New routes towards organocatalysis using the Corey-Chaykovsky aziridination reaction

PhD Thesis

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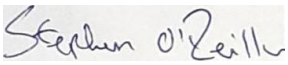
Signed:  Name: Stephen O'Reilly

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Contents

Abbreviations

ABCN	1,1′-Azobis(cyclohexanecarbonitrile)
ACN	Acetonitrile
AIBN	Azobisisobutyronitrile
API	Active Pharmaceutical Ingredient
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1′-Bi-2-naphthol
Boc	*tert*-Butyloxycarbonyl
COSY	Crrelation Spectroscopy
CWR	Catalytic Wittig Reaction
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DEPT	Distortion Enhancement by Polarisation Transfer
DHBT	2,3-Dihydrobenzothiophene
DIBAL	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine
DMF	Dimethylformamide
DMSO	Dimethyl Sulfoxide
DMSO-d_6	Dimethylsulfoxide d6
DOPA	3,4-Dihydroxyphenylalanine
dr	Diastereomeric Ratio
EDG	Electron-Donating Group
ee	Enantiomeric Excess
EWG	Electron-Withdrawing Group
Hex	Hexane
hfacac	Hexafluoroacetylacetone
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence

LVT	Low-Valence Titanium
NMR	Nuclear Magnetic Resonance
PMI	Process Mass Intensity
rt	Room Temperature
Sln	Solution
SOMO	Singly Occupied Molecular Orbital
TBDMS	*tert*-Butyldimethylsilyl
TEA	Triethylamine
THF	Tetrahydrofuran
THP	Tetrahydropyridine
THT	Tetrahydrothiophene
TLC	Thin Layer Chromatography
TMG	1,1,3,3-Tetramethylguanidine
Tol	Toluene
Ts	Tosylate

Abstract

New routes towards organocatalysis using the Corey-Chaykovsky aziridination reaction, by Stephen O'Reilly

Organocatalysis and green chemistry are major areas of modern research. The current project aims to apply these concepts to development of a catalytic Corey-Chaykovsky reaction.

Chapter 1 provides an extensive review of current literature and an outline of the goals of the current research. In Chapter 2, a method has been developed for the Corey-Chaykovsky aziridination reaction using imine and sulfonium salt starting materials for the selective synthesis of vinylaziridine or aryl pyrroline. It has been shown that the choice of base used in the reaction plays a crucial role for product selectivity. Further investigations suggest that a rearrangement of vinylaziridine to pyrroline is unlikely, and the base used may activiate the intermediate molecule.

In Chapter 3, a synthetic pathway has been developed for three target dihydrobenzothiophene sulfides to be used in the Corey-Chaykovsky reaction (one chiral sulfide). The core structure was synthesised but the sulfonium salt derivative could not be formed. Substituted derivatives not synthesised due to crucial steps being unsuccessful. However, the five new compounds were prepared and fully characterised, and alternative synthetic pathways have been proposed.

In Chapter 4, three derivatives of pyrroline were synthesised with a future goal of using them as organocatalysts. A detosylation study was performed and needs further optimisation. The methods developed are adaptable for asymmetric synthesis to obtain enantiomerically pure samples of pyrrolidine suitable for use as an organocatalysts.

In Chapter 5, the shortcomings of the working chapters (2-4) have been addressed and alternative synthetic strategies suggested, with particular emphasis on obtaining enantiomerically pure compounds, all with appropriate reference to evidence and precedent from the literature.

Acknowledgements

I would like to thank the Irish Research Council and DCU for my funding as well as the incredible technical staff at the DCU School of Chemical Sciences, especially Veronica Dobbyn, Damien McGuirk, John McLoughlin and Ambrose May. I also thank my supervisor, Dr. Emma Coyle. I would also like to hugely thank the incredible Dr. Kieran Nolan, as well as Dr. Nessan Kerrign, Dr. Aoife Morrin, Dr. Jamie Walsh and Dr. Hasim Ibrahim. And of course a bit thanks to all my colleagues and friends in DCU, and of course my family and girlfriend for putting up with me.

Chapter 1

Chapter 1 Introduction and literature review

1.1. Introduction

The goal of the modern synthetic organic chemist is not just to find new routes to desired molecules, but finding methods that are cost effective, robust, environmentally friendly and stereospecific. Organocatalysis has, in the last 20 years, attempted to address this by using chiral organic molecules as catalysts rather than metal complexes, which can be expensive and environmentally threatening. The explosion of interest in organocatalysis in the last two decades coincides with the newly emerged area of green chemistry, which aims to make synthetic chemistry in the pharmaceutical industry sustainable, affordable and reusable in the future while also minimising waste and pollution as defined by the twelve principles of green chemistry.[1]

It is not just, however, the aim of green chemistry to find new methods for forming new molecules, but also redeveloping old methods to align them with the fundamental twelve principles. Examples recently include the development of the catalytic Wittig reaction (CWR),[2] which redeveloped the decades old method for synthesising alkenes from carbonyls into an efficient catalytic process with reusability and stereocontrol of the products. A similar approach to develop a catalytic cycle around the Corey-Chaykovsky aziridination process is thus the aim of this current research. This will facilitate the efficient, and asymmetric, synthesis of highly useful aziridines for use as synthons, as well as making aryl pyrrolines, which themselves have great potential as organocatalysts. The Corey-Chaykovsky reaction uses sulfur ylides, and the proposed catalytic cycle would use an organosulfur precatalyst as the reusable component. The reaction must first be optimised to selectively synthesise each of the two possible products, before developing a catalytic cycle, which would use more complex sulfide structures to induce stereoselectivity and 'tune' the ylide. The aryl pyrroline from the reaction can then itself be further modified and functionalised to use as an organocatalyst in other reactions.

This interdisciplinary project has the potential to help develop many new areas of organic chemistry such as organocatalysis, asymmetric synthesis and green chemistry. This literature review will examine modern organocatalysis and green chemistry and discuss the limitations and advantages that have arose. Also reviewed will be the Corey-Chaykovsky reaction, and how the aziridination reaction has been overshadowed by the analogous epoxidation. Great potential resides in the aziridination as well as the vinylaziridine to pyrroline rearrangement that has been noted under various circumstances in numerous publications. Pyrrolines being the major product of the Corey-Chaykovsky aziridination is not well known, but would be highly useful if it could be optimised.

1.2. Organocatalysis

Organocatalysis describes the use of small, chiral organic molecules for asymmetric catalytic processes as an alternative to the more mainstream methods of organometallic and enzymatic catalysis. There have been several examples of this form of chemistry throughout the twentieth century, such as the use of alkaloids from the cinchona plant for nucleophilic addition to aldehydes[3] and the Hajos-Parrish-Eder-Sauer-Weichert asymmetric aldol reaction which produces starting materials for the synthesis of steroids.[4] Organocatalysis, however, was never considered a major field in synthesis and new synthetic methods were normally expected to be found with biological and organometallic chemistry.[5] This began to change in the late 1990s, with two landmark papers in 2000 effectively launching organocatalysis to mainstream attention. The first was by List *et al*. who demonstrated the use of the cyclic amino acid (*S*)-proline (**A1**) for asymmetric aldol reactions.[6] The second was by MacMillan *et al*. who reported on an enantioselective organocatalytic Diels-Alder reaction using more complex N-containing heterocycles (**A2 and A3**) (**Figure 1**).[7]

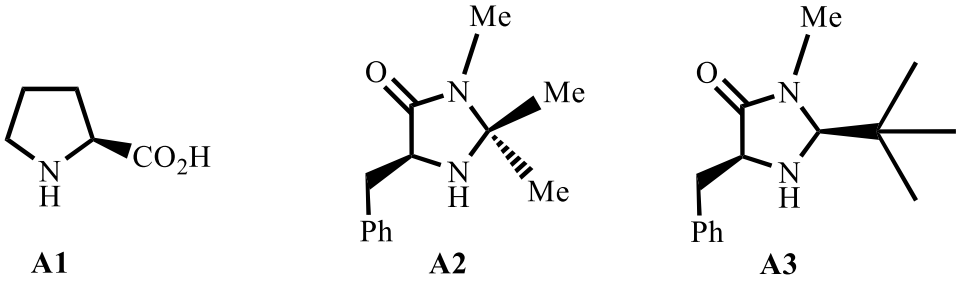


Figure 1: (*S*)-proline (A1, left) and MacMillan organocatalysts (A2 and A3, right)

Organocatalysts can generally be defined by their activation mode. That is, the transition state that forms when the substrate binds to the catalyst. Catalysis by (*S*)-proline, as developed by List, forms an enamine activation mode, whereas the MacMillan catalysts form an iminium intermediate. The discovery of the imine (**A5**) and enamine (**A5**) activation modes (**Figure 2**) attracted much interest as it meant both catalysts could be applied to a much more diverse range of reactions. It was for this reason that the 2000's saw an explosion of interest in this new chemistry field but also was the significant advantages organocatalysts offers over conventional catalysts. Compared to metal catalysts, they tend to be cheaper, much easier to handle and have less environmental impact and they avoid the biological complexities and hazards associated with enzymatic catalysis and are easier to use.[8]

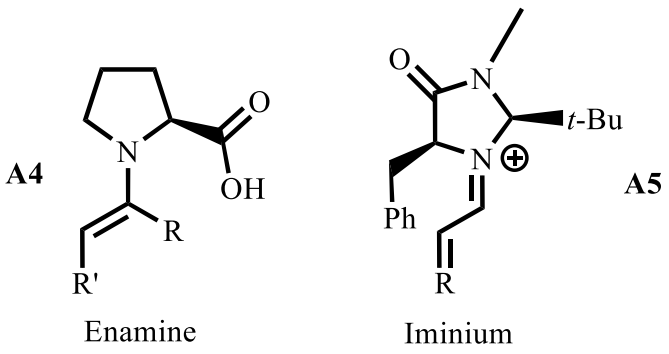


Figure 2: Enamine (left) and iminium (right) activation modes

The newfound interest in the topic led to the enhancement and expansion of the iminium and enamine activation mode catalysts, as well as the discovery of new modes. (*S*)-proline enamine catalysis has been applied to many more reactions, notably the Mannich and Michael reactions, while MacMillan's iminium catalysis has been applied to conjugate amination, oxygenation and sulphenylation reactions, among others.[8] New modes that have been discovered include hydrogen-bonding catalysis which is applicable to carbonyl and imine containing substrates that can intermolecularly interact with the H on the catalysts' amine groups, enhancing stereoselectivity.[9] Another mode was later developed by MacMillan called singly occupied molecular orbital (SOMO) catalysis where a carbonyl substrate (**A6**) binds to the amine group on the catalyst (**A3**) producing a radical, cationic species (**A7**) with three π electrons which is then susceptible to nucleophilic attack in the α position (**Figure 3**).[10]

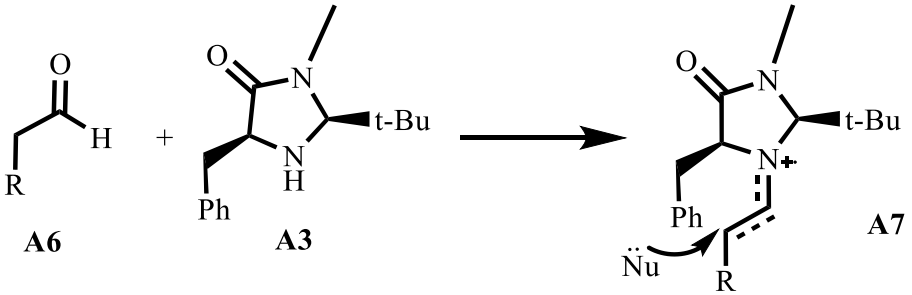


Figure 3: SOMO Activation mode; carbonyl compound combined with MacMillan catalyst to form a radical, cationic activation mode which is susceptible to nucleophilic attack

Chiral thioureas are a highly utilised class of organocatalysts that operate via a through bond activation mode where the hydrogens on the two amine groups of the thiourea moiety coordinate to the substrate. Early research groups to publish work on thiourea organocatalysis were led by Schreiner,[11] Jacobsen[12] and Takemoto.[13] An early application by Schreiner is the Diels-Alder of an α, β-unsaturated aldehyde (**A8**) (**Figure 4**)

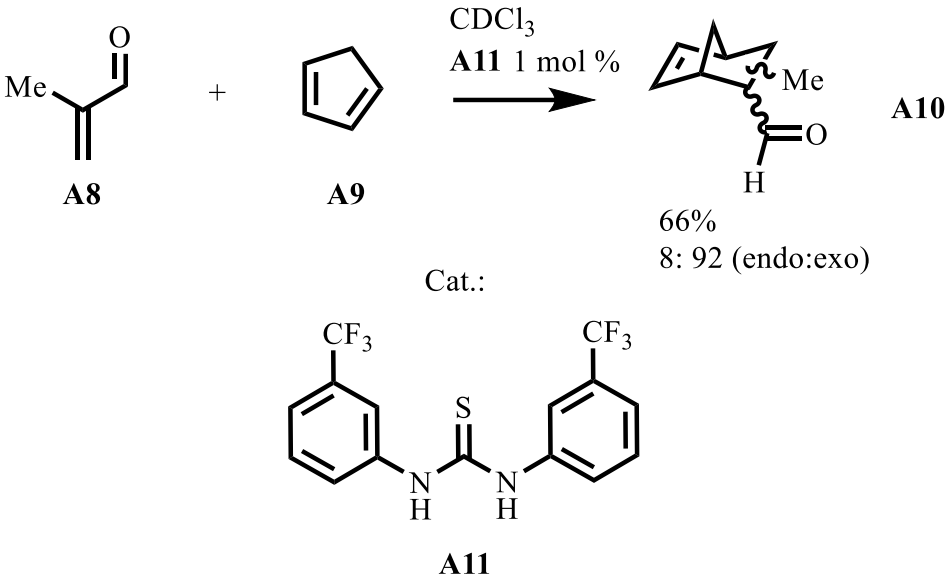


Figure 4: Schreiner's thiourea A11 catalysed Diels-Alder reaction

Jacobsen has applied chiral thiourea catalysts to the Mannich reaction, achieving excellent yields of up to 89% with ee values as high as 98% (**Figure 5**).[14]

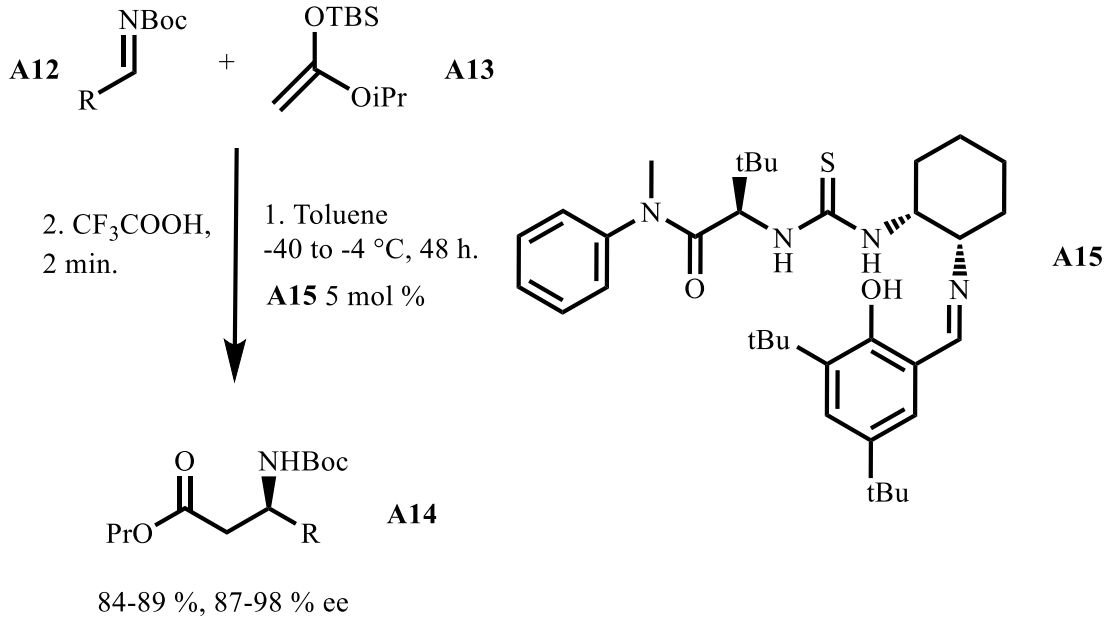


Figure 5: Jacobsen chiral thiourea catalysed Mannich reaction

An interesting recent application of thiourea organocatalysts was reported by Li *et al.*[15] where a bifunctional catalyst (**A18**), with two moieties with separate catalytic functions, was used to synthesise cyclic carbonates (**A17**) from an epoxide (**A16**) and CO_2 (**Figure 6).** The first catalytic moiety features a charged ammonium group with a counter anion. This counter anion opens the epoxide ring, and the resulting transition state coordinates to the thiourea moiety before CO_2 addition. The best performing counter anion was bromide but this was not studied extensively. The chain length between the charged ammonium group and the thiourea group was also crucial for catalytic performance, but only varying alkyl linkers were tested. Aryl and allyl linkers would be a more complete study.

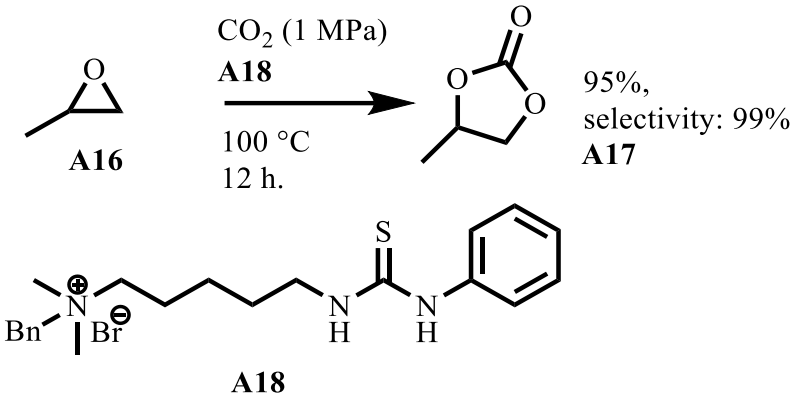


Figure 6: Li et al. cyclic carbonate synthesis using a bifunctional thiourea catalyst

Isothiourea through bond organocatalysis emerged as a progression from thiourea catalysis,[16] with early pioneering research reported by Birman *et al.*[17] Isothioureas have a thiourea group locked in a ring structure. Smith *et al*. reported in 2014 a Mannich application of a chiral isothiourea catalyst (**A21**) using tosylated aryl imines with aryl carboxylic acids (**A19**) to synthesise **A20** and achieved excellent ee values of 95% (**Figure 7)**.

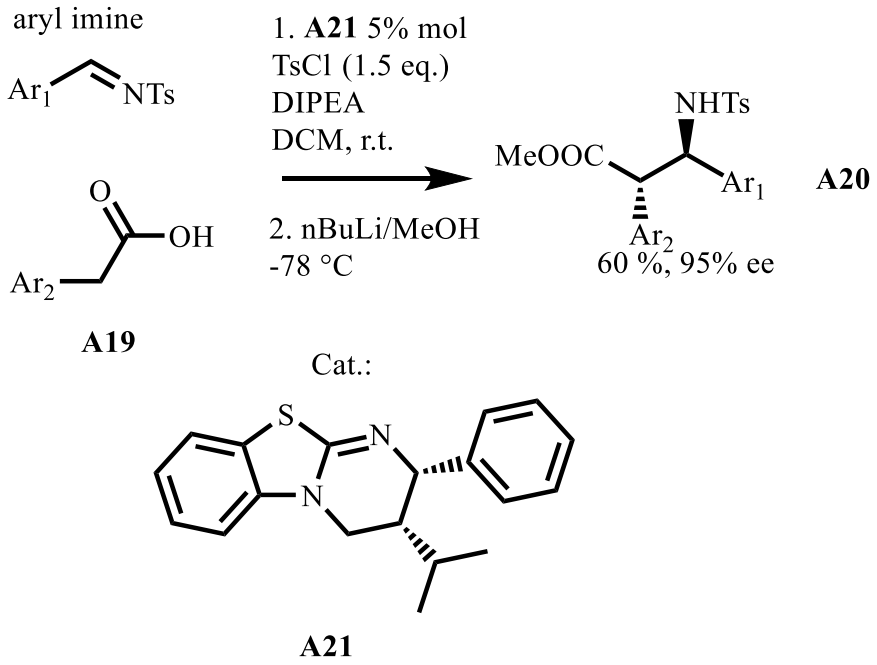


Figure 7: Smith et al. Mannich reaction using chiral isothiourea catalysis

Medicinal applications of organocatalysis have become increasingly common in the last decade. The absence of metals is particularly desirable for pharmaceuticals that cannot tolerate metal contamination. It is also widely accepted that the more steps involved in the synthesis of an active pharmaceutical ingredient (API) the higher the drug cost, generally.[18] Therefore, new synthetic routes are constantly being sought after, particularly for drugs needed in third world areas, where high drug prices remains a major issue.

Tetrahydropyridines (THPs, **A27**) have been synthesised by using (*S*)-proline (**A1**) to form an enamine activation mode with a β-ketoester (**A22**), which in turn reacts with an aromatic

aldehyde and then an aniline to form a new enamine. Concurrently, an imine is formed with the reaction of the aldehyde and the aniline, which in turn undergoes a Diels-Alder reaction with the enamine to form the final THP product (**A27**, **Figure 8**). These THPs have been screened extensively for anti-malarial activity against *plasmodium falciparum* in vitro, with promising results (*p*-methoxy groups on the aryl substituents provided best hits) and structure activity relationship (SAR) studied.[19] It has also been reported that guanidine derivatives have been synthesised using quinine alkaloids as organocatalysts in an imine activation mode, with *p*-halogen aryl substituents providing best hits against a range of malaria-causing parasites.[20]

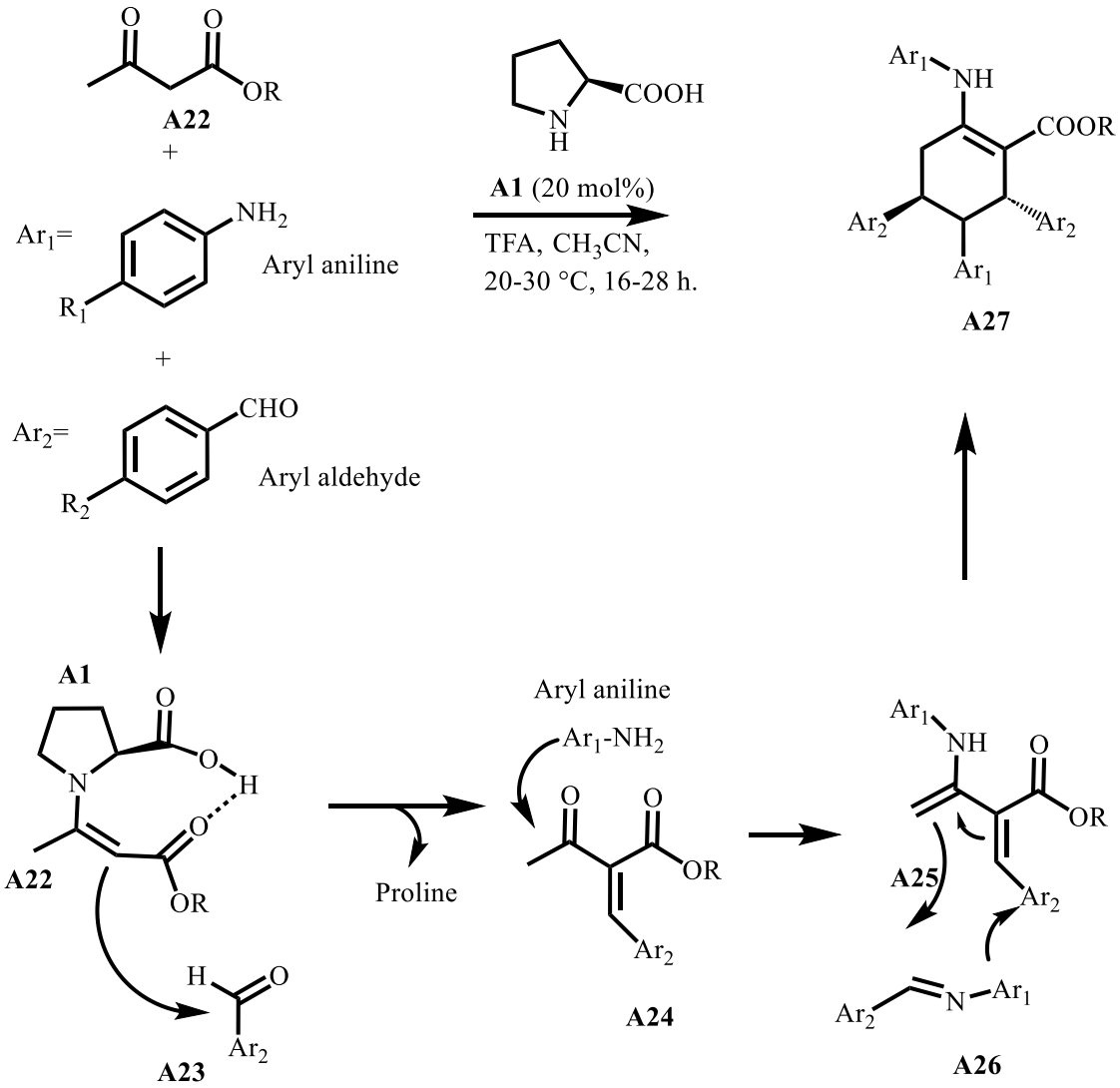
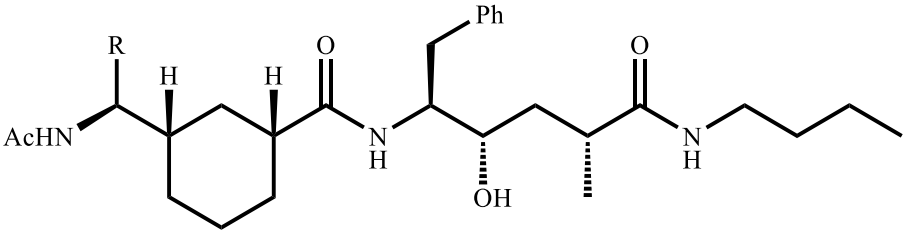


Figure 8: THT compound A27 synthesised from β-ketoester (A22), aryl aniline and aromatic aldehyde using (*S*)-proline (A1) via an enamine activation

Hanessian *et al*. have designed a series of peptide mimetics (**A22**, **Figure 9**) (small molecules with amino acid groups which can 'mimic' proteins) for use as β-secretase (BACE) inhibitors.[21] BACE are proteases which have been theorised to play a role in amyloid plaque accumulations in the brain, a potential major cause of Alzheimer's disease. The mimetics had a general structure of a small peptide chain attached to a cyclohexane moiety with an amino group. The first step in the synthesis of these mimetics was the 1,4-

addition of a nitroalkane to cyclohexenone to form the cyclohexane moiety, from which the amino acid chain could be added. This key step was catalysed with proline to induce asymmetry, utilising an imine activation mode. High branching with *i*-Pr at the nitro side of the cyclohexane was proved to be crucial for inhibition of the protease.

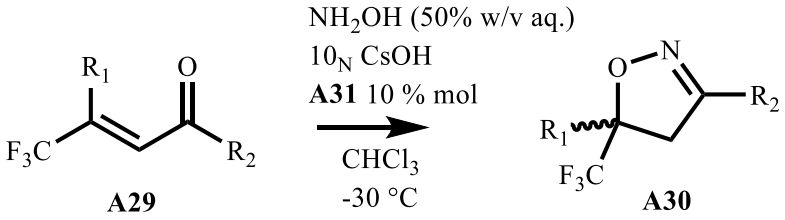


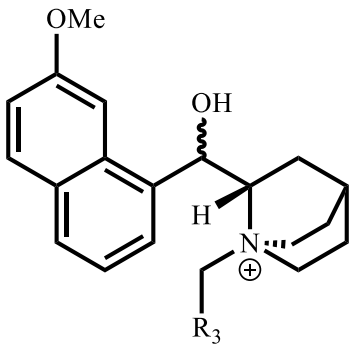
A28

Figure 9: General structure of the Hanessian designed peptide mimetic A28

Gilead Sciences Inc., reported in 2015 of the synthesis of a starting material in the synthesis of a useful hepatitis C virus inhibitor. The cyclohexene product is synthesised by a Diels-Alder reaction with use of an oxazaborolidine organocatalyst for enantioselectivity using a Lewis acid-base activation mode.[22]

Asymmetric synthesis of isoxazolines is an important process for making insecticides in veterinary medicine. Nissan Chemicals Industries filed a patent in 2009 using charged cinchona alkaloids (**A31**) as organocatalysts for isoxazoline (**A30**) synthesis using trifluoromethyl substituted α, β unsaturated ketones/esters (**A29**) as starting material and proceeding through addition/cyclisation/dehydration reaction sequence (**Figure 10**).[23-24] Yields of 98% with 78% enantiomeric excess (ee) were recorded.





A31

Figure 10: Isoxazoline (A30) synthesis using charged cinchola alkaloids (A31) as a catalyst

The use of organocatalysis in modern medicinal chemistry has been recognised as substantial, particularly in recent years, with many examples being reported in the

literature. The reactions above, along with most in modern industry, are performed in batch production. However, continuous flow reactions have garnered considerable interest in recent years due to major advantages it offers over batch production, which include better mixing quality, improved operational safety, real time reaction monitoring and easier reaction optimisation and scalability. Flow reactions have thus been recently applied to organocatalytic processes with the aim of improving reaction efficiency.[25] Perhaps the most famous reaction in organocatalysis is the asymmetric aldol reaction using (*S*)-proline.[26] This reaction was performed using flow in 2009 by Odedra *et al*. where the catalyst (**A32**) was loaded on a glass microreactor and the starting materials and solvent was passed through with syringe pumps under homogeneous conditions (**Figure 11**). The reported yield of the aldol product (**A33**) and ee was an improvement on batch production. The reaction was also reported using heterogeneous conditions, by loading a range of organocatalysts to silica.[27] The flow process has been extended to include a range of different catalysts and other reactions, such as the Michael addition[28] and Mannich reaction,[26] where yields often matched or improve on batch production, and reaction time is generally shorter and milder conditions can be tolerated. Flow organocatalysis is still very much in its infancy but these recent results present the topic as a very interesting research area for the future and will certainly attract the attention of industry for competing with batch production.

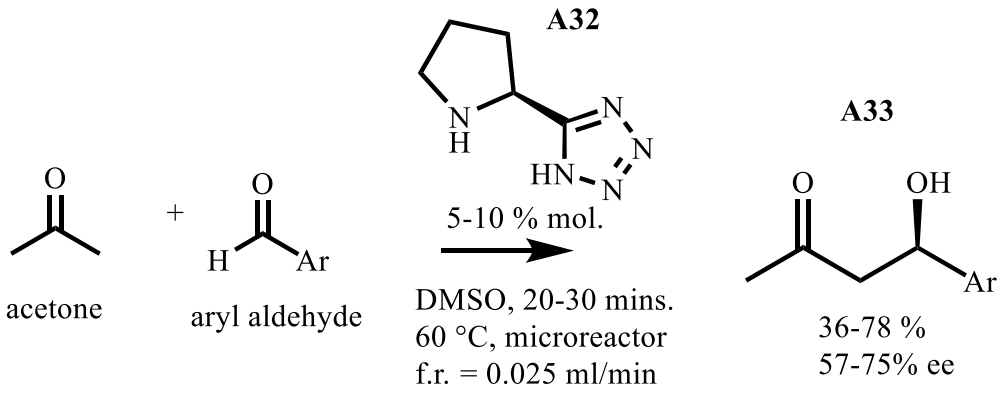


Figure 11: Asymmetric aldol (A33) organocatalytic synthesis by flow chemistry using (*S*)-proline derivative (A32)

Along with flow chemistry, a recent area of research is merging organocatalysis with photochemistry. Normal organocatalytic processes involve a two-electron activation mode, but photo organocatalysis aims to use a one-electron process generating a radical. These one-electron activation modes offer unique transformations and can enhance enantioselectivity. Two types of reactions of light in organocatalysis have emerged. The first is dual catalysis, where an organocatalyst works in conjunction with a photosensitive metal catalyst to generate a radical species under relatively mild conditions. The newly generated radical activation mode has thus expanded its potential functionality.[29] MacMillan reported in 2008 the use of a dual catalyst approach for the α-alkylation of aldehydes using a ruthenium photocatalyst. The first step of this process proceeds as normal, where the aldehyde (**A35**) bonds with the organocatalyst (**A34**) to generate the enamine activation mode (**A36**). Next the alkyl halide (**A41**) is reduced by the ruthenium complex (**A42**) which has been activated by visible light, generating an alkyl radical (**A37**) which in turn bonds to the enamine organocatalytic transition molecule (**A36**) creating a

'stereoselective radical trap'(**A38**). The single electron is then transferred back to the metal complex and the newly generated molecule (**A43**) hydrolyses to form product **A44** and the organocatalyst (**A34**, **Figure 12**).[30]

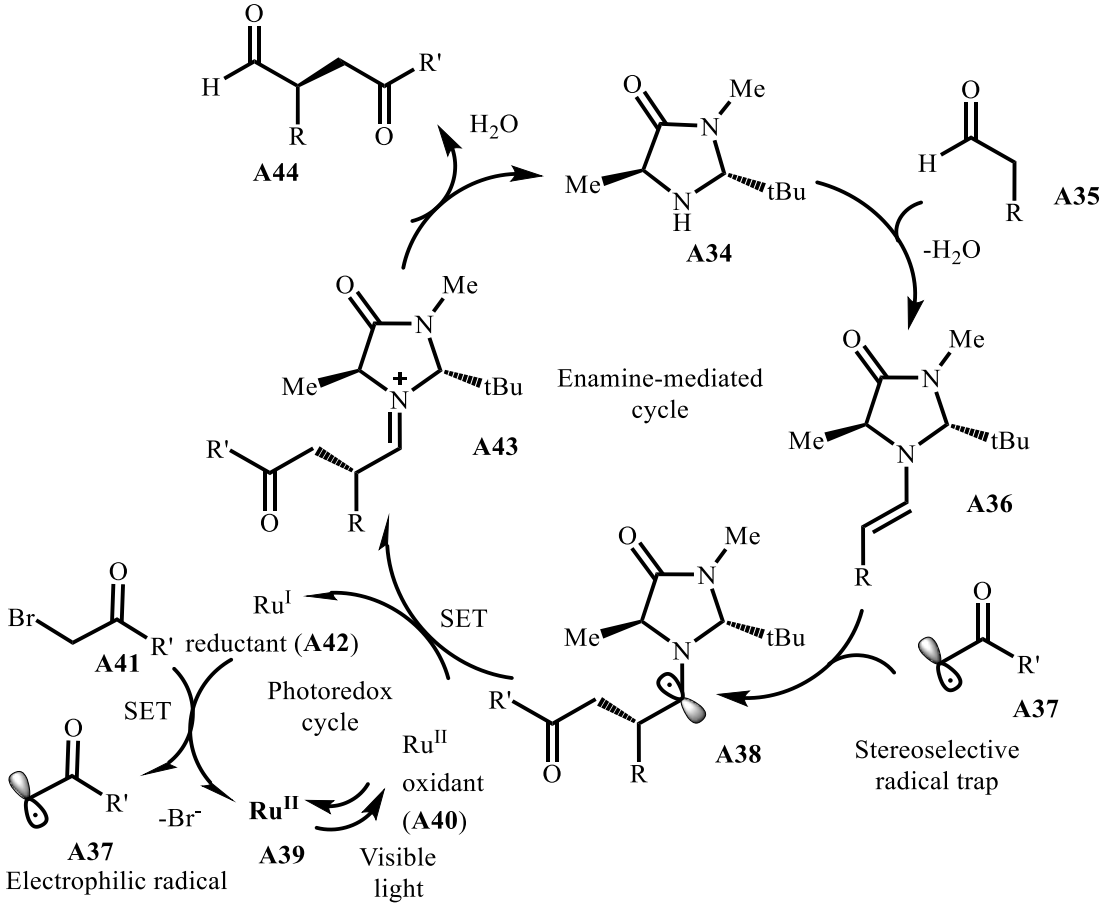


Figure 12: Photo organocatalysis; dual catalytic approach cycle with the enamine activation mode (A36) attacked by radical A37 to form new mode A38. A38 is in turn oxidised by the Ru complex to form the charged mode A43, which produces product A44. The reduced Ru complex is then oxidised by light generate more of radicals A37

This dual catalyst approach has been applied to SOMO and imine activation modes as well. The second type of photo organocatalysis is single catalysis which involves the photo excitation of organocatalysts themselves, generating radical activation modes to enhance enantioselectivity.[29] In 2013, Arceo *et al.* reported using an enamine activation mode for α-alkylation of aldehydes. The process involves more complex organocatalysts with increased conjugation along with additional reagents to assist the radical chain reaction.[31] Single photo organocatalysis, along with dual photo organocatalysis, are still very much in their infancy, like flow organocatalysis. This is likely to be the next major area of organocatalytic research, with major developments expected in the coming years, according to a 2018 review by Silvi *et al.*[29] Single photo organocatalysis appears particularly attractive as it uses no metals, reducing cost and environmental impact, and can directly compete with metal photocatalysts, which themselves have become a major area in synthetic and inorganic chemistry.

Acridinium salts have also emerged as a major type of organic photoredox catalysts and function without the need for a metal co-catalyst. These catalysts have been used for the

same reactions used with the much more widely utilised ruthenium and iridium redox catalysts, such as the decarboxylative conjugation of an (*S*)-proline derivative (**A44**) with **A45** to a dimethyl maleate derivative (**A46**) using catalyst **A47** (**Figure 13**). Yields recorded were as high as 88%, similar to those reported with ruthenium redox catalysts but stereoselectivity was not reported.[32]

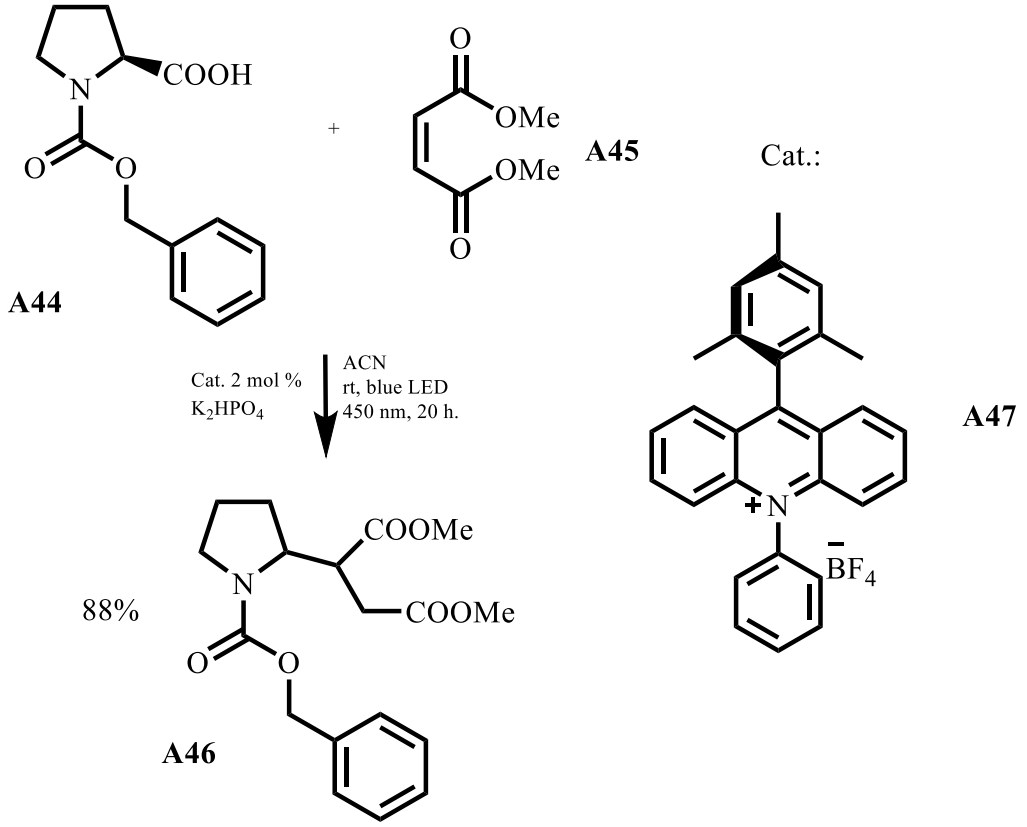


Figure 13: Decarboxylative conjugation of (*S*)-proline derivative A44 using an acridinium salt co-catalyst A47

These are just two examples of photo organocatalysis but a large number of examples are reported in the literature with extensive work reported by Nicewicz[33] and Fukuzumi.[34]

There are many recent examples of different synthetic reactions that have utilised organocatalysis which are given as examples below;

It was noted by Gallier *et al.* in a recent review that organocatalysis has emerged as a highly useful route towards rare and non-natural carbohydrates as well as stereoselective glycosylation reactions.[35] A recent example is the synthesis of a phenyl substituted D-ribose derivative (**A50**) using acetal protected acetone (**A48**) and a phenyl aldehyde which undergoes an α-chlorination with *N*-chlorosuccinimide while simultaneously forming an enamine activation mode with (*S*)-proline to form chlorinated aldol (**A49**) in low enantiomeric excess, which is then cyclised to form the ribose (**A50**, **Figure 14**).[36]

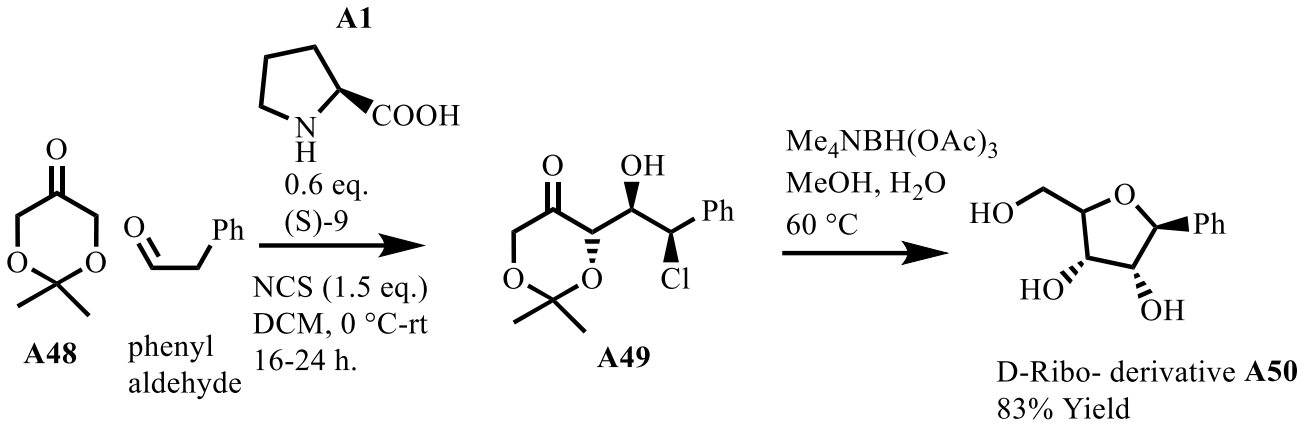


Figure 14: D-Ribose derivative (A50) synthesised using (*S*)-proline (A1) organocatalysis and acetal protected acetone (A48) and a phenyl aldehyde which forms the chloro aldol A49

The glycosylation reaction of carbohydrate monomers has been described as one of the most important but also most difficult in synthesis.[35] An organocatalytic alternative has recently been reported using chiral phosphoric acids, such as the Akiyama–Terada catalyst shown in **Figure 15**. The method reports the need to prepare glucoside trichloroacetimidate starting material, which is subsequently reacted with the relevant alcohol at -40 °C to form a glycosylated carbohydrate. The chiral phosphoric acid coordinated with both the glucoside starting material and the alcohol to coordinate the direction the molecules couple at. While yields for the sugar product were lower than the non-organocatalytic alternative of BF_3.OEt (but still as high as 88%) the stereocontrol of the reaction was better, with β/α ratio reported as high as 70:1. It was also noted that catalytic equivalence needed was higher, however, with 0.6 equivalence needed for some reactions (**Figure 15)**.[37–39]

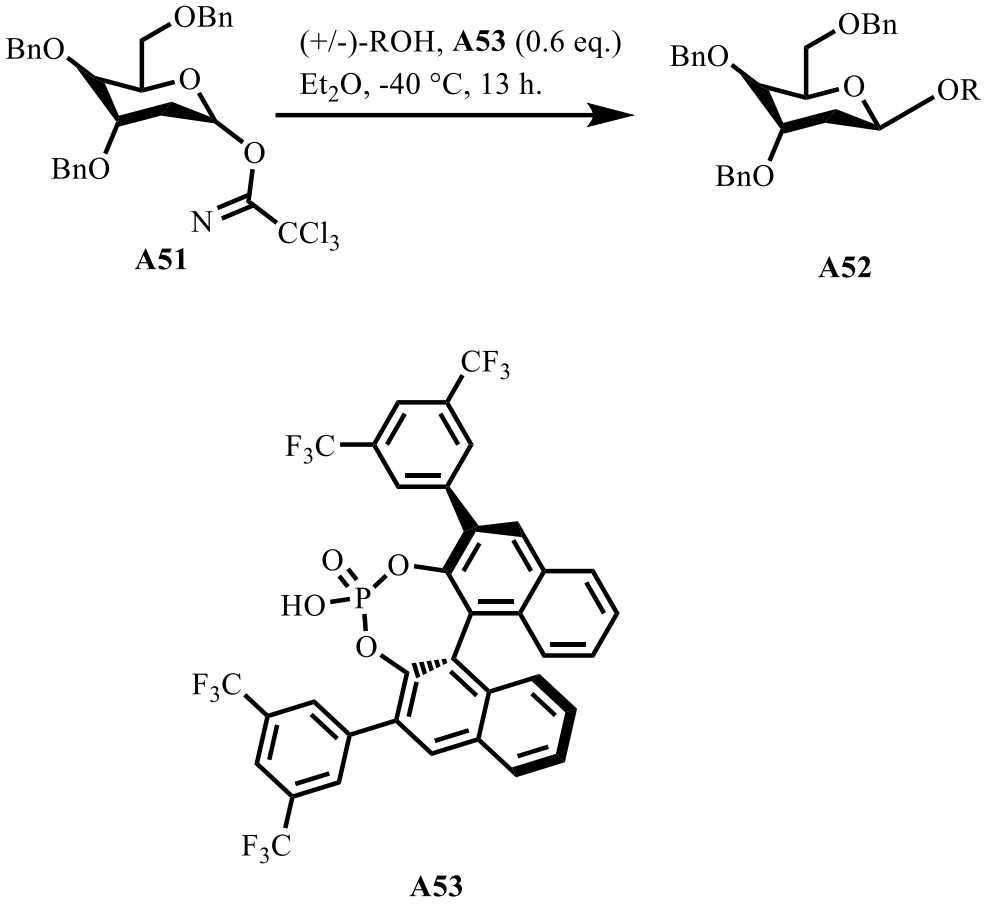
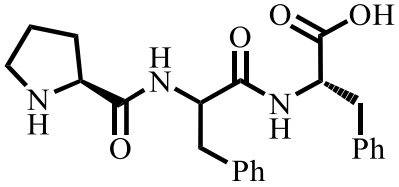


Figure 15: Synthesis of glycosylated sugar A52 from the glucoside trichloroacetimidate starting material A51 using a chiral phosphoric organocatalyst A53

An interesting recent development was noted by Sinibaldi *et al.* which uses a tripeptide consisting of *D*-proline and two *L*-phenylalanines (called PFF, **A54**, **Figure 16**).[40] It was reported that this structure has the effect of accelerating the organocatalytic rate of a Michael reaction (isovaleraldehyde addition to β-nitrostyrene). The conversion rate of the product was reported to be over 60% after 24 hours, compared to 29% using just (*S*)-proline, with ee values of the purified product as high as 71% when using phosphate buffered saline (PBS) as a solvent. It was theorised that the tripeptide places the organocatalytic moiety in a supramolecular state, which in turn forms a more organised lipophilic pocket with cooperative interactions to accelerate the catalysis.



PFF (D-Pro-L-Ph-L-Ph)

A54

Figure 16: PFF (A54)

While (*S*)-proline (**A1**) is still widely used and being researched as an organocatalysis, the next generation of (*S*)-proline derivatives have been noted recently.[41] Diamine derivatives

of (*S*)-proline have been synthesised and used in numerous reactions. One example is the enantioselective reduction of chiral ketones using borane as a mediator, where the boron coordinates to both amine groups. Yields for the synthesis of the catalyst **A58** was reported as 99% with an ee value of 84%. The synthesis is outlined in **Figure 17**.[41,42]

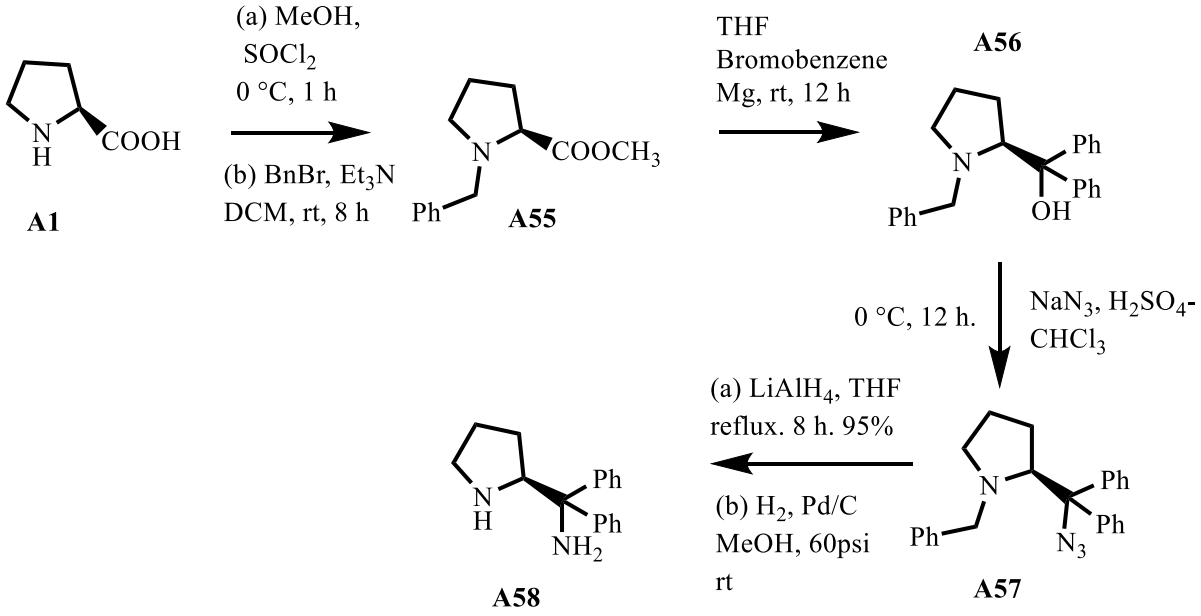
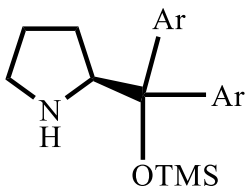


Figure 17: Synthesis of diamine derivative of (*S*)-proline (A58) for use as an organocatalyst for the borane mediated reduction of chiral ketones

α-α and α-β dipeptide derivatives of (*S*)-proline have also been recently reported as new novel organocatalysts.[41,43] These derivatives have been reported in the synthesis of novel heterocycles, and it was noted that there is a constant search for new (*S*)-proline like structures that can be evaluated as catalysts. Interesting it was noted that when using an α-α dipeptide of (*S*)-proline conjugated to (*S*)-phenylglycine for a novel aldol synthesis the catalyst could be used under solvent-free conditions using a technique called high speed ball milling, with 70% yields reported and 95% ee. It was theorised that the solvent-free conditions maximise the π-π interactions with the substrate.[41,44]

Jørgensen–Hayashi catalysts are widely used (*S*)-proline-derived catalysts (**A59, Figure 18**) that have a silyl and two aromatic functional groups in place of the carboxylic acid moiety to improve solubility of the catalyst in organic solvent as well as improving the activation of the amine group.[45, 46]



A59

Figure 18: Jørgensen–Hayashi catalysts

A major issue noted when using (*S*)-proline as an organocatalyst is its poor solubility in many organic solvents, making it difficult to find a solvent mix that can effectively dissolve both the catalyst and the substrate. Recovery of the catalyst can be difficult too. The use of

additives has been explored recently, such as the use of solvate ionic liquids (SILs).[47] These most often consist of an alkaline metal cation , such as Li^+, added to a glyme moiety which in turn form a complex, which is added to the regular solvent mixture. It was noted in a novel aldol reaction that yields were boosted from 60% to 90% compared to not using the SIL, and % ee values were increased slightly, and the catalyst was more easily recoverable.[22]

It has been reported recently in the literature that *N*,*N*′-bis(triflyl)phosphoramidimidates (PADIs) have been used as Bronsted acid catalysts for the stereoselective synthesis of vinyl ether (VE) polymers. The organocatalyst uses a cationic reversible addition fragmentation transfer (RAFT) process and is the first such of its kind reported. The catalyst is used in a 0.1 eq. with 100 eq. of the vinyl ether monomer and 1.0 eq. of the chain-transfer agent (CTA). The reaction was broadly tolerable with different side groups on the VEs with M_n values ranging from 70000-160000 daltons and very good weight distributions recorded as low as 1.20 D.[48]

1.3. Corey-Chaykovsky reaction

In 1962, EJ Corey and Michael Chaykovsky at Harvard University published their work on carbanions, specifically those substituted with alkylsufinyl groups. They reported on the ease of synthesis and great stability of these ylides.[49-50] Most ylides, defined as an overall neutral molecule with one positively charged heteroatom and one adjacent negatively charged carbon atom, reported to this point were phosphonium ylides used in the Wittig reaction for the synthesis of alkenes from carbonyl groups. The carbonyl on the sulfinyl group provided conjugation and, as noted by A. William Johnson *et al*., whose group's work with sulfur ylides coincided with Corey and Chaykovsky, the vacant, low energy d orbitals of the sulfur, which are also present in phosphorous, play a key role in the stability of the ylide.[51] Corey and Chaykovsky also noted the unexpected result of epoxide formation when treating benzaldehydes with this stable ylide (**Figure 19**),[49 50] as opposed to phosphonium ylides which formed alkenes. Interested in the chemistry of this unique carbanion, Corey and Chaykovsky undertook an extensive investigation of this reaction.

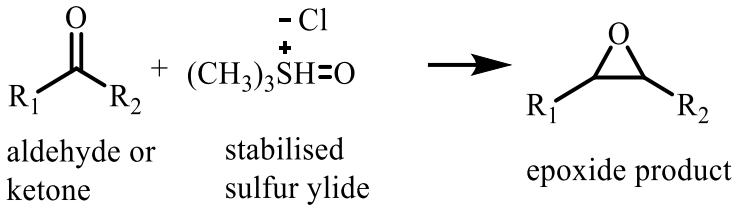


Figure 19: Epoxidation of an aldehyde or ketone by a sulfoxonium salt, as first noted by Corey and Chaykovsky in 1962

First they reported on the unique chemical properties of the oxosulfonium ylide.[52] It was again noted that this ylide is quite stable due to the attached oxygen on the sulfur, allowing delocalisation of the electrons. Another interesting observation was when this ylide was reacted with esters, which generally led to the formation of β-keto sulfoxides. This reaction was quite general, tolerating aryl and alkyl groups in very good yield. These β-keto

sulfoxides were noted as being highly useful synthetic intermediates, most usefully they can easily be converted to ketones by removal of the sulfinyl group by replacing it with a hydrogen. Thus, this paper reported a very useful and general method for converting esters to ketones.

A subsequent paper was more extensive and dealt with the interesting observation noted in the 1962 communication regarding the formation of epoxides from ketones using the oxosulfonium ylide.[53] The paper also reported on the synthesis of the sulfonium ylide, which was similar to the oxosulfonium ylide but lacked the oxygen group on the sulfur, preventing the delocalisation of electrons, thus the ylide was much more unstable (**Figure 20**).

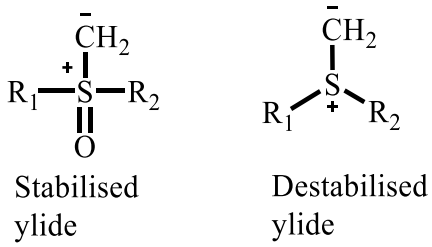


Figure 20: Oxosulfonium stabilised ylide (left) and sulfonium destabilised ylide

The team firstly examined the ketone to epoxide reaction and developed the method. Both ylides can firstly be synthesised as sulfonium salts using an akyl halide. The ylide can then be generated in situ by treating the salt with a base (NaH), deprotonating the α-carbon. The ylide is then added to the ketone and the epoxide is synthesised (**Figure 21,** epoxidation). It was noted that the sulfonium ylide was much more powerful and gave higher yields. This is down to its greater instability and thus is easier to react with the ketone. The general mechanism for the epoxidation was also suggested (**Figure 22**).

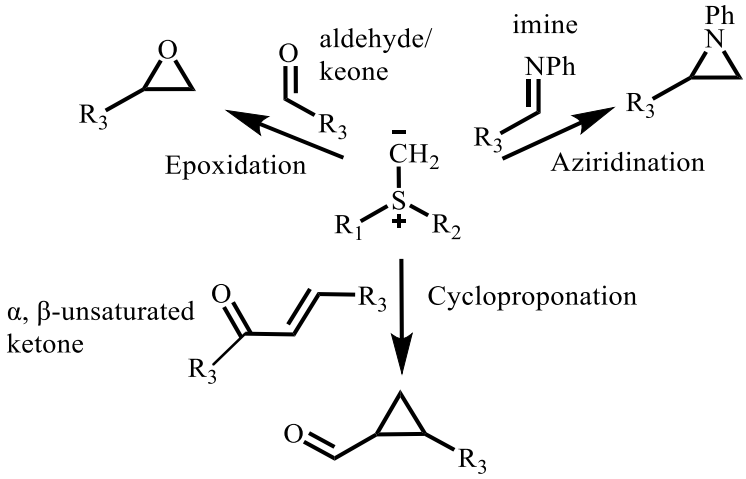


Figure 21: Corey Chaykovsky epoxidation, aziridination and cyclopropanation using a destabilised ylide. Note that destabilised ylides work best for the aziridination, while stabilised ylides are best for the cyclopropanation and the epoxidation tolerates both well.

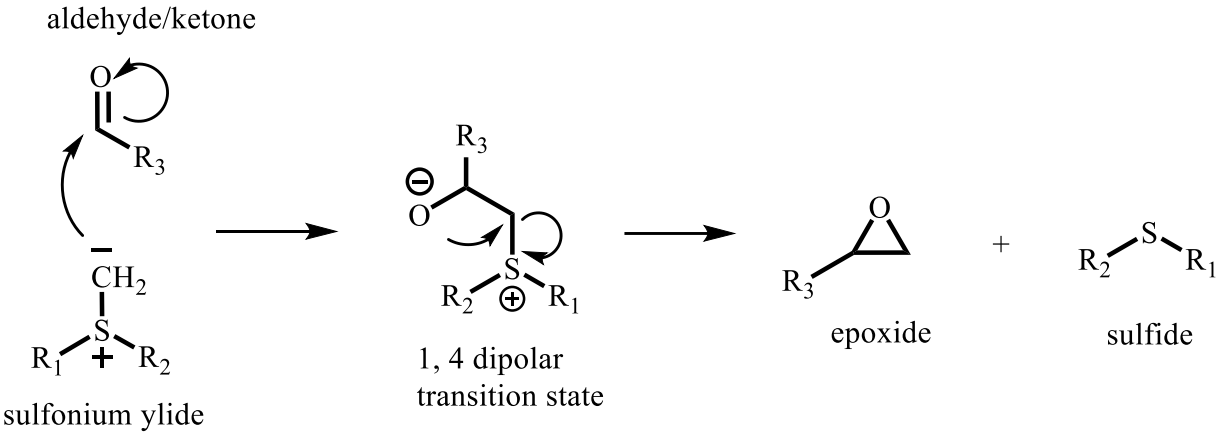


Figure 22: General epoxidation mechanism suggested by Corey and Chaykovsky

The team then extended the reaction to imines to synthesise aziridines, analogous to the epoxidation. The sulfonium ylide was reacted with benzalaniline (where the nitrogen is protected with a phenyl group). This reaction gave a good yield with the sulfonium ylide, however when using the oxosulfonium ylide the reaction was much more sluggish and gave a series of by-products. Also tested were α, β-unsaturated ketones. Interestingly, when using the sulfonium ylide, the major product was the epoxide, but when using the oxosulfonium ylide the major product was the cyclopropane, with the methyl group from the ylide adding across the carbon-carbon double bond. (**Figure 21,** aziridination and cyclopropanation) This study revealed the control over the ylide reaction.[53] Alkene groups do not generally react with the ylide unless part of an α, β-unsaturated ketone and using an oxosulfonium ylide. Imine to aziridine needs a protection group on the nitrogen and only proceeds smoothly with a sulfonium ylide. The imines also need to be conjugated with an aryl group. Ketones and aldehydes undergo epoxidation with both sulfonium and oxosulfonium ylides, with sulfonium providing the best yields.

With this landmark study, the Corey-Chaykovsky reaction became part of mainstream organic chemistry. Because of the contribution of the group led by A. William Johnson,[51] the reaction is often referred to as the 'Johnson-Corey-Chaykovsky reaction'. Corey and Chaykovsky also acknowledged the work of Franzen and Driessen who also reported on the sulfonium ylide mediated epoxidation and aziridination around the same time.[54]

The Corey-Chaykovsky reaction has since been used extensively in chemical synthesis due the convenience, reliability, and broad diversity of substrates tolerable. Though the cyclopropanation and aziridination are frequently utilised and highly pragmatic, by far the most performed version of the reaction is the epoxidation. As a great number of molecules used in synthesis contain a carbonyl group, the epoxidation can be adopted frequently. Epoxides are very practical precursors, as they possess high ring strain and the polarised C-O bond. Epoxides themselves are present in many biologically active molecules, rendering them important in medicinal chemistry. One of the most notable contemporary applications of the epoxidation is in a key step in the total synthesis of baccatin III and taxol by Danishefsky *et al.*[55] Taxol, a complex molecule isolated from the pacific yew tree, was first noted in the 1960's as an effective chemotherapeutic drug. Baccatin III is also isolated from the yew tree and is in a much more plentiful supply and acts as a precursor to taxol.

Other modern application of the epoxidation includes Kavanagh *et al.* who used the sulfide in catalytic amount (20% mol) to produce the ylide in situ with the aldehyde/ketone in the presence of methyl triflate and an organic base to produce epoxides in good yield.[56] The reaction tolerated both aliphatic and aromatic aldehydes/ketones and the sulfide could be used as a catalyst. Also treating the sulfide as a catalyst, Sone *et al.* reported on the synthesis of highly useful disubstituted terminal epoxides (**A70**) from ketone **A60** using a heterobimetallic La-Li(3)-BINOL complex (LLB) to promote methylene transfer, with excellent ee values of 92-97% reported (**Figure 23**).[57] Notably this was done using an oxosulfonium ylide. In 2009, Szostack *et al.*, successfully synthesised epoxides from twisted amides, yielding highly useful and often difficult to produce aminoepoxides which have reactivity very different from normal epoxides.[58]

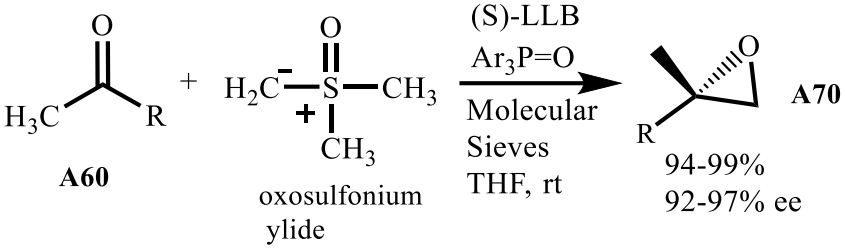


Figure 23: Sone *et al* asymmetric synthesis of epoxides using an LLB catalyst

The Corey-Chaykovsky aziridination has been much used much less frequently used relative to the epoxidation but due to the usefulness of aziridines, both in synthesis and biological applications it warrants more attention and research. Aggarwal *et al*. in 1996 reported on the development of a sulfide catalytic cycle using diazo compounds and metal salts to produce sulfides in situ from sulfonium salt instead of a base, which were then added to a series of aryl imines to produce the corresponding aziridine. The reported yields were as high as 96%, but the aryl imines were limited to phenyl, *p*-Me-C_6H_4 and *p*-Cl-C_6H_4 and all imines were protected using Ts, *N*-(diphenylphosphinyl)benzaldimines (DPP) and *β*-(trimethylsilyl)ethanesulfonyl (SES). An attempted control of enantioselectivity was performed using (+)-camphorsulfonyl ylides and achieved 97% ee, but yields were significantly decreased.[59]

Dai *et al.* synthesised highly useful vinylaziridines using allylic sulfonium ylides. The ylides were produced in situ using KOH from the corresponding allylic sulfonium salts with both Br^- and ClO_4^-.[60] The starting materials used included aromatic, heteroaromatics and α, β-unsaturated imines as well as a range of allylic sulfonium ylides with phenyl, methyl, ethyl and camphor side groups (**Figure 24**). Yields were good across this diverse range of functional groups, although attempts at stereoselectivity were disappointing. A pyrroline side product, speculated to be the result of a rearrangement of the vinylaziridine was also reported in small yields in some cases. Arsonium and telluronium ylides were also tested as an alternative to sulfur. The study was extensive and provides a highly useful method for vinylaziridines synthesis, which are highly useful starting materials in a range of reactions. Though only one each of the arsonium and telluronium ylides were used, sulfur ylides were concluded to be more useful. The reaction is highly convenient as it proceeds at room temperature and takes no longer than 30 mins, depending on the starting materials used.

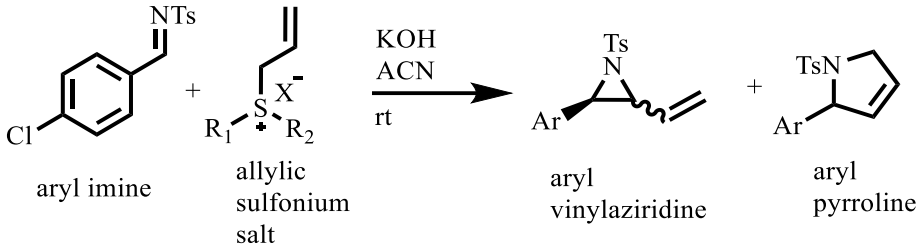


Figure 24: Dai *et al* vinylaziridine synthesis with aryl pyrroline minor by-product

1.4. Aziridines

Aziridines are three-membered, N-containing heterocycles sometimes referred to as ethyleneamines and are analogous to epoxides. Aziridines are present in a large number of natural products, and are an attractive synthetic reagent due to their polarised C-N bond and high ring strain which renders them susceptible to nucleophilic attack, providing a convenient starting point for the synthesis of a range of amine containing compounds. They are also attractive because of their basicity, being more basic than arylamines and less so than alkylamines. Aziridines are often overshadowed by the more popular epoxide, which possesses the more polarised C-O bond and boasts a larger number of methods for synthesis (**Figure 25**).[61]

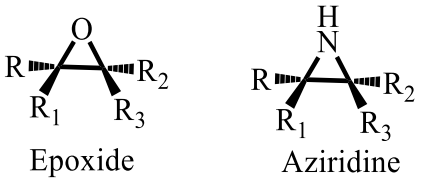


Figure 25: Epoxide (left), Aziridine (right)

A large number of methods exist in the current literature for aziridine synthesis, many of which are highly reliant on the adjoining functional groups. Inevitably this is often compared to the far more extensive range and more widely applicable epoxidation reactions. Of particular comparison is the epoxidation of alkenes, which is highly convenient and an extremely popular reaction in organic chemistry. The corresponding aziridination of alkenes ,however, is more difficult due the stability of N-N and N-O bonds, compared to the high instability of peroxycarboxylic acids used in the epoxidation (RCOOOH).[62]

Carbene additions to imines is a popular method for aziridine formation. Jacobsen *et al*. reported in 1995 the use of copper catalysts to generate carbenes in situ before addition to protected imines.[63] Though successful, the resulting aziridines lacked acceptable enantiomeric excess (ee) values. This was improved by the use of (*R*)-Tol-BINAP by Juhl *et al*., who reported ee values of 72% for aziridine **A72** using starting material **A71** (**Figure 26**).[64]

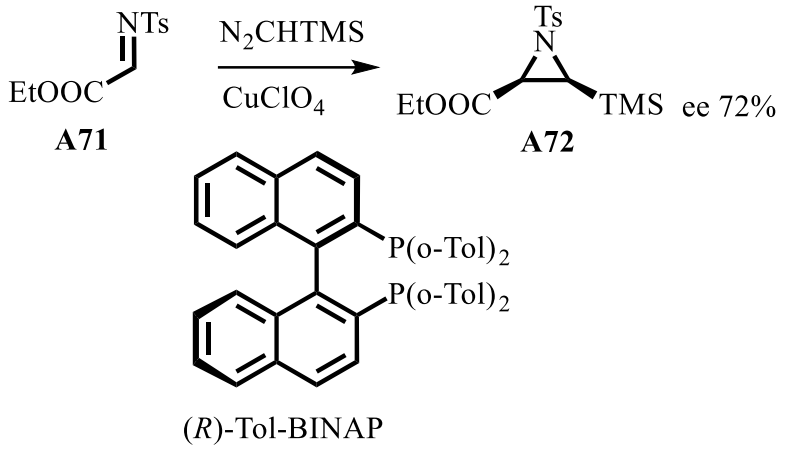


Figure 26: Juhl *et al.* carbene addition to imine using (*R*)-Tol-BINAP

Aziridination by nitrene addition to alkenes is also reported in the literature,[65,66] but is not as widely used as carbenes. Dauban *et al*. reported on the aziridination of styrene using PhI=O, tosylated amine and a copper catalyst with ligand **A74**, previously employed for carbene reactions (**Figure 27**) with an excellent yield of aziridine **A73** of 86% and an ee of 59%.[67]

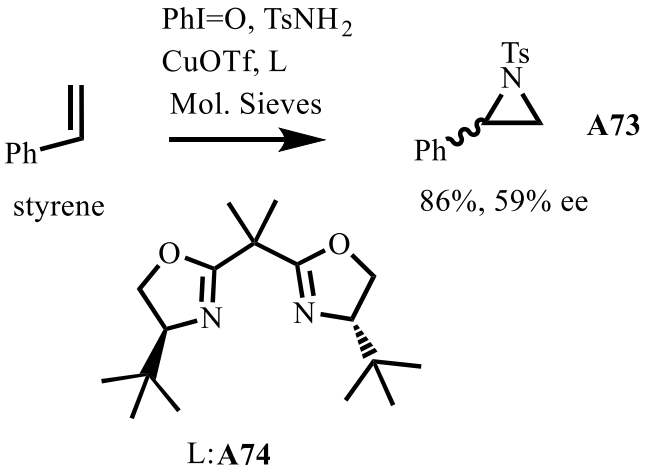


Figure 27: Dauban *et al*. aziridination of styrene using nitrene

Trost *et al*. reported on the synthesis of crucial aziridine-containing precursor to (+)-agelastatin (**A76**), a molecule with potential anti-tumour properties that has also been investigated as a treatment for Alzheimer's disease, using a nitrene addition to an alkene bond on **A75** with a copper catalyst with ligand **A77** and PhI=NTs (**Figure 28**).[68]

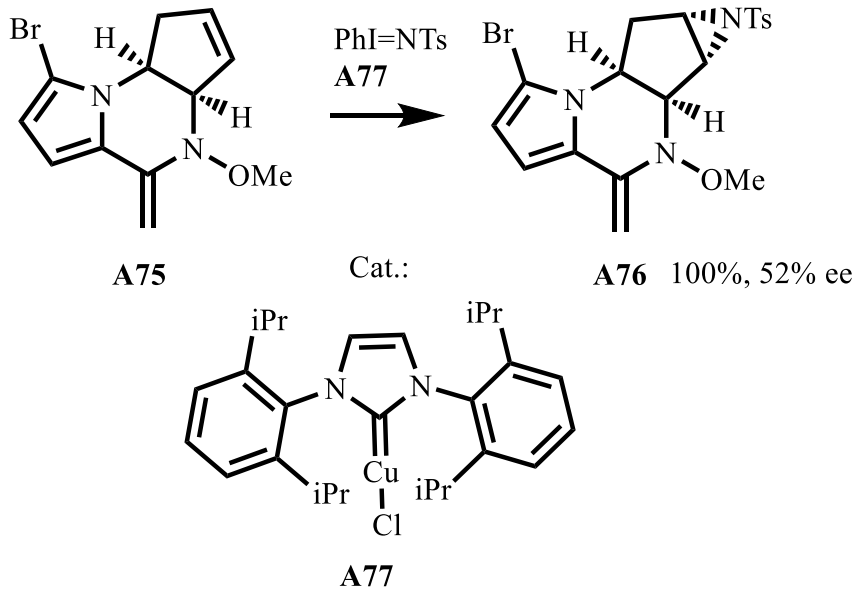


Figure 28: Trost et al. aziridination using nitrene

Luo et al. reported recently about C-H aziridination of allylic molecules using a sulfur mediated process. The reaction uses an allylic molecule (**A78**) which is reacted with a sulfur compound (**A79**) which is oxidised using Tf_2O, which bonds directly to the C-H group next to the alkene bond. The sulfoxide is converted to an ylide using DBU, which leads to aziridine (**A80**) formation when an aryl imine is added. This reaction, which is a direct variation of the Corey-Chaykovsky, was also extended to epoxidation and arylation of the same C-H group using the same method (**Figure 29**). The yields of these aziridines varied but were as high as 58% with cis/trans ratio of up to 73/27.[69]

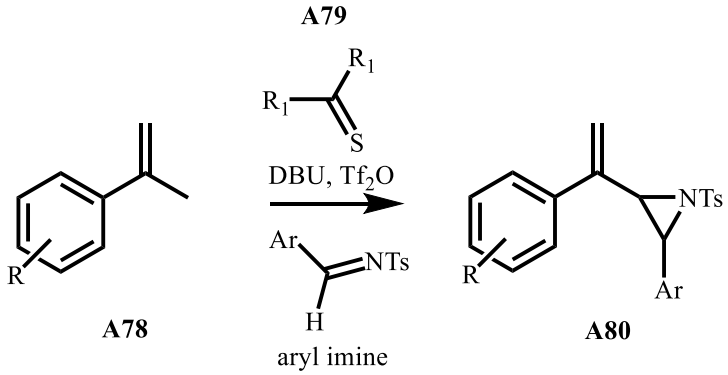


Figure 29: Allylic aziridine (A80) synthesis using a C-H allylic molecule (A78), a sulfide (A79) and an imine

Illa *et al.* reported on the aziridination of various tosyl protected aryl imines using a novel sulfur ylide (**A81**).[70] This produced aziridines (**A82**) with two aryl substituents with excellent stereoisomer control; the cis/trans ratio of the synthesised aziridines were reported as high as 99:1 and ee values of up to 98% and yields were as high as 80% (**Figure 30**). This is an excellent example of asymmetric aziridine synthesis using the Corey-Chaykovsky reaction. Note that stoichiometric quantities of sulfide were used.

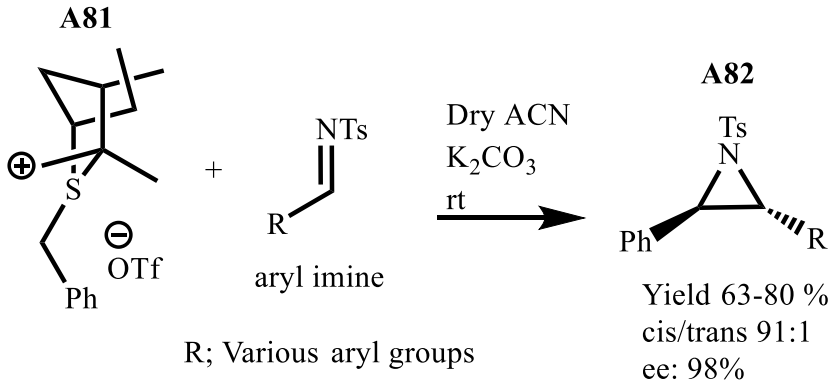


Figure 30: Illa et al. asymmetric Corey-Chaykovsky aziridine synthesis

As previously mentioned, the Corey-Chaykovsky reaction, first reported in the mid-1960s, provides a convenient azirdination using destabilised sulfur ylides to add CH_2 groups across the unsaturated C=N imine bond, with protecting groups on the N necessary.[53] The analogous epoxidation reaction attracted much more attention and has been studied more extensively, leaving significant scope for studies of the aziridine reaction. Aggarwal examined this reaction with focus on catalytic cycles,[59] and Dai synthesised aryl vinylaziridines with KOH.[60] Both reported though on the stereoselectivity shortcomings. This leaves the Corey-Chaykovsky aziridination with still a lot of scope for further study. Whether using carbenes or ylides to produce aziridines to from imines, a vital requirement is the protection of the N group, both to prevent side reaction with the free amine, and indeed to activate the N. These protecting groups are commonly Tosyl, *β*-(trimethylsilyl)ethanesulfonyl (SES) or Boc.[61, 71]

An interesting approach to stereochemistry problems has been reported by use of enantiomerically pure epoxides. Epoxidations have endured much greater success for stereocontrol and the approach attempts to exploit this. Nitrenes are used to open the pure epoxide enantiomer to produce the corresponding hydroxyazide which in is treated with a phosphine to produce oxazaphospholidines which is heat treated to form an enantiomerically pure aziridine.[72]

Catalytic asymmetric aziridine synthesis has attracted significant attention in more recent years as a method for stereocontrol, due to ongoing improvements in catalytic ligands. High asymmetric control is deemed a basic requirement in modern synthetic chemistry as products are often used for further asymmetric processes or indeed used for medicinal purposes. Huang *et al.* reported the use of (*R*)-VANOL to synthesise trisubstituted aziridines (**A84**) using Boc protected imines and α-diazo-N-acyloxazolidinone (**A83**) as added side group (**Figure 31**).[73] The synthesis was convenient and tolerable towards a large range of imines, with yields as high as 83% and % ee values up to 98%, a considerable improvement on previous studies. One trisubstituted aziridine formed had potential to act as a precursor to L-methyldopa, an anti-hypertensive agent. Huang *et al.* had previously reported on the asymmetric catalytic synthesis of disubstituted aziridines using a similar approach which produced a highly useful precursor to L-DOPA, used for treatment of Parkinson's disease.[74]

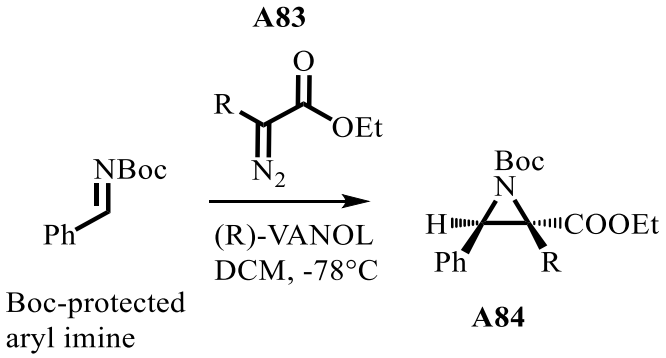


Figure 31: Hung *et al.* trisubstituted aziridine synthesis using (R)-VANOL

Polymerisation of aziridines to form amino polymers is one of the most sought after uses of aziridines. Zhou *et al.* recently reported on an organocatalytic polymerisation of N-tosyl aziridines using N-heterocyclic olefins such as **A85** in **Figure 32.** The organocatalytic process was used for various N-tosyl aziridines and had excellent conversion, with >99% reported for each and excellent dispersity, with D values as low as 1.12.[75]

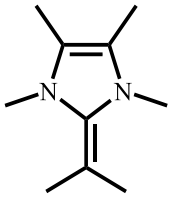


Figure 32: N-Heterocyclic olefin A85 used as an organocatalyst for polymerisation of aziridines

A recent review from Li *et al.* highlighted the importance of N-sulfonyl aziridines in polymer chemistry. It discussed a new technique for synthesising the highly useful polymer polyethyleneimines (PEIs) using solvent and catalytic free conditions with excellent conversion of >99%. The PEIs synthesised are fluorescent and can be used to capture metal ions such as Fe^{3+}, Co^{2+}, Cu^{2+}, and Zn^{2+}.[76]

As previously mentioned, key to aziridines' usefulness as a synthon in organic chemistry is both the polarised C-N bond (not as polarised however as epoxide's C-O bond) and the high ring strain, with a Bayer strain value reported to be around 111 kJ/mol. The unstable bond angles in the ring combined with the polarity allows aziridines to readily undergo ring opening under favourable reaction parameters. Often key to the success of aziridine reactions is the substituent attached to the nitrogen, which highlights a key difference to the reactions of epoxides.[61]

For nucleophilic aziridine reactions, a bare N-H group in the ring readily allows for unwanted side reactions, therefore protection is needed to allow nucleophilic addition to occur at the desired carbon. Also, aziridine ring-opened reaction intermediate ions are stabilised by N-substituents. Therefore, aziridines need to be adequately protected and activated by an appropriate functional group. Commonly used protecting groups fall into categories such as sulfonyl (e.g. tosyl, SES), phosphoryl and carbonyl (Boc), with sulfonyl groups being by far the most used.[61, 71]

Sulfonyl groups, most commonly tosyl groups, are popular due to the fact that *N*-sulfonyl aziridines (**Figure 33**) are convenient to prepare, especially for large scale processes and the groups are effective at protecting the nitrogen as well as activating the aziridine and stabilising the ring-opened product. A disadvantage however is that tosyl group can often be difficult to remove, and ring opening steps, often the first step when using aziridines as synthons, can be difficult, sometimes requiring harsh conditions and strong acids.[77]

N-tosyl protected aziridine

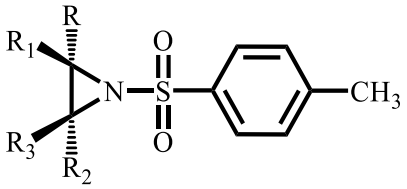


Figure 33: N-tosyl protected aziridine

Numerous examples of highly useful and impressive synthetic processes involving aziridine starting materials exist in the literature, with one example being Zhang et al. who reported of the synthesis of highly useful α-amino aryl ketones using a range of *N*-sulfonyl aziridines and catalytic amounts of 2-methylquinoline.[78] Jung et al. reported on the synthesis of (*S*)-3-methylamino-3-[(*R*)-pyrrolidin-3-yl]propanenitrile, a crucial component in several fluoroquinolone antibiotics which is often difficult form.[79] The approach employed *N*-methylative aziridine ring opening as well as addition of a methyl group to the nitrogen. The *N*-methylative aziridine ring opening had been previously utilised to synthesise other bioactive molecules such as ephedrine[80] and hygrine.[81] Also, β-aryl- and β-heteroarylamines, which are of considerable interest in medicinal chemistry, have been conveniently synthesised using tosyl-protected aziridines and a range of Grignard reagents and copper catalysts, as reported by Nenajdenko *et al.* in 2001.[82]

Aziridines occur frequently in nature and are present in many biologically active molecules as well as synthetic active pharmaceutical ingredients (APIs). A study by Ismail *et al.* in 2009 examined natural molecules containing aziridine functional groups, particularly aziridine alkaloids. It was reported that at least 130 natural compounds containing aziridines exhibited a range of medicinal functions, such as antimicrobial activity (e.g. an azirinomycin isolated from a type of *streptomyces aureus* exhibited broad-spectrum antibiotic activity) and antitumour properties (e.g. molecules isolated from s*treptomyces sandaensis*).[83] Peptides containing aziridine-2,3-dicarboxylic acid have been reported as very useful cysteine protease inhibitors, used to treat a variety of conditions such as tumours and cardiovascular disease. [84] Mitomycin C, isolated from a range of microorganisms, contains an aziridine group and is a widely used chemotherapeutic agent.[85] Synthetic drugs that contain aziridines include thiotepa, an alkylating agent (**Figure 34**).[86]

Thiotepa

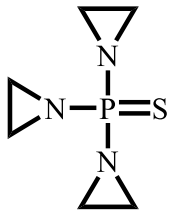


Figure 34: Thiotepa, a chemotherapeutic alkylating agent

A recent review by Qiu *et al.* highlighted the importance of new methods of aziridine synthesis due to their importance in biologically active compounds. The review highlighted a new click method with palladium on activated carbon (Pd/C) for direct C-H functionalisation that converts *N*-containing heterocycles to functionalised aziridines that can be used as drug precursors. Yield of the aziridines using this method were above 80% and one of the molecules made is a potential precursor to aziridinylquinone, a biologically active quinone derivative.[87]

Vinylaziridines are a notable and widely used class of aziridines which incorporate an allyl group attached to one of the carbons in the three membered ring (**Figure 35**).

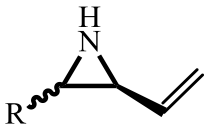


Figure 35: Vinylaziridine

Vinylaziridines offer additional usefulness as synthons due to the numerous additional reactions that can occur with the vinylic group, as well as providing extra stability by facilitating charge distribution. Synthesis of vinylaziridines often follow those of general aziridine synthesis, such as nitrene addition to dienes and carbine addition imines. The Corey-Chaykovsky aziridination of imines using allylic ylides has also been widely applied, most notably by Dai *et al.* in 1996, as previously discussed.[60] A different approach employed by Hirner *et al.* uses benzylic aldehydes to produce the corresponding chlorohydrin using allyl chloride and a chiral borate catalyst, which in turn underwent aminolysis followed by ring closing and tosyl protection to afford enantiomerically pure benzylic vinylaziridine.[88] Unique processes vinylaziridines can undergo compared to regular aziridines are numerous in amount, one example includes reduction with hydride to produce allyl amines, but perhaps the most notable, specifically for the purposes of this review, is the vinylaziridine rearrangement to the corresponding 3-pyrroline.[89]

1.5. Vinylaziridine to 3-pyrroline rearrangement

The interesting phenomenon of vinylaziridines rearranging to the corresponding 3-pyrroline was noted as early as 1967 in separate publications by Scheiner[90] and Atkinson *et al.*[91] A similar process of vinylcyclopropanes rearranging to the five membered cyclohexene ring had been well known at the time and is understood to occur via a diradical

intermediate when treated with heat. Scheiner noted this rearrangement with *N*-aryl vinylaziridines but also observed ring fusion, the result of a Claisen rearrangement, which occurred in higher yields.[90] Atkinson *et al.* worked with simpler vinylaziridines with a protecting group on the nitrogen, and they observed the rearrangement occurring readily upon heat treatment (**Figure 36**), while non-vinylic aziridines remained structurally stable under the same conditions.[91]

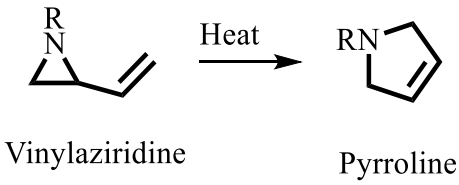


Figure 36: Scheiner and Atkinson reported on the vinylaziridine to pyrroline rearrangement upon heat treatment

Interestingly, the heat needed ranged from 100-200 °C, compared to the much higher 300-500 °C needed for the vinylcyclopropane. The group noted that higher alkyl substitution on the aziridine ring led to higher conversion rates to the pyrroline, leading them to postulate that the same diradical intermediate process that occurs in the vinylcyclopropane rearrangement occurs here as the increased alkyl substitution would stabilise the radical. This diradical intermediate is also favourable due to the presence of the nitrogen and the vinylic group. Scheiner and Atkinson both noted that the same transformation occurs when the vinylaziridine undergoes nucleophilic addition with iodide, but in smaller yields **(Figure 37**). This led both to conclude that the diradical intermediate, which would not occur with the nucleophilic addition, is favourable and responsible for higher pyrroline yields.[90-91]

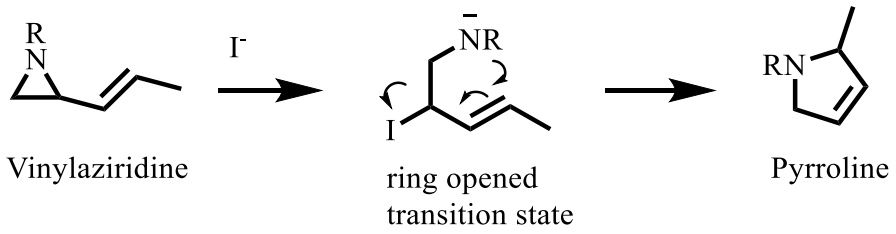


Figure 37: Iodide nucleophilic attack on a vinylaziridine, followed by pyrroline formation, as noted by Scheiner and Atkinson

Fugami *et al.* reported the rearrangement of dienylaziridines with tosyl protection on the nitrogen (**A86**) with the use of palladium and tin catalysts to vinylpyrrolines (**A87**) under very mild conditions (**Figure 38**).[92] The reaction tolerated a range of functional groups and was extended to dienylazetidines rearranging to vinylpiperidines. The group had previously studied the vinylcyclopropane rearrangement, and reported the use of palladium catalysts allowed smooth transition at 50 °C. Both the aziridine and cyclopropane rearrangement was reported to occur through a diradical intermediate, with the metal catalysts inducing radicalisation therefore allowing the reaction to occur under much milder conditions.

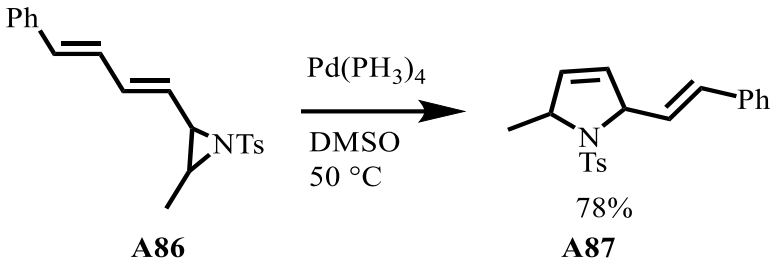


Figure 38: Dienylaziridine with tosyl protection rearangment to pyrroline, as reported by Fugami *et al*. with use of a palladium catalyst

As previously mentioned, Dai *et al*. reported on the occurrence of the pyrroline when synthesising aryl vinylaziridines from aryl imines and allylic sulfur ylides. This only occurred in small yields and mainly with a ClO_4^- anion on the sulfonium salt prior to ylide formation, and it wasn't clear why this was the case and no further study was undertaken.[60]

Hirner *et al.* reported on the highly efficient microwave-assisted rearrangement of vinylaziridines (**A88**) to 3-pyrrolines (**A89**) using iodide as a nucleophile (**Figure 39**).[88]

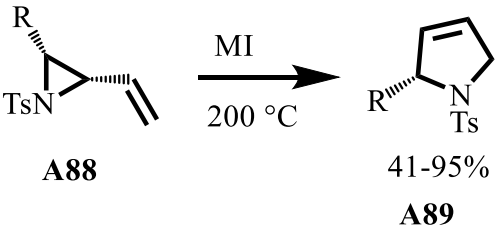


Figure 39: Hirner *et al.* tosyl protected vinylaziridine (A88) to pyrroline (A89) rearrangement using iodide nucleophile and microwave irradiation

The study also noted that the cis and trans isomers of **A88** can interchange by microwave irradiation. Interestingly, the experimental observations noted that when a pure sample of cis **A88** was subjected to irradiation, pyrroline **A89** was the major product, but when trans **A88** was irradiated, cis **A88** was the major product, with **A89** the minor. The author suggested that this may mean that cis **A88** is more thermodynamically stable, which would be unexpected. The study of different aziridines was extensive, but only looked at one aryl vinylaziridine, with an unsubstituted phenyl group which, and although the pyrroline was the main product, unidentified side-products formed which discouraged use of other aryl vinylaziridines. The article also noted that this convenient microwave method was employed for the synthesis of the antibiotic (-)-anisomycin, demonstrating the usefulness of the vinylaziridine to pyrroline rearrangement.[88]

More recently, Baktharaman *et al*. synthesised a range of stereochemically rich *N*-containing heterocycles from chiral vinylaziridines by utilising a ring opening and ring closing mechanism, which included a 7-membered enamine cyclic intermediate.[93] Brichacek *et al*. reported on the stereospecific ring expansion of chiral vinylaziridines (**A90**) with the use of a copper catalyst to form a large range of functionalised 3-pyrrolines (**A91**),[94] one example of which is given in **Figure 40**.

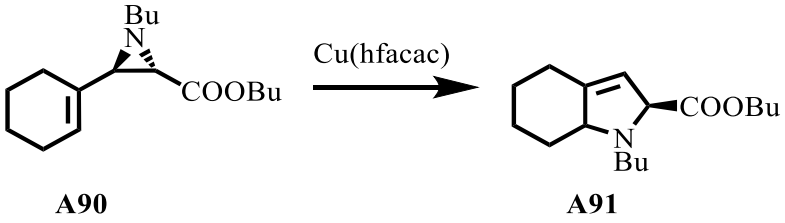


Figure 40: Brichacek *et al.* synthesis of functionalised 3-pyrrolines (A91) from chiral vinylaziridines (A90) with use of a Cu catalyst with hfacac (hexafluoroacetylacetone) ligand

1.6. 3-Pyrrolines

3-Pyrroline is one of three possible isomers of the five membered, heterocyclic, *N*-containing monounsaturated ring (**Figure 41**).

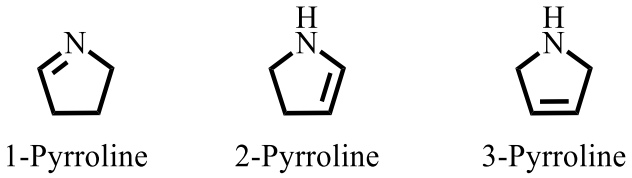


Figure 41: The three isomer of pyrroline

Pyrrolines are present in many biological compounds and are extremely practical intermediates in synthesis. One noteworthy example of 3-pyrroline's usefulness as an intermediate is in the synthesis (+)-lactacystin, a highly useful proteasome inhibitor. Once the enantiomerically pure 3-pyrroline intermediate has been isolated, known as the 'Baldwin intermediate' (**Figure 42**) the remaining steps of the reaction are highly convenient to make the inhibitor.[95]

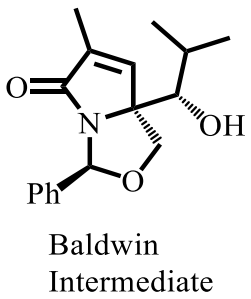
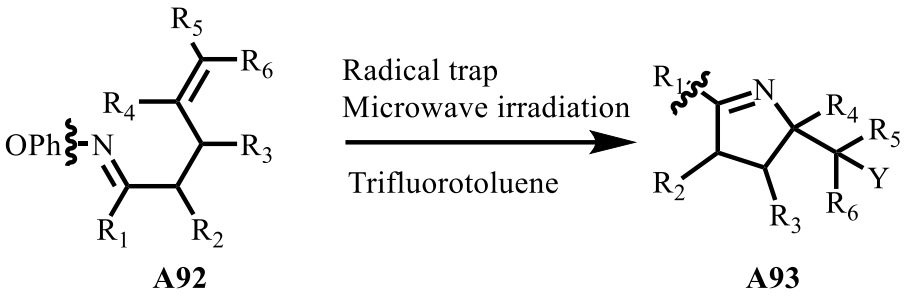


Figure 42: The 'Baldwin intermediate', a pyrroline containing intermediate in the synthesis of (+)-lactacystin

Biologically active compounds containing 3-pyrrolines include monoamine oxidase inhibitors,[96] NMDA (*N*-Methyl-D-aspartate) receptor agonists,[97] κ-opioid receptor agonists[98] and antitumour agents.[99] The usefulness of 3-pyrrolines in synthesis and biological applications renders new methodologies for their synthesis of great importance.

A highly useful and interesting technique for synthesising 1-pyrrolines was reported recently by Singh *et al.* which used an O-phenyloxime (**A92**) starting material coupled to an alkene which was then subjected with microwave irradiation.[100] Toluene or 1-

trifluoromethylbenzene was used as both a solvent and an ion trap, and the ring closed 1-pyrroline product (**A93**) was obtained in up to 72% yield. The intermediate formed by the irradiation was a 5-exo-trig iminyl radical with an unpaired electron on the nitrogen which readily ring closes to the alkene group **(Figure 43**). While this reaction was not extended to 3-pyrrolines, the technique used leaves room for such reactions. It is also noteworthy of the amount of functionality in the pyrroline ring the product has, and excellent stereocontrol was reported with these group with dr values of 15:1. This reaction could be extended to synthesising functionalised 3-pyrroline. The low amount of solvent, heat and lack of purification makes this a green reaction.



A92 **A93**

Figure 43: Synthesis of functionalised 1-pyrrolines (A93) using microwave irradiation from an O-phenyloxime coupled alkene starting material (A92)

The regioselective functionalisation of 3-pyrrolines using nickel catalysts has been reported recently by Xu *et al.* The nickel catalysts, which can have one of two organic ligands, can perform a hydroalkylation on a protected 3-pyrroline. If ligand **A97** is used, the alkyl group (in this case a cycloalkyl group) is added in the 2-position to form a functionalised 3-pyrroline (**A95**), if catalyst **A98** is used the cycloalkyl group is added in the 3-position and thus breaks the double bond, and the product is a functionalised pyrrolidine (**A96**, **Figure 44).**[101]

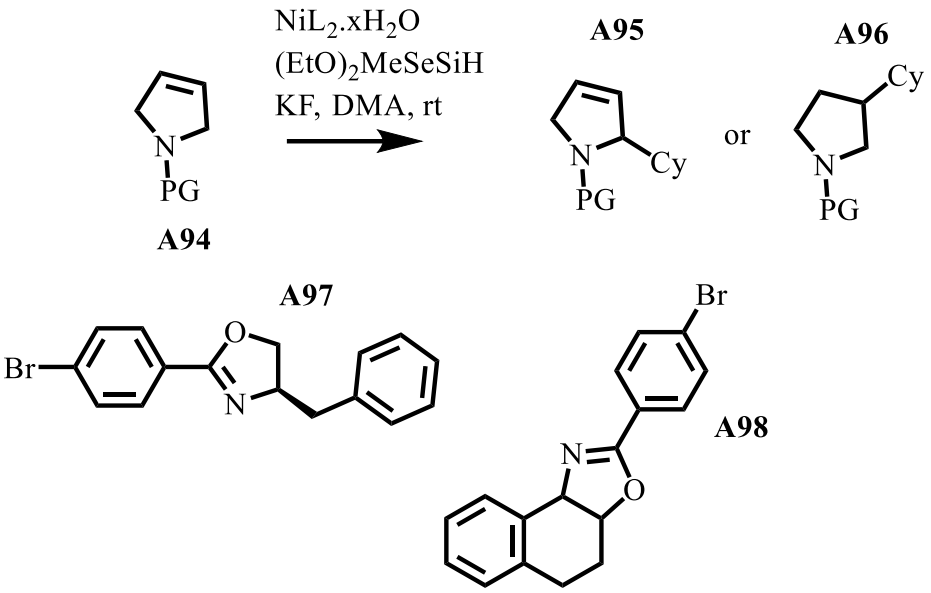


Figure 44: Functionalisation of 3-pyrroline A94 using nickel catalyst. Using ligand A97 leads to formation of functionalised 3-pyrroline A95, whereas use of ligand A98 leads to functionalised pyrrolidine A96

3-Pyrrolines with an aryl substituent in the 2-position have great similarity to many organocatalysts, as seen earlier in this review. The unsaturated bond in the ring also leaves opportunity for adding substituents to the ring, allowing for the making of a structurally diverse library of compounds that can be investigated for use as organocatalysts. Therefore, an optimised synthetic pathway for aryl pyrrolines would be highly useful for making new organocatalysts, as well as a more convenient pathway to already existing ones. Optimisation of the vinylaziridine rearrangement is one possible way of achieving this, but aryl vinylaziridines rearranging to aryl pyrrolines hasn't been widely reported, except in the earlier discussed article by Dai *et al.* where it was an unexpected by-product of the aziridination of aryl imines with allylic sulphur ylides.[60] The reasons for the pyrroline formation was unknown, but if it can be discovered and the reaction subsequently optimised to produce the aryl pyrroline over the vinylaziridine, it would produce a very convenient pathway for synthesis of this highly useful compound for further use as an organocatalyst (**Figure 45**).

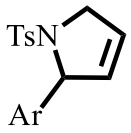


Figure 45: Tosyl protected aryl pyrroline

1.7. Green chemistry

In the last 30 years, chemists have realised that the success of a synthetic process isn't just determined based upon the yield of the desired product, but also the costs, environmental impact, waste generated, robustness, efficiency and reusability of the reagents. These considerations aim to make large scale chemical synthesis sustainable and environmentally

friendly for the future. This has led to the birth of 'green chemistry', which is defined by twelve key principles which were outlined by Paul Anastas and John Warner in their 1998 book entitled 'Green Chemistry: Theory and Practice';[1]

1. *Prevention*: It is better to prevent chemical waste prior to conducting a reaction rather than attempt to clean up waster afterwards.
2. *Atom Economy*: It should always be aimed to include all or most of the reagents used in a synthesis in the final product
3. *Less hazardous chemical synthesis*: A chemical synthesis used should ideally not produce toxic by-products
4. *Designing safer chemicals*: Ideally it should not be sought to synthesise toxic chemicals
5. *Safer solvents and auxiliaries:* Solvents and auxiliaries should be used as little as possible, and where they are necessary they should always be non-toxic to both humans and the environment
6. *Design for energy efficiency:* Use of energy should be carefully considered for environmental impact and kept to a minimum
7. *Use of renewable feedstock*: Renewable reagents should always be used when possible
8. *Reduce derivatives*: While making of derivatives often assists in synthetic processes, they add steps and reagents and should be kept to a minimum or not at all
9. *Catalysis*: Use of reagents in catalytic rather than stoichiometric quantities should always be aimed
10. *Design for degradation*: When a chemical has been used, it should be designed to break down and degrade naturally
11. *Real time analysis for polluting prevention*: Processes should be measured in real-time to detect potentially hazardously substances forming
12. *Inherently safer chemistry for accident prevention*: Chemicals should ideally not be chosen for use if they have the potential for dangers such as toxicity, damage, explosiveness, etc.

Thus, with principles defined, green chemistry has become part of mainstream science and an area of intense interest and research. Green chemistry is an attractive prospect for both industry and academia for the potential money savings, environmental protection reducing waste and increasing safety. Many recent research examples exist in the literature of green chemistry techniques developed for different processes, trying to adhere to one or more of the twelve principles. An early example of green chemistry was the ibuprofen synthetic method developed by the chemical company Hoechs AG in the 1980's, which cut reaction steps down to three and used much less reagents, generated little waste and actually improved yields.[102] It was a massive improvement on the original method developed by Boots in the 1960's, with 77% of the atoms used as reagents being present in the final product and almost all the remaining were reusable, thus addressing several green chemistry principles (**Figure 46**). It also had an improved 'E-factor', defined as the mass of waste produced divided by the mass of the desired product synthesised.[103] However, it used a palladium catalyst, which addresses the catalysis principle but adds cost, and metals can often be toxic to

humans and/or the environment, demonstrating how in green chemistry a 'balancing acts' are often needed.

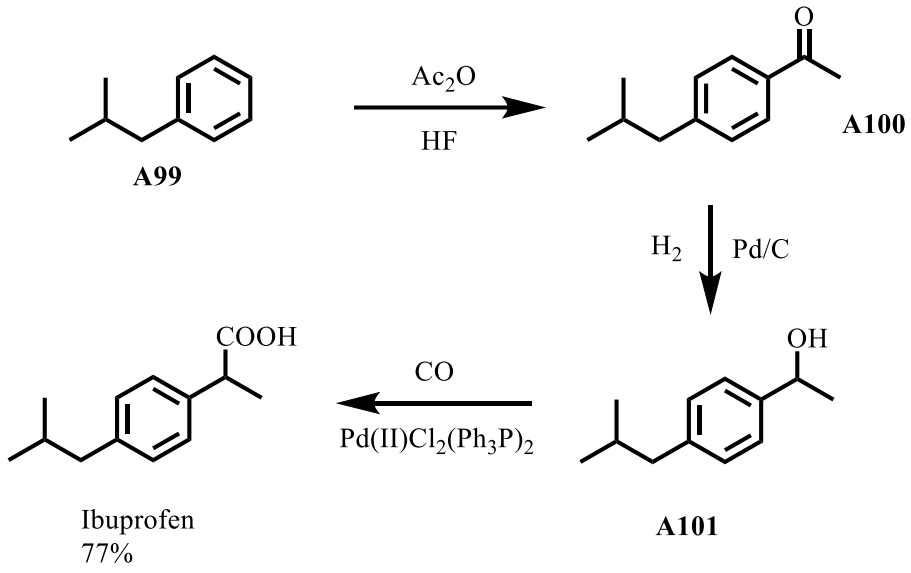


Figure 46: Hoesch ibuprofen synthesis

Another example is the method developed by Jeon *et al.* for the catalytic asymmetric addition of alkyl groups to ketones using solvent-free conditions. The method addresses the catalysis and solvent principles of green chemistry, as well as generating less waste.[104] Once again this method uses a metal catalyst. Addressing the solvent principle was also reported by Coyle *et al.* involving the photooxygenation of 1-naphthols using microemulsions of water, ethanol and ethyl acetate using sodium dodecyl sulfate as a surfactant, as opposed to the usual method of using toxic solvents of dichloromethane, due to the use of the more non-polar sensitiser tetraphenylporphyrin (TPP, **Figure 47**).[105] This study represents an example of the sub-category of green photochemistry, and it does not use a metal catalyst.

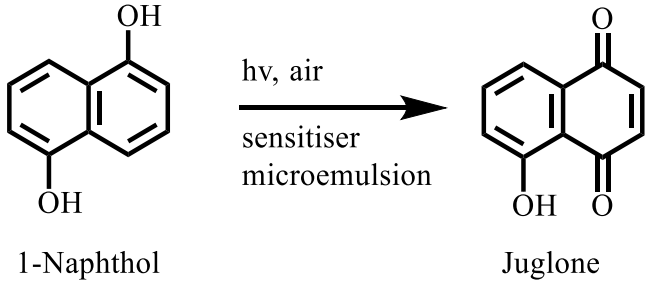


Figure 47: Photooxygenation of 1-naphthols to juglone using microemulsions

Green chemistry has recently become increasingly important in the pharmaceutical industry, as noted in a recent review by Becker *et al.* with particular focus on reducing the product mass index (PMI), which measures the total mass of materials used to make a product, and reducing waste and time in producing APIs.[106] Takeda have recently developed a new technique for synthesising a patented 5-HT4 receptor (5-hydroxytryptamine receptor 4) agonist drug, TAK-954. The new synthetic method uses no organic solvents, using instead water with micelles. The result was an overall yield of 30%,

similar to the older technique, with the PMI factor reducing from 350 to 79.[107] The review also made note of a recent development by Merck, which adjusted the synthetic pathway of a new drug candidate, MK 7264 that is in phase III trials as a treatment for chronic bronchitis. The new pathway reduced the synthetic steps from 8 to 4, greatly reducing waste and time.[108] Glaxo Smith Kline recently reported on a new technique for synthesising paroxetine, an anti-anxiety drug, using a biocatalyst. It was noted that that waste from this API synthesis was greatly reduced.[109]

Patial *et al.* reported recently on the development of covalent organic frameworks, 3D organic molecular structures, which can reduce or even eliminate the need for solvents and/or catalysts.[110]

An interesting new green synthetic technique that has been garnering attention recently is the use of solvent and catalyst-free 'mechanochemistry' for certain reactions. Mechanochemistry refers to the physical grinding of two solid (or solid-liquid) reagents together, often by mortar and pestle, to drive a reaction to completion. Banerjee *et al.* reported on several such reactions, including a Diels-Alder reaction (**Figure 48**), which tolerated many different side group and was completed in 1-30 minutes with excellent yields (75-100%). However, formation of isomers was a significant problem, with recrystallisation being effective for separation in some cases.[111]

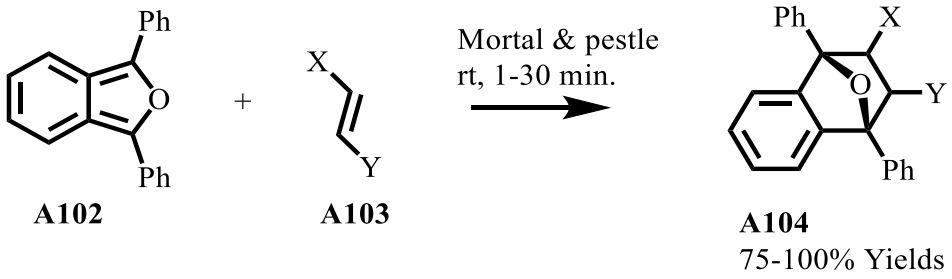


Figure 48: Diels-Alder reaction by mechanochemistry using a mortar and pestle

These are just a few examples of the many and ever-increasing green chemistry methods developed in synthesis. With greater concern for the environment, as well as cost saving and reagent efficiency, green chemistry is and will continue to become of major importance in modern industry and academic research. Organocatalysis, discussed in detail earlier in this review, can be considered a major area of modern green chemistry due to the catalysis principle and making catalysts that are non-toxic, compared to them many metal-based catalysts which are toxic and harmful to the environment and indeed expensive.

1.8. Organosulfur chemistry

Sulfur is one of the most abundant elements that occur in nature, mainly in the form of the molecular ion sulfate (SO_4^{2-}) or sulfite (SO_3^{2-}), but sulfur also has a large role in organic and medicinal chemistry. Sulfur is present in the core structure of penicillin antibiotics, as well as sulfa drugs. Perhaps the most widely known organosulfur compound is sulfur mustard which, although originally used in chemical warfare, was an early chemotherapeutic agent (**Figure 49**).[112]

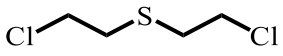


Figure 49: Sulfur mustard

Organosulfur compounds can form a series of functional groups, among the most common are thiols (RS-H), which are relatively strong nucleophiles and sulfides (RS-R'). Disulfides have the functional group RS-SR', and play a role in tertiary structure of proteins, making disulfide bonds between sulfur-containing amino acids. The lone pair present on sulfur, being a group 16 element, renders it a good nucleophile and useful reagent. As sulfur is a third-row element and is non-metallic, it can form expanded octets when bonded to highly electronegative atoms, therefore its valence is variable. An example of this is the sulfoxide functional group, a notable example of which is the highly useful polar solvent dimethyl sulfoxide (DMSO, **Figure 50**).[113]

Figure 50: DMSO

These properties of sulfur render it an important component in organic chemistry. An example is the thioester (RC(O)-SR'), which plays a role in a number of synthetic reactions in biochemistry, and also in a highly efficient ketone synthesis method developed by Fukuyama *et al.* which employs the use of a palladium catalyst and an organic zinc halide.[114]

Organosulfur molecules also make up a large amount of organocatalysts. Perhaps the most renowned use of sulfur organocatalysts are thiourea and isothioureas, which have been discussed in detail earlier in this review. Other organosulfur catalysts are plentiful in the literature. For example, Rowlands *et al.* developed an asymmetric synthesis of useful aryl cyanohydrins using conveniently synthesised isoxazoline-based sulfoxide organocatalysts (**A105**, **Figure 51**).[115]

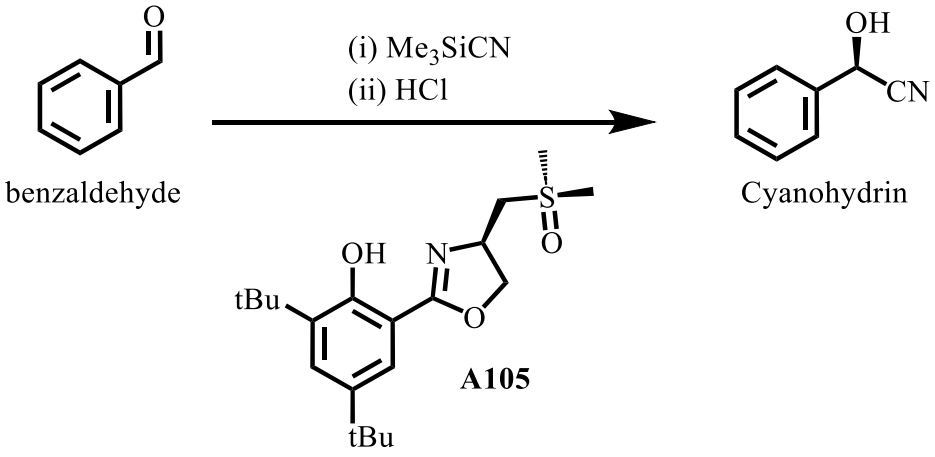


Figure 51: Asymmetric synthesis of cyanohydrin from benzaldehyde using isooxazoline-based sulfur organocatalyst (A105), as developed by Rowland *et al.*

Bolm *et al.* developed a high-yielding, asymmetric Diels-Alder cycloaddition of 1,3-cyclohexadiene and ethyl glyoxalate using sulfoximines (sulfoxide group with an added double bond to nitrogen, bringing its valence to six).[116] The varying valence of sulfur gives

it unique properties that can compete with metals for adding ligands. Sulfur thus provides a cheaper and more environmentally friendly alternative to metals in catalysis.

A class of organosulfur compounds getting more attention recently is sulfonimidates (**Figure 52**) which are chiral sulfur-based organic compounds with oxygen and nitrogen side groups that can be used as precursors for many other sought after chiral organic molecules. Sulfonimidates can be prepared from the reaction of chlorosulfoxides and chiral alkyl amines. A great diversity of cyclic and acyclic chiral compounds can be synthesised using sulfonimidates as precursors. An example is given in **Figure 53** in which a cyclic sulfonimidates (**A106**) is added to an allylic Grignard reagent (**A107**), followed by ring closing of intermediate **A108** to form a highly functionalised, chiral pyrrolidine (**A109**).[117,118]

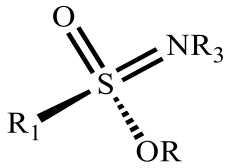


Figure 52: Sulfonimidates general structure

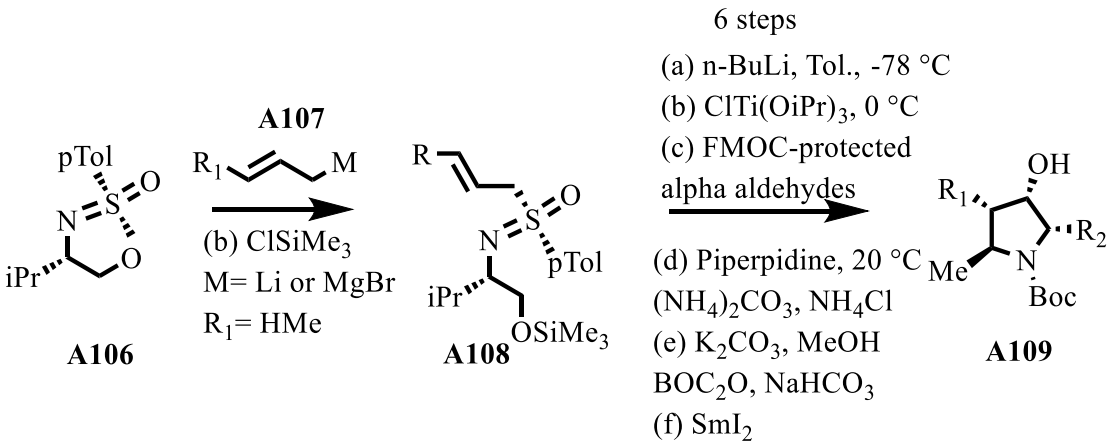


Figure 53: A substituted, chiral pyrrolidine (A109) is synthesised using a cyclic sulfonimidates (A106) with an allylic chiral sulfoxide intermediate (A108)

Again highlighting organosulfur compound's usefulness as a synthetic reagent, Bisag *et al.* recently reported on the synthesis of highly useful benzofurans from salicylaldehydes (**A110**) and sulfoxides in yields up to 72% (**Figure 54**). The reaction conditions can also be adjusted to selectively synthesise 2-*H*-chromenes instead of the benzofuran.[119]

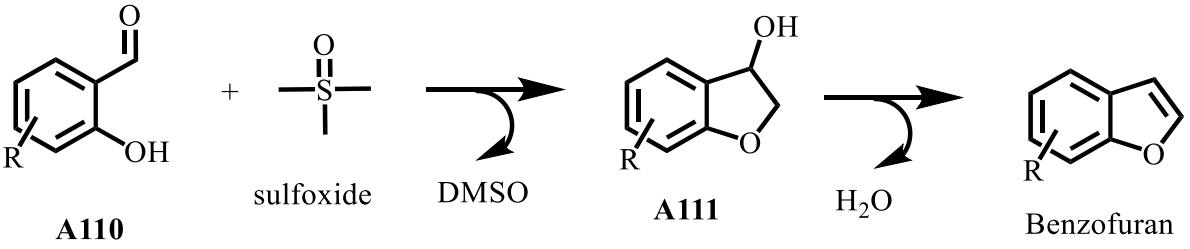


Figure 54: Synthesis of Benzofurans from Salicyaldehydes (A110) and sulfoxides

Ye *et al.* reported recently on the synthesis of polysubstituted olefins (**A114**) in 77% yield using a light-promoted sulfur ylide reaction. Aryl diazoacetates (**A112**) are used as a starting material and the light is theorised to break the sulfur ylide up to form a carbene, which in turn adds alpha to the acetate group in a radical process with the elimination of nitrogen. (**Figure 55**).[120]

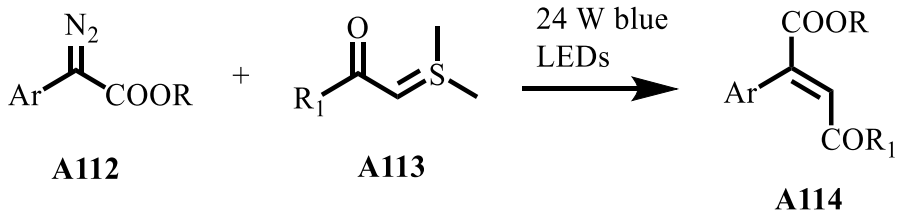


Figure 55: Polysubstituted olefin (A114) synthesis using aryl diazoacetates (A112) and a sulfur ylide precursor (A113)

It was highlighted in a recent review that organosulfur compounds are becoming increasingly important in green chemistry due to their low-toxicity, inexpensiveness and stability and may be able to be used as a replacement for metal complexes. It was also noted how sulfur is an intensive part of current research in the pharmaceutical industry due to organosulfur compound's ability to aid in metabolism, solubility and conjugation with other molecules due to disulfide bond formation. It was also noted how polysulfides are being currently researched to discover sulfur's role in proteins.[121]

Sulfur, along with phosphorous and nitrogen, can form ylides where it is positively charged and the adjacent carbon is negatively charged, allowing the carbon to act as a nucleophile. Sulfur ylides are most widely used in the Corey-Chaykovsky reaction, as discussed earlier in this review (**Figure 56**).

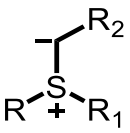


Figure 56: A destabilised sulfur ylide, commonly used in the Corey-Chaykovsky aziridination

Another example of a use of sulfur ylides, is the rearrangement of sulfonium ylides to sulfides, commonly known as the Stevens rearrangement.[122]

It is thus shown that organosulfur compounds possess many unique and useful properties of great importance in organic chemistry, and provide a cheaper and more environmentally friendly alternative in catalysis.

1.9. Development of organocatalytic cycles from known reactions: catalytic Wittig reaction (CWR)

An enormous amount of organic reactions have been developed over the last century to synthesise new molecule of known usefulness in further synthesis and biological, industrial, agricultural applications among many others. For many years, the simple act of discovering

a method to make a new molecule of interest was deemed satisfactory, but that has changed in recent years as the crucial factors such as price, environmental impact, reusability and robustness have become apparent. It is thus a major part of modern synthetic chemistry to develop previously discovered reactions to cheaper, more robust, reusable and environmentally friendly forms. This links in heavily with green chemistry and organocatalysis, as previously discussed. The development of organocatalytic cycles of known reactions meats all of this criteria, and can compete with the more widespread metal catalysts. One of the best examples of this in recent years is the development of the catalytic Wittig reaction (CWR).

The Wittig reaction was first reported by German chemist George Wittig in the 1950s and it has since become one of the most convenient and widely used method of forming alkenes, which are highly useful synthons and are present in many drug molecules and precursors. In its simplest form, a phosphine ylide (**A116**) is produced in situ with a triphenyl group as well as an organic group. This ylide (**A116**) then adds to the carbonyl of an aldehyde or ketone (**A115**), and the generated negatively charged oxygen adds to the charged phosphorous atom to produce a four membered cyclic transition state (**A118**), which in turn rearranges to yield the desired alkene (**A119**) and triphenylphosphine oxide (**A120**) by product (**Figure 57**).[123]

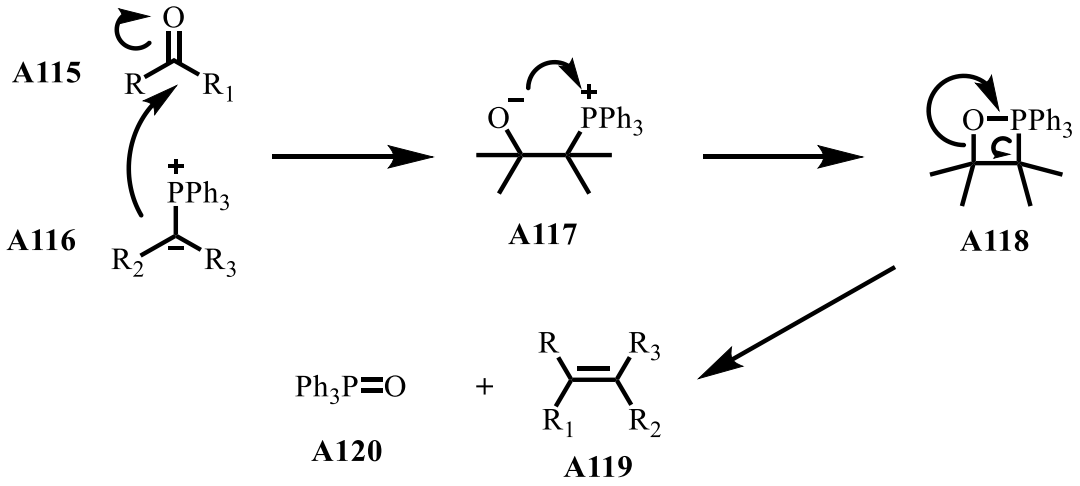


Figure 57: Wittig reaction; phosphonium ylide A116 adds to aldehyde/ketone (A115) to form intermediate A117, which in turn forms cyclic structure A118, which rearranges to form alkene product A119 and phosphine oxide A120[123]

The reaction has many variants, including different groups rather than triphenyl on the phosphine. While highly useful, the Wittig reaction has some significant shortcomings such as the phosphine oxide being difficult to recover and thus reusability being impossible, the base used for ylide formation can result in ineffective deprotonation or indeed side reaction as well as stereoselectivity between the *E* and *Z* isomers of the alkene not always being possible.

These shortcomings have been addressed by O'Brien *et al.* in a series of publications on the development of the CWR. The initial article in 2009 reported on the first ever known CWR, which was developed by using phosphine oxide as a 'precatalyst', which is reduced in the cycle to the phosphine catalyst using diphenyl silane. A phosphonium salt is generated next by addition of an organobromide (with the organic group being the R group

adding to the carbonyl further on in the cycle). Base then adds to the cycle next to generate the ylide, which is added to an aldehyde carbonyl and the alkene is generated, with the phosphine oxide leftover which was recoverable. A high temperature of 100 °C was required however to recover the phosphine oxide. Notably, triphenylphosphine was not used, instead was 3-methyl-1-phenylphospholane-1-oxide, which is more easily reduced and thus a better precatalyst. A large number of aryl and alkyl aldehydes were thus employed leading to a diverse library of compounds, while the organobromide generally needed electron withdrawing groups in order to add to the phosphine (catalytic cycle, **Figure 58,** an example reaction, **Figure 59)**.[125]

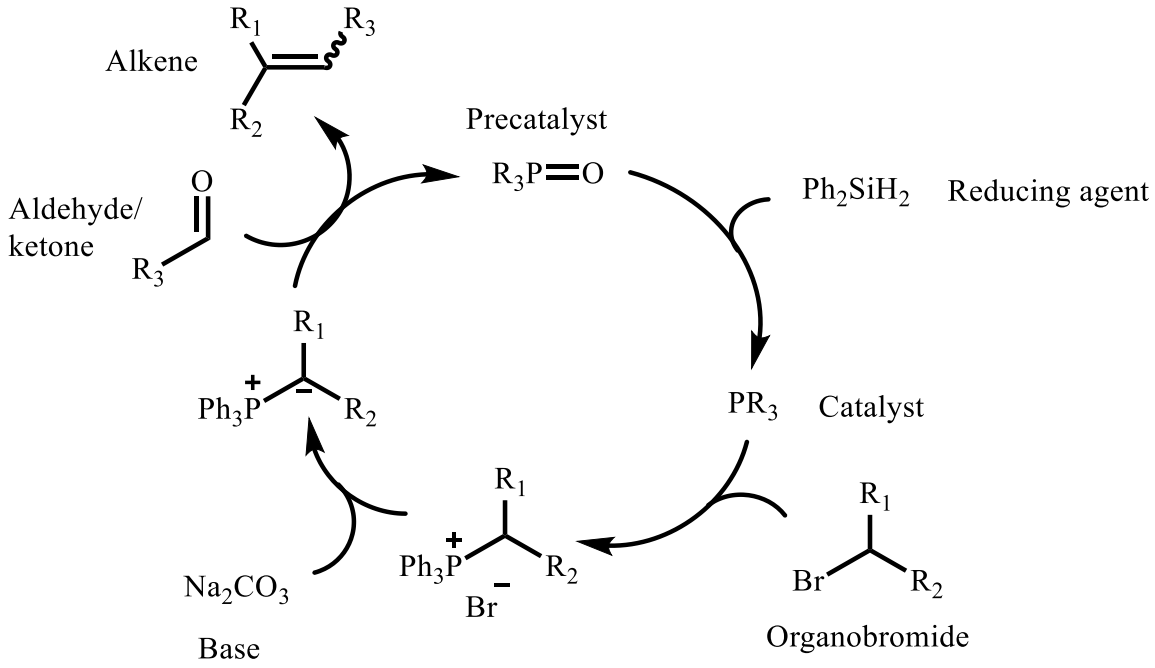


Figure 58: O'Brien *et al.* developed catalytic Wittig reaction (CWR) cycle

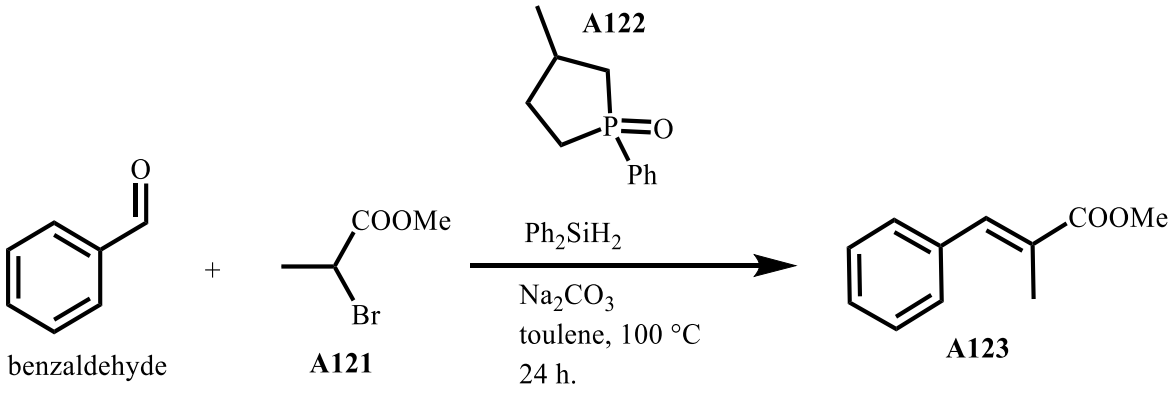
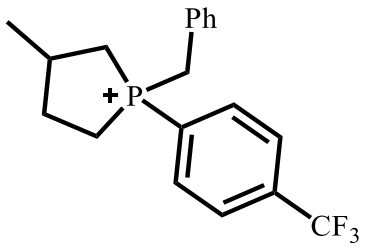


Figure 59: An example of one of many alkenes (A123) synthesised by the CWR using a stabilised phosphonium ylide (ylide precursor A122)

The cycle was further developed in a follow up paper in 2013 where it was found the inclusion of 4-nitrobenzoic acid, acting as a Lewis acid, helped increase the rate of reduction of the phosphine oxide to phosphine, and thus the catalytic cycle could be

performed at room temperature. This led to more choice for the phosphine precatalyst, which no longer required a cyclic structure, and enabled use of other side groups to induce stereoselectivity, with *E/Z* ratios as high as 95:5 reported.[126] It was thus proposed that the phosphine itself plays a role in rearranging the *Z*-isomer of the starting material to the *E*-conformation by performing a 1,4-addition to the alkene bond which is facilitated by the adjacent carbonyl, allowing the free rotation to the *E*-conformation, before elimination of the phosphine and reformation of the alkene bond.[127]

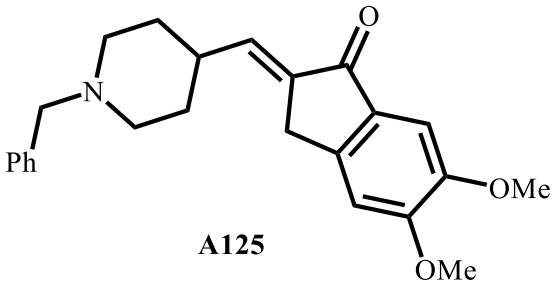
The final major shortcoming of this CWR was the fact it only facilitated stabilised ylides, so the organic group addition to the aldehyde to form the alkene needed a carbonyl or cyano group to stabilise the ylide. Without the stabilisation, the phosphonium salt, precursor to the ylide, could not sufficiently deprotonate. To overcome this, 'ylide-tuning' was employed, whereby electron withdrawing substituents, such as CF_3 containing phenyl rings, were included on the phosphine to reduce electron density on the phosphorous, and thus lower the pK_a on the ylide-forming proton (**A124** in **Figure 60**).[2]



A124

Figure 60: An example of one of the 'tuned' phosphonium precatalysts (A124) with an electron withdrawing phenyl group which lowers the pKa of the ylide forming alpha proton.

Also needed was a 'masked base' such as $NaOCO_2tBu$ which releases the base NaO*t*Bu slowly in solution to avoid the problematic side reactions, while also maintaining the sufficient strength. The lowering of the pK_a had side-effect of reducing the nucleophilicity of the phosphine, therefore higher temperatures were once again required. However, this was the first reported case of a CWR using semistabilised and nonstabilised ylides, and an impressive library of alkene compounds was prepared, with a greater diversity of substituents on attached to the double bond due to the nonstabilised ylides being employed. One of the most notable compounds produced during this whole study was a precursor to donepezil hydrochloride (**A125**), a widely used drug in the treatment of Alzheimer's disease (**Figure 61**).[2]



A125

Figure 61: The alkene donepezil precursor (A125), synthesised using the CWR with a stabilised phosphonium ylide

The extensive CWR study has made the Wittig reaction more environmentally friendly, cheaper, robust, metal-free and reusable thanks to the phosphine oxide precatalyst and has been employed by other research groups.[2] Similar approaches can thus be used for other ylide organic reactions, such as the Corey-Chaykovsky as previously discussed in this review.

1.10. Conclusion of literature review

This review has shown how organocatalysis and green chemistry have become a major part of mainstream chemistry in recent years how they are critical for sustainable growth of the chemical and pharmaceutical industries, as well as academic research. The review has highlighted the usefulness of aziridines and examples of how they have been asymmetrically synthesised. The usefulness of the Corey-Chaykovsky reaction, and how the aziridination branch is in need of further development has been noted, over 50 years since it was first reported. The catalytic Wittig reaction (CWR) has demonstrated how existing synthetic processes can be developed to incorporate organocatalysis and green chemistry, making the reaction more sustainable, environmentally friendly and asymmetric. A similar approach could be used to asymmetrically and organocatalytically synthesise aziridines using the Corey-Chaykovsky reaction, developing next generation sulfide catalysts and flow chemistry in the process. The forming of aryl pyrrolines when attempting to make vinylaziridines could also be developed as aryl pyrrolines have great potential as organocatalysts. A critical part of modern organocatalysis is being able to efficiently and indeed asymmetrically synthesise the catalysts themselves. This approach would be synthesising organocatalysts through organocatalysis.

1.11. Introduction to research project

Developing new and efficient methods of producing asymmetric molecules of medicinal, industrial and research interest while also reducing costs, waste and environmental impact is one of the highest goals of the modern synthetic chemist. As was discussed in the literature review**,** organocatalysis has become a major area of modern synthetic chemistry in the last 20 years as it addresses these criteria, and is continuing to develop into new and innovating areas, such as flow and photo organocatalysis. Developing organocatalytic capabilities of existing, highly useful reactions to boost efficiency, reduce waste and enhance asymmetric synthesis is of upmost importance to making organic chemistry sustainable in the future. A recent example of this was with the development of the catalytic Wittig reaction (CWR).

The literature review highlighted the history and highly useful capabilities of the Corey-Chaykovsky reaction. While the epoxidation branch of this reaction has been extensively studied, the aziridination has been less so. Various methods of asymmetric aziridine synthesis have been highlighted, including those using the Corey-Chaykovsky reaction. It is thus aimed in this project to develop and optimise the Corey-Chaykovsky aziridination

reaction, paving the way for catalytic cycles in the future, where the sulfide would act as the precatalyst and form the sulfonium salt in situ, followed by ylide formation, addition to an imine to form the aziridine and recovery of the sulfide for reuse, as can be seen in the proposed catalytic cycle in **Figure 62.**

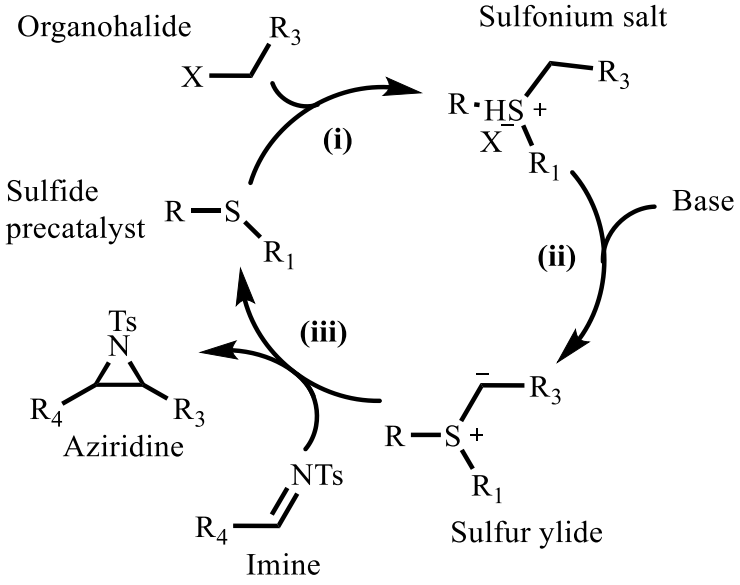


Figure 62: Proposed cycle for a catalytic Corey-Chaykovsky reaction

The aziridination reaction must be first optimised with a focus on reaction conditions and stoichiometry with sulfides, such as tetrahydrothiophene (THT) and diethyl sulfide, before developing larger, more complex sulfides which can be more easily reused and induce asymmetry of the aziridine. These sulfides can be described as next-generation sulfur organocatalysts; examples of possible sulfide structures are given in **Figure 63**. Note the hydroxy group on each of these sulfides, which would be useful for loading in flow chemistry applications.

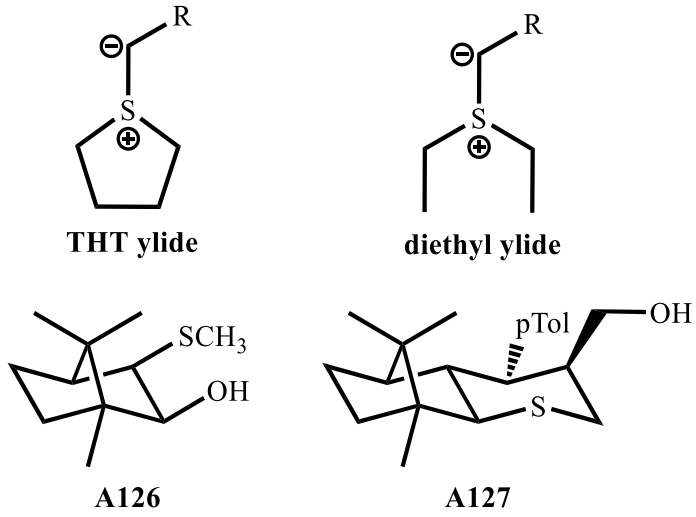


Figure 63: THT and diethyl destabilised sulfur ylides. A126[60] and A127[59] are previously developed next generation sulfide catalysts

Flow chemistry has in recent years become a desirable approach for bulk synthesis and directly competes with, and holds notable advantages over, more traditional batch production. Aziridines are one of the most useful synthons in organic chemistry for producing nitrogen containing compounds. Once the Corey-Chaykovsky aziridination reaction has been fully optimised with respect to asymmetry, it could facilitate a future flow chemistry method by immobilising the next-generation sulfur catalysts to a capillary hollow monoPLOT reactor[128] (**Figure 64**), and then flowing the reactants through, which will elute the asymmetric aziridine.

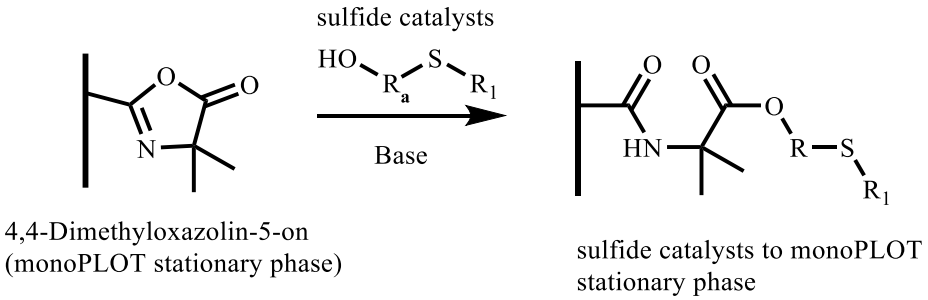


Figure 64: Proposed loading of sulfide catalyst to monoPLOT column

A recent observation by the Coyle research group at DCU when studying the aziridination reaction was the formation of aryl pyrroline when using an aryl imine, an allyl THT sulfonium ylide and the strong organic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (**Figure 65**). An allyl ylide was used as the corresponding vinylaziridine is highly useful, and the use of organic bases for deprotonation of the sulfonium salt to form the ylide had not been widely reported in the literature.

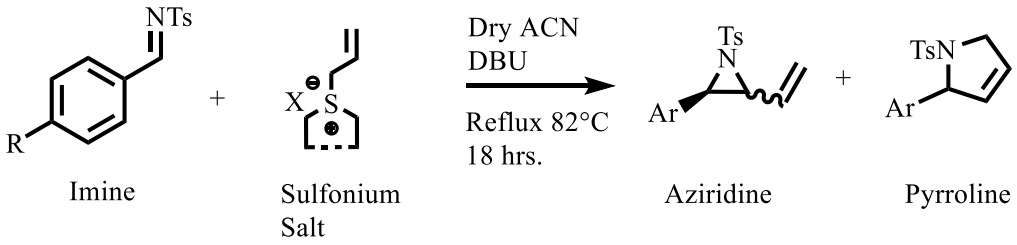


Figure 65: DBU mediated aziridination, with the unexpected aryl pyrroline formation

Although initially this was seen as an unwanted side-product, it was realised that this aryl pyrroline does in fact bear striking resemblance to many existing organocatalysts, such as those developed by MacMillan, as it is a five membered, *N*-containing heterocycle with an aryl group in the two position (discussed in the literature review). It is thus theorised that optimising the reaction to develop this pyrroline over the aziridine may produce an important new pathway to synthesis of new organocatalysts. The double bond on the pyrroline ring offers many opportunities for extensive and diverse functionalisation of the ring, and a library of catalysts could be produced, one example being the hydrogenation of the double bond to form the corresponding aryl pyrrolidine (**Figure 66**).

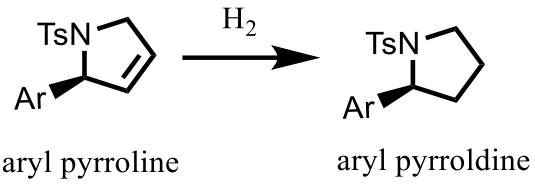


Figure 66: Proposed hydrogenation of the aryl pyrroline double bond

As organocatalysts require enantiomerically pure compounds, the enantiomers of aryl pyrroline will have to be resolved, which may be achieved through reaction to form separable diastereomeric molecules. These aryl pyrrolines could be investigated for their potential as catalysts with the asymmetric aldol synthesis as shown in **Figure 67**, before being extended to the many organocatalytic processes in current use, as well as development of new ones.

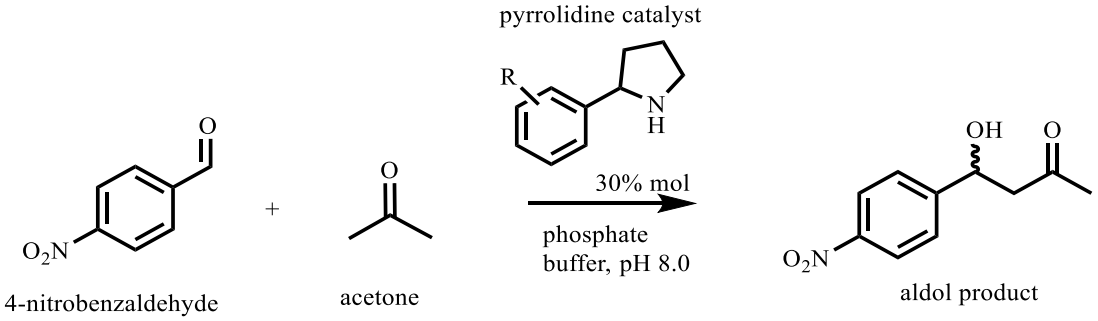


Figure 67: Organocatalytic asymmetric aldol synthesis using a deprotected aryl pyrrolidine catalyst

This project is thus multidisciplinary. In the first working chapter, **Chapter 2**, it will be aimed to optimise the Corey-Chaykovsky aziridination reaction to selectively produce both aziridines and aryl pyrrolines, investigating in detail which factors of the reaction affect the product that is formed, as well as factors that may influence the cis/trans selectivity of the aziridines.

In the second working chapter, **Chapter 3**, it is aimed to develop a synthetic pathway towards development of next generation sulfides that could be used as catalysts in the Corey-Chaykovsky aziridination reaction. A pathway that can synthesise a core structure and allow the synthesis of many derivatives is envisioned. Such derivatives should be able to incorporate chiral centres and different electron withdrawing/donating groups to allow a wide range of catalytic parameters possible. If sulfide organocatalysts can be synthesised, the next target is to develop a method for a catalytic (in sulfide) Corey-Chaykovsky aziridination reaction.

In the third and final working chapter, **Chapter 4**, the aryl pyrrolines synthesised from the method developed in **Chapter 2** will be looked at. It is aimed to develop a synthetic pathway for making derivatives of the aryl pyrrolines, and examine how these may be used as organocatalysts for different reactions.

Chapter 2 Investigation of the Corey-Chaykovsky aziridination reaction

2.1. Introduction

The Corey-Chaykovsky aziridination reaction, using *p*-aryl imines (**1**) and allylic sulfonium salts (**2**) as starting materials, has been shown to produce the expected vinylaziridines (**3**) product and occasionally aryl pyrrolines (**4**) as a minor product (**Figure 68**). It was aimed to study the reaction and identify how to selectivity synthesise both **3** and **4.** To achieve this goal, several of the reaction parameters were investigated, which included the ylide used, and the effect of different counteranions of the sulfonium salt were examined. The solvent for the reaction, acetonitrile, being aprotic and polar, has already been shown to be the most suitable , however, parameters such as base, temperature, work-up/purification were examined. The mechanism of the formation of **4** was also examined to determine if **4** is synthesised directly in the reaction or by the rearrangement of **3**, as this is not known.

The baseline conditions to selectively synthesise **3** and **4** in the Corey Chaykovsky reaction will form the basis for a future catalytic study.

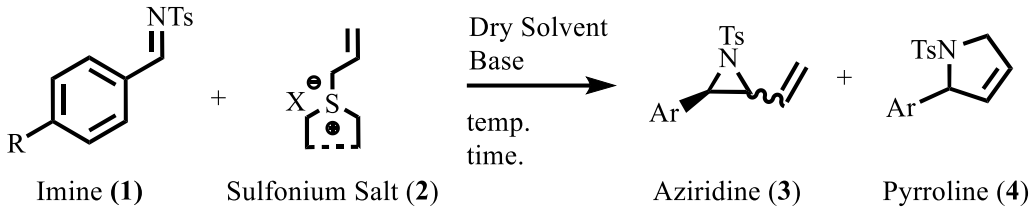
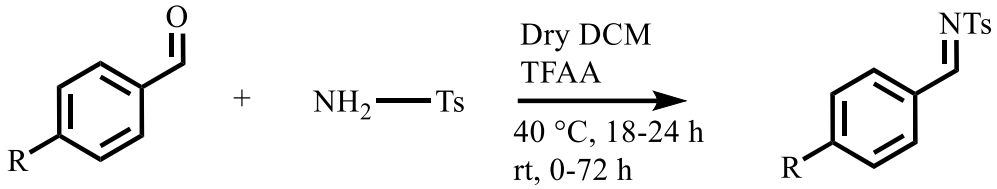


Figure 68: Corey-Chaykovsky vinylaziridine and aryl pyrroline general reaction scheme

2.2. Imine synthesis

The first of the two starting materials to be synthesised were the para-substituted, tosyl protected aryl imines which employed a method reported by Lee *et al*.,[129] which was further optimised. The reaction involved the addition of *para*-toluenesulfonamide to the appropriate *para*-substituted benzaldehyde to yield the analogous tosyl protected imine, while using trifluoroacetic anhydride as a dehydrating agent. The reaction was carried out under an inert atmosphere with dried glassware and solvent, with dry dichloromethane. Seven imines (**1a-h**) were synthesised with different times at reflux and stirring at room temperature (**Table 1**). Products **1a-h** were characterised by ^{1}H NMR spectroscopy with comparison to spectra from the literature, as follows; **1a-c**,[130] **1d** and **1f**,[131] **1e**,[132] **1g**[133] and **1h**[134]. The ^{1}H NMR spectrum for **1a** is provided in **Figure 69**, and all other imine spectra are included in the Appendix.

Table 1: Synthesis of tosyl protected aryl imines



1

Imine	R	Conditions (Temperature + time)	% Yield
1a	CF_3	40 °C 24 h., rt 72 h	72
1b	OMe	40 °C 24 h., rt 24 h	62
1c	Cl	40 °C 18 h., rt 24 h	57
1d	Me	40 °C 24 h	43
1e	H	40 °C 18 h., rt 5 h	63
1f	NO_2	40 °C 24 h., rt 48 h.	20
1g	CN	40 °C 24 h., rt 48 h	40
1h	$C(O)OCH_3$	40 °C 24 h., rt 48 h	30

All reactions were performed at 5-10 mmol scale with 5-10 mL of dry DCM, followed by purification by recrystallisation with ethyl acetate and hexane. See Experimental Methods for further details.

The purification of the imines was performed with an ethyl acetate and hexane recrystallisation. Yields for the imines ranged from 20-72%. Substituent electronic effects did not appear to have a major influence on the yield as good yields were recorded for **1a** and **2b** (electron-withdrawing CF_3- and electron-donating OMe-substituted imines, respectively) although reaction times were different. Imines **1f, 1f** and **1h** had poorer yields of 20-40% but as these were only required for a single study pursuing further optimisation was deemed not necessary.

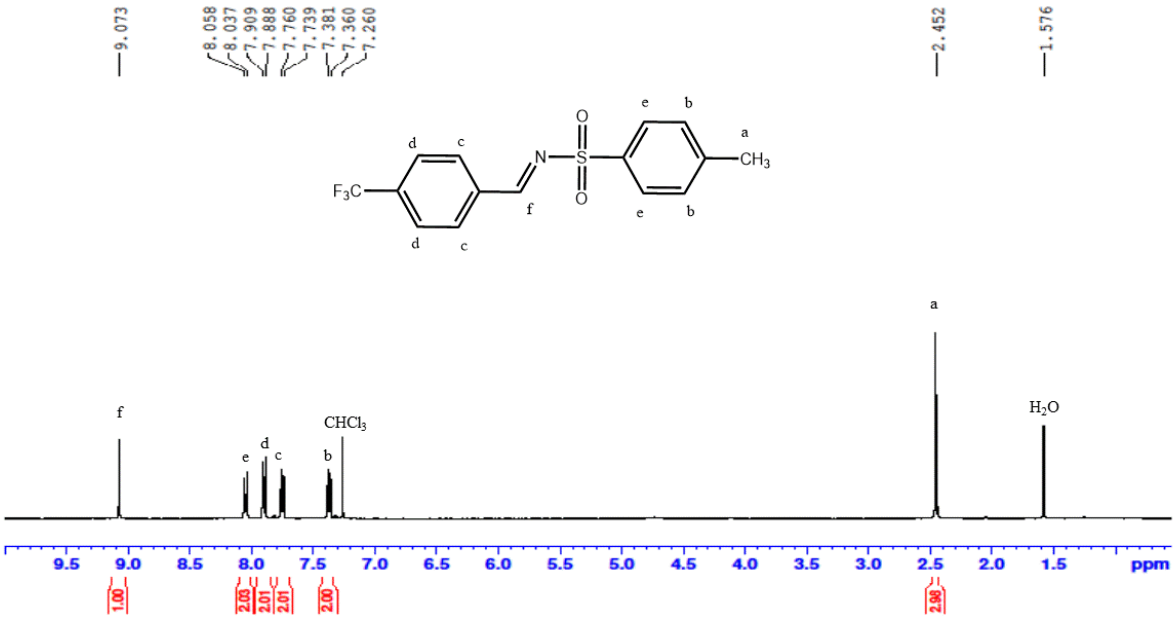
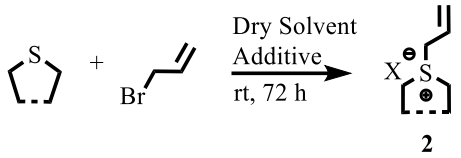


Figure 69: ^{1}H NMR of imine 1a

2.3. Sulfonium salt synthesis

The second starting materials to be prepared were the allyl sulfonium salts that are required for sulfur ylide formation. For establishing the baseline conditions of the reaction, two sulfides were chosen, tetrahydrothiophene (THT) and diethyl sulfide. THT has a locked ring conformation, while diethyl sulfide has free rotation about its' two ethyl groups, so this may provide insight as to the effect of conformation on the reaction. Both sulfides react readily with allyl bromide in dry DCM at room temperature over 72 hours to yield the sulfonium salt with bromide as the counter anion (**Table 2**). Very dry glassware is critical to the success of the reaction, so appropriate flame drying is needed. It has been previously reported by Dai *et al.*[60] that an allyl sulfonium salt with ClO_4^- counter anions yielded a small amount of pyrroline along with the target vinylaziridine product. Therefore, counter anion exchanges were also employed using silver salts ($AgClO_4$ and $AgBF_4$) to yield the THT and diethyl salts to determine if this may boost yields. The counter anion exchanged sulfonium salt synthesis worked best in dry acetonitrile (ACN) instead of DCM, and underwent alumina plug filtration as a post reaction workup to remove AgBr. The methods used were based on those used by Dai *et al.*[60] as well as Sokka *et al.*[135] for trialkyl sulfonium salt synthesis and la Rochelle *et al.*[136] for the counter anion inclusion. Salts **2a-f** were characterised by ^{1}H NMR and high resolution mass spectrometry (HRMS). **2a** and **2d** were compared to ^{1}H NMR of the same compound from the literature.[137] **2b-c** and **2e-f** were not found in the literature and are new but differ to **2a** and **2d** only by the counter anion, and therefore were also compared to the same literature spectra. The ^{1}H NMR of **2a** (**Figure 70**) and **2d** (**Figure 71**) are given below, and all ^{1}H NMR and HRMS spectra for salts **2a-f** are included in the Appendix.

Table 2 Sulfonium salt synthesis



2

Salt	Sulfide	Dry Solvent	Additive	X	% Yield
2a	Et_2	DCM	-	Br	91
2b	Et_2	ACN	$AgClO_4$	ClO_4	90
2c	Et_2	ACN	$AgBF_4$	BF_4	96
2d	THT	DCM	-	Br	49
2e	THT	ACN	$AgClO_4$	ClO_4	57
2f	THT	ACN	$AgBF_4$	BF_4	99

All reactions were performed at a 10-20 mmol scale with 10-20 mL of dry solvent. Salts **2a** and **2d** were purified by vigorous stirring with EtOAc, the rest underwent no purification. See Experimental Methods for further details.

Yields of the three diethyl salts (**2a-c**) were over 90%, with the BF_4^- at 96%, marginally better than the other two. Two of the THT salts (**2d-e**) had lower yields but the THT BF_4^- salt was obtained in 99% yield. From these results it can be concluded that the BF_4^- counter anion produces the highest yields for THT-based sulfonium salt formation. There was no observable difference in yields for the diethyl salts with the different counter anions used.

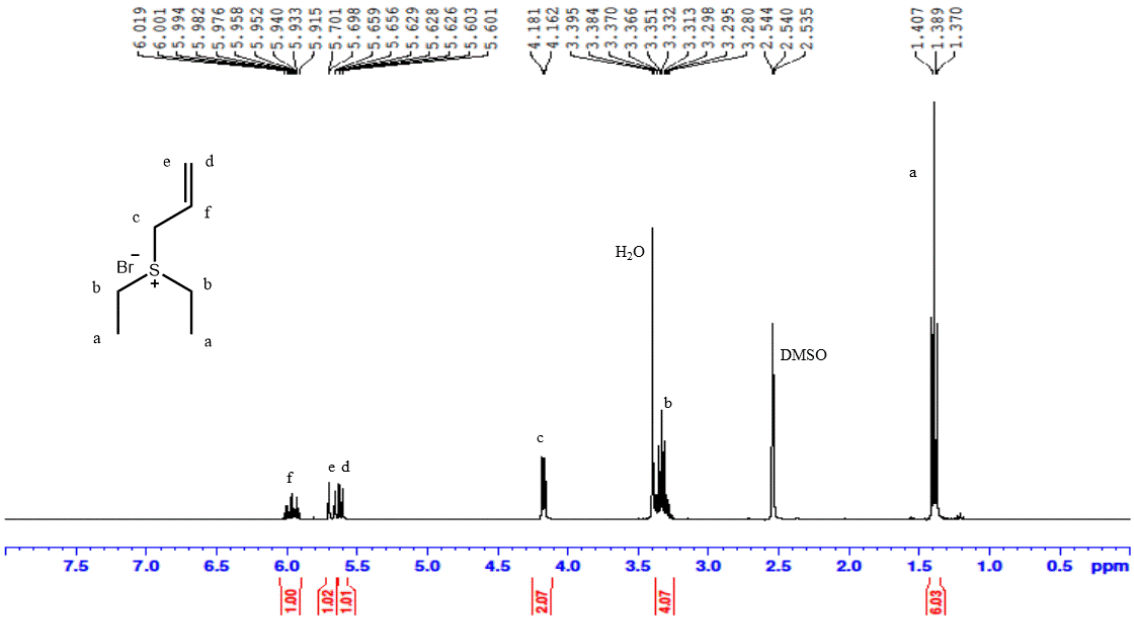


Figure 70: ^{1}H NMR of salt 2a

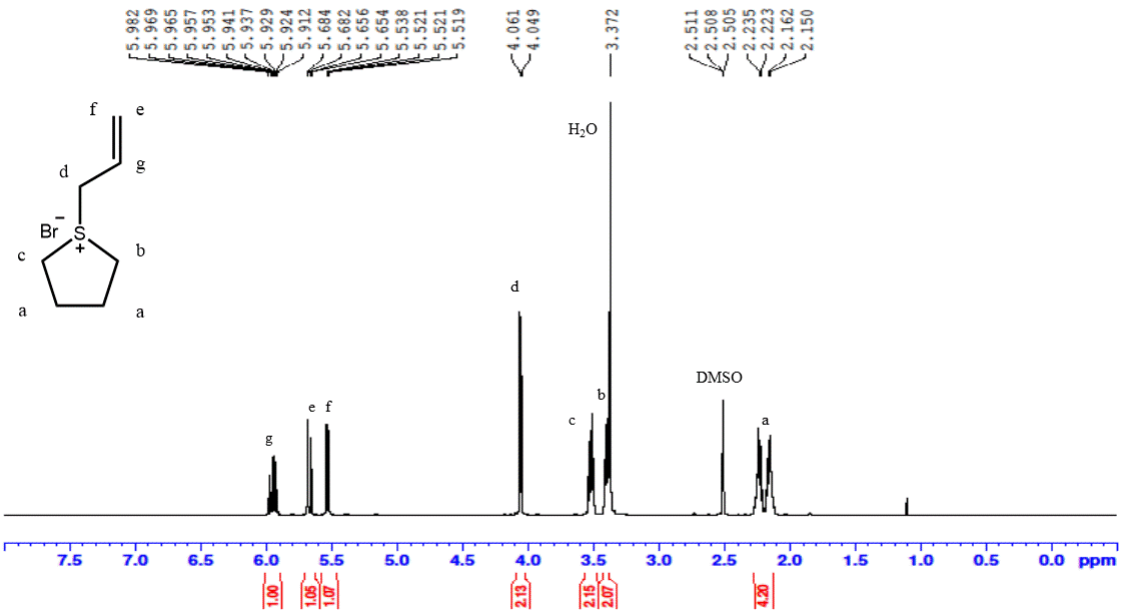
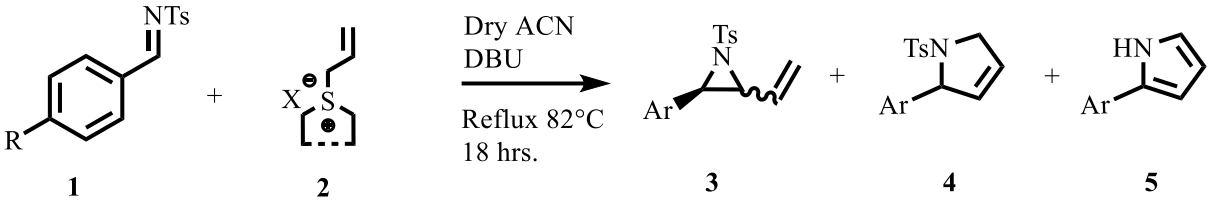


Figure 71: ^{1}H NMR spectrum of salt 2d

2.4. Initial aziridination studies with DBU and a range of imines and salts

As an initial study it was decided to examine the Corey Chaykovsky aziridination reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a strong, bicyclic, organic non-nucleophilic base. DBU has been used for Corey-Chaykovsky aziridination reactions previously in the literature.[69] It had been previously found in an initial study in our research group that this base tended to favour the formation of the aryl pyrroline (**4**) rather than the aziridine (**3**). Interestingly, the base in this reaction is in theory supposed to merely deprotonate the sulfonium salt and produce the corresponding ylide in situ, however our earlier results may suggest DBU performs a further role. This initial study carried out used ten different *p*-aryl imines (**Table 3**). Also, a range of sulfonium salts were used and all reactions performed at a 0.5 mmol scale with a standard work-up of a celite and alumina plug filtration. The study aimed to identify the preference for forming the pyrroline (**4**) and aziridine (**3**) using different starting materials with DBU as well as possibly identify side products that may give clues as to the reaction mechanism. Results are given in **Table 3**.

Table 3: Initial DBU aziridination study reaction conditions



1 **2** **3** **4** **5**

Entry	Imine (**1**)	R	Salt (**2**)	Counter anion (**X**)	% Yield Aziridine (**3**) (cis/trans)	% Yield Pyrroline (**4**)	% Yield Pyrrole (**5**)
1	a	CF_3	2d, THT	Br^-	-	4	11
2	c	Cl	2d, THT	Br^-	-	12	-
3	b	OMe	2d, THT	Br^-	-	10	-
4	d	Me	2d, THT	Br^-	-	7	-
5	e	H	2d, THT	Br^-	-	4	-
6	a	CF_3	2a, Diethyl	Br^-	-	5	20
7	b	OMe	2a, Diethyl	Br^-	-	12	-
8	a	CF_3	2d, THT	ClO_4^-	-	3	9
9	b	OMe	2d, THT	ClO_4^-	-	6	-

All reactions were performed in duplicate at a 0.5 mmol scale with 1 mL of dry ACN and a standard work-up of filtering through a celite and alumina plug followed by column chromatography. See Experimental Methods for further details.

This initial study used each of the imines with the sulfonium salt **2d**, as well as testing the diethyl Br^- (**2a**) and the THT ClO_4^- (**2e**). It was found that the crude ^{1}H NMR spectra for all entries were problematic for interpretation due to the high concentration of DBU and its conjugate acid which is present between 1-4ppm on the NMR spectra. In many of the purified pyrroline and pyrrole samples, DBU still remained in varying amounts despite passing through the silica chromatography column in a non-polar mobile phase. A brief study to improve the reaction work-up was carried out by washing the crude material with water and/or 1 M HCl to remove the DBU, but this led to a significant loss of product. However, it was then found that using a longer silica stationary phase with a less polar initial mobile phase with a gradual gradient led to DBU successfully being removed. The pyrrolines (**4**) and pyrrole (**5**) synthesised in **Table 3** were characterised by ^{1}H NMR and compared to spectra of the same compounds from the literature; **4a** and **4c** [138] **4b, 4d-e** [139] and **5a** [140]. **4a** and **4b** were additionally characterised by ^{13}C, COSY, DEPT and HSQC NMR as well as HRMS. The ^{1}H NMR of **4a** (**Figure 73**) and **5a** (**Figure 74**) are given below as examples, the remaining NMR and HRMS spectra can be found in the Appendix.

Once products could be isolated pure it was found that no aziridine **3** (expected product) was formed in any of the reactions. All reactions produced the pyrroline (**4**) in varyingly low yields. The diethyl salt **2a** boosted yields slightly, as seen in entry **6** and **7**. The ClO_4^- salt **2e** did not improve yields (entry **8** and **9**) implying the role of the counter anion may not be significant. Unexpectedly, each time the imine **1a** was used it produced the

corresponding pyrrole (**5**), instead of the pyrroline, as the major product. As this did not occur for any of the other imines, it seems likely that the electron-withdrawing effect of the CF_3 substituent is responsible. A plausible explanation is that the electron-withdrawing aryl group renders the adjoining proton on the pyrroline ring electron deficient, or acidic, allowing DBU to remove this proton, leading to detosylation and the formation of 2*H*-pyrrole, which in turn aromatises to the more stable tautomer, 1*H*-prrole, as is shown in **Figure 72**. The fact that DBU was used in a 2 eq. to the 1 eq. of imine allows for excess DBU to perform the detosylation.

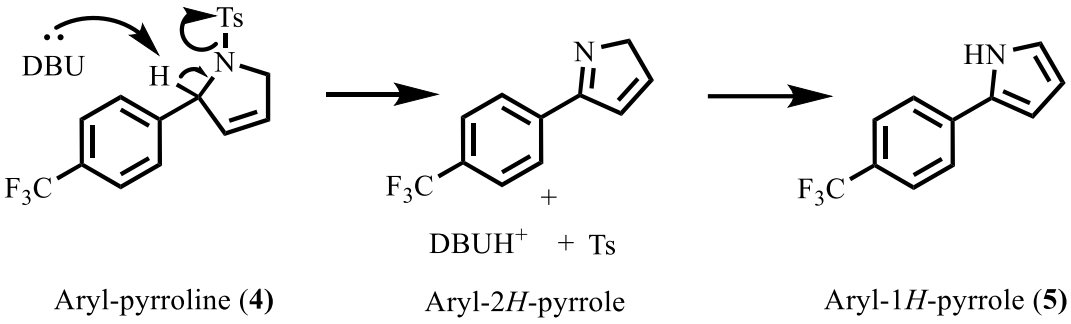


Figure 72: Proposed mechanistic formation of aryl-1*H*-pyrrole from the corresponding aryl-pyrroline

Thus, a follow up study using different imines bearing electron-withdrawing groups was conducted to confirm this theory. Also, a study using other organic bases was carried out to see if aromatisation to the pyrrole is unique to DBU.

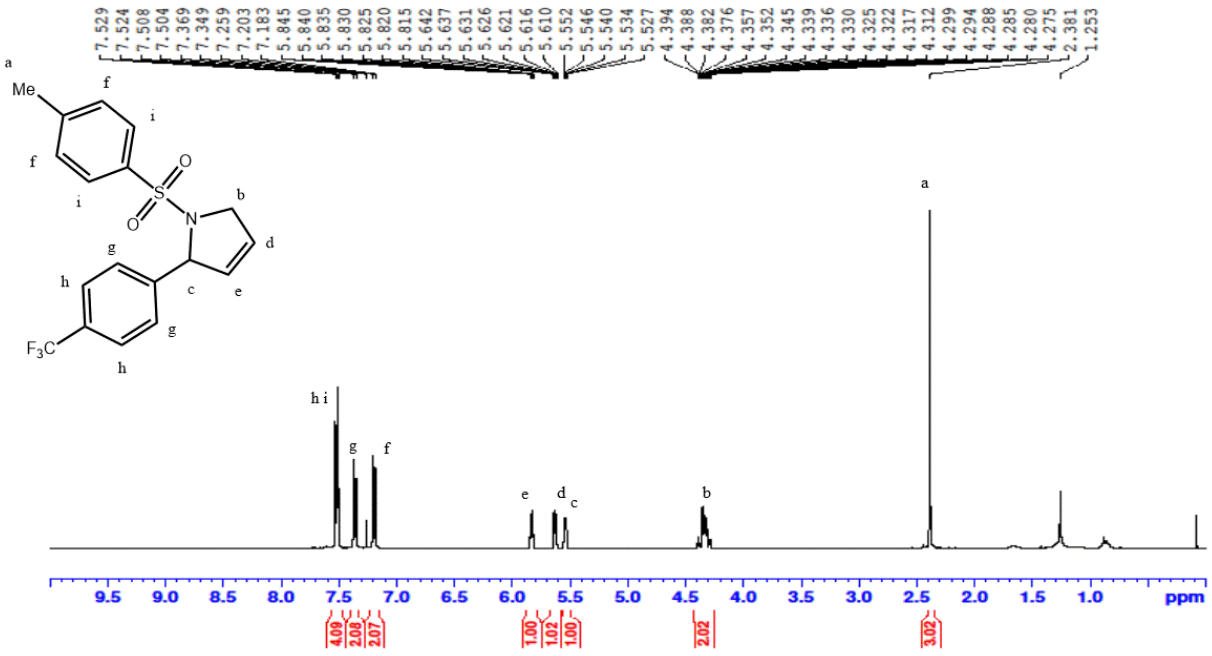


Figure 73: ^{1}H NMR of pyrroline 4a

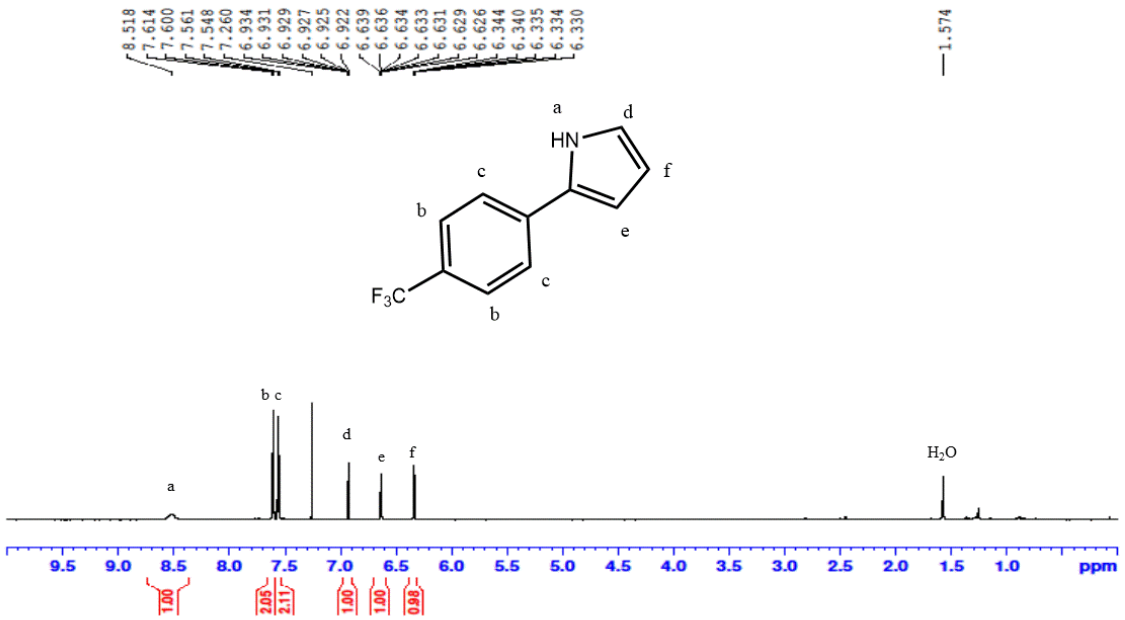
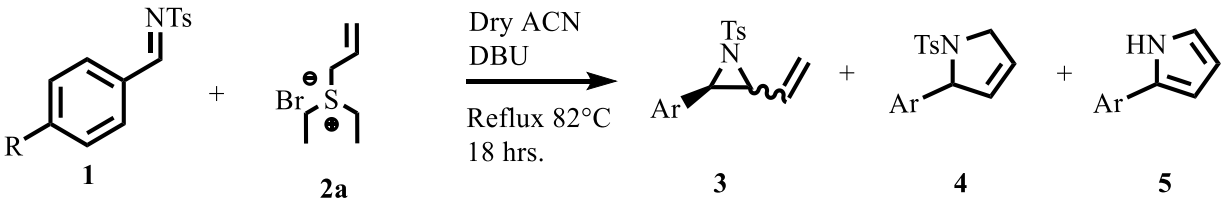


Figure 74: ^{1}H NMR of pyrrole 5a

2.5. Electron-withdrawing substituent study

In order to test the theory that the electron withdrawing nature of the CF_3 substituent on the imine **1a** is responsible for pyrrole formation during the aziridination reaction with DBU as base, three additional imines were synthesised bearing electron-withdrawing groups – NO_2 (**1f**), CN (**1g**) and $C(O)CH_3$ (**1h**) – and were tested in the aziridination reaction. The results of this study are shown in **Table 4**.

Table 4: Electron-withdrawing substituent study



1 **2a** **3** **4** **5**

Entry	Imine (**1**) (**R**)	% Yield Aziridine (cis/trans) (**3**)	% Yield Pyrroline (**4**)	% Yield Pyrrole (**5**)
1	NO_2	-	-	0
2	CN	-	-	0
3	$C(O)OCH_3$	-	-	0

All reactions were performed in duplicate at a 0.5 mmol scale with 1 mL of dry ACN and a standard work-up of filtering through a celite and alumina plug, followed by extraction. See Experimental Methods for further details.

The crude ^{1}H NMR spectra for entries 1,2 and 3 strongly suggested that pyrrole (**5**) formed as splitting patterns were present that were very similar to that observed for pyrrole **5a**, but purification was not carried out so this was not confirmed. The crude ^{1}H NMRs for entries 1-3 showed no evidence of **3** or **4**. It was thus concluded that it likely that **5** was the major product in all three reactions. This study suggests the electron-withdrawing substituent on **1** leads to **5** in the reaction when using DBU as a base at 82 °C.

2.6. Study of crude NMR spectra under different temperatures and bases

With the recurring problem of pyrrole (**5**) formation and no aziridine forming with DBU, it was decided to perform a study with different organic bases of varying strength. It was unclear at this point what impact the base was having on the pyrroline formation. The bases chosen for this study were; 1, 1, 3, 3-tetramethylguanadine (TMG, *p*K$_a$ 13.6) and diisopropylethylamine (DIPEA/Hünig's base, *p*K$_a$ 10) which are on either side of the strength of DBU (*p*K$_a$ 12 in DMSO). Also tested were triethylamine (TEA, *p*K$_a$ 9) and 1,4-diazabicyclo[2.2.2]octane (DABCO, *p*K$_a$ 2.97, 8.93) (**Figure 75**).[141]

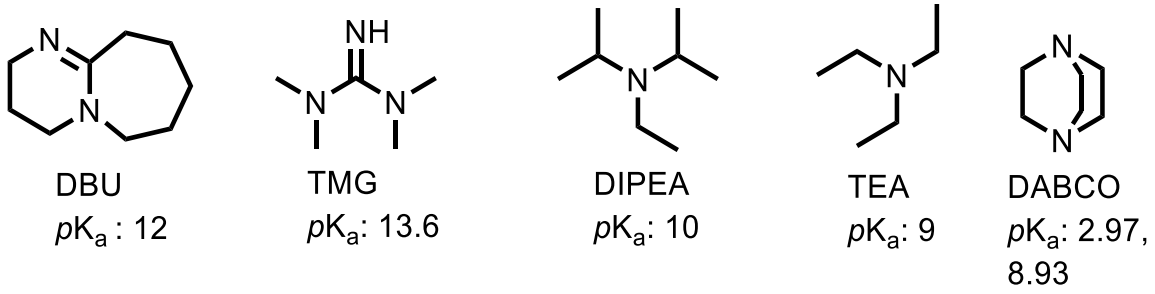


Figure 75: Range of organic bases tested in the aziridination reaction

For the study it was also decided to test each aziridination with each base at three different temperatures; 82°C (reflux temperature of acetonitrile which was currently being used), 50 °C and room temperature to see if this has an impact on which product forms. The imine **1a**, which formed the pyrrole (**5a**) with DBU, was chosen for the study as well as the salt **2a**. The study simply looked at the ratio of the characteristic peak of **3** and **4** from ^{1}HNMR spectra of the crude materials to see which conditions favoured forming which product best (**Table 5**). As is shown in **Figure 76,** the proton on the aziridine ring next to the aryl group appears as a doublet of doublets, but the trans isomers shows this distinctive peak slightly more upfield at 3.27 ppm compared to the cis at 3.67 ppm, because the trans proton is more shielded by the anisotropic effect of the vinylic group (**Figure 77**). The coupling constants are also slightly different for the cis and trans isomers. (**Figure 78**) The identification of these characteristic peaks is based on the studies conducted by Dai *et al.*[60] and Aggarwal *et al.*[59]

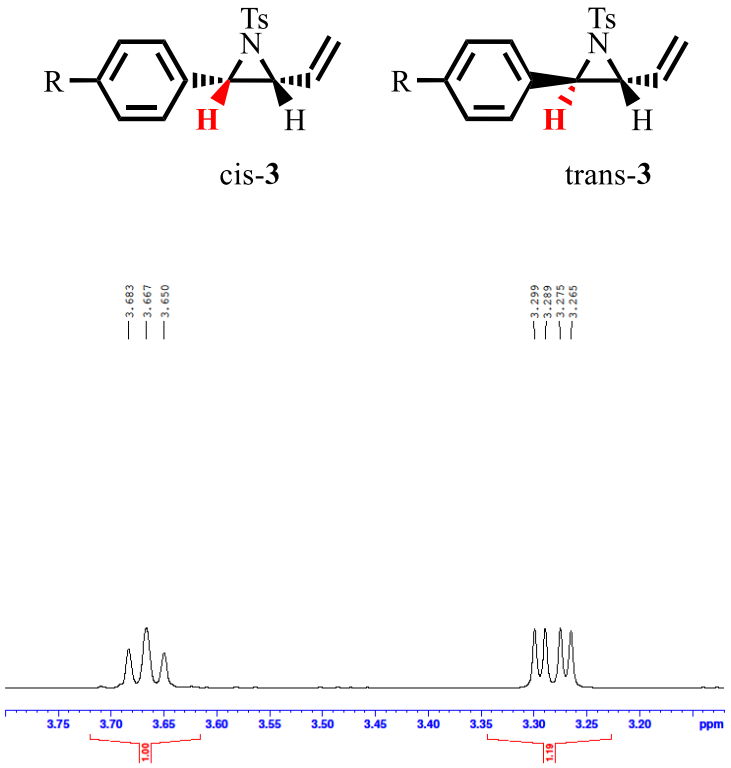


Figure 76: cis- and trans-3 with ^{1}H NMR spectrum showing characteristic peaks for cis/trans aziridine, at 3.67 ppm and 3.27 ppm, respectively. The characteristic peak is representative of the proton highlighted in red in the cis- or trans-aziridine, shown above

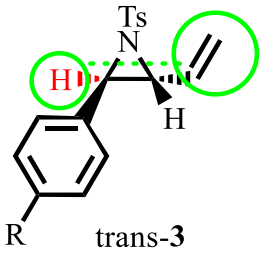


Figure 77: Illustration of the anisotropic effect the vinylic group has on the proton of the trans aziridine isomer, leading to shielding and this the proton's peak being more upfield

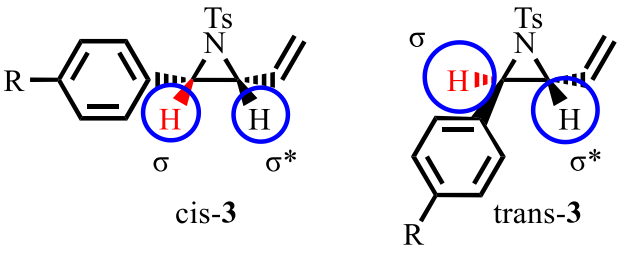
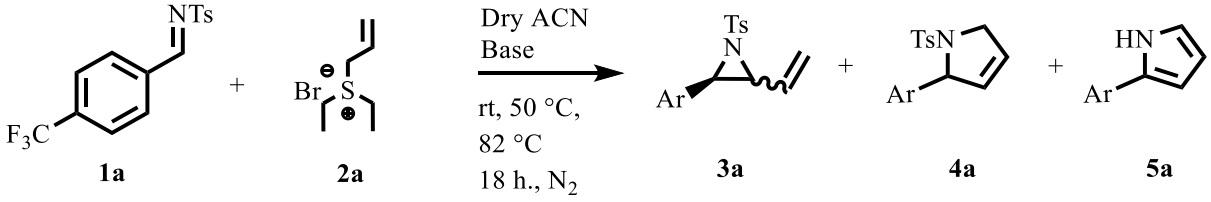


Figure 78: Illustration of the protons coupled about the aziridine ring. The σ to σ* overlap is slightly more pronounced in the cis isomer, leading to a higher coupling constant.

This characteristic splitting allows the cis/trans ratio of the vinylaziridines **3a** to be determined by ^{1}H NMR. In the below study (**Table 5**) the ^{1}H NMR spectra of the crude materials of each reaction were examined, and the distinctive peak of the cis and trans aziridine (**3a**) as well as the distinctive peak for the pyrroline **4a** and pyrrole **5a** which were

previously characterised by ^{1}H NMR were identified and the ratios of the peaks recorded to give an indication of the abudance of one product over another. An example crude ^{1}H NMR is given below (**Figure 79**). Note that in this study **3a** is a new compound, and was identified by the literature spectrum of the very similar vinylaziridine reported by Dai *et al.*[60] which differed only by a Cl substituent in placed of the CF_3 in **3a**. **3a** was later isolated fully characterised by NMR and HRMS to confirm the structure, and spectra are included in the Appendix.

Table 5: Temperature-organic base study of crude ^{1}H NMR spectra



1a **2a** **3a** **4a** **5a**

Entry	Base	Temp. (°C)	Ratio of characteristic peaks in crude ^{1}H NMR			
			Aziridine (**3a**)		Pyrroline (**4a**)	Pyrrole (**5a**)
			cis	trans		
1	DBU	rt	-	-	1	-
2	DBU	50	-	-	1	0.5
3	DBU	82	-	-	0.4	1
4	TMG	rt	-	-	1	-
5	TMG	50	-	-	1	-
6	TMG	82	-	-	1	-
7	DIPEA	rt	1	0.75	0.3	-
8	DIPEA	50	0.8	0.9	1	-
9	DIPEA	82	0.9	1	1	-
10	TEA	rt	0.9	1	0.5	-
11	TEA	50	-	-		-
12	TEA	82	-	-	-	-
13	DABCO	rt	-	-	-	-
14	DABCO	50	-	-	-	-
15	DABCO	82	-	-	-	-

All reactions were performed in duplicate at a 0.5 mmol scale with 1 mL of dry ACN and a standard work-up of filtering through a celite and alumina plug, followed by extraction. See Experimental Methods for further details.

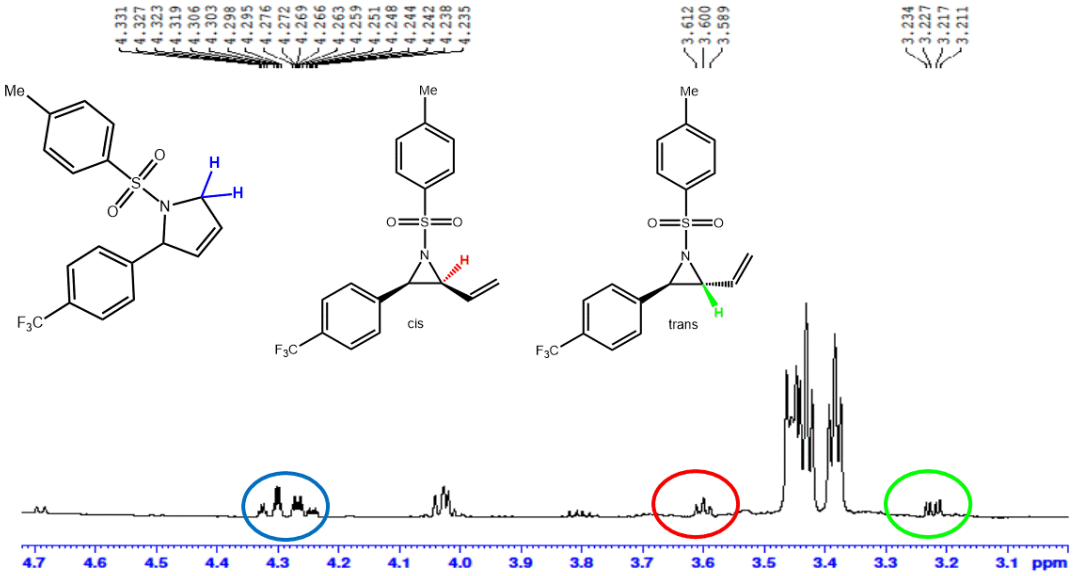


Figure 79: Example Crude ^{1}H NMR showing the identifiable peaks of 3a (cis and trans isomers) and 4a

Entries 1-3 using DBU revealed the pyrrole (**5**) only forms as the major product at 82 °C, as a minor product at 50 °C and not at all at room temperature. This means the suspected pyrroline (**4a**) deprotonation with electron-withdrawing substituents only occurs at higher temperatures. Pyrrole (**5**) also did not form for any of the other organic bases, meaning DBU, along with electron-withdrawing group on the imine and heat, is needed for pyrrole formation. TMG in entries 4-6 showed exclusive preference for the pyrroline (**4a**) and did not go to full completion at room temperature. DIPEA formed an equal distribution of cis and trans aziridine and pyrroline in entries **7-9** and the reaction did not go to completion at room temperature since there was remaining starting material. TEA and DABCO did not appear to show distinctive peaks of any of the products, with strong evidence of starting material still present after reaction completion. This study shows that the strength of the base has a significant effect on product distribution. Stronger bases (DBU and TMG) tend to form the pyrroline (**4a**), while slightly weaker bases (DIPEA) tend to form the aziridine (**3a**) and even weaker bases (TEA and DABCO) do not work. TMG appears best for making the pyrroline (**4a**) as it only requires 50 °C and does not produce the pyrrole (**5**), or indeed any aziridine (**3a**), according to the crude ^{1}H NMR spectra. DIPEA appears best for forming the aziridine (**3a**), with 50 °C again only needed for the reaction to go to completion. In each case approximately 50:50 cis/tans ratio of **3a** was found. However, a significant amount of pyrroline (**4a**) also formed, although much less than observed using TMG or DBU. For the TMG reaction, two minor side products are also formed which are unidentified, although one may be the cis aziridine with peaks shifted in the NMR spectra (though this is purely speculative). The DIPEA reaction also has one unidentified minor side product, along with the cis/trans aziridine (**3a**) and pyrroline (**4a**). As TMG formed (**4a**) only, while DIPEA produced the aziridine (**3a**) and pyrroline (**4a**) as well, it may suggest that the aziridine forms first before rearranging, rather than the pyrroline forming straight from the charged 1, 4 dipolar intermediate that forms when the ylide reacts with the imine. This will be investigated later.

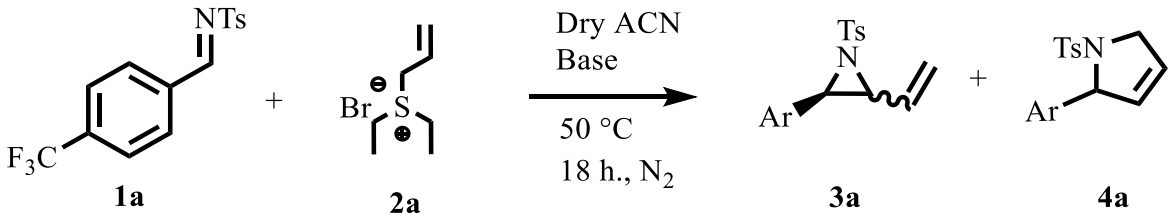
The study shows that choice of base plays a profound role in the products formed, despite the fact that, in theory, the only role they are supposed to play is deprotonation of the salt to form the ylide. Interestingly, 50 °C seems to suit the formation of both products using the respective bases, increasing to reflux (82 °C) has no observed benefit but room temperature stops the reaction from going to completion.

A brief study on the work-up of several of the reactions in **Table 5** suggested washing the crude material with water and/or 1 M HCl was successful at removing leftover organic base and did not significantly change the ratio of products, but significantly reduced the quantity of the crude material, so it was decided to not perform a work-up and simply purify the crude material by column chromatography.

2.7. Scale ups

Although TMG and DIPEA at 50 °C appear best for forming **4a** and **3a**, respectively, purification tests at a 0.5 mmol scale produced relatively poor yields (20-30%) for each compound. As this was such a small scale, it was decided to test each at a larger 2 mmol scale (**Table 6**). The ^{1}H NMR for **3a** is given below, which is a mix of the cis and trans isomers (**Figure 80**) as well as a ^{1}H NMR spectrum of purely cis **3a** (**Figure 81**). This spectrum was compared to the very similar aziridine reported by Dai *et al.* which differed only with a Cl instead of a CF_3 substituent on the aryl ring. Furthermore, a pure sample of the cis isomer of **3a** was fully characterised by ^{1}H, ^{13}C, COSY, DEPT and HSQC NMR and HRMS and is included in the Appendix.

Table 6: TMG and DIPEA scale-up aziridinations at 2 mmol



Entry	Base	% Yield	
		Aziridine (cis:trans)	Pyrroline
1	TMG	5 (100:0)	40
2	DIPEA	38 (52:48)	11

All reactions were carried out at a 2 mmol scale with 4 mL of dry ACN and no work up followed by purification by column chromatography. See Experimental Methods for further details.

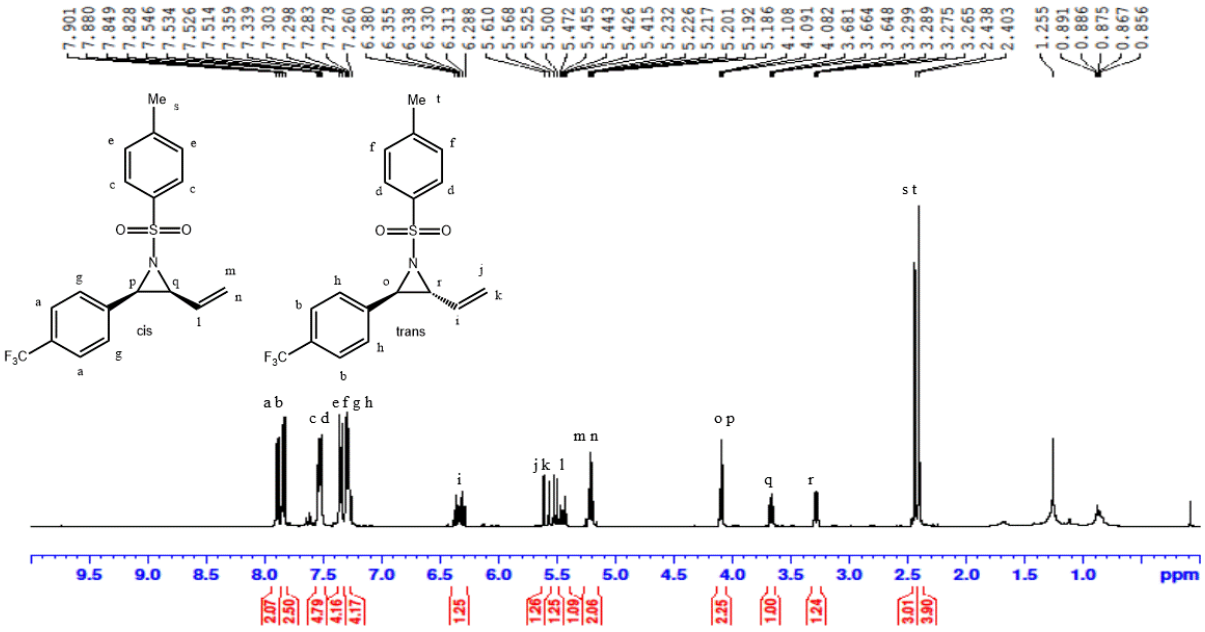


Figure 80: ^{1} H NMR spectra of a cis/trans mixture of aziridine 3a

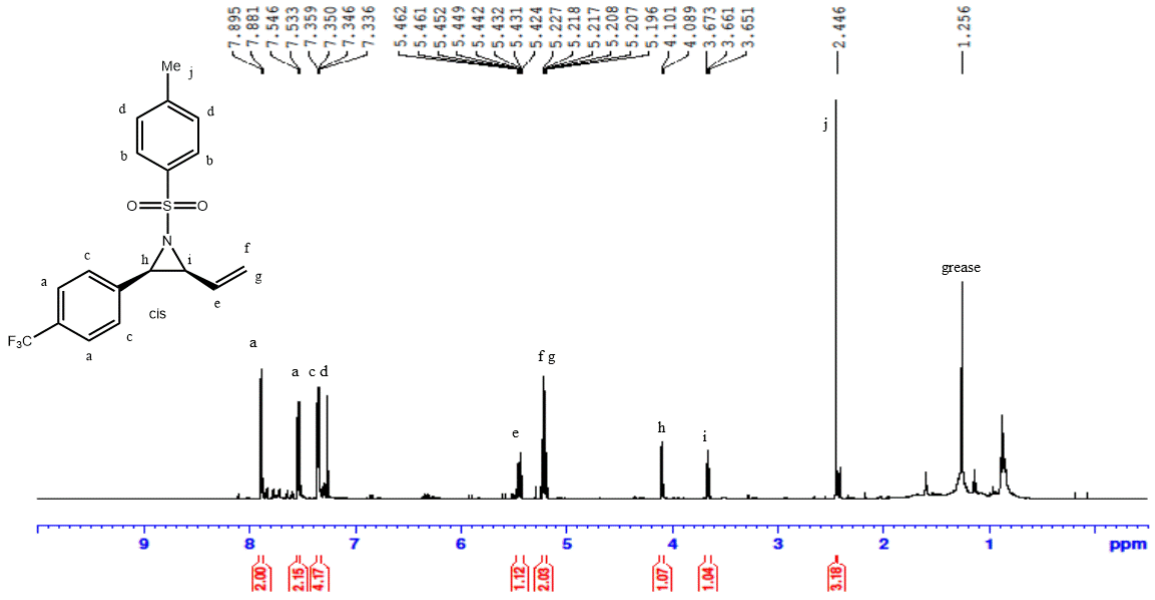


Figure 81: ^{1} NMR spectra a pure cis aziridine 3a

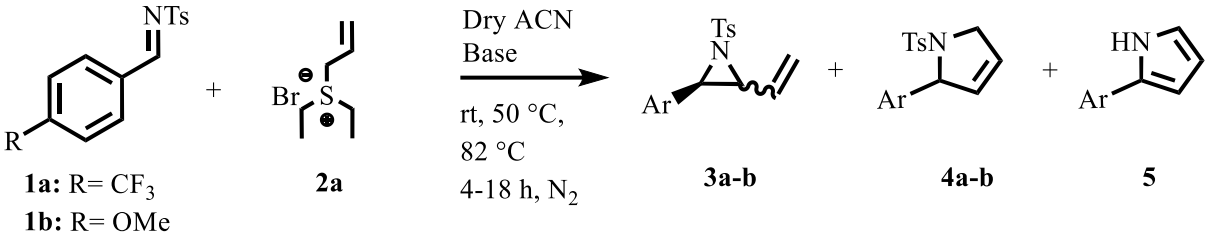
The results of the scale up reactions showed an increase in yield, up to 40% for **4a** and **3a**. Interestingly, a small yield of cis aziridine (5%) was obtained for the TMG reaction, which was not observed for the smaller scale. The DIPEA showed a near 50:50 distribution of cis and trans **3a** and pyrroline was obtained in 11% yield. A notable insight is that for the optimal conditions for synthesising **3a,** the cis/tans ratio is 50:50 and a significant amount

of **4a** forms too. For optimal **4a** formation (with TMG) a much smaller amount of **3a** minor product forms, and its stereochemistry is 100% cis. This may suggest that in both cases, aziridine forms first, then rearranges to pyrroline, but the trans isomer rearranges to **4a** quicker and not remaining. The scale also shows that in the absence of work-up increase yields and no base/conjugate acid was left over after purification. Purification was carried out by column chromatography with an initial mobile phase of 98% hexane with ethyl acetate, which was gradually increased in polarity by gradient to 85% hexane, 15% ethyl acetate. This technique ensured the leftover base remained on the column and good separation of the products occurred.

2.8. Temperature-base studies with **1a** and **1b**

In an effort to boost yields of both the aziridine **3** and pyrroline **4** products, and indeed explain why the 40% yield threshold cannot be surpassed, a base/temperature study was conducted with the five organic bases previously employed (DBU, TMG, DIPEA, TEA and DABCO) as well as an inorganic base study with NaH, KOH and Na_2CO_3. Included also in this study was the imine **1b** as this is the most electron-donating imine, compared with the electron-withdrawing **1a**. Results of the temperature-organic base study is given in **Table 7** below.

Table 7: Temperature-base study with purifications for imine 1a and 1b



1a: R= CF_3 **1b:** R= OMe **2a** **3a-b** **4a-b** **5**

Entry	Base	Imine (**1**)	Time (h)	Temp. (°C)	% Yield Aziridine (**3**) (cis:trans)	% Yield Pyrroline (**4**)
1	DBU	**1a**	4	rt	-	19
2	DBU	**1a**	4	50	-	22
3	DBU	**1a**	4	82	-	24
4	TMG	**1a**	4	rt	-	11
5	TMG	**1a**	4	50	-	29
6	TMG	**1a**	4	82	-	22
7	DIPEA	**1a**	8	rt	21 (48:52)	9
8	DIPEA	**1a**	8	50	29 (51:49)	14
9	DIPEA	**1a**	8	82	26 (50:50)	13
10	TEA	**1a**	18	rt	-	-
11	TEA	**1a**	18	50	3 (56:44)	3
12	TEA	**1a**	18	82	5(51:49)	-
13	DBU	**1b**	4	rt	-	14
14	DBU	**1b**	4	50	-	28
15	DBU	**1b**	4	82	-	24
16	TMG	**1b**	4	rt	-	17
17	TMG	**1b**	4	50	-	22
18	TMG	**1b**	4	82	-	22
19	DIPEA	**1b**	18	rt	16	8
20	DIPEA	**1b**	18	50	27 (64:36)	14
21	DIPEA	**1b**	18	82	22 (59:41)	15
22	DABCO	**1b**	18	rt	-	-
23	DABCO	**1b**	18	50	2 (60:40)	1
24	DABCO	**1b**	18	82	2 (60:40)	2

All reactions were carried out at a 0.5mmol scale in duplicate with 1mL of dry ACN and combined before purification by column chromatography. See Experimental Methods for full details.

For both imines, TMG and DBU reactions (entries 1-6 and 13-18) only 4 hours were needed to complete reaction. Notable the pyrrole **5** does not form in entry 3 as was normally the case at the usual reaction time of 18 hours, thereby concluding that **5** only forms with an electron withdrawing substituent with DBU at 82°C for 18 hours. However, TMG at 50°C remains the best condition for forming the pyrroline (**4**) as is seen in entry 5 for imine **1a**. Likewise, DIPEA at 50°C is the optimum for forming the aziridine (**3**) for both imines

(entries 8 and 20) but this requires 8 hours. DBU at 50°C appears better for forming **4b** than TMG. As is now confirmed, room temperature is not sufficient for forming any product in good yields, with 50 °C being optimal (reflux at 82°C lowered yields in some cases). Interestingly, the imine **1b** requires 18 hours for forming **3b** with DIPEA (entries 19-21), but only needs 4 hours with DBU (entries 13-15) or TMG (entries 16-18) to form **4**. Yields for reactions using TEA (entries 10-12) and DABCO (entries 22-24) are very poor. The stronger bases (DBU and TMG) are best for forming the pyrroline, while the weaker base, DIPEA, is best for forming the aziridine. TEA and DABCO both formed the aziridine as the major product, but yields were low. For optimal aziridine conditions, the **3a** forms a 50:50 mixture of the cis and trans, while the **3b** seems to favour the cis isomer. **3b** was characterised by ^{1}H NMR and compared to the spectra of the same compound in the literature.[142] The ^{1}H NMR spectrum of **3b** is given below (**Figure 82**, cis:trans ratio 1:0.5). The ^{1}H NMR spectrum of a purely cis isomer of **3b** is also shown (**Figure 83**).

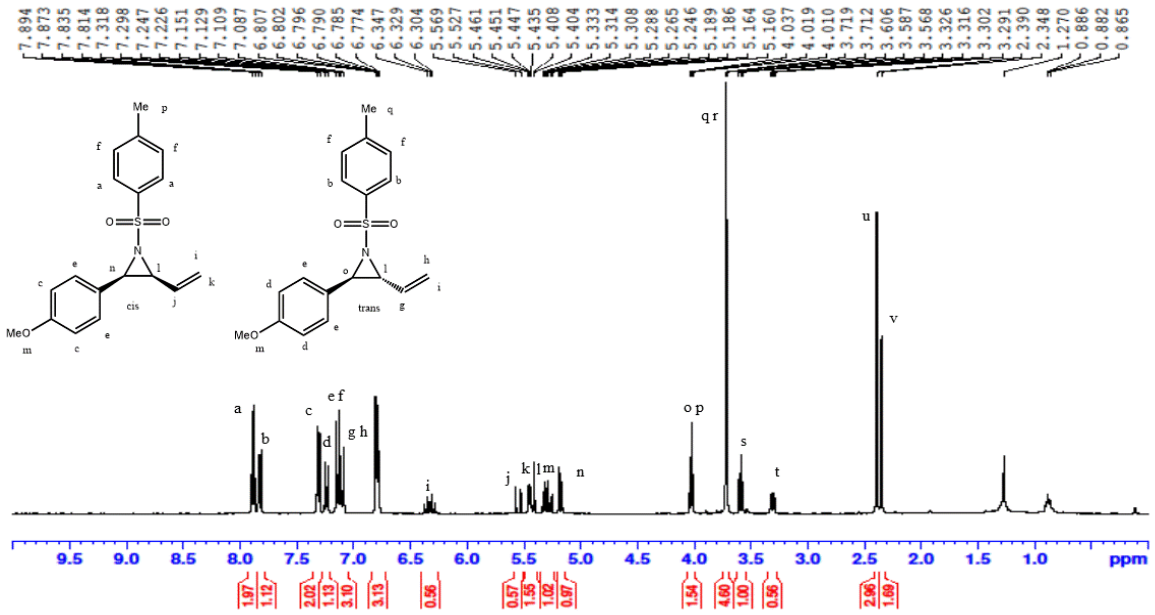


Figure 82: ^{1}H NMR of a cis/trans mixture of aziridine 3b

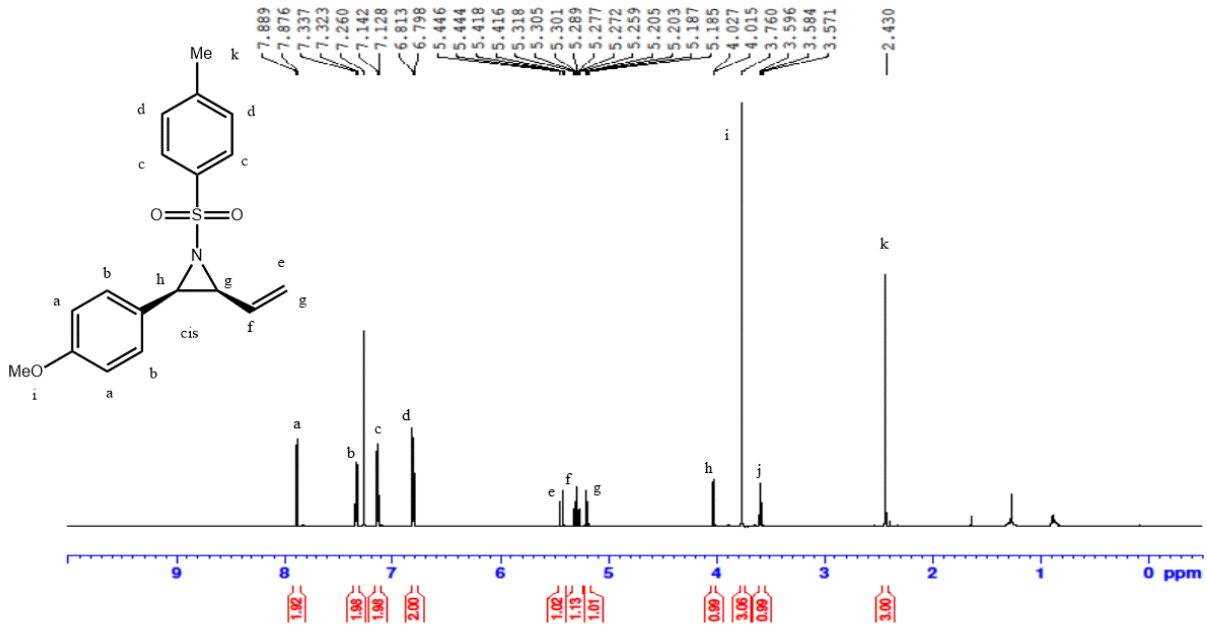
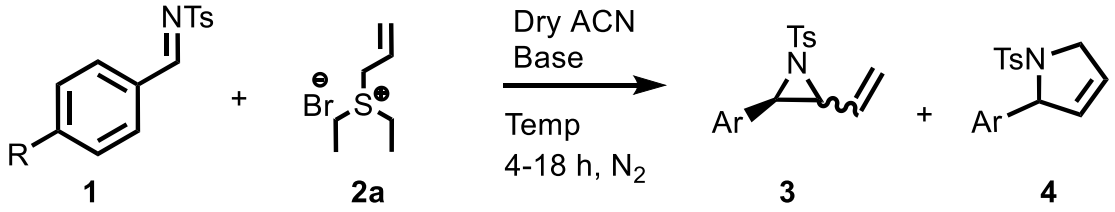


Figure 83: ^{1}H NMR spectrum of a purely cis-aziridine 3b

An area not examined up until now was the use of inorganic bases, which are more standard for the Corey-Chaykovsky reaction. KOH has been most widely used in the literature for the aziridination,[59,60] but NaH and Na_2CO_3 were also examined in this work. Time and temperature were also varied. The most noteworthy results are given in **Table 8.** Note that a work-up of filtering the crude mixture through an alumina plug is necessary for the inorganic bases to remove residual inorganic salts (NaBr or KBr).

Table 8: Inorganic temperature-base study with imines 1a and 1b



					% Yield	
Entry	Base	Imine	Time (h.)	Temp. (°C)	Aziridine (cis:trans)	Pyrroline
1	NaH	**1a**	8	rt	22 (50:50)	14
2	NaH	**1a**	8	50	26 (50:50)	16
3	NaH	**1a**	8	82	25 (51:49)	16
4	NaH	**1b**	8	rt	14 (61:39)	7
5	NaH	**1b**	8	50	29 (65:35)	14
6	NaH	**1b**	8	82	18 (60:40)	8
7	NaH	**1a**	4	0	12 (47:53)	4
8	NaH	**1b**	4	0	10 (37:63)	5
9	Na_2CO_3	**1a**	18	50	-	-
10	KOH	**1a**	4	0	15 (51:49)	8
11	KOH	**1a**	18	50	19 (50:50)	11
12	KOH	**1b**	4	0	18 (34:66)	11
13	KOH	**1b**	18	50	20 (62:38)	16

All reactions were carried out at a 0.5 mmol scale in duplicate with 1 mL of dry ACN with a standard work-up of filtering through an alumina plug, before being combined and purified by column chromatography. See Experimental Methods for further details.

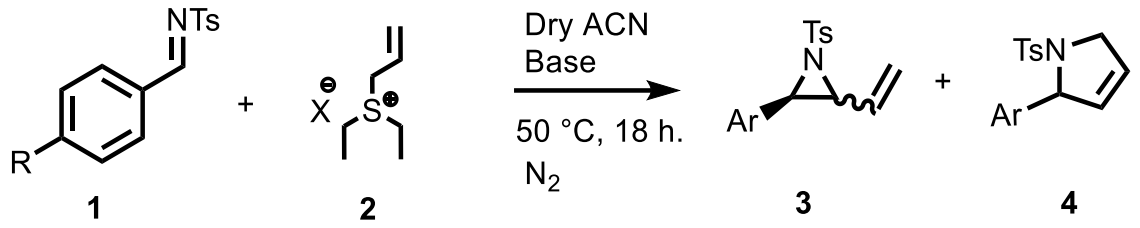
This study showed that NaH appears as good as DIPEA for forming both aziridines (**3a-b**), and in the same cis/trans ratio as previously seen. Similar yields for the pyrroline (**4a-b**) minor product were also obtained. Once again, 50 °C was the optimal temperature. KOH yields were lower but also favoured **3**. Na_2CO_3 was too weak a base and did not work so it was not further examined. NaH required 8 hours for **3a-b** formation, this is an improvement for **3b** which required 18 hours using DIPEA, and yields improved. The 0 °C reactions gave surprising results, yields of **3** and minor product **4** were lower, but the cis/trans ratio for **3a** changed to 34:66 in favour of trans (entry 12), which is the opposite of the 50 or 82 °C conditions which is the same ratio in favour of the cis, but no change was observed for **3b**.

This extensive study has now established the optimal base and temperature for each imine (**1a-b**) starting material. **1a** requires DIPEA at 50°C for 8 hours to make **3a** in a 50:50 cis/trans ratio, and TMG at 50 °C for 4 hours to make **4a**. For **1b**, NaH or DIPEA works best for **3b** formation at 50 °C with cis being favoured, but NaH requiring the shorter time of 8 compared to 18 hours for the DIPEA. For **4b** DBU or TMG at 50 °C for 4 hours work relatively equally well, with perhaps DBU being slightly better. The final parameter to be examined to boost yield or control the stereochemistry of **3** will be to examine a range of sulfonium salts (**2**).

2.9. Salt study with imines **1a** and **1b** and TMG, DIPEA and NaH and final scale-up reactions

For the temperature-base studies outlined previously, the diethyl allyl salt with the bromide counter anion (**2a**) has been used. This diethyl salt had been established to produce better yields than the cyclic THT salts **2d-f**. Initial studies with the ClO_4^- (**2b**) and BF_4^- (**2c**) showed no changes in yield, but now that the optimal base/temperature conditions have been established, it was decided to do a more extensive study. Thus, TMG, DIPEA and NaH were tested with salts **2b** and **2c** and imines **1a** and **1b** at 50 °C followed by purification (**Table 9**). A time study was not performed so all reactions were at 18 hours.

Table 9: Salt study with sulfonium salts 2a-c and imines 1a-b



Entry	Base	Imine (**1**)	Salt (**2**) (**X**)	% Yield Aziridine (cis:trans)	Pyrroline
1	TMG	**1a**	**2b** (ClO_4^-)	-	30
2	DIPEA	**1a**	**2b** (ClO_4^-)	25 (52:48)	11
3	NaH	**1a**	**2b** (ClO_4^-)	20	12
4	TMG	**1a**	**2c** (BF_4^-)	-	9
5	DIPEA	**1a**	**2c** (BF_4^-)	10 (54:46)	5
6	NaH	**1a**	**2c** (BF_4^-)	12 (56:44)	5
7	TMG	**1b**	**2b** (ClO_4^-)	-	21
8	DIPEA	**1b**	**2b** (ClO_4^-)	21 (60:40)	10
9	NaH	**1b**	**2b** (ClO_4^-)	23 (60:40)	12
10	TMG	**1b**	**2c** (BF_4^-)	-	8
11	DIPEA	**1b**	**2c** (BF_4^-)	16 (50:50)	8
12	NaH	**1b**	**2c** (BF_4^-)	18 (49:51)	9

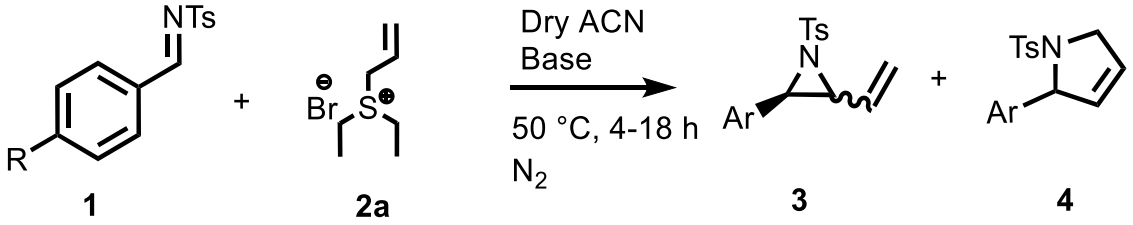
All reactions were carried out at a 0.5 mmol scale in duplicate with 1 mL of dry ACN, with a standard work-up of filtering through an alumina plug for entries 3, 6, 9 and 12, before being combined and purified by column chromatography. See Experimental Methods for further details.

The results from this study show that for salt **2b**, the ClO_4^- counter anion does not produce any observed benefit, as the cis/trans ratio of the aziridine using both the **1a** and **1b** imine starting material is the same as that obtained using the Br^- salt **2a**. Yields for both the aziridine and the pyrroline are about the same if not slightly less. Salt **2c** shows a decrease in yield for the aziridine and pyrroline using both imines, however, the cis/trans ratio when using imine **1b** is about 50:50, (instead of favouring the cis which is the case for the other

salts **2a** and **2b)** and there is no change in the cis/trans ratio when using imine **1a**. This result is interesting as the cis/trans ratio, when forming the aziridine at its' optimised conditions, appears constant at 50:50, when using imine **1a.** However, when using imine **1b** the cis/trans ratio appears easier to manipulate, as it normally favours the cis, but lowering the reaction temperature to 0 °C favours formation of the trans product (**Table 8,** entry 12). Using the BF_4^- counter anion leads to a 50:50 mixture of isomers, albeit with significantly decreased yields. It can be concluded from this study that when using salt **2b**, the reaction proceeds similarly to that using the standard salt **2a**, but with slightly decreased yields for reactions of both imines **1a** and **1b**. Salt **2c** leads to significantly decreased yields but changes the cis/trans of the aziridine when using imine **1b** to 50:50, instead of favouring the cis. Thus, the BF_4^- may be interesting to investigate further when using catalytic sulfides to induce stereoselectivity in a later chapter.

Now that extensive studies have been done with regard to the salts, base, temperature, time, imine, work-up and purification with the aim of maximising yields and controlling which product forms, a final scale up for the best conditions to form the aziridine and pyrroline for imine **1a** and **1b** were undertaken**.** As seen throughout this chapter, the electronics of the imine has a profound effect on the reaction, so **1a**, bearing the electron-withdrawing CF_3 group and **1b**, bearing the electron-donating OMe group were examined again. The results of the scaled-up reaction are shown in **Table 10.**

Table 10: Scaled-up reactions under optimised conditions for imines 1a and 1b



Entry	Base	Imine	Time (h.)	% Yield Aziridine (cis:trans)	Pyrroline
1	TMG	**1a**	4	11 (100:0)	39
2	DIPEA	**1a**	8	38 (52:48)	14
3	DBU	**1b**	4	-	31
4	NaH	**1b**	8	33 (61:39)	11

All reactions were performed at a 2 mmol scale with 4 mL of dry ACN, and a standard work-up of filtering through an alumina plug for entry 4, before purification by column chromatography. See Experimental Methods for further details.

The results correlate with the previous scaled-up reactions. In entry 1, **1a** forms the pyrroline **4a** with TMG at 50 °C for 4 hours at close to 40% yield with the minor aziridine product at 11% and being all cis. In entry 2, the aziridine is the major product at a 52:48 cis/trans ratio and a 14% pyrroline yield, this using DIPEA at 50 °C for 8 hours. Entry 3 uses DBU with the methoxy imine **1b** at 50 °C for 4 hours to produce pyrroline at a 31% yield with no aziridine, and entry 4 forms the aziridine at a 61:39 cis/trans ratio with a yield of 33% using NaH at 50 °C for 8 hours with the pyrroline minor product at an 11% yield.

While the extensive study has optimised yields and exerted control over which product forms, yields for either product do not exceed 40%, and under best conditions the combined yields of the aziridine and pyrroline are around 50% for imine **1a** and less for **1b**. This means that approximately half the reaction mixture is going unaccounted for. While some unidentified by-products have been identified during purification, they are in very small amounts. The literature would suggest that the aziridine forms first, followed by rearrangement to pyrroline. The choice of base is crucial to which is the major product, so it is highly suspected that this plays a role in the rearrangement. There may be competition between the base for the ylide formation and the aziridine rearrangement. It is also possible that the pyrroline **4** forms directly from the reaction of **1** and **2** and does not undergo a rearrangement. If the mechanism of the pyrroline formation and the impact that the base has can be determined, then yields may be boosted, and this will be examined next.

2.10. Aziridine to pyrroline rearrangement study

Up until now, the aziridination reaction has been studied extensively to produce the best conditions for forming the aziridine **3** and/or pyrroline **4**, but it remains unclear why one product forms over another. In the mechanism of the Corey-Chaykovsky reaction, only the aziridine should form. Pyrroline **4** has been reported in small yields in the literature, but never as the major product. Pyrroline **4** is the preferred product when using strong organic bases such as TMG and DBU, while the weaker organic base DIPEA favours aziridine **3** and the strong inorganic base NaH favours **3** also. It thus seems certain that the choice of base, rather than other factors, such as electronics of the substituents, salt choice or temperature, plays a fundamental role in the formation of either product. It was theorised that a competing mechanism may be present after the ylide attacks the imine, as the negatively charged nitrogen in the 1,4-dipolar intermediate could attack the carbon adjacent to the charged sulfur, as expected, and expel the sulfide in pathway **A**, or indeed the nitrogen attaches the vinylic bond at the end of the chain, causing the double bond to shift, expelling the sulfide and then forming the pyrroline in pathway **B** (**Figure 84**). Searches in the literature did not find any studies of the vinylaziridine to pyrroline rearrangement. Dai *et al*. had theorised a rearrangement mediated by nucleophilic ring opening of the aziridine by the sulfonium salt (**2**) anion, but this was not confirmed.[60]

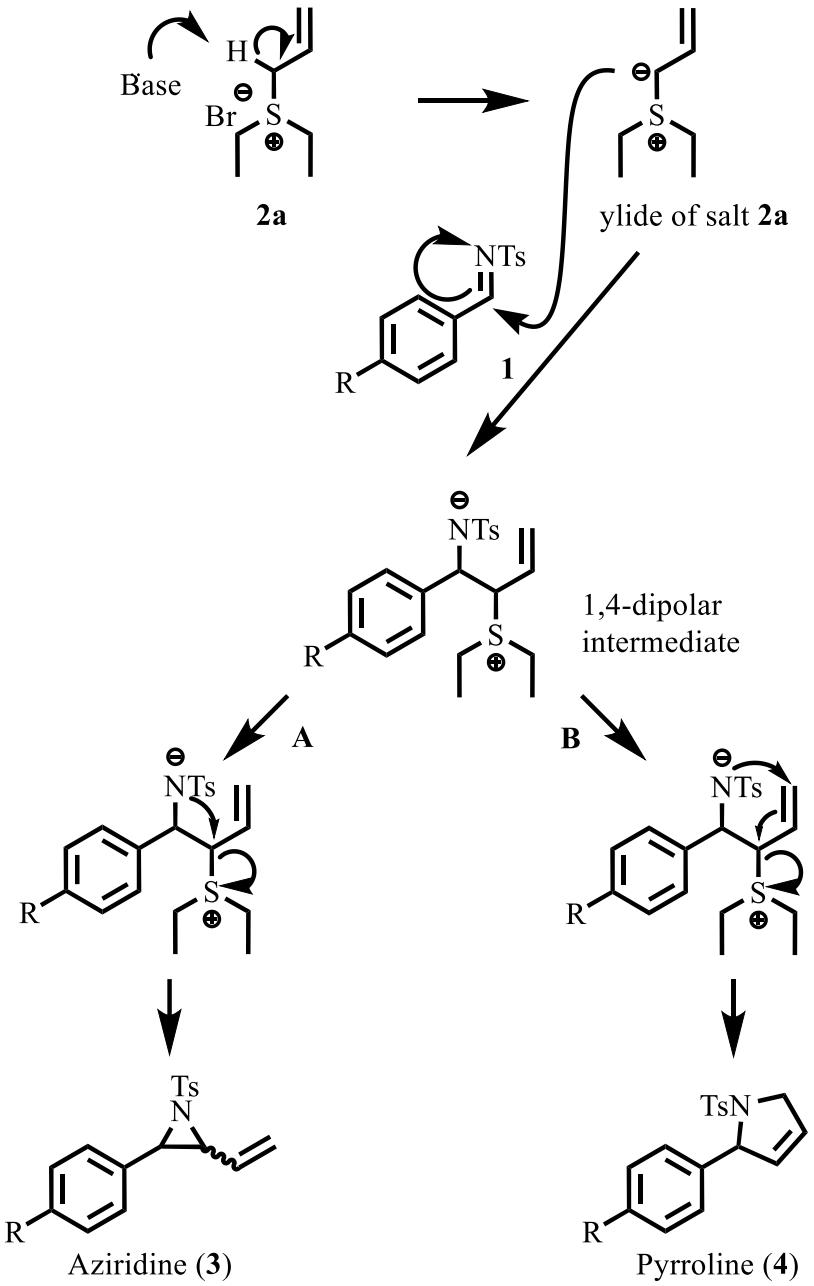


Figure 84: Proposed aryl pyrroline formation; proposed competitive reaction pathways for forming the vinylaziridine or the aryl pyrroline. Pathway A shows attack on the carbon α to the positively charged sulfur, as would be normally expected. Pathway B shows attack on the vinylic bond, followed by a new double bond formation

This mechanism is plausible but it seems unlikely as attack by the negatively charged nitrogen on the carbon next to the sulfur would be favoured electronically, and this theory fails to account for the role played by the base. Also, the evidence from the reaction results would suggest that the aziridine forms first, followed by rearrangement. The best conditions for forming the aziridine always produce the pyrroline as a minor product, but this is not always the case for the best conditions for pyrroline, as often no aziridine is formed. For the pyrroline **4b** formation, which is best with DBU or TMG, no aziridine **3b** has ever been isolated or observed. For the pyrroline **4a** formation, a small amount of aziridine is usually isolated but not always, and the stereochemistry has changed, being all the cis isomer rather than 50:50 cis/trans when using the ideal conditions for **3a** formation . These results could

suggest that when using the stronger bases, the aziridine **3** forms first, followed by rapid transformation to the pyrroline **4**. For the weaker bases, **3** forms, with pyrroline as a minor product. Also, the 100:0 cis/trans aziridine minor product suggests that the trans aziridine may first transform to the cis isomer, before rearranging, and this theory is speculated by Hirner *et al.*[88] as previously discussed in the literature review. The postulated reaction scheme for this transformation is shown in **Figure 85.**

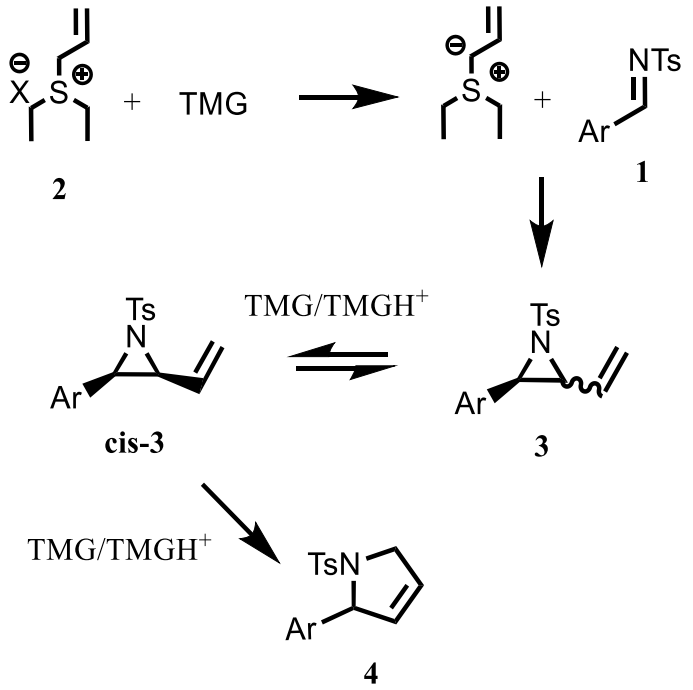


Figure 85: Proposed aryl pyrroline formation; cis/trans aziridine 3 forms, followed by trans-cis conversion and rearrangement to aryl-pyrroline 4

Also evident in this scheme is that a competitive reaction may be taking place between the ylide formation and the aziridine to pyrroline rearrangement where both need the base (TMG shown as an example in Figure). It may also be the case that the conjugate acid, $TMGH^+$ in this example, is responsible for the rearrangement after the base has deprotonated the sulfonium salt.

Three proposed mechanisms for the aziridine (**3**) to pyrroline (**4**) rearrangement are given in **Figure 86.** Pathway **A** involves deprotonation (possibly by the base) followed by ring opening to form a diene, which in turn forms the pyrroline **4** by the nitrogen lone pair attacking the end of the double bond, and the proton on the carbon alpha to the nitrogen is reinstated. Pathway **B** involves the lone pair on the nitrogen attacking the vinylic group followed by reformation leading to the pyrroline **4**. Pathway **C** suggests a nucleophile, which may be the sulfide or the anion of the starting material **2**, attacking a carbon of the aziridine ring, leading to ring opening and a negatively charged nitrogen, which in turn adds to the double bond and pyrroline is formed.

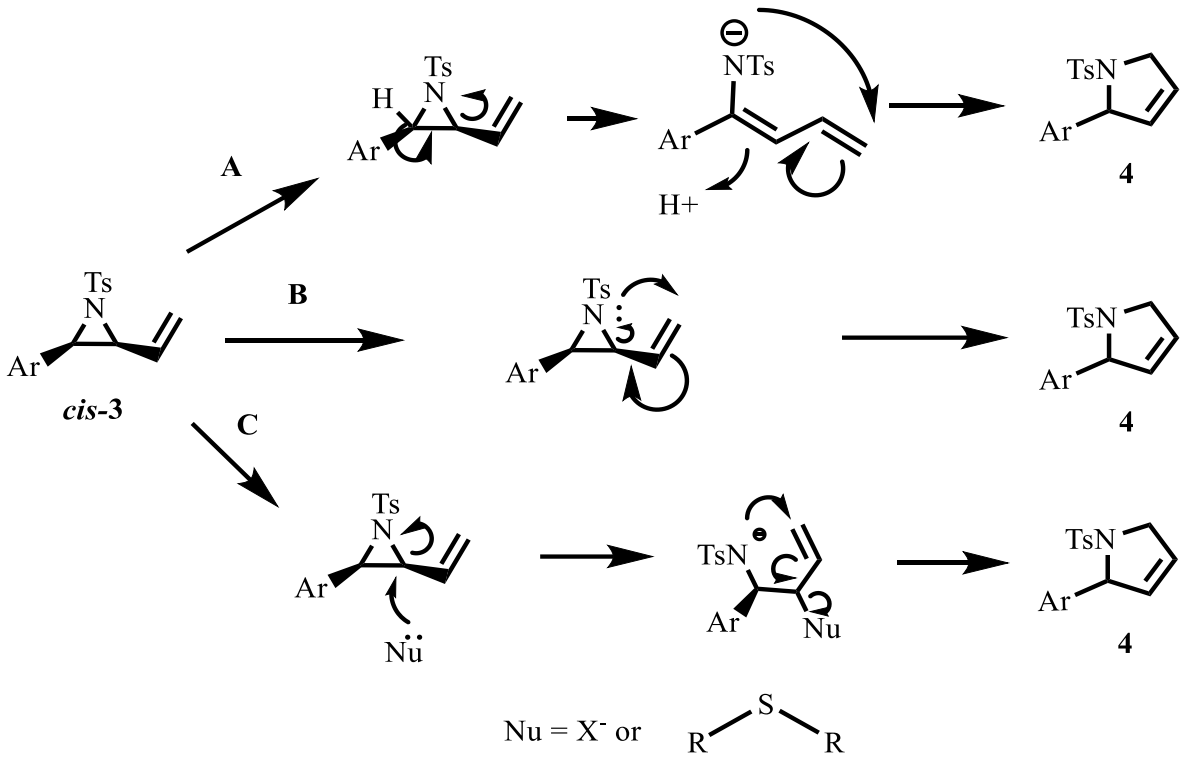
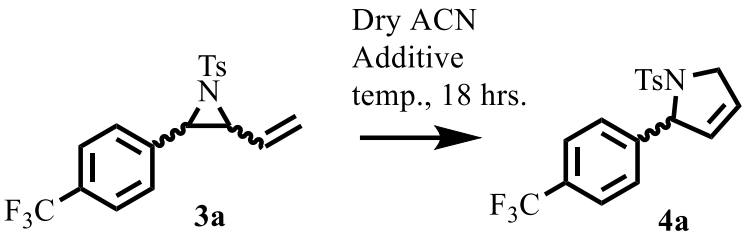


Figure 86: Proposed aryl pyrroline formation; Pathway A shows deprotonation of the vinylaziridine to form a ring-opened diene, leading to 4. Pathway B shows the aziridine nitrogen's nucleophilic attack on the vinylic bond, followed by bond reformation to form 4. Pathway C shows nucleophilic attack on the aziridine, leading to negatively charged ring opened product, which forms 4.

Pathway **C** may account for the role of the base if it is the nucleophile, and perhaps nucleophilic addition is only favourable to the cis-aziridine. Route **C** is analogous to the iodine nucleophilic addition to vinylaziridine followed by pyrroline formation, as previously seen in the literature, so this may be the most likely route to formation of **4**.

A study was performed to investigate the rearrangement of **3** to **4**. A sample of **3a** was stirred under N_2 overnight under various conditions, as outlined in **Table 11.** The conditions investigated were heat, the base (in this case TMG), the bases' conjugate acid (formed by adding a stoichiometric amount of HCl to the TMG), the sulfide (as this may act as a nucleophile when leftover after ylide addition) and bromide anions (which could also act as a nucleophile). After each experiment was complete, the sample was examined by ^{1}H NMR to see if any **4a** had formed. If so, the peak area of one distinctive proton would be compared to that of any **3a** that was leftover.

Table 11: Aziridine (3a) to pyrroline (4a) rearrangement study



Entry	Temp. (°C)	Additive	Pyrroline (**4**):Aziridine (**3**) from peak ratio in ^{1}H NMR
1	rt	-	No evidence of formation of **4a**
2	82	-	No evidence of formation of **4a**
3	50	TMG	No evidence of formation of **4a**
4	50	TMG + HCl	No evidence of formation of **4a**
5	50	Diethyl sulfide	No evidence of formation of **4a**
6	50	**2d**	No evidence of formation of **4a**

All reactions were performed at a 0.1 mmol scale with 1 mL of dry ACN. Crude products were dried by rotary evaporation and ^{1}H NMR spectra obtained. See Experimental Methods for further details.

The purpose of entry 1 was a negative control, as it was simply stirred overnight at room temperature with no additives. Entry 2 has the same conditions as entry 1 but 82 °C was applied, and the crude ^{1}H NMR spectrum showed only **3a**, with no evidence of **4a** formation. Entry 3 was applied with 50 °C heat with an addition of 1.1 eq. TMG. The NMR showed no evidence of **4a**. As it was theorised that the conjugate acid of TMG may play a role in the rearrangement, TMG was mixed with an equal amount of HCl and this mixture was applied to **3a**. Because HCl is an aqueous acid, this experiment added water to the mixture which adds more variables and is inconsistent with the other experiments. ^{1}H NMR analysis of entry 4 showed no evidence of **4a** formation. Entry 5 and 6 included additives that were possible nucleophiles which could open the aziridine ring and lead to the pyrroline forming. Diethyl sulfide in entry 5 was used as this would be leftover after the ylide adds in the reaction, and the lone pair on the sulfur renders it a good nucleophile. However, this experiment showed no evidence of **4a** in the crude ^{1}H NMR. Salt **2d** was used as an additive in entry 6 as source of bromide anions was added in entry 6, and again showed no evidence of **4a** formation. Thus, the conclusion of this preliminary study is that a rearrangement from **3** to **4** is unlikely, and the formation of **4** is most likely to come from the theorised pathway **B** in **Figure 84**.

Since pathway **B** in **Figure 84** is considered the most likely route to form the observed pyrroline products, it was theorised what role the choice of base plays in the selectivity of product **3** and **4**. It was demonstrated in the temperature-base study in **Table 5** and **Table 7** that the choice of base is key to product selectivity. It was theorised that stronger bases favoured formation of pyrroline **4**, but this correlation did not hold up in the studies. Organic bases TMG and DBU favoured pyrroline **4**, while organic base DIPEA favoured

formation of aziridines **3** and the strong base NaH favoured **3** also. It is plausible that the organic bases coordinate to the 1,4-dipolar intermediate in the reaction and the rigid structures of DBU and TMG favour **4** and only allows the formation of pure cis-aziridine **3** as a minor product (as was observed experimentally) and DIPEA, that has three freely rotating groups, favours **3** as the major product with a cis/trans ratio of 50:50 and **4** is a minor product (**Figure 87**). This theory is supported by Bai *et al.* who demonstrated in a study that the charged conjugate acid of DBU hydrogen bonds to a charged transition intermediate and facilitates a crucial ring closing step with stereoselectivity.[143]

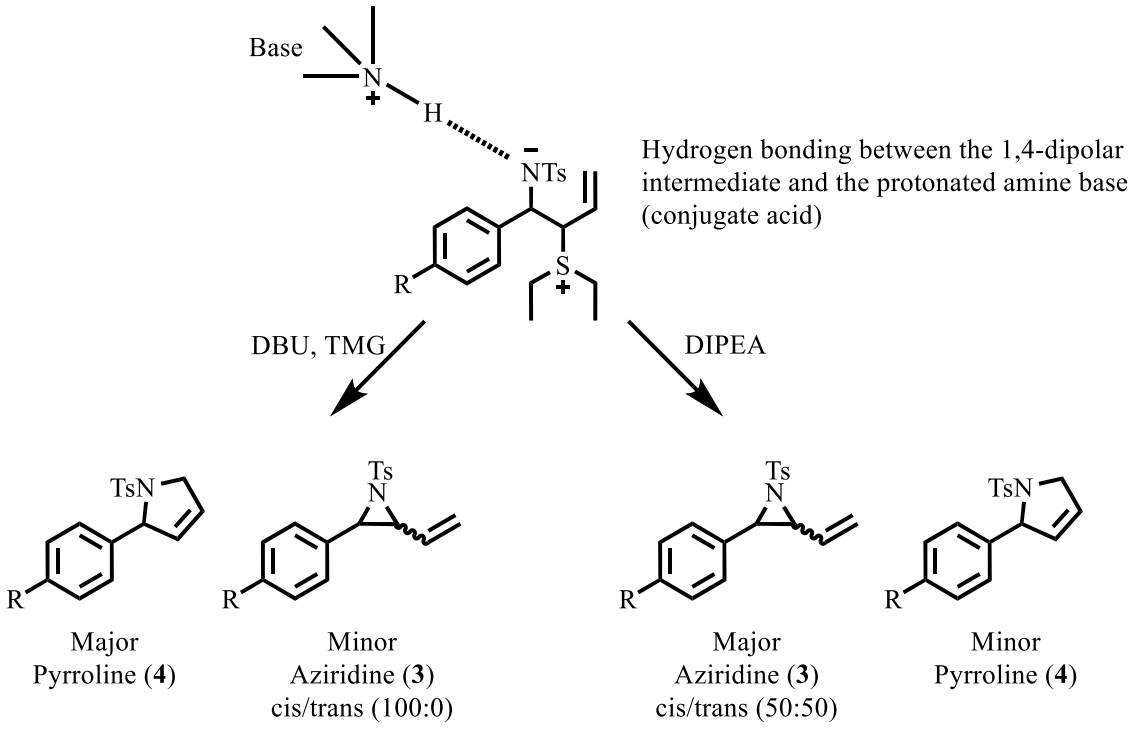


Figure 87: Theorised H-bonding between the charged organic base and the 1,4-dipolar intermediate influencing selectivity of product 3 and 4

Once the nature of the rearrangement is established, it may offer a method of improving yields, as thus far only about half the reaction mixture for aziridine and pyrroline formation is being accounted for, this suggests the base may be used competitively between ylide formation and the rearrangement and thus is used up, but in each case starting material is always fully consumed so this may not be the case.

2.11. Conclusion

A method has been developed for the synthesis of a range of aryl imines (**1**) (yields up to 72%) and sulfonium salts (**2**) (yields up to 99%). The Corey-Chaykovsky aziridination reaction using starting materials **1** and **2** has been intensively studied and a method for selective synthesis of vinylaziridine **3** and/or aryl pyrroline **4** has been developed. The optimal conditions for selectively synthesising **3** or **4** are as follows;

- **3a:** imine **1a**, salt **2a**, base DIPEA, 50 °C, 8 hr. (**3a** cis:trans 50:50, **4a** minor product)
- **3b:** imine **1b**, salt **2a**, base NaH, 50 °C, 8 hr. (**3b** cis:trans 50:50, **4b** minor product)
- **4a:** imine **1a**, salt **2a**, base TMG, 50 °C, 4 hr. (**3a** as minor product, cis:trans 100:0)
- **4b:** imine **1b**, salt **2a**, base DBU, 50 °C, 4 hr. (**3b** as minor product, cis:trans 100:0)

It has been shown through experimental observations that the choice of base used in the reaction plays a crucial role for product selectivity. A study has shown that rearrangement from **3** to **4** is unlikely. It has been suggested, by evidence in the literature, that the conjugate acid of the organic base can stabilise the 1,4-dipolar intermediate through hydrogen bonding, and effects the ring closure and thus the product formed. This, however, requires further study.

There was tentative evidence that changing the anion on **2** from Br^- to BF_4^- affects the cis/trans ratio of **3** formed, as does lowering the temperature to 0 °C.

3a is a new compound and was fully characterised by NMR and HRMS.

Chapter 3 Synthetic pathway development for next-generation sulfur catalysts

3.1. Introduction

Until now, relatively simple sulfides (THT and diethyl sulfides, **2**) have been used in order to optimise the Corey-Chaykovsky aziridination reaction. These sulfides were successful in developing the synthesis, but do not induce stereoselectivity in the aziridine or enantioselectivity of the pyrroline and they are difficult to reuse due to their low boiling points and the fact that they often get retained on the silica during column chromatography. It is thus aimed to synthesise more complex catalytic sulfides that include chiral centres for asymmetric synthesis in the Corey-Chaykovsky reaction, as well as having an electronic 'tuning' ability, similar to that achieved with phosphonium ylides in the CWR,[2] discussed in Chapter 1.

After the establishment of baseline conditions for the Corey-Chaykovsky aziridination, the next focus of the research was the synthesis of sulfide catalysts, which could be used in the aziridination reaction in catalytic amount, and reused afterwards. The catalysts themselves should be able to facilitate different side groups that can withdraw or donate electron density on the sulfur atom, allowing 'ylide tuning', and contain a chiral centre to induce asymmetry to the aziridination process. The chosen core structure is a 2, 3-dihydrobenzothiophene (DHBT) derivative (**6** in **Figure 88**) which was a desirable choice as the phenyl ring would allow electron-withdrawing/donating substituents to be added close to the sulfur centre (**7** in **Figure 88)**. While examples of DHBT sulfonium salts were not found in the literature Dai *et al.*[60] demonstrated that sulfides with aromatic groups alpha to the sulfur could form sulfonium salts (albeit with lower yields than alkyl groups), and there are more recent examples of sulfonium salt synthesis with aromatic sulfides.[144]

Also, an additional step on the synthetic pathway would allow substituents to be added on the 5-membered aliphatic ring, alpha to the sulfide, providing a chiral centre for the catalyst (**8** in **Figure 88**). The core structure also includes a hydroxyl group on the phenyl ring which could be used for catalyst loading for future flow chemistry (note that in **Figure 88** this hydroxy group is protected with TBDMS which is necessary during the proposed synthetic pathway, but can be removed easily with TBAF when needed). The proposed synthesis is based on a method from the literature,[145] with additional steps added for the inclusion of side groups. It is aimed to optimise the synthetic pathway, followed by method development for the side group additions. It is intended to synthesise a family of compounds, with the basic core structure being the first, followed by several with different inductive and steric effects. Once the first sulfide **6** is synthesised, a study of formation of the sulfonium salt derivative is proposed, using the same method developed for the synthesis of salts **2** in Chapter 2. It is then aimed to evaluate these sulfides (**6, 7** and **8**) in the Corey-Chaykovsky aziridination.

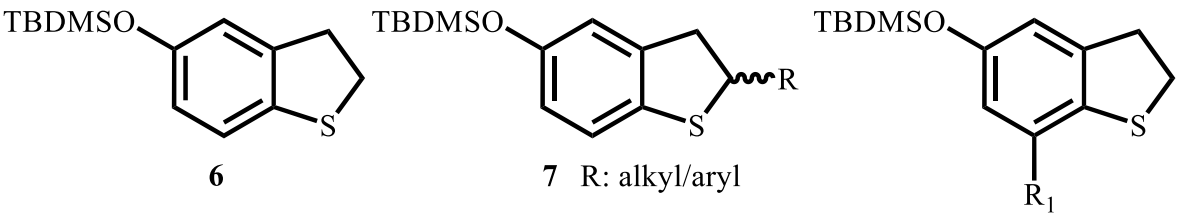


Figure 88: Proposed sulfide (6) which will be the core structure. 7 is a proposed set of derivatives with alkyl/aryl substituents alpha to the sulfide. 8 is a proposed set of derivatives with EWG/EDGs. Note the hydroxy group on the phenyl ring, whose purpose is to facilitate future flow chemistry, is protected with TBDMS

A synthetic pathway of the proposed sulfide **6** was reported by Malmstrom *et al*. using a phenolic ester (**9, Figure 89**).[145] This sulfide with a fused phenyl ring offers great opportunity as a potential precatalyst for the catalytic Corey-Chaykovsky reaction. The allylic group can be added to it to make the sulfonium salt, and deprotonation to the sulfur ylide for the aziridination reaction. The hydroxyl group on the phenyl ring allows immobilisation to a polymer support (capillary monoPLOTs or submicron beads under slug flow conditions) for future flow chemistry. The structure and synthesis of the sulfide leaves room to add functional groups that can 'tune' the ylide by withdrawing or donating electron density on the sulfur (**8** in **Figure 88**), adjusting the *p*K_a of the neighbouring proton, and functional groups that add bulk to induce stereoselectivity (**7** in **Figure 88**).

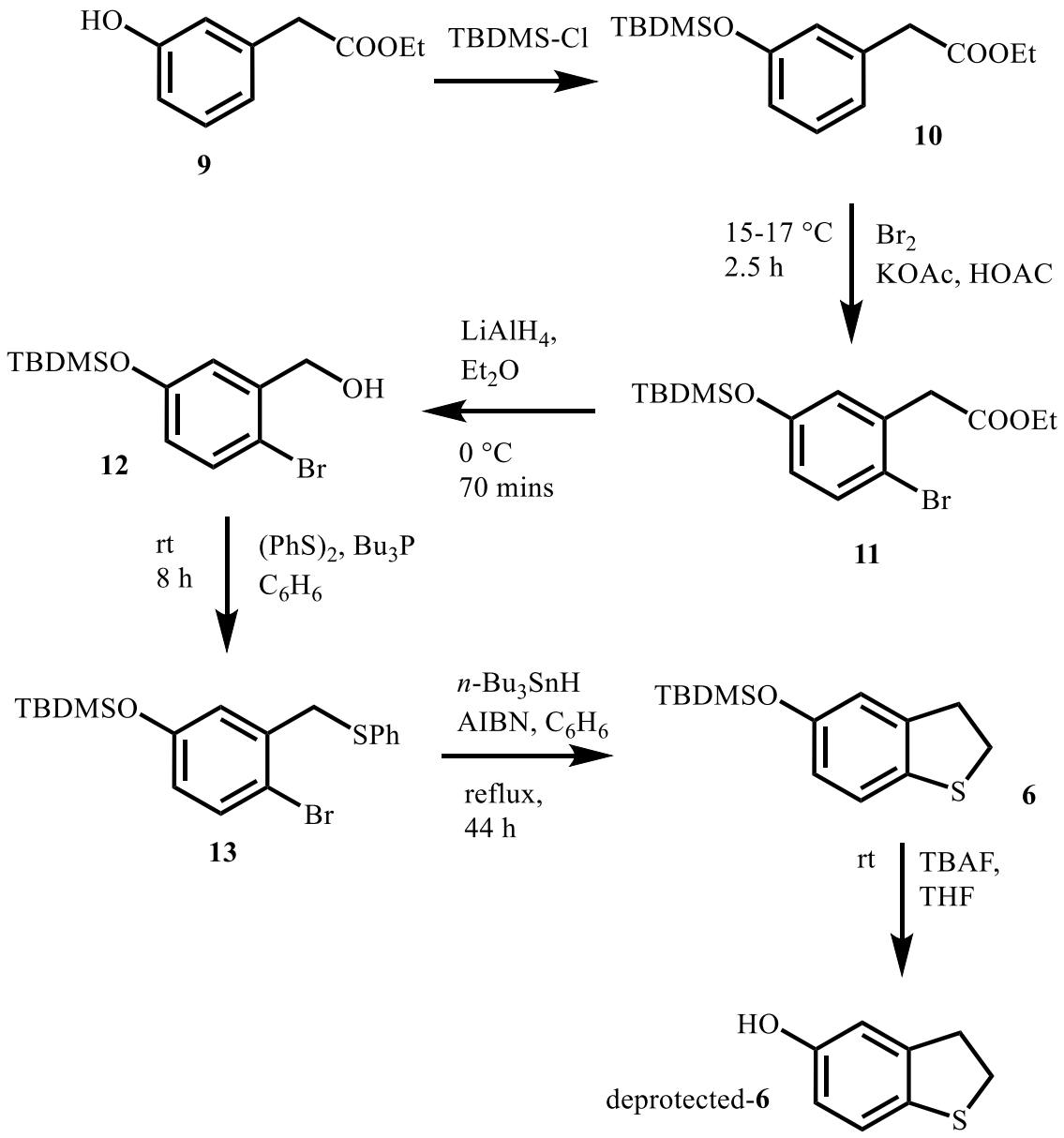


Figure 89: Synthesis of the proposed sulfide (6) as reported by Malmstrom *et al.* This sulfide itself can be used to form an allylic sulfur ylide, and it offers plenty of opportunity for further functionisation

A proposed synthetic route for preparation of new alkyl/aryl functionalised sulfides **7** (alpha to the sulfur) is shown in **Figure 90**. During the reduction of the ester group on **11**, the use of diisobutylaluminium hydride (DIBAL) can reduce to an aldehyde **14** rather than the alcohol **12**. Nucleophilic addition can now take place here before moving on to the next step of the synthesis. The proposed synthesis in **Figure 90** show an R group being added to **14** via a Grignard reaction. The resulting alcohol (**15**), which has a newly formed chiral center, can then proceed through the rest of the synthetic pathway in **Figure 89** before ring closure to form **7**. The resulting isomers of the sulfides can thus be separated thereafter.

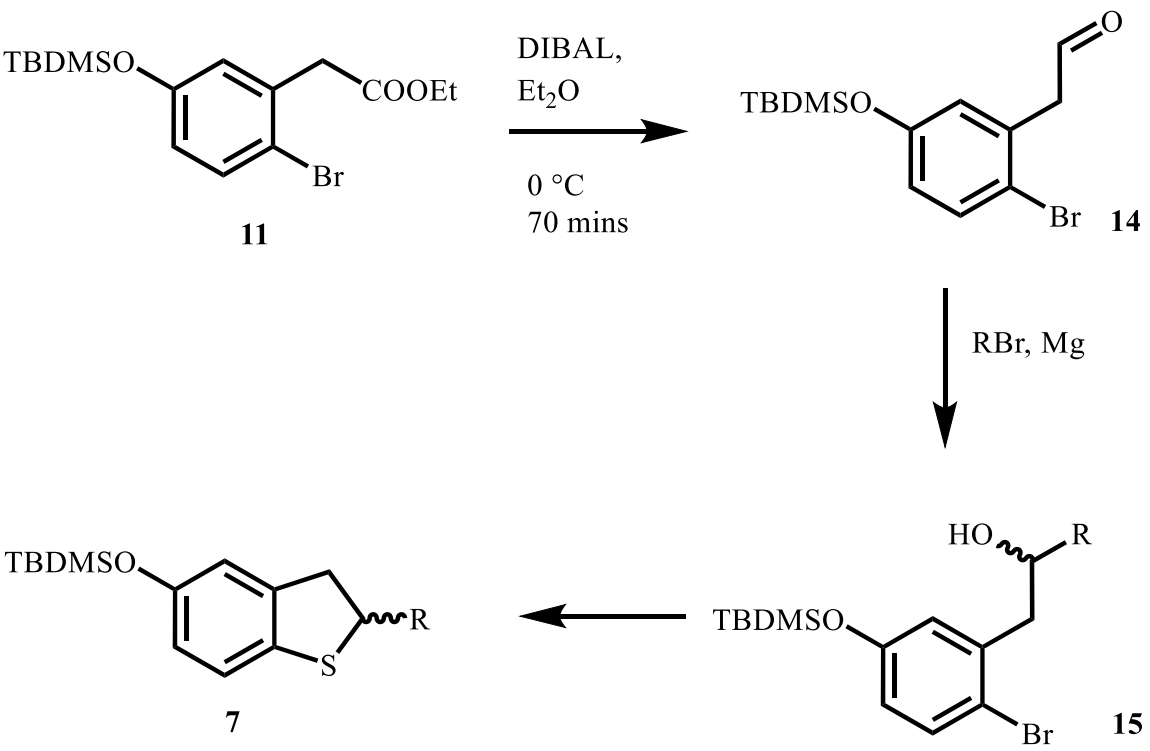


Figure 90: Proposed synthesis of sulfide derivatives 7 by using a DIBAL-H reduction to form 14, followed by a Grignard reaction to form 15 before continuation of the synthetic pathway to introduce a chiral centre alpha to the sulfur

As well as adding groups alpha to the sulfur (DHBT derivatives **7**), functionalisation can be added to the phenyl ring (DHBT derivatives **8**). Attempting to add groups to the phenyl ring during the synthetic pathway would interfere with the synthesis, therefore it is aimed to add groups directly to the final sulfide product **6**. One convenient method to achieve this is to directly nitrate sulfide **6**. Not only is the nitro group a strong electron-withdrawing group, the nitro group can also be converted to other functionalities via reduction and diazotisation as is outlined in **Figure 91.**

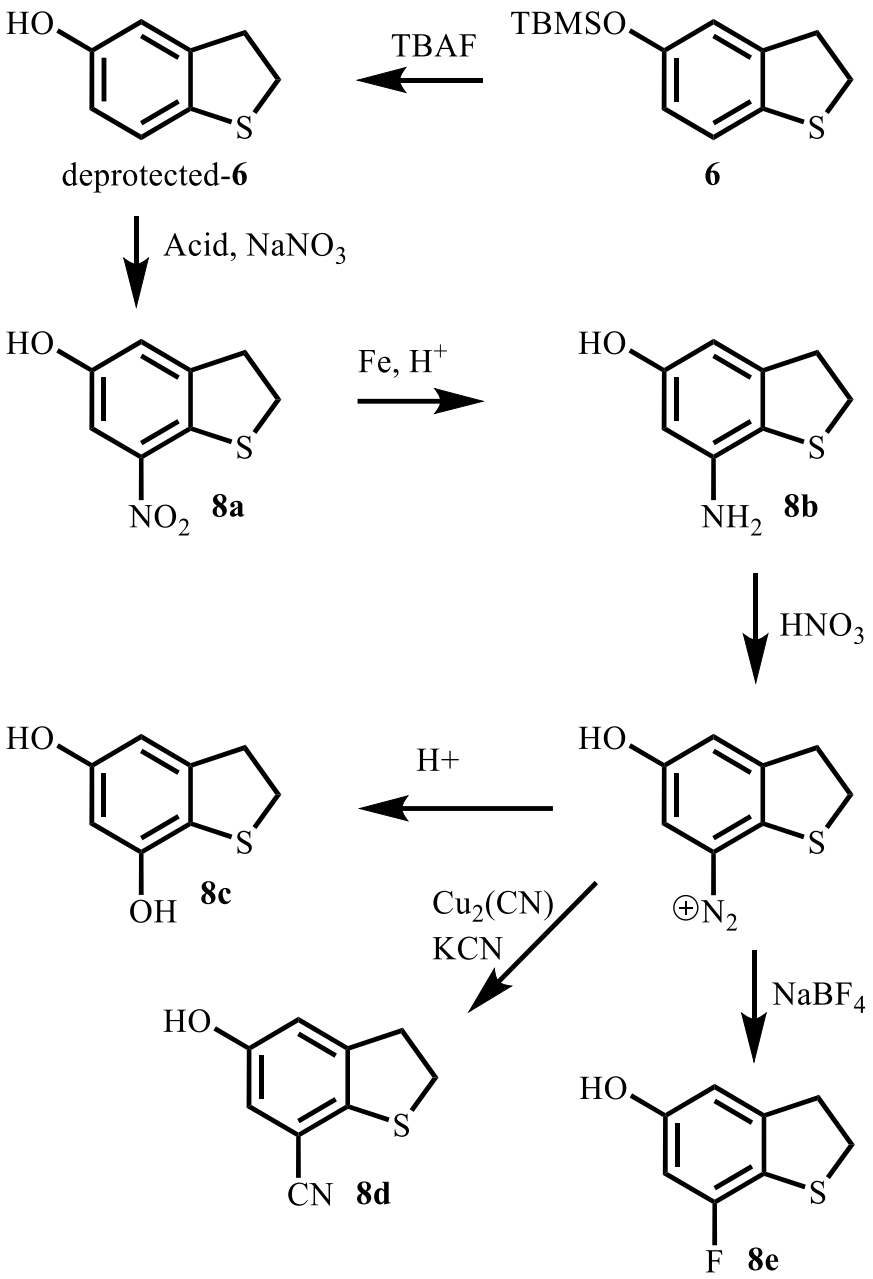


Figure 91: Proposed synthesis of sulfide derivatives 7 by direct nitration of sulfide 6, followed by reduction of nitro group to an amine. This amine group can now undergo a diazonium salt reaction to form various functional groups.

As stated in the literature review, flow chemistry is becoming increasing popular for bulk asymmetric synthesis due to the many advantages it holds over batch production The chosen sulfide (**6**) and its derivatives (**7** and **8**) possess a phenol group on the phenyl ring, which could facilitate immobilisation into a flow reactor in the future, by allowing loading on the catalyst on a suitable column, such as a capillary monoPLOT (**Figure 92**). monoPLOT colums have a tubular instead of packed stationary phase, which allows smoother flow with less risk of high back pressure and blockages and the stationary phase is a monolithic porous polymer layer, which allows the solvent mixture to easily flow in and out and cover a large surface area.[128] For flow chemistry, it is proposed to load the

sulfide catalysts to a polymer stationary phase of a monoPLOT column, and the reagents through to synthesise the aziridine (**3**) or aryl pyrroline (**4**) product with stereoselectivity.

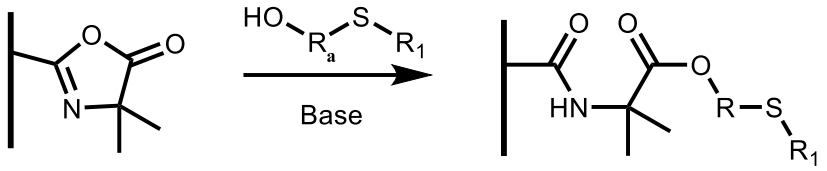
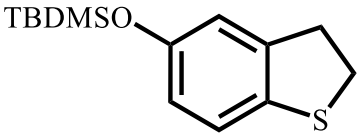


Figure 92: Proposed loading of sulfur catalyst to a monoPLOT column. Note the importance of the hydroxyl group on the sulfide catalyst.

3.2. First Target compound (**6**) synthetic pathway development and optimisation

The first target compound of this chapter is the DHBT derivative **6**. The synthetic pathway, based on a method from the literature, was optimised. It was then investigated how this compound could be used in the Corey-Chaykovsky aziridination reaction.



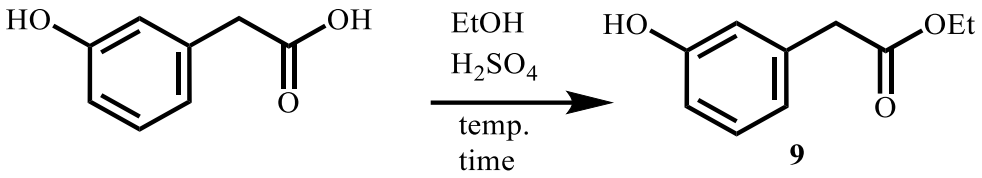
9

Figure 93: First target compound

3.2.1. Synthesis of ethyl 2-(3-hydroxy)phenylacetate (**9**)

The first step of the synthesis was the esterification of 3-hydroxyphenylacetic acid to ethyl 2-(3-hydroxy)phenylacetate (**9**). Such esterification of carboxylic acids is a very well established reaction in synthetic chemistry and involves reflux of the starting material in alcohol (in this case ethanol to provide the desired ethyl group) with a catalytic amount of H_2SO_4.[146] A brief optimisation study was performed as seen in **Table 12** below. **9** is a new compound as it could not be found in the literature, and was characterised by ^{1}H, ^{13}C, COSY, DEPT and HSQC NMR and HRMS. The ^{1}H NMR of the product is given in **Figure 94** below, with the remaining spectra given in the Appendix.

Table 12: Optimisation study of esterification of 3-hydroxyphenylacetic acid to form ester 9



9

Entry	Temperature (°C)	Time (h)	% Yield
1	78	18	91
2	rt	18	78
3	78	4	81
4	rt	4	80

Reactions were performed at various mmol scales with a standard work up of rotary evaporation to remove most ethanol, followed by the addition of water and ethyl acetate, extraction with ethyl acetate and washing with water and brine. See Experimental Methods for further details.

The best yield was recorded when refluxed overnight (entry 1, **Table 12**) so this was chosen as the optimal method. The reaction required a brief work-up to remove remaining acid and water but no further purification was required.

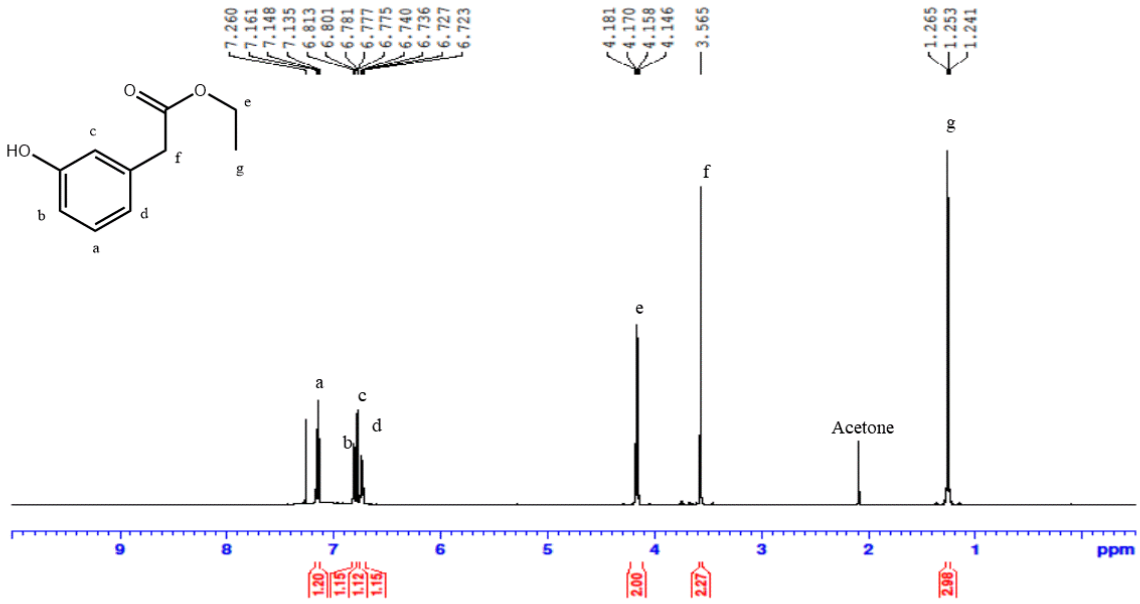


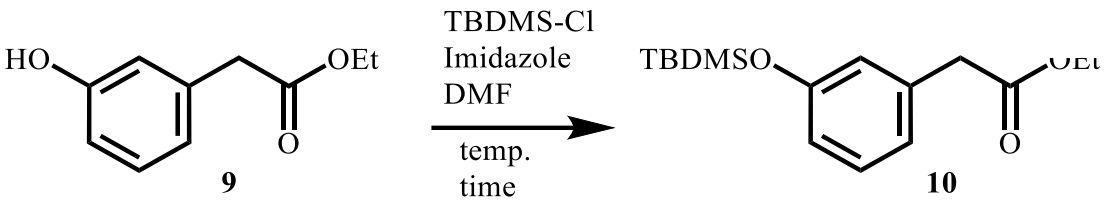
Figure 94: ^{1}H NMR spectrum of ester 9

3.2.2. Synthesis of ethyl 3-(tert-butyldimethylsilyloxy)phenyl acetate (**10**)

The next step of the synthesis is the protection of the hydroxyl group on the phenyl ring with a *tert*-butyldimethylsilane (TBDMS) group. TBDMS is an appropriate protecting

group as it can readily add to alcohols and will not interfere with later synthetic steps, and the group can be conveniently removed when needed with a fluoride ion source, such as tetra-n-butylammonium fluoride (TBAF). The synthetic method chosen is based on methods found in the literature.[147] Dimethylformamide (DMF) is chosen as an appropriate reaction solvent as it will dissolve the water soluble imidazole and the starting material, while not interfering with the reaction due to being polar aprotic. An optimisation study was carried out as seen in **Table 13** below with focus on the amount of excess of TBDMS-Cl and imidazole needed, as well as temperature and time (**Table 13**). A reference spectrum for **10** could not be found in the literature and therefore the product is new and characterised by ^{1}H, ^{13}C, COSY, DEPT and HSQC NMR and HRMS. The ^{1}H NMR spectrum of **10** is given in **Figure 95** below, and the remaining spectra are given in the Appendix.

Table 13: Optimisation of synthesis of ethyl 3-(tert-butyldimethylsilyloxy)phenyl acetate 10



9 **10**

Entry	TBDMS-Cl eq.	Imidazole eq.	Temperature (°C)	Time (h)	Yield (%)
1	1.3	3.0	rt	4	44
2	1.3	3.0	rt	18	51
3	1.3	3.0	50	18	49
4	1.3	3.0	80	18	66
5	1.1	3.0	80	18	68
6	1.1	3.0	80	4	49
7	1.1	2.0	80	18	52

Reactions were performed at various mmol scale with a standard work-up of quenching in ice-cold water, extraction with diethyl ether and washing with water and brine. See Experimental Methods for further details.

The first results of the optimisation study showed that leaving the reaction overnight produced slightly better yields (entry 2), and a significant increase in yield was seen when the temperature was increased from ambient to 80 °C (entry 4). Interestingly, yields were very similar when using 1.3 or 1.1 mole equivalence of TBDMS-Cl (entry 4 and 5), whereas using 2.0 instead of 3.0 equivalence of imidazole lead to a decrease in yield (entry 7). It was therefore concluded from this study that optimal conditions were 80 °C for 18 hours, with 1.1 eq. of TBDMS-Cl and 3.0 eq. of imidazole. Purification by column chromatography using a mobile phase of 100% hexane gave good separation of the product.

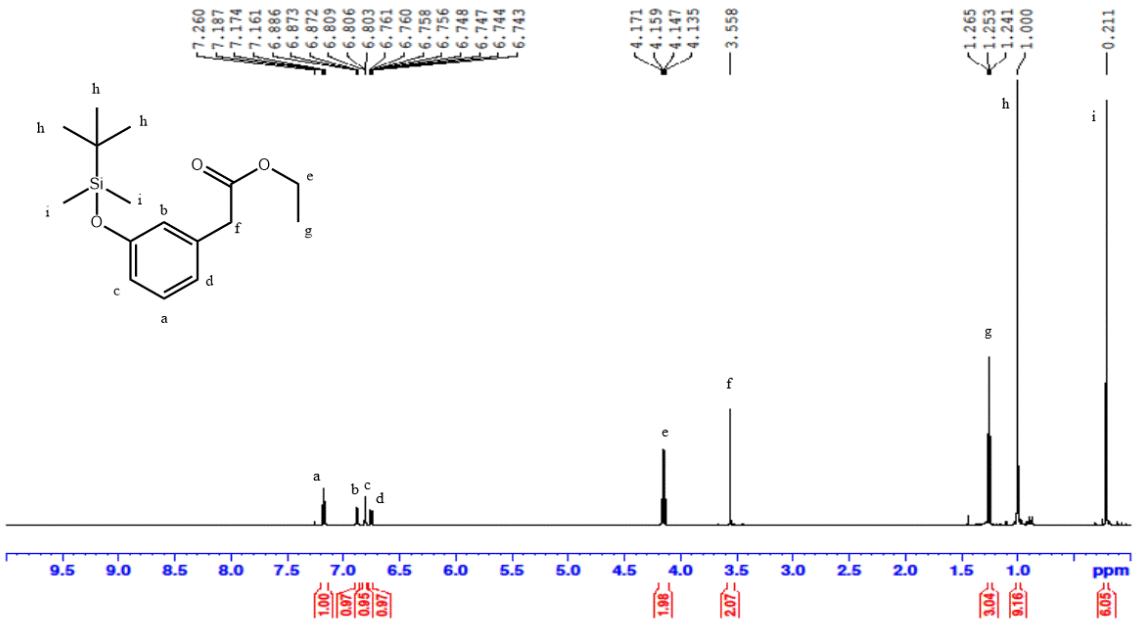
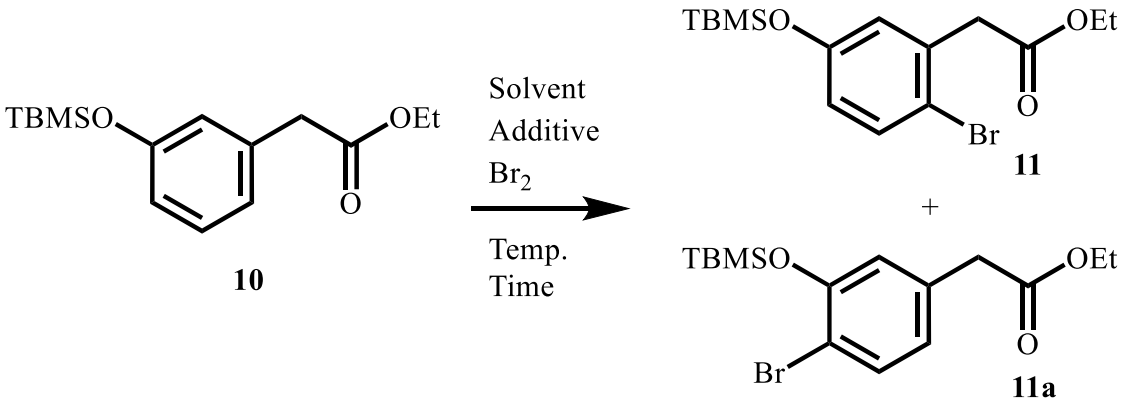


Figure 95: ^{1}H NMR spectrum of 10

3.2.3. Synthesis of ethyl 6-bromo-3-(tert-butyldimethylsilyloxy)phenyl acetate (**11**)

The next step of the synthesis was the bromination of the phenyl ring which will facilitate the sulfide ring closing step later in the pathway. The position the bromine adds to on the phenyl ring is determined by the nature of the ring's two substituents, which are both electron-donating in nature, and therefore will direct the bromine into the *ortho*- and *para*-positions. As the two current substituents are *meta* to one another, the bromine will either add *ortho* to the ethyl acetate substituents or *ortho* to the TBDMS protected oxygen, so it is expected to get a mix of both possible products, which may lead to a difficult purification. Most methods for bromination of phenyl rings in the literature use Fe(III)Br_3 produced in situ with a suitable solvent such as DCM. This method uses pure bromine (Br_2) with acetic acid as a suitable solvent that can dissolve both the starting material and bromine, and uses a suitable amount of sodium acetate as a buffer. An optimisation study was conducted, and results are given in **Table 14** below. Confirmation of the product **11** was based on ^{1}H NMR analysis and comparison with the literature.[145] The ^{1}H NMR spectrum of the confirmed product **11** is given in **Figure 96** below.

Table 14: Synthesis of ethyl 6-bromo-3-(tert-butyldimethylsilyloxy)phenyl acetate 11



Entry	Solvent	Br_2 eq.	Temp. (°C)	Time (h)	Yield	
					11	**11a**
1	AcOH	1.0	rt	2.5	57	0
2	AcOH	2.0	rt	2.5	41	0
3	AcOH	1.0	60	2.5	44	0
4	DCM	1.0	rt	2.5	0	0
5	AcOH	1.0	rt	16	0	0

Reactions were performed at various mmol scale with 1.0 eq. NaOAc as an additive. The standard work-up involved three extractions with Et_2O, neutralising the combined organic layers with saturated $NaHCO_3$ solution, washing with water and brine and drying over $MgSO_4$. See Experimental Methods for further details.

Interestingly, in this study the results show for each of the conditions examined in **Table 14** that the undesired side product **11a** did not form, and that the only product present was the desired **11**. This shows that the reaction is regioselective. Increasing the equivalence of bromine (entry 2) did not increase the yield, either did increasing the temperature (entry 3). Using DCM, instead of AcOH, as a solvent led to the formation of no product, and no product also formed when the reaction was left stir overnight (entry 5). The best yields achieved were just over 50%, and no purification was necessary but the work-up for this reaction was problematic. The acetic acid often formed an emulsion with the diethyl ether in the work-up. Filtering through celite sometimes led to this being resolved. When neutralising the organic layer with saturated sodium bicarbonate solution to remove remaining AcOH, a very large number of washes were typically needed and often led to intense effervescence due to the released CO_2 gas. Also, the TBDMS protecting group was sometimes removed if the work-up went on too long (such as leaving the emulsified reaction mixture overnight to separate out). This was probably due to the acidic conditions that can remove TBDMS group if left for long enough. The quality of the bromine reagent is also critically important, as the product did not form on several occasions, which after investigation it was discovered the bromine solution being used was degraded. Keeping the bromine solution refrigerated when being stored was found to be critically important.

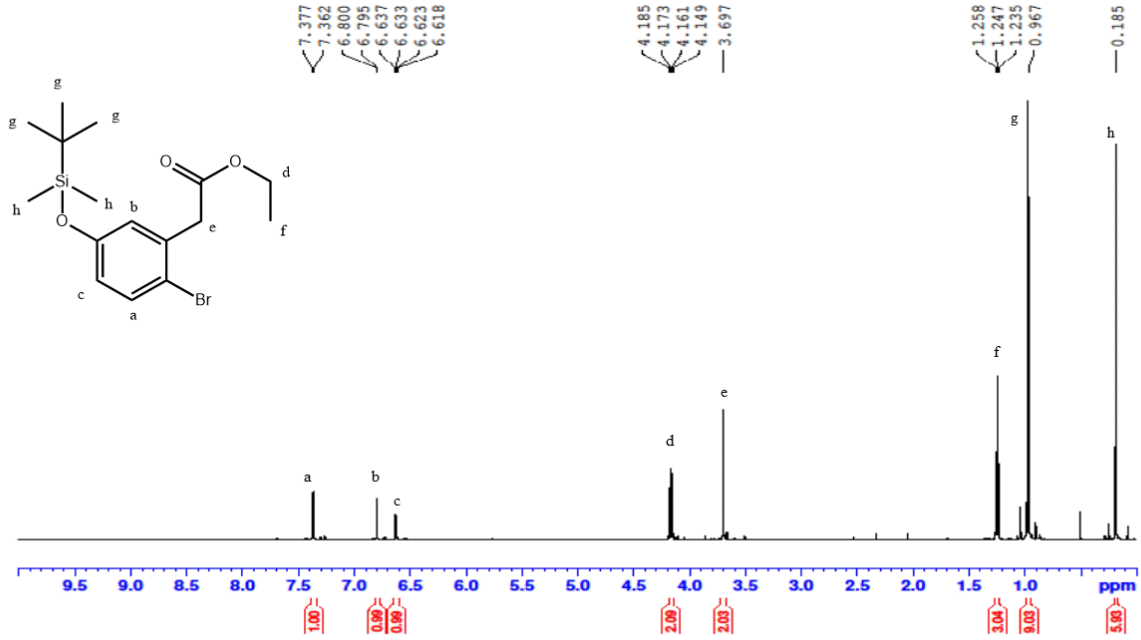


Figure 96: ^{1}H NMR spectrum of 11

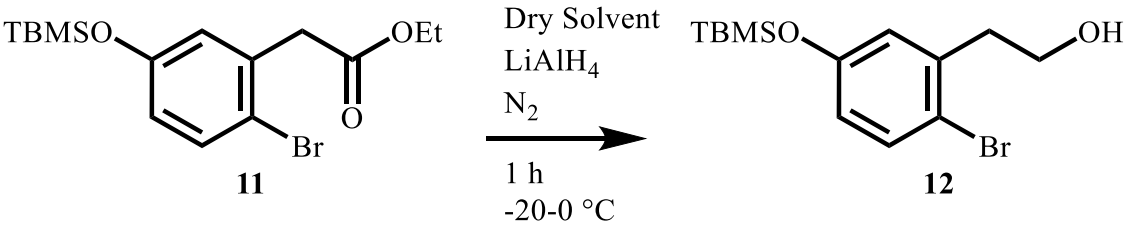
3.2.4. Synthesis of 4-bromo-3-(2-hydroxyethyl)phenyl tert-butyldimethylsilyl ether (**12**)

The next step of the synthetic pathway was the reduction of the ester group to an alcohol. Two methods were attempted using lithium aluminium hydride (method 1) and sodium borohydride (method 2).

3.2.4.1. Method 1: $LiAlH_4$ as reducing agent

Lithium aluminium hydride is a very commonly used reagent for the reduction of esters to alcohols, while sodium borohydride is used for reducing aldehydes and ketones to alcohols. An optimisation study was performed results shown in **Table 15** using $LiAlH_4$ (2.4 M in THF) and powder form. Formation of **12** was confirmed by ^{1}H NMR analysis and comparison with the same compound from the literature.[145] The ^{1}H NMR spectrum of the confirmed product is given in **Figure 97** below.

Table 15: Synthesis of 4-bromo-3-(2-hydroxyethyl)phenyl *tert*-butyldimethylsilyl ether 12 using $LiAlH_4$ reduction



Entry	Dry Solvent	$LiAlH_4$ eq.	$LiAlH_4$ formulation	% Yield
1	THF	1.1	Powdered	82
2	THF	1.5	Powdered	80
3	Et_2O	1.1	Powdered	58
4	THF	1.1	2.4 M in dry THF	79

All reactions were performed at various mmol scale under N_2 with flame dried glassware with an ice/water/NaCl bath and a standard work-up of neutralisation with 1 M HCl, extraction with EtOAc and wash with water and brine. See Experimental Methods for further details.

The results of the study show excellent yields when using dry THF as a solvent, but are reduced significantly when using dry Et_2O (entry 3). No significant increase in yields was seen when increasing the equivalence of $LiAlH_4$ (entry 2) and the yield was very similar when using 2.4 M $LiAlH_4$ in dry THF (entry 4). Entry 4 was thus seen as the optimal conditions as it produced high yields and was easier and safer. No further purification was necessary for this reaction.

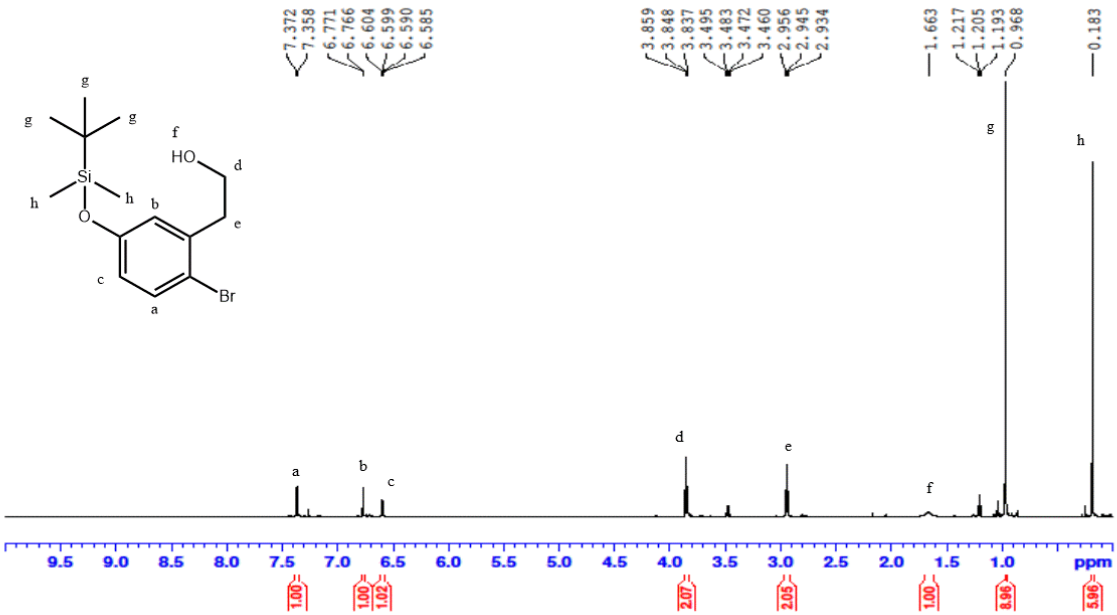
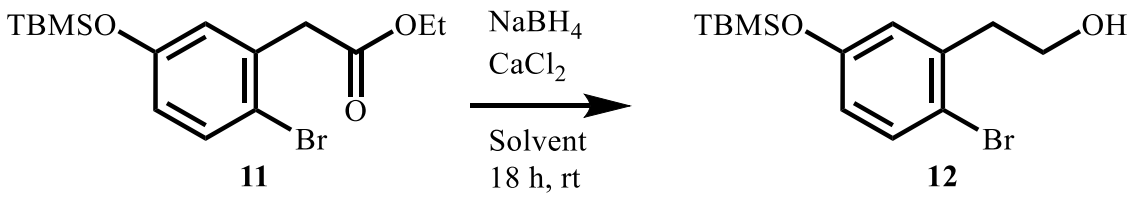


Figure 97: ^{1}H NMR spectrum of 12

3.2.4.2. Method 2: $NaBH_4$ as reducing agent

$NaBH_4$ was also investigated since it is cheaper, safer and easier to use than $LiAlH_4$. The method used has $NaBH_4$ in larger excess than usual, and uses a combination of THF and EtOH to dissolve as much of the reducing reagent as possible. $CaCl_2$ is used as an additive to absorb the water given off in the reaction and ensure it doesn't interfere with the action of $NaBH_4$. The results of the study are given in **Table 16** below.

Table 16: Synthesis of 4-bromo-3-(2-hydroxyethyl)phenyl *tert*-butyldimethylsilyl ether 12 using $NaBH_4$ reduction



11 **12**

Entry	Solvent	$NaBH_4$ eq.	Yield
1	THF+EtOH	2.5	24
2	THF+EtOH	3.5	39
3	THF	3.5	0

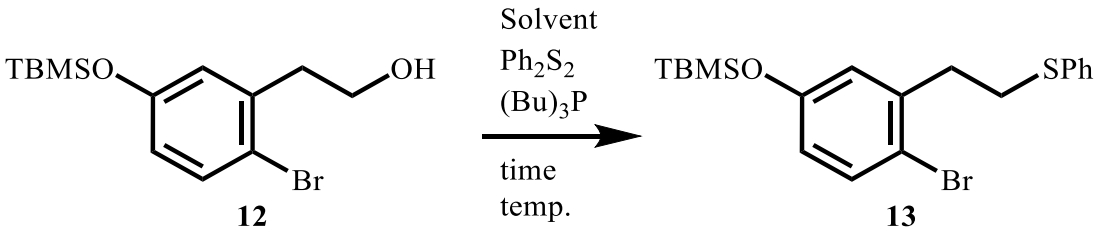
All reactions were performed at 1 mmol scale with a standard work-up of neutralisation with 1 M HCl, extraction with EtOAc and wash with water and brine. See Experimental Methods for further details

The results of the study showed that full reduction of the ester group is possible with $NaBH_4$, although at greatly reduced yields. In entry 3 the reaction was tried with just THF and no product was formed, highlighting the importance of the EtOH for this reaction to move towards completion. Yield of the product was significantly higher with a greater equivalence of $NaBH_4$ (entry 2) but the yields were still a great deal lower than $LiAlH_4$.

3.2.5. Synthesis of 4-bromo-3-[2-(phenylthio)ethyl]phenyl tert-butyldimethylsilyl ether (**13**)

The next step in the synthetic pathway is the substitution of the hydroxy group with a phenyl sulfide (SPh). This phenyl sulfide will facilitate the ring closing in the final step, when a radical reaction with the bromine will form a 5 membered ring with elimination of the bromine and phenyl group. Nucleophilic substitution of a hydroxy group can be a difficult reaction but variously reported methods are in the literature. This method uses tributylphosphine to facilitate the hydroxy group's replacement with phenyl sulfide. The reaction must proceed under inert conditions due to tributylphosphine's sensitivity to oxygen. An optimisation study was carried out as seen in **Table 17**. Product formation of **13** was confirmed by ^{1}H NMR and comparison with the literature.[145] The ^{1}H NMR spectrum of the confirmed product is given in **Figure 98**.

Table 17: Synthesis of 4-bromo-3-[2-(phenylthio)ethyl]phenyl *tert*-butyldimethylsilyl ether (13)



Entry	Dry Solvent	$(Bu)_3P$ eq.	Ph_2S_2	Time (h)	Temp. (°C)	% Yield
1	Benzene	1.1	1.1	8	rt	31
2	Toluene	1.1	1.1	8	rt	38
3	THF	1.1	1.1	8	rt	37
4	THF	1.5	1.5	8	rt	0
5	THF	1.1	1.1	18	rt	42
6	THF	1.1	1.1	18	66	32

Reactions were performed at various mmol scale under inert conditions with a nitrogen atmosphere with flame dried glassware. Standard work-up involved quenching the reaction mixture with saturated $NaHCO_3$ solution, followed by washing with saturated $NaHCO_3$ solution, water and brine followed by drying over $MgSO_4$ and rotary evaporation. See Experimental Methods for further details.

In entry 1 of **Table 17** dry benzene was used as a solvent in accordance with the literature, however it would be highly preferable if an alternative solvent can be used due to benzene's carcinogenicity and difficulty in purchasing. Dry toluene was used in entry 2, and THF in entry 3. Both of these solvents produced similar yields. THF is preferable as it is easier to remove in the work-up due to its far lower boiling point. Increasing the equivalence of both reagents led to decreased yields (entry 4) with impurities present in the ^1H NMR. A slight increase in yield was observed when reaction time was increased to 18 hours (overnight) as seen in entry 5, but yields decreased when increasing temperature to THF reflux (66 ° C) in entry 6. It was thus concluded the reaction conditions in entry 5 were optimal. In each case, column chromatography was used for purification.

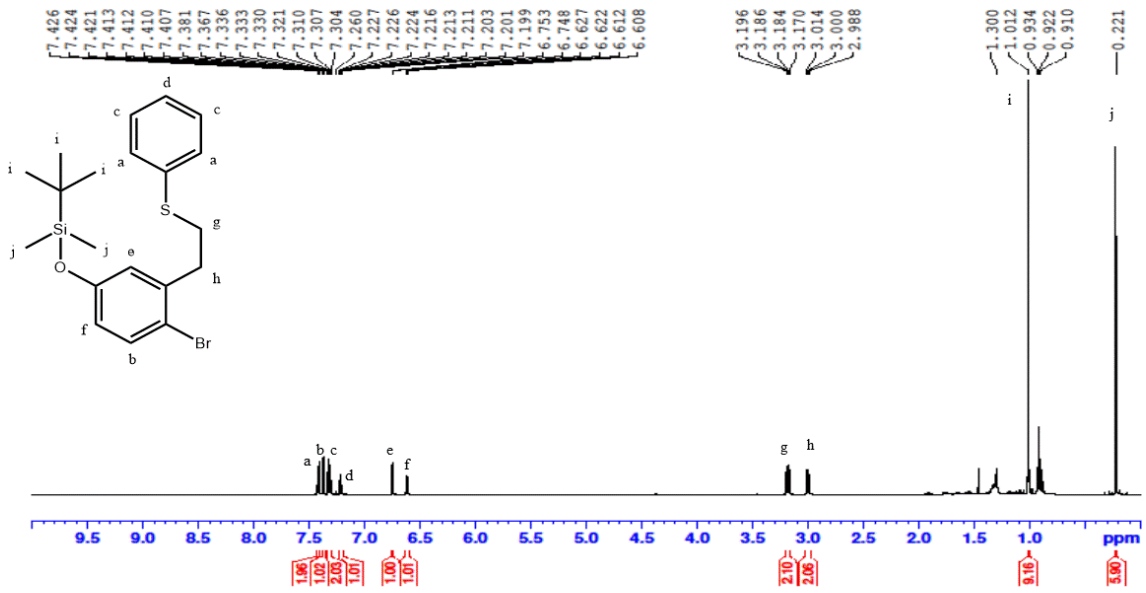


Figure 98: ^{1}H NMR spectrum of 13

3.2.6. Synthesis of 5-(tert-butyldimethylsilyloxy)-2,3-dihydrobenzo[b]thiophene (**6**)

The final step in making the DHBT sulfide **6** is the ring closing of **13**. A radical initiated process is used, with an initiator used in conjunction with tributyltin hydride to generate a tributyl tin radical. The initiator used in the literature was azobisisobutyronitrile (AIBN), but due to limited availability an alternative, 1,1′-azobis(cyclohexanecarbonitrile) (ABCN) was used. The reaction mechanism is outlined in **Figure 99**.

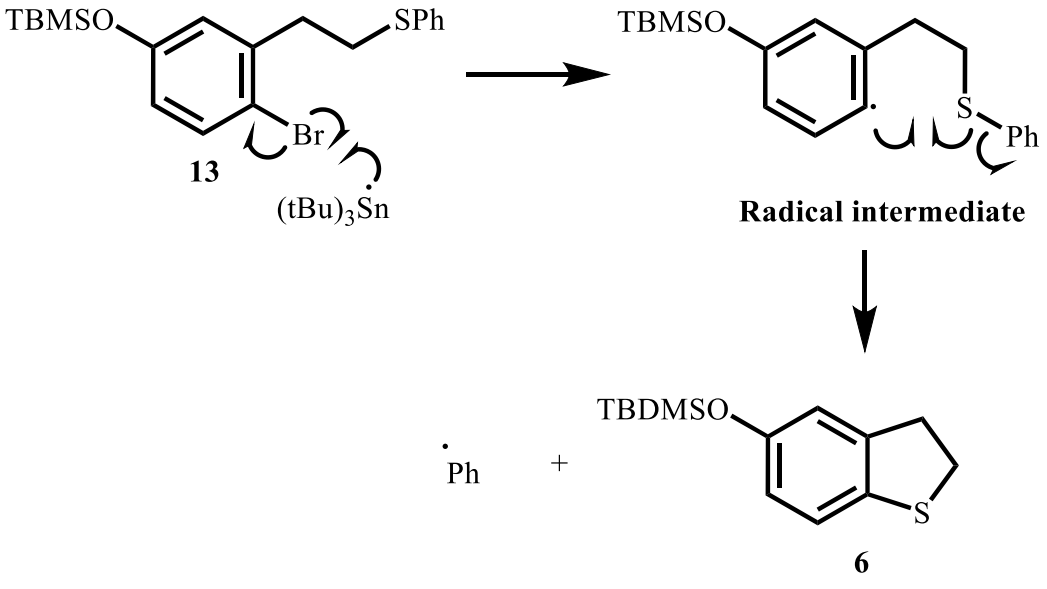


Figure 99: Reaction mechanism for the radical synthesis of 6

In the literature,[145] dry benzene is used as a solvent which was available in the lab but due to its' carcinogenic nature was undesirable to use. Thus, a solvent study was performed comparing dry benzene, toluene, ACN and THF. The reaction is monitored by ^{1}H NMR every 24 hours to observe the gradually decreasing intensity of the triplets representing the starting material and the emerging upshifted triplets representing the ring closed product. (**Figure 100**).

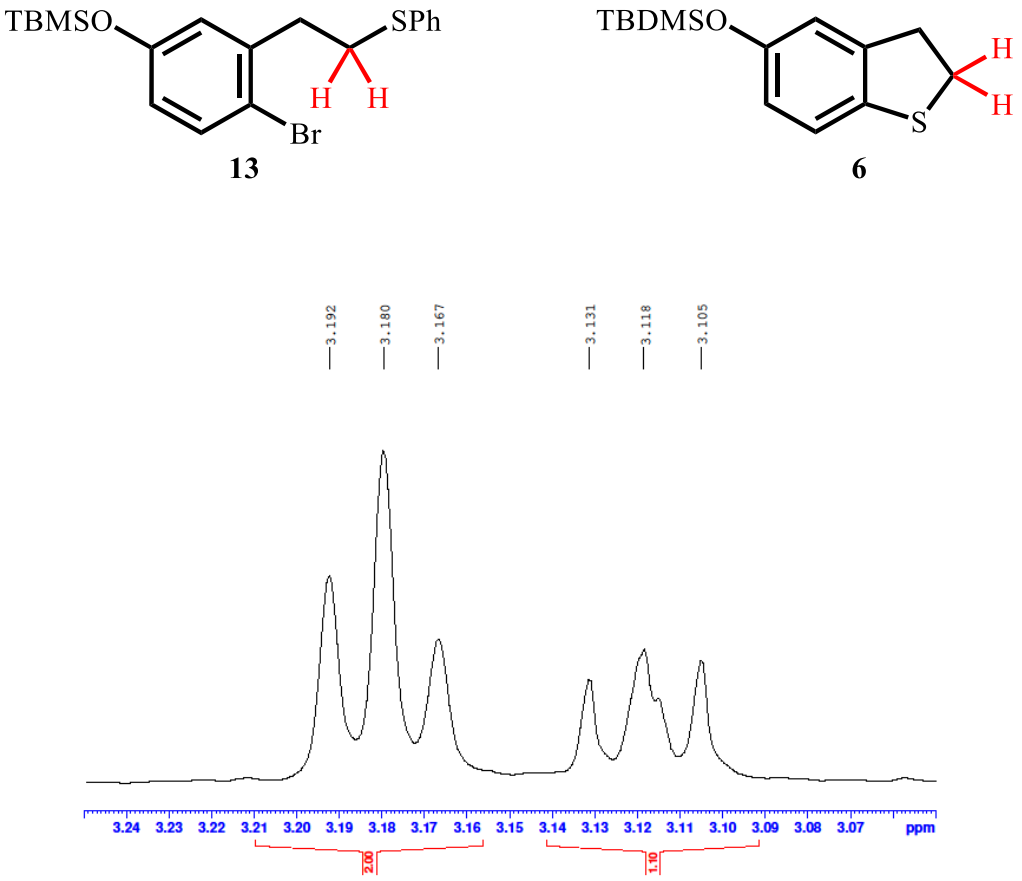
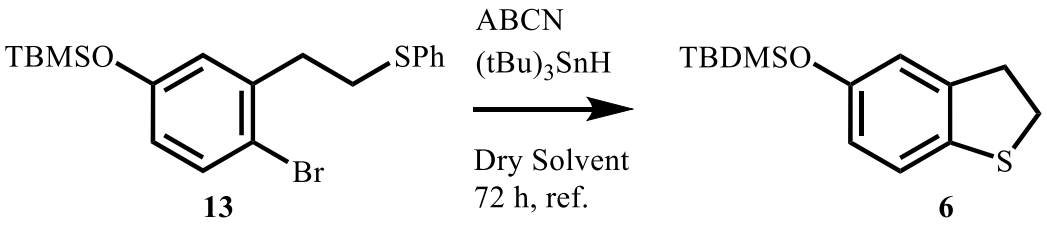


Figure 100: ^{1}H NMR snapshot showing the characteristic triplet peak of product 6 at 3.18 ppm as compared to starting material 13 at 3.12 ppm. 1H NMR spectra were recorded as reaction was ongoing.

It was thus decided for the purpose of this study, the reactions would be run for 3 days and the ratio of the product peak to the starting material peak in the ^{1}H NMR compared. The results of the study are shown in **Table 18** below.

Table 18: Time study for the synthesis of 6



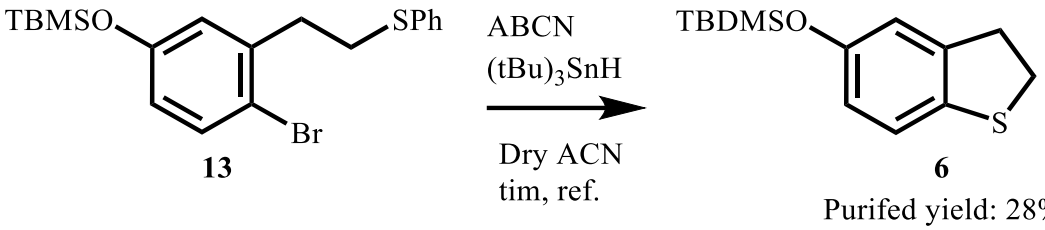
Entry	Dry Solvent	Ratio of product peak to starting material peak in ^{1}H NMR
1	Benzene	0.35
2	Toluene	0
3	ACN	0.56
4	THF	0

Reactions were performed at various mmol scale under inert conditions with a nitrogen atmosphere with flame dried glassware. Standard work-up involved rotary evaporation of the reaction mixture. See Experimental Methods for further details.

The results of the study how that both toluene and THF failed to work. Toluene was unsurprising giving its' methyl group is susceptible to radical. THF may have also have been unsuitable as a radical could form from the ther linkage. Dry ACN was observed to produce a higher proportion of the product than benzene. As ACN performed better and is far safer, it was decided to use this as the solvent. ACN can in theory form radicals too along the carbon-nitrogen triple bond, but this was not observed.

For the reaction optimisation study, the reaction was run over several days, with the tributyltin hydride and ABCN being added to the mixture every 24 hours as well as an aliquot of the crude material being extracted from the flask and analysed by ^{1}H NMR. When the ring closing stops proceeding any further, the reaction is deemed finished and worked-up and purified. Results of this time study are shown in **Table 19** below. A ^{1}H NMR spectrum of the isolated product **6** is given in **Figure 101** below. The ^{1}H NMR spectrum of **6** was compared to the spectra of the same compound in the literature.[145]

Table 19: Optimisation study for the synthesis of 5-(*tert*-butyldimethylsilyloxy)-2,3-dihydrobenzo[*b*]thiophene (6)



Entry	Time (h)	Ratio of product peak to starting material peak in ^{1}H NMR
1	18	0.35
2	42	0.51
3	66	0.56
4	90	0.77
5	114	1.04
6	138	1.17
7	162	1.56
8	186	1.60

Reactions were performed at various mmol scale under inert conditions with a nitrogen atmosphere with flame dried glassware. Standard work-up involved rotary evaporation of the reaction mixture. See Experimental Methods for further details.

The time study shows that after 8 days, the ring closing ceases, and no more of the starting material will form the ring closed product. The purification of this compound was done by column chromatography, and was very difficult. The literature recommends a mobile phase of hexane, but this led to both the starting material and the product co-eluting. Adding a small amount of Et_2O did not help the separation, and several other solvents in various ratios were attempted. It was then decided to use a small amount of toluene added to hexane (98:2 Hex:Tol). As the starting material has an extra phenyl group, it should be better retained by the mobile phase. This mobile phase did work at separating the starting material and the product was isolated with an overall purified yield of 28%, which is low and needs more optimisation. Incresing the percent of toluene in the mobile phase led to co-elution, and reducing the toluene percentage in the mobile phase less led to both materials becoming ‘stuck’ on the column. With the product eventually purified, the next step was to see if this sulfide can form an allyl sulfonium salt for use in the Corey-Chaykovsky reaction.

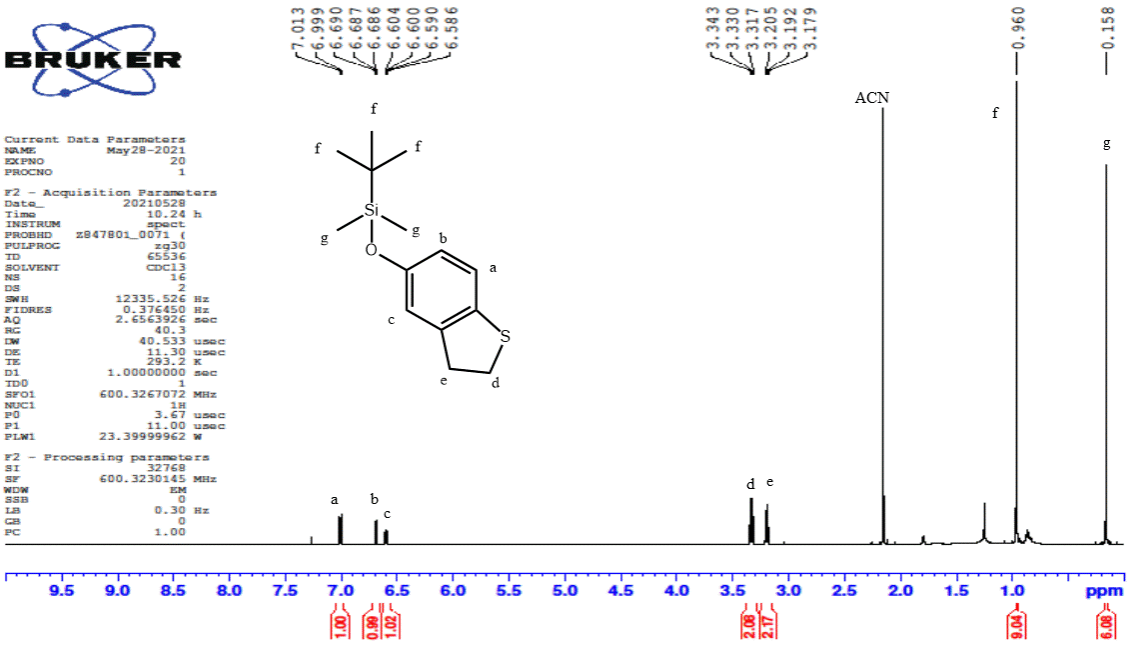
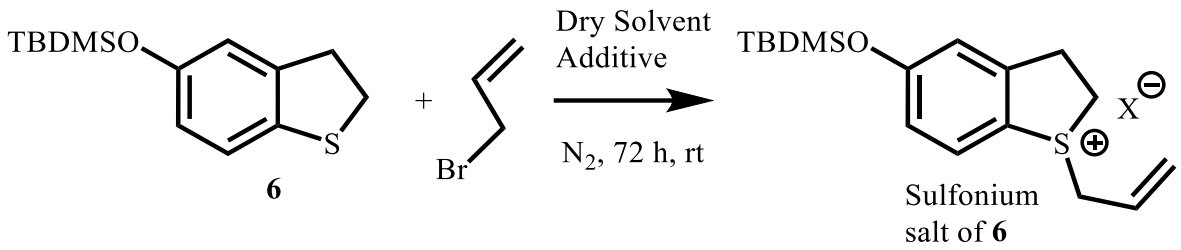


Figure 101: ^{1}H NMR spectrum of target compound 6

3.2.7. Synthesis study of sulfonium salt from 5-(tert-butyldimethylsilyloxy)-2,3-dihydrobenzo[b]thiophene (**6**)

It is planned to use the synthesised sulfide in the Corey-Chaykovsky reaction for aziridine synthesis. However, it must first be determined if the desired allyl sulfonium salt derivative of **6** can form, and if so, its formation reaction should be optimised. Once this has been achieved, the salt can be formed in situ with the aziridination reaction, with the sulfide in a catalytic amount and be recoverable afterwards. Due to a limited amount of **6** available, an extensive study could not be carried out but two reactions were tried based on the sulfonium salt (**2**) optimal conditions determined in Chapter 2**.** Results are given in **Table 20** below.

Table 20: Synthesis study of sulfonium salt from 5-(*tert*-butyldimethylsilyloxy)-2,3-dihydrobenzo[*b*]thiophene (6)



Entry	Dry Solvent	Additive	X	% Yield
1	DCM	-	Br	0
2	ACN	$AgBF_4$	BF_4	0

All reactions were performed at a 0.05 mmol scale. Entry 2 has a work-up of filtering through an alumina plug. Both entry 1 and 2 were purified by vigorous stirring with EtOAc. See Experimental Methods for synthesis of **2**

In entry 1 of **Table 20**, the optimal conditions for forming the diethyl sulfonium salt from Chapter 2 were tried, with allyl bromide in dry solvent under nitrogen in dry glassware for 72 hours. The ^{1}H NMR of the crude material appeared to show remaining starting material, with purification attempts unsuccessful. In entry 2 the optimal conditions for synthesising the THT sulfonium salt were tried, which the conditions are the same except for the addition of silver tetrafluoroborate. The tetrafluoroborate undergoes an anion exchange with the bromine and helps to drive the reaction towards completion. The THT sulfonium salt contained a locked 5 membered ring, similar to this sulfide, so it was suspected that this may help the salt formation with this sulfide. The crude ^{1}H NMR appeared to show that a small amount of the salt did form, but this was unconfirmed, and remaining starting material was present. Purification attempts were unsuccessful too. It may be the case that the aryl side group next to the sulfide reduces the nucleophillicity of the lone pair of electrons on the sulfur. In the literature, an example of a benzothiophene sulfonium salt could not be found. However, aromatic sulfides have been shown in the literature to form sulfonium salts.[60,144] This suggests the sulfonium salt of sulfide **6** is suitable to form but requires a far more extensive optimisation study.

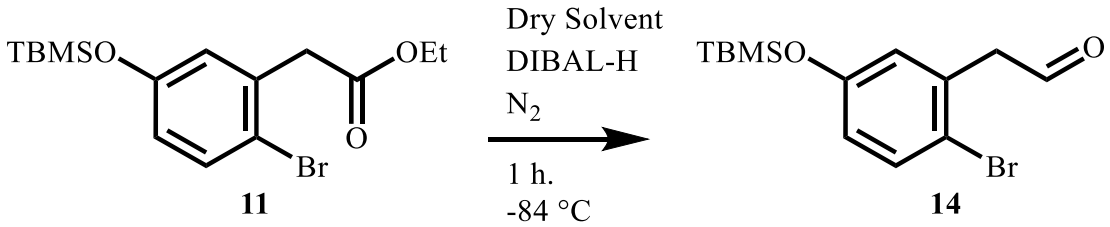
3.3. Second target compound (**7**) synthetic pathway development and optimisation

The second target compound of this chapter is a derivative of DHBT **6**, with a side group added next to the sulfide to include a chiral centre (**7**). This target compound would be a novel chiral sulfide and is aimed to be used as a catalyst in the Corey-Chaykovsky reaction

3.3.1. Synthesis of 4-bromo-3-(2-acetaldehyde)phenyl tert-butyldimethylsilyl ether (**14**)

The starting point for the synthesis of this target sulfide is reducing ester **11** with diisobutylaluminium hydride (DIBAL-H) instead of $LiAlH_4$, to give the desired aldehyde product **14** instead of the alcohol **12**. DIBAL-H reacts very readily with water, so having flame dried glassware under a nitrogen atmosphere is key to the reaction's success, and the temperature must be maintained at very low temperatures (-84°C) as the reaction is both highly exothermic and at temperatures higher than this the fully reduced alcohol is much more likely to form. This low temperature can be achieved with an an ethyl acetate bath that is frozen and continuously topped up with liquid nitrogen. An optimisation study was carried out of this reaction and is shown below in **Table 21**. Compound **14** is new and was characterised by ^{1}H, ^{13}C, COSY, DEPT and HSQC NMR and HRMS. The ^{1}H NMR spectrum of **14** is given in **Figure 102** below and the remaining spectra can be found in the Appendix

Table 21: Synthesis of 4-bromo-3-(2-acetaldehyde)phenyl *tert*-butyldimethylsilyl ether 14



Entry	Dry Solvent	DIBAL-H eq.	Yield (%)
1	DCM	1.1	48
2	DCM	1.5	68
3	THF	1.5	59

All reactions were performed under nitrogen in flame dried glassware in a bath of EtOAc and liquid nitrogen with a standard work-up of quenching with MeOH, stirring in saturated potassium sodium tartate solution before extracting with EtOAc and washing with water and brine. See Experimental Methods for further details.

The results of the study showed that the aldehyde was readily formed under the stated conditions. Surprisingly, no alcohol by product or ester starting material was evident in the ^{1}H NMR. Dry DCM gave better yields than THF and a significant boost to yield was observed when increasing the mole equivalence of DIBAL-H from 1.1 to 1.5 (entry 2). The reaction was performed at -84 °C and the DIBAL-H was added dropwise over 30 mins, then allowed to stir for 30 mins, all while maintaining the bath at the low temperature with continued addition of liquid nitrogen. Potassium sodium tartrate solution was used in the work-up to remove the ethoxide complex and excess DIBAL-H leftover. No further purification was necessary.

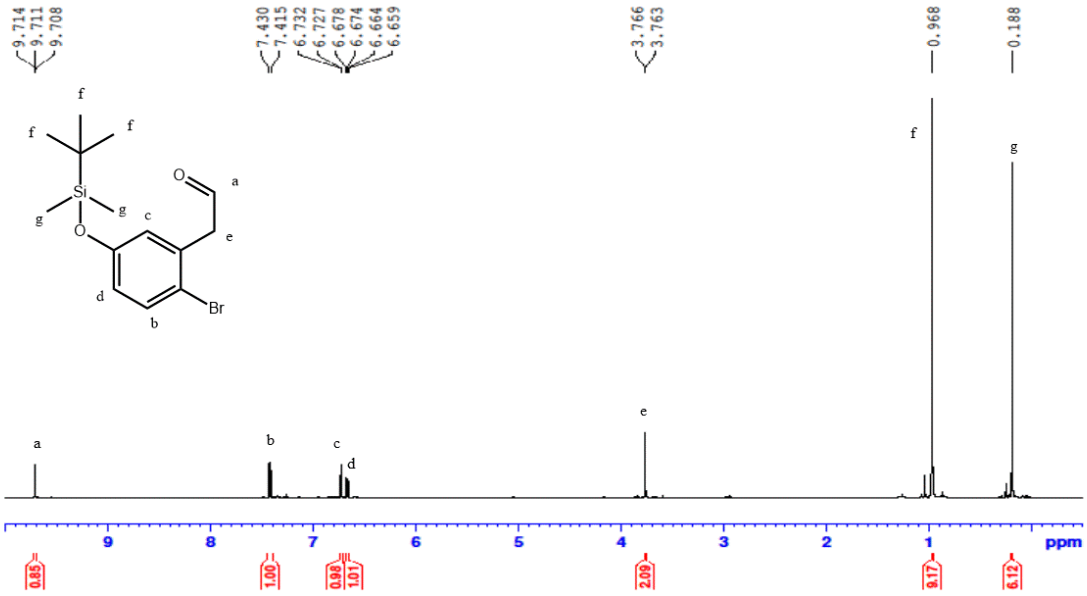
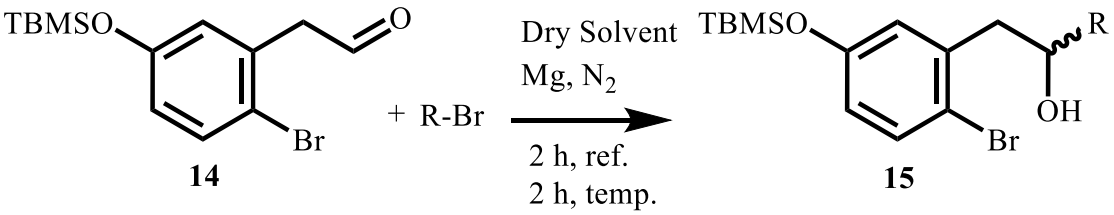


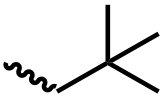
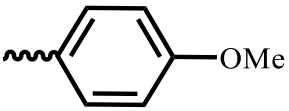
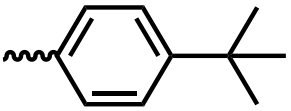
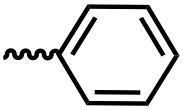
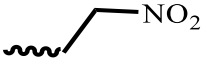
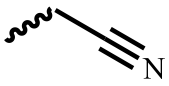
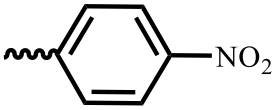
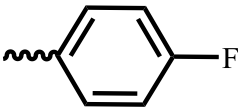
Figure 102: ^{1}H NMR spectrum of 14

3.3.2. Grignard study on **14** for synthesis of alpha-substituted sulfide derivatives (synthesis of **15**)

The next step in the synthetic pathway involves a Grignard addition to the synthesised aldehyde **14**. This was based on methods from the literature.[148,149] It was decided to have three organobromides whose R group, when added to the sulfide precursor, would give either an electron-donating effect (entries 1-5 in **Table 22**) or electron-withdrawing effect (entries 6-9 in **Table 22**). The standard conditions for this reaction involved preparing the Grignard reagent in flame dried glassware under nitrogen by the addition of the organobromide to magnesium, dry ether (either THF or Et_2O) with an iodine crystal to remove oxidised magnesium. This was typically done for 2 hours followed by the addition of the aldehyde in dry ether, and refluxing the entire reaction mixture for 2 hours. A variety of conditions were screened as outlined in **Table 22** below.

Table 22: Synthesis of Grignard derivatives 15



Entry	R	Product	Dry Solvent	Conditions	% Yield
1		**15a**	THF	2 h. ref, 2 h. ref.	31
2		**15b**	THF	2 h. ref, 2 h. ref.	28
3		**15c**	Et_2O	2 h. ref, 6 h. ref.	0
4		**15d**	THF	2 h. ref, 2 h. ref.	0
5		**15e**	THF	2 h. ref, 18 h. ref.	0
6		**15f**	THF	2 h. ref, 18 h. ref.	0
7		**15g**	Et_2O	2 h. ref, 2 h. ref.	0
8		**15h**	THF	2 h. ref, 2 h. ref.	0
9		**15i**	THF	2 h. ref, 2 h. ref.	0

Reactions were performed at 0.2-0.6 mmol scale with a standard work-up of neutralising the reaction mixture in ice cold saturated ammonium chloride solution followed by extraction with Et_2O (×3), washing with saturated ammonium chloride solution, water and brine and drying over $MgSO_4$. Purification was performed by column chromatography with varying ratios of hexane/Et_2O. See Experimental Methods for further details.

The reaction proved difficult, especially at the relatively small scales that were performed due to starting material availability. 2 hours was generally used to form the Grignard reagent with assistance of the heat gun to start the reaction, followed by refluxing. After

the addition of the aldehyde, the reactions were run for between 2-18 hours. TLC monitoring was carried at both stages of the reaction but was also difficult, with cluttered spots that were hard to separate and the added problem of trying not to contaminate the reaction flask, as the Grignard reaction is highly water sensitive. A 1.5 equivalence of the organobromide relative to the aldehyde was used in all the reactions in **Table 22** as initial studies with 1.1 eq. produced no yields. Purification also proved difficult, as a typical crude material contained multiple compounds in the ^{1}H NMR, most probably the aldehyde and a small amount organobromide starting materials, the alcohol product as well as various unknown impurities. Entries 1 and 2 show the only successfully purified alcohol products that involved a long silica column, initially with 100% hexane mobile phase, with gradual introduction of 1-2% diethyl ether. Typically, the organobromide eluted first followed by various unknown impurities, and the desired product and aldehyde starting material eluting next close together. Entries 1 and 2 of **Table 22** contained the bulky t-butyl R group (**15a**) and *para*-anisole (**15b**). Compounds **15a** and **15b** from **Table 22** are both new and were characterised by ^{1}H, ^{13}C, COSY, DEPT and HSQC NMR and HRMS. The ^{1}H NMR of **15a** is given in **Figure 103** below, and the remaining spectra are contained in the Appendix. For entries 3-5 of **Table 22**, there was tentative evidence from the crude ^{1}H NMRs that the desired alcohol formed, but purification was unsuccessful so this was not confirmed. Entries 6-9 of **Table 22** did not work at all. The two alcohols that were formed and successfully purified were used to proceed to the next step of replacing the hydroxy group with phenyl sulfide.

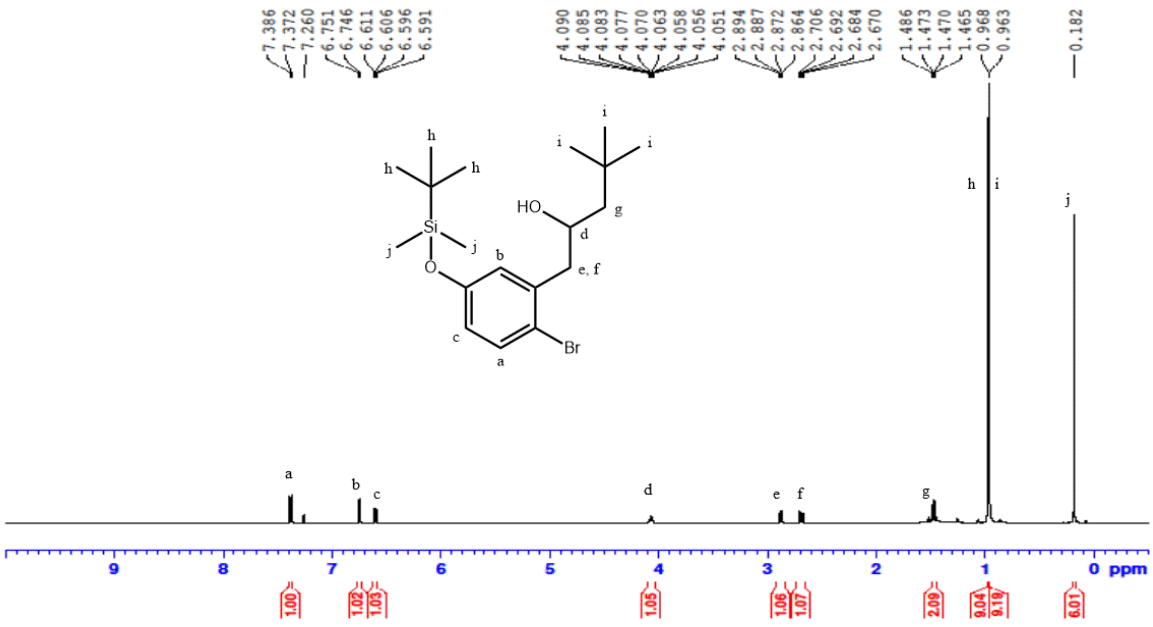
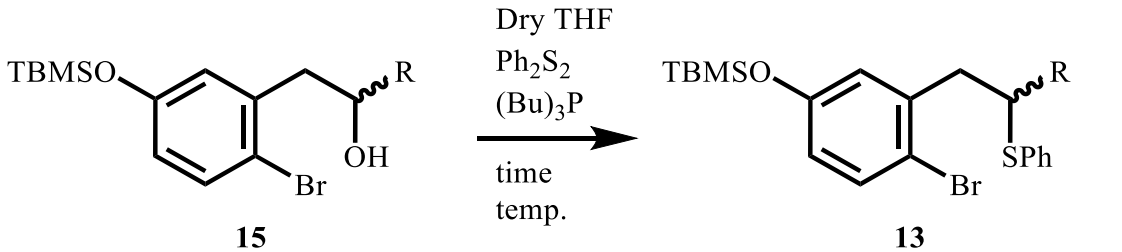


Figure 103: ^{1}H NMR spectrum of 15a

3.3.3. Sulfonation study of Grignard products (**15a** and **15b**) to form substituted sulfide (**13a** and **13b**)

Having made two alcohol derivatives with the Grignard method (**15a** and **15b**), the next step was to replace the hydroxy group with phenyl sulfide using the same method optimised for the synthesis of **13** when synthesising the previous target sulfide. The reaction was studied as outlined in **Table 23** below.

Table 23: Synthesis study of 10a and 10b from Grignard products 13a and 13b



15
15a: R = tBu
15b: R = 4-methoxyphenyl

13
13a: R = tBu
13b: R = 4-methoxyphenyl

Entry	Starting Material	Product	$(Bu)_3P$ eq.	Ph_2S_2	Time (h)	Temp. (°C)	% Yield
1	**15a**	**13a**	1.1	1.1	8	rt	0
2	**15b**	**13b**	1.1	1.1	8	rt	0
3	**15a**	**13a**	1.1	2.0	8	rt	0
4	**15b**	**13b**	1.1	2.0	8	rt	0
5	**15a**	**13a**	2.0	2.0	8	rt	0
6	**15a**	**13a**	1.1	2.0	18	66	0

Reactions were performed at various mmol scale under inert conditions with a nitrogen atmosphere with flame dried glassware. Standard work-up involved quenching the reaction mixture with saturated $NaHCO_3$ solution, followed by washing with saturated $NaHCO_3$ solution, water and brine followed by drying over $MgSO_4$ and rotary evaporation. See Experimental Methods for the synthesis of **13** for further details

This reaction proved far more difficult compared to the unsubstituted alcohol (**9**). The same reaction conditions were tried with the tert-butyl (**15a**) and *para*-anisole (**15b**) R groups in entry 1 and 2 of **Table 23** and produced no product, with crude ^1H NMR spectra showing what appears to be leftover starting material, with this being confirmed by column chromatography where starting material was recovered. Increasing the equivalence of the diphenyl disulfide also produced the same result (entry 3 and 4), as did increasing the amount of $(Bu)_3P$ (entry 5) and reaction temperature and time (entry 6). A plausible explanation as to why this reaction does not work is the added steric hindrance when using the **15a** and **15b** starting material, as can be seen when looking at the proposed reaction mechanism, as outlined in **Figure 104.** The tributylphosphine as a nucleophile to break the

disulfide bond on the diphenyldisulfide to produce a charged phosphine bonded to a phenyl sulfide as well as a thiophenolate anion. From here, the alcohol acts as a nucleophile, attacking the phosphine and producing a charged hydroxy. The carbon attached to the newly charged hydroxy group can now itself undergo nuclephilic attack with the thiophenolate anion produced earlier, with expulsion of the hydroxy phosphine group. This key nucleophilic step is likely hindered by the bulky R groups present in **15a** and **15b** alcohol starting materials, but proceeds without issue when using the unhindered alcohol **12.** As this method didn't work with the substituted alcohols, alternative methods for nucleophilic substitution of hydroxy for phenyl sulfide will be attempted.

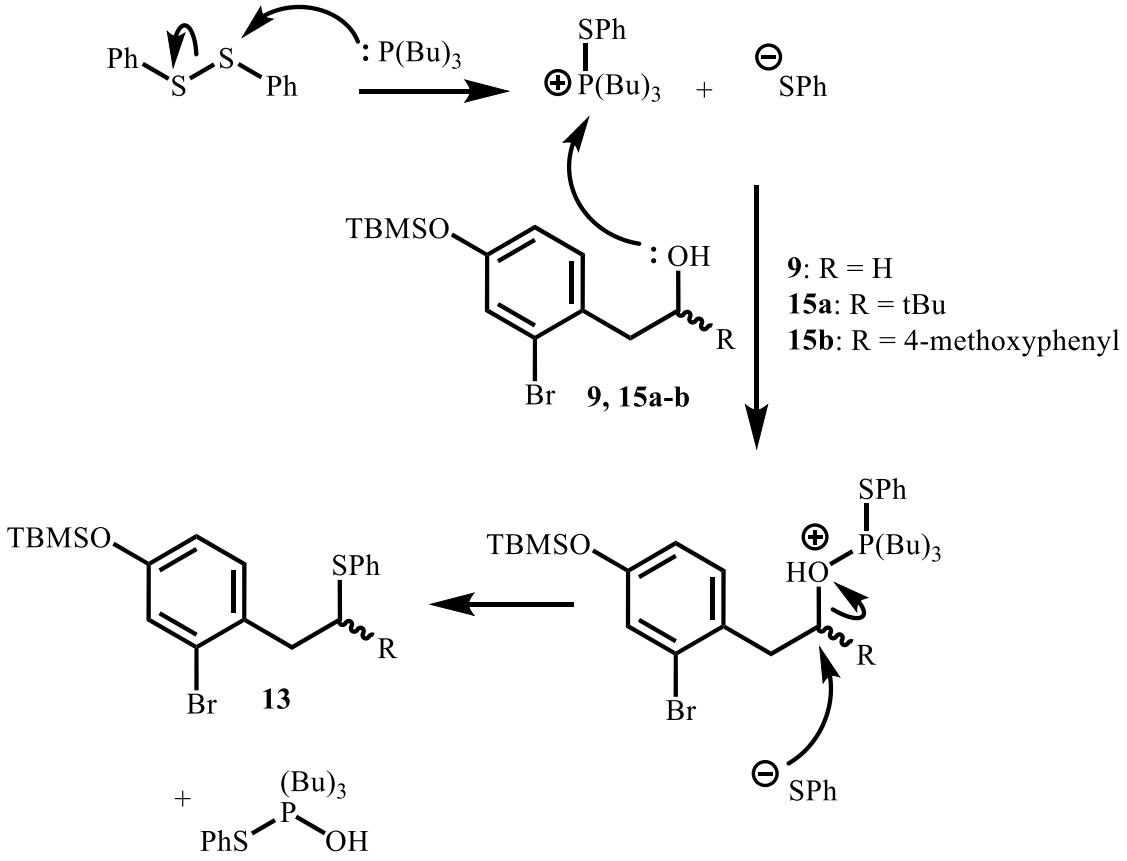
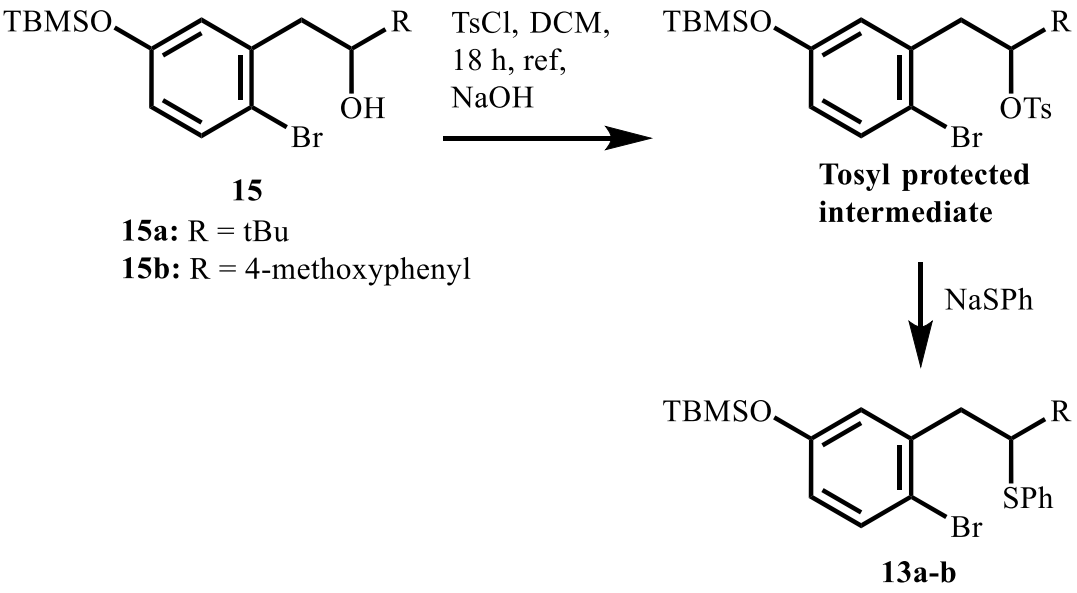


Figure 104: Reaction mechanism for synthesis of phenyl sulfide derivatives from alcohol starting materials 9, 15a and 15b

A new method attempted to add the phenyl sulfide to the secondary alcohols was based on a method from the literature.[150] It involves converting the hydroxy group to a good leaving group by tosylation. The proposed reaction scheme is shown in **Figure 105** below.

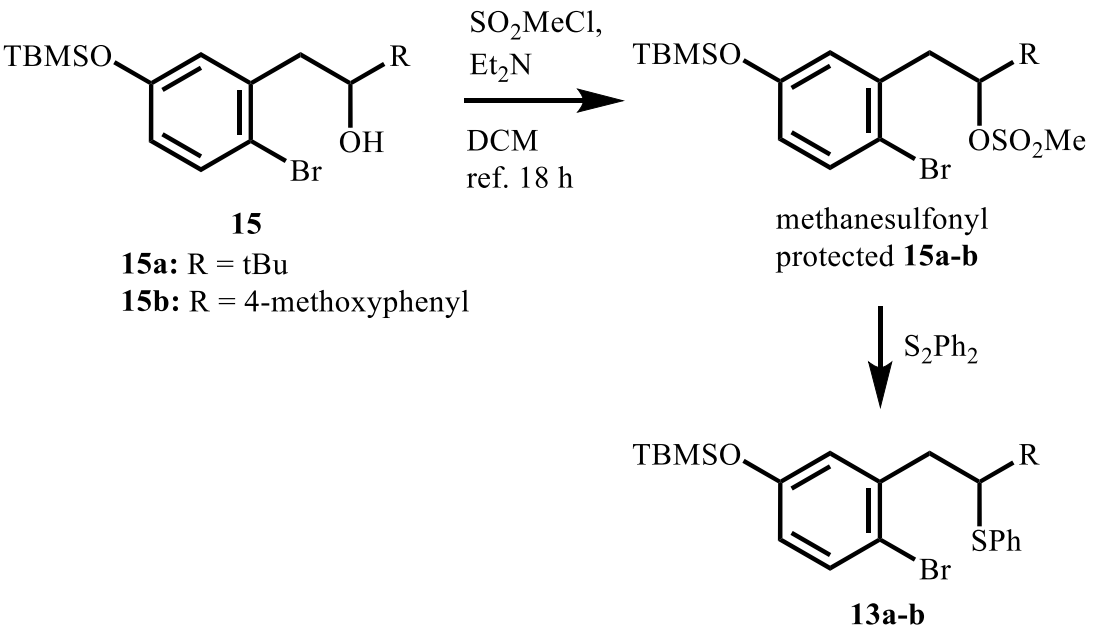


15
15a: R = tBu
15b: R = 4-methoxyphenyl

Figure 105: Theorised reaction scheme of tosyl protection alternative startegy to synthesisng 13a-b

The first step of this reaction was attempted with the tert-butyl and *para*-anisole R group secondary alcohols but did not produce the tosyl protected alcohol, therefore, the method was discontinued and another sought.

Another alternative method found in the literature[151] was used for similarly structured secondary alcohols and involved replacing the hydroxyl with a methanesulfonyl group using methanesulfonyl chloride, this methanesulfonyl group can then be more easily replaced with phenylsulfide. The proposed scheme is shown in **Figure 106.**



15
15a: R = tBu
15b: R = 4-methoxyphenyl

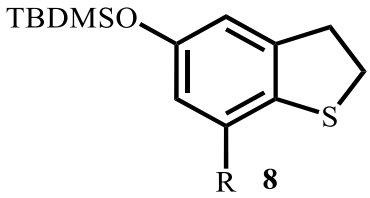
Figure 106: Theorised reaction scheme of methanesulfonyl alternative startegy to synthesisng 13a-b

Several attempts to add the methanesulfonyl group with the tert-butyl secondary alcohol failed and this method was set aside. The target chiral sulfide **7** was therefore not

synthesised by these explored methods, so alternative routes will be needed. This will be discussed further in Chapter 5.

3.4. Third target compounds (DHBT derivatives **8**) synthetic pathway development and optimisation

The third target compound of this chapter is a derivative of of **6**, with a side group added ortho to the sulfide on the phenyl ring (**8, Figure 107**). A substituent here may be able to withdraw/donate electron density onto the sulfur atom, and allow ylide tuning.

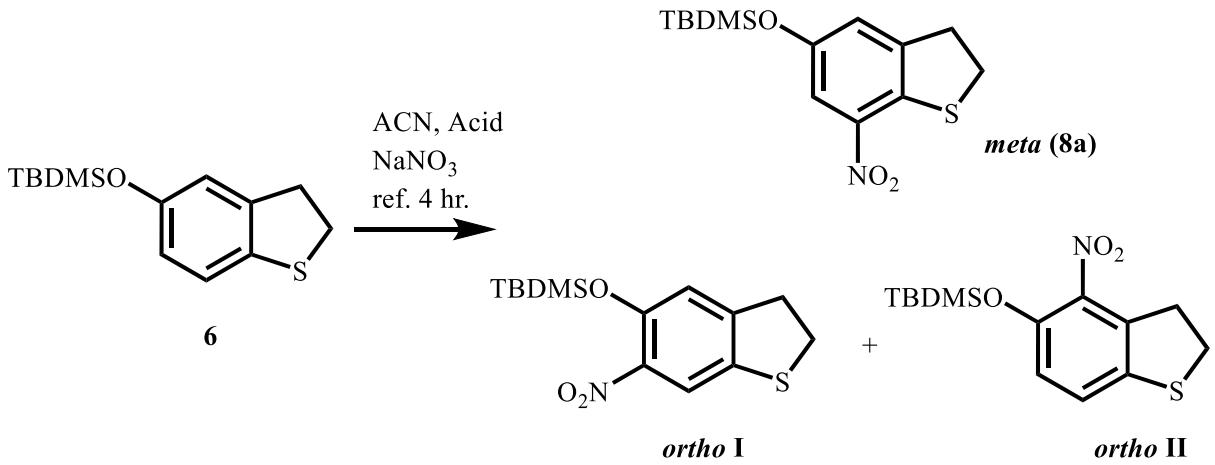


8

Figure 107: Third target sulfide, DHBT derivatives 8

As outlined in this chapter's introduction, it was decided to make the sulfide **6** first, and then nitrate the phenyl ring ortho to the sulfide. The nitro group is interesting and it can also be converted by reduction/diazotisation to a variety of group possessingelectron withdrawing or donating potentials. Any attempt to nitrate the phenyl ring earlier in the synthetic pathway would result in nitration in the wrong position or altering of the existing group (for example, nitrating with acidic conditions would remove the TBDMS protecting group). With a limited amount of sulfide available, three separate nitrations were tested using the well-established method of an acid with sodium nitrate salt.[152,153] The three different acids used were nitric acid (HNO_3, strong acid, pK_a: -1.4), trifluroacetic acid (strong acid, pK_a: 0.52) and acetic acid (weak acid, pK_a: 4.76). The favoured position of the nitro group is expected to be *ortho* to the electron-donating substituent OTBDMS, but the sulfide also has *ortho-para* directing abilities so it is hoped the desired product can form. The study details are shown in **Table 24** below, with the three possible nitrated products.

Table 24: Study of the nitration of sulfide DHBT 6



Entry	Acid	Salt	% Yield		
			***meta* (8a)**	***ortho I***	***ortho II***
1	HNO_3	$NaNO_3$	0	0	0
2	TFA	$NaNO_3$	0	0	0
3	AcOH	$NaNO_3$	0	0	0

All reactions were performed at a 0.05 mmol scale with a standard work-up of quenching the reaction mixture with ice cold 4M NaOH solution, followed by extraction with EtOAc and washing with water and brine. See Experimental Methods for further details.

The results of the study show that when using HNO_3 and AcOH (entries 1 and 3, respectively), no nitrated product at all formed. In entry 2, when using TFA, the crude ^1H NMR spectrum showed the possible formation of ortho-**I** based of the splitting in the aromatic region, however this was unconfirmed. The desired product was not observed. Given the limited amount of **6** product available, it was decided to seek an alternative route to forming a more simplified sulfide with the nitro group attached (**16a, Figure 108**).

It was theorised that the TBDMS protected phenol group on the 2,3-dihydrothiophene derivative (**8**) could be interfering with the nitration. Therefore, it was decided to attempt to synthesise unsubstituted 2,3-dihydrobenzothiophene **16** (which was not commercially available) sacrificing the phenol group which was planned to allow catalyst loading on a column. The proposed synthesis is given in **Figure 108** below. It utilises a similar reaction pathway used for the synthesis of **8**, but with phenylacetic acid as a starting material. Also, to ensure the crucial bromination step adds ortho to the carboxylic acid group, it was proposed to first sulfonate the phenylacetic acid in the *para*-position. This sulfonation will block the bromine adding in the *para*-position and guide it to the *ortho*-position (which is *meta* with respect to the sulfonate group). Once the bromination occurs in the correct position, the sulfonate group can be removed and the synthesis can proceed in the same manner as the pathway for **8**. Once**16** has been synthesised, it was proposed to directly nitrate the phenyl ring to form **16a**.

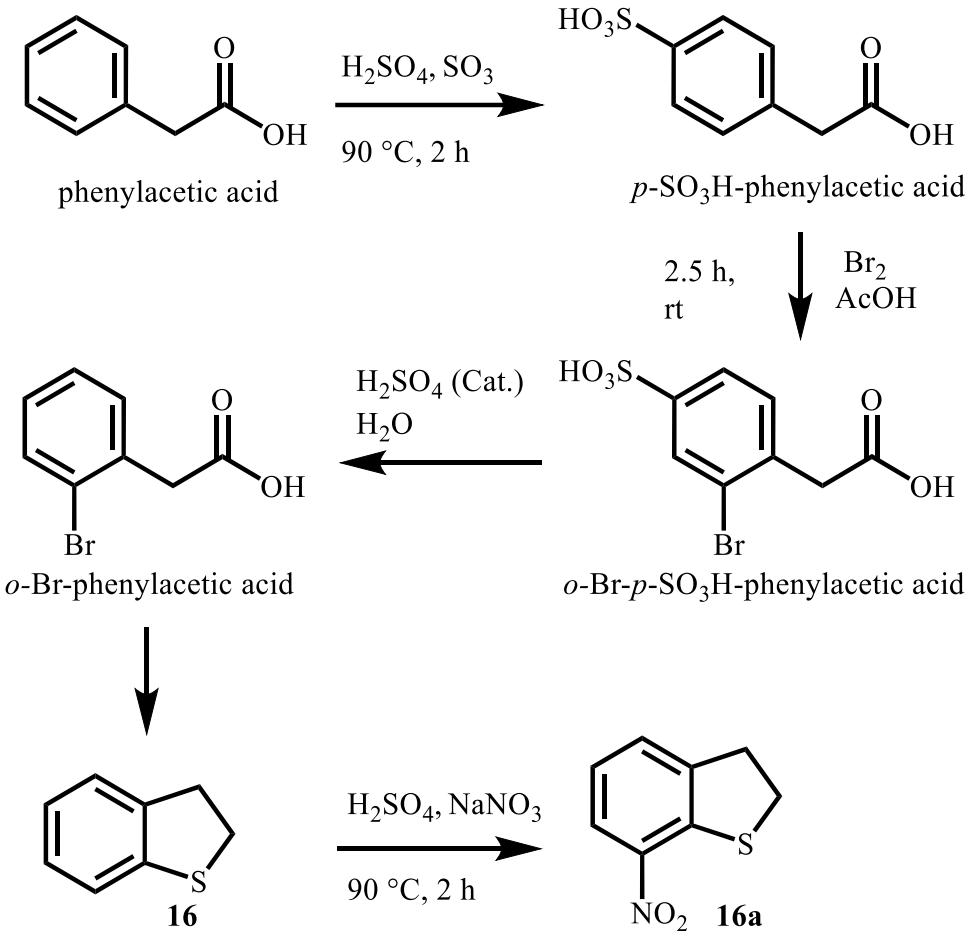
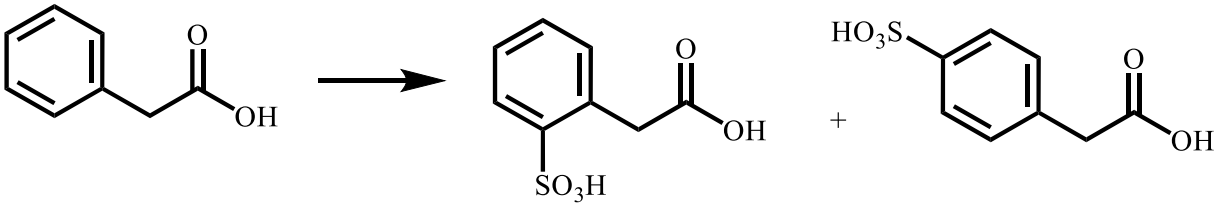


Figure 108: Proposed synthesis of 2,3-dihydrobenzothiophene (DHBT 16) using a similar method to the synthesis of 8

The first step of this new synthetic pathway is sulfonating of the phenyl acetic acid. A study was performed in **Table 25** below. Three different conditions were examined with sulfuric acid and/or fuming sulphuric acid (oleum).[154–156] The two expected products were the *ortho* and *para* substituted phenyl acetic acids.

Table 25: Study of the sulfonation of phenylacetic acid



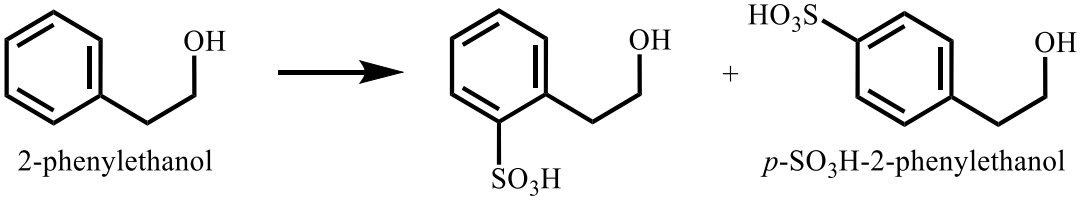
phenylacetic acid *o*-SO_3H-phenylacetic acid *p*-SO_3H-phenylacetic acid

Entry	Conditions	Temp. (° C)	Time (h)	% Yield	
				o	***p***
1	H_2SO_4	120	18	0	0
2	H_2SO_4	80	4	0	0
3	H_2SO_4 / SO_3	80	4	0	0

All reactions were performed at a 2 mmol scale with a standard work-up of quenching the reaction mixture with ice cold 4M NaOH solution, followed by extraction with EtOAc and washing with water and brine. See Experimental Methods for further details.

As is seen in the results from **Table 25** the desired *para* substituted did not form according to the crude ^{1}H NMR spectra, with only tentative evidence of the undesired *ortho* substituted product (this was not confirmed). Use of fuming sulfuric acid in entry 3 did not produce any of the desired *para* product. The carboxylic acid group could be hindering formation of the desired product. Therefore, it was decided to do another study but with the reduced phenyl acetic acid, 2-phenylethanol. 2-phenylethanol was available commercially. This study looked at using sulfuric acid at 120 °C and fuming sulfuric acid at 80 ° and results are shown in **Table 26** below.

Table 26: Sulfonation study of 2-phenylethanol



2-phenylethanol *o*-SO_3H-2-phenylethanol *p*-SO_3H-2-phenylethanol

Entry	Conditions	Temp. (° C)	% Conversion	
			o-	***p-***
1	H_2SO_4	120	0	0
2	H_2SO_4 / SO_3	80	0	0

All reactions were performed at a 2 mmol scale with a standard work-up of quenching the reaction mixture with ice cold 4 M NaOH solution, followed by extraction with EtOAc and washing with water and brine. See Experimental Methods for further details.

This study did not yield the desired product. The ^{1}H NMR spectra appeared to show remaining starting material and another material with *para* substitution (**Figure 109**), which would be consistent with the desired product, however, purification was unsuccessful so this was not confirmed, with further optimisation and purification studies needed.

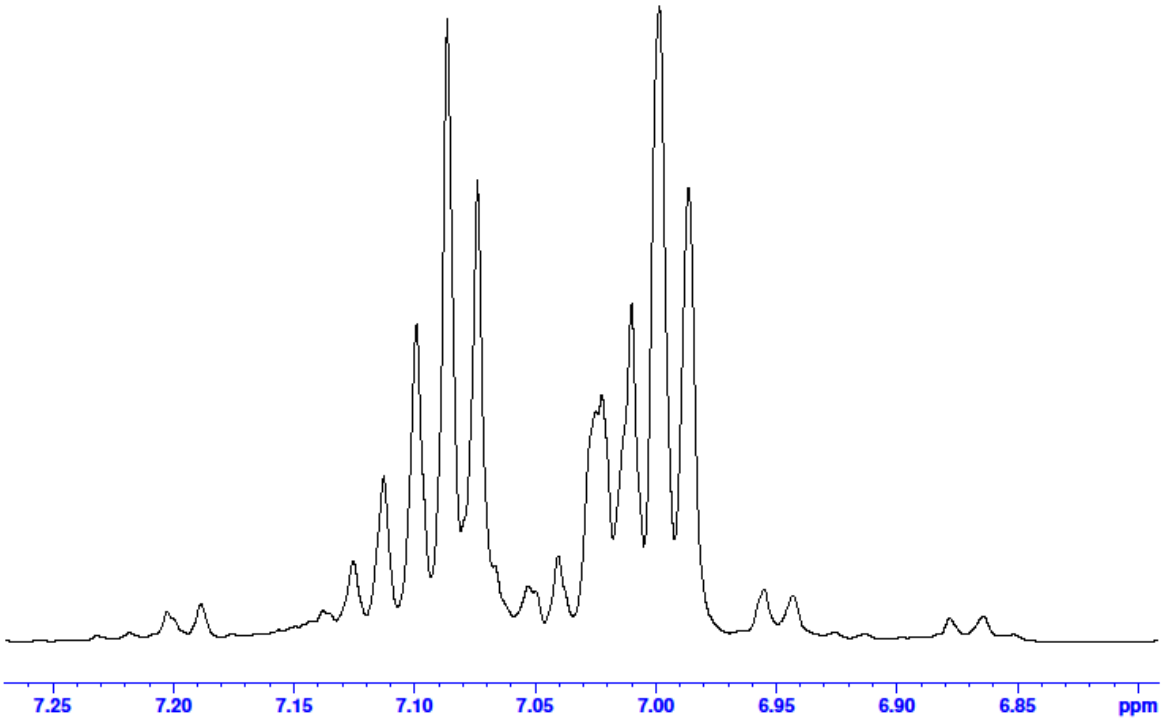
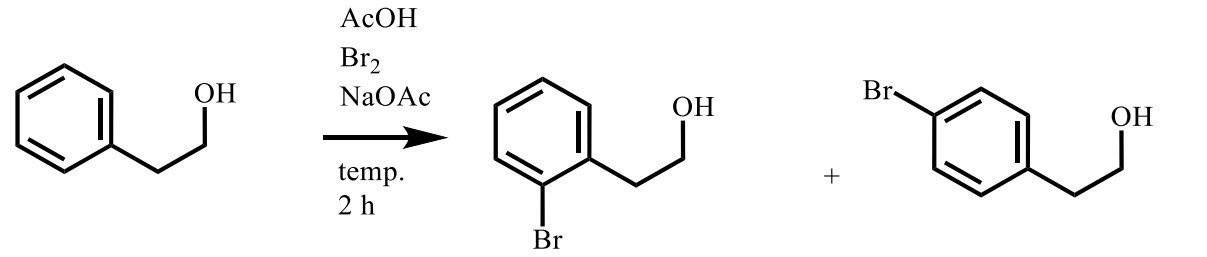


Figure 109: Crude ^{1} H NMR aromatic region for the sulfonation attempt of 2-phenylethanol, showing tentative evidence of para-splitting, but this was unconfirmed.

Another alternative route to 2,3-dihydrobenzothiophene **16** would be directly brominating 2-phenylethanol, with the aim of isolating the *ortho*-substituted product.. A study was carried out in **Table 27** using the same bromination method used for the synthesis of **11**, which used bromine and acetic acid as a solvent with sodium acetate present at room temperature.

Table 27: Bromination of 2-phenylethanol using bromine and acetic aid method



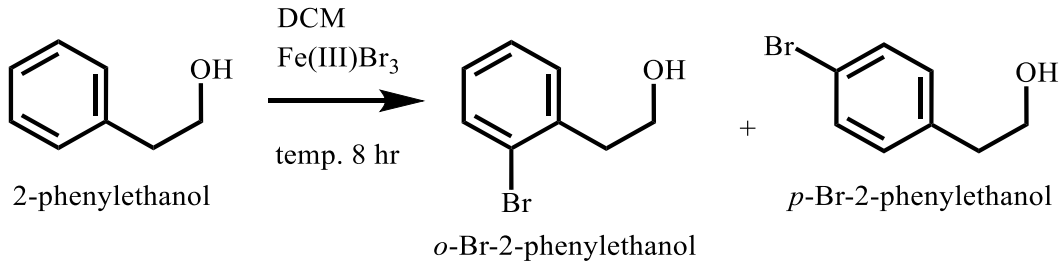
2-phenylethanol *o*-Br-2-phenylethanol *p*-Br-2-phenylethanol

Entry	Temp. (° C)	% Yield	
		o-	***p-***
1	rt	0	0
2	0	0	0

Reaction were performed at 2.0 mmol scale with 1.0 eq. NaOAc as an additive. The standard work-up involved three extractions with Et_2O, neutralising the combined organic layers with saturated $NaHCO_3$ solution, washing with water and brine and drying over $MgSO_4$. See Experimental Methods for further details.

This study did not yield the desired *ortho*-brominated 2-phenylethanol product. The ^1H NMR spectrum showed a mixture of materials, with evidence of *para* splitting in the aromatic region which would be consistent with the undesired *para*-brominated product. However, this was unconfirmed due to unsuccessful purification. It was thus decided to try the more widely used bromination method in the literature,[157] which uses Fe(III)Br_3. It was noted in the literature that temperature can play a role in the substitution regioselectivity, therefore the reaction was tried at room temperature and 0-20 °C and results are shown in **Table 28** below.

Table 28: Bromination of 2-phenylmethanol using Fe(III) bromide method



2-phenylethanol

o-Br-2-phenylethanol

p-Br-2-phenylethanol

Entry	Temp. (° C)	% Conversion	
		o-	***p-***
1	Rt	0	0
2	0	0	0

Reactions were performed at 2.0 mmol scale. The standard work-up neutralising with saturated $NaHCO_3$ solution, extraction with Et_2O and washing with water and brine and drying over $MgSO_4$. See Experimental Methods for further details.

The study did not yield the desired product, but evidence from the ^1H NMR spectra suggested a mix of *ortho* and *para* substituted product based on splitting in the aromatic region (**Figure 110**), though this was unconfirmed as purification was unsuccessful. At 0 °C it appeared the ortho substituted product was more favoured, but this was also unconfirmed due to unsuccessful purification. It may suggest, however, that the use of $Fe(III)Br_3$ at lower temperature could favour *ortho* substitution. This will need a more extensive study and isolation and characterisation of products.

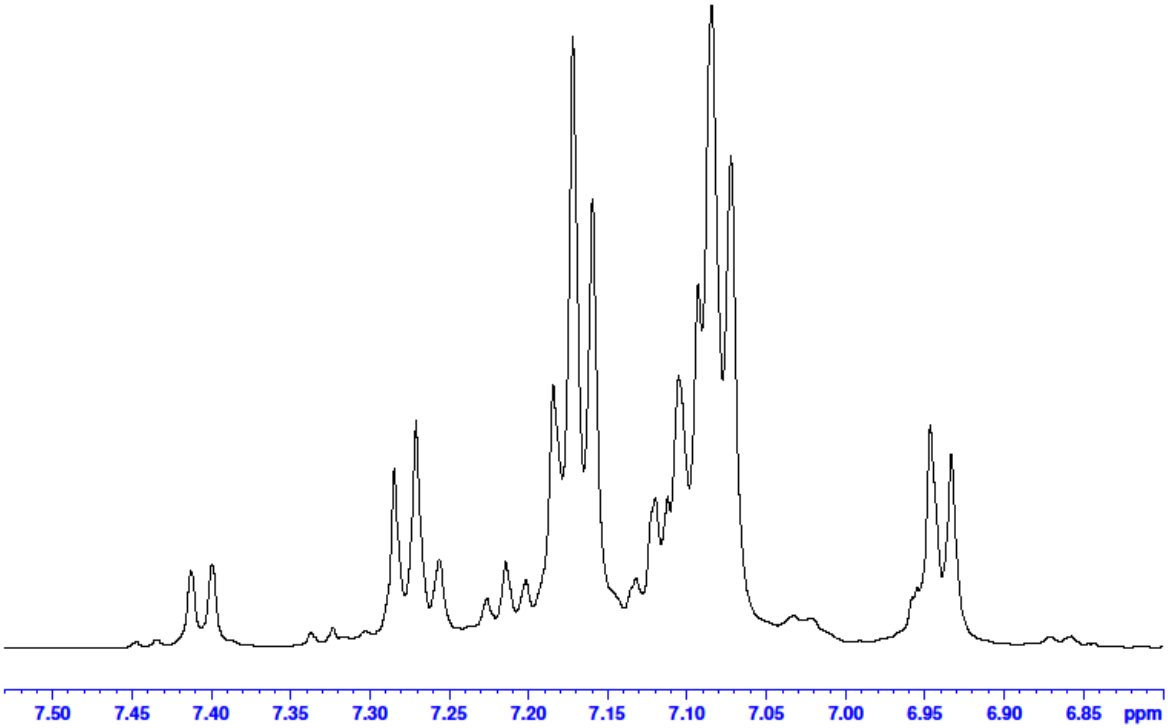


Figure 110: Crude ^{1}H NMR spectrum showing the aromatic region of the Fe(III)Br$_3$ bromination attempt of 2-phenylethanol, with tentative evidence of both *ortho* and *para* splitting. This is, however, unconfirmed.

The synthetic pathway development did not proceed beyond this point, with the final products of **7** and **8** not being synthesised and sulfide **6** still in need of optimisation to form the sulfonium salt before being used in the Corey-Chaykovsky aziridination. The shortcomings and proposed solution as well as future work of this working chapter are addressed in Chapter 5.

3.5. Conclusion

For the first target compound **6**, a synthetic pathway has been optimized. A preliminary study to form the sulfonium salt derivative of **6** was unsuccessful, however, evidence from the literature shows that aromatic sulfides with fused ring structures can form sulfonium salts and ylides which demonstrates that **6** is a viable sulfide for the core-chaykovsky reaction. Further optimisation is needed.

The second target compound **7** was not synthesised. Compounds **13a-b** in the synthetic pathway were not successfully formed from **15a-b**, most likely due to steric hindrance. Several alternative strategies were attempted but were also unsuccessful. New synthetic strategies for synthesising **7** are suggested in Chapter 5.

The third target compound **8** was also not synthesised as the nitration step did not work. It is likely that the phenol group on **6** affects the regioselectivity of the nitro group. Attempts to synthesise **16** was also unsuccessful and this was not commercially available. New synthetic strategies are suggested in Chapter 5.

This chapter yielded the new compounds **9, 10, 14, 15a** and **15b**, which were all fully characterised by NMR and HRMS.

Chapter 4 Pyrrolines for new organocatalysts

4.1. Introduction

The aryl pyrroline products **4** (**Figure 111**) from the aziridination reaction optimised in Chapter 2 provide an opportunity for synthesis of organocatalysts. New, convenient methods of organocatalysis synthesis are constantly being sought. Therefore, having established optimal baseline conditions for the synthesis of aryl pyrrolines **4** through the Corey-Chaykovsky reaction, as was achieved in Chapter 2, this chapter will aim to synthesise new organocatalysts using the aryl pyrrolines **4** as a starting material. The pyrrolines that have been synthesised are 5-membered, *N*-containing heterocycles with an aryl side group with both electron-withdrawing and donating groups possible. The structure bears resemblance to many other organocatalysts seen in the literature, and the double bond can facilitate a range of different functionalities. There are two target classes of compound aimed to be synthesised, as shown in **Figure 111.** The first is a simple pyrroldine, which will only have the aryl side group as a substituent. The second target compound is a pyrrolidiol, which will have the aryl side group and two hydroxys as substituents. These hydroxys could also facilitate further functionalisation in the future. As it is also aimed to facilitate a future catalytic cycle for the Corey-Chaykovsky aziridination reaction, this research could allow in the future a unique organocatalytic synthesis through organocatalysis itself. **Figure 112** shows their possible use in an asymmetric aldol reaction.

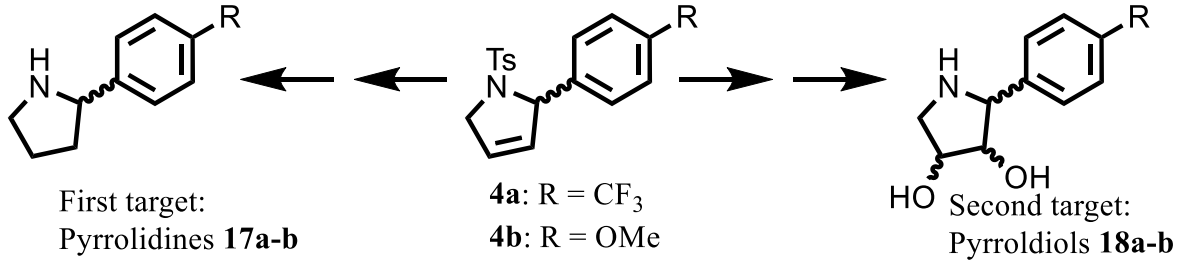


Figure 111: The aryl pyrroline starting materials that will be used to synthesise organocatalyst target compounds 17 and 18

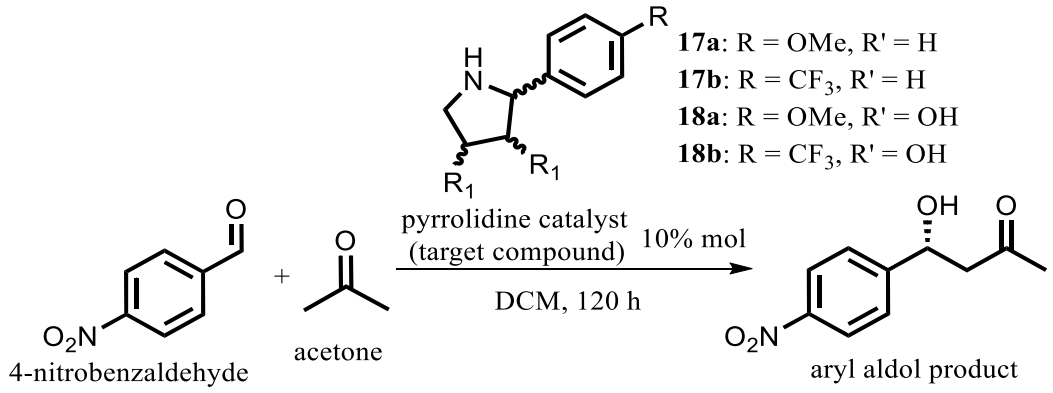


Figure 112: Asymmetric aldol synthesis using the aryl pyrrolidine/pyrrolidiol target compounds

The aims for developing the synthesis of the first target compounds, the pyrrolidines (**17**), are outlined in **Figure 113.** The first step is hydrogenating the aryl pyrroline **4**, which is a racemic mixture, to form **19**. The next step is to optimise a detosylation method to form **17**. The tosyl group is necessary for the pyrroline synthesis, and any attempt to remove it with the double bond in the pyrroline ring present will lead to the stable aromatic pyrrole. Therefore, a method must be developed to remove it after hydrogenation. The last step is resolving the stereoisomers to yield enantiomerically pure pyrrolidine, suitable for use as a catalyst. The stereoisomer resolution could be achieved through a kinetic resolution method, or by including a chiral co-catalyst in the hydrogenated method to induce asymmetry.

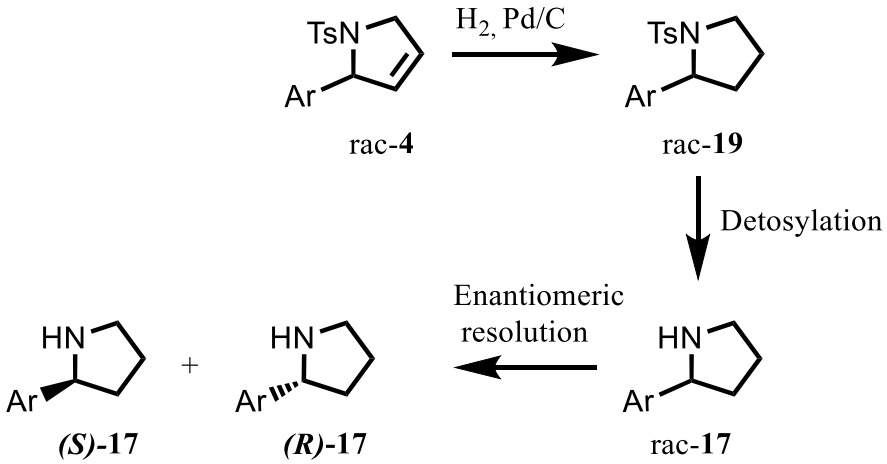


Figure 113: Synthesis plan for compounds 17a-b

The aims for developing the second target compounds, the pyrrolidiol (**18**), is outlined in **Figure 114**. The first step will be developing a method for dihydroxylating the pyrroline ring to form **20**, which in turn will be detosylated to form **18**, followed by enantiomeric resolution. The dihydroxylation step will add to new chiral centres, therefore, the dihydroxylated product will have 8 possible stereoisomers. It will be examined how best to develop the synthesis to obtain an enantiomerically pure pyrrolidiol (**18**) product. This could be achieved by a kinetic resolution reaction or by using an asymmetric dihydroxylation method.

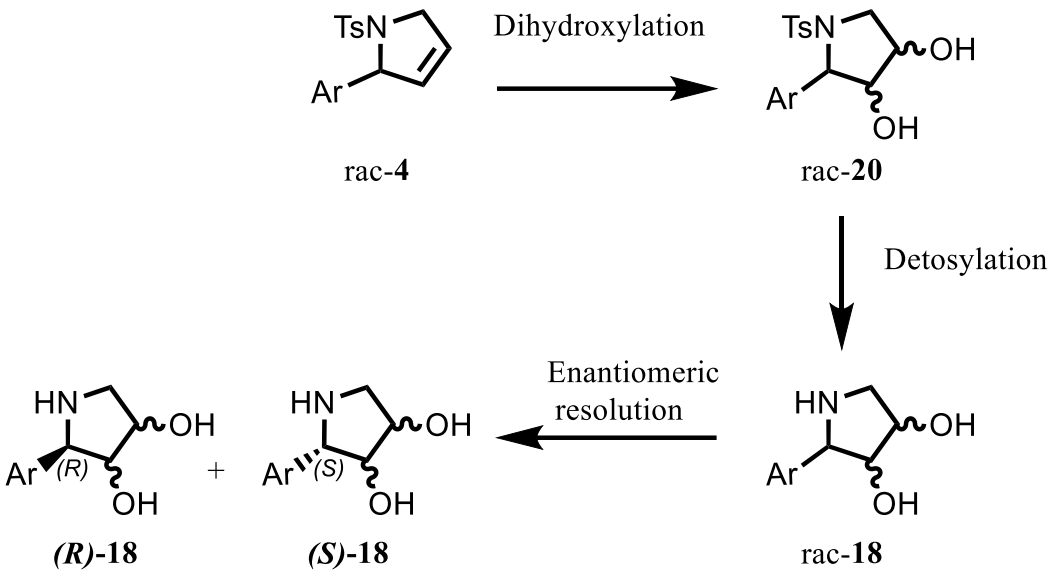


Figure 114: Proposed synthesis plan for compounds 18a-b

A standard dihydroxylation using $KMnO_4$ as an oxidizing agent will lead to 8 stereoisomers of **20**, as outlined in **Figure 115.** However, this could be reduced to 4 stereoisomers if a syn-addition is performed using a Sharpless dihydroxylation, which employs $KOsO_4.2H_2O$ as an oxidizing agent, which ensures a concerted addition to the alkene bond and thus both hydroxy groups add on the same side, as outlined in **Figure 116.** Also, if a Sharpless dihydroxylation method can be optimised, it could be further developed to include a chiral quinine ligand on the osmium to induce a Sharpless asymmetric dihydroxylation that will produce just one stereoisomer of the pyrrolidiol (**20**) product. It thus decided to use the Sharpless method.

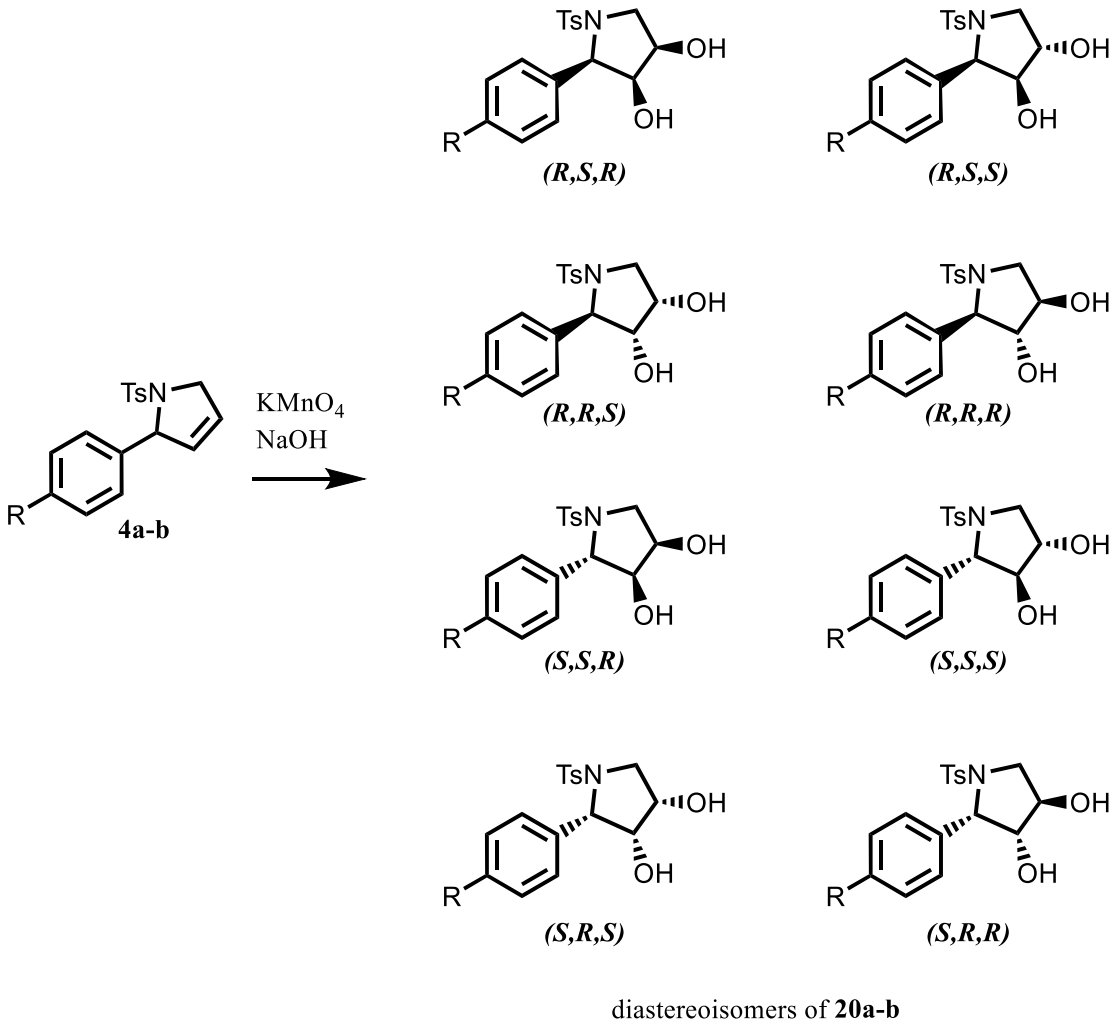


Figure 115: Proposed dihydroxylation of the aryl pyrroline (4) using $KMnO_4$, leading to eight isomers of diol product (20)

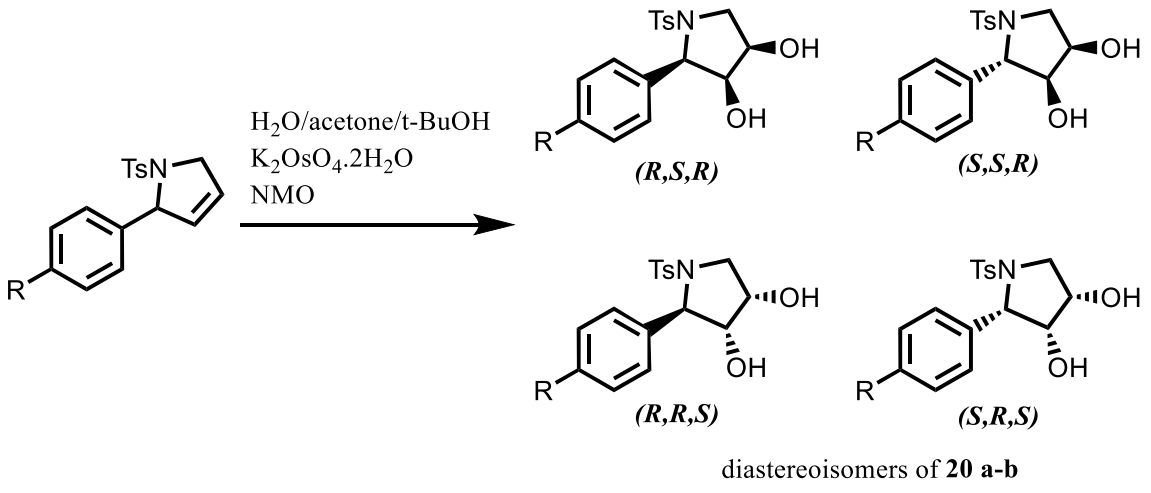


Figure 116: Sharpless dihydroxylation of aryl pyrroline 4 to pyrrolidine diol 20. This method leads to 4 stereoisomer products

If a series of aryl pyrroline-based, enantiomerically-pure organocatalysts can be synthesised, it is aimed to test them in an organocatalytic reaction from the literature (**Figure 112**).

4.2. Development of synthetic pathway for aryl pyrroline based organocatalysts

4.2.1. First target compound; tosyl-protected aryl pyrrolidines (**19**)

The first aryl pyrroline derivative to be synthesised was the pyrroldine (**19**), where the alkene bond on the pyrroline ring was converted to a single bond using a non-asymmetric hydrogenation with palladium on carbon at atmospheric pressure, based on a method from the literature.[127] Both the *R* and *S* stereoisomers of the racemic starting material, **4**, should be equally hydrogenated (**Figure 117**) An optimisation of the reaction conditions was carried out.

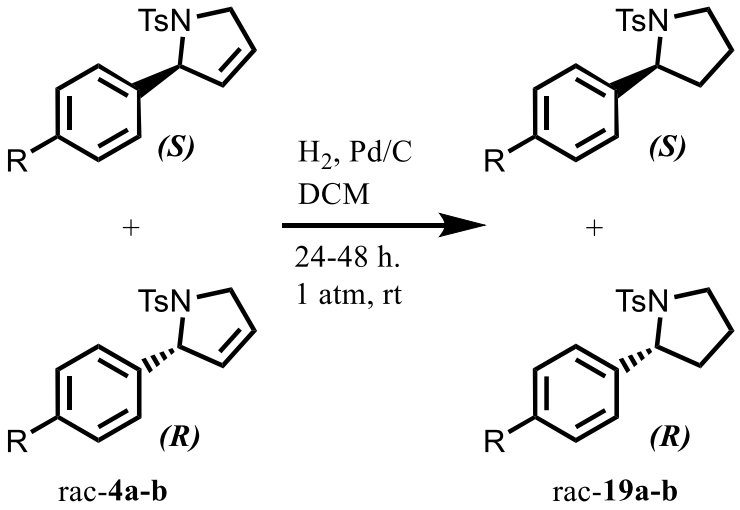
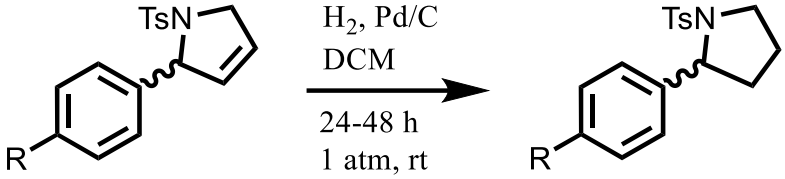


Figure 117: Hydrogenation of aryl pyrroline 4 to pyrrolidine 19

The initial method studied was a room temperature and pressure, hydrogenation with the results given in **Table 29.** Reactions were carried out at various scales with a standard work-up of filtering through a celite plug, mixing with charcoal before filtering through a celite plug again and rotary evaporation. **19a** and **19b** were fully characterised by ^{1}H, ^{13}C, COSY, DEPT and HSQC NMR and **19b** was also characterised by HRMS. **19a** and **19b**, however, are not new and have been reported in the literature,[158] and the NMR spectra for both were compared for confirmation. has been reported in the literature and its spectra was also compared for confirmation [159] ^{1}H NMR spectrum for **19a** is given in below as an example (**Figure 118**), the rest of the spectra for **19a** and **19b** are given in the Appendix.

Table 29: Hydrogenation of aryl pyrrolines study



4a-b **19a-b**

Entry	R	Product	Time (h.)	% Yield
1	CF_3	**19a**	48	78
2	OMe	**19b**	48	71
3	OMe	**19b**	24	0

Reactions were performed at various mmol scale with a standard work-up of filtering reaction through a celite plug, washing with water and extraction with EtOAc. See Experimental Methods for further details.

The results of the study showed very good yields for both the aryl pyrrolines being studied (entry 1 and 2), and no further purification was necessary beyond the work-up. Performing a shortened time of 24 hours (entry 3) was tried once but resulted in an incomplete reaction, based on the crude ^{1}H NMR spectrum where a mixture of both the product and starting material was found to be present. With the reaction conditions for the hydrogenation decided upon, these hydrogenated pyrrolines **19** can now be studied for detosylation to form **17**.

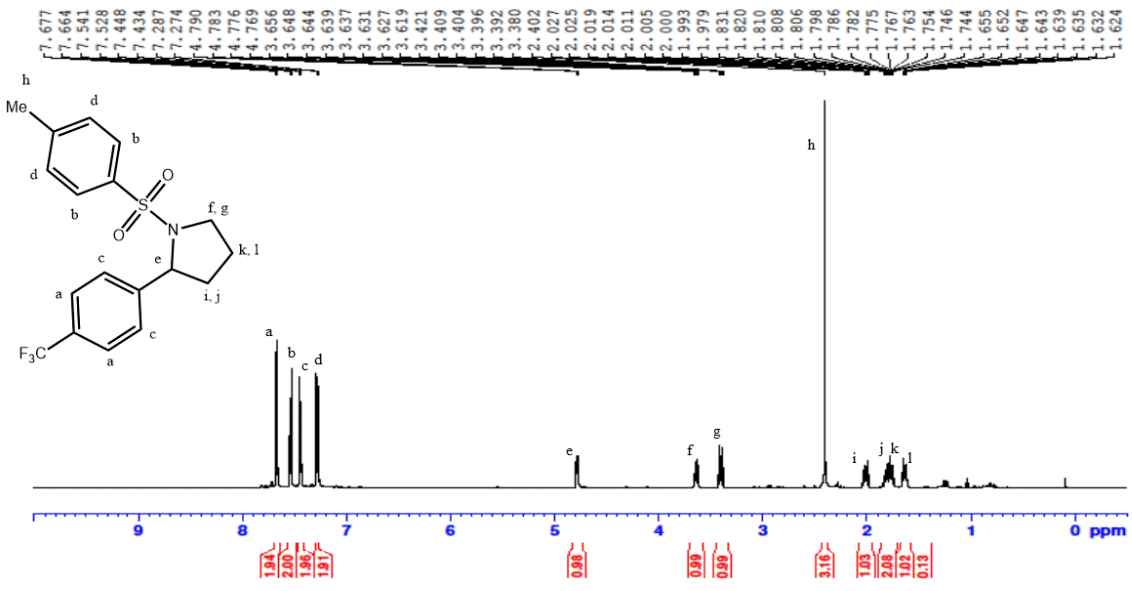


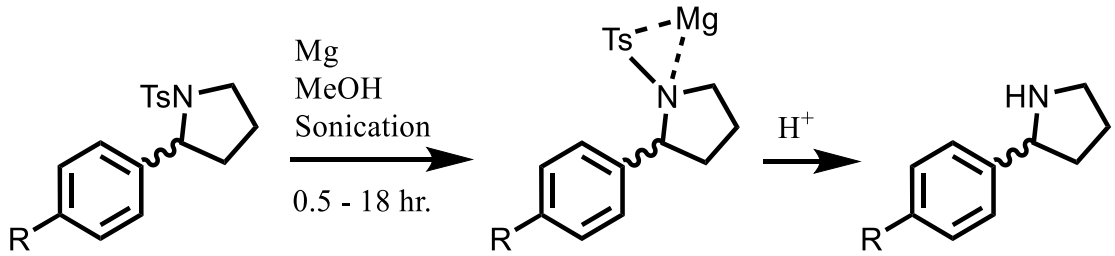
Figure 118: ^{1}H NMR spectrum of 19a

4.2.1.1. First target compound; aryl pyrrolidines (**17**) via detosylation of **19a-b**

The nitrogen group on both the aryl pyrroline **4** and vinylaziridines **3** is protected with a toluenesulfonyl (tosyl) group. The tosyl group provides activation of the nitrogen for the aziridination reaction and protects the imine starting material from unwanted side reactions in the aziridination process. However, this protecting group must be removed from the aryl pyrroline to allow for the formation of the enamine or imium activation modes in the organocatalytic reactions.

The first study performed for the detosylation of the saturated pyrrolidine ring was using a method found in the literature[158] and previously used for detosylating nitrogen atoms in unsaturated heterocycles. The method involves dissolving the pyrrolidine in methanol and adding magnesium powder. The solution is then subjected to sonication. The proposed mechanism of the method is that the sonication helps break up the magnesium powder and allows it to coordinate with both the nitrogen atom on the pyrrolidine ring and the oxygen atom attached to the sulfur on the tosylate protecting group. This coordination weakens the *N*-Ts bond which can then be cleaved with H^+ cations provided by acidic addition (in this case HCl) to leave an unprotected NH on the pyrrolidine ring and TsCl. Results of the study are given in Table 30 below.

Table 30: Detosylation study using Mg/MeOH with sonication method



19a-b **17a-b**

Entry	R	Solvent	Time (h)	Mg	% Yield
1	CF_3	MeOH	1	Powdered	0
2	CF_3	Dry MeOH	18	Powdered + Turnings	0
3	OMe	MeOH	1	Powdered	0
4	OMe	Dry MeOH	1	Powdered	0
5	OMe	Dry MeOH	18	Powdered + Turnings	0

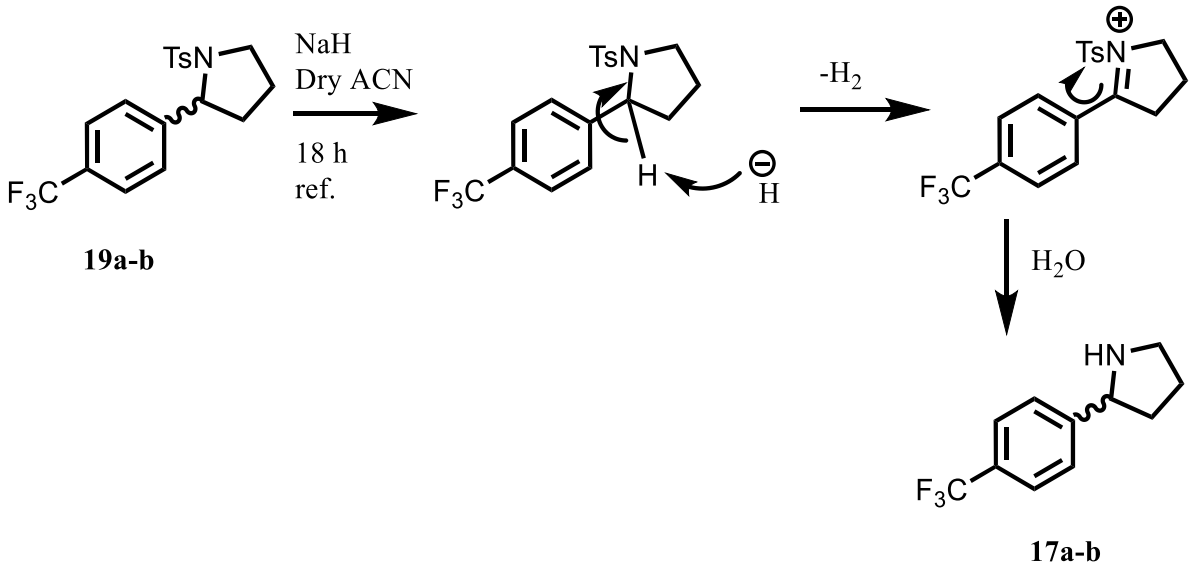
All reactions were performed at a 0.1 mmol scale with a sonicator bath in MeOH (both dry and bench) followed by a standard work-up of quenching reaction in 1M HCl and extraction with EtOAc. See Experimental Methods for further details.

The study was run with the 4-CF_3 and 4-OMe pyrrolidines (**19a** and **19b**, respectively). In entry 1 and 3 from **Table 30** bench methanol was used. In both these cases there was no evidence of detosylation in the crude ^{1}H NMR spectra. It was concluded from these results that dry MeOH should be used as the magnesium would have more affinity to coordinate

with water. Entry 4 used the 4-OMe pyrrolidine (**19b**) with magnesium in dry MeOH, and the crude ^{1}H NMR spectrum suggested a small amount of detosylated product, but this was not confirmed. It was theorised that the process may need more time so the same reaction was run over night. Also, some fresh magnesium turnings were added with the powdered magnesium to see if this impacted the reaction. These conditions are seen in Entry 5 which showed nearly identical results. These conditions were replicated in Entry 2 with the 4-CF_3 pyrroline (**19a**) and showed no evidence of detosylation. It was clear from this study that the magnesium coordination is hard to achieve. Perhaps more intense sonications are needed to adequately break up the magnesium, such as with a High-Performance Ultra Sonicator, which was not available. The reaction is also very sensitive to water and magnesium used in the lab may have been slightly oxidised which would significantly interfere with the reaction. It was decided to explore alternative methods for detosylation due to the poor results of this study.

Another method studied was refluxing **19a** in NaH. This method had been detailed in the literature for the detosylation of functionalised indoles,[160] and requires the rearrangement of the indole's double bond. While these pyrrolidines do not have a double bond, it was theorised that the acidic proton alpha to the nitrogen next to the phenyl ring could be cleaved by a hydride anion (reaction mechanism in **Table 31**). This had been previously observed in Chapter 2 when the electronic withdrawing influence of the CF_3 group led to the rearrangement of the 4-CF_3 pyrroline (**4a**) to the pyrrole (**5a**), removing the tosyl group in the process. It was theorised that after the removal of the acidic alpha proton, a double bond and thus a positive charge would form on the nitrogen, which should be able to cleave the tosyl group in aqueous conditions. A brief study is shown with the proposed mechanism in **Table 31** below.

Table 31: Detsolyaltion study with NaH method



19a-b

17a-b

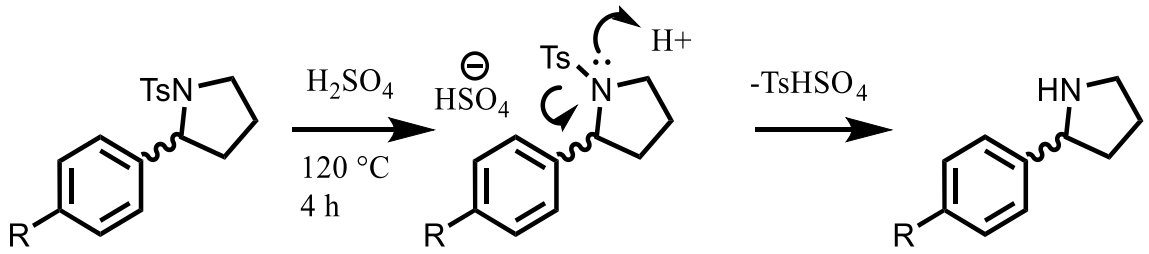
Entry	Time (h)	% Yield
1	4	0
2	18	0

All reactions were performed at a 0.1 mmol scale with a standard work-up of quenching with water, neutralisation with 1 M HCl, extraction with EtOAc and washing with water and brine. See Experimental Methods for further details.

The reaction was performed for 4 hours, with no conversion seen in the ^{1}H NMR spectrum (entry 1) and again at 18 hours (entry 2) with the same results. These results show that with the absence of a double bond in the pyrrolidine ring the alpha proton cannot be cleaved with the subsequent rearrangement taking place.

The next method studied is the most common method seen in the literature for detosylation of amines,[161] using a strong acid. The large presence of H^+ cations in the strong acidic conditions is enough for the stabilised nitrogen to be able to donate its' lone pair to the proton. This action subsequently promotes the cleaving of the tosylate group which forms a salt with the acid's anion (in this case, HSO_4^-). The study used H_2SO_4, being the strongest acid available in the lab. It should be noted that in the literature this reaction is often performed with HBr. This acid was not available in the lab is very unsafe so it was not desired to purchase. The results of the study are shown in Table 32 below. The study used both the 4-CF_3 and 4-OMe pyrrolidine (**19a** and **19b**, respectively). The reaction conditions involved refluxing the relevant pyrrolidine in sulphuric acid for 4 hours before a work-up of neutralisation and extraction.

Table 32: Detosylation study with H_2SO_4 method



19a-b **17a-b**

Entry	R	% Yield
1	CF_3	0
2	OMe	0

All reactions were performed at a 0.1 mmol scale with a standard work up of quenching with ice-cold water, neutralisation with saturated $NaHCO_3$ solution and extraction with EtOAc. See Experimental Methods for further details.

Disappointingly, neither experiment resulted in detosylation of **19a-b** to form **17a-b**. The study appears to show that, in this case, the highly stabilised tosylated nitrogen is not able to donate its' pair of electrons to the proton even under very strong acidic conditions. Use of HBr may work due to being an even stronger acid, but it was decided to avoid this compound before alternative methods were studied.

The next method studied employed an interesting technique involving low-valence titanium (LVT). LVT can be defined as titanium with an oxidation state less than +4, with +3 being the most common and lower states such as +2, +1 and 0 rarer. LVTs have a strong affinity to accept pairs of electrons owing to its' empty d orbitals. Electron rich environments, such

as on sulfonamide protected amines are ideal candidates for reaction with LVTs. Shohji *et al*. reported on an interesting study using LVTs to cleave nitrogen and oxygen from sulfonyl groups, having best success with aromatic sulfonamides, for which tosyl groups belong.[162] The author had previously reported on using LVTs for cleaving allyl and propargyl from oxygen in alcohol and ether compounds. Normally, LVTs are generated by inorganic reagents in a heterogenous mixture such as by mixing $TiCl_4$ in zinc or lithium. Interestingly, however, it was reported that instead the LVTs were produced by a cleaner and more convenient, mainly homogeneous mixture of titanium isopropoxide, trimethylsilyl chloride and powdered magnesium. The mechanism by which the LVTs are produced using these reagents isn't certain but theorised and is outlined in **Figure 119.** The titanium complex reacts with a chloride anion from the trimethylsilyl chloride molecule to form a new complex featuring the chloride, which can now be reduced by the magnesium to form a lower valence titanium, most likely Ti(III). This process can be iterated to generate even lower valance titanium species (Ti(II), Ti(I), Ti(O)). The sulfonanyl group thus binds to the very reactive LVT species which has a high affinity for electrons, and thus the deprotection step is complete. It is probable that remaining trimethylsilyl groups add to the nitrogen after the cleaving of the sulfonyl group.

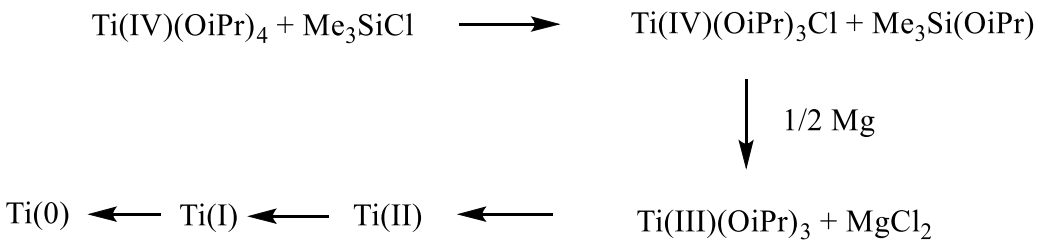
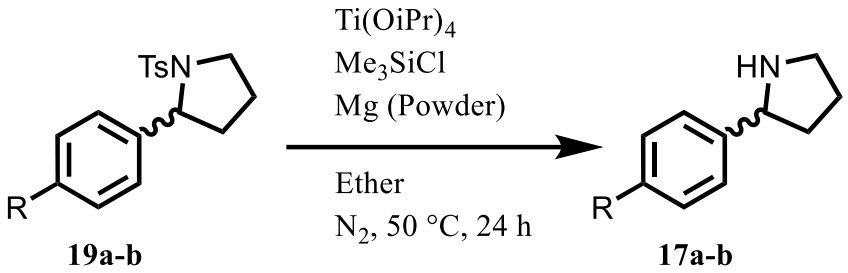


Figure 119: Theorised low valence titanium (LVT) generation mechanism

The silyl group is then removed in the work-up by mixing with fluoride anions provided by KF. Due to titanium's high affinity for oxygen, the reaction must be performed under very dry and inert conditions and with a suitable coordinating solvent such as diethyl ether or tetrahydrofuran. A study of this process on both the pyrrolidines **19a** (CF_3) and **19b** (OMe) as well as the results are given in **Table 33** below. Note that confirmation of the product formation was by ^{1}H NMR spectroscopy and comparison to the literature for product **17a** and **17b.**[163]

Table 33: Study of detosylation of 19 with $Ti(OiPr)_4$ method



19a-b **17a-b**

Entry	R	$Ti(OiPr)_4$ eq.	Solvent	% CrudeYield
1	CF_3	1.0	Dry THF	38
2	OMe	1.0	Dry THF	51
3	CF_3	1.2	Dry THF	34
4	OMe	1.2	Dry THF	41
5	CF_3	1.0	Et_2O	0
6	OMe	1.0	Et_2O	0

Reactions were performed at various mmol scale with a standard work up of adding 3 M NaOH solution, Et_2O, celite and KF to the reaction mixture before stirring, then filtering through a celite plug before addition of more 3 M NaOH solution and extraction with EtOAc and washing with 3 M NaOH solution, water and brine and drying over $MgSO_4$ and rotary evaporated See Experimental Methods for further details.

Entry 1 and entry 2 shows the results from the 4-CF_3 and 4-OMe pyrrolidines (**19a** and **19b**, respectively). Both led the desired detosylated product according to the crude ^{1}H NMR spectra and comparison to the same compound from the literature.[163] However, significant impurities remain and purification attempts with column chromatography and recrystallisation did not adequately purify, therefore the reported yields in **Table 33** are crude yields. The crude ^{1}H NMR spectras for **16a** (**Figure 120**) and **16b** (**Figure 121**) are given below. The conclusion of this study is that while the detosylation was successful, a more extensive study is needed to optimise purity. It is likely the presence of leftover tosylate and methylsilyl groups as well as side reactions from the $Ti(OiPr)_4$ render purification difficult.

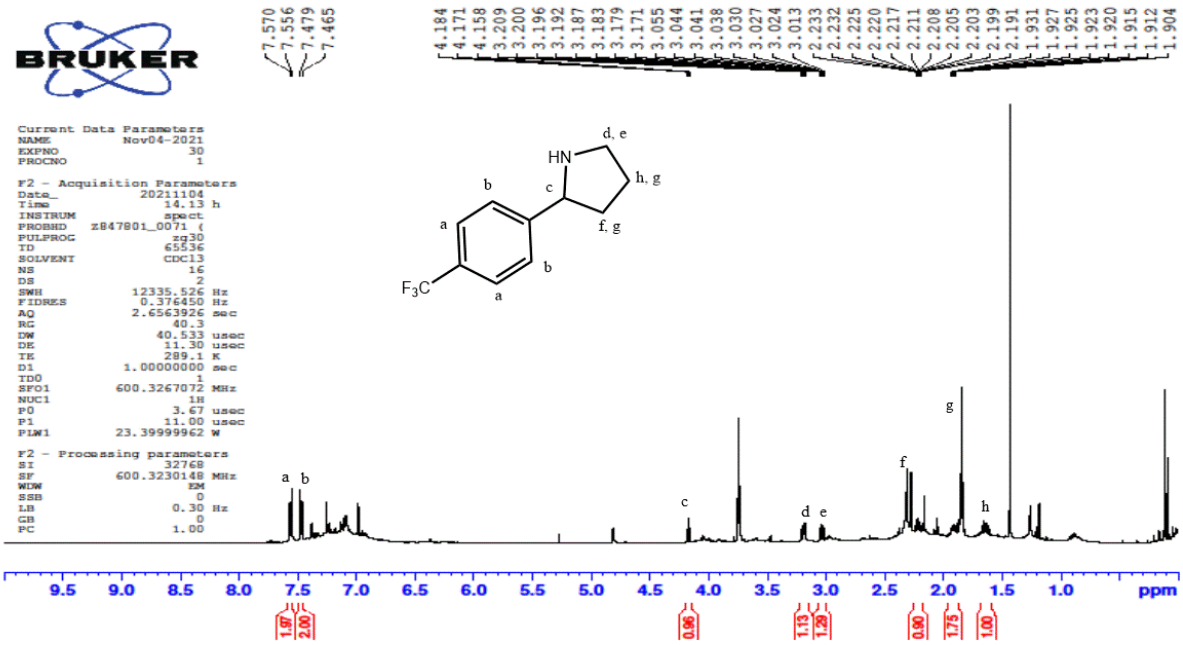


Figure 120: Crude ^{1}H NMR spectrum for the synthesis of 17a

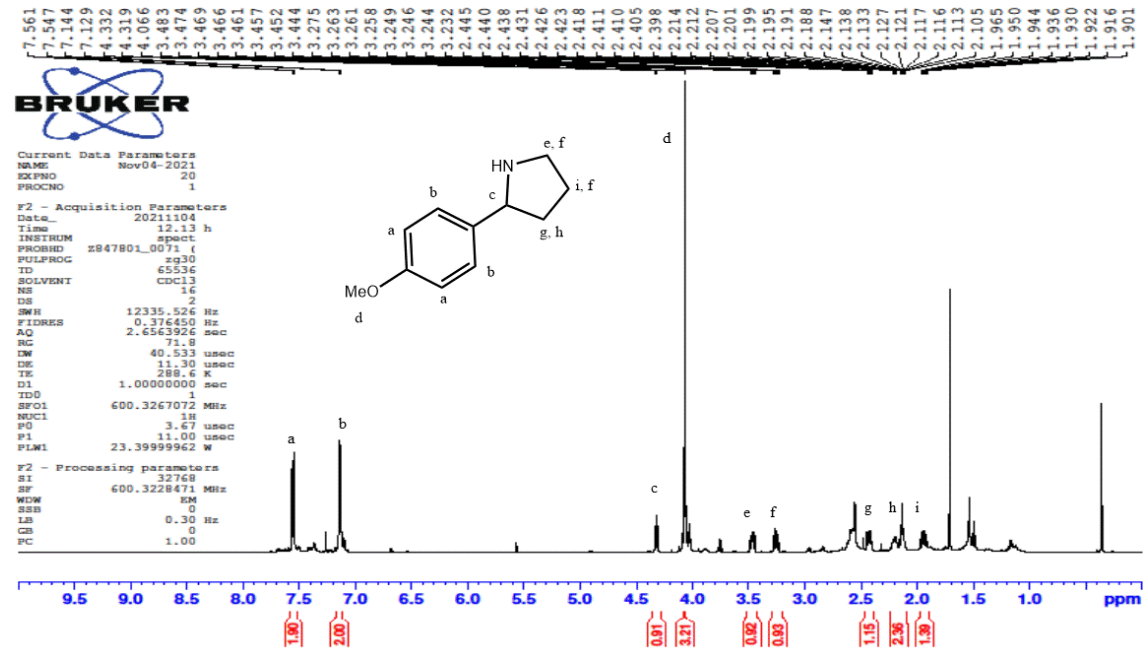


Figure 121: Crude ^{1}H NMR spectrum for the synthesis of 17b

4.2.2. Attempted separation of pyrrolidine **17a** and **17b** enantiomers by using D-alanine through kinetic resolution

With the pyrrolidine detosylated (**17a** and **17b**) in crude form, it was decided to perform a brief preliminary study on separation of the enantiomers of **17a** and **17b** by kinetic resolution to facilitate the future synthesis of enantiomerically pure **17**. While using an asymmetric hydrogenation method for the synthesis of **17** was planned, it was decided to investigate a kinetic resolution method. The secondary amine group (NH) on the pyrroline ring is potentially a good binding site for a chiral resolving agent. The amine's basic nature means an acidic group should be chosen to bind. D-Alanine was used to study how it can bind to the aryl pyrrolines, both the-CF_4 and 4-OMe (**17a** and **17b**, respectively), based on a method in the literature,[164] where the chiral amino acid forms an ionic bond with one enantiomer of the pyrrolidine, but not the other. Initial attempts using this method were unsuccessful, with no evidence from NMRs or TLCs of the amino acid binding. The addition of a small amount of HCl, in order to protonate the amine group was also tried to no success. It was postulated that the coupling of the D-alanine with itself (the carboxylic acid group binding to the NH_2) may be more favourable than binding to the pyrrolines NH group. To solve this problem, *tert*-butyloxycarbonyl protected (BOC-protected) D-Alanine was used instead but it was very unclear from NMRs and TLCs if binding occurred. A much more extensive study with larger amount of pyrroline, and different Boc-protected chiral amino acid will need to be carried out in future work. This method notably does not use a coupling agent. Inclusion of a coupling agent may also a covalent amide bond linkage, instead of forming a salt. Many coupling exist in the literature. A convenient method from the literature for coupling of secondary amines with a carboxylic acid uses a tris(2,2,2-trifluoroethyl) borate coupling agent and could be tried for this kinetic resolution reaction.[165] Also, using one of many other chiral acids for amide coupling along with a coupling agent would have been a better strategy.

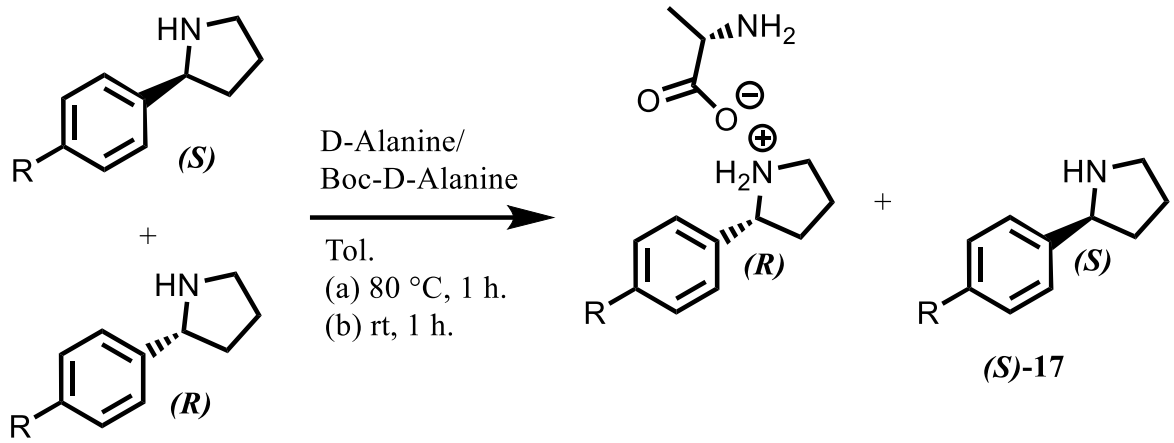


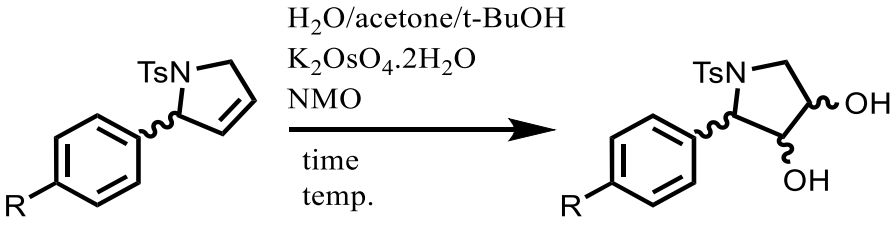
Figure 122: Proposed use of D-alanine for separating the enantiomers of the pyrroline

4.2.3. Second target compound; tosyl-protected pyrrilidiol (**20**)

The second aryl pyrroline derivative to be synthesised was the pyrroldiol (**15**). While several methods exist in the literature of the conversion of an alkene to a dihydoxylated form, it was decided to employ a Sharpless dihydroxylation reaction, as discussed in this chapter's introduction using the $K_2OsO_4.2H_2O$.[166] This reaction has the advantage of adding the hydroxy groups in syn addition, therefore cutting the number of stereoisomer products to four, rather than eight when using a standard oxidation method. This method, as shown in **Figure 116**, will be optimised first and if successful then the Sharpless asymmetric dihydroxylation, using a chiral quinine co-catalyst will be attempted to try and produce a single stereoisomer.

An optimisation study on both the aryl pyrrolines is shown below in **Table 34** below. The study focused on reaction temperature and time. The amount of osmium reagent was not studied (due to its' expense and toxicity) and thus the *N*-methylmorpholine-*N*-oxide (NMO) was also kept at a constant 3.0 eq. Results are given in **Table 34**. **20a** and **20b** are new and were characterised by ^1H, ^{13}C, COSY, DEPT and HSQC NMR and HRMS. The ^1H NMR of **20b** is given below as an example. The remaining spectra for **20a** and **20b** are contained in the Appendix.

Table 34: Dihydroxylation study on aryl pyrrolines 4a-b



4a-b **20a-b**

Entry	R	Product	Time (h.)	Temp. (°C)	% Yield
1	CF_3	**20a**	18	rt	0
2	OMe	**20b**	18	rt	0
3	CF_3	**20a**	48	rt	41
4	OMe	**20b**	48	rt	44
5	CF_3	**20a**	48	50	57
6	OMe	**20b**	48	50	46

Reactions were carried out at various mmol scales with a standard work-up of quenching the reaction miture with saturated $NaHSO_3$ solution, before extraction with EtOAc and washing with saturated $NaHSO_3$ solution, water and brine, drying over $MgSO_4$ and rotary evaporation. See Experimental Methods for further details.

The initial reactions of both aryl pyrrolines (**4a-b**) were performed overnight at room temperature (entry 1 and 2) and ^1H NMR analysis of the crude material showed what appeared to be the product with impurities present, however the product could not be

purified. By extending the reaction time to 48 hours (entries 3 and 4) a higher purity product was produced. Yields were increased for the **20a** when temperature was increased to 50 °C (entry 5). Yields were similar for the **20b** pyrroline at 50 °C (entry 6) compared to room temperature. The solvent mixture was also kept constant during the study. The solvent mixture used included water, mixed with acetone and t-butyl alcohol (ratio 12:5:4, respectively) which ensures the dissolution of both the osmium reagent and the pyrroline starting material. With the optimal conditions found it was now necessary to focus on developing a method for the removal of the tosyl protection groups from the 124ehydroxylated pyrrolines to form target compounds **18**. If developed then these optimised conditions can be applied to a Sharpless asymmetric dihydroxylation to obtain pure stereoisomers in future work.

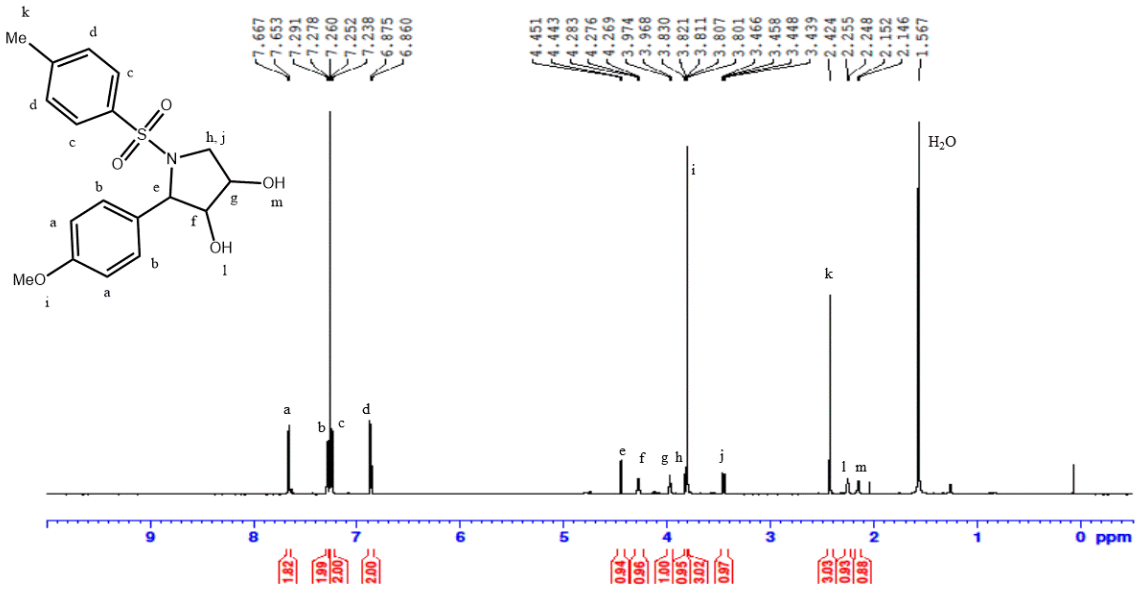
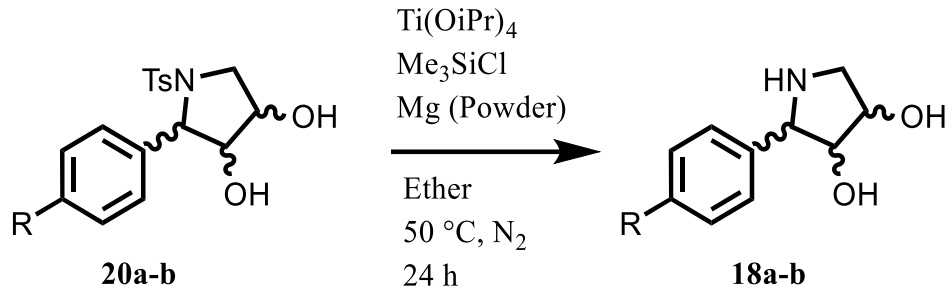


Figure 123: [1] H NMR spectrum of 20a

Several detosylation methods were studied previously on **19a-b** and the successful method was using low-valence titanium (LVT). This method was attempted on the pyrroldiols **20**, with the results of the study given in **Table 35** below.

Table 35: Detosylation study of 20 with $Ti(OiPr)_4$ method



20a-b **18a-b**

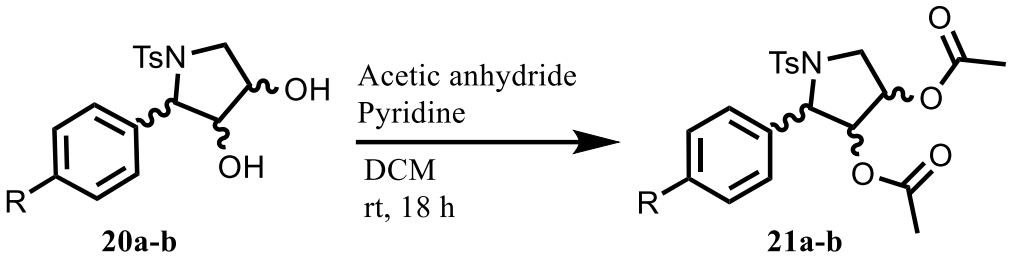
Entry	R	R_1	Product	$Ti(OiPr)_4$ eq.	Solvent	%Yield
5	CF_3	OH	**18a**	1.0	Dry THF	0
6	OMe	OH	**18b**	1.0	Dry THF	0

Reactions were performed at various mmol scale with a standard work up of adding 3 M NaOH solution, Et_2O, celite and KF to the reaction mixture before stirring, then filtering through a celite plug before addition of more 3 M NaOH solution and extraction with EtOAc and washing with 3M NaOH solution, water and brine and drying over $MgSO_4$ and rotary evaporated. See Experimental Methods for synthesis of **17** for further details

Unfortunately, the method produced no yield of the detosylated product. This would suggest that the two hydroxyl groups on the pyrrolidine ring interact with the titanium and its' low valence form more favourably than with the tosyl group. This was not entirely unexpected as titanium has a strong affinity for oxygen.

It was therefore concluded that in order to detosylate the pyrrolidiols (**20a-b**), the OH groups would have to be protected first. A convenient method for this would be addition of an acyl group to the hydroxys using acetic anhydride and a suitable base. This was for both the 4-OMe and 4-CF_3 dihydroxylated pyrrolidines (**20a** and **20b**, respectively) with results given in **Table 36** below. **21a** and **21b** are new and were characterised by ^1H, ^{13}C, COSY, DEPT and HSQC NMR and HRMS. The ^1H NMR of **21b** is given below as an example, and the remaining spectras for **21a** and **21b** are contained in the Appendix.

Table 36: Acylation of dihydroxylated pyrrolidines 20



20a-b **21a-b**

Entry	R	% Yield
1	CF_3	77
2	OMe	80

Reactions were performed at various mmol scale with a standard work up of mixing the reaction mixture with 2 M HCl solution and stirring, before extraction with EtOAc and washing with saturated $NaHCO_3$ solution, water and brine and drying over $MgSO_4$ and rotary evaporated See Experimental Methods for further details.

The method used for the acylation from the literature[167] ses pyridine as a base with acetic anhydride in 2.5 equivalence and DCM as solvent. The reaction proceeded smoothly with yields for both dihydroxylated pyrrolidines ranging from 77-80%. Interestingly, the results of these reactions show that the electron-withdrawing or donating effects of the phenyl group on both pyrrolidines has no effect on the acylation process.

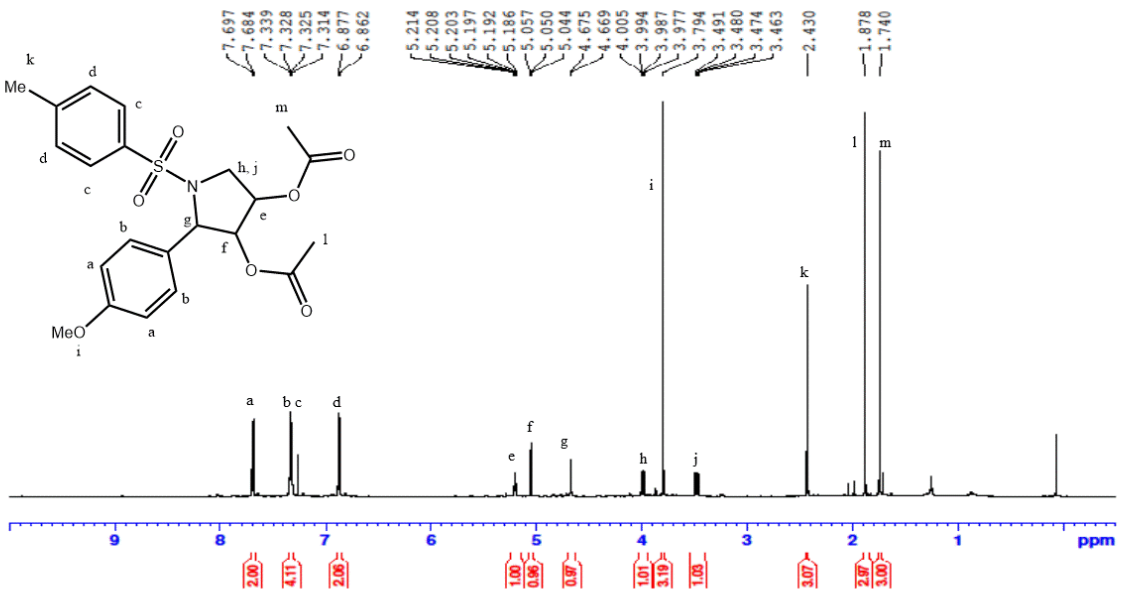


Figure 124: ^{1}H NMR spectrum of 21b

Another method possible for protecting the hydroxy groups is an acetalation reaction, which would bind the two hydroxy groups would be formation of a ketal (**Figure 125**). Attempts at this reaction, using a method from the literature,[168] at room temperature and at reflux were unsuccessful. A more extensive study would be needed, but seeing as the

acylation reaction worked for protecting the hydroxy groups this method was put aside but may be considered in future work.

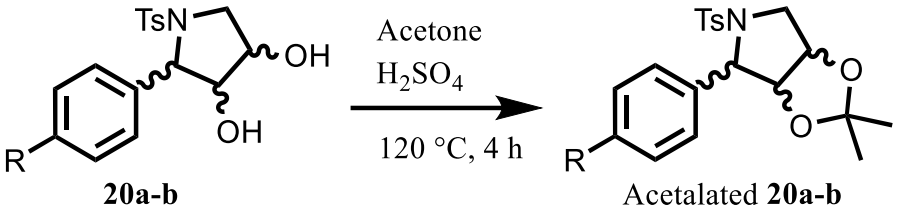


Figure 125: Proposed acetalation of 20a-b

Now that the dihydroxylated pyrrolidines have been acylated (**21a** and **21b**), the LVT detosylation method was tried (**Figure 126**). Unfortunately, the reaction did not work. The ^{1}H NMR spectra appeared to show a removal of the tosylate group, but also the acyl group (though this was not confirmed), which is consistent with the mechanistic action of titanium isopropoxide. The crude mixture contained many impurities, however, and was extremely difficult to purify. This was true for both **21a** and **21b**. It was thus decided to leave aside the dihydroxylated pyrrolidines for now and the dihydroxylated pyrrolidines (**20**) can be returned to in future work.

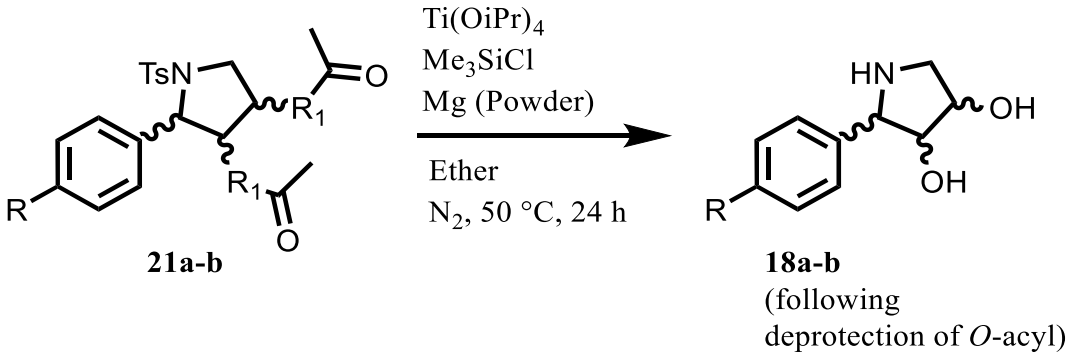


Figure 126: Attempted detosylation of 21a and 21b. Note that the product formed is theorised and not confirmed due to heavy impurities and no purification

4.3. Conclusion

For the first target compound, the tosyl-protected precursors **19a-b** were synthesised by an optimised hydrogenation method from **4a-b**. Enantiomerically pure samples of **19a-b** were not made, but the hydrogenation method developed is adaptable to asymmetric synthesis by the inclusion of a chiral co-catalyst, which is further discussed with literature evidence in Chapter 5. A detosylation study of **19a-b** was carried out, with the only successful method being the use of titanium (IV) isopropoxide to form crude samples of **17a-b**. Further optimisation of the detosylation is needed to improve yields, reliability and purity.

For the second target compound, a Sharpless dihydroxylation method for synthesising **20a-b** from **4a-b** has been optimised. Enantiomerically pure samples of **20a-b** were not made, but the dihydroxylation method developed is adaptable to asymmetric synthesis by the inclusion of a chiral co-catalyst (Sharpless asymmetric dihydroxylation). This is discussed

further in Chapter 5. Attempts at detosylating **20a-b** using the same method for synthesising **17a-b** were unsuccessful. Acylated derivatives **21a-b** were also synthesised, but detosylation was also unsuccessful.

This chapter has demonstrated the viability of using **4a-b** to synthesise potential pyrrolidine catalysts, but further work is required to obtain enantiomerically pure, detosylated product.

This chapter yielded the new compounds **20a-b** and **21a-b**, which were fully characterised by NMR and HRMS.

Chapter 5 Future work

5.1. Introduction

This chapter will outline what further work could be done on the assuming the research project is to continue. There are three sections, each dedicated to each working chapter and addresses what further experiments can be performed, and how shortcomings in the aims may be addressed. Future work is based on work from the lab as well as extensive research in the literature.

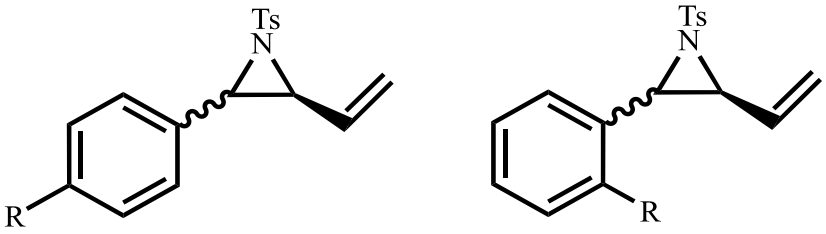
While many of the aims of Chapter 2 were achieved it will be looked at here what further aziridines can be synthesised and what further aspects the reaction studied can be examined.

Chapter 3 proved challenging. It will be proposed alternative pathways towards synthesising sulfide derivatives **7** and **8** as well as how to separate enantiomers of **7**, and how a catalytic Corey-Chaykovsky reaction may be developed if these sulfides can be made.

For Chapter 4, it will be suggested as how best to achieve enantiomerically pure pyrrolidines as well as how new derivatives of aryl pyrroline **4** could be synthesised and used as organocatalysts.

5.2. Future work for investigation of the Corey-Chaykovsky aziridination reaction (Chapter 2)

Future work with the aziridines can look at broadening the scope of the aryl vinylaziridines (**3**) to incorporate different side groups. For this research the focus remained with the highly electron withdrawing CF_3 substituent (**3a**) and electron donating OMe substituent (**3b**) in the para position on the phenyl ring, but other groups, based on imines that were synthesised. It can also be further studied (**Figure 127**). The para substituted phenyl groups were used to narrow the focus of the study to the electronics, but ortho substituted aziridines can be synthesised too, which would add sterics as an obstacle in the aziridination process (**Figure 127**). Asymmetric aziridine synthesis, an original goal of the research, can only be tried when chiral sulfides are synthesised. This process required more work (see sulfides in future work).



3 R = Cl, Me, H, NO_2, $C(O)OCH_3$, CN

Figure 127: Future vinylaziridines (3) to synthesise

Also, as previously mentioned, the effect the sulfonium salt counteranion has on the 1,4-dipolar intermediate and the cis/trans selectivity of the aziridines should be further investigated. It was also mentioned that the vinylaziridine to pyrroline rearrangement needs to be investigated further, as well as the more likely reaction pathway where **4** forms directly from the 1,4 dipolar intermediate. It was theorised, with precedent from the literature,[143] that the organic base's conjugate acid may play a hydrogen bonding mediating role.

The research also focused solely on the allylic donor group on the sulfonium ylides. This led to the formation of the useful vinylaziridines **3** as well as the pyrrolines **4**, but other organobromide groups can be added to the sulfonium ylide, examples given below in **Figure 128** (**A126-129**) which can be used to make ylides and thus aziridines with tert-butyl and aryl side groups.

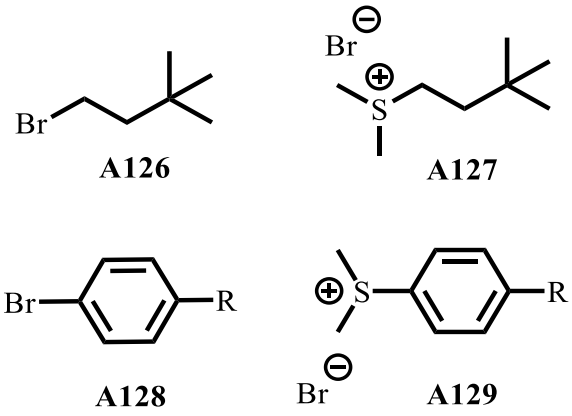


Figure 128: Potential organobromides A126, A127, A128 and A129 to use for the preparation of sulfonium ylides

As had been discussed in the literature review, there are many uses for aziridines, and asymmetric aziridines can be used as synthons for making chiral amino acids and other biologically active molecules.

One of the most interesting potential uses for the synthesised aziridines is polymerisation, with the ring strain of the molecule making this a convenient process. Polymerisation of tosyl protected aziridines was reported recently by Zhou *et al.* using an organocatalyst instead of metal regents giving good control of molecular weights of up to 83 kg/mol and a molecular weight distribution of D = 1.10-1.16.[75] A range of *N*-heterocyclic olefins, such as the example given in **Figure 129**. This method could be used for the vinylaziridines

synthesised in this research to make polyethylenimines (PEIs) through an organocatalytic methods. A metal-, solvent- and catalyst-free method of polymerisation of aziridines was recently reported by Li *et al.* and this method could also be used. [124]

A85

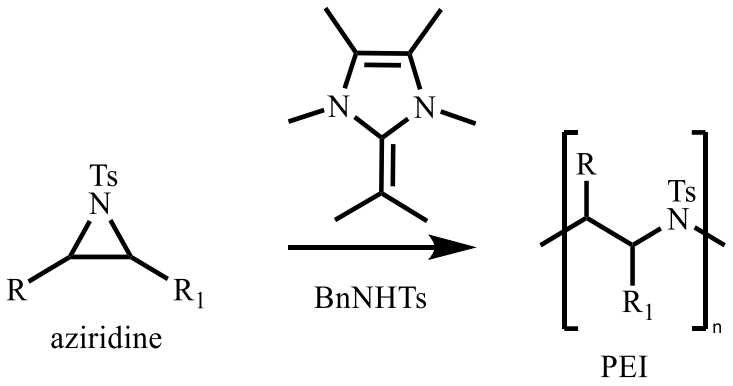


Figure 129: Organocatalyzed polymerisation of tosyl protected aziridines

5.3. Future work for synthetic pathway development for next-generation sulfur catalysts (Chapter 3)

One of the biggest challenges of Chapter 3 has been the failure to substitute the hydroxy group for phenyl sulfide on **15a-b** to form **13a-b**. Hydroxy groups are poor leaving groups and secondary alcohols with the R group are further stabilised. A potential new method to try would be the used of boron trifluoride etherate. This reagent is often used to promote hydroxys as leaving groups, as the empty orbital in the boron can accept the lone pair on the oxygen of the alcohol and allow the hydroxy to leave, leaving a carbocation which can then undergo nucleophilic attack with an appropriate nucleophile. This reagent has been used in the literature for highly stable tertiary alcohols,[169] using methanol as a solvent with the appropriate nucleophile. For this proposed reaction (**Figure 130**) either diphenyl disulfide or sodium thiophenolate could be used as a nucleophile, although diphenyl disulfide may need the additive $(t\text{-}Bu)_3P$ to break the disulfide bond.

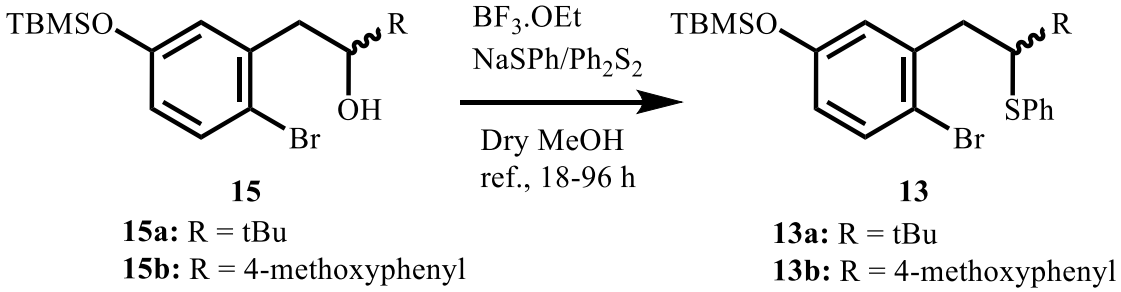


Figure 130: Proposed nucleophilic substitution reaction of the secondary alcohols 15a-b using BF_3.OEt

Another alternative method to synthesising the sulfides with an R-substituent in the alpha position (**7**) would be to oxidise the sulfur on the completed, ring closed unsubstituted

sulfide **6** to form a sulfone and/or sulfoxide. From here, a reaction can be tried due to the strong electron withdrawing effect of the oxidised sulfur, which will render the protons on the alpha carbon acidic, and a carbanion can form with an appropriate base such as LDA. This charged compound can then be used as a nucleophile to add to a carbonyl. Jalba *et al.*recently reported on an enantioselective technique for oxidising sulfides with one aromatic and one alkyl side groups using Fe/6,6′-bis(4-isopropyloxazolin-2-yl)-2,2′-bipyridine complexes which are generated in situ with iron chloride and the appropriate ligand (**A130**) with hydrogen peroxide as a strong oxidising agent.[170] The sulfoxides were obtained in good yields of up to 61% with an excellent ee value of 97%. The sulfones were also synthesised but with smaller yields and ee values. It is proposed to apply this reaction to sulfide **6** to generate sulfoxides. **(Figure 131**).

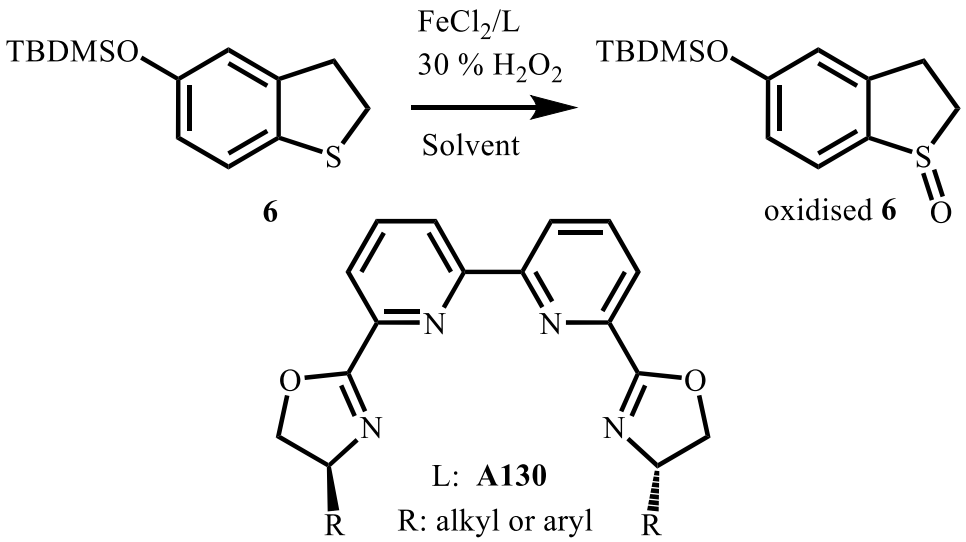


Figure 131: Proposed enantioselective oxidation of the sulfides

It is proposed that if this reaction can be applied to sulfide **6**, then an enolate reaction can be then tried by addition of LDA to the sulfoxide to generate the enolate, followed nucleophilic addition to an appropriate carbonyl containing compound with a bulky R group, such as 2,2-dimethylpropanal (**Figure 132**). If this reaction is successful, the sulfoxide can then be reduced back to the sulfide using triphenylphosphine and thionyl chloride to generate the desired alpha substituted sulfide derivative (**7**).

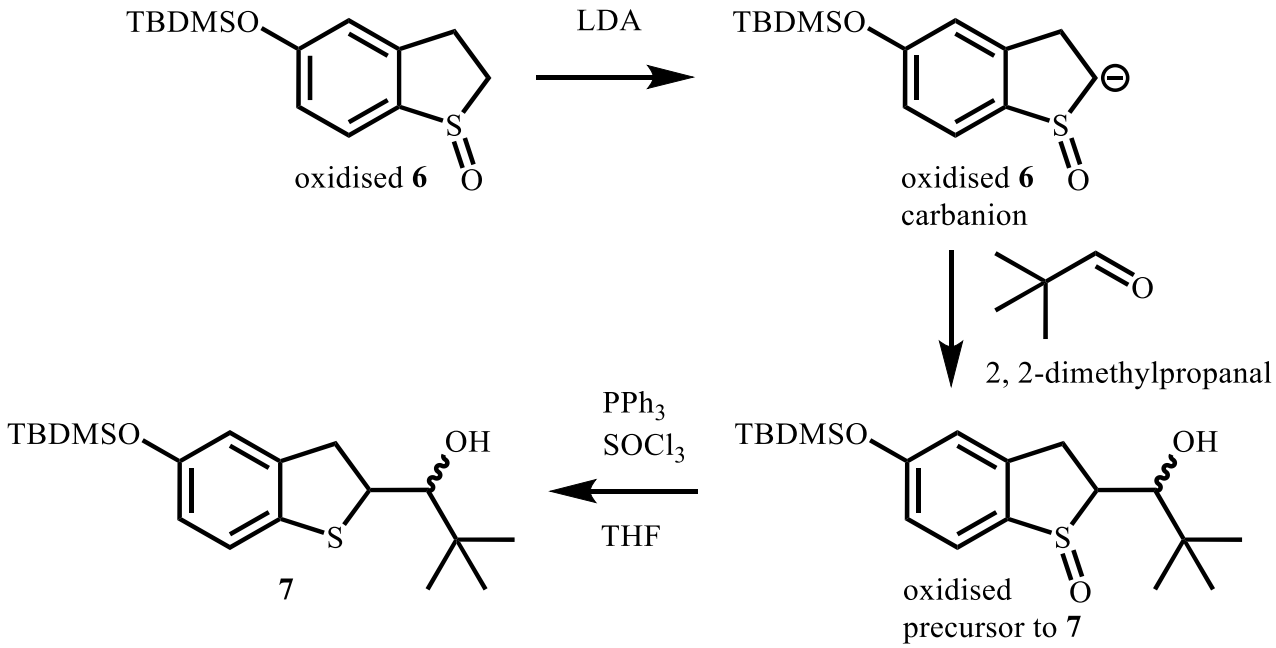


Figure 132: Proposed alternative synthesis of target compound 7

It is also envisaged to synthesise other chiral sulfides other than the core structure chosen. Many exist in the literature that could be applied to the Corey-Chaykovsky aziridination reaction, including Isothiocineole, synthesised by Illa *et al.*[70] by the reaction of limonene and γ-terpinene with elemental sulfur (**Figure 133**). From here, the allyl sulfonium salts can be made. Illa *et al.* applied this chiral sulfide to the Corey-Chaykovsky epoxidation and aziridination reactions (yields up to 78% with 99% ee) but using non-allylic sulfonium salts and in non-catalytic amounts. Therefore future work could look at applying this sulfide to vinylaziridine and/or pyrroline synthesis and the sulfide's use as a catalysts, as well as potentially adding more functionality to the sulfide (e.g. by the sulfur oxidation method).

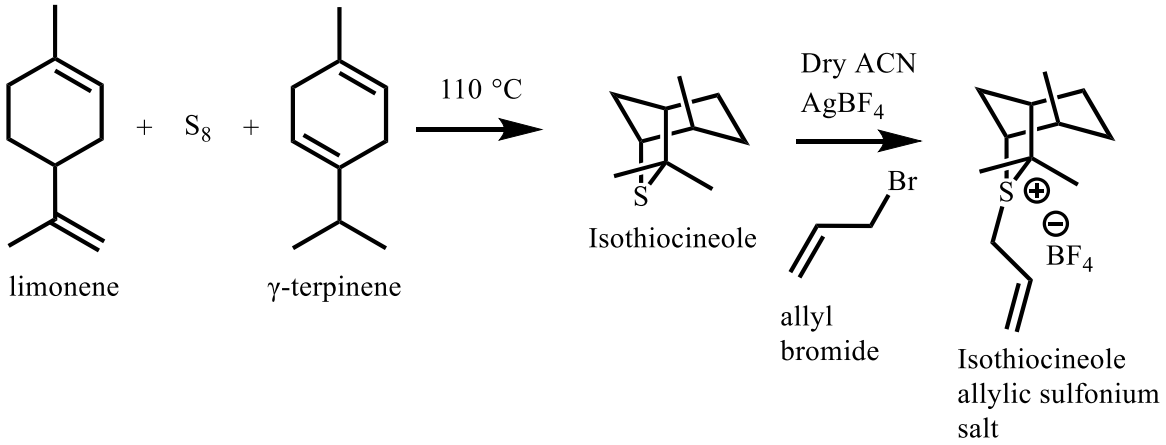


Figure 133: Synthesis of Isothiocineole and proposed synthesis of allylic sulfonium salts

Okada *et al.* also recently reported on the use of BINOL-derived sulfides for use as catalysts in the synthesis of 3,3-disubstituted phthalides.[171] The sulfides (core structure given in **Figure 134**) can be synthesised from readily available BINOL and are easily recoverable after their catalytic reaction. The structure also allows for many derivatives to be made as many functional groups can be added. This sulfide could thus be investigated for use as an aziridination catalyst.

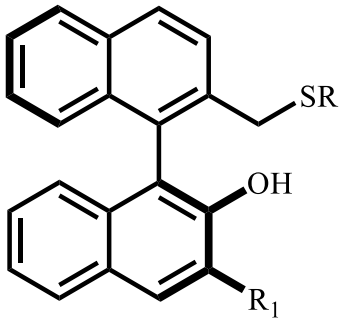


Figure 134: Okada *et al.* BINOL derived sulfide catalysts

It was also not possible to synthesise derivatives of the sulfide with functional group on the phenyl ring ortho to the sulfur (sulfide derivatives **8**). Electron-withdrawing/donating groups in this position can withdraw/donate electron density from the sulfur and adjust its' pK_a and thus its' catalytic performance. By nitrating the sulfide in this position, it would allow a diazonium salts process to add a variety of different group. The TBDMS protected hydroxy group on the phenyl ring however prevented nitration in the appropriate position. It is thus proposed to simplify the sulfide and sacrifice the TBDMS protected hydroxy which was envisaged to play a role in future work for flow chemistry. As previously discussed, optimisations and purification studies are needed on the brominated 2-phenylethanol. Purification of the *ortho*- and *para*-brominated products with β-cyclodextrin column chromatography is proposed. Once the *ortho*-brominated 2-phenylethanol is isolated, it can then be sulfonated and ring closed (**Figure 135**). This new structure should allow nitration in the correct *ortho*-position, followed by the diazonium salt reaction which can produce a range of the sulfide derivatives (**21**) with various group in this position. As seen in **Figure 135** the proposed R groups in this position are NO_2, Cl, CN, Br, OH, F and I. A NH_2 can also be added here by directly reducing the nitro group without having to perform the diazonium salt reaction. These sulfides (**16**) will have different electron-withdrawing/donating abilities so it is envisaged to determine the pK_a of the sulfur on each of the derivatives, and then evaluate what impact the pK_a value has on the sulfonium salt as well as the sulfur ylide formation. It is proposed to determine these pK_a values by UV-vis spectrophotometric acid-base titrations, based on a method from the literature,[172] where the UV-vis of the appropriate sulfide is constantly read as an appropriate electron acceptor (Lewis acid) is added over time. This produces an 'S' shaped titration curve in which the pK_a can be calculated.

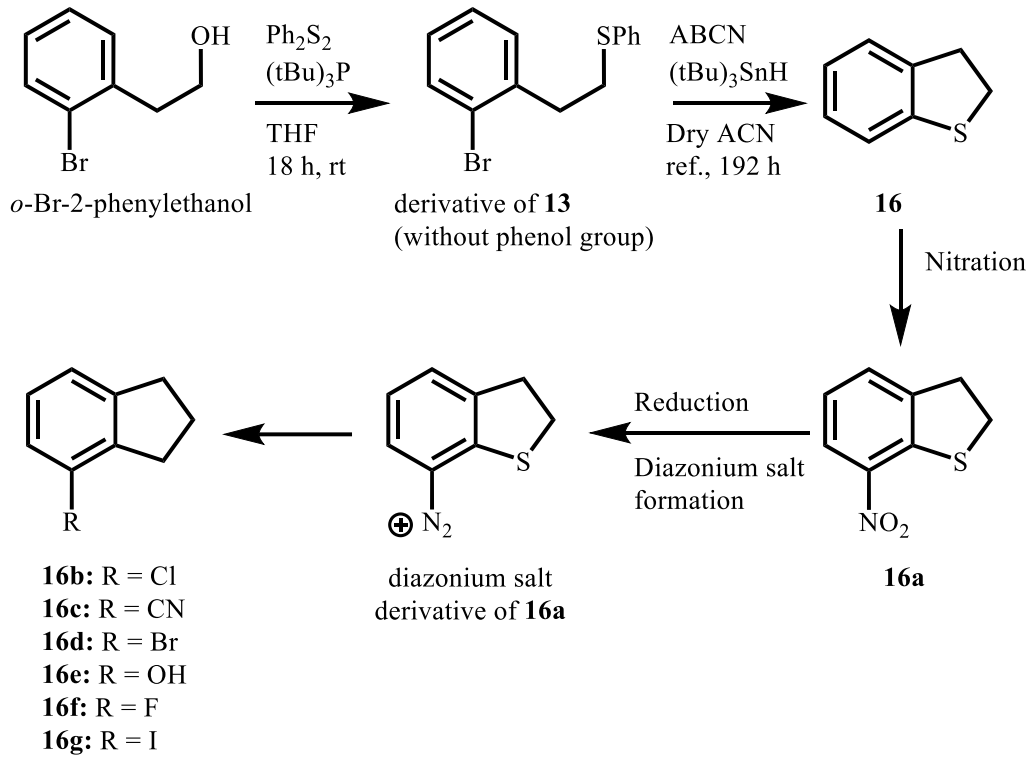


Figure 135: Synthesis of sulfide derivatives 21 using nitration followed by diazonium salts

Using natural chiral compounds to derive chiral sulfides that can be used as sulfide catalysts is potentially another research topic in future work. A very interesting chiral sulfide was synthesised by Saito *et al.* from (+)-camphor (**A131, Figure 136**).[173] This sulfide is bulky and has high ring strain, and was applied to epoxidation reaction with excellent stereoselectivity (96:4 trans/cis) and good ee values of 51%, with yields reported as high as 99%. This sulfide could be applied to the aziridination reaction, and can also be applied to allylic sulfonium salts and investigated for use in a catalytic amount.

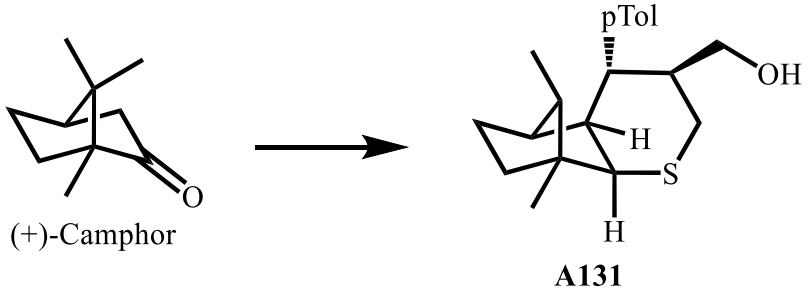


Figure 136: Saito *et al.* synthesis of chiral sulfides from (+)-camphor

The envisaged use the chiral sulfides is for asymmetric aziridine synthesis in the Corey-Chaykovsky reaction based on the conditions optimised in Chapter 2. Once a suitable selection of sulfides has been made, catalytic performance can then be evaluated. The proposed cycle is given in **Figure 137** below. As discussed in Chapter 3, the synthesis of the sulfonium salt from the sulfide **6** must be optimised, but it is estimated that the BF_4^- counteranion will be best as it proved to be for the ring closed THT sulfonium salts **2d-f**. The catalytic reaction will start with the generation of this sulfonium salt in a reaction vessel, before the addition of the relevant base to generate the ylide. Then the imine can be

added, and as the aziridine is produced, the sulfide starting material is regenerated, which can then reform the sulfonium salt and ylide, and produce more aziridine. A large and comprehensive study will be undertaken to evaluate the performance of each of the sulfides, and compare and contrast the impact of each of the functional groups. The sulfides with the electron-donating group on the phenyl ring may form the sulfonium salt easier, but the ylide more slowly and vice versa for the electron-withdrawing groups, and this may affect overall yield. The bulky groups on the sulfide ring in the alpha position are hoped to have an impact on the asymmetry of the reaction, for controlling the cis/trans ratio and also the enantiomeric excess (ee).

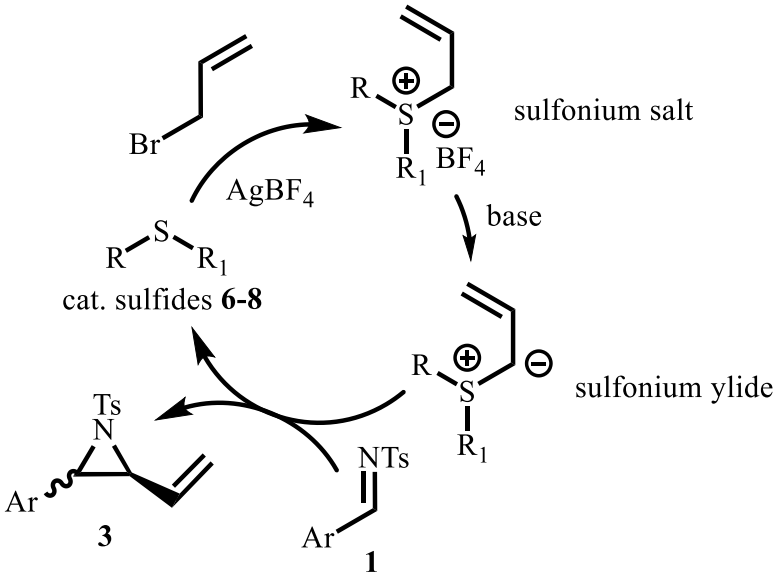


Figure 137: Proposed Corey-Chaykovsky catalytic cycle

The sulfides with the alpha side groups (**7**) will have to be enantiomerically pure. The alternative method discussed above involving sulfide oxidation to sulfoxide is an enantiomerically pure process, therefore this method could be used if dealing with an enantiomer mix of two alpha substituted sulfides, as asymmetric sulfoxide formation will oxidise only one of the sulfide enantiomers. Therefore a mix of one sulfoxide and one sulfide will remain, which could be separated, as seen in **Figure 138**.

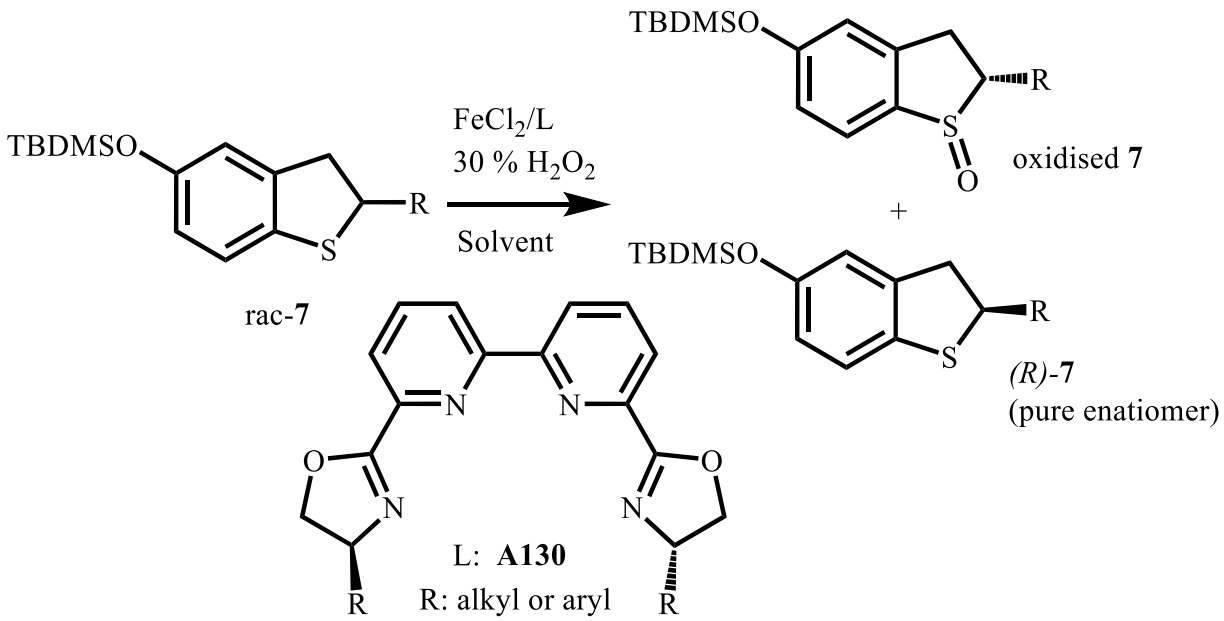


Figure 138: Asymmetric oxidation of 7, where only one enantiomer is oxidised

5.4. Future work for pyrrolines as new organocatalysts (Chapter 4)

A major challenge in the synthesis of pyrrolidine-based organocatalysts from Chapter 4 has been the inability to produce enantiomerically pure product. For the synthesis of **19a-b** the hydrogenation method has been optimised using palladium on carbon, so it can now be adjusted to an asymmetric hydrogenation, where only one enantiomer is hydrogenated. Many examples exist in the literature, usually using platinum group transition metal catalysts. A method reported by Duan *et al.* used palladium with several chiral co-catalysts. [178] One chiral catalyst used, (*R*)-BINAP, is widely available commercially. A proposed method based on this palladium optimised method is given in **Figure 139** below.

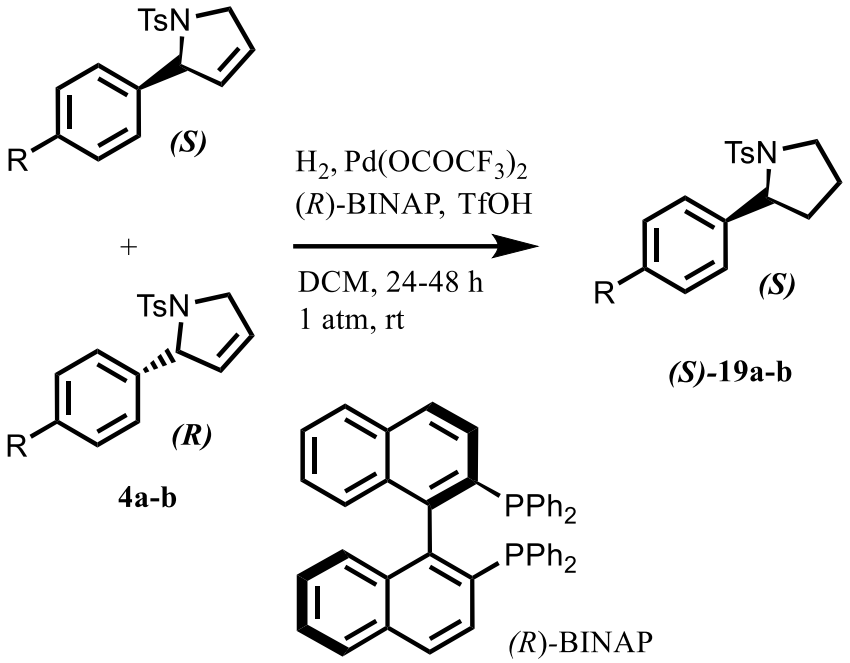


Figure 139**: Proposed asymmetric hydrogenation of 4a-b to 19a-b**

Attempts using D-alanine for kinetic resolution on the crude samples of **19a-b** proved unsuccessful. The purity of the pyrrolines after detosylation may have been an issue in this reaction, so optimisation of that reaction and purification needs to be looked at.

The Sharpless dihydroxylation method used in this research for the synthesis of **20a-b** used $K_2OsO_4.2H_2O$ as a strong oxidising agent and ensured a syn addition of the two hydroxy groups across the alkene bond, however it was not asymmetric as both enantiomer. If the alkene bond is considered in a flat plane, the hydroxy group both add from the same side but can add from the top or bottom. The addition of a quinine based ligand can be used to produce asymmetry.[174] The chiral ligand, which is usually a dimer dihydroquinine bridged by phthalazine, has two pseudo-enantiomeric forms; $(DHQ)_2Phal$ or $(DHQD)_2Phal$ where one forms one enantiomer of the dihydroxylated product, and the other forms the second, as seen in **Figure 140**. Once the enantiomerically pure dihydroxylated product is formed, a study must be performed to detosylate. Use of HBr acid should be used, as the other methods explored in Chapter 4 did not work.

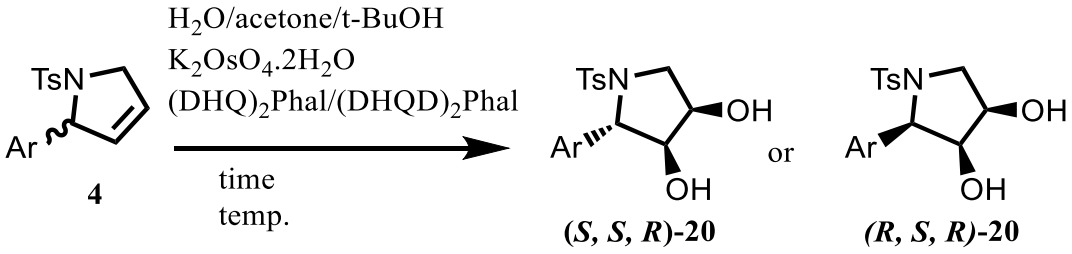


Figure 140: Sharpless asymmetric dihydroxylation of 4 to form diols 20

If the asymmetric hydrogenation and dihydroxylation of **19** and **20** can be achieved, the enantiomeric excess can be determined by chiral chromatography and measuring specific rotation by polarimetry. For both **19** and **20**, a detosylation method must be fully optimised before testing them as organocatalysts.

While the focus of the current research has been on the hydrogenated and dihydroxylated pyrrolines, the alkene bond on the 5-membered ring offers a wide variety of other reactions which can be performed, such as the dibromination, which proceeds in an anti-syn manner (**Figure 141**). With bromines' characteristic as being good leaving group, this dibrominated pyrroline offers the potential for additional functionalisation of the ring.

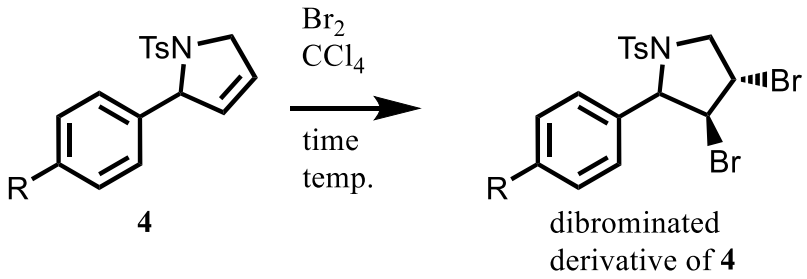


Figure 141: Proposed dibromination of 4

Another reaction of the pyrroline that is proposed is a hydroboration, a well-established reaction in synthesis where diborane is added to the more substituted carbon on the alkene bond.[175] The diborane can then be replaced with a hydroxy group with a suitable oxidising agent such as hydrogen peroxide, to form a regioselective monohydroxylated pyrroline derivative, which itself can be further derivative. This reaction opens a range of new pyrroline-based catalysts that can be synthesised with just one substituent on the ring.

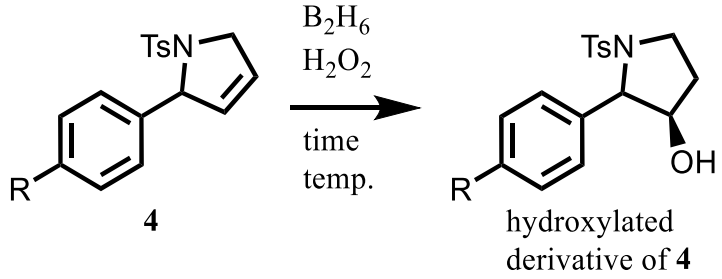


Figure 142: Proposed hydroboration and oxidation of 4

A major focus of future work will be analysis to demonstrate the enantiomeric purity of synthesised compounds. There are several classes of molecules that will need this analysis; the aziridines from the catalytic asymmetric synthesis using the sulfides, the chiral sulfides with the alpha substitution, the synthesised pyrrolines which have been enantiomerically purified, and the products of the organocatalytic reactions tried with the pyrrolines as catalysts. Methods to determine the prevalence of one enantiomer over the other (the % ee value) will include chiral HPLC, linear polarimetry and circular dichroism spectroscopy (circular polarimetry).

Once enantiomerically pure pyrrolidine derivatives can be obtained, it is envisaged to apply them to the asymmetric aldol reaction, as outlined in Chapter 4 as well as the numerous (*S*)-proline organocatalytic reactions detailed Chapter 1**.**

5.5. Conclusion

For Chapter 2, future work should focus on broadening the scope of derivatives of **3** and **4** that can be made, as well as studying in more detail the synthetic selectivity of **3** and **4**, and what role organic bases, particularly their conjugate acids, play in the reaction pathway.

For Chapter 3, sulfonium salt synthesis from **6** should be the focus of future work, as well as developing the alternative synthetic strategies for **7, 8** and **16** that have been outlined in this chapter. Resolving enantiomers of **8** can be performed through asymmetric oxidation of the sulfide group, or by kinetic resolution. Once achieved, the performance of sulfides **6, 7, 8** and **16** in the Corey-Chaykovsky reaction, both stochiometrically and catalytically, should be evaluated.

For Chapter 4, adapting the optimised synthesis of **19, 20** and **21** towards asymmetry has been suggested for future work, as has development of the detosylation method. Once enantiomerically pure samples can be obtained, their performance in organocatalytic reactions should be evaluated.

Overall Conclusion

To conclude, the Corey-Chaykovsky aziridination has been successfully redeveloped to selectively synthesise vinylaziridines (**3**) and aryl pyrrolines (**4**), with the key reaction parameters identified, with the most important being choice of base. These conditions can be used for future asymmetric aziridine synthesis and as a starting point for synthesising pyrrolidine organocatalysts.

A synthetic strategy has been partially developed for synthesising sulfides **6, 7, 8** and **16** which can be used for future synthesis of **3** and **4,** both catalytically and asymmetrically, as well as other aziridines and pyrrolines.

Pyrroline **4** has been used to synthesise derivatives **19, 20** and **21**. The optimised conditions for the synthesis of these three compounds is adaptable to asymmetric synthesis. A detosylation method has been partially developed, but needs more study. These compounds can form the basis for future organocatalysts.

This project has yielded a number of new compounds; **2b-c, 2e-f**, **3a**, **9, 10, 14, 15a-b, 20a-b, 21a-b**, all of which were characterised by NMR and HRMS.

An extensive plan of future work has also been detailed.

This project has highlighted the ability of redeveloped known synthetic reactions to incorporate organocatalysis and to make synthetic greener and more efficient. However, it has also highlighted the extensive optimisation studies that are required as well as the volume of metals and solvents are needed to synthesise organocatalysts, which is not in line with green chemistry.

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Experimental methods

All reagents were purchased from commercial sources and were used without further purification, unless otherwise stated. Commercial dry solvents were purchased from Sigma Aldrich and Acros Chemicals and handled under nitrogen. Deuterated solvents were purchased from Sigma Aldrich. Thin Layer Chromatography (TLC) was performed on Merck TLC silica gel w/UV 254 aluminium-backed plates, and spots were visualized using UV light and/or potassium permanganate. Column chromatography purifications were carried out using the flash technique. NMR spectra were recorded on Bruker Advance 400 or 600. The chemical shifts (δ) for ^{1}H and ^{19}F are given in parts per million (ppm) and referenced to the residual proton signal of the deuterated solvent (CHCl3 at δ 7.26 ppm) and coupling constants are expressed in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, td = triplet of doublets, tq = triplet of quartets, q = quartet, qt = quartet of triplets, qn = quintet, ddt = doublet of doublets of triplets.

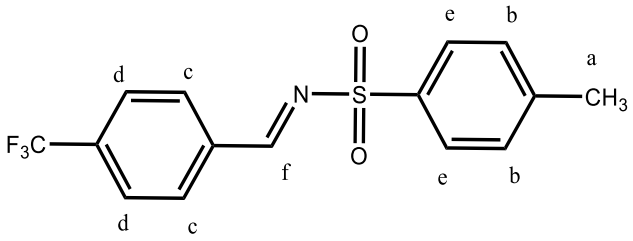
6.1. Chapter 2 methods

6.1.1. General experimental

All experiments were conducted under an atmosphere of nitrogen unless otherwise noted, using Schlenk technique 1. Cis and trans refer to the stereochemistry of the bond formed during the reaction.

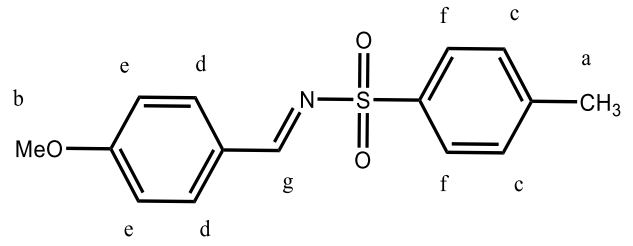
6.1.2. General procedure for imine synthesis

To a flame dried round bottomed flask, of p-toluenesulfonamide (840 mg, 1.0 eq) was added along with dry DCM (5 mL) under nitrogen. Substituted benzaldehyde (1.1 eq) was then added and the reaction flask was heated up to reflux temperature. As heating proceeded, trifluoroacetic anhydride (1.04 mL, 1.5 eq) was added dropwise. The reaction was then refluxed followed by stirring at rt under nitrogen. When reaction time was complete, the mixture was quenched with 10 mL of ice-cold water and 5 mL of DCM. After placing in a separating funnel, the mixture was extracted with 3× 5 mL of DCM, washed with 10 mL of water and dried over $MgSO_4$. Rotary evaporation yielded the crude product which was purified by recrystallisation. This was performed by dissolving the crude material in a minimum of hot EtOAc followed by the dropwise addition of hexane until a cloud of precipitate was observed. After allowing the flask to cool to rt, the purified product was isolated by vacuum filtration and allowed to dry. Characterisation was performed by ^{1}H NMR spectroscopy in $CDCl_3$.



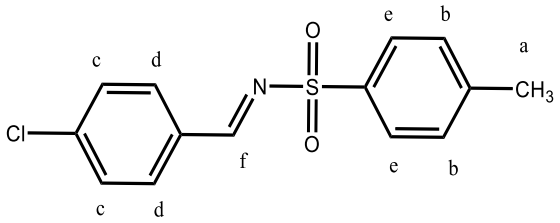
4-Methyl-*N*-[[4-(trifluoromethyl)phenyl]methylene]benzenesulfonamide (1a); was obtained by the general procedure from the reaction of p-toluenesulfonamide (840 mg, 1.0 eq) and 4-(trifluromethyl)benzaldehyde (0.75 mL, 1.1 eq) with trifluoroacetic anhydride (1.04 mL, 1.5 eq) in dry DCM (5 mL). The reaction mixture went a pale yellow upon heating, and was refluxed for 24 h. followed by stirring at rt under nitrogen for 72 h. Purification was performed by recrystallisation by dissolving the crude material in a minimum of hot EtOAc followed by the dropwise addition of hexane. Purified material was a white, fluffy solid (72%).

^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H, Ha), 7.37 (d, J= 8.4Hz, 2H, Hb), 7.75 (d, J= 8.4Hz, 2H, Hc), 7.90 (d, J= 8.4Hz, 2H, Hd), 8.05 (d, J= 8.4 Hz, 2H, He), 9.07 (s, 1H, Hf) (**Spectrum 1**) Data is consistent with literature values. [130]



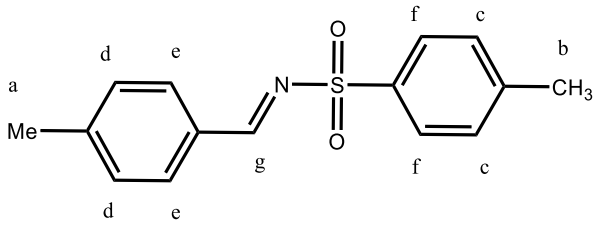
4-Methyl-*N*-[[4-(methoxy)phenyl]methylene]benzenesulfonamide (1b); was obtained by the general procedure from the reaction of p-toluenesulfonamide (840 mg, 1.0 eq) and 4-methoxybenzaldehyde (0.67 mL, 1.1 eq) with trifluoroacetic anhydride (1.04 mL, 1.5 eq) in dry DCM (5 mL). The reaction mixture went a deep purple upon heating, and was refluxed for 24 h. followed by stirring at rt under nitrogen for 24 h. Purification was performed by recrystallisation by dissolving the crude material in a minimum of hot EtOAc followed by the dropwise addition of hexane. Purified material was a flaky, yellow/white solid (62%).

^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H, Ha), 3.88 (s, 3H, Hb), 6.96 (d, J= 8.8 Hz, 2H, Hc), 7.31 (d, J= 8 Hz, 2H, Hd), 7.86-7.89 (m, 4H, He, Hf), 8.94 (s, 1H, Hg) (**Spectrum 2).** Data is consistent with literature values. [130]



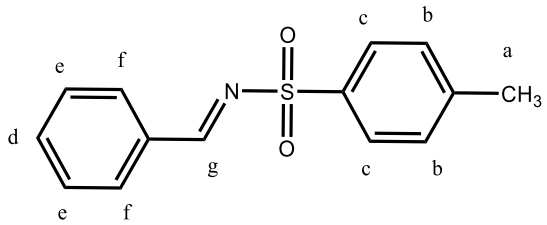
4-Methyl-*N*-[[4-(chloro)phenyl]methylene]benzenesulfonamide (1c); was obtained by the general procedure from the reaction of p-toluenesulfonamide (840 mg, 1.0 eq) and 4-chlorobenzaldehyde (773 mg , 1.1 eq) with trifluoroacetic anhydride (1.04 mL, 1.5 eq) in dry DCM (5 mL). The reaction mixture went a pale yellow upon heating, and was refluxed for 18 h. followed by stirring at rt under nitrogen for 24 h. Purification was performed by recrystallisation by dissolving the crude material in a minimum of hot EtOAc followed by the dropwise addition of hexane. Purified material was a fine, white/yellow powder (57%).

^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H, Ha), 7.35 (d, J= 8 Hz, 2H, Hb), 7.47 (d, J= 8.4 Hz, 2H, Hc) 7.87 (m, 4H, Hd, He), 8.99 (s, 1H, Hf). (**Spectrum 3**). Data is consistent with literature values. [130]



4-Methyl-*N*-[[4-(methyl)phenyl]methylene]benzenesulfonamide (1d); was obtained by the general procedure from the reaction of p-toluenesulfonamide (840 mg, 1.0 eq) and 4-methylbenzaldehyde (0.65 mL , 1.1 eq) with trifluoroacetic anhydride (1.04 mL, 1.5 eq) in dry DCM (5 mL). The reaction mixture went a bright red upon heating, and was refluxed for 18 h. Purification was performed by recrystallisation by dissolving the crude material in a minimum of hot EtOAc followed by the dropwise addition of hexane. Purified material was a flaky, white/yellow solid (43%).

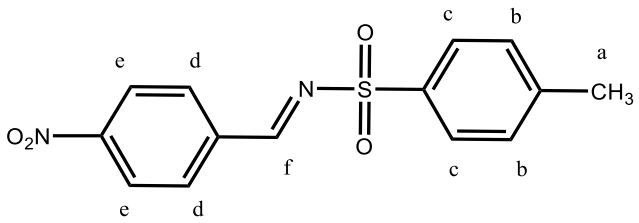
^{1}H NMR ($CDCl_3$) δ 2.24 (s, 3H, Ha), 2.43 (s, 3H, Hb), 7.28 (d, J= 8Hz, 2H, Hc), 7.37 (d, J= 8.4 Hz, 2H, Hd), 7.81 (d, J= 8.4 Hz, 2H, He), 7.88 (d, J= 8 Hz, 2H, Hf), 8.98 (s, 1H, Hg) (**Spectrum 4**). Data is consistent with literature values. [131]



4-Methyl-*N*-[(phenyl)methylene]benzenesulfonamide (1e); was obtained by the general procedure from the reaction of p-toluenesulfonamide (840 mg, 1.0 eq) and benzaldehyde (0.56 mL , 1.1 eq) with trifluoroacetic anhydride (1.04 mL, 1.5 eq) in dry DCM (5 mL). The reaction mixture went a pale yellow upon heating, and was refluxed for 18 h. followed by stirring at rt under nitrogen for 5 h. Purification was performed by recrystallisation by

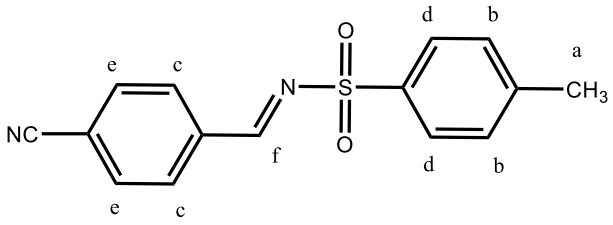
dissolving the crude material in a minimum of hot EtOAc followed by the dropwise addition of hexane. Purified material was a fine, white/yellow powder (63%).

^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H, Ha), 7.50 (d, J= 8 Hz, 2H, Hb), 7.48 (dd, J= 7.8 Hz, 7.6 Hz, 2H, Hc), 7.62 (t, 7.6 Hz, 1H, Hd), 7.91 (m, 4H, He, Hf), 9.03 (s, 1H, Hg). (**Spectrum 5**). Data is consistent with literature values. [132]



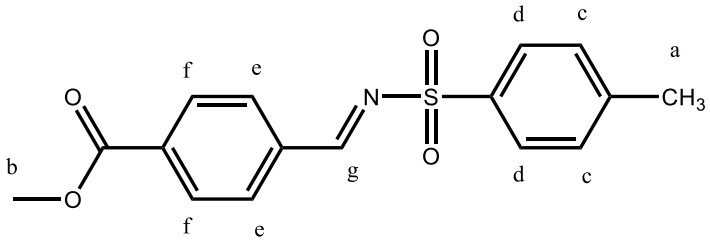
4-Methyl-*N*-[[4-(nitro)phenyl]methylene]benzenesulfonamide (1f); was obtained by the general procedure from the reaction of p-toluenesulfonamide (840 mg, 1.0 eq) and 4-nitrobenzaldehyde (919 mg , 1.1 eq) with trifluoroacetic anhydride (1.04 mL, 1.5 eq) in dry DCM (5 mL). The reaction mixture went a deep, cloudy yellow upon heating with solid residue remaining, and was refluxed for 24 h. followed by stirring at rt under nitrogen for 72 h. Solid residue was removed upon completion by filtration. Purification was performed by recrystallisation by dissolving the crude material in a minimum of hot EtOAc followed by the dropwise addition of hexane. Purified material was a flaky, yellow solid (20%).

^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H, Ha), 7.39 (d, J= 8Hz, 2H, Hb), 7.91 (d, J= 8 Hz, 2H, Hc), 8.11 (d, J= 8.8 Hz, 2H, Hd), 8.34 (d, J= 8.8 Hz, 2H, He), 9.1 (s, 1H, Hf). (**Spectrum 6**). Data is consistent with literature values. [131]



4-Methyl-*N*-[[4-(cyano)phenyl]methylene]benzenesulfonamide (1g); was obtained by the general procedure from the reaction of p-toluenesulfonamide (840 mg, 1.0 eq) and 4-cyanobenzaldehyde (831 mg , 1.1 eq) with trifluoroacetic anhydride (1.04 mL, 1.5 eq) in dry DCM (5 mL). The reaction mixture went a pale yellow upon heating, and was refluxed for 24 h. followed by stirring at rt under nitrogen for 72 h. Purification was performed by recrystallisation by dissolving the crude material in a minimum of hot EtOAc followed by the dropwise addition of hexane. Purified material was a fine, white solid (40%).

^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H, Ha), 7.37 (d, J= 8 Hz, 2H, Hb), 7.78 (d, J= 8.4 Hz, 2H, Hc), 7.89 (d, 8.4 Hz, 2H, Hd), 8.03 (d, J= 8.4 Hz, 2H, He), 9.05 (s, 1H, Hf) (**Spectrum 7**). Data is consistent with literature values. [133]

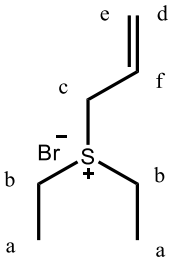


***N*-[[4-(Methoxycarbonyl)phenyl]]methylene]-4-methylbenzenesulfonamide (1h);** was obtained by the general procedure from the reaction of p-toluenesulfonamide (840 mg, 1.0 eq) and methyl 4-formylbenzoate (903 mg , 1.1 eq) with trifluoroacetic anhydride (1.04 mL, 1.5 eq) in dry DCM (5 mL). The reaction mixture went a pale white upon heating, and was refluxed for 24 h. followed by stirring at rt under nitrogen for 72 h. Purification was performed by recrystallisation by dissolving the crude material in a minimum of hot EtOAc followed by the dropwise addition of hexane. Purified material was a fine, white solid (30%).

^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H, Ha), 3.95 (s, 3H, Hb), 7.37 (d, J= 8 Hz, 2H, Hc), 7.90 (d, J= 8.4 Hz, 2H, Hd), 7.99 (d, J= 8.4 Hz, 2H, He), 8.14 (d, J= 8.4 Hz, 2H, Hf), 9.1 (s, 1H). (**Spectrum 8**). Data is consistent with literature values. [134]

6.1.3. General procedure for sulfonium salt synthesis

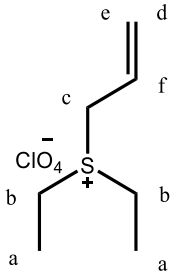
To a flamed dried round bottomed flask, dry ACN was added along with sulfide (1 eq) and allyl bromide (2 eq.) The mixture was left to stir at rt for 72 h. under nitrogen. Upon completion, the mixture was rotary evaporated to yield fine brown/white crystals or a brown oil. This crude material was then stirred vigorously with EtOAc (approximately 10 mL) to remove impurities. The EtOAc was then carefully decanted off to leave the wet material, which was dried by rotary evaporation and then under high vacuum to yield fine brown/white crystals. Characterisation was performed by ^{1}H NMR spectroscopy in $CDCl_3$ or DMSO.



1-Allyldiethylium bromide (2a); was obtained by the general procedure from the reaction of diethyl sulfide (1.58 mL, 1 eq) and allyl bromide (1.73 mL, 2 eq) in dry DCM (10 mL) which was stirred at rt for 72 h. under nitrogen. Reaction mixture was a pale brown. Purification was from vigorous stirring in EtOAc, followed by decanting of EtOAc and drying of product under vacuum. Product was fine, white/brown crystals (91%).

^{1}H NMR (DMSO-d6) δ 3.40 (t, J= 7.2 Hz, 6H, Ha), 3.33 (sep, J= 7.6 Hz, 4H, Hb), 4.17 (d, J= 7.3 Hz, 2H, Hc), 5.61 (d, J= 10.3 Hz, 1H, Hd), 5.68 (d, J= 17.1 Hz, 1H, He), 5.97 (tdd, J= 7.3, 17.1, 10 Hz, 1H, Hf) (**Spectrum 9**). Data is consistent with literature values. [137]

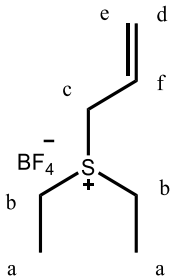
HRMS: M^{+}: 131.0889, 79.0290 m/z (**Spectrum 10**).



1-Allyldiethylium perchlorate (2b); was obtained by the general procedure from the reaction of diethyl sulfide (4.31 mL, 4 eq) and allyl bromide (1.73 mL, 1 eq) in dry ACN (10 mL) with a solid additive, silver perchlorate (4164 mg, 1 eq.) which was stirred at rt for 72 h. under nitrogen. Reaction mixture went a cloudy green colour upon stirring. Upon completion, mixture was filtered through a alumina plug to remove inorganic salts. The filtrate was rotary evaporated and placed under vacuum on the high pump, to yield a viscous, green/brown semi-solid, which was not further purified (90%).

^{1}H NMR (DMSO-d6) δ 1.39 (t, J= 7.6 Hz, 6H, Ha), 7.31 (sep, J= 7.6 Hz, 4H, Hb), 7.14 (d, J= 7.4 Hz, 2H, Hc), 5.62 (d, J= 10 Hz, 1H, Hd), 5.67 (d, J= 16 Hz, 1H, He), 5.95 (tdd, J= 7.4, 9.9, 16.7 Hz, 1H, Hf) (**Spectrum 11**).

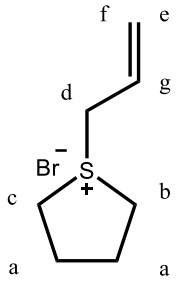
HRMS: M^{+}: 131.0889, 99.0231 m/z (**Spectrum 12**).



1-Allyldiethylium tetrafluoroborate (2c); was obtained by the general procedure from the reaction of diethyl sulfide (4.31 mL, 4 eq) and allyl bromide (1.73 mL, 1 eq) in dry ACN (10 mL) with a solid additive, silver tetrafluoroborate (3893 mg, 1 eq.) which was stirred at rt for 72 h. under nitrogen. Reaction mixture went a cloudy green colour upon stirring. Upon completion, mixture was filtered through a alumina plug to remove inorganic salts. The filtrate was rotary evaporated and placed under vacuum on the high pump, to yield a viscous, green/brown semi-solid, which was not further purified (96%).

^{1}H NMR (DMSO-d6) δ 1.39 (t, J= 7.6 Hz, 6H, Ha), 3.30 (sep, 7.2 Hz, 4H, Hb), 4.12 (d, J= 7.4 Hz, 2H, Hc), 5.61 (d, J= 10.1 Hz, 1H, Hd), 5.68 (d, J= 16.9 Hz, 1H, He), 5.95 (tdd, J= 7.4, 17.1, 10 Hz, 1H, Hf). (**Spectrum 13).**

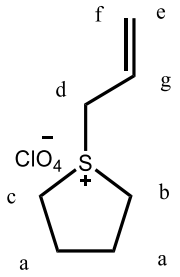
HRMS: M^+: 131.0682, 89.0561 m/z (**Spectrum 14**)



1-Allytetrahydrothiophenium bromide (2d); was obtained by the general procedure from the reaction of tetrahydrothiophene (1.33 mL, 1 eq) and allyl bromide (1.73 mL, 2 eq) in dry DCM (10 mL) which was stirred at rt for 72 h. under nitrogen. Reaction mixture was clear brown. Purification was from vigorous stirring in EtOAc, followed by decanting of EtOAc and drying of product under vacuum. Product was brown crystals (49%).

^{1}H NMR (DMSO-d6) δ 6.00-5.90 (m, 1H, Hg), 5.67 (d, J= 16.9 Hz, Hf), 5.53 (d, J= 10.3 Hz), 4.06 (d, J= 7.5 Hz, Hd), 3.55-3.48 (m, 2H, Hc), 3.42-3.38 (m, 2H, Hb), 2.28-2.10 (m, 4H, Ha) (**Spectrum 15**). Data is consistent with literature values. [137]

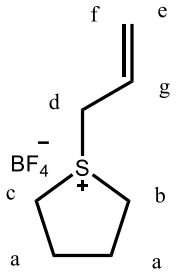
HRMS: M^+: 129.0732, 79.0980 m/z (**Spectrum 16**).



1-Allytetrahydrothiophenium perchlorate (2e); was obtained by the general procedure from the reaction of tetrahydrothiophene (5.32 mL, 4 eq) and allyl bromide (1.73 mL, 1 eq) in dry ACN (10 mL) with a solid additive, silver perchlorate (4164 mg, 1 eq.) which was stirred at rt for 72 h. under nitrogen. Reaction mixture went a cloudy green colour upon stirring. Upon completion, mixture was filtered through a alumina plug to remove inorganic salts. The filtrate was rotary evaporated and placed under vacuum on the high pump, to yield a viscous, green/brown semi-solid, which was not further purified (57%).

^{1}H NMR (DMSO-d6) δ 2.17 (m, 4H, Ha), 3.33 (m, 2H, Hb), 3.46 (m, 2H, Hc), 3.94 (d, J= 7.4 Hz, 2H, Hd), 5.54 (d, J= 10.1 Hz, 1H, He), 5.63 (d, 17.1 Hz, 1H, Hf), 5.92 (tdd, J= 7.3, 16.9, 10 Hz, 1H, Hg). (**Spectrum 17**).

HRMS: M^+: 129.0732, 98.9750 m/z (**Spectrum 18**).



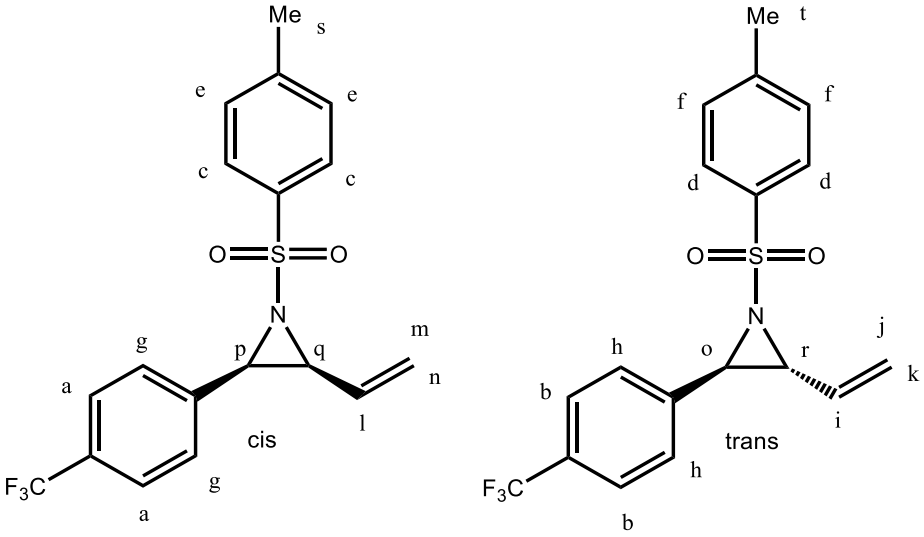
1-Allytetrahydrothiophenium tetrafluroborate (2f); was obtained by the general procedure from the reaction of tetrahydrothiophene (5.32 mL, 4 eq) and allyl bromide (1.73 mL, 1 eq) in dry ACN (10 mL) with a solid additive, silver tetrafluoroborate (3893 mg, 1 eq.) which was stirred at rt for 72 h. under nitrogen. Reaction mixture went a cloudy green colour upon stirring. Upon completion, mixture was filtered through a alumina plug to remove inorganic salts. The filtrate was rotary evaporated and placed under vacuum on the high pump, to yield a viscous, green/brown semi-solid, which was not further purified (99%).

^{1}H NMR ($CDCl_3$) δ 2.40 (m, 4H, Ha), 3.46 (m, 2H, Hb), 3.68 (m, 2H, Hc), 4.04 (d, J= 7.3 Hz, 2H, Hd), 5.65 (d, 10 Hz, 1H, He), 5.70 (d, J= 16.6 Hz, 1H, Hf), 5.88 (tdd, J= 7.3, 17.1, 9.9 Hz, 1H, Hg) (**Spectrum 19**).

HRMS: M^+: 129.0733, 86.9960 m/z (**Spectrum 20**).

6.1.4. General procedure for aziridination reaction (synthesis of **3**, **4** and **5**)

To a flame dried round bottomed flask under nitrogen, imine (1.0 eq) was added along with of sulfonium salt (1.1 eq) and dry ACN (1 mL) and heat and stirring commenced under reflux. Base (1.1 eq) was added dropwise as reaction heated up. When using a solid base, this was added with the imine and salt. Reaction was refluxed at relevant temperature for the relevant time. Upon completion, the mixture was rotary evaporated and dried under high action pump and crude mixture was characterised by NMR in $CDCl_3$. Mixture was then purified by column chromatography, and the fractions were characterised by NMR in $CDCl_3$.



1-[(4-Methylphenyl)sulfonyl]-2-(1-ethylene)-3-[4-(trifluoromethyl)phenyl]aziridine (3a); was obtained by the general procedure from the reaction of 4-CF_3 imine (**1a**) (164 mg, 1.0 eq) and diethyl Br^- allyl sulfonium salt (**2a**) (116 mg, 1.1 eq) in dry ACN (1 mL). Upon initiation of heat and stirring under nitrogen, diisopropylethyamine (0.1 mL, 1.1 eq) was added dropwise. The reaction mixture went a dark yellow/brown, and was stirred for 8 h. at 50 °C. Upon completion, the crude mixture was rotary evaporated and characterised by ^1H and ^{19}F NMR in $CDCl_3$. The crude mixture was then purified by column chromatography, using a dry loading method in 98% hexane in Et_2O, which was gradually changed down to 85%. The column fraction were constantly monitored by TLC. The appropriate fractions were collected, rotary evaporated and dried on the high pump. Product was a viscous, bright yellow semi-solid (38%).

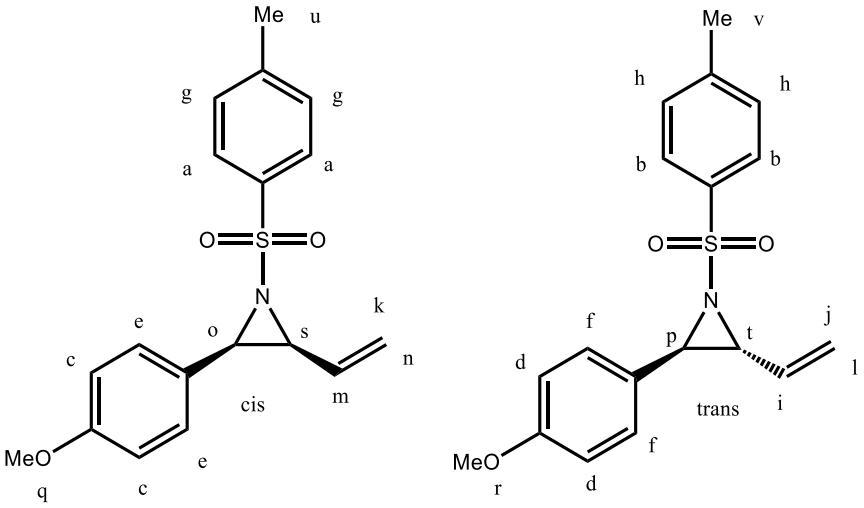
^1H NMR ($CDCl_3$) cis/trans (1:1.25) δ 7.89 (d, J= 8.2 Hz, 2H, Ha), 7.84 (d, J= 8.3 Hz, 2.5H, Hb), 7.57-7.49 (m, 4.75H, Hc, Hd), 7.35 (d, J= 8 Hz, 4H, He, Hf), 7.29 (d, J= 8.2 Hz, 4H, Hg, Hh), 6.40-6.27 (m, 1.25H, Hi), 5.59 (d, J= 16.9 Hz, 1.25H, Hj), 5.51 (d, J= 10.3 Hz, 1.25H, Hk), 5.49-5.40 (m, 1H, Hl), 5.27-5.15 (m, 2H, Hm, Hn), 4.13-4.06 (m, 2.25H, Ho, Hp), 3.70-3.63 (m, 1H, Hq), 3.28 (dd, J= 4, 9.4 Hz, 1.25H, Hr), 2.44 (s, 3H, Hs), 2.40 (s, 3.75H, Ht) (**Spectrum 21**).

^{19}F NMR ($CDCl_3$) cis/trans (1:1.18) δ -62.60 (1), -62.63 (1.18) (**Spectrum 22**)

^1H NMR ($CDCl_3$) cis/trans (1:0) δ 7.89 (d, J= 8.5 Hz, 2H, Ha), 7.54 (d, J= 8 Hz, 2H, Hb), 7.37-7.33 (m, 4H, Hc, Hd), 5.47-5.41 (m, 1H, He), 5.24-5.19 (m, 2H, Hf, Hg), 4.10 (d, J= 7.2 Hz, 1H, Hh), 3.68-3.65 (m, 1H, Hi), 2.45 (s, 3H, Hj) (**Spectrum 23**)

^{13}C NMR ($CDCl_3$) cis/trans (1:0) δ 145.07, 136.85, 134.98, 130.02, 129.28, 128.08, 128.03, 125.55-125.39, 122.58, 47.42, 45.75, 29.50, 21.82 (**Spectrum 25**)

HRMS: $[M-H]^+$ 366.0781 m/z (**Spectrum 28**)



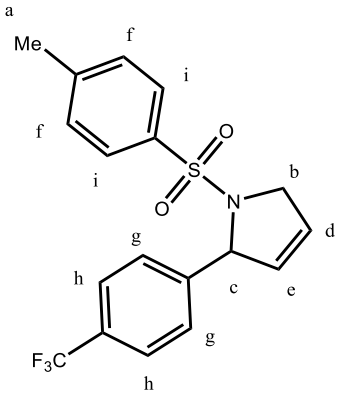
1-[(4-Methylphenyl)sulfonyl]-2-(1-ethylene)-3-[4-(methoxy)phenyl]aziridine (3b); was obtained by the general procedure from the reaction of 4-OMe imine (**1b**) (145 mg, 1.0 eq) and diethyl Br^- allyl sulfonium salt (**2a**) (116 mg, 1.1 eq) in dry ACN (1 mL). NaH (60% dispersion in oil) (25 mg, 1.1 eq) was also added. Heat and stirring was initiated under nitrogen, The reaction mixture went bright/cloudy yellow, and was stirred for 8 h. at 50 °C. Upon completion, the crude mixture was filtered through an alumina plug, and then rotary evaporated and characterised by ^1H and NMR in $CDCl_3$. The crude mixture was then purified by column chromatography, using a dry loading method in 98% hexane in Et_2O, which was gradually changed down to 85%. The column fraction were constantly monitored by TLC. The appropriate fractions were collected, rotary evaporated and dried on the high pump. Product was a viscous, bright yellow semi-solid (33%).

δ^1H NMR ($CDCl_3$) cis/trans (1:0.5) δ 7.88 (d, J= 8.3 Hz, 2H, Ha), 7.82 (d, J= 8.3 Hz, 1H, Hb), 7.31 (d, J= 8.2 Hz, 2H, Hc), 7.24 (d, J= 8.2 Hz, 1H, Hd), 7.17-7.06 (m, 3H, He, Hf), 6.84-6.75 (m, 3H, Hg, Hh), 6.39-6.27 (m, 0.5H, Hi), 5.55 (d, J= 16.8 Hz, 0.5H, Hj), 5.49-5.38 (m, 1.5H, Hk, Hl), 5.35-5.23 (m, 1H, Hm), 5.17 (d, J= 10.4 Hz, 1H, Hn), 4.06-3.99 (m, 1.5H, Ho, Hp), 3.74-3.70 (m, 4.5H, Hq, Hr), 3.62-3.55 (m, 1H, Hs), 3.31 (dd, J= 4.1, 9.5 Hz, 0.5H, Ht), 2.39 (s, 3H, Hu), 2.35 (s, 1.5H, Hv) (**Spectrum 29**). Data is consistent with literature values. [142]

^1H NMR ($CDCl_3$) cis/trans (1:0) δ 7.88 (d, J= 8.2 Hz, 2H, Ha), 7.33 (d, J= 8.2 Hz, 2H, Hb), 7.14 (d, J= 8.4 Hz, 2H, Hc), 6.80 (d, J= 8.5 Hz, 2H, Hd), 5.45-5.40 (m, 1H, He), 5.33-5.25 (m, 1H, Hf), 5.21-5.17 (m, 1H, Hg), 4.02 (d, J= 7.2 Hz, 1H, Hh), 3.76 (s, 3H, Hi), 3.60-3.57 (m, 1H, Hj), 2.43 (s, 3H, Hk) (**Spectrum 30**)

^{13}C NMR ($CDCl_3$) cis/trans (1:0) δ 159.45, 144.67, 135.30, 130.05, 129.86, 128.77, 127.95, 124.64, 121.88, 113.86, 55.34, 47.43, 46.13, 21.77 (**Spectrum 32**)

HRMS: $[M-H]^+$ 328.1013 m/z (**Spectrum 35**)



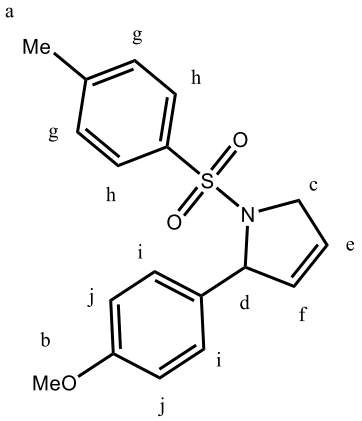
2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(trifluoromethyl)phenyl]-3-pyrroline (4a); was obtained by the general procedure from the reaction of 4-CF_3 imine (**1a**) (164 mg, 1.0 eq) and diethyl Br^- allyl sulfonium salt (**2a**) (116 mg, 1.1 eq) in dry ACN (1 mL). Upon initiation of heat and stirring under nitrogen, 1,1,3,3-Tetramethylguanidine (0.07 mL, 1.1 eq) was added dropwise. The reaction mixture went a dark red/brown, and was stirred for 4 h. at 50 °C. Upon completion, the crude mixture was rotary evaporated and characterised by ^1H and ^{19}F NMR in $CDCl_3$. The crude mixture was then purified by column chromatography, using a dry loading method in 98% hexane in EtAcO, which was gradually changed down to 85%. The column fraction were constantly monitored by TLC. The appropriate fractions were collected, rotary evaporated and dried on the high pump. Product was a fine, white powder (40%).

^1H NMR ($CDCl_3$) δ 2.38 (s, 3H, Ha), 4.41-4.27 (m, 2H, Hb), 5.56-5.51 (m, 1H, Hc), 5.63 (ddd, J= 6.4, 3.2, 2.1 Hz, 1H, Hd), 5.83 (ddd, J= 6.2, 2.9, 2 Hz, 1H, He), 7.19 (d, 8 Hz, 2H, Hf), 7.36 (d, 8.1 Hz, 2H, Hg), 7.52 (m, 4H, Hh) (**Spectrum 36**). Data is consistent with literature values. [138]

^{13}C NMR ($CDCl_3$) δ 144.56, 143.64, 135.47, 130.07, 129.69, 127.71, 127.34, 125.63-125.54, 125.49, 69.80, 55.71, 21.58 (**Spectrum 38)**

^{19}F NMR ($CDCl_3$) δ -62.50 (**Spectrum 41**)

HRMS: $[M-H]^+$ 366.0781 m/z (**Spectrum 42**)

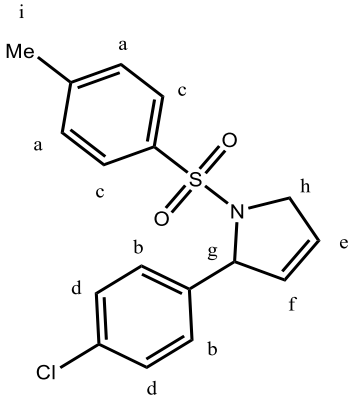


2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(methoxy)phenyl]-3-pyrroline (4b); was obtained by the general procedure from the reaction of 4-OMe imine (**1b**) (145 mg, 1.0 eq) and diethyl Br^- allyl sulfonium salt (**2a**) (116 mg, 1.1 eq) in dry ACN (1 mL). Upon initiation of heat and stirring under nitrogen, 1,8-diazabicyclo[5.4.0]undec-7-ene (0.08 mL, 1.1 eq) was added dropwise. The reaction mixture went a dark red/brown, and was stirred for 4 h. at 50 °C. Upon completion, the crude mixture was rotary evaporated and characterised by ^1H and NMR in $CDCl_3$. The crude mixture was then purified by column chromatography, using a dry loading method in 98% hexane in EtAcO, which was gradually changed down to 85%. The column fraction were constantly monitored by TLC. The appropriate fractions were collected, rotary evaporated and dried on the high pump. Product was a fine, white powder (31%).

^1H NMR ($CDCl_3$) δ 2.37 (s, 3H, Ha), 3.78 (s, 3H, Hb), 4.34-4.18 (m, 2H, Hc), 5.50-5.45 (m, 1H, Hd), 5.61 (ddd, J= 6.4, 3.1, 2.1 Hz, 1H, He), 5.77 (ddd, J= 6.1, 2.9, 2 Hz, 1H, Hf), 6.80 (d, J= 8.7 Hz, 2H, Hg), 7.18 (m, 4H, Hh), 7.51 (d, J= 8.3 Hz, 2H, Hi) (**Spectrum 43**). Data is consistent with literature values. [139]

^{13}C NMR ($CDCl_3$) δ 159.44, 143.14, 135.89, 132.69, 130.83, 129.53, 128.74, 127.37, 124.48, 113.94, 69.82, 55.45, 55.34, 21.61 (**Spectrum 45**)

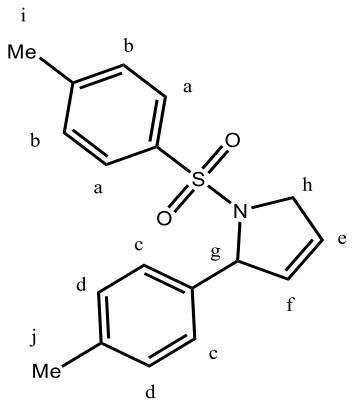
HRMS: $[M+H]^+$ 330.1158 m/z (**Spectrum 48**)



2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(chloro)phenyl]-3-pyrroline (4c); was obtained by the general procedure from the reaction of 4-Cl imine (**1c**) (147 mg, 1.0 eq) and THT Br^- allyl sulfonium salt (**2d**) (115 mg, 1.1 eq) in dry ACN (1 mL). Upon initiation

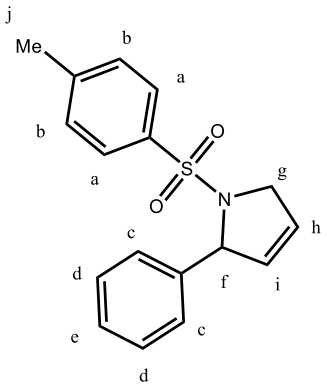
of heat and stirring under nitrogen, 1,8-diazabicyclo[5.4.0]undec-7-ene (0.15 mL, 2.0 eq) was added dropwise. The reaction mixture went a dark red/brown, and was stirred for 18 h. at 82 °C. Upon completion, the crude mixture was filtered through a celite and alumina plug and then rotary evaporated and characterised by ^{1}H NMR in $CDCl_3$. The crude mixture was then purified by column chromatography, using a wet loading method in 85% hexane in EtAcO The column fraction were constantly monitored by TLC. The appropriate fractions were collected, rotary evaporated and dried on the high pump. Product was white powder (12%).

^{1}H NMR ($CDCl_3$) δ 7.52 (d, 8.4 Hz, 2H, Ha), 7.24 (d, 8.6 Hz, 2H, Hb), 7.21 (d, 8.4 Hz, 2H, Hc), 7.18 (d, 8.6 Hz, 2H, Hd), 5.80 (ddd, J= 6.2, 3, 1.9 Hz, 1H, He), 5.61 (ddd, 6.4, 3.3, 2.2 Hz, 1H, Hf), 5.49-5.46 (m, 1H, Hg), 4.35-4.24 (m, 2H, Hh), 2.40 (s, 3H, Hi). (**Spectrum 49**). Data is consistent with literature values. [138]



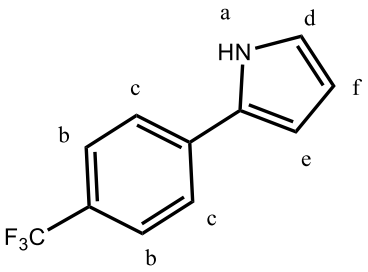
2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(methyl)phenyl]-3-pyrroline (4d); was obtained by the general procedure from the reaction of 4-Me imine (**1d**) (137 mg, 1.0 eq) and THT Br^- allyl sulfonium salt (**2d**) (115 mg, 1.1 eq) in dry ACN (1 mL). Upon initiation of heat and stirring under nitrogen, 1,8-diazabicyclo[5.4.0]undec-7-ene (0.15 mL, 2.0 eq) was added dropwise. The reaction mixture went a dark red/brown, and was stirred for 18 h. at 82 °C. Upon completion, the crude mixture was filtered through a celite and alumina plug and then rotary evaporated and characterised by ^{1}H NMR in $CDCl_3$. The crude mixture was then purified by column chromatography, using a wet loading method in 85% hexane in EtAcO The column fraction were constantly monitored by TLC. The appropriate fractions were collected, rotary evaporated and dried on the high pump. Product was white powder (7%).

^{1}H NMR ($CDCl_3$) δ 7.52 (d, 8.2 Hz, 2H, Ha), 7.19 (d, 8.2 Hz, 2H, Hb), 7.14 (d, 8 Hz, 2H, Hc), 7.09 (d, 8 Hz, 2H, Hd), 5.77 (ddd, 6, 2.9, 1.9 Hz, 1H, He), 5.63 (ddd, 6.4, 3.4, 2.2 Hz, 1H, Hf), 5.48-5.40 (m, 1H, Hg), 4.34-4.22 (m, 2H, Hh), 2.39 (s, 3H, Hi), 2.33 (s, 3H, Hj) (**Spectrum 50**). Data is consistent with literature values. [139]



2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-phenyl]-3-pyrroline (4e); was obtained by the general procedure from the reaction of 4-H imine (**1e**) (130 mg, 1.0 eq) and THT Br^- allyl sulfonium salt (**2d**) (115 mg, 1.1 eq) in dry ACN (1 mL). Upon initiation of heat and stirring under nitrogen, 1,8-diazabicyclo[5.4.0]undec-7-ene (0.15 mL, 2.0 eq) was added dropwise. The reaction mixture went a dark red/brown, and was stirred for 18 h. at 82 °C. Upon completion, the crude mixture was filtered through a celite and alumina plug and then rotary evaporated and characterised by ^{1}H NMR in $CDCl_3$. The crude mixture was then purified by column chromatography, using a wet loading method in 85% hexane in EtAcO The column fraction were constantly monitored by TLC. The appropriate fractions were collected, rotary evaporated and dried on the high pump. Product was white powder (4%).

^{1}H NMR ($CDCl_3$) δ 7.51 (d, 8.3 Hz, 2H, Ha), 7.30-7.23 (m, 5H, Hb), 7.19 (d, 7.9 Hz, 2H, Hc), 5.79 (ddd, J= 6, 3, 2.3 Hz, 1H, Hd), 5.65 (ddd, 6.3, 3.3, 2.2 Hz, 1H, He), 5.53-5.50 (m, 1H, Hf), 4.38-4.23 (m, 2H, Hg), 2.38 (s, 3H, Hh) (**Spectrum 51**). Data is consistent with literature values. [139]



2-[4-(Trifluoromethyl)phenyl]-3-pyrrole (5a); was obtained by the general procedure from the reaction of 4-CF_3 imine (**1a**) (164 mg, 1.0 eq) and THT Br^- allyl sulfonium salt (**2d**) (115 mg, 1.1 eq) in dry ACN (1 mL). Upon initiation of heat and stirring under nitrogen, 1,8-diazabicyclo[5.4.0]undec-7-ene (0.15 mL, 2.0 eq) was added dropwise. The reaction mixture went a dark red/brown, and was stirred for 18 h. at 82 °C. Upon completion, the crude mixture was filtered through a celite and alumina plug and then rotary evaporated and characterised by ^{1}H NMR in $CDCl_3$. The crude mixture was then purified by column chromatography, using a wet loading method in 85% hexane in EtAcO The column fraction were constantly monitored by TLC. The appropriate fractions were collected, rotary evaporated and dried on the high pump. Product was white/red powder (20%).

^{1}H NMR ($CDCl_3$) δ 8.52 (s, 1H, Ha), 7.61 (d, J= 8.3 Hz, 2H, Hb), 7.55 (d, J= 8.3 Hz, 2H, Hc), 6.95-6.91 (m, 1H, Hd), 6.65-6.62 (m, 1H, He), 6.65-6.32 (m, 1H, Hf) (**Spectrum 52**). Data is consistent with literature values. [140]

^{19}F NMR ($CDCl_3$) δ -62.32 (**Spectrum 53**)

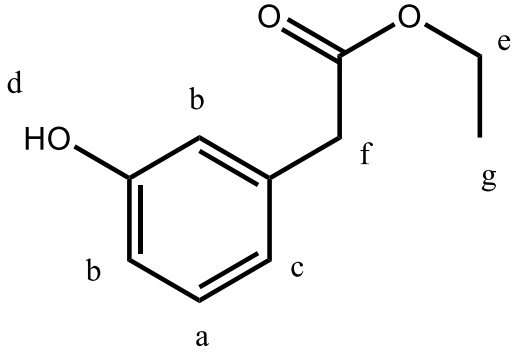
6.1.5. Additional methods

Crude analysis of aziridination reaction: to a flame dried round bottom flask under N_2, imine (**1**) (1.0 eq) and sulfonium salt (**2**) (1.1-2.0 eq) were added with dry ACN. Upon initiation of heat and stirring under nitrogen, base (1.0-2.0 eq) was added dropwise. The reaction mixture went a dark yellow/brown, and was stirred for varying time and temperature. Upon completion, the crude mixture was rotary evaporated and characterised by ^{1}H NMR in $CDCl_3$.

Aziridine (3) to pyrroline (4) rearrangement study: to a flame dried round bottom flask under N_2, aziridine **3a** (1.0 eq.) was added with dry ACN (1 mL) and additive (1.1 eq.). The reaction mixture was stirred at rt or heated for 18 hours. Upon completion, the crude mixture was rotary evaporated and characterised by ^{1}H NMR in $CDCl_3$.

6.1. Chapter 3 methods

6.1.1. Synthesis of ethyl 2-(3-hydroxy)phenylacetate (**9**)



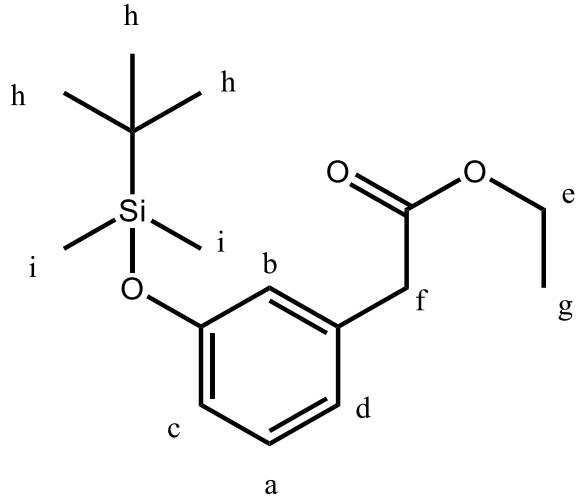
Ethyl 2-(3-hydroxyphenyl)acetate (9); was obtained by placing 3-hydroxyphenylacetic acid (10 g) in a 500 mL round bottom flask with the addition of EtOH (200 mL) and H_2SO_4 (6.1 mL). The reaction mixture was stirred under reflux for 18 h and was pale brown. Upon completion, the mixture was rotary evaporated before the addition of EtAcO (30 mL) , followed by washing with H_2O (3×10 mL) and brine (10 mL) and drying over $MgSO_4$. Rotary evaporation of the organic layer yielded a dark brown oil which was not further purified (91 %).

^{1}H NMR ($CDCl_3$) δ 7.15 (t, J= 7.8 Hz, 1H, Ha), 6.82-6.79 (m, 2H, Hb), 6.78-6.76 (d, J= 8.9 Hz, 1H, Hc), 6.75-6.71 (m, 1H, Hd), 4.16 (s, q, J= 7.1 Hz, 2H, He), 3.57 (s, 2H, Hf), 1.25 (t, J= 7.1 Hz, 3H, Hg) (**Spectrum 54**)

^{13}C NMR ($CDCl_3$) δ 172.80, 156.13, 135.31, 129.80, 121.37, 116.37, 114.42, 61.45, 41.36, 14.10 (**Spectrum 56**)

HRMS: $[M-H]^+$ 179.0714 m/z (**Spectrum 59**)

6.1.2. Synthesis of ethyl 2-(3-tert-butyldimethylsilyloxy)phenyl acetate (**10**)



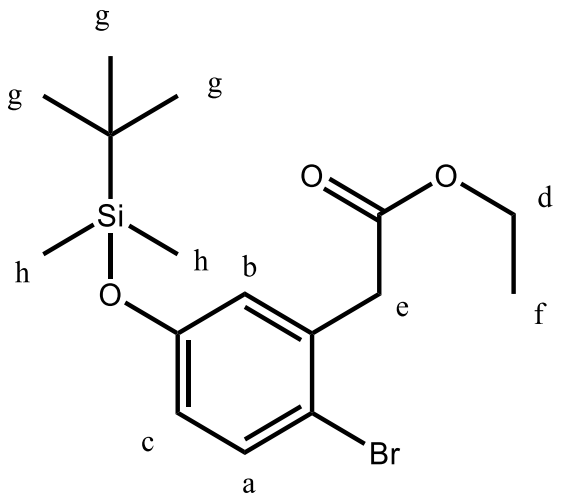
Ethyl 2-(3-tert-butyldimethylsilyloxy)phenyl acetate (10); was obtained by adding imidazole (100 mmol, 3.0 eq.) to a round bottomed flask containing compound **9** (33 mmol, 1.0 eq.) in DMF (12 mL) and allowing to stir at room temperature for 15 mins. A solution of tert-Butylmethylsilyl Chloride (36 mmol, 1.1 eq.) in DMF (10 mL) was then added dropwise over 10 mins, before heating the reaction mixture to 80 °C for 18 h., at which point the mixture was pale brown. The reaction was quenched with the addition of ice cold H_2O (10 mL) followed by extraction with Et_2O (2×10 mL) and washing with H_2O (10 mL) and brine (10 mL), drying over $MgSO_4$ and rotary evaporation The crude material was a pale brown oil, and was purified by column chromatography with silica gel and a mobile phase of 100% Hex. Purified product was a clear oil (71%).

^{1}H NMR ($CDCl_3$) δ 7.17 (t, J= 7.9 Hz, 1H, Ha), 6.88 (d, J= 7.7 Hz, 1H, Hb), 6.82-6.79 (m, 1H, Hc), 6.75 (d, J, 8.1 Hz, 1H, Hd), 4.15 (q, J= 7.1 Hz, 2H, He), 3.56 (s, 2H, Hf), 1.25 (t, J= 7.1 Hz, 3H, Hg), 1.0 (s, 9H, Hh), 0.21 (s, 6H, Hi) (**Spectrum 60)**

^{13}C NMR ($CDCl_3$) δ 171.53, 155.83, 135.61, 129.43, 122.30, 121.16, 118.81, 60.89, 41.46, 25.78, 18.29, 14.27, -4.33 (**Spectrum 62**)

HRMS: $[M-H]^+$ 293.1578 m/z (**Spectrum 65**)

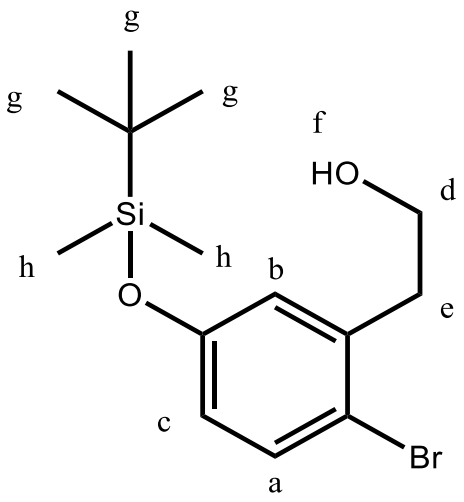
6.1.3. Synthesis of ethyl 6-bromo-3-(tert-butyldimethylsilyloxy)phenyl acetate (**11**)



Ethyl 6-bromo-3-(*tert*-butyldimethylsilyloxy)phenyl acetate (11); was prepared by dissolving compound **10** (17 mmol, 1.0 e.) in AcOH (96 mL) with NaOAc (17 mmol, 1.0 eq) and allowing to stir in a round bottom flask at room temperature for 15 mins. This was followed by the dropwise addition of a solution of Br_2 (17 mmol, 1.0 eq) in AcOH (51 mL). The reaction mixture was stirred at room temperature for 2.5 h. at which point it was wine red/brown. Reaction was quenched with the addition of H_2O (30 mL) and Et_2O (30 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were washed with of H_2O (2×30 mL) and saturated $NaHCO_3$ solution (9×15 mL) before an additional washing with H_2O (30 mL) and brine (30 mL), followed by drying over $MgSO_4$ and rotary evaporation. The crude material was an orange/brown oil and purification was performed with column chromatography with silica gel and a mobile phase of 98% Hex, 2% Et_2O. Purified material was clear, light brown oil (57%).

^{1}H NMR ($CDCl_3$) δ 7.37 (d, J= 8.6 Hz, 1H, Ha), 6.80 (d, J= 2.9 Hz, 1H, Hb), 6.63 (dd, 8.6, 2.9 Hz, 1H, Hc), 4.17 (q, J= 7.1 Hz, 2H, Hd), 3.70 (s, 2H, He), 1.25 (t, J= 7.1 Hz, 3H, Hf), 0.97 (s, 9H, Hg), 0.18 (s, 6H, Hh) (**Spectrum 66**). Data is consistent with literature values.[145]

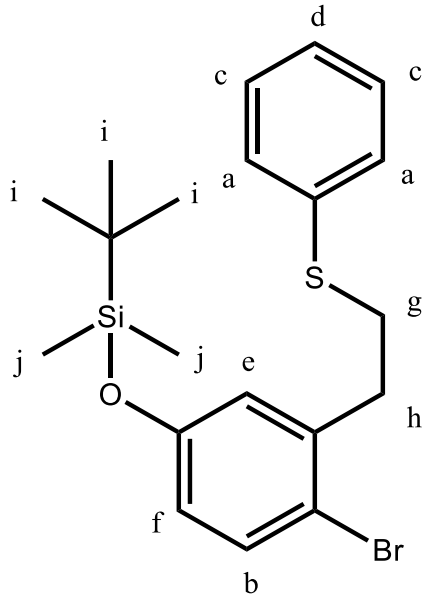
6.1.4. Synthesis of 4-bromo-3-(2-hydroxyethyl)phenyl tert-butyldimethylsilyl ether(**12**)



4-Bromo-3-(2-hydroxyethyl)phenyl *tert*-butyldimethylsilyl ether (12); was prepared by the addition of compound **11** (3.3 mmol, 1.0 eq) in Dry Et_2O (37 mL) to a flame dried round bottom flask under N_2. The flask was cooled to -20 °C in a bath of ice, water and NaCl. $LiAlH_4$ (4.4 mmol, 1.1 eq.) was then added and the reaction was stirred at 0 °C for 70 mins under N_2. The cloudy white reaction mixture was then quenched with 25 mL of 1 M HCl, and 1 M HCl was then added dropwise until any remaining $LiAlH_4$ was neutralized. The organic phase was then removed and the aqueous phase was extracted with Et_2O (3×15 mL). The combined organic phase were then washed with H_2O (15 mL) and brine (15 mL) and dried over $MgSO_4$ before rotary evaporation to yield a clear, colourless/pale yellow oil (79%).

^1H NMR ($CDCl_3$) δ 7.37 (d, J= 8.6 Hz, 1H, Ha), 6.77 (d, J= 2.9 Hz, 1H, Hb), 6.59 (dd, J= 8.6, 2.9 Hz, 1H, Hc), 3.85 (t, J= 6.8 Hz, 2H, Hd), 2.95 (t, J= 6.8 Hz, 2H, He), 1.66 (s, 1H, Hf), 0.97 (s, 9H, Hg), 0.18 (s, 6H, Hh) (**Spectrum 67**). Data is consistent with literature values. [145]

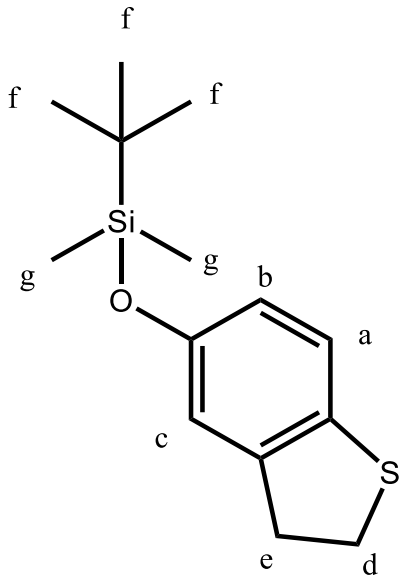
6.1.5. Synthesis of 4-bromo-3-[2-(phenylthio)ethyl]phenyl tert-butyldimethylsilyl ether (**13**)



4-Bromo-3-[2-(phenylthio)ethyl]phenyl *tert*-butyldimethylsilyl ether (13); was prepared by dissolving compound **12** (5.7 mmol, 1.0 eq) in dry THF (45 mL) in a flame dried round bottom flask under N_2 followed by the addition of Diphenyl disulfide (6.3 mmol, 1.1 eq.) and Tri-*n*-butylphosphine (6.3 mmol, 1.1 eq.). Reaction was stirred at reflux for 1 h., followed by stirring at room temperature for a further 18 h., all while under N_2. The mixture was clear brown, and reaction was quenched with the addition of saturated $NaHCO_3$ solution (20 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2×10 mL). The combined organic layers were then washed with saturated $NaHCO_3$ solution (10 mL), H_2O (10 mL) and brine (10 mL) before drying over $MgSO_4$ and rotary evaporation. Crude material was a clear brown oil. Purification was performed by column chromatography with silica gel and a mobile phase of 97% Hex., 3% Et_2O, which was gradually change to 93% Hex., 7% Et_2O. Purified material was a clear, colurless/pale brown oil (49%)

^{1}H NMR ($CDCl_3$) δ 7.42 (d, J= 7.9 Hz, 2H, Ha), 7.34 (d, J= 8.6 Hz, 1H, Hb), 7.32 (t, J= 7.5 Hz, 2H, Hc), 7.21 (t, J= 7.4 Hz, 1H, Hd), 6.75 (d, J= 2.9 Hz, 1H, He), 6.62 (dd, J= 8.6, 2.9 Hz, 1H, Hf), 3.18 (t, J= 7.5 Hz, 2H, Hg), 3.00 (t, J= 7.5 Hz, 2H, Hh), 1.01 (s, 9H, Hi), 0.22 (s, 6H, Hj). (**Spectrum 68**). Data is consistent with literature values. [145]

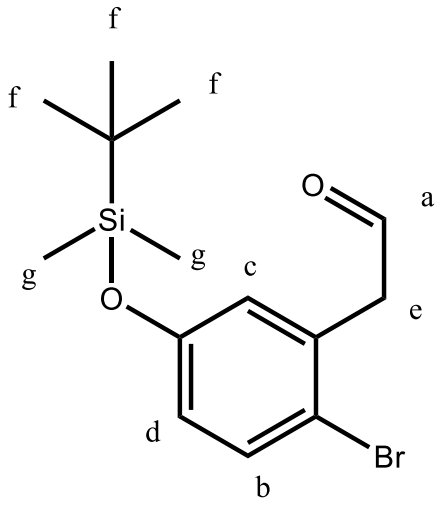
6.1.6. Synthesis of 5-(tert-butyldimethylsilyloxy)-2,3-dihydrobenzo[b]thiophene (**6**)



5-(*tert*-Butyldimethylsilyloxy)-2,3-dihydrobenzo[*b*]thiophene (6); was prepared by dissolving 4-bromo-3-[2-(phenylthio)ethyl]phenyl *tert*-butyldimethylsilyl ether (**13**) (1.0 eq, 0.1 mmol) in dry ACN (9 mL) in a flame dried round bottom flask under N_2. ABCN (0.075 eq., 0.0075 mmol) was then added and the reaction mixture was heated to reflux before the addition of $(tBu)_3SnH$ (1.2 eq., 0.12 mmol). The reaction mixture was then refluxed for 18 hr. before the addition of the same quantities of ABCN and $(tBu)_3SnH$. The reaction then proceeded at reflux for a further 168 hr. with the addition of the same quantities of ABCN and $(tBu)_3SnH$ every 24 hr. The crude reaction mixture was also monitored by ^1H NMR by the extraction of approximately 0.1 mL of the mixture via syringe and needle and rotary evaporating the aliquot and dissolving in $CDCl_3$ and submitting for NMR. At completion, the reaction flask was cooled and rotary evaporated to leave a crude material of a clear, colourless oil which was purified by column chromatography using a silica stationary phase and a mobile phase of 95% Hex., 5 % Tol. The purified product was a clear, colurless oil (28%)

^1H NMR ($CDCl_3$) δ 7.01 (d, J= 8.4 Hz, 1H, Ha), 6.70-6.68 (m, 1H, Hb), 6.61-6.58 (m, 1H, Hb), 6.61-6.58 (m, 1H, Hc), 3.33 (t, J= 7.6 Hz, 2H, Hd), 3.19 (t, J= 7.6 Hz, 2H, He), 0.96 (s, 9H, Hf), 0.16 (s, 6H, Hg) (**Spectrum 69**). Data is consistent with literature values. [145]

6.1.7. Synthesis of 4-bromo-3-[2-(acetaldehyde)phenyl] tert-butyldimethylsilyl ether (**14**)



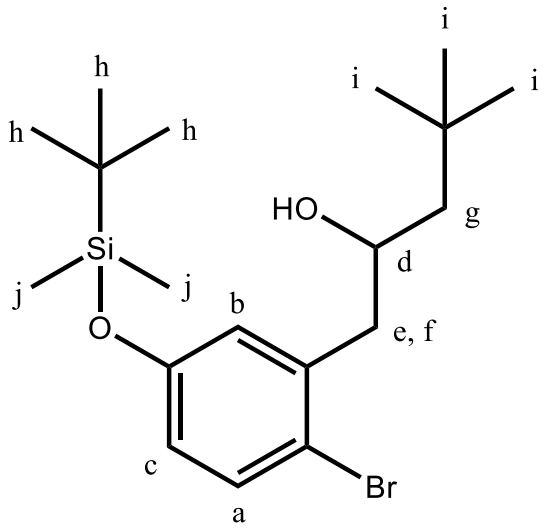
4-Bromo-3-[2-(acetaldehyde)phenyl] *tert*-butyldimethylsilyl ether (14); was prepared by dissolving 4-bromo-3-(2-hydroxyethyl)phenyl *tert*-butyldimethylsilyl ether (**11**) (1.0 eq. 11 mmol) in dry DCM (24 mL) in a flame dried round bottom flame under N_2. The flask was then placed in a bath of EtOAc, before liquid N_2 was slowly added to the EtOAc bath until the EtOAc was frozen solid. Liquid N_2 was continuously added to the EtOAc bath every 2-4 mins for the entirety of the reaction, to keep the bath temperature at -84 °C. DIBAL-H, 2.4 M in dry Toluene (1.5 eq., 16.75 mL) was then added dropwise over 30 mins. The reaction mixture was then allowed to stir for an additional 30 mins, before removing the round bottom flask from the bath and quenching the reaction with bench MeOH (13 mL). The reaction mixture was then poured into a conical flask containing saturated Potassium Sodium Tartrate solution (Rochelle's solution) (77 mL). The mixture was allowed to stir for 1 hr. The organic layer was then removed in a separating funnel, and the aqueous phase was extracted with EtOAc (3×20 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL) before drying over $MgSO_4$ and rotary evaporation. The product was a clear, yellow oil/semi-solid which required no further purification (68%)

^{1}H NMR ($CDCl_3$) δ 9.71 (t, J= 1.8 Hz, 1H, Ha), 7.42 (d, J= 8.4 Hz, 1H, Hb), 6.73 (d, J= 2.9 Hz, 1H, Hc), 6.67 (d, J= 8.4, 2.9 Hz, 1H, Hd), 3.77 (d, J= 1.8 Hz, 2H, He), 0.97 (s, 9H, Hf), 0.19 (s, 6H, Hg) (**Spectrum 70**)

^{13}C NMR ($CDCl_3$) δ 198.24, 155.46, 133.64, 133.55, 123.55, 121.09, 116.15, 50.57, 25.69, 18.25, -4.39 (**Spectrum 72**)

HRMS: $[M-H]^+$ 327.0421 m/z (**Spectrum 75**)

6.1.8. Synthesis of 4-bromo-3-(2-hydroxy-4, 4, 4-trimethylbutyl)phenyl tert-butyldimethylsilyl ether (**15a**)



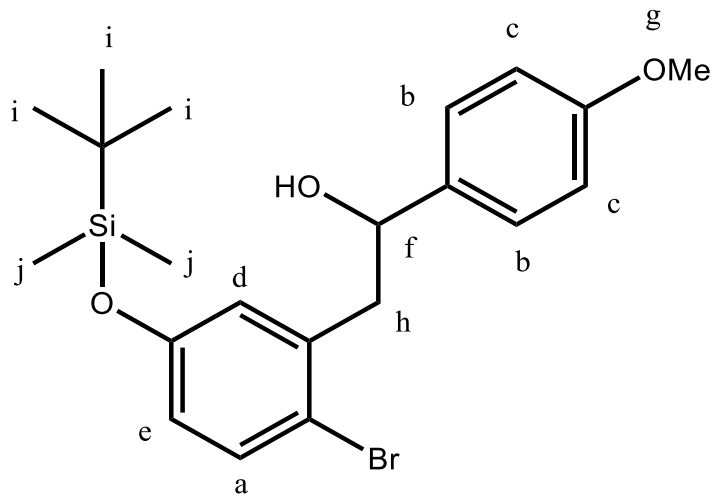
4-Bromo-3-(2-hydroxy-4, 4, 4-trimethylbutyl)phenyl *tert*-butyldimethylsilyl ether (15a); was prepared by dissolving 1-bromo-2, 2-dimethylpropane (1.5 eq, 1.9 mmol) in dry THF (1 mL) in a flame dried round bottom flask under N_2 with Mg turnings (2.0 eq.) and an iodine crystal. The solution was stirred and heated with the heat gun for approximately 1 min before placing the flask under reflux heat for 2 hr. In a separate flask under N_2 4-bromo-3-[2-(acetaldehyde)phenyl] *tert*-butyldimethylsilyl ether (**14)**, (1.0 eq. 1.3 mmol) was dissolved in dry THF (1 mL). This was then added dropwise to the main reaction mixture with a syringe and needle, with an additional 1 mL of dry THF used to wash the flask and transfer washings to the reaction flask. The reaction was refluxed for 2 hr. Upon completion, the mixture was poured into a saturated solution of NH_4Cl (5 mL) and cooled to 0 °C with ice and stirred. The aqueous layer was then extracted with Et_2O (3 × 5 mL) and the combined organic phases were washed with water (5 mL) and brine (5 mL) before drying over $MgSO_4$ and rotary evaporation. The crude material was a yellow/orange oil which was purified by column chromatography using a silica gel stationary phase and a mobile phase of 99% Hex, 1% Et_2O to yield a the product which was clear, yellow oil (31%)

^{1}H NMR ($CDCl_3$) δ 7.38 (d, J= 8.6 Hz, 1H, Ha), 6.75 (d, J= 2.9 Hz, 1H, Hb), 6.60 (dd, J= 2.9, 8.6 Hz, 1H, Hc), 4.10-4.04 (m, 1H, Hd), 2.88 (dd, J= 4.3, 13.5 Hz, 1H, He), 2.69 (dd, J= 8.7, 13.5 Hz, 1H, Hf), 1.49-1.46 (m, 2H, Hg), 0.97 (s, 9H, Hh), 0.96 (s, 9H, Hi), 0.18 (s, 6H, Hj) (**Spectrum 76**)

^{13}C NMR ($CDCl_3$) δ 155.09, 139.28, 133.63, 123.86, 120.21, 116.20, 68.95, 50.70, 46.26, 30.50, 30.24, 25.79, 18.14, -4.30 (**Spectrum 78**)

HRMS: M^+ 383.1400 m/z (**Spectrum 81**)

6.1.9. Synthesis of 4-bromo-3-[2-hydroxy-2-(p-anisole)]phenyl tert-butyldimethylsilyl ether (**15b**)



4-Bromo-3-[2-hydroxy-2-(p-anisole)]phenyl *tert*-butyldimethylsilyl ether (15b); was prepared by dissolving 4-bromoanisole (1.5 eq, 1.9 mmol) in dry THF (1 mL) in a flame dried round bottom flask under N_2 with Mg turnings (2.0 eq.) and an iodine crystal. The solution was stirred and heated with the heat gun for approximately 1 min before placing the flask under reflux heat for 2 hr. In a separate flask under N_2, 4-bromo-3-[2-(acetaldehyde)phenyl] *tert*-butyldimethylsilyl ether (**14**) (1.0 eq. 1.3 mmol) was dissolved in dry THF (1 mL). This was then added dropwise to the main reaction mixture with a syringe and needle, with an additional 1 mL of dry THF used to wash the flask and transfer washings to the reaction flask. The reaction was refluxed for 2 hr. Upon completion, the mixture was poured into a saturated solution of NH_4Cl (5 mL) and cooled to 0 °C with ice and stirred. The aqueous layer was then extracted with Et_2O (3 × 5 mL) and the combined organic phases were washed with water (5 mL) and brine (5 mL) before drying over $MgSO_4$ and rotary evaporation. The crude material was a yellow/orange oil which was purified by column chromatography using a silica gel stationary phase and a mobile phase of 99% Hex, 1% Et_2O to yield a the product which was clear, yellow oil (28%)

^{1}H NMR ($CDCl_3$) δ 7.38 (d, J= 8.6 Hz, 1H, Ha), 7.31 (d, J= 8.6 Hz, 2H, Hb), 6.88 (d, J= 8.6 Hz, 2H, Hc), 6.63 (d, J= 3 Hz, 1 H, Hd), 6.60 (dd, J= 8.6, 3 Hz, 1H, He), 4.98-4.94 (m, 1H, Hf), 3.80 (s, 3H, Hg), 3.11-3.01 (m, 2H, Hh), 1.87 (d, J= 2.9 Hz, Hi, 1H) 0.95 (s, 9H, Hj), 0.12 (s, 6H, Hk) **(Spectrum 82)**

^{13}C NMR ($CDCl_3$) δ 159.29, 155.05, 138.74, 136.06, 133.47, 127.20, 123.91, 120.31, 116.19, 113.98, 73.22, 55.42, 46.35, 25.77, 18.31, -4.38 (**Spectrum 84**)

HRMS: M^+ 433.0840 m/z (**Spectrum 86**)

6.1.10. Additional Methods

Method for nitration of 6: To a round bottom flask, **6** (1.0 eq., 0.05 mmol) was added along with ACN (0.5 mL), acid (2.0 eq) and $NaNO_3$ (2.0 eq.) and the reaction was refluxed for 4 hours before quenching the reaction mixture with a mix of ice cold water and 4M

NaOH followed by extraction with EtOAc (3×1 mL) and washing with water (1 mL) and brine (1 mL) before drying over $MgSO_4$ followed by rotary evaporation. The material was submitted for NMR or analysis.

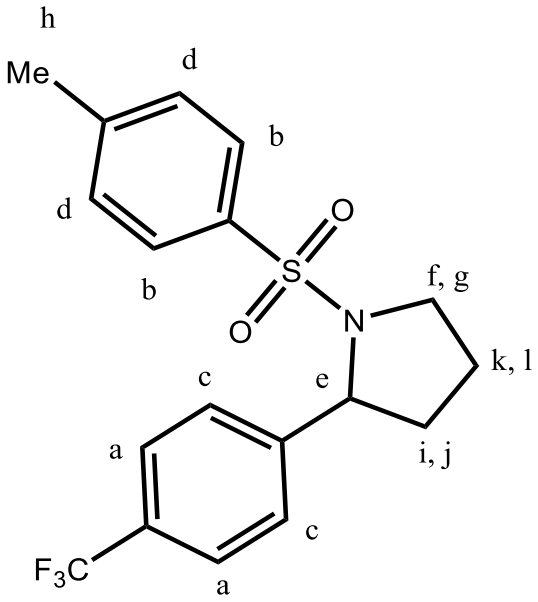
Sulfonation of phenylacetic acid: To a round bottom flask, phenylacetic acid (1.0 eq., 2 mmol) was added along with sulfuric acid or oleum (4 mL) and was heated to 80-120°C for 4-18 hours before quenching the reaction mixture with a mix of ice cold water and 4M NaOH followed by extraction with EtOAc (3×5 mL) and washing with water (5 mL) and brine (5 mL) before drying over $MgSO_4$ followed by rotary evaporation. The material was submitted for NMR or analysis.

Sulfonation of 1-phenylethanol: To a round bottom flask, 1-phenylethanol (1.0 eq., 2 mmol) was added along with sulfuric acid or oleum (4 mL) and was heated to 80-120°C for 4-18 hours before quenching the reaction mixture with a mix of ice cold water and 4M NaOH followed by extraction with EtOAc (3×5 mL) and washing with water (5 mL) and brine (5 mL) before drying over $MgSO_4$ follwed by rotary evaporation. The material was submitted for NMR or analysis.

Bromination of 1-phenylethanol using Fe(III)Br_3: To a round bottom flask, 1-phenylethanol (1.0 eq., 2 mmol) was added along with DCM (10 mL) and powdered iron (~1g) before the dropwise addition of Br_2 (1.0 eq.) dissolved in DCM (3-4 mL). The reaction mixture was stirred at room temperature or cooled to 0° in an ice bath. Upon completion, the reaction mixture passed through filter paper to remove residual iron powder before neutralising with saturated $NaHCO_3$ and extraction with Et_2O (3×5 mL) and washing with water (5 mL) and brine (5 mL) before drying over $MgSO_4$ followed by rotary evaporation. The material was submitted for NMR analysis.

6.2. Chapter 4 methods

6.2.1. Synthesis of 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl] pyrrolidine (**19a**)

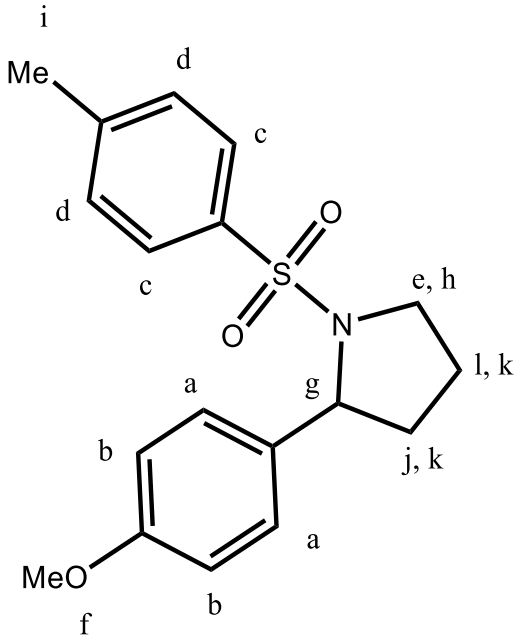


1-[(4-Methylphenyl)sulfonyl] 2-[4-(trifluoromethyl] pyrrolidine (19a); was prepared by dissolving 2,5-dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(trifluoromethyl)phenyl]-3-pyrroline (**4a) (**1.0 eq., 1.0 mmol) in DCM (5 mL) under an atmosphere of N_2. Pd/C (0.06 eq., 0.06 mmol) was then added with the addition of another 5 mL of DCM. The reaction mixture was then placed under an atmosphere of H_2 and stirred at room temperature for 48 hr. Upon completion, the reaction mixture was filtered through a celite plug. The filtrate was then placed in a conical flask with the addition of a spatula tip of charcoal and stirred for 1 h. This was then filtered through a celite plug and the resulting filtrate was rotary evaporated to yield a clear, colurless, oily semi solid which was not further purified (78%).

^{1}H NMR ($CDCl_3$) δ 7.67 (d, J= 8.3 Hz, 2H, Ha), 7.54 (d, J= 8 Hz, 2H, Hb), 7.44 (d, J= 8.2 Hz, 2H, Hc), 7.28 (d, J= 8 Hz, 2H, Hd), 4.80-4.76 (m, 1H, He), 3.67-3.61 (m, 1H, Hf), 3.43-3.37 (m, 1H, Hg), 2.40 (s, 3H, Hh), 2.05-1.97 (m, 1H, Hi), 1.85-1.72 (m, 2H, Hj, Hk), 1.67-1.60 (m, 1H, Hl) (**Spectrum 87**). Data is consistent with literature values. [158]

^{13}C NMR ($CDCl_3$) δ 147.29, 143.73, 134.94, 129.80, 127.63, 126.66, 125.51-125.40, 62.99, 49.62, 39.95, 24.14, 21.63 (**Spectrum 89**)

6.2.2. Synthesis of 1-[(4-methylphenyl)sulfonyl] 2-[4-(methoxy] pyrrolidine (**19b**)



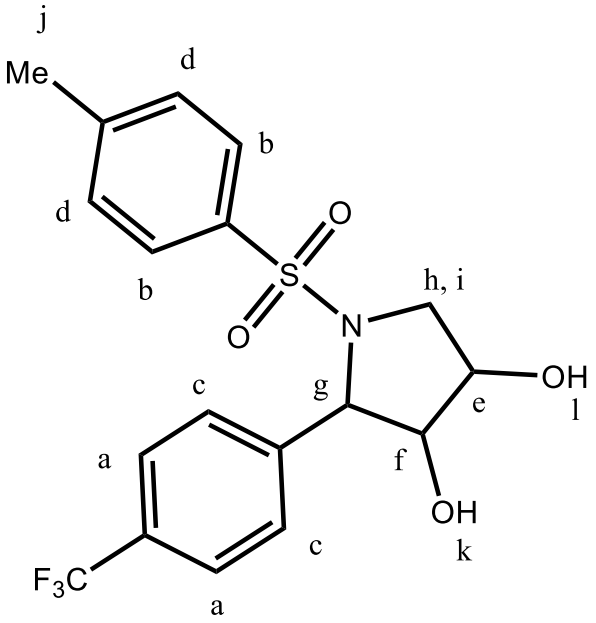
1-[(4-Methylphenyl)sulfonyl] 2-[4-(methoxy] pyrrolidine (19b); was prepared by dissolving 2,5-dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(methoxy)phenyl]-3-pyrroline (**4b) (**1.0 eq., 1.0 mmol) in DCM (5 mL) under an atmosphere of N_2. Pd/C (0.06 eq., 0.06 mmol) was then added with the addition of another 5 mL of DCM. The reaction mixture was then placed under an atmosphere of H_2 and stirred at room temperature for 48 hr. Upon completion, the reaction mixture was filtered through a celite plug. The filtrate was then placed in a conical flask with the addition of a spatula tip of charcoal and stirred for 1 h. This was then filtered through a celite plug and the resulting filtrate was rotary evaporated to yield clear, white crystals which were not further purified (71%)

^{1}H NMR ($CDCl_3$) δ 7.66 (d, J= 8.2 Hz, 2H, Ha), 7.27 (d, J= 8 Hz, 2H, Hb), 7.22 (d, J= 8.3 Hz, 2H, Hc), 6.83 (d, J= 8.5 Hz, 2H, Hd), 4.75-4.71 (m, 1H, He), 3.79 (s, 3H, Hf), 3.62-3.57 (m, 1H, Hg), 3.44-3.37 (m, 1H, Hh), 2.42 (s, 3H, Hi), 1.99-1.91 (m, 1H, Hj), 1.90-1.76 (m, 2H, Hk, Hl), 1.68-1.62 (m, 1H, Hl) (**Spectrum 92**). Data is consistent with literature values. [158]

^{13}C NMR ($CDCl_3$) δ 158.78, 143.30, 135.37, 135.26, 129.64, 127.61, 127.45, 113.81, 62.94, 55.41, 49.42, 35.90, 24.11, 21.63 (**Spectrum 94**)

HRMS: $[M+H]^+$ 332.1326 (**Spectrum 96**)

6.2.3. Synthesis of 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl]-3,4-dihydroxypyrrolidine (**20a**)



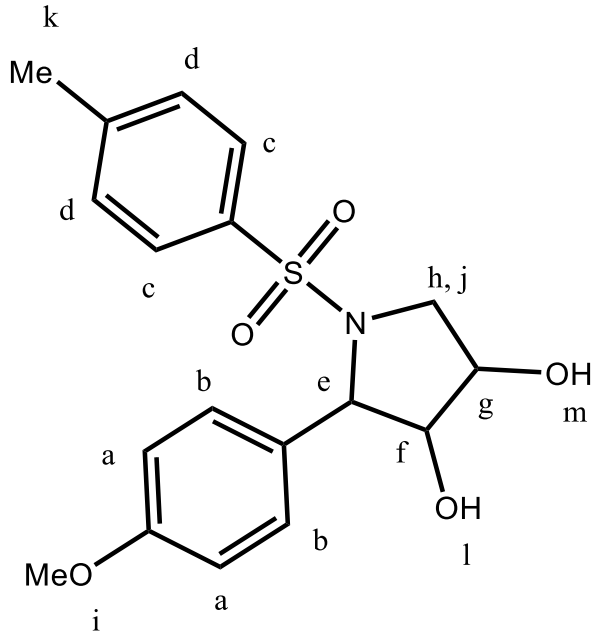
1-[(4-Methylphenyl)sulfonyl] 2-[4-(trifluoromethyl]-3,4-dihydroxypyrrolidine (20a); was prepared by disolving 2,5-dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(trifluoromethyl)phenyl]-3-pyrroline (**4a**) (1.0 eq., 2.9 mmol) in a solvent mixture of water/acetone/t-BuOH (6 mL: 2.5 mL: 2 mL) in a round bottom flask followed by the addition of NMO (3.0 eq., 9.0 mmol) and $K_2OsO_4.2H_2O$ (0.1 eq., 0.3 mmol). The reaction mixture was stirred at 50 °C for 48 h. Upon completion, saturated $NaHSO_3$ solution was added (5 mL) to the mixture and stirred. The aqueous phase was extracted with EtOAc (3×5 mL) and the combined organic phases were washed with water, brine and saturated $NaHSO_3$ solution before drying over $MgSO_4$ and rotary evaporation. The crude material was a grey-white semi-solid and was purified by column chromatography using a silica stationary phase and a mobile phase of Hexane 40%, EtOAc 60 % to yield the purified product as white crystals (57 %)

^{1}H NMR ($CDCl_3$) δ 7.66 (d, J= 7.8 Hz, 2H, Ha), 7.59 (d, J= 8.2 Hz, 2H, Hb), 7.48 (d, J= 7.8 Hz, 2H, Hc), 7.29 (d, J= 8.2 Hz, 2H, Hd), 4.52 (d, J= 5 Hz, 1H, He), 4.28-4.24 (m, 1H, Hf), 4.00-3.97 (m, 1H, Hg), 3.84 (dd, J= 11.3, 5 Hz, 1H, Hh), 3.53 (dd, J= 11.3, 4.4 Hz, 1H, Hi), 2.43 (s, 3H, Hj), 2.32 (s, 1H, Hc), 2.10 (s, 1H, Hl) **H_2O:** δ 1.56 (s) (**Spectrum 97**)

^{13}C NMR ($CDCl_3$) δ 129.72, 128.09, 127.01, 125.77, 80.03, 69.90, 67.79, 53.02, 21.72 (**Spectrum 99**)

HRMS: $[M+1]^+$ 402.0981 (**Spectrum 101**)

6.2.4. Synthesis of 1-[(4-methylphenyl)sulfonyl] 2-[4-(methoxy]-3,4-dihydroxypyrrolidine (**20b**)



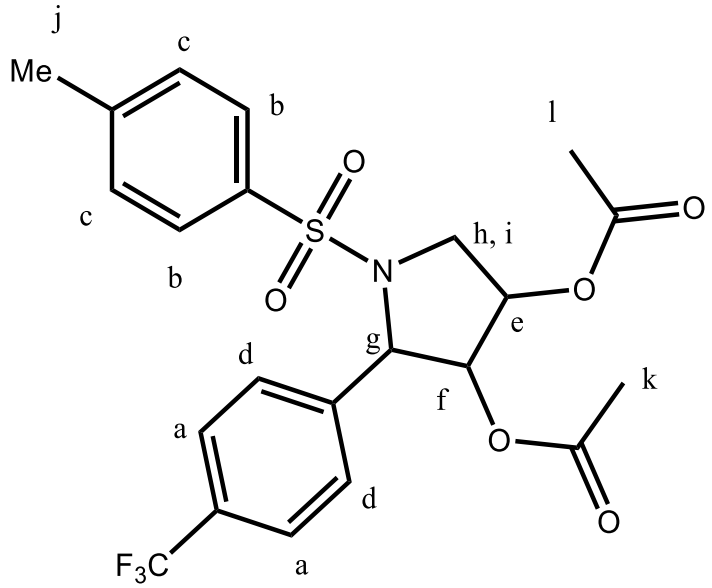
1-[(4-Methylphenyl)sulfonyl] 2-[4-(methoxy]-3,4-dihydroxypyrrolidine (20b); was prepared by disolving 2,5-dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(methoxy)phenyl]-3-pyrroline (**4b**) (1.0 eq., 2.9 mmol) in a solvent mixture of water/acetone/t-BuOH (6 mL: 2.5 mL: 2 mL) in a round bottom flask followed by the addition of NMO (3.0 eq., 9.0 mmol) and $K_2OsO_4.2H_2O$ (0.1 eq., 0.3 mmol). The reaction mixture was stirred at 50 °C for 48 hr. Upon completion, saturated $NaHSO_3$ solution was added (5 mL) to the mixture and stirred. The aqueous phase was extracted with EtOAc (3×5 mL) and the combined organic phases were washed with water, brine and saturated $NaHSO_3$ solution before drying over $MgSO_4$ and rotary evaporation. The crude material was a grey-white semi-solid and was purified by column chromatography using a silica stationary phase and a mobile phase of hexane 40%, EtOAc 60% to yield the purified product as white crystals (46%)

^{1}H NMR ($CDCl_3$) δ 7.66 (d, J= 8 Hz, 2H, Ha), 7.28 (d, J= 8 Hz, 2H, Hb), 7.25 (d, J= 8.3 Hz, 2H, 2H, Hc), 6.87 (d, J= 8.3 Hz, 2H, Hd), 4.45 (d, J= 4.4 Hz, 1H, He), 4.30-4.25 (m, 1H, Hf), 3.99-3.95 (m, 1H, Hg), 3.84-3.80 (m, 1H, Hh), 3.80 (s, 3H, Hi), 3.45 (d, J= 5 Hz, 1H, Hj), 2.24 (s, 3H, Hk), 2.25 (d, J= 4.4 Hz, Hl), 2.15 (d, J= 4.4 Hz, Hm). **H_2O:** 1.57 (s) (**Spectrum 102**)

^{13}C NMR ($CDCl_3$) δ 159.38, 143.73, 134.27, 131.36, 129.59, 128.04, 127.82, 114.20, 79.81, 69.54, 68.00, 55.46, 52.80, 21.71 (**Spectrum 104**)

HRMS: $[M-H]^+$ 362.1068 (**Spectrum 106**)

6.2.5. Synthesis of 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl)]-3,4-pyrrolidinedione, 3, 4 diacetate (**21a**)



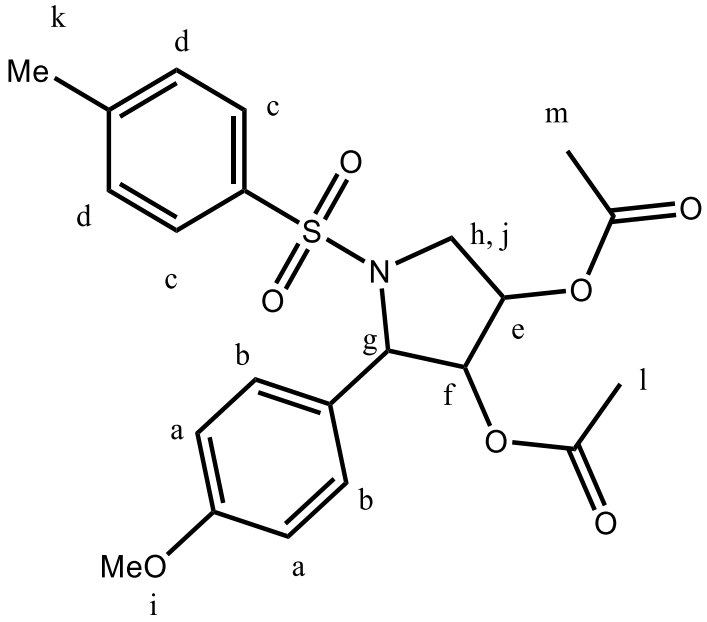
1-[(4-Methylphenyl)sulfonyl] 2-[4-(trifluoromethyl)]-3,4-pyrrolidinedione, 3, 4 diacetate (21a); was prepared by dissolving 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl]-3,4-dihydroxypyrrolidine (**20a**) (1.0 eq., 0.85 mmol) in DCM (35 mL) with acetic anhydride (2.5 eq., 2.1 mmol) and pyrridine (3.5 mL). The reaction mixture was stirred at room temperature for 18 hr. Upon completion, the reaction micture was added to a beaker containing 2M HCl solution (25 mL) and ice, and was stirred for 5-10 mins. The aqueous layer was then extracted with EtOAc (3×15 mL) and the combined organic layers were washed with saturated $NaHCO_3$ solution (6×15 mL), water (15 mL) and brine (15 mL) before drying over $MgSO_4$ and rotary evaporation to yield a clear, colourless oil which was not further purified (77%)

^{1}H NMR ($CDCl_3$) δ 7.69 (d, J= 8.3 Hz, 2H, Ha), 7.61 (d, J= 8.3 Hz, 2H, Hb), 7.56 (d, J= 8.3Hz, 2H, Hc), 7.35 (d, J= 8.3 Hz, 2H, Hd), 5.19-5.15 (m, 1H, He), 5.04 (t, J= 3.9 Hz, 1H, Hf), 4.75 (d, J= 3.9 Hz, 1H, Hg), 4.02 (dd, J= 10.5, 5.9 Hz, 1H, Hh), 3.54 (dd, J= 10.5, 3.5 Hz, 1H, Hi), 2.44 (s, 3H, Hj), 1.88 (s, 3H, Hk), 1.78 (s, 3H, Hl) (**Spectrum 107**)

^{13}C NMR ($CDCl_3$) δ 169.79, 169.69, 144.24, 142.07, 133.89, 129.87, 128.87, 128.05, 127.01, 125.90-125.85, 78.06, 69.10, 65.83, 50.14, 21.61, 20.50, 20.45 (**Spectrum 109**)

HRMS: $[M+H]^+$ 486.1193 (**Spectrum 111**)

6.2.6. Synthesis of 1-[(4-methylphenyl)sulfonyl] 2-[4-(methoxy)]-3,4-pyrrolidinedione, 3, 4 diacetate (**21b**)



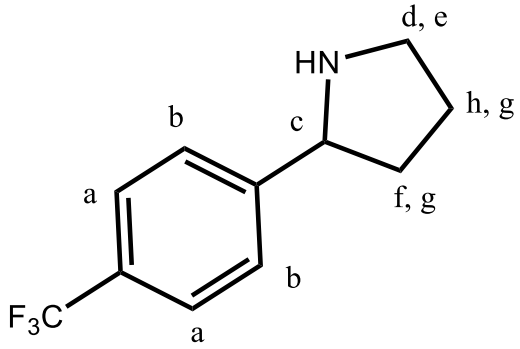
1-[(4-Methylphenyl)sulfonyl] 2-[4-(methoxy)]-3,4-pyrrolidinedione, 3, 4 diacetate (21b); was prepared by dissolving 1-[(4-methylphenyl)sulfonyl] 2-[4-(methoxy]-3,4-dihydroxypyrrolidine (**20b**) (1.0 eq., 0.85 mmol) in DCM (35 mL) with acetic anhydride (2.5 eq., 2.1 mmol) and pyrridine (3.5 mL). The reaction mixture was stirred at room temperature for 18 hr. Upon completion, the reaction micture was added to a beaker containing 2M HCl solution (25 mL) and ice, and was stirred for 5-10 mins. The aqueous layer was then extracted with EtOAc (3×15 mL) and the combined organic layers were washed with saturated $NaHCO_3$ solution (6×15 mL), water (15 mL) and brine (15 mL) before drying over $MgSO_4$ and rotary evaporation to yield a clear, colourless oil which was not further purified (80%)

^{1}H NMR ($CDCl_3$) δ 7.69 (d, J= 8.2 Hz, 2H, Ha), 7.34 (m, 4H, Hb, Hc), 6.87 (d, J= 8.6 Hz, Hd), 5.23-5.18 (m, 1H, He), 5.06-5.03 (m, 1H, Hf), 4.68-4.66 (m, 1H, Hg), 4.01-3.97 (m, 1H, Hh), 3.79 (s, 3H, Hi), 3.50-3.46 (m, 1H, Hj), 2.43 (s, 3H, Hk), 1.87 (s, 3H, Hl), 1.74 (s, 3H, Hm) (**Spectrum 112)**

^{13}C NMR ($CDCl_3$) δ 169.83, 169.75, 159.55, 143.80, 134.33, 129.86, 129.71, 128.00, 127.72, 114.26, 78.18, 69.25, 65.95, 55.43, 49.90, 21.60, 20.54, 20.49. **EtOAc:** 171.28, 60.51, 21.16, 14.31 (**Spectrum 114**)

HRMS: $[M+H]^+$ 448.1425 (**Spectrum 116**)

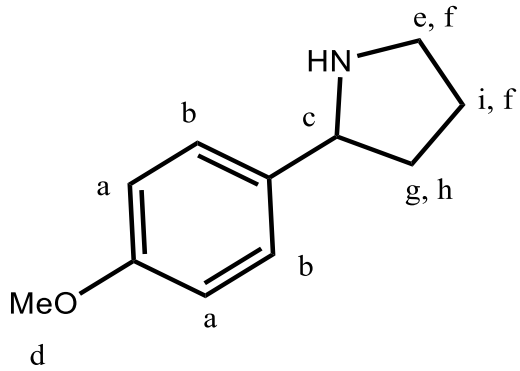
6.2.7. Synthesis of 2-[4-(trifluoromethyl)phenyl] pyrrolidine **17a**



2-[4-(Trifluoromethyl)phenyl] pyrrolidine (17a); was prepared by dissolving 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl] pyrrolidine (**16a)** (1.0 eq., 1.1 mmol) in dry THF (5 mL) in a flame dried round bottom flask under N_2 with the addition of powdered Mg (5.0 eq., 5.5 mmol), $Ti(OiPr)_4$ (1.0 eq., 1.1 mmol) and Me_3SiCl (1.5 eq., 1.7 mmol). The reaction mixture was heated to 50 °C and stirred for 18 hr. The reaction was monitored by TLC. Upon completion, 3 M NaOH solution (1 mL) was added to the mixture along with Et_2O (5 mL), celite (1.1 g) and KF (1.1 g). The mixture was stirred for 1 hr. before passing through a celite plug. 3M NaOH solution (17 mL) was then added to the filtrate and the aqueous phase was extracted with Et_2O (2×10 mL) and the combined organic layers were washed with water (10 mL), brine (10 mL) and 3M NaOH solution (10 mL) before drying over $MgSO_4$ and rotarty evaporation. The resulting product was a pale yellow, clear semi-solid which was not further purified (Crude: 38%).

^{1}H NMR ($CDCl_3$) δ 7.56 (d, J= 8.2 Hz, 2H, Ha), 7.47 (d, J= 8.2 Hz, 2H, Hb), 4.19-4.15 (m, 1H, Hc), 3.21-3.16 (m, 1H, Hd), 3.06-3.01 (m, 1H, He), 2.25-2.20 (m, 1H, Hf), 1.91-1.81 (m, 2H, Hg), 1.70-1.60 (m, 1H, Hh) (**Spectrum 117**)

6.2.8. Synthesis of 2-[4-(methoxy)phenyl] pyrrolidine (**17b**)



2-[4-(Methoxy)phenyl] pyrrolidine (17b); was prepared by dissolving 1-[(4-methylphenyl)sulfonyl] 2-[4-(methoxy] pyrrolidine (**16b)** (1.0 eq., 1.1 mmol) in dry THF (5 mL) in a flame dried round bottom flask under N_2 with the addition of powdered Mg (5.0 eq., 5.5 mmol), $Ti(OiPr)_4$ (1.0 eq., 1.1 mmol) and Me_3SiCl (1.5 eq., 1.7 mmol). The reaction mixture was heated to 50 °C and stirred for 18 hr. The reaction was monitored by

TLC. Upon completion, 3 M NaOH solution (1 mL) was added to the mixture along with Et_2O (5 mL), celite (1.1 g) and KF (1.1 g). The mixture was stirred for 1 hr. before passing through a celite plug. 3M NaOH solution (17 mL) was then added to the filtrate and the aqueous phase was extracted with Et_2O (2×10 mL) and the combined organic layers were washed with water (10 mL), brine (10 mL) and 3M NaOH solution (10 mL) before drying over $MgSO_4$ and rotarty evaporation. The resulting product was a pale yellow, clear semi-solid which was not further purified (Crude yield: 51%).

^{1}H NMR ($CDCl_3$) δ 7.55 (d, J= 8.6 Hz, 2H, Ha), 7.14 (J= 8.6 Hz, 2H, Hb), 4.34-4.28 (m, 1H, Hc), 4.07 (s, 3H, Hd), 3.45-3.43 (m, 1H, He), 3.29-3.22 (m, 1H, Hf), 2.46-2.39 (m, 1H, Hg), 2.25-2.09 (m, 2H, Hh), 1.97-1.89 (m, 1H, Hi) (**Spectrum 118**)

6.2.9. Additional Methods

Mg in MeOH with sonication method: To a dried round bottom flask, **19** (1.0 eq) was added with MeOH (1 mL) and Mg (5.0 eq) and the flask was placed in a sonicator at the highest setting for 1-18 hours. Upon completion, reaction mixture was quenched with 1M HCl and extracted with EtOAc (3×3 mL) before drying over $MgSO_4$ follwed by rotary evaporation. The material was submitted for NMR or analysis.

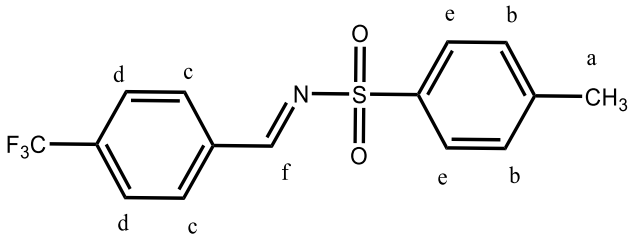
NaH reflux method: To a flame dried round bottom flask under nitrogen, **19** (1.0 eq) was added with dry ACN (1 mL) and NaH (1.5 eq) and refluxed for 4-18 hours. Upon completion reaction mixture was quenched with water and nuetralised with the dropwise addition of 1M HCl. The aqueous layer was then extracted with EtOAc (3×3 mL), washed with water (3 mL) and brine (3mL) before drying over $MgSO_4$ followed by rotary evaporation. The material was submitted for NMR or analysis.

H_2SO_4 method: To a round bottom flask, **19** (1.0 eq) was added with concentrated H_2SO_4 (1 mL) the flask heated to 120 °C and stirred for 4 hours. Upon completion, the reaction mixture was quenched with ice-cold water and neutralised with saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc (3×3 mL) before drying over $MgSO_4$ followed by rotary evaporation. The material was submitted for NMR or analysis.

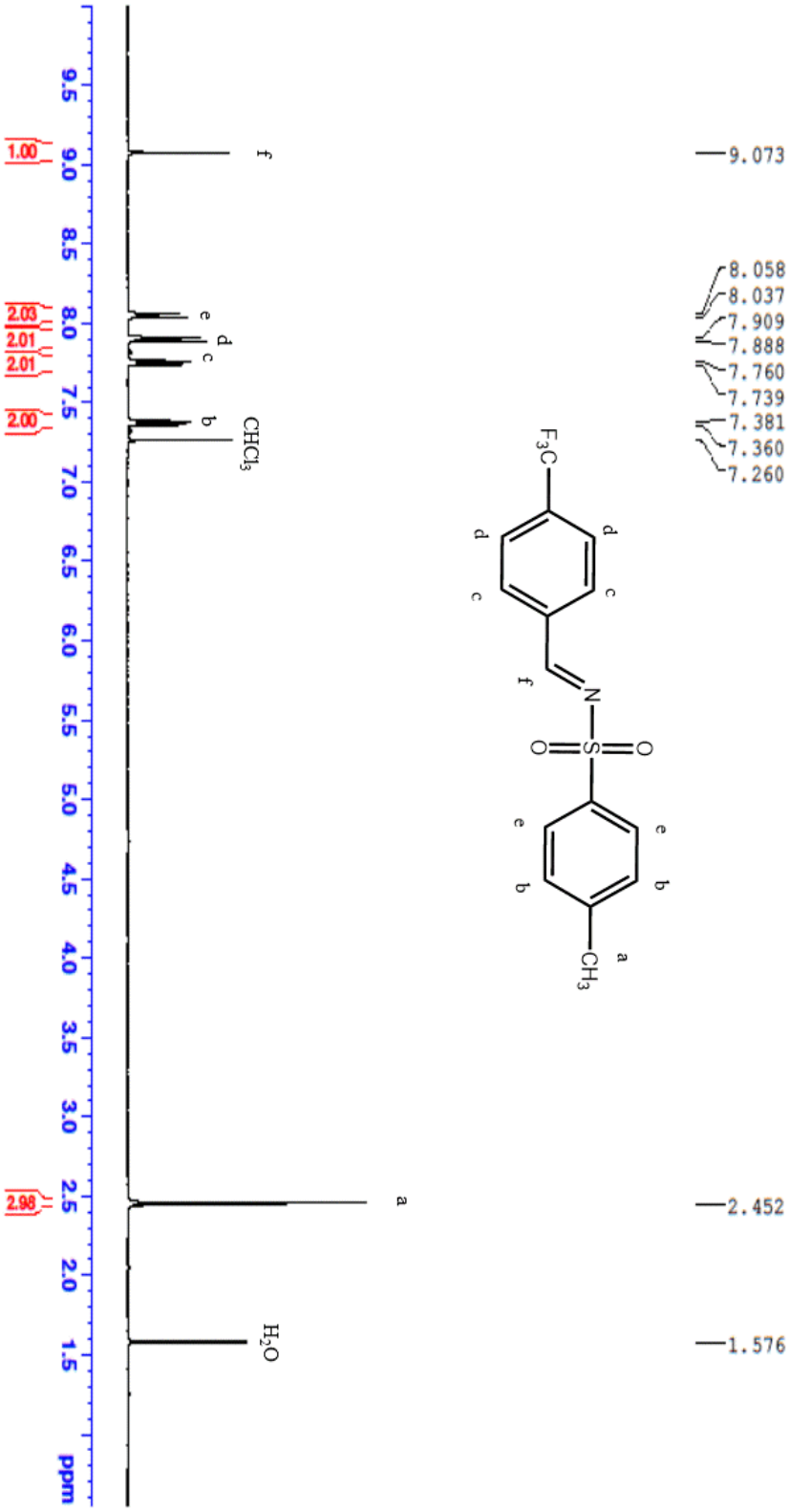
Appendix

7.1. Data for compounds from Chapter 2

7.1.1. 4-Methyl-N-[[4-(trifluoromethyl)phenyl]methylene]benzenesulfonamide **1a**

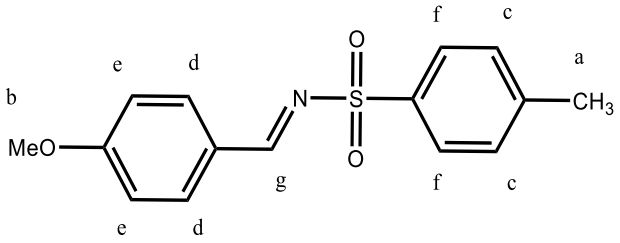


^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H, Ha), 7.37 (d, J= 8.4Hz, 2H, Hb), 7.75 (d, J= 8.4Hz, 2H, Hc), 7.90 (d, J= 8.4Hz, 2H, Hd), 8.05 (d, J= 8.4 Hz, 2H, He), 9.07 (s, 1H, Hf). **H_2O**: ^{1}H NMR ($CDCl_3$) δ 1.59 (s) (**Spectrum 1**)

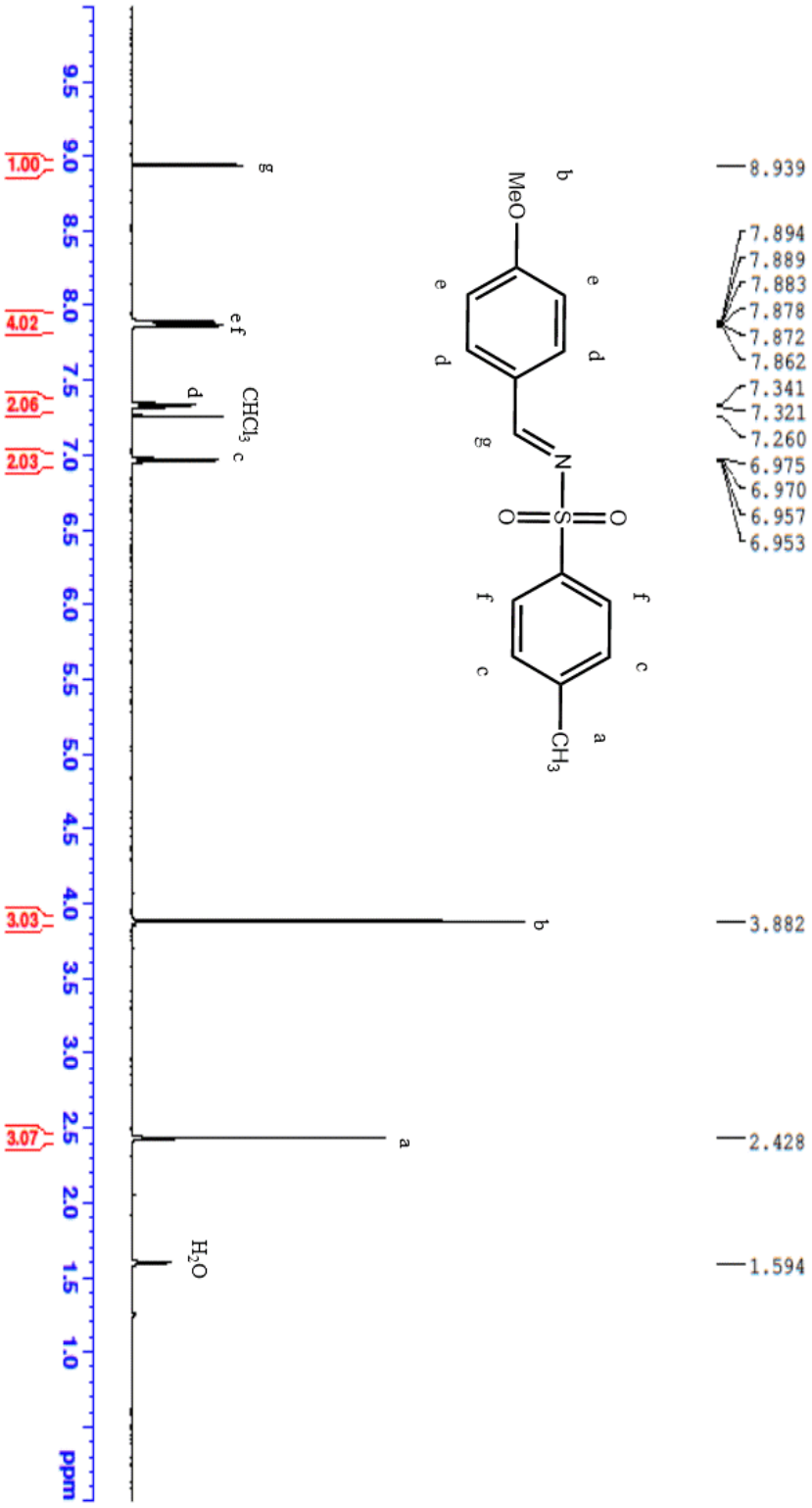


Spectrum 1: ^{1}H NMR spectrum 4-Methyl-*N*-[[4-(trifluoromethyl)phenyl]methylene]benzenesulfonamide 1a

7.1.2. 4-Methyl-N-[[4-(methoxy)phenyl]methylene]benzenesulfonamide **1b**

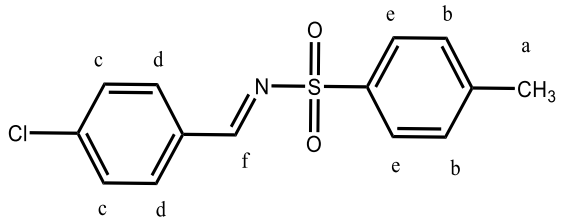


^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H, Ha), 3.88 (s, 3H, Hb), 6.96 (d, J= 8.8 Hz, 2H, Hc), 7.31 (d, J= 8 Hz, 2H, Hd), 7.86-7.89 (m, 4H, He, Hf), 8.94 (s, 1H, Hg) **H_2O**: ^{1}H NMR ($CDCl_3$) δ 1.59 (s) (**Spectrum 2)**

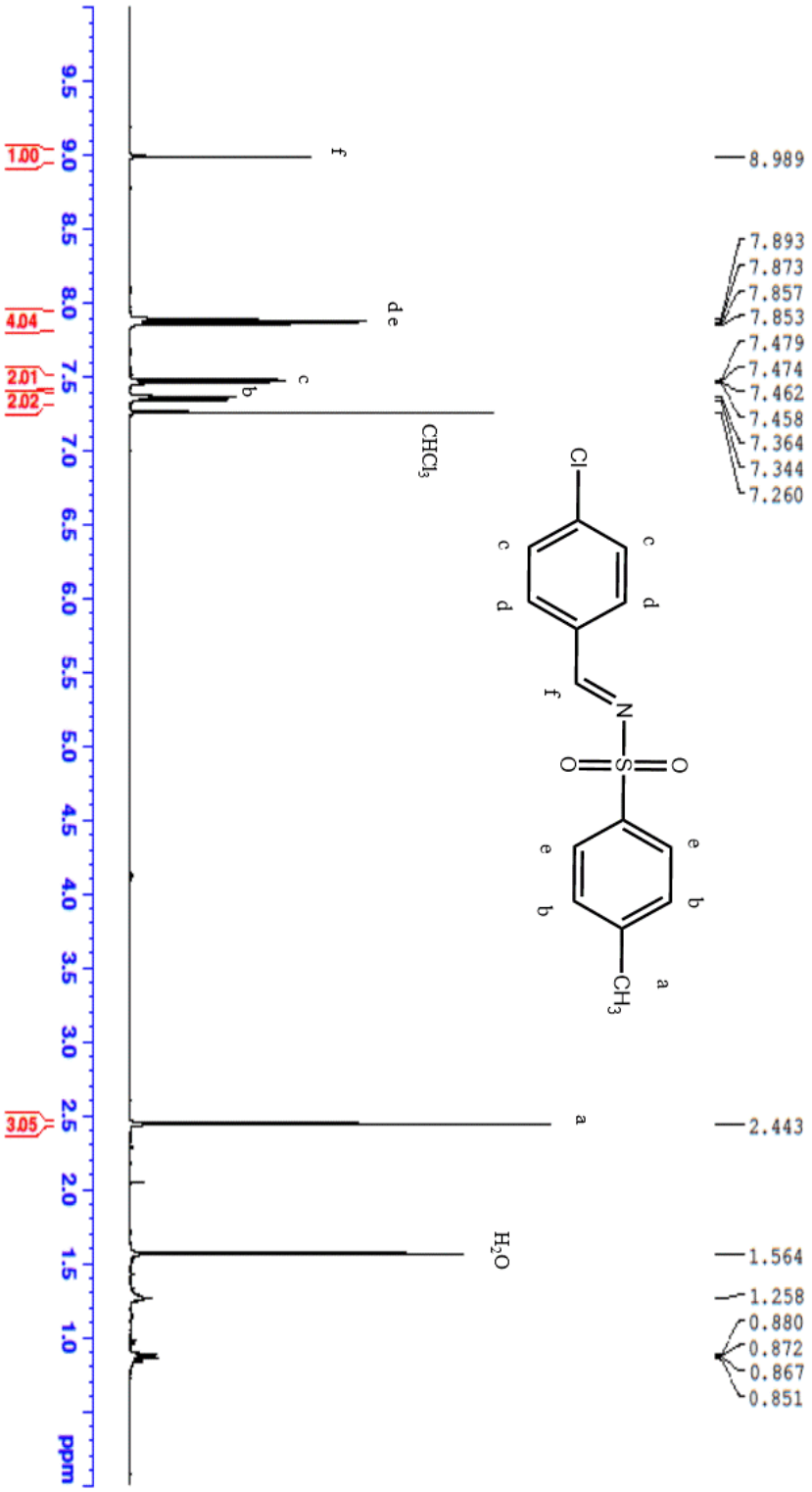


Spectrum 2: ^{1}H NMR spectrum of 4-Methyl-*N*-[[4-(methoxy)phenyl]methylene]Benzenesulfonamide 1b

7.1.3. 4-Methyl-N-[[4-(chloro)phenyl]methylene]benzenesulfonamide **1c**

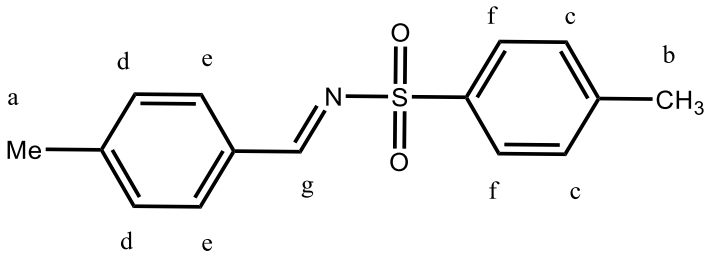


^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H, Ha), 7.35 (d, J= 8 Hz, 2H, Hb), 7.47 (d, J= 8.4 Hz, 2H, Hc) 7.87 (m, 4H, Hd, He), 8.99 (s, 1H, Hf). **H_2O**: ^{1}H NMR ($CDCl_3$) δ 1.56 (s) (**Spectrum 3**)

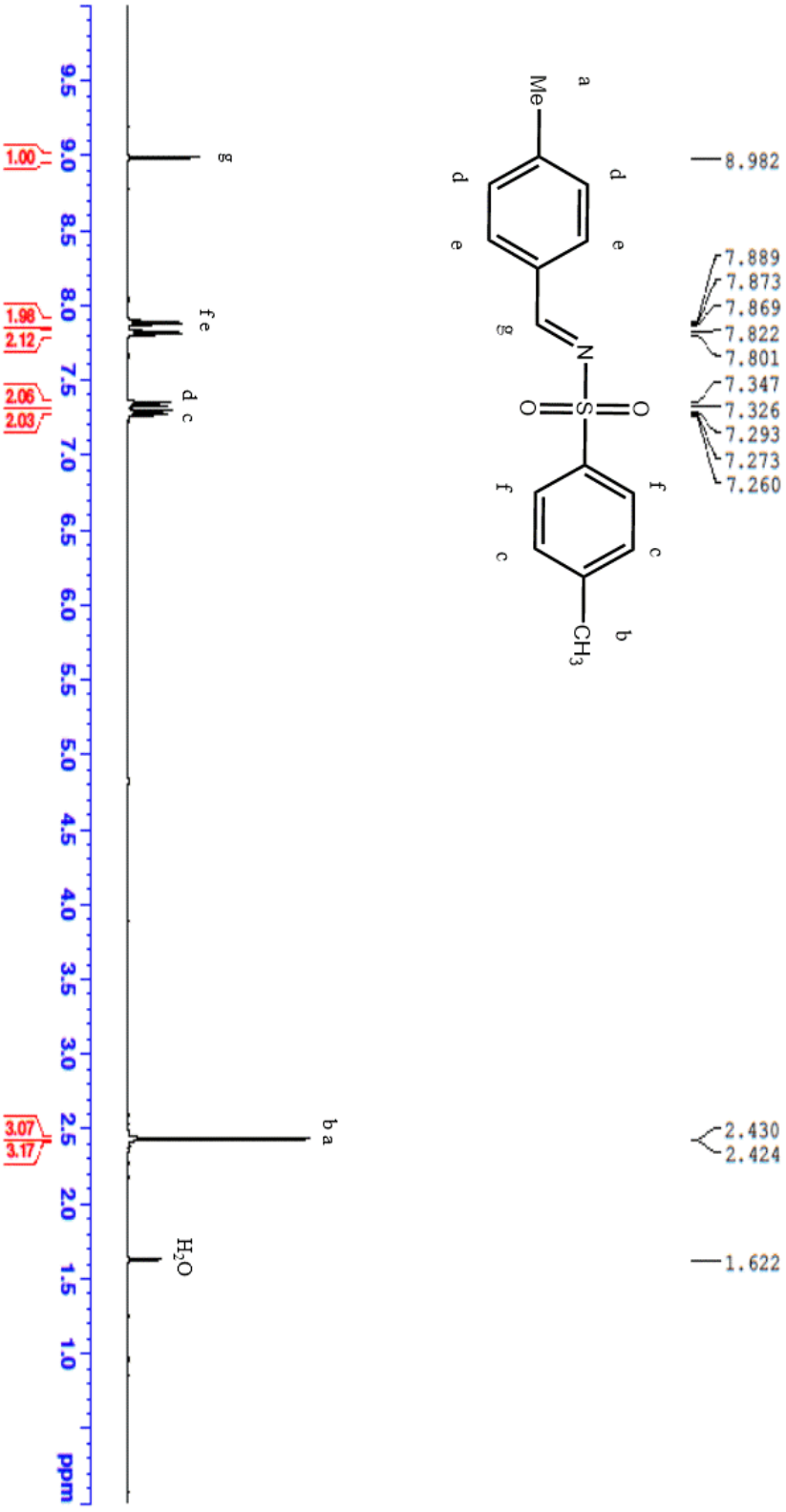


Spectrum 3: ^{1}H NMR spectrum 4- of Methyl-*N*-[[4-(chloro)phenyl]methylene]benzenesulfonamide 1c

7.1.4. 4-Methyl-N-[[4-(methyl)phenyl]methylene]benzenesulfonamide **1d**

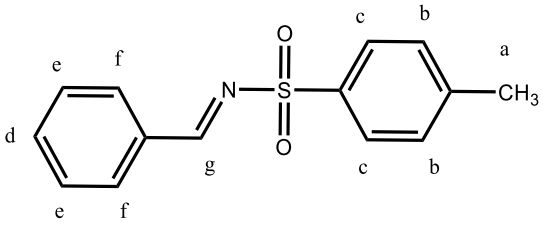


^{1}H NMR ($CDCl_3$) δ 2.24 (s, 3H, Ha), 2.43 (s, 3H, Hb), 7.28 (d, J= 8Hz, 2H, Hc), 7.37 (d, J= 8.4 Hz, 2H, Hd), 7.81 (d, J= 8.4 Hz, 2H, He), 7.88 (d, J= 8 Hz, 2H, Hf), 8.98 (s, 1H, Hg).
H_2O: ^{1}H NMR ($CDCl_3$) δ 1.62 (s) (**Spectrum 4**)

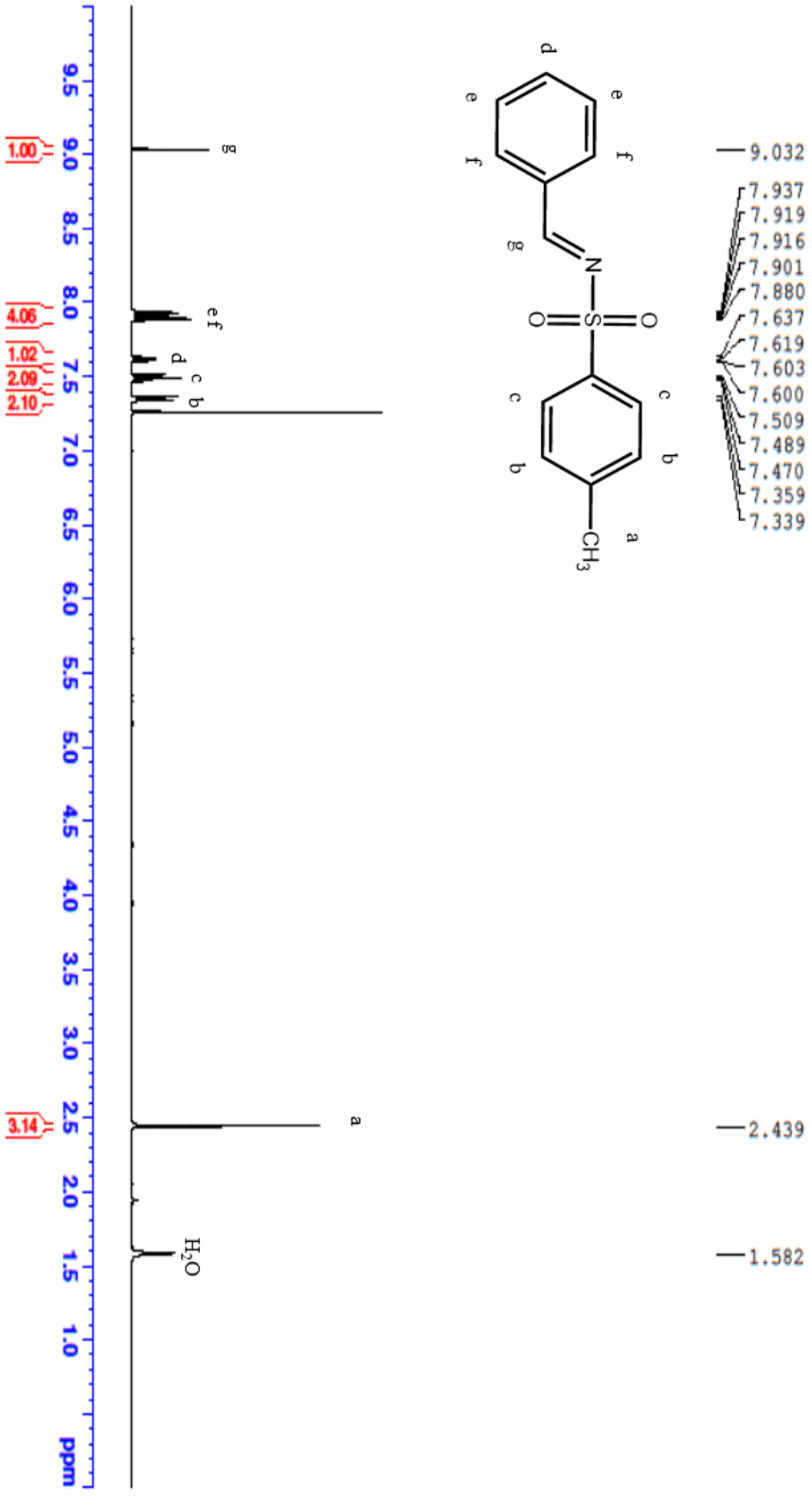


Spectrum 4: **^{1}H NMR spectrum of 4-Methyl-*N*-[[4-(methyl)phenyl]methylene]benzenesulfonamide 1d**

7.1.5. 4-Methyl-N-[(phenyl)methylene]benzenesulfonamide **1e**

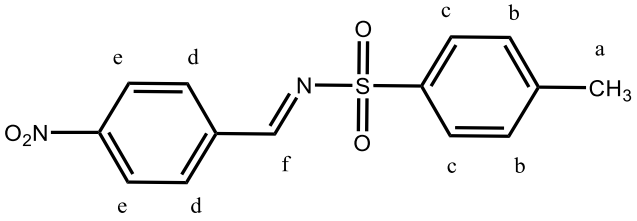


^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H, Ha), 7.50 (d, J= 8 Hz, 2H, Hb), 7.48 (dd, J= 7.8 Hz, 7.6 Hz, 2H, Hc), 7.62 (t, 7.6 Hz, 1H, Hd), 7.91 (m, 4H, He, Hf), 9.03 (s, 1H, Hg). **H_2O**: ^{1}H NMR ($CDCl_3$) δ 1.59 (s) (**Spectrum 5**)

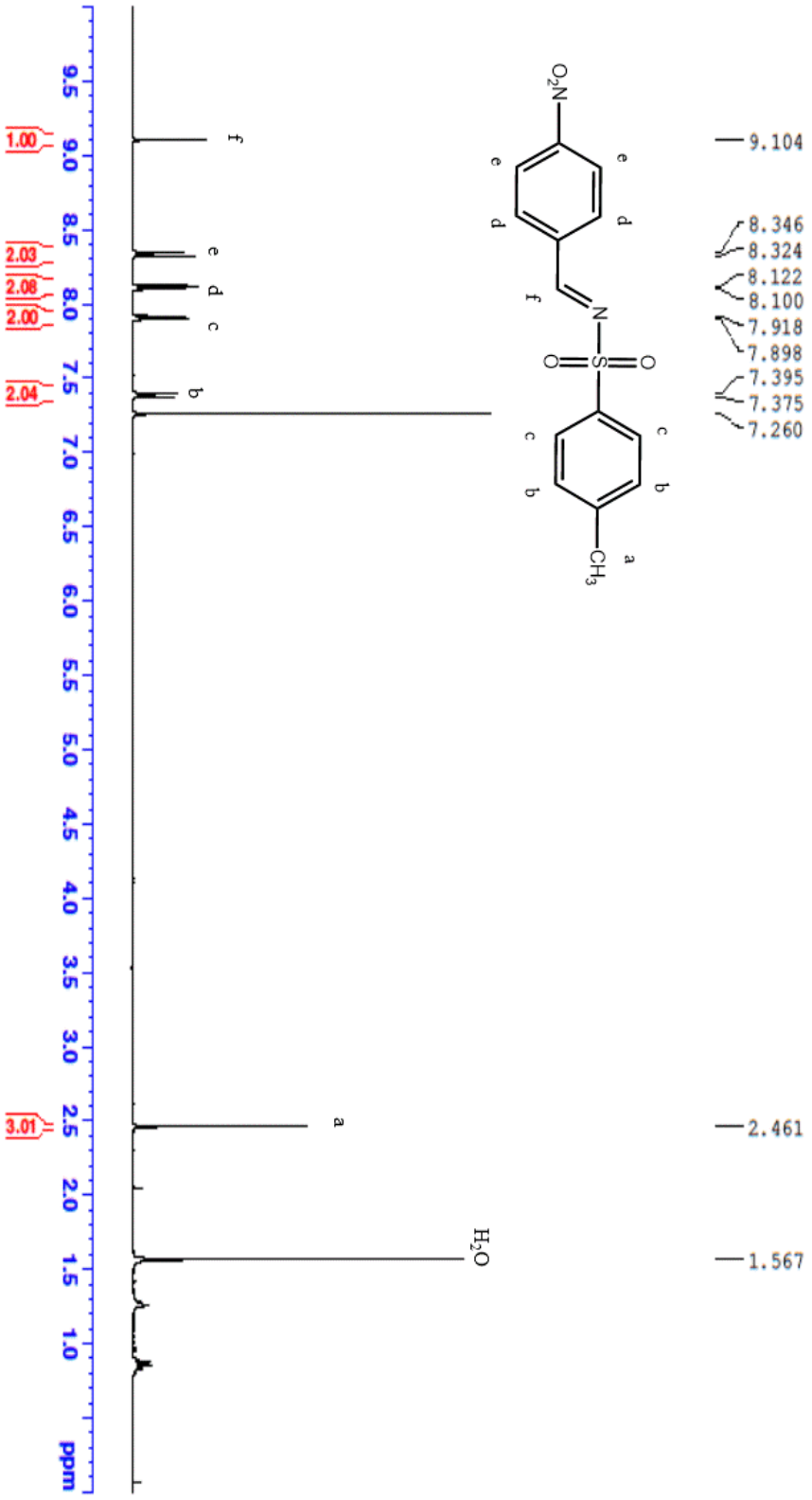


Spectrum 5: ^{1}H NMR spectrum of 4-Methyl-*N*-[(phenyl)methylene]benzenesulfonamide 1e

7.1.6. 4-Methyl-N-[[4-(nitro)phenyl]methylene]benzenesulfonamide **1f**

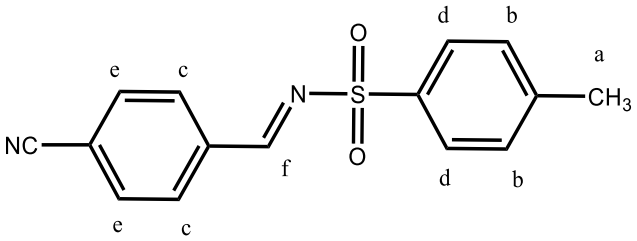


^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H, Ha), 7.39 (d, J= 8Hz, 2H, Hb), 7.91 (d, J= 8 Hz, 2H, Hc), 8.11 (d, J= 8.8 Hz, 2H, Hd), 8.34 (d, J= 8.8 Hz, 2H, He), 9.1 (s, 1H, Hf). **H_2O**: ^{1}H NMR ($CDCl_3$) δ 1.57 (s) (**Spectrum 6**)

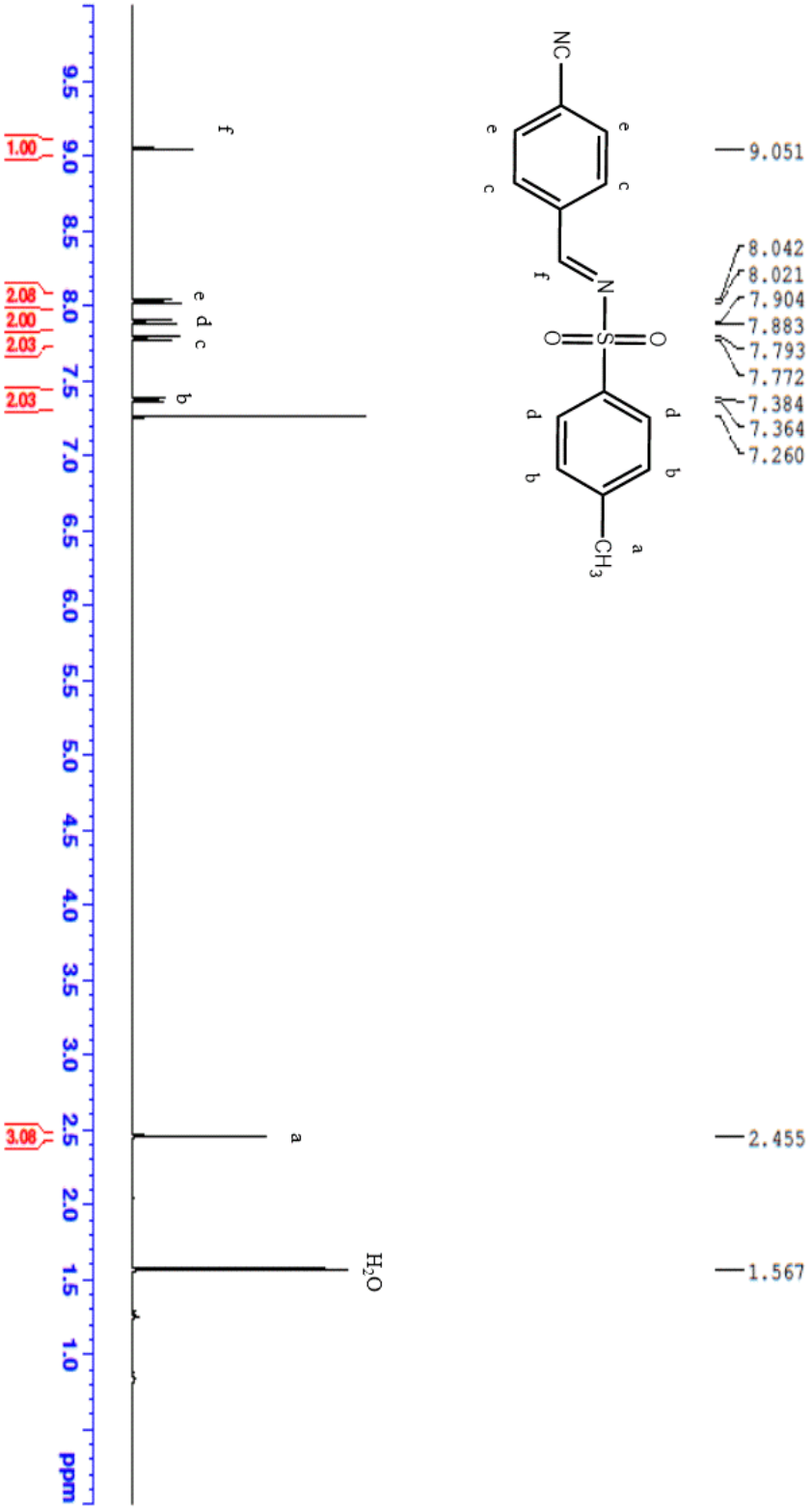


Spectrum 6: ^{1}H NMR spectrum of 4-Methyl-*N*-[[4-(nitro)phenyl]methylene]benzenesulfonamide 1f

7.1.7. 4-Methyl-N-[[4-(cyano)phenyl]methylene]benzenesulfonamide **1g**

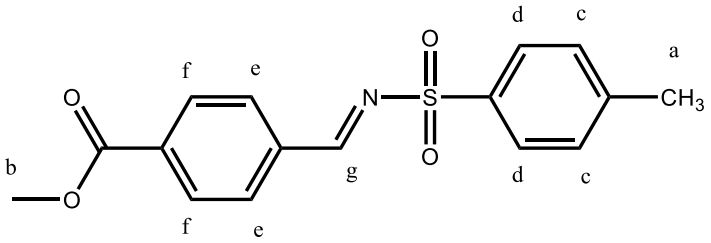


^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H, Ha), 7.37 (d, J= 8 Hz, 2H, Hb), 7.78 (d, J= 8.4 Hz, 2H, Hc), 7.89 (d, 8.4 Hz, 2H, Hd), 8.03 (d, J= 8.4 Hz, 2H, He), 9.05 (s, 1H, Hf). **H_2O**: ^{1}H NMR ($CDCl_3$) δ 1.57 (s) (**Spectrum 7**)

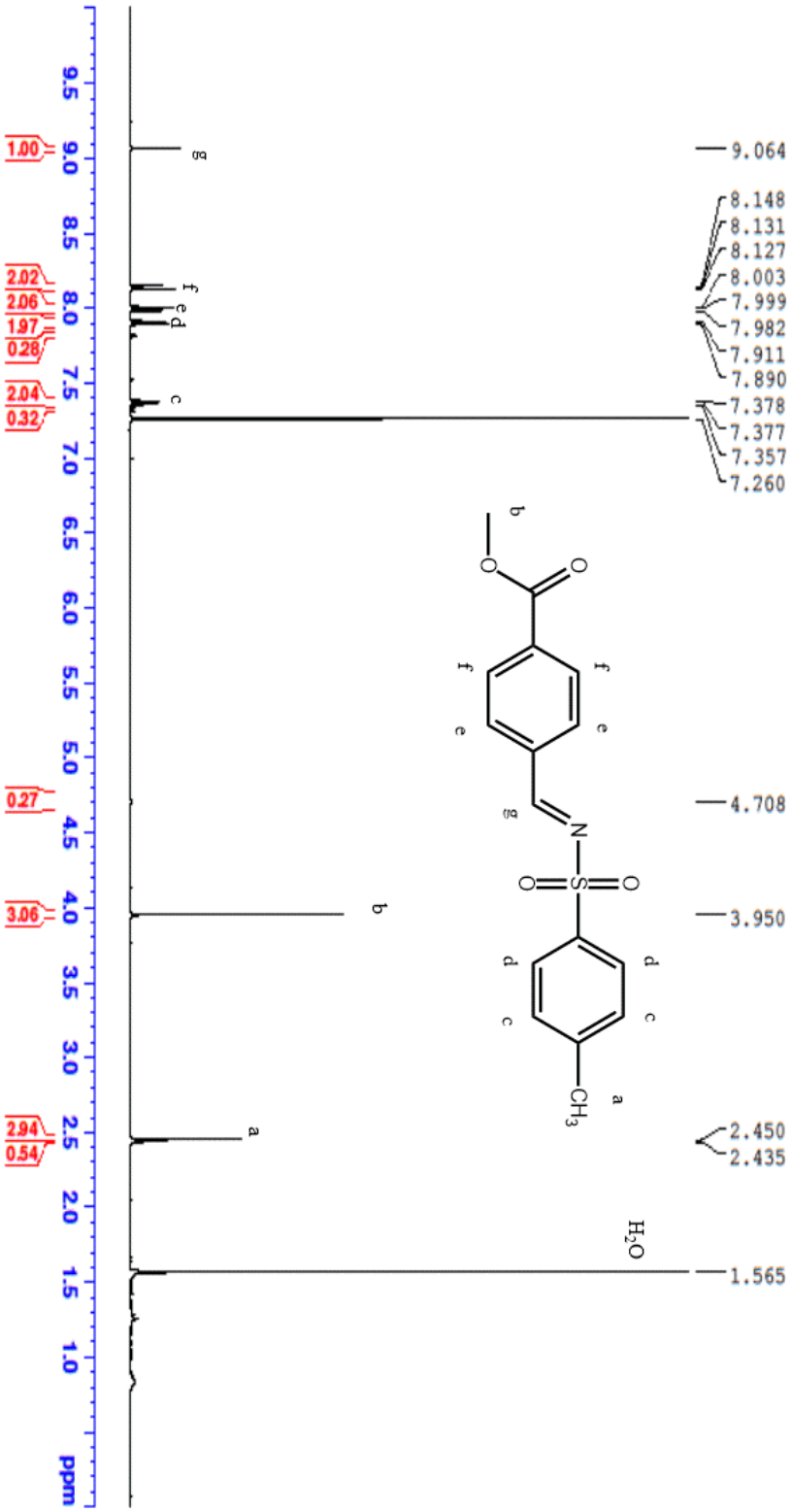


Spectrum 7: ^{1}H NMR spectrum of 4-Methyl-*N*-[[4-(cyano)phenyl]methylene]benzenesulfonamide 1g

7.1.8. N-[[4-(Methoxycarbonyl)phenyl]]methylene]-4-methylbenzenesulfonamide **1h**

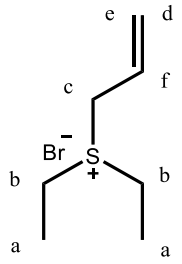


^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H, Ha), 3.95 (s, 3H, Hb), 7.37 (d, J= 8 Hz, 2H, Hc), 7.90 (d, J= 8.4 Hz, 2H, Hd), 7.99 (d, J= 8.4 Hz, 2H, He), 8.14 (d, J= 8.4 Hz, 2H, Hf), 9.1 (s, 1H). **H_2O**: ^{1}H NMR ($CDCl_3$) δ 1.57 (s) (**Spectrum 8**)



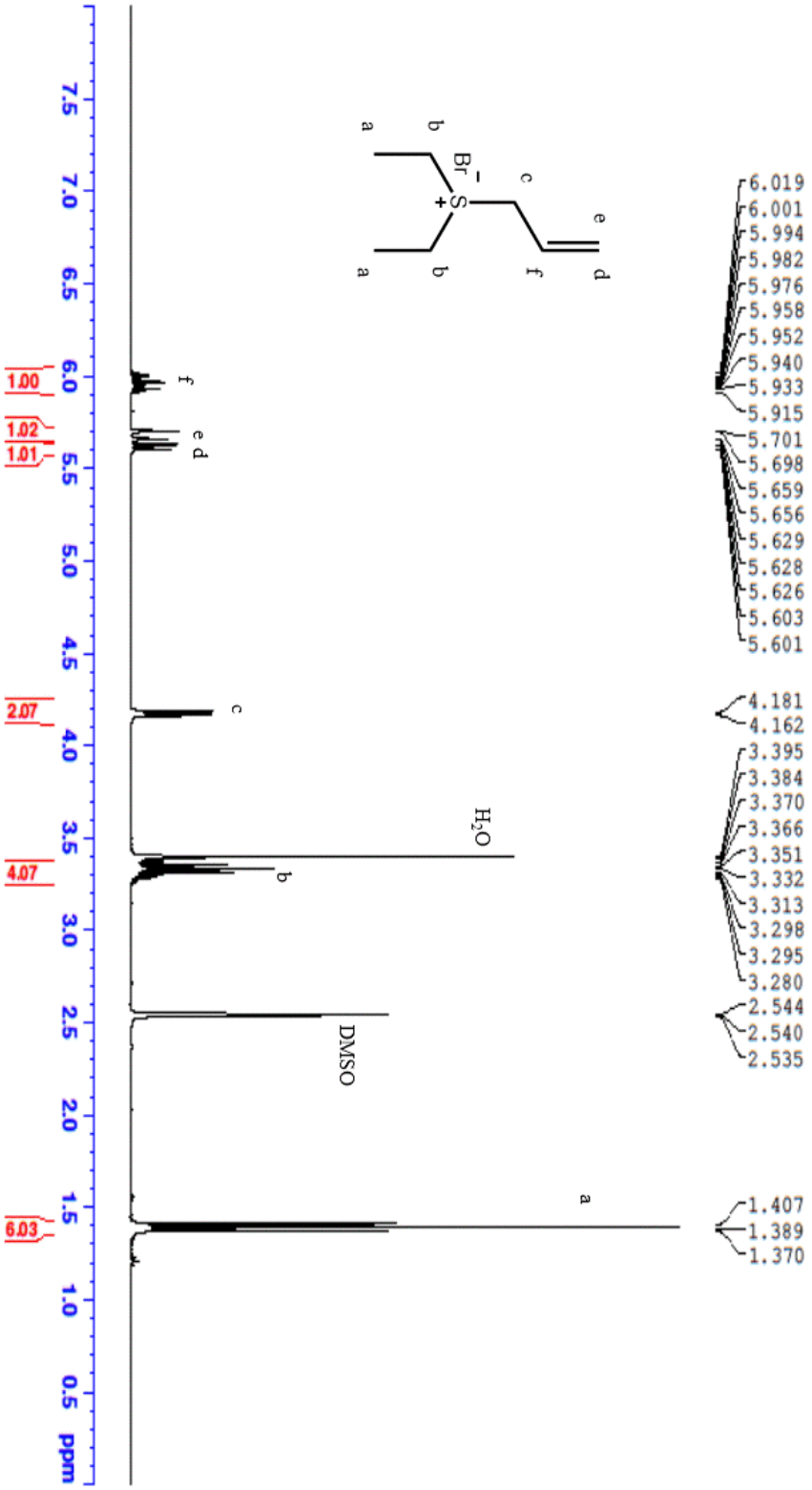
Spectrum 8: ^{1}H NMR spectrum of *N*-[[4-(Methoxycarbonyl)phenyl]]methylene]-4-methylbenzenesulfonamide 1h

7.1.9. 1-Allyldiethylium bromide **2a**



^{1}H NMR (DMSO-d6) δ 3.40 (t, J= 7.2 Hz, 6H, Ha), 3.33 (sep, J= 7.6 Hz, 4H, Hb), 4.17 (d, J= 7.3 Hz, 2H, Hc), 5.61 (d, J= 10.3 Hz, 1H, Hd), 5.68 (d, J= 17.1 Hz, 1H, He), 5.97 (tdd, J= 7.3, 17.1, 10 Hz, 1H, Hf). **H_2O**: ^{1}H NMR (DMSO-d6) δ 3.40 (s) **Spectrum 9**).

HRMS: M^+: 131.0889, 79.0290 m/z (**Spectrum 10**).



Spectrum 9: ^{1}H NMR spectrum of 1-Allyldiethylium bromide 2a

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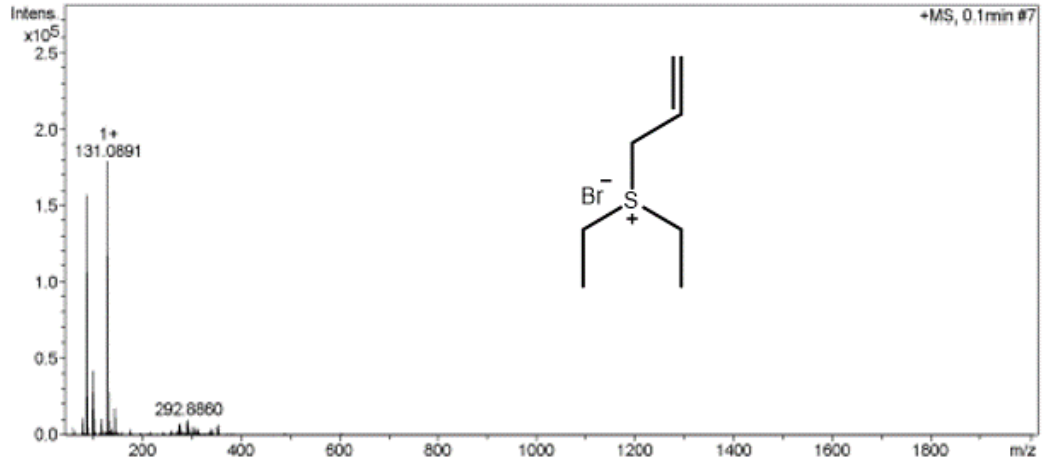
Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SOR_47A_GA7_01_32454.d	Acquisition Date	15/03/2023 15:44:13
Sample Description			



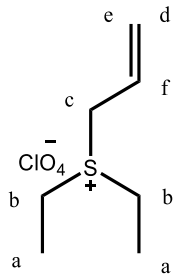
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
131.089118	1	C7H15S	131.088898	0.2	1.7	0.5	ok	even	2.9

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

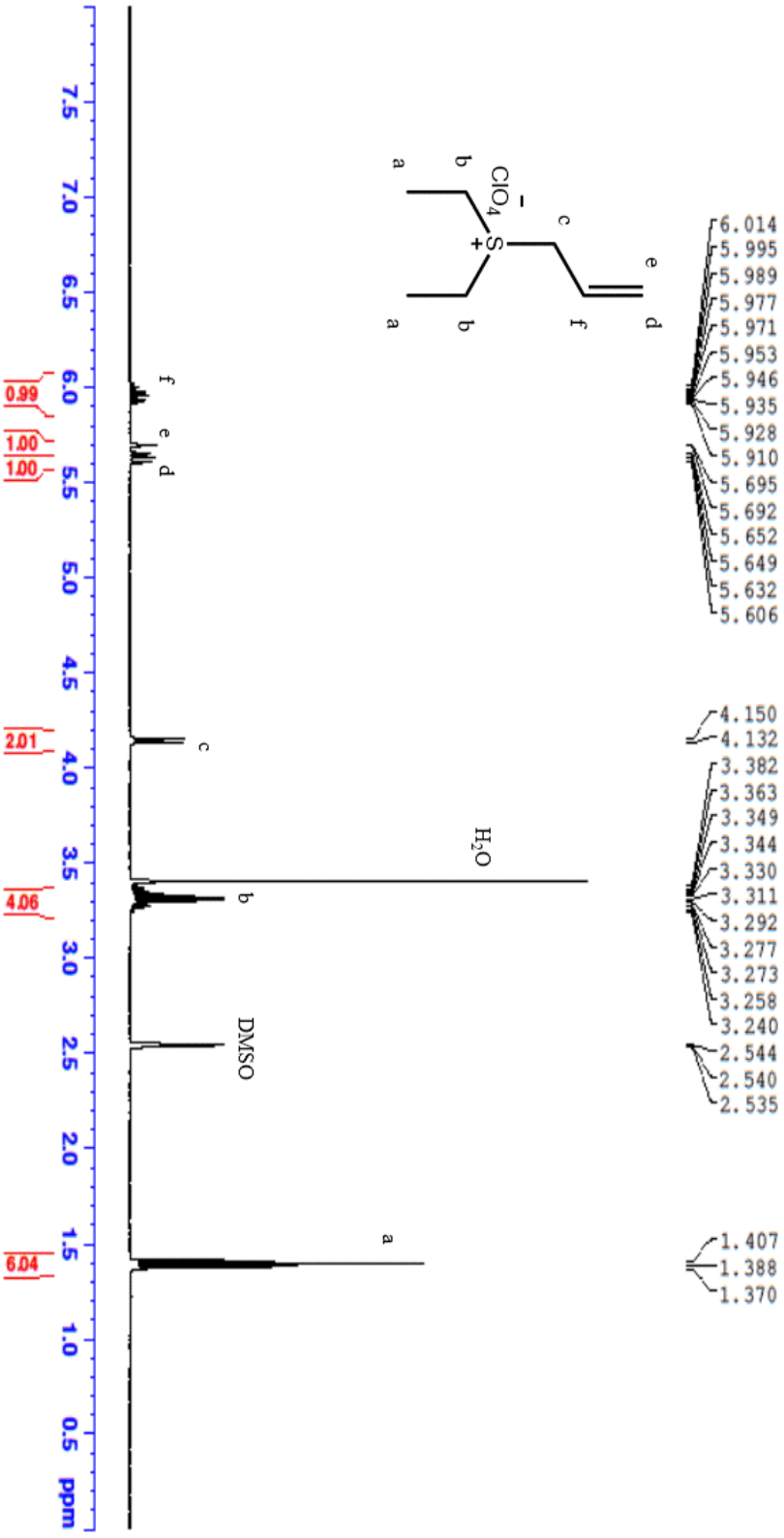
Spectrum 10: HRMS spectrum of 1-Allyldiethylium bromide 2a

7.1.10. 1-Allyldiethylium perchlorate **2b**



^{1}H NMR (DMSO-d6) δ 1.39 (t, J= 7.6 Hz, 6H, Ha), 7.31 (sep, J= 7.6 Hz, 4H, Hb), 7.14 (d, J= 7.4 Hz, 2H, Hc), 5.62 (d, J= 10 Hz, 1H, Hd), 5.67 (d, J= 16 Hz, 1H, He), 5.95 (tdd, J= 7.4, 9.9, 16.7 Hz, 1H, Hf). **H_2O**: ^{1}H NMR (DMSO-d6) δ 3.38 (s) (**Spectrum 11**).

HRMS: M^+: 131.0889, 99.0231 m/z (**Spectrum 12**).



Spectrum 11: ^{1}H NMR spectrum of 1-Allyldiethylium perchlorate 2b

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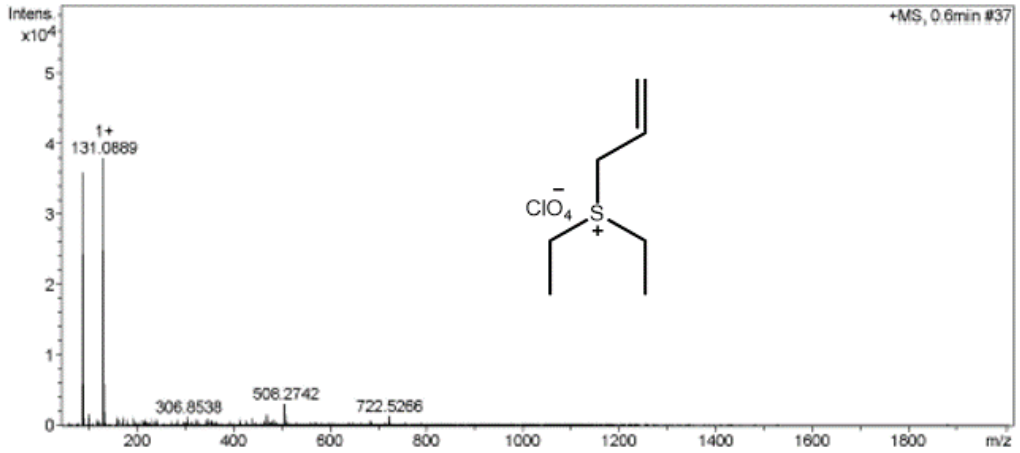
Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SOR_44B_GA2_01_32449.d	Acquisition Date	15/03/2023 15:28:01
Sample Description			



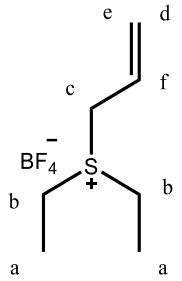
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
131.088868	1	C7H15S	131.088898	0.0	0.2	0.5	ok	even	5.1

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

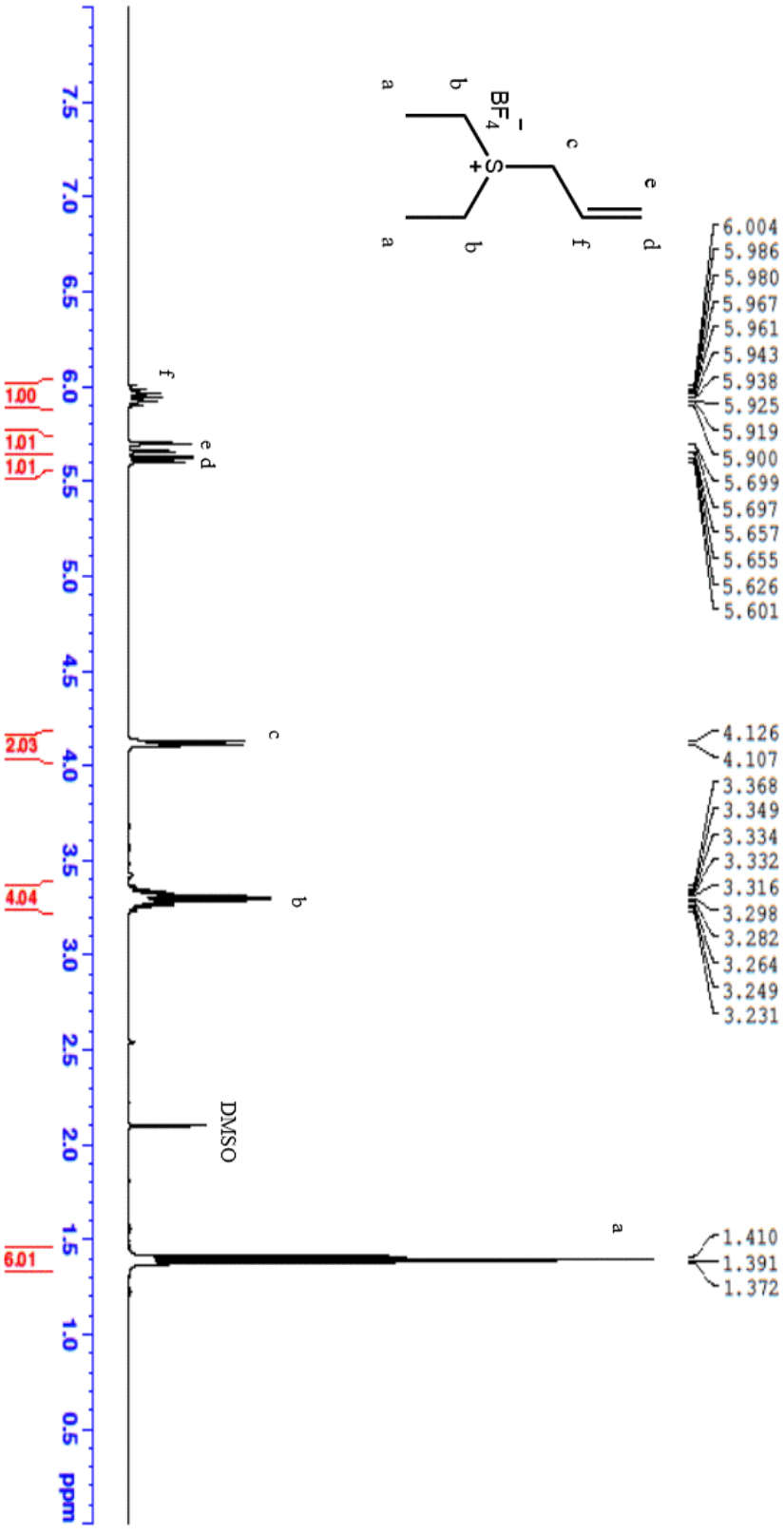
Spectrum 12: HRMS spectrum of 1-Allyldiethylium perchlorate 2b

7.1.11. 1-Allyldiethylium tetrafluoroborate **2c**



^{1}H NMR (DMSO-d6) δ 1.39 (t, J= 7.6 Hz, 6H, Ha), 3.30 (sep, 7.2 Hz, 4H, Hb), 4.12 (d, J= 7.4 Hz, 2H, Hc), 5.61 (d, J= 10.1 Hz, 1H, Hd), 5.68 (d, J= 16.9 Hz, 1H, He), 5.95 (tdd, J= 7.4, 17.1, 10 Hz, 1H, Hf). **ACN**: ^{1}H NMR (DMSO-d6) δ 2.1 (s) (**Spectrum 13).**

HRMS: M^{+}: 131.0682, 89.0561 m/z (**Spectrum 14**)



Spectrum 13: ^{1}H NMR spectrum of Allyldiethylium tetrafluoroborate 2c

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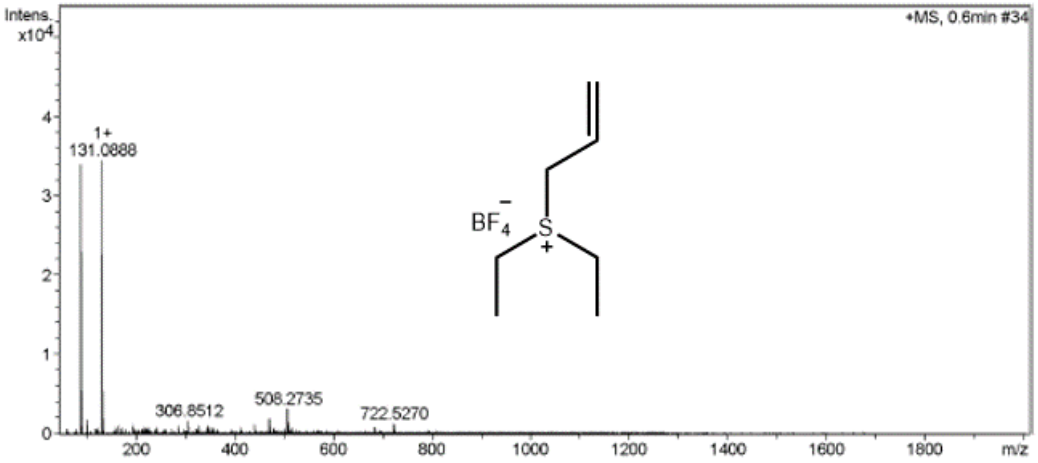
Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SOR_44A_GA1_01_32448.d	Acquisition Date	15/03/2023 15:24:47
Sample Description			



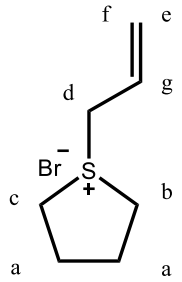
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
131.088832	1	C7H15S	131.088898	-0.1	-0.5	0.5	ok	even	3.4

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

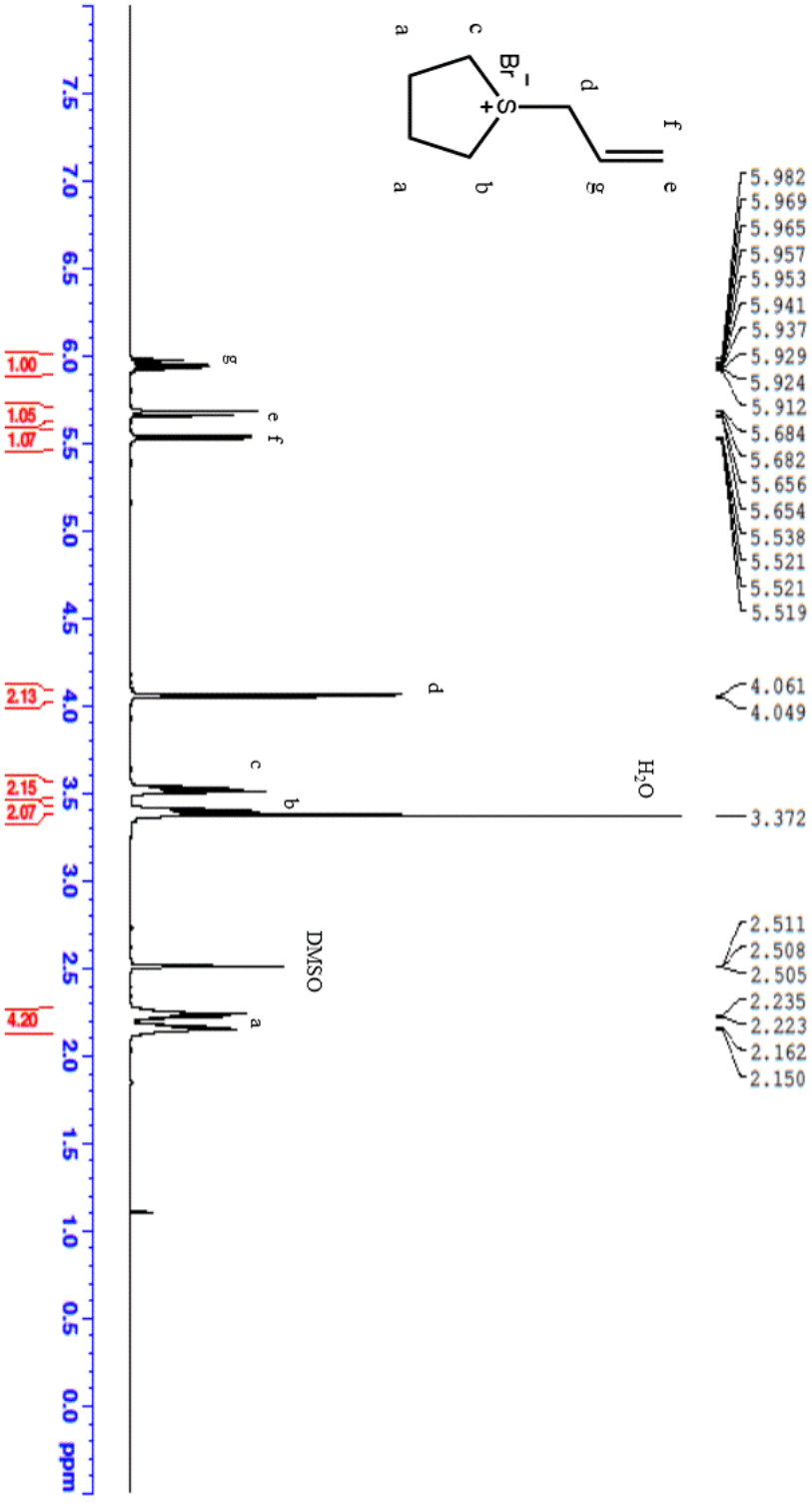
Spectrum 14: HRMS spectrum of Allyldiethylium tetrafluoroborate 2c

7.1.12. 1-Allytetrahydrothiophenium bromide **2d**



^{1}H NMR (DMSO-d6) δ 6.00-5.90 (m, 1H, Hg), 5.67 (d, J= 16.9 Hz, Hf), 5.53 (d, J= 10.3 Hz), 4.06 (d, J= 7.5 Hz, Hd), 3.55-3.48 (m, 2H, Hc), 3.42-3.38 (m, 2H, Hb), 2.28-2.10 (m, 4H, Ha). **H_2O**: 3.37 (s) (**Spectrum 15**).

HRMS: M^+: 129.0732, 79.0980 m/z (**Spectrum 16**).



Spectrum 15: ^{1}H NMR spectrum of 1-Allytetrahydrothiophenium bromide 2d

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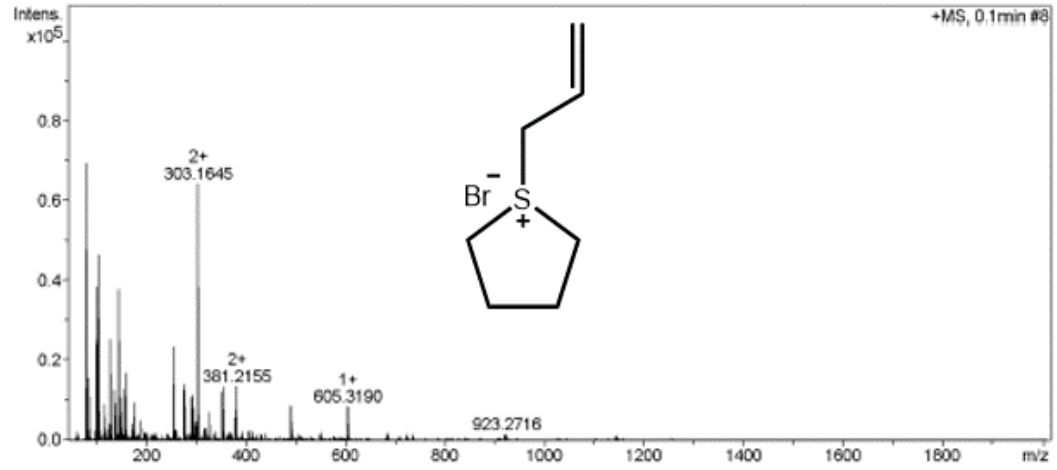
Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SOR_47B_GA5_01_32452.d	Acquisition Date	15/03/2023 15:37:44
Sample Description			



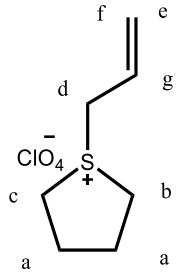
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
129.073356	1	C7H13S	129.073248	-0.1	-0.8	1.5	ok	even	5.7

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

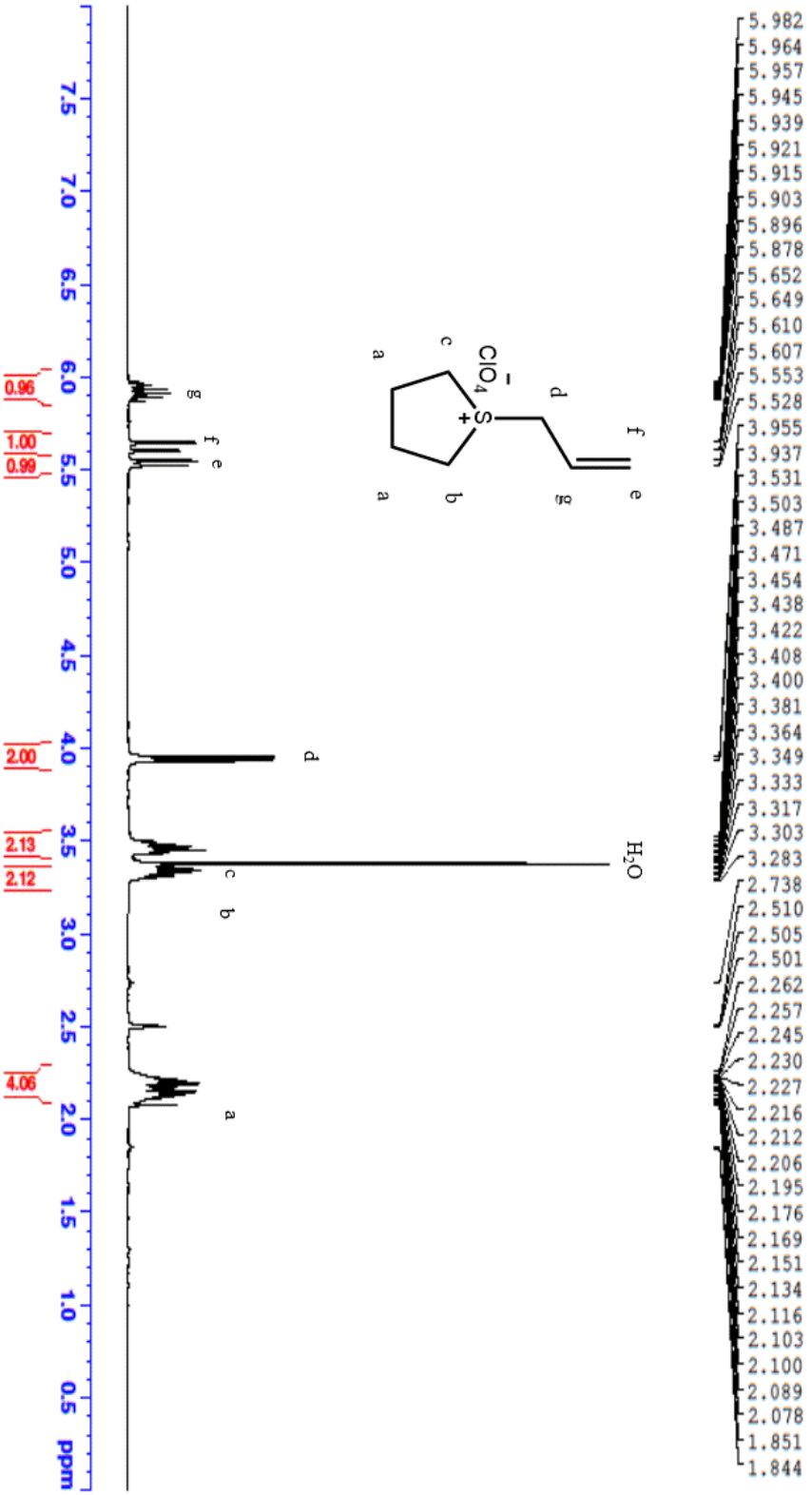
Spectrum 16: HRMS spectrum of 1-Allytetrahydrothiophenium bromide 2d

7.1.13. 1-Allytetrahydrothiophenium perchlorate **2e**



^{1}H NMR (DMSO-d6) δ 2.17 (m, 4H, Ha), 3.33 (m, 2H, Hb), 3.46 (m, 2H, Hc), 3.94 (d, J= 7.4 Hz, 2H, Hd), 5.54 (d, J= 10.1 Hz, 1H, He), 5.63 (d, 17.1 Hz, 1H, Hf), 5.92 (tdd, J= 7.3, 16.9, 10 Hz, 1H, Hg). **H_2O**: ^{1}H NMR (DMSO-d6) δ 3.38 (s) (**Spectrum 17**).

HRMS: M^+: 129.0732, 98.9750 m/z (**Spectrum 18**).



Spectrum 17: ^{1}H NMR spectrum of 1-Allytetrahydrothiophenium perchlorate 2e

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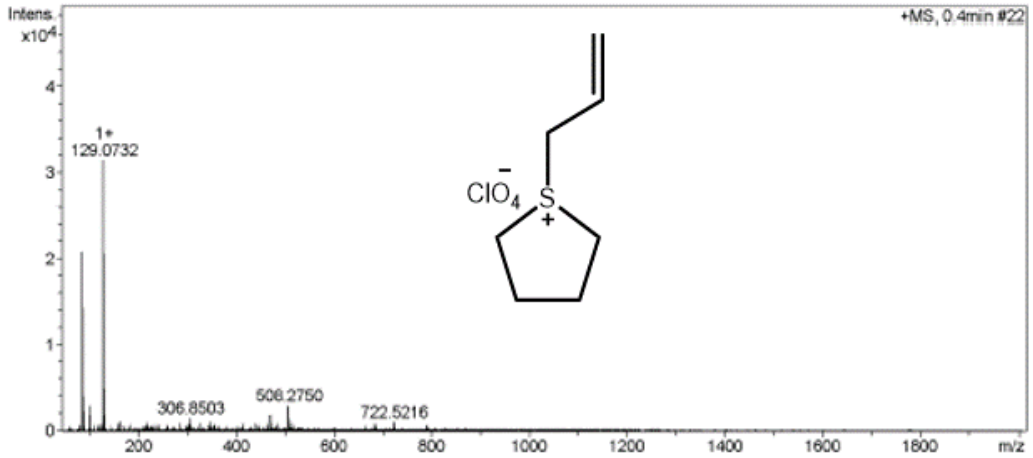
Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SOR_45B_GA4_01_32451.d	Acquisition Date	15/03/2023 15:34:29
Sample Description			



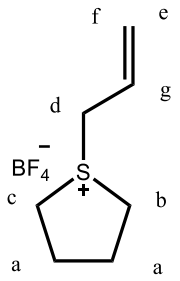
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
129.073242	1	C7H13S	129.073248	0.0	0.0	1.5	ok	even	23.4

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

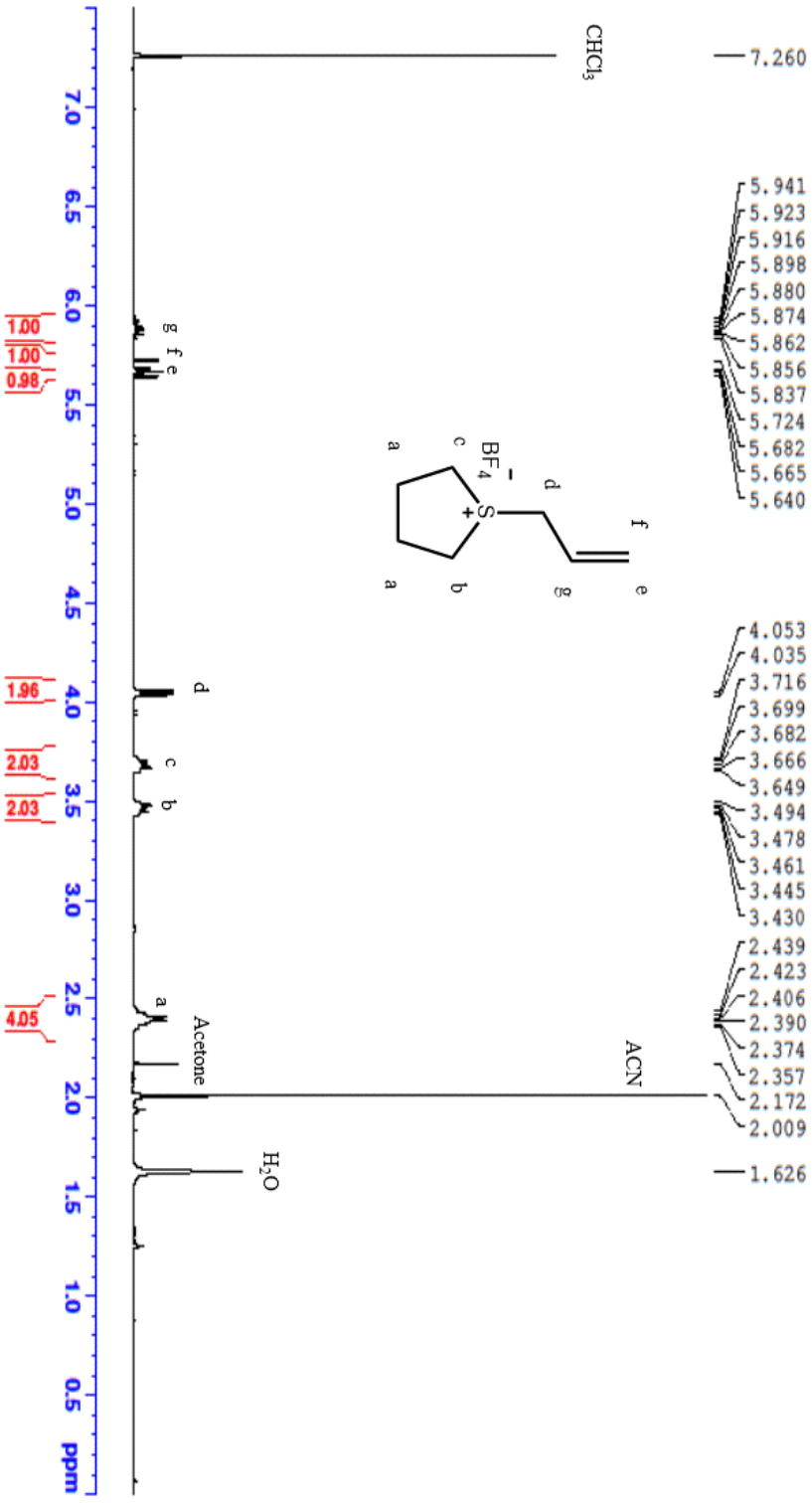
Spectrum 18: HRMS spectrum of 1-Allytetrahydrothiophenium perchlorate 2e

7.1.14. 1-Allytetrahydrothiophenium tetrafluoroborate **2f**



^{1}H NMR ($CDCl_3$) δ 2.40 (m, 4H, Ha), 3.46 (m, 2H, Hb), 3.68 (m, 2H, Hc), 4.04 (d, J= 7.3 Hz, 2H, Hd), 5.65 (d, 10 Hz, 1H, He), 5.70 (d, J= 16.6 Hz, 1H, Hf), 5.88 (tdd, J= 7.3, 17.1, 9.9 Hz, 1H, Hg). **H_2O**: ^{1}H NMR ($CDCl_3$) δ 1.64 (s). **ACN**: ^{1}H NMR ($CDCl_3$) δ 2.01 (s). **Acetone**: ^{1}H NMR ($CDCl_3$) δ 2.17 (s) (**Spectrum 19**).

HRMS: M^+: 129.0733, 86.9960 m/z (**Spectrum 20**).



Spectrum 19: ^{1}H NMR spectrum of 1-Allytetrahydrothiophenium tetrafluoroborate 2f

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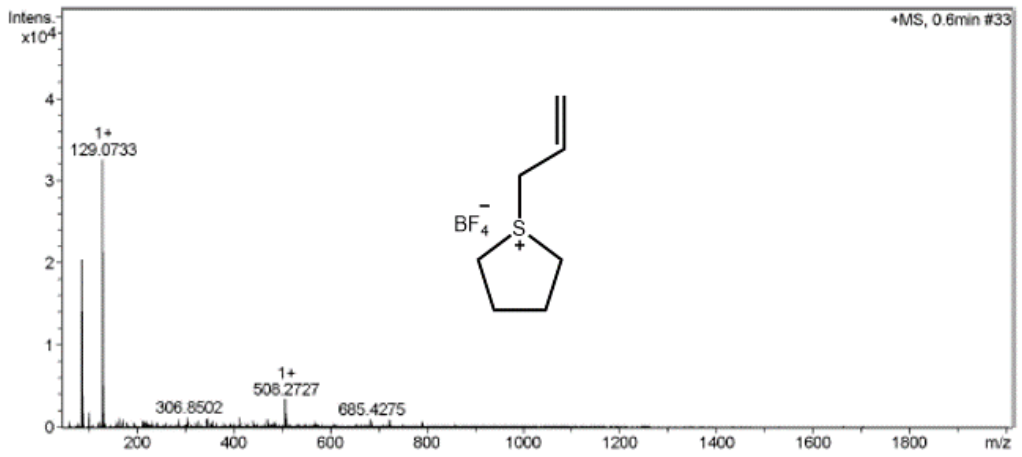
Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SOR_45A_GA3_01_32450.d	Acquisition Date	15/03/2023 15:31:14
Sample Description			



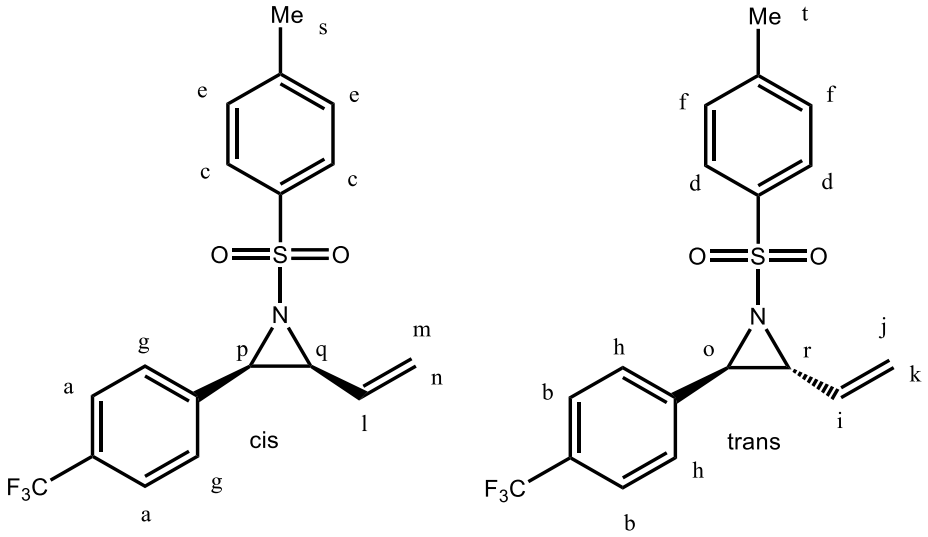
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
129.073335	1	C7H13S	129.073248	0.1	0.7	1.5	ok	even	18.9

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

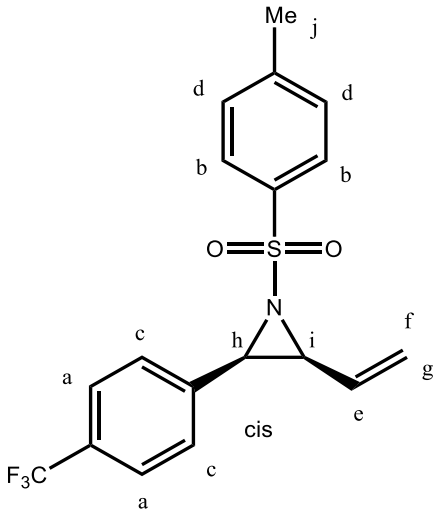
Spectrum 20: HRMS spectrum of 1-Allytetrahydrothiophenium tetrafluoroborate 2f

7.1.15. 1-[(4-Methylphenyl)sulfonyl]-2-(1-ethylene)-3-[4-(trifluoromethyl)phenyl]aziridine **3a**



^{1}H NMR ($CDCl_3$) cis/trans (1:1.25) δ 7.89 (d, J= 8.2 Hz, 2H, Ha), 7.84 (d, J= 8.3 Hz, 2.5H, Hb), 7.57-7.49 (m, 4.75H, Hc, Hd), 7.35 (d, J= 8 Hz, 4H, He, Hf), 7.29 (d, J= 8.2 Hz, 4H, Hg, Hh), 6.40-6.27 (m, 1.25H, Hi), 5.59 (d, J= 16.9 Hz, 1.25H, Hj), 5.51 (d, J= 10.3 Hz, 1.25H, Hk), 5.49-5.40 (m, 1H, Hl), 5.27-5.15 (m, 2H, Hm, Hn), 4.13-4.06 (m, 2.25H, Ho, Hp), 3.70-3.63 (m, 1H, Hq), 3.28 (dd, J= 4, 9.4 Hz, 1.25H, Hr), 2.44 (s, 3H, Hs), 2.40 (s, 3.75H, Ht) (**Spectrum 21**).

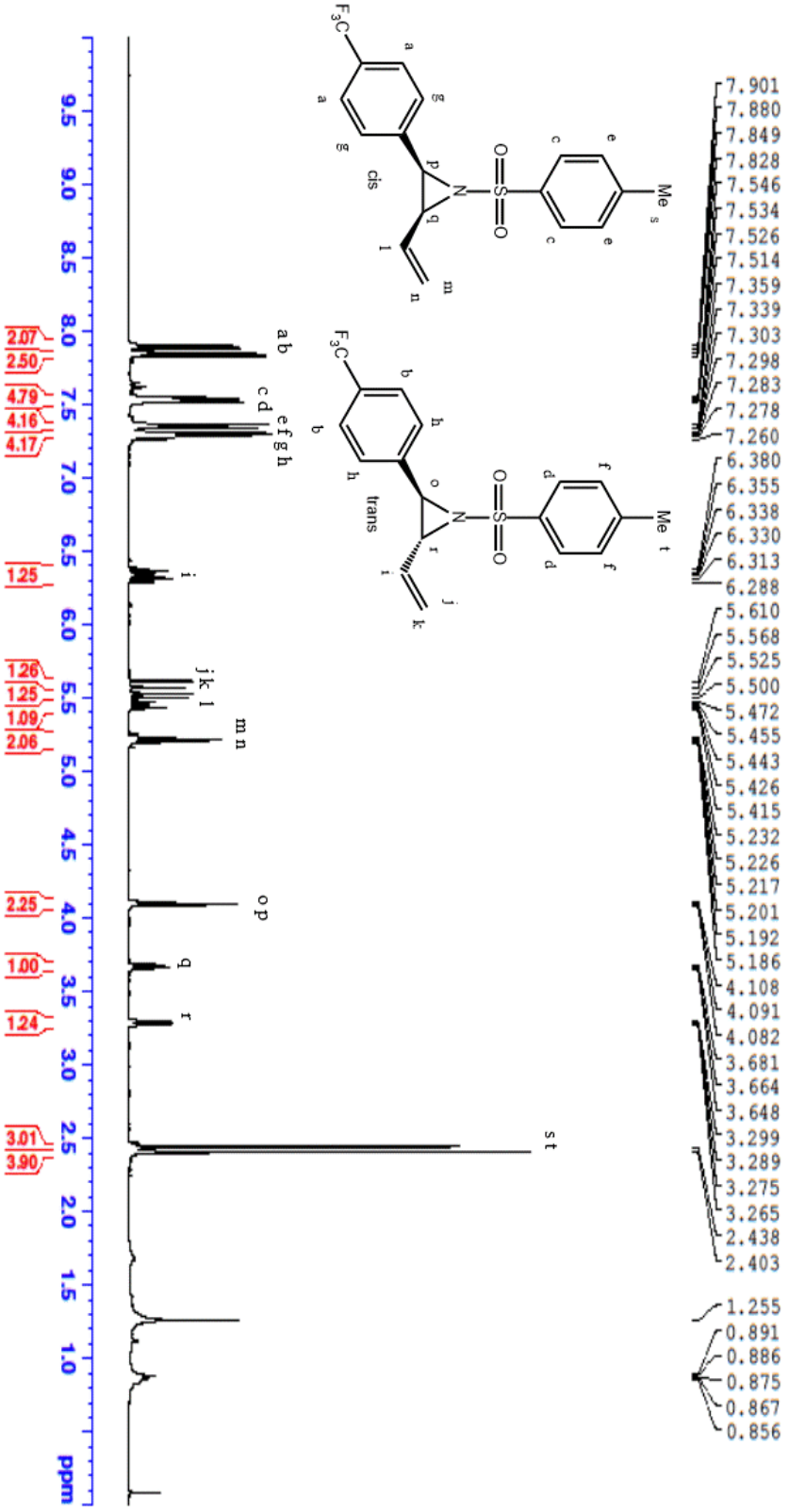
^{19}F NMR ($CDCl_3$) cis/trans (1:1.18) δ -62.60 (1), -62.63 (1.18) (**Spectrum 22**)



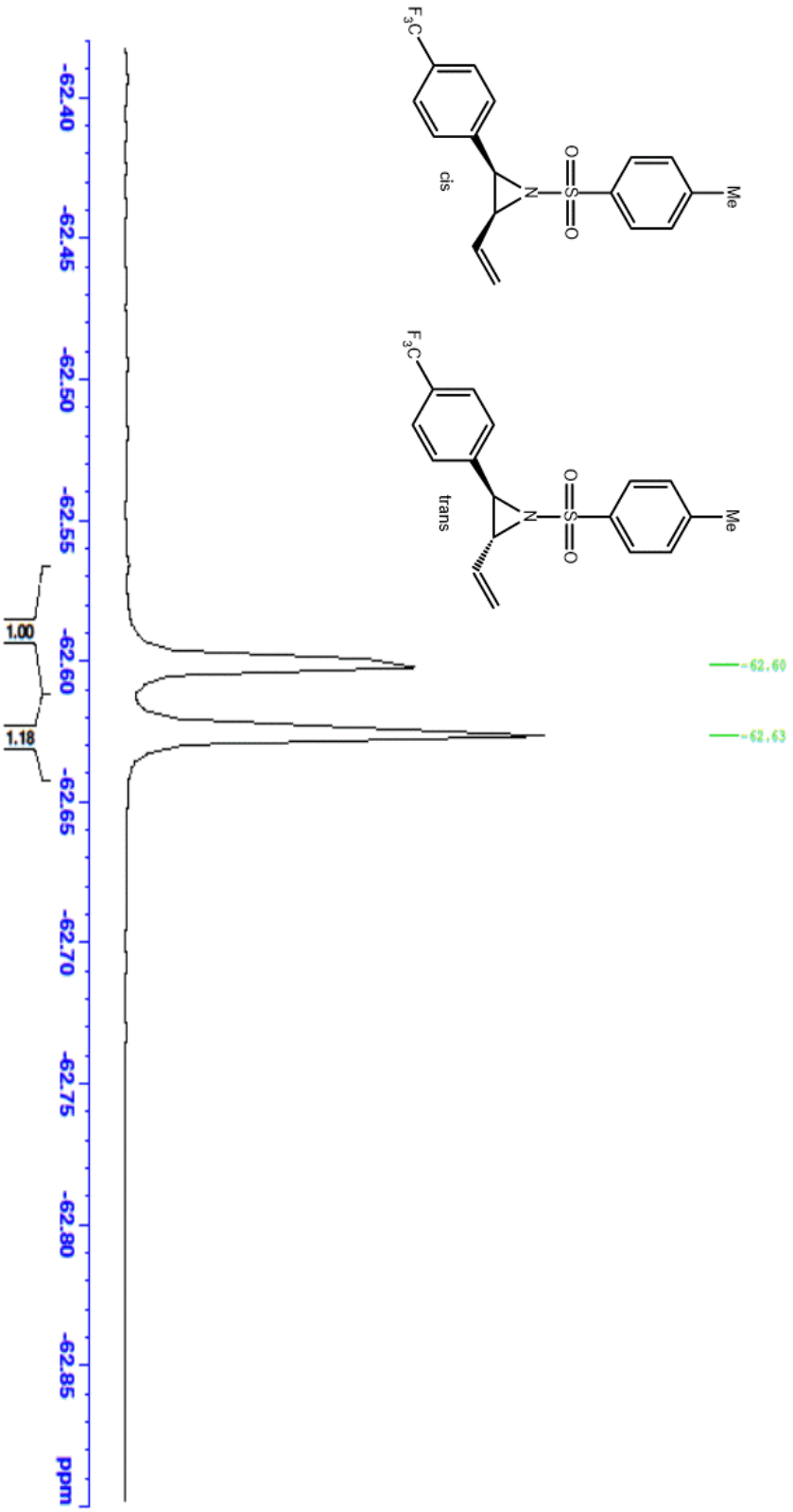
^{1}H NMR ($CDCl_3$) cis/trans (1:0) δ 7.89 (d, J= 8.5 Hz, 2H, Ha), 7.54 (d, J= 8 Hz, 2H, Hb), 7.37-7.33 (m, 4H, Hc, Hd), 5.47-5.41 (m, 1H, He), 5.24-5.19 (m, 2H, Hf, Hg), 4.10 (d, J= 7.2 Hz, 1H, Hh), 3.68-3.65 (m, 1H, Hi), 2.45 (s, 3H, Hj) (**Spectrum 23**)

^{13}C NMR ($CDCl_3$) cis/trans (1:0) δ 145.07, 136.85, 134.98, 130.02, 129.28, 128.08, 128.03, 125.55-125.39, 122.58, 47.42, 45.75, 29.50, 21.82. **Hexane**: 32.07, 22.83, 14.25. **Grease:** 29.84 (**Spectrum 25**)

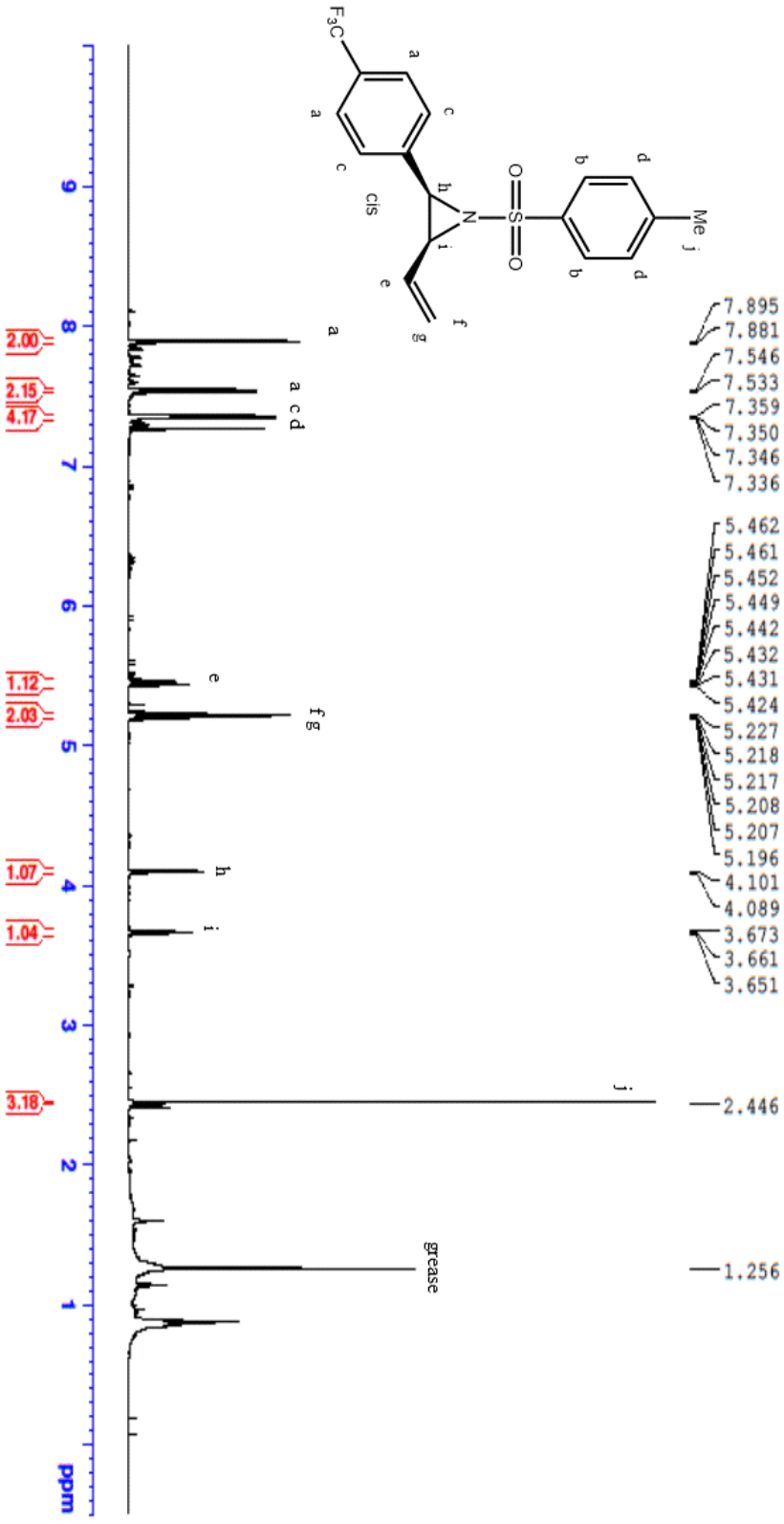
HRMS: $[M-H]^+$ 366.0781 m/z (**Spectrum 28**)



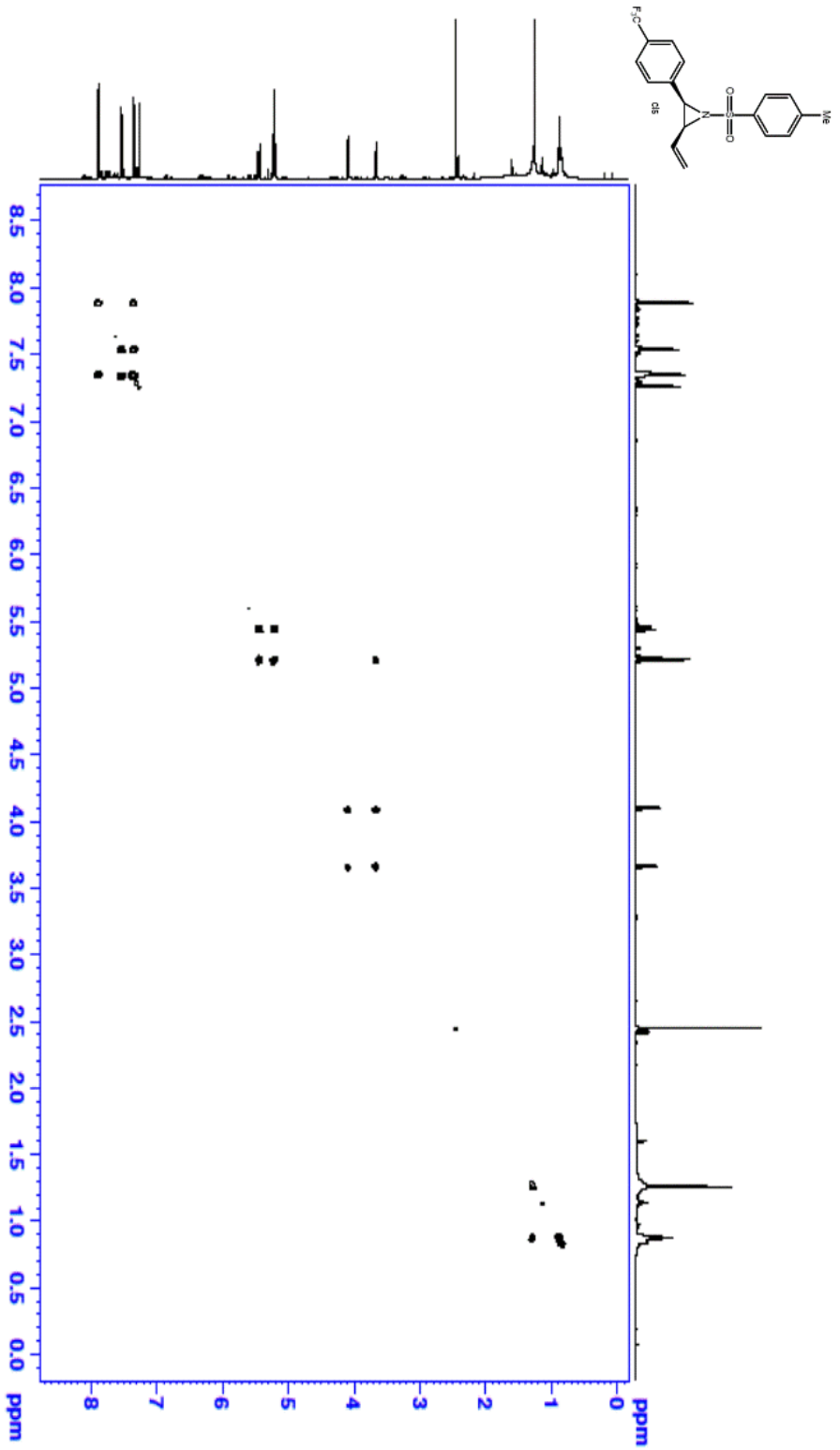
Spectrum 21: ^{1}H NMR of cis/trans mix of 1-[(4-Methylphenyl)sulfonyl]-2-(1-ethylene)-3-[4-(trifluoromethyl)phenyl]aziridine 3a



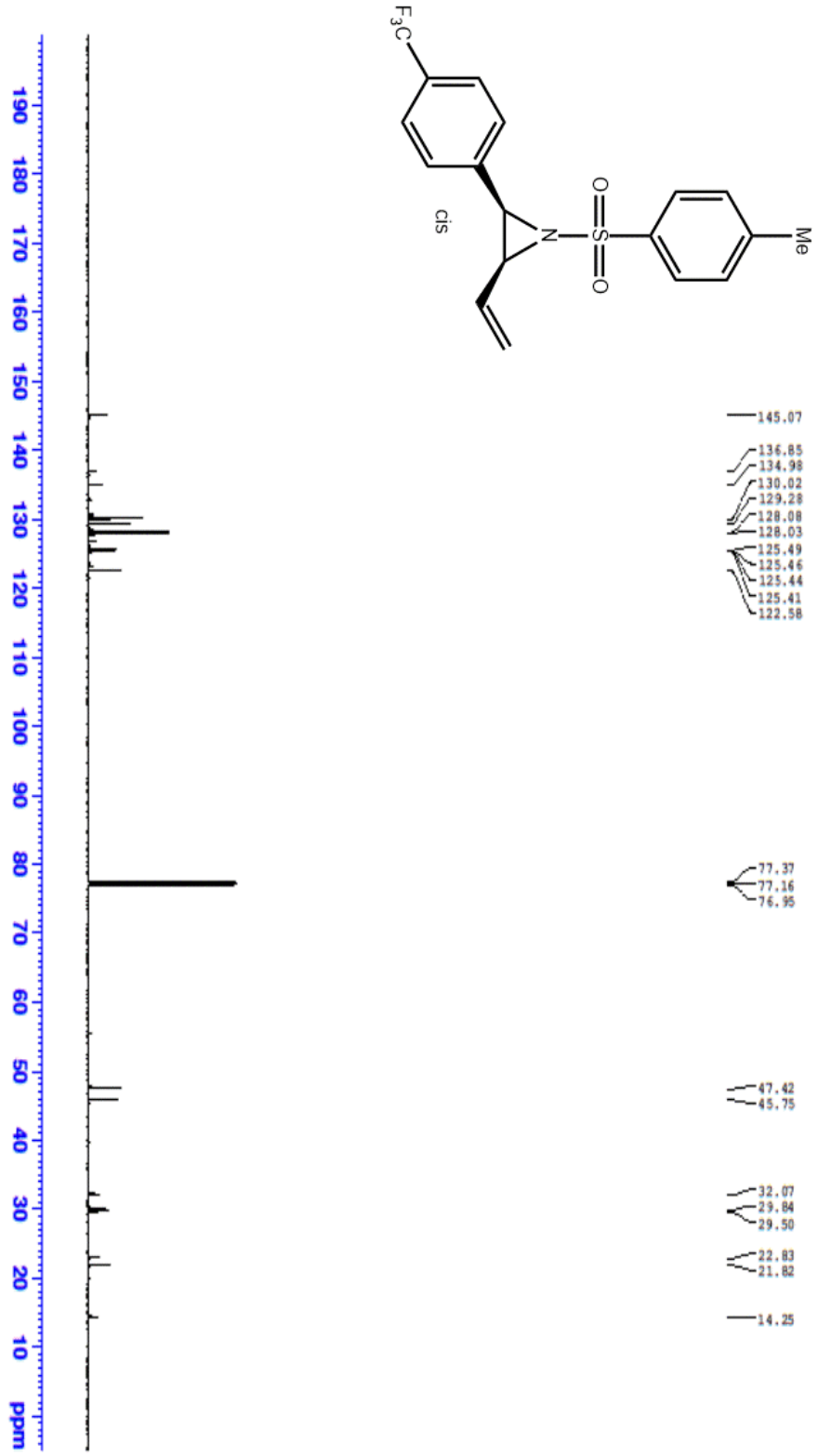
Spectrum 22: ^{19}F NMR of cis/trans mix of 1-[(4-Methylphenyl)sulfonyl]-2-(1-ethylene)-3-[4-(trifluoromethyl)phenyl]aziridine 3a



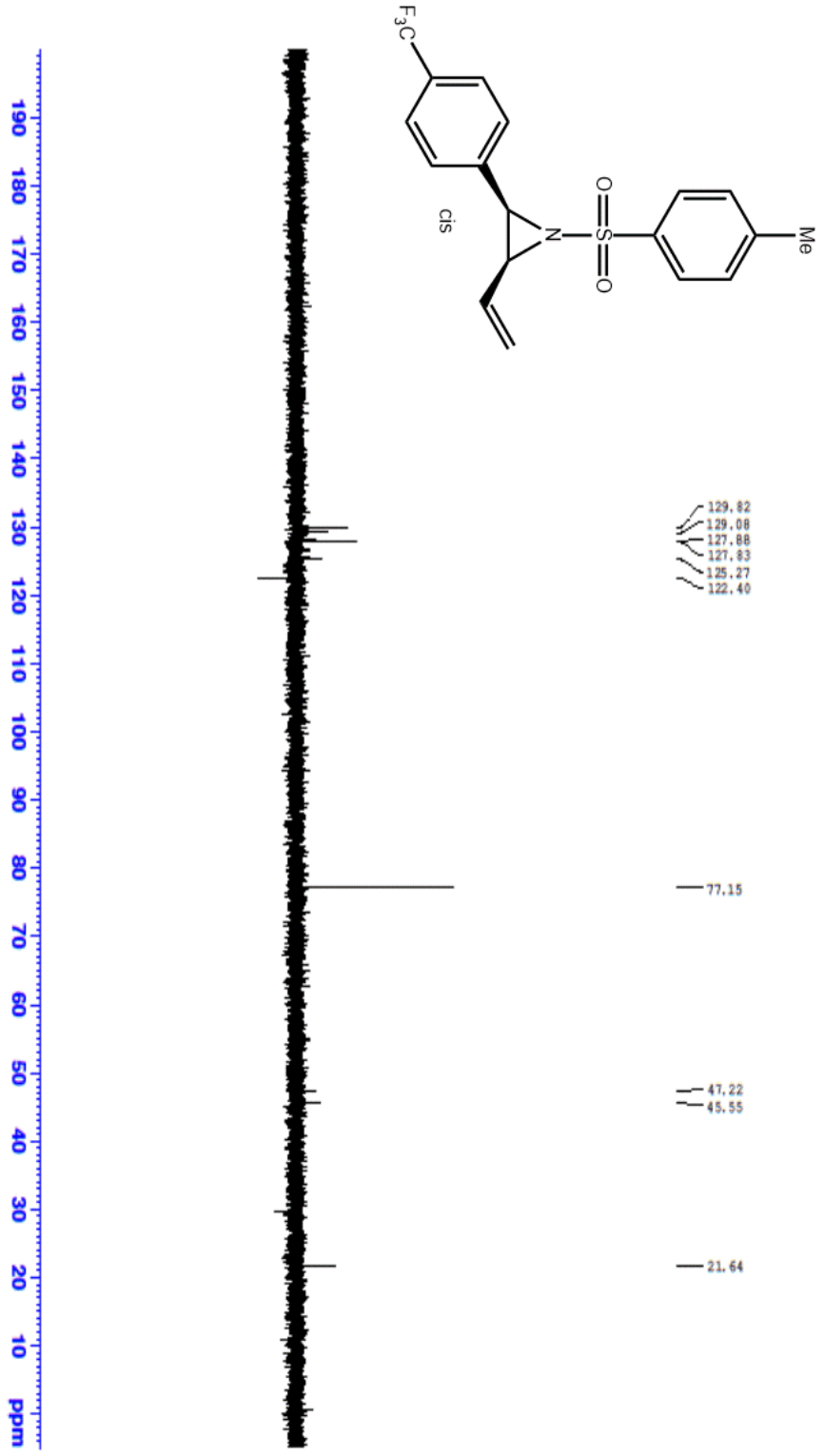
Spectrum 23: ^{1}H NMR spectrum of cis 1-[(4-Methylphenyl)sulfonyl]-2-(1-ethylene)-3-[4-(trifluoromethyl)phenyl]aziridine 3a



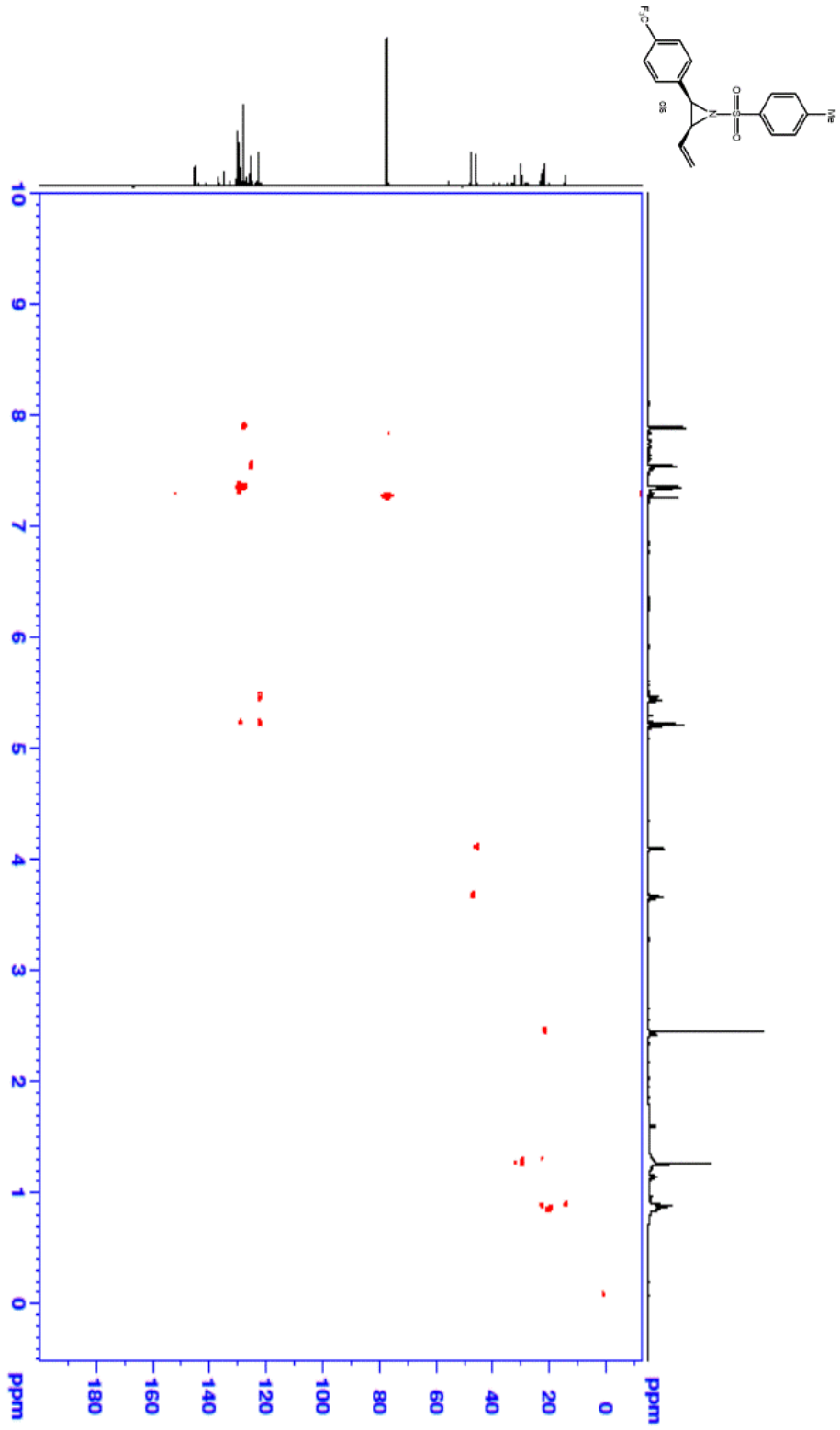
Spectrum 24: COSY NMR spectrum of cis 1-[(4-Methylphenyl)sulfonyl]-2-(1-ethylene)-3-[4-(trifluoromethyl)phenyl]aziridine 3a



Spectrum 25: ^{13}C NMR spectrum of cis 1-[(4-Methylphenyl)sulfonyl]-2-(1-ethylene)-3-[4-(trifluoromethyl)phenyl]aziridine 3a



Spectrum 26: DEPT NMR spectrum of cis 1-[(4-Methylphenyl)sulfonyl]-2-(1-ethylene)-3-[4-(trifluoromethyl)phenyl]aziridine 3a



Spectrum 27: HSQC NMR spectrum of cis 1-[(4-Methylphenyl)sulfonyl]-2-(1-ethylene)-3-[4-(trifluoromethyl)phenyl]aziridine 3a

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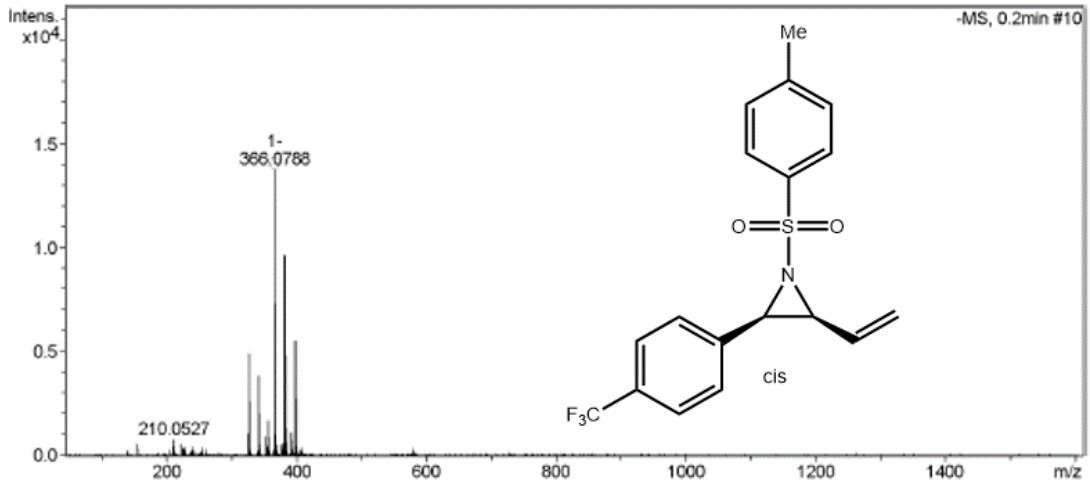
Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SOR_34C_RB6_01_32600.d	Acquisition Date	21/03/2023 14:26:47
Sample Description			



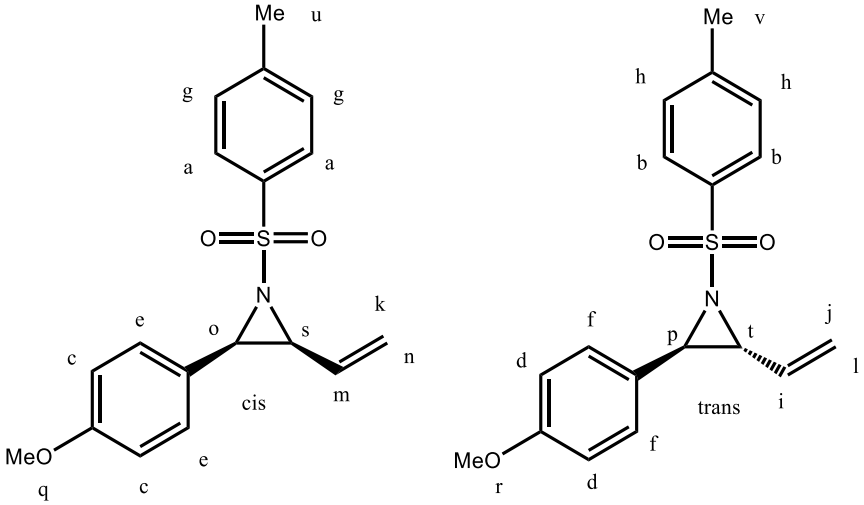
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
366.078757	1	C18H15F3NO2S	366.078108	0.6	1.8	10.5	ok	even	5.8

SmartFormula Settings

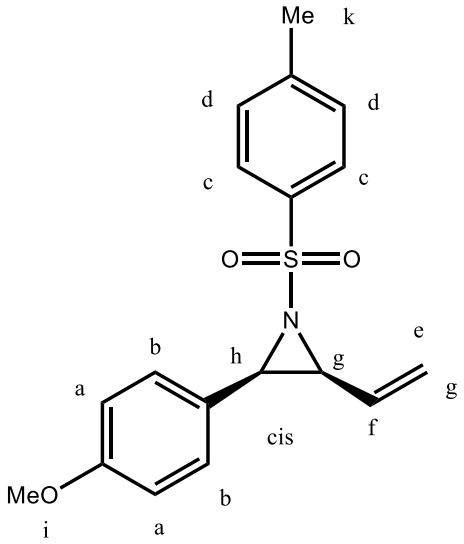
Low value of mSigma indicates good isotopic pattern match

Spectrum 28: HRMS spectrum of cis 1-[(4-Methylphenyl)sulfonyl]-2-(1-ethylene)-3-[4-(trifluoromethyl)phenyl]aziridine 3a

7.1.16. 1-[(4-Methylphenyl)sulfonyl]-2-(1-ethylene)-3-[4-(methoxy)phenyl]aziridine **3b**



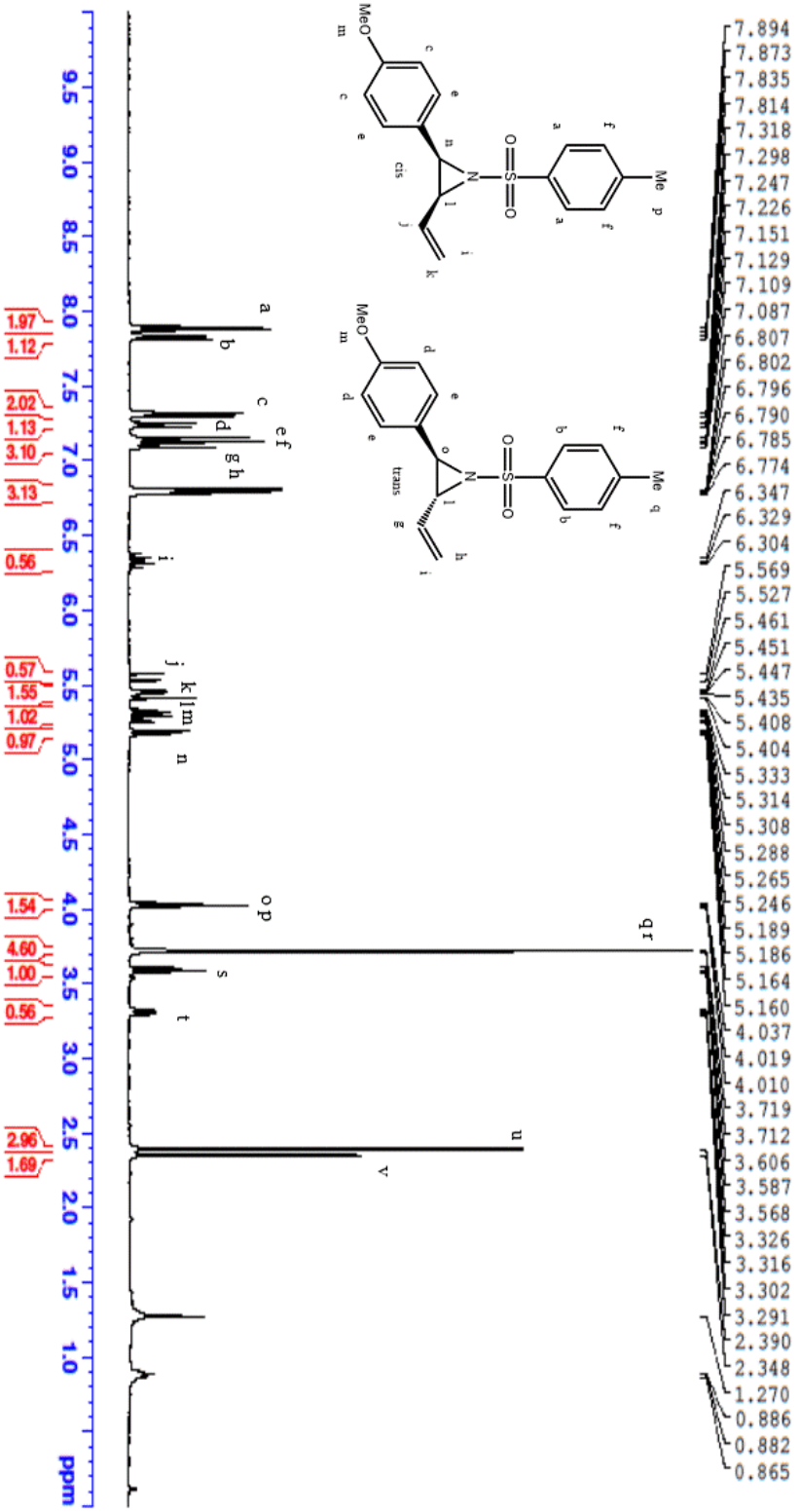
^{1}H NMR ($CDCl_3$) cis/trans (1:0.5) δ 7.88 (d, J= 8.3 Hz, 2H, Ha), 7.82 (d, J= 8.3 Hz, 1H, Hb), 7.31 (d, J= 8.2 Hz, 2H, Hc), 7.24 (d, J= 8.2 Hz, 1H, Hd), 7.17-7.06 (m, 3H, He, Hf), 6.84-6.75 (m, 3H, Hg, Hh), 6.39-6.27 (m, 0.5H, Hi), 5.55 (d, J= 16.8 Hz, 0.5H, Hj), 5.49-5.38 (m, 1.5H, Hk, Hl), 5.35-5.23 (m, 1H, Hm), 5.17 (d, J= 10.4 Hz, 1H, Hn), 4.06-3.99 (m, 1.5H, Ho, Hp), 3.74-3.70 (m, 4.5H, Hq, Hr), 3.62-3.55 (m, 1H, Hs), 3.31 (dd, J= 4.1, 9.5 Hz, 0.5H, Ht), 2.39 (s, 3H, Hu), 2.35 (s, 1.5H, Hv) (**Spectrum 29**)



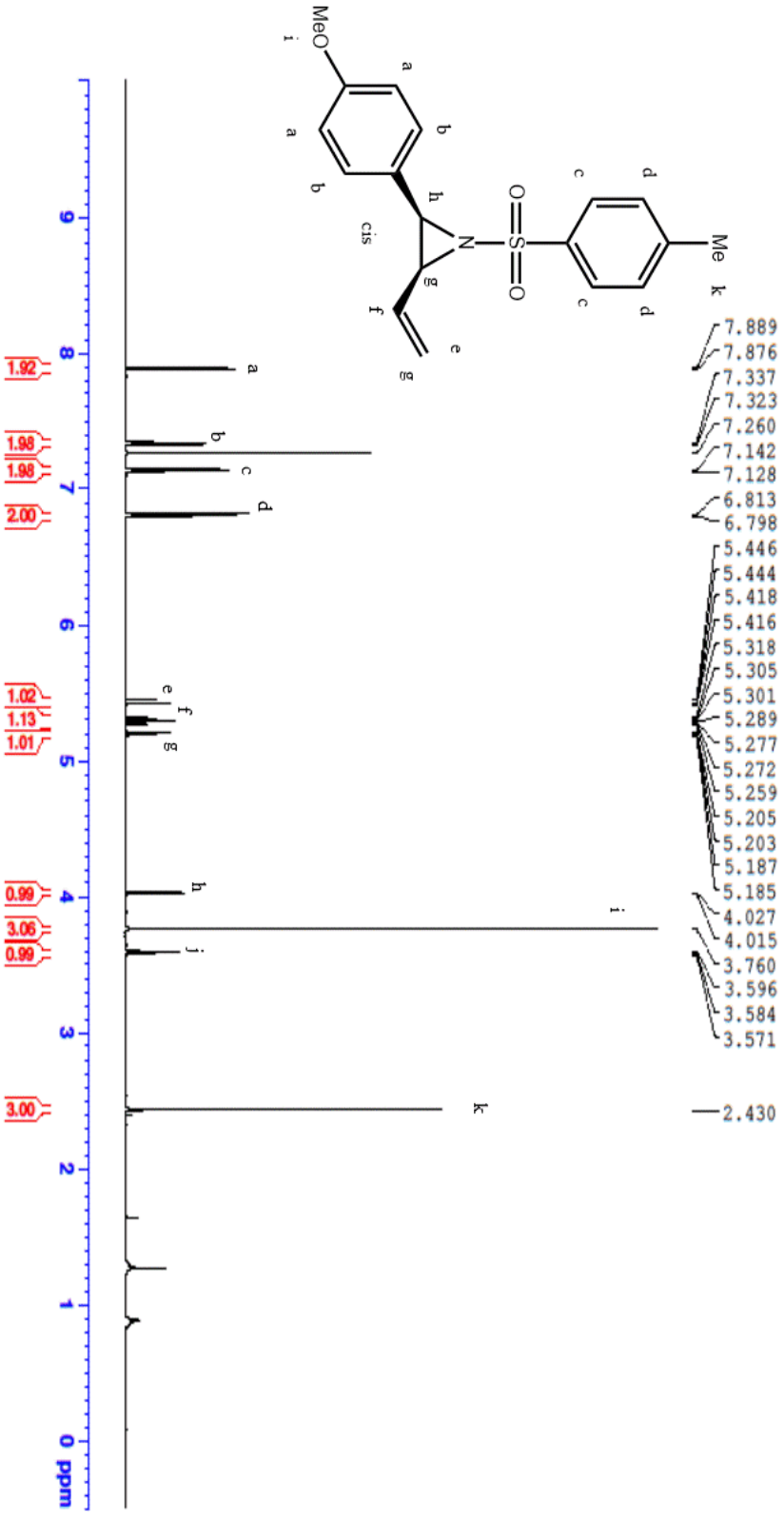
^{1}H NMR ($CDCl_3$) cis/trans (1:0) δ 7.88 (d, J= 8.2 Hz, 2H, Ha), 7.33 (d, J= 8.2 Hz, 2H, Hb), 7.14 (d, J= 8.4 Hz, 2H, Hc), 6.80 (d, J= 8.5 Hz, 2H, Hd), 5.45-5.40 (m, 1H, He), 5.33-5.25 (m, 1H, Hf), 5.21-5.17 (m, 1H, Hg), 4.02 (d, J= 7.2 Hz, 1H, Hh), 3.76 (s, 3H, Hi), 3.60-3.57 (m, 1H, Hj), 2.43 (s, 3H, Hk) (**Spectrum 30**)

^{13}C NMR ($CDCl_3$) cis/trans (1:0) δ 159.45, 144.67, 135.30, 130.05, 129.86, 128.77, 127.95, 124.64, 121.88, 113.86, 55.34, 47.43, 46.13, 21.77 (**Spectrum 32**)

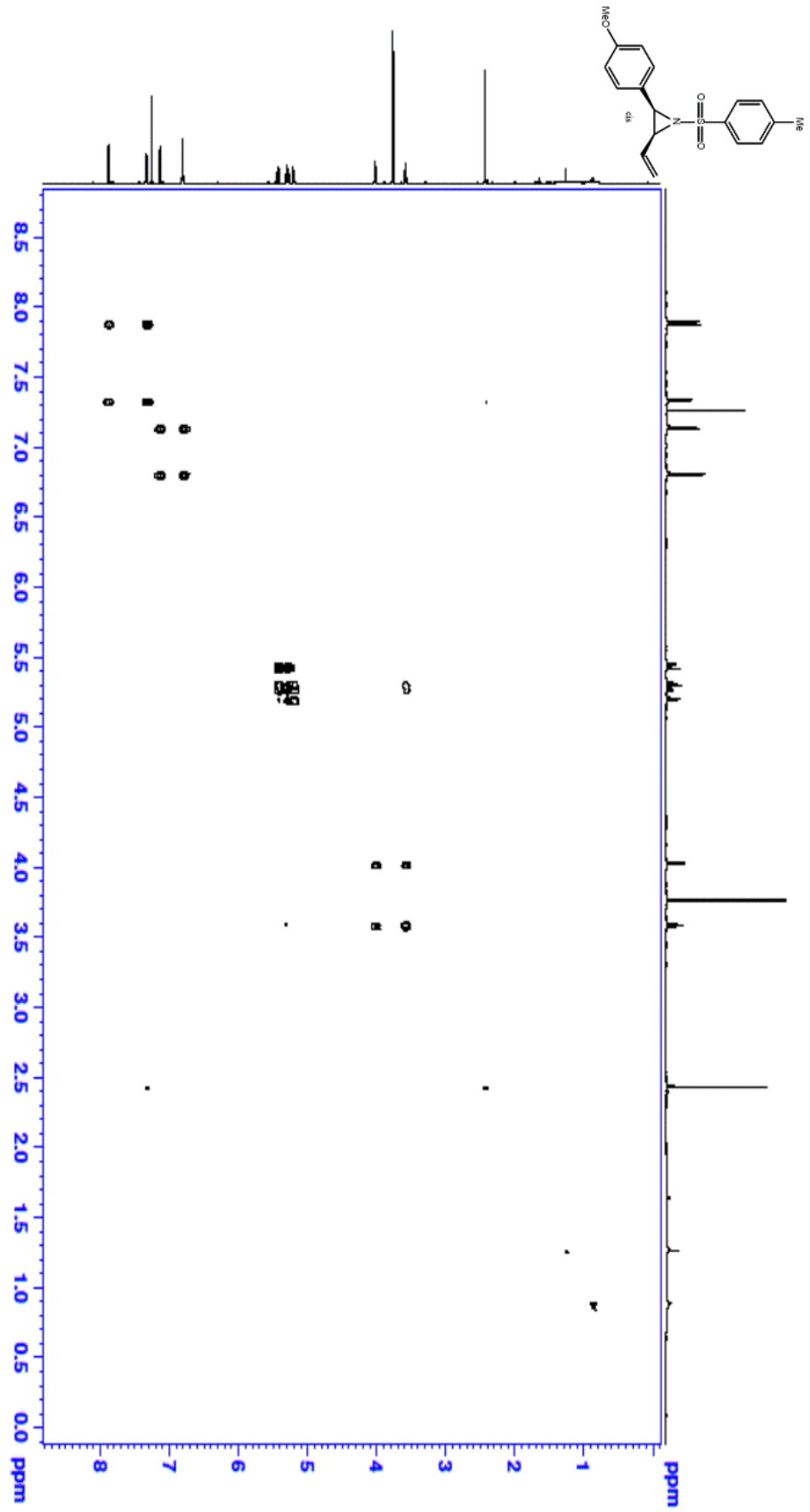
HRMS: $[M-H]^+$ 328.1013 m/z (**Spectrum 35**)



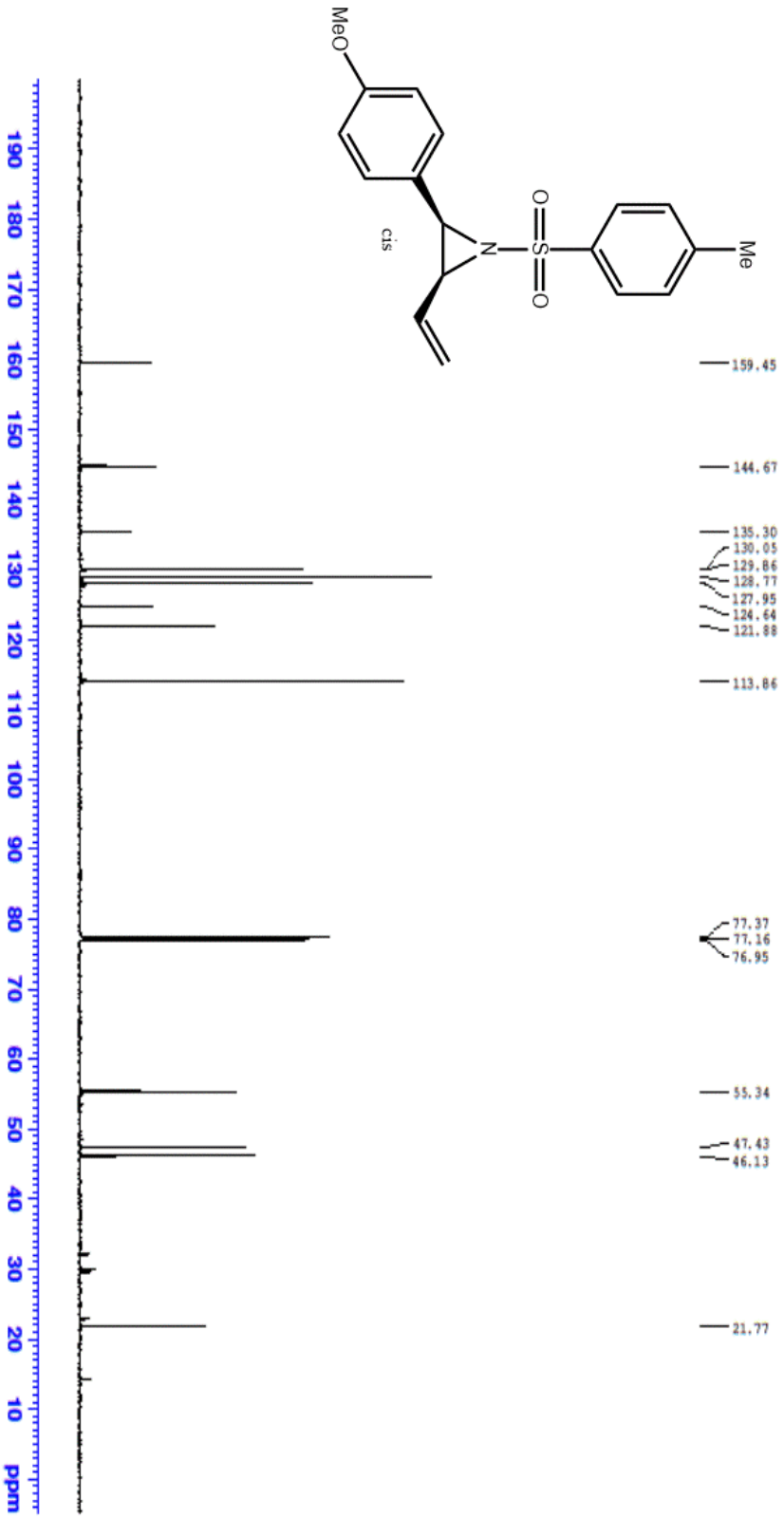
Spectrum 29: ^{1}H NMR spectrum of cis/trans mix of 1-[(4-Methylphenyl)sulfonyl]-2-(1-ethylene)-3-[4-(methoxy)phenyl]aziridine 3b



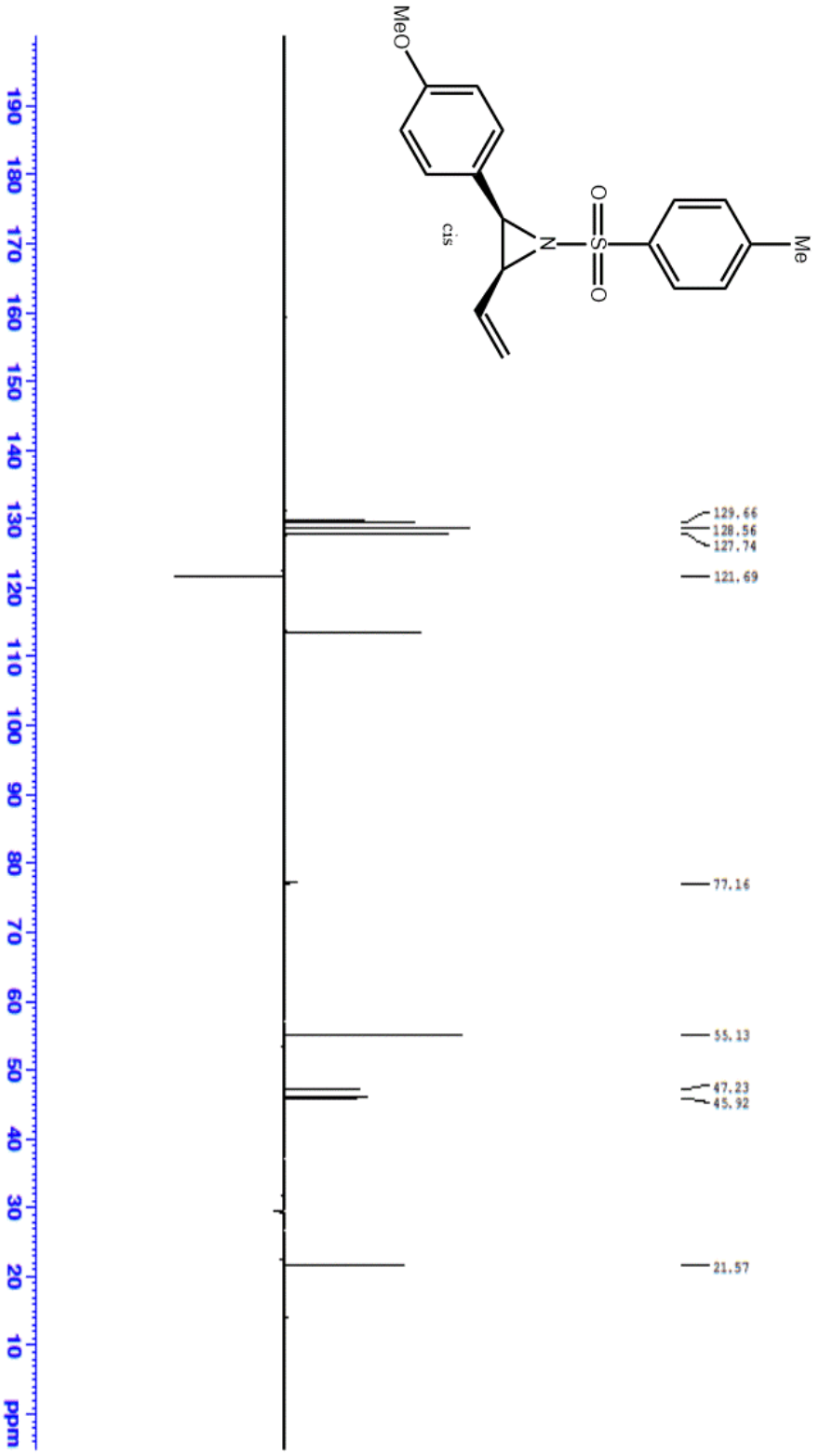
Spectrum 30: ^{1}H NMR spectrum of cis 1-[(4-Methylphenyl)sulfonyl]-2-(1-ethylene)-3-[4-(methoxy)phenyl]aziridine 3b



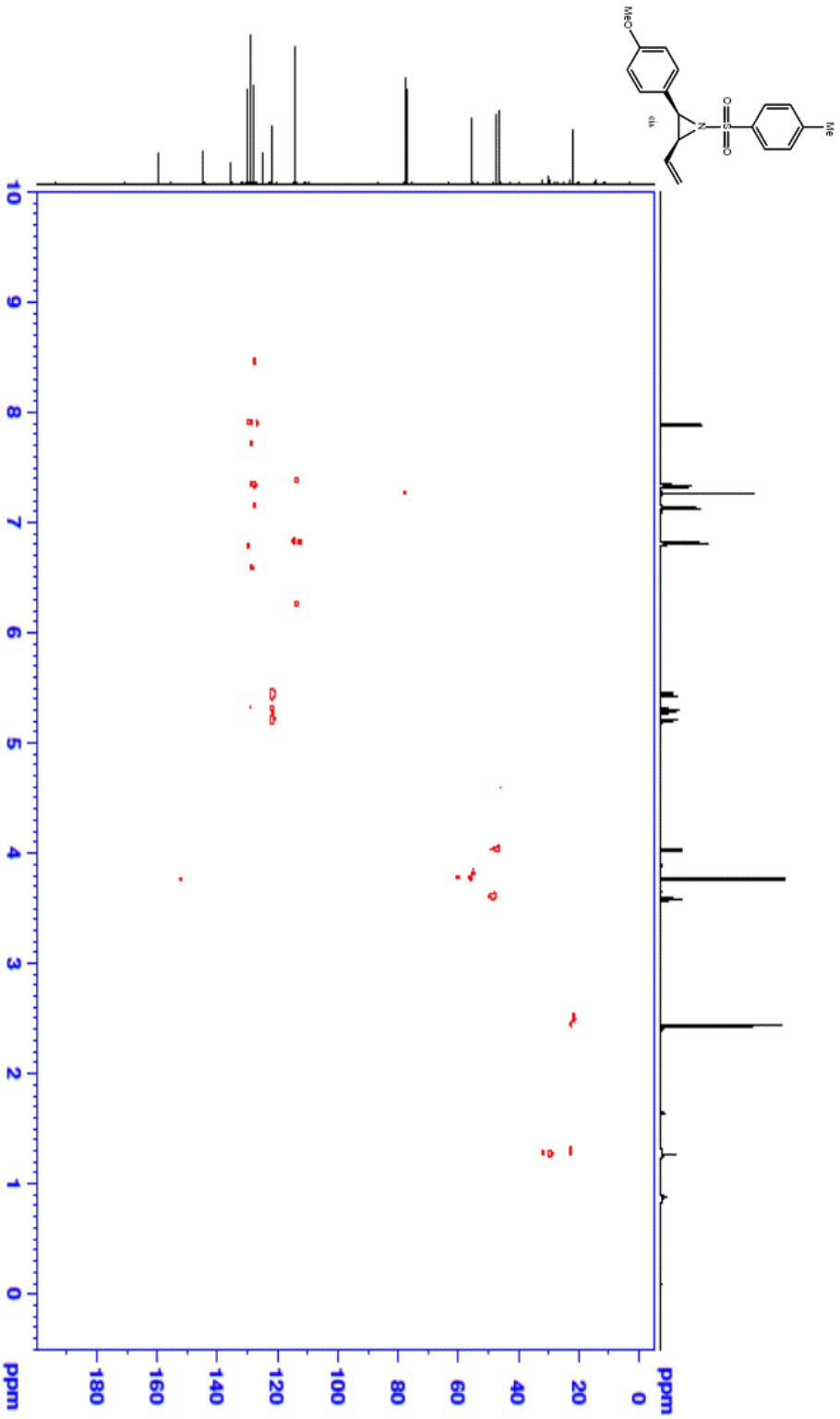
Spectrum 31: COSY NMR spectrum of cis 1-[(4-Methylphenyl)sulfonyl]-2-(1-ethylene)-3-[4-(methoxy)phenyl]aziridine 3b



Spectrum 32: ^{13}C NMR spectrum of cis 1-[(4-Methylphenyl)sulfonyl]-2-(1-ethylene)-3-[4-(methoxy)phenyl]aziridine 3b



Spectrum 33: DEPT NMR spectrum of cis 1-[(4-Methylphenyl)sulfonyl]-2-(1-ethylene)-3-[4-(methoxy)phenyl]aziridine 3b



Spectrum 34: HSQC NMR spectrum of cis 1-[(4-Methylphenyl)sulfonyl]-2-(1-ethylene)-3-[4-(methoxy)phenyl]aziridine 3b

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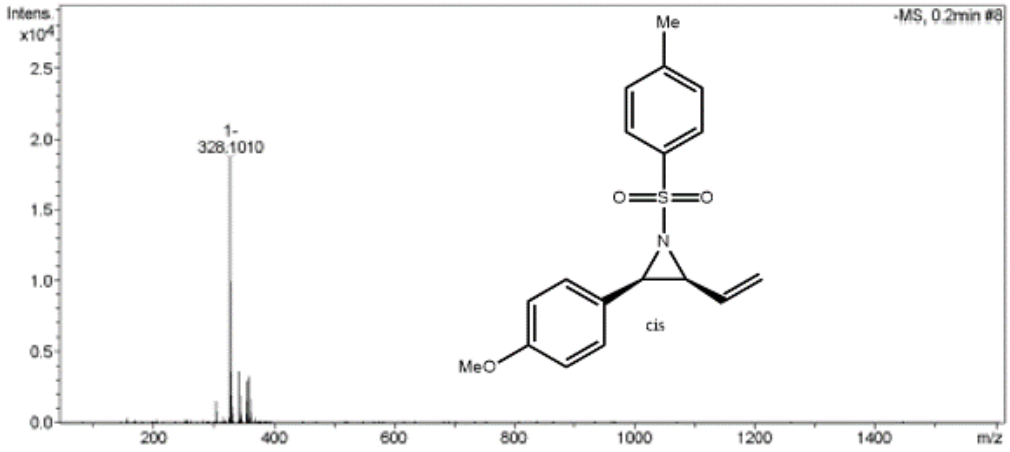
Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SOR_28B_RB2_01_32596.d	Acquisition Date	21/03/2023 14:13:51
Sample Description			



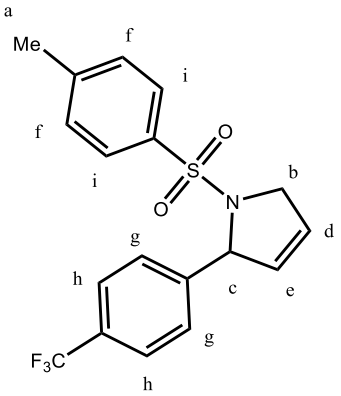
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
328.101049	1	C18H18NO3S	328.101288	-0.2	-0.7	10.5	ok	even	9.4

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

Spectrum 35: HRMS of spectrum of cis 1-[(4-Methylphenyl)sulfonyl]-2-(1-ethylene)-3-[4-(methoxy)phenyl]aziridine 3b

7.1.17. 2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(trifluoromethyl)phenyl]-3-pyrroline **4a**

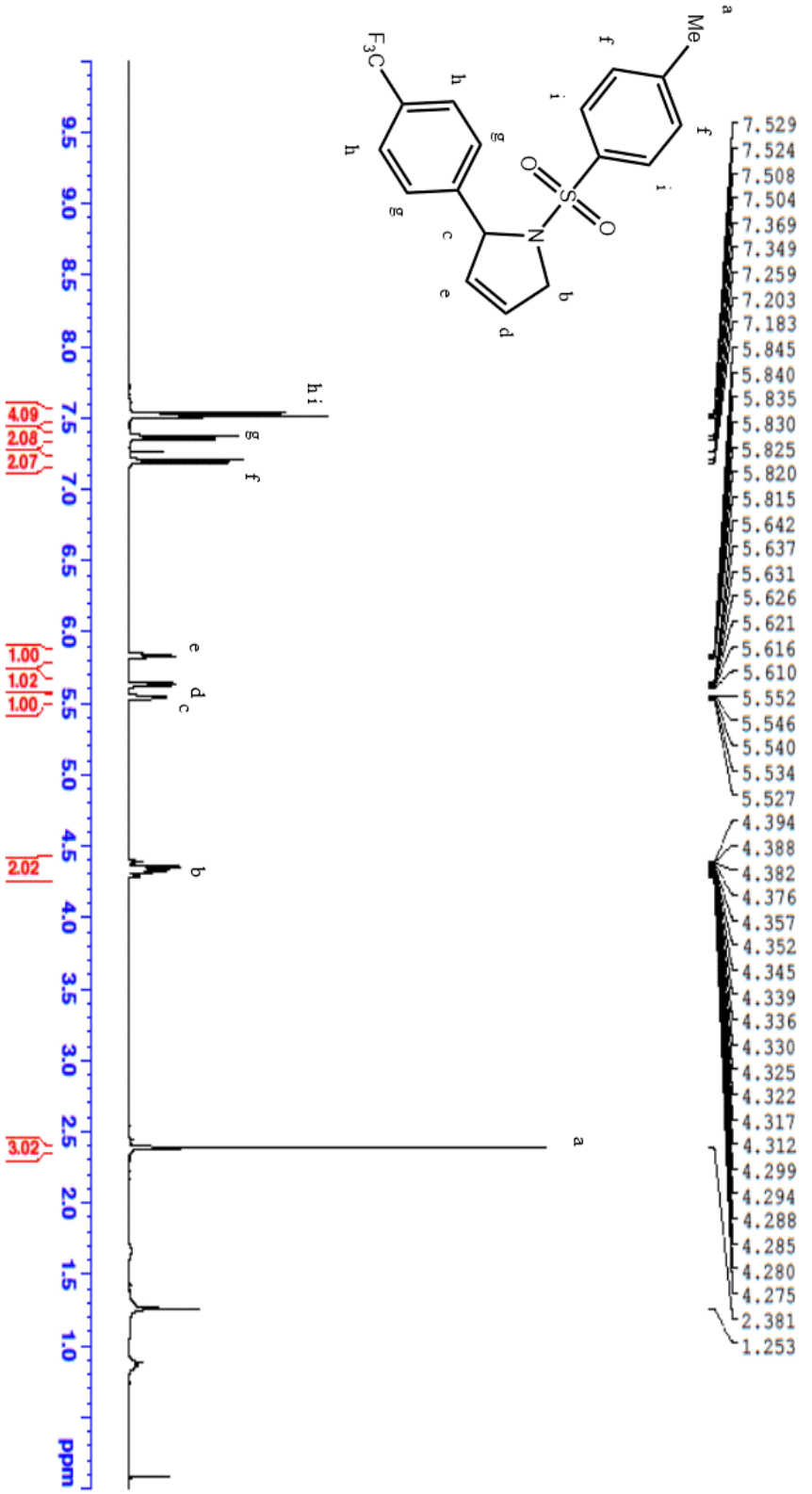


^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H, Ha), 4.41-4.27 (m, 2H, Hb), 5.56-5.51 (m, 1H, Hc), 5.63 (ddd, J= 6.4, 3.2, 2.1 Hz, 1H, Hd), 5.83 (ddd, J= 6.2, 2.9, 2 Hz, 1H, He), 7.19 (d, 8 Hz, 2H, Hf), 7.36 (d, 8.1 Hz, 2H, Hg), 7.52 (m, 4H, Hh) (**Spectrum 36**)

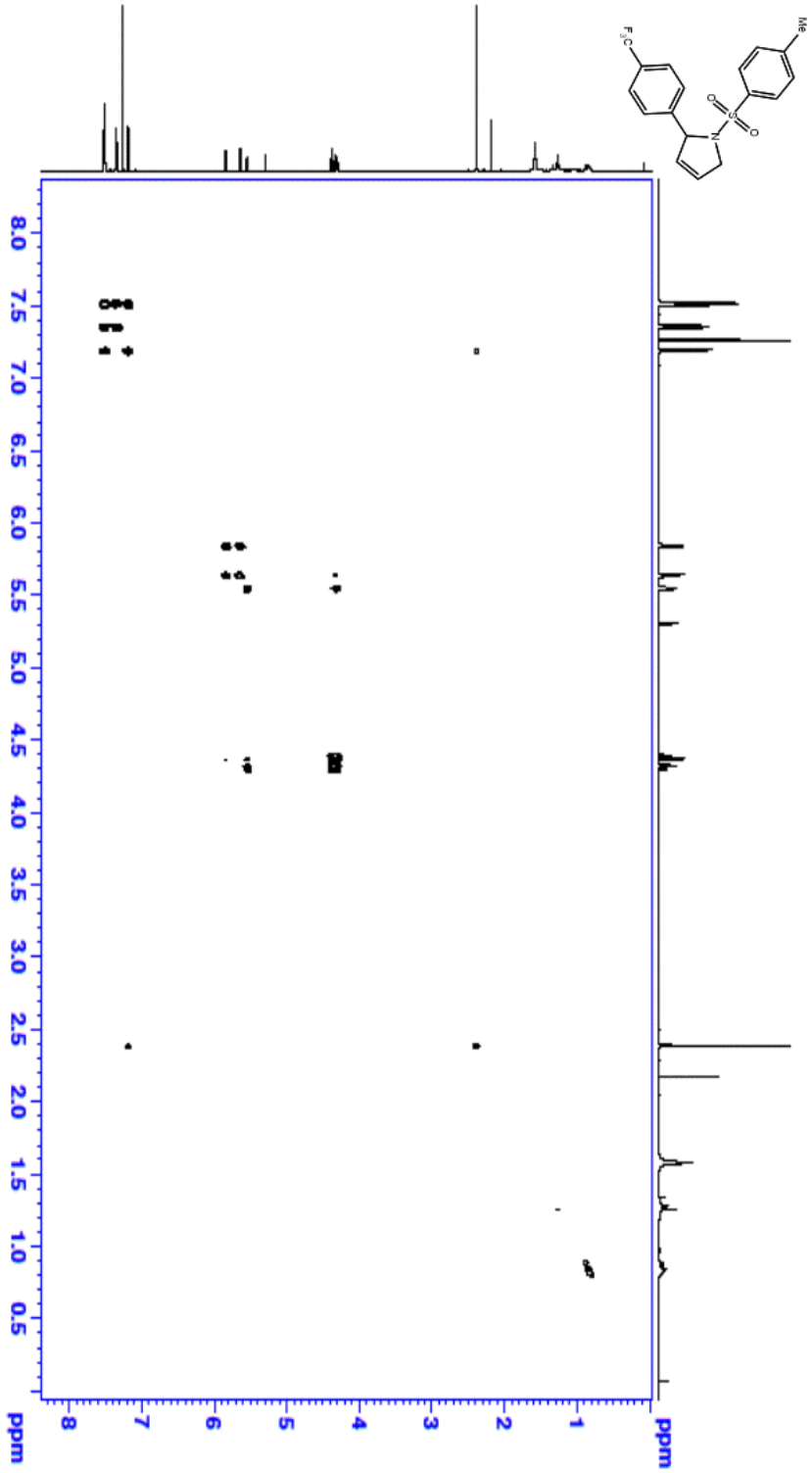
^{13}C NMR ($CDCl_3$) δ 144.56, 143.64, 135.47, 130.07, 129.69, 127.71, 127.34, 125.63-125.54, 125.49, 69.80, 55.71, 21.58 (**Spectrum 38)**

^{19}F NMR ($CDCl_3$) δ -62.50 (**Spectrum 41**)

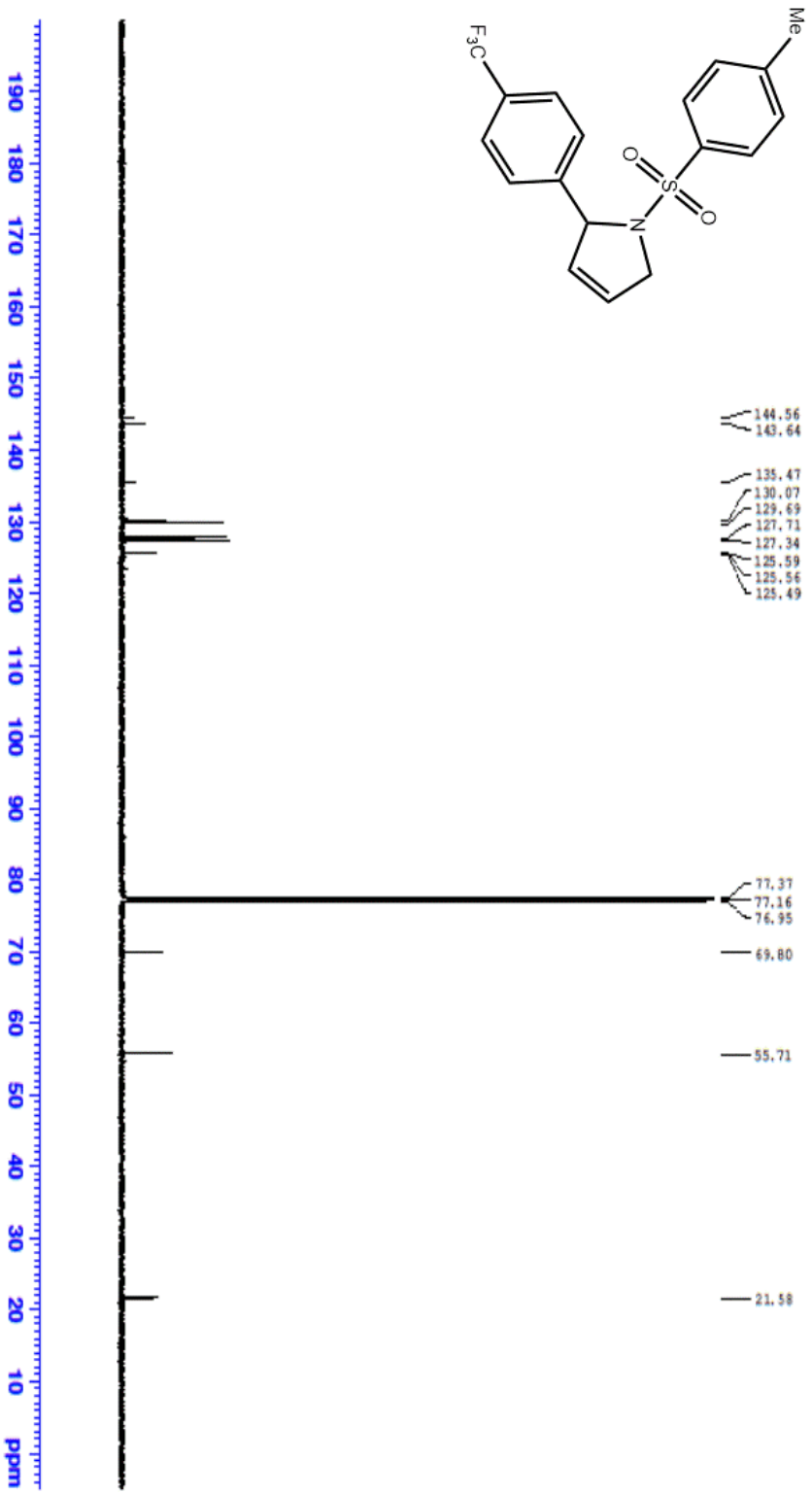
HRMS: $[M-H]^+$ 366.0781 m/z (**Spectrum 42**)



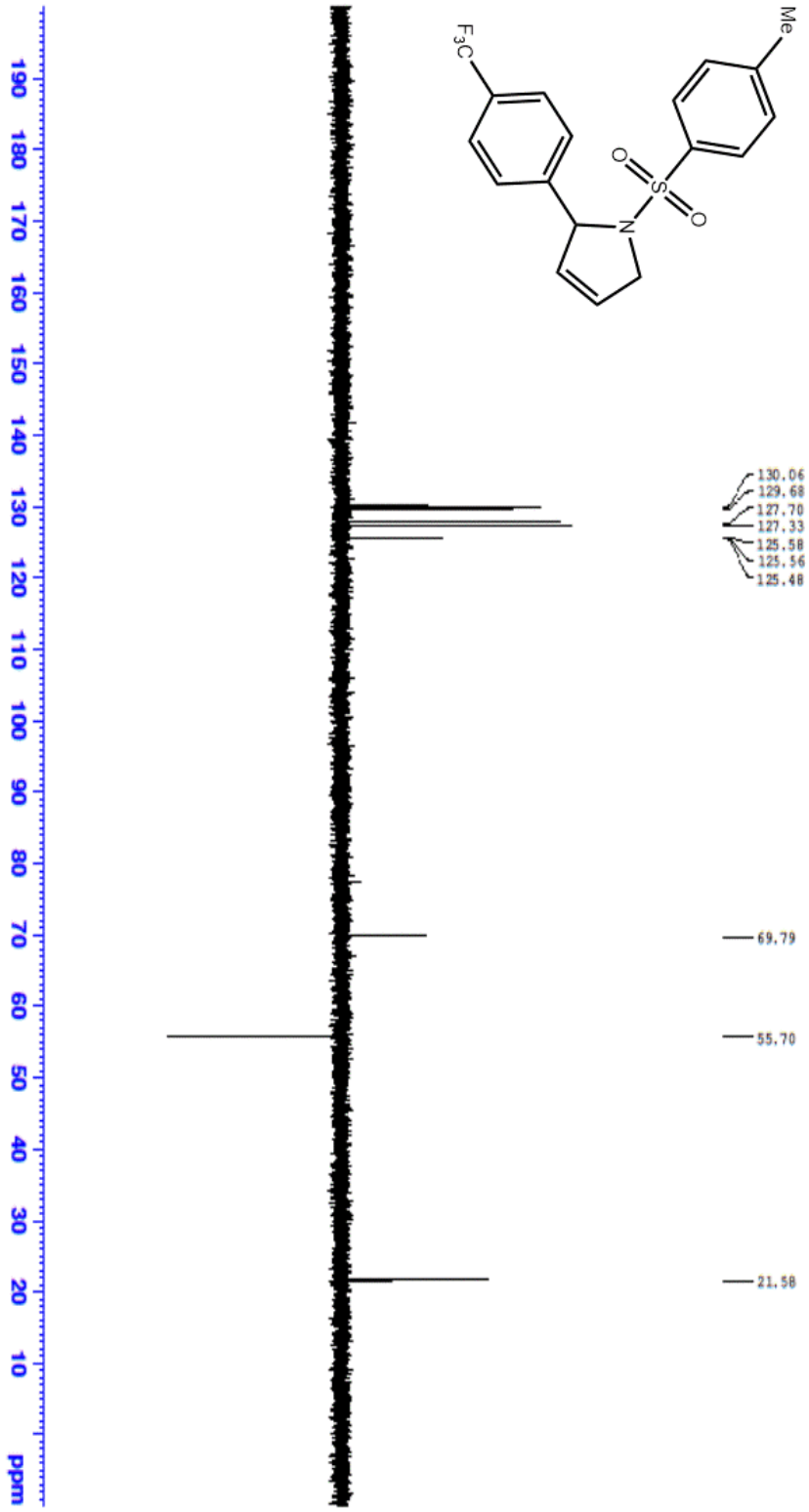
Spectrum 36: ^{1}H NMR spectrum of 2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(trifluoromethyl)phenyl]-3-pyrroline 4a



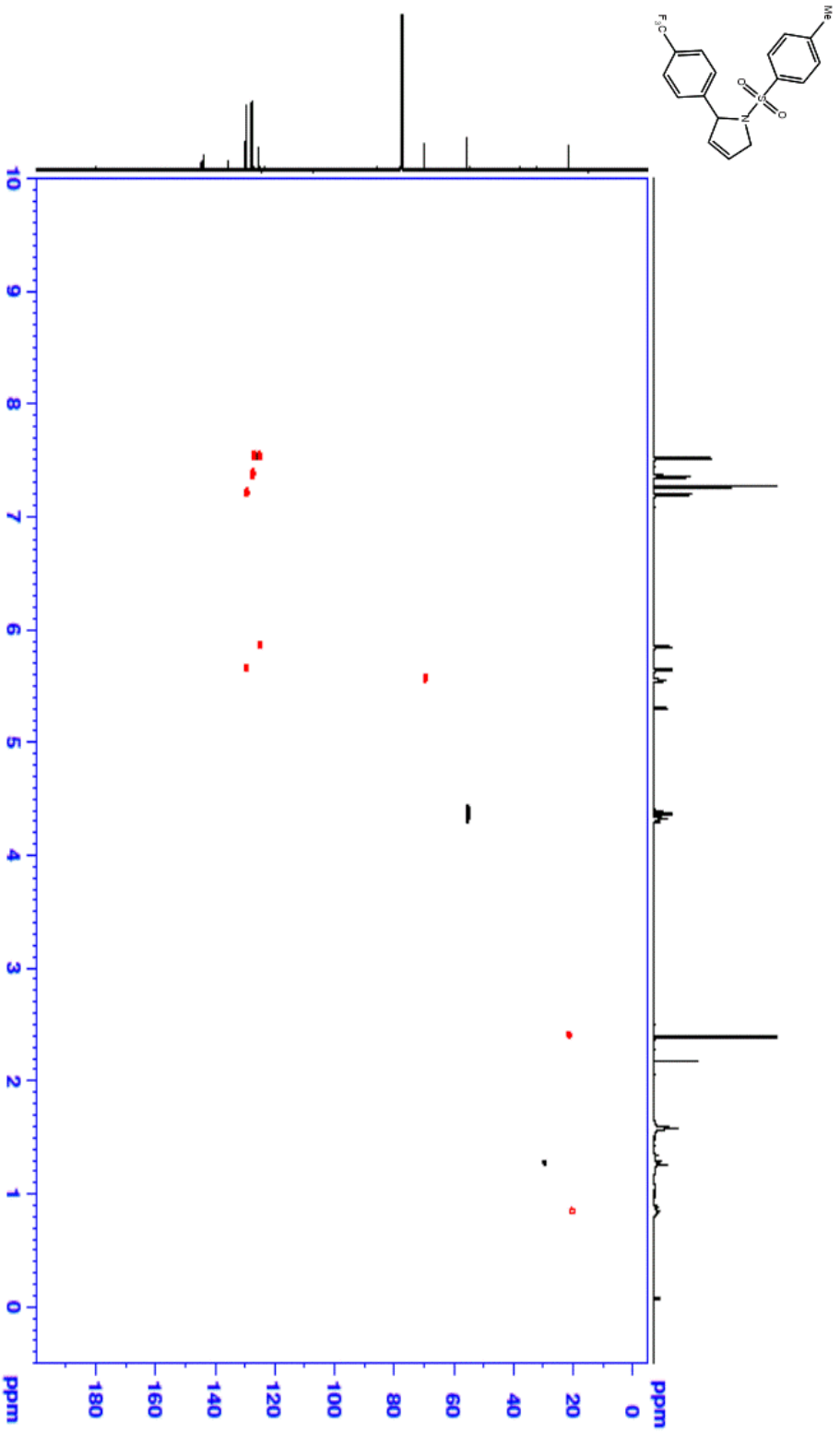
Spectrum 37: COSY NMR spectrum of 2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(trifluoromethyl)phenyl]-3-pyrroline 4a



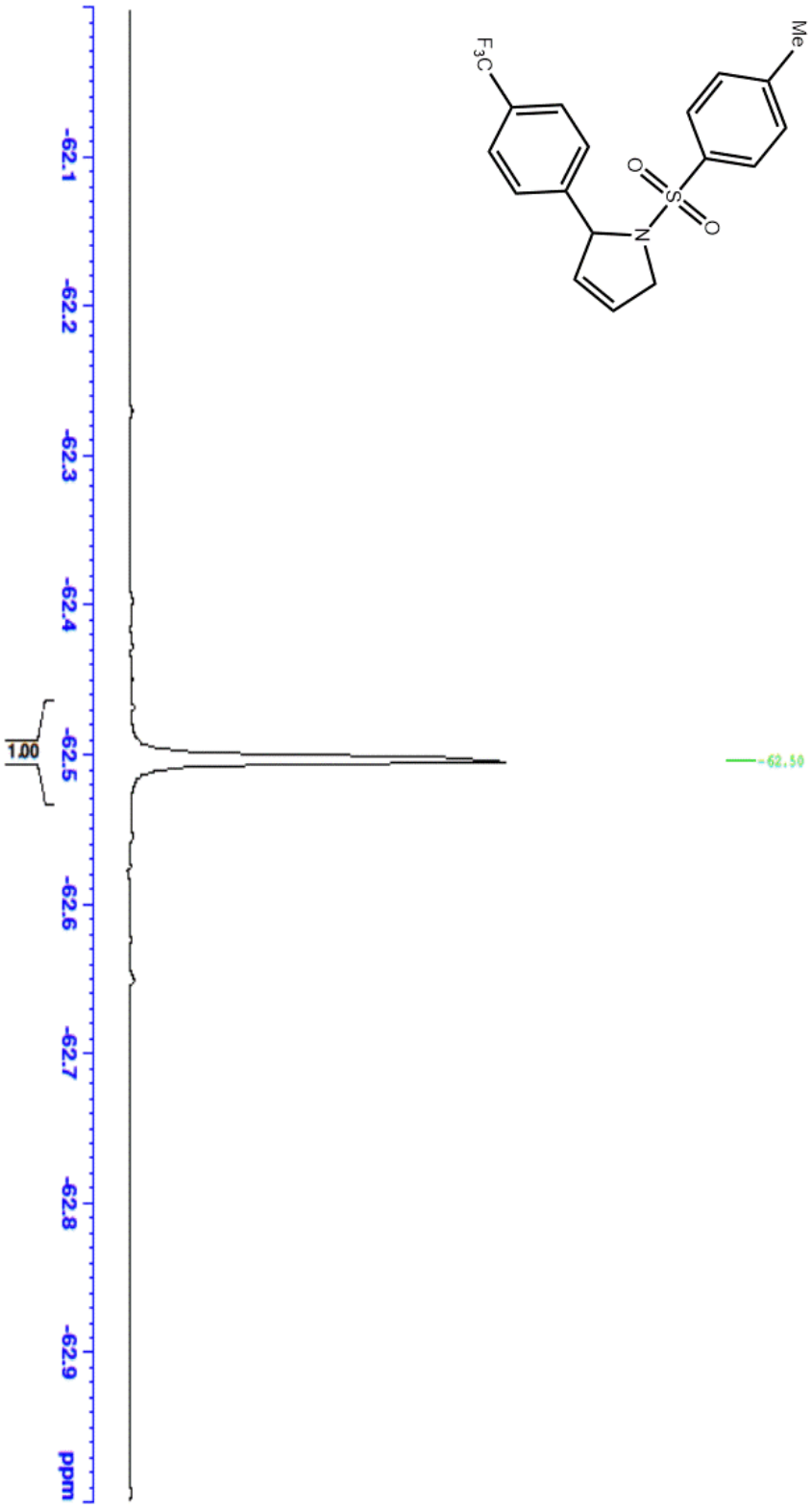
Spectrum 38: ^{13}C NMR spectrum of 2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(trifluoromethyl)phenyl]-3-pyrroline 4a



Spectrum 39: DEPT NMR spectrum of 2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(trifluoromethyl)phenyl]-3-pyrroline 4a



Spectrum 40: HSQC NMR spectrum of 2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(trifluoromethyl)phenyl]-3-pyrroline 4a



Spectrum 41: ^{19}F NMR spectrum of 2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(trifluoromethyl)phenyl]-3-pyrroline 4a

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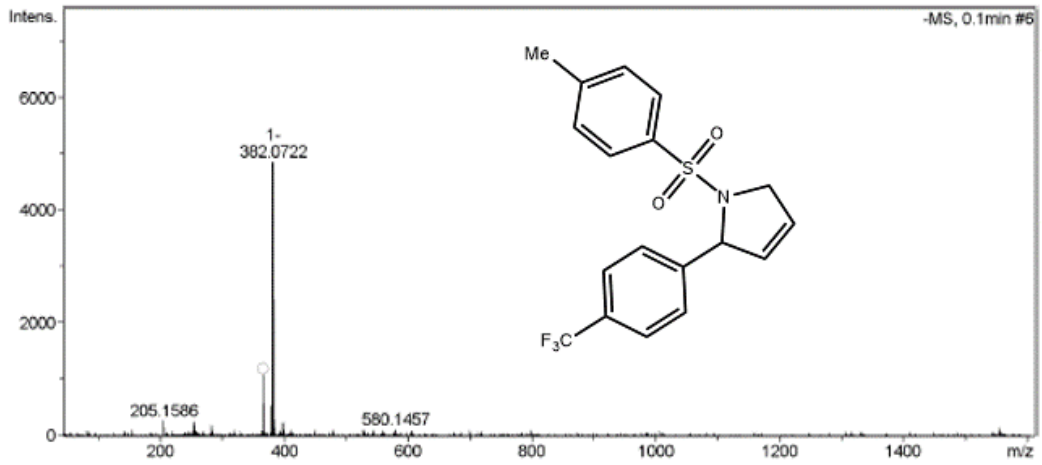
Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SOR_22B_RB1_01_32595.d	Acquisition Date	21/03/2023 14:10:36
Sample Description			



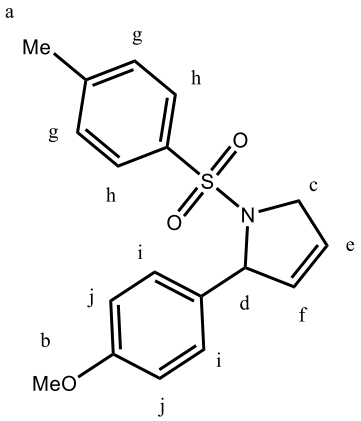
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
366.078386	1	C18H15F3NO2S	366.078108	-0.3	-0.8	10.5	ok	even	31.4

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

Spectrum 42: HRMS spectrum of 2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(trifluoromethyl)phenyl]-3-pyrroline 4a

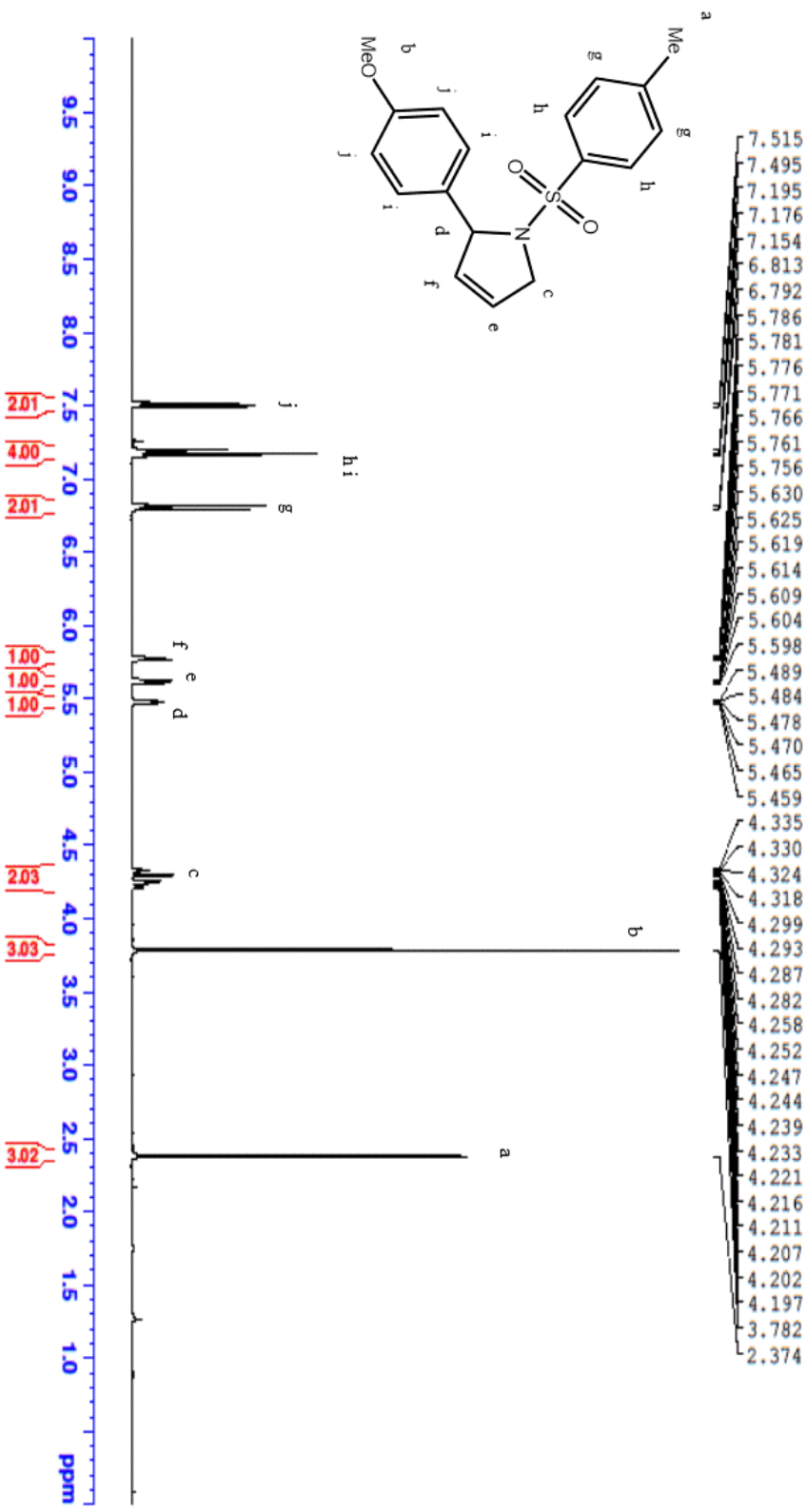
7.1.18. 2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(methoxy)phenyl]-3-pyrroline **4b**



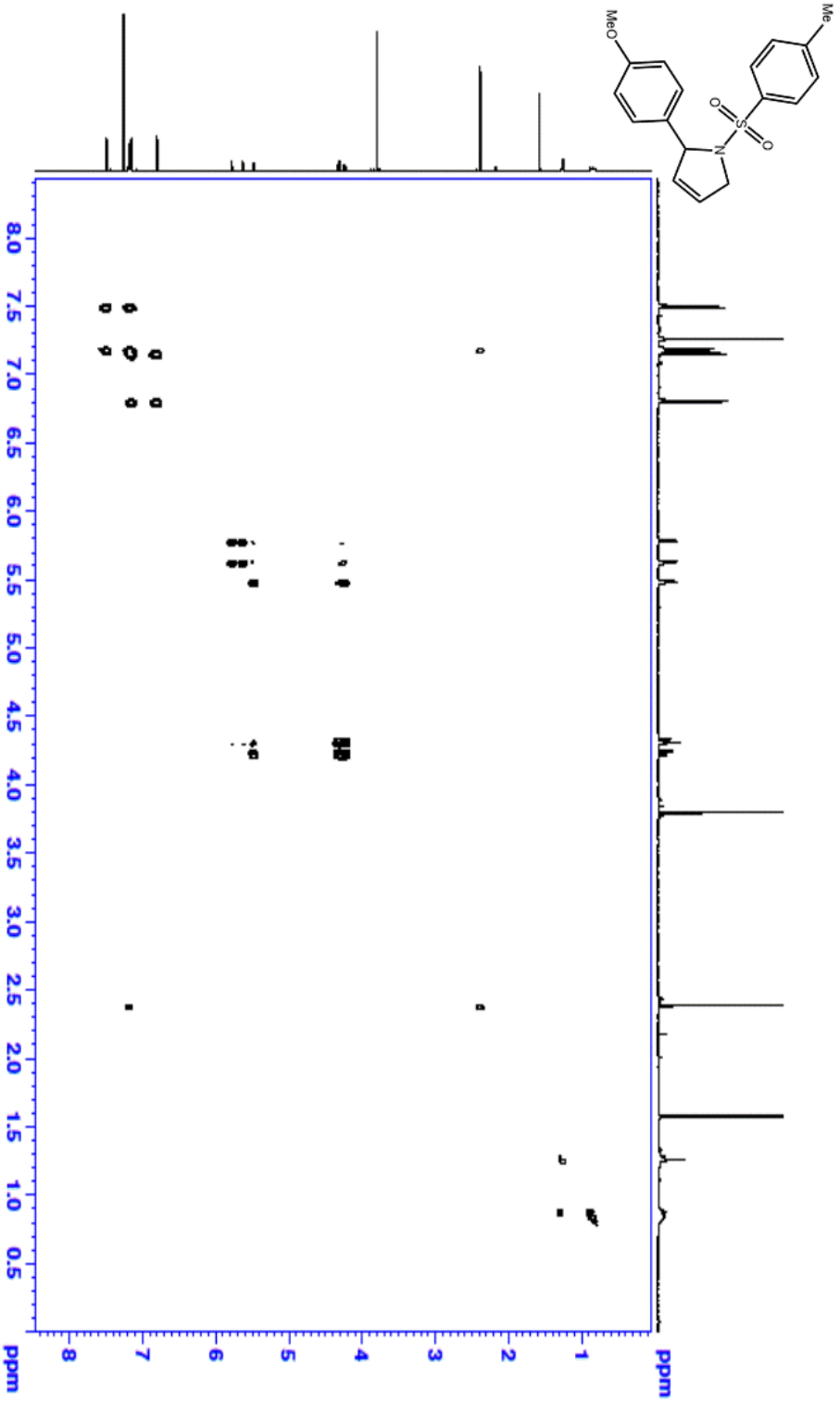
^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H, Ha), 3.78 (s, 3H, Hb), 4.34-4.18 (m, 2H, Hc), 5.50-5.45 (m, 1H, Hd), 5.61 (ddd, J= 6.4, 3.1, 2.1 Hz, 1H, He), 5.77 (ddd, J= 6.1, 2.9, 2 Hz, 1H, Hf), 6.80 (d, J= 8.7 Hz, 2H, Hg), 7.18 (m, 4H, Hh), 7.51 (d, J= 8.3 Hz, 2H, Hi) (**Spectrum 43**)

^{13}C NMR ($CDCl_3$) δ 159.44, 143.14, 135.89, 132.69, 130.83, 129.53, 128.74, 127.37, 124.48, 113.94, 69.82, 55.45, 55.34, 21.61(**Spectrum 45**)

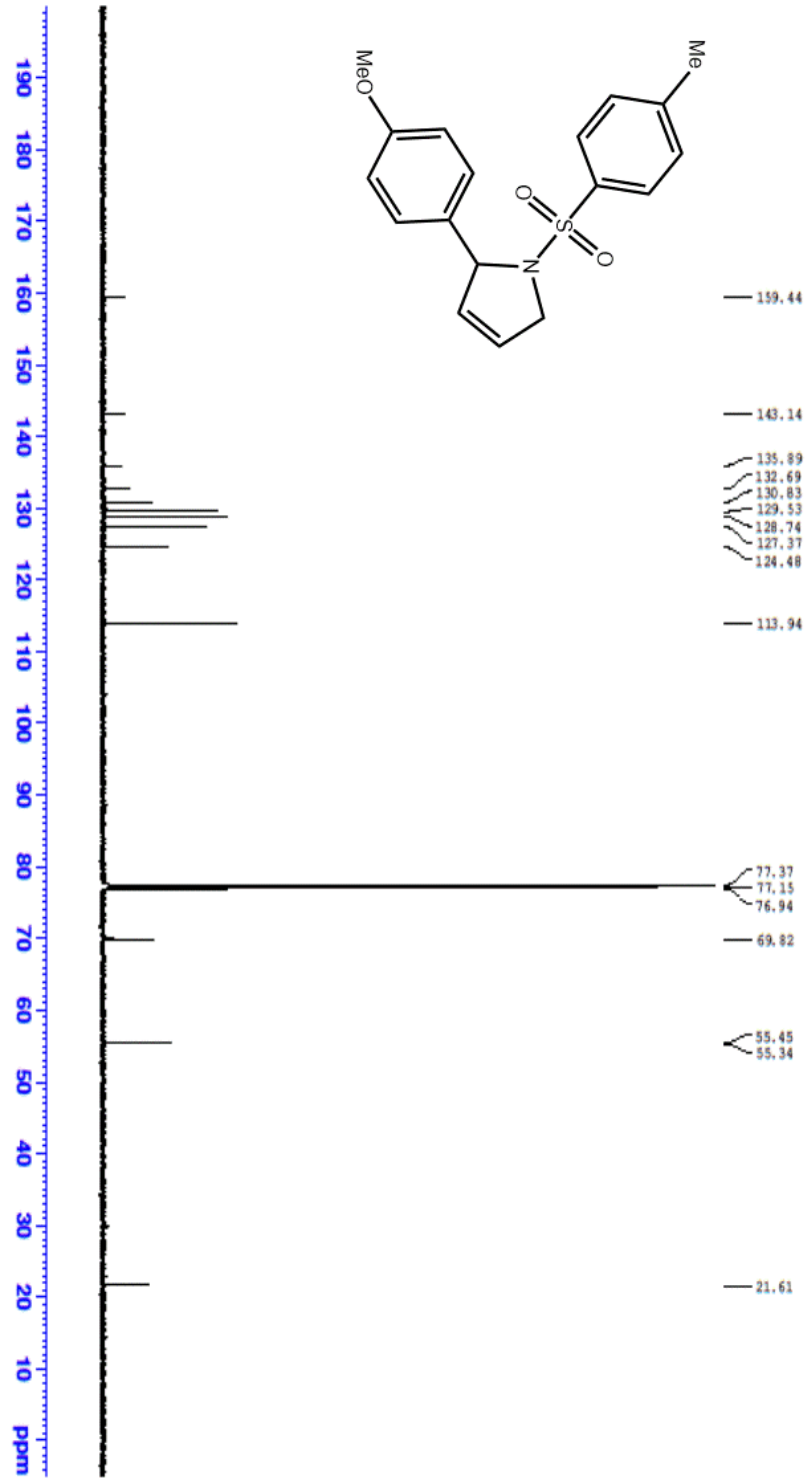
HRMS: $[M+H]^+$ 330.1158 m/z (**Spectrum 48**)



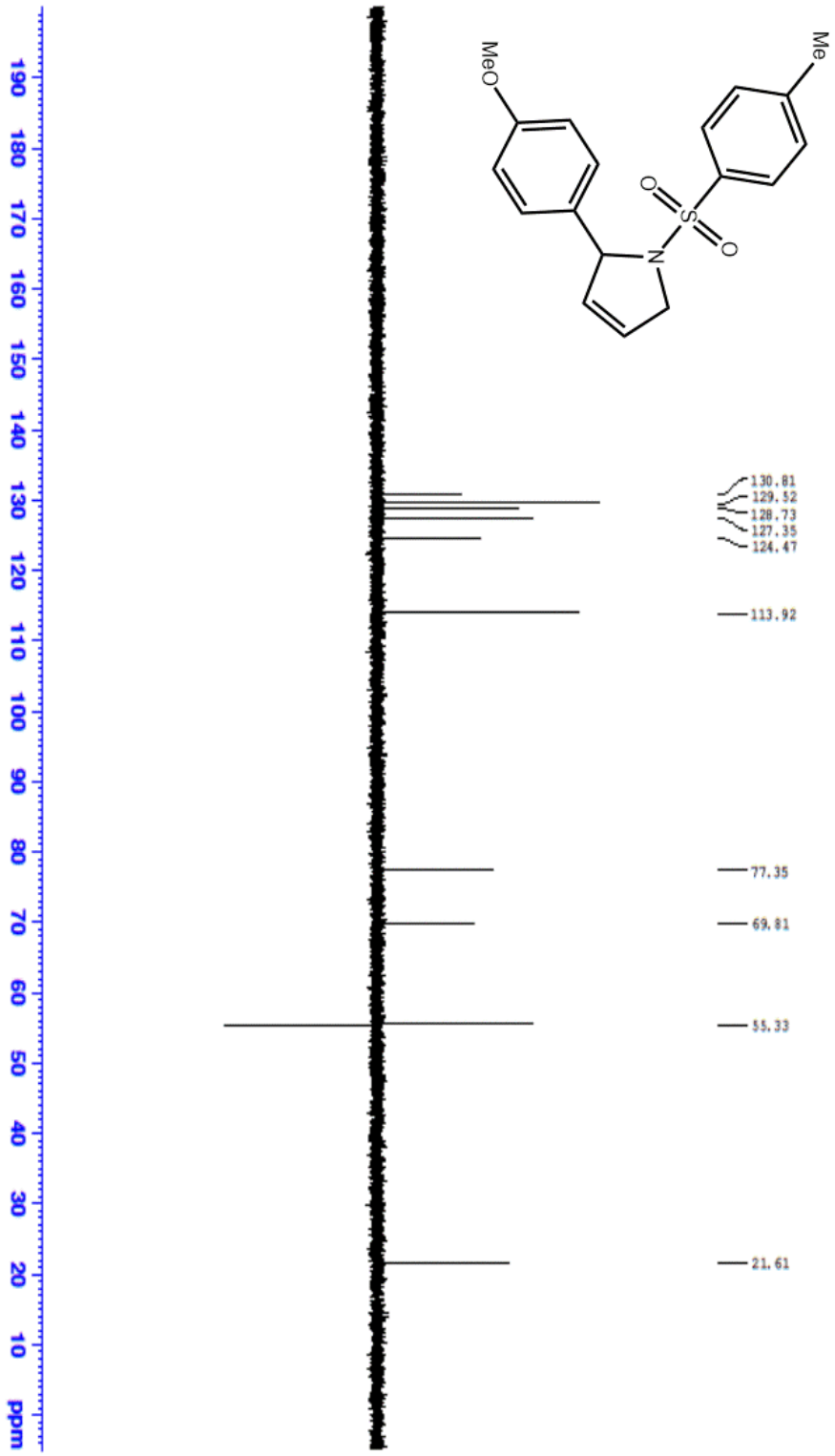
Spectrum 43: ^{1}H NMR spectrum of 2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(methoxy)phenyl]-3-pyrroline 4b



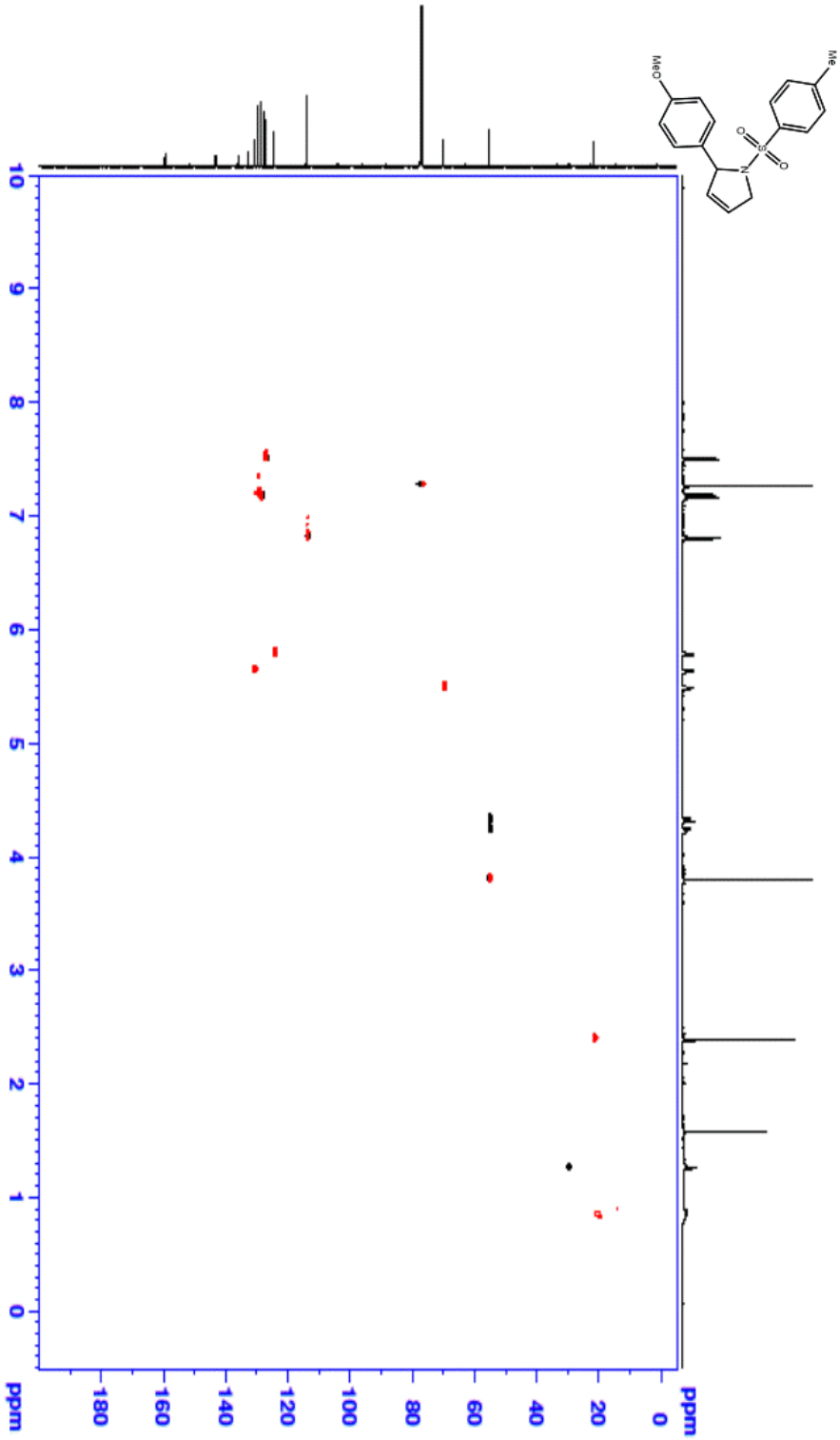
Spectrum 44: COSY NMR spectrum of 2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(methoxy)phenyl]-3-pyrroline 4b



Spectrum 45: ^{13}C NMR spectrum of 2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(methoxy)phenyl]-3-pyrroline 4b



Spectrum 46: DEPT NMR of spectrum of 2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(methoxy)phenyl]-3-pyrroline 4b



Spectrum 47: HSQC NMR spectrum of 2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(methoxy)phenyl]-3-pyrroline 4b

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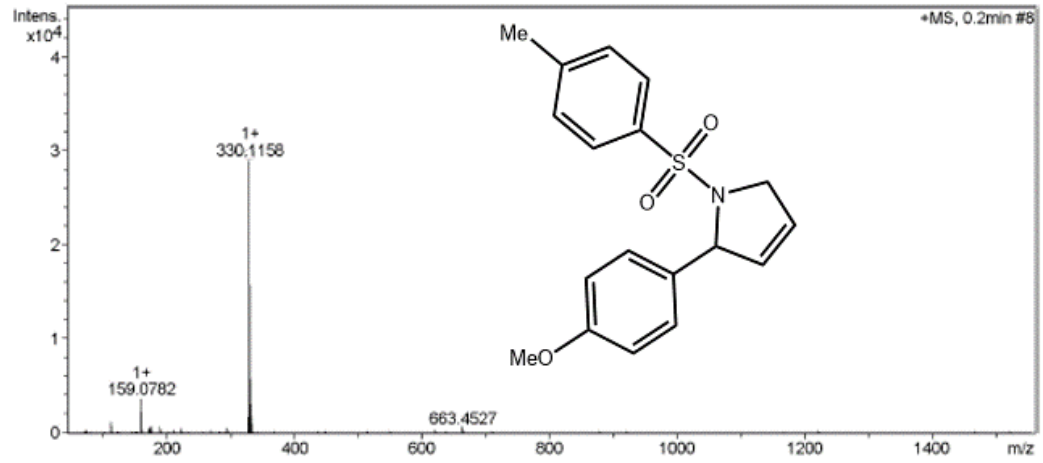
Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SOR_28C_RB3_01_32508.d	Acquisition Date	20/03/2023 13:35:17
Sample Description			



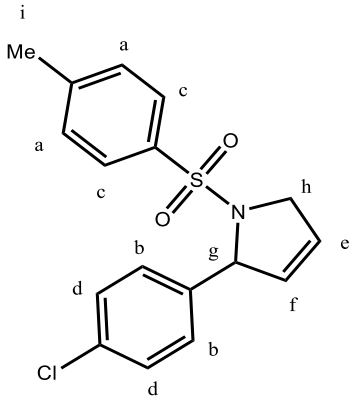
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
330.115818	1	C18H20NO3S	330.115841	-0.0	-0.1	9.5	ok	even	5.7

SmartFormula Settings

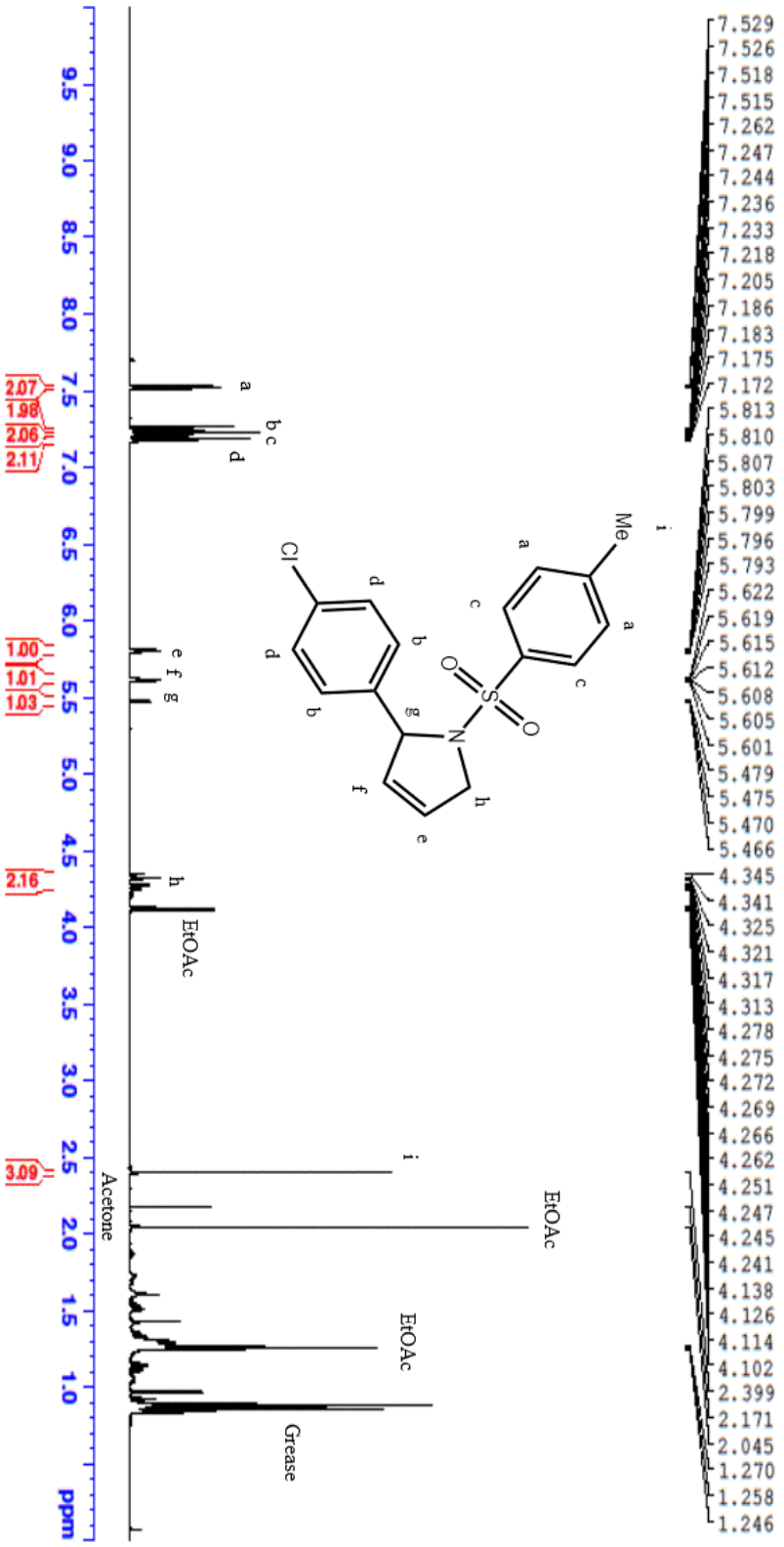
Low value of mSigma indicates good isotopic pattern match

Spectrum 48: HRMS spectrum of 2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(methoxy)phenyl]-3-pyrroline 4b

7.1.19. 2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(chloro)phenyl]-3-pyrroline **4c**

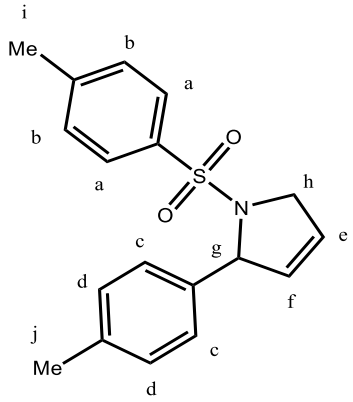


^{1}H NMR ($CDCl_3$) δ 7.52 (d, 8.4 Hz, 2H, Ha), 7.24 (d, 8.6 Hz, 2H, Hb), 7.21 (d, 8.4 Hz, 2H, Hc), 7.18 (d, 8.6 Hz, 2H, Hd), 5.80 (ddd, J= 6.2, 3, 1.9 Hz, 1H, He), 5.61 (ddd, 6.4, 3.3, 2.2 Hz, 1H, Hf), 5.49-5.46 (m, 1H, Hg), 4.35-4.24 (m, 2H, Hh), 2.40 (s, 3H, Hi). **EtOAc**: ^{1}H NMR ($CDCl_3$) δ 4.12 (q, J= 7.1 Hz, 2H), 2.05 (s, 3H), 1.26 (t, J= 7.1 Hz, 3H). **Acetone**: ^{1}H NMR ($CDCl_3$) δ 2.17 (s). (**Spectrum 49**)

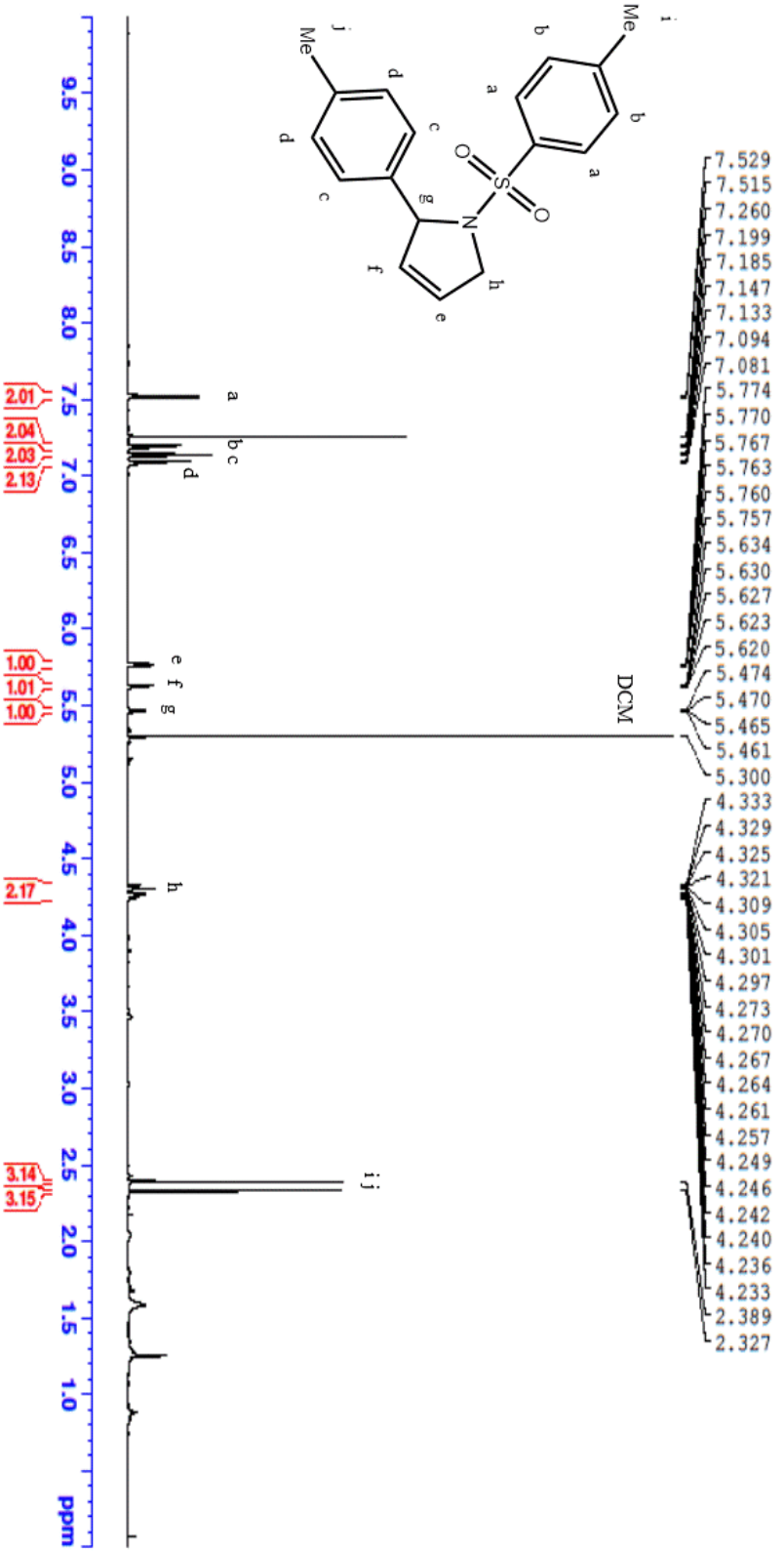


Spectrum 49: ^{1}H NMR spectrum of 2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(chloro)phenyl]-3-pyrroline 4c

7.1.20. 2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(methyl)phenyl]-3-pyrroline **4d**

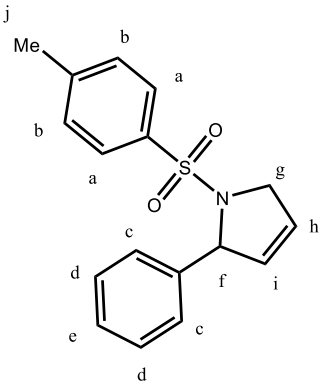


^{1}H NMR ($CDCl_3$) δ 7.52 (d, 8.2 Hz, 2H, Ha), 7.19 (d, 8.2 Hz, 2H, Hb), 7.14 (d, 8 Hz, 2H, Hc), 7.09 (d, 8 Hz, 2H, Hd), 5.77 (ddd, 6, 2.9, 1.9 Hz, 1H, He), 5.63 (ddd, 6.4, 3.4, 2.2 Hz, 1H, Hf), 5.48-5.40 (m, 1H, Hg), 4.34-4.22 (m, 2H, Hh), 2.39 (s, 3H, Hi), 2.33 (s, 3H, Hj) (**Spectrum 50**)

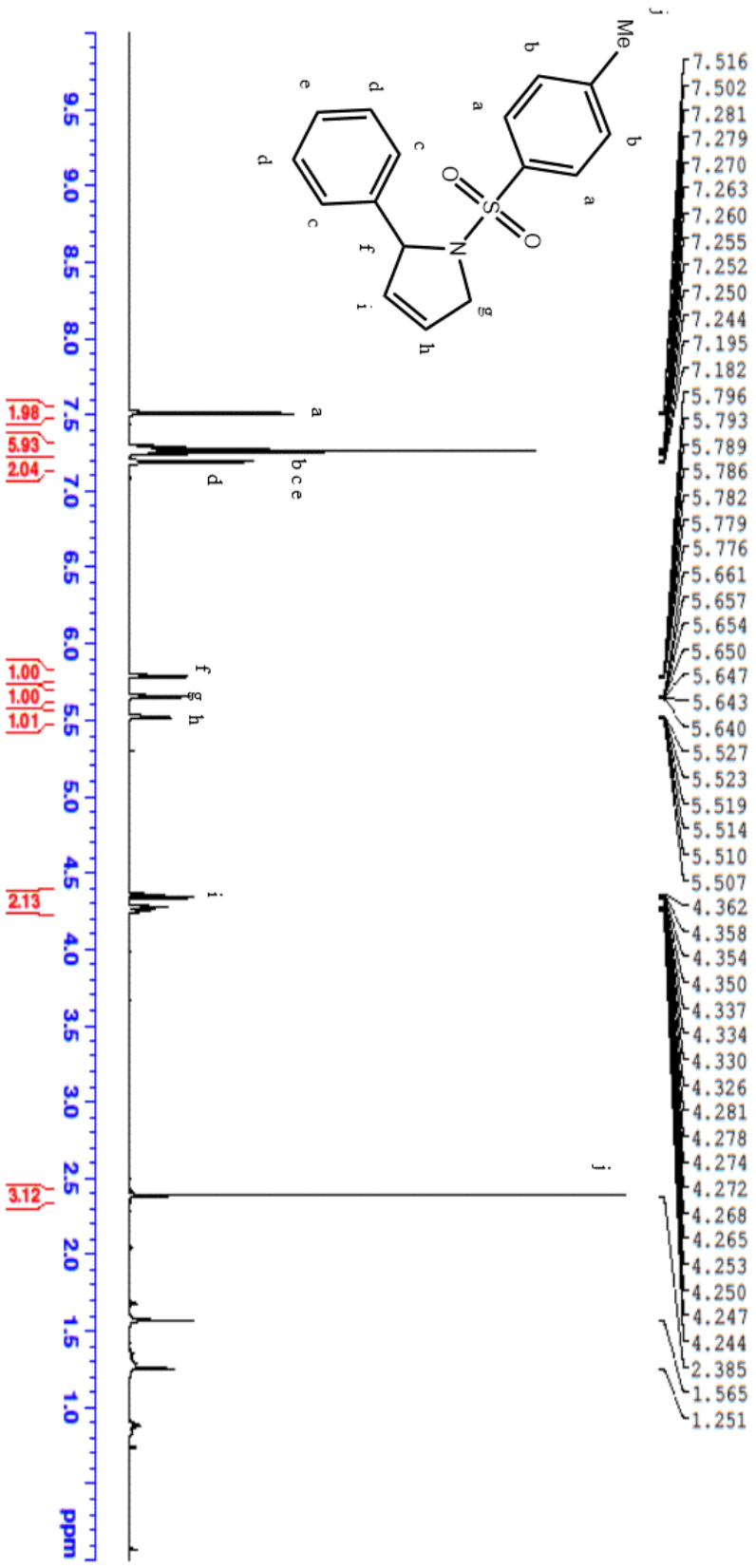


Spectrum 50: ^{1}H NMR spectrum of 2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-(methyl)phenyl]-3-pyrroline 4d

7.1.21. 2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-phenyl]-3-pyrroline **4e**

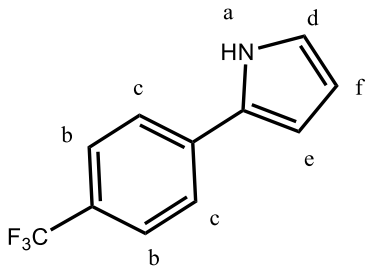


^{1}H NMR ($CDCl_3$) δ 7.51 (d, 8.3 Hz, 2H, Ha), 7.30-7.23 (m, 5H, Hb), 7.19 (d, 7.9 Hz, 2H, Hc), 5.79 (ddd, J= 6, 3, 2.3 Hz, 1H, Hd), 5.65 (ddd, 6.3, 3.3, 2.2 Hz, 1H, He), 5.53-5.50 (m, 1H, Hf), 4.38-4.23 (m, 2H, Hg), 2.38 (s, 3H, Hh). **H_2O**: ^{1}H NMR ($CDCl_3$) δ 1.57 (s) (**Spectrum 51**)



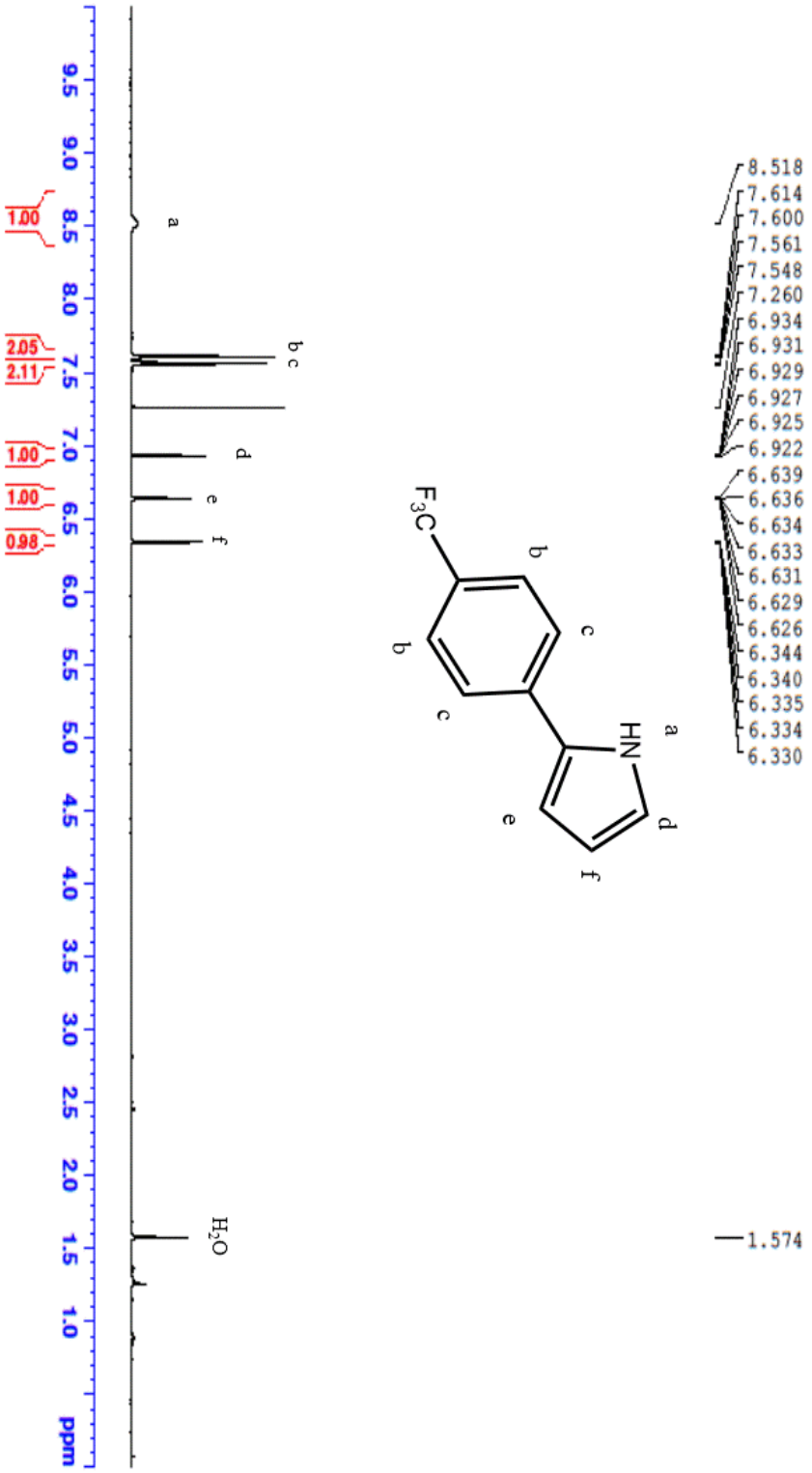
Spectrum 51: ^{1}H NMR spectrum of 2,5-Dihydro-1-[(4-methylphenyl)sulfonyl]-2-[4-phenyl]-3-pyrroline 4e

7.1.22. 2-[4-(Trifluoromethyl)phenyl]-3-pyrrole **5a**

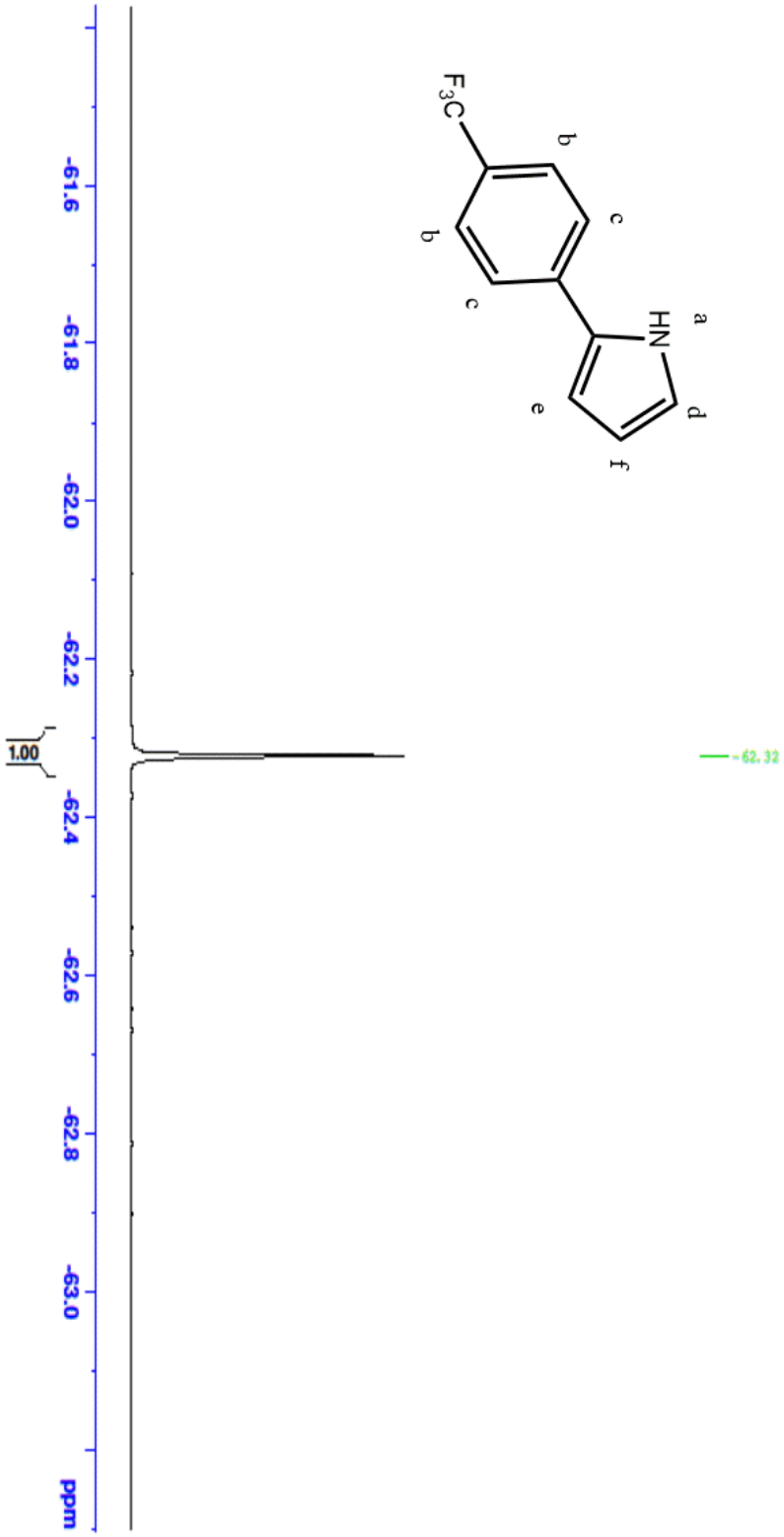


^{1}H NMR ($CDCl_3$) δ 8.52 (s, 1H, Ha), 7.61 (d, J= 8.3 Hz, 2H, Hb), 7.55 (d, J= 8.3 Hz, 2H, Hc), 6.95-6.91 (m, 1H, Hd), 6.65-6.62 (m, 1H, He), 6.65-6.32 (m, 1H, Hf) **H_2O**: ^{1}H NMR ($CDCl_3$) δ 1.57 (s) (**Spectrum 52**)

^{19}F NMR ($CDCl_3$) δ -62.32 (**Spectrum 53**)



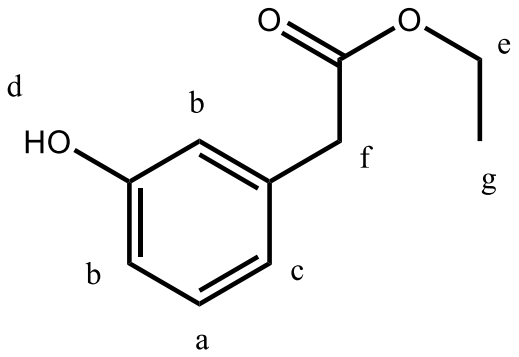
Spectrum 52: ^{1}H NMR spectrum of 2-[4-(Trifluoromethyl)phenyl]-3-pyrrole 5a



Spectrum 53: ^{19}F NMR spectrum of 2-[4-(Trifluoromethyl)phenyl]-3-pyrrole 5a

7.2. Data for compounds from Chapter 3:

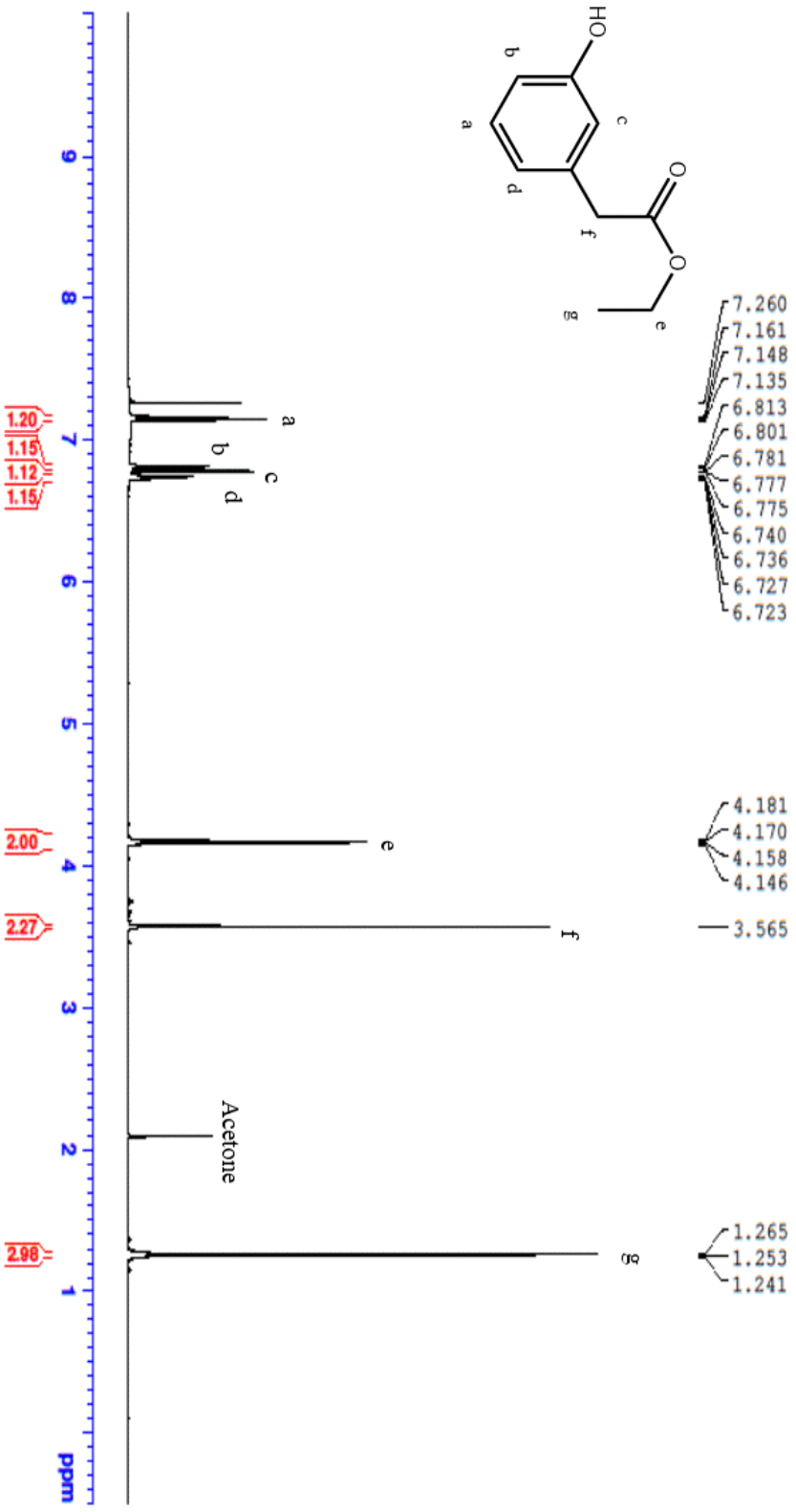
7.2.1. Ethyl 2-(3-hydroxyphenyl)acetate **9**



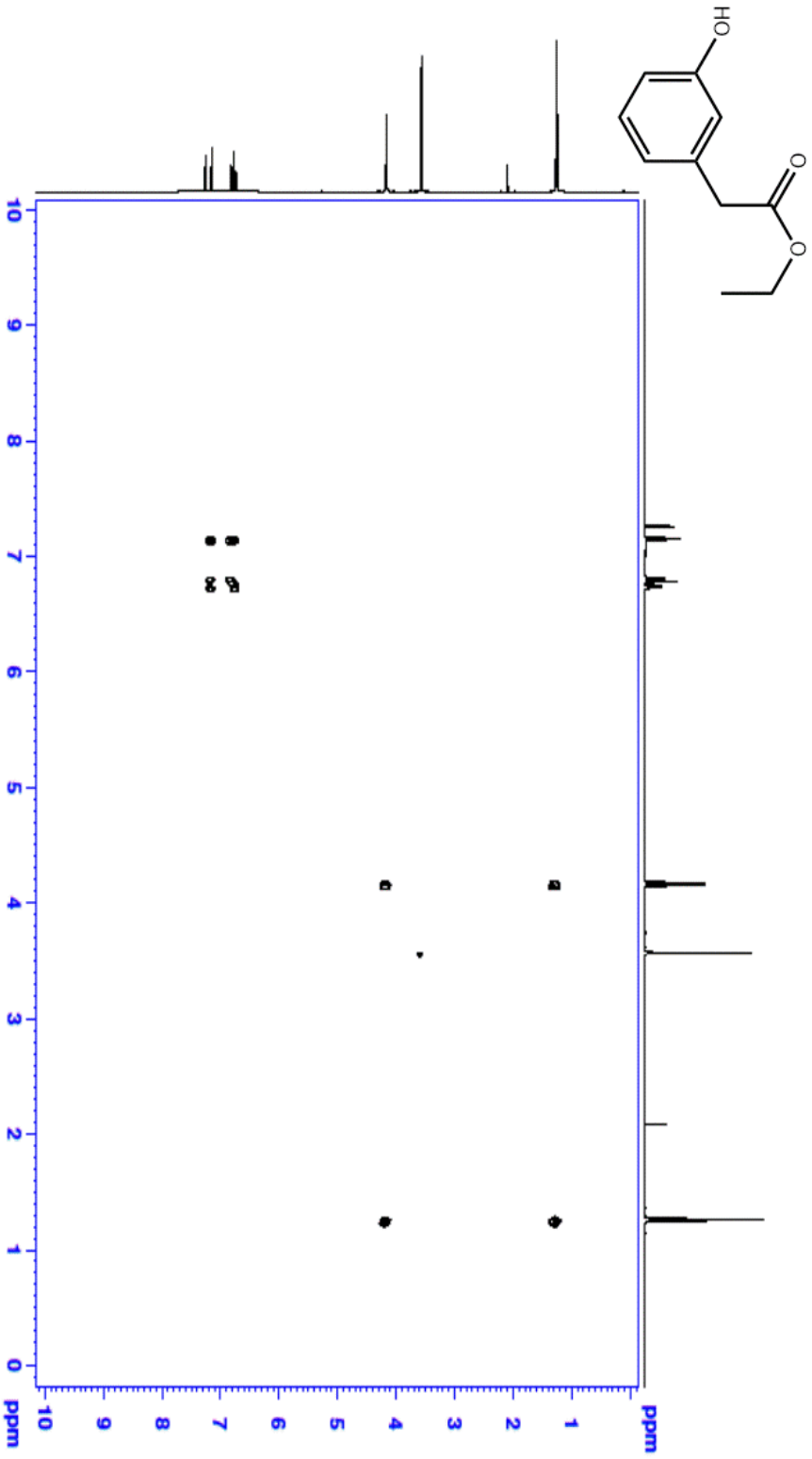
^{1}H NMR ($CDCl_3$) δ 7.15 (t, J= 7.8 Hz, 1H, Ha), 6.82-6.79 (m, 2H, Hb), 6.78-6.76 (d, J= 8.9 Hz, 1H, Hc), 6.75-6.71 (m, 1H, Hd), 4.16 (s, q, J= 7.1 Hz, 2H, He), 3.57 (s, 2H, Hf), 1.25 (t, J= 7.1 Hz, 3H, Hg). **Acetone:** 2.10 (s) (**Spectrum 54**)

^{13}C NMR ($CDCl_3$) δ 172.80, 156.13, 135.31, 129.80, 121.37, 116.37, 114.42, 61.45, 41.36, 14.10 (**Spectrum 56**)

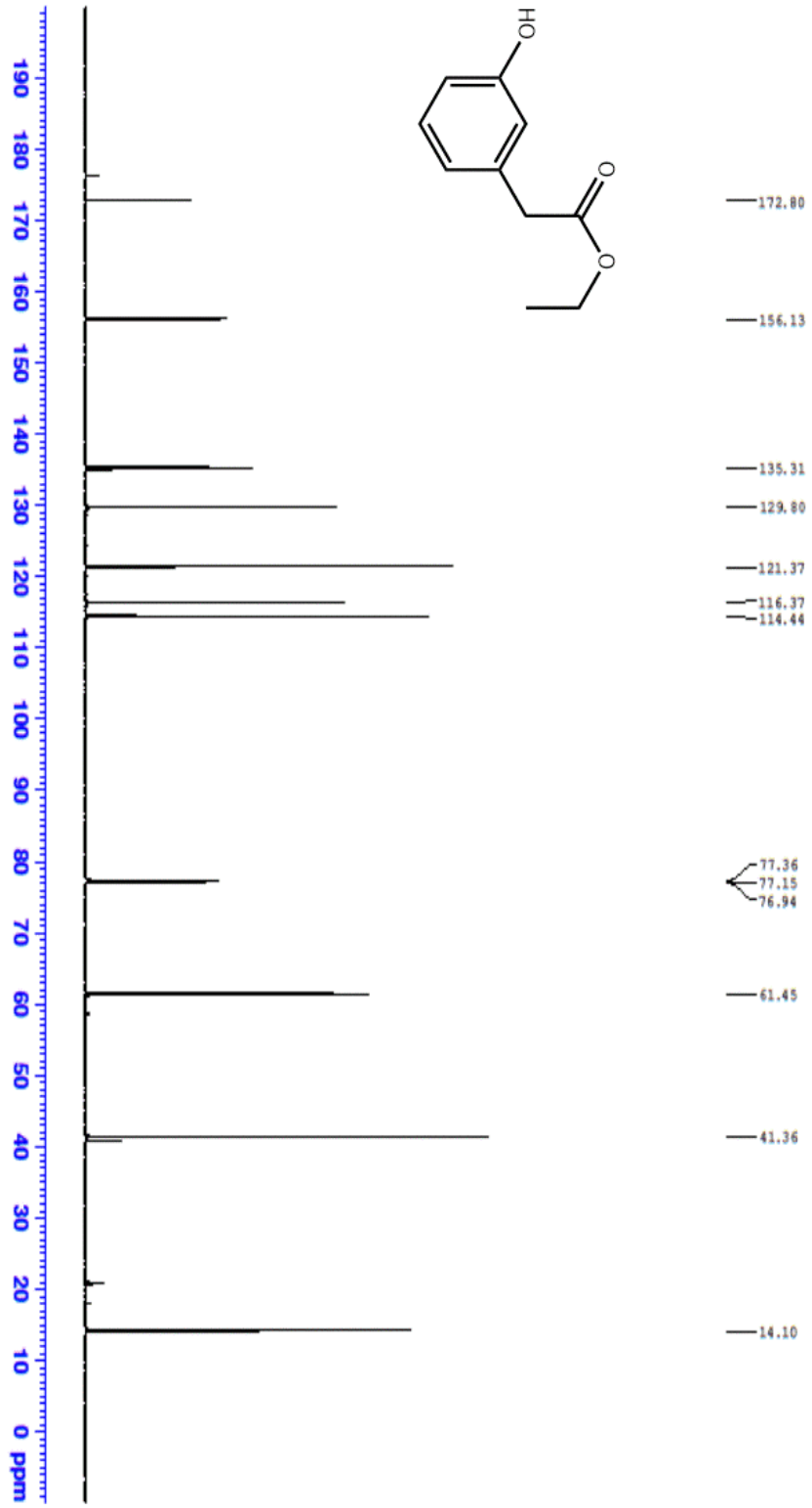
HRMS: $[M-H]^+$ 179.0714 m/z (**Spectrum 59**)



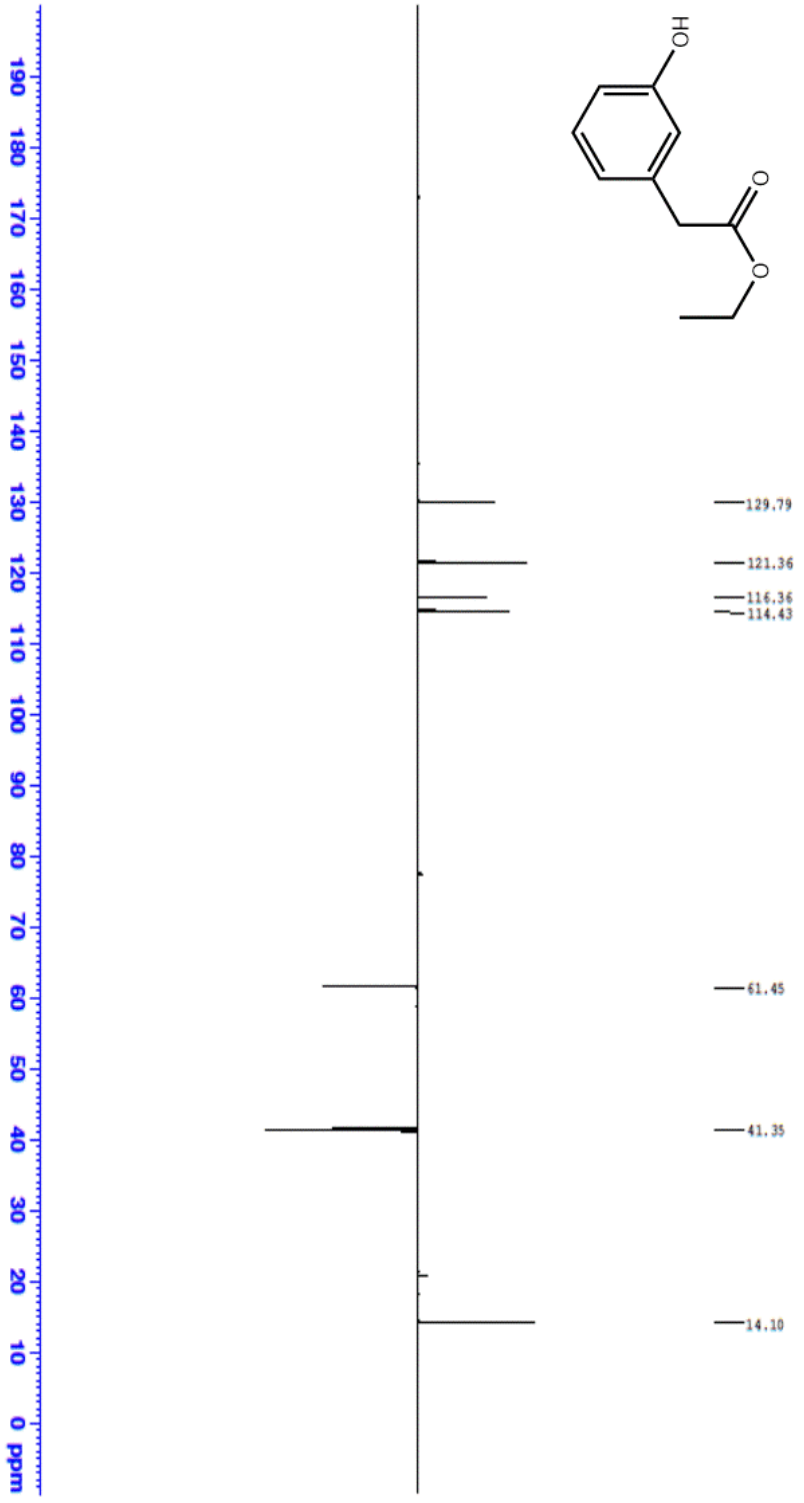
Spectrum 54: ^{1}H NMR spectrum of Ethyl 2-(3-hydroxyphenyl)acetate 9



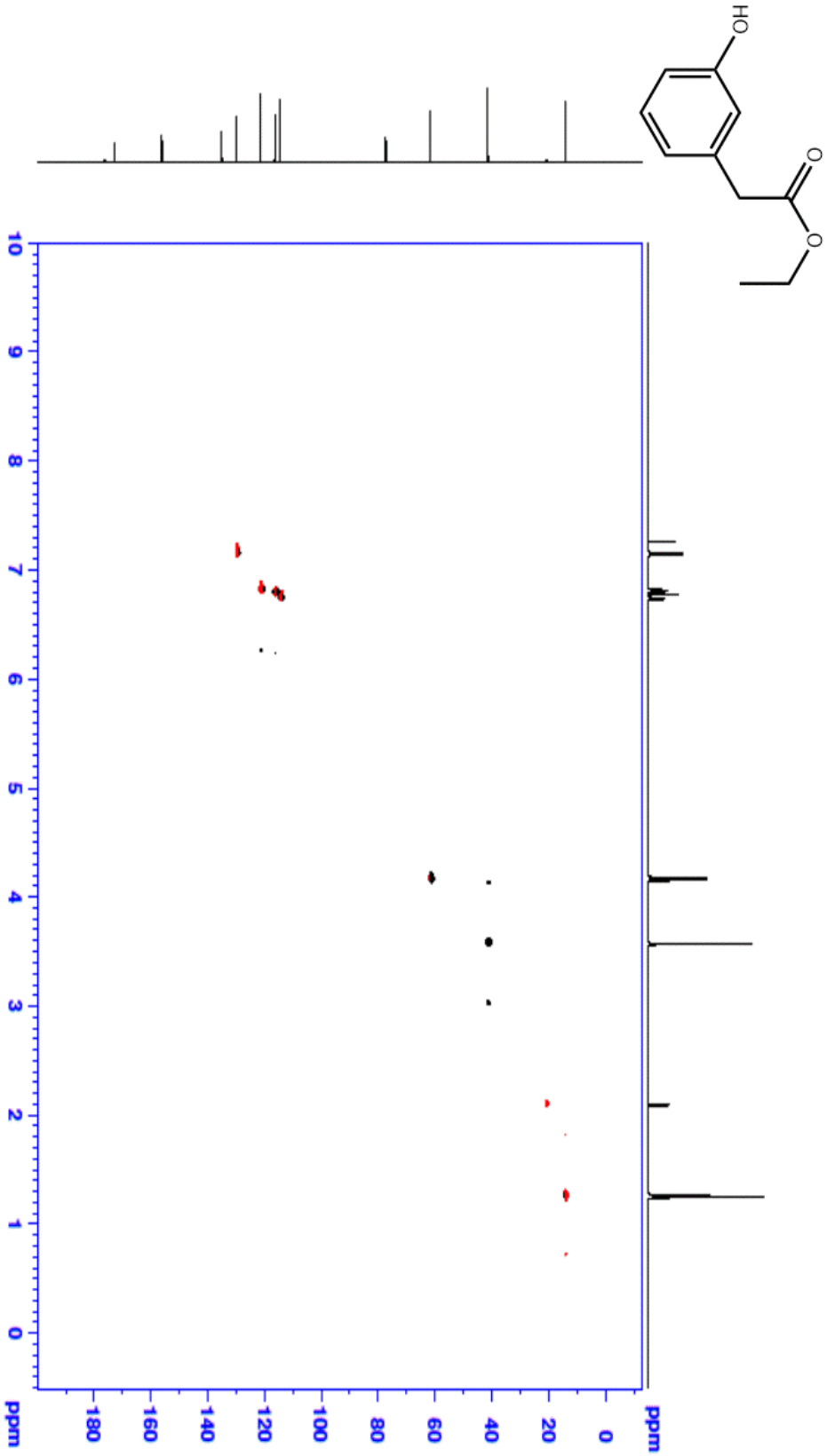
Spectrum 55: COSY NMR spectrum of Ethyl 2-(3-hydroxyphenyl)acetate 9



Spectrum 56: ^{13}C NMR spectrum of Ethyl 2-(3-hydroxyphenyl)acetate 9



Spectrum 57: DEPT NMR spectrum of Ethyl 2-(3-hydroxyphenyl)acetate 9

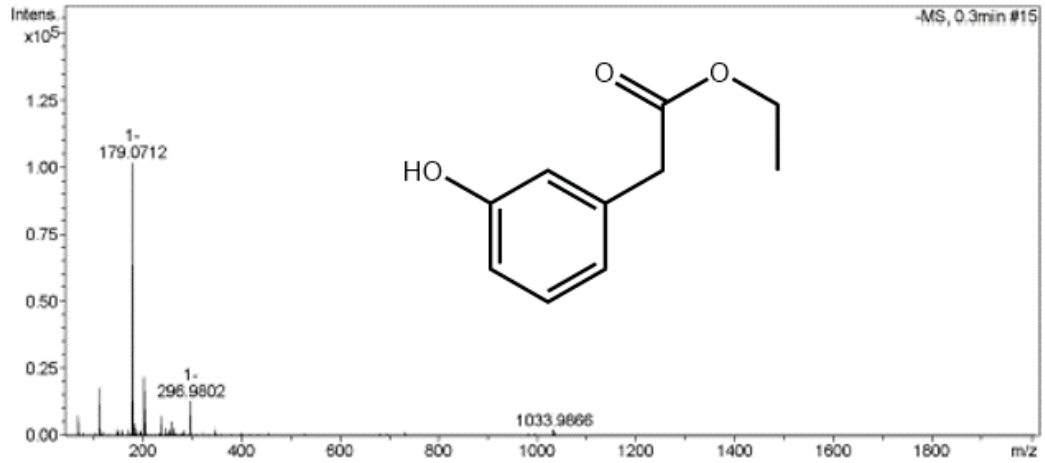


Spectrum 58: HSQC NMR spectrum of Ethyl 2-(3-hydroxyphenyl)acetate 9

Trinity College Dublin

School of Chemistry Mass Spectrometry Unit

Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SOR_28D_RE1_01_32469.d	Acquisition Date	15/03/2023 16:32:57
Sample Description			



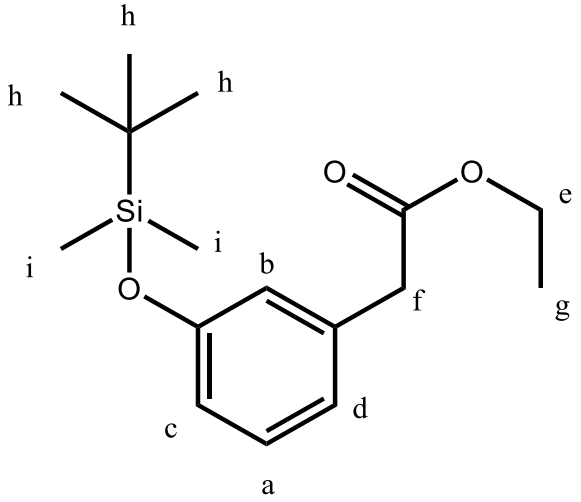
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
179.071217	1	C10H11O3	179.071368	0.2	0.8	5.5	ok	even	5.7

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

Spectrum 59: HRMS spectrum of Ethyl 2-(3-hydroxyphenyl)acetate 9

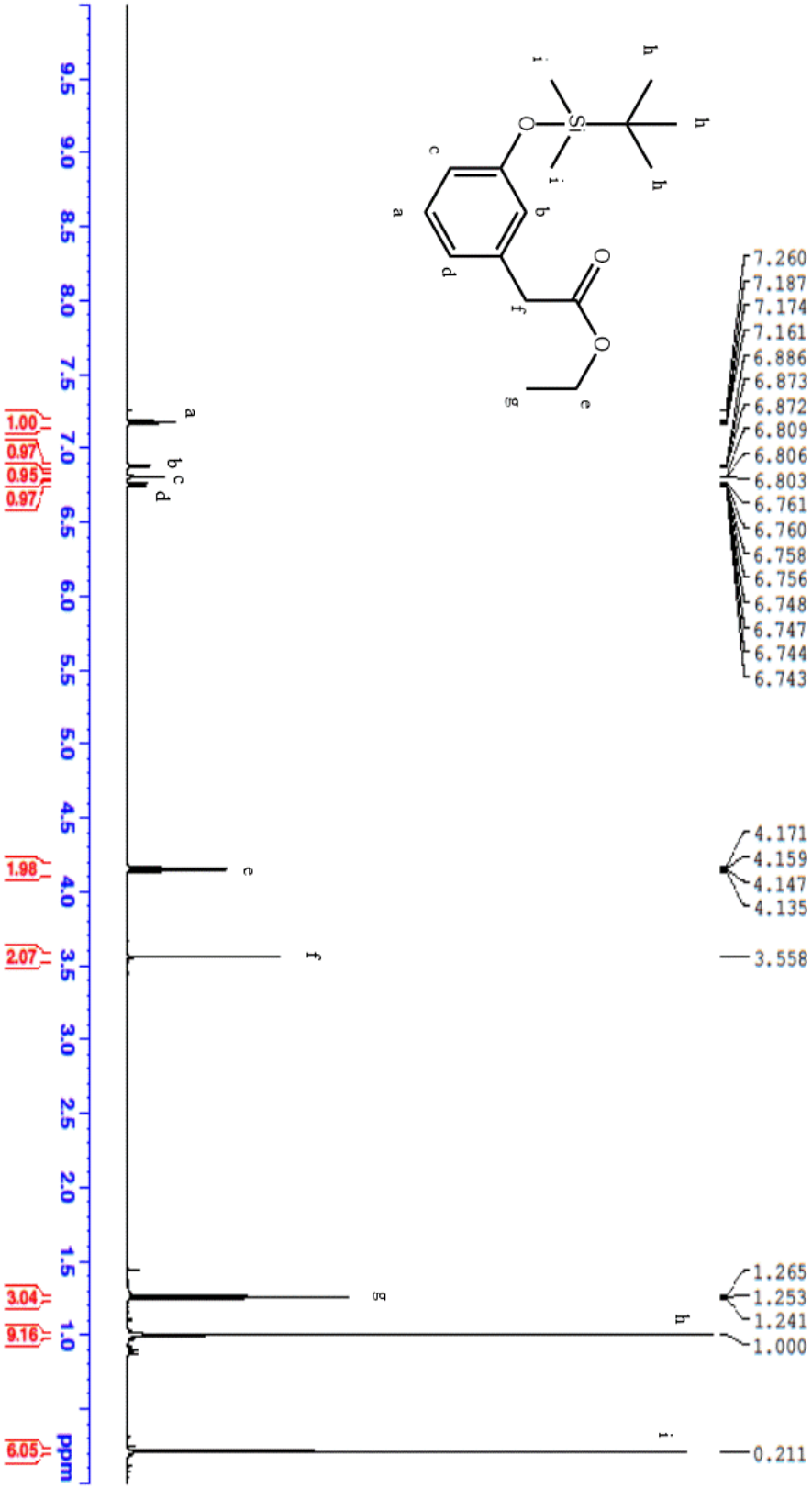
7.2.2. Ethyl 2-(3-tert-butyldimethylsilyloxy)phenyl acetate **10**



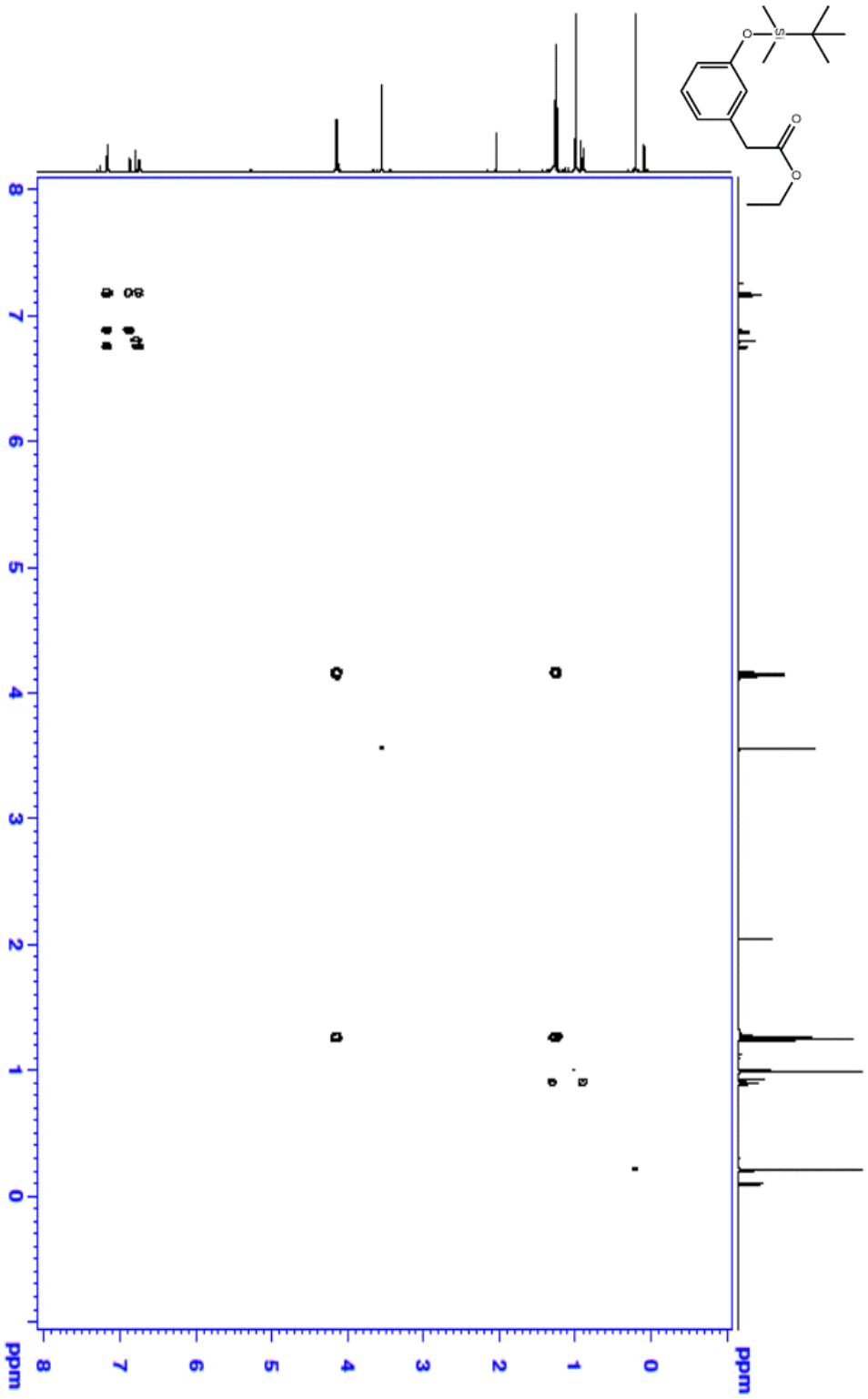
^{1}H NMR ($CDCl_3$) δ 7.17 (t, J= 7.9 Hz, 1H, Ha), 6.88 (d, J= 7.7 Hz, 1H, Hb), 6.82-6.79 (m, 1H, Hc), 6.75 (d, J, 8.1 Hz, 1H, Hd), 4.15 (q, J= 7.1 Hz, 2H, He), 3.56 (s, 2H, Hf), 1.25 (t, J= 7.1 Hz, 3H, Hg), 1.0 (s, 9H, Hh), 0.21 (s, 6H, Hi). (**Spectrum 60)**

^{13}C NMR ($CDCl_3$) δ 171.53, 155.83, 135.61, 129.43, 122.30, 121.16, 118.81, 60.89, 41.46, 25.78, 18.29, 14.27, -4.33 **Hexane:** 31.70, 22.76, 14.21 (**Spectrum 62**)

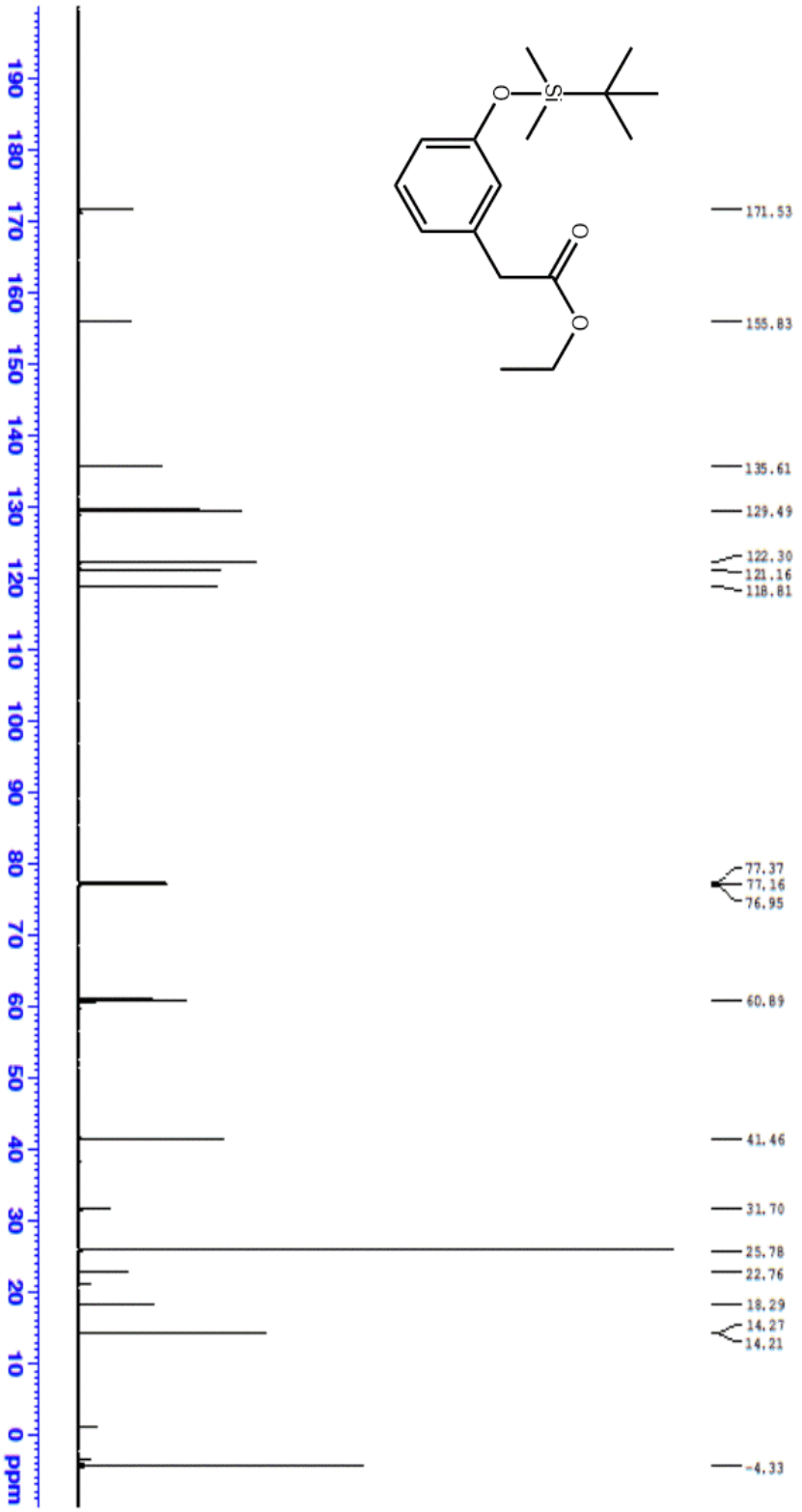
HRMS: $[M-H]^+$ 293.1578 m/z (**Spectrum 65**)



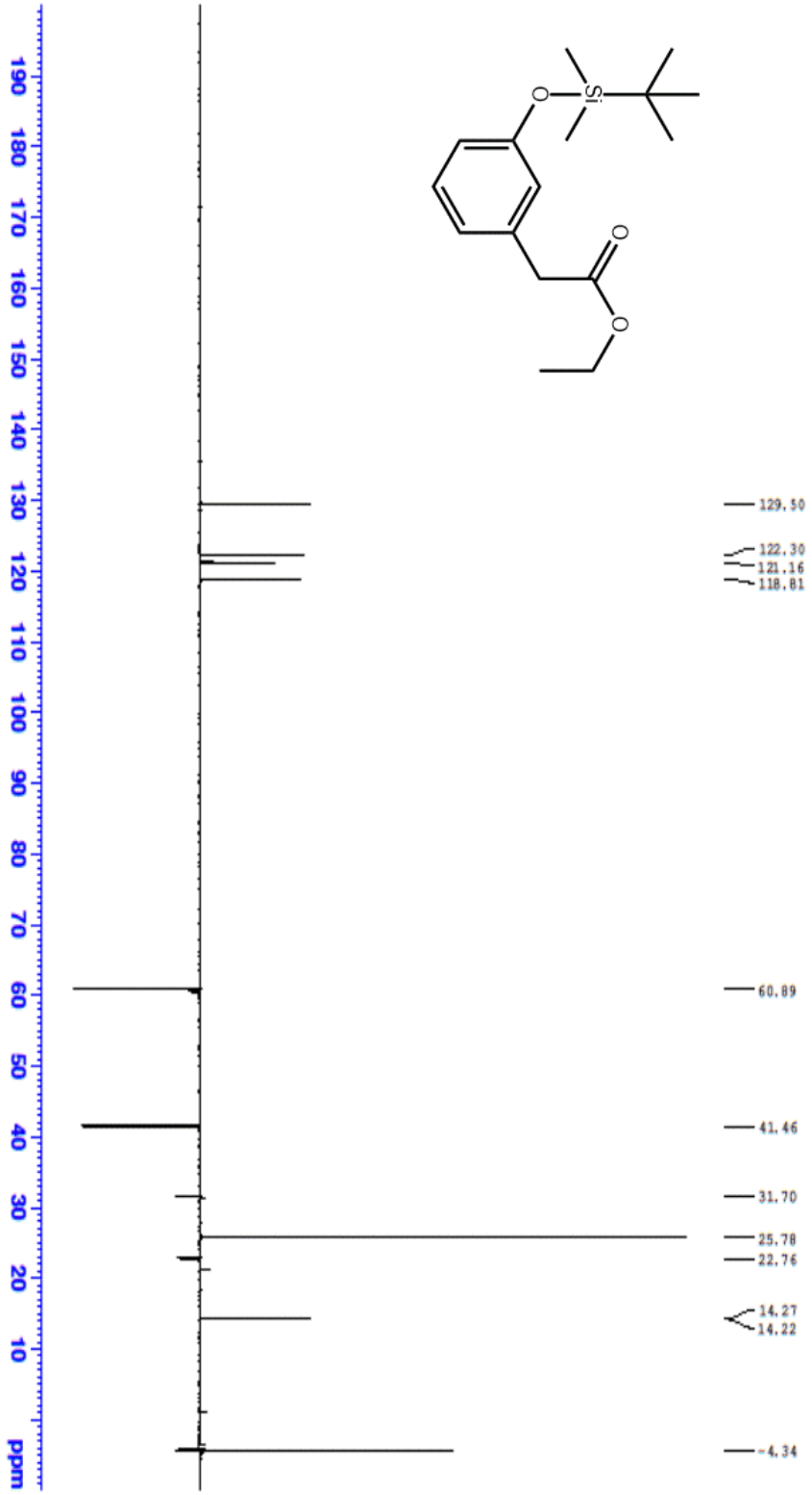
Spectrum 60: ^{1}H NMR spectrum of Ethyl 2-(3-tert-butyldimethylsilyloxy)phenyl acetate 10



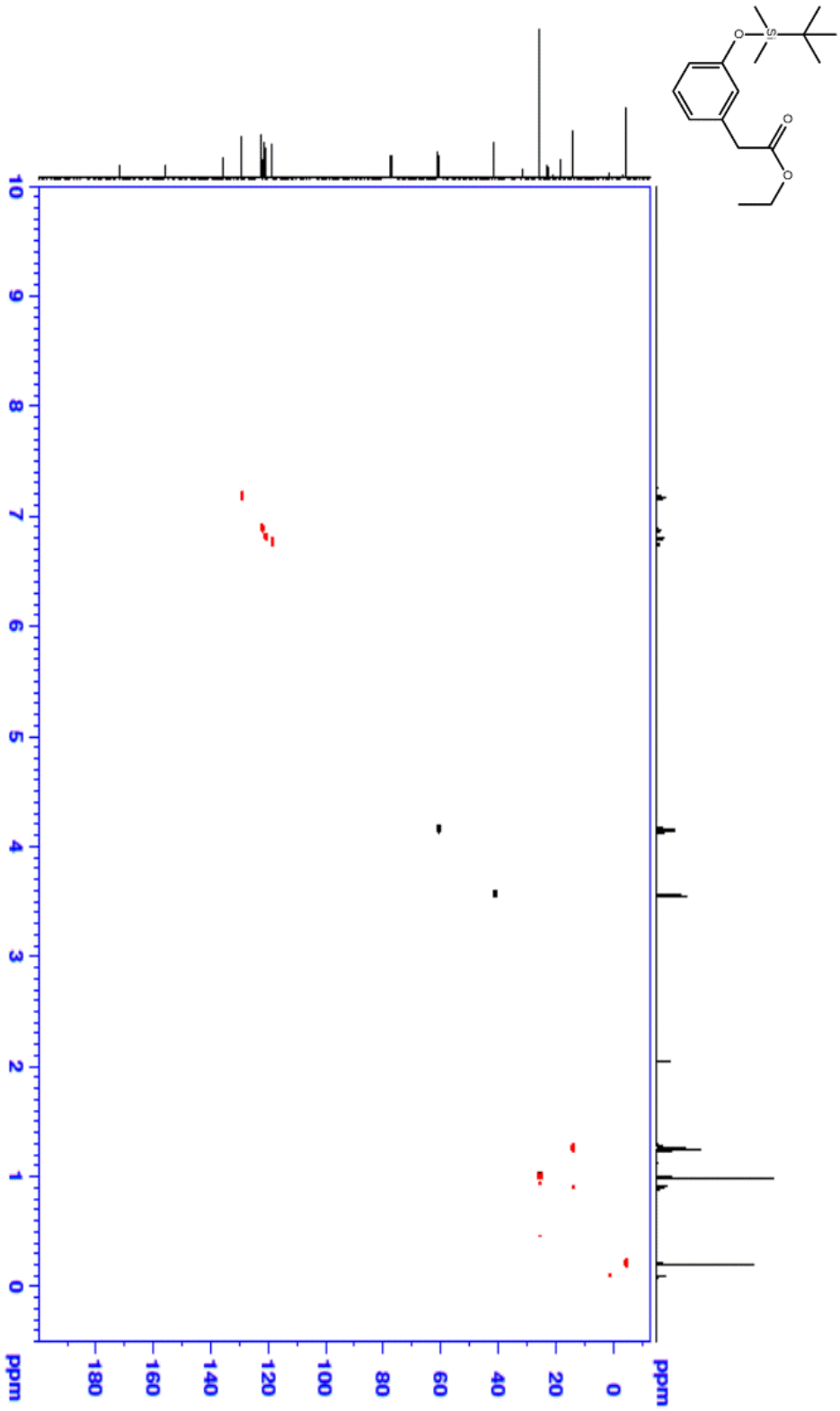
Spectrum 61: COSY NMR spectrum of Ethyl 2-(3-tert-butyldimethylsilyloxy)phenyl acetate 10



Spectrum 62: ^{13}C NMR spectrum of Ethyl 2-(3-tert-butyldimethylsilyloxy)phenyl acetate 10



Spectrum 63: DEPT NMR spectrum of Ethyl 2-(3-tert-butyldimethylsilyloxy)phenyl acetate 10

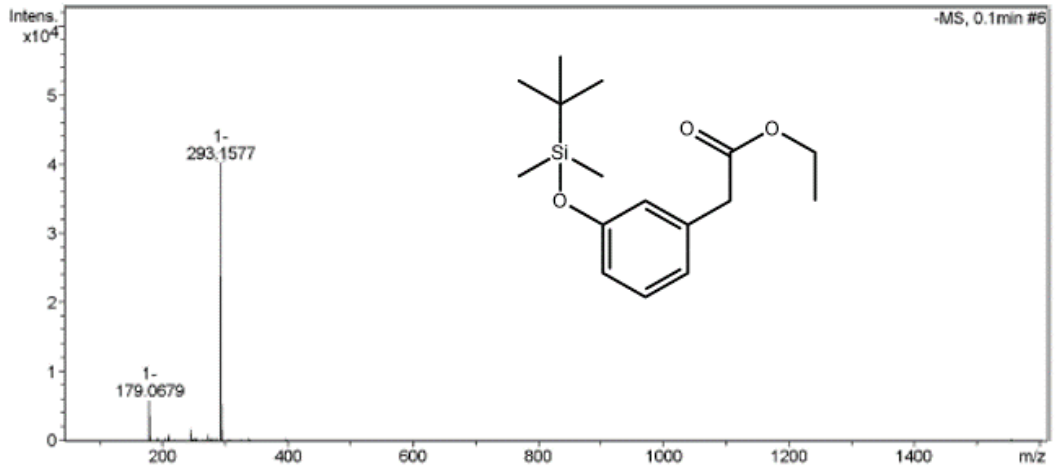


Spectrum 64: HSQC NMR spectrum of Ethyl 2-(3-tert-butyldimethylsilyloxy)phenyl acetate 10

Trinity College Dublin

School of Chemistry Mass Spectrometry Unit

Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SOR_36_RB8_01_32602.d	Acquisition Date	21/03/2023 14:33:14
Sample Description			



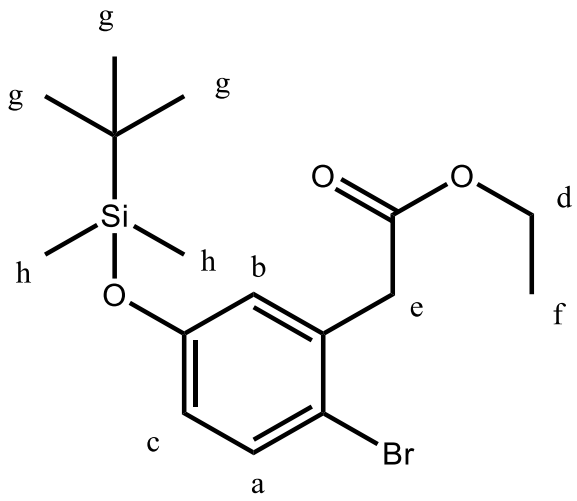
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
293.157721	1	C16H25O3Si	293.157845	-0.1	-0.4	5.5	ok	even	27.8

SmartFormula Settings

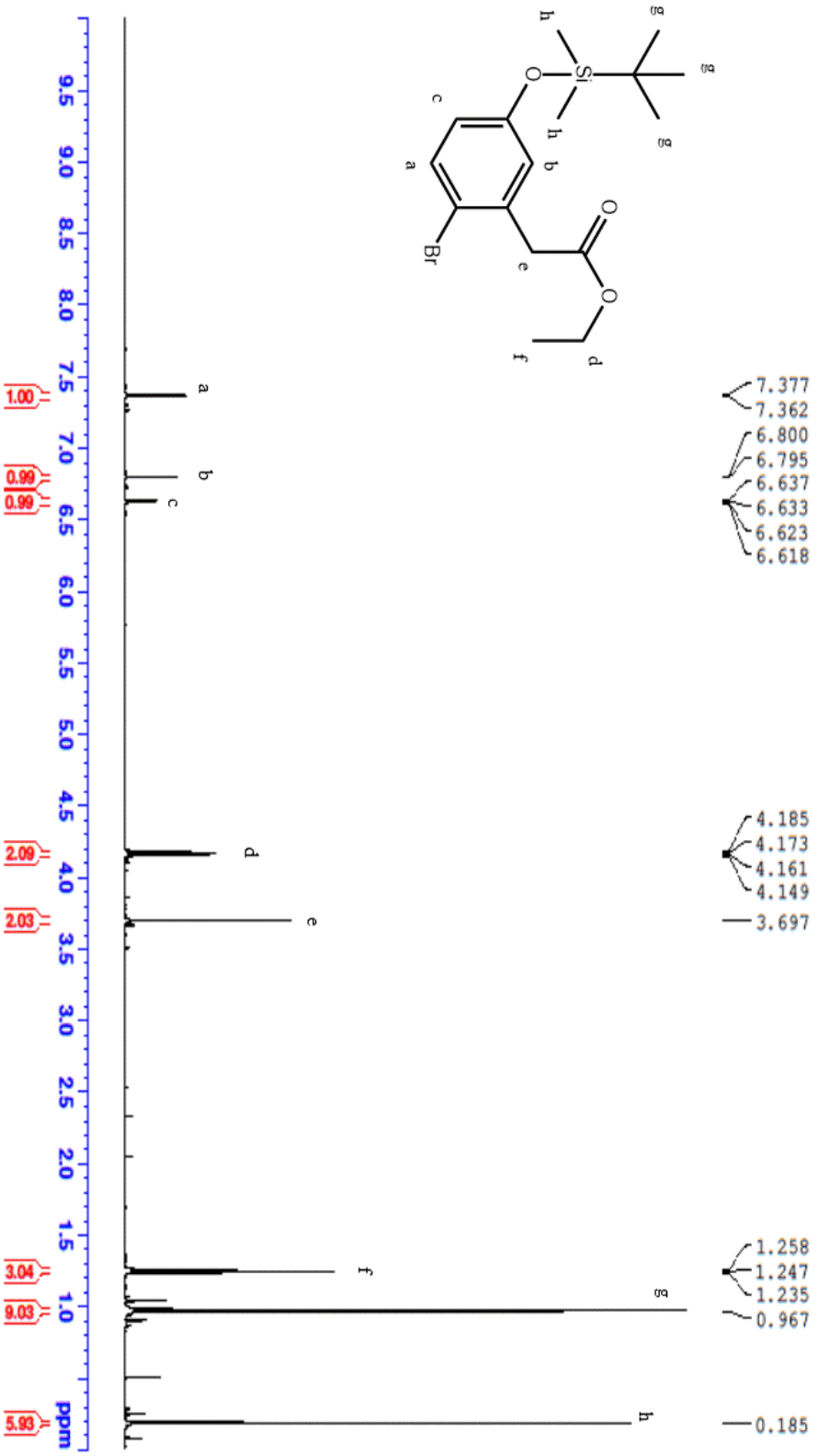
Low value of mSigma indicates good isotopic pattern match

Spectrum 65: HRMS spectrum of Ethyl 2-(3-tert-butyldimethylsilyloxy)phenyl acetate 10

7.2.3. Ethyl 6-Bromo-3-(tert-butyldimethylsilyloxy)phenyl acetate **(11)**

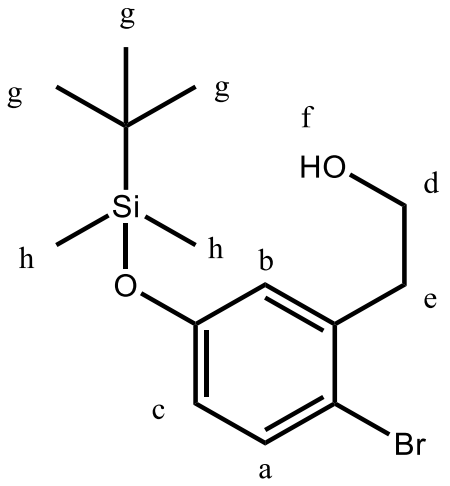


^{1}H NMR ($CDCl_3$) δ 7.37 (d, J= 8.6 Hz, 1H, Ha), 6.80 (d, J= 2.9 Hz, 1H, Hb), 6.63 (dd, 8.6, 2.9 Hz, 1H, Hc), 4.17 (q, J= 7.1 Hz, 2H, Hd), 3.70 (s, 2H, He), 1.25 (t, J= 7.1 Hz, 3H, Hf), 0.97 (s, 9H, Hg), 0.18 (s, 6H, Hh) (**Spectrum 66**)

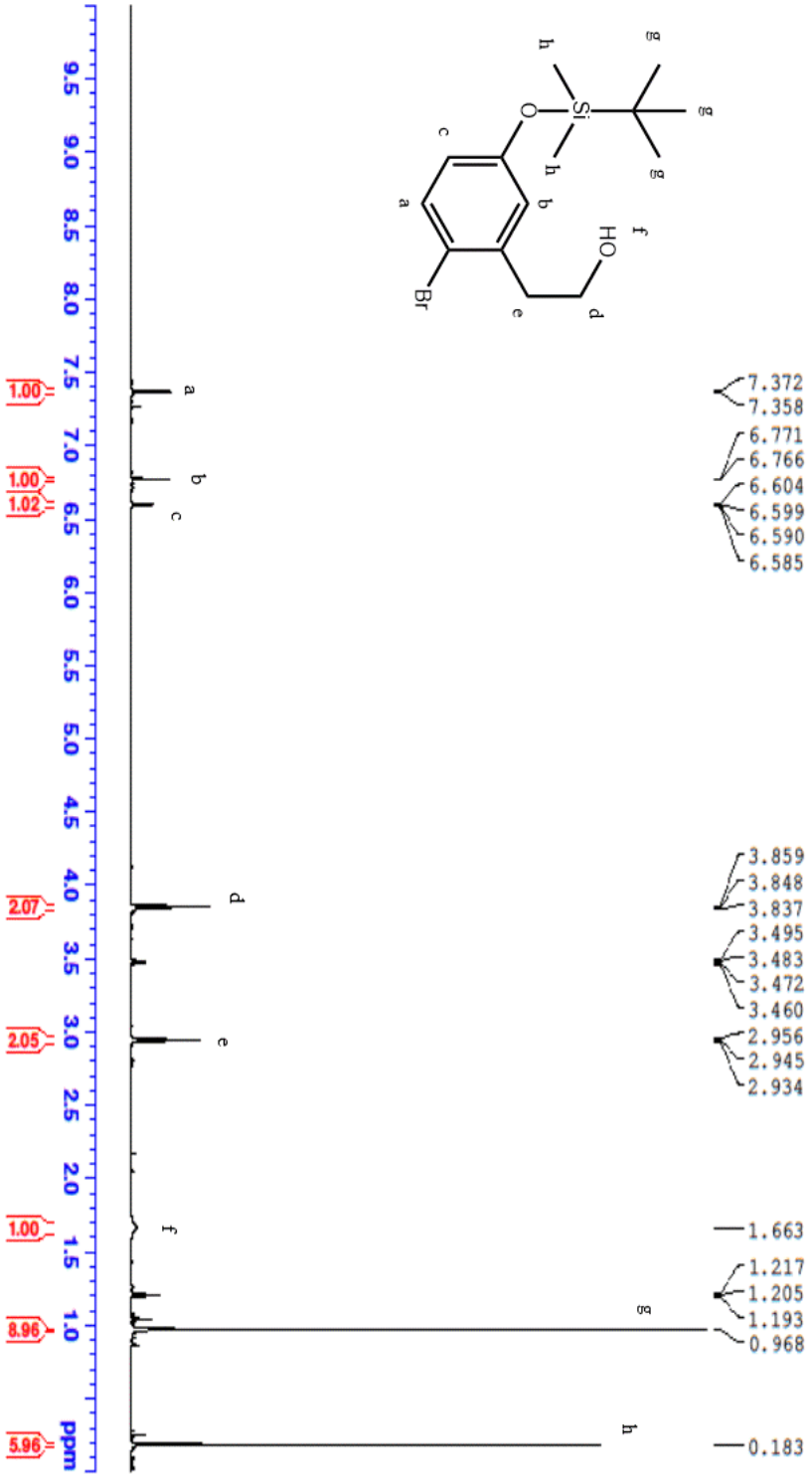


Spectrum 66: ^{1}H NMR spectrum of Ethyl 6-Bromo-3-(*tert*-butyldimethylsilyloxy)phenyl acetate (11)

7.2.4. 4-Bromo-3-(2-hydroxyethyl)phenyl tert-Butyldimethylsilyl Ether **12**

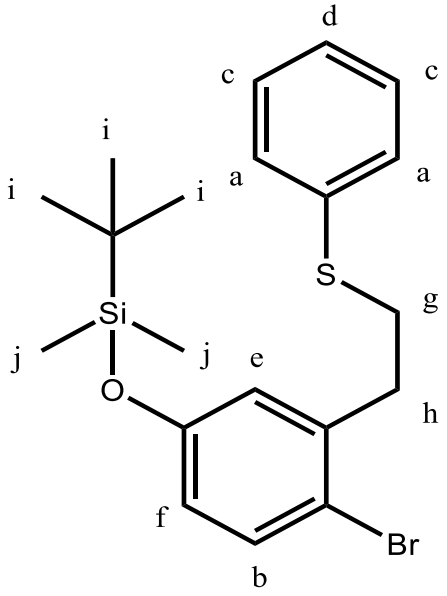


^{1}H NMR ($CDCl_3$) δ 7.37 (d, J= 8.6 Hz, 1H, Ha), 6.77 (d, J= 2.9 Hz, 1H, Hb), 6.59 (dd, J= 8.6, 2.9 Hz, 1H, Hc), 3.85 (t, J= 6.8 Hz, 2H, Hd), 2.95 (t, J= 6.8 Hz, 2H, He), 1.66 (s, 1H, Hf), 0.97 (s, 9H, Hg), 0.18 (s, 6H, Hh). **Et_2O**: 3.48 (q, J- 3.5 Hz, 4H), 1.21 (t, J= 7.1 Hz, 6H) (**Spectrum 67**)

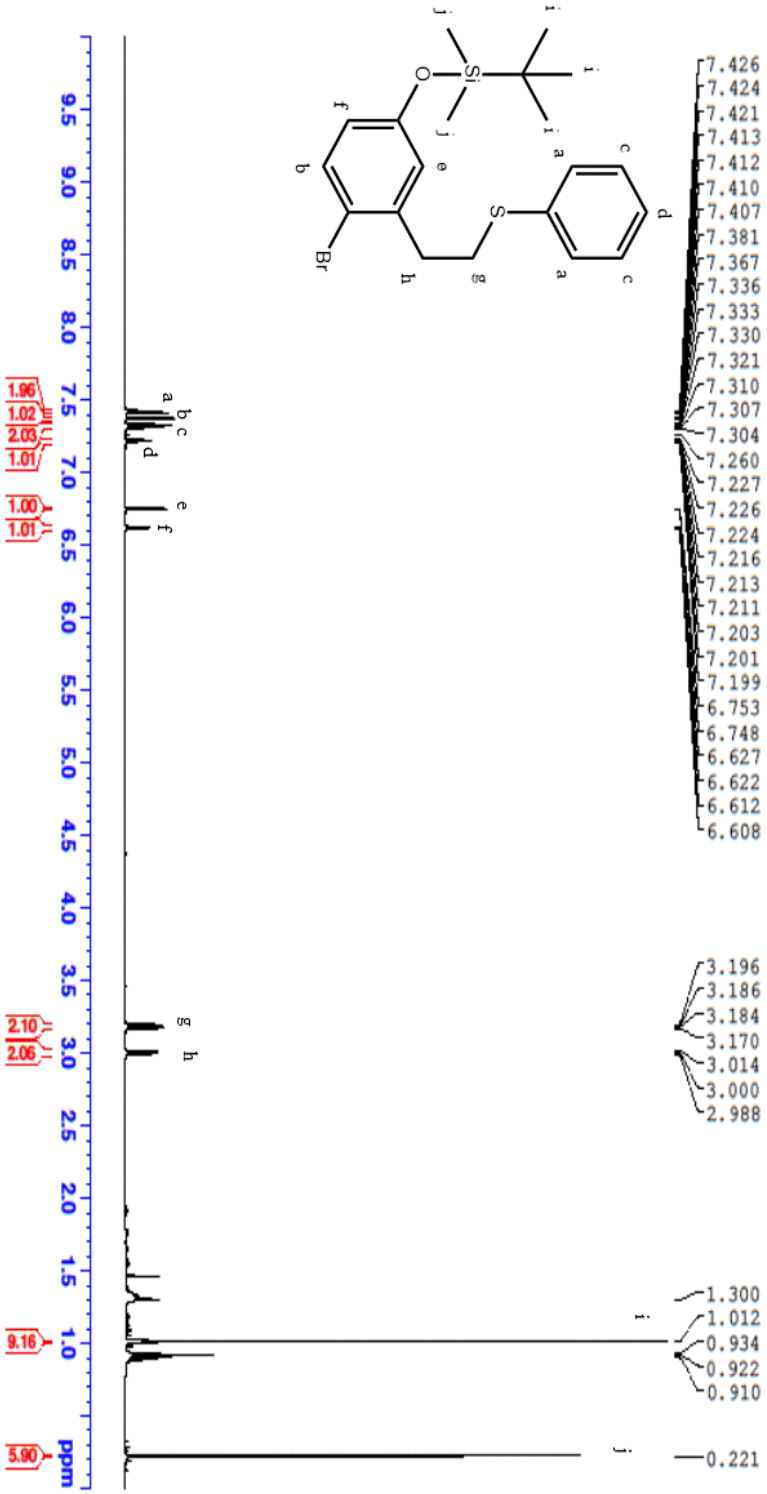


Spectrum 67: ^{1}H NMR spectrum of 4-Bromo-3-(2-hydroxyethyl)phenyl *tert*-Butyldimethylsilyl Ether 12

7.2.5. 4-Bromo-3-[2-(phenylthio)ethyl]phenyl tert-Butyldimethylsilyl Ether **(13)**

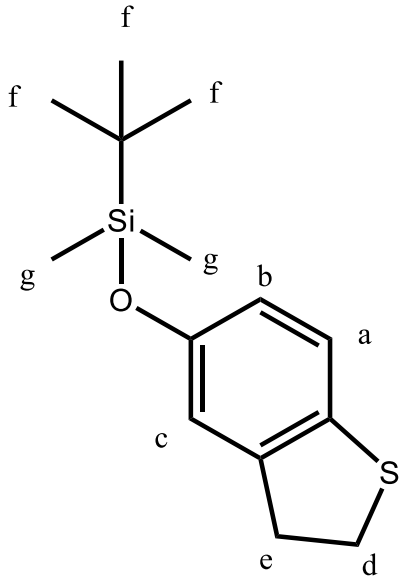


^{1}H NMR ($CDCl_3$) δ 7.42 (d, J= 7.9 Hz, 2H, Ha), 7.34 (d, J= 8.6 Hz, 1H, Hb), 7.32 (t, J= 7.5 Hz, 2H, Hc), 7.21 (t, J= 7.4 Hz, 1H, Hd), 6.75 (d, J= 2.9 Hz, 1H, He), 6.62 (dd, J= 8.6, 2.9 Hz, 1H, Hf), 3.18 (t, J= 7.5 Hz, 2H, Hg), 3.00 (t, J= 7.5 Hz, 2H, Hh), 1.01 (s, 9H, Hi), 0.22 (s, 6H, Hj). **Hex**.: 1.31-1.29 (m), 0.94-0.90 (m) (**Spectrum 68**)

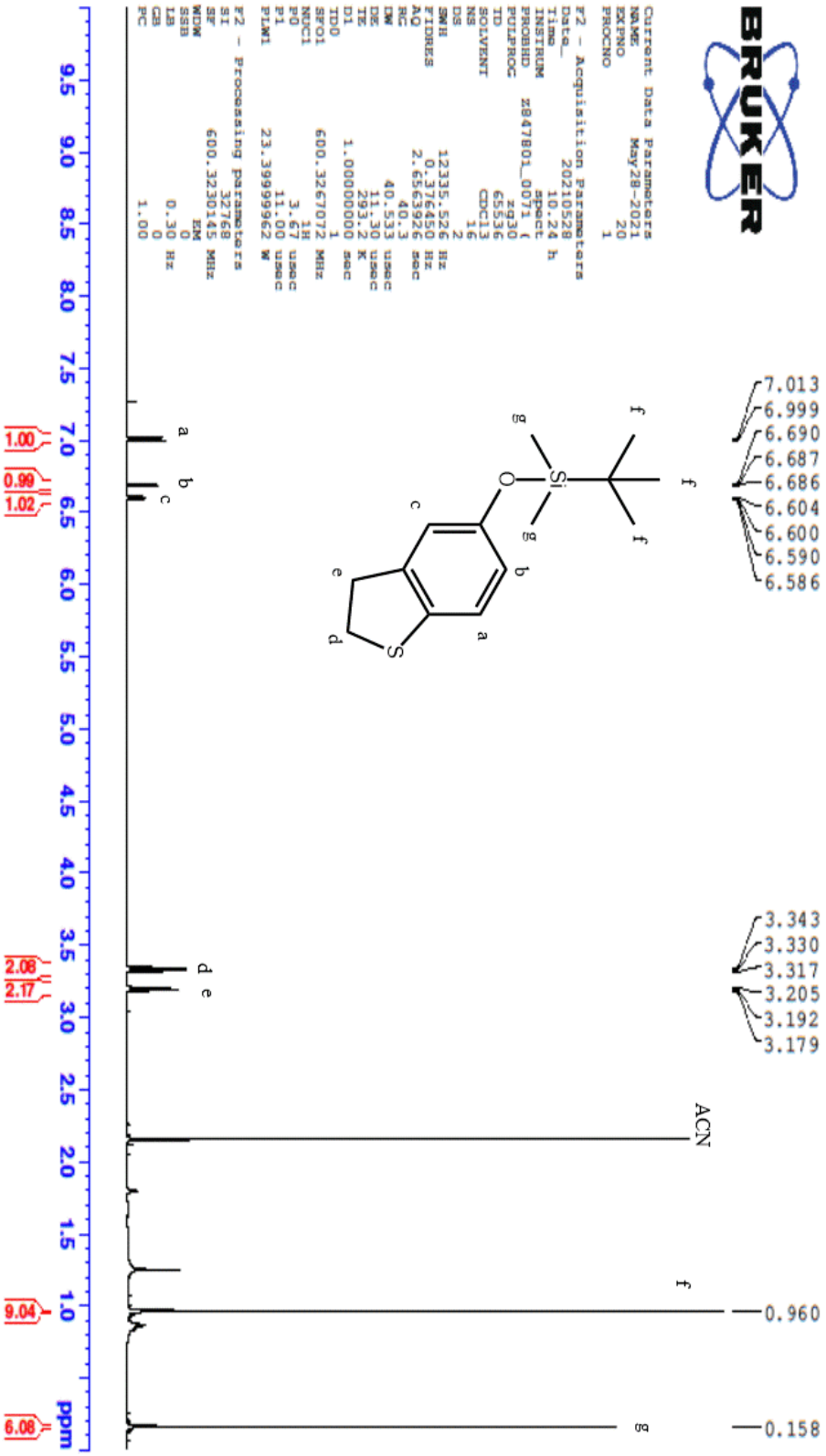


Spectrum 68: ^{1}H NMR of 4-Bromo-3-[2-(phenylthio)ethyl]phenyl *tert*-Butyldimethylsilyl Ether 13

7.2.6. 5-(tert-Butyldimethylsilyloxy)-2,3-dihydrobenzo[b]thiophene **(6)**

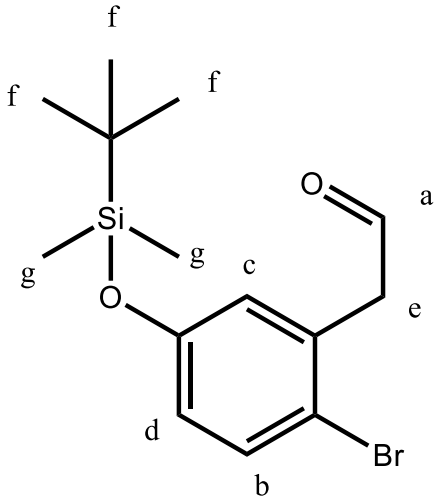


^{1}H NMR ($CDCl_3$) δ 7.01 (d, J= 8.4 Hz, 1H, Ha), 6.70-6.68 (m, 1H, Hb), 6.61-6.58 (m, 1H, Hb), 6.61-6.58 (m, 1H, Hc), 3.33 (t, J= 7.6 Hz, 2H, Hd), 3.19 (t, J= 7.6 Hz, 2H, He), 0.96 (s, 9H, Hf), 0.16 (s, 6H, Hg). **Acetone** ^{1}H NMR ($CDCl_3$) δ 2.15 (s) (**Spectrum 69**)



Spectrum 69: ^{1}H NMR spectrum of 5-(*tert*-Butyldimethylsilyloxy)-2,3-dihydrobenzo[*b*]thiophene 6

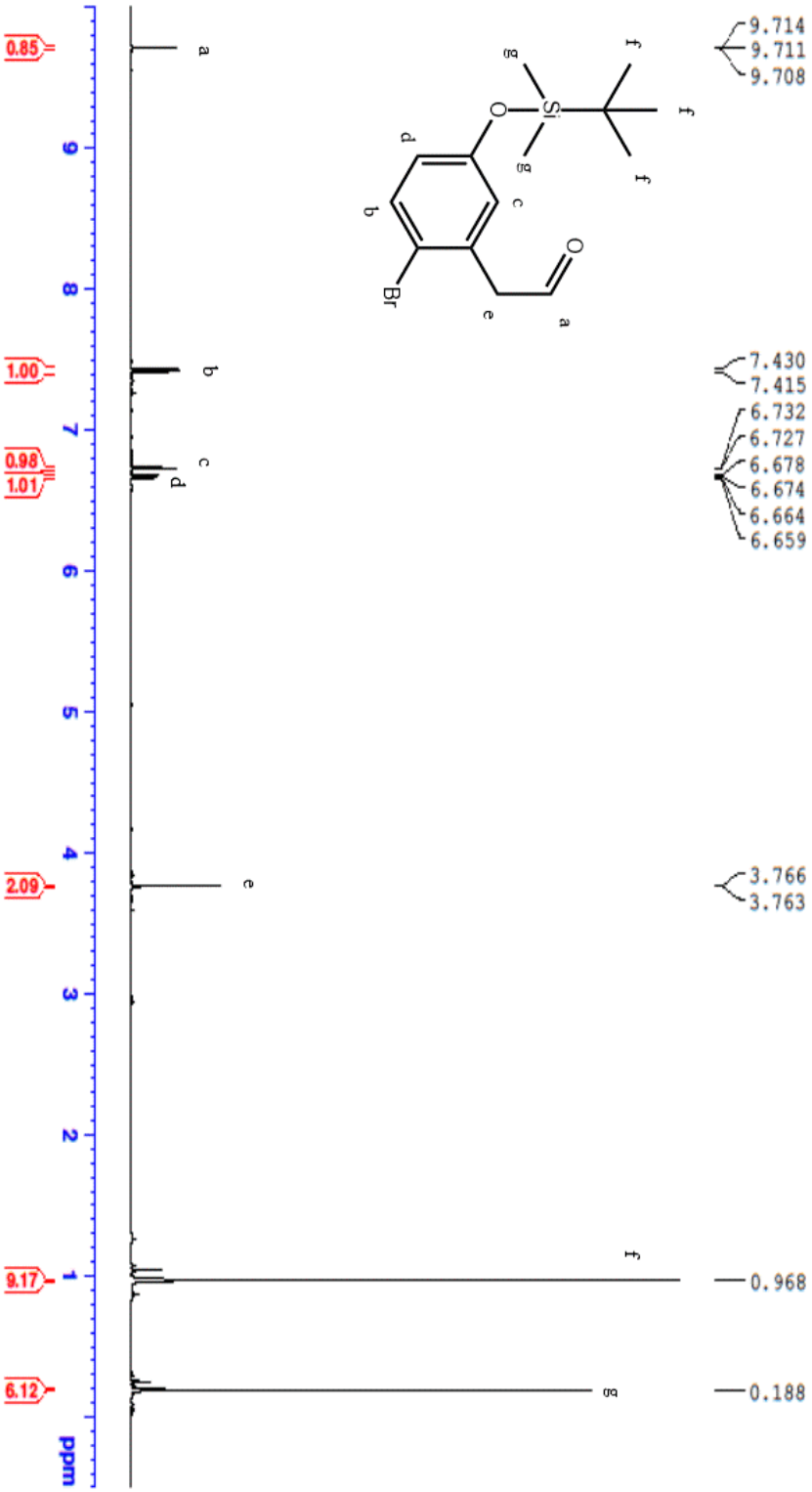
7.2.7. 4-Bromo-3-[2-(acetaldehyde)phenyl] tert-Butyldimethylsilyl Ether **(14)**



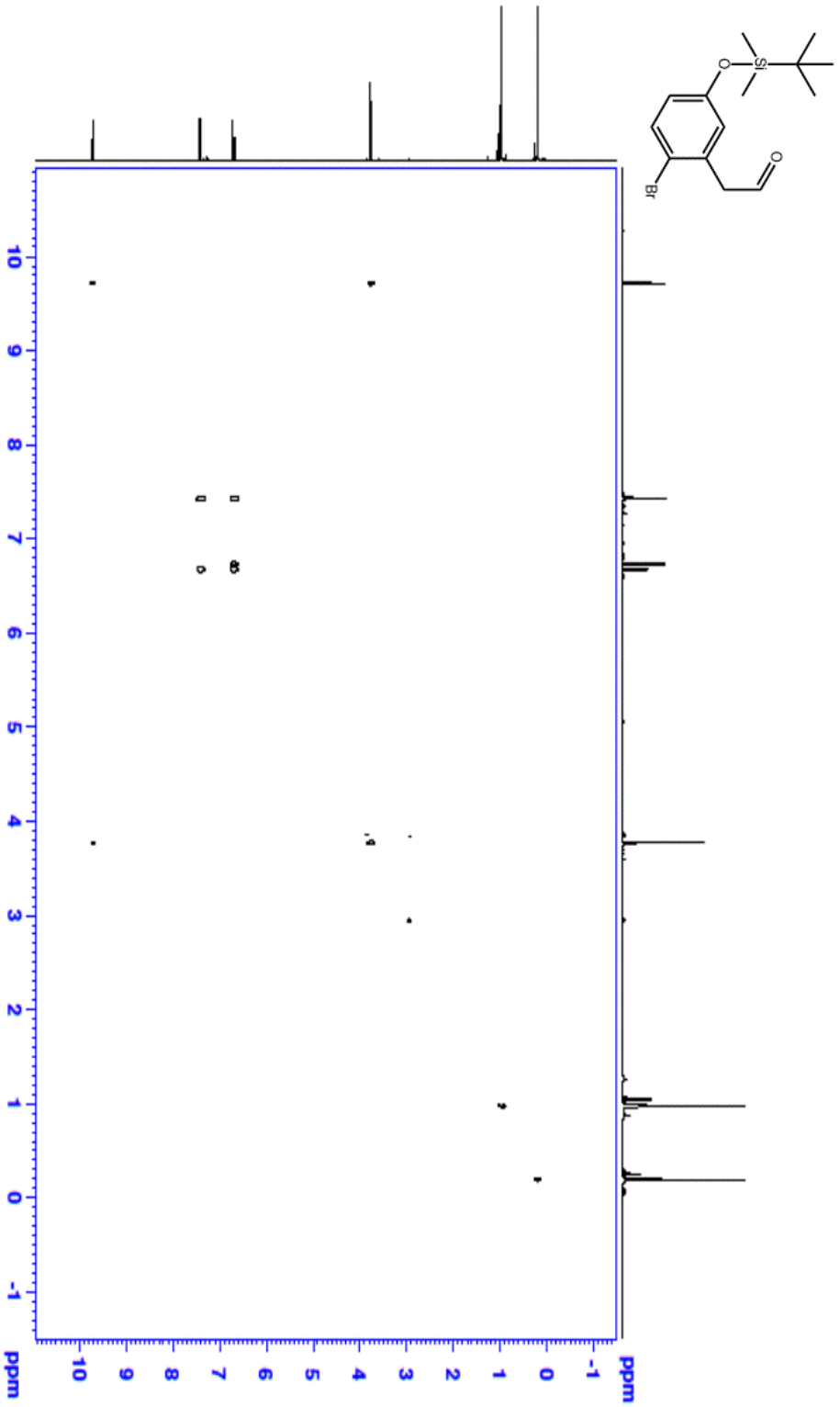
^{1}H NMR ($CDCl_3$) δ 9.71 (t, J= 1.8 Hz, 1H, Ha), 7.42 (d, J= 8.4 Hz, 1H, Hb), 6.73 (d, J= 2.9 Hz, 1H, Hc), 6.67 (d, J= 8.4, 2.9 Hz, 1H, Hd), 3.77 (d, J= 1.8 Hz, 2H, He), 0.97 (s, 9H, Hf), 0.19 (s, 6H, Hg) (**Spectrum 70**)

^{13}C NMR ($CDCl_3$) δ 198.24, 155.46, 133.64, 133.55, 123.55, 121.09, 116.15, 50.57, 25.69, 18.25, -4.39 (**Spectrum 72**)

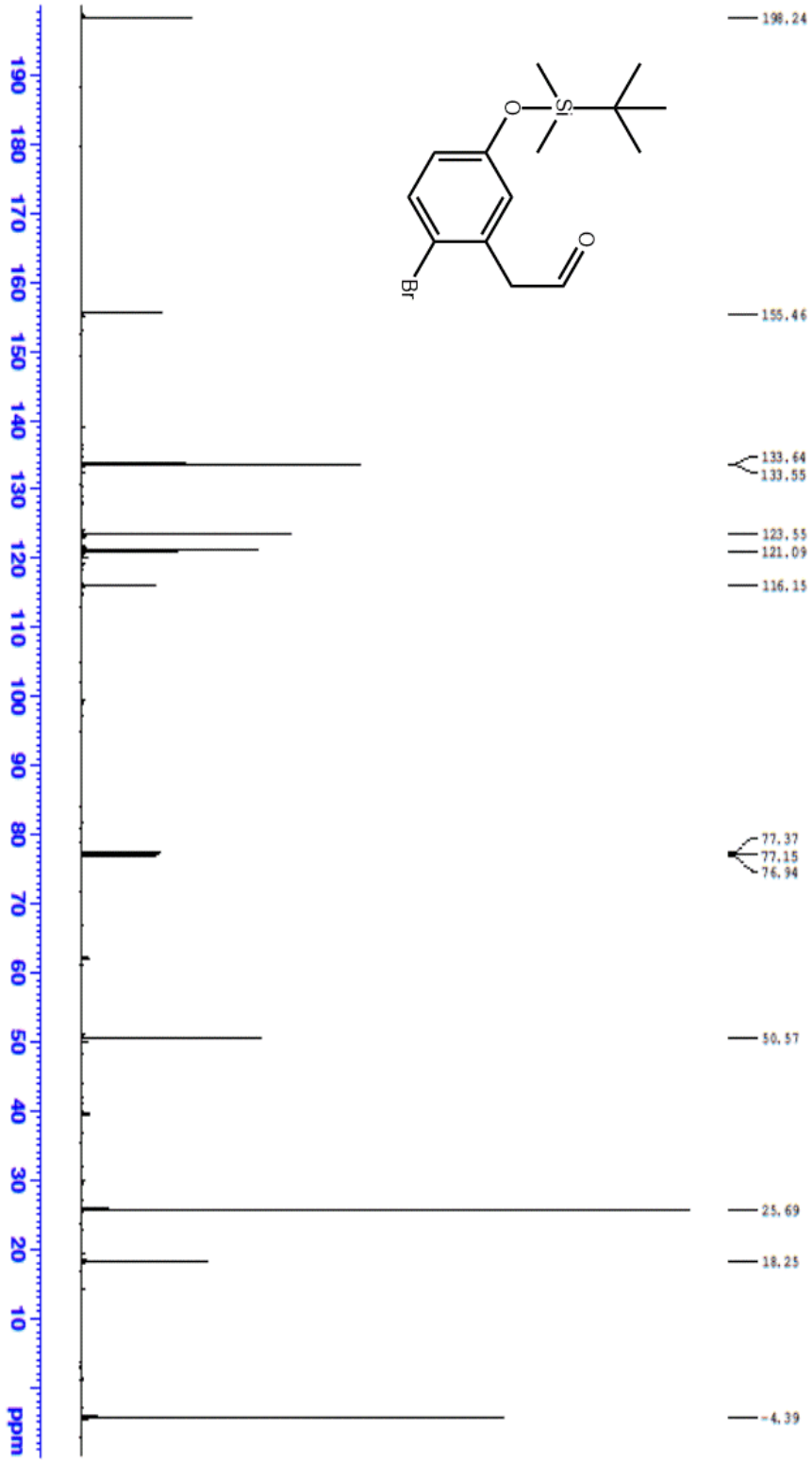
HRMS: $[M-H]^+$ 327.0421 m/z (**Spectrum 75**)



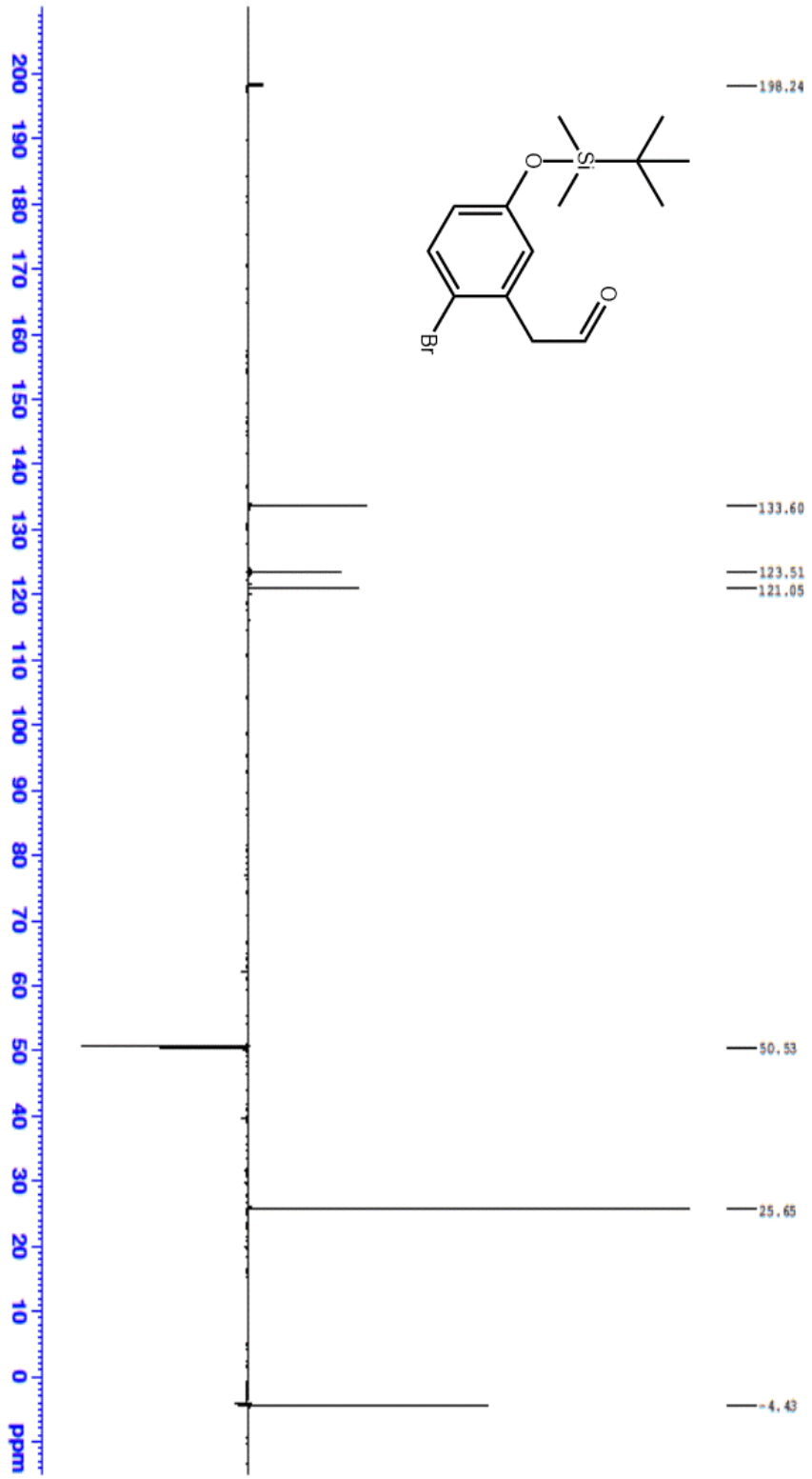
Spectrum 70: ^{1}H NMR spectrum of 4-Bromo-3-[2-(acetaldehyde)phenyl] *tert*-Butyldimethylsilyl Ether 14



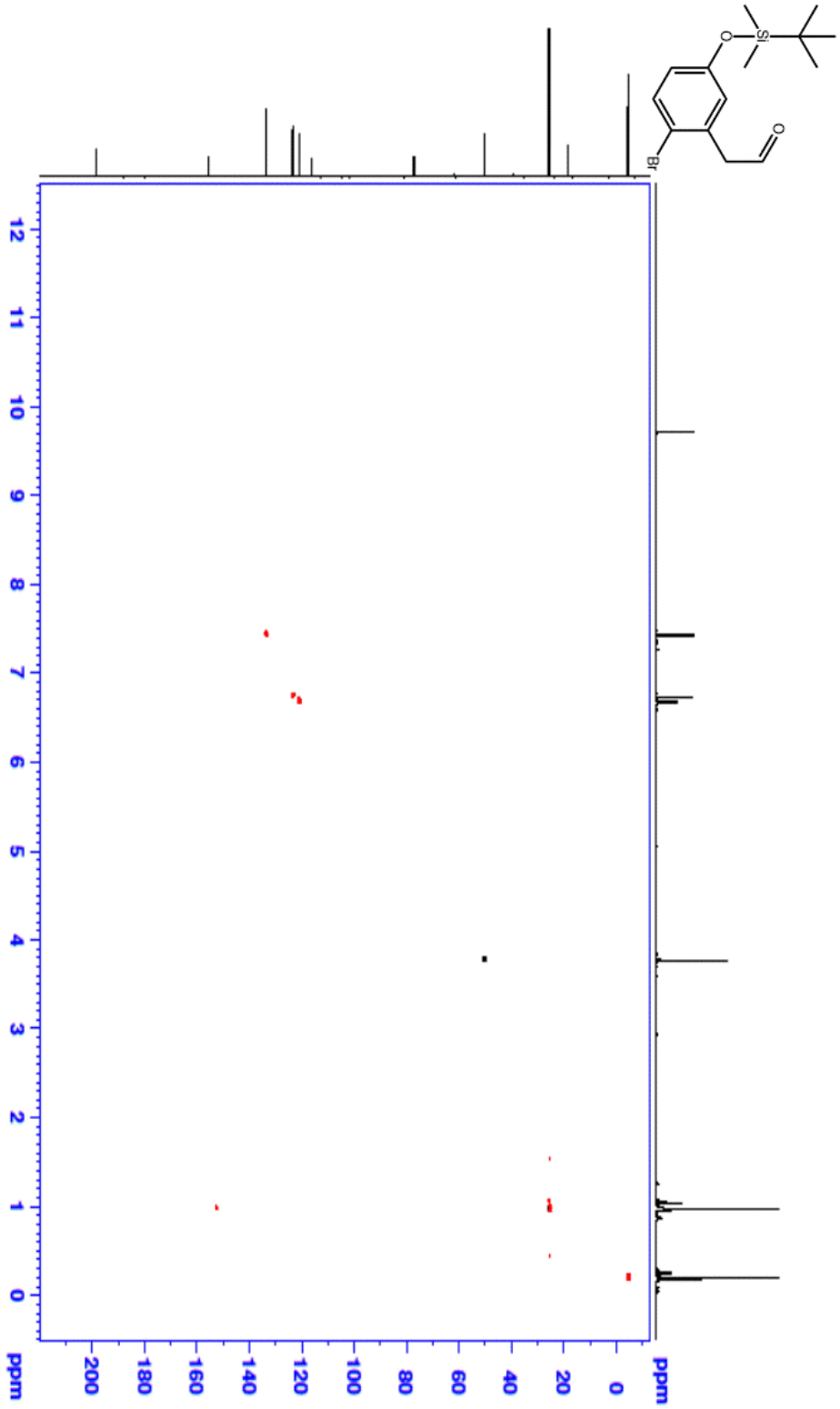
Spectrum 71: COSY NMR spectrum of 4-Bromo-3-[2-(acetaldehyde)phenyl] *tert*-Butyldimethylsilyl Ether 14



Spectrum 72: ^{13}C NMR spectrum of 4-Bromo-3-[2-(acetaldehyde)phenyl] *tert*-Butyldimethylsilyl Ether 14



Spectrum 73: DEPT NMR spectrum of 4-Bromo-3-[2-(acetaldehyde)phenyl] *tert*-Butyldimethylsilyl Ether 14



Spectrum 74: HSQC NMR spectrum of 4-Bromo-3-[2-(acetaldehyde)phenyl] *tert*-Butyldimethylsilyl Ether 14

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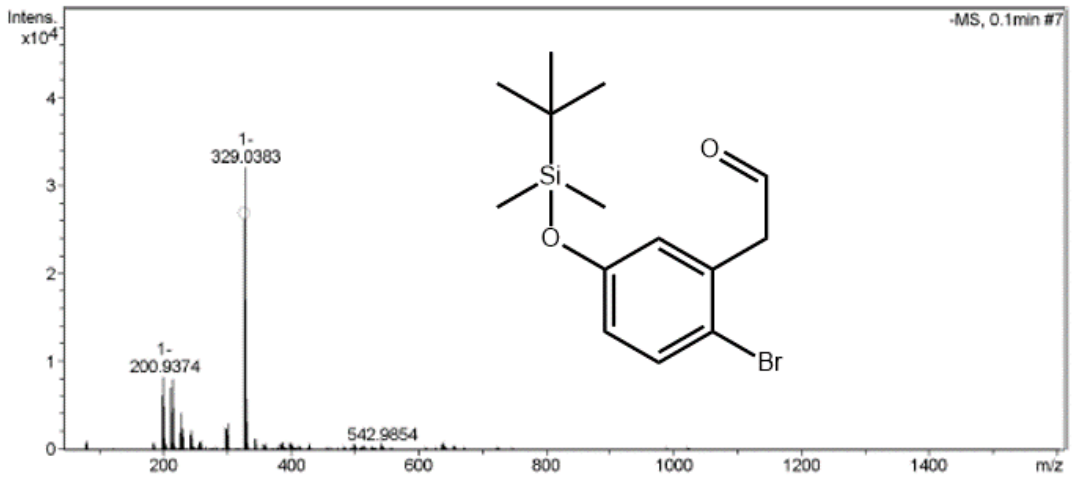
Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SOR_21_RA8_01_32594.d	Acquisition Date	21/03/2023 14:07:20
Sample Description			



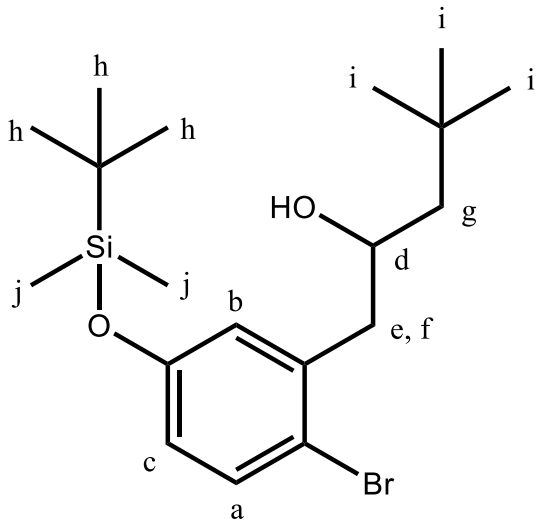
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
327.042056	1	C14H20BrO2Si	327.042142	0.1	0.3	5.5	ok	even	77.5

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

Spectrum 75: HRMS spectrum of 4-Bromo-3-[2-(acetaldehyde)phenyl] *tert*-Butyldimethylsilyl Ether 14

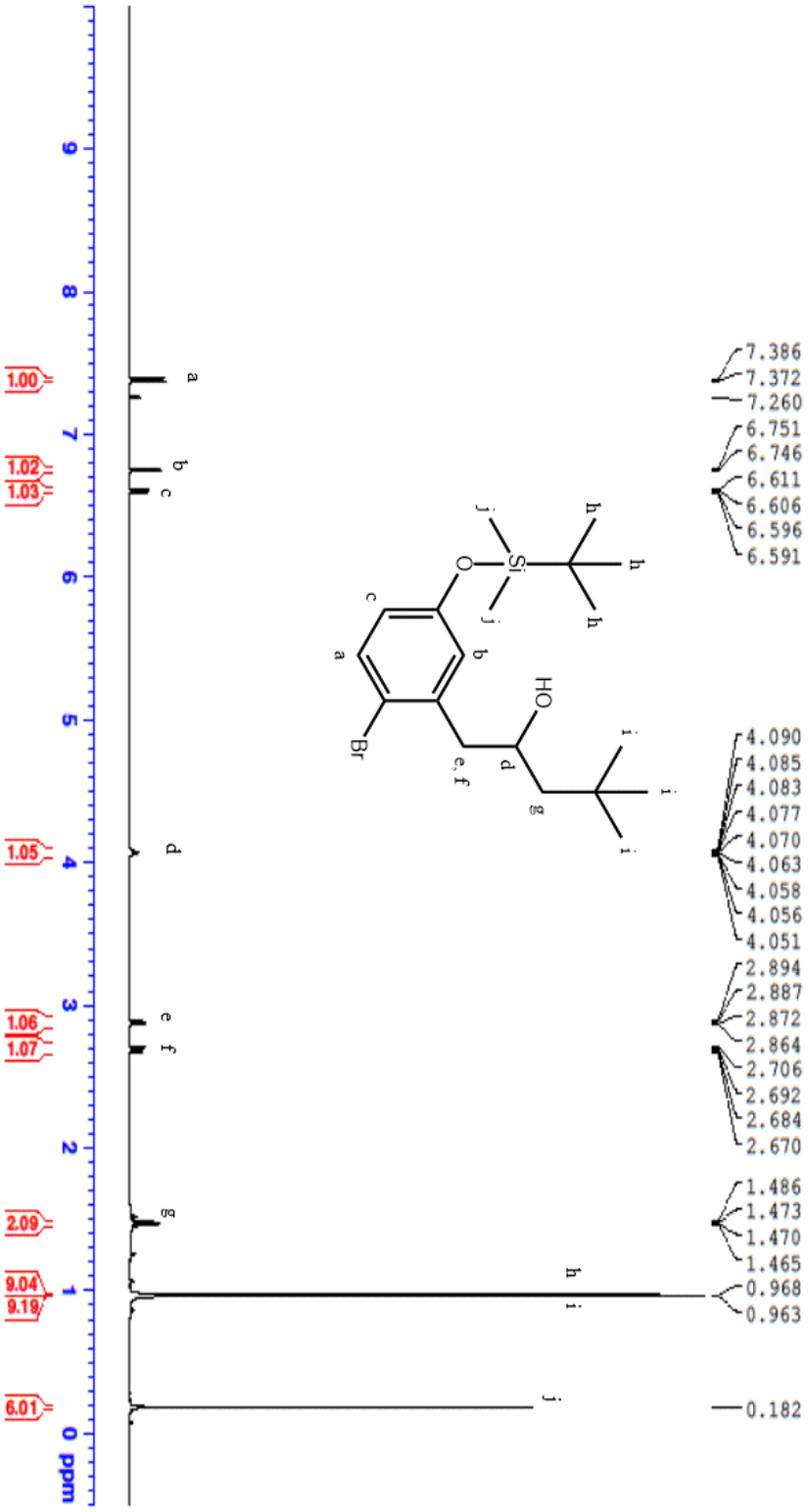
7.2.8. 4-Bromo-3-(2-hydroxy-4, 4, 4-trimethylbutyl)phenyl tert-Butyldimethylsilyl Ether **15a**



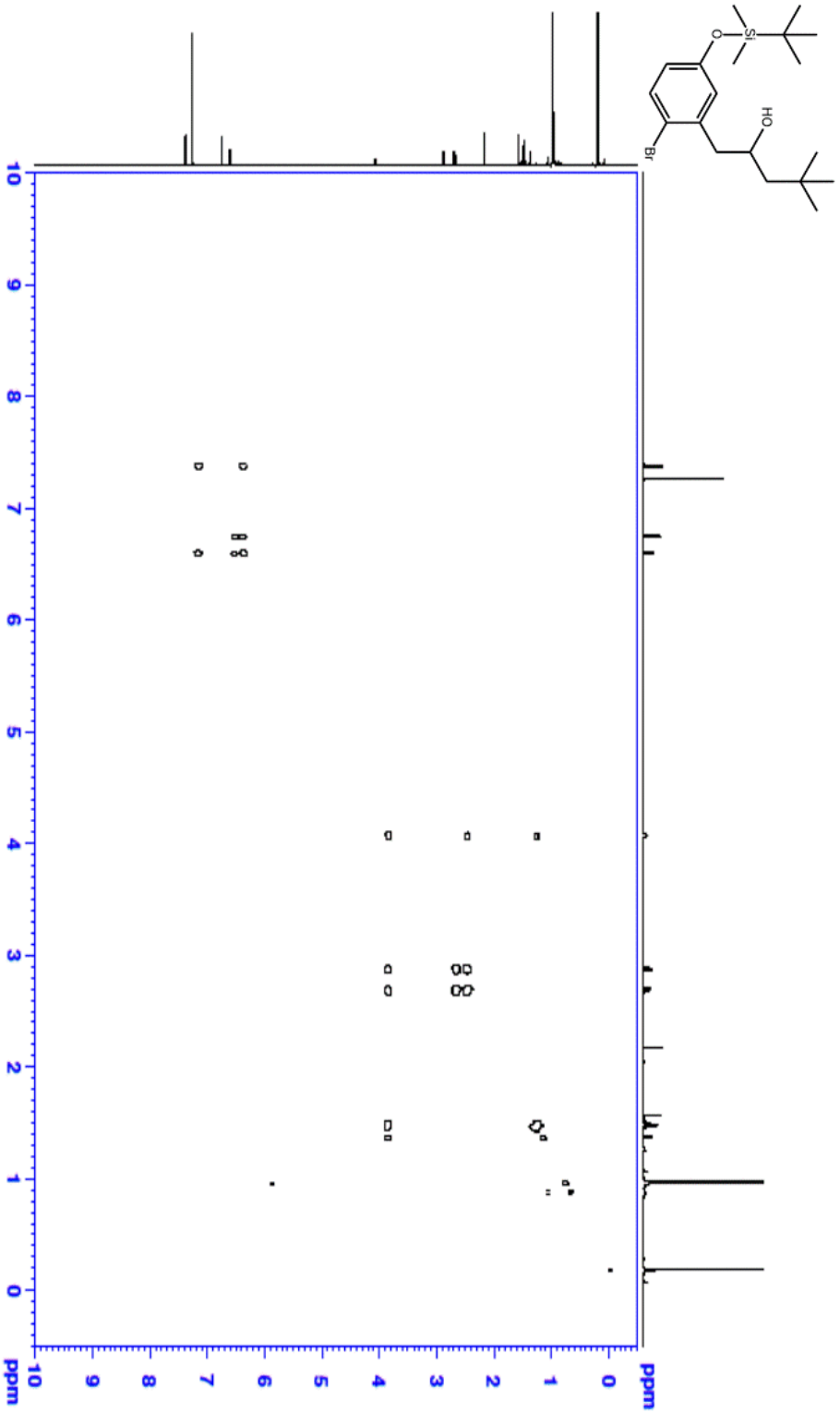
^{1}H NMR ($CDCl_3$) δ 7.38 (d, J= 8.6 Hz, 1H, Ha), 6.75 (d, J= 2.9 Hz, 1H, Hb), 6.60 (dd, J= 2.9, 8.6 Hz, 1H, Hc), 4.10-4.04 (m, 1H, Hd), 2.88 (dd, J= 4.3, 13.5 Hz, 1H, He), 2.69 (dd, J= 8.7, 13.5 Hz, 1H, Hf), 1.49-1.46 (m, 2H, Hg), 0.97 (s, 9H, Hh), 0.96 (s, 9H, Hi), 0.18 (s, 6H, Hj) (**Spectrum 76**)

^{13}C NMR ($CDCl_3$) δ 155.09, 139.28, 133.63, 123.86, 120.21, 116.20, 68.95, 50.70, 46.26, 30.50, 30.24, 25.79, 18.14, -4.30 (**Spectrum 78**)

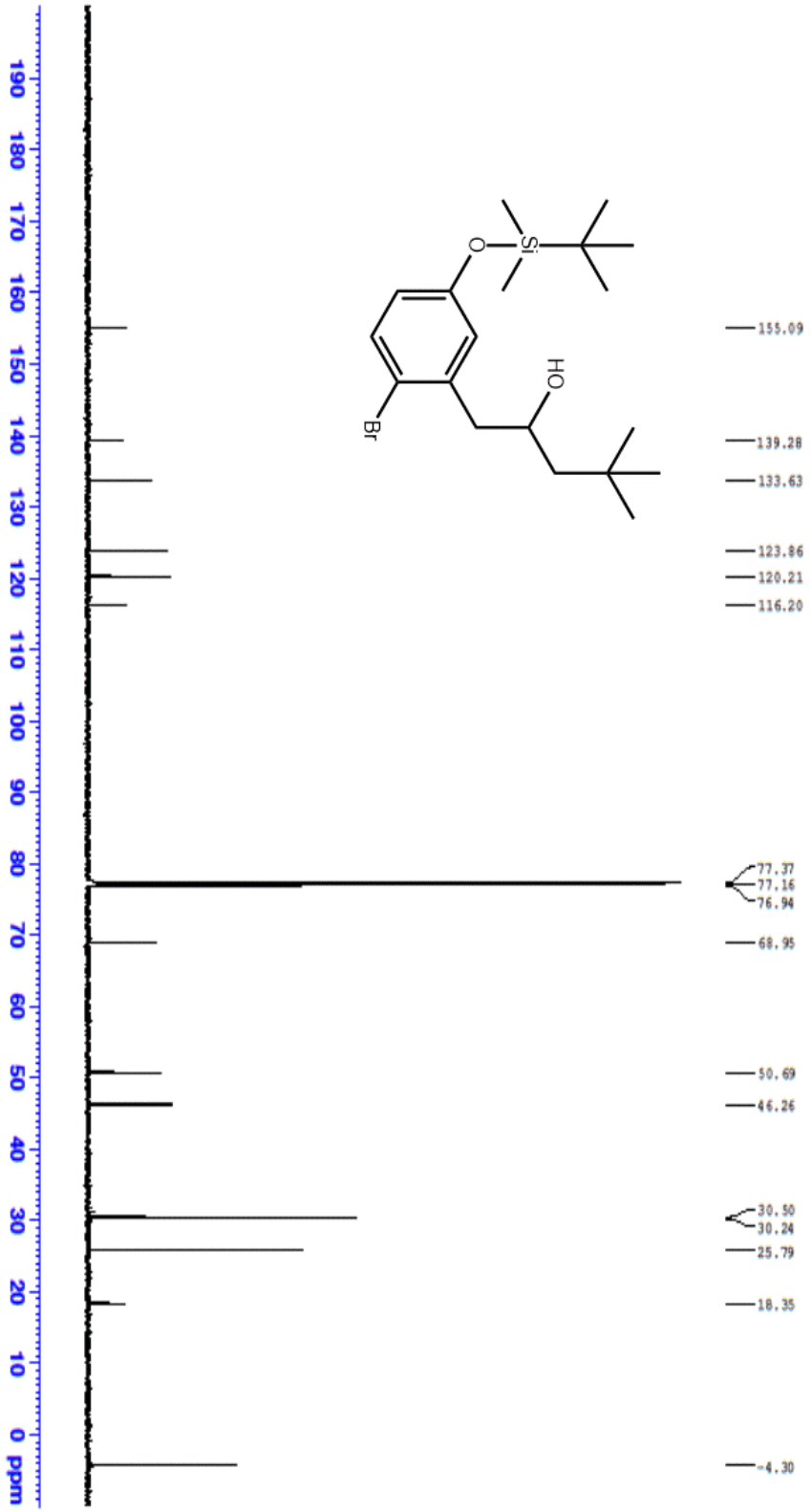
HRMS: M^+ 383.1400 m/z (**Spectrum 81**)



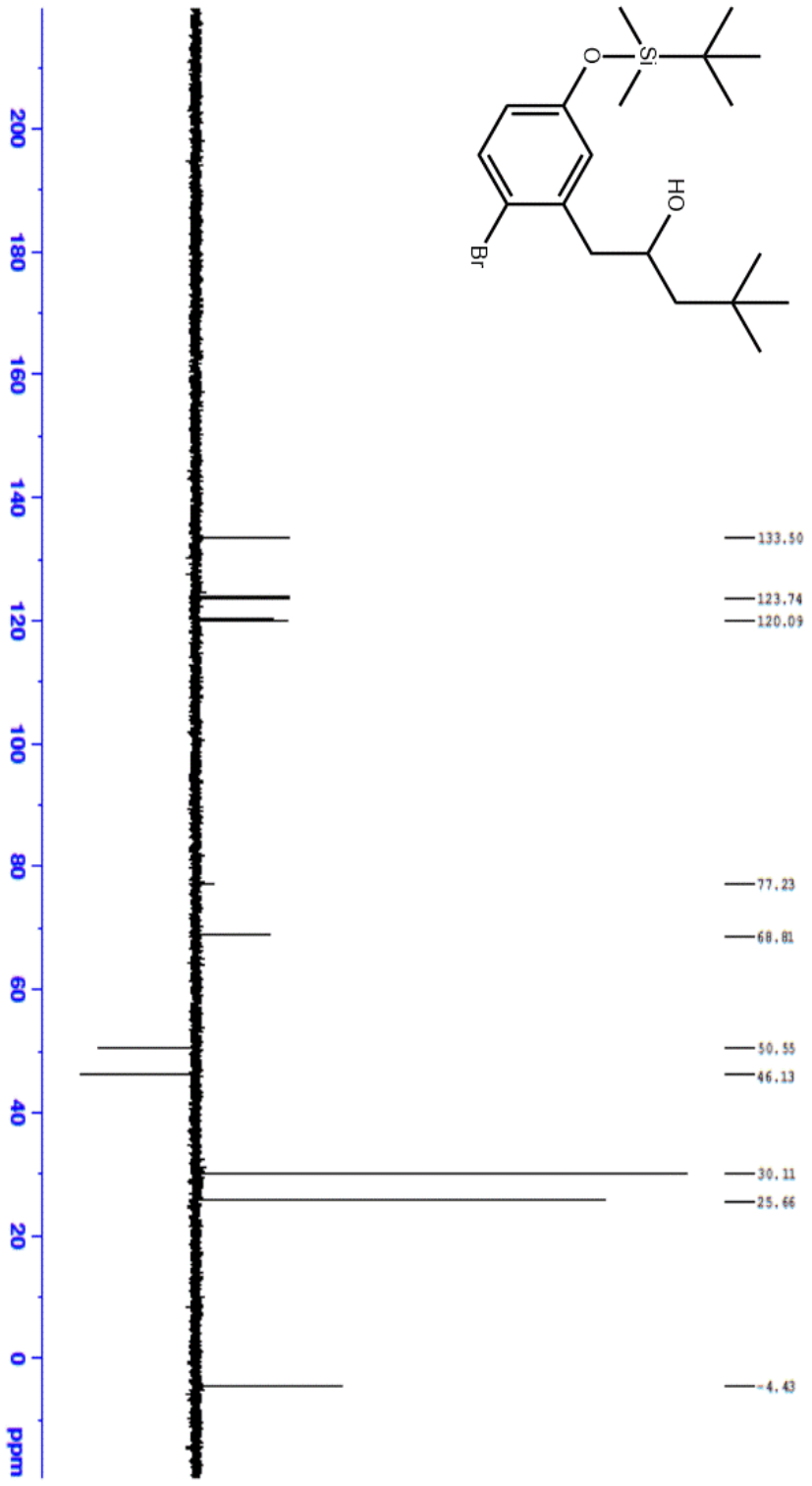
Spectrum 76: ^{1}H NMR spectrum of 4-Bromo-3-(2-hydroxy-4, 4, 4-trimethylbutyl)phenyl *tert*-Butyldimethylsilyl Ether 15a



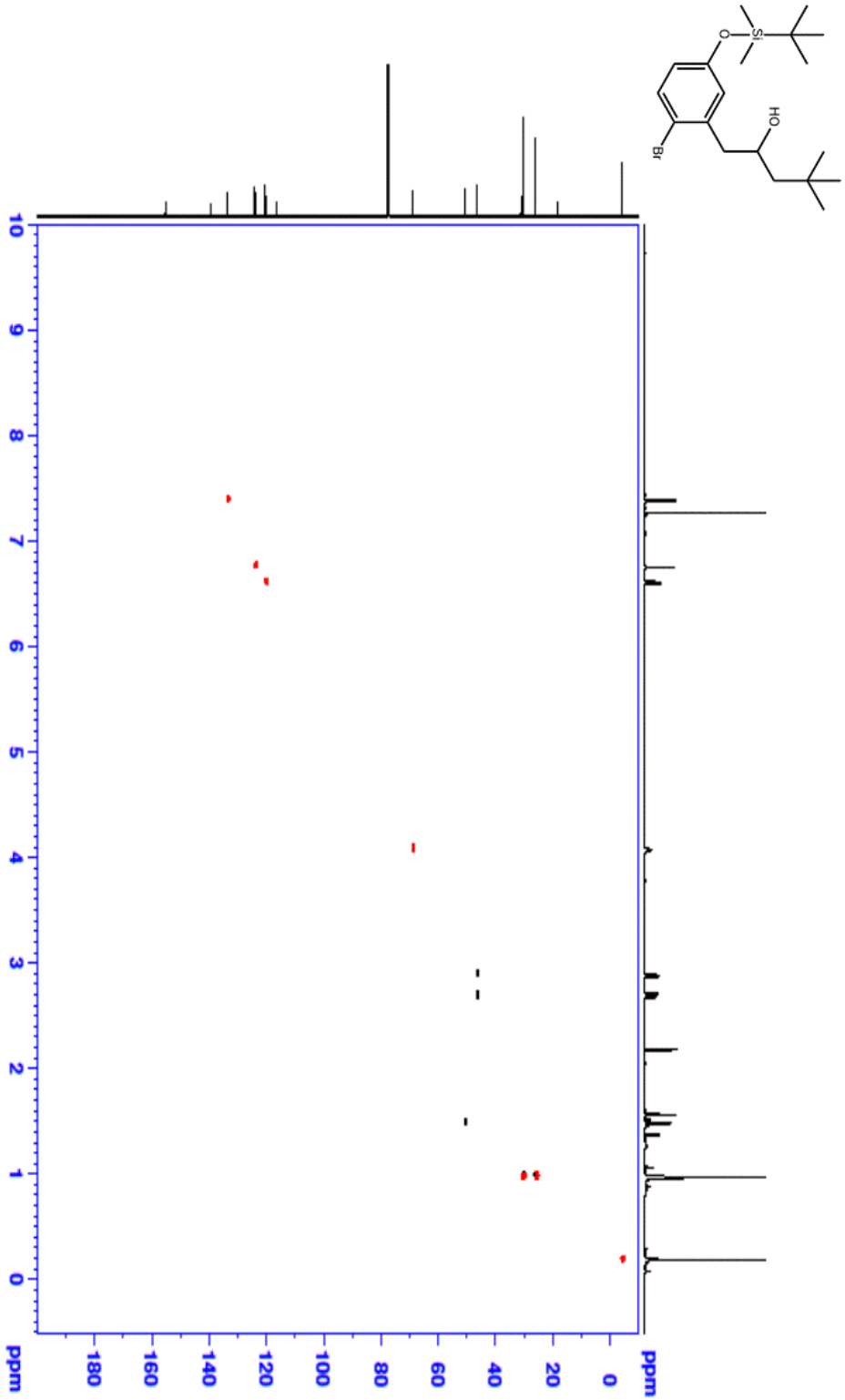
Spectrum 77: COSY NMR spectrum of 4-Bromo-3-(2-hydroxy-4, 4, 4-trimethylbutyl)phenyl *tert*-Butyldimethylsilyl Ether 15a



Spectrum 78: ^{13}C NMR spectrum of 4-Bromo-3-(2-hydroxy-4, 4, 4-trimethylbutyl)phenyl *tert*-Butyldimethylsilyl Ether 15a



Spectrum 79: DEPT NMR spectrum of 4-Bromo-3-(2-hydroxy-4, 4, 4-trimethylbutyl)phenyl *tert*-Butyldimethylsilyl Ether 15a



Spectrum 80: HSQC NMR spectrum of 4-Bromo-3-(2-hydroxy-4, 4, 4-trimethylbutyl)phenyl *tert*-Butyldimethylsilyl Ether 15a

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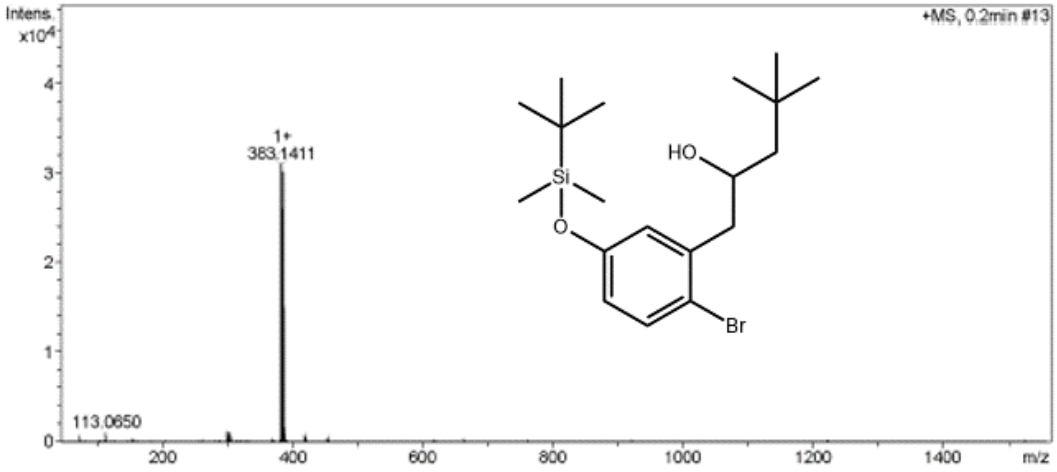
Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SOR_41B_RC2_01_32515.d	Acquisition Date	20/03/2023 13:57:58
Sample Description			



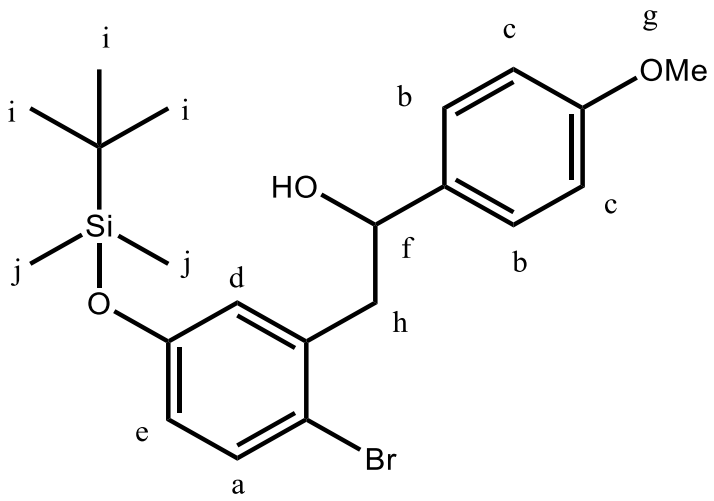
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
383.141112	1	C19H32BrOSi	383.140031	1.1	2.8	4.5	ok	even	22.8

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

Spectrum 81: HRMS spectrum of 4-Bromo-3-(2-hydroxy-4, 4, 4-trimethylbutyl)phenyl *tert*-Butyldimethylsilyl Ether 15a

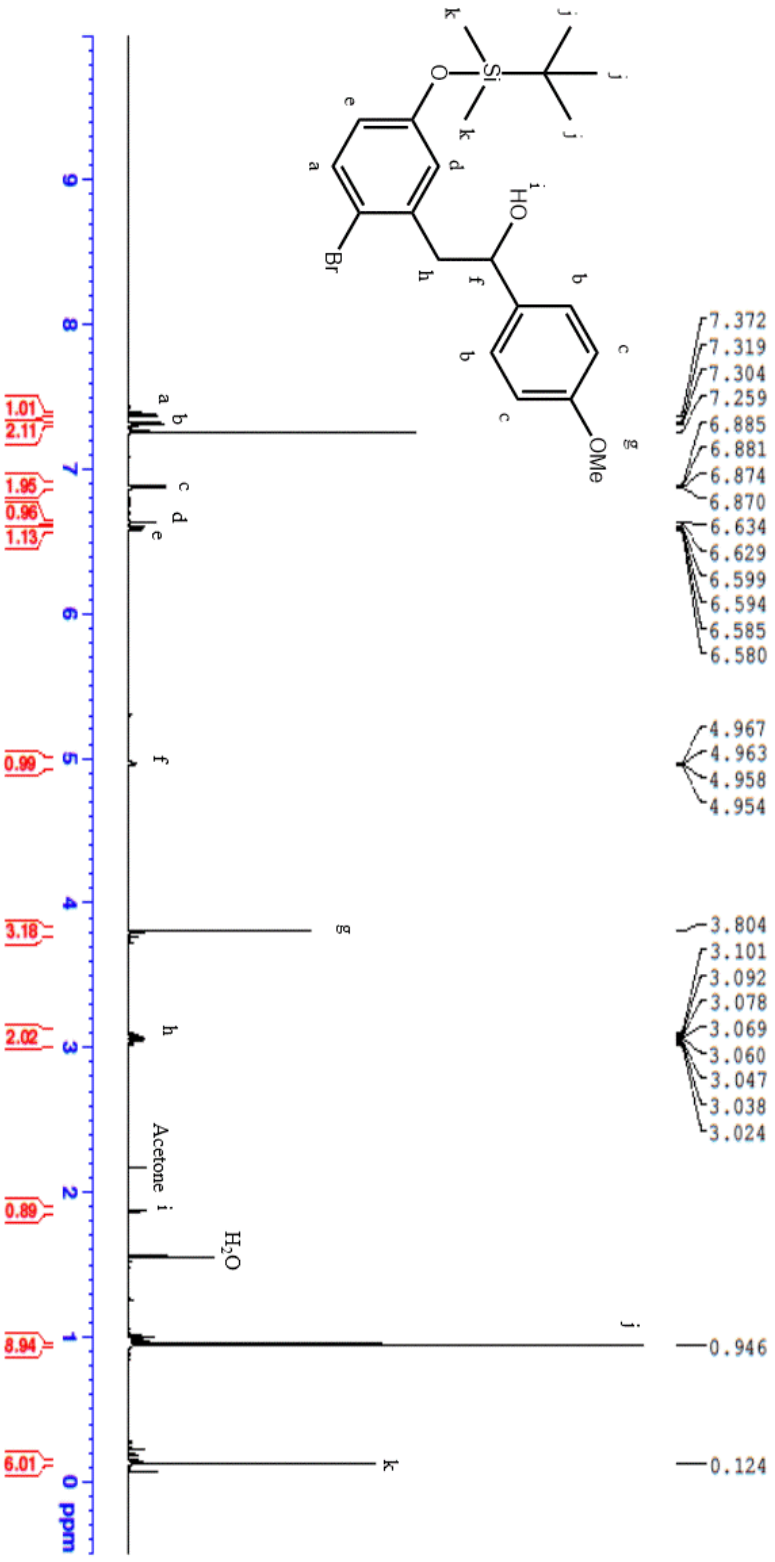
7.2.9. 4-Bromo-3-[2-hydroxy-2-(p-anisole)]phenyl tert-Butyldimethylsilyl Ether **15b**



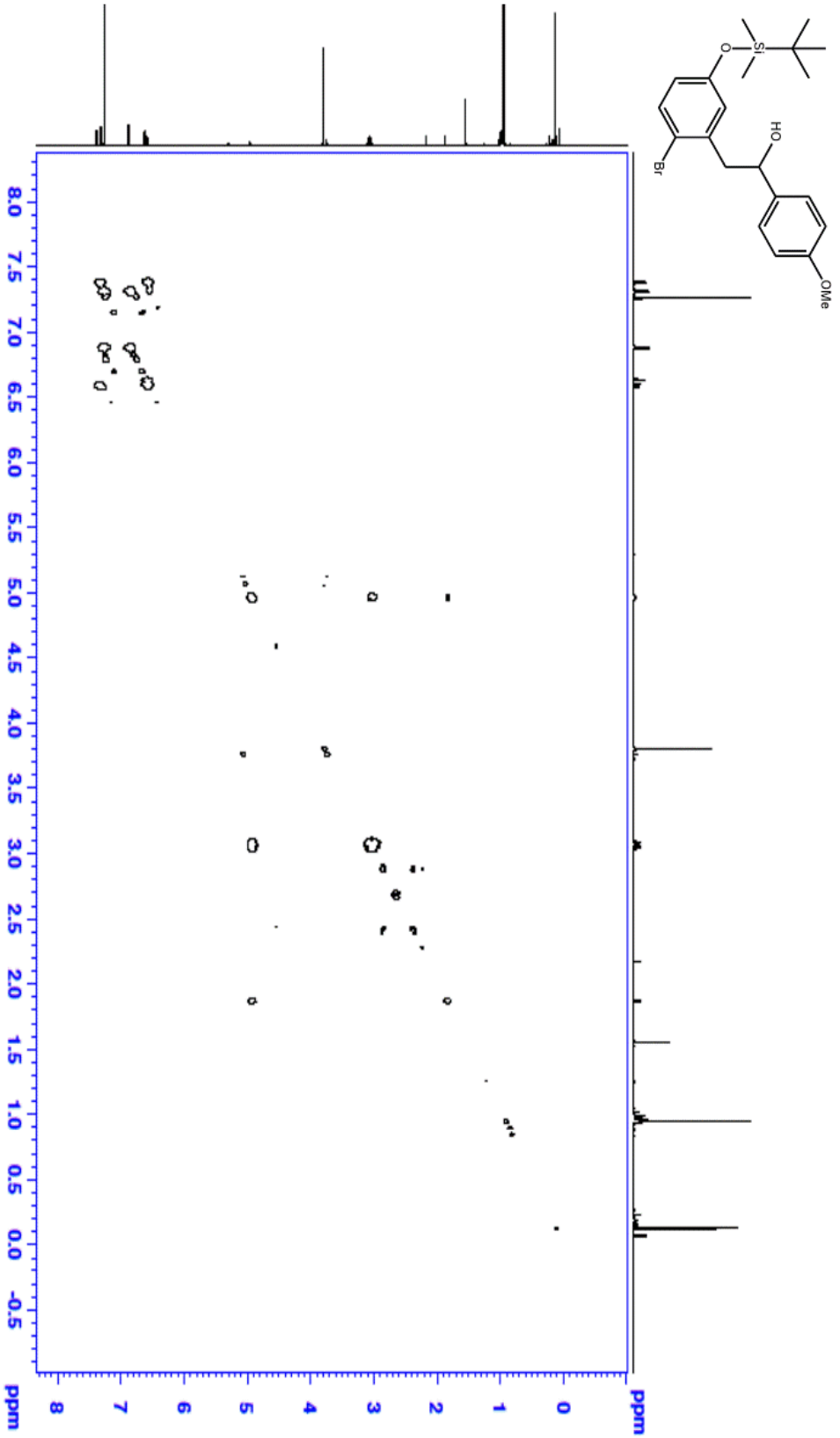
^{1}H NMR ($CDCl_3$) δ 7.38 (d, J= 8.6 Hz, 1H, Ha), 7.31 (d, J= 8.6 Hz, 2H, Hb), 6.88 (d, J= 8.6 Hz, 2H, Hc), 6.63 (d, J= 3 Hz, 1 H, Hd), 6.60 (dd, J= 8.6, 3 Hz, 1H, He), 4.98-4.94 (m, 1H, Hf), 3.80 (s, 3H, Hg), 3.11-3.01 (m, 2H, Hh), 1.87 (d, J= 2.9 Hz, Hi, 1H) 0.95 (s, 9H, Hj), 0.12 (s, 6H, Hk) **H_2O**: 1.55 (s), **Acetone**: 2.17 (s) **(Spectrum 82)**

^{13}C NMR ($CDCl_3$) δ 159.29, 155.05, 138.74, 136.06, 133.47, 127.20, 123.91, 120.31, 116.19, 113.98, 73.22, 55.42, 46.35, 25.77, 18.31, -4.38 (**Spectrum 84**)

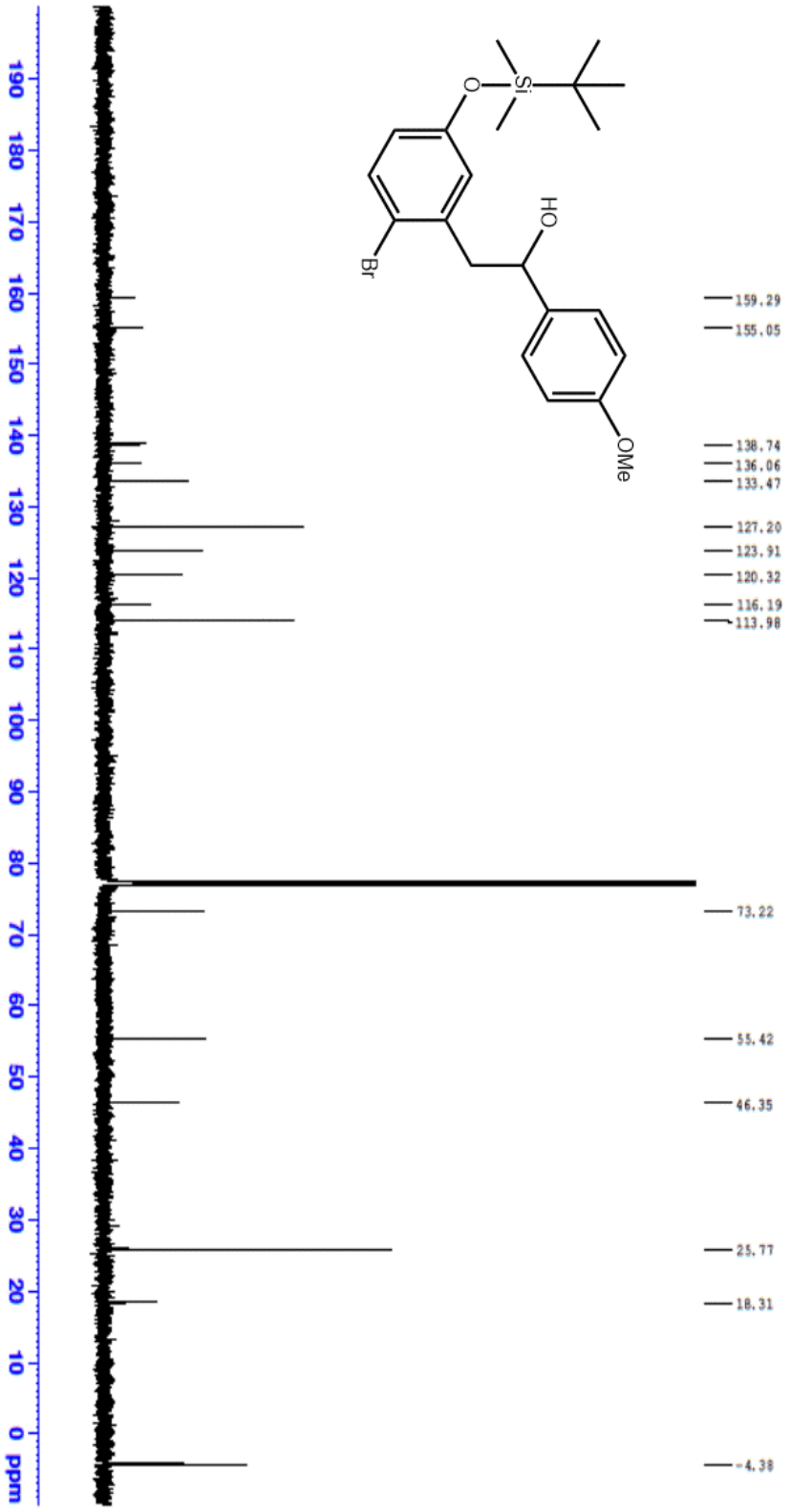
HRMS: M^+ 433.0840 m/z (**Spectrum 86**)



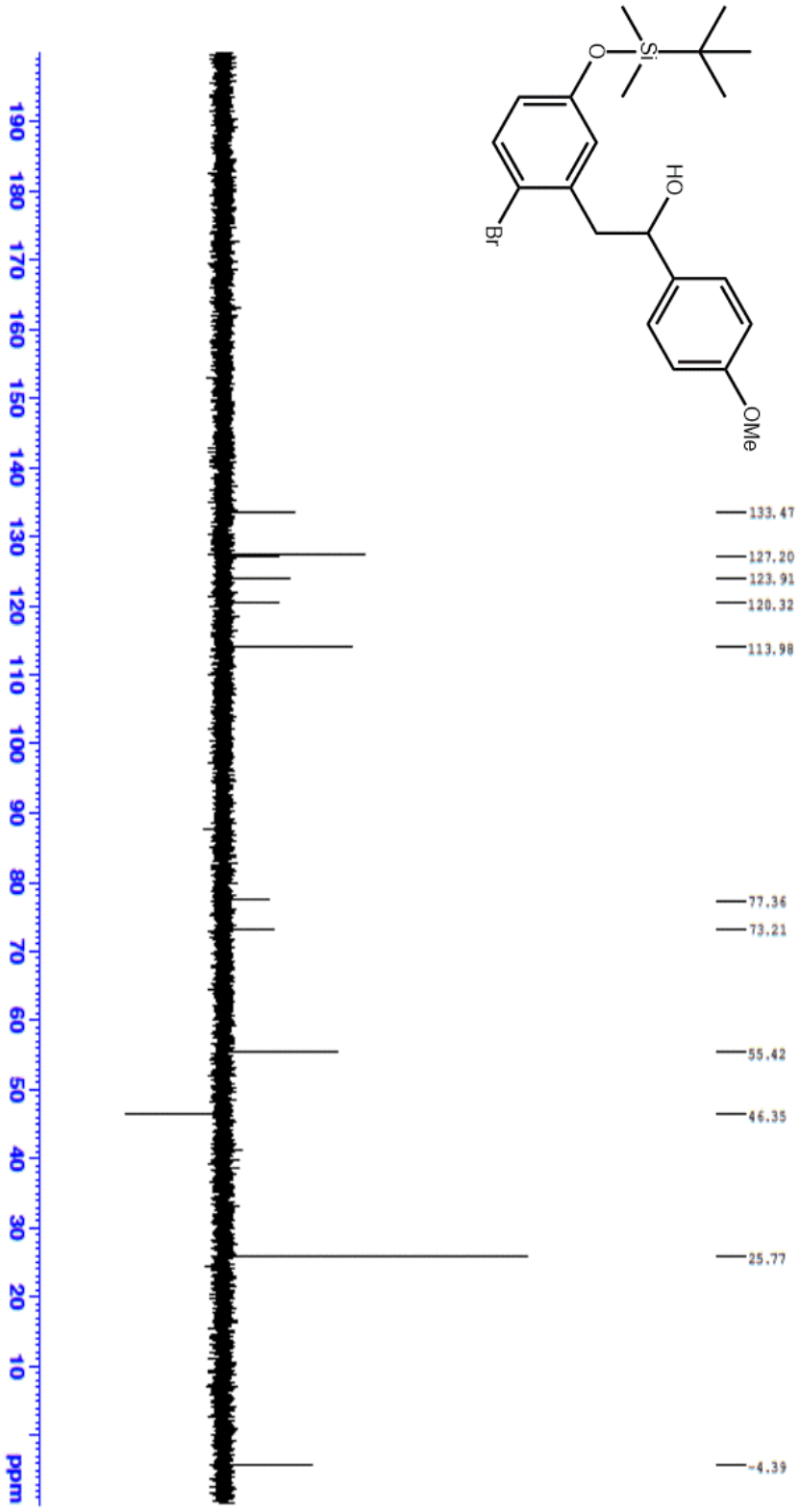
Spectrum 82: ^{1}H NMR spectrum of 4-Bromo-3-[2-hydroxy-2-(p-anisole)]phenyl *tert*-Butyldimethylsilyl Ether 15b



Spectrum 83: COSY NMR spectrum of 4-Bromo-3-[2-hydroxy-2-(p-anisole)]phenyl *tert*-Butyldimethylsilyl Ether 15b



Spectrum 84: ^{13}C NMR spectrum of 4-Bromo-3-[2-hydroxy-2-(p-anisole)]phenyl *tert*-Butyldimethylsilyl Ether 15b



Spectrum 85: DEPT NMR spectrum of 4-Bromo-3-[2-hydroxy-2-(p-anisole)]phenyl *tert*-Butyldimethylsilyl Ether 15b

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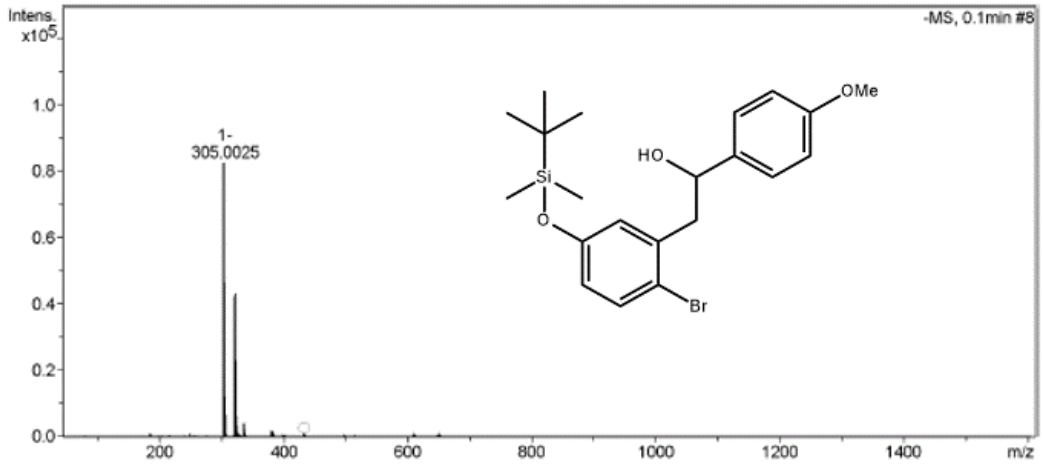
Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SOR_40_RC1_01_32603.d	Acquisition Date	21/03/2023 14:36:27
Sample Description			



Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
433.083126	1	C21H26BrO3Si	433.084007	-0.9	-2.0	9.5	ok	even	62.7

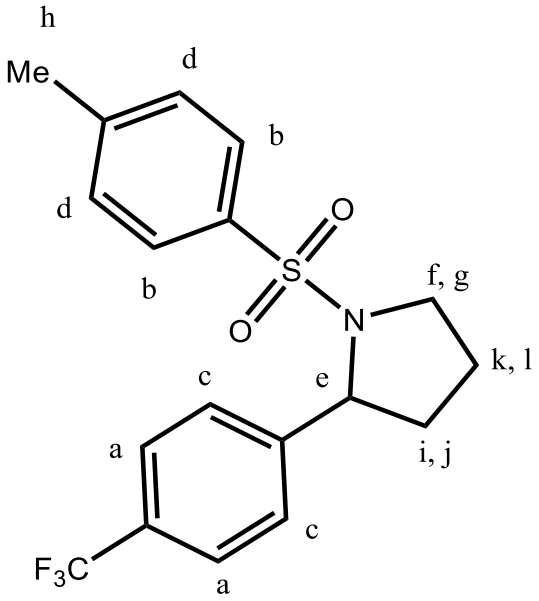
SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

Spectrum 86: HRMS spectrum of 4-Bromo-3-[2-hydroxy-2-(p-anisole)]phenyl *tert*-Butyldimethylsilyl Ether 15b

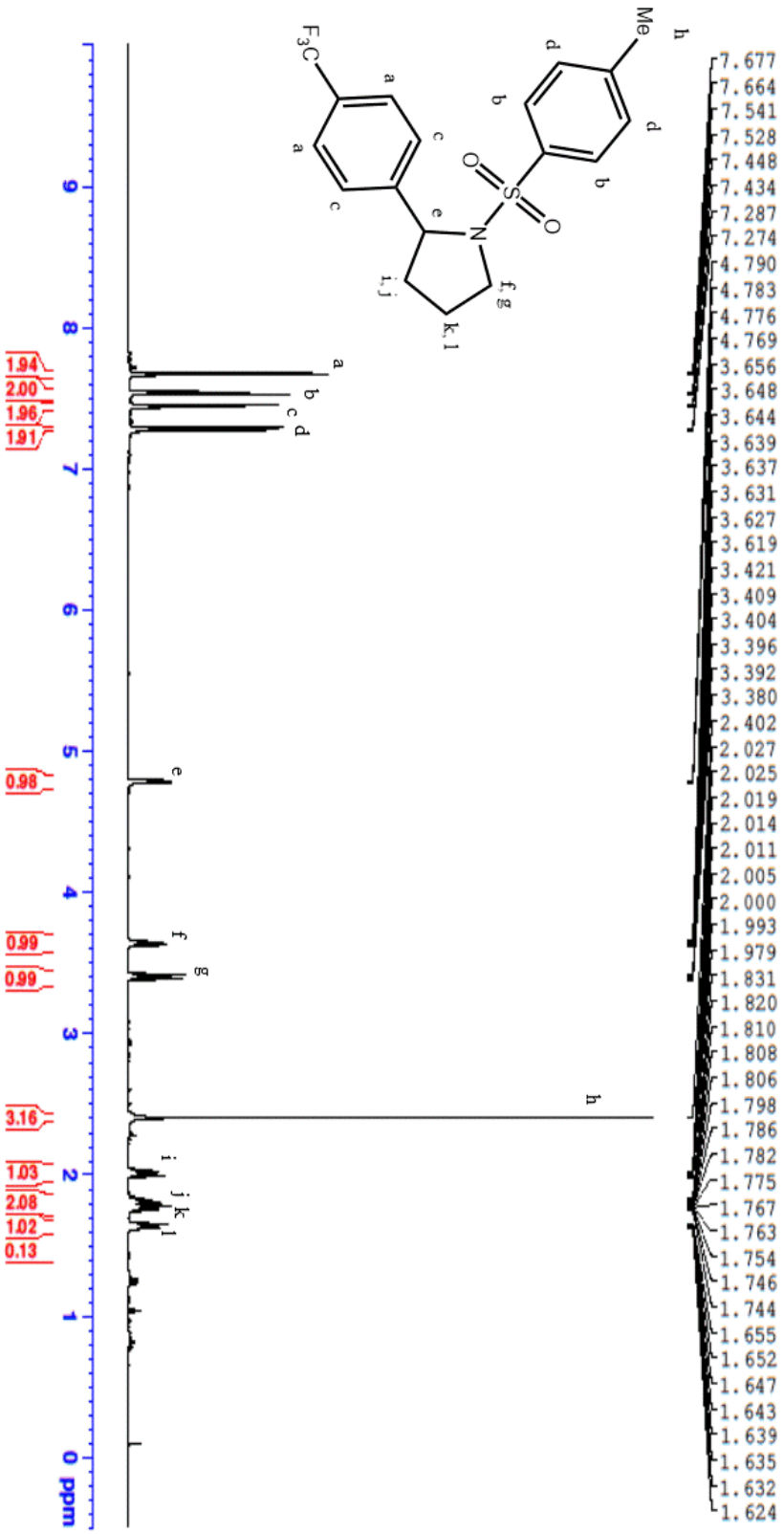
7.3. Data for compounds from Chapter 4

7.3.1. 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl] pyrrolidine **19a**

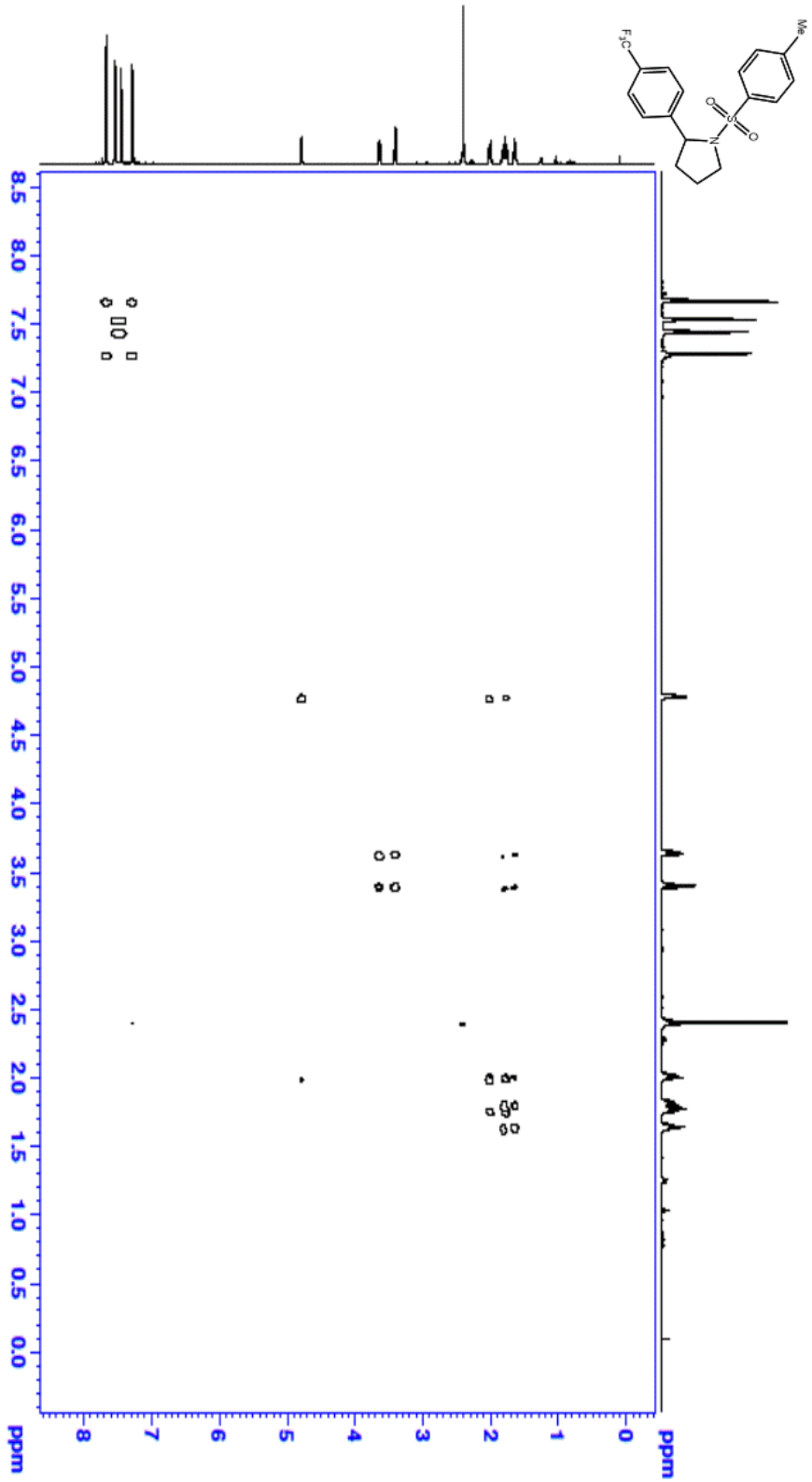


^{1}H NMR ($CDCl_3$) δ 7.67 (d, J= 8.3 Hz, 2H, Ha), 7.54 (d, J= 8 Hz, 2H, Hb), 7.44 (d, J= 8.2 Hz, 2H, Hc), 7.28 (d, J= 8 Hz, 2H, Hd), 4.80-4.76 (m, 1H, He), 3.67-3.61 (m, 1H, Hf), 3.43-3.37 (m, 1H, Hg), 2.40 (s, 3H, Hh), 2.05-1.97 (m, 1H, Hi), 1.85-1.72 (m, 2H, Hj, Hk), 1.67-1.60 (m, 1H, Hl). (**Spectrum 87**)

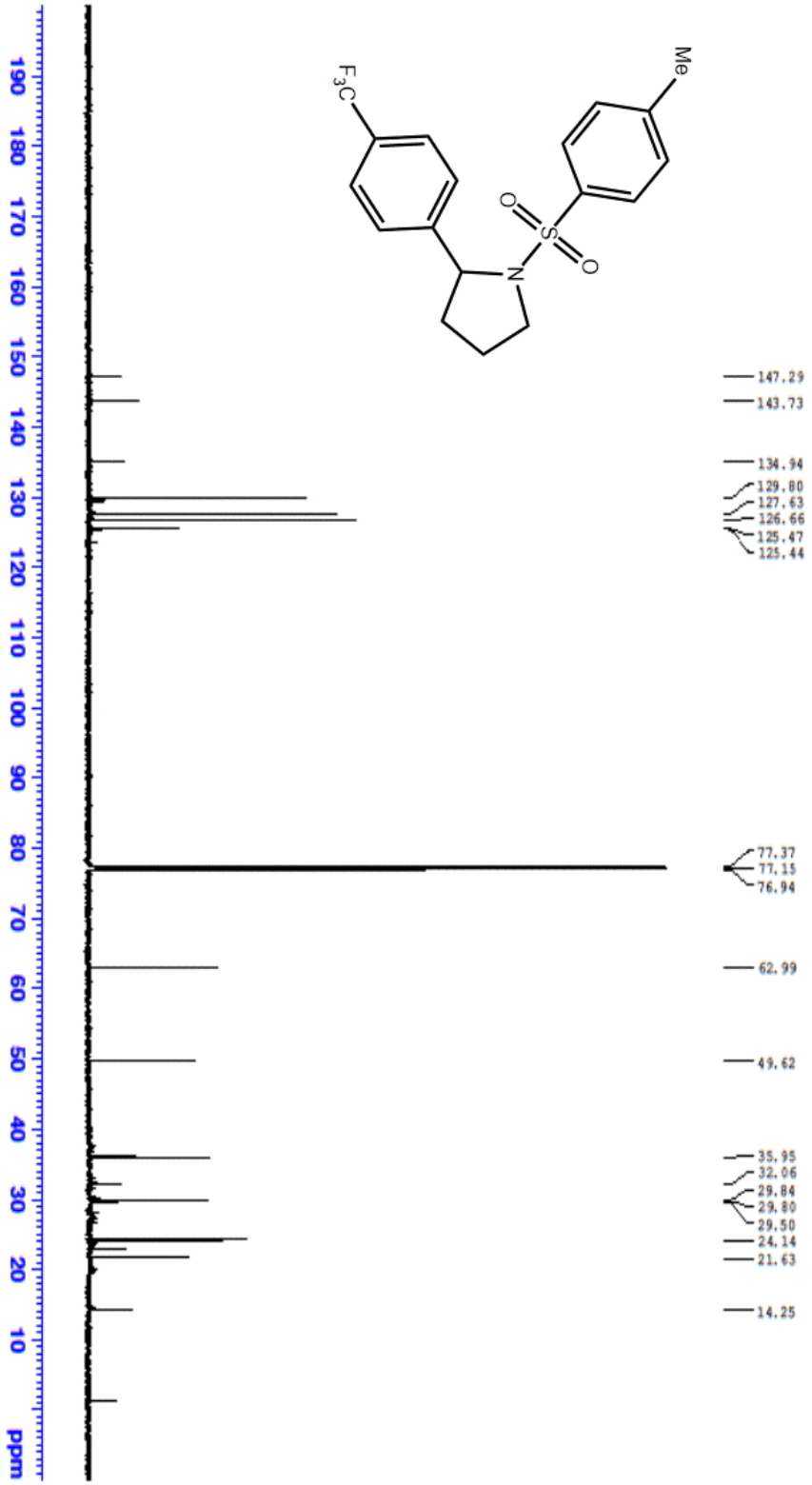
^{13}C NMR ($CDCl_3$) δ 147.29, 143.73, 134.94, 129.80, 127.63, 126.66, 125.51-125.40, 62.99, 49.62, 39.95, 24.14, 21.63. **Hexane:** 32.06, 22.83, 14.25. **Grease:** 29.84 (**Spectrum 89**)



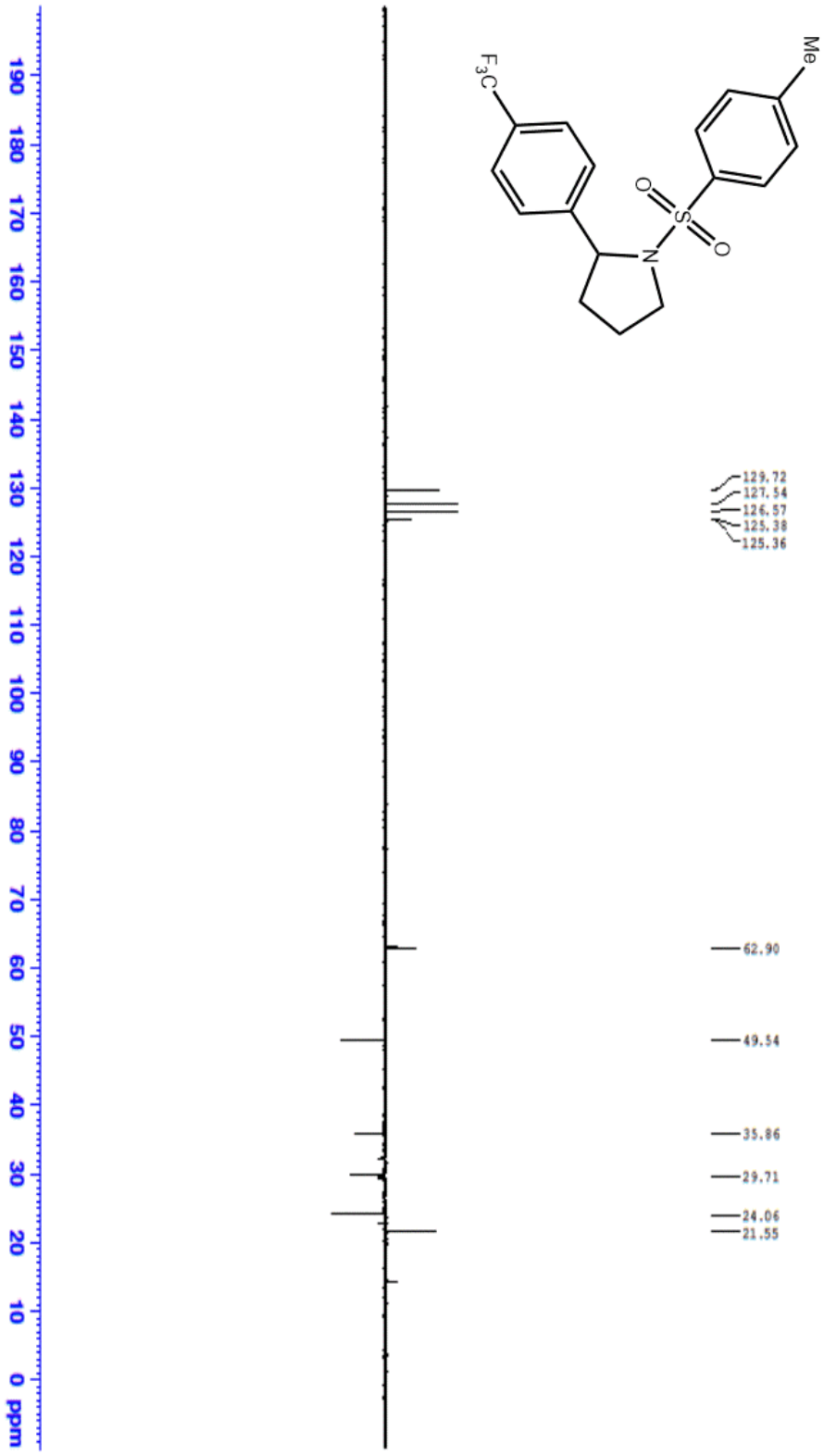
Spectrum 87: ^{1}H NMR spectrum of 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl] pyrrolidine 19a



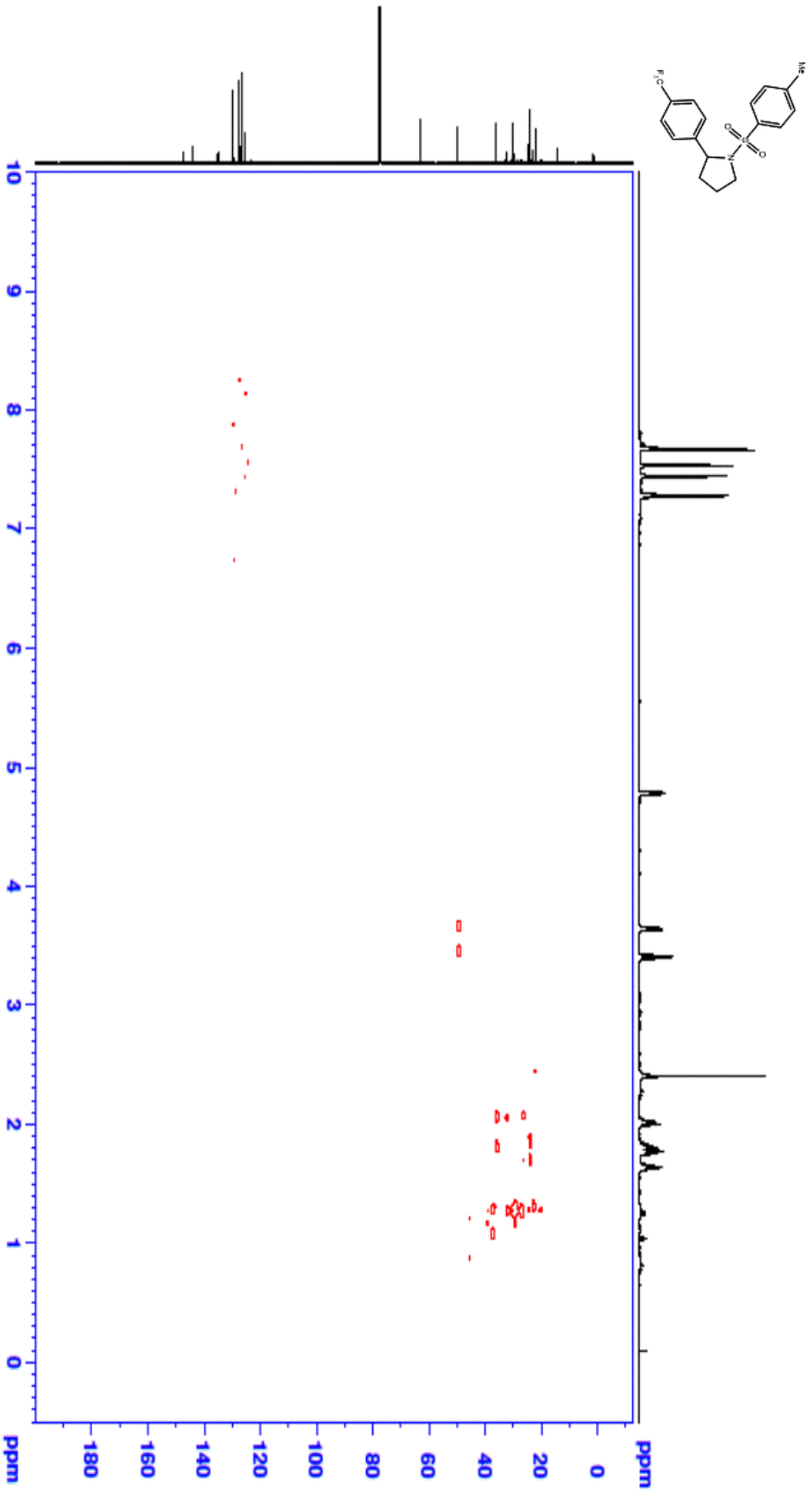
Spectrum 88: COSY NMR spectrum of 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl] pyrrolidine 19a



Spectrum 89:^{13}C NMR spectrum of 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl] pyrrolidine 19a

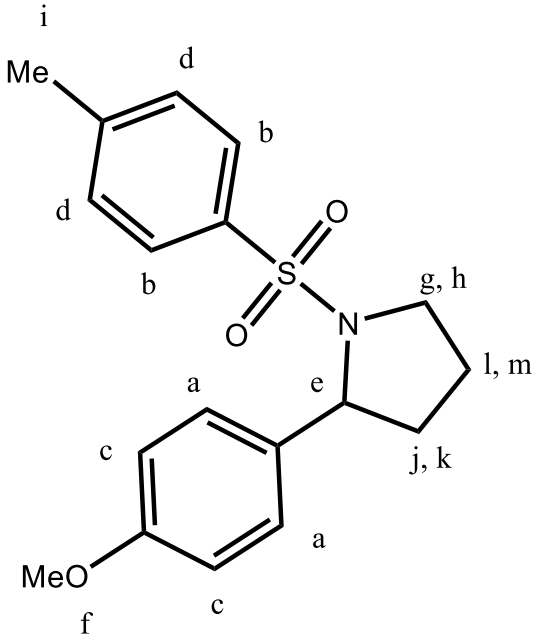


Spectrum 90: DEPT NMR spectrum of 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl] pyrrolidine 19a



Spectrum 91: HSQC NMR spectrum of 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl] pyrrolidine 19a

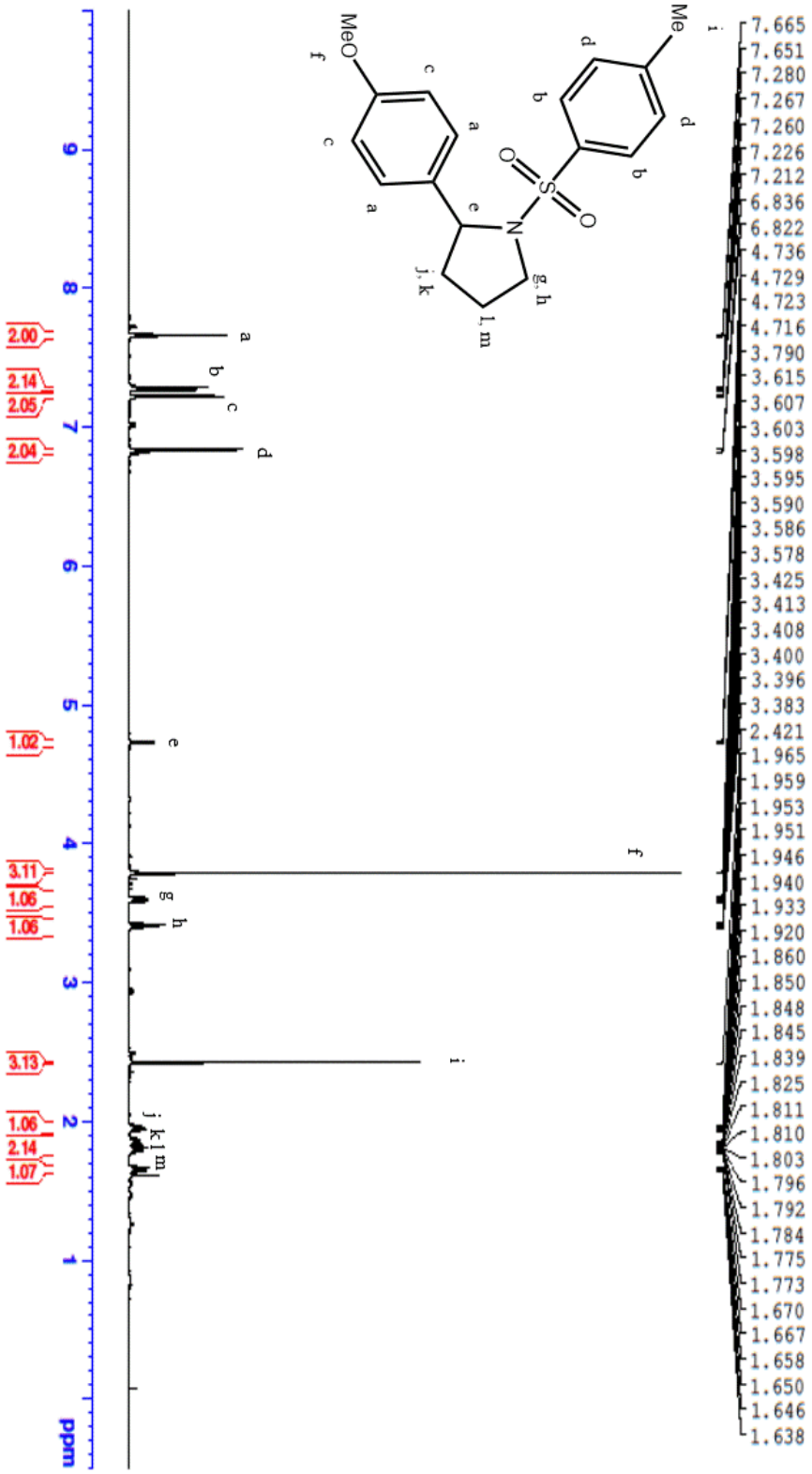
7.3.2. 1-[(4-methylphenyl)sulfonyl] 2-[4-(methoxy] pyrrolidine **19b**



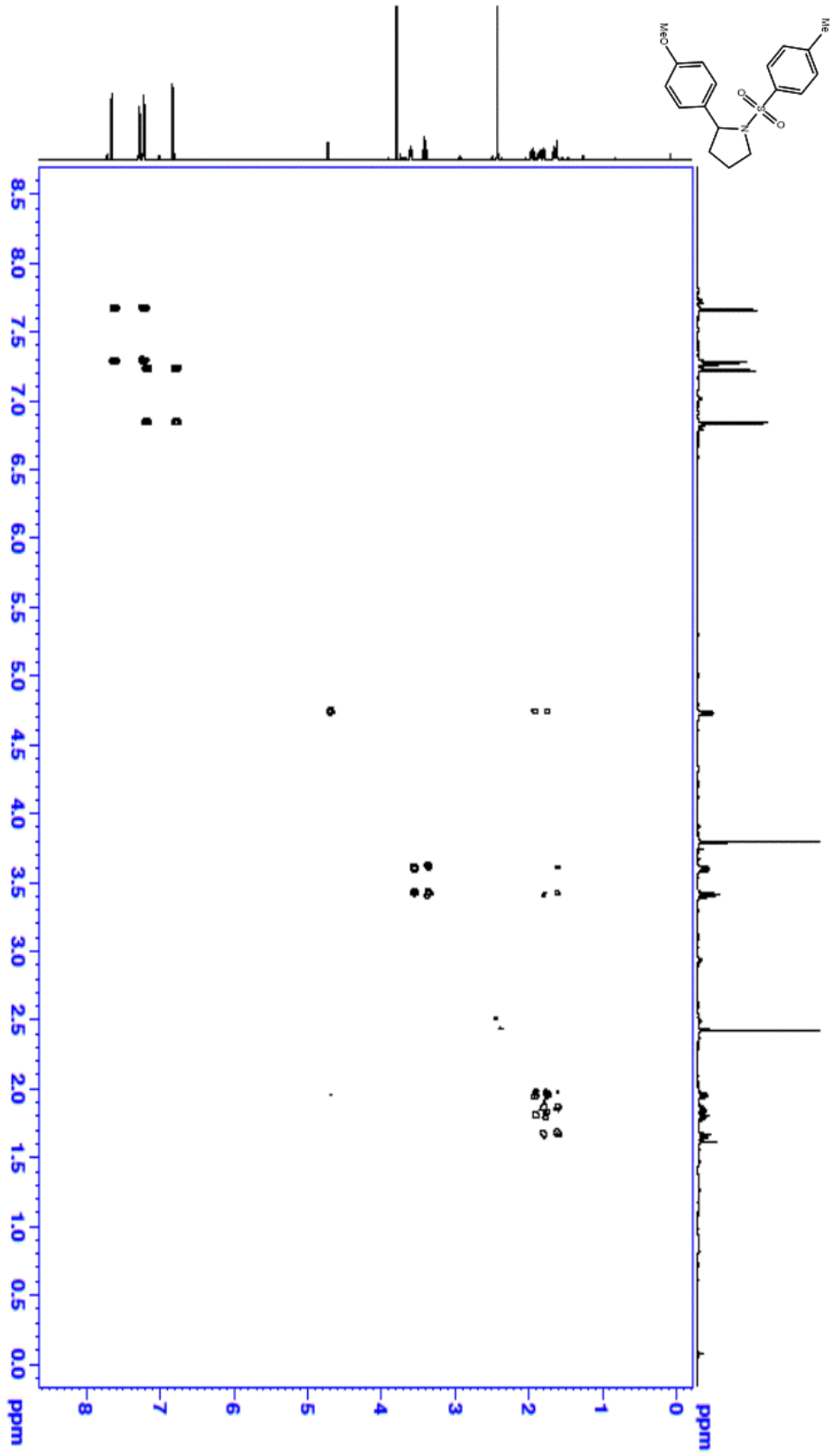
^{1}H NMR ($CDCl_3$) δ 7.66 (d, J= 8.2 Hz, 2H, Ha), 7.27 (d, J= 8 Hz, 2H, Hb), 7.22 (d, J= 8.3 Hz, 2H, Hc), 6.83 (d, J= 8.5 Hz, 2H, Hd), 4.75-4.71 (m, 1H, He), 3.79 (s, 3H, Hf), 3.62-3.57 (m, 1H, Hg), 3.44-3.37 (m, 1H, Hh), 2.42 (s, 3H, Hi), 1.99-1.91 (m, 1H, Hj), 1.90-1.76 (m, 2H, Hk, Hl), 1.68-1.62 (m, 1H, Hl) (**Spectrum 92**)

^{13}C NMR ($CDCl_3$) δ 158.78, 143.30, 135.37, 135.26, 129.64, 127.61, 127.45, 113.81, 62.94, 55.41, 49.42, 35.90, 24.11, 21.63 (**Spectrum 94**)

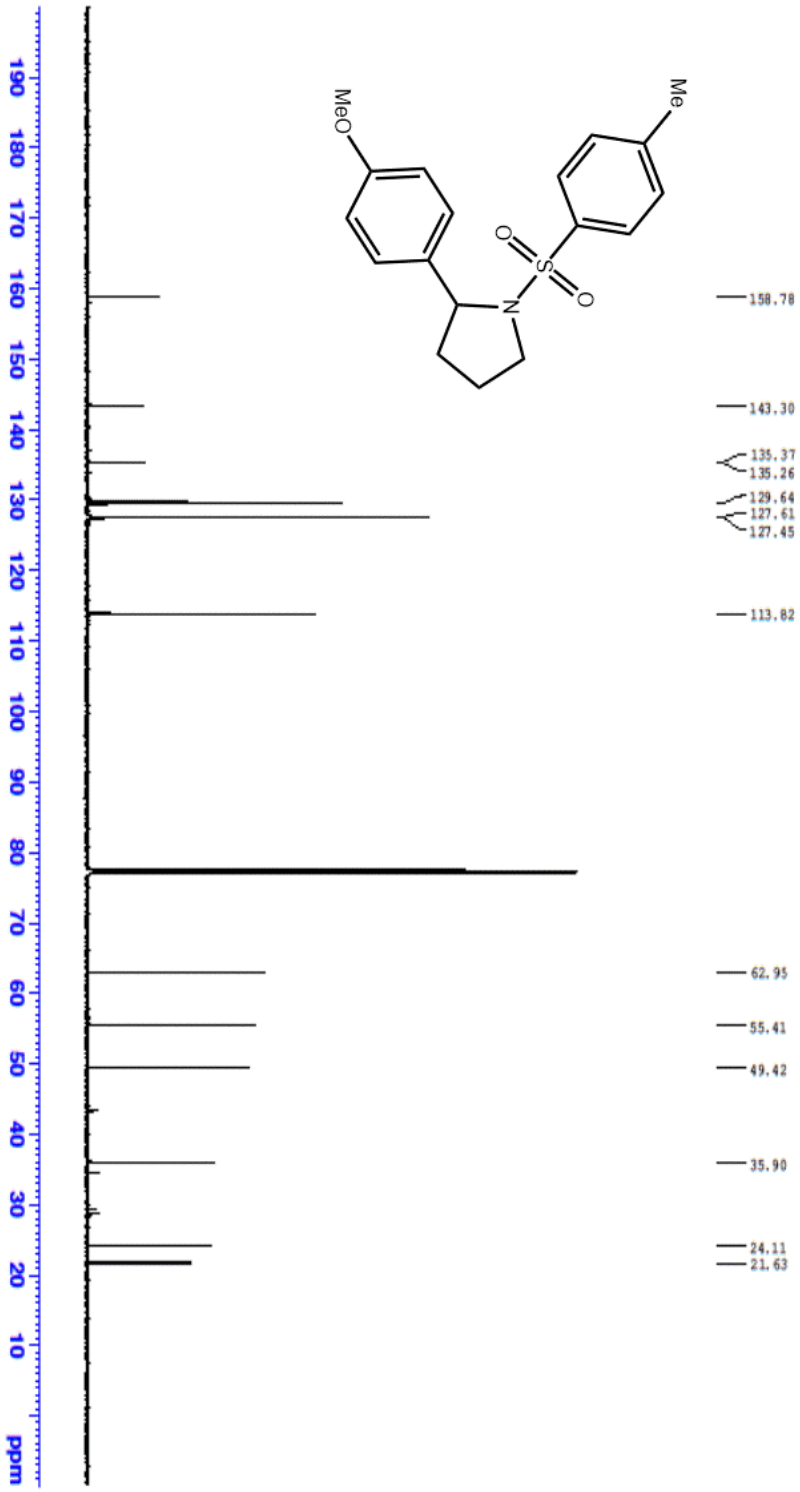
HRMS: $[M+H]^+$ 332.1326 m/z (**Spectrum 96**)



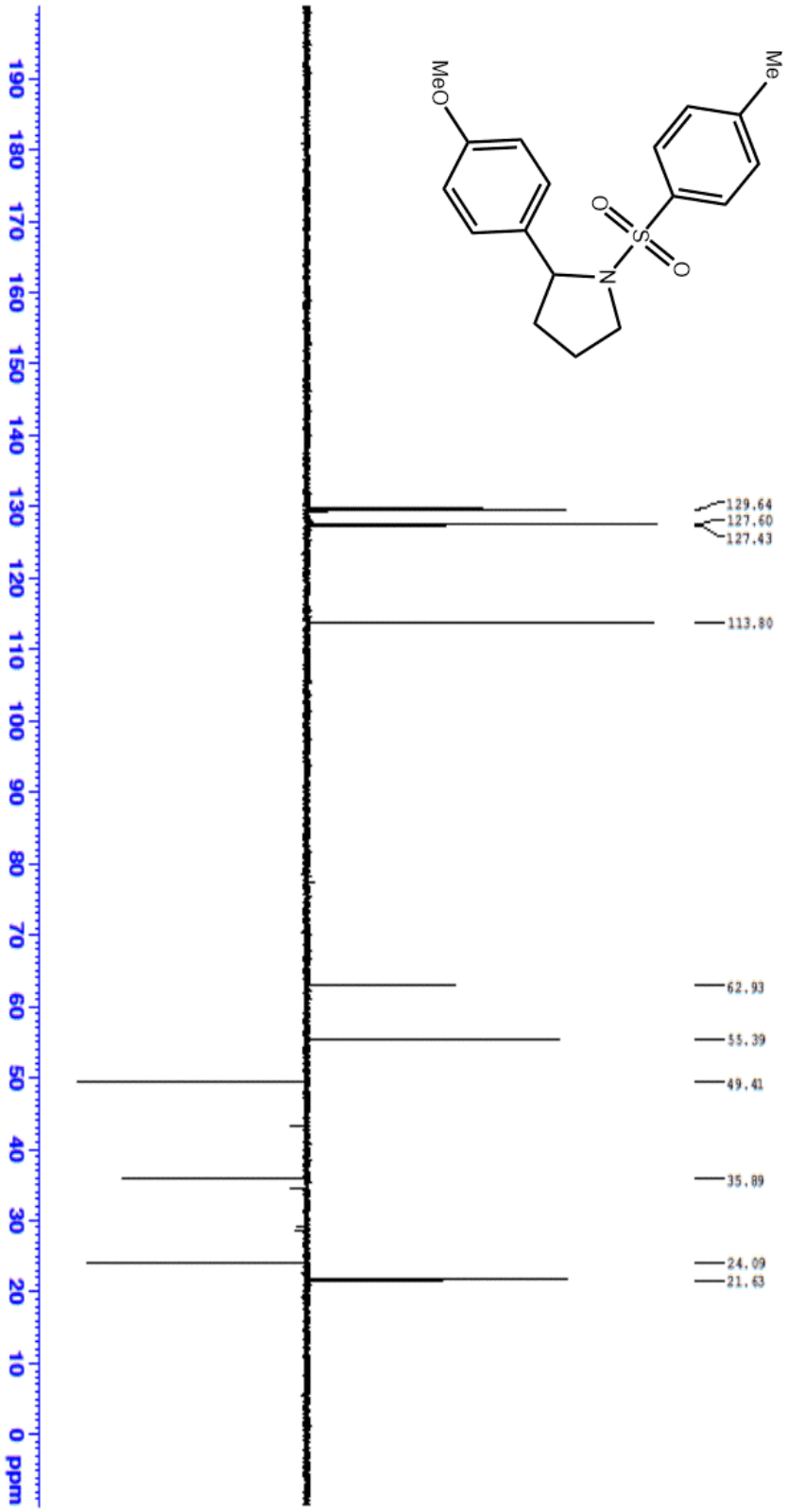
Spectrum 92: ^{1}H NMR spectrum of 1-[(4-methylphenyl)sulfonyl] 2-[4-(methoxy] pyrrolidine 19b



Spectrum 93: COSY NMR spectrum 1-[(4-methylphenyl)sulfonyl] 2-[4-(methoxy] pyrrolidine 19b



Spectrum 94: ^{13}C NMR spectra of 1-[(4-methylphenyl)sulfonyl] 2-[4-(methoxy] pyrrolidine 19b



Spectrum 95: DEPT NMR spectra of 1-[(4-methylphenyl)sulfonyl] 2-[4-(methoxy] pyrrolidine 19b

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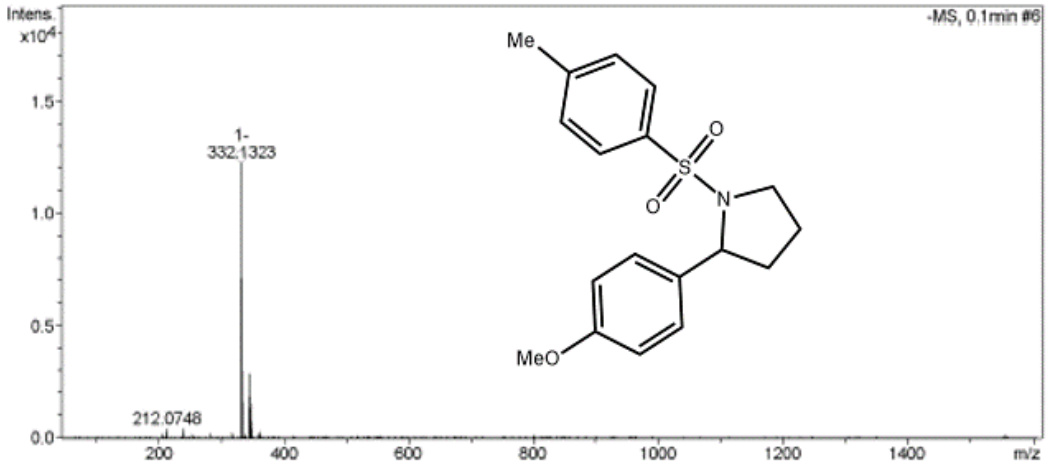
School of Chemistry Mass Spectrometry Unit

Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SOR_34B_RB5_01_32599.d	Acquisition Date	21/03/2023 14:23:33
Sample Description			



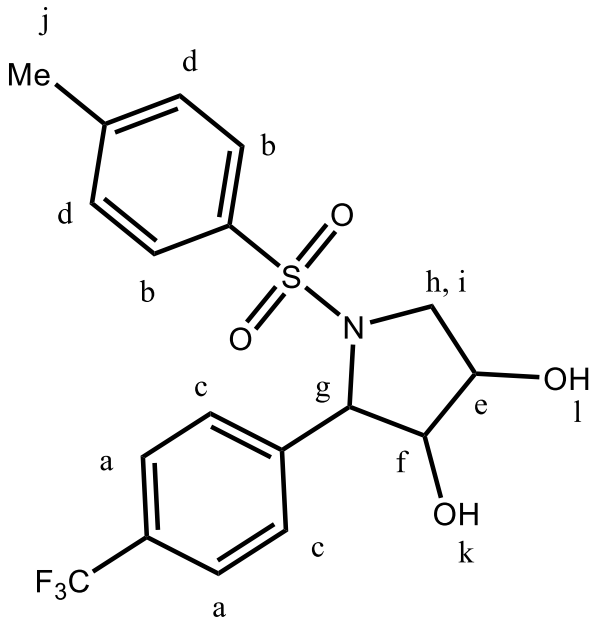
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
332.132344	1	C18H22NO3S	332.132588	0.2	0.7	8.5	ok	even	18.1

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

Spectrum 96: HRMS spectra of 1-[(4-methylphenyl)sulfonyl] 2-[4-(methoxy] pyrrolidine 19b

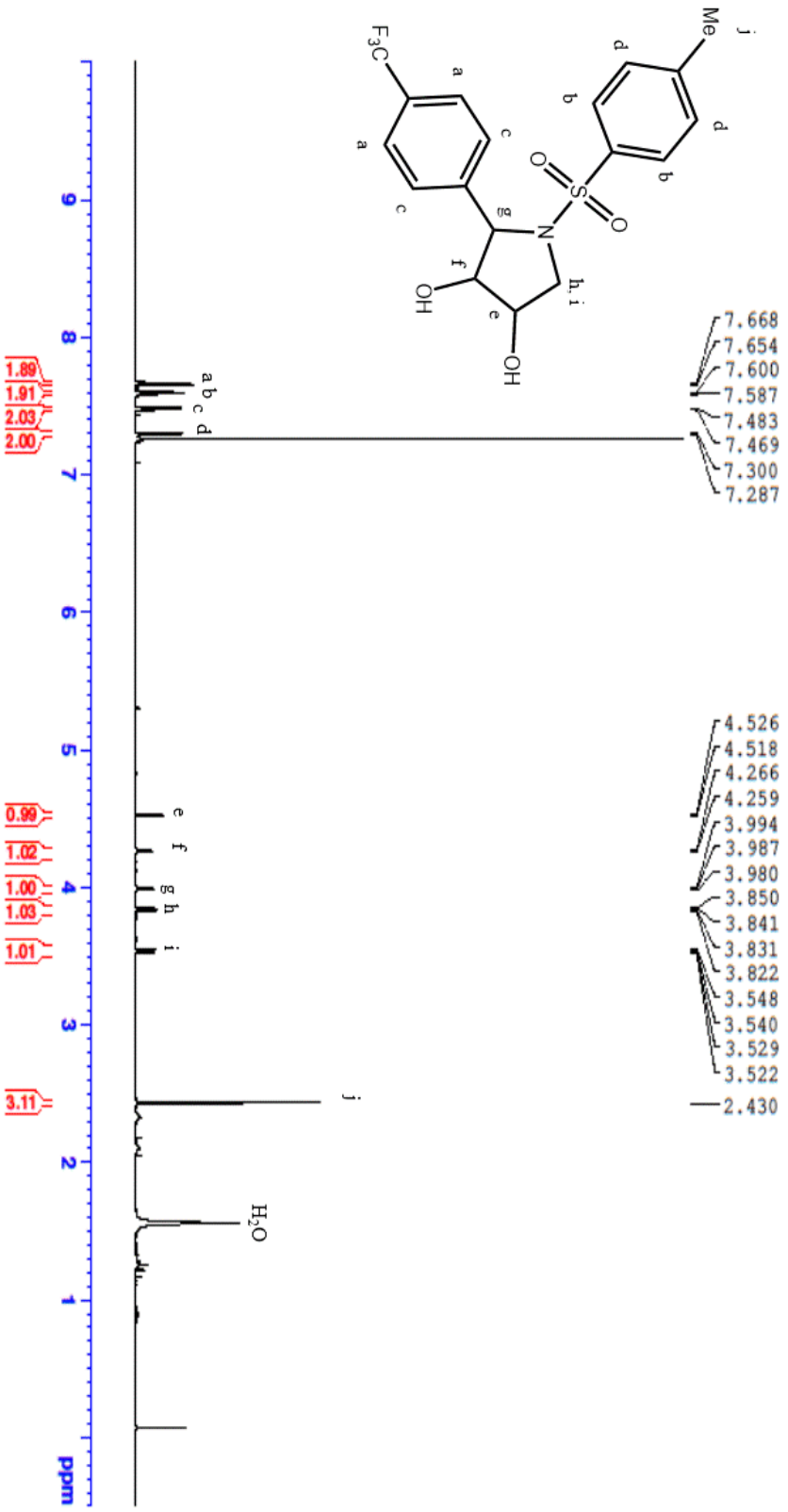
7.3.3. 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl]-3,4-dihydroxypyrrolidine **20a**



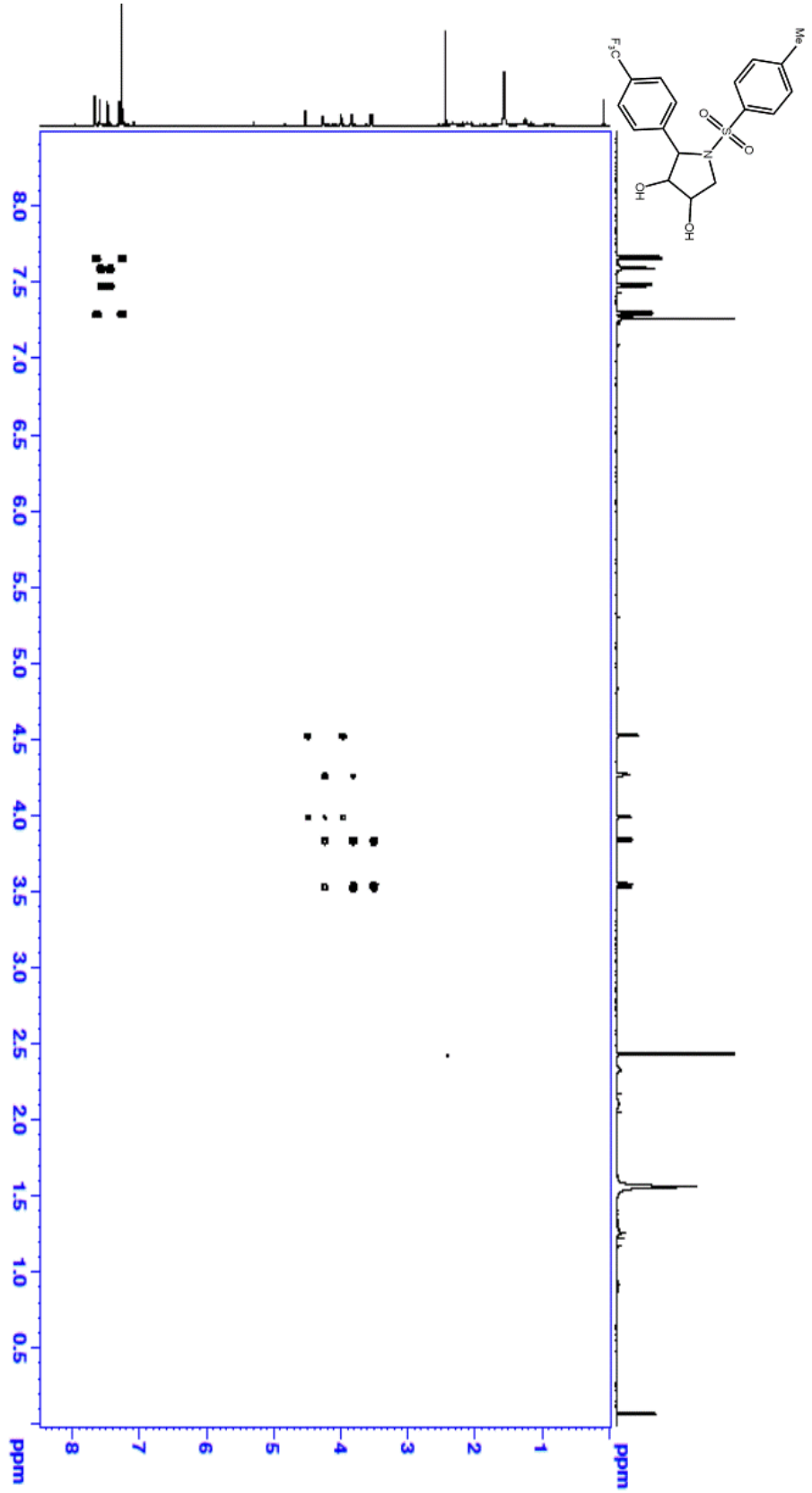
^{1}H NMR ($CDCl_3$) δ 7.66 (d, J= 7.8 Hz, 2H, Ha), 7.59 (d, J= 8.2 Hz, 2H, Hb), 7.48 (d, J= 7.8 Hz, 2H, Hc), 7.29 (d, J= 8.2 Hz, 2H, Hd), 4.52 (d, J= 5 Hz, 1H, He), 4.28-4.24 (m, 1H, Hf), 4.00-3.97 (m, 1H, Hg), 3.84 (dd, J= 11.3, 5 Hz, 1H, Hh), 3.53 (dd, J= 11.3, 4.4 Hz, 1H, Hi), 2.43 (s, 3H, Hj), 2.32 (s, 1H, Hc), 2.10 (s, 1H, Hl) **H_2O:** δ 1.56 (s) (**Spectrum 97**)

^{13}C NMR ($CDCl_3$) δ 129.72, 128.09, 127.01, 125.77, 80.03, 69.90, 67.79, 53.02, 21.72 (**Spectrum 99**)

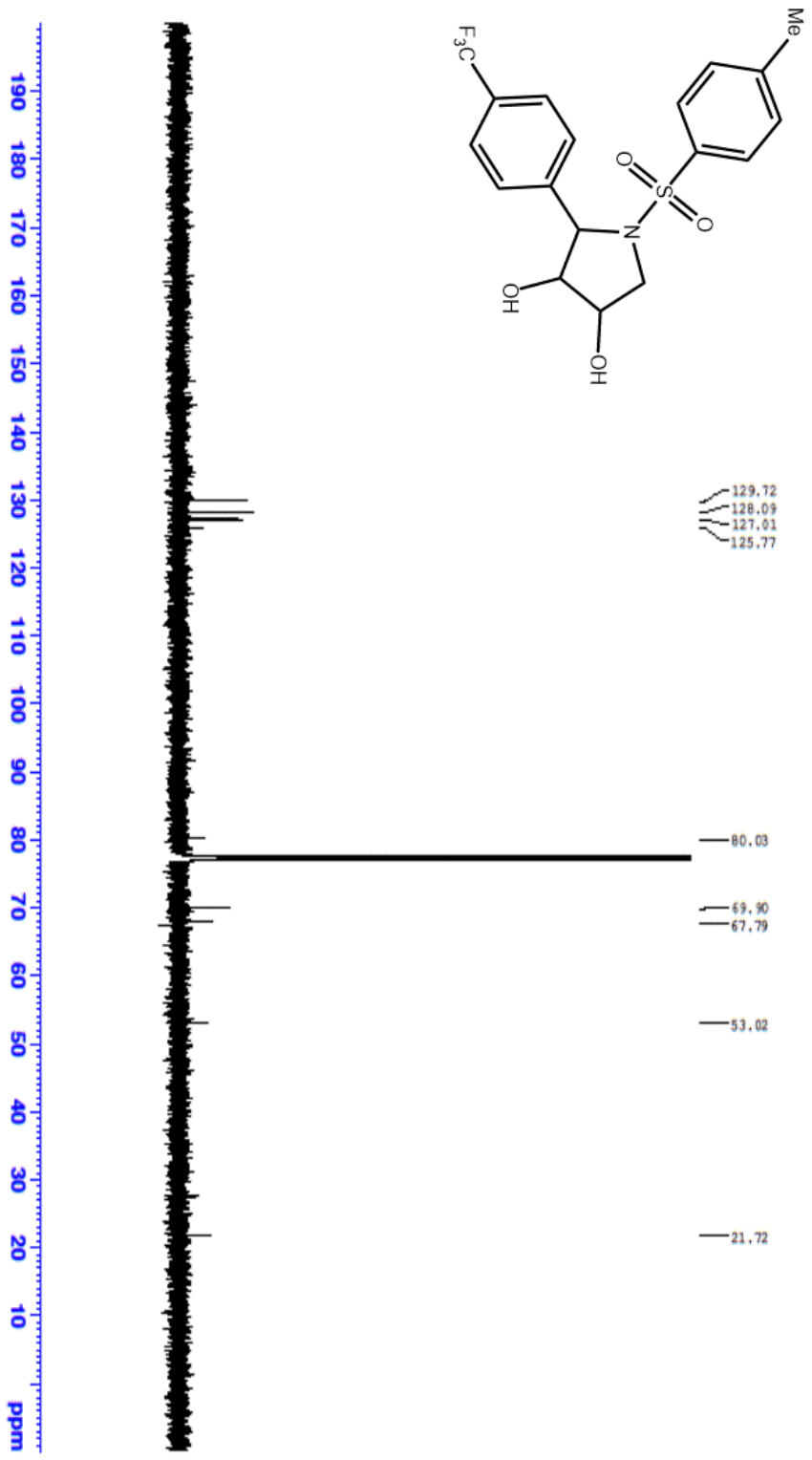
HRMS: $[M+1]^+$ 402.0981 m/z (**Spectrum 101**)



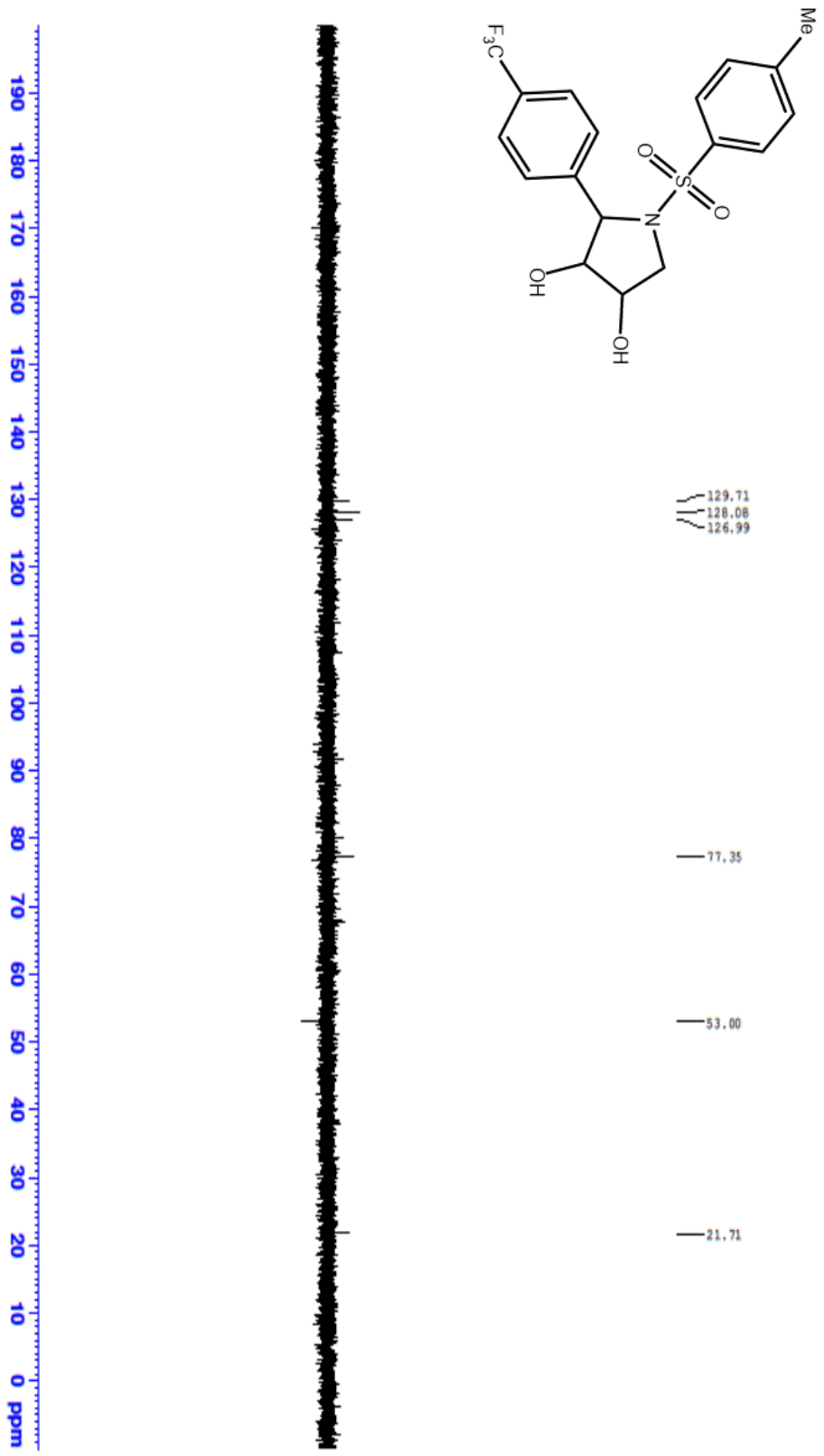
Spectrum 97: ^{1}H NMR spectrum of 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl]-3,4-dihydroxypyrrolidine 20a



Spectrum 98: COSY NMR spectrum of 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl]-3,4-dihydroxypyrrolidine 20a



Spectrum 99: ^{13}C NMR spectrum of 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl]-3,4-dihydroxypyrrolidine 20a



Spectrum 100: DEPT NMR spectrum of 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl]-3,4-dihydroxypyrrolidine 20a

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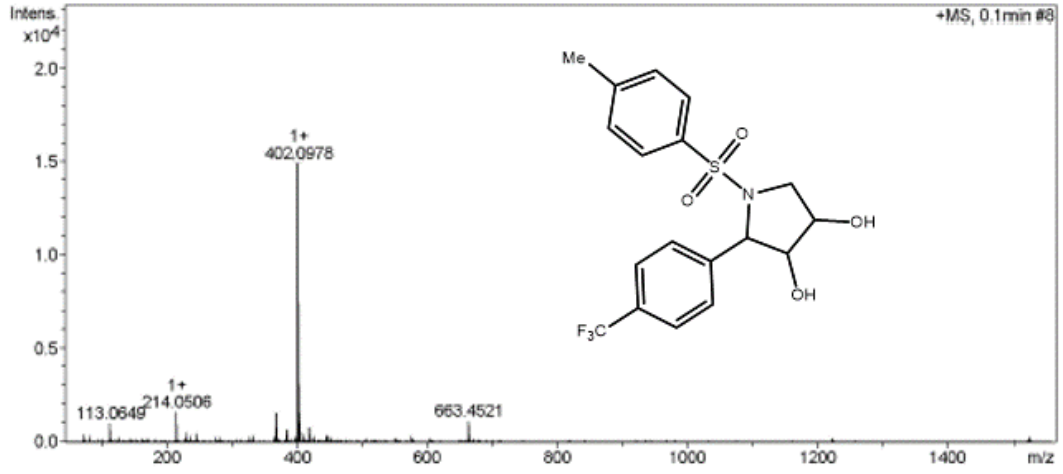
Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SOR_35_RB7_01_32512.d	Acquisition Date	20/03/2023 13:48:14
Sample Description			



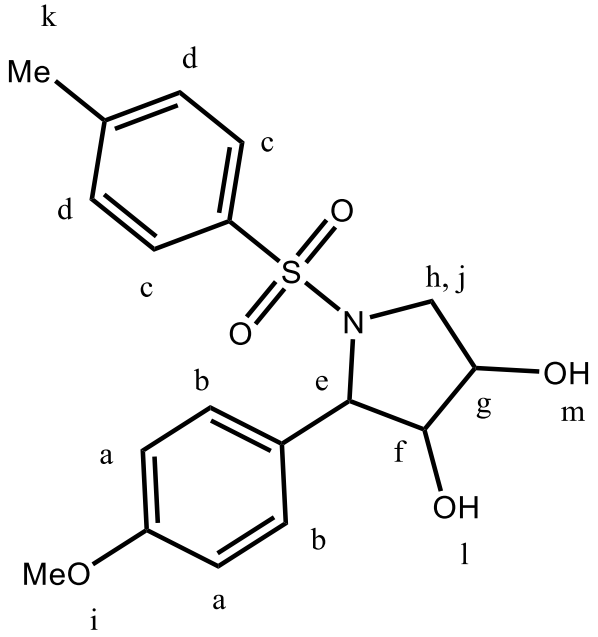
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
402.097754	1	C18H19F3NO4S	402.098140	-0.4	-1.0	8.5	ok	even	3.5

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

Spectrum 101: HRMS spectrum of 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl]-3,4-dihydroxypyrrolidine 20a

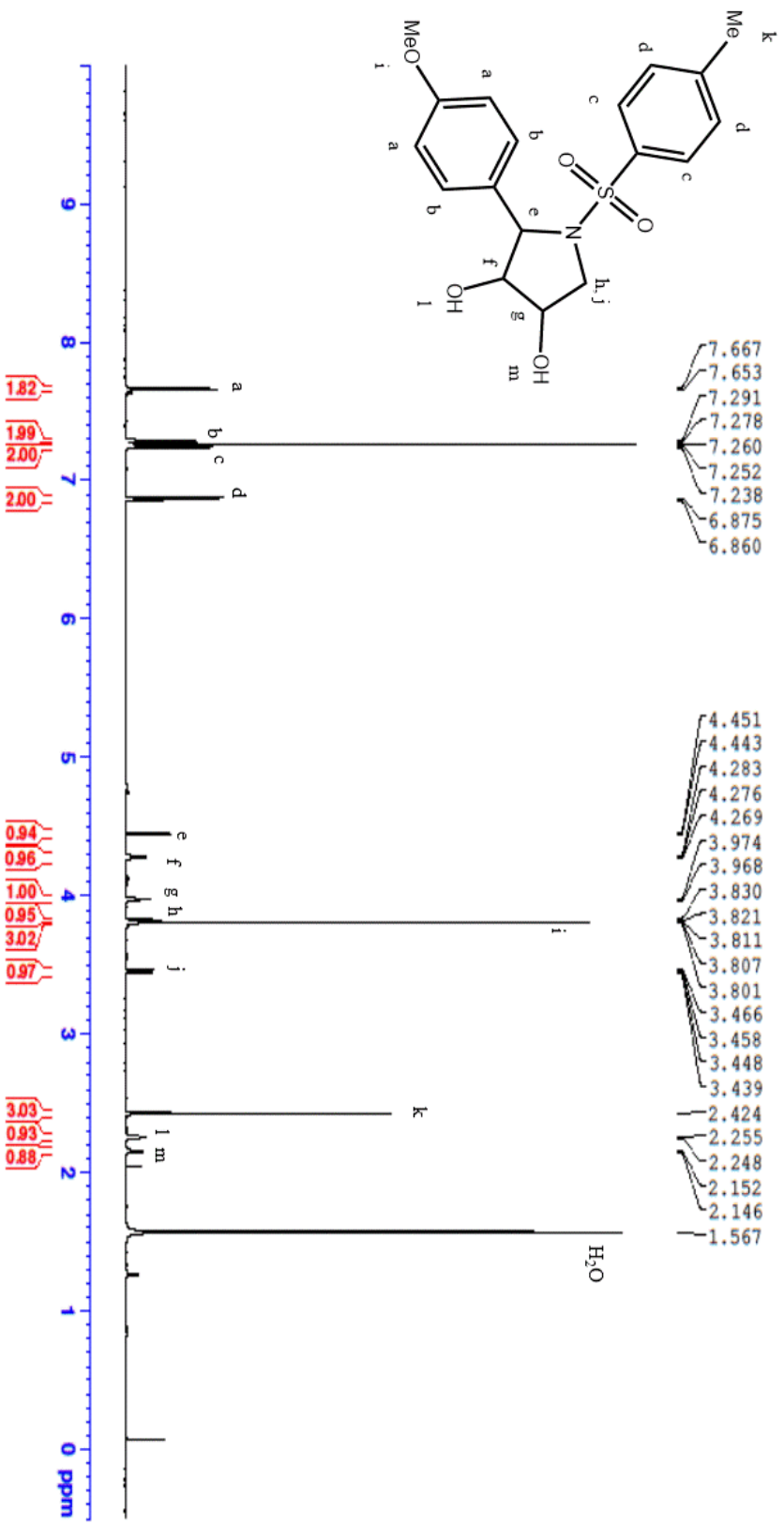
7.3.4. 1-(4-methylphenyl)sulfonyl] 2-[4-(methoxy]-3,4-dihydroxypyrrolidine **20b**



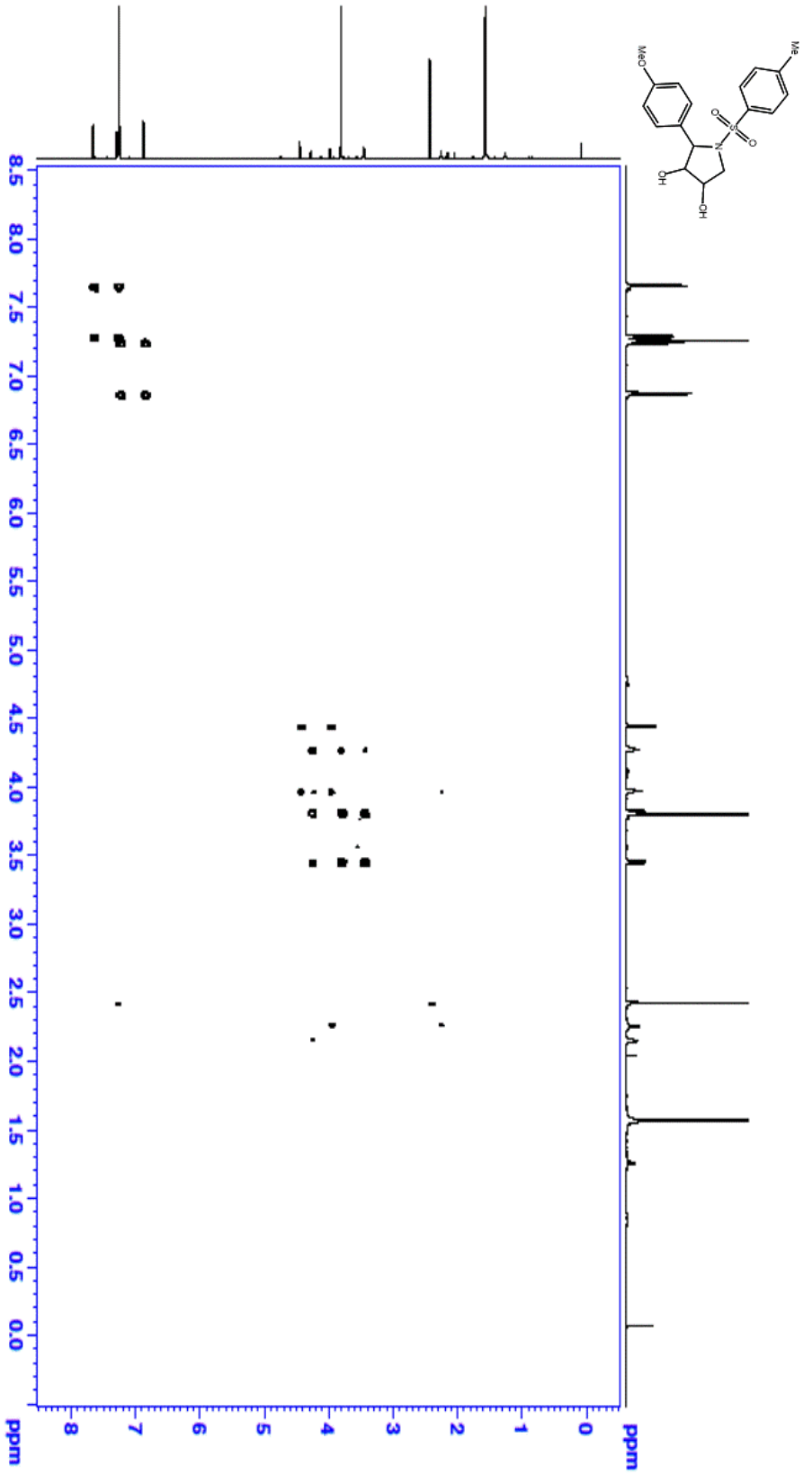
^{1}H NMR ($CDCl_3$) δ 7.66 (d, J= 8 Hz, 2H, Ha), 7.28 (d, J= 8 Hz, 2H, Hb), 7.25 (d, J= 8.3 Hz, 2H, 2H, Hc), 6.87 (d, J= 8.3 Hz, 2H, Hd), 4.45 (d, J= 4.4 Hz, 1H, He), 4.30-4.25 (m, 1H, Hf), 3.99-3.95 (m, 1H, Hg), 3.84-3.80 (m, 1H, Hh), 3.80 (s, 3H, Hi), 3.45 (d, J= 5 Hz, 1H, Hj), 2.24 (s, 3H, Hk), 2.25 (d, J= 4.4 Hz, Hl), 2.15 (d, J= 4.4 Hz, Hm). **H_2O:** 1.57 (s) (**Spectrum 102**)

^{13}C NMR ($CDCl_3$) δ 159.38, 143.73, 134.27, 131.36, 129.59, 128.04, 127.82, 114.20, 79.81, 69.54, 68.00, 55.46, 52.80, 21.71 (**Spectrum 104**)

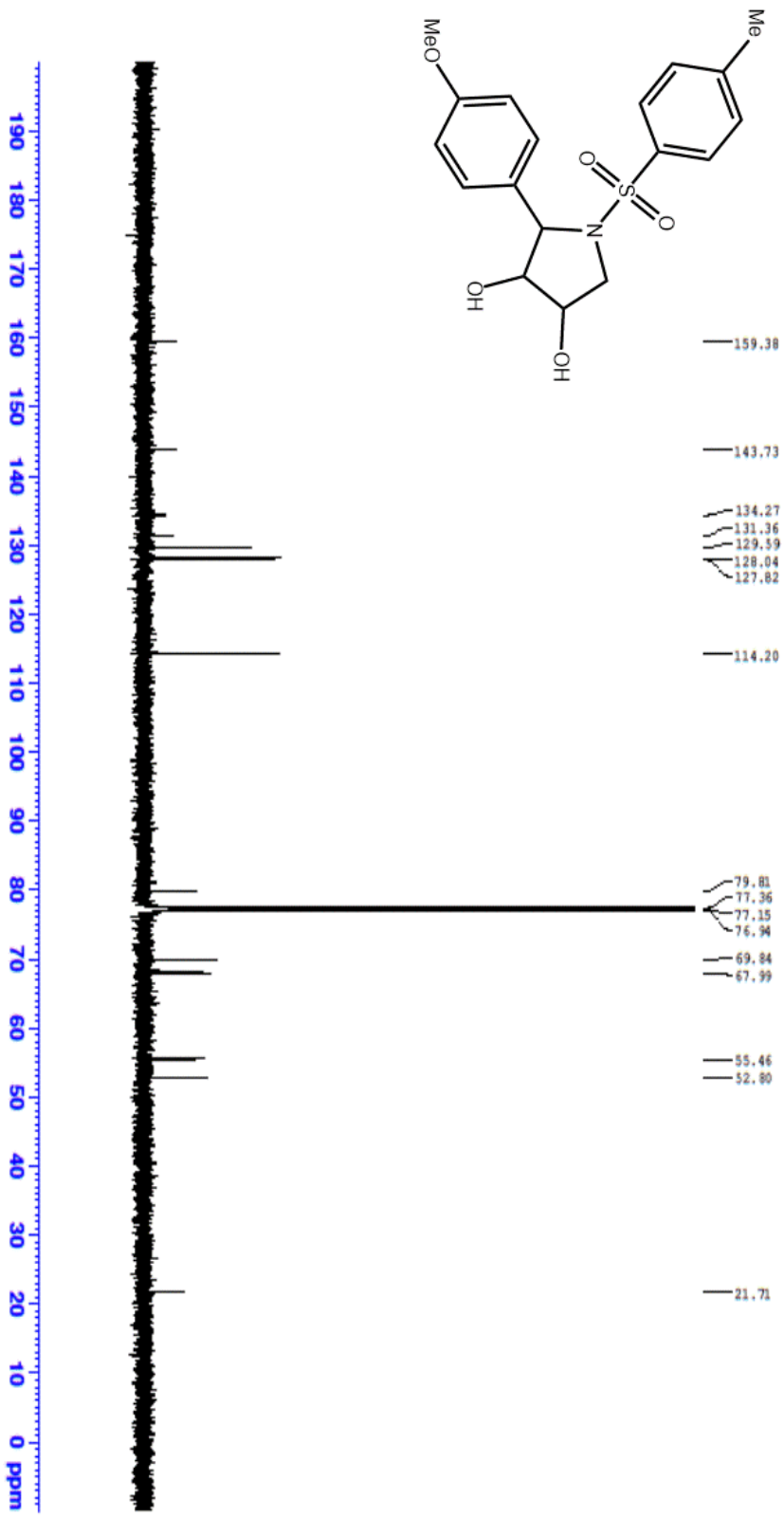
HRMS: $[M-H]^+$ 362.1068 m/z (**Spectrum 106**)



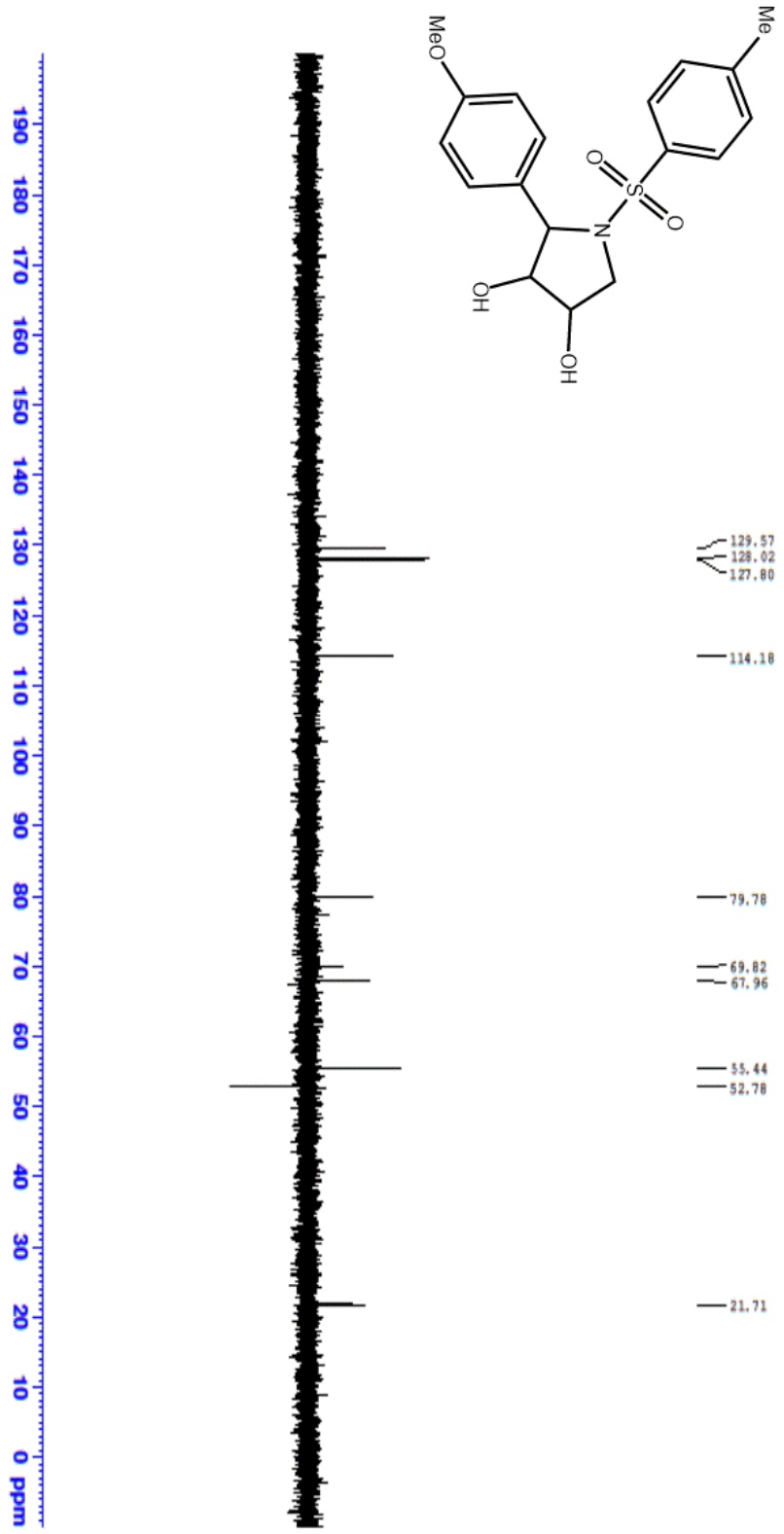
Spectrum 102: ^{1}H NMR spectrum of [(4-methylphenyl)sulfonyl] 2-[4-(methoxy]-3,4-dihydroxypyrrolidine 20b



Spectrum 103: COSY NMR spectrum of [(4-methylphenyl)sulfonyl] 2-[4-(methoxy]-3,4-dihydroxypyrrolidine 20b



Spectrum 104: ^{13}C NMR spectrum of [(4-methylphenyl)sulfonyl] 2-[4-(methoxy]-3,4-dihydroxypyrrolidine 20b



Spectrum 105: DEPT NMR spectrum of [(4-methylphenyl)sulfonyl] 2-[4-(methoxy]-3,4-dihydroxypyrrolidine 20b

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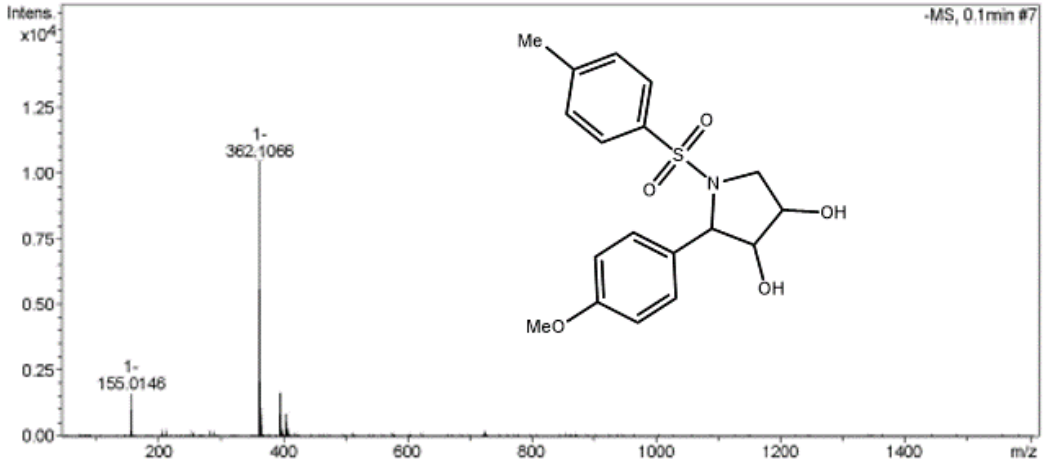
Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SOR_20B_RA7_01_32593.d	Acquisition Date	21/03/2023 14:04:07
Sample Description			



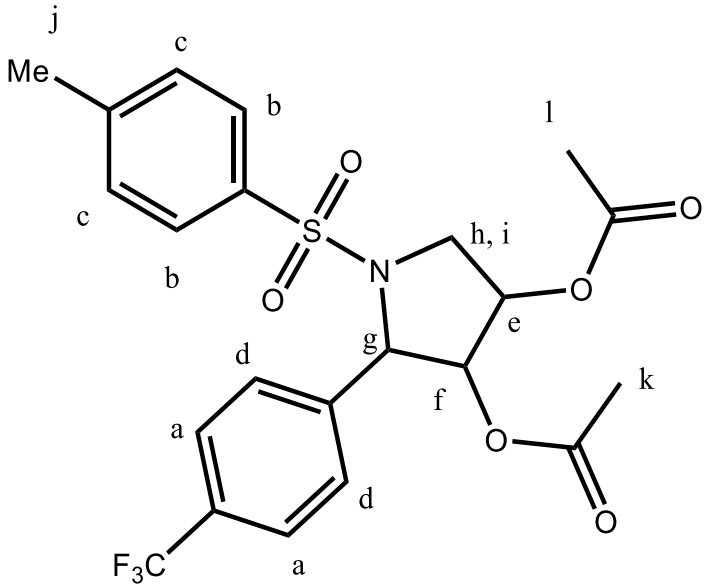
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
362.106556	1	C18H20NO5S	362.106767	0.2	0.6	9.5	ok	even	5.8

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

Spectrum 106: HRMS spectrum of [(4-methylphenyl)sulfonyl] 2-[4-(methoxy]-3,4-dihydroxypyrrolidine 20b

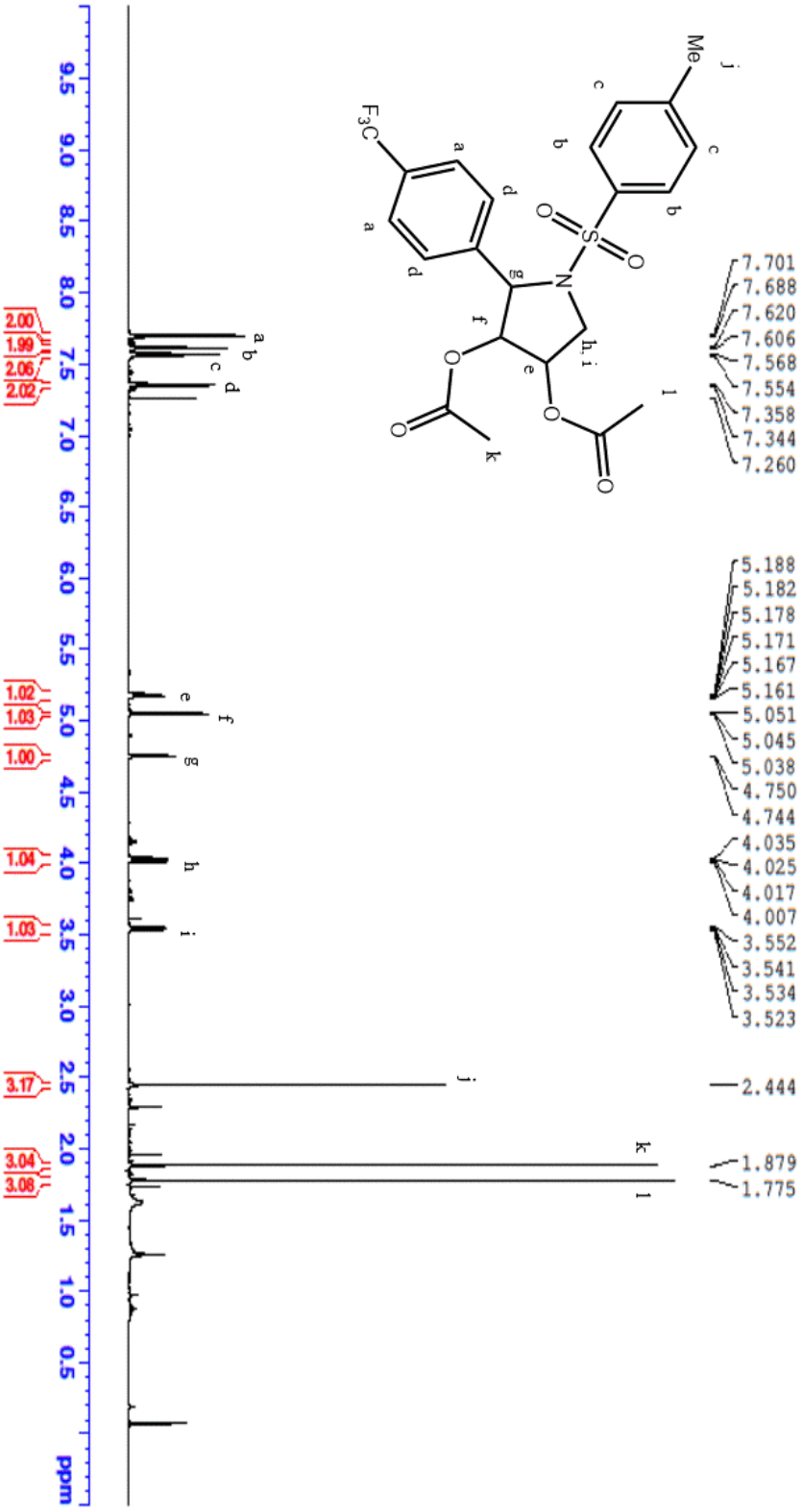
7.3.5. 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl)]-3,4-pyrrolidinedione, 3, 4 diacetate **21a**



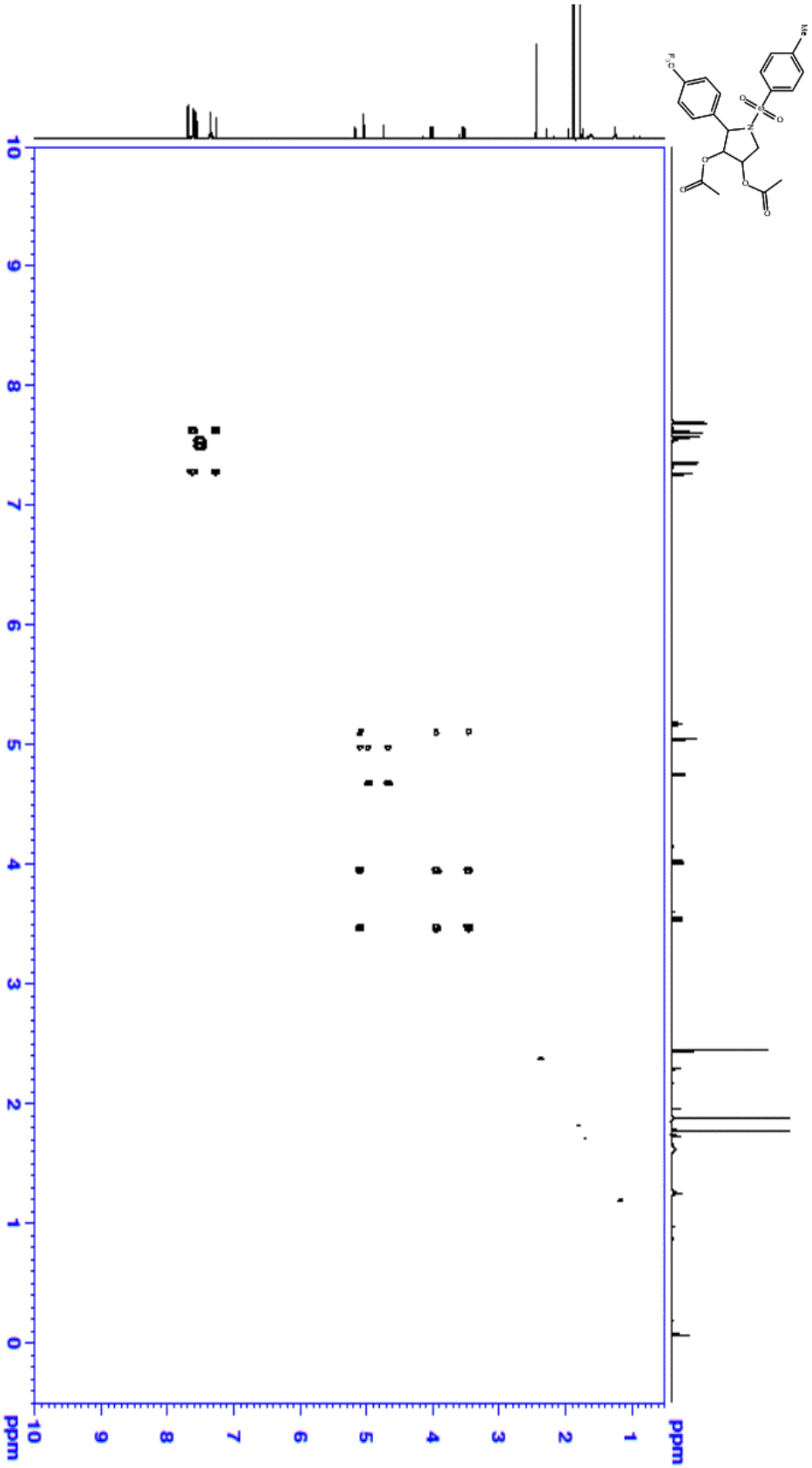
^{1}H NMR ($CDCl_3$) δ 7.69 (d, J= 8.3 Hz, 2H, Ha), 7.61 (d, J= 8.3 Hz, 2H, Hb), 7.56 (d, J= 8.3Hz, 2H, Hc), 7.35 (d, J= 8.3 Hz, 2H, Hd), 5.19-5.15 (m, 1H, He), 5.04 (t, J= 3.9 Hz, 1H, Hf), 4.75 (d, J= 3.9 Hz, 1H, Hg), 4.02 (dd, J= 10.5, 5.9 Hz, 1H, Hh), 3.54 (dd, J= 10.5, 3.5 Hz, 1H, Hi), 2.44 (s, 3H, Hj), 1.88 (s, 3H, Hk), 1.78 (s, 3H, Hl) (**Spectrum 107**)

^{13}C NMR ($CDCl_3$) δ 169.79, 169.69, 144.24, 142.07, 133.89, 129.87, 128.87, 128.05, 127.01, 125.90-125.85, 78.06, 69.10, 65.83, 50.14, 21.61, 20.50, 20.45 (**Spectrum 109**)

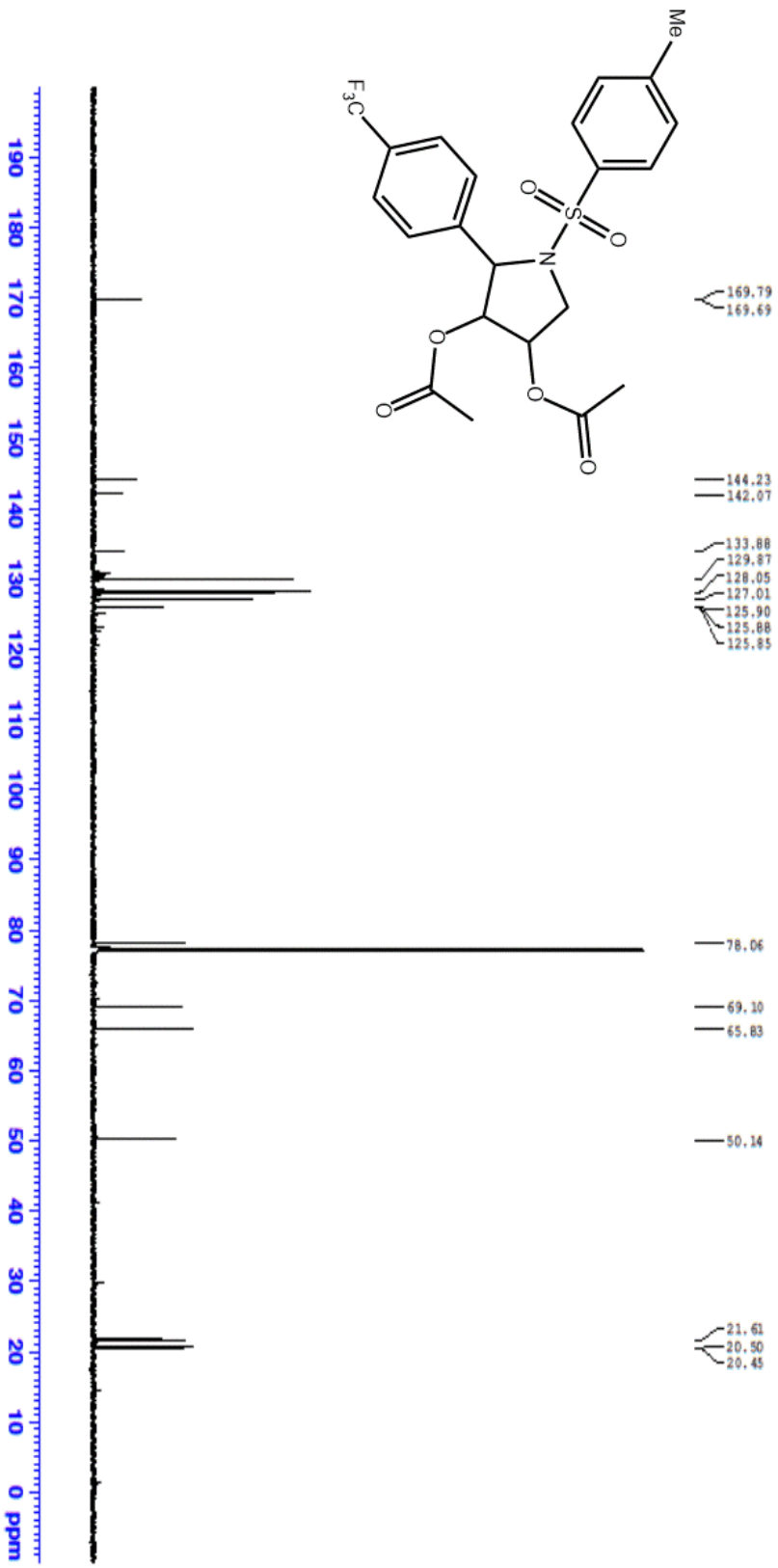
HRMS: $[M+H]^+$ 486.1193 m/z (**Spectrum 111**)



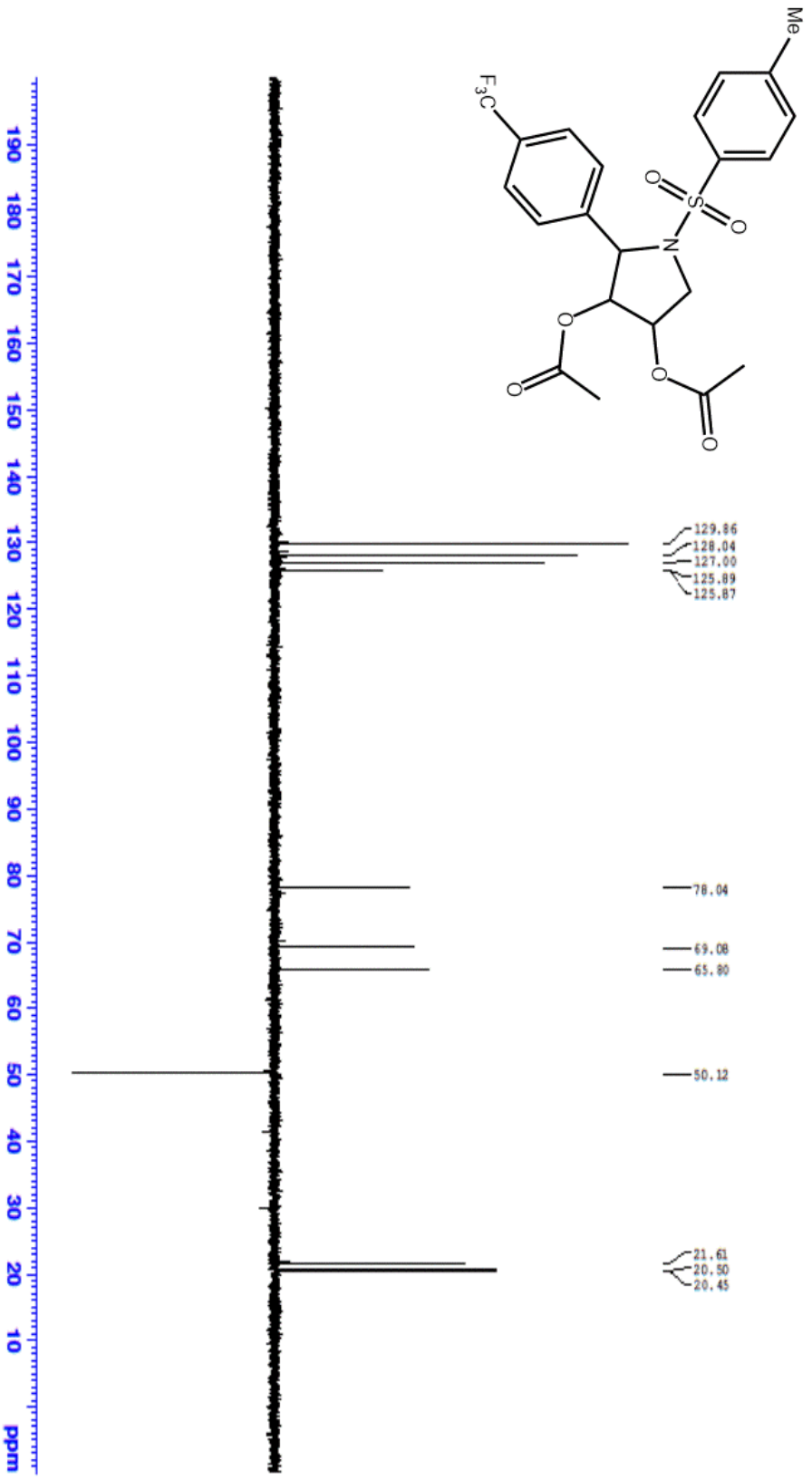
Spectrum 107: ^{1}H NMR spectrum of 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl)]-3,4-pyrrolidinedione, 3, 4 diacetate 21a



Spectrum 108: COSY NMR spectrum of 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl)]-3,4-pyrrolidinedione, 3, 4 diacetate 21a



Spectrum 109: ^{13}C NMR spectrum of 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl)]-3,4-pyrrolidinedione, 3, 4 diacetate 21a



Spectrum 110: DEPT NMR spectrum of 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl)]-3,4-pyrrolidinedione, 3, 4 diacetate 21a

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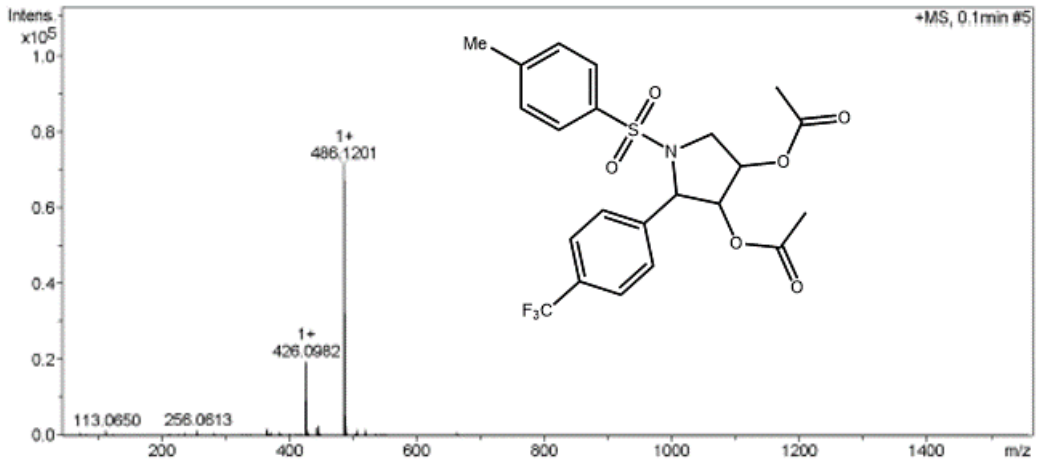
Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SOR_46_RD1_01_32522.d	Acquisition Date	20/03/2023 14:20:36
Sample Description			



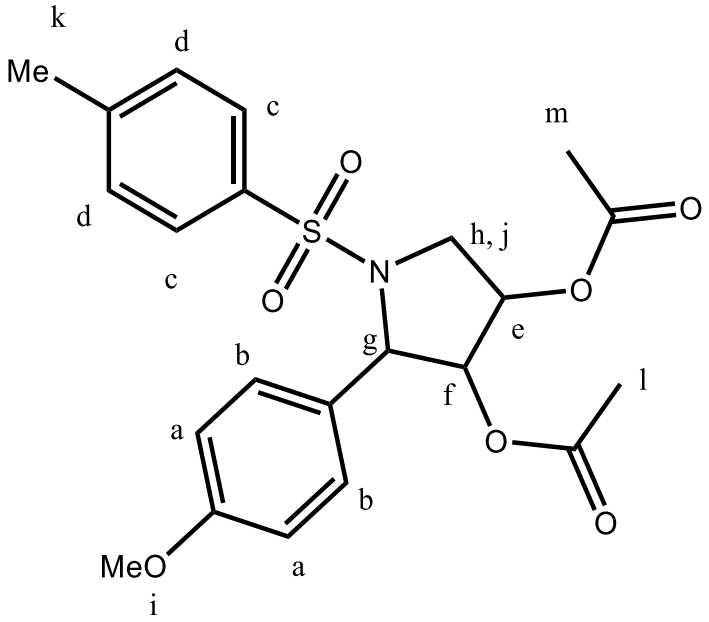
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
486.120107	1	C22H23F3NO6S	486.119270	-0.8	-1.7	10.5	ok	even	12.2

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

Spectrum 111: HRMS spectrum of 1-[(4-methylphenyl)sulfonyl] 2-[4-(trifluoromethyl)]-3,4-pyrrolidinedione, 3, 4 diacetate 21a

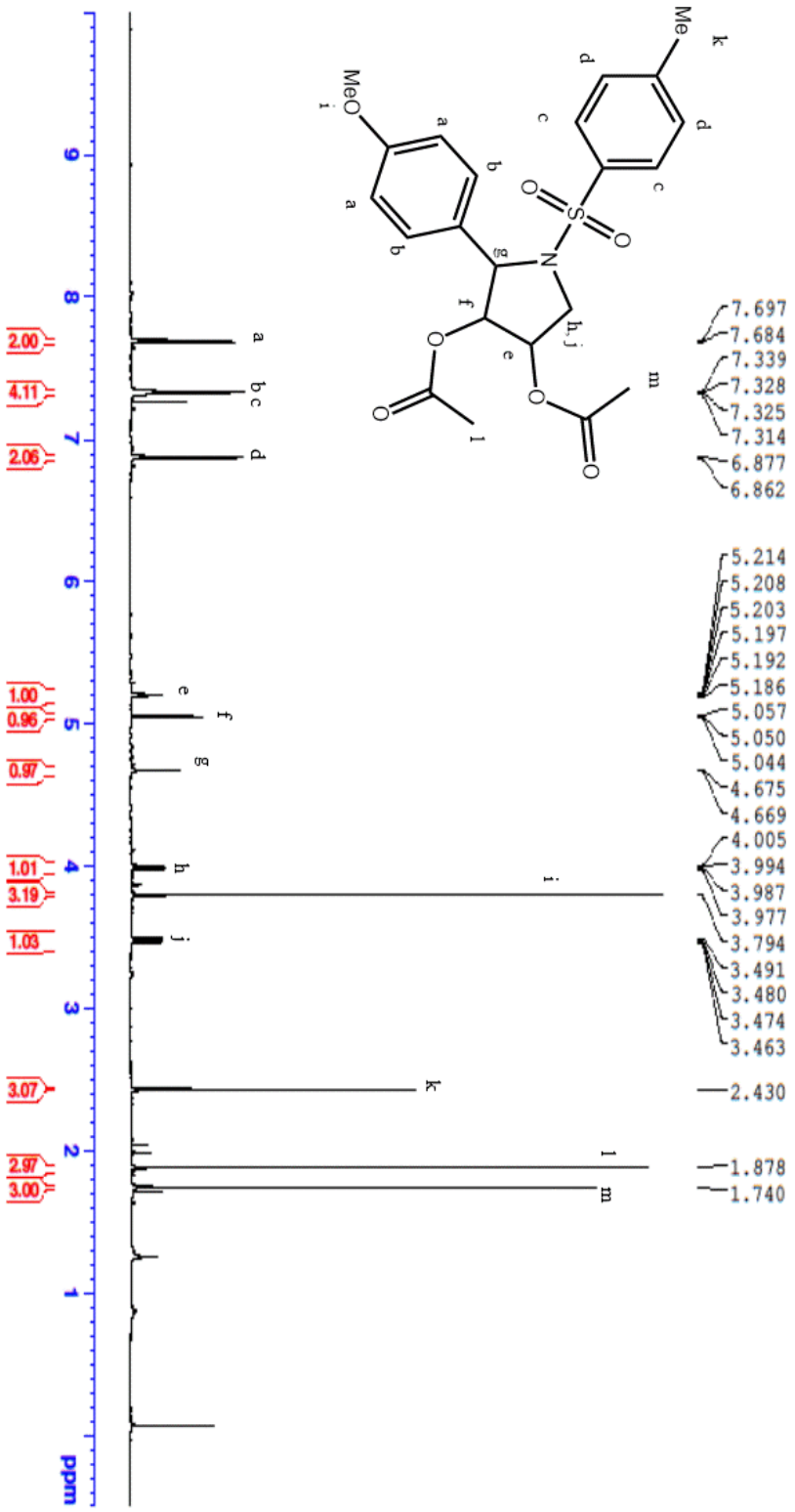
7.3.6. 1-[(4-methylphenyl)sulfonyl] 2-[4-(methoxy)]-3,4-pyrrolidinedione, 3, 4 diacetate **21b**



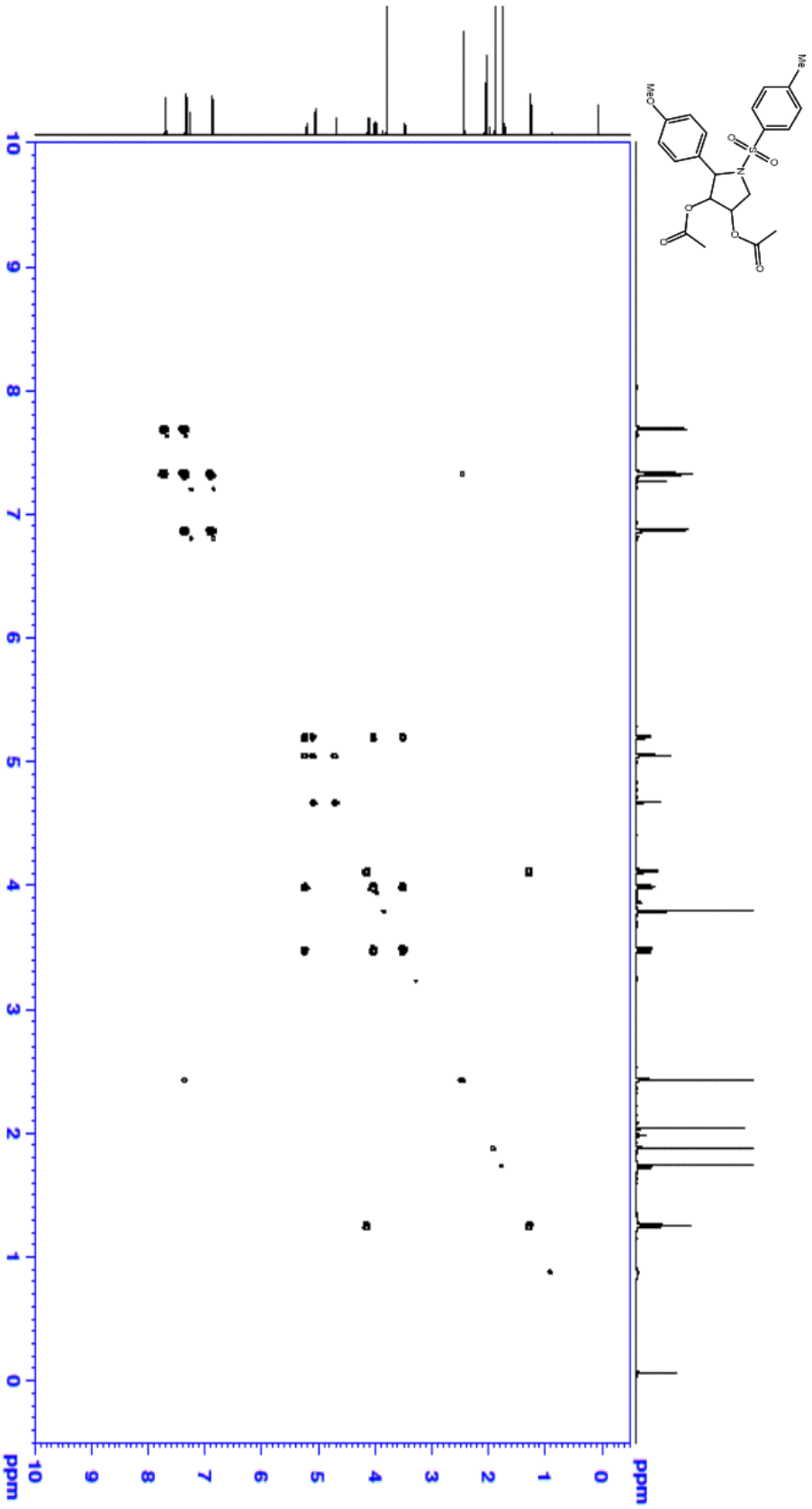
^{1}H NMR ($CDCl_3$) δ 7.69 (d, J= 8.2 Hz, 2H, Ha), 7.34 (m, 4H, Hb, Hc), 6.87 (d, J= 8.6 Hz, Hd), 5.23-5.18 (m, 1H, He), 5.06-5.03 (m, 1H, Hf), 4.68-4.66 (m, 1H, Hg), 4.01-3.97 (m, 1H, Hh), 3.79 (s, 3H, Hi), 3.50-3.46 (m, 1H, Hj), 2.43 (s, 3H, Hk), 1.87 (s, 3H, Hl), 1.74 (s, 3H, Hm). (**Spectrum 112)**

^{13}C NMR ($CDCl_3$) δ 169.83, 169.75, 159.55, 143.80, 134.33, 129.86, 129.71, 128.00, 127.72, 114.26, 78.18, 69.25, 65.95, 55.43, 49.90, 21.60, 20.54, 20.49. **EtOAc:** 171.28, 60.51, 21.16, 14.31 (**Spectrum 114**)

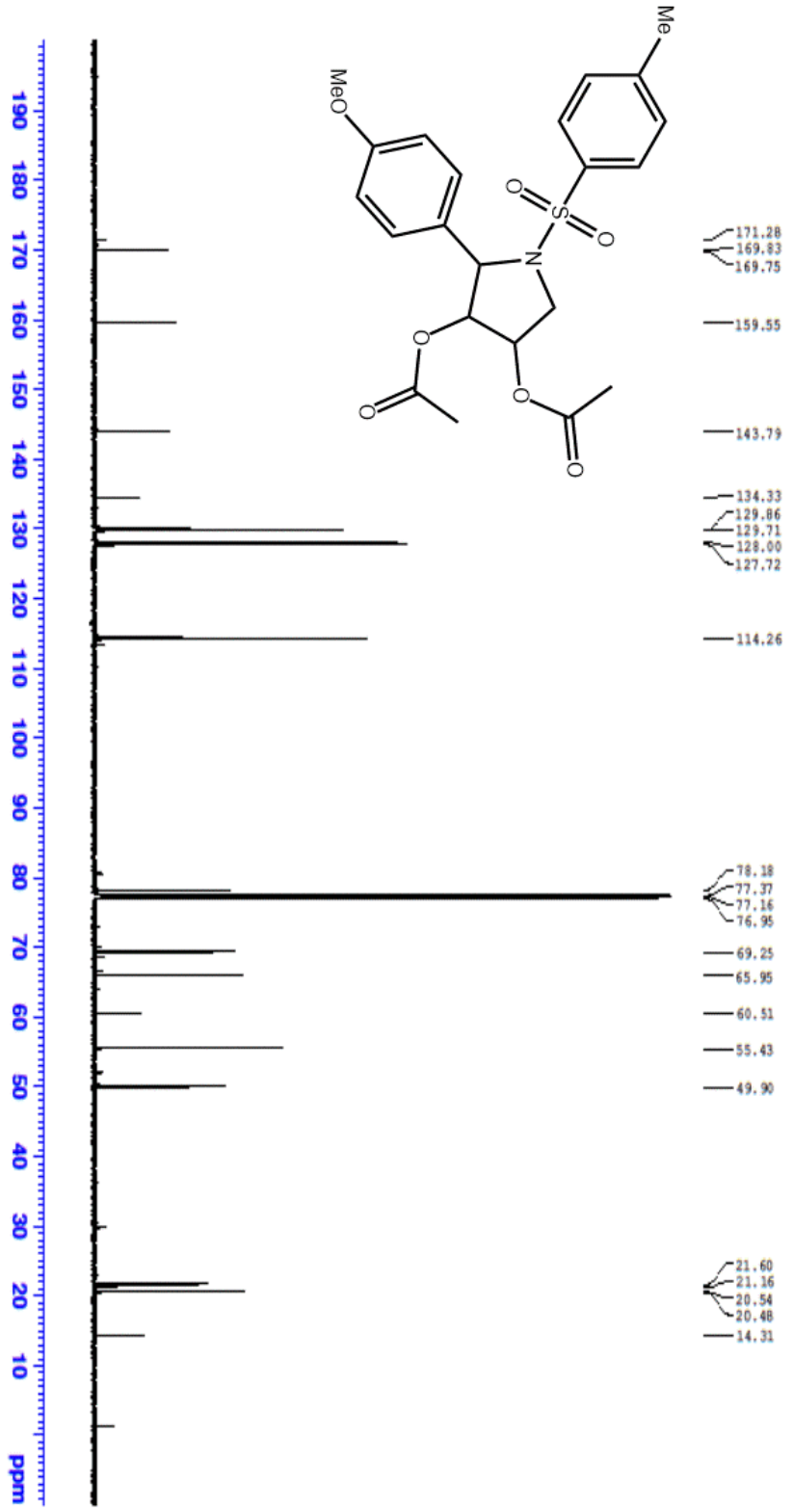
HRMS: $[M+H]^+$ 448.1425 m/z (**Spectrum 116**)



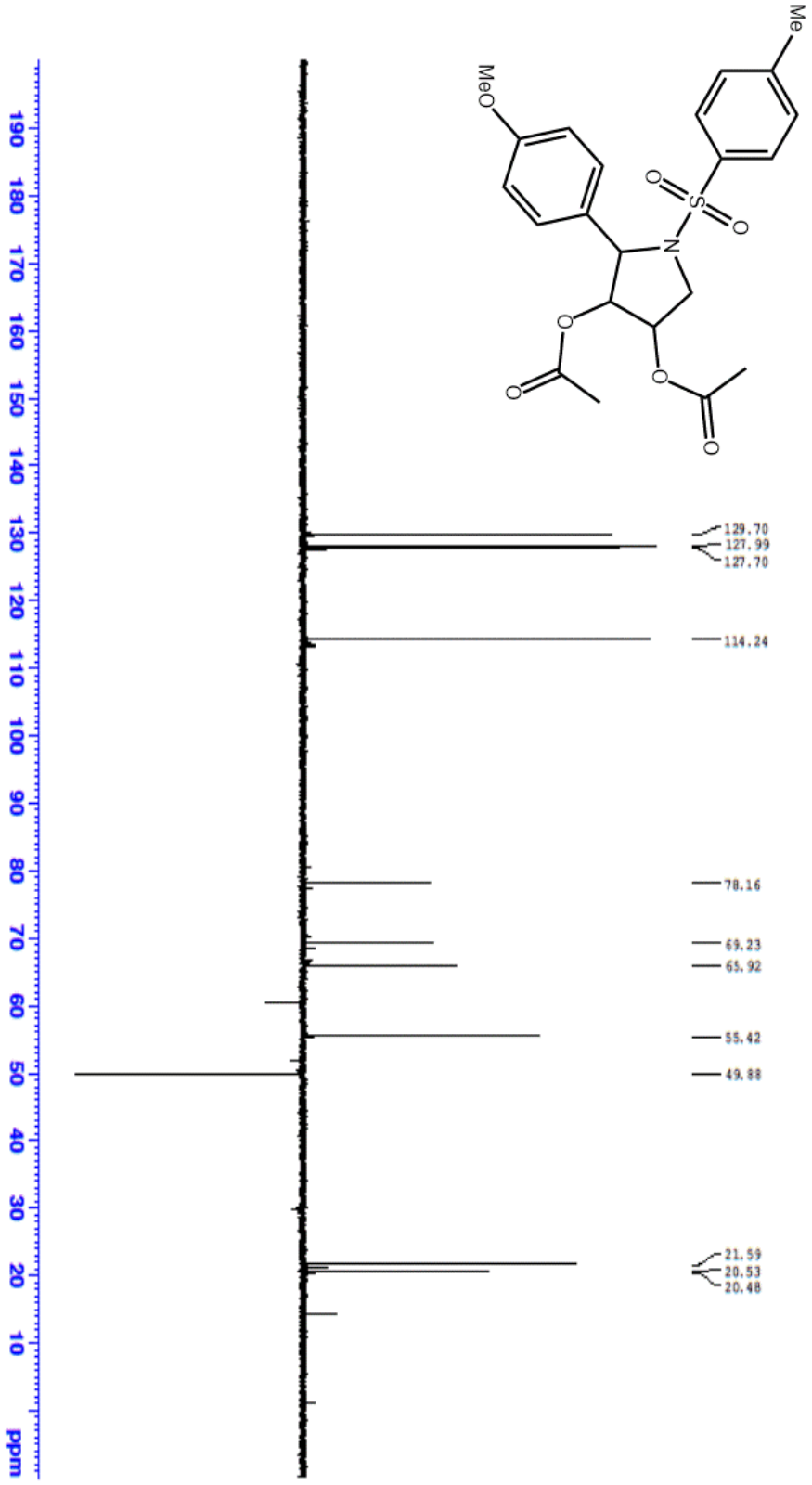
Spectrum 112: ^{1}H NMR spectrum of 1-[(4-methylphenyl)sulfonyl] 2-[4-(methoxy)]-3,4-pyrrolidinedione, 3, 4 diacetate 21b



Spectrum 113: COSY NMR spectrum of 1-[(4-methylphenyl)sulfonyl] 2-[4-(methoxy)]-3,4-pyrrolidinedione, 3, 4 diacetate 21b



Spectrum 114: ^{13}C NMR spectrum of 1-[(4-methylphenyl)sulfonyl] 2-[4-(methoxy)]-3,4-pyrrolidinedione, 3, 4 diacetate 21b



Spectrum 115: DEPT NMR spectrum of 1-[(4-methylphenyl)sulfonyl] 2-[4-(methoxy)]-3,4-pyrrolidinedione, 3, 4 diacetate 21b

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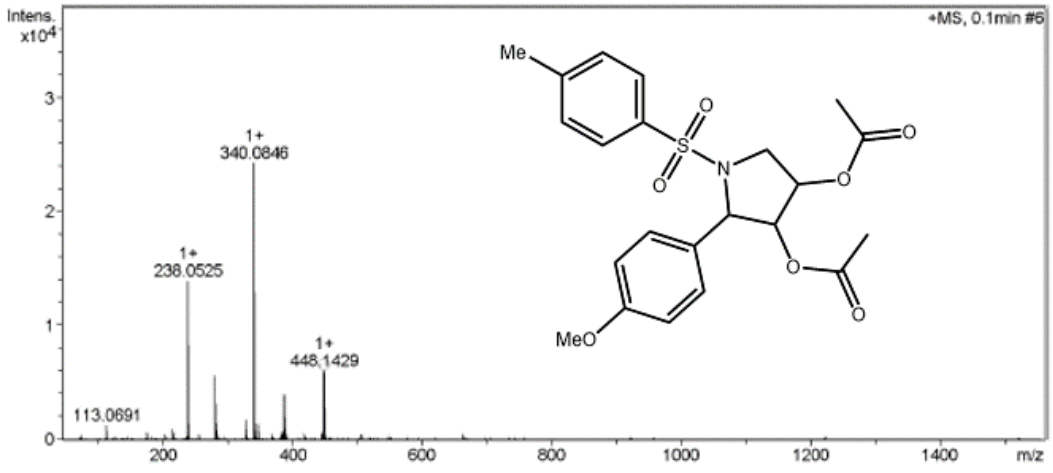
Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SOR_42_RC3_01_32516.d	Acquisition Date	20/03/2023 14:01:12
Sample Description			



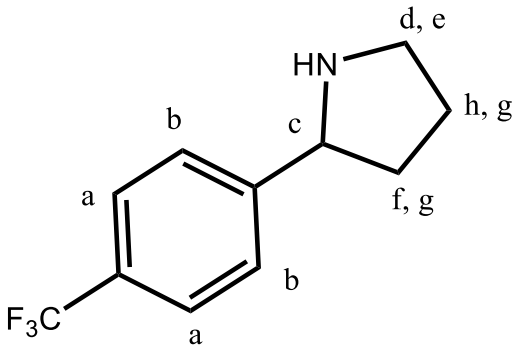
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
448.142863	1	C22H26NO7S	448.142450	-0.4	-0.9	10.5	ok	even	10.5

SmartFormula Settings

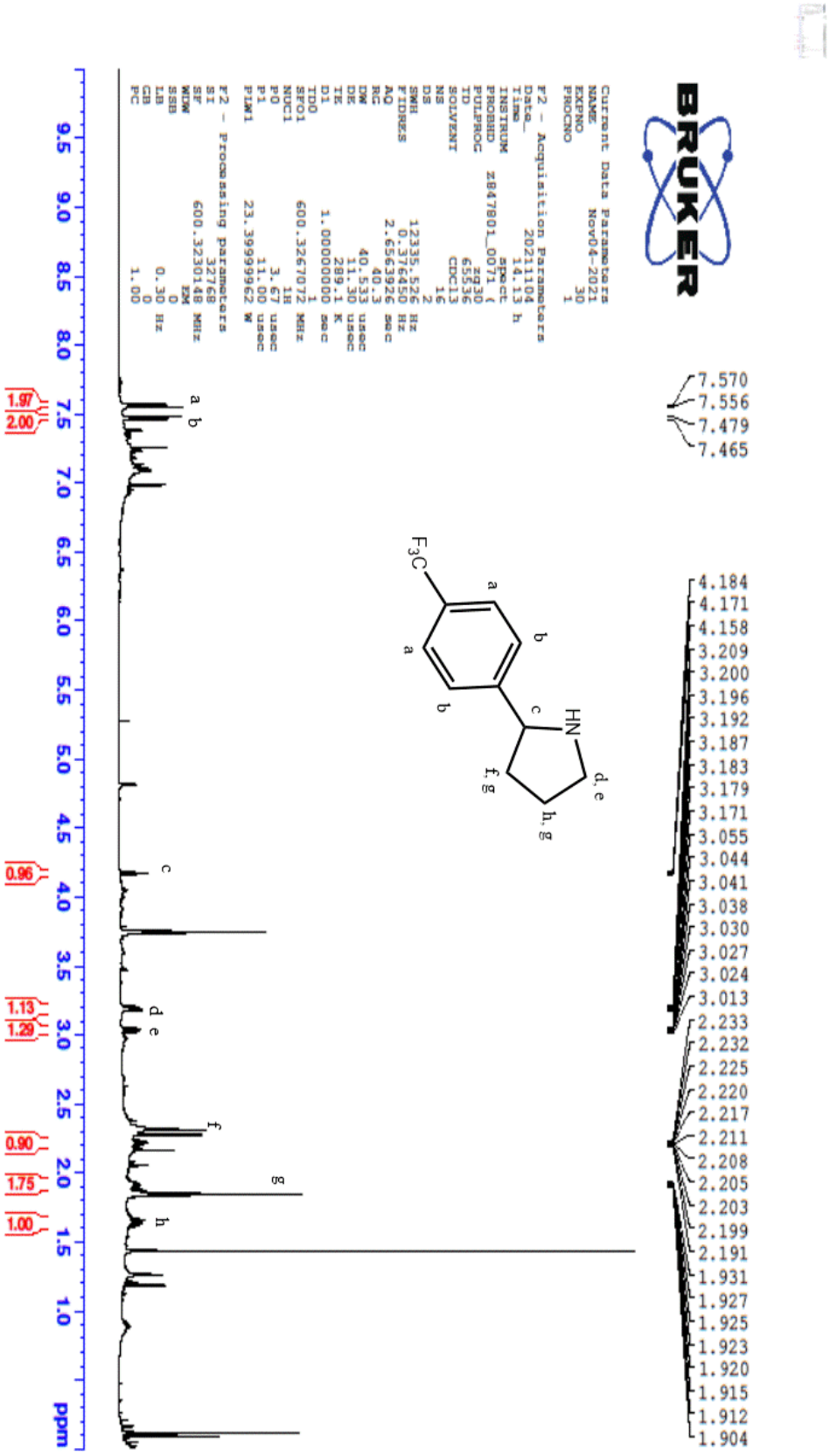
Low value of mSigma indicates good isotopic pattern match

Spectrum 116: HRMS spectrum of 1-[(4-methylphenyl)sulfonyl] 2-[4-(methoxy)]-3,4-pyrrolidinedione, 3, 4 diacetate 21b

7.3.7. 2-[4-(trifluoromethyl)phenyl] pyrrolidine **17**a (crude)

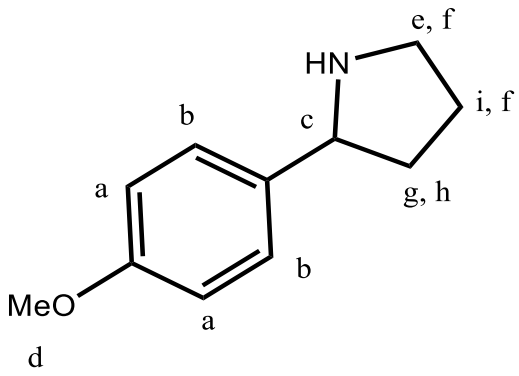


^{1}H NMR ($CDCl_3$) δ 7.56 (d, J= 8.2 Hz, 2H, Ha), 7.47 (d, J= 8.2 Hz, 2H, Hb), 4.19-4.15 (m, 1H, Hc), 3.21-3.16 (m, 1H, Hd), 3.06-3.01 (m, 1H, He), 2.25-2.20 (m, 1H, Hf), 1.91-1.81 (m, 2H, Hg), 1.70-1.60 (m, 1H, Hh) (**Spectrum 117**)

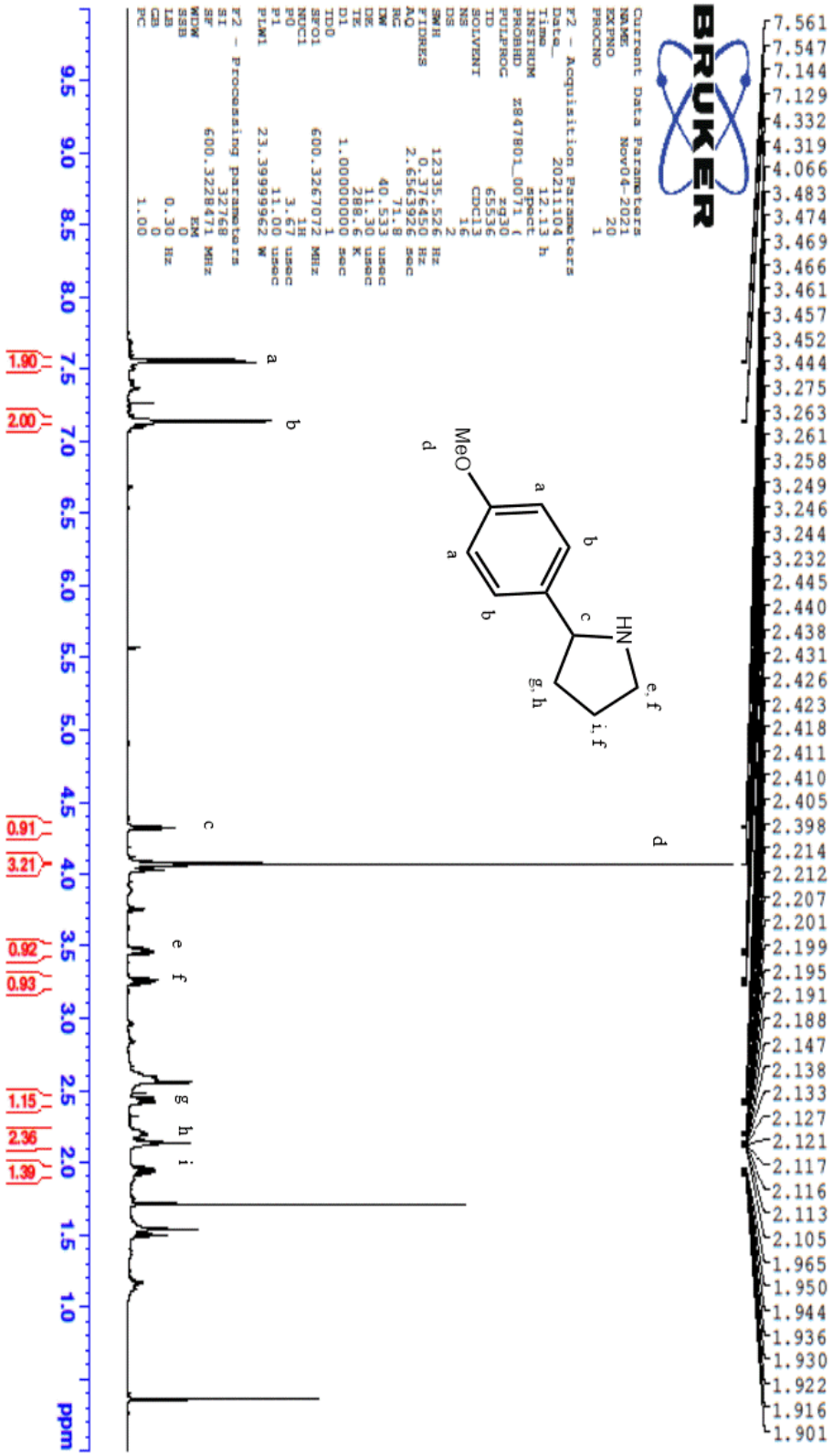


Spectrum 117: Crude ^{1}H NMR spectrum of 2-[4-(trifluoromethyl)phenyl] pyrrolidine 17a

7.3.8. 2-[4-(methoxy)phenyl] pyrrolidine **17b**



^{1}H NMR ($CDCl_3$) δ 7.55 (d, J= 8.6 Hz, 2H, Ha), 7.14 (J= 8.6 Hz, 2H, Hb), 4.34-4.28 (m, 1H, Hc), 4.07 (s, 3H, Hd), 3.45-3.43 (m, 1H, He), 3.29-3.22 (m, 1H, Hf), 2.46-2.39 (m, 1H, Hg), 2.25-2.09 (m, 2H, Hh), 1.97-1.89 (m, 1H, Hi) (**Spectrum 118**)



Spectrum 118: Crude ^{1}H NMR spectrum of 2-[4-(methoxy)phenyl] pyrrolidine 17b