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Synthesis towards thioridazine

Erling Berge Monsen

M-KJEMI

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Be excellent to each other.

Ås 2019

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Introduction

Aim of Study

The aim of this master project was to synthesize the phenothiazine thioridazine (1), as shown in figure 1. The compound is known as an anti-psychosis drug with several interesting microbial effects.

It has been shown that the two enantiomers of thioridazine have different effects, and studies of these can be useful for further development. As of today, there are no good synthetic strategies towards the two enantiomers.

The aim of this master thesis was to develop a short, concise synthetic approach towards both enantiomers.

Phenothiazines

The neuroleptic drugs (also called antipsychotic drugs, or major tranquilizers) are mainly used in treatment of schizophrenia. They are also effective in treatment of other psychotic states such as manic states with psychotic symptoms incorporating states as grandiosity or paranoia, hallucinations and delirium. Typical low potency neuroleptics include thioridazine (**1**), chlorpromazine (**2**) and prochlorperazine (**3**). All of them derivates of the tricyclic thiazine-class compound phenothiazine (**4**).

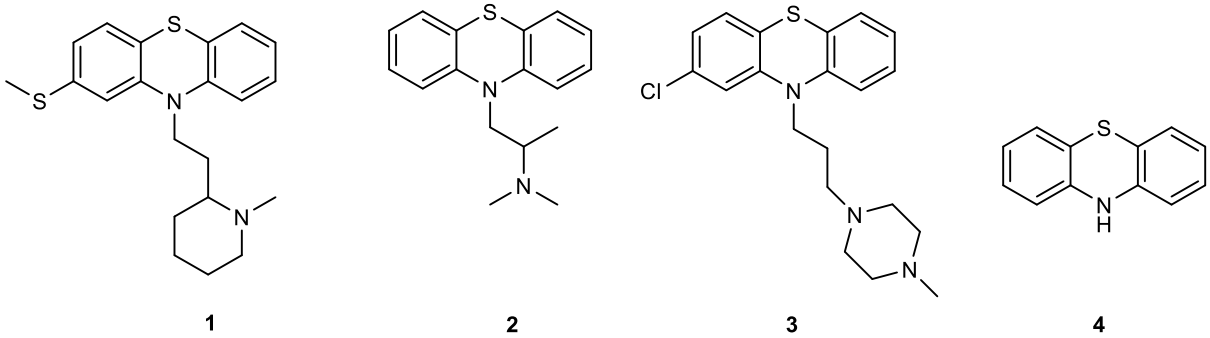


Figure 1. Structures of the typical, low potency neuroleptics 1-4.

These antipsychotic drugs alleviate symptoms by decreasing dopaminergic and/or serotonergic neurotransmission. The traditional neuroleptic drugs (also called conventional or first-generation antipsychotics) by competitive inhibition at a variety of receptors, but their antipsychotic effect reflects blocking of the dopamine receptors. These drugs are not curative and do not eliminate and chronic thought disorder, but they often decrease the intensity of

hallucinations and delusions which permits the person with schizophrenia to function in a supportive environment.[1]

The neuroleptic drugs represent several, diverse structures with markedly different potencies. The tricyclic phenothiazine derivative chlorpromazine was the first neuroleptic drug used in treatment of schizophrenia, a particular kind of psychosis caused by permanent dysfunction of the brain.[1]

Phenothiazines belong to the oldest, synthetic antipsychotic drugs, to which their precursor do not come from natural compounds.[2] Heinrich August Bernthsen was the first to synthesize **4**, along with its characterisation**,** in 1883, after which he deduced the structure of the phenothiazine derivatives dyes methylene blue (5) and thionine (Lauth's violet) (6).[3-5]

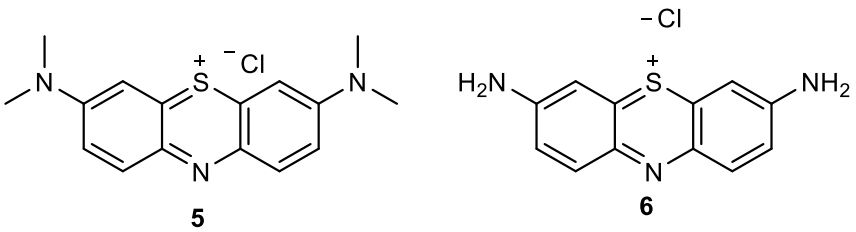


Figure 2 Structures of methylene blue and Lauth's violet.

In the 1880s Ehrlich and his collaborators found that **5** would preferentially stain plasmodia in the bloodstream, and as such became the first synthetic antimalarial drug.[6,7] Investigations of **5** as an analgesic and antipsychotic drug were also conducted.[8]
Phenothiazine has anti-insecticidal properties shown to be more toxic than rotenone.[9]
Therefore widely tested on a wide arsenal of insects, replacing lead arsenate as a fruit spray in the late 1930s.[10]

Phenothiazine and derivatives showed to have *in vitro,* bacteristatic effects on the growth of the tubercle bacilli *Mycobacterium tuberculosis.*[11] Though the bacteriostatic effects were diminished, they were still significant. Other investigations demonstrated effect against *Escherichia coli* in both rabbits and rats,[12,13] attributing its effect on phenothiazine or its metabolites. Mammals administered with phenothiazine excreted several metabolites, including phenothiazone and thionol.[14] These compounds are the ones that appear to possess

the antiseptic properties, moreover thionol itself has displayed *in vitro* bacteriocidal effect against *Staphylococcus aureus.*[13]

1.1.1 Mechanism of action

Clinical efficacy of the typical neuroleptic drugs correlates closely to their relative ability to block D_2 receptors in the mesolimbic system of the brain. Many of these drugs also block cholinergic, adrenergic and histaminergic receptors. It's unknown if these interactions have any role in alleviating symptoms of psychosis. However, the undesirable effects of these agents are often linked with the actions of these receptors. All the drugs have a calming effect and reduction in physical movement but does not depress intellectual capabilities as much as central nervous system depressants, as well as minimal decrease in motor incoordination. [1]

Thioridazine

Thioridazine (**1**) is a piperidine type phenothiazine antipsychotic, 10-derivative, previously used in the treatment of schizophrenia and psychosis.

Thioridazine had for many years used in the treatment of schizophrenia. However, in December 2000, the Committee on Safety of Medicines advised a restricted use of thioridazine. This was in response to accumulating data corresponding thioridazine use causing dose related QTc interval prolongation that predisposes to potentially fatal ventricular arrhythmia, *Torsades de Pointes*.[15] In 2005 Novartis voluntarily withdrew thioridazine from the world market. Although, the drug is still available for patients unable to withdraw from thioridazine. However, prescribing it to a new patient will be by specialist only.[15]

The development of thioridazine as antibacterial has not succeeded into clinical use, probably due to scare of the well-known side effects. However, renewed interest in thioridazine, has arisen due to its effect on multi-drug resistant tuberculosis.[16] Thioridazine has shown to increase the sensitivity of drug resistant *Mycobacterium tuberculosis* and methicillin-resistant *Staphylococcus aureus*.[17,18] Suggested mechanism of action is by disruption of the bacterial efflux pumps.[17]

Thioridazine has been shown to concentrate in macrophages. Infections prone to develop in macrophage-rich tissue include tuberculosis. Therefore, a treatment of such infections with thioridazine would be expected to require lower doses compared to treatment of psychosis.[19]

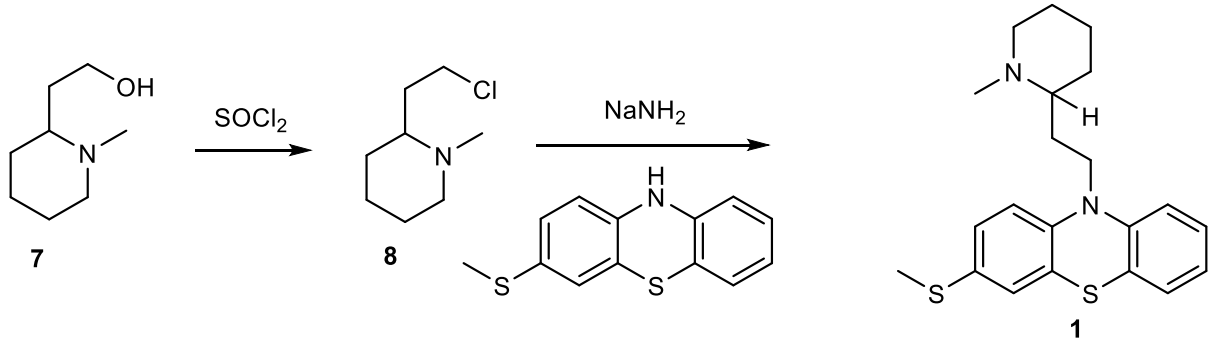
Interestingly thioridazine has also shown to suppress the growth of several cancer cell types. Recent studies revealed thioridazine to selectively target cancer stem cells. [20] Moreover, it has been demonstrated that thioridazine make multidrug-resistant cancer cells vulnerable to cytotoxic agents they originally resisted.[21]

Investigations into differences in action of enantiomers has increased through the years, so it is not surprising that examination of the enantiomers of thioridazine has also been undertaken. Trials in rat brains has shown that (+)-thioridazine has approximately 2.7 greater affinity to the D_2 dopamine receptor than the (-)-enantiomer. Interaction with the D_2 receptor is the cause for the antipsychotic effect of thioridazine. Additionally, the (+)-enantiomer has 4.5 times higher affinity to norepinephrine α1, whereas the (-)-enantiomer shows 10 times higher affinity for the D_1 dopamine receptor. In rabbits (-)-thioridazine has shown to cause significantly lower QTc interval prolongation. [22]

Previous synthetic work on thioridazine:

A few published procedures on the preperation of enantiomers of thioridazine excist. [2,23]

The synthesis of thioridazine was first reported by Bourquin *et al.*, starting with racemic piperidine alcohol (X) shown in scheme X. The resulting enantiomers were separated via chiral resolution employing di-*p*-toluyl-*L*-tartaric acid as the chiral derivatizing agent.[23] Bourquin also prepared the enantiomers from optically active X.



Scheme 1 Synthesis by Bourquin *et. al.* of enantiopure thioridazine.

Patrick *et al.* used enantiomerically pure pipecolinic acid to prepare (-)-X whereby its specific rotation was used to determine the absolute chemistry of (+)-1 and (-)-1 as *R* and *S,* respectively.[24] It is also mention that alcohol piperidine (-) has been made through chiral resolution, but an arduous nine recrystallizations were needed for adequate purity.

The strategy reported by Choi *et al.* involves preparation of the menthyl carbamate of thioridazine. The diastereomeric pair can then be separated by chromatography. However, the carbamate hydrolyses easily which complicates the resolution in upscaling. The following reduction of the carbamates, with $LiAlH_4$, gives good enantiomeric excess, but with overall low yields.[25]

A third strategy has been also reported of the isotope-labelled synthesis of racemic thioridazine.[26,27] Also, synthesis of several analogues has been published. [28,18]

Asymmetric synthesis

Development of asymmetric synthesis strategies of detrimental importance in the mass production of useful natural products such as amino acids. Asymmetric synthesis is a key area in modern organic chemistry.[29]

Asymmetric synthesis is key to modern organic chemistry and of vital importance in the field of pharmaceuticals, as the different enantiomers or diastereomers can have widely different biological effects. In some cases, their effects can be remedial whilst the opposite stereoisomer can be devastating. A well-known and disastrous example is the prescription drug thalidomide, produced racemic in the 50s and early 60s claiming to treat anxiety, insomnia, gastritis, and tension and that it was safe and harmless for pregnant women.[30] More then 10 000 infants in 46 countries were born with deformities, such as phocomelia, or even perished due to mother's ingestion of the racemic drug mixture during pregnancy.[31]

In asymmetric synthesis (stereoselective synthesis) the reaction produces one or more chiral centre(s) with enantiomeric excess or diastereomeric ratio in unequal proportions. It refers to a compendium of transformations which are not necessarily a synthesis. The stereoselective process can also be breaking of certain bonds into two or more species.

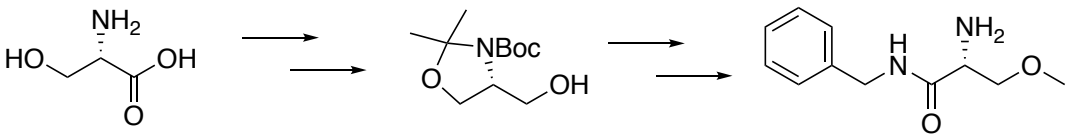
Chiral resolution

The racemic mixture is modified with an appropriate chiral moiety. Easy to attach and to remove. Hence the new diastereomeric pair can be separated by for example chromatography.

Chiral pool synthesis

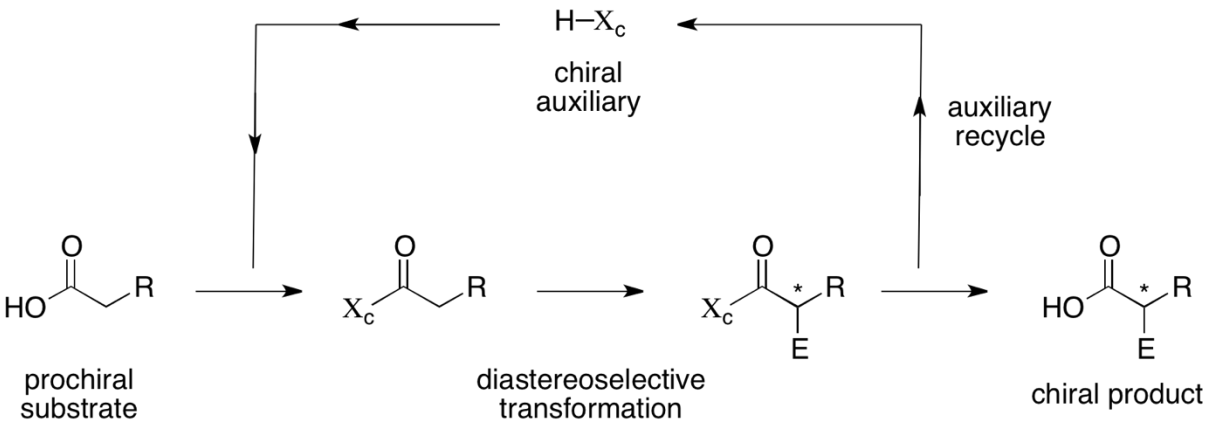
Chiral pool synthesis is a strategy that aims to improve the efficiency of enantioselective synthesis. It starts with a complex enantiopure chemical compound. These are commonly amino acids and monosaccharides. The built-in chirality is then preserved in the remainder of the reaction sequence.

One example is the synthesis of antiepileptic drug (*R*)-lacosamide by Aratikatla and Bhattacharya, as depicted in scheme 2.[32]



Scheme 2 Synthesis of the antiepileptic drug (*R*)-lacosamide by Aratikatla and Bhattacharya.

Chiral auxiliary modification



Scheme 3 Chiral auxiliary modification

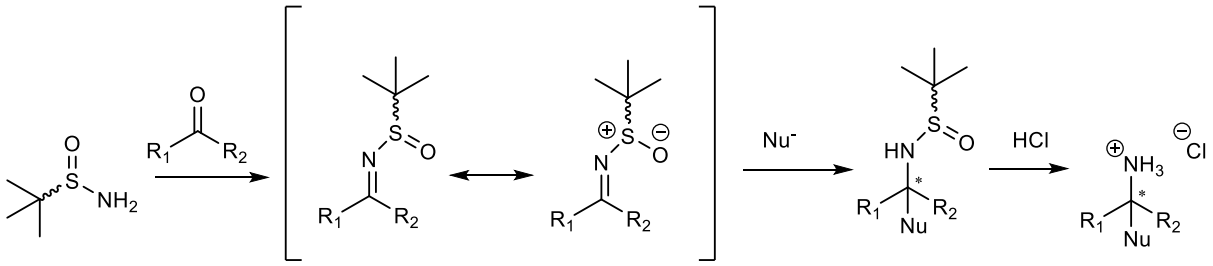
Problems can incur with the chiral pool approach caused by the very origin of these substrates. posing limitations to the applicability, both in terms of the substitution patterns and their stereochemical configurations. The use of a chiral auxiliary approach can circumvent this problem .A chiral auxiliary is a enantiomerically pure molecule, with a well-defined

absolute configuration, covalently bonded to a usually achiral substrate. The resultant molecule is an enantioenriched molecule can undergo a stereo controlled reaction, after which the auxiliary is removed to give the desired product.

Ellman's sulfinamide

The amine functionality exists in the large majority of all drugs and drug candidates,[33] pointing towards the importance of reliable asymmetric synthetic methods for organic compounds with a chiral amine functionality. The use of the Ellman's sulfinamide (X) (*tert*-butanesulfinamide), a chiral amine reagent, has become one of the most extensively used in synthetic approaches for both discovery and production of drug candidates.[33] The popularity can mostly be attributed to its typically robust, easy and the broad scope of reactions that can be done with Ellman's sulfinamide.

The sulfinamide X undergoes direct condensation (scheme 4) with aldehydes and ketones resulting in high yields under mild conditions granting *N*-*tert*-butanesulfinyl aldimines or ketimines, which are significantly less hydrolytically labile or prone to tautomerization than most *N*-alkyl, aryl, acyl, or carbamoyl imines.[33]



Scheme 4 Direct condensation of Ellman's sulfonamide with a carbonyl.

N-*tert*-Butanesulfinyl imines, are despite their stability, significantly more electrophilic than typical *N*-alkyl of aryl imines. This can be explained by the notable positive charge on the sulphur atom. The more significant electrophilicity enablees robust and high yielding additions of a diverse range of nucleophiles, such as organo-magnesium, lithium, zinc, silicon, indium, cerium, and boron reagents stabilized carbanions, and including noncarbon nucleophiles such as phosphorus, boron, tin and silicon derivatives as well as hydride reagents. Additions to α-heteroatom imines usually proceeds in high yields. Moreover, with an α-stereocenter present, doesn't undergo epimerization. [33]

The Ellman's sulfinamide is capable of metal coordination, resulting in high diasteroselectivities. And is a versatile protecting group, stable in a wide array of conditions including strong bases, nucleophiles, and a variety of transition metal catalysed reactions such as olefin metathesis and Pd-mediated cross-coupling. Finally, the sulfinamide is easily cleaved by simple treatment of non-aqueous HCl, producing the amine hydrochloride. [33]

Allylation in aqueous media

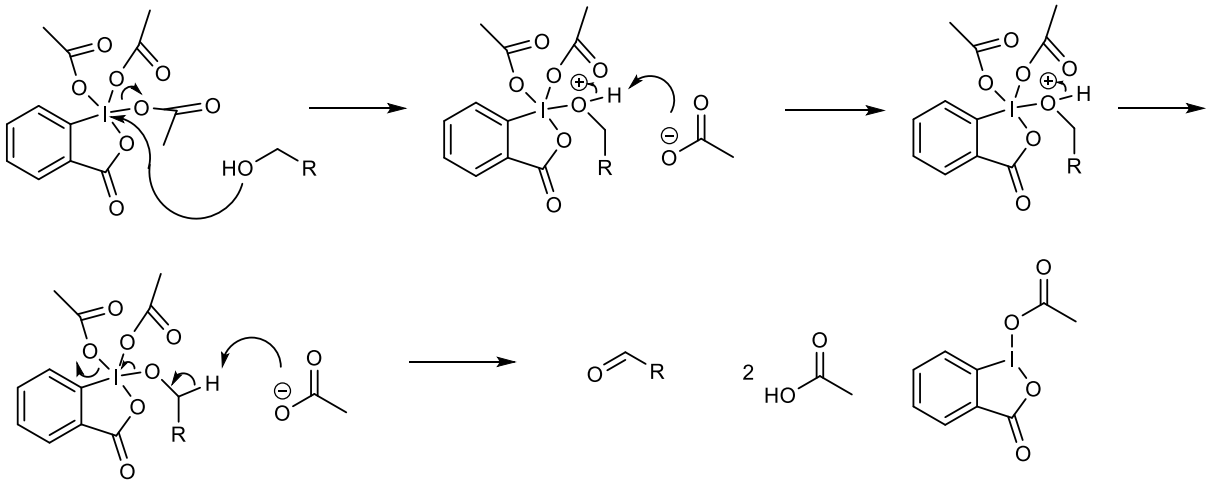
Interest in usage of performing organic reactions in aqueous media, without organic cosolvent, is of great interest for the significant environmental and economic advantages over standard reactions with organic solvents.[34,35] Although problems with imines arises as they are often easily hydrolysed in aqueous media.[36] By using a saturated aqueous NaBr and indium environment, Sun *et al.* discovered that asymmetric synthesis of homoallylic amines proceeded at ambient temperatures and excellent yields and diastereoselectivities (up to 99:1).

Oxidation and reduction

Oxidation-reduction (redox) is usually referred to reactions with loss and gain of electrons. In organic chemistry compounds experience gain or loss of electron density, usually by gain or loss of oxygen bonds and/or hydrogen.[37]

Oxidation with Dess-Martin periodate

Primary and secondary can be oxidized to aldehydes and ketones, respectively, by use of mild oxidizing agents such as pyridinium chlorochromate (PCC) or Dess-Martin periodate (DMP). DMP has several advantages over other methods[38], such as chromium based oxidizers, avoiding long reaction times, difficult workup procedures and need for large excess of oxidizing agent.



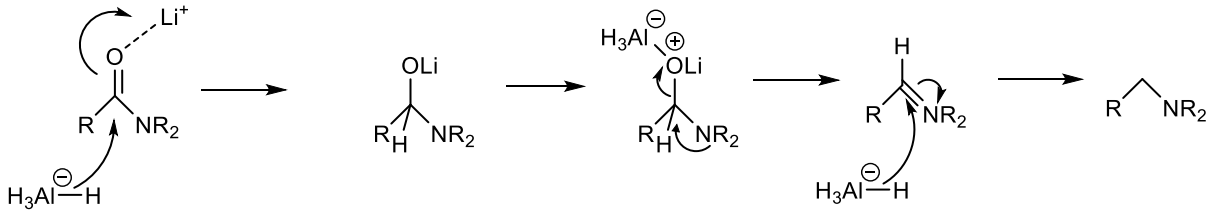
Scheme 4 Proposed mechanism for oxidation by DMP.

Oxidation using DMP occurs with high chemoselectivity[39] producing the aldehyde or ketone, two equivalents of acetic acid and one equivalent of iodinane (Scheme 4).

Reduction with lithium aluminium hydride

$LiAlH_4$ (LAH) is a strong reducing agent, capable of reducing a vast array of different functional groups such as amides, esters, acid chlorides, chlorides etc.

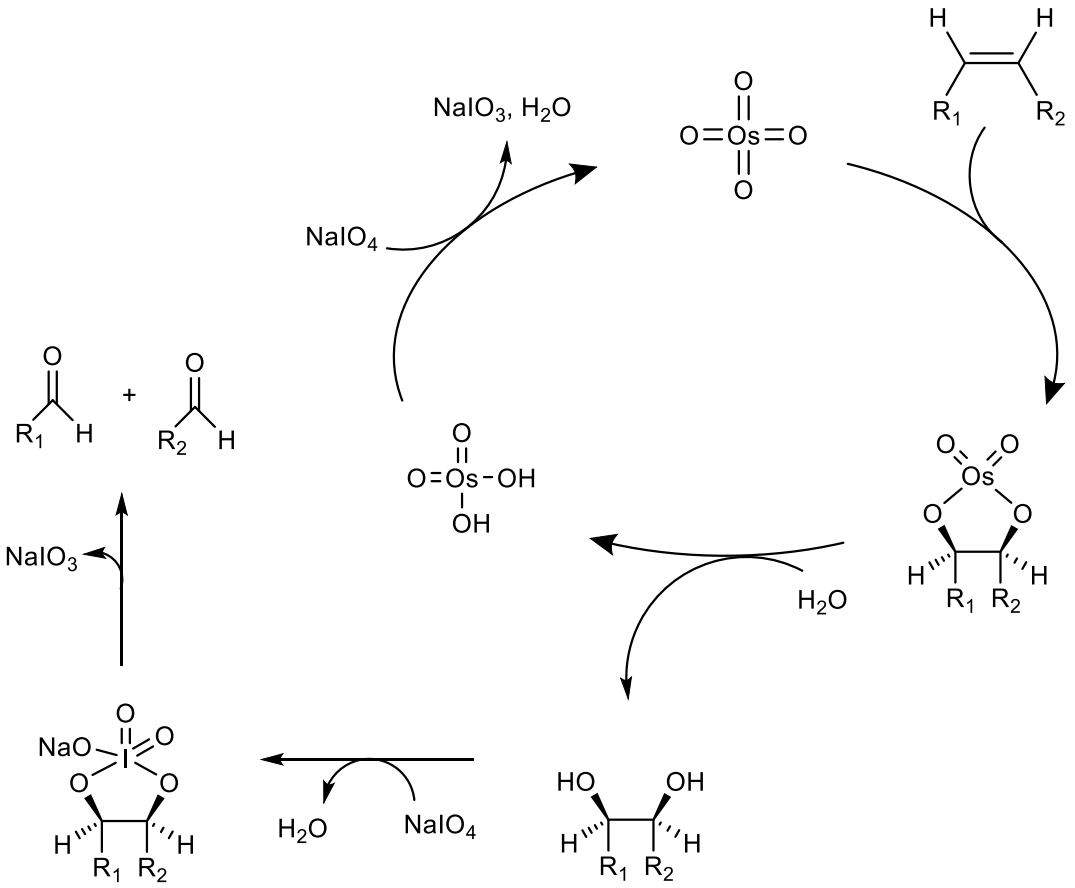
Carbamates can be reduced to the corresponding *N*-methyl species.



Scheme 5 Mechanism for reduction of a amide.

Lemieux-Johnson oxidation

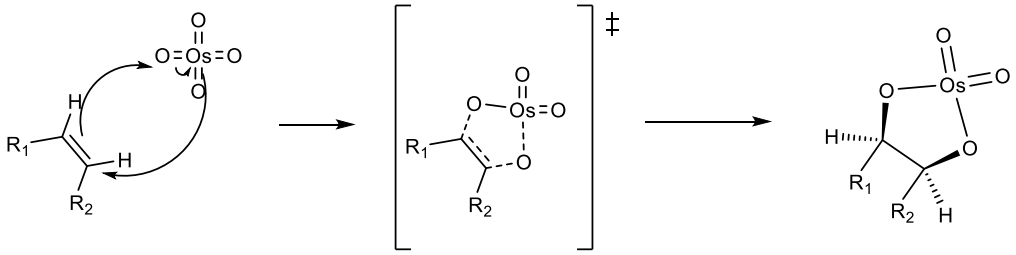
Lemieux-Johnson oxidation is an osmium tetroxide-sodium periodate technique, cleaving olefinic bonds, with the advantage of not proceeding beyond the aldehydic oxidation state. [40] Thereby affording the same product as in ozonlysis followed by reductive cleavage. Only catalytic amounts of osmium tetroxide is need as the periodate oxidizes osmium(VI) to regain tetroxide, thus regenerating the hydroxylating agent (se scheme X).[40] Thereby omitting the need to use large amounts of expensive and highly poisonous osmium tetroxide.



Scheme 6 Lemieux-Johnson oxidation catalytic cycle.[41]

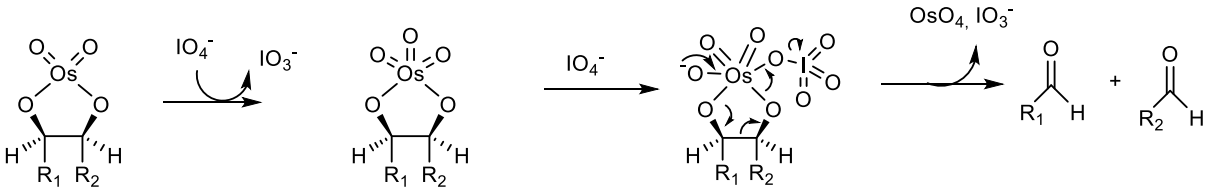
Proposed Mechanism

Without the sodium periodate, by OsO_4 reacts with olefins forming cyclic diesters which after hydrolyzation is converted into vicinal *cis*-diols. It's therefore probable that sodium periodate further oxidizes the osmium species and causes cleavage of the carbon-carbon bond to give the aldehydic pair.[42]



Scheme 6 Mechanism of formation of the cyclic diester.[43]

Generally it is accepted that the reaction proceeds through a concerted mechanism ([3 + 2], scheme 7) to the cyclic diester.[43] However, a [2 + 2]-reaction creating a metallooxetane, which then undergoes rearrangement into the cyclic diester has also been suggested.[44,45]



Scheme 7 Proposed interaction of periodate. [42]

Modification

The Osmium(VI) complex is usually written as a tetrahedral species like **X**.[43,46] Structure **X** may exist as a transient species in solution,[45] as no examples of tetrahedral d^2 stereochemistry exist for third-row transition metals. In addition there is expected severe strain in the cyclic osmate ester due to the long osmium-oxygen bonds (2.2 Å).[47,48]

Experiencing low yields, due to formation of side products, using the standard OsO_4- $NaIO_4$ protocol, Yu *et al.* decided to try and improve the classic Lemieux-Johnson reaction. It has been observed that excess addition of a non-nucleophilic tertiary amine, such as pyridine, could greatly increase the rate of formation of Osmium(VI) complexes.[49,50] Thereby stabilizing the transient species of the osmium(VI) complex into a octahedral stereochemistry (figure 3).

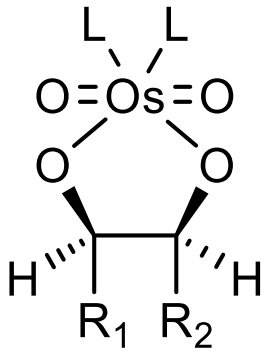


Figure 3 Ligand stailizing Osmium(VI) complex.

Epimerization can be observed with the use of pyridine[51], leading to investigation of 2,6-lutidine as the base. It showed to be an «ideal base» for the purpose which suppressed side products, whilst also being faster and without epimerization product. Though in cases where epimerization isn't an issue pyridine is still a viable option.[51]

Microwave assisted heating

The principles of microwave heating were first established in the post second world war period.[52] Reports of use in syntheses date back to at least 1981[53], but exploration into organic chemistry began in 1986[54,55] with Gedye *et al.* and Giguere *et al.* resulting with expansion into nearly all chemical areas.[52] Microwave irradiation can be used to speed many chemical reactions which has led to investigation of the mechanism of microwave dielectric heating, and advantages of the technique for chemical synthesis.[56]

Traditional heating is usually slow and inefficient method of transferring heat into the reaction mixture. It depends on the convection currents and thermal connectivity of the various materials that must be penetrated, resulting in reaction vessels usually warmer than the reaction mixture itself.[57] Microwave radiation simultaneously heats the reaction mixture, without concern of reaction vessel, liquid in the bath or surrounding gas.

The ability of a molecule to interact with microwave radiation is a function of its molecular polarizability (i.e. a function of its dipole moment). Only polar molecules tend to interact with microwave energy, see table 1, whilst less polar compounds are poorly absorbing. It has also been suggested that if only the solvent absorb energy and not the substrate, only moderate reaction rate increases, relative to those with conventional energy, will be observed. However, if the microwave energy is absorbed selectively by a reactant (by a complex or an intermediate during the rate determining step) a large rate increase may be observed.

Table 1 Microwave heating of organic solvents (50 cm^3, 560 W for 1 minute).[58]

Solv.	Temp./^{O}C	bp./^{O}C	Solv.	Temp./^{O}C	bp./^{O}C
Water	81	100	Acetic acid	110	119
Methanol	65	65	Ethyl acetate	73	77
Ethanol	78	78	Chloroform	49	61
1-Propanol	97	97	Acetone	56	56
1-Butanol	109	117	DMF	131	153
1-Pentanol	106	137	Diethyl ether	32	35
1-Hexanol	92	158	Hexane	25	68
1-Chlorobutane	76	78	Heptane	26	98
1-Bromobutane	95	101	CCl_4	28	77

Results and discussion

The main goal was the preparation of enantiopure piperidine alcohol **7.** First, we envisioned a strategy using *L*-aspartic, a chiral pool approach. However, the strategy was discarded early as even the first step with protecting the side chain carboxyl with a benzyl group proved problematic. The product was even hard to confirm as it would not dissolve in any available deuterated solvents. Previous experiences also show how easily α-amino acids can racemize during elongation.[59]

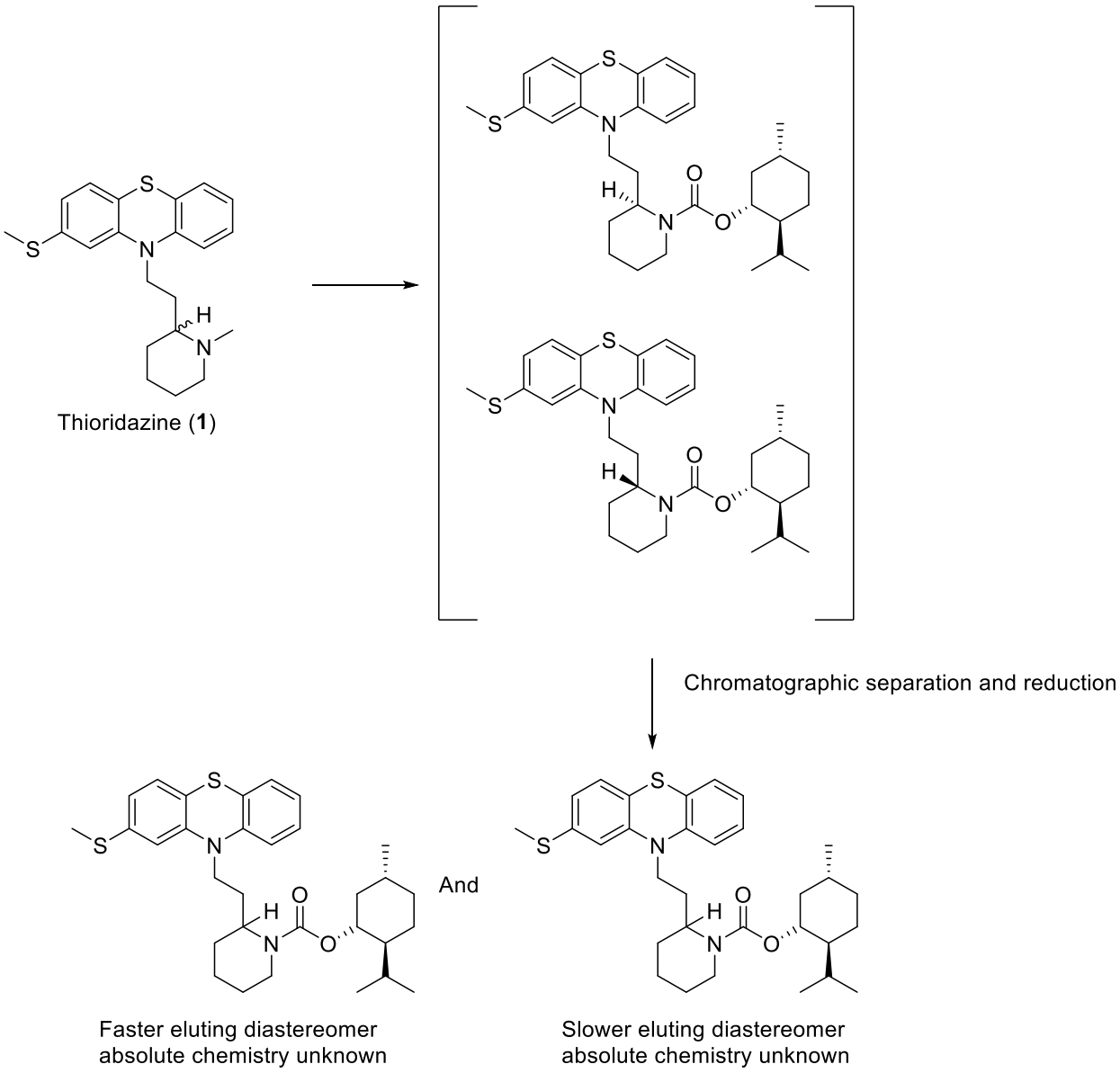
Chiral resolution:

As the hydrochloride of racemic thioridazine is commercially available, the most obvious approach to get enantiopure thioridazine is chiral resolution.

The first reported chiral resolution of thioridazine was by Bourquin *et al.* in 1958.[60] In this procedure, thioridazine is reacted with di-*p*-toluyl-*L*-tartaric acid. Previous master students proved this to be laborious. Several recrystallizations were found to be necessary for sufficient purity.

However, another chiral resolution is reported by Schlauderer *et al*.[61] This relies on the acid chloride of a chiral terpenoid, *R*-(-)-menthyl chloroformate.

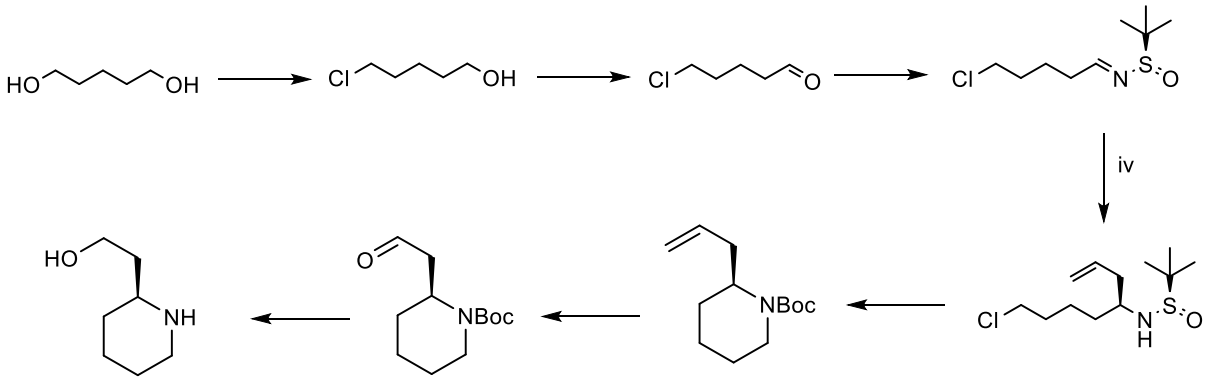
First the commercially available **1**-HCl salt is turned into the free base and reacted with the chiral auxiliary. With the diastereomer pair, a normal flash chromatography was carried out and the pair were successfully separated with a small portion coeluting. 84 mg of **(-)1** was obtained and 91 mg of **(+)1** from 800 mg of racematic **1** (11 % **(-)1**, 11% **(+)1**). The optical rotation measured was -21° for the enantiomer yielded from the faster eluting diastereomer, and +19° for the enantiomer yielded from the slower eluting diastereomer.



Scheme 8 Chiral resolution of thioridazine.

Total synthesis of thioridazine:

Starting from cheap 1,5-pentadiol giving the correct carbon skeleton in piperidine, we eventually decided to use a chiral auxiliary to insert the desired stereochemistry. Enantiopure Ellman *tert*-butane sulfinamide proved excellent for this purpose, and with added utility of inserting the amine group in the molecule. The allyl motive was chosen as it's easily handled, and through oxidative cleavage, can easily be oxidized to the aldehyde followed by reduction to the target molecule **7**. The cyclisation was mainly done by microwave irradiation. Both this and the chiral auxiliary usage was heavily inspired by Senter *et. al.*



Scheme 9 Reactions done in this thesis

Synthesis of 5-chlorpenta-1-ol

The reaction was carried out with commercial 1,5-pentadiol, as a simple S_N2 reaction, using concentrated aqueous HCl. Using azeotropic distillation with a water-toluene mixture thereby removing water from the HCl reagent and reaction. With a Dean-Stark apparatus the reaction went well with the use of simple reagents, though the yield was at a meagre 47 %. Purification by distillation distillation under reduced pressure proved difficult as the mixture was prone to bumping. Pure product distilled over at 84-88 ^{O}C at 12 mbar. ^{1}H-NMR and ^{13}C-NMR spectra showed no symmetry as was in the starting material. It was in accordance with literature except for the alcohol group which came a lot more upfield.[62]

Synthesis of 5-chlorpentanal

The reaction was carried out using both PCC and DMP. Using DMP the reactions yield was quantitative, though in subsequent tries the crude was used limiting the aldehydes exposure time.

Synthesis of (*S,E*)-N-(5-Chloropentylidene)-2-methylpropane-2-sulfinamide and (*R,E*)-N-(5-Chloropentylidene)-2-methylpropane-2-sulfinamide

The *tert*-butylsulfinyl aldimines were prepared by simple $CuSO_4$ mediated condensation. The reaction gave the desired product, in high yields of 81 % over two steps. When the condensation was done in one stop with purified chloroaldehyde the yield was 92 %. The specific rotation indicated that the asymmetric reaction was successful with specific optical rotation + 230.7^{O} and -235.9^{O} for (*S*) and respectively. UV-spectroscopy showed clear absorbance at 243-248.9 nm contributed by the conjugated system from the carbonyl group to the C-N double bond. In addition, IR showed the classic sulfoxide peak at 1085 cm^{1}.

(S)-N-(R)-8-Chlorookt-1-en-4-yl-2-methylpropane-2-sulfinamide and (R)-N-(S)-8-Chlorookt-1-en-4-yl-2-methylpropane-2-sulfinamide

Elemental indium mediated Allylation in an aqueous environment went well with yields towards 95 %. As expected the specific optical rotation was similar at + 56.6^{O} and -57.2^{O} for *S*,*R* and *R*,*S* respectively.

(S)-2-Allyl piperidine hydrochloride and (R)-2-Allyl piperidine hydrochloride

The cyclisation was performed by first deprotecttion with acid, where ^{1}H- NMR showed full consumption of the starting material. Intramolecular cyclisation was performed by use of microwave irradiation. The reaction seemed to go well though there was significant difficulties in purifying the product. Purification by distillation of the free amine would be preferential though this option was not tried as the amounts of product was so small. Instead protecting the amine directly after cyclisation was performed to the *tert*-butyl carbamate, thusly circumventing the purifying step.

(S)-N-tert-butyl 2-allylpiperidine-1-carboxylate and (R)-N-tert-butyl 2-allylpiperidine-1-carboxylate

The reaction was performed in three steps to prevent previously mentioned problems. The amine was protection to the *tert*-butyl carbamate to circumvent possible *N*-oxide products, during Lemieux-Johnson oxidation step, and at the same time creating a convenient path to the *N*-methyl in the target molecule. The reaction was also performed using crude X (2 allyl piperidine hydrochloride) though overall the three-step approach was easier and allowed for better yields up to 88 %. The specific optical rotation was -41.7 ^{O} and + 38.9 ^{O} for S X and R X respectively, not concurrent with previously reported values[63]. But more in line with results reported with a 78:22 e.e.[64]

(S)-N-tert-butyl 2-etanalpiperidine-1-carboxylate and *(R)-N-tert*-Butyl 2-Etanalpiperidine-1-carboxylate

The allyl piperidine carboxylates were cleaved oxidatively under modified Lemieux-Johnson conditions producing quantitative yields. The reaction went really well and was easily purified. Specific optical rotation wasn't theperformed.

(R)-*N*-2-ethanolpiperidine and *(S)*-*N*-2-ethanolpiperidine

The carbamate aldehydes were reduced to the target molecule, but there were severe issues with the purifying step. Regrettably only (*S*)-product was successfully made, and purified. The optical rotation of + 11.4 ^{o} points high enantiomeric excess.

5 Experimental procedure

5.1 General methods

Chemicals were obtained from commercial sources without further purification

All reactions were carried under a N_2- atmosphere unless otherwise specified.

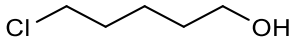
Most reactions were observed by thin layer chromatography of the type TLC Silica gel 60 F254 plates produced by Merck. For detection a $KMnO_4$-dip, UV (UVGL-25 Mineralight lamp produced by UVP) and a dinitrophenylhydrazine-dip.

Flash chromatography was performed using glass columns packed with silica gel of the type Silica Gel 60 (0.040-0.063 mm) from Merck.
NMR spectra were recorded with a Bruker AscendTM 400 at 400 MHz for ^{1}H- NMR and 100 MHz for ^{13}C- NMR, using $CDCl_3$ as solvent calibrated at 7.26 ppm and 77.16 ppm respectively.
IR-spectra (4000 – 600 cm^{-1}) were recorded on an Agilent Technologies 5500 series FTIR and a diamond ATR-cell.

Specific optical rotation was measured on a Perkin Elmer 341 polarimeter in a cell with a path length of 1.0 dm.

The microwave used was of the type «Start synth Microwave synthesis labstation» by Milestone Laboratory systems.

UV spectra were recorded with a Biochrom Libra S32 PC.5.1 Synthesis of 5-chloropentan-1-ol



To a solution of 1,5-pentanediol (41.4 g, 39.8 mmol) in 250 mL toluene was added 37 % HCl (117 mL, 51,9 mmol). The mixture was heated for 3 days whilst water was routinely removed. The chloropentanol was isolated by distillation under reduced pressure (82-88 ^{O}C, 12 Torr) to yield a clear oil (22.8 g, 47 %).
R_f: 0.2 (4:1 hex/EtOAc)
^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.66 (t, *J* = 6.3 Hz, 2H), 3.55 (t, *J* = 6.7 Hz, 2H), 1.81 (p, *J* = 6.7 Hz, 2H), 1.66 – 1.46 (m, 4H), 1.37 (s, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 62.80, 45.08, 32.48, 32.06, 23.28.

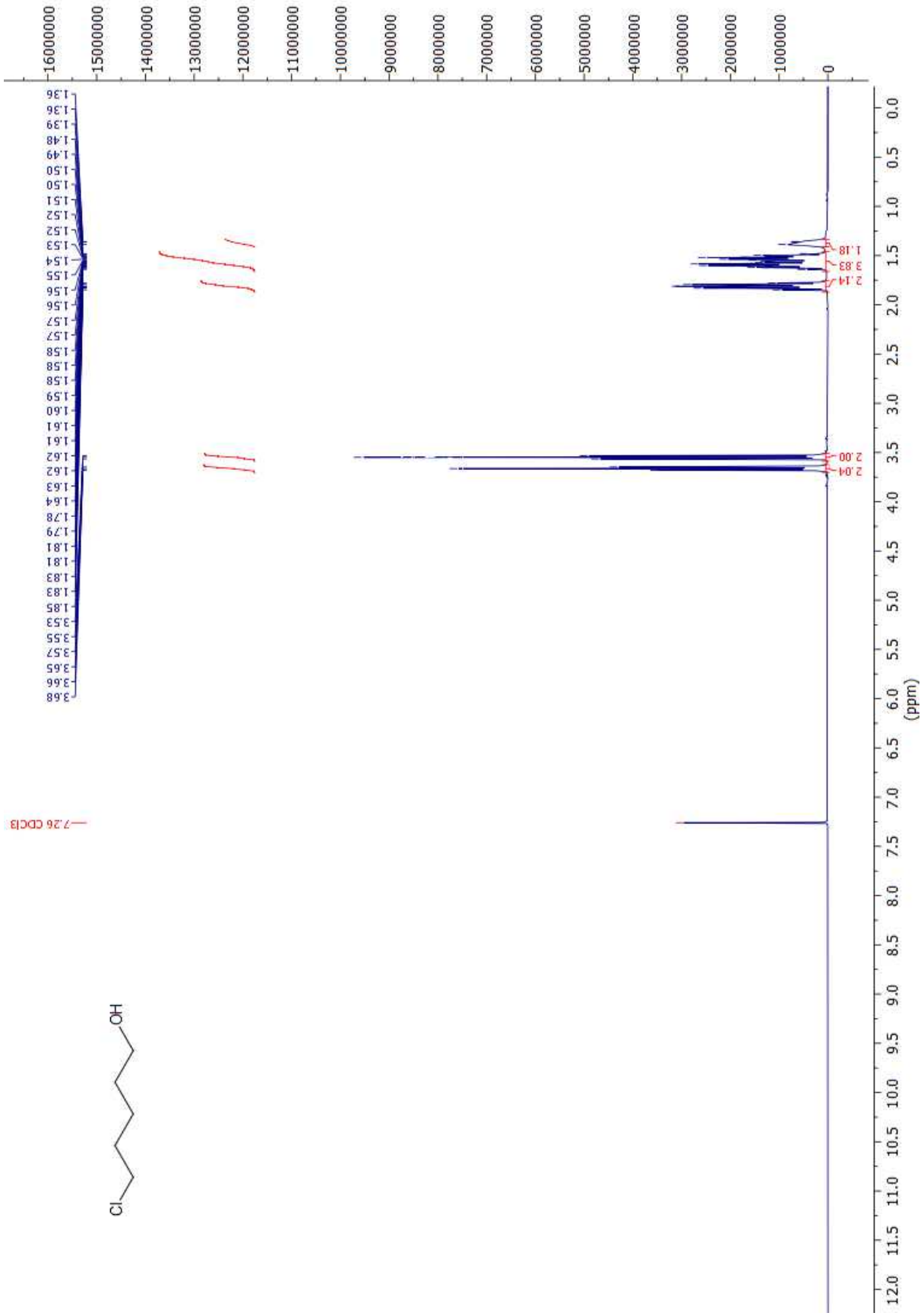


Figure 4 ^{1}H-NMR specterof 5-chloro-1-pentanol

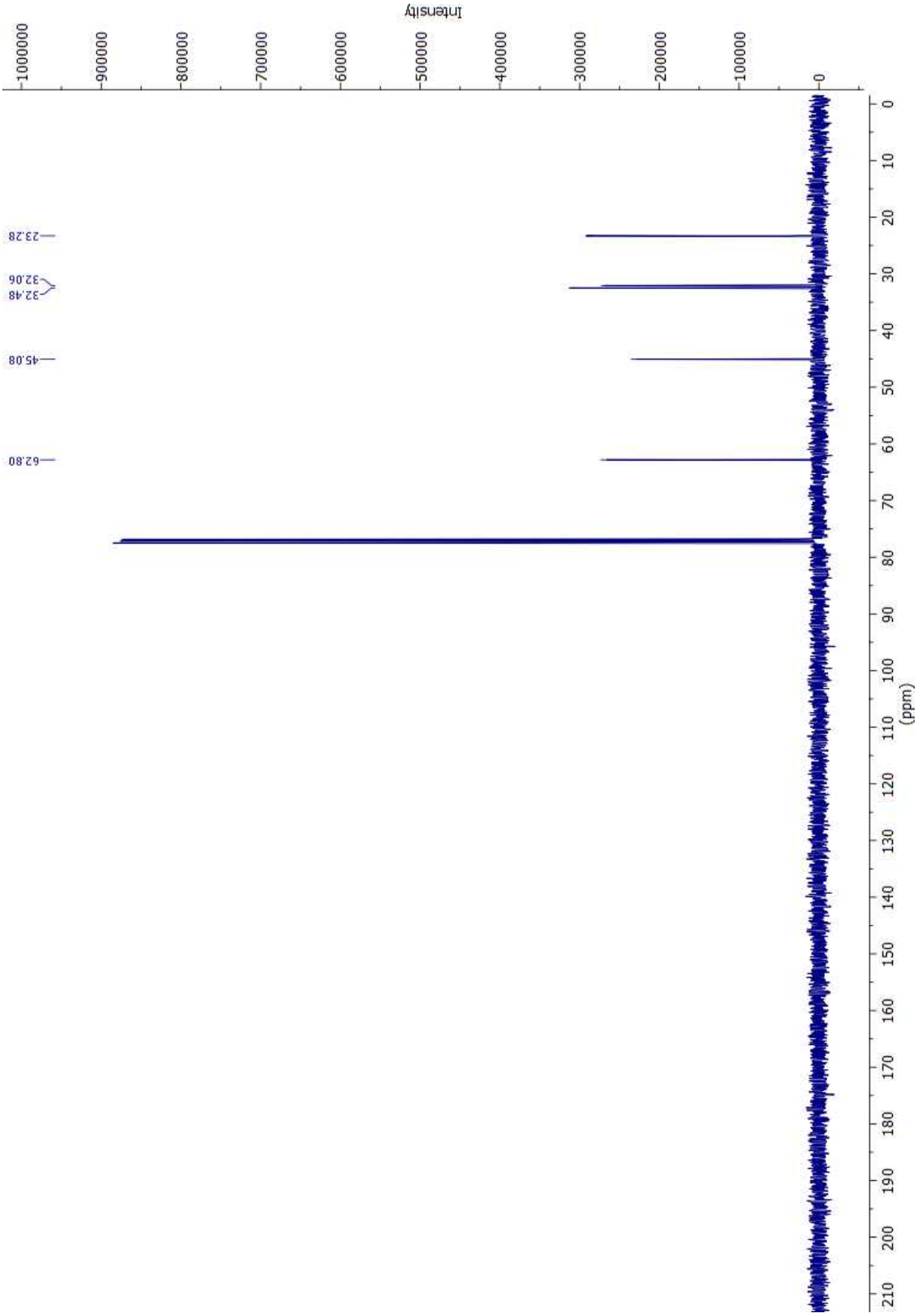
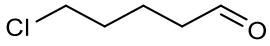


Figure 5 ^{13}C-NMR spectre of 5-chloro-1-pentanol

5.2 Synthesis of 5-chloropentanal



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Chloroalcohol (4.1 mmol, 0.50 g, 0.48 mL) was diluted with CH_2Cl_2 (30 mL) and carefully added DMP (2.25 g, 5.3 mmol, 1.3 eq.) dissolved in 20 mL CH_2Cl_2. The reaction was stirred at ambient temperature for 1.5 h, whereupon TLC analysis showed full consumption of the alcohol. The reaction was diluted successively with sat. $NaHCO_3$ (12.5 mL) and sat. $Na_2S_2O_3$ (12.5 mL), extracted with CH_2Cl_2 (3x 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure at 0 ^{O} C. The concentrated heterogenous mixture was purified by flash chromatography yielding the desired aldehyde as a clear oil.

Yield: 0.45 g, 91 %.

R_f: 0.48 (4:1 hex/EtOAc).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.76 (q, *J* = 1.9 Hz, 1H), 3.54 (qd, *J* = 6.1, 4.9, 1.9 Hz, 2H), 2.48 (td, *J* = 5.9, 5.5, 3.3 Hz, 2H), 1.79 (dh, *J* = 6.4, 3.0 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.89, 44.55, 43.06, 31.87, 19.46.

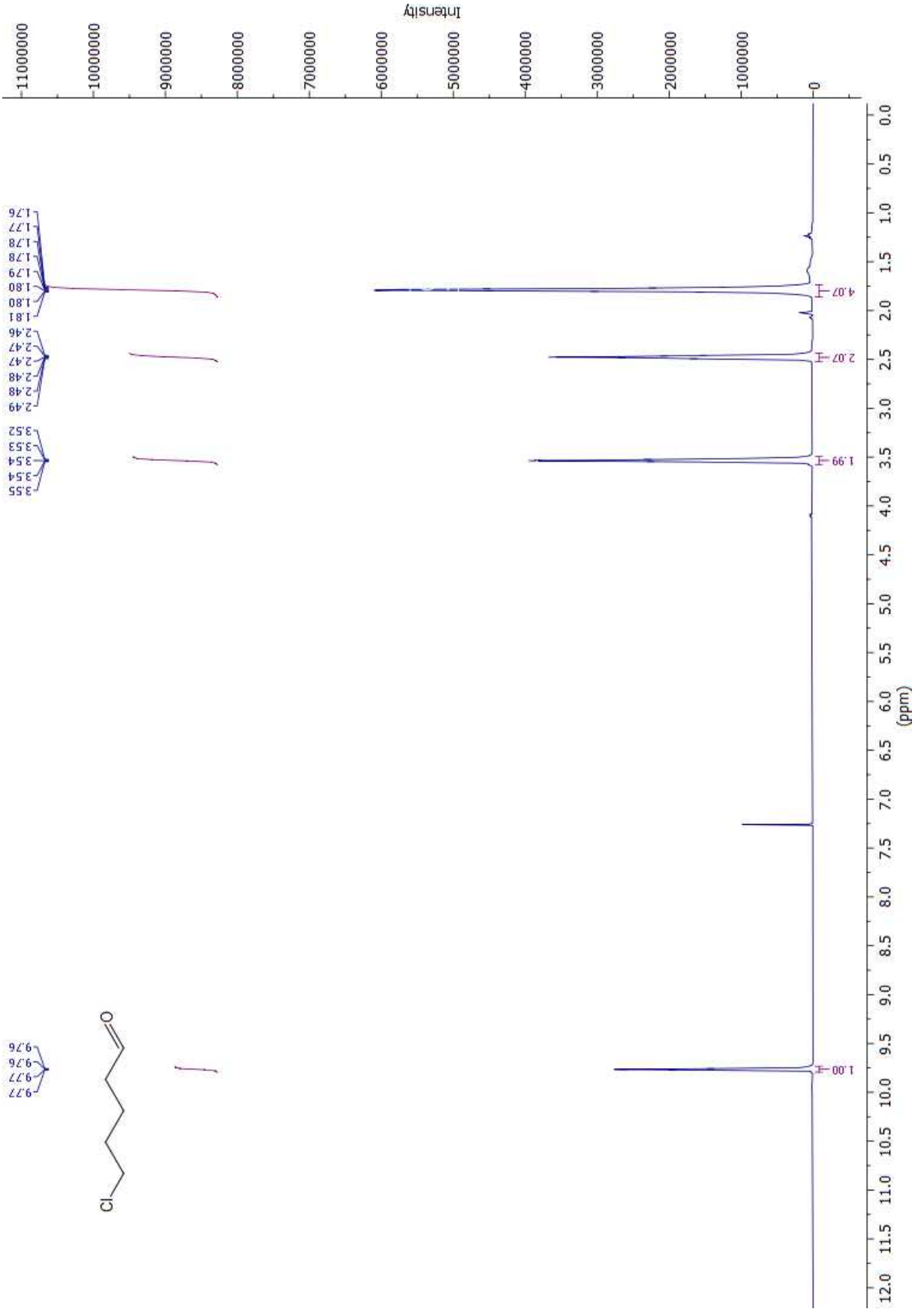


Figure 6 ^{1}H-NMR spectre of 5-chloropentanal

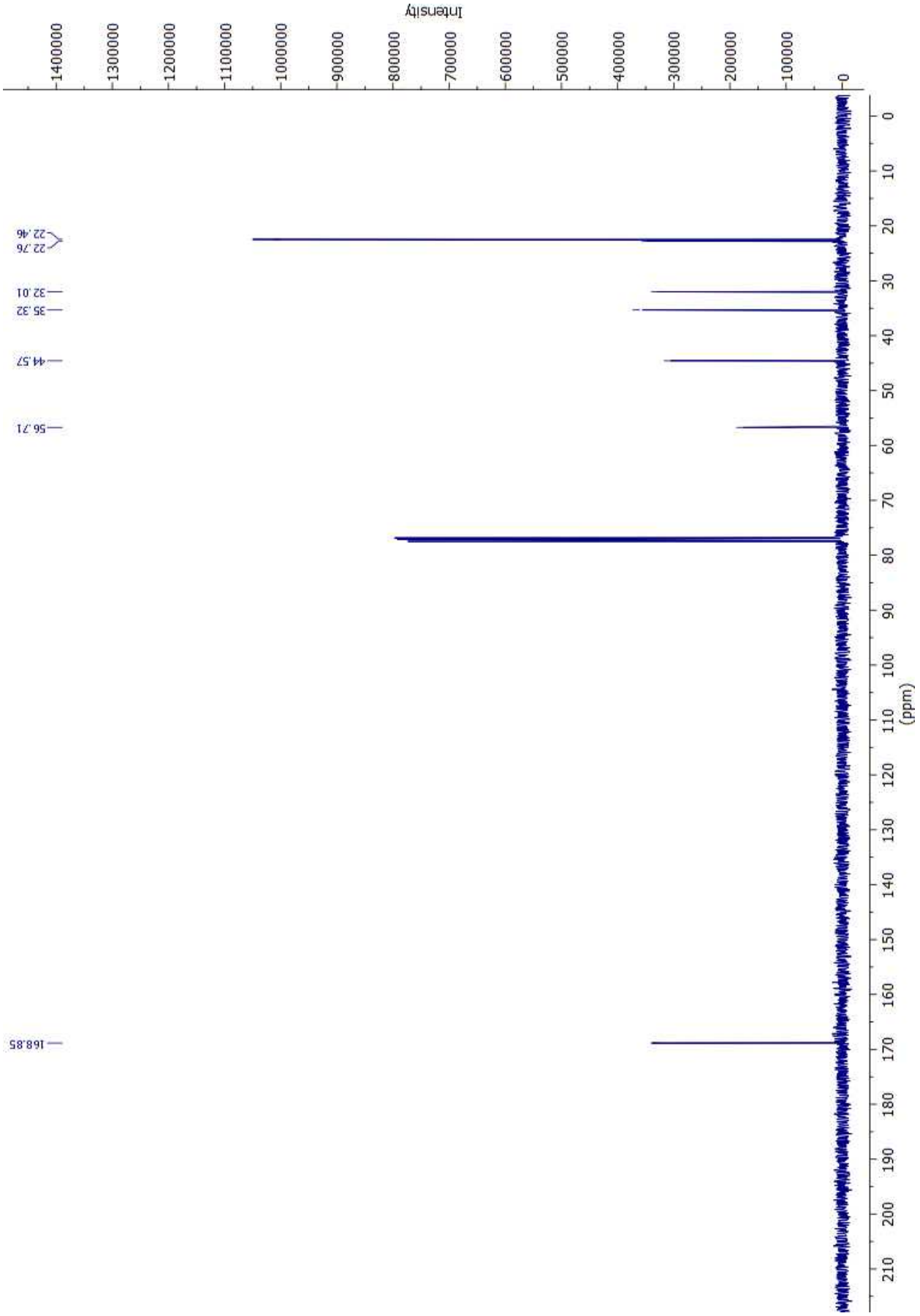
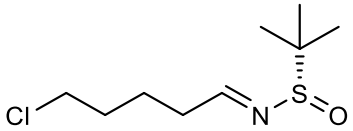


Figure 7 ^{13}C-NMR spectre of 5-chloropentanol

5.3 Synthesis of (S,E)-N-(5-Chloropentylidene)-2-methylpropane-2-sulfinamide



To a solution of 5-chloropentan-1-ol (0.7215 g, 5,885 mmol) in DCM (50 mL), DMP (3.25 g, 7.65 mmol, 1.3 eq.) diluted in CH_2Cl_2 (25 mL) was carefully added and stirred for 1.5 h. whereupon TLC analysis showed full consumption of the alcohol. The mixture was diluted with 20 mL sat. $Na_2S_2O_3$ and 20 mL sat. $NaHCO_3$ and extracted 3x in CH_2Cl_2 (3x 30 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure resulting in a heterogenous mixture filtered through a silica plug. The crude solution of 5-chloropental was added CH_2Cl_2 (100 mL) and anhydrous $CuSO_4$ powder (2.16 g, 13.54 mmol, 2.3 eq.) followed by (S)-2-methylpropane-2-sulfinamide (0.87 g, 7.18 mmol, 1.2 eq.). The reaction was stirred overnight, and TLC analysis showed full consumption of the aldehyde. The heterogeneous mixture was filtered through a silicapad, concentrated under reduced pressure and purified by flash chromatography to yielding the desired product as an amber, viscous oil.

Yield: 1.07 g, 81 %

R_f: 0.21 (4:1 hex/EtOAc)

$[\alpha]_D^{20}$: +230.7° (c 1.2 g/100 mL, CH_3Cl).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 (td, *J* = 4.4, 2.0 Hz, 1H), 3.55 (qd, *J* = 6.3, 1.9 Hz, 2H), 2.55 (tdd, *J* = 6.8, 4.4, 1.8 Hz, 2H), 1.89 – 1.76 (m, 5H), 1.19 (d, *J* = 2.0 Hz, 10H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.85, 56.71, 44.57, 35.32, 32.01, 22.76, 22.46.

UV absorption: A_{243} = 3597, : A_{249} = 3601

IR: 2958, 2869, 1622, 1460, 1085 cm^{-1}

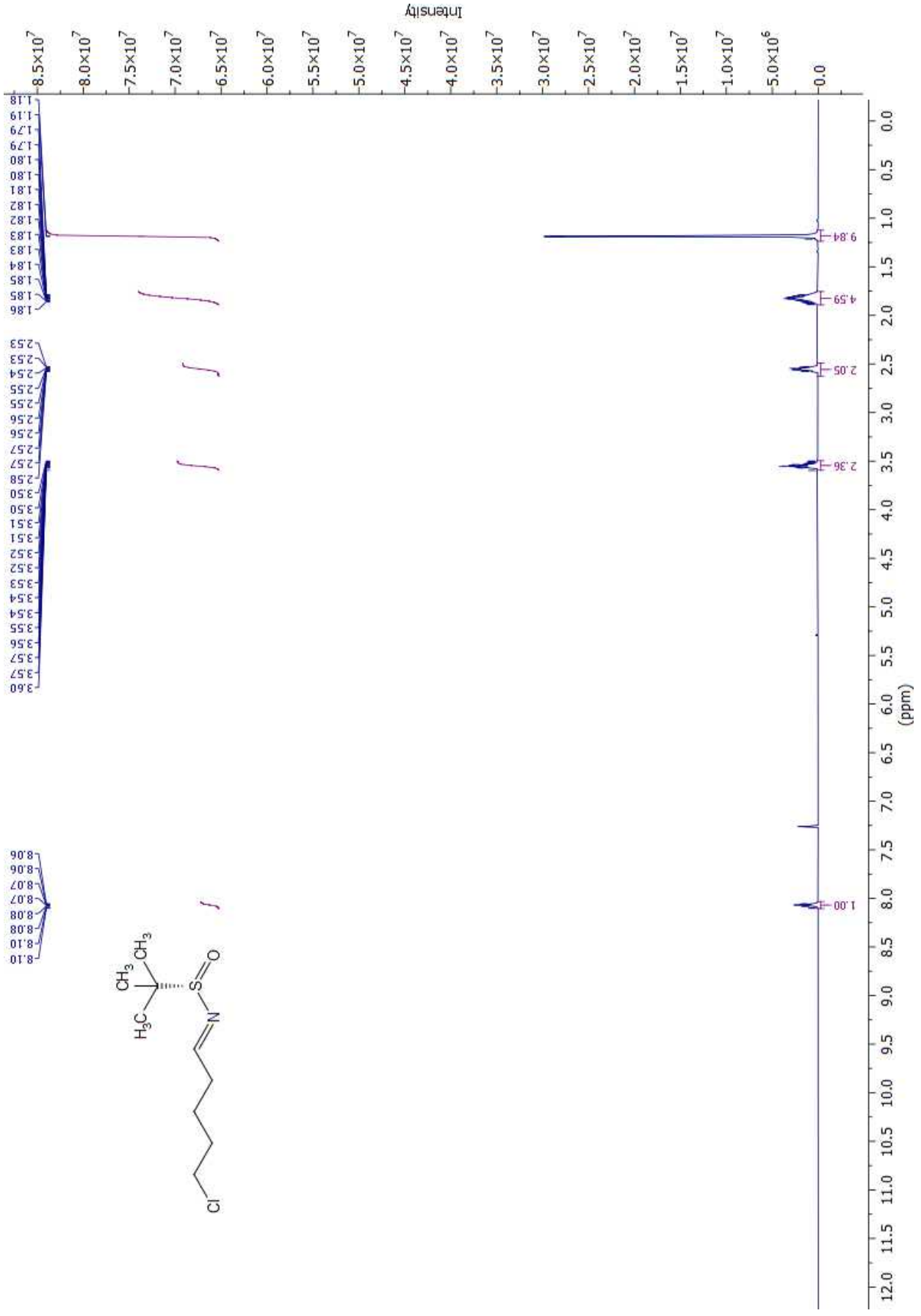


Figure 8 ^{1}H-NMR spectre of *(S,E)-N-(5-Chloropentylidene)*-2-methylpropane-2-

sulfinamide

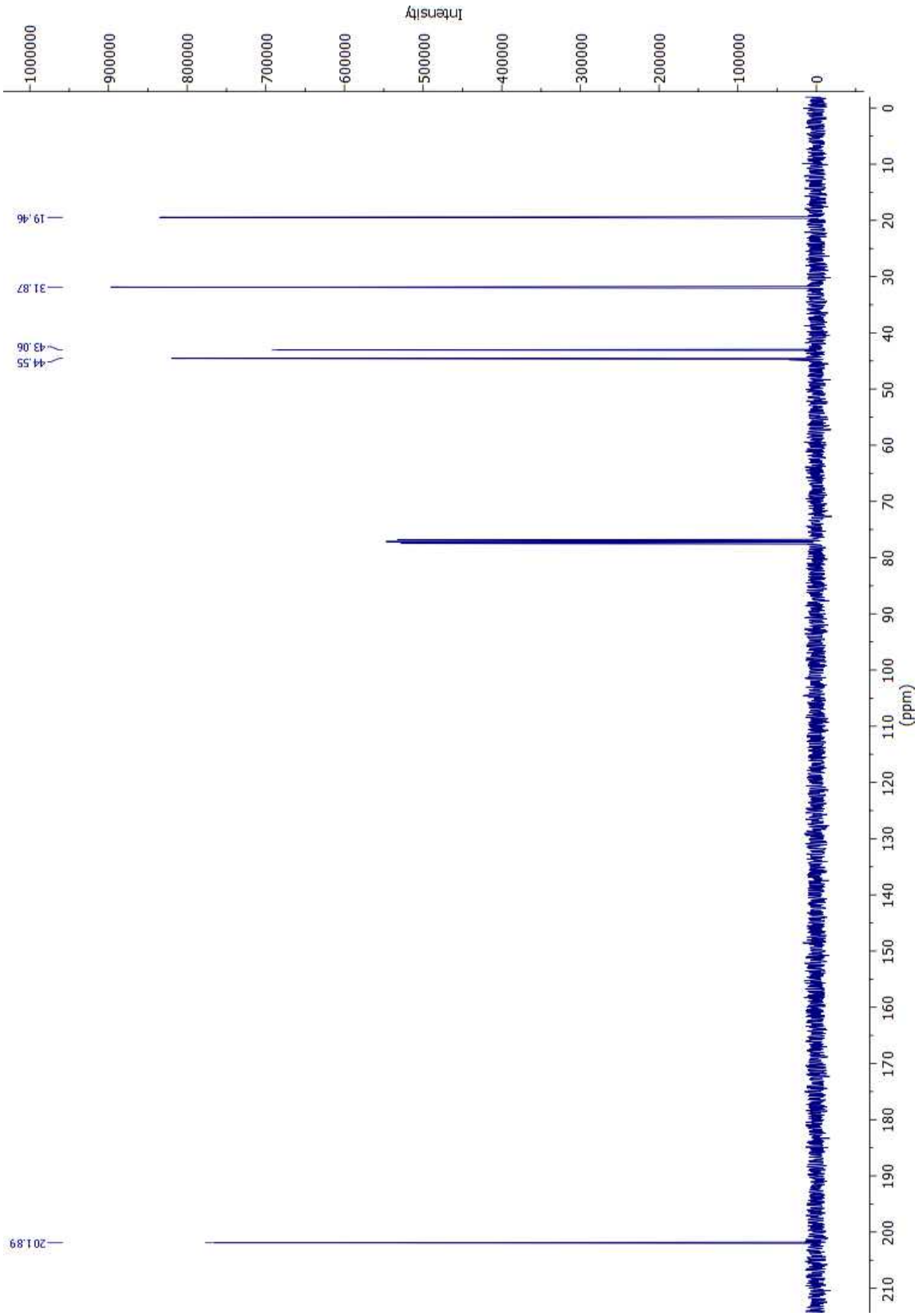


Figure 9 ^{13}C-NMR spectre of *(S,E)-N-(5-Chloropentylidene)*-2-methylpropane-2-sulfinamide

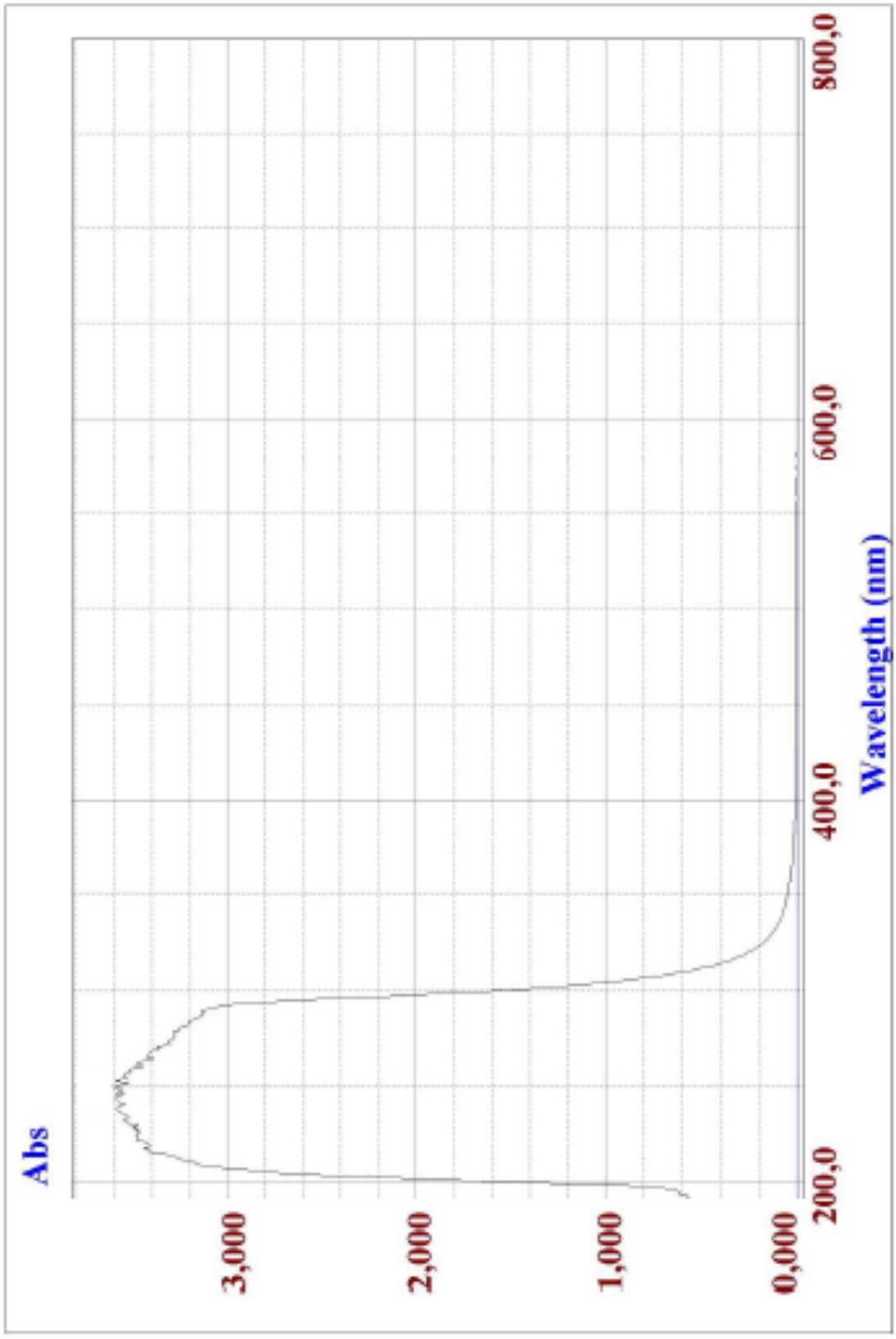


Figure X UV-spectre of *(S,E)-N-(5-Chloropentylidene)*-2-methylpropane-2-sulfinamide

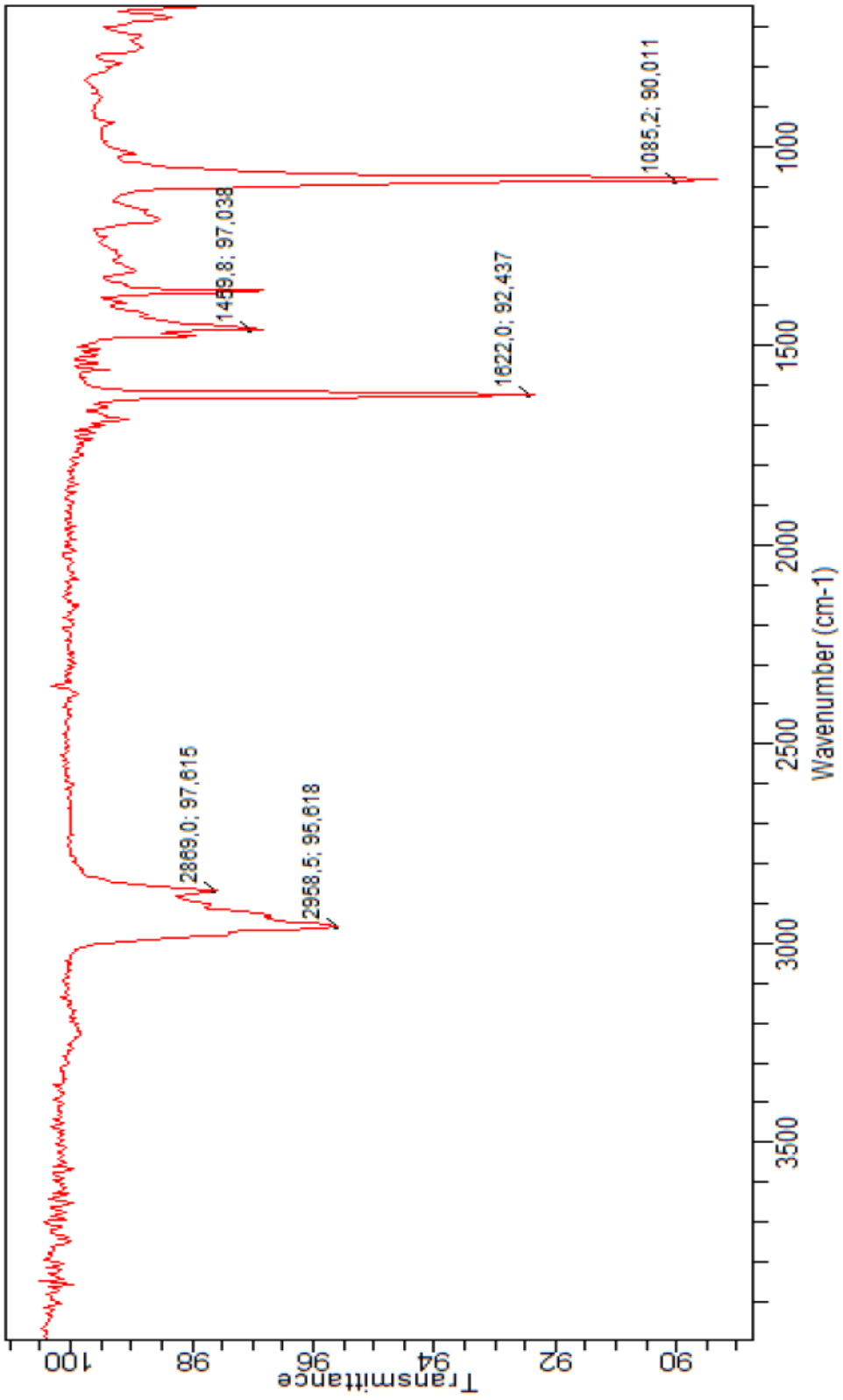
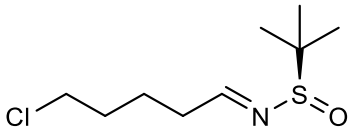


Figure X IR-spectre of *(S,E)-N-(5-Chloropentylidene)*-2-methylpropane-2-sulfinamide

5.4 Synthesis of (R,E)-N-(5-Chloropentylidene)-2-methylpropane-2-sulfinamide



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Synthesized as XX using instead the enantiomer Ellman reagent, (*R*)-2-methylpropane-2-sulfinamide, yielding an amber, viscous oil.

Yield: 1.09 g, 91 %

R_f: 0.21 (4:1 hex/EtOAc)
$[\alpha]_D^{20}$: -235.9° (c 1.25 g/100 mL, CH_3Cl).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 (q, *J* = 4.3 Hz, 1H), 3.55 (td, *J* = 5.7, 3.4 Hz, 2H), 2.55 (tq, *J* = 6.0, 3.7 Hz, 2H), 1.83 (ddtd, *J* = 16.5, 12.3, 8.8, 7.5, 4.1 Hz, 4H), 1.24 – 1.16 (m, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.85, 56.71, 44.57, 35.32, 32.02, 22.76, 22.47.

UV absorption: A_{231} = 3475, : A_{243} = 3507

IR: 2958, 2869, 1622, 1460, 1085 cm^{-1}

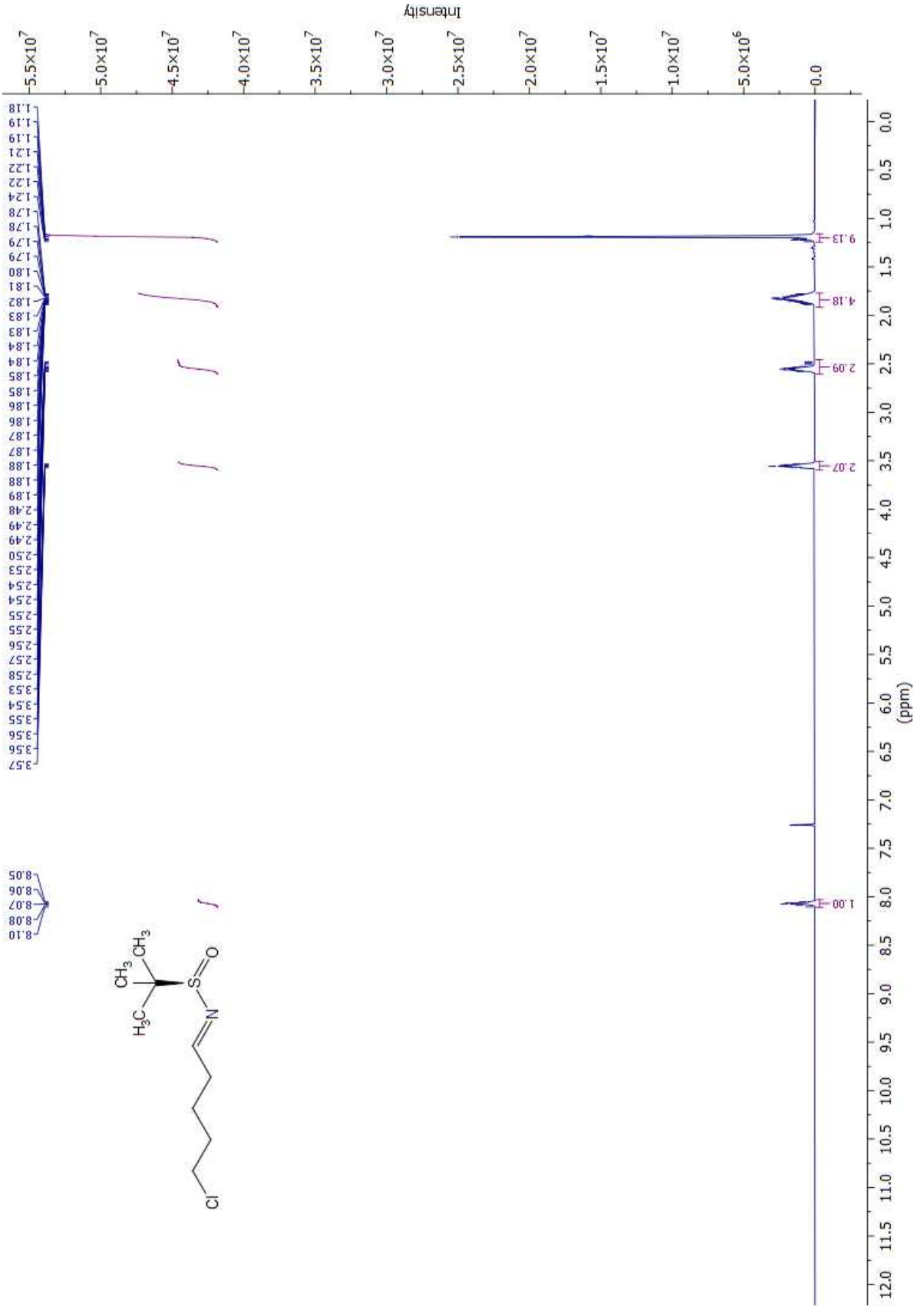


Figure [1]H-NMR spectre of *(R,E)-N-(5-Chloropentylidene)*-2-methylpropane-2-sulfinamide

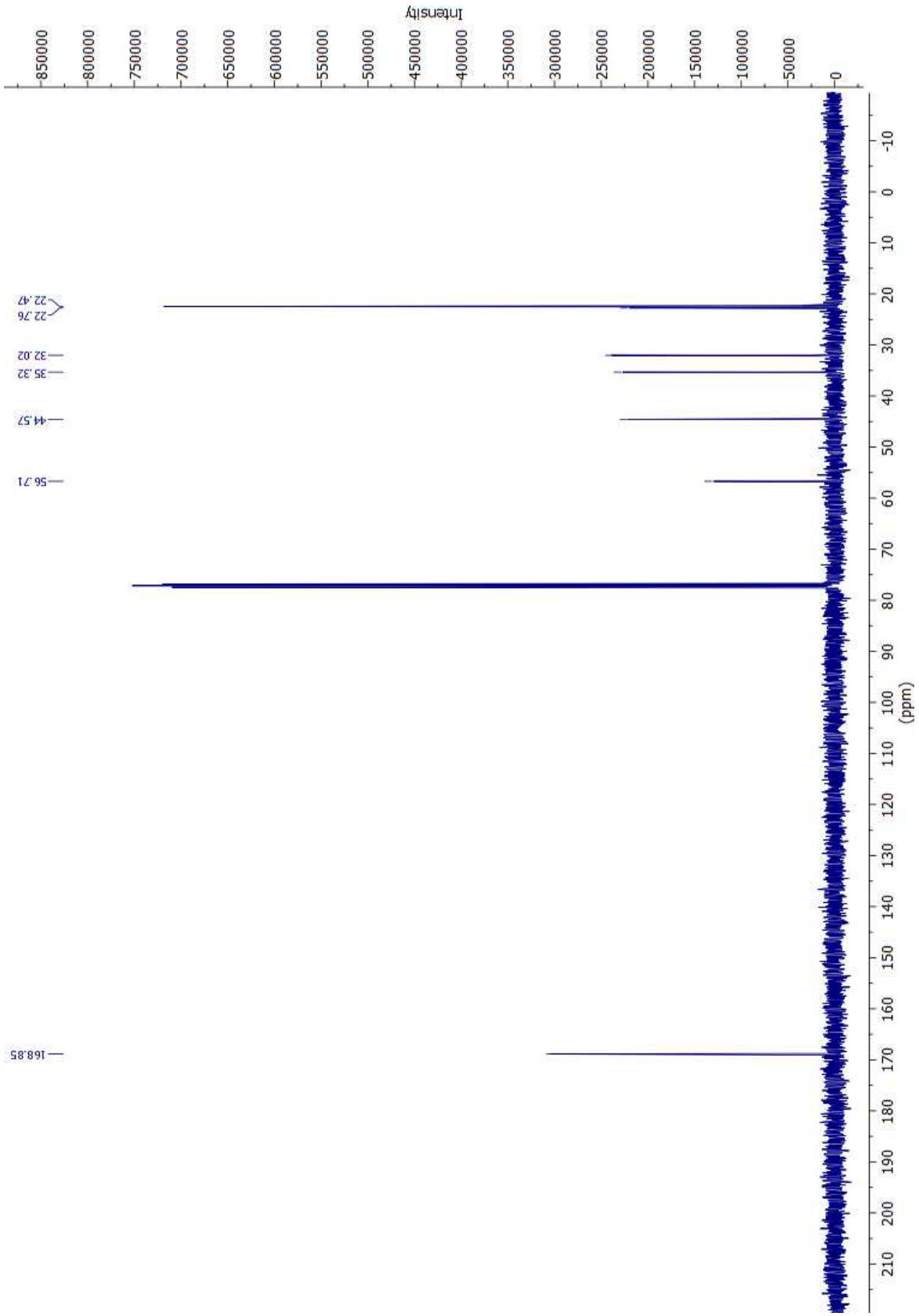


Figure ^{13}C-NMR spectre of *(S,E)-N-(5-Chloropentylidene)*-2-methylpropane-2-sulfinamide

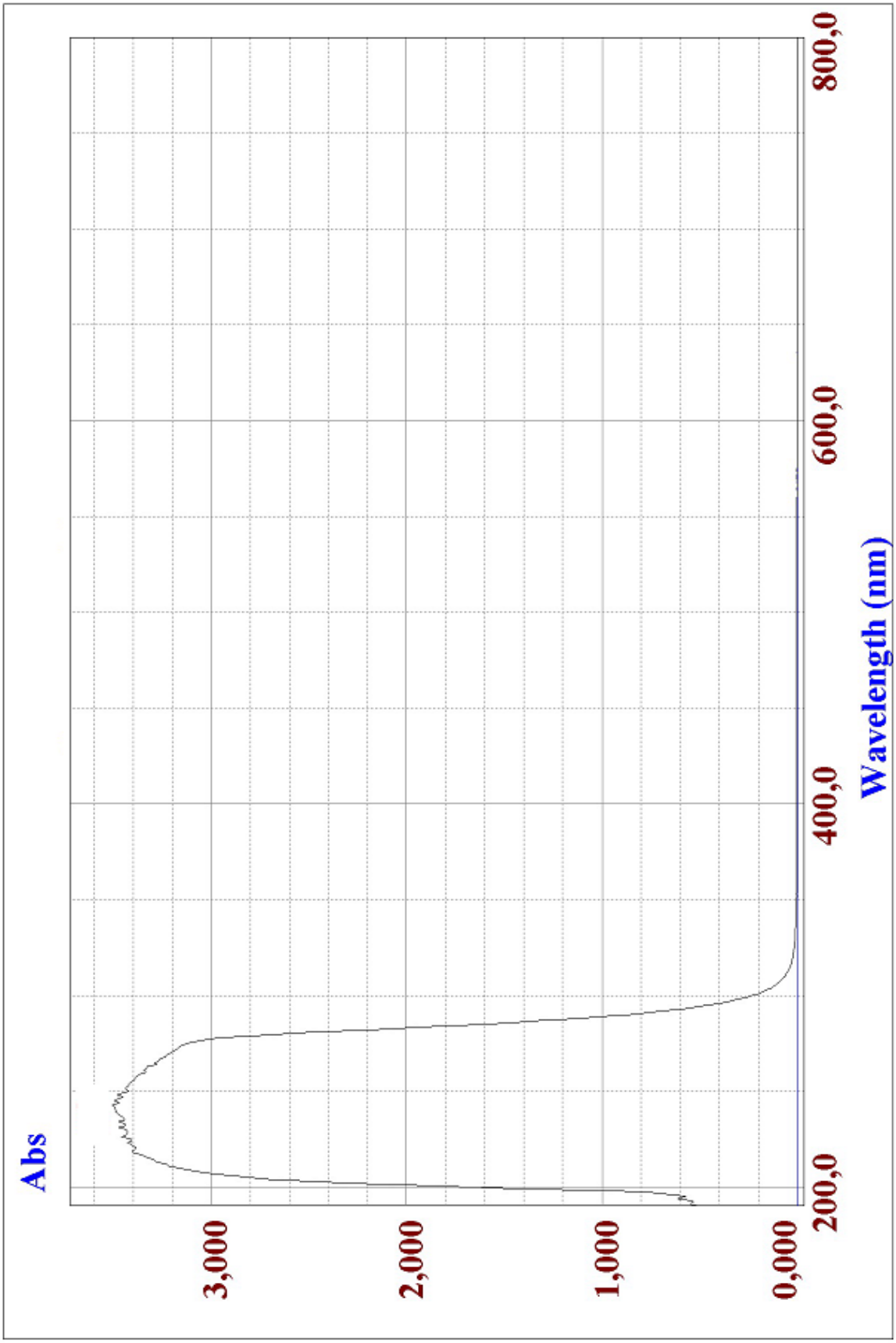


Figure X UV-spectre of *(R,E)-N-(5-Chloropentylidene)*-2-methylpropane-2-sulfinamide

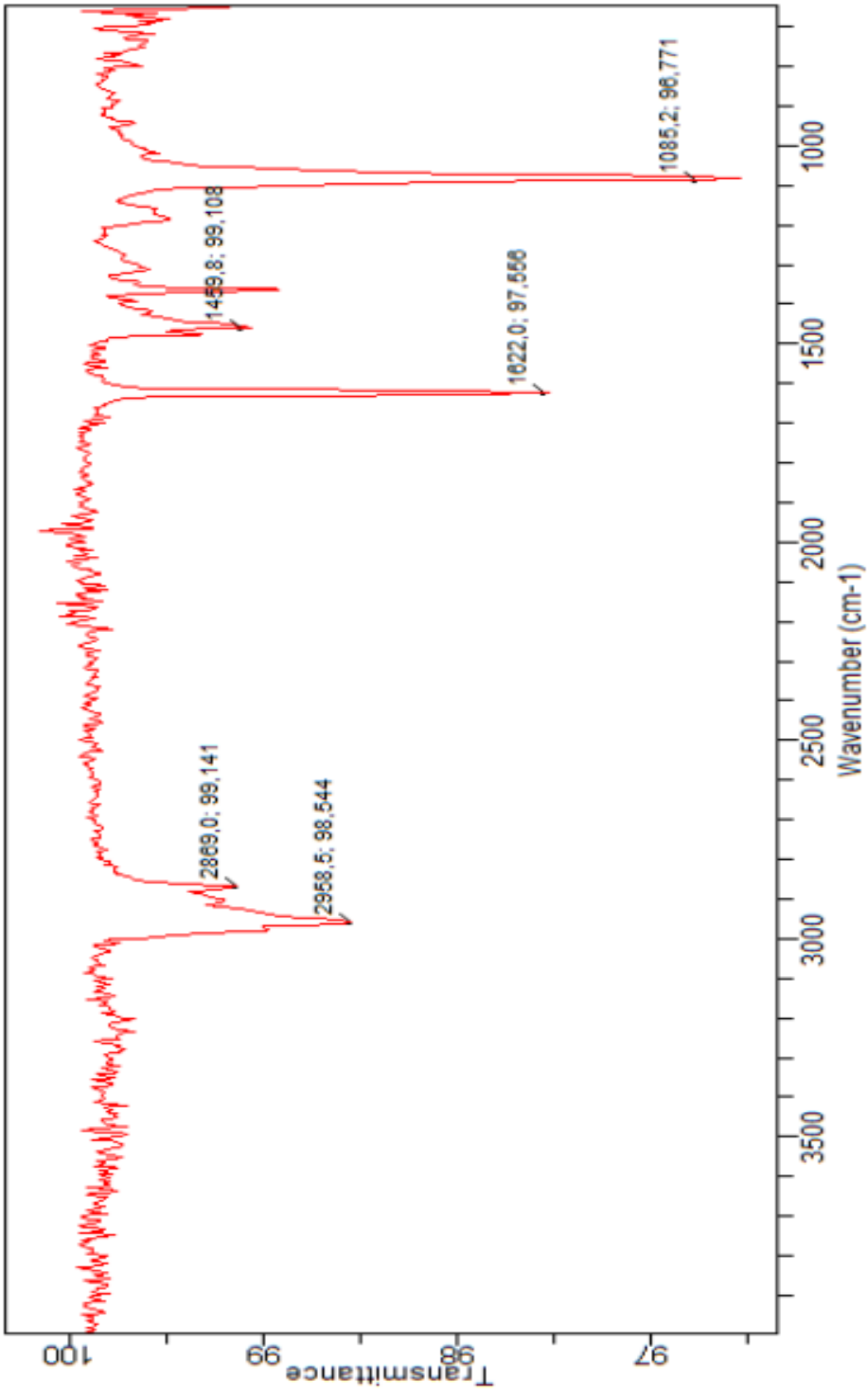
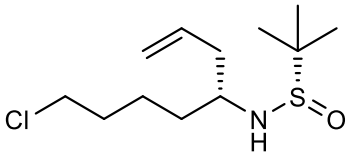


Figure X IR-spectre of *(R,E)-N-(5-Chloropentylidene)*-2-methylpropane-2-sulfinamide

5.X Synthesis of (S)-N-(R)-8-Chlorookt-1-en-4-yl-2-methylpropane-2-sulfinamide



NaBr (38 g) was dissolved in H_2O (84 mL, Millii-Q) and the resulting saturated NaBr solution was added to the sulfinimine X (1.0681 g, 4.773 mmol) followed by indium powder (2.2 g, 19 mmol, 4 eq.). The heterogenous mixture was stirred vigorously for 10 min. and then added allylbromide (2.3 g, 1.65 mL, 19 mmol, 4 eq.). The mixture was stirred overnight whereupon TLC showed full consumption of the starting material. The reaction mixture was quenched with sat. $NaHCO_3$ (40 mL), extracted with EtOAc (6x 40 mL) and washed with brine (40 mL). The collected organic fractions were dried over Na_2SO_4 and concentrated under reduced pressure to yield a crude oil purified by flash chromatography affording the desired product as an amber, viscous oil.

Yield: 1.08 g, quantitative

R_f: 0.33 (1:1 hex/EtOAc)
$[\alpha]_D^{20}$ +56.6° (*c* 0.4 g/100 mL, $CHCl_3$)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.84 – 5.69 (m, 1H), 5.20 – 5.08 (m, 2H), 3.56 – 3.48 (m, 2H), 3.34 – 3.17 (m, 1H), 2.46 – 2.25 (m, 2H), 1.83 – 1.69 (m, 2H), 1.60 – 1.43 (m, 4H), 1.29 – 1.17 (m, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 133.99, 119.09, 55.81, 54.61, 44.85, 40.39, 34.13, 22.66.

UV absorption: A_{216} = 2946.

IR: 3232, 2953, 2869, 1639, 1454, 1057 cm^{-1}

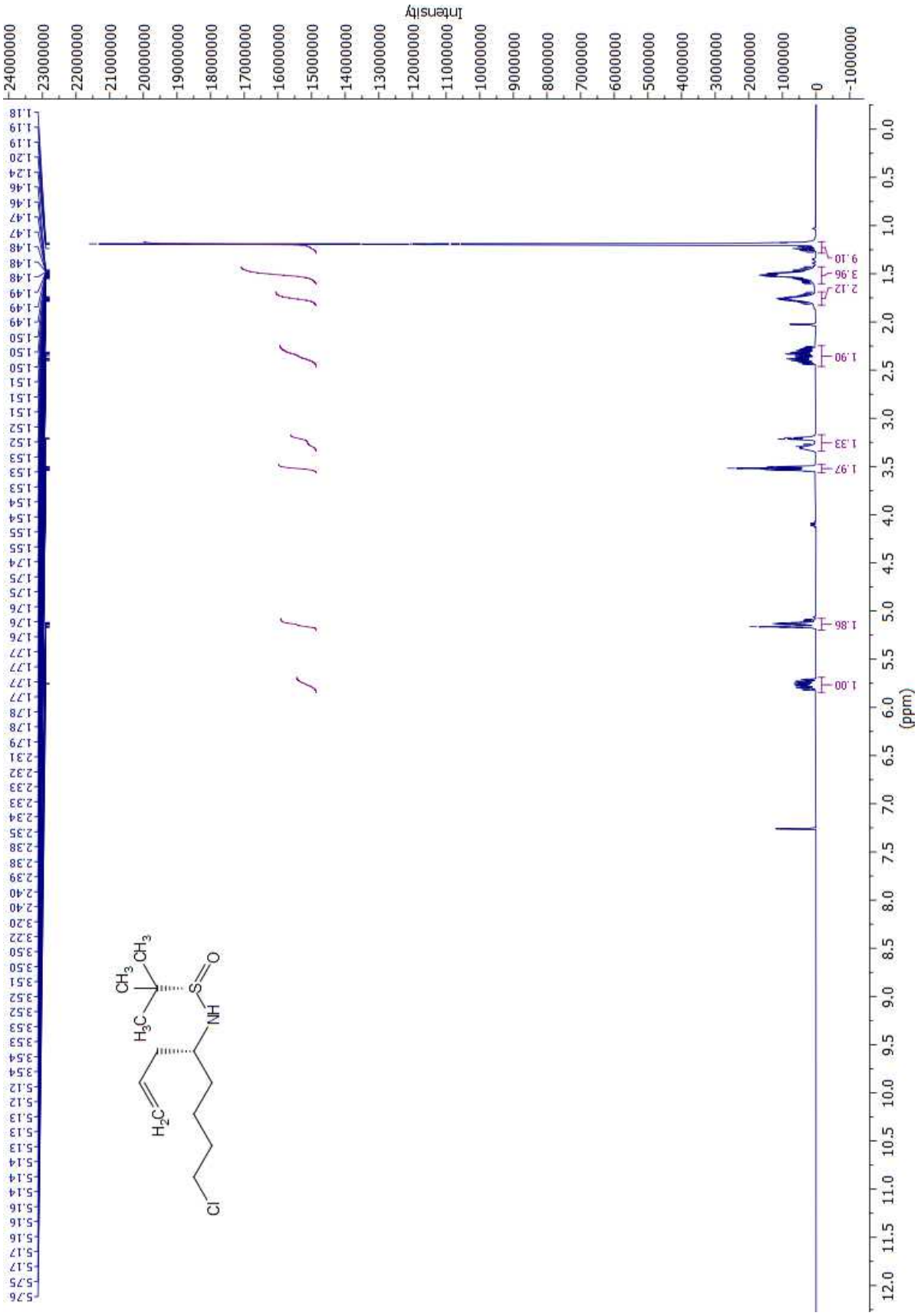


Figure X ^{1}H NMR-spectre of *(S)-N-(R)-8-Chlorookt-1-en-4-yl-2-methylpropane-2-sulfinamide*

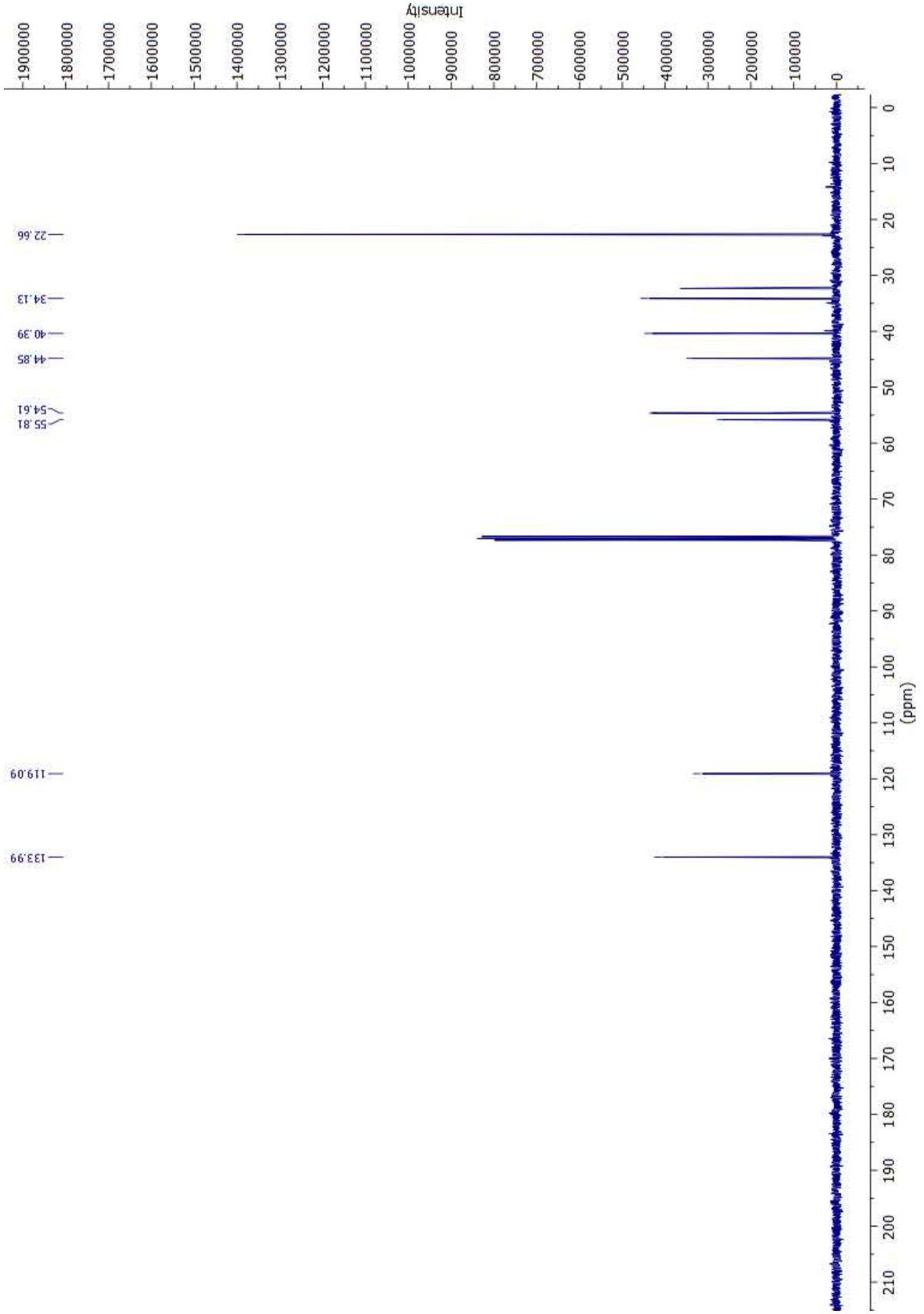
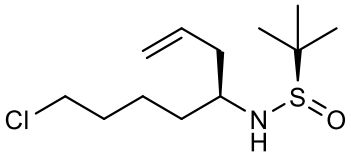


Figure X ^{13}C NMR-spectre of *(S)-N-(R)-8-Chlorookt-1-en-4-yl-2-methylpropane-2-sulfinamide*

5.X Synthesis of (R)-N-(S)-8-Chlorookt-1-en-4-yl-2-methylpropane-2-sulfinamide



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Synthesized with the same procedure as XX. Yielded a lightly yellow oil.

Yield: 1.20 g, 93 %

R_f: 0.33 (1:1 hex/EtOAc)

$[\alpha]_D^{20}$ -57.2° (*c* 0.4 g/100 mL, $CHCl_3$)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.85 – 5.70 (m, 1H), 5.21 – 5.11 (m, 2H), 3.54 (t, *J* = 6.5 Hz, 2H), 3.27 (dd, *J* = 45.9, 6.1 Hz, 2H), 2.47 – 2.27 (m, 2H), 1.78 (dt, *J* = 13.0, 4.9 Hz, 2H), 1.63 – 1.42 (m, 4H), 1.21 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 134.13, 119.25, 55.95, 54.73, 45.00, 40.52, 34.28, 32.47, 22.81.

UV absorption: A_{216} = 2946.

IR: 3232, 2953, 2869, 1639, 1454, 1057 cm^{-1}

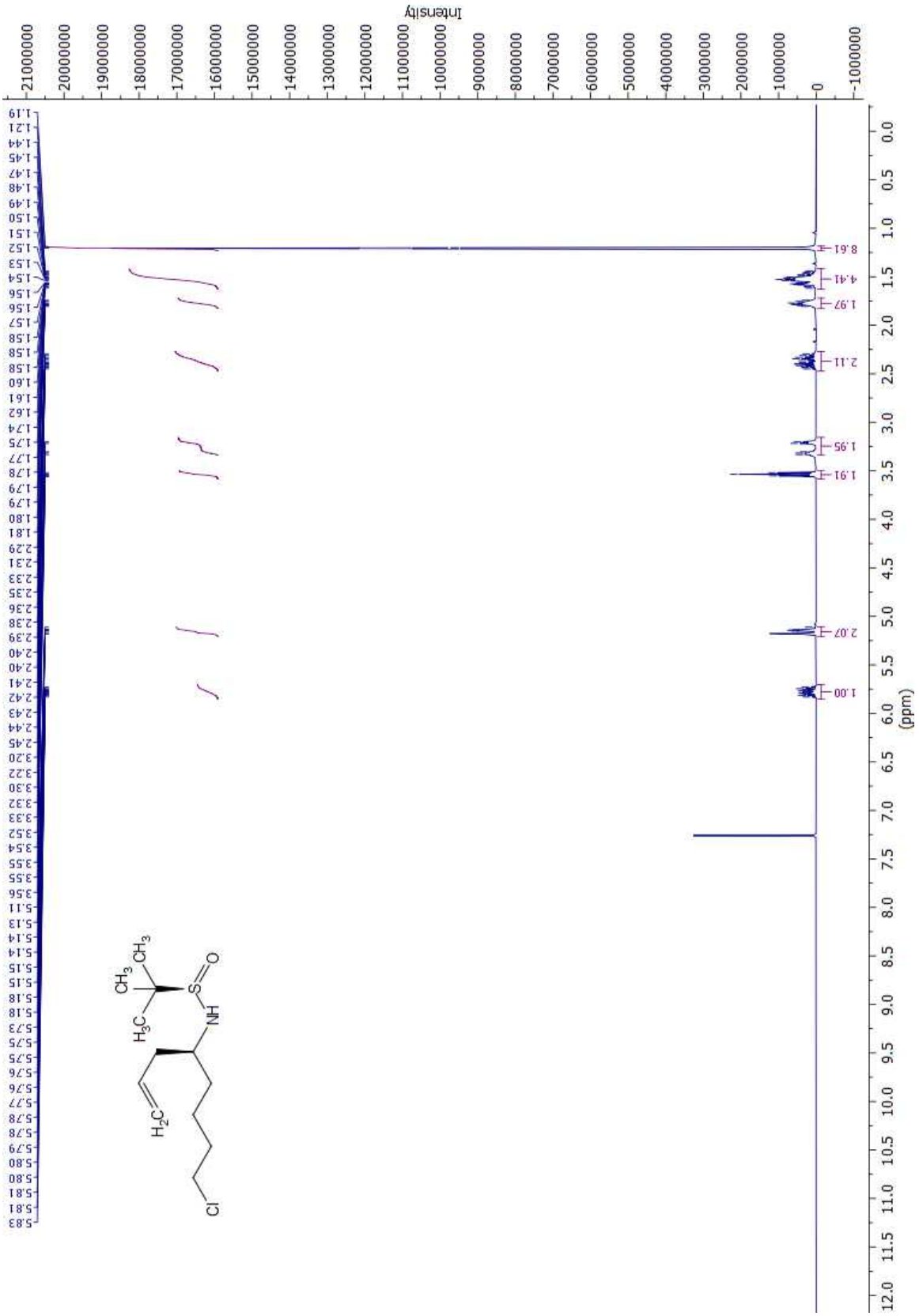


Figure X ^{1}H NMR-spectre of *(R)-N-(S)-8-Chlorookt-1-en-4-yl-2-methylpropane-2-sulfinamide*

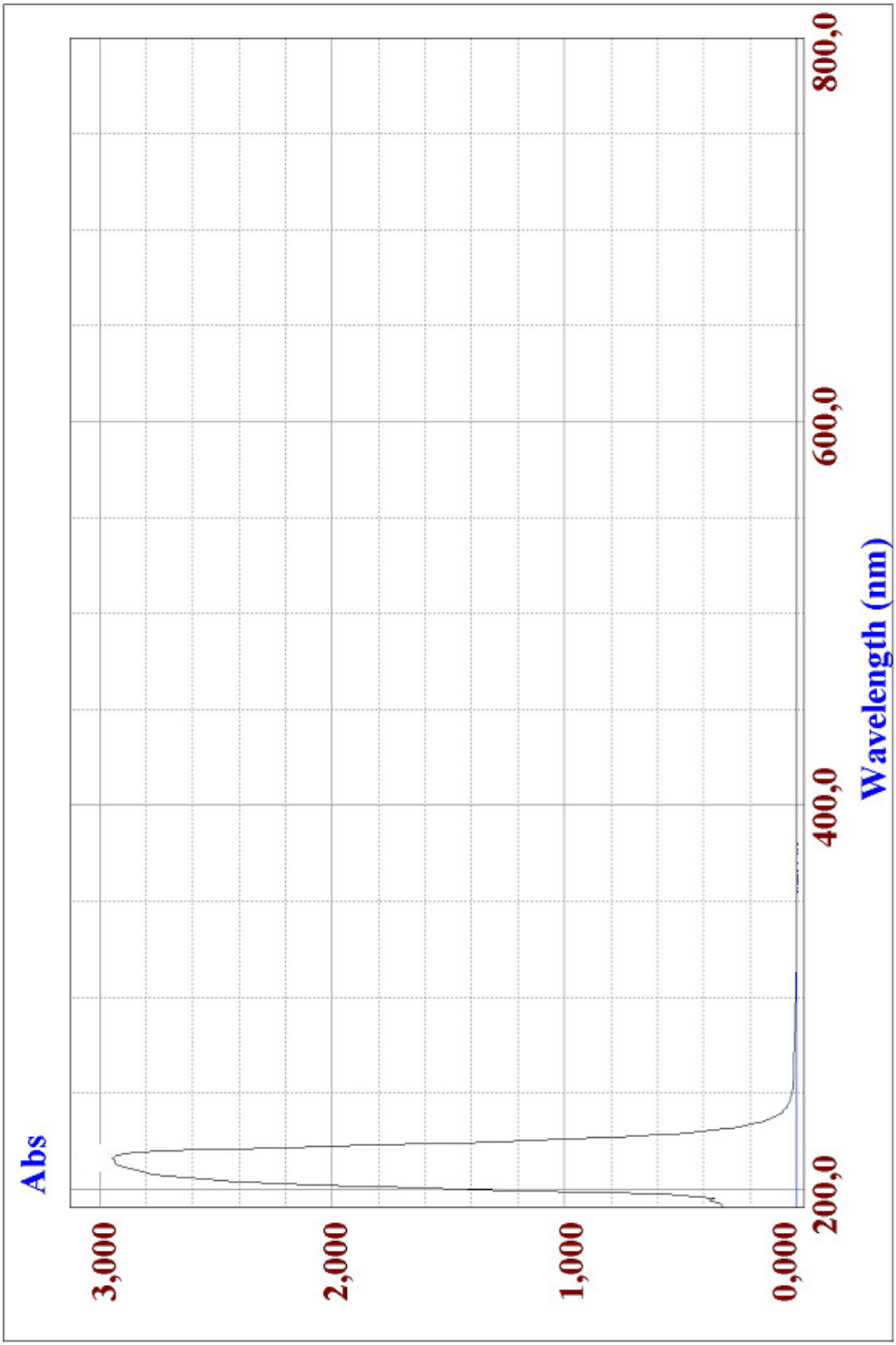


Figure X UV-spectre of *(R)-N-(S)-8-Chlorookt-1-en-4-yl-2-methylpropane-2-sulfinamide.*

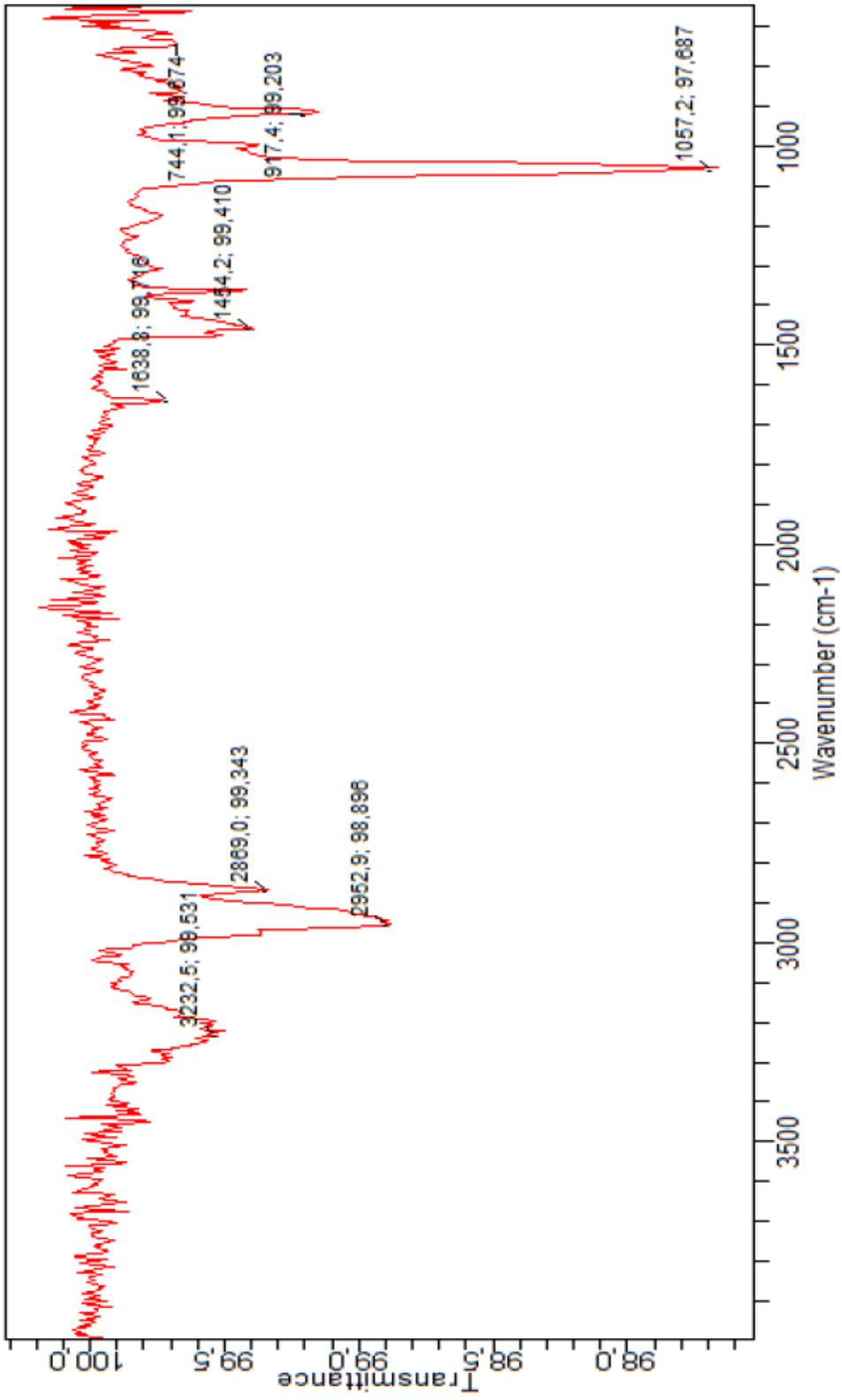
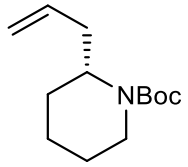


Figure X IR-spectre of *(R)-N-(S)-8-Chlorookt-1-en-4-yl-2-methylpropane-2-sulfinamide*

5.X Synthesis of *(R)-N-tert*-Butyl 2-Allylpiperidine-1-carboxylate



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A solution of HCl/dioxane solution (4 M, 1.6 mL) at 0 ^{O}C was added to the sulfinamide X (0.2134 g, 0.803 mmol) and stirred for 1 hour at room temperature, where ^{1}H-NMR specter analysis showed the amine salt fully deptrotected. The mixture was concentrated at reduced pressure. The amine salt was dissolved in DMF (5 mL), transferred to a microwave vial and added K_2CO_3 (0.222 g, 1.61 mmol) and NaI (0.132 g, 0.807 mmol) in succession. The vial was sealed and stirred for 5 minutes before submission to microwave irradiation at 120 ^{O}C for 15 minutes. The mixture was cooled to 0 ^{O}C and added aqueous sat. K_2CO_3 (10 mL) and Boc_2O dissolved in THF (10 mL) and stirred at ambient temperature overnight. The mixture was extracted with EtOAc (3x 10 mL), washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The compound was purified by flash chromatography to yield a colourless oil (0.118 g, 65 %).

Yield: 118 mg, 65 %

R_f: 0.47 (1:1 hex/EtOAc)

$[\alpha]_D^{20}$ -41.7^{o} (*c* 1.0 g/100 mL, $CHCl_3$)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.73 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 5.07 – 4.93 (m, 2H), 4.26 (s, 1H), 4.00 – 3.91 (m, 1H), 2.75 (td, *J* = 13.1, 2.7 Hz, 1H), 2.38 (dddt, *J* = 13.7, 8.3, 7.1, 1.3 Hz, 1H), 2.27 – 2.15 (m, 1H), 1.65 – 1.48 (m, 5H), 1.44 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.23, 135.76, 116.69, 79.21, 50.20, 39.01, 34.59, 28.59, 27.73, 25.62, 18.96.

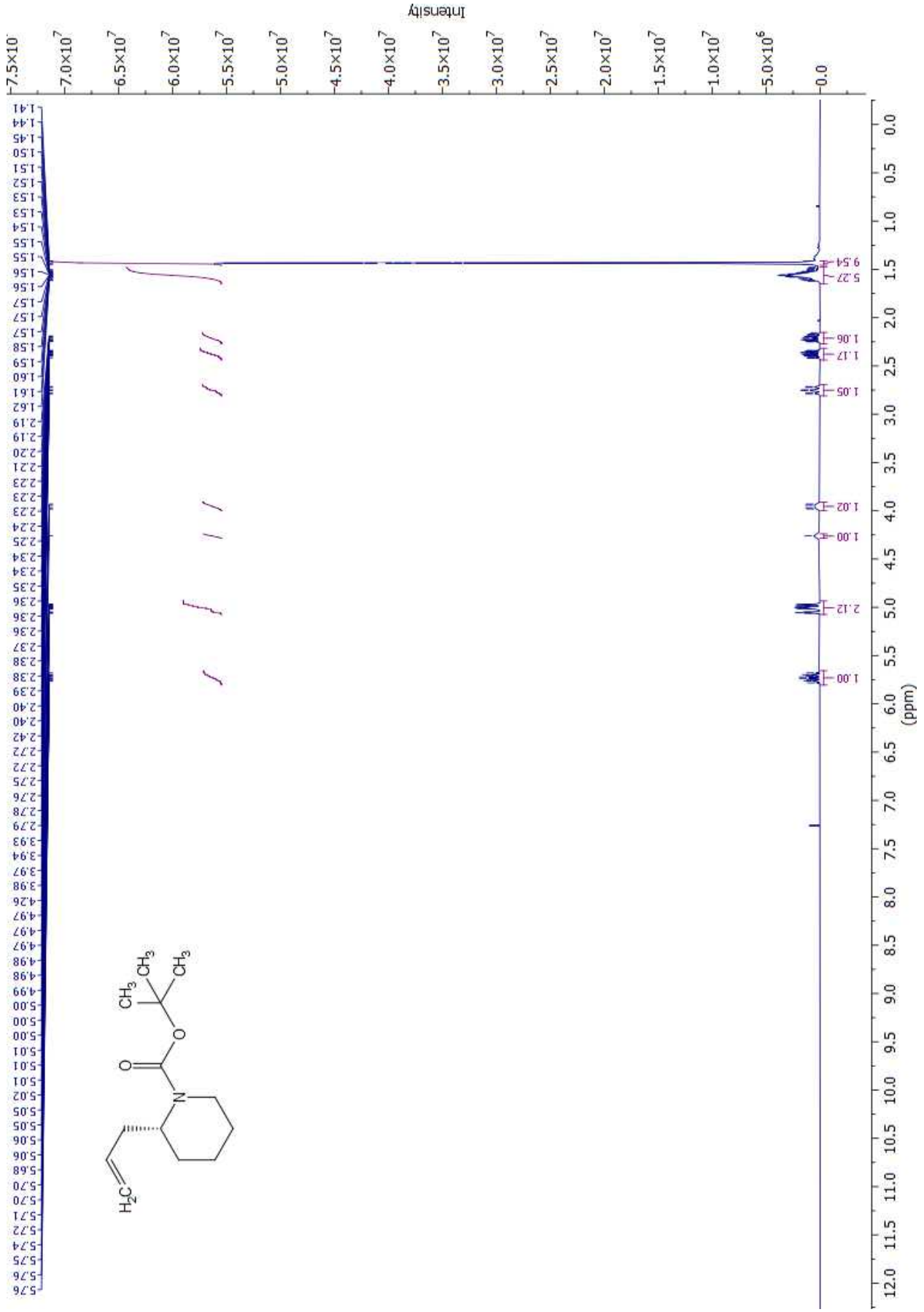


Figure X ^{1}H-NMR spectre of *(R)-N-tert*-Butyl 2-Allylpiperidine-1-carboxylate

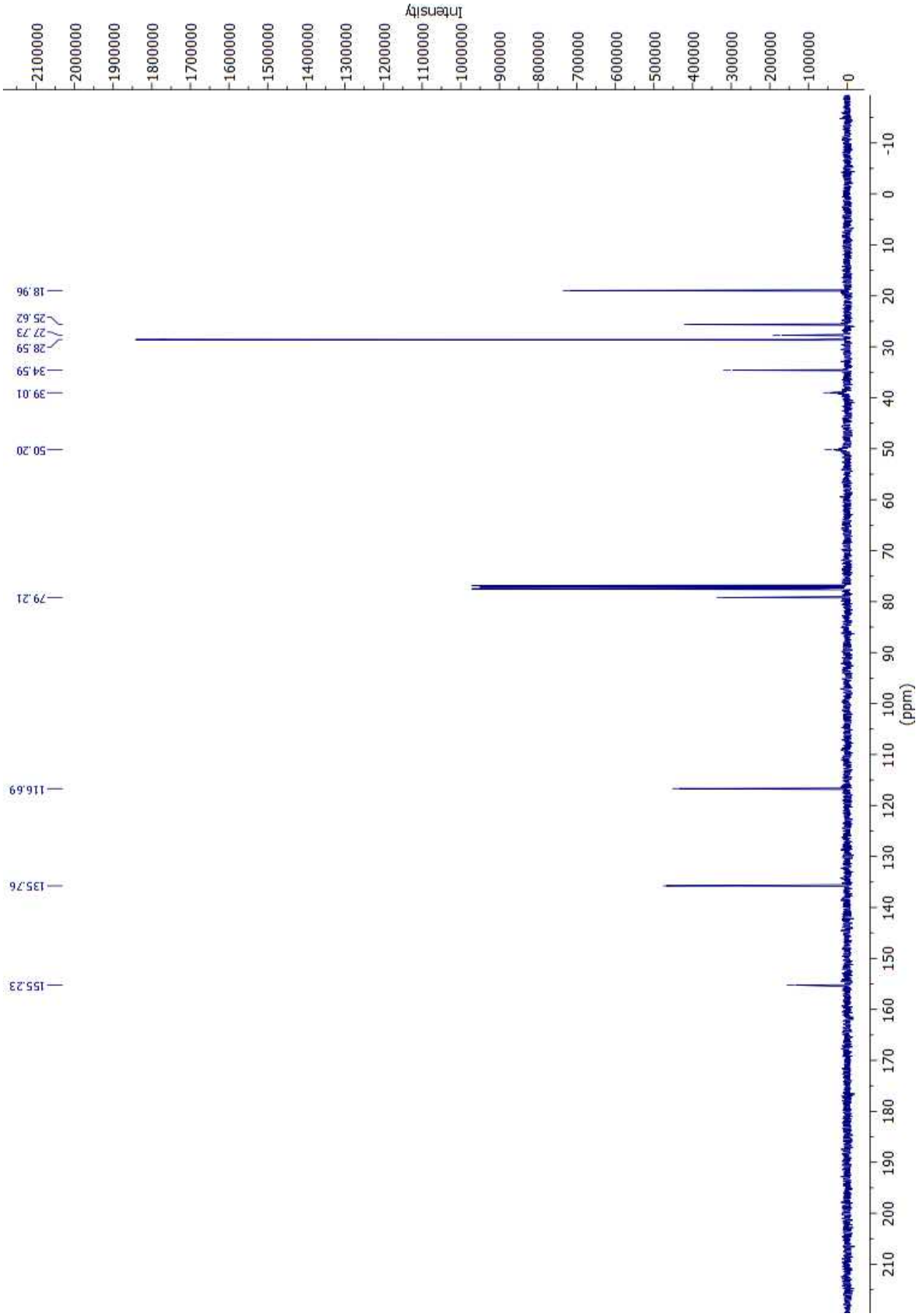
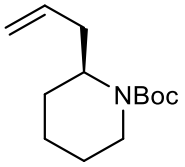


Figure X ^{13}C-NMR spectre of *(R)-N-tert*-Butyl 2-Allylpiperidine-1-carboxylate

5.X Synthesis of *(S)-N-tert*-Butyl 2-Allylpiperidine-1-carboxylate



XXXXXX

Synthesized with the same procedure as XX, with one exception where the reaction mixture was transferred to a round bottom flask, after microwave irradiation, before the next reaction step. Yielded a colourless oil.

Yield: 0.61 g, 88 %

R_f: 0.47 (1:1 hex/EtOAc)

$[\alpha]_D^{20}$ +38.9° (*c* 1.2 g/100 mL, $CHCl_3$)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.74 (ddt, *J* = 17.2, 10.1, 7.2 Hz, 1H), 5.10 – 4.93 (m, 2H), 4.27 (s, 1H), 3.96 (d, *J* = 13.6 Hz, 1H), 2.76 (td, *J* = 13.1, 2.7 Hz, 2H), 2.46 – 2.33 (m, 1H), 2.21 (dd, *J* = 14.0, 7.2 Hz, 1H), 1.64 – 1.51 (m, 7H), 1.44 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.80, 154.67, 79.90, 45.86, 44.64, 39.24, 28.88, 28.36, 25.21, 18.91.

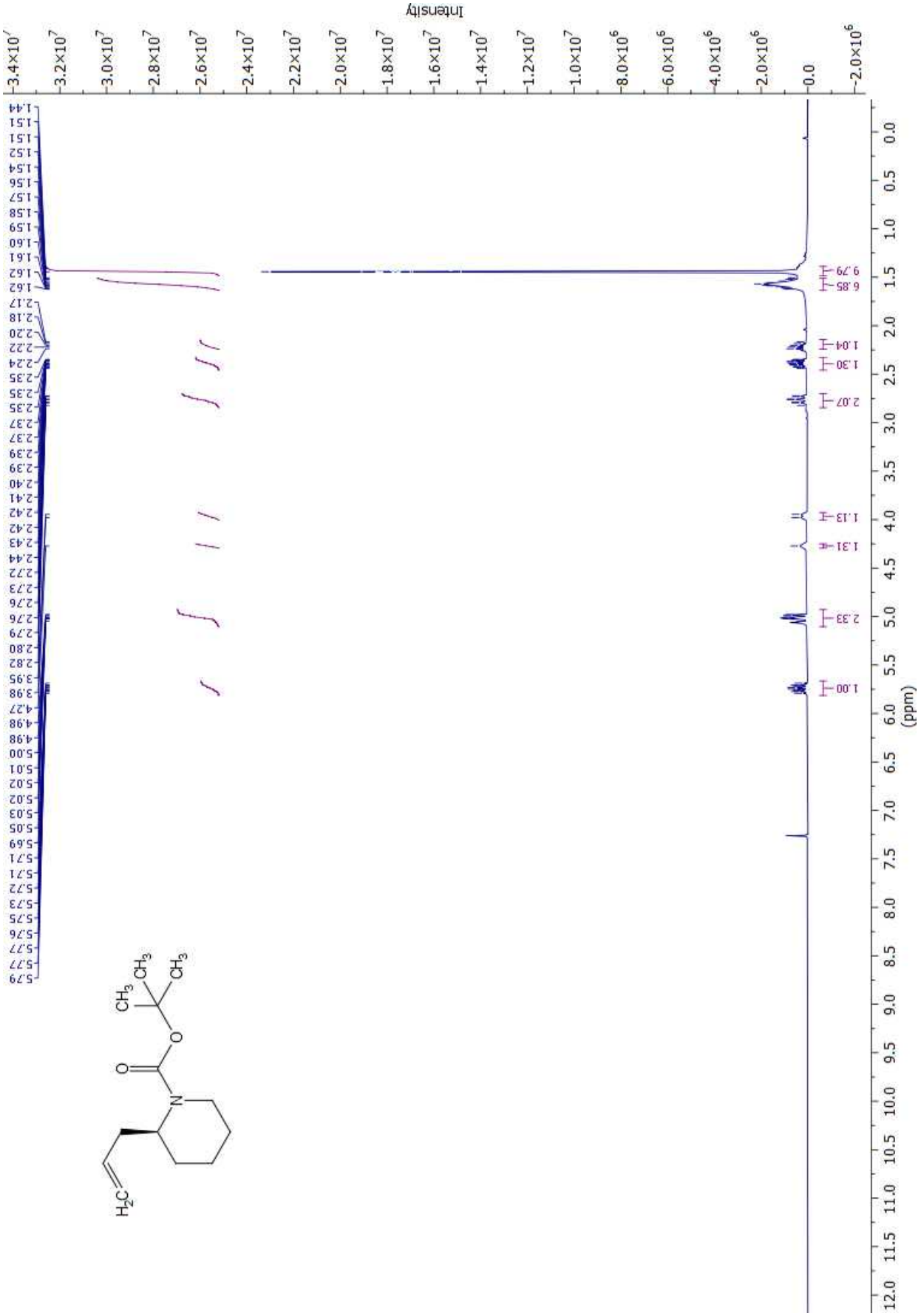


Figure X Figure X ^{1}H-NMR spectre of *(S)-N-tert*-Butyl 2-Allylpiperidine-1-carboxylate

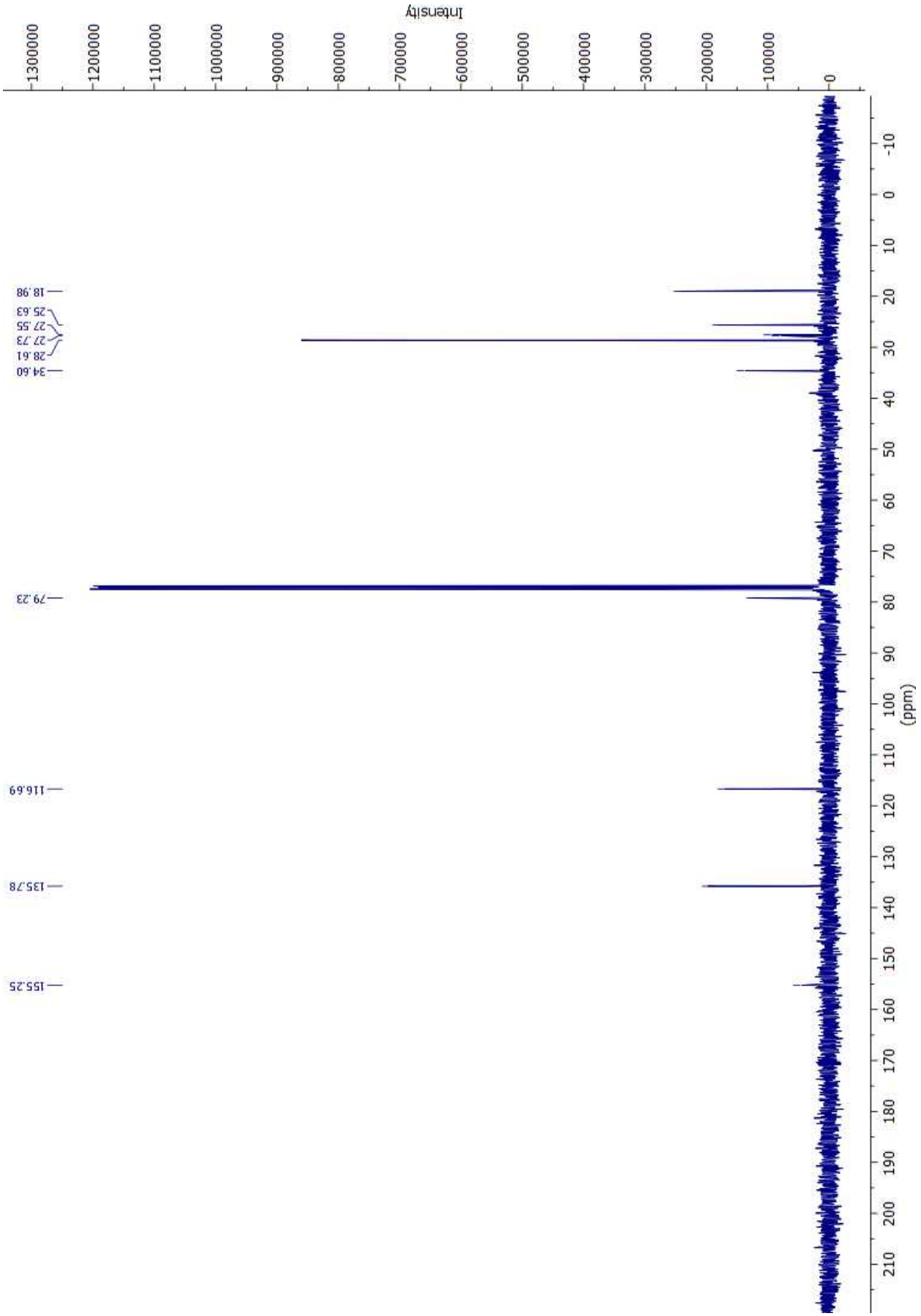
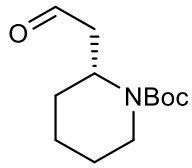


Figure X ^{13}C-NMR spectre of *(S)-N-tert*-Butyl 2-Allylpiperidine-1-carboxylate.

5.X Synthesis of tert-butyl (2S)-2-(2-oxoethyl)-piperidine-1-carboxylate



Allyl piperidine X (36.5 mg, 0.162 mmol) was added dioxane (9.5 mL) and stirred vigorously for 10 min and then added 2,6-lutidine (0.038 mL, 2 eq.), 2.5 wt% OsO_4 in *tert*-butanol (0.047 mL, 0.02 mol%), H_2O (3.2 mL, Milli-Q), $NaIO_4$ (0.14 g, 0,65 mmol, 4 eq.) and stirred for 5 hours whereupon TLC analysis showed full consumption of the starting material. The mixture was added water (8 mL) and CH_2Cl_2 (16 mL). The organic fraction was separated and the aqueous fraction extracted with CH_2Cl_2 (3x 8 mL). The combined organic fractions were washed with brine (16 mL), dried over Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography to yield a colourless oil

Yield: 36 mg, quantitative

R_f: 0.31 (7:3 hex/EtOAc)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.71 (dd, *J* = 3.3, 2.2 Hz, 1H), 4.81 (d, *J* = 8.9 Hz, 1H), 3.97 (d, *J* = 13.8 Hz, 1H), 2.81 – 2.66 (m, 2H), 2.51 (ddd, *J* = 15.3, 6.4, 2.2 Hz, 1H), 1.58 (dddd, *J* = 16.5, 14.4, 10.5, 5.5 Hz, 2H), 1.42 (s, 10H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.80, 154.67, 79.90, 45.86, 44.64, 39.24, 28.88, 28.36, 25.21, 18.91.

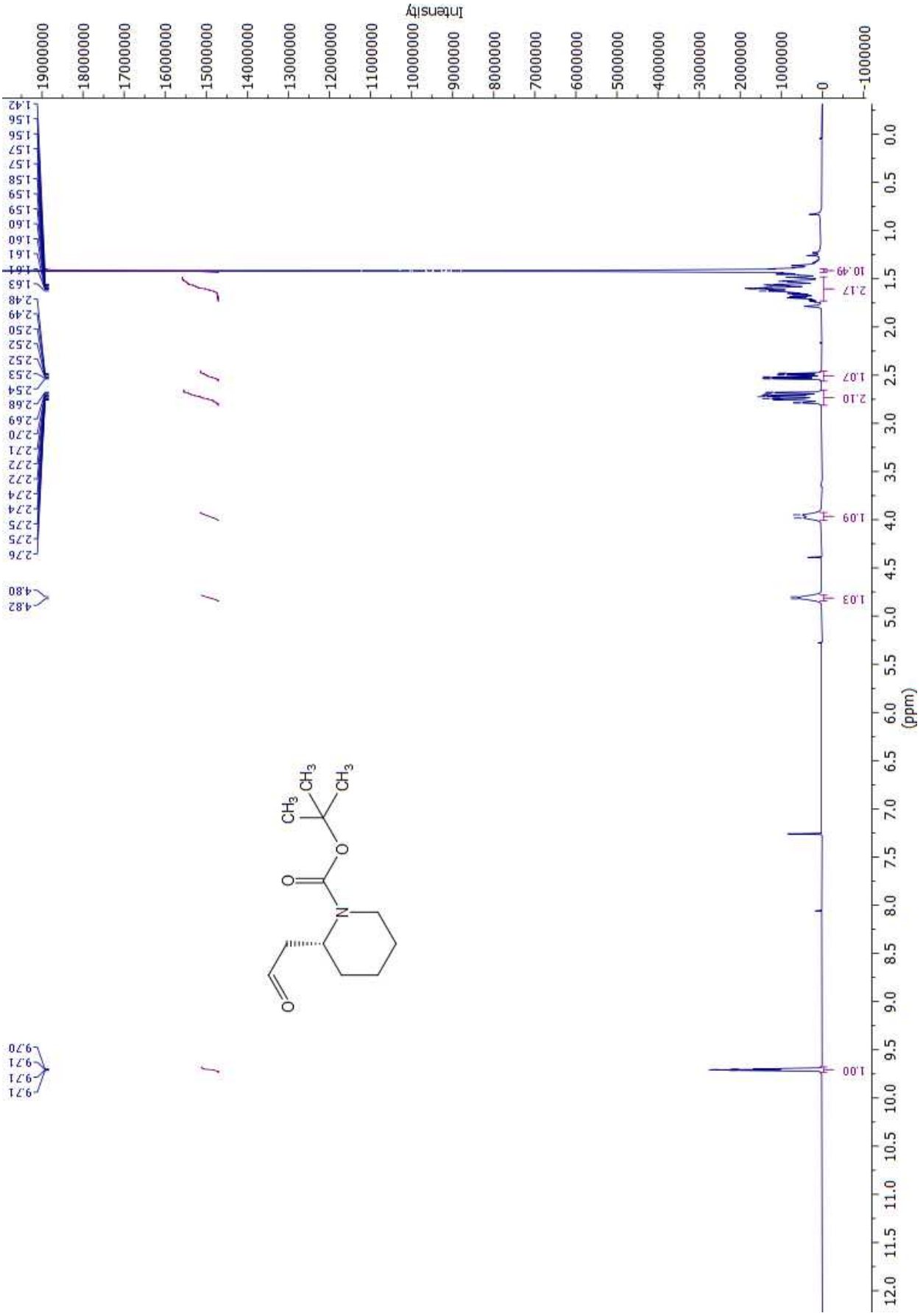


Figure X ^{1}H-NMR spectre of *tert*-butyl (2*S*)-2-(2-oxoethyl)-piperidine-1-carboxylate

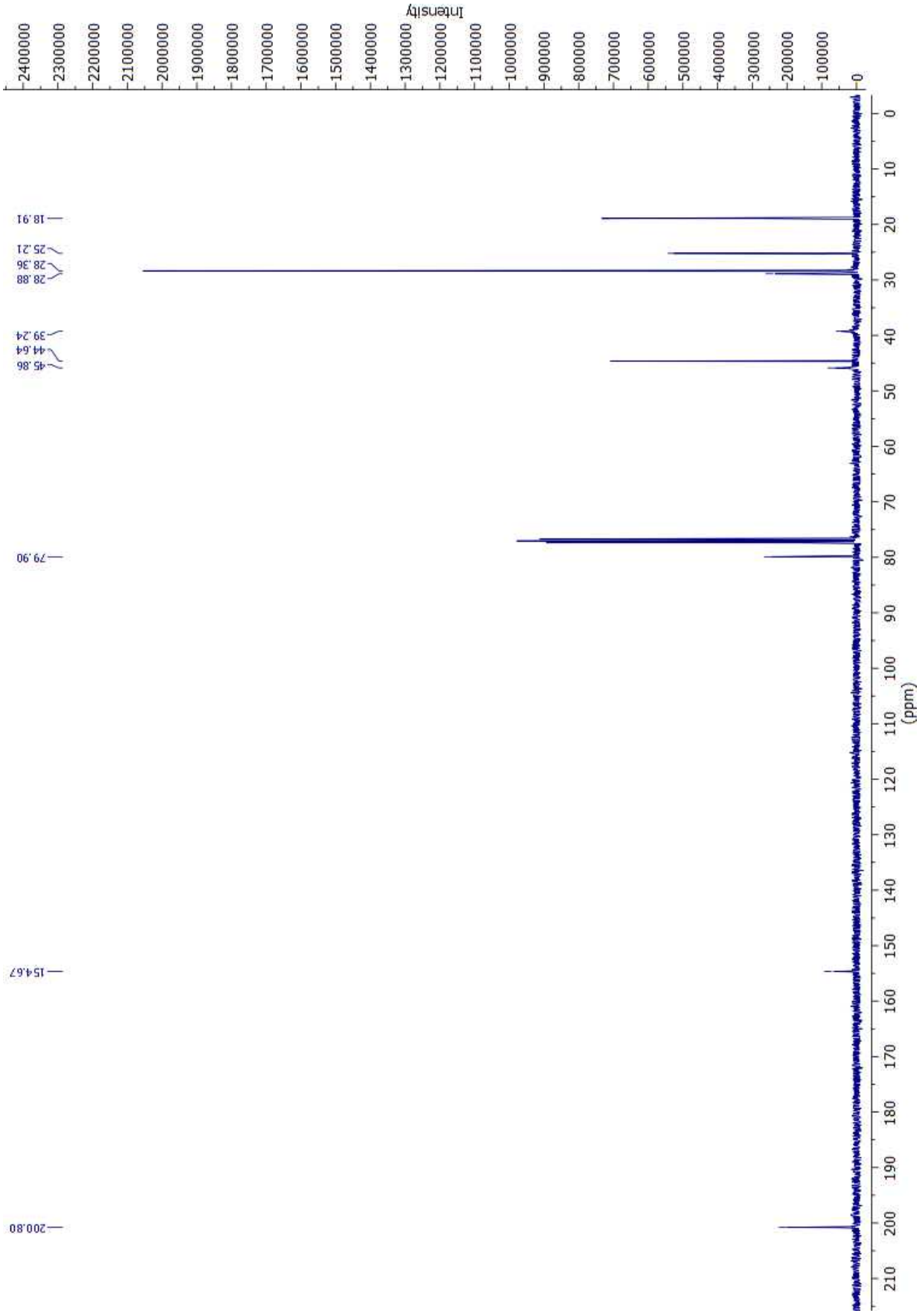
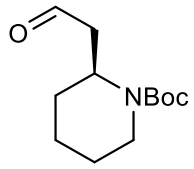


Figure X ^{13}C-NMR spectre of *tert*-butyl (2*S*)-2-(2-oxoethyl)-piperidine-1-carboxylate

5.X Synthesis of *tert*-butyl (2*R*)-2-(2-oxoethyl)-piperidine-1-carboxylate



XXXXXXXXXX

Synthesized with the same procedure as XX.

Yield: 140 mg, 93 %

R_f: 0.31 (7:3 hex/EtOAc)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.73 (dd, *J* = 3.2, 2.2 Hz, 1H), 4.83 (s, 1H), 3.99 (d, *J* = 13.8 Hz, 1H), 2.83 – 2.68 (m, 2H), 2.53 (ddd, *J* = 15.3, 6.4, 2.2 Hz, 1H), 1.79 – 1.46 (m, 7H), 1.44 (s, 11H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.99, 80.06, 61.36, 44.80, 29.02, 28.51, 25.36, 19.06.

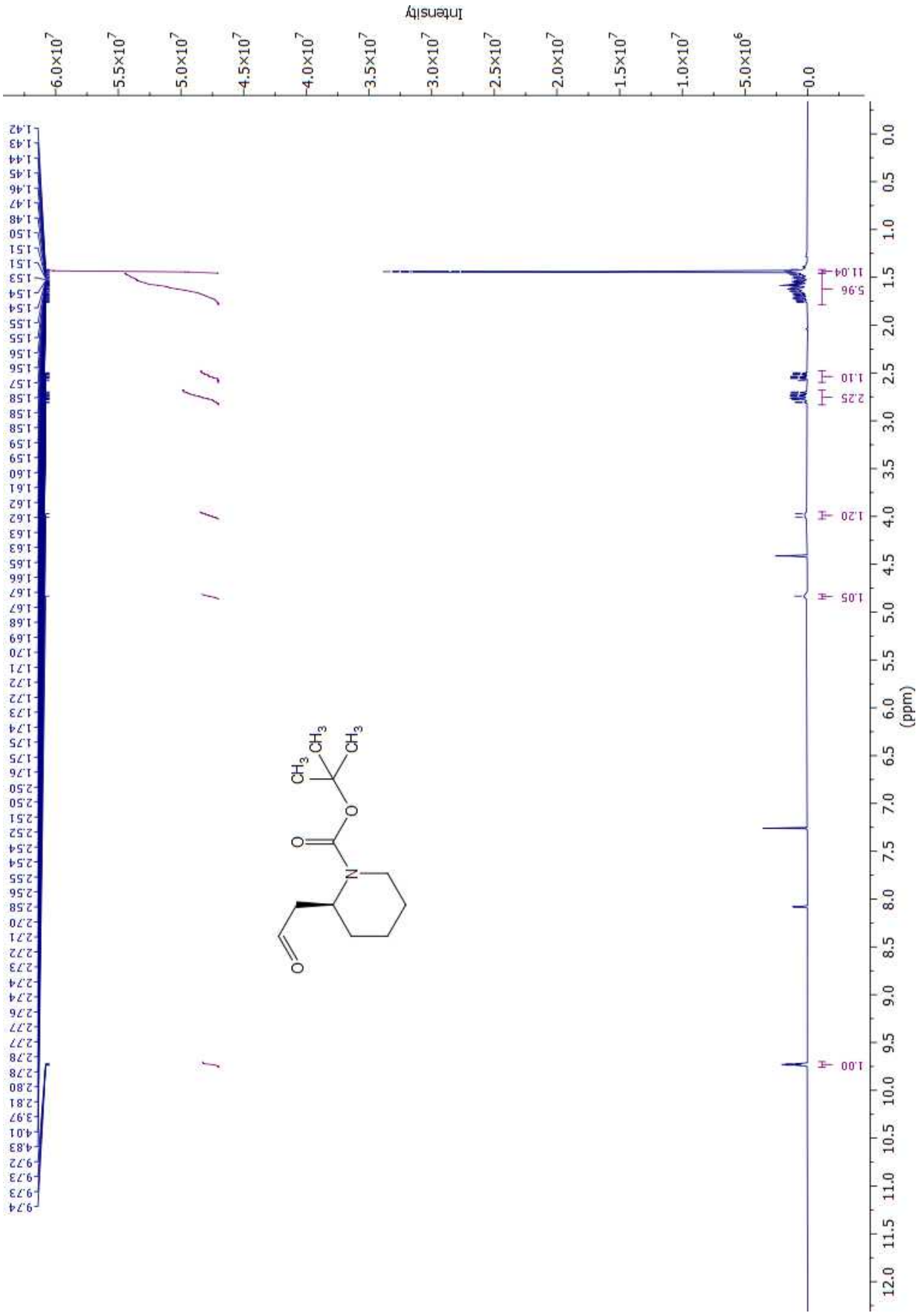


Figure X ^{1}H-NMR spectre of *tert*-butyl (2*R*)-2-(2-oxoethyl)-piperidine-1-carboxylate

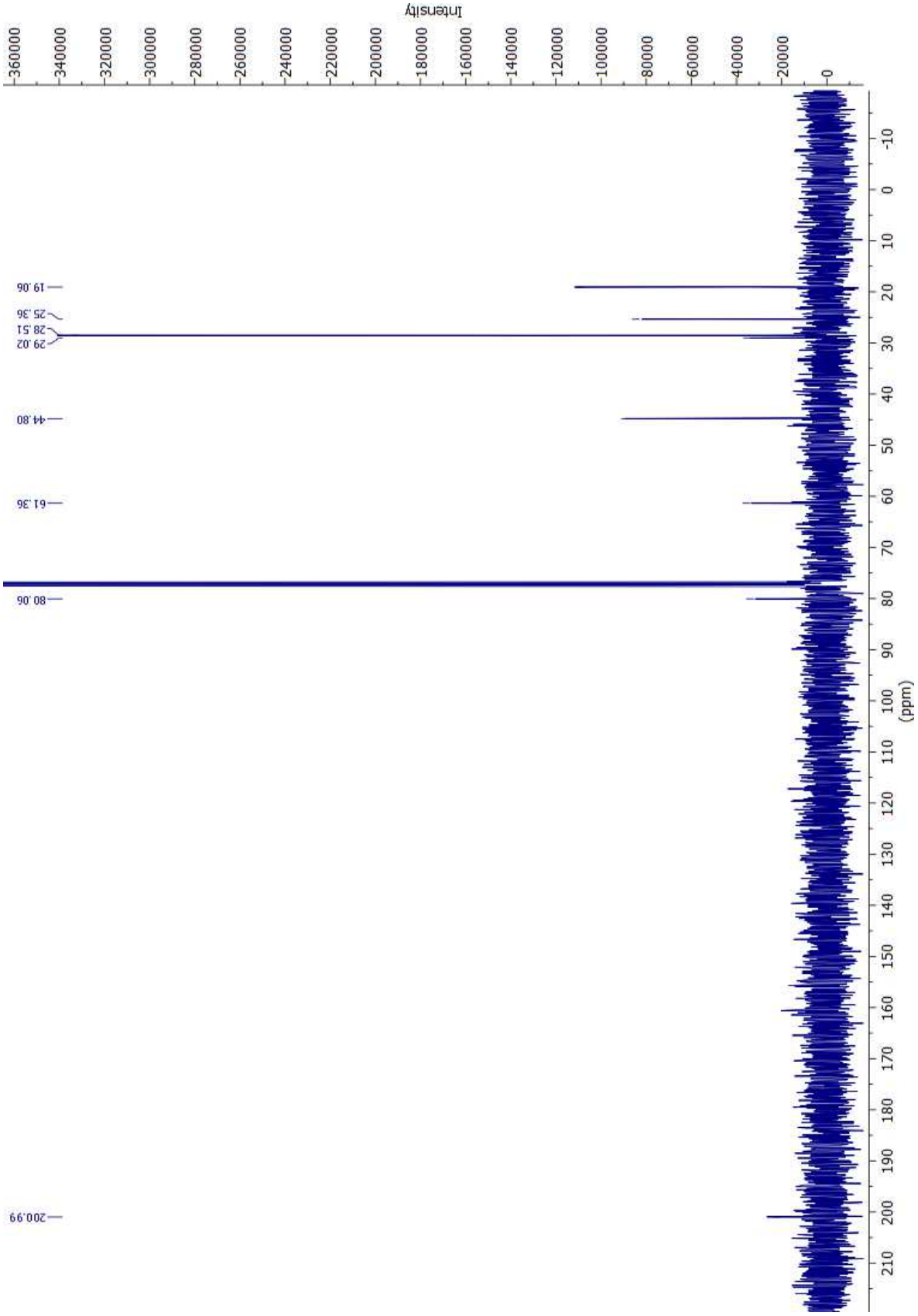
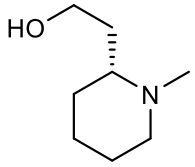


Figure X ^{13}C-NMR spectre of *tert*-butyl (2*R*)-2-(2-oxoethyl)-piperidine-1-carboxylate

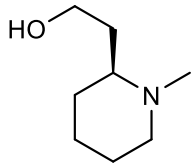
5.X Synthesis of *(R)-N*-methyl 2-Etanolpiperidine



XXXX

Aldehyde (36 mg, 0.16 mmol) XX was added dry THF (25 mL) and carefully added $LiAlH_4$-solution (0.5 mL, 2 M, 6.2 eq.) at 0 ^{O}C. The reaction mixture was then heated to reflux for 10 hours. It was then cooled to at 0 ^{O}C and added H_2O (1 mL), aqueous NaOH (3 mL, 15 % w/w) and H_2O (10 mL). The mixture was extracted with Et_2O (3 x 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to yield the desired product with impurities.

5.X Synthesis of *(S)-N*-methyl 2-Etanolpiperidine



Aldehyde (150 mg, 0.66 mmol) XX was added dry THF (40 mL) and carefully added $LiAlH_4$-solution (2.0 mL, 2 M, 6 eq.) at 0 ^{O}C. The reaction mixture was then heated to reflux for 10 hours. It was then cooled to at 0 ^{O}C and slowly added aqueous NaOH (15 mL).The mixture was extracted with Et_2O (3 x 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by flash chromatography to yield a white crystalline solid.

Yield: 58.6 mg, 62 %

R_f: 0.03 (9:1 CH_2Cl_2/MeOH)

$[\alpha]_D^{20}$ +11.4^{o} (*c* 0.4 g/100 mL, $CHCl_3$)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.59 (s, 1H), 3.74 (ddd, *J* = 10.8, 8.1, 5.8 Hz, 1H), 3.54 (ddd, *J* = 10.8, 6.4, 5.4 Hz, 1H), 2.75 (dtd, *J* = 11.7, 3.7, 1.5 Hz, 1H), 2.10 – 2.00 (m, 1H), 2.00 – 1.89 (m, 1H), 1.77 (ddt, *J* = 14.3, 8.1, 6.1 Hz, 1H), 1.67 – 1.29 (m, 5H), 1.24 – 1.07 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 62.01, 59.99, 56.61, 43.00, 33.38, 29.44, 25.08, 24.01.

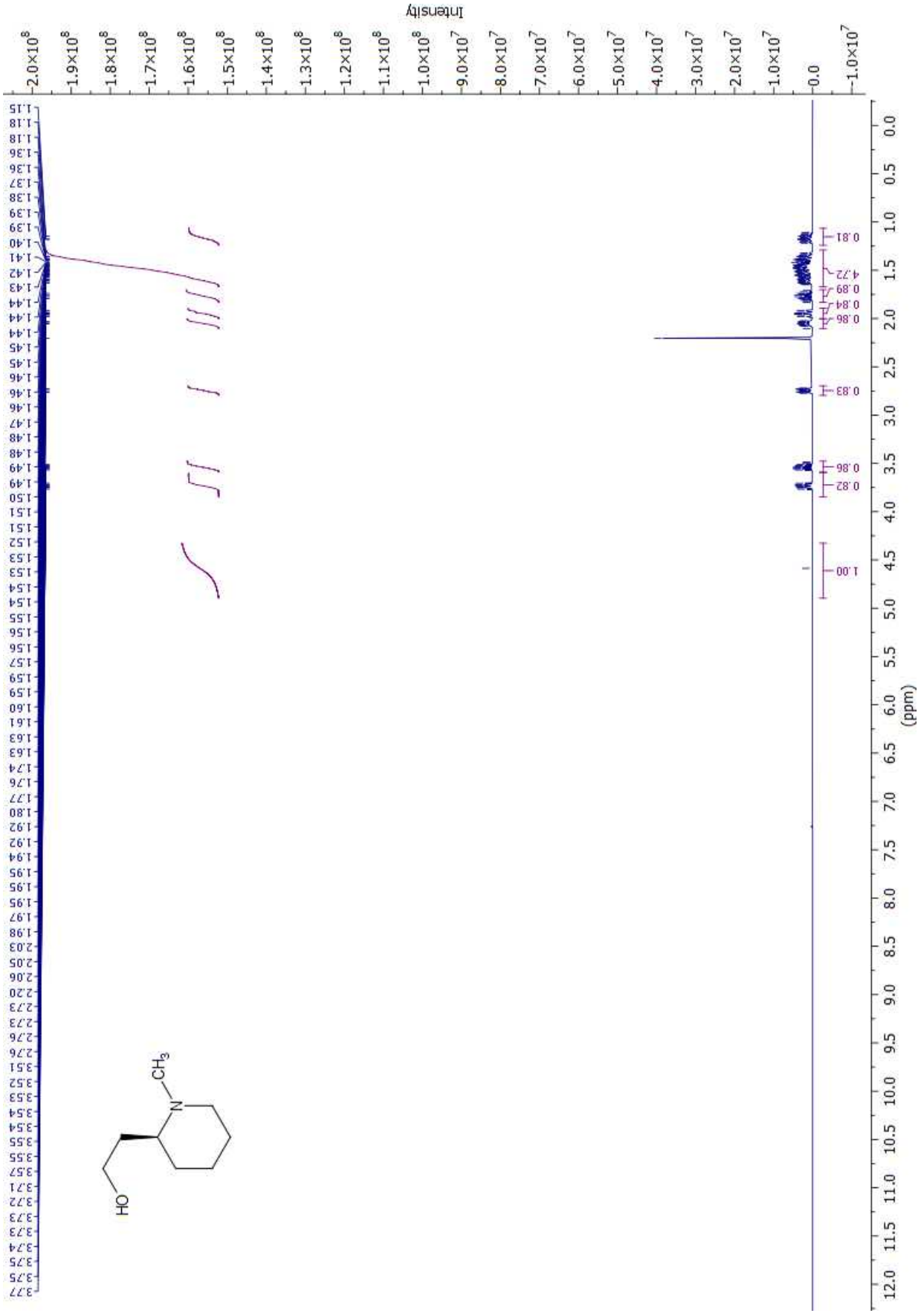


Figure X ^{1}H-NMR spectre of *(S)-N*-methyl 2-Etanolpiperidine.

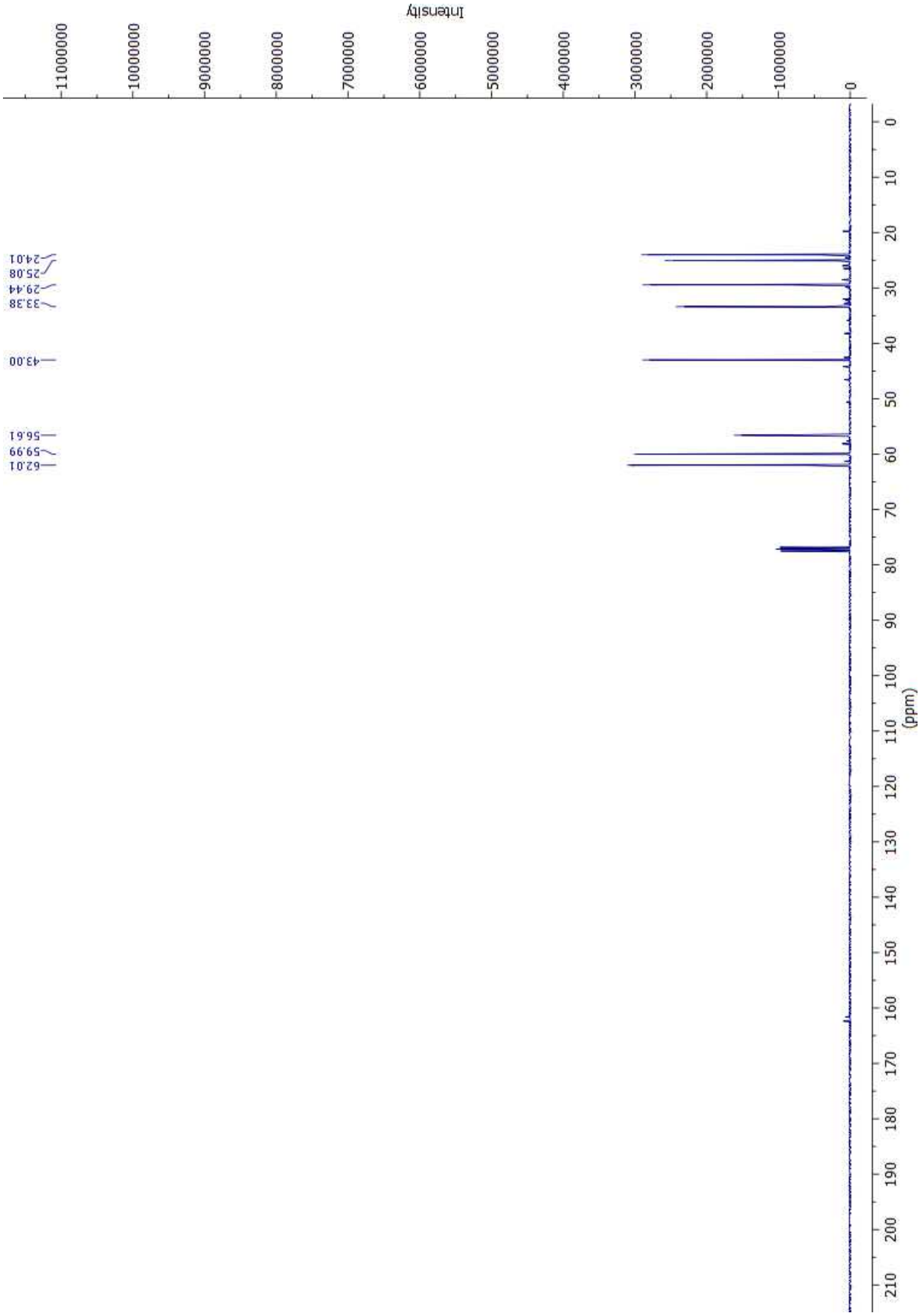
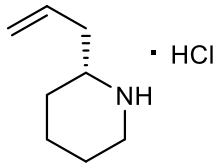


Figure X ^{13}H-NMR spectre of *(S)-N*-methyl 2-Etanolpiperidine.

5.X Synthesis of *(R)*-2-Allyl piperidine hydrochloride



A solution of HCl/dioxane (4 M, 3.8 mL) at 0 ^{O}C was added to the sulfinamide X (0.513 g, 1.93 mmol) and stirred for 1 hour at room temperature. The mixture was concentrated at reduced pressure. The amine salt was dissolved in DMF (17.5 mL), transferred to a microwave vial and added K_2CO_3 (0.222 g, 1.61 mmol) and NaI (0.132 g, 0.807 mmol) in succession. The vial was sealed and stirred for 5 minutes before submission to microwave irradiation at 120 ^{O}C for 15 minutes. The reaction mixture was added aqueous LiCl-solution (15 mL 10 % w/w), extracted with Et_2O (5x 15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was cooled to 0 ^{O}C, slowly added HCl/dioxane (4 M, 3.8 mL) and concentrated under reduced pressure to yield a white solid with impurities. The mixture was added Et_2O, filtered and washed thoroughly with Et_2O yielding a white solid with impurities.

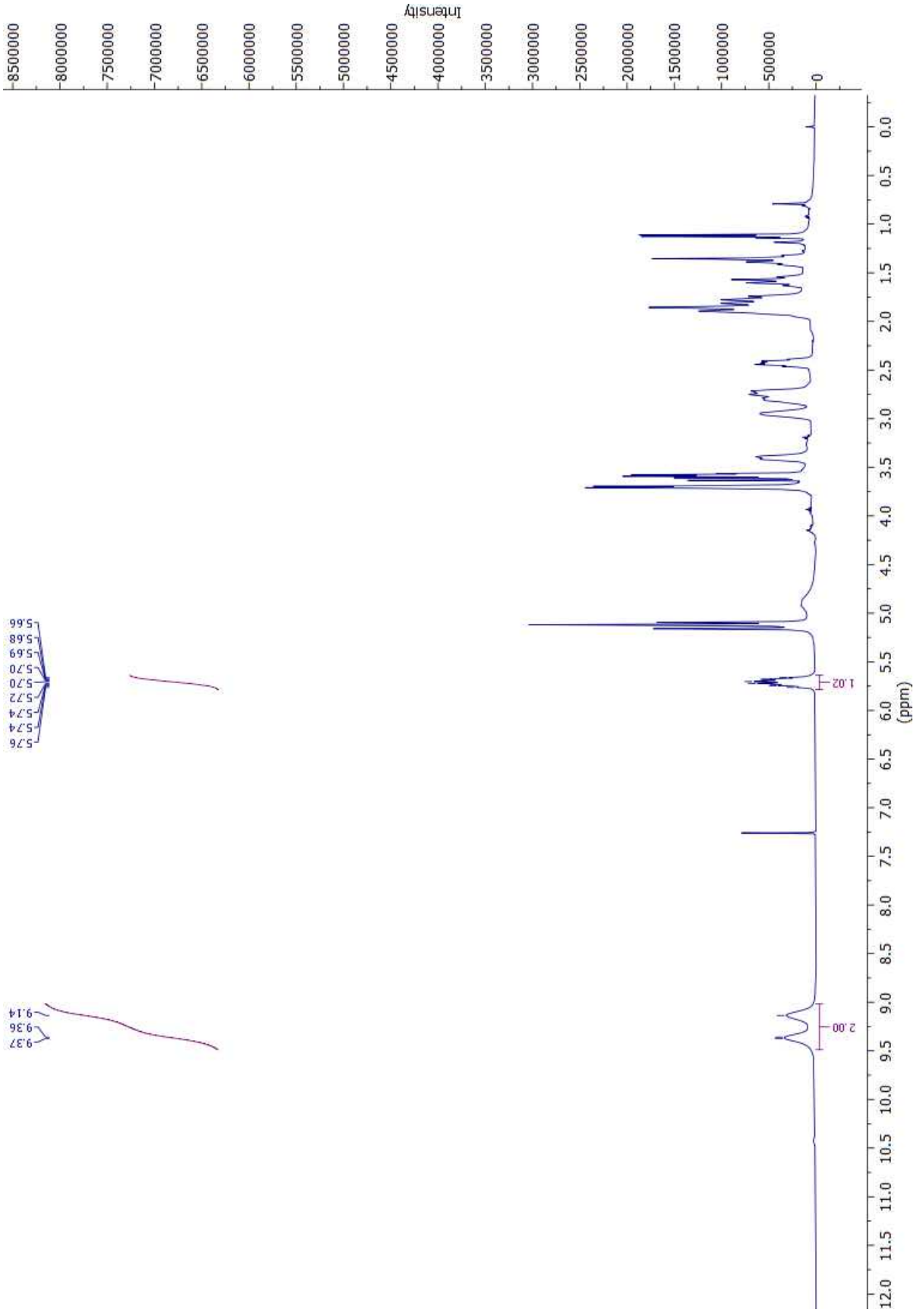


Figure X ^{1}H-NMR spectre of impure *(R)*-2-Allyl piperidine hydrochloride.

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