University of HUDDERSFIELD

- **Synthesis of 8-alkylthioguanine as GTP cyclohydrolase (I) inhibitors for the treatment of cancer pain.**

- **Towards amino acids: asymmetric [1,2]-Stevens rearrangements and [2,3]-sigmatropic rearrangements.**

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A thesis submitted to the University of Huddersfield in partial fulfilment of the requirements for the degree of Doctor of Philosophy

March 2018

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Abstract

Pain is a major symptom of patients with advanced cancer[21]. Tetrahydrobiopterin (BH4) has been found to be a key modulator of cancer pain.[23,30] Two enzymes GTP cyclohydrolase I (EC 3.5.4.16; GTPCH1) and sepiapterin reductase (EC 1.1.1.153; SR) are required for the biosynthesis of BH4.[18,19,20,23] This link between BH4 synthesis and pain provides a new approach for treating neuropathic and other forms of chronic pain[24]. GTPCH1 and SPR enzymes are drug targets based on active site characterization of these two enzymes. Therefore, we wish to develop inhibitors of GTPCH1, SPR key enzymes in the synthesis of BH4 that could potentially be targeted in the treatment of cancer pain. Our work will be focused on the inhibition of GTPCH1 by thiopurines.[30] 8-(alkylthio) guanine and an extensive range of 8-(substituted benzyl thio) guanines were synthesised using traditional reactions of purine chemistry in 13-98% yields. The target compounds are accessible from readily available nucleosides.

This part of thesis describes research towards the synthesis of amino acids *via* [1,2]-Stevens rearrangements of benzylic ammonium ylids and [2,3]-sigmatropic rearrangements of allylic heteroatoms. Firstly, [1,2]-Stevens rearrangements using camphorsultam as the chiral auxiliary, it was found that yields were improved when BTPP, 5 Å molecular serves and DMSO as solvent were used. We have reported 12 examples of [1,2]-Stevens rearrangement of benzylic ammonium ylids with different benzyl substituted (61-89% total yields) as well as three examples of non-coded amino acids (32-39%). Finally, we have reported the metal catalysed [2,3]-sigmatropic rearrangements of allylic heteroatoms (N,I,S). The investigation was done *via* using diazo attached to a chiral auxiliary (camphorsultam and benzyl oxazolidinone), allyl heteroatoms and catalysts (5,10,15,20-Tetrakis(pentafluorophenyl)-21H,23H-porphyrin iron(III) chloride and rhodium(II) acetate). Reactions of the diazo oxazolidinone and the diazo chiral benzyl oxazolidinone worked well with highly reactive iron(III) porphyrin catalyst in the presence of the *N,N* dimethylallylamine and gave high yields (70%, 86% respectively), although diastereoselectivity was poor (1:1.5). Rhodium(II) acetate catalysed decomposition of the diazoaceyl camphorsultam in the presence of the ally iodide and produced high yield (>90%) and excellent diastereoselectivity (5.6:1).

Acknowledgements

I respect everyone, especially those who have the scientific knowledge and experience and they try to transfer them to others.

Firstly, I would like to thank my supervisor, Professor Joe Sweeney, for the patient guidance, encouragement and advice. I need to thank him for giving me the opportunity to carry out my PhD within his group. Secondly, I would like to thank Dr. Duncan Gill, who has acted as a second supervisor. I need to thank him for his proofreading of this manuscript and his advice.

I would like to thank the past and present members of the Sweeney group for their help, advice and exchange of ideas. Special thanks must go to Julien Doulcet for his proofreading and the HPLC help, Anthony Ball for his help.

I would like to thank Dr. Patrick McHugh and Ben Moore, Department of Biology, University of Huddersfield who have carried out all biological testing.

I would like to thank the staff of the University of Huddersfield: Dr. Jack Blackburn for running an excellent mass spec service, Dr. Neil McLay for his efforts in keeping the NMR machine running.

My final thanks, must go to my family (mother, wife, daughter, son, sisters and brothers) for their support and encouragements during my time at University of Huddersfield to produce of this work.

List of abbreviations

Ac	Acetyl
Acac	Acetylacetonate
ADP	adenosine diphosphate
AIBN	Azobisisobutyronitrile
AIDS	acquired immune deficiency syndrome.
App	Apparent
Ar	Aromatic
ATP	adenosine triphosphate
BH4	Tetrahydrobiopterin
br	Broad
BTPP	(tert-Butylimino)tris(pyrrolidino)phosphorane
cAMP	cyclic adenosine monophosphate
DAHP	diaminohydroxypyrimidine
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethene
DCM	Dichloromethane
de	diastereoisomeric excess
DHP	Dihydropteridine
DMAc	dimethyl acetamide
DME	Dimethoxyethane
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DPPF	bis(diphenylphosphino)ferrocene
d.r.	diastereoisomeric ratio
EC	enzyme commission number
EDA	ethyl diazoacetate
ee	enantiomeric excess
ELISA	enzyme-linked immunosorbent assay
eq.	Equivalents
GDP	guanosine diphosphate
GMP	guanosine monophosphate
GTP	guanosine-5'-triphosphate
GTPCH1 or GCH1	guanosine triphosphate cyclohydrolase I
HOMO	highest occupied molecular orbital

HPLC	high-performance liquid chromatography
IR	Infrared
LiHMDS	lithium hexamethyldisilamide
LUMO	lowest unoccupied molecular orbital
m.p.	melting point
MS	molecular sieves
NAD	nicotinamide adenine dinucleotide
NADP	nicotinamide adenine dinucleotide phosphate
NBS	*N*-bromosuccinimide
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
PE	petroleum ether
PTPS	6-pyruvoyl tetrahydropterin synthase
R_f	retention factor
RNA	ribonucleic acid
RT or r.t.	room temperature
SN_{Ar}	nucleophilic aromatic substitution
SPR	sepiapterin reductase
TBAF	tetra-n-butylammonium fluoride
THF	Tetrahydrofuran
TLC	thin-layer chromatography
t_R	retention time
Z	carboxybenzyl

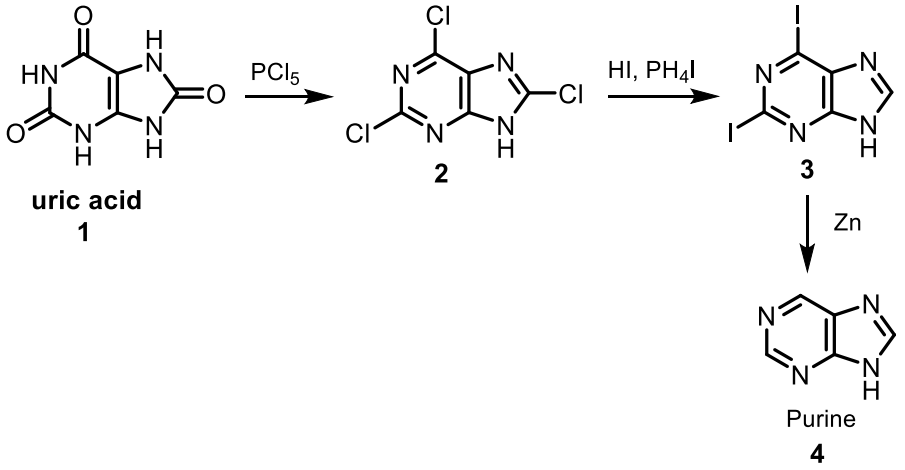
Chapter 1

1. Introduction

In recent years, there has been an increased interest in the synthesis of purine compounds for many reasons. One reason is that they act as neurotransmitters and hormones. The second is that they often have therapeutic activity. Lastly, they are subunits of some molecules, for instance DNA and RNA, which are essential in biological processes. Purine compounds have several applications for example as inducers of interferon and, for the treatment of virus infection and AIDS.

1.1 Purine

In 1899, Emil Fischer synthesized a colourless, crystalline weak base for first time and named it purine.[1] He synthesised purine from uric acid (**1**), which was reacted with PCl_5 to give 2,6,8-trichloropurine (**2**), and was then converted to 2,6-diiodopurine (**3**) by reaction with HI and $PH_4^+I^-$. Finally, this compound was reduced with zinc to give purine (Scheme 1).[1]



Scheme 1. Original synthesis of purine from uric acid.

Purine is a heterocyclic compound which contains four nitrogen atoms within a skeleton of two fused rings, an imidazole and a pyrimidine as shown in Figure 1.

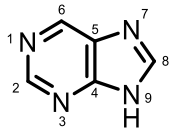


Figure 1. Purine (imidazole [4, 5-*d*] pyrimidine) ring.

The imidazole ring of purine can undergo nucleophilic (c) and electrophilic (b) reactions whereas the pyrimidine ring only undergoes nucleophilic (d) reactions. This is due to the possible prototropic tautomerism as illustrated in Figure 2 (a).[2]

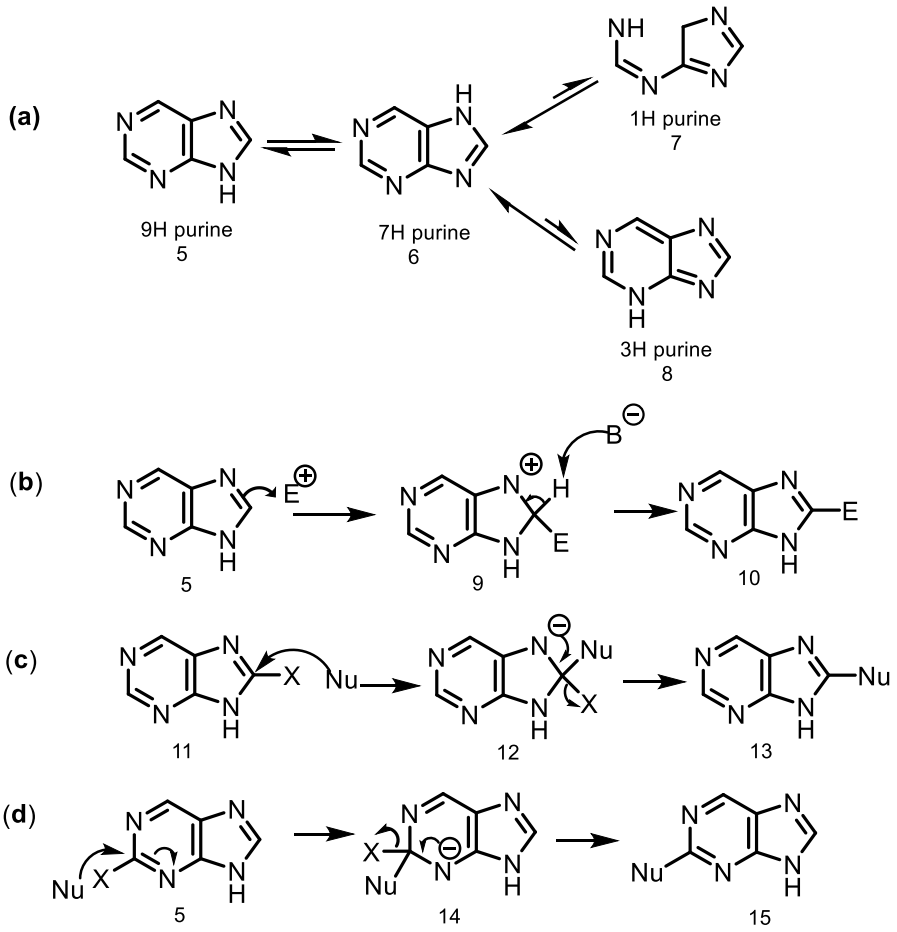


Figure 2. a) The possible tautomerism of purine. **b**) Electrophilic reaction on imidazole ring. **c**) Nucleophilic reaction on imidazole ring. **d**) Nucleophilic reaction on pyrimidine ring.

1.1.1 Classification of purines

There are many purine derivatives, which may be classified into three groups according to the following descriptions: [2,3]

a) Hydroxy or oxy purines which contain a carbonyl or enol form, such as uric acid, xanthine **16** and **17** (Figure 3).

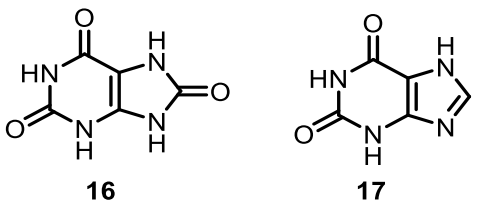


Figure 2. Chemical structure: Uric acid (16). b) Xanthine (17).

b) Amino purines:

These contain an amine group at positions 2-, 6- or 8- of the purine skeleton. An example of an amino purine is adenine (**18**) (Figure 4).

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Figure 4. Chemical structure of adenine.

c) Amino and oxo purines:

These contain an amino and carbonyl group at positions 2, 6- or 8- of purine, for instance guanine (**19**) (Figure 5).

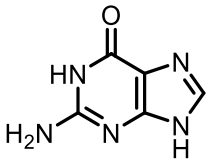

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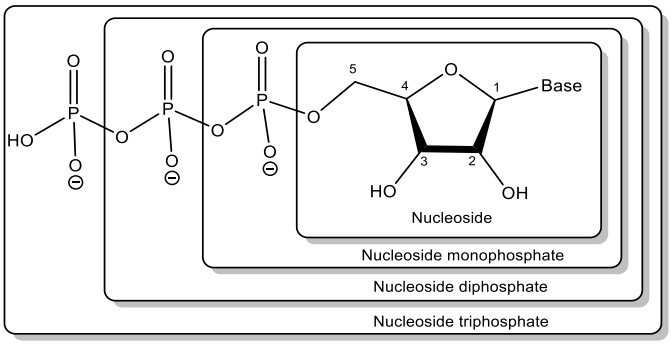
Figure 5. Chemical structure of guanine.

1.1.2 Biochemistry of purines

As mentioned above, purine derivatives are essential in biological processes because they are basic units in the composition of DNA and RNA. In addition, purines are cofactors associated with many enzymes and receptors, such as ATP, GTP, GDP, GMP, cAMP, ADP, NAD and NADP, which play important roles in the cell cycle.[4] To explain further, some basic points will be illustrated.

1.1.2.1 Nucleosides and nucleotides

A nucleoside is a nitrogenous base, in this case purine compounds, attached to a sugar (ribose) but without the phosphate group. A nucleotide consists of a nitrogenous base, a sugar (ribose) and one to three phosphate groups, as shown in (Figure 6).



Base= Adenine, Guanine.

Nucleoside= Ribose + Base

Nucleotide=Ribose + Base + Phosphate.

Or Nucleoside + Phosphate.

Figure 6. Nucleoside and nucleotide.

To further explain what has been described above, we will use Guanine, which has a structure as shown in Figure 5, and as a basis for further explanation about the role of purine compounds in biological processes Figure 7.[2]

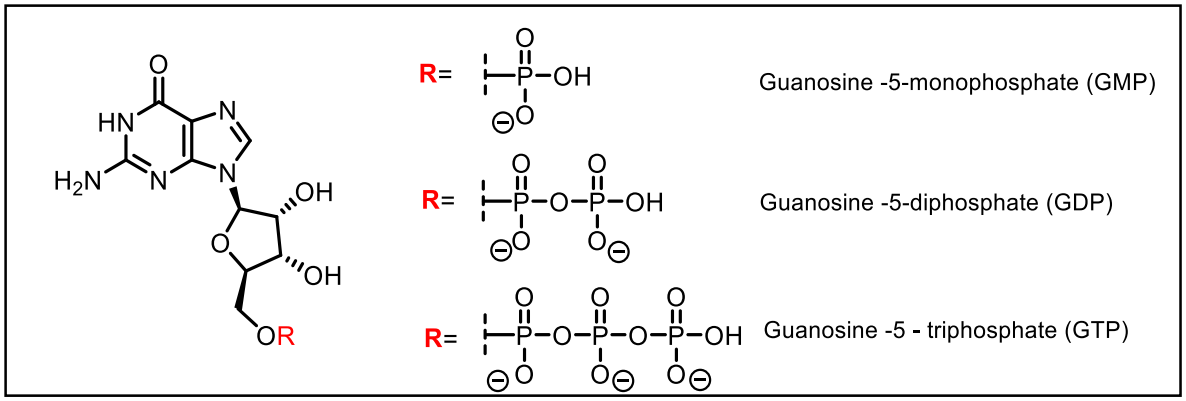
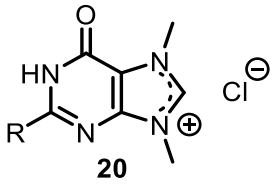


Figure 7. Guanine nucleotide.

1.1.3 Biological activity of purine analogues

The purine rings have biological importance for example Heteromines were isolated from the Chinese climber *Heterostemma brownii*. These plants are used in Taiwan as a folk medicine for the treatment of certain tumors (Figure 8).[5]



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R= NH_2, NHMe, NMe_2

Figure 8. Chemical structure of Heteromines.

In 1980**,** Fuhrman has reported that 1-methylguanosine (dordosine, **21**), which was isolated from marine sponges, reduced heart rate in anesthetized mice by 50% for many hours (Figure 9).[6]

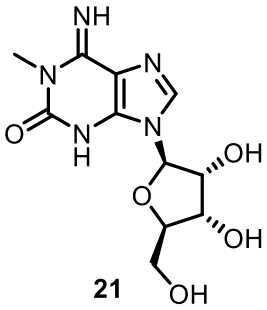

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Figure 9. Chemical structure of Dordosine**.**

There is a class of plant growth substances (Phytohormones) called cytokinins. One of them is zeatin (**22**), which is isolated from *Zea mays*. Zeatin in the E configuration shows phytohormone activity. Isopentenyl adenine (**23**) is present as a component part of isopentenyl adenosine (**24**). It has strong antimetabolic and anti-cancer activities (Figure 9a).[7, 8]

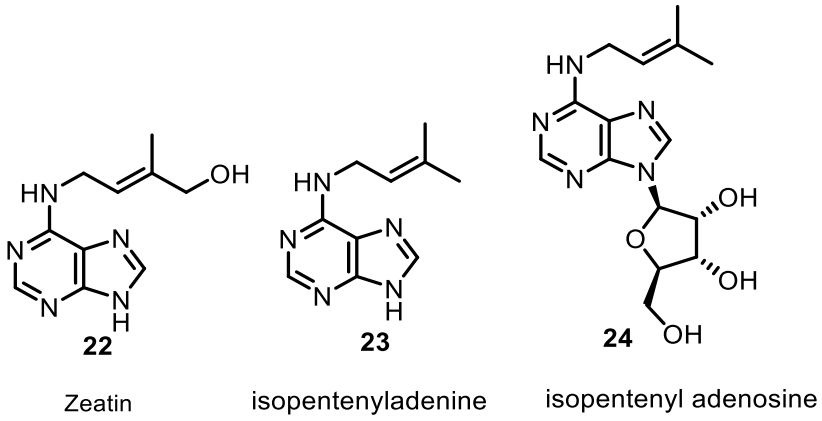


Figure 9a. Chemical structures of cytokinins.

In 1998, Kashman and co-worker found that asmarines (**25, 26, 27**), which are tricyclic purine derivatives, have cyotoxic activity against cell cultures of leukemia, lung carcinoma and colon carcinoma (Figure 10).[9]

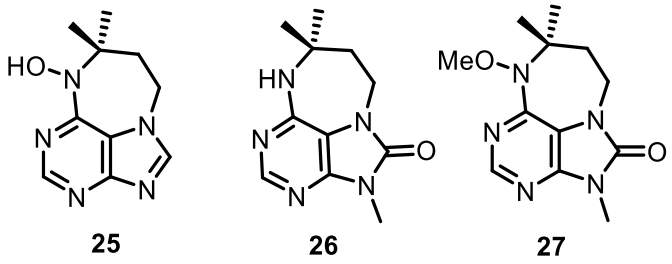
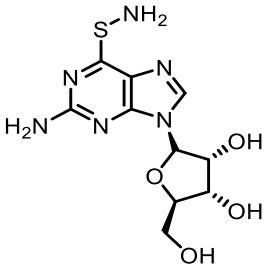
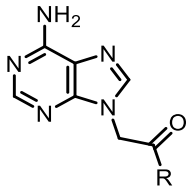
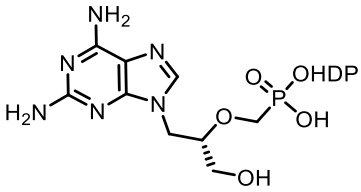
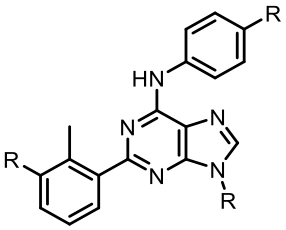
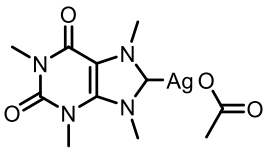
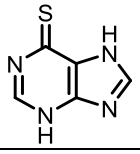
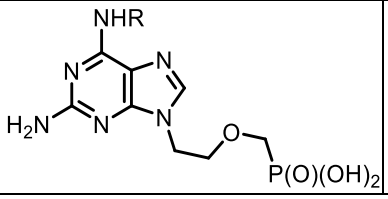


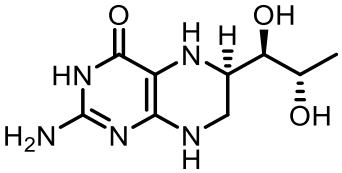
Figure 10. Chemical structures of asmarines.

There are a large number of examples which are represented use of purine and its derivatives in biological activity and the table 1 shows some purines derivatives structures and their biological activity.

Table 1

Compound structure	Biological activity (Ref)	Compound structure	Biological activity (Ref)
	Antileukemic (10)		Antineoplastic (14)
	Anti-HIV (11)		Inhibitor for autoimmune diseases (15)
	Antimicrobial (12)		Antileukemic (16)
	Antiviral (13)		

1.2 Tetrahydrobiopterin (BH4)



BH4

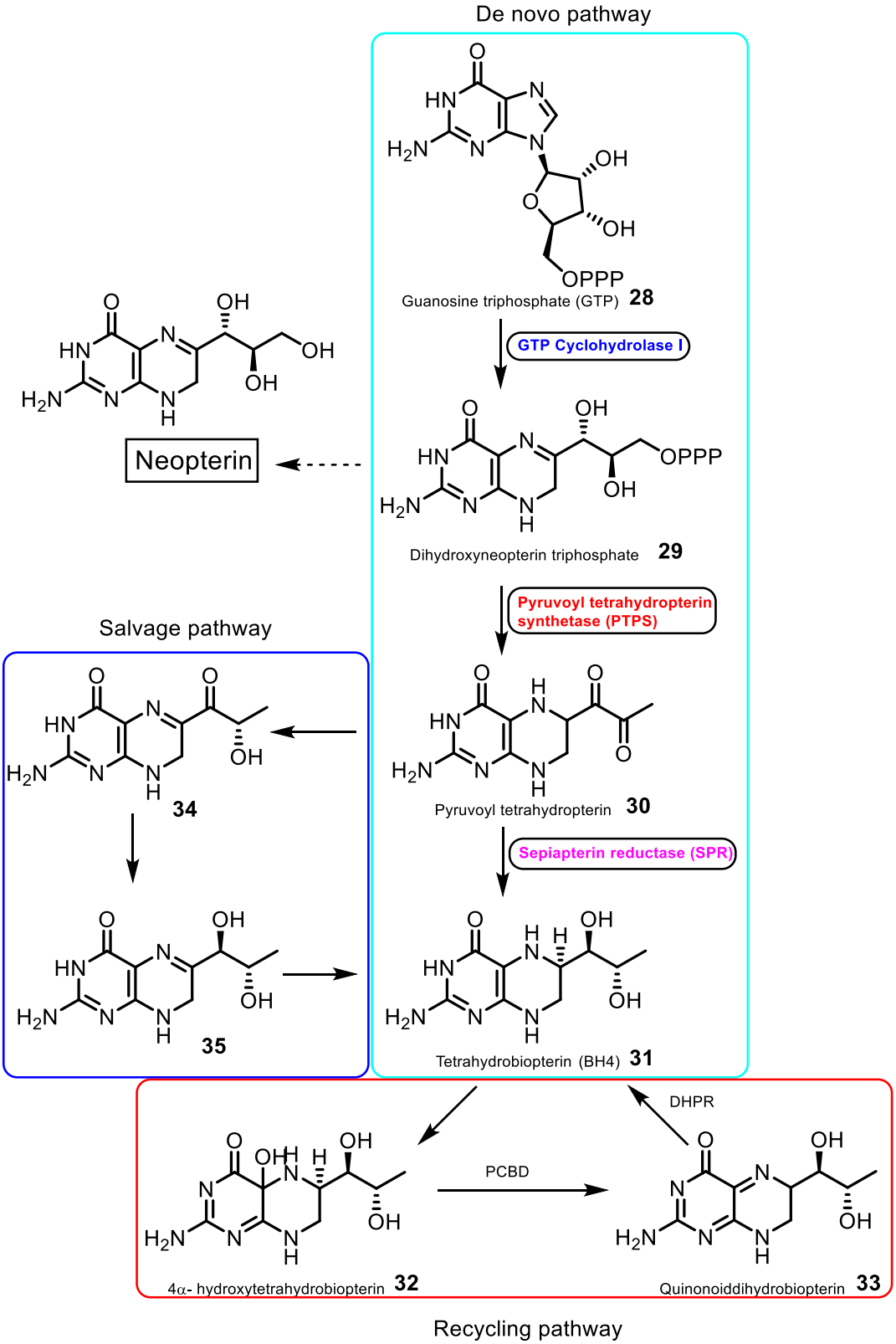
Tetrahydrobiopterin (BH4) is essential for different processes and is present in all tissues of higher organisms. It has found to play a role as an enzymatic cofactor. BH4 is the natural cofactor required for the hydroxylation of the aromatic amino acids phenylalanine, tyrosine, and tryptophan.

1.2.1 Biosynthesis of BH4

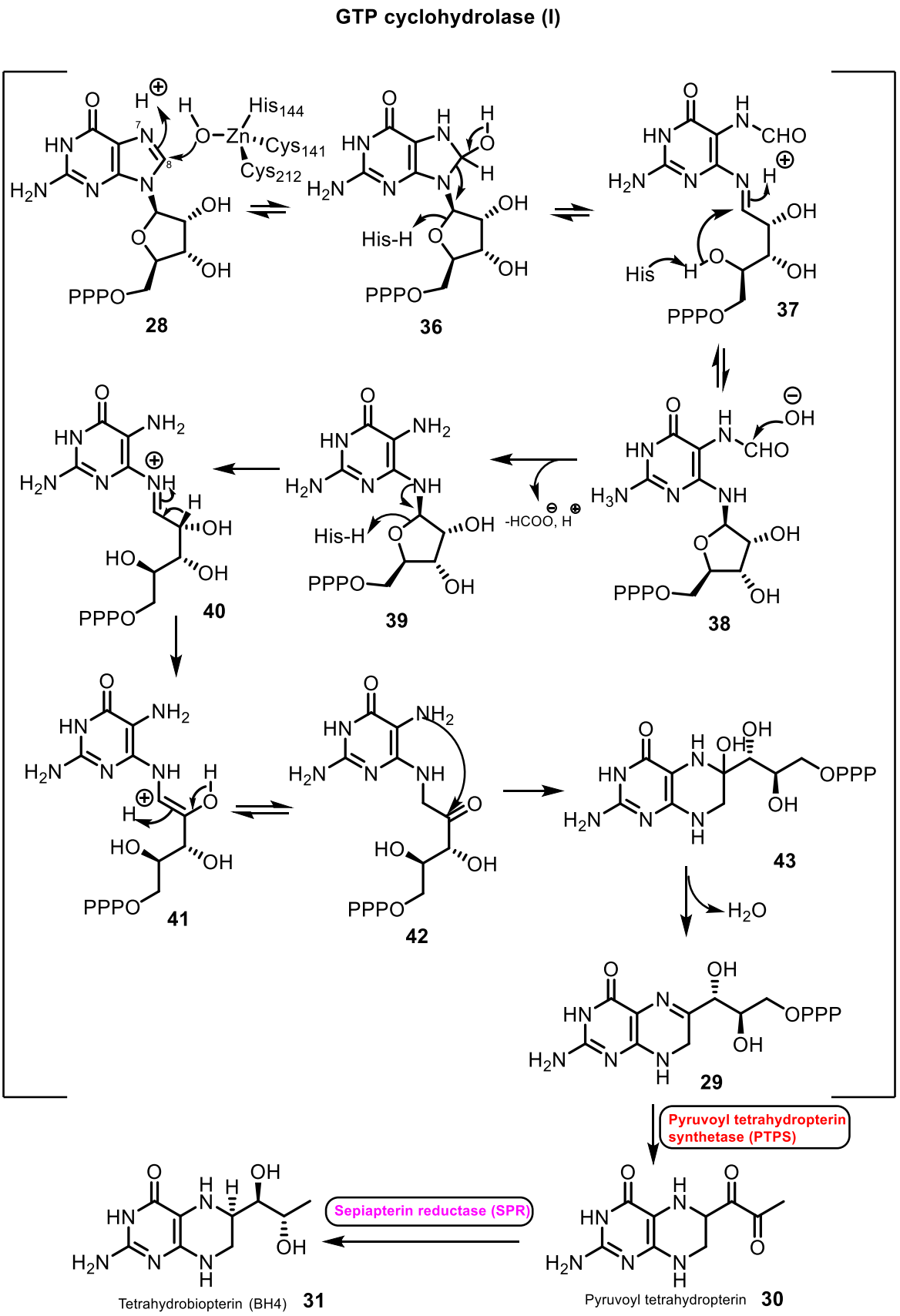
BH4 is biosynthesized from several pathways, including the *de novo* synthesis pathway, salvage and the recycling pathway. The *de novo* pathway is a common form of BH4 biosynthesis which is carried out by three enzymes as shown in Scheme 2.

1.2.2 GTP reaction mechanism of de novo pathway

In the *de novo* pathway (Scheme 1), three enzymes GTP cyclohydrolase (I) (EC 3.5.4.16; GTPCH), pyruvoyl tetrahydropterin synthase (EC 4.6.1.10; PTPS), and sepiapterin reductase (EC 1.1.1.153; SPR) are required to form BH4. The first part of the pathway is carried out by GTP cyclohydrolase (I), which is responsible for the hydrolysis of guanosine triphosphate (GTP)(**28**) to form dihydroneopterin triphosphate (**29**). GTP cyclohydrolase (I) contains a single zinc ion, which present in the active site. The mechanism of GTP cyclohydrolase (I) on GTP (**28**) requires that the zinc ion acting as a Lewis acid and polarizing water ligand, thus forming a hydroxyl nucleophile which attacks carbon 8 of the GTP substrate, while His-210 can donate a proton and acts as a proton donor at position 7 of GTP. This leads to the opening of the imidazole ring at carbon 8; in addition, protonation of the ribose ring by His-143 leads to the formation of a Schiff base at the N9-glycoside. Next, cleavage of the formamide bond occurs, catalyzed by zinc. After that comes the opening of the sugar ring and the formation of an Amadori product, (via a re-arrangement of the Schiff base), and the creation of an enol tautomerises to the ketone. Finally, condensation (the amino group at position 7 attacks the carbonyl, before loss of a molecule of water) which leads to the formation of the final product (**29**) (Scheme 3).[17, 18, 19, 20]



Scheme 2. BH4 pathways.



Scheme 3. GTP reaction mechanism of *De novo* pathway.

1.3 Tetrahydrobiopterin (BH4) and cancer pain

From pharmacological viewpoints, chronic pain exists in two forms. One of them is inflammatory pain and the second is neuropathic pain. Cancer derived neuropathic pain is common in cancer patients as a direct result of the effect of the cancer on peripheral nerves (e.g. compression by a tumour), or as a side effect of chemotherapy, radiation injury or surgery.

Lötsch *et al* have reported[21] that most of cancer patients with advanced cancer suffer pain. Genetically, the results obtained in their study suggest that the reduction of GTP cyclohydrolase 1, which is responsible for the first step of biosynthesis of BH4, leads to a decrease in the need for opioid therapy in cancer patients. They analysed data of 251 cancer patients (including men and women and aged 29-89) (Figure 11).

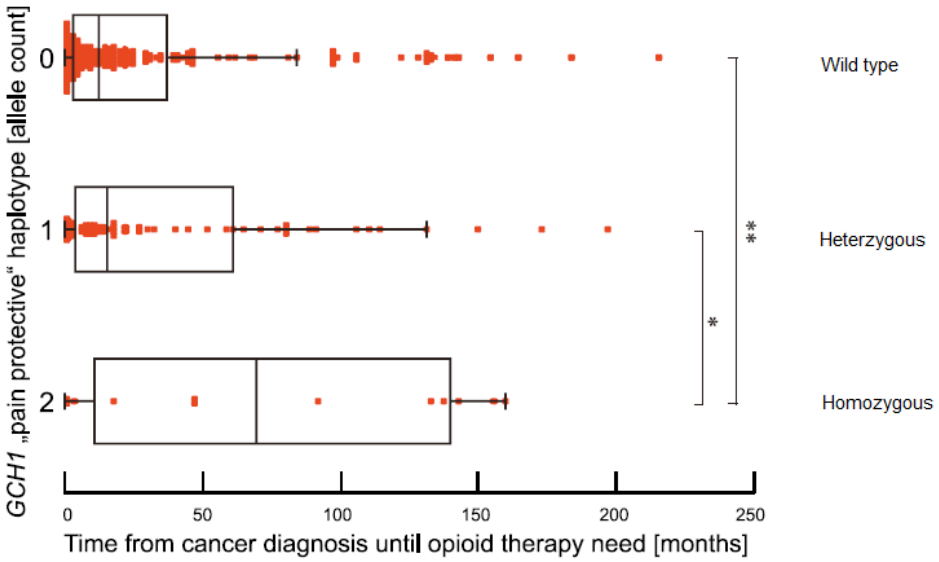


Figure 11. Consequences of the GCH1 ‘‘pain protective” haplotype in 251 patients treated for chronic cancer pain in tertiary care (**Taken out of ref 21 without permission**).

In the same context, Nasser has pointed out[22] that GCH1 variants or GCH1 gene mutations are the most important factors for decrease pain sensitivity and chronic pain. Perhaps this linkage may provide potential new targets for analgesic drugs.

Tegeder *et al.* have enhanced and indicated that blocking the increased BH4 tetrahydrobiopterin synthesis by inhibiting both GCH1 and SPR might reduce neuropathic pain. They have demonstrated that 2,4-diamino-6-hydroxypyrimidine (DAHP) has shown great promise as GTPCH1 inhibitor.[23]

Naylor *et al.* have stated that the discovered relationship between BH4 and pain provide new insights for treating neuropathic pain and that reducing the action of two enzymes (GCH1 and SPR) makes them a target for drugs according to the active site of two enzymes. Small molecules which include guanine and its derivatives or those which have a similar structure to guanine are capable inhibition of GCH1 in high efficiency. In other words, these molecules bind to the active site in the enzyme, which contains zinc, and inhibits the action of the enzyme (Table 2).[24]

Table 2.

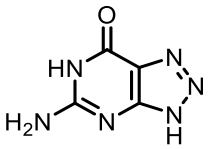
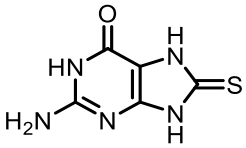
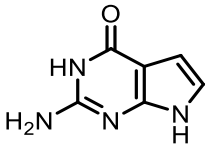
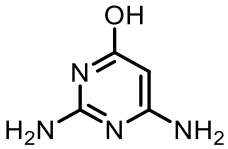
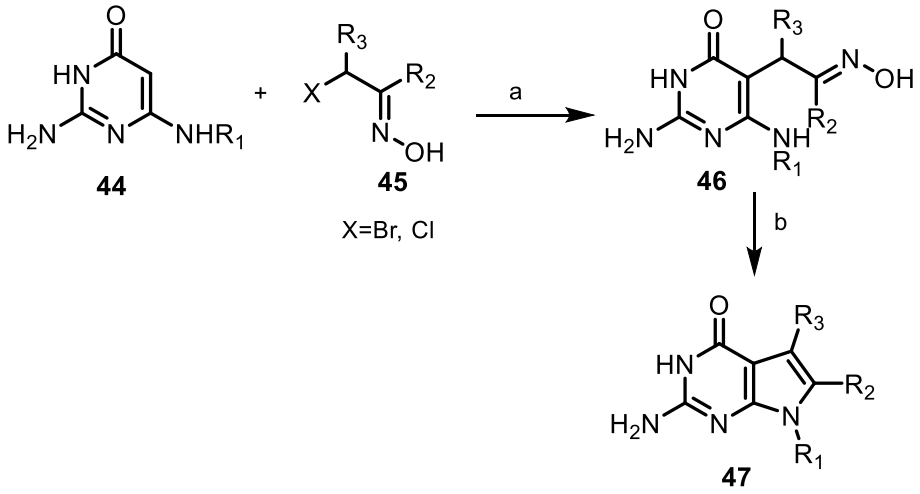
Compound	Structure	Mechanism of action	Reference
8-azaguanine		Competitive	24
8-mercaptoguanine		Competitive	24
7-deazaguanine		Unknown	25
2,4-diamino-6-hydroxypyrimidine		GFRP regulatory	26

Table 2 shows that both 8-azaguanine and 8-mercaptoguanine are competitive inhibitors. They are molecules with similar shape to the substrate (GTP) therefore inhibitors and substrate compete to react with the enzyme through active sites.

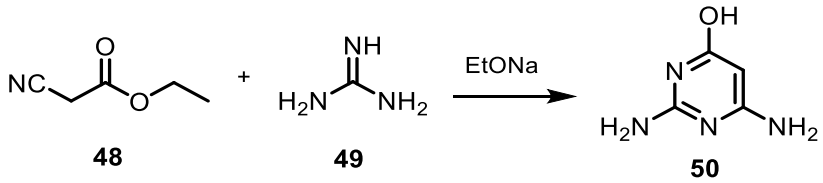
Some of the first examples of GTPCH1 inhibitors are 7-deazaguanine derivatives which have been prepared using a novel two steps synthesis, starting from diaminopyrimidinones and α-halooximes to give (**46**). In the second step transoximation (cleavage oxime which reacts with aldehyde) occurs, to give 7-deazaguanine derivatives in 41-65 % yield (Scheme 4).[27]



Reagents and conditions:
a) Base, DMF, r.t. 4-72 h. **b**) EtOH-H_2O, benzaldehyde or acetaldehyde, Cat HCl, heat, 24-72 h.

Scheme 4. Synthesis of 7-deazaguanine derivatives.

The second example of a GTPCH1 inhibitor is diaminohydroxypyrimidine (DAHP) which has been reported as a selective inhibitor of GCH1 in the *de novo* pathway with an IC_{50} in the range of 0.3-1 mM. DAHP has been reported to have a dual activity, binding at GTP site/GFRP interaction site at low concentrations but directly inhibiting the GTP binding site at high concentrations. DAHP can be prepared from reaction of guanidine and ethyl cyanoacetate in the presence of sodium ethoxide (Scheme 5).[28]



Scheme 5. Synthesis of diaminohydroxypyrimidine.

Firstly, considering the previously mentioned biological activity of purine compounds and due to the similarity between the purine skeleton and GTP substrate (see scheme 2) which is the starting point of BH4 biosynthesis. Secondly, according to many studies about cancer pain, tetrahydrobiopterin (BH4) has been found to be a key modulator of cancer pain. Therefore, our attention turned to find out whether the purine compounds have activity against or reduce chronic pain which is associated with cancer patients.

Aim

The aim of this project is therefore to explore the relationship between biosynthesis of BH4 and cancer pain and develop inhibitors of GTPCH1, the key enzyme in the production of BH4 that could potentially be targeted in the treatment of cancer pain and could reduce the need for opioids. In the first stage, efforts will be focused on the synthesis of 8-mercaptoguanine derivatives as inhibitors for GTPCH1 enzyme. In parallel, pharmaceutical testing (in collaboration with Dr. McHugh at the University of Huddersfield) will be carried out.

2. Organic synthesis of GTPCH1 inhibitors

2.1 Methodology

The chemical starting points chosen were guanine (**51**), 2-amino-4-chloro-6–hydroxy pyrimidine (**62**), 5-amino-1H-imidazol-4-carboxamide hydrochloride (**65**) and guanosine (**69**). The introduction of sulfur at the 8- position, where the GTPCH1 enzyme reacts with GTP, of guanine is thought to improve the therapeutic effect and block the reaction at this position (Figure 12).[29]

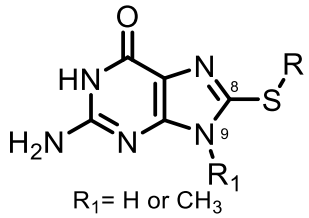


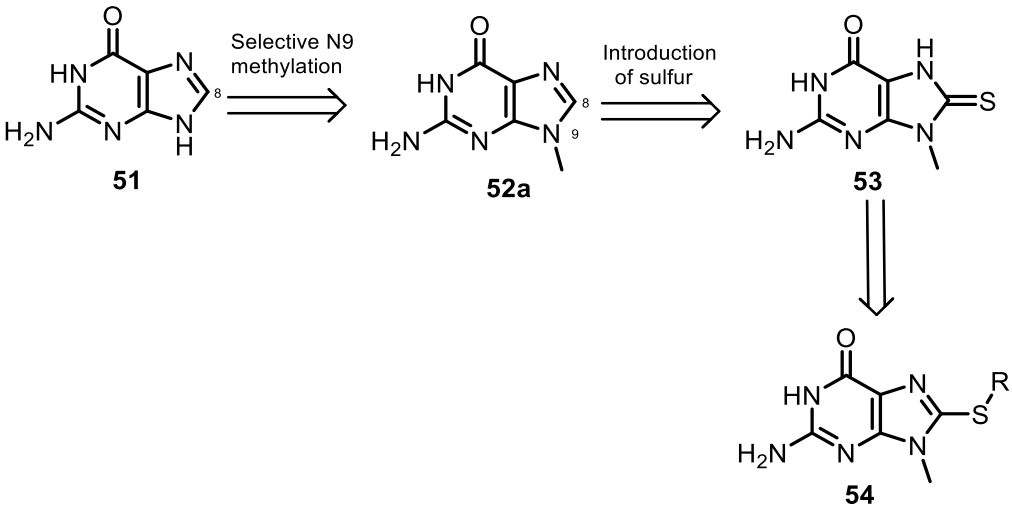
Figure 12. The target compounds.

2.2 Results and discussion

2.2.1 Towards 9-methyl-8-mercaptoguanine derivatives

2.2.1.1 First approach: guanine route (plan A)

Original efforts were focused on the synthesis of 9-methyl-8-mercaptoguanine (**53**) using guanine (**51**) as starting material. A retrosynthesis is presented in Scheme 6. The key steps of the retrosynthesis are the introduction of a directing group, enabling the methylation of the correct nitrogen, and the introduction of sulfur using thiourea. Once 9-methyl-8-mercaptoguanine (**53**) would be obtained, it would serve as the starting material for derivatisation.



Scheme 6. General strategy for the synthesis of **54**

Several points have to be considered for the synthesis of **53** when using guanine as starting material. These are:

- Protection of the amino group.
- The insertion of a methyl group at N9 is essential for successful bromination at C-8 in order to facilitate the introduction of a sulfur-function by nucleophilic displacement.

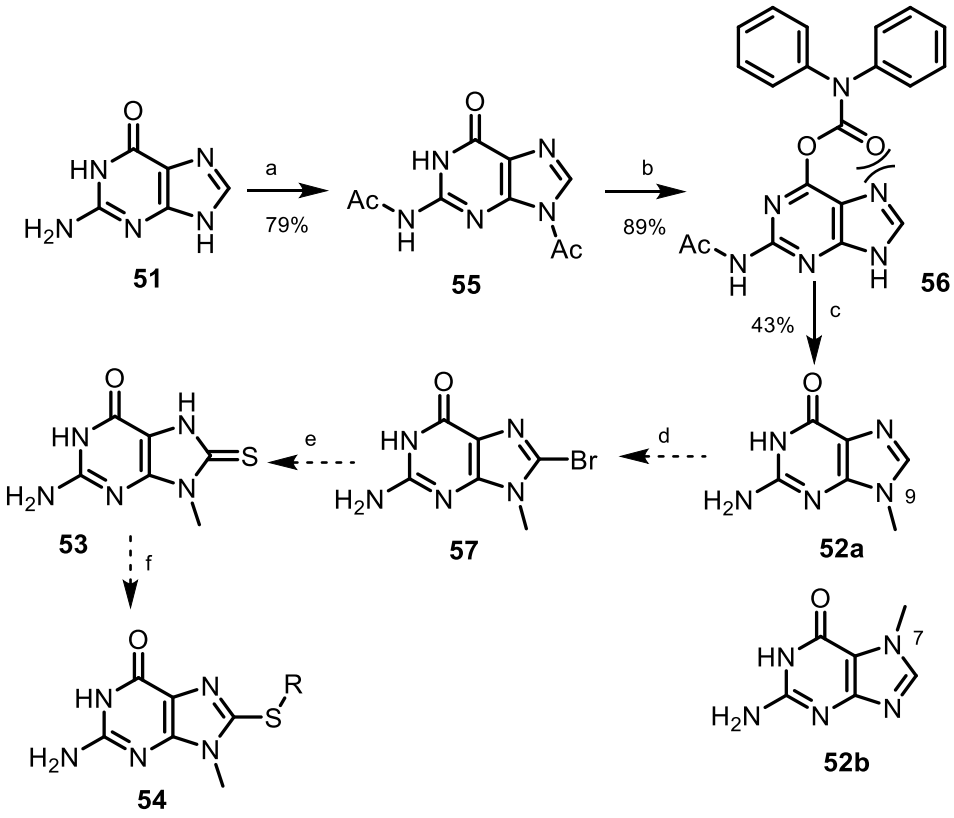
Direct methylation of guanine produces N7, N9 isomeric mixtures that are difficult to separate, due to the limited solubility of these compounds in organic solvents. Therefore, the selective N9 methylation of guanine is important and this may be achieved by using a steric shield at position 6 to give enhancement of N9 methyl.

The protection of amino group was done as reported by Zou [30]. Three different solvents were evaluated (**55**) as shown in table 3.

Table 3

Start material	Conditions	% yield	Chemical shifts (in ppm)		
			2NAc	N9Ac	C8-H
Guanine	Ac_2O, DMAc, 160 °C, 7 h	79%	2.21	2.81	8.44
Guanine	Ac_2O, NMP, 160 °C, 7 h	75%	2.20	2.79	8.44
Guanine	Ac_2O, AcOH, 135 °C, 7.5 h	77%	2.18	2.79	8.41

Subsequently, amide group was protected by formation of the *N*,*N*-diphenyl carbamate (**56**) in 89% yield. We have assumed that there were many advantages to introduce *N, N*-diphenyl carbamate, one of them was to block the methylation at the N7 position. Secondly, to increase solubility of guanine derivatives *via* increase polarity.[30] Next, deprotecton of N9 using mixture of EtOH/H_2O. *N*-methylation of **56** was done *via* methyl iodide and NaH as base.



Reagents and conditions:

a) Ac_2O, DMAc, 160 °C, 7 h. **b**) (i) Ph_2NCOCl / $EtN(i\text{-}Pr)_2$ / pyridine. (ii) EtOH / H_2O.
c) (i) MeI, NaH, DMF, 3 days. (ii) 30% ammonia / MeOH, 60 °C. **d**) Br_2, AcOH.
e) Thiourea, EtOH, reflux . **f**) NaOH (0.5 M), R-Br.

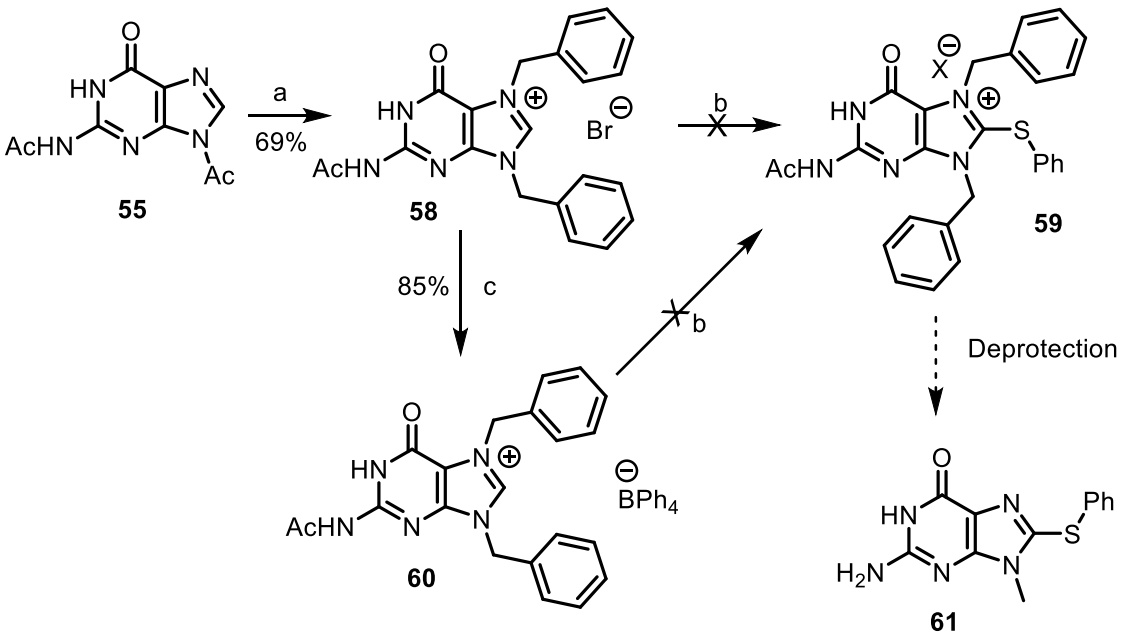
Scheme 7. Proposed preparation of the target compounds via guanine.

Unfortunately, all attempts to produce single desired N9 methyl guanine product (**52a**) failed. The reaction produced the mixture of N7 and N9 methyl guanine **52a** and **52b**

which were difficult to separate using column chromatography especially because these compounds are insoluble in organic solvents. It was supposed to carry on with bromination C8-H of **52a** or **52b** by Br_2 and AcOH mixture to give (**57**), thiolation using thiourea and the target compounds (**54**) using sodium hydroxide (0.5M) and haloalkyl (Scheme 7).

2.2.1.2 Second approach: guanine route (plan A)

Compound (**58**) obtained from (**55**) using benzyl bromide (69% yield) and was subsequently treated with base in the presence of diphenyl disulfide. However, no desired product (**59**) was observed. Due to the poor solubility of **58**, the counter ion was switched from bromide ($^-$Br) to tetraphenylborate ($^-BPh_4$) using reported procedure[60] within our group (Scheme 8), nonetheless reaction with diphenyl disulfide failed to provide the desired product (**59**).



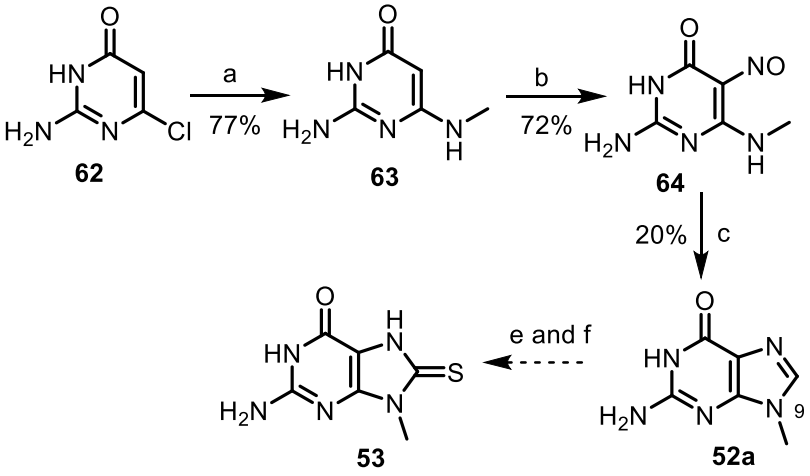
Reagents and conditions:
a) BnBr, DMAc, 120 °C, 2h. **b**) ^{t}BuOK, $(SPh)_2$, DCM, rt . **c**) $NaBPh_4$, H_2O.

Scheme 8. Proposed preparation of the target compounds *via* guaninium salts (58 and 60).

2.2.1.3 Pyrimidine route (plan B)

To solve the problem, which was the production of the mixture of N7 and N9 methyl guanine (Scheme 7), we turned to another route (plan B), which was reported by Blagg,[29] to synthesis N9 methyl guanine (Scheme 9). In plan B, the formation of N9 methyl guanine was accomplished in 20% yield by introducing the methylamino group

to pyrimidine ring *via* S_NAr of chloropyrimidine (**62**) followed by nitrosylation (72% yield), reduction and cyclization of the imidazole ring, was performed using a mixture of formamide and formic acid.[30, 31]

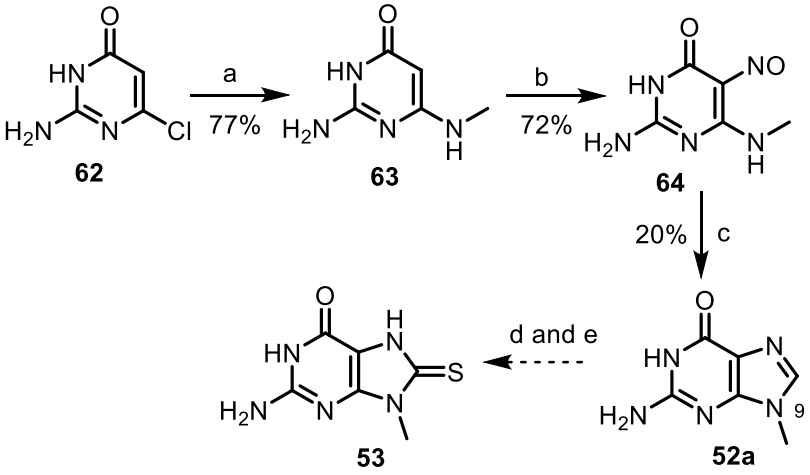


Reagents and conditions:
a) CH_3NH_2, 120 °C. **b**) $NaNO_2$, H_2O. **c**) $HCONH_2$, HCO_2H, $Na_2S_2O_4$, 70 °C, 3 h.
e) Br_2, AcOH. f) Thiourea, EtOH, reflux.

Scheme 9. Plan B: Proposed formation of N9-methyl guanine by cyclization of the imidazole ring.

2.2.1.4 Imidazole route (plan C)

The yield of N9 methyl guanine (**52a**) obtained by the previous route was low, therefore our attention turned to plan C (Scheme 10), which was reported by Alhede,[32] where methylation of the *N*-imidazole ring occurs before formation of the pyrimidine ring. Preparation of the potassium salt of **65** in DMF using KOH powder followed by addition of iodomethane allowed the introduction of the N-Me substituent in 41% yield. Subsequently, It was supposed to carry on with bromination C8-H of **52a** by Br_2 and AcOH mixture and the introduction of sulfur using thiourea to give **53**.



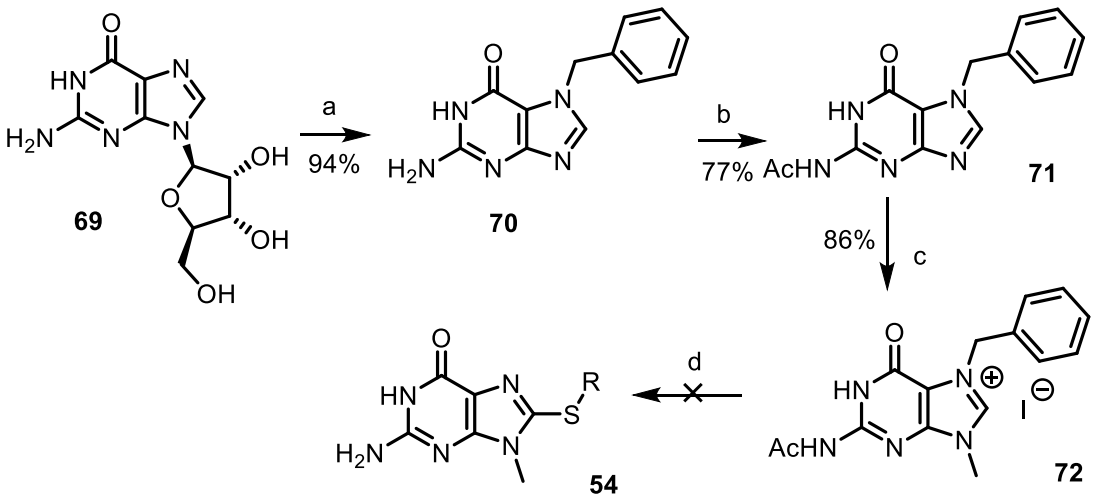
Reagents and conditions:
a) CH_3NH_2, 120 °C. **b**) $NaNO_2$, H_2O. **c**) $HCONH_2$, HCO_2H, $Na_2S_2O_4$, 70 °C, 3 h.
d) Br_2, AcOH. e) Thiourea, EtOH, reflux.

Scheme 10. Plan C: Proposed formation of N9-methyl guanine *via* cyclization of the pyrimidine ring.

Next, the treatment of N1-methyl imidazole (**66**) with benzoyl isothiocyanate in acetone afforded the corresponding thiourea (**67**), 65% yield. Finally, the cyclization catalysed by copper(II) acetate, allowed construction of the pyrimidine ring, and compound (**52a**) was obtained in 76% yield.[32]

2.2.1.5 Guanosine route (plan D)

Other methods to prepare 9-methyl guanine having proved unsatisfying a pathway using guanosine (**69**) was chosen, using to our advantage the regioselective benzylation on N^7 on guanosine (**69**). Acid hydrolysis of the sugar ring afforded (**70**) in 94% yield, protection of the amino group using acetic anhydride gave (**71**) in 77% yield[33] and treatment of N^7 benzyl guanine with methyl iodide gave guaninium salt (**72**) in 86% yield. The last in turn, dissolved in DMSO then ^{t}BuOK was added as base which presumably resulted in the formation of carbanion that was reacted with S-S bond and getting the target compounds (Scheme 11). Guaninium salt (**72**) was reacted with the base but the desired product was not observed.



Reagents and conditions:
a) i) BnBr, DMSO, r.t, 24 h. ii) HCl conc. b) Ac_2O, DMAc, 150 °C, 1 h.
c) MeI, DMAc, 40 °C, 3 days. d) i) ^{t}BuOK, $(SR)_2$, DMSO, rt. ii) Deprotection

Scheme 11. Proposed preparation of the target compounds *via* guaninium salt.

Attempts to transform guaninium salts (**72**), (and as previously presented **58** and **60**) to 9-methyl-8-mercaptoguanine derivatives using base and diphenyl disulfide were unsuccessful. After adding the base (^{t}BuOK), the colour changed from colourless to yellow. In order to understand the colour change, NMR analysis was performed for the reaction mixture which contained the salt (**72**) and the base (^{t}BuOK). The ^{1}H NMR spectrum of the reaction mixture showed the absence of the proton at position 8 (at 9.6 ppm) in the starting material (**72**), but no reaction with Ph-S-S-Ph (Figure 13). Mass spectrometry also support this observation (Figure13a). Mass spectrometry data analysis for guaninium salt (**72**) $[M]^+$ = 298.1296, while mass spectrometry data analysis for the product was $[M+H]^+$ = 298.1292 corresponding to loss of one proton. We assumed that either N-H of amide or C8-H was deprotonated. In case C8-H was deprotonated the resulting compound was carbene.

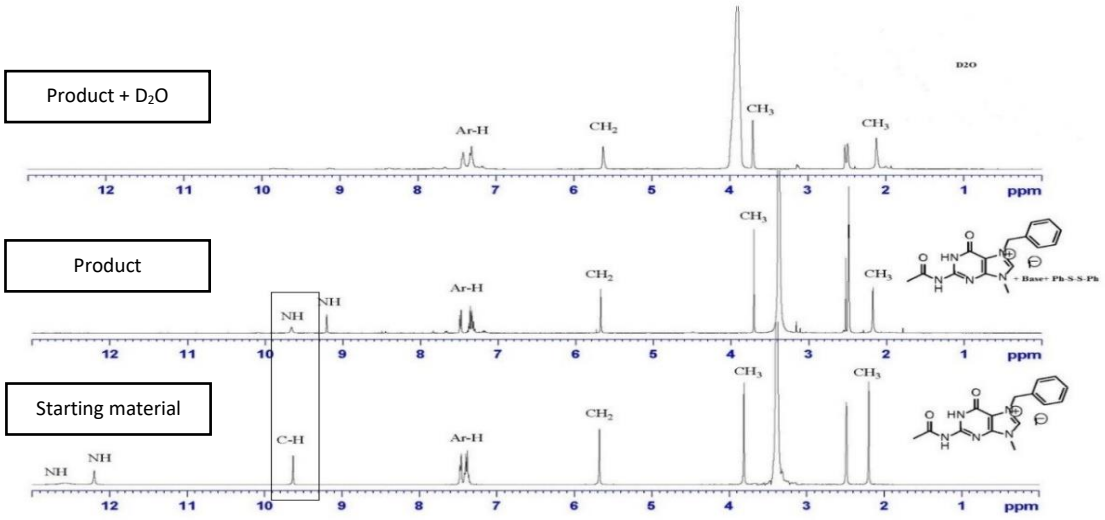


Figure 13. NMR spectrum of guaninium salt (**72**) and unknown product (DMSO-d6).

Mass Spectrum:

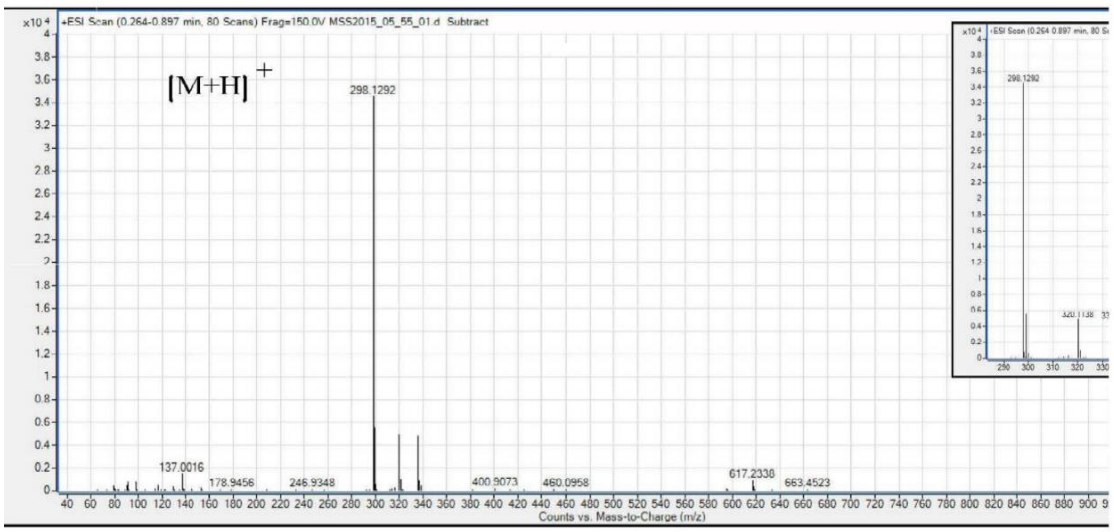
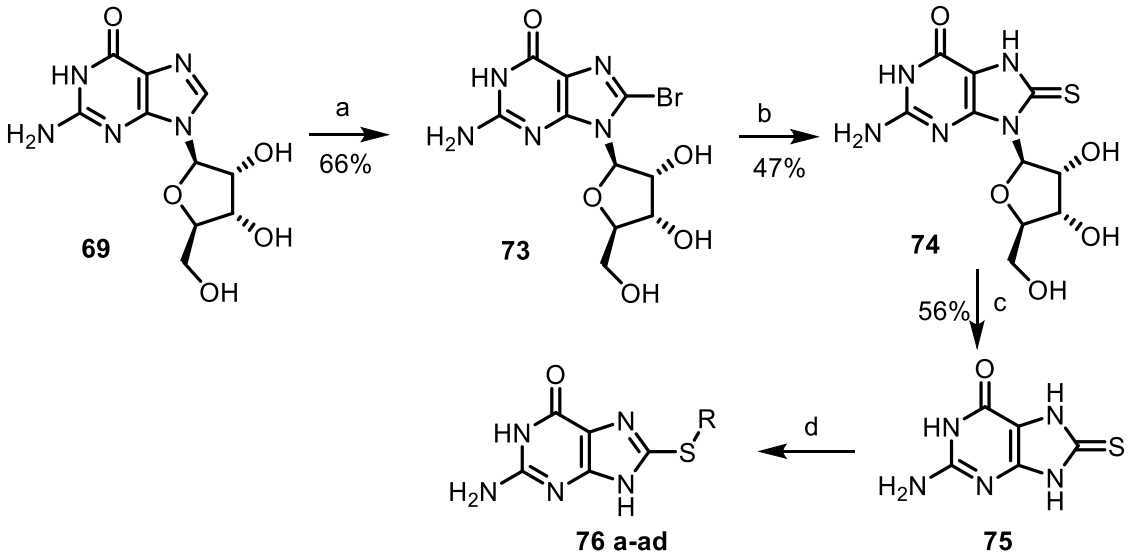


Figure 13a. Mass spectrometry of unknown product.

2.2.2 Synthesis of 8-mercaptoguanine

Finally, the target compounds were obtained in four steps using guanosine (**69**). The presence of sugar group at N9 is essential for successful bromination at C8 by NBS and DMF as solvent, [34] and compound (**73**) was obtained in good (66%) yield. Then, guanosine bromide (**73**) underwent nucleophilic substitution with thiourea and after acid hydrolysis of the sugar ring by HCl, 8-mercaptoguanine (**75**) was obtained in 56% yield (Scheme 12).

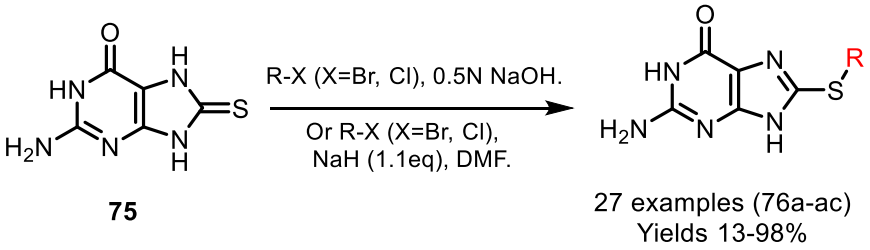


Reagents and conditions:
a) NBS, DMF, r.t overnight. b) Thiourea, EtOH, reflux. c) 3 N HCl, 100 °C.
d) R-Br or R-Cl, 0.5 M NaOH Or NaH (1.1eq), DMF, r.t.

Scheme 12. Preparation of the target compounds *via* guanosine.

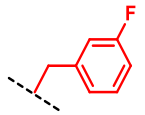
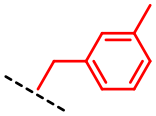
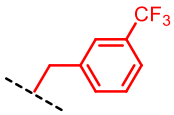
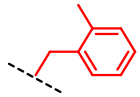
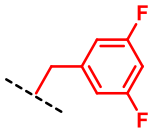
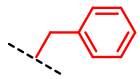
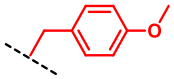
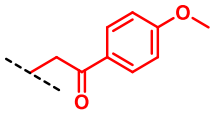
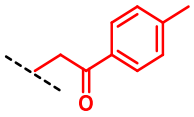
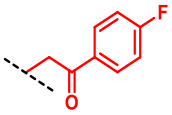
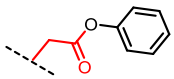
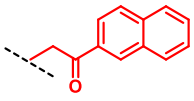
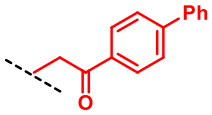
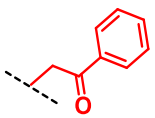
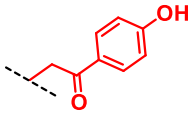
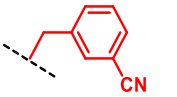
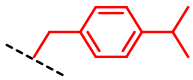
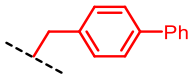
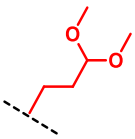
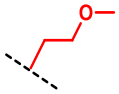
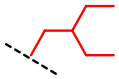
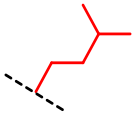
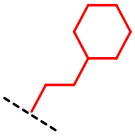
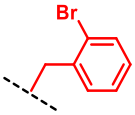
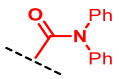
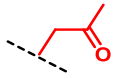
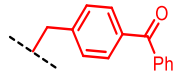
2.2.3 Synthesis of 8-mercaptoguanine derivatives

The target compounds, represented by formula (**76**), were prepared by the reaction of compound (**75**) with several alkyl bromides and chlorides using sodium hydroxide base for the deprotonation of the imidazole N-H (Scheme13 and table 4).



Scheme 13

Table 4

Entry	R-X	Comp	Yield (%)	Time	(%) of inhibition
1		76a	44	2 h	44
2		76b	64	3 h	43
3		76c	62	15 h	9
4		76d	72	2 h	52
5		76e	75	5 h	33
6		76f	65	17 h	59
7		76g	20 [a]	30 min	41
8		76h	82	4 h	35
9		76i	81	6 h	30
10		76j	57	6 h	37
11		76k	88	16 h	41
12		76l	62	1 day	44
13		76m	69[b]	18 h	41
14		76n	98	15 h	31
15		76o	98	17 h	31
16		76p	44	20 h	44
17		76q	13	16 h	7
18		76r	58	16 h	28
19		76u	58	3 days	48
20		76v	73	18 h	41
21		76w	95	20 h	52
22		76x	82	3 days	52
23		76y	37	3 days	41
24		76z	60	3 days	44
25		76aa	23[a]	5 h	67
26		76ab	37[a]	19 h	70
27		76ac	30	1 day	- [b]

[a] Using chloride derivatives. [b] No biological test for this compound.

The difference in the physical and chemical properties of halo compounds led to the use of different procedures for the preparation of the target compounds. The sulfur atom was substituted successfully with alkyl and benzyl groups bearing a wide range

of functionalities (ketone, ether, amide, cyano, hydroxyl, ester, ketal). From the previous table it is not easy to explain the reason of the high yield and there are no obvious trends. Generally, α-bromoacetophenone derivatives (Entry 8, 9, 14 and 15) gave good yields and this is due to the benzoyl group (as withdrawing group) increasing the electrophilicity of the carbon neighbour. Secondly, bromide derivatives gave better than chlorides derivatives (entry 7, 27 and 29) and this is due to the bromide (Br^-) is good leaving group than chloride (Cl^-).

All 8-mercaptoguanine derivatives **76a-76ab** were subjected to biological testing in THP-1 monocyte cell line (in vitro) performed using ELISA experiments. Neopterin, which is first product in the BH4 pathway, can be used as a marker of GTP cyclohydrolase (I) enzyme activity (Scheme 2). Biological experiments were run using the Neopterin ELISA kit (total n=9 for stimulated/ stimulated+ DAHP/non-stimulated samples and n=6 for all other 26 compounds at 10 μM concentration in stimulation media). Neopterin concentrations increased from non-stimulated THP-1 cell lysates of 2.75 ± 2.19 nM to 64.63 ± 10.77 nM in stimulated THP-1 lysates.

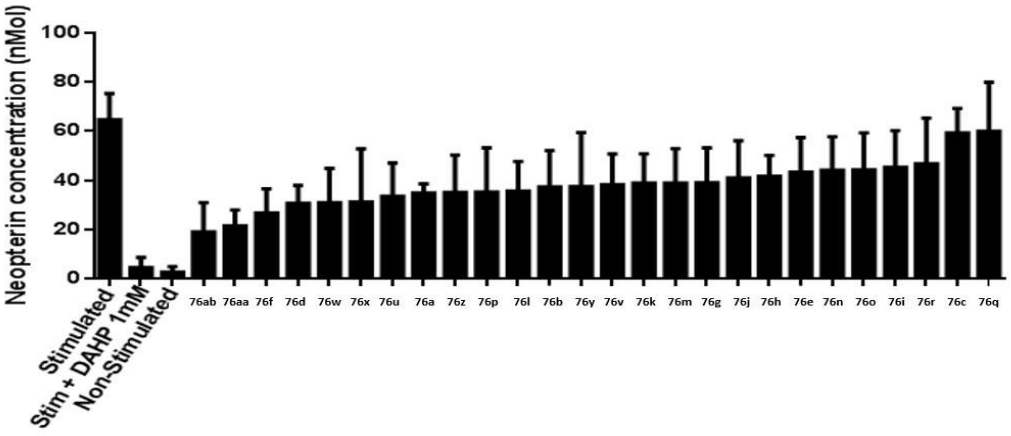
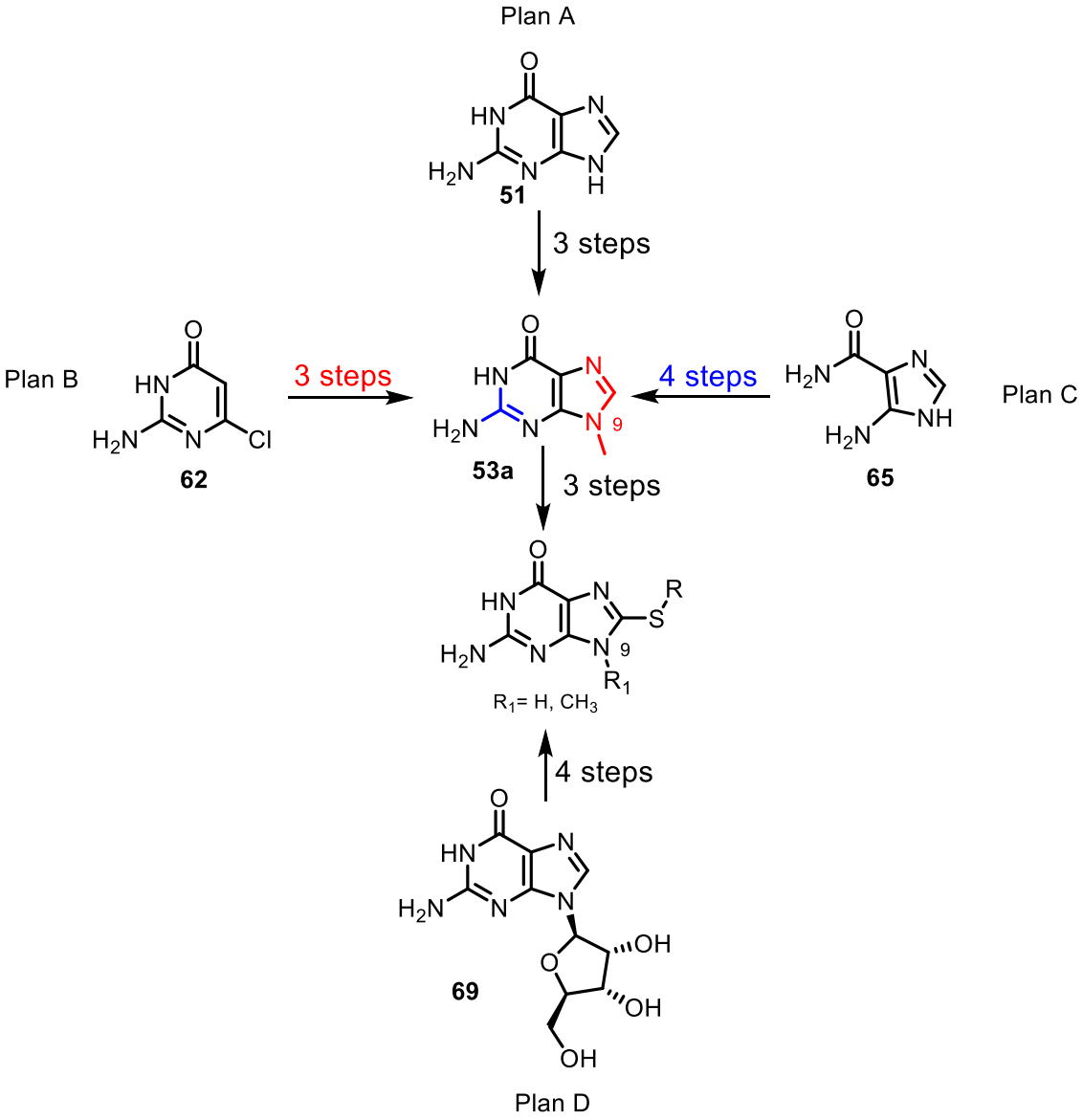


Figure 14. Data obtained from biological testing.

Figure 14 presents preliminary data obtained for subjecting compounds **76a-76ab** to THP-1 monocyte cell line and monitoring the formation of Neopterin. It represents Neopterin concentration when the target compounds were subjected, the biological method described above were obtained from Dr. Patrick McHugh and Ben Moore at the University of Huddersfield. It can be seen that the target compounds have shown inhibition activity against the formation of Neopterin which represents the activity of GTPCH1 enzyme. The compound (76ab) has showed the best activity against the formation of Neopterin which means the reduction of biosynthesis of BH4.

3. Conclusion

Summing up the results, toward the target compounds, the initial attempts were to prepare N9 methyl guanine. The latter in turn, was synthesised by three different plans (Scheme 14). The problem with the plan (A) was in that the reaction produced a mixture of N7/N9 methyl guanine which were difficult to separate them. On the other hand, plans (B) and (C), which involved the cyclisation of pyrimidine and imidazole rings, took 3 and 4 steps to prepare N9 methyl guanine which additionally will take 3 steps to produce the target compounds. Finally, instead of use N9 methyl guanine, our attention turned to use guanosine as starting material to prepare the desired compounds.



Scheme 14

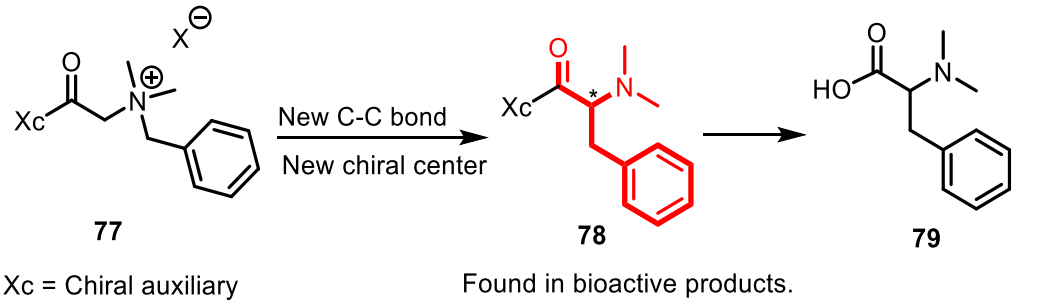
In conclusion, a library of 8-mercaptoguanine derivatives (**76a-76ab**) were successfully synthesised in four-steps using traditional purine chemistry reactions in moderate to high yields (13-98%). The target compounds are accessible from readily available nucleosides.

Chapter 2

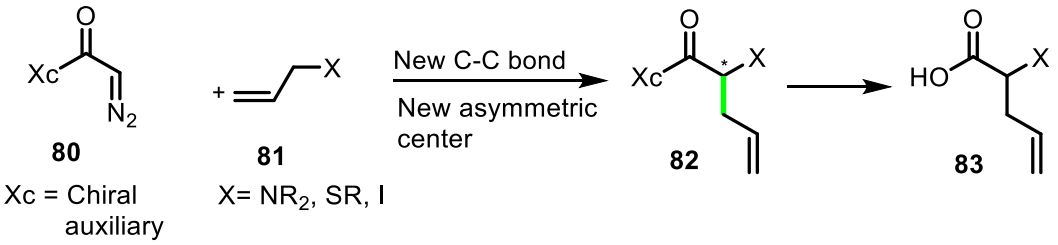
Towards amino acids: asymmetric [1,2]-Stevens rearrangements and [2,3]-sigmatropic rearrangements of onium ylides

4. Introduction

Our group has been interested in [1,2]-Stevens rearrangement of benzyl ammonium and [2,3]-sigmatropic rearrangement for many reasons, firstly that it is a good strategy for construction of carbon-carbon bonds, quickly converting accessible C-N bonds into a new C-C bonds. For example, the rearrangement of benzyl ammonium salts might be an efficient way to generate α-benzylated chiral amino acid derivatives, by using chiral auxiliaries such as camphorsultam (Scheme 15). In the case of allyl onium ylids (Scheme 16), the [2,3]-sigmatropic rearrangement affording α-allylated chiral amino acid in which the double bond could be converted into many other functional groups. Moreover, the presence of the dialkyl phenyl alanine skeleton in many natural bioactive cyclopeptides such as Sanjoinine and Lasiodine which are isolated from plants (Figure 16).[35]



Scheme 15



Scheme 16

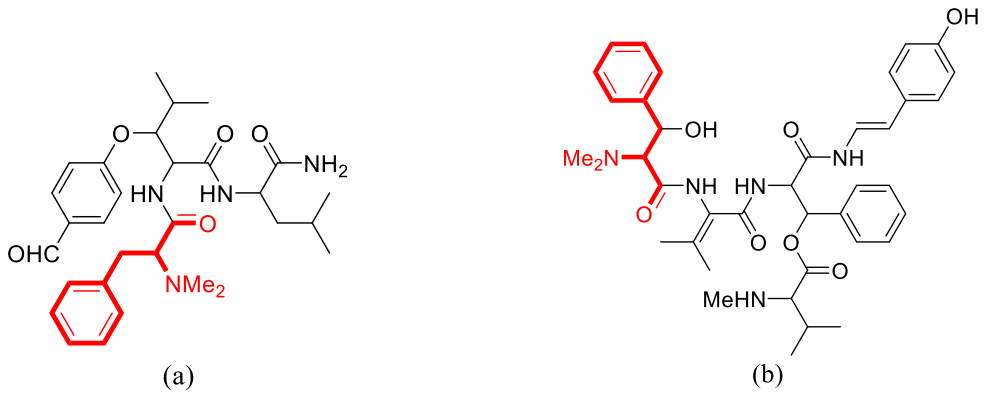
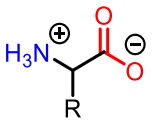


Figure 16. (a) Structure of Sanjoinine. (b) Structure of Lasiodine.

4.1 Amino acids

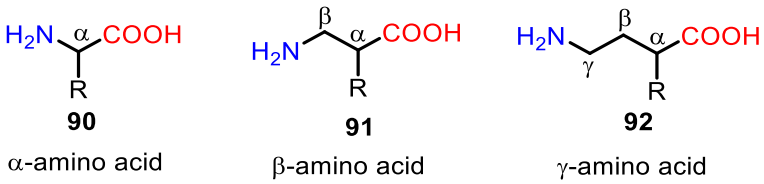
Amino acids are a class of organic compounds, which contain carboxyl and amine group and a side chain, which is specific to each amino acid (Figure 17).



90

Figure 17.

Amino acids can be classified according to the position of the amino group, which may be attached to carbon alpha- (α-), beta- (β-) or gamma- (γ-) to the carboxylic acid (Figure 18). About 700 amino acids are known in nature and some of them exist in free form or bound into large molecules. Although, there are so many amino acids, only 20 appear in the genetic code (proteinogenic) and under control of genes for synthesis of proteins in human body.[36]



90 α-amino acid

91 β-amino acid

92 γ-amino acid

Figure 18

4.1.1 Examples of α-amino acids

Shown below the chemical structures and names for 20 coded amino acids (proteinogenic). Except for glycine (**93**), all amino acids have at least one asymmetric carbon, which leads to the presence of amino acids in two isomeric forms, because of the possibility of forming two different enantiomers (stereoisomers) around the central carbon atom. In addition, all amino acids have a primary amino group (except for proline, **108**) and a carboxylic acid group attached to α-carbon atom (Figure 19).

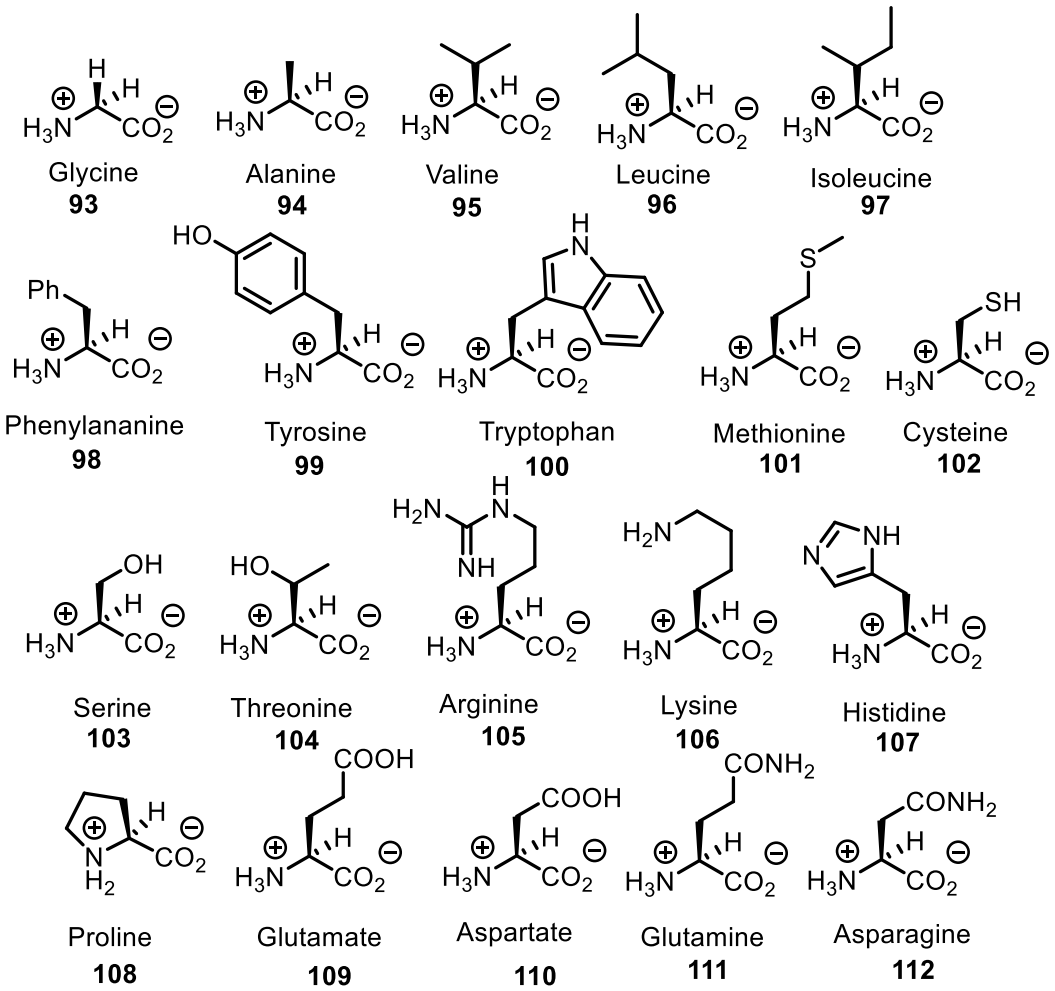
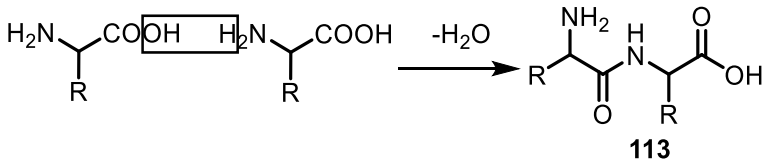


Figure 19

4.1.2 Peptide linkage

As mentioned earlier, proteins are built by amino acids, which are linked together. The carboxylic acid group of one amino acid is linked to the basic amino group of another with elimination of water (Scheme 20).[37]

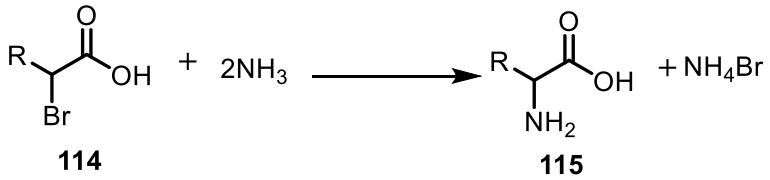


Scheme 17

4.1.3 The synthesis of amino acids

There is a lot of interest in the synthesis of coded and non-coded amino acids because of their importance in biosynthesis and their medicinal properties. In the past, synthesis of amino acids produced amino acids as racemic mixture. There are many

methods for synthesis of α-amino acids. One of them is amination, in which the amino group is introduced into α-bromocarboxylic acids (**114**), as illustrated in scheme 18.[38]

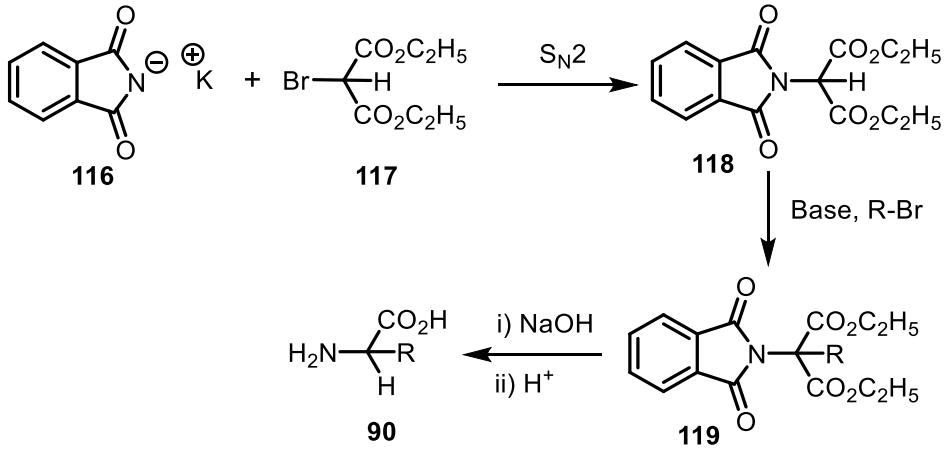


114 **115**

Scheme 18

4.1.3.1 Gabriel synthesis

Traditionally, Gabriel synthesis of α-amino acid begins with potassium phthalimide (**116**), which is the source of the amino group and serves as nucleophile, and diethyl bromomalonate (**117**). The phthalimide substituted malonic ester **118** has an acidic hydrogen, (activated by two ester groups), this compound can be deprotonated and reacted in nucleophilic substitution (S_{N2}) fashion with electrophiles to install the side chain of the amino acid. Finally, base hydrolysis of the phthalimide derivatives (**119**) followed by acid catalysed decarboxylation, produces an amino acid (Scheme 19).

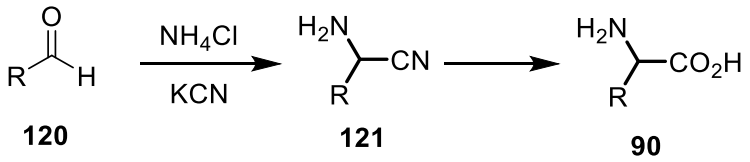


116 **117** **118** **119** **90**

Scheme 19

4.1.3.2 Strecker synthesis

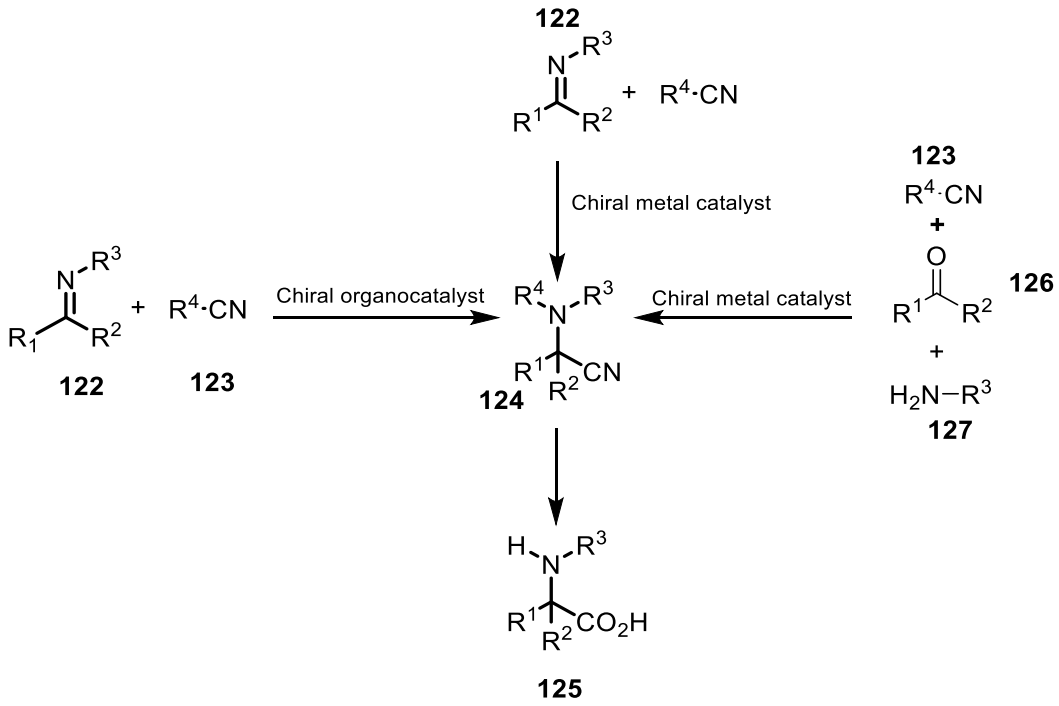
By this method, amino acids are produced from an aldehyde (**120**), which is reacted with ammonium chloride (the amine precursor) in the presence of potassium cyanide (the carboxyl precursor) to form α-aminonitrile (**121**) which can be subsequently, hydrolysed to an amino acid (Scheme 20).[39]



120 **121** **90**

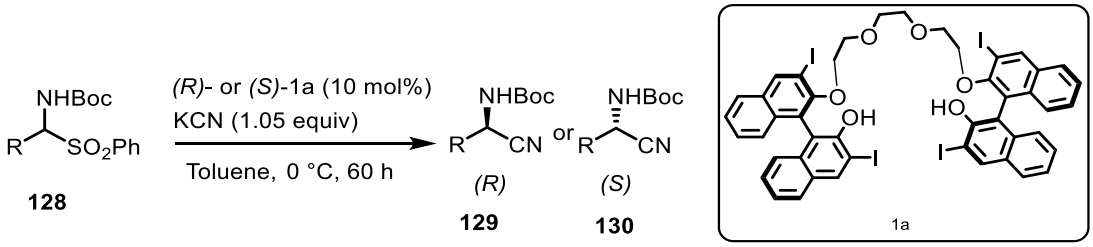
Scheme 20

Unfortunately, using Strecker synthesis in this manner, only gives a racemic mixture of amino acids. Therefore, there has been extensive attention developed towards an asymmetric Strecker reaction that would be used to produce optically pure non-proteinogenic amino acids. There are several methods in this context, for instance, enantioselective Strecker reaction using organocatalysts and metal catalysts (Scheme 21).[39]



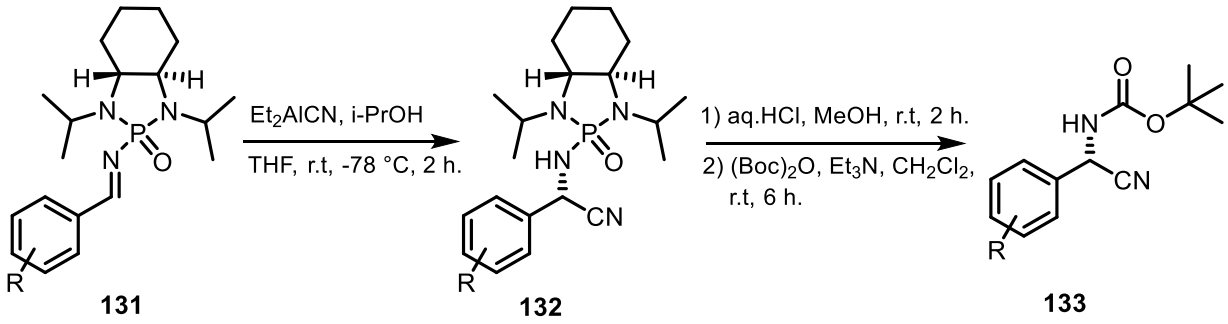
Scheme 21

In 2012, Woong Lee and co-worker have reported an organcatalytic asymmetric Strecker reactions using oligoethylene glycol (**1a**) as catalyst and KCN. They were able to transform various α-amido sulphone substrates (**128**) (alkyl, aryl and heteroaryl) into optically active amino nitriles, which were hydrolysed to afford amino acids, with enantionselectivities and excellent yields (Scheme 22).[40]



Scheme 22

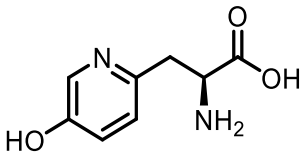
In 2011, Li and co-workers found that chiral *N*-phosphonylimines (**131**) were good electrophiles for reaction with diethylaluminium cyanide. The reaction gives chiral α-aminonitriles (**132**) in excellent yield (94-98 %) and diastereoselectivity (95:5 to > 99:1 d.r.). The *N*-phosphonyl group was cleaved by HCl in methanol, which was followed by treatment with Boc anhydride to give Boc-α- aminonitrile (**133**) that can be hydrolysed to amino acids (Scheme 21).[41]



Scheme 21

The limited benefit of Strecker reaction might be due to many factors. The most important factor is the use of hazardous cyanide sources in high stoichiometric amounts, which reduce application to large-scale.

4.1.3.3 Total synthesis of L-azatyrosine



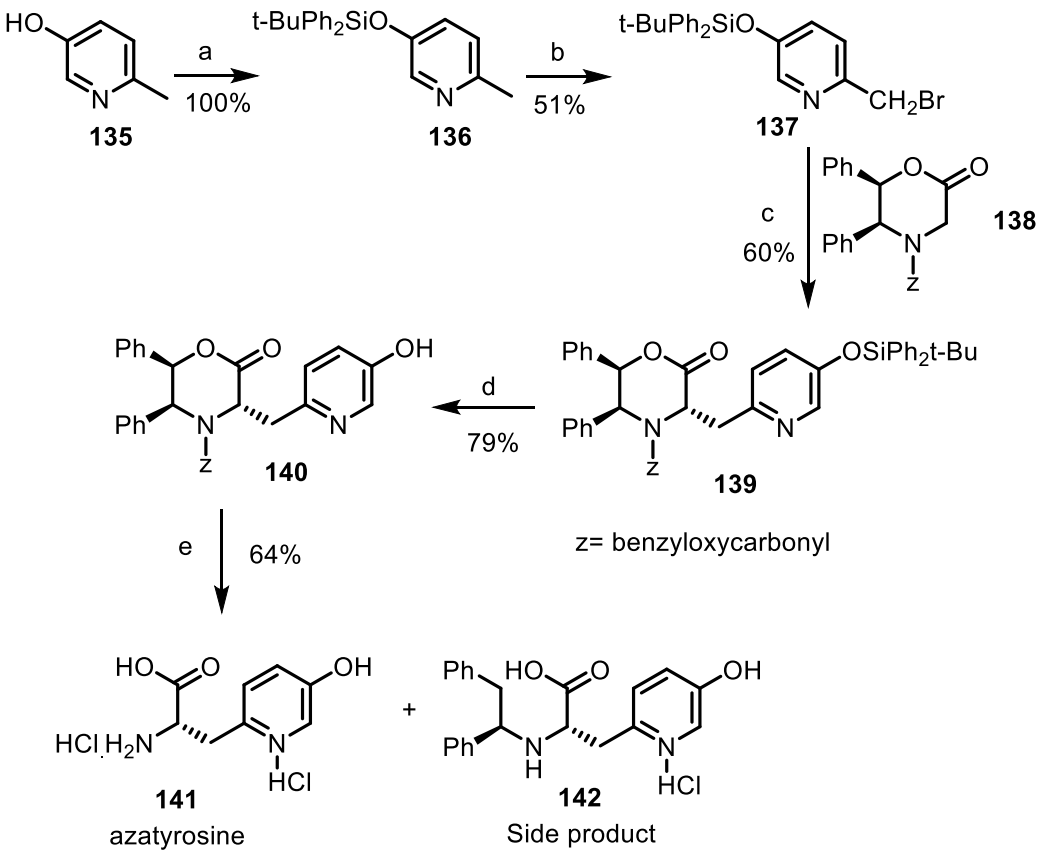
134

Figure 20

As an example of α-amino acids, *L*-azatyrosine (Figure 20) was obtained from a fermentation broth of *Streptomyces chibanesis,* which was isolated from soil in Japan.

It is an antibiotic which has showed anti-cancer activity. Many total syntheses of *L*-azatyrosine have been achieved since its discovery.

In 1994, Schow and co-workers have reported a distereoselective synthesis of L-azatyrosine (**134**). They started with the silyl protection of 5-hydroxy-2-methyl pyridine (**135**), which is commercially available. Subsequent bromination of the methyl group using NBS followed by S_N2 displacement of the bromide by the enolate of chiral glycine derivative **138**[42] produced azatyrosine precursor **139**. Next, deprotection of silyl group using TBAF and hydrogenation over Pearlman's catalyst to remove diphenylethylene and gave mixture of azatyrosine (**141**) and side product **142**. To solve this problem, the mixture was treated with HCl and continued hydrogenation in water over 5 % Pd/C to yield azatyrosine.HCl (Scheme 22).[43]

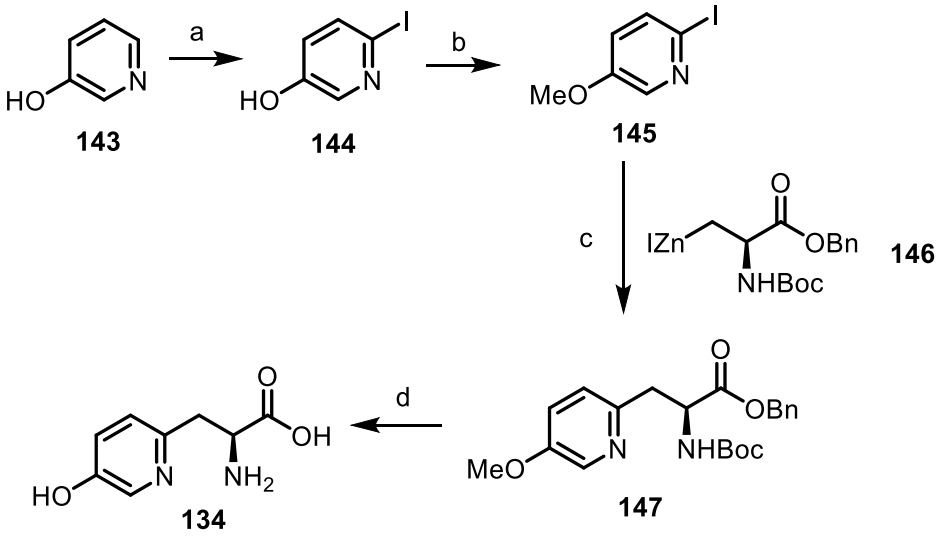


Reagents and conditions:

a) Ph_2t-BuSiCl, imidazol, DMF. b) NBS, AIBN, CCl_4. c) $NaN(SiMe3)_2$, THF.
d) TBAF, THF. e) $Pd(OH)_2/C$, H_2, THF, Pd/C, HCl/H_2O.

Scheme 22

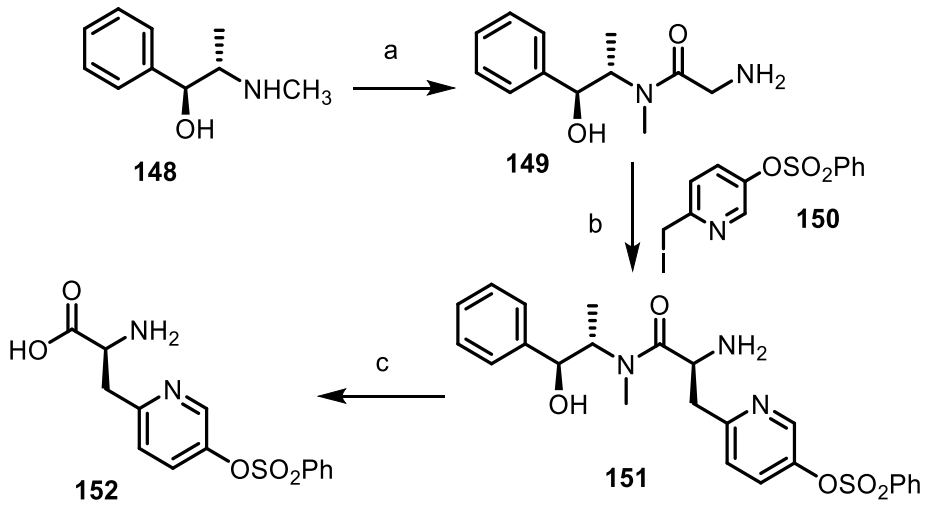
One year later, Westwell published a total synthesis of *L*-azatyrosine in three steps, starting with 3-hydroxypyridine (**143**) which was converted to 2-iodo-5-hydroxypyridine (**144**) using NaI, NaOCl, NaOH. The next step was a Negishi coupling with organozinc **146**[44] followed by deprotection to give the desired amino acid **134** (Scheme 23).[45]



Reagents and condition:
a) i) NaI, NaOCl, MeOH, 0 °C. b) CH_2N_2, Et_2O, 0 °C.
c) $PdCl_2(PPh_3)_2$, DMAC, THF, 0 °C. d) BBr_3, CH_2Cl_2, 0 °C.

Scheme 23

Myers *et al.* described a practical synthesis of *L*-azatyrosine and showed that it can be prepared from pseudoephedrine glycinamide (**149**), (which is produced from pseudo ephedrine (**148**) using base and LiCl in the presence of GlyOMe).



Reagents and conditions:
a) n-BuLi, LiCl, GlyOMe. b) LDA, LiCl. c) NaOH, H_2O.

Scheme 24

Alkylation of **149** with iodo derivative **150** gave protected L-azatyrosine **151**, which was deprodected using NaOH affording sulfonate **152** (Scheme 24).[46]

4.2 Rearrangement reaction

As mentioned previously, our group is interested in the [1,2]-Stevens rearrangement and the [2,3]-sigmatropic rearrangement of ammonium ylids (often referred to as the [2,3]-Stevens rearrangement) because they offer an efficient way to generate α- chiral amino acid therefore our attention will focus on them.

A rearrangement reaction is a type reaction where bonds are changed of order to produce a structural isomer.

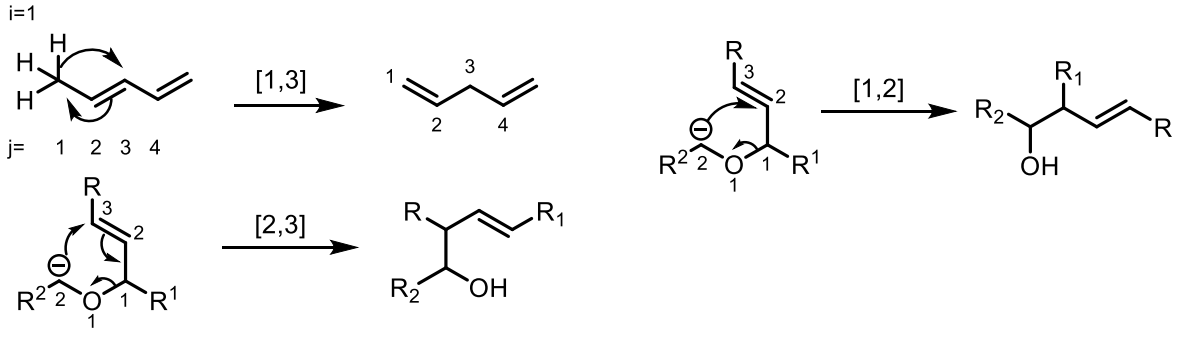
4.2.1 Pericyclic reactions

Pericyclic reactions are rearrangement reactions where the order of bonds change. This reaction includes mechanism through cyclic geometry of the transition state where flow of electrons occurs through a cyclic transition state and according to Woodward–Hoffmann rules, which can predict the stereochemical outcome of pericyclic reactions. They can be classified into following four categories:

Sigmatropic rearrangements, cycloaddition, electrocyclic reactions and group transfer reactions

4.2.2 Sigmatropic rearrangements

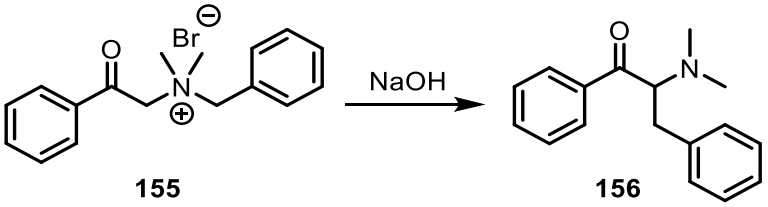
Sigmatropic rearrangement is a type of pericyclic reaction where the number of σ and π bonds in the product and the starting material is unchanged and a σ-bond migrates with rearrangement of the π-framework. The Woodward–Hoffmann notation describe sigmatropic rearrangement by an order term [i,j] which means σ-bond moves to one or more π bonds for example [1,3]-shift which means σ-bond moves from position 1 to position 3. There are many types of this rearrangement, includes [1,2]- and [2,3]-rearrangements (Scheme 25).



Scheme 25

4.2.2.1 [1,2]-Stevens rearrangement

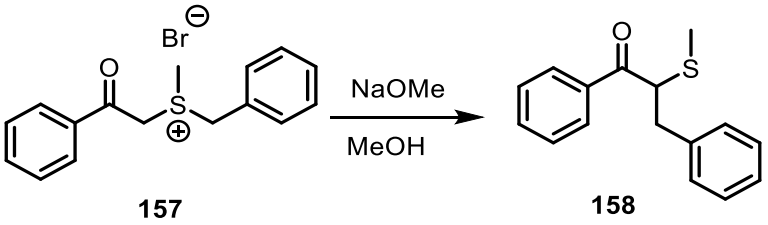
In 1928, the [1,2]-rearrangement of benzyl ammonium salts was first reported by T. S. Stevens who observed the 1,2-shift of quaternary ammonium salt while attempting amine protection. Ammonium salt **155** was converted to 1-benzoyl-2-benzyldimethylamine (**156**) upon treatment with aqueous sodium hydroxide (Scheme 26).[47]



155 **156**

Scheme 26

A few years later, Stevens reported an analogous reaction with sulfonium salt **157** and sodium methoxide as base to get the corresponding sulfide **158** (Scheme 27).

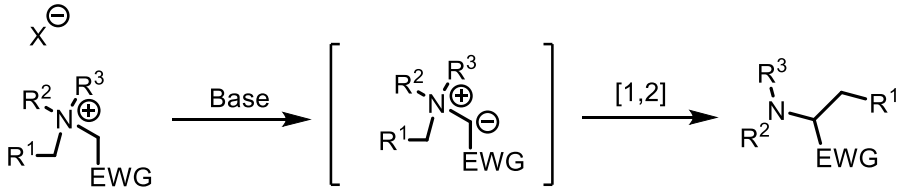


157 **158**

Scheme 27

4.2.2.1.1 [1,2]-Stevens rearrangement mechanism

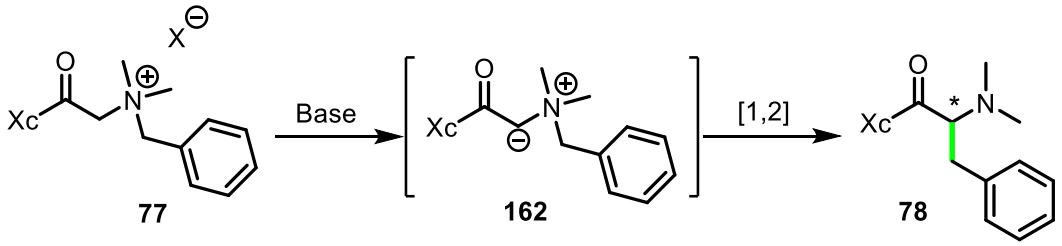
To produce [1,2]-Stevens rearrangement products, ammonium salts must be prepared first. Then, addition of base allows for deprotonation of the most acidic proton and forms the ammonium ylides (**160**). As the σ^*-orbitals of C-N bond have little stabilization by the negative charge adjacent to the onium centre, ammonium ylides tend to rearrange to obtain thermodynamic stabilization (Scheme 28).



159 **160** **161**

Scheme 28

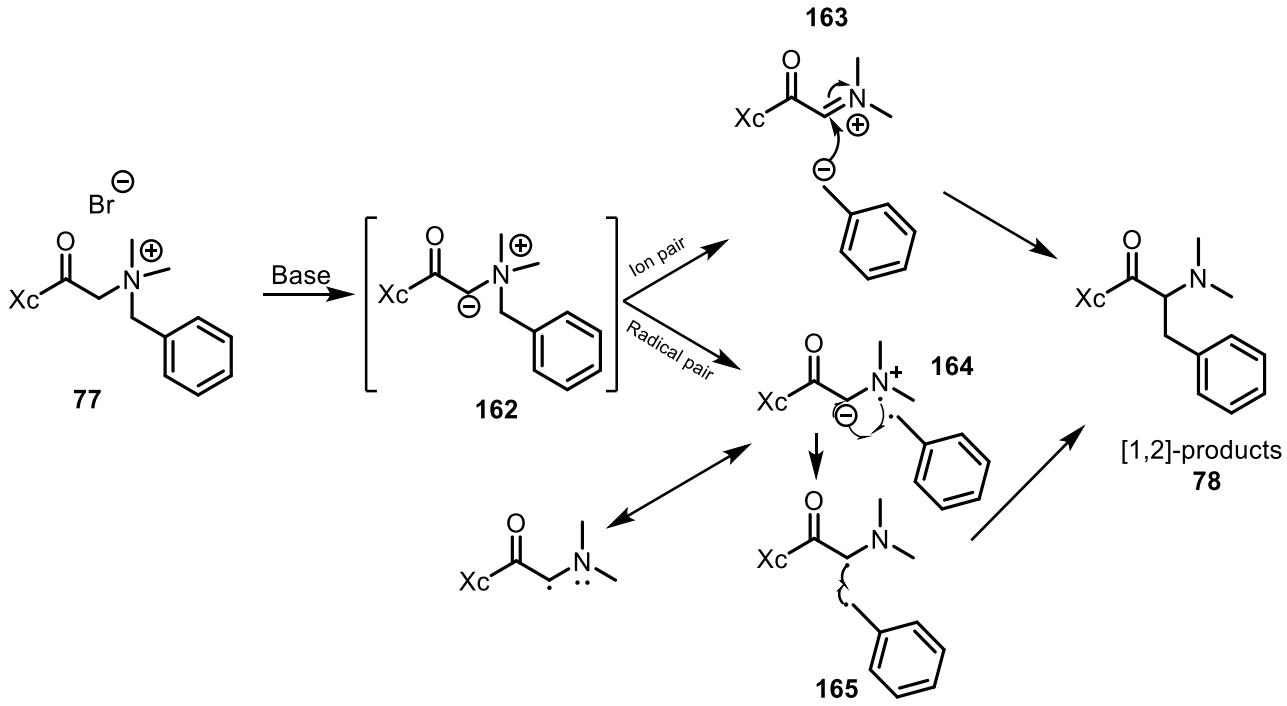
To explain the [1,2]-Stevens rearrangement mechanism, we will use a chiral auxiliary which hopefully control stereochemistry of the newly formed chiral centre (Scheme 29).



Xc = Chiral auxiliary

Scheme 29

There are two proposed mechanisms for the [1,2]-Stevens rearrangement, whether the reaction proceeds *via* an ion-pair or a radical-pair. A number of views and evidence[48] support the [1,2]-shift occurs through radical mechanism which includes homolytic cleavage of C-N bond to stable carbon a radical and forming a radical pair that is held tightly together by a solvent cage. Next, rapid recombination of a radical pair to provide the Stevens [1,2]-shift products. Stereoselectivity should be considered when a radical pair recombine (Scheme 30).[49]

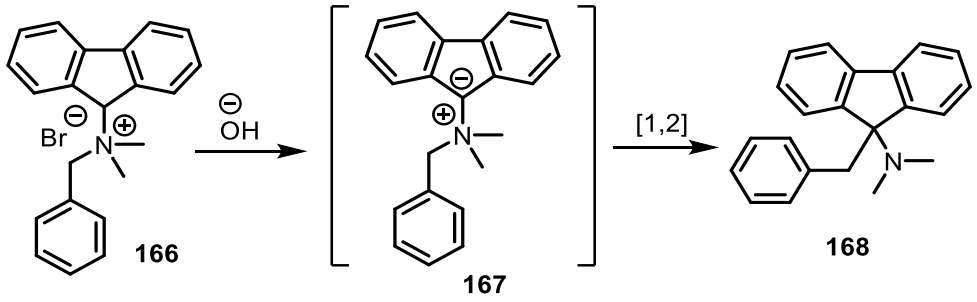


Scheme 30

In 1975, Ollis and co-workers reported the influence of solvent and reaction temperature on the stereoselectivity and intramolecularity of the Stevens [1,2] rearrangement. They investigated the stereoselectivity using different solvents and temperature. The results led to the following conclusion: firstly, the stereoselectivity and intramolecularity of the Stevens [1,2] rearrangement decreases when the solvent used has low viscosity; secondly, at high temperature, intramolecularity of the Stevens [1,2] rearrangement decreases. These results seem to indicate that the high viscosity of the solvent favours the solvent cage effect.[50]

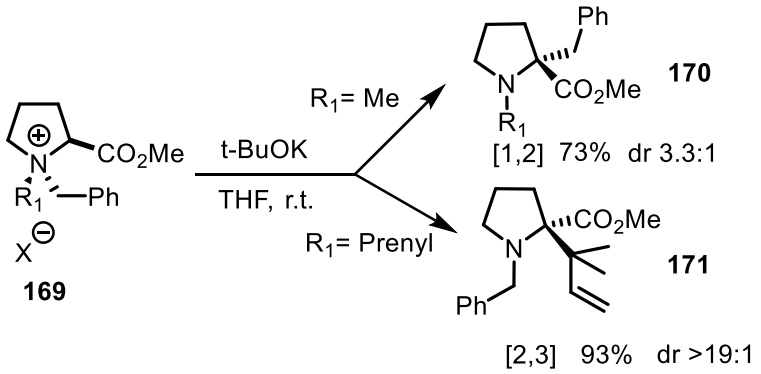
4.2.2.1.2 Previous work

In 1952, Stevens reported the [1,2]-rearrangement of benzyl fluorenyl dimethyl ammonium salt (**166**) in the presence of base to give 9-benzyl-9-dimethylamine fluorine (**168**) through a zwitterionic intermediate (**167**) (Scheme 31).[51]



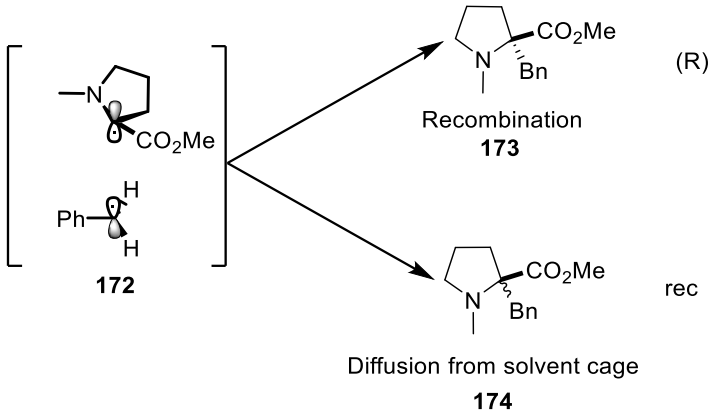
Scheme 31

In the same context and using cyclic ammonium salts, West and coworkers obtained chirality transfer from heteroatom to carbon. They used ammonium salts of proline (**169**), which was treated with base to yield [1,2] or [2,3]-rearrangement depending on R group attached to nitrogen. The products were obtained in 73 and 95% yield and good enantioselectivity (Scheme 32).[52]



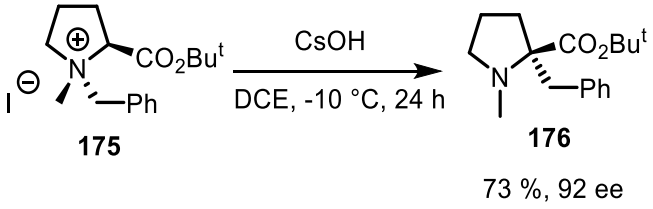
Scheme 32

Diastereoselectivity of [1,2]-shift of cyclic ammonium salts reaction was low (3:1), which was due to the rate of the diffusion was competitive with the rate of recombination (Scheme 33).[52]



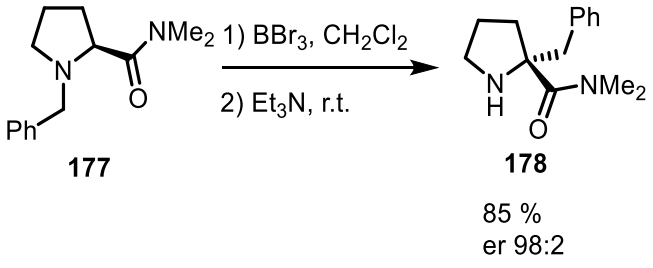
Scheme 33

Tayama investigated [1,2]- rearrangement of proline ammonium salt (**175**), which was treated with CsOH in 1,2-dichloroethane as solvent to form the desired products with high enantiopurities and high yield (Scheme 34).[53]



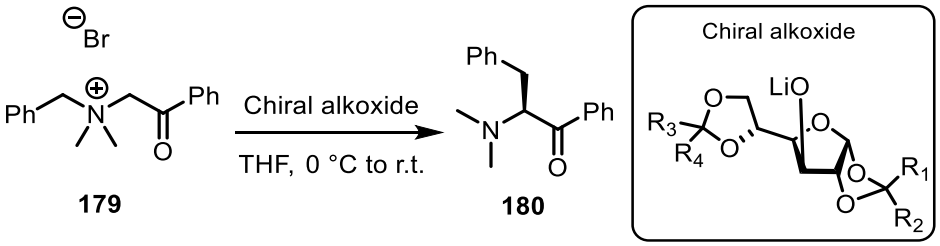
Scheme 34

The [1,2]- rearrangement of proline derivatives can be promoted by Lewis acids. Treatment of *N*-benzyl proline amide (**177**) with BBr_3 produces an intermediate where BBr_3 coordinates to the oxygen and nitrogen on the same side (cis). Subsequent deprotonation with Et_3N, homolytic cleavage of the C-N bond, recombination of radicals, and finally hydrolysis gives the desired product (**178**) in excellent yield and enantioselectivities (Scheme 35).[54]



Scheme 35

Tomooka and co-workers achieved the first example of [1,2]-Stevens rearrangement using D-glucose-derived lithium alkoxide as a chiral promoter. The reactions were carried out in the presence of chiral alkoxides at 0 °C to room temperature to give enantiomerically enriched products (4-61 % ee) (Scheme 36).[55]

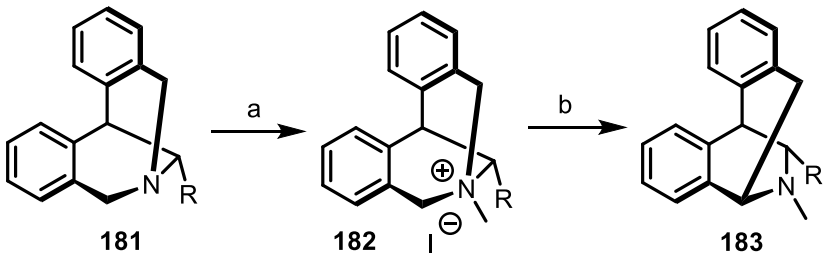


179 **180**

Scheme 36

4.2.2.1.3 Synthetic applications of the Stevens rearrangement of ammonium ylides

Towards the synthesis of functionalized isopavines, which are morphinomimetics, Hanessian has reported highly distereoselective intermolecular [1,2]-rearrangement of ammonium salt (**182**) (Scheme 37). The salt **182** was prepared from amine **181** with methyl iodide then subsequently it was reacted in basic conditions to form desired [1,2]-product **183**.

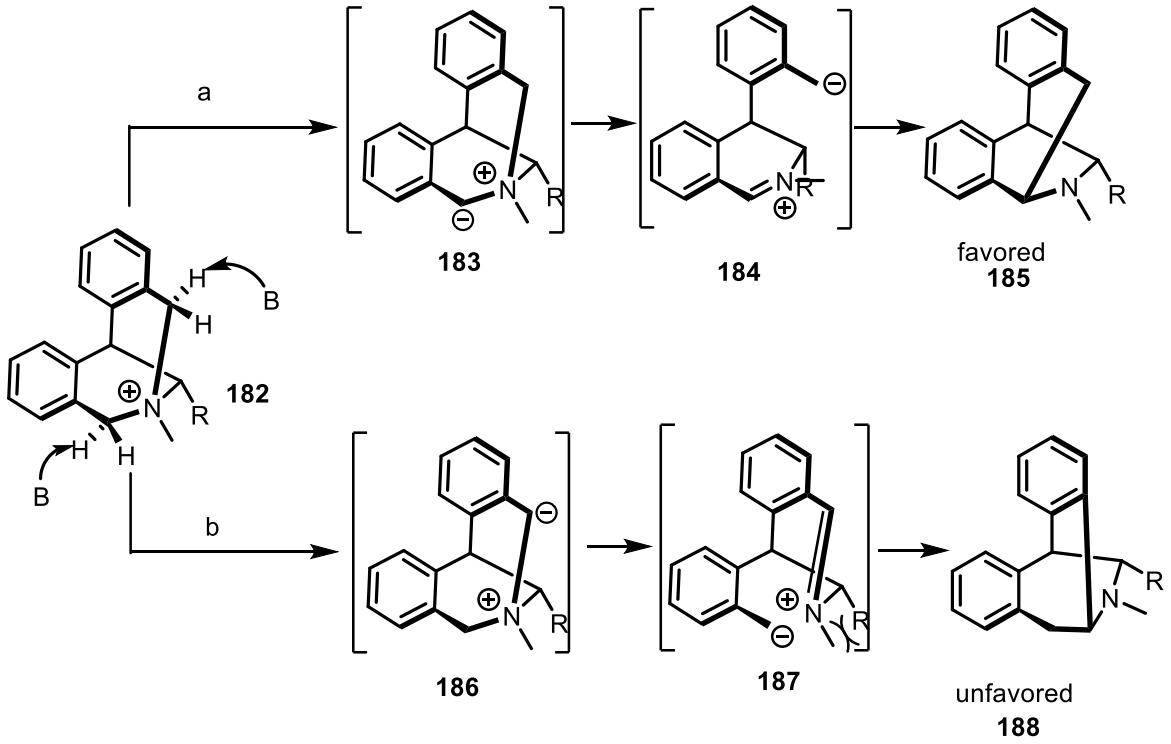


181 **182** **183**
Isopavine

Reagents and conditions:
a) MeI, acetone, reflux. b) ^{t}BuOK, 1,4-dioxane, 80 °C, 1 h.

Scheme 37

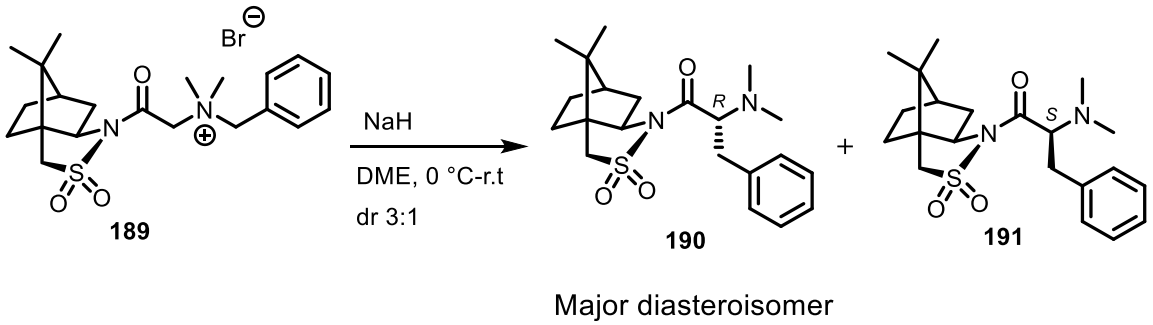
Hanessian proposed two possible pathways as resulting from deprotonation at two different benzylic positions (Scheme 38). Pathway **a** (giving **184**) is a favoured over pathway **b** (giving **187**) due to 1,2 allylic strain.[56]



Scheme 38

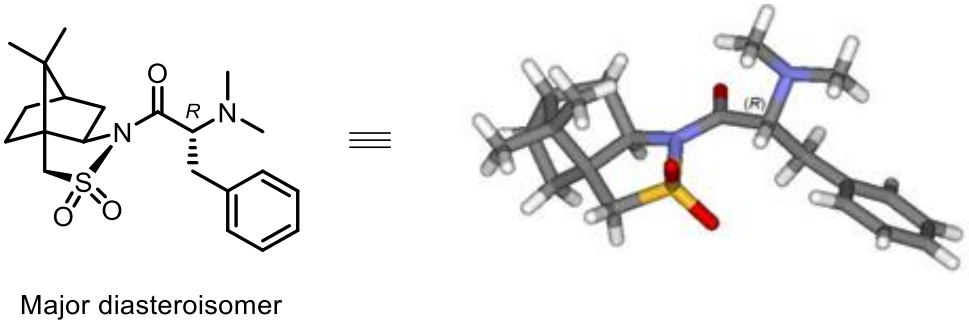
4.2.2.1.4 Previous work in the Sweeney group

The asymmetric [1,2]-Stevens rearrangement of *N*-benzylic ammonium salts has been of prime interest in the Sweeney group. Initial investigation from the Sweeney group was conducted by Neil Garrido, who tested [1,2]-Stevens rearrangement using the camphorsultam ammonium salt **189** which was treated with NaH, in DME at 0 °C (Scheme 39).[57,58]



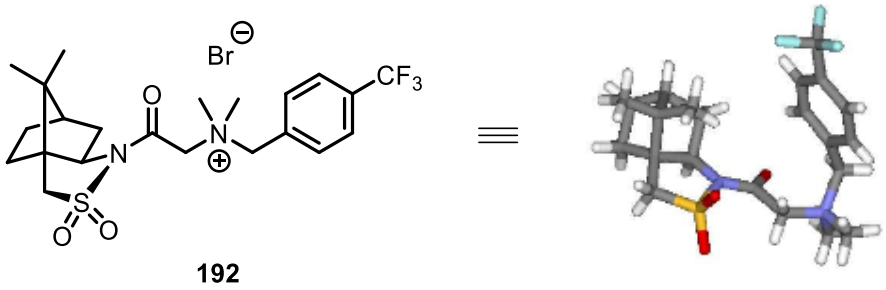
Scheme 39

The stereochemistry of the major diastereoisomer, which was (2*R*), was confirmed by X-ray crystallography (Figure 21). An X-ray (crystal) structure of the camphorsultam ammonium salt **192** was also obtained (Figure 22).[58]



Major diasteroisomer

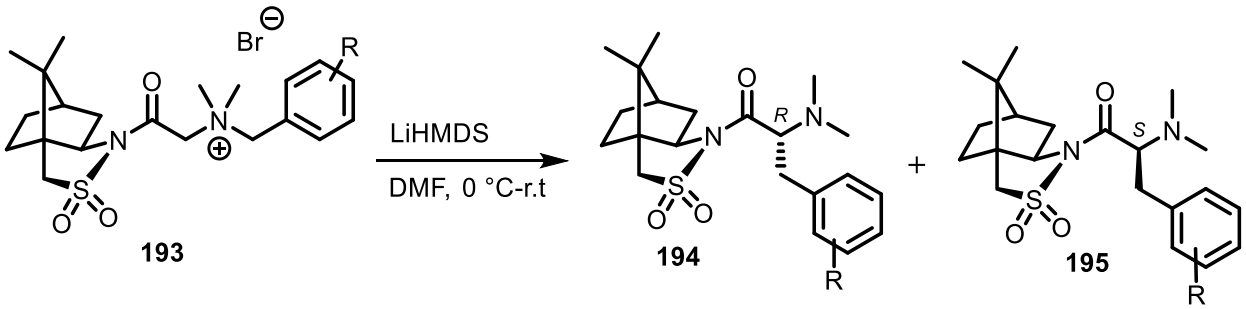
Figure 21



192

Figure 22

The crystallographic data (Figure 21) suggested that the carbonyl C=O double bond is anti-parallel to the nitrogen-sulfonamide bond and is vertical to *N,N* dimethyl amine group in the product, so as to minimize dipole interactions. An ammonium salt **189** did not fully dissolve in DME therefore Garrido changed the base to LiHDMS and used DMF as solvent (Scheme 40). He reported 11 examples using different substituents on the benzyl ring (Table 5).[58]



193 **194** **195**

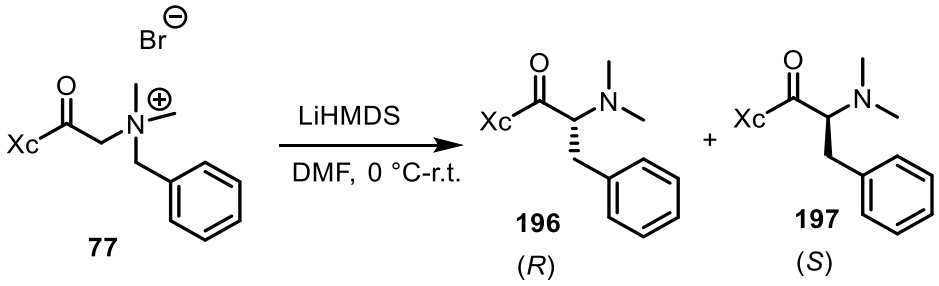
Scheme 40

Table 5

Entry	R	2R (%)[a]	2S (%)[a]
1	4-OMe	6	-
2	4-F	8	4
3	4-CF_3	34	6
4	4-NO_2	43	-
5	3-OMe	8	-
6	2-Me	9	-
7	4-Me	13	-
8	2-NO_2	44	-
9	3-NO_2	9	-
10	3-F	6	-
11	3-CF_3	25	-

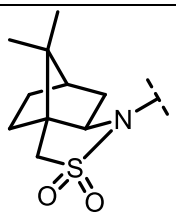
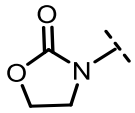
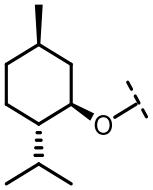
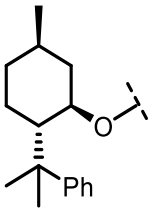
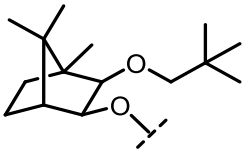
[a] Isolated yield.

The results showed that the presence of electron withdrawing groups (CF_3, NO_2) on the aromatic ring gave best results (entries 3, 4, 8, 11), albeit low yields where obtained. In addition, these experiments showed that the cleavage of the chiral auxiliary was a competitive side reaction. To solve this problem, they continued to examine several chiral auxiliaries as shown in table 6 and scheme 41.[59,60]

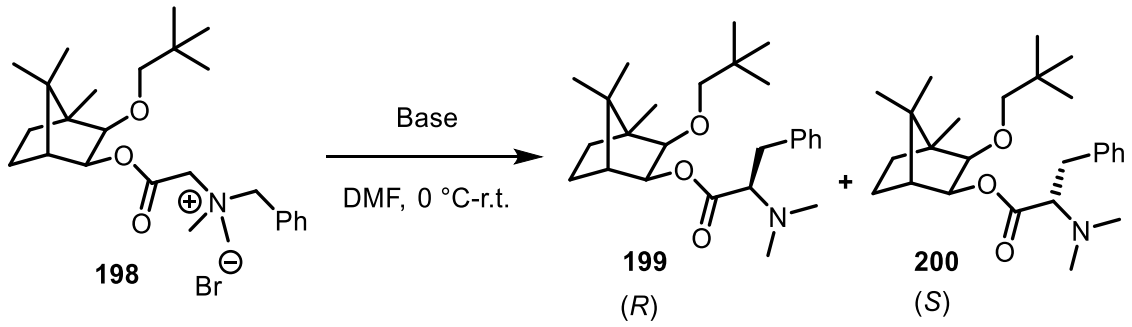


Scheme 41

Table 6

Entry	Xc	Yield (%)	d.r (*R*):(*S*)	Cleaved Xc
1		64	3:1	33
2		25	nd	63
3		60	1:1	traces
4		51	1:2	traces
5		60	9:1	6

From table above, it is clear that camphorsultam gave a good yield in rearrangement, whereas oxazolidinone gave low yield with maximal auxiliary cleavage. Menthol and phenyl menthol showed only a trace of cleavage product with decreased stereocontrol. Camphene-derived auxiliary (entry 5) gave the best selectivity (9:1 d.r.) with minimal auxiliary cleavage (6%) and good yield (60%). Therefore, camphorsultam and camphene-derived as a chiral auxiliary were used for further investigation. Our group moved to test a number of bases, which were applied to camphene-derived ammonium salt (Scheme 42 and Table 7).[59,60]



Scheme 42

Table 7

Entry	Base	eq.	Yield (%)	d.r (*R*):(*S*)	Cleaved Xc
1	LiHMDS	1.05	60	9:1	6
2	BTPP	1.05	38	19:1	13
3	BTPP	2.00	66	8:1	traces
4	BTPP	2.00	44	5:1	10
5	BTPP	2.00	22	10:1	22
6	BTPP	1.75	64	12:1	36
7	P_2-^{t}Bu	1.05	21	2:1	Traces
8	P_2-^{t}Bu	2.00	0	n/a	39

The table lists four types of bases with different number of equivalents. Overall, it can be seen that the best results obtained when BTPP is used (highest yield 66% entry 3, 8:1 d.r.), however, the reaction yield dropped (Entry 7, 8) when stronger phosphazene bases (Figure 23) were used.

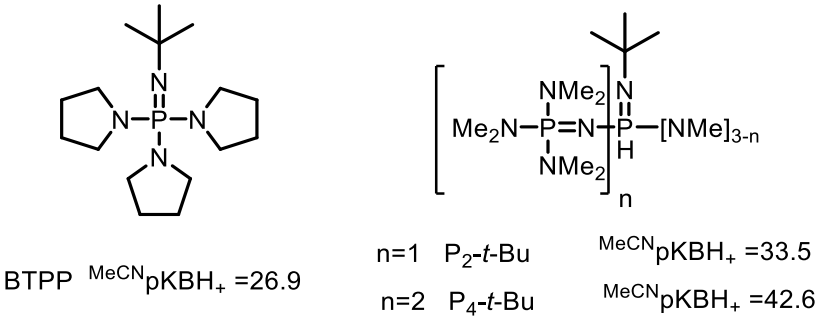
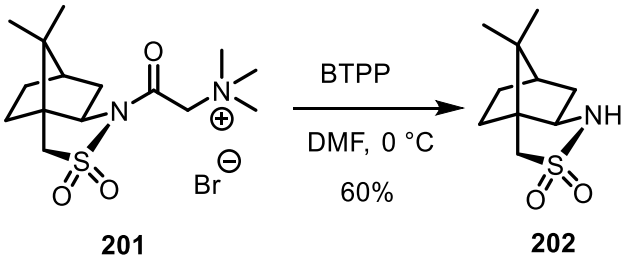


Figure 23. Phosphazene bases.

Further studies were conducted to explain the mechanism behind the cleavage of chiral auxiliary. They used optimised conditions with camphorsultam *N*-trimethyl ammonium salt **201**, which is unstable and yielded cleaved camphorsultam in good yield (Scheme 43).[59,60]



201 **202**

Scheme 43

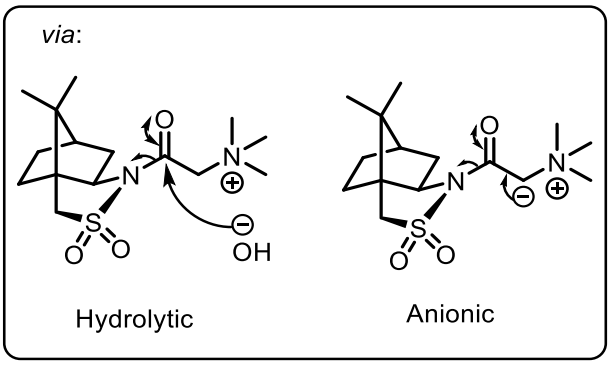
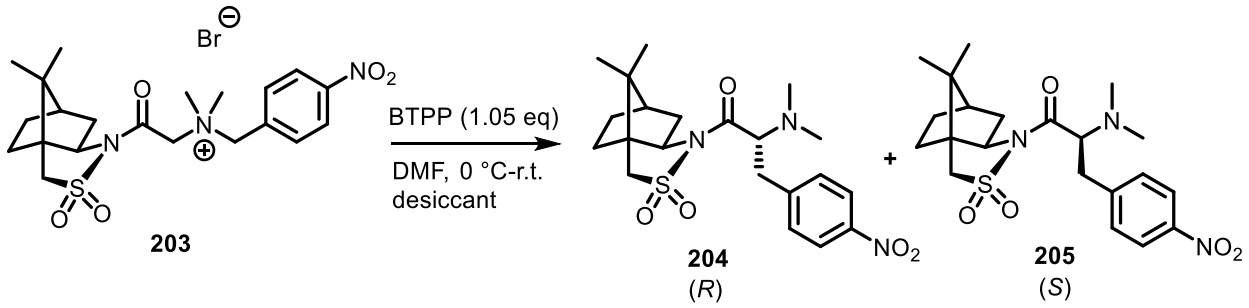


Figure 24

The reaction in scheme 43 allowed to us to suggest two possible mechanisms for the cleavage of the camphorsultam unit through anionic or hydrolysis cleavage (Figure 24). If there is a trace of water in the reaction mixture as well as base, hydroxide anions could be produced that lead to cleavage camphorsultam.[59,60]

In order to assess the hypothesis of hydroxide mediated cleavage of the auxiliary several desiccants were used in the reaction of the *p*-nitro camphorsultam ammonium salt (**203**) as shown in (Scheme 44 and Table 8).[59]



203 **204** (*R*) **205** (*S*)

Scheme 44

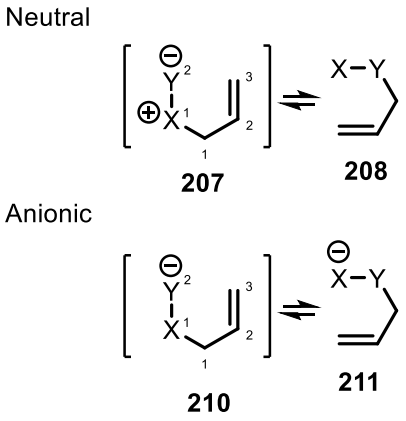
Table 8

Desiccants	Yield (%)	d.r (*R*):(*S*)	Cleaved Xc
-	41	3:1	22
3 Å MS	50	5:1	8
4 Å MS	53	4:1	5
5 Å MS	65	5.5:1	10
Na_2SO_4	55	4:1	12
$CuSO_4$	0	n/a	71

The results showed decrease of the camphorsultam cleavage and increase in yield in most cases (except when $CuSO_4$ was used). It can be noted that 5 Å molecular sieves gave the best result with 65% yield and 5.5:1 ratio of diastereoisomers. It is worth noting that copper sulfate, which is powerful desiccant, did not give any of the desired products. This may be because it acts as a Lewis acid and thus favours the cleavage of camphorsultam.

4.2.1.2 [2,3]-Sigmatropic rearrangement

The [2,3]-sigmatropic rearrangement is a type of sigmatropic rearrangement and can be categorized into two types, neutral and anionic (Scheme 45). Moreover, the scaffold always contains at least one heteroatom (N, O, S).

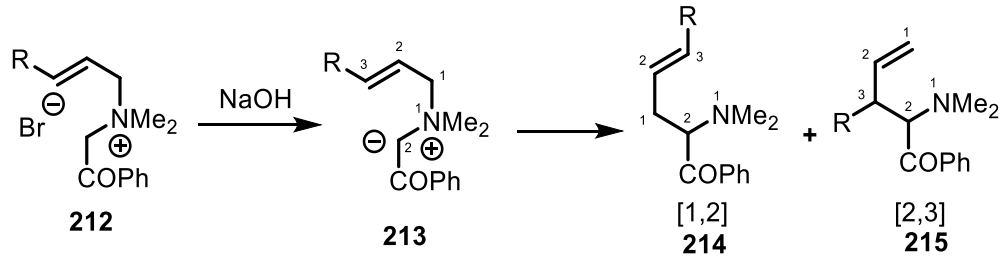


Scheme 45

The [2,3]-sigmatropic rearrangement is an important reaction in organic synthesis because it can form carbon-carbon bonds diastero- and enantioselectively. Most stereoselective [2,3]-rearrangements involve the presence of either a stereocentre within the starting material, chiral catalysts, chiral ligands or chiral auxiliaries. The most

widely reported [2,3]-sigmatropic rearrangements are either base catalysed or metal catalysed.[61]

In the 1960s, Stevens discovered the [2,3]-sigmatropic rearrangement of allyl ammonium salts (allylic analogues to the [1,2]-Stevens rearrangement of benzyl ammonium salts); this rearrangement will be referred to as the [2,3]-Stevens rearrangement in the following parts of the thesis (Scheme 46).[62]

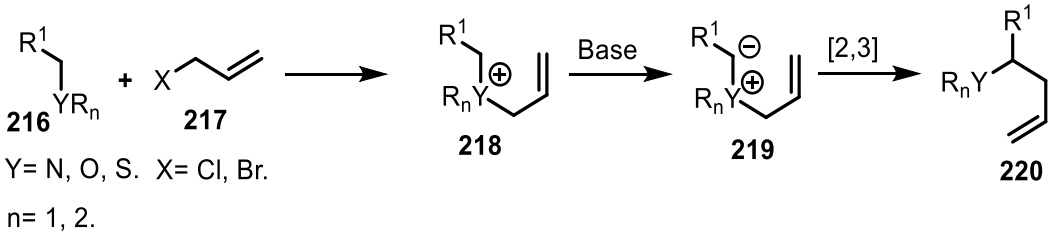


Scheme 46

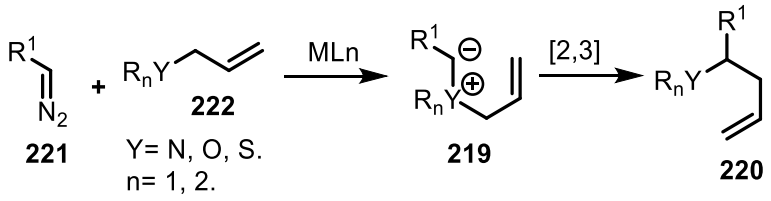
When he warmed cinnamyl (R = Ph) ammonium salt with NaOH and he observed the production of a mixture of [1,2] and [2,3]-rearrangement product, while the crotyl analogue (R=Me) gave only [2,3]-rearrangement. Years later, Ollis and Rautenstrauch examined the reaction and showed that the [2,3]-rearrangement dominates at low temperature.[63,64]

4.2.1.2.1 Generation of allylic onium ylides

There are two important strategies to form onium ylides. One of them is alkylation of the heteroatom using allyl halides followed deprotonation by base (Scheme 47). On the other hand, an alternative approach that shows a great promise is trapping metal carbenoids will allylic nucleophiles (Scheme 48). However, the last strategy can sometime be associated with cyclopropanation issues.[61]



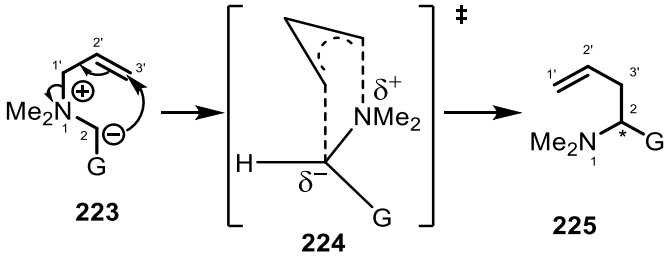
Scheme 47. Onium ylides from quaternary salts



Scheme 48. Onium ylides from metal carbenoids

4.2.1.2.2 [2,3]-Rearrangement mechanism

To explain the mechanism, ammonium ylides will be used as an example. The reaction mechanism occurs through a six-electron and five-membered transition state. The process involves breaking of heteroatom-carbon σ bond and formation of a new carbon-carbon σ bond. In addition, new stereocentres (at least one) are generated during this transformation (Scheme 49).[61,65,66]



Scheme 49

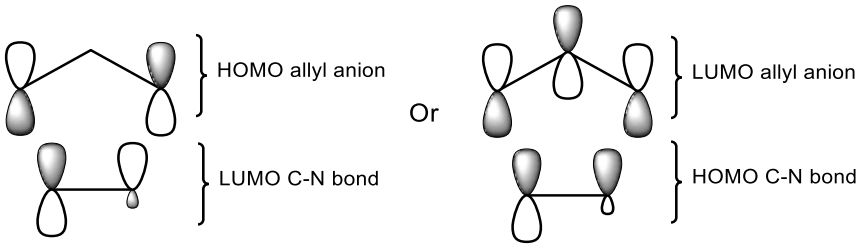


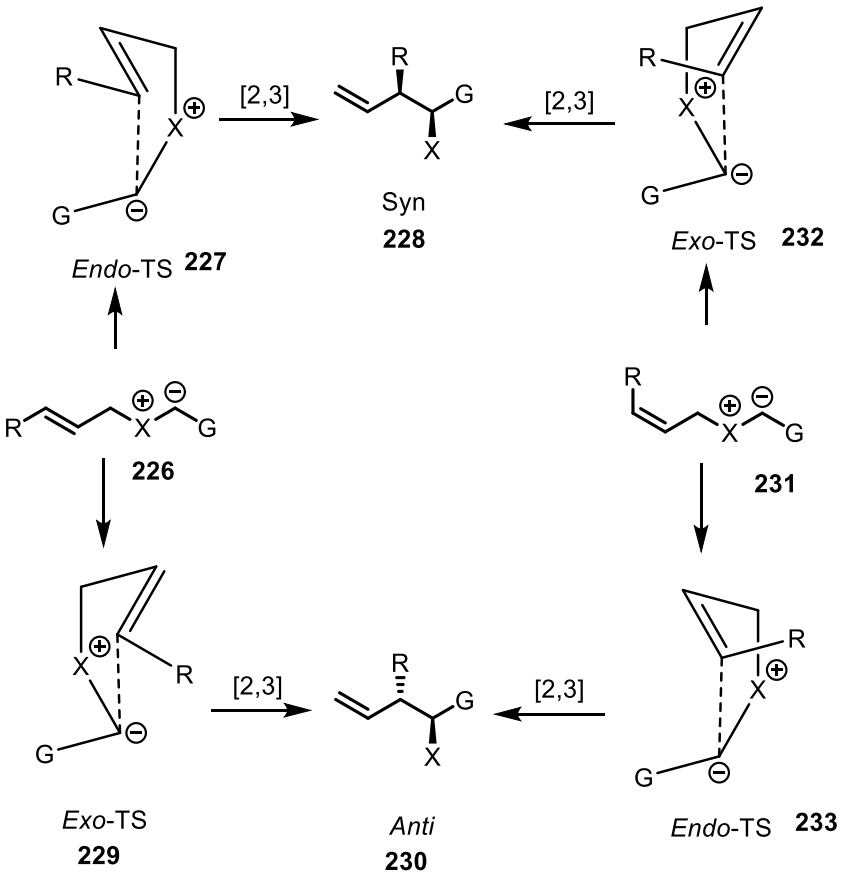
Figure 25

From a molecular orbitals viewpoint, the rearrangement can be explained through overlap between the HOMO of the allyl anion and the LUMO of carbon-nitrogen double bond (or opposite). The maximized overlap can be obtained when bonds are parallel as shown in the transition state structure (Figure 25).[61,65,66]

4.2.1.2.3 Diastereoselectivity in the rearrangement

As mentioned earlier, in [2,3]-rearrangements new stereocentres can be formed (at least one). In the case of two stereocentres, the formation and stereoselectivity of the

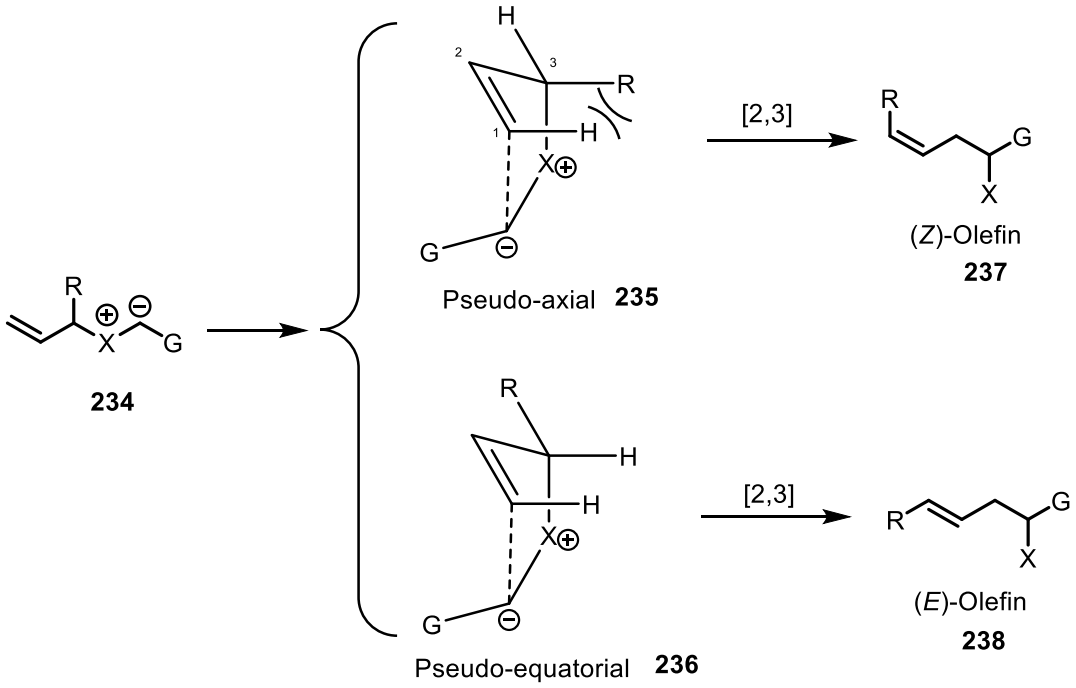
two new stereocentres (*syn* and *anti*) is determined by the conformation of the transition state (*Exo*-TS and *Endo*-TS), R group on alkene and geometric isomerism (*cis* or *trans*) of reactants (Scheme 50).[61]



Scheme 50

4.2.1.2.4 Stereochemistry of the newly formed double bond

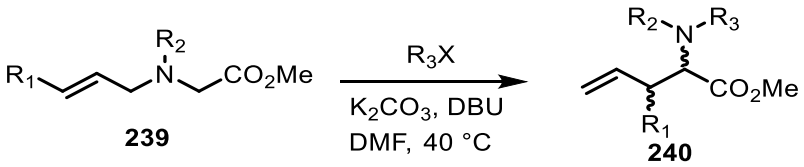
Generally, [2,3]-rearrangements of allyl salts with substituents at the vinyl position occur to give (E)- selectivity for the new formed double bond (Scheme 51). From the five-membered transition state, one can observe that the pseudo-equatorial orientation is preferred to the pseudo-axial orientation to minimise 1,3-allylic strain which is the strain energy arises from interaction between a substituent on one end of an alkene with an allylic substituent.[61]



Scheme 51

4.2.1.2.5 Base-mediated [2,3]-rearrangement

Coldham *et al.* developed a one-pot procedure using K_2CO_3, DBU and DMF, where *N*-alkylation of *N*-allyl α-amino esters was followed by [2,3]-rearrangement (Scheme 52 and Table 9).[67]

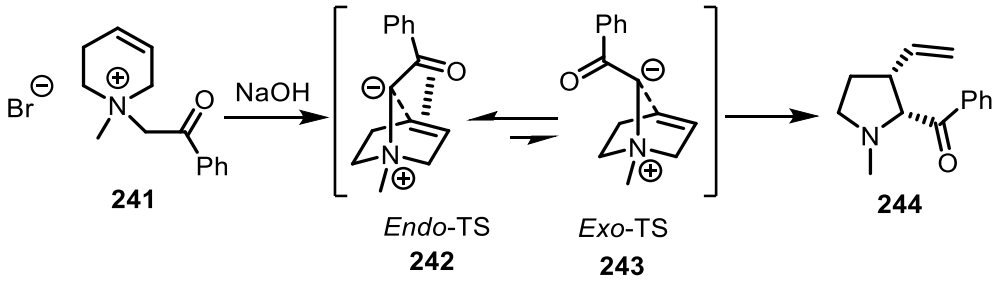


Scheme 52

Table 9

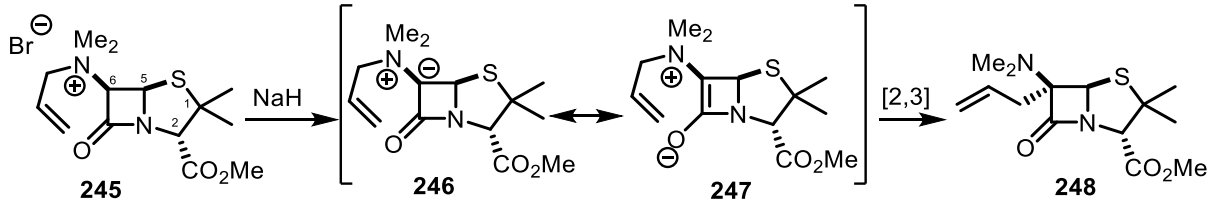
Entry	R_1	R_2	R_3X	Yield	Ratio (anti:syn)
1	H	Me	MeI	48	-
2	Me	Me	MeI	53	60:40
3	H	Me	$PhCH_2Br$	52	-
4	Me	Me	$PhCH_2Br$	65	60:40
5	H	$PhCH_2Br$	MeI	51	-
6	Me	$PhCH_2Br$	MeI	63	60:40

Another example of [2,3]-rearrangement which is catalysed by base, is the rearrangement of 1,2,5,6-tetrahydropyrdinium salt in the presence of NaOH. The reaction afforded highly *syn*-selective rearrangement and with concomitant formation of the pyrrolidine ring. Ollis suggested that this selectivity occurs due to interaction between the carbonyl and double bond leading to stabilization of the endo-TS (Scheme 53).[68]



Scheme 53

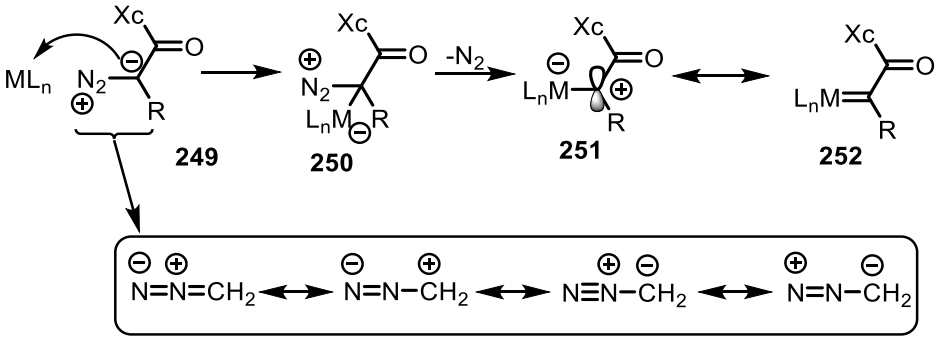
In the same context, Kaiser and co-worker have reported the stereospecific alkylation of a penicillin at C6 using [2,3]-rearrangement (Scheme 54). The reaction was carried out with 1.5 eq of sodium hydride in DMF-benzene (2:5) at room temperature for 30 min, affording **248** in 75 % yield, as the single rearrangement product.[69]



Scheme 54

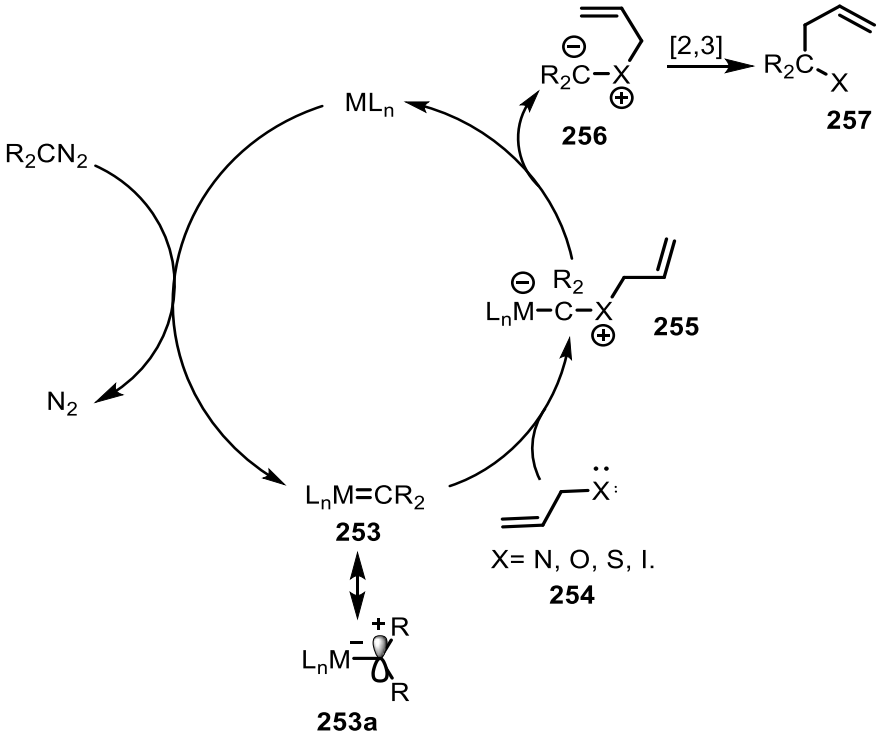
4.2.1.2.6 Metal-catalysed rearrangements

An alternative methodology to base-mediated [2,3]-rearrangement has been reported, where a metal catalyst promotes the generation of onium ylides which in turn undergo rapid [2,3]-rearrangement. Rhodium(II) and copper(II) are common catalysts used to generate onium ylides. Firstly, the metal catalyst reacts with the carbene precursor (in this case diazo compound **249**), to form metal carbenoid **252**, which is a reactive electrophilic carbene complex (Scheme 55).



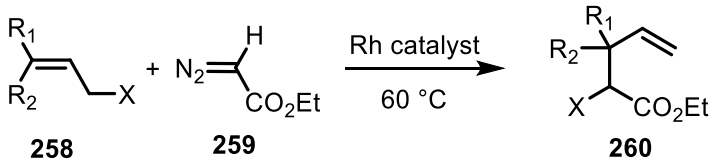
Scheme 55

Subsequently, the reactive electrophilic carbenoid (**252** or **253**) is reacted with a nucleophile (for example hetero-allyl nuclephiles) leading to regeneration of the metal catalyst as well as formation of onium ylid **256** which undergoes the [2,3]-rearrangement (Scheme 56).



Scheme 56

As reported by Doyle *et al*., rhodium and copper catalysts catalyse the decomposition of ethyl diazoacetate in the presence of methyl allyl sulfide, allylic tertiary amines and allyl halides to give the [2,3]-rearrangement and cyclopropanation products (Schemes 57 and 58, Tables 10 and 11).[70]



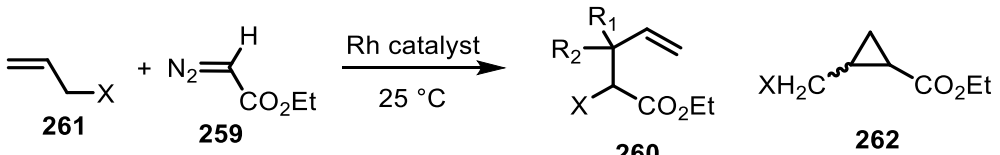
258 **259** **260**

Scheme 57

Table 10

X	R_1	R_2	Catalyst (mol %)	Yield (%)
SMe	H	H	$Rh_2(CO)_{16}$ (0.5)	96
SMe	H	H	$Rh_2(OAc)_4$ (0.5)	91
NMe_2	H	H	$Rh_2(CO)_{16}$ (0.5)	82
NMe_2	H	H	$Rh_2(OAc)_4$ (1.0)	60
NMe_2	CH_3	CH_3	$Rh_2(CO)_{16}$ (0.4)	49
NMe_2	CH_3	CH_3	$Rh_2(OAc)_4$ (1.0)	37
NMe_2	CH_3	H	$Rh_2(CO)_{16}$ (0.2)	36 (77:23)[a]
NMe_2	CH_3	H	$Rh_2(OAc)_4$ (0.5)	79 (75:25)[a]
NMe_2	C_6H_5	H	$Rh_2(CO)_{16}$ (0.5)	78 (72:28)[a]
NMe_2	C_6H_5	H	$Rh_2(OAc)_4$ (0.5)	59 (75:25)[a]

[a] anti:syn ratio



261 **259** **260** **262**

X=Cl, Br, I.

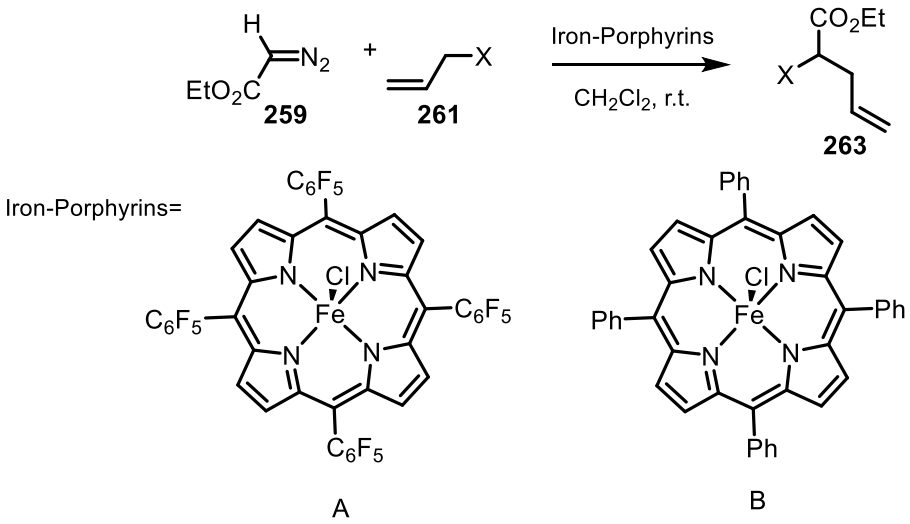
Scheme 58

Table 11

Allyl halide	Catalyst (0.5 mol %)	Yield (%)[a] of 260	Ratio of 260/262 trans/cis [b]
CH_2=$CHCH_2I$	$Rh_2(CO)_{16}$	89	100:0
CH_2=$CHCH_2I$	$Rh_2(OAc)_4$	98	100:0
CH_2=$CHCH_2Br$	$Rh_2(CO)_{16}$	41	27:73 (1.13)
CH_2=$CHCH_2Br$	$Rh_2(OAc)_4$	76	28:72 (1.12)
CH_2=$CHCH_2Cl$	$Rh_2(CO)_{16}$	26	7:93 (1.22)
CH_2=$CHCH_2Cl$	$Rh_2(OAc)_4$	95	5:95 (1.16)

[a] Isolated product yield.
[b] Ratio of cyclopropane geometrical isomers

From the results obtained by Doyle, it can be observed that cyclopropanation is a side reaction when allyl bromide and chloride are used. Allyl iodide and methyl allyl sulfide are similar in ability to react with carbenoid intermediates. In like manner, Gross reported the unique, fast and efficient [2,3]-rearrangement of dimethyl allylamine and ethyl diazoacetate (EDA) catalysed by iron(III) porphyrins affording products in excellent yields (Scheme 59 and Table 12). In addition to allylamine, this reaction works efficiently with allyl sulfide.[71]



Scheme 59

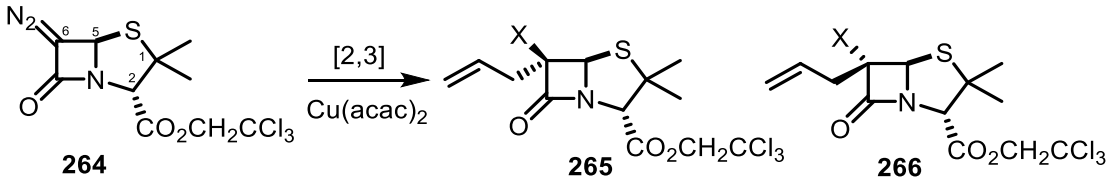
Table 12

X	Catalyst	Time	Yield (%)
NMe_2	A	1 min	96[a]
NMe_2	B	24 h	92[a]
SMe	A	1 h	91[b]

[a] Catalyst/EDA/substrate 1:500:500.
[b] Catalyst/EDA/substrate 1:100:100.

All of these reactions reported by Gross were faster and used lower catalyst loadings than other metal catalysed [2,3]-rearrangements.

Another example of carbenoid mediated [2,3]-rearrangements, complementary to the work of Kaiser on penicillin salts (Scheme 54), was reported by Giddings, who investigated intermolecular [2,3]-rearrangement of diazopenicilliin (Scheme 60). Copper(II) acetylacetonate ($Cu(acac)_2$) catalysed formation of the ylide using allylic sulphides and selenides followed by [2,3]-rearrangement afforded products in good yields.[72]



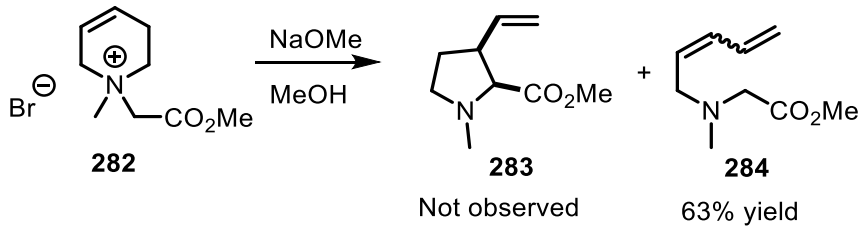
Scheme 60

Table 13

X	dr (ratio)	Yield (%)
PhS	87:13	65
MeS	80:20	60
PhSe	50:50	64

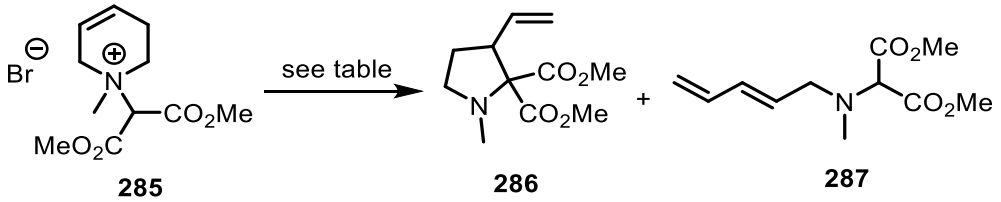
4.2.1.2.7 Previous work in the Sweeney group

Following Stevenson's work,[76,77] who reported that the reaction of didehydro-piperidinium salt **282** with base in an alcohol solvent gave elimination product **284** rather than [2,3] rearrangement (Scheme 61), our group optimised the reaction to favour [2,3] rearrangement over elimination processes. Reaction optimisation was carried out by screening various solvent and bases (Scheme 62 and Table 14).[78]



Scheme 61

Our group's work

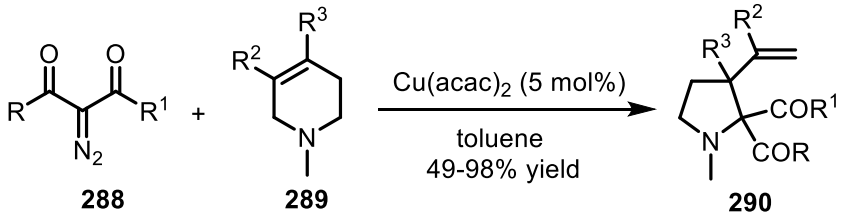


Scheme 62

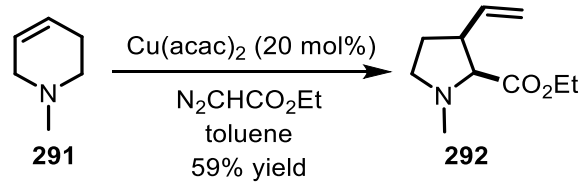
Table 14

Solvent	Base	Reaction °C	Yield (286) %	Yield (287) %
THF	NaH	Reflux	30	0
THF	BuLi	-78 °C to reflux	46	0
THF	DBU	Reflux	73	0
DME	NaH	Reflux	57	0
DME	DBU	Reflux	79	0

One year later, Sweeney's group continued to investigate the [2,3]-rearrangement (metal-catalysed rearrangements) of tetrahydropyridine derivatives **289** with diazo malonate compounds **288** in the presence of copper catalysts and reported many examples proceeding in high yields, using different substituents (R^1 and R^2) on *N*-methyl tetrahydropyridine (Scheme 63).[79] In addition, they examined the reaction using ethyl diazoacetate giving pyrrolidine **292** in 59% yield (Scheme 64).[80]

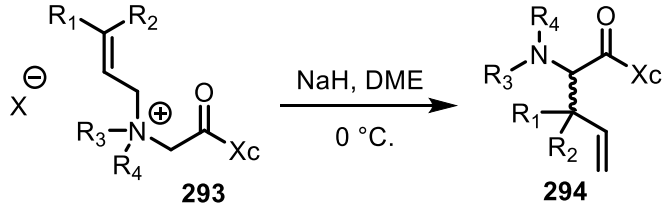


Scheme 63



Scheme 64

Highly diastereo-enantioselective [2,3]-rearrangements of simple allylic ammonium ylides in excellent yields were reported by the Sweeney group. The reaction catalysed by NaH produces the [2,3] rearrangement of allylic sultam ammonium salts using DME as solvent. A range of substituents have been used to generate allyl glycine derivatives **294** (Scheme 64 and Table 15).[81]



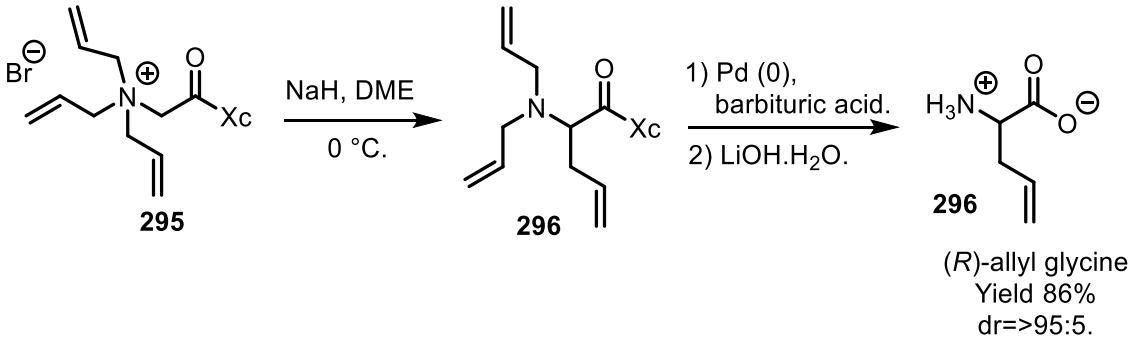
Xc= camphorsultam (2*R* or 2*S*)

Scheme 64

Table 15

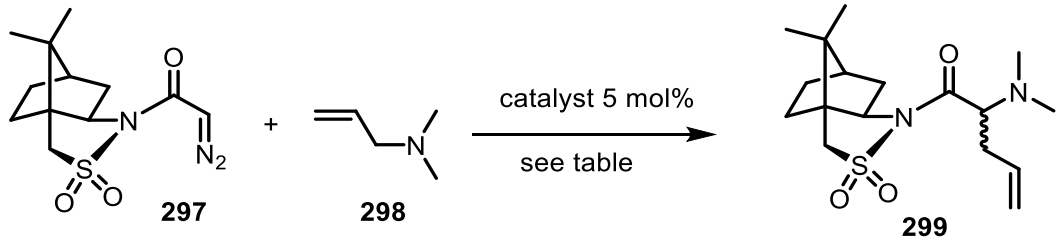
R1	R2	R3	R4	Yield (%)	Anti:syn	dr (*R*:*S*)
H	H	Me	Me	99	-	2:98
H	H	Me	Allyl	99	-	97:3
H	H	Allyl	allyl	86	-	97:3
H	H	Bn	allyl	80	-	>99:1
Me	H	Me	Me	86	>99:1	96:4
Me	Me	Me	Me	70	-	97:3
MeO_2C	H	Me	Me	64	>99:1	>99:1

The previous method can be used to prepare (*R*)-allyl glycine simply using triallyl ammonium salt **295** (Scheme 65).[81]



Scheme 65

As reported by Doyle who examined the reaction of dimethyl allyl amine with ethyl diazoacetate, our group proposed to further study this reaction using a chiral diazo camphorsultam. The reaction was optimised using different solvents, catalysts, reaction temperature and addition rate (Scheme 66 and Table16).[58]

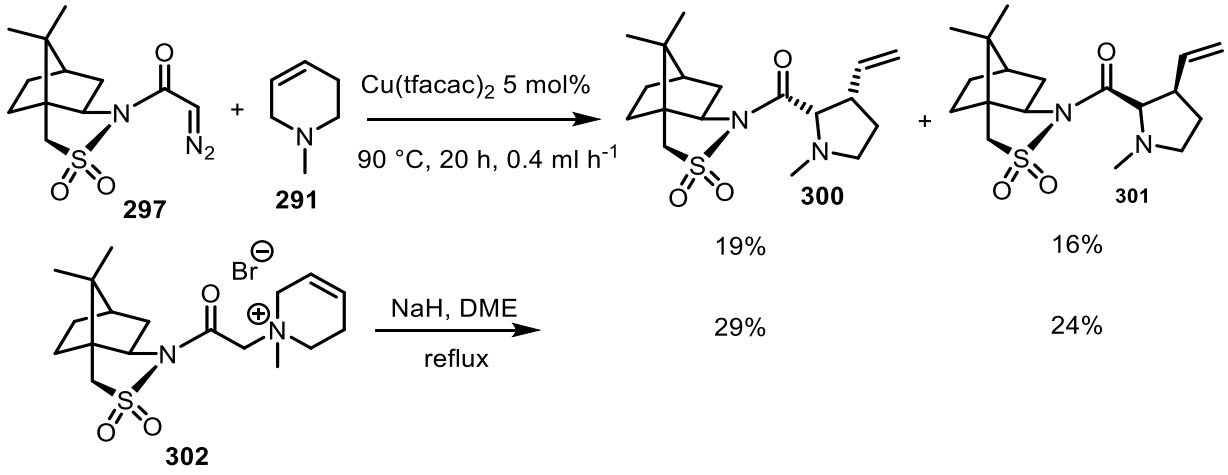


Scheme 66

Table 16

Entry	Solvent	Catalyst	°C	Addition rate (ml h^{-1})	Yield	d.r. (2*S*:2*R*)
1	PhMe	$Cu(acac)_2$	90	0.397	44	84:16
2	DCE	$Cu(acac)_2$	reflux	0.397	<5	100:0
3	DME	$Cu(acac)_2$	90	0.397	<5	100:0
4	PhMe	$Cu(acac)_2$	90	120	38	76:24
5	PhMe	$Cu(OTF)_2$	90	0.397	57	88:12
6	PhMe	$Cu(OTF)_2$	90	120	52	73:27
7	PhMe	$Rh_2(OAc)_4$	90	0.397	58	84:16
8	PhMe	$Rh_2(OAc)_4$	90	120	47	83:17

As shown in table 16, high temperature is required to accelerate the reaction and activate the diazo compound. Secondly, the best yields were obtained by using toluene as solvent and $Rh_2(OAc)_4$ as catalyst (Entry 7, Table 16) with very good diastereoselectivity (84:16). In contrast 1,2-dichloroethene (DCE, Entry 2, Table 16) and dimethoxyethane (DME, Entry 3, Table 16) gave very low yields but with excellent diastereoselectivity. Next, our group turned attention to examine the reaction of cyclic amines with a chiral diazocamphorsultam which would allow to compare the results obtained in the carbenoid pathway with previously obtained base mediated ones. The results show that both approaches were similar, giving *syn* products with low diastereoselectivity (Scheme 67).[58]

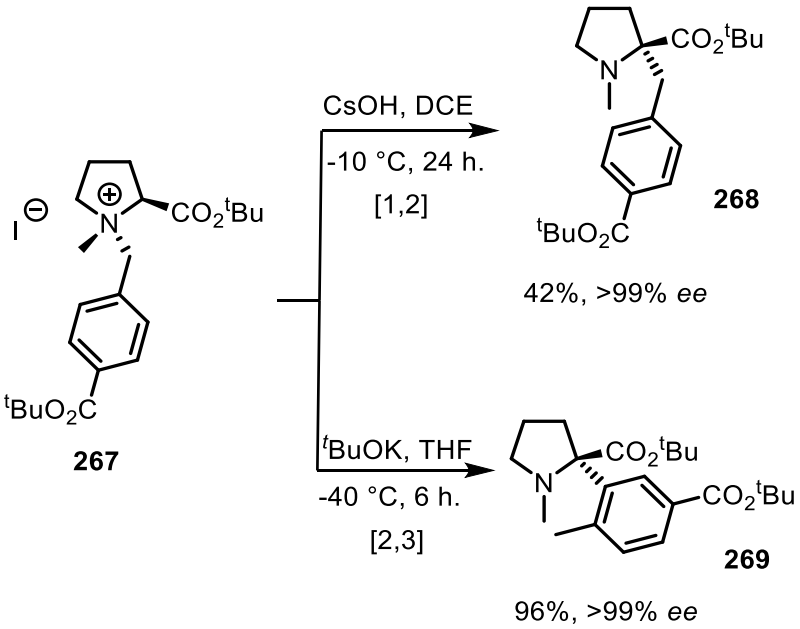


Scheme 67

4.2.1.3 Competion between [1,2]- and [2,3]-processes

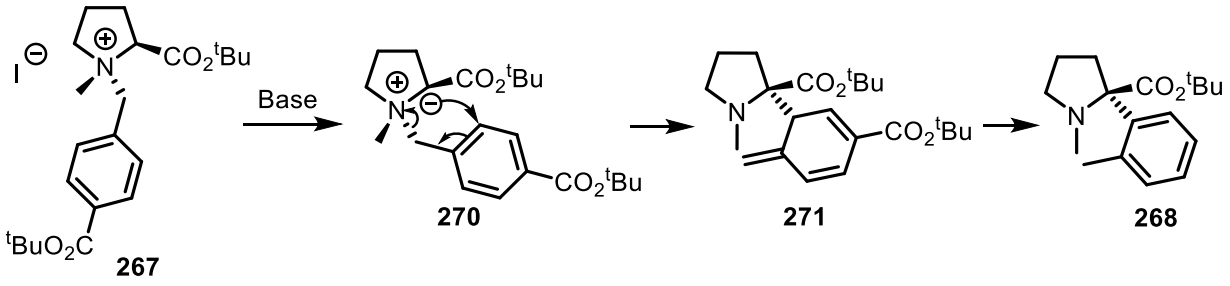
In the case of benzyl ammonium salts, which normally undergo [1,2]-Stevens rearrangements, a competing [2,3]-rearrangement known as the Sommerlet-Hauser rearrangement can occur. This [2,3]-rearrangement competes with [1,2]-Stevens

rearrangement depending on the reaction conditions and the steric and electronic properties of the substrates. For example, Tayama has shown that either rearrangements can be obtained by carefully tuning the reaction conditions. *N*-Benzyl proline ammonium salt **267**, underwent both rearrangements depending on the reaction conditions chosen (Scheme 68).[73]



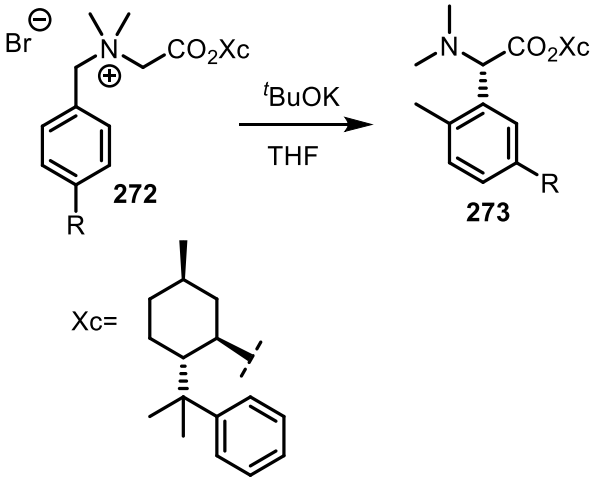
Scheme 68

The [1,2]-Stevens rearrangement mechanism proceeds, as mentioned previously, *via* a radical-pair which formed through homolytic cleavage of the C-N bond followed fast recombination of the radical-pair to give [1,2] products. On the other hand, from the ylide, the [2,3]-rearrangement proceeds via an anionic mechanism where concomitant nucleophilic attack of the negatively charged carbon of the ylide on the benzene ring and cleavage of the carbon-nitrogen bond (affording a rearranged product with an exo double bond) followed by rearomatisation of the benzene ring afford the rearranged product (Scheme 69).[73]



Scheme 69

Tayama extended the study of the [2,3]-rearrangement to benzylammonium ylides bearing a (-)-8-phenylmenthol chiral auxiliary and various *para* substituents on the benzene ring. The reaction proceeded in excellent yields and high stereoselectivity (Scheme 70 and Table 17). In addition, electron withdrawing substituents were shown to be essential for the reaction to proceed as no desired product was formed when using electron rich benzyl groups (entry 7) .[73]

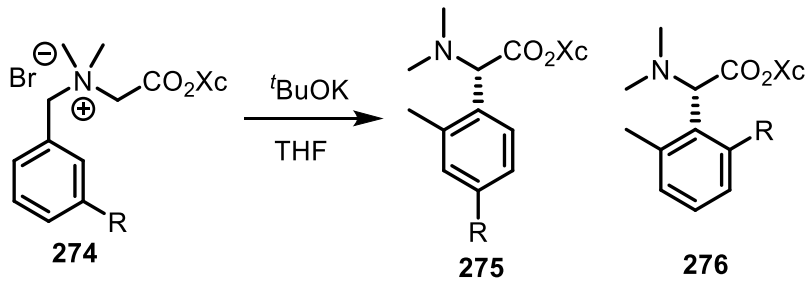


Scheme 70

Table 17

Entry	R	T (°C)	Time	Yield (%)	d.r. ratio (*S*:*R*)
1	$CO_2{}^tBu$	-40	4 h	95	>98:2
2	CN	-60	4 h	82	97:3
3	CO_2CH_3	-60	8 h	85	>98:2
4	COPh	-60	8 h	82	>98:2
5	CF_3	-60	15 h	93	>98:2
6	H	-40	15 h	46	>98:2
7	OCH_3	-40	15 h	0	-

In the same publication, the authors also carried out the reaction with *meta* substituted benzylammonium salts (CN and CF_3) obtaining almost completely selectively ortho/para substituted products **275** (Scheme 71 and Table 18).[73]

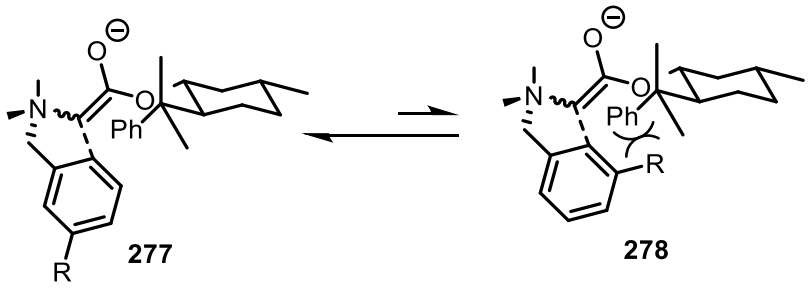


Scheme 71

Table 18

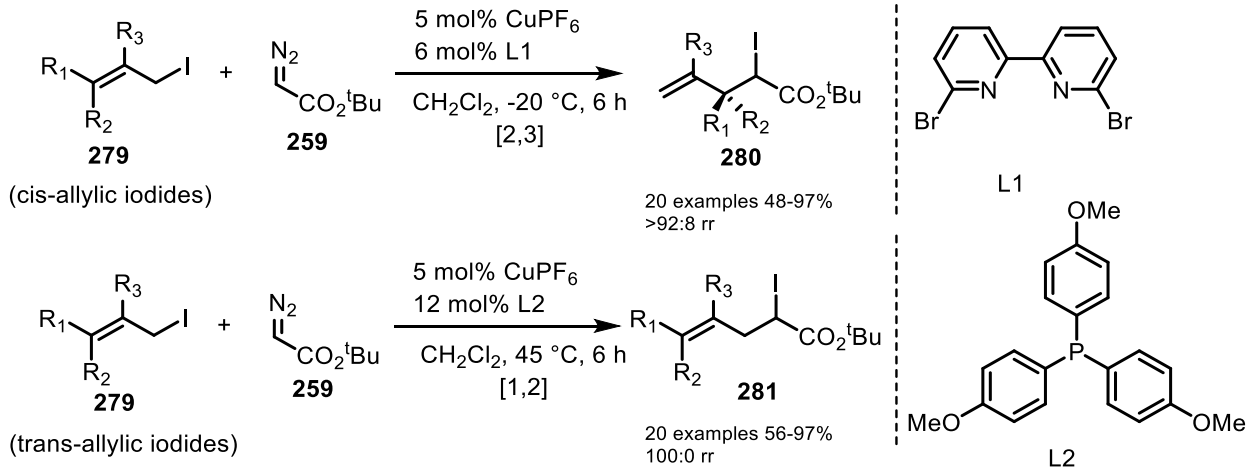
R	T (°C)	Yield (%) (275) d.r.	Yield (%) (276) d.r.
CN	-60	63 (>98:2)	6 (>98:2)
CF_3	-40	90 (>98:2)	0

The explanation given for the regioselectivity of the transformation (Scheme 72) was based on the favourable formation of less sterically hindered intermediate **277**.[73]



Scheme 72

A switch in selectivity from [2,3] to [1,2] metal catalysed carbenoid rearrangement of iodonium ylide from metal carbenoid was reported by Tamber. The selectivity of the rearrangement of allylic iodonium ylides was controlled by the choice of ligand using the same metal catalyst. The reaction afforded either of the products in high yield and stereoselectivity using various allyl-iodides (Scheme 73).[74,75]



Scheme 73

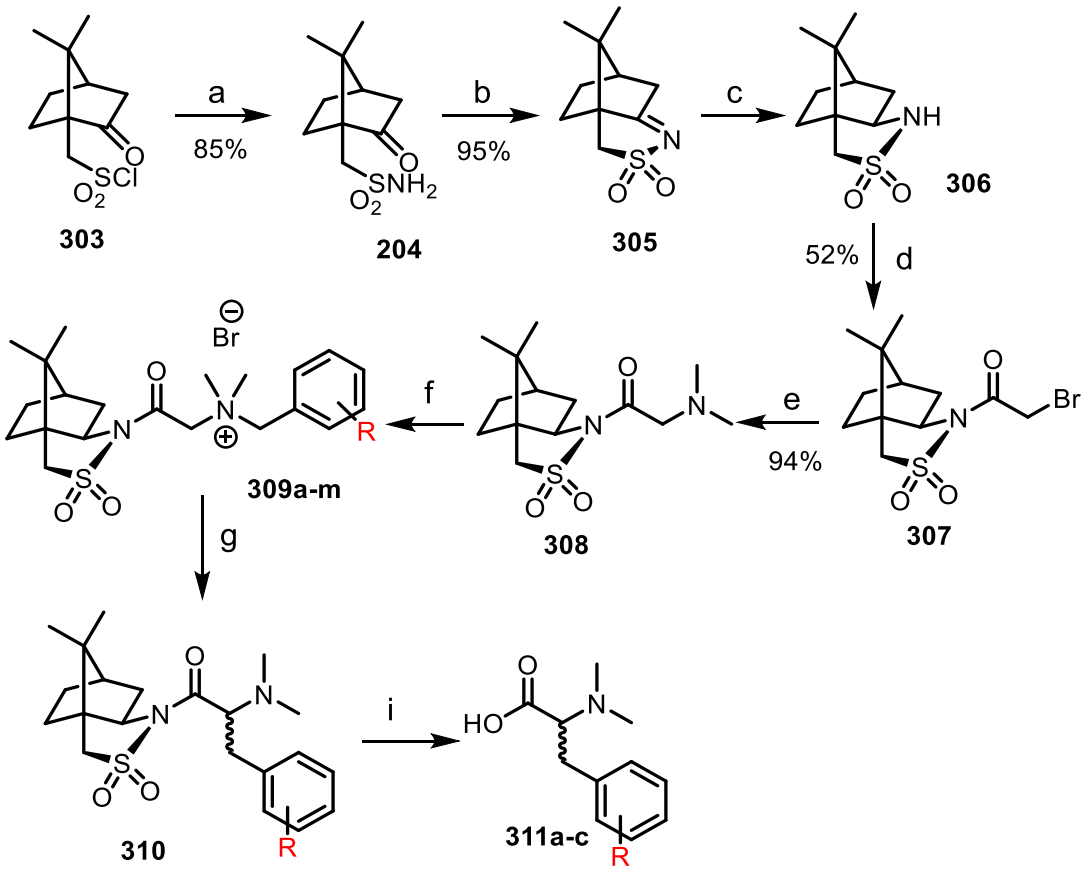
Aims

The aim of the work described in this chapter is to highlight and expand the scope of the [1,2]-Stevens rearrangement of benzylic ammonium salts and of the [2,3]-Stevens rearrangement of allylic onium ylids. This work should provide access towards novel amino acids and is complementary to other work done within our group.

5. Results and discussion

5.1 Asymmetric [1,2]-Stevens rearrangement

In general, our synthetic strategy toward α-benzylated amino acids is shown in scheme 74.



Reagents and conditions:
(a) NH_4OH, DCM, 0 °C. (b) Amberlyst, toluene, reflux, 4 h. (c) $LiALH_4$, dry THF, 80 °C, 4 h.
(d) NaH, Bromoacetyl bromide, dry toluene, 0 °C-r.t., 72 h. (e) Dimethylamine hydrochloride, THF, 0 °C-r.t., 12 h. (f) $ArCH_2Br$, 50 °C, 75 h. (g) BTPP, DMSO, r.t. (i) $LiOH.H_2O$ (2eq), THF/H_2O (4:1).

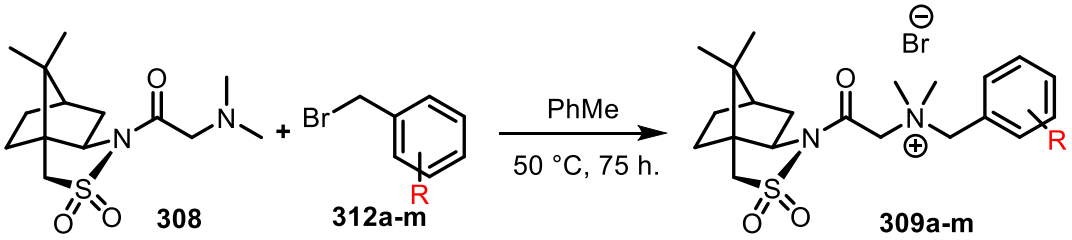
Scheme 74

5.1.1 Synthesis of Oppolzer's chiral auxiliary

The synthesis outlined in Scheme 74 (as reported by Davis)[82] began with (1*S*)-(+)-10-camphorsulfonyl chloride (**303**), which was treated with an ammonia solution to give camphorsulfonamide (**304**) in 85% isolated yield. Without any purification **304** was used in the next step, where Amberlyst 15 ion-exchange resin was used as acid catalyst for the imine formation using Dean-Stark conditions and affording camphorsulfonimine (**305**) in excellent yield (95%). The latter in turn, underwent reduction with $LiAlH_4$ in THF to afford camphorsultam (**306**), also known as Oppolzer's chiral auxiliary.

5.1.2 Synthesis of benzylic ammonium salts

Subsequently, reaction of camphorsultam **306** with bromoacetyl bromide gave compound **307**, which was reacted with *N,N*-dimethylamine to produce amine **308**. Ammonium salts **309** can be synthesized efficiently in high yield by treatment of **308** with benzyl bromide derivatives at 50 °C for 75 h. After such time, the salt, which is hygroscopic, was precipitated and collected by filtration (Scheme 75 and Table 19).



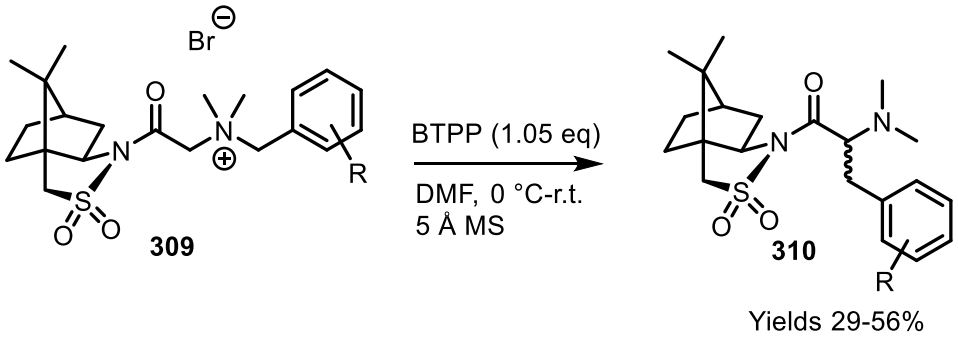
Scheme 75

Table 19

Entry	R	Yield (%)	Product No
1	H	95	**309a**
2	4-OMe	98	**309b**
3	4-COMe	75	**309c**
4	2,5-diF	98	**309d**
5	4-COPh	97	**309e**
6	4-CO_2Me	95	**309f**
7	2,4-diF	96	**309g**
8	3,5-diF	82	**309h**
9	2,4,6-triF	95	**309i**
10	3-F	98	**309j**
11	4-Ph	72	**309k**
12	2-CN	96	**309l**

5.1.3 [1,2]-Stevens rearrangement of benzylic ammonium salts

As described in the introduction of this chapter, the optimized conditions towards the [1,2]-Stevens rearrangement of benzylic ammonium salts were obtained within our group, and use BTPP as base, DMF as solvent, and 5 Å molecular sieves as a water scavenger in order to avoid cleavage of the chiral auxiliary (Scheme 76).[59]



Scheme 76

Moreover, the results obtained by Ollis and co-workers on the influence of solvent and reaction temperature on the stereoselectivity and intramolecularity of the [1,2]-Stevens rearrangement, suggested that the high viscosity of the solvent favours the solvent cage effect. The latter in turn, might increase yield. For next stage, we chose to limit our initial focus to improve the yield. For that purpose, we hypothesized that the use of a high viscosity solvent, could lead to increased yield (Table 20).

Table 20

Solvent	Viscosity at 20 °C
DMF	0.92 cP
DMSO	1.996 cP

Furthermore, in order to further understand the effect of solvent on the [1,2]-Stevens rearrangement it is worth looking at the solvent's chemical structure (Figure 26). When considering DMF and DMSO, it is clear that DMF has a partial negative charge on oxygen and partial positive on nitrogen, whereas DMSO has negative charge on oxygen and positive on sulfur.

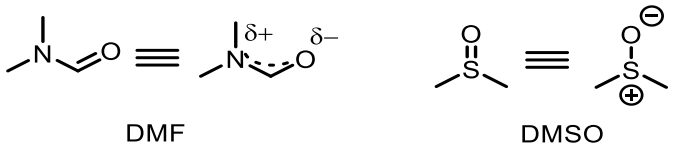


Figure 26

According to intermediate **162**, which is formed during the [1,2]-Stevens rearrangement (as shown in Scheme 30), it can be observed that the structure of DMSO, where the delocalisation of the charge is increased, stabilises further the formation of ylide **162** thus should allow to improve the yield (Figure 27).

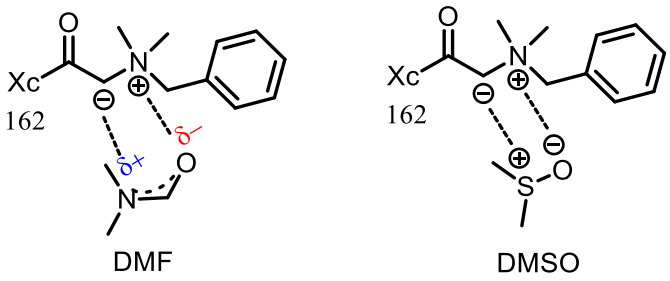
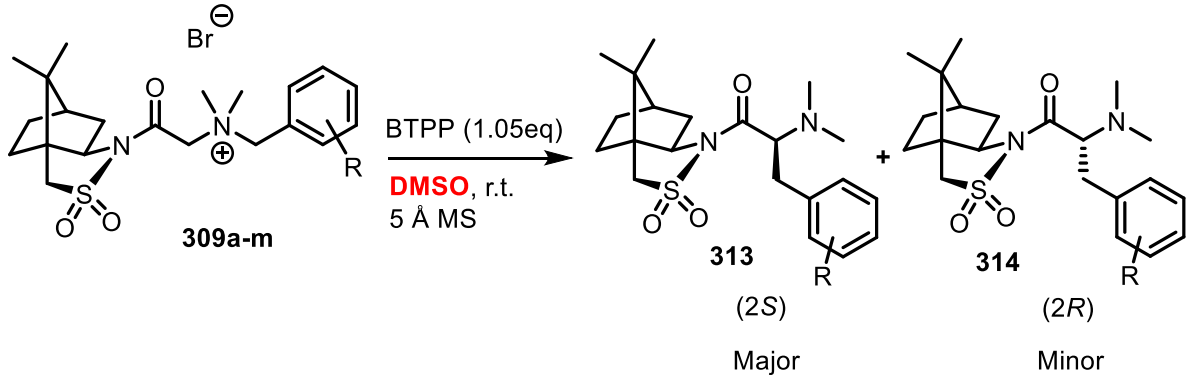


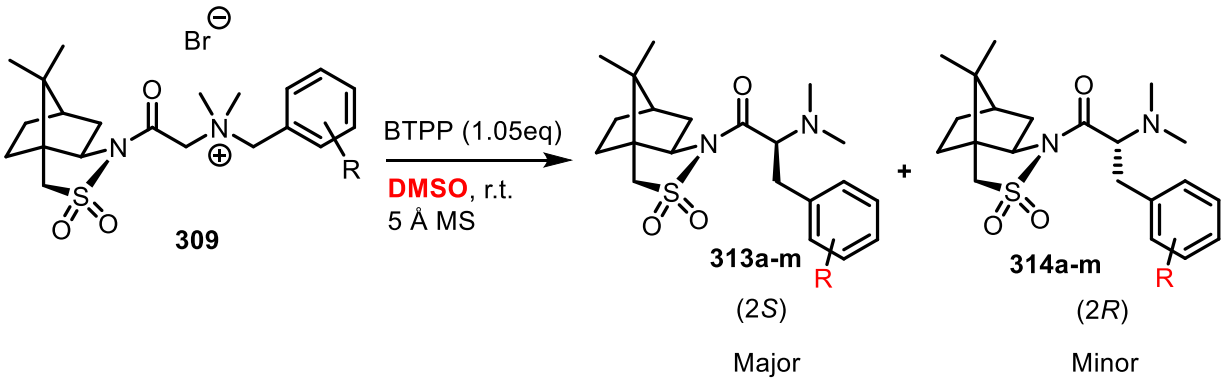
Figure 27

Therefore, we carried out [1,2]-Stevens rearrangement of benzylic ammonium salts using the previous conditions except for the use of DMSO as solvent instead of DMF (Scheme 77).



Scheme 77

The results obtained show that the reaction's efficiency was increased and products were obtained in high yields compared with those obtained with DMF. We expanded the scope of the [1,2]-rearrangement to different substituted benzylic ammonium salts. Products were generated in 61-89 yields and with a degree of diastereoselectivity in the presence of several functional groups on the aromatic ring (methoxy, ketone, ester, phenyl, cyano, haloalkyl) and using various substitution patterns (Scheme 78 and Table 21, Appendix 9, Pages 122-138).



Scheme 78

Table 21

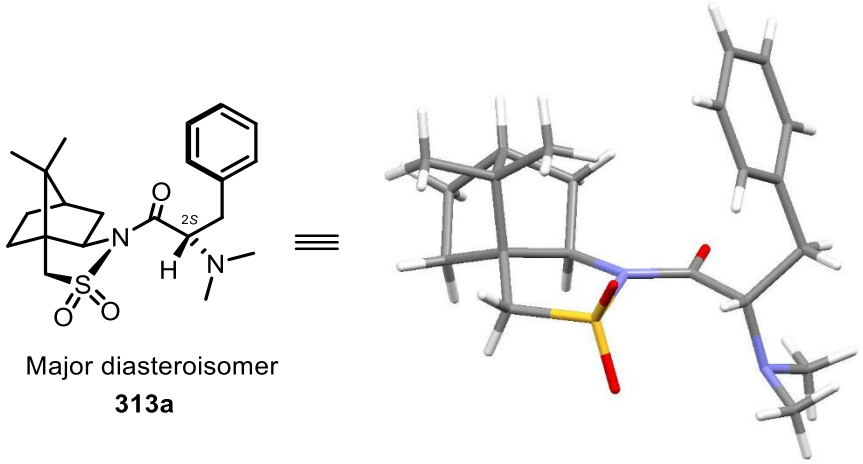
Entry	R	% of [1,2] pure products			(dr) ratio (2*S*:2*R*)	
		(2*S*)	(2*R*)	Total yield	^{1}H NMR [a]	HPLC [b]
1	H	54%	11% [c]	**65%**	83:17	81:19
2	4-OMe	50%	15%	**65%**	79:21	79:21
3	4-COMe	57%	11%	**68%**	75:25	78:22
4	2,5-diF	60%	29%	**89%**	78:22	71:29
5	4-COPh	43%	17%	**60%**	38:62	44:56
6	4-CO_2Me	41%	22%	**63%**	78:22	75:25
7	2,4-diF	42%	19%	**61%**	80:20	79:21
8	3,5-diF	55%	32%	**87%**	80:20	72:28
9	2,4,6-triF	41%	24%	**65%**	84:16	85:15
10	3-F	65%	23% [c]	**88%**	71:29	67:33
11	4-Ph	41%	22% [c]	**63%**	80:20	77:23
12	2-CN	47% [d]	30%	**77%**	66:18[e]	63:19[f]

[a] The ratio determined from ^{1}H NMR spectrum of the crude, by integration of *N*- dimethyl resonances for two diastereoisomers.
[b] The ratio determined from HPLC spectrum of the crude by calculation of peak area for two diastereoisomers.
[c] (2*R*)-[1,2]-product and camphorsultam as an inseparable mixture.
[d] (2*S*)-[1,2]-product and [2,3]-product as an inseparable mixture.
[e] 16 % [2,3]-rearrangement.
[f] 18 % [2,3]-rearrangement.

The ratio of diastereoisomers was calculated by ^{1}H NMR and HPLC analysis of the crude product. Generally, the best results were obtained with fluorine substituted compounds. The presence of competing [2,3]-rearrangement products was possible for all compounds, however, noticeably just one example, (2-CN, Entry 12), gave [2,3]-rearrangement along with [1,2]-Stevens rearrangement. Furthermore, camphorsultam was recovered in most reactions in 1-5% showing little hydrolysis had occurred.

The stereochemistry of the major product was confirmed by X-ray of single-crystal (a, Figure 28). The X-ray data showed that the carbonyl C=O double bond is opposite to sulfonamide (N-S) bond in the product, to minimize dipole interactions. In addition, C-NMe_2 bond is inclined at approximately 90° to SO_2-N-C=O bonds.

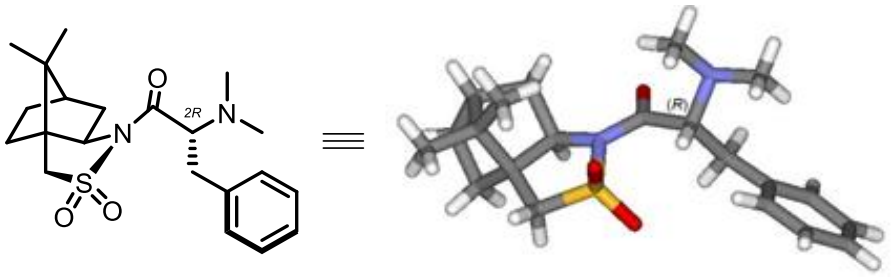
a) Our work (BTPP as base and DMSO as solvent, Appendix 9, Pages 122)



Major diasteroisomer

313a

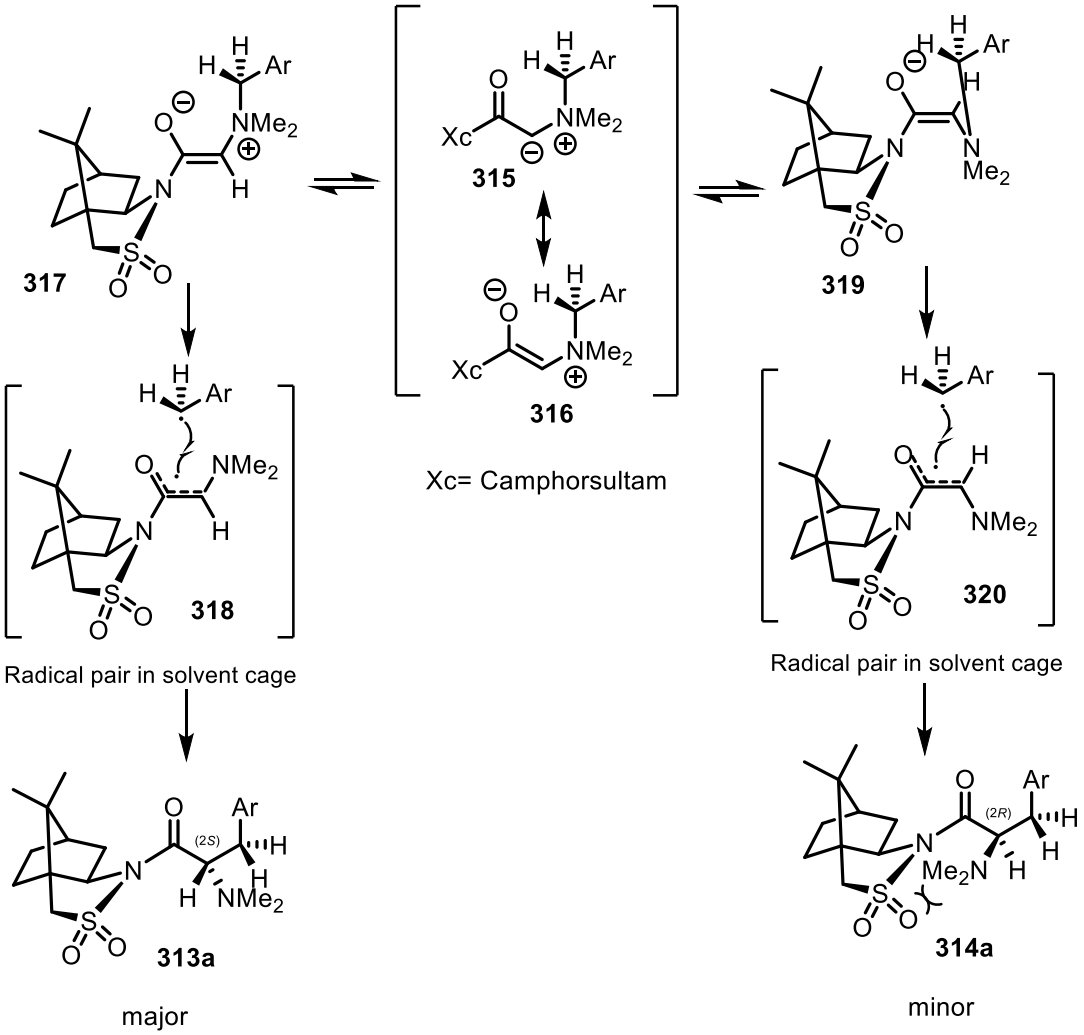
b) Previous work within Sweeney group (NaH as base and DME as solvent)



Major diasteroisomer

Figure 28

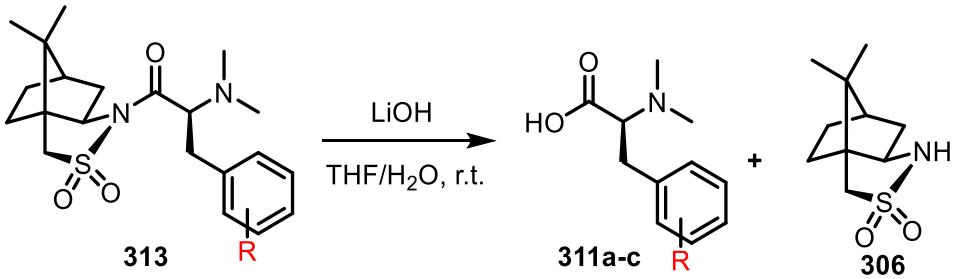
Based on the configuration of the product, we can provide an explanation for diastereocontrol of this reaction. Presumably, the benzyl radical recombines from the upper face, leading to the observed stereoselectivity. We assume that recombination is faster when the NMe_2 group is anti to S=O bonds (Scheme 79). Surprisingly, our X-ray structure shows that there is the difference in an absolute configuration of the major product which prepared by two methods (Figure 28) (two different conditions). In other words the major product, which was prepared by the previous work within our group using NaH as base and DME as solvent, has absolute configuration (2*R*) whereas the major product, which was prepared by this work using BTPP as base and DMSO as solvent has absolute configuration (2*S*).



Scheme 79

5.1.4 Cleavage of the auxiliary

[1,2]-Stevens rearrangement products can be hydrolysed to give the corresponding amino acids. The hydrolysis reactions were performed according to a known procedure (with minor modifications), which was previously reported by the Sweeney group.[83] The reaction was carried out using lithium hydroxide monohydrate in THF/H_2O (4:1) giving amino acids in 311a-c (Scheme 80 and Table 22, Appendix 9, Pages 139-140).



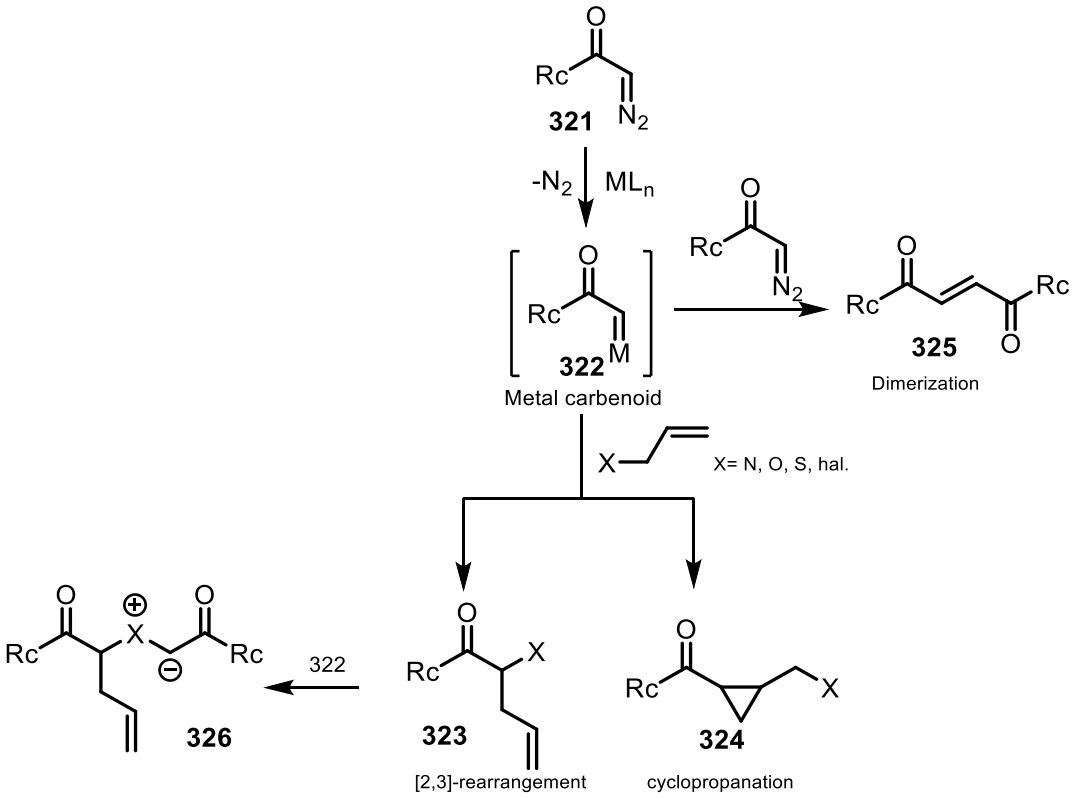
Scheme 80

Table 22

Entry	R	Yield (%)
1	H	32
2	2,4-diF	39
3	4-Ph	35

5.2 [2,3]-Rearrangement of allylic onium ylids

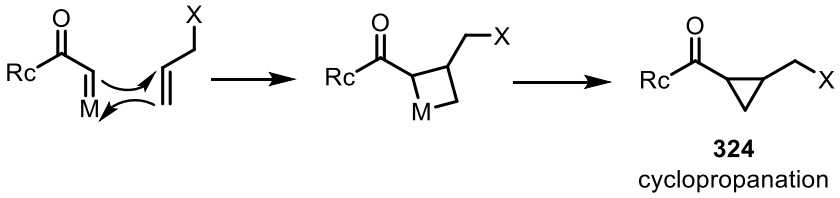
Regarding the [2,3]-rearrangement, we reported earlier that the Sweeney group had previously obtained excellent results in the case of base-mediated allyl ammonium salt rearrangements (Scheme 71). Our goal was to further examine the rearrangement reaction but using metal-catalysed rearrangements instead, which is expected to obviate the need to use of the base and hygroscopic salts. Optimization of the [2,3]-rearrangements of allylic ylids using metal catalysts and diazo compounds (carbene precursors) can be challenging because many different species compete for addition to the metal carbenoid (Scheme 81).



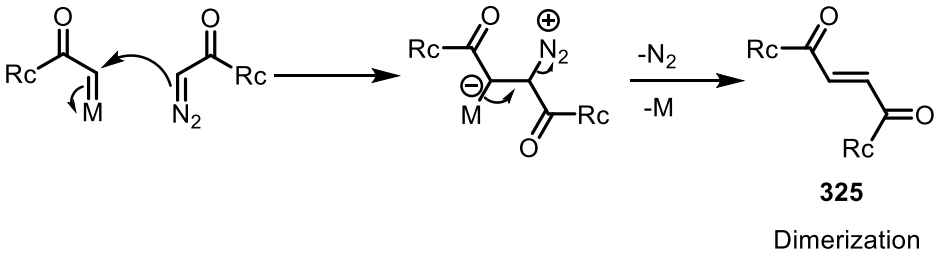
Scheme 81

The metal carbenoid species (**322**) can react with the allylic heteroatom to produce allylic onium ylids, which undergo [2,3]-rearrangements (Scheme 56 and Scheme 81).

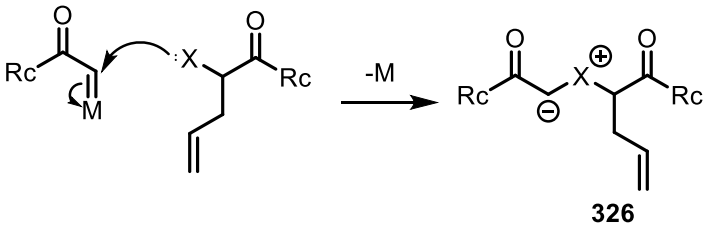
On the other hand, the metal carbenoid species (**322**) can also react with the double bond giving a cyclopropanation, which is concerted addition of the metal carbene to the alkene to form cyclopropane ring, species side reaction (formation of **324**)(Scheme 81a). Moreover, the electron-deficient carbon, which is attached to metal, can undergo to the nucleophilic attack by another diazo to form dimerization compound **325**)(Scheme 81b). Finally, [2,3]-products might react with metal carbenoid species as nucleophile to form another side product (**326**)(Scheme 81c).



Scheme 81a



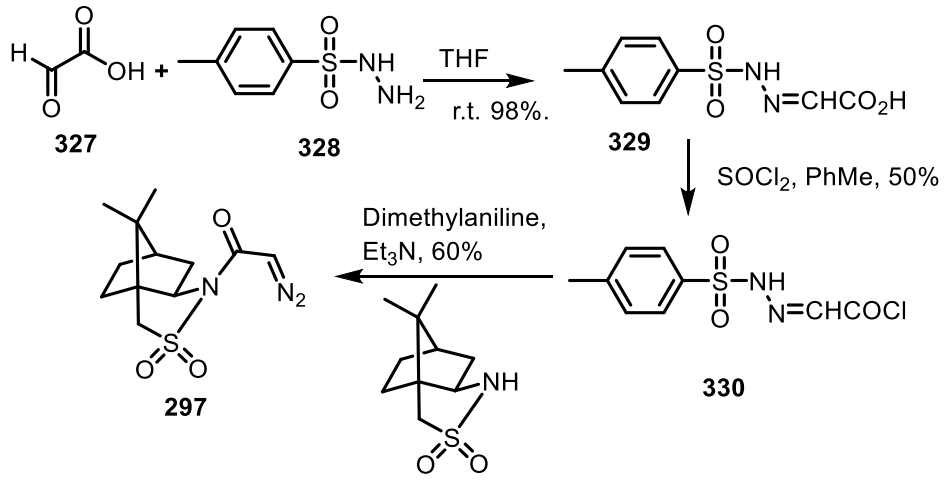
Scheme 81b



Scheme 81c

5.2.1 Synthesis of the diazoacetyl camphor sultam

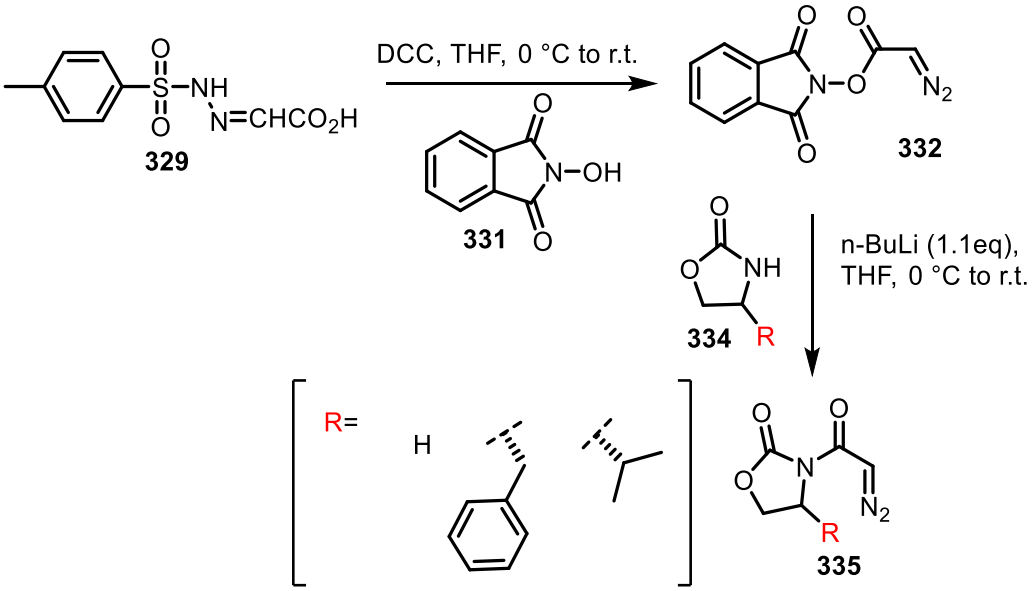
As outlined in Scheme 82, glyoxylic acid chloride *p*-toluenesulfonyl hydrazone (**330**) was prepared by procedure reported by Atkinson.[84] The synthesis started with glyoxylic acid (**327**) which was reacted with *p*-toluenesulfonyl hydrazide (**328**) to produce glyoxylic acid *p*-toluenesulfonyl hydrazone (**329**) in 98% yield. Subsequently, **329** was converted into glyoxylic acid chloride *p*-toluenesulfonyl hydrazone (**330**) using freshly distilled thionyl chloride. Finally, the desired diazo compound **297** was prepared in 60% yield using a modified procedure from Myers.[58,85]



Scheme 82

5.2.2 Synthesis of *N*-α-diazoacyl oxazolidinones

Different diazo oxazolidinones were synthesized according to reported procedures.[86,87] The synthesis began with the conversion of *N*-hydroxyphthalimide into diazo phthalimide obtained in 71% yield followed by addition of oxazolidinone or substituted oxazolidinone under basic conditions (Scheme 83 and Table 23).



Scheme 83

Table 23

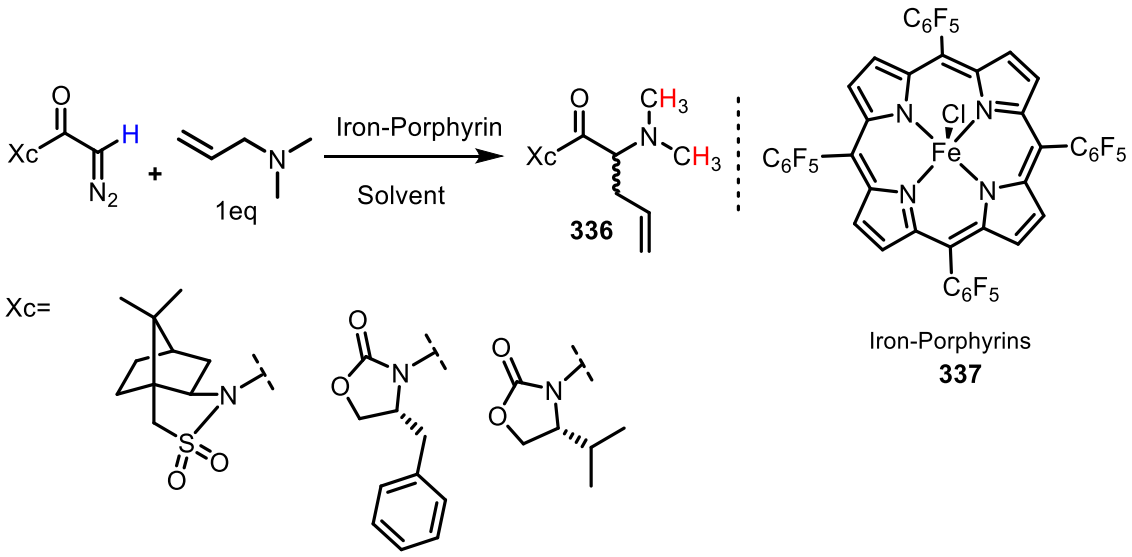
Entry	R	Yield (%)
1	H	75
2	Benzyl	57
3	Isopropyl	55

5.5.3 [2,3]-Rearrangements of allylic onium ylids

The example reported by Gross (Scheme 59), suggested it was worth investigating [2,3]-rearrangements of allylic ammonium ylides using iron(III) porphyrin catalysts and a diazoacyl moiety attached to a chiral auxiliary. The use of the auxiliary, might allow access to range of products with high diastereoselectivity.

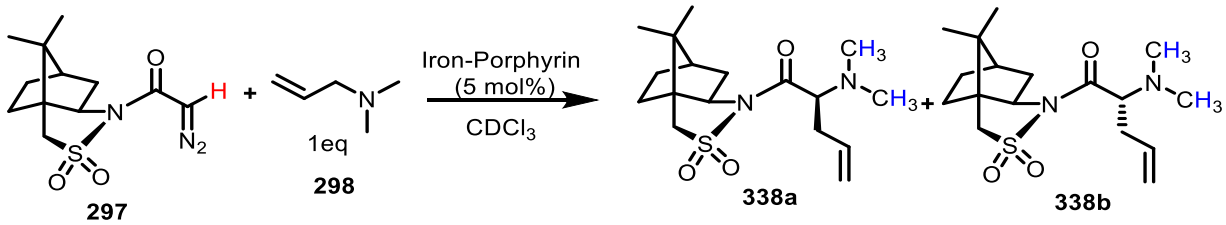
5.5.3.1 [2,3]-rearrangements of allylic ammonium ylids

Our initial idea was to examine [2,3]-rearrangements using dimethyl allylamine and diazoacyl group attached to different chiral auxiliaries in the presence of a highly reactive iron(III) porphyrin catalyst **337** (Scheme 84).



Scheme 84

[2,3]-Rearrangements using dimethyl allylamine and diazoacyl camphorsultam **297** in the presence iron(III) porphyrins were initially studied (Scheme 85). The reaction was carried out according to reported procedures.[71] The first reaction was carried out using low catalyst loading (0.2 mol%), one equivalent of *N,N* dimethylallylamine and $CDCl_3$ as the reaction solvent. The reaction mixture was monitored by ^1H NMR and TLC analysis.



Scheme 85

The conversion from diazoacyl camphorsultam to [2,3]-rearrangement products was determined at a series of time points from the ^{1}H NMR spectrum of the reaction mixture recorded in $CDCl_3$ by integration of *N,N*-dimethyl resonances for each isomer product and α-proton (substrate) (Figure 29).

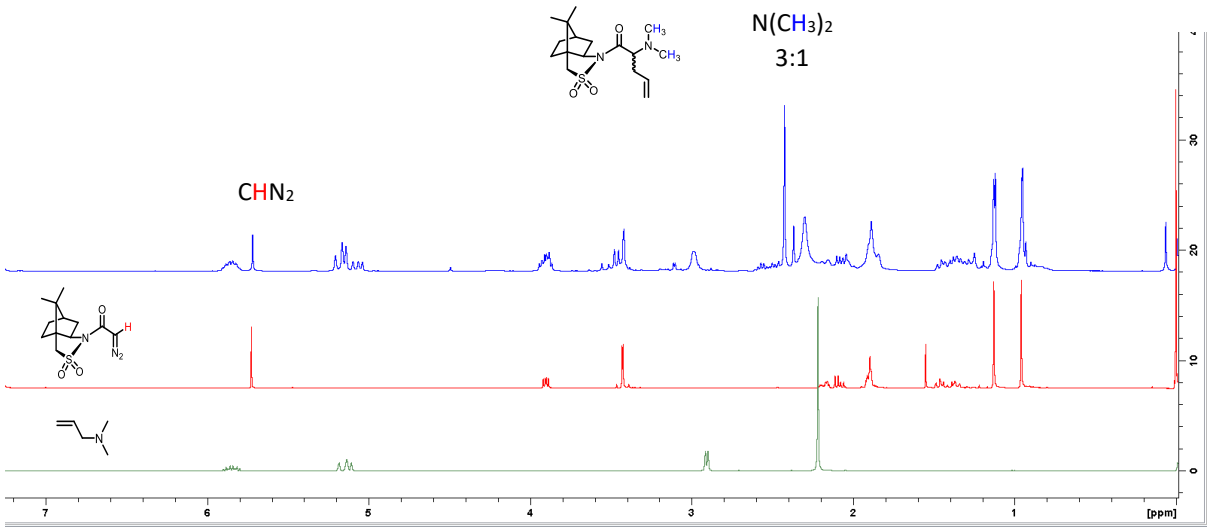
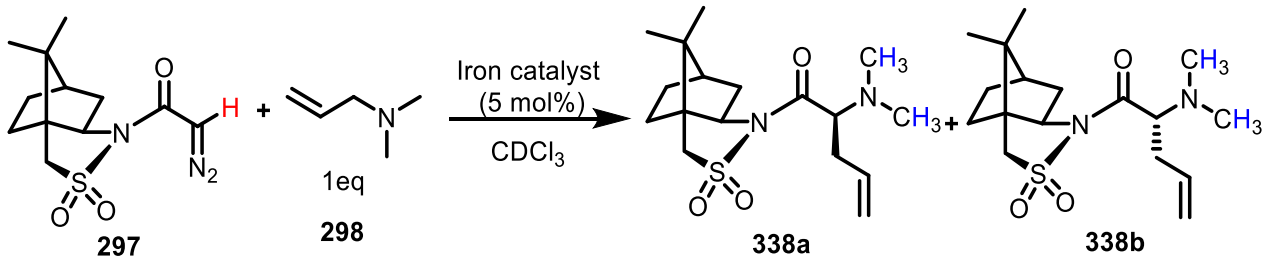


Figure 29. ^{1}H NMR for the reaction mixture.

The results showed that the reaction provided the desired product albeit very slowly. In order to optimise the reaction, a combination of catalyst loading (1, 5, 10, 20, 40 mol%) and one equivalent of *N,N* dimethylallylamine were used (Chart 1).

Chart 1

From the previous chart, it is clear that increasing the amount of catalyst (Stoichiometry) led to increased conversion. After two days and using 40 mol% of catalyst loading at room temperature, 90% of starting material was consumed and the product was obtained as diastereoisomers in a 3:1 ratio. Secondly, increasing number of equivalents of *N,N* dimethyl allyl amine (1eq, 5 eq, 10 eq) gave the same results. Generally, the reaction worked slowly and requires a high loading of catalyst. The reason for this might be the steric hindrance between the catalyst and diazo camphorsultam. Therefore, our focus turned to other iron catalysts as shown scheme 86 and table 24.



Scheme 86

Table 24

Entry	Catalyst	Time (h)	Conversion[a]
1	Iron (III) 1,3-diphenyl-1,3-propanedionate	21	0
2	Iron(III) tris(2,2,6,6-tetramethyl-3,5-heptanedionate)	21	0
3	$Fe(acac)_3$	24	0
4	$FeBr_3$	50	0
5	DPPF	50	0

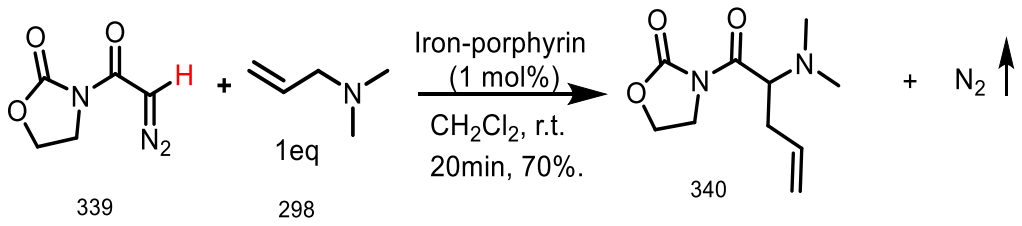
[a] According to the consumption of diazo and alkene peaks (^{1}H NMR for crude).

[b] DPPF= bis(diphenylphosphino)ferrocene.

The results of this investigation (Table 24) show that there is no conversion to the desired products and only starting materials were recovered from all reactions. Based on this, we did not continue the investigation of the [2,3]-rearrangement with diazo-camphorsultam, and we moved to examine another chiral auxiliary.

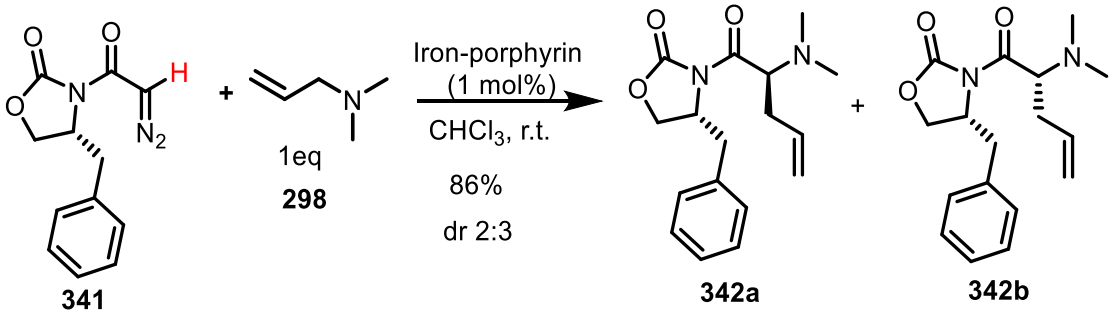
Our next goal was to test iron(III) porphyrin catalyst with diazoacyl oxazolidinones in the presence of *N,N* dimethylallylamine (Scheme 87). The reaction was carried out using 1 mol% of iron(III) porphyrin catalyst, one equivalent of *N,N*-dimethylallylamine and CH_2Cl_2 as solvent at room temperature. The initial reaction worked efficiently

affording the desired product in 70% yield. The reaction was performed by addition of a solution of diazo **339** and allylamine into a solution of catalyst in one portion and it took 20 min for the nitrogen bubbles to stop (showing no more diazo compound was consumed).



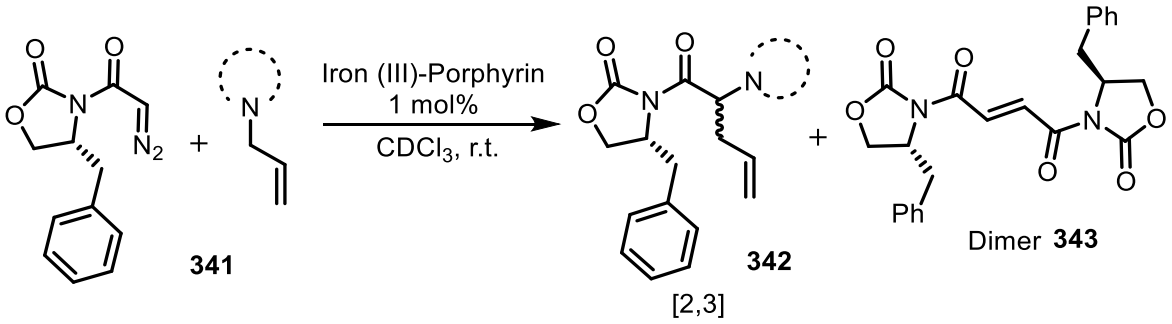
Scheme 87

This was a promising start and led to further investigation using different substrates. Next, the chiral diazo-oxazolidinone **341** was used in the reaction (Scheme 88).



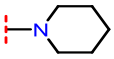
Scheme 88

Iron (III) porphyrin catalysed the decomposition of diazo benzyl oxazolidinone **341** in the presence of *N,N*-dimethylallylamine to produce [2,3]-products **342a** and **342b** in high 86% yield (Appendix 9, Pages 145-146), although diastereoselectivity was poor (2:3). The reaction was carried out at room temperature, 0 °C and -78 °C as a means to improving the diastereoselectivity. Unfortunately, all the reactions gave the same ratio of diastereoisomers. Next, the reaction was carried out using another chiral oxazolidinone, which employed (*R*)-isopropyl oxazolidinone, and *N,N*-dimethylallylamine to give the product in poor diastereoselectivity (1:1.7, see appendix 9, Page 263, Crude 20). In addition, the reaction was done using cyclic allyl amines and the obtained results are shown in scheme 89 and table 25.



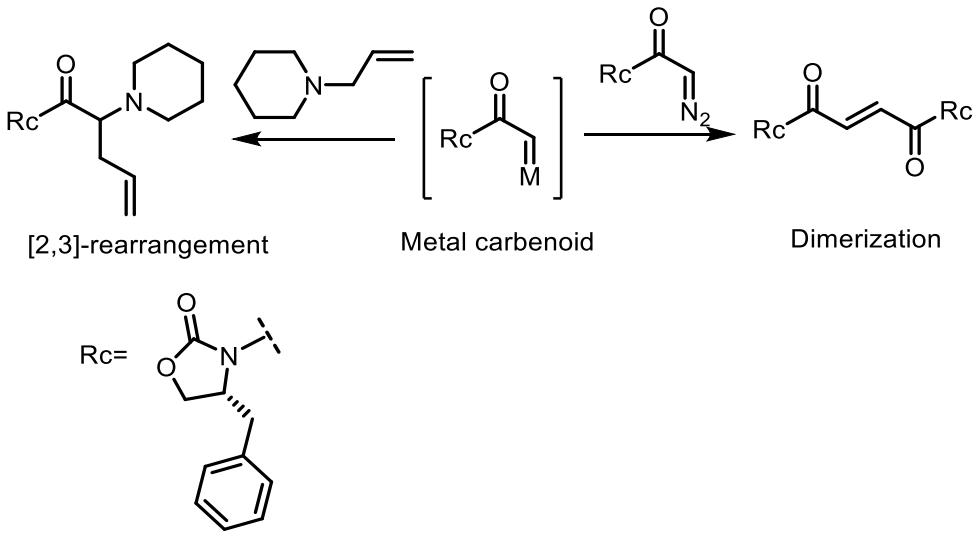
Scheme 89

Table 25

Entry	Ally amine	[2,3] (dr) ratio	Ratio ([2,3]:dimer)	Total yield (%)
1		1:1.5[a]	-	86
2		1:1.3[a]	-	- [c]
3		1:1[b]	2:1[a]	62

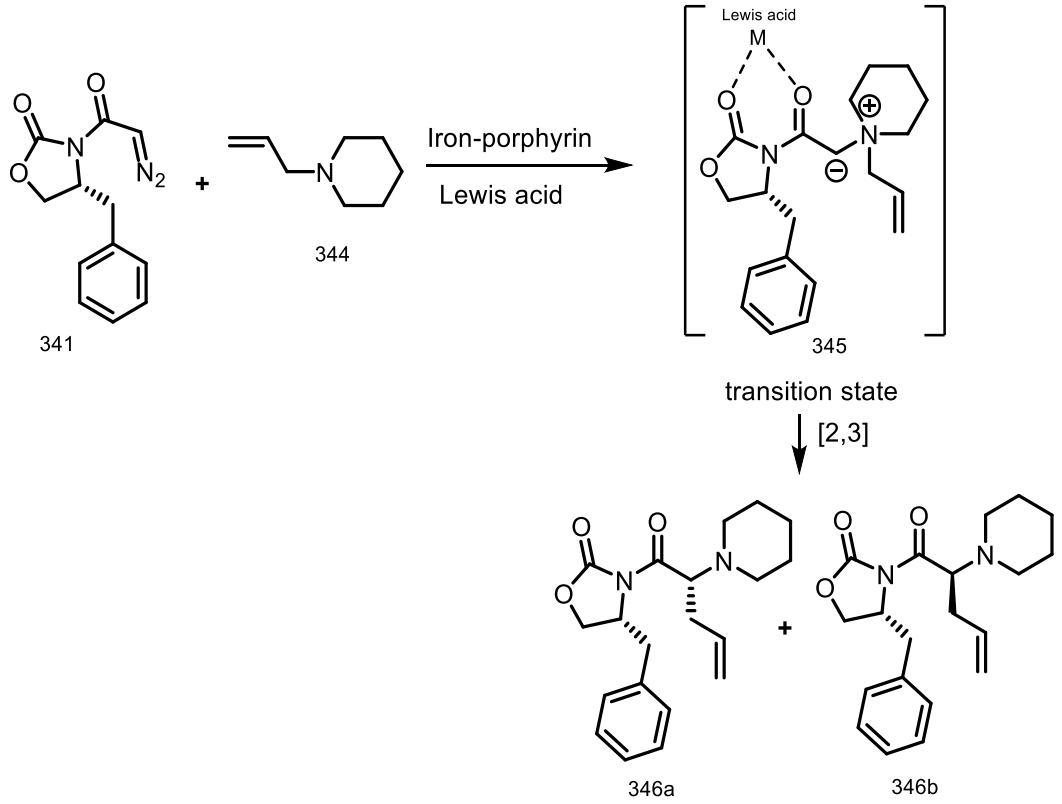
[a] The ratio determined from ^{1}H NMR spectrum of the crude, by integration of one proton of C$\underline{H_2}$Ph resonances for [2,3]-products and dimer.
[b] The ratio determined from HPLC spectrum of the crude by calculation of peak area for two diastereoisomers.
[c] Could not estimate yield.

We assume that the steric hindrance around nitrogen atom affects its ability to nucleophilically attack to the metal carbenoid. As result of this, dimerization of the diazo compound occurred (Entry 3, Table 25) when N-allylpiperidine was used in reaction. Perhaps due to the high reactivity of the iron catalyst and the steric effect around the nitrogen reaction the formation of the dimerized product competed with the [2,3]-rearrangement (Scheme 90).



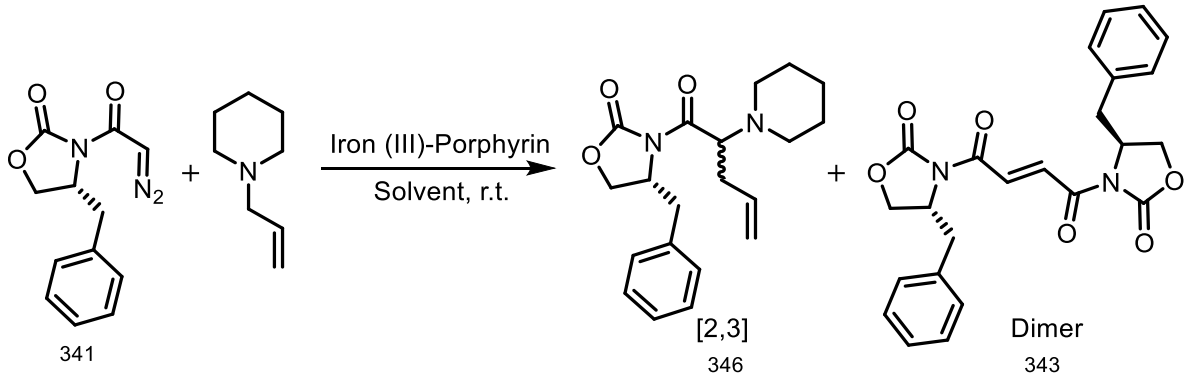
Scheme 90

To shine some light on the previous reaction, we hypothesised that improvement of diastereoselectivity of the iron(III) porphyrin catalysed rearrangement could be achieved by using Lewis acids that would bind to both carbonyl oxygens and therefore force the rearrangement to proceed in a “more asymmetric” environment as illustrated in transition state (345) (Scheme 91).



Scheme 91

Before employing a Lewis acid within the reaction, it was necessary to test a range of solvents as result of the limited solubility of Lewis acids in chloroform (Scheme 92 and table 26).

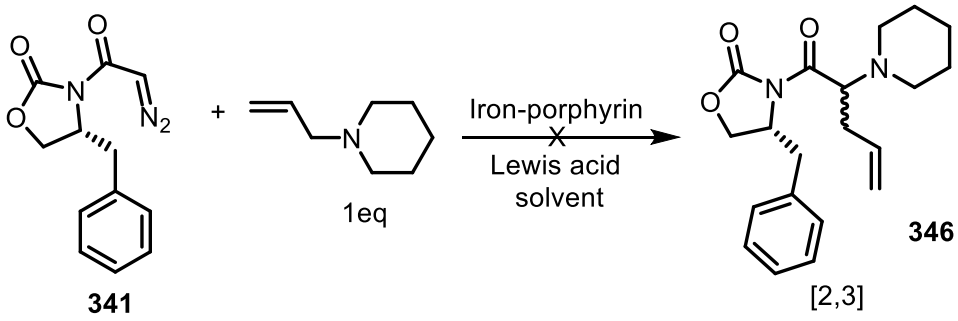


Scheme 92

Table 26

Entry	Solvent	[2,3]:Dimer
1	EtOH	0:1
2	DMSO	-
3	MeCN	3:1
4	$CHCl_3$	2:1

It is worth noting that acetonitrile (Entry 3, Table 26) reduces the formation of dimer and supports the formation of [2,3]-rearrangement whereas ethanol did not give any [2,3]-products. Next, a range of Lewis acids were used the reaction along with iron catalyst (Scheme 95 and table 27).



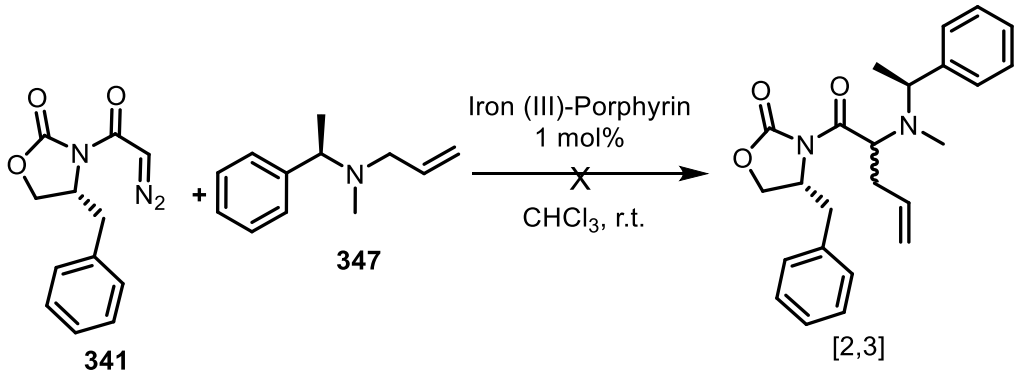
Scheme 93

Table 27

Entry	Lewis acid	solvent	[2,3]-products
1	$MgCl_2$	$CHCl_3$	-
2	$AlCl_3$	$CHCl_3$	-
3	$FeCl_3$	$CHCl_3$	-
4	Bu_2BOTf	$CHCl_3$	-
5	$Mg(ClO_4)_2$	MeCN	-
6	$MgBr_2.OEt_2$	MeCN	-

According to ^1H NMR for all the previous reactions, it was clear there were no [2,3]-rearrangement products. However, diazo benzyl oxazolidinone (**341**) was fully consumed in all reactions.

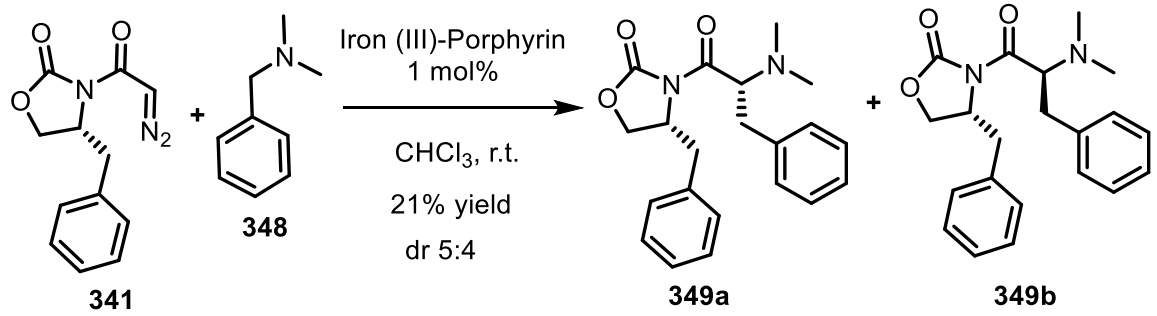
As another possible means to improve the diastereoselectivity of the reaction we thought of using chiral allylamines. *N*,α-Dimethylbenzylallylamine (**347**) was therefore examined in the reaction with the chiral diazo benzyl oxazolidinone (**341**) in the presence of the iron(III) porphyrin catalyst (Scheme 94).



Scheme 94

Unexpectedly, when diazo compound (**341**) was treated with one equivalent of chiral amine **347** (in chloroform at room temperature), [2,3]-rearrangement products were not observed.

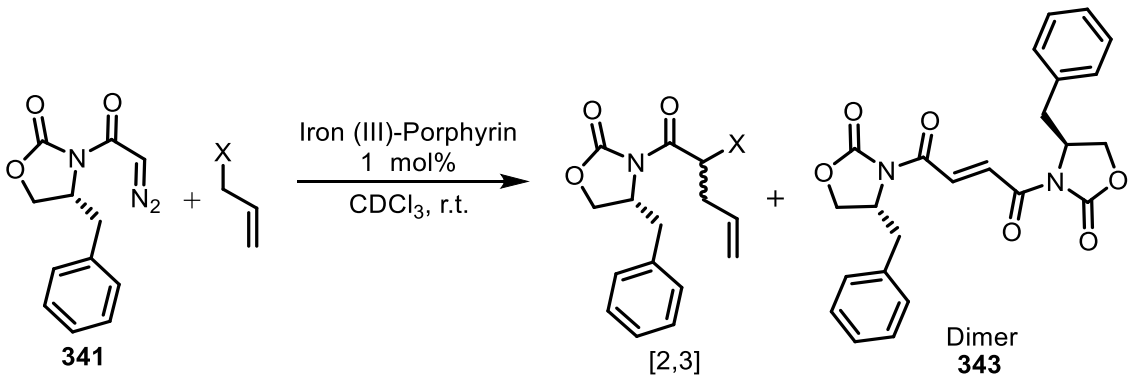
We were also interested in testing whether the reaction of *N,N*-dimethylbenzylamine (**348**) with diazo benzyl oxazolidinone would undergo the [1,2]-Stevens rearrangement or not. The reaction was carried out using iron porphyrin catalyst at room temperature and gave desired compound **349** in 21% yield, in a 5:4 ratio of diastereoisomers (Scheme 95).



Scheme 95

5.5.3.2 [2,3]-rearrangements of allylic onium ylids

To increase the coverage of the study of chiral diazo oxazolidinones, we proposed to carry out the reaction of diazo benzyl oxazolidinone **341** with other allylic nucleophiles as illustrated in scheme 96 and table 28.

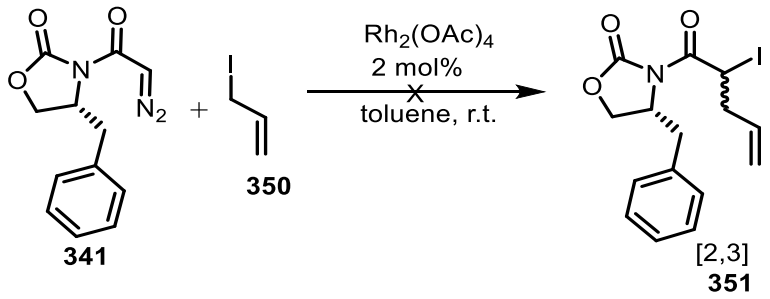


Scheme 96

Table 28

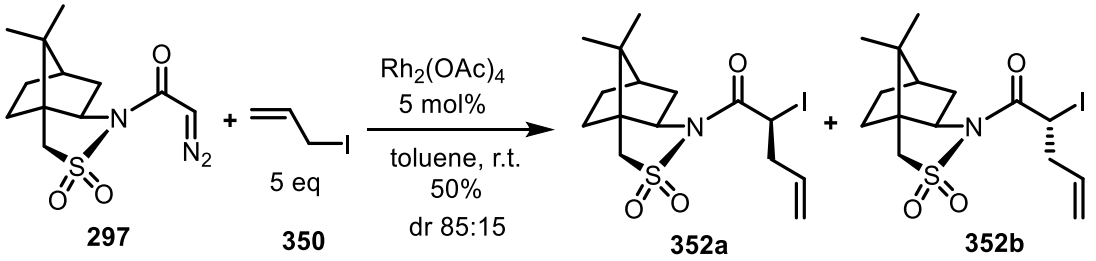
Entry	X	[2,3]: Dimer
1	OH	0:1
2	OCH_3	0:1
3	I	0:1

Based on the results shown in table 28, the formation of the dimerization product overcame the formation of [2,3]-rearrangement products. The high reactivity of iron(III) porphyrin catalyst with diazo compounds would make dimerization occur faster than nucleophilic attack of allylic nucleophiles on the metal carbenoid compound. These findings may be explained by the increased nucleophilicity of nitrogen than oxygen and iodine. To tune the balance between the reactivity of catalyst and the ability of nucleophilic attack, firstly we proposed to use a less activating catalyst such as $Rh_2(OAc)_4$, which is used widely in metal carbenoid chemistry. Secondly, the rate of addition of the diazo precursor to solution mixture of catalyst and allylic nucleophiles should affect the production of the dimer (diazo solution can be added slowly, and allylic nucleophiles can be used in excess). The next idea was to test if $Rh_2(OAc)_4$ catalyse decomposition of diazo chiral oxazolidinone in the presence of excess allyl iodide (Scheme 97).



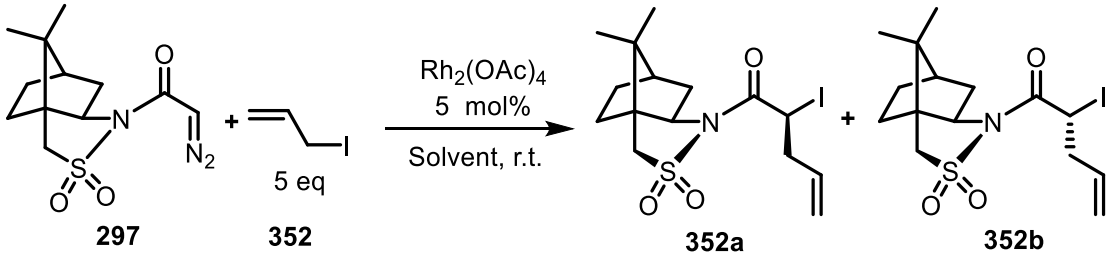
Scheme 97

Various reagents addition order were evaluated. Firstly, the solution of diazo compound was dropwise to a solution of catalyst and allyl iodide (5 eq.). Secondly, the solution of catalyst was dropwise to a solution of diazo (**341**) and allyl iodide (5 eq.). Unfortunately, attempts to produce desired [2,3]-products failed. To solve this problem, we examined the use diazocamphorsultam with the Rh(II) catalyst in the presence of excess allyl iodide and toluene as solvent at room temperature (Scheme 98). The initial reaction afforded products in 50% yield with 85:15 diastereoselectivity.



Scheme 98

This reaction was done with slow addition of the diazocamphorsultam solution (0.1g in 10 mL solvent over 24 h) to the solution of $Rh_2(OAc)_4$ and five equivalents of allyl iodide. Next, we focued on improving the yield by tuning the reaction conditions. To optimise the reaction, various factors were investigated. Firstly, the reaction was carried out using different solvents and the results are shown in table 29.



Scheme 99

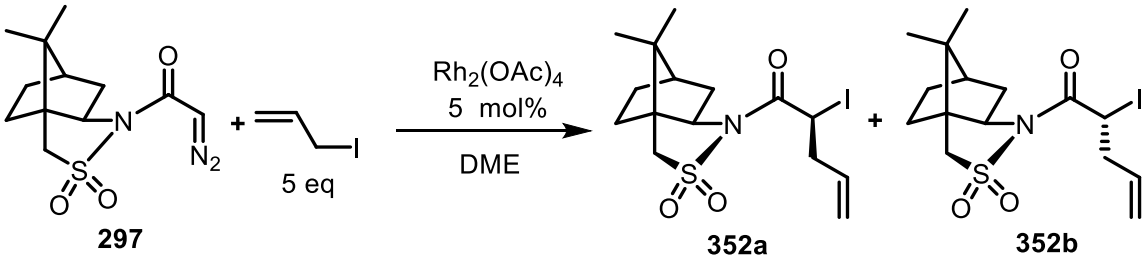
Table 29. Solvent screen.

Entry	Solvent	Addition time (mL.h^{-1})[d]	Conversion[a]	Total yield (%)	d.r.[b,c]
1	Toluene	0.397	100	50	85:15
2	DCM	0.397	100	73	85:15
3	THF	0.397	100	55	85:15
4	MeCN	0.397	44	-[e]	85:15
5	DMF	0.397	0	-	-
6	DME	0.397	100	>90	85:15

[a] According to the consumption of diazo. [b] Calculated by HPLC. [c] Approximate ratio. [d] A solution of diazo (100 mg) in solvent (10 mL). [e] Analytical reaction carried out without purification.

As can be seen from table 29, the best results were obtained in DME, as **352** was obtained in 90% yield and 5.6:1 d.r (Appendix 9, Pages 243-245). In contrast DMF did not give any desired products. In addition, acetonitrile (MeCN) gave 40% conversion in the same reaction time.

The second factor that might affect the diastereoselectivity is the reaction temperature (Scheme 100 and Table 30).



Scheme 100

Table 30

Solvent	Temp (°C)	Addition time (mL.h^{-1})	dr ratio[a,b]	Total yield (%)
DME	0	0.397	85:15	>90
DME	-20	0.397	85:15	>90
DME	-40	0.397	85:15	>90

[a] Calculated by HPLC. [b] Approximate ratio.

Clearly, the results above show that lowering the temperature did not affect the diastereoselectivity and conversion of the reaction.

Stability of 352 at room temperature

The carbon-iodine bond (C-I) is weak (bond dissociation energy = 57.6 kcal/mol). In other words, iodide is very good leaving group and iodide compounds are light sensitive. Therefore, iodide compounds have to be stored in a dark bottle, which prevent light from reaching to sample, and in the fridge.

Method

To monitor the stability of camphorsultam iodide (**352**), a quantity (solid) of camphorsultam iodide (**352**) was divided into 6 vials each one containing 10 mg. All vials were covered with aluminium foil to protect them from the light. Monitoring of stability was done by ^{1}H NMR of the mixture of two diastereoisomers during 24 days (24 h, 48 h, 5, 6, 7 and 24 days) (Figure 30).

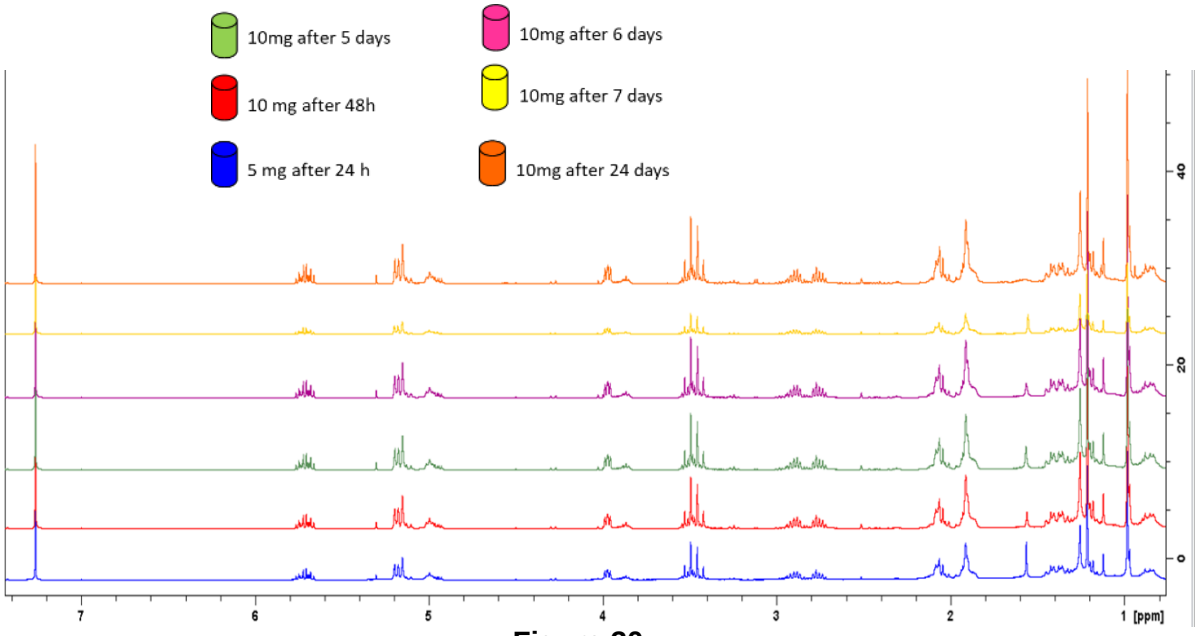


Figure 30

In the meantime, one of these samples, left in solution in $CDCl_3$ was monitored by ^1H NMR (Figure 31).

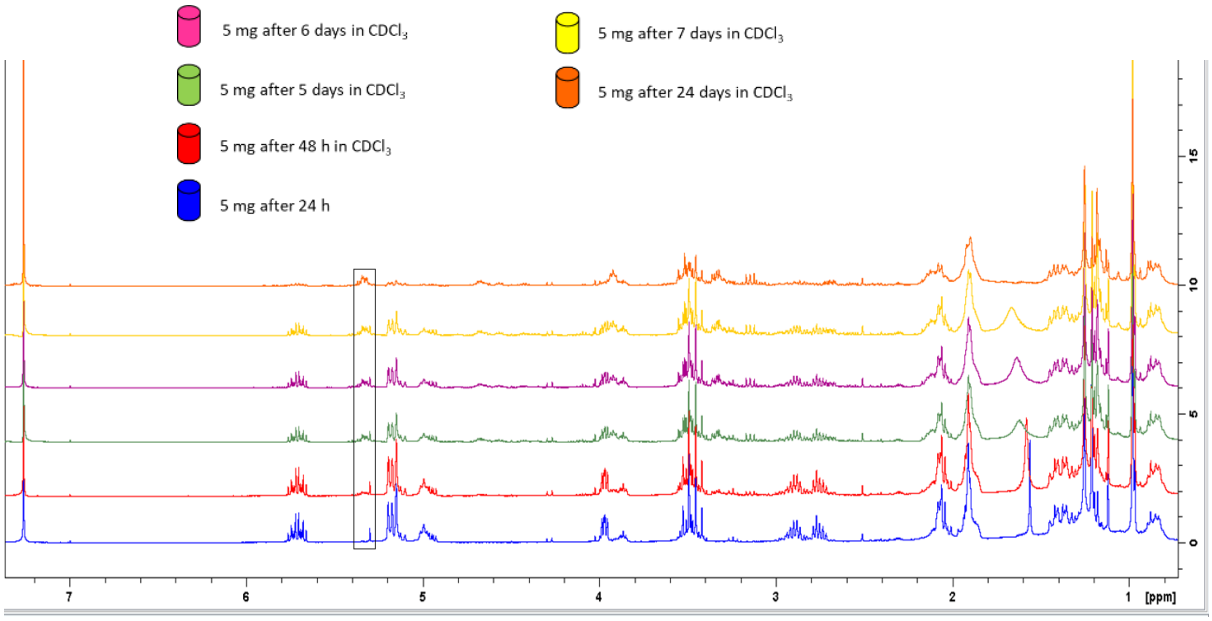
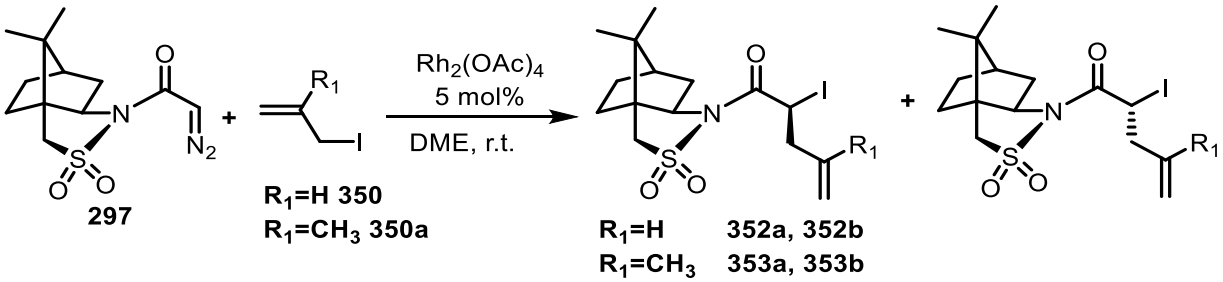


Figure 31. (In $CDCl_3$).

This study has demonstrated that **352** (solid) is stable at room temperature (at least for 24 days) (Figure 30), whereas it started to decompose after 48 h when stored at r.t. in a $CDCl_3$ solution (Figure 31). This can be more simply noticed from the colour of

the solution that turned to pink, and the colour intensity increased dramatically over the 7 days.

To further expand the scope of the [2,3]-rearrangements of iodonium ylides, we carried out the reaction with substituted allyl iodides (Scheme 101). Products were generated in high yields and good diastereoselectivities (Table 31).



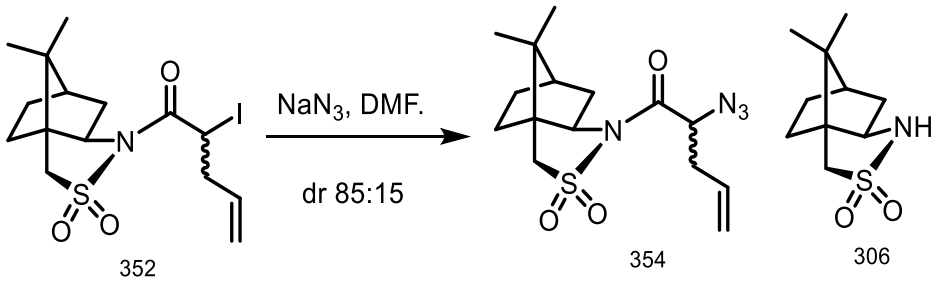
Scheme 101

Table 31

R_1	Ratio (dr)	Total yield (%)
H	85:15[a]	95
Me	84:16[a,b]	90

[a] Calculated by HPLC.
[b] Calculated by ^{1}H NMR and HPLC.

As mentioned above, iodide is very good leaving group and it should be easy to transform the newly made iodide rearrangement product into amino acids. For this, acetyl camphorsultam iodide **352** was reacted with sodium azide in DMF (Scheme 102).



Scheme 102

The reaction was carried out using the crude mixture of the two diastereoisomers of **352** directly with sodium azide (1 eq.) at 60 °C and room temperature. According to the ^{1}H NMR spectrum for the crude product, we observed the corresponding peaks of

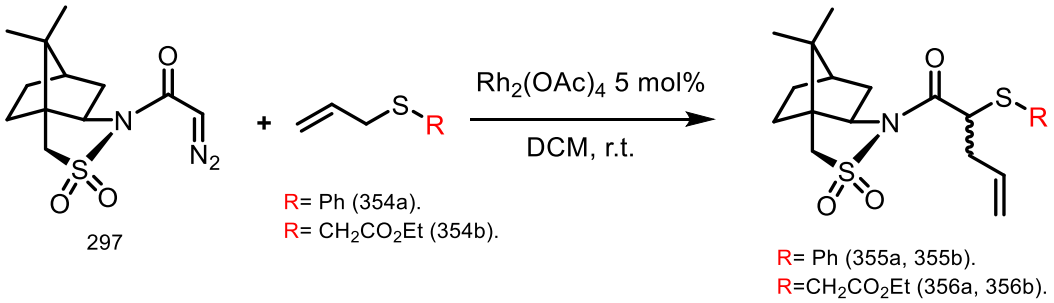
the cleaved chiral auxiliary (Scheme 102 and Table 32), therefore reaction had to be carried out carefully. We were pleased to see that a 4 h reaction at room temperature afforded desired compound **354** in 70% yield.

Table 32

Tem (°C)	Time	Ratio (354:306)[a]	Total yield (%) 354
60	Overnight	1:1	41
RT	Overnight	5:1	-
RT	4 h	8:1	70

[a] The ratio determined from ^{1}H NMR spectrum of the crude, by integration of $CH_2CH{=}C\underline{H}_2$ for azide products and $C\underline{H}_2SO_2$ for the cleaved sultam.

Finally, we turned to examine another allylic nucleophile with diazocamphorsultam and $Rh_2(OAc)_4$ catalyst. The next reactions carried out using two examples of allyl sulfide with diazocamphorsultam in the presence of a Rh(II) catalyst at room temperature gave [2,3]-rearrangement products in low to good yield but with low diastereoselectivity (1:1 d.r.) (Scheme 103 and Table 33).



Scheme 103

Table 33

Entry	R	d.r.	Total yield (%)
1	Ph	1:1[a]	80
2	CH_2CO_2Et	1:1[b]	28

[a] The ratio determined from ^{1}H NMR spectrum of the crude. [b] The ratio determined from HPLC of the crude

In the case of phenyl allyl sulfide we have done the reaction with two solvents, DCM and DME. The best results were obtained with DCM.

6. Conclusion

We have shown that the [1,2]-Stevens rearrangement of benzylic ammonium ylids can carried out in excellent yield and diastereoselectivity. We have reported 12 examples with the [1,2]-Stevens rearrangement of benzylic ammonium ylids in good to excellent yields (61-89%). These results can be achieved by using phosphazene base (BTPP) in DMSO in the presence of 5 Å molecular sieves to decrease product hydrolysis. As expected, the use of DMSO as the reaction solvent improved the [1,2]-Stevens rearrangement yield by at least 19% compared to DMF (results previously obtained within our group). Finally, the [2,3]-sigmatropic rearrangement of allylic onium ylids catalysed by metal catalysts has been investigated and applied successfully to allylamines, allyl iodides and allyl sulfides. 5,10,15,20-Tetrakis(pentafluorophenyl)-21H,23H-porphyrin iron(III) chloride catalyst showed high reactivity with a chiral diazo oxazolidinone towards [2,3]-rearrangement while diazocamphorsultam worked slowly. Rhodium(II) acetate [$Rh_2(OAc)_4$] worked well with diazocamphorsultam and allyl iodide. Finally, acetyl camphorsultam iodide can be transformed into new non-coded amino acids.

Chapter 3

7. General experimental methods

Spectrometry:

The NMR spectra were recorded with a Bruker 400 MHz spectrometer using $CDCl_3$, DMSO-d_6 and D_2O as the solvents. Chemical shifts (δ) in ^1H NMR are reported in ppm, downfield from TMS, and as in ^{13}C NMR, are referenced to the residual solvent peak. Multiplicities are reported as a singlet (s), doublet (d), triplet (t), quartet (q) and combinations thereof, or multiplet (m). Coupling constants (J) are quoted in Hertz. All melting points were obtained using a Stuart SMP10 melting point apparatus. The Infrared spectra were recorded on Thermo Electron Corporation FT-IR Nicolet 380 and Omnic software. Mass spectrometry was performed using a Agilent 6210 TOF MS instrument with electrospray ionisation in the positive mode.

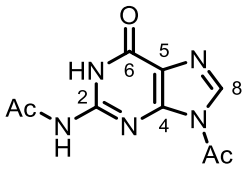
Reagents

All the solvents and reagents used were supplied by Sigma–Aldrich, Fisher Scientific and Tokyo Chemical Industry.

Chromatography

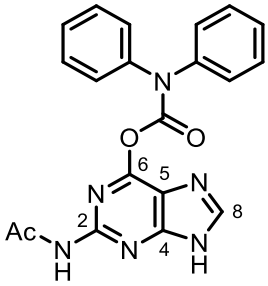
Thin layer chromatography (TLC) was carried out using silica gel 60 F_{254} aluminium sheets. Spots were visualised by quenching UV irradiation at 254 nm, and by staining with solution of $KMnO_4$ (3.0 g), K_2CO_3 (20.0 g) and NaOH (0.2 g in 5 mL water) in 250 mL water. Flash column chromatography was carried out using silica gel 60 A, 70-230 mesh, 63-200 µm obtained from Sigma–Aldrich. The HPLC analysis was conducted on a Chiralpack IB-3, IF-3 columns (Dimensions: 4.6 mm×250 mm; particle size: 3 µm). The UV detection was at wavelengths of 200, 210, 220, 230 and 254. Solvents were employed; Hexane, 2-propanol and Ethanol and flow rate of 1mL/min.

2-N, 9-diacetyl guanine (55).[29]



Guanine (3.75 g, 25 mmol), 60 mL of dry DMAc and 13 mL of Ac_2O were stirred at 160 °C for 7 h. After this time, the solution was left to cool. The precipitated solid was filtrated and washed by acetone to give (4.6 g, 79%)**. m.p.**= 262-264 °C (lit 251-256). **H^1 NMR** (400 MHz, DMSO-d_6) δ_H: 2.21 (s, 3H, 2NCOC<u>H</u>$_3$), 2.81 (s, 3H, N9COC<u>H</u>$_3$), 8.44 (s, 1H, C8<u>H</u>), 11.75 (s, 1H, exchange with D_2O, AcN<u>H</u>), 12.21 (s, 1H, exchange with D_2O, N<u>H</u>). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 24.3 (<u>C</u>H$_3$CO), 25.1 (N9CO<u>C</u>H$_3$), 121.9 (C5), 137.9 (C8), 148.3 (C4), 148.9 (C2), 155.1 (C6), 168.5 (N9-<u>C</u>O), 174.2 (N^2<u>C</u>O). **IR** ν_{max}/cm^{-1}: 3148 (NH), 3113 (NH), 1742 (CO), 1702 (CO), 1675 (CO).
MS *m/z* (ESI$^+$) calculated for ($C_9H_9N_5O_3$) $[M+H]^+$; 236.0778 found 236.0785.

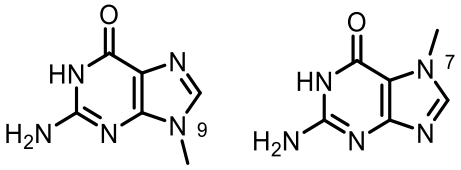
2-acetamido-9H-purin-6-yl diphenylcarbamate (56).[29]



(4.5 g, 19 mmol) of 2-*N*, 9-diacetylguanine in (7 mL, 40 mmol) of EtN(i-Pr)$_2$ and 100 mL of dry pyridine was treated with (4.9 g, 21 mmol) of diphenyl carbamoyl chloride for 1 hour at room temperature. Water (7 mL) was added and stirring for 20 min. The solvents were evaporated *in vacuo* and coevaporation (3 x 20 mL of PhCH$_3$). The residue was heating at 100 °C with 300 mL of EtOH/H_2O (1:1) for 1.5 hours. After this it was left to cool for 24 h, followed by filtration, washing (EtOH), and drying to give (6.5 g, 89%)**. m.p.**= 241-242 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 2.14 (s, 3H, 2NCOC<u>H</u>$_3$), 7.32-7.49 (10H, ArC<u>H</u>), 8.40 (s, 1H, C8<u>H</u>), 10.63 (s, 1H, exchange with D_2O, N-<u>H</u>), 13.57 (s, 1H, exchange with D_2O, N-<u>H</u>). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 24.8 (<u>C</u>H$_3$CO), 117.3 (C5), 127.7-129.8 (10×Ar<u>C</u>H), 142.1 (2×Ar<u>C</u>), 144.4 (C8), 150.7 (C6), 152.4 (C4), 155.4 (C2), 156.4 (O<u>C</u>ON), 169.0 (CH$_3$<u>C</u>O). **IR** ν_{max}/cm^{-1}: 3327 (NH),

3161 (NH), 1714 (CO), 1629 (CO). **MS** *m/z* (ESI$^+$); calculated for ($C_{20}H_{16}N_6O_3$) $[M+H]^+$; 389.1357 found 389.1359.

N9 and N7-methyl guanine (52a and 52b)

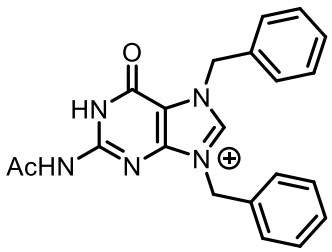


To cold mixture of NaH (1.1 eq) in 30 mL DMF was added (**56**) (1 g, 2.5 mmol). After 30 min iodomethane (1.2 eq) was added and the mixture was stirred at room temperature for 3 days under nitrogen. The solvent was evaporated under reduced pressure. Next, 50 mL EtOAc and 50 mL H_2O were poured to the residue. The organic layer was separated, washed with brine (50 ml × 2), dried over $MgSO_4$ and concentrated under pressure. Deprotection step was done by adding 60 mL (1:1) NH_3/MeOH to the product, reflux overnight. The solvent was removed under reduced pressure, and the residue was suspended in DCM (20 mL) and stirred for 30 min. Then the solid was filtered and washed with DCM to obtain the mixture of (**52a and 52b**) (0.18 g, 43%).

52a ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 3.50 (s, 3H, N9C$\underline{H}_3$), 6.07 (s, 2H, N$\underline{H}_2$), 7.61(s, 1H imidazole, C8$\underline{H}$).

52b ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 3.80 (s, 3H, N7C$\underline{H}_3$), 6.40 (s, 2H, N$\underline{H}_2$), 7.80 (s, 1H imidazole, C8$\underline{H}$).

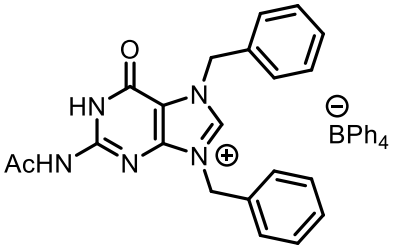
N^{2}acetyl-7,9-dibenzylguaninium bromide (58).[33]



2-N,9-diacetyl guanine (1.54 g, 6.5 mmol), DMAc (5 ml) and benzyl bromide (1.6 ml, 13.3 mmol) were added respectively. The reaction mixture was heated at 120 °C for 3 hours. The solution was poured into hot EtOAc (50 mL) with stirring. After cooling of the mixture, the solid began to separate after 2 hours then filtered and washed by acetone to give (2.0 g, 69%) of (**58**). **m.p.**= 213-214 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 2.19 (s, 3H, C$\underline{H}_3$CO), 5.47 (s, 2H, NC$\underline{H}_2$), 5.68 (s, 2H, NC$\underline{H}_2$), 7.21-7.48 (10H,

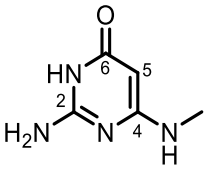
ArC<u>H</u>), 9.75 (s, 1H, C8<u>H</u>), 12.11 (s, 1H, ,exchange with D_2O, NH), 12.60 (s, 1H, exchange with D_2O, AcN<u>H</u>) .**^{13}C NMR** (100 MHz, DMSO-d_6) δ_C : 24.4 (<u>C</u>H_3CO), 48.9 (CH_2Ph), 52.1 (CH_2Ph), 110.9 (C5), 128.0-134.6 (10×Ar<u>C</u>H and 2×Ar<u>C</u>), 140.3 (C8), 148.0 (C4), 151.1 (C2), 151.8 (C6), 174.6 (CH_3<u>C</u>ON). **IR** ν_{max} /cm^{-1}: 3034 (NH), 1717 (CO), 1686 (CO). **MS** *m/z* (ESI$^+$); calculated for ($C_{21}H_{20}N_5O_2$) [M-Br]$^+$; 374.1612 found 374.1606.

2-acetamido-7,9-dibenzyl-6-oxo-6,9-dihydro-1H-purin-7-ium tetraphenylborate (60).



To a stirred solution of N^{2}acetyl-7,9-dibenzylguaninium bromide (1.0 g, 2.2 mmol) in 10 mL water was added a solution of sodium tetraphenylborate (0.75 g, 2.2 mmol) in 10 mL water, then filtration and drying in oven at 50 °C overnight to give (1.28g, 85%) of (**60**). **m.p.** = 174-175 °C (dec). **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 2.19 (s, 3H, C<u>H</u>$_3$CO), 5.45 (s, 2H, NC<u>H</u>$_2$), 5.67(s, 2H, NC<u>H</u>$_2$), 6.74-7.47 (30H, ArC<u>H</u>), 9.7 (s, 1H, C8<u>H</u>), 12.09 (br, s, 1H, exchange with D_2O, NH), 12.59 (br, s, 1H, exchange with D_2O, NH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 24.4 (<u>C</u>H_3CO), 48.9 (<u>C</u>H_2Ph), 52.2 (<u>C</u>H_2Ph), 110.9 (C5), 121.9 (4× tetraphenylborate Ar<u>C</u>H), 125.9 (8× tetraphenylborate Ar<u>C</u>H), 127.0-134.9 (Ar<u>C</u>H), 135.9 (8× tetraphenylborate Ar<u>C</u>H), 140.3 (C8), 148.0 (C2), 151.2 (C4), 151.9 (tetraphenylborate Ar<u>C</u>), 163.0 (tetraphenylborate Ar<u>C</u>), 163.5 (tetraphenylborate Ar<u>C</u>), 164.0 (tetraphenylborate Ar<u>C</u>), 164.5 (C6), 174.2 (CH_3<u>C</u>ON). **IR** ν_{max} /cm^{-1}: 3281(N-H), 3052 (CH), 1698 (CO).

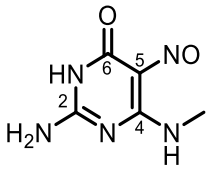
2-amino-6-hydroxy-4-methylamine pyrimidine (63).[30]



2-amino-6-chloro-4-hydroxy pyrimidine (1.0 g, 6.87 mmol) and ethanolic methylamine (5 mL) were heated in sealed tube at 120 °C for 5 hours. The solution was cooled, and precipitate was collected to give (0.74 g, 77%) of (**63**)**. m.p.**= 255-256 °C (lit 255-257).

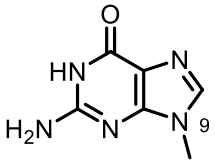
^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 2.65 (s, 3H, NC<u>H</u>$_3$), 4.34 (s, exchange with D_2O, N<u>H</u>), 6.10 (s, 2H, exchange with D_2O, NH_2), 6.26 (s, 1H, C<u>H</u>), 9.63 (s, 1H, exchange with D_2O, N<u>H</u>). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 28.3 (N<u>C</u>H$_3$), 75.0 (<u>C</u>5H), 155.1 (C4), 163.5 (C2), 165.3 (C6O). **IR** ν_{max} /cm^{-1}: 3345 (NH), 3112 (NH), 2909 (CH). **MS** *m/z* (ESI$^+$); calculated for ($C_5H_8N_4O$) $[M+H]^+$;141.0771 found 141.0774.

2-amino-6-hydroxy-4-methylamine -5-nitros pyrimidine (64).[30]



(0.75 g, 5.3 mmol) of (**63**) in 1:1 mixture of H_2O/AcOH (20 mL) was added $NaNO_2$ (0.73 g, 10.6 mmol) in H_2O (10 mL) at 0 °C. After that, the mixture was stirred to room temperature for 1.5 hour. After such time, the reaction flask was put in ice to cool to 0 °C and the precipitated was collected by filtration and washed by ethanol to give (0.65 g, 72%) of (**64**)**. m.p.**>300 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 2.86 (d, *J* 4.8 Hz, 3H, NC<u>H</u>$_3$), 6.86 (s, 2H, exchange with D_2O, N<u>H</u>$_2$), 10.78 (s, exchange with D_2O, N<u>H</u>), 12.27 (s, 1H, exchange with D_2O, N<u>H</u>). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 26.9 (<u>C</u>H3), 141.1 (C5), 153.3 (C4), 156.6 (C2), 161.8 (C6O). **IR** ν_{max} /cm^{-1}: 3524 (N-H), 3322 (NH), 2991 (CH), 1727 (CO), 1582 (str, N=O). **MS** *m/z* (ESI$^+$); calculated for ($C_5H_7N_5O_2$) $[M+H]^+$;170.0673 found 170.0673.

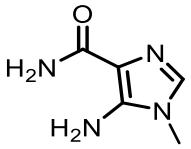
N^9 methyl guanine (52a).[30]



To mixture of (**64**) (0.9 g, 5.3 mmol), $HCONH_2$ (4.5 mL) and 90% HCO_2H (3.5 mL) was heated for 1 h. Next, $Na_2S_2O_4$ (1.0 g, 5.7 mmol) was added then the mixture was heated to 70 °C for 3 hours. After such time, the mixture was left to cool to room temperature and cooled to 0 °C. The precipitated was collected by filtration. Then it was dissolved in 1N HCl and neutralized with NH_4OH. The precipitated solid was collected by filtration to give (0.17 g, 20%) of (**52a**). **m.p.**>300 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 3.50 (s, 3H, NC<u>H</u>$_3$), 6.43 (s, 2<u>H</u>, exchange with D_2O, NH_2), 7.61 (s, 1H, C8<u>H</u>), 10.53 (s, 1H, exchange with D_2O, NH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 26.7 (<u>C</u>H$_3$), 116.8 (C5), 138.5 (C8), 151.9 (C4), 153.9 (C2), 157.2 (C6O). **MS** *m/z* (ESI$^+$);

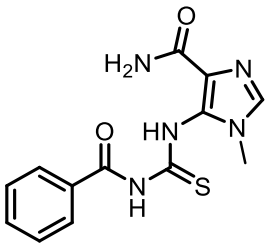
calculated for ($C_6H_7N_5O$) $[M+H]^+$;166.0723 found 166.0724. **IR** ν_{max} /cm^{-1}: 3315 (NH), 3160 (CH), 1618 (CO).

5-amino-1-methyl -1H- imidazol-4-carboxamide (66).[32]



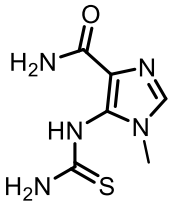
90 % KOH powder (0.88 g, 15.8 mmol) was added to solution of 5-amino- 1H-imidazol-4-carbobamide. HCl (**65**) (1 g, 7.92 mmol) in 10 mL DMF. At 0 °C on ice bath, the mixture was stirred for 5 hours. Next, iodomethane (0.5 mL, 7.92 mmol) was added dropwise over 2 hours at 0 °C. The precipitated product was separated by filtration and washed with MeOH to give (0.45 g, 41%) of (**66**)**. m.p.**= 258-259 (lit 251-255) °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 3.36 (s, 3H, NC<u>H</u>$_3$), 5.70 (s, 2H, exchange with D_2O, NH_2), 6.56 (s, 2H exchange with D_2O, NH_2), 7.04 (s, 1H, CH). **MS** *m/z* (ESI$^+$); calculated for ($C_5H_8N_4O$) $[M+H]^+$;141.0771 found 141.0769. **IR** ν_{max} /cm^{-1}: 3355 (NH), 3191 (CH), 1607 (CO).

5-(3-benzoylthioureido)-1-methyl-1H-imidazole-4-carboxamide (67).[32]



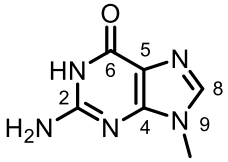
The mixture of (**66**) (0.43 g, 3.0 mmol), benzoyl isothiocyanate (0.5 mL, 3.7 mmol) and acetone (7 mL) were refluxed for 6 hours. After such time, the mixture was cooled on ice bath and the precipitated solid was filtrated and washed with acetone to give (0.56 g, 61%) of (**67**). **m.p.**= 198-200 °C (lit 194-6). **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 3.53 (s, 3H, NC<u>H</u>$_3$), 7.07 (s, 2H, exchange with D_2O, NH_2), 7.52-7.69 (5H, ArC<u>H</u>), 7.97(d, *J* 7.3 Hz, 1H, CH), 11.97 (s, 1H, exchange with D_2O, N-H), 12.05 (s, 1H, exchange with D_2O, NH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 31.7 (<u>C</u>H$_3$N), 127 (C4, imidazole), 129.0, 129.2, (Ar<u>C</u>H), 129.8 (Ar<u>C</u>), 132.3 (C5, imidazole), 133.8, 135.9 (Ar<u>C</u>H), 135.9 (CH, imidazole), 164.1 (CO), 168.6 (CO), 183.0 (C=S). **MS** *m/z* (ESI$^+$); calculated for ($C_{13}H_{13}N_5O_2S$) $[M+H]^+$; 304.0863 found 304.0861. **IR** ν_{max}/cm^{-1}: 3353 (NH), 3148 (CH), 1667 (CO), 1599 (CO).

1-methyl-5-thioureido-1H-imidazole-4-carboxamide (68).[32]



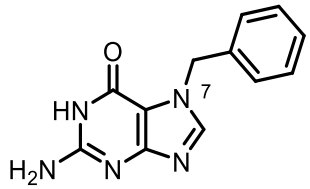
Potassium carbonate (0.11 g, 0.83 mmol) in water 2 mL was added to 5-(3-benzoylthioureido)-1-methyl-1H-imidazole-4-carboxamide (**67**) (0.5 g,1.64 mmol) in acetone – methanol (1:1, 8 mL). The reaction mixture was heated at 70 °C to reflux under nitrogen for 5 hours. After this time, 0.1 mL of acetic acid was added, cooling on ice bath, filtration and washing by acetone to give (0.21 g, 65%) of (**68**). **m.p.**= 254 °C (dec). **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 3.45 (s, 3 H, NC$\underline{H}_3$), 7.03 (s, 2H, NH_2), 7.18 (s, 2H, NH_2), 7.57 (s, 1H, CH), 9.19 (s, 1H, NH). **MS** *m/z* (ESI^+); calculated for ($C_6H_9N_5OS$) $[M+H]^+$; 200.0601 found 200.0600. **IR** ν_{max} /cm^{-1}: 3268 (NH), 3154 (CH), 1659 (CO).

N^9 methyl guanine (52a).[32]



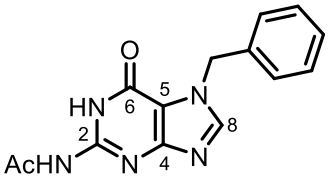
Copper (II) acetate monohydrate (0.3 g, 1.5 mmol) was added to 1-methyl-5-thioureido-1H-imidazole-4-carboxamide (**68**) (0.2 g, 1 mmol) in 1N NaOH (50 mL). The reaction mixture was heated to reflux for 1.5 h. After this time, the mixture cooled to 50 °C then filtered and the solid residue was washed by 1N NaOH. The filtrate was acidified with acetic acid to pH 5 and the precipitated product was filtered and dried in oven at 50 °C to give (0.12 g, 76%) of (**52a**). **m.p.**>300 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 3.50 (s, 3H, NC$\underline{H}_3$), 6.42 (s, 2H, exchange with D_2O, NH_2), 7.61 (s, 1H, C8$\underline{H}$), 10.51 (s, 1H, exchange with D_2O, NH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 29.7 ($\underline{C}H_3$), 116.9 (C5), 138.5 (C8), 151.9 (C4), 153.9 (C2), 157.3 (C6O). **IR** ν_{max} /cm^{-1}: 3348 (NH), 3171 (CH), 1678 (CO). **MS** *m/z* (ESI^+); calculated for ($C_6H_7N_5O$) $[M+H]^+$; 166.0723 found 166.0721.

N7- Benzyl guanine (70).[33]



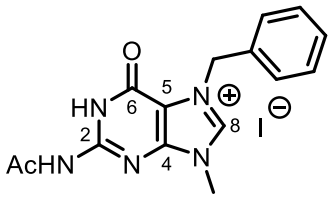
In 100 mL flask, guanosine (5 g, 17.6 mmol) was dissolved in 50 mL DMSO. After that, benzyl bromide (5 mL, 21 mmol) was added dropwise. The reaction was stirred overnight at room temperature. Then, 15 mL of HCl 37% was added in one portion at 60 °C. After stirring for 1 hour, the solution was poured into 300 mL methanol and was left one day for crystallization then the solid was collected by filtration. The product was dissolved in HCl (6M) and neutralized by 6M NaOH to give (4.0 g, 94%) of (**70**). **m.p.**>300 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 5.38 (s, 2H, NC<u>H</u>$_2$), 6.11 (s, 2H, exchange with D_2O, NH_2), 7.25-7.33 (5H, ArC<u>H</u>), 8.05 (s, 1H, C8H), 10.71 (s, 1H, exchange with D_2O, NH). **MS** *m/z* (ESI$^+$); calculated for ($C_{12}H_{11}N_5O$) $[M+H]^+$; 242.1036 found 242.1035. **IR** ν_{max} /cm^{-1}: 3401 (NH), 3126 (CH), 1706 (CO).

N^2-Acethyl - 7- benzyl guanine (71).[33]



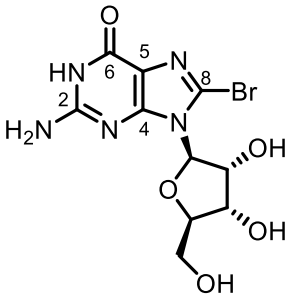
To suspension of (**70**) (1g, 4.1 mmol) in DMAc (10 mL) was added of Ac_2O (0.6 mL, 6.3 mmol). The reaction mixture was heated at 150 °C for 2 hours. The solvent was removed under reduced pressure and EtOAc (10 mL) was added to residue followed by filtration and washing by acetone to give (0.9 g, 77%) of (**71**)**. m.p.**= 238-239 °C (lit 236-238). **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 2.13 (s, 3H, C<u>H</u>$_3$CO), 5.48 (s, 2H, NC<u>H</u>$_2$), 7.26-7.33 (5H, ArC<u>H</u>), 8.33 (s, 1H, C8-<u>H</u>), 11.56 (s, 1H, exchange with D_2O, N-<u>H</u>), 12.09 (s, 1H, exchange with D_2O, AcN<u>H</u>). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 24.2 (<u>C</u>H$_3$CO), 49.6 (<u>C</u>H$_2$Ph), 111.6 (C5), 128.0 (2×Ar<u>C</u>H), 129.1 (2×Ar<u>C</u>H), 137.8 (Ar<u>C</u>), 144.6 (C8), 147.7 (C2), 157.7 (C6O), 173.6 (NH<u>C</u>OCH$_3$). **MS** *m/z* (ESI$^+$); calculated for ($C_{14}H_{13}N_5O_2$) $[M+H]^+$; 284.1142 found 284.1139. **IR** ν_{max} /cm^{-1}: 3138 (NH), 1713 (CO), 1684 (CO)**.**

2-acetamido-7-benzyl-9-methyl-6-oxo-6,9-dihydro-1H-purin-7-ium bromide (72).



To a suspension of (**71**) (0.85 g, 3.0 mmol) in DMF (5 mL) was added iodomethane (0.18 mL, 3.0 mmol). The reaction mixture was heated 40 °C and stirred for 3 days. After this time the solvent was removed *in vacuo* and the solid was washed by acetone to give (0.97 g, 86%) of (**72**). **m.p.**= 264 °C (dec). **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 2.19 (s, 3H, C$\underline{H}_3$CO), 3.808 (s, 3H, NC$\underline{H}_3$), 5.67 (s, 2H, NC$\underline{H}_2$), 7.19-7.47 (5H, ArC$\underline{H}$), 9.58 (s, 1H, C8$\underline{H}$), 12.19 (s, 1H, exchange with D_2O, N$\underline{H}$), 12.57 (s, 1H, exchange with D_2O, AcN$\underline{H}$). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 24.4 ($\underline{C}H_3CO$), 31.1 (N9$\underline{C}H_3$), 51.9 ($\underline{C}H_2Ph$), 110.4 (C5), 128.7 (2×Ar$\underline{C}$H), 129.3 (2×Ar$\underline{C}$H), 134.7 (Ar$\underline{C}$), 140.9 (C8), 148.4 (C4), 151.0 (C2), 151.8 (CO), 174.5 ($CH_3\underline{C}O$). **IR** ν_{max} /cm^{-1}: 3130 (NH), 3017 (CH), 1714 (CO), 1693 (CO). **MS** *m/z* (ESI$^+$); calculated for ($C_{15}H_{16}N_5O_2$) [M-I]$^+$; 298.1299 found 298.1296.

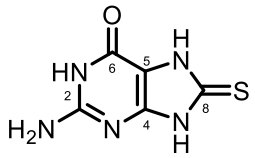
8-Bromoguanosine (73).[34]



To suspension of guanosine (2.0 g, 7.0 mmol) in 30 mL of dry DMF was added *N*-bromosuccinimide (1.4 g, 7.8 mmol) and the reaction mixture was stirred over the 3 days at room temperature. After such time. The mixture was concentrated in *vacuo*, then cold water added to the mixture and the precipitated solid was filtered and washed by acetone to give (1.64 g, 66%) of (**73**). **m.p.**= 210-211 °C (dec), (lit 201-203). **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 3.49 (m, 1H, C$\underline{H}_2$), 3.63 (m, 1H, C$\underline{H}_2$), 3.83 (m, 1H, C$\underline{H}$), 4.11 (m, 1H, C$\underline{H}$), 4.93 (t, *J* 5.5 Hz, 1H, OH), 4.99 (m, 1H, C$\underline{H}$), 5.1 (d, *J* 5.2 Hz, 1H, OH), 5.45 (d, *J* 6.2 Hz, 1H, OH), 5.66 (d, *J* 6.0 Hz., 1H, C$\underline{H}$) , 6.49 (s, 2H, NH_2), 10.82 (s, 1H, NH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 62.4 ($\underline{C}H_2$), 70.7 ($\underline{C}$H), 70.9 ($\underline{C}$H), 86.3 ($\underline{C}$H), 90.1 ($\underline{C}$H), 117.9 (C5), 121.6 (C8), 152.5 (C4), 153.9 (C2), 155.9

(C6O). **MS** *m/z* (ESI$^+$); calculated for ($C_{10}H_{12}BrN_5O_5$) $[M+H]^+$; 362.0095 found 362.0091. **IR** ν_{max} /cm^{-1}: 3118 (NH), 2933 (CH), 1680 (CO).

8-mercaptoguanine (75).



A mixture of 8-bromoguanosine (**73**) (1.0 g, 2.7 mmol) and thiourea (0.5 g, 6.5 mmol) in anhydrous ethanol (15 mL) was refluxed for 24 h. The mixture was cooled to room temperature; the solid was filtered, dried to give (0.4 g, 47%) of (**74**).

A mixture of 8-mercaptoguanosine (**74**) (0.4 g, 1.2 mmol) and 15 mL of 3N HCl was heated to 100 °C for 1.5 hours. The precipitated solid was filtrated and washed by acetone to give (0.11 g, 56%) of (**75**). **m.p.**>300 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 6.49 (s, 2H, NH_2), 10.8 (s, 1H, NH), 12.34 (s, 1H, NH), 12.52 (s, 1H, NH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 105.3 (C5), 151.1 (C4), 151.2 (C2), 154.4 (C6), 164.5 (C8). **IR** ν_{max} /cm^{-1}: 3407 (NH). **MS** *m/z* (ESI$^+$); calculated for ($C_5H_5N_5OS$) $[M+H]^+$; 184.0288 found 184.0281.

Preparation of compounds from 76a to 76ac.

General procedure (A): 76a-76g, 76q, 76t, 76u, 76w and 76x.

To a solution of 8-mercaptoguanine (0.1 g, 0.54 mmol) in 0.5N NaOH (3 mL) was added bromide derivative (0.61 mmol). The reaction mixture was stirred for time at room temperature. At this time, the solution was acidified by acetic acid and the precipitated solid was filtrated and washed by water then acetone to give product.

General procedure (B): 76h-76o, 76r, 76y and 76ac.

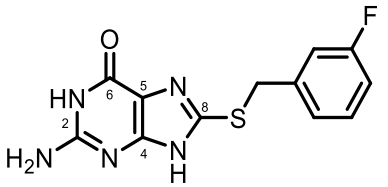
To a solution of 8-mercaptoguanine (0.1 g, 0.54 mmol) in 0.5N NaOH (3 mL) was added bromide derivative (0.61 mmol) in ethanol or acetone (0.8 mL). The reaction mixture was stirred for time at room temperature. At this time, the solution was acidified by acetic acid and the precipitated solid was filtrated and washed by water then acetone to give product.

General procedure (C): 76s, 76v, 76z and 76aa.

To a stirred solution of sodium hydride (1.1 eq) in DMF (3 mL) was added via syringe a solution of 8-mercaptoguanine (0.1 g, 0.54 mmol) in DMF (3 mL) and the reaction was stirred for 30 min. Bromide derivative (0.61 mmol) was added dropwise, and after complete addition the reaction was stirred for time at room temperature. At this time,

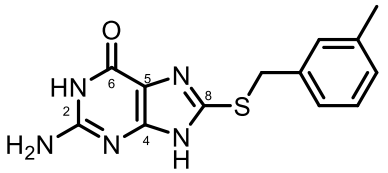
the solvent was removed by vacuum and the residue was quenched by water, the solid was filtered and washed by acetone.

2-amino-8-((3-fluorobenzyl)thio)-1,9-dihydro-6H-purin-6-one (76a).



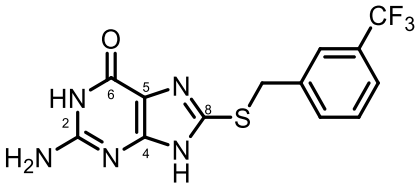
Following procedure (A) outlined above, the product (**76a**) was isolated as solid (69 mg, 44%, Table 4, Entry 1). **m.p.**= 229 °C (dec). **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 4.37 (s, 2H, SC<u>H</u>$_2$), 6.32 (s, 2H, exchange with D_2O, N<u>H</u>$_2$), 7.03-7.34 (4H, ArC<u>H</u>), 10.54 (br, 1H exchange with D_2O, NH), 12.54 (s, exchange with D_2O, NH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 35.5 (S<u>C</u>H$_2$), 114.4 (d, *J* 20.5 Hz, Ar<u>C</u>H), 115.8 (d, *J* 21.5 Hz, Ar<u>C</u>H), 117.7 (C5), 125.3 (Ar<u>C</u>H), 130.7 (d, *J* 8.5 Hz, Ar<u>C</u>H), 141.2 (d, *J* 7.5 Hz, Ar<u>C</u>), 148.7 (C8), 153.7 (C4), 154.0 (C2), 156.2 (C6O), 162.4 (d, *J* 242.0 Hz, Ar<u>C</u>F). ^{19}F **NMR** (376.5 MHz, DMSO-d_6) δ_F -113.3 (Ar-F). **IR** ν_{max} /cm^{-1}: 3315(NH), 3099 (CH), 1651(CO). **MS** *m/z* (ESI$^+$); calculated for ($C_{12}H_{10}FN_5O$) $[M+H]^+$; 292.0663 found 292.0667.

2-amino-8-((3-methylbenzyl)thio)-1,9-dihydro-6H-purin-6-one (76b).



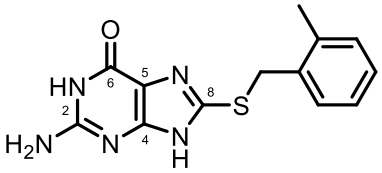
Following procedure (A) outlined above, the product (**76b**) was isolated as solid (100 mg, 64%, Table 4, Entry 2). **m.p.**= 280 °C (dec). **H^{1} NMR** (400 MHz, DMSO-d_6) δ_H: 2.23 (s, 3H, C<u>H</u>$_3$Ar), 4.33 (s, 2H, C<u>H</u>$_2$Ar), 6.50 (s, 2H, N<u>H</u>$_2$), 7.02-7.17 (m, 4H, ArC<u>H</u>), 11.09 (s, br ,1H, N<u>H</u>). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 21.3 (<u>C</u>H$_3$Ar), 36.1 (<u>C</u>H$_2$Ar), 115.6 (C5), 126.3 (Ar<u>C</u>H), 128.3 (ArCH), 128.8 (Ar<u>C</u>H), 129.8 (Ar<u>C</u>H), 137.9 (Ar<u>C</u>), 138.0 (Ar<u>C</u>), 143.5 (C8), 153.7 (C4), 155.7 (C2, C6O). **MS** *m/z* (ESI$^+$); calculated for ($C_{13}H_{13}N_5OS$) $[M+H]^+$; 288.0914 found 288.0913. **IR** ν_{max} /cm^{-1}: 3311 (NH), 3072 (CH), 2862 (CH), 1651 (CO).

2-amino-8-((3-(trifluoromethyl)benzyl)thio)-1,9-dihydro-6H-purin-6-one (76c).



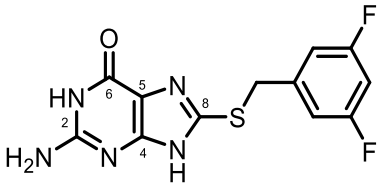
Following procedure (A) outlined above, the product (**76c**) was isolated as solid (107 mg, 62%, Table 4, Entry 3). **m.p.**= 275 °C (dec). **H[1] NMR** (400 MHz, DMSO-d_6) δ_H: 4.45 (s, 2H, C<u>H</u>$_2$Ar), 6.30 (s, 2H, N<u>H</u>$_2$), 7.51-7.71 (m, 4H, ArC<u>H</u>), 10.63 (s, br, 1H, N<u>H</u>), 12.59 (s, br, 1H, N<u>H</u>). **MS** *m/z* (ESI$^+$); calculated for ($C_{13}H_{10}F_3N_5OS$) $[M+H]^+$; 342.0631 found 342.0626. **IR** ν_{max} /cm^{-1}: 3308 (NH), 3136 (CH), 2873 (CH), 1651 (CO), 1329 ($ArCF_3$), 1115 (CF).

2-amino-8-((2-methylbenzyl)thio)-1,9-dihydro-6H-purin-6-one (76d).



Following procedure (A) outlined above, the product (**76d**) was isolated as solid (103 mg, 72%, Table 4, Entry 4). **m.p.**= 290 °C (dec). **H[1] NMR** (400 MHz, DMSO-d_6) δ_H: 2.34 (s, 3H, C<u>H</u>$_3$), 4.37 (s, 2H, C<u>H</u>$_2$), 6.38 (s, br, 2H, N<u>H</u>$_2$), 7.09-7.28 (m, 4H, ArC<u>H</u>), 10.81 (s, br, 1H, N<u>H</u>), 12.66 (s, br, 1H, N<u>H</u>). **^{13}C NMR** (100MHz, DMSO-d_6) δ_C: 19.2 (<u>C</u>H$_3$Ar), 34.6 (<u>C</u>H$_2$Ar), 115.9 (C5), 126.4 (Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 130.1 (Ar<u>C</u>H), 130.7 (Ar<u>C</u>H), 135.5 (Ar<u>C</u>), 137.0 (C4), 143.5 (C8), 153.8 (C2), 155.9 (C6O). **MS** *m/z* (ESI$^+$); calculated for ($C_{13}H_{13}N_5OS$) $[M+H]^+$; 288.0914 found 288.0914. **IR** ν_{max} /cm^{-1}: 3304 (NH), 3066 (CH), 2856 (CH), 1658 (CO).

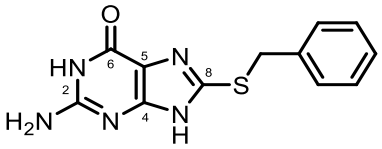
2-amino-8-((3,5-difluorobenzyl)thio)-1,9-dihydro-6H-purin-6-one (76e).



Following procedure (A) outlined above, the product (**76e**) was isolated as solid (116 mg, 75%, Table 4, Entry 5). **m.p.**= 293 °C (dec). **H[1] NMR** (400 MHz, DMSO-d_6) δ_H: 4.38 (s, 2H, CH_2Ar), 6.63 (s, br, 2H, N<u>H</u>$_2$), 7.07-7.10 (m, 3H, ArC<u>H</u>), 11.01 (s, br, 1H, N<u>H</u>), 12.65 (s, br, 1H, N<u>H</u>). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 35.0 (<u>C</u>H$_2$Ar), 103.1 (t, *J* 25.5 Hz, Ar<u>C</u>H), 112.2 (d, *J* 6.5 Hz, Ar<u>C</u>H), 112.4 (d, *J* 6.5 Hz, Ar<u>C</u>H), 116.3 (C5),

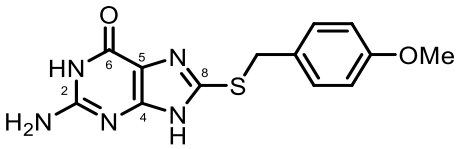
143.2 (ArC), 143.3 (C4), 143.4 (C8), 153.9 (C2), 155.6 (C6O), 161.2 (d, *J* 13.5 Hz, CF), 163.7 (d, *J* 13.5 Hz CF). ^{19}F **NMR** (376.5 MHz, DMSO-d$_6$) δ_F: -110.03 (Ar-F). **MS** *m/z* (ESI$^+$); calculated for ($C_{12}H_9F_2N_5OS$) $[M+H]^+$; 310.0569 found 310.0558. **IR** ν_{max} /cm^{-1}: 3322 (NH), 3164 (CH), 2858 (CH), 1658 (CO), 1113 (C-F).

2-amino-8-(benzylthio)-1,9-dihydro-6H-purin-6-one (76f).



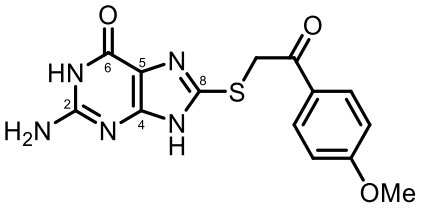
Following procedure (A) outlined above, the product (**76f**) was isolated as solid (92 mg, 65%, Table 4, Entry 6). **m.p.**= 295 °C (dec). **H^1 NMR** (400 MHz, DMSO-d$_6$) δ_H: 4.36 (s, 2H, C<u>H</u>$_2$), 6.33 (s, br, 2H, N<u>H</u>$_2$), 7.24-7.34 (5H, ArC<u>H</u>), 10.71 (s,, br, 1H, N<u>H</u>), 12.55 (br, 1H, N<u>H</u>). **^{13}C NMR** (100 MHz, DMSO-d$_6$) δ_C: 36.1 (SCH_2), 116.8 (C5), 127.7 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>H), 129.2 (Ar<u>C</u>H), 138.1 (Ar<u>C</u>), 142.0 (C8), 153.6 (C2), 155.5 (C6O). **MS** *m/z* (ESI$^+$); calculated for ($C_{12}H_{11}N_5OS$) $[M+H]^+$; 274.0757 found 274.0755. **IR** ν_{max} /cm^{-1}: 3306 (NH), 3027 (CH), 2684 (CH), 1651 (CO).

2-amino-8-((4-methoxybenzyl)thio)-1,9-dihydro-6H-purin-6-one (76g).



Following procedure (A) outlined above, the product (**76g**) was isolated as solid (33 mg, 20%, Table 4, Entry 7). **m.p.**= 242 °C (dec). **^{1}H NMR** (400 MHz, DMSO-d$_6$) δ_H: 3.69 (s, 3H, OC<u>H</u>$_3$), 4.29 (s, 2H, C<u>H</u>$_2$), 6.51 (s, br, 2H, N<u>H</u>$_2$), 6.83 (d, *J* 8.2 Hz, 2H, ArC<u>H</u>), 7.26 (d, *J* 8.1 Hz, 2H, ArC<u>H</u>), 10.97 (s, br, 1H, N<u>H</u>), 12.07 (br, 1H, N<u>H</u>). **MS** *m/z* (ESI$^+$); calculated for ($C_{13}H_{13}N_5O_2S$) $[M+H]^+$; 304.0863 found 304.0863. **IR** ν_{max} /cm^{-1}: 3081 (NH), 2752 (CH), 1607 (CO), 1029 (OMe).

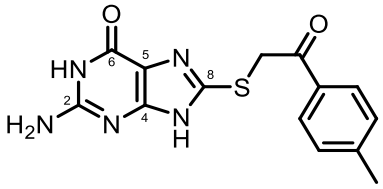
2-amino-8-((2-(4-methoxyphenyl)-2-oxoethyl)thio)-1,9-dihydro-6H-purin-6-one (76h).



Following procedure (B) outlined above, the product (**76h**) was isolated as solid (146 mg, 82%, Table 4, Entry 8). **m.p.**= 280 °C (dec). **^{1}H NMR** (400 MHz, DMSO-d$_6$) δ_H:

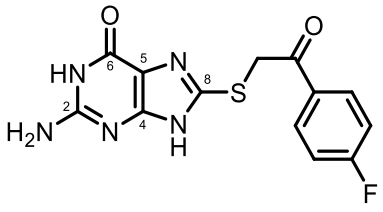
3.83 (s, 3H, OC<u>H</u>$_3$), 4.78 (s, 2H, C<u>H</u>$_2$), 6.26 (s, br, 2H, N<u>H</u>$_2$), 7.04 (d, *J* 8.7 Hz, 2H, ArC<u>H</u>), 8.00 (d, *J* 8.6 Hz, 2H, ArC<u>H</u>), 10.66 (br, 1H, N-<u>H</u>), 12.49 (br, 1H, N-<u>H</u>). **^{13}C NMR** (100 MHz, DMSO-d$_6$) δ_C: 31.1 (S-<u>C</u>H$_2$), 56.0 (O<u>C</u>H$_3$), 114.6 (Ar<u>C</u>H), 114.7 (Ar<u>C</u>H), 115.6 (C5), 128.6 (Ar<u>C</u>), 131.2 (2×Ar<u>C</u>H), 140.7 (C8), 151.3 (C2), 154.4 (C6O), 163.7 (Ar<u>C</u>), 192.3 (CO). **MS** *m/z* (ESI$^+$); calculated for ($C_{14}H_{13}N_5O_3S$) $[M+H]^+$; 332.0812 found 332.0808. **IR** ν_{max}/cm^{-1}: 3322 (NH), 3081(CH), 2923 (CH), 1651 (CO), 1700 (CO), 1021 (OMe).

2-amino-8-((2-oxo-2-(p-tolyl)ethyl)thio)-1,9-dihydro-6H-purin-6-one (76i).



Following procedure (B) outlined above, the product (**76i**) was isolated as solid (137 mg, 81%, Table 4, Entry 9). **m.p.**= 271 °C (dec). **^{1}H NMR** (400 MHz, DMSO-d$_6$) δ_H: 2.37 (s, 3H, ArC<u>H</u>$_3$), 4.83 (s, 2H, C<u>H</u>$_2$), 6.26 (s, br, 2H, N<u>H</u>$_2$), 7.34 (d, *J* 8.0 Hz, 2H, ArC<u>H</u>), 7.90 (d, *J* 8.0 Hz, 2H, ArC<u>H</u>), 10.52 (br, 1H, N-<u>H</u>), 12.51 (br, 1H, N-<u>H</u>).). **^{13}C NMR** (100 MHz, DMSO-d$_6$) δ_C: 21.6 (Ar<u>C</u>H$_3$), 39.9 (S-<u>C</u>H$_2$), 117.5 (C5), 128.9 (2×Ar<u>C</u>H), 129.5 (2×Ar<u>C</u>H), 133.2 (Ar<u>C</u>), 140.7 (C8), 144.6 (Ar<u>C</u>), 153.7 (C2), 156.0 (C6O), 193.5 (CO). **MS** *m/z* (ESI$^+$); calculated for ($C_{16}H_{13}N_5O_2S$) $[M+H]^+$; 316.0863 found 316.0868. **IR** ν_{max} /cm^{-1}: 3331 (NH), 3161(CH), 2919 (CH), 1651 (CO), 1680 (CO).

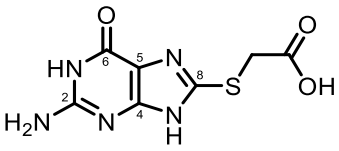
2-amino-8-((2-(4-fluorophenyl)-2-oxoethyl)thio)-1,9-dihydro-6H-purin-6-one (76j).



Following procedure (B) outlined above, the product (**76j**) was isolated as solid (98 mg, 57%, Table 4, Entry 10). **m.p.**= 263 °C (dec). **^{1}H NMR** (400 MHz, DMSO-d$_6$) δ_H: 4.80 (s, 2H, C<u>H</u>$_2$), 6.57 (s, br, 2H, N<u>H</u>$_2$), 7.36 (t, *J* 8.8 Hz, 2H, ArC<u>H</u>), 8.1 (dd, *J* 5.6 Hz, 8.6 Hz, 2H, ArC<u>H</u>), 10.51 (br, 1H, N<u>H</u>), 12.53 (br, 1H, N<u>H</u>). **^{13}C NMR** (100 MHz, DMSO-d$_6$) δ_C: 31.1 (S<u>C</u>H$_2$), 105.3 (C5), 116.3 (d, *J* 22.0, 2×Ar<u>C</u>H), 131.9 (d, *J* 9.5, 2×Ar<u>C</u>H), 132.6 (Ar<u>C</u>), 151.1 (C8), 153.6 (C2), 154.6 (C6O), 164.4 (d, *J* 3.5, CF), 192.6 (CO).

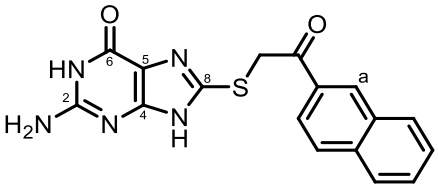
^{19}F NMR (376.5 MHz, DMSO-d_6) δ_F: -105.2 (Ar-F). **MS** *m/z* (ESI$^+$); calculated for ($C_{13}H_{10}FN_5O_2S$) $[M+H]^+$; 320.0612 found 320.0617. **IR** ν_{max} /cm^{-1}: 3324 (NH), 3078 (CH), 2923 (CH), 1650 (CO), 1156 (C-F).

S-(2-amino-6-oxo-6,9-dihydro-1H-purin-8-yl) 2-hydroxyethanethioate (76k).



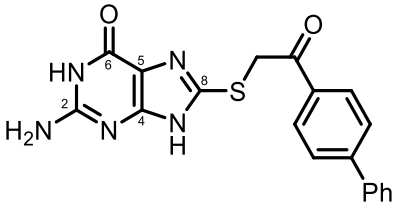
Following procedure (B) outlined above, the product (**76k**) was isolated as solid (114 mg, 88%, Table 4, Entry 11). **m.p.**>300 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 3.96 (s, 2H, C$\underline{H}_2$), 6.24 (s, br, 2H, N$\underline{H}_2$), 10.51 (s, br, 1H, N-$\underline{H}$), 12.88 (br, 1H, N-$\underline{H}$). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 34.1 (S-$\underline{C}H_2$), 115.4 (C5), 143.2 (C8), 153.6 (C2), 155.4 (C6O), 170.2 (CO). **MS** *m/z* (ESI$^+$); calculated for ($C_7H_7N_5O_3S$) $[M+H]^+$; 242.03 found 242.0338. **IR** ν_{max} /cm^{-1}: 3081 (NH), 2921 (CH), 1673 (CO).

2-amino-8-((2-(naphthalen-2-yl)-2-oxoethyl)thio)-1,9-dihydro-6H-purin-6-one (76l).



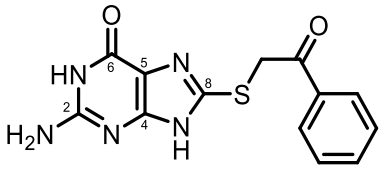
Following procedure (B) outlined above, the product (**76l**) was isolated as solid (117 mg, 62%, Table 4, Entry 12). **m.p.**= 241 °C (dec). **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 4.97 (s, 2H, C$\underline{H}_2$), 6.11 (s, br, 2H, N$\underline{H}_2$), 7.59-8.69 (2H, ArC$\underline{H}$), 7.98-8.03 (3H, ArC$\underline{H}$), 8.09-8.11 (1H, ArCH), 8.80 (s, 1H, ArC$\underline{H}_a$), 10.38 (s, 1H, N-$\underline{H}$), 12.48 (1H, N$\underline{H}$). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 39.9 (S$\underline{C}H_2$), 115.8 (C5), 124.1 (Ar$\underline{C}$H), 127.5 (Ar$\underline{C}$H), 128.1 (Ar$\underline{C}$H), 128.8 (Ar$\underline{C}$H), 129.3 (Ar$\underline{C}$H), 130.1 (Ar$\underline{C}$H), 131.1 (Ar$\underline{C}$H), 132.5 (Ar$\underline{C}$), 133.1 (Ar$\underline{C}$), 135.6 (Ar$\underline{C}$), 143.7 (C8), 153.5 (C4), 155.6 (C2), 156.5 (C6O), 194.1 (CO). **MS** *m/z* (ESI$^+$); calculated for ($C_{17}H_{13}N_5O_2S$) $[M+H]^+$; 352.0863 found 352.0864. **IR** ν_{max} /cm^{-1}: 3306 (NH), 3121 (CH), 1667 (CO), 1620 (CO).

8-((2-([1,1'-biphenyl]-4-yl)-2-oxoethyl)thio)-2-amino-1,9-dihydro-6H-purin-6-one (76m).



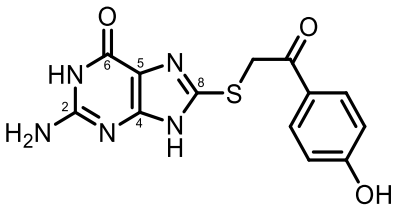
Following procedure (B) outlined above, the product (**76m**) was isolated as solid (141 mg, 69%, Table 4, Entry 13). **m.p.**= 261 °C (dec). **^{1}H NMR** (400 MHz, DMSO-d$_6$) δ_H: 4.83 (s, 2H, C<u>H</u>$_2$), 6.18 (s, 2H, N<u>H</u>$_2$), 7.40-7.44 (m, 3H, ArC<u>H</u>), 7.52 (d, *J* 7.8 Hz, 2H, ArC<u>H</u>), 7.76 (d, *J* 8 Hz, 2H, ArC<u>H</u>), 8.11 (d, *J* 8 Hz, 2H, ArC<u>H</u>), 10.53 (s, br,1H, N<u>H</u>), 12.63 (s, br,1H, N<u>H</u>). **^{13}C NMR** (100 MHz, DMSO-d$_6$) δ_C: 39.7 (S<u>C</u>H$_2$), 117.4 (C5), 127.1 (Ar<u>C</u>H), 127.3 (2×Ar<u>C</u>H), 127.5 (2×Ar<u>C</u>H), 129.5 (2×Ar<u>C</u>H), 129.6 (2×Ar<u>C</u>H), 130.1 (Ar<u>C</u>), 134.7 (Ar<u>C</u>), 139.3 (Ar<u>C</u>), 145.2 (C8), 152.6 (C4), 156.4 (C2), 158.8 (C6O), 194.5 (CO). **MS** *m/z* (ESI$^+$); calculated for ($C_{19}H_{15}N_5O_2S$) $[M+H]^+$; 378.1019 found 378.1038. **IR** ν_{max} /cm^{-1}: 3317 (NH), 3104 (CH), 2914 (CH), 1650 (CO), 1600 (CO).

2-amino-8-((2-oxo-2-phenylethyl)thio)-1,9-dihydro-6H-purin-6-one (76n).



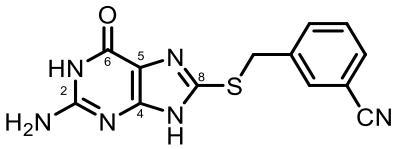
Following procedure (B) outlined above, the product (**76n**) was isolated as solid (159 mg, 98%, Table 4, Entry 14). **m.p.**= 265 °C (dec). **^{1}H NMR** (400 MHz, DMSO-d$_6$) δ_H: 4.84 (s, 2H, C<u>H</u>$_2$), 6.35 (s, 2H, N<u>H</u>$_2$), 7.51-7.55 (2H, ArC<u>H</u>), 7.64-7.68 (1H, ArC<u>H</u>), 8.00-8.02 (2H, ArC<u>H</u>), 10.84 (s, br, 1H, N<u>H</u>), 12.39 (s, br, 1H, N<u>H</u>). **^{13}C NMR** (100 MHz, DMSO-d$_6$) δ_C: 39.9 (S-<u>C</u>H$_2$), 117.0 (C5), 128.8 (2×Ar<u>C</u>H), 129.2 (2×Ar<u>C</u>H), 134.1 (Ar<u>C</u>H), 135.8 (Ar<u>C</u>), 144.1 (C8), 153.6 (C4 and C2), 155.6 (C6O), 194.0 (CO). **MS** *m/z* (ESI$^+$); calculated for ($C_{13}H_{11}N_5O_2S$) $[M+H]^+$; 302.0706 found 302.0711. **IR** ν_{max} /cm^{-1}: 3312 (NH), 3114 (CH), 2910 (CH), 1650 (CO).

2-amino-8-((2-(4-hydroxyphenyl)-2-oxoethyl)thio)-1,9-dihydro-6H-purin-6-one (76o).



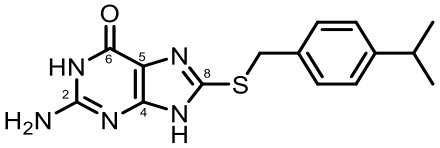
Following procedure (B) outlined above, the product (**76o**) was isolated as solid (167 mg, 98%, Table 4, Entry 15). **m.p.**= 234 °C (dec). **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 4.77 (s, 2H, C$\underline{H}_2$), 6.26 (s, 2H, N$\underline{H}_2$), 6.85 (d, *J* 8.1 Hz, 2H, ArC$\underline{H}$), 7.88 (d, *J* 8.1 Hz, 2H, ArC$\underline{H}$), 10.47 (s, 1H, N$\underline{H}$), 10.53 (s, 1H, OH), 12.51 (s, br, 1H, N$\underline{H}$). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 39.7 (S$\underline{C}$H$_2$), 115.8 (2×Ar$\underline{C}$H), 116.0 (C5), 127.2 (Ar$\underline{C}$), 131.5 (2×Ar$\underline{C}$H), 152.3 (C8), 153.5 (C4), 154.0 (C2), 155.5 (C6O), 162.9 (Ar$\underline{C}$), 191.9 (CO). **MS** *m/z* (ESI$^+$); calculated for ($C_{13}H_{11}N_5O_3S$) $[M+H]^+$; 318.0655 found 318.0650. **IR** ν_{max} /cm^{-1}: 3115 (NH), 2915 (CH), 1651 (CO), 1578 (CO).

3-(((2-amino-6-oxo-6,9-dihydro-1H-purin-8-yl)thio)methyl)benzonitrile (76p).



Following procedure (A) outlined above, the product (**76p**) was isolated as solid (71 mg, 44%, Table 4, Entry 16). **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 4.40 (s, 2H, C$\underline{H}_2$), 6.33 (2H, N$\underline{H}_2$), 7.35-7.94 (4H, ArC$\underline{H}$), 10.67 (s, br, 1H, N$\underline{H}$), 12.53 (s, br, 1H, N$\underline{H}$). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 35.19 ($\underline{C}$H$_2$), 110.2 (C5) 111.7, (Ar$\underline{C}$CN), 119.1 (Ar$\underline{C}$N), 128.7 (Ar$\underline{C}$H), 130.1 (Ar$\underline{C}$H), 132.8 (Ar$\underline{C}$H), 134.2 (Ar$\underline{C}$H), 138.2 (Ar$\underline{C}$), 140.42 (C8), 153.7 (C4), 155.8 (C2) 156.0 (C6O). **MS** *m/z* (ESI$^+$); calculated for ($C_{13}H_{10}N_6OS$) $[M+H]^+$; 299.071 found 299.0719. **IR** ν_{max} /cm^{-1}: 3320 (NH), 3090 (CH), 2873 (CH), 2228 (CN), 1650 (CO).

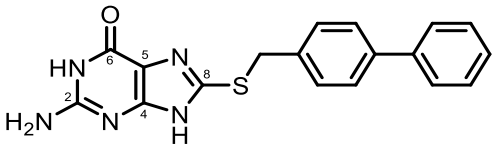
2-amino-8-((4-isopropylbenzyl)thio)-1,9-dihydro-6H-purin-6-one (76q).



Following procedure (A) outlined above, the product (**76q**) was isolated as solid (22 mg, 13%, Table 4, Entry 17). **m.p.**= 291 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 1.15 (d, *J* 6.6 Hz, 6H, 2×C$\underline{H}_3$), 2.82 (m, 1H, CH), 4.31 (s, 2H, C$\underline{H}_2$), 6.30 (2H, N$\underline{H}_2$), 7.14-

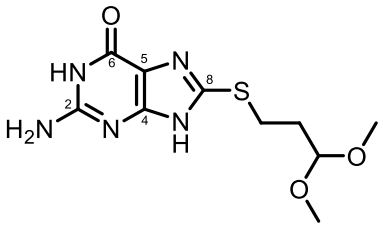
7.35 (4H, ArC<u>H</u>), 10.17 (s, 1H, N<u>H</u>), 12.49 (s, 1H, N<u>H</u>). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 24.3 (2×CH_3), 33.5 (CH), 35.8 (SCH_2), 117.6 (C5), 125.1 (2×Ar<u>C</u>H), 129.2 (Ar<u>C</u>H), 129.2 ((2×Ar<u>C</u>H), 135.4 (Ar<u>C</u>), 141.1 (C8), 147.9 (ArC), 153.6 (C4), 154.5 (C2), 156.2 (C6O). **MS** *m/z* (ESI^+); calculated for ($C_{15}H_{17}N_5OS$) $[M+H]^+$; 316.1227 found 316.1224. **IR** ν_{max} /cm^{-1}: 3301 (NH), 3147 (CH), 2957 (CH), 2868 (CH), 1666 (CO).

8-(([1,1'-biphenyl]-4-ylmethyl)thio)-2-amino-1,9-dihydro-6H-purin-6-one (76r).



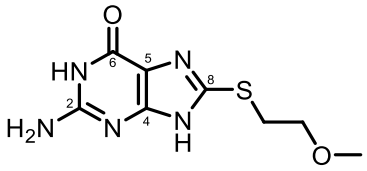
Following procedure (B) outlined above, the product (**76r**) was isolated as solid (105 mg, 58%, Table 4, Entry 18). **m.p.**>300 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 4.42 (s, 2H, C<u>H</u>$_2$Ar), 6.34 (2H, N<u>H</u>$_2$), 7.30-7.62 (9H, ArC<u>H</u>), 10.68 (s, br, 1H, N<u>H</u>), 12.57 (s, br, 1H, N<u>H</u>). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 35.7 (S<u>C</u>H$_2$), 117.3 (C5), 127.0 (2×Ar<u>C</u>H), 127.2 (2×Ar<u>C</u>H), 127.8 (Ar<u>C</u>H), 129.3 (2×Ar<u>C</u>H), 129.8 (Ar<u>C</u>H), 137.5 (Ar<u>C</u>), 139.5 (Ar<u>C</u>), 140.3 (Ar<u>C</u>), 144.3 (C8), 153.6 (C4 and C2), 155.84 (C6). **MS** *m/z* (ESI^+); calculated for ($C_{18}H_{15}N_5OS$) $[M+H]^+$; 350.107 found 350.1073. **IR** ν_{max} /cm^{-1}: 3317 (NH), 3150 (CH), 2871 (CH), 1651 (CO).

2-amino-8-((3,3-dimethoxypropyl)thio)-1,9-dihydro-6H-purin-6-one (76u).



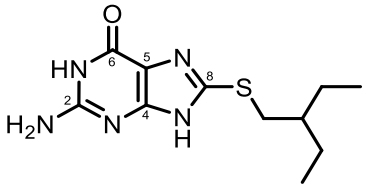
Following procedure (A) outlined above, the product (**76u**) was isolated as solid (89 mg, 58%, Table 4, Entry 19). **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 1.86 (q, 2H, SCH_2C<u>H</u>$_2$), 3.06 (t, *J* 7.2 Hz, 1H, C<u>H</u>), 3.20 (s, 6H, 2 × C<u>H</u>$_3$), 4.43 (t, *J* 5.5 Hz, 2H, SC<u>H</u>$_2$), 6.28 (s, 2H, N<u>H</u>$_2$), 10.58 (s, 1H, N<u>H</u>). 12.45 (s, 1H, N<u>H</u>). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 27.5 (<u>C</u>H$_2$S), 32.9 (SCH_2<u>C</u>H$_2$), 53.1 (2×O<u>C</u>H$_3$), 103.5 (<u>C</u>H), 116.5 (C5), 143.9 (C8), 154.0 (C4), 155.6 (C2), 156.4 (C6O). **MS** *m/z* (ESI^+); calculated for ($C_{10}H_{15}N_5O_3S$) $[M+H]^+$; 286.0968 found 286.0982. **IR** ν_{max} /cm^{-1}: 3305 (NH), 3142 (CH), 2934 (CH).

2-amino-8-((2-methoxyethyl)thio)-1,9-dihydro-6H-purin-6-one (76v).



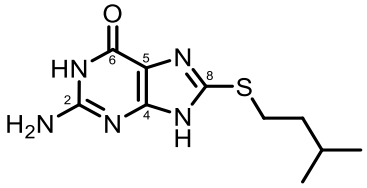
Following procedure (A) outlined above, the product (**76v**) was isolated as solid (95 mg, 73%, Table 4, Entry 20). **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 3.23 (s, 3H, C$\underline{H}_3$O), 3.25 (t, *J* 6.4 Hz, 2H, C$\underline{H}_2$), 3.54 (t, *J* 6.4 Hz, 2H, SC$\underline{H}_2$), 6.67 (2H, N$\underline{H}_2$), 11.61 (s, br, 1H, N$\underline{H}$). **MS** *m/z* (ESI$^+$); calculated for ($C_8H_{11}N_5O_2S$) $[M+H]^+$; 242.0706 found 242.0711. **IR** ν_{max} /cm^{-1}: 3330 (NH), 3099 (CH), 1674 (CO), 1098 (OMe).

2-amino-8-((2-ethylbutyl)thio)-1,9-dihydro-6H-purin-6-one (76w).



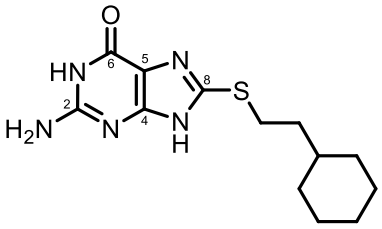
Following procedure (C) outlined above, the product (**76w**) was isolated as solid (137 mg, 95%, Table 4, Entry 21). **m.p.**>300 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 0.82 (t, *J* 7.3 Hz, 6H, 2× C$\underline{H}_3$), 1.35 (m, 4H, 2 × C$\underline{H}_2$), 1.49 (m, 1H, C$\underline{H}$), 3.12 (d, *J* 4.8 Hz, 2H, SC$\underline{H}_2$), 6.24 (s, 2H, N$\underline{H}_2$), 10.49 (s, 1H, N$\underline{H}$), 12.47 (s, 1H, N$\underline{H}$). **MS** *m/z* (ESI$^+$); calculated for ($C_{11}H_{17}N_5OS$) $[M+H]^+$; 268.1227 found 268.1231. **IR** ν_{max} /cm^{-1}: 3325 (NH), 3089 (CH), 2960 (CH), 2870 (CH), 1650 (CO).

2-amino-8-(isopentylthio)-1,9-dihydro-6H-purin-6-one (76x).



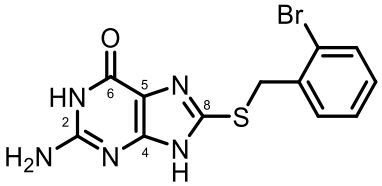
Following procedure (A) outlined above, the product (**76x**) was isolated as solid (112 mg, 82%, Table 4, Entry 22). **m.p.**= 293 °C (dec). **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 0.85 (d, *J* 6.6 Hz, 6H, 2×C$\underline{H}_3$), 1.48 (m, 2H, C$\underline{H}_2$), 1.63 (m, 1H, CH), 3.09 (2H, SC$\underline{H}_2$), 6.31 (s, 2H, N$\underline{H}_2$), 10.63 (s, 1H, N$\underline{H}$). 12.47 (s, 1H, N$\underline{H}$). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 22.5 (2×$\underline{C}$H$_3$), 27.2 ($\underline{C}$H), 30.1 (CH$\underline{C}$H$_2$), 38.6 (S$\underline{C}$H$_2$), 117.6 (C5), 141.5 (C8), 153.5 (C4 and C2), 156.1 (C6O). **MS** *m/z* (ESI$^+$); calculated for ($C_{10}H_{15}N_5OS$) $[M+H]^+$; 254.107 found 254.1076. **IR** ν_{max} /cm^{-1}: 3306 (NH), 3122 (CH), 2934 (CH), 2867 (CH), 1657 (CO).

2-amino-8-((2-cyclohexylethyl)thio)-1,9-dihydro-6H-purin-6-one (76y).



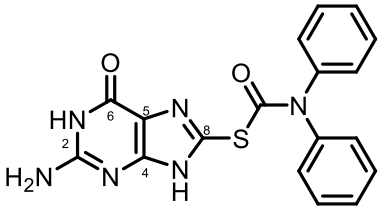
Following procedure (A) outlined above, the product (**76y**) was isolated as solid (59 mg, 37%, Table 4, Entry 23). **m.p.**= 286 °C (dec). **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 0.81-2.06 (13H, 6 × C$\underline{H}_2$ and 1× C$\underline{H}$), 3.08 (t, *J* 7.6 Hz, 2H, SC$\underline{H}_2$), 6.23 (s,4.8 2H, N$\underline{H}_2$), 10.69 (s,1H, N$\underline{H}$). 12.46 (s, 1H, N$\underline{H}$). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 26.1 (2×$\underline{C}H_2$), 26.5 ($\underline{C}H_2$), 29.7 ($\underline{C}H_2$), 32.8 (2×$\underline{C}H_2$), 36.6 ($\underline{C}H$), 37.1 (S$\underline{C}H_2$), 116.0 (C5), 144.1 (C8), 153.7 (C4 and C2), 155.8 (C6O). **MS** *m/z* (ESI$^+$); calculated for ($C_{13}H_{19}N_5OS$) $[M+H]^+$; 294.1383 found 294.1384. **IR** ν_{max} /cm^{-1}: 3318 (NH), 3155 (CH), 2918 (CH), 1657 (CO).

2-amino-8-((2-bromobenzyl)thio)-1,9-dihydro-6H-purin-6-one (76z).



Following procedure (B) outlined above, the product (**76z**) was isolated as solid (114 mg, 60%, Table 4, Entry 24). **m.p.**= 284 °C (dec). **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 4.44 (s, 2H, C$\underline{H}_2$), 6.31 (s, br, 2H, N$\underline{H}_2$), 7.18-7.62 (4H, ArC$\underline{H}$), 10.71 (s, br, 1H, N$\underline{H}$), 12.59 (s, br, 1H, N$\underline{H}$). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 36.8 (S$\underline{C}H_2$), 116.1 (C5), 124.4 ($\underline{C}$-Br), 128.3 (Ar$\underline{C}$H), 130.0 (Ar$\underline{C}$H), 131.5 (Ar$\underline{C}$H), 133.1 (Ar$\underline{C}$H), 137.4 (Ar$\underline{C}$), 143.2 (C8), 153.8 (C4 and C2), 156.1 (C6O). **MS** *m/z* (ESI$^+$); calculated for ($C_{12}H_{10}BrN_5OS$) $[M+H]^+$; 351.9862 found 351.9878. **IR** ν_{max} /cm^{-1}: 3305 (NH), 3098 (CH), 2900 (CH), 1657 (CO).

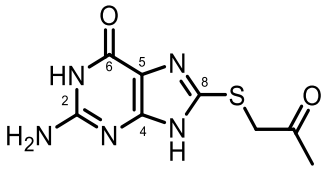
S-(2-amino-6-oxo-6, 9-dihydro-1H-purin-8-yl) diphenylcarbamothioate (76aa).



Following procedure (C) outlined above, the product (**76aa**) was isolated as solid (47 mg, 23%, Table 4, Entry 25). **m.p** >300 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 6.39 (s,

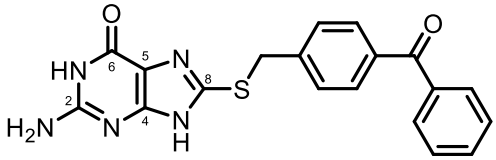
br, 2H, N<u>H</u>$_2$), 7.38-7.46 (10H, ArC<u>H</u>), 10.59 (s, br, 1H, N<u>H</u>), 12.81 (s, br, 1H, N<u>H</u>). **^{13}C NMR** (100 MHz, DMSO-d$_6$) δ_C: 118.7 (C5), 128.58 (2×Ar<u>C</u>), 130.07 (10×Ar<u>C</u>H), 141.3 (C8), 154.1 (C4), 154.8 (C2), 156.7 (C6O), 165.0 (CO). **MS** *m/z* (ESI$^+$); calculated for ($C_{18}H_{14}N_6O_2S$) $[M+H]^+$; 379.0972 found 379.0982. **IR** ν_{max} /cm^{-1}: 3323 (NH), 3158 (CH), 1673 (CO), 1659 (CO).

2-amino-8-((2-oxopropyl)thio)-1,9-dihydro-6H-purin-6-one (76ab).



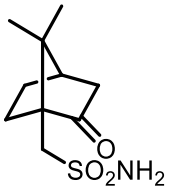
Following procedure (C) outlined above, the product (**76ab**) was isolated as solid (48 mg, 37%, Table 4, Entry 26). **m.p.**>300 °C. **^{1}H NMR** (400 MHz, DMSO-d$_6$) δ_H: 2.22 (s, 3H, C<u>H</u>$_3$), 4.15 (s, 2H, C<u>H</u>$_2$), 6.34 (s, br, 2H, N<u>H</u>$_2$), 10.58 (s, br, 1H, N<u>H</u>), 12.51 (s, br, 1H, N<u>H</u>). **^{13}C NMR** (100 MHz, DMSO-d$_6$) δ_C: 29.1 (<u>C</u>H$_3$), 42.2 (<u>C</u>H$_2$), 114.8 (C5), 142.8 (C8), 153.6 (C4), 155.0 (C2), 155.8 (C6O), 202.7 (CO). **MS** *m/z* (ESI$^+$); calculated for ($C_8H_9N_5O_2S$) $[M+H]^+$; 240.055 found 240.0571. **IR** ν_{max} /cm^{-1}: 3308 (NH), 3111 (CH), 2911 (CH), 1676 (CO), 1650 (CO).

2-amino-8-((4-benzoylbenzyl)thio)-1,9-dihydro-6H-purin-6-one (76ac).



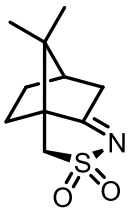
Following procedure (A) outlined above, the product (**76ac**) was isolated as solid (61 mg, 30%, Table 4, Entry 27). **^{1}H NMR** (400 MHz, DMSO-d$_6$) δ_H: 4.47 (s, 2H, SC<u>H</u>$_2$), 6.30 (s, 2H, N<u>H</u>$_2$), 7.51-7.55 (m, 4H, ArC<u>H</u>), 7.63-7.70 (m, 5H, ArC<u>H</u>), 10.53 (s, br, 1H, N<u>H</u>), 12.55 (s, br, 1H, N<u>H</u>). **^{13}C NMR** (100 MHz, DMSO-d$_6$) δ_c: 35.8 (S<u>C</u>H$_2$), 117.7 (C5), 129.0 (2×Ar<u>C</u>H), 129.3 (2×Ar<u>C</u>H), 130.0 (2×Ar<u>C</u>H), 130.3 (2×Ar<u>C</u>H), 133.0 (Ar<u>C</u>H), 136.2 (Ar<u>C</u>), 137.4 (Ar<u>C</u>), 140.5 (Ar<u>C</u>), 143.4 (C8), 153.8 (C4), 154.0 (C2), 156.2 (CO), 195.7 (CO). **MS** *m/z* (ESI$^+$); calculated for ($C_{19}H_{15}N_5O_2S$) $[M+H]^+$; 378.1019 found 378.1017. **IR** ν_{max} /cm^{-1}: 3315 (NH), 3111 (CH), 1655 (CO), 1605 (CO).

((1R,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonamide (304).[82]



In 250 mL round bottomed flask, which immersed in crushed ice bath, was placed 50 mL of ammonium hydroxide NH_4OH. A solution of (1*S*)-(+)-10-Camphorsulfonyl chloride (5 g, 19.7 mmol) in 50 mL dichloromethane (DCM) was added dropwise over 2 hours to NH_4OH. After this time, the mixture was transferred to separating funnel and shaking many times then the lower dichloromethane layer was separated, and the aqueous layer was extracted (2×50 mL) with dichloromethane. The organic layers dried over $MgSO_4$ and solvent was removed in *vacuo* to give (3.8 g, 85%) of (**304**). **m.p.**= 123-124 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 0.93 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.00 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.44-2.26 (m, 7H, $C\underline{H}_2C\underline{H}_2C\underline{H}C\underline{H}_2$), 3.11 (d, *J* 15.0 Hz, 1H, $C\underline{H}_2SO_2$), 3.45 (d, *J* 15.0 Hz, 1H, $C\underline{H}_2SO_2$), 5.36 (br, 2H, $N\underline{H}_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 19.3 ($(\underline{C}H_3)_2CR_2$), 19.9 ($(\underline{C}H_3)_2CR_2$), 26.8 ($CH_2\underline{C}H_2CHCH_2$), 27.0 ($\underline{C}H_2CH_2CHCH_2$), 42.8 ($CH_2CH_2\underline{C}HCH_2$), 43.0 ($CH_2CH_2CH\underline{C}H_2$), 49.1 ($\underline{C}$ $(CH_3)_2$), 54.0 ($\underline{C}H_2SO_2$), 59.3 ($\underline{C}CH_2SO_2$), 217.7 (CO). **IR** ν_{max} /cm^{-1}: 3301(NH), 2962 (CH), 1729 (CO), 1151, 1334 (SO_2). **MS** *m/z* (ESI^+); calculated for ($C_{10}H_{17}NO_3S$) $[M+Na]^+$; 254.0821 found 254.0817.

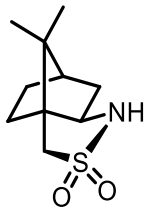
(3aR,6R)-8,8-dimethyl-4,5,6,7-tetrahydro-3H-3a,6-methanobenzo[c]isothiazole 2,2-dioxide (305).[82]



In round -bottomed flask placed 0.7 g of Amberlyst 15 ion - exchange resin, (5 g, 21.6 mmol) of camphorsulfonamide (**304**) and 200 mL toluene. Dean- Stark trap and reflux condenser were fitted with the flask. The mixture was stirred and reflux for 5 hours. After this time, the heat was stopped, and 100 mL dichloromethane was added. Solvents were removed in *vacuo* to give 95 % of (**305**). **m.p.**= 229 230 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 0.87 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.08 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.45-2.80

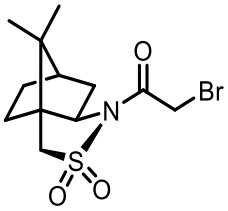
(7H, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>C<u>H</u>$_2$), 2.95 (d, *J* 13.2 Hz, 1H, C<u>H</u>$_2$SO$_2$), 3.06 (d, *J* 13.2 Hz, 1H, C<u>H</u>$_2$SO$_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 18.9 ((<u>C</u>H$_3$)$_2$C), 19.4 ((<u>C</u>H$_3$)$_2$C), 26.6 (CH$_2$<u>C</u>H$_2$CHCH$_2$), 28.3 (<u>C</u>H$_2$CH$_2$CHCH$_2$), 35.9 (CH$_2$CH$_2$CH<u>C</u>H$_2$), 44.5 (CH$_2$CH$_2$<u>C</u>HCH$_2$), 47.9 (<u>C</u>(CH$_3$)$_2$), 49.4 (<u>C</u>H$_2$SO$_2$), 64.4 (<u>C</u>CH$_2$SO$_2$), 195.3 (C=N). **IR** ν_{max} /cm^{-1}: 2964 (CH), 1731 (C=N), 1133, 1318 (SO_2). **MS** *m/z* (ESI$^+$); calculated for ($C_{10}H_{15}NO_2S$) $[M]^+$; 214.0896 found 214.0900.

(3aR,6R)-8,8-dimethylhexahydro-3H-3a,6-methanobenzo[c]isothiazole 2,2-dioxide (306).[82]



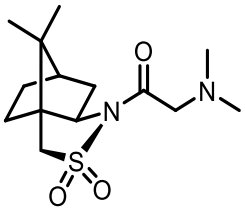
(0.88 g, 23.5 mmol) of $LiALH_4$ and 250 mL dry THF were placed in round -bottomed flask, which was fitted with Soxlet extraction apparatus and condenser with nitrogen. (5.0 g, 23.5 mmol) of camphorsulfonimine (**305**) was placed into the Soxlet extraction apparatus. The reaction mixture was heated (100 °C) overnight. After this time, the reaction mixture allowed to cool. (1N) HCl was added to react with the unreacted $LiALH_4$. The contents were transferred to separation funnel, the lower aqueous silver layer was separated and washed by (3×100) dichloromethane then the organic layers were dried over $MgSO_4$. The solvents were removed in *vacuo* to afford of (**306**). **m.p.**= 165-166 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 0.93 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$), 1.13 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$), 1.25-2.00 (7H, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>C<u>H</u>$_2$), 3.07 (d, *J* 13.4 Hz, 1H, C<u>H</u>$_2$SO$_2$), 3.11 (d, *J* 13.4 Hz, 1H, C<u>H</u>$_2$SO$_2$), 3.40 (q, *J* 7.0 Hz, 1H, NC<u>H</u>), 4.01 (br, 1H, N<u>H</u>). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 20.4 ((<u>C</u>H$_3$)$_2$CR$_2$), 20.5 ((<u>C</u>H$_3$)$_2$CR$_2$), 26.8 (CH$_2$<u>C</u>H$_2$CHCH$_2$), 31.8 (<u>C</u>H$_2$CH$_2$CHCH$_2$), 36.0 (CH$_2$CH$_2$CH<u>C</u>H$_2$), 44.7 (CH$_2$CH$_2$<u>C</u>HCH$_2$), 47.4 (<u>C</u>(CH$_3$)$_2$), 50.3 (<u>C</u>H$_2$SO$_2$), 55.0 (<u>C</u>CH$_2$SO$_2$), 62.8 (<u>C</u>HN). **IR** ν_{max} /cm^{-1}: 3287 (NH), 2955 (CH), 1133, 1328 (SO_2). **MS** *m/z* (ESI$^+$); calculated for ($C_{10}H_{17}NO_2S$) $[M+H]^+$; 216.1053 found 216.1051.

2-bromo-1-((3aR,6R)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6 methanobenzo [c]isothiazol-1(4H)-yl)ethan-1-one (307).



Camphorsultam **(306)** (2.5 g, 11.6 mmol) in dry toluene (20 mL) was added to a solution of Sodium hydride (0.5 g, 12.76 mmol) in dry toluene (20 mL) at 0 °C. After the addition was completed, the reaction was stirred for 1 hour at room temperature. Next, Bromoacetyl (1.1 eq.) was added dropwise over 2 hours at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 72 hours. After this time, the reaction was quenched by careful addition of water (25 mL) and extracted with ethyl acetate (25 mL). The organic layer was washed with brine (15 mL), dried over sodium sulfate and filtered. The solvent was removed *in vacuo* to yield crude which was subjected to column chromatography to give (2.0 g, 52%) of (**307**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 0.98 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.16 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.33-2.18 (7H, $C\underline{H}_2C\underline{H}_2C\underline{H}C\underline{H}_2$), 3.44 (d, *J* 13.8 Hz, 1H, $C\underline{H}_2SO_2$), 3.51 (d, *J* 13.8 Hz, 1H, $C\underline{H}_2SO_2$), 3.90 (q, *J* 5.0 Hz, 1H, $NC\underline{H}$), 4.19 (d, *J* 13.0 Hz, 1H, $COC\underline{H}_2$), 4.32 (d, *J* 13.0 Hz, 1H, $COC\underline{H}_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 19.8 ($(\underline{C}H_3)_2CR_2$), 20.7 ($(\underline{C}H_3)_2\ CR_2$), 26.4 ($CH_2\underline{C}H_2CHCH_2$), 27.5 ($\underline{C}H_2CH_2CHCH_2$), 32.8 ($CH_2CH_2CH\underline{C}H_2$), 37.9 ($CO\underline{C}H_2$), 44.5 ($CH_2CH_2\underline{C}HCH_2$), 47.8 ($\underline{C}(CH_3)_2$), 49.0 ($\underline{C}CH_2SO_2$), 57.7 ($\underline{C}H_2SO_2$), 65.4 ($\underline{C}HN$), 164.5 ($N\underline{C}OCH_2$). **MS** *m/z* ($ESI^+$); calculated for ($C_{12}H_{18}BrNO_3S$) $[M+H]^+$; 336.0264 found 336.0262. **TLC** R_f = 0.25 (EtOAc:PE, 1:4).

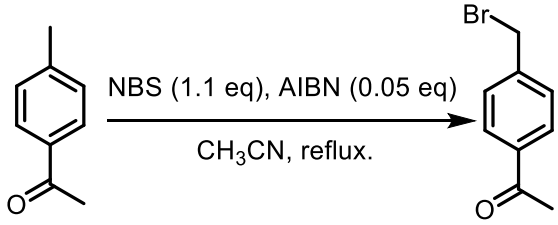
1-((6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6 methanobenzo [c]isothiazol-1(4H)-yl)-2-(dimethylamino)ethan-1-one (308).



To a solution of (**307**) (1.34 g, 4 mmol) in THF (20 mL) at 0 °C was added in three portions dimethylamine hydrochloride (12 mmol) and triethylamine (20 mmol) over a period of 10 minutes. The reaction was allowed to stir for 12 hours, then was allowed

to warm to room temperature. It was filtered through a celite plug, washed with THF (30 mL) and concentrated under reduced pressure to give crude (1.6 g, 94%) of (**308**)**,** which was purified by flash column chromatography. **m.p.**= 121-122 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 0.95 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.13 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.31-1.42 (m, 2H, $C(R)_2HC\underline{H}_2C\underline{H}_2$), 1.83-2.15 (m, 5H, $C\underline{H}_2C(R)\underline{H}C\underline{H}_2C\underline{H}_2$), 2.36 (s, 6H, $2\times N(C\underline{H}_3)_2$), 3.40 (d, *J* 13.7 Hz, 1H, $C\underline{H}_2SO_2$), 3.46 (d, *J* 13.7 Hz, 1H, $C\underline{H}_2SO_2$), 3.55 (s, 2H, $NC\underline{H}_2CO$), 3.88 (t, *J* 5.2 Hz, 1H, $NC\underline{H}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 19.8 ($(\underline{C}H_3)_2CR_2$), 20.8 ($(\underline{C}H_3)_2$ CR_2), 26.4 ($CH_2\underline{C}H_2CHCH_2$), 32.8 ($\underline{C}H_2CH_2CHCH_2$), 38.4 ($CH_2CH_2CH\underline{C}H_2$), 44.6 ($CH_2CH_2\underline{C}HCH_2$), 45.5 ($2\times$ $N(\underline{C}H_3)_2$), 47.8 ($\underline{C}(CH_3)_2$), 48.8 ($\underline{C}CH_2SO_2$), 52.9 ($C\underline{C}H_2SO_2$), 61.2 ($CO\underline{C}H_2N$), 65.2 ($\underline{C}HN$), 169.3 (CO). **IR** ν_{max} /cm^{-1}**:** 2956 (CH), 1706 (CO), 1306, 1131 (SO_2). **MS** *m/z* (ESI^+) calculated for $C_{14}H_{24}N_2O_3S$ $[M+H]^+$; 301.158 found 301.1581.

Preparation of 4-(Bromomethyl)acetophenone.

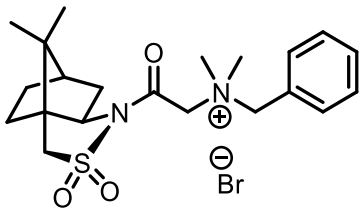


A suspension of methyl *p*-tolyl ketone (2.5 g, 18.6 mmol, 1 eq.), NBS (3.64 g, 20.5 mmol, 1.1 eq.) and AIBN (0.15 g, 0.93 mmol, 0.05 eq.) in CH_3CN (30 mL) was reflux for 3 hours. The solvent was removed in *in vacuo* then toluene (15 mL) was added to the residue, filtered and concentrated *in vacuo* to give 4-(Bromomethyl) acetophenone (3.5 g, 90%)**. ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 2.60 (s, 3H, $ArCOC\underline{H}_3$), 4.50 (s, 2H, $ArC\underline{H}_2Br$),7.47 (d, *J* 8.3 Hz, 2H, $ArC\underline{H}$), 7.47 (d, *J* 8.3 Hz, 2H, $ArC\underline{H}$).

General procedure (D) for synthesis of ammonium bromide salts (309a-m).

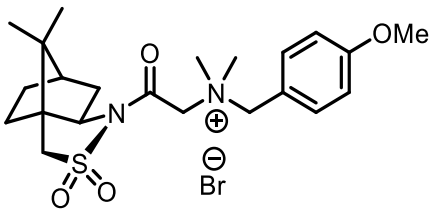
(0.2 g, 0.66 mmol, 1 eq.) of (**308**), aryl bromide (1.9 mmol, 3 eq.) and toluene (10 mL) were heated to 50 °C for 3 days. The formed precipitate was collected over a glass sinter, washed with hexane, and dried *in vacuo* to give the crude salt, which was used without purification.

_N_-benzyl-2-((6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo [c] isothiazol-1(4H)-yl)-_N,N_-dimethyl-2-oxoethan-1-aminium (309a).



Following procedure (D) outlined above, the product (**309a**) was isolated as solid (0.297 g, 95%, Table 19, Entry 1). **m.p.**= 124-126 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 0.88 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.03 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.32-1.45 (m, 2H, $C(R)_2HC\underline{H}_2C\underline{H}_2$), 1.75-1.88 and 2.13 (m, 5H, $C\underline{H}_2C\underline{H}_2C(R)\underline{H}C\underline{H}_2$), 3.46 (m, 8H, 2×$N(C\underline{H}_3)_2$ and $C\underline{H}_2SO_2$), 4.10 (br, m, 1H, $NC\underline{H}$), 4.66 (d, *J* 16.5 Hz, $NC\underline{H}_2Ar$), 5.02-5.12 (br, m, 1H, $NC\underline{H}_2Ar$), 5.17 (d, *J* 13.4 Hz, 1H, $COC\underline{H}_2N$), 5.20 (d, *J* 13.4 Hz, 1H, $COC\underline{H}_2N$), 7.32-7.42 ((m, 3H, $ArC\underline{H}$), 7.54 (d, *J* 7.2 Hz, 2H, $ArC\underline{H}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 19.8 ($(\underline{C}H_3)_2CR_2$), 21.0 ($(\underline{C}H_3)_2CR_2$), 26.0 ($CH_2\underline{C}H_2CHCH_2$), 32.8 ($\underline{C}H_2CH_2CHCH_2$), 38.2 ($CH_2CH_2CH\underline{C}H_2$), 44.9 ($CH_2CH_2\underline{C}HCH_2$), 48.0 ($\underline{C}(CH_3)_2$), 49.4 ($\underline{C}CH_2SO_2$), 50.7 ($N(\underline{C}H_3)_2$), 51.1 ($N(\underline{C}H_3)_2$), 52.6 ($\underline{C}H_2SO_2$), 60.9 ($N\underline{C}H_2Ar$), 64.6 ($N\underline{C}H$), 67.9 ($CO\underline{C}H_2N$), 126.9 ($Ar\underline{C}$), 129.2 (2 x $Ar\underline{C}H$), 130.9 ($Ar\underline{C}H$), 133.2 (2 x $Ar\underline{C}H$), 163.4 (CO). **IR** ν_{max} /cm^{-1}**:** 2958 (CH), 1692 (CO), 1336, 1136 (SO_2).

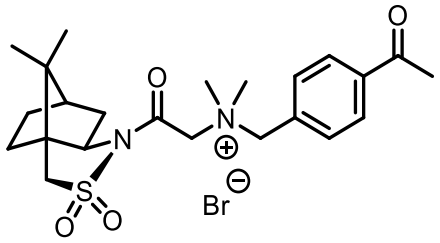
2-((3aR,6R)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo [c]isothiazol-1(4H)-yl)-_N_-(4-methoxybenzyl)-N,N-dimethyl-2-oxoethan-1-aminium bromide (309b).



Following procedure (D) outlined above, the product (**309b**) was isolated as solid (0.328 g, 98%, Table 19, Entry 2). **m.p.**= 130-132 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H**:** 0.95 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.11 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.41-1.52 (m, 2H, $C(R)_2HC\underline{H}_2C\underline{H}_2$), 1.84-1.96 and 2.17 (m, 5H, $C\underline{H}_2C(R)\underline{H}C\underline{H}_2C\underline{H}_2$), 3.49 (s, 3H, $N(C\underline{H}_3)_2$), 3.51 (app s, 5H, $N(C\underline{H}_3)_2$ and $C\underline{H}_2SO_2$), 3.80 (s, 3H, $OC\underline{H}_3$), 4.17 (br, m, 1H, $NC\underline{H}$), 4.53 (d, *J* 16.8 Hz, 1H, $NC\underline{H}_2Ar$), 5.02-5.11 (br, m, 1H, $NC\underline{H}_2Ar$), 5.16 (d, *J* 12.6 Hz , 1H, $COC\underline{H}_2N$),

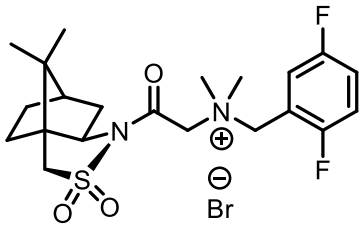
5.21 (d, *J* 12.6 Hz, 1H, COC<u>H</u>$_2$N), 6.90 (d, *J* 8.6 Hz, 2H, ArC<u>H</u>), 7.52(d, *J* 8.6 Hz, 2H, ArC<u>H</u>). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 19.8 ((<u>C</u>H$_3$)$_2$CR$_2$), 21.0 ((<u>C</u>H$_3$)$_2$CR$_2$), 26.1 (CH$_2$<u>C</u>H$_2$CHCH$_2$), 32.8 (<u>C</u>H$_2$CH$_2$CHCH$_2$), 38.2 (CH$_2$CH$_2$CH<u>C</u>H$_2$), 44.9 (CH$_2$CH$_2$<u>C</u>HCH$_2$), 48.1 (<u>C</u>(CH$_3$)$_2$), 49.4 (<u>C</u>CH$_2$SO$_2$), 50.6 (N(<u>C</u>H$_3$)$_2$), 51.0 (N(<u>C</u>H$_3$)$_2$), 52.6 (<u>C</u>H$_2$SO$_2$), 55.4 (O<u>C</u>H$_3$), 60.6 (N<u>C</u>H$_2$Ar), 64.7 (N<u>C</u>H), 68.2 (CO<u>C</u>H$_2$N), 114.7 (2×Ar<u>C</u>H), 118.6 (Ar<u>C</u>), 134.7 (2×Ar<u>C</u>H), 161.5 (Ar<u>C</u>), 163.3 (CO). **IR** ν_{max} /cm^{-1}**:** 2942 (CH), 1697 (CO), 1341, 1140 (SO_2), 1026 (OMe). **MS** *m/z* (ESI$^+$) calculated for $C_{22}H_{33}N_2O_4S$ [M-Br]$^+$; 416.2156 found 416.2151.

***N*-(4-acetylbenzyl)-2-((6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-*N,N*-dimethyl-2-oxoethan-1-aminium (309c).**



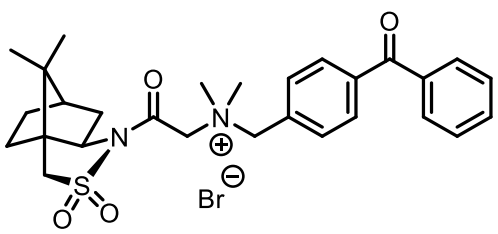
Following procedure (D) outlined above, the product (**309c**) was isolated as solid (0.255 g, 75%, Table 19, Entry 3). **m.p.**= 140-143 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 0.96 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$), 1.10 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$), 1.40-1.51 (m, 2H, CHC<u>H</u>$_2$C<u>H</u>$_2$), 1.88-1.96 (m, 3H, CH$_2$C<u>H</u>C<u>H</u>$_2$C<u>H</u>$_2$), 2.18 (br, 2H, C<u>H</u>$_2$CHCH$_2$CH$_2$), 2.61 (s, 3H, ArCOC<u>H</u>$_3$) 3.45 (d, *J* 8.4 Hz, 1H, C<u>H</u>$_2$SO$_2$), 3.53 (d, *J* 8.4 Hz, 1H, C<u>H</u>$_2$SO$_2$), 3.57 (s, 3H, N(C<u>H</u>$_3$)$_2$), 3.63 (s, 3H, N(C<u>H</u>$_3$)$_2$), 4.12-4.21 (br m, 1H, NC<u>H</u>), 4.65 (d, *J* 16.7 Hz, 1H, NC<u>H</u>$_2$Ar), 5.05-5.14 (br m, 1H, NC<u>H</u>$_2$Ar), 5.39 (d, *J* 12.5 Hz, 1H, COC<u>H</u>$_2$N), 5.44 (d, *J* 12.5 Hz, 1H, COC<u>H</u>$_2$N), 7.79 (d, *J* 8.0 Hz, 2H, ArCH), 7.97 (d, *J* 8.0 Hz, 2H, ArCH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 19.8 ((<u>C</u>H$_3$)$_2$CR$_2$), 21.0 ((<u>C</u>H$_3$)$_2$CR$_2$), 26.1 (CH$_2$<u>C</u>H$_2$CHCH$_2$), 26.8 (ArCO<u>C</u>H$_3$), 32.8 (<u>C</u>H$_2$CH$_2$CHCH$_2$), 38.2 (CH$_2$CH$_2$CH<u>C</u>H$_2$), 44.8 (CH$_2$CH$_2$<u>C</u>HCH$_2$), 48.1 (<u>C</u>(CH$_3$)$_2$), 49.5 (<u>C</u>CH$_2$SO$_2$), 51.1 (N(<u>C</u>H$_3$)$_2$), 51.5 (N(<u>C</u>H$_3$)$_2$), 52.7 (<u>C</u>H$_2$SO$_2$), 61.1 (N<u>C</u>H$_2$Ar), 64.9 (N<u>C</u>H), 67.3 (CO<u>C</u>H$_2$N), 129.0 (2 x Ar<u>C</u>H), 131.6 (Ar<u>C</u>), 133.7 (2×Ar<u>C</u>H), 138.8 (Ar<u>C</u>COCH$_3$), 163.0 (CO), 197.3 (Ar<u>C</u>OCH$_3$). **IR** ν_{max} /cm^{-1}**:** 2948 (CH), 1685 (CO), 1341, 1140 (SO_2). **MS** *m/z* (ESI$^+$) calculated for $C_{23}H_{33}N_2O_4S$ [M-Br]$^+$; 433.2156 found 433.2158.

***N*-(2,5-difluorobenzyl)-2-((6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-*N,N*-dimethyl-2-oxoethan-1-aminium bromide (309d).**



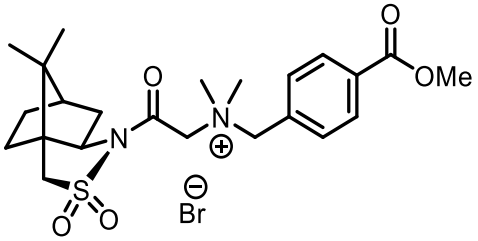
Following procedure (D) outlined above, the product (**309d**) was isolated as solid (0.33 g, 98%, Table 19, Entry 4). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 0.99 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.15 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.41-1.52 (m, 2H, $CHC\underline{H}_2C\underline{H}_2$), 1.94-1.96 (m, 3H, $CH_2C\underline{H}C\underline{H}_2C\underline{H}_2$), 2.19 (br, 2H, $C\underline{H}_2CHCH_2CH_2$), 3.48 (d, *J* 14.4 Hz, 1H, $C\underline{H}_2SO_2$), 3.50 (d, *J* 14.4 Hz, 1H, $C\underline{H}_2SO_2$), 3.58 (s, 3H, $N(C\underline{H}_3)_2$), 3.71 (s, 3H, $N(C\underline{H}_3)_2$), 4.09 (br, 1H, $NC\underline{H}$), 4.46 (d, *J* 16.8 Hz, 1H, $NC\underline{H}_2Ar$), 5.02 (br, 1H, NCH_2Ar), 5.44 (d, *J* 14.4 Hz, 1H, $COC\underline{H}_2N$), 5.51 (d, *J* 14.4 Hz, 1H, $COC\underline{H}_2N$), 7.14-7.26 (3H, $ArC\underline{H}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 19.8 ($(\underline{C}H_3)_2CR_2$), 20.1 ($(\underline{C}H_3)_2CR_2$), 26.1 ($CH_2\underline{C}H_2CHCH_2$), 32.8 ($\underline{C}H_2CH_2CHCH_2$), 38.1 ($CH_2CH_2CH\underline{C}H_2$), 44.9 ($CH_2CH_2\underline{C}HCH_2$), 48.0 ($\underline{C}(CH_3)_2$), 49.5 ($\underline{C}CH_2SO_2$), 51.5 ($N(\underline{C}H_3)_2$), 51.9 ($N(\underline{C}H_3)_2$), 52.6 ($\underline{C}H_2SO_2$), 60.5 ($N\underline{C}H_2Ar$), 61.4 ($N\underline{C}H$), 64.8 ($CO\underline{C}H_2N$), 116.1 (dd, J_{CF} 16.2, 7.5, ArC), 117.7 (dd, J_{CF} 24.8, 8.3, ArCH), 120.3 (dd, J_{CF} 23.7, 8.9, ArCH), 122.0 (dd, J_{CF} 24.5, 2.1, ArCH), 157.1 (dd, J_{CF} 35.5, 2.5, ArCF), 159.5 (dd, J_{CF} 36.9, 2.1, ArCF), 162.9 (CO). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -117.62 – -118.35 (m, 1F, ArCF), -115.26 – -116.00 (m, 1F, ArCF). **IR** ν_{max} /cm^{-1}**:** 2943 (CH), 1692 (CO), 1336, 1136 (SO_2). **MS** *m/z* (ESI^+) calculated for $C_{21}H_{29}F_2N_2O_3S$ $[M\text{-}Br]^+$; 427.1861 found 427.1862.

***N*-(4-benzoylbenzyl)-2-((6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-*N,N*-dimethyl-2-oxoethan-1-aminium (309e).**



Following procedure (D) outlined above, the product (**309e**) was isolated as solid (0.371 g, 97%, Table 19, Entry 5). **m.p.**= 121-123 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 0.94 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.10 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.40-1.51 (m, 2H, $CHC\underline{H}_2C\underline{H}_2$), 1.86-1.95 (m, 5H, $C\underline{H}_2C\underline{H}C\underline{H}_2C\underline{H}_2$), 3.49 (d, *J* 14.2 Hz, 1H, $C\underline{H}_2SO_2$), 3.54 (d, *J* 14.2 Hz, 1H, $C\underline{H}_2SO_2$), 3.61 (s, 3H, $N(C\underline{H}_3)_2$), 3.66 (s, 3H, $N(C\underline{H}_3)_2$), 4.14 (br, 1H, $NC\underline{H}$), 4.70 (d, *J* 16.7 Hz, 1H, $NC\underline{H}_2Ar$), 5.09-5.15 (br, m, 1H, $NC\underline{H}_2Ar$), 5.42 (d, *J* 12.4 Hz, 1H, $COC\underline{H}_2N$), 5.47 (d, *J* 12.4 Hz, 1H, $COC\underline{H}_2N$), 7.45 (t, *J* 7.4 Hz, 2H, $ArC\underline{H}$), 7.58 (t, *J* 7.4 Hz, 1H, $ArC\underline{H}$), 7.75 (d, *J* 7.8 Hz, 2H, $ArC\underline{H}$), 7.80 (d, *J* 7.8 Hz, 2H, $ArC\underline{H}$), 7.82 (d, *J* 8.4 Hz, 2H, $ArC\underline{H}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 19.8 ($(\underline{C}H_3)_2CR_2$), 21.0 ($(\underline{C}H_3)_2CR_2$), 26.1 ($CH_2\underline{C}H_2CHCH_2$), 32.8 ($\underline{C}H_2CH_2CHCH_2$), 38.2 ($CH_2CH_2CH\underline{C}H_2$), 44.9 ($CH_2CH_2\underline{C}HCH_2$), 48.0 ($\underline{C}(CH_3)_2$), 49.5 ($\underline{C}CH_2SO_2$), 51.1 ($N(\underline{C}H_3)_2$), 51.5 ($N(\underline{C}H_3)_2$), 52.7 ($\underline{C}H_2SO_2$), 61.1 ($N\underline{C}H_2Ar$), 64.8 ($N\underline{C}H$), 67.4 ($CO\underline{C}H_2N$), 128.5 (2 x $Ar\underline{C}H$), 130.1 (2 x $Ar\underline{C}H$), 130.5 ($Ar\underline{C}H$), 130.9 ($Ar\underline{C}$), 133.1 ($Ar\underline{C}H$), 133.4 ($Ar\underline{C}H$), 136.6 ($Ar\underline{C}H$), 139.8 (2 x $Ar\underline{C}$), 163.2 (CO), 195.7 (ArCO). **IR** ν_{max} /cm^{-1}**:** 2959 (CH), 1690 (CO), 1655 (CO), 1335, 1136 (SO_2). **MS** *m/z* (ESI^+) calculated for $C_{28}H_{35}N_2O_4S$ $[M\text{-}Br]^+$; 495.2318 found 495.2312.

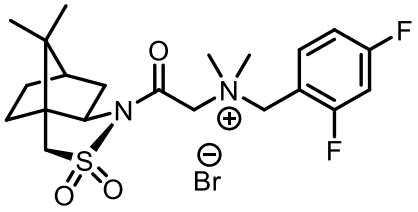
2-((3aR,6R)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo [c]isothiazol-1(4H)-yl)-*N*-(4-(methoxycarbonyl)benzyl)-*N,N*-dimethyl-2-oxoethan-1-aminium bromide (309f).



Following procedure (D) outlined above, the product (**309f**) was isolated as solid (0.281 g, 95%, Table 19, Entry 6). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 0.98 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.13 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.41-1.53 (m, 2H, $CHC\underline{H}_2C\underline{H}_2$), 1.88-2.09 (m, 5H, $C\underline{H}_2C\underline{H}C\underline{H}_2C\underline{H}_2$) 3.48 (d, *J* 12.3 Hz, 1H, $C\underline{H}_2SO_2$), 3.55 (d, *J* 12.3 Hz, 1H, $C\underline{H}_2SO_2$), 3.57 (s, 3H, $N(C\underline{H}_3)_2$), 3.66 (s, 3H, $N(C\underline{H}_3)_2$), 3.94 (s, 3H, $ArCOOC\underline{H}_3$), 4.12 (br, 1H, $NC\underline{H}$), 4.47 (d, *J* 16.8 Hz, 1H, $NC\underline{H}_2Ar$), 4.89-5.26 (br, m, 1H, $NC\underline{H}_2Ar$), 5.41 (d, *J* 11.6 Hz, 1H, $COC\underline{H}_2N$), 5.48 (d, *J* 11.6 Hz, 1H, $COC\underline{H}_2N$), 7.75 (d, *J* 8.2 Hz, 2H, $ArC\underline{H}$), 8.09 (d, *J* 8.2 Hz, 2H, $ArC\underline{H}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 19.8 ($(\underline{C}H_3)_2CR_2$), 21.0 ($(\underline{C}H_3)_2CR_2$), 26.1 ($CH_2\underline{C}H_2CHCH_2$), 32.8 ($\underline{C}H_2CH_2CHCH_2$), 38.2

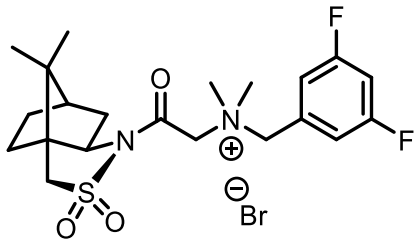
($CH_2CH_2CH\underline{C}H_2$), 44.8 ($CH_2CH_2\underline{C}HCH_2$), 48.1 ($\underline{C}(CH_3)_2$), 49.5 ($\underline{C}CH_2SO_2$), 51.2 ($N(\underline{C}H_3)_2$), 51.6 ($N(\underline{C}H_3)_2$), 52.5 ($ArCOO\underline{C}H_3$) 52.6 ($\underline{C}H_2SO_2$), 61.1 ($N\underline{C}H_2Ar$), 64.7 ($N\underline{C}H$), 67.3 ($CO\underline{C}H_2N$), 130.3 (2 x Ar$\underline{C}$H), 131.4 ($Ar\underline{C}COOCH_3$), 132.5 (Ar$\underline{C}$), 133.4 (2 x Ar$\underline{C}$H), 166.0 (CO), 194.8 ($Ar\underline{C}OOCH_3$).

***N*-(2,4-difluorobenzyl)-2-((6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-*N,N*-dimethyl-2-oxoethan-1-aminium bromide (309g).**



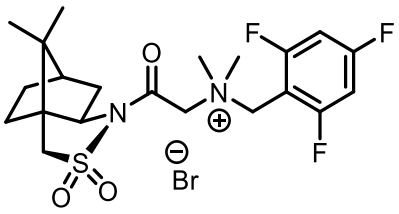
Following procedure (D) outlined above, the product (**309g**) was isolated as solid (0.324 g, 96%, Table 19, Entry 7). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 0.98 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.14 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.40-1.52 (m, 2H, $C(R)_2HC\underline{H}_2C\underline{H}_2$), 1.88-1.98 and 2.19 (m, 5H, $C\underline{H}_2C(R)\underline{H}C\underline{H}_2C\underline{H}_2$), 3.35 (s, 3H, $N(C\underline{H}_3)_2$), 3.45-3.58 (m, 5H, $N(C\underline{H}_3)_2$ and $C\underline{H}_2SO_2$), 3.67 (s, 3H, $N(C\underline{H}_3)_2$), 4.10 (br, m, 1H, $NC\underline{H}$), 4.52 (d, *J* 16.8 Hz, 1H, $NC\underline{H}_2Ar$), 4.49-5.20 (br, m, 1H, $NC\underline{H}_2Ar$), 5.29-5.48 (m, 2H, $COC\underline{H}_2N$), 6.93 (td, *J* 9.3 Hz, 2.2 Hz, 1H, Ar$\underline{C}$H), 7.05 (td, *J* 8.3 Hz, 2.1 Hz, 1H, Ar$\underline{C}$H), 8.13-8.19 (m, 1H, Ar$\underline{C}$H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 19.8 ($(\underline{C}H_3)_2CR_2$), 20.9 ($(\underline{C}H_3)_2CR_2$), 26.1 ($CH_2\underline{C}H_2CHCH_2$), 32.8 ($\underline{C}H_2CH_2CHCH_2$), 38.1 ($CH_2CH_2CH\underline{C}H_2$), 44.8 ($CH_2CH_2\underline{C}HCH_2$), 48.0 ($\underline{C}(CH_3)_2$), 49.4 ($\underline{C}CH_2SO_2$), 51.2 ($N(\underline{C}H_3)_2$), 51.6 ($N(\underline{C}H_3)_2$), 52.6 ($\underline{C}H_2SO_2$), 60.6 ($N\underline{C}H_2Ar$), 61.1 ($N\underline{C}H$), 64.8 ($CO\underline{C}H_2N$), 104.8 (t, J_{CF} 25.5, ArCH), 110.9 (dd, J_{CF} 14.5, 4.0, ArC), 113.0 (dd, J_{CF} 20.3, 2.1, ArCH), 137.4 (dd, J_{CF} 9.3, 3.1, ArCH), 162.3 (dd, J_{CF} 223.7, 2.2, ArCF), 164.7 (CO), 164.8 (dd, J_{CF} 225.8, 12.0, ArCF). **^{19}F NMR** (376.5MHz, $CDCl_3$): δ -103.0 – -103.8 (m, 1F, ArCF), -106.8 – -108.2 (m, 1F, ArCF). **IR** ν_{max} /cm^{-1}**:** 2960 (CH), 1692 (CO), 1337, 1137 (SO_2). **MS** *m/z* (ESI$^+$) calculated for $C_{21}H_{29}F_2N_2O_3S$ $[M\text{-}Br]^+$; 427.1861 found 427.1861.

***N*-(3,5-difluorobenzyl)-2-((6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-*N,N*-dimethyl-2-oxoethan-1-aminium bromide (309h).**



Following procedure (D) outlined above, the product (**309h**) was isolated as solid (0.276 g, 96%, Table 19, Entry 8). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 0.97 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.12 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.42-1.50 (m, 2H, $CHC\underline{H}_2C\underline{H}_2$), 1.90-1.96 (m, 3H, $CH_2C\underline{H}C\underline{H}_2C\underline{H}_2$), 2.19 (br, 2H, $C\underline{H}_2CHCH_2CH_2$), 3.53 (d, *J* 12.8 Hz, 1H, $C\underline{H}_2SO_2$), 3.59 (d, *J* 12.8 Hz, 1H, $C\underline{H}_2SO_2$), 3.60 (s, 3H, $N(C\underline{H}_3)_2$), 3.68 (s, 3H, $N(C\underline{H}_3)_2$), 4.09 (br, 1H, $NC\underline{H}$), 4.65 (d, *J* 16.8 Hz, 1H, $NC\underline{H}_2Ar$), 5.08 (br, 1H, $NC\underline{H}_2Ar$), 5.42 (d, *J* 12.4 Hz, 1H, $COC\underline{H}_2N$), 5.49 (d, *J* 12.4 Hz, 1H, $COC\underline{H}_2N$), 6.96 (t, J_{HF} 8.6, 2.2 Hz, 1H, $ArC\underline{H}$), 7.15-7.30 (m, 2H, $ArC\underline{H}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C**:** 19.8 ($(\underline{C}H_3)_2CR_2$), 20.9 ($(\underline{C}H_3)_2CR_2$), 26.1 ($CH_2\underline{C}H_2CHCH_2$), 32.8 ($\underline{C}H_2CH_2CHCH_2$), 38.1 ($CH_2CH_2CH\underline{C}H_2$), 44.8 ($CH_2CH_2\underline{C}HCH_2$), 48.0 ($\underline{C}(CH_3)_2$), 49.5 ($\underline{C}CH_2SO_2$), 51.2 ($N(\underline{C}H_3)_2$), 51.6 ($N(\underline{C}H_3)_2$), 52.6 ($\underline{C}H_2SO_2$), 61.1 ($N\underline{C}H_2Ar$), 64.9 ($N\underline{C}H$), 66.3 ($CO\underline{C}H_2N$), 106.8 (t, J_{CF} 24.5, ArCH), 116.4 (dd, J_{CF} 19.8, 7.4, 2 x ArCH), 130.3 (t, J_{CF} 9.8, ArC), 163.0 (dd, J_{CF} 250.6, 12.4, 2 x ArCF). **^{19}F NMR** (376.5MHz, $CDCl_3$): δ -106.61 (br s, 2F, ArCF). **IR** ν_{max} /cm^{-1}**:** 2962 (CH), 1689 (CO), 1320, 1136 (SO_2). **MS** *m/z* (ESI$^+$) calculated for $C_{21}H_{29}F_2N_2O_3S$ $[M\text{-}Br]^+$; 427.1861 found 427.1862.

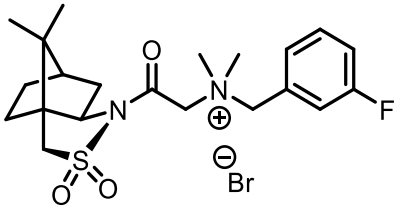
2-((6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-*N,N*-dimethyl-2-oxo-*N*-(2,4,6-trifluorobenzyl)ethan-1-aminium bromide (309i).



Following procedure (D) outlined above, the product (**309i**) was isolated as solid (0.332 g, 95%, Table 19, Entry 9). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 0.97 (s, 3H,

(C<u>H</u>$_3$)$_2$CR$_2$), 1.16 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$), 1.44-1.54 (m, 2H, CHC<u>H</u>$_2$C<u>H</u>$_2$), 1.89-1.98 (m, 3H, CH$_2$C<u>H</u>C<u>H</u>$_2$C<u>H</u>$_2$), 2.25 (br, 2H, C<u>H</u>$_2$CHCH$_2$CH$_2$), 3.48 (d, *J* 13.7 Hz, 1H, C<u>H</u>$_2$SO$_2$), 3.55 (d, *J* 13.7 Hz, 1H, C<u>H</u>$_2$SO$_2$), 3.63 (s, 3H, N(C<u>H</u>$_3$)$_2$), 3.64 (s, 3H, N(C<u>H</u>$_3$)$_2$), 4.21 (br, 1H, NC<u>H</u>), 4.71 (d, *J* 16.9 Hz, 1H, NC<u>H</u>$_2$Ar), 5.12 (d, *J* 13.6 Hz, 1H, COC<u>H</u>$_2$N), 5.22 (d, *J* 13.6 Hz, 1H, COC<u>H</u>$_2$N), 5.50 (br, 1H, NC<u>H</u>$_2$Ar), 6.86 (t, J_{HF} 8.2 Hz, 2H, ArC<u>H</u>). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 19.8 ((<u>C</u>H$_3$)$_2$CR$_2$), 21.0 ((<u>C</u>H$_3$)$_2$CR$_2$), 26.1 (CH$_2$<u>C</u>H$_2$CHCH$_2$), 32.9 (<u>C</u>H$_2$CH$_2$CHCH$_2$), 38.1 (CH$_2$CH$_2$CH<u>C</u>H$_2$), 44.9 (CH$_2$CH$_2$<u>C</u>HCH$_2$), 48.1 (<u>C</u>(CH$_3$)$_2$), 49.4 (<u>C</u>CH$_2$SO$_2$), 51.7 (N(<u>C</u>H$_3$)$_2$), 52.3 (N(<u>C</u>H$_3$)$_2$), 52.7 (<u>C</u>H$_2$SO$_2$), 56.0 (N<u>C</u>H$_2$Ar), 61.6 (N<u>C</u>H), 64.8 (CO<u>C</u>H$_2$N), 100.9 (d, J_{CF} 21.6 Hz, ArC), 101.8 (td, J_{CF} 25.9, 3.4, 2xArCH), 163.1 (dt, J_{CF} 127.8, 11.8, 3xAr<u>C</u>F), 163.8 (CO). **^{19}F NMR** (376.5MHz, $CDCl_3$): δ-98.8 (br s, 1F, ArCF), -103.2 (s, 2F, ArCF). **IR** ν_{max} /cm^{-1}**:** 2960 (CH), 1689 (CO), 1338, 1138 (SO_2). **MS** *m/z* (ESI$^+$) calculated for $C_{21}H_{28}F_3N_2O_3S$ [M-Br]$^+$; 445.1773 found 445.1768.

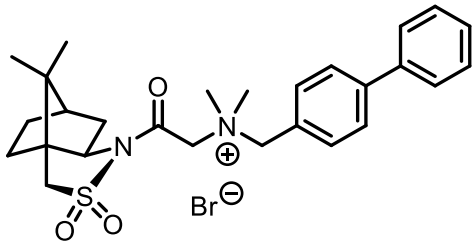
2-((6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c] isothiazol-1(4H)-yl)-N-(3-fluorobenzyl)-*N,N*-dimethyl-2-oxoethan-1-aminium bromide (309j).



Following procedure (D) outlined above, the product (**309j**) was isolated as solid (0.319 g, 98%, Table 19, Entry 10). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 0.98 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$), 1.13 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$), 1.41-1.53 (m, 2H, C(R)$_2$HC<u>H</u>$_2$C<u>H</u>$_2$), 1.88-1.98 and 2.19 (m, 5H, C<u>H</u>$_2$C(R)<u>H</u>C<u>H</u>$_2$C<u>H</u>$_2$), 3.51 (d, *J* 11.8 Hz, 1H, CH$_2$SO$_2$), 3.55 (d, *J* 11.8 Hz, 1H, CH$_2$SO$_2$), 3.58 (s, 3H, N(CH$_3$)$_2$), 3.65 (s, 3H, N(CH$_3$)$_2$), 4.13 (br, 1H, NCH), 4.54 (d, *J* 16.8 Hz, 1H, NCH$_2$Ar), 4.97 (br, 1H, NCH$_2$Ar), 5.36 (d, *J* 12.5 Hz, 1H, COCH$_2$N), 5.42 (d, *J* 12.5 Hz, 1H, COCH$_2$N), 7.16-7.23 (m, 4H, ArC<u>H</u>). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 19.8 ((<u>C</u>H$_3$)$_2$CR$_2$), 21.0 ((<u>C</u>H$_3$)$_2$CR$_2$), 26.1 (CH$_2$<u>C</u>H$_2$CHCH$_2$), 32.8 (<u>C</u>H$_2$CH$_2$CHCH$_2$), 38.2 (CH$_2$CH$_2$CH<u>C</u>H$_2$), 44.8 (CH$_2$CH$_2$<u>C</u>HCH$_2$), 48.1 (<u>C</u>(CH$_3$)$_2$), 49.5 (<u>C</u>CH$_2$SO$_2$), 51.2 (N(<u>C</u>H$_3$)$_2$), 51.6 (N(<u>C</u>H$_3$)$_2$), 52.6 (<u>C</u>H$_2$SO$_2$), 61.0 (N<u>C</u>H$_2$Ar), 64.9 (N<u>C</u>H), 67.2 (CO<u>C</u>H$_2$N), 118.3 (d, J_{CF} 21.3 Hz, ArCH), 120.0 (d, J_{CF} 22.1 Hz, ArCH), 129.0 (d, J_{CF} 6.9 Hz, ArCH), 129.2 (d, J_{CF} 3.1 Hz, ArCH), 131.1 (d, J_{CF} 8.3 Hz, ArC),

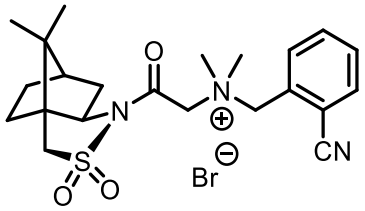
161.4 (ArCF), 163.9 (CO). **^{19}F NMR** (376.5MHz, $CDCl_3$): δ -110.05 – -110.09 (m, 1F, ArCF),

***N*-([1,1'-biphenyl]-4-ylmethyl)-2-((6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-*N,N*-dimethyl-2-oxoethan-1-aminium bromide (309k).**



Following procedure (D) outlined above, the product (**309k**) was isolated as solid (0.262 g, 72%, Table 19, Entry 11). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 0.99 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.15 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.43-1.58 (m, 2H, $C(R)_2HC\underline{H}_2C\underline{H}_2$), 1.94-1.96 and 2.17 (m, 5H, $C\underline{H}_2C(R)\underline{H}C\underline{H}_2C\underline{H}_2$), 3.49 (d, *J* 13.8 Hz, 1H, $C\underline{H}_2SO_2$), 3.56 (d, *J* 13.8 Hz, 1H, $C\underline{H}_2SO_2$), 3.59 (s, 3H, $N(C\underline{H}_3)_2$), 3.66 (s, 3H, $N(C\underline{H}_3)_2$), 4.16 (br, 1H, $NC\underline{H}$), 4.38 (d, *J* 16.8 Hz, 1H, $NC\underline{H}_2Ar$), 5.04 (br, 1H, $NC\underline{H}_2Ar$), 5.33 (d, *J* 12.3 Hz, 1H, $COC\underline{H}_2N$), 5.39 (d, *J* 12.3 Hz, 1H, $COC\underline{H}_2N$), 7.38-7.71 (m, 9H, $ArC\underline{H}$).

***N*-(2-cyanobenzyl)-2-((3aR, 6R)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-*N,N*-dimethyl-2-oxoethan-1-aminium bromide (309l).**



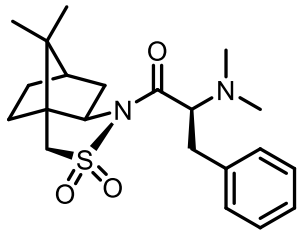
Following procedure (D) outlined above, the product (**309l)** was isolated as solid (0.286 g, 96%, Table 19, Entry 12). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 0.98 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.14 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.397-1.512 (m, 2H, $C(R)_2HC\underline{H}_2C\underline{H}_2$), 1.88-1.99 (m, 3H, $C\underline{H}_2C\underline{H}_2C\underline{H}CH_2$), 2.18 (d, 2H, *J* 5.8, $CH_2CH_2CHC\underline{H}_2$), 3.47 (d, *J* 13.9 Hz, 1H, $C\underline{H}_2SO_2$), 3.53 (d, *J* 13.9 Hz, 1H, $C\underline{H}_2SO_2$), 3.58 (s, 3H, $N(C\underline{H}_3)_2$), 3.69 (s, 3H, $N(C\underline{H}_3)_2$), 4.10 (br, 1H, $NC\underline{H}$), 4.59 (d, *J* 16.6, 1H, $NC\underline{H}_2Ar$), 5.23-5.44 (br, 1H, $NC\underline{H}_2Ar$), 5.50 (d, *J* 12.9 Hz, 1H, $COC\underline{H}_2N$), 5.81 (d, *J* 12.9 Hz, 1H, $COC\underline{H}_2N$), 7.66 (td, *J* 7.1, 8.2, 1H, $ArC\underline{H}$), 7.81-7.86 (m, 2H, $ArC\underline{H}$), 8.47 (d, *J* 8.0 Hz, 1H, $ArC\underline{H}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 19.8 ($(\underline{C}H_3)_2CR_2$), 21.0 ($(\underline{C}H_3)_2CR_2$), 26.2 ($CH_2\underline{C}H_2CHCH_2$), 32.9 ($\underline{C}H_2CH_2CHCH_2$), 38.0 ($CH_2CH_2CH\underline{C}H_2$), 46.0

($CH_2CH_2\underline{C}HCH_2$), 48.0 (($\underline{C}(CH_3)_2$), 49.4 ($\underline{C}CH_2SO_2$), 51.0 ($N(\underline{C}H_3)_2$), 51.9 ($N(\underline{C}H_3)_2$), 52.7 ($\underline{C}H_2SO_2$), 61.9 ($N\underline{C}H_2Ar$), 65.1 (N$\underline{C}$H camphor), 65.3 ($CO\underline{C}H_2N$), 115.7 (Ar$\underline{C}$N), 117.4 (Ar$\underline{C}$CN), 130.0 (Ar$\underline{C}$), 131.7 (Ar$\underline{C}$H), 134.0 (Ar$\underline{C}$H), 134.1 (Ar$\underline{C}$H), 136.4 (Ar$\underline{C}$H), 167.0 (CO). **IR** ν_{max} /cm^{-1}**:** 2950 (CH), 2223 (CN), 1689 (CO), 1335, 1136 (SO_2). **MS** *m/z* (ESI$^+$) calculated for $C_{22}H_{30}N_3O_3S$ [M-Br]$^+$; 416.2002 found 416.2006.

General procedure (E) for [1,2]-Stevens rearrangement.

To a solution benzylic ammonium bromide salt (**309a-m**) (100 mg, 1 eq.) in DMSO (3 mL) at room temperature with 5Å molecular sieves was added phosphazene bases (BTPP) (1.05 eq.). The reaction mixture was allowed to stir overnight. The crude mixture was filtered through a small pad of Celite and washed with Et_2O. The organic layer was extracted with water (10 mL) and aqueous layer extracted with Et_2O (3×15 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude rearranged product, which was injected to HPLC then purified by flash chromatography.

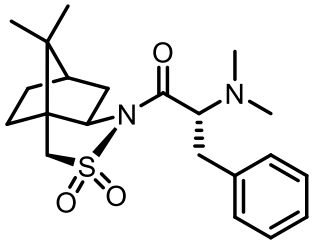
***N*-[(2*S*)-*N,N*-Dimethylphenylalanine]bornane-10,2-sultam (313a).**



Following General procedure (E) outlined above, it was isolated as solid (46 mg, 54%, Table 21, Entry 1). **m.p.**= 190-191 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.66 (s, 3H, $(C\underline{H}_3)_2CR_2$), 0.87 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.26-1.36 (m, 2H, $C(R)_2HC\underline{H}_2C\underline{H}_2$), 1.75-1.86 (m, 4H, $C\underline{H}_2C(R)\underline{H}C\underline{H}_2C\underline{H}_2$), 1.99 (dd, *J* 13.7 Hz, 7.8 Hz, 1H, $C\underline{H}_2C(R)HCH_2CH_2$), 2.50 (s, 6H, $2\times N(C\underline{H}_3)_2$), 2.97 (dd, *J* 13.2 Hz, 7.5 Hz, 1H, Ar-$C\underline{H}_2$), 3.08 (dd, *J* 13.3 Hz, 7.5 Hz, 1H, Ar-CH_2), 3.37 (s, 2H, $C\underline{H}_2SO_2$), 3.81 (b m, 1H, NC$\underline{H}$ camphor), 4.19 (t, *J* 7.5 Hz, 1H, $C\underline{H}CH_2Ar$) 7.14-7.18 (m, 1H, ArCH), 7.22-7.26 (m, 4H, ArCH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.8 (($\underline{C}H_3)_2CR_2$), 20.4 (($\underline{C}H_3)_2CR_2$), 26.4 ($CR_2H\underline{C}H_2CH_2CR_3$), 32.8 ($CR_2HCH_2\underline{C}H_2CR_3$), 34.2 ($\underline{C}H_2Ar$), 38.2 ($CR_2H\underline{C}H_2C(R)HN$), 41.6 ($2\times N(\underline{C}H_3)_2$), 44.5 ($CH_2CH_2\underline{C}HCH_2$), 47.5 ($\underline{C}(CH_3)_2$), 48.0 ($\underline{C}CH_2SO_2$), 53.0 ($\underline{C}H_2SO_2$), 65.0 (N$\underline{C}$H camphor), 67.1 ($N\underline{C}HCH_2Ar$), 126.5 (Ar$\underline{C}$H), 128.3 ($2\times$Ar$\underline{C}$H), 129.5 ($2\times$Ar$\underline{C}$H), 137.3 (Ar$\underline{C}$), 172.2 (CO). **IR** ν_{max} (thin film, cm^{-1}): 2947 (CH), 1686

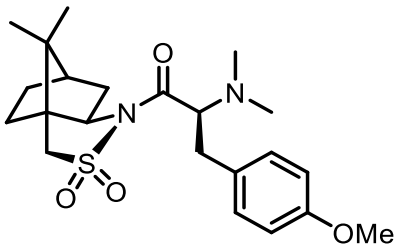
(CO), 1323, 1137 (SO_2). **MS** *m/z* (ESI$^+$) calculated for $C_{21}H_{30}N_2O_3S$ $[M+H]^+$; 391.205 found 391.2051. **TLC** R_f = 0.5 (Toluene:EtOAc, 4:1). **HPLC** t_R = 7.84 min.

***N*-[(2*R*)-*N,N*-Dimethylphenylalanine]bornane-10,2-sultam (314a).**



Following General procedure (E) outlined above, it was impure includes camphorsultam product. Partial characterisation was only possible, as the product was not isolated pure (11%, Table 21, Entry 1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.96 (s, 3H, $(CH_3)_2CR_2$), 1.18 (s, 3H, $(CH_3)_2CR_2$), 1.25-1.51 (m, 2H, $C(R)_2HCH_2CH_2$), 1.84-2.13 (m, 5H, $CH_2C(R)HCH_2CH_2$), 2.38 (s, 6H, 2×$N(CH_3)_2$), 2.88 (dd, *J* 14.0 Hz, 7.2 Hz, 1H, Ar-CH_2), 3.04 (dd, *J* 14.0 Hz, 7.2 Hz, 1H, Ar-CH_2), 3.37 (d, *J* 13.7 Hz, 1H, CH_2SO_2), 3.46 (d, *J* 13.7 Hz, 1H, CH_2SO_2), 3.89 (dd, *J* 7.4 Hz, 5.2 Hz, 1H, NCH camphor), 4.17 (t, *J* 7.0 Hz, 1H, $CHCH_2Ar$) 7.16-7.29 (m, 5H, ArCH).

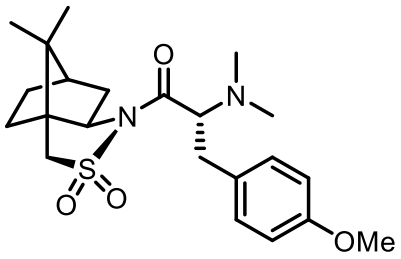
***N*-[(2*S*)-*N,N*-dimethylamino-4-methoxyphenylphenylalanine]bornane-10,2-sultam (313b).**



Following General procedure (E) outlined above, it was isolated as solid (41 mg, 50%, Table 21, Entry 2). **m.p.**= 120-121 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.66 (s, 3H, $(CH_3)_2CR_2$), 0.87 (s, 3H, $(CH_3)_2CR_2$), 1.25-1.35 (m, 2H, $C(R)_2HCH_2CH_2$), 1.74-1.92 (m, 4H, $CH_2C(R)HCH_2CH_2$), 1.99 (dd, *J* 13.7 Hz, 7.7 Hz, 1H, $CH_2C(R)HCH_2CH_2$), 2.49 (s, 6H, 2×$N(CH_3)_2$), 2.92 (dd, *J* 13.3 Hz, 7.6 Hz, 1H, Ar-CH_2), 3.01 (dd, *J* 13.3 Hz, 7.6 Hz, 1H, Ar-CH_2), 3.37 (s, 2H, CH_2SO_2), 3.75 (s, 3H, $ArOCH_3$), 3.80 (b m, 1H, NCH camphor), 4.13 (t, *J* 7.5 Hz, 1H, $CHCH_2Ar$), 6.78 (d, *J* 8.5 Hz, 2H, ArCH), 7.16 (d, *J* 8.5 Hz, 2H, ArCH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.8 ($(CH_3)_2CR_2$), 20.3 ($(CH_3)_2CR_2$), 26.4 ($CR_2HCH_2CH_2CR_3$), 32.8 ($CR_2HCH_2CH_2CR_3$), 33.6 (CH_2Ar), 38.2

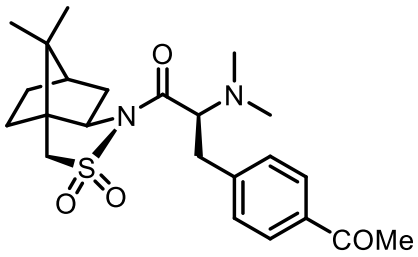
($CR_2HCH_2C(R)HN$), 41.7 (2×$N(CH_3)_2$), 44.5 ($CH_2CH_2CHCH_2$), 47.5 ($C(CH_3)_2$), 48.0 (CCH_2SO_2), 53.0 (CH_2SO_2), 55.2 ($ArOCH_3$), 65.0 (NCH camphor), 67.3 ($NCHCH_2Ar$), 113.7 (2×ArCH), 129.2 (ArC), 130.5 (2×ArCH), 158.3 (ArC), 172.4 (CO). **IR** ν_{max} (thin film, cm^{-1}): 2939 (CH), 1686 (CO), 1325, 1136 (SO_2), 1035 (OMe). **MS** *m/z* (ESI^+) calculated for $C_{22}H_{32}N_2O_4S$ $[M+H]^+$; 421.2156 found 421.2160. **TLC** R_f = 0.1 (PE:EtOAc, 7:3). **HPLC** t_R = 11.29 min.

***N*-[(2*R*)-*N,N*-dimethylamino-4-methoxyphenylphenylalanine]bornane-10,2-sultam (314b).**



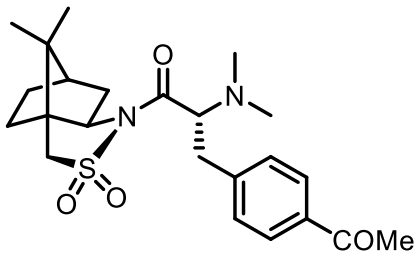
Following General procedure (E) outlined above, it was isolated as solid (12 mg, 15%, Table 21, Entry 2). **m.p.**= 139-141 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.96 (s, 3H, $(CH_3)_2CR_2$), 1.18 (s, 3H, $(CH_3)_2CR_2$), 1.32-1.47 (m, 2H, $C(R)_2HCH_2CH_2$), 1.84-2.13 (m, 5H, $CH_2C(R)HCH_2CH_2$), 2.38 (s, 6H, 2×$N(CH_3)_2$), 2.83 (dd, *J* 14.1 Hz, 7.2 Hz, 1H, Ar-CH_2), 2.97 (dd, *J* 14.1 Hz, 7.2 Hz, 1H, Ar-CH_2), 3.38 (d, *J* 13.7 Hz, 1H, CH_2SO_2), 3.47 (d, *J* 13.7 Hz, 1H, CH_2SO_2), 3.77 (s, 3H, $ArOCH_3$), 3.90 (dd, *J* 7.2 Hz, 5.3 Hz, 1H, NCH camphor), 4.12 (t, 7.5 Hz, 1H, $CHCH_2Ar$), 6.81 (d, *J* 8.5 Hz, 2H, ArCH), 7.17 (d, *J* 8.5 Hz, 2H, ArCH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.9 ($(CH_3)_2CR_2$), 21.0 ($(CH_3)_2CR_2$), 26.4 ($CR_2HCH_2CH_2CR_3$), 32.4 ($CR_2HCH_2CH_2CR_3$), 33.0 (CH_2Ar), 39.1 ($CR_2HCH_2C(R)HN$), 41.3 (2×$N(CH_3)_2$), 44.9 ($CH_2CH_2CHCH_2$), 47.7 ($C(CH_3)_2$), 48.2 (CCH_2SO_2), 53.2 (CH_2SO_2), 55.1 ($ArOCH_3$), 65.4 (NCH camphor), 67.4 ($NCHCH_2Ar$), 113.7 (2×ArCH), 130.2 (ArC), 130.3 (2×ArCH), 158.0 (ArC), 171.6 (CO). **IR** ν_{max} (thin film, cm^{-1}): 2960 (CH), 1682 (CO), 1326, 1176 (SO_2), 1032 (OMe). **MS** *m/z* (ESI^+) calculated for $C_{22}H_{32}N_2O_4S$ $[M+H]^+$; 421.2156 found 421.2160. **TLC** R_f = 0.20 (PE:EtOAc, 7:3). **HPLC** t_R = 7.05 min.

***N*-[(2*S*)-*N,N*-dimethylamino-4-acetylphenylphenylalanine]bornane-10,2-sultam (313c).**



Following General procedure (E) outlined above, it was isolated as solid (48 mg, 57%, Table 21, Entry 3). **m.p.**= 136-137 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.62 (s, 3H, $(C\underline{H}_3)_2CR_2$), 0.86(s, 3H, $(C\underline{H}_3)_2CR_2$), 1.25-1.37 (m, 2H, $C(R)_2HC\underline{H}_2C\underline{H}_2$), 1.75-1.89 (m, 4H, $C\underline{H}_2C(R)\underline{H}C\underline{H}_2C\underline{H}_2$), 2.00 (dd, *J* 13.7 Hz, 7.8 Hz, 1H, $C\underline{H}_2C(R)HCH_2CH_2$), 2.49 (s, 6H, $2\times N(C\underline{H}_3)_2$), 2.56 (s, 3H, $ArCOC\underline{H}_3$), 3.02 (dd, *J* 13.2 Hz, 7.5 Hz, 1H, $Ar\text{-}C\underline{H}_2$), 3.13 (dd, *J* 13.2 Hz, 7.5 Hz, 1H, $Ar\text{-}CH_2$), 3.38 (s, 2H, $C\underline{H}_2SO_2$), 3.84 (dd, *J* 7.0 Hz, 4.9 Hz, 1H, NC<u>H</u> camphor), 4.21 (t, *J* 7.5 Hz, 1H, $C\underline{H}CH_2Ar$), 7.35 (d, *J* 8.2 Hz, 2H, ArC<u>H</u>), 7.85 (d, *J* 8.2 Hz, 2H,ArC<u>H</u>). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.7 ($(\underline{C}H_3)_2CR_2$), 20.2 ($(\underline{C}H_3)_2CR_2$), 26.3 ($CR_2H\underline{C}H_2CH_2CR_3$), 26.6 ($CO\underline{C}H_3$), 32.8 ($CR_2HCH_2\underline{C}H_2CR_3$), 34.2 ($\underline{C}H_2Ar$), 38.2 ($CR_2H\underline{C}H_2C(R)HN$), 41.6 ($2\times N(\underline{C}H_3)_2$), 44.4 ($CH_2CH_2\underline{C}HCH_2$), 47.5 ($\underline{C}(CH_3)_2$), 48.1 ($\underline{C}CH_2SO_2$), 53.0 ($\underline{C}H_2SO_2$), 65.1 (NC<u>H</u> camphor), 66.8 ($N\underline{C}HCH_2Ar$), 128.4 ($2\times Ar\underline{C}H$), 129.7 ($2\times Ar\underline{C}H$), 135.5 (Ar<u>C</u>), 143.3 (Ar<u>C</u>), 171.0 (<u>C</u>O), 197.8 (Ar<u>C</u>O). **IR** ν_{max} (thin film, cm^{-1}): 2954 (CH), 1681 (CO), 1605 (CO), 1324, 1136 (SO_2). **MS** *m/z* (ESI$^+$) calculated for $C_{22}H_{32}N_2O_4S$ $[M+H]^+$; 433.2156 found 433.2158. **TLC** R_f = 0.07 (PE:EtOAc, 7:3). **HPLC** t_R = 41.64 min.

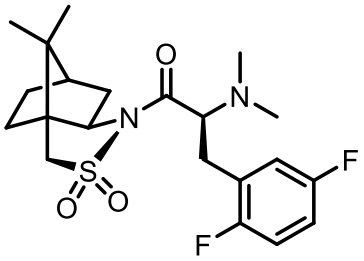
***N*-[(2*R*)-*N,N*-dimethylamino-4-acetylphenylphenylalanine]bornane-10,2-sultam (314c).**



Following General procedure (E) outlined above, it was isolated as solid (10 mg, 11%, Table 21, Entry 3). **m.p.**= 144-146 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.96 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.18 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.31-1.41 (m, 2H, $C(R)_2HC\underline{H}_2C\underline{H}_2$), 1.86-2.16 (m, 5H, $C\underline{H}_2C(R)\underline{H}C\underline{H}_2C\underline{H}_2$), 2.38 (s, 6H, $2\times N(C\underline{H}_3)_2$), 2.56 (s, 3H, $ArCOC\underline{H}_3$), 2.94 (dd, *J* 14.0 Hz, 7.2 Hz, 1H, $Ar\text{-}C\underline{H}_2$), 3.07 (dd, *J* 14.0 Hz, 7.2 Hz, 1H, $Ar\text{-}CH_2$), 3.38 (d, *J* 13.7 Hz, 1H, $C\underline{H}_2SO_2$), 3.48 (d, *J* 13.7 Hz, 1H, $C\underline{H}_2SO_2$), 3.89 (dd, *J* 7.4 Hz, 5.2 Hz, 1H, NC<u>H</u> camphor), 4.19 (t, *J* 7.2 Hz, 1H, $C\underline{H}CH_2Ar$), 7.33 (d, *J* 8.1 Hz, 2H, ArC<u>H</u>), 7.86 (d, *J* 8.1 Hz, 2H, ArC<u>H</u>). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.9 ($(\underline{C}H_3)_2CR_2$), 21.0 ($(\underline{C}H_3)_2CR_2$), 26.4 ($CR_2H\underline{C}H_2CH_2CR_3$), 26.5 ($CO\underline{C}H_3$), 33.0 ($CR_2HCH_2\underline{C}H_2CR_3$), 33.2 ($\underline{C}H_2Ar$), 39.0 ($CR_2H\underline{C}H_2C(R)HN$), 41.2 ($2\times N(\underline{C}H_3)_2$), 44.8 ($CH_2CH_2\underline{C}HCH_2$), 47.7 ($\underline{C}(CH_3)_2$), 48.2 ($\underline{C}CH_2SO_2$), 53.1 ($\underline{C}H_2SO_2$), 65.4 (NC<u>H</u> camphor), 66.9 ($N\underline{C}HCH_2Ar$), 128.4 ($2\times Ar\underline{C}H$), 129.6 ($2\times Ar\underline{C}H$), 135.3 (Ar<u>C</u>), 144.2 (Ar<u>C</u>), 171.1 (<u>C</u>O), 197.9 (Ar<u>C</u>O).

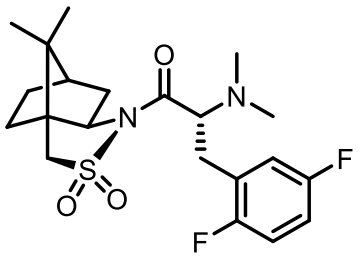
IR ν_{max} (thin film, cm^{-1}): 2933 (CH), 1679 (CO), 1603 (CO), 1330, 1149 (SO_2). **MS** *m/z* (ESI^+) calculated for $C_{22}H_{32}N_2O_4S$ $[M+H]^+$; 433.2156 found 433.2152. **TLC** R_f = 0.15 (PE:EtOAc, 7:3). **HPLC** t_R = 34.13 min.

***N*-[(2*S*)-*N,N*-dimethylamino-2,5-difluorophenylphenylalanine]bornane-10,2-sultam (313d).**



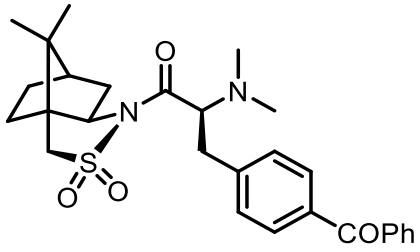
Following General procedure (E) outlined above, it was isolated as solid (50 mg, 60%, Table 21, Entry 4). **m.p.**= 133-135 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.71 (s, 3H, $(C\underline{H}_3)_2CR_2$), 0.88 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.24-1.42 (m, 2H, $C(R)_2HC\underline{H}_2C\underline{H}_2$), 1.79-1.94 (m, 4H, $C\underline{H}_2C(R)\underline{H}C\underline{H}_2C\underline{H}_2$), 2.04 (dd, *J* 13.6 Hz, 7.8 Hz, 1H, $C\underline{H}_2C(R)HCH_2CH_2$), 2.49 (s, 6H, $2\times N(C\underline{H}_3)_2$), 2.96 (dd, *J* 13.4 Hz, 7.3 Hz, 1H, Ar-$C\underline{H}_2$), 3.11 (dd, *J* 13.4 Hz, 7.3 Hz, 1H, Ar-CH_2), 3.38 (s, 2H, $C\underline{H}_2SO_2$), 3.86 (dd, *J* 7.4 Hz, 5.2 Hz, 1H, NC<u>H</u> camphor), 4.17 (dd, *J* 7.8 Hz, 7.0 Hz, 1H, $C\underline{H}CH_2Ar$), 6.79-6.85 (m, 1H, ArC<u>H</u>), 6.91-6.98 (m, 2H, ArC<u>H</u>). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.7 ($(\underline{C}H_3)_2CR_2$), 20.2 ($(\underline{C}H_3)_2CR_2$), 26.3 ($CR_2H\underline{C}H_2CH_2CR_3$), 27.0 ($CR_2HCH_2\underline{C}H_2CR_3$), 32.9 ($\underline{C}H_2Ar$), 38.2 ($CR_2H\underline{C}H_2C(R)HN$), 41.5 ($N(\underline{C}H_3)_2$), 42.8 ($N(\underline{C}H_3)_2$), 44.5 ($CH_2CH_2\underline{C}HCH_2$), 47.5 ($\underline{C}(CH_3)_2$), 48.1 ($\underline{C}CH_2SO_2$), 52.9 ($\underline{C}H_2SO_2$), 65.2 (N<u>C</u>H camphor), 65.5 (N<u>C</u>HCH$_2$Ar), 114.5 (dd, J_{CF} 23.8 Hz, 8.5 Hz, Ar<u>C</u>H), 116.2 (dd, J_{CF} 25.1Hz, 8.7 Hz, Ar<u>C</u>H), 117.7 (dd, J_{CF} 23.8 Hz, 4.6 Hz, Ar<u>C</u>H), 126.2 (dd, J_{CF} 18.2 Hz, 8.0 Hz, Ar<u>C</u>), 156.7 (dd, J_{CF} 110.5 Hz, 2.4 Hz, Ar<u>C</u>F), 159.1 (dd, J_{CF} 110.4 Hz, 2.3 Hz, Ar<u>C</u>F), 170.5 (CO). **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F –119.57 (1F, ArC<u>F</u>), –123.53 (1F, ArC<u>F</u>). **IR** ν_{max} (thin film, cm^{-1}): 2946 (CH), 1682 (CO), 1327, 1135 (SO_2). **MS** *m/z* (ESI^+) calculated for $C_{21}H_{28}N_2O_3F_2S$ $[M+H]^+$; 427.1861 found 427.1866. **TLC** R_f = 0.15 (PE:EtOAc, 7:3). **HPLC** t_R = 36 min.

***N*-[(2*R*)-*N,N*-dimethylamino-2,5-difluorophenylphenylalanine]bornane-10,2-sultam (314d).**



Following General procedure (E) outlined above, it was isolated as solid (27 mg, 29%, Table 21, Entry 4). **m.p.**= 100-101 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.96 (s, 3H, $(CH_3)_2CR_2$), 1.18 (s, 3H, $(CH_3)_2CR_2$), 1.31-1.41 (m, 2H, $C(R)_2HCH_2CH_2$), 1.86-2.05 (m, 4H, $CH_2C(R)HCH_2CH_2$), 2.11 (dd, *J* 13.6 Hz, 7.6 Hz, 1H, $CH_2C(R)HCH_2CH_2$), 2.38 (s, 6H, 2×$N(CH_3)_2$), 2.93 (dd, *J* 14.0 Hz, 7.2 Hz, 1H, Ar-CH_2), 3.02 (dd, *J* 14.0 Hz, 7.2 Hz, 1H, Ar-CH_2), 3.36 (d, *J* 13.6 Hz, 1H, CH_2SO_2), 3.46 (d, *J* 13.6 Hz, 1H, CH_2SO_2), 3.89 (dd, *J* 7.3 Hz, 5.3 Hz, 1H, NCH camphor), 4.18 (t, *J* 7.0 Hz, 1H, $CHCH_2Ar$), 6.81-6.87 (m, 1H, ArCH), 6.91-7.00 (m, 2H, ArCH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.9 ($(CH_3)_2CR_2$), 21.0 ($(CH_3)_2CR_2$), 26.4 ($CR_2HCH_2CH_2CR_3$) and ($CR_2HCH_2CH_2CR_3$), 33.0 (CH_2Ar), 39.0 ($CR_2HCH_2C(R)HN$), 41.2 (2×$N(CH_3)_2$), 44.9 ($CH_2CH_2CHCH_2$), 47.7 ($C(CH_3)_2$), 48.1 (CCH_2SO_2), 53.1 (CH_2SO_2), 65.3 (NCH camphor), 65.8 ($NCHCH_2Ar$), 114.2 (dd, J_{CF} 23.7 Hz, 8.7 Hz, ArCH), 115.9 (dd, J_{CF} 25.3 Hz, 8.4 Hz, ArCH), 118.0 (dd, J_{CF} 23.8 Hz, 4.4 Hz, ArCH), 126.9 (d, J_{CF} 8.0 Hz, ArC), 156.7 (dd, J_{CF} 87.0 Hz, 2.0 Hz, ArCF), 159.1 (d, J_{CF} 87.2, 2.2 Hz, ArCF), 170.8 (CO). **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −119.69 (s, 1F, ArCF), −123.71 (s, 1F, ArCF). **IR** ν_{max} (thin film, cm^{-1}): 2942 (CH), 1686 (CO), 1327, 1131 (SO_2). **MS** *m/z* (ESI^+) calculated for $C_{21}H_{28}N_2O_3F_2S$ $[M+H]^+$; 427.1861 found 427.1862. **TLC** R_f = 0.32 (PE:EtOAc, 7:3). **HPLC** t_R = 23.55 min.

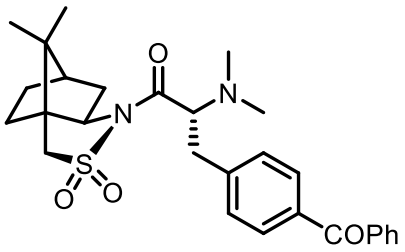
***N*-[(2*S*)-*N,N*-dimethylamino-4-benzoylphenylphenylalanine]bornane-10,2-sultam (313e).**



Following General procedure (E) outlined above, it was isolated as solid (37 mg, 43%, Table 21, Entry 5). **m.p.**= 179-181 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.69 (s, 3H, $(CH_3)_2CR_2$), 0.87 (s, 3H, $(CH_3)_2CR_2$), 1.25-1.38 (m, 2H, $C(R)_2HCH_2CH_2$), 1.77-1.89 (m, 4H, $CH_2C(R)HCH_2CH_2$), 2.02 (dd, *J* 13.7 Hz, 7.8 Hz, 1H, $CH_2C(R)HCH_2CH_2$), 2.52 (s, 6H, 2×$N(CH_3)_2$), 3.07 (dd, *J* 13.2 Hz, 7.4 Hz, 1H, Ar-CH_2), 3.17 (dd, *J* 13.2 Hz, 7.4 Hz, 1H, Ar-CH_2), 3.39 (s, 2H, CH_2SO_2), 3.85 (dd, *J* 6.9 Hz, 7.0 Hz, 1H, NCH camphor), 4.25 (t, *J* 7.4 Hz, 1H, $CHCH_2Ar$), 7.38 (d, *J* 8.0 Hz, 2H, ArCH), 7.47 (t, *J* 7.4 Hz, 1H,

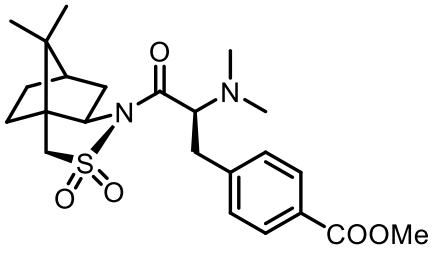
ArC<u>H</u>), 7.57 (t, *J* 7.3 Hz, 1H, ArC<u>H</u>), 7.72 (d, *J* 8.0 Hz, 2H, ArC<u>H</u>), 7.77 (d, *J* 7.2 Hz, 2H, ArCH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.7 (($\underline{C}H_3)_2CR_2$), 20.4 (($\underline{C}H_3)_2CR_2$), 26.3 ($CR_2H\underline{C}H_2CH_2CR_3$), 32.8 ($CR_2HCH_2\underline{C}H_2CR_3$), 34.1 ($\underline{C}H_2Ar$), 38.2 ($CR_2H\underline{C}H_2C(R)HN$), 41.6 (2×N($\underline{C}H_3)_2$), 44.4 ($CH_2CH_2\underline{C}HCH_2$), 47.6 ($\underline{C}(CH_3)_2$), 48.1 ($\underline{C}CH_2SO_2$), 53.0 ($\underline{C}H_2SO_2$), 65.1 (N<u>C</u>H camphor), 66.8 (N<u>C</u>HCH$_2$Ar), 128.2 (2×Ar<u>C</u>H), 129.5 (2×Ar<u>C</u>H), 129.9 ((2×Ar<u>C</u>H), 130.3 (2×Ar<u>C</u>H), 132.2 (Ar<u>C</u>H), 135.8 (Ar<u>C</u>), 137.7 (Ar<u>C</u>), 143.5 (Ar<u>C</u>), 171.5 (<u>C</u>O), 196.2 (Ar<u>C</u>O). **IR** ν_{max} (thin film, cm^{-1}): 2948 (CH), 1683 (CO), 1655 (CO), 1324, 1135 (SO_2). **MS** *m/z* (ESI$^+$) calculated for $C_{28}H_{34}N_2O_4S$ [M+H]$^+$; 495.2312 found 495.2318. **TLC** R_f = 0.08 (PE:EtOAc, 7:3). **HPLC** t_R = 10.80 min.

***N*-[(2*R*)-*N,N*-dimethylamino-4-benzoylphenylphenylalanine]bornane-10,2-sultam (314e).**



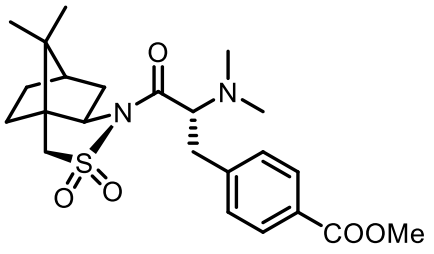
Following General procedure (E) outlined above, it was isolated as solid (14.5 mg, 17%, Table 21, Entry 5). **m.p.**= 124-126 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.97 (s, 3H, ($C\underline{H}_3)_2CR_2$), 1.19 (s, 3H, ($C\underline{H}_3)_2CR_2$), 1.33-1.47 (m, 2H, C(R)$_2$HC$\underline{H}_2C\underline{H}_2$), 1.84-2.17 (m, 5H, $C\underline{H}_2C(R)\underline{H}C\underline{H}_2C\underline{H}_2$), 2.40 (s, 6H, 2×N($C\underline{H}_3)_2$), 2.98 (dd, *J* 13.9 Hz, 7.2 Hz, 1H, Ar-C$\underline{H}_2$), 3.10 (dd, *J* 13.7 Hz, 7.2 Hz, 1H, Ar-C$\underline{H}_2$), 3.38 (d, *J* 13.6, 1H, C$\underline{H}_2SO_2$), 3.49 (d, *J* 13.6, 1H, C$\underline{H}_2SO_2$), 3.91 (dd, *J* 7.2 Hz, 5.4 Hz, 1H, NC<u>H</u> camphor), 4.22 (t, *J* 6.8 Hz, 1H, C<u>H</u>CH$_2$Ar), 7.37 (d, *J* 7.8 Hz, 2H, ArC<u>H</u>), 7.48 (t, *J* 7.8 Hz, 1H, ArC<u>H</u>), 7.56 (t, *J* 7.4 Hz, 1H, ArC<u>H</u>), 7.73 (d, *J* 7.6 Hz, 2H, ArCH), 7.78 (d, *J* 7.6 Hz, 2H, ArCH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.9 (($\underline{C}H_3)_2CR_2$), 21.0 (($\underline{C}H_3)_2CR_2$), 26.4 ($CR_2H\underline{C}H_2CH_2CR_3$), 33.0 ($CR_2HCH_2\underline{C}H_2CR_3$), 33.3 ($\underline{C}H_2Ar$), 39.1 ($CR_2H\underline{C}H_2C(R)HN$), 41.2 (2×N($\underline{C}H_3)_2$), 44.9 ($CH_2CH_2\underline{C}HCH_2$), 47.7 ($\underline{C}(CH_3)_2$), 48.2 ($\underline{C}CH_2SO_2$), 53.1 ($\underline{C}H_2SO_2$), 65.4 (N<u>C</u>H camphor), 67.0 (N<u>C</u>HCH$_2$Ar), 128.1 (2×Ar<u>C</u>H), 129.3 (2×Ar<u>C</u>H), 130 ((2×Ar<u>C</u>H), 130.2 ((2×Ar<u>C</u>H), 132.1 (Ar<u>C</u>H), 135.5 (Ar<u>C</u>), 137.9 (Ar<u>C</u>), 143.6 (Ar<u>C</u>), 171.1 (<u>C</u>O), 196.5 (Ar<u>C</u>O).**IR** ν_{max} (thin film, cm^{-1}): 2957 (CH), 1684 (CO), 1654 (CO), 1326, 1131 (SO_2). **MS** *m/z* (ESI$^+$) calculated for $C_{28}H_{34}N_2O_4S$ [M+H]$^+$; 495.2312 found 495.2319. **TLC** R_f = 0.18 (PE:EtOAc, 7:3). **HPLC** t_R = 6.31 min.

***N*-[(2*S*)-*N,N*-dimethylamino-4-methoxycarbonylphenyl)phenylalanine]bornane-10,2-sultam (313f).**



Following General procedure (E) outlined above, it was isolated as solid (32 mg, 41%, Table 21, Entry 6). **m.p.**= 133-134 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.62 (s, 3H, $(C\underline{H}_3)_2CR_2$), 0.86 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.24-1.36 (m, 2H, $C(R)_2HC\underline{H}_2C\underline{H}_2$), 1.75-1.85 (m, 4H, $C\underline{H}_2C(R)\underline{H}C\underline{H}_2C\underline{H}_2$), 2.00 (dd, *J* 13.8 Hz, 7.8 Hz, 1H, $C\underline{H}_2C(R)HCH_2CH_2$), 2.48 (s, 6H, $2\times N(C\underline{H}_3)_2$), 3.01 (dd, *J* 13.2 Hz, 7.5 Hz, 1H, Ar-$C\underline{H}_2$), 3.12 (dd, *J* 13.2 Hz, 7.5 Hz, 1H, Ar-CH_2), 3.37 (s, 2H, $C\underline{H}_2SO_2$), 3.83 (br dd, *J* 7.8 Hz, 4.9 Hz, 1H, NC<u>H</u> camphor), 3.89 (s, 3H, COO$C\underline{H}_3$), 4.20 (t, *J* 7.5 Hz, 1H, $C\underline{H}CH_2Ar$), 7.33 (d, *J* 8.2 Hz, 2H, ArC<u>H</u>), 7.92 (d, *J* 8.2 Hz, 2H, ArC<u>H</u>). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.7 ($(\underline{C}H_3)_2CR_2$), 20.2 ($(\underline{C}H_3)_2CR_2$), 26.3 ($CR_2H\underline{C}H_2CH_2CR_3$), 32.8 ($CR_2HCH_2\underline{C}H_2CR_3$), 34.1 ($\underline{C}H_2Ar$), 38.2 ($CR_2H\underline{C}H_2C(R)HN$), 41.6 ($2\times N(\underline{C}H_3)_2$), 44.4 ($CH_2CH_2\underline{C}HCH_2$), 47.5 ($\underline{C}(CH_3)_2$), 48.1 ($\underline{C}CH_2SO_2$), 52.0 (COO<u>C</u>H3), 53.0 ($\underline{C}H_2SO_2$), 65.1 (N<u>C</u>H camphor), 66.8 (N<u>C</u>HCH_2Ar), 128.4 (Ar<u>C</u>), 129.6 ($2\times Ar\underline{C}H$), 129.6 (($2\times Ar\underline{C}H$), 143.0 (Ar<u>C</u>), 167.0 (Ar<u>C</u>O), 171.7 (<u>C</u>O). **IR** ν_{max} (thin film, cm^{-1}): 2948 (CH), 1715 (CO), 1683 (CO), 1324, 1136 (SO_2). **MS** *m/z* (ESI^+) calculated for $C_{23}H_{32}N_2O_5S$ $[M+H]^+$; 449.2105 found 449.2110 . **TLC** R_f = 0.48 (PE:EtOAc, 4:1). **HPLC** t_R = 9.41 min.

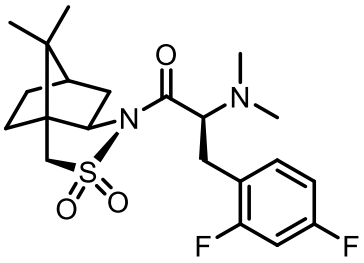
***N*-[(2*R*)-*N,N*-dimethylamino-4-methoxycarbonylphenyl)phenylalanine]bornane-10,2-sultam (314f).**



Following General procedure (E) outlined above, it was isolated as solid (16 mg, 22%, Table 21, Entry 6). **m.p.**= 161-162 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.96 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.18 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.25-1.46 (m, 2H, $C(R)_2HC\underline{H}_2C\underline{H}_2$), 1.86-2.17 (m, 5H, $C\underline{H}_2C(R)\underline{H}C\underline{H}_2C\underline{H}_2$), 2.38 (s, 6H, $2\times N(C\underline{H}_3)_2$), 2.93 (dd, *J* 13.9 Hz, 7.2 Hz, 1H, Ar-$C\underline{H}_2$), 3.07 (dd, *J* 13.9 Hz, 7.2 Hz, 1H, Ar-CH_2), 3.37 (d, *J* 13.7, 1H, $C\underline{H}_2SO_2$), 3.47

(d, *J* 13.7, 1H, C<u>H</u>$_2$SO$_2$), 3.87 (dd, *J* 12.1 Hz, 6.2 Hz, 1H, NC<u>H</u> camphor), 3.88 (s, 3H, COO<u>C</u>H$_3$), 4.18 (t, *J* 6.8 Hz, 1H, C<u>H</u>CH$_2$Ar), 7.32 (d, *J* 8.1 Hz, 2H, ArC<u>H</u>), 7.94 (d, *J* 8.1 Hz, 2H, ArC<u>H</u>). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.9 ((<u>C</u>H$_3$)$_2$CR$_2$), 21.0 ((<u>C</u>H$_3$)$_2$CR$_2$), 26.4 (CR$_2$H<u>C</u>H$_2$CH$_2$CR$_3$), 31.8 (CR$_2$HCH$_2$<u>C</u>H$_2$CR$_3$), 33.0 (<u>C</u>H$_2$Ar), 39.0 (CR$_2$H<u>C</u>H$_2$C(R)HN), 41.2 (2×N(<u>C</u>H$_3$)$_2$), 44.9 (CH$_2$CH$_2$<u>C</u>HCH$_2$), 47.7 (<u>C</u>(CH$_3$)$_2$), 48.2 (<u>C</u>CH$_2$SO$_2$), 51.9 (COO<u>C</u>H3), 53.1 (<u>C</u>H$_2$SO$_2$), 65.4 (N<u>C</u>H camphor), 67.0 (N<u>C</u>HCH$_2$Ar), 128.1 (Ar<u>C</u>), 129.4 (2×Ar<u>C</u>H), 129.5 (2×Ar<u>C</u>H), 143.9 (Ar<u>C</u>), 167.1 (Ar<u>C</u>O), 171.1 (<u>C</u>O). **IR** ν_{max} (thin film, cm^{-1}): 2953 (CH), 1718 (CO), 1688 (CO), 1327, 1133 (SO$_2$). **MS** *m/z* (ESI$^+$) calculated for $C_{23}H_{32}N_2O_5S$ $[M+H]^+$; 449.2105 found 449.2108 . **TLC** R_f = 0.26 (PE:EtOAc, 7:3). **HPLC** t_R = 5.89 min.

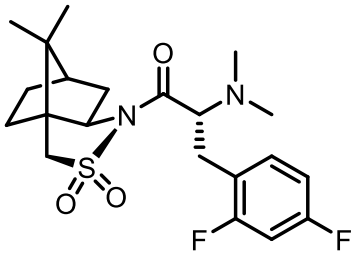
***N*-[(2*S*)-*N,N*-dimethylamino-2,4-difluorophenylphenylalanine]bornane-10,2-sultam (313g).**



Following General procedure (E) outlined above, it was isolated as solid (35.9 mg, 42%, Table 21, Entry 7). **m.p.**= 129-130 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.67 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$), 0.88 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$), 1.24-1.37 (m, 2H, C(R)$_2$HC<u>H</u>$_2$C<u>H</u>$_2$), 1.77-1.87 (m, 4H, C<u>H</u>$_2$C(R)<u>H</u>C<u>H</u>$_2$C<u>H</u>$_2$), 2.02 (dd, *J* 13.7 Hz, 7.8 Hz, 1H, C<u>H</u>$_2$C(R)HCH$_2$CH$_2$), 2.49 (s, 6H, 2×N(C<u>H</u>$_3$)$_2$), 2.97 (dd, *J* 13.3 Hz, 7.6 Hz, 1H, Ar-C<u>H</u>$_2$), 3.09 (dd, *J* 13.3 Hz, 7.6 Hz, 1H, Ar-CH$_2$), 3.37 (s, 2H, C<u>H</u>$_2$SO$_2$), 3.84 (dd, *J* 7.6 Hz, 4.8 Hz, 1H, NC<u>H</u> camphor), 4.16 (dd, *J* 8.2 Hz, 6.6 Hz, 1H, C<u>H</u>CH$_2$Ar), 6.71-6.77 (m, 2H, 2×ArC<u>H</u>), 7.18-7.24 (m, 1H, ArC<u>H</u>). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.7 ((<u>C</u>H$_3$)$_2$CR$_2$), 20.2 ((<u>C</u>H$_3$)$_2$CR$_2$), 26.3 (CR$_2$H<u>C</u>H$_2$CH$_2$CR$_3$), 26.7 (CR$_2$HCH$_2$<u>C</u>H$_2$CR$_3$), 32.9 (<u>C</u>H$_2$Ar), 38.2 (CR$_2$H<u>C</u>H$_2$C(R)HN), 41.60 (2×N(<u>C</u>H$_3$)$_2$), 44.5 (CH$_2$CH$_2$<u>C</u>HCH$_2$), 47.5 (<u>C</u>(CH$_3$)$_2$), 48.0 (<u>C</u>CH$_2$SO$_2$), 52.9 (<u>C</u>H$_2$SO$_2$), 65.1 (N<u>C</u>H camphor), 65.6 (N<u>C</u>HCH$_2$Ar), 103.7 (t, J_{CF} 25.5 Hz, ArC<u>H</u>), 111.0 (dd, J_{CF} 20.2 Hz, 4.1 Hz, ArC<u>H</u>), 120.2 (dd, J_{CF} 15.5 Hz, 4.0 Hz, Ar<u>C</u>), 132.1 (dd, J_{CF} 9.3 Hz, 6.4 Hz, ArC<u>H</u>), 160.4 (dd, J_{CF} 59.2 Hz, 12.6 Hz, Ar<u>C</u>F), 162.9 (dd, J_{CF} 57.0 Hz, 12.1 Hz, Ar<u>C</u>F), 171.6 (CO). **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −112.86 - −112.74 (m, 2F, ArC<u>F</u>). **IR** ν_{max} (thin film, cm^{-1}): 2948 (CH), 1685 (CO),

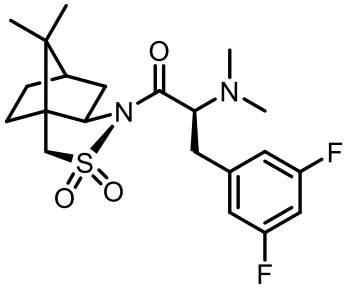
1330, 1138 (SO_2). **MS** *m/z* (ESI$^+$) calculated for $C_{21}H_{28}N_2O_3F_2S$ $[M+H]^+$; 427.1861 found 427.1864. **TLC** R_f = 0.2 (PE:EtOAc, 4:1). **HPLC** t_R = 9.42 min.

***N*-[(2*R*)-*N,N*-dimethylamino-2,4-difluorophenylphenylalanine]bornane-10,2-sultam (314g).**



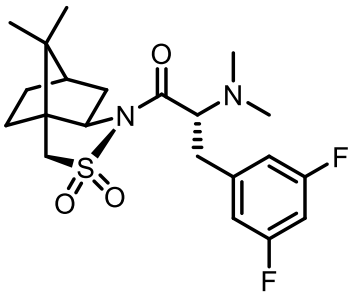
Following General procedure (E) outlined above, it was isolated as solid (14.77mg, 19%, Table 21, Entry 7). **m.p.**= 125-126 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.96 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.17(s, 3H, $(C\underline{H}_3)_2CR_2$), 1.25-1.41 (m, 2H, $C(R)_2HC\underline{H}_2C\underline{H}_2$), 1.86-2.04 (m, 4H, $C\underline{H}_2C(R)\underline{H}C\underline{H}_2C\underline{H}_2$), 2.10 (dd, *J* 13.6 Hz, 7.7 Hz, 1H, $C\underline{H}_2C(R)HCH_2CH_2$), 2.38 (s, 6H, 2×$N(C\underline{H}_3)_2$), 2.93 (dd, *J* 14.0 Hz, 7.2 Hz, 1H, Ar-$C\underline{H}_2$), 3.00 (dd, *J* 14.0 Hz, 7.2 Hz, 1H, Ar-CH_2), 3.36 (d, *J* 13.7 Hz, 1H, $C\underline{H}_2SO_2$), 3.46 (d, *J* 13.7 Hz, 1H, $C\underline{H}_2SO_2$), 3.87 (dd, *J* 7.2 Hz, 5.2 Hz, 1H, NC<u>H</u> camphor), 4.15 (t, *J* 7.1 Hz, 1H, $C\underline{H}CH_2Ar$), 6.72 (m, 2H, 2×ArC<u>H</u>), 7.19-7.25 (m, 1H, ArC<u>H</u>). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.9 ($(\underline{C}H_3)_2CR_2$), 21.0 ($(\underline{C}H_3)_2CR_2$), 26.4 ($CR_2H\underline{C}H_2CH_2CR_3$), 33.0 ($\underline{C}H_2Ar$ and $(CR_2HCH_2\underline{C}H_2CR_3$), 39.0 ($CR_2H\underline{C}H_2C(R)HN$), 41.2 (2×$N(\underline{C}H_3)_2$), 44.9 ($CH_2CH_2\underline{C}HCH_2$), 47.7 ($\underline{C}(CH_3)_2$), 48.1 ($\underline{C}CH_2SO_2$), 53.1 ($\underline{C}H_2SO_2$), 65.3 (N<u>C</u>H camphor), 66.0 (N<u>C</u>HCH_2Ar), 103.2 (t, J_{CF} 25.2 Hz, Ar<u>C</u>H), 110.9 (dd, J_{CF} 20.6 Hz, 3.6 Hz, Ar<u>C</u>H), 120.8 (dd, J_{CF} 15.6 Hz, 3.9 Hz, Ar<u>C</u>), 132.3 (dd, J_{CF} 9.1 Hz, 6.4 Hz, Ar<u>C</u>H), 160.3 (dd, J_{CF} 20.0 Hz, 12.6 Hz, Ar<u>C</u>F), 162.9 (dd, J_{CF} 35.5 Hz, 23.1 Hz, Ar<u>C</u>F), 170.9 (CO). **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −113.01 (m, 1F, ArC<u>F</u>), −113.29 (br, m, 1F, ArC<u>F</u>). **IR** ν_{max}(thin film, cm^{-1}): 2956 (CH), 1686 (CO), 1329, 1133 (SO_2). **MS** *m/z* (ESI$^+$) calculated for $C_{21}H_{28}N_2O_3F_2S$ $[M+H]^+$; 427.1861 found 427.1866. **TLC** R_f = 0.37 (PE:EtOAc, 4:1). **HPLC** t_R = 4.65 min.

***N*-[(2*S*)-*N,N*-dimethylamino-3,5-difluorophenylphenylalanine]bornane-10,2-sultam (313h).**



Following General procedure (E) outlined above, it was isolated as solid (46.6 mg, 55%, Table 21, Entry 8). **m.p.**= 173-175 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.78 (s, 3H, ($C\underline{H}_3$)$_2$CR$_2$), 0.90 (s, 3H, ($C\underline{H}_3$)$_2$CR$_2$), 1.25-1.39 (m, 2H, C(R)$_2$HC$\underline{H}_2$C$\underline{H}_2$), 1.80-1.91 (m, 4H, C$\underline{H}_2$C(R)$\underline{H}$C$\underline{H}_2$C$\underline{H}_2$), 2.04 (dd, *J* 13.8 Hz, 7.8 Hz, 1H, C$\underline{H}_2$C(R)HCH$_2$CH$_2$), 2.48 (s, 6H, 2×N($C\underline{H}_3$)$_2$), 2.93 (dd, *J* 13.4 Hz, 7.5 Hz, 1H, Ar-C$\underline{H}_2$), 3.05 (dd, *J* 13.4 Hz, 7.5 Hz, 1H, Ar-CH$_2$), 3.37 (d, *J* 14.0 Hz, 1H, C$\underline{H}_2$SO$_2$), 3.41 (d, *J* 14.0 Hz, 1H, C$\underline{H}_2$SO$_2$), 3.86 (dd, *J* 7.6 Hz, 5.0 Hz, 1H, NC$\underline{H}$ camphor), 4.15 (t, *J* 7.5 Hz, 1H, C$\underline{H}$CH$_2$Ar), 6.59 (app t, J_{HF} 9.0, 1H, ArC$\underline{H}$), 6.78 (app d, J_{HF} 6.2, 2H, ArC$\underline{H}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.7 (($\underline{C}$H$_3$)$_2$CR$_2$), 20.2 (($\underline{C}$H$_3$)$_2$CR$_2$), 26.3 (CR$_2$H$\underline{C}$H$_2$CH$_2$CR$_3$), 32.8 (CR$_2$HCH$_2\underline{C}$H$_2$CR$_3$), 33.9 ($\underline{C}$H$_2$Ar), 38.2 (CR$_2$H$\underline{C}$H$_2$C(R)HN), 41.5 (2×N($\underline{C}$H$_3$)$_2$), 44.5 (CH$_2$CH$_2\underline{C}$HCH$_2$), 47.6 ($\underline{C}$(CH$_3$)$_2$), 48.1 ($\underline{C}$CH$_2$SO$_2$), 52.9 ($\underline{C}$H$_2$SO$_2$), 65.1 (N$\underline{C}$H camphor), 66.6 (N$\underline{C}$HCH$_2$Ar), 102.0 (t, J_{CF} 25.1 Hz, Ar$\underline{C}$H), 112.3 (dd, J_{CF} 18.2 Hz, 6.5 Hz, Ar$\underline{C}$H), 141.4 (t, J_{CF} 9.2 Hz, Ar$\underline{C}$), 161.6 (d, J_{CF} 12.7 Hz, Ar$\underline{C}$F), 164.1 (d, J_{CF} 12.9 Hz, Ar$\underline{C}$F), 171.6 (CO). **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −110.55 (t, J_{HF} 8.6 Hz, 2F, ArC$\underline{F}$). **IR** ν_{max} (thin film, cm^{-1}): 2950 (CH), 1685 (CO), 1321, 1135 (SO_2). **MS** *m/z* (ESI$^+$) calculated for $C_{21}H_{28}N_2O_3F_2S$ $[M+H]^+$; 427.1861 found 427.1861. **TLC** R_f = 0.04 (PE:EtOAc, 4:1). **HPLC** t_R = 39.33 min.

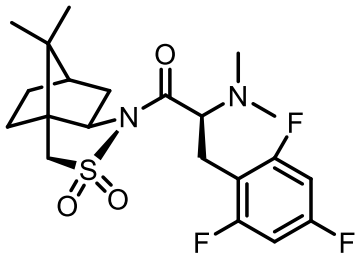
***N*-[(2*R*)-*N,N*-dimethylamino-3,5-difluorophenylphenylalanine]bornane-10,2-sultam (314h).**



Following General procedure (E) outlined above, it was isolated as solid (27.4 mg, 32%, Table 21, Entry 8). **m.p.**= 136-137 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.97 (s, 3H, ($C\underline{H}_3$)$_2$CR$_2$), 1.19 (s, 3H, ($C\underline{H}_3$)$_2$CR$_2$), 1.25-1.42 (m, 2H, C(R)$_2$HC$\underline{H}_2$C$\underline{H}_2$), 1.87-2.07 (m, 4H, C$\underline{H}_2$C(R)$\underline{H}$C$\underline{H}_2$C$\underline{H}_2$), 2.11 (dd, *J* 13.7 Hz, 7.6 Hz, 1H, C$\underline{H}_2$C(R)HCH$_2$CH$_2$), 2.37 (s, 6H, 2×N($C\underline{H}_3$)$_2$), 2.86 (dd, *J* 14.1 Hz, 6.6 Hz, 1H, Ar-C$\underline{H}_2$), 2.98 (dd, *J* 14.1 Hz, 6.6 Hz, 1H, Ar-CH$_2$), 3.39 (d, *J* 13.7 Hz, 1H, C$\underline{H}_2$SO$_2$), 3.49 (d, *J* 13.7 Hz, 1H, C$\underline{H}_2$SO$_2$), 3.89 (dd, *J* 7.4 Hz, 5.2 Hz, 1H, NC$\underline{H}$ camphor), 4.13 (t, *J* 6.7 Hz, 1H, C$\underline{H}$CH$_2$Ar), 6.62 (app t, J_{HF} 9.0, 1H, ArC$\underline{H}$), 6.78 (app d, J_{HF} 6.4, 2H, ArC$\underline{H}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.9 (($\underline{C}$H$_3$)$_2$CR$_2$), 21.0 (($\underline{C}$H$_3$)$_2$CR$_2$), 26.4 (CR$_2$H$\underline{C}$H$_2$CH$_2$CR$_3$), 33.0

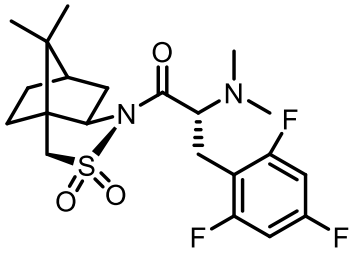
($CR_2HCH_2\underline{C}H_2CR_3$), 33.1 ($\underline{C}H_2Ar$), 39.0 ($CR_2H\underline{C}H_2C(R)HN$), 41.2 ($2\times N(\underline{C}H_3)_2$), 44.8 ($CH_2CH_2\underline{C}HCH_2$), 47.7 ($\underline{C}(CH_3)_2$), 48.2 ($\underline{C}CH_2SO_2$), 53.1 ($\underline{C}H_2SO_2$), 65.4 (N$\underline{C}$H camphor), 66.7 (N$\underline{C}HCH_2$Ar), 101.7 (t, J_{CF} 25.1 Hz, Ar$\underline{C}$H), 112.2 (dd, J_{CF} 18.0 Hz, 6.4 Hz, Ar$\underline{C}$H), 142.2 (t, J_{CF} 9.3 Hz, Ar$\underline{C}$), 161.5 (d, J_{CF} 12.8 Hz, Ar$\underline{C}$F), 164.0 (d, J_{CF} 12.8 Hz, Ar$\underline{C}$F), 170.9 (CO). **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −112.86 (t, J_{HF} 8.2 Hz, 2F, ArC$\underline{F}$). **IR** ν_{max} (thin film, cm^{-1}): 2954 (CH), 1686 (CO), 1325, 1132(SO_2). **MS** *m/z* (ESI$^+$) calculated for $C_{21}H_{28}N_2O_3F_2S$ $[M+H]^+$; 427.1861 found 427.1860. **TLC** R_f = 0.14 (PE:EtOAc, 4:1). **HPLC** t_R = 20.40 min.

***N*-[(2*S*)-*N,N*-dimethylamino-2,4,6-trifluorophenylphenylalanine]bornane-10,2-sultam (313i).**



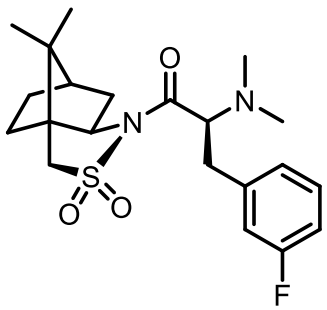
Following General procedure (E) outlined above, it was isolated as solid (35 mg, 41%, Table 21, Entry 9). **m.p.**= 135-136 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.69 (s, 3H, ($C\underline{H}_3)_2CR_2$), 0.88 (s, 3H, ($C\underline{H}_3)_2CR_2$), 1.23-1.41 (m, 2H, $C(R)_2HC\underline{H}_2C\underline{H}_2$), 1.79-1.95 (m, 4H, $C\underline{H}_2C(R)\underline{H}C\underline{H}_2C\underline{H}_2$), 2.05 (dd, *J* 13.8 Hz, 7.8 Hz, 1H, $C\underline{H}_2C(R)HCH_2CH_2$), 2.50 (s, 6H, $2\times N(C\underline{H}_3)_2$), 2.96 (dd, *J* 13.3 Hz, 7.3 Hz, 1H, Ar-$C\underline{H}_2$), 3.17 (dd, *J* 13.3 Hz, 7.3 Hz, 1H, Ar-CH_2), 3.36 (s, 2H, $C\underline{H}_2SO_2$), 3.86 (dd, *J* 7.7 Hz, 5.1 Hz, 1H, NC$\underline{H}$ camphor), 4.17 (dd, *J* 9.5 Hz, 5.2 Hz, 1H, C$\underline{H}CH_2Ar$), 6.55-6.62 (m, 2H, 2×ArC$\underline{H}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.7 (($\underline{C}H_3)_2CR_2$), 20.3 ($\underline{C}H_2Ar$), 21.4 (($\underline{C}H_3)_2CR_2$), 26.3 ($CR_2H\underline{C}H_2CH_2CR_3$), 32.9 ($CR_2HCH_2\underline{C}H_2CR_3$), 38.2 ($CR_2H\underline{C}H_2C(R)HN$), 41.6 ($2\times N(\underline{C}H_3)_2$), 44.5 ($CH_2CH_2\underline{C}HCH_2$), 47.5 ($\underline{C}(CH_3)_2$), 47.9 ($\underline{C}CH_2SO_2$), 53.0 ($\underline{C}H_2SO_2$), 64.4 (N$\underline{C}$H camphor), 65.3 (N$\underline{C}HCH_2$Ar), 99.7 -100.2 (m, 2×Ar$\underline{C}$H), 109.2 (td, J_{CF} 20.3 Hz, 5.0 Hz, Ar$\underline{C}$), 160.4 (dd, J_{CF} 14.2 Hz, 3.5 Hz, Ar$\underline{C}$F), 162.9 (dd, J_{CF} 15.4 Hz, 4.0 Hz, 2× Ar$\underline{C}$F), 170.6 (CO). **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −110.72 (t, J_{HF} 6.7, 2F, ArC$\underline{F}$), −110.54 - −110.58 (br m, 1F, ArC$\underline{F}$). **IR** ν_{max} (thin film, cm^{-1}): 2960 (CH), 1694 (CO), 1329, 1135 (SO_2). **MS** *m/z* (ESI$^+$) calculated for $C_{21}H_{27}N_2O_3F_3S$ $[M+H]^+$; 445.1767 found 445.1767. **TLC** R_f = 0.31 (PE:EtOAc, 1:1). **HPLC** t_R = 6.8 min.

***N*-[(2*R*)-*N,N*-dimethylamino-2,4,6-trifluorophenylphenylalanine]bornane-10,2-sultam (314i).**



Following General procedure (E) outlined above, it was isolated as solid (20 mg, 24%, Table 21, Entry 9). **m.p.**= 145-146 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.96 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.19 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.25-1.43 (m, 2H, $C(R)_2HC\underline{H}_2C\underline{H}_2$), 1.86-2.04 (m, 4H, $C\underline{H}_2C(R)\underline{H}C\underline{H}_2C\underline{H}_2$), 2.12 (dd, *J* 13.7 Hz, 7.7 Hz, 1H, $C\underline{H}_2C(R)HCH_2CH_2$), 2.36 (s, 6H, $2\times N(C\underline{H}_3)_2$), 2.96 (dd, *J* 14.1 Hz, 7.4 Hz, 1H, Ar-$C\underline{H}_2$), 3.03 (dd, *J* 14.1 Hz, 7.4 Hz, 1H, Ar-CH_2), 3.36 (d, *J* 13.6 Hz, 1H, $C\underline{H}_2SO_2$), 3.46 (d, *J* 13.6 Hz, 1H, $C\underline{H}_2SO_2$), 3.89 (dd, *J* 7.6 Hz, 5.0 Hz, 1H, NC<u>H</u> camphor), 4.24 (t, *J* 7.3 Hz, 1H, $C\underline{H}CH_2Ar$), 6.60 (t, J_{HF} 8.0, 2H, 2×ArC<u>H</u>). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.9 ($(\underline{C}H_3)_2CR_2$), 20.7 (CH_2Ar), 21.0 ($(\underline{C}H_3)_2CR_2$), 26.4 ($CR_2H\underline{C}H_2CH_2CR_3$), 33.0 ($CR_2HCH_2\underline{C}H_2CR_3$), 39.0 ($CR_2H\underline{C}H_2C(R)HN$), 41.3 ($2\times N(\underline{C}H_3)_2$), 44.8 ($CH_2CH_2\underline{C}HCH_2$), 47.7 ($\underline{C}(CH_3)_2$), 48.0 ($\underline{C}CH_2SO_2$), 53.2 ($\underline{C}H_2SO_2$), 64.7 (N<u>C</u>H camphor), 65.4 (N<u>C</u>HCH$_2$Ar), 99.6 -100.1 (m, 2×Ar<u>C</u>H), 110.1 (dd, J_{CF} 20.2 Hz, 4.6 Hz, Ar<u>C</u>), 160.6 (d, J_{CF} 11.3 Hz, Ar<u>C</u>F), 163.1 (t, J_{CF} 14.7 Hz, 2× Ar<u>C</u>F), 170.6 (CO). **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −110.70 (t, J_{HF} 6.8, 2F, ArC<u>F</u>), −110.85 - −110.93 (br m, 1F, ArC<u>F</u>). **IR** ν_{max} (thin film, cm^{-1}): 2953 (CH), 1683 (CO), 1322, 1134 (SO_2). **MS** *m/z* (ESI^+) calculated for $C_{21}H_{27}N_2O_3F_3S$ $[M+H]^+$; 445.1767 found 445.1769. **TLC** R_f = 0.62 (PE:EtOAc, 1:1). **HPLC** t_R = 4.83 min.

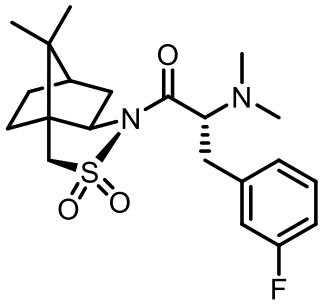
***N*-[(2*S*)-*N,N*-dimethylamino-3-fluorophenylphenylalanine]bornane-10,2-sultam (313j).**



Following General procedure (E) outlined above, it was isolated as solid (52.6 mg, 65%, Table 21, Entry 10). **m.p.**= 197-199 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.71 (s,

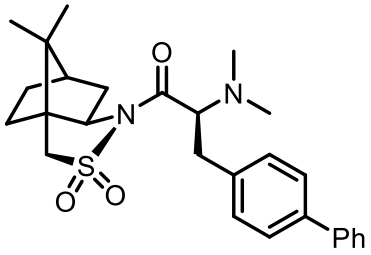
3H, ($C\underline{H}_3$)$_2$CR_2), 0.88 (s, 3H, ($C\underline{H}_3$)$_2$CR_2), 1.25-1.38 (m, 2H, C(R)$_2$HC$\underline{H}_2$C$\underline{H}_2$), 1.77-1.89 (m, 4H, C$\underline{H}_2$C(R)$\underline{H}$C$\underline{H}_2$C$\underline{H}_2$), 2.02 (dd, *J* 13.7 Hz, 7.8 Hz, 1H, C$\underline{H}_2$C(R)HCH_2CH_2), 2.49 (s, 6H, 2×N($C\underline{H}_3$)$_2$), 2.96 (dd, *J* 13.3 Hz, 7.5 Hz, 1H, Ar-C$\underline{H}_2$), 3.07 (dd, *J* 13.3 Hz, 7.5 Hz, 1H, Ar-CH_2), 3.39 (s, 2H, C$\underline{H}_2$SO_2), 3.84 (dd, *J* 6.8 Hz, 5.1 Hz, 1H, NC$\underline{H}$ camphor), 4.17 (t, *J* 7.5 Hz, 1H, C$\underline{H}$CH_2Ar), 6.86 (app d, *J* 2.3 Hz, 1H, ArC$\underline{H}$), 6.94 (d, *J* 11.4 Hz, 1H, ArC$\underline{H}$), 7.03 (d, *J* 7.6 Hz, 1H, ArC$\underline{H}$), 7.18-7.23 (m, 1H, ArC$\underline{H}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.8 (($\underline{C}H_3$)$_2$CR_2), 20.3 (($\underline{C}H_3$)$_2$CR_2), 26.3 (CR_2H$\underline{C}H_2$CH_2CR_3), 32.8 (CR_2HC$H_2$$\underline{C}H_2CR_3$), 33.9 ($\underline{C}H_2$Ar), 38.2 (C$R_2H\underline{C}H_2$C(R)HN), 41.6 (2×N($\underline{C}H_3$)$_2$), 44.5 (C$H_2CH_2$$\underline{C}HCH_2$), 47.5 ($\underline{C}$(C$H_3$)$_2$), 48.1 ($\underline{C}CH_2SO_2$), 53.0 ($\underline{C}H_2SO_2$), 65.1 (N$\underline{C}$H camphor), 66.9 (N$\underline{C}HCH_2$Ar), 113.4 (d, *J* 20.8 Hz, Ar$\underline{C}$H), 116.4 (d, *J* 21.1 Hz, Ar$\underline{C}$H), 125.2 (d, *J* 2.7 Hz, Ar$\underline{C}$H), 129.7 (d, *J* 8.2 Hz, Ar$\underline{C}$H), 139.9 (d, *J* 7.3 Hz, Ar$\underline{C}$), 162.75 (dd, *J* 243.8 Hz, Ar$\underline{C}$F), 171.8 (CO). **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −113.72 (1F, ArC$\underline{F}$). **IR** ν_{max} (thin film, cm^{-1}): 2952 (CH), 1686(CO), 1323, 1136 (SO_2). **MS** *m/z* (ESI$^+$) calculated for $C_{21}H_{29}FN_2O_3S$ [M+H]$^+$; 409.1956 found 409.1957. **HPLC** t_R = 11.50 min. **TLC** R_f = 0.47 (Toluene:EtOAc, 4:1).

***N*-[(2*R*)-*N,N*-dimethylamino-3-fluorophenylphenylalanine]bornane-10,2-sultam (314j).**



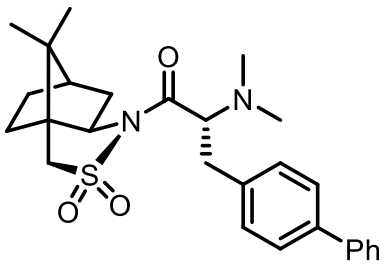
Following General procedure (E) outlined above, it was impure includes camphorsultam product. Partial characterisation was only possible, as the product was not isolated pure (23%, Table 21, Entry 10). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.94 (s, 3H, ($C\underline{H}_3$)$_2$CR_2), 1.13 (s, 3H, ($C\underline{H}_3$)$_2$CR_2), 1.25-1.48 (m, 2H, C(R)$_2$HC$\underline{H}_2$C$\underline{H}_2$), 1.84-2.10 (m, 5H, C$\underline{H}_2$C(R)$\underline{H}$C$\underline{H}_2$C$\underline{H}_2$), 2.38 (s, 6H, 2×N($C\underline{H}_3$)$_2$), 2.87 (dd, *J* 14.1 Hz, 7.2 Hz, 1H, Ar-C$\underline{H}_2$), 3.02 (dd, *J* 14.1 Hz, 7.2 Hz, 1H, Ar-CH_2), 3.38 (d, *J* 13.7 Hz, 1H, C$\underline{H}_2$SO_2), 3.48 (d, *J* 13.7 Hz, 1H, C$\underline{H}_2$SO_2), 3.89 (dd, *J* 7.3 Hz, 5.1 Hz, 1H, NC$\underline{H}$ camphor), 4.15 (t, *J* 7.1 Hz, 1H, C$\underline{H}$CH_2Ar), 6.88 (app d, *J* 2.0 Hz, 1H, ArC$\underline{H}$), 6.96 (d, *J* 9.9 Hz, 1H, ArC$\underline{H}$), 7.03 (d, *J* 7.5 Hz, 1H, ArC$\underline{H}$), 7.19-7.23 (m, 1H, ArC$\underline{H}$).

***N*-[(2*S*)-*N,N*-dimethylamino-biphenylphenylalanine]bornane-10,2-sultam (313k).**



Following General procedure (E) outlined above, it was isolated as solid (35.4 mg, 41%, Table 21, Entry 11). **m.p.**= 142-143 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.61 (s, 3H, $(C\underline{H}_3)_2CR_2$), 0.84 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.25-1.35 (m, 2H, $C(R)_2HC\underline{H}_2C\underline{H}_2$), 1.72-1.85 (m, 4H, $C\underline{H}_2C(R)\underline{H}C\underline{H}_2C\underline{H}_2$), 1.97 (dd, *J* 13.8 Hz, 7.8 Hz, 1H, $C\underline{H}_2C(R)HCH_2CH_2$), 2.53 (s, 6H, $2\times N(C\underline{H}_3)_2$), 3.00 (dd, *J* 13.2 Hz, 7.6 Hz, 1H, $ArCH_2$), 3.09 (dd, *J* 13.2 Hz, 7.6 Hz, 1H, $ArCH_2$), 3.37 (s, 2H, $C\underline{H}_2SO_2$), 3.82 (b, 1H, NC<u>H</u> camphor), 4.21 (dd, *J* 7.5 Hz, 7.4 Hz, 1H, $C\underline{H}CH_2Ar$), 7.32-7.34 (m, 3H, ArC<u>H</u>), 7.44 (t, *J* 7.7 Hz, 2H, ArC<u>H</u>), 7.48 (d, *J* 7.7 Hz, 2H, ArC<u>H</u>), 7.54 (d, *J* 7.7 Hz, 2H, ArC<u>H</u>). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.8 ($(\underline{C}H_3)_2CR_2$), 20.2 ($(\underline{C}H_3)_2CR_2$), 26.3 ($CR_2H\underline{C}H_2CH_2CR_3$), 32.8 ($CR_2HCH_2\underline{C}H_2CR_3$), 34.0 ($\underline{C}H_2Ar$), 38.2 ($CR_2H\underline{C}H_2C(R)HN$), 41.7 ($2\times N(\underline{C}H_3)_2$), 44.5 ($CH_2CH_2\underline{C}HCH_2$), 47.5 ($\underline{C}(CH_3)_2$), 48.06($\underline{C}CH_2SO_2$), 53.0 ($\underline{C}H_2SO_2$), 65.1 (N<u>C</u>H camphor), 67.0 (N<u>C</u>HCH_2Ar), 127.0 (5×Ar<u>C</u>H), 128.7 (2×Ar<u>C</u>H), 130.0 (2×Ar<u>C</u>H), 136.3 (Ar<u>C</u>), 139.4 (Ar<u>C</u>), 141.1 (Ar<u>C</u>), 172.1 (CO). **IR** ν_{max} (thin film, cm^{-1}): 2958 (CH), 1692 (CO), 1328, 1132 (SO_2). **MS** *m/z* (ESI^+) calculated for $C_{27}H_{34}N_2O_3S$ $[M+H]^+$; 467.2363 found 467.2366. **TLC** R_f = 0.39 (Toluene:EtOAc, 4:1). **HPLC** t_R = 11.43 min.

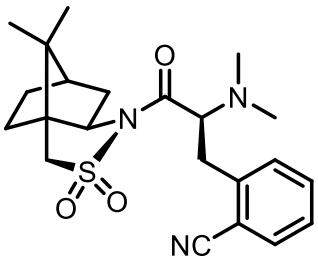
***N*-[(2*R*)-*N,N*-dimethylamino-biphenylphenylalanine]bornane-10,2-sultam (314k).**



Following General procedure (E) outlined above, it was impure includes camphorsultam. Partial characterisation was only possible, as the product was not isolated pure (22%, Table 21, Entry 11). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.97 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.19 (s, 3H, $(C\underline{H}_3)_2CR_2$), 1.30-1.40 (m, 2H, $C(R)_2HC\underline{H}_2C\underline{H}_2$), 1.84-2.14 (m, 5H, $C\underline{H}_2C(R)\underline{H}C\underline{H}_2C\underline{H}_2$), 2.41 (s, 6H, $2\times N(C\underline{H}_3)_2$), 2.94 (dd, *J* 14.1 Hz, 7.2 Hz, 2H, $ArCH_2$), 3.06 (dd, *J* 14.1 Hz, 7.2 Hz, 2H, $ArCH_2$), 3.40 (d, *J* 13.6 Hz, 1H, $C\underline{H}_2SO_2$),

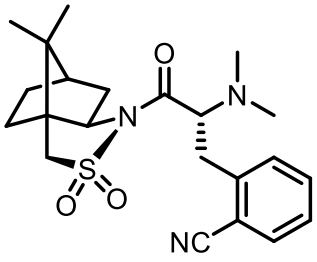
3.49 (d, *J* 13.6 Hz, 1H, C<u>H</u>$_2$SO$_2$), 3.92 (dd, *J* 7.4 Hz, 5.2 Hz, 1H, NC<u>H</u> camphor), 4.22 (t, *J* 6.5 Hz, 1H, C<u>H</u>CH$_2$Ar), 7.29-7.35 (m, 3H, ArC<u>H</u>), 7.41 (t, *J* 7.8 Hz, 2H, ArC<u>H</u>), 7.51 (d, *J* 7.6 Hz, 2H, ArC<u>H</u>), 7.57 (d, *J* 7.6 Hz, 2H, ArC<u>H</u>).

N-[(2*S*)-*N,N*-dimethylamino-2-cyanophenylphenylalanine]bornane-10,2-sultam (313l).



Following General procedure (E) outlined above, it was impure includes [2,3]-product. Partial characterisation was only possible, as the product was not isolated pure (47%, Table 21, Entry 12). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.67 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$), 0.87 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$), 1.21-1.37 (m, 2H, C(R)$_2$HC<u>H</u>$_2$C<u>H</u>$_2$), 1.71-1.97 (m, 4H, C<u>H</u>$_2$C(R)<u>H</u>C<u>H</u>$_2$C<u>H</u>$_2$), 2.04 (dd, *J* 13.7 Hz, 7.8 Hz, 1H, C<u>H</u>$_2$C(R)HCH$_2$CH$_2$), 2.52 (s, 6H, 2×N(C<u>H</u>$_3$)$_2$), 3.23 (dd, *J* 13.6 Hz, 7.4 Hz, 2H, ArCH$_2$), 3.30 (dd, *J* 13.6 Hz, 7.4 Hz, 2H, ArCH$_2$), 3.37 (s, 2H, C<u>H</u>$_2$SO$_2$), 3.84 (dd, *J* 7.4 Hz, 5.1 Hz, 1H, NC<u>H</u> camphor), 4.27 (t, *J* 6.9 Hz, 1H, C<u>H</u>CH$_2$Ar), 7.28 (dd, *J* 7.0 Hz, 1.1 Hz, 1H, ArC<u>H</u>), 7.43-7.49 (m, 2H, ArC<u>H</u>), 7.59 (dd, *J* 7.4 Hz, 0.7 Hz, 1H, ArC<u>H</u>).

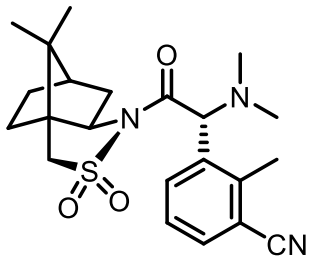
***N*-[(2*R*)-*N,N*-dimethylamino-2-cyanophenylphenylalanine]bornane-10,2-sultam (314l).**



Following General procedure (E) outlined above, it was isolated as solid (20 mg, 30%, Table 21, Entry 12). **m.p.**= 128-130 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.96 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$), 1.17 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$), 1.24-1.40 (m, 2H, C(R)$_2$HC<u>H</u>$_2$C<u>H</u>$_2$), 1.86-2.04 (m, 4H, C<u>H</u>$_2$C(R)<u>H</u>C<u>H</u>$_2$C<u>H</u>$_2$), 2.08 (dd, *J* 13.6 Hz, 7.7 Hz, 1H, C<u>H</u>$_2$C(R)HCH$_2$CH$_2$), 2.42 (s, 6H, 2×N(C<u>H</u>$_3$)$_2$), 3.15 (dd, *J* 14.1 Hz, 7.0 Hz, 1H, ArCH$_2$), 3.21 (dd, *J* 14.1 Hz, 7.0 Hz, 1H, ArCH$_2$), 3.34 (d, *J* 13.7 Hz, 1H, C<u>H</u>$_2$SO$_2$), 3.44 (d, *J* 13.7 Hz, 1H, C<u>H</u>$_2$SO$_2$), 3.88 (dd, *J* 7.4 Hz, 5.2 Hz, 1H, NC<u>H</u> camphor), 4.19 (t, *J* 7.0 Hz, 1H, C<u>H</u>CH$_2$Ar), 7.29 (dd, *J* 7.4 Hz, 1.2, 1H, ArC<u>H</u>), 7.44 (br d, *J* 7.0 Hz, 1H, ArC<u>H</u>), 7.49 (td, *J* 7.3 Hz, 1.2

Hz, 1.3 Hz, 1H, ArCH), 7.59 (dd, *J* 7.6 Hz, 0.8 Hz, 1H, ArCH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.9 ($(CH_3)_2CR_2$), 21.0 ($(CH_3)_2CR_2$), 26.4 ($CR_2HCH_2CH_2CR_3$), 33.0 ($CR_2HCH_2CH_2CR_3$ and CH_2Ar), 39.0 ($CR_2HCH_2C(R)HN$), 41.4 ($2\times N(CH_3)_2$), 44.9 ($CH_2CH_2CHCH_2$), 47.7 ($C(CH_3)_2$), 48.2 (CCH_2SO_2), 53.1 (CH_2SO_2), 65.2 (NCH camphor), 66.8 ($NCHCH_2Ar$), 113.3 (ArCN), 118.1 (ArCCN), 126.7 (ArCH), 130.7 (ArCH), 132.6 (ArCH), 132.7 (ArCH), 142.3 (ArC), 170.3 (CO). **IR** ν_{max} (thin film, cm^{-1}): 2956 (CH), 1686 (CO), 2223 (CN), 1327, 1132 (SO_2). **MS** *m/z* (ESI^+) calculated for $C_{22}H_{29}N_3O_3S$ $[M+H]^+$; 416.2002 found 416.2005. **TLC** R_f = 0.45 (PE:EtOAc, 1:1). **HPLC** t_R = 7.03 min.

***N*-[(2*R*)-*N,N*-dimethylamino-3-cyano-2-methylphenylphenylalanine]bornane-10,2-sultam (313m).**



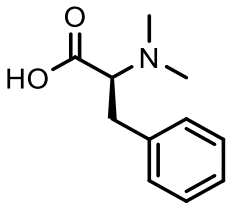
Following General procedure (E) outlined above, it was impure includes [1,2]- (2S) product. Partial characterisation was only possible, as the product was not isolated pure (Table 21, Entry 12). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.69 (s, 3H, $(CH_3)_2CR_2$), 0.88(s, 3H, $(CH_3)_2CR_2$), 1.25-1.37 (m, 2H, $C(R)_2HCH_2CH_2$), 1.71-1.97 (m, 4H, $CH_2C(R)HCH_2CH_2$), 2.02 (dd, *J* 13.7 Hz, 7.8 Hz, 1H, $CH_2C(R)HCH_2CH_2$), 2.25 (s, 6H, $2\times N(CH_3)_2$), 2.52 (s, 3H, $ArCH_3$), 3.46 (d, *J* 2.6 Hz, 2H, CH_2SO_2), 3.93 (dd, *J* 7.5 Hz, 4.6 Hz, 1H, NCH camphor), 4.53 (s,1H, CHAr), 7.28 (dd, *J* 7.0 Hz, 1.1 Hz, 1H, ArCH), 7.67 (dd, *J* 8.0 Hz, 1.8 Hz, 1H, ArCH), 7.80 (d, *J* 1.7 Hz, 1H, ArCH).

General procedure (F) for sultam hydrolysis.

The substituted sulfonamide (0.13 - 0.16 mmol, 1 eq.) was dissolved in THF/H_2O (4:1 3.25 ml) and lithium hydroxide monohydrate (2 eq.) was added in one portion. The reaction mixture was allowed to stir for 22 hours. The organic solvent was removed by concentration under reduced pressure and the residue dissolved in sat. aq. sodium bicarbonate (19 ml) and extracted with chloroform (3 x 15 ml). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to yield recovered sultam. The aqueous layer was neutralised to pH7 with 6M hydrochloric acid and then extracted with *n*-butanol (3 x 10 ml). The combined organics were dried (Na_2SO_4) and

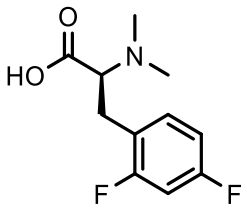
concentrated under reduced pressure. The residue was triturated with acetone (10 ml), filtered and concentrated under reduced pressure to yield desired product.

***N,N*-Dimethyl-L-phenylalanine (311a).**



Following the general procedure (F) *N*-[(2*S*)-*N*,*N*-Dimethylphenylalanine]bornane-10,2-sultam (**313a**) (50.0 mg, 0.13 mmol) was hydrolysed to yield the product (8.0 mg, 32 %, Table 22, Entry 1) as a colourless solid. **m.p.**= 229 - 231 °C. **^{1}H NMR** (400 MHz, D_2O) δ_H 2.67 (s, 6H, 2NC$\underline{H}_3$), 2.96 (dd *J* 13.6, 9.7 Hz, 1H, C$\underline{H}_2$Ar), 3.13 (dd *J* 13.6, 5.8 Hz, 1H, C$\underline{H}_2$Ar), 3.57 (dd *J* 9.7, 5.8 Hz, 1H, C$\underline{H}$CH$_2$Ar), 7.19 - 7.32 (m, 5H, 5×ArC$\underline{H}$). **^{13}C NMR** (100 MHz, D_2O) δ_C 34.6 (2N$\underline{C}$H$_3$), 41.5 ($\underline{C}$H$_2$Ar), 72.4 (CH), 127.2 (Ar$\underline{C}$H), 128.9 (Ar$\underline{C}$H), 129.2 (Ar$\underline{C}$H), 136.2 (Ar$\underline{C}$), 173.9 (CO). **IR** ν_{max} / cm^{-1}: 3352 (OH), 1621 (CO). **MS** *m/z* (ESI$^+$) calculated for $C_{11}H_{16}NO_2$ $[M+H]^+$; 194.1136, found 194.1176.

***N,N*-Dimethyl-2,4-difluoro-L-phenylalanine (311b).**

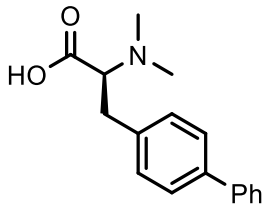


Following the general procedure (F) *N*-[(2*S*)-*N*,*N*-Dimethylamino-2,4-difluorophenylalanine]bornane-10,2-sultam (**313g**) (58.0 mg, 0.14 mmol) was hydrolysed to yield the product (12.0 mg, 39 %, Table 22, Entry 2) as a colourless hygroscopic solid.

^{1}H NMR (400 MHz, D_2O) δ_H 2.82 (s, 6H, 2NC$\underline{H}_3$), 2.92 (dd *J* 10.3, 13.4 Hz, 1H, C$\underline{H}_2$Ar), 3.26 (dd *J* 13.4, 5.2 Hz, 1H, C$\underline{H}_2$Ar), 3.65 (dd *J* 10.3, 5.2 Hz, 1H, C$\underline{H}$CH$_2$Ar), 6.80 - 6.90 (m, 2H, 2×ArC$\underline{H}$), 7.18 (m, 1H, ArC$\underline{H}$). **^{13}C NMR** (100 MHz, D_2O) δ_C 27.5 (2NCH$_3$), 41.5 ($\underline{C}$H$_2$Ar), 72.4 (CH), 103.7 (t, *J* 25.8 Hz, CF$\underline{C}$HCF), 111.5 (dd, *J* 21.3, 3.6 Hz, CFCHCF$\underline{C}$H), 118.3 (dd, *J* 15.5, 3.6 Hz, CF$\underline{C}$CH), 132.2 (dd, *J* 9.8, 5.9 Hz, C$\underline{C}$HCH), 160.9 (dd, *J* 245, 12.3 Hz, CCFCH$\underline{C}$F), 162.2 (dd, *J* 244, 12.3 Hz, C$\underline{C}$F), 172.3 (CO). **^{19}F NMR** (376 MHz, D_2O) δ_F -111.9 (d, *J* 7.4 Hz CF), -113.8 (d, *J* 7.4 Hz CF). **IR** ν_{max}

/cm^{-1}: 3357 (OH), 1632 (CO). **MS** *m/z* (ESI$^+$) calculated for $C_{11}H_{13}F_2NO_2$ $[M+H]^+$; 230.0987, found 230.0987.

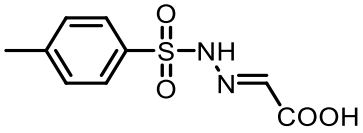
***N,N*-Dimethyl-2phenyl-L-phenylalanine (311c).**



Following the general procedure (F) *N*-[(2*S*)-*N*,*N*-Dimethylamino-biphenyl phenylalanine]bornane-10,2-sultam (**313k**) (75.0 mg, 0.16 mmol) was hydrolysed to yield the product (15.0 mg, 35 %, Table 22, Entry 3) as a colourless solid. **m.p.**= 220 - 222 °C. **^{1}H NMR** (400 MHz, D_2O) δ_H 2.25 (s, 6H, $2NCH_3$), 2.78 - 2.93 (m, 2H, C$\underline{H}_2$Ar), 3.17 (dd *J* 6.3, 9.1 Hz, 1H, C$\underline{H}$C$\underline{H}_2$Ar), 7.21 - 7.30 (m, 3H, 3ArCH), 7.37 (t *J* 7.6 Hz, 2H, 2ArCH), 7.49 (d *J* 8.0 Hz, 2H, 2ArCH), 7.56 (t *J* 8.0 Hz, 2H, 2ArCH). **^{13}C NMR** (100 MHz, D_2O) δ_C 35.7 ($2NCH_3$), 41.1 ($\underline{C}H_2$Ar), 72.7 (CH), 126.8 (2×Ar$\underline{C}$H), 126.9 (2×Ar$\underline{C}$H), 127.5 (Ar$\underline{C}$H), 129.1 (2×Ar$\underline{C}$H), 129.7 (2×Ar$\underline{C}$H), 137.9 (Ar$\underline{C}$), 138.6 (Ar$\underline{C}$), 140.3 (Ar$\underline{C}$), 177.7 (CO). **IR** ν_{max} /cm^{-1}: 3371 (OH), 1607 (CO).

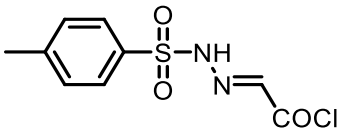
MS *m/z* (ESI$^+$) calculated for $C_{17}H_{19}NO_2$ $[M+H]^+$; 270.1489, found 270.1487

Glyoxylic acid *p*-toluenesulfonyl hydrazone (329).[84]



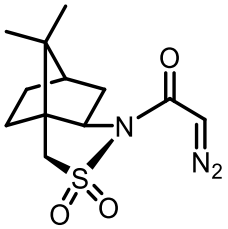
A mixture of glyoxylic acid (2.5 g, 27.2 mmol) and *p*-toluenesulfonyl hydrazide (5.11g, 27.2 mmol) in 50 mL of dry THF was stirred overnight at room temperature. The solvent was removed under reduced pressure and 150 mL cold water was added to the residue. The precipitated solid was filtered and washed by cold water, acetone and dried for 2 days in oven at 45 °C to give (6.4 g, 98%). The yield was used without any purifications. **^{1}H NMR** (400 MHz, DMSO, d_6) δ_H 2.36 (s, 3H, ArC$\underline{H}_3$), 7.17 (s, 1H, C$\underline{H}$COOH), 7.40 (d, *J* 8.1 Hz, 2H, ArC$\underline{H}$), 7.68 (d, *J* 8.2 Hz, 2H, ArC$\underline{H}$), 12.28 (s, 1H, COO$\underline{H}$). **^{1}C NMR** (100 MHz, $CDCl_3$) δ_C 21.4 (Ar$\underline{C}H_3$), 127.5 (Ar$\underline{C}$H), 130.3 (Ar$\underline{C}$H), 136.1 (Ar$\underline{C}$), 137.9 (Ar$\underline{C}$), 144.5 ($\underline{C}$HCOOH), 164.0 (CO). **IR** ν_{max} /cm^{-1}: 3168 (OH), 1694 (CO), 1348, 1081 (SO_2). **MS** *m/z* (ESI$^+$) calculated for $C_9H_{10}N_2O_4S$ $[M+H]^+$; 243.0434 found 243.1434.

Glyoxylic acid chloride *p*-toluenesulfonyl hydrazine (330).[84]



A mixture of glyoxylic acid *p*-toluenesulfonyl hydrazone (1.0 g, 4.12 mmol) and thionyl chloride (0.5 mL, 6.89 mmol) in 20 mL of dry toluene was stirred and heated to 90 °C overnight. The solvent was removed under reduced pressure to give (0.48 g, 50%). The yield was used immediately without any purifications. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.46 (s, 3H, ArC<u>H</u>$_3$), 7.22 (s, 1H, C<u>H</u>COCl), 7.38 (d, *J* 8.2 Hz, 2H, ArC<u>H</u>), 7.87 (d, *J* 8.2 Hz, 2H, ArC<u>H</u>), 8.86 (s, 1H, NH). **IR** ν_{max} (thin film, cm^{-1}): 1744 (CO), 1353, 1079 (SO_2).

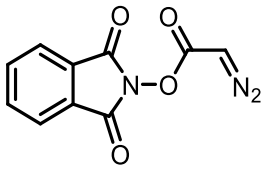
Diazo Camphorsultam (297).[58]



(1*S*)- camphorsultam (**306**) (0.84 g, 3.8 mmol, 1eq) in 10 mL $CHCl_3$ was added to cooled glyoxylic acid chloride *p*-toluenesulfonylhydrazone (1.0 g, 7.6 mmol, 2 eq) in $CHCl_3$ (10 mL). Dimethylaniline (0.98 mL, 7.8 mmol, 2.1 eq) was added dropwise over 3 hours. Triethylamine (2.72 mL, 19 mmol, 5 eq) was added dropwise. After completing the addition, the mixture was stirred for 1 hour at room temperature before water (16 mL) was added and the mixture concentrated *in vacuo*. Saturated citric acid (32 mL) and EtOAc-hexane (3:2) v/v, 32 mL) were added and the layers were separated. The organic layers were dried over $MgSO_4$ and filtered and the solvents were removed *in vacuo.* The crude was purified via column chromatography (4:1, PE:EtOAc) to give yellow solid (0.64 g, 60%). **m.p.**= 159-161 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.95 (s, 3H, C(C<u>H</u>$_3$)$_2$), 1.12 (s, 3H, C(C<u>H</u>$_3$)$_2$), 1.33-1.48 (m, 2H, C<u>H</u>$_2$C<u>H</u>$_2$CHCH$_2$), 1.85-1.94 (m, 3H, C<u>H</u>$_2$C<u>H</u>$_2$CHC<u>H</u>$_2$), 3.40 (d, 1H, *J* 13.8 Hz, C<u>H</u>$_2$SO$_2$), 3.44 (d, 1H, *J* 13.8 Hz, C<u>H</u>$_2$SO$_2$), 3.89 (dd, 1H, *J* 7.6 Hz, 4.8 Hz, C<u>H</u>N), 5.72 (s, 1H, C<u>H</u>N$_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.9 (C<u>C</u>H$_3$)$_2$, 20.4 (C<u>C</u>H$_3$)$_2$, 26.5 (CH$_2$<u>C</u>H$_2$CHCH$_2$), 32.4 (<u>C</u>H$_2$CH$_2$CHCH$_2$), 38.1 (CH$_2$CH$_2$CH<u>C</u>H$_2$), 44.4 (CH$_2$CH$_2$<u>C</u>HCH$_2$), 47.9 (<u>C</u>(CH$_3$)$_2$), 48.7 (<u>C</u>CH$_2$SO$_2$), 49.8 (<u>C</u>HN$_2$), 52.5 (<u>C</u>H$_2$SO$_2$), 64.8 (N<u>C</u>H), 162.9 (CO). **MS** *m/z* (ESI$^+$) calculated for $C_{12}H_{17}N_3O_3S$ [M+Na]$^+$; 306.0883

found 206.0882. **IR** ν_{max} /cm^{-1}: 3124 (CH), 2956 (CH), 2127 (NΞN), 1637(CO), 1394, 1126 (SO_2). **TLC** R_f = 0.15 (PE:EtOAc, 4:1).

Diazoacyl phthalimide (332).[86,87]

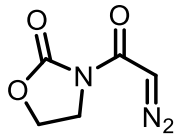


To a solution of *N*-hydroxyphthalimide (2.0 g, 12.4 mmol, 1eq) and glyoxylic acid p-toluenesulfonyl hydrazone (3.0 g, 12.4 mmol, 1eq) in dry THF (100 mL). At 0 °C was added dropwise a solution of DCC in 20 mL THF. The mixture was allowed to warm to room temperature and stirring was continued overnight. DCU was filtered off and filtrate was concentrated under reduced pressure. The crude was purified by flash chromatography (PE:EtOAc, 7:3) to give (2.0 g, 71%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 5.18 (s br, 1H, COC<u>H</u>), 7.77-7.81 (m, 2H, ArC<u>H</u>), 7.87-7.91 (m, 2H, ArC<u>H</u>). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 45.0 (CO<u>C</u>HN_2), 124.0 (2×Ar<u>C</u>H), 128.8 (2×Ar<u>C</u>H), 134.8 (2×Ar<u>C</u>), 162.1 (3×<u>C</u>O). **IR** ν_{max} /cm^{-1}: 3099 (CH), 2145 (NΞN), 1796, 1704 (CO). **MS** *m/z* (ESI$^+$) calculated for $C_{10}H_5N_3O_4$ [M+Na]$^+$; 254.0172 found 254.0172. **TLC** R_f = 0.22 (PE:EtOAc, 7:3).

General procedure (G) for synthesis of *N*-α-diazoacyl oxazolidinones.[87]

To a solution of oxazolinone or oxazolinone derivatives (1.0 eq) in THF (50 mL) was added *n*-BuLi (1.6 M in hexane, 1.1 eq) dropwise at 0 °C. After stirring hour, a solution of diazoacyl phthalimide (1.0 eq) was added. The mixture was stirred at room temperature overnight. The resulting mixture was quenched with saturated $NaHCO_3$, and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude was purified by flash chromatography.

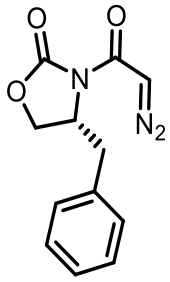
3-(2-diazoacetyl)oxazolidin-2-one (339).



Following General procedure (G) outlined above, it was isolated as solid (0.25 g, 75%, Table 23, Entry 1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.06 (t, *J* 7.8 Hz, 2H, C<u>H</u>$_2$N), 4.42 (t, *J* 8.3 Hz, 2H, C<u>H</u>$_2$O), 6.56 (s, 1H, COC<u>H</u>N_2). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 42.5 (N<u>C</u>H$_2$), 49.6 (<u>C</u>HN_2), 62.3 (<u>C</u>H$_2$O), 153.7 (CO), 164.1 (CO). **IR** ν_{max} /cm^{-1}: 3131 (CH),

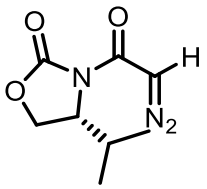
2109 (NΞN), 1764, 1739 (CO). **MS** *m/z* (ESI$^+$) calculated for $C_5H_5N_3O_3$ $[M+Na]^+$; 178.0223 found 178.0223. **TLC** R_f = 0.21 (PE:EtOAc, 7:3).

(*R*)-4-benzyl-3-(2-diazoacetyl) oxazolidin-2-one (341).



Following General procedure (G) outlined above, it was isolated as solid (0.8 g, 57%, Table 23, Entry 2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.83 (dd, *J* 13.3 Hz, 6.2 Hz, 1H, ArC$\underline{H}_2$), 3.34 (dd, *J* 13.3 Hz, 6.2 Hz, 1H, ArC$\underline{H}_2$), 4.17-4.25 (m, 2H, CHC$\underline{H}_2$O), 4.72-4.78 (m, 1H, C$\underline{H}$CH$_2$), 6.62 (s, 1H, C$\underline{H}$N$_2$), 7.21-7.34 (5H, ArC$\underline{H}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 38.2 (Ar$\underline{C}$H$_2$), 49.9 ($\underline{C}$HN$_2$), 55.2 ($\underline{C}$HCH$_2$), 66.4 ($\underline{C}$H$_2$O), 127.4 (Ar$\underline{C}$H), 128.9 (2×Ar$\underline{C}$H), 129.4 (2×Ar$\underline{C}$H), 135.1 (Ar$\underline{C}$), 153.5 (CO), 164.0 (CO). **IR** ν_{max}/cm^{-1}: 3116 (CH), 2114 (NΞN), 1772, 1754 (CO). **MS** *m/z* (ESI$^+$) calculated for $C_{12}H_{11}N_3O_3$ $[M+Na]^+$; 268.0693 found 268.0694. **TLC** R_f = 0.25 (PE:EtOAc, 7:3).

(*R*)-3-(2-diazoacetyl)-4-isopropyloxazolidin-2-one (341a)



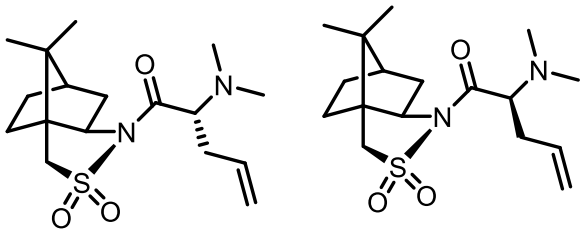
Following General procedure (G) outlined above, it was isolated as solid (0.165 g, 55%, Table 23, Entry 2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.88 (d, *J* 6.8 Hz, 3H, CHC$\underline{H}_3$), 0.93 (d, *J* 7.0 Hz, 3H, CHC$\underline{H}_3$), 2.34-2.48 (m, 1H, C$\underline{H}$(CH$_3$)$_2$, 4.23 (dd, *J* 9.0 Hz, 5.7 Hz, 1H, OC$\underline{H}_2$), 4.29 (dd, *J* 9.0 Hz, 5.7 Hz, 1H, OC$\underline{H}_2$), 4.48-4.52 (m, 1H, CH$_2$C$\underline{H}$CH), 6.62 (s, 1H, C$\underline{H}$N$_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 14.6 (CH$\underline{C}$H$_3$), 17.9 (CH$\underline{C}$H$_3$), 28.7 ($\underline{C}$H(CH$_3$)$_2$), 49.8 $\underline{C}$HN$_2$), 58.6 (CH$_2\underline{C}$HCH) 63.6 (O$\underline{C}$H$_2$). **IR** ν_{max} (thin film, cm^{-1}): 2963 (CH), 2111 (NΞN), 1762, 1732 (CO). **MS** *m/z* (ESI$^+$) calculated for $C_8H_{11}N_3O_3$ $[M+Na]^+$; 220.0693 found 220.0693. **TLC** R_f = 0.31 (PE:EtOAc, 7:3).

General procedure (H) for reaction of allyl tertiary amines with diazo compounds

A solution of diazo (100 mg, 1 eq) and allyl tertiary amines (1eq) in CH_2Cl_2 or $CHCl_3$ (1 mL) was added in a single portion to a solution of the catalyst (iron(III) porphyrins)

(0.2-40 mol%), in 1.5 mL CH_2Cl_2 or $CHCl_3$. The solvent was removed to produce crude, which was subjected to column chromatography.

(2*R*)-1-((6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6 methanobenzo [c]isothiazol-1(4H)-yl)-2-(dimethylamino)pent-4-en-1-one (338a) and **(2*S*)-1-((6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c] isothiazol-1(4H)-yl)-2-(dimethylamino)pent-4-en-1-one (338b).**

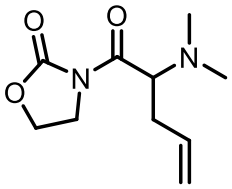


Following procedure (H) above the major diastereoisomer was isolated as solid (14 mg, 25%) and the second was impure with camphorsultam.

The first diastereoisomer

m.p.= 129-131 °C**. ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.96 (s, 3H, C(C<u>H</u>$_3$)$_2$), 1.13 (s, 3H, C(C<u>H</u>$_3$)$_2$), 1.23-1.42 (m, 2H, C<u>H</u>$_2$CH$_2$C<u>H</u>CH$_2$), 1.84-2.08 (m, 5H, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>C<u>H</u>$_2$), 2.43 (s, 6H, 2×N(CH$_3$)$_2$, 2.47-2.61 (m, 2H, NCHC<u>H</u>$_2$), 3.42 (d, 1H, *J* 13.7 Hz, C<u>H</u>$_2$SO$_2$), 3.48 (d, 1H, *J* 13.7 Hz, C<u>H</u>$_2$SO$_2$), 3.87-3.94 (m, 2H, N(CH$_3$)$_2$C<u>H</u>, C<u>H</u>N), 5.05 (d, *J* 13.0 Hz, 1H, C<u>H</u>$_2$=CH), 5.12 (d, *J* 13.0 Hz, 1H, C<u>H</u>$_2$=CH), 5.85 (ddt, *J* 17.0, 10.1, 7.0, 1H, C<u>H</u>=CH$_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.9 (C<u>C</u>H$_3$)$_2$, 20.8 (C<u>C</u>H$_3$)$_2$, 26.4 (CH$_2$<u>C</u>H$_2$CHCH$_2$), 32.9 (<u>C</u>H$_2$CH$_2$CHCH$_2$), 34.5 (<u>C</u>H$_2$CH=CH$_2$), 38.3 (CH$_2$CH$_2$CH<u>C</u>H$_2$), 41.8 (2×N(<u>C</u>H$_3$)$_2$), 44.5 (CH$_2$CH$_2$<u>C</u>HCH$_2$), 47.7 (<u>C</u>(CH$_3$)$_2$), 48.2 (<u>C</u>CH$_2$SO$_2$), 53.2 (<u>C</u>H$_2$SO$_2$), 65.2 (N<u>C</u>H), 66.1 (N(CH$_3$)$_2$<u>C</u>H), 117.8 (CH$_2$CH=<u>C</u>H$_2$), 133.9 (CH$_2$<u>C</u>H=CH$_2$), 172.8 (CO). **IR** ν_{max} (thin film, cm^{-1}): 2765 (CH), 1683 (CO). **MS** *m/z* (ESI$^+$) calculated for $C_{17}H_{28}N_2O_3S$ $[M+H]^+$; 341.1893 found 341.1892. **R_f** = 0.35 (PE: EtOAc, 2:1).

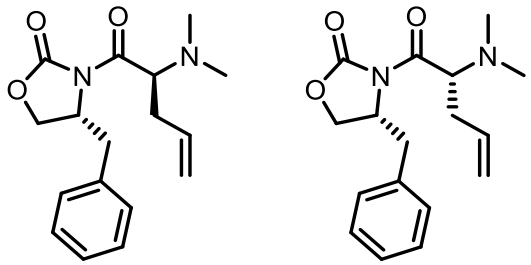
3-(2-(dimethylamino)pent-4-enoyl)oxazolidin-2-one (340).



Following procedure (H) above, the product was isolated as oil (96 mg, 70%, Scheme 87). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.38 (s, 6H, N(C<u>H</u>$_3$))$_2$, 2.42 (m, 1H, CHC<u>H</u>$_2$CH), 2.56 (m, 1H, CHC<u>H</u>$_2$CH), 4.00-4.04 (m, 2H, NCH$_2$), 4.40 (t, *J* 8.0 Hz, 2H, COOC<u>H</u>$_2$),

4.75 (dd, *J* 8.9 Hz, 5.6 Hz, 1H, COC<u>H</u>N(CH$_3$)$_2$), 5.05 (d, *J* 10.0 Hz, 1H, CH=C<u>H</u>$_2$), 5.11 (dd, *J* 17.0 Hz, 1.3 Hz, 1H, CH=C<u>H</u>$_2$), 5.77 (ddt, *J* 17.3 Hz, 10.2 Hz, 7.5 Hz, 1H, C<u>H</u>=CH$_2$). **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 30.8 (CH<u>C</u>H$_2$CH), 41.3 (N(<u>C</u>H$_3$)$_2$), 42.4 (N<u>C</u>H$_2$CH$_2$O), 61.8 (NCH$_2$<u>C</u>H$_2$O), 62.7 (CO<u>C</u>HN(CH$_3$)$_2$), 117.6 (CH=<u>C</u>H$_2$), 134.4 (<u>C</u>H=CH$_2$), 153.1 (O<u>C</u>ON), 172.1 (N<u>C</u>OCH). **IR** ν_{max} (thin film, cm^{-1}): 2923 (CH), 1750 (CO), 1694 (CO). **MS** *m/z* (ESI$^+$) calculated for $C_{10}H_{16}N_2O_3$ [M+H]$^+$; 213.1234 found 213.1234. **TLC** R_f = 0.21 (EtOAc).

(*R*)-4-benzyl-3-((*S*)-2-(dimethylamino)pent-4-enoyl)oxazolidin-2-one (342a) and **(*R*)-4-benzyl-3-((*R*)-2-(dimethylamino)pent-4-enoyl)oxazolidin-2-one (342b).**



Following procedure (H) above, the combined yield was isolated as oil (**342a+342b** =106 mg, 86%, Scheme 88, Table 25, Entry 1).

The first diastereoisomer

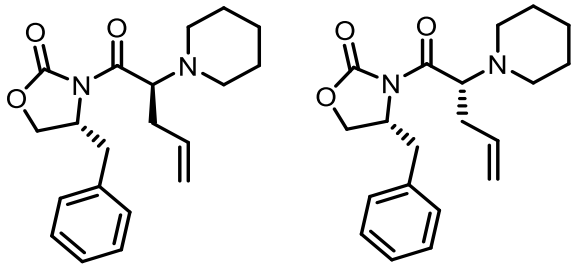
^{1}H NMR (400 MHz, CDCl$_3$) δ_H 2.35-2.41 (m, 1H, CHC<u>H</u>$_2$CH), 2.43 (s, 6H, N(C<u>H</u>$_3$))$_2$, 2.53-2.60 (m, 1H, CHC<u>H</u>$_2$CH), 2.71 (dd, *J* 13.2 Hz, 6.6 Hz, 1H, CHC<u>H</u>$_2$Ar), 3.37 (dd, *J* 13.2 Hz, 6.6 Hz, 1H, CHC<u>H</u>$_2$Ar), 4.12-4.18 (m, 2H, COOC<u>H</u>$_2$), 4.67-4.79 (m, 1H, COOCH$_2$C<u>H</u>), 4.78 (dd, *J* 8.9 Hz, 5.7 Hz, 1H, COC<u>H</u>N), 5.05 (d, *J* 13.4 Hz, 1H, CH=C<u>H</u>$_2$), 5.12 (d, *J* 13.4 Hz, 1H, CH=C<u>H</u>$_2$), 5.78 (ddt, *J* 17.2 Hz, 10.1 Hz, 7.1 Hz, 1H, C<u>H</u>=CH$_2$). **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 31.1 (CH<u>C</u>H$_2$CH), 38.4 (<u>C</u>H$_2$Ar) 41.3 (N(<u>C</u>H$_3$)$_2$), 55.8 (N<u>C</u>HCH$_2$O), 62.8 (CO<u>C</u>HN(CH$_3$)$_2$), 66.1 (NCH$_2$<u>C</u>H$_2$O), 117.6 (CH=<u>C</u>H$_2$), 127.3 Ar<u>C</u>H), 128.9 (2×Ar<u>C</u>H), 129.4 (2×Ar<u>C</u>H), 134.4 (<u>C</u>H=CH$_2$), 135.3 (Ar<u>C</u>),153.1 (O<u>C</u>ON), 172.0 (N<u>C</u>OCH). **IR** ν_{max} (thin film, cm^{-1}): 2785 (CH), 1773 (CO), 1693 (CO). **MS** *m/z* (ESI$^+$) calculated for $C_{17}H_{22}N_2O_3$ [M+H]$^+$; 303.1703 found 303.1703. **TLC** R_f = 0.38 (PE:EtOAc, 1:1). **HPLC** t_R = 4.9 min (50:50, Hex:IPA).

The second diastereoisomer

^{1}H NMR (400 MHz, CDCl$_3$) δ_H 2.33-2.46 (m, 1H, CHC<u>H</u>$_2$CH), 2.39(s, 6H, N(C<u>H</u>$_3$))$_2$, 2.59-2.67 (m, 1H, CHC<u>H</u>$_2$CH), 2.71 (dd, *J* 13.2 Hz, 6.4 Hz, 1H, CHC<u>H</u>$_2$Ar), 3.27 (dd, *J* 13.2 Hz, 6.4 Hz, 1H, CHC<u>H</u>$_2$Ar), 4.13-4.22 (m, 2H, COOC<u>H</u>$_2$), 4.66-4.72 (m, 1H,

COOCH$_2$CH), 4.77 (dd, *J* 5.5 Hz, 8.9 Hz, 1H, COCHN), 5.09 (d, *J* 10.0 Hz, 1H, CH=CH$_2$), 5.16 (dd, *J* 17.1 Hz, 1.3 Hz, 1H, CH=CH$_2$), 5.84 (ddt, *J* 17.1 Hz, 10.1 Hz, 6.9 Hz, 1H, CH=CH$_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 30.8 (CHCH$_2$CH), 37.8 (CH$_2$Ar) 41.3 (N(CH$_3$)$_2$), 55.4 (NCHCH$_2$O), 62.7 (COCHN(CH$_3$)$_2$), 66.0 (NCH$_2$CH$_2$O), 117.7 (CH=CH$_2$), 127.3 ArCH), 128.9 (2×ArCH), 129.4 (2×ArCH), 134.4 (CH=CH$_2$), 135.3 (ArC),153.1 (OCON), 172.0 (NCOCH). **IR** ν_{max} (thin film, cm^{-1}): 2783 (CH), 1772 (CO), 1696(CO). **MS** *m/z* (ESI$^+$) calculated for $C_{17}H_{22}N_2O_3$ $[M+H]^+$; 303.1703 found 303.1704. **TLC** R_f = 0.14 (PE:EtOAc, 1:1). **HPLC** t_R = 5.6 min (50:50, Hex:IPA).

(*R*)-4-benzyl-3-((*S*)-2-(piperidin-1-yl)pent-4-enoyl)oxazolidin-2-one (346a) and **(*R*)-4-benzyl-3-((*R*)-2-(piperidin-1-yl)pent-4-enoyl)oxazolidin-2-one (346b).**



Following procedure (H) above, the combined yield was isolated as oil (**346a+346b** = 86.5 mg, 62%, Scheme 89, Table 25, Entry 3).

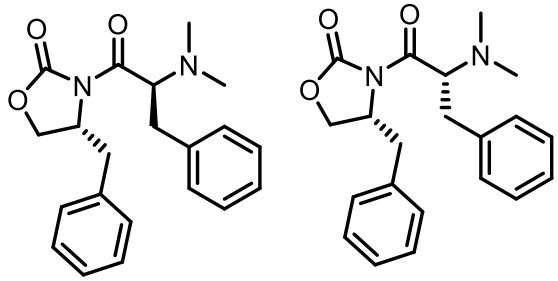
The first diastereoisomer

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.43-1.44 (m, 2H, NCH$_2$CH$_2$CH$_2$), 1.53-1.57 (m, 4H, NCH$_2$CH$_2$CH$_2$), 2.42 (ddd, *J* 12 Hz, 6.0 Hz, 6.0 Hz, 1H, CH$_2$=CHCH$_2$), 2.55-2.71 (m, 1H, CH$_2$=CHCH$_2$ and 4H, 2×NCH$_2$), 2.75 (dd, *J* 13.3 Hz, 6.3 Hz, 1H, CH$_2$Ph), 3.28 (dd, *J* 13.3 Hz, 6.3 Hz, 1H, CH$_2$Ph), 4.10-4.17 (m, 2H, OCH$_2$CH), 4.72 (m, 1H, CHCH$_2$Ph), 4.79 (dd, J 9.7 Hz, 5.1 Hz, 1H, COCHNR$_2$), 5.02 (d, *J* 13.6 Hz, 1H, CH=CH$_2$), 5.10 (d, *J* 13.6 Hz, 1H, CH=CH$_2$), 5.77 (ddt, *J* 17.1 Hz, 10.1 Hz, 7.4 Hz, 1H, CH=CH$_2$), 7.26-7.35 (m, 5H, ArH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 24.6 (NCH$_2$CH$_2$CH$_2$), 26.6 (2×CH$_2$), 30.9 (CH$_2$CHN), 38.2 (CH$_2$Ph), 50.4 (2×NCH$_2$), 55.13 (NCHCH$_2$Ph), 63.4 (COCHN), 65.8 (CH$_2$O), 117.42 (CH$_2$=CH), 127.3 (ArCH), 128.9 (2×ArCH), 129.5 (2×ArCH), 134.8 (ArC), 135.3 (CH$_2$=CH), 153.0 (CO), 171.8 (CO). **IR** ν_{max} (thin film, cm^{-1}): 2928 (CH), 1774 (CO), 1693(CO). **MS** *m/z* (ESI$^+$) calculated for $C_{20}H_{26}N_2O_3$ $[M+H]^+$; 343.2016 found 343.2015. **TLC** R_f = 0.29 (PE:EtOAc, 4:1). **HPLC** t_R = 8.3 min (95:5, Hex:IPA).

The second diastereoisomer

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.39-1.41 (m, 2H, $NCH_2CH_2C\underline{H}_2$), 1.50-1.54 (m, 4H, $NCH_2C\underline{H}_2CH_2$), 2.44 (ddd, *J* 12.5 Hz, 6.1 Hz, 6.3 Hz, 1H, CH_2=$CHC\underline{H}_2$), 2.56-2.66 (m, 1H, CH_2=$CHC\underline{H}_2$ and 4H, 2×$NC\underline{H}_2$), 2.69 (dd, *J* 13.3 Hz, 6.5 Hz, 1H, $C\underline{H}_2Ph$), 3.28 (dd, *J* 13.3 Hz, 6.5 Hz, 1H, $C\underline{H}_2Ph$), 4.12-4.19 (m, 2H, $OC\underline{H}_2CH$), 4.67 (m, 1H, $C\underline{H}CH_2Ph$), 4.79 (dd, J 9.5 Hz, 5.2 Hz, 1H, $COC\underline{H}NR_2$), 5.06 (d, *J* 13.7 Hz, 1H, CH=$C\underline{H}_2$), 5.13 (d, *J* 13.7 Hz, 1H, CH=$C\underline{H}_2$), 5.84 (ddt, *J* 17.1 Hz, 10.1 Hz, 7.5 Hz, 1H, $C\underline{H}$=CH_2), 7.21-7.34 (m, 5H, ArH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 24.4 ($NCH_2CH_2\underline{C}H_2$), 26.2 (2×$\underline{C}H_2$), 31.5 ($\underline{C}H_2CHN$), 37.8 ($\underline{C}H_2Ph$), 50.6 (2×$N\underline{C}H_2$), 55.6 ($N\underline{C}HCH_2Ph$), 63.2 ($CO\underline{C}HN$), 66.0 ($\underline{C}H_2O$), 117.8 ($\underline{C}H_2$=CH), 127.3 (ArCH), 128.9 (2×ArCH), 129.4 (2×ArCH), 135.4 (ArC), 135.9 (CH_2=$\underline{C}H$), 153.1 (CO), 158.9 (CO). **IR** ν_{max} (thin film, cm^{-1}): 2927 (CH), 1774 (CO), 1696(CO). **MS** *m/z* (ESI^+) calculated for $C_{20}H_{26}N_2O_3$ $[M+H]^+$; 343.2016 found 343.2020. **TLC** R_f = 0.16 (PE:EtOAc, 4:1). **HPLC** t_R = 10.2 min (95:5, Hex:IPA).

(*R*)-4 benzyl-3-(dimethyl-L-phenylalanyl)oxazolidin-2-one (349a) and **(*R*)-4-benzyl-3-(dimethyl-D-phenylalanyl)oxazolidin-2-one (349b).**



Following procedure (H) above, the combined yield was isolated as oil (**349a+349b** = 30 mg, 21%, Scheme 95).

The first diastereoisomer

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.50 (s, 6H, $N(CH_3)_2$), 2.67 (dd, *J* 13.1 Hz, 9.8 Hz, 1H, $C\underline{H}_2Ph$), 2.98 (dd, *J* 12.9 Hz, 5.1 Hz, 1H, $C\underline{H}_2Ph$), 3.09 (dd, *J* 12.8 Hz, 10.4 Hz, 1H, $C\underline{H}_2Ph$), 3.29 (dd, *J* 13.2 Hz, 3.2 Hz, 1H, $C\underline{H}_2Ph$), 3.78 (t, *J* 8.3 Hz, 1H, $OC\underline{H}_2$), 3.98 (dd, *J* 8.9 Hz, 2.4 Hz, 1H, $OC\underline{H}_2$), 4.43 (td, *J* 10.1 Hz, 3.0 Hz, 1H, $CH_2C\underline{H}NCO$), 5.01 (dd, *J* 10.3 Hz, 5.1 Hz, 1H, $COC\underline{H}N$), 7.16-7.33 (m, 10H, $ArC\underline{H}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 33.3 ($\underline{C}H_2Ar$), 38.2 ($\underline{C}H_2Ar$), 41.6 ($N(\underline{C}H_3)_2$), 55.3 $CH_2\underline{C}HNCO$), 64.7 ($CO\underline{C}HN$), 65.8 ($O\underline{C}H_2$), 126.4 (2×$Ar\underline{C}H$), 127.3 (2×$Ar\underline{C}H$), 128.4 (2×$Ar\underline{C}H$), 128.9 (2×$Ar\underline{C}H$), 129.3 (2×$Ar\underline{C}H$), 129.4 (2×$Ar\underline{C}H$), 135.3 ($Ar\underline{C}$), 137.8 ($Ar\underline{C}$), 152.8 (CO), 172.2 (CO). **TLC** R_f = 0.35 (PE:EtOAc, 1:1).

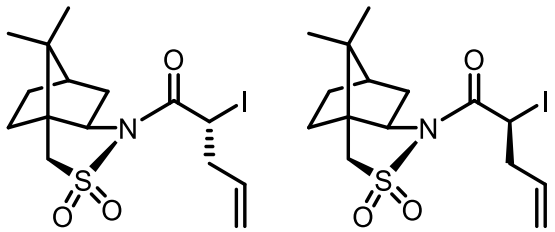
The second diastereoisomer

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.48 (s, 6H, $N(CH_3)_2$), 2.94 (1H, CH_2Ph and 2H, CH_2Ph), 3.21 (dd, *J* 12.9 Hz, 10.6 Hz, 1H, CH_2Ph), 4.06 (dd, *J* 9.0 Hz, 2.0 Hz, 1H, OCH_2), 4.16 (dd, *J* 8.6 Hz, 8.2 Hz, 1H, OCH_2), 4.66 (td, *J* 8.2 Hz, 8.0 Hz, 1H, CH_2CHNCO), 5.12 (dd, *J* 10.3 Hz, 4.1 Hz, 1H, $COCHN$), 7.13-7.37 (m, 10H, ArCH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 31.8 (CH_2Ar), 37.2 (CH_2Ar), 41.4 ($N(CH_3)_2$), 54.9 CH_2CHNCO), 64.4 ($COCHN$), 65.6 (OCH_2), 126.5 (2×ArCH), 127.2 (2×ArCH), 128.4 (2×ArCH), 128.8 (2×ArCH), 129.3 (2×ArCH), 129.6 (2×ArCH), 135.0 (ArC), 137.8 (ArC), 152.8 (CO), 171.3 (CO).

General procedure (I) for reaction of allyl iodide with diazo compounds.

A solution of diazo (100 mg) in DME (10 mL) was added dropwise by syringe pump (0.397 $mL.h^{-1}$) to solution of allyl iodide or allyl sulfide (5 eq) and $Rh_2(OAc)_4$ (5 mol%) in DME (3 mL). The solvent was removed to produce crude which was subjected to column chromatography.

(2*R*)-1-((6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo [c]isothiazol-1(4H)-yl)-2-iodopent-4-en-1-one (352a) and **(2*S*)-1-((6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6 methanobenzo [c] isothiazol-1(4H)-yl)-2-iodopent-4-en-1-one (352b).**



Following procedure (I) above, the combined yield was isolated as solid (**352a+352b** = 141 mg, 95%, Scheme 100, Table 29, Entry 6).

The first diastereoisomer

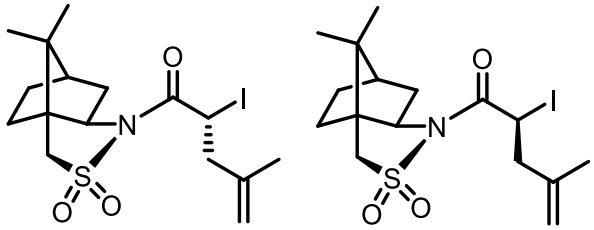
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.98 (s, 3H, $C(CH_3)_2$), 1.21 (s, 3H, $C(CH_3)_2$), 1.32-1.45 (m, 2H, $CH_2CH_2CHCH_2$), 1.85-2.21 (m, 5H, $CH_2CH_2CHCH_2$), 2.75 (ddd, *J* 21.5 Hz, 14.2 Hz, 7.2 Hz, 1H, $CHCH_2CH$), 2.90 (ddd, *J* 21.5 Hz, 14.2 Hz, 7.2 Hz, 1H, $CHCH_2CH$), 3.43 (d, *J* 13.7 Hz, 1H, CH_2SO_2), 3.51 (d, *J* 13.7 Hz, 1H, CH_2SO_2), 3.97 (dd, *J* 7.4 Hz, 5.2 Hz, 1H, NCH), 4.99 (app t, *J* 7.3 Hz, 1H, CHI), 5.15 (d, *J* 1.8 Hz, 1H, CH_2=CH), 5.18 (d, *J* 7.5 Hz, 1H, CH_2=CH), 5.80 (ddt, *J* 16.8 Hz, 10.2 Hz, 6.7 Hz, 1H, $CH=CH_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.9 ($CCH_3)_2$, 20.3 (CHI), 20.6 ($CCH_3)_2$,

26.5 ($CH_2\underline{C}H_2CHCH_2$), 32.7 ($\underline{C}H_2CH_2CHCH_2$), 37.0 ($\underline{C}H_2CH=CH_2$), 39.3 ($CH_2CH_2CH\underline{C}H_2$), 44.3 ($CH_2CH_2\underline{C}HCH_2$), 47.8 ($\underline{C}(CH_3)_2$), 48.7 ($\underline{C}CH_2SO_2$), 53.0 ($\underline{C}H_2SO_2$), 64.8 (N$\underline{C}$H), 118.8 ($CH_2CH=\underline{C}H_2$), 134.5 ($CH_2\underline{C}H=CH_2$), 169.5 (CO). **IR** ν_{max} (thin film, cm^{-1}): 2940 (CH), 1678 (CO), 1325, 1136 (SO_2). **MS** *m/z* (ESI^+) calculated for $C_{15}H_{22}INO_3S$ $[M+H]^+$; 424.0438 found 424.0422. **HPLC** t_R = 13.7 min (96:4, Hex:IPA).

The second diastereoisomer

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.96 (s, 3H, C(C$\underline{H}_3$)$_2$), 1.12 (s, 3H, C(C$\underline{H}_3$)$_2$), 1.32-1.43 (m, 2H, C$\underline{H}_2$CH$_2$C$\underline{H}$CH$_2$), 1.85-2.08 (m, 5H, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}$C$\underline{H}_2$), 2.75 (ddd, *J* 21.5 Hz, 14.2 Hz, 7.2 Hz, 1H, CHC$\underline{H}_2$CH), 2.90 (ddd, *J* 21.5 Hz, 14.2 Hz, 7.2 Hz, 1H, CHC$\underline{H}_2$CH), 3.47 (d, *J* 12.2 Hz, 1H, C$\underline{H}_2$SO$_2$), 3.51 (d, *J* 12.2 Hz, 1H, C$\underline{H}_2$SO$_2$), 3.86 (app t, *J* 6.5 Hz, 1H, NCH), 4.94 (dd, *J* 9.2 Hz, 5.7 Hz, 1H, C$\underline{H}$I), 5.15 (m, 2H, C$\underline{H}_2$=CH), 5.71 (ddt, *J* 17.1 Hz, 10.1 Hz, 7.2 Hz, 1H, C$\underline{H}$=CH$_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.1 (C$\underline{C}$H$_3$)$_2$, 19.9 ($\underline{C}$HI), 20.8 (C$\underline{C}$H$_3$)$_2$, 26.3 ($CH_2\underline{C}H_2CHCH_2$), 32.9 ($\underline{C}H_2CH_2CHCH_2$), 38.2 ($\underline{C}H_2CH=CH_2$), 42.1 ($CH_2CH_2CH\underline{C}H_2$), 44.6 ($CH_2CH_2\underline{C}HCH_2$), 47.8 ($\underline{C}(CH_3)_2$), 48.6 ($\underline{C}CH_2SO_2$), 52.6 ($\underline{C}H_2SO_2$), 65.9 (N$\underline{C}$H), 119.1 ($CH_2CH=\underline{C}H_2$), 134.2 ($CH_2\underline{C}H=CH_2$), 168.5 (CO). **HPLC** t_R = 26.5 min (96:4, Hex:IPA).

(2*R*)-1-((6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo [c]isothiazol-1(4H)-yl)-2-iodo-4-methylpent-4-en-1-one(353a) and **(2*S*)-1-((6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c] isothiazol-1(4H)-yl)-2-iodo-4-methylpent-4-en-1-one (353b).**



Following procedure (I) above, the combined yield was isolated as solid (**353a+353b** = 135 mg, 90%, Scheme 101, Table 31, Entry 2).

The first diastereoisomer

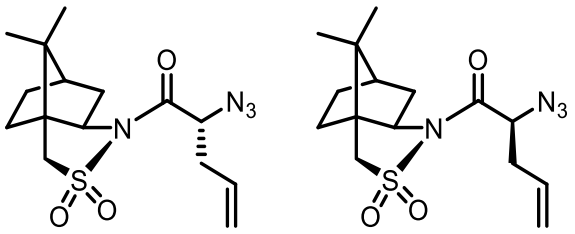
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.97 (s, 3H, C(C$\underline{H}_3$)$_2$), 1.21 (s, 3H, C(C$\underline{H}_3$)$_2$), 1.31-1.48 (m, 2H, C$\underline{H}_2$CH$_2$C$\underline{H}$CH$_2$), 1.75 (s, 3H, CH$_2$=C(C$\underline{H}_3$)CH$_2$), 1.84-2.16 (m, 5H, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}$C$\underline{H}_2$), 2.71 (dd, *J* 14.6 Hz, 7.4 Hz, 1H, C$\underline{H}_2$CHI), 2.91 (dd, *J* 14.6 Hz, 7.4 Hz, 1H, C$\underline{H}_2$CHI), 3.43 (d, *J* 13.7 Hz, 1H, C$\underline{H}_2$SO$_2$), 3.51 (d, *J* 13.7 Hz, 1H, C$\underline{H}_2$SO$_2$),

3.96 (dd, *J* 7.5 Hz, 5.0 Hz, 1H, NCH), 4.82 (s, 1H, C$\underline{H}_2$=CH), 4.88 (s, 1H, C$\underline{H}_2$=CH), 5.14 (app t, *J* 7.2 Hz, 1H, C$\underline{H}$I). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.6 (C$\underline{C}H_3)_2$, 19.9 (C$\underline{H}$I), 20.6 (C$\underline{C}H_3)_2$, 22.1 CH_2=C(C$\underline{H}_3$)CH_2), 26.5 ($CH_2\underline{C}H_2CHCH_2$), 32.7 ($\underline{C}H_2CH_2CHCH_2$), 37.0 ($\underline{C}H_2CH$=$CH_2$), 43.2 ($CH_2CH_2CH\underline{C}H_2$), 44.3 ($CH_2CH_2\underline{C}HCH_2$), 47.8 ($\underline{C}(CH_3)_2$), 48.7 ($\underline{C}CH_2SO_2$), 52.9 ($\underline{C}H_2SO_2$), 64.8 (N$\underline{C}$H), 114.42 ($\underline{C}H_2$=C($CH_3$)$CH_2$), 141.9 ($CH_2$=$\underline{C}$($CH_3$)$CH_2$), 169.5 (CO). **TLC** R_f = 0.22 (PE:EtOAc, 4:1). **HPLC** t_R = 16.1 min (95:5, Hex:EtOH).

The second diastereoisomer

Partial characterisation was only possible, as the product was not isolated pure. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.96 (s, 3H, C(C$\underline{H}_3)_2$), 1.10 (s, 3H, C(C$\underline{H}_3)_2$), 1.32-1.44 (m, 2H, C$\underline{H}_2$CH_2C$\underline{H}$CH_2), 1.76 (s, 3H, CH_2=C(C$\underline{H}_3$)CH_2), 1.84-2.07 (m, 5H, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}$C$\underline{H}_2$), 2.71 (dd, *J* 13.8 Hz, 7.8 Hz, 1H, C$\underline{H}_2$CHI), 3.06 (dd, *J* 13.8 Hz, 7.8 Hz, 1H, C$\underline{H}_2$CHI), 3.47 (d, *J* 4.4 Hz, 1H, C$\underline{H}_2SO_2$), 3.49 (d, *J* 4.4 Hz, 1H, C$\underline{H}_2SO_2$), 3.86 (dd, *J* 6.5 Hz, 6.1 Hz, 1H, NCH), 4.79 (s, 1H, C$\underline{H}_2$=CH), 4.81 (s, 1H, C$\underline{H}_2$=CH), 5.06 (dd, *J* 10.2 Hz, 5.2 Hz, 1H, C$\underline{H}$I). **HPLC** t_R = 21.1 min (95:5, Hex:EtOH).

(2*R*)-2-azido-1-((6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo [c] isothiazol-1(4H)-yl)pent-4-en-1-one (354a) and **(2*S*)-2-azido-1-((6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c] isothiazol-1(4H)-yl)pent-4-en-1-one (354b).**



The mixture of diastereoisomers of camphorsultam iodide (**354**) (0.295 g, 0.69 mmol) was dissolved in DMF (5 mL) and sodium azide (45.34 mg, 0.697 mmol) was added, the mixture was stirred at room temperature for 4 h, after which it was taken to the ethyl acetate and extracted with water (3×50 mL) and brine (1× 50 mL). The combined organic layers were dried using anhydrous $MgSO_4$. The solvent was removed to produce crude which was subjected to column chromatography to afford (**354a+354b** = 0.165 g, 70%, Scheme 102, Table 32) total yield.

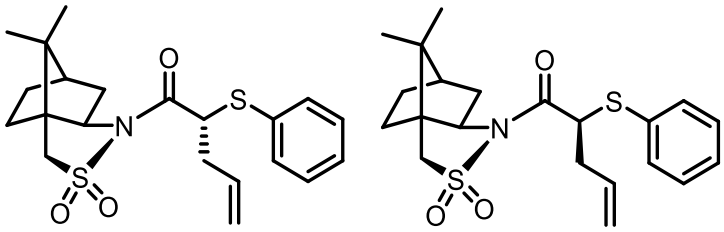
The first diastereoisomer

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.97 (s, 3H, C(C$\underline{H}_3$)$_2$), 1.12 (s, 3H, C(C$\underline{H}_3$)$_2$), 1.32-1.45 (m, 2H, C$\underline{H}_2$CH$_2$C$\underline{H}$CH$_2$), 1.87-2.12 (m, 5H, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}$C$\underline{H}_2$), 2.59 (ddd, *J* 21.2 Hz, 14.1 Hz, 7.2 Hz, 1H, CHC$\underline{H}_2$CHN$_3$), 2.69 (ddd, *J* 21.2 Hz, 14.1 Hz, 7.2 Hz, 1H, CHC$\underline{H}_2$CHN$_3$), 3.47 (d, *J* 13.8 Hz, 1H, C$\underline{H}_2$SO$_2$), 3.52 (d, *J* 13.8 Hz, 1H, C$\underline{H}_2$SO$_2$), 3.94 (dd, *J* 7.6 Hz, 5.0 Hz, 1H, NCH), 4.42 (dd, *J* 7.1 Hz, 6.5 Hz, 1H, C$\underline{H}$N$_3$), 5.15 (d, *J* 10.0 Hz, 1H, C$\underline{H}_2$=CH), 5.21 (d, *J* 17.0 Hz, 1H, C$\underline{H}_2$=CH), 5.80 (ddt, *J* 17.2 Hz, 10.0 Hz, 7.0 Hz, 1H, C$\underline{H}$=CH$_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.8 (C$\underline{C}$H$_3$)$_2$, 20.7 (C$\underline{C}$H$_3$)$_2$, 26.3 (CH$_2$$\underline{C}H_2$CHCH$_2$), 32.8 ($\underline{C}H_2CH_2$CHCH$_2$), 36.7 ($\underline{C}H_2$CH=CH$_2$), 38.0 (CH$_2CH_2CH\underline{C}H_2$), 44.5 (CH$_2CH_2$$\underline{C}HCH_2$), 47.8 ($\underline{C}$(CH$_3$)$_2$), 48.7 ($\underline{C}CH_2SO_2$), 52.9 ($\underline{C}H_2SO_2$), 60.3 ($\underline{C}HN_3$), 65.2 (N$\underline{C}$H), 119.6 (CH$_2$CH=$\underline{C}H_2$), 131.6 (CH$_2$$\underline{C}$H=CH$_2$), 169.5 (CO). **IR** ν_{max}/cm^{-1}: 2952 (CH), 2101 (C=N$_3$), 1688 (CO), 1323, 1135 (SO$_2$). **MS** *m/z* (ESI$^+$) calculated for $C_{15}H_{22}N_4O_3S$ [M+Na]$^+$; 361.1305 found 361.1311. **TLC** R_f = 0.17 (PE:EtOAc, 4:1).

The second diastereoisomer

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.97 (s, 3H, C(C$\underline{H}_3$)$_2$), 1.12 (s, 3H, C(C$\underline{H}_3$)$_2$), 1.32-1.45 (m, 2H, C$\underline{H}_2$CH$_2$C$\underline{H}$CH$_2$), 1.87-2.12 (m, 5H, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}$C$\underline{H}_2$), 2.59 (ddd, *J* 21.2 Hz, 14.1 Hz, 7.2 Hz, 1H, CHC$\underline{H}_2$CHN$_3$), 2.69 (ddd, *J* 21.2 Hz, 14.1 Hz, 7.2 Hz, 1H, CHC$\underline{H}_2$CHN$_3$), 3.48 (d, *J* 7.6 Hz, 1H, C$\underline{H}_2$SO$_2$), 3.51 (d, *J* 7.6 Hz, 1H, C$\underline{H}_2$SO$_2$), 3.86-3.93 (m, 1H, NCH), 4.34 (dd, *J* 8.6 Hz, 5.4 Hz, 1H, C$\underline{H}$N$_3$), 5.15 (d, *J* 10.0 Hz, 1H, C$\underline{H}_2$=CH), 5.24 (d, *J* 15.5 Hz, 1H, C$\underline{H}_2$=CH), 5.80 (ddt, *J* 17.2 Hz, 10.0 Hz, 7.0 Hz, 1H, C$\underline{H}$=CH$_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 20.8 (C$\underline{C}$H$_3$)$_2$, 22.1 (C$\underline{C}$H$_3$)$_2$, 26.4 (CH$_2$$\underline{C}H_2$CHCH$_2$), 31.9 ($\underline{C}H_2CH_2$CHCH$_2$), 34.5 ($\underline{C}H_2$CH=CH$_2$), 38.2 (CH$_2CH_2CH\underline{C}H_2$), 44.7 (CH$_2CH_2$$\underline{C}HCH_2$), 47.8 ($\underline{C}$(CH$_3$)$_2$), 48.8 ($\underline{C}CH_2SO_2$), 53.0 ($\underline{C}H_2SO_2$), 60.2 ($\underline{C}HN_3$), 65.2 (N$\underline{C}$H), 119.4 (CH$_2$CH=$\underline{C}H_2$), 132.0 (CH$_2$$\underline{C}$H=CH$_2$), 168.4 (CO).

(2*R*)-1-((6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo [c]isothiazol-1(4H)-yl)-2-(phenylthio)pent-4-en-1-one (355a) and **(2*S*)-1-((6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo [c]isothiazol-1(4H)-yl)-2-(phenylthio)pent-4-en-1-one (355b).**



Following procedure (I) above, the combined yield was isolated as solid (**355a+355b** = 114.5 mg, 80%, Scheme 103, Table 33).

The first diastereoisomer

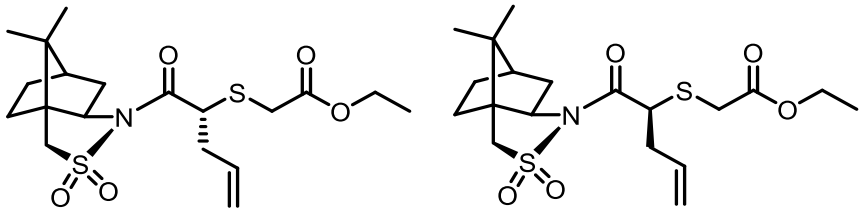
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.93 (s, 3H, C(C$\underline{H}_3$)$_2$), 1.00 (s, 3H, C(C$\underline{H}_3$)$_2$), 1.33-1.41 (m, 2H, C$\underline{H}_2$CH$_2$C$\underline{H}$CH$_2$), 1.84-2.02 (m, 5H, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}$C$\underline{H}_2$), 2.47 (ddd, *J* 21.5 Hz, 14.3 Hz, 7.1 Hz, 1H, CHC$\underline{H}_2$CHSPh), 2.68 (ddd, *J* 21.5 Hz, 14.3 Hz, 7.1 Hz, 1H, CHC$\underline{H}_2$CHSPh), 3.40 (d, *J* 13.7 Hz, 1H, C$\underline{H}_2$SO$_2$), 3.47 (d, *J* 13.7 Hz, 1H, C$\underline{H}_2$SO$_2$), 3.88 (dd, *J* 7.6 Hz, 5.0 Hz, 1H, NCH), 4.34 (dd, *J* 6.6 Hz, 6.2 Hz, 1H, C$\underline{H}$SPh), 5.09 (d, *J* 11.2 Hz, 1H, C$\underline{H}_2$=CH), 5.13 (d, *J* 17.1 Hz, 1H, C$\underline{H}_2$=CH), 5.83 (ddt, *J* 17.1 Hz, 10.1 Hz, 7.0 Hz, 1H, C$\underline{H}$=CH$_2$), 7.28-7.30 (m, 3H, ArCH), 7.49-7.51 (m, 2H, ArCH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.8 (C$\underline{C}$H$_3$)$_2$, 20.7 (C$\underline{C}$H$_3$)$_2$, 26.4 (CH$_2$$\underline{C}H_2$CHCH$_2$), 32.8 ($\underline{C}H_2CH_2$CHCH$_2$), 35.4 ($\underline{C}H_2$CH=CH$_2$), 38.2 (CH$_2CH_2CH\underline{C}H_2$), 44.6 (CH$_2CH_2$$\underline{C}HCH_2$), 47.7 ($\underline{C}$(CH$_3$)$_2$), 48.3 ($\underline{C}CH_2SO_2$), 49.5 ($\underline{C}$HSPh), 53.1 ($\underline{C}H_2SO_2$), 65.1 (N$\underline{C}$H), 118.2 (CH$_2$CH=$\underline{C}H_2$), 128.6 (ArCH), 128.8 (4×ArCH), 133.8 (ArC), 134.8 (CH$_2$$\underline{C}$H=CH$_2$), 170.3 (CO). **IR** ν_{max} /cm^{-1}: 2922 (CH), 1689 (CO), 1330, 1132 (SO_2). **MS** *m/z* (ESI$^+$) calculated for $C_{21}H_{27}NO_3S_2$ [M+H]$^+$; 406.1505 found 406.1511. **TLC** R_f = 0.20 (PE:EtOAc, 4:1).

The second diastereoisomer

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.96 (s, 3H, C(C$\underline{H}_3$)$_2$), 1.13 (s, 3H, C(C$\underline{H}_3$)$_2$), 1.25-1.43 (m, 2H, C$\underline{H}_2$CH$_2$C$\underline{H}$CH$_2$), 1.84-2.09 (m, 5H, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}$C$\underline{H}_2$), 2.61 (ddd, *J* 20.9 Hz, 14.1 Hz, 6.8 Hz, 1H, CHC$\underline{H}_2$CHSPh), 2.68 (ddd, *J* 20.9 Hz, 14.1 Hz, 6.8 Hz, 1H, CHC$\underline{H}_2$CHSPh), 3.45 (d, *J* 13.8 Hz, 1H, C$\underline{H}_2$SO$_2$), 3.50 (d, *J* 13.8 Hz, 1H, C$\underline{H}_2$SO$_2$), 3.93 (dd, *J* 6.7 Hz, 6.1 Hz, 1H, NCH), 4.45 (dd, *J* 7.8 Hz, 5.7 Hz, 1H, C$\underline{H}$SPh), 5.04 (d, *J* 10.2 Hz, 1H, C$\underline{H}_2$=CH), 5.10 (d, *J* 17.1 Hz, 1H, C$\underline{H}_2$=CH), 5.79 (ddt, *J* 16.8 Hz,

10.1 Hz, 6.5 Hz, 1H, C<u>H</u>=CH_2), 7.28-7.33 (m, 3H, ArCH), 7.53-7.55 (m, 2H, ArCH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.9 ($C\underline{C}H_3)_2$, 20.8 ($C\underline{C}H_3)_2$, 26.3 ($CH_2\underline{C}H_2CHCH_2$), 32.8 ($\underline{C}H_2CH_2CHCH_2$), 38.2 ($\underline{C}H_2CH=CH_2$), 38.3 ($CH_2CH_2CH\underline{C}H_2$), 44.5 ($CH_2CH_2\underline{C}HCH_2$), 47.7 ($\underline{C}(CH_3)_2$), 48.4 ($\underline{C}CH_2SO_2$), 50.6 ($\underline{C}HSPh$), 53.0 ($\underline{C}H_2SO_2$), 65.6 (N<u>C</u>H), 118.5 ($CH_2CH=\underline{C}H_2$), 128.1 (ArCH), 128.9 (2×ArCH), 132.6 (ArC), 133.4 ($CH_2\underline{C}H=CH_2$), 133.9 (2×ArCH), 169.9 (CO). **IR** ν_{max} /cm^{-1}: 2957 (CH), 1670 (CO), 1356, 1137 (SO_2). **MS** *m/z* (ESI$^+$) calculated for $C_{21}H_{27}NO_3S_2$ $[M+H]^+$; 406.1505 found 406.1512.

Ethyl 2-(((2R)-1-((6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methano-benzo [c]isothiazol-1(4H)-yl)-1-oxopent-4-en-2-yl)thio)acetate (356a) and **ethyl 2-(((2S)-1-((6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo [c]isothiazol-1(4H)-yl)-1-oxopent-4-en-2-yl)thio)acetate (356b).**



Following procedure (I) above, the combined yield was isolated as solid (356a+356b = 41 mg, 28%, Scheme 103, Table 33).

The first diastereoisomer

m.p.= 97-99 °C**. ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.97 (s, 3H, C($C\underline{H}_3)_2$), 1.20 (s, 3H, C($C\underline{H}_3)_2$), 1.27 (t, J 7.2 Hz, 3H, $COOCH_2C\underline{H}_3$) 1.31-1.44 (m, 2H, $C\underline{H}_2CH_2C\underline{H}CH_2$), 1.85-2.16 (m, 5H, $C\underline{H}_2C\underline{H}_2C\underline{H}C\underline{H}_2$), 2.53 (ddd, *J* 21.6 Hz, 14.1 Hz, 6.9 Hz, 1H, $CHC\underline{H}_2CHSCH_2$), 2.74 (ddd, *J* 21.6 Hz, 14.1 Hz, 6.9 Hz, 1H, $CHC\underline{H}_2CHSCH_2$), 3.33-3.52 (2H, $C\underline{H}_2SO_2$ and 2H, $COC\underline{H}_2S$), 3.91 (dd, *J* 7.6 Hz, 4.9 Hz, 1H, NCH), 4.02 (app t, *J* 7.0 Hz, 1H, $COC\underline{H}SCH_2$), 4.17 (q, *J* 7.1 Hz, 2H, $COOC\underline{H}_2$), 5.09 (d, *J* 10.1 Hz, 1H, $C\underline{H}_2$=CH), 5.15 (d, *J* 17.0 Hz, 1H, $C\underline{H}_2$=CH), 5.80 (ddt, *J* 17.0 Hz, 10.0 Hz, 6.8 Hz, 1H, C<u>H</u>=CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 14.1 ($COOCH_2\underline{C}H_3$), 19.9 ($C\underline{C}H_3)_2$, 20.7 ($C\underline{C}H_3)_2$, 26.5 ($CH_2\underline{C}H_2CHCH_2$), 32.0 ($S\underline{C}H_2COO$), 32.7 ($\underline{C}H_2CH_2CHCH_2$), 35.1 ($\underline{C}H_2CH=CH_2$), 37.9 ($CH_2CH_2CH\underline{C}H_2$), 44.6 ($CH_2CH_2\underline{C}HCH_2$), 45.7 ($CO\underline{C}HS$), 47.8 ($\underline{C}(CH_3)_2$), 48.5 ($\underline{C}CH_2SO_2$), 53.1 ($\underline{C}H_2SO_2$), 61.5 ($COO\underline{C}H_2CH_3$), 65.0 (N<u>C</u>H), 118.2 ($CH_2CH=\underline{C}H_2$), 133.6 ($CH_2\underline{C}H=CH_2$), 169.7 (CO), 170.0 (CO). **IR** ν_{max} /cm^{-1}: 2942 (CH), 1731 (CO), 1323, 1133 (SO_2). **MS** *m/z* (ESI$^+$) calculated for $C_{19}H_{29}NO_5S_2$

$[M+Na]^+$; 438.1379 found 438.1377. **TLC** R_f = 0.27 (PE:EtOAc, 7:3). **HPLC** t_R = 11.5 min (90:10, Hex:IPA).

The second diastereoisomer

m.p.= 72-74 °C**.** **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.95 (s, 3H, $C(C\underline{H}_3)_2$), 1.12 (s, 3H, $C(C\underline{H}_3)_2$), 1.27 (t, J 7.2 Hz, 3H, $COOCH_2C\underline{H}_3$) 1.31-1.45 (m, 2H, $C\underline{H}_2CH_2C\underline{H}CH_2$), 1.84-2.08 (m, 5H, $C\underline{H}_2C\underline{H}_2C\underline{H}C\underline{H}_2$), 2.63 (ddd, *J* 21.0 Hz, 14.0 Hz, 7.0 Hz, 1H, $CHC\underline{H}_2CHSCH_2$), 2.70 (ddd, *J* 21.0 Hz, 14.0 Hz, 7.0 Hz, 1H, $CHC\underline{H}_2CHSCH_2$), 3.38-3.52 (2H, $C\underline{H}_2SO_2$ and 2H, $COC\underline{H}_2S$), 3.92 (dd, *J* 6.5 Hz, 6.5 Hz, 1H, NCH), 4.17 (q, J 7.0 Hz, 2H, $COOC\underline{H}_2$), 4.23 (dd, *J* 8.3 Hz, 5.9 Hz, 1H, $COC\underline{H}SCH_2$), 5.04 (d, *J* 10.2 Hz, 1H, $C\underline{H}_2$=CH), 5.12 (d, *J* 17.0 Hz, 1H, $C\underline{H}_2$=CH), 5.80 (ddt, *J* 16.8 Hz, 10.1 Hz, 6.2 Hz, 1H, $C\underline{H}$=CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 14.1 ($COOCH_2\underline{C}H_3$), 19.9 ($C\underline{C}H_3)_2$, 20.8 ($C\underline{C}H_3)_2$, 26.3 ($CH_2\underline{C}H_2CHCH_2$), 32.8 ($S\underline{C}H_2COO$), 32.9 ($\underline{C}H_2CH_2CHCH_2$), 38.0 ($\underline{C}H_2CH$=$CH_2$), 38.2 ($CH_2CH_2CH\underline{C}H_2$), 44.6 ($CH_2CH_2\underline{C}HCH_2$), 46.6 ($CO\underline{C}HS$), 47.7 ($\underline{C}(CH_3)_2$), 48.4 ($\underline{C}CH_2SO_2$), 53.0 ($\underline{C}H_2SO_2$), 61.5 ($COO\underline{C}H_2CH_3$), 65.6 ($N\underline{C}H$), 118.5 ($CH_2CH$=$\underline{C}H_2$), 133.3 ($CH_2\underline{C}H$=$CH_2$), 170.0 (CO), 170.4 (CO). **IR** ν_{max} /cm^{-1}: 2941 (CH), 1731 (CO), 1327, 1133 (SO_2). **MS** *m/z* (ESI^+) calculated for $C_{19}H_{29}NO_5S_2$ $[M+Na]^+$; 438.1379 found 438.1381. **HPLC** t_R = 44.1 min (90:10, Hex:IPA).

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9. Appendix

Table 33. Comparison of δ C<u>H</u>CH$_2$Ar (^{1}H NMR, CDCl$_3$) of the major and the minor diastereoisomers.

Product *2S*/*2R*	**Ar**	**δ (2*S*)-product (major)**	**δ (2*R*)-product (minor)**
313a/314a	H	4.19 (t, *J* 7.5 Hz, 1H)	4.17 (t, *J* 7.0 Hz, 1H)
313b/314b	4-OMe	4.13 (t, *J* 7.5 Hz, 1H)	4.12 (t, *J* 7.5 Hz, 1H)
313c/314c	4-COMe	4.21 (t, *J* 7.5 Hz 1H)	4.19 (t, *J* 7.2 Hz, 1H)
313d/314d	2,5-diF	4.17 (dd, *J* 7.0, 6.5, 1H)	4.18 (t, *J* 7.0 Hz, 1H)
313e/314e	4-COPh	4.25 (t, *J* 7.4 Hz, 1H)	4.22 (t, *J* 6.8 Hz, 1H)
313f/314f	4-COOMe	4.20 (t, *J* 7. Hz, 1H)	4.18 (t, *J* 6.8 Hz, 1H)
313g/314g	2,4-diF	4.16 (dd, *J* 8.2, 6.6 Hz, 1H)	4.15 (t, *J* 7.1 Hz, 1H)
313h/314h	3,5-diF	4.15 (t, *J* 7.5 Hz, 1H)	4.13 (t, *J* 6.7 Hz, 1H)
313i/314i	2,4,6-triF	4.18 (dd, *J* 9.5, 5.1 Hz, 1H)	4.24 (t, *J* 7.3 Hz, 1H),
313j/314j	3-F	4.17 (t, *J* 7.5 Hz, 1H)	4.15 (t, *J* 7.1 Hz, 1H)
313k/314k	4-Ph	4.21 (t, *J* 7.5 Hz, 1H)	4.22 (t, *J* 6.5 Hz, 1H)
313l/314l	2-CN	4.27 (t, *J* 6.9 Hz, 1H)	4.19 (t, *J* 7.0 Hz, 1H)

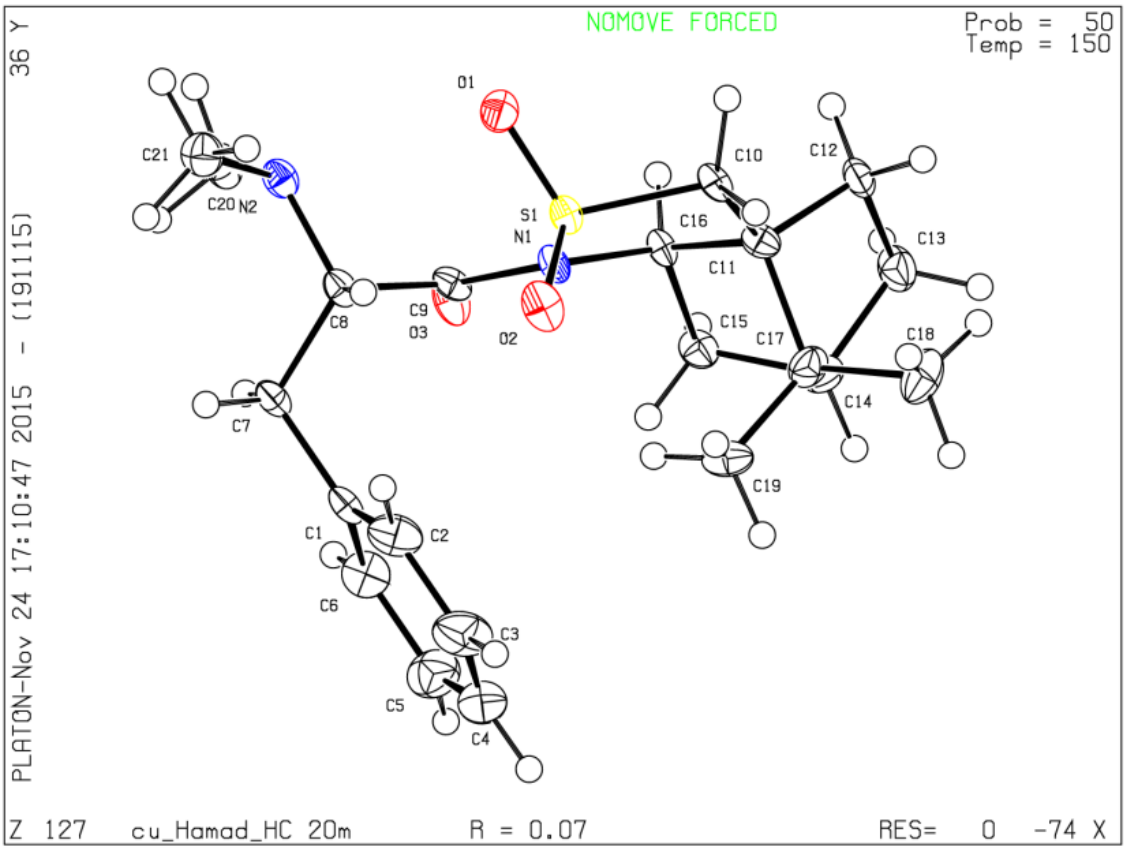
Table 34. Comparison of δ CHC<u>H</u>$_2$Ar (^{1}H NMR, $CDCl_3$) of the major and the minor diastereoisomers.

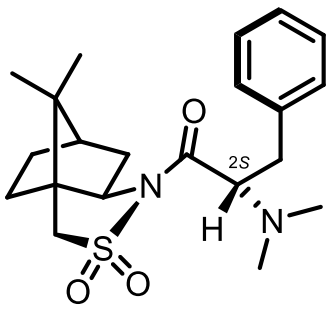
Product 2*S*/2*R*	**Ar**	**δ (2*S*)-product (major)**	**δ (2*R*)-product (minor)**
313a/314a	H	2.97 (dd, *J* 13.2, 7.5, 1H) 3.08 (dd, *J* 13.2, 7.5, 1H)	2.88 (dd, *J* 14.0, 7.2, 1H) 3.04 (dd, *J* 14.0, 7.2, 1H)
313b/314b	4-OMe	2.92 (dd, *J* 13.3, 7.6, 1H) 3.01 (dd, *J* 13.3, 7.6, 1H)	2.83 (dd, *J* 14.1, 7.2, 1H) 2.97 (dd, *J* 14.1, 7.2, 1H)
313c/314c	4-COMe	3.02 (dd, *J* 13.2, 7.5, 1H) 3.13 (dd, *J* 13.2, 7.5, 1H)	2.94 (dd, *J* 14.0, 7.2, 1H) 3.07 (dd, *J* 14.0, 7.2, 1H)
313d/314d	2,5-diF	2.96 (dd, *J* 13.4, 7.3, 1H) 3.11 (dd, *J* 13.4, 7.3, 1H)	2.93 (dd, *J* 14.0, 7.2, 1H) 3.02 (dd, *J* 14.0, 7.2, 1H)
313e/314e	4-COPh	3.07 (dd, *J* 13.2, 7.4, 1H) 3.17 (dd, *J* 13.2, 7.4, 1H)	2.98 (dd, *J* 13.8, 7.2, 1H) 3.10 (dd, *J* 13.8, 7.2, 1H)
313f/314f	4-COOMe	3.01 (dd, *J* 13.2, 7.5, 1H) 3.12 (dd, *J* 13.2, 7.5, 1H)	2.93 (dd, *J* 13.9, 7.2, 1H) 3.07 (dd, *J* 13.9, 7.2, 1H)
313g/314g	2,4-diF	2.97 (dd, *J* 13.3, 7.6, 1H) 3.09 (dd, *J* 13.3, 7.6, 1H)	2.93 (dd, *J* 14.0, 7.2, 1H) 3.00 (dd, *J* 14.0, 7.2, 1H)
313h/314h	3,5-diF	2.93 (dd, *J* 13.4, 7.5, 1H) 3.05 (dd, *J* 13.4, 7.5, 1H)	2.86 (dd, *J* 14.1, 6.6, 1H) 2.98 (dd, *J* 14.1, 6.6, 1H)
313i/314i	2,4,6-triF	2.96 (dd, *J* 13.4, 7.5, 1H) 3.17 (dd, *J* 13.4, 7.5, 1H)	2.96 (dd, *J* 14.1, 7.4, 1H) 3.03 (dd, *J* 14.1, 7.4, 1H)
313j/314j	3-F	2.96 (dd, *J* 13.3, 7.5, 1H) 3.07 (dd, *J* 13.3, 7.5, 1H)	2.87 (dd, *J* 14.1, 7.2, 1H) 3.02 (dd, *J* 14.1, 7.2, 1H)
313k/314k	4-Ph	3.00 (dd, *J* 13.2, 7.6, 1H) 3.09 (dd, *J* 13.2, 7.6, 1H)	2.94 (dd, *J* 14.1, 7.2, 2H) 3.06 (dd, *J* 14.1, 7.2, 2H)
313l/314l	2-CN	3.23 (dd, *J* 13.6, 7.4, 2H) 3.30 (dd, *J* 13.6, 7.4, 2H)	3.15 (dd, *J* 14.1, 7.0, 1H) 3.21 (dd, *J* 14.1, 7.0, 1H)

Table 35. Comparison of δ $C\underline{H}_2SO_2$ (^{1}H NMR, $CDCl_3$) of the major and the minor diastereoisomers**.**

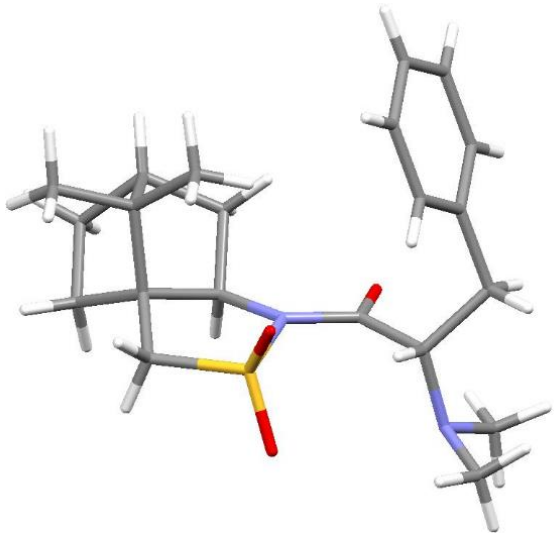
Product 2*S*/2*R*	**Ar**	**δ (2*S*)-product (major)**	**δ (2*R*)-product (minor)**
313a/314a	H	3.37 (s, 2H)	3.37 (d, *J* 13.7, 1H) 3.46 (d, *J* 13.7, 1H)
313b/314b	4-OMe	3.37 (s, 2H)	3.38 (d, *J* 13.7, 1H) 3.47 (d, *J* 13.7, 1H)
313c/314c	4-COMe	3.38 (s, 2H)	3.38 (d, *J* 13.7, 1H) 3.468 (d, *J* 13.7, 1H)
313d/314d	2,5-diF	3.38 (s, 2H)	3.36 (d, *J* 13.6, 1H) 3.46 (d, *J* 13.7, 1H)
313e/314e	4-COPh	3.39 (s, 2H)	3.38 (d, *J* 13.6, 1H) 3.49 (d, *J* 13.7, 1H)
313f/314f	4-COOMe	3.37 (s, 2H)	3.37 (d, *J* 13.7, 1H) 3.47 (d, *J* 13.7, 1H)
313g/314g	2,4-diF	3.37 (s, 2H)	3.36 (d, *J* 13.7, 1H) 3.46 (d, *J* 13.7, 1H)
313h/314h	3,5-diF	3.37 (s, 2H)	3.39 (d, *J* 13.7, 1H) 3.49 (d, *J* 13.7, 1H)
313i/314i	2,4,6-triF	3.36 (s, 2H)	3.36 (d, *J* 13.6, 1H) 3.46 (d, *J* 13.6, 1H)
313j/314j	3-F	3.39 (s, 2H)	3.38 (d, *J* 13.7, 1H) 3.48 (d, *J* 13.7, 1H)
313k/314k	4-Ph	3.37 (s, 2H)	3.40 (d, *J* 13.7, 1H) 3.48 (d, *J* 13.6, 1H)
313l/314l	2-CN	3.37 (s, 2H)	3.34 (d, *J* 13.7, 1H) 3.44 (d, *J* 13.7, 1H)

X-Ray crystallographic data for (313a)

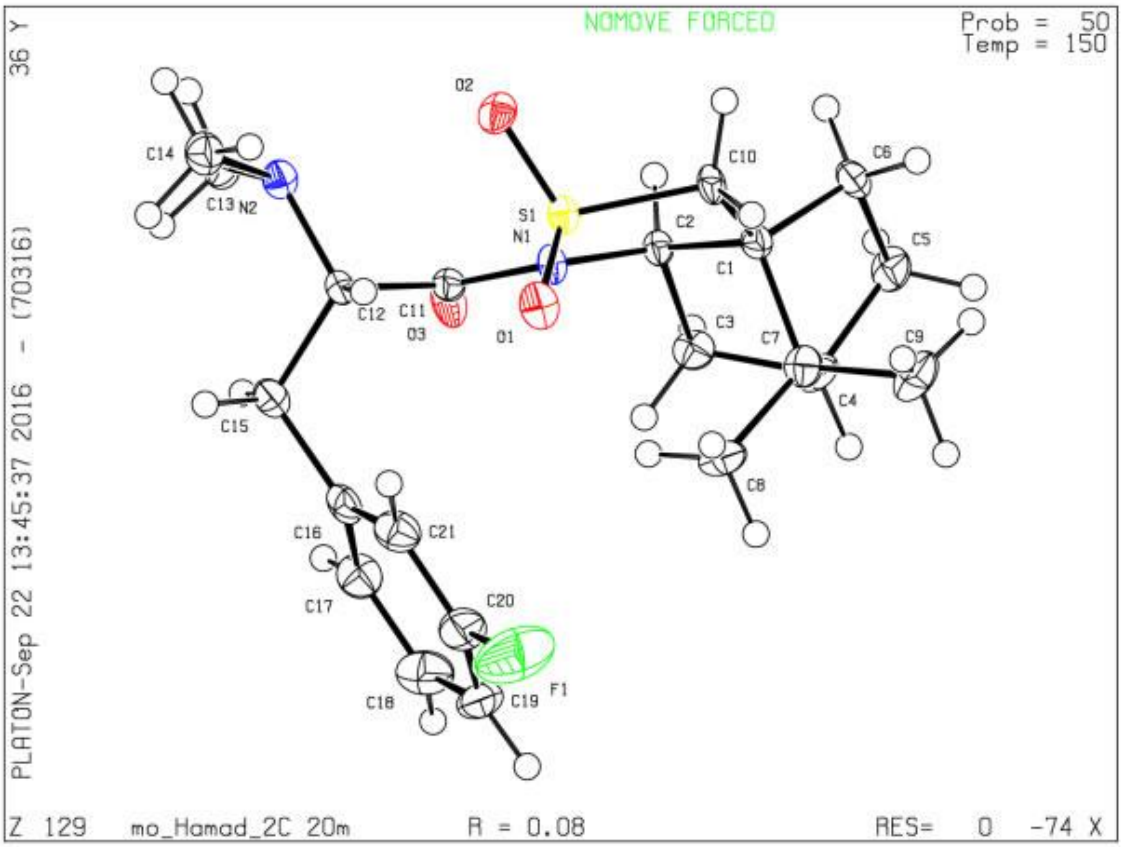


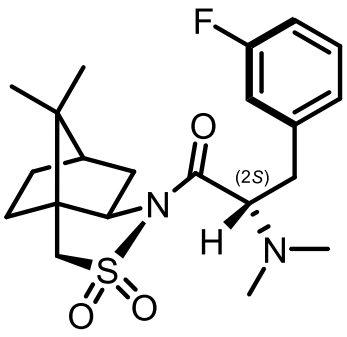


Major diasteroisomer

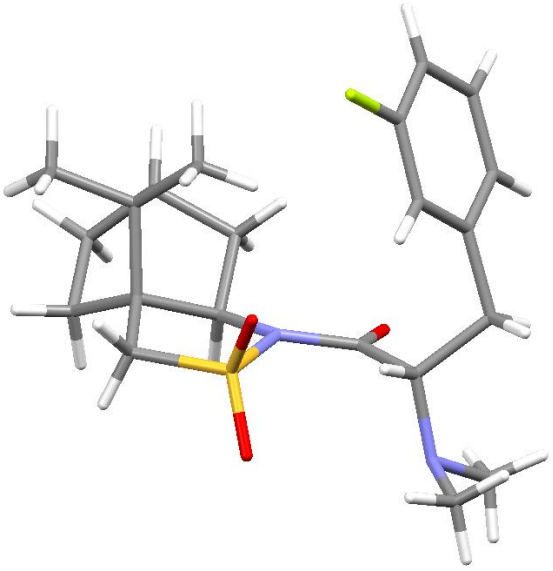


X-Ray crystallographic data for (313j)

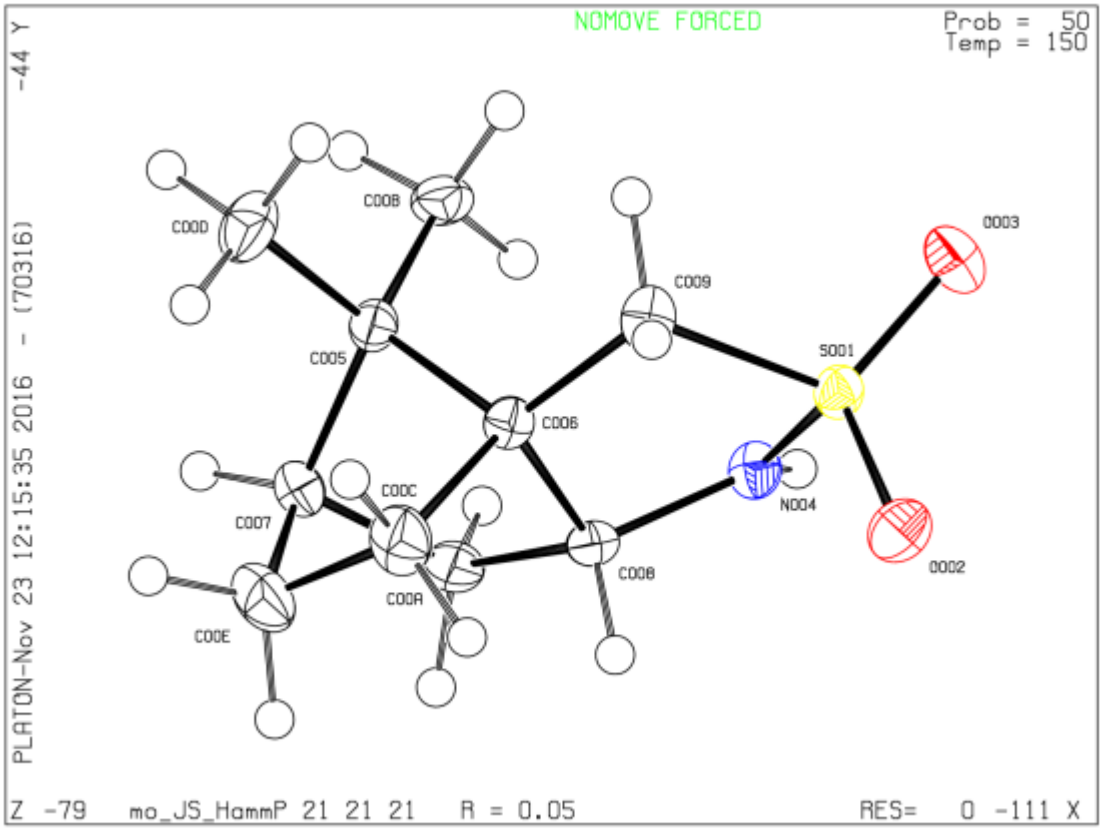


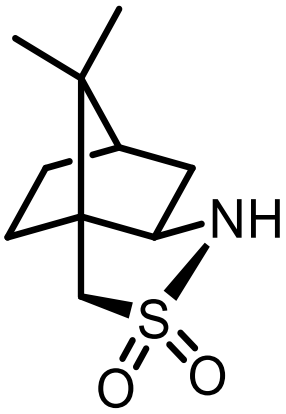


Major diasteroisomer

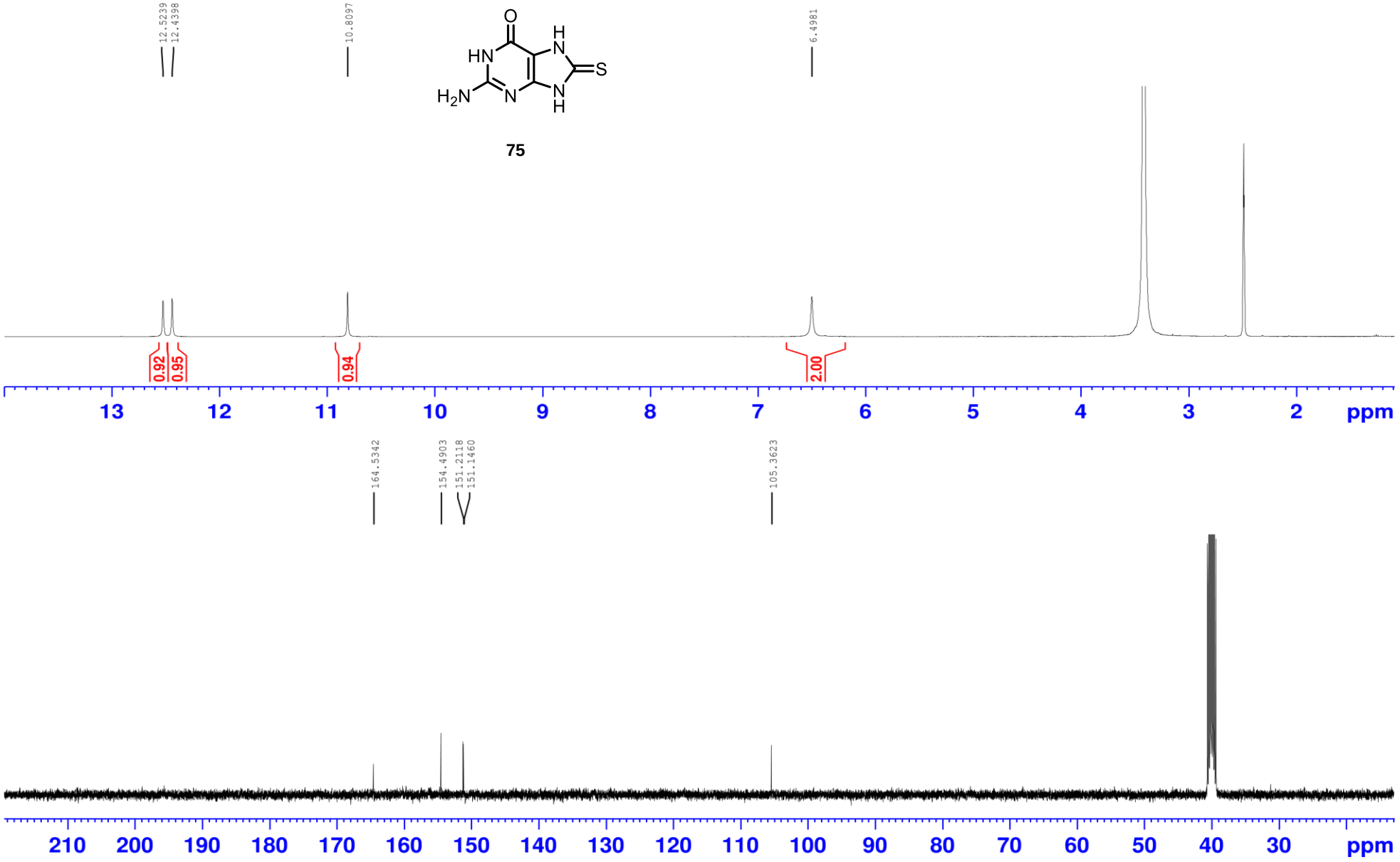


X-Ray crystallographic data for (306)



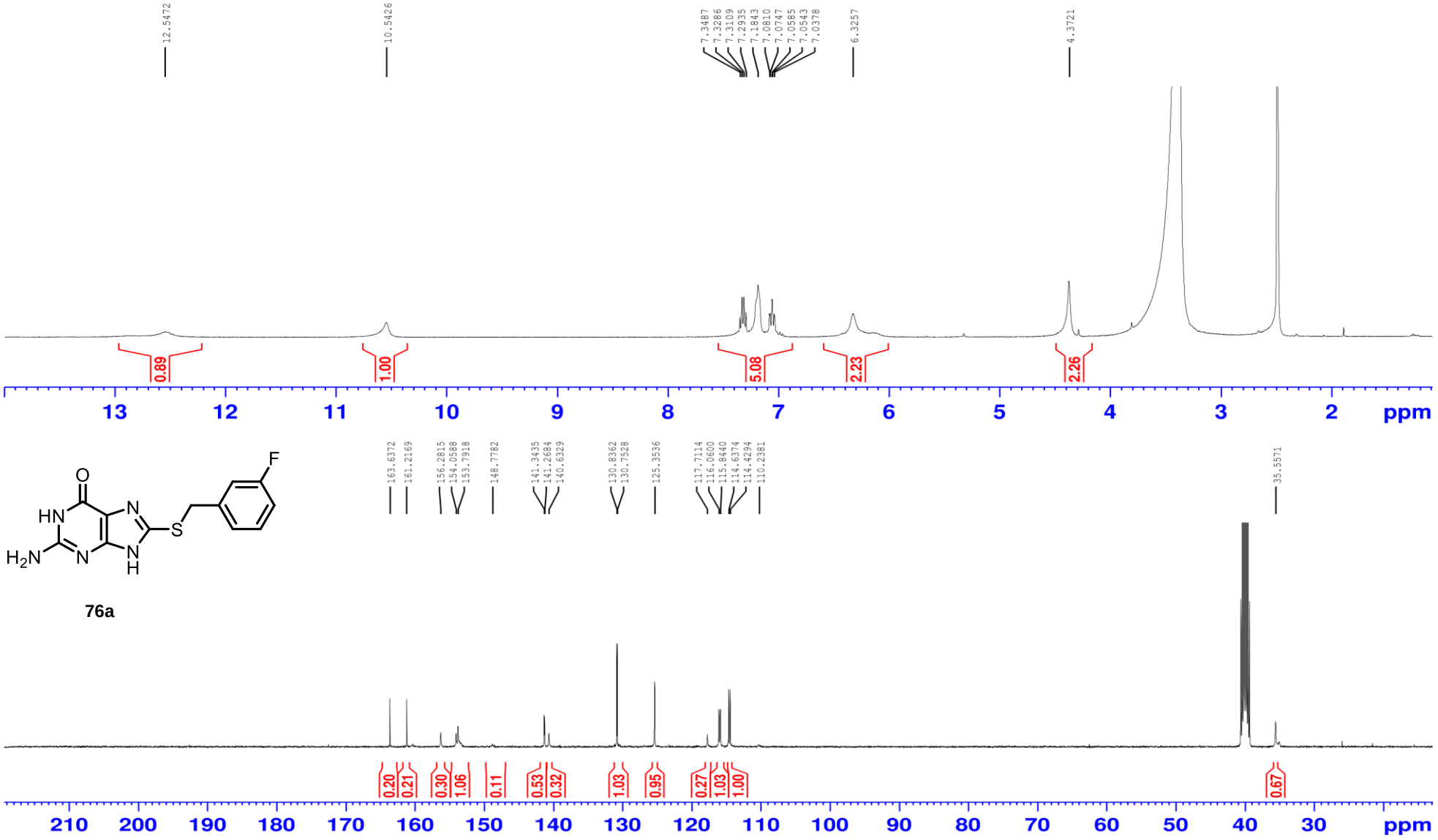


^{1}H and ^{13}C NMR (DMSO-d_6)



75

^{1}H and ^{13}C NMR (DMSO-d_6)



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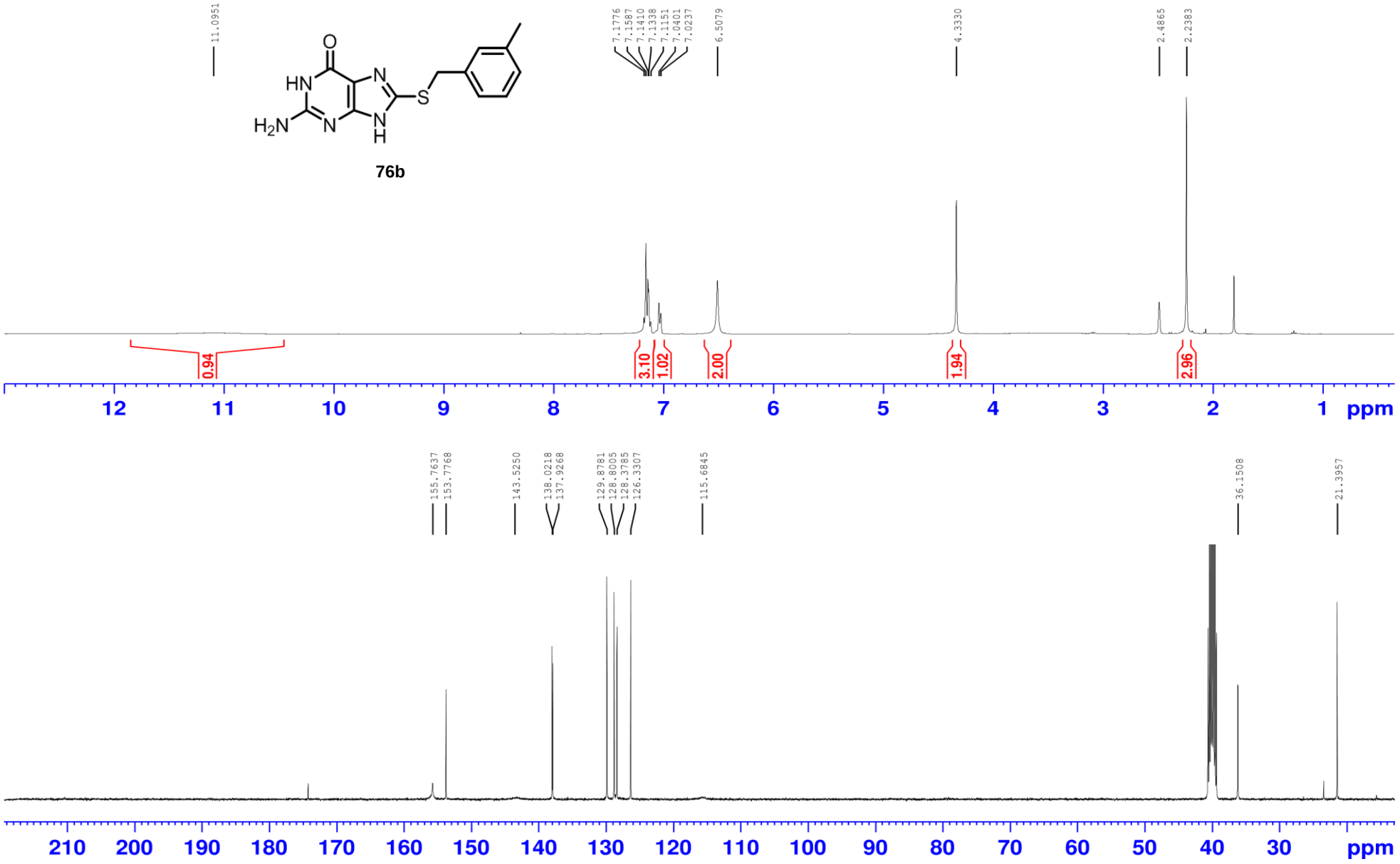

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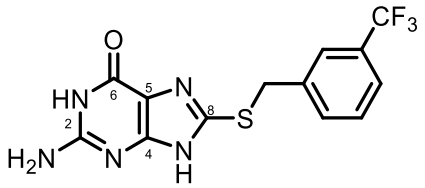
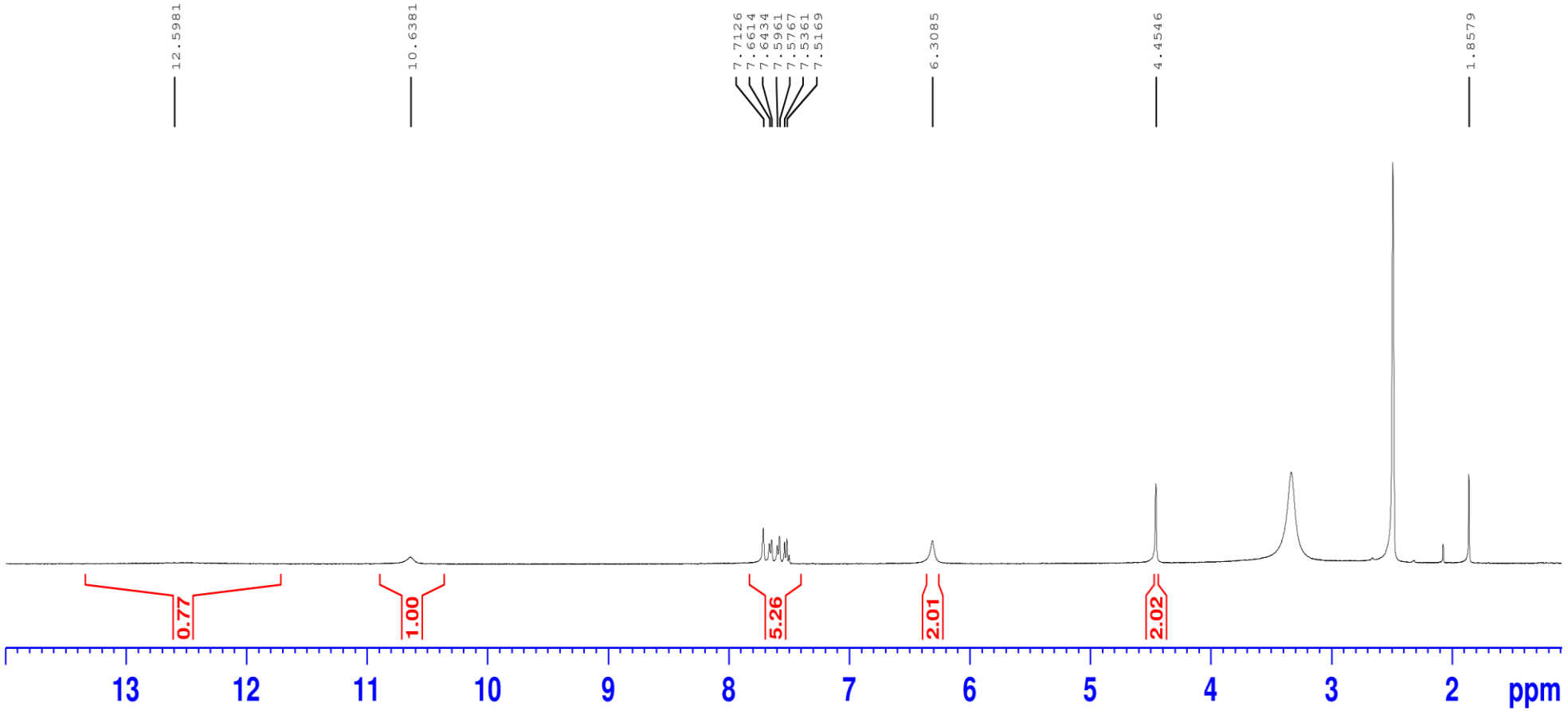


76c



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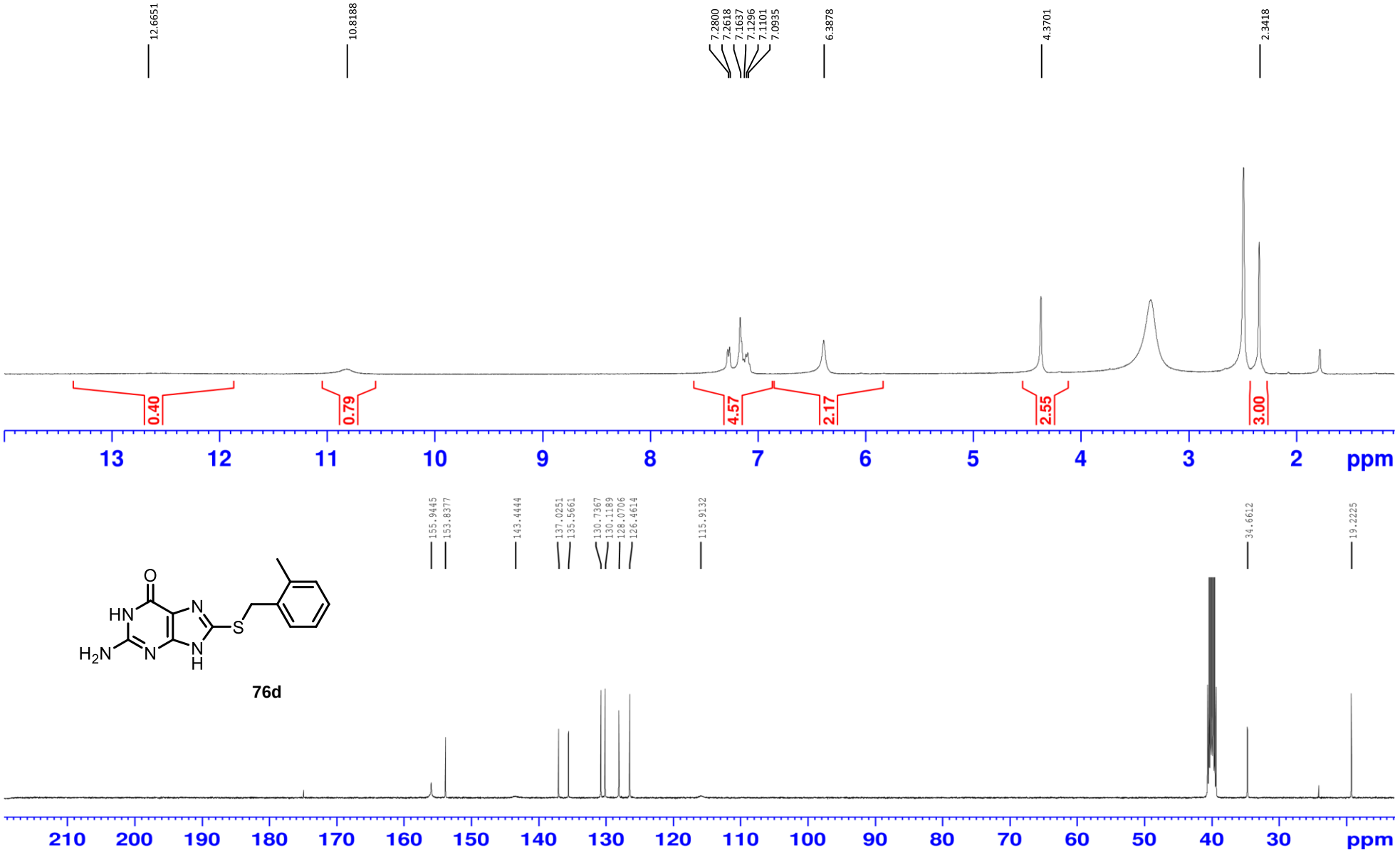

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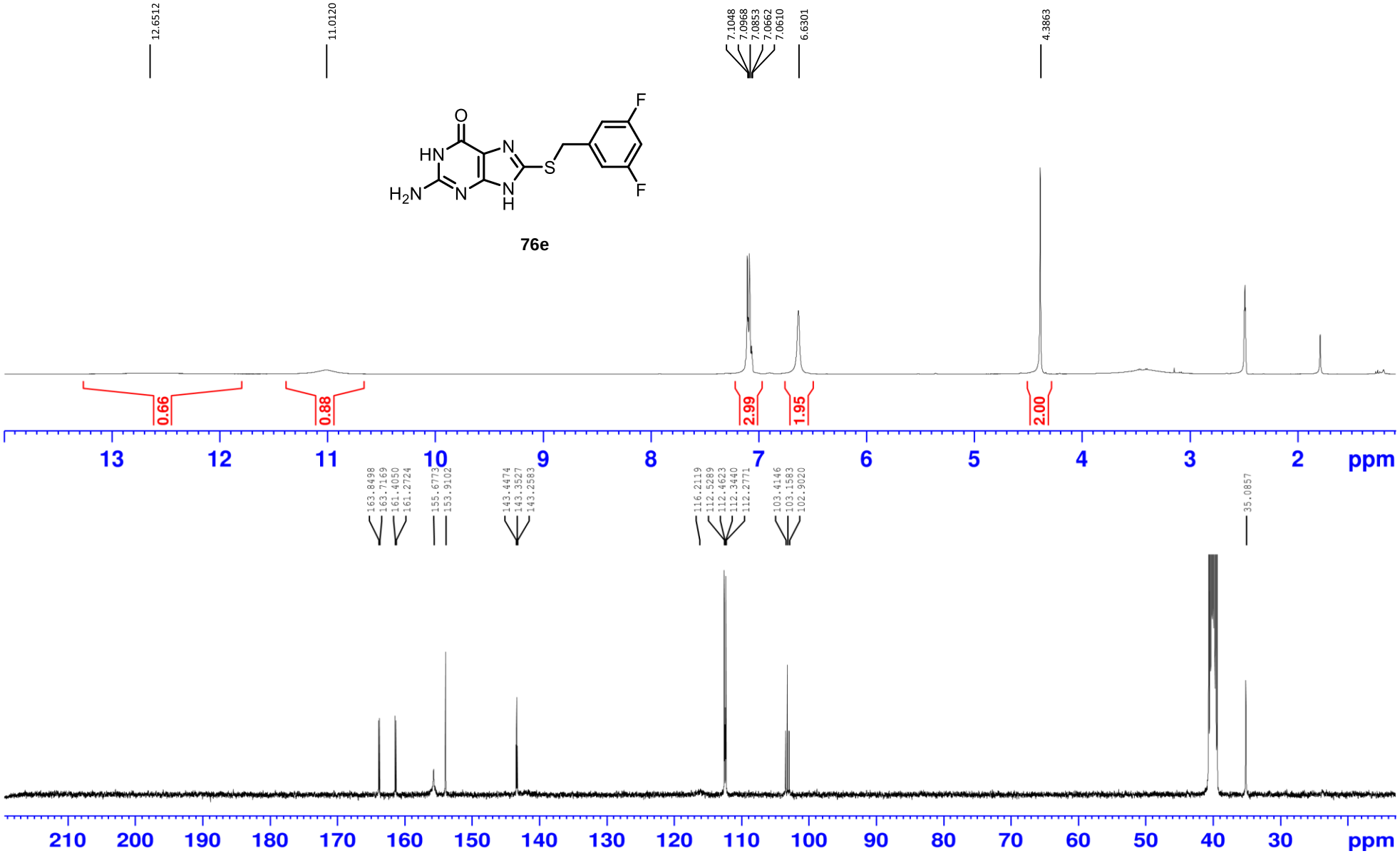

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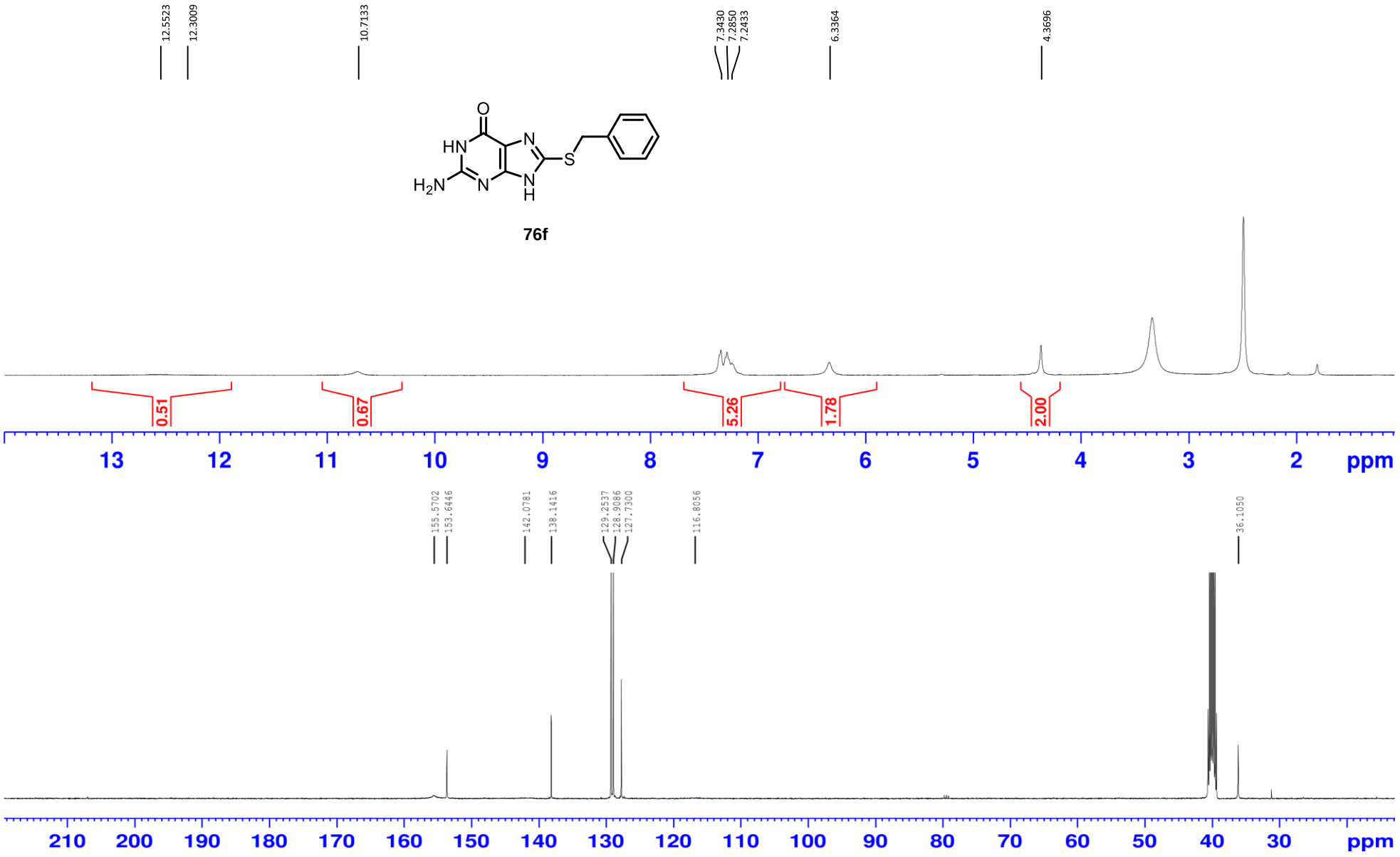

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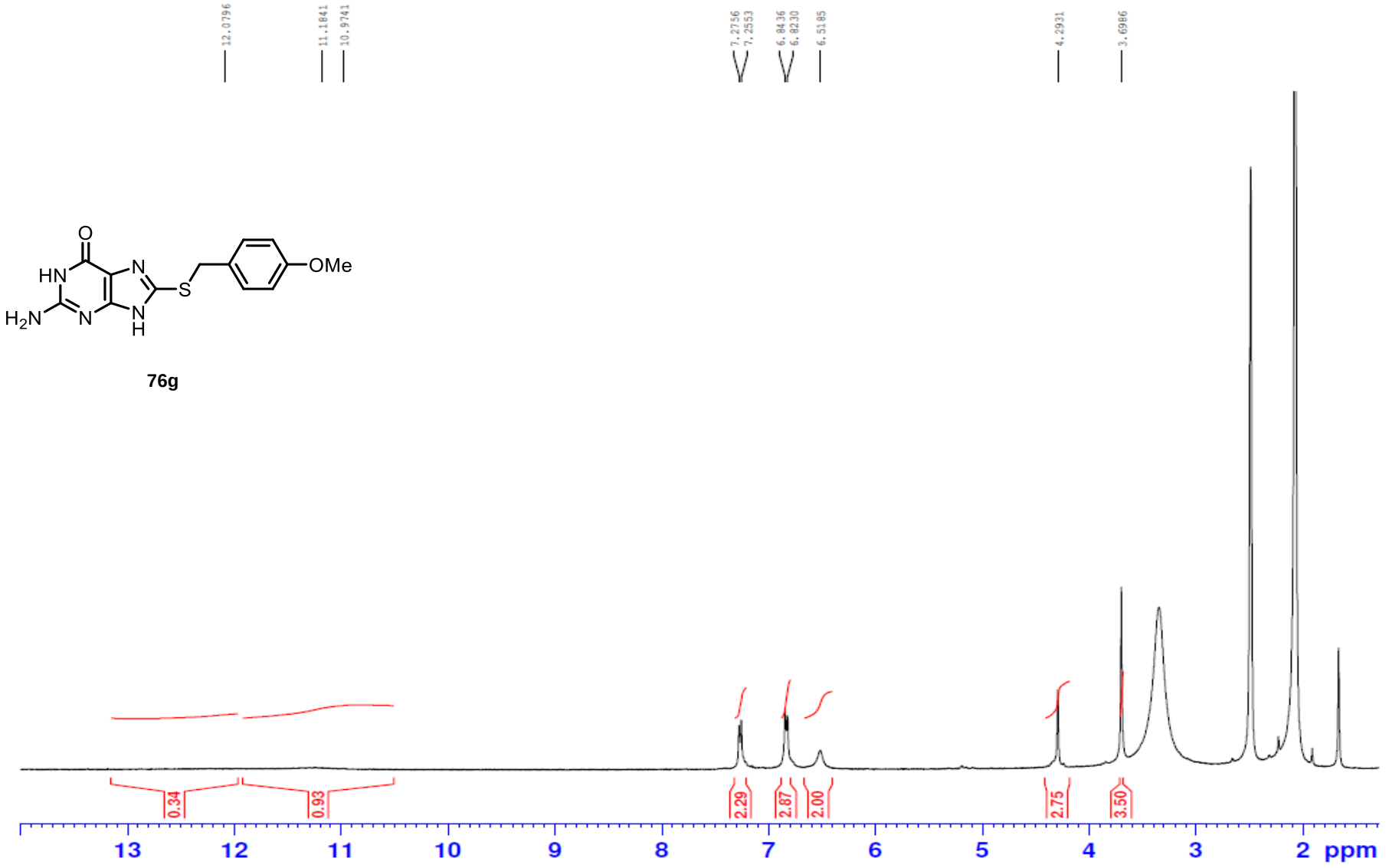
^{1}H and ^{13}C NMR (DMSO-d_6)



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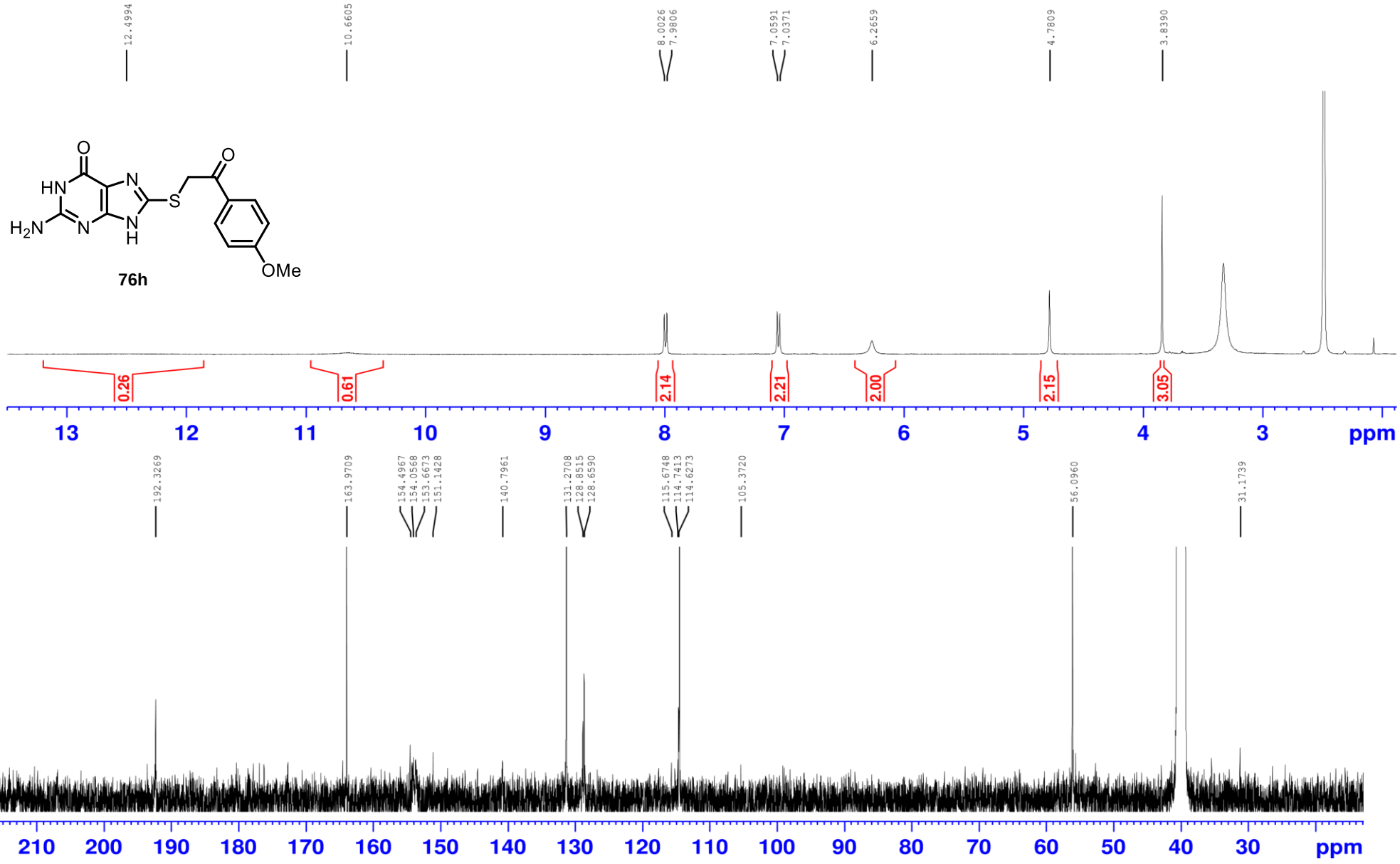

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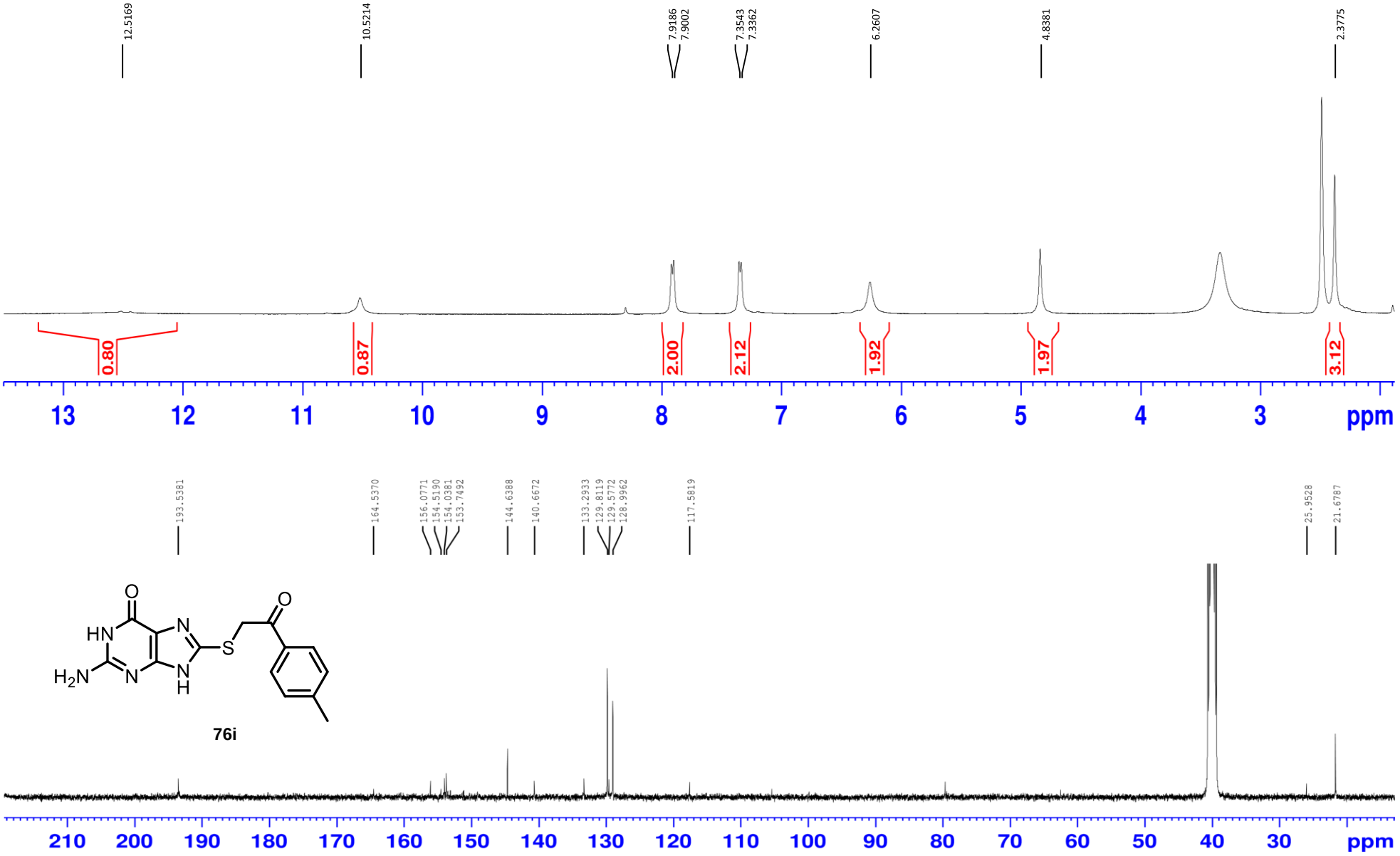

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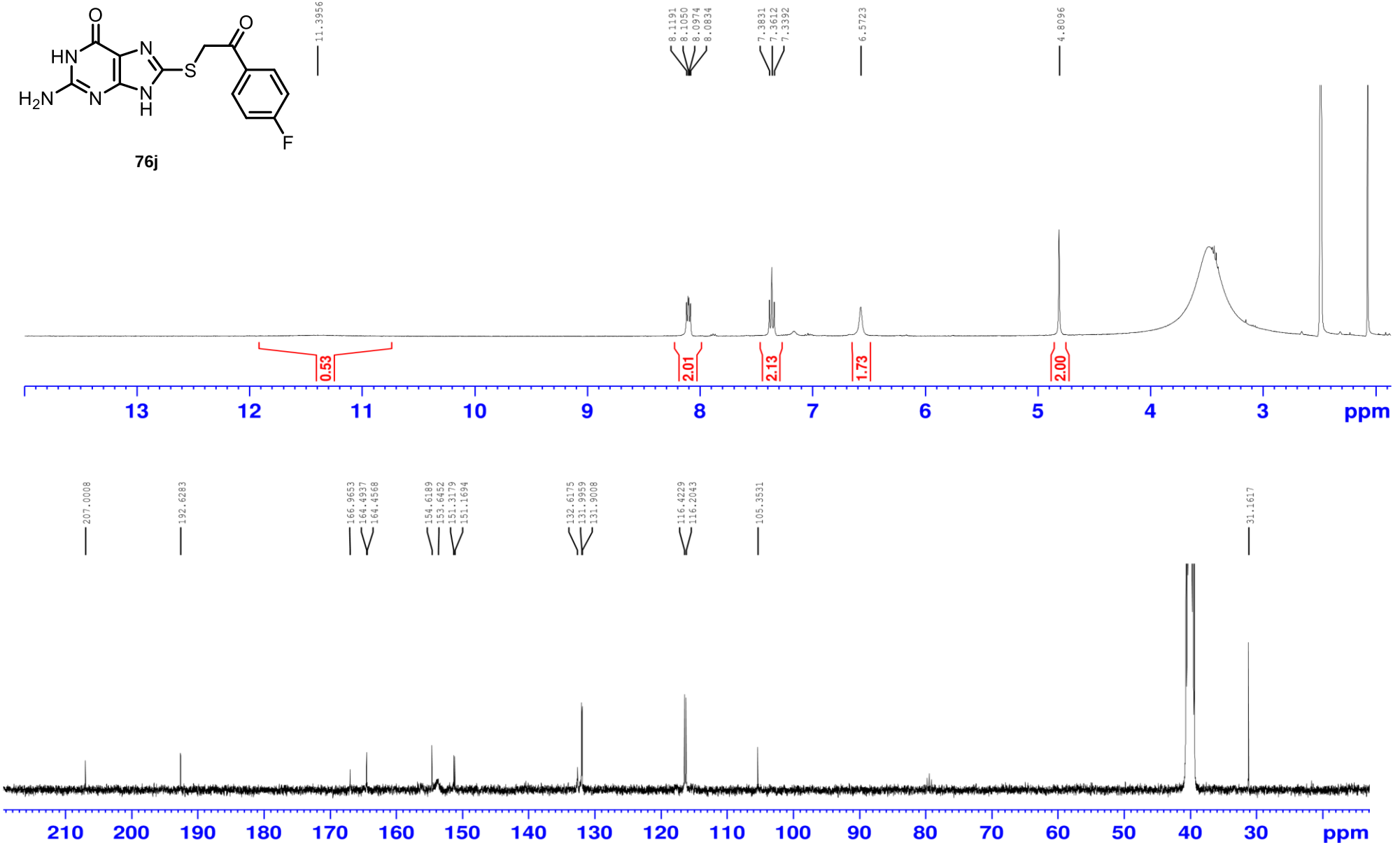

76j

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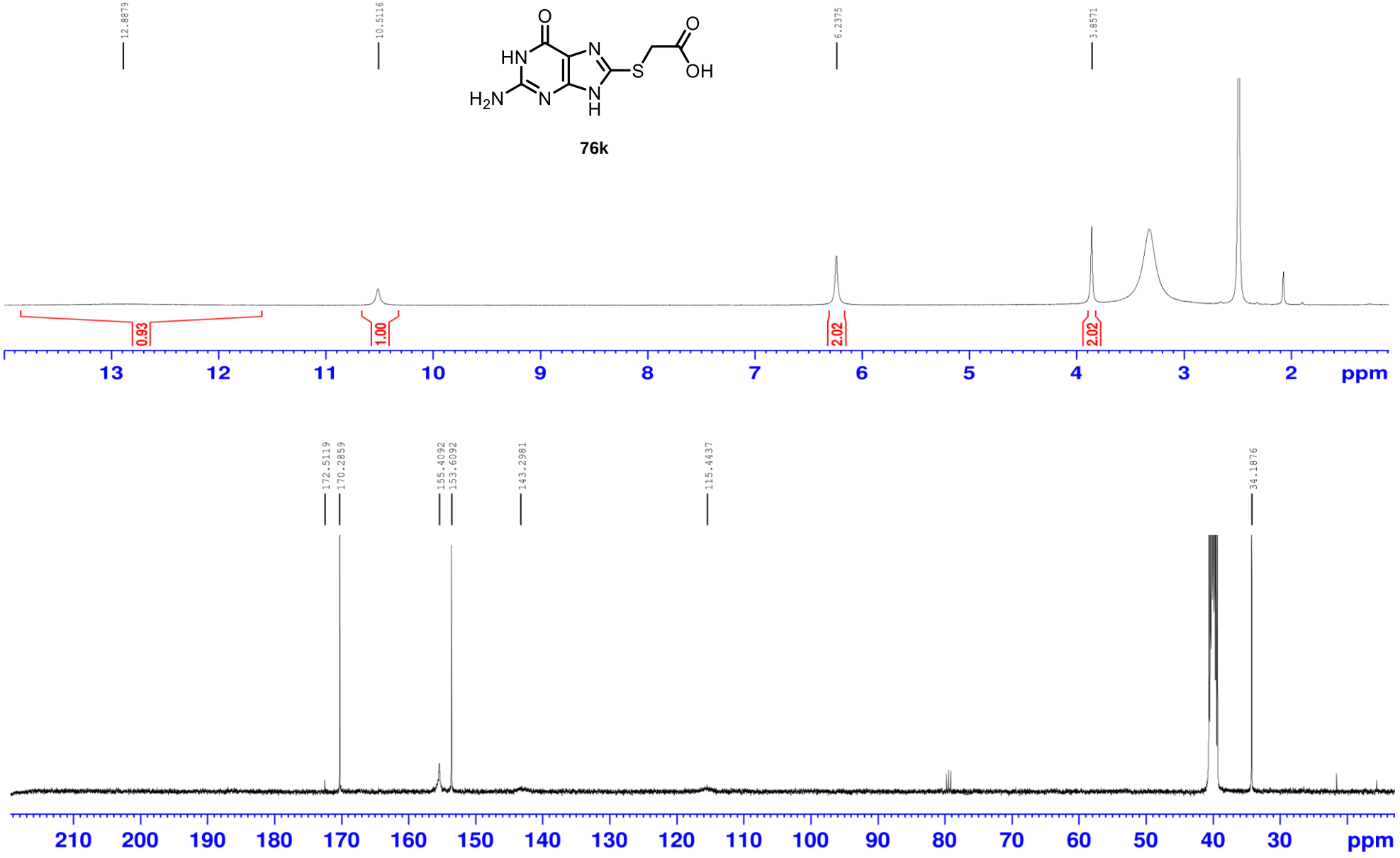

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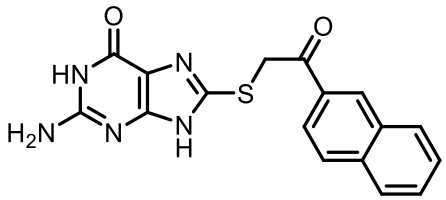
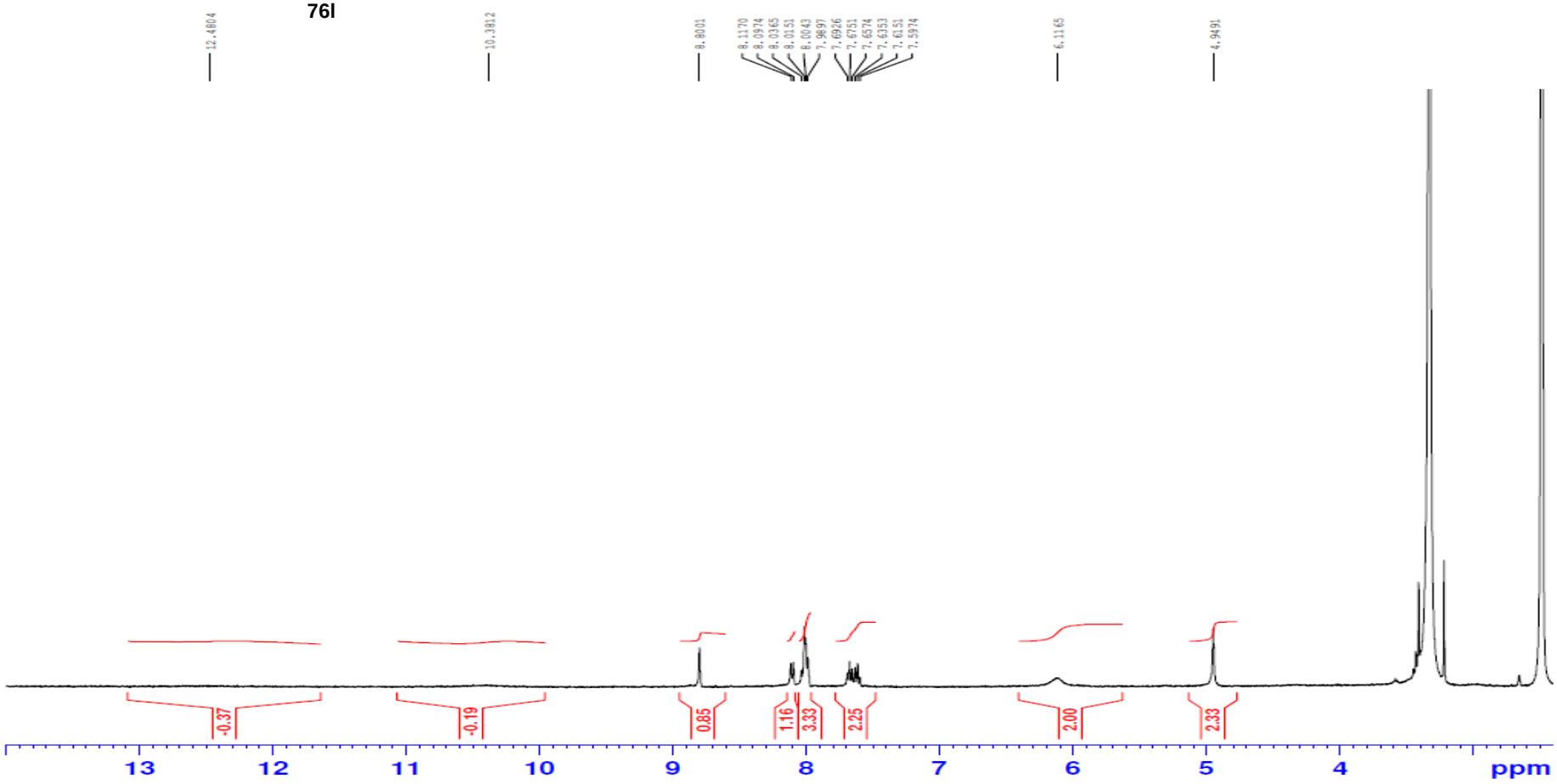


76l



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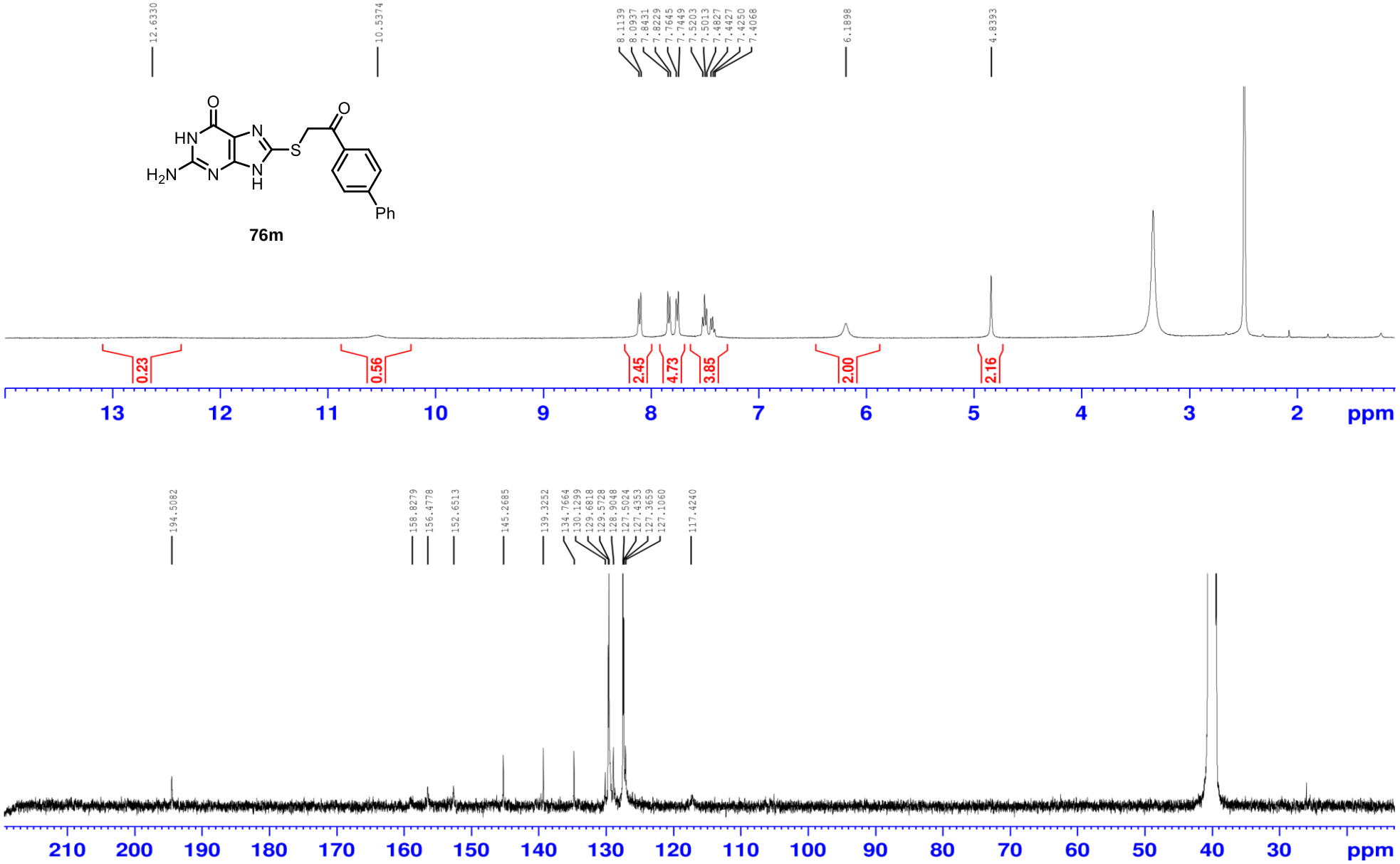
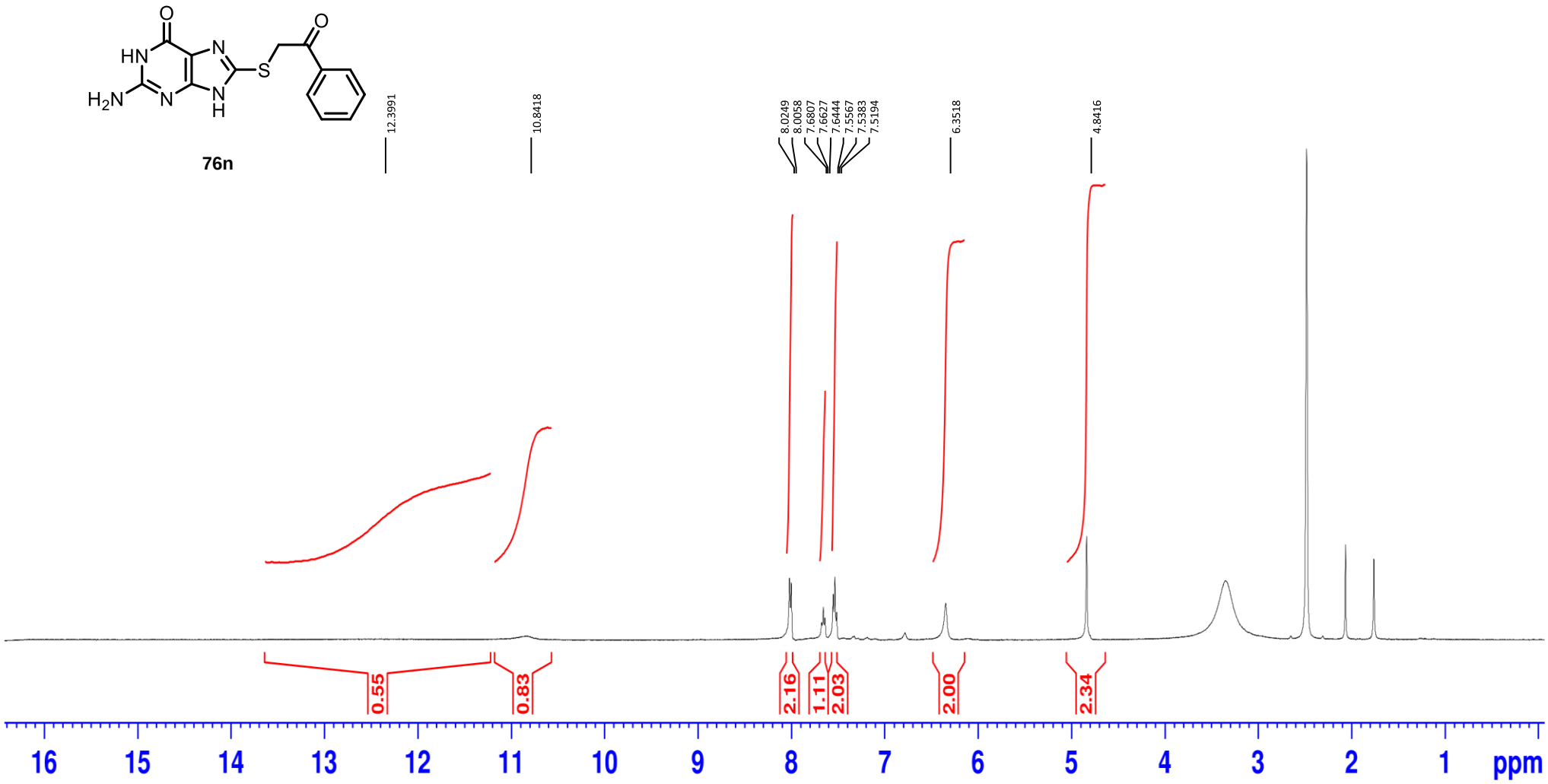
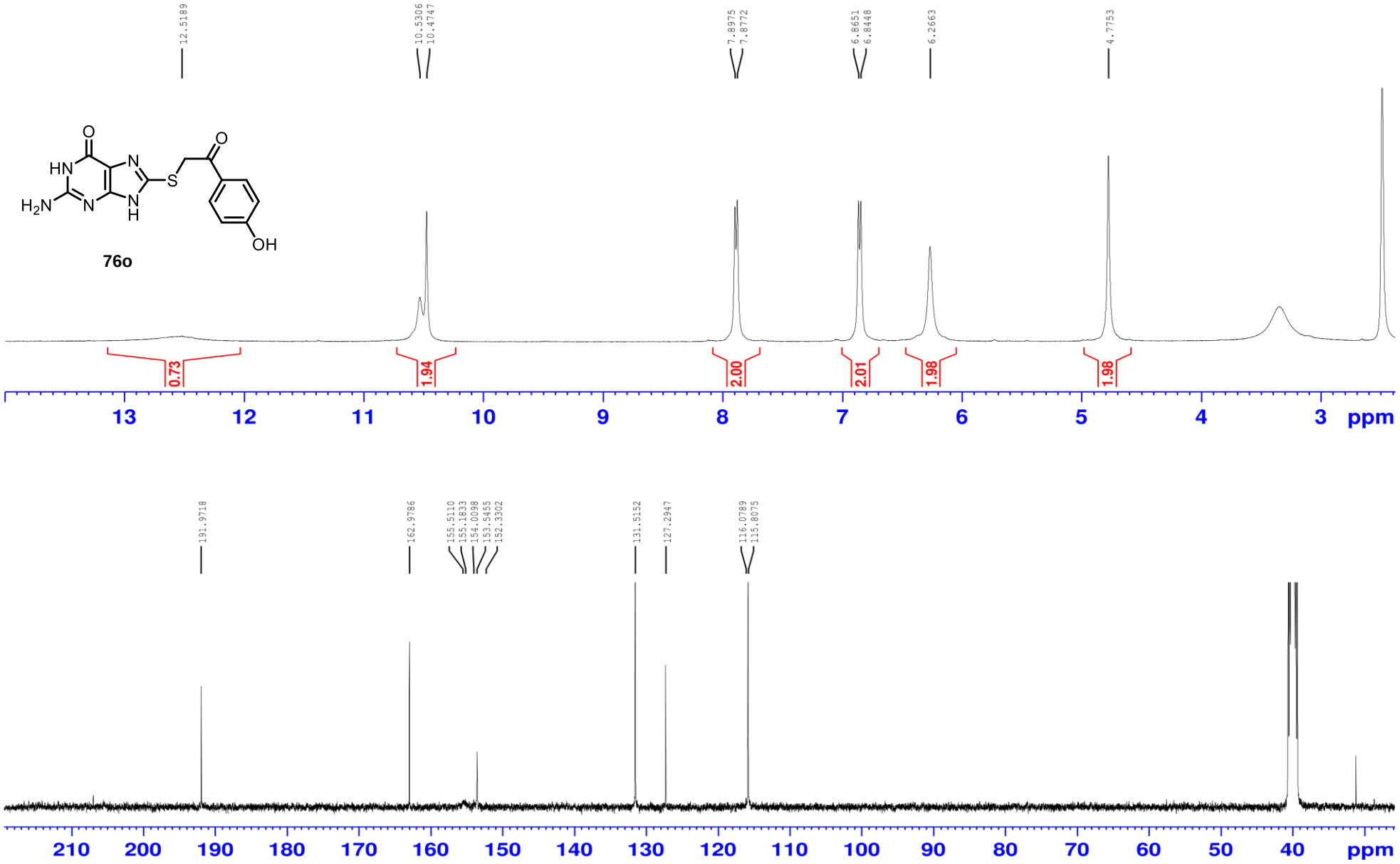


76m

^{1}H and ^{13}C NMR (DMSO-d_6)



^{1}H and ^{13}C NMR (DMSO-d_6)



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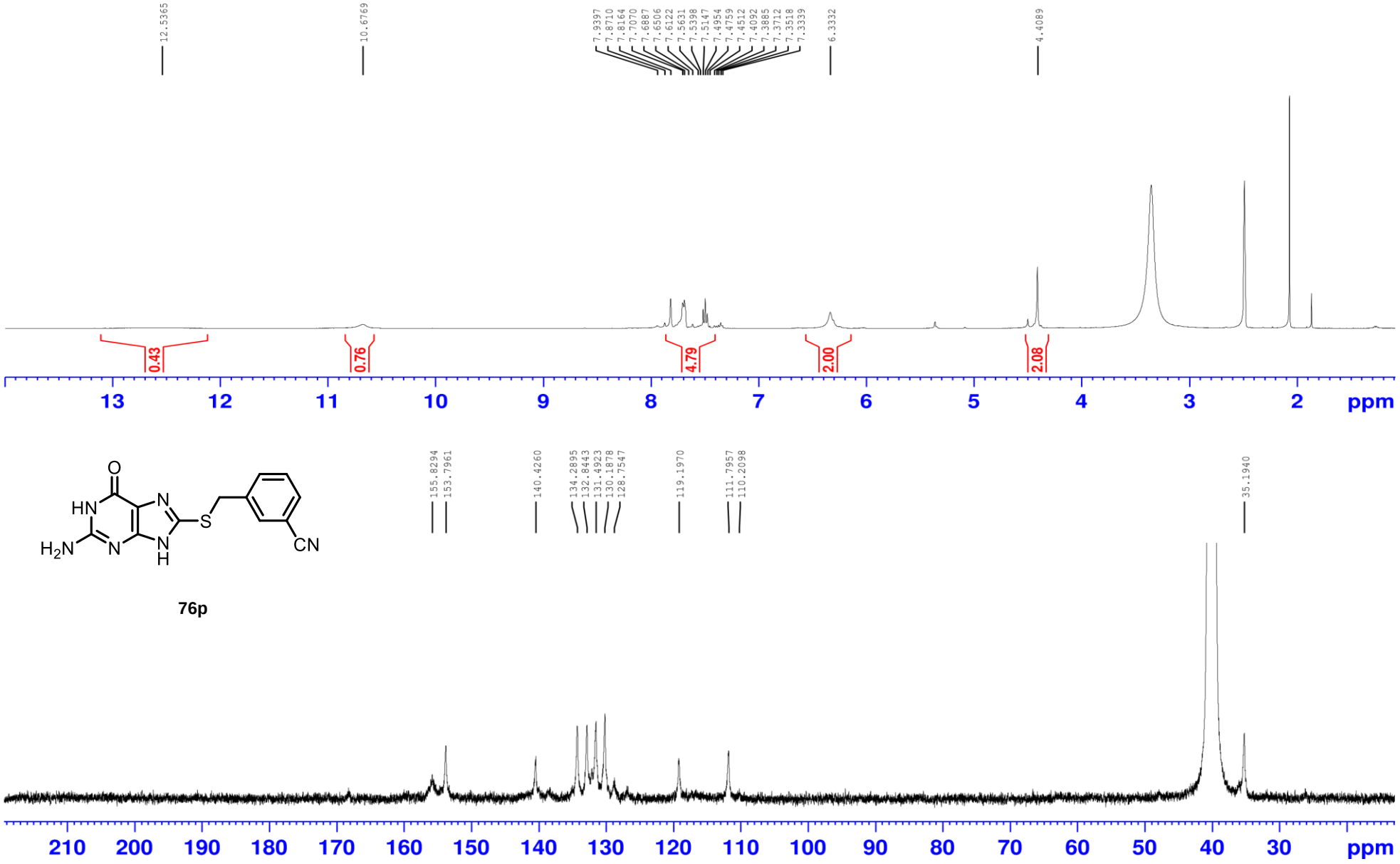
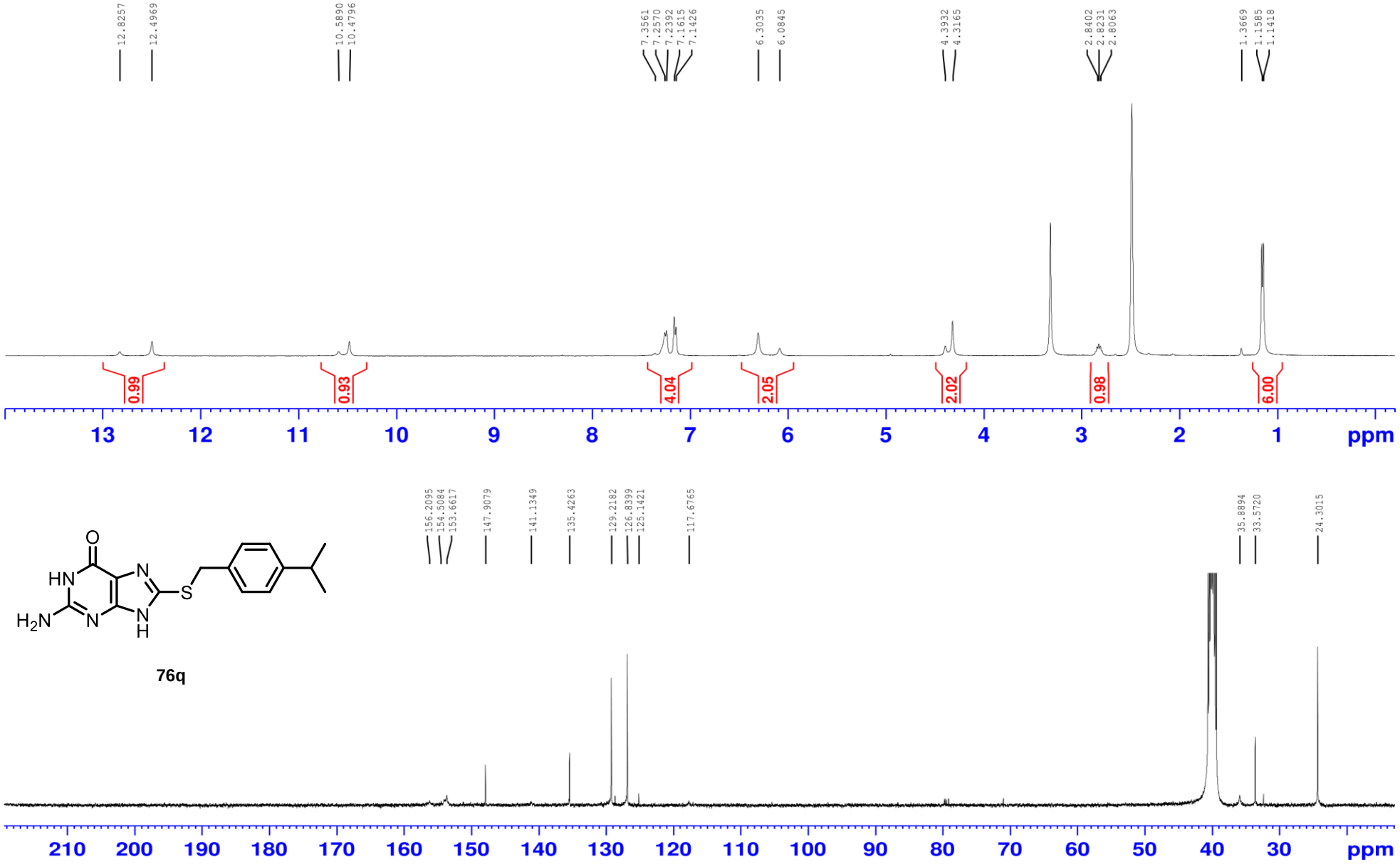


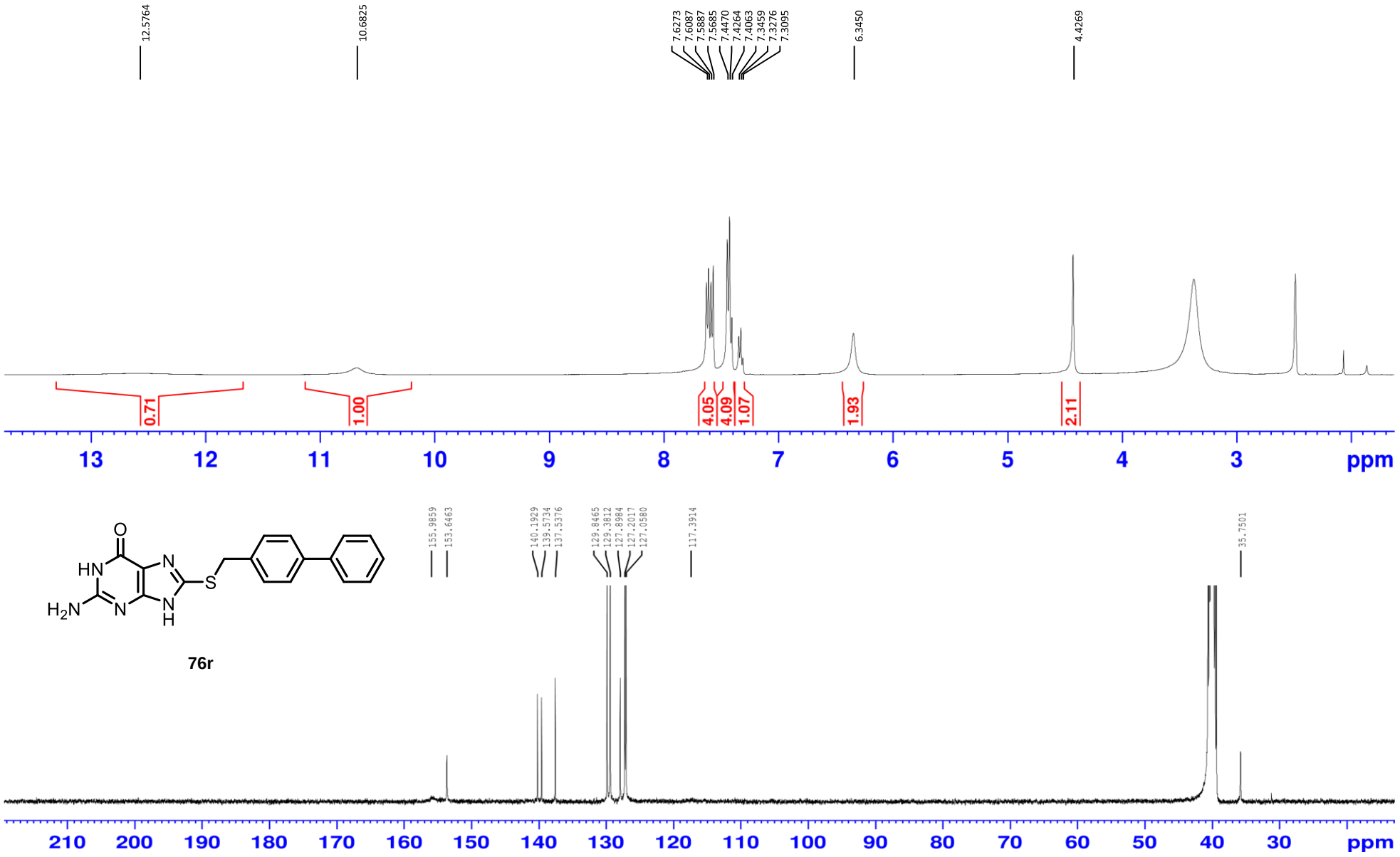
76p

^{1}H and ^{13}C NMR (DMSO-d_6)



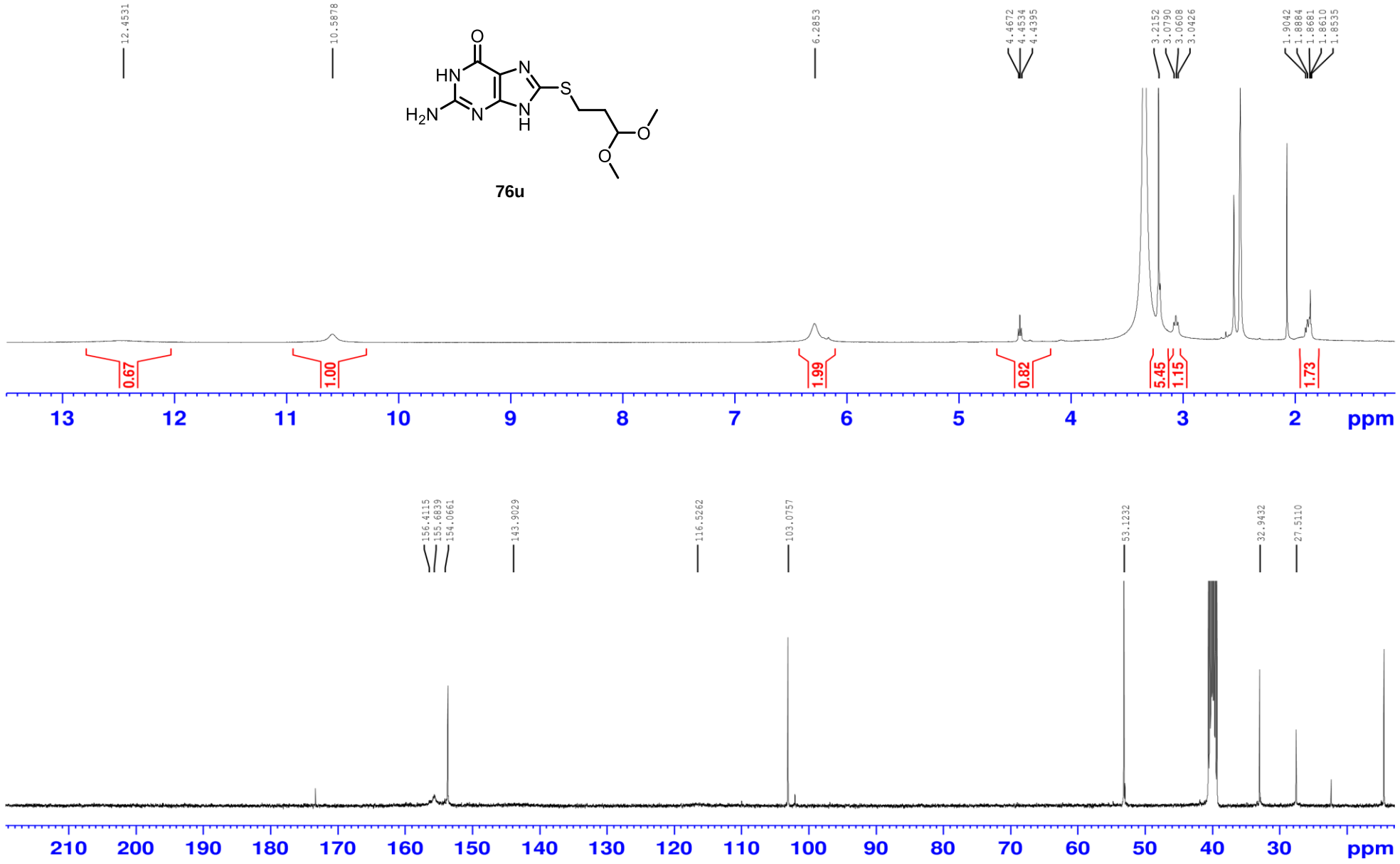
76q

^{1}H and ^{13}C NMR (DMSO-d_6)



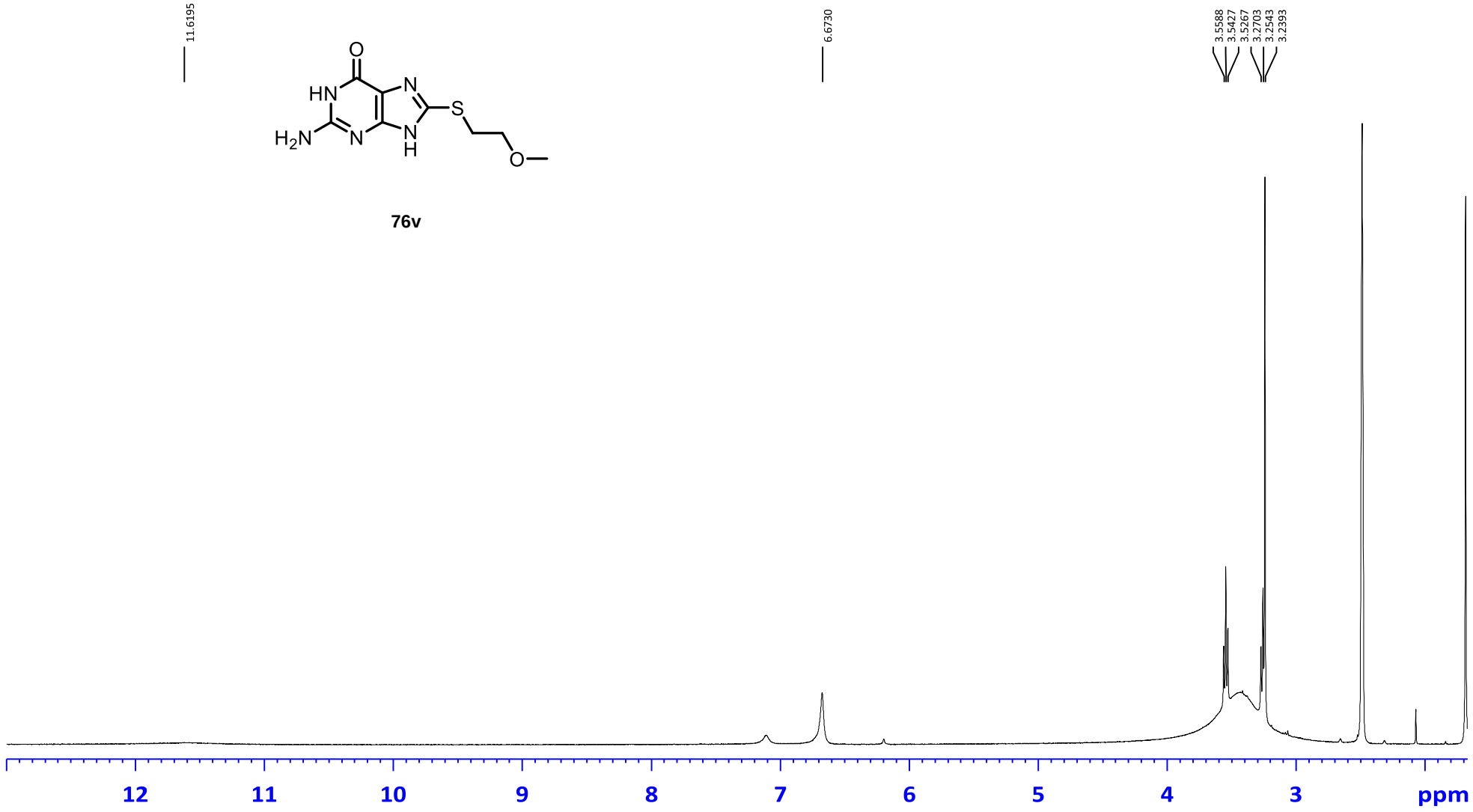
76r

^{1}H and ^{13}C NMR (DMSO-d_6)



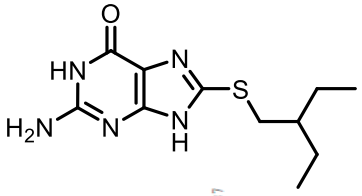
76u

^{1}H and ^{13}C NMR (DMSO-d_6)

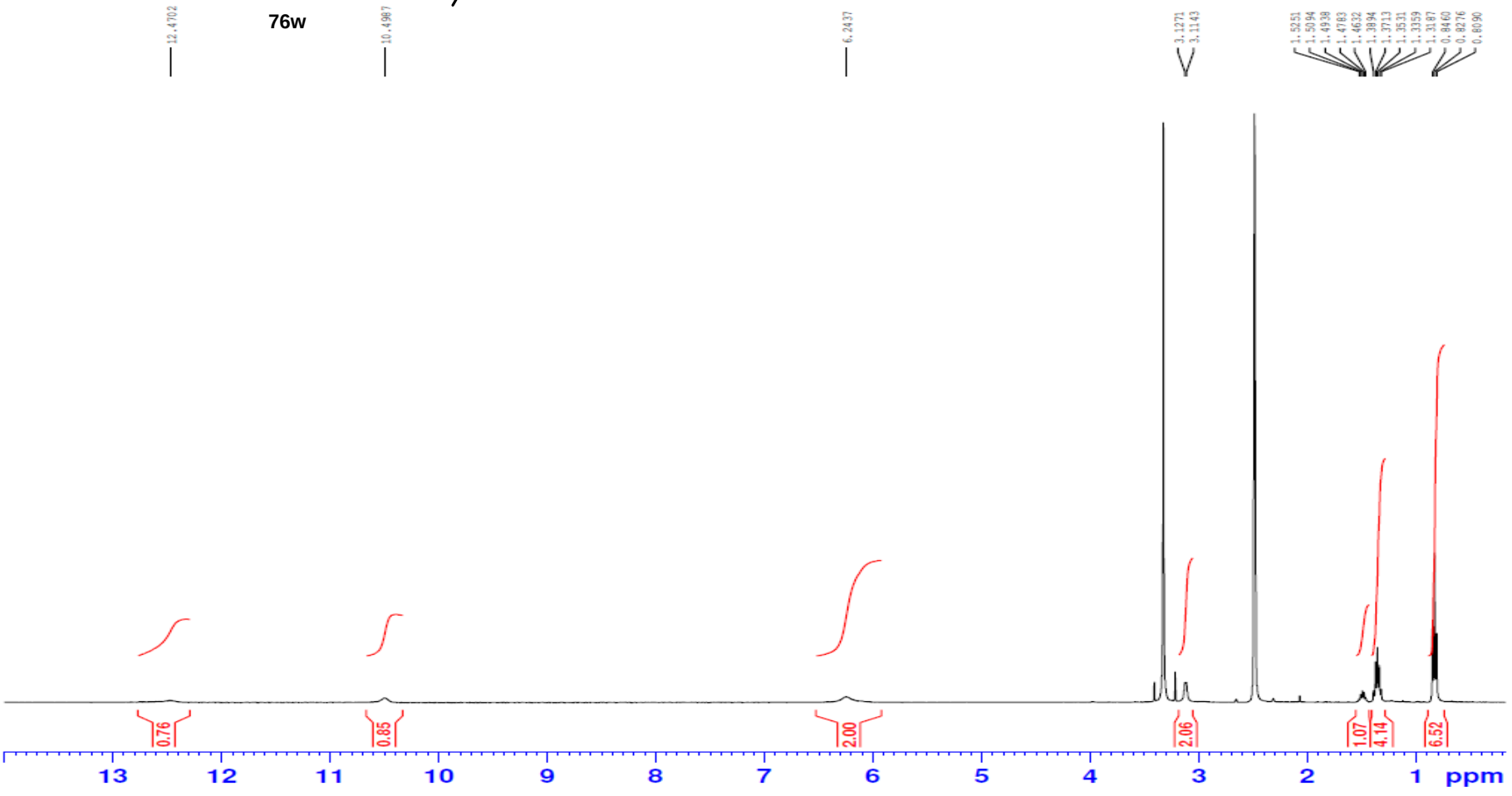


76v

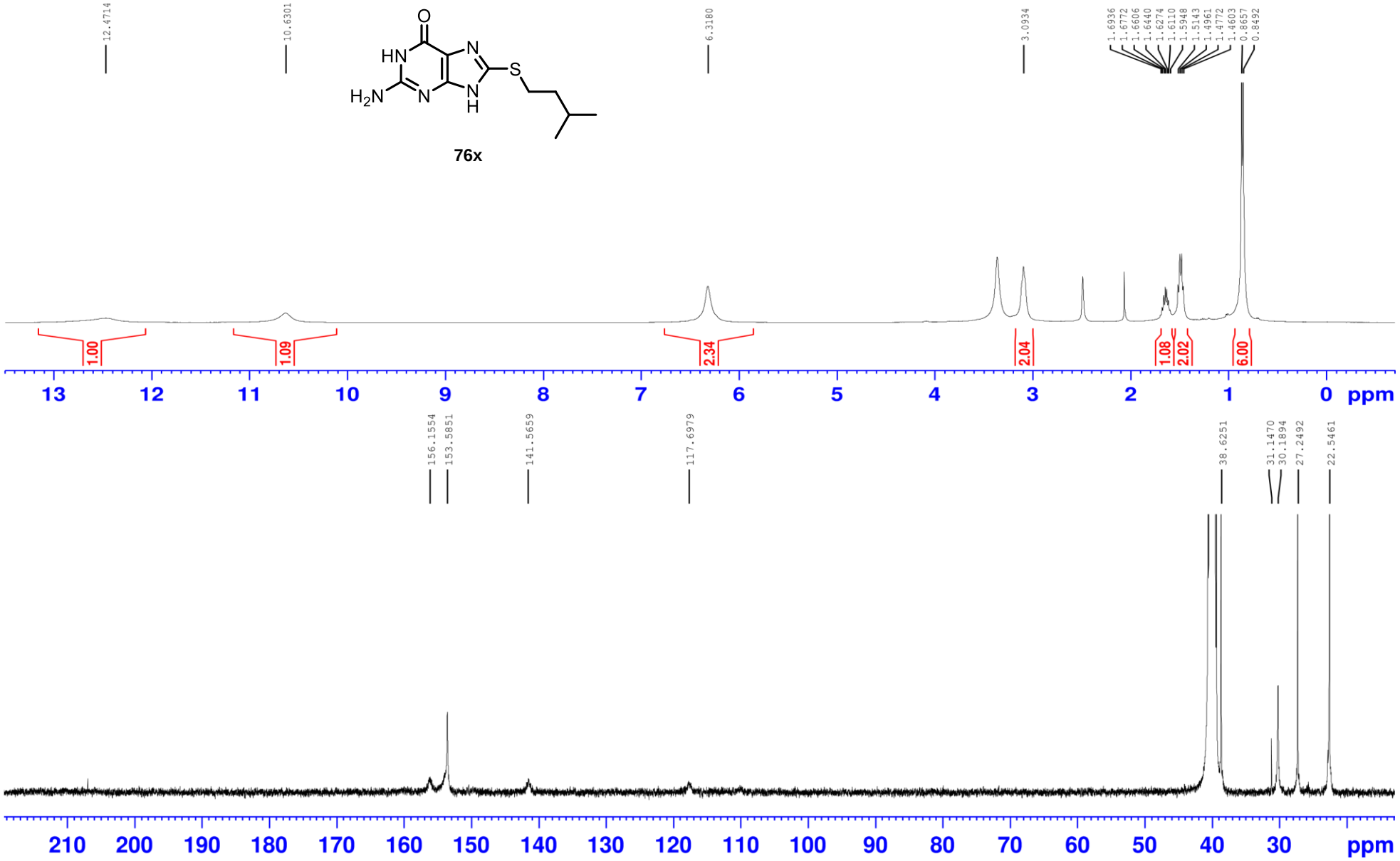
^{1}H and ^{13}C NMR (DMSO-d_6)



76w

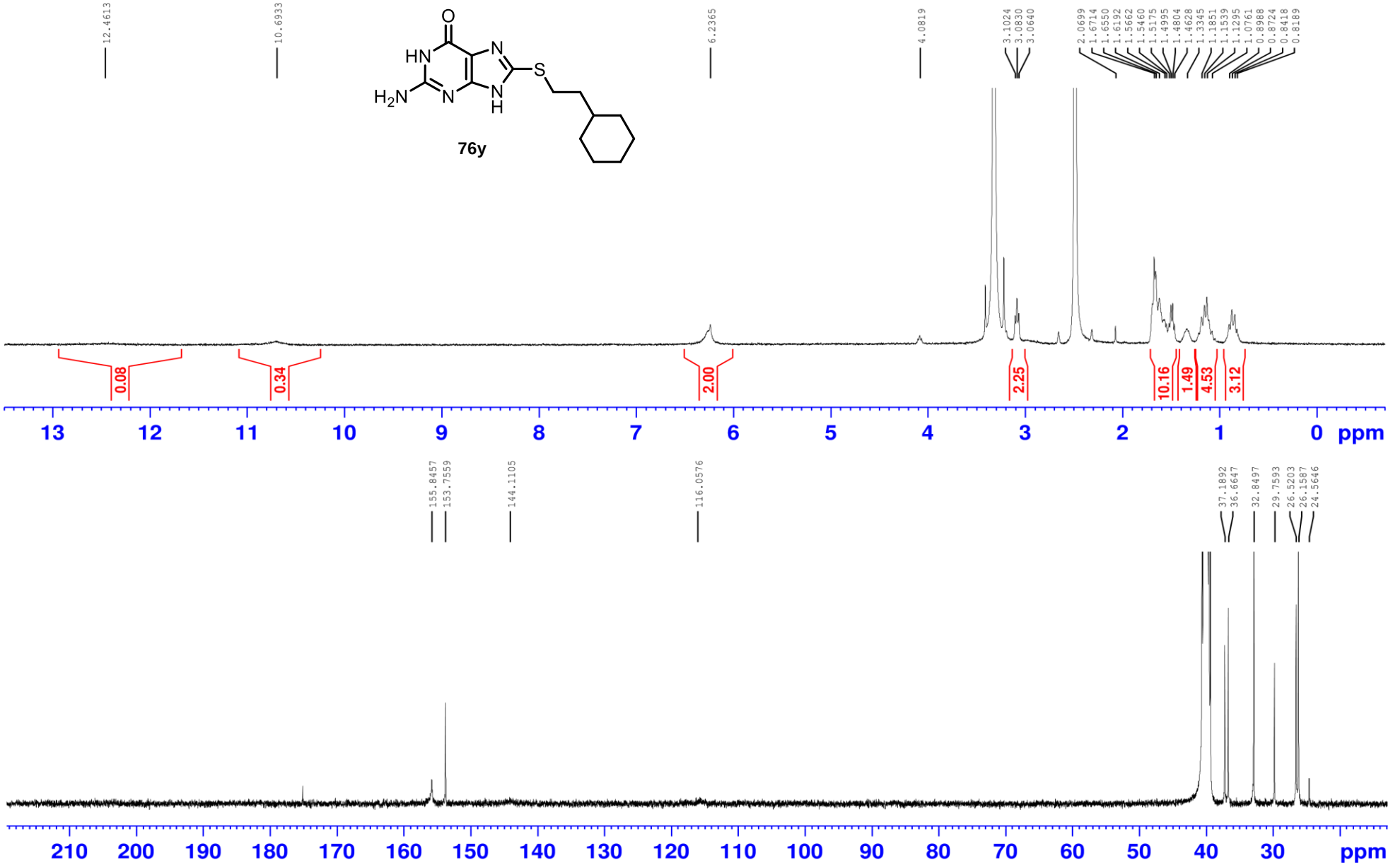


^{1}H and ^{13}C NMR (DMSO-d_6)



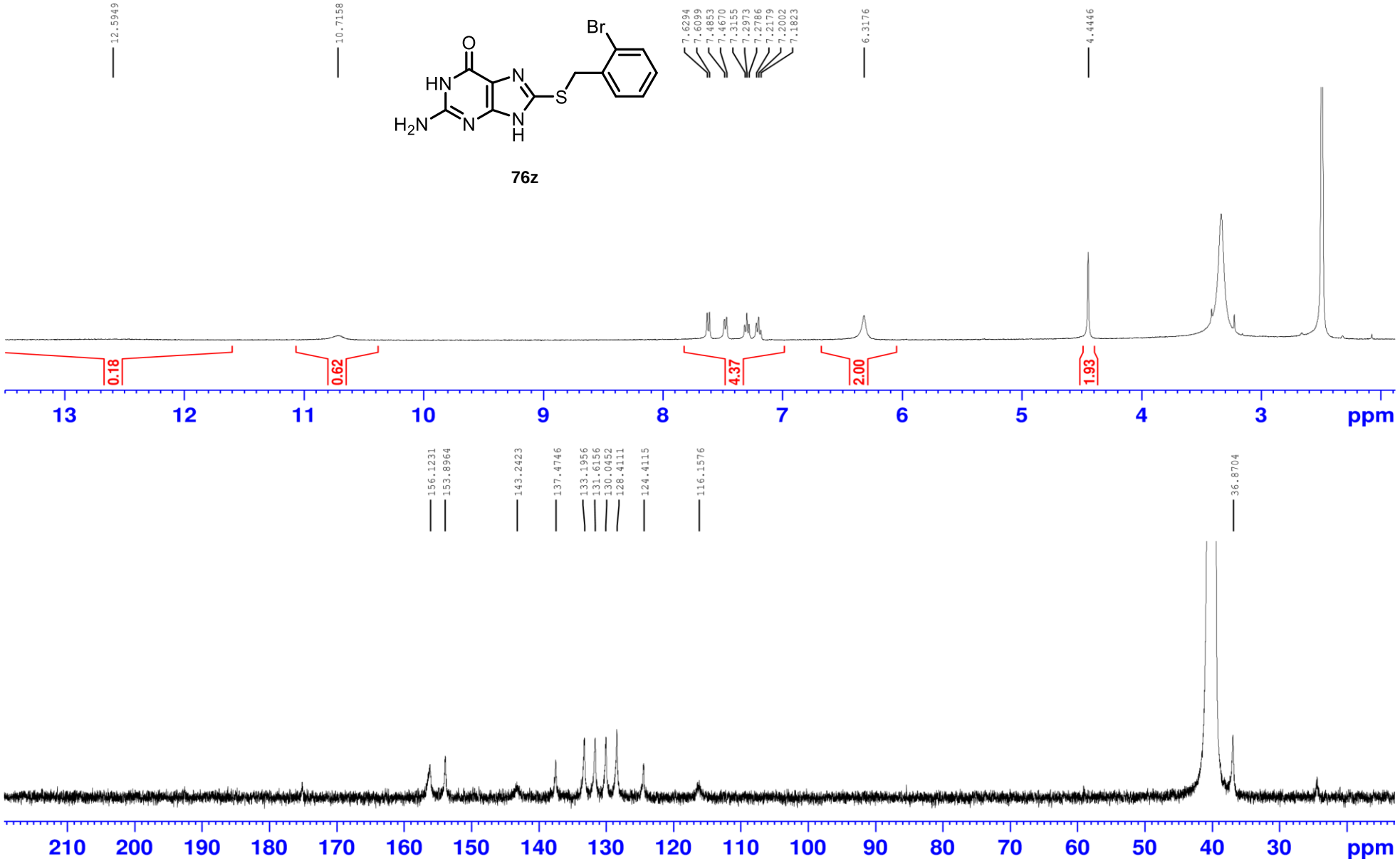
76x

^{1}H and ^{13}C NMR (DMSO-d_6)



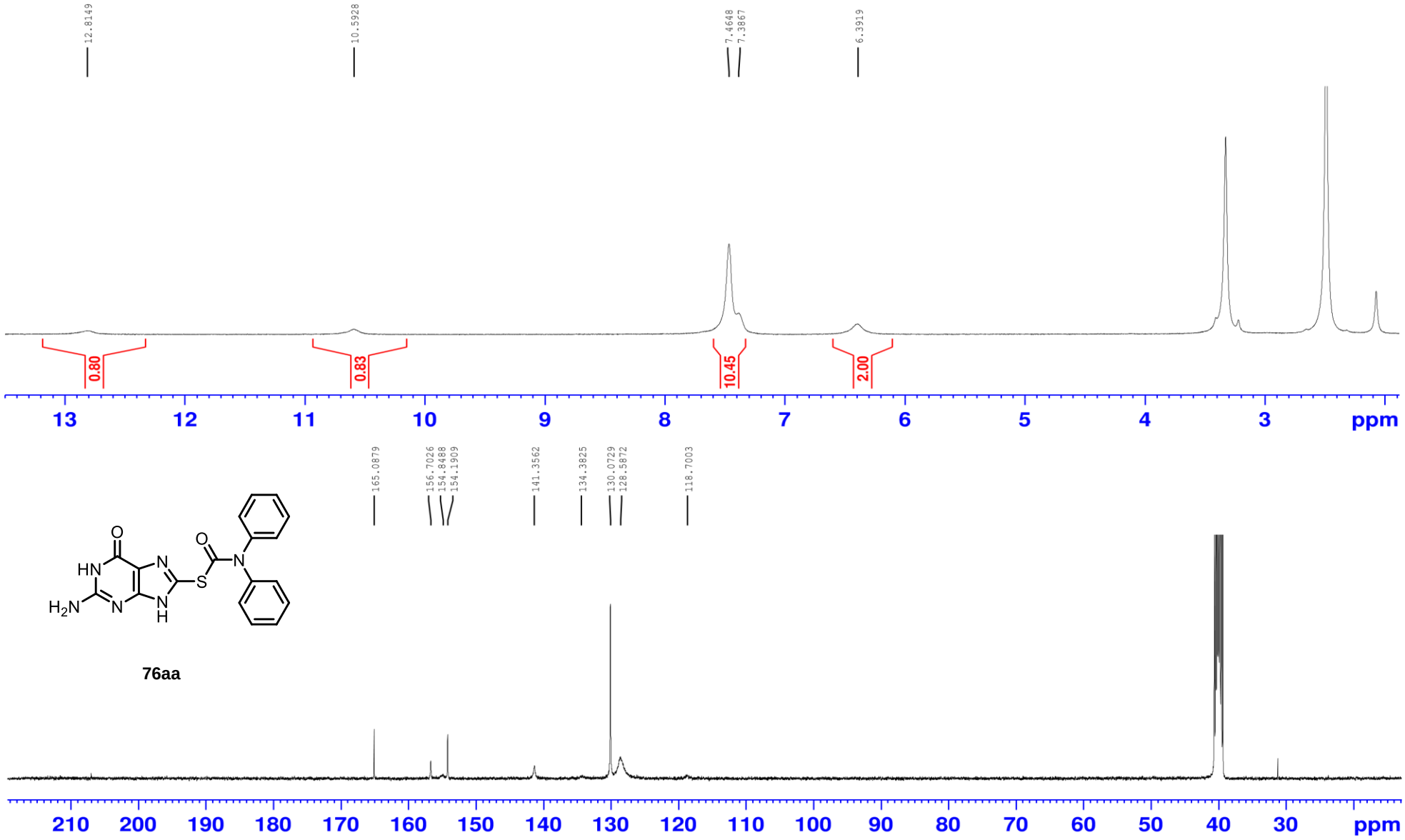
76y

^{1}H and ^{13}C NMR (DMSO-d_6)



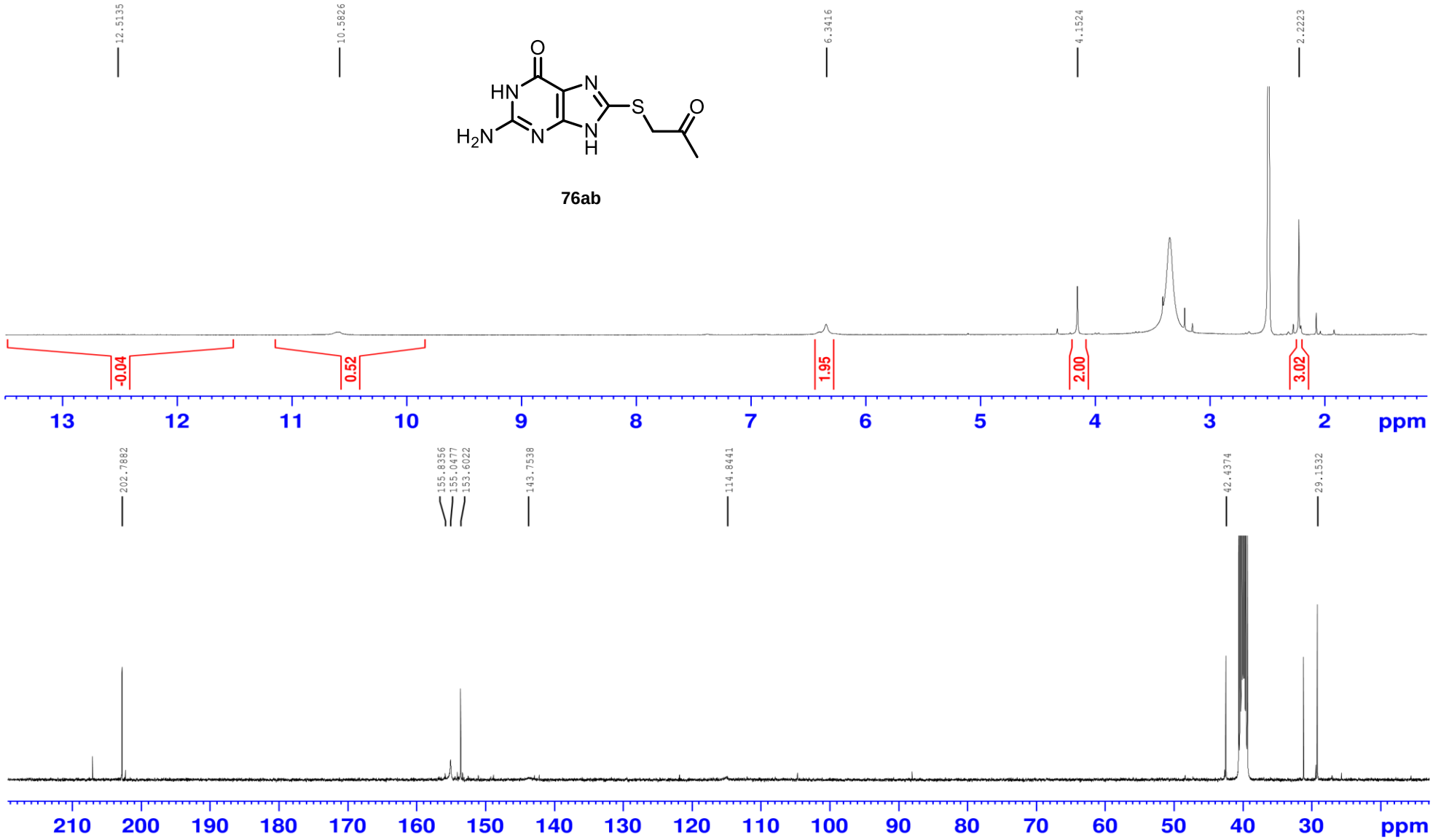
76z

^{1}H and ^{13}C NMR (DMSO-d_6)



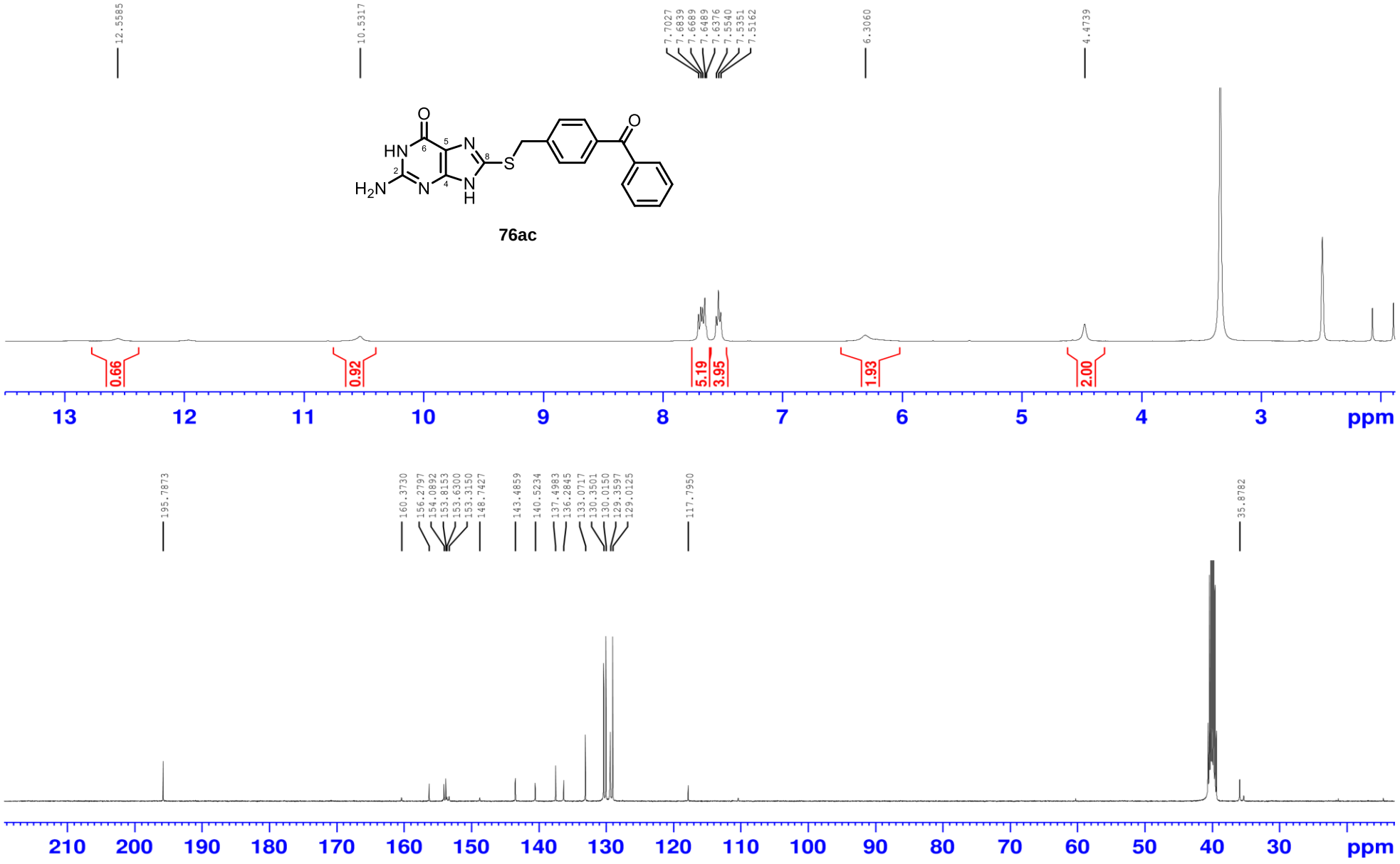
76aa

^{1}H and ^{13}C NMR (DMSO-d_6)

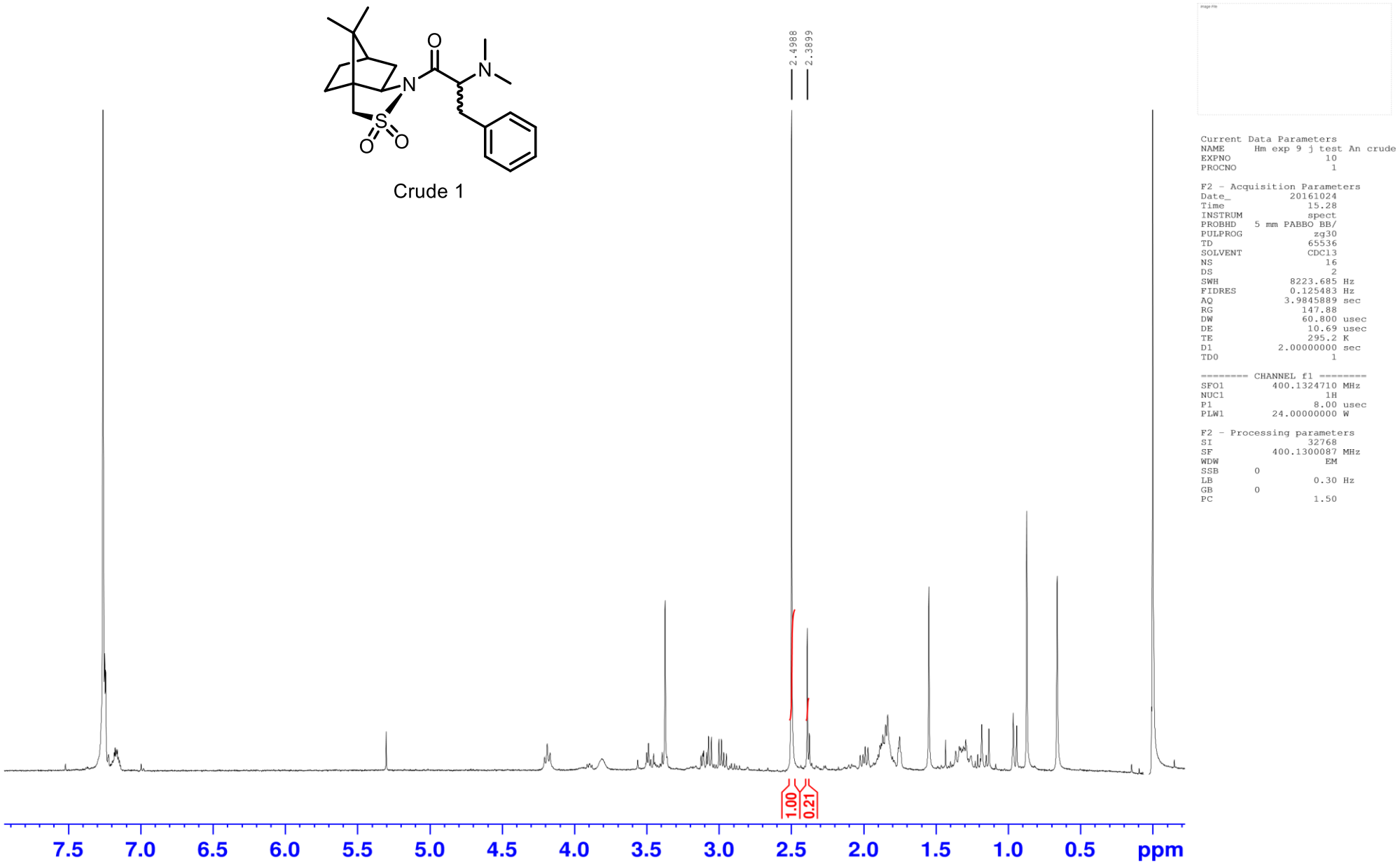


76ab

^{1}H and ^{13}C NMR (DMSO-d_6)



76ac



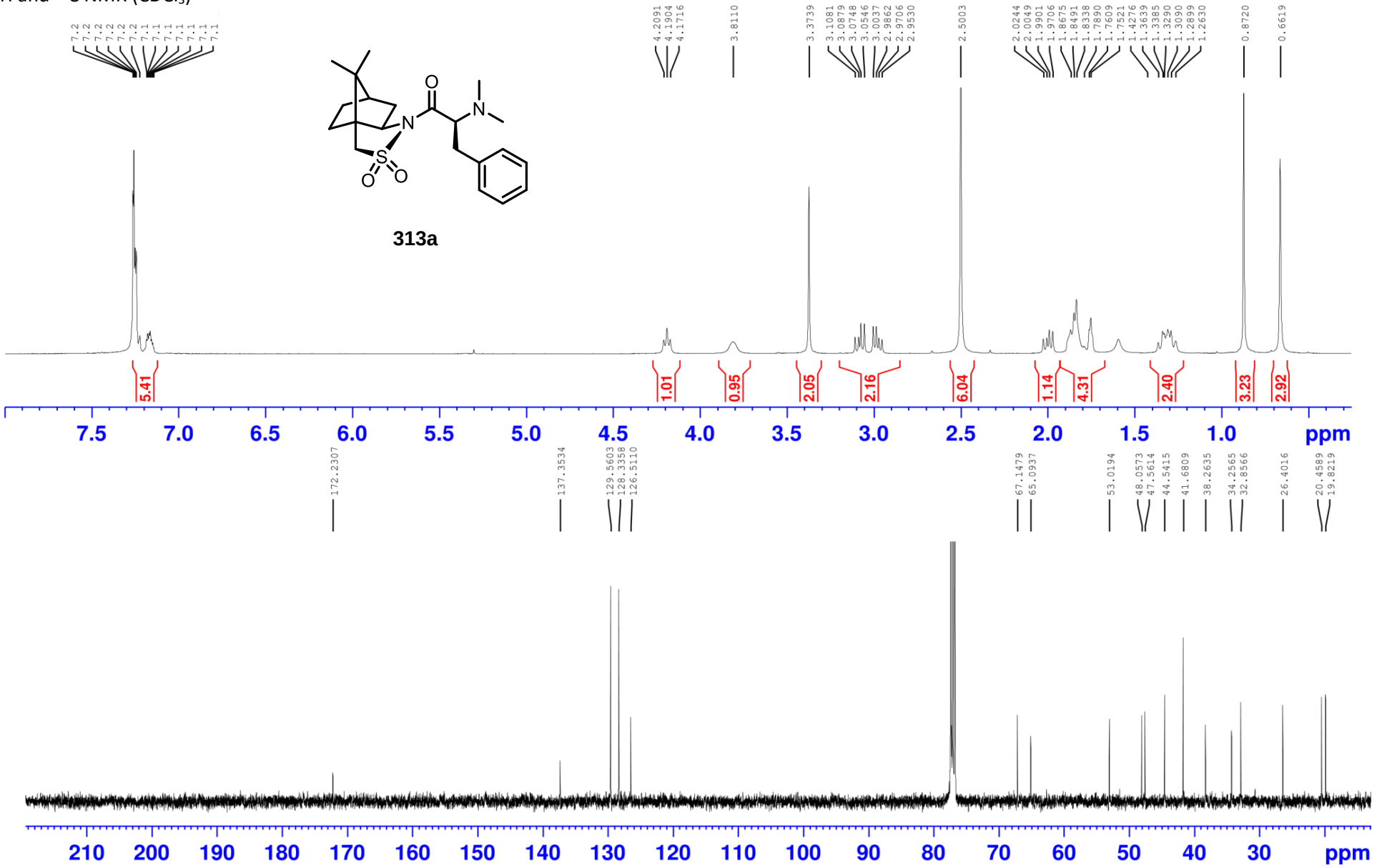

```
Current Data Parameters
NAME      Hm exp 9 j test An crude
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20161024
Time                15.28
INSTRUM             spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH              8223.685 Hz
FIDRES           0.125483 Hz
AQ               3.9845889 sec
RG                 147.88
DW                 60.800 usec
DE                 10.69 usec
TE                 295.2 K
D1              2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          400.1324710 MHz
NUC1                  1H
P1                 8.00 usec
PLW1          24.00000000 W

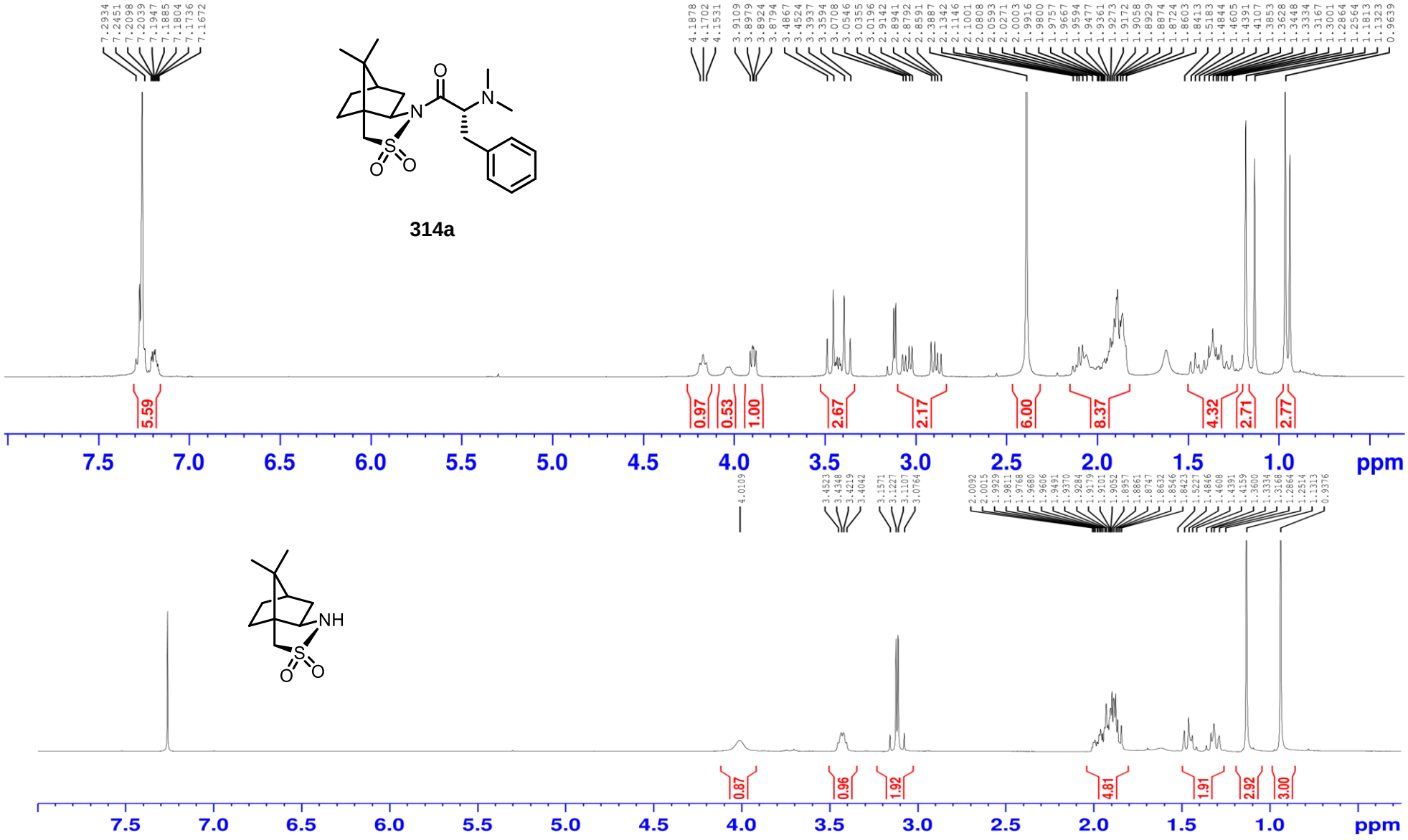
F2 - Processing parameters
SI                 32768
SF            400.1300087 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.50
```

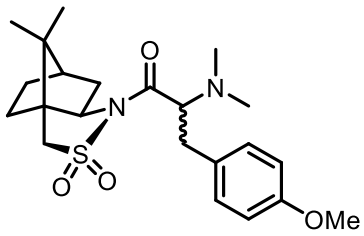
^{1}H and ^{13}C NMR ($CDCl_3$)



313a

^{1}H and ^{13}C NMR ($CDCl_3$)





Crude 2

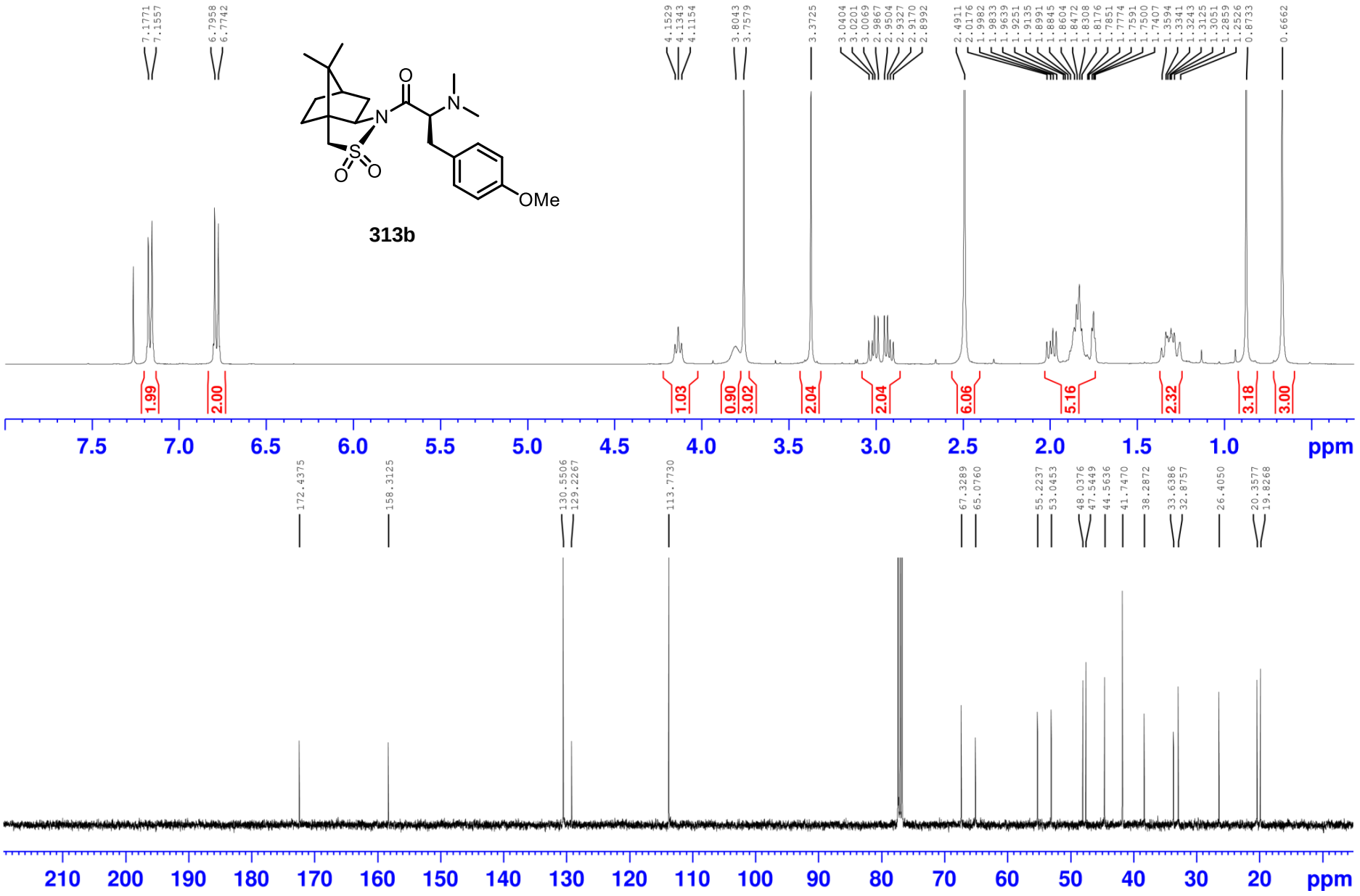

```
Current Data Parameters
NAME      Hm exp 9 j 6 crude
EXPNO                   10
PROCNO                   1

F2 - Acquisition Parameters
Date_            20160323
Time                14.47
INSTRUM             spect
PROBHD   5 mm PABBO BB/
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8223.685 Hz
FIDRES           0.125483 Hz
AQ               3.9845889 sec
RG                  147.88
DW                  60.800 usec
DE                  10.69 usec
TE                  293.6 K
D1              2.00000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1         400.1324710 MHz
NUC1                   1H
P1                  8.00 usec
PLW1        24.00000000 W

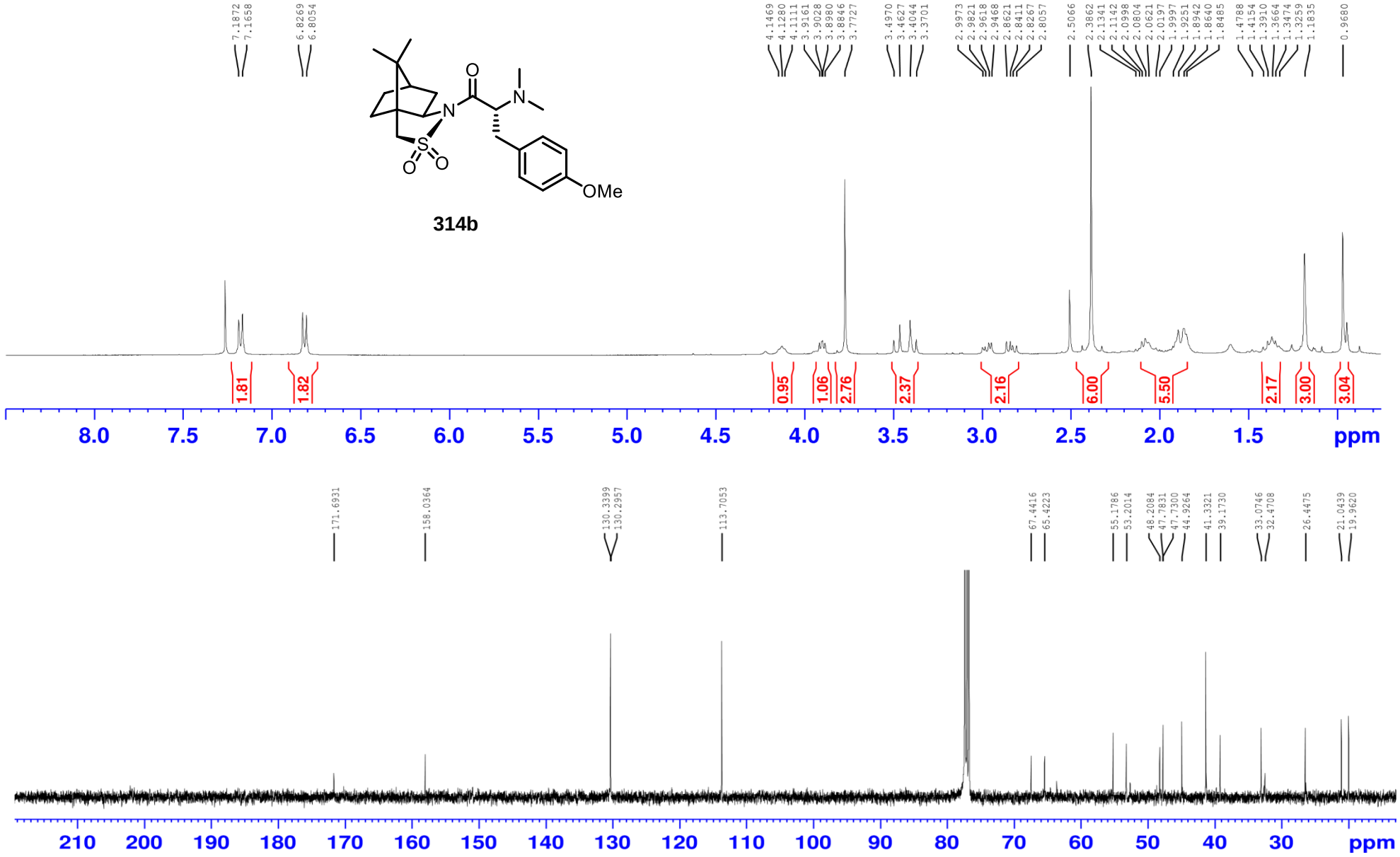
F2 - Processing parameters
SI                  32768
SF           400.1300087 MHz
WDW                    EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.50
```

^{1}H and ^{13}C NMR ($CDCl_3$)

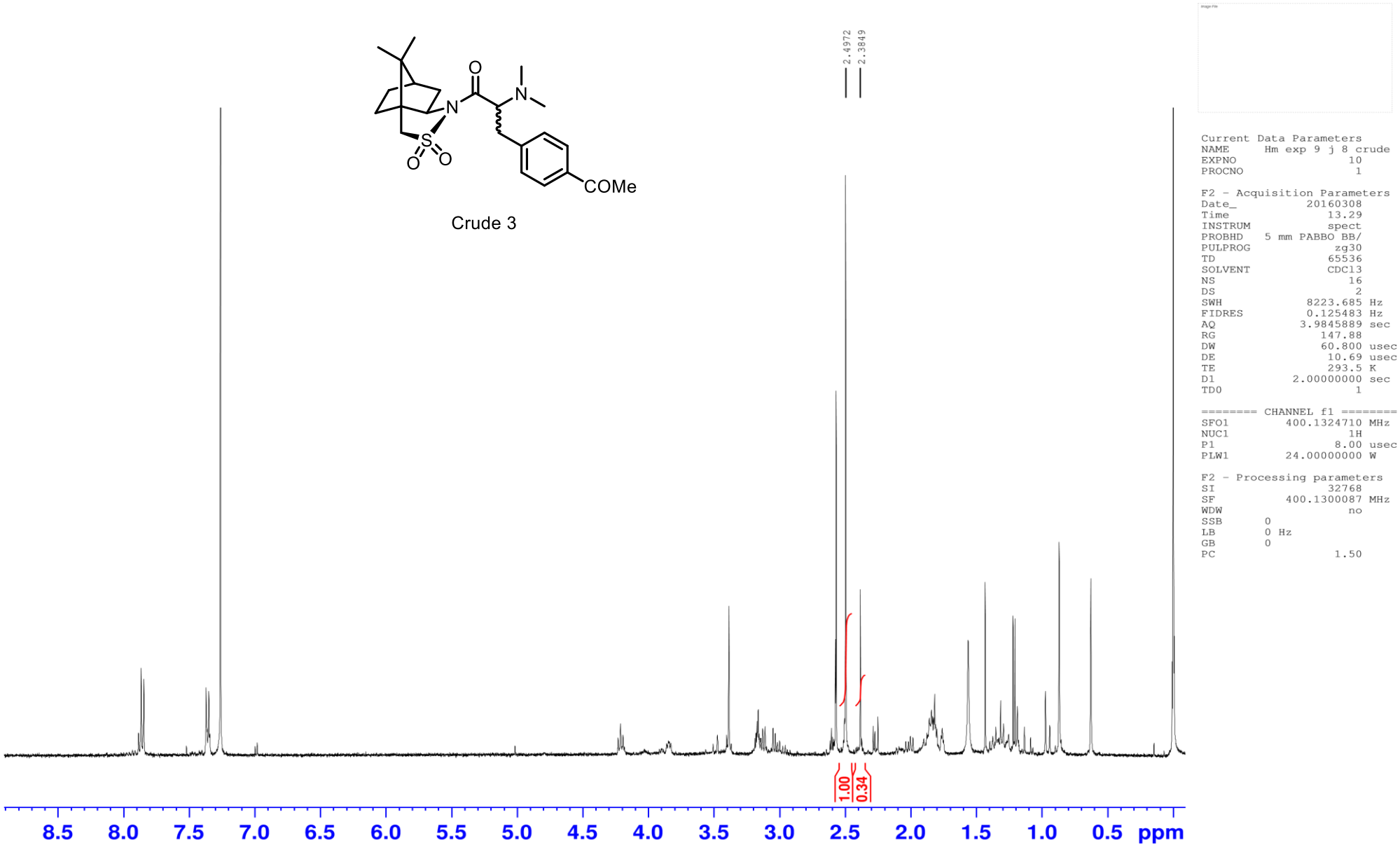


313b

^{1}H and ^{13}C NMR ($CDCl_3$)



314b



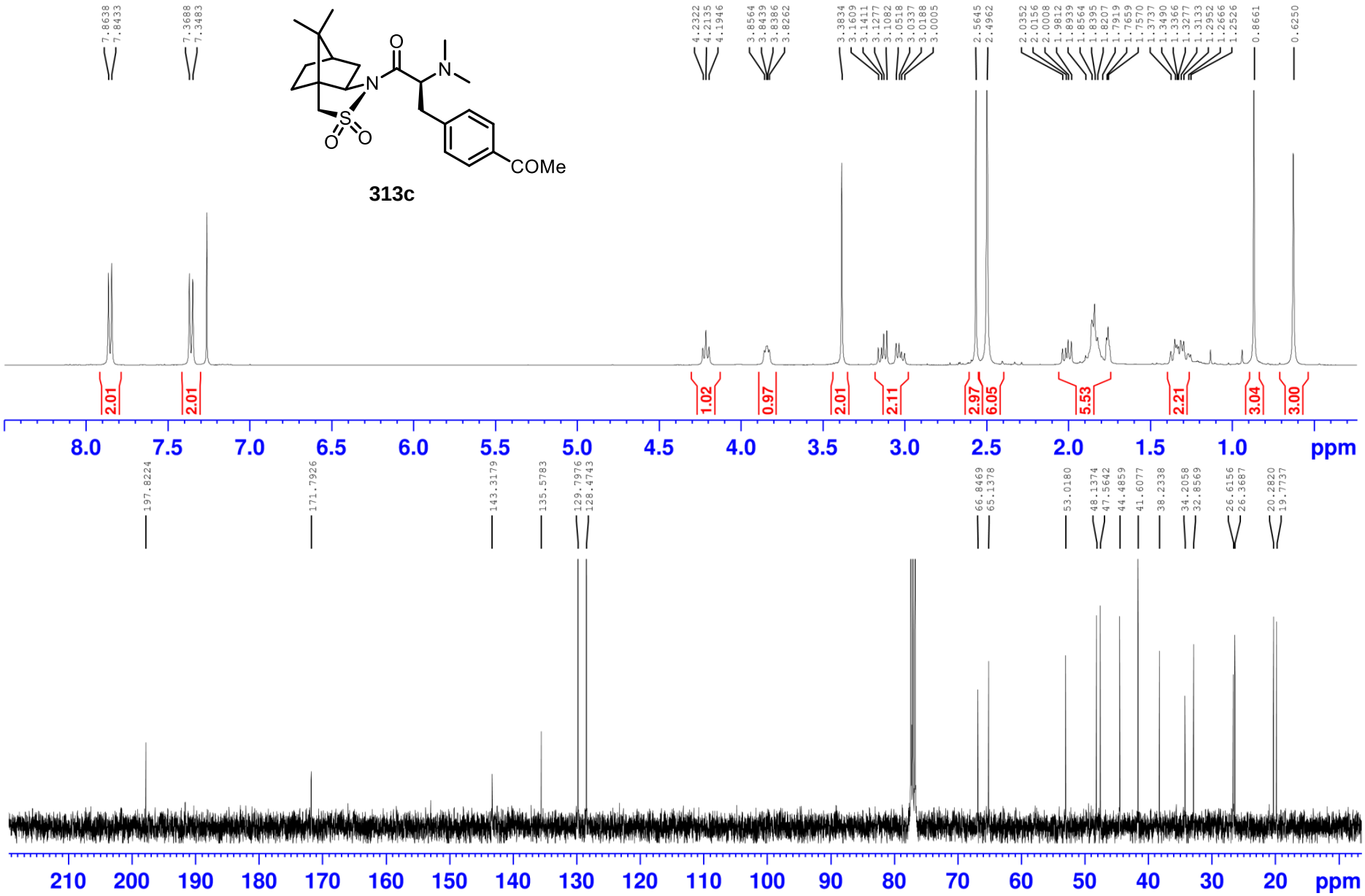

```
Current Data Parameters
NAME      Hm exp 9 j 8 crude
EXPNO                   10
PROCNO                   1

F2 - Acquisition Parameters
Date_           20160308
Time               13.29
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9845889 sec
RG                147.88
DW                60.800 usec
DE                10.69 usec
TE                293.5 K
D1             2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         400.1324710 MHz
NUC1                   1H
P1                  8.00 usec
PLW1        24.00000000 W

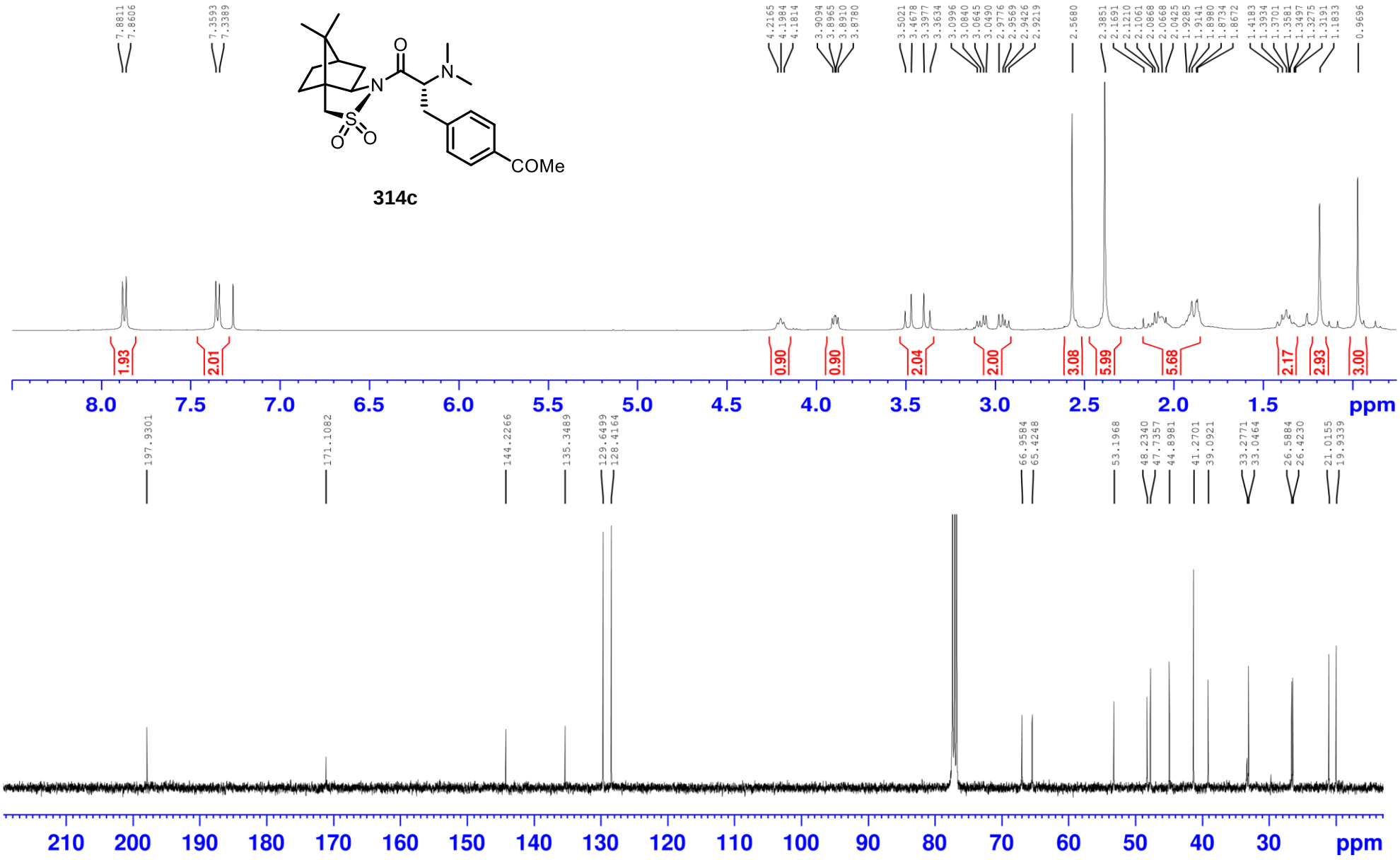
F2 - Processing parameters
SI                 32768
SF            400.1300087 MHz
WDW                   no
SSB       0
LB        0 Hz
GB        0
PC                  1.50
```

^{1}H and ^{13}C NMR ($CDCl_3$)

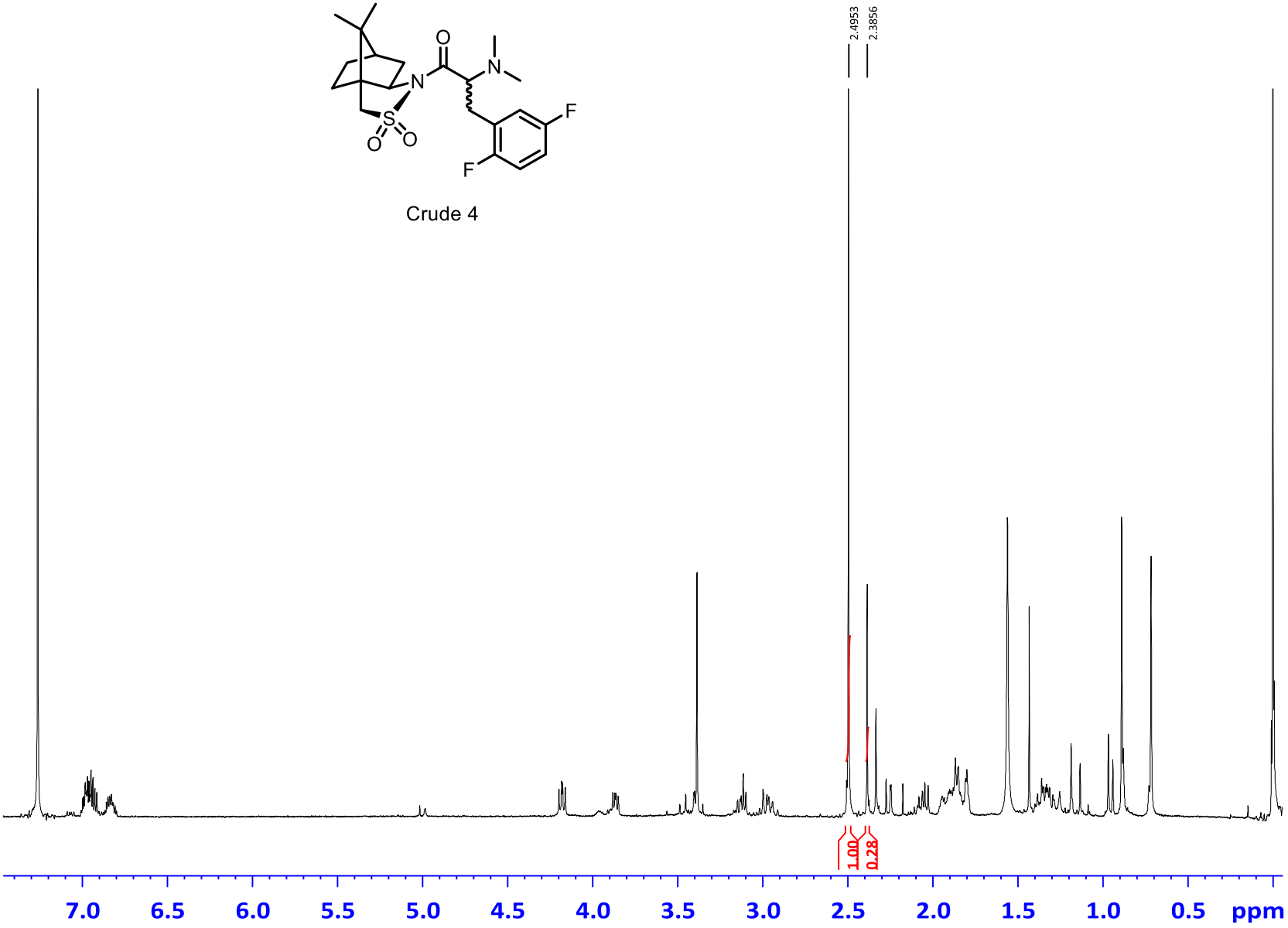


313c

^{1}H and ^{13}C NMR ($CDCl_3$)



314c



Crude 4

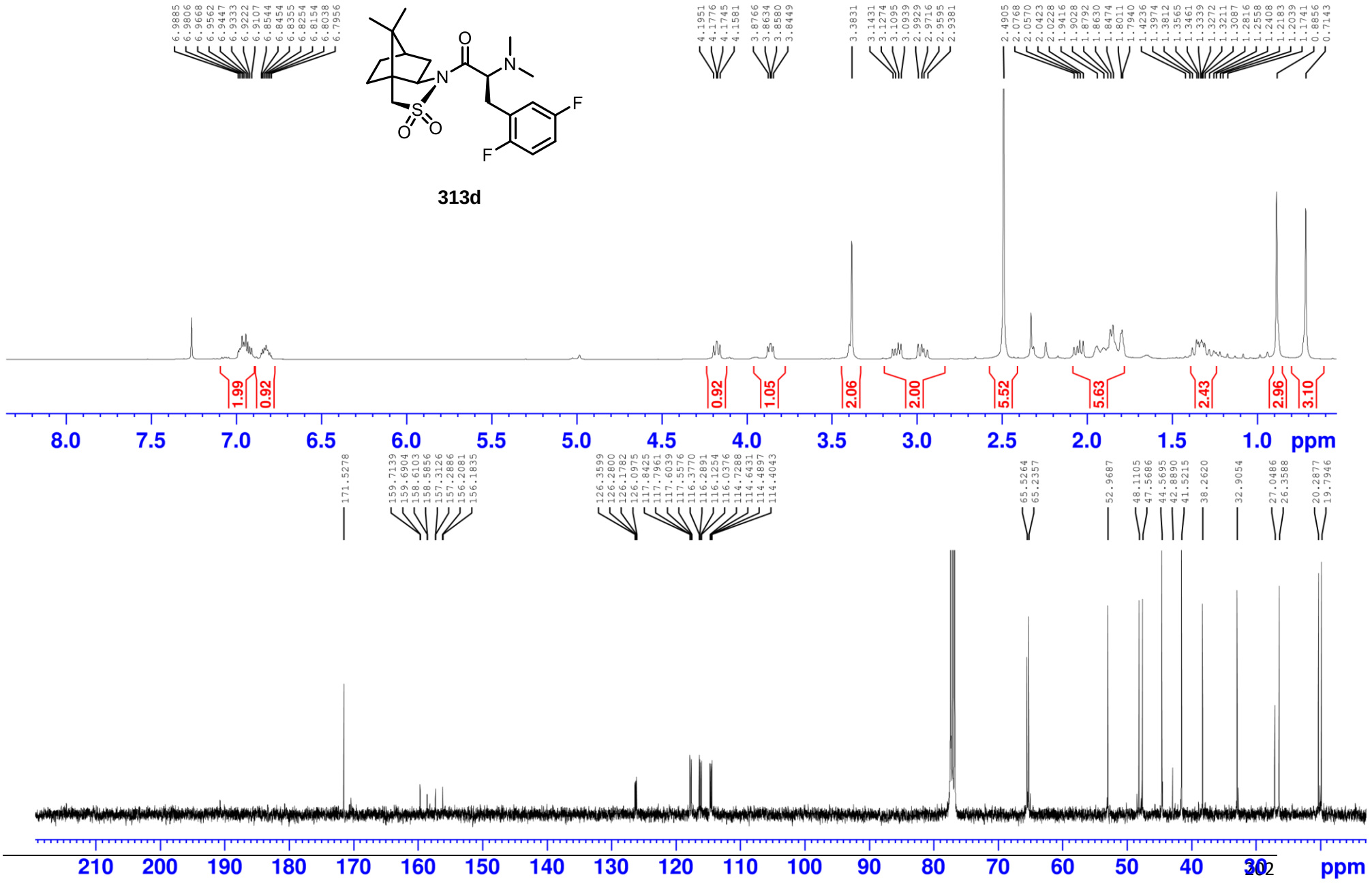
Current Data Parameters
NAME Hm exp 9 j 15 crude
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160303
Time 8.24
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9845889 sec
RG 147.88
DW 60.800 usec
DE 10.69 usec
TE 293.7 K
D1 2.00000000 sec
TD0 1

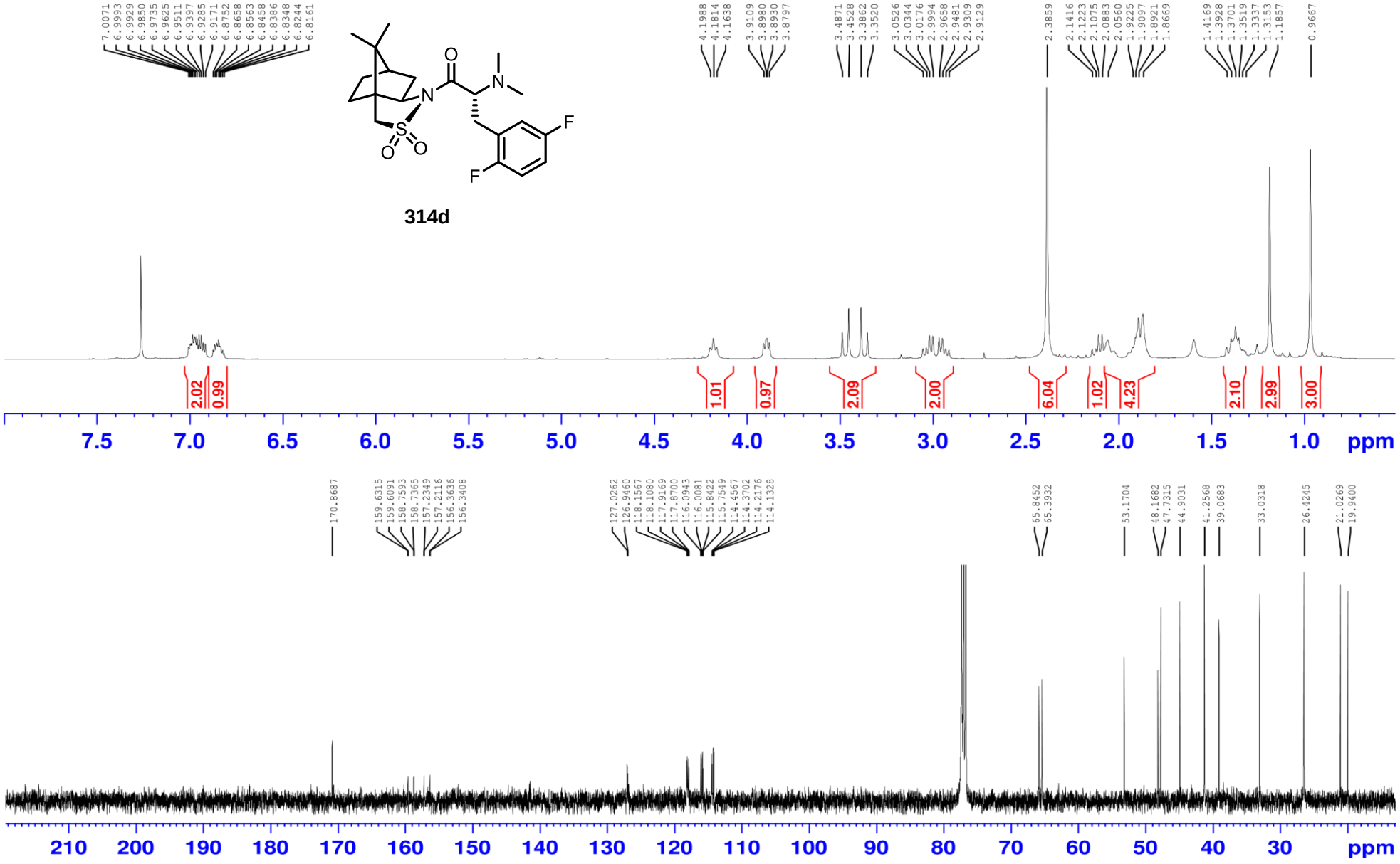
======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 8.00 usec
PLW1 24.00000000 W

F2 - Processing parameters
SI 32768
SF 400.1300087 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.50

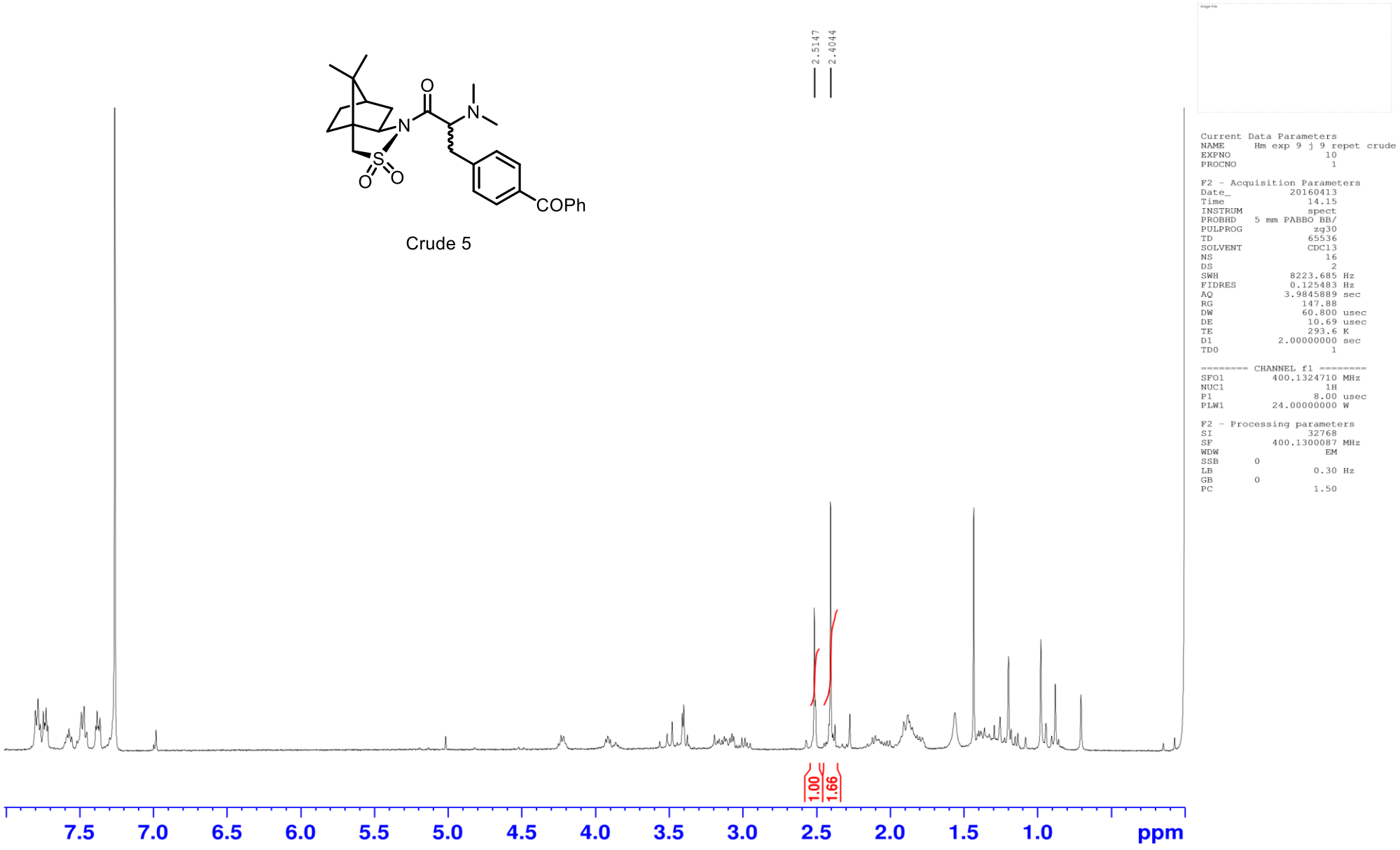
^{1}H and ^{13}C NMR ($CDCl_3$)



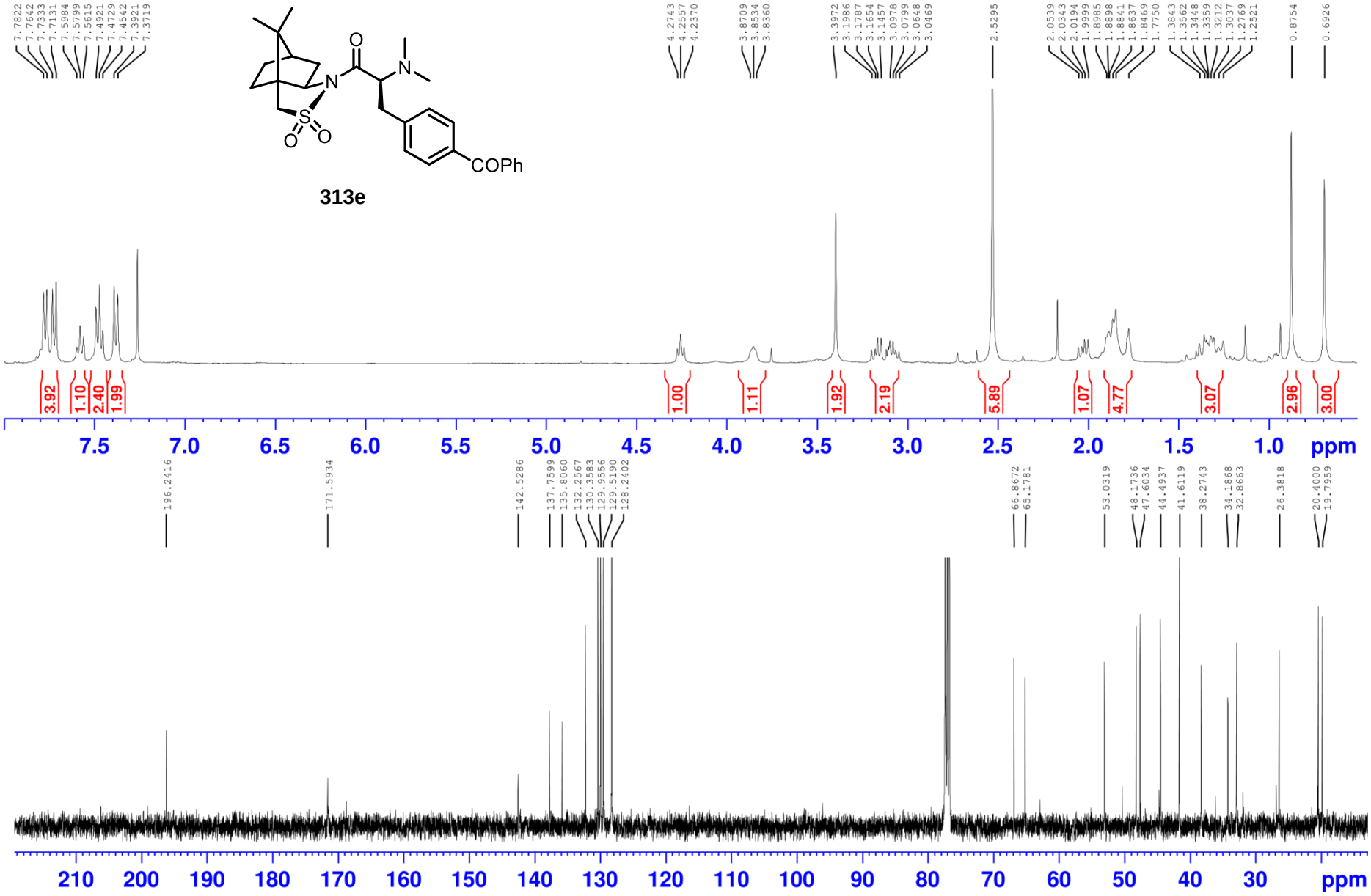
^{1}H and ^{13}C NMR ($CDCl_3$)



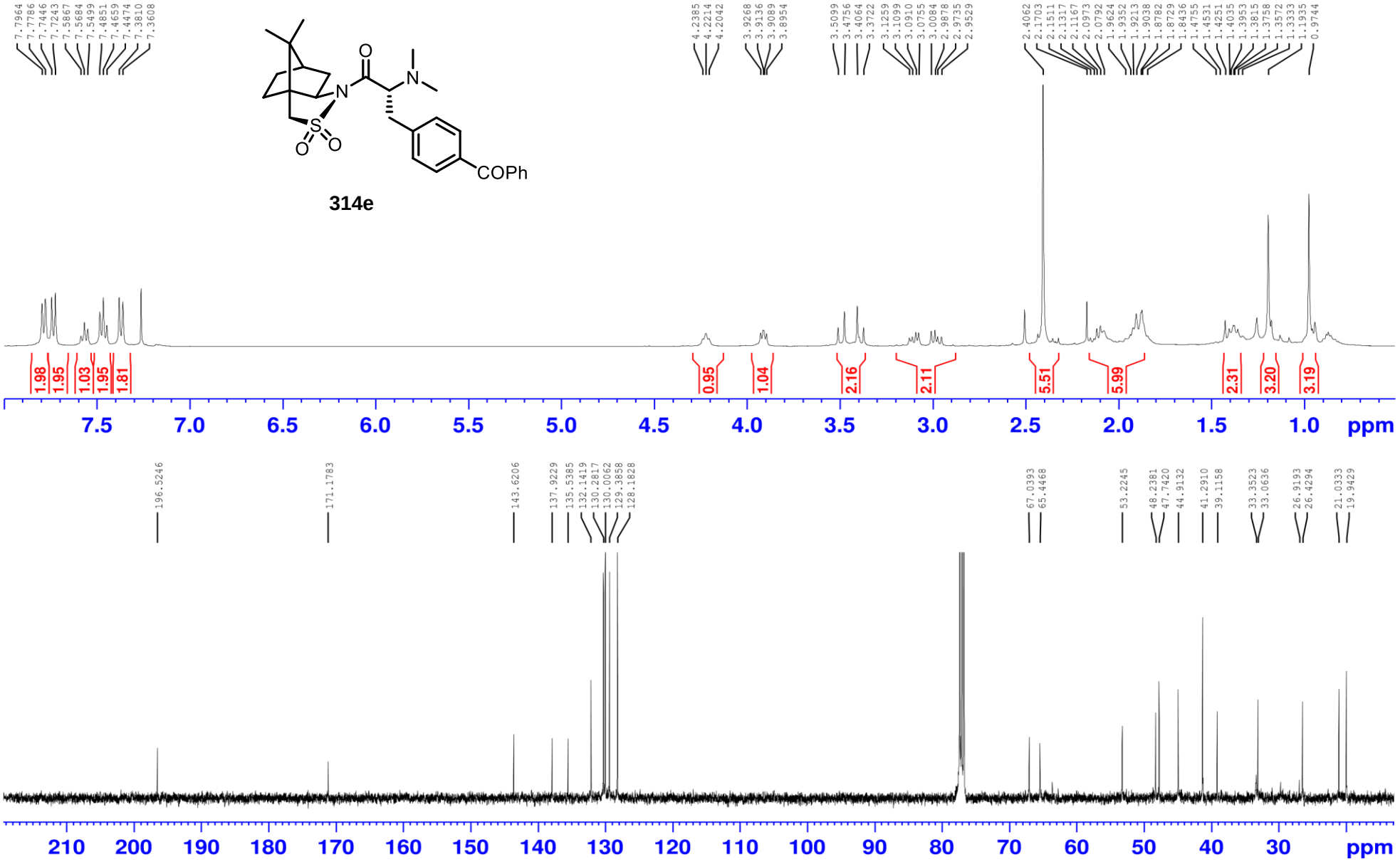
314d

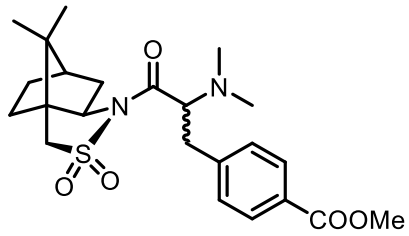

2.5147
2.4044
O
N
N
S
O
O
COPh
Crude 5
1.00
1.66
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
Current Data Parameters
NAME Hm exp 9 j 9 repet crude
EXPNO 10
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160413
Time 14.15
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9845889 sec
RG 147.88
DW 60.800 usec
DE 10.69 usec
TE 293.6 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 8.00 usec
PLW1 24.00000000 W
F2 - Processing parameters
SI 32768
SF 400.1300087 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.50

^{1}H and ^{13}C NMR ($CDCl_3$)



^{1}H and ^{13}C NMR ($CDCl_3$)





Crude 6

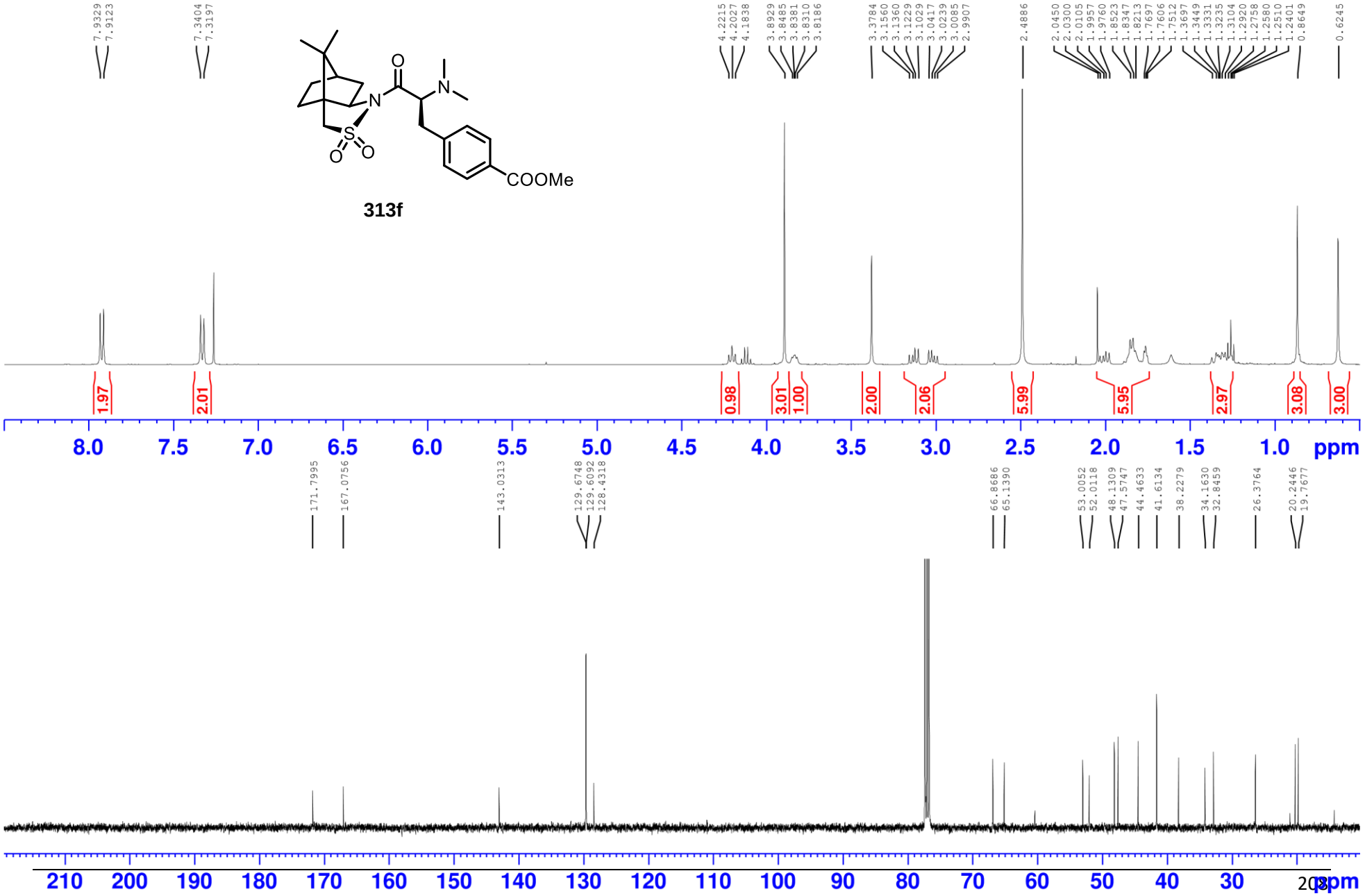

```
Current Data Parameters
NAME      Hm exp 9 j 6 Et2O layer
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160131
Time              12.06
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG           zg30
TD             65536
SOLVENT          CDCl3
NS                16
DS                 2
SWH            8223.685 Hz
FIDRES        0.125483 Hz
AQ            3.9845889 sec
RG               120.59
DW              60.800 usec
DE              10.69 usec
TE               293.8 K
D1          2.00000000 sec
TD0                1

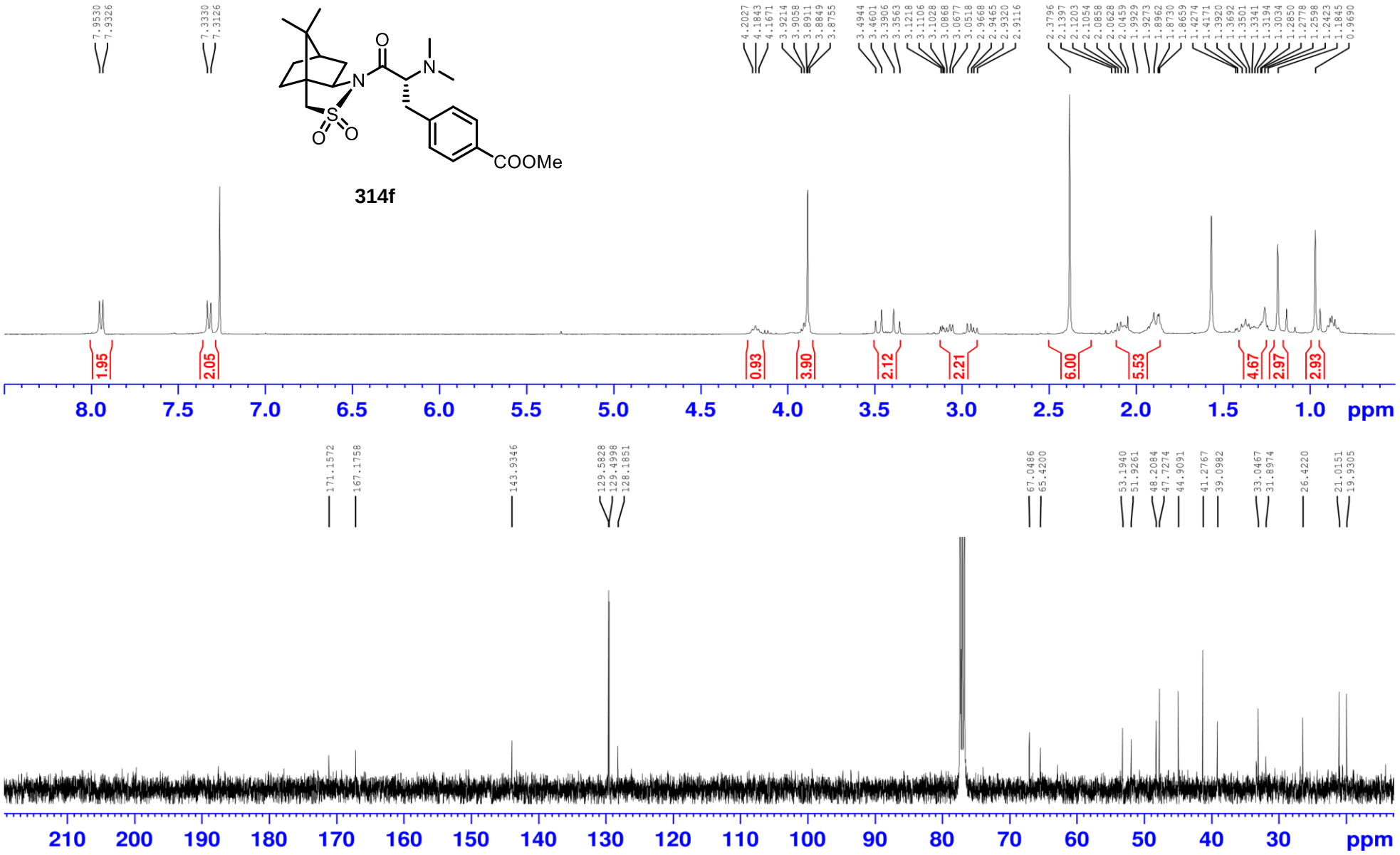
======== CHANNEL f1 ========
SFO1       400.1324710 MHz
NUC1              1H
P1              8.00 usec
PLW1       24.00000000 W

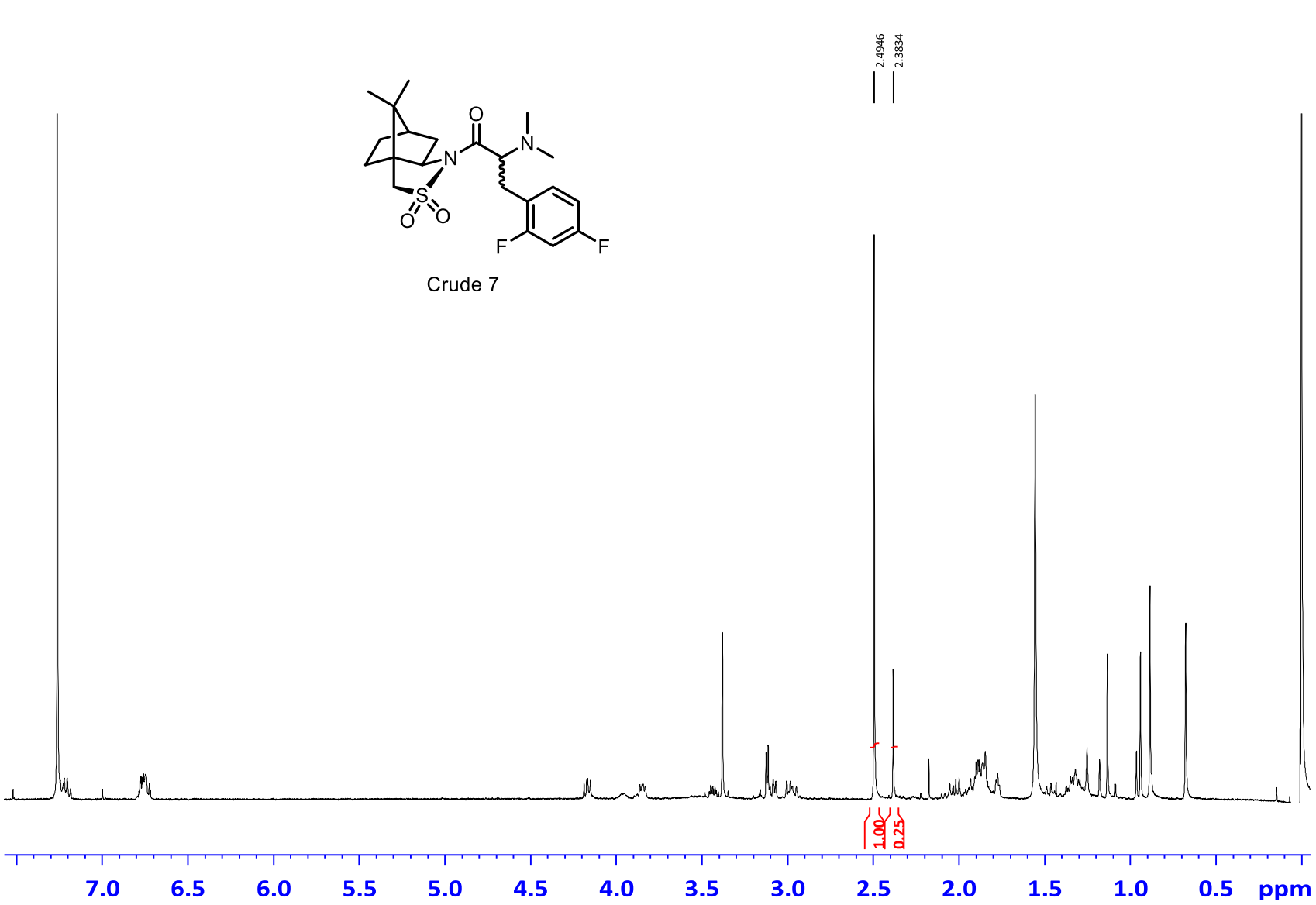
F2 - Processing parameters
SI             32768
SF         400.1300087 MHz
WDW               EM
SSB       0
LB              0.30 Hz
GB        0
PC              1.50
```

^{1}H and ^{13}C NMR ($CDCl_3$)



^{1}H and ^{13}C NMR ($CDCl_3$)





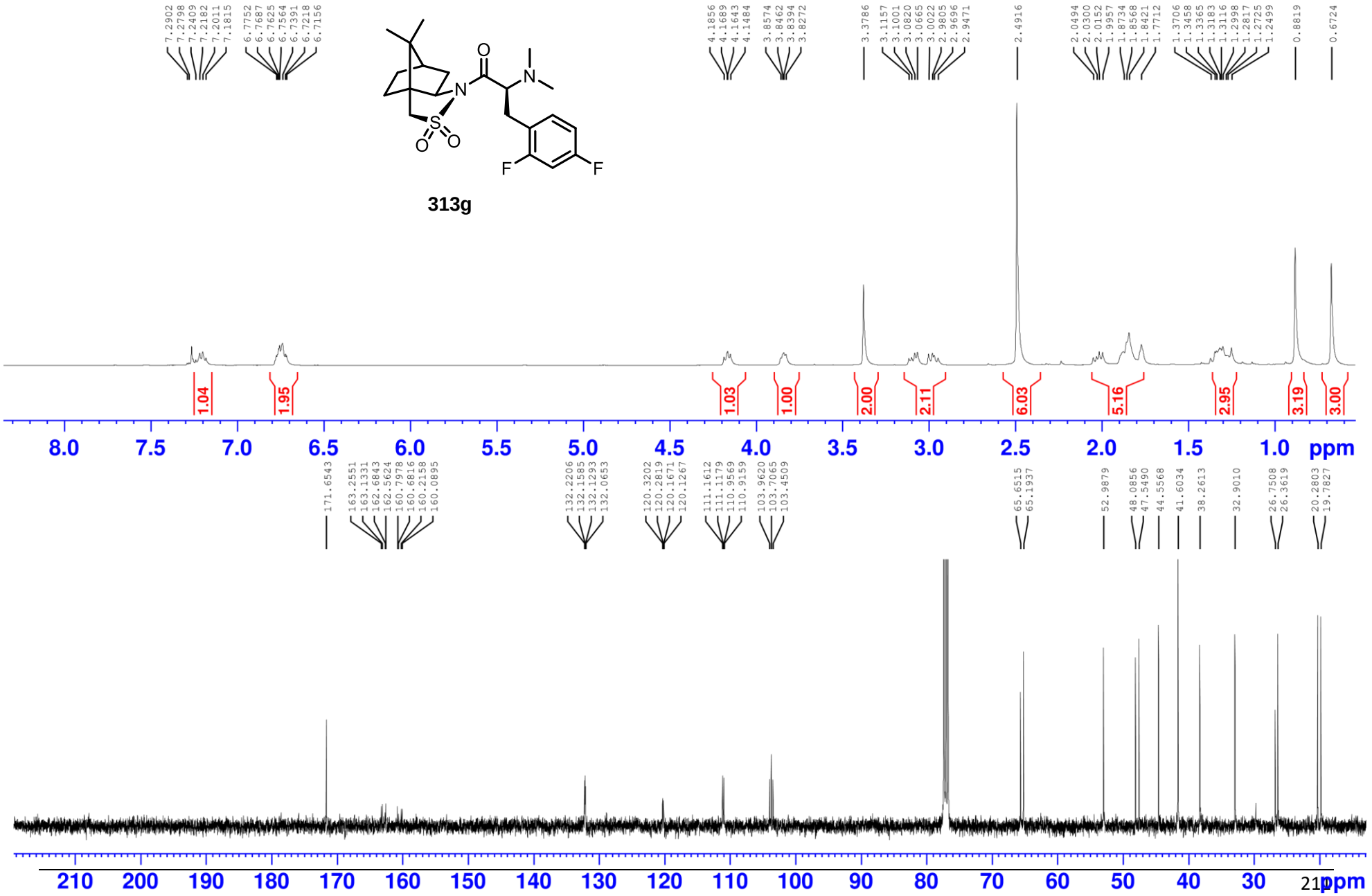
Current Data Parameters
NAME Hm exp 9 i 7 crude
EXPNO 24
PROCNO 1

F2 - Acquisition Parameters
Date 20160130
Time 5.26
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9845889 sec
RG 147.88
DW 60.800 usec
DE 10.69 usec
TE 294.0 K
D1 2.00000000 sec
TD0 1

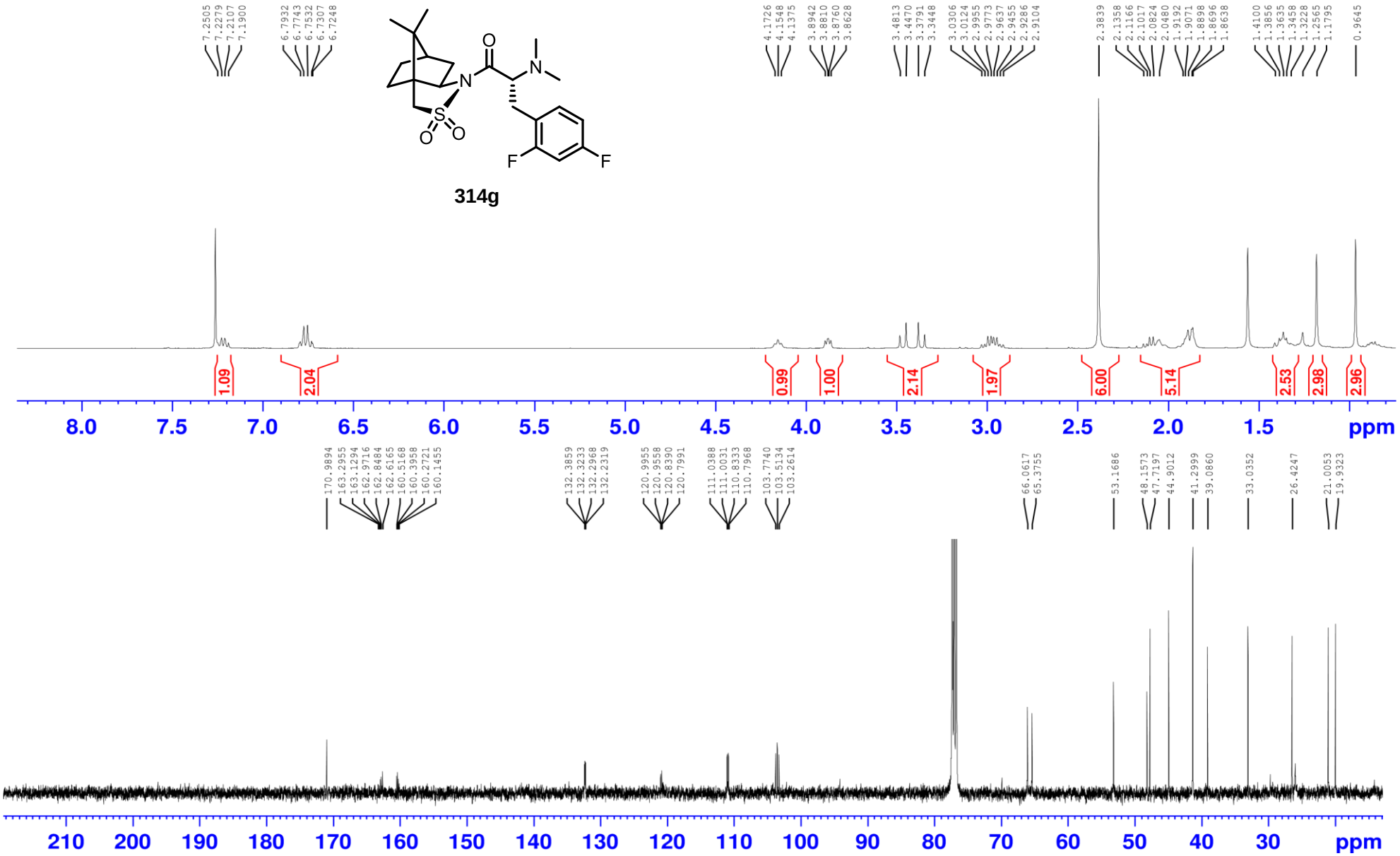
======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 8.00 usec
PLW1 24.00000000 W

F2 - Processing parameters
SI 32768
SF 400.1300087 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.50

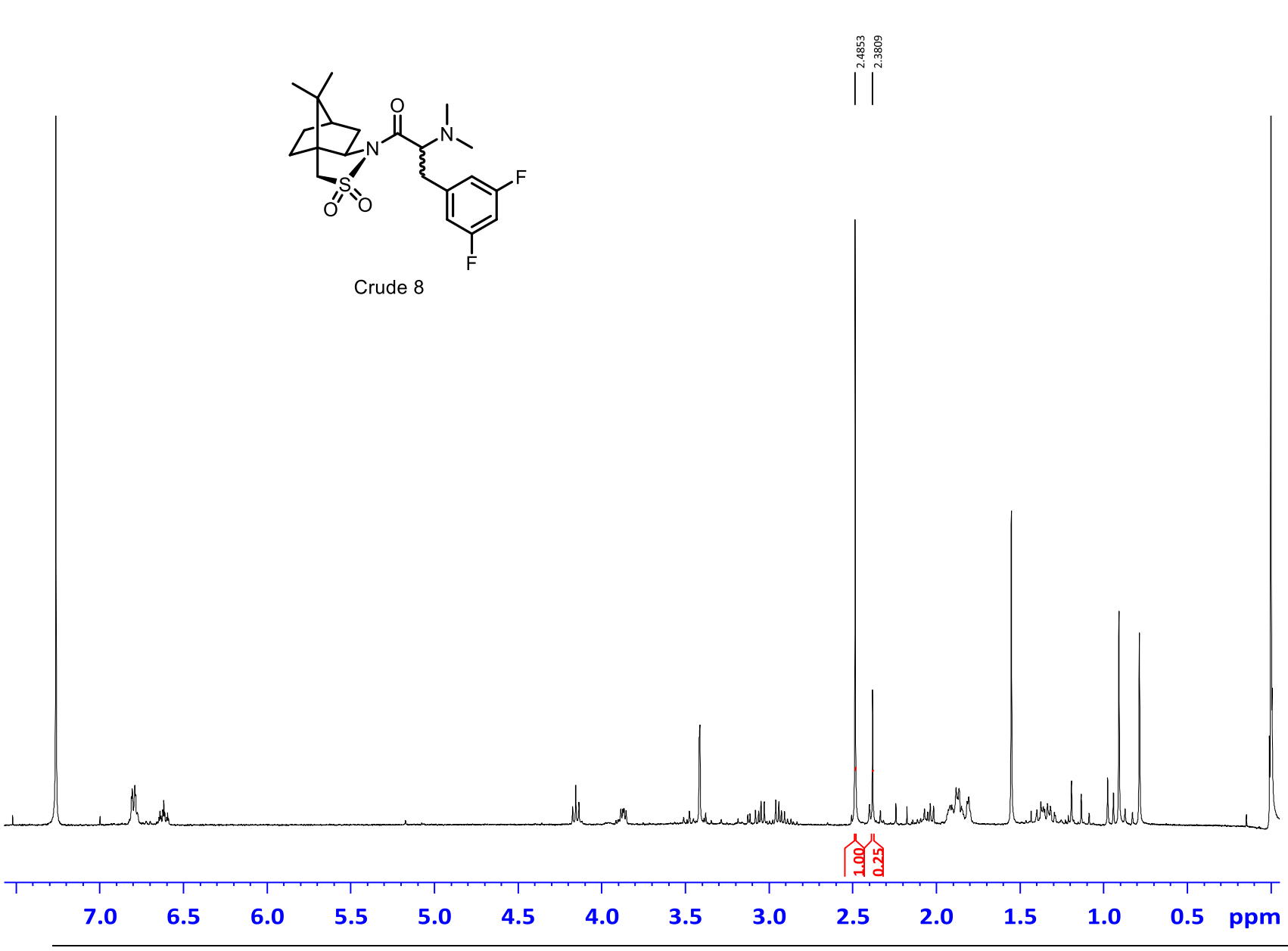
^{1}H and ^{13}C NMR ($CDCl_3$)



^{1}H and ^{13}C NMR ($CDCl_3$)



314g



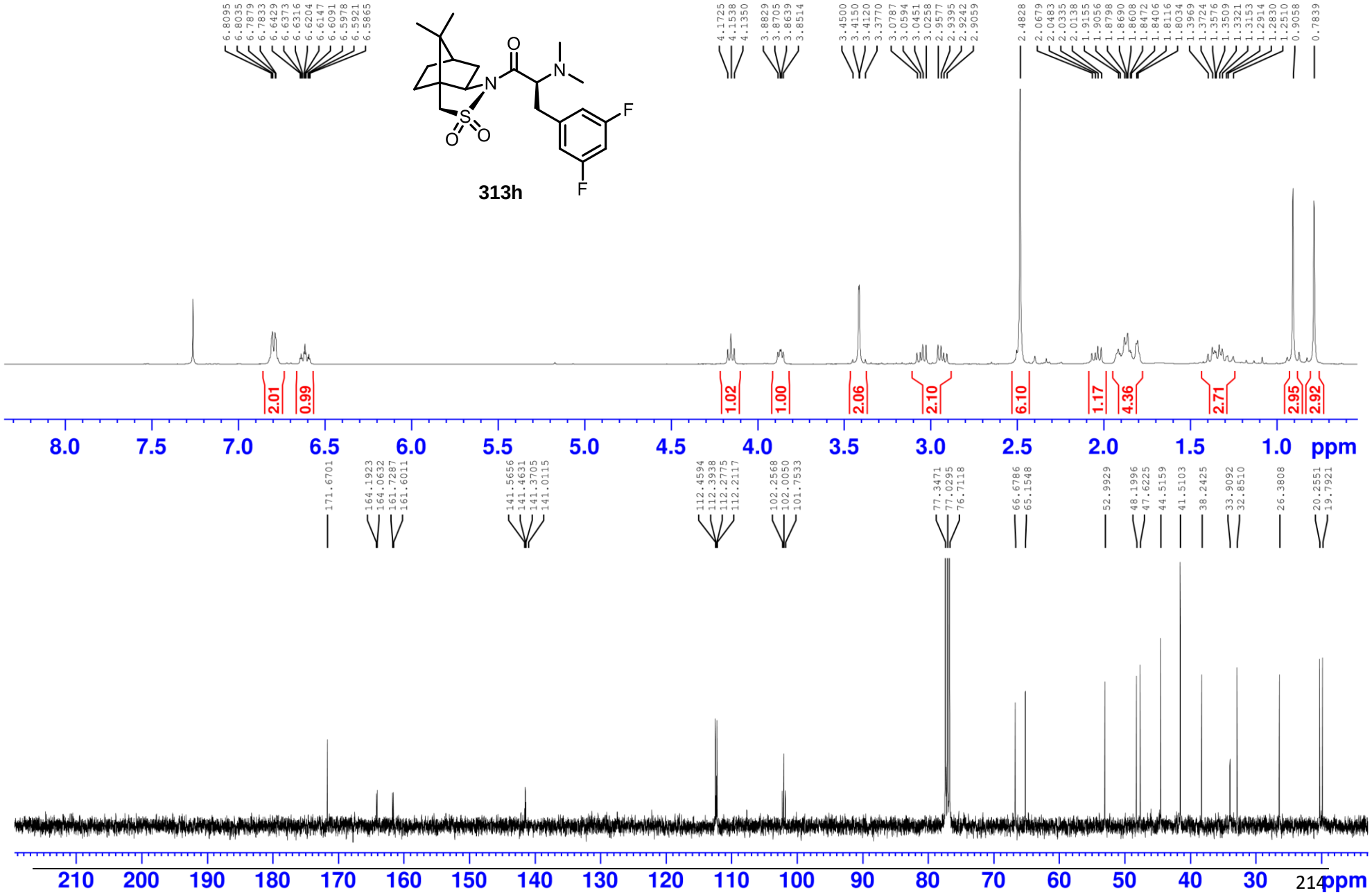
Current Data Parameters
NAME Hm exp 9 j 14 crude
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date 20160226
Time 13.24
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9845889 sec
RG 147.88
DW 60.800 usec
DE 10.69 usec
TE 293.7 K
D1 2.00000000 sec
TD0 1

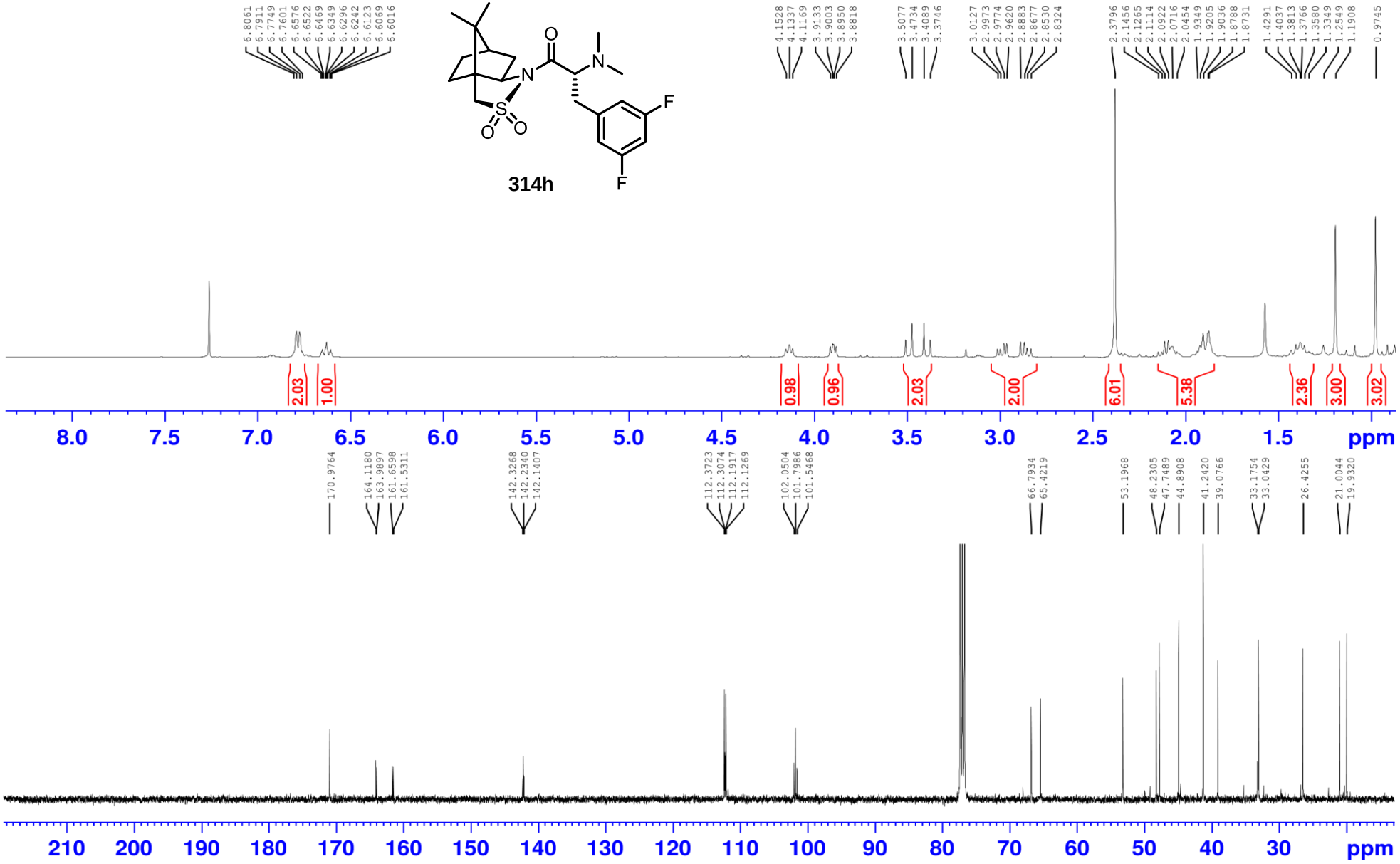
======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 8.00 usec
PLW1 24.00000000 W

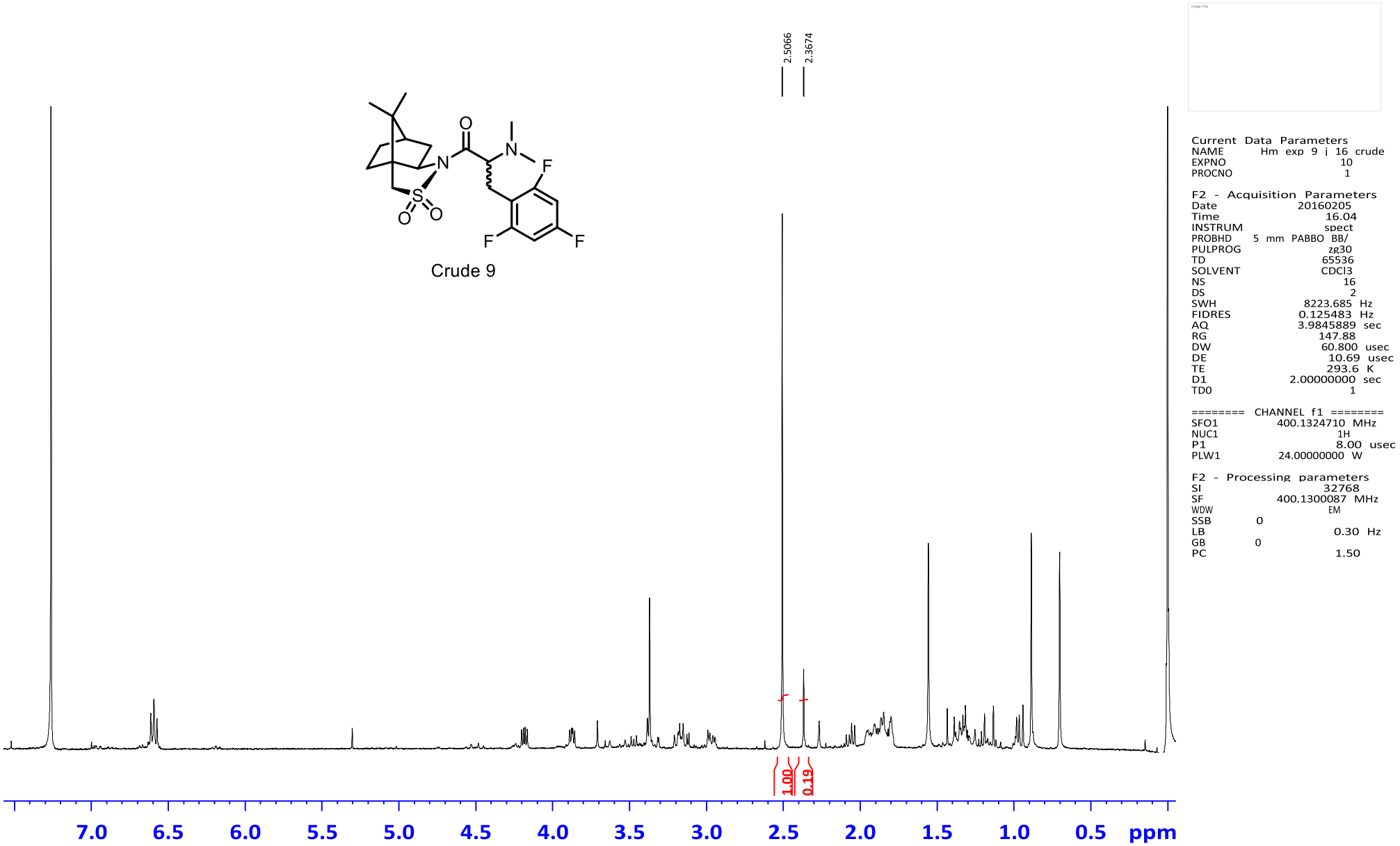
F2 - Processing parameters
SI 32768
SF 400.1300087 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.50

^{1}H and ^{13}C NMR ($CDCl_3$)



^{1}H and ^{13}C NMR ($CDCl_3$)





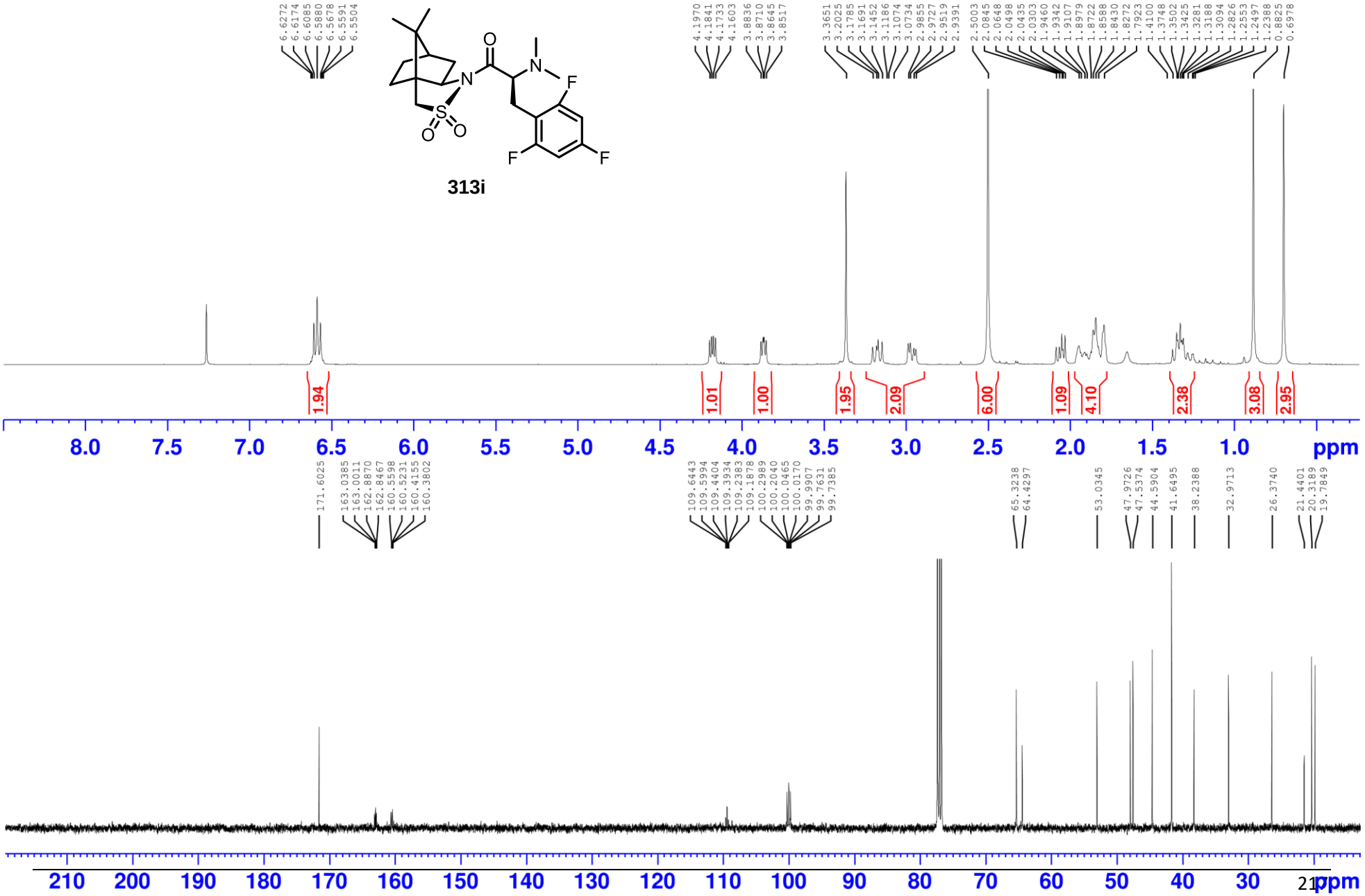
Current Data Parameters
NAME Hm exp 9 i 16 crude
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date 20160205
Time 16.04
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9845889 sec
RG 147.88
DW 60.800 usec
DE 10.69 usec
TE 293.6 K
D1 2.00000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 8.00 usec
PLW1 24.00000000 W

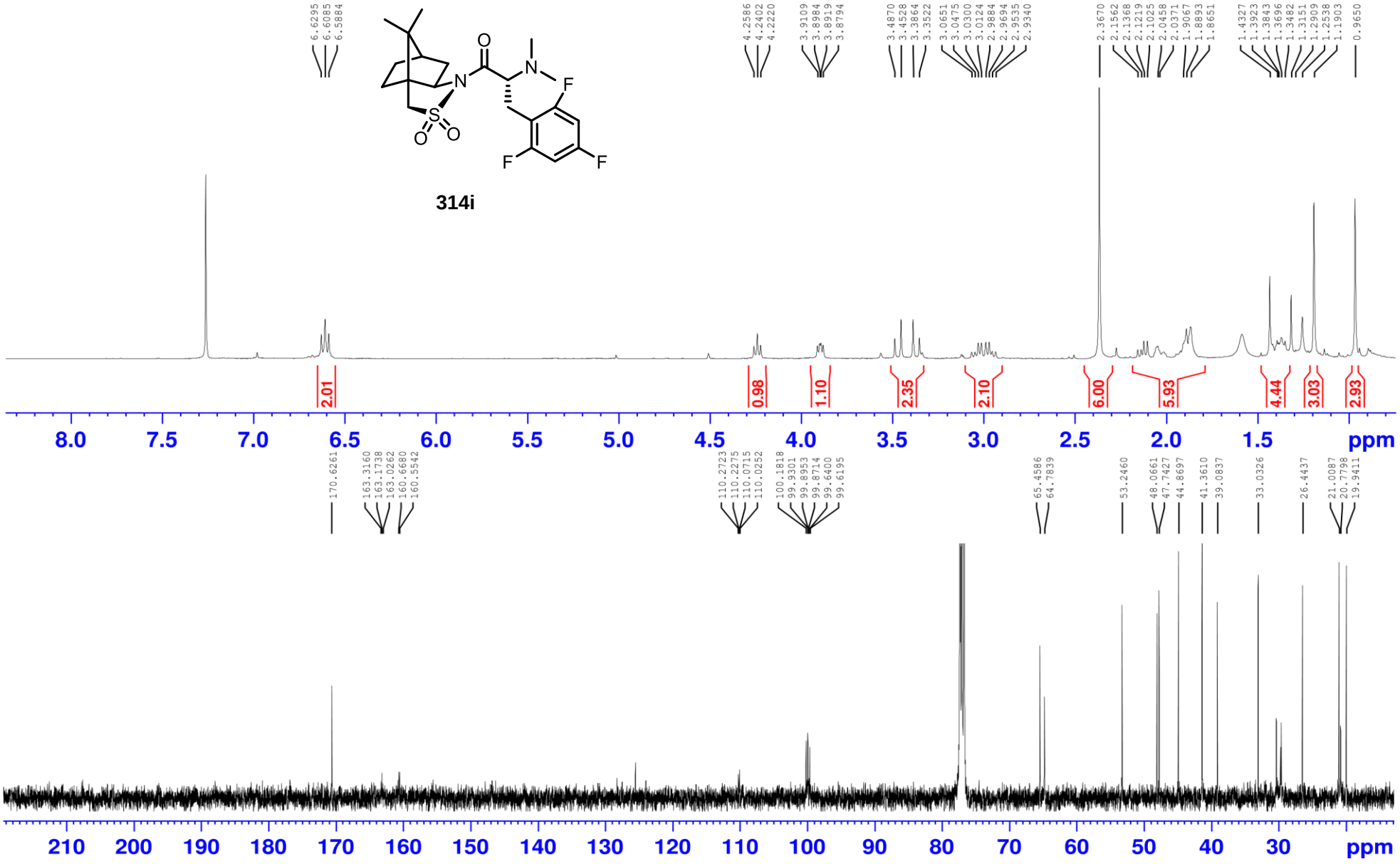
F2 - Processing parameters
SI 32768
SF 400.1300087 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.50

^{1}H and ^{13}C NMR ($CDCl_3$)

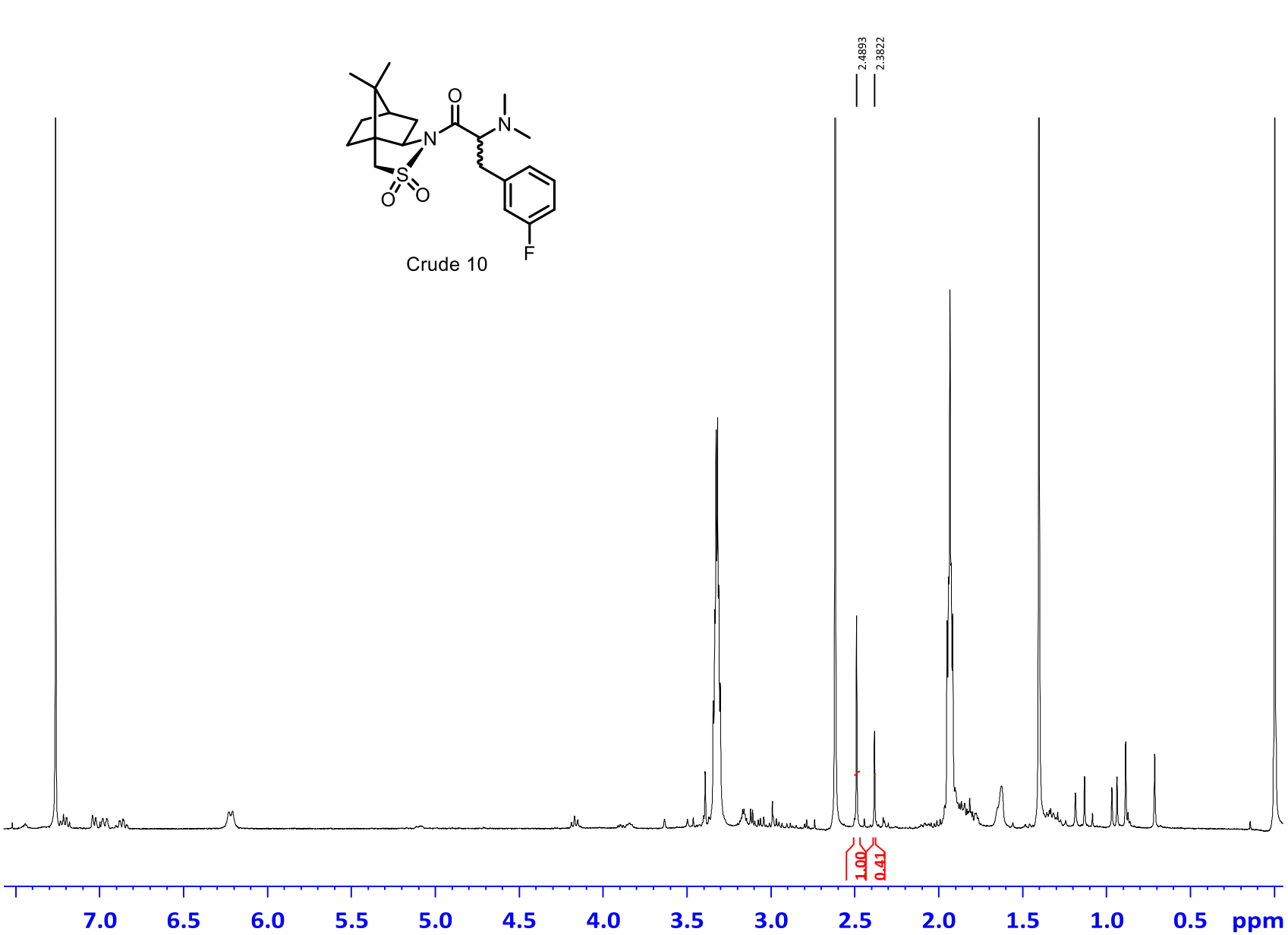


313i

^{1}H and ^{13}C NMR ($CDCl_3$)



314i



Current Data Parameters
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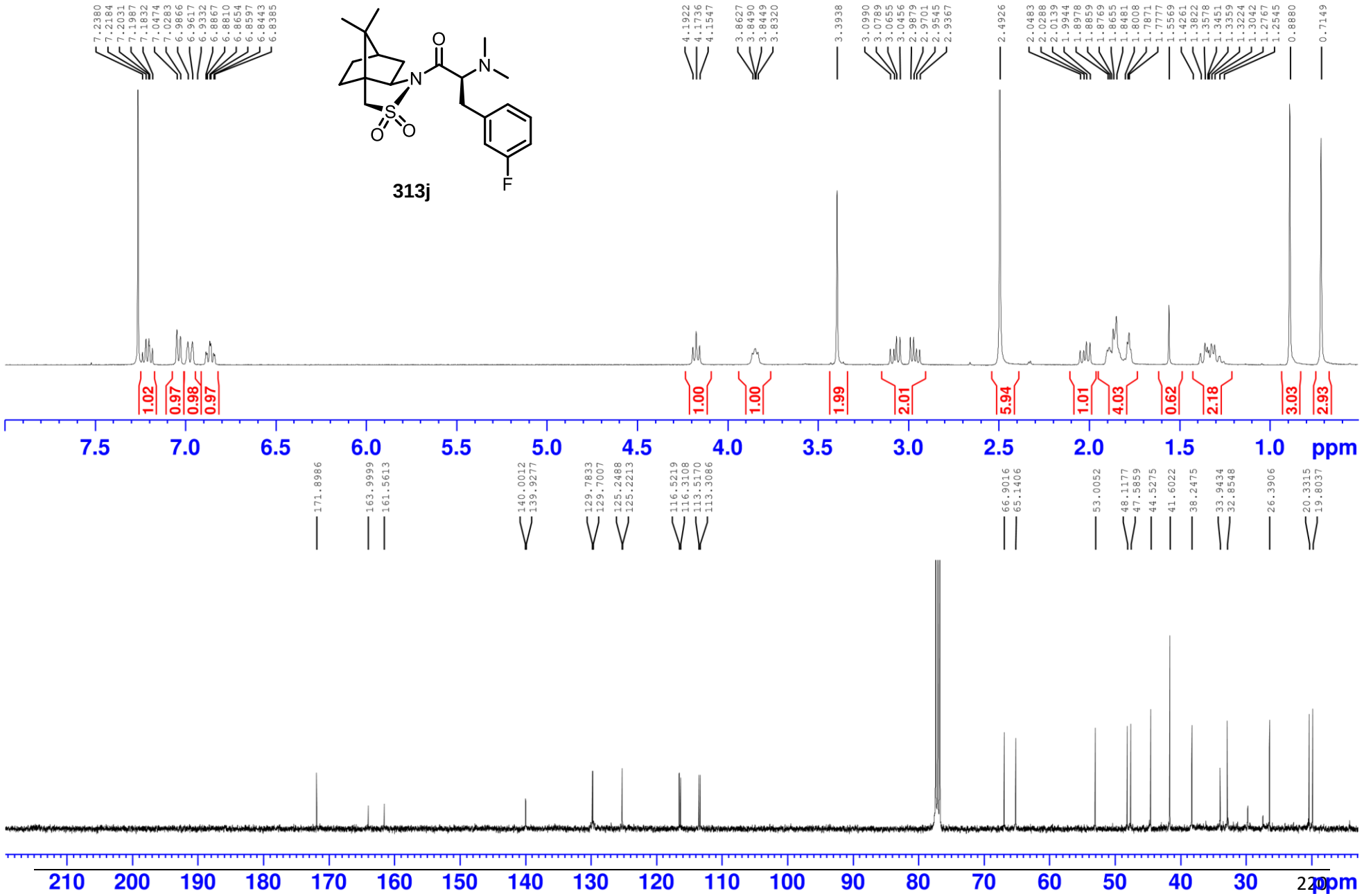
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date 20151208
Time 15.36
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9845889 sec
RG 147.88
DW 60.800 usec
DE 10.69 usec
TE 293.6 K
D1 2.00000000 sec
TD0 1

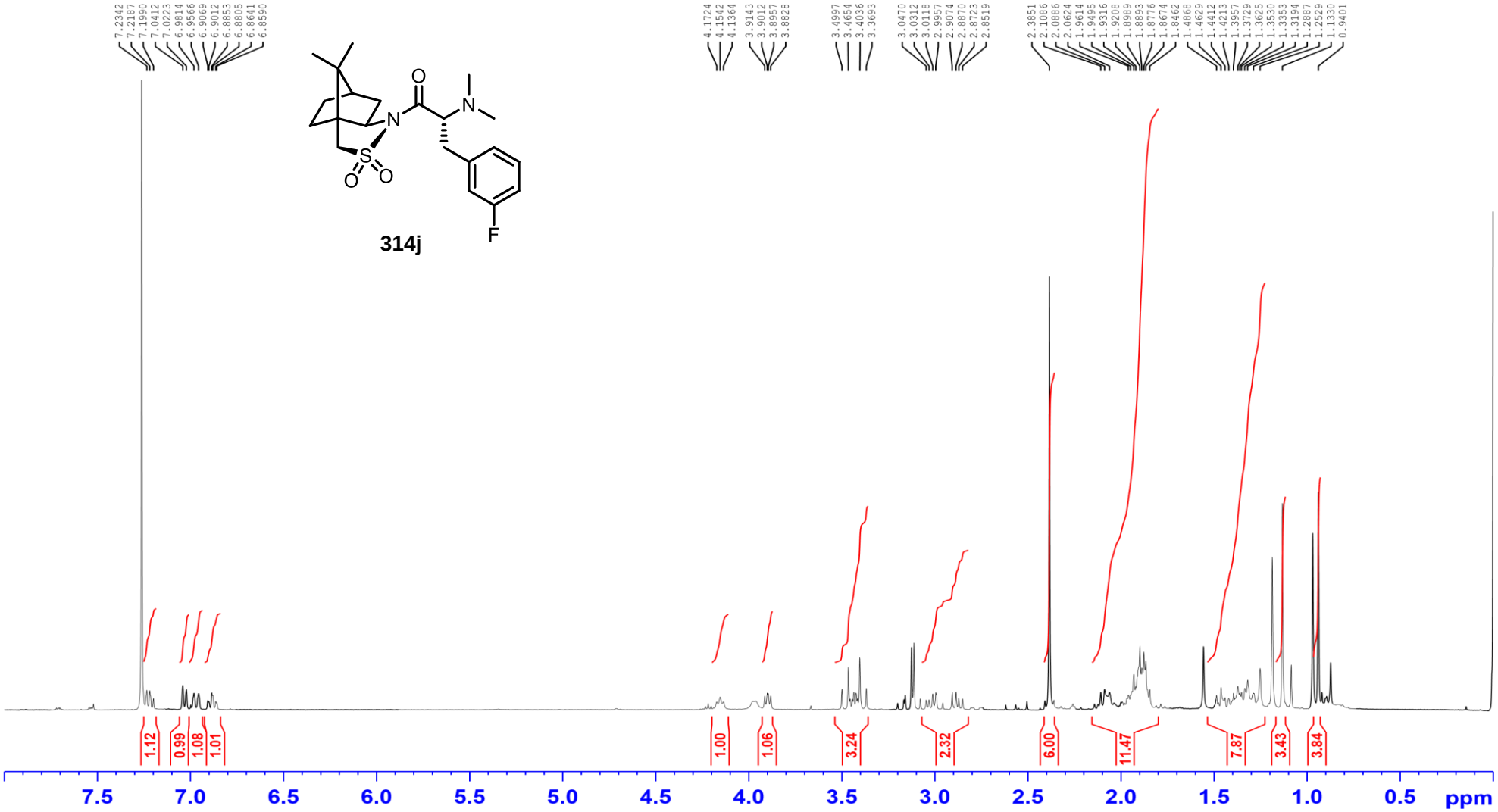
======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 8.00 usec
PLW1 24.00000000 W

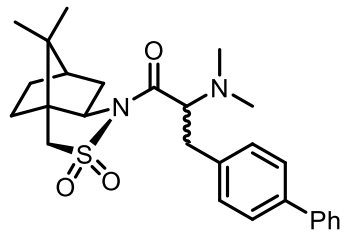
F2 - Processing parameters
SI 32768
SF 400.1300087 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.50

^{1}H and ^{13}C NMR ($CDCl_3$)



^{1}H and ^{13}C NMR ($CDCl_3$)





Crude 11

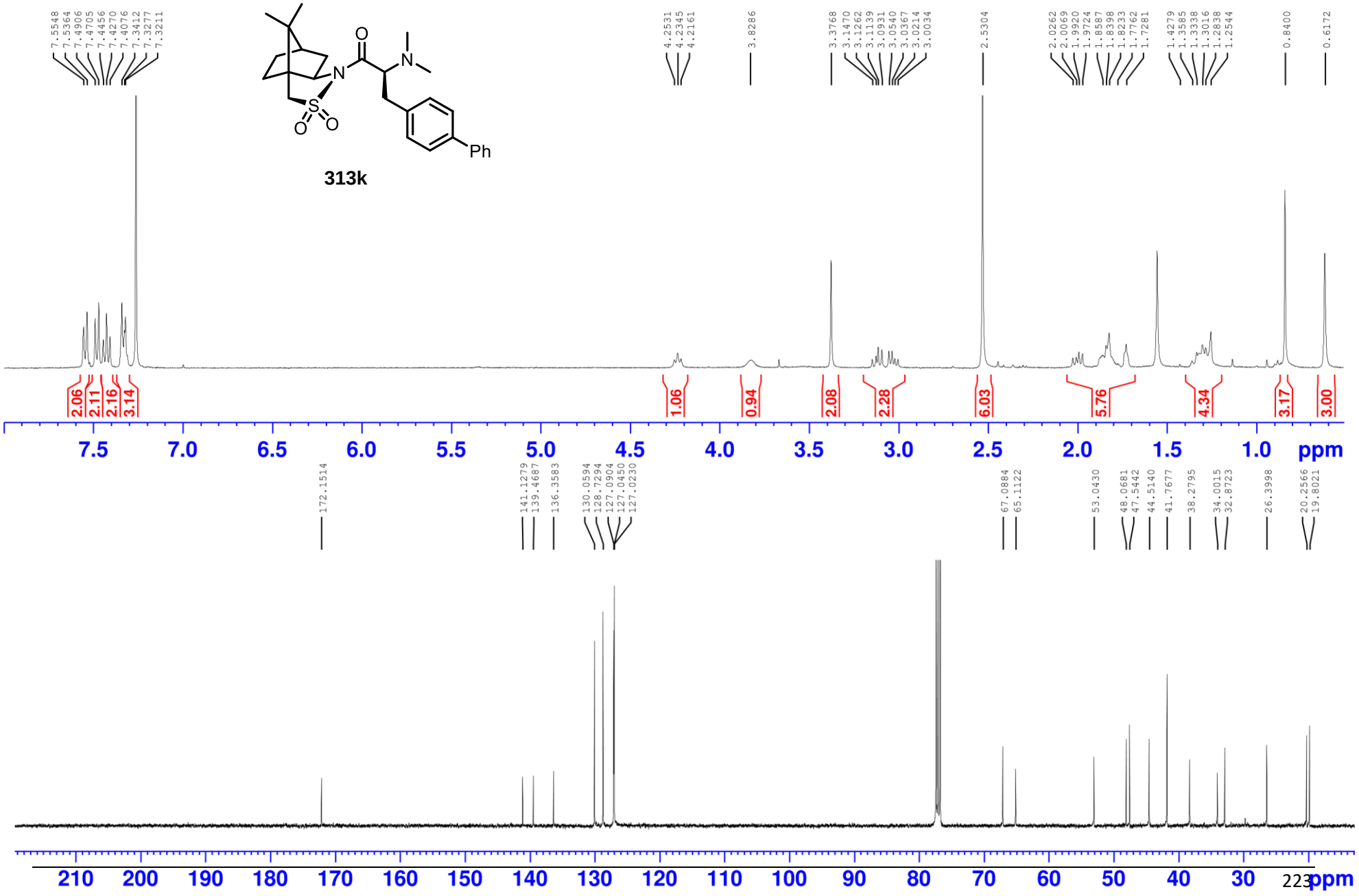

```
Current Data Parameters
NAME      Hm exp 9 j 2 crude
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20151214
Time               15.40
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9845889 sec
RG                147.88
DW                60.800 usec
DE                10.69 usec
TE                293.7 K
D1             2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          400.1324710 MHz
NUC1                  1H
P1                 8.00 usec
PLW1          24.00000000 W

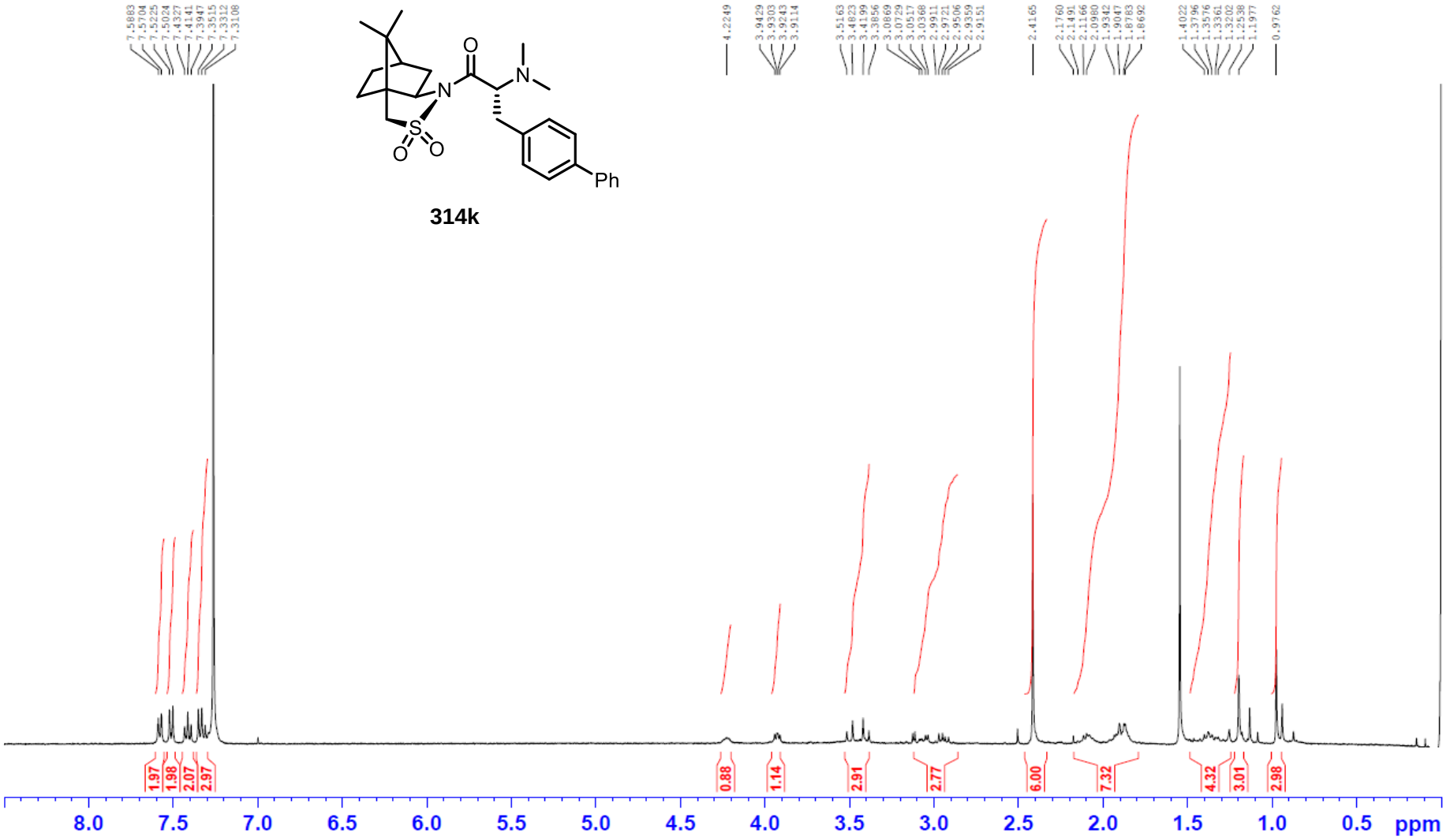
F2 - Processing parameters
SI                 32768
SF            400.1300087 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.50
```

^{1}H and ^{13}C NMR ($CDCl_3$)

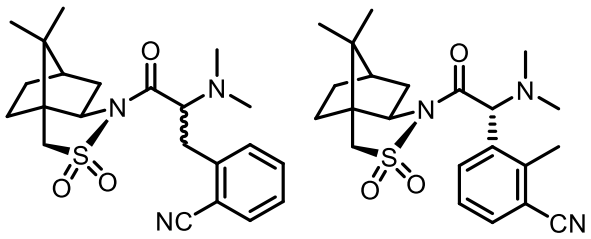


313k

^{1}H and ^{13}C NMR ($CDCl_3$)



314k



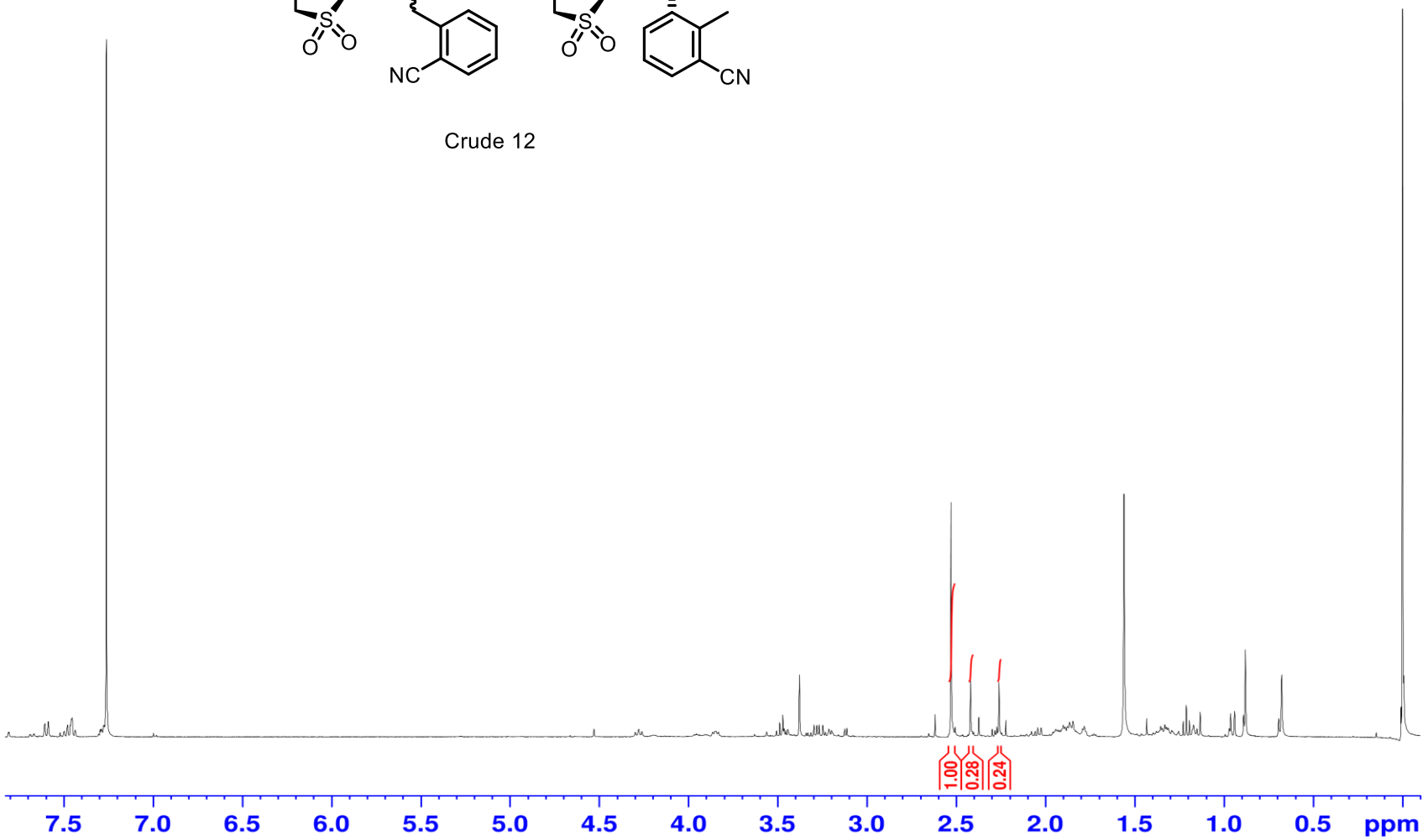
Crude 12


```
Current Data Parameters
NAME      Hm exp 9 j 5 crude
EXPNO                   10
PROCNO                   1

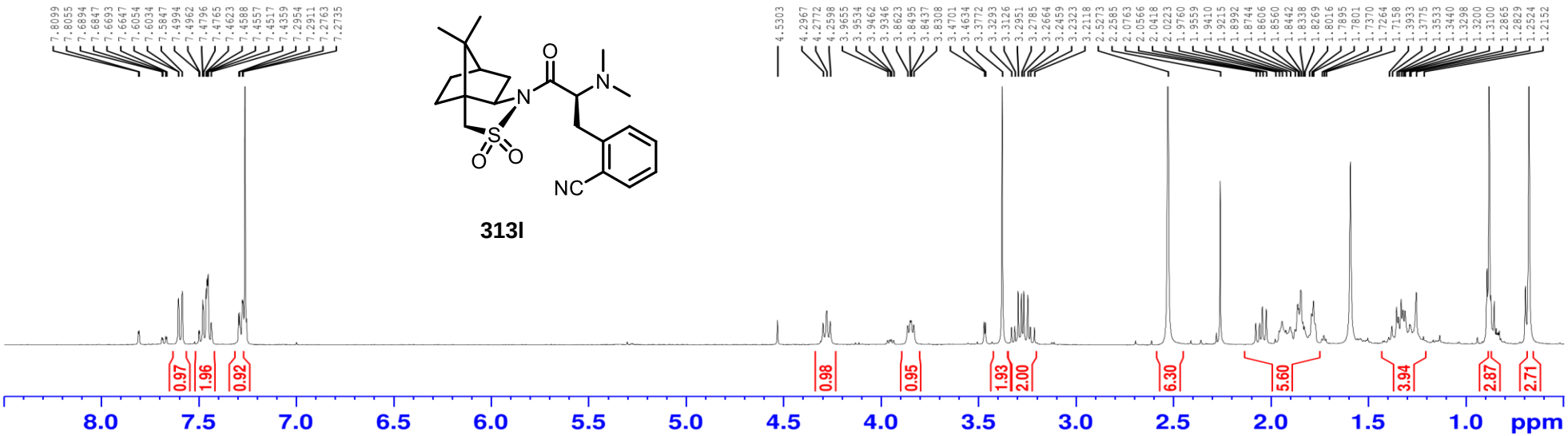
F2 - Acquisition Parameters
Date_           20160201
Time                1.46
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 65536
SOLVENT            CDC13
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9845889 sec
RG                147.88
DW                60.800 usec
DE                10.69 usec
TE                294.1 K
D1             2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          400.1324710 MHz
NUC1                  1H
P1                 8.00 usec
PLW1          24.00000000 W

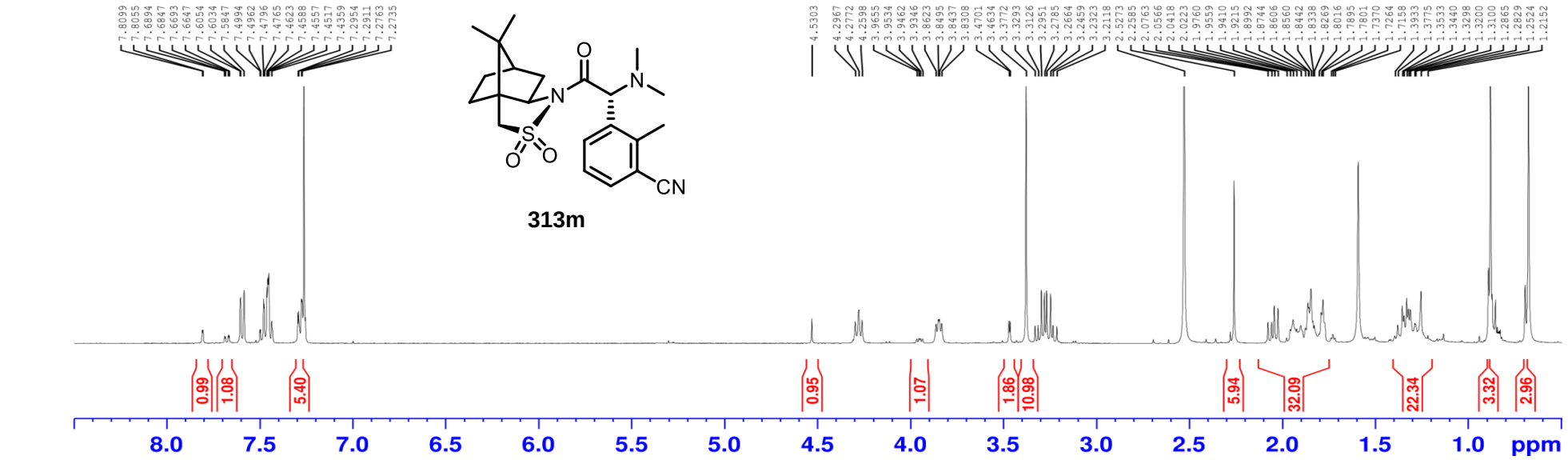
F2 - Processing parameters
SI                 32768
SF            400.1300087 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.50
```



^{1}H and ^{13}C NMR ($CDCl_3$)

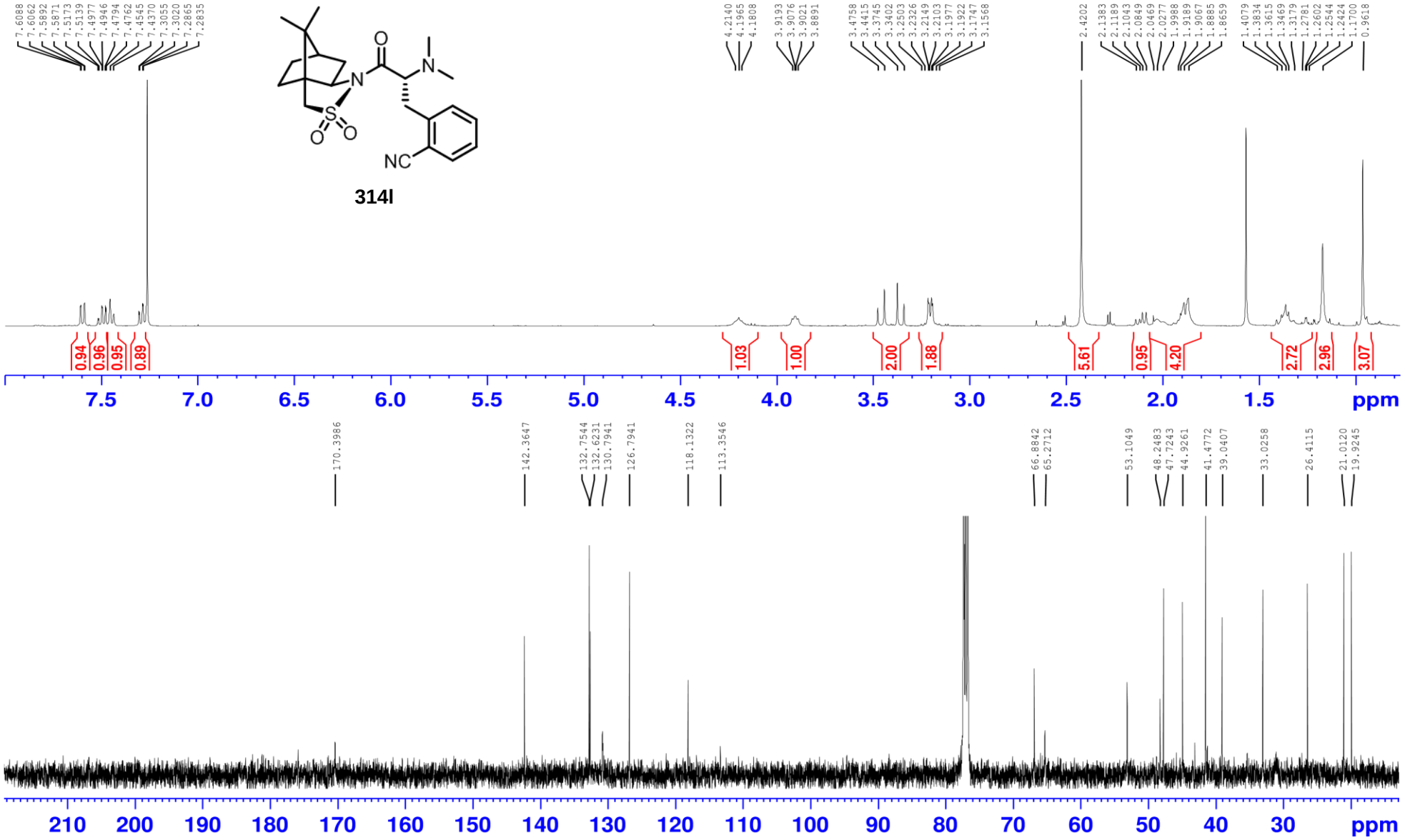


313l



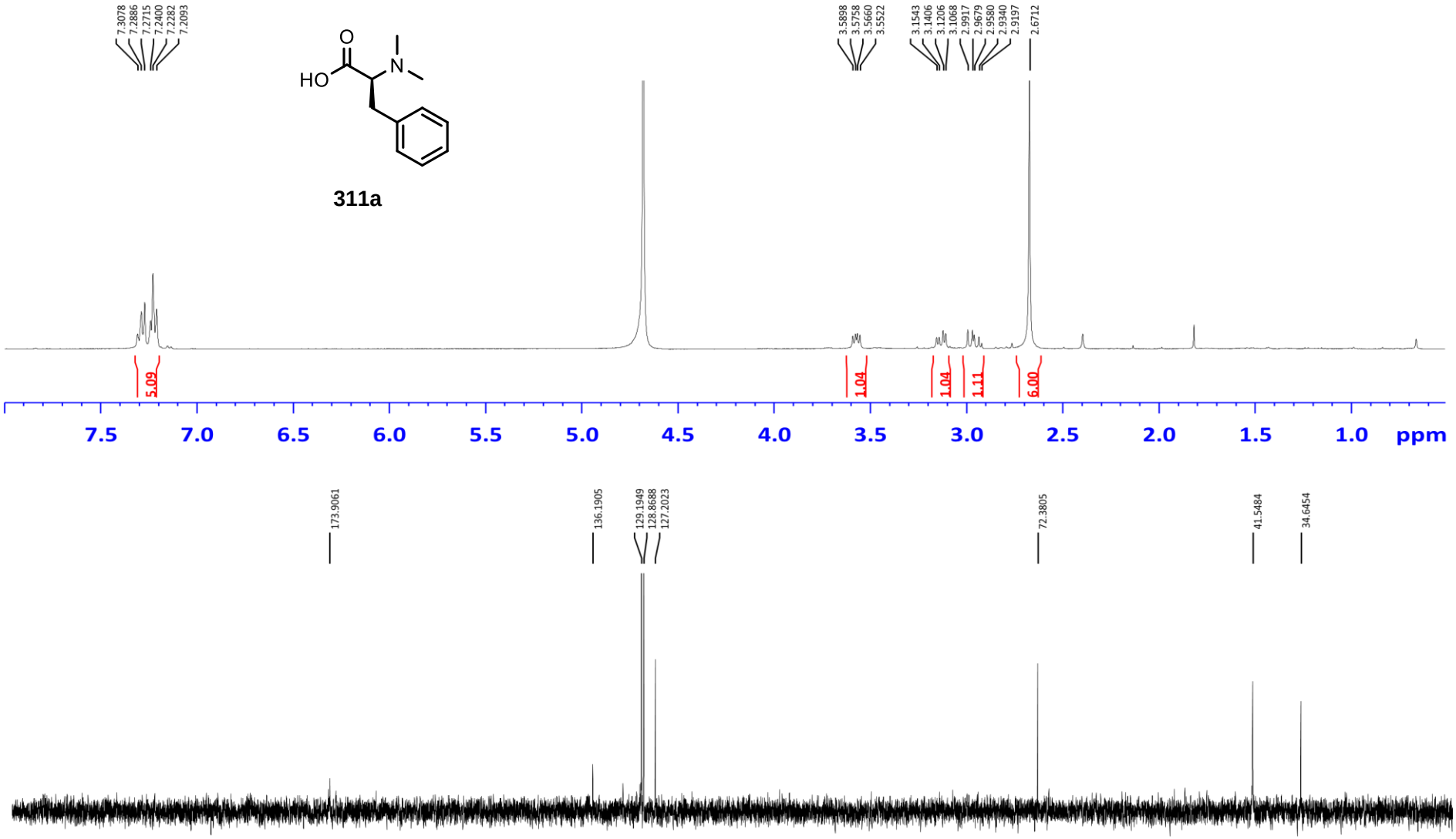
313m

^{1}H and ^{13}C NMR ($CDCl_3$)

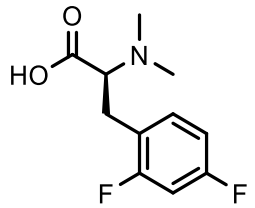


314l

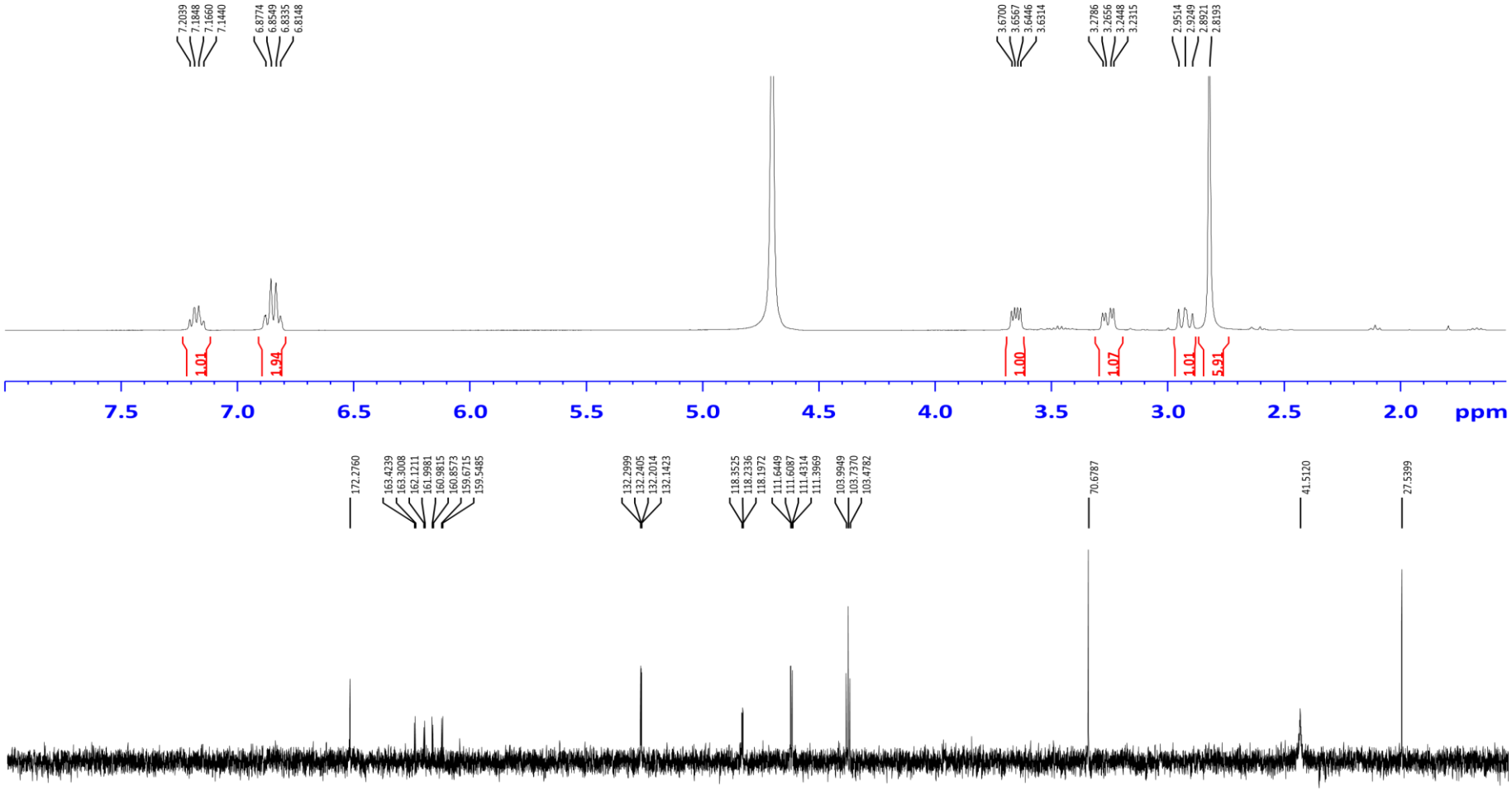
^{1}H and ^{13}C NMR (D_2O)



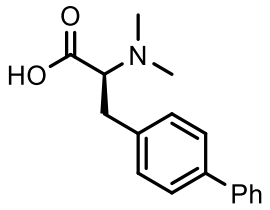
^{1}H and ^{13}C NMR (D_2O)



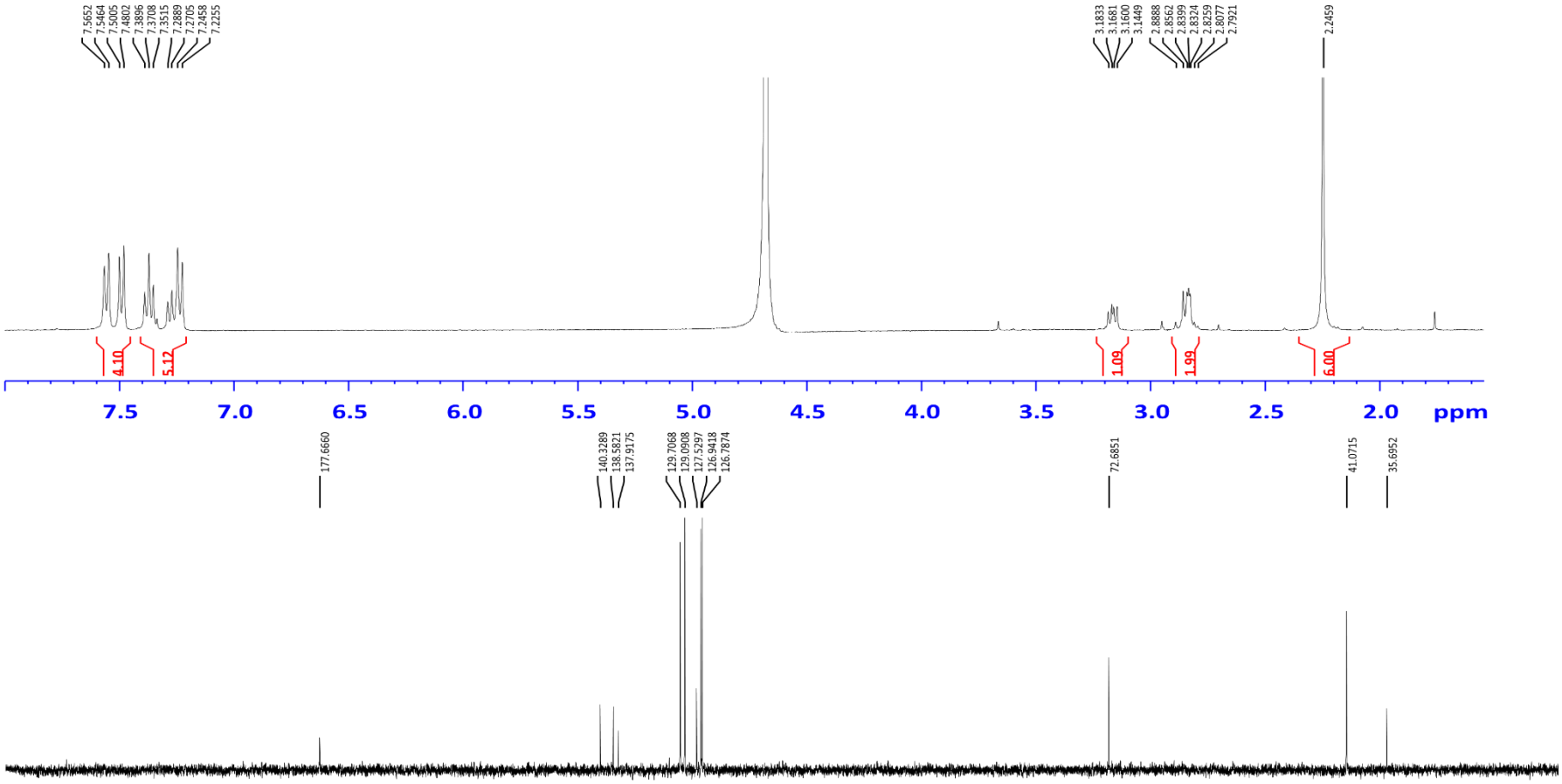
311b



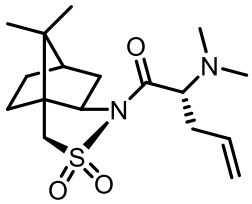
^{1}H and ^{13}C NMR (D_2O)



311c

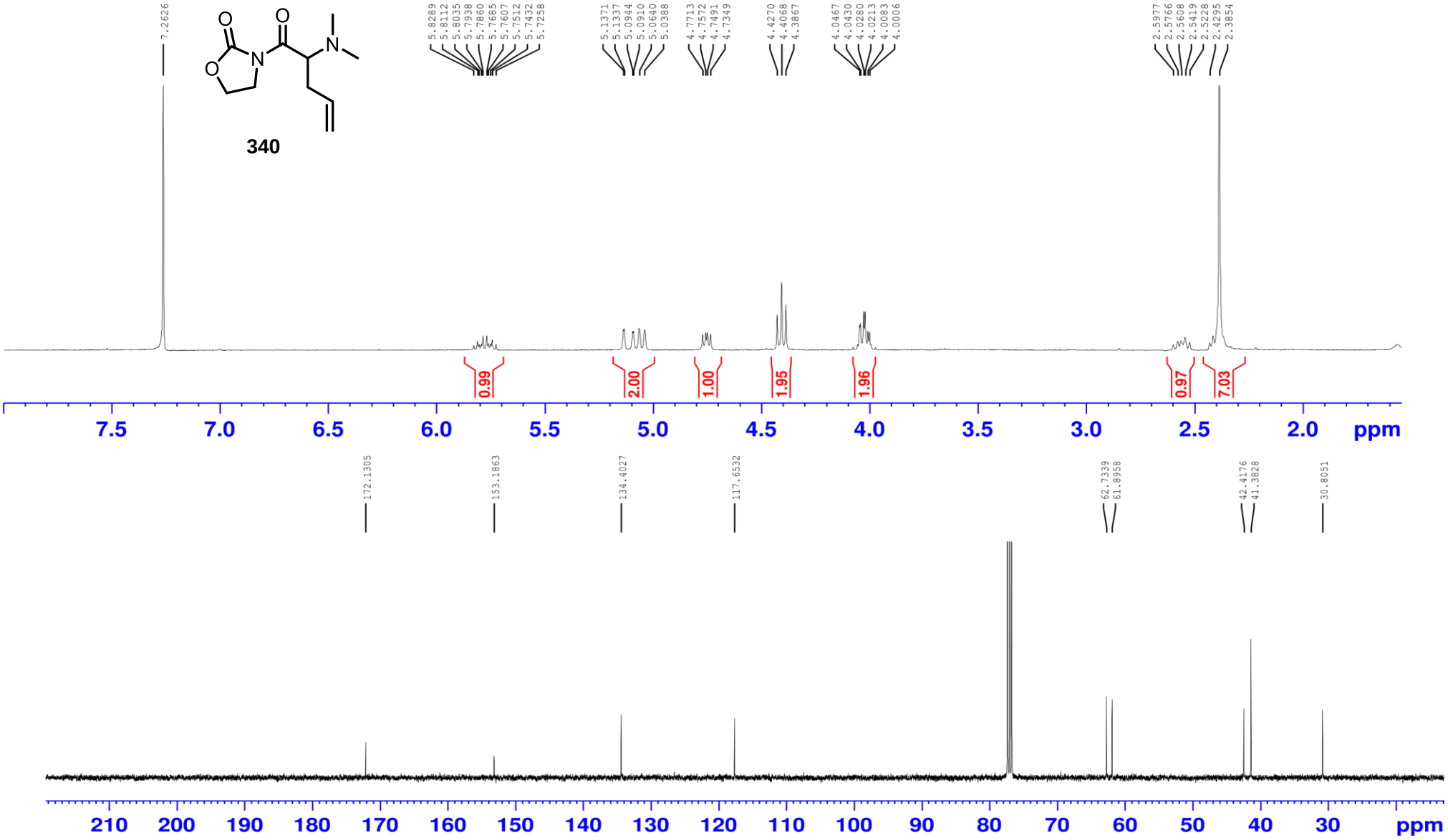


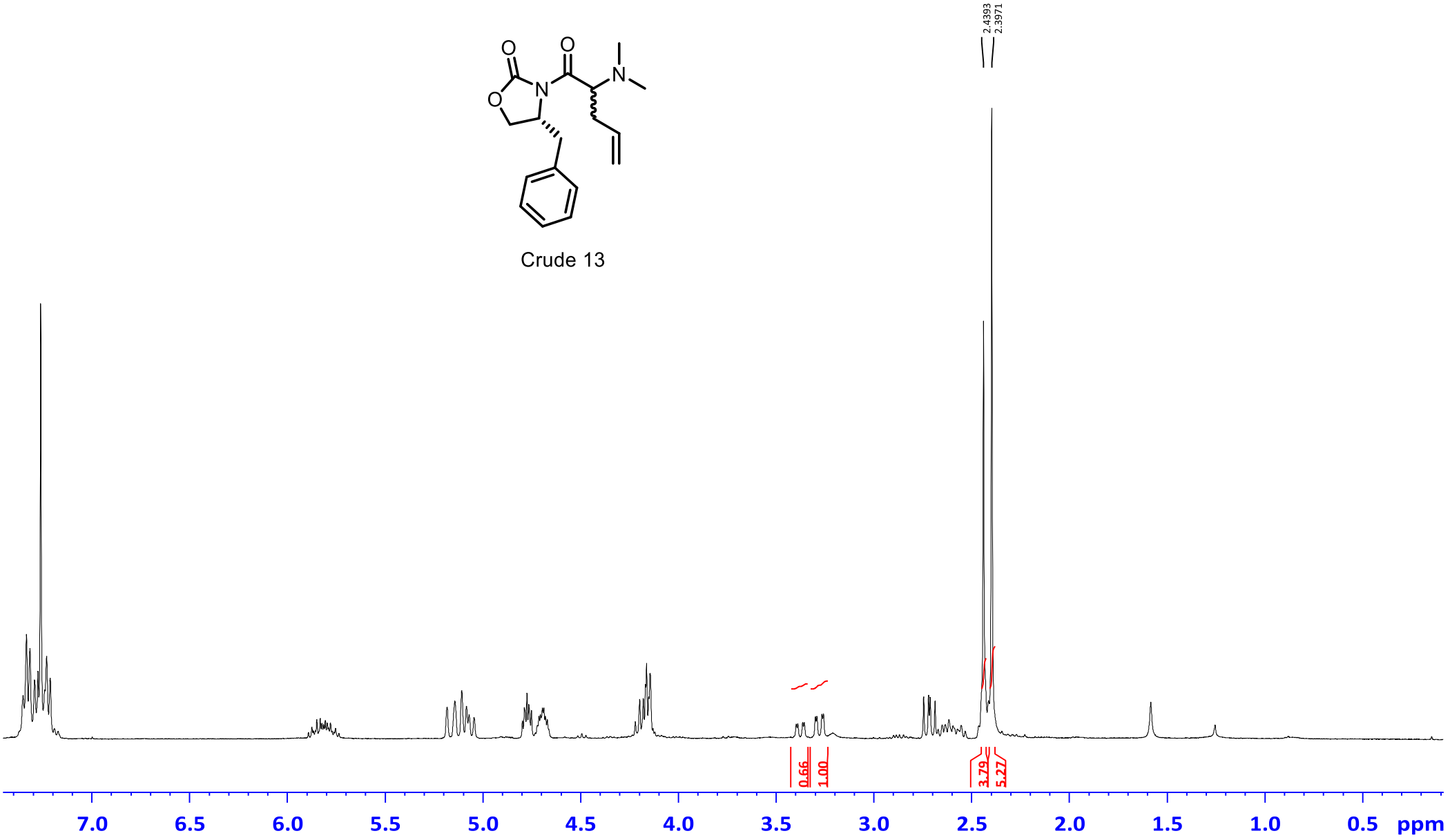
^{1}H and ^{13}C NMR ($CDCl_3$)



338a

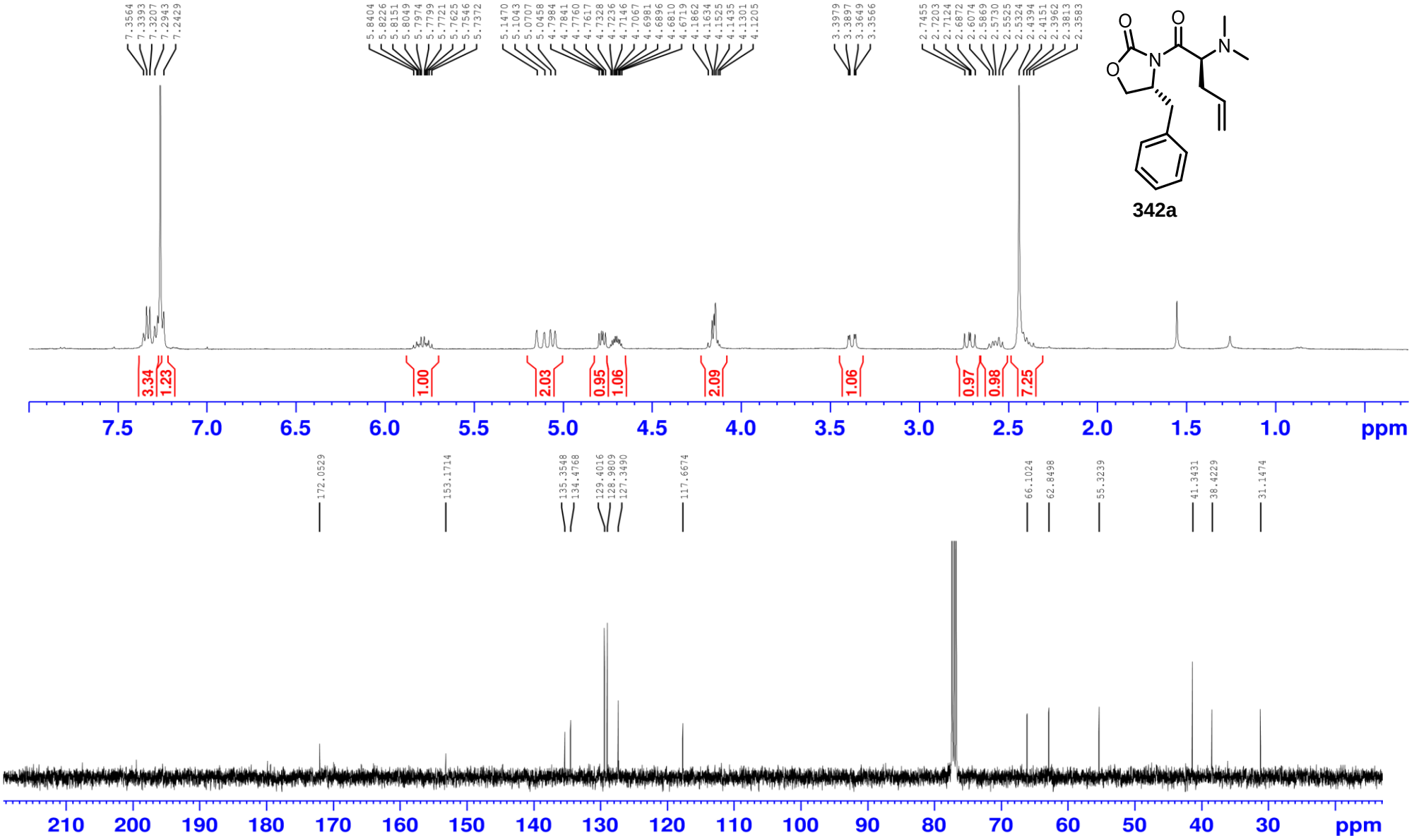
^{1}H and ^{13}C NMR ($CDCl_3$)



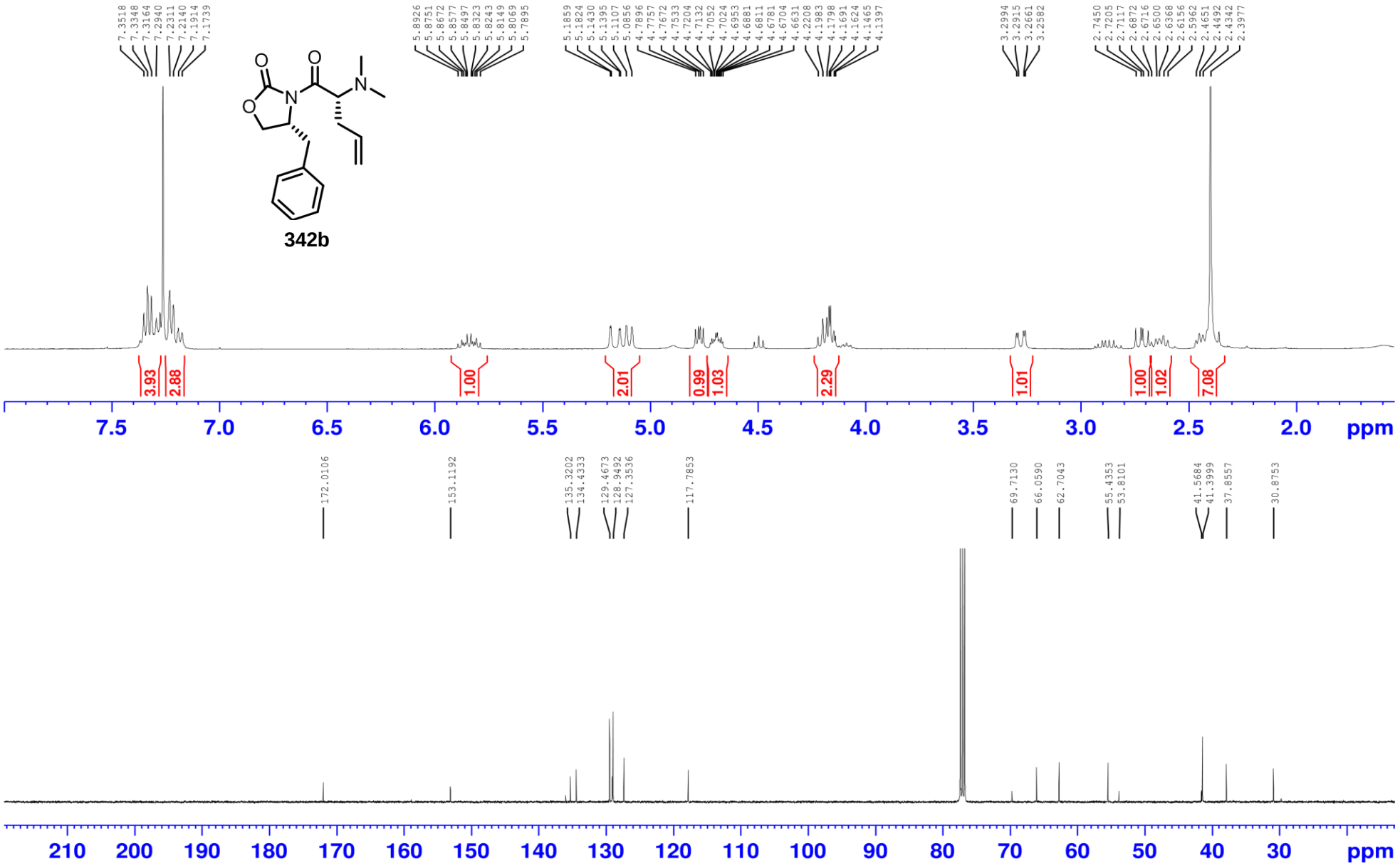

2.4393
2.3971
0.66
1.00
3.79
5.27
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

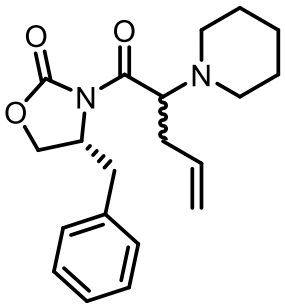
Crude 13

^{1}H and ^{13}C NMR ($CHCl_3$)

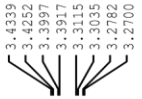


^{1}H and ^{13}C NMR ($CHCl_3$)





Crude 14

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Current Data Parameters
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PROCNO                       1

F2 - Acquisition Parameters
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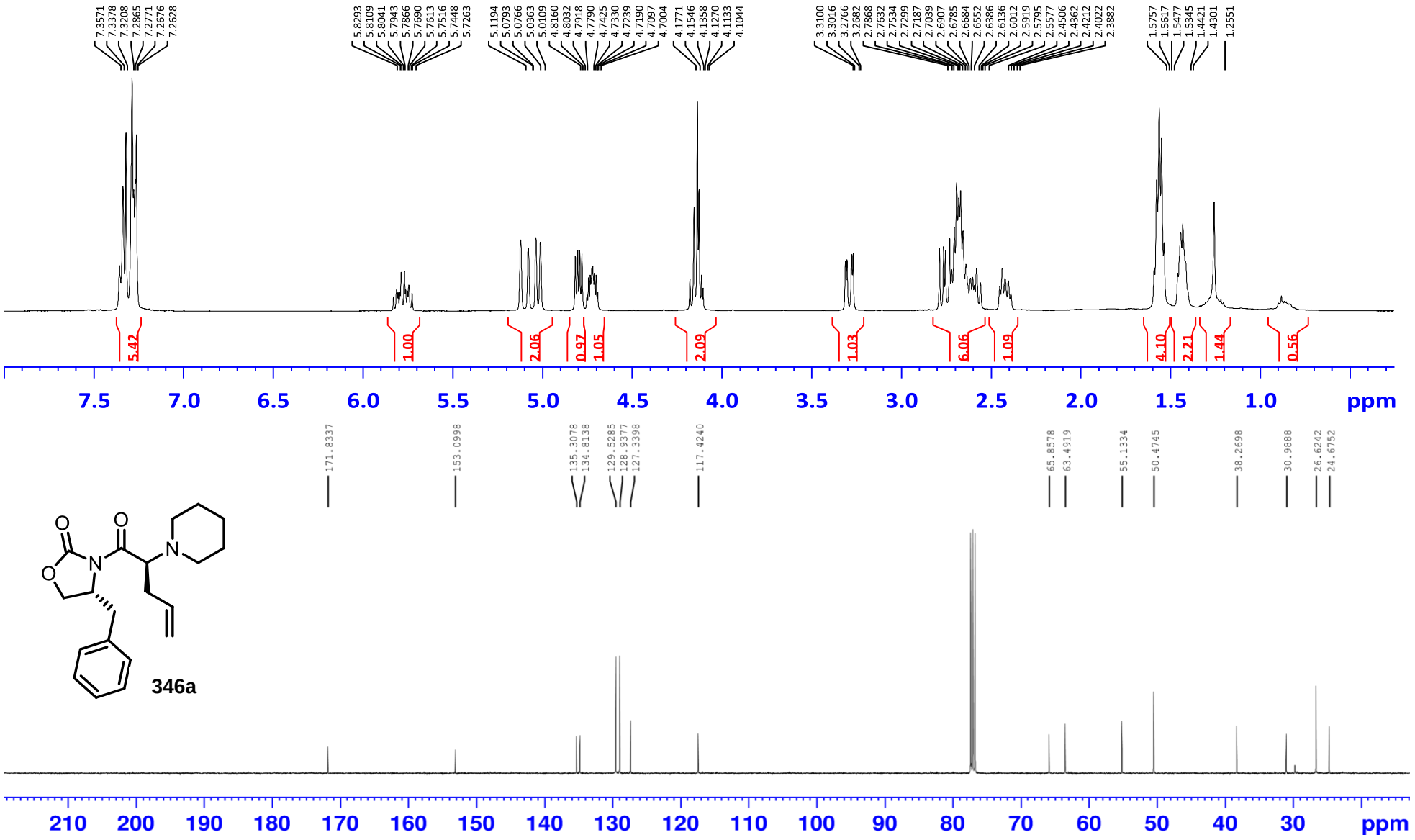
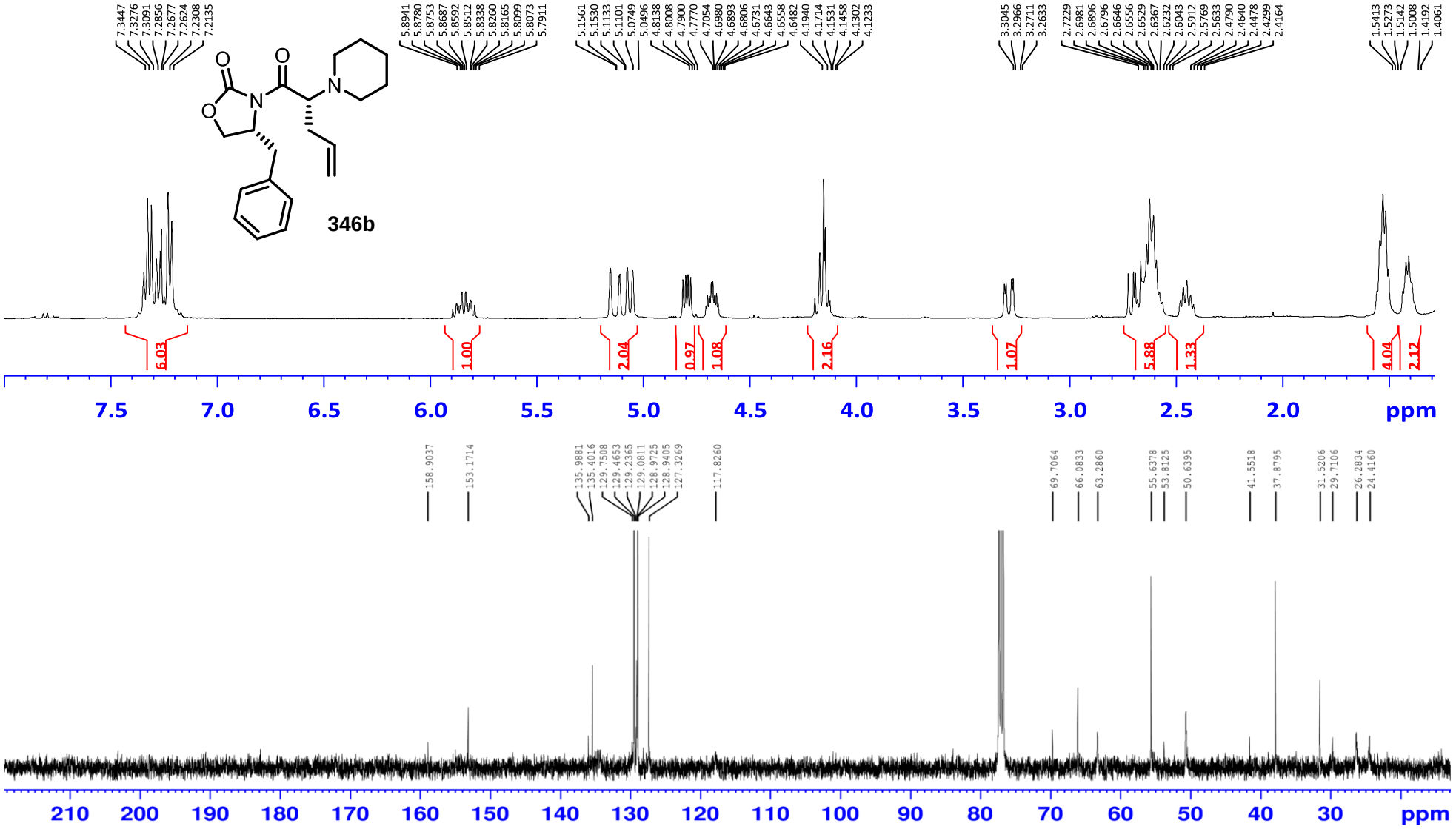
Time                     17.17 h
INSTRUM                  spect
PROBHD    Z116098_0048 (
PULPROG                  zg30
TD                      65536
SOLVENT                 CDCl3
NS                         16
DS                          2
SWH                   8223.685 Hz
FIDRES                0.250967 Hz
AQ                    3.9845889 sec
RG                       147.88
DW                       60.800 usec
DE                       10.69 usec
TE                       295.0 K
D1                  2.00000000 sec
TD0                          1
SFO1                400.1324710 MHz
NUC1                        1H
P1                       8.00 usec
PLW1               24.00000000 W

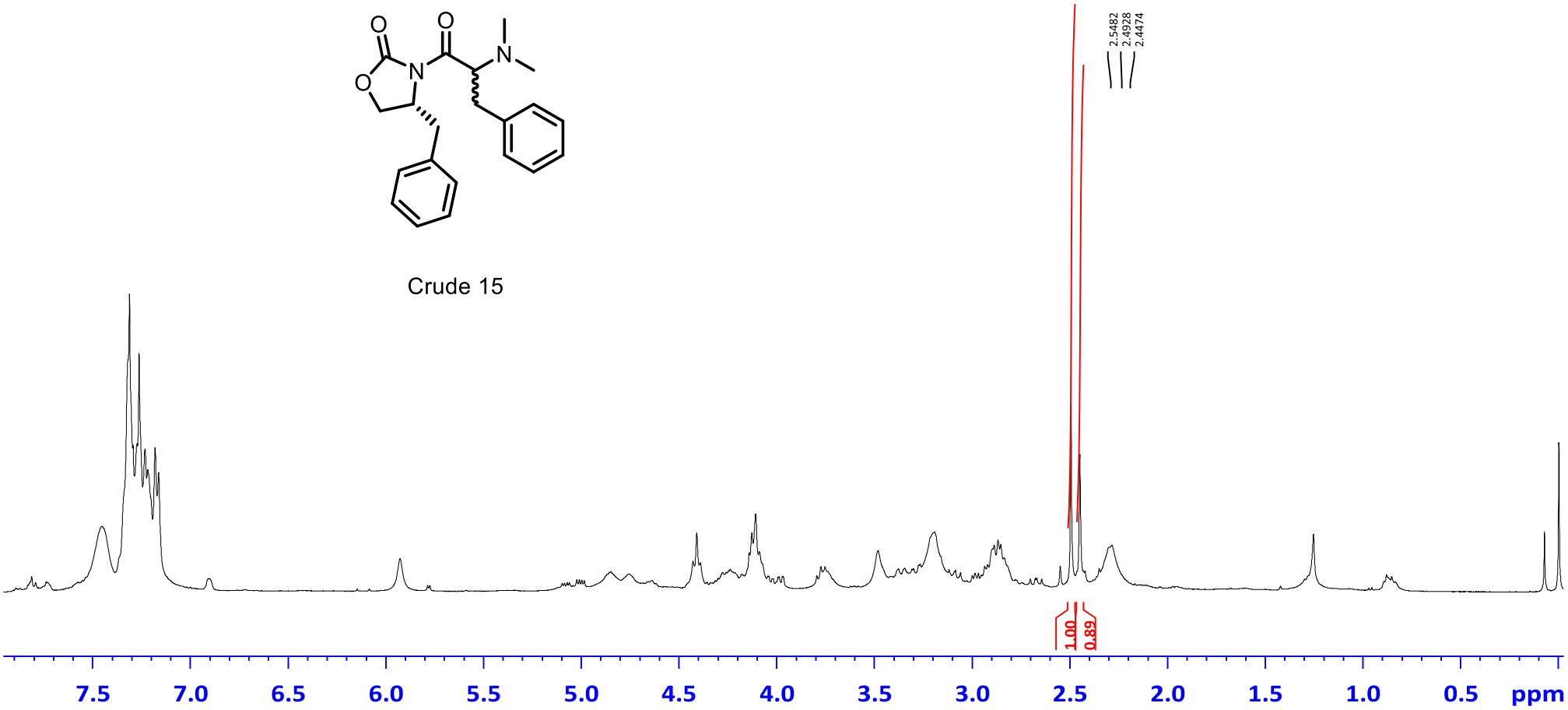
F2 - Processing parameters
SI                       32768
SF                  400.1300087 MHz
WDW                         EM
SSB          0
LB                       0.30 Hz
GB           0
PC                       1.50
```

^{1}H and ^{13}C NMR ($CDCl_3$)

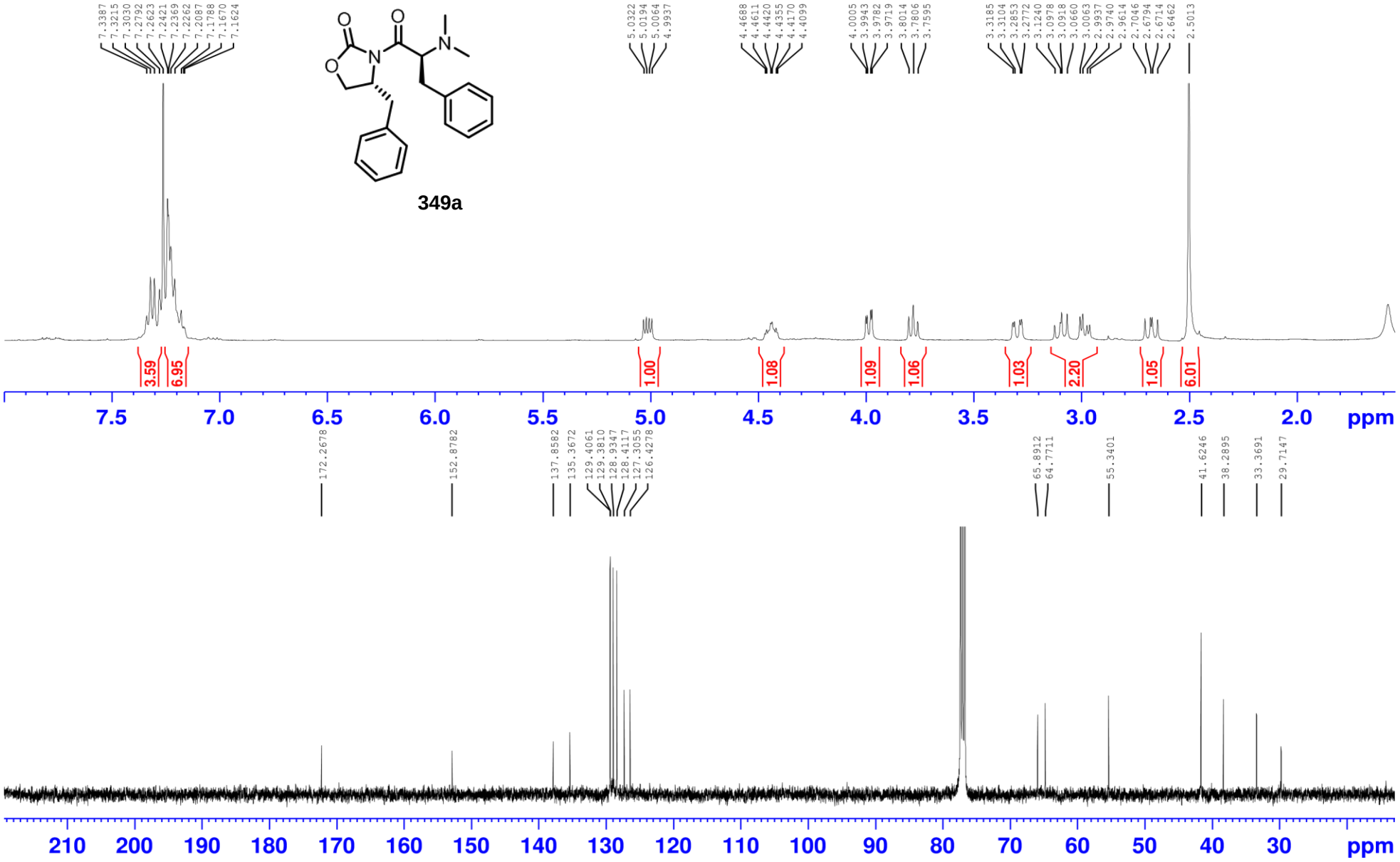


^{1}H and ^{13}C NMR ($CDCl_3$)



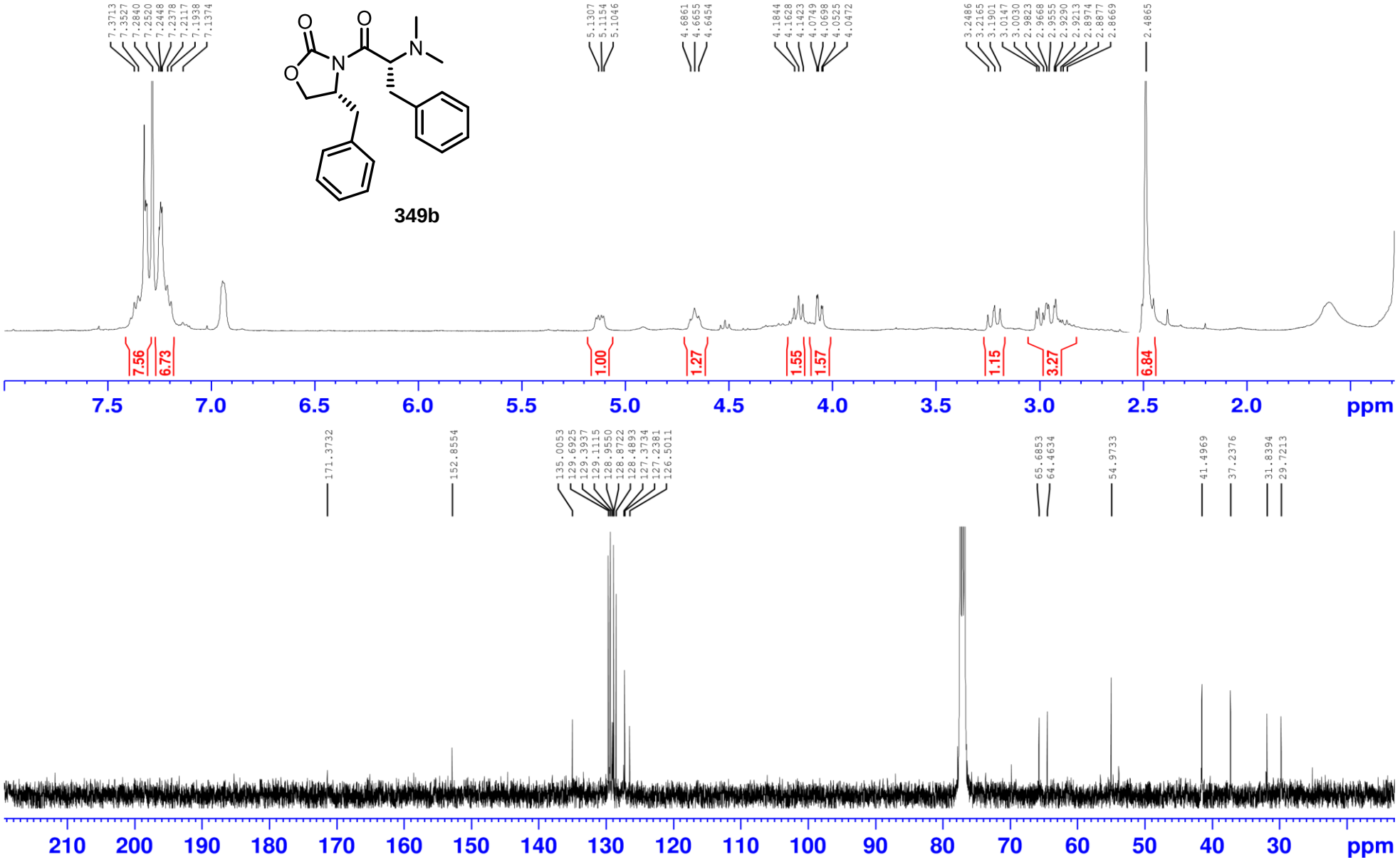

Crude 15
2.5482
2.4928
2.4474
1.00
0.89
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

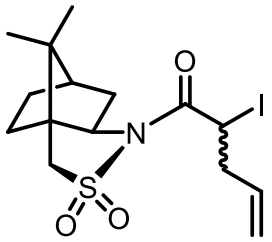
^{1}H and ^{13}C NMR ($CDCl_3$)



349a

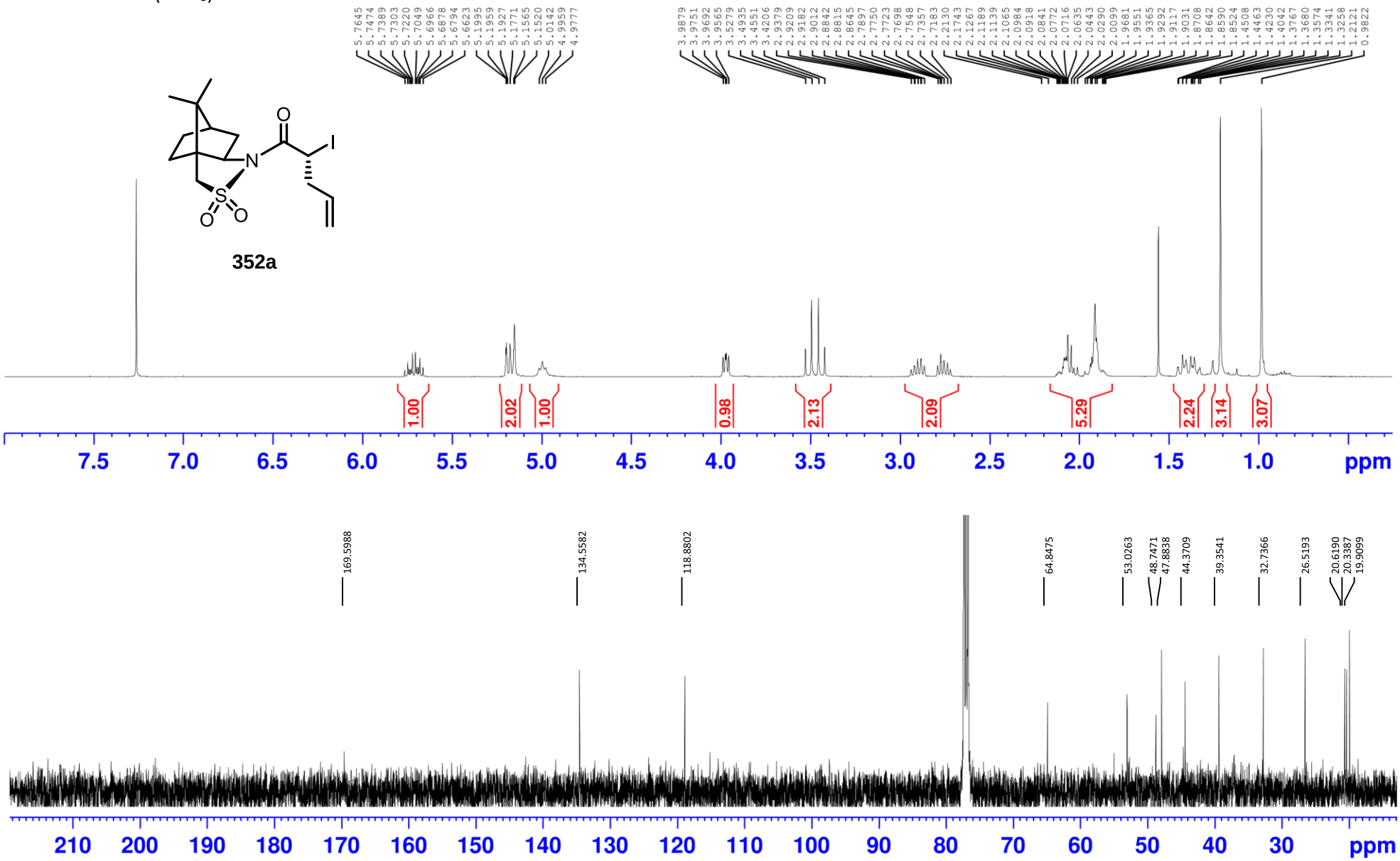
^{1}H and ^{13}C NMR ($CDCl_3$)



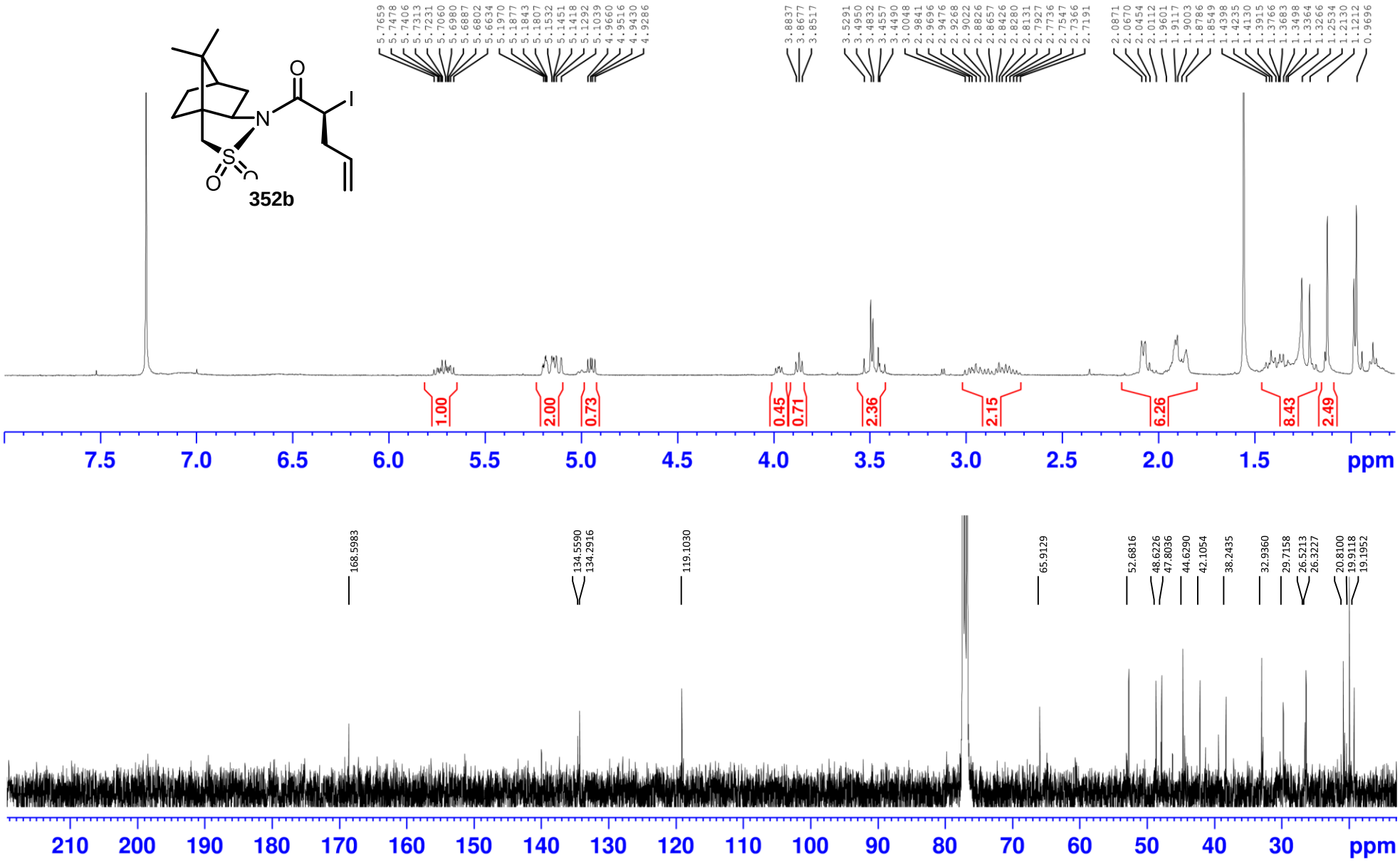


Crude 16

^{1}H and ^{13}C NMR ($CDCl_3$)

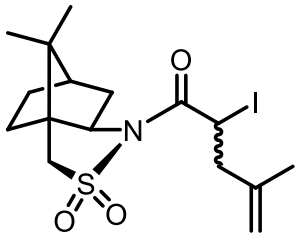


^{1}H and ^{13}C NMR ($CDCl_3$)



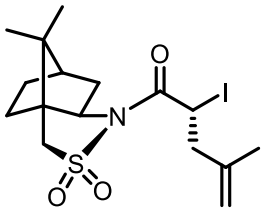
"Hm exp cam 12 R crude" 10 1 \\nas02\Stusapphome\u1151221\Desktop\NMR

Hm exp cam 12 R crude



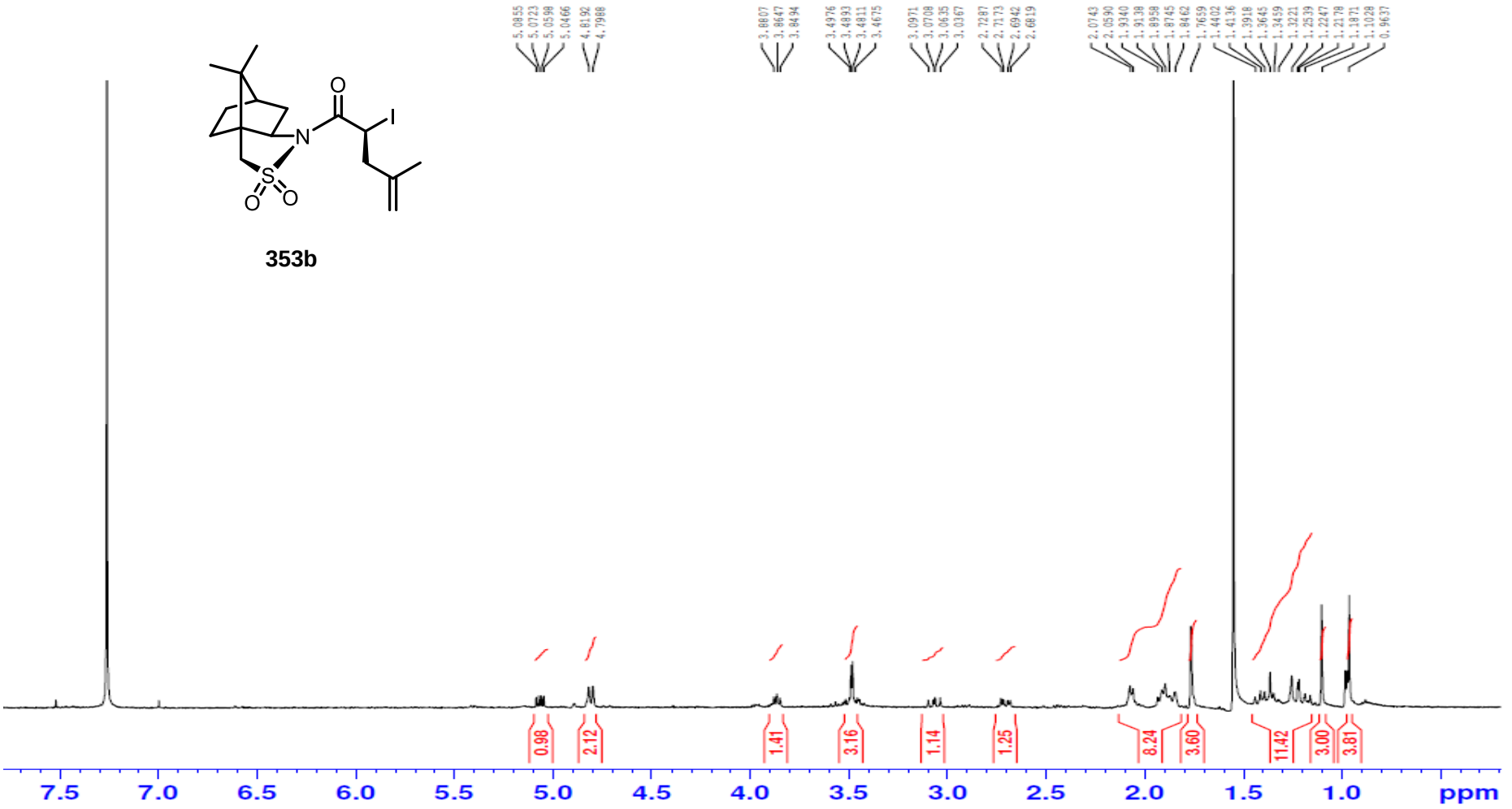
Crude 17

^{1}H and ^{13}C NMR ($CDCl_3$)



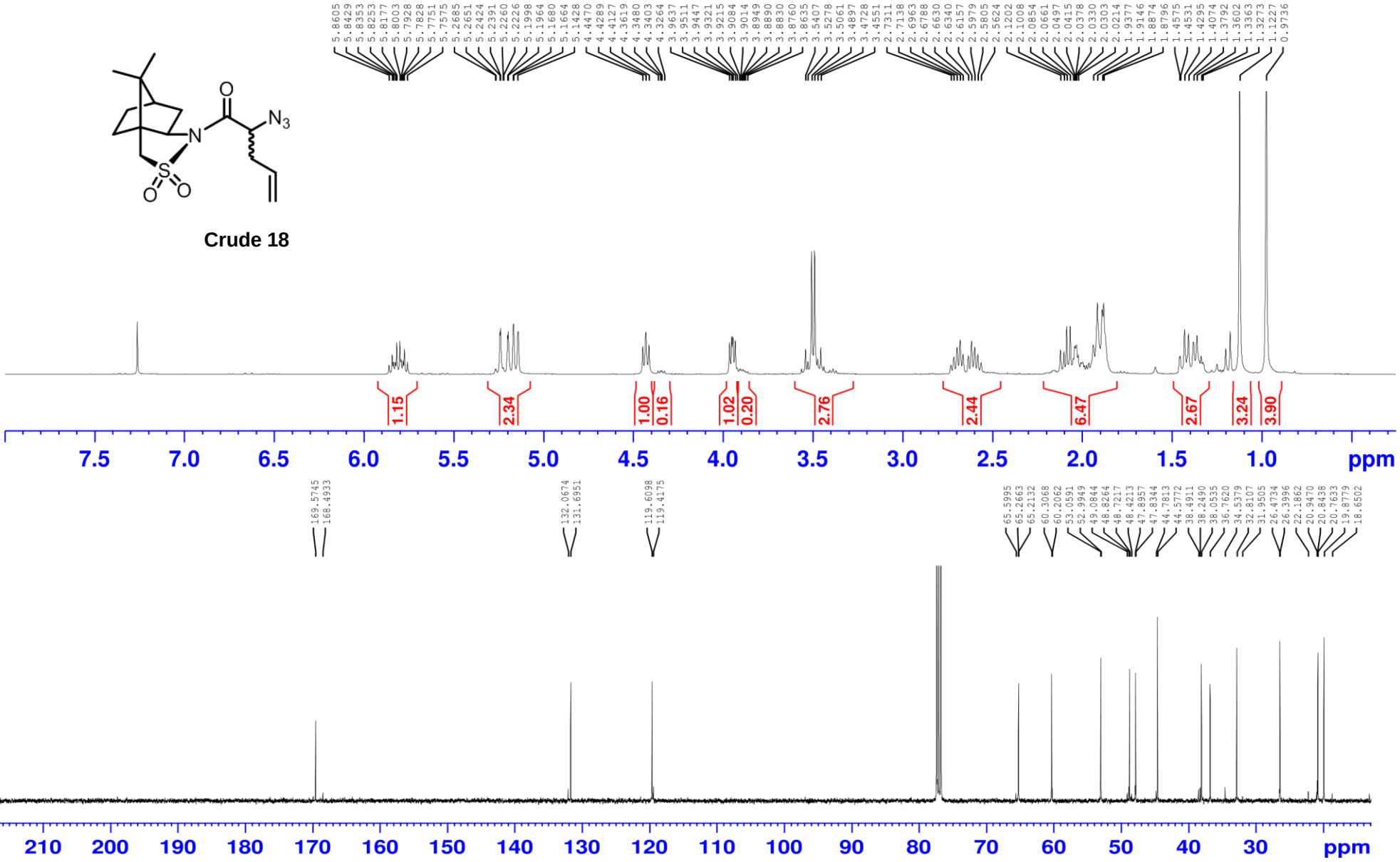
353a

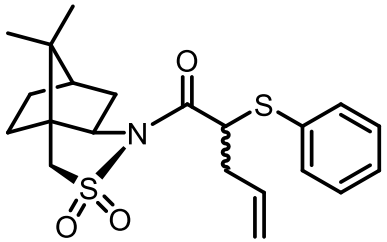
^{1}H and ^{13}C NMR ($CDCl_3$)



353b

^{1}H and ^{13}C NMR ($CHCl_3$)

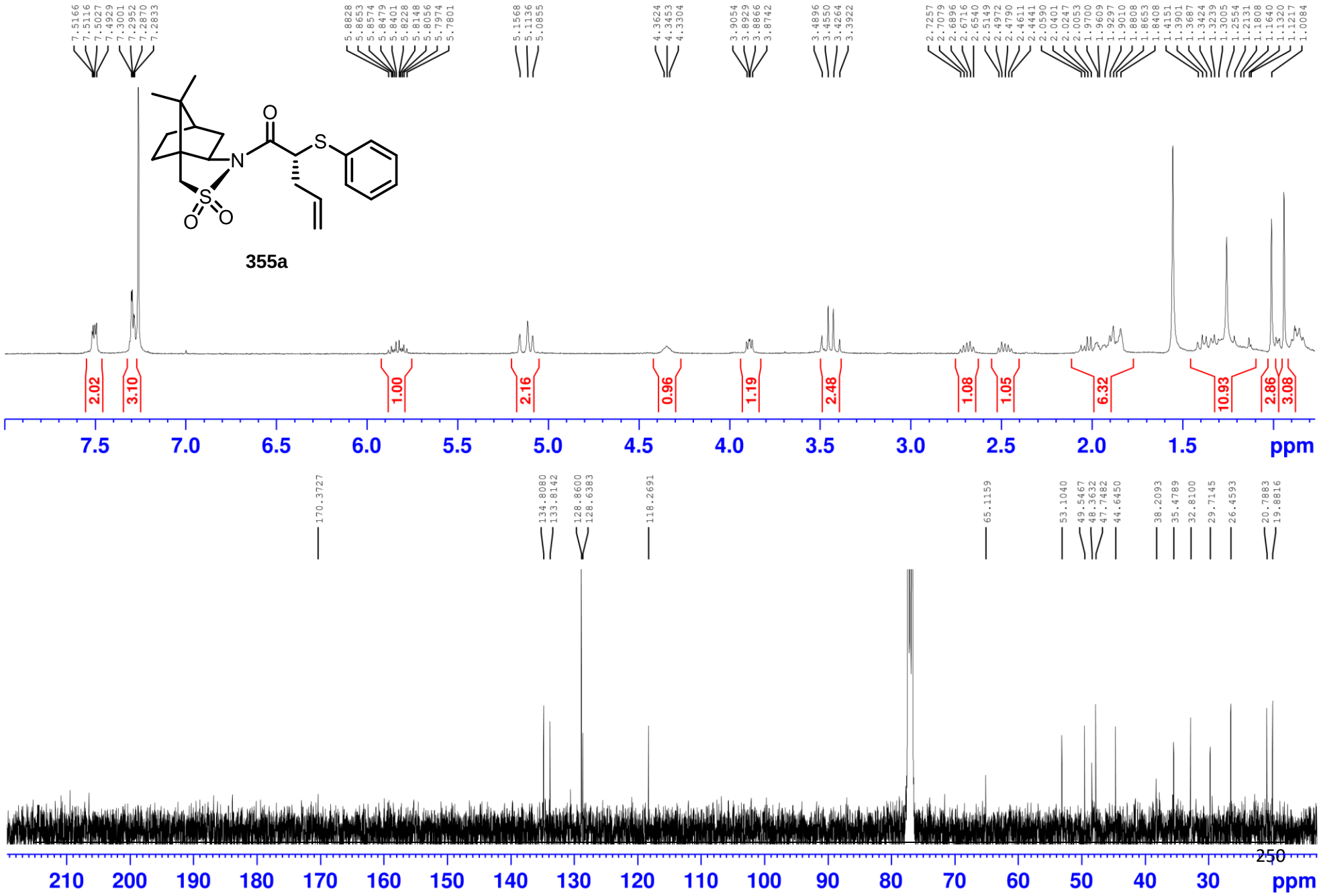



O
N
S
S
O
O

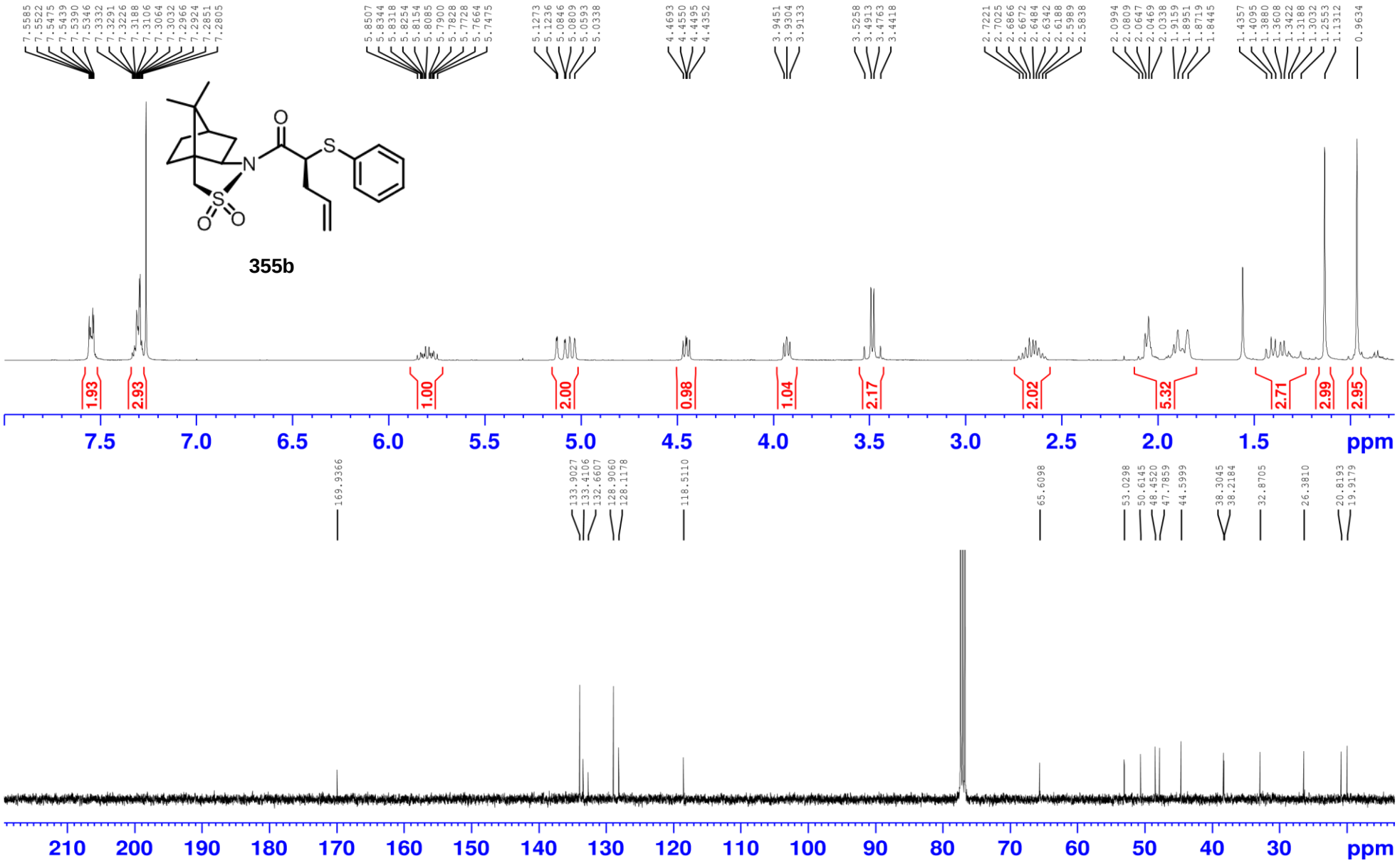
Crude 19

4.4660
4.4516
4.4463
4.4319
4.3423
1.00
1.10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

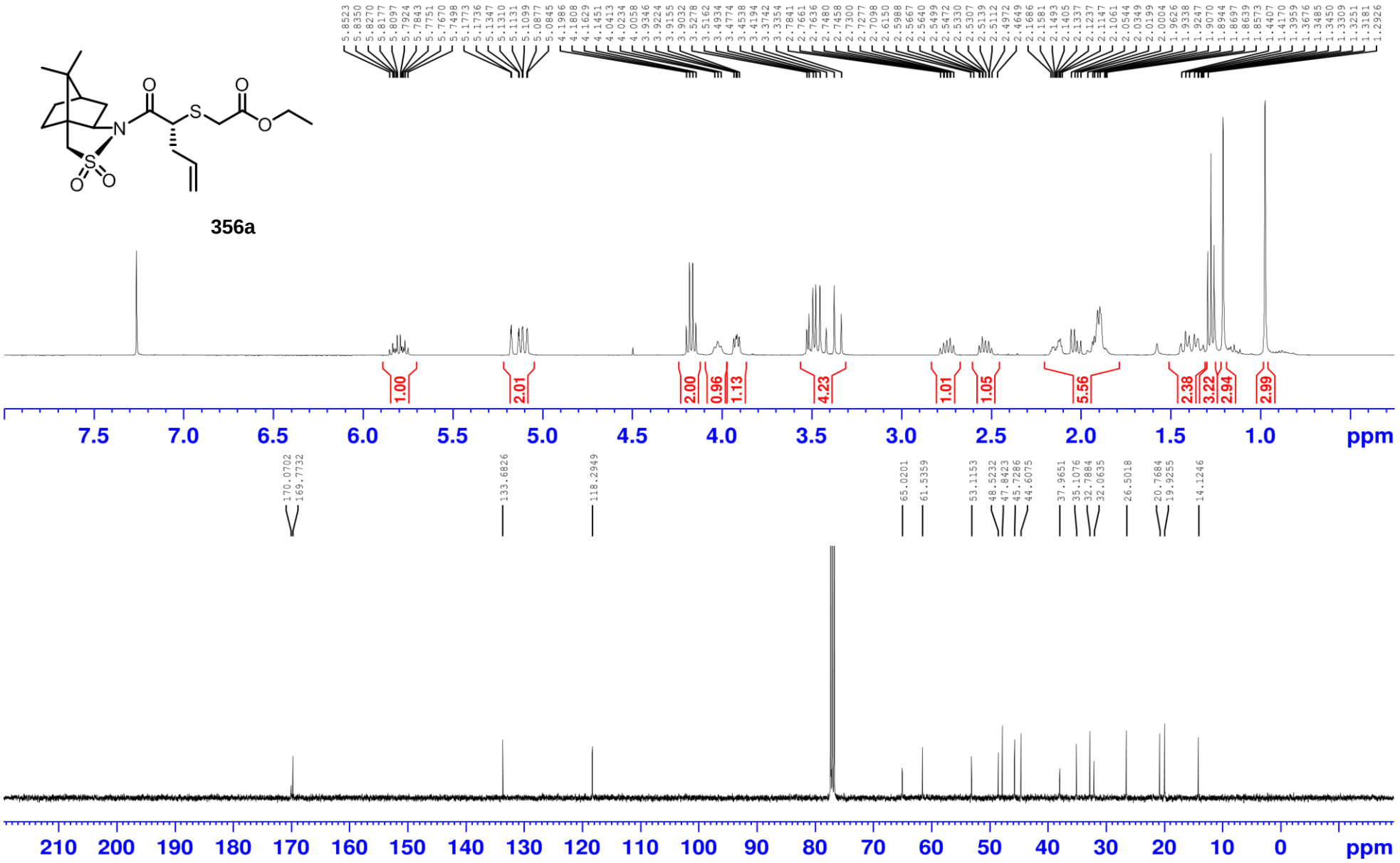
^{1}H and ^{13}C NMR ($CDCl_3$)



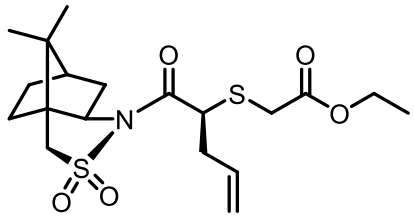
^{1}H and ^{13}C NMR ($CDCl_3$)



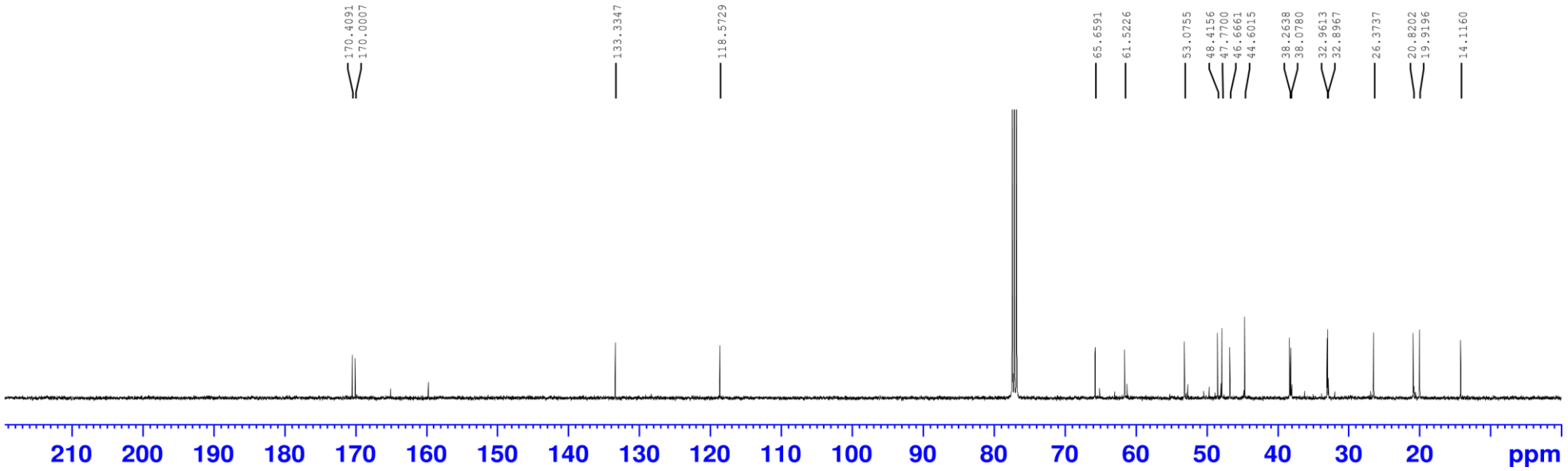
^{1}H and ^{13}C NMR ($CDCl_3$)

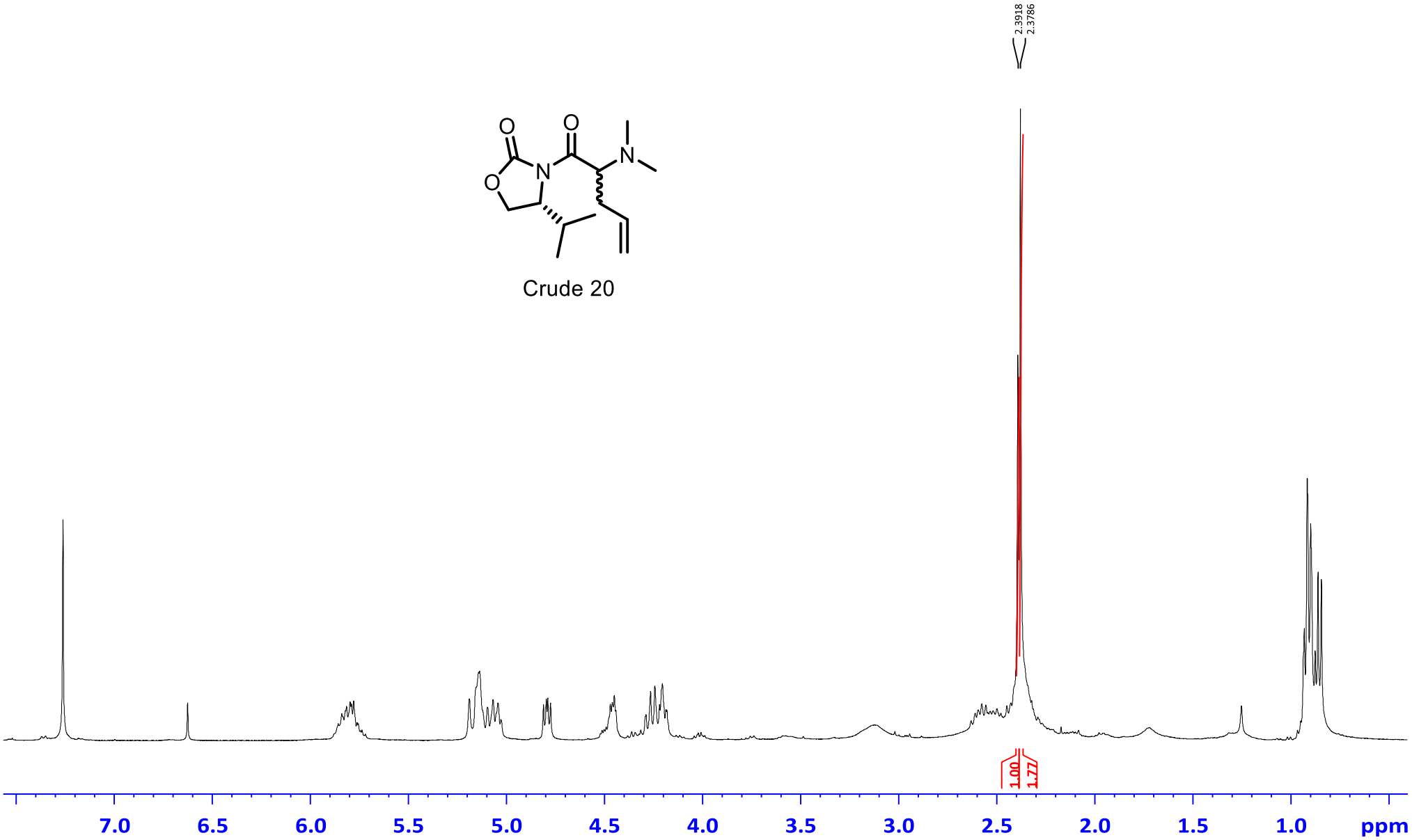


^{1}H and ^{13}C NMR ($CDCl_3$)



356b




2.3918
2.3786
O
O
N
N
O
Crude 20
1.00
1.77
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm