DESIGN AND SYTHESIS OF NOVEL CHIRAL BASE

by

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Dedicated to my family and friends.

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I'd like to thank my research advisor Professor Mark Lipton. His mentorship has allowed me to achieve the success that I have achieved today. He believes that graduate should be what you make of it. Regarding that, he lets his students research topics that interest them. He gives us space to conduct our research but is always available if we need any advice. He is concerned about his student's well-being and has taken us on ski trips, group dinners, and Christmas parties to ensure it. He has been a wonderful research advisor and mentor, and I couldn't have asked for better.

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µL	microliter
aq	aqueous
BMS	borane dimethyl sulfide
Boc	t-butyloxycarbonyl
cat	catalytic
d	doublet
DCC	N,N'-dicyclohexylcarbodiimide
dd	doublet of doublets
DIPEA	diisopropylethylamine
DMF	dimethylformamide
dp	doublet of pentets
dq	doublet of quartets
EDCI	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
EtOAc	ethyl acetate
EWG	electron withdrawing group
g	grams
GC	gas chromatography
h	hour
HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b] pyridinium-3-oxide hexafluorophosphate
HBTU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b] pyridinium-3-oxide hexafluorophosphate
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	hydroxybenzotriazole
Hz	hertz
J	coupling constant
LDA	lithium diisopropylamine

$LiAlH_4$	lithium aluminum hydride
M	molar
Me	methyl
MeCN	acetonitrile
MeOD	deuterated methanol
MeOH	methanol
Mg	milligrams
MHz	megahertz
mL	milliliters
mmol	millimoles
mp	melting point
MS	mass spectrometer
nBuLi	n-butyllithium
NMR	nuclear magnetic resonance
NR	no reaction
OMe	methoxy
o/n	overnight
pd	pentet of doublets
PyBOP	(benzotriazol-1-yloxytripyrrolidinophosphonium) hexafluorophosphate
qd	quartet of doublets
RT	room temperature
s	singlet
t	triplet
td	triplet of doublets
THF	tetrahydrofuran
TFA	trifluoracetic acid
TLC	thin-layer chromatography
TMS	trimethysilyl
TMSCl	trimethylsilyl chloride

ABSTRACT

In organic synthesis, controlling stereochemistry can be a challenge whether you are working with small molecules or larger natural products. Current chiral bases, such as Sparteine, are difficult to make or expensive to purchase. Their other drawback is that many chiral bases only can access one stereochemical configuration, not both. In the work presented here, progress has been made towards developing a chiral base from an amino acid derivative, L-valine. The chiral base has been fully synthesized. The use of the amino acid starting material, allows for us to make both the R and S selective amino acid. Efforts are being made to determine the efficacy of the base to control stereochemistry.

CHAPTER 1. DESIGN OF A NOVEL CHIRAL BASE

1.1 Introduction to Chiral Bases

Stereogenic carbons are important features in the synthesis of many drugs and natural products.[1,2,3] Often in nature, enzymes selectively interact with only one stereoisomer of a given ligand. When building libraries for screening potential drug candidates, all stereoisomers are considered and must be synthesized to determine the most effective inhibitor.[2,3] Additionally, enantiomers tend to be difficult to separate by standard purification methods. Thus, the ability to conduct a stereoselective synthesis is essential to organic chemistry.[2] A variety of approaches have been taken to accomplish this; one such method is the use of a chiral base. Chiral bases involve a basic functional group nearby a stereocenter with a bulky substituent, effectively only allowing the removal a proton from one face of a prochiral or achiral substrate.

The biggest problem with lithium diisopropylamide is its inability to remove the proton stereoselectivity, resulting in racemic mixtures. Chiral bases provide an alternative pathway to stereoselectivity. By using a chiral base, the proton can be stereoselectively removed, which can result in a chiral product (Figure 1-1).[4]

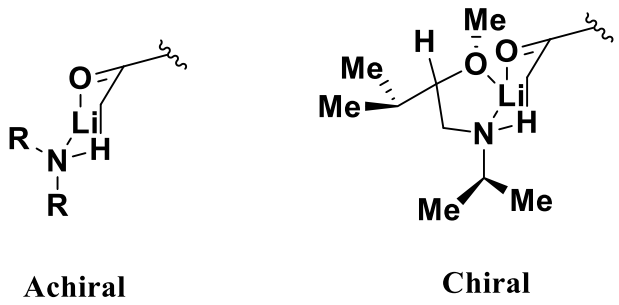


Figure 1-1: Unbiased vs. Selective Deprotonation of Achiral and Chiral Base Transition State

A common chiral base is sparteine. Sparteine is a natural product that is derived from bitter lupine seed in 1851, but its total chemical synthesis was achieved in the late 1940's by Nelson and Beyler from the University of Illinois.[4,5,6] In the 1950's, several other papers were published by Nelson and Arnet explaining other synthetic strategies to produce sparteine.[4,6]

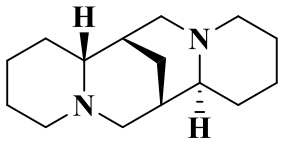


Figure 1-2: Structure of (-)-Sparteine

Scientists were able to show that they could form a chiral product with over 95% ee.[5] Major problems with sparteine include a lengthy synthesis and difficulty accessing the other enantiomer.[6] The synthesis of sparteine starts with L-lysine, a natural amino acid.[5]

Since lithium diisopropylamide has been used successfully to exhibit achiral behavior, researchers have developed chiral lithium amides. In 1980, Whitesell and Felman were able to demonstrate enantioselective deprotonation with chiral lithium amide bases.[7] Their work showed moderate enantioselectivity, but they noticed that the highest levels of asymmetric induction involved compounds with enhanced steric bulk. Hodgson and Gibbs[8,9] took the research a bit further, and began to test other chiral lithium amides, including proline, which is also an amino acid. Unfortunately, they are only able to use the (S) enantiomer.

In our work, we hope to also use an unhindered amino acid as a building block to access a chiral base through a more concise synthesis, but also use the design of the chiral lithium amides to take advantage of the simplicity of testing conditions.

1.2 Design of Novel Chiral Base

The design of our material draws inspiration from lithium diisopropylamide following the general guidelines of chiral base structure. To mimic diisopropylamide, our goal is to have two isopropyl groups on each side. The isopropyl groups will act as our bulky substituent. There will be a stereocenter near the amine. The stereocenter will need to have and a chelating group (X) to stabilize the other hydrogen on the same face. Figure 1-2 shows the general design of what the ideal chiral base should look like.

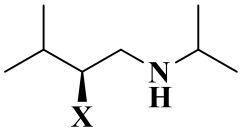
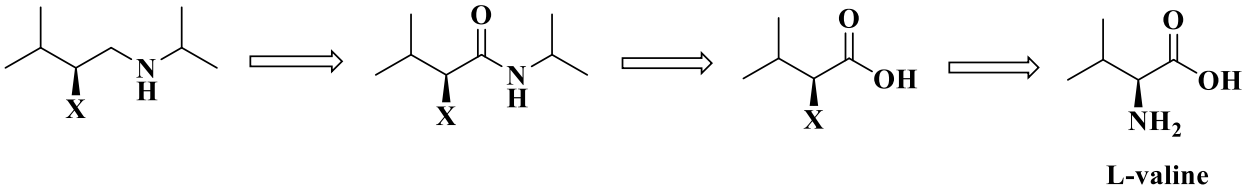


Figure 1-3: General Design of the Chiral Base

The ideal starting materials is an unhindered amino acid. This will allow for both the R and S enantiomers to be formed depending on the stereochemistry of the original amine. When examining the compound retrosynthetically, we determined the amino acid we should use is L-valine (Scheme 1-1).

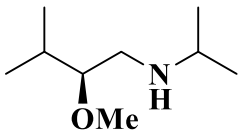


L-valine

Scheme 1-1: Retrosynthetic Analysis of Target Chiral Base

L-valine is the ideal molecule since one of the bulky isopropyl substituents is already present. The other half of the molecule could be converted into an amide with isopropylamine and then reduced to the target base.

The chelating agent can be introduced early on. Since having two amines would not be conducive to our focus, the original amine in valine needs to be converted. The material can be converted to an alcohol using a diazotization/ hydrolysis reaction. The resulting hydroxyl group is both an electron donor and acceptor, and our target base needs to only have a chelating ligand. By converting the alcohol into an ether, we can access a chelating ligand that is only an electron donor. This approach led us to the target chiral base molecule shown in Figure 1-4.



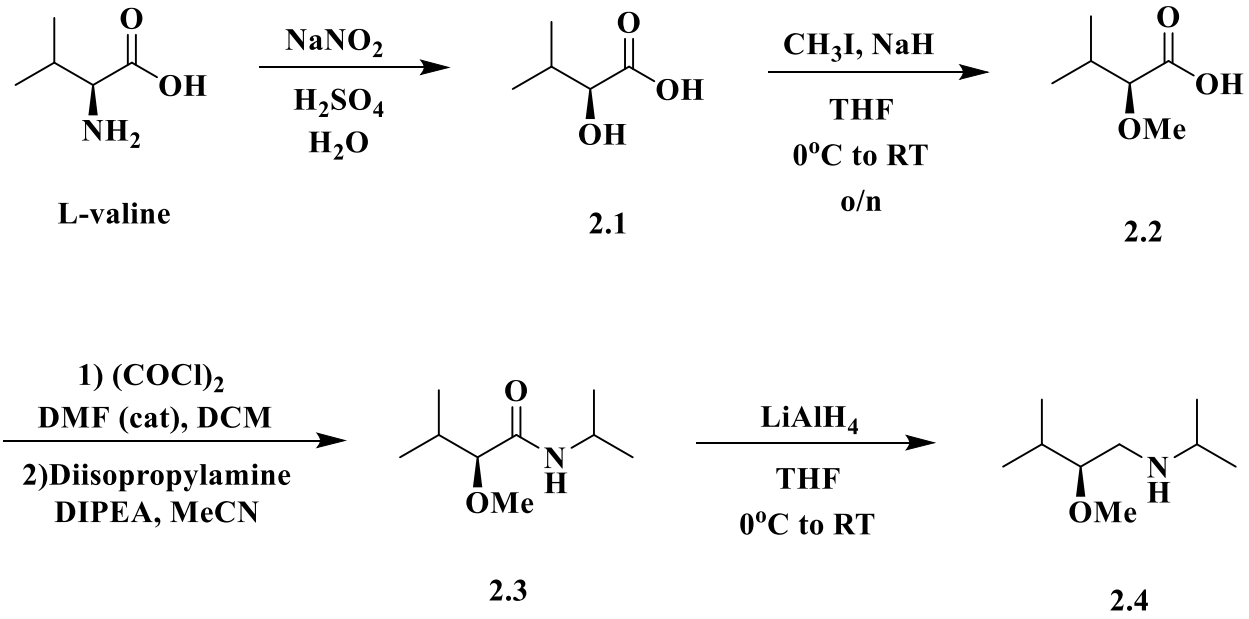
Target Chiral Base

Figure 1-4: Final Design of Target Chiral Base

CHAPTER 2. SYNTHESIS OF A NOVEL CHIRAL BASE

2.1 Initial Approach of the Synthesis

When we first began our approach, we had decided to use L-valine as our starting material. It mimics half of diisopropylamine, which is our achiral amine, with the isopropyl group already present. Our original approach involved converting the amine on L-valine into a hydroxyl group by a diazotization reaction. Compound **2.1** would be subjected to Williamson ether conditions to form the ether group. Compound **2.2** could then be converted into the acid chloride, which would then react with isopropylamine. This would install the other isopropyl group and give use compound **2.3**. The amide (**2.3)** would be reduced with $LiAlH_4$ to result in compound **2.4**, which is our target amine. This theoretical approach is summarized in Scheme 2-1.

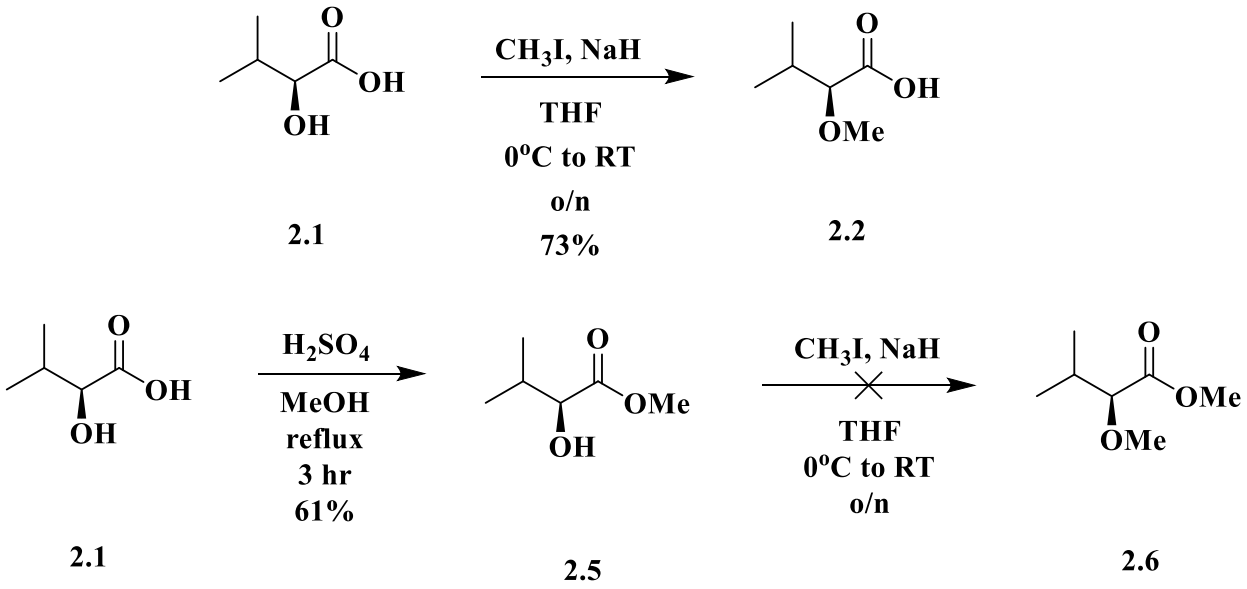


Scheme 2-1: Initial Approach to Form the Chiral Amine

We discovered that we could purchase compound **2.1**, so the need to synthesize it was unnecessary.

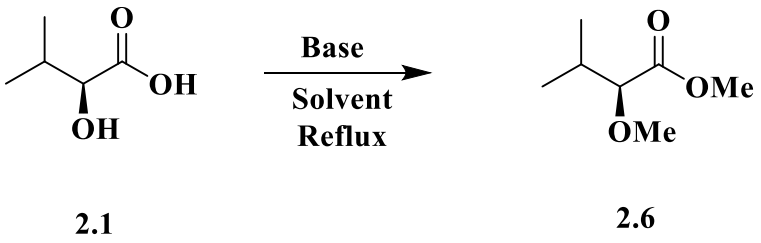
2.2 Synthesis of the Ether

One of the main reactions was the synthesis of the ether group on carbon two. Our first approach was to use Williamson ether synthesis reaction conditions (Scheme 2-2).[10] The Williamson ether synthesis conditions provided a 73% yield of compound **2.2.** The product was a light-yellow oil. The first few times the reaction was run, the NaH was not rinsed with hexanes, which may have negatively impacted the reaction. This led us to look at alternative routes. Later, the same conditions were tried again, but the NaH was washed and there was an improvement in yield from less than 10% to 73%. The reaction continued to go forward smoothly and worked, even on a large scale.



Scheme 2-2: Williamson Ether Synthesis and Fisher Esterification

Another approach was taken early on (Scheme 2-2). Compound **2.1** was subjected to a Fisher esterification[11,12], then the Williamson ether conditions were examined to see if the overall yield would be improved. The yield of the Fisher esterification was 61%**.** Compound **2.5** was then subjected to Williamson etherification conditions, but compound **2.6** was not formed.



2.1 **2.6**

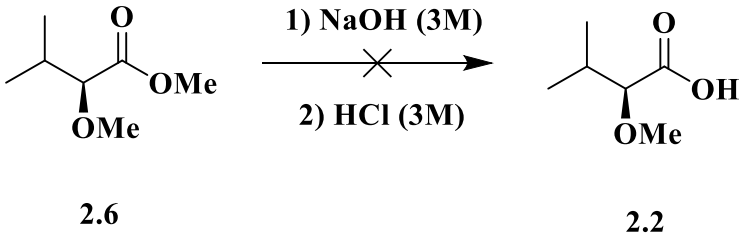
Scheme 2-3: Formation of the Methyl Ester and Ether Simultaneously

The other alternative, was to form the ether and the ester simultaneously (Scheme 2-3). Compound **2.1** was subjected to the conditions summarized in table 2-1.

Table 2-1:Screening conditions for simultaneous synthesis of methyl ester and ether

Base	Solvent	Yield (%)
K_2CO_3	MeCN	NR
K_2CO_3	DMF	NR
Cs_2CO_3	MeCN	<12
Cs_2CO_3	DMF	15

We discovered that K_2CO_3 was not a strong enough base for these reaction conditions, but Cs_2CO_3 was sufficient. When the reaction was run in MeCN, there was formation of the some of the product, but the ^{1}HNMR showed that the product was not pure. The same issue occurred when the reaction was run in DMF. Removing the DMF proved to be nearly impossible. Yields were very low, once the product was able to be purified, and did not get over 15%. Heating the reaction to reflux did not result in an improved yield. With compound **2.6**, we attempted to saponify to reform the carboxylic acid (Scheme 2-4).[13]



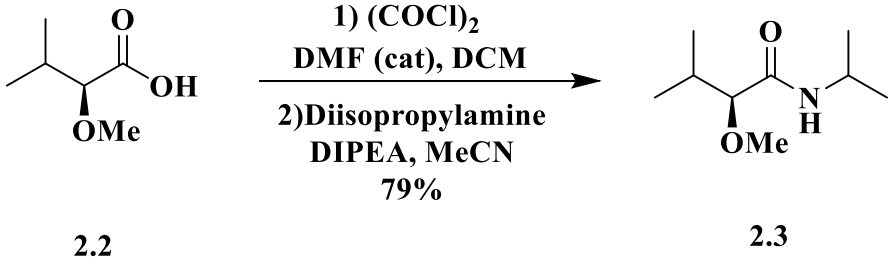
2.6 **2.2**

Scheme 2-4: Saponification of Methyl Ester **2.6**

The saponification of **2.6** did not result in formation of compound **2.2**. This may have been due to the small amount of starting material used. In the end, the Williamson ether conditions provided us with the original product (**2.2)** we had targeted, so we continued forward with that method.

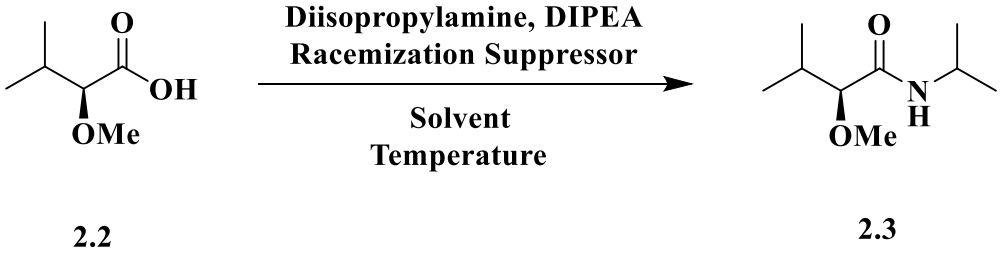
2.3 Formation of the Amide

The next step in our synthesis was to form the amide. Using the compound **2.2**, we looked at two pathways to form the amide (**2.3**). The first approach was to form the acyl chloride, followed by the subsequent addition of the amine (Scheme 2-5).[14] The product produced was a colorless solid in 70-80% yield. The product had a melting point of 39-41°C.



Scheme 2-5: Conditions for Acid Chloride Coupling

The other approach was to use coupling reagents in a one-step approach. The goal was to simplify the overall synthesis of the material (Scheme 2-6).[15]



Scheme 2-6: General Reaction for the Synthesis of Amide **2.3**

We attempted to use several coupling agents: EDCI, DCC, HATU, HBTU, and PyBOP (Table 2-2). To suppress racemization, HOBt and HOAt were used.

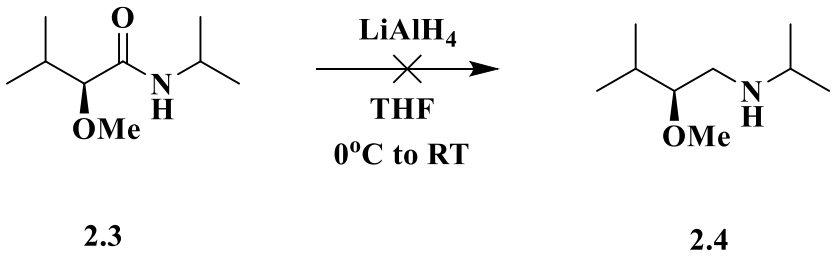
Table 2-2. Table of Amide Coupling Conditions

Coupling Agent	Racemization Suppressant	Solvent	Temperature (°C)	Yield (%)
EDCI	HOBt	DMF	25	73
EDCI	HOBt	MeCN	25	84*
EDCI	-	MeCN	0	NR
DCC	HOBt	MeCN	25	0*
DCC	-	MeCN	0	NR
HATU	HOAt	MeCN	25	78
HBTU	HOBt	MeCN	25	0*
HBTU	-	MeCN	0	NR
PyBOP	-	MeCN	0	NR

When using EDCI, the reaction proceeded with a higher yield if the reaction was run in MeCN than in DMF. The issue with DMF, was the inability to remove it from the sample before, during, and after purification. Brine washes and column chromatography were insufficient. In MeCN, the reaction proceeded more cleanly, but when the reaction was scaled up, there was a water impurity that remained. The used of Na_2SO_4 was unable to remove the excess water. The water issue was also present when HBTU and DCC were used. We believed this may be due to the presence of the HOBt hydrate. To circumvent this, we attempted to lower the temperature of the reaction, so the additive was not needed. These reactions did not result in any product. The use of PyBop did not result in any conversion of starting material. HATU did not have the same problem. The reaction proceeded forward cleanly and resulted in a yield of 78%. The use of HATU and formation of the chloride both cleanly resulted in compound **2.3** with high yields.

2.4 Reduction of the Amide

The first attempt to reduce the amide was to expose compound **2.5** to $LiAlH_4$ to reduce the amide as shown in Scheme 2-7**.** [16]

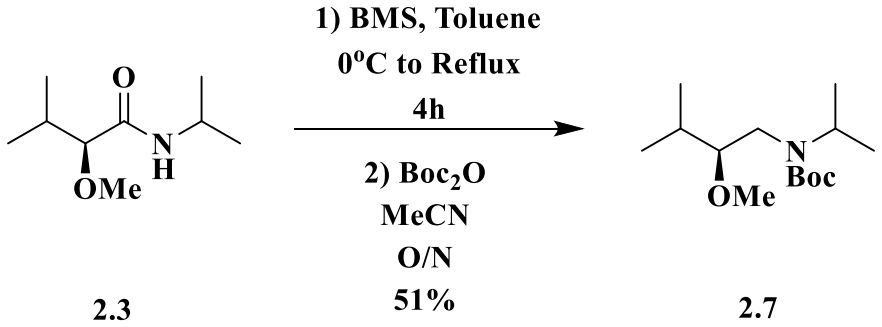


2.3 **2.4**

Scheme 2-7: Attempted Reduction of Amide

The reduction of **2.3** resulted in some challenges. $LiAlH_4$ should cleanly reduce the amide (Scheme 2-7), but it did not. There were issues in separating the amine from the aluminum salts. Several different attempts were made to purify the product but were unsuccessful. The secondary amine was not stable enough to be exposed to silica, so a different alternative had to be taken.

The other reaction examined was a reduction using $BH_3 \bullet SMe_2$ (Scheme 2-8). The solvent was changed from THF to toluene, when papers indicated that toluene was a better solvent to use. The reflux temperature could be increased, which sped the reaction up from 12 hours to 4 hours. Fewer equivalents of $BH_3 \bullet SMe_2$ were needed.[17, 18]



2.3 **2.7**

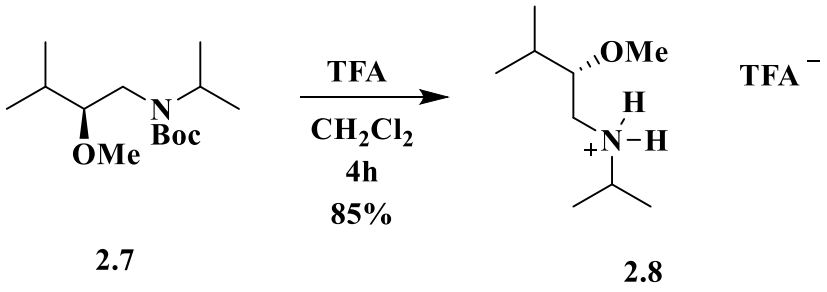
Scheme 2-8: Reduction of Amide and Protection Step

When purification was attempted at this step, there were other impurities within the sample as indicated by NMR. By protecting the amine as a Boc carbamate, we were able to synthesize compound **2.7.**[19] This compound was more stable and therefore able to be purified. The yield over the two steps was increased from 26% to 51% with the solvent change. We believe the increase in yield was primarily due to the solvent change in the reduction step, since the Boc protections showed 100% conversion via TLC. The product recovered was a yellow oil. Determining the

presence of compound **2.7** was difficult since the product is a mixture of two rotamers. The ^{1}H-NMR and ^{13}C-NMR were not definitive, but MS confirmed the presence of compound **2.7**.

2.5 Deprotection of the Amine

The amine (**2.7**) was deprotected using TFA in CH_2Cl_2. The resultant TFA salt was neutralized using basic water and extracted into CH_2Cl_2 (Scheme 2-9).[19] The product is the TFA salt and is a white solid. The material is stored and used as a salt. The yield of the reaction was approximately 85%.

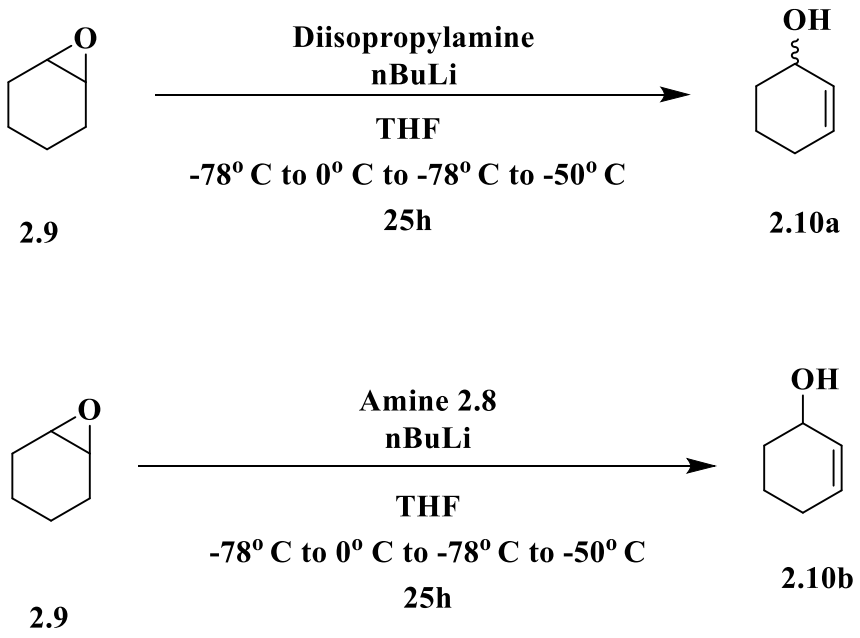


2.7 **2.8**

Scheme 2-9: Deprotection of Amine **2.7**

2.6 Testing the Chiral Amine

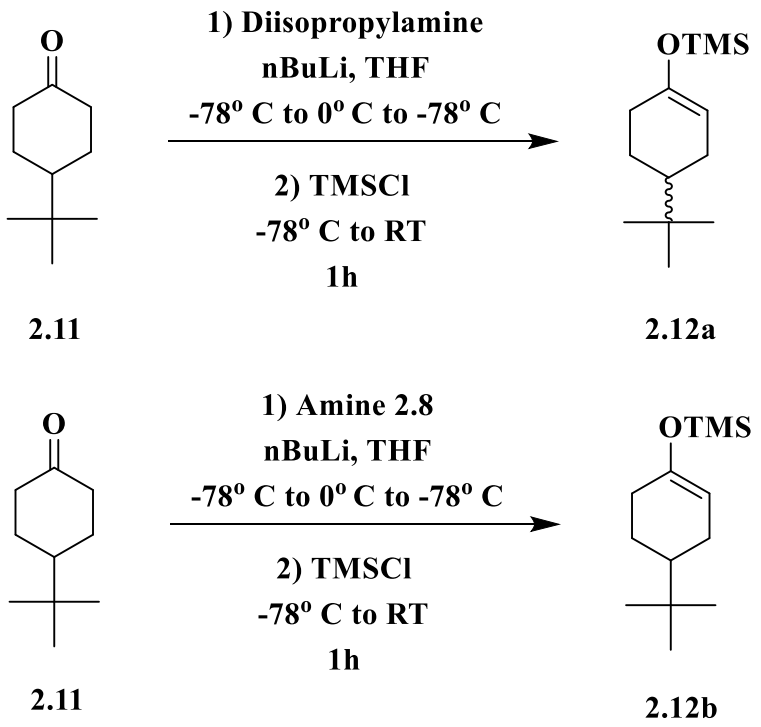
To test the efficacy of the chiral amine, we tested it in two model reactions. The first was the base-promoted ring opening of an achiral epoxide and the other was a selective enolization of an achiral ketone. We used LDA as our achiral comparison. For the epoxide opening, cyclohexene oxide (**2.9**) was chosen as the test system.[20] The amine of interest was deprotonated by n-BuLi in THF and cooled to -78°C, after which cyclohexene oxide was added to the solution and reacted at -50° C for 25 hours (Scheme 2-10).



Scheme 2-10: Formation of the Allylic Alcohol from Achiral Epoxide Opening

The formation of the allylic alcohol results in a slightly yellow oil. The yield is about 30% for both the LDA and chiral amine examples. To test for % ee, the purified compounds of **2.10a** and **2.10b** are analyzed with a chiral GC.[21] The chiral GC can separate the enantiomers, unlike traditional chromatographic techniques. You can identify the two peaks using the racemic sample that was synthesized with LDA. The area under the curve gives you the amounts of each of the enantiomers. The amounts are compared to determine the % ee of the resulting product. The racemic mixture is needed to determine what the retention time of the product is, so when looking at the chiral sample, it is easy to find. This study is still ongoing for this system.

For the enolization study, 4-tert-butylcyclhexanone (**2.11**) was chosen as the model system.[22] The amine of interest was deprotonated by n-BuLi in THF and cooled to -78°C, after which 4-*tert*-butylcyclohexanone was added to the solution and reacted for 30 minutes. TMSCl was subsequently added and reacted for 1 hour (Scheme 2-11).



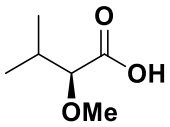
Scheme 2-11 Formation of the Enolate from Achiral Ketone

The formation of the silyl enol ether showed full conversion via TLC. However, the instability of the silyl enol ether prevented purification, and therefore percent yield determination. This material is subjected to chiral GC crude. The results to determine % ee are still ongoing.

2.7 Conclusion

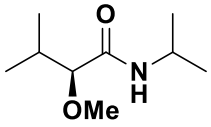
We have successfully synthesized a new chiral base. The advantage of this design is that the amine can be made in either the R or S configuration. Unlike sparteine, both enantiomers can be accessed. This eliminates the need for complex chiral auxiliaries that help control the stereochemistry if a chiral base is inaccessible. The simplicity of the synthesis also makes it a viable solution. The overall yield of the synthesis is 12%, but there is still room for improvement. The efficacy of the material is still undetermined currently as chiral GC data is still being collected.

APPENDIX A. EXPERIMENTAL PROCEDURES



(S)-2-methoxy-3-methylbutanoic acid (2.2).

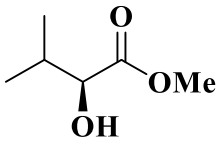
Sodium hydride (1.02 g, 25.4 mmol) was added to a round bottom flask and was cooled to 0°C. In a separate flask, starting material (1.00 g, 8.47 mmol) was dissolved in THF (21.2 mL). The resulting solution was added dropwise to the flask containing the sodium hydride. After 30 minutes, iodomethane (2.63 mL, 42.3 mmol) was added dropwise to the solution. The raction was stirred and warmed to room temperature (12 h). The reaction was quenched with water and acidified to pH 2 with 6M HCl, after which it was extracted with ethyl acetate and dried over sodium sulfate. Purification by flash chromatography (40% ethyl acetate/ hexanes) afforded the product as a yellow oil, in 73% yield. (815 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 3.54 (d, J= 4.9 Hz, 1H), 3.40 (s, 3H), 2.08 (pd, J= 4.9 Hz, 1H), 0.96 (dd, J= 15.8, 6.9 Hz, 6H) ppm; ^{13}C NMR 100 MHz, $CDCl_3$) δ 177.57, 85.31, 58.77, 31.28, 18.53, 17.12; ESI-MS M/z 132



***(S)-N*-isopropyl-2-methoxy-3-methylbutanamide (2.3).**

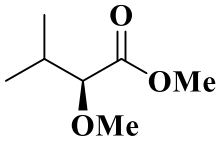
Method 1: To a solution of *(S)*-2-methoxy-3-methylbutanoic acid (945 mg, 7.2 mmol) in dichloromethane (35.7 mL, 0.2M) was added a catalytic amount of dimethylformamide. The solution was cooled to 0° C and oxalyl chloride (1.23 mL, 12.3 mmol) was added dropwise. Once complete (1h), the solvent was removed in vacuo and the crude oil was redissolved in acetonitrile (17.9 mL). DIPEA (2.50 mL, 14.3 mmol) was added, after 5 min isopropylamine (1.20 mL, 14.3 mmol) was added and stirred overnight (12h). Method 2: (*S*)-2-methoxy-3-methylbutanoic acid (815 mg, 6.2 mmol) was dissolved in acetonitrile (15.4 mL) along with HATU (3.52 g, 9.3 mmol), HOAt (1.26 g, 9.3 mmol), and DIPEA (3.22 mL, 18.5 mmol). After 5 min, isopropylamine (2.65

mL, 30.8 mmol) was added and the reaction stirred overnight (12 h). Acetonitrile and excess amine were evaporated, and 3M NaOH was added to adjust the pH to 12. The aqueous solution was extracted with ethyl acetate and dried over sodium sulfate. Purification by flash chromatography (30% ethyl acetate/ hexanes) afforded the product as a colorless solid in 69% yield (732 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.27 (s, 1H), 4.11 (dp, J= 8.5 Hz, 1H), 3.40-3.34 (m, 4H), 2.06 (pd, J= 6.9 Hz, 1H), 1.16 (dd, J= 8.9, 6.6 Hz, 6H), 0.98 (d, J= 6.9 Hz, 3H), 0.87 (d, J= 6.8 Hz, 3H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.9, 87.3, 59.2, 40.5, 31.3, 22.8, 22.7, 18.9, 16.6; ESI-MS M/z 173; mp≈ 39-41° C



Methyl-(*S*)-2-hydroxy-3-methylbutanoate (2.5)

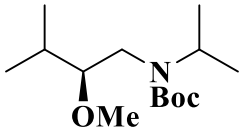
(*S*)-2-methoxy-3-methylbutanoic acid (50 mg, 0.42 mmol) was dissolved in MeOH (2.1 mL) and H_2SO_4 (225 µL, 4.23 mmol) was added dropwise. The reaction was heated to reflux for 3h. The reaction was cooled, and pentane added to azeotrope H_2SO_4 in vacuo. The crude product was diluted with Et_2O and washed with saturated $NaHCO_3$ (3x) and brine. The organic layer was dried over sodium sulfate and concentrated in vacuo and afforded the product as a yellow oil in 61% yield (34 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.03 (d, *J* = 3.6 Hz, 1H), 3.77 (s, 3H), 2.71 (s, 1H), 2.05 (td, *J* = 6.9, 3.6 Hz, 1H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, Chloroform-*d*) δ 175.27, 74.94, 52.25, 32.04, 18.62, 15.89.



Methyl-(*S*)-2-methoxy-3-metylybutanoate (2.6)

To a flame-dried round bottom, was added Cs_2CO_3 (414 mg, 1.30 mmol). (*S*)-2-methoxy-3-methylbutanoic acid (50 mg, 0.42 mmol) was dissolved in anhydrous DMF (1.1 mL) and the solution added to the reaction flask dropwise. The reaction was stirred for 30 minutes CH_3I (131

µL, 2.12 mmol) was added dropwise. The reaction was stirred overnight (12h, after which it was diluted with water and extracted with Et_2O. The organic layer was washed with brine (3X) and dried over sodium sulfate and evaporated in vacuo Purification with flash chromatography (10% ethyl acetate/ hexanes) afforded the product in 31% yield (18 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.77 (d, *J* = 4.4 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 2.24 (td, *J* = 6.9, 4.4 Hz, 1H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 155.4, 79.8, 79.4, 55.0, 52.1, 51.9, 30.1, 30.0, 18.5, 16.9.

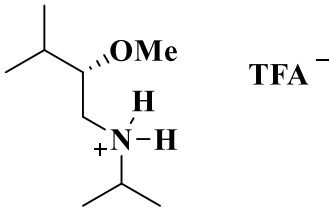


***tert*-Butyl-*(S)*-*N*-isopropyl-*N*-((2-methoxy-3-methyl)butyl)-carbamate (2.7).**

In a flame-dried flask under nitrogen, *(S)*-*N*-isopropyl-2-methoxy-3-methylbutanamide (730 mg, 4.21 mmol) was dissolved in toluene (10.5 mL) and cooled to 0°C. BMS was added dropwise to the reaction (4.0 mL, 42 mmol) and the reaction was warmed to room temperature and heated to reflux (40°C) for 4h. The reaction was cooled to -10°C and quenched by the dropwise addition of cold methanol. The pH was adjusted to 12 by the addition of 3M NaOH, and extracted with EtOAc, and dried over sodium sulfate and reduced in vacuo.

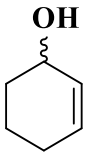
The resulting oil was dissolved in THF (10.5 mL) and Boc_2O was added (4.60 g, 21.1 mmol) to the reaction flask. The reaction was run overnight (12 h), after which water was added to the flask and the pH adjusted to 12 with 3M NaOH, extracted with EtOAc, and dried over sodium sulfate. Purification by flash chromatography (10% ethyl acetate/hexanes) afforded the product as a yellow oil and in 51 % yield (216 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (t, J = 6.7 Hz, 0H), 3.82 – 3.77 (m, 1H), 3.69 (td, J = 10.2, 4.2, 3.3 Hz, 1H), 3.40 (d, J = 2.0 Hz, 3H), 3.33 (dd, J = 12.6, 2.0 Hz, 2H), 3.23 – 3.10 (m, 1H), 2.87 – 2.63 (m, 1H), 2.59 – 2.42 (m, 2H), 2.01 (qd, J = 6.7, 2.1 Hz, 2H), 1.49 (s, 6H), 1.46 – 1.37 (m, 1H), 1.37 – 1.26 (m, 2H), 1.30 – 1.25 (m, 1H), 1.25 – 1.19 (m, 3H), 1.18 (dd, J = 7.0, 3.4 Hz, 2H), 1.14 (td, J = 5.5, 4.1, 2.1 Hz, 5H), 1.00 – 0.92 (m, 1H), 0.96 – 0.81 (m, 11H), 0.79 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.0, 146.6, 85.0, 82.3, 80.0, 79.1, 63.8, 63.4, 60.2, 58.4, 57.9, 56.8, 55.9, 54.1, 51.7, 50.80, 49.9, 40.7, 36.1, 31.1, 30.1, 29.6,

28.5, 28.1, 27.8, 27.3, 26.4, 26.1, 22.4, 22.4, 22.1, 22.0, 21.8, 20.8, 18.7, 18.4, 18.2, 18.0, 17.8, 17.7, 17.6, 17.4, 16.1, 16.0, 15.3, 14.1; ESI-MS M/z 259



***(S)-N*-isopropyl-2-methoxy-3-methylbutan-1-ammonium trifluoroacetate (2.8).**

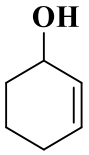
Tert-Butyl-*(S)*-*N*-isopropyl-*N*-((2-methoxy-3-methyl)butyl)-carbamate (216 mg, 0.83 mmol) was added to a reaction flask and dissolved in CH_2Cl_2 (5.0 mL). TFA (5.00 mL) was added dropwise to the solution and the reaction stirred for 4h. TFA was removed by washing the crude product with CH_2Cl_2. The resulting solid was suspended in MeOH and filtered through glass wool. The filtrate was evapoarated to dryness under educed pressure to afford the product as a white solid in 85% yield (113 mg); ^{1}H NMR (400 MHz, MeOD) δ 3.41 (s, 2H), 3.31 – 3.20 (m, 1H), 3.01 – 2.91 (m, 1H), 2.85 (dd, J = 12.7, 9.7 Hz, 1H), 2.08 (pd, J = 7.0, 4.8 Hz, 1H), 1.33 – 1.24 (m, 5H), 0.97 (dd, J = 6.7, 0.9 Hz, 3H), 0.92 (d, J = 7.0 Hz, 2H) ppm; ^{13}C NMR (100 MHz, MeOD) δ 81.7, 56.3, 50.1, 45.0), 28.0, 21.1, 18.5, 18.0, 16.9, 15.1; ESI-MS M/z 273



2-cyclohexen-1-ol (2.10a)

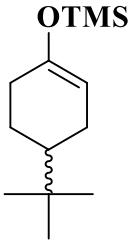
Diisopropylamine (86 µL, 0.61 mmol) was dissolved in anhydrous THF (2.04 mL) and cooled to -78°C. n-BuLi (0.35 mL, 0.56 mmol) was added dropwise to the solution, which was warmed to 0°C over 30 min and then cooled to -78°C. Cyclohexenoxide (52 µL, 0.51 mmol) was added dropwise to the reaction, which was warmed to -50°C and allowed to react for 25h. The reaction was quenched by the addition of aqueous NH_4Cl (5M) and extracted with Et_2O. The combined organic layer was washed with H_2O followed by brine. The organic layer was dried over sodium

sulfate and purified by flash chromatography (25% acetone/hexanes) to afford the product as a yellow oil in 15% yield.



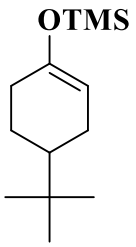
2-Cyclohexen-1-ol (2.10b)

Compound **2.8** (167 mg, 0.61 mmol) was dissolved in anhydrous THF (2.04 mL) and cooled to -78°C. n-BuLi (0.70 mL, 1.12 mmol) was added dropwise to the solution, which was warmed to 0°C over 30 min and then cooled to -78°C. Cyclohexenoxide (52 µL, 0.51 mmol) was added dropwise to the reaction, which was warmed to -50°C and allowed to react for 25h. The reaction was quenched by the addition of aqueous NH_4Cl (5M) and extracted with Et_2O. The combined organic layer was washed with H_2O followed by brine. The organic layer was dried over sodium sulfate and purified by flash chromatography (25% acetone/hexanes) to afford the product as a yellow oil in 21% yield.



***rac*-4-*tert*-butyl-cyclohex-1-en-1-yl-oxy-trimethylsilane (2.12a)**

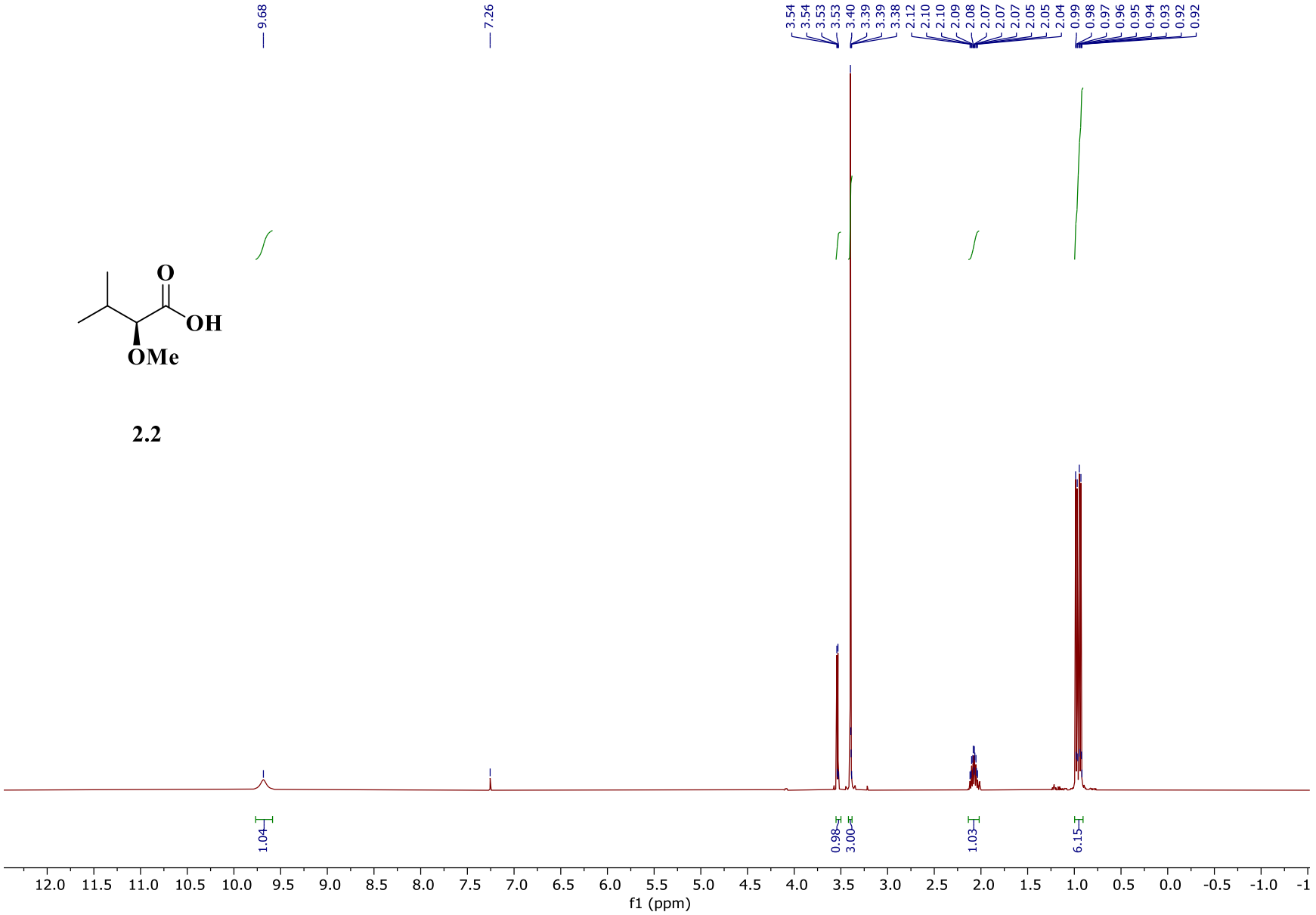
Diisopropylamine (22 µL, 0.16 mmol) was dissolved in anhydrous THF (0.52 mL and cooled to -78°C. n-BuLi (89 µL, 0.14 mmol) was added dropwise to the reaction, which was warmed to 0° C over 30 min then cooled to -78°C. A solution of 4-*tert*-butylcyclohexanone (20 mg, 0.13 mmol) in THF was added dropwise to the reaction, which then stirred for 30 min. TMSCl (31 µL, 0.25 mmol) was added dropwise to the reaction, which was allowed to stir and warm to room temperature over 1h. The crude silyl enol ether was used for the chiral GC studies.



4-*tert*-butyl-cyclohex-1-en-1-yl-oxy-trimethylsilane (2.12a)

Diisopropylamine (22 µL, 0.16 mmol) was dissolved in anhydrous THF (0.52 mL and cooled to -78°C. n-BuLi (178.0 µL, 0.29 mmol) was added dropwise to the reaction, which was warmed to 0° C over 30 min then cooled to -78°C. A solution of 4-*tert*-butylcyclohexanone (20 mg, 0.13 mmol) in THF was added dropwise to the reaction, which then stirred for 30 min. TMSCl (31 µL, 0.25 mmol) was added dropwise to the reaction, which was allowed to stir and warm to room temperature over 1h. The crude silyl enol ether was used for the chiral GC studies.

APPENDIX B. NMR DATA



2.2

Figure B1: ^{1}HNMR of Compound 2.2

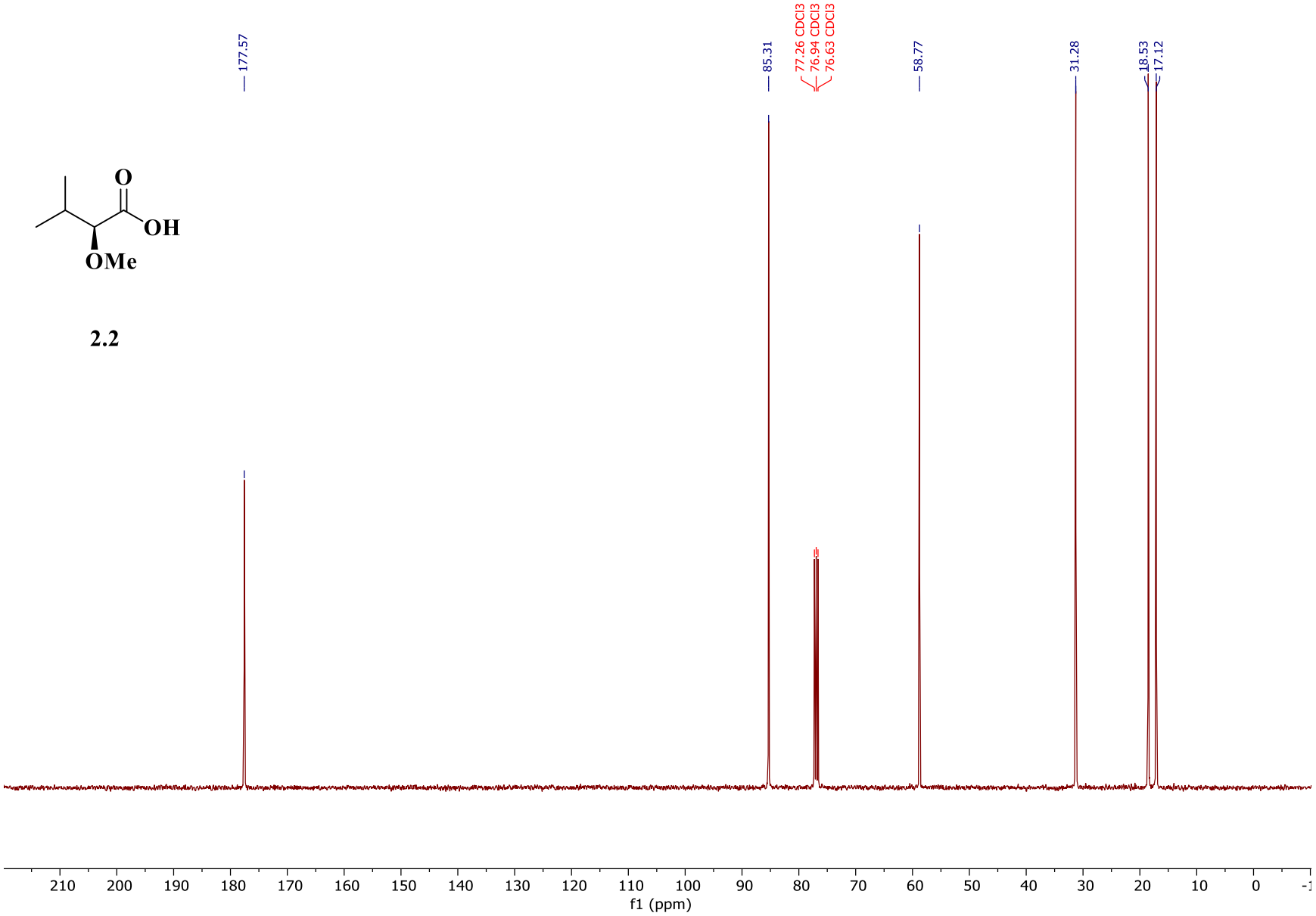
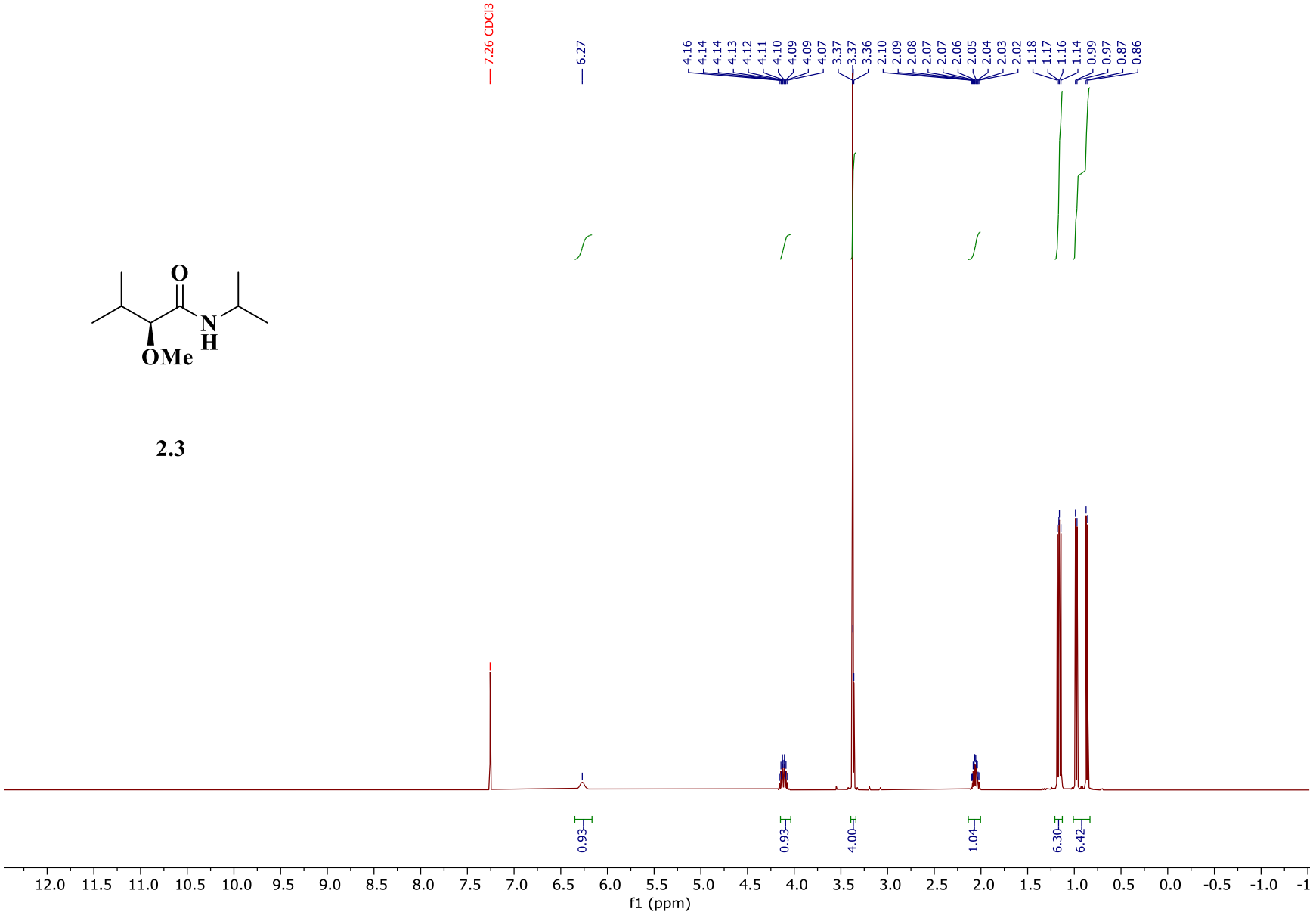


Figure B2: ^{13}CNMR of Compound 2.2



2.3

Figure B3: ^{1}HNMR of Compound 2.3

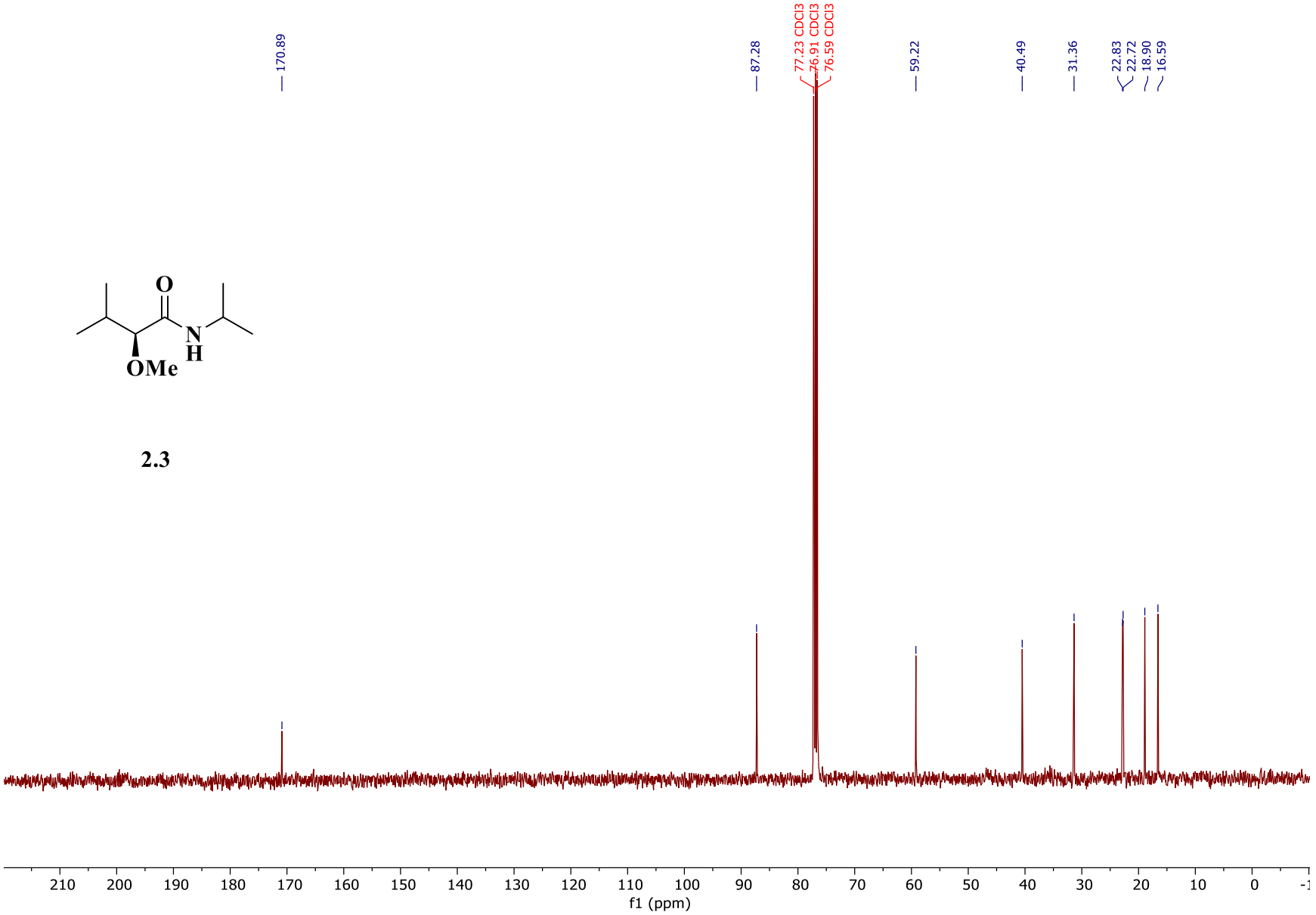


Figure B4: ^{13}CNMR of Compound 2.3

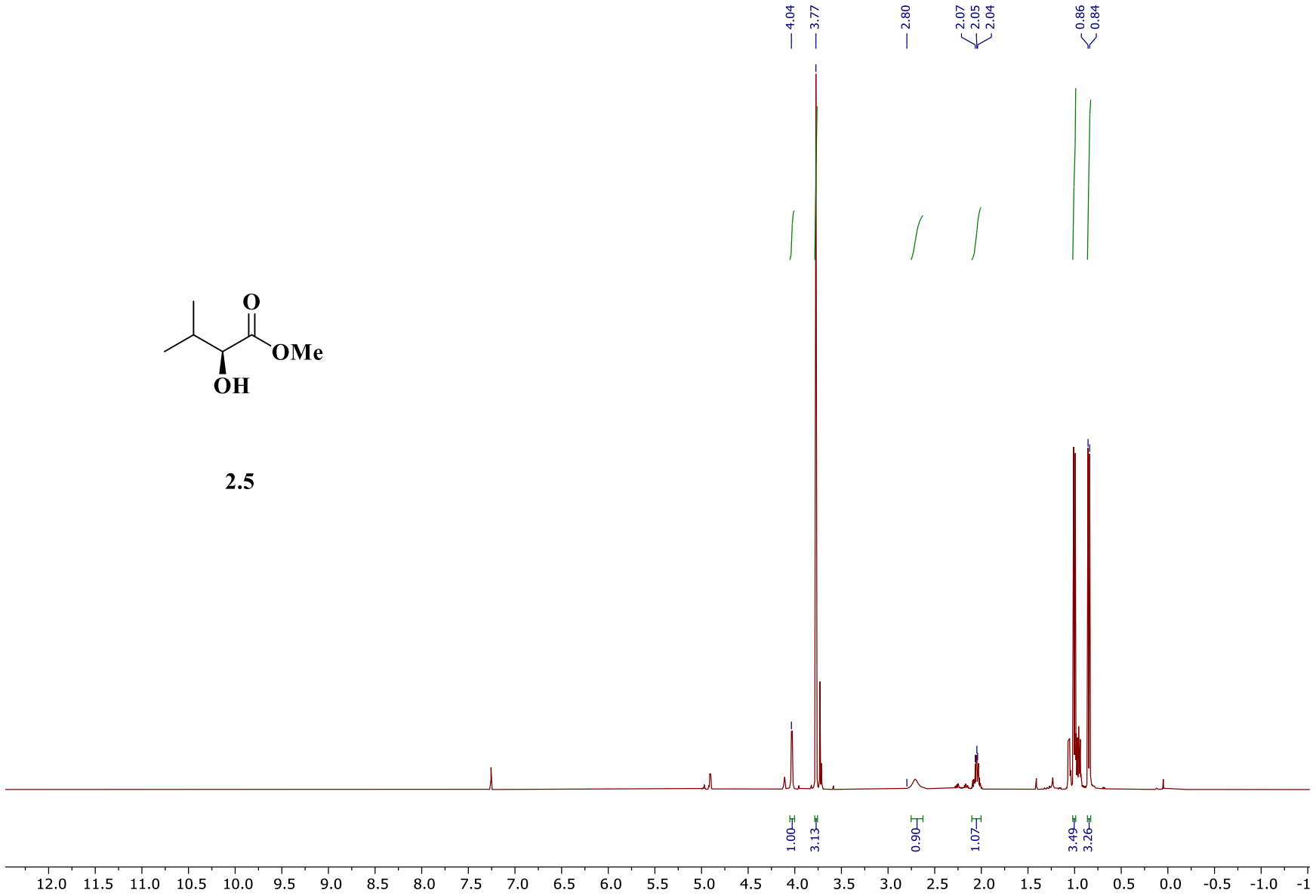


Figure B5: ^{1}HNMR of Compound 2.5

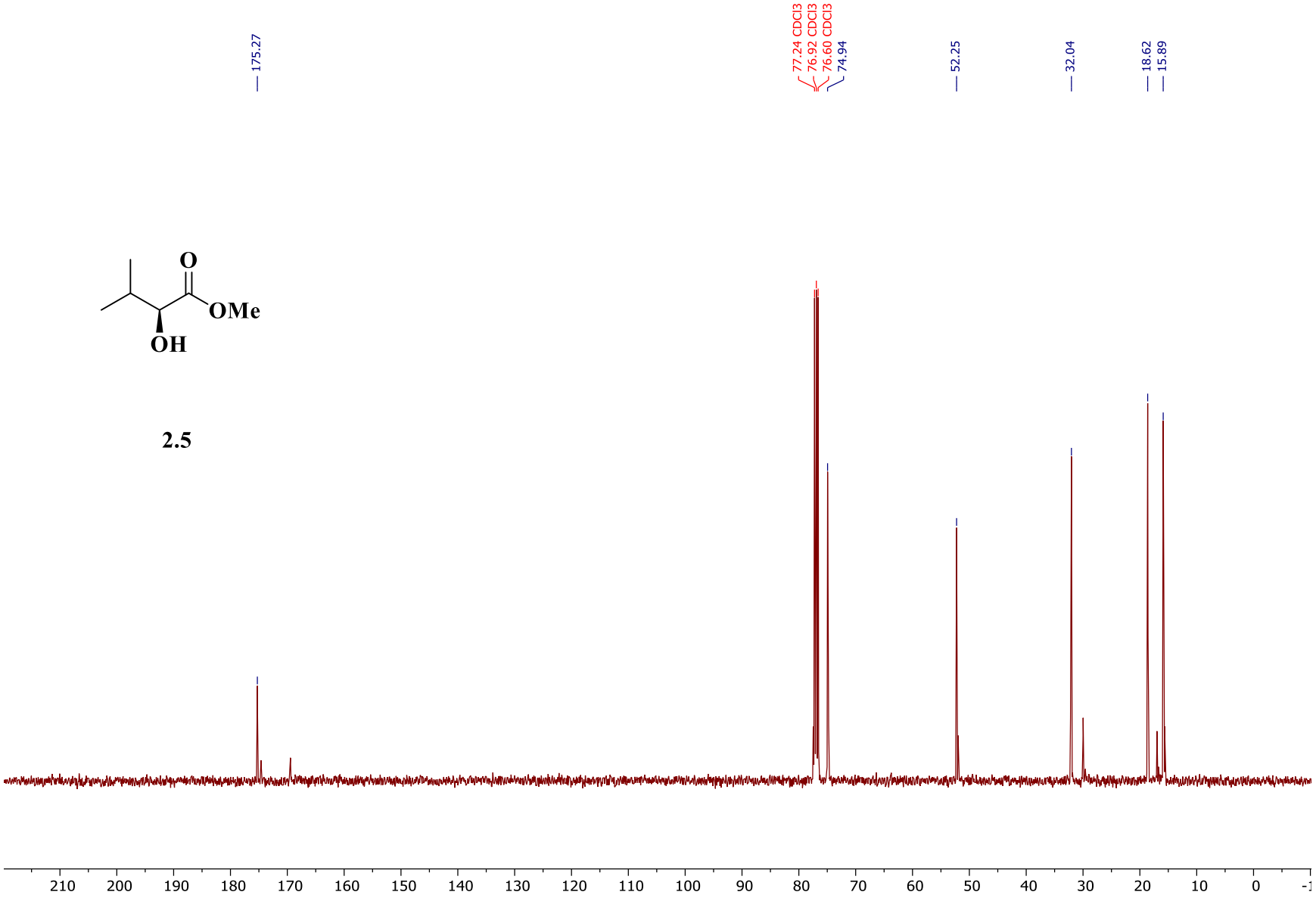


Figure B6: ^{13}CNMR of Compound 2.5

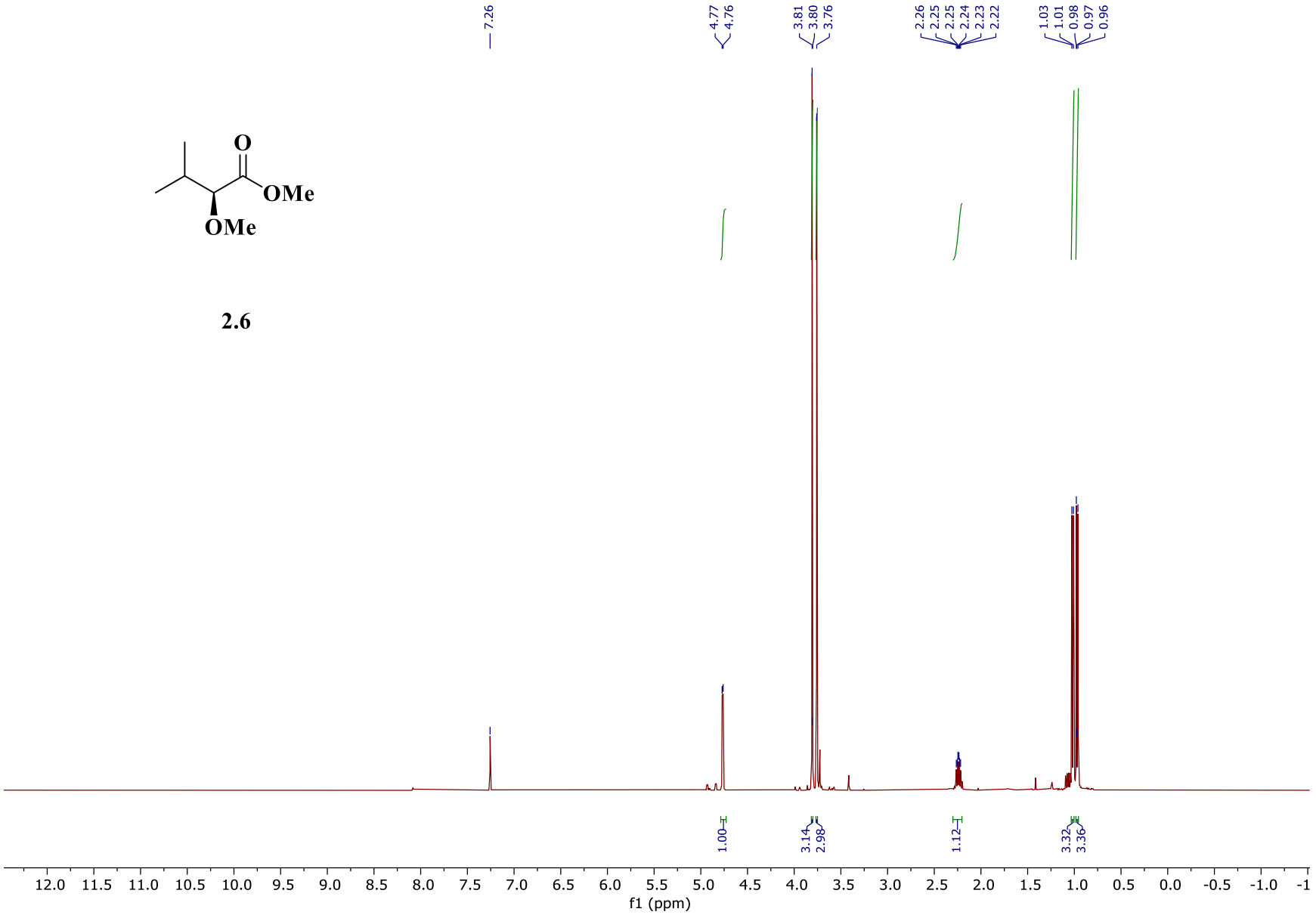


Figure B7: ^{1}HNMR of Compound 2.6

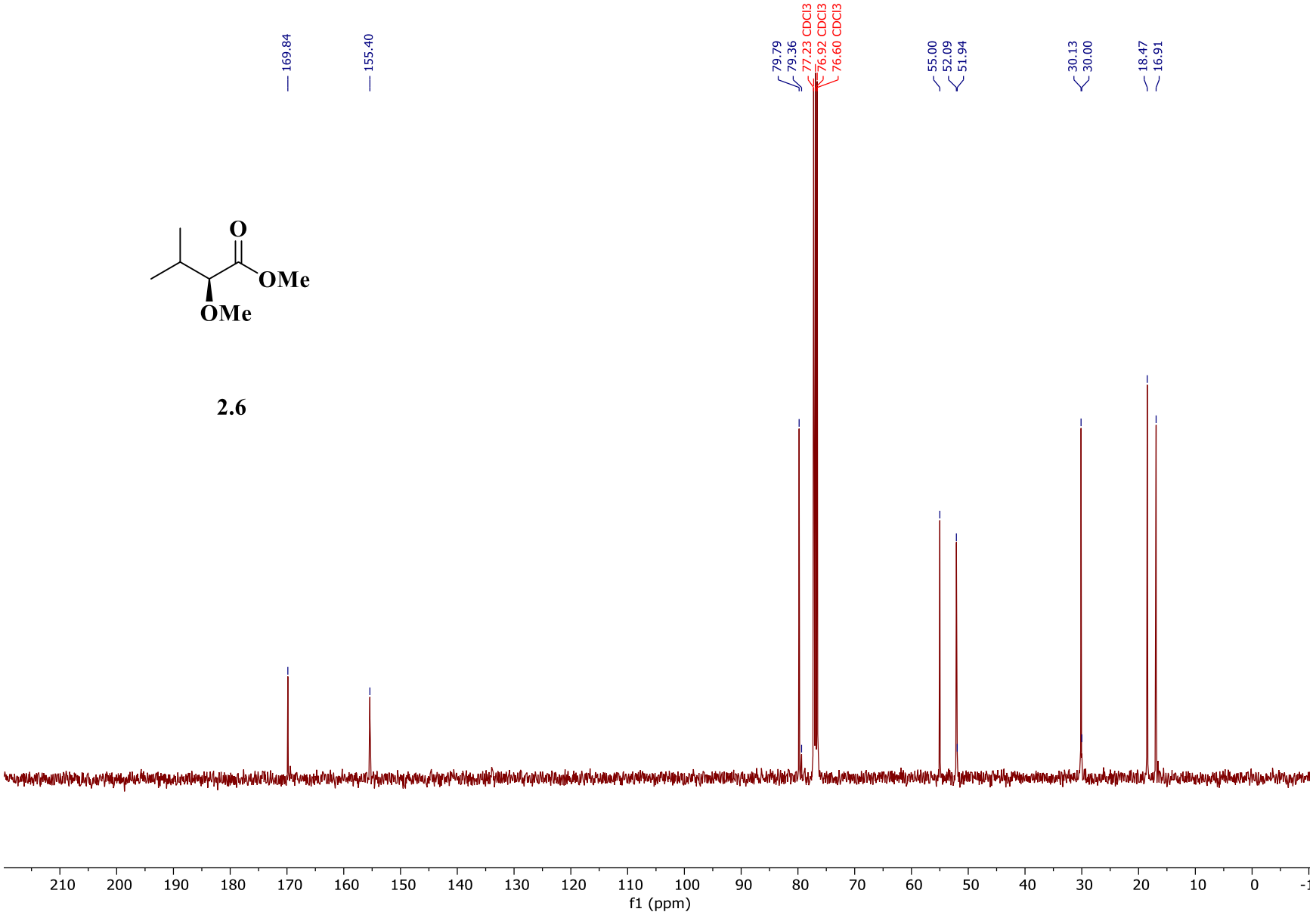
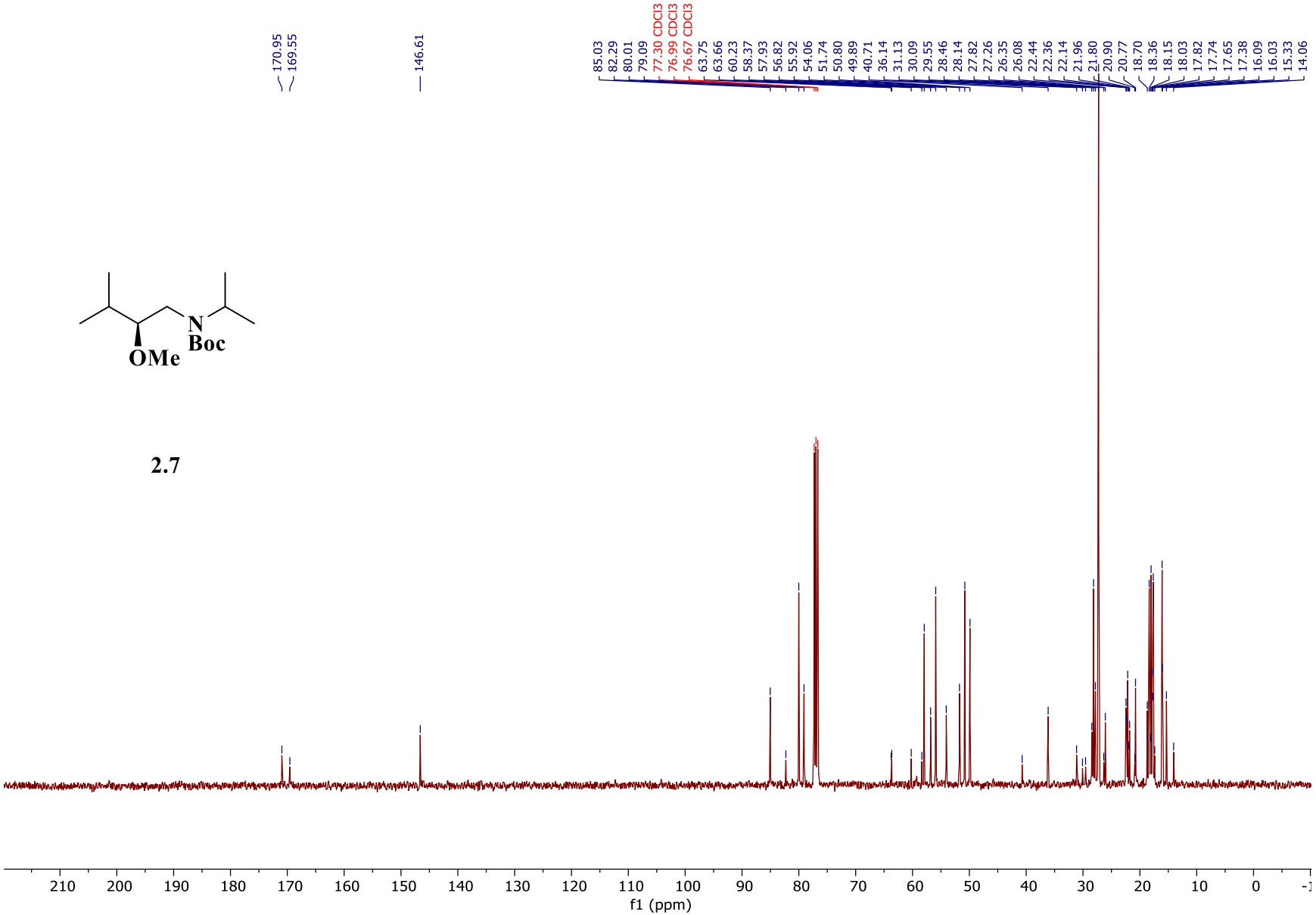


Figure B8: ^{13}CNMR of Compound 2.6



2.7

Figure B9: ^{13}CNMR of Compound 2.7

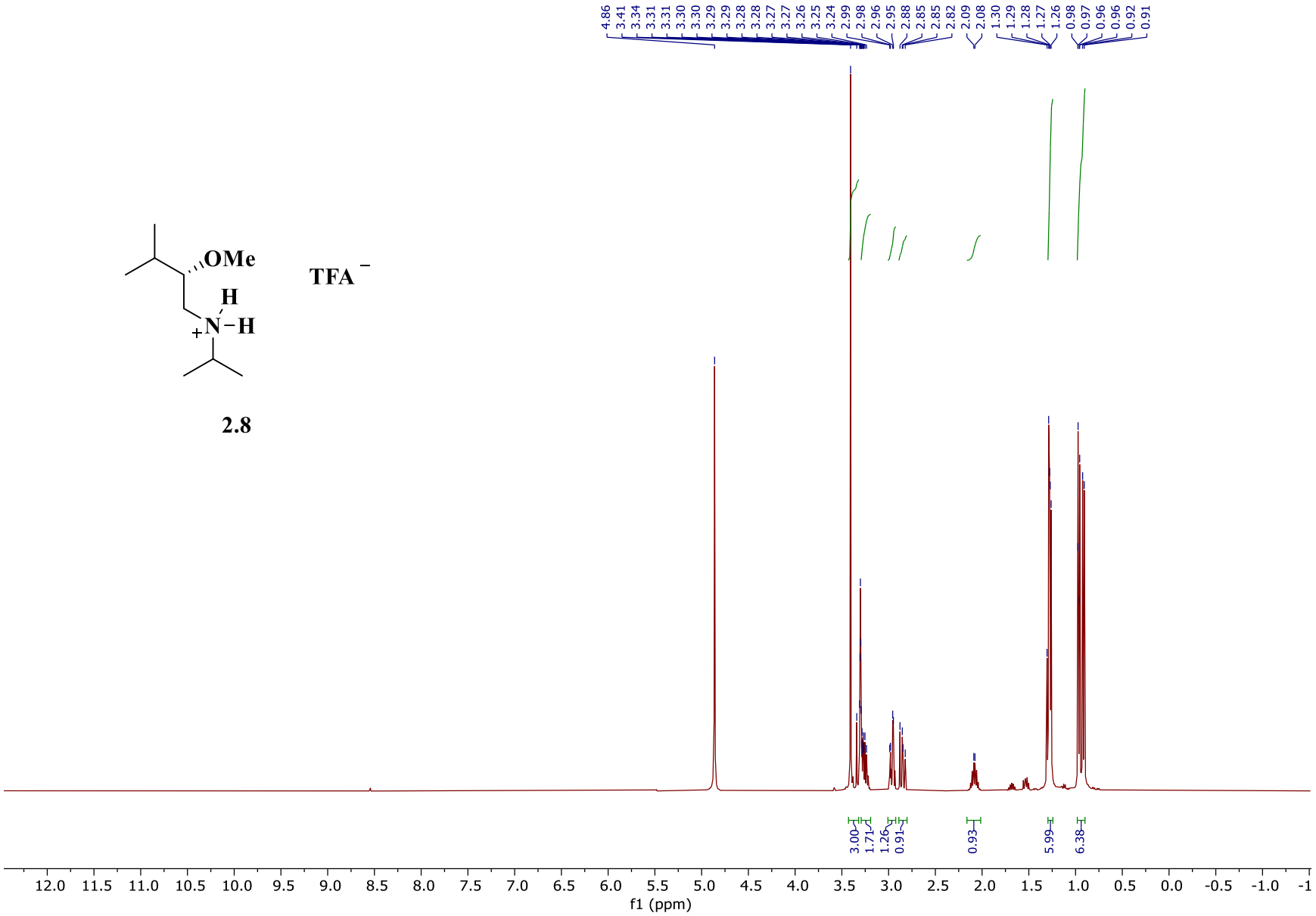


Figure B10: ^{1}HNMR of Compound 2.8

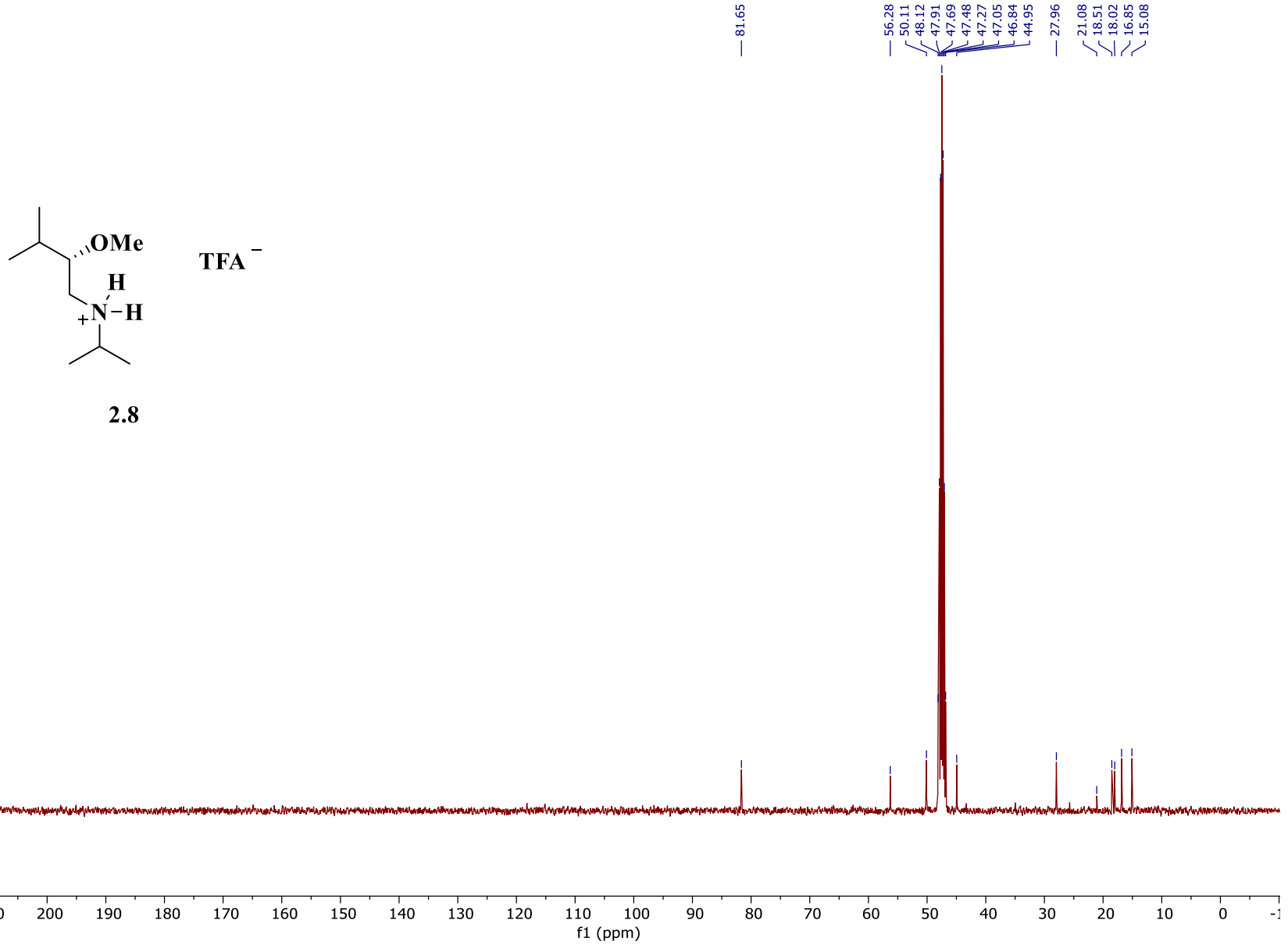


Figure B11: ^{13}CNMR of Compound 2

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