Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Natural Sciences
Department of Chemistry

Mikael Sverre Rui

# Synthetic exploration towards total synthesis of Fusolanone B

Master's thesis in Chemistry
Supervisor: Eirik Johansson Solum
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## Abstract

The γ-pyrone Fusolanone B (**28**), previously isolated by fungi, has shown potential use as an antibiotic. In this project retrosynthesis inspired by biosynthesis of polyketides has been carried out, and two different reaction pathways for synthesizing Fusolanone B were investigated and adjusted. Due to the chirality of the target compound, Evans auxiliares were used in combination with aldol reactions, followed up by Barton-McCombie deoxygenation. The deoxygenation turned out to be problematic for the second reaction pathway, where the olefin was destroyed. Attempts to avoid the problem were made, but unsuccessfully.

# Innhold

# 1. Introduction

## Polyketides in fungi[1]

Many bioactive secondary metabolites are polyketides. In fungi aromatic polyketides are produced by non-reducing iterative polyketide synthetase (PKS).[2] Polyketide synthetase is an multidomain enzyme that facilitates a catalysed claisen condensation to produce a wide range of different polyketides. PKS consists of three main domain, the β-ketosynthase (KS), the acyl-transferase (AT) and the acyl-carrier proteinn (ACP). KS catalyze the condensation of acyl-CoA via Claisen condensation, AT delivers the correct substrate to to the enzyme and ACP facilitates movement of substrate and products between active sites (figure 1).

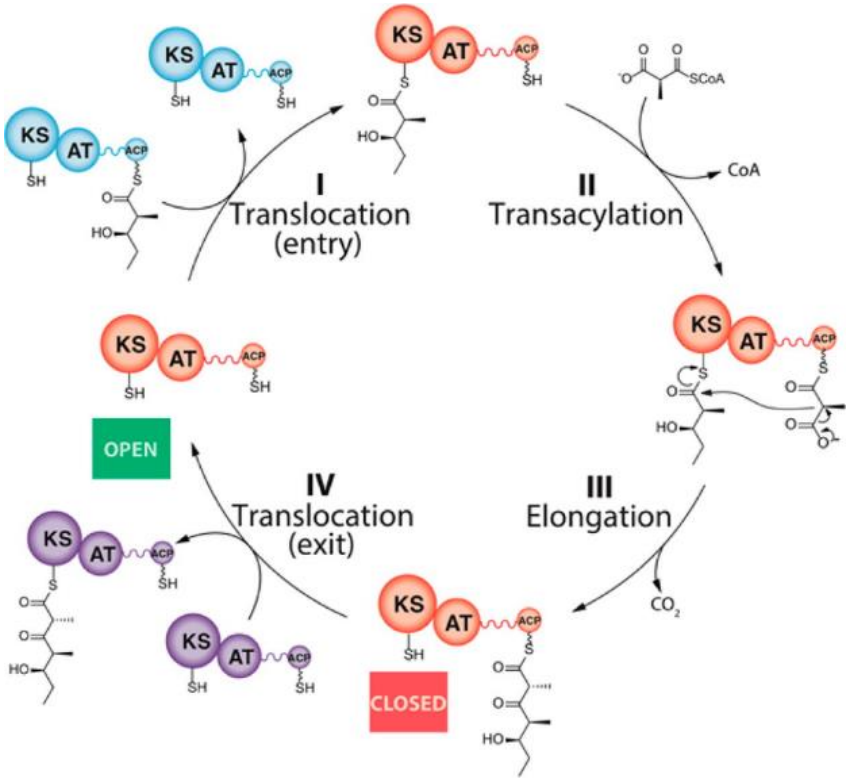



Figure 1.1.[3]: The basic cyclus of polyketide synthetase. Figure from Lowry et al. under CC license.

Beyond the three main domains, other domains can aid in further modification. Ketone can be reduced to hydroxyl by β-ketoreductae (KR), hydroxyl can be reduced to enoyl by dehydrogenase (DH), enoyl can be reduced to alkyl by enoyl reductase (ER). Thioesterase (TE) releases the product with water, and Claisen cyclase (CYC) release the product by an intramolecular reaction, which often leads to an aromatic compound.

## Fusolanone[4]

Seven compounds were isolated from the fungi Fusarium solani and tested for antimicrobal activity. From these compounds, Fusalonone B (Figure 1.2) showed the highest activity with MIC value 6.25 µg/mL on Vibrio parahaemolytic.

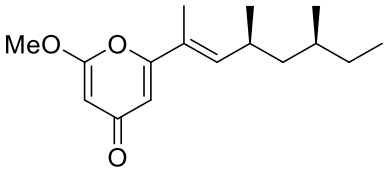



Figure 1.2:

In this project, Fusolanone B will be attempted synthesized, and if succeeded, tested for antibacterial activity.

## Biomimetic (polyketide) Cyclication[5]

Cyclization of polyketides can be done biologically in fungi. A chemical approach to the cyclization of 3.5-diketoesters is described by Onda et al. The proposed mechanism is shown in Figure 1.3.

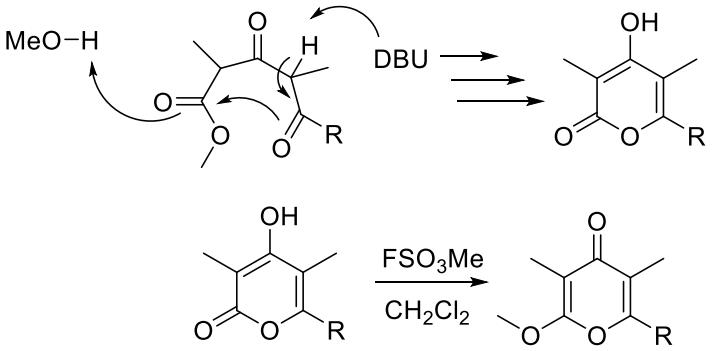



**Figure 1.3: proposed cyclization mechanism of 3,5-diketoester, followed by methylation.**

## Hoover-Stahl oxidation mechanism

Jessica Hoover and Shannon Stahl reported a highly selective oxidation of primary alcohol with good yield.[6] The oxidation uses TEMPO as oxidizing agent, catalyzed by copper(I) with bpy as ligand and NMI as base. The proposed mechanism for the oxidation is shown in figure 1.4.

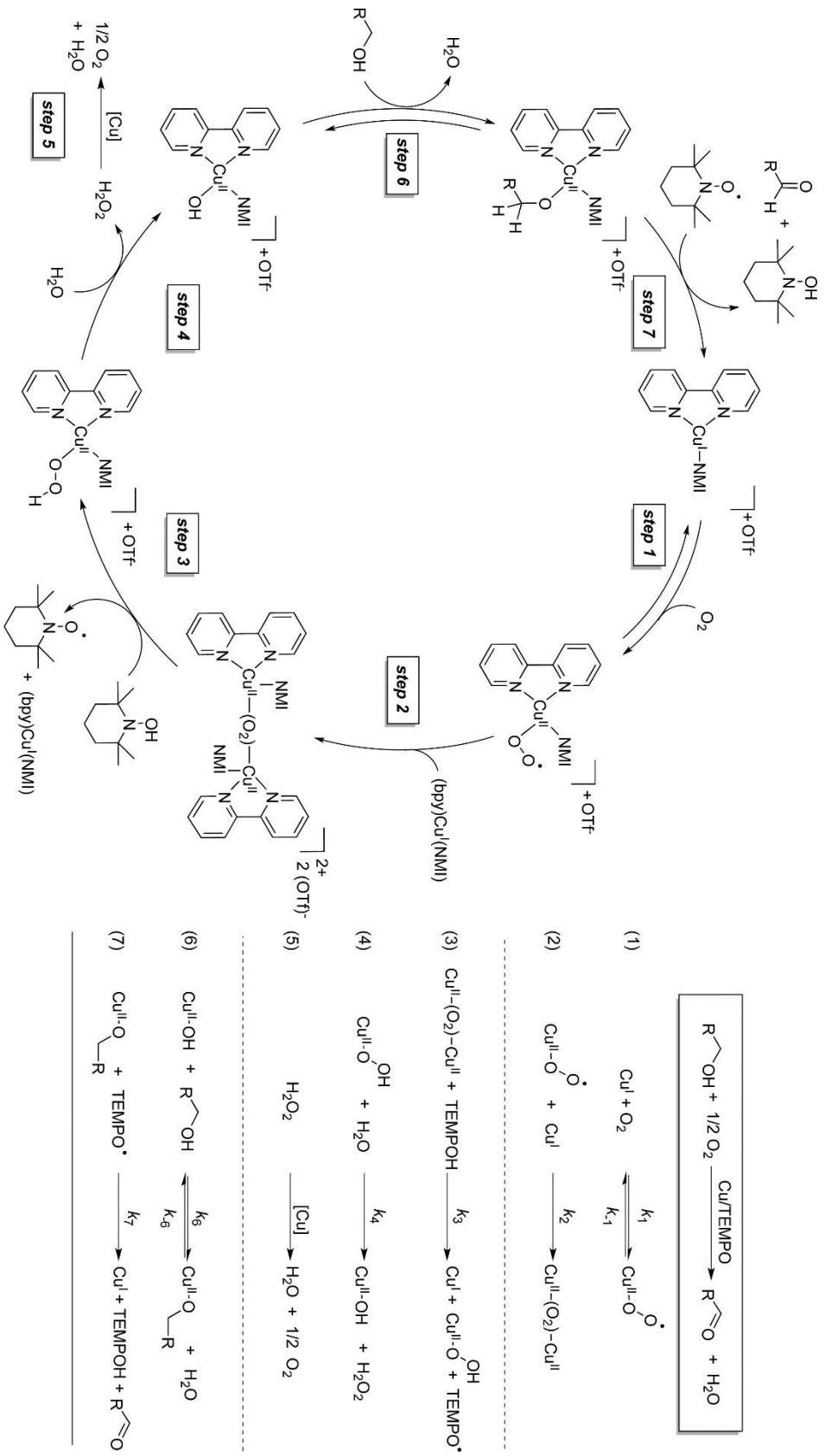
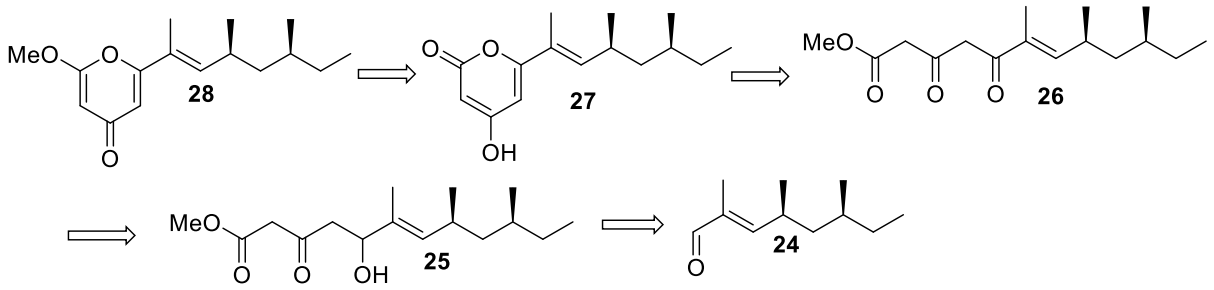



**Figure 1.4:** Proposed mechanism of the Copper(I)/TEMPO-Catalyzed aerobic alcohol oxidation by Jessica Hoover and Shannon Stahl. Reprinted with permission from [7]. Copyright (2013) American Chemical Society.

### Oxazolidinone as stereodirecting group

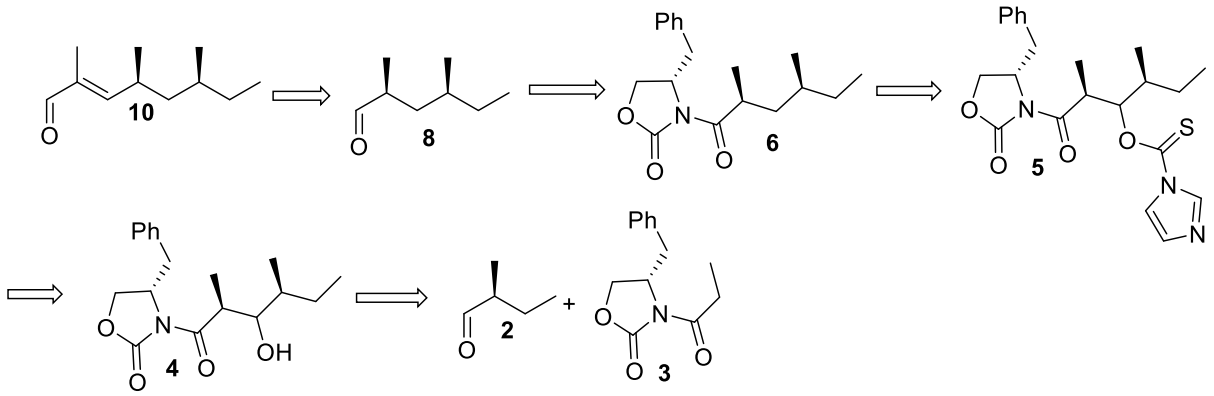
Bioactive compounds often have chiral senters, which can be an extra challenge when synthesizing a compound. A way to solve this is sterically hindering the unwanted reaction site. One way of doing this is adding a oxazolidinone with a bulky group to your compound, to block the unwanted enantiomer to be synthetized.

## 2. Retrosynthesis



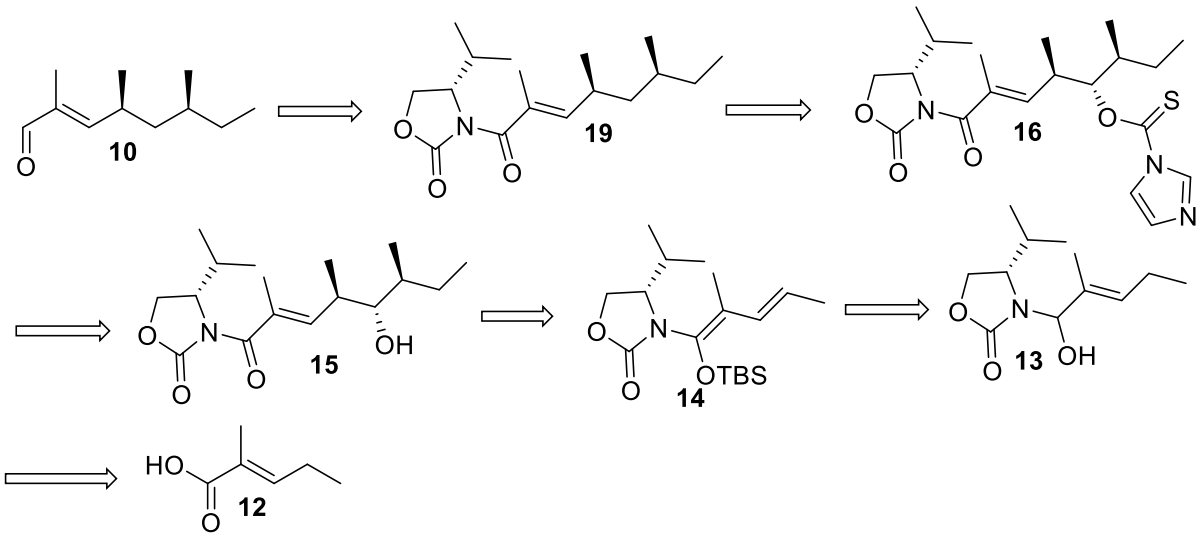

Scheme 2.1: Retrosynthesis from Fusolanone B (**28**)

Scheme 2.1 shows retrosynthesis from fusolanone B **28**. Similar products have been synthesized by cyclization of 3,5 diketoesters (**26**), followed by an methylation of the cyclic compound (**27**).[5] **26** can be made by an aldol reaction between **24** and an enolate of methyl acetoacetate to yield **25**, which in turn can be oxidized to **26**.




Scheme 2.2: alternative a

Compound **10** has both an olefin and two chiral senters. Based on similar compounds, **10** can be synthesized by a wittig reaction 2-(Triphenylphosphoranylidene)propionaldehyde and the aldehyde **8**.[8] The aldehyd **8** has two chiral senters, where a chiral oxazolidinone can be used to hinder the synthesis of the unwanted enantiomer.

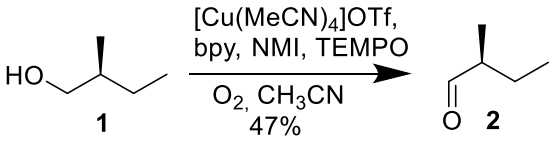



Scheme 2.3: alternative b

A different approach is to not do a wittig reaction, by choosing a different starting compound.

# 3. Results and discussion

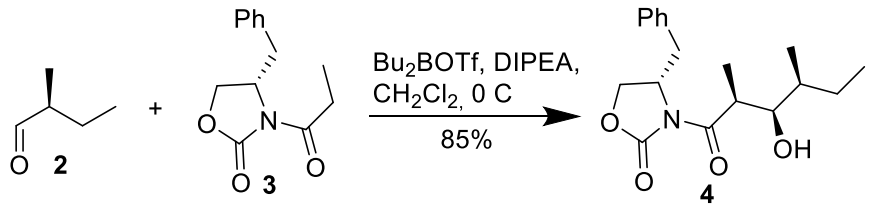
## Oxidation of primary alcohol[6]




Scheme 3.1:

2S-methylbutanal **2** was obtained by oxidizing 2S-methylbutanol with TEMPO as oxidizing agent with a copper catalyst. The procedure was first described by Jessica Hoover and Shannon Stahl, where good yield and selectivity had been reported for primary alcohols. Despite nmr analysis of the reaction mixture indicating full conversion of the alcohol to aldehyde, the yield was at first very low. This was due to the high volatility of the product. This was resolved by not evaporating all of the solvent (DCM) from the sample. The yield obtained was 47% in DCM.

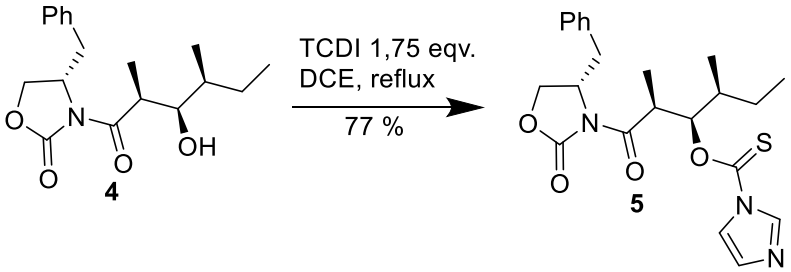
## Aldol reaction




Scheme 3.2:

(S)-4-benzyl-3-((2S,3R,4S)-3-hydroxy-2,4-dimethylhexanoyl)oxazolidin-2-one **4** (4.52 g, 14.2 mmol) was obtained by an aaldol condensation between the enolate of **3** (3.897 g, 16.7 mmol) and the aldehyde **2** (1.72 g, 20 mmol) in 85% yield.

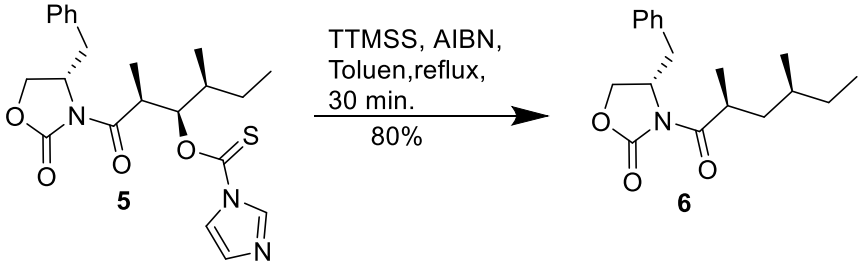
## Barton McCombie




Scheme 3.3:

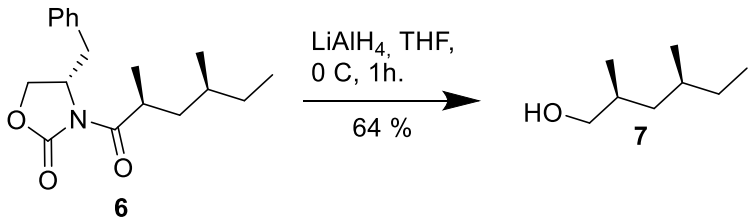
compound **5** (2.25 g, 5.23 mmol) was obtained from the alcohol **4** (2.17 g, 6.8 mmol) and TCDI (1.75 eqv.) in 77 % yield.

## Deoxygenation



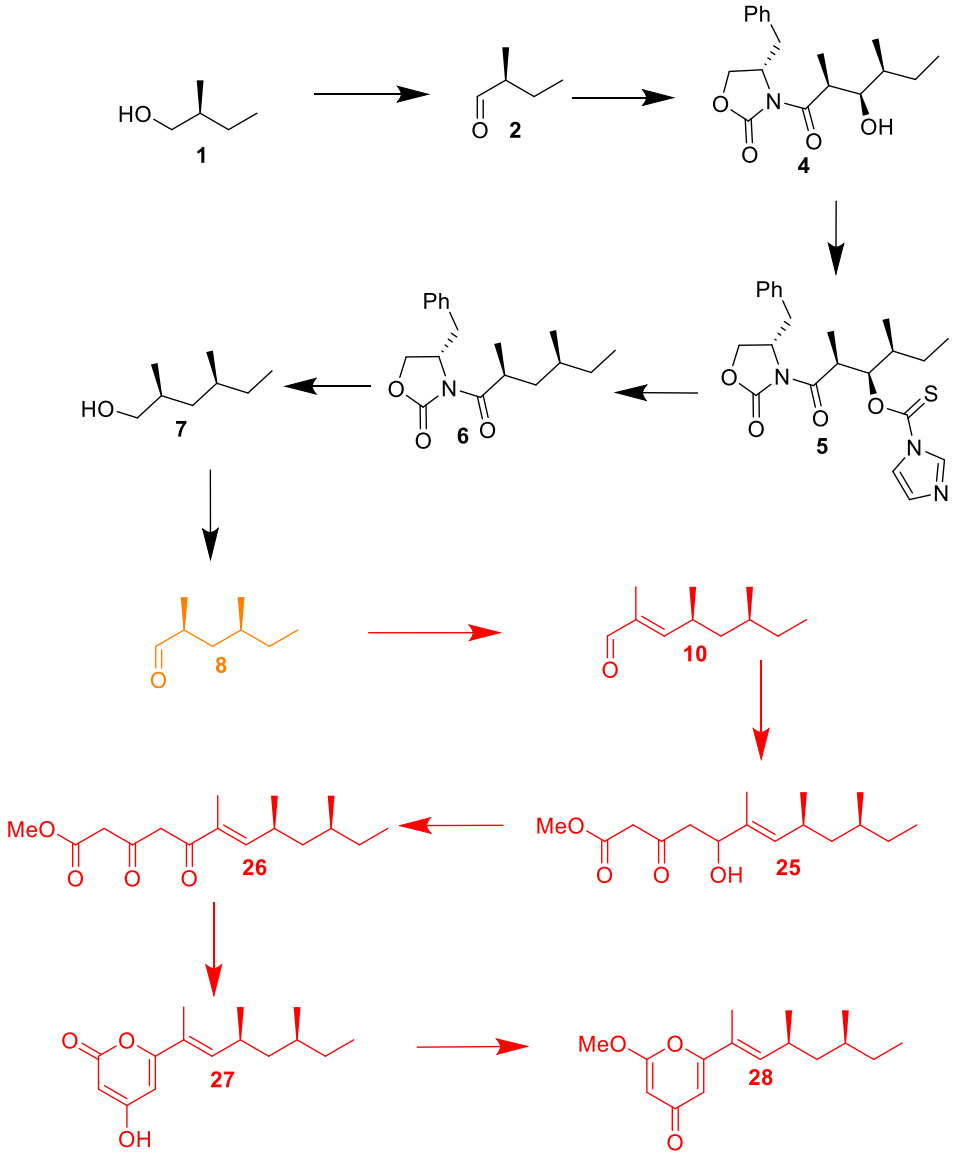

Scheme 3.4:

The thioester **5** (1.6 g, 3.73 mmol) was reduced to **6** (0.9 g, 2.97 mmol) at 80 % yield, by radical initiated deoxygenation, where AIBN was used as the initiator and trimethylsilylsilan as the reducing agent.




Scheme 3.5

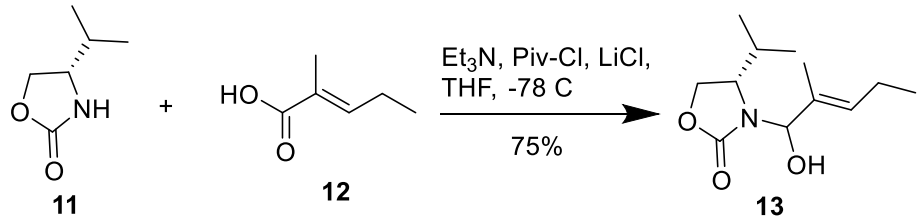
**6** (1.1 g, 3.6 mmol) reduced by $LiAlH_4$ to yield the alcohol **7** (0.3 g, 2.3 mmol, 64%) as a colorless oil.




Scheme 3.6: Reaction pathway for synthesizing Fusolanone B, based on the experimental results obtained. The red compounds was not obtained, and therefore is uncertain.

## Alternative reaction pathway

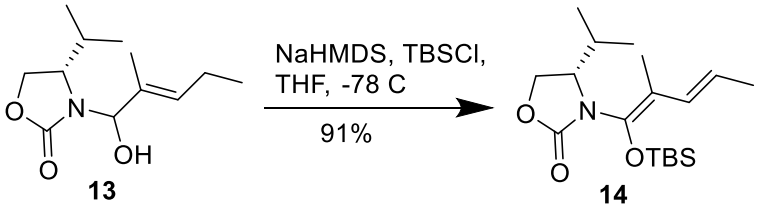
### Aldol reaction




Scheme 3.7:

(4S)-3-((E)-1-hydroxy-2-methylpent-2-en-1-yl)-4-isopropyloxazolidin-2-one **12** was obtained in 75% yield.

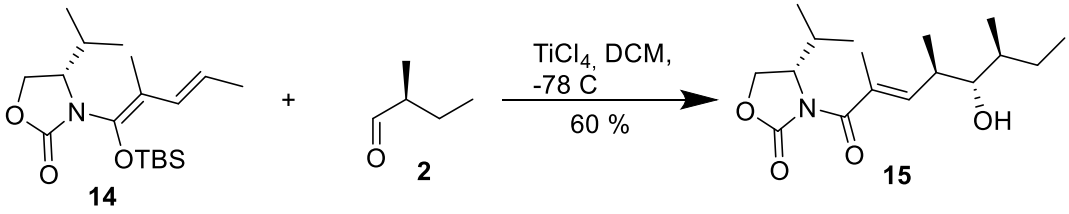
### (S)-3-((1Z,3E)-1-((tert-butyldimethylsilyl)oxy)-2-methylpenta-1,3-dien-1-yl)-4-isopropyloxazolidin-2-one (14)




Scheme 3.8

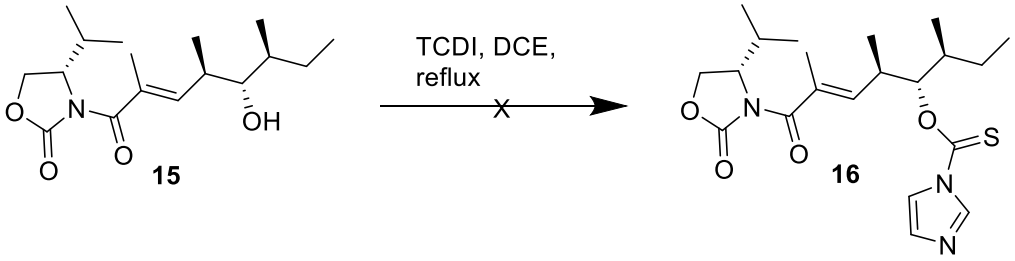
Adding TBS to the alcohol gave **14** in very good yield of 91%.

### (S)-3-((4R,5S,6S,E)-5-hydroxy-2,4,6-trimethyloct-2-enoyl)-4-isopropyloxazolidin-2-one (15)



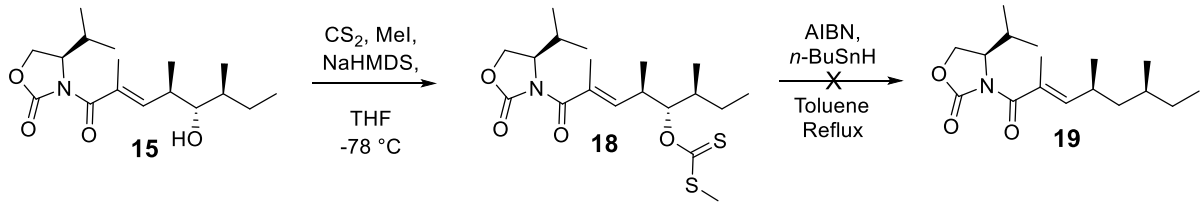

Scheme 3.9:

The product **15** was obtained in 60 % yield. The reaction was very slow (16h), and had to proceed under -78 °C to avoid significant amount of byproducts. The product was a clear oil.



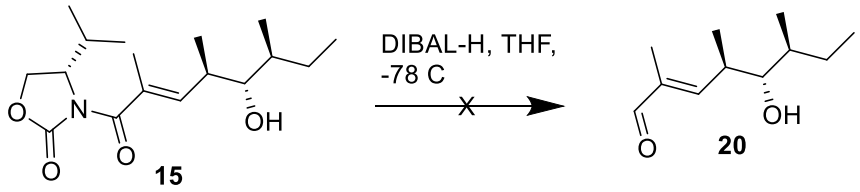

Scheme 3.10:

The conditions for thioesterification of **4** to give 77% of **5** was applied to **15**. unfortunately, **14** did not react with the 1.1'- thiocarbonyldiimidazole.



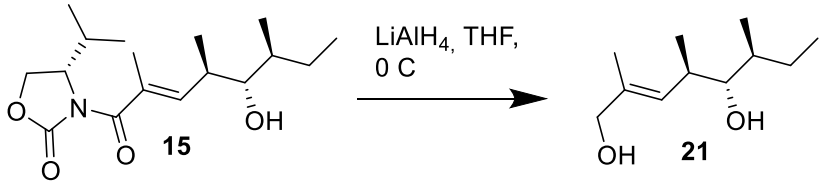

Scheme 3.11.Reaction for attempted deoxygenation of **15**.

An alternate Barton-Mccombie reaction was carried out to give **18** in low yield. The crude had a yellow impurity that was hard to purify, and might explain the low yield. After purification, deoxygenation with AIBN was carried out with AIBN and n-BuSnH. NMR samples of the fractions after purification indicated that the olefin in **18** (and **15**) had been broken. This is substantiated by Carey and Sundberg (p. 966).[9]



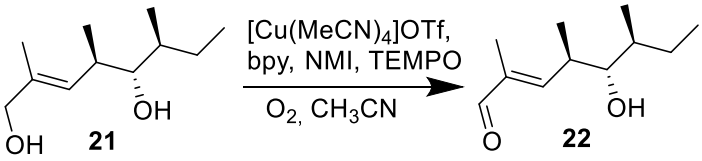

Scheme 3.12: Reaction conditions for attempted cleavage of oxazolidinone.

To avoid using a radical reaction while the oxazolidinone group was still atached, removal of the oxazolidinone-group by DIBAL-H was attempted. Compound **15** did not react with DIBAL-H, which is believed to be due to steric hinderance.



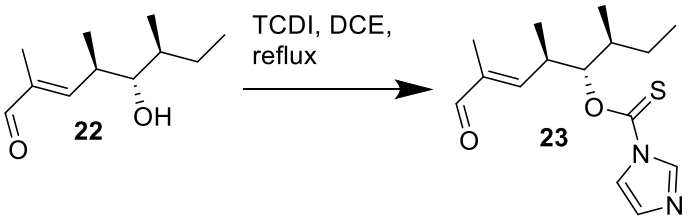

Scheme 3.13: Reaction condition for reduction of **15.**

The much less hindered $LiAlH_4$ was attempted as a substitute for DIBAL-H. The reaction gave the diol **21** in 65 % yield. Impurities of the oxazolidinone **11** was not separated from **21** even at fraction 50. The next reaction was carried out with these impurities.




Scheme 3.14: Reaction condition for selective oxidation of **21**.

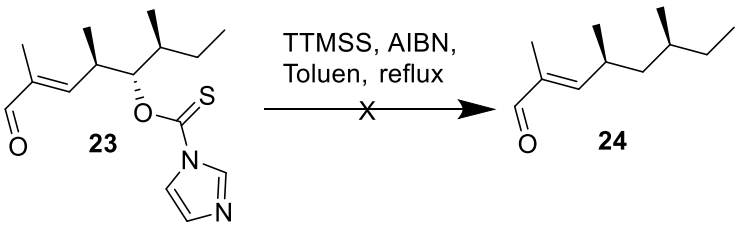
Hoover-Stahl oxidation was used to selectively oxidize the primary alcohol of the diol **21** to yield **22**. The starting material had impurities of the oxazolidinone **11**, but it was successfully separated from the product without interference in the reaction.




Scheme 3.15:

The original Barton-McCombie with TCDI was applied on **22** under the same conditions applied to the secondary alcohol **4**. **23** was obtained in 45% yield. The formation of **23** indicates that steric hinderence might be the problem for reacting **15** with TCDI, where the reaction did not occur.

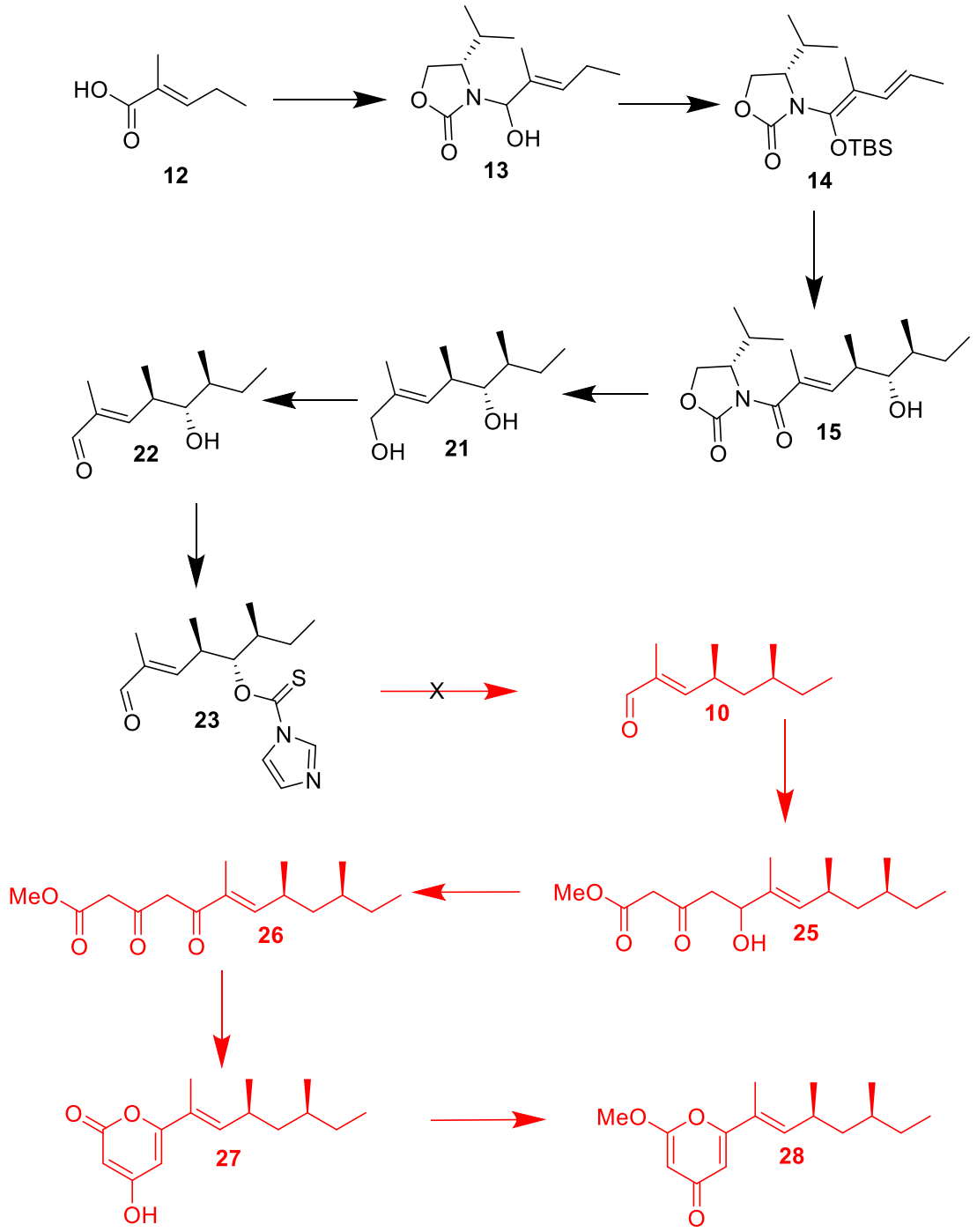
## Attempted deoxygenation




Scheme 3.16: Reaction conditions for attempted deoxygenation of **23.**

Deoxygenation of the thioester **23** under the same conditions used on **5** was attempted. NMR analysis after purification did not show sign of the olefin.

Due to the failed deoxygenation of both **18** and **23**, a different approach need to be made to obtain **10.** The successfull reactions, and the remaining steps to synthesize Fusolanone B is shown in sheme 3.17.




Scheme 3.17: Reaction pathway for synthesizing Fusolanone B (**28**), base experimental data obtained. The compounds in red was not obtained.

# 4. Spectroscopy

## (S)-2-methylbutanol

Table 1 shows assigned $^{1}H$ NMR shifts for (S)-2-methylbutanol (figure 1)

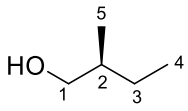



Figure 4.1: (S)-2-methylbutanol with numbering of carbons

Table 1: $^{1}H$ NMR shifts for (S)-2-methylbutanol

| Carbon no. | δ H (ppm) | M | [Hz] | Integral |
|---|---|---|---|---|
| 1 | 3.44 | m | - | 2 |
| 2 | 1.13 | m | - | 1 |
| 3 | 1.49 | m | - | 2 |
| 4 | 0.90 | t | 7.4 | 3 |
| 5 | 0.90 | d | 6.7 | 3 |

## (S)-2-methylbutanal

Table 2 shows assigned $^{1}H$ NMR shifts for (S)-2-methylbutanal (figure 2)

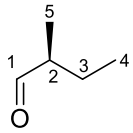



Figure 4.2: (S)-2-methylbutanal with numbered carbons

Table 2: Assigned shift for (S)-2-methylbutanal

| Carbon no. | δ H (ppm) | M | [Hz] | Integral |
|---|---|---|---|---|
| 1 | 9.61 | d | 1.9 | 1 |
| 2 | 2.27 | dsex | 1.8, 6.9 | 1 |
| 3 | 1.74 | sep | 7.1 | 1 |
| 3 | 1.42 | sep | 7.1 | 1 |
| 4 | 1.08 | d | 7.0 | 3 |
| 5 | 0.94 | t | 7.5 | 3 |

Compared to the spectra of (S)-2-methylbutanol, (S)-2-methylbutanal shows no sign of the sign of the multipled with integral 2 at 3.44, but instead has peak at 9.61 with integral 1. This indicates an oxidation to an aldehyde.

## (S)-4-isopropyloxazolidin-2-one

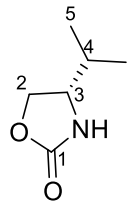


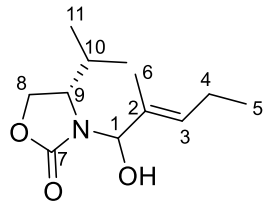

Figure 4.3

Table 3: NMR shift of compound 11.

| Carbon no. | δ H (ppm) | M | [Hz] | integral |
|---|---|---|---|---|
| 1 | - | - | - | - |
| 2 | 4.42, 4.08 | t, dd | 8.7, - | 2 |
| 3 | 3.60 | m | - | 1 |
| 4 | 1.70 | m | 6.7 | 1 |
| 5 | 0.91 | 2 x d | 6.7, 6.7 | 3+3 |
| N | 7.15 | s, broad | - | 1 |

## (4S)-3-((E)-1-hydroxy-2-methylpent-2-en-1-yl)-4-isopropyloxazolidin-2-one

Table 4 shows assigned $^{1}$H NMR shifts for (4S)-3-((E)-1-hydroxy-2-methylpent-2-en-1-yl)-4-isopropyloxazolidin-2-one (figure x)




*Figur 4.43*

Table 4: nmr shift of compound 12

| Carbon no. | δ H (ppm) | M | [Hz] | Integral |
|---|---|---|---|---|
| 1 | - | - | - | - |
| 2 | - | - | - | 0 |
| 3 | 6.09 | t | 7.3 | 1 |
| 4 | 2.22 | qv | 7.5 | 2 |
| 5 | 1.07 | t | 7.5 | 3 |
| 6 | 1.91 | s | - | 3 |
| 7 | - | - | - | - |
| 8 | 4.33, 4.18 | t, dd | 8.8, 5.3, 8.8 | 1 + 1 |
| 9 | 4.53 | m | | 1 |
| 10 | 2.38 | m | | 1 |
| 11 | 0.93 | t | 6.5 | 6 |

## (S)-3-((1Z,3E)-1-((tert-butyldimethylsilyl)oxy)-2-methylpenta-1,3-dien-1-yl)-4-isopropyloxazolidin-2-one

Chemical shift for compound **13** (figure 4.5) is shown in table 5.

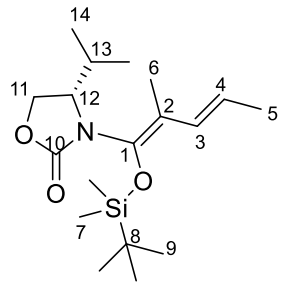



Figure 4.5

Table 5: NMR shift of compound 13.

| Carbon no. | δ H (ppm) | M | [Hz] | Integral |
|---|---|---|---|---|
| 1 | - | - | - | - |
| 2 | - | - | - | - |
| 3 | 6.23 | d | 15.4 | 1 |
| 4 | 5.65 | dq | 15.4, 6.6 | 1 |
| 5 | 1.80 | m | | 3’ |
| 6 | 1.80 | m | | 3’ |
| 7 | 0.2 | | | 6 |
| 8 | - | - | - | - |
| 9 | 1.00 | s | - | 9 |
| 10 | - | - | - | - |
| 11 | 4.0-4.4 | | | 2 |
| 12 | 4.0-4.4 | | | 1 |
| 13 | 1.97 | m | - | 1 |
| 14 | 0.95 | d | 6.9 | 6 |

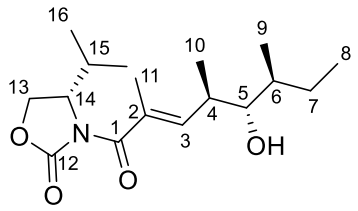
Compared to **13**, **14** does not have a qvintet at 2.22 ppm, but a doublet of quartet at 5.65. it also shows a doublet at 6.23 ppm with integral 1, while **13** shows a triplet. The low shift at 0.2 indicates the silyl.

## (S)-3-((4R,5S,6S,E)-5-hydroxy-2,4,6-trimethyloct-2-enoyl)-4-isopropyloxazolidin-2-one

For this compound (figur 6, **15**) $^{1}H$, $^{13}C$, COSY, HMBC and HSQC was carried out to determine shift for both proton and carbon. Table 6 show the assigned shifts, and figure 4.6 shows the carbon numbering of the compound analysed.

## (S)-3-((4R,5S,6S,E)-5-hydroxy-2,4,6-trimethyloct-2-enoyl)-4-isopropyloxazolidin-2-one

Chemical shift for compound **15** (figure 4.6) is shown in table 6.




Figur 4.6: carbon numbering of compound 15

Table 6: NMR shift of compound **15**

| Carbon no. | Δ H (ppm) | M | [Hz] | Integral | 13C |
|---|---|---|---|---|---|
| 1 | - | - | - | - | 172 |
| 2 | - | - | - | - | 132 |
| 3 | 5.71 | dd | 1.3, 10.3 | 1 | 143 |
| 4 | 2.66 | | | | 38 |
| 5 | 3.21 | dt | 2.0, 8.9 | 1 | 77 |
| 6 | 1.47 | m | | 1 | 36 |
| 7 | 1.30, 1.42 | m | | 2 | 27 |
| 8 | 0.86 | m | | 3 | |
| 9 | 0.86 | m | | 3 | |
| 10 | 0.86 | m | | 3 | |
| 11 | 1.86 | d | 1.3 | 3 | |
| 12 | - | - | - | - | 155 |
| 13 | 4.26, 4.10 | | | 2 | 63 |
| 14 | 4.49 | | | 1 | 58 |
| 15 | 2.27 | | | 1 | 28 |
| 16 | 0.86 | | | 6 | |

For the proton shifts at 0.9 and the belonging carbon shifts could not be assigned precisely due to the closeness of the shifts.

## (4R,5S,6S,E)-2,4,6-trimethyloct-2-ene-1,5-diol

The assigned shifts of the diol **21** (figure 4.7) is shown in table 7.

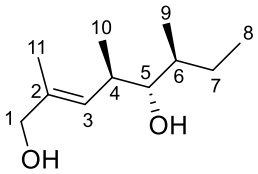



Figure 4.7:

Table 7: NMR shift of compound **21**

| Carbon no. | δ H (ppm) | M | [Hz] | Integral |
|---|---|---|---|---|
| 1 | 2.99 | s | - | 2 |
| 2 | - | - | - | -- |
| 3 | 5.30 | d | 9.9 | 1 |
| 4 | 2.56 | m | - | 1 |
| 5 | 3.24 | dd | 3.22, 8.16 | 1 |
| 6 | 1.51 | m | - | 1 |
| 7 | 1.43, 1.30 | m, m | - | 2 |
| 8 | 0.9 | - | - | 3* |
| 9 | 0.9 | - | - | 3* |
| 10 | 0.9 | - | - | 3* |
| 11 | 1.68 | s | - | 3 |

*impurities of oxazolidinone **11** is corrected for.

## (4R,5S,6S,E)-5-hydroxy-2,4,6-trimethyloct-2-enal

Table 8 shows assigned $^{1}H$ shifts for compound **22** (Figure 4.8).

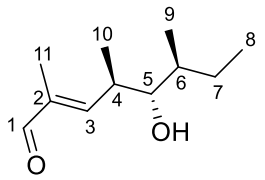



Figure 4.8:

Table 8: NMR shift of compound **22**

| Carbon no. | δ H (ppm) | M | [Hz] | integral |
|---|---|---|---|---|
| 1 | 9.43 | s | - | 1 |
| 2 | - | - | - | - |
| 3 | 6.54 | d(d) | 9.8, (1.2) | 1 |
| 4 | 2.91 | m | - | 1 |
| 5 | 3.46 | broad | - | 1 |
| 6 | 1.51 | m | - | 1 |
| 7 | 1.44, 1.26 | m | - | 1 + 1 |
| 8 | 0.92 | | 7.4 | 3 |
| 9 | 0.93 | d | 6.7 | 3 |
| 10 | 1.07 | d | 6.9 | 3 |
| 11 | 1.79 | s(d) | -, (1.2) | 3 |

The difference between the shifts of **22** and that of **21** is the singlet at 9.43 ppm at **22** and the singlet at 2.99 ppm with integral 2 at **21**, indicating successfull selective oxidation of primary alcohol.

## O-((3S,4S,5R,E)-3,5,7-trimethyl-8-oxooct-6-en-4-yl) 1H-imidazole-1-carbothioate

NMR shift of compound **23** (Figure 4.9) is shown in table 9.

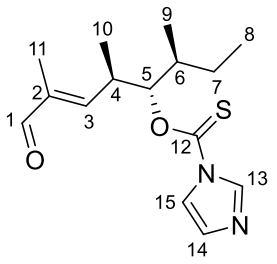



Figure 4.9

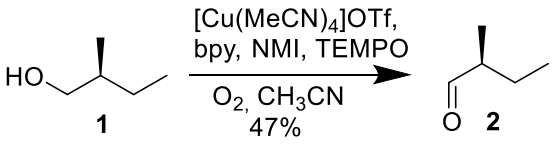
Table 9: NMR shift of compound **23**

| Carbon no. | δ H (ppm) | M | [Hz] | integral |
|---|---|---|---|---|
| 1 | 9.39 | s | - | 1 |
| 2 | - | - | - | - |
| 3 | 6.45 | d(d) | 10.2, (1.4) | 1 |
| 4 | 3.33 | m | - | 1 |
| 5 | 5.84 | dd | 4.3, 7.5 | 1 |
| 6 | 1.92 | m | - | 1 |
| 7 | 1.47, 1.27 | m, m | - | 1 + 1 |
| 8 | 0.98 | t | 7.4 | 3 |
| 9 | 1.08 | d | 6.8 | 3 |
| 10 | 1.19 | d | 6.8 | 3 |
| 11 | 1.75 | s(d) | (1.3) | 3 |
| 12 | - | - | - | - |
| 13 | 8.31 | s | - | 1 |
| 14 | 7.59 | s | - | 1 |
| 15 | 7.06 | s | - | 1 |

# 5. Experimental

## Oxidation of 2(S)-methylbutanol

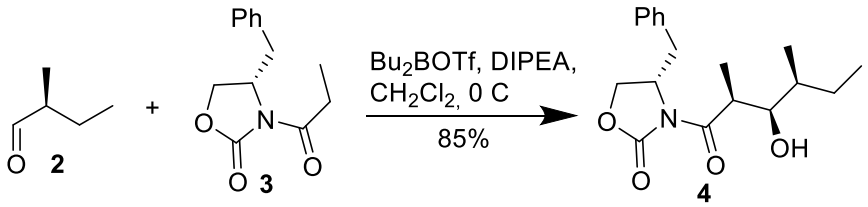
The procedure is based on copper-catalysed oxidation reported by Jessica Hoover and Shannon Stahl.[6]




2(S)-methylbutanol (**1**, 4.6 g) was dissolved in $CH_3CN$, and added $[Cu(MeCN)_4]OTf$ (5 mol% in $CH_3CN$), bpy (5 mol% in $CH_3CN$), TEMPO (5 mol% in $CH_3CN$) and NMI (10 mol% in $CH_3CN$). A balloon with $O_2$ was connected to the stirred reaction mixture, and the mixture was left stirring for 24 hours. When NMR showed no sign of alcohol, the reaction was evoporated and purified on a silica column, using DCM. Because of the volatile nature of the product, all of the DCM was not attempted to be removed. Product **2** was obtained dissolved in DCM (2.11 g, 47% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ = 9.65 (1H, s), 2.06 (1H, m), 1.52 (1H, m), 1.21 (1H, m), 0.84 (3H, d), 0.72 (3H, t).

## (S)-4-benzyl-3-((2S,3R,4S)-3-hydroxy-2,4-dimethylhexanoyl)oxazolidin-2-one (4)

This procedure follows

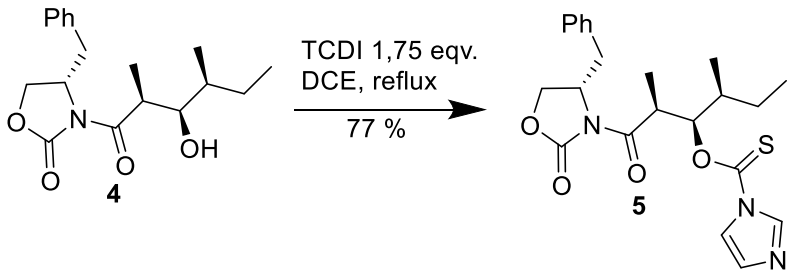



Scheme 5.1

The acylated oxazolidinone **3** ( 3.90 g, 16 mmol) was dissolved in $CH_2Cl_2$, in a dry flask under $N_2$ at 0 °C. 1M dibutylboron triflate in $CH_2Cl_2$ (1.2 eqv.) was added dropwise, followed by slow addition of DIPEA (1.3 eqv.). The solution was cooled to -78 °C, and 2(S)-methylbutanal **2** (1.1 eqv) was added. The solution was stirred for 30 minutes, before it was warmed to 0 °C and stirred for an additional 60 minutes. The reaction was quenched by addition of phosphate buffer and methanol, and stirred for an additional hour. The mixture was concentrated in vacuo, and the resulting slurry was extracted with $Et_2O$ (3 x 25 mL), washed with $Na_2CO_{2(aq)}$, brine, dried over $MgSO_4$ and concentrated in vacuo. Purification on silica column (20 % EtOAc/Pentan) to give the product **4** as a colorless oil (4.52 g, 85%). $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.3 (5H, m), 4.72 (1H, m), 4.22 (2H, m), 4.01 (1H, m), 3.71 (1H, dd), 3.28 (1H, dd), 2.81 (1H, dd), 1.51 (2H, m), 1.29 (3H, d), 1.15 (1H, m), 1.01 (3H, d), 0.93 (3H, t). $^{13}$C NMR(400 MHz, $CDCl_3$) δ = 178, 163, 136, 129, 129, 128, 75, 66, 55, 40, 38, 37, 25, 15, 11, 11.

## O-((2S,3R,4S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2,4-dimethyl-1-oxohexan-3-yl) 1H-imidazole-1-carbothioate

Barton mccombie deoxygenation[10]

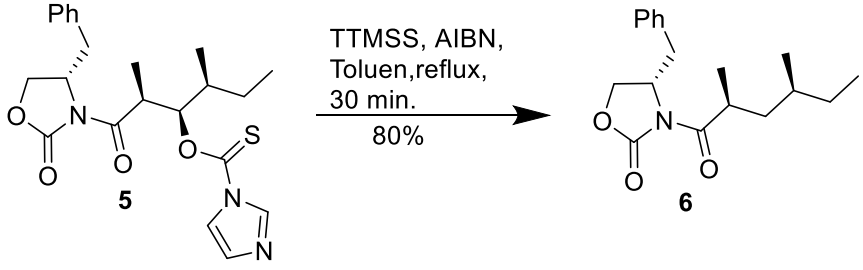



Scheme 5.2

The alcohol **4** (2.17 g, 6.8 mmol) and 1,1'-thiocarbonyldiimidazole (TCDI) (1.75 eqv.) was dissolved in 1,2-dichloroethane and heated under reflux for 5 hours. The solvent was evaporated and the crude was dissolved in $CH_2Cl_2$, washed with 5 % w/v tartaric acid, $H_2O$ and saturated $NaHCO_3$, dried over $MgSO_4$, and evaporated. Purification by silica column (20 % EtOAc/pentan) to give **5** as a yellow oil (2.25 g, 5.23 mmol, 77% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ = 8.38 (1H, s), 7.64 (1H, s), 7.31 (5H, m), 7.09 (1H, s), 6.09 (1H, t), 4.54 (1H, m), 4.42 (1H, m), 4.22 (2H, m), 3.27 (1H, dd), 2.79 (1H, dd), 1.94 (1H, m), 1.63 (1H, m), 1.34 (4H, d + m), 1.00 (6H, m). ). $^{13}$C NMR(400 MHz, $CDCl_3$) δ = 173, 153, 135, 131, 129, 129, 127, 87, 66, 56, 40, 38, 37, 25, 15, 11, 11.

## (S)-4-benzyl-3-((2S,4S)-2,4-dimethylhexanoyl)oxazolidin-2-one

Radical deoxygenation[11]

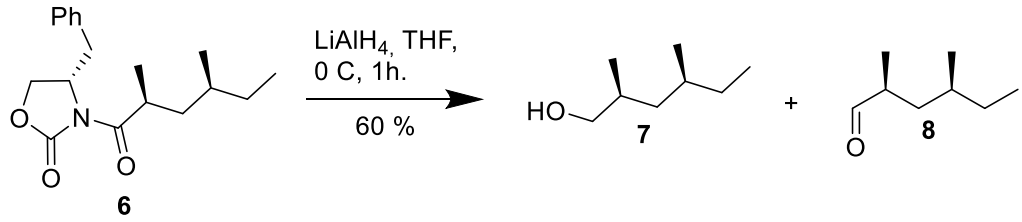



Scheme 5.3

The carbothioate **5** (1.6 g) was dissolved in toluene, and AIBN (0.3 eqv.) and tris(trimethylsilyl)silane (1.2 eqv.) were added. The mixture was slowly heated, and refluxed for 30 min under $N_2$. After cooling, the mixture was added $NaHCO_{3(aq)}$ (20 % w/w) and extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over $MgSO_4$,

consentrated in vacuo and purafied by silica column (EtOAc/pentan). Purification resulted in **6** (0.9 g) as a colorless oil 80 % yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ = 7.29 (5H, m), 4.69 (1H, m), 4.18 (2H, m), 3.90 (1H, m), 3.28 (1H, dd), 2.79 (1H, dd), 1.89 (1H, m), 1.36 (2H, m), 1.24 (3H, d), 1.17 (2H, m), 0.90 (6H, m). $^{13}$C NMR(400 MHz, $CDCl_3$) δ = 177, 153, 135, 129, 129, 127, 66, 55, 40, 38, 35, 32, 29, 19, 18, 11.

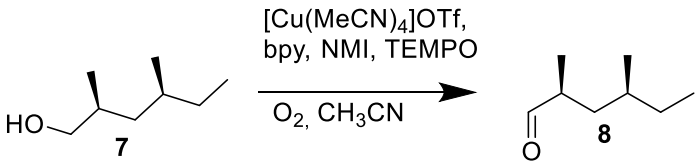
## Removal of oxazolidinone group by reduction




Scheme 5.4

The oxazolidinone **6** dissolved in dry THF was added $LiAlH_4$ slowly, at 0 °C. After 45 minutes, the reaction was quenched by addition of methanol, and the reaction was allowed to stir for 30 minutes, before water and NaOH (1M) was added slowly. The mixture was extracted with EtOAc (3x), washed with $NaHCO_3$, dried over $MgSO_4$, concentrated in vacuo and purified by silica column (EtOAc/Pentan). Purification resulted in both the alcohol **7,** and the aldehyde **8** (60 % total). $^{1}$H NMR (400 MHz, $CDCl_3$) δ = 3.46 (2H, m), 1.72 (1H, m), 1.35 (3H, m), 1.10 (1H, m), 0.95 (10H, m). $^{13}$C NMR(400 MHz, $CDCl_3$) δ = 69, 41, 34, 32, 30, 20, 18, 17.

## Hoover-Stahl oxidation

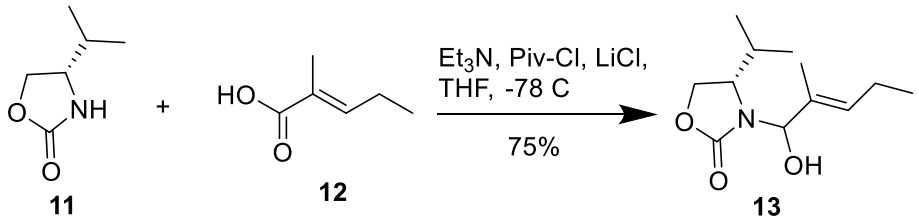



Scheme 5.5

The alcohol **7** was dissolved in $CH_3CN$, and added $[Cu(MeCN)_4]OTf$ (5 mol% in $CH_3CN$), bpy (5 mol% in $CH_3CN$), TEMPO (5 mol% in $CH_3CN$) and NMI (10 mol% in $CH_3CN$). A balloon with $O_2$ was connected to the stirred reaction mixture, and the mixture was left stirring for 24 hours. When NMR showed no sign of alcohol, the reaction was evoporated and purified on a silica column, using DCM. NMR indicated aldehyde, but further purification is needed.

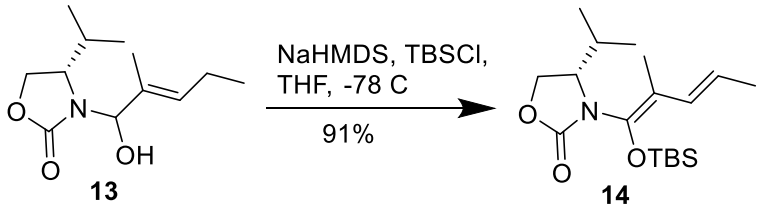
# Alternative path

## Aldol[12]



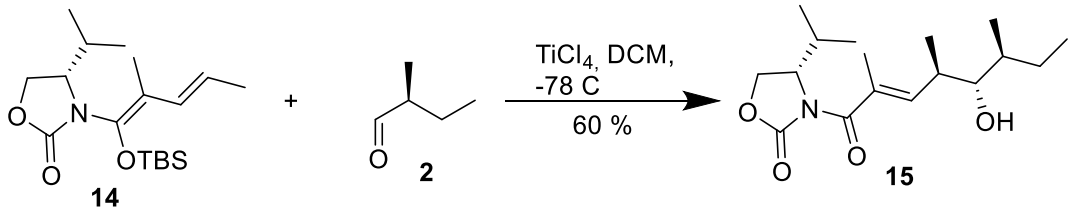

A stirred solution of (E)-methyl-2-pentenoic acid **12** (2.79 g, 24.4 mmol) in THF (110 mL) was added triethylamine (9 mL) and cooled to -78 °C. Trimethylacetyl acetyl chloride (3.1 mL) was then added slowly over 10 minutes, before the mixture was allowed to warm to room temperature and stirred for 60 minutes. The mixture was added LiCl (1.234 g) and (S)—4-isopropyloxazolidin-2-one **11** (2.62 g, 20 mmol mmol). After TLC indicated no starting material (3 days), the reaction was quenched with 1:1 water:sat.$NH_4Cl$ solution. The layers were separated, and the aqueous layer was extracted with $Et_2O$. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and consentrated in vacuo. Purified by silica column (20% EtOAc in pentan) to result in (4S)-3-((E)-1-hydroxy-2-methylpent-2-en-1-yl)-4-isopropyloxazolidin-2-one **13** (3.8 g, 75%). $^1$H NMR (400 MHz, $CDCl_3$) δ = 6.09 (1H, t, J = 7.3 Hz), 4.53 (1H, m), 4.33 (1H, m), 4.18 (1H, m), 2.38 (1H, m), 2.22 (2H, qv, J = 7.5 Hz), 1.91 (3H, s), 1.07 (3H, t, J = 7.5 Hz), 0.93 (6H, t, J = 6.5 Hz. $^{13}$C NMR (400 MHz, $CDCl_3$) δ = 172, 154, 141, 130, 63, 58, 28, 22, 18, 15, 13, 13.

## TBS



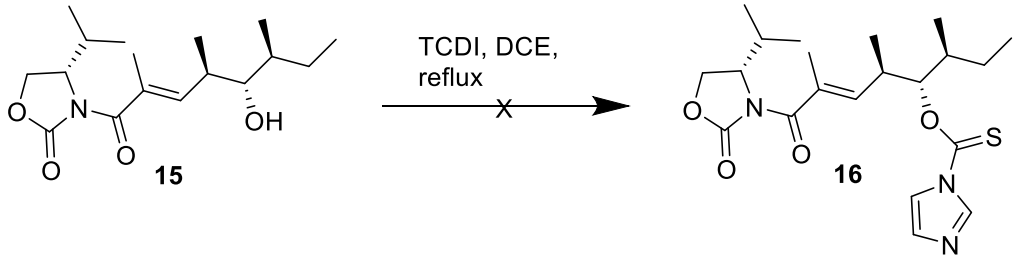

(4S)-3-((E)-1-hydroxy-2-methylpent-2-en-1-yl)-4-isopropyloxazolidin-2-one **13** (3.7 g, 16.44 mmol) in THF (150 mL) at -78 C was added NaHMDS (25 mmol) slowly, before the solution was stirred for 135 minutes at -78 C. TBSCl (xx g, xx mmol) in THF (xx mL) was added slowly and the mixture was stirred for addition 120 minutes at -78 C, before it was quenched with $NH_4Cl$, and warmed to room temperature. Layers were separated and aqueous layer was extracted with EtOAc, before it was washed with brine, dried over $MgSO_4$, filtered, and consentrated in vacuo. Purification by silica column (20 %EtOAc in pentan) to yield **14** (5, 06 g, 91%) as a colorles oil). $^1$H NMR (400 MHz, $CDCl_3$) δ = 6.23 (1H, d, J = 15.4 Hz), 5.65 (1H, dq, J = 15.4, 6.6 Hz), 4.34 (1H, m), 4.15 (1H, t), 4.01 (1H, m), 1.97 (1H, m), 1.80 (6H, m), 1.00 (9H, s), 0.95 (6H, d, J = 6.9 Hz), 0.2 (6H). $[\alpha]_D^{20}$ = -7.89 ($CHCl_3$, *c* = 2.0)

## Mukaiyama aldol[13]



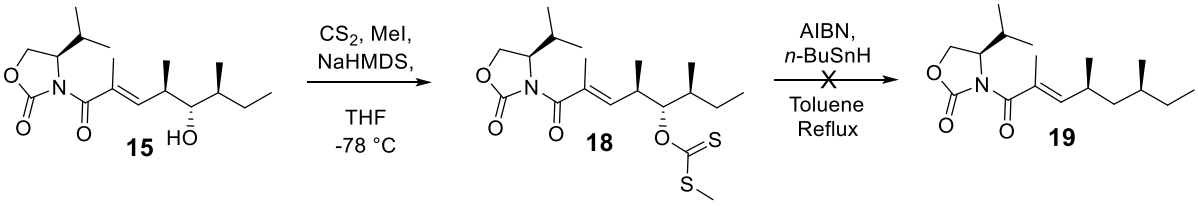

The aldehyde **2** (xx g, xx mmol, 2 eqv.) in $CH_2Cl_2$ (xx mL) was cooled to -78 C, before TiCl (xx g, xx mmol) and the silyl N,O-acetal **14** (xx g, xx mmol) were added. The reaction was stirred for 16 hours before it was quenched with tartaric acid (aq), and saturated $NaHCO_{3(aq)}$. The mixture was allowed to warm to r.t. while stirring, before extracting with EtOAc. The organic layers were washed with brine, dried over $MgSO_4$, filtered and consentrated in vacuo. Purification by silica column (20 % EtOAc in pentan) to yield **15** as a colorless oil (60 %). $^1$H NMR (400 MHz, $CDCl_3$) δ = 5.7 (1H, dd, J = 10.3, 1.3 Hz), 4.51 (1H, m), 4.45 (1H, m) 4.10 (1H, m), 3.21 (1H, dt, J = 8.9, 2.0), 2.66 (1H, m), 1.86 (3H, d, J = 1.3 Hz), 1.47 (1H, m), 1.42 (1H, m), 1.30 (1H, m), 0.86 (15H, m). $^{13}$C NMR(400 MHz, $CDCl_3$) δ = 172, 155, 143, 131, 77, 63, 58, 37, 36, 28, 27, 18, 16, 15, 14, 12, 12. IR: 3526, 2962, 2933, 2875, 1766, 1683, 1205. $[\alpha]_D^{20}$ = + 3.3 ($CHCl_3$, *c* = 2.0)

## McCombie




The alcohol **4** and 1,1'-thiocarbonyldiimidazole (TCDI) (1.75 eqv.) was dissolved in 1,2-dichloroethane and heated under reflux for 5 hours. The solvent was evaporated and the crude was dissolved in $CH_2Cl_2$, washed with 5 % w/v tartaric acid, $H_2O$ and saturated $NaHCO_3$, dried over $MgSO_4$, and evaporated. Purification by silica column (20 % EtOAc/pentan) indicated that no reacted had occured.

## Alternate McCombie deoxygenation[14]

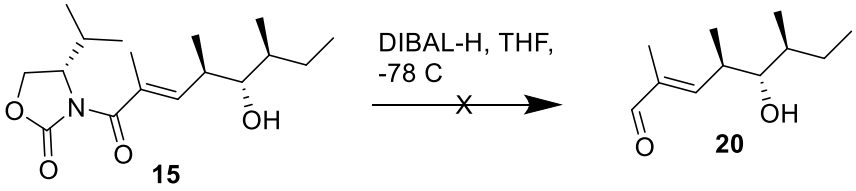



The secondary alcohol **15** (3 mmol) in anhydrous THF (15 mL) was cooled to -78 C, and stirred for 30 min. $CS_2$ (60 mmol) was added, and the solution was stirred for another 30 minutes, before MeI (90 mmol) was added and the solution was stirred for another 15

minutes. The reaction was quenched with $H_2O$ before it was allowed to warm to room temperature. Extracted by EtOAc, before the organic phases was washed with brine, dried over $MgSO_4$, filtered and consentrated in vacuo. Purification by silica column (10% EtOAc in pentan) to give **18** (low yield). $^1$H NMR (400 MHz, $CDCl_3$) δ =

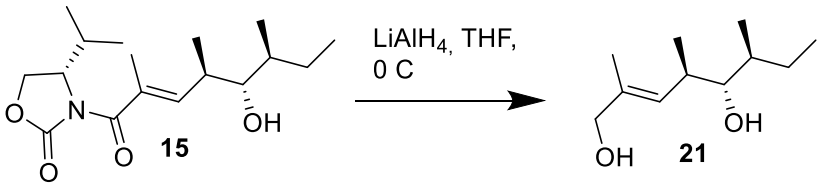
Compound **18**, $Bu_3SnH$ and AIBN was mixed together and stirred unter reflux at 120 C for 1 h. The reaction was quenched by addition of $H_2O$, extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and consentrated in vacuo. Purification by silica column (EtOAc gradient in pentane) did not give the expected compound.

## Reduction by DIBAL-H [15]




The secondary alcohol **15**(0.3 g) in THF (15 mL) was cooled to -78 C, and added DIBAL-H (1,2 mL, 1M) under inert athmosphere. The reaction was stirred for 2 hours, but no sign of any reaction was indicated by nmr.

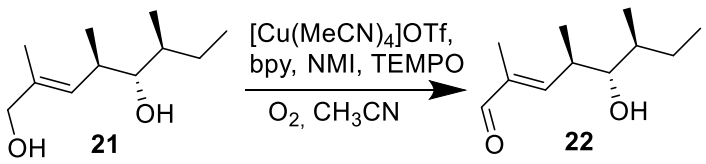
## Removal of oxazolidinone[12]




Same procedure as Scheme 5.4. diol **21** in 65% yield.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 5.30 (1H, d, J = 9.9 Hz), 3.24 (1H, dd, J = 8.2, 3.2 Hz), 2.99 (2H, s), 2.56 (1H, m), 1.68 (3H, s), 1.51 (1H, m), 1.43 (1H, m), 1.30 (1H, m), 0.9 (9H). $^{13}$C NMR (400 MHz, $CDCl_3$) δ = 137, 129, 78, 68, 36, 36, 27, 17, 14, 12, 12.

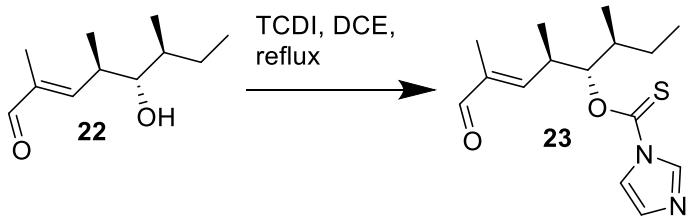
## Selective oxidation of primary alcohol[6]




The diol **21** was dissolved in $CH_3CN$, and added $[Cu(MeCN)_4]OTf$ (5 mol% in $CH_3CN$), bpy (5 mol% in $CH_3CN$), TEMPO (5 mol% in $CH_3CN$) and NMI (10 mol% in $CH_3CN$). A balloon with $O_2$ was connected to the stirred reaction mixture, and the mixture was left stirring for 24 hours.

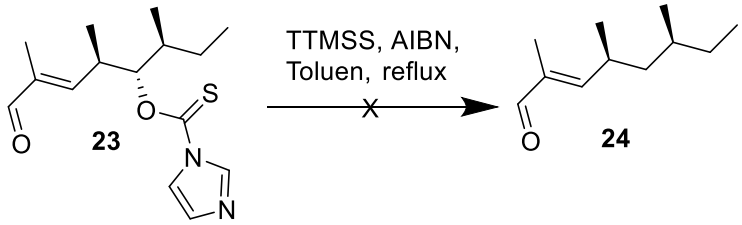
When NMR showed no sign of alcohol, the reaction was evoporated and purified on a silica column, using DCM. The purification resulted in the aldehyde **22.** $^{1}$H NMR (400 MHz, $CDCl_3$) δ = 9.43 (1H s), 6.54 (1H, dd, J = 9.8, 1.2 Hz), 3.46 (1H, b), 2.91 (1H, m), 1.79 (3H, d, J = 1.2), 1.51 (1H, m), 1.44 (1H, m), 1.26 (1H, m), 1.07 (3H, d, J = 6.9 Hz), 0.92 (6H, d + t, J = 6.7, 7.4 Hz). $^{13}$C NMR (400 MHz, $CDCl_3$) δ = 195, 157, 139, 78, 37, 37, 26, 17, 13, 12, 9.

## McCombie[10]




The alcohol **22** and 1,1'-thiocarbonyldiimidazole (TCDI) (1.75 eqv.) was dissolved in 1,2-dichloroethane and heated under reflux for 5 hours. The solvent was evaporated and the crude was dissolved in $CH_2Cl_2$, washed with 5 % w/v tartaric acid, $H_2O$ and saturated $NaHCO_3$, dried over $MgSO_4$, and evaporated. Purification by silica column (20 % EtOAc/pentan) to give **23** (xx%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ = 9.39 (1H, s), 8.31 (1H, s), 7.59 (1H, s), 7.06 (1H, s), 6.45 (1H, dd, J = 10.2, 1.4 Hz), 5.84 (1H, dd, J = 7.5, 4.3 Hz), 3.33 (1H, m), 1.92 (1H, m), 1.75 ( 3H, d, J = 1.3 Hz), 1.47 (1H, m) 1.27 (1H, m), 1.19 (3H, d, J = 6.8 Hz), 1.08 (3H, d, J = 6.8 Hz), 0.98 (3H, t, J = 7.4 Hz). $^{13}$C NMR(400 MHz, $CDCl_3$) δ = 195, 185, 153, 140, 131, 118, 89, 37, 36, 26, 17, 14, 12, 9.

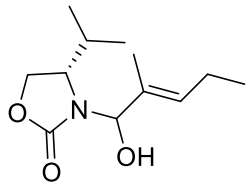
## Deoxygenation




Same conditions that was carried out on **5**, but did not yield the expected compound (**24**).

# 6. Spectra

## Spectra of compound **13**



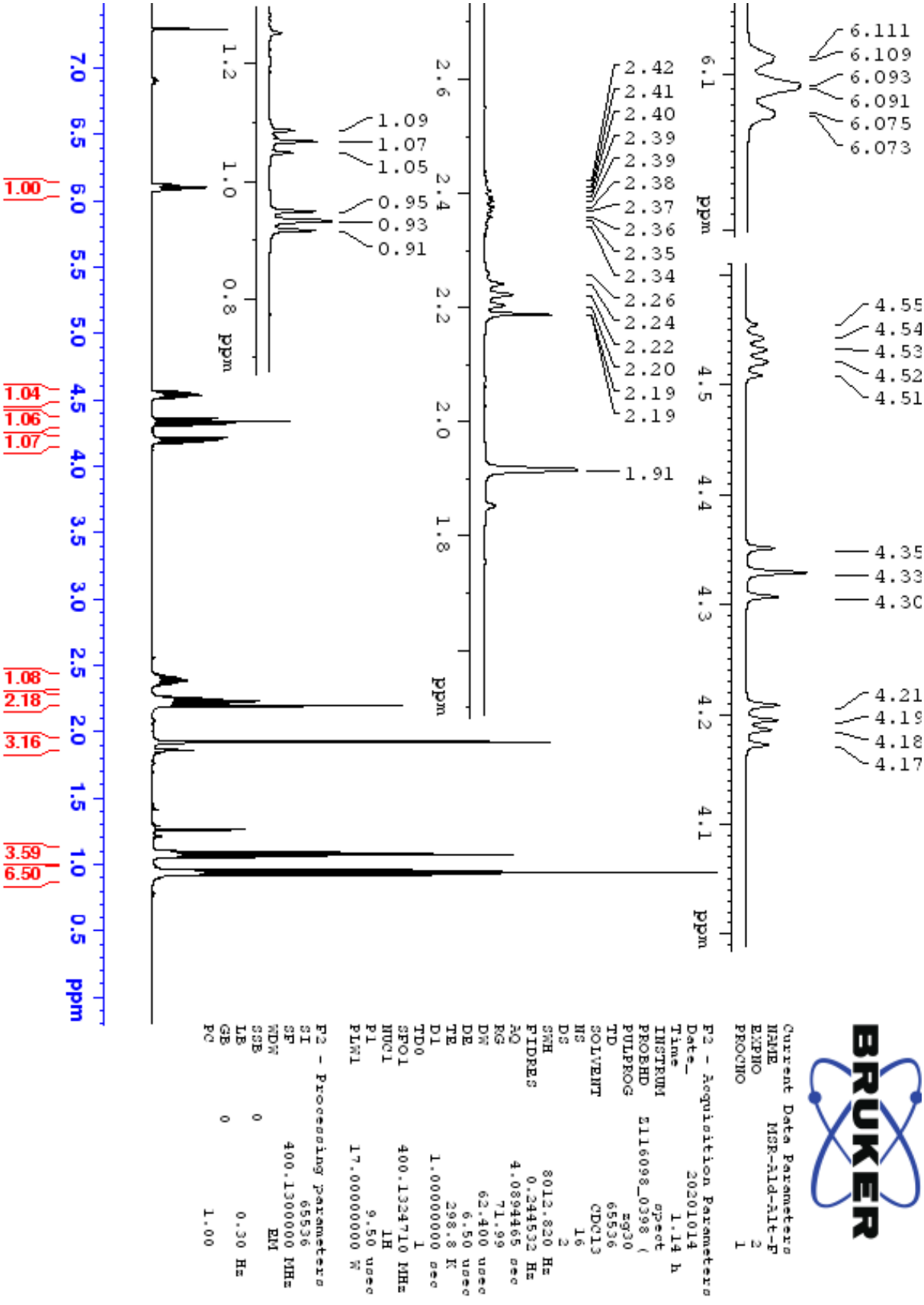



Figure 6.1: $^{1}$H NMR of **13**

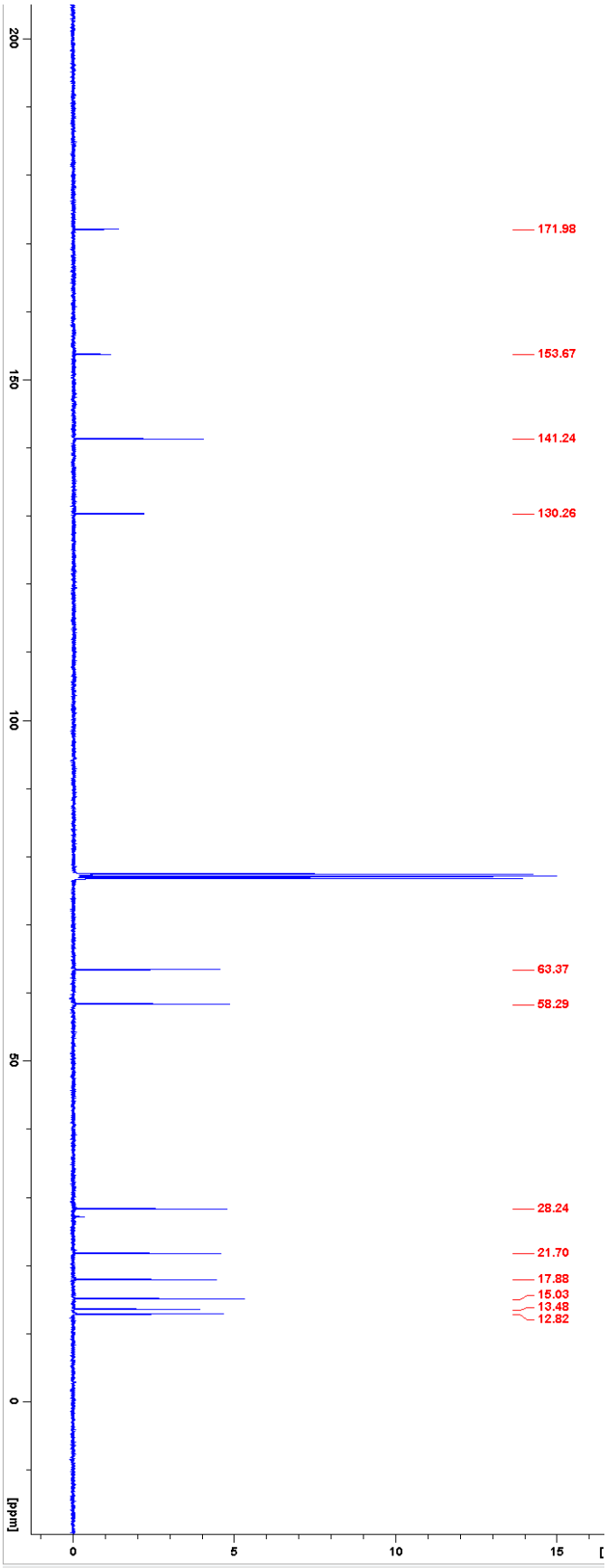
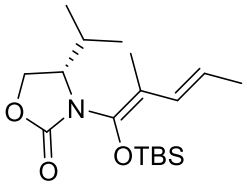



Figure 6.2: $^{13}C$ nmr of **13**

## Spectra of compound 14



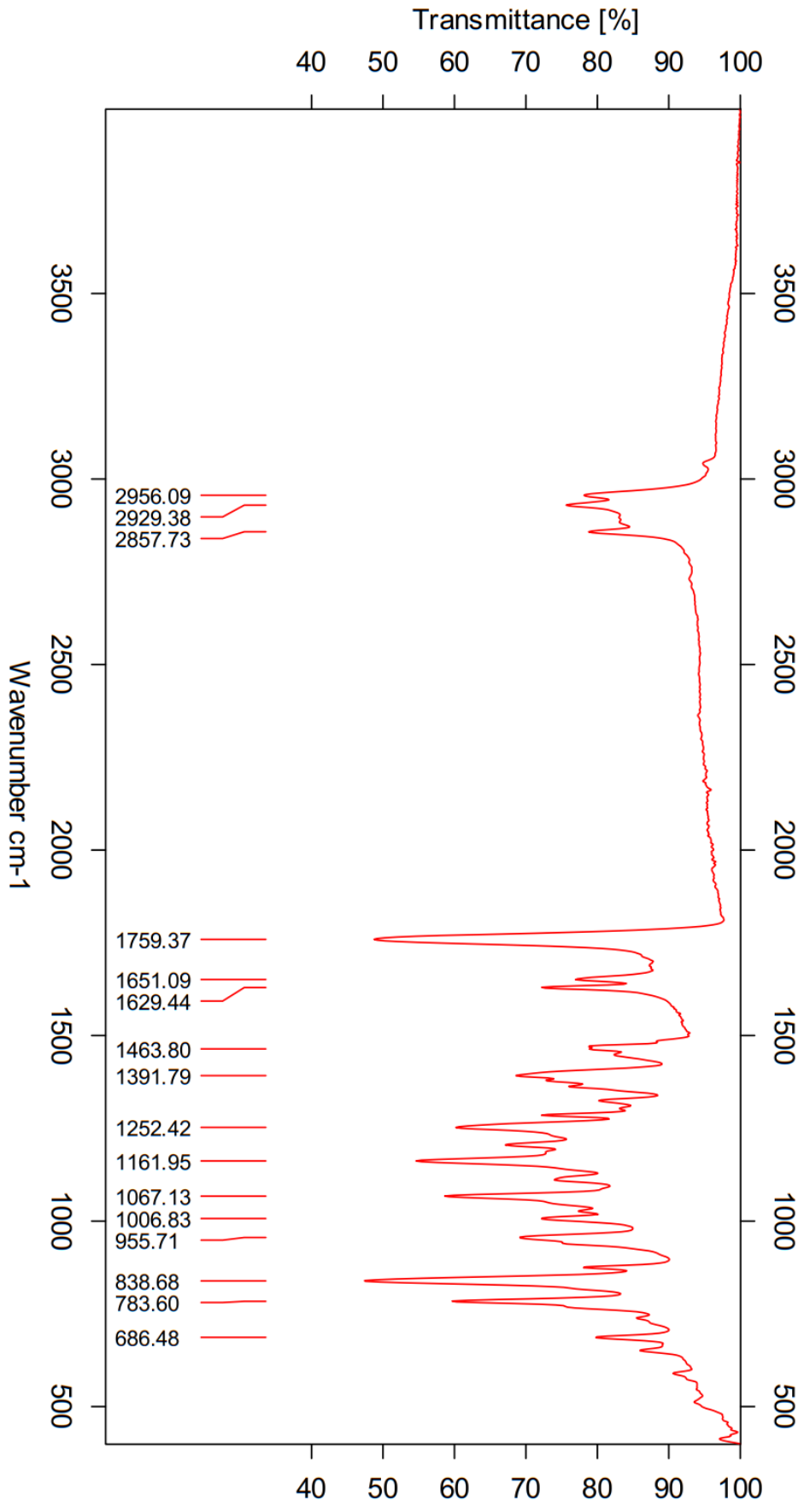



Figure 6.3: ir of **14**

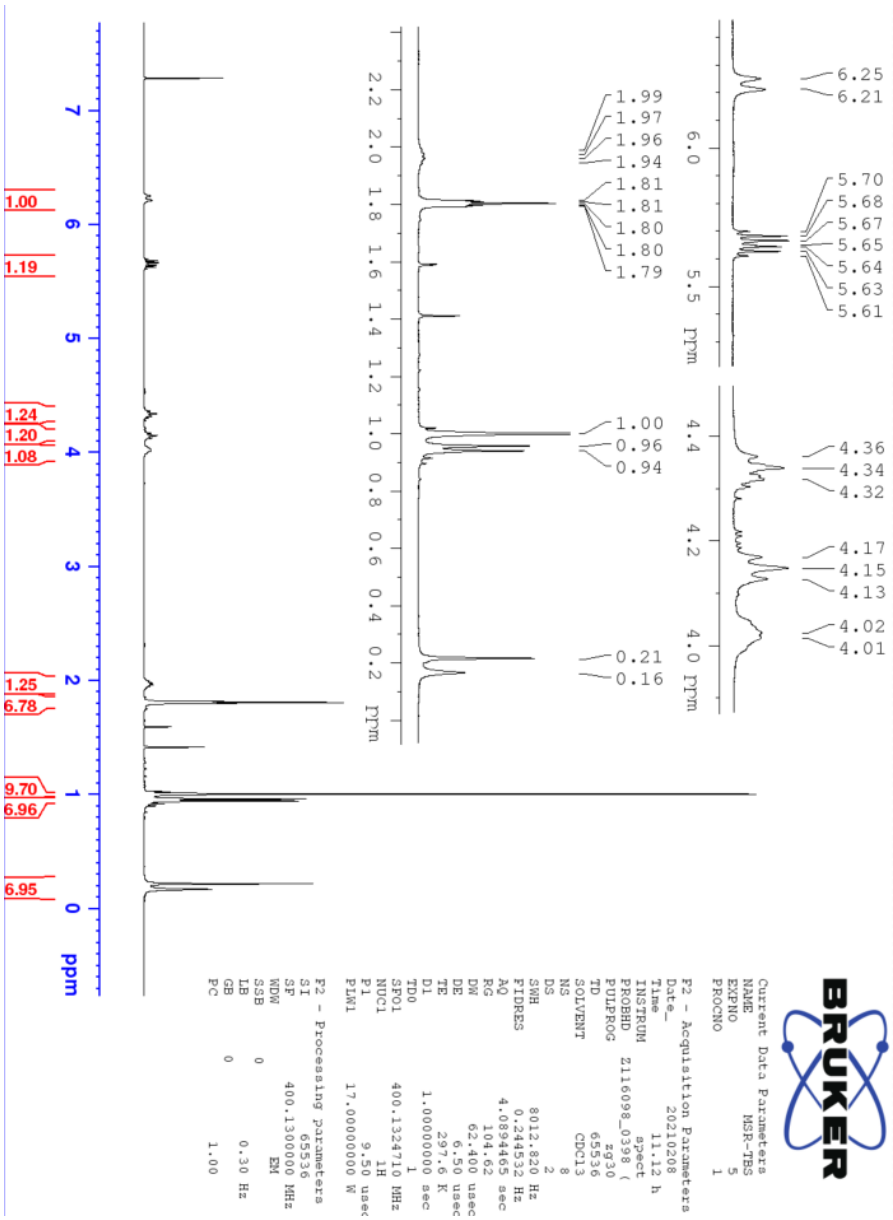
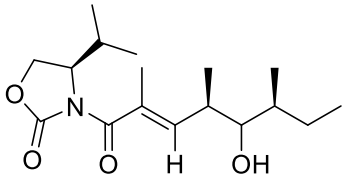


Figure 6.4: $^{1}$H NMR of compound **14**

## Spectra of compound 15



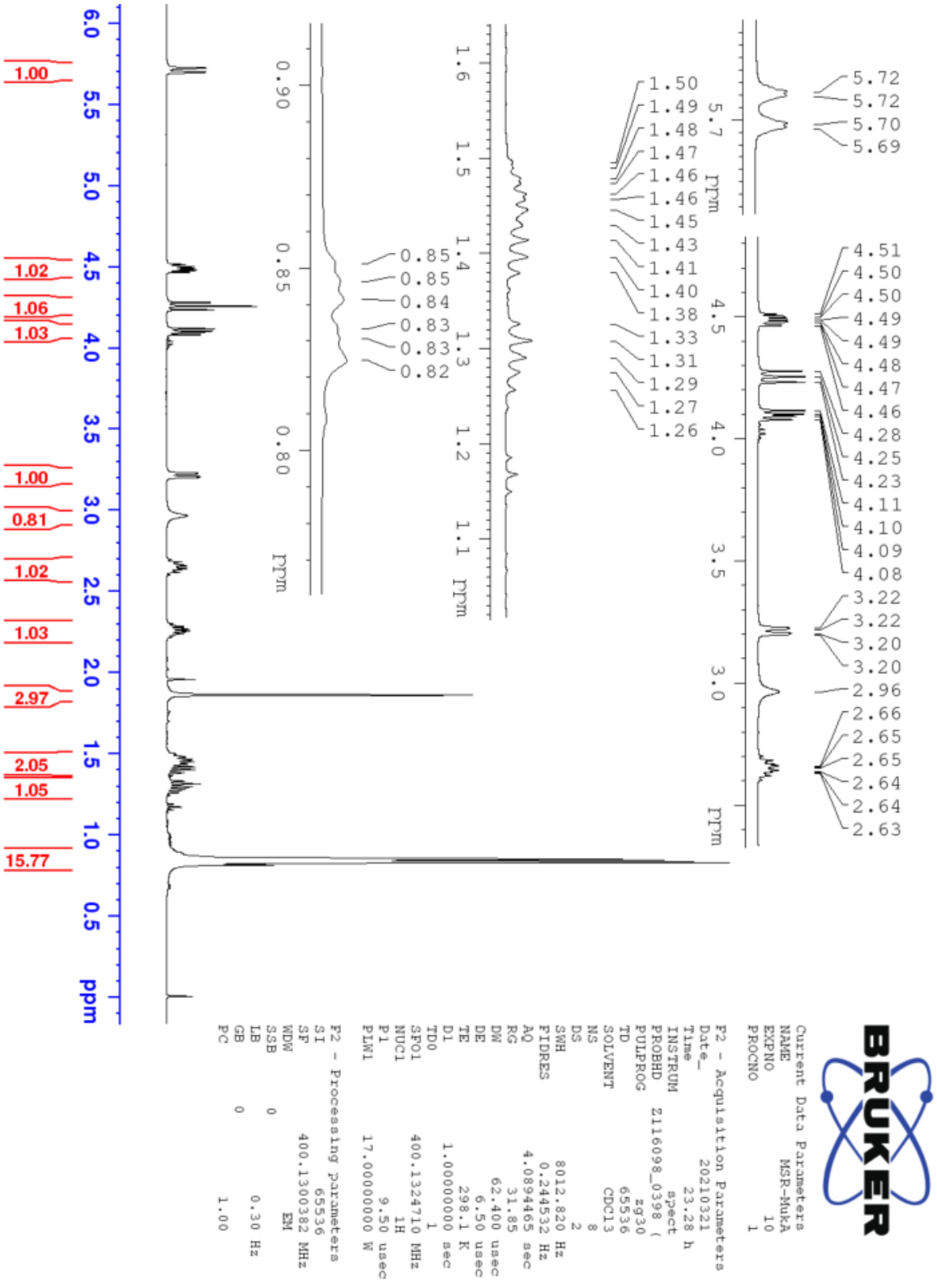



Figure 6.5: $^{1}$H NMR spectra of compound 15

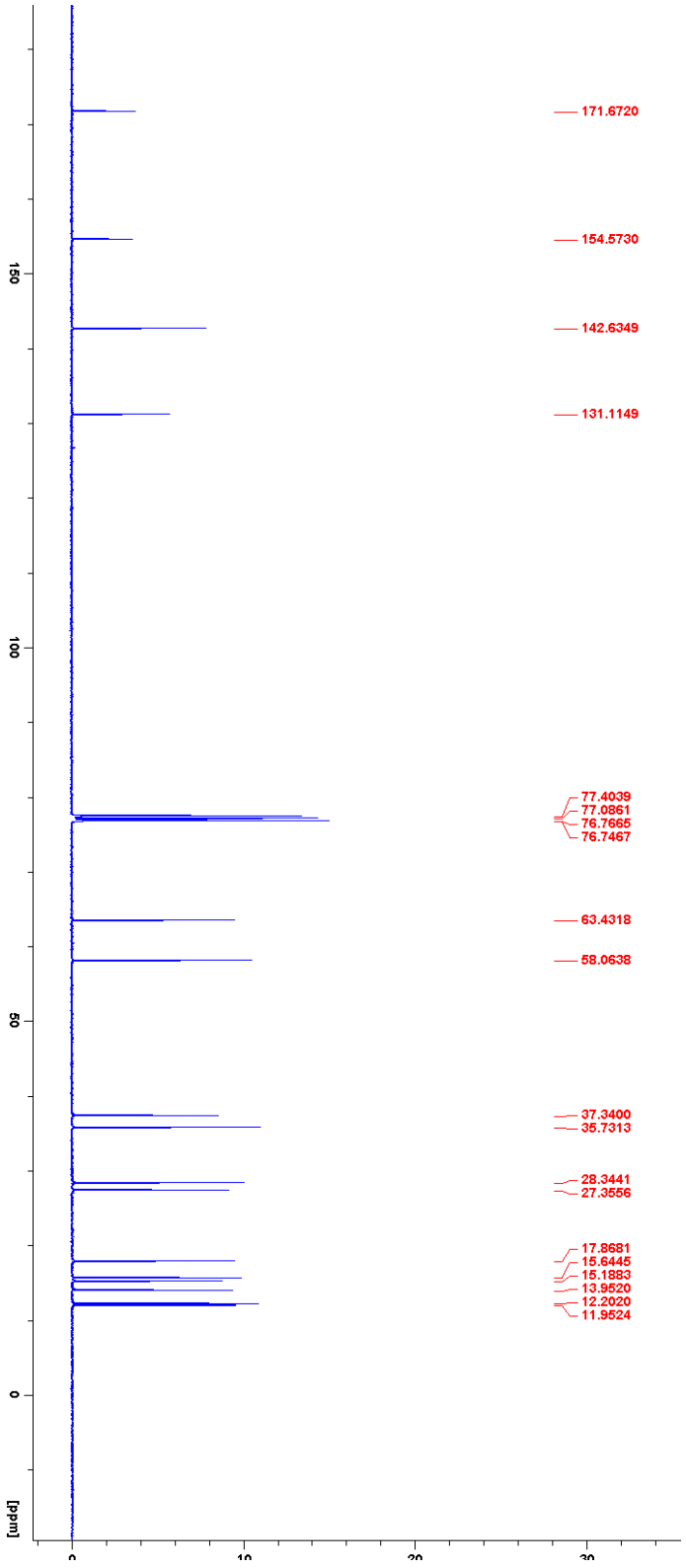



Figure 6.6: $^{13}C$ NMR spectra of **15**

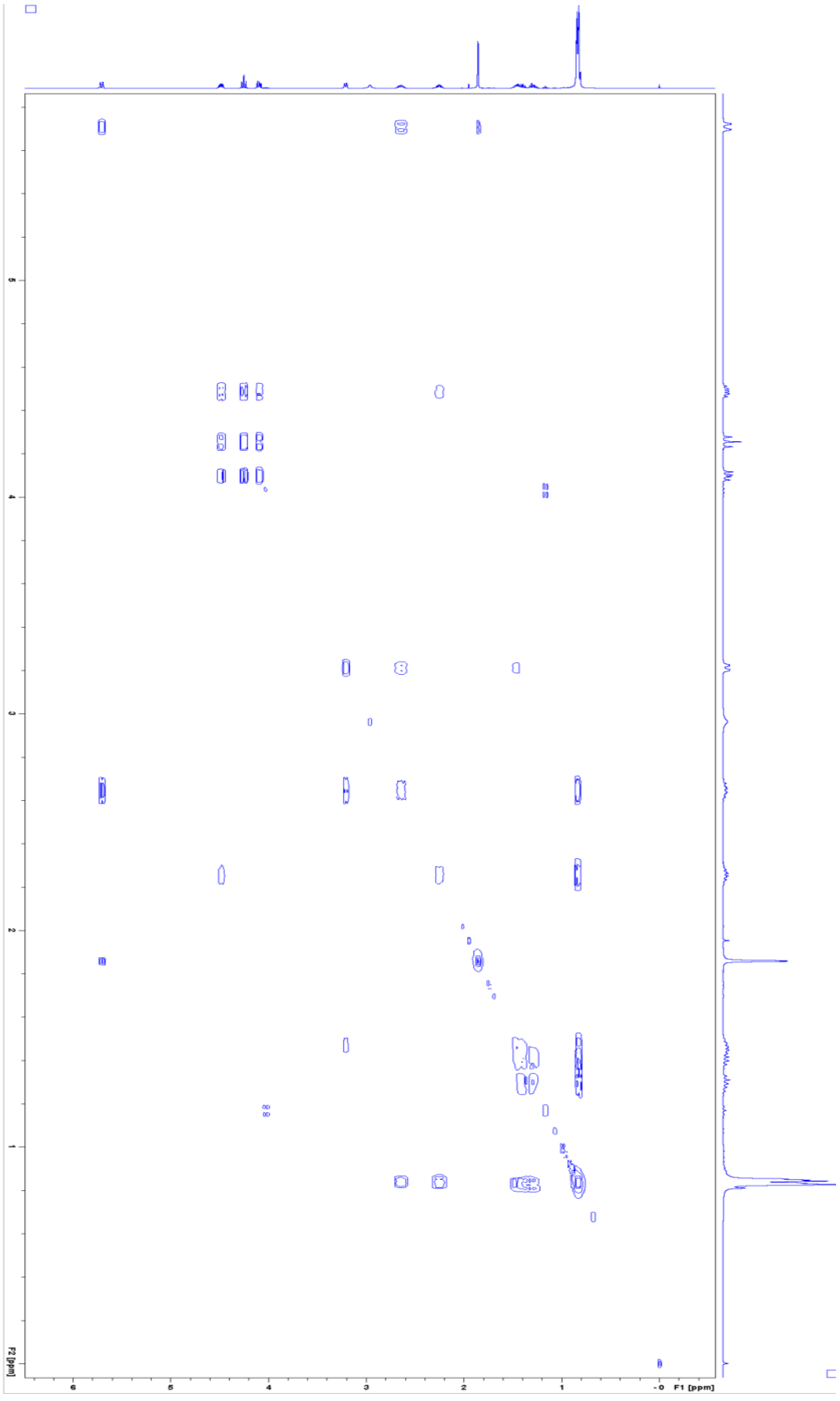



Figure 6.7: COSY spectra of compound **15**

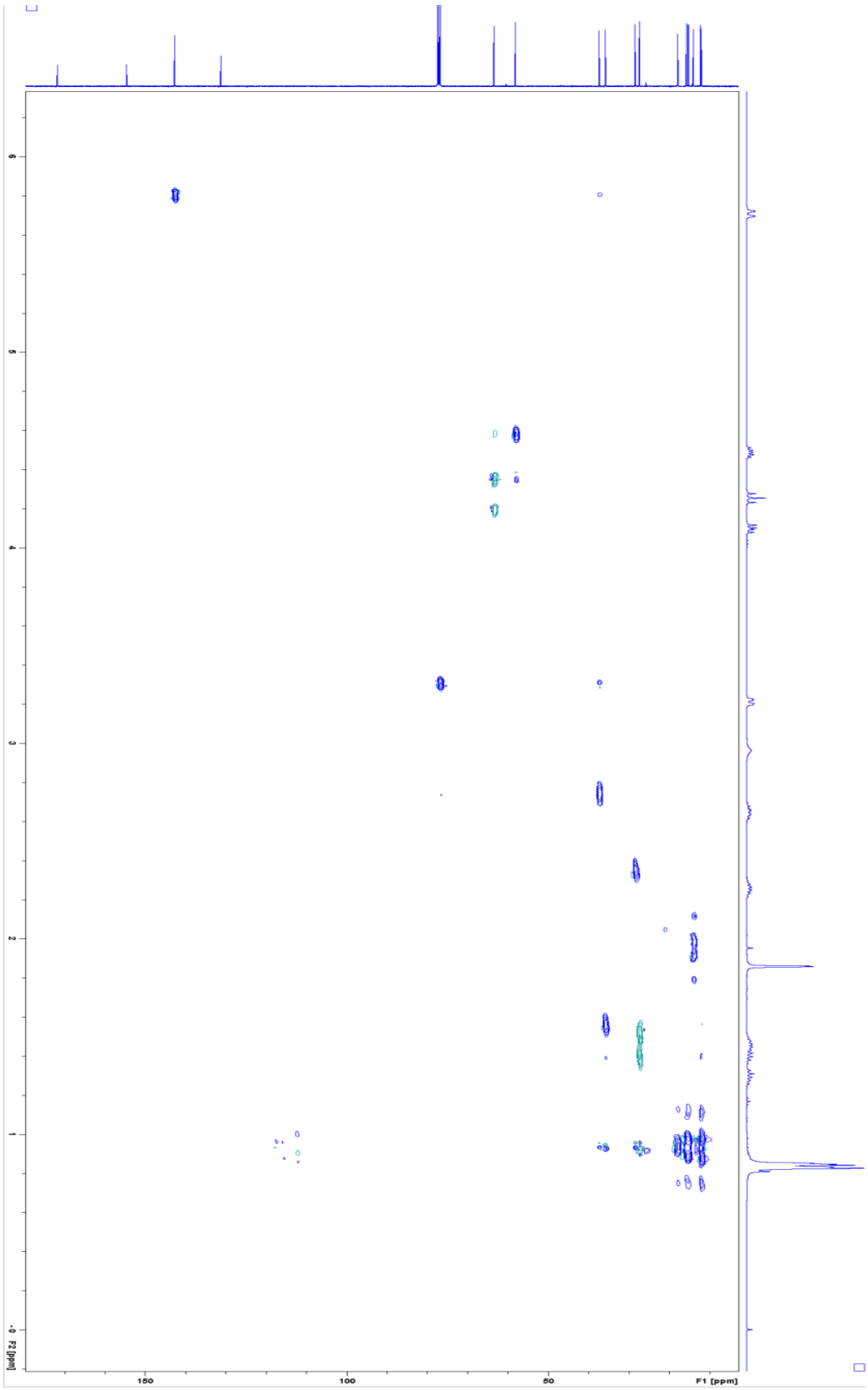



Figure 6.8: HSQC spectra of compound **15**.

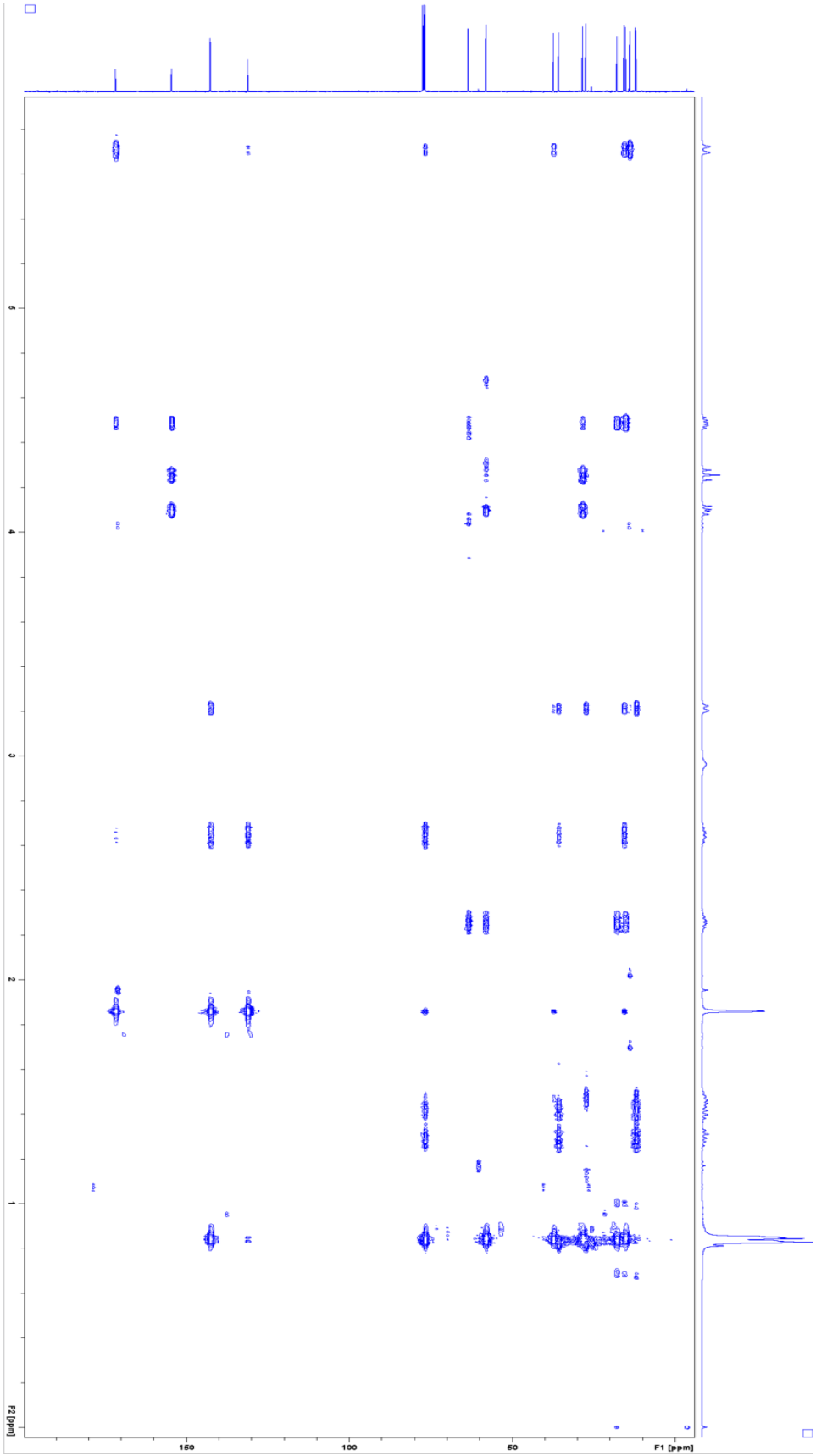



Figure 6.9: HMBC spectra of compound **15**

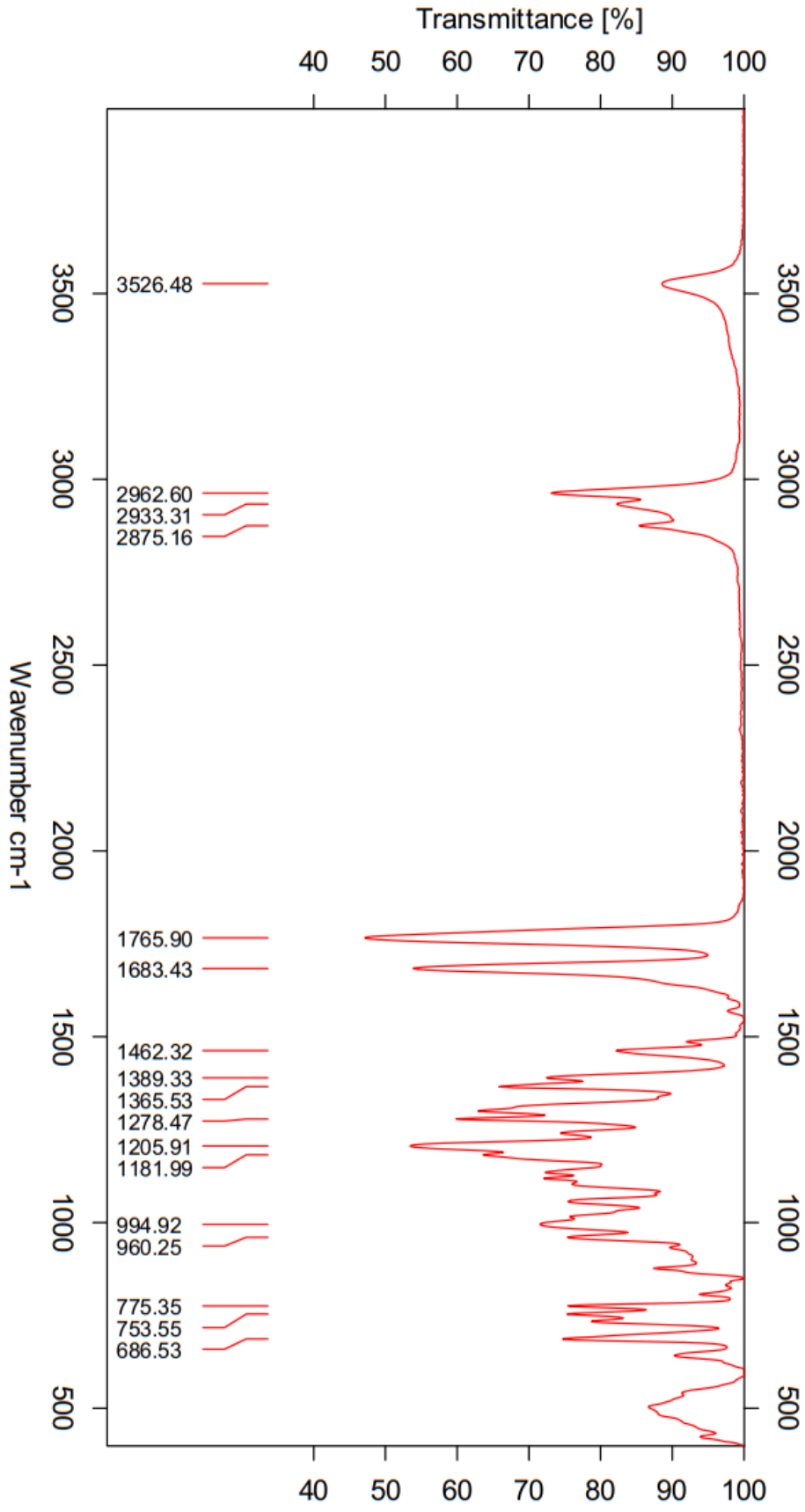
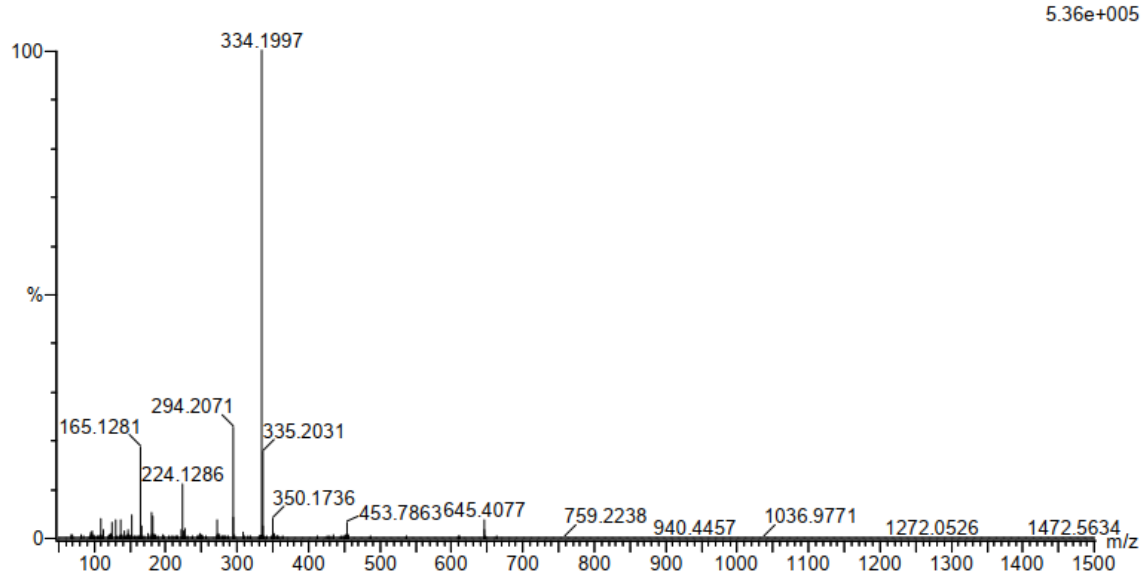



Figure 6.10: IR spectra of compound **15**.

**Elemental Composition Report** **Page 1**

**Single Mass Analysis**
Tolerance = 2.1 PPM / DBE: min = -10.0, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 6

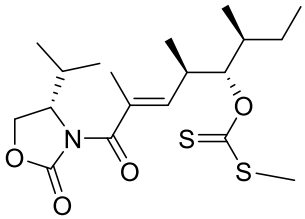
Monoisotopic Mass, Even Electron Ions
221 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-100 N: 0-1 O: 0-10 Na: 0-1
2021-118 56 (0.536) AM2 (Ar,35000.0,0.00,0.00); Cm (49:56)
1: TOF MS ES+




| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Minimum: | | | | -10.0 | | | | |
| Maximum: | | 5.0 | 2.1 | 50.0 | | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Norm | Conf(%) | Formula |
| 334.1997 | 334.1994 | 0.3 | 0.9 | 3.5 | 1918.6 | n/a | n/a | C17 H29 N O4 Na |

Figure 6.11: MS analysis of compound **15**.

## Spectra of compound 18



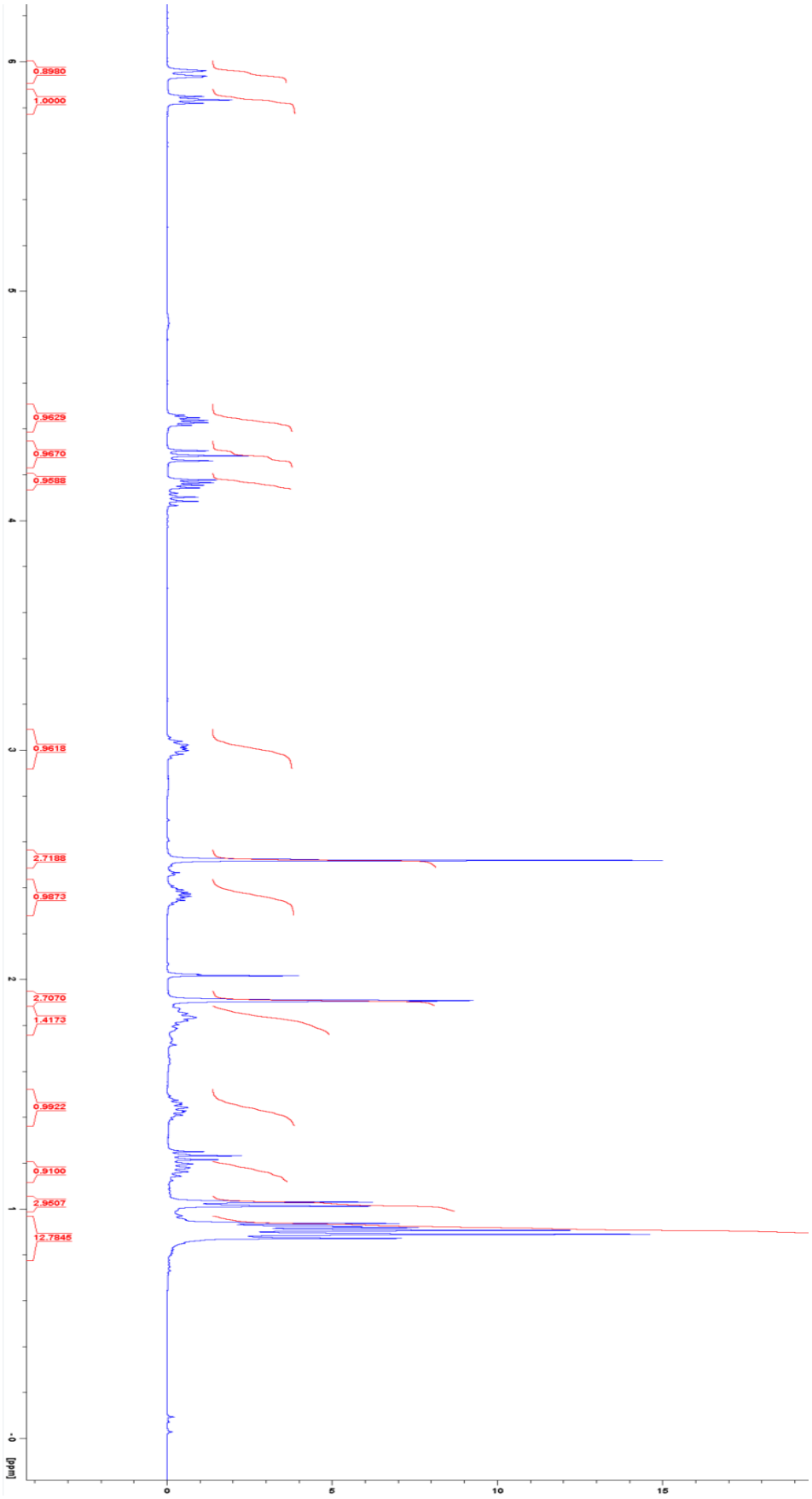



Figure 6.12: $^{1}$H NMR spectra of compound **18.**

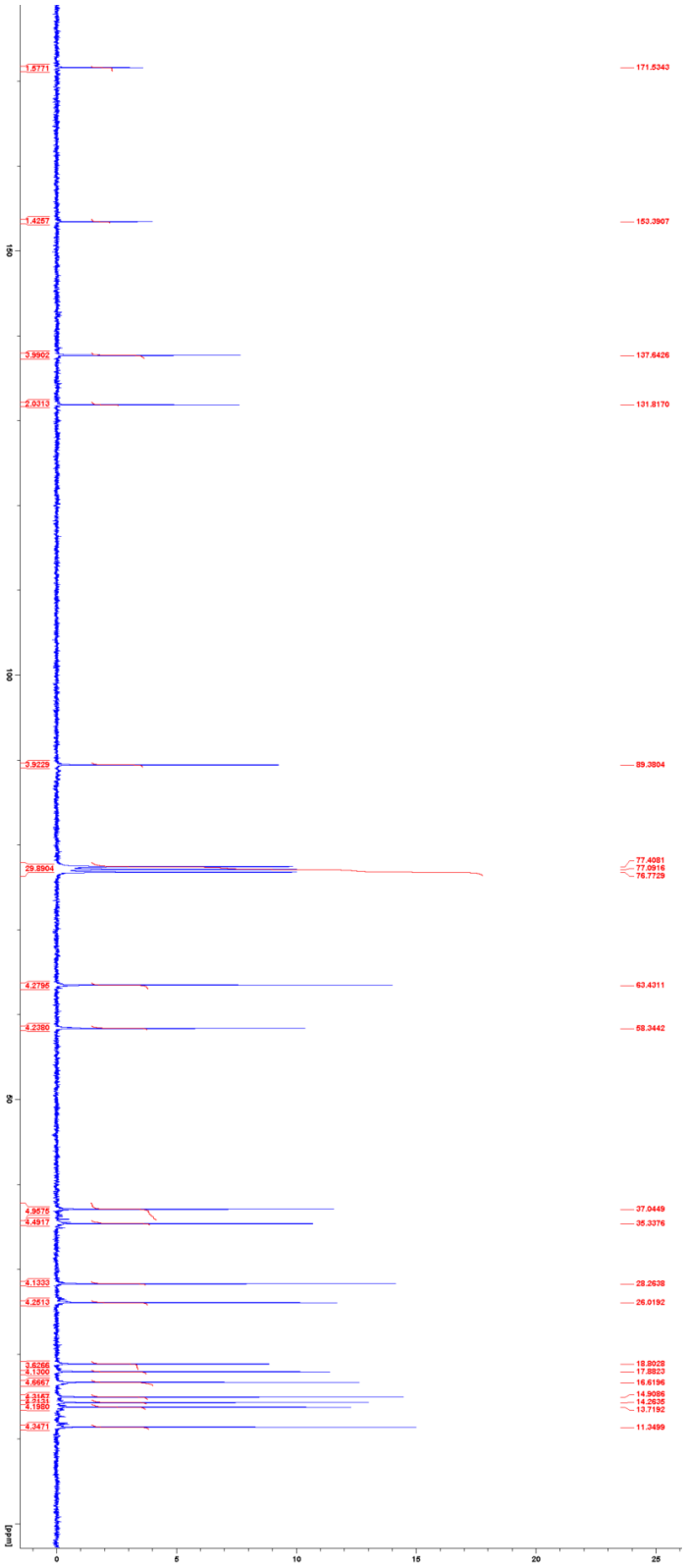



Figure 6.13: $^{13}C$ NMR spectra of compound **18**

## Spectra of compound **21**

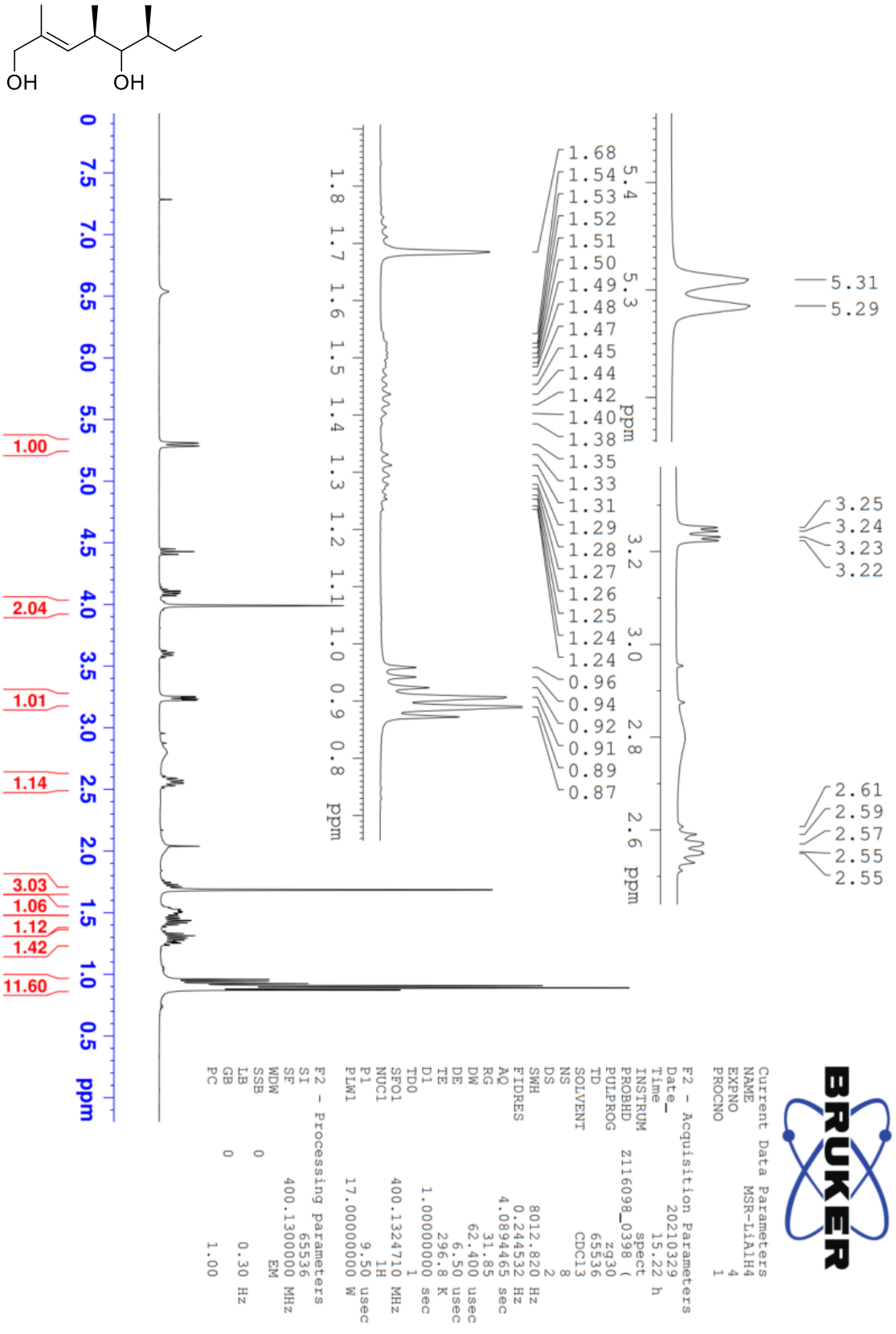



Figure 6.14: $^{1}$H spectra of compound **21.**

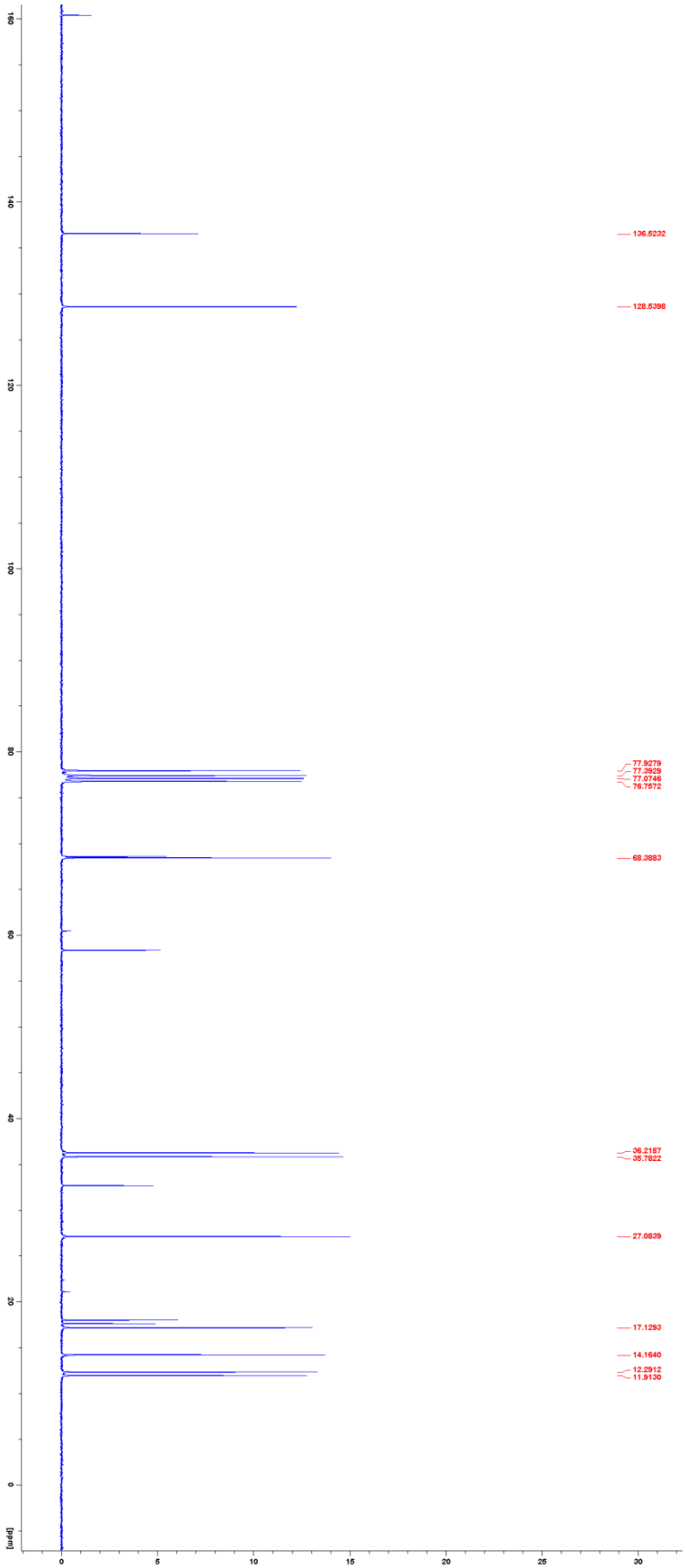
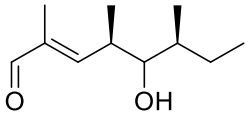



Figure 6.15: $^{13}C$ NMR spectra of compound **21**.

## Spectra of compound **22**



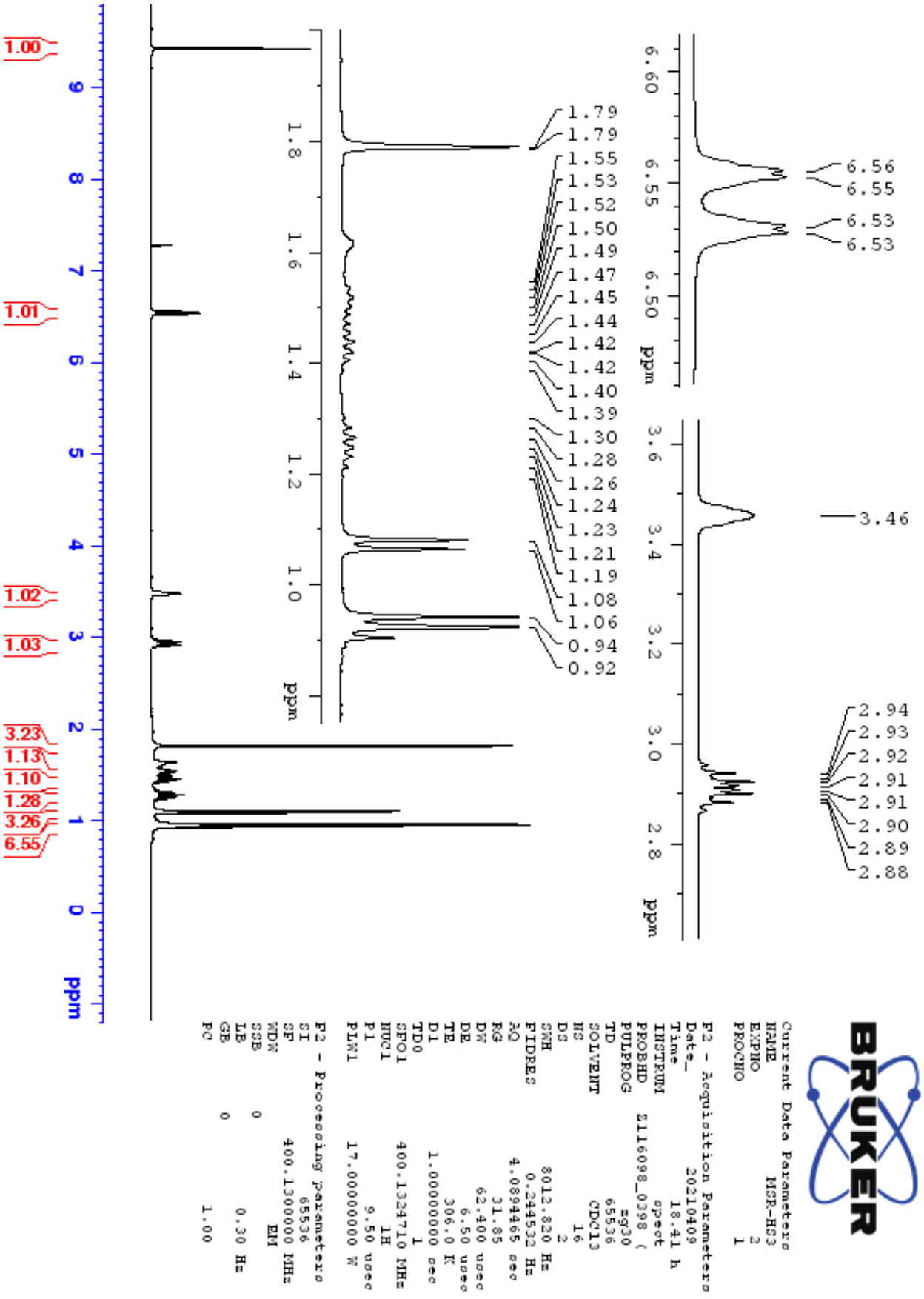



Figure 6.16: $^{1}$H NMR spectra of compound **22**

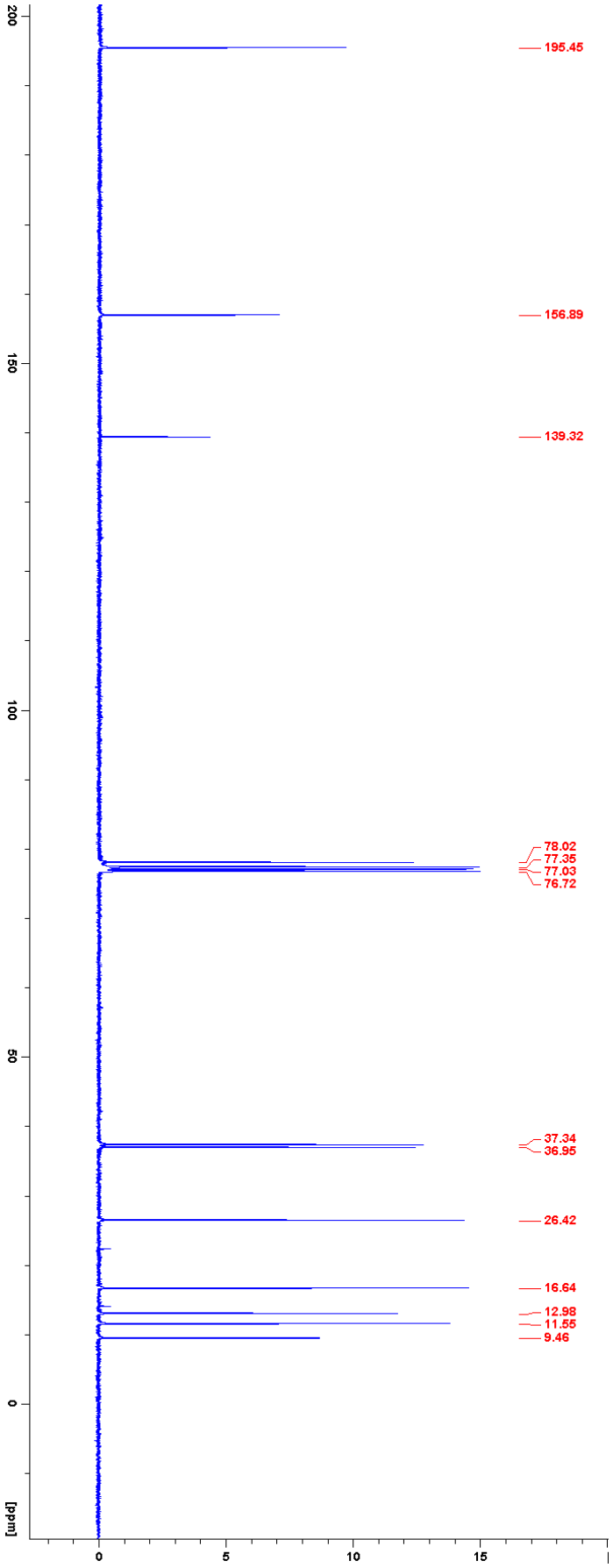
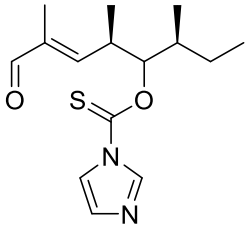



Figure 6.17: $^{13}C$ NMR spectra of compound **22**.

## Spectra of compound 23



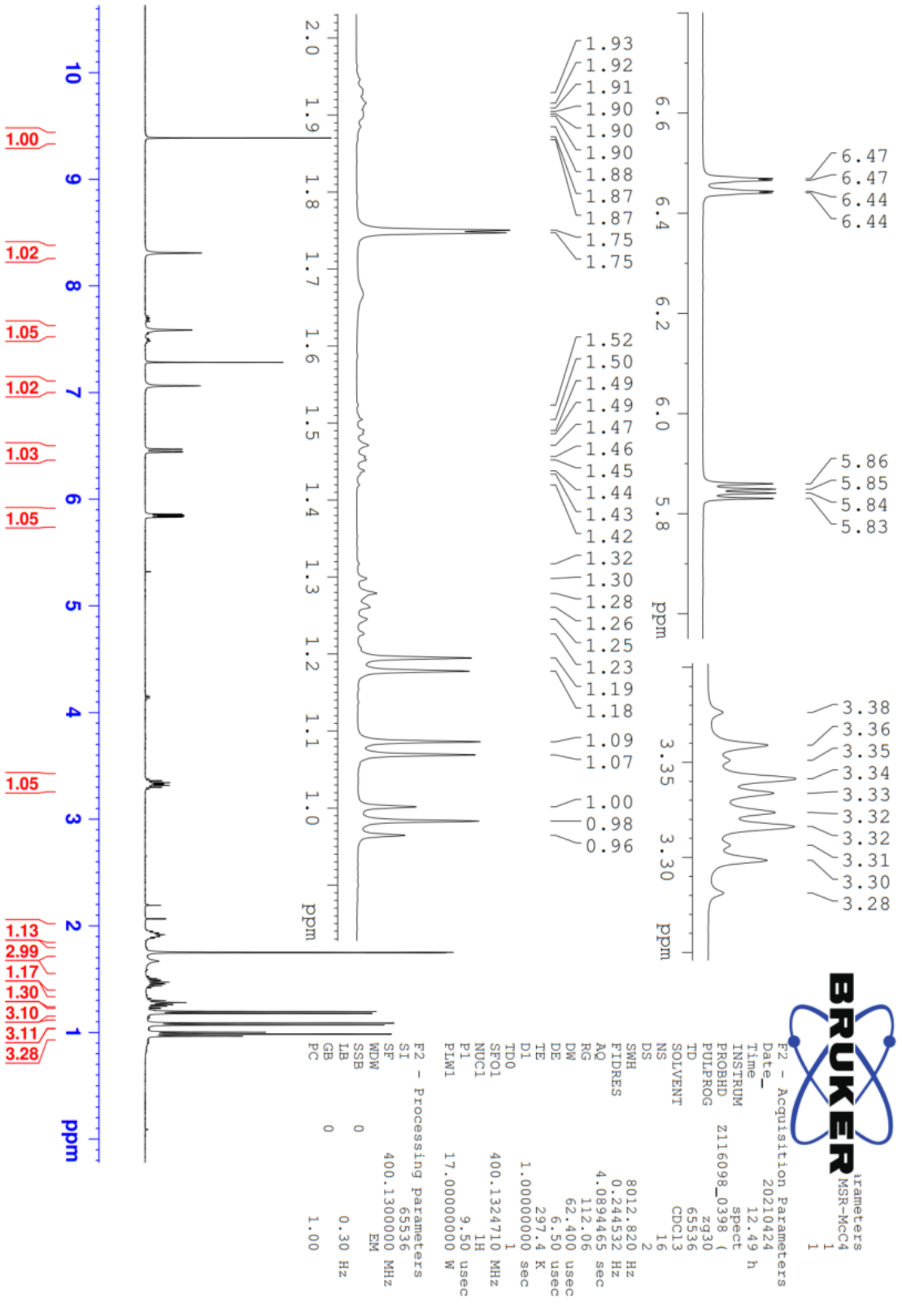


Figure 6.18: $^{1}$H NMR spectra of compound **23.**

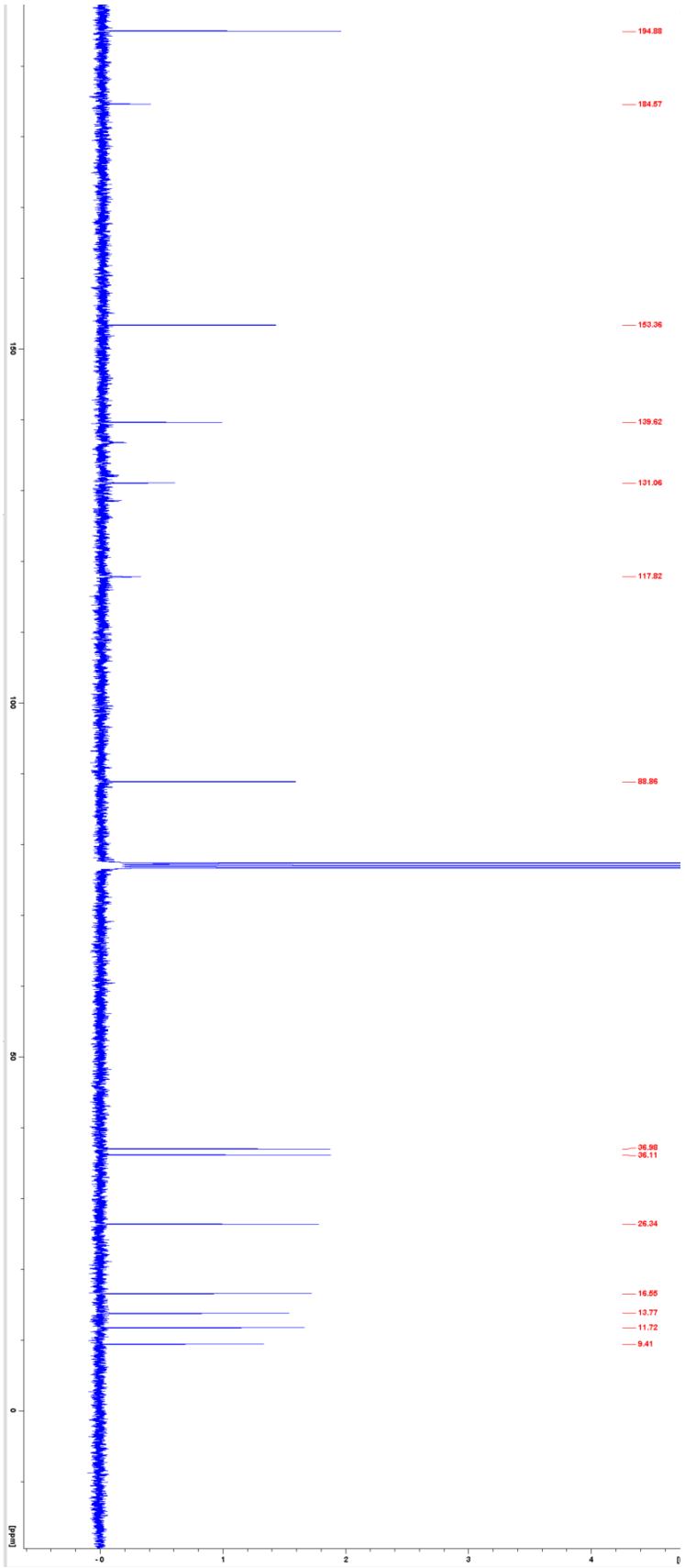
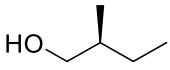



Figure 6.19: $^{13}C$ NMR spectra of compound **24.**

## Spectra of compound **1**



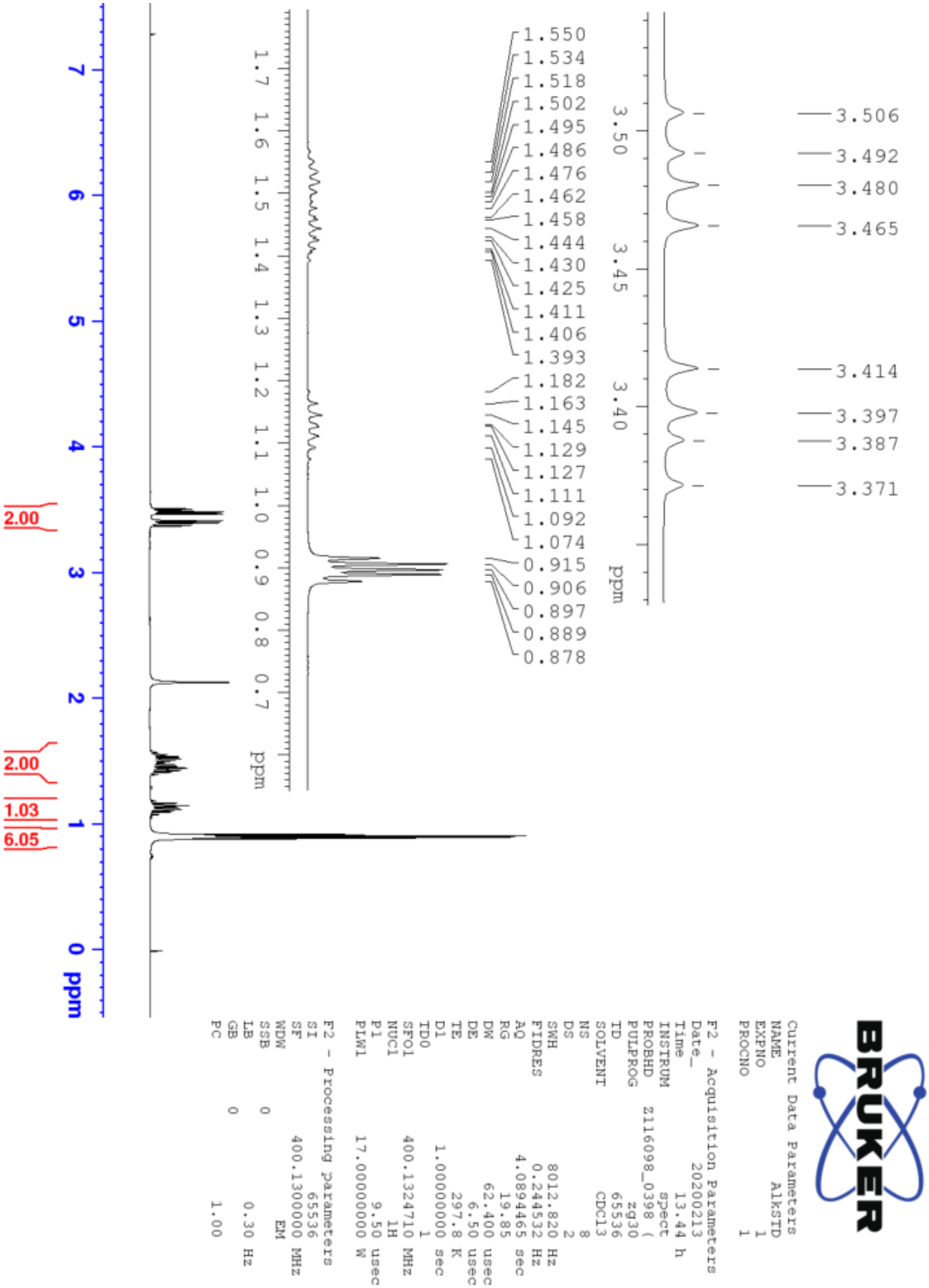
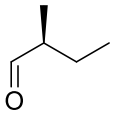



Figure 6.20: $^{1}$H NMR spectra of compound **1**.

## Spectra of compound **2**



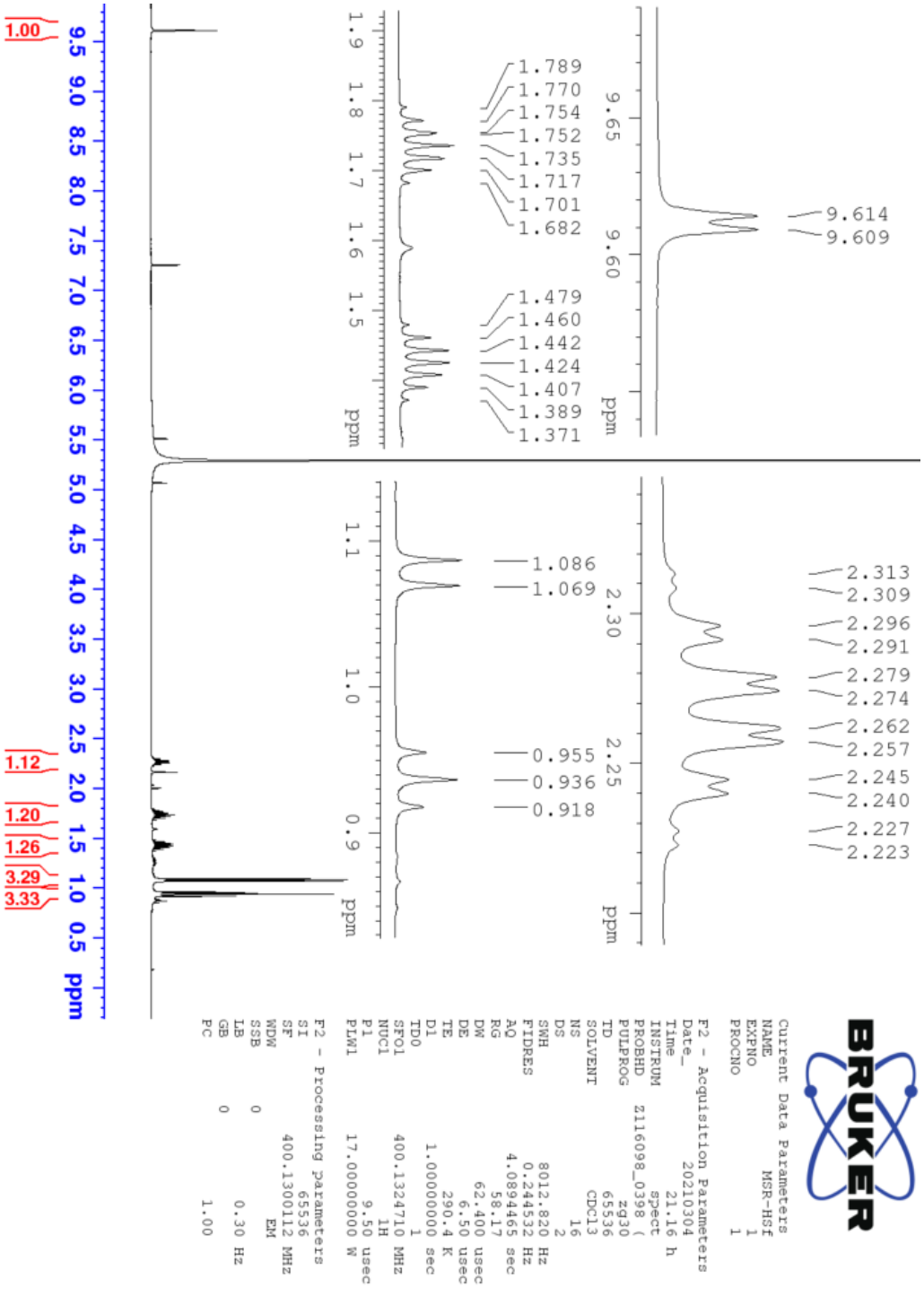
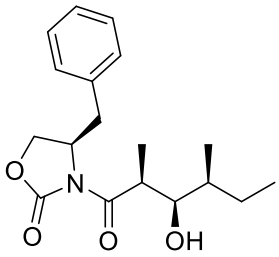



Figure 6.21: $^{1}$H NMR spectra of compound **2** (in DCM).

## Spectra of compound **4**



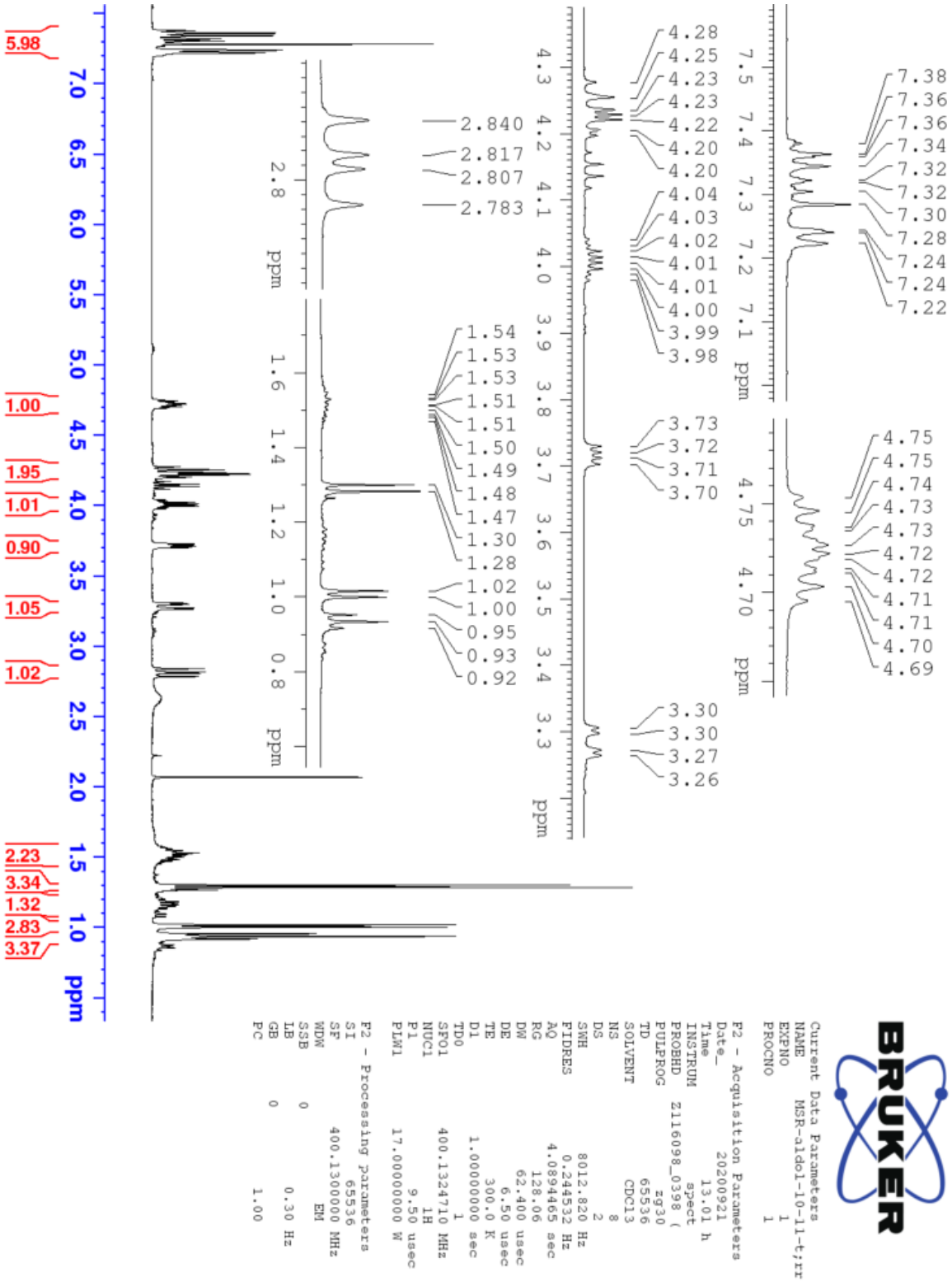



Figure 6.22: $^{1}$H NMR spectra of compound **4**.

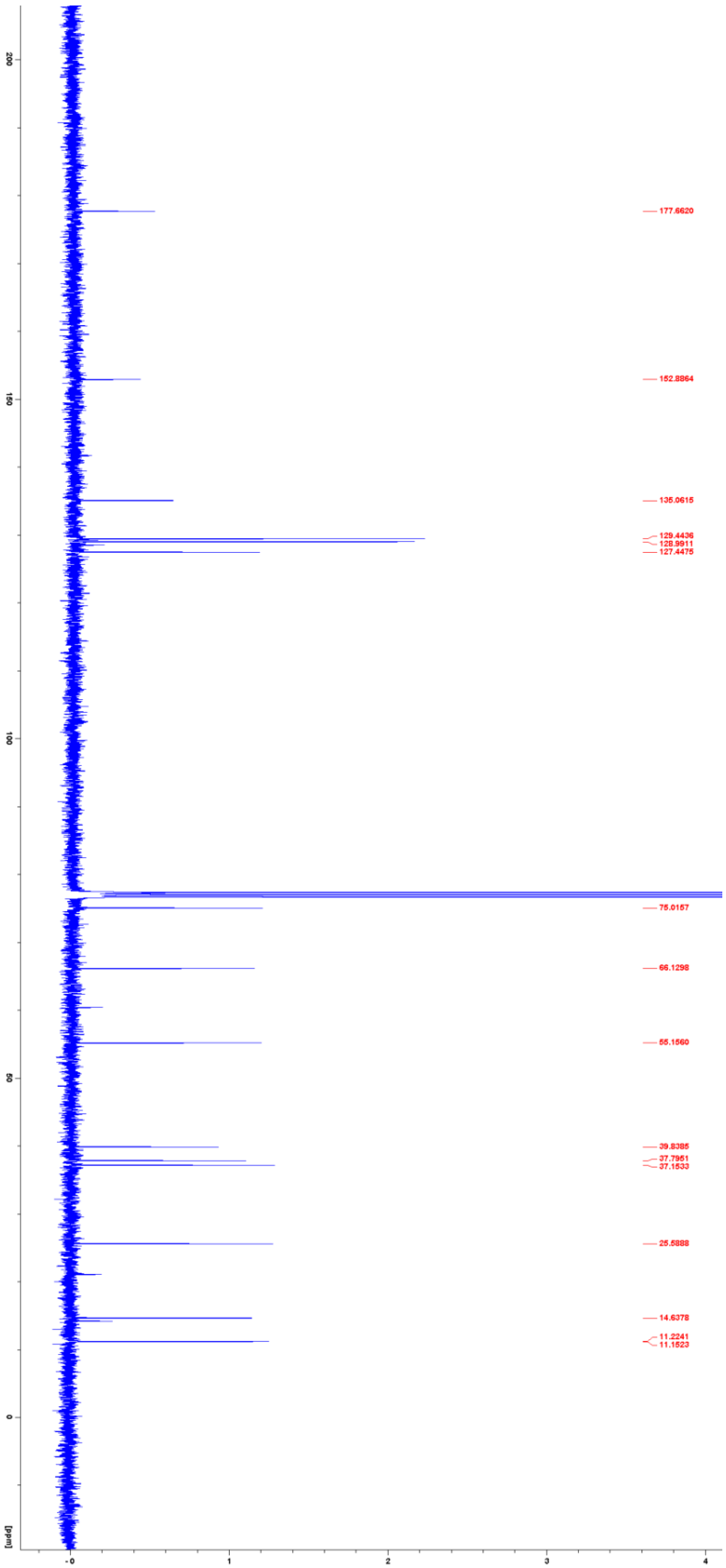



Figure 6.23: $^{13}C$ NMR spectra of compound **4**.

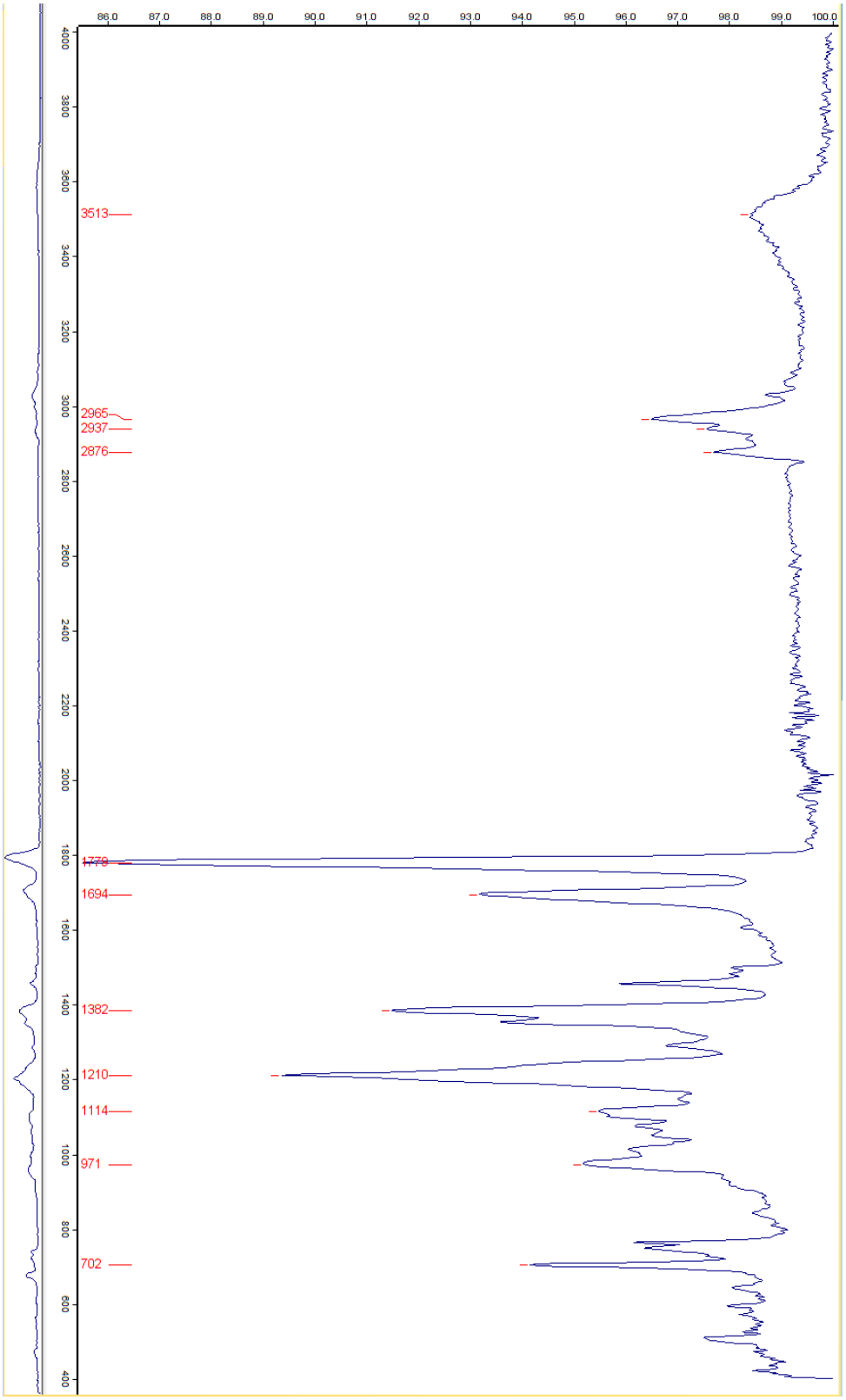
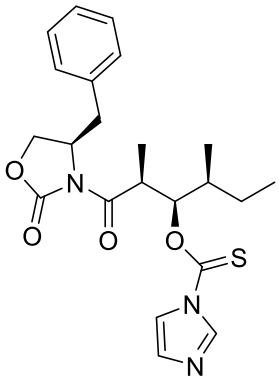



Figure 6.24: IR spectra of compound **4.**

## Spectra of compound **5**



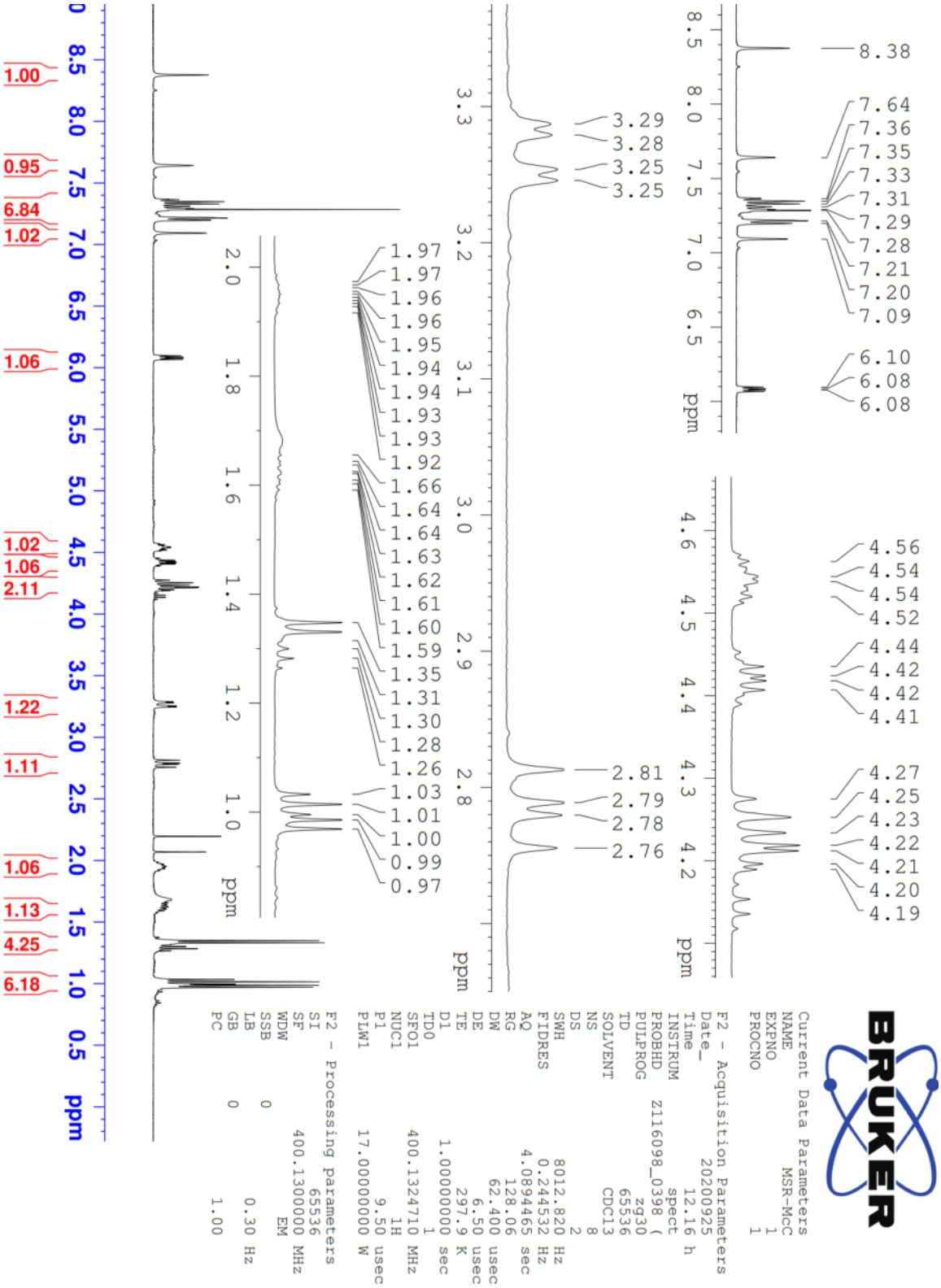



Figure 6.25: $^{1}$H NMR spectra of compound **5**.

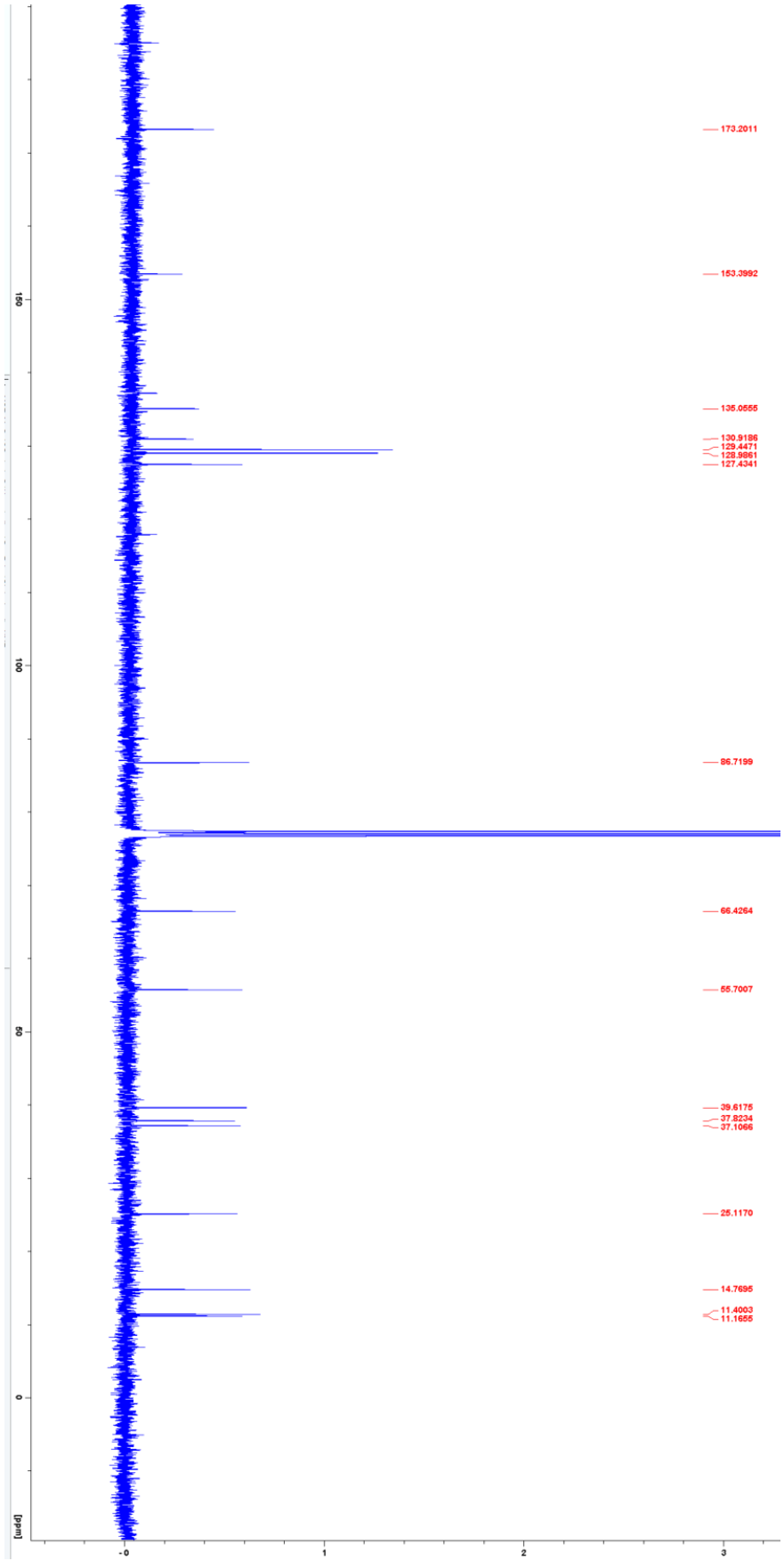



Figure 6.26: $^{13}C$ NMR spectra of compound **5.**

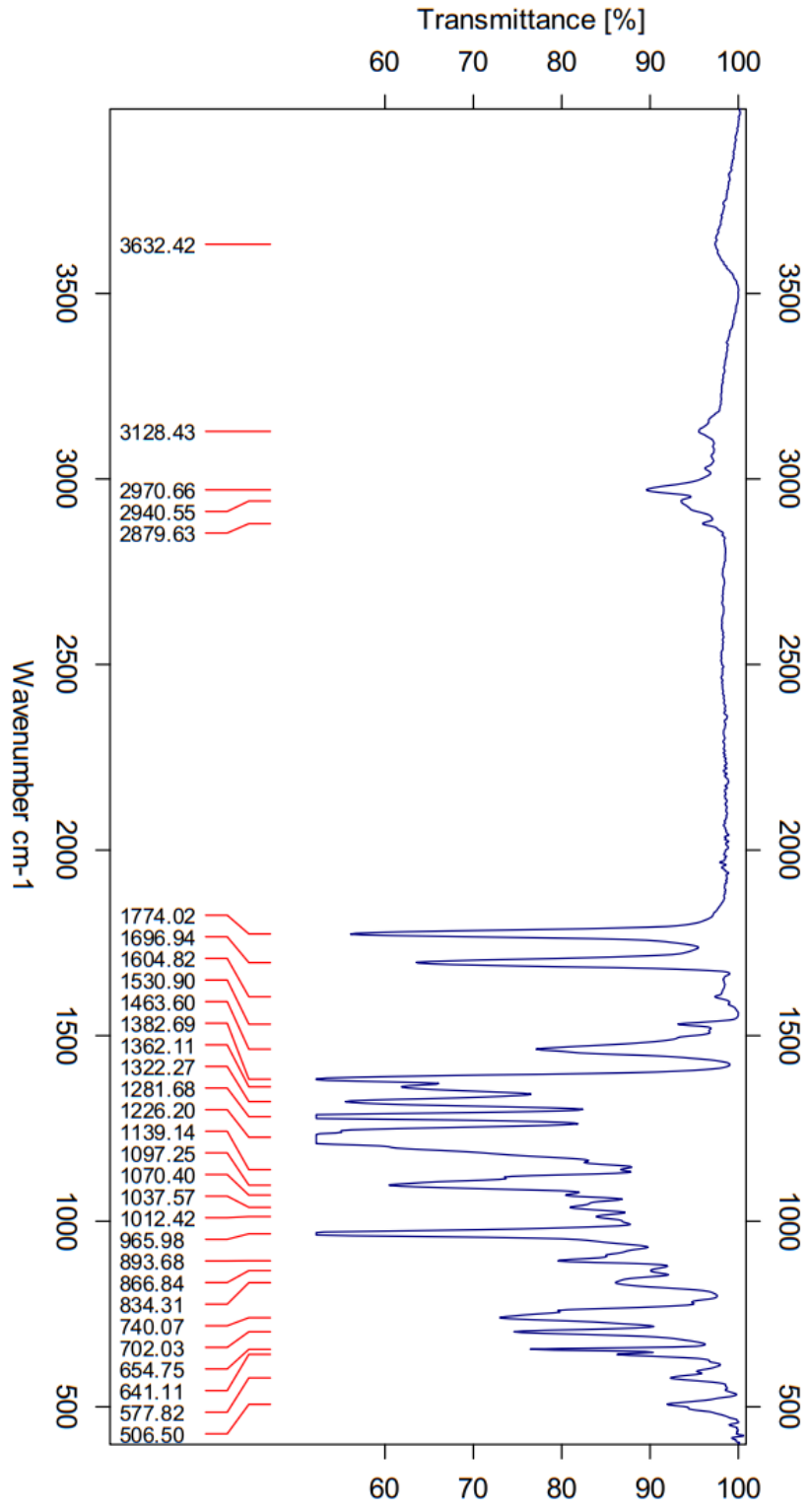
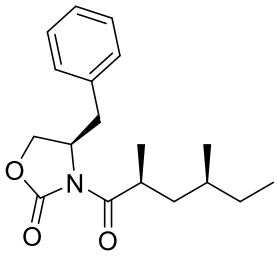



Figure 6.27: IR spectra of compound **5.**

## Spectra of compound **6**



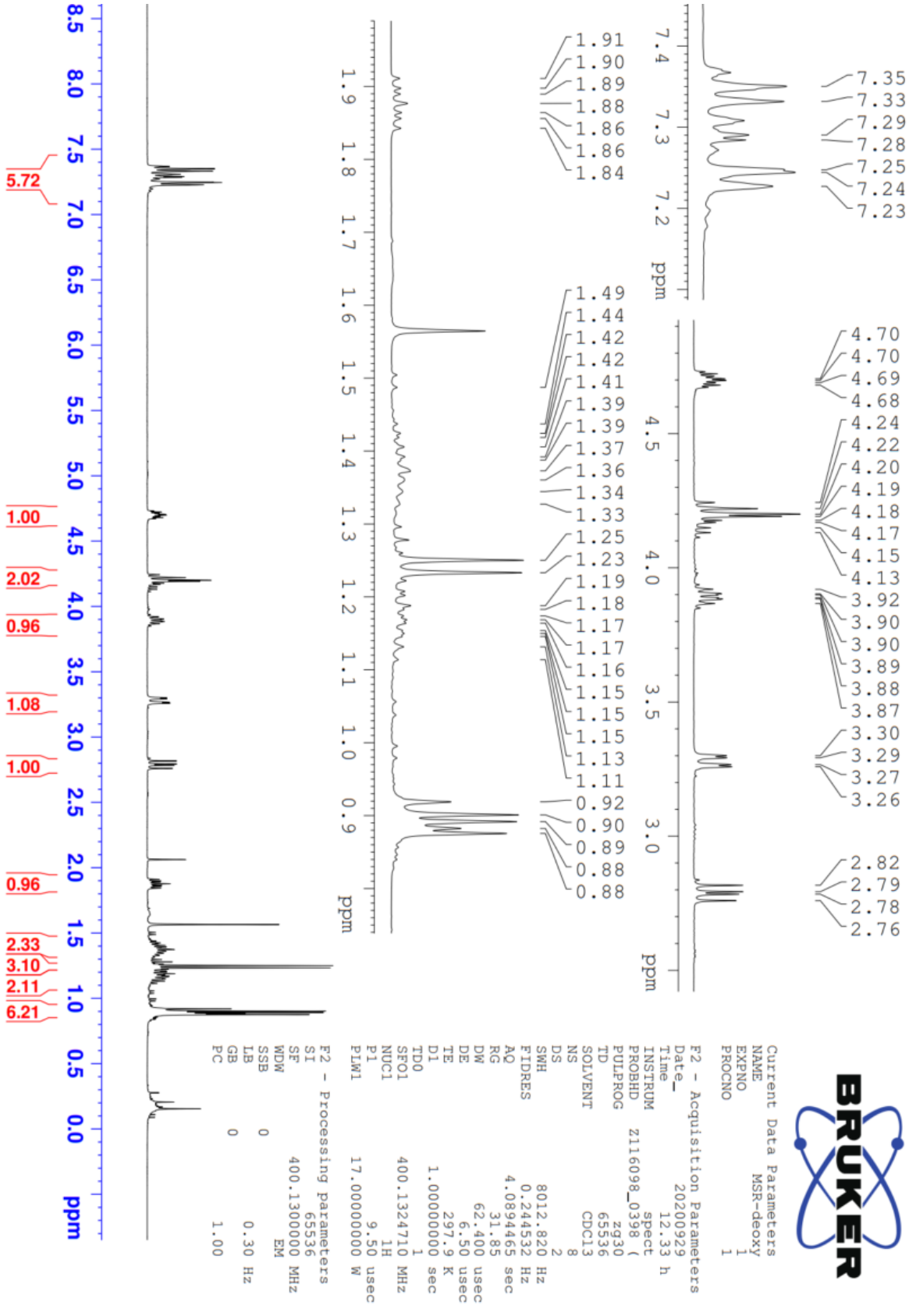



Figure 6.28: $^{1}$H NMR spectra of compound 6.

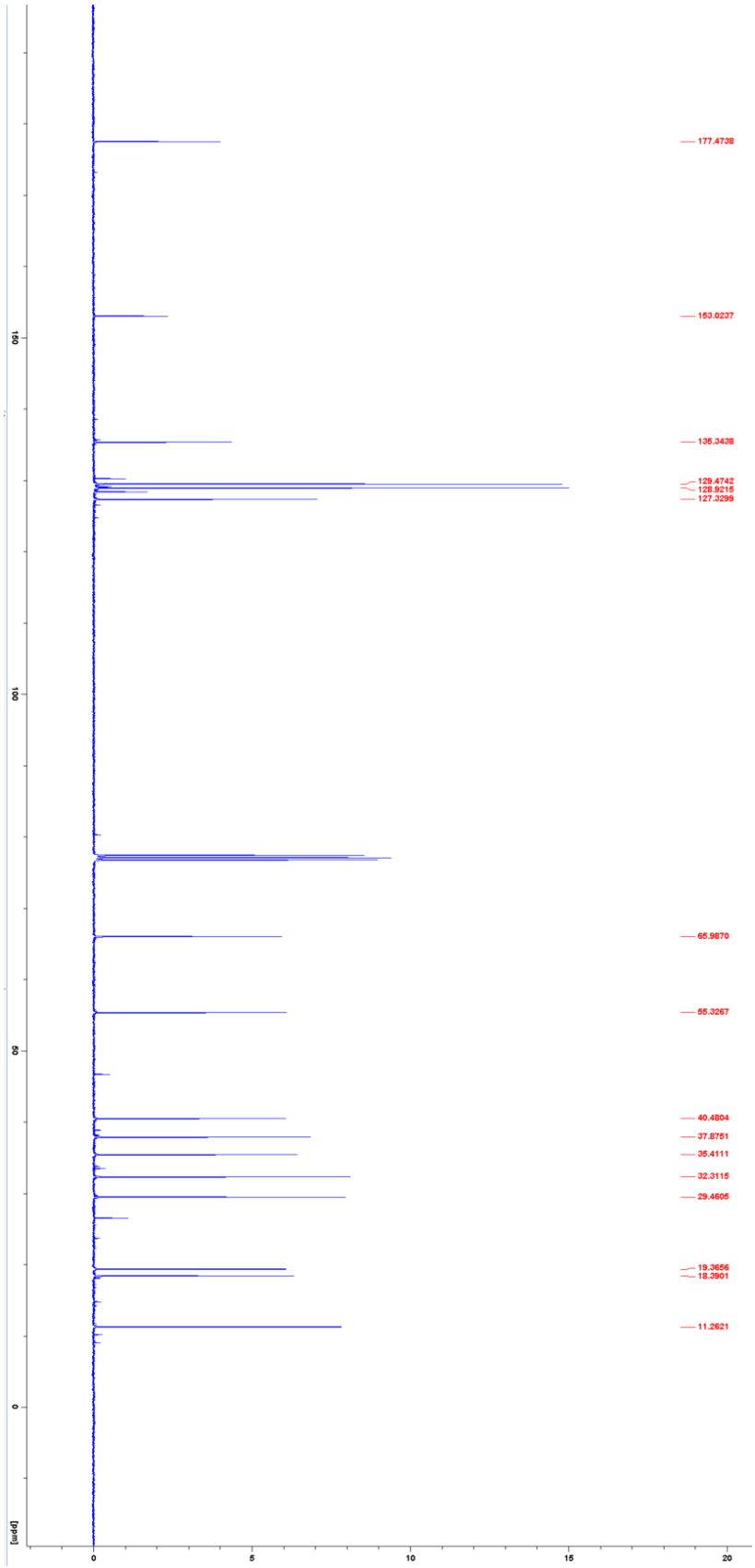



Figure 6.29: $^{13}C$ NMR spectra of compound **6**.

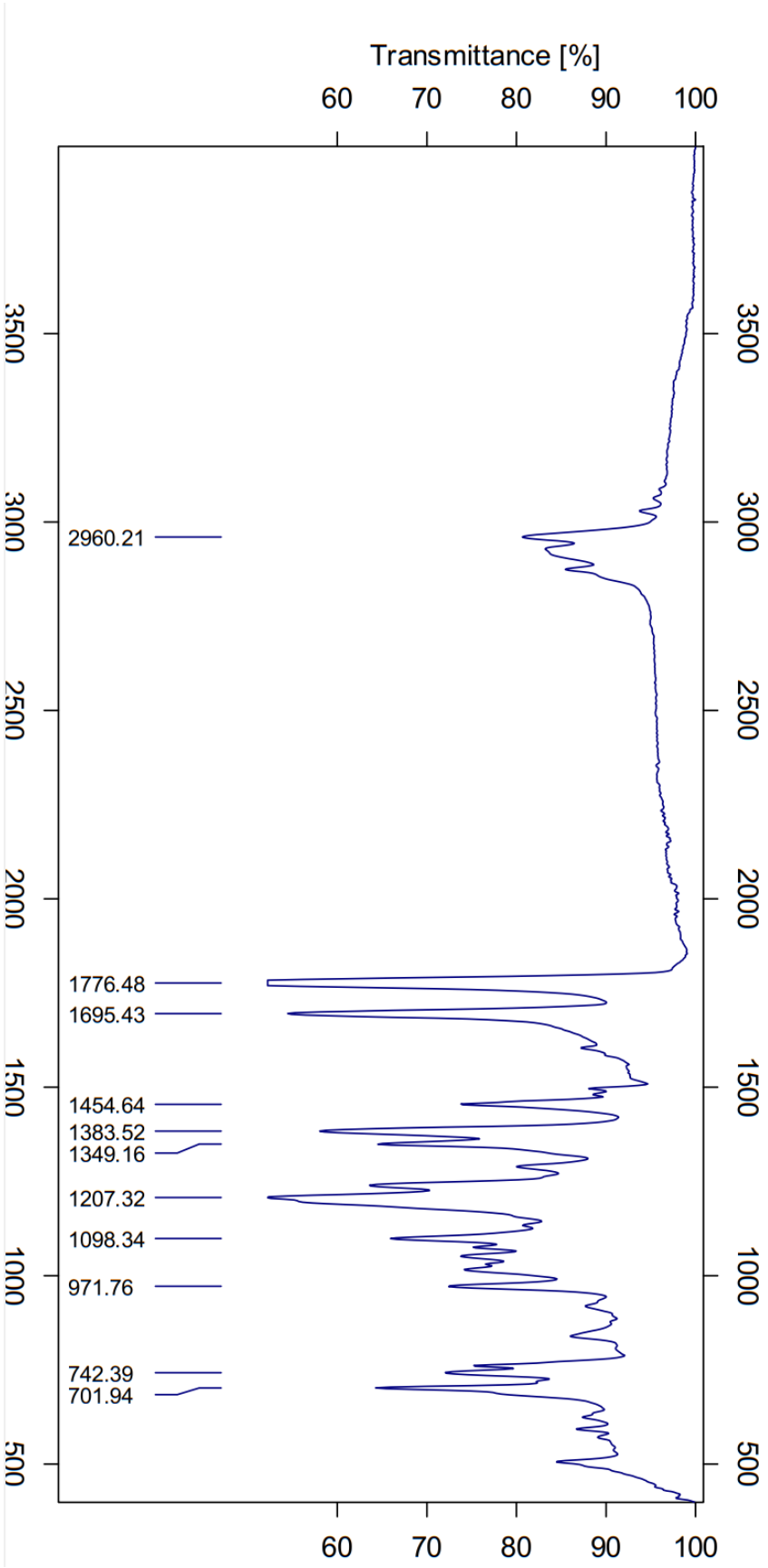



Figure 6.30: IR spectra of compound **6**.

## Spectra of compound **7**

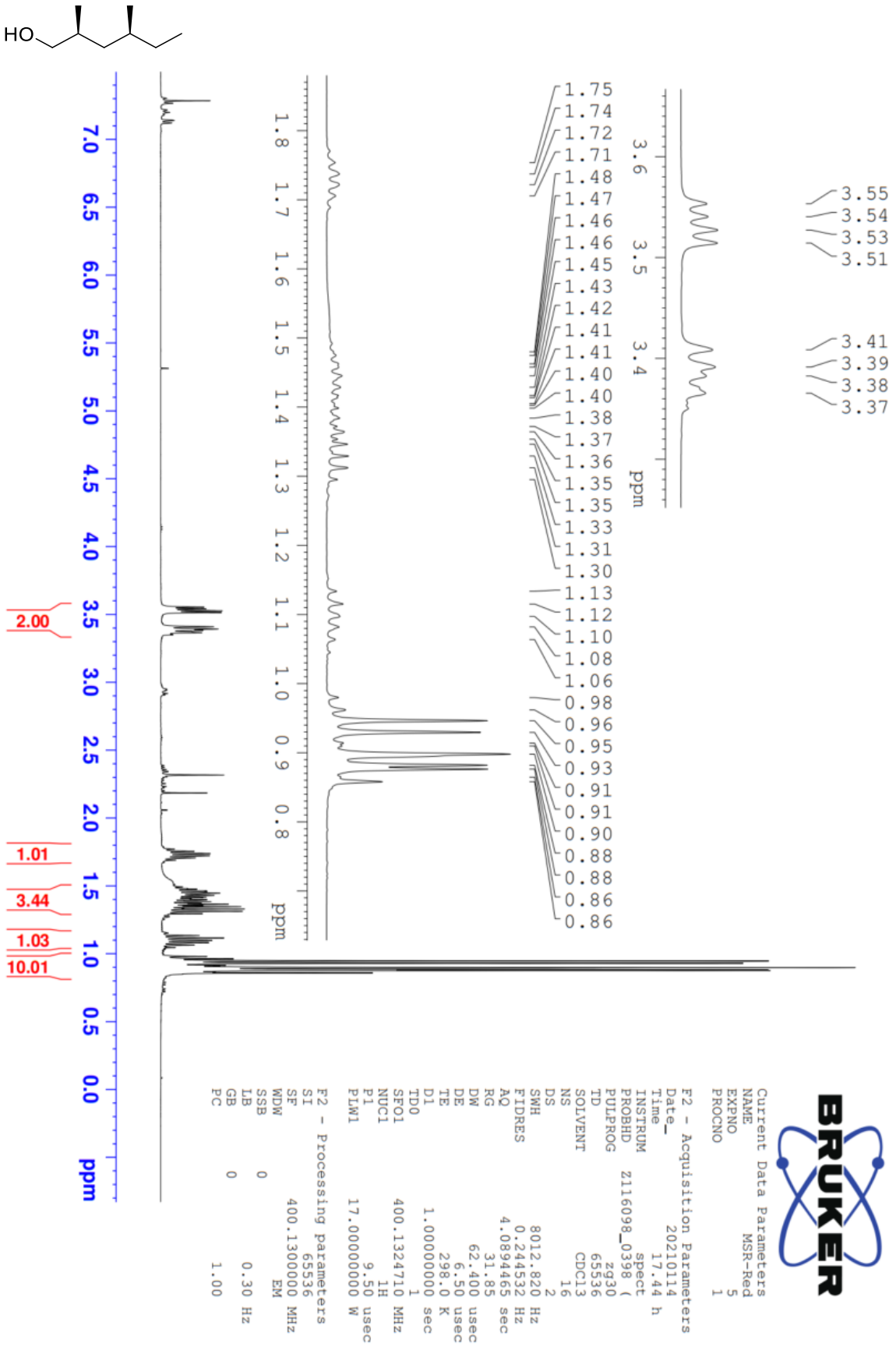
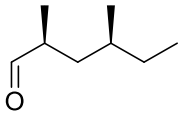



Figure 6.31: $^{1}$H NMR spectra of compound **7**.


Figure 6.32: $^{13}C$ NMR spectra of compound **7**.

## Spectra of compound 8



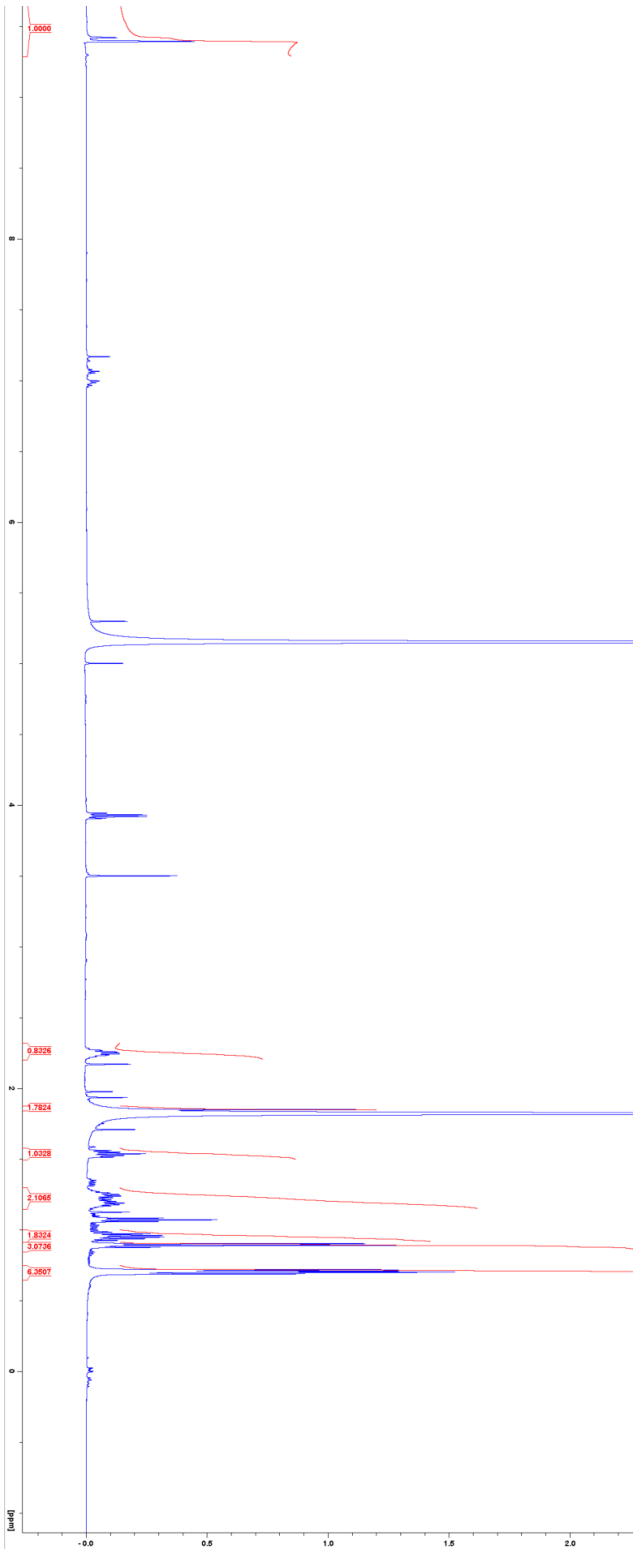




Figure 6.33: $^{1}$H NMR spectra of compound **8**.

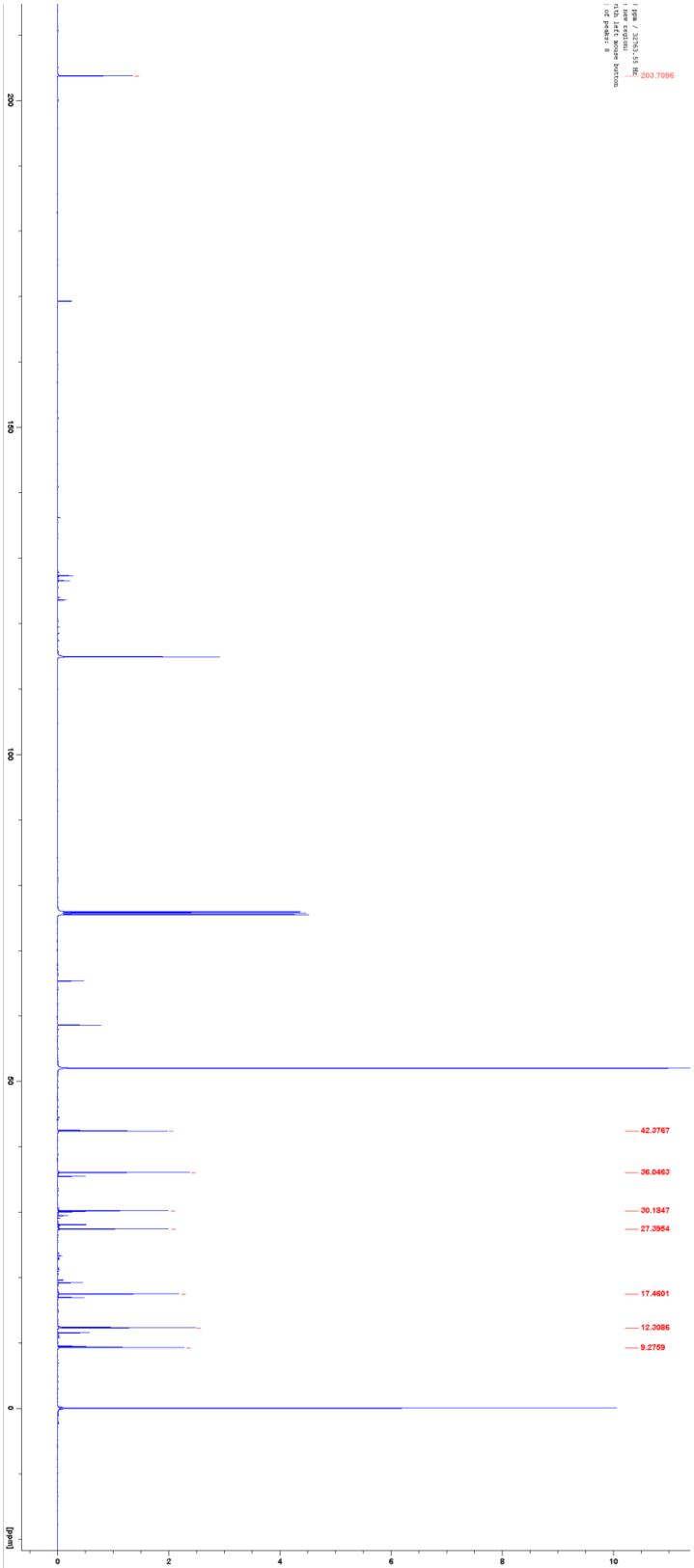
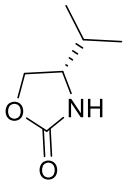



Figure 6.34: $^{13}C$ NMR spectra of compound **8**.

## Spectra of compound **11**



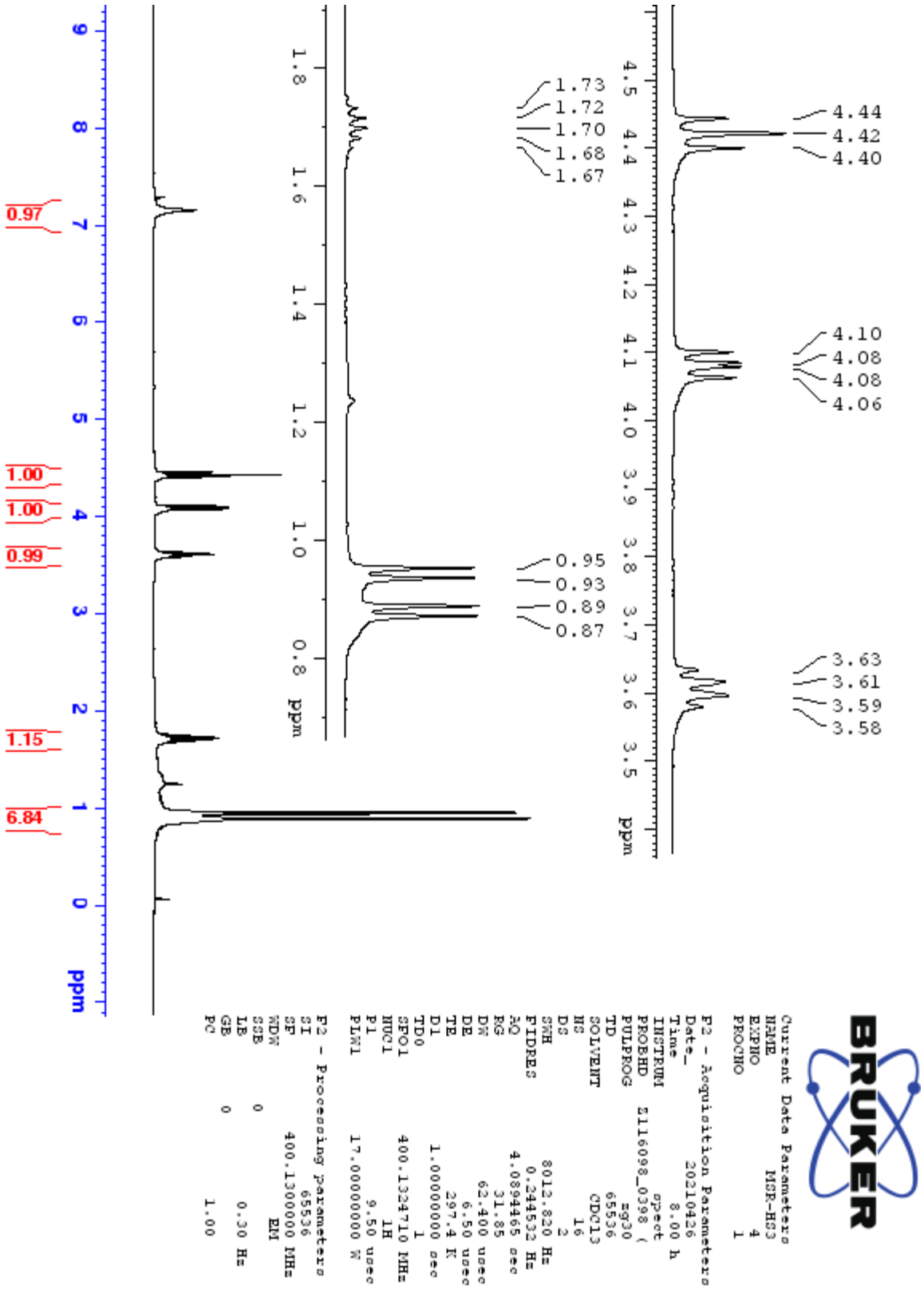



Figure 6.35: $^{1}$H NMR spectra of compound **11**.

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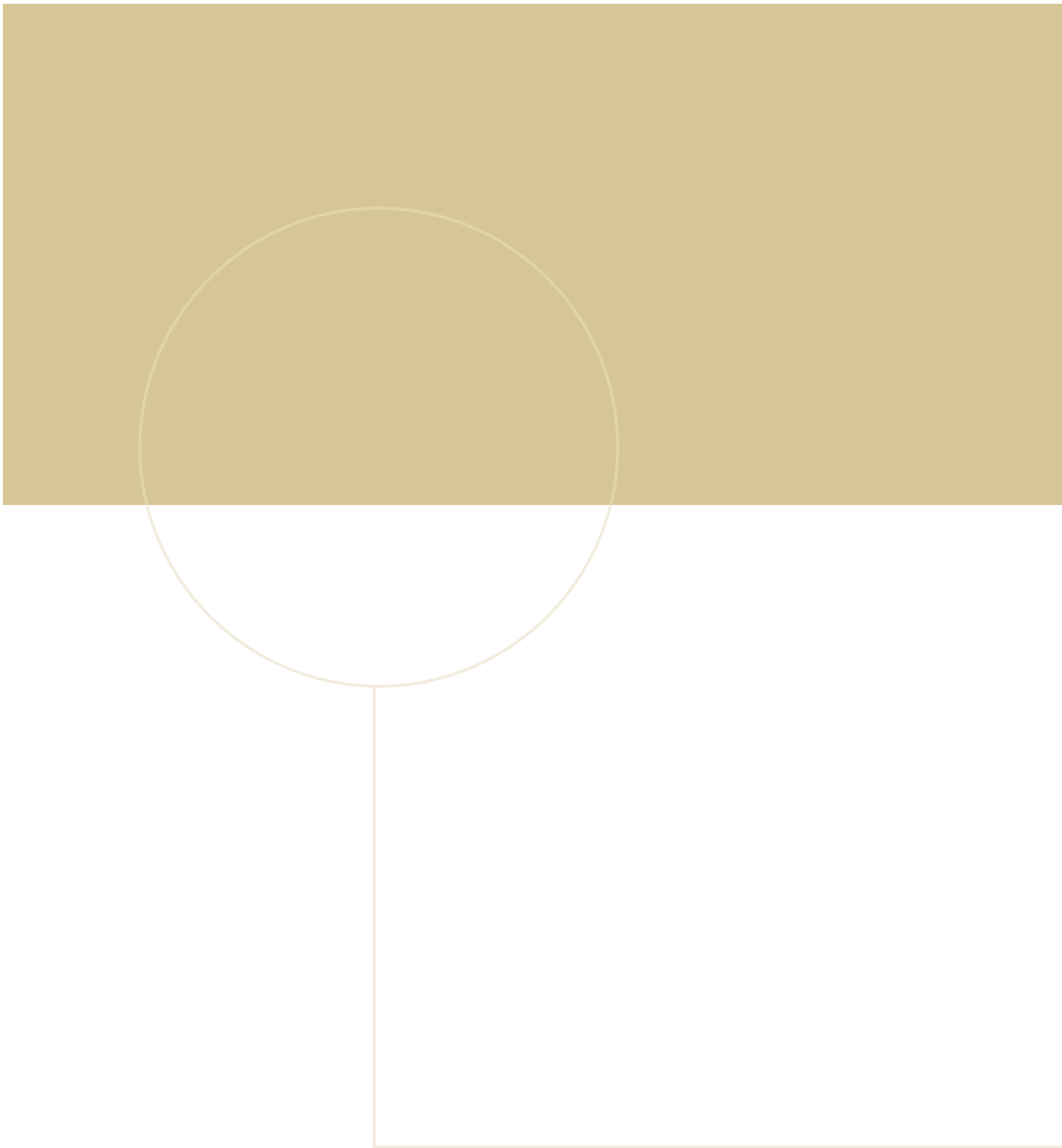

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