Project Number: MQP- JPD-0001

Synthesis of a Novel Multicyclic Organic Scaffold via a Photoinitiated Intramolecular Ylide-Alkene Cycloaddition Reaction

A Major Qualifying Project Report

Submitted to the Faculty

Of the

WORCESTER POLYTECHNIC INSTITUTE

In partial fulfillment of the requirements for the

Degree of Bachelor of Science

By

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Submitted: April 30, 2009

Approved:

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Adviser

Department of Chemistry

Abstract

When developing potentially medicinally relevant compounds it is important to utilize efficient synthetic methods, control stereochemistry, liphophilicity, acidity, and the incorporation of bioisosteres. The synthesis of a bioisosteric analog of morphine was studied utilizing an intramolecular ylide-alkene cycloaddition as the final step to establish the six stereocenters and three of the rings of the molecule. This multicyclic scaffold is expected to produce biologically active compounds from a brief, modifiable synthesis and simple starting materials.

Acknowledgements

I would like to thank Professor James P. Dittami for the use of his laboratory, extensive guidance, thoughtful advice, and help throughout the year. I would also like to thank Ilie Fishtik and Victor Kiryak for their counsel and assistance throughout the research process. Finally I would like to thank my mother for her continuing support and encouragement.

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Background

The heterocyclization reaction of aryl vinyl sulfides, aryl vinyl ethers, and aryl vinyl amines was reported to proceed via ylide intermediates.[1-4]

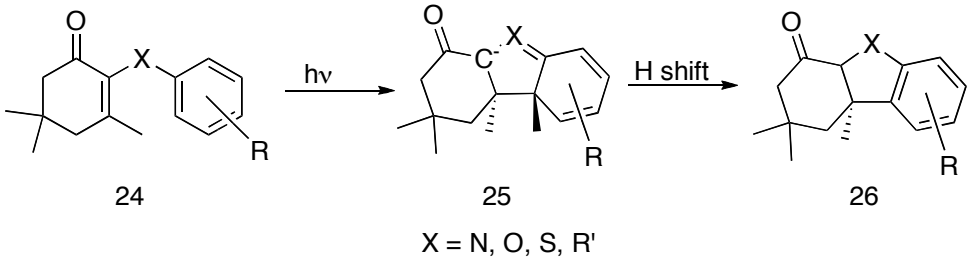


Figure 1: Dihydrofuran product resulting from hydrogen shifts discovered by Schultz

This was considered a potentially useful reaction to create a carbon-carbon bond on an aromatic ring. The ylide intermediate rearrangment proceeds via a series of hydrogen shifts to provide dihydrofuran, dihydrothiophene and dihydroindole products. Usual methods for the generation of the carbonyl ylide species have involved thermolysis and photolysis of oxirane rings,[5]carbine addition to carbonyl groups,[6] and extrusion reactions such as the thermolysis of oxadiazolines.[7] The use of aryl vinyl sulfides and aryl vinyl ethers to generate a ylide intermediate was considered a novel and potentially very reaction.

Our group was interested in beta-naphthol ring forming reactions proceeding via intermediate ylides with a pendant dipolaophile. This set the precedence for the use of aryl vinyl ethers for photocyclization and intramolecular ylide-alkene [3+2]

[1-4] Schultz, A.G.; Detar, M. B., *J. Am. Chem. Soc.* **1976**, *98*, 3574.,Schults, A. G. *Acc. Chem. Res.* **1983**, *16,* 210., Wolff, T. J. *J. Org. Chem.* **1981**, *46*, 978-983.,Herkstroeter, W. G.; Shultz, A. G. *J. Am. Chem. Soc.* **1984**, *106*, 5563.
[5] Eberbach, W.; Brokatzky, J.; Fritz, H. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 47.
[6] Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100.
[7] Shimizu, N.; Bartlett, P. D. *J. Am. Chem. Soc.* **1978**, *100,* 4260.

cycloaddition reactions. It was reported by Dittami et. al. that aryl vinyl ethers bearing a pendant alkene side chain undergo [3+2] photocycilization and subsequent intramolecular ylide-alkene addition.[8]

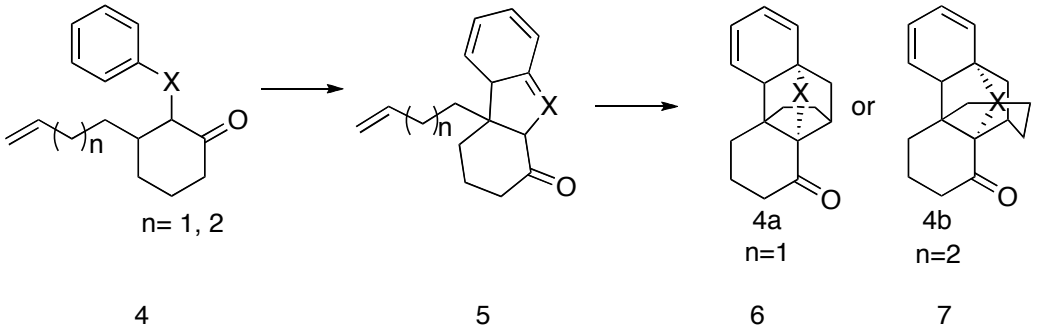


Figure 2: Intramolecular ylide-alkene[3+2] cycloaddition reaction

This was viewed as a potentially rapid and powerful way to construct complex multicyclic scaffolds forming up to six-chiral centers and three rings with excellent stereocontrol . The Dittami group utilized this reaction to test whether they could create complex and useful [3+2] cycloaddition products. Early work with aryl vinyl sulfides did not provide the expected [3+2] cycloaddition product. However, work with aryl vinyl ethers yielded the desired [3+2] product.[9]

[8] Dittami, J. P.; Nie, X,-Y.; Nie, H.; Ramanathan, H.; Breining, S.; Bordner, J.; Decosta, D.; Kiplinger, J.; Rieche, P.; Ware, R. *J. Org. Chem.* **1991**, 56, 5572.
[9] Dittami, J. P.; Nie, X,-Y.; Nie, H.; Ramanathan, H.; Buntel, C.; Rigatti, S. *J. Org. Chem.* **1992**, 57, 1151-1158.

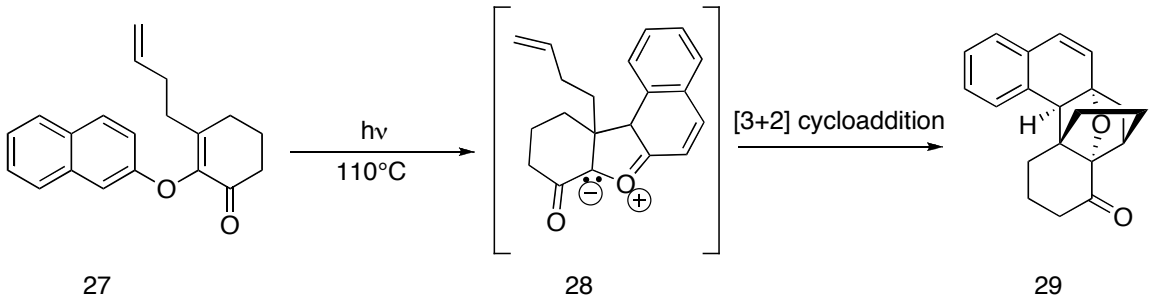


Figure 3: Aryl vinyl ethers provide the [3+2] cycloaddtion product

It was found that many factors such as heat, heteroatom (i.e. O vs. S), and aromatic ring (naphthyl versus phenyl) greatly affected the kinds of intramolecular addition products observed. It was found that carbonyl ylides can undergo intramolecular cycloaddition reactions with a lower activation barrier and higher purity when an electron withdrawing group is added to the pendant alkene.[5] Through studies it was determined that naphthyl vinyl ethers with electron deficient alkenes provide the highest yield of [3+2] cycloaddition products. [8]

These results lead to an interest in incorporating biologically active aromatic systems other than the naphthol group.

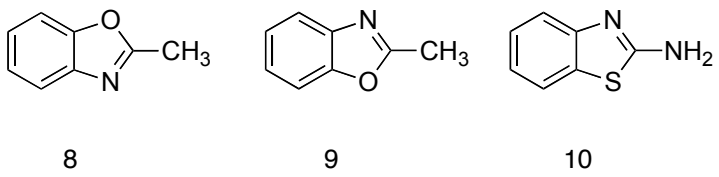
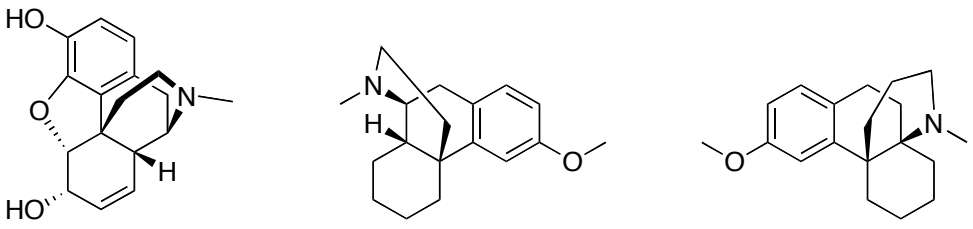


Figure 4: Various benzoxazoles and a benzothazole that could be utilized in the cycloaddition reaction

By incorporating benzoxazoles (**8** and **9**) and benzothiazoles **10** into the multicyclic scaffold it may be possible to create new compounds that exhibit useful biological utility from very simple starting materials. This paper will focus on the photoprecursor created utilizing 2-methylbenzo[d]oxazol-6-ol **9**.



11 morphine 12 dextromethorphan 13 llevomethorphan

Figure 5:Pharmaceutical drugs with similar structures to that of the scaffold created by the [3+2] cycloaddition reaction.

Many pharmaceutical drugs rely on a specific motif to imbue biological activity. Different compounds incorporating the same motif will often exhibit similar biological activity. Thus the same multicyclic scaffold is found in the structures of morphine **11**, dextromethorphan **12**, and levomethorphan **13**. The goal of this project was to prepare multicyclic scaffolds similar to that found in the opiods which also incorporate a bioisosteric replacement for the catechol group utilized by morphine and its analogs.

The following synthetic scheme will be used:

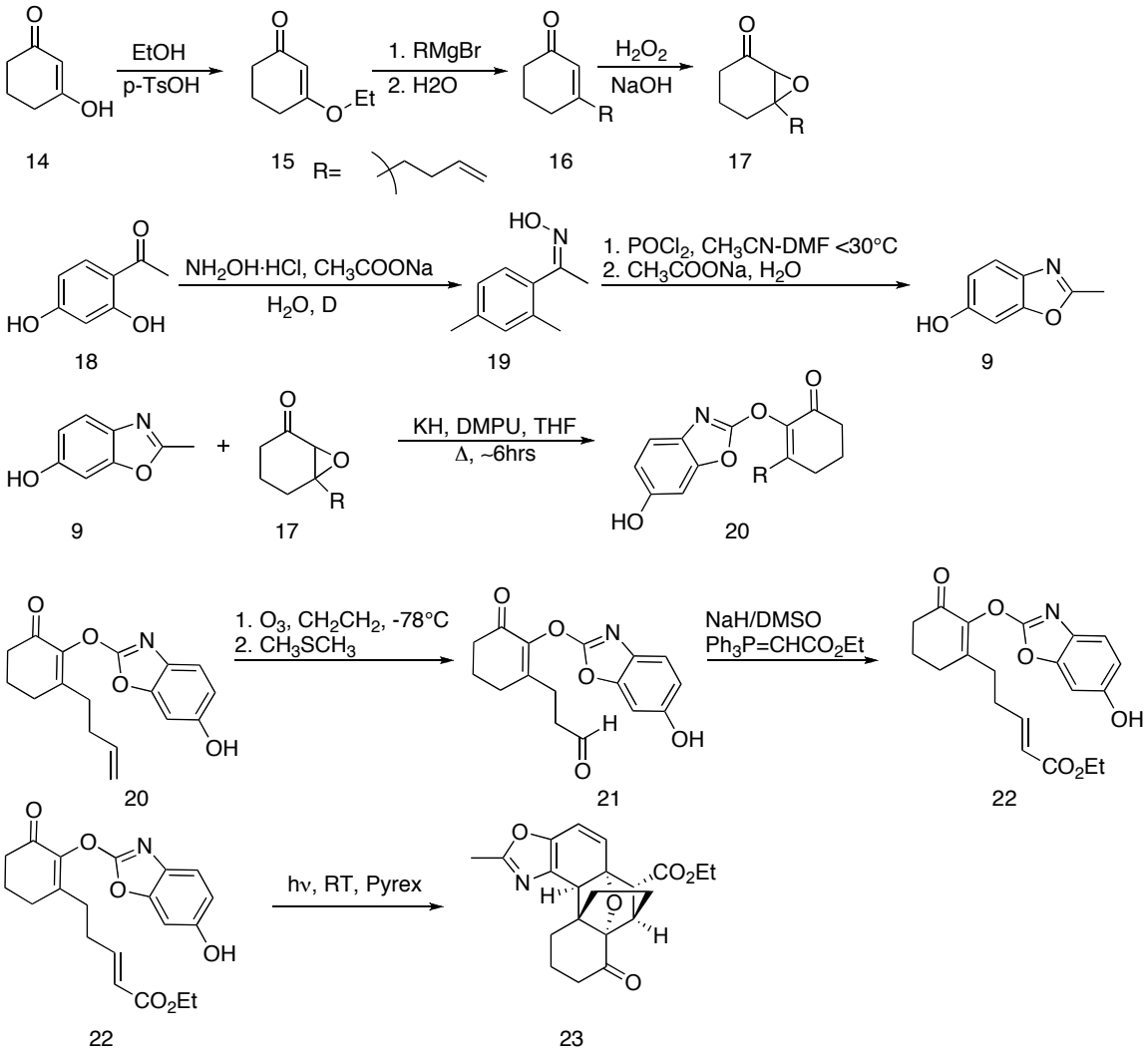


Figure 6: Synthetic scheme followed and discussed in this paper

Results and Discussion:

In order to prepare photoprecursors for the Photoinitated Intramolecular Ylide-Alkene Cycloaddition Reaction, the following general synthetic method was utilized.[9]

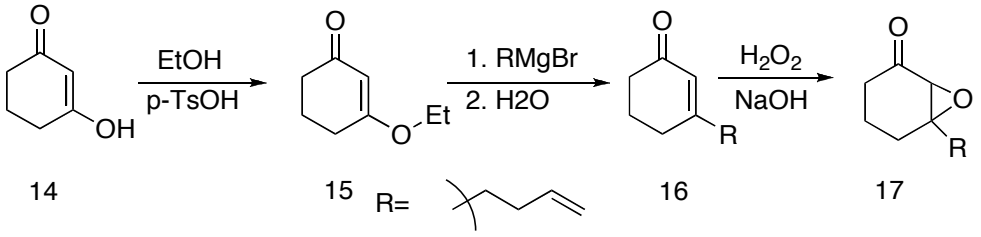


Figure 7: Synthetic route for the production of 6-(3-butenyl)-7-oxabicyclo[4.1.0]heptan-2-one

Compound **14** was treated with *p*-toluene sulfonic acid to provide **15**. This compound underwent a Grignard reaction to form **16**. This reaction was initially difficult as it was found that the solvent used was wet and quenched the Grignard product as soon as it was formed. Once anhydrous solvent was obtained this reaction proceeded with good purity and yield (73%). Facial epoxidation of **16** provided **17** in 33% yield. The epoxide **17** can be used as a starting point for synthesis of a variety of substituted alkene systems, which can be further employed in the photoinitiated intramolecular ylide-alkene cycloaddition reaction.

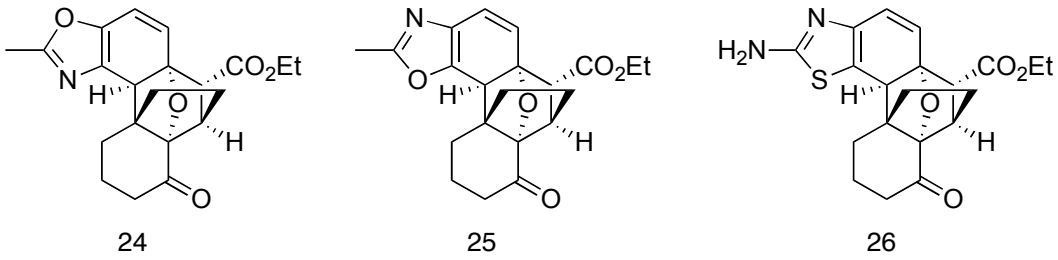
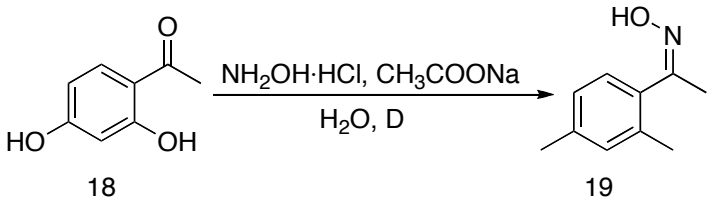


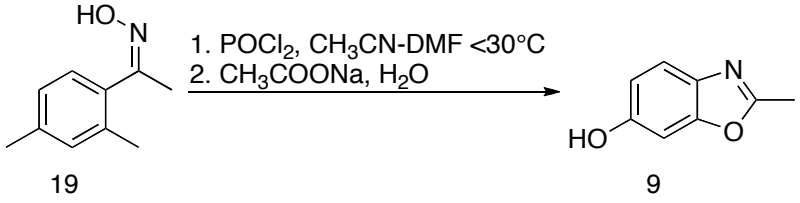
Figure 8: Proposed products of [3+2] cycloaddition reaction utilizing various benzoxazoles and a benzothiazole

In this case **17** was coupled with 3-(but-3-enyl)-2-(2-methylbenzo[d]oxazol-6-yloxy)cyclohex-2-enone **9** to create **18**. Compound **9** was made through a treatment of 2,4-Dihydroxyacetophenone **18** with hydroxylamine hydrochloride and sodium acetate in water at room temperature to produce (E)-1-(2,4-dihydroxyphenyl)ethanone oxime **19** in 91% yield.[10]



18 19

Compound **19** was then treated further with N,N-Dimethylacetamide and Phosphorus oxychloride to produce 3-(but-3-enyl)-2-(2-methylbenzo[d]oxazol-6-yloxy)cyclohex-2-enone **9** (67% yield).



19 9

The epoxide **17** was then coupled, via a base catalyzed epoxide opening, with **9** to give rise to **20** which will be further treated to provide a photoprecursor that can be utilized to complete the [3+2] photoinitiated ylide-alkene cycloaddtion reaction.

[10] Fujita, S.; Koyama, K.; Inagaki, Y. *Synthesis* **1982**, *1*, 68.

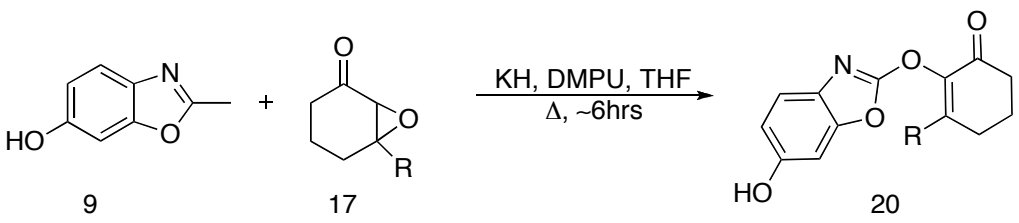
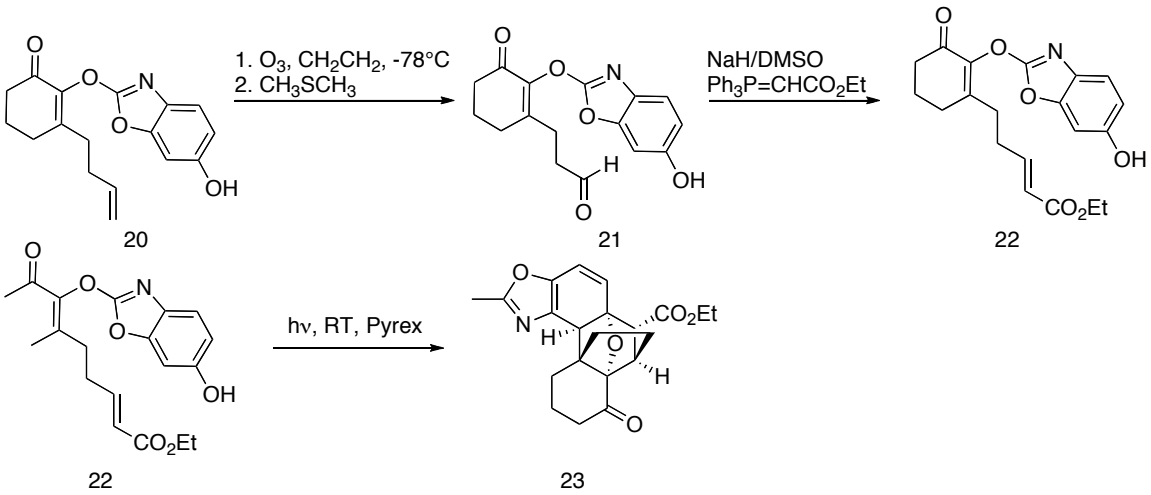


Figure 9: Synthetic route for the production of 3-(but-3-enyl)-2-(2-methylbenzo[d]oxazol-6-yloxy)cyclohex-2-enone

Compound **20** was first produced in fairly low yield and without very good purity.

After **20** has been purified the side chain will be converted an aldehyde which in turn will undergo the Wittig reaction to provide photoprecursor **23**.

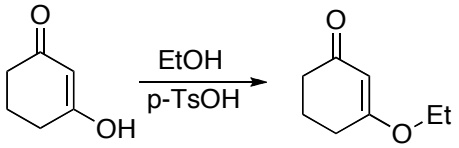


Once this has been done, and **23** has been purified, a sample will be sent for biological testing to determine whether this product has any medically relevant biological activity.

Methodology:

General Methods. High resolution ^{1}H NMR spectra were obtained using a Bruker 500MHz NMR spectrometer. Chemical shifts are reported in ppm (δ) relative to tetramethysilane at 0.00. The general experimental procedures included equipment, analytical methods, and solvent and chemical purification processes that have been reported elsewhere.[8] Unless otherwise noted, solvent removal was carried out on a rotary evaporator at reduced pressure. Infrared spectra were recorded on a Bruker Vertex 70 Infrared Spectrometer with a 4 cm^{-1} resolution scanning from 4000 to 650 cm^{-1} over 10 scans. Analytical thin-layer chromatography were done on pre-coated silica gel plates (0.25mm thickness) with a 254nm fluorescent indicator and were visualized under a UV lamp and/or by staining with *p*-anisaldehyde. Flash chromatography was run in a silica gel column on an AnaLogix IntelliFlash 280.

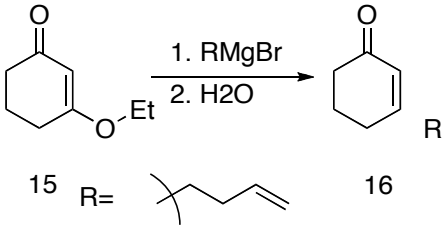
3-ethoxy-3-cyclohexenone (AEV-I-002)



14 15

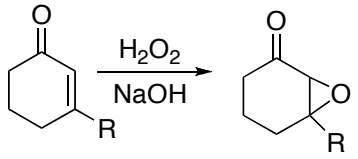
1,3-cyclohexanedione **14** (67.5 g, 602 mol) was dissolved in 100 mL of ethanol over low heat. This was added to p-toluene sulfonic acid monohydride (2.76 g, 14.5 mmol) dissolved in 900 mL of toluene, and heated in a three-neck round bottom flask (2 L) fitted with a dean stark trap and cold-water condenser. The reaction was heated at reflux for 1.5 h and the azeotrope of toluene and ethanol (~15 mL) was removed approximately every 10 min. The mixture was washed four times with 100 mL portions of 10% NaOH in saturated NaCl water. The aqueous layer was washed with 100 mL portions of water until the pH tested neutral. The aqueous phase was dried (Mg_2SO_4). Removal of solvent followed by distillation provided a pale yellow oil, 3-ethoxy-2-cyclohexenone **15** (50.4 g, 60%). ^{1}H NMR (CDCl3, 600 MHz) δ 1.36 (t, 3H), 1.97 (t, 2H), 2.37 (dt, 4H), 3.90 (q, 2H), 5.34 (s, 1H).

3-(3-Butenyl)-2-cyclohexenone (AEV-I-012)



To a vigorously dried 100-mL round-bottom flask fitted with a Claisen adapter and water-cooled reflux condenser, under nitrogen, was added finely chopped Magnesium (2.52 g, 104 mmol) in anhydrous THF (18 mL). 4-Bromo-1-butene (6.95 mL, 68.4 mmol) was added dropwise via syringe. A vigorous exothermic reaction was observed, after which an additional portion of anhydrous THF (18 mL) was added. The mixture was stirred under exothermic heat until the reaction subsided, and subsequently stirred at room temperature, for a total of 30 min. 2-cyclohexenone **15** (7.06 mL, 47.0 mmol) was added dropwise, and upon addition the formerly cloudy reaction mixture clarified becoming olive-green in color, with the evolution of heat. The reaction mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution (20 mL) was added. The product was partitioned between DCM and saturated aqueous oxalic acid. The aqueous phase was further washed with water and brine and dried (Mg_2SO_4). The product was determined to be 3-(3-Butenyl)-2-cyclohexenone **16** (7.06 g, 47.0 mmol, 73.2 % yield).^{1}H NMR(CDCl3, 600 MHz) δ 2.00 (m, 2H), 2.30 (m, 5H), 2.37 (t, 2H), 5.00 (dq, 1H), 5.06 (dq, 1H, 5.79 (m, 1H), 5.89 (t, 1H).

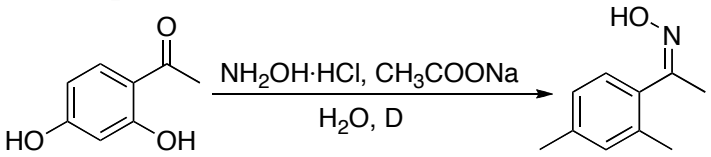
6-(3-butenyl)-7-oxabicyclo[4.1.0]heptan-2-one (AEV-I-026)



16 17

Aqueous hydrogen peroxide (1.567 mL, 33.3 mmol) was added to a solution of enone **16** (5 g, 33.3 mmol) in methanol (6.285 mL). The mixture was cooled to 0°C with stirring. Aqueous sodium hydroxide (0.571 mL, 3.43 mmol) was added dropwise to the reaction mixture. The reaction flask was then warmed to room temperature, and stirred for 2 h. TLC analysis (on silica gel) of the reaction mixture after one hour at room temperature showed the appearance of a product spot (hexanes-ethyl acetate (6:4)). The resulting mixture was partitioned between methylene chloride and water. The product was extracted with DCM. The combined organic phases were then washed with water and brine, and then dried (Mg_2SO_4). Product was characterized and determined to be 6-(3-butenyl)-7-oxabicyclo[4.1.0]heptan-2-one **17** (0.073 g, 33.33%). ^{1}H NMR (CDCl3, 600 MHz) δ 1.60-2.24 (m, 10H), 2.51 (dt, 1H), 3.11 (s, 1H), 5.04 (q, 2H), 5.74-5.85 (m, 1H).

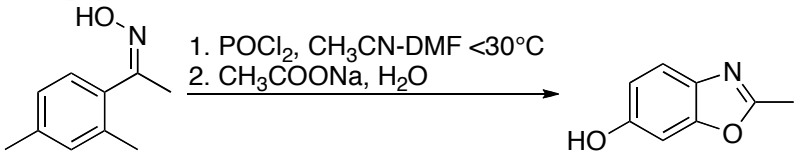
(E)-1-(2,4-dihydroxyphenyl)ethanone oxime (AEV-I-019a)



18 19

To a solution of hydroxylamine hydrochloride (2.71 mL, 65.1 mmol) and sodium acetate (9.06 g, 110 mmol) in water (15 mL) was added 2,4-Dihydroxyacetophenone **18** (3.00 g, 19.7 mmol) and water (20 mL). The solution was heated at reflux temperature for 75 min after which product was extracted with ethyl acetate. The combined organic phases were washed with water, brine, and dried (Na_2SO_4). Removal of solvent provided (E)-1-(2,4-dihydroxyphenyl)ethanone oxime **19** (3.00 g, 91% yield) as a light orange solid. ^{1}H NMR(DMSO-d6, 600 MHz) δ 2.19 (s, 3H), 6.24 (s, 1H), 6.32 (d, 1H), 7.29 (d, 1H), 9.70 (broad s, 1H), 11.20 (broad s, 1H), 11.76, (s, 1H).

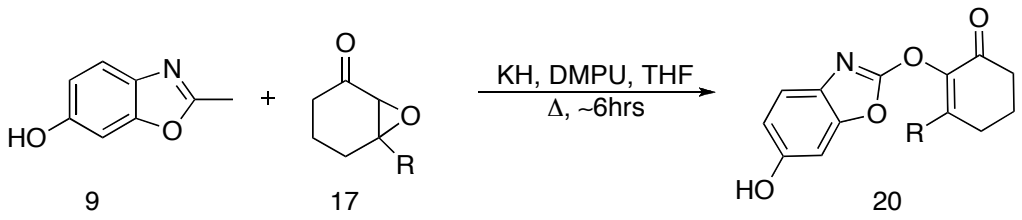
2-methylbenzo[d]oxazol-6-ol (AEV-I-021)



19 9

A solution of (E)-1-(2,4-dihydroxyphenyl)ethanone oxime **19** (4 g, 23.93 mmol) in dry acetonitrile (7 mL) and dry N,N-dimethylacetamide (15 mL) was treated with phosphorus oxychloride (3.67 g, 23.93 mmol) over a period of 2 min. During the addition, the temperature was maintained below 30 °C. The resulting mixture was stirred at room temperature for 75 min. Aqueous Sodium acetate (1.96 g, 47.86 mmol) was added and stirring was continued for 5 min. The crude product was extracted with ethyl acetate. The combined organic phases were washed with water, brine and dried (Na_2SO_4). Removal of solvent provided a brown solid. Recrystallization from acetonitrile yielded 2-methylbenzo[d]oxazol-6-ol as a light brown solid. **9** (2.41 g, 67.6%) ^{1}H NMR (DMSO-d6, 600 MHz) δ 2.52 (s, 3H), 6.76 (d, 1H), 6.96 (s, 1H), 7.41 (d, 1H), 9.65 (s, 1H).

3-(but-3-enyl)-2-(2-methylbenzo[d]oxazol-6-yloxy)cyclohex-2-enone (AEV-I-023flash)



9 17 20

In a 25-mL round bottom flask under nitrogen, 2-methylbenzo[d]oxazol-6-ol **9** (0.027 g, 0.180 mmol) was dissolved in dry THF (3 mL). The flask was cooled to 0 °C on an ice bath. A suspension of potassium hydride (0.023 g, 0.2 mmol) in THF (2 mL) was added to the flask. Gas evolution was observed. After 5 minutes, a solution of 6-(3-butenyl)-7-oxabicyclo[4.1.0]heptan-2-one **17** (0.03 g, 0.180 mmol) in dry THF (2 mL) was added. DMPU (0.1 mL, 0.180 mmol) was added and the mixture was heated to reflux for 4h. TLC on silica gel (hexanes-ethyl acetate (1:2)) showed that the epoxide had been consumed. The residue was partitioned between ether and water. The organic extracts were washed with water, with brine, and dried over anhydrous (Mg_2SO_4). Removal of solvent gave a yellow semisolid (0.023g, 42%). Chromatography of the resulting oil on silica gel (hexanes-ethyl acetate (6:4)) provided **20** (0.013 g, 24.3%). IR (film) 3102, 2927, 1681, 1619 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.10 (m, 2H), 2,26 (q, 2H), 2.46 (t, 2H), 2.56 (m, 7H), 4.90 (dd, 1H), 5.04 (dd, 1H), 5.75 (m, 1H), 6.88 (dd, 1H), 6.94 (d, 1H), 7.50 (d, 1H). ^{13}C NMR ($CDCl_3$) δ 14.2, 14.4, 21.0, 22.2, 29.7, 30.9, 31.2, 38.4, 97.1, 112.0, 115.6, 119.3, 136.1, 137.1, 144.3, 151.5, 151.7, 155.7, 163.1, 193.0s. LC/MS *m/e* 298.9 (M+).

References

1. Schultz, A.G.; Detar, M. B., *J. Am. Chem. Soc.* **1976**, *98*, 3574.
2. Schultz, A. G. *Acc. Chem. Res.* **1983**, *16,* 210.
3. Wolff, T. J. *J. Org. Chem.* **1981**, *46*, 978-983.
4. Herkstroeter, W. G.; Shultz, A. G. *J. Am. Chem. Soc.* **1984**, *106*, 5563.
5. Eberbach, W.; Brokatzky, J.; Fritz, H. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 47.
6. Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100.
7. Shimizu, N.; Bartlett, P. D. *J. Am. Chem. Soc.* **1978**, *100,* 4260.
8. Dittami, J. P.; Nie, X,-Y.; Nie, H.; Ramanathan, H.; Breining, S.; Bordner, J.; Decosta, D.; Kiplinger, J.; Rieche, P.; Ware, R. *J. Org. Chem.* **1991**, 56, 5572
9. Dittami, J. P.; Nie, X,-Y.; Nie, H.; Ramanathan, H.; Buntel, C.; Rigatti, S. *J. Org. Chem.* **1992**, 57, 1151-115
10. Fujita, S.; Koyama, K.; Inagaki, Y. *Synthesis* **1982**, *1*, 68.

Spectra

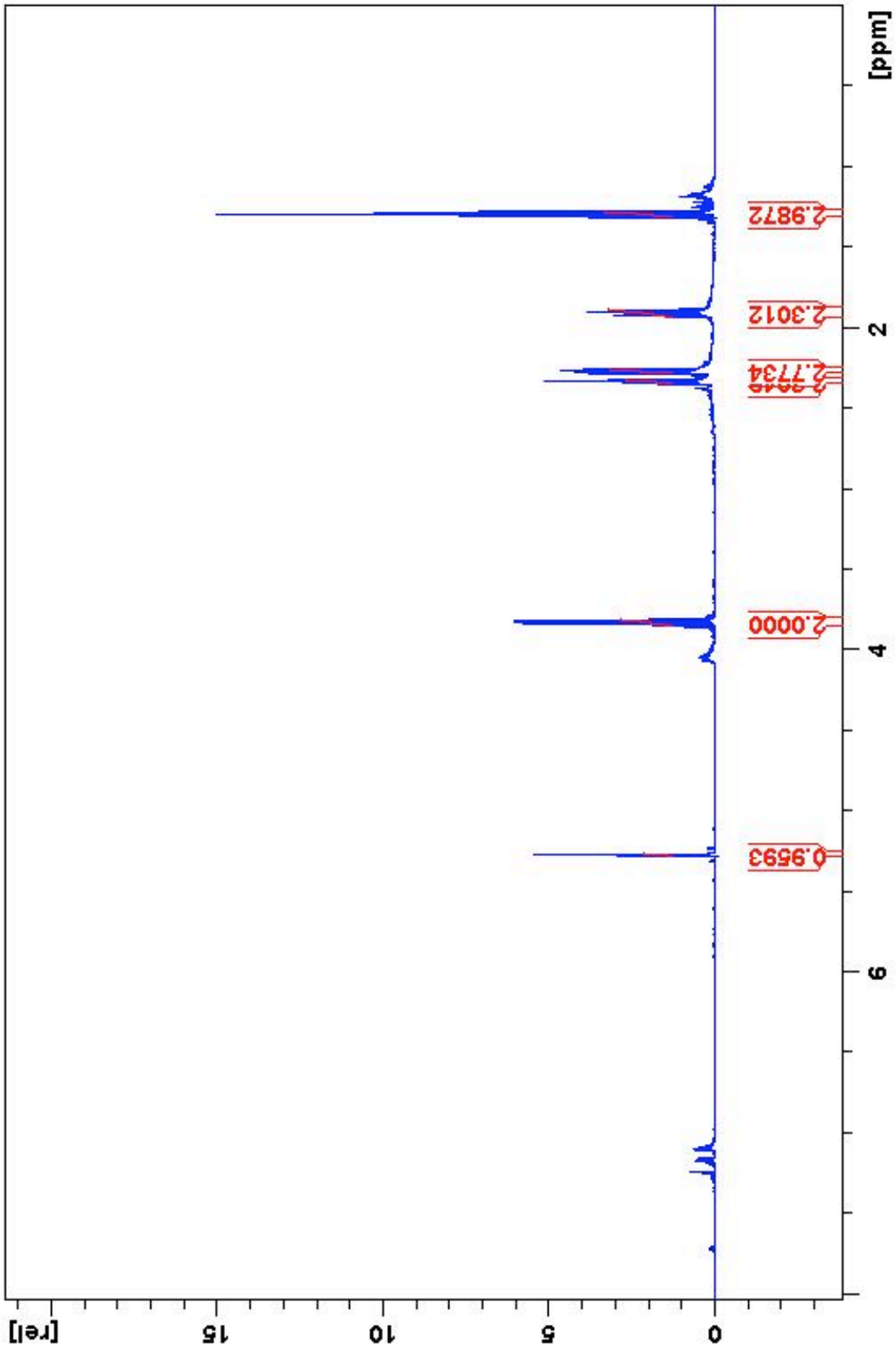


Figure 10: ^{1}H NMR 3-ethoxy-3-cyclohexenone (BCC-i-001c)

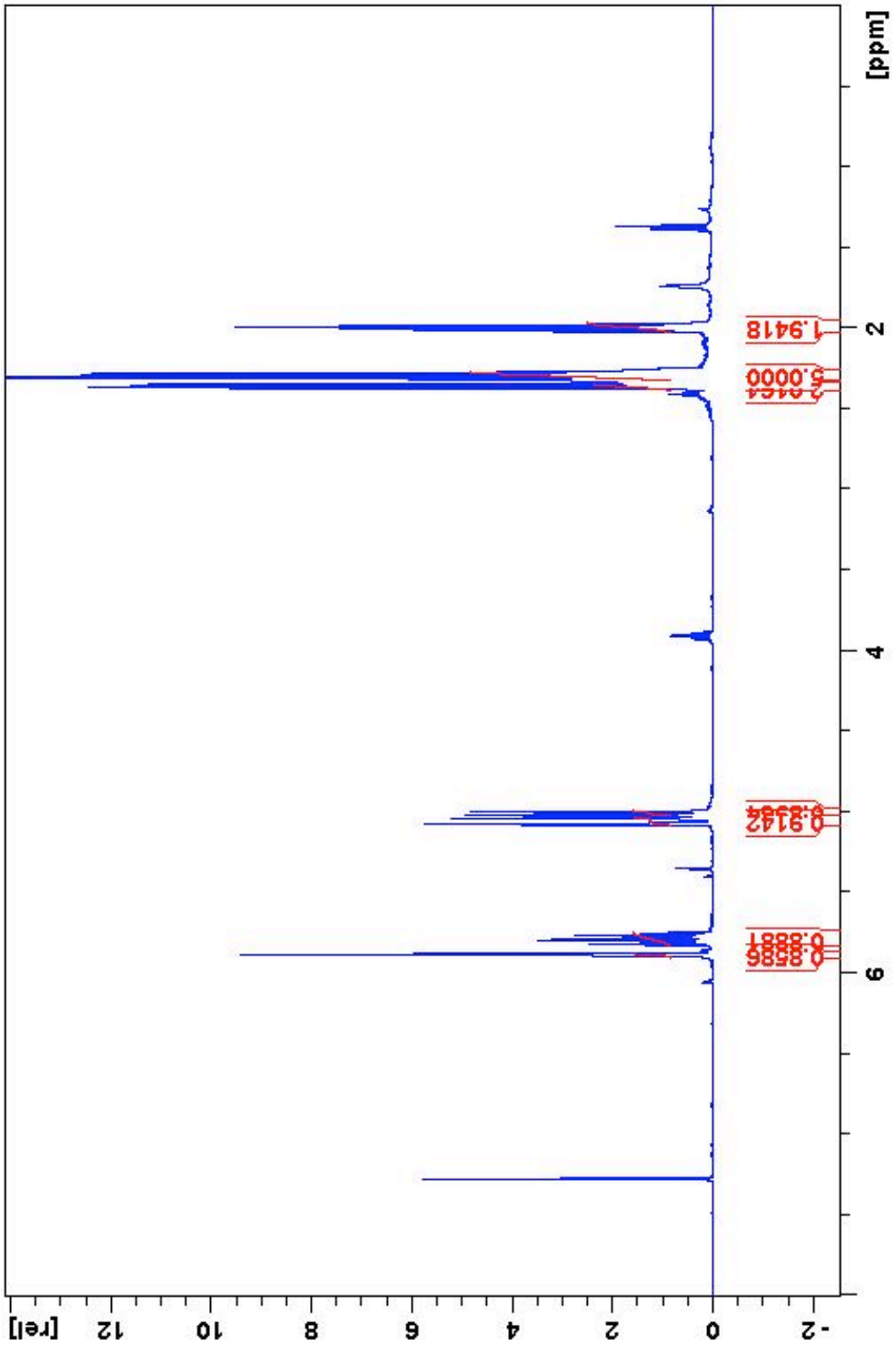


Figure 11: ^{1}H NMR 3-(3-Butenyl)-2-cyclohexenone (BCC-I-011b)

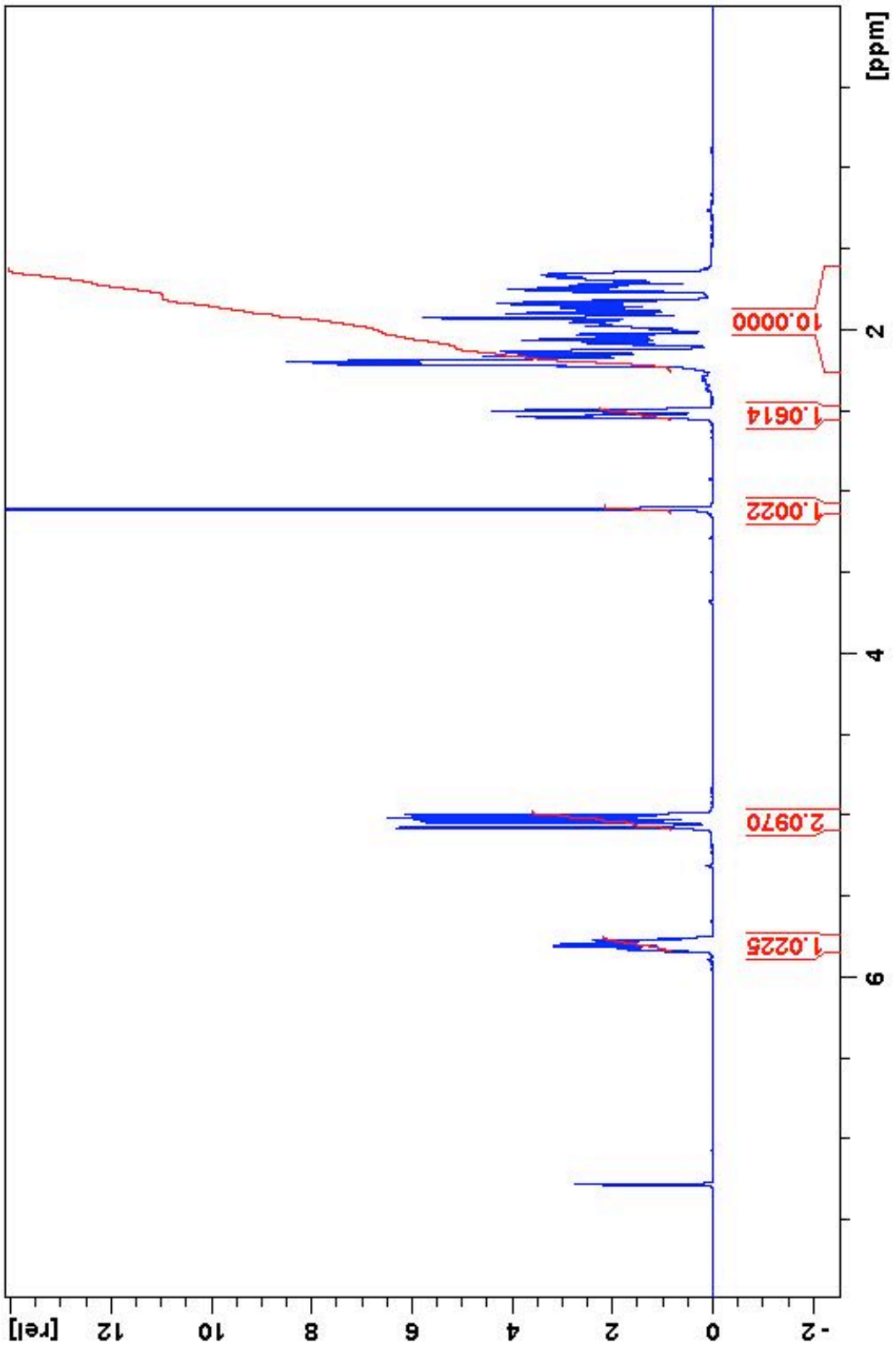


Figure 12: ^{1}H NMR 6-(3-butenyl)-7-oxabicyclo[4.1.0]heptan-2-one (BCC-I-016)

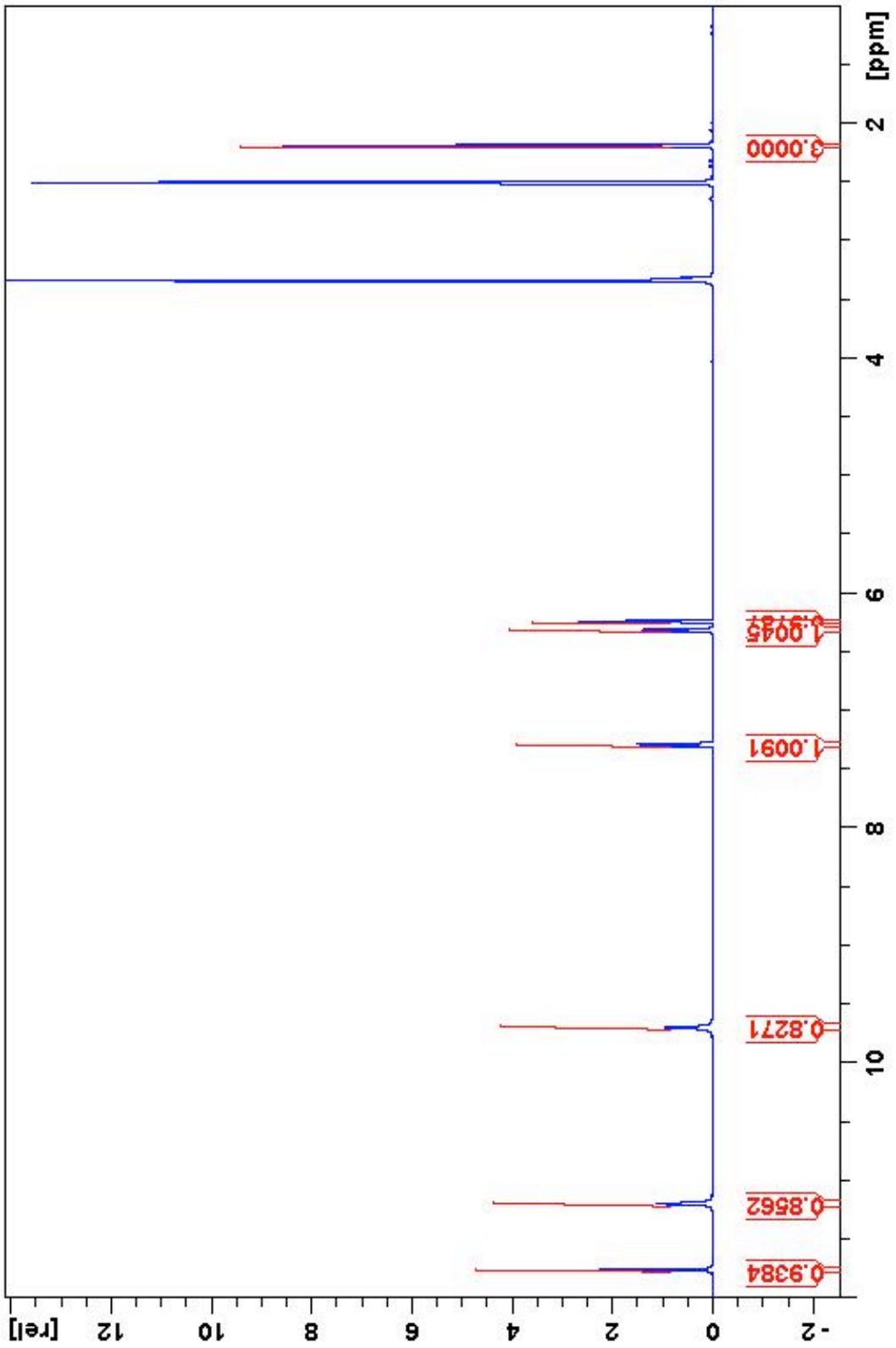


Figure 13: ^{1}H NMR (E)-1-(2,4-dihydroxyphenyl)ethanone oxime (AEV-I-019)

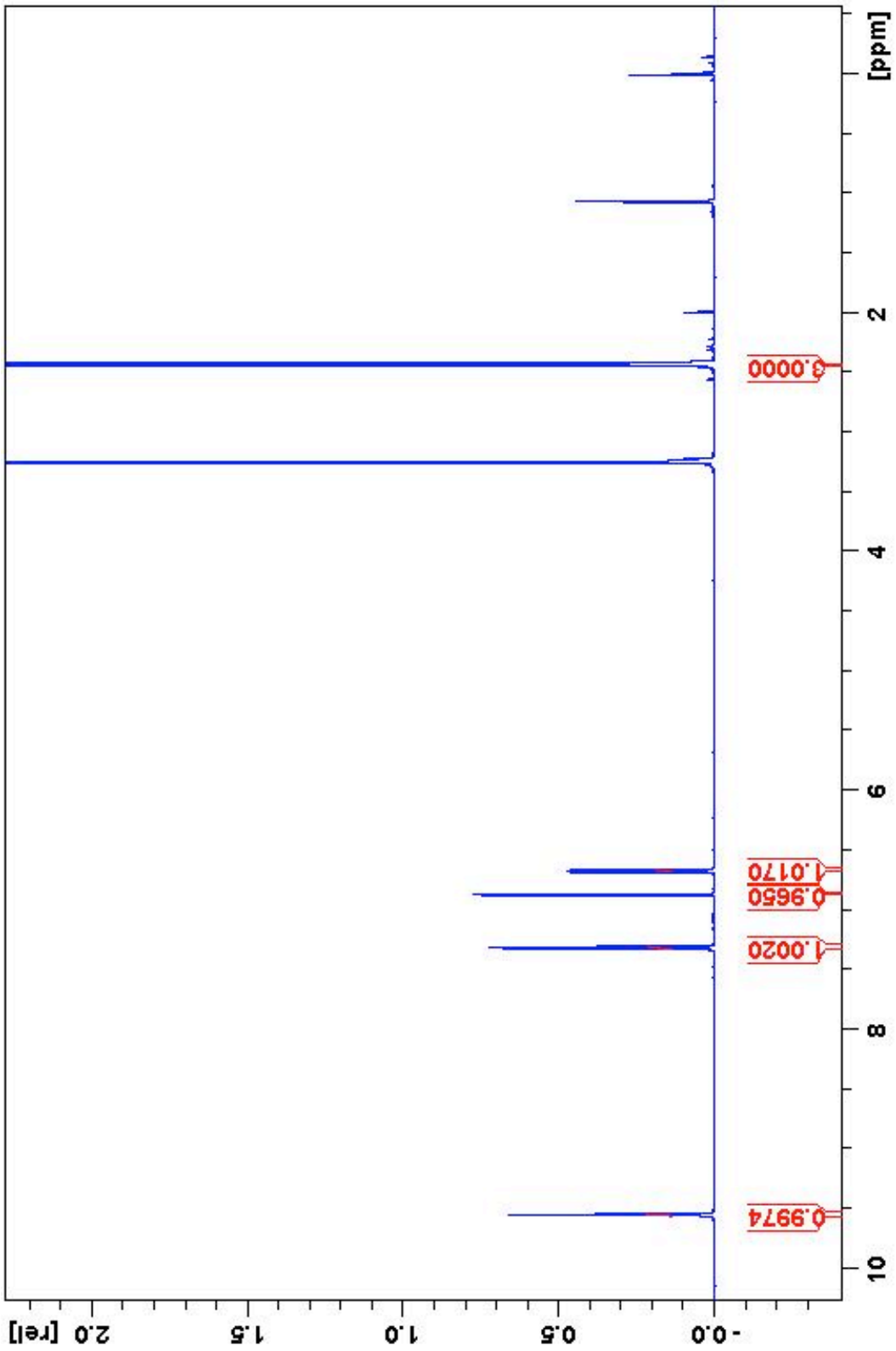


Figure 14: ^{1}H NMR 2-methylbenzo[d]oxazol-6-ol (AEV-I-021)

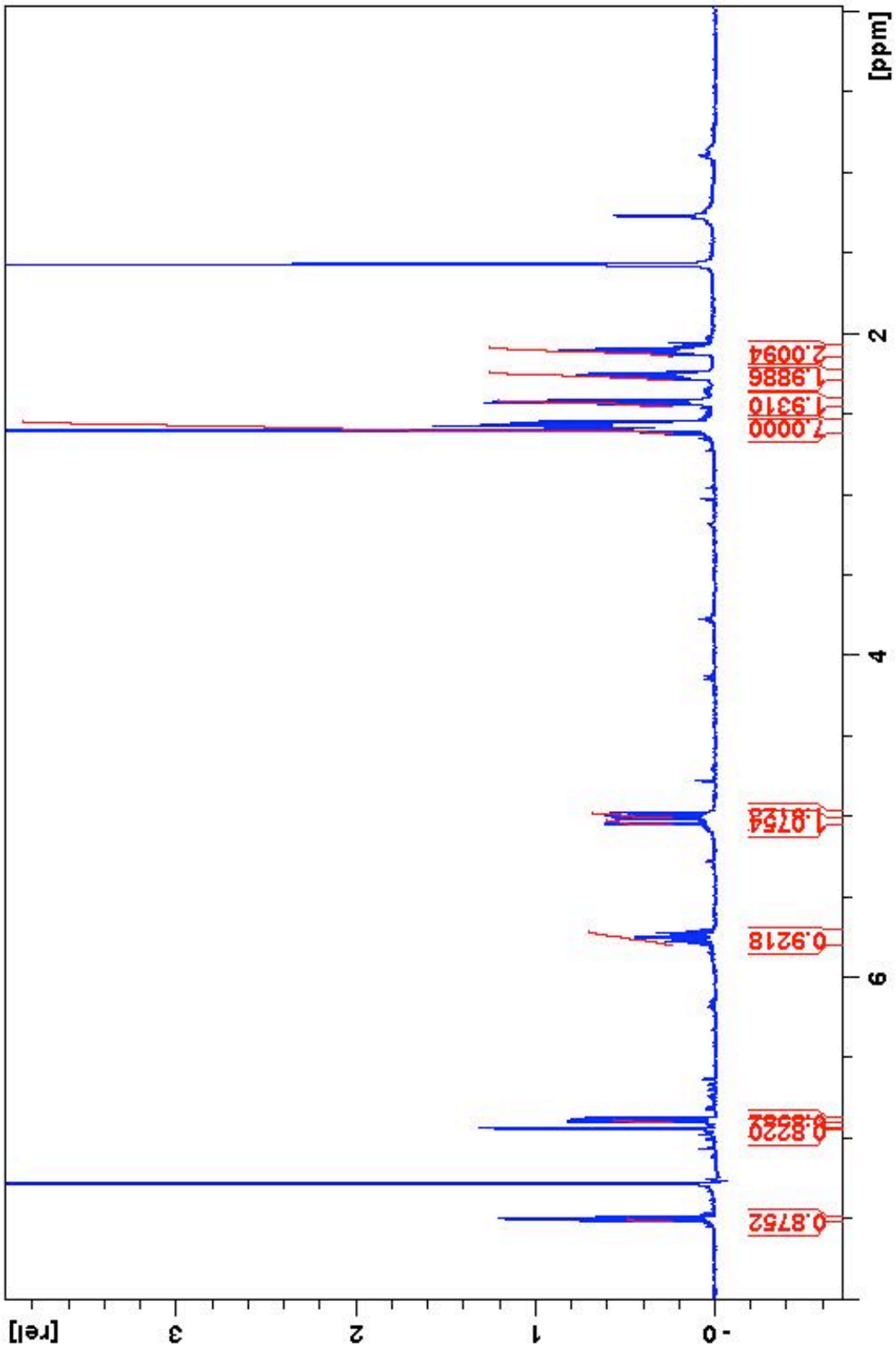


Figure 15: ^{1}H NMR 3-(but-3-enyl)-2-(2-methylbenzo[d]oxazol-6-yloxy)cyclohex-2-enone (AEV-I-023flash)

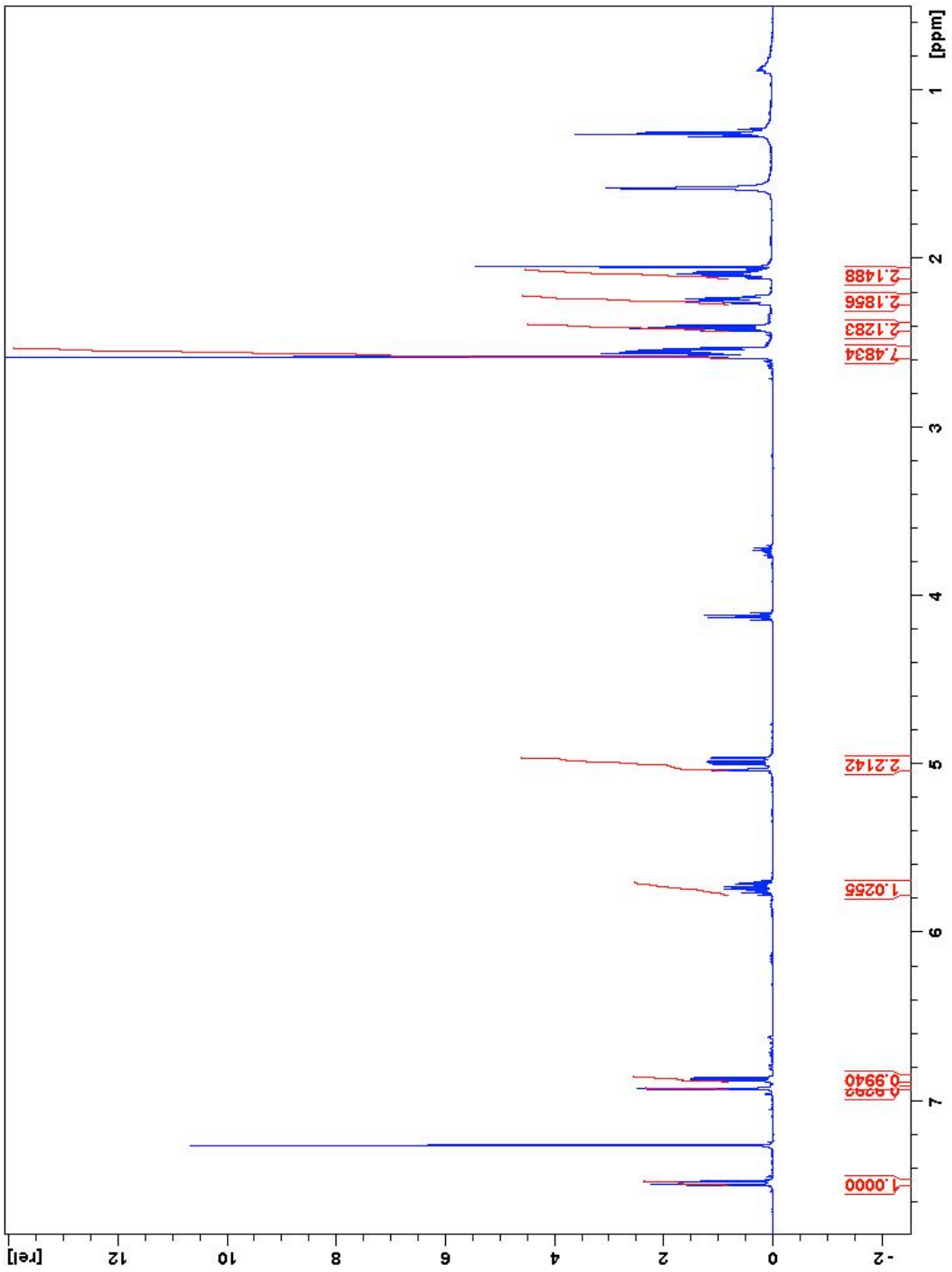


Figure 16: ^{1}H NMR 3-(but-3-enyl)-2-(2-methylbenzo[d]oxazol-6-yloxy)cyclohex-2-enone from microwave reaction (AEV-1-027a)

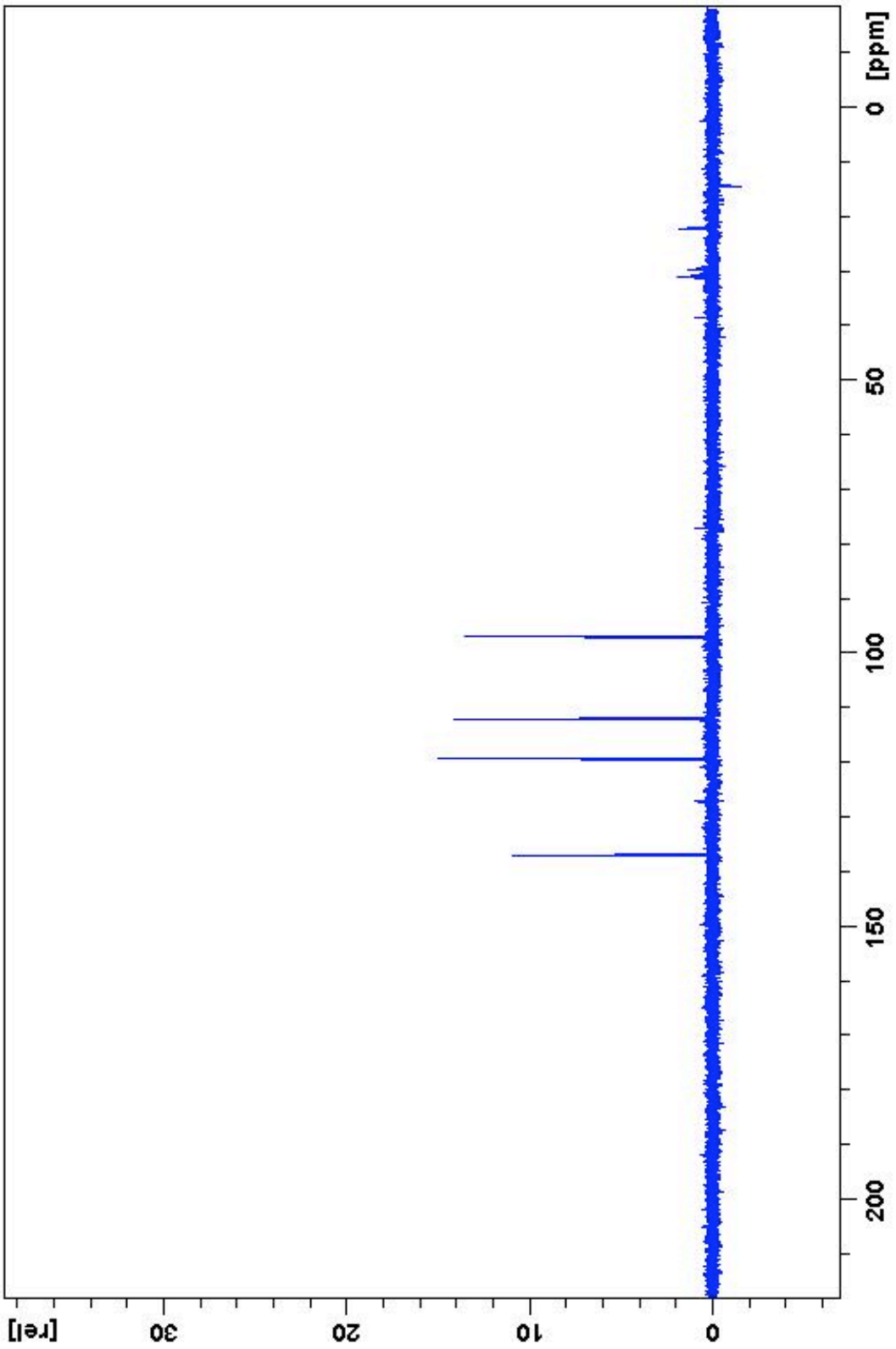


Figure 17: Dept90 NMR of3-(but-3-enyl)-2-(naphthalen-2-yloxy)cyclohex-2-enone (AEV-I-027b)

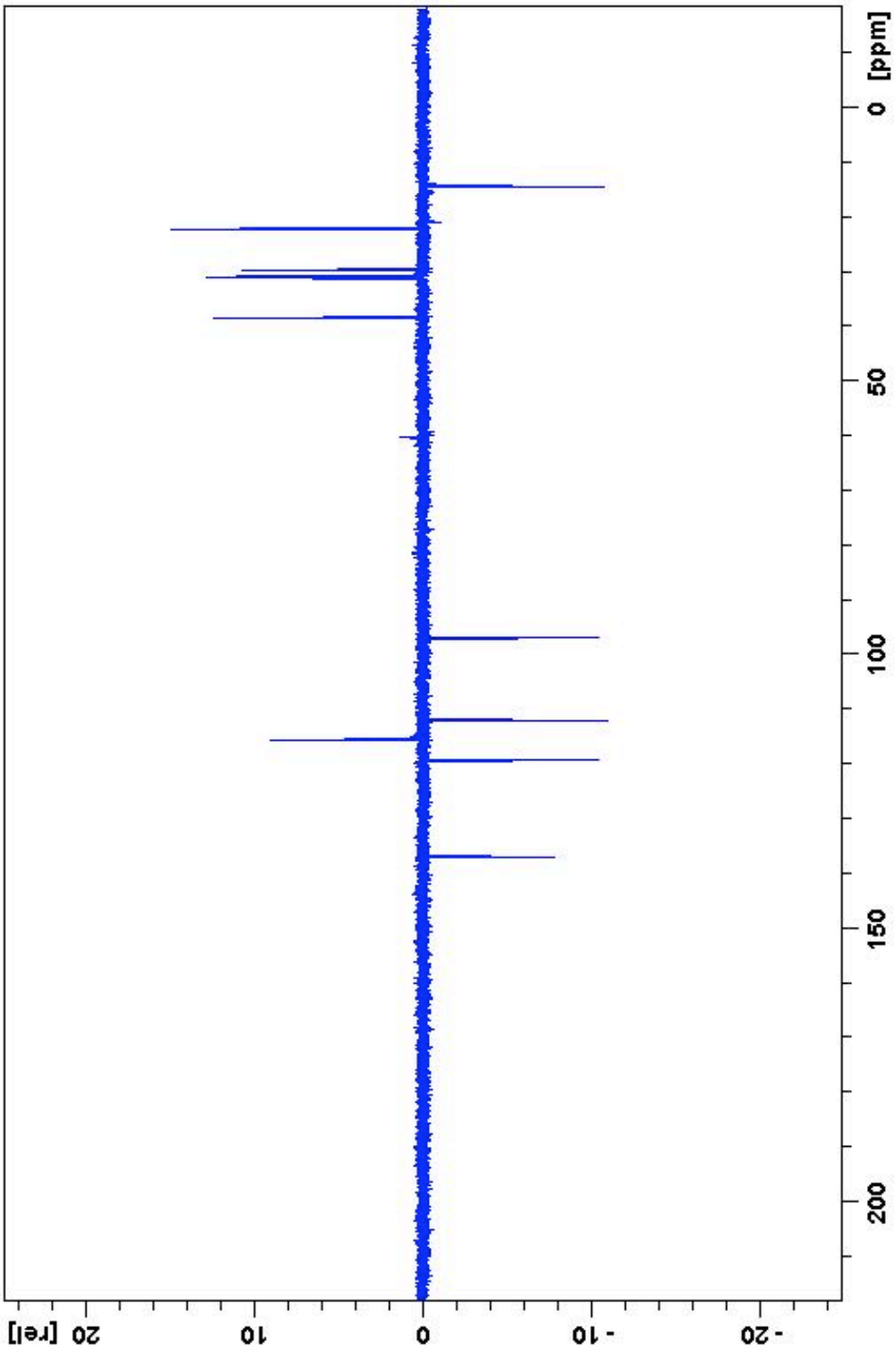


Figure 18: Dept135 of 3-(but-3-enyl)-2-(naphthalen-2-yloxy)cyclohex-2-enone (AEV-I-027b)

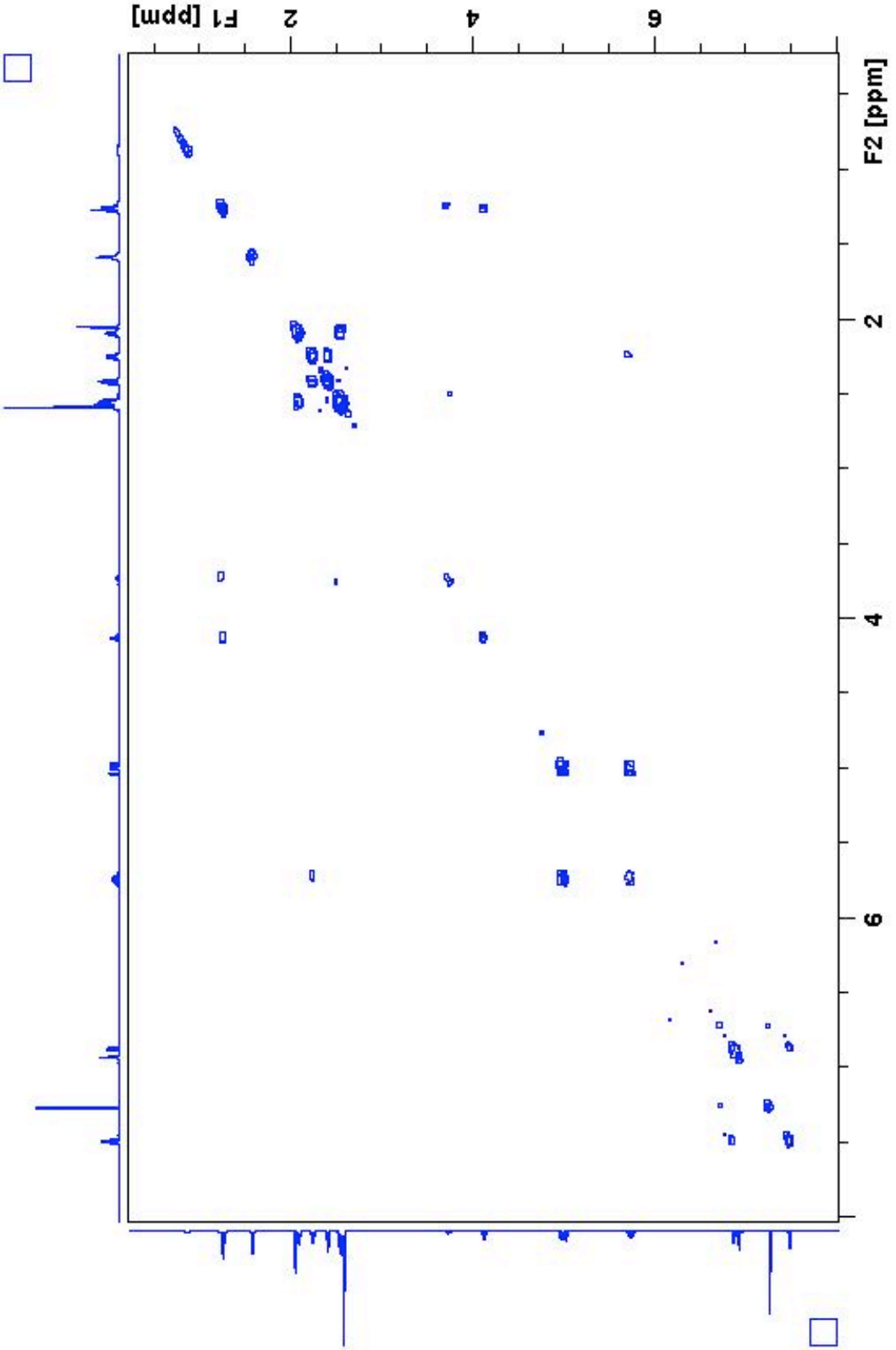


Figure 19: COSEY NMR of 3-(but-3-enyl)-2-(naphthalen-2-yloxy)cyclohex-2-enone (AEV-I-027b)

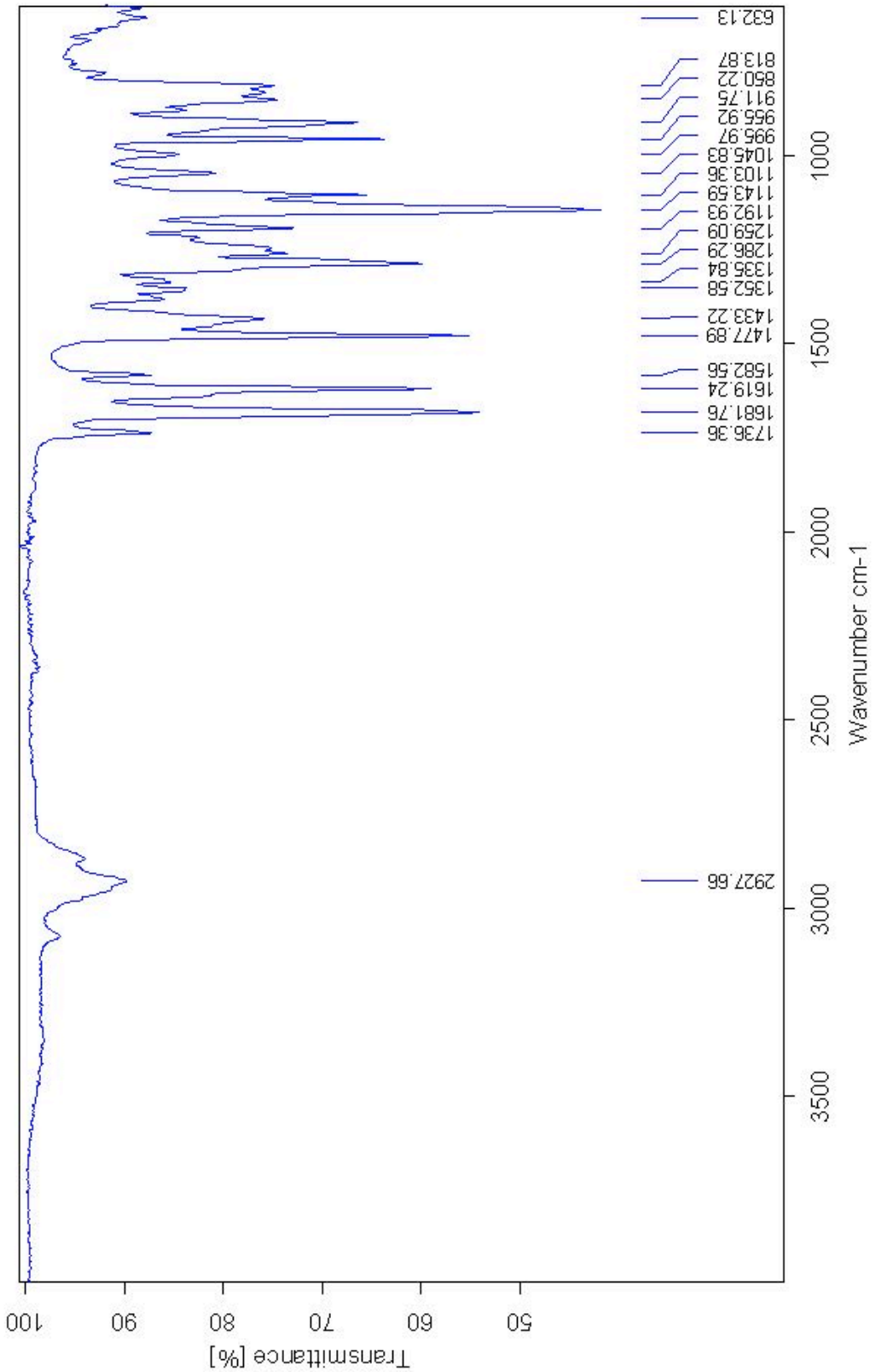


Figure 20: IR spectra of3-(but-3-enyl)-2-(naphthalen-2-yloxy)cyclohex-2-enone

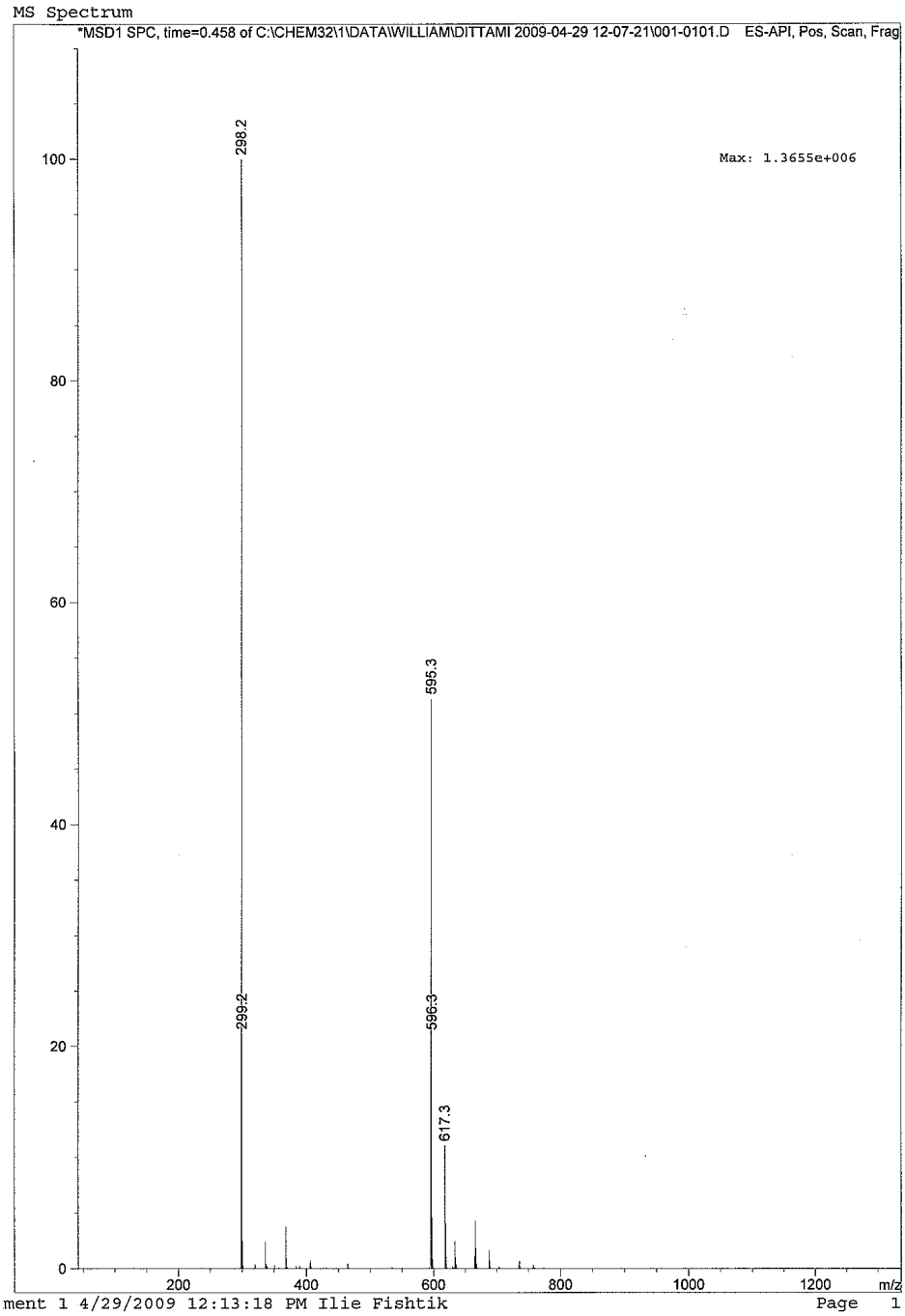


Figure 21: LCMS of of3-(but-3-enyl)-2-(naphthalen-2-yloxy)cyclohex-2-enone