Project Number: MQP – JPD – 0701

Synthesis of Novel Materials Containing Catechol Bioisosteres

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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_____
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Abstract

The “photoinitiated intramolecular ylide-alkene cycloaddition reaction” which was developed in our laboratory provides a method for construction of up to three rings and six chiral centers in a single experimental operation from relatively simple starting materials. This project has attempted to utilize this reaction to quickly synthesize novel materials which incorporate catechol bioisosteres into the organic scaffold in the hopes of imparting potentially useful bio-activity to the new molecules.

Acknowledgements

We would like to thank Professor James P. Dittami for allowing us to use his laboratory and for providing support and guidance to us throughout the year. We also wish to thank Brian Costa and Shira Rockowitz for their effort on this project. Without their help, we would not have been able to push as far as we had in our work. We wish to thank our peers for providing us with laughter and stress relief throughout the past four years. Lastly, we wish to thank our families for their support over the past twenty-two years.

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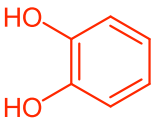
Introduction

Catechol **1** is a commonly seen motif in many active medicinal compounds such as Morphine **2,** and Dopamine **3**.



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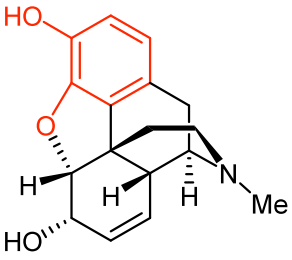
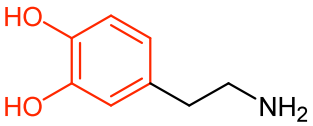
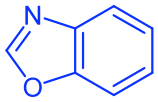


Morphine 2

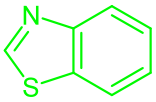


Dopamine 3

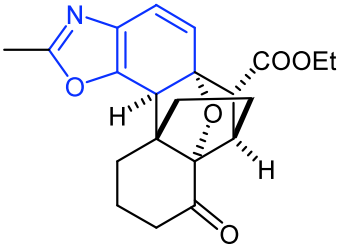
Bioisosteres of catechol, including benzoxazole **4** and benzothiazole **5** also commonly occur as motifs in a wide range of antibacterial, antifungal, non-narcotic analgesic, anti-inflammatory, anticancer, anti-HIV-1, and antimicrobial agents[1, 2].



Benzoxazole 4



Benzothiazole 5



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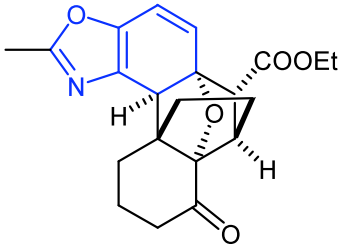

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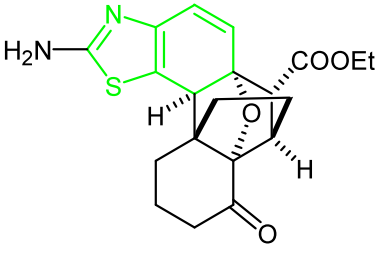
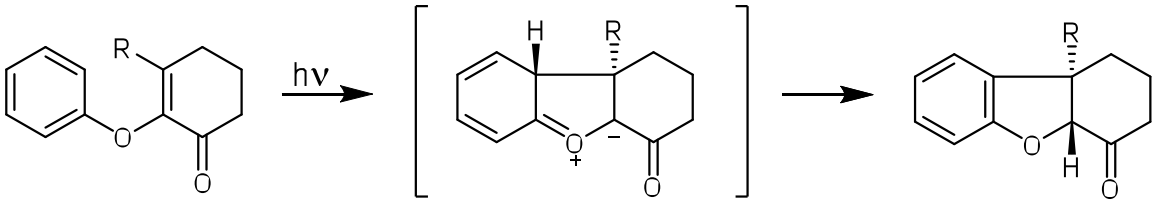


8

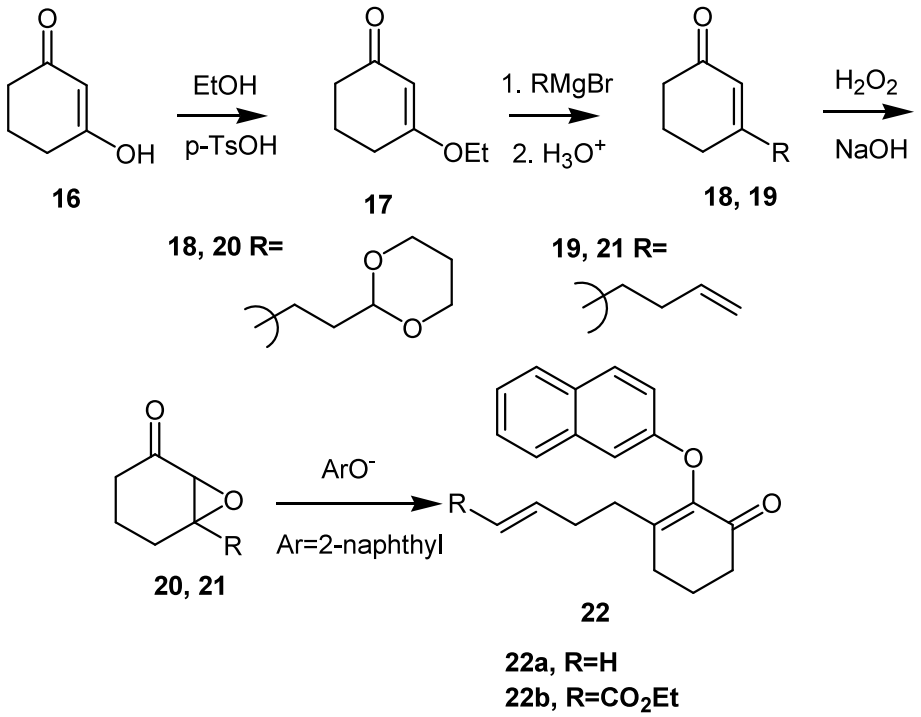
A common method used for development of new drugs from known active compounds is via the introduction of bioisosteres. Bioisosteres are groups or molecules that have chemical and physical similarities producing broadly similar biological properties. Thus if one knows the pharmacophores, or groups in a molecule which are responsible for biological activity, one could systematically replace these with bioisosteric groups to generate new compounds with potentially improved therapeutic profiles. Thus novel compounds **6**, **7**, and **8** are logical targets for the development of new medicines.

Our group has actively pursued development of procedures to build multicyclic scaffolds similar to those found in natural products[3, 4]. The method is based on a photoarylation procedure pioneered by A.G. Schultz and exemplified via the conversion **13→15**[5].

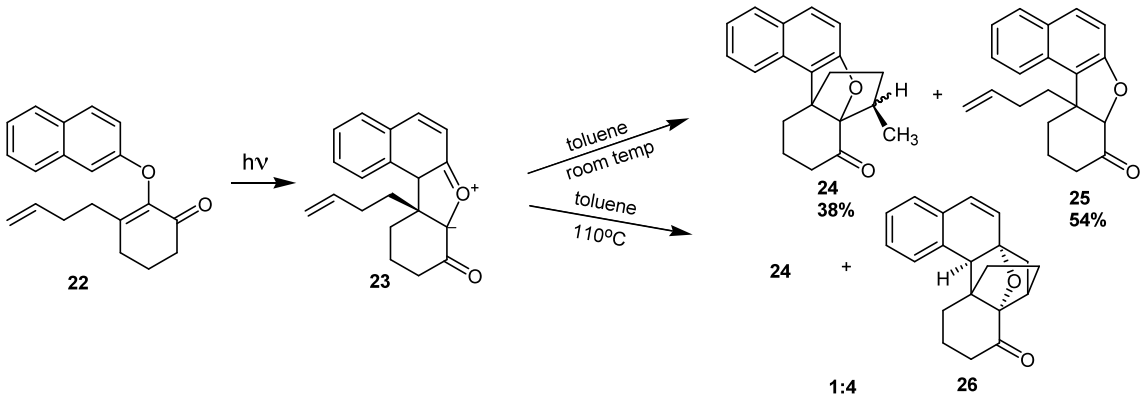


13 **14** **15**

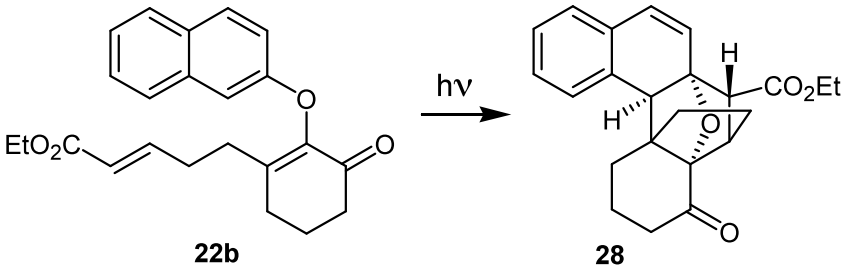
We sought to take advantage of the reactive ylide intermediate by appending a dipolarophile to the enone system as in **22**. Synthesis of **22** is representative of the methods used in preparation of all photoprecursors used in this study.



Upon photolysis it was observed that **22** underwent ring closure and subsequent intramolecular ylide alkene addition. At room temperature the predominant product **25** was consistent with ring closure to provide an ylide which underwent hydrogen shift as in Schultz's model **13→14→15**. A second product **24** arising from ylide alkene addition was also observed. At higher temperature we observed exclusively ylide alkene addition products **26** and **24** in a 4:1 ratio[3,4].

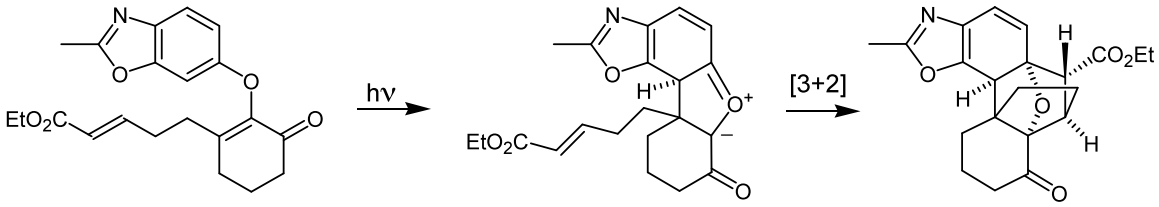


Formation of the [3+2] products can be enhanced by addition of electron withdrawing groups on the side chain of **22**. Therefore, photolysis of **22b** in toluene (0.001 M) provides **28** as the only product, even at room temperature. Compound **22b** was prepared from the acetal derivative of **22** via (1) acetal hydrolysis followed by (2) Wittig addition to the resulting aldehyde[3,4].



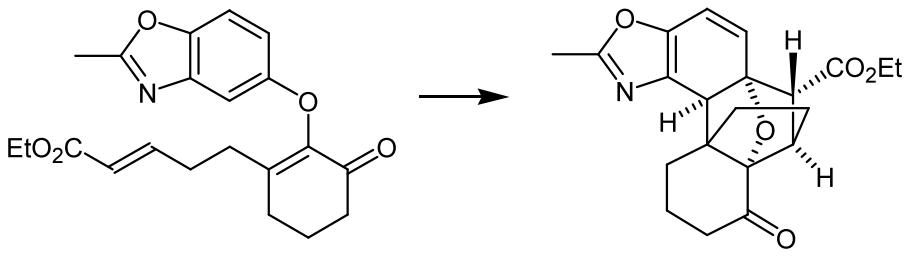
22b **28**

With this established precedent, we predicted photolysis of **9** would provide carbonyl ylide intermediate **10** which would be expected to undergo a [3+2] intramolecular ylide-alkene cycloaddition to give **6**[3, 4].

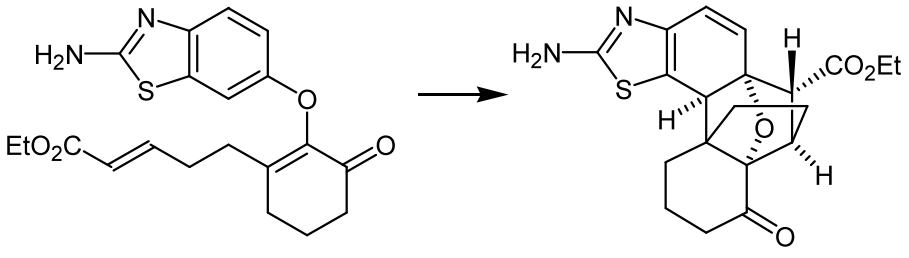


9 **10** **6**

Similarly, precursors **11** and **12** are expected to undergo the same transition to give products **7** and **8** respectively.

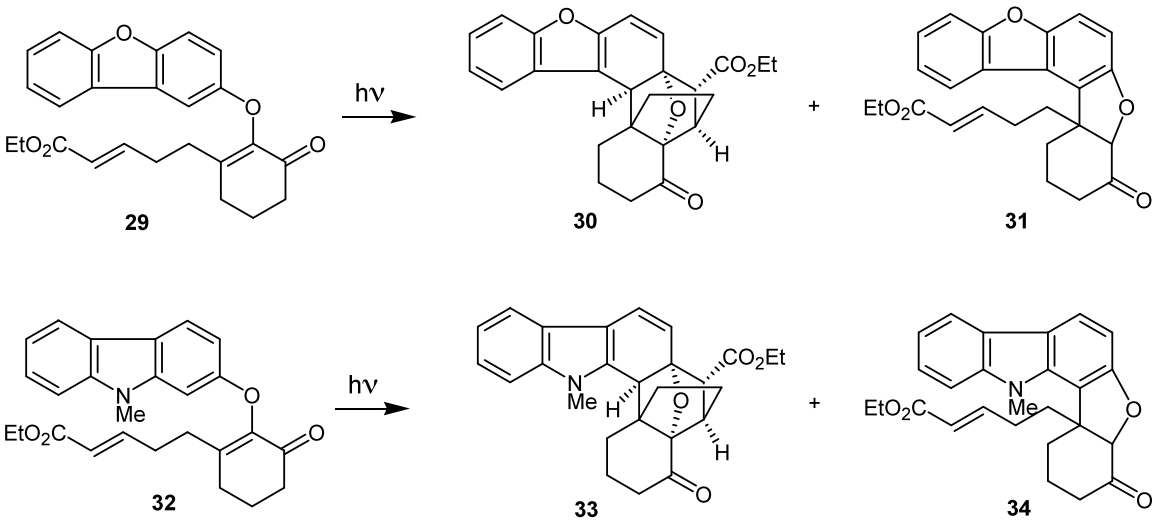


11 **7**



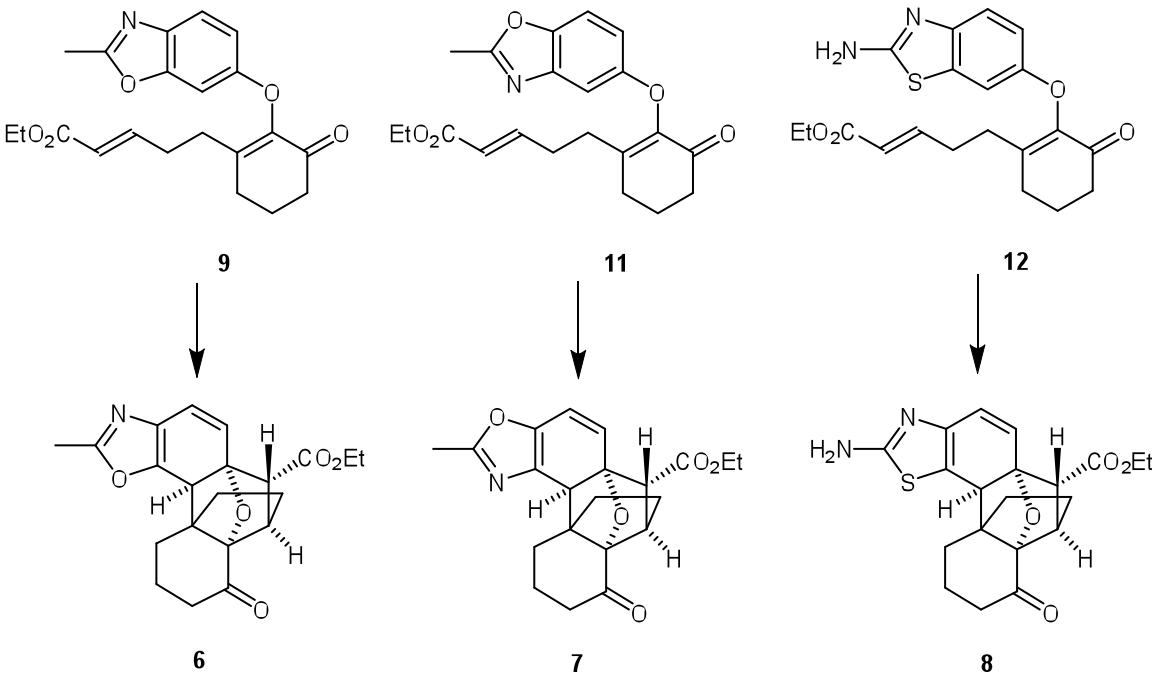
12 **8**

Former researchers in our lab have prepared substrates **29** and **32**, which both contain heteroaromatic groups, in order to test the feasibility of performing a [3+2] ylide alkene cycloaddition on compounds similar to the target benzoxazole and benzothiazole derivatives. Photolysis of **29** in toluene at room temperature provided **30** in 60% yield and **31** in 30%. Similarly, photolysis of **32** in xylene at reflux gave **33** in 10% yield and **34** in 60%.



29 30 31 32 33 34

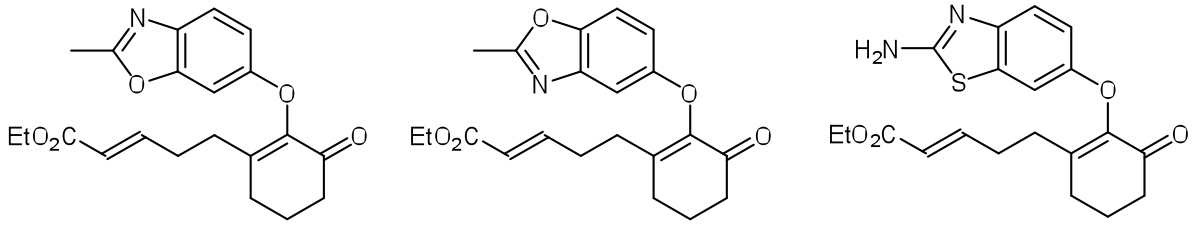
The successful formation of **30** and **33** shows the feasibility of using heteroaromatic systems to promote the photoinitiated intramolecular [3+2] cycloaddition reaction. With this demonstrated precedent, it is likely that photoprecursors **9**, **11**, and **12** will undergo similar transformations to give the desired [3+2] cycloaddition products **6**, **7** and **8** respectively.



9 11 12 6 7 8

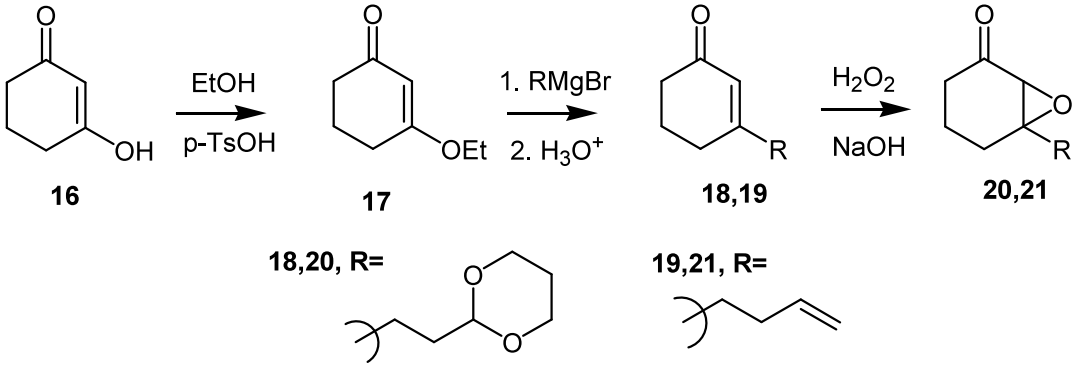
Results and Discussion

As noted in our introduction, this project addresses the synthesis and photochemical reactions of products **9**, **11** and **12** as a means to prepare complex multi-cyclic scaffolds.

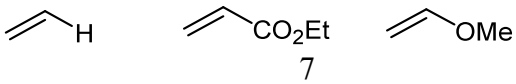


9 **11** **12**

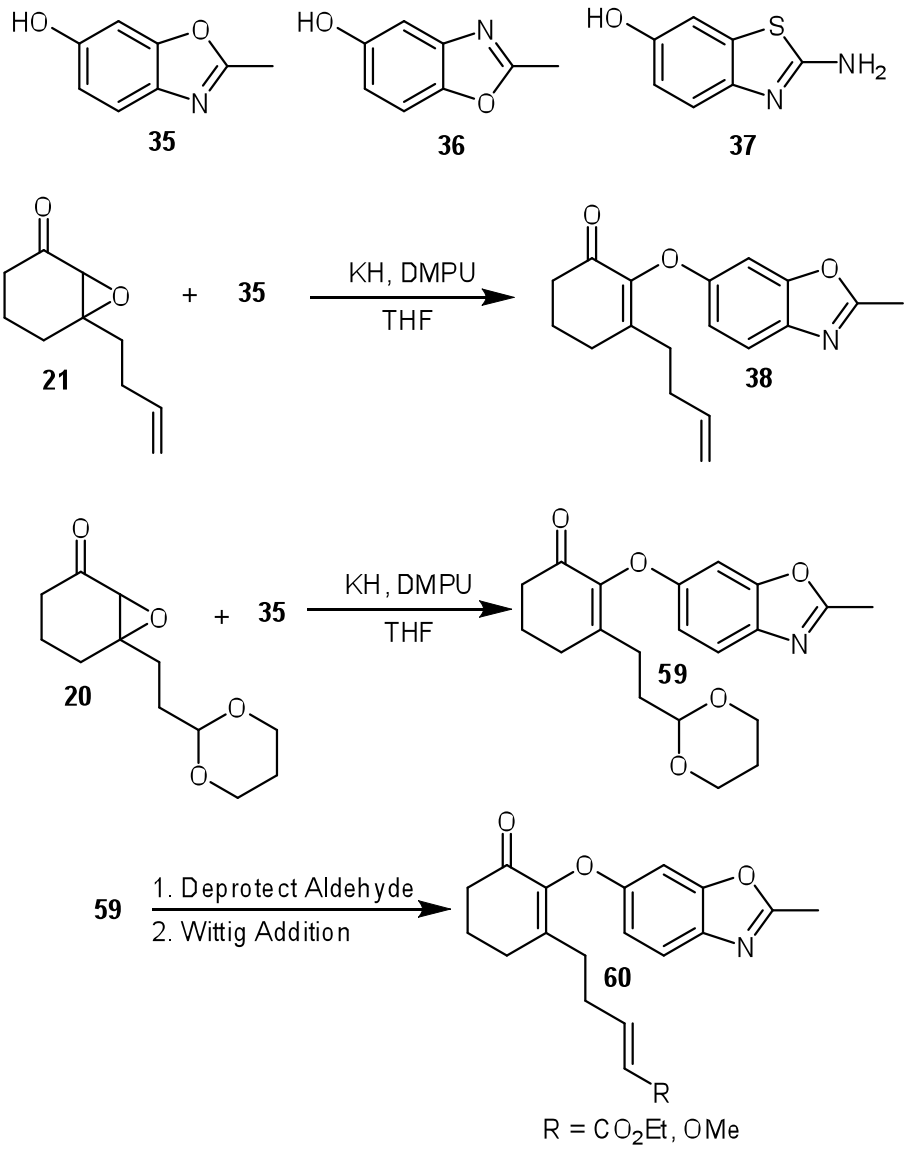
In order to achieve maximum versatility in substrates for our studies, we selected the following general method of synthesis.



Thus, synthesis of either epoxide **20** or **21** can give rise to a variety of substituted or non-substituted alkene systems such as:

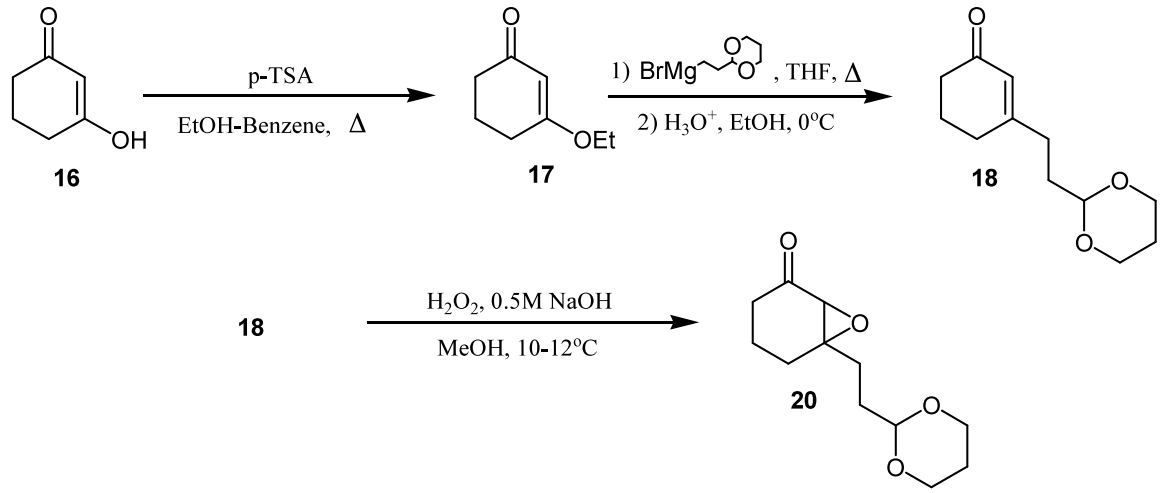


Coupling of either epoxide with one of the three aromatic systems as shown gives rise to an array of aryl-vinyl ether photo precursors for use in our studies.

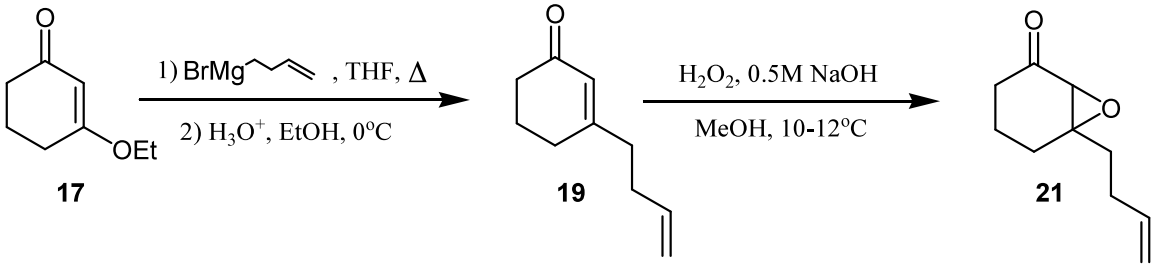


Synthesis of epoxide **20** was achieved as follows. Reaction of **16** with *p*-toluene sulfonic acid (*p*-TsOH) in ethanol-benzene provided **17**[6]. Grignard addition of (2-(1,3-dioxan-2-yl)ethyl)magnesium bromide and subsequent acid workup yielded **18**. Facile epoxidation of **18**

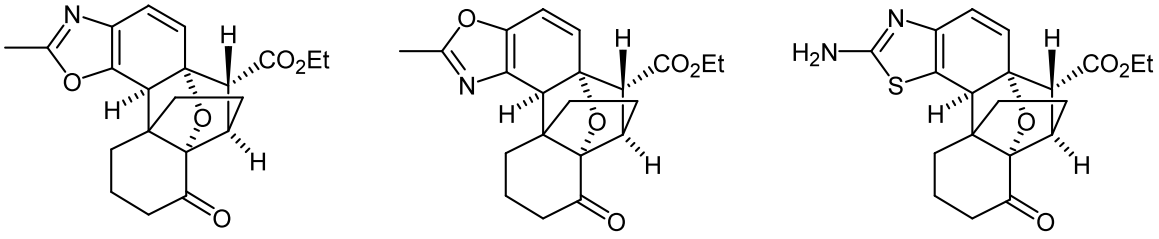
under basic conditions gave **20** in a 54% yield. Compound **20** shows peaks in the ^{1}H NMR at δ 1.17-1.39 (2 H), 1.72-2.41 (10 H), 3.68-3.80 (2 H), 4.02-4.15 (2 H), 4.45-4.53 (1 H), and 5.80-5.88 (1 H).



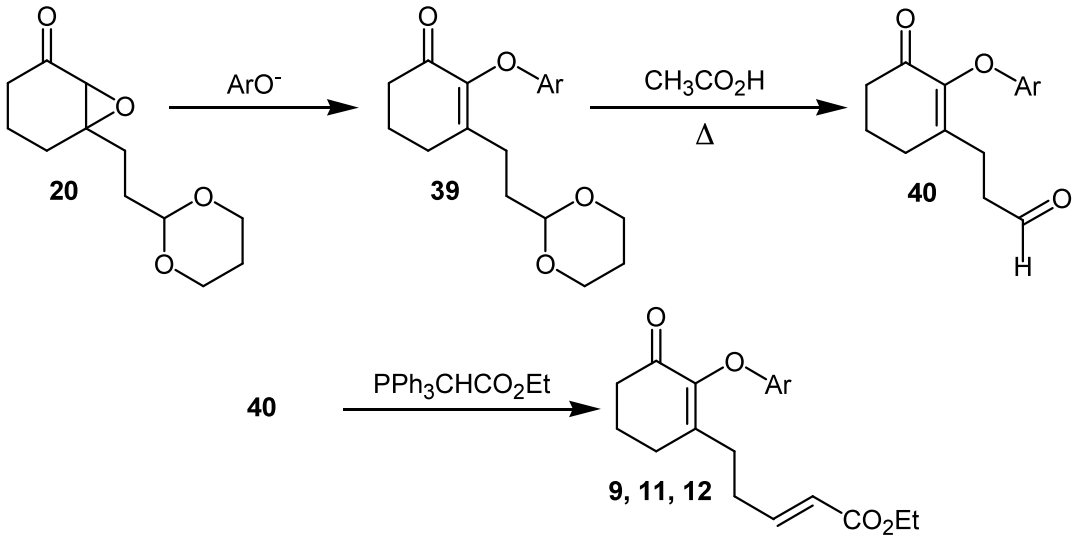
Similarly, epoxide **21** was prepared via Grignard addition of but-3-enylmagnesium bromide to **17** followed by acid catalyzed hydrolysis to give **19** and subsequent treatment with basic hydrogen peroxide provided **21** in 74% yield. **21** showed peaks in the ^{1}H NMR at δ 1.87-2.45 (10 H), 4.87-5.10 (2 H), and 5.68-5.90 (2 H).



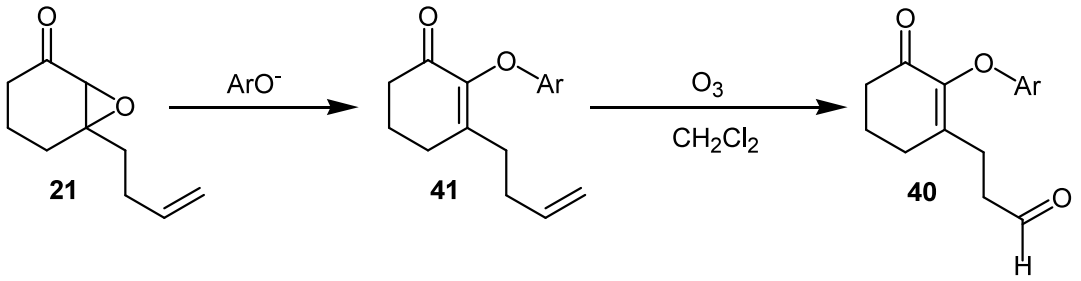
Epoxide **21** incorporates a simple alkene side chain. Epoxide **20** incorporates a protected aldehyde which can subsequently be converted to a substituted alkene, where R can be electron withdrawing or electron donating (e.g. CO_2Et or OMe respectively, illustrated below).



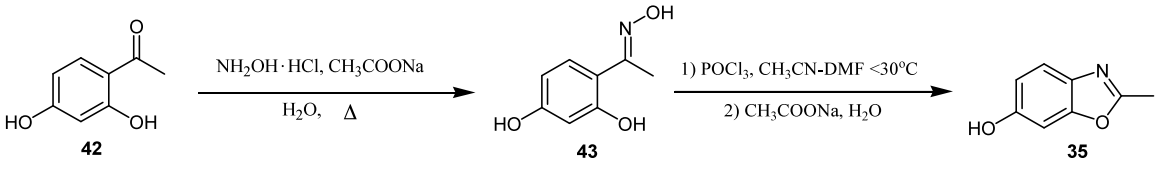
Much of the prior successful work on building scaffolds similar to **6**, **7** and **8** in our lab was conducted using the ethyl buteonate side chain. Accordingly, we selected the series of compounds **9**, **11** and **12** as initial synthesis targets.



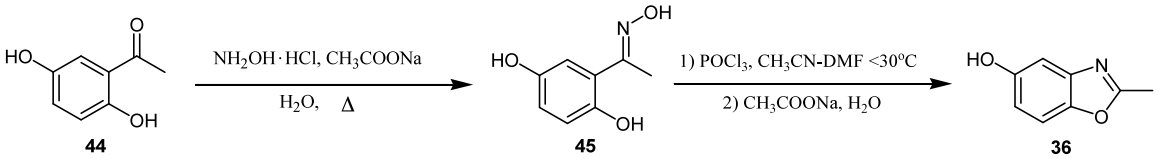
It was noted that benzoxazoles hydrolyzed under acidic conditions. Given the instability of benzoxazole toward acid and the need for an acid workup of **39** to form aldehyde **40**, we turned our attention to an alternative approach to **40** via epoxide **21**. This approach takes advantage of ozonolysis of the side chain olefin late in the synthesis to provide aldehyde **40** as shown[7, 8].



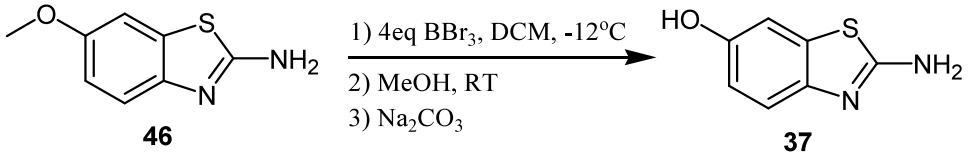
Synthesis of the bioisostere containing aryl groups **35**, **36**, and **37** was easily accomplished from commercially available materials. Compound **35** was synthesized via a two-step published procedure[9, 10]. Thus, addition of **42** to a mixture of hydroxylamine hydrochloride and sodium acetate in water provided **43**. Treatment of **43** with phosphorous oxychloride ($POCl_3$) in acetonitrile and dimethylformamide, followed by aqueous sodium acetate gave rise to **35** in 43% yield. Compound **35** displays ^{1}H NMR peaks at δ 2.57 (3 H), 6.75 (1 H), 6.97 (1 H), 7.37 (1 H), and 9.67 (1 H).



Similarly, **36** was obtained in 85% yield via the same procedure starting with commercially available **44** and shows ^{1}H NMR peaks at δ 2.53 (3 H), 6.65 – 6.75 (1 H), 6.82 – 6.84 (1 H), 7.43 – 7.42 (1 H), and 9.48 (1 H).

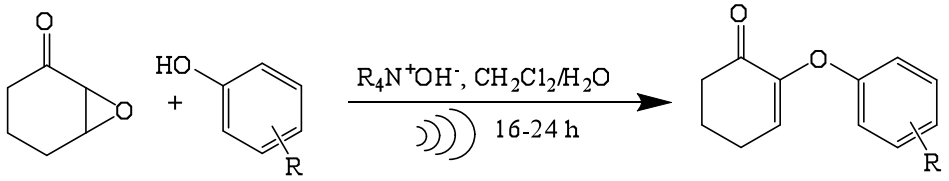


Benzothiazole **37** was obtained in a 70% yield from the commercially-available **46** upon treatment with 4 equivalents of BBr_3 in methylene chloride, followed by slow addition of methanol and neutralization with sodium bicarbonate. Previous research in our laboratory found a temperature of -12°C was essential for the reaction to proceed in high yield[11]. Benzothiazole **37** exhibits ^{1}H NMR peaks at δ 2.42 – 2.48 (2 H), 6.64 – 6.66 (1 H), 7.02 – 7.22 (2 H), and 9.17 (1 H).

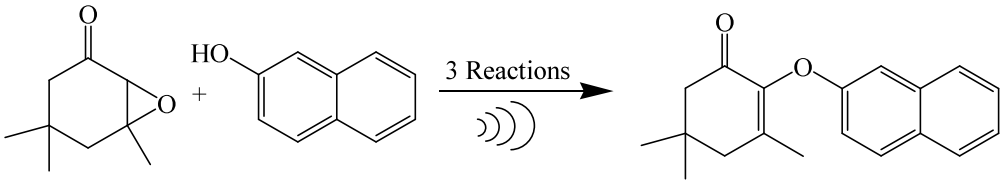


Once both the epoxide and the aryl-oxy systems were synthesized, we turned our attention to determine methods to couple the two systems together via an epoxide-opening reaction. Although procedures for preparing aryl-vinyl ether systems from epoxide **21** and various phenols had been developed in our laboratory, we chose to investigate some other attractive procedures

in the hopes of attaining higher yields. In one published report, epoxides were successfully coupled with phenols to provide aryl-vinyl ether systems as shown below[12, 13].



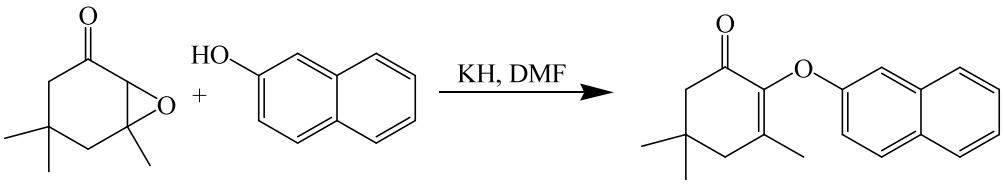
In our trials however, this approach failed to provide product under a variety of concentrations and conditions.



47 **48** **49**

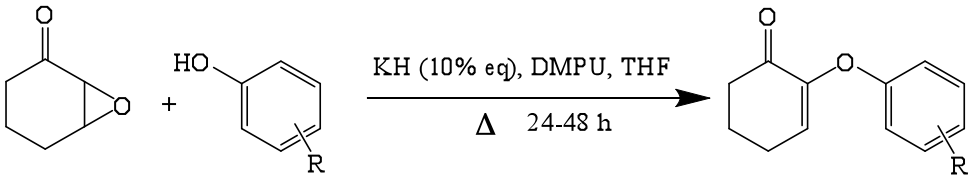
Reaction 1: (CH3)4NI, NaOH, CH2Cl2 / H2O, 0.1 M, 5 d
Reaction 2: (CH3)4NI, NaOH, CH2Cl2 / H2O, 1.0 M, 5 d
Reaction 3: NaOH, CH2Cl2, 1.0 M, 5 d

In another approach, we attempted to affect the coupling between 47 and 48 with potassium hydride (30% by weight in mineral oil) and dimethylformamide.

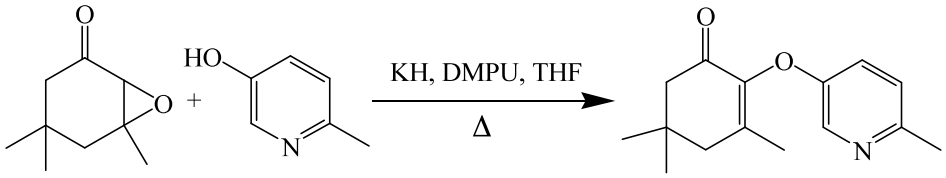


47 **48** **49**

When this attempt failed, we turned our attention to the method previously developed in our laboratory and typified by the scheme below[5].

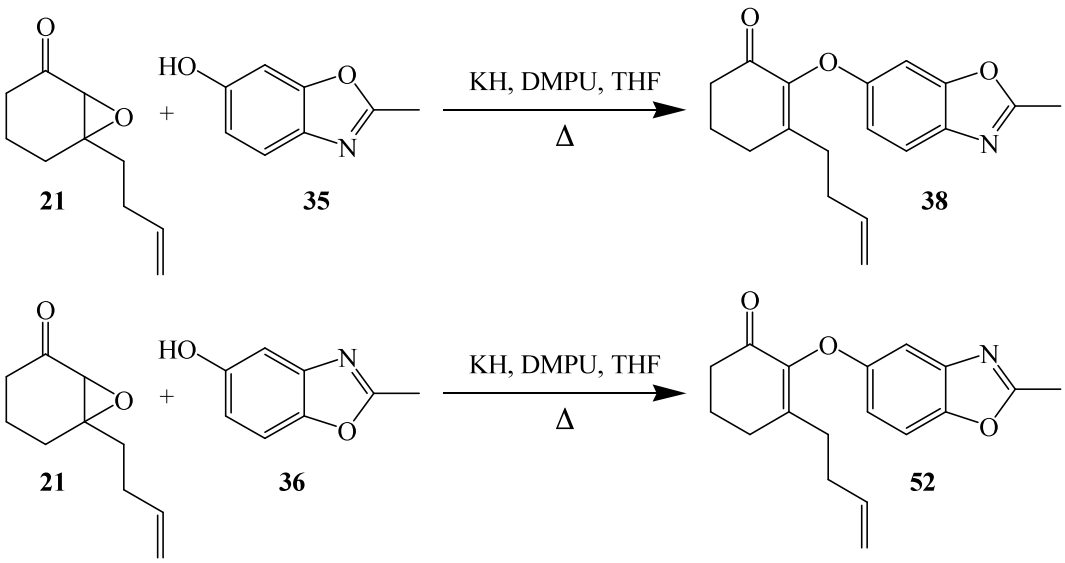


In order to evaluate this method for use with heterocyclic aromatic systems, we tested the conditions for synthesis of **51** from the readily available **47** and **50**.

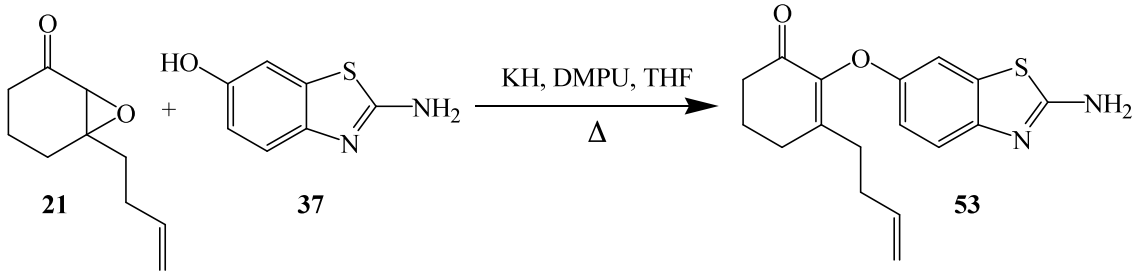


47 **50** **51**

After heating at reflux temperature for one day, followed by standard workup, aryl-vinyl ether **51** was collected in 47% yield. Following this success, coupling was done using epoxide **21** with the two benzoxazoles and one benzothiazole under the same conditions.

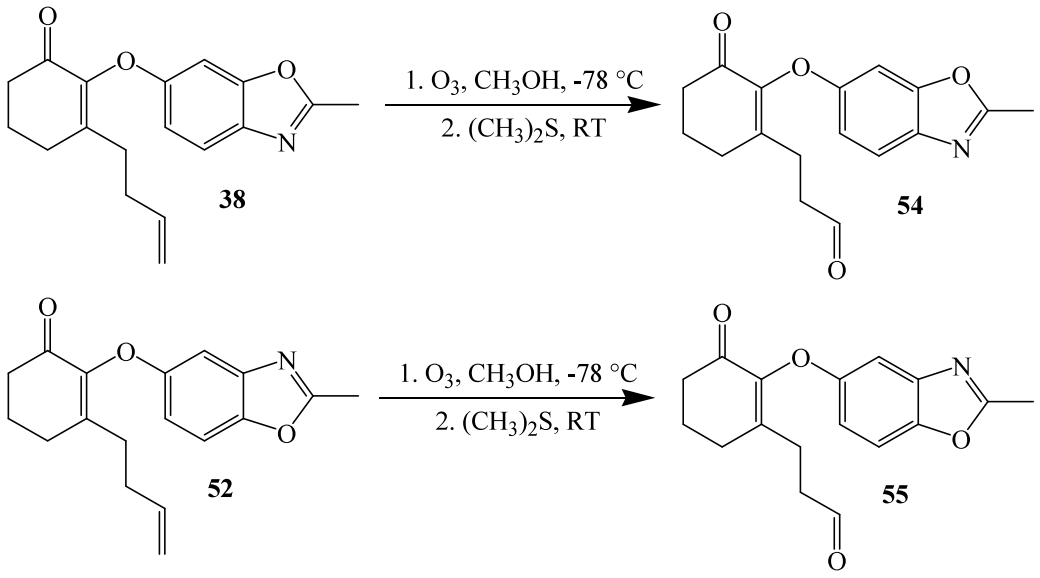


Epoxide **21** and benzoxazole **35** were allowed to heat at reflux temperature for two days, after which, a standard workup and a wash with 1 N sodium hydroxide were performed to afford aryl-vinyl ether **38** in a 35% yield. Compound **38** shows ^{1}H NMR peaks at δ 2.05 – 2.14 (10 H), 2.57 (3 H), 4.99 – 5.04 (2 H), 5.75 – 5.80 (1 H), 6.87 – 6.89 (1 H), 6.93 – 6.95 (1 H), and 7.65 – 7.69 (1 H). This same procedure was used to couple epoxide **21** and benzoxazole **36** to afford aryl-vinyl ether **52** in 40% yield. Compound **52** displays ^{1}H NMR peaks at δ 1.54-2.17 (10 H), 2.53 (3 H), 4.88-5.01 (2 H), 5.65-5.78 (1 H), 6.74-6.79 (1 H), 7.04-7.07 (1 H), and 7.18-7.25 (1 H).

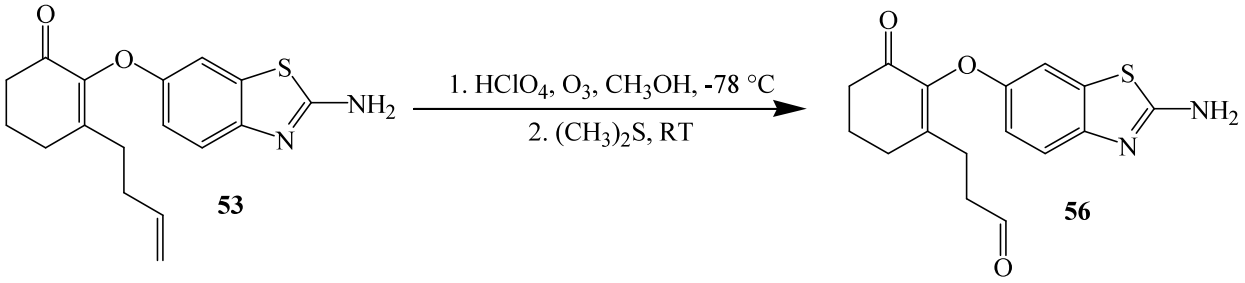


Epoxide **21**and benzothiazole **37** were heated at reflux temperature for two days using the standardized procedure of KH and DMPU in THF. A standard workup and purification by column chromatography on silica gel (methylene chloride : methanol (98:2)) afforded pure aryl-vinyl ether **53** in 45% yield. Aryl-vinyl ether **53** showed peaks in the ^{1}H NMR at δ 2.06-2.12 (2 H), 2.22-2.28 (2 H), 2.42 (2 H), 2.54-2.58 (4 H), 4.98 (1 H), 5.03 (1 H), 5.09 (2 H), 5.70-5.79 (1 H), 6.86 (1 H), 7.07 (1 H), and 7.42 (1 H).

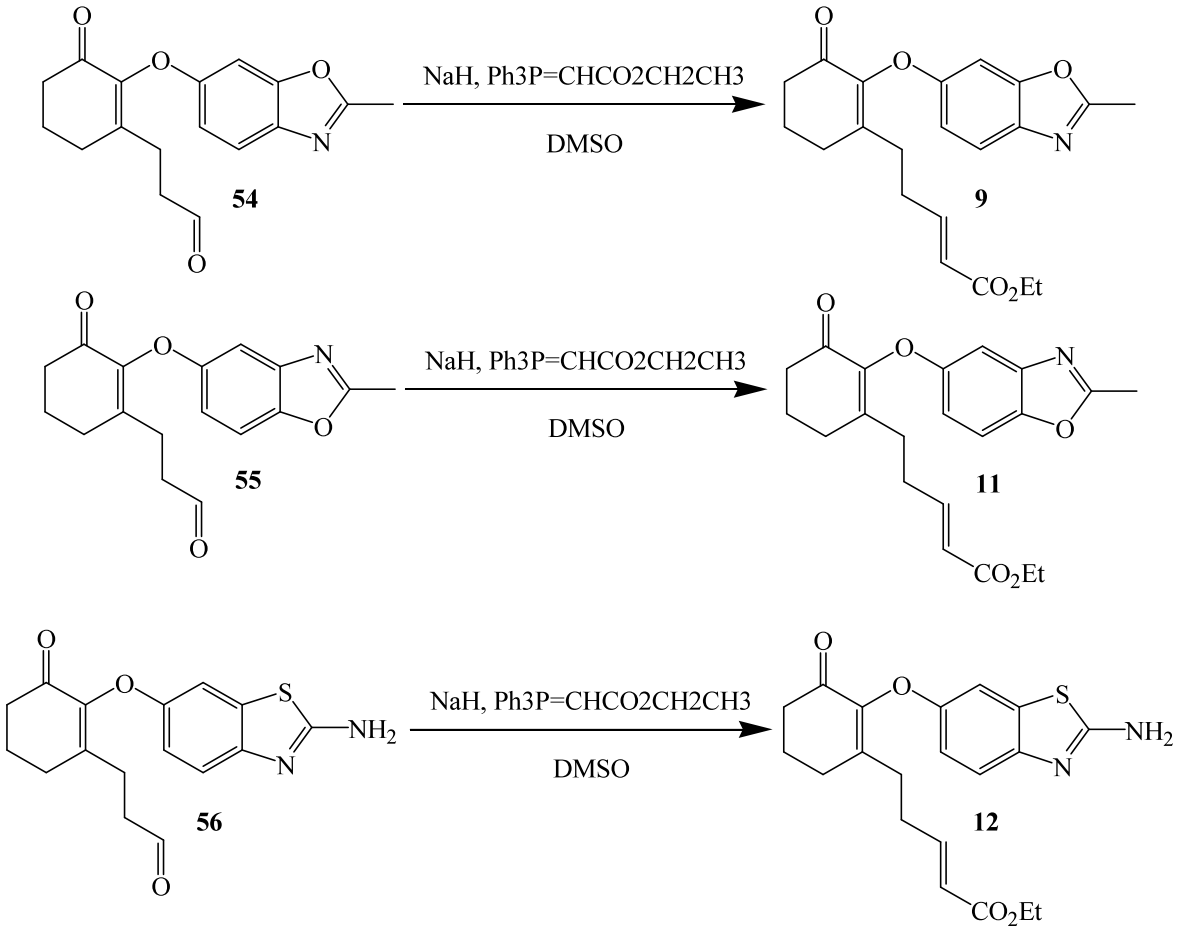
The next step in the synthesis is to oxidize the simple alkene side-chain to an aldehyde via ozonolysis followed by a reductive workup using dimethylsulfide[7]. Compounds **38** and **52** may be converted to compounds **54** and **55** through simple ozonolysis at -78 °C.



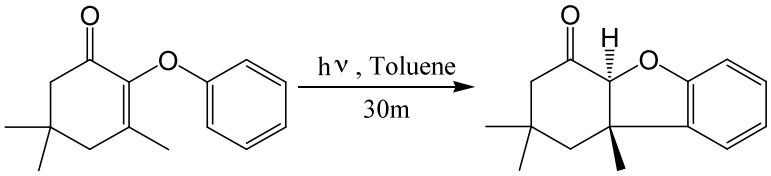
Compound **53** may be converted to compound **56** through ozonolysis; however, the primary amine group on **53** must first be protected as the amine salt using perchloric acid[8].



Following the formation of aldehydes **54**, **55**, and **56**, Wittig addition may provide a convenient path to photolysis precursors, **9, 11,** and **12** respectively.

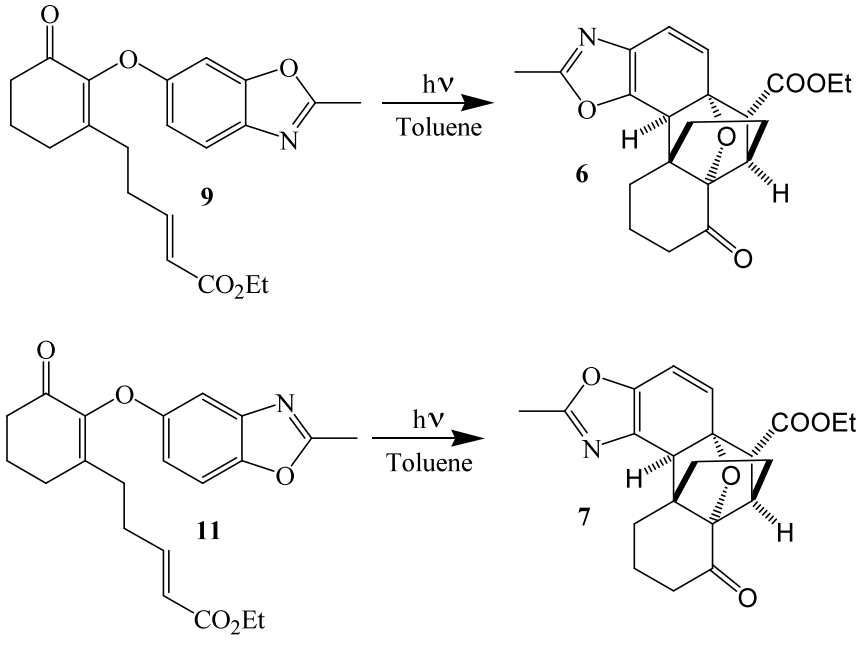


Before attempting photocyclization of our precursors, and in order to gain experience, aryl-vinyl ether **57** was dissolved in toluene and irradiated for thirty minutes. ^{1}H-NMR shows that the compound formed from the photoreaction was the *trans*-product, **58**.

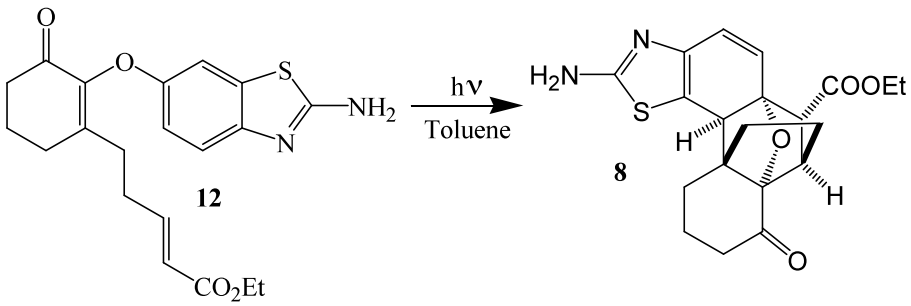


57 **58**

The photo precursors synthesized in our lab will be irradiated in toluene according to conditions used previously and are expected to undergo photocyclization followed by an intramolecular [3+2] cycloaddition to form products **6**, **7** and **8**.



9 **6** **11** **7**



In conclusion, aryl-vinyl ether systems **38**, **52**, and **53** were successfully synthesized. Future work will entail conversion of these substrates to photoprecursors **9**, **11**, and **12**, which will be employed to construct multi-cyclic scaffolds via photochemical methods developed in our laboratory to provide **6**, **7**, and **8**.

Experimental

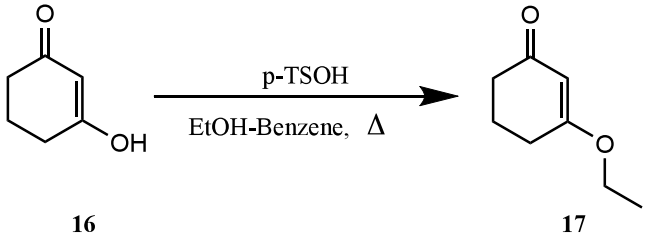
General Methods

^{1}H NMR spectra were recorded on a Bruker 400 (400 MHz) NMR Spectrometer or a Bruker 500 (500 MHz) NMR Spectrometer. Chemical shifts (δ) are reported in ppm relative to tetramethylsilane (TMS) at 0.00. ^{13}C NMR spectra were recorded at 100.61 MHz.

Infrared spectra (IR) were recorded on a Bruker Vertex 70 Infrared Spectrometer with a 4 cm^{-1} resolution, scanning from 4000 to 650 cm^{-1} over 4 scans.

Analytical thin-layer chromatography were done on precoated silica gel plates (0.25 mm thickness) with a 254 nm fluorescent indicator and were visualized under a UV lamp and/or by staining with either iodine or a *p*-anisaldehyde stain.

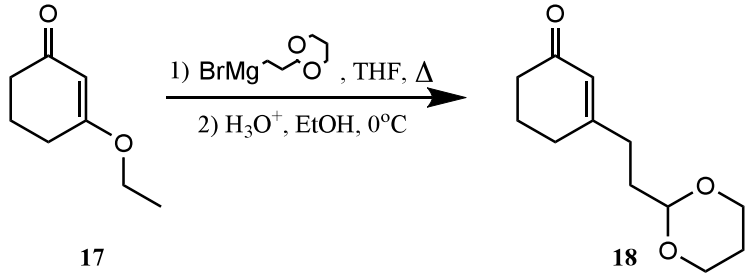
3-ethoxy-2-cyclohexenone (17)



16 **17**

To a 500-mL two-neck flask equipped with a reflux condenser and Dean Stark trap was added 3-hydroxycyclohex-2-enone **16** (10.3 g, 91.6 mmol), ethanol (50 mL), benzene (175 mL) and *p*-toluene sulfonic acid monohydrate (441 mg, 2.3 mmol). The resulting solution was stirred at room temperature for 4 h. The resulting clear, amber solution was heated at reflux temperature for 2 h after which it was allowed to cool to room temperature. Solvent was removed under reduced pressure and the resulting oil was dissolved in ethyl acetate, washed with a sodium hydroxide solution (10% aqueous saturated with sodium chloride), followed by water until neutral and then washed with brine. The organic layer was collected, dried (Na_2SO_4) and the solvent was removed under reduced pressure to yield **17** as an amber colored oil (8.66 g, 67.5%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (t, 3 H), 1.89-2.42 (m, 6 H), 3.91 (q, 2 H), 5.37 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ14.5, 21.6, 29.5, 37.1, 64.6, 103.1, 178.4, 200.4.

3-(2-(1,3-dioxan-2-yl)ethyl)cyclohex-2-enone (18)

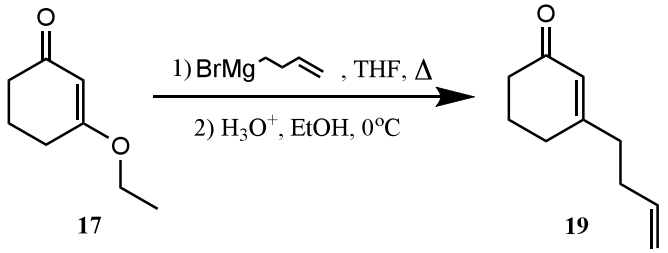


17 **18**

Magnesium turnings (2.31 g, 95.2 mmol) were added to a dry 250-mL three-neck flask under nitrogen. Anhydrous tetrahydrofuran (THF, 10 mL) followed by 2-(2-bromoethyl)-1,3-dioxane (9.26 mL, 13.3 g, 68.3 mmol) was added along with additional THF (40 mL). The reaction mixture was allowed to reflux under exothermic heat for 10 min and the resulting mixture was refluxed with heating for an additional 30 min. The reaction mixture was cooled to 0 ^{o}C and a solution of **17** (8.25 g, 58.8 mmol) in THF (40ml) was added dropwise over 30 min. The resulting solution was allowed to stir at room temperature over the weekend and was neutralized with saturated aqueous ammonium chloride, and the solvent removed under reduced pressure. The resulting oil was dissolved in ethyl acetate, washed with water and brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to yield an amber oil, which was diluted in ethanol, cooled to 0 °C, and slowly treated with aqueous hydrochloric acid (3.7%, 13.3 mL). The resulting solution was allowed to warm to room temperature and stirred for 4 h. The resulting solution was neutralized with saturated aqueous sodium bicarbonate and concentrated under reduced pressure. The resulting oil was diluted with ethyl acetate and washed with water, brine, and dried (Na_2SO_4). Removal of solvent under reduced pressure yielded **18** as an amber oil

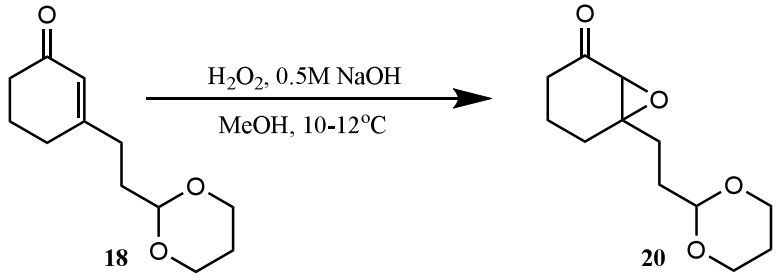
(9.31 g, 75.3%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.17-1.39 (m, 2 H), 1.72-2.41 (m, 10 H), 3.68-3.80 (m, 2 H), 4.02-4.15 (m, 2 H), 4.45-4.53 (m, 1 H), 5.80-5.88 (m, 1 H).

3-(but-3-enyl)cyclohex-2-enone (19)



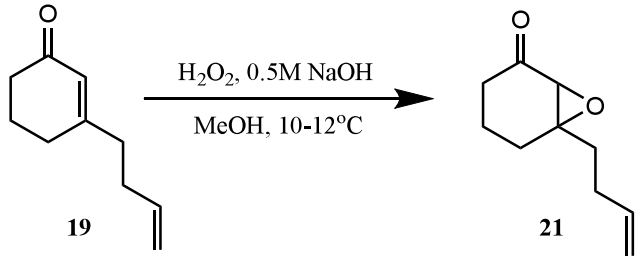
To a mixture of magnesium turnings (0.28 g, 12 mmol) in dry THF (2 mL) under nitrogen was added 4-bromo-1-butene (0.85 mL, 8.3 mmol) in THF (4 mL). The mixture was maintained at reflux temperature for 45 min, after which it was cooled to 0 °C and compound **17** (0.96 mL, 7.12 mmol) in THF (5 mL) was added. The solution was stirred at room temperature for 22 h and then was filtered. To the filtrate was added saturated aqueous ammonium chloride (5 mL) and the solvent was removed under reduced pressure. The crude product was taken up in ethyl acetate, washed with water, brine, and dried (Na_2SO_4) and the solvent was removed under reduced pressure. The resulting oil was taken up in ethanol and cooled to 0 °C. Aqueous hydrochloric acid (3.7%, 1.7 mL) was added dropwise and the mixture was stirred at 0 °C for 3 h, allowed to warm to room temperature, neutralized with saturated aqueous sodium bicarbonate and concentrated under reduced pressure. Product was extracted from the resulting liquid with ethyl acetate and the organic layer was washed with water, brine and dried (Na_2SO_4). Solvent was removed under reduced pressure to yield **19** as a yellow oil (638 mg, 62 %): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.87-2.45 (m, 10 H), 4.87-5.10 (m, 2 H), 5.68-5.90 (m, 2 H).

6-(2-(1,3-dioxan-2-yl)ethyl)-7-oxabicyclo[4.1.0]heptan-2-one (20)



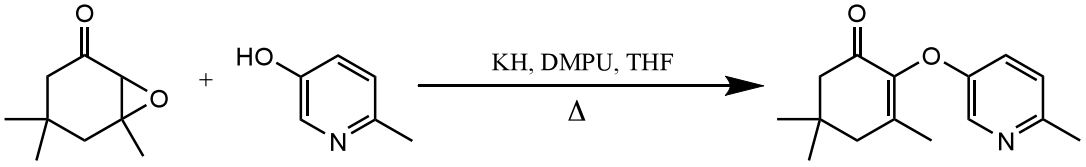
To a 500-mL flask containing methanol (147 mL) at 10 ^{o}C was added **18** (9.28 g, 44.1 mmol) and hydrogen peroxide (35%, 9.9 mL, 115 mmol). Aqueous sodium hydroxide (0.5 M, 98 mL) was added over 75 min and the temperature was maintained at 10-12 ^{o}C. The resulting solution was allowed to stir an additional 50 min at 10-12 ^{o}C, after which it was extracted with dichloromethane. The combined organic layers were washed with brine and dried (Na_2SO_4). Solvent was removed under reduced pressure to yield **20** as a yellow colored oil (5.38 g, 53.9%): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.18-1.38 (m, 2 H), 1.75-2.38 (m, 10 H), 3.12 (s, 1 H), 3.68-3.80 (m, 2 H), 4.03-4.16 (m, 2 H), 4.45-4.52 (m, 1 H).

6-(but-3-enyl)-7-oxabicyclo[4.1.0]heptan-2-one (21)



A solution of **19** (638 mg, 4.3 mmol) in methanol was cooled to 10 °C and hydrogen peroxide (35%, 0.98 mL, 11 mmol) was added dropwise. Aqueous sodium hydroxide (0.5 M, 10 mL) was added over 16 min via addition funnel and stirring was continued for 1 h at 10-12 °C. The reaction mixture was extracted with dichloromethane and the combined organic layers were washed with brine and dried (Na_2SO_4). Solvent was removed under reduced pressure to yield **21** as an oil (540 mg, 74 %): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45-2.57 (m, 10 H), 3.11 (s, 1 H), 4.89-5.10 (m, 2 H), 5.69-5.92 (m, 1 H).

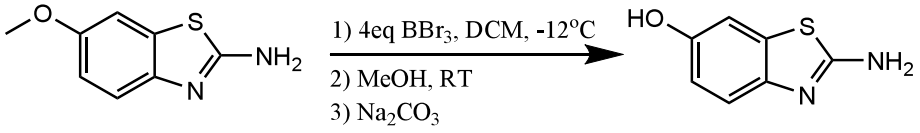
3,5,5-trimethyl-2-(6-methylpyridin-3-yloxy)cyclohex-2-enone (51)



47 **50** **51**

To a solution of 3-hydroxy-6-methylpyridine **50** (600 mg, 5.5 mmol) in anhydrous THF (10 mL) was added potassium hydride (30% by weight in mineral oil, 6 drops). The resulting mixture was stirred for 10 min after which isophorone oxide **47** (0.78 mL, 5.0 mmol) was added followed by 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU, 0.66 mL, 5.5 mmol). The resulting solution was stirred at reflux temperature for 25 h. The resulting mixture was cooled to room temperature and partitioned between ethyl acetate and water. The organic phase was washed with water, brine, dried (Na_2SO_4), and the solvent was removed under reduced pressure. The resulting oil was dissolved in hexane, filtered, and washed with sodium hydroxide (1 N), water, and brine. The organic layer was collected, dried (Na_2SO_4). The solvent was removed under reduced pressure to yield **51** as an amber colored oil (0.58 g, 47.4%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (s, 6 H), 1.63 (s, 3 H), 2.14 (s, 2 H), 2.18 (s, 2 H), 2.25 (s, 3 H), 6.86 (m, 2 H), 7.88 (m, 1 H).

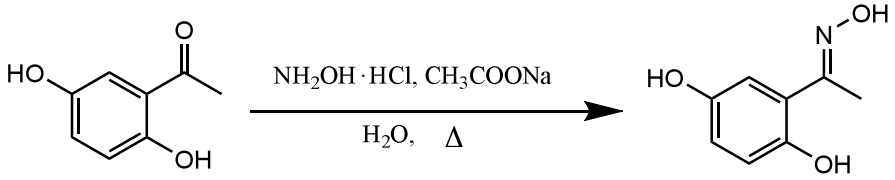
2-aminobenzo[*d*]thiazol-6-ol (37)



46 **37**

To a 100-mL round-bottom flask was added compound **46** (1.002 g, 5.56 mmol) in anhydrous dichloromethane (5.6 mL). The resulting solution was stirred at -12 ^{o}C. boron tribromide (1.0 M in methylene chloride, ~28 mL, 28 mmol) was added dropwise under nitrogen and the resulting reaction mixture was stirred at -9 to -12 ^{o}C for 3 h, at which point, starting material was no longer visible by thin layer chromatography (TLC) analysis (Hexanes : Ethyl Acetate (50:50)). Methanol (2.8 mL, 69.1 mmol) was slowly added, resulting in formation of a white gas. A light colored solid slowly formed and the flask was allowed to warm to room temperature with stirring. After 2.5 h, the solid was collected, dissolved in water and washed with ethyl acetate. The aqueous layer was collected and neutralized with saturated aqueous sodium bicarbonate. Evolution of gas was observed with concomitant formation of light grey solid. The mixture was filtered to yield **37** as a light grey solid (0.6454 g, 69.8%): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.42 – 2.48 (m, 2 H), 6.64 – 6.66 (m, 1 H), 7.02 – 7.22 (m, 2 H), 9.17 (s, 1 H).

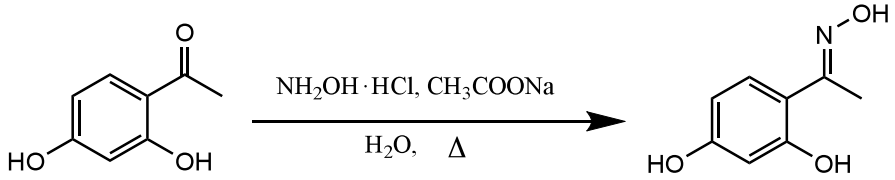
(*E*)-1-(2,5-dihydroxyphenyl)ethanone oxime (45)



44 **45**

To a mixture of hydroxylamine hydrochloride (5.14 g, 73.9 mmol) and sodium acetate (10.2 g, 125 mmol) in water (15 mL) was added a solution of 2',5'-dihydroxyacetophenone **44** (3.00 g, 19.7 mmol) in water (15 mL). The mixture was heated at reflux temperature for 2 h, and the crude mixture was extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried (Na_2SO_4). The solvent was removed under reduced pressure to yield **45** as a brown solid (3.20 g, 97%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.19 (s, 3 H), 6.68 (d, 2 H), 6.83 (s, 1 H), 8.96 (s, 1 H), 10.86 (dd, 1 H), 11.53 (d, 1 H).

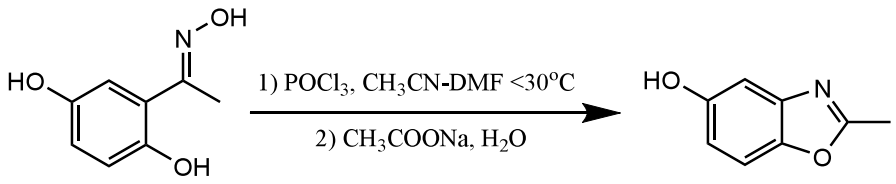
(*E*)-1-(2,4-dihydroxyphenyl)ethanone oxime (43)



42 **43**

To a solution of hydroxylamine hydrochloride (4.61 g, 66 mmol) and sodium acetate (9.18 g, 112 mmol) in water (15 mL) was added 2',4'-dihydroxyacetophenone **42** (3.00 g, 20 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 **43** as a light orange solid (3.10 g, 94%): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.19 (s, 3 H), 6.24 (t, J=2.78 Hz, 1 H), 6.31 (m, 1 H), 7.28 (m, 1 H), 9.82 (broad s, 1 H), 11.26 (broad s, 1 H), 11.78 (s, 1 H).

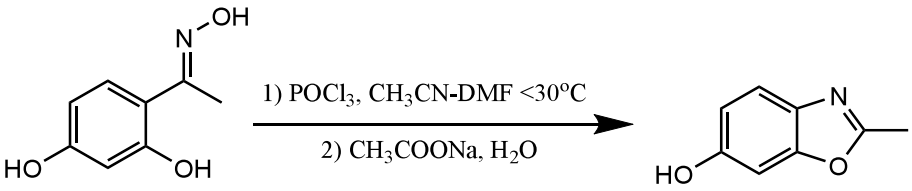
2-methylbenzo[*d*]oxazol-5-ol (36)



45 **36**

A solution of oxime **45** (1.50 g, 9 mmol) in dry acetonitrile (1.8 mL) and dry dimethylformide (5.4 mL) was treated with phosphorous oxychloride (0.85 mL, 9.1 mmol) over a period of 3 min. During the addition, the temperature was maintained below 30 °C. The resulting mixture was stirred at room temperature for 60 min. Aqueous sodium acetate (1.75 M, 15 mL) 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 **36** as a tan solid (1.14 g, 85 %): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.53 (s, 3 H), 6.65 – 6.75 (m, 1 H), 6.82 – 6.84 (m, 1 H), 7.43 – 7.42 (m, 1 H), 9.48 (s, 1 H).

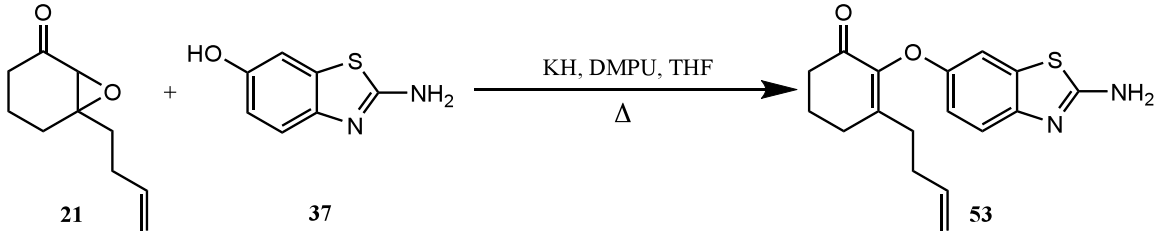
2-methylbenzo[*d*]oxazol-6-ol (35)



43 **35**

A solution of oxime **43** (1.50 g, 9 mmol) in dry acetonitrile (1.8 mL) and dry dimethylformide (5.4 mL) was treated with phosphorous oxychloride (0.84 mL, 9 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 (1.32 M, 20 mL) 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 (2.07 g) and recrystallization from acetonitrile yielded **35** as a light brown solid (.582 g, 43%): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.57 (s, 3 H), 6.75 (m, 1 H), 6.97 (m, 1 H), 7.37 (m, 1 H), 9.67 (s, 1 H).

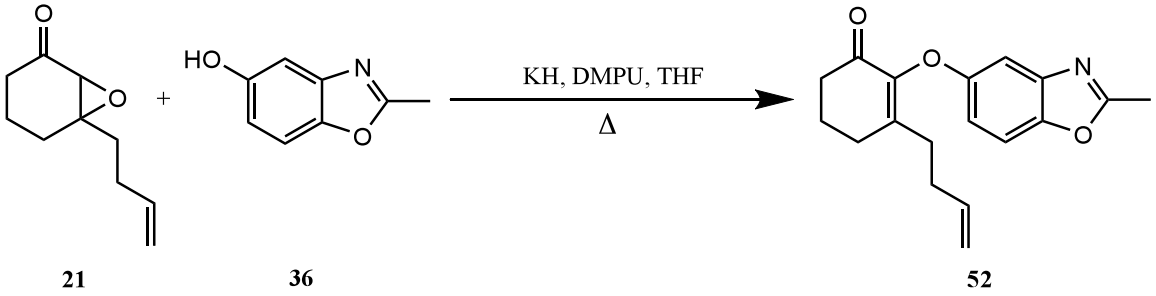
2-(2-aminobenzo[*d*]thiazol-6-yloxy)-3-(but-3-enyl)cyclohex-2-enone (53)



21 37 53

To a solution of phenol **37** (0.2205 g, 1.33 mmol) in dry THF (2.4 mL) at 0 ^{o}C was added potassium hydride (30% by weight in mineral oil, 2 drops), resulting in a green cloudy reaction mixture. Compound **21** (0.20 mL, 1.20 mmol) and DMPU (0.16 mL, 1.32 mmol) were added and the mixture was stirred for 10 min at 0 ^{o}C. The reaction mixture was heated at reflux temperature for 63 h. The resulting dark brown reaction mixture was cooled to room temperature, after which the solvent was removed under reduced pressure. The resulting dark oil was dissolved in ethyl acetate, washed with water, brine, and dried (Na_2SO_4). Solvent was removed under reduced pressure to yield a viscous brown oil (0.5709 g), which was dissolved in chloroform and filtered (solid 0.0590 g). The brown filtrate was concentrated under reduced pressure to yield a brown-orange residue (0.4259 g). Purification by column chromatography over silica gel (methylene chloride : methanol (98:2)) provided **53** as a brown solid (0.161 g, 44.7%): IR (film) 3382, 3107, 2954, 1676, 1633 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.06-2.12 (m, 2 H), 2.22-2.28 (m, 2 H), 2.42 (t, 2 H), 2.54-2.58 (m, 4 H), 4.98 (dq, 1 H), 5.03 (dq, 1 H), 5.09 (broad s, 2 H), 5.70-5.79 (m, 1 H), 6.86 (dd, 1 H), 7.07 (d, 1 H), 7.42 (d, 1 H).

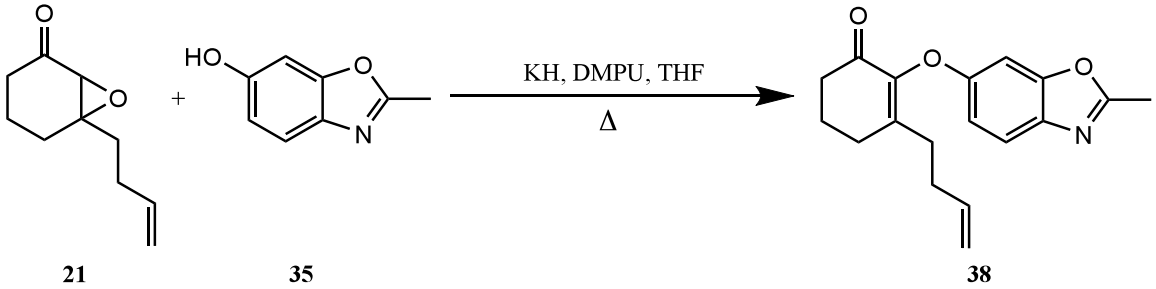
3-(but-3-enyl)-2-(2-methylbenzo[*d*]oxazol-5-yloxy)cyclohex-2-enone (52)



21 **36** **52**

A solution of alcohol **36** (155.6 mg, 1.05 mmol), dry tetrahydrofuran (1.5 mL) and potassium hydride (35% in mineral oil, 222 mg, 0.14 mmol) was stirred at ice-bath temperature under a nitrogen environment while a solution of epoxide **21** (156.0 mg, 0.95 mmol) in dry THF (0.4 mL) was added over 2 min. The mixture was heated at reflux temperature for 24 h after which product was extracted with ethyl acetate. The organic phase was washed with water, brine and dried (Na_2SO_4). Removal of solvent yielded **52** as an impure dark brown solid (263.5 mg, 85%): IR (film) 3076, 2927, 1680, 1618 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.54-2.17 (m, 10 H), 2.53 (s, 3 H), 4.88-5.01 (m, 2 H), 5.65-5.78 (m, 1 H), 6.74-6.79 (m, 1 H), 7.04-7.07 (m, 1 H), 7.18-7.25 (m, 1 H).

3-(but-3-enyl)-2-(2-methylbenzo[*d*]oxazol-6-yloxy)cyclohex-2-enone (38)



21 **35** **38**

A solution of alcohol **35** (302.8 mg, 1.82 mmol), dry tetrahydrofuran (THF, 3 mL) and potassium hydride (35% in mineral oil, 11.07 mg, 0.28 mmol) was stirred at ice-bath temperature under a nitrogen environment while a solution of epoxide **21** (304.7 mg, 0.95 mmol) in dry THF (0.6 mL) was added over 2 min. The mixture was heated at reflux temperature for 48 h after which product was extracted with ethyl acetate. The organic phase was washed with water, sodium hydroxide (1 N), brine and dried (Na_2SO_4). Removal of solvent followed by purification by column chromatography over silica gel (methylene chloride : methanol (99:1)) yielded **38** as a viscous yellow liquid (188 mg, 35%): IR (film) 3078, 2945, 2859, 1711, 1613 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.05 – 2.14 (m, 10 H), 2.57 (s, 3 H), 4.99 – 5.04 (m, 2 H), 5.75 – 5.80 (m, 1 H), 6.87 – 6.89 (m, 1 H), 6.93 – 6.95 (m, 1 H), 7.65 – 7.69 (m, 1 H).

References

1. Rida S.M.; Ashour F.A.; El-Hawash S.A.M.; Elsemary M.M.; Badr M.H.; Shalaby M.A. *European J. Med. Chem*. **2005**, *40*, 949.

2. Rana A.; Siddiqui N.; Khan S.A. *Indian J. Pharm. Sci.* **2007**, *169*, 10.

3. Dittami J.P.; Nie X.Y.; Nie H.; Ramanathan H.; Breining S.; Bordner J.; Decosta D.L.; Kiplinger J.; Reiche P.; Ware R. "Intramolecular Addition Reactions of Carbonyl Ylides Formed during Photocyclization of Aryl Vinyl Ethers" *J. Org. Chem*. **1991**, *56*, 5572.

4. Dittami J.P.; Nie X.Y.; Nie H.; Ramanathan H.; Buntel C.; Rigatti S.; Bordner J.; Decosta D.L.; Willard P. "Tandem Photocyclization-Intramolecular Addition Reactions of Aryl Vinyl Sulfides. Observation of a Novel [2+2] Cycloaddition-Allylic Sulfide Rearrangement" *J. Org. Chem.* **1992**, *57*, 1151.

5. Schultz A.G.; Lucci R.D.; Fu W.Y.; Berger M.H.; Erhardt J.; Hagmann W.K. "Heteroatom Directed Photoarylation. Synthetic Potential of the Heteroatom Oxygen" *J. Am. Chem. Soc.* **1978**, *100*, 2150.

6. Gannon, W.F.; House, H.O., *Organic Synthesis Coll.*, **1973**, *5*, 539.

7. Schultz A.G.; Napier J.J.; Ravichandran R. "Synthetic Applications of Heteroatom-Directed Photoarylation. Benzo[b]furan Ring Construction" *J. Org. Chem.* **1983**, *48*, 3408.

8. Schultz A.G.; Lucci R.D.; Napier J.J.; Kinoshita H.; Ravichandran R.; Shannon P.; Yee Y.K. "Studies Directed at a Synthesis of the Morphine Alkaloids. A Photochemical Approach" *J. Org. Chem.* **1985**, *50*, 217.

9. Corma, A.; García, H. Leyva, A. “Comparison between polyethylenlycol and imidazolium ionic liquids as solvents for developing a homogeneous and reusable palladium catalytic system for the Suzuki and Sonogashira coupling” *Tetrahedron*, **2005**, 61, 9848.

10. Fujita, S.; Koyama, K.; Inagaki, Y. “The Beckmann Rearrangement by Means of Phosphoryl Chloride/N,N-Dimethylacetamide; A Novel and Convenient Method for Preparing Benzoxazoles” *Synthesis*, **1982**, 68.

11. Conditions developed by Brian Costa during summer 2007 fellowship work.

12. Jung M.E.; Starkey L.S. "New Preparation of o-Aryloxyphenols via Cyclohexenone Oxides" *Tetrahedron Lett.* **1995**, 7363.

13. Jung M.E.; Starkey L.S. "Total Synthesis of (S,S)-Isodityrosine" *Tetrahedron*, **1997**, *53*, 8815.

Spectra

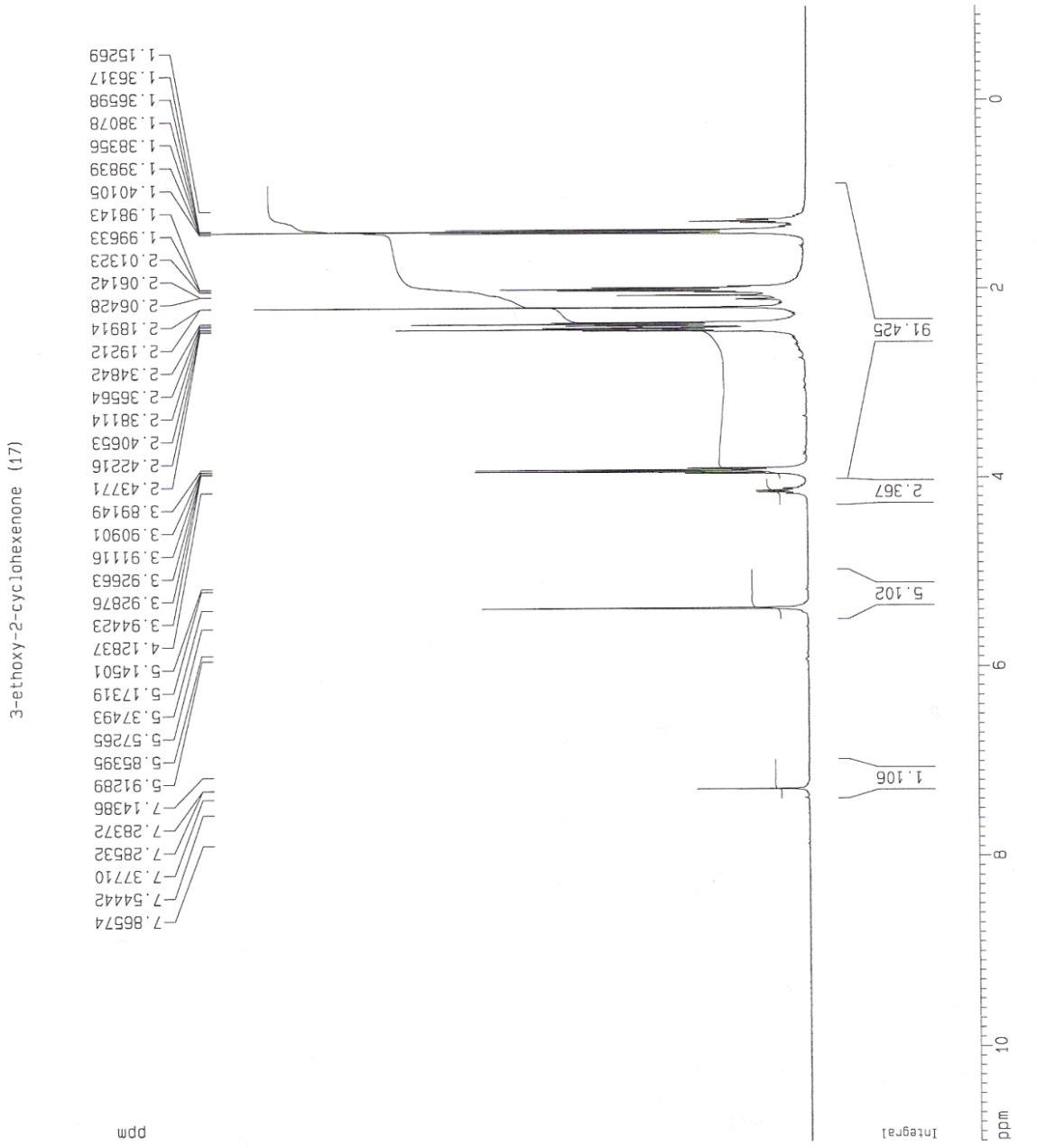


Figure 1 ^{1}H NMR Spectra of 3-ethoxy-2-cyclohexenone (17)

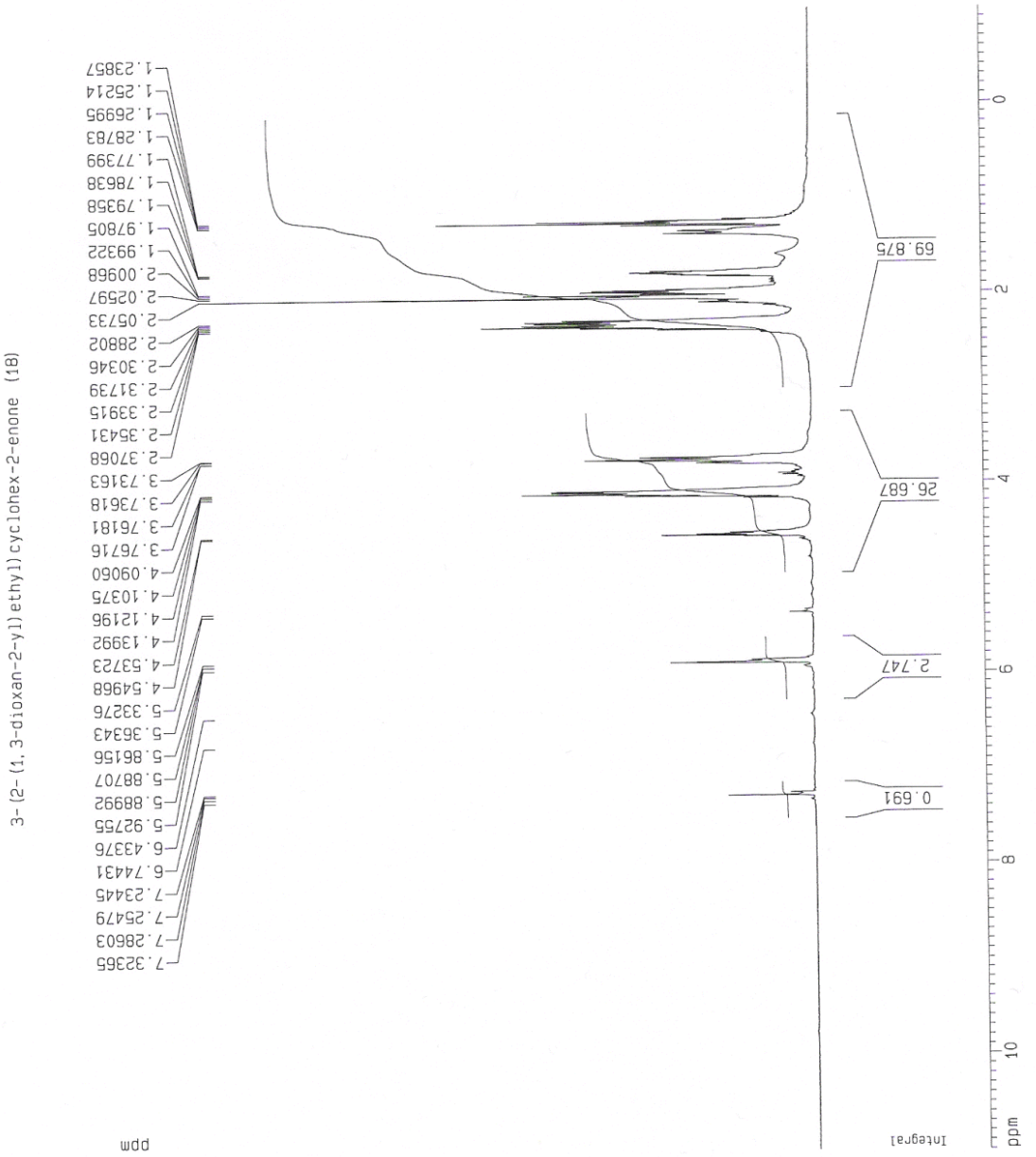


Figure 2 ^{1}H NMR Spectra of 3-(2-(1,3-dioxan-2-yl)ethyl)cyclohex-2-enone (18)

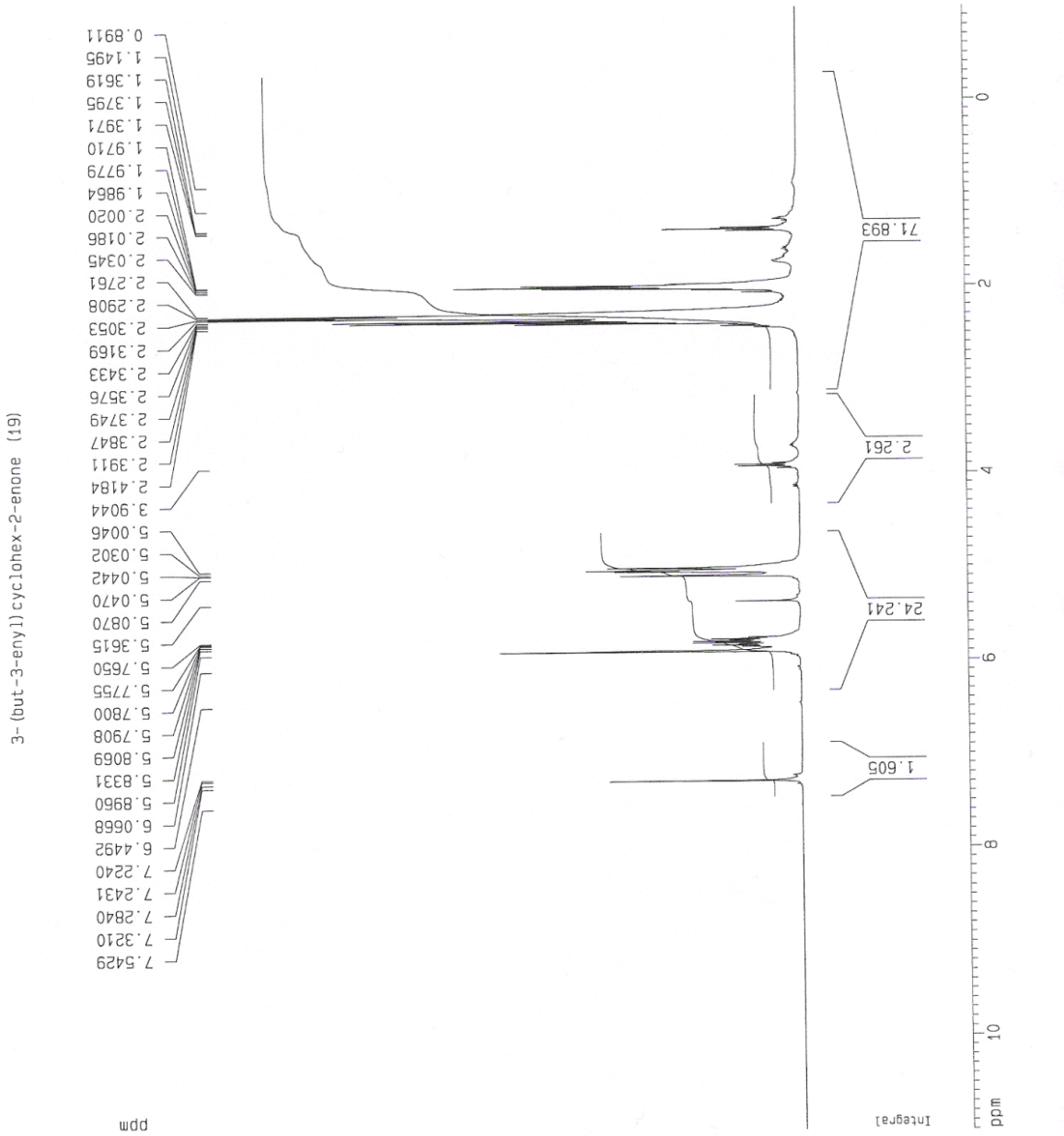


Figure 3 ^{1}H NMR Spectra of 3-(but-3-enyl)cyclohex-2-enone (19)

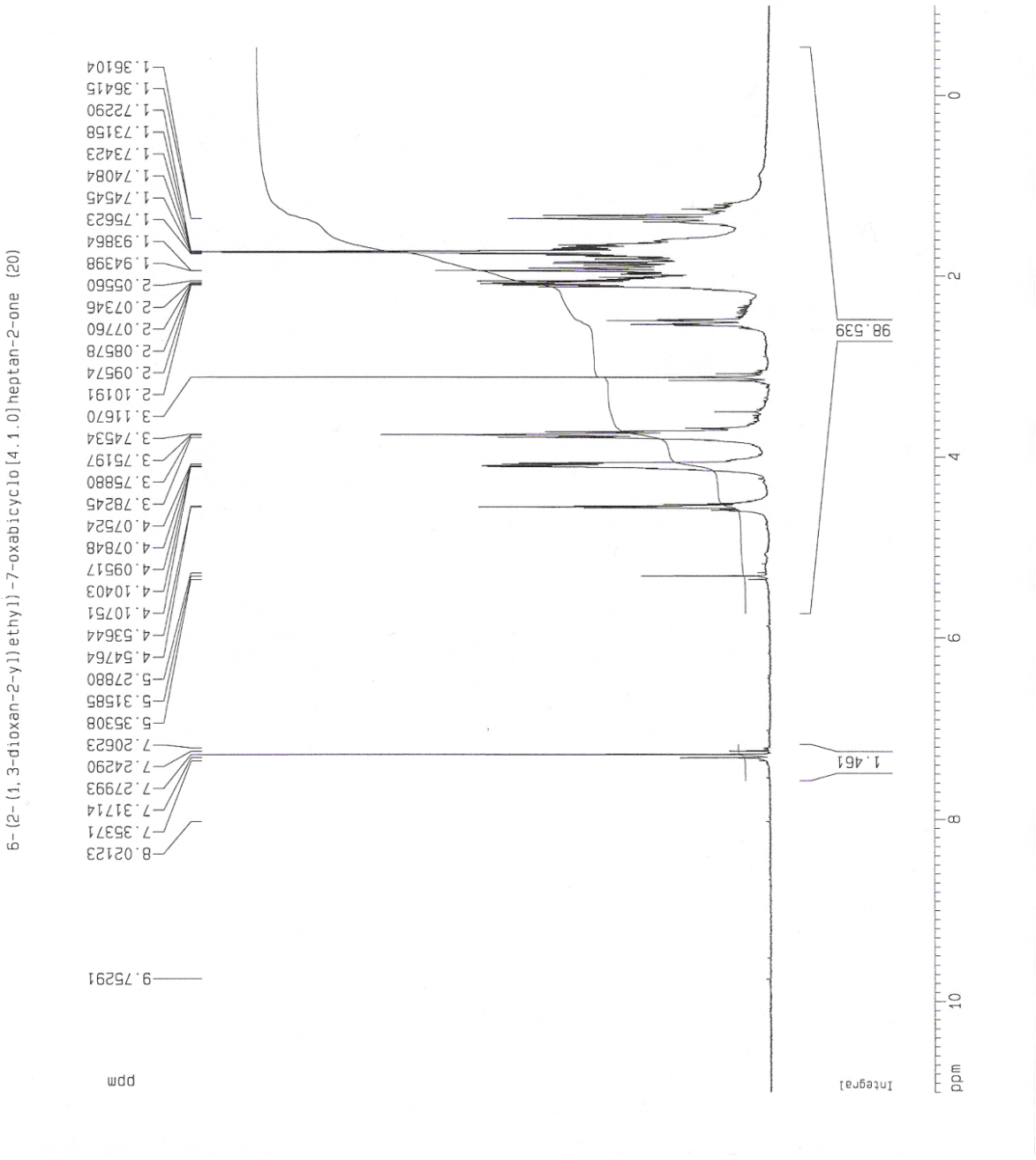


Figure 4 ^{1}H NMR Spectra of 6-(2-(1,3-dioxan-2-yl)ethyl-7-oxabicyclo[4.1.0]heptan-2-one (20)

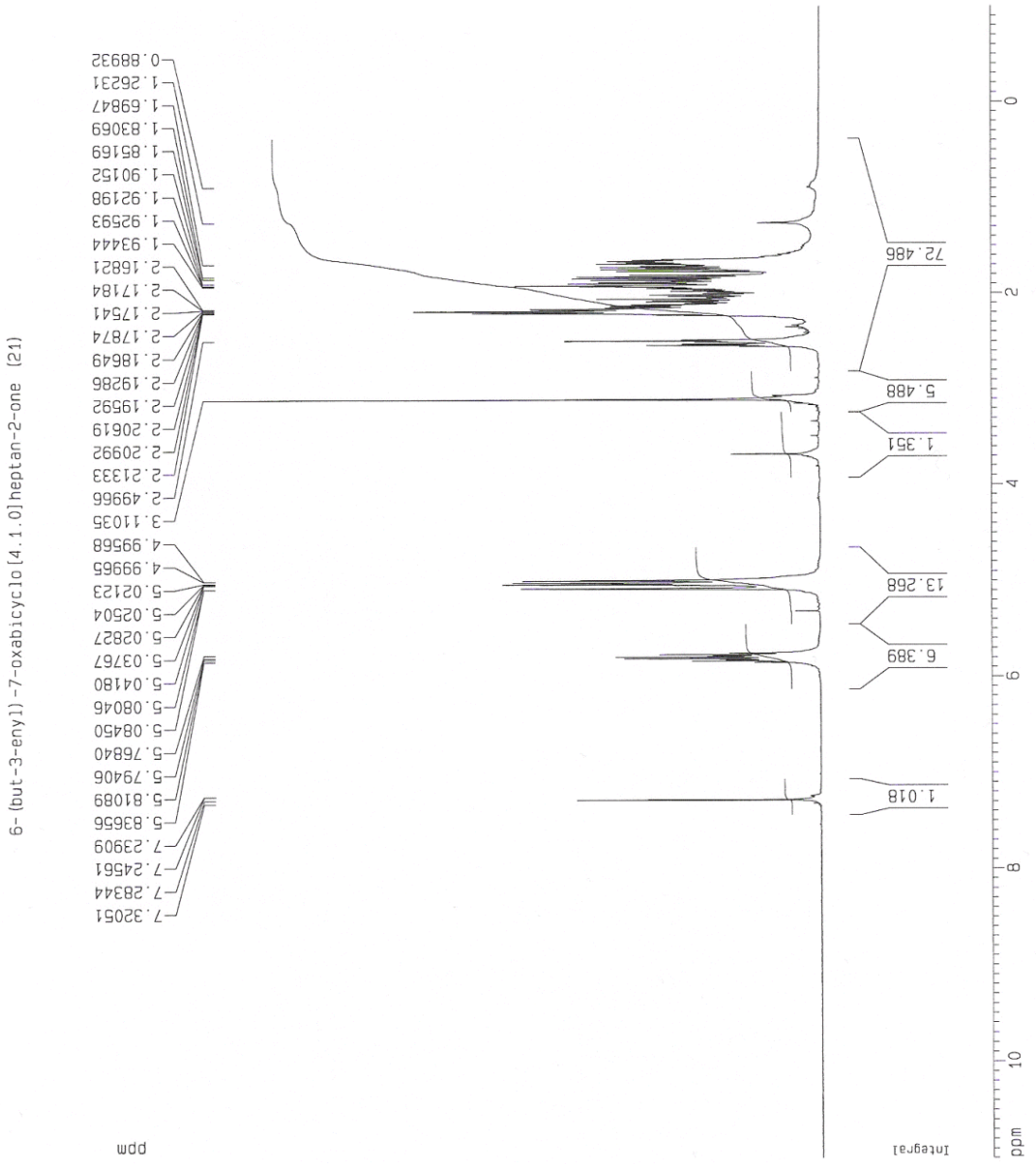


Figure 5 ^{1}H NMR Spectra of 6-(but-3-enyl)-7-oxabicyclo[4.1.0]heptan-2-one (21)

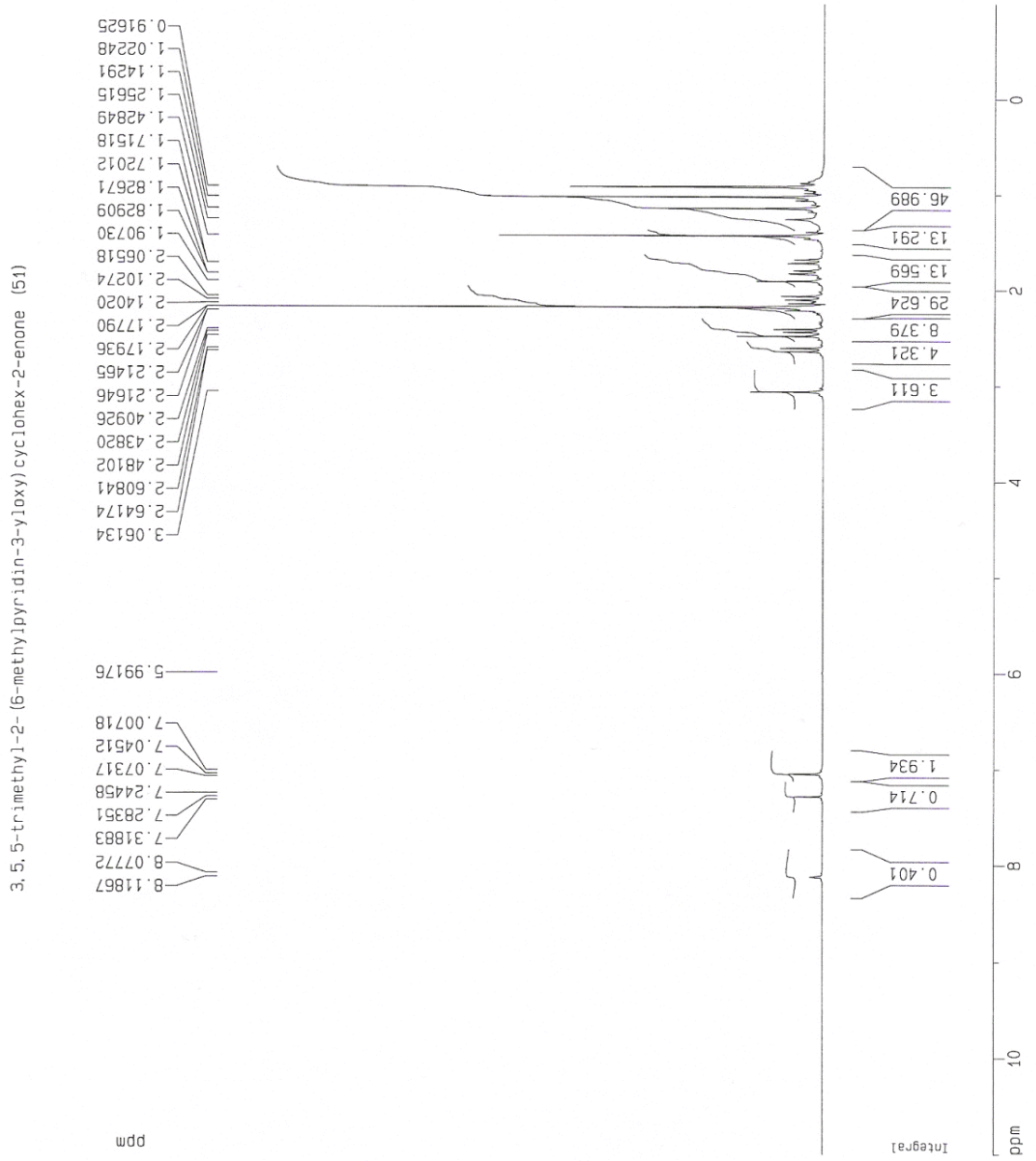


Figure 6 ^{1}H NMR Spectra of 3,5,5-trimethyl-2-(6-methylpyridin-3-yloxy)cyclohex-2-enone (51)

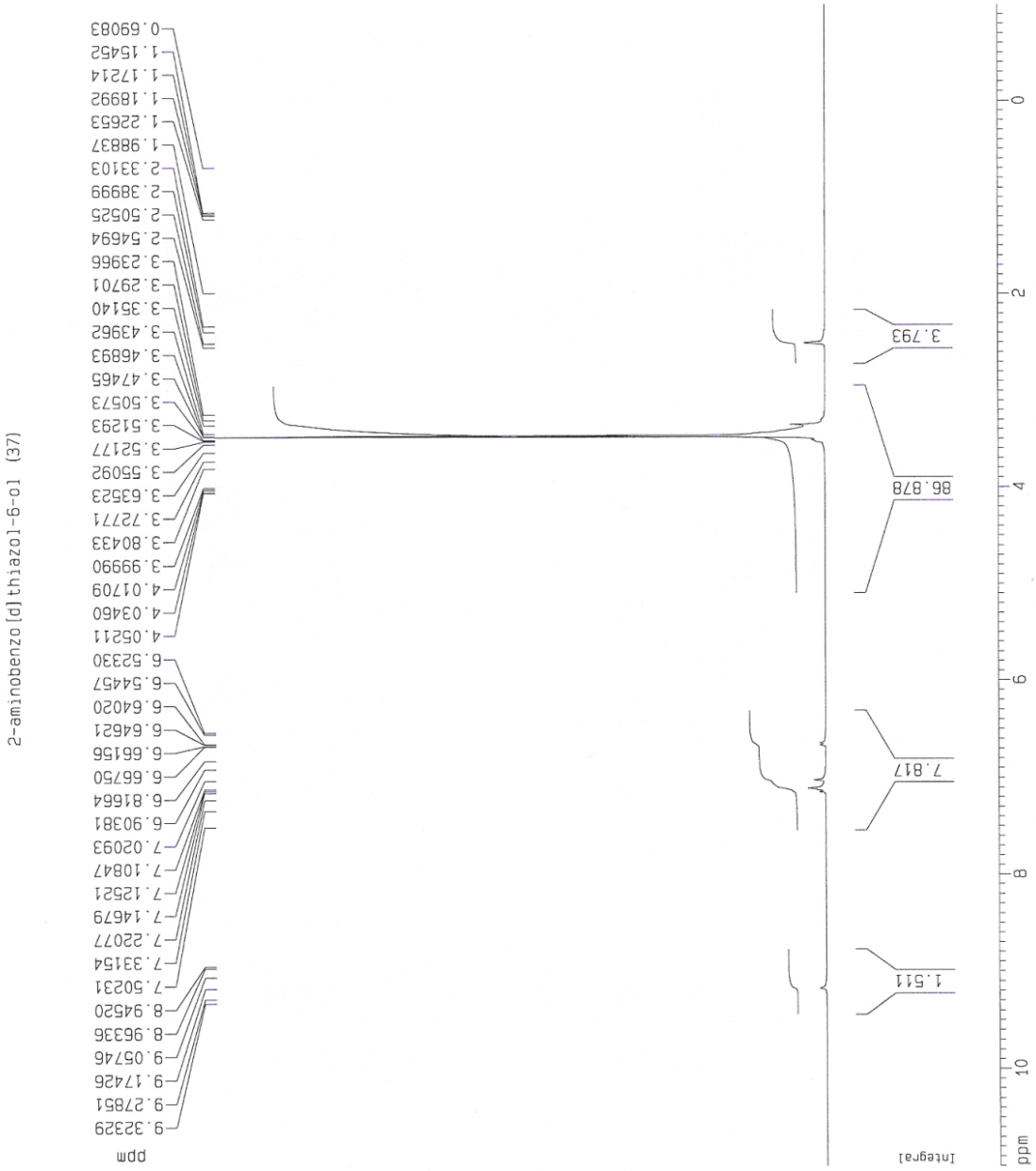


Figure 7 ^{1}H NMR Spectra of 2-aminobenzo[*d*]thiazol-6-ol (37)

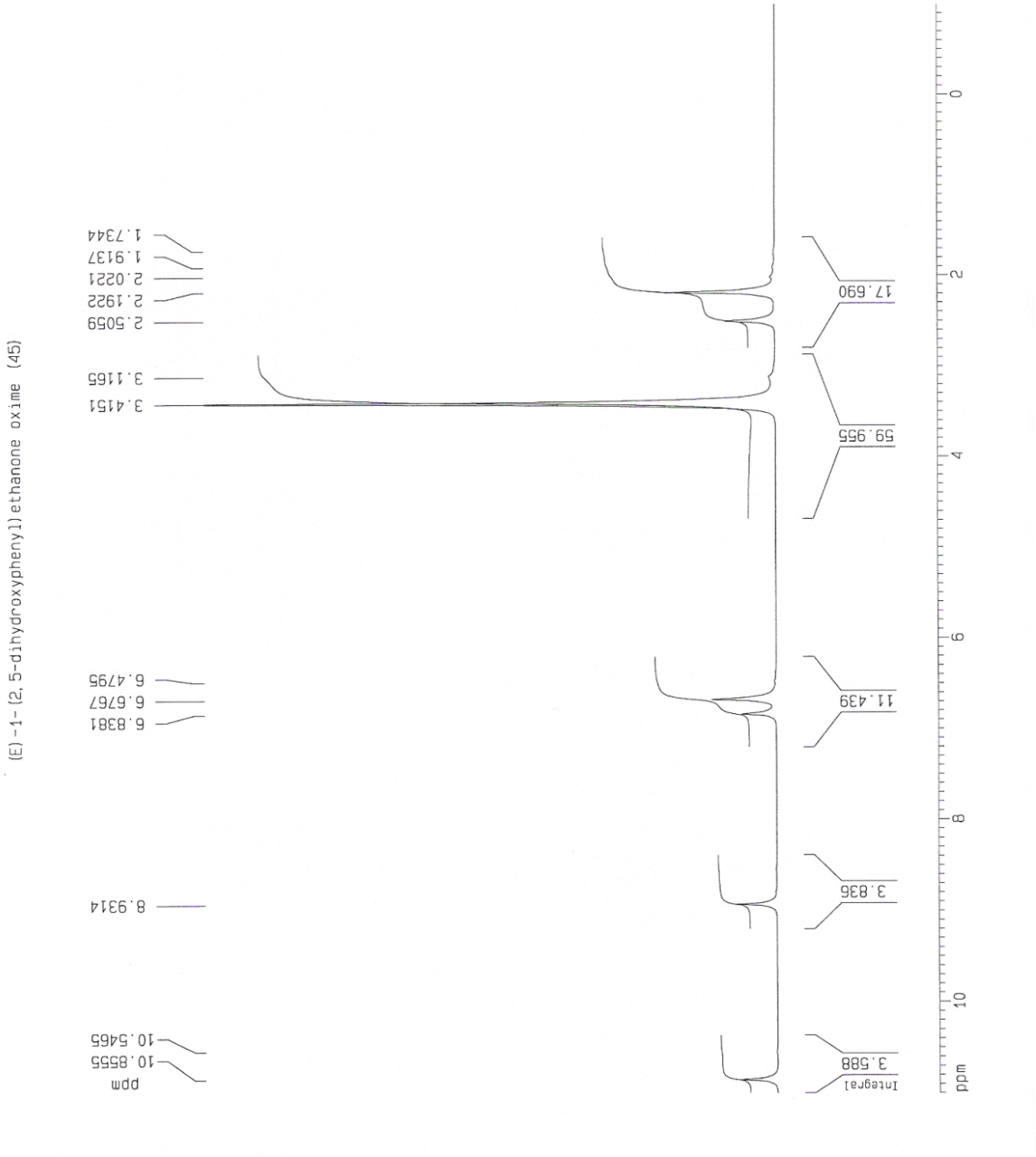


Figure 8 ^{1}H NMR Spectra of (*E*)-1-(2,5-dihydroxyphenyl)ethanone oxime (45) (-1 to 11 ppm)

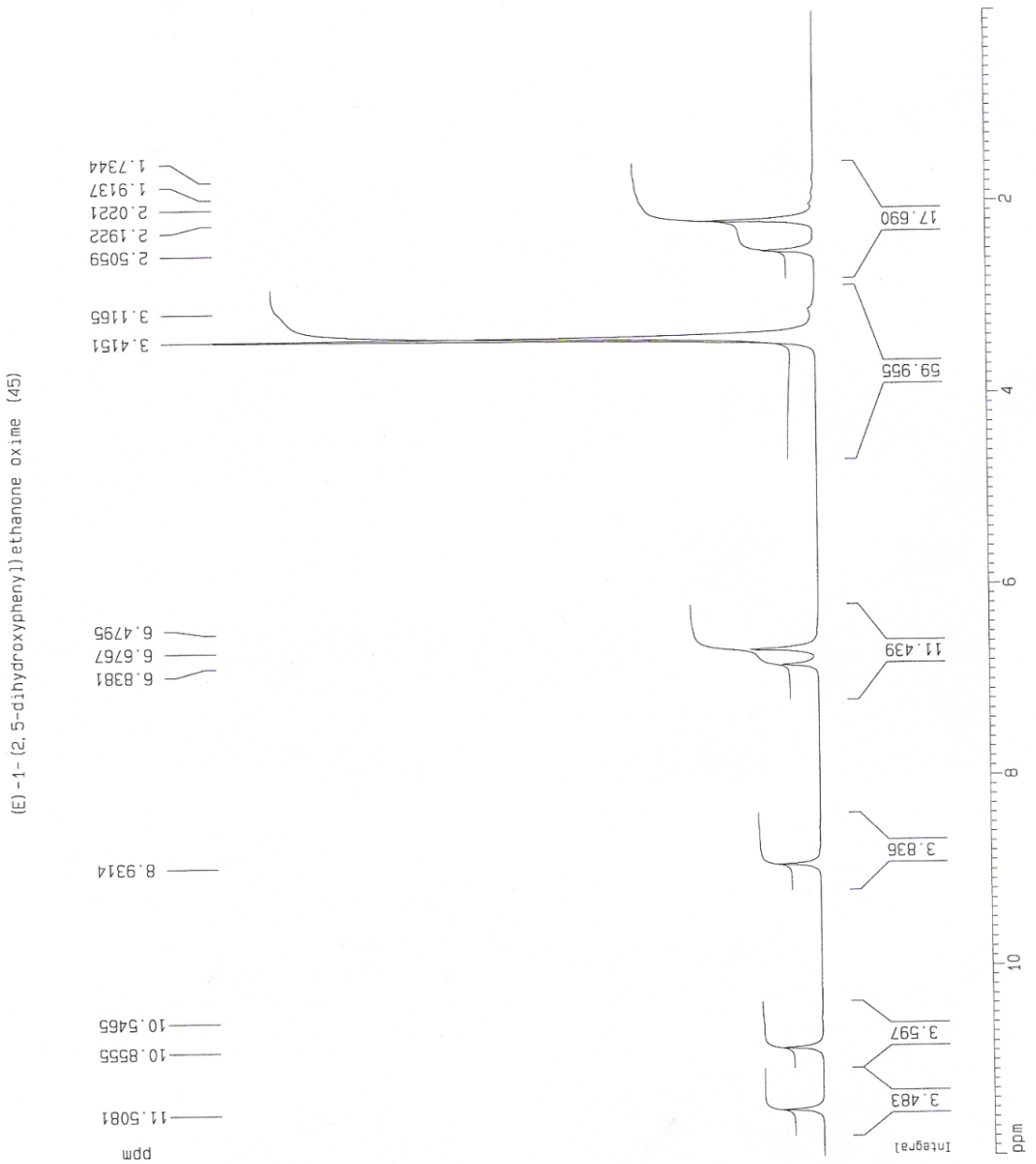


Figure 9 ^{1}H NMR Spectra of (*E*)-1-(2,5-dihydroxyphenyl)ethanone oxime (45) (0 to 12 ppm)

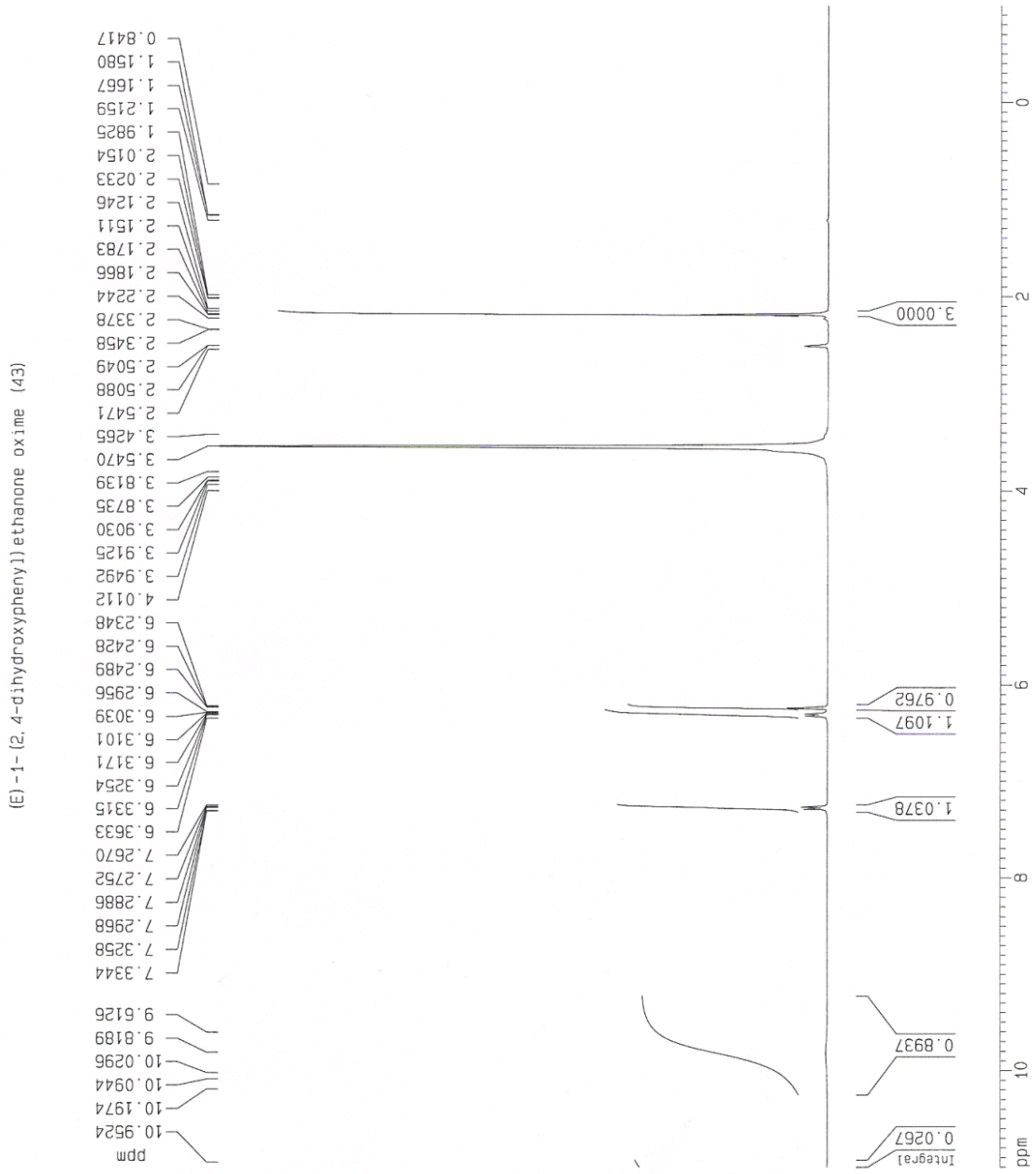


Figure 10 ^{1}H NMR Spectra of (*E*)-1-(2,4-dihydroxyphenyl)ethanone oxime (43) (-1 to 11 ppm)

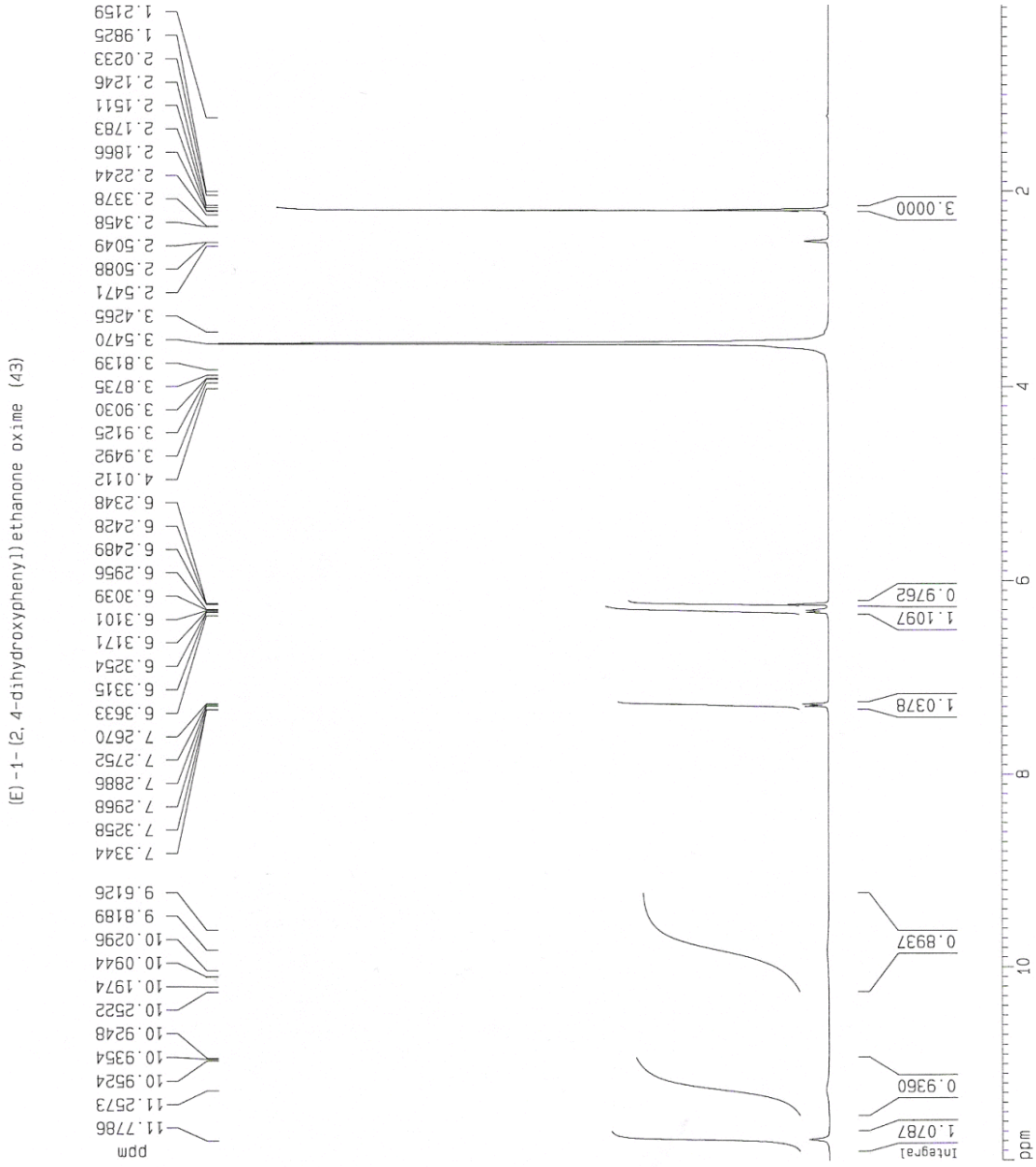


Figure 11 ^{1}H NMR Spectra of (*E*)-1-(2,4-dihydroxyphenyl)ethanone oxime (43) (0 to 12 ppm)

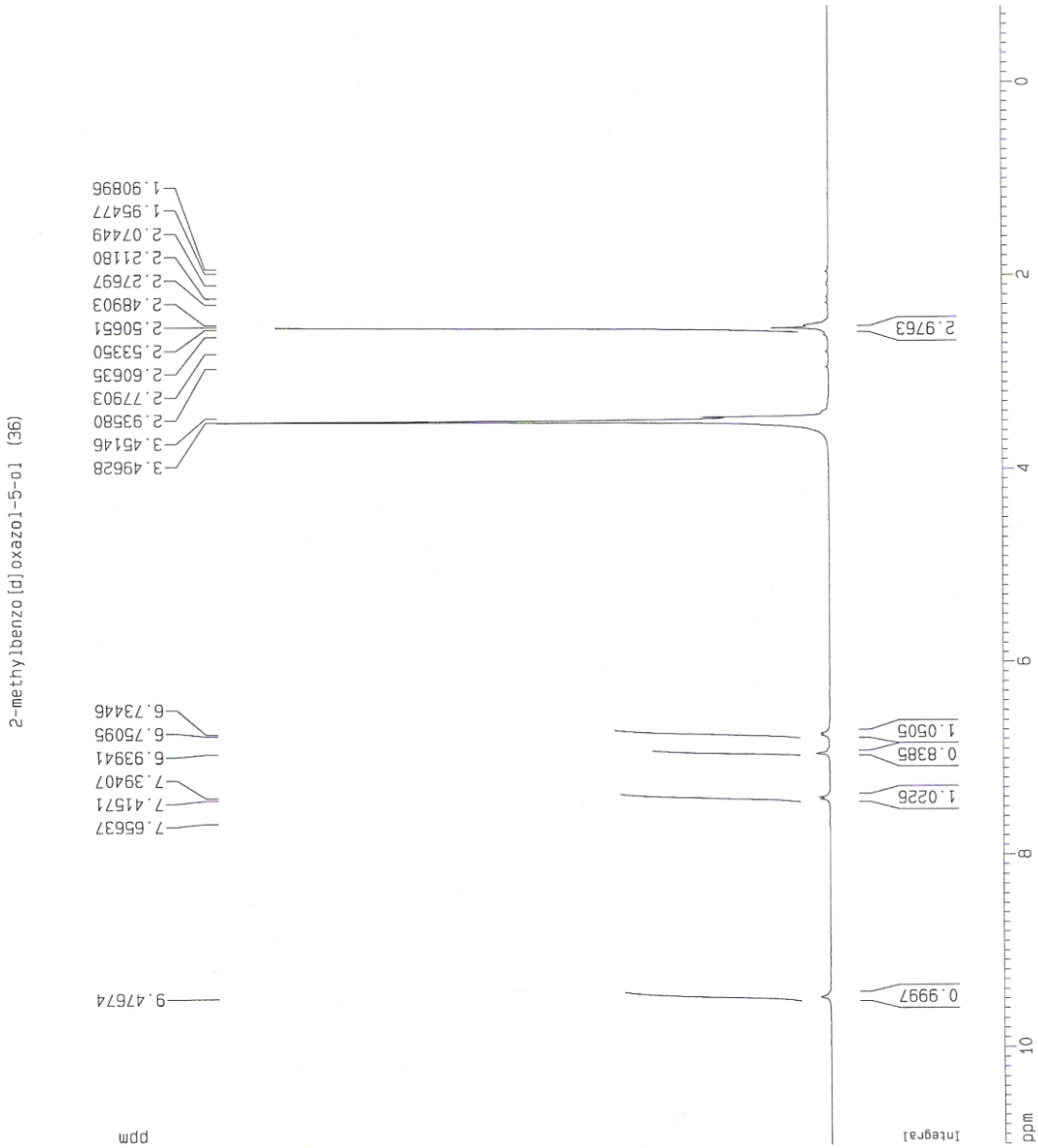


Figure 12 ^{1}H NMR Spectra of 2-methylbenzo[*d*]oxazol-5-ol (36)

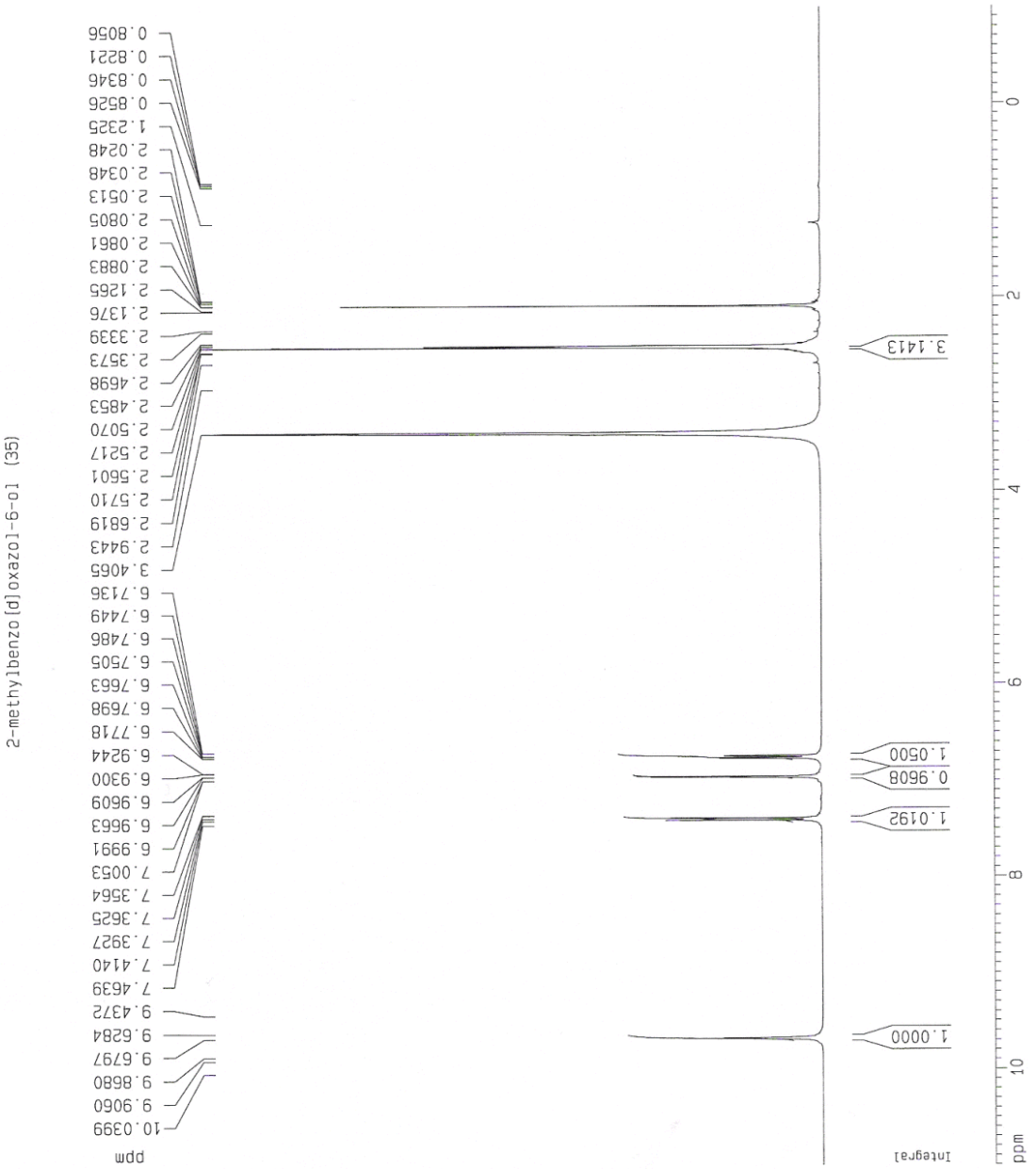


Figure 13 ^{1}H NMR Spectra of 2-methylbenzo[*d*]oxazol-6-ol (35)

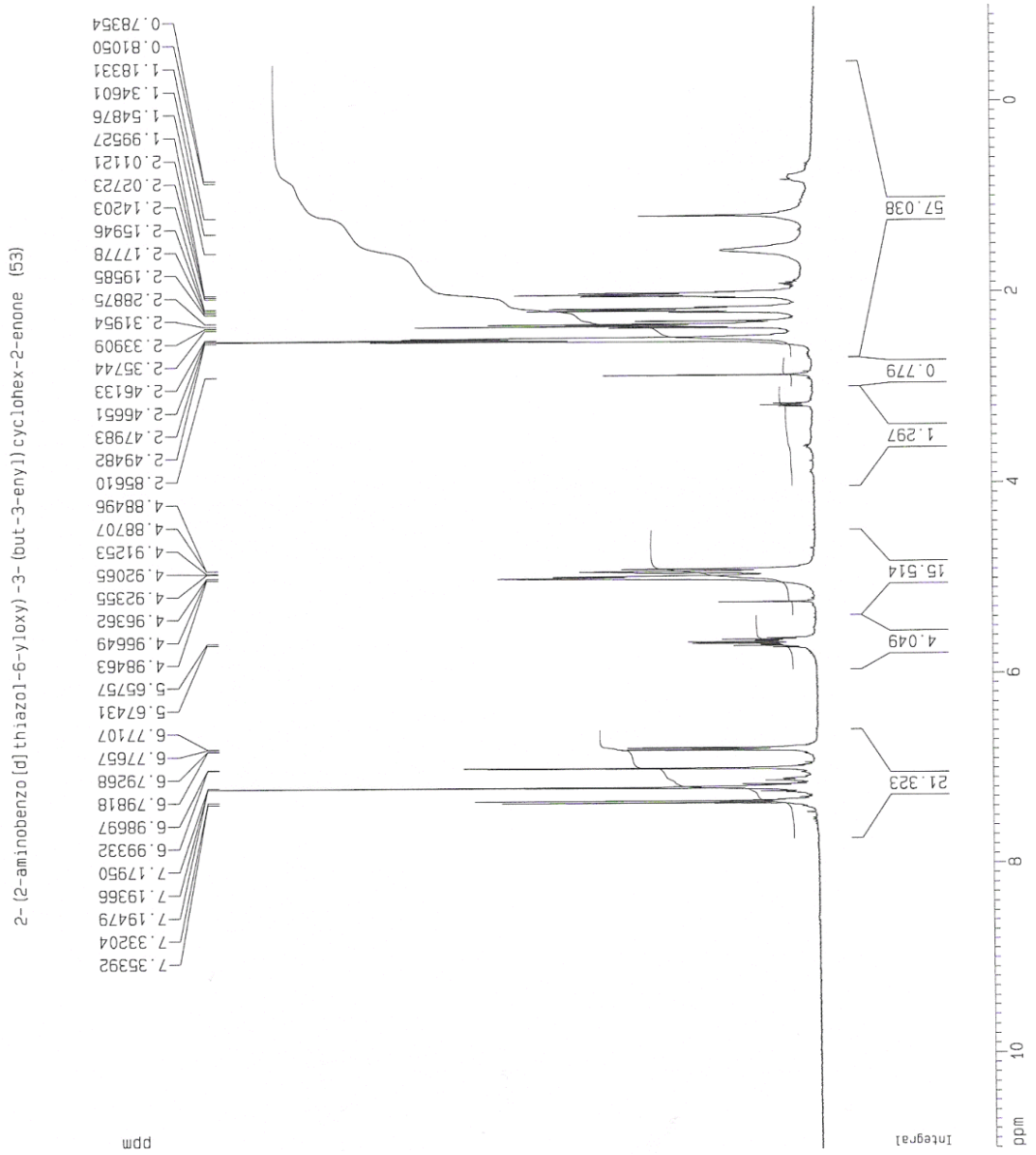


Figure 14 ^{1}H NMR Spectra of 2-(2-aminobenzo[*d*]thiazol-6-yloxy)-3-(but-3-enyl)cyclohex-2-enone (53)

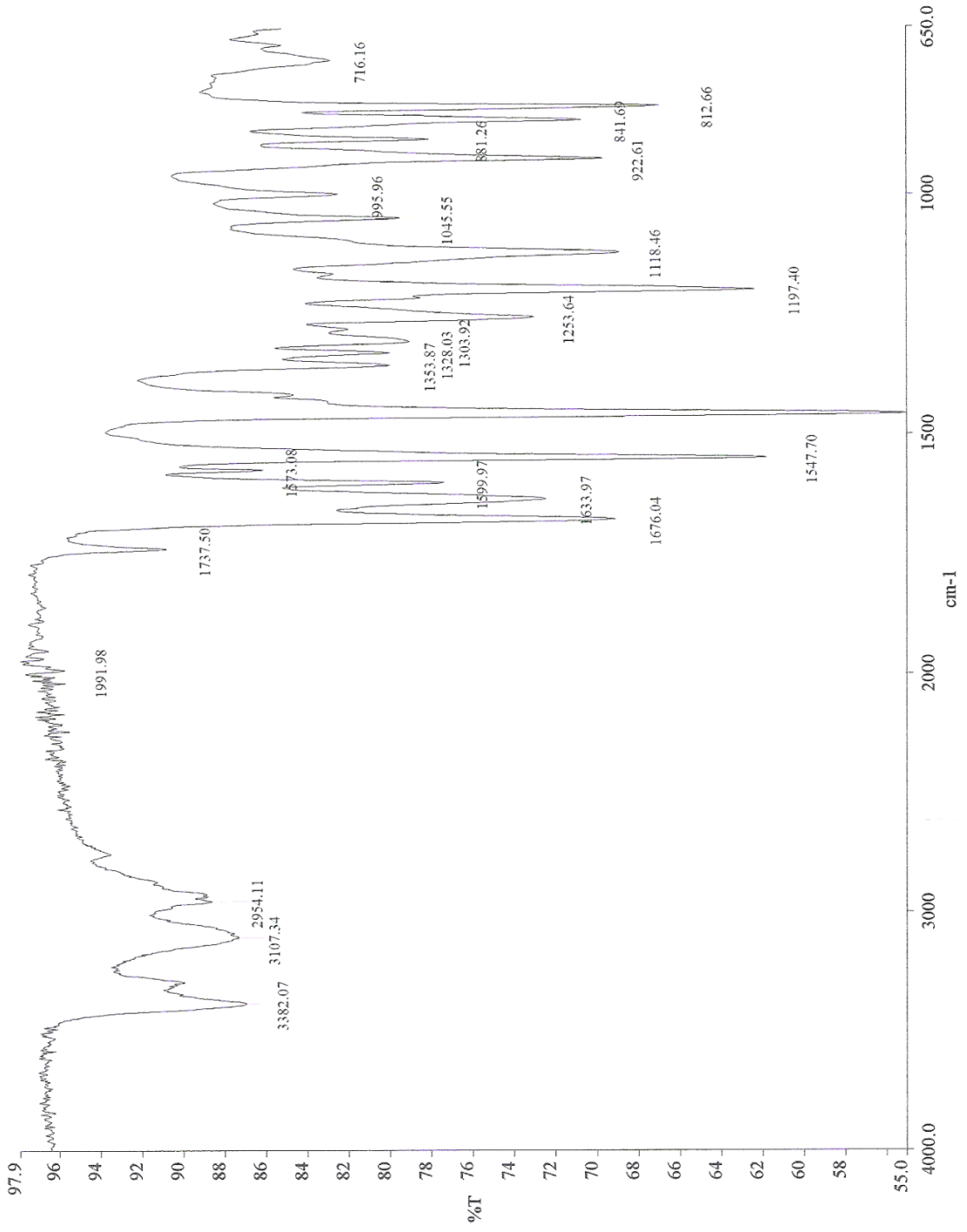


Figure 15 IR Spectra of 2-(2-aminobenzo[*d*]thiazol-6-yloxy)-3-(but-3-enyl)cyclohex-2-enone (53)

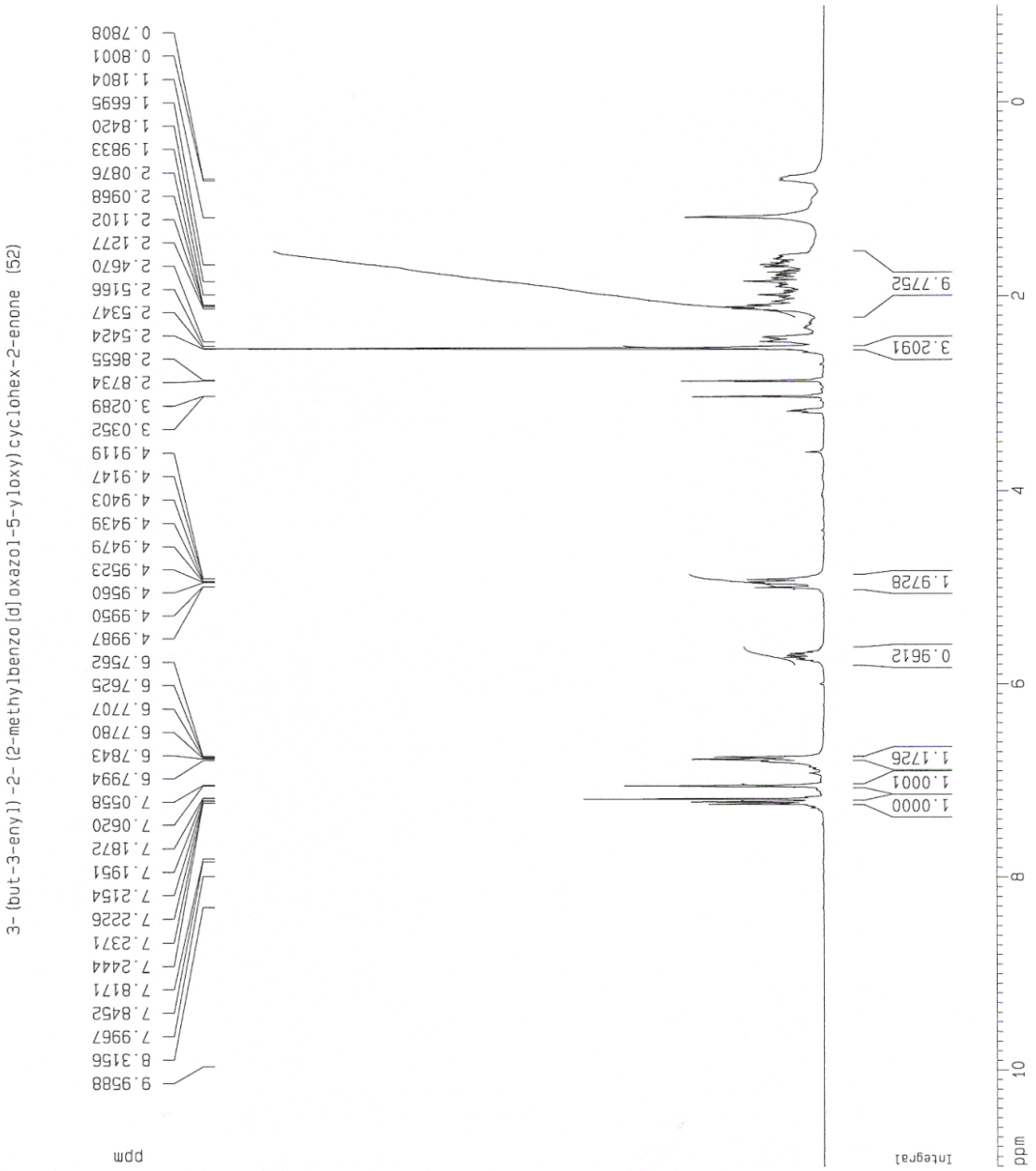


Figure 16 ^{1}H NMR Spectra of 3-(but-3-enyl)-2-(2-methylbenzo[*d*]oxazol-5-yloxy)cyclohex-2-enone (52)

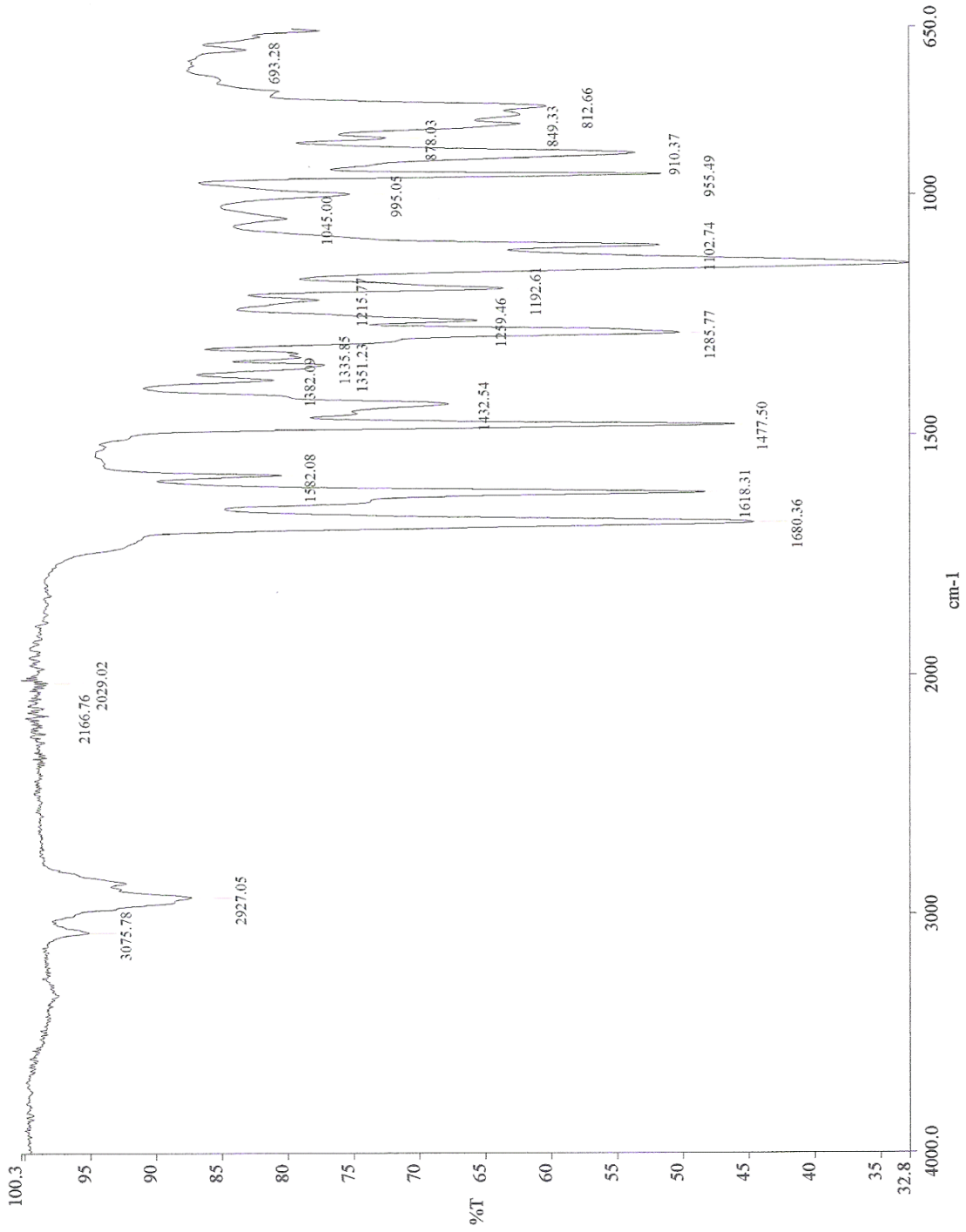


Figure 17 IR Spectra of 3-(but-3-enyl)-2-(2-methylbenzo[*d*]oxazol-5-yloxy)cyclohex-2-enone (52)

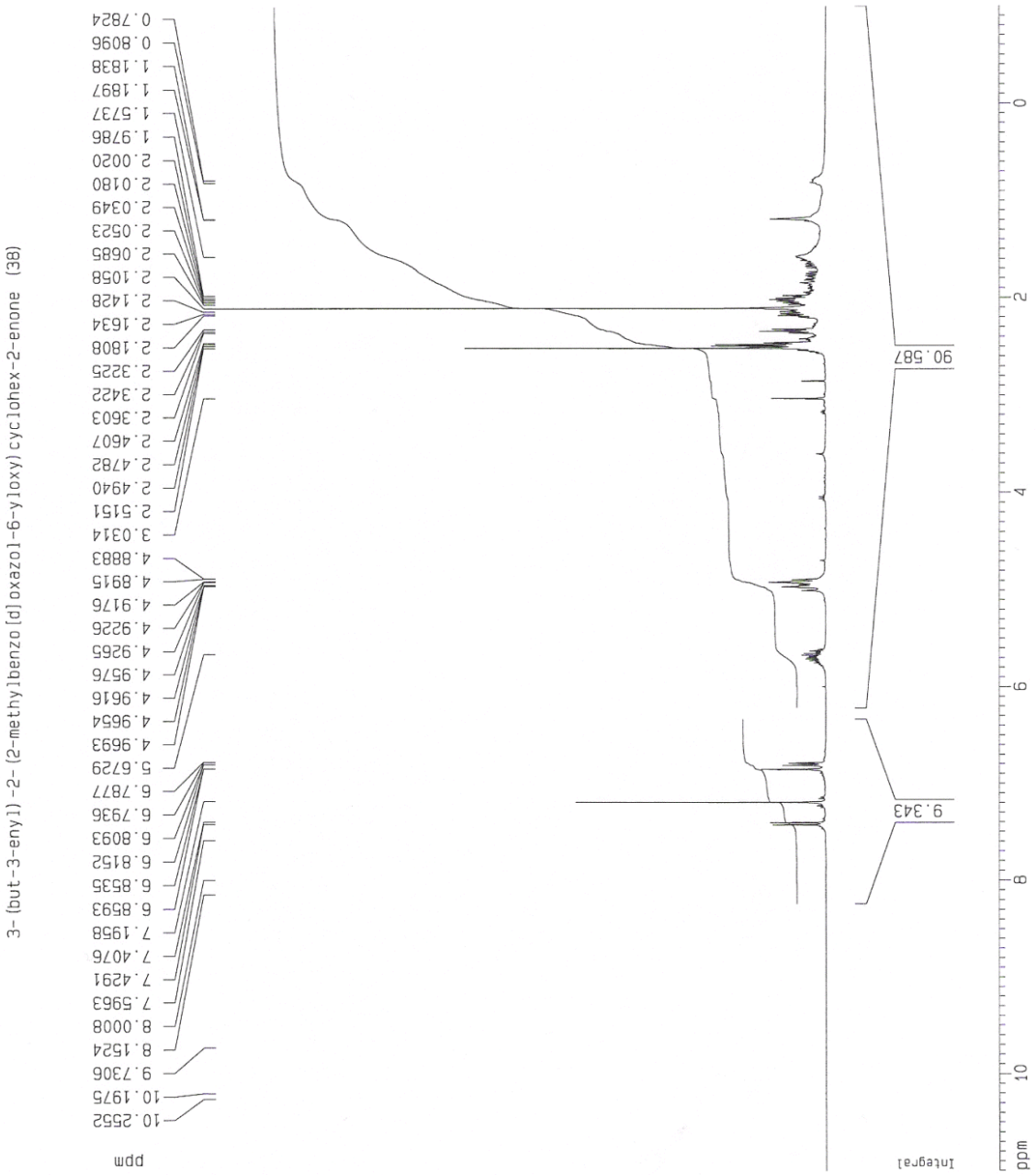


Figure 18 ^{1}H NMR Spectra of 3-(but-3-enyl)-2-(2-methylbenzo[*d*]oxazol-6-yloxy)cyclohex-2-enone (38)

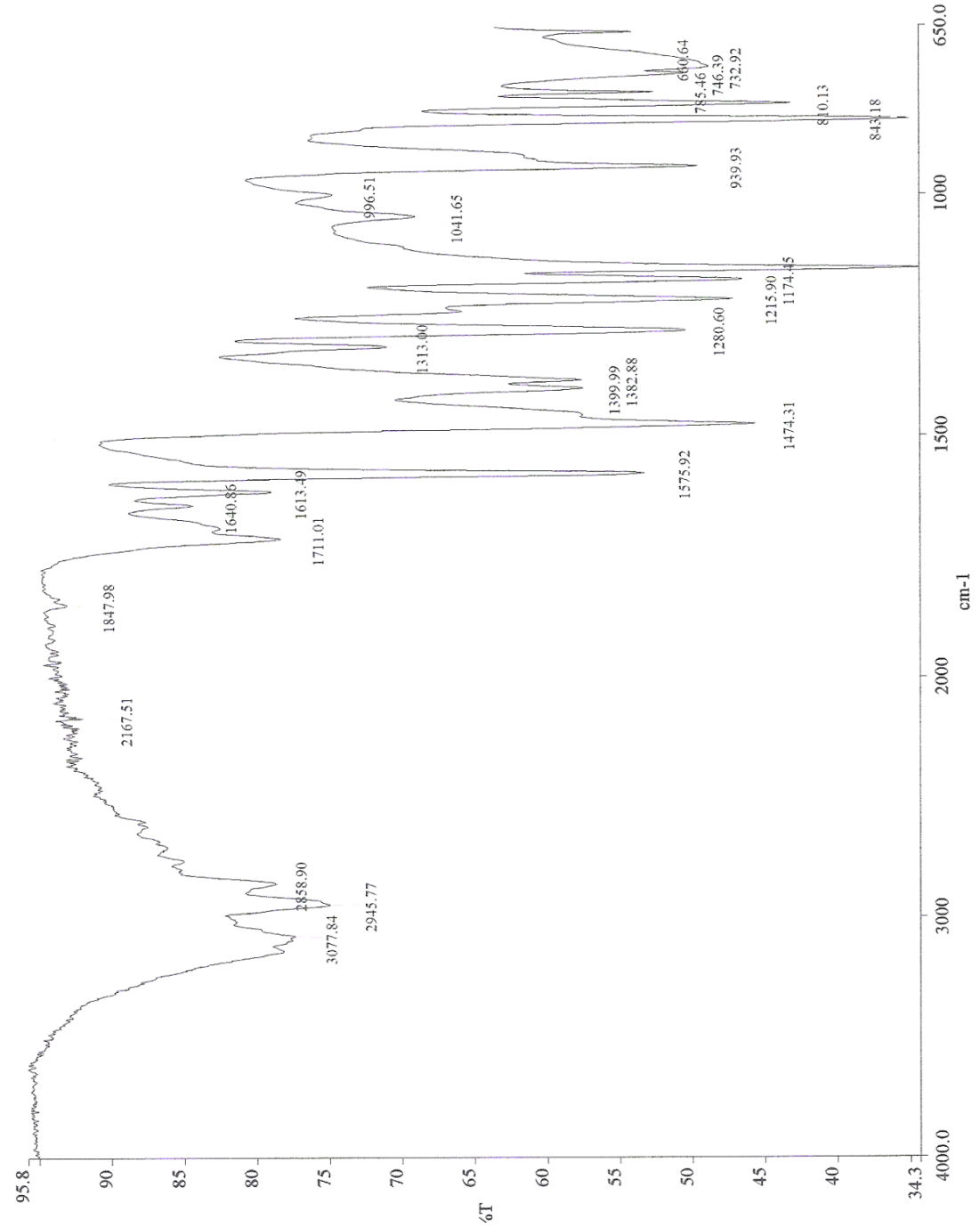


Figure 19 IR Spectra of 3-(but-3-enyl)-2-(2-methylbenzo[*d*]oxazol-6-yloxy)cyclohex-2-enone (38)