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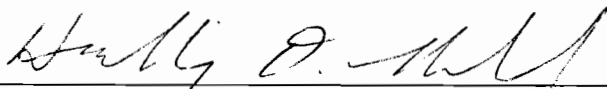
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Rhodium Catalyzed Intramolecular Hydroacylation of Sulfur and Nitrogen  
Containing Compounds

Presented to the Faculty of Lycoming College  
For Departmental Honors  
by

Tara Tiley  
Lycoming College  
April 24, 2002

Approved by:



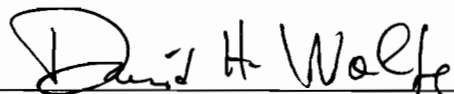
Dr. Holly Bendorf, Assistant Professor, Lycoming College Chemistry Department



Dr. Chriss McDonald, Associate Professor, Lycoming College Chemistry Department



Dr. Edward Gabriel, Associate Professor, Lycoming College Biology Department



Dr. David Wolfe, Associate Professor, Lycoming College Physics Department

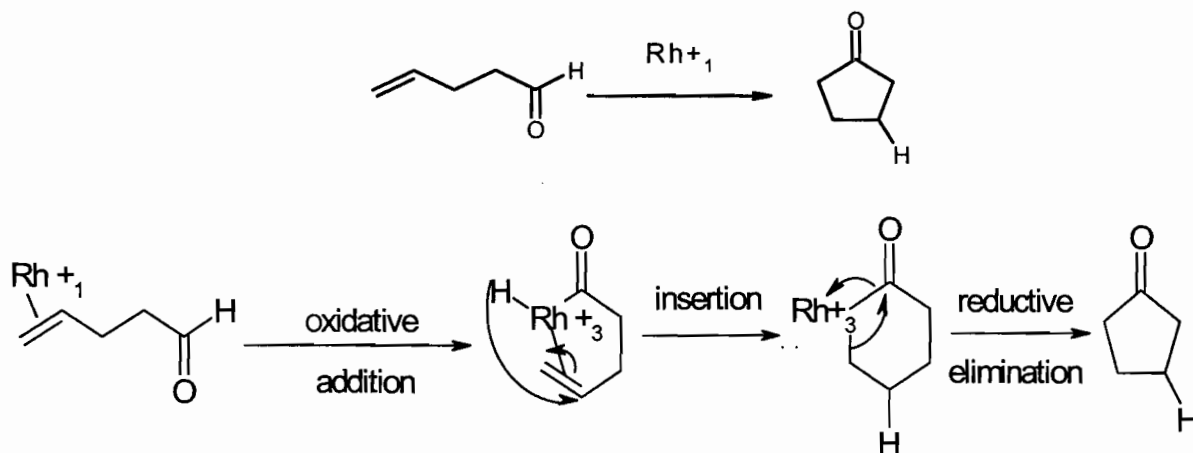
## Abstract

The goal of this research is to synthesize medium ring heterocycles using chelation-assisted intramolecular hydroacylation. This is accomplished by reacting Wilkinson's catalyst with substrates that contain a "tether atom" such as oxygen, nitrogen, and sulfur. However, sulfur-containing compounds have been the only substrates successful in cyclizations because amides, amines, and oxygen-containing compounds unfortunately have not cyclized. The cyclized products that have been formed have ranged in yields from trace amounts to 92% and have been produced by alkyl alkenals, aryl alkenals, and aryl alkynals.

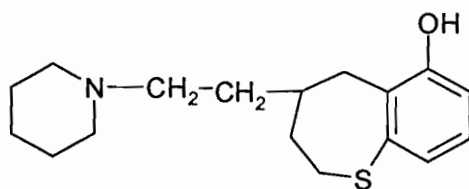
## Introduction

Intramolecular hydroacylation is a well-known technique for creating rings using a metal-containing catalyst. A procedure developed by Sakai used  $\text{RhCl}(\text{PPh}_3)_3$ , also known as Wilkinson's catalyst, to create five-membered rings.<sup>1</sup> This mechanism is shown below in Scheme 1.

Scheme 1



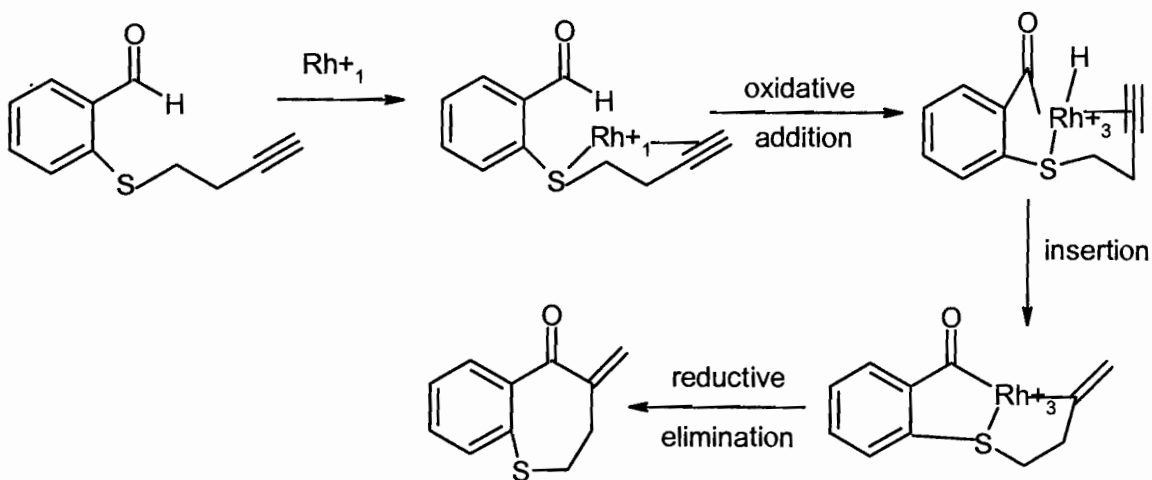
Five-membered rings are historically the only products that can be formed because any number lower creates too much ring strain during insertion and rings of six carbons or greater can not be constructed due to competitive decarbonylation as the size of the ring increases and the rate of oxidative addition and/or insertion decreases.<sup>4</sup> The method would be very useful if it could make medium rings (C<sub>7</sub>-C<sub>11</sub>), but the cyclization rates would be slow because the reaction to form larger rings is not kinetically favorable.<sup>1</sup> A useful modification of this procedure would be the inclusion of tether atoms, for instance oxygen, sulfur, or nitrogen, in the medium ring structure in order to facilitate the synthesis of the medium ring for a facile synthesis of medium ring heterocycles. These compounds are of interest because many compounds of biological importance and potential pharmaceutical application contain this structure. Medium ring heterocycles are found in many compounds with desirable biological activity such as urinary incontinence, high blood pressure, and they have had some effects against the HIV virus. The compound shown below has been used to lower blood pressure.



The goal of this research is to develop a methodology to use intramolecular hydroacylation to make medium ring heterocycles. This will be performed by reacting a rhodium-containing catalyst with substrates that contain tether atoms and which possess the requisite aldehyde functionality. This project focuses mainly on sulfur containing compounds in which the sulfur atom is attached to both a benzene ring and an alkyne or alkene carbon chain. The proposed mechanism for a typical substrate is shown below in

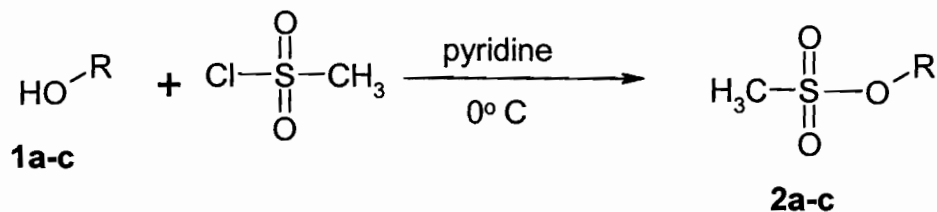
Scheme 2. The rhodium binds to the alkyne and tether atom first. The molecule then goes through oxidative addition where the rhodium reacts with the aldehyde. It then goes through insertion which means the rhodium is incorporated into the ring, and then reductive elimination in which the rhodium is removed and the result (as seen below) is a cycloheptanone.

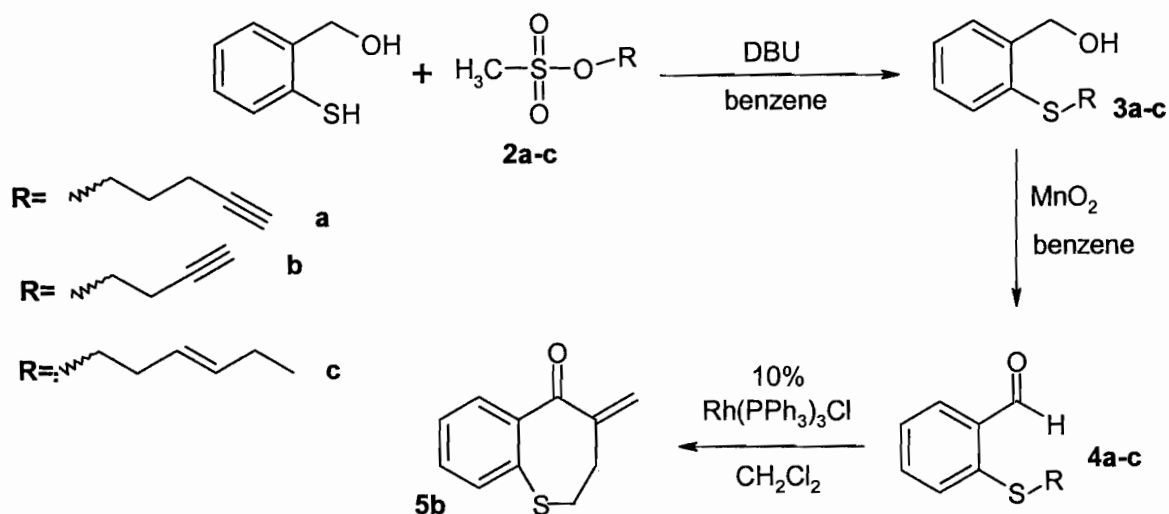
Scheme 2



The cyclization substrates must first be synthesized. The proposed reaction pathway to obtain the substrate follows in Scheme 3.

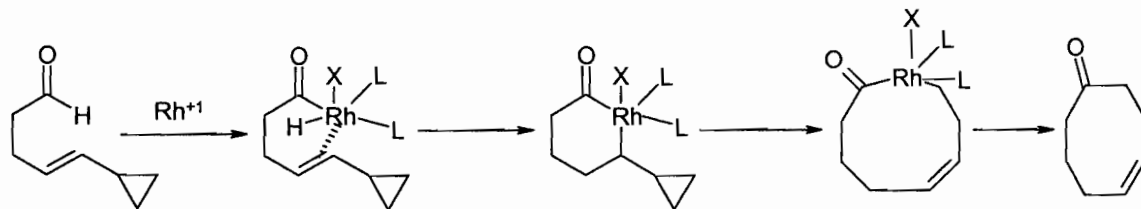
Scheme 3





## Literature Review

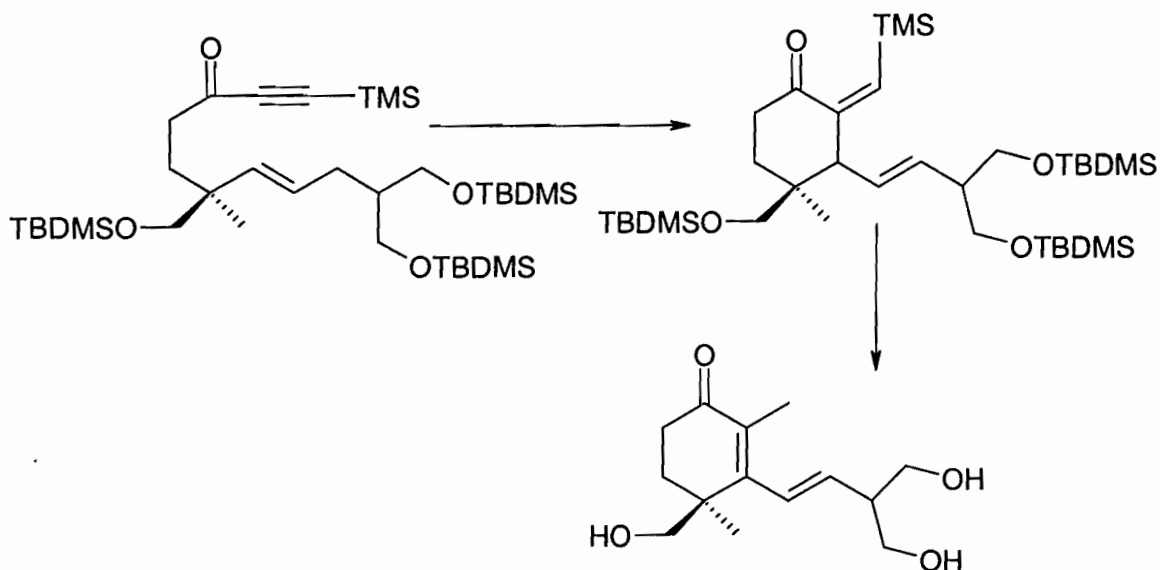
Medium rings have been made using intramolecular hydroacylation, but with the starting material having an appropriately located cyclopropane that can fragment. A rhodium catalyst coordinates to both the aldehyde and the cyclopropylalkene, and then the cyclopropane ring opens before insertion. The process continues through insertion and reductive elimination to form a cyclooctenone. The proposed mechanism is shown below.



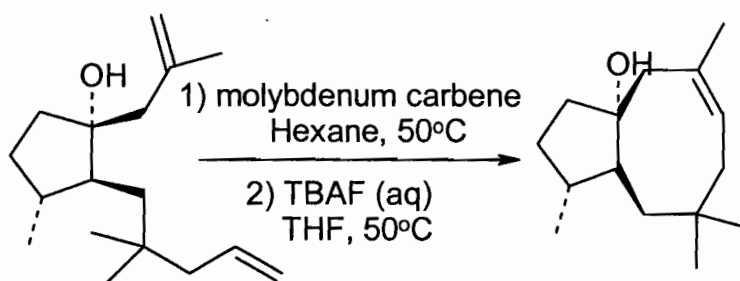
Thus, intramolecular hydroacylation can be used to form eight-membered rings.<sup>1</sup>

There have been many other successes creating medium rings with other procedures. A six-membered ring, cassiol, although not a medium ring, was made using

palladium catalyzed allylic alkylation and cycloisomerization.<sup>1</sup> It is a thirteen step reaction sequence with the last three steps shown below.

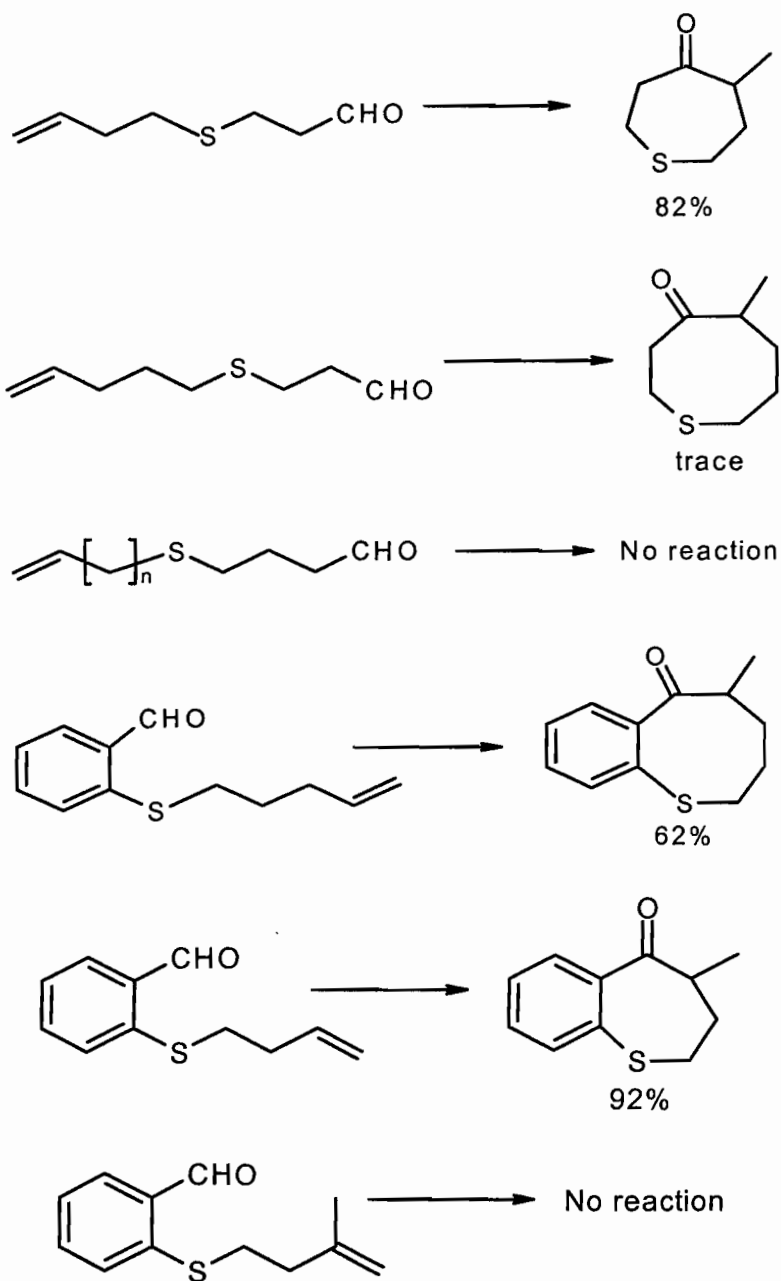


Dactyolol, which contains an 8-membered ring was formed using molybdenum carbene. Dactyolol is derived from humulene and is concentrated by mollusks.<sup>2</sup> Dactyolol is shown below as the product.



Some work that has been performed with sulfur has been successful and they have been performed in Dr. Bendorf's lab. Below in Scheme 4 are reactions that have been previously attempted in the lab.

Scheme 4<sup>5</sup>



From these above reactions much information has been obtained. It has been shown that intramolecular hydroacylation does occur with sulfur containing substrates, however there are some limitations. On a straight chain substrate it is found that if there are four or five carbons are on the alkene side and three carbons on the aldehydic side, cyclization will occur. Once either side of the chain is modified beyond these limits, then



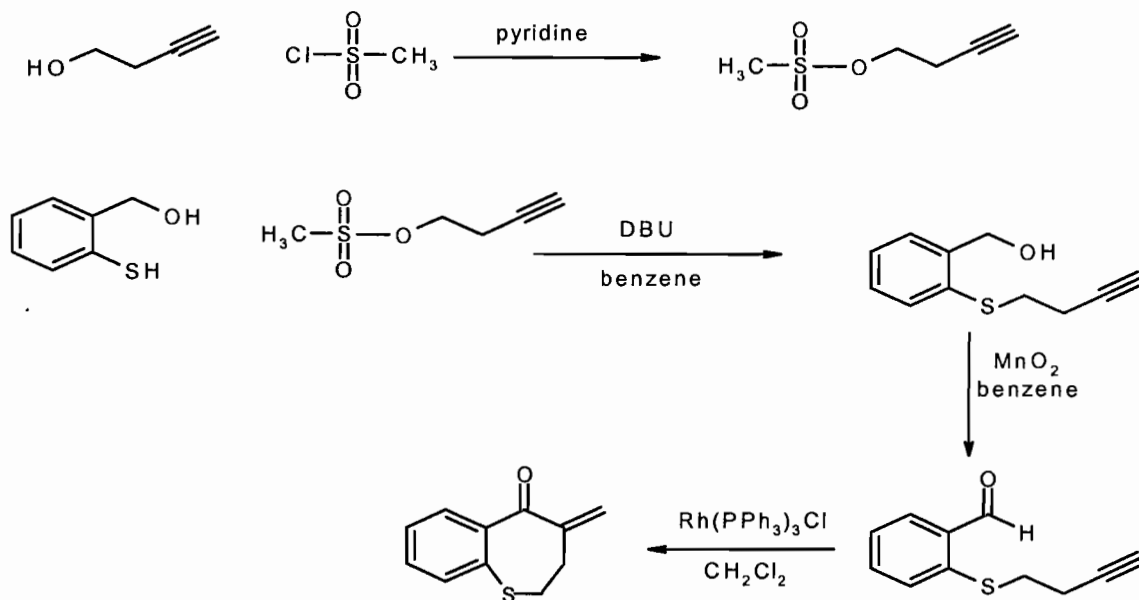
the reaction will not produce a cyclized product ( $n=1,2,3$ ). Ring formation is restricted if the chain is shorter because of ring strain and it is restricted when the chain is longer because cyclization is kinetically unfavorable. These results are consistent with the aromatic substrates as well. It is also shown that steric congestion on the proximal end of the alkene prevents cyclization. Nitrogen and oxygen have also been tested as tether atoms, but these attempts have not been successful. Some nitrogen reactions are incorporated into this paper in addition to the sulfur work.

## **Results and Discussion**

This project focused mainly on sulfur compounds containing a benzene ring and an alkyne or alkene carbon chain and the compounds are not available to be purchased, all of the substrates had to be synthesized. The synthesis involved alkylation as well as oxidation. Once the substrate had been synthesized and purified, it was then tested for cyclization.

## Synthesis and Cyclization of 2-But-3-ynylsulfanylbenzaldehyde(Scheme 5)

Scheme 5



The first step was to prepare a mesylate from 3-butyn-1-ol.<sup>6</sup> The alcohol was reacted with methanesulfonyl chloride in pyridine. The product was purified using column chromatography and obtained in an 83% yield. NMR spectroscopy confirmed the mesylate had been made because of a singlet at 3.0 ppm corresponding to the CH<sub>3</sub> of methane sulfonyl group, which integrated to three hydrogens and also a triplet at 2.08 ppm that integrated to one hydrogen corresponding to the alkyne. The mesylate was then used to alkylate 2-mercaptobenzyl alcohol in the presence of DBU and benzene.<sup>7</sup> The product was purified and then characterized by NMR. A singlet at 2.1 ppm that integrated to one hydrogen, the alkyne hydrogen, confirmed the alkylation. The reaction had a 55% yield. The alcohol on this product was then oxidized to an aldehyde.<sup>8</sup> This was accomplished with manganese dioxide in benzene and the product was obtained in a

75% yield. NMR spectroscopy revealed an aldehyde singlet at 10.5 ppm, confirming the presence of the functional group. Cyclization was attempted using the standard procedure involving the substrate and Wilkinson's catalyst in methylene chloride under argon and the dissolved gasses removed with the freeze/thaw technique. Immediately after adding the Wilkinson's catalyst the solution turned yellow. For the next few hours the solution continuously turned darker. Presumably, this is due to the rhodium complexing to the sulfur and alkyne. The reaction was monitored by gas chromatography. The starting material had a retention time of 17.030 min. while the product had a retention time of 17.815 min. It was purified by column chromatography and characterized by NMR spectroscopy. The NMR showed many peaks that indicated cyclization had occurred. For instance two singlets at 5.5 and 6.5 ppm each integrated for one hydrogen and correlate to the two alkene hydrogens. Also, two triplets around 2.7 and 3.1 ppm that integrated to two hydrogens correspond to ring hydrogens. However a mixture of products seemed to be present since there were many different small peaks spread throughout the baseline. There also may have been some starting material still present as well. The NMR spectrum can be seen in Appendix A (Fig. 1). Mass spectroscopy (CI) was also used to characterize the product and a peak with an  $m/z = 191.2$  was seen. The product that was attempted had a molecular mass of 190.256g/mol. Therefore, the GC/MS data was promising however, the starting material also has a molecular mass of 190.256 g/mol. The reaction had a 62% recovery.

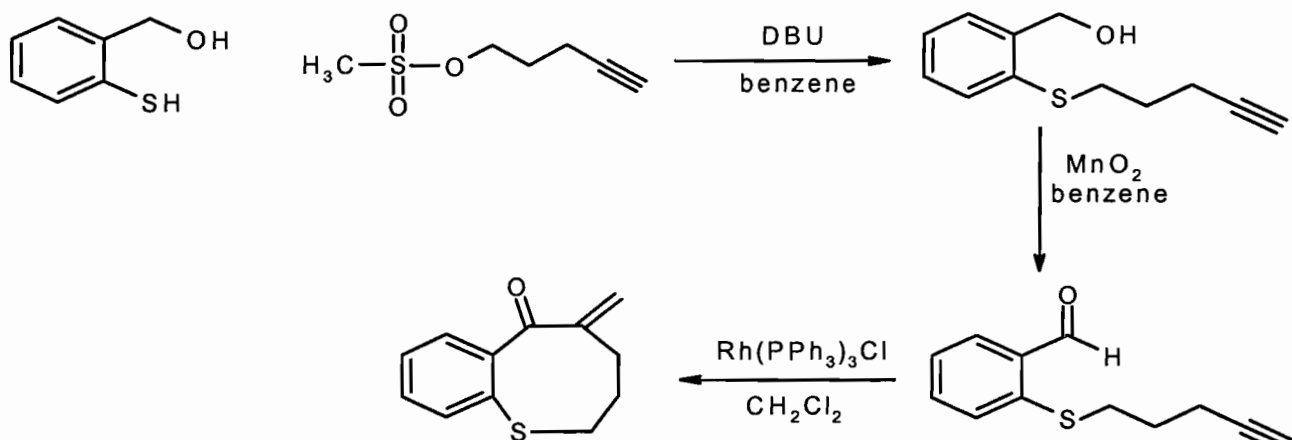
The reaction was later tried again, but using Kugelrohr distillation for purification. The NMR showed a more complex mixture of products probably caused

from heating the rhodium. The recovery also decreased to 57%. This NMR spectrum can also be seen in Appendix A (Fig. 2).

Another cyclization reaction was run analogous to the above reactions, however this time it was monitored very closely. During this reaction, it was found that when the solution containing the product and the rhodium was exposed to air another product was formed as seen as a separate peak on a GC chromatogram. To avoid this problem another reaction was performed and the reaction mixture was transferred via syringe into a methylene chloride column under  $N_2$ . This produced a pure 7-membered heterocycle in a 54% yield. The product was characterized by NMR and there are 2 singlets around 5.5 ppm and 6.5 ppm that represent the two alkene hydrogens, and two triplets around 2.7 ppm and 3.1 ppm that correlate to the four hydrogens on the newly formed ring. The absence of baseline peaks suggests a single product was formed. The spectrum can be seen in Appendix A (Fig.3).

#### Synthesis and Cyclization of 2-Pent-4-ynylsulfanylbenzaldehyde (Scheme 6)

**Scheme 6**



Because the four-carbon alkyne had cyclized, the next step was to try a five-carbon alkyne. The five-carbon alkyne substrate was synthesized in a manner analogous to the 4-carbon alkyne starting with 4-pentyn-1-ol. The mesylate was characterized by NMR and was obtained in a 97% yield.<sup>6</sup> The alkylation was successful as indicated by the NMR.<sup>7</sup> A singlet at 2.1 ppm that integrated to one hydrogen indicated the presence of the alkyne. This reaction resulted in an 83% yield. The oxidation from the alcohol to the aldehyde was also successful with an NMR peak for the aldehyde hydrogen at 10.4 ppm.<sup>8</sup> The yield was 83% for this reaction. For cyclization, again the solution turned immediately yellow, however it did not become darker gradually over time, instead after around two hours the solution turned dark at once. At this point a GC was taken to monitor the reaction, here the retention time for the starting material was 18.585 min., while the reaction mixture showed a single peak (other than solvent) at 19.225 min. The mixture was purified twice, once in a methylene chloride column and again in a hexane/ethyl acetate column. An NMR was taken and two singlets, one at 5.5 ppm and the other at 6.3 ppm looked very promising to be the alkene hydrogens on the product, but the rest of the NMR was difficult to interpret probably again because of a mixture of products. This spectrum can be seen in Appendix A (Fig. 4). A GC/MS (CI) was also taken and a peak with an  $m/z = 205.0$ g (the product should have a mass of 204.294g) was observed. The yield for this reaction was 67%.

Since the mixture of products had been obtained, the next cyclization attempt involved transferring the product directly from the reaction vessel to a methylene chloride column under  $N_2$ . This however did not result in a single product. The NMR characterization spectrum still showed the presence of a mixture of products.

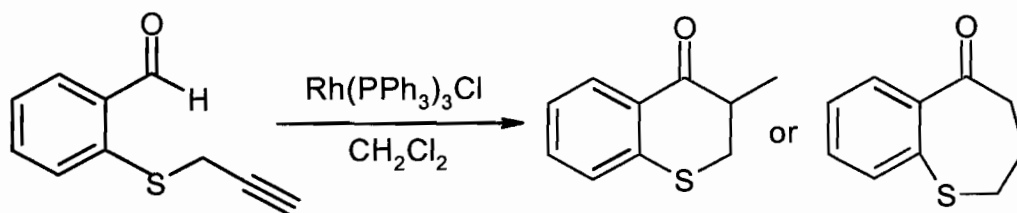
The next attempt to obtain a pure product for this cyclization involved heating the reaction in dichloroethane. This could help push the reaction to produce the thermodynamic product and possibly result in a cleaner reaction. The reaction solution was purified using a methylene chloride column. Again, a mixture of products, similar to the other attempts, was obtained. This can be seen from the NMR spectra, all attempts yield a similar mixture of products. A GC/MS (CI) spectrum was also taken and a peak at  $m/z = 220$  was not consistent with any possible product, however  $m/z = 205.0$  was still present and was the most prominent peak.

In the last attempt to purify the product, the reaction was run as previously described under the standard cyclizations conditions, but to purify it in a column with fluorosil as the stationary phase rather than silica gel. Fluorosil is less acidic than silica gel and products are less likely to isomerize through it, if that is what is causing the problem. This however also did not work as seen in the NMR spectrum.

#### Attempted Cyclization of 2-Prop-2-ynylsulfanylbenzaldehyde

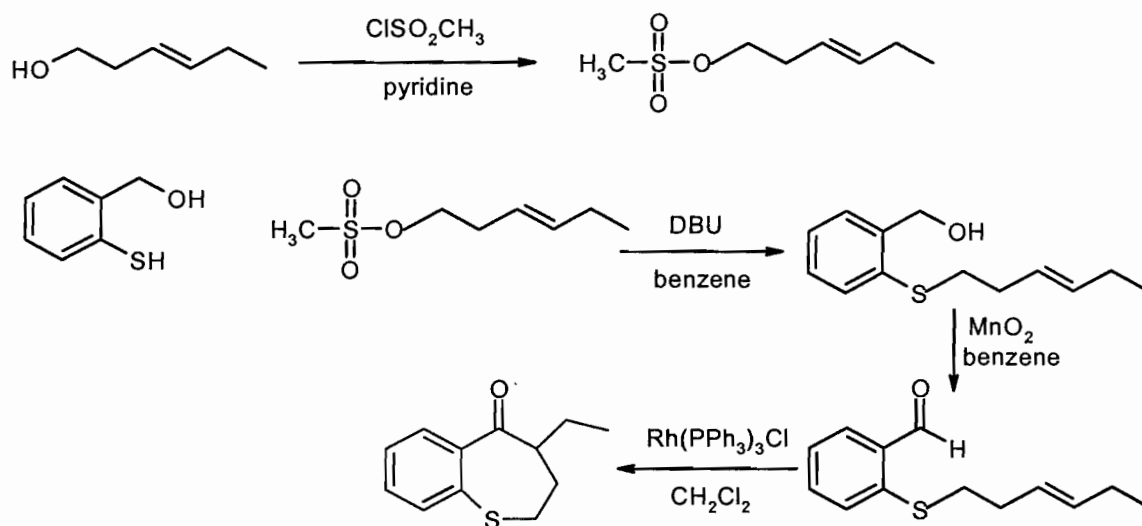
A three-carbon chain alkyne had already been synthesized in same manner as the four and five carbon alkynes. A cyclization attempt (Scheme 7) did not work as evidenced by spectroscopy NMR where only starting material peaks was observed. This is probably due to the allyl group being too short and creating too much ring strain for the substrate to cyclize.

**Scheme 7**



Synthesis and Attempted Cyclization of 2-Hex-3-enylsulfanylbenzaldehyde (Scheme 8)

**Scheme 8**

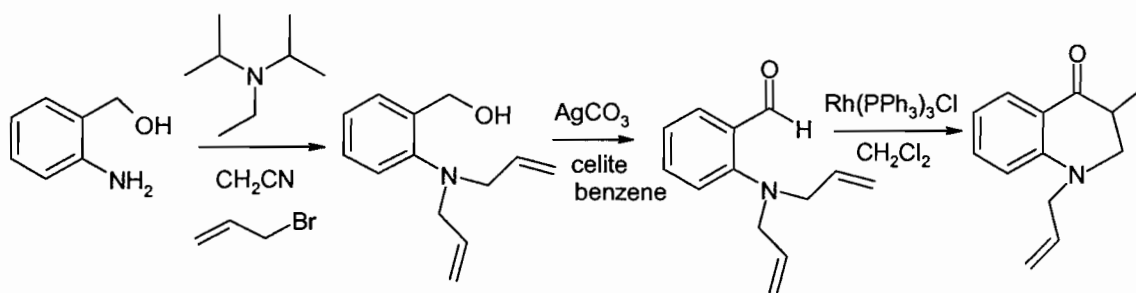


Since the alkynes cyclized and alkenes have been shown to cyclize, disubstituted alkenes were attempted next to test the limitations of the reaction. Again a mesylate was prepared using the standard reaction<sup>6</sup> yielding 97% product. The alkylation<sup>7</sup> of 2-mercaptobenzyl alcohol was proven successful by NMR spectroscopy characterization. The reaction yielded 74% product. The oxidation of the alcohol with manganese dioxide<sup>8</sup> in benzene was also successful and revealed by a peak around 10 ppm in the NMR spectrum. An 81% yield was obtained for this reaction. The product was purified and

then tested for cyclization using the standard reaction. The reaction was monitored by GC, but both the starting material and the reaction mixture gave approximately the same retention times of 19.945 min. and 19.831 respectively. The alkene did not cyclize because the alkene may have been located in the carbon chain too deep to react with the aldehyde group or the substituent on the alkyne created steric hindrance, which probably prevents insertion of the alkene into the Rh-H bond.

### Synthesis of 2-Diallylaminobenzaldehyde (Scheme 9)

**Scheme 9**



This compound was synthesized in two steps starting with, 2-aminobenzyl alcohol. Refluxing with 4-bromo-but-1-ene and ethyl diisopropylamine in acetonitrile produces the amine in 81% yield. The product was characterized by NMR and a multiplet at 5.85ppm, another multiplet at 5.17ppm and a doublet at 3.62 ppm confirmed the alkylation. Oxidation of the alcohol to an aldehyde was accomplished using 50% silver carbonate on celite with a 61% yield. Again the product was characterized by NMR and a peak at 10.38ppm confirmed that the alcohol had been oxidized to the aldehyde. The substrate was then ready for a cyclization attempt and was reacted with Wilkinson's catalyst in dichloromethane under argon. An NMR taken after purification showed a possible mixture of products, but mainly starting material. The possible explanation for

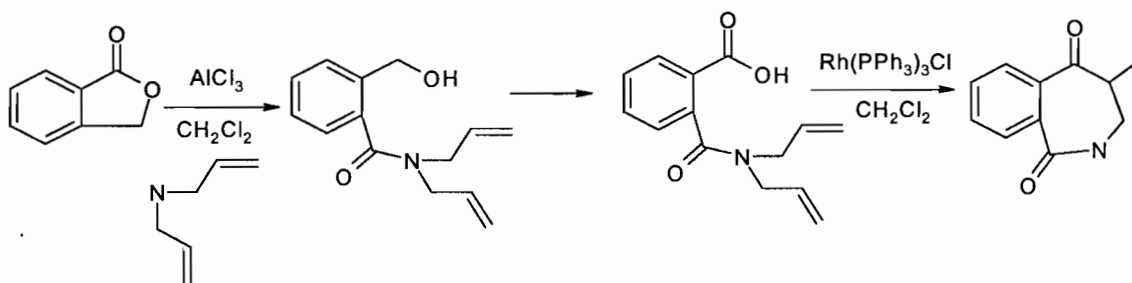


this substrate not cyclizing is that the allyl groups on the nitrogen are too short.

Unfortunately, we did not obtain the desired cyclized product.

### Synthesis of 2-Diallylamidebenzaldehyde

**Scheme 10**



Synthesis of this substrate began with nucleophilic acyl substitution on phthalide with aluminum chloride, diisopropylamine, and in methylene chloride. The product was characterized by NMR and two multiplet peaks, one at 5.87ppm and the other at 5.68ppm showed the desired product was obtained with a yield of 50%. Oxidation of the alcohol was then accomplished with  $\text{MnO}_2$  in benzene. An NMR peak at 10.13ppm proved that oxidation had occurred (53% yield).  $\text{MnO}_2$  was used because the usual chromium or swern oxidation would have affected the nitrogen on the amide. A cyclization was then attempted, but only starting material was present in the NMR. Again this probably did not work because the allyl groups are too short and too much ring strain is inhibiting cyclization.

### Conclusions

Cyclizations using butynyl and pentynyl substrates were successful. Unfortunately though, the cyclooctanone product is not pure which could be a result of a side reaction

producing other products. Isolation of a pure cyclooctanone from the cyclization of 2-Pent-4-ynylsulfanylbenzaldehyde is definitely part of the future work for this project. The reason the propargyl substrate did not cyclize was because the chain length was too short and rigid to react to form a ring. Other areas to investigate include trying other tether atoms, for instance thioacetals and thioesters and the inclusion of amines and amides to try to achieve a substrate containing a propene or butyne chain to test cyclization.

### **Experimental Section**

**General.** Anhydrous methylene chloride was refluxed over calcium hydride and distilled immediately prior to use. Chromatographic purifications were performed on silica gel, Merck grade 60, by flash technique. TLC plates covered with silica gel were viewed under UV light and developed in iodine. Coupling constants (J) are in Hz. GC conditions were Initial time=2min. Rate=10°C/min, Initial Temp.=70°C, Final time=15 mins. and Final Temp.=220°C

**General procedure for the preparations of mesylates (2a-c).**<sup>6</sup> The alcohol (10 mmol) and distilled pyridine (10mL, ~1M) was added to a flamed flask. The mixture was then cooled to 0°C and mesyl chloride was added (11mmol). The mixture was stirred for 4 hrs. at 0°C and then was added to H<sub>2</sub>O and CH<sub>2</sub>Cl<sub>2</sub> in a separatory funnel. The organic layer was washed several times with H<sub>2</sub>O (3x15 mL), 10% HCl (3x15 mL), brine (3x20 mL), and dried over Na<sub>2</sub>SO<sub>4</sub>. The solution was then concentrated.

**3-butynyl methanesulfonate (2a).** The product was a clear, colorless oil, 1.377 g of **2a**, 83% yield.  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ) 4.29(2H, t,  $J=6.6$ ), 3.04(3H, s), 2.65(2H, td,  $J=8.5$ ,  $J=2.1$ ), 2.08(1H, t,  $J=2.64$ ).

**4-pentynyl methanesulfonate (2b).** A clear, colorless oil was produced, 1.5821 g of **2b**, 97% yield.  $^1\text{H}$  NMR 4.33(2H, t,  $J=6.1$ ), 3.01(3H, s), 2.35(2H, td,  $J=6.9$   $J=2.3$ ), 2.01(1H, t,  $J=4.7$ ), 1.92(2H, quint.,  $J=6.1$ ).

**3-hexenyl methanesulfonate (2c).** The product was a clear, colorless oil, 1.726 g of **2c**, 97% yield.  $^1\text{H}$  NMR 5.57(1H, m), 5.32(1H, m), 4.21(2H, t,  $J=6.9$ ), 3.01(3H, s), 2.51(2H, qd,  $J=7.20$   $J=0.7$ ), 2.06(2H, qd,  $J=7.40$   $J=0.8$ ), 0.97 (3H, t,  $J=7.55$ ).

**Preparation of (2-Mercapto-phenyl)-methanol.** To a dry 200 mL round bottom flask added  $\text{LiAlH}_4$  (79.0 mmol). A dropping funnel was added onto the flask and the system was flushed with Ar. THF (50 mL) was then added via syringe to the dropping funnel and slowly added to  $0^\circ\text{C}$   $\text{LiAlH}_4$ . The solution of the 2-mercapto-benzoic acid (38.9 mmol) and THF (50 mL) was then added dropwise over 60 minutes. The solution was warmed to room temperature and stirred overnight. The following day the solution was cooled to  $0^\circ\text{C}$  and 15 mL of ethyl acetate and 60 mL of 10%  $\text{H}_2\text{SO}_4$  was added. The solution was then warmed to room temperature again and gravity filtered into an argon flushed flask. This filtrate was poured into an argon flushed separatory funnel and distilled water and ethyl acetate were added. The aqueous layer was then drained and the organic layer was then washed twice with 50 mL brine. The solution was then dried over  $\text{Na}_2\text{SO}_4$ , concentrated on the rotovap and vacuum pumped for 2 hours. The product was kept under Ar at all times because it is very air sensitive. The product was an off-

white solid, 4.690 g of 2-mercaptobenzoic acid, 86% yield.  $H^1$  NMR 7.36(2H, m), 7.22(2H, m), 4.76(2H, s), 3.71(1H, s), 1.94(1H, s).

**General procedure for alkylation of 2-mercaptobenzyl alcohol (3a-c).**<sup>7</sup> An Ar flushed round bottom flask was charged with alcohol (3.5 mmol). Benzene (30 mL) and DBU (4.1 mmol) were then added and a precipitated formed. The mesylate (4.1 mmol) was added. The mixture was stirred for 48 hrs. The solution was washed with  $H_2O$  (2x50 mL), 10% HCl (2x30 mL), brine (2x 30 mL), and dried over  $Na_2SO_4$ . The solution was then concentrated, and then the product was dissolved in ether, filtered, and concentrated. The filter paper was then rinsed with benzene and this solution was collected and concentrated. This product was then dissolved in ether and a TLC was taken. It was transferred into the other flask that contained product and concentrated. The product was then purified using flash chromatography (100% Methylene Chloride). The solution was then concentrated.

**2-carboxalphenyl-3-butynyl sulfide (3a).** A yellow oil was produced, 0.3387g of **3a**, 55% yield.  $H^1$  NMR 7.45(2H, m), 7.29(2H,m) 4.80(2H, d, J=6.1), 3.09(2H, t, J=7.3), 2.59(1H, t, J=6.3), 2.49(2H, td, J=7.3 J=2.6), 2.08(1H, t, J=2.6).

**2-carboxalphenyl-4-pentynyl sulfide (3b).** The product was a yellow oil, 0.6142g of **3b**, 83% yield., 7.37(2H, td, J=5.75), 7.22(2H, quint d, J=7.72 J=1.9) 4.72(2H, d, J=3.84), 3.34(1H, s), 3.00(2H, t, J=8.7), 2.33(2H, td, J=6.9 J=2.6), 2.02(1H, d, J=2.6), 1.84(2H, quint., J=7.0),

**2-carboxalphenyl-3-hexenyl sulfide (3c).** A yellow oil product resulted, 0.5961g of **3c**, 74% yield.  $H^1$  NMR 7.39(2H, m), 7.26(2H, quint. D, J=11.2 J=1.7), 5.48

(2H, m), 4.77(2H, d, J=6.3), 2.96(2H, t, J=7.3), 2.65(1H, d, J=6.3), 2.40(2H, q, J=6.9), 2.05(3H, quint., J=7.4), 0.98(3H, t, J=7.5).

**General procedure for oxidation of alcohols (4a-c).**<sup>8</sup> To a flask charged with the alcohol (3 mmol) and flushed with argon, benzene (80 mL) and MnO<sub>2</sub> (45 mmol) was added. The reaction was stirred for 48 hrs and then a TLC was taken. The mixture was then filtered through a fritted funnel with a pad of celite, and washed with 100 mL of benzene. The solution was concentrated and then purified using flash chromatography (70:30 hexane/EtOAc). The solution was then concentrated.

**2-carboxaldehydephenyl-3-butynyl sulfide (4a).** The product was a yellow oil, 0.2783g of **4a**, 75% yield. H<sup>1</sup> NMR 10.41 (1H, s), 7.86(1H, dd, J=7.6 J=1.5), 7.52 (1H, m), 7.45(1H, d, J=7.96), 7.33 (1H, m), 3.12(2H, t, J=7.3), 2.55(2H, td, J=5.56 J=2.05), 2.08(1H, t, J=2.64).

**2-carboxaldehydephenyl-4-pentynyl sulfide (4b).** A yellow oil was produced, 0.4924g of **4b**, 81%. H<sup>1</sup> NMR 10.39(1H, s), 7.85(1H, dd, J=7.3 J=1.5), 7.53(2H, quint, J=7.1), 7.31(1H, m), 3.11(2H, q, J=7.1), 2.39(2H, m), 2.04(1H, m), 1.92(2H, t, J=7.5).

**2-Hex-3-enylsulfanyl-benzaldehyde (4c).** The product was a yellow oil, 0.4983g of **4c**, 84% yield. H<sup>1</sup> NMR 10.41(1H, s), 7.85(1H, dd, J=7.7 J=0.3), 7.51(2H, m), 7.31(1H, t, J=0.5), 5.46(2H, m), 2.99(2H, t, J=7.3), 2.43(2H, qd, J=8.0 J=0.9), 2.03(2H, quint., J=7.5), 0.96(3H, t, J=7.5).

**General procedure for cyclization (6b & 2-Pent-4-ynylsulfanylbenzaldehyde).** To a Schlenk flask flushed with argon the aldehyde (0.3 mmol) and the solvent (~0.25 M) is added. Freezing it in liquid nitrogen and vacuum pumping then degassed the mixture. This was performed twice. Wilkinson's catalyst (0.03 mmol) was then added under Ar

flush. The mixture was stirred and was monitored by GC. The mixture was then purified using several different techniques in order to isolate one product and increase yield.

**2-But-3-ynylsulfanylbenzaldehyde (6b).** The mixture was concentrated and then purified using flash chromatography (100% Methylene Chloride). However, there was some overlapping of products in the fractions. A second purification was conducted again using flash chromatography (90:10 hexane/EtOAc). The product was a yellow oil, 0.0360g of **6b**, 62% yield. A second attempt of this reaction was conducted. The mixture was concentrated and then Kugel Rohr distilled. The product was a yellow oil, 0.0343g of **6b**, 57% yield.  $H^1$  NMR information is attached in Appendix A (Fig. 2).

A third attempt was then conducted. The mixture was concentrated on the vacuum pump so only a few milliliters remained. This mixture was then transferred to a column (100% Methylene Chloride, under  $N_2$  (g)) from the reaction tube via syringe. The product was a yellow oil, 0.01610g of **6b**, 54% yield.  $H^1$  NMR 7.65(1H, m), 7.53(1H, m), 7.46(2H, m), 6.36(1H, d,  $J=1.62$ ), 5.51(1H, d,  $J=1.63$ ,  $J=0.83$ ), 3.03(2H, t,  $J=6.67$ ), 2.67(2H, t,  $J=6.09$ ). This spectra can be found in Appendix A (Fig. 3).

**2-Pent-4-ynylsulfanylbenzaldehyde.** The mixture was concentrated and then purified using flash chromatography (100% Methylene Chloride), and then purified again using the same method with 90:10 hexane/EtOAc. The product was a yellow oil, 0.0338g of **2-Pent-4-ynylsulfanylbenzaldehyde**, 67% yield.  $H^1$  NMR information is included in Appendix A (Fig. 4).

The second attempt for this reaction involved concentrating the reaction mixture on the vacuum pump so that only a few milliliters remained. This concentrated mixture was then transferred to a column (100% Methylene Chloride, under  $N_2$  (g)) via syringe.

The product was a yellow oil, 0.01183g of **2-Pent-4-ynylsulfanylbenzaldehyde**, 75% yield.  $H^1$  NMR information is included in Appendix A (Fig. 5).

Another attempt involved using dichloroethane instead of dichloromethane in the reaction mixture and then heating the reaction. The reaction was monitored by GC and refluxed for 48hrs. It was then concentrated on the vacuum pump and transferred into a column (100% Methylene Chloride, under  $N_2$  (g)) via syringe. The product was a yellow oil, 0.0254g of **2-Pent-4-ynylsulfanylbenzaldehyde**, 96% yield.  $H^1$  NMR information is included in Appendix A (Fig. 6).

A fourth attempt was made and this mixture was concentrated on the vacuum pump and transferred to a column (100% Methylene Chloride, under  $N_2$  (g)) however the stationary phase was fluorisil instead of silica gel. The product was a yellow oil, 0.0320g of **2-Pent-4-ynylsulfanylbenzaldehyde**, 64% yield.  $H^1$  and  $C^{13}$  NMR information is included in Appendix A (Fig. 7&8)

### **Synthesis and cyclization of 2-Diallylaminobenzaldehyde**

**2-aminobenzyl alcohol** was purchased and used from the bottle. The alcohol (0.804 mmol) was added to a round bottom flask under  $N_2$ . 40 milliliters of acetonitrile were then added to the flask via syringe and shortly after that addition, 4-bromo-but-1-ene (5.62 mmol) and ethyldiisopropylamine were added as well. The reaction was heated and refluxed for 48hours. The dark pink solution was then concentrated to yield a dark pink solid. This solid was then dissolved in distilled water and ether and a milliliter of sodium bicarbonate was added and it was all separated in a separatory funnel. The organic layer was washed with saturated sodium bicarbonate, water, and brine, and then allowed to dry over sodium sulfate. To purify the product it was run through a column

(70:30 hexane/EtOAc). After removing the solvent the product was a yellow oil and 81% yield.  $^1\text{H}$  NMR 7.19(4H, m), 5.86(2H, m), 5.23(1H, s), 5.19(4H, m), 4.84(2H, s), 3.62(4H, d,  $J=6.5$ ).

The next step in the synthesis is oxidation of the alcohol in which to an oven dried round bottom flask  $\text{AgCO}_3/\text{Celite}$  (5.20 mmol) and the alcohol (0.196 mmol) are added.<sup>9</sup> The reaction takes place in dry benzene (18 mL) however, half of the benzene was distilled off of the reaction, and the concentrated reaction solution was then allowed to reflux overnight. It was then cooled to RT and then filtered and washed with ethyl acetate. The solution was concentrated and the product was purified in a 70:30 hexane/ethyl acetate column. Again it was concentrated and the reaction had a 61% yield of **2-diallyamino-benzaldehyde**.  $^1\text{H}$  NMR 10.38(1H, s), 7.82(1H, dd,  $J=7.7$   $J=1.7$ ), 7.48(1H, td,  $J=1.7$   $J=0.7$ ), 7.28(1H, s), 7.13(1H, m), 5.83(2H, m), 5.20(4H, m), 3.81(4H, dd,  $J=5.9$   $J=1.3$ ).

The **2-diallyamino-benzaldehyde** was then tested for cyclization using the general procedure above. NMR showed a possible a mixture and the spectra can be seen Appendix A (Fig. 9).

### Synthesis and Cyclization of 2-Diallyamidebenzaldehyde

To start this synthesis a round bottom flask is flushed with  $\text{N}_2$  and  $\text{AlCl}_3$  (2.49 mmol) is added and the contents are flushed again with  $\text{N}_2$ . Distilled dichloromethane (4 mL) was then added and the system was cooled to  $0^\circ\text{C}$ . The amine (4.77 mmol) was then added with solvent and the system was warmed up to RT again. At this point the lactone (1.87 mmol) was added and a solid was formed. It was then allowed to stir overnight. For work-up the system was cooled to  $0^\circ\text{C}$  and then 10 mL of saturated



NaHCO<sub>3</sub> was slowly added. The solution was then gravity filtered into a separatory funnel and the product was extracted twice with methylene chloride and dried over sodium sulfate. The product was concentrated and purified in a column (85:15-60:40 hexane/EtOAc). The product was concentrated and a 50% yield was obtained. <sup>1</sup>H NMR 7.46-7.27(4H, m), 5.87(1H, m), 5.68(1H, m), 5.27(4H, quint., J=2.98), 4.53(2H, s), 4.11(2H, q,d J=7.2 J=1.8), 3.77(2H, d, J=5.28).

The next step was to oxidize the alcohol to an aldehyde, this was done analogous to the above oxidations for the S containing compounds. The product was purified in a column (70:30 hexane/EtOAc) and it was concentrated for a 44% yield of 2-

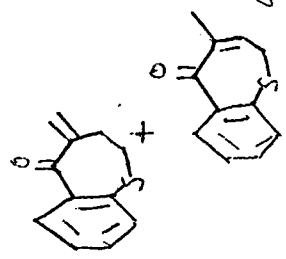
**Diallylamidebenzaldehyde.** <sup>1</sup>H NMR 10.13(1H, s), 7.94(1H, dd, J=7.6 J=1.5), 7.62(3H, m), 5.92(1H, m), 5.59(1H, m), 5.07(4H, q,d J=17.1 J=1.5), 4.22(1H, d, J=5.98), 3.68(1H, d, J=5.6).

**2-Diallylamidebenzaldehyde** was then tested for cyclization under the standard conditions given in the general experimental, the reaction solution was found by NMR to be just starting material with same peaks and coupling constants as above.

- 
- (1) Trost, B.; Li, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6625.
  - (2) Furstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746.
  - (4) Larock, R.C.; Oertle, K.; Potter, G. J. *J. Am. Chem. Soc.* **1980**, *102*, 190
  - (5) Bendorf, H.; Dixon, L.; Marchetti, M.; Matukonis, A.; Musselman, J. Lycoming College, Williamsport, PA. Unpublished work, 1995.
  - (6) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5<sup>th</sup> ed.; Longman Scientific & Technical: UK, 1989; pp 573.
  - (7) Ono, N.; Miyake, H.; Saito, T.; Kaji, A. *Communications.* **1980**, 952-953
  - (8) Kasmai, H. S., Mischke, S. G. *Synthesis*, **1989**, 763
  - (9) Frye, Leah L.; Robinson, Cecil H. *J. Org. Chem.* **1990**, *55*, 1579-1584

## **Appendix A**

TAT-I-6-19  
 off  
 2nd column



mixture containing

after 2  
 Column  
 (pg 8+19)

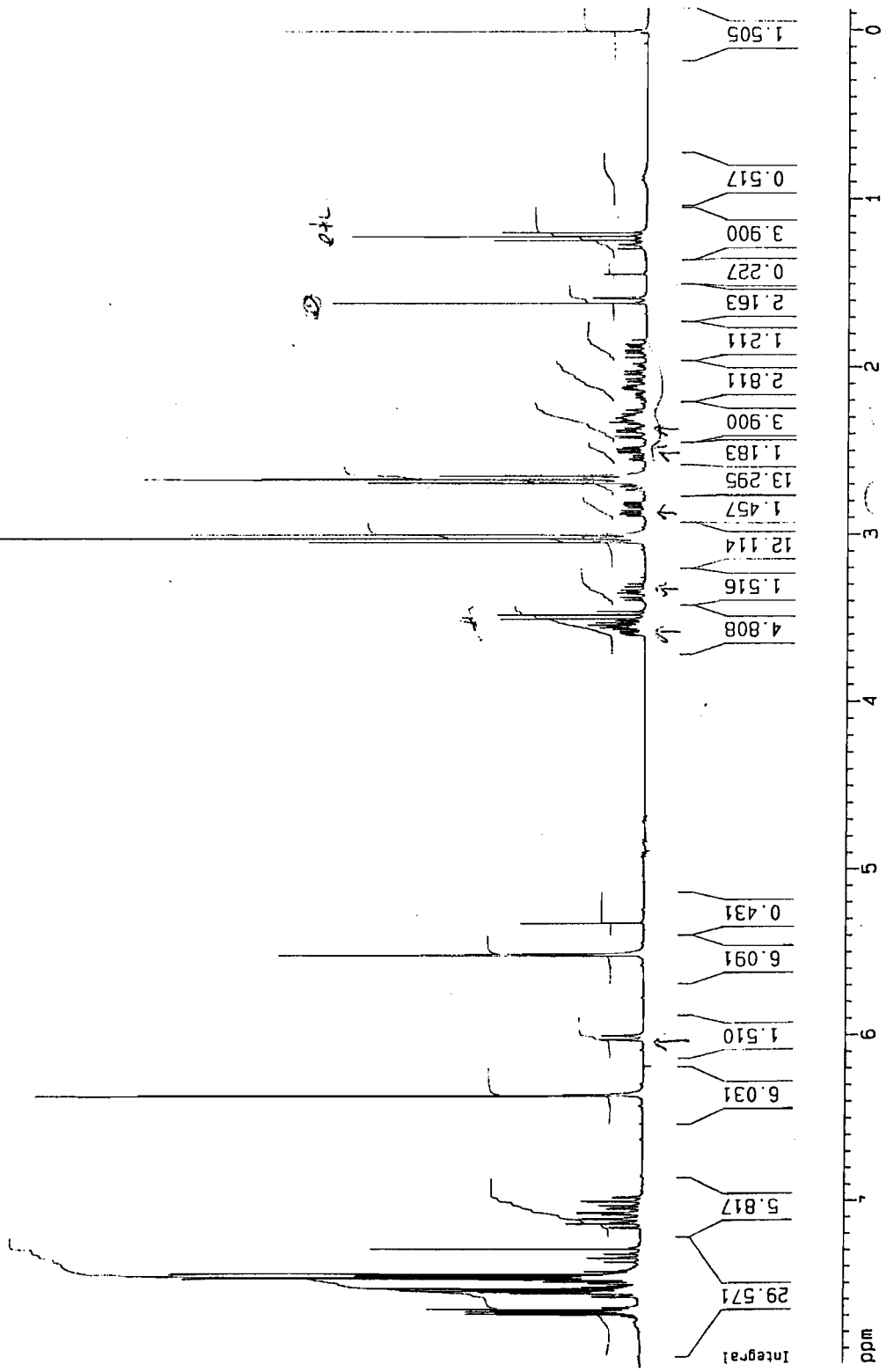
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 NAME tat169  
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 PROCNO 1

F2 - Acquisition Parameters  
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 INSTRUM spect  
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 PULPROG zg30  
 TD 65536  
 SOLVENT CDCl3  
 NS 16  
 DS 2  
 SWH 6172.839 Hz  
 FIDRES 0.094190 Hz  
 AQ 5.3084660 sec  
 RG 362  
 CW 81.000 usec  
 DE 6.00 usec  
 TE 300.0 K  
 D1 1.0000000 sec

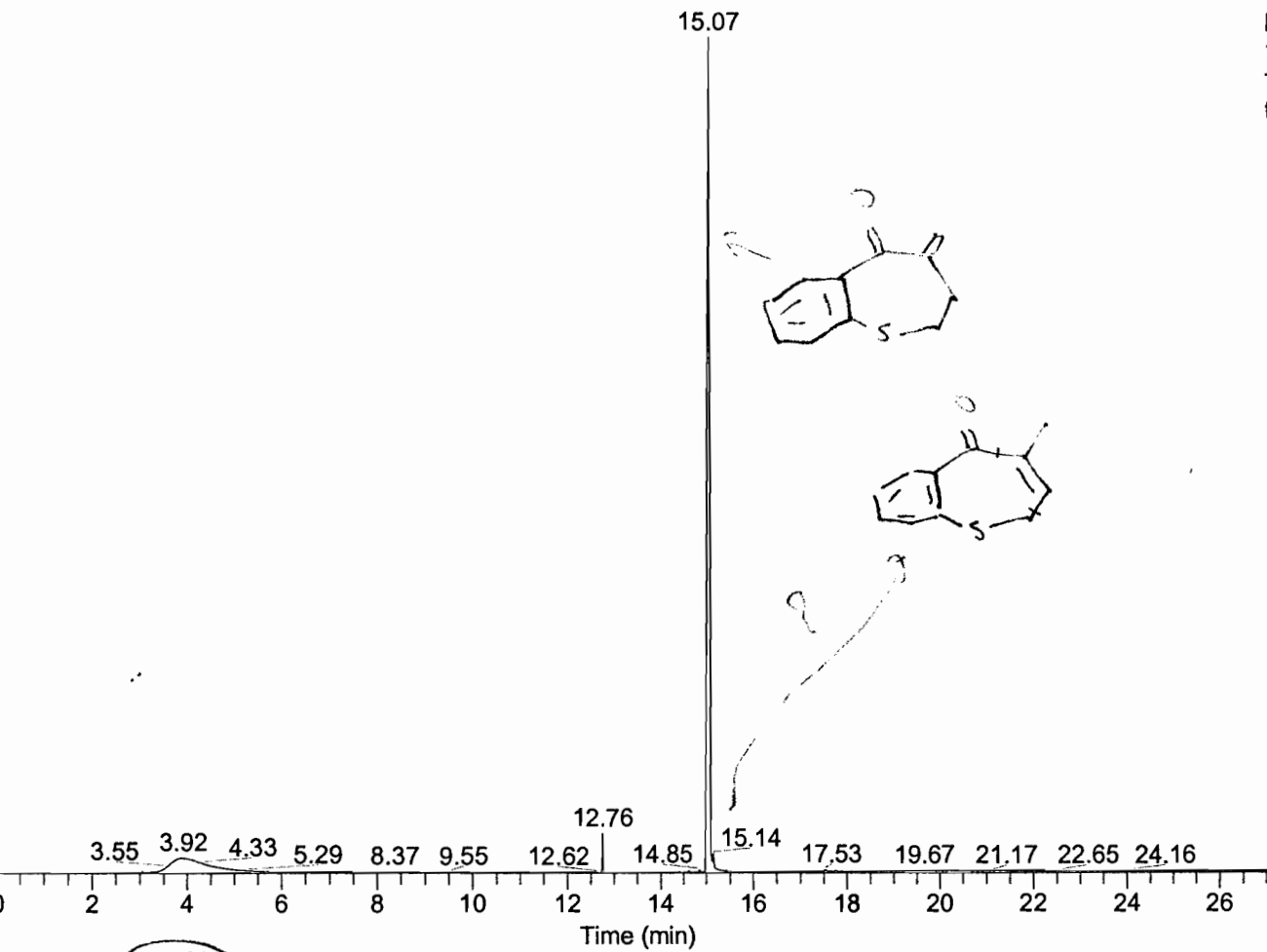
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 P1 11.00 usec  
 PL1 0.00 dB  
 SF01 300.1318534 MHz

F2 - Processing parameters  
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 MCM no  
 SSB 0  
 LB 0.00 Hz  
 GB 0  
 PC 1.00

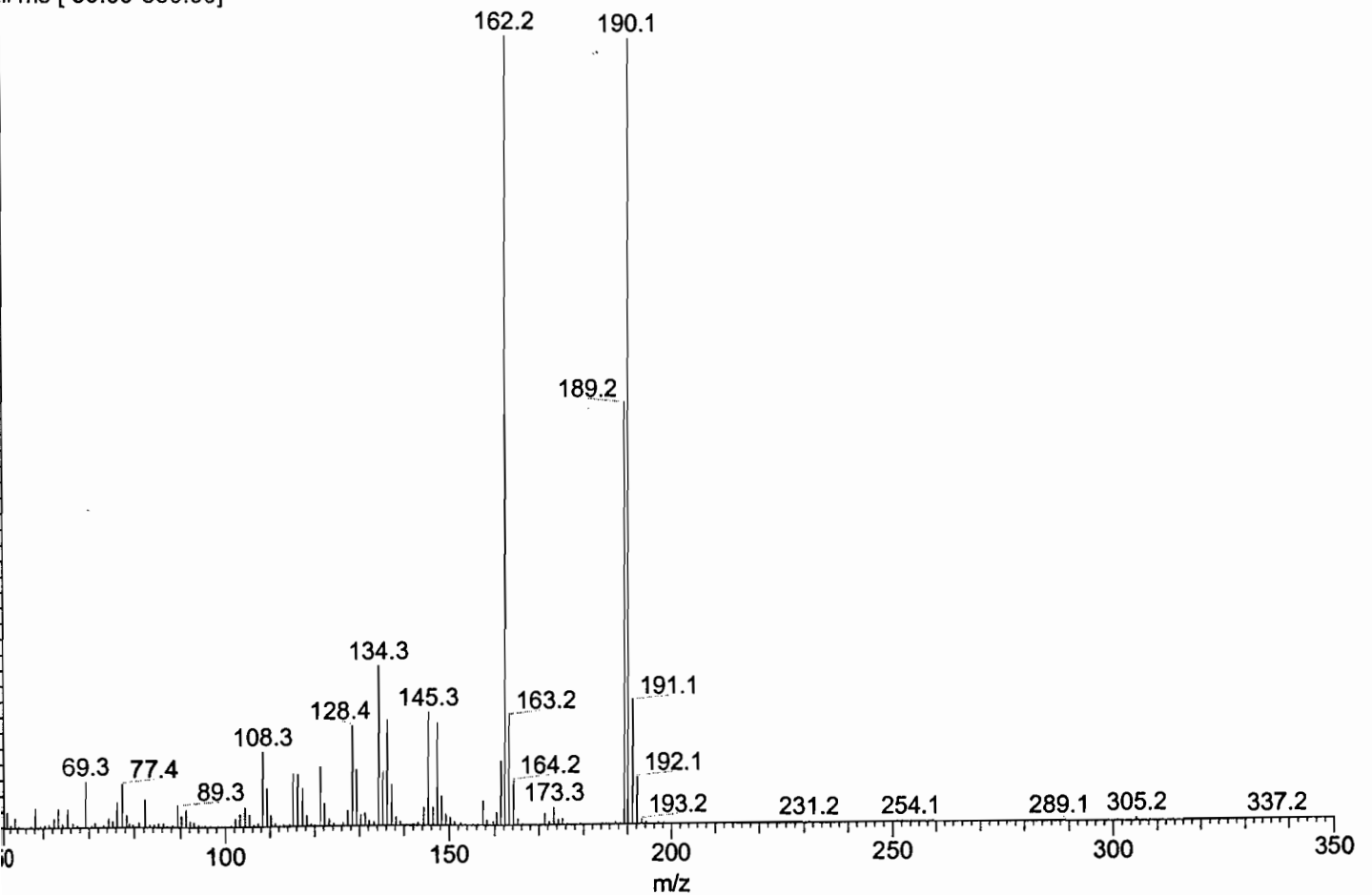
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 F2P -0.124 ppm  
 F2 -37.08 Hz  
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 HZCM 121.85609 Hz/cm

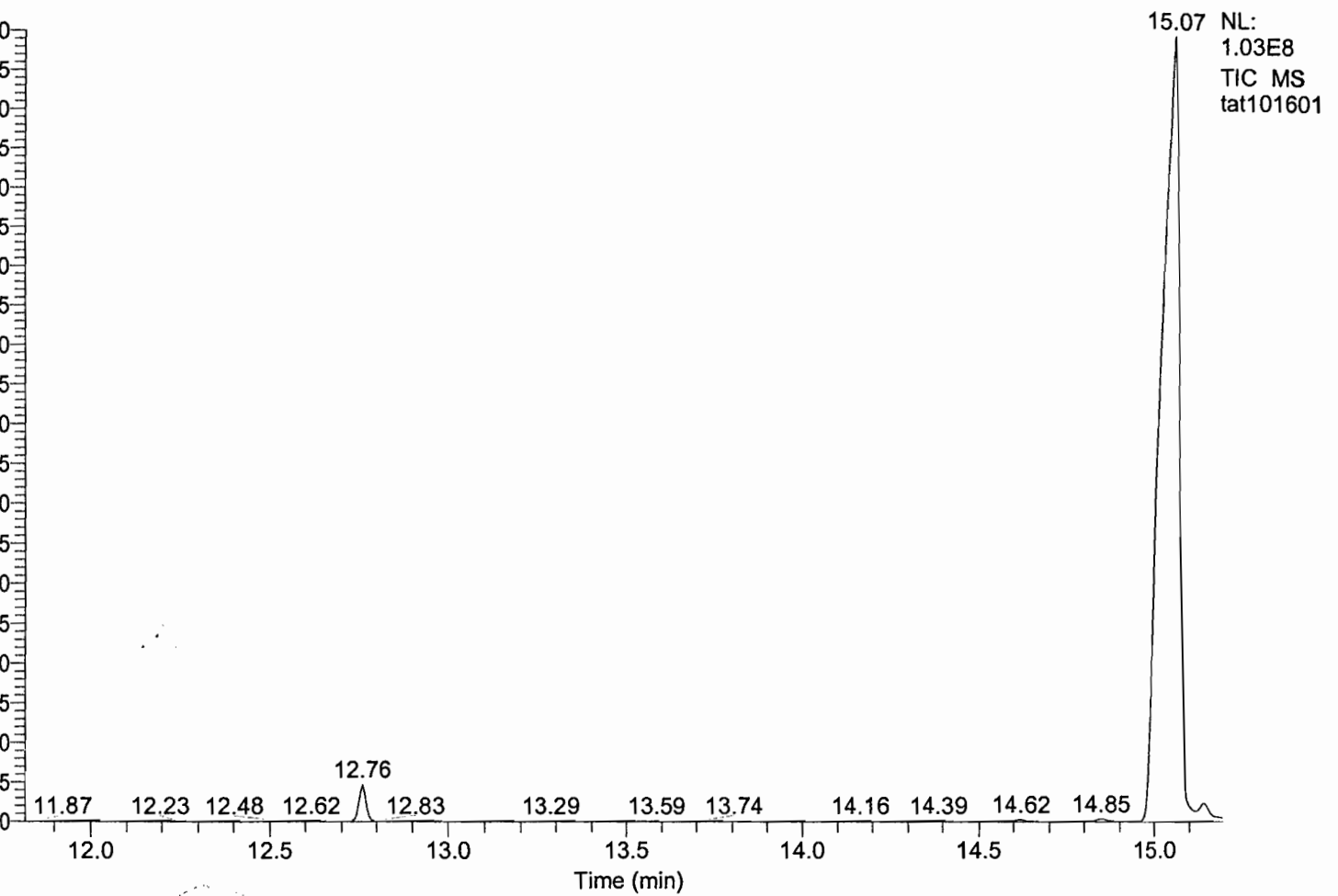


NL:  
1.03E8  
TIC MS  
tat101601

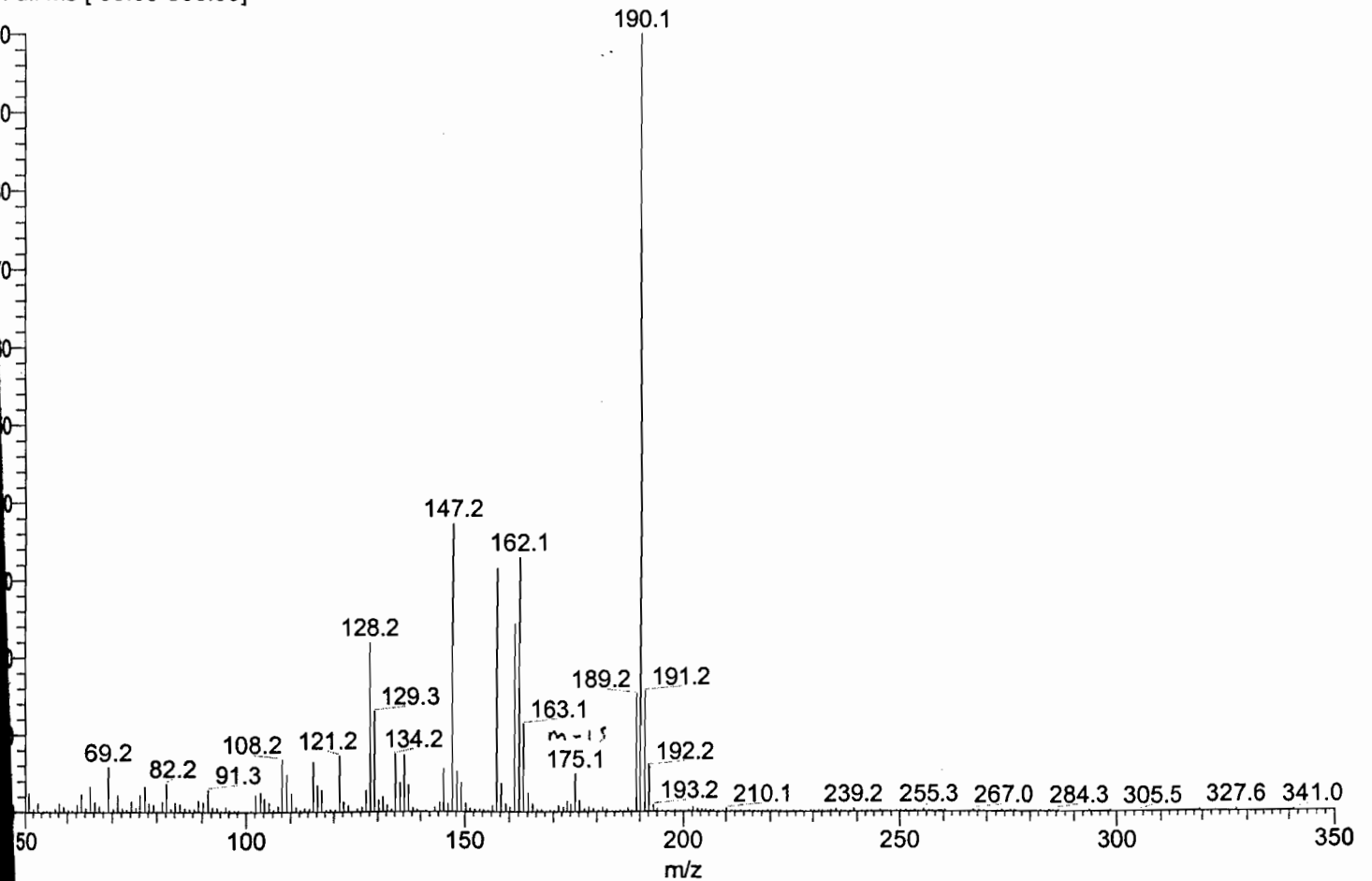


1 #1768 RT: 15.07 AV: 1 NL: 1.93E7  
ll ms [ 50.00-350.00]





601 #1780 RT: 15.14 AV: 1 NL: 4.82E5  
Full ms [ 50.00-350.00]



2  
after Kugel

Mixture containing  
C1=CC=C2C(=C1)C(=O)C2 +  
C1=CC=C2C(=C1)C(=O)C2  
after Kugel

Robt  
distillation  
(Pg 8+19)

Current Data Parameters  
NAME tat169  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20011018  
Time 14.00

INSTRUM spect  
PROBHD 5 mm 880 BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDC13  
NS 16  
DS 2  
SWH 6172.839 Hz  
FIDRES 0.094190 Hz  
AQ 5.3084660 sec  
RG 287.4  
DW 81.000 usec  
DE 6.00 usec  
TE 300.0 K  
D1 1.0000000 sec

\*\*\*\*\* CHANNEL f1 \*\*\*\*\*  
NUC1 1H  
P1 11.00 usec  
PL1 0.00 dB  
SF01 300.1318534 MHz

F2 - Processing parameters  
SI 32768  
SF 300.1300000 MHz  
WDW no  
SSB 0  
LB 0.00 Hz  
GB 0  
PC 1.00

F2 - NMR plot parameters  
CX 20.00 cm  
F1P 8.273 ppm  
F1 2482.84 Hz  
F2P -0.217 ppm  
F2 -65.16 Hz  
PP4CM 0.42448 ppm/cm  
HZCM 127.40013 Hz/cm

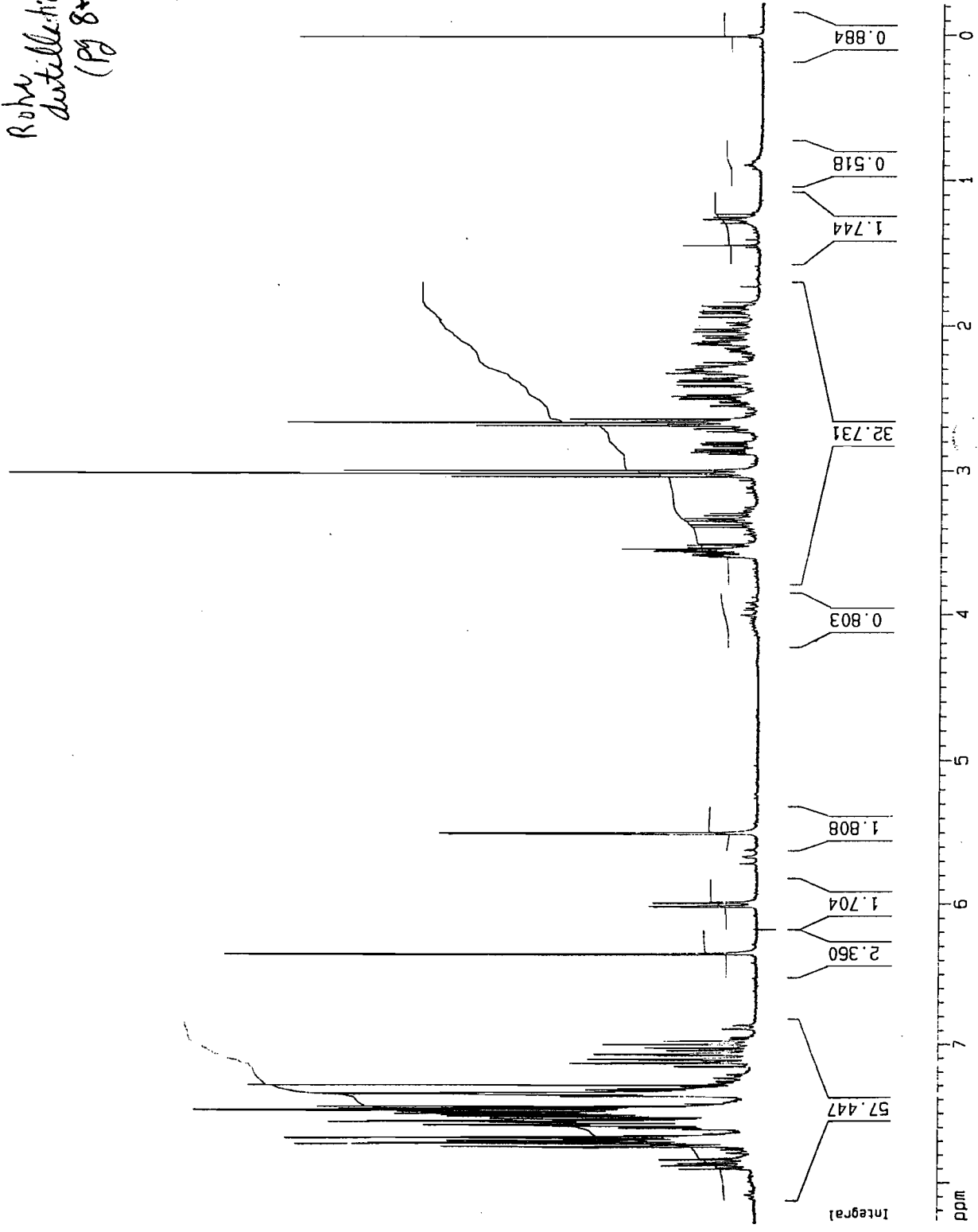
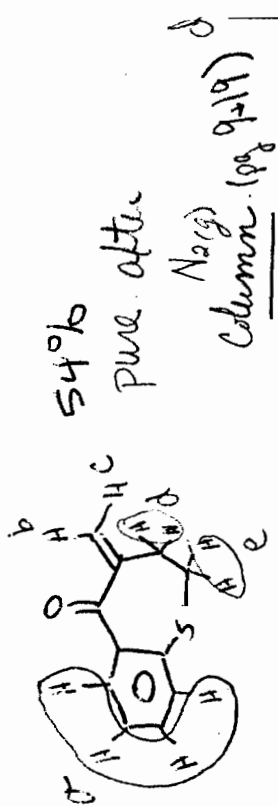


Figure 3



Current Data Parameters  
 NAME tat187  
 EXPNO 1  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20020117  
 Time 17.02  
 INSTRUM spect  
 PROBHD 5 mm BBO BB-  
 PULPROG zg30  
 TD 65536  
 SOLVENT CDC13  
 NS 16  
 DS 2  
 SMH 6172.839 Hz  
 FIDRES 0.094190 Hz  
 AQ 5.3084660 sec  
 RG 456.1  
 DM 81.000 usec  
 DE 6.00 usec  
 TE 300.0 K  
 D1 1.00000000 sec

\*\*\*\*\* CHANNEL f1 \*\*\*\*\*  
 NUC1 1H  
 P1 11.00 usec  
 PL1 0.00 dB  
 SF01 300.1318534 MHz

F2 - Processing parameters  
 SI 32768  
 SF 300.1300000 MHz  
 WDW no  
 SSB 0  
 LB 0.00 Hz  
 GB 0  
 PC 1.00

1D NMR plot parameters  
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 F1 2444.93 Hz  
 F2 -0.141 ppm  
 F2 0.41438 ppm/cm  
 PPMCM 124.36679 Hz/cm

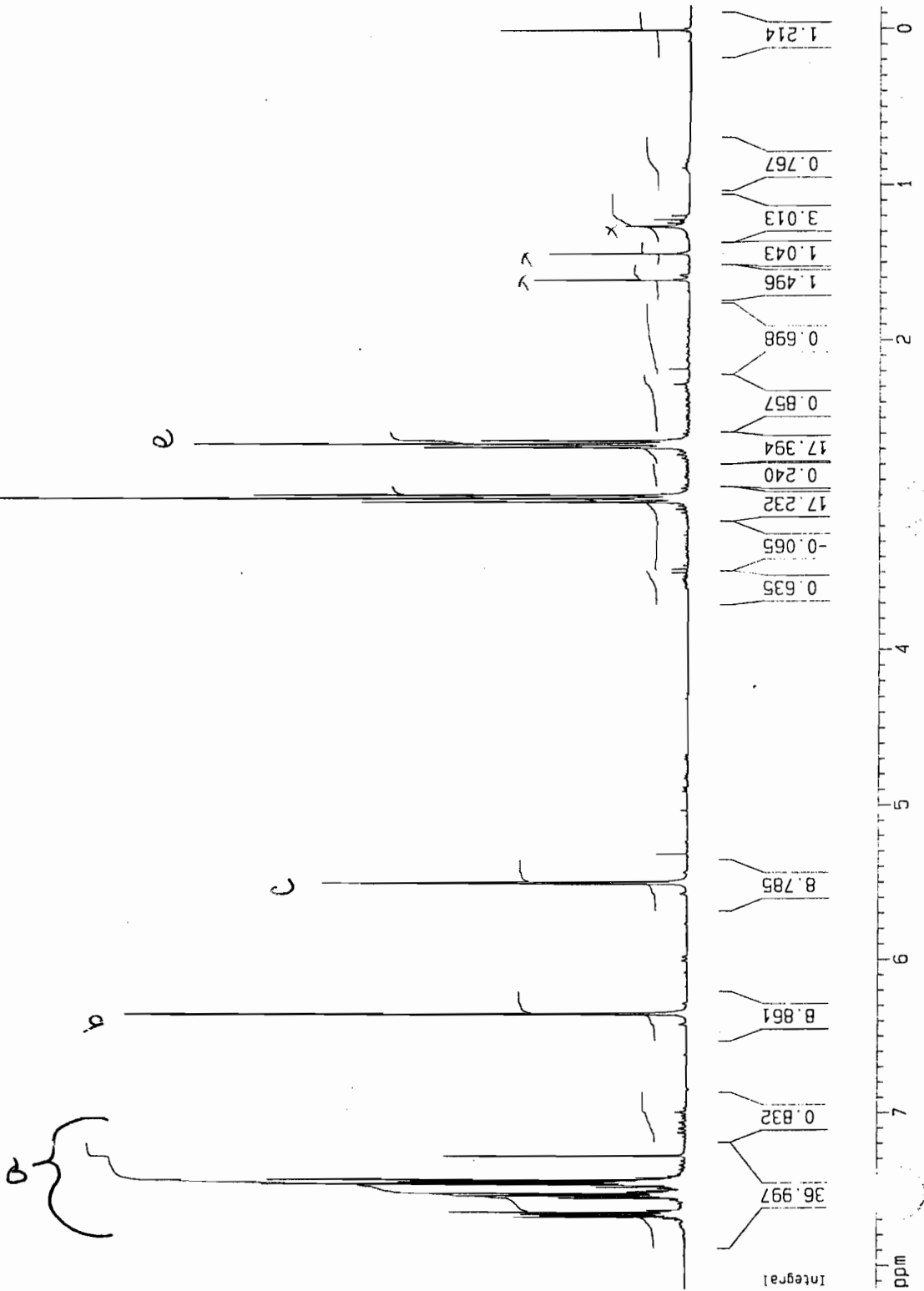
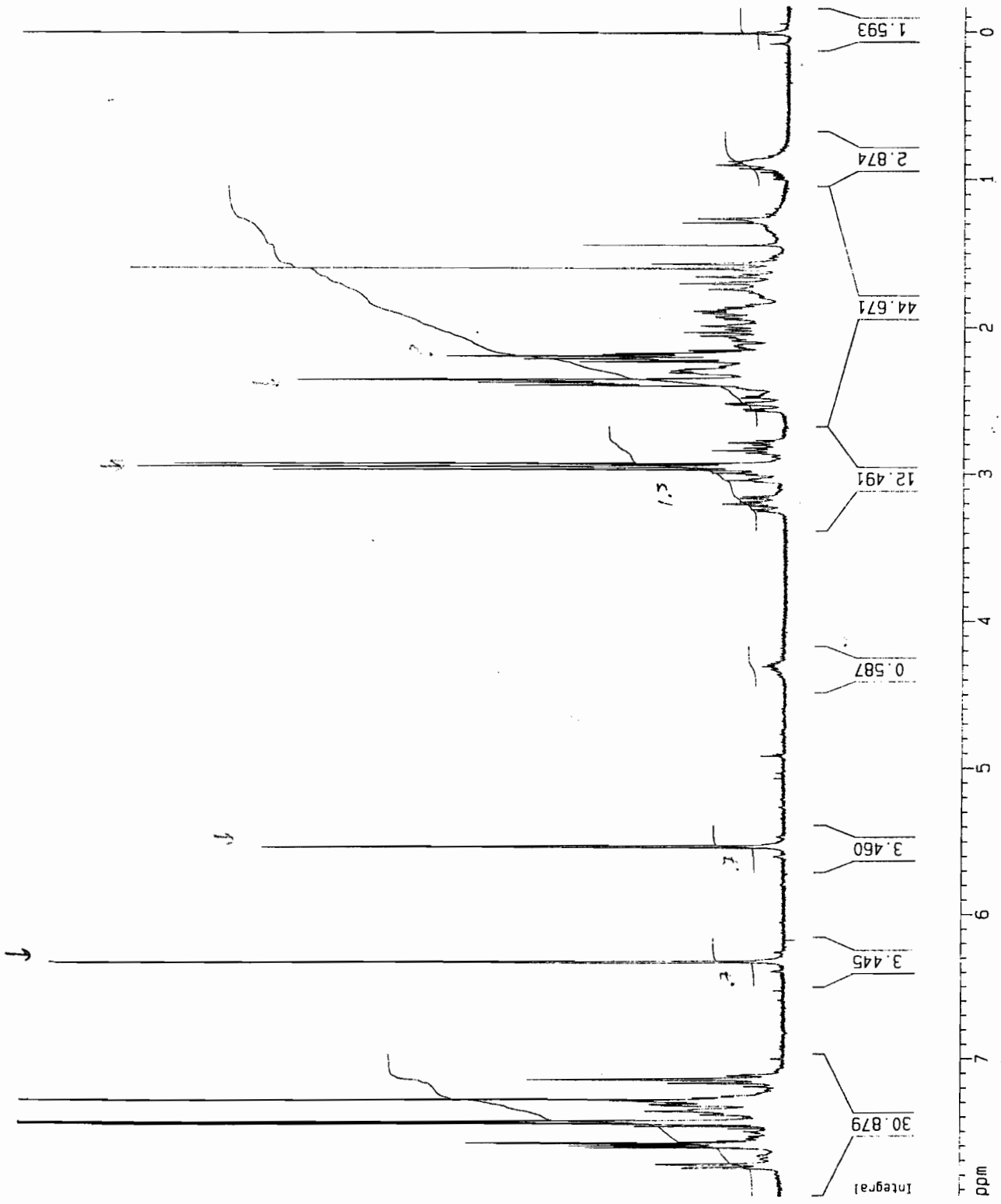


Figure 4

After 2 columns (pg 19-20)

Mixture Containing



Current Data Parameters  
NAME tat179  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20011120  
Time 9.46  
INSTRUM spect  
PROBHD 5 mm BBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 16  
DS 2  
SWH 6172.839 Hz  
FIDRES 0.094190 Hz  
AQ 5.3084660 sec  
RG 322.5  
DM 81.000 usec  
DE 6.00 usec  
TE 300.0 K  
D1 1.0000000 sec

\*\*\*\*\* CHANNEL f1 \*\*\*\*\*  
NUC1 1H  
P1 11.00 usec  
PL1 0.00 dB  
SF01 300.1318534 MHz

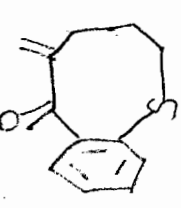
F2 - Processing parameters  
SI 32768  
SF 300.1300000 MHz  
WDW no  
SSB 0  
LB 0.00 Hz  
GB 0  
PC 1.00

1D NMR plot parameters  
CX 20.00 cm  
F1P 7.944 ppm  
F1 2384.26 Hz  
F2p -0.167 ppm  
F2 -49.99 Hz  
PPMCH 0.40553 ppm/cm  
HZCM 121.71262 Hz/cm



Figures

mixture containing  
after NMR column (pg 20).



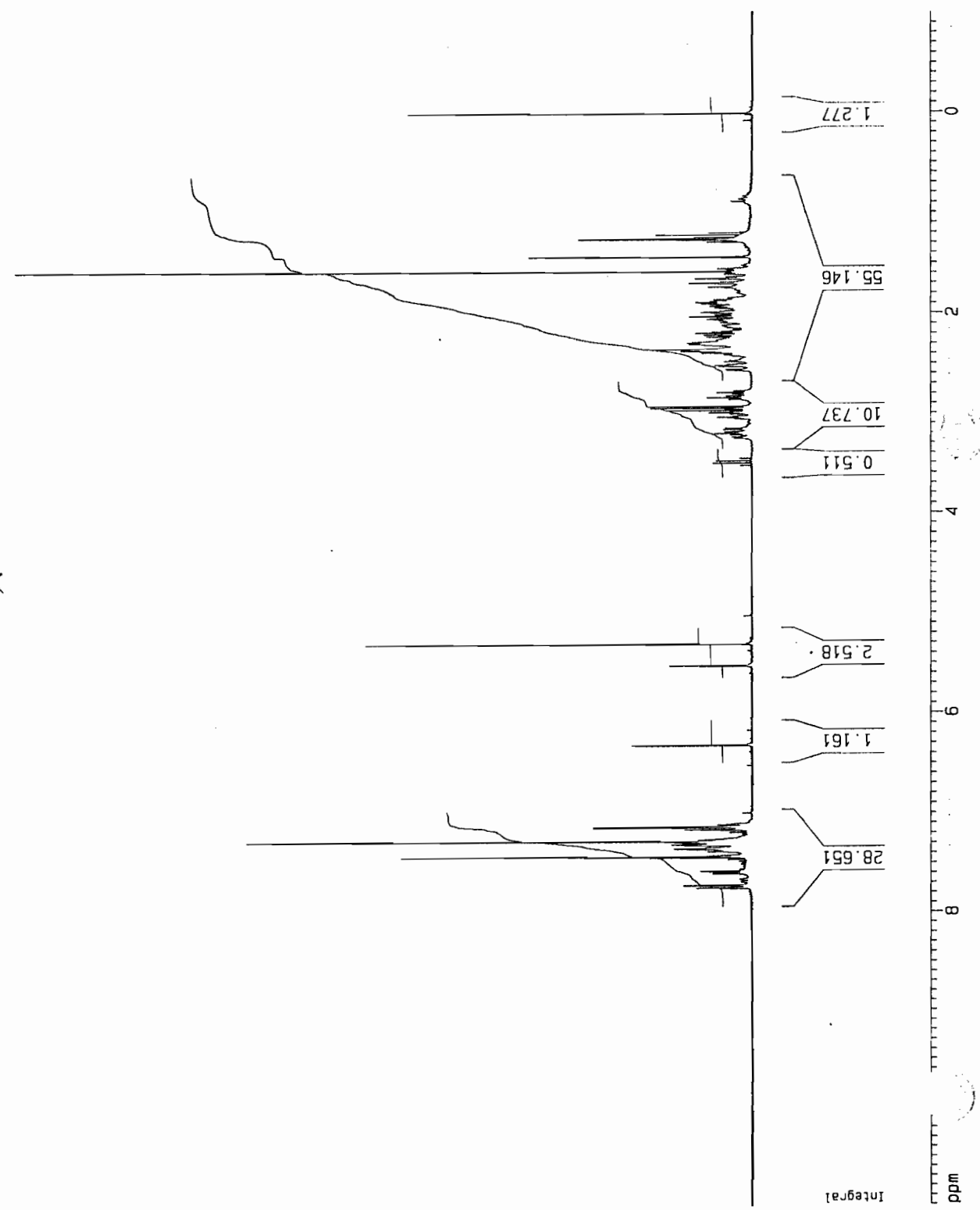
Current Data Parameters  
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 EXPNO 1  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20020124  
 Time 14.30  
 INSTRUM spect  
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 PULPROG zg30  
 TD 65536  
 SOLVENT CDC13  
 NS 16  
 DS 2  
 SWH 6172.839 Hz  
 FIDRES 0.094190 Hz  
 AQ 5.3084660 sec  
 RG 406.4  
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 DE 6.00 usec  
 TE 300.0 K  
 O1 1.00000000 sec

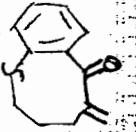
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 SFO1 300.1318534 MHz

F2 - Processing parameters  
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 SF 300.1300000 MHz  
 WDW no  
 SSB 0  
 LB 0.00 Hz  
 GB 0  
 PC 1.00

10 NMR plot parameters  
 CX 20.00 cm  
 F1P 11.000 ppm  
 F1 3301.43 Hz  
 F2P -1.000 ppm  
 F2 -300.13 Hz  
 PPMCM 0.60000 ppm/cm  
 HZCM 180.07800 Hz/cm



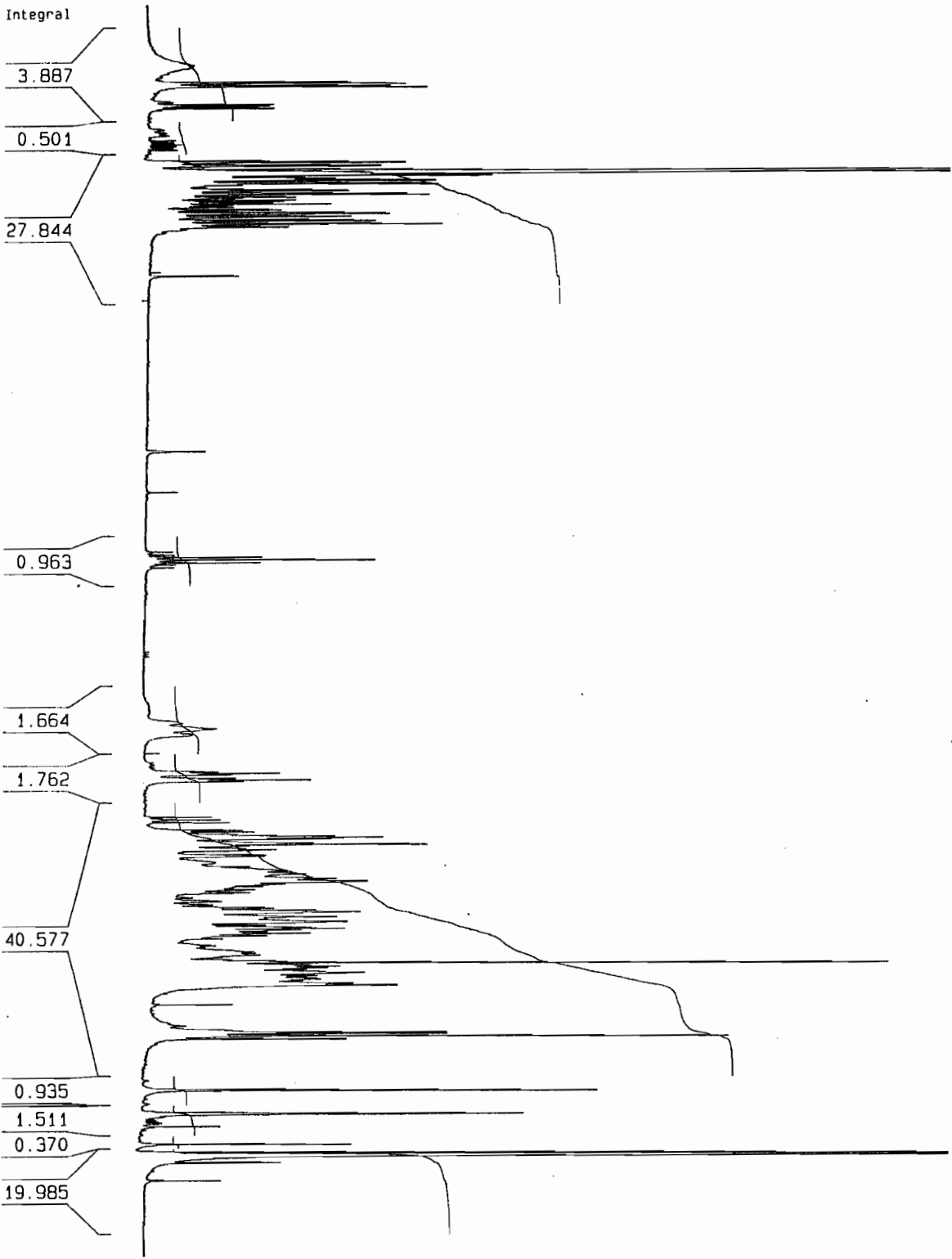
mixture containing  
after heating



(pg 20)

MT-I-91  
C<sub>6</sub>D<sub>6</sub>

Figure 6



Current Data Parameters  
NAME lat191a  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20020129  
Time 18.29

INSTRUM spect  
PROBHD 5 mm BBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 128  
DS 0

SWH 6172.839 Hz  
FIDRES 0.094190 Hz  
AQ 5.3084660 sec  
RG 203.2  
DM 81.000 usec  
DE 6.00 usec  
TE 300.0 K  
D1 2.00000000 sec

\*\*\*\*\* CHANNEL f1 \*\*\*\*\*  
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P1 11.00 usec  
PL1 0.00 dB  
SFO1 300.1318534 MHz

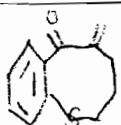
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WDW no  
SSB 0  
LB 0.00 Hz  
GB 0  
PC 1.00

10 NMR plot parameters  
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F2P -0.773 ppm  
F2 -231.99 Hz  
PPMCM 0.45733 ppm/cm  
HZCM 137.25847 Hz/cm

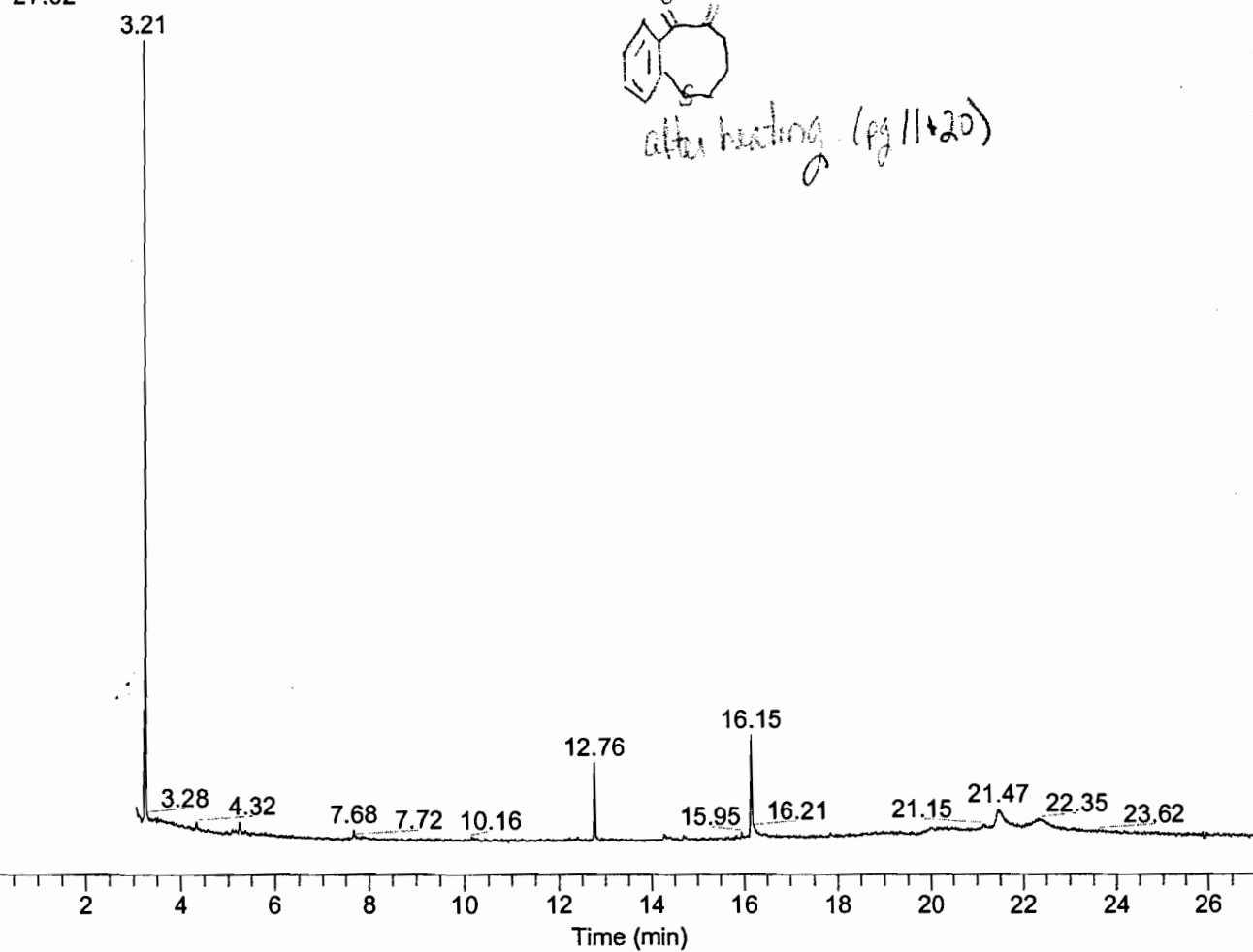
27.02

2002 02:00:00 M

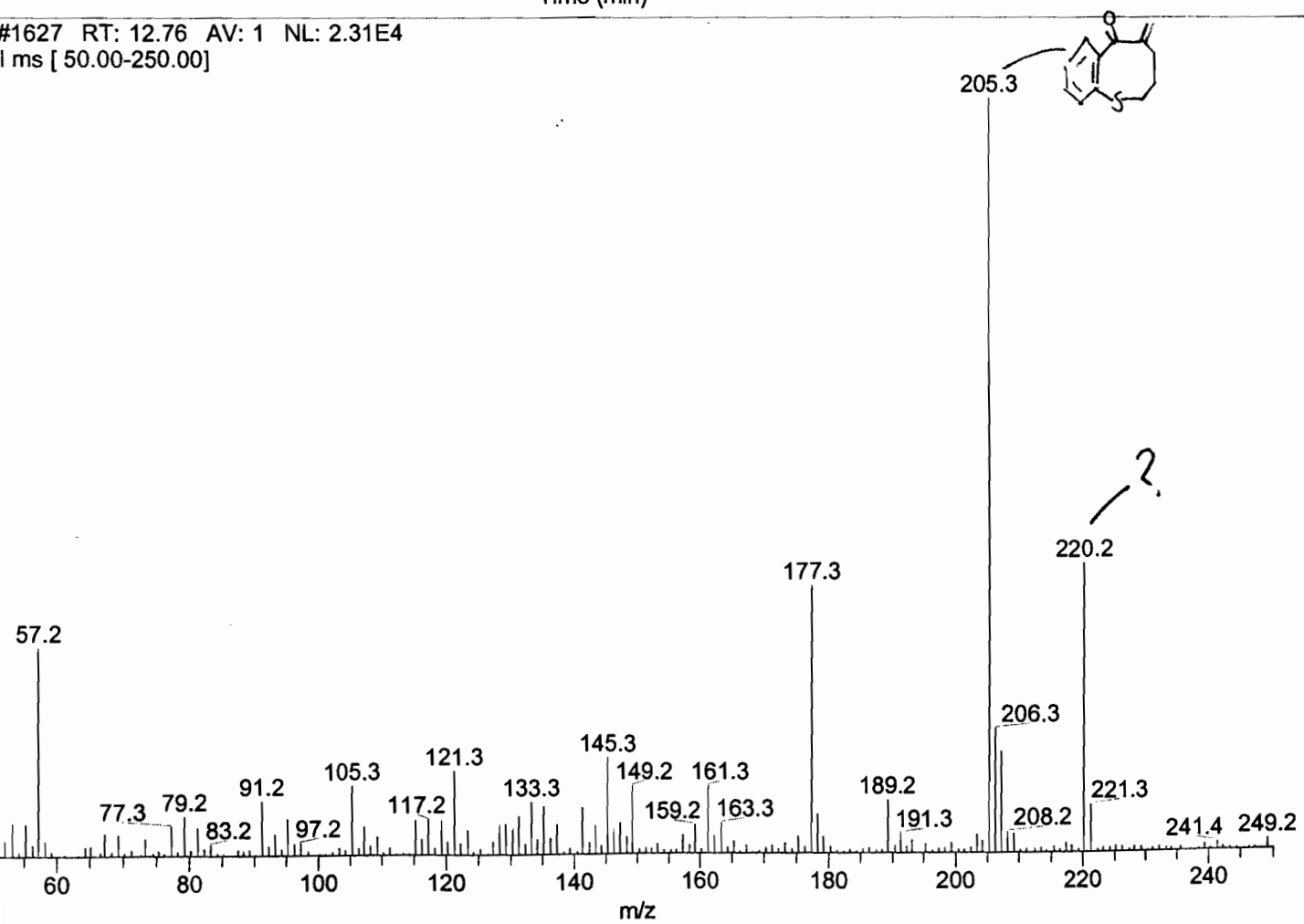
NL:  
9.58E5  
TIC MS  
tat91b01



after heating (pg 11+20)



#1627 RT: 12.76 AV: 1 NL: 2.31E4  
1 ms [ 50.00-250.00]





# Figure 8

Current Data Parameters  
 NAME lat1103C  
 EXPNO 10  
 PROCNO 1

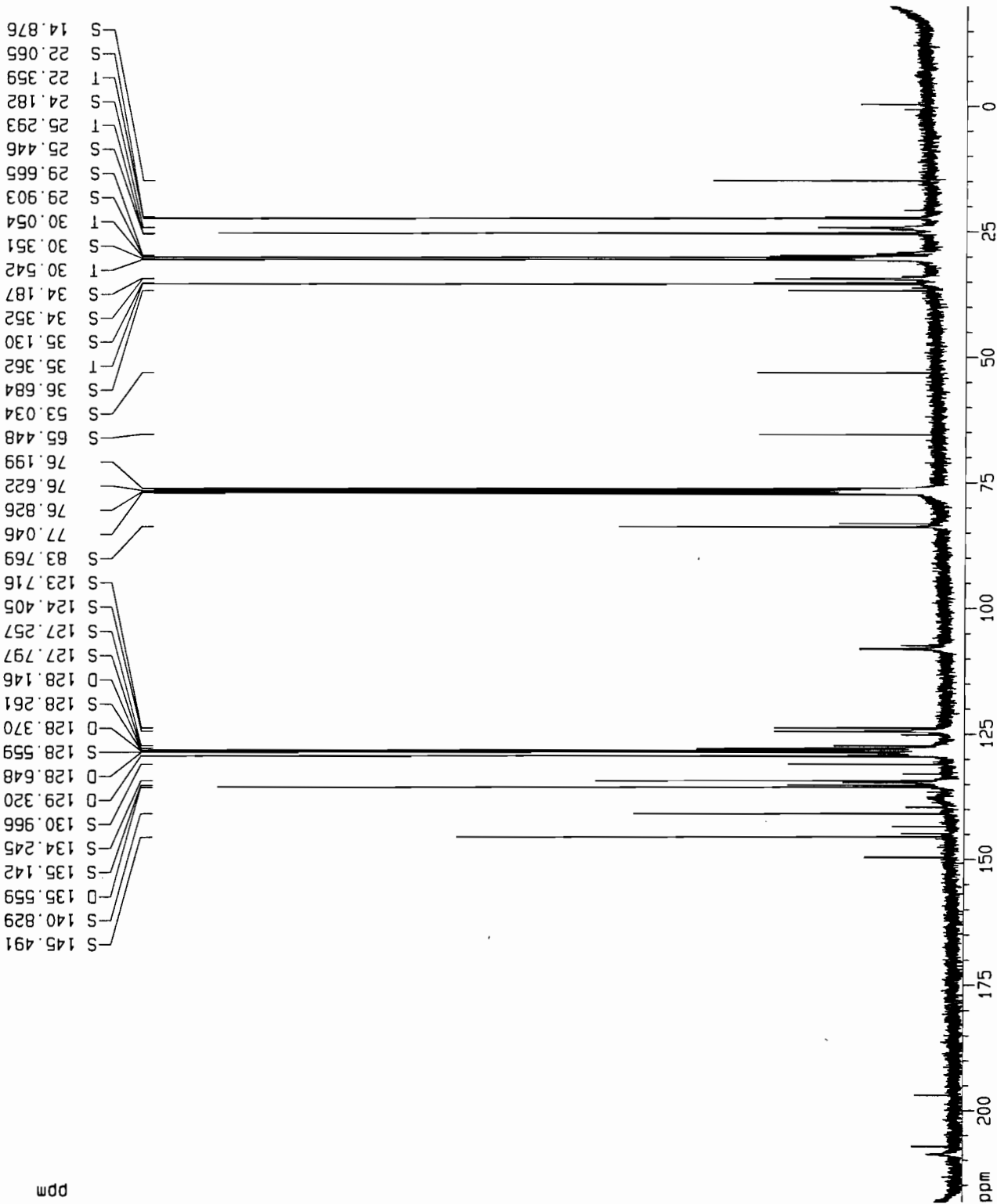
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 SOLVENT CDCl3  
 NS 20000  
 DS 2  
 SWH 17985.611 Hz  
 FIDRES 0.274439 Hz  
 AQ 1.8219508 sec  
 RG 16384  
 DW 27.800 usec  
 DE 6.00 usec  
 TE 300.0 K  
 D1 2.00000000 sec  
 d11 0.03000000 sec  
 d12 0.00002000 sec

===== CHANNEL f1 =====  
 NUC1 13C  
 P1 7.10 usec  
 PL1 -1.50 dB  
 SF01 75.4752653 MHz

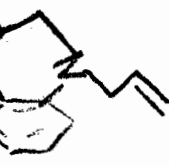
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 PL12 18.00 dB  
 PL13 18.00 dB  
 SF02 300.1312005 MHz

F2 - Processing parameters  
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 SF 75.4677812 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.40

1D NMR plot parameters  
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 F1 16476.84 Hz  
 F2P -19.992 ppm  
 F2 -1508.77 Hz  
 PPMCK 11.91609 ppm/cm  
 HZCM 899.28058 Hz/cm



2-diallylamine = benzene amine (1 g)



Current Data Parameters  
 NAME tat057  
 EXPNO 1  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20010801  
 Time 14.37  
 INSTRUM spect  
 PROBHD 5 mm BBO BB-  
 PULPROG zg30  
 TO 65536  
 SOLVENT CDC13  
 NS 16  
 DS 2  
 SWH 6172.839 Hz  
 FIDRES 0.094190 Hz  
 AQ 5.3084660 sec  
 RG 143.7  
 DW 81.000 usec  
 DE 6.00 usec  
 TE 300.0 K  
 D1 1.0000000 sec

===== CHANNEL f1 =====  
 NUC1 1H  
 P1 11.00 usec  
 PL1 0.00 dB  
 SF01 300.1318534 MHz

F2 - Processing parameters  
 SI 32768  
 SF 300.1300000 MHz  
 WDW no  
 SSB 0  
 LB 0.00 Hz  
 GB 0  
 PC 1.00

ID NMR plot parameters  
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 F1 3248.14 Hz  
 F2P -0.526 ppm  
 F2 -157.82 Hz  
 PPMCM 0.56741 ppm/cm  
 HZCM 170.29820 Hz/cm

