Rhodium Catalyzed Hydroacylation: Synthesis of Biologically Active Benzothiepinones

Presented to the faculty of Lycoming College in partial fulfillment of the requirements for Departmental Honors in Chemistry

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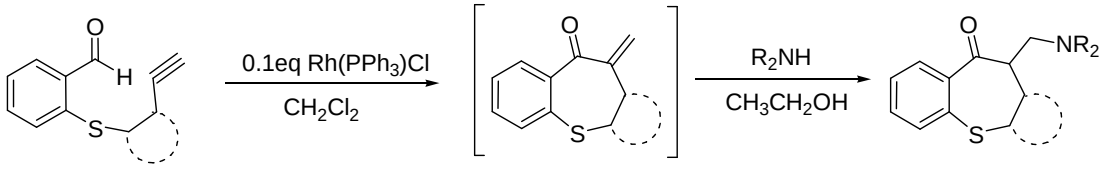
Abstract

Previous research in our lab has revealed that Ω-alkynals that contain a sulfide functional group can be cyclized via a chelation-assisted intramolecular hydroacylation, affording high yields of benzothiepinone products. We have now used this chemistry to develop a rapid route into aminomethylbenzothiepinones, and analogous tricyclic ring systems, by tandem intramolecular hydroacylation-Michael addition (Scheme 1). In this procedure Ω-alkynals cyclize to an enone intermediate that can then undergo Michael addition with a variety of secondary amines. Using this one-pot procedure, we avoid isolation of the reactive enone intermediate. Isolation of the aminomethyl-substituted benzothiepinone products is facile and yields for the two step sequence are good.

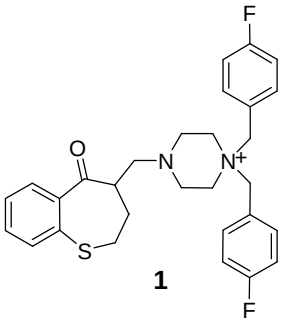
Scheme 1



Introduction and Background

Historically, the synthesis of medium rings has proven to be difficult, due to entropic factors and non-bonding interactions that occur at the transition state of the cyclization. Medium rings are core structures in many biologically active compounds and natural products; therefore, an efficient methodology for their synthesis is desired. Transition metal-catalyzed cyclizations have proven to be some of the most attractive strategies for the synthesis of medium-ring compounds.[1] Therefore, we hope to develop a facile synthesis of aminomethylbenzothiepinones and analogous tricyclic ring systems using a rhodium catalyzed hydroacylation strategy.

A variety of aminomethylbenzothiepinones and dibenzothiepinones, which contain a 7-membered ring, are under patent or investigation as potential pharmaceuticals.[2] For example, compound **1** is patented as a potential vasodilator, compound **2** as a potential analgesic, and compound **3** as a muscle relaxant.[3,4,5] Compounds **1** and **2** were previously



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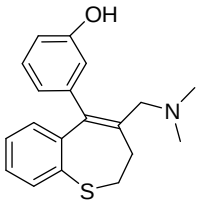

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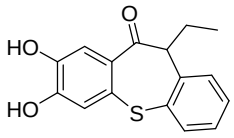
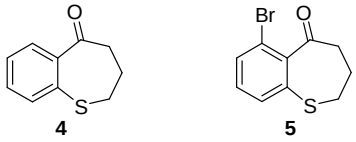


3

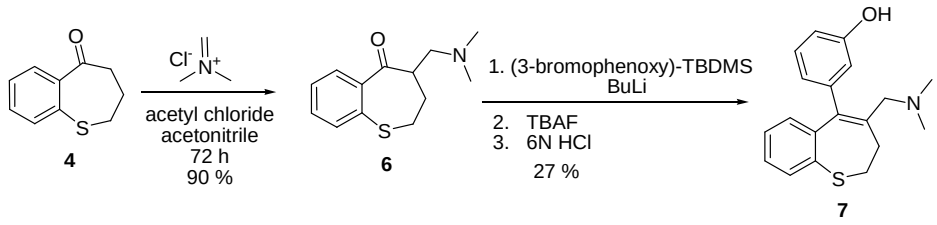
prepared from 3,4-dihydro-2H-benzo[b]thiepin-5-one, **4**, which is presently not commercially available. Methods for the construction of the 3,4-dihydro-2H-benzo[b]thiepin-5-one core involve harsh reaction conditions such as the polyphophoric acid mediated ring closure of phenylthiobutyric acid,[6,7,8,9] and the multi-step protocol for

ring expansion of thiochromanes.[10,11] The bromine-substituted analog, **5**, is available by special request from Focus Synthesis LLC at a cost of $1900/g. The synthesis of compound **2** is illustrated in Scheme 1.[4] Treating **4** with dimethylmethyleneimmonium



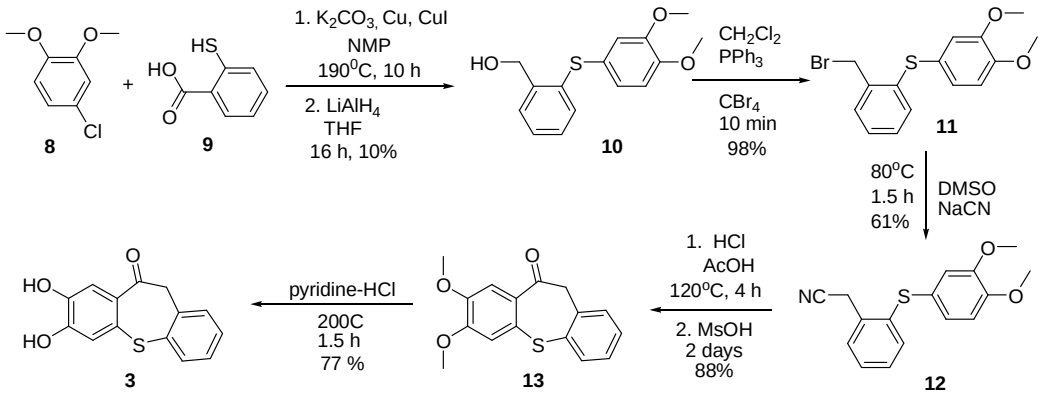
chloride in the presence of acetylchloride yields the corresponding aminomethylbenzothiepinone, **6**. Compound **6** was then treated with TBDMS-protected 3-bromophenol and butyl lithium. The addition product was then desilylated by the addition of 1M tetrabutylammonium fluoride in THF, and treated with 6N HCl to eliminate water yielding the desired product, **7**. Similarly, compounds in the

Scheme 1



dibenzothiepine class such as **3** require lengthy, inefficient syntheses which make use of harsh conditions and long reaction times (Scheme 2).[5]

Scheme 2

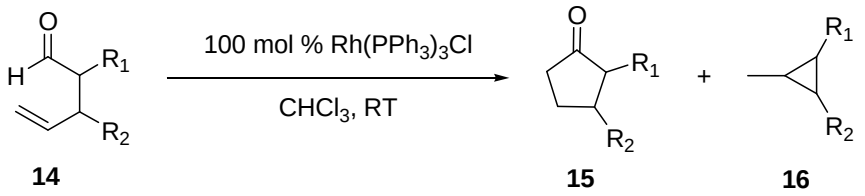


4-Chloro-1,2-dimethoxybenzene, **8**, is coupled to 2-mercapto-benzoic acid, **9**, via a Cu-promoted coupling reaction which yields only 10% product and requires long reaction times and high temperatures. The alcohol, **10**, is then treated with PPh_3 and CBr_4 to produce the corresponding bromide, **11**, which then undergoes substitution with NaCN to form nitrile, **12.** The nitrile, **12,** is then heated in hydrochloric acid and acetic acid to form a 7-membered immine species which upon stirring in methanesulfonic acid is hydrolyzed to the ketone yielding dimethoxybenzothiepinone, **13**. Heating **13** with pyridine hydrochloride furnishes the desired compound, **3**, in 4% overall yield. Clearly a more efficient synthesis of these compounds would be beneficial for further studies.

Rhodium(I) catalyzed hydroacylation has been used to form cyclopentanones from unsaturated aldehydes, but has had limited success in the construction of larger ring systems.[6-8] We have examined the utility of rhodium catalyzed hydroacylation and tandem hydroacylation-Michael addition reactions in the synthesis of aminomethyl-substituted benzothiepinones and analogous tricyclic ring systems. These reactions employ a new method in the formation of medium ring compounds via chelation-assisted hydroacylation, which makes use of a Lewis-basic tether atom.

Rhodium-catalyzed hydroacylation was first reported by Sakai in 1972 in which a Rh(I)-mediated hydroacylation of 4-alkenals, afforded cyclopentanone products, with cyclopropane derivatives as the significant by-products due to decarbonylation of the substrate (Scheme 3).[12] The proposed mechanism by which rhodium converts 4-pentenals

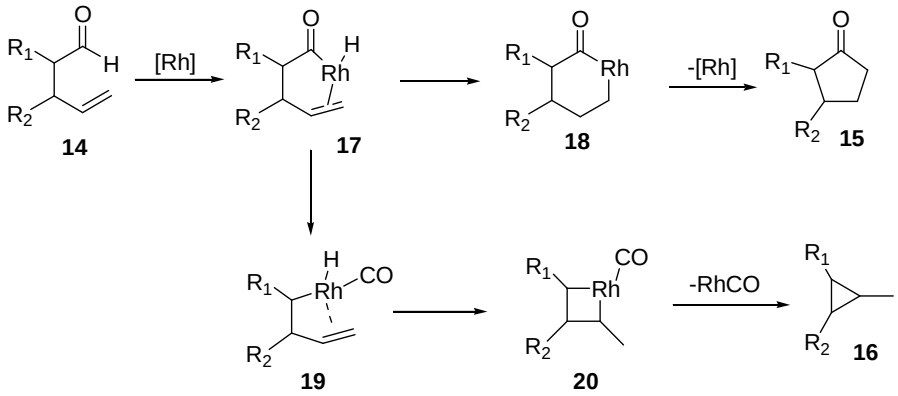
Scheme 3



14 **15** **16**

to cyclopentanones through hydroacylation (Scheme 4) involves oxidative addition of rhodium(I) into the aldehyde C-H bond to give the acylhydridorhodium(III) complex, **17**. Next, the alkene undergoes insertion into the rhodium-hydride bond, followed by reductive elimination of the metal to yield the cyclopentanone product, **15**, and regenerate the rhodium(I) catalyst.[13] Cyclopropane by-products presumably result from decarbonylation, which is a competing pathway in hydroacylation. It is likely that deinsertion of the carbonyl before insertion of the alkene will lead to the metallocyclobutane intermediate, **20**. This intermediate can then undergo reductive elimination to form cyclopropane derivative, **16**. This reaction was low yielding (30 % for cyclopentanone), non-catalytic, and was limited to the synthesis of 5-membered carbocycles.

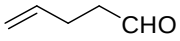
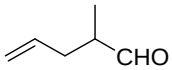
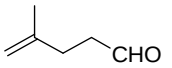
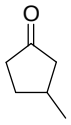
Scheme 4



14 **17** **18** **15** **19** **20** **16**

Lochow and Miller subsequently reported a catalytic version of the cyclization. Using 10 mol % of Wilkinson's catalyst in ethylene-saturated chloroform, a 72 % yield of cyclopentanone was obtained.[14] Ethylene occupies any open coordination sites on the metal, preventing decarbonylation of the substrate. Larock has also reported a synthesis of cyclopentanones via rhodium(I)-catalyzed intramolecular hydroacylation of unsaturated aldehydes, using a variety of $RhCl(PAr_3)_3$ catalysts to afford cyclopentanones in up to 98 % yield (Table 1).[15]

Table 1

Aldehyde	ligand	% catalyst	product	% yield
	$P(PhOCH_3)_3$	50 10		98 88
	$P(PhOCH_3)_3$	50 10		51 24
	$P[Ph(N(CH_3)_2)]_3$	50		98

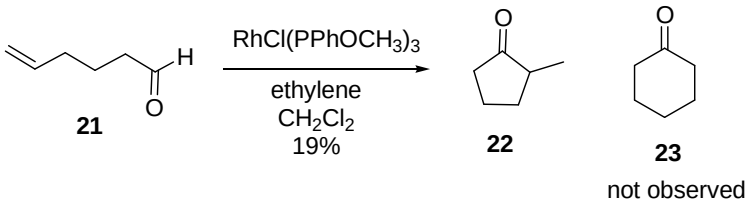
A catalyst screening showed that rhodium complexes of the form $RhCl(PAr_3)_3$ were unsurpassed in reactivity compared to other rhodium complexes such as $RhI(PPh_3)_3$, $RhNO(PPh_3)_3$, or those prepared in situ by the addition of $AgClO_4$ and $AgBF_4$ to $RhCl(PPh_3)_3$. Other metal complexes utilizing Ru(II), Ir(I), Pd(0), and Pd(II) showed no reactivity (Table 2). A variety of phosphine ligands were also screened for the complex $RhCl(PAr_3)_3$ in which three triaryl phosphines looked promising, namely tri-*p*-tolylphosphine, tri-*p*-anisylphosphine, and tris(*p*-di-methylaminophenyl)phosphine. The

Table 2

Complex	Yield of Cyclopentanone
$RhCl(PPh_3)_3$	47
$RhI(PPh_3)_3$	27
$Rh(NO)(PPh_3)_3$	0
$RhCl(PPh_3)_3 + AgClO_4$	11
$RhCl(PPh_3)_3 + AgBF_4$	0
$RhCl(CH_2{=}{=}CH_2)[P(c\text{-}C_6H_{11})_3]_2$	trace
$RhCl(N_2)[P(c\text{-}C_6H_{11})_3]_2$	0
$RhCl(CO)(PPh_3)_3$	0
$RhCl(CO)[P(Ph\text{-}p\text{-}OMe)_3]_2$	0
$RhH(CO)(PPh_3)_3$	trace
$RhH(PPh_3)_4$	0
$RhCl(H)(PPh_3)_3$	0
$IrH(CO)(PPh_3)_3$	0
$IrCl(N_2)(PPh_3)_2$	0
$Pd(PPh_3)_4$	0
$PdCl_2(PPh_3)_2$	0

basicity of the ligand seemed to have the most important influence on reactivity. Less basic arylphosphines, such as the four described previously, were more efficient than more basic trialkylphosphines such as triethyl, tributyl, and tricyclohexyl phosphine. In an attempt to apply this chemistry to the synthesis of α,β-unsaturated ketones, acetylenic aldehydes such as 4-pentynal, 5-hexynal, and 5-heptynal were treated with 50 mol % of rhodium(I) catalyst. After 2 days, the reactions yielded no cyclic ketones; only decarbonylation products were observed. Larock also showed that reacting hexenal **21** with a rhodium catalyst produces only the methylcyclopentanone, **22**, and not the corresponding cyclohexanone, **23**, as would be expected (Scheme 5). Functional group compatibility was screened by running the reaction in the presence of additives containing various functional groups. Cyclopentane product was obtained when carboxylic acids, esters, nitriles, ketones, primary bromides, and alcohols were present

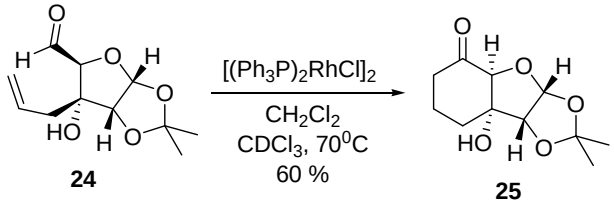
Scheme 5



but amines gave significantly reduced yields. Amines could affect the reaction by complexing to the catalyst and inactivating it. Also, allyl amines are prone to isomerization to the corresponding enamine by rhodium catalysts.

About a decade after Larock had shown that hexenals undergo hydroacylation to form methylcyclopentanones, Gable stumbled upon the discovery that some strained systems may cyclize to form cyclohexanones.[16] In an attempt to cyclize 3-C-alkenyl pentodialose derivatives to form 5-5-5 fused ring systems, a 6-5-5 ring system resulted (Scheme 6).

Scheme 6

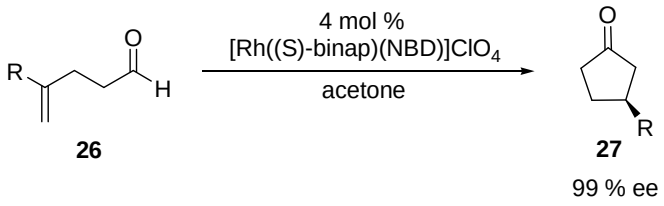


This result can most likely be explained by the formation of the much less strained 6-5-5 ring system in preference to the 5,5,5 ring system. Presently, this is the only example of 6-membered carbocycle formation via hydroacylation.

The work of Bosnich has uncovered an asymmetric version of rhodium catalyzed hydroacylation which uses chiral phosphine ligands as the source for chirality transfer.

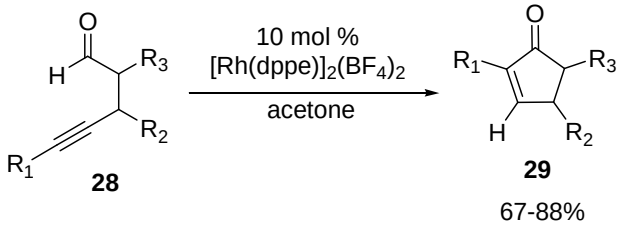
Using this method, 3-substituted cyclopentanones **27** can be synthesized in about 90 % yield with ee's up to 99 % using (S)-binap as the ligand (Scheme 7).[17]

Scheme 7



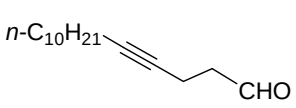
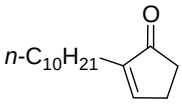
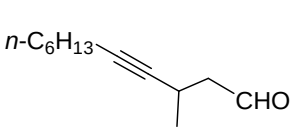
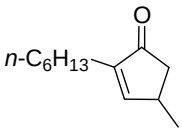
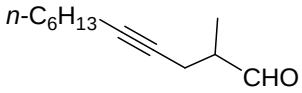
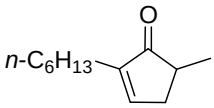
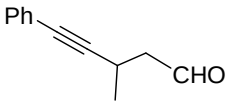
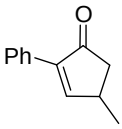
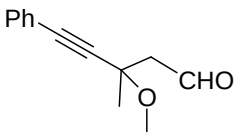
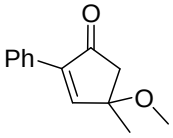
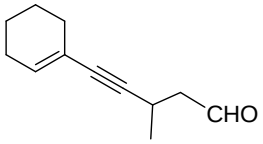
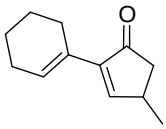
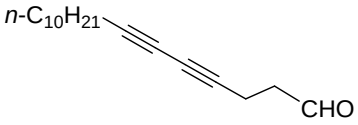
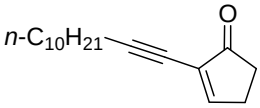
Most recently, Fu has demonstrated that hydroacylation is also applicable to the synthesis of highly substituted cyclopentenones **29** from alkynals **28** (Scheme 8).[18] Previously

Scheme 8



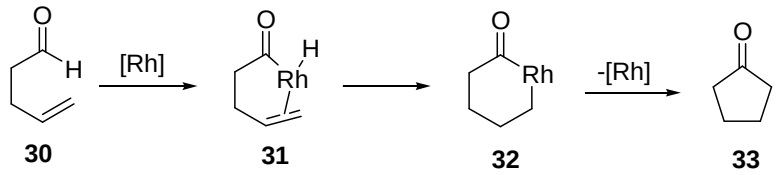
Larock had shown that 4-alkynals did not cyclize under the same conditions used for the hydroacylation of 4-alkenals. One potential difficulty in the hydroacylation of 4-alkynals is the need for a trans-addition of a metal hydride to an alkyne.[19] The facility of this step may be influenced not only by alkyne substitution but also catalyst geometry. It has thus been shown that by using a cationic Rh-ligand complex like Bosnich, the transformation of substituted alkynals can be achieved. The reaction tolerates alkyl, phenyl, alkynyl, and cycloalkene substituents on the alkyne, and methyl and methoxy substituents α and β to the carbonyl (Table 3).

Table 3

Substrate	Product	% Yield
		67
		75
		67
		88
		75
		84
		76

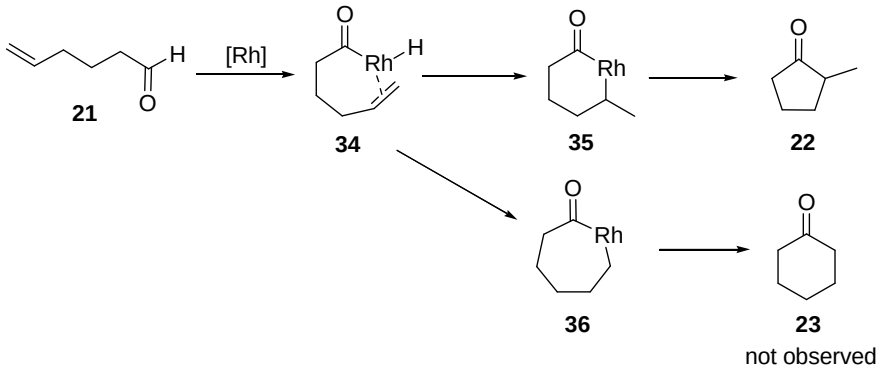
It was long known that hydroacylation could be used to construct cyclopentanone derivatives, but attempts to synthesize medium rings using this method have only recently been developed. Because the mechanism of Rh-catalyzed hydroacylation (Scheme 9) had been thoroughly investigated by many, most notably by Bosnich and coworkers[20], strategies which take advantage of this information could then be employed. Larock showed that hexenals do not undergo hydroacylation to form cyclohexanones but

Scheme 9



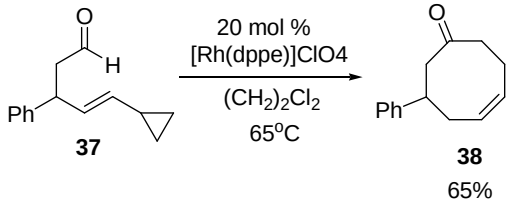
instead form methylcyclopentanones. This result can be rationalized by the formation of the less strained 6-membered metallacycle intermediate, **35**, over the 7- membered metallacycle, **36**, (Scheme 10). As the ring size increases the rate of hydroacylation

Scheme 10



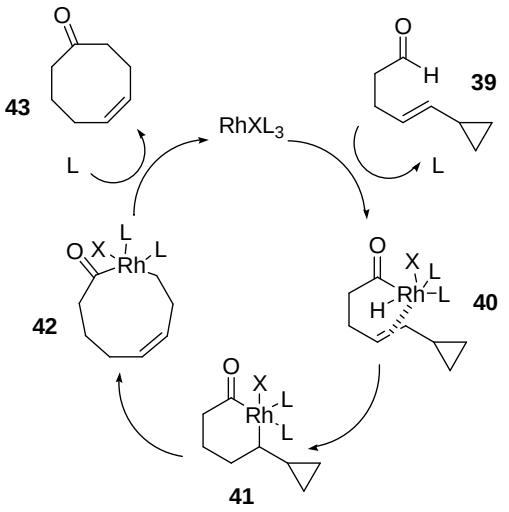
slows prohibitively, leading solely to decarbonylation products as shown by Larock.[4] It was not until Shair reported his synthesis of cyclooctenones using intramolecular hydroacylation in 2000, that hydroacylation could be used to assemble medium rings. By using a strategy similar to that originally used by Wender[21] and Trost[22] in transition metal-catalyzed [5+2] cycloadditions, Shair strategically placed a cyclopropane ring capable of fragmentation, and thus ring expansion, in the starting material (Scheme 11).[23]

Scheme 11



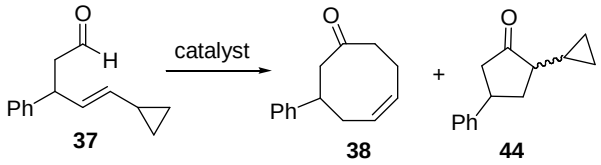
Because a 4-pentenal derivative is used, a 6-membered intermediate is formed intially, which avoids direct formation of the 9-membered metallacycle. Subsequent ring expanison yields the corresponding cyclooctenone, **43** (Scheme 12). Using the same model system as described in Scheme 12, a variety of catalysts were screened to affect

Scheme 12



the desired transformation including $Rh(PPh_3)_3Cl$, $[Rh(dppe)]ClO_4$, and[Rh(dppe)]OTf (Scheme 13).

Scheme 13

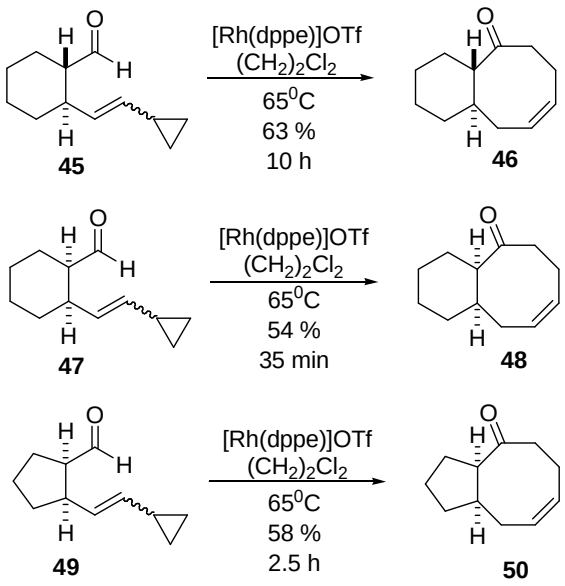


$Rh(Ph_3P)_3Cl$	7%	44%
$[Rh(dppe)]ClO_4$	65%	0%
[Rh(dppe)]OTf	50%	0%

Wilkinson's catalyst ($Rh(PPh_3)_3Cl$) gave mostly cyclopropyl-substituted cyclopentanone **44** which arises from reductive elimination before ring expansion. The use of Rh-dppe complexes $[Rh(dppe)]ClO_4$, and[Rh(dppe)]OTf gave moderate yields of the desired cyclooctenone, **38**. This hydroacylation chemistry developed by Shair is limited in

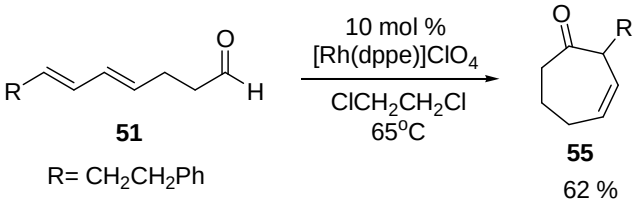
scope, given that it can only be used to produce 8-membered carbocycles, although it was successfully applied to the synthesis of both cis and trans fused 6-8 and 5-8 ring systems with good yields (Scheme 14).

Scheme 14



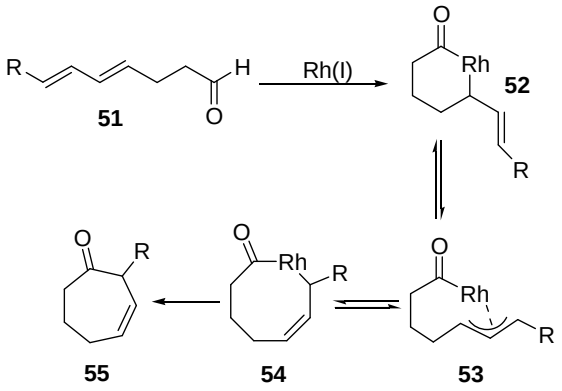
Another advancement in syntheses of medium rings via hydroacylation was made by Mori in 2002 (Scheme15).[24] It was speculated that if a double bond was conjugated to a

Scheme 15



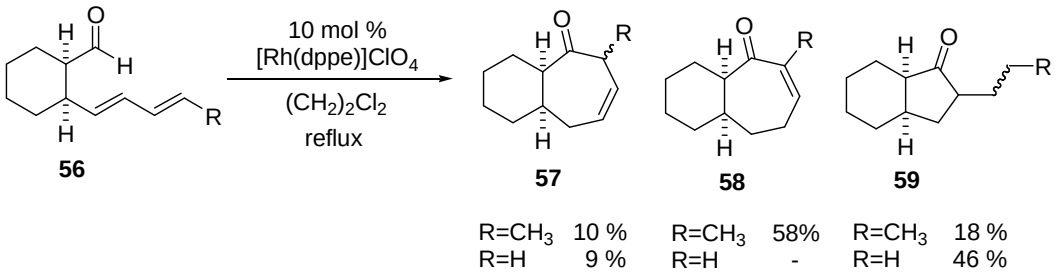
Rh-C bond in rhodacycle **52,** an 8-membered rhodacycle intermediate, **54**, could be formed via a π-allylrhodium intermediate, **53.** Reductive elimination from **54** would then lead to the cycloheptenone product, **55** (Scheme 16). Cis fused 6-7 ring systems have

Scheme 16



been synthesized using this method as well, although mixtures of hydroacylation products are observed (Scheme 17).

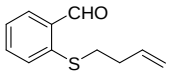
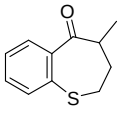
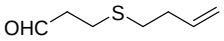
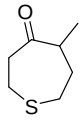
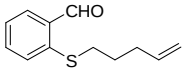
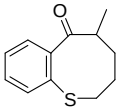
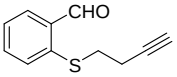
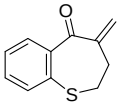
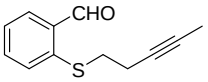
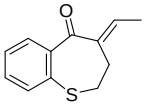
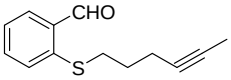
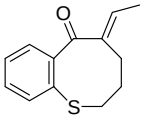
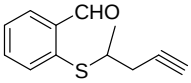
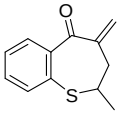
Scheme 17



Only cycloheptenones have been synthesized using this method, to date; thus efforts in our laboratory have been focused on a broad scope methodology for the synthesis of medium rings of various sizes using hydroacylation.

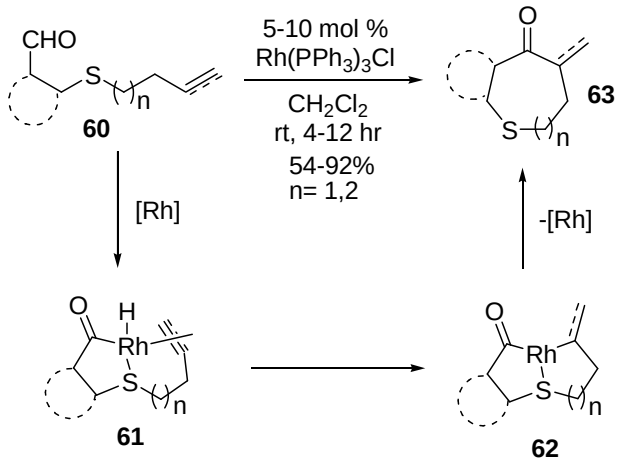
In 2002, our laboratory reported a method to synthesize medium ring sulfur heterocycles, using a chelation-assisted hydroacylation.[25] By treating ω-alkenals and alkynals which contain a Lewis basic tether atom such as sulfur, with Wilkinson's catalyst, a variety of 7 and 8-membered sulfur heterocycles have been prepared (Table 4). Unlike previous

Table 4

Entry	Substrate	Hydroacylation Product	% Yield
1			92
2			82
3			62
4			54
5			89
6			86
7			65

attempts to construct medium rings using hydroacylation, our method uses sulfur as a tether atom, along with an alkene or alkyne, to coordinate to the metal center. This coordination, promotes oxidative addition of the aldehyde via proximal assistance and most likely forms a metallabicyclic intermediate, **61**. The alkene or alkyne then inserts in to the rhodium-hydride bond to give intermediate **62.** Reductive elimination of the metal affords the heterocycle, **63** (Scheme 18). Similar to hexenals, insertion occurs such that the hydride

Scheme 18



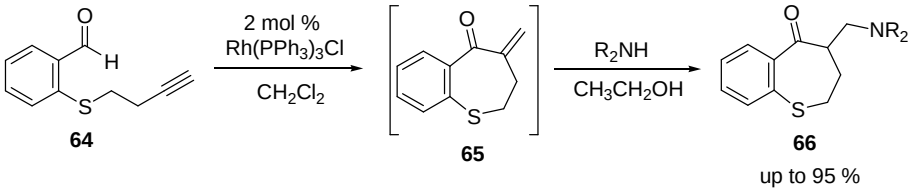
ligand is delivered to the distal position of the alkene or alkyne. The regiochemistry of the insertion is opposite that seen for pentenals thus the 5-membered metallacycle must be preferred to the 6-membered metallacycle inermediate. Substitution of the alkyl chain α to the sulfur atom, or on the terminal position of the alkyne is tolerated. In contrast, substitution on the alkene is not tolerated. It should be noted that the transformations of both methyl-substituted and terminal alkynes (Table 4, Entries 4,5) are quantitative by GC. Isolation of the unsubstituted benzothiepinone product (Table 4, Entry 4) gives dramatically reduced yields where as isolated yields of the methyl-substituted product (Table 4, Entry 5) are much higher. This is primarily due to the ability of benzothiepinones to dimerize.[20] More hindered enones such as that in entry 5 dimerize much slower and are thus easier to isolate in good yield. This method represents the first route to heterocycles via hydroacylation.

By applying this novel method to the formation of aminomethylbenzothiepinones and other tricyclic ring systems possessing biological activity we have developed a facile entry into this class of compounds.

Results and Discussion

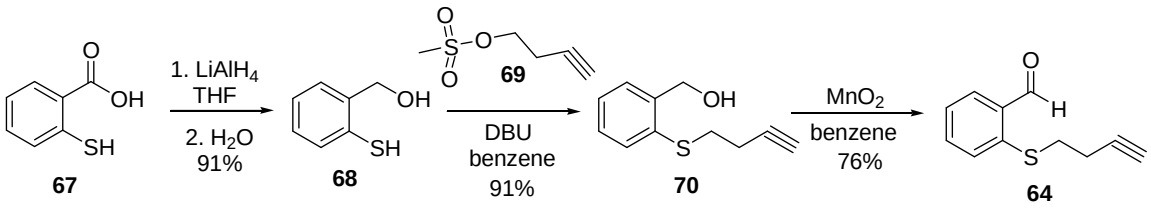
With the goal of applying the chelation assisted hydoacylation to the synthesis of aminomethylsubstituted benzothiepines, we have developed a tandem hydroacylation-Michael addition strategy. By cyclizing ω-alkynals using Wilkinson's catalyst, enone products are formed. The enones are unstable due to their ability to dimerize,[20] and attempts to isolate them directly results in poor yields and mixtures, thus a one-pot procedure is needed. Treatment of enone intermediates, **65**, with amines produces aminomethyl-substituted heterocycles, **66**, in high yields (Scheme 19). The

Scheme 19



hydroacylation substrate, **64**, was synthesized via the route outlined in Scheme 20.

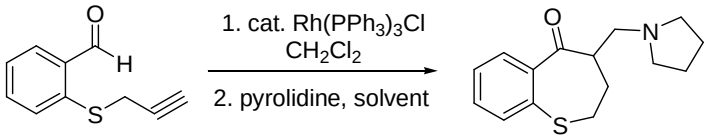
Scheme 20



Benzyl alcohol **70** is prepared by reducing 2-mercaptobenzoic acid, **67**, then alkylating with mesylate **69** in the presence of DBU. Alcohol **70** is then oxidized with MnO_2 to yield alkynal **64**. Mesylate **69** is synthesized from commercially available but-3-ynol via mesylation by methanesulfonyl chloride.

Initial work on this project focused on optimizing the conditions for the tandem hydroacylation-Michael addition and examining the scope and limitations of the reaction. In the first trials of the project the solvent for the Michael addition was investigated; addition of the amine directly to the reaction yielded very little product. Because polar solvents are the most efficient choice for Michael additions, the amine was added as an ethanol solution to the enone (Table 5, Entry 2). Later, it was found that yields of the product were drastically increased when the methylene chloride was stripped from the enone prior to the addition of the ethanol solution of the amine (Table 5, Entries 3-5). Acetonitrile was also used as a solvent, although the yields in these cases were significantly reduced (Table 5, Entry 1). In general, no significant change in yield was observed when decreasing the equivalents from 5 to 1.5 (Table 5, Entries 3-5).

Table 5



64 **71**

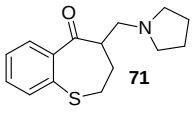
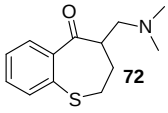
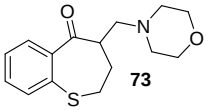
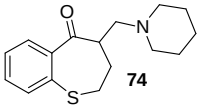
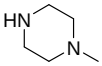
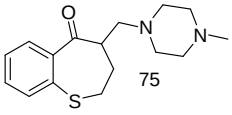
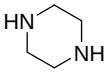
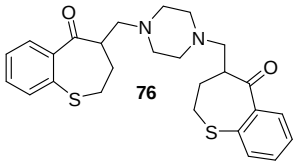
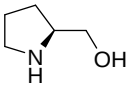
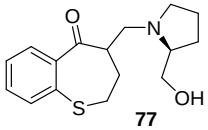
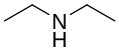
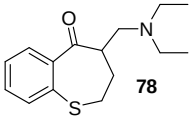
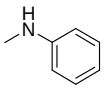
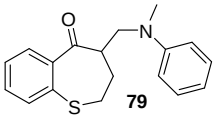
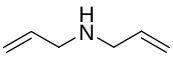
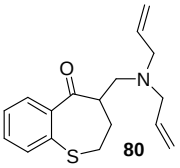
Entry	Solvent	Eq. Pyrrolidine	% Yield*
1	CH_3CN/CH_2Cl_2	5.0	37
2	CH_3CH_2OH/CH_2Cl_2	5.0	47
3	CH_3CH_2OH	5.0	94
4	CH_3CH_2OH	2.5	95
5	CH_3CH_2OH	1.5	94

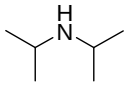
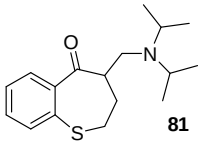
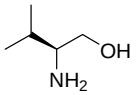
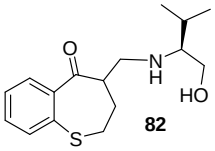
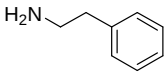
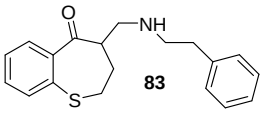
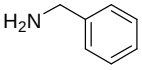
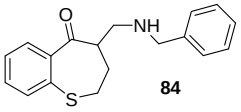
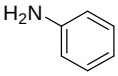
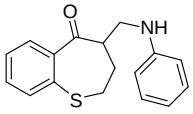
* isolated yield via column chromatography

The scope of the reaction was then investigated in hopes that it would tolerate a variety of secondary amines (Table 6). Most cyclic secondary amines reacted smoothly; where as more hindered secondary amines such as diisopropylamine were slower and gave low

yields of product. Primary amines gave slightly lower yields than did the secondary amines. When chiral amines were used such as prolinol and leucinol, mixtures of

Table 6

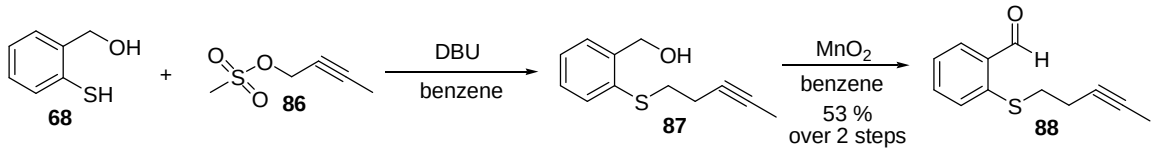
Amine	Product	% Yield
	 **71**	95
	 **72**	93
	 **73**	90
	 **74**	86
	 75	87
	 **76**	64
	 **77**	52
	 **78**	52
	 **79**	17
	 **80**	15

Amine	Product	% Yield
	 **81**	4
	 **82**	74
	 **83**	75
	 **84**	76
	 **85**	76

diastereomers were obtained with ratios of 1.8:1 and 1:1, respectively. Addition of allyl amine gave poor yields which could be caused by potential isomerization to the enamine. All yields in table 6 are optimized and are based on isolation by silica gel chromatography.[26] An aqueous extraction method has also been used to isolate the product albeit with slightly lower yields.

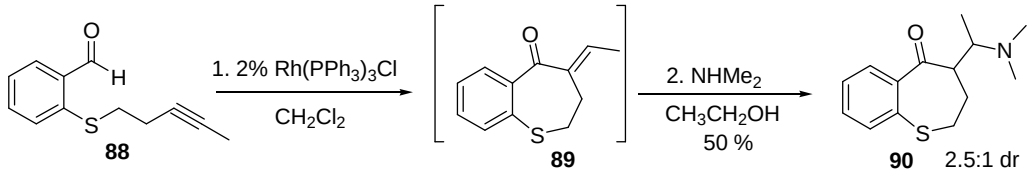
We have also applied this chemistry to 1-aminoethyl-substituted benzothiepinones through the formation of the more stable methyl substituted enone intermediate, **89** (Scheme 22). The alkynal, **88**, was synthesized by a similar route to that used for alkynal **64** (Scheme 21). 2-Mercaptobenzyl alcohol, **68**, is alkylated with mesylate **86** in the presence of DBU to yield benzyl alcohol **87**. The alcohol, **87**, is then oxidized with

Scheme 21



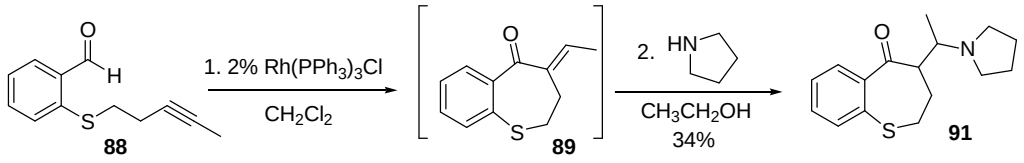
MnO_2 to yield alkynal **88**. Mesylate **86** is prepared by mesylation of pent-3-yn-1-ol with methanesulfonyl chloride in the presence of pyridine. Even with relatively unhindered secondary amines such as dimethylamine, yields are significantly lower than those

Scheme 22



obtained with the terminal alkyne (Scheme 22).[20] Cyclic secondary amines such as pyrrolidine produce even lower yields (Scheme 23). The methyl group hinders approach

Scheme 23

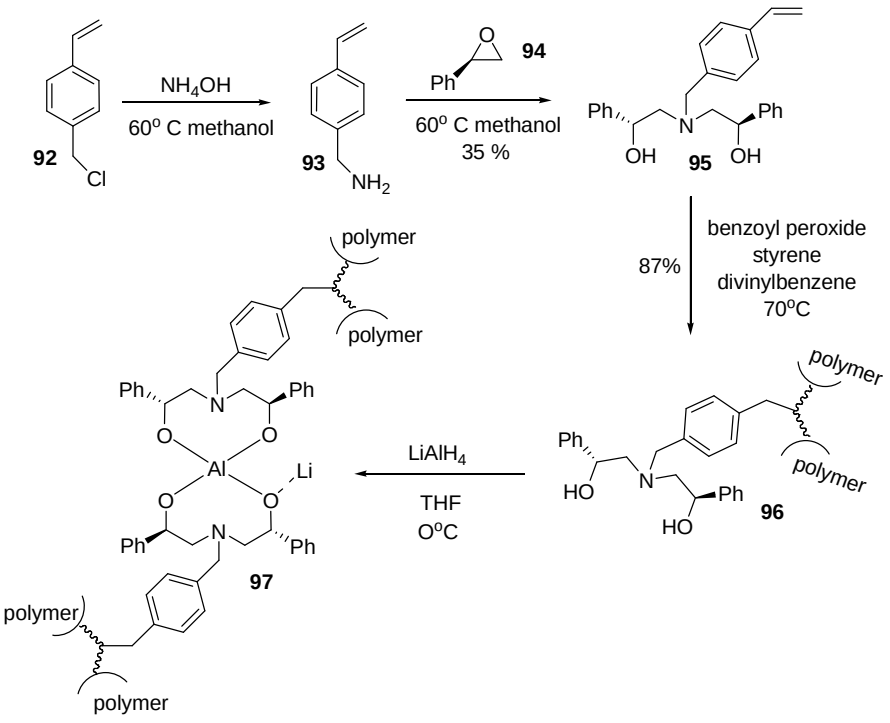


of the amine during Michael addition. Although these reactions are lower yielding, a modest degree of selectivity is seen. Dimethyl amine reacts to form the 1-aminoethyl-substituted benzothiepinone, **90**, with a diastereomeric ratio of 2.5:1.

Since previous attempts to increase diastereoselectivity gave poor results, a more selective method was desired. Chiral Lewis base catalysts have been studied intensely for use as asymmetric Michael addition catalysts.[27] Homogeneous catalysts are

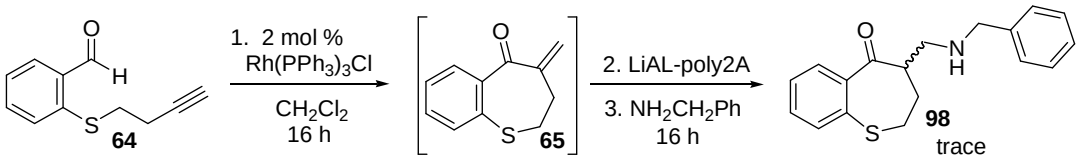
sometimes difficult to separate from the product so polymer supported catalysts have many advantages. Sundararajan and coworkers have developed a polymer bound asymmetric Michael addition catalyst which has been used to direct the addition of malonates and thiophenols to cyclic and acyclic enones.[28] To investigate the potential use of this catalyst in our tandem hydroacylation-Michael addition reaction, LiAl-poly2A was synthesized as outlined in Scheme 24 and then tested in our reaction. 1-(Chloromethyl) styrene, **92**, is treated with concentrated ammonium hydroxide to afford

Scheme 24



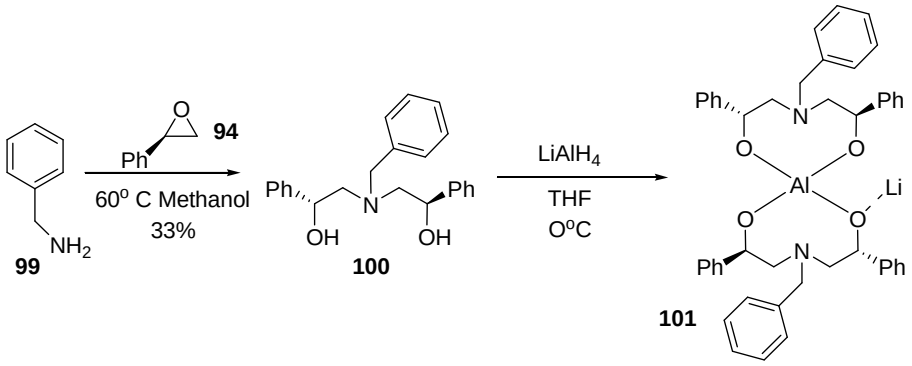
benzyl amine **93**. (R)-Styrene oxide, **94**, is then opened with benzyl amine **93** to produce the C_2-symmetric aminodiol ligand. Polymerization of the ligand, **95**, is accomplished by treating with benzoyl peroxide, styrene, and divinylbenzene. As a test reaction, alkynal **64** was subjected to hydroacylation conditions for 16 h. The polymer supported ligand **97** was then activated in *situ* with $LiAlH_4$, and added to the reaction mixture. After

Scheme 25



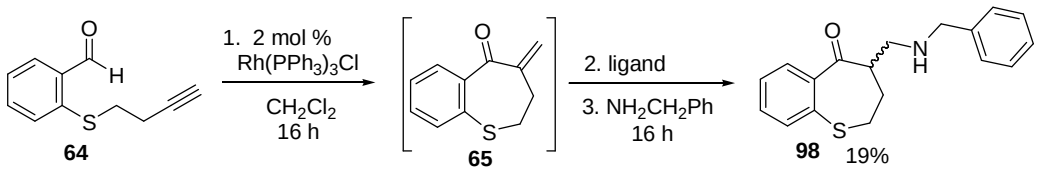
stirring the mixture for 5 minutes, benzylamine was added via syringe. The reaction was stirred overnight upon which only trace amounts of product **98** were present (Scheme 25). The non-polymer supported ligand complex **101** was also synthesized in a similar method (Scheme 26) and

Scheme 26



tested in the reaction. (R)-Styrene oxide, **94**, was opened with benzyl amine **99** to produce the C_2-symmetric aminodiol ligand, **100**, which was activated *in situ* with $LiAlH_4$. The non-polymer bound ligand was then activated and subjected to the same conditions as previously described (Scheme 27). After 16 h, 19% of the product, **98**, was

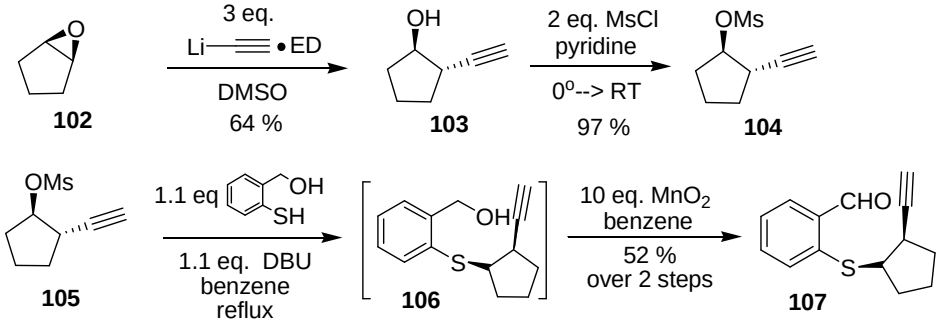
Scheme 27



isolated. This reaction was not pursued further due to the lack of reactivity.

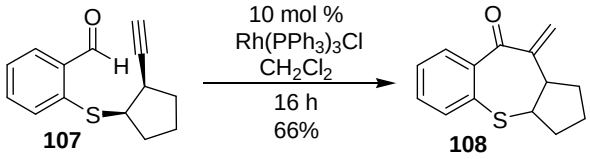
We also explored steric control of the Michael addition by the addition of a ring alpha to the sulfur atom. A ring substituent could direct the Michael addition through sterics and may offer some selectivity. The substrate under investigation was synthesized using the route outlined in Scheme 28. Preparation of the mesylate used for alkylation was

Scheme 28



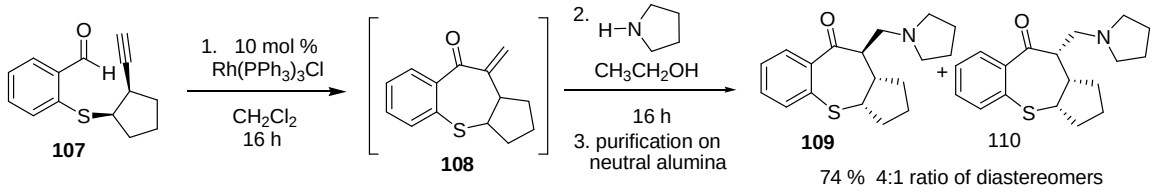
accomplished by opening of cyclopentene oxide, **102,**[16] with lithium ethylenediamine acetylide, followed by treatment of the product, **103**, with methanesulfonyl chloride in pyridine. Alkylation of 2-mercapto-benzyl alcohol, was accomplished by reacting it with mesylate, **105**, in the presence of DBU to yield alcohol **106**. Because the product and starting material had a similar R_f on silica gel, the product was not purified after the alkylation. Instead, the crude product was treated with MnO_2 and the resultant alkynal **107** was purified on silica gel. To test our hypothesis, the alkynal, **107**, was subjected to Wilkinson's catalyst in CH_2Cl_2 for 16 h. The initial cyclization product, **108**, via hydroacylation, could be isolated but only in moderate yields, most likely due to its inherent instability and tendency to dimerize (Scheme 29).[29] The solvent was then removed and pyrrolidine was added as a solution in ethanol and stirred for 16 h. The

Scheme 29



crude reaction mixture contained two diastereomers, **109,** and **110**, of an unassigned ratio of 1.2:1. After purification on neutral alumina, a the diastereomeric aminomethylbenzothiepinones were obtained in 74% yields and in a ration of 4:1 (Scheme 30). Attempts of purification on silica gel were unsuccessful and decomposition

Scheme 30



to the enone, **108**, was prevalent. To test the stability of the product on different media, and also to assess the relative equilibration between diastereomers, an original mixture of ratio 1.2:1 was stirred in different media overnight in ether. The results are outlined in

Table 7

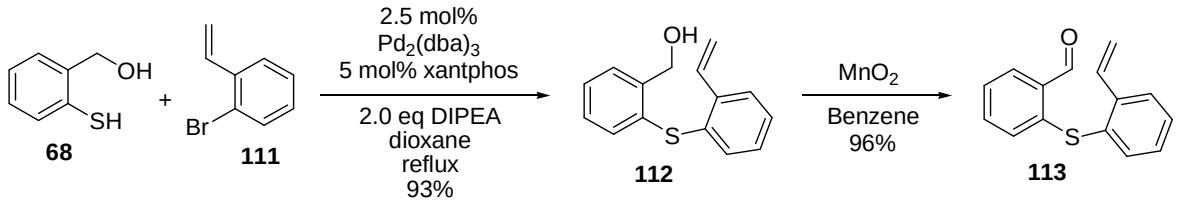
Media	Compounds (9,10)	Compound (11)
10% HCl	1.2:1	0
10% NaOH	1.2:1	0
Fluorisil	-	Major
Silica	3.1:1	1
Neutral Alumina	11.1:1	3

the table above (Table 7). Decomposition to the enone, **108**, prevailed when fluorisil was used. Neutral alumina gave the highest ratio and the least decomposition thus it was chosen as the media for purification. The major diastereomer obtained in the crude

reaction mixture is also the major diastereomer after purification. It is reasonable to assume it is the most thermodynamically stable product. We were unable to assign the structure of the major diastereomer but MM2 calculations of torsional energy suggest that compound **109,** is energetically more stable. Steric considerations argue that **109** would be the least strained where the cis fused 5-membered ring is trans to the aminomethyl substituent.

Following the successful synthesis of a tricyclic benzothiepinone using this methodology, a possible new route to dibenzothiepinones became evident. By introducing a benzene ring α to the sulfur atom, dibenzothiepinone derivatives could be produced. To first test our hypothesis and gain entry into methyl-substituted dibenzothiepinones, the hydroacylation substrate, **113**, was synthesized via the following route (Scheme 31).

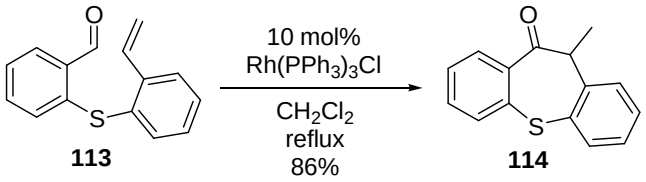
Scheme 31



First, 2-mercapto-benzylalcohol, **68**, was coupled to 1-bromovinylbenzene, **111**, via a palladium cross coupling reaction using Buchwald conditions.[30] Alcohol **112** was then oxidized with MnO_2 to yield the desired hydroacylation substrate, **113**, in high yield. Substrate **113** was then subjected to normal hydroacylation conditions using 10 mol% $Rh(PPh_3)_3Cl$ in dichloromethane and allowed to stir at room temperature overnight. After approximately 16 hours mostly starting material was present, although a crude NMR showed a small amount of hydroacylation product. Substrate **113** was subjected to

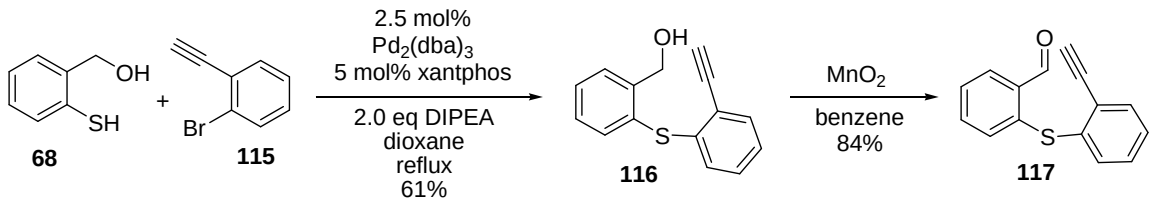
the same conditions as described previously but at refluxing temperatures. After 16 hours, substrate **113** was completely consumed and an 86% yield of dibenzothiepinone **114** was obtained after purification by silica gel chromatography (Scheme 32). To test the applicability of this method to the

Scheme 32



synthesis of aminomethyl-substituted dibenzothiepinones using the tandem hydroacylation-Michael addition strategy, the hydroacylation substrate, **117**, was synthesized using a route similar to that of **113** (Scheme 33). First, 2-mercapto-benzylalcohol, **68**, was condensed with 1-bromo-ethynylbenzene **115** via a palladium

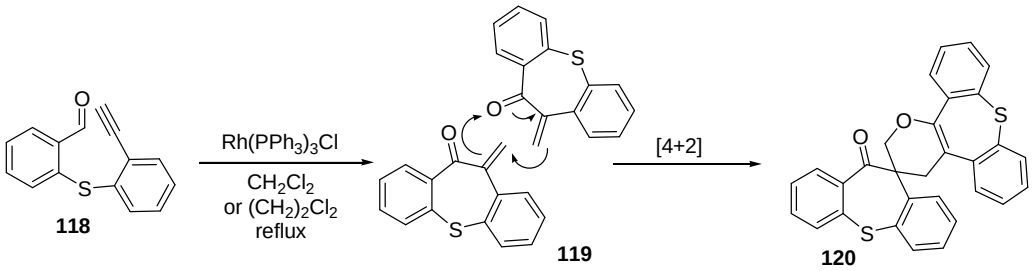
Scheme 33



cross coupling reaction using Buchwald conditions.[31] The alcohol, **116**, was then oxidized with MnO_2 to yield the desired hydroacylation substrate, **117**, in high yield. Subjecting substrate **117** to 10 mol% Wilkinson's catalyst in dichloromethane yielded no isolable hydroacylation product after 2 days. Refluxing the reaction in either dichloromethane or dichloroethane for 16 h also showed no sign of hydroacylation product. After further analysis by mass spectrometry and time-resolved NMR experiments, it seems that the hydroacylation product may be formed, but just as quickly

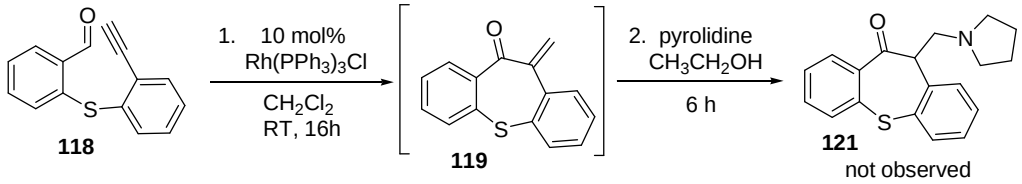
dimerizes (most likely via an intermolecular hetero-Diels-Alder reaction)[20] to form compound **120**, especially at elevated temperatures (Scheme 34). The ability of

Scheme 34



these compounds to dimerize was what led to the development of the tandem hydroacylation-Michael addition reaction initially. In hopes of using this strategy for the synthesis of aminomethyl-substituted dibenzothiepinones, hydroacylation of **118** was then followed by addition of pyrrolidine as a solution in ethanol (Scheme 35). After 6 hours none of the desired product, **121**, was detected, thus it seems that this particular

Scheme 35



enone dimerizes rapidly and we have not been able to find proper conditions for its isolation or further reaction.

Conclusion

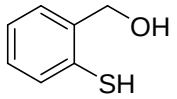
In conclusion, we have described an efficient one-pot method for the synthesis of a variety of biologically active benzothiepinones. ω-Alkynals undergo hydroacylation rapidly to form cyclic enones which react with a variety of amines to produce

aminomethybenzothiepinones in high yields. Although we have only had modest success in making the reaction selective, our efforts have introduced us to a novel method for the synthesis of dibenzothiepinones, which we have been able to prepare in good yields.

Experimental

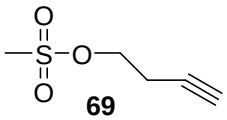
General Methods. All reactions were carried out under either nitrogen or argon atmosphere, using oven dried glassware, unless otherwise noted. All reagents were used as received without further purification, unless otherwise noted. Tetrahydrofuran was distilled from from sodium benzophenone ketyl; and CH_2Cl_2 from CaH_2. Pyridine, pyrrolidine, and triethylamine were distilled prior to use and stored over molecular sieves. Rhodiumtris(triphenylphosphine) chloride (Wilkinson's catalyst) was prepared using a literature procedure.[32] Reaction products were purified using column chromatography on silica gel (70-230 mesh) using hexanes/ethyl acetate mixtures as the mobile phase. Thin layer chromatography was performed using Analtech glass-backed TLC plates (250 microns), and visualized using I_2, UV light (254 nm), anisaldehyde stain, and phosphomolybdic acid stain.

Spectral Data. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded using a Bruker Avance DPX-300 NMR Spectrometer in $CDCl_3$ unless otherwise noted. Mass spectrometry data was recorded using a Thermo Polaris Q Gas Chromatograph- Mass Spectrometer.



68

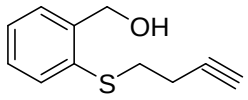
2-Mercaptobenzyl alcohol. An oven dried flask, fitted with a dropping funnel, was charged with $LiAlH_4$ (3.94 g, 103.8 mmol) and evacuated and backfilled with argon gas. The flask was then cooled to 0^{o}C in an ice bath upon which THF (40 mL) was added. A solution of 2-mercaptobenzoic acid (6.40 g, 41.5 mmol) in THF (40 mL) was then added drop wise over approximately 1 h. The reaction was then allowed to warm to room temperature and was stirred for 16 h. Once again the reaction mixture was cooled to 0^{o}C in an ice bath and ethyl acetate (15 mL) and 10% H_2SO_4 (60 mL) were added. The gray mixture was then filtered into a argon flushed flask, and extracted in an argon flushed seperatory funnel containing brine (20 mL) using ethyl acetate (3 x 20 mL). The organic layer was then dried over Na_2SO_4 and concentrated *in vacuo* to yield 5.30 g, (27.6 mmol, 91%) of the desired product as a pale yellow solid and used without any further purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.29 (2H, m), 7.14 (2H, m), 4.64 (2H, s), 3.65 (1H, s), 2.71 (1H, bs).



69

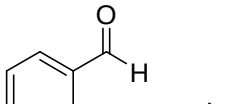
Prop-2-ynyl methanesulfonate. To an oven dried flask was added but-3-yne-1-ol (4.00 g, 57.1 mmol), and pyridine (60 mL) which was then cooled to 0^{o}C in an ice bath. Methanesulfonyl chloride (4.42 mL, 57.1 mmol) was added via syringe and the bright yellow solution allowed to stir at room temperature for 3 h. The resultant orange solution was added to water (50 mL), extracted using CH_2Cl_2 (3 x 30 mL), washed with 10% HCl

(3 x 20 mL) and brine (3 x 20mL), dried over Na_2SO_4, and concentrated *in vacuo* to yield 7.36 g, (49.7 mmol, 87%) of the desired product as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 4.31 (2H, t, *J*=6.7 Hz), 3.07 (3H, s), 2.67 (2H, td, *J*=6.7, 2.7 Hz), 2.10 (1H, tm, *J*=2.7 Hz).



70

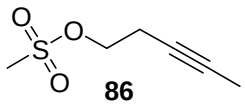
2-(But-3-ynylthio)benzyl alcohol. 2-Mercaptobenzyl alcohol (5.30 g, 37.8 mmol), prop-2-ynyl methanesulfonate (6.16 g, 41.6 mmol), and benzene (250 mL) were added to an oven dried flask. To the yellow solution was added DBU (5.40 mL, 41.0 mmol) via syringe, and the mixture was stirred at room temperature for 16 h. Water (100 mL) was then added and the reaction was washed with 10% HCl (3 x 30 mL), saturated $NaHCO_3$ (3 x 30 mL), brine (3 x 30 mL), and then dried over Na_2SO_4. The extract was then concentrated *in vacuo* to yield 6.58 g, (34.3 mmol, 91%) of the desired product as a pale solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.42 (2H, m), 7.28 (2H, m), 4.81 (2H, d, *J*=6.4 Hz), 3.09 (2H, m), 2.48 (2H, td, *J*=7.2, 2.7, Hz), 2.07 (1H, t, *J*=2.7 Hz), 1.57 (1H, s).



64

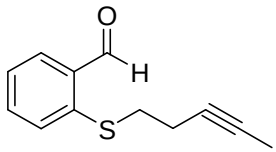
2-(But-3-ynylthio)benzaldehyde. 2-(3-Butynylthio)benzyl alcohol (6.58 g, 34.3 mmol), benzene (350 mL), and MnO_2 (33.9 g, 343 mmol) were added to an oven dried flask and stirred at room temperature for 16 h. The mixture was then filtered through celite and

concentrated *in vacuo*. The crude product was purified by silica gel chromatography using 50% CH_2Cl_2 in hexanes, to yield 4.94 g, (26.0 mmol, 76%) of the desired product as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 10.43 (1H, s), 7.86 (1H, m), 7.55 (1H, m), 7.46 (1H, m), 7.35 (1H, tm, *J*=7.2 Hz), 3.13 (2H, t, 7.6 Hz), 2.55 (2H, td, *J*=7.6, 2.7 Hz), 2.08 (1H, t, *J*=2.7 Hz).



86

Pent-3-ynyl methanesulfonate. To an oven dried flask was added 3-pentyne-1-ol (2.47 g, 29.4 mmol), and pyridine (30 mL) which was then cooled to 0^{o}C in an ice bath. Methanesulfonyl chloride (2.28 mL, 29.4 mmol) was added via syringe and the bright yellow solution allowed to stir at room temperature for 3 h. The resultant orange solution was added to water (20 mL), extracted using CH_2Cl_2 (3 x 15 mL), washed with 10% HCl (3 x 15 mL) and brine (3 x 15mL), dried over Na_2SO_4, and concentrated *in vacuo* to yield 3.33 g, (20.6 mmol, 70%) of the desired product as a clear oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 4.27 (2H, t, *J*=6.8), 3.05 (3H, s), 2.60 (2H, m), 1.79 (2H, t, *J*=2.9).

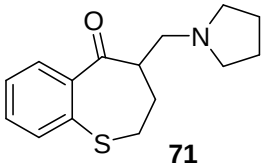


88

2-(3-Pentynylthio)benzaldehyde. 2-Mercaptobenzyl alcohol (1.00 g, 7.33 mmol), 3-pentynyl methanesulfonate (1.27 g, 7.85 mmol), and benzene (75 mL) were added to an oven dried flask. To the yellow solution was added DBU (1.02 mL, 7.85 mmol) via

syringe, and the mixture was stirred at room temperature for 16 h. Water (50 mL) was then added and the reaction was washed with 10% HCl (3 x 15 mL), saturated $NaHCO_3$ (3 x 15 mL), brine (3 x 15 mL), and then dried over Na_2SO_4. The crude product was then dissolved in benzene (90 mL) and MnO_2 (8.62 g, 87.3 mmol) was added. The mixture was let stir for 3 days at which point it was filtered through celite and concentrated *in vacuo*. The crude product was then purified by silica gel chromatography using 20% CH_2Cl_2 in hexanes to yield 0.766 g, (3.71 mmol, 53%) of the desired product as a pale yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 10.48 (1H, s), 7.86 (1H, dd, *J*=7.7, 1.6 Hz), 7.54 (1H, m), 7.48 (1H, m), 7.34 (1H, tm, *J*=7.7 Hz), 3.09 (2H, t, *J*=7.4 Hz), 2.49 (2H, m), 1.77 (3H, s).

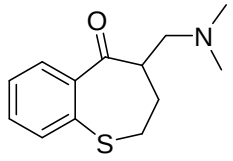
General Method for the tandem hydroacylation-Michael addition reaction:



71

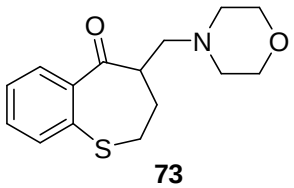
3,4-Dihydro-4-((pyrrolidin-1-yl)methyl)benzo[b]thiepin-5(2H)-one. $Rh(PPh_3)_3Cl$ (0.012 g, 0.013 mmol) was added to an oven dried Schlenk flask and then evacuated and filled with argon gas. 2-(3-butynylthio)benzaldehyde (0.120 g, 0.631 mmol) was then added as a solution in CH_2Cl_2 (7 mL) and the reaction was stirred for 16 h upon which the solvent was removed and pyrrolidine (0.132 mL, 1.58 mmol) was added as a solution in anhydrous ethanol (1.5 mL). The mixture was allowed to stir at room temperature for an additional 4 h at which time the solvent was removed and the crude residue purified by silica gel chromatography using a 60:35:5 mixture of hexanes/ethyl acetate/methanol to

yield 0.165 g, (0.631 mmol, 95%) of the desired product as an amber oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.75 (1H, dd, *J*=7.7, 1.7 Hz), 7.43 (1H, dm, *J*=7.8 Hz), 7.31 (1H, td, *J*=7.8, 1.7 Hz), 7.23 (1H, m), 3.73 (1H, m), 3.15 (1H, ddm, *J*=14.7, 6.4 Hz), 2.95 (1H, m), 2.75 (2H, m), 2.43 (5H, m), 1.98 (1H, m), 1.71 (4H, m). **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 205.10, 142.15, 138.67, 130.95, 130.66, 129.89, 126.03, 56.29, 54.76, 48.71, 37.20, 34.21, 23.89. **IR** (neat) 2957, 2784, 1677, 1585, 1457, 1430, 1387, 1351, 1260, 1199, 1146, 1129, 1078, 1037, 947, 875, 784 cm^{-1}. **MS** m/z (calcd for $C_{15}H_{20}NOS$, 262.1266) obsd 262.1261.



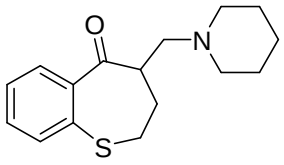
72

4-((Dimethylamino)methyl)-3,4-dihydrobenzo[b]thiepin-5(2H)-one. Refer to general procedure for tandem hydroacylation-Michael Addition. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.77 (1H, dm, *J*=7.7 Hz), 7.44 (1H, m), 7.31 (1H, tm, *J*=8.2 Hz), 7.23 (1H, tm, *J*=7.7 Hz), 3.71 (2H, m), 3.16 (1H, dd, *J*=14.7, 6.4 Hz), 2.91 (1H, m), 2.75 (1H, td, *J*=19.2, 5.3 Hz), 2.34 (1H, sep, *J*=6.4 Hz), 2.17 (6H, s), 1.95 (1H, m). **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 204.44, 141.66, 138.20, 130.60, 130.36, 129.49, 125.67, 59.51, 46.90, 45.78, 36.52, 33.81. **IR** (neat) 3055, 2941, 2855, 2817, 2765, 1678, 1585, 1457, 1430, 1267, 1224, 1197, 1032, 951, 784. **MS** m/z (calcd for $C_{13}H_{18}NOS$, 236.1109) obsd 236.1104.



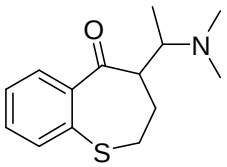
73

3,4-Dihydro-4-(morpholinomethyl)benzo[b]thiepin-5(2H)-one. Refer to general procedure for tandem hydroacylation-Michael Addition. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.75 (1H, dd, *J*=9.4, 1.7 Hz), 7.44 (1H, m), 7.32 (1H, td, *J*=7.7, 1.7 Hz), 7.24 (1H, m), 3.77 (1H, m), 3.62 (4H, m), 3.16 (1H, ddd, *J*=14.8, 6.4, 1.2 Hz), 2.99 (1H, dd, *J*=12.6, 7.7 Hz), 2.75 (1H, m), 2.55 (1H, m), 2.40 (5H, m), 1.95 (1H, m). **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 204.39, 141.57, 138.23, 130.63, 130.21, 129.51, 125.73, 66.98, 58.64, 53.77, 46.20, 36.44, 33.76.



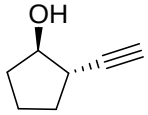
74

3,4-Dihydro-4-((piperidin-1-yl)methyl)benzo[b]thiepin-5(2H)-one. Refer to general procedure for tandem hydroacylation-Michael Addition. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.72 (1H, dd, *J*=7.7, 1.7 Hz), 7.43 (1H, m), 7.31 (1H, td, *J*=7.6, 1.7), 7.25 (1H, m), 3.76 (1H, m), 3.14 (1H, ddd, *J*=14.8, 6.3, 1.2 Hz), 2.95 (1H, m), 2.73 (1H, td, *J*=14.8, 5.3 Hz), 2.55 (1H, m), 2.30 (5H, m), 1.97 (1H, m), 1.47 (5H, m), 1.36 (1H, m). **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 204.93, 141.50, 138.38, 130.49, 130.23, 129.46, 125.64, 58.95, 54.67, 46.55, 36.83, 33.77, 26.02, 24.21.



90

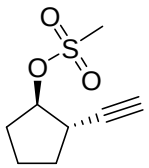
4-(1-(Dimethylamino)ethyl)-3,4-dihydrobenzo[b]thiepin-5(2H)-one. Refer to general procedure for tandem hydroacylation-Michael Addition. Major diastereomer: **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.65 (1H, m), 7.41 (1H, m), 7.31 (1H, m), 7.23 (1H, m). 3.56 (1H, m), 3.27 (1H, m), 3.13 (1H, m), 2.74 (1H, td, *J*=12.3, 4.9 Hz), 2.51 (1H, sept, J=6.8 Hz), 2.23 (6H, m), 2.02 (1H, m), 0.79 (3H, m).



103

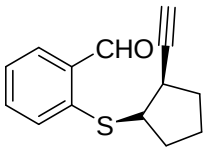
Trans-2-ethynylcyclopentanol[33] To an oven dried flask was added lithium ethylenediamine acetylide (12.66 g, 34.38 mmol) as a 25% w/w slurry in toluene. The toluene was evaporated *in vacuo*, followed by addition of anhydrous DMSO (10 mL) and cyclopentene oxide (0.964 g, 11.5 mmol). The brown mixture was allowed to stir at room temperature for 96 h, at which point saturated aqueous NH_4Cl was added (25 mL) and then the mixture was extracted with Et_2O (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, concentrated *in vacuo*, and subjected to column chromatography using 10% EtOAc in hexanes. Due to inseparable impurities, the residue was then purified using Kugelrohr distillation (100° C, 14 mm) to yield 0.726 g, (6.67 mmol, 58%) of the desired product as a clear viscous oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 4.22 (1H, q,

J=5.6 Hz), 2.57 (1H, m), 2.08 (4H, m), 1.68 (4H, m); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 86.33, 79.23, 69.58, 39.24, 33.42, 30.73, 21.67.



104

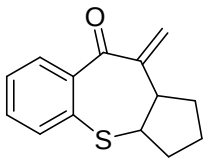
Trans-2-ethynylcyclopentyl methanesulfonate. Trans-2-ethynylcyclopentanol (0.400 g, 3.63 mmol) was added to an oven dried flask containing freshly distilled pyridine (5 mL). The solution was cooled to 0° C in an ice bath at which point methanesulfonyl chloride (0.211 mL, 2.72 mmol) was added via syringe and the mixture allowed to warm to room temperature, and stirred for 16 h. Water (10 mL) and CH_2Cl_2 (10 mL) were then added to the reaction mixture and the organic layer washed with 10% HCl (3 x 10 mL), dried over Na_2SO_4, and concentrated *in vacuo* to yield 0.663 g, (3.52 mmol, 97 %) of the desired product as a viscous yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 5.02 (1H, m), 3.08 (3H, s), 2.96 (1H, m), 2.20 (2H, m), 1.84 (4H, m), 1.59 (1H, s); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 87.95, 84.31, 71.38, 38.76, 37.47, 32.53, 31.23, 22.44.



107

Cis-2-(2-ethynylcyclopentylthio)benzaldehyde. Trans-2-ethynylcyclopentyl methanesulfonate (0.100 g, 0.531 mmol), and 2-mercaptobenzyl alcohol (0.068 g, 0.48 mmol) were added to an oven dried flask containing benzene (5 mL). To the resultant

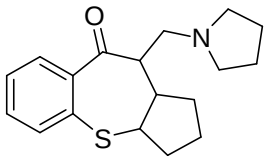
solution, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.070 mL, 0.53 mmol) was added via syringe, upon which the reaction mixture immediately became yellow and was refluxed for 16 h. Water (10 mL) and CH_2Cl_2 (10 mL) were then added and the organic layer washed with 10% HCl (3 x 10 mL), saturated aqueous $NaHCO_3$, and dried over Na_2SO_4. The resultant extract was concentrated *in vacuo* and dissolved in benzene (5 mL). To this solution was added MnO_2 (0.430 g, 4.31 mmol) and the heterogeneous mixture was allowed to stir at room temperature for 72 h. Upon completion, the reaction was filtered through celite, concentrated *in vacuo*, and purified by silica gel chromatography using 5% EtOAc in hexanes, to yield 0.052 g, (0.28 mmol, 52%) of the desired product as an off-white crystalline solid. . **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 10.70 (1H, s), 7.89 (1H, dd, *J*=7.7, 1.2 Hz), 7.56 (2H, dd, *J*=7.9, 1.1 Hz), 7.36 (1H, m), 3.62 (1H, q, *J*=7.2 Hz), 3.07 (1H, m), 2.20 (1H, d, *J*= 2.5 Hz), 2.00 (5H, m), 1.70 (1H, m). **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 192.41, 141.54, 135.97, 134.31, 132.59, 130.47, 127.13, 84.33, 72.61, 51.91, 36.51, 32.62, 32.10, 22.87.



108

3,4-Dihydro-cyclopenta[f]-4-methylenebenzo[b]thiepin-5(2H)-one. Rhodium tris(triphenylphosphine) chloride (0.030 g, 0.033 mmol) was added to an oven dried Schlenk flask, and the flask was then evacuated and backfilled with argon. A solution of cis-**(**2-ethynylcyclopentylthio)benzaldehyde (0.075 g, 0.33 mmol) in dry CH_2Cl_2 (4 mL) was then added. The reaction was stirred at room temperature for 16 h. Upon

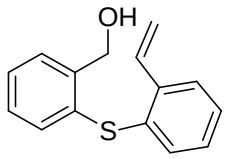
completion, the solvent was removed *in vacuo,* and the residue purified by silica gel chromatography using 0 -2% EtOAc in hexanes, to yield 0.050 g, (0.22 mmol, 66%) of the desired product as a near colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.88 (1H, m), 7.51 (1H, m), 7.41 (2H, m), 5.97 (1H, s), 5.35 (1H, s), 3.67 (1H, q, *J*=7.8 Hz), 3.19 (1H, m), 2.19 (1H, m), 1.85 (2H, m), 1.63 (3H, m). **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 197.64, 150.78, 141.50, 136.08, 134.52, 132.58, 130.92, 128.76, 120.98, 51.00, 49.19, 32.20, 29.65, 25.71.



109, 110

3,4-Dihydro-4-((pyrrolidin-1-yl)methyl)-cyclopenta[f]benzo[b]thiepin-5(2H)-one. Rhodium tris(triphenylphosphine) chloride (0.033 g, 0.036 mmol) was added to an oven dried Schlenk flask, and the flask was then evacuated and backfilled with argon. A solution of cis-**(**2-ethynylcyclopentylthio)benzaldehyde (0.083 g, 0.36 mmol) in dry CH_2Cl_2 (4 mL) was then added. The reaction was stirred at room temperature for 16 h upon which the solvent was removed *in vacuo,* and a solution of pyrrolidine (0.064 g, 0.90 mmol) in dry ethanol (4 mL) was added via syringe. The mixture was stirred for an additional 16 h and the solvent removed *in vacuo*. This residue was then purified by column chromatography using Brockman Activity I Neutral alumina and 5% EtOAc in hexanes as the eluent to yield 0.080 g, (0.27 mmol, 74%) of the desired product as 4:1 mixture of diastereomers. Major diastereomer: **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.72 (1H, ddd, *J*=7.8, 1.6, 0.5 Hz), 7.39 (1H, m), 7.32 (1H, m), 7.23 (1H, m), 3.63 (1H, td,

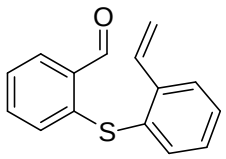
J=10.0, 2.5 Hz), 3.54 (1H, m), 3.31 (1H, dd, *J*=12.0, 10.0 Hz), 2.62 (1H, dd, *J*=12.0, 2.2 Hz), 2.38 (4H, m), 2.22 (2H, m), 2.06 (1H, m), 1.85 (1H, m), 1.68 (7H, m). **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 204.92, 140.89, 138.45, 131.02, 130.38, 129.44, 126.02, 55.49, 54.80, 53.81, 53.69, 52.79, 32.68, 29.41, 24.61, 23.90. Minor diastereomer: **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 8.0 (1H, ddd, *J*=7.9, 1.7, 0.5 Hz), 7.50 (1H, m), 7.39 (1H, td, *J*=7.2, 1.7 Hz), 7.30 (1H, m), 3.89 (1H, m), 3.47 (1H, m), 3.17 (1H, m), 2.86 (1H, m), 2.76 (1H, m), 2.55 (2H, m), 2.45 (2H, m), 1.74 (6H, m), 1.27 (4H, m).



112

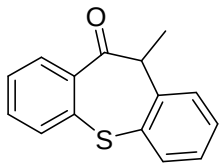
2-(2-Vinylphenylthio)benzyl alcohol. 2-mercaptobenzyl alcohol (0.300 g, 2.14 mmol), 1-bromo-2-vinylbenzene (0.276 mL, 2.14 mmol), diisopropylethylamine (0.750 mL, 4.29 mmol), and dioxane (20.0 mL) was added to an oven dried round bottom Schlenk flask with condenser attached. The solution was then degassed 3 times and backfilled with argon gas, at which point trisdibenzylidene acetone dipalladium (0.048 g, 0.054 mmol), and xantphos (0.063 g, 0.108 mmol) were added and the light brown mixture was again degassed and backfilled with argon gas. After refluxing for 16 h the mixture was filtered through silica gel and purified by silica gel chromatography using 10% EtOAc in hexanes, to yield 0.483 g, (2.01 mmol, 94 %) of the desired product as a viscous yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.61 (1H, dd, *J*=7.7, 1.5 Hz), 7.52 (1H, dm, *J*=9.5 Hz), 7.22 (7H, m), 5.75 (1H, dd, *J*=17.4, 1.2 Hz), 5.36 (1H, dd, *J*=11.0, 1.2 Hz), 4.81 (2H, s), 2.12 (1H, broad-s). **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 141.58, 139.18, 134.61,

133.78, 133.66, 132.71, 132.14, 128.99, 128.93, 128.81, 128.14, 128.06, 126.70, 116.95, 63.97.



113

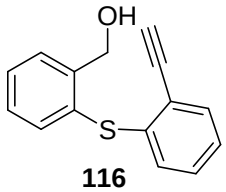
2-(2-Vinylphenylthio)benzaldehyde. To a solution of 2-(2-vinylphenylthio)benzyl alcohol (0.483 g, 1.99 mmol) in benzene (20 mL) was added 88% active manganese oxide (1.97 g, 19.9 mmol) and the mixture was then stirred for 3 days at room temperature. The mixture was then filtered through celite and the filtrate concentrated *in vacuo*. This crude residue was then purified by silica gel chromatography using 5 % EtOAc in hexanes to yield 0.459 g, (1.91 mmol, 96 %) of the desired product as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 10.36 (1H, s), 7.87 (1H, dd, *J*=7.5, 1.8 Hz), 7.72 (1H, dd, *J*=7.8, 1.4 Hz), 7.45 (2H, m), 7.32 (2H, m), 7.22 (1H, d, *J*=11.0 Hz), 7.16 (1H, d, *J*=11.0 Hz), 6.83 (1H, dm, *J*=7.9 Hz), 5.75 (1H, dd, *J*=17.4, 1.1 Hz), 5.30 (1H, dd, *J*=10.2, 1.1 Hz).



114

3,4-Dihydro-2,3-benzo-4-methylbenzo[b]thiepin-5(2H)-one. To a degassed solution of 2-(2-vinylphenylthio)benzaldehyde (0.100 g, 0.416 mmol) in dry CH_2Cl_2 (4 mL) was added Rhodiumtris(triphenylphosphine) chloride (0.038 g, 0.042 mmol). The brick red

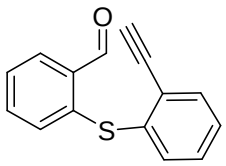
solution was degassed, backfilled with argon gas, and refluxed for 16 h in an oven dried Schlenk flask with condenser attached. Upon completion the solvent was removed *in vacuo*, and the crude residue purified by silica gel chromatography using 30% CH_2Cl_2 in hexanes to yield 0.0863 g, (0.358 mmol, 86 %) of the desired product as a pale yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 8.18 (1H, dd, *J*=7.9, 1.7 Hz), 7.69 (1H, dm, *J*=12.4 Hz), 7.62 (1H, dd, *J*=7.8, 1.3), 7.44 (3H, m). 7.32 (1H, m), 7.20 (1H, m), 4.96 (1H, q, *J*=6.7 Hz), 1.73 (3H, d, *J*=6.7). **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 193.65, 141.80, 140.47, 136.53, 135.03, 132.51, 131.93, 131.52, 130.75, 130.47, 127.07, 126.91, 126.51, 49.28, 13.39.



116

(2-(2-Ethynylphenylthio)phenyl)methanol. (2-Mercaptophenyl)methanol (0.300 g, 2.14 mmol), 1-bromo-2-ethynylbenzene (0.208 mL, 2.14 mmol), diisopropylethylamine (0.750 mL, 4.29 mmol), and dioxane (20.0 mL) was added to an oven dried round bottom Schlenk flask with condenser attached. The solution was then degassed 3 times and backfilled with argon gas, at which point trisdibenzylidene acetone dipalladium (0.048 g, 0.054 mmol), and xantphos (0.063 g, 0.108 mmol) were added and the light brown mixture was flushed with argon gas. After refluxing for 16 h the mixture was filtered through silica gel and purified by silica gel chromatography using 10% EtOAc in hexanes, to yield 0.314 g, (1.31 mmol, 61 %) of the desired product as a viscous oil. **^{1}H**

NMR (300 MHz, $CDCl_3$) δ: 7.60 (1H , m), 7.48 (3H, m), 7.36 (1H, m), 7.14 (2H, qm, *J*=7.5 Hz), 6.77 (1H, dm, *J*=9.2 Hz), 4.80 (2H, s), 3.48 (1H, s), 2.15 (1H, broad-s).



117

2-(2-Ethynylphenylthio)benzaldehyde. To a solution of (2-(2-ethynylphenylthio)phenyl)methanol (0.314 g, 1.31 mmol) in benzene (15 mL) was added 88% active manganese oxide (1.29 g, 13.1 mmol) and the mixture was then stirred for 3 days at room temperature. The mixture was then filtered through celite and the filtrate concentrated *in vacuo*. This crude residue was then purified by silica gel chromatography using 2-5 % Et_2O in hexanes to yield 0.262 g, (1.10 mmol, 84 %) of the desired product as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 10.48 (1H, s), 7.96 (1H, dd, *J*=7.5, 1.8 Hz), 7.59 (1H, m), 7.52 (1H, m), 7.43 (1H, m), 7.29 (3H, m), 7.19 (1H, m), 3.35 (1H, s).

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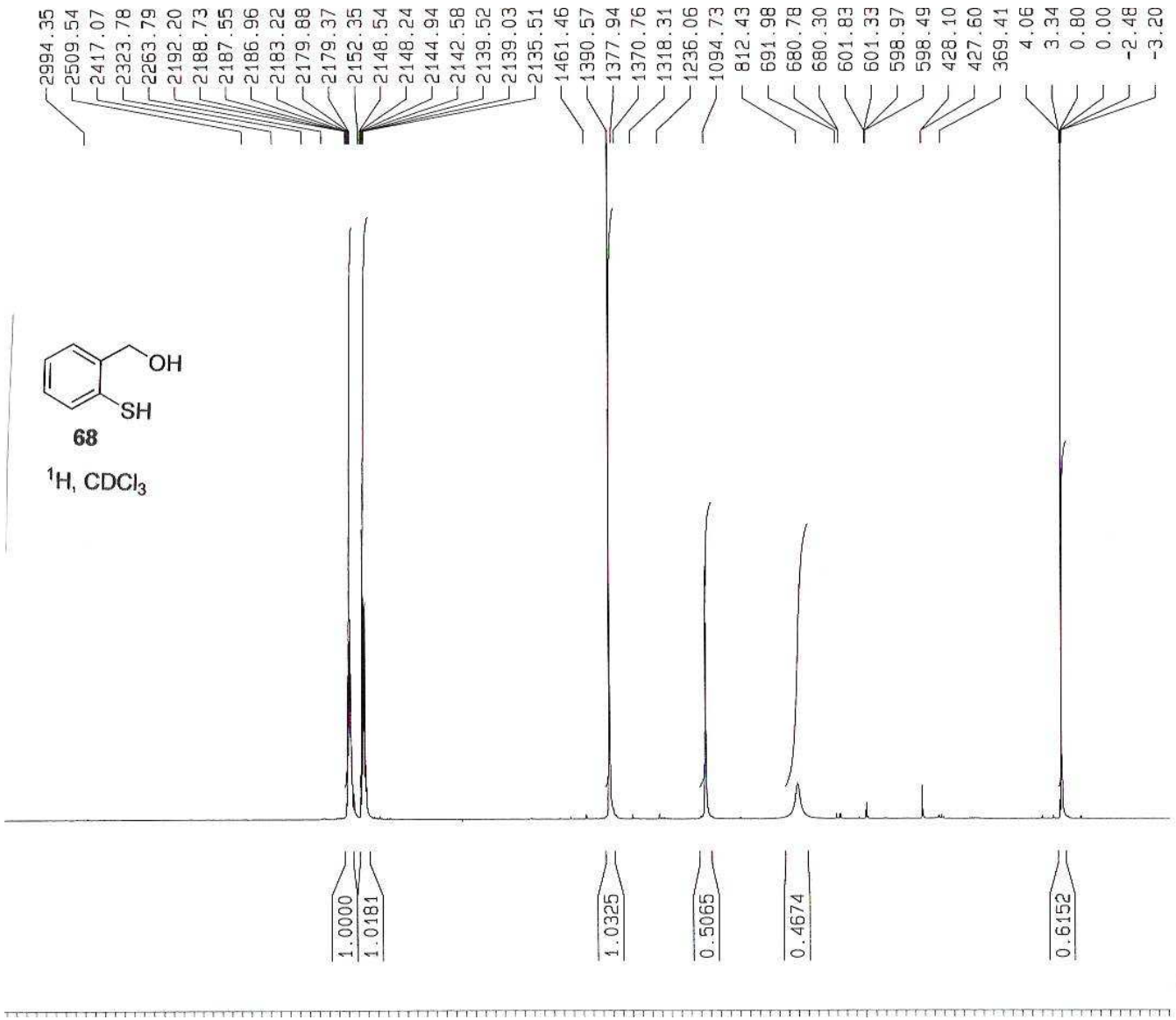
Appendix A

Spectral Data



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PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839
FIDRES	0.094190
AQ	5.3084660
RG	90.5
DW	81.000
DE	6.00
TE	300.0
D1	1.00000000
========== CHANNEL f1	
NUC1	1H
P1	11.00
PL1	0.00
SFO1	300.1318534
F2 - Processing paramet	
SI	32768
SF	300.1300124
WDW	nc
SSB	0
LB	0.00
GB	0
PC	1.00
1D NMR plot parameters	
CX	20.00
F1P	11.991
F1	3598.83
F2P	-1.108
F2	-332.44
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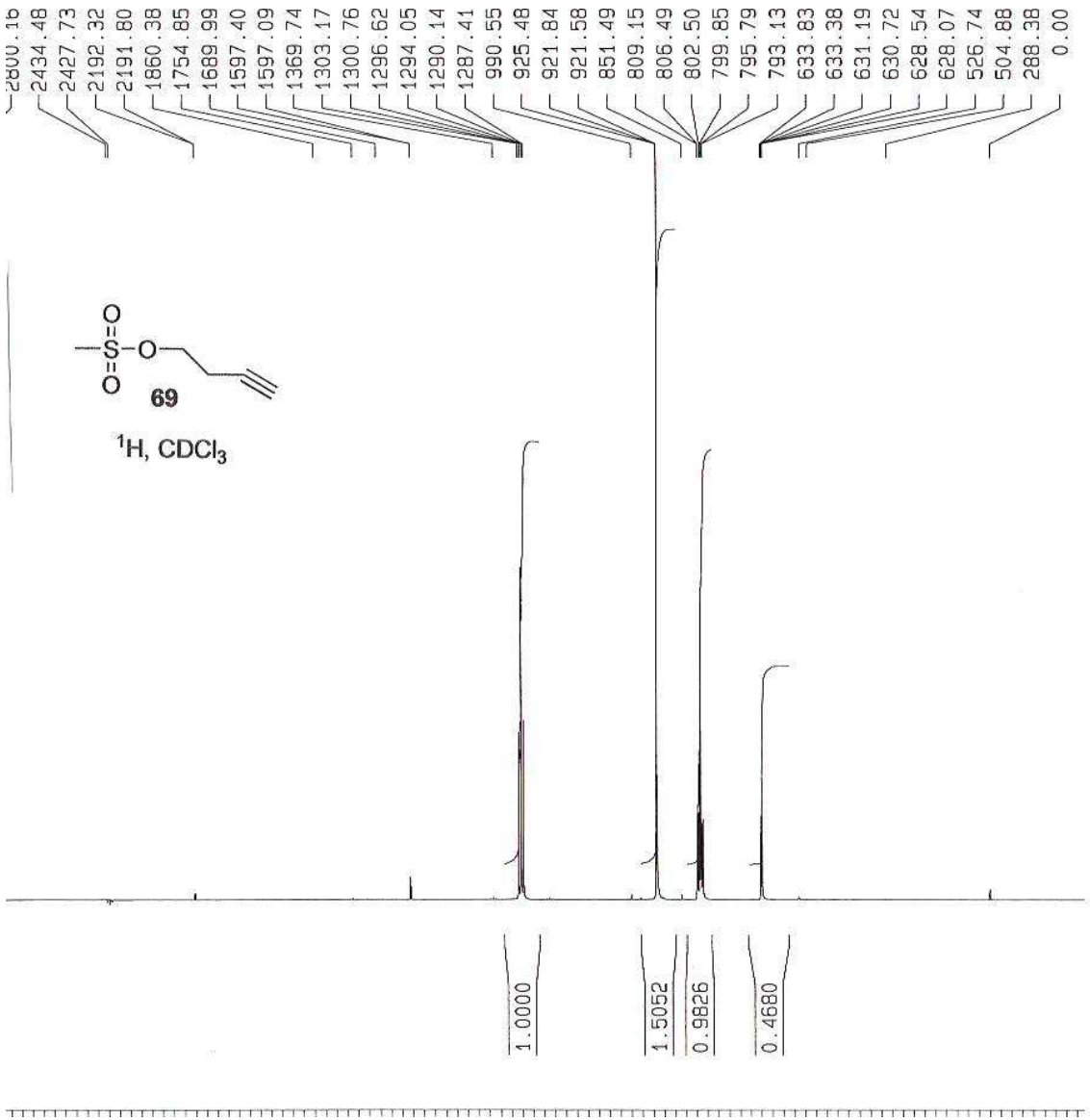
HZCM	196.56339

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PROCNO                1

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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 se
RG                71.8
DW               81.000 us
DE                6.00 us
TE               300.0 K
D1           1.00000000 se

============ CHANNEL f1 ==
NUC1                 1H
P1                11.00 us
PL1                0.00 dE
SFO1        300.1318534 MH

F2 - Processing parameters
SI                32768
SF          300.1299928 MH
WDW                  no
SSB                   0
LB                 0.00 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX                20.00 cm
F1P               12.056 pp
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F2P               -0.861 pp
F2              -258.32 Hz
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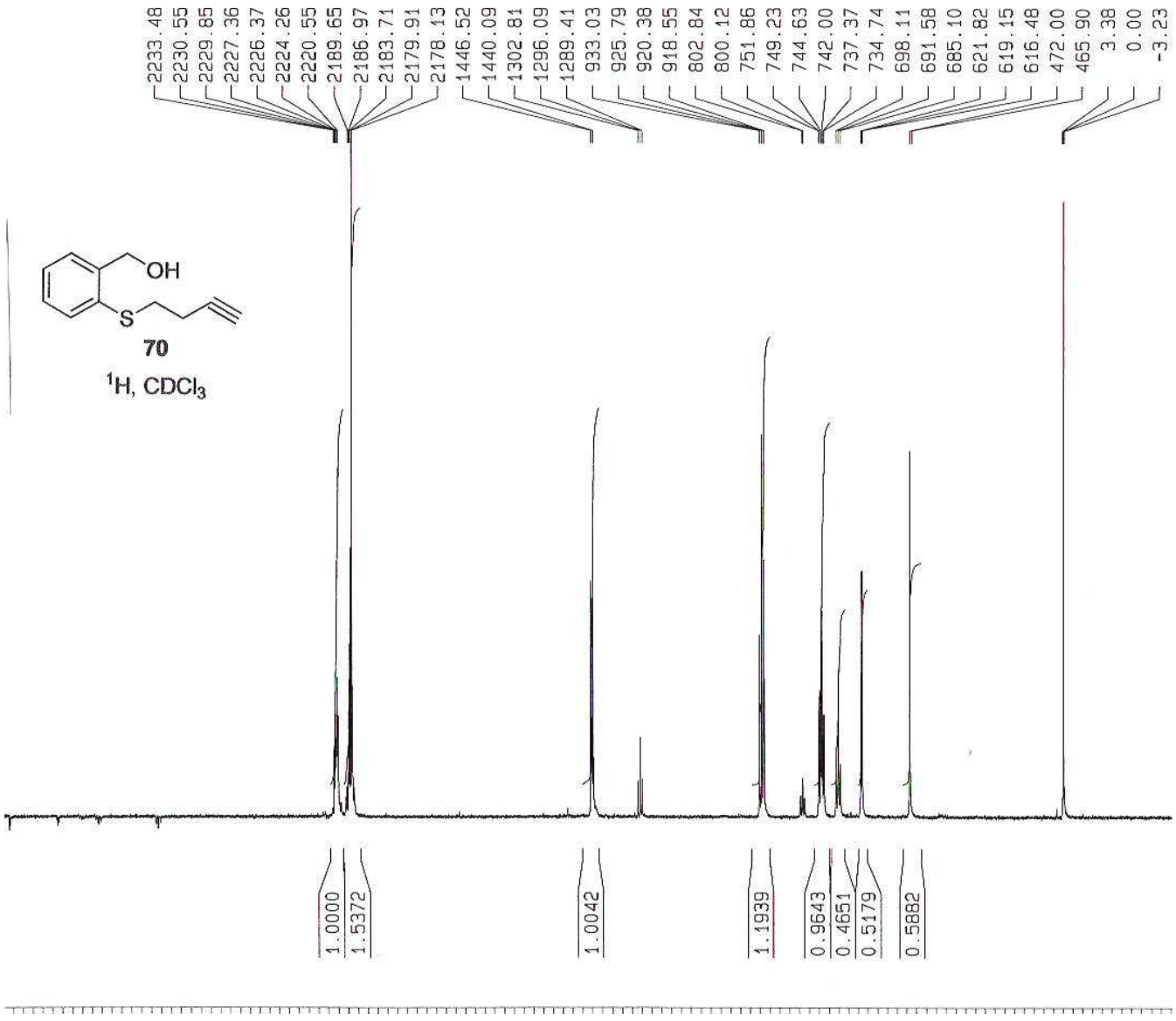


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PROCNO                1

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TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             6172.839
FIDRES          0.094190
AQ              5.308466
RG                912.3
DW                81.000
DE                 6.00
TE                300.0
D1             1.0000000

============ CHANNEL f1
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P1                 11.00
PL1                 0.00
SFO1          300.1318534

F2 - Processing paramet
SI                 32768
SF          300.1300052
WDW                   no
SSB                    0
LB                  0.00
GB                     0
PC                  1.00

1D NMR plot parameters
CX                 20.00
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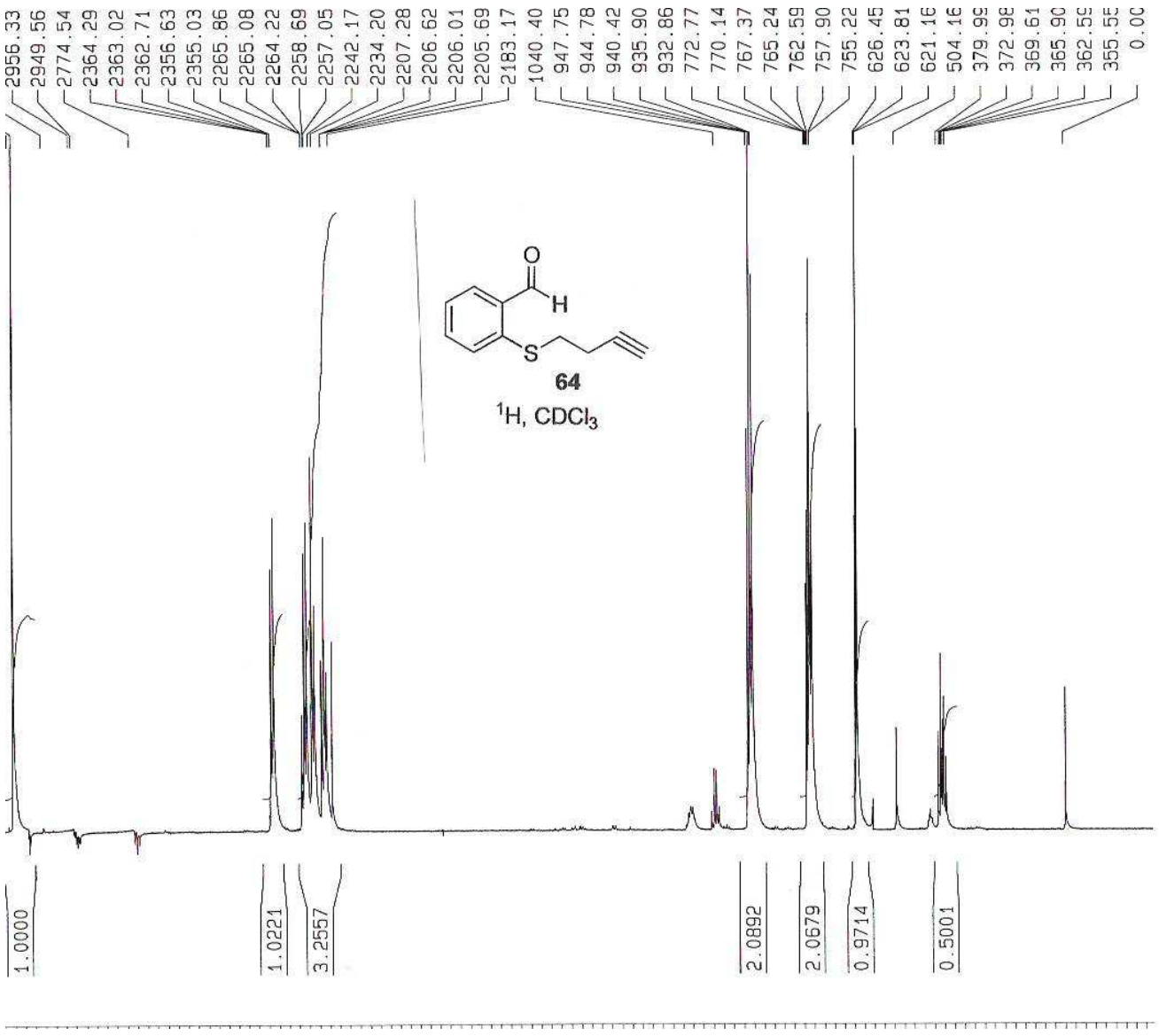

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TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839
FIDRES	0.094190
AQ	5.3084660
RG	143.7
DW	81.000
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TE	300.0
D1	1.00000000
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SF	300.1300021
WDW	nc
SSB	0
LB	0.00
GB	0
PC	1.00
1D NMR plot parameters	
CX	20.00
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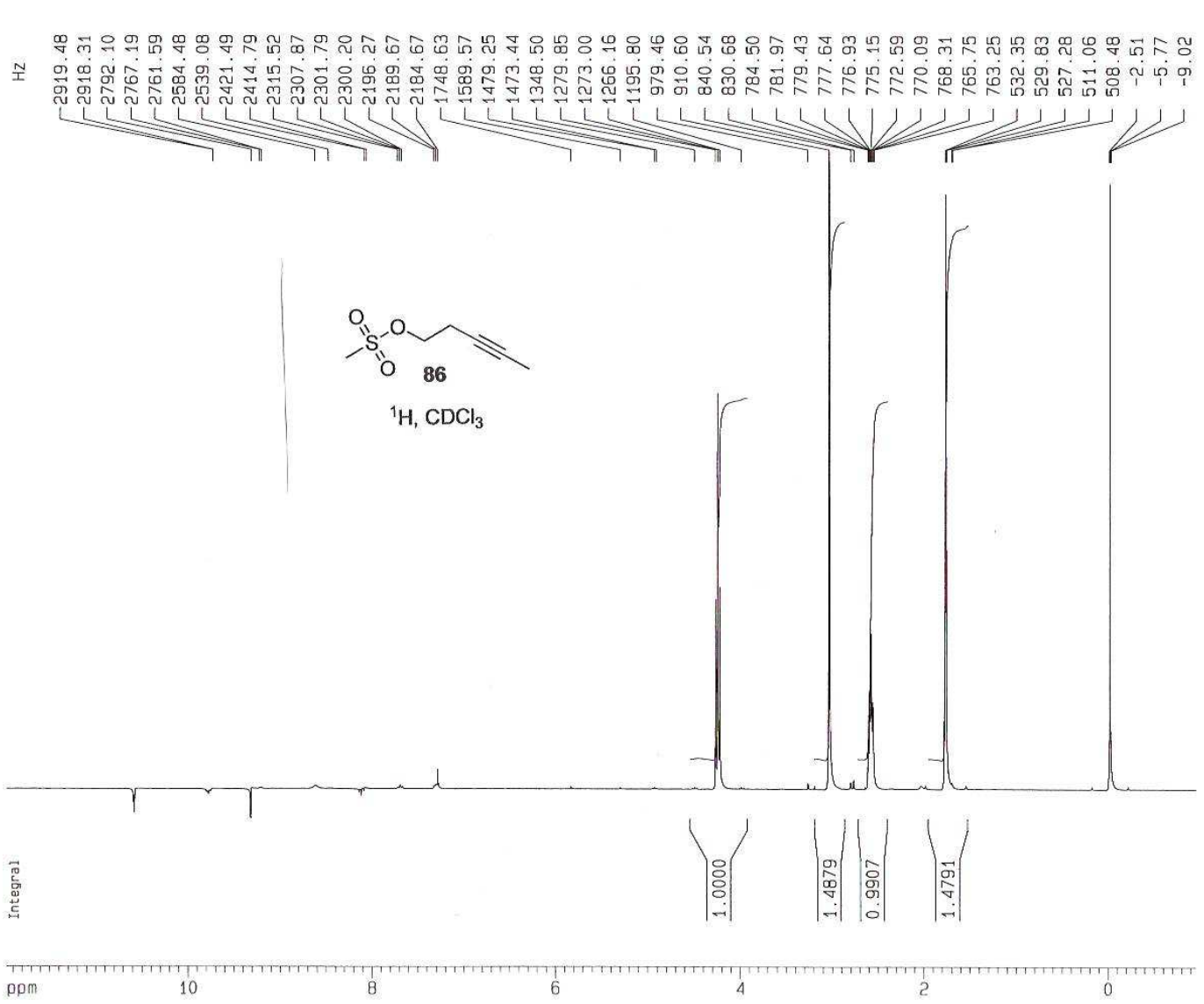

Current Data Parameters

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PROCNO	1

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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	71.8
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

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PL1	0.00 dB
SFO1	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	11.964 ppm
F1	3590.81 Hz
F2P	-0.953 ppm
F2	-285.95 Hz
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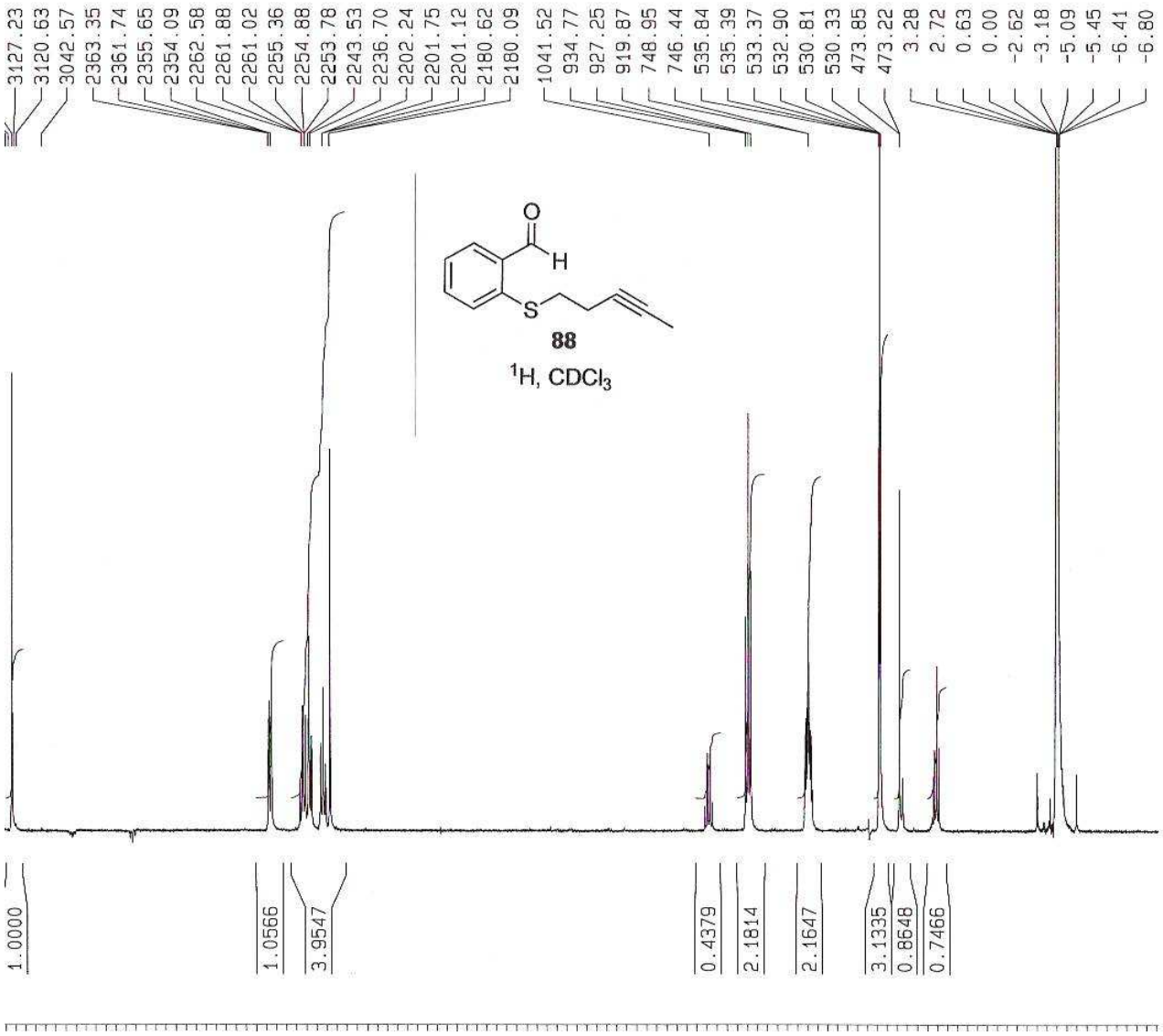
HZCM	193.83807 Hz/cm



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PULPROG	zg30
TD	37036
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839
FIDRES	0.166671
AQ	2.9999659
RG	362
DW	81.000
DE	6.00
TE	300.0
D1	1.00000000
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NUC1	1H
P1	11.00
PL1	0.00
SFO1	300.1318534
F2 - Processing paramet	
SI	32768
SF	300.1300045
WDW	no
SSB	0
LB	0.00
GB	0
PC	1.00
1D NMR plot parameters	
CX	20.00
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F1	3586.29
F2P	-1.013
F2	-304.10
PPMCM	0.64812
HZCM	194.51938

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729.07
727.24
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PROCNO 1
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PULPROG zg30
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SOLVENT CDCl3
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FIDRES 0.166671 Hz
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RG 128
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F2 - Processing parameters
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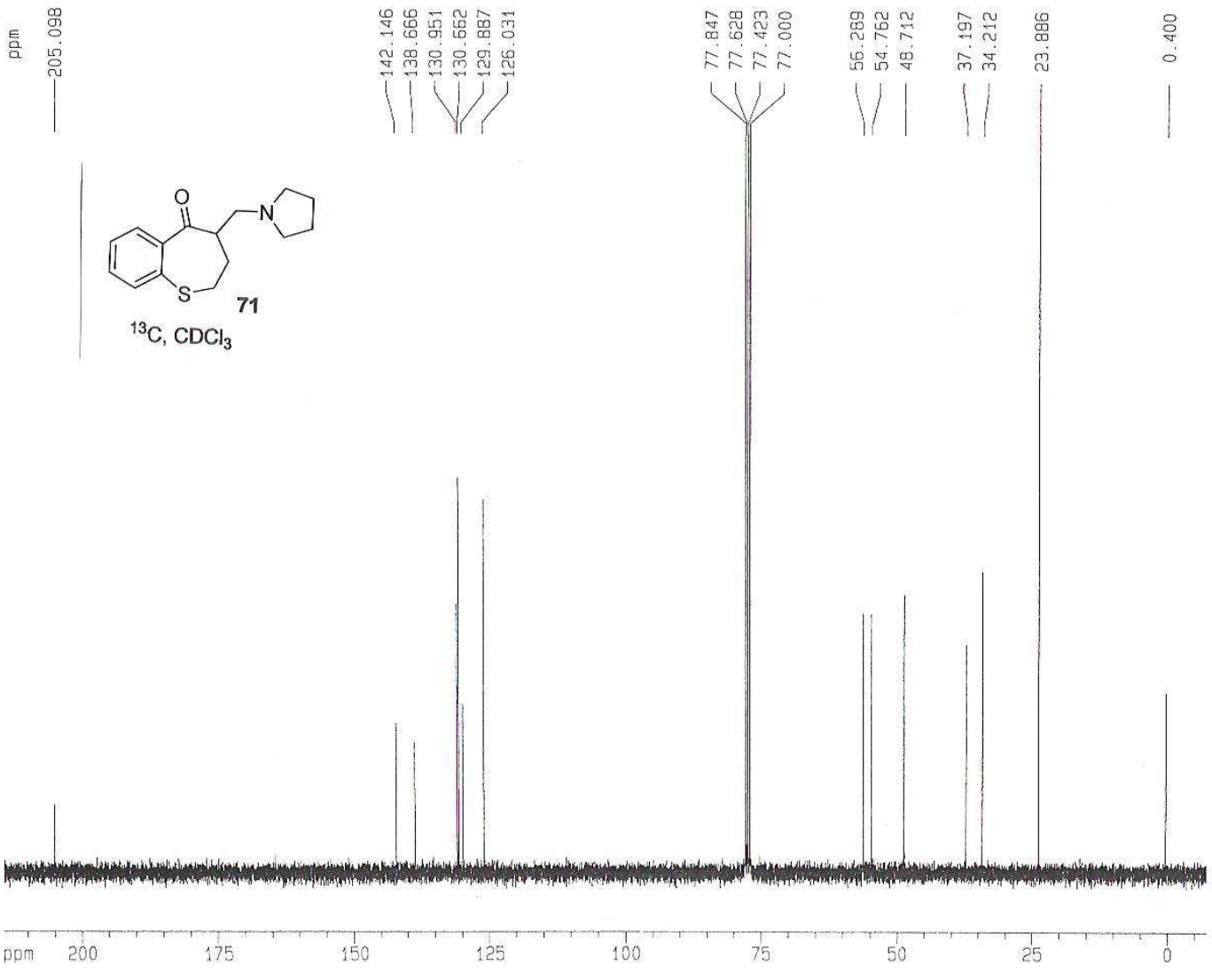


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NS                    2048
DS                       4
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AQ               1.7400308 sec
RG                 4597.6
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TE                 300.0 K
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NUC1                  13C
P1                  7.10 usec
PL1                -1.50 dB
SFO1           75.4760200 MHz

============ CHANNEL f2 ============
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PL2                 0.00 dB
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PL13               18.00 dB
SFO2          300.1312005 MHz

F2 - Processing parameters
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SF             75.4677190 MHz
WDW                    no
SSB                     0
LB                   0.00 Hz
GB                      0
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1D NMR plot parameters
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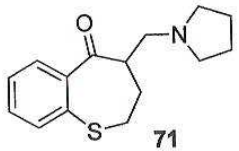

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FT-IR

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Peak#	10	11	12	13	14	15	16	17	18
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Height	66.958	74.043	71.284	75.932	76.796	73.592	77.887	73.295	36.038

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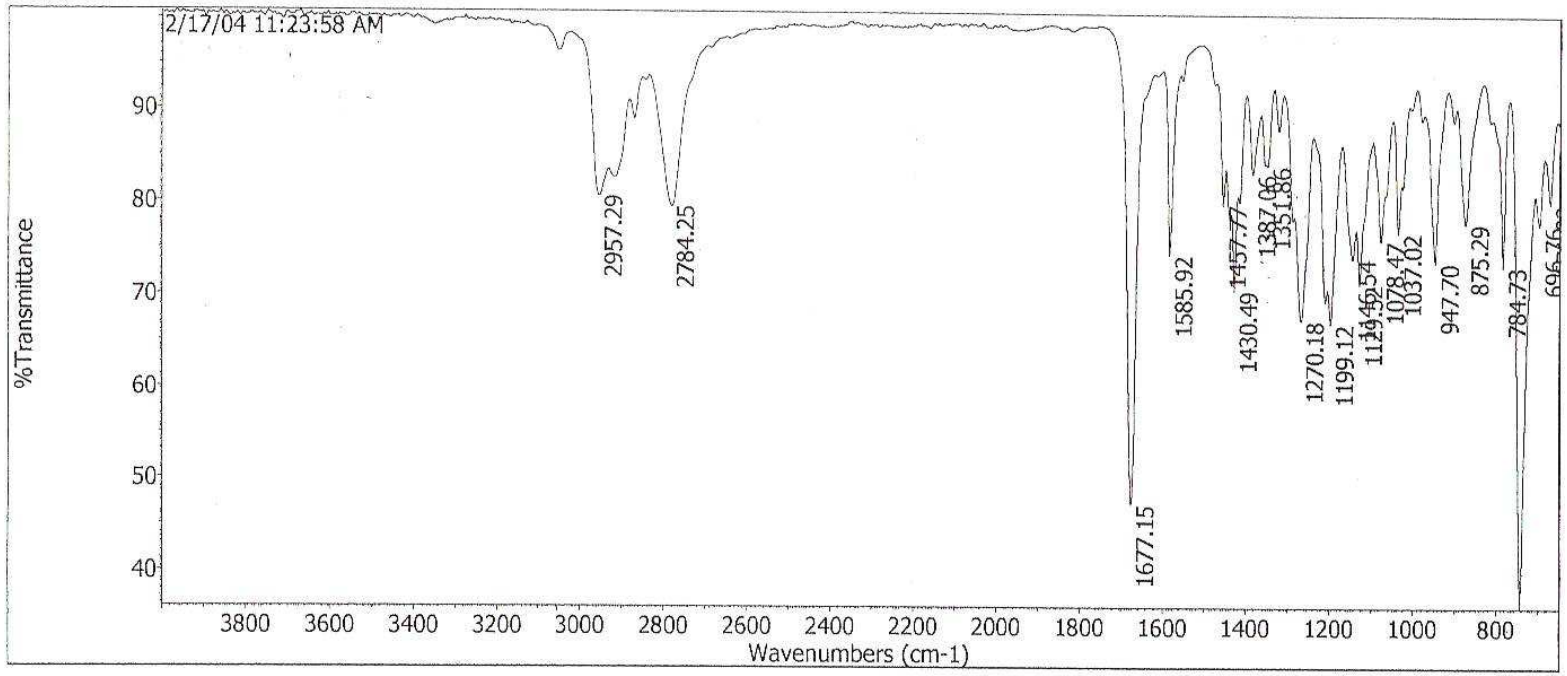

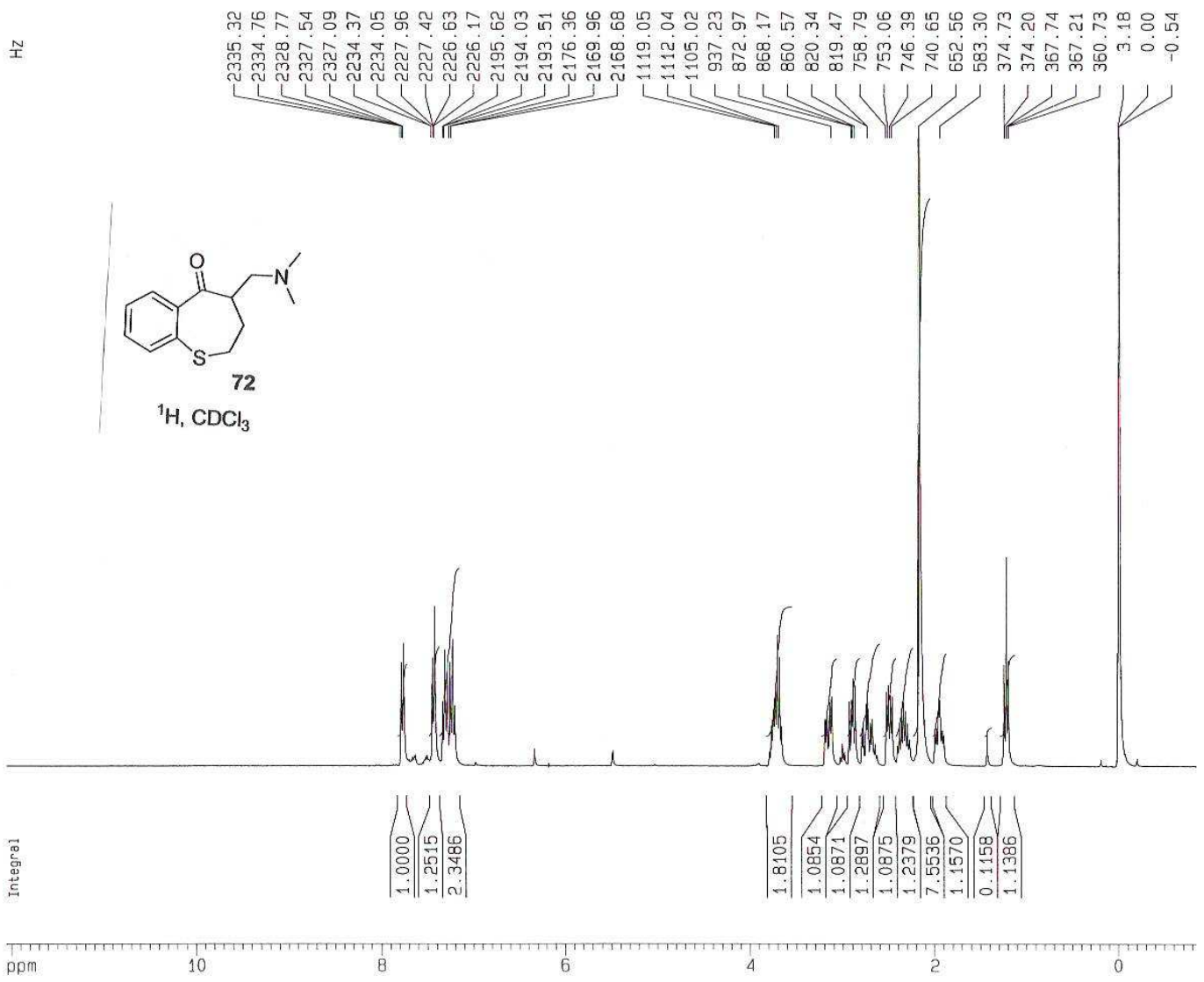

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DS	2
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FIDRES	0.094190 Hz
AQ	5.3084660 sec
RG	114
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
========== CHANNEL f1 =========	
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PL1	0.00 dB
SFO1	300.1318534 MHz
F2 - Processing parameters	
SI	32768
SF	300.1299997 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.00
1D NMR plot parameters	
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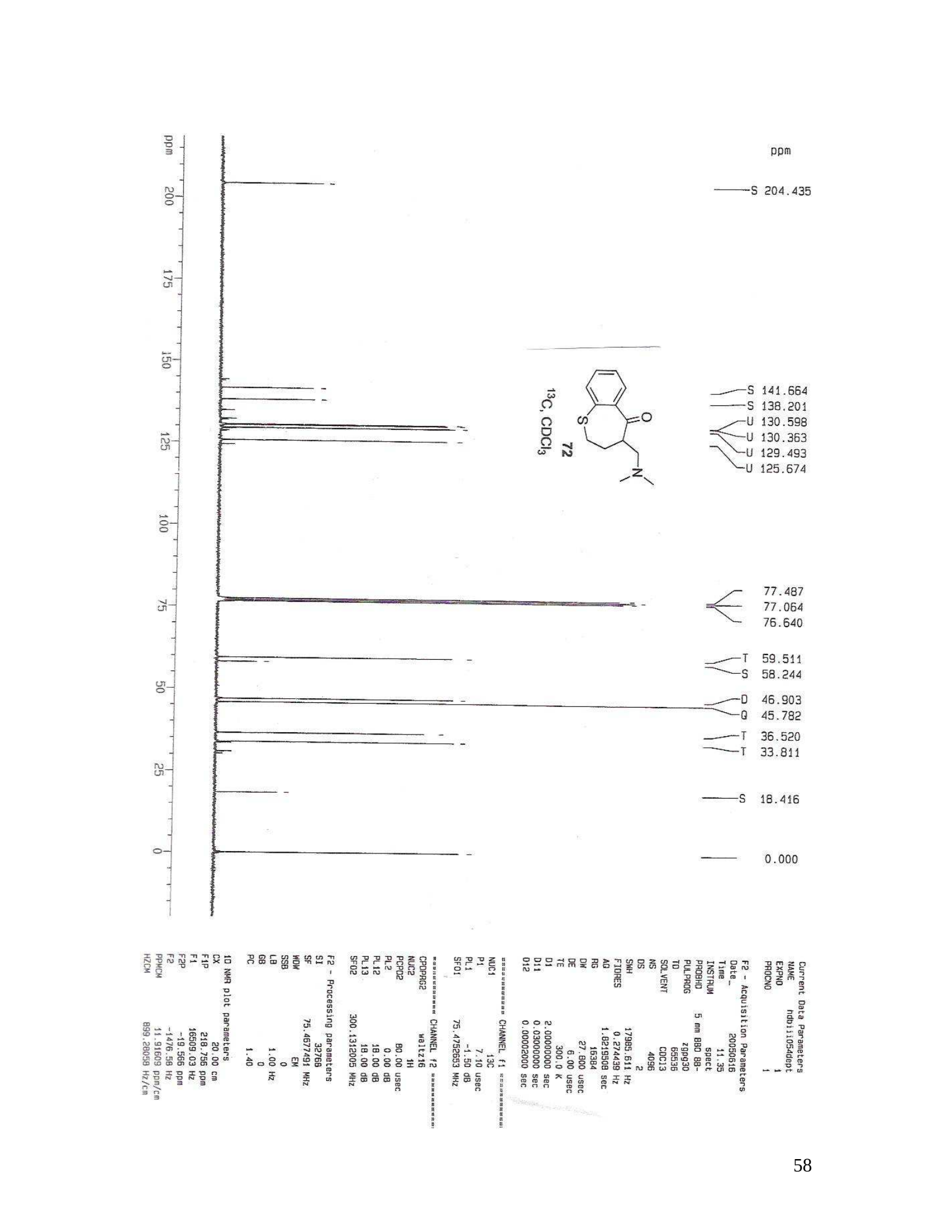
F2P	-0.838 ppm
F2	-251.63 Hz
PPMCM	0.64471 ppm/cm
HZCM	193.49741 Hz/cm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13C, CDCl3
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PROCNO 1
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DE 6.00 usec
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D11 0.03000000 sec
D12 0.00002000 sec
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SFO1 75.4752693 MHz
CHANNEL f2
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NUC2 1H
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PL2 0.00 dB
PL12 18.00 dB
PL13 18.00 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
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SSB 0
LB 1.00 Hz
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F2P -19.566 ppm
F2 -1476.58 Hz
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HZCM 899.28058 Hz/cm

Peak#	1	2	3	4	5	6	7	8	9
Position	3055.65	2941.50	2855.48	2817.88	2765.17	1678.19	1585.96	1457.54	1430.83
Height	95.750	83.401	89.043	83.307	81.177	46.856	73.537	68.005	67.431

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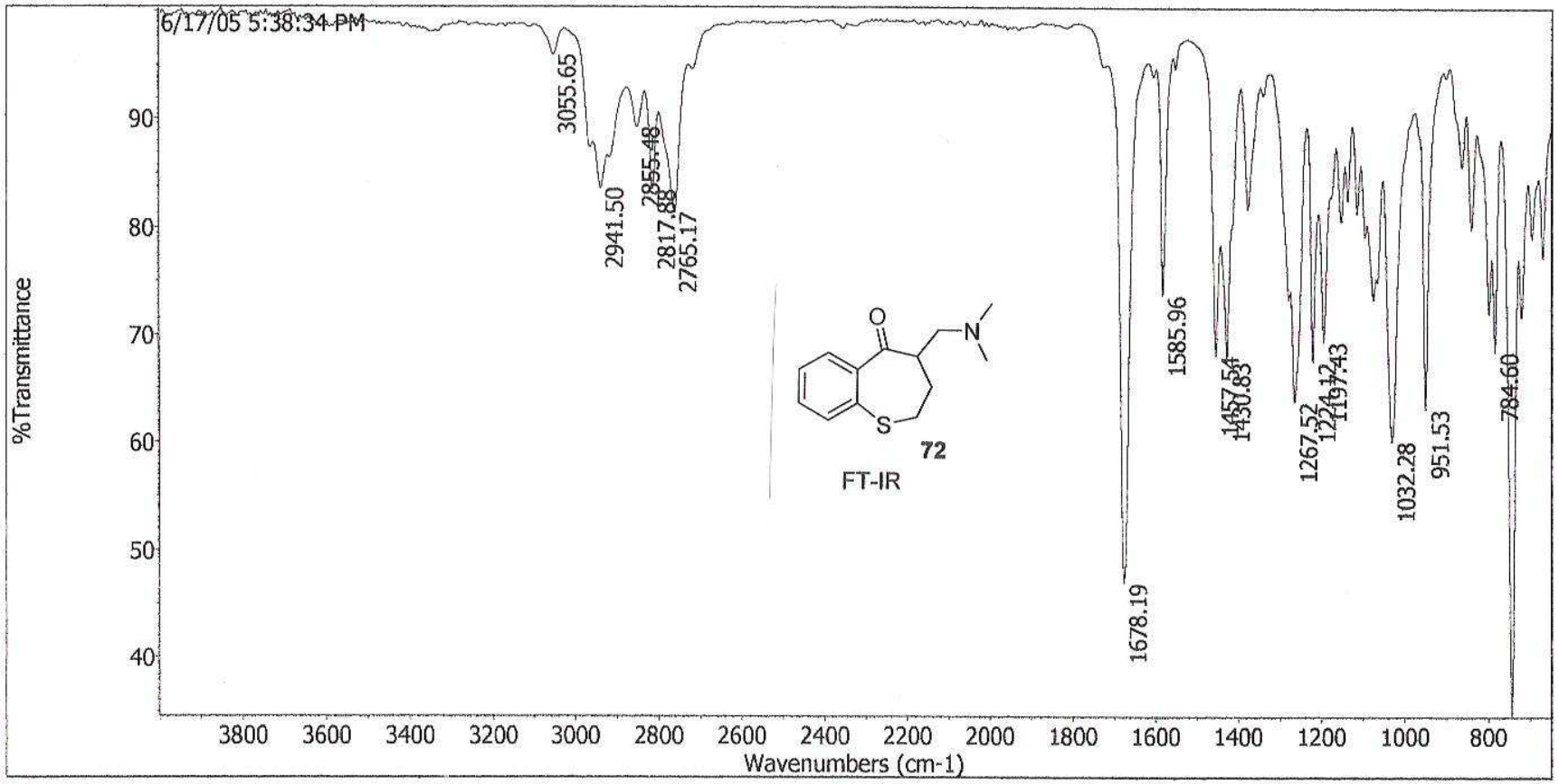
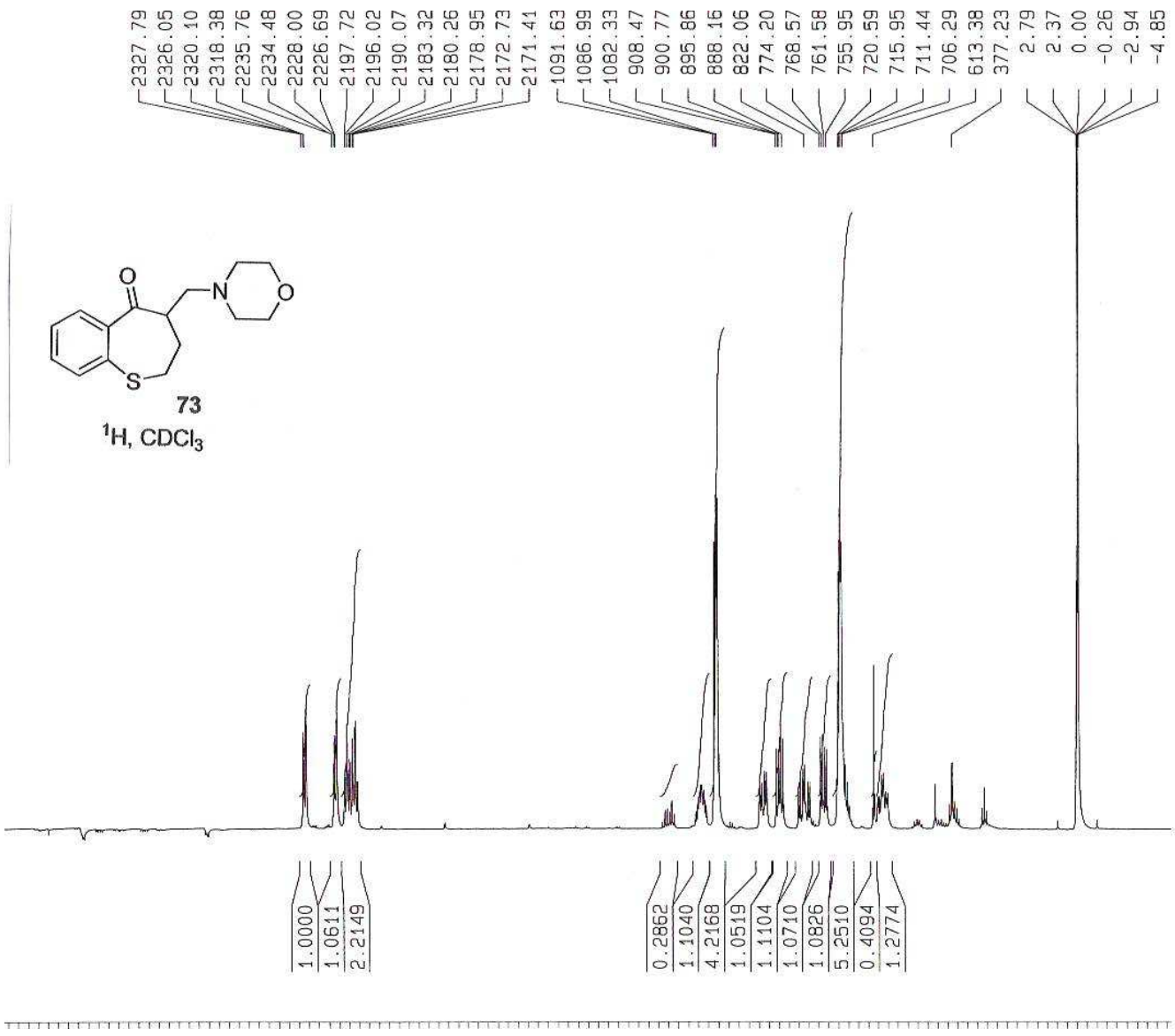
Position	1267.52	1224.12	1197.43	1032.28	951.53	784.60	743.00		
Height	63.695	67.458	69.289	60.046	63.013	68.356	34.352		





EXPNO	1
PROCNO	1
F2 - Acquisition Parame	
Date_	20050812
Time	19.12
INSTRUM	spect
PROBHD	5 mm BBO BB-
PULPROG	zg30
TD	37036
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839
FIDRES	0.166671
AQ	2.9999659
RG	128
DW	81.000
DE	6.00
TE	300.0
D1	1.00000000
========== CHANNEL f1	
NUC1	1H
P1	11.00
PL1	0.00
SFO1	300.1318534
F2 - Processing paramet	
SI	32768
SF	300.1300018
WDW	no
SSB	0
LB	0.00
GB	0
PC	1.00
1D NMR plot parameters	
CX	20.00
F1P	12.004
F1	3602.65
F2P	-0.938
F2	-280.93
PPMCM	0.64698
HZCM	194.17873

NAME mdbii077dept
EXPNO 1
PROCNO 1

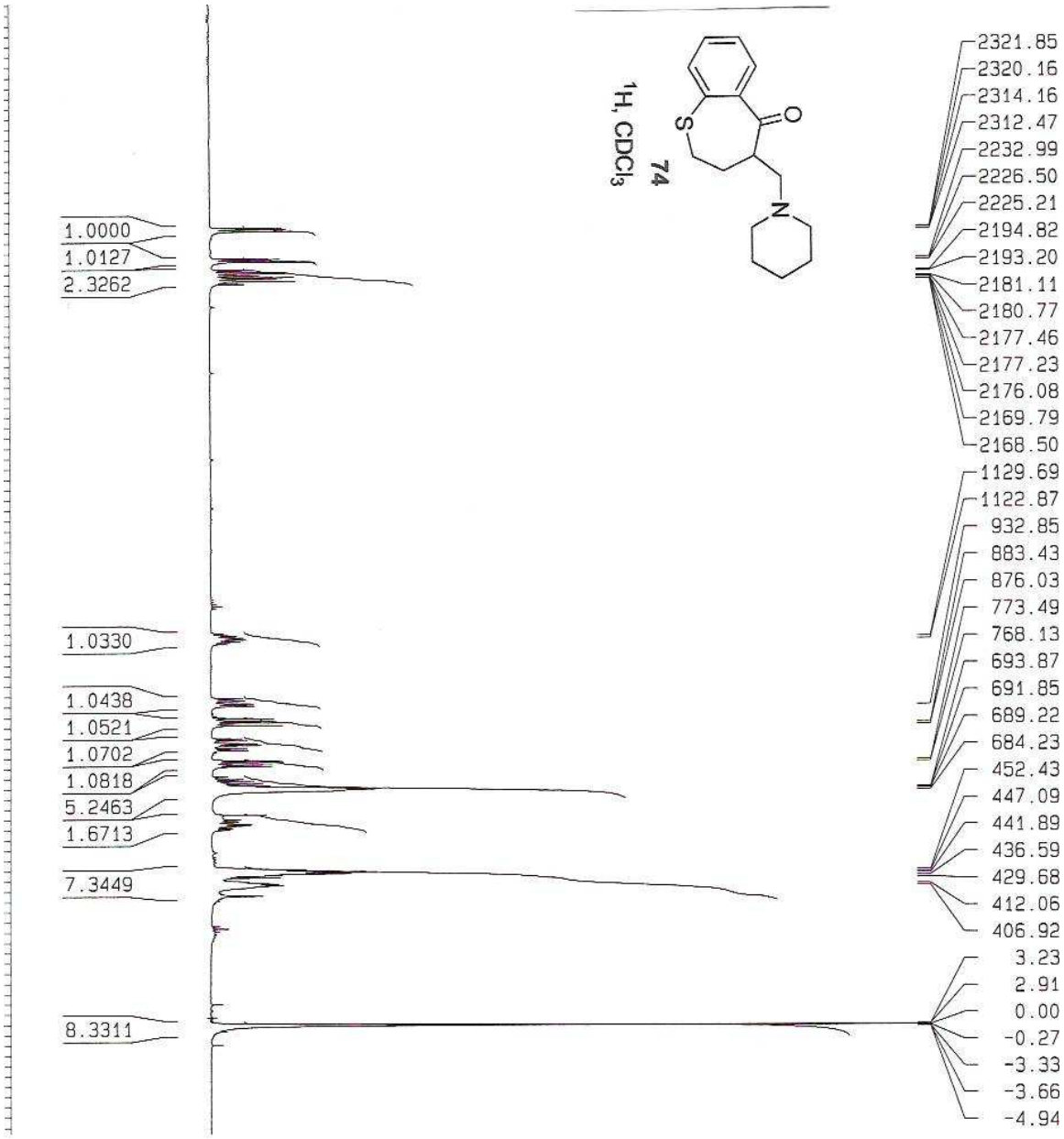
F2 - Acquisition Parame
Date_ 20050813
Time 14.57
INSTRUM spect
PROBHD 5 mm BBO BB-
PULPROG zpgp30
TD 65536
SOLVENT CDCl3
NS 6144
DS 2
SWH 17985.611
FIDRES 0.274435
AQ 1.821950
RG 16384
DW 27.800
DE 6.00
TE 300.0
D1 2.000000
D11 0.030000
D12 0.000020

======== CHANNEL f1
NUC1 13C
P1 7.10
PL1 -1.50
SF01 75.475265

======== CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00
PL2 0.00
PL12 18.00
PL13 18.00
SF02 300.131200

F2 - Processing parame
SI 32768
SF 75.467749
WDW EM
SSB 1.00
LB 0.00
GB 0
PC 1.40

1D NMR plot parameters
CX 20.00
F1P 218.75
F1 16508.6
F2P -19.57
F2 -1476.9

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EXPNO                 1
PROCNO                1

F2 - Acquisition Parame
Date_              20050811
Time                  19.29
INSTRUM                spect
PROBHD     5 mm BBO BB-
PULPROG               zg30
TD                   37036
SOLVENT              CDCl3
NS                      16
DS                       2
SWH                6172.839
FIDRES            0.166671
AQ                2.9999659
RG                      128
DW                 81.000
DE                  6.00
TE                 300.0
D1                 1.00000000

========== CHANNEL f1
NUC1                   1H
P1                 11.00
PL1                 0.00
SFO1          300.1318534

F2 - Processing paramet
SI                   32768
SF            300.1300040
WDW                     no
SSB                      0
LB                    0.00
GB                       0
PC                    1.00

1D NMR plot parameters
CX                   20.00
F1P                11.928
F1                 3579.98
F2P                -1.057
F2                 -317.24
PPMCM              0.6492
HZCM             194.8600
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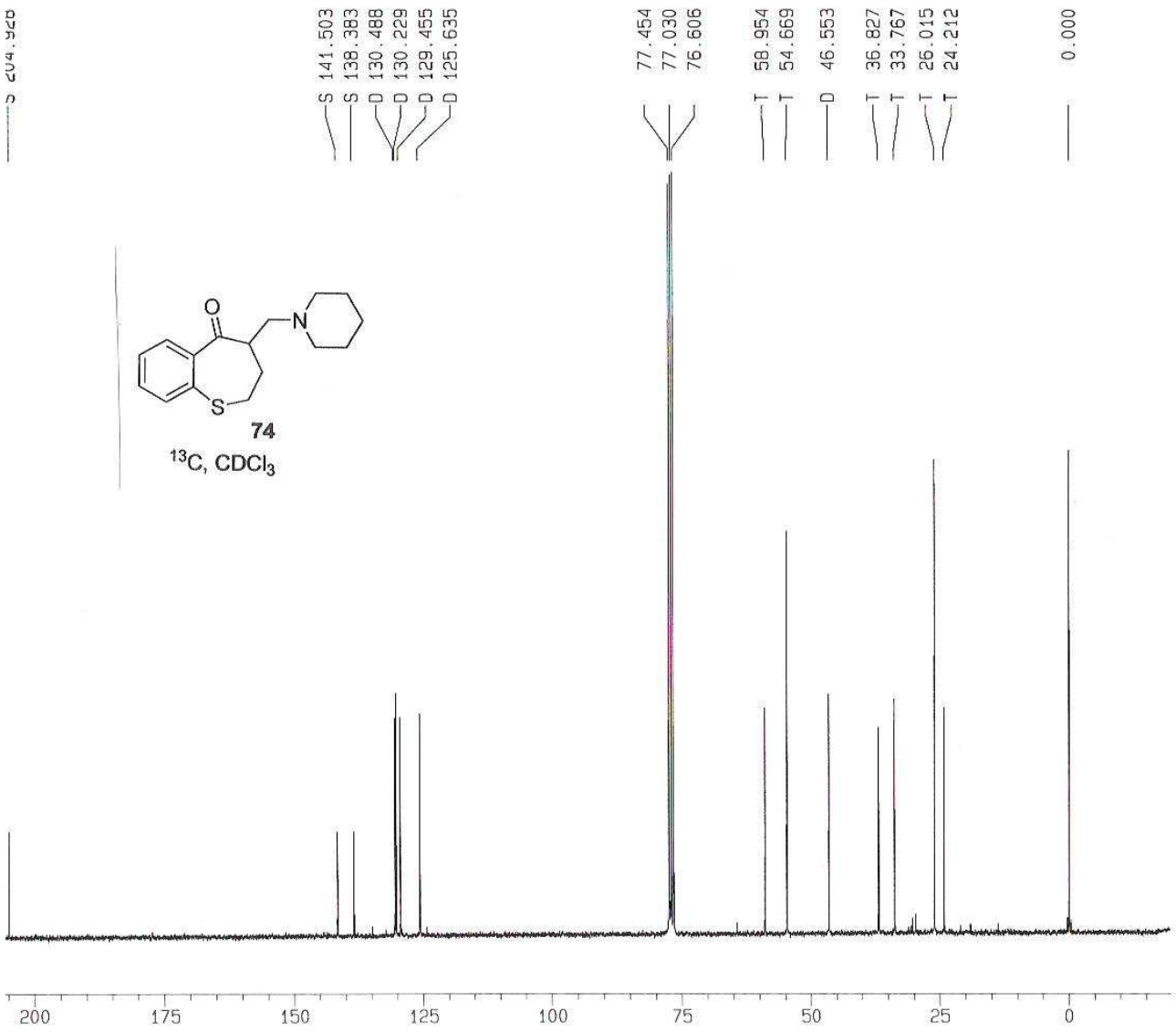


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Current Data Parameters
NAME        hdbiii076dept
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parame
Date_            20050812
Time                13.19
INSTRUM             spect
PROBHD     5 mm BBO BB-
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   512
DS                     2
SWH             17985.611
FIDRES          0.274435
AQ              1.821950E
RG                  1638
DW                 27.800
DE                  6.00
TE                 300.0
D1              2.000000C
D11             0.030000C
D12             0.000200C

============ CHANNEL f1
NUC1                  13C
P1                   7.10
PL1                  -1.50
SFO1            75.475265

============ CHANNEL f2
CPDPRG2           waltz16
NUC2                   1H
PCPD2                80.0
PL2                   0.0
PL12                 18.0
PL13                 18.0
SFO2            300.131200

F2 - Processing paramet
SI                  32768
SF              75.467749
WDW                    EM
SSB                     0
LB                   1.00
GB                      0
PC                   1.40

1D NMR plot parameters
CX                   20.0
F1P                218.75
F1                16509.0
F2P                -19.56
F2                -1476.5
PPMCM             11.9160
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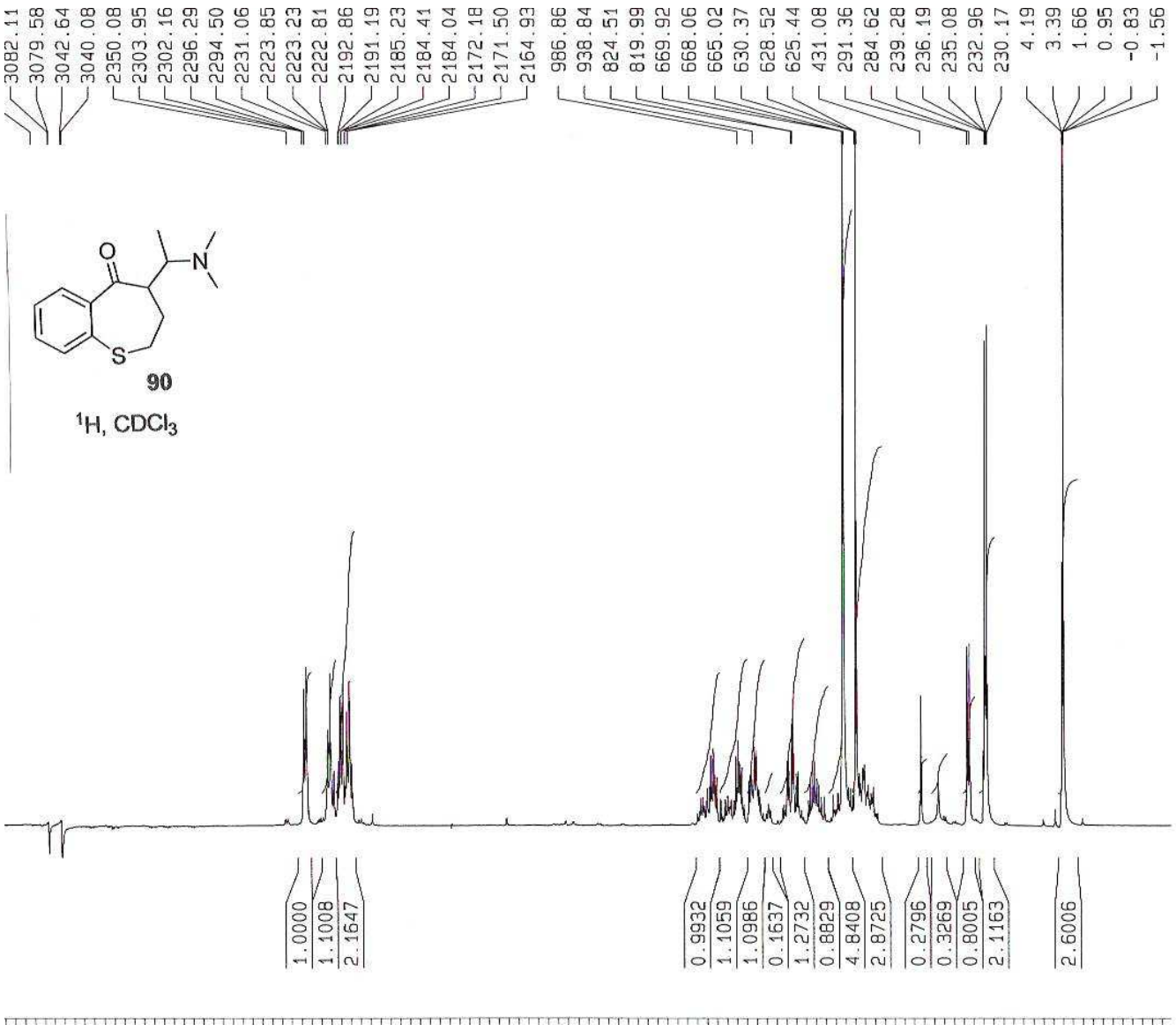
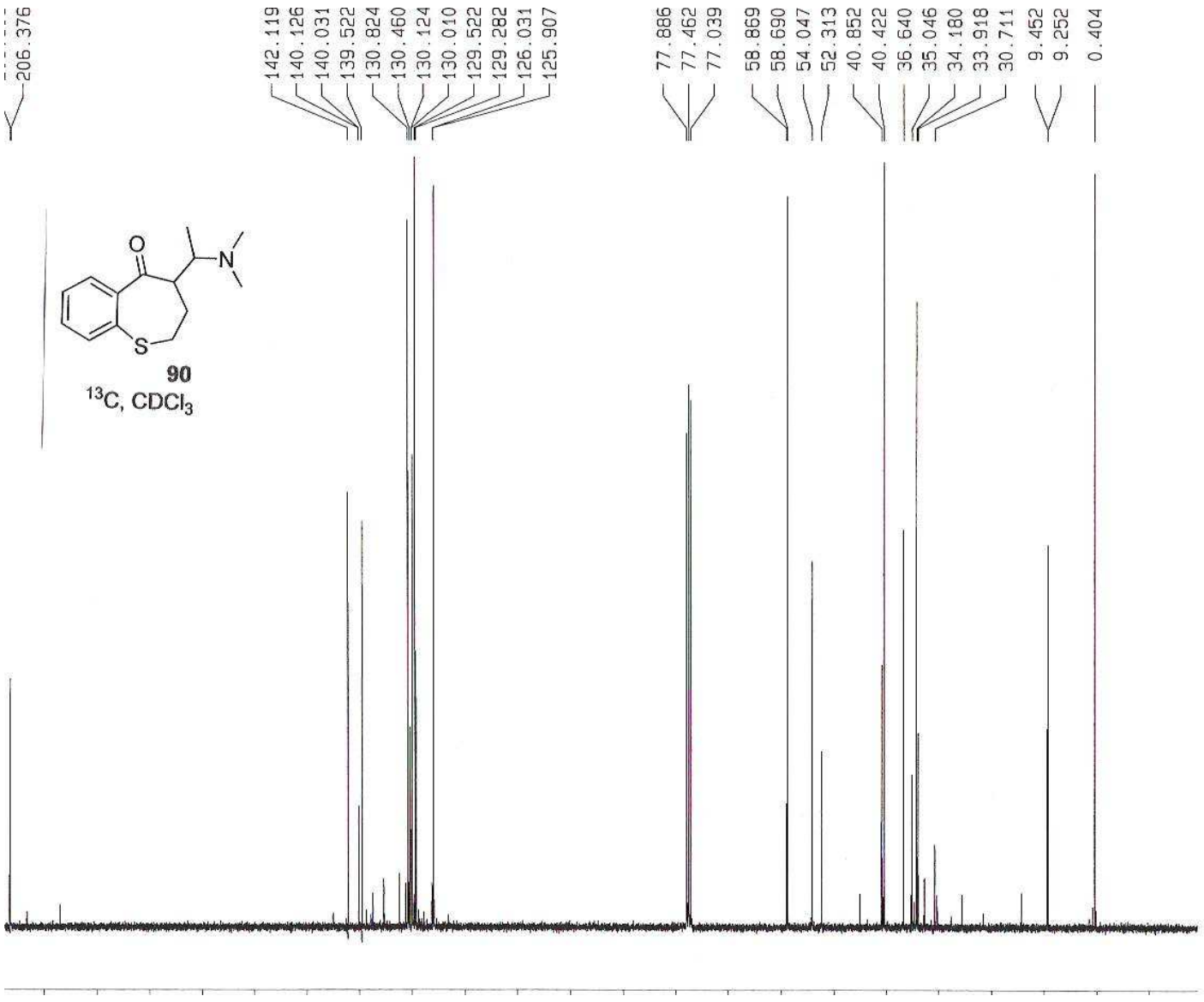
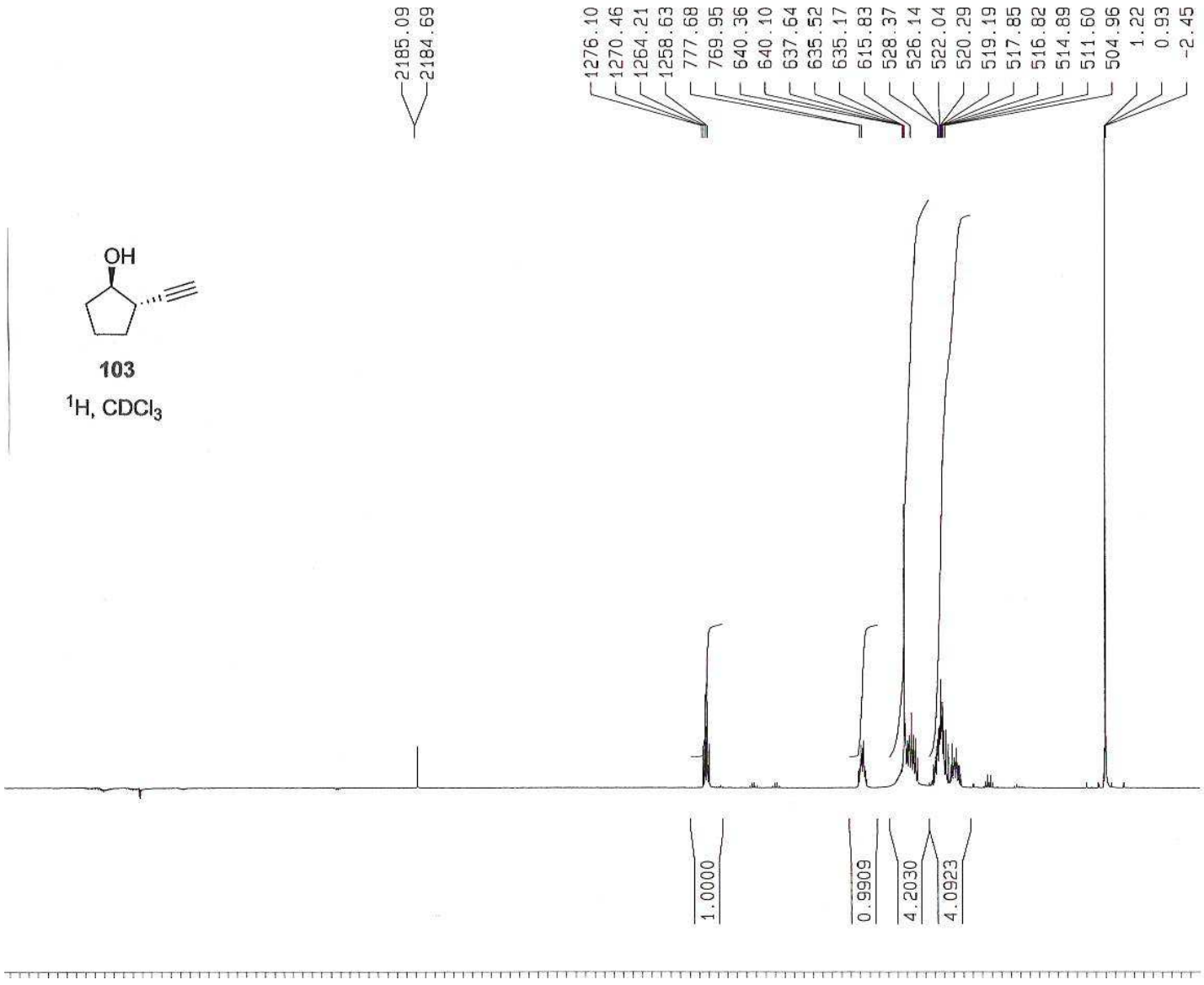


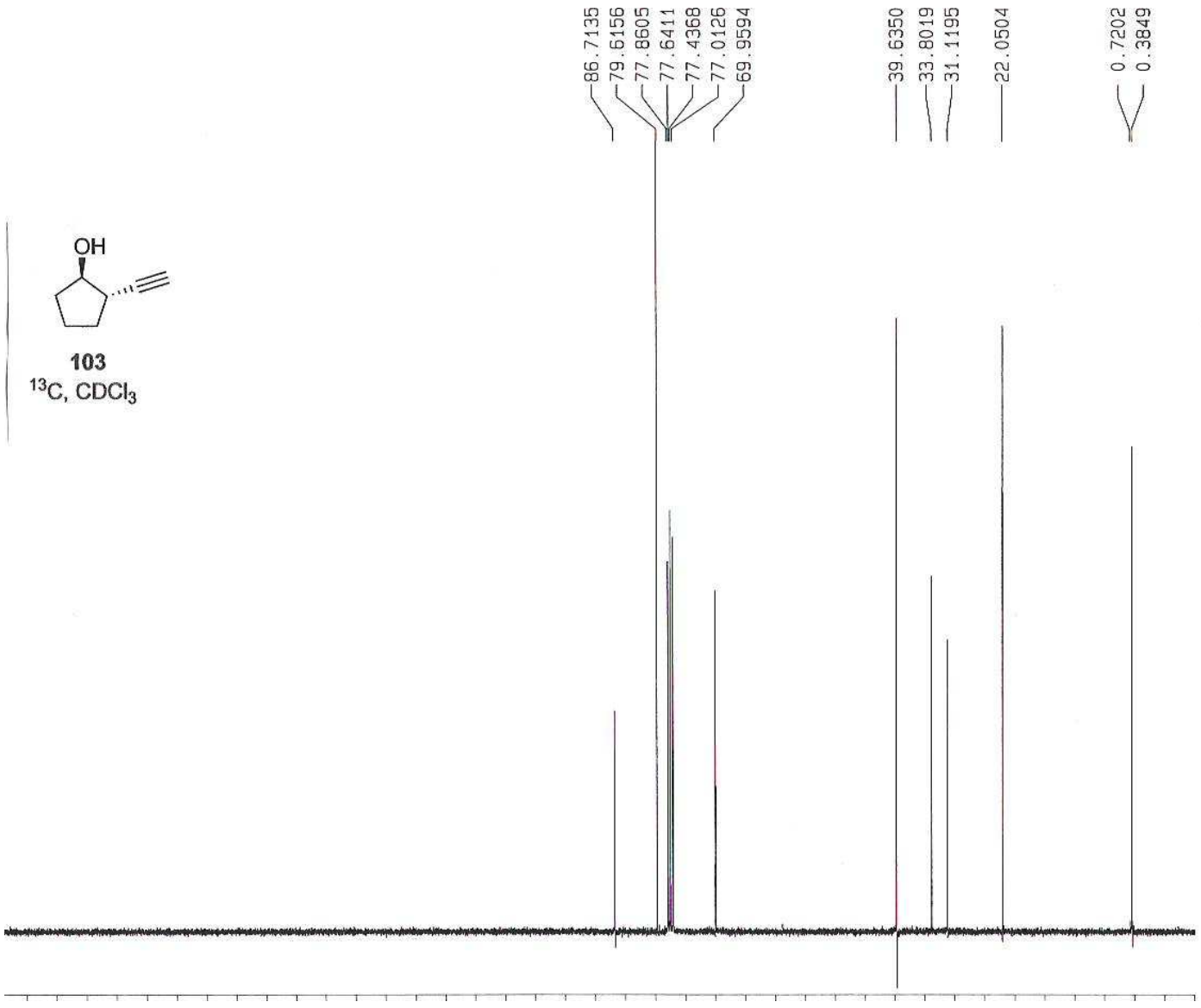
EXPNO	1
PROCNO	1
F2 - Acquisition Parame	
Date_	20050808
Time	21.04
INSTRUM	spect
PROBHD	5 mm BBO BB-
PULPROG	zg30
TD	37036
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839
FIDRES	0.166671
AQ	2.9999659
RG	90.5
DW	81.000
DE	6.00
TE	300.0
D1	1.00000000
========== CHANNEL f1	
NUC1	1H
P1	11.00
PL1	0.00
SFO1	300.1318534
F2 - Processing paramet	
SI	32768
SF	300.1300000
WDW	no
SSB	0
LB	0.00
GB	0
PC	1.00
1D NMR plot parameters	
CX	20.00
F1P	11.941
F1	3584.00
F2P	-1.089
F2	-326.83
PPMCM	0.65152
HZCM	195.54140



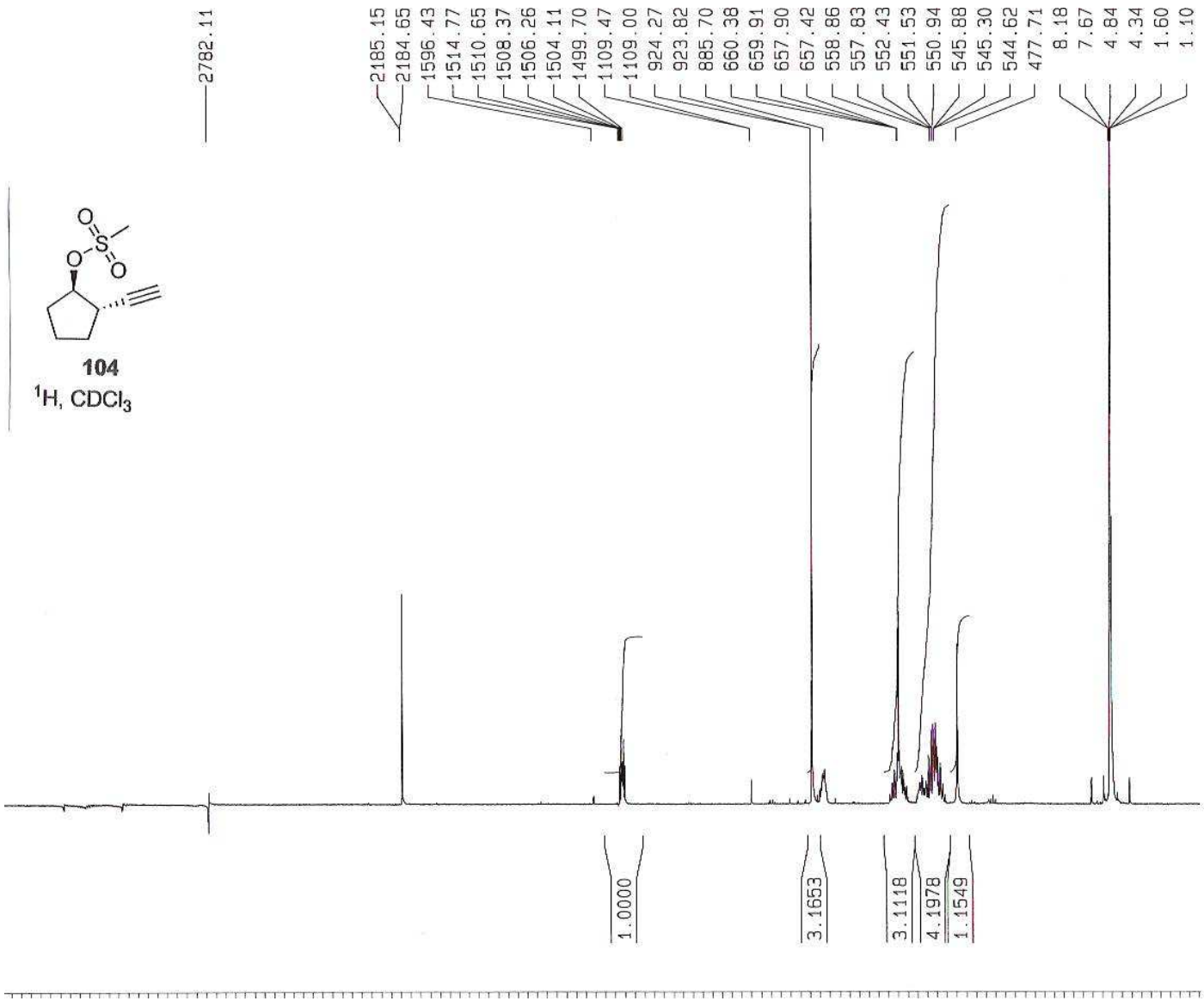
EXPNO	1
PROCNO	1
F2 - Acquisition Parame	
Date_	20050809
Time	13.29
INSTRUM	spect
PROBHD	5 mm BBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	5120
DS	2
SWH	17985.611
FIDRES	0.274439
AQ	1.8219508
RG	16384
DW	27.800
DE	6.00
TE	300.0
D1	2.00000000
D11	0.03000000
D12	0.00002000
========== CHANNEL f1	
NUC1	13C
P1	7.10
PL1	-1.50
SFO1	75.4752653
========== CHANNEL f2	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00
PL2	0.00
PL12	18.00
PL13	18.00
SFO2	300.1312005
F2 - Processing paramet	
SI	32768
SF	75.4677190
WDW	no
SSB	0
LB	0.00
GB	0
PC	1.40
1D NMR plot parameters	
CX	20.00
F1P	219.154
F1	16539.09
F2P	-19.167
F2	-1446.52



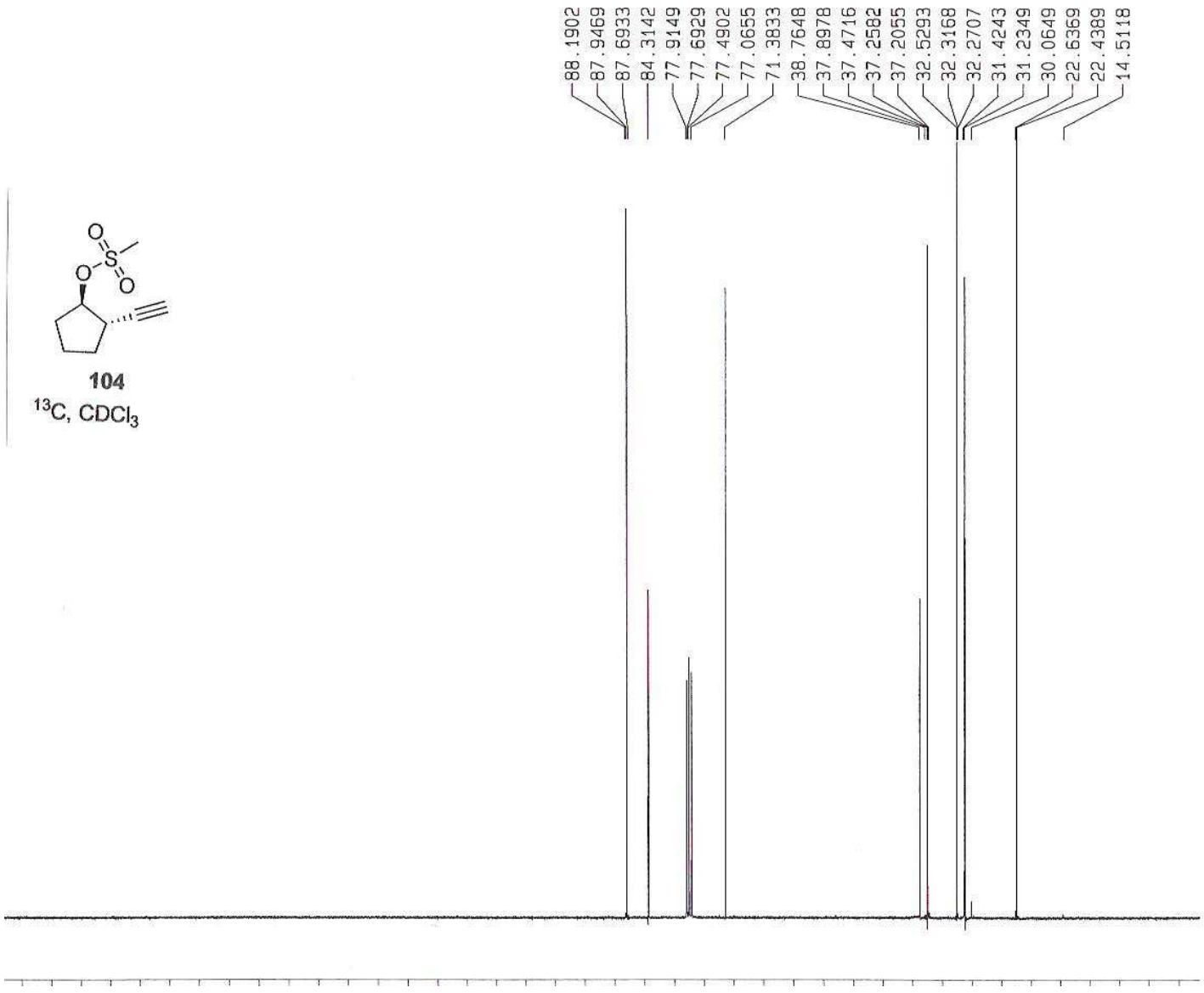
EXPNO	9999
PROCNO	1
F2 - Acquisition Parame	
Date_	20060921
Time	13.43
INSTRUM	spect
PROBHD	5 mm BBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839
FIDRES	0.094190
AQ	5.3084660
RG	128
DW	81.000
DE	6.00
TE	300.0
D1	1.00000000
========== CHANNEL f1	
NUC1	1H
P1	11.00
PL1	0.00
SFO1	300.1318534
F2 - Processing paramet	
SI	32768
SF	300.1300000
WDW	no
SSB	0
LB	0.00
GB	0
PC	1.00
1D NMR plot parameters	
CX	20.00
F1P	12.010
F1	3604.44
F2P	-0.998
F2	-299.57
PPMCM	0.65039
HZCM	195.2007



EXPNO	9999
PROCNO	1
F2 - Acquisition Parameter	
Date_	20060921
Time	16.40
INSTRUM	spect
PROBHD	5 mm BBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	2508
DS	4
SWH	18832.393 Hz
FIDRES	0.287360 Hz
AQ	1.7400308 se
RG	8192
DW	26.550 us
DE	6.00 us
TE	300.0 K
D1	2.00000000 se
D11	0.03000000 se
D12	0.00002000 se
========== CHANNEL f1 ==	
NUC1	13C
P1	7.10 us
PL1	-1.50 dB
SFO1	75.4760200 MH
========== CHANNEL f2 ==	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 us
PL2	0.00 dB
PL12	18.00 dB
PL13	18.00 dB
SFO2	300.1312005 MH
F2 - Processing parameters	
SI	32768
SF	75.4677190 MH
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.40
1D NMR plot parameters	
CX	20.00 cm
F1P	199.785 pp
F1	15077.29 Hz
F2P	-10.095 pp
F2	-761.87 Hz



EXPNO	9999
PROCNO	1
F2 - Acquisition Parame	
Date_	20060928
Time	14.17
INSTRUM	spect
PROBHD	5 mm BBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839
FIDRES	0.094190
AQ	5.3084660
RG	322.5
DW	81.000
DE	6.00
TE	300.0
D1	1.0000000
========== CHANNEL f1	
NUC1	1H
P1	11.00
PL1	0.00
SFO1	300.131853
F2 - Processing paramet	
SI	32768
SF	300.130000
WDW	no
SSB	0
LB	0.00
GB	0
PC	1.00
1D NMR plot parameters	
CX	20.00
F1P	11.964
F1	3590.81
F2P	-0.907
F2	-272.32
PPMCM	0.64358
HZCM	193.1567



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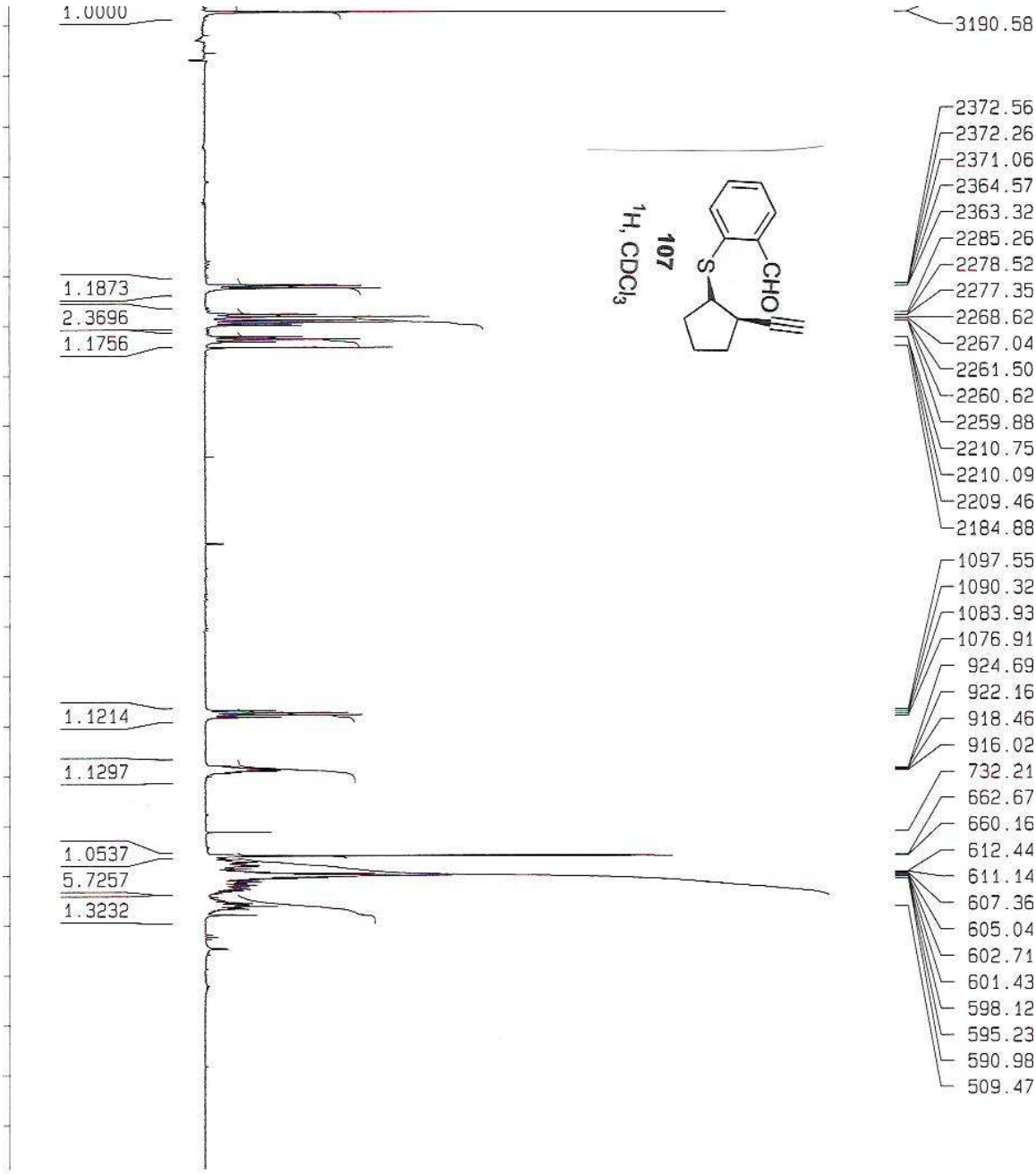
^{13}C, $CDCl_3$

EXPNO	1
PROCNO	1
F2 - Acquisition Parameter	
Date_	20061018
Time	2.40
INSTRUM	spect
PROBHD	5 mm BBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	7168
DS	4
SWH	18832.393 Hz
FIDRES	0.287360 Hz
AQ	1.7400308 se
RG	16384
DW	26.550 us
DE	6.00 us
TE	300.0 K
D1	2.00000000 se
D11	0.03000000 se
D12	0.00002000 se
========== CHANNEL f1 ==	
NUC1	13C
P1	7.10 us
PL1	-1.50 dB
SFO1	75.4760200 MH
========== CHANNEL f2 ==	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 us
PL2	0.00 dB
PL12	18.00 dB
PL13	18.00 dB
SFO2	300.1312005 MH
F2 - Processing parameters	
SI	32768
SF	75.4677190 MH
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.40
1D NMR plot parameters	
CX	20.00 cm
F1P	200.336 pp
F1	15118.87 Hz
F2P	-8.443 pp
F2	-637.15 Hz

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EXPNO                  9999
PROCNO                    1

F2 - Acquisition Parame
Date_               20061009
Time                   19.42
INSTRUM                spect
PROBHD     5 mm BBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                6172.839
FIDRES            0.094190
AQ                5.3084660
RG                    322.5
DW                   81.000
DE                     6.00
TE                    300.0
D1                1.0000000

======== CHANNEL f1 ========
NUC1                     1H
P1                    11.00
PL1                    0.00
SFO1              300.1318534

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

1D NMR plot parameters
CX                     20.00
F1P                    12.123
F1                   3638.51
F2P                   -0.930
F2                   -279.13
PPMCM                 0.65266
HZCM                195.88206
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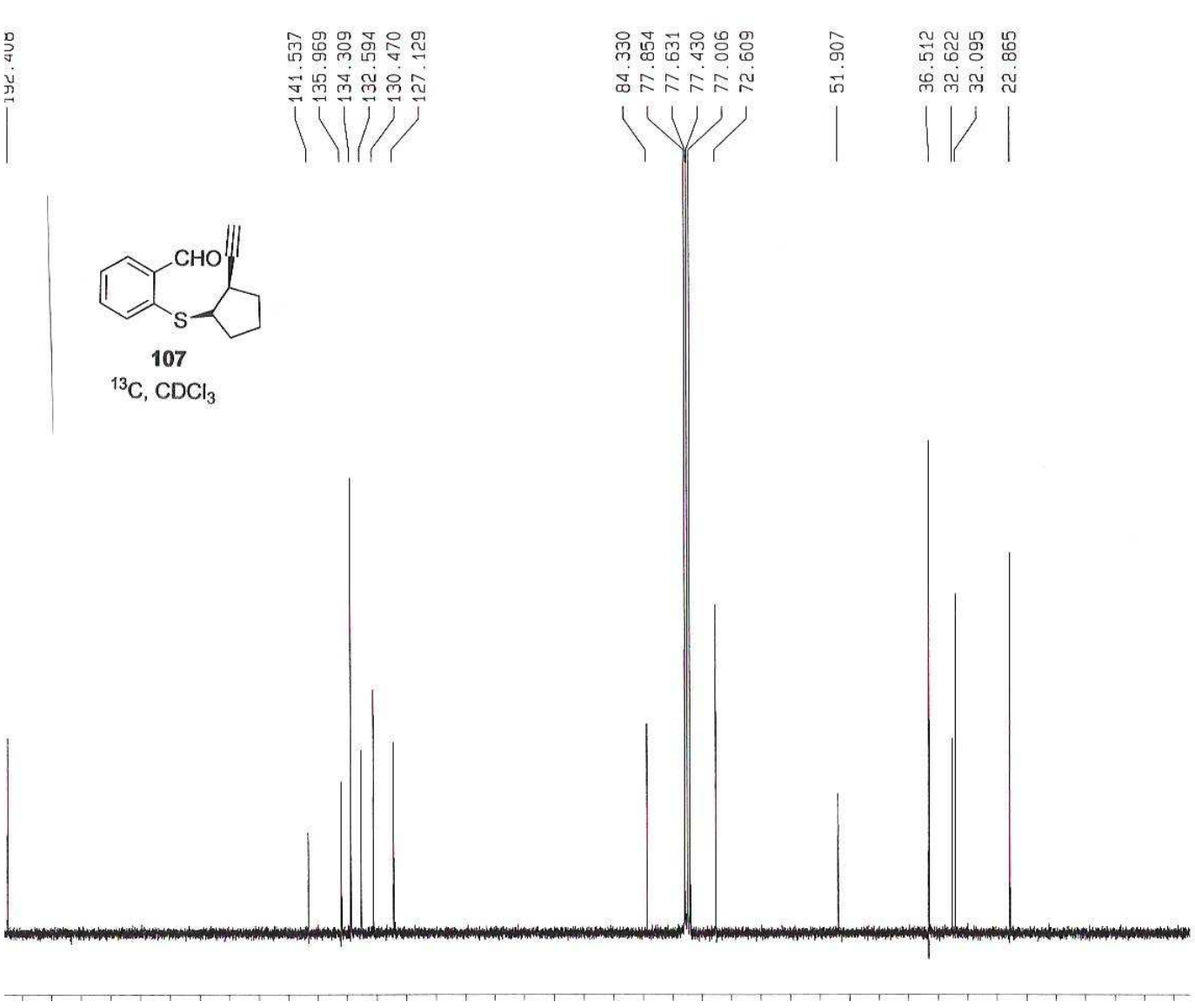


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Current Data Parameters
NAME      dad-3-11-carbo
EXPNO              9999
PROCNO                1

F2 - Acquisition Parameter
Date_          20061010
Time               1.20
INSTRUM           spect
PROBHD     5 mm BBO BB-
PULPROG         zgpg30
TD              65536
SOLVENT          CDCl3
NS                5120
DS                   4
SWH          18832.393 Hz
FIDRES        0.287360 Hz
AQ            1.7400308 se
RG                16384
DW               26.550 us
DE                6.00 us
TE               300.0 K
D1           2.00000000 se
D11          0.03000000 se
D12          0.00002000 se

============ CHANNEL f1 ==
NUC1               13C
P1                7.10 us
PL1              -1.50 dB
SFO1         75.4760200 MH

============ CHANNEL f2 ==
CPDPRG2         waltz16
NUC2               1H
PCPD2             80.00 us
PL2                0.00 dB
PL12              18.00 dB
PL13              18.00 dB
SFO2        300.1312005 MH

F2 - Processing parameters
SI                32768
SF           75.4677190 MH
WDW                  no
SSB                   0
LB                 0.00 Hz
GB                    0
PC                 1.40

1D NMR plot parameters
CX                20.00 cm
F1P              200.336 pp
F1             15118.87 Hz
F2P              -7.616 pp
F2             -574.79 Hz
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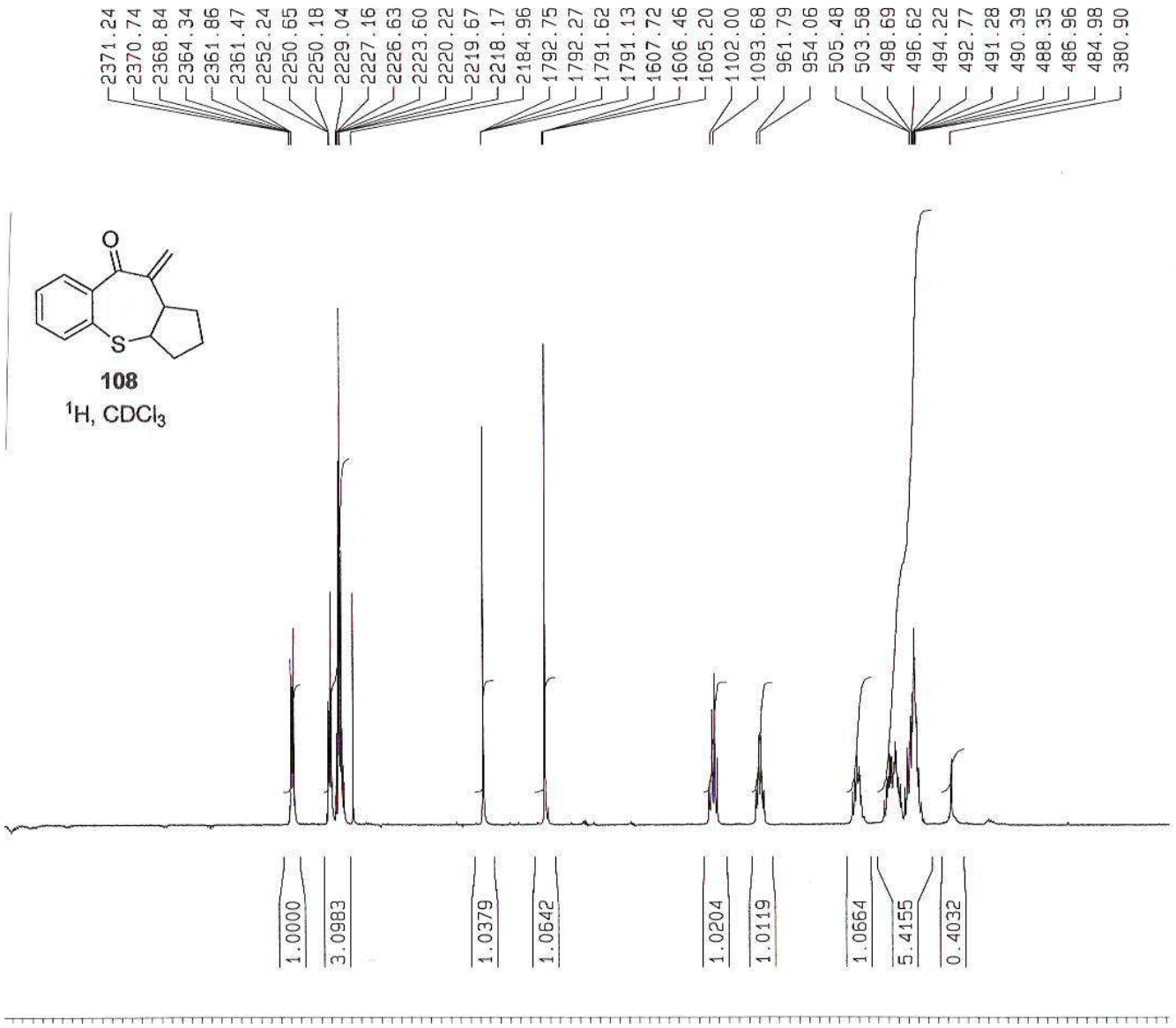
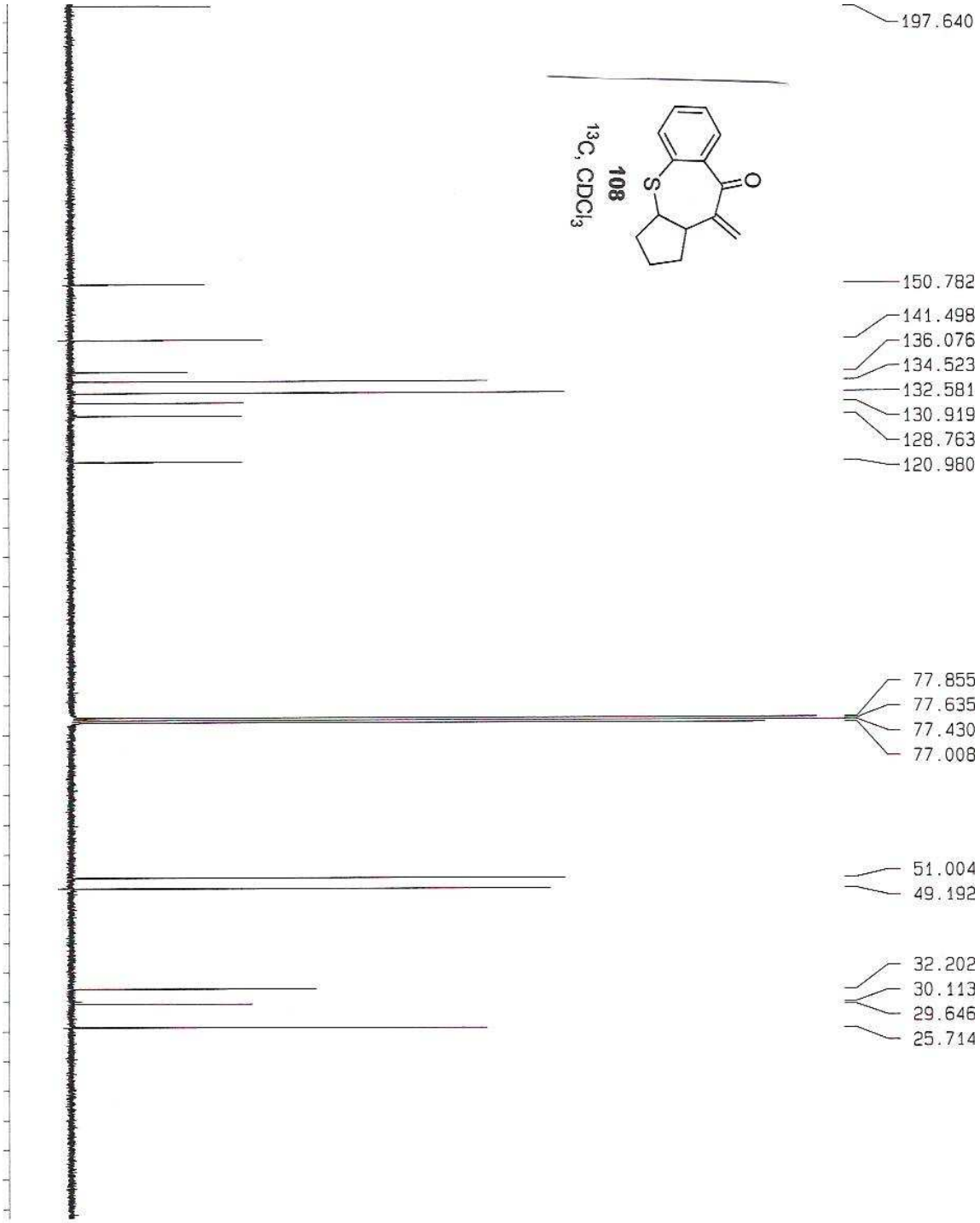


EXPNO	1
PROCNO	1
F2 - Acquisition Parame	
Date_	20061107
Time	14.42
INSTRUM	spect
PROBHD	5 mm BBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839
FIDRES	0.094190
AQ	5.3084660
RG	287.4
DW	81.000
DE	6.00
TE	300.0
D1	1.00000000
========== CHANNEL f1	
NUC1	1H
P1	11.00
PL1	0.00
SFO1	300.1318534
F2 - Processing paramet	
SI	32768
SF	300.1300000
WDW	no
SSB	0
LB	0.00
GB	0
PC	1.00
1D NMR plot parameters	
CX	20.00
F1P	12.010
F1	3604.44
F2P	-0.930
F2	-279.13
PPMCM	0.64698
HZCM	194.17873

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EXPNU                                   1
PROCNO                                  1

F2 - Acquisition Parameter
Date_                            20061108
Time                                2.59
INSTRUM                             spect
PROBHD                5 mm BBO BB-
PULPROG                          zgpg30
TD                                65536
SOLVENT                           CDCl3
NS                                  7168
DS                                     4
SWH                           18832.393 Hz
FIDRES                         0.287360 Hz
AQ                             1.7400308 se
RG                                  8192
DW                                26.550 us
DE                                 6.00 us
TE                                300.0 K
D1                            2.00000000 se
D11                           0.03000000 se
D12                           0.00002000 se

============== CHANNEL f1 ==
NUC1                                  13C
P1                                  7.10 us
PL1                                -1.50 dB
SFO1                       75.4760200 MH

============== CHANNEL f2 ==
CPDPRG2                         waltz16
NUC2                                  1H
PCPD2                              80.00 us
PL2                                 0.00 dB
PL12                               18.00 dB
PL13                               18.00 dB
SFO2                       300.1312005 MH

F2 - Processing parameters
SI                                 32768
SF                         75.4677190 MH
WDW                                   no
SSB                                    0
LB                                  0.00 Hz
GB                                     0
PC                                  1.40

1D NMR plot parameters
CX                                 20.00 cm
F1P                               201.162 pp
F1                               15181.23 Hz
F2P                                -6.515 pp
F2                               -491.65 Hz
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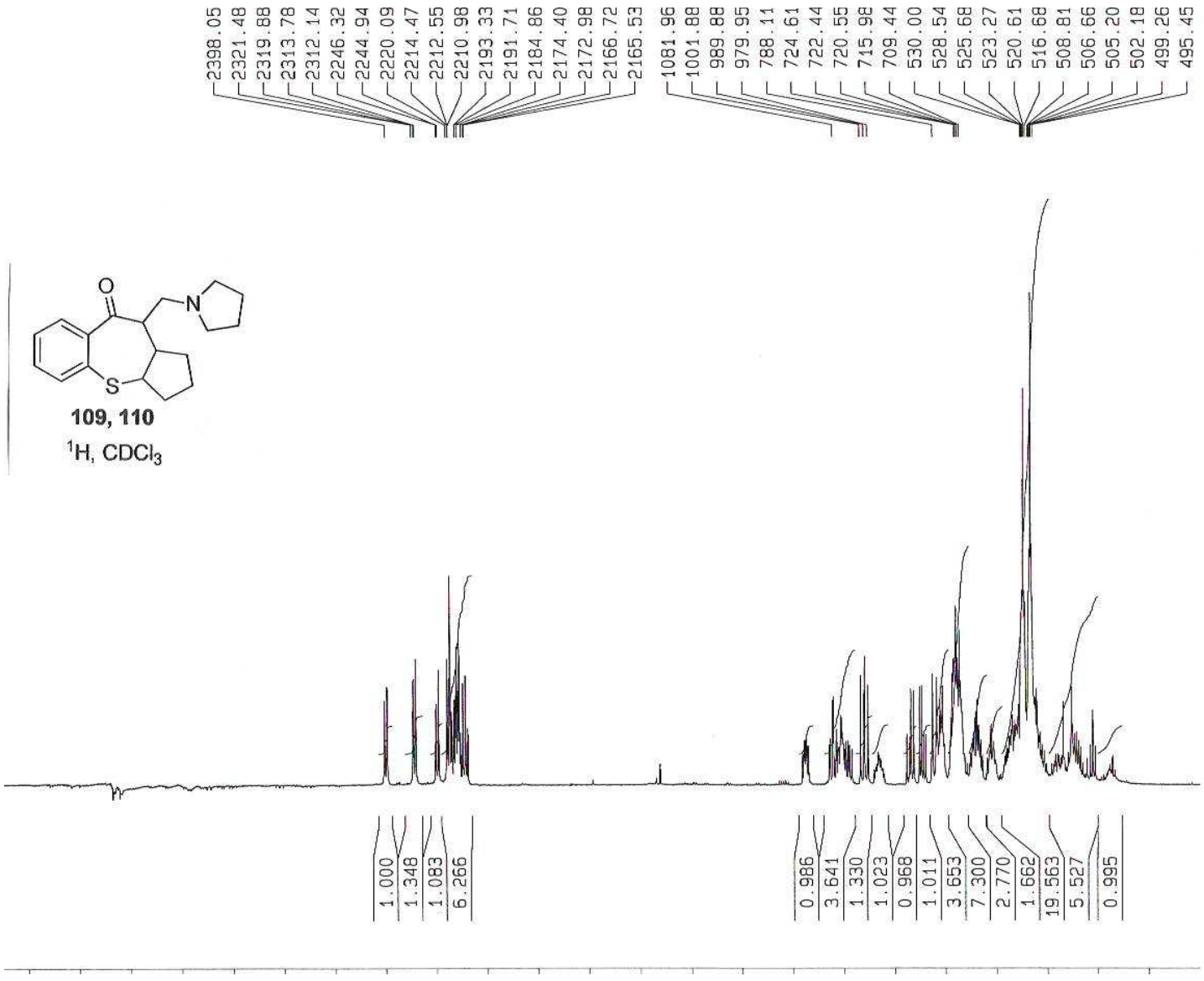
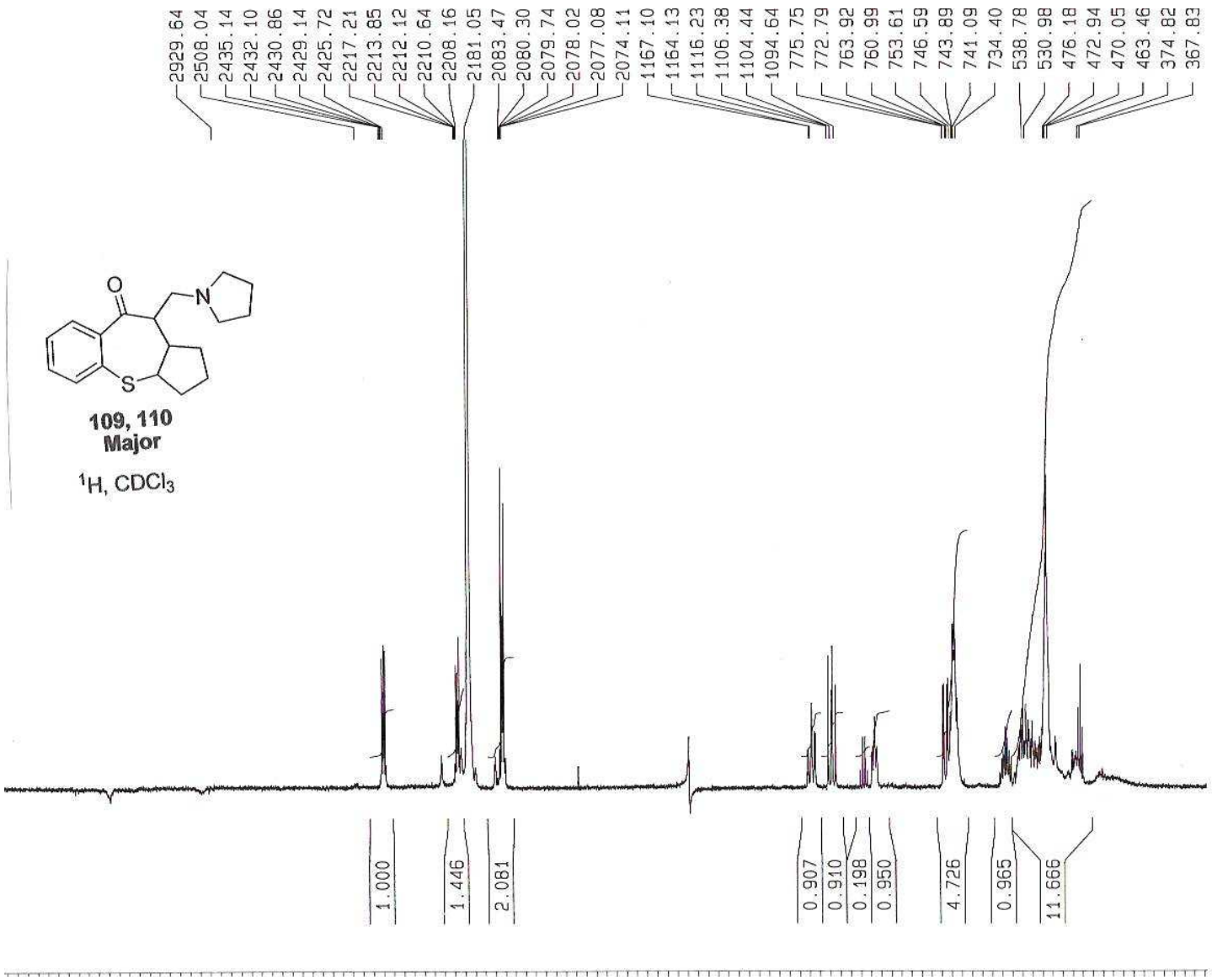
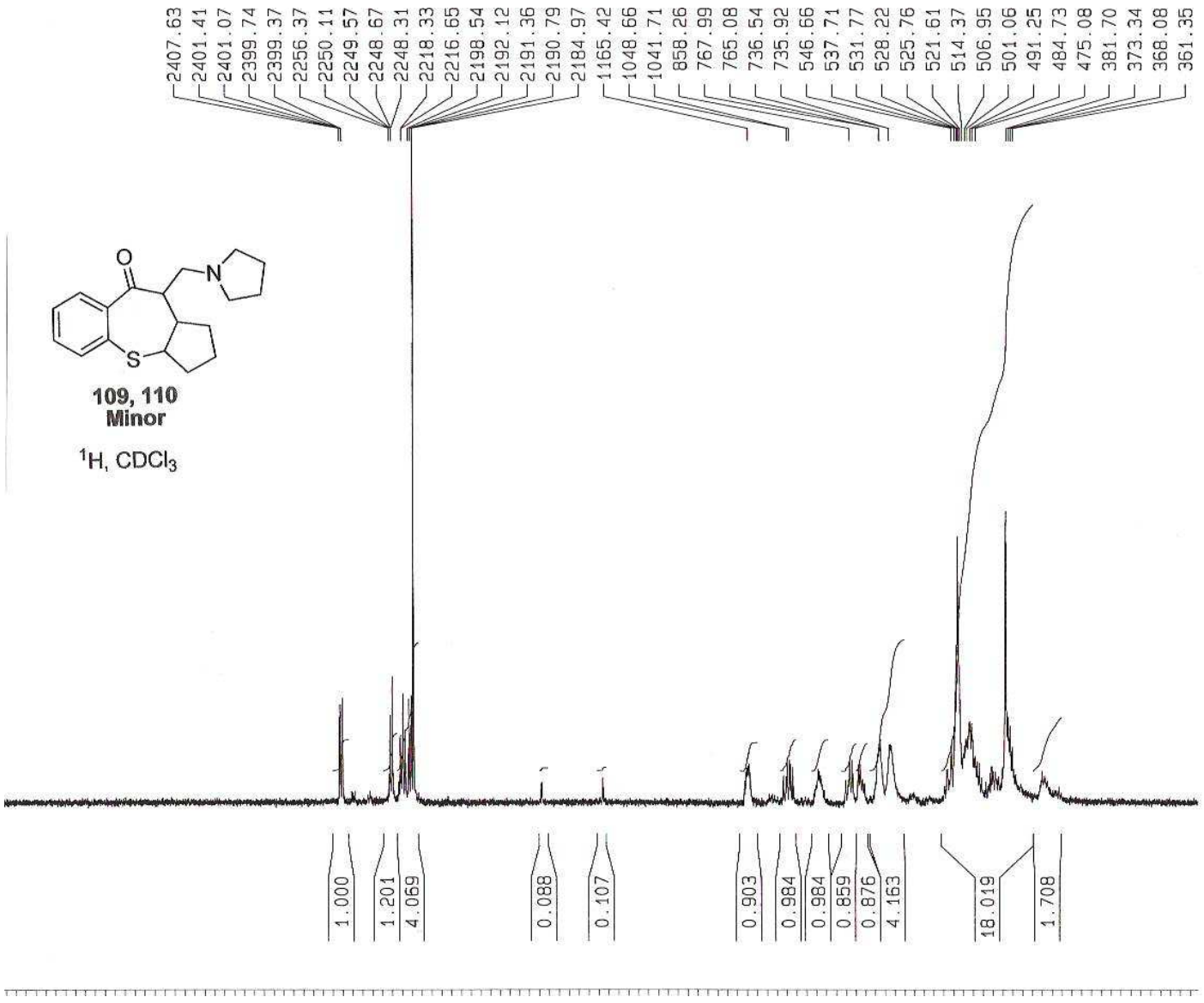


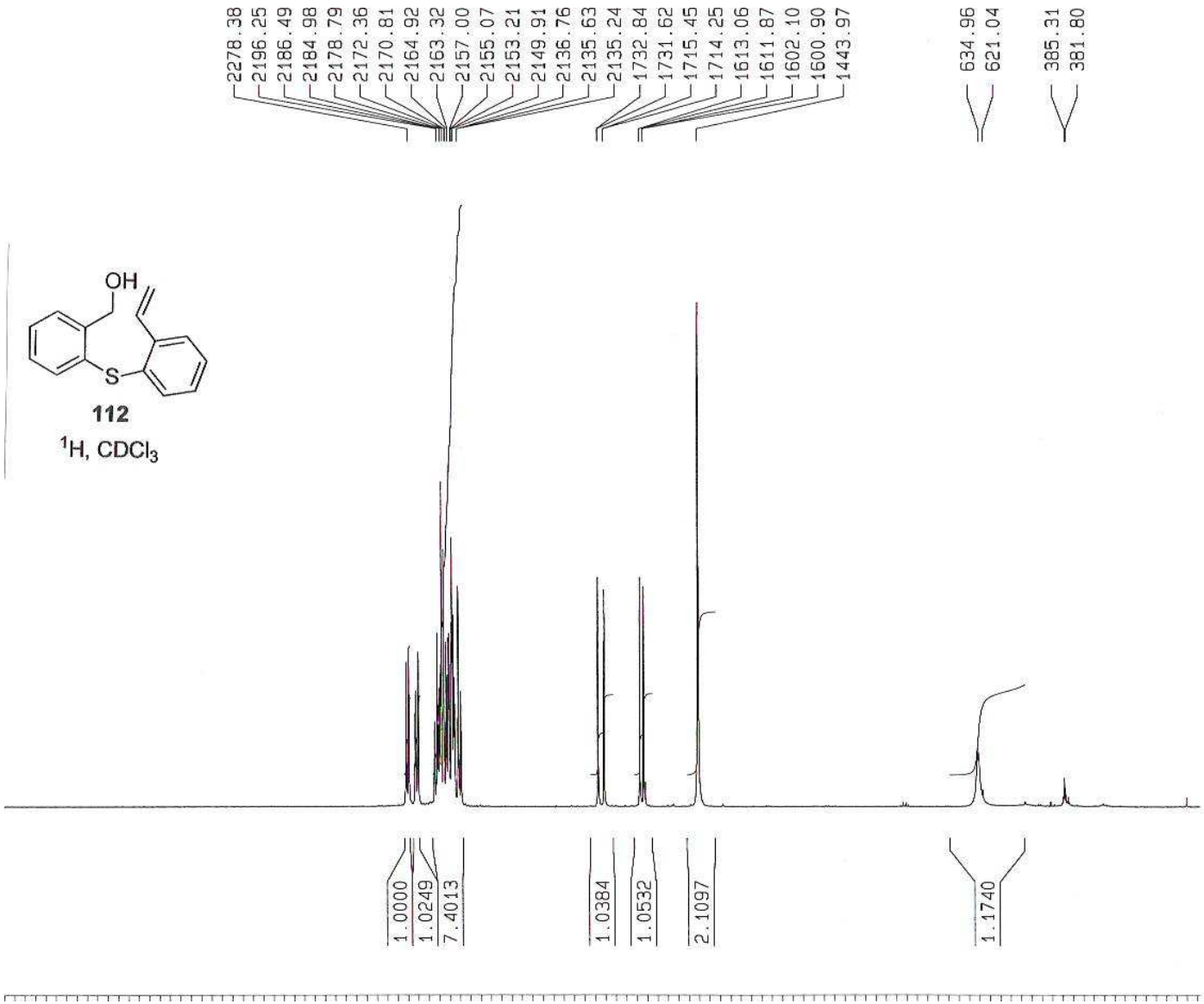
EXPNO	9999
PROCNO	1
F2 - Acquisition Parame	
Date_	20061010
Time	15.00
INSTRUM	spect
PROBHD	5 mm BBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839
FIDRES	0.094190
AQ	5.3084660
RG	128
DW	81.000
DE	6.00
TE	300.0
D1	1.00000000
========== CHANNEL f1	
NUC1	1H
P1	11.00
PL1	0.00
SFO1	300.1318534
F2 - Processing paramet	
SI	32768
SF	300.1300000
WDW	no
SSB	0
LB	0.00
GB	0
PC	1.00
1D NMR plot parameters	
CX	20.00
F1P	12.055
F1	3618.07
F2P	0.001
F2	0.21
PPMCM	0.60271
HZCM	180.89282



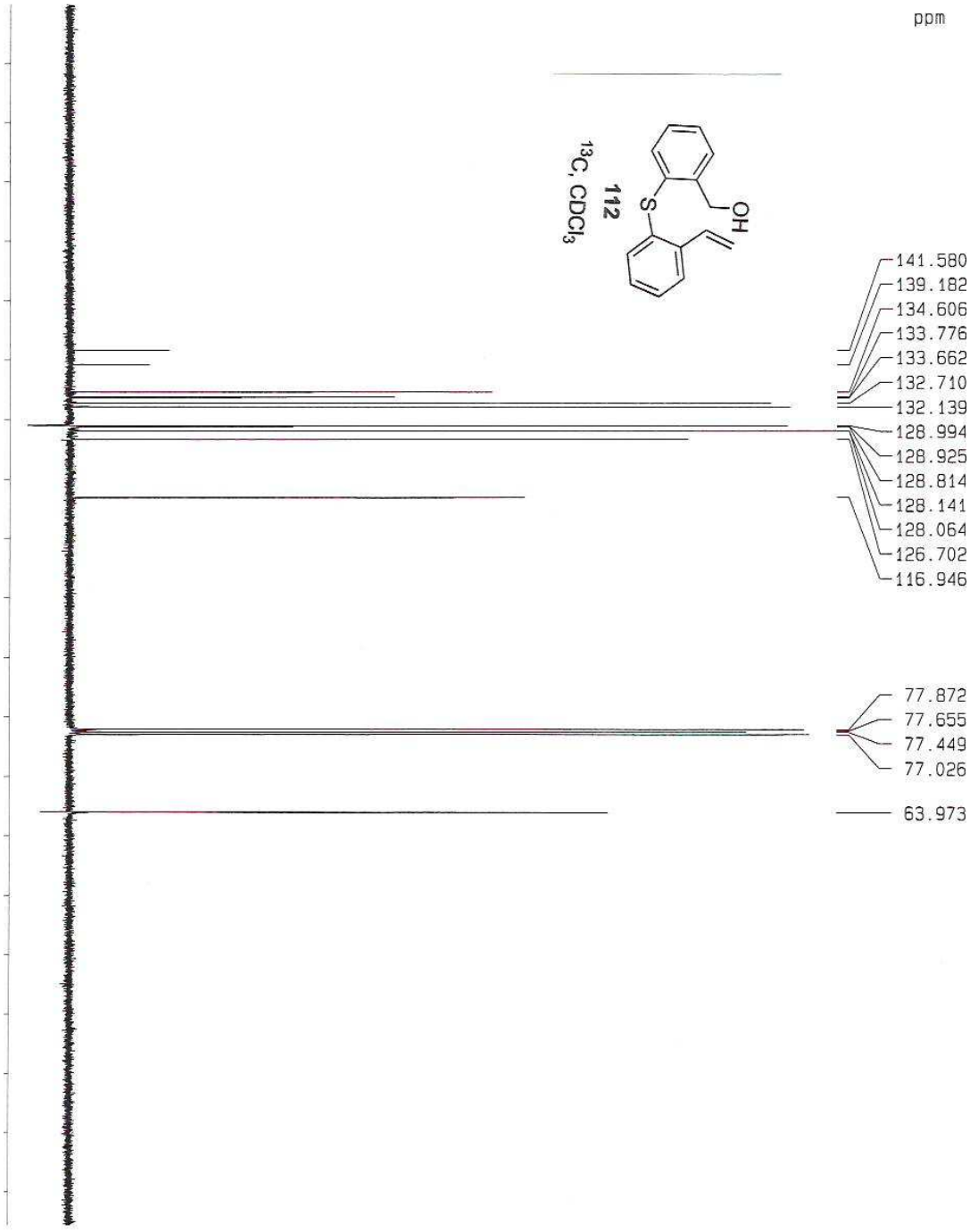
EXPNO	9999
PROCNO	1
F2 - Acquisition Parame	
Date_	20061017
Time	14.28
INSTRUM	spect
PROBHD	5 mm BBO BB-
PULPROG	zg30
TD	65536
SOLVENT	C6D6
NS	16
DS	2
SWH	6172.839
FIDRES	0.094190
AQ	5.3084660
RG	406.4
DW	81.000
DE	6.00
TE	300.0
D1	1.00000000
========== CHANNEL f1	
NUC1	1H
P1	11.00
PL1	0.00
SFO1	300.1318534
F2 - Processing paramet	
SI	32768
SF	300.1300000
WDW	no
SSB	0
LB	0.00
GB	0
PC	1.00
1D NMR plot parameters	
CX	20.00
F1P	12.100
F1	3631.69
F2P	-0.022
F2	-6.60
PPMCM	0.60612
HZCM	181.91481



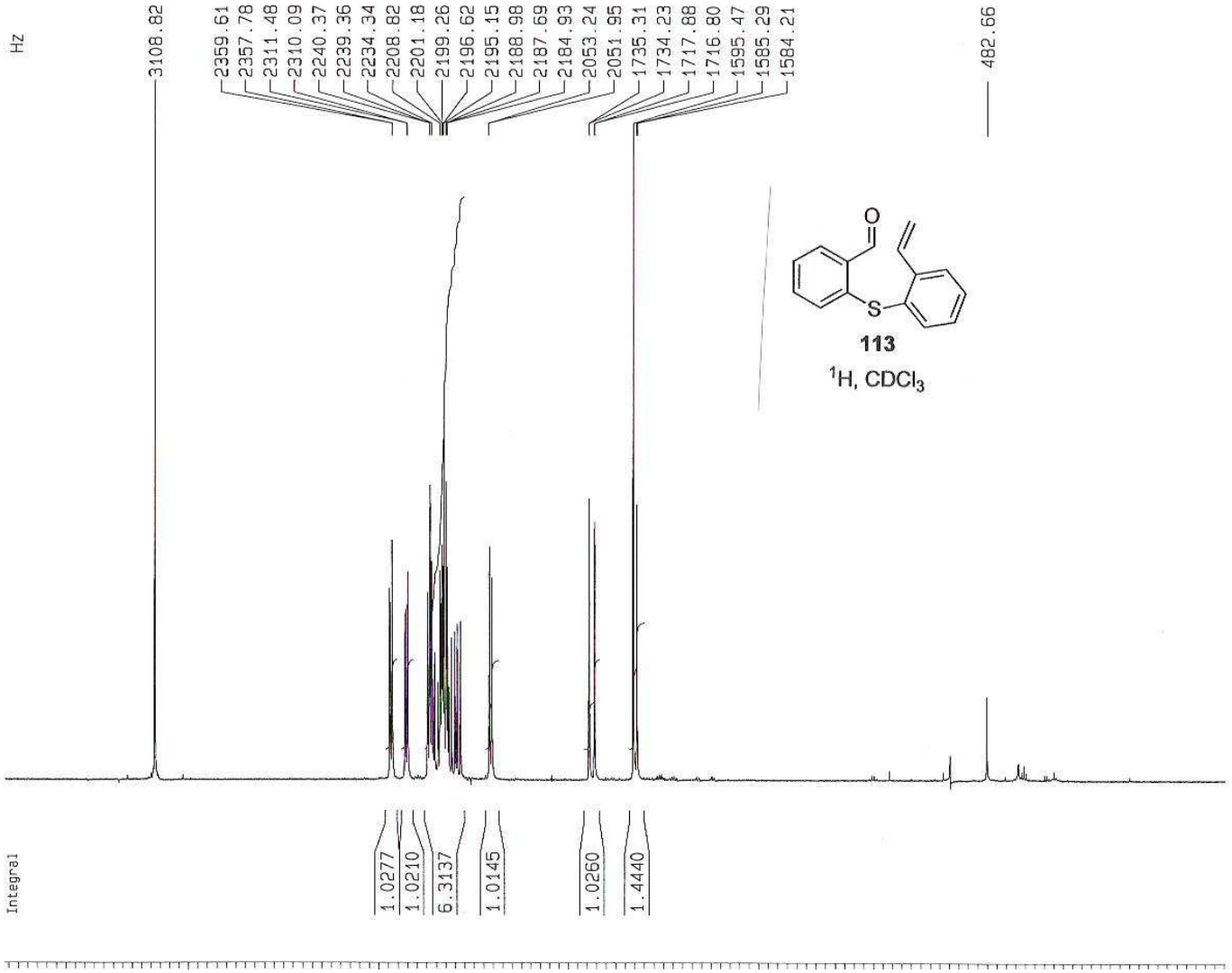
EXPNO	1
PROCNO	1
F2 - Acquisition Parame	
Date_	20061016
Time	19.42
INSTRUM	spect
PROBHD	5 mm BBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839
FIDRES	0.094190
AQ	5.3084660
RG	724.1
DW	81.000
DE	6.00
TE	300.0
D1	1.00000000
========== CHANNEL f1	
NUC1	1H
P1	11.00
PL1	0.00
SFO1	300.1318534
F2 - Processing paramet	
SI	32768
SF	300.1300000
WDW	no
SSB	0
LB	0.00
GB	0
PC	1.00
1D NMR plot parameters	
CX	20.00
F1P	12.032
F1	3611.25
F2P	-0.680
F2	-204.19
PPMCM	0.63563
HZCM	190.77209



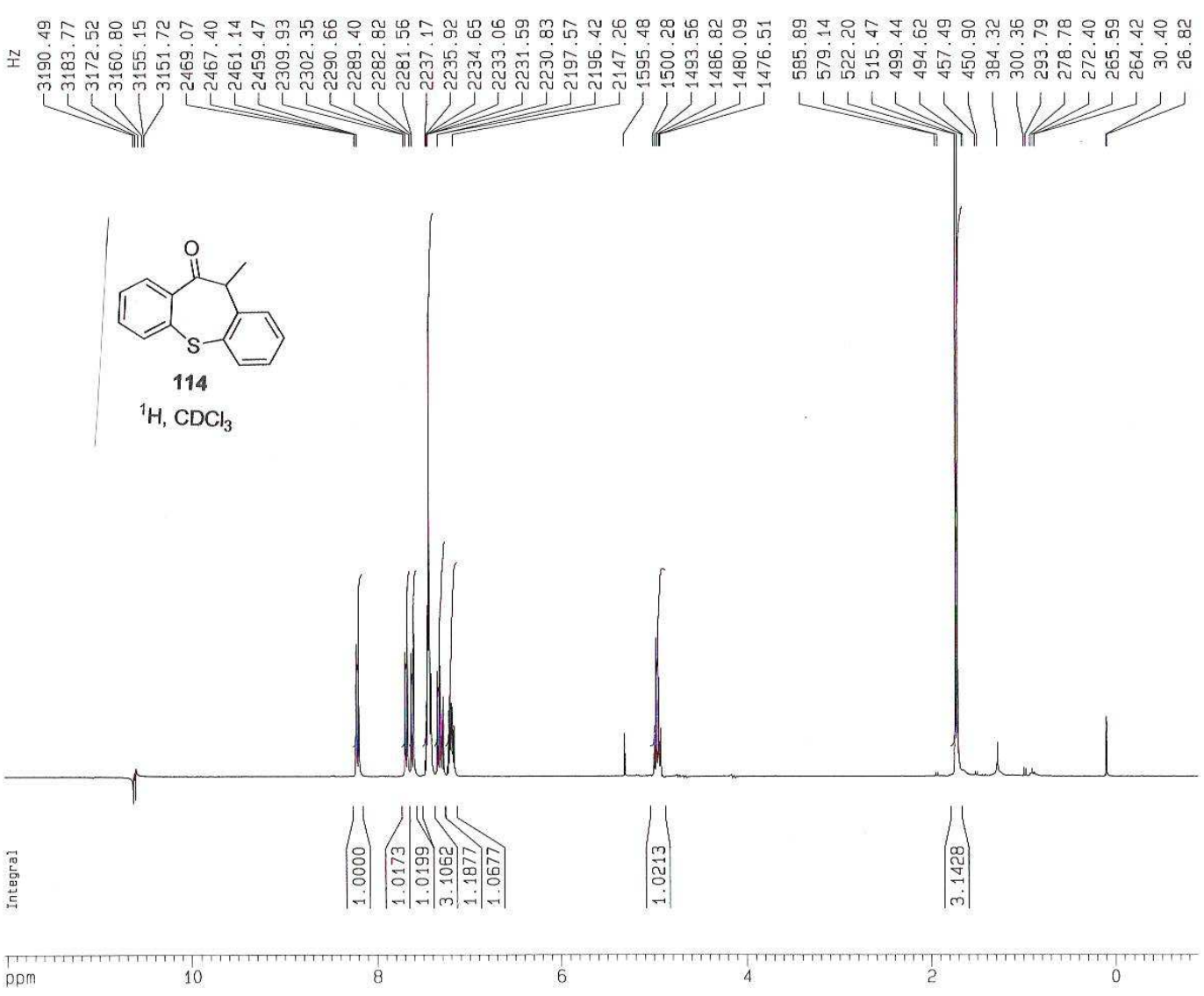
EXPNO	1
PROCNO	1
F2 - Acquisition Parame	
Date_	20070117
Time	19.33
INSTRUM	spect
PROBHD	5 mm BBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839
FIDRES	0.094190
AQ	5.3084660
RG	181
DW	81.000
DE	6.00
TE	300.0
D1	1.00000000
========== CHANNEL f1	
NUC1	1H
P1	11.00
PL1	0.00
SFO1	300.1318534
F2 - Processing paramet	
SI	32768
SF	300.1300000
WDW	no
SSB	0
LB	0.00
GB	0
PC	1.00
1D NMR plot parameters	
CX	20.00
F1P	12.100
F1	3631.69
F2P	-0.022
F2	-6.60
PPMCM	0.60612
HZCM	181.91481



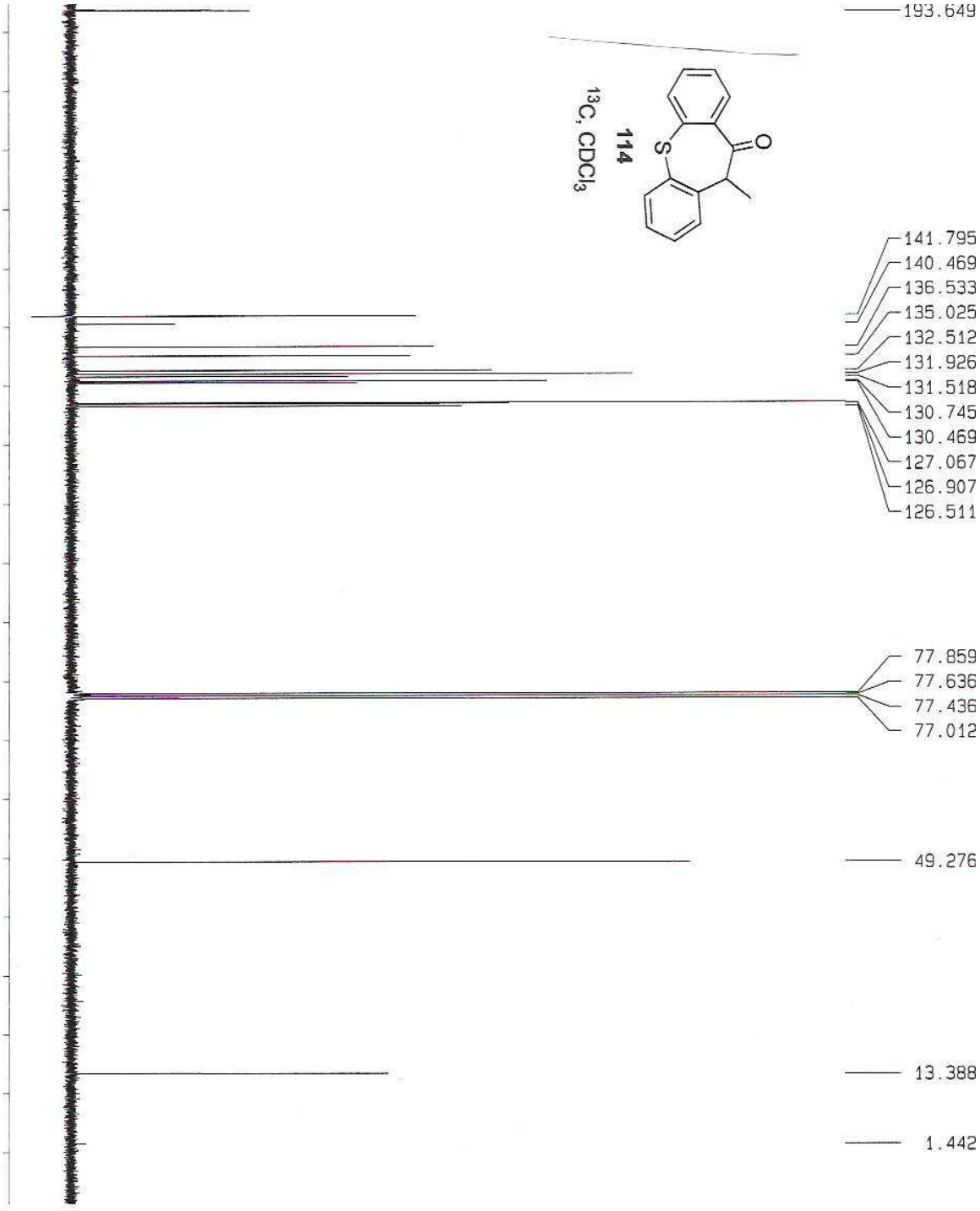

```
EXPNO                 1
PROCNO                1

F2 - Acquisition Parame
Date_          20070119
Time_              0.28
INSTRUM            spect
PROBHD  5 mm BBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                 5120
DS                    4
SWH           18832.393
FIDRES        0.287360
AQ            1.740030
RG                16384
DW                26.550
DE                 6.00
TE                300.0
D1            2.00000000
D11           0.03000000
D12           0.00002000

============ CHANNEL f1
NUC1                13C
P1                 7.10
PL1               -1.50
SFO1          75.4760200

============ CHANNEL f2
CPDPRG2         waltz16
NUC2                1H
PCPD2             80.00
PL2                0.00
PL12              18.00
PL13              18.00
SFO2          300.1312005

F2 - Processing paramet
SI                32768
SF            75.4677190
WDW                  no
SSB                   0
LB                 0.00
GB                    0
PC                 1.40

1D NMR plot parameters
CX                20.00
F1P              199.785
F1             15077.30
F2P               -5.688
F2              -429.29
```



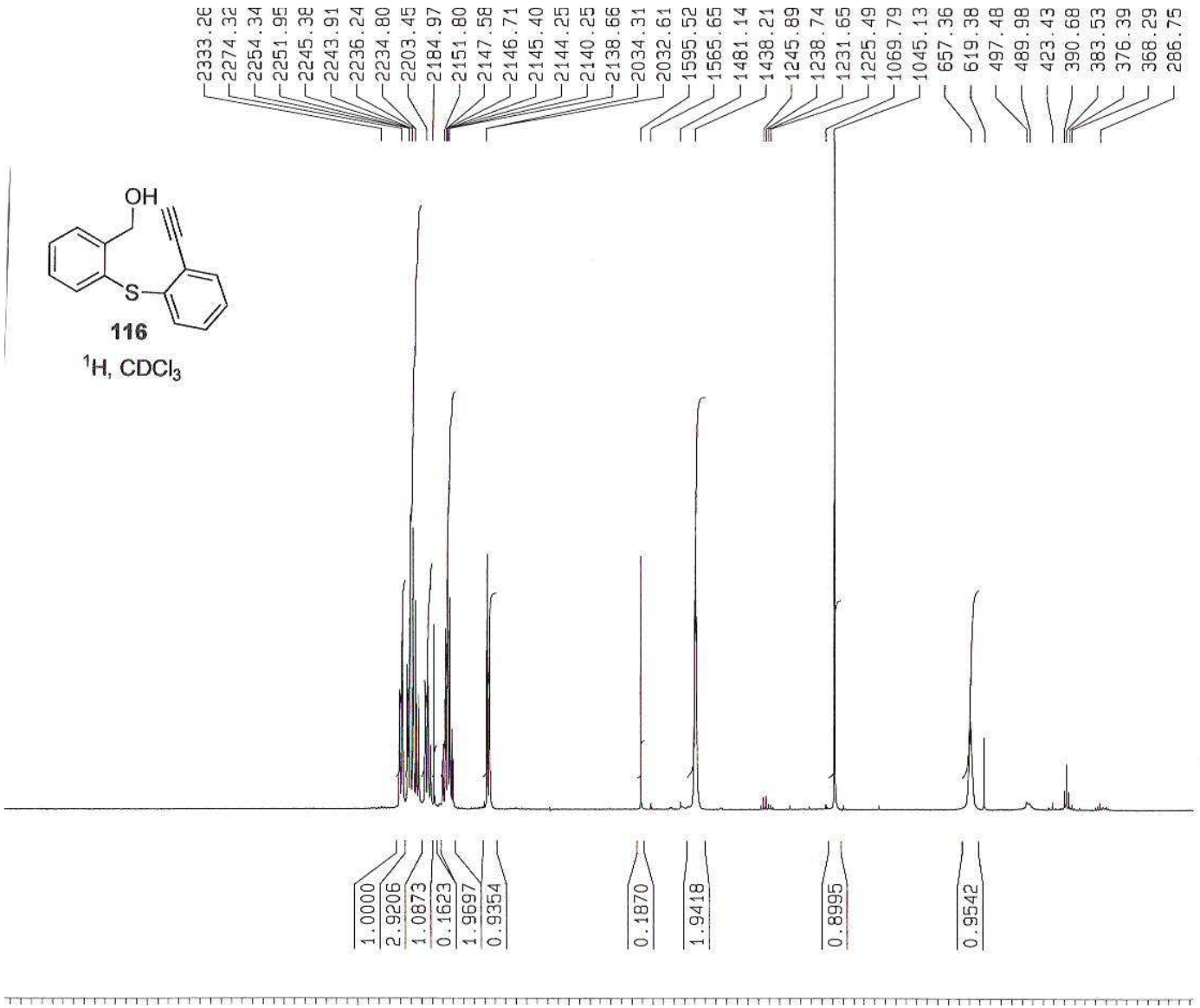
EXPNO	1
PROCNO	1
F2 - Acquisition Parame	
Date_	20070130
Time	14.07
INSTRUM	spect
PROBHD	5 mm BBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839
FIDRES	0.094190
AQ	5.3084660
RG	203.2
DW	81.000
DE	6.00
TE	300.0
D1	1.00000000
========== CHANNEL f1	
NUC1	1H
P1	11.00
PL1	0.00
SFO1	300.1318534
F2 - Processing paramet	
SI	32768
SF	300.1300000
WDW	no
SSB	0
LB	0.00
GB	0
PC	1.00
1D NMR plot parameters	
CX	20.00
F1P	11.941
F1	3584.00
F2P	-0.907
F2	-272.32
PPMCM	0.64244
HZCM	192.81607



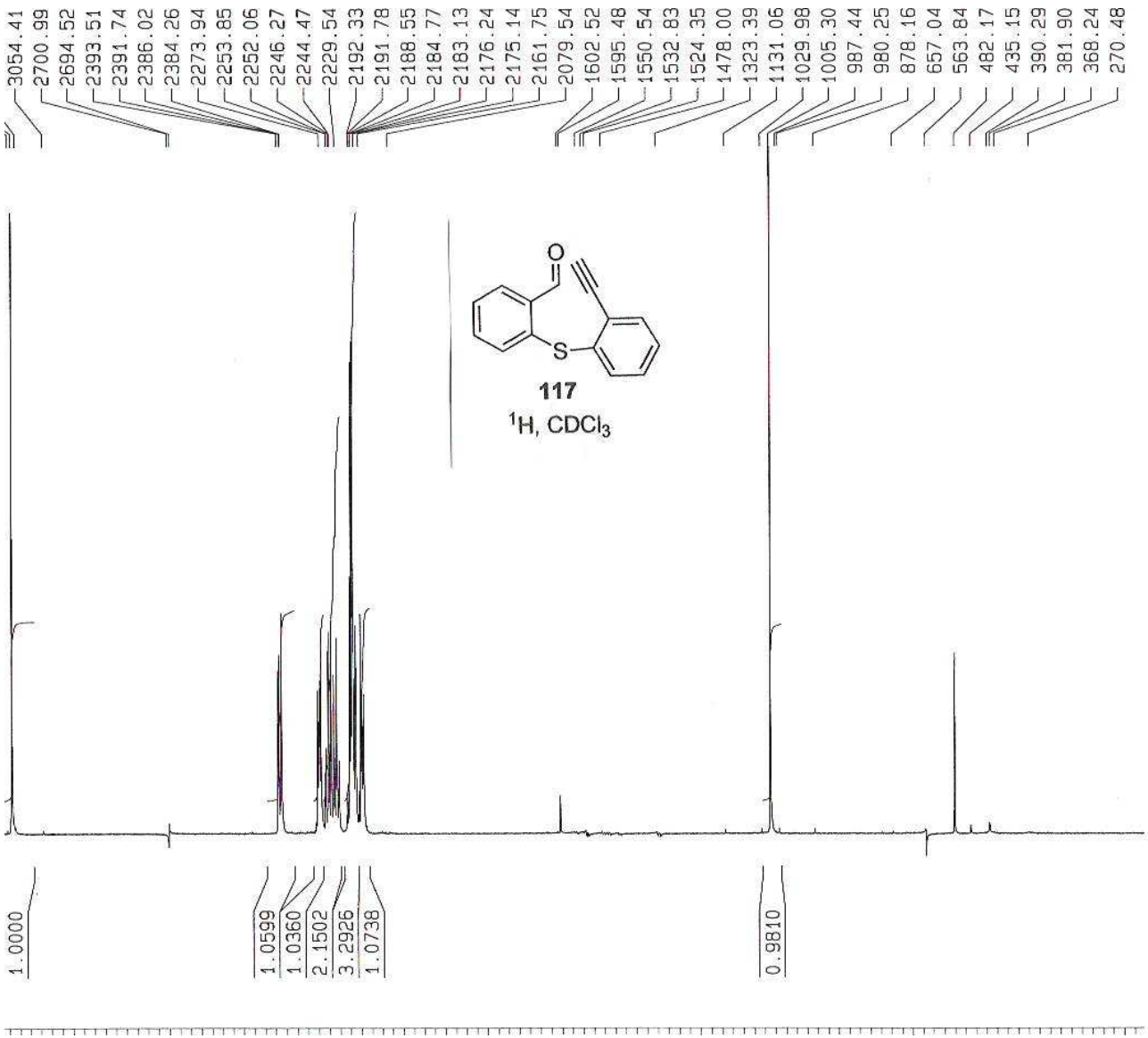

```
NAME          dad-3-28-pure
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20070201
Time                 20.05
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                   287.4
DW                 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
SFO1          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                 12.032 ppm
F1                3611.25 Hz
F2P                 -0.885 ppm
F2                -265.51 Hz
PPMCM             0.64585 ppm/cm
HZCM            193.83807 Hz/cm
```



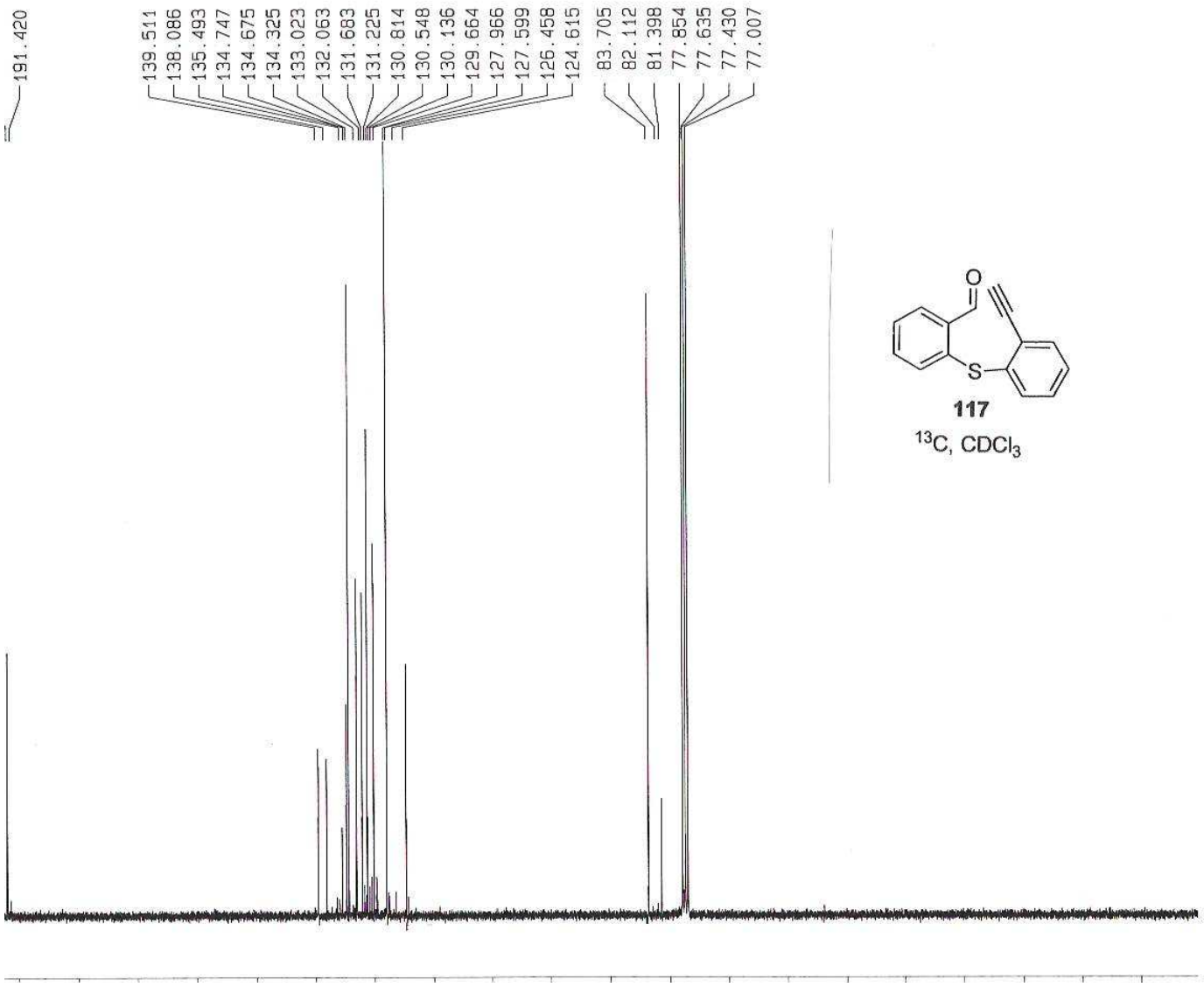

```
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameter
Date_           20070202
Time                1.31
INSTRUM             spect
PROBHD   5 mm BBO BB-
PULPROG           zpgp30
TD                 65536
SOLVENT             CDCl3
NS                   5120
DS                      4
SWH           18832.393 Hz
FIDRES         0.287360 Hz
AQ             1.740308 se
RG                  16384
DW                 26.550 us
DE                  6.00 us
TE                300.0 K
D1             2.00000000 se
D11            0.03000000 se
D12            0.00002000 se

============ CHANNEL f1 ==
NUC1                  13C
P1                   7.10 us
PL1                -1.50 dB
SFO1          75.4760200 MH

============ CHANNEL f2 ==
CPDPRG2           waltz16
NUC2                  1H
PCPD2              80.00 us
PL2                0.00 dB
PL12              18.00 dB
PL13              18.00 dB
SFO2          300.1312005 MH

F2 - Processing parameters
SI                  32768
SF            75.4677190 MH
WDW                    no
SSB                     0
LB                0.00 Hz
GB                      0
PC                   1.40

1D NMR plot parameters
CX                 20.00 cm
F1P               200.886 pp
F1              15160.44 Hz
F2P                -8.718 pp
F2               -657.94 Hz
```




```
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameter
Date_           20070306
Time               16.55
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 se
RG                203.2
DW               81.000 us
DE                6.00 us
TE               300.0 K
D1           1.00000000 se

============ CHANNEL f1 ==
NUC1                  1H
P1                11.00 us
PL1                0.00 dE
SFO1        300.1318534 MH

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

1D NMR plot parameters
CX                20.00 cm
F1P               12.078 pp
F1              3624.88 Hz
F2P                0.069 pp
F2                20.65 Hz
PPMCM             0.60044 pp
HZCM            180.21149 Hz
```



EXPNO	1
PROCNO	1
F2 - Acquisition Parameters	
Date_	20070312
Time	15.49
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
DW	81.000 use
DE	6.00 use
TE	300.0 K
D1	1.00000000 sec
========== CHANNEL f1 ===	
NUC1	1H
P1	11.00 use
PL1	0.00 dB
SFO1	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	12.078 ppm
F1	3624.88 Hz
F2P	-0.181 ppm
F2	-54.30 Hz
PPMCM	0.61293 ppm
HZCM	183.95880 Hz/



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^{13}C, $CDCl_3$

```
Current Data Parameters
NAME      dad-3-30-carbo
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parame
Date_           20070210
Time                5.57
INSTRUM            spect
PROBHD     5 mm BBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                10240
DS                    4
SWH           18832.393
FIDRES        0.287360
AQ            1.7400308
RG                16384
DW                26.550
DE                 6.00
TE                300.0
D1            2.00000000
D11           0.03000000
D12           0.00002000

============ CHANNEL f1
NUC1                13C
P1                 7.10
PL1               -1.50
SFO1          75.4760200

============ CHANNEL f2
CPDPRG2         waltz16
NUC2                1H
PCPD2              80.00
PL2                0.00
PL12               18.00
PL13               18.00
SFO2         300.1312005

F2 - Processing paramet
SI                 32768
SF          75.4677190
WDW                   no
SSB                    0
LB                 0.00
GB                     0
PC                 1.40

1D NMR plot parameters
CX                 20.00
F1P              200.060
F1             15098.08
F2P               -9.544
F2              -720.30
```