Exploration into the Novel Generation of Carbon Radicals

Presented to the faculty of Lycoming College
in partial fulfillment of the requirements
for departmental honors in Chemistry

by
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26 April 2004

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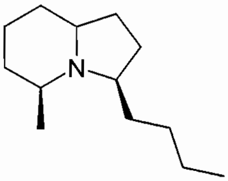
Abstract

A novel approach toward the formation of nitrogen containing heterocycles, and more recently, radical cyclization of sulfur containing, alkyl chains was examined. The first method used substituted, electron-deficient pyridine rings that were alkylated on the nitrogen with strong electrophiles by S_N2 means. This generated pyridinium cations that were treated with SmI_2 to cause a one electron reduction on the ring and induce cyclization onto a pendant alkene or alkyne. The cyclized product then underwent another one electron reduction and subsequent protonation to form the desired heterocycles. The generation and reduction of the pyridinium intermediates has proven to be successful, although final products have been very difficult to separate and fully characterize due to formation of a mixture of diastereomers and regioisomers that rapidly undergo air oxidation. More success has been achieved with the radical cyclization of sulfur-substituted compounds. This scheme involved performing a Pummerer rearrangement that added a trifluoroacetate substituent adjacent to the sulfur on the alkyl chain. Treatment with SmI_2 generated a radical at the site of loss of the trifluoroacetate, followed by homogenic bond formation between the radical and electron withdrawing portion, terminal on the alkyl chain, and finally, reduction and protonation of the molecule. Efforts concerning this chemistry are aimed at examining yield optimization and characterization of reaction byproducts.

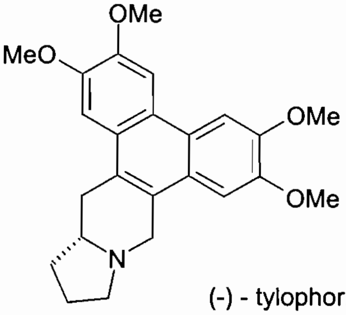
Introduction

The chemistry of pyridines has been extensively investigated for well over one hundred years and thus, numerous reviews on this subject are readily available.[1,2] However, very little attention has been given to bicyclic systems formed via pyridinyl radical precursors. In this paper, we examine a novel approach for the formation of nitrogen containing heterocycles. This method, which calls for an intramolecular cyclization of a pyridinyl radical onto a pendant alkene or alkyne, may prove to be useful in natural product synthesis where classes of alkaloids such as indolizidines and phenanthroindolizidines possess skeletal structures similar to those we are attempting to construct. Examples of these include the indolizidine, monomorine (**1**), which is the trail pheromone of *Monomorium pharaosis* and the phenanthroindolizidine, (-) – tylophorine (**2**), which exhibits a wide range of biological properties including antitumor activity.[3] Though the use of pyridinium cations as electrophiles is nothing new, examples of single-electron addition to these cations are almost nonexistent. This project will examine the potential utility of SmI_2 as a one-electron reductant for substituted pyridine rings and their concomitant cyclizations onto carbon-carbon multiple bonds.



monomorine

1



(-) - tylophorine

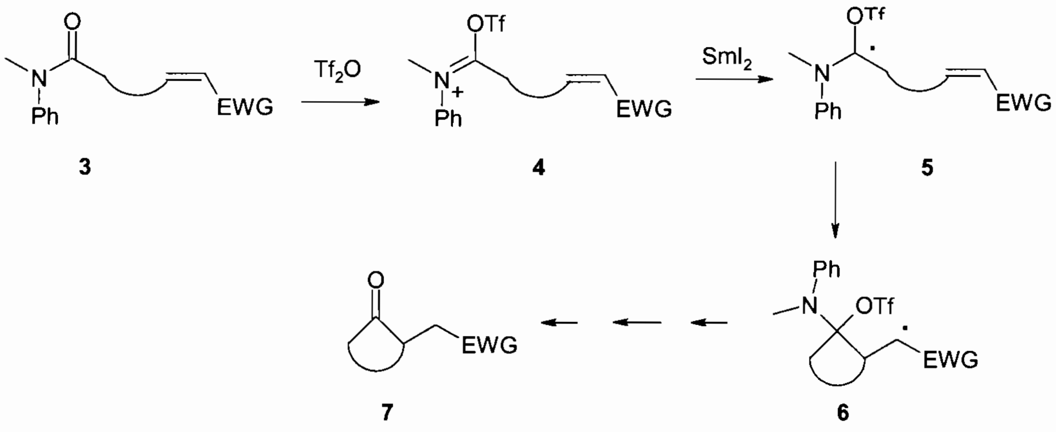
2

The latter segment of this project delves into the formation of sulfur-substituted rings. Although this involves much less direct biological significance than the pyridinium chemistry, it may prove very useful from the standpoint of using SmI_2 on other systems. That is, the capabilities of this one-electron reductant have by no means been fully explored, and thus, research on its applications and limitations with various organic moieties still falls within the realm of our laboratory research. This research could also prove to be useful for intermediate synthesis, because the products of this novel cyclization are sufficiently functionalized to allow for a variety of subsequent chemistry.

Literature Review

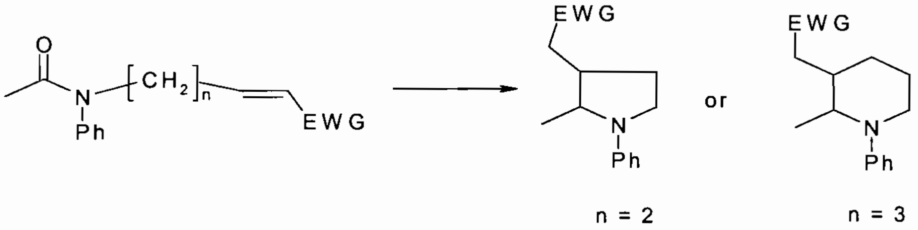
Previous work in this laboratory has shown that the SmI_2-initiated reduction of amides to form acyl radical equivalents has been moderately successful in the subsequent intramolecular cyclization onto substituted olefins.[4]

Scheme 1



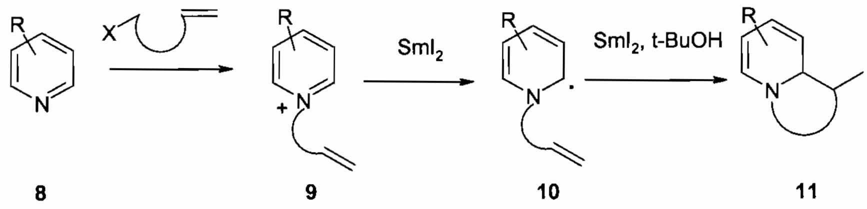
Here, treatment of the amide (**3**) with an electrophile, such as triflic anhydride affords an iminium triflate intermediate (**4**). Next, a one-electron reduction by samarium diiodide generates an acyl radical equivalent (**5**), which can then cyclize to form **6**. Finally, another one-electron reduction, followed by protonation by *t*-butanol and hydrolysis gives the final cyclic ketone (**7**). Further research has indicated that having an internal nitrogen to the forming ring provides an avenue toward the synthesis of five and six-membered heterocyclic systems (Scheme 2).[5]

Scheme 2



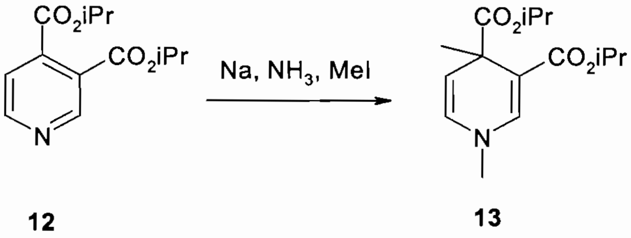
There are, however, several limitations to both of these reactions. For example, strong electrophiles are needed to form the iminium cation, but are sometimes incompatible with sensitive functionalities. Furthermore, we have only been able to form five and six-membered rings via *exo*-trig mechanisms. Finally, for cyclization to occur, the pendant alkene must be sufficiently electron deficient. With these drawbacks in mind, we would like to determine if pyridinyl ring systems could be used in an analogous manner to the preceding amides as radical precursors for heterocyclic formations. It is envisioned that we can N-alkylate on a substituted pyridine (**8**) by S_N2 means to generate an activated pyridinium cation (**9**). This species could then accept an electron from an appropriate reductant, such as SmI_2, to create a radical (**10**) and initiate cyclization with a pendant alkene or alkyne (**11**).

Scheme 3



Work by Donohoe, et.al. has uncovered the necessity of electron-withdrawing groups on the pyridine ring for reductions to take place in a related reaction. As seen in Scheme 4, they have treated disubstituted pyridine rings (**12**) with sodium, ammonia and methyl iodide under reductive alkylation conditions to generate the dialkylated product (**13**).[6]

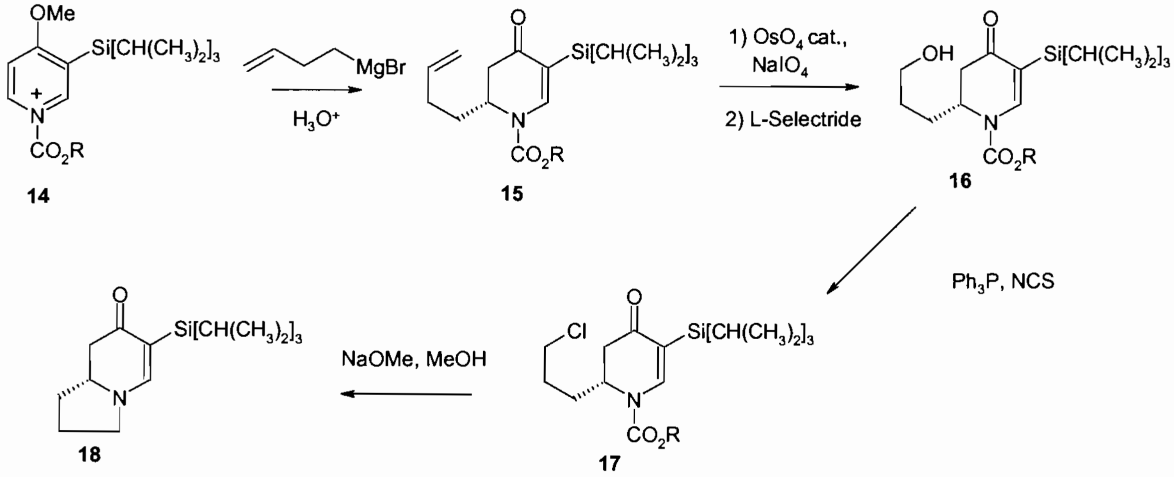
Scheme 4



Problems with this procedure include having two one-electron reductions occur and then two alkylations, which is not applicable to our work. In other work, Donohoe's group uses these alkyl groups to perform either base-induced or Bu_3SnH-mediated cyclizations onto the pre-existing ring at the least hindered alkene.[7] These cyclizations, however, only afford moderate yields due to the difficulties in separating the products from tin residues[8] and none of the reactions involve SmI_2 as a reductant, which is one of the goals of our research, though they may provide insight about the regioselectivity of our cyclizations.

More pertinent to our work is that done by Comins and colleagues. In their work, nucleophilic attack of a pyridinium ring (**14**) with a Grignard reagent followed by hydrolysis, yields the allane (**15**). Oxidative cleavage and reduction with L-Selectride transforms the alkene to an alcohol (**16**). The alcohol is converted to the chloride (**17**) upon treatment with triphenylphosphine and N-chlorosuccinimide. Lastly, the chloride was treated with sodium methoxide in methanol to eliminate the carbamate protecting group and afford cyclization to yield an indolizidine (**18**) similar to those previously discussed.[9]

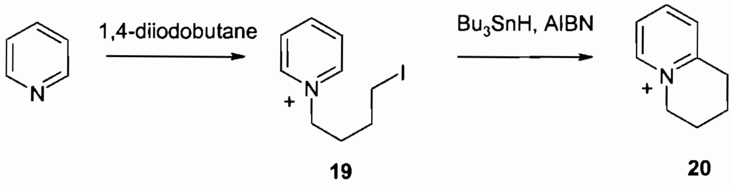
Scheme 5



Although this is very useful in terms of providing a mechanism for enantioselective cyclization, a drawback to this procedure is that it takes at least four steps to accomplish and probably more considering the functionality of the starting material, whereas our intended process takes only two steps.

Finally, Murphy and Sherburn have also shown comparable methods for the formation of bicyclic compounds via radical intermediates.[10] They also make use of a pyridinium cation intermediate (**19**) as seen in the first step in Scheme 6. This intermediate is treated with tributyltin hydride and the radical initiator AIBN to provide a 6,6-fused ring system (**20**) in only two steps.

Scheme 6



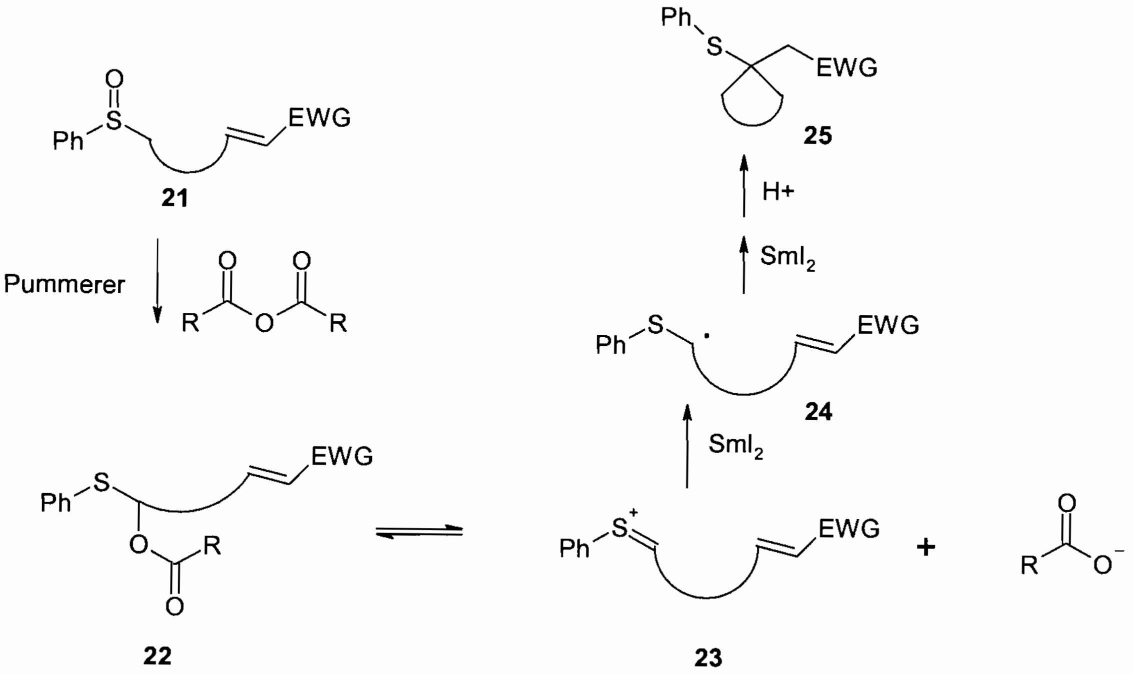
Although cyclization occurs in only two steps, there are several issues with this chemistry that could be problematic. For example, ionic character is retained in the final products because the radical is generated on the chain, external to the ring, which allows the ring to serve as the radical acceptor.[11] In addition, substitution has been found to occur at both ends of the alkyl chain in the first step, leading to unwanted bis-pyridinium byproducts. Reagent related problems stem from the use of tributyltin hydride and other sources of tin hydride, which tend to cause purification problems, as mentioned before.

Lastly, the final products generated in this manner were sometimes contaminated with undesired reductive deiodination salts.[12]

In a method similar to those previously discussed, we hope to develop and characterize a novel approach for the generation of bicyclic systems from pre-existing pyridine complexes in only two steps and with control of regioselectivity of alkylation and ring formation.

A second aspect of this research also focuses on generating carbon radicals, but this time, in hopes of eliciting cyclization to create sulfur substituted ringed systems. Like the methods previously discussed, samarium diiodide will be used as a one-electron reductant to produce a carbon radical, which will then cyclize onto the π-bond of a nearby electron withdrawing group. The basic procedure for this synthesis is depicted in Scheme 7.

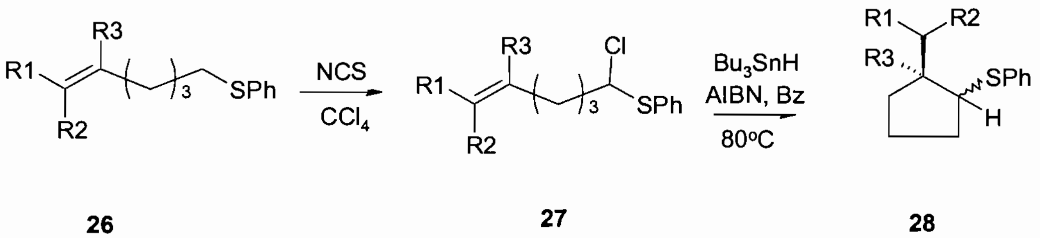
Scheme 7



Here, a sulfoxide (**21**) is subjected to Pummerer rearrangement conditions to create compound **22**, which is in equilibrium with the radical acceptor unit (**23**).[13] Compound **23** is treated with SmI_2 to induce a one-electron reduction to generate the radical (**24**). We then envision the intramolecular cyclization to occur between the radical and double bond of the electron withdrawing group to afford an intermediate cyclized product. The final step involves another one electron reduction and subsequent proton abstraction from the *t*-butyl alcohol to generate the final product (**25**).

There has been other interest creating carbon radicals and intramolecular cyclizations of organosulfur compounds over the last fifteen years, with some of the most important work being conducted by Yeun-Min Tsai and colleagues. In their initial research, they studied α-sulfenyl radical generation from α-chlorosulfides or dithioacetals and the effect of olefinic substituents on intramolecular cyclization.[14]

Scheme 8



In this relatively simple procedure, the α-chlorosulfide (**27**) is synthesized after treating the sulfide (**26**) with N-chlorosuccinamide in carbon tetrachloride. The desired α-sulfenyl radical intermediate was generated by treating the chlorosulfide with tributyltin hydride and AIBN in benzene to afford a 35/65 mixture of *cis* and *trans* isomers (**28**). In this synthesis the substituted R-groups varied from all hydrogens to combinations of hydrogens and methyl groups or ethyl esters. Analogous procedures involved making dithioacetals as radical precursors, which simply replace the chloro group with another thiophenol in compound **27**.

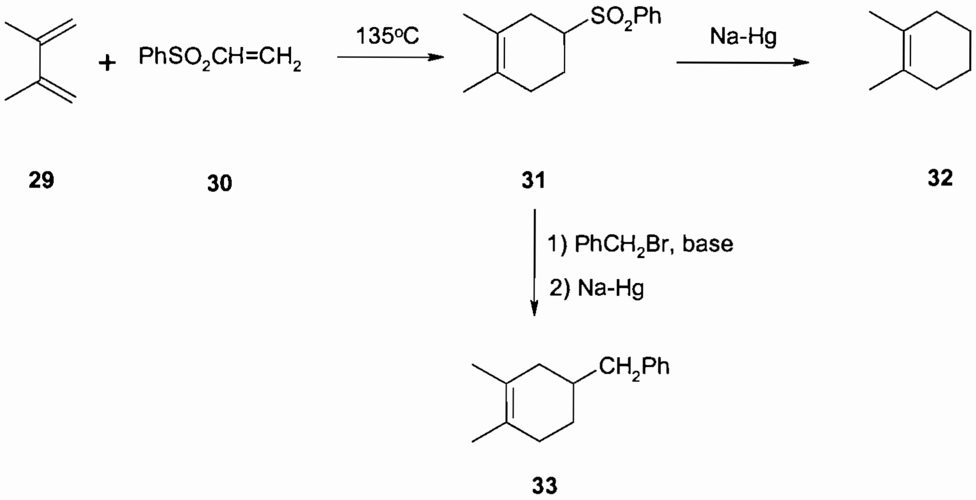
From this research, it was found that electron-deficient olefins increased the rate of cyclization and that more dilute conditions lead to an increased recovery of starting material. This method of cyclization is very useful because of the limited number of steps involved and the use of common reagents. However, tin complexes have been known to complicate purification of final products and AIBN may be very toxic and possibly carcinogenic.

More recent research by this same group, again studied the effects of this intramolecular cyclization, but with emphasis on the 5-*exo* cyclization because the 6-*endo* type was not observed in previous work.[15] This latter work also proved that the cyclization is most successful when the olefin is terminally substituted with an ester group. The *cis*/*trans* ratio of the cyclized product varied according to reaction rates. That is, when faster cyclization occurred, the *cis*-isomer was favored and vice versa.[16] Aside from the other problems with this synthesis discussed earlier, the group ran into problems with the stability of chlorosulfide and dithioacetal intermediates, as they readily decomposed due to their moisture sensitivity.

Our work in the synthesis of sulfur-substituted cyclic systems could provide a better means of generating intermediate compounds that possess great utility when used in conjunction with a nearly infinite variety of other procedures. For example, Leo

Paquette and his team have been actively generating similar compounds to those we wish to make by employing Diels-Alder [4+2] π cycloadditions.

Scheme 9



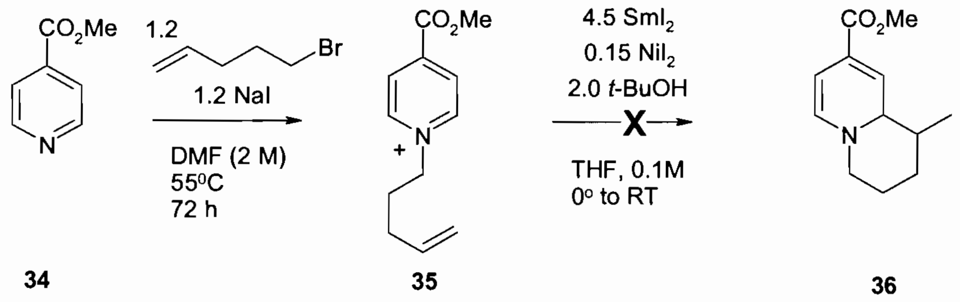
In their procedures, they react the diene (**29**) with a sulfonated dienophile (**30**) to make the cyclic sulfone (**31**). Compounds such as this are very similar to the ones we envision making. While Paquette's chemistry generates six-membered, sulfone-substituted rings, our chemistry will focus on five-membered, sulfide-substituted rings. Any differences in the reactivity of their intermediates could be compensated for in our lab by using different starting materials, or easily oxidizing our final products to make the sulfone. In Paquette's group, reductive desulfonylation was accomplished using sodium amalgam to afford compound **32**.[17] In another procedure electrophilic addition to the ring was followed by desulfonylation to generate compound **33**.[18] Both of these methods provided high yields of products, many in excess of 90%. These basic examples demonstrate just some of the potential utilities of the intermediates we wish to create.

In methods analogous to those previously described, we wish to undertake an innovative approach for generating carbon radicals of sulfide intermediates through one-electron reductions using samarium diiodide. We envision intramolecular cyclization of these free radicals with properly substituted olefins to yield cyclic sulfides that possess considerable utility in other organic mechanisms and handles for further functionalization.

Results and Discussion

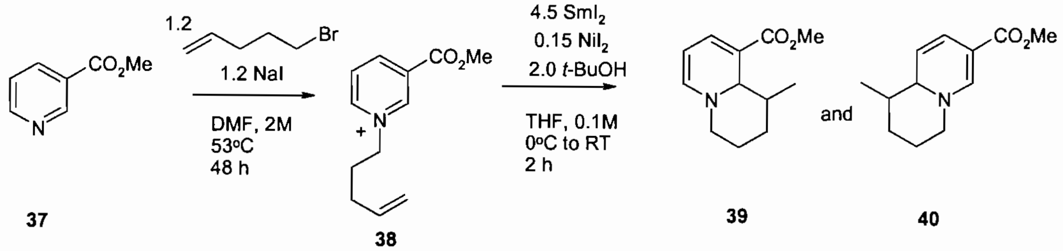
The initial approach is depicted in Scheme 10. Here, methyl isonicotinate (**34**) is reacted with an excess of sodium iodide and 1-bromo-4-pentene for 72 hours at 55°C in DMF to generate the pyridinium intermediate (**35**). In the next step, a catalytic amount of NiI_2, along with a large excess of SmI_2 was added to the flask at 0°C, quickly followed by the addition of *t*-butanol. The contents were allowed to stir for two hours and warm to room temperature in the hopes that a one-electron reduction would occur, inducing cyclization at the two-position of the ring with the terminal π-bond from the alkyl substituent. Then, another one-electron reduction would occur to form an anion, which would be immediately protonated by the *t*-butanol. The reduction and cyclization, however, were unsuccessful as ^{1}H-NMR showed mostly starting material remained.

Scheme 10



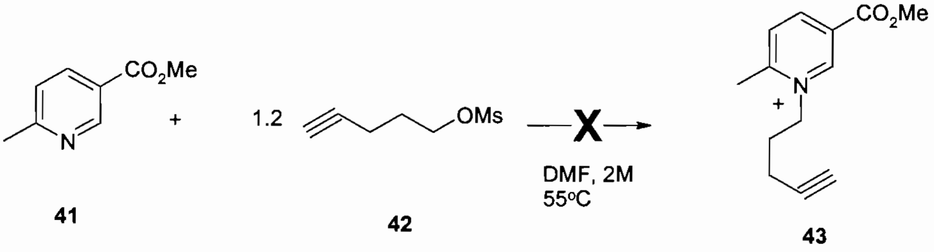
The same strategy was then applied to methyl nicotinate (**37**). This time, the analogous pyridinium intermediate (**38**) was formed, and reduction occurred in the next step. These reduced products, however, were unable to be separated and fully characterized due to the complexity of the contents, which was most likely a mixture of diastereomers and regioisomers (**39**, **40**), as reduction and cyclization could also take place at carbon-6 on the pyridinium ring as seen in Scheme 11. Difficulties may also have arisen from the unstable nature of the product dihydropyridine ring systems.

Scheme 11



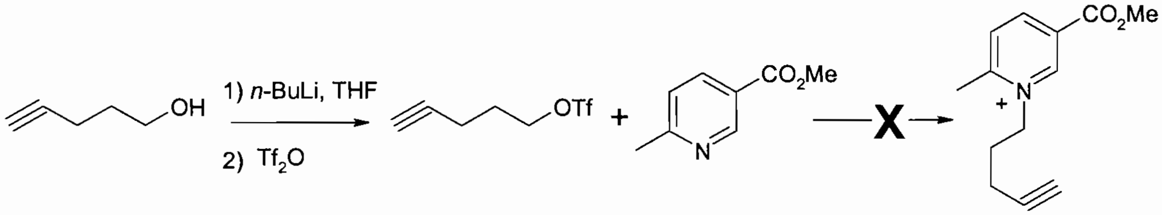
To try to generate intermediates at faster rates and reduce the number of potential products, several modifications were made. First, methyl 6-methyl nicotinate (**41**) was used as the starting material. The methyl group on C-6 was expected to hinder one mode of cyclization. In addition, 4-pentyn-1-methanesulfonate (**42**) was used as the electrophile because it was hoped that this compound would be more electrophilic than the bromide. Also, the presence of a terminal alkyne was expected to eliminate the possibility of diastereomers in the final cyclized products. Thirdly, it had a defined counterion to the pyridinium cation in the mesylate group that made molar calculations easier in the cyclization step. However, when a slight molar excess of **42** was reacted with **41**, at 55°C in DMF, the reaction was only 10-15% complete after four days and was thus, scrapped. The extremely long reaction time can probably be attributed to the increased steric bulk of the pyridine nucleophile.

Scheme 12



In the next approach, synthesis of a different electrophile with a triflate, instead of mesylate leaving group was attempted. The method involved reacting 4-pentyn-1-ol (**44**) with butyllithium and triflic anhydride in THF and then forming the cationic intermediate *in situ* by adding compound **41** to the flask after ten minutes and allowing the final contents to stir overnight. ^{1}H-NMR of an aliquot of this reaction showed very little desired product being formed, with the majority of the contents being apparent electrophilic addition to the THF, followed by nucleophilic attack of **41** and subsequent ring opening. This problem has come up in previous laboratory work and is due to the triflate being extremely electrophilic, and thus, incompatible with this particular solvent.

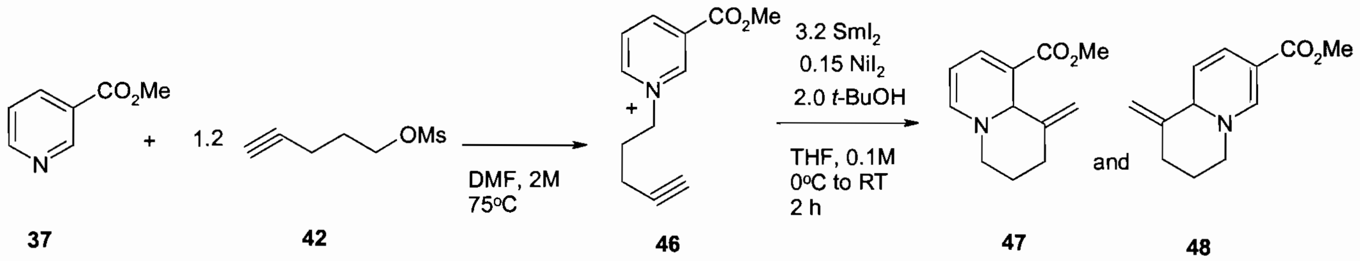
Scheme 13



44 **45** **41** **43**

Going back to the original approach for cation formation, compounds **37** and **42** were mixed together under the same conditions in Scheme 11. This reaction took approximately a week to complete and required heating to reach about 75°C over the last four days. The desired cation (**46**) was generated and then treated with SmI_2, NiI_2, and *t*-butyl alcohol, as stated in Scheme 11. The only change in this reaction was that 3.2 equivalents of the samarium diiodide were used, as opposed to 4.5 equivalents used in previous reactions, for fear of over-reduction. ^{1}H-NMR again indicated that reduction had occurred. Many signals corresponding to alkenyl protons appeared in the crude product spectrum. Also, the terminal alkyne proton had vanished, suggesting that reduction, and possibly cyclization had occurred as hoped. Further evidence of desired products was given by CI-MS, which showed an M +1 peak that had the molecular weight of our theorized heterocyclic products. TLC spotting showed two major compounds in the final mixture, but attempted column chromatographic separation was unsuccessful, as the presumed products were apparently destroyed on the column.

Scheme 14

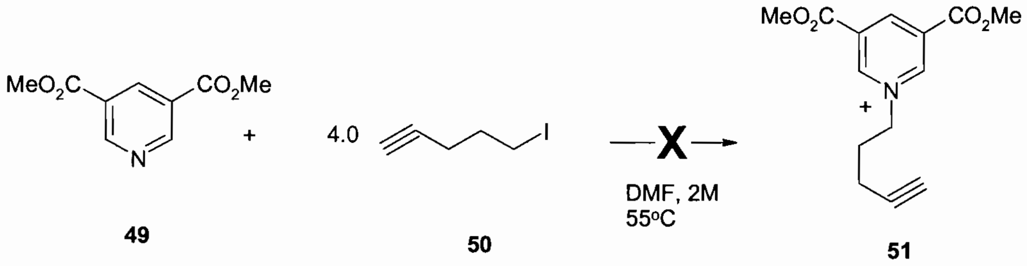


The exact same procedure was then attempted with emphasis placed on purifying the material as quickly as possible to prevent decomposition. Again, two major compounds were seen from TLC, and mass spectroscopy showed molecular weight of the desired products. The two compounds were moderately separated, but in very low yields, and with oxidation already occurring. In fact, much lower than expected yields were realized over the last two reaction sequences. This led us to believe that either the cationic intermediates were being over-reduced or that preferred reduction was incomplete. Since, no starting material could be recovered from this reaction; it seemed probable that over-reduction was occurring. Thus, in the next sequence, the same intermediate was only reacted with the SmI_2 for thirty minutes, instead of the usual two hours.

After the reaction had taken place over a half-hour, a crude weight of the contents taken was much less than expected, even before purification. ^{1}H-NMR spectra of the aqueous layer from extraction did not reveal anything that would indicate the majority of products being reduced or converted to inorganic materials, and thus ruled out all of our speculations as to why such poor yields from this reduction step were happening. A ^{13}C-NMR was taken in an attempt to get a better idea of what may be occurring here, but not enough material had been produced to give an identifiable spectrum.

At this point, we began to focus on new starting materials that were symmetric, so that only one mode of cyclization was possible.

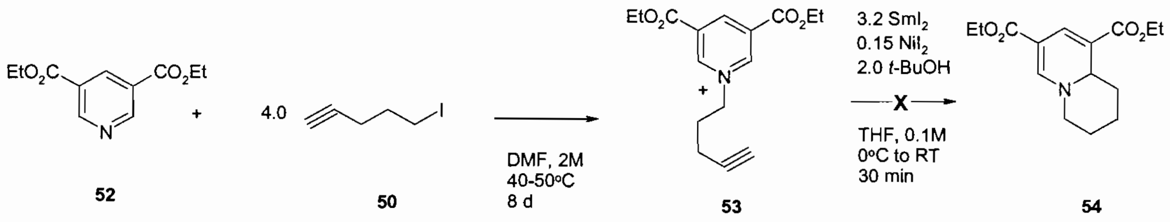
Scheme 15



Here, a second carbomethoxy electron-withdrawing group was added at the five position on the ring to create symmetry in compound **49**. This will presumably attenuate the nucleophilicity of the starting material, and thus compound **42** was converted to the iodide **(50)** to promote better reactivity between the species. After heating the mixture for 2.5 days, it appeared by NMR, that some of the desired product was synthesized but the contents may have heated too long and some unwanted materials were also being generated.

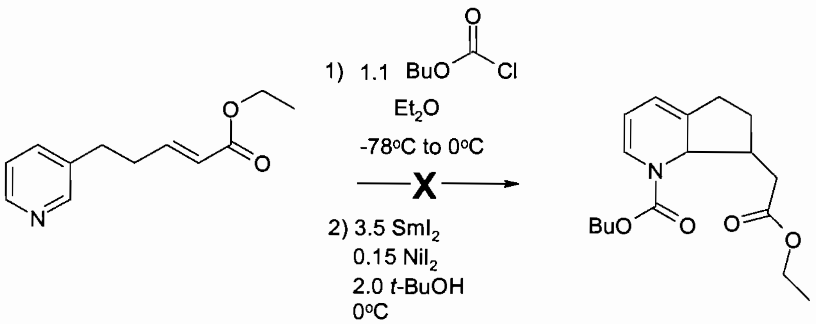
To correct this problem, the contents were heated at a lower temperature for a shorter period, but heating was not properly controlled and got to about 59°C, and again led to undesired products. The diethyl ester analog of compound **49** was generated in hopes of achieving better stability and used in the same manner as depicted in Scheme 15. This reaction stirred for a total of eight days while being heated between 40-50°C to make the cation (**53**). After this, compound **53** was subjected to the same reduction conditions using 3.2 equivalents of the samarium diiodide. The contents were left stirring at 0°C for only thirty minutes because reduction would probably occur at a faster rate due to the presence of two electron-withdrawing groups on the pyridine ring. After quenching the reaction, spectroscopic data indicated disappointing results. First, ^{1}H-NMR did not show any shifts between 5.0 and 6.0 ppm, which is where we would have expected several peaks due to the loss of aromaticity. The spectrum showed that mostly the pyridinium starting material remained, with some reductive elimination to form compound **52** as well. Also, CI-MS spectral data did not possess any major fractions having the desired molecular weight of the cyclized products. A TLC spot showed a very complicated mixture of products, which contained many more byproducts than expected. Due to the complexity of the final mixture, no hypotheses have been made as to what unintended reactions are occurring and how to fix them.

Scheme 16



The next approach was aimed at promoting cyclization of our final products by adding an electron withdrawing group, terminal to the alkenyl chain, which should help cyclization to occur after the initial one-electron reduction. Also, the radical accepting portion of the tethered chain could also stem from the three-position of the ring, as opposed to all previous tethers originating off the nitrogen atom, or one-position. Prior to this, a carbamate protecting group would be used to acylate on the nitrogen and generate a cation. After the reduction, cyclization, another reduction and protonation occur, this protecting group could be oxidized off to yield desired products. The rationale behind this method is to generate intermediates that are not as air-sensitive so that we could more easily characterize them.

Scheme 17



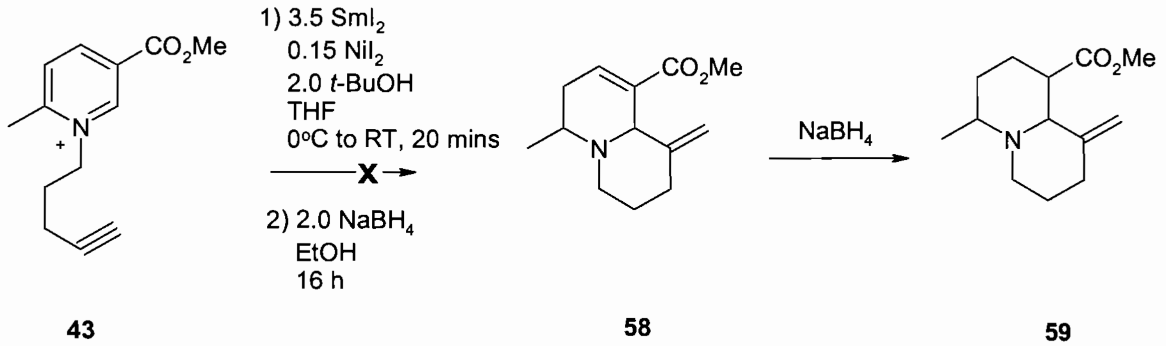
55 **56**

In this scheme, the substituted pyridine **(55)** was dissolved in dry ether in a nitrogen-filled flask with the NiI_2 already added, and then cooled to around -78°C in a chloroform/liquid nitrogen bath. Butyl chloroformate was then added via syringe and the contents in the vessel solidified almost immediately, indicating that the cation had formed. The flask was then allowed to warm to 0°C, at which point 3.5 equivalents of the samarium diiodide was added to the flask. The deep blue color of the SmI_2 solution vanished after only five seconds, so another 2.0 equivalents of the solution was added. Again, the blue color vanished quickly and turned to a cloudy, yellow-green mixture. Finally, the *t*-butanol was added and the contents were left to stir for twenty minutes. After this, an aqueous workup was employed after filtering off inorganic solids and the organic layers were collected and stripped to dryness. A crude TLC showed a complex mixture of products, while a crude NMR spectrum indicated that the reaction had led to mostly the reformation of starting material. Reduction had presumably occurred at the acyl pyridinium carbon, which resulted in the pyridine being reductively eliminated, as opposed to reduction of the ring, itself.

This procedure was attempted one more time, but without adding the extra 2.0 equivalents of SmI_2. Again, the contents turned to a black solid after adding the butyl chloroformate. When adding the SmI_2, the blue color did not dissipate as quickly, as it took about a minute for the solution to turn a dull yellow color. The *t*-butyl alcohol was added after about thirty seconds and the solution turned to a maroon color, a physical event that did not occur in the previous reaction. After a similar workup, a TLC spotting showed a much simpler product mix, but NMR spectral data again indicated that the vast majority of products was starting material.

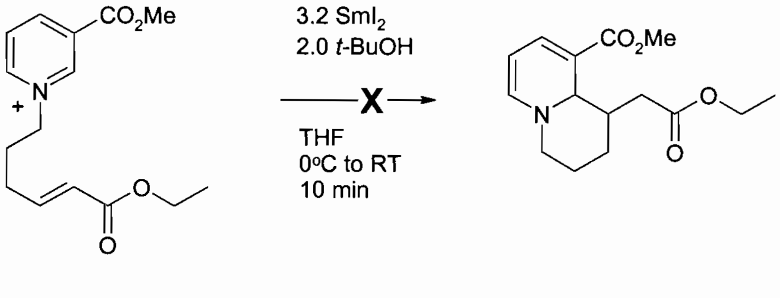
We decided to move away from this type of starting material and pursue new methods with our previous pyridinium structures that have the radical acceptor tethered to the nitrogen. The first change in our typical procedure was made during the workup of the reduction products. After treating the pyridinium salt, which in this case was the 6-methyl substituted pyridinium that possessed a tethered alkyne (**43**), with 3.5 equivalents of samarium diiodide, 0.15 equivalents of the nickel diiodide and 2.0 equivalents of the *t*-butyl alcohol, and allowing the contents to stir for 20 minutes, approximately 8 mL of ethanol was added to the flask along with 2.0 equivalents of sodium borohydride. The idea behind this is that the hydride will be able to reduce one or both of the double bonds in the formerly aromatic ring (**58**, **59**), which would lead to better stability and less susceptibility to oxidations during aqueous workup. After the borohydride was added, gas evolution was immediately noticed, as expected, and the contents were left to stir overnight. In the morning, the solution had turned yellowish in tint, and had become much clearer. After a typical workup, crude TLC showed that the product mixture was even more complex than before. Chemical ionization mass spectral data did show ions having the desired mass, but due to the increased complexity of the mixture, no efforts were made to separate and further characterize the components.

Scheme 18



The last efforts made for the cyclization of pyridiniums with samarium diiodide as the reductant were performed without the use of the nickel diiodide electron transfer catalyst. General reaction conditions were employed other than NiI_2 being absent. It should also be noted that the radical-accepting portion of the pyridinium (**60**) also possesses a terminal electron-withdrawing group that should promote cyclization to afford the final product (**61**). After dissolving the pyridinium (**60**), cooling the reaction vessel to 0°C, and adding the samarium diiodide, the contents turned yellow in color, indicating oxidation of the samarium, even without the catalyst. Approximately 1.5 more equivalents of the samarium diiodide were added slowly, and this time the blue color persisted for several minutes. The *t*-butanol was added and the contents stirred for another ten minutes before aqueous workup conditions. After removing the solids by filtering through celite, extracting with ether and stripping the organic layers a crude NMR was taken. Although some reduction was apparent in the spectrum, there still existed a large amount of aromatic material. The absence of the nickel catalyst also did not enhance the reaction in terms of simplicity of final product mixture. At this time, it was decided that efforts would be focused on using different one-electron reductants to elicit the generation of carbon radicals and adjusting reaction conditions to limit byproducts.

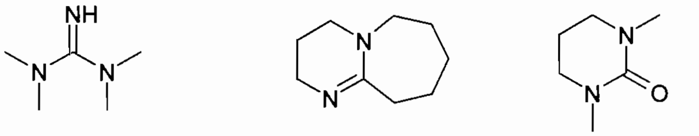
Scheme 19



60 **61**

Should attention be placed on using SmI_2 again in the future, there are a variety of articles available that demonstrate how the reductive capacity of the samarium diiodide can be enhanced. These mostly include the formation of samarium (II) complexes formed with both added ligands and the solvent. The most popular of these is the THF/HMPA complex formed with the SmI_2. Although the addition of HMPA to a THF solution does lead to a significant increase in the electron-donating abilities of SmI_2,[19] HMPA is known to be a carcinogen and poses obvious dangers that we would rather not deal with. Therefore, less toxic complexes, such as $Sm[N(SiMe_3)_2]_2$ could be used. This complex behaves similarly to SmI_2 and has proven to be a very reactive reductant.[20] This complex is also soluble in a variety of solvents from THF to hexane, which is beneficial because THF is sometimes known to be a good hydrogen atom donor, and thus terminate certain radical reactions. Other ligands that can also be used in enhancing the reductive capacity of this system include, but are not limited to, TMG (**62**), DBU (**63**), DMPU (**64**), and Et_3N.[21] However, the most promising system, in terms of compatibility with our research, toxicity of reagents, and speed of reduction, is the SmI_2/water/amine system developed by Dahlen and Hilmersson, who show that most reductions occur instantaneously.[22]

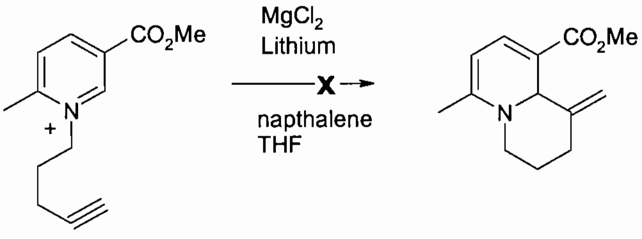
Scheme 20



62 **63** **64**

The first method employed to generate carbon radicals without using a samarium reductant was done with magnesium metal. The process to make this reductant was taken from Sugimoto and colleagues, who used it in conjunction with the addition of electrophiles to halomagnesium pyridines.[23] By their methods, dry magnesium dichloride was mixed with 2.0 equivalents of naphthalene and lithium ribbon under inert atmosphere in THF solvent. The mixture turned a black color after three minutes of stirring at room temperature, but it was allowed to stir overnight. The next day, a metal coating all around the bottom of the flask was apparent, so the pyridinium (**43**) was added directly to the flask. There may have been a slight exotherm upon addition of the pyridinium, but otherwise, there were no other physical signs of reaction taking place. The contents were allowed to stir for about two hours, before aqueous workup with sodium bicarbonate. A crude TLC showed only two main products in the mixture, but neither having the polarity that one would expect if the desired compounds were generated. A crude NMR indicated that very little starting material had been reduced. Nonetheless, a chemical ionization mass spectrum was taken and only one compound was seen, which could be attributed to the naphthalene. Because little, if any, reduction had occurred, no more reactions were performed with a magnesium reductant, and the last attempted reductions of the pyridiniums were done with cobalt complexes.

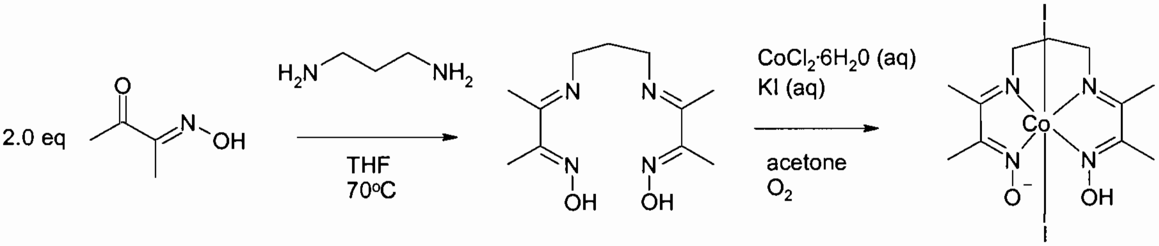
Scheme 21



43 **47**

Though not very common, we were able to find some precedents in the literature for generating alkyl radicals with cobalt complexes, with some even going further to form saturated radical cyclization products.[24] From these articles, we came across several simple procedures that outline the construction of the cobalt complexes. Our adapted procedure for generating these complexes is outlined in Scheme 22.

Scheme 22



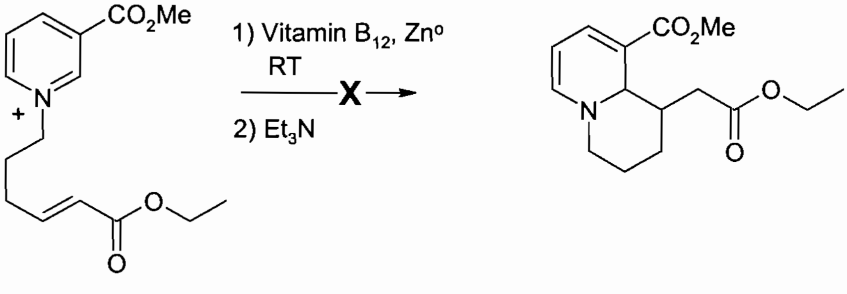
65 **66** **67**

In the first step, diacetylmonoxime (**65**) was dissolved in THF and then a proportional amount of 1,3-diaminopropane added via syringe.[25] The mixture was then heated in a water bath to about 70°C and then cooled back to room temperature. In the first attempt to synthesize compound **66**, the mixture was heated for about two hours before cooling. Nothing, however, precipitated out of solution as the mixture cooled, nor when the flask was left in the freezer overnight. The solvent was stripped off and hexane was added. Although some crystals did form around the edges of the flask, most of the mass remained a yellowish, pudding-like substance. This was probably due to overheating, so in the next reaction, the vessel was only heated at the aforementioned temperature for twenty minutes, but the results were the same. A third attempt was made with heating to 60°C for ten minutes. This time, crystals did begin to precipitate out of solution as the mixture was cooled in an ice bath, instead of letting it cool slowly to room temperature. The solids were washed with ice-cold ether and all volatiles were removed on the vacuum pump. An NMR spectrum was taken and showed a complex mixture of products. Therefore, efforts to recrystallize the solid with a mix of ethyl acetate and hexane and separately, with butyl ether were made, but no improvement to the clarity of the NMR spectrum was achieved. Due to the time that had already been spent on this portion of the project, it was decided that the products would be used as/is in the next step of the reaction sequence.

In the second step the 1,3-bis(diacetylmonoxime-imino)propane (**66**) was reacted with cobalt (II) chloride hexahydrate and potassium iodide in acetone, with a constant source of oxygen gas being present.[26] The starting material (**66**) was dissolved in acetone, while the cobalt chloride and potassium iodide were dissolved in small amounts of deionized water. The aqueous solutions were added to **66** slowly by pipette to produce a deep magenta color from the cobalt in solution. The contents stirred for one hour and then the solids were filtered off and washed with cold water and then cold ethanol to leave behind dark green crystals. The crystals were left to air-dry overnight before an NMR was taken. The NMR, although very clean, did not show representative peaks of the target compound **(67)**, leading us to believe that the proper starting materials were never synthesized in the first place. Because of the difficulties with this particular cobalt complex, this reaction scheme was scrapped.

Because the previous cobalt complexes were derived from vitamin B_{12} models, and vitamin B_{12} has been used by other labs for radical formation[27], we decided to try this reductant, especially since it is commercially available.

Scheme 23



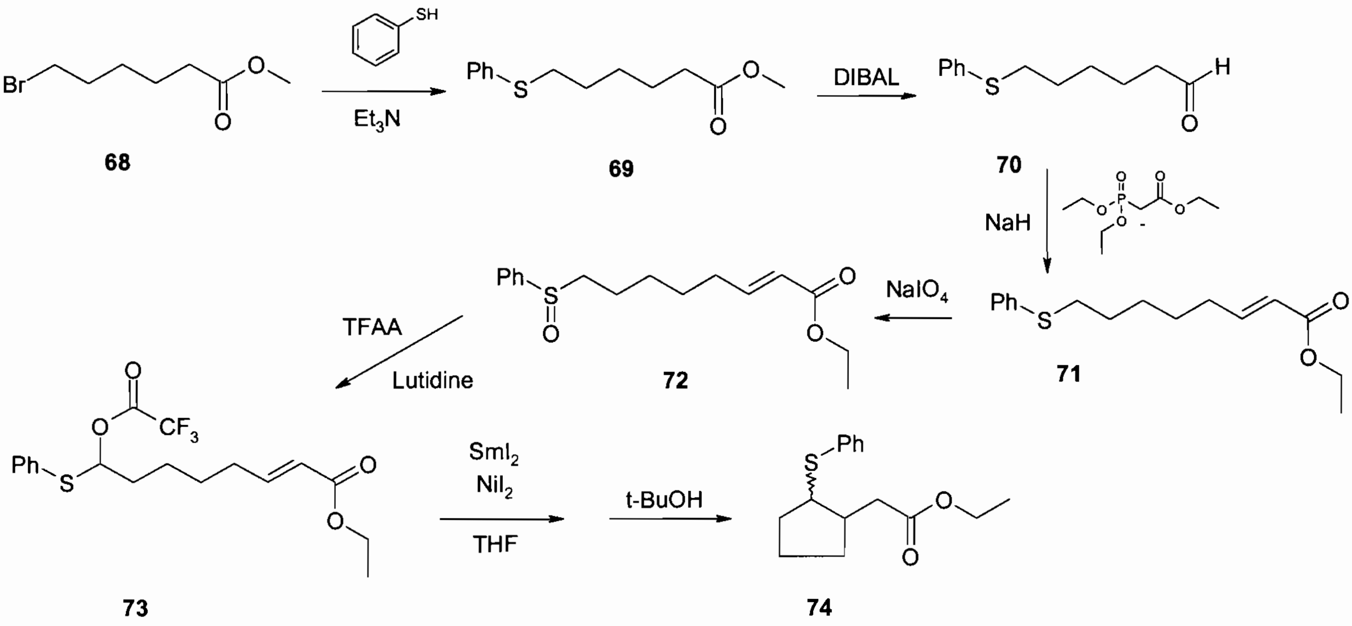
60

61

In this process, activated zinc metal and the vitamin B_{12} were mixed together. The zinc was first activated by treating it with 2N HCl (2x10mL) followed by washing with water (2x10mL) and diethyl ether (2x10mL) and then finally dried.[28] The reactants were mixed with distilled DMF and stirred vigorously. To help dissolution of this heterogeneous mixture, a sonicator bath was used. As the cobalt complex is reduced, a color change from deep red to dark green should be observed, however, this was not the case in our experience. After three hours, it was decided that the pyridinium **(60)** should be added to the reduced cobalt solution anyway. This was accomplished by dissolving the cation in minimal amounts of DMF and transferring via syringe. Shortly after this, triethylamine was added and the mixture stirred overnight. No visible changes occurred after 24 hours and the reaction was quenched with water, filtered, acidified and extracted with ether. The organic collections were washed with water, dried with magnesium sulfate, filtered and stripped. A crude NMR of this material shows that reduction may have occurred. However, when this same reaction was performed without the vitamin B_{12}, a similar spectrum resulted. From this it can be concluded that the activated zinc was responsible for any reduction to the radical precursor (**60**), and that the vitamin B_{12} complex was probably never reduced, as evidence by the lack of dark green solution. Unfortunately, this failure led to the culmination of research using the pyridinium compounds, as more successful research in the carbon radical generation of sulfur-containing compounds came into focus. Although the pyrdinium chemistry could have had tremendous biological impact if successful, we decided not to pursue it any further.

The sulfur chemistry possesses direct correlation to the initial chemistry performed in the lab, where SmI_2 was first used by our group as a reductant, which is depicted in Scheme 1. Both methods demonstrate how carbon radicals can be formed adjacent to heteroatoms. Thus, our current work is based on the exploration of the generation of carbon radicals with other heteroatomic systems, beginning with sulfur-containing compounds.

Scheme 24



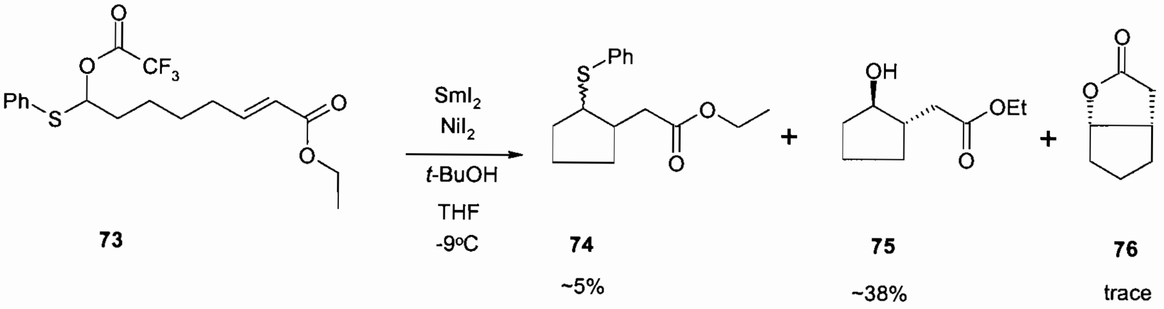
Thus, the first task was to construct an appropriate sulfoxide radical precursor tethered to a radical acceptor. To accomplish this, we first used an S_N2 displacement of the bromide leaving group in compound **68** with thiophenol to generate the sulfide ester (**69**) in 85% yield. In the next step a DIBAL reduction is used to create the aldehyde (**70**), and the radical acceptor unit (**71**) is introduced via a Wadsworth-Emmons reaction for an overall, two-step, yield of 48%. Treatment of this compound with 1.05 equivalents of sodium periodate oxidizes the sulfur to a sulfoxide group in excess of 90% yield.[29,30] Compound **72** is then subjected to Pummerer rearrangement conditions by treating it with trifluoroacetic anhydride and then lutidine, a mild base, to synthesize compound **73**.[31] After stripping off all volatiles, compound **73** is transferred into a THF solution of SmI_2 to induce a one-electron reduction after loss of the trifluoroacetate ion. We then envision the intramolecular cyclization to occur between the thio-substituted carbon radical and double bond of the electron withdrawing group to afford an intermediate cyclized product. The final step involves another one-electron reduction and subsequent proton removal from the *t*-butyl alcohol to generate the final product (**74**).

In our initial workings of this procedure we concentrated on optimizing reaction conditions in the two most important steps, which are the Pummerer rearrangement and subsequently, the reduction and cyclization step. In the Pummerer reaction, the sulfoxide was dried under vacuum, and then the flask was filled with argon. Then trifluoroacetic anhydride was added via syringe to make a one molar solution. After one minute, lutidine was added via syringe, which resulted in the solution immediately turning to a yellow/green color as vapors arose in the flask. The flask was stoppered, sealed, and allowed to stir at room temperature for 45 minutes. The reaction was monitored by NMR, and after 45 minutes it showed that sulfoxide was no longer present. In the next step, NiI_2 was transferred to a Schlenk flask and dried under vacuum, and then the SmI_2 was added to this flask. After the volatiles had been stripped from the Pummerer product, it was dissolved in dry THF and transferred to the Schlenk flask at room temperature. After thirty seconds, the *t*-BuOH was added to the flask as well. The contents stirred for only about twenty minutes as the solution turned to a yellowish color, indicating that the samarium diiodide had been consumed very quickly. The reaction was quenched with water and extracted with 1:1 ether/hexane mixture. A TLC in pure hexane showed mainly one nonpolar spot, but a large spotting of polar material that never moved from the baseline. The crude product was purified on a silica column. When this reaction was performed at room temperature, a 26% yield of the desired cyclized product

(74) was attained, with a *cis*/*trans* ratio of approximately 2.9:1. Since this was only a probe reaction, no efforts were made to characterize any of the byproducts.

Results looked promising, but due to the relatively poor yield of only 26%, efforts were made to optimize this reaction and also characterize the byproduct. Therefore, the reaction was performed as before, except that the Pummerer product was added to the Schlenk flask at 0°C. It, again, took about 20 minutes for the deep blue color of the solution to dissipate, after which point, the solution was taken out of the ice bath and allowed to warm to room temperature for ten minutes. The same workup and purification methods were used, but the column was overloaded with polar solvent during the transfer of crude product to the column, resulting in a non-optimal separation. Even with this problem the desired product **(74)** was obtained in 24% yield with trace impurities. The *cis*/*trans* ratio did, however, improve to almost 4:1. The final reaction performed as part of this project was the same thing, but at an even lower temperature of -9°C, as shown in Scheme 25.

Scheme 25



This reaction took much longer for the samarium to be oxidized with a time of one hour, compared to the previous twenty minutes. A better separation was attained this time, but only 5% of the cyclized sulfide was generated. On a positive note, other cyclized material became apparent in NMR spectral data of the more polar byproducts. Compound **75** was identified by GC-CI/EIMS and ^{1}H-NMR spectra compared to literature references. COSY-NMR was first used to analyze this compound, but the results were inconclusive, probably because the mixture was too dilute. Chemical ionization mass spectroscopy did provide some insight into the identity of this product, which in this reaction was the major product with 38% yield. In this spectrum, main peaks at m/z = 173, 155 and 127 were observed. The first is indicative of the molecular ion and the one at 155 would be expected for loss of H_2O. The peak at m/z = 127 shows loss of CH_3CH_2OH to leave the corresponding acylium cation, $C_7H_{11}O_2^+$. ^{1}H-NMR and ^{13}C-NMR were also compared to literature references where the same compound was synthesized and characterized.[32,33] Comparison of our spectra against the literature references unambiguously identified our primary byproduct as the hydroxyl-substituted cyclized product (**75**), and proved that through our procedure a bimodal cyclization mechanism is possible. The stereochemistries of compounds **75** and **76** were made based on the literature precedence and well-known knowledge that if the ester and hydroxyl substituents are *cis* to each other, then intramolecular acyl substitution readily ensues to generate **76**. It is believed that compound **76** may have been produced in trace quantities because of reasonable chemical ion peaks seen in the mass spectral data. If it was actually produced, most of it may have been stripped off by vacuum during the purification process, which is why only traces of it may have been seen.

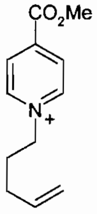
As of now, the nucleofugacity of this mechanism is not sufficiently selective, so we need to develop strategies that favor or disfavor the loss of either the thiophenoxide or the trifluoroacetate ions. Either mechanism proceeds quickly within the 0°C to room temperature range. Some future possibilities to control the mechanistic pathway of the reaction could be to find Lewis acids that will selectively bind to one of the leaving groups, and therefore facilitate its loss. In addition, we could attempt to retard the loss of the thiophenoxide by substituting on the aromatic ring, or analogously, use different anhydrides that may prevent loss of the carboxylate leaving group. By employing a combination of these possibilities, with temperature variations and stoichiometric optimization of reactants we hope to further characterize the products of this reaction, develop methods to control mechanistic pathway and selectivity of *cis/trans* isomers, and most importantly, enhance yield.

Conclusions

Reduction of the pyridinium intermediates was successful, however, desired cyclization has not been proven and yields from these reactions have tended to be very poor. Several methods were employed in an attempt to optimize yield and simplify final product mixture, such as using different reductants or treating the reduction products with sodium borohydride to make the products more stable. Again, the desired reduction was apparent, however, no gains were made in terms of complexity and stability of final products. Therefore, research efforts were focused on forming carbon radicals in sulfur-containing systems. Initial efforts in these sulfide cyclizations have been successful, but at low yields. Most interesting is the observance of a bimodal mechanistic pathway toward radical generation and subsequent cyclization. Current methods, however, are not selective for each individual mode of cyclization. Therefore we need to develop strategies that favor/disfavor loss of the trifluoroacetate or thiophenoxide ions. Finally, we also need to continue developing methods to increase product yield and control stereoselectivity of final products.

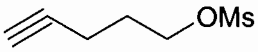
Experimental

General Methods. All reactions were carried out under nitrogen or argon atmosphere, using anhydrous solvents and oven-dried glassware, unless otherwise noted. Syringes were oven-dried, and cooled in nitrogen or argon-filled, septa-sealed flasks. Commercially available compounds were used without further purification, unless documented. Solvents and other reagents were dried employing the following methods: DMF distilled from CaH_2 using water aspiration, THF distilled from Na/benzophenone under N_2, *t*-BuOH distilled from CaH_2 under N_2, using a short-path condenser without circulating water, pyridine distilled from CaH_2 under N_2, lutidine distilled from CaH_2 under N_2, and triethylamine distilled from CaH_2 under N_2 . Reaction mixtures were cooled to 0°C using an ice-water bath and to approximately -10°C with a salt/ice bath. Purification of the cationic intermediates was carried out by triturating with hexane and/or diethyl ether. Other compounds were purified by silica gel chromatography, using 70-270 mesh silica gel, and specified proportions of EtOAc/Hexane as the mobile phase. Thin layer chromatography was performed using Analtech glass-backed TLC plates, and visualized using both I_2 chambers and UV-VIS. Nuclear Magnetic Resonance spectra were obtained using the Bruker Avance DPX-300 NMR Spectrometer. ^1H spectra were recorded at 300 MHz, using $CDCl_3$ as the solvent and are reported in ppm downfield from TMS (δ=0).



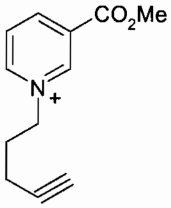
35

Methyl 4-carboxylate N-(1'-pent-4'-ynyl) pyridinium bromide/iodide. Methyl isonicotinate (0.750g, 5.47mmol) was weighed into a 10-mL round-bottom flask, followed by dry sodium iodide (0.983g, 6.56mmol). Dry DMF (2.75mL) and 5-bromo-1-pentene (0.78mL, 6.6mmol) were then added at room temperature via syringe. A reflux condenser was attached and the contents were allowed to stir at 55° C for 48 hours. After this, more 5-bromo-1-pentene (0.32mL, 2.7mmol) was added and the mixture stirred for 24 more hours. The viscous brown mixture was vacuum pumped to concentrate and triturated with a 2:1 hexane/ether mix. These solvents were vacuum pumped off and the contents were washed with pure hexane twice more and dried by vacuum to obtain an orange/brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (d, 2H, J = 6.0Hz), 8.54 (d, 2H, J = 6.0 Hz), 5.08 (m, 4H), 5.78 (m, 1H), 4.08 (s, 3H), 2.23 (m, 4H).



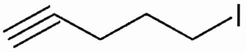
42

4-Pentyn-1-O-methanesulfonate. 4-pentyn-1-ol (1.50g, 0.0178mol) was weighed into a dry 50-mL round-bottom flask, followed by dry pyridine (18mL). The flask was cooled to 0° C under N_2 and then methanesulfonyl chloride (1.52mL, 0.0196mol) was added via pipette to produce a yellow/orange color in the flask. The mixture was stirred for four hours at 0° C. At this time, the contents were poured into a separatory funnel and extracted with dichloromethane and water. The organic layer was collected and washed with water (3x20mL), 10% HCl (2x15mL) and brine (2x15mL). The organic layer was then dried over sodium sulfate, filtered, stripped with the rotovap, and vacuum pumped for 45 minutes to produce a yellowish liquid in 82% yield (2.371g, 0.0146mol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35 (t, 2H, $J = 6.3$ Hz), 3.04 (s, 3H), 2.36 (m, 2H), 2.06 (t, 1H, $J = 2.7$ Hz), 1.97 (quint, 2H, $J = 6.3$ Hz).



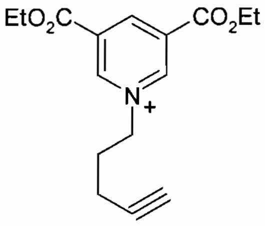
46

Methyl 3-carboxylate N-(1'-pent-4'-ynyl) pyridinium methanesulfonate. Methyl nicotinate (0.75g, 5.47mmol) was weighed into a 10-mL round-bottom flask, followed by 4-pentyn-1-O-methane sulfonate (1.06g, 6.56mmol). Dry DMF (2.75mL) was then added at room temperature via syringe. A reflux condenser was attached and the contents were allowed to stir and heated intermittently at 55° C for 72 hours. After this, more 4-pentyn-1-O-methane sulfonate (0.410g, 2.52mmol) was added and the mixture stirred for 72 more hours at 75° C. The viscous brown mixture was rotovapped to concentrate and triturated with hexane and then diethyl ether. These solvents were vacuum pumped off to obtain a brown gummy substance in 67% yield (1.09g, 3.64mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1H), 9.03 (s, 1H), 8.69 (s, 1H), 8.43 (app. s, 1H), 5.07 (s, 2H), 4.07 (s, 3H), 3.05 (s, 3H), 2.38 (m, 4H), 2.06 (s, 1H).



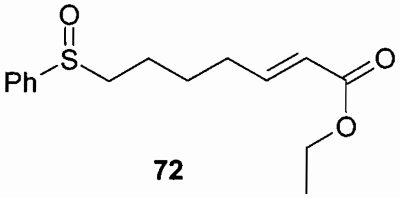
50

1-Iodo-4-pentyne. Dry sodium iodide (8.01g, 0.0534mol) was added to 4-pentyn-1-O-methanesulfonate (**42**) (5.78g, 0.0356mol). Then sieve-dried acetone (18mL) was added to the flask via syringe and a condenser was attached before allowing the contents to reflux. White precipitate fell out solution as the reaction stirred for 90 minutes. Solids were filtered off with ether through celite in a sintered glass funnel. Next, the ether and acetone were removed by distillation off using a vigreaux column. Purification was performed by Kugelrohr distillation, in which the product boiled at about 110°C, and was collected in an ice-cooled flask, yielding a viscous, yellow liquid in 47% yield (3.24g, 0.0167mol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.30 (t, 2H, J = 6.7 Hz), 2.33 (m, 2H), 1.99 (m, 3H).



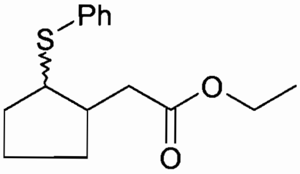
53

Diethyl 3,5-dicarboxylate N-(1'-pent-4'-ynyl) pyridinium iodide. Diethyl 3,5-pyridinedicarboxylate (0.141g, 6.32x10^{-4} mol) was added to a 5-mL round bottom flask. This was followed by 1-iodo-4-pentyne (0.490g, 0.00253mol) via pipette and DMF (0.211mL) via syringe. A glass stopper was attached and then parafilmed as the content were heated to 40°C and stirred in an oil bath. After 24 hours, the color of the reaction began to change from yellow to light orange and the orange color intensified as the reaction progressed further. The temperature was increased to 50°C after two days and continued to stir at this temperature until complete after eight days. To drive the reaction to completion, four drops of the alkyne were added to the flask on days six and seven. Progression was checked by both GC and ^{1}H-NMR. After completion the solvent was stripped off, first by rotovap, then by vacuum pump. The contents were triturated with ether three times, each time vacuuming off the ether to leave an orange, gummy solid in 46.3% yield (0.122g, 2.92x10^{-4}mol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.96 (app. s, 2H), 9.36 (s, 1H), 5.33 (t, 2H, J = 6.5 Hz), 4.57 (quart, 4H, J = 7.1 Hz), 2.49 (m, 4H), 2.11 (s, 1H), 1.49 (m, 6H).



72

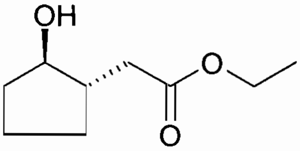
Ethyl *trans*-7-phenylsulfinyl-2-heptenoate. Ethyl *trans*-7-phenylthio-2-heptenoate (0.205g, 7.77×10^{-4}mol) was dissolved in methanol. This solution was cooled to 0°C and to it was added a 4 mL aqueous solution of sodium periodate (0.175g, 8.16×10^{-4}mol). The contents stirred overnight for about 16 hours. Progress of the reaction was monitored by TLC, which showed only trace amounts of starting material. The mixture was worked up by filtering off the solids and washing them with methylene chloride. The filtrate was partitioned with water and extracted with 3x15mL washings of methylene chloride. The organic layers were washed with a 15mL fraction of water and rotovapped down. The crude product was purified on a six inch 24/40 column with 300mL of 20% EtOAc/hexane followed by 300mL of 50% EtOAc/hexane to give a yellow, viscous oil in 91% yield (0.198g, 7.08×10^{-4}mol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (m, 2H), 7.53 (m, 3H), 6.89 (dt, 1H, J = 7.0, 15.6 Hz), 5.80 (d, 1H, J = 15.6 Hz), 4.18 (quart., 2H, J = 7.1 Hz), 2.79 (m, 2H), 2.22 (m, 2H), 1.78 (m, 1H), 1.61 (m, 3H), 1.29 (t, 3H, J = 7.1 Hz).



74

2-Phenylthiocyclopentaneacetic acid ethyl ester. T*rans*-7-phenylsulfinyl-2-heptenoate (0.105g, 3.75x10^{-4}mol) was transferred to a 5mL pear bottom flask, vacuum pumped, filled with argon and sealed. Trifluororacetic anhydride (0.375mL, 1.0M) was added via syringed followed by distilled lutidine (0.087mL, 7.5x10^{-4}mol) one minute later. The flask was parafilmed and the contents stirred at room temperature for 45 minutes. The contents were then placed on the vacuum pump to remove volatiles. Meanwhile NiI_2 (0.013g, 3.75x10^{-5}mol) was transferred to a dry Schlenk flask and pumped on for 45 minutes. The flask was then filled with argon and SmI_2 was added via syringe (15.0mL, 1.50x10^{-3}mol). The Pummerer product, ethyl *trans*-7-phenylthio-7-trifluoroacetoxy-2-heptenoate, **73**, was dissolved in minimal quantities of distilled THF and quantitatively transferred to the Schlenk flask. After thirty seconds, t-butyl alcohol was added via syringe (0.072mL, 7.50x10^{-4}mol). After 25 minutes of stirring the solution turned a green-brown color, at which point the flask was taken out of the ice bath and allowed to warm to room temperature for ten minutes. The reaction was quenched with water and extracted with 1:1 ether/hexane mix (4x20mL). The organic layers were filtered through celite and volatiles were removed by rotary evaporation. A TLC in pure hexane showed one relatively non-polar product, and a large spotting of more polar material that did not move from the baseline. The crude product was separated in 15mL fractions on a long, 14/20 column by the following methods: 150mL pure hexane→

100mL 1% EtOAc/hexane → 100mL 3% EtOAc/hexane → 100mL 15% EtOAc/hexane. The column was overloaded with polar solvent during the transfer of crude material to the column. Fractions one and two were collected and stripped down to leave behind a yellow liquid in 24% yield (0.025g, 9.46x10^{-5}mol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (m, 5H), 4.01(m, 2H), 3.70 (m, 1H), 2.58 (m, 2H), 2.28 (m, 1H), 1.98 (m, 2H), 1.75 (m, 2H), 1.55 (m, 2H), 1.15 (m, 3H). ^{13}C NMR (300MHz, $CDCl_3$) δ 172.1, 135.5, 130.2, 127.8, 125.5, 59.3, 50.8, 39.3, 34.8, 31.6, 29.0, 20.8, 13.2.



75

***Trans*-2-hydroxy-cyclopentaneacetic acid ethyl ester.** T*rans*-7-phenylsulfinyl-2-heptenoate (0.100g, 3.57x10^{-4}mol) was transferred to a 5mL pear bottom flask and reacted under the same conditions and proportions of reagents as above. The only difference was that ethyl *trans*-7-phenylthio-7-trifluoroacetoxy-2-heptenoate, **73**, was dissolved and added to the SmI_2 solution at -9°C. The blue color of this solution dissipated after one hour of stirring, and was allowed to warm to room temperature, at which point the mixture was worked up and separated by the methods outlined above. A yellow liquid was obtained fractions 31-37 in 38% yield (0.023g, 1.34x10^{-4}mol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (m, 2H), 3.87(m, 1H), 2.82 (m, 1H), 2.45 (m, 2H), 1.97 (m, 2H), 1.71 (m, 2H), 1.62 (m, 3H), 1.27 (m, 3H). ^{13}C NMR (300MHz, $CDCl^3$) δ 174.3, 79.0, 61.2, 44.4, 38.5, 34.3, 30.8, 23.4, 14.2.

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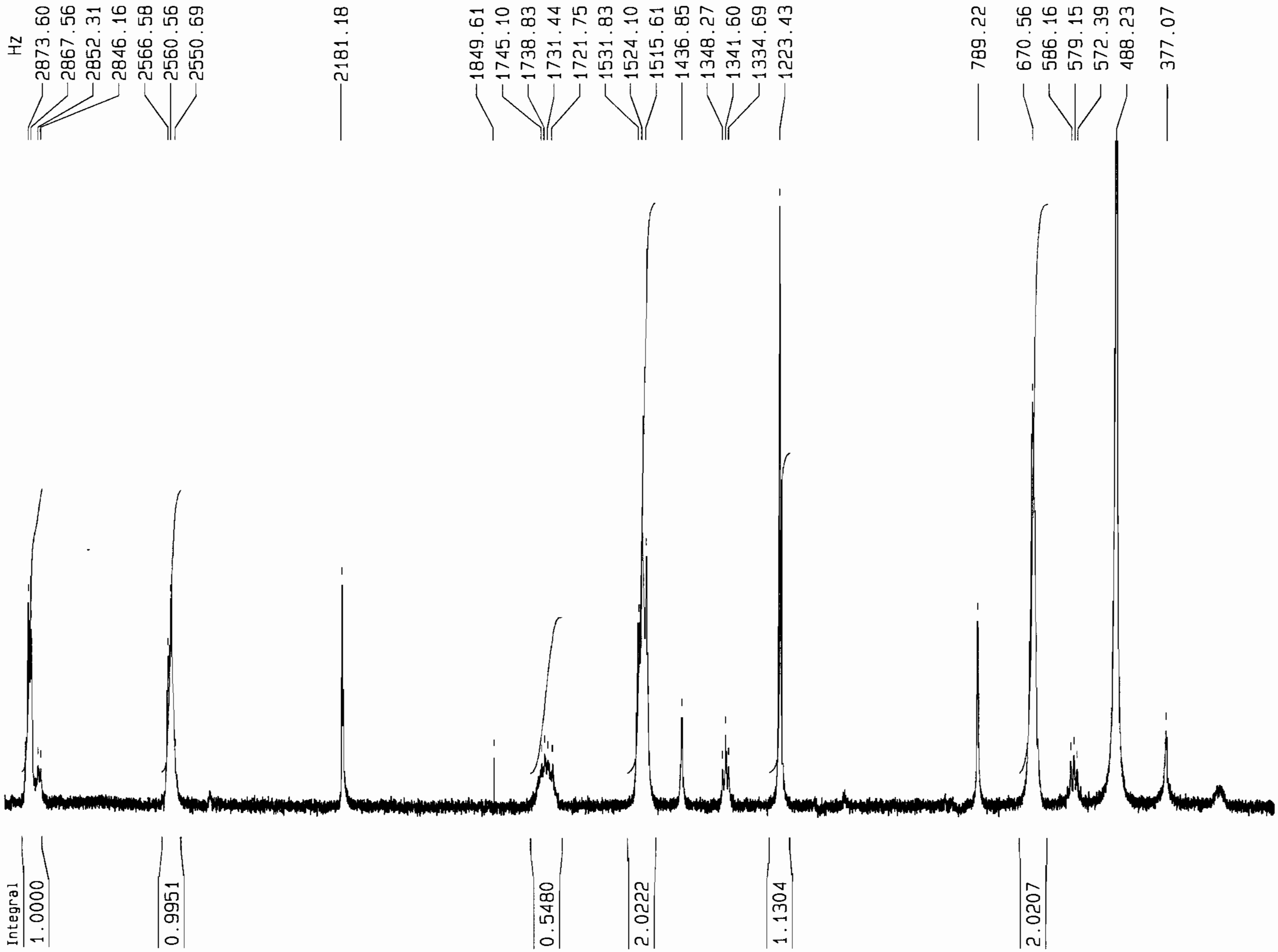
Compound 35



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PROCNO                   1

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DS                       2
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FIDRES          0.094190 Hz
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RG                   912.3
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
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WDW                     no
SSB                      0
LB                    0.00 Hz
GB                       0
PC                    1.00

1D NMR plot parameters
CX                   20.00 cm
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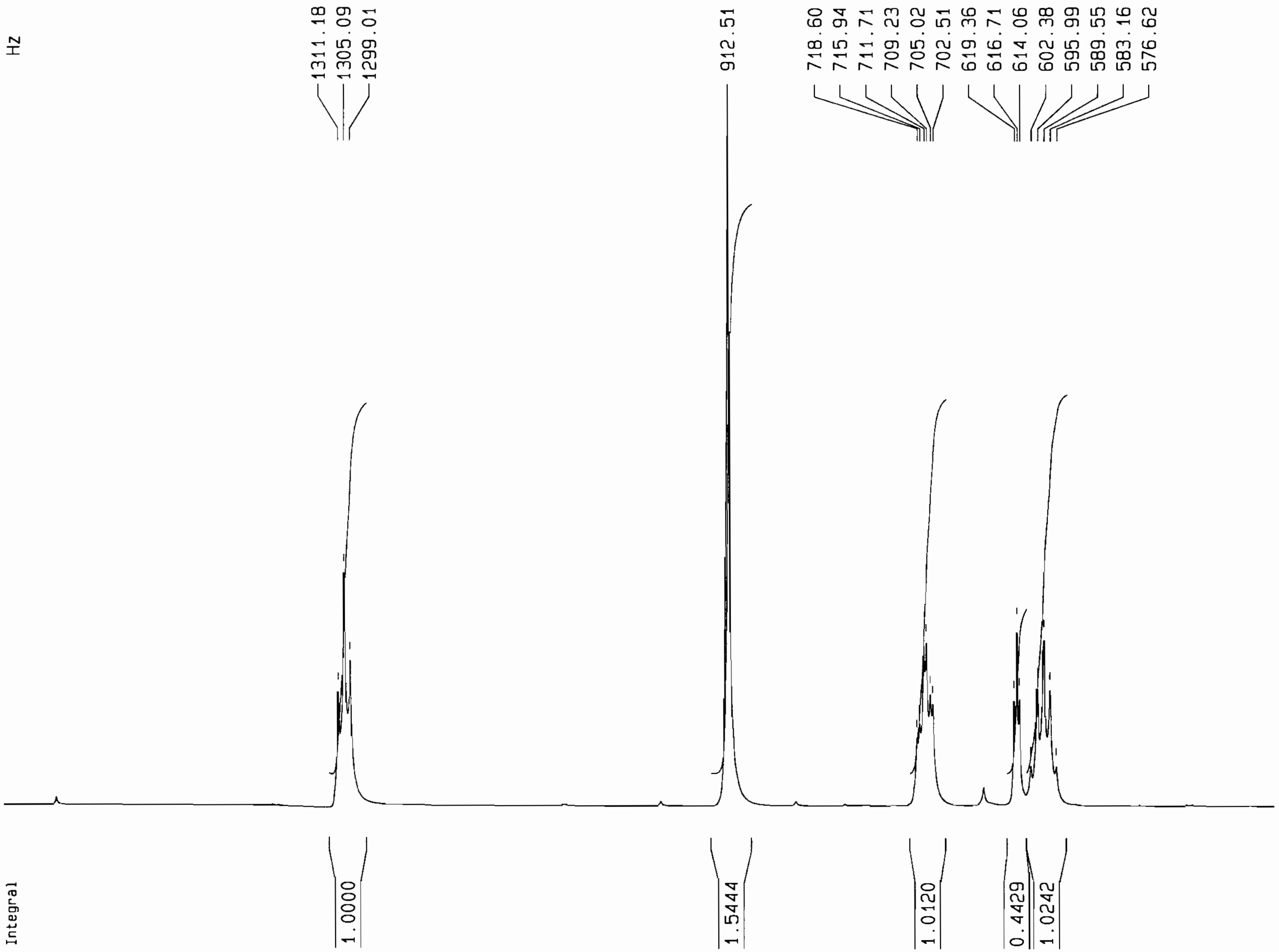
Compound 42



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TD                 32768
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NS                    32
DS                     2
SWH             8389.262 Hz
FIDRES          0.256020 Hz
AQ             1.9530228 sec
RG                  40.3
DW                59.600 usec
DE                  6.00 usec
TE                 300.0 K
D1            1.00000000 sec

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PL1                 0.00 dB
SFO1         300.1325021 MHz

F2 - Processing parameters
SI                 16384
SF           300.1299829 MHz
WDW                   no
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX                 20.00 cm
F1P                5.513 ppm
F1               1654.64 Hz
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F2                352.49 Hz
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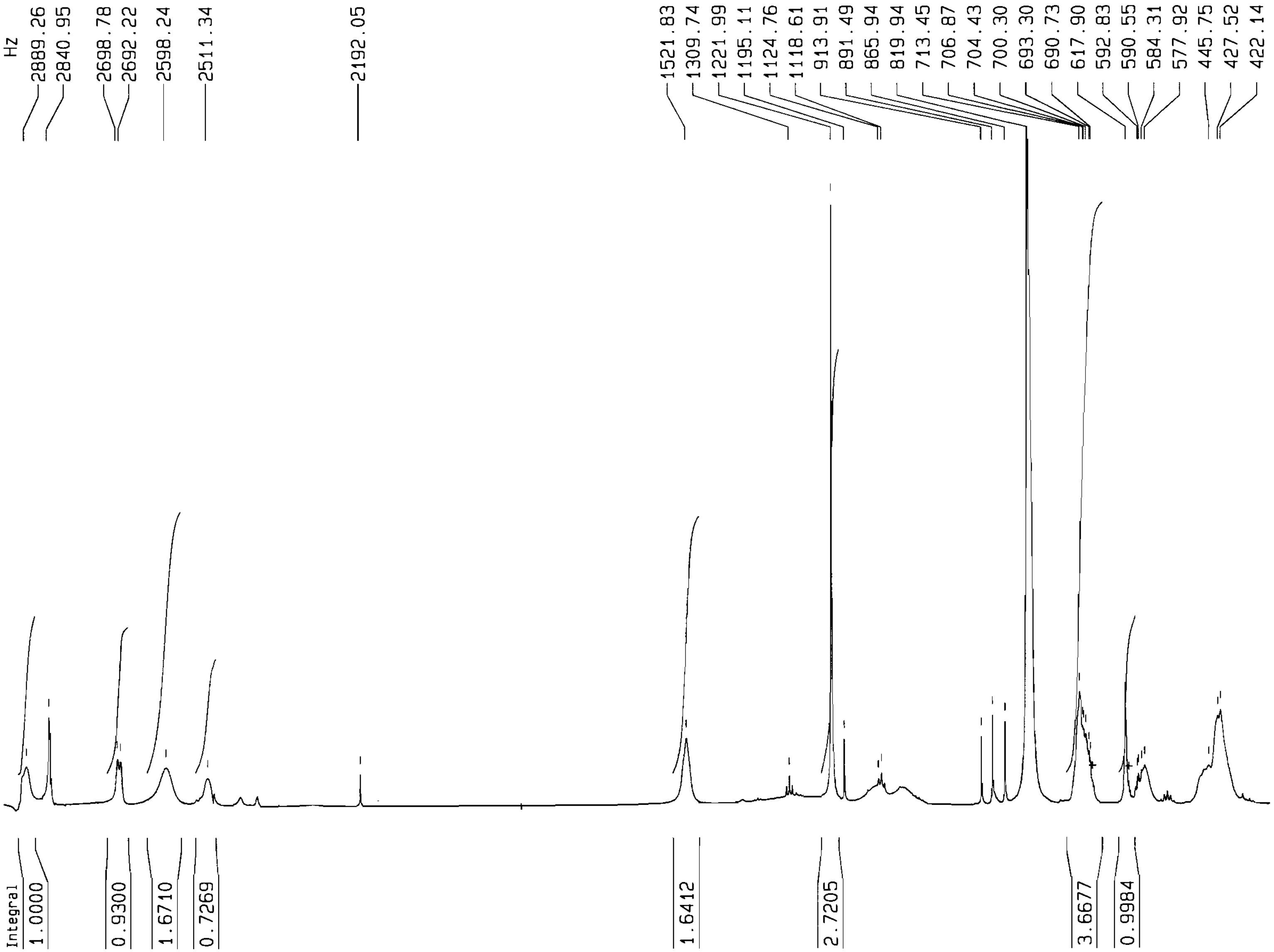
Compound 46



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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                   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
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WDW                   no
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX                 20.00 cm
F1P                9.784 ppm
F1               2936.46 Hz
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F2                321.25 Hz
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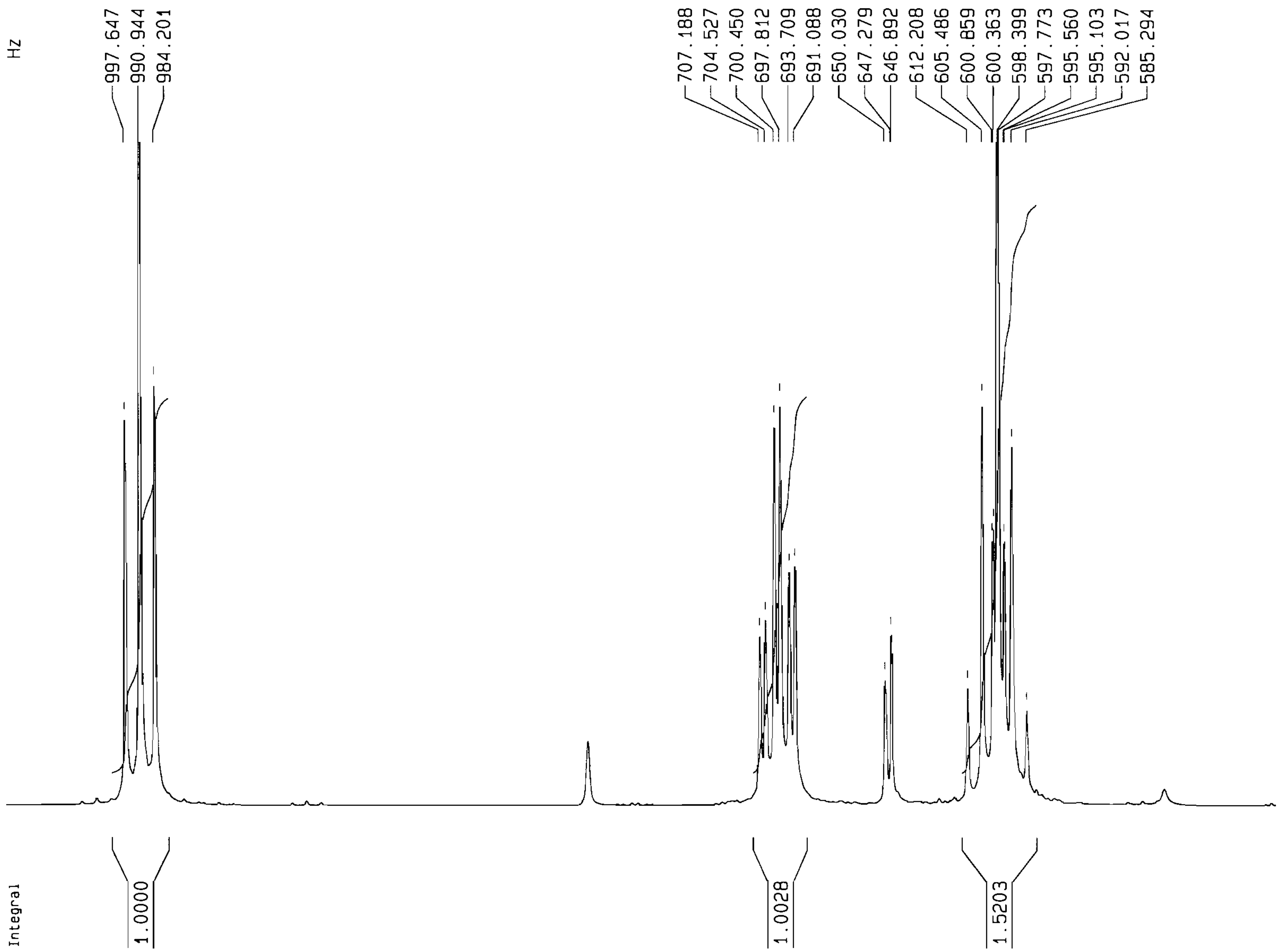
Compound 50



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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                     57
DW               81.000 usec
DE                 6.00 usec
TE                300.0 K
D1           1.00000000 sec

============ CHANNEL f1 ========
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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                 3.506 ppm
F1                1052.37 Hz
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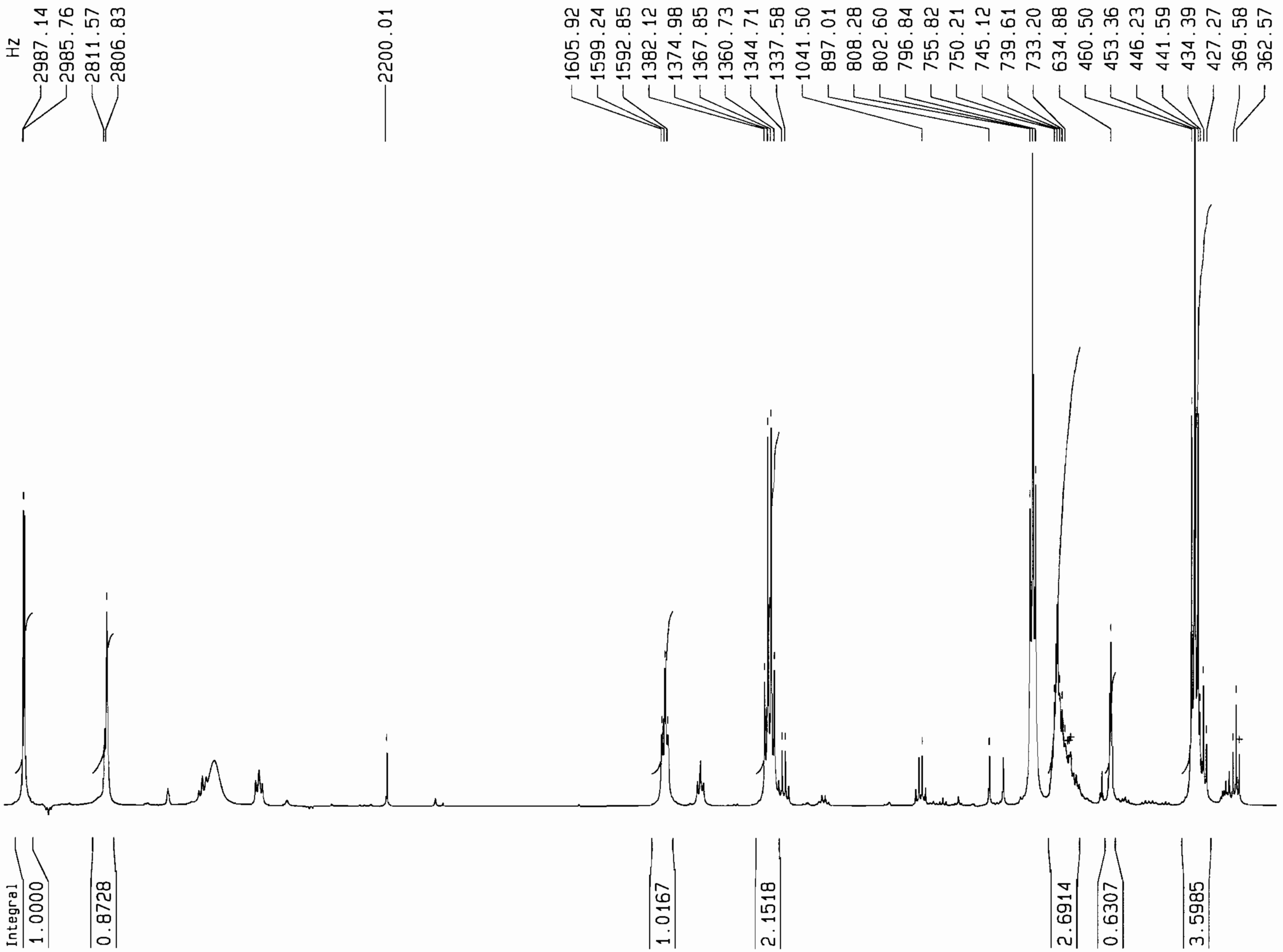
Compound S3



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PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       32
DS                        2
SWH                6172.839 Hz
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 ========
NUC1                     1H
P1                    11.00 usec
PL1                    0.00 dB
SFO1            300.1318534 MHz

F2 - Processing parameters
SI                    32768
SF              300.1299852 MHz
WDW                      no
SSB                       0
LB                     0.00 Hz
GB                        0
PC                     1.00

1D NMR plot parameters
CX                    20.00 cm
F1P                  10.097 ppm
F1                  3030.54 Hz
F2P                   0.913 ppm
F2                   273.97 Hz
PPMCM               0.45923 ppm/cm
HZCM              137.82867 Hz/cm
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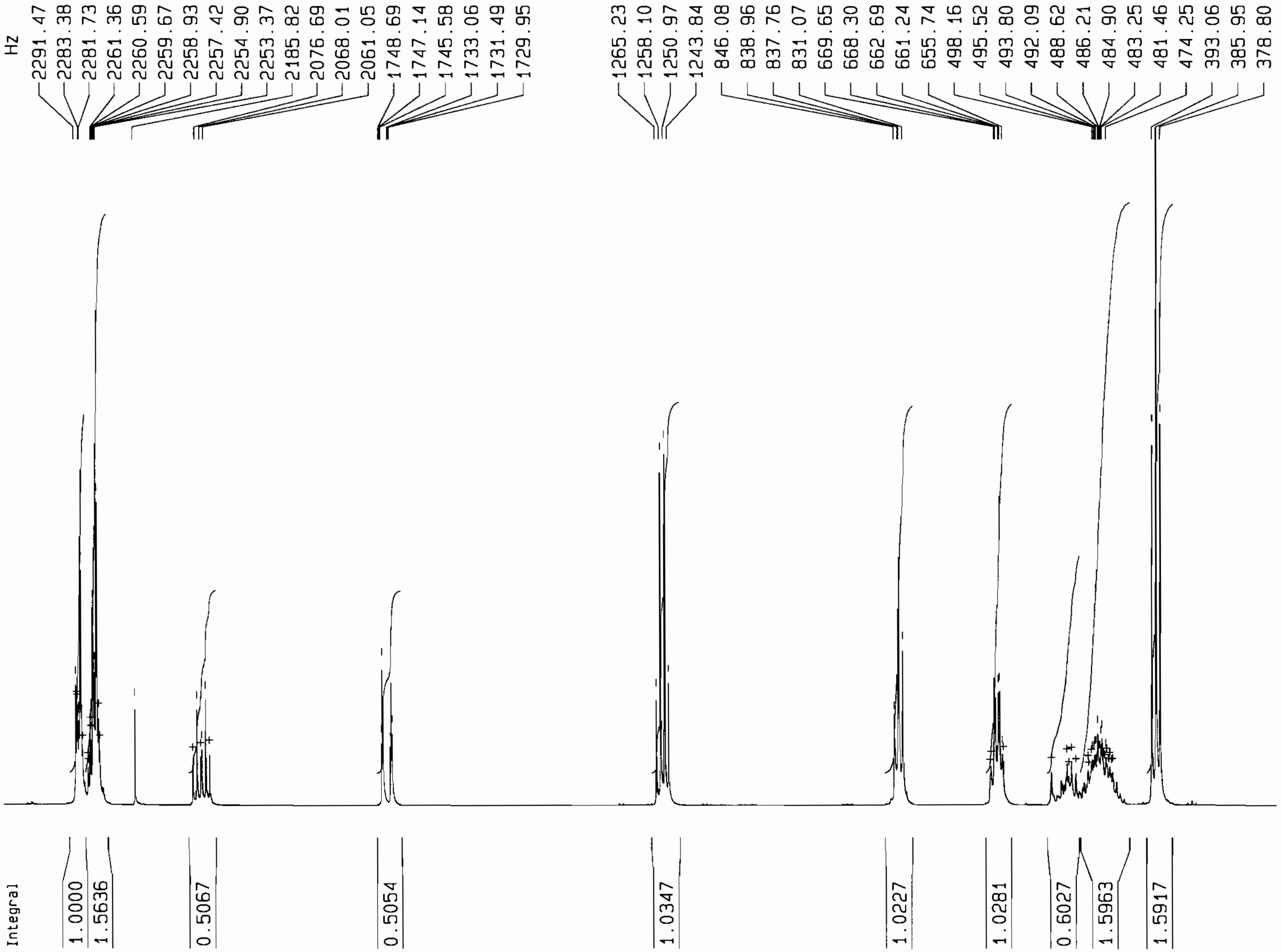
Compound 72



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RG                       128
DW                    81.000 usec
DE                      6.00 usec
TE                     300.0 K
D1                2.00000000 sec

============ CHANNEL f1 ========
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P1                     11.00 usec
PL1                     0.00 dB
SFO1             300.1318534 MHz

F2 - Processing parameters
SI                     32768
SF               300.1299992 MHz
WDW                       no
SSB                        0
LB                      0.00 Hz
GB                         0
PC                      1.00

1D NMR plot parameters
CX                     20.00 cm
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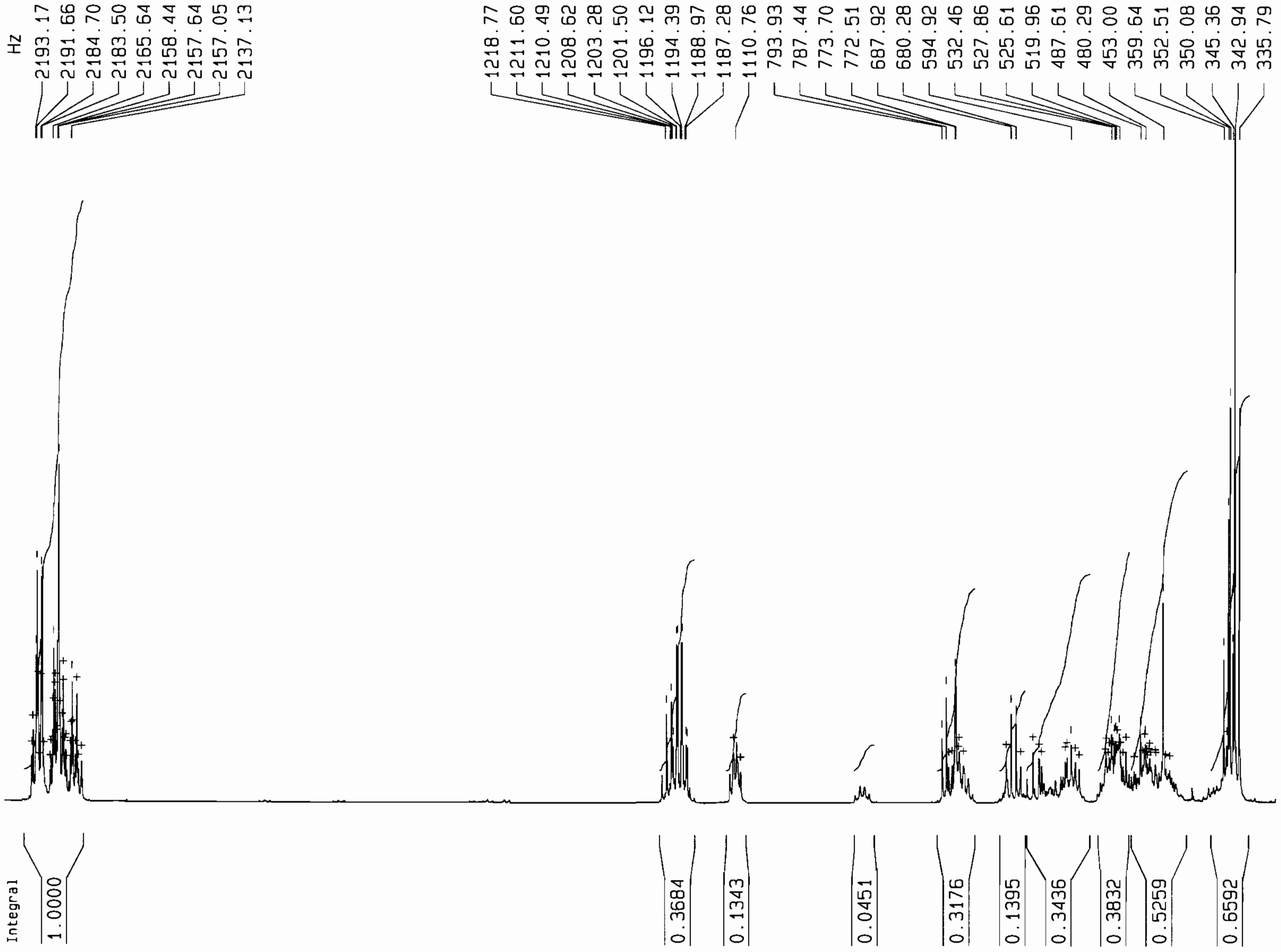
Compound 74



Current Data Parameters

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FIDRES	0.094190 Hz
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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	300.1300273 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
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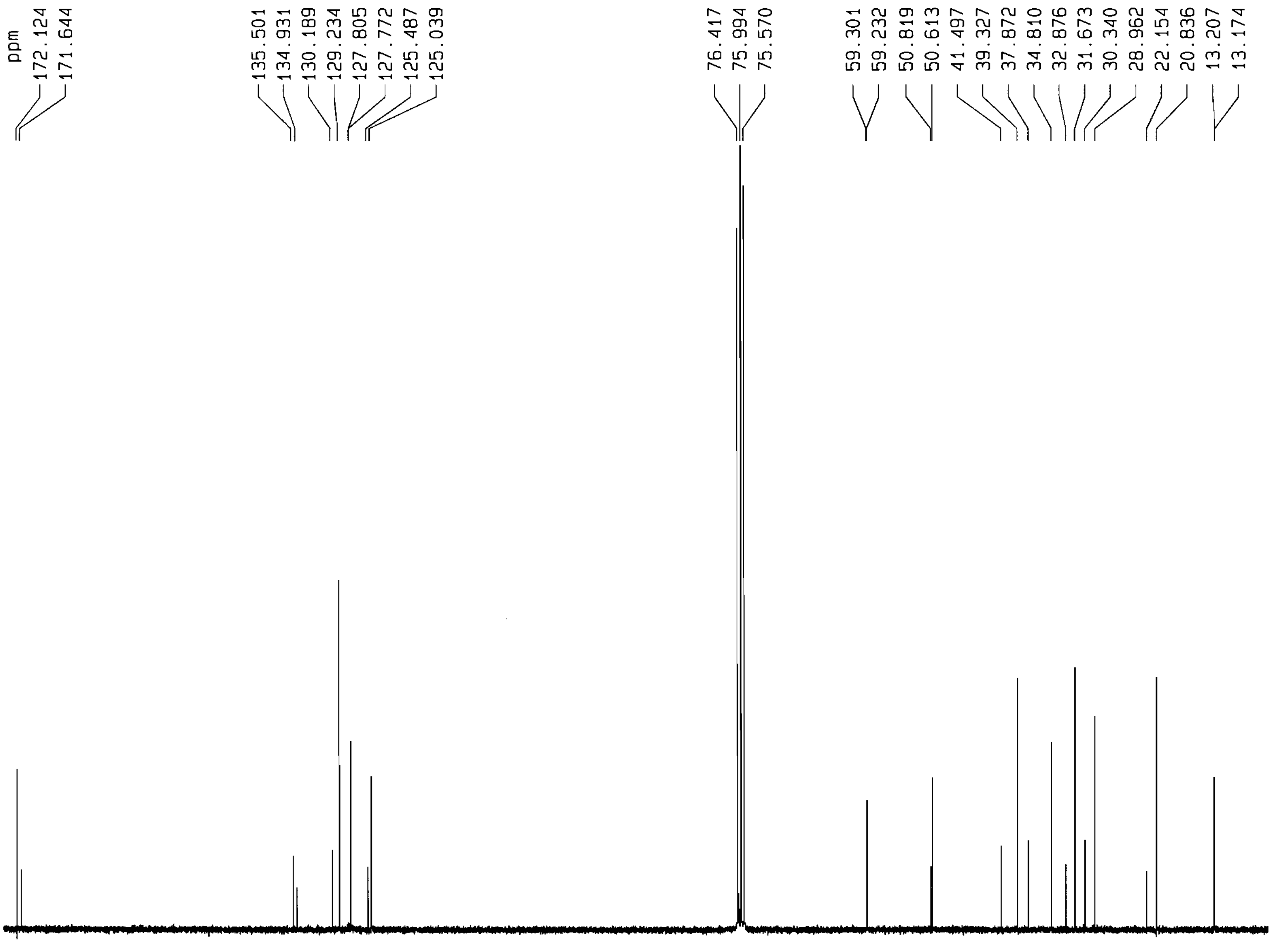
HZCM	98.16856 Hz/cm

Compound 74



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D1           2.00000000 sec
d11          0.03000000 sec
d12          0.00002000 sec

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PL1               -1.50 dB
SFO1         75.4760200 MHz

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PL12              18.00 dB
PL13              18.00 dB
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F2 - Processing parameters
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SF           75.4678257 MHz
WDW                  no
SSB                   0
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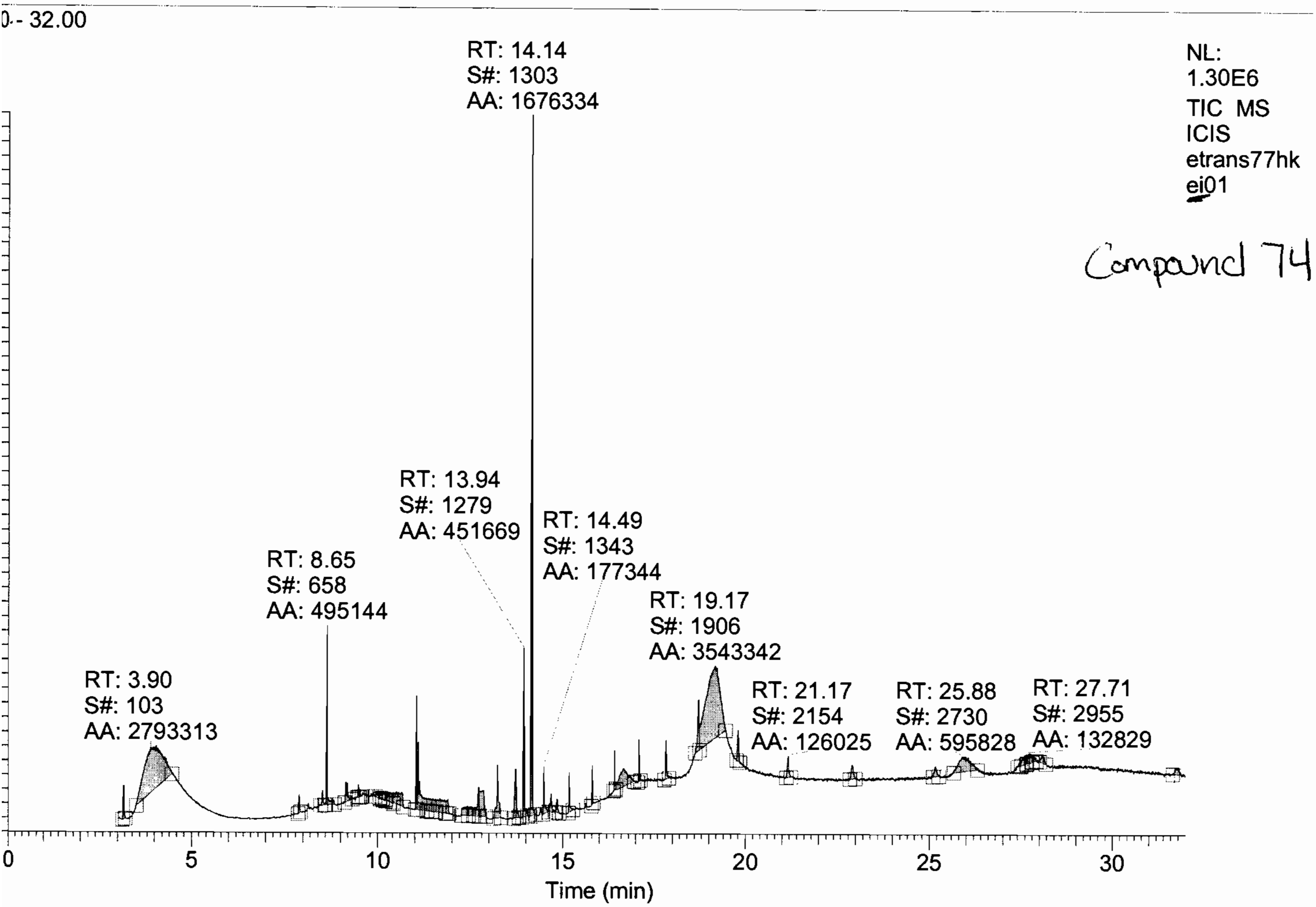
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RT: 8.65
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AA: 495144
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S#: 1906
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RT: 3.90
S#: 103
AA: 2793313
RT: 21.17
S#: 2154
AA: 126025
RT: 25.88
S#: 2730
AA: 595828
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S#: 2955
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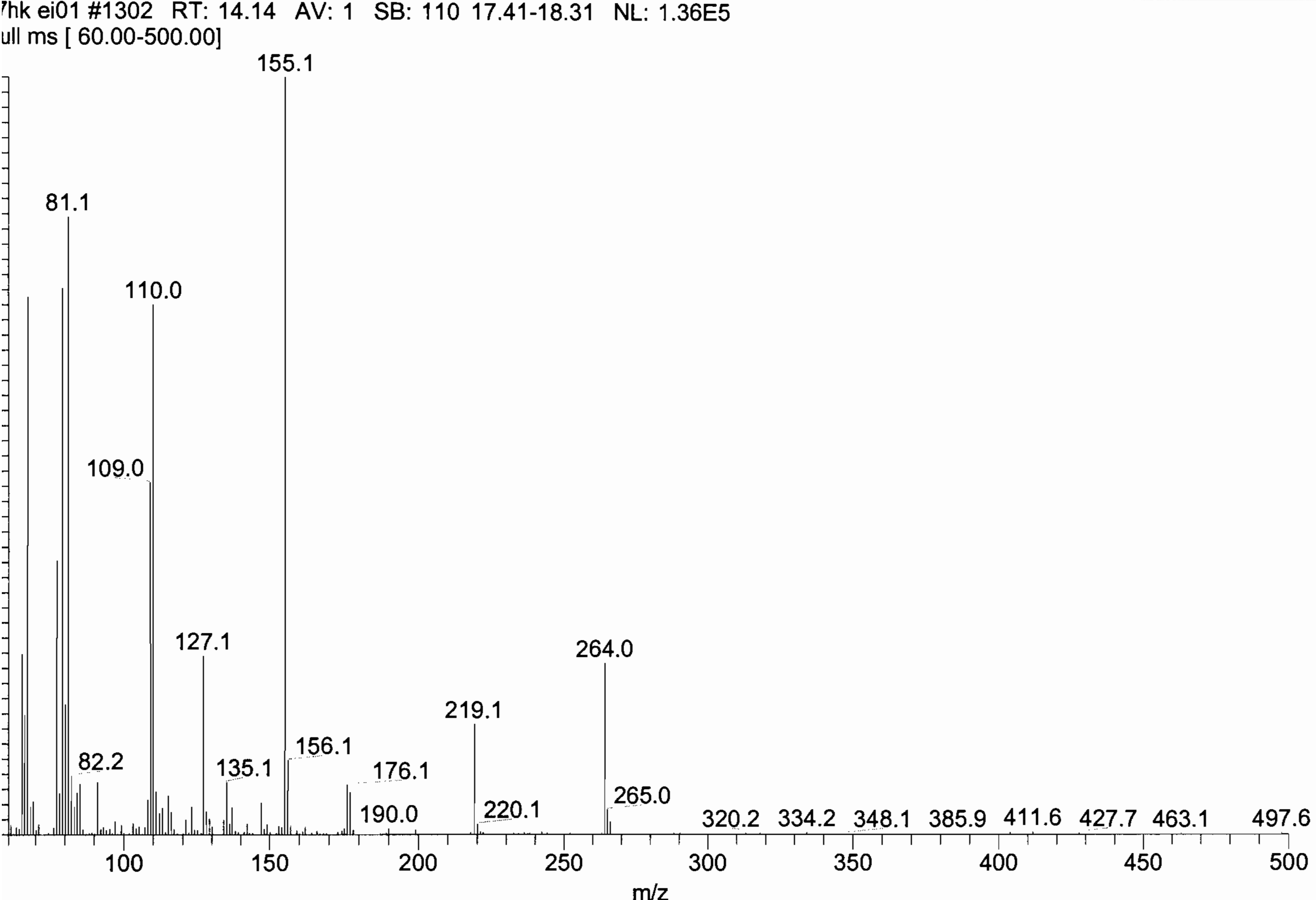
0
5
10
15
20
25
30
Time (min)

Compound 74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127.1
264.0
219.1
82.2
135.1
156.1
176.1
190.0
220.1
265.0
320.2
334.2
348.1
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463.1
497.6
100
150
200
250
300
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400
450
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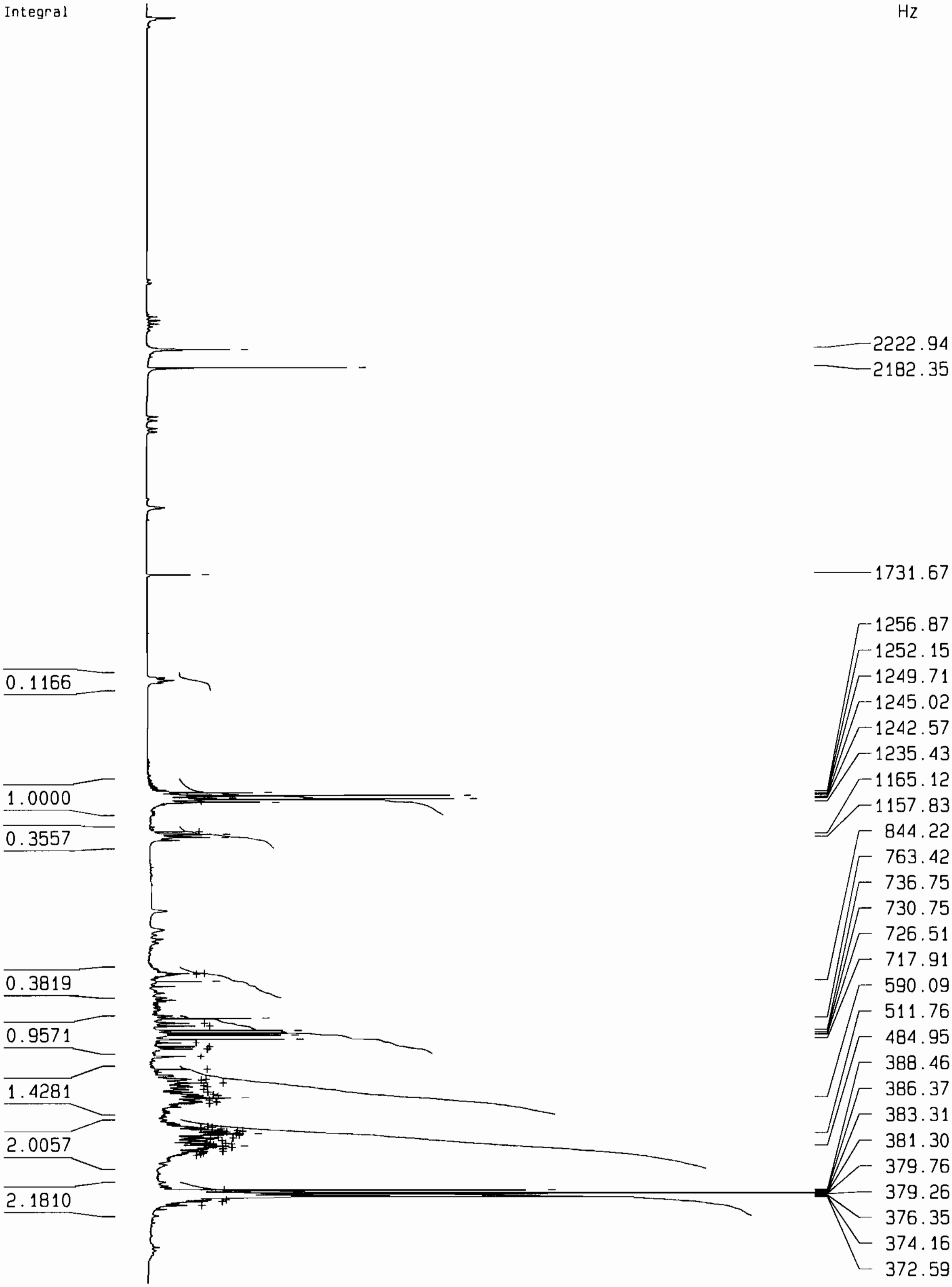

Compound 75

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PROCNO                    1

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NS                       32
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FIDRES             0.094190 Hz
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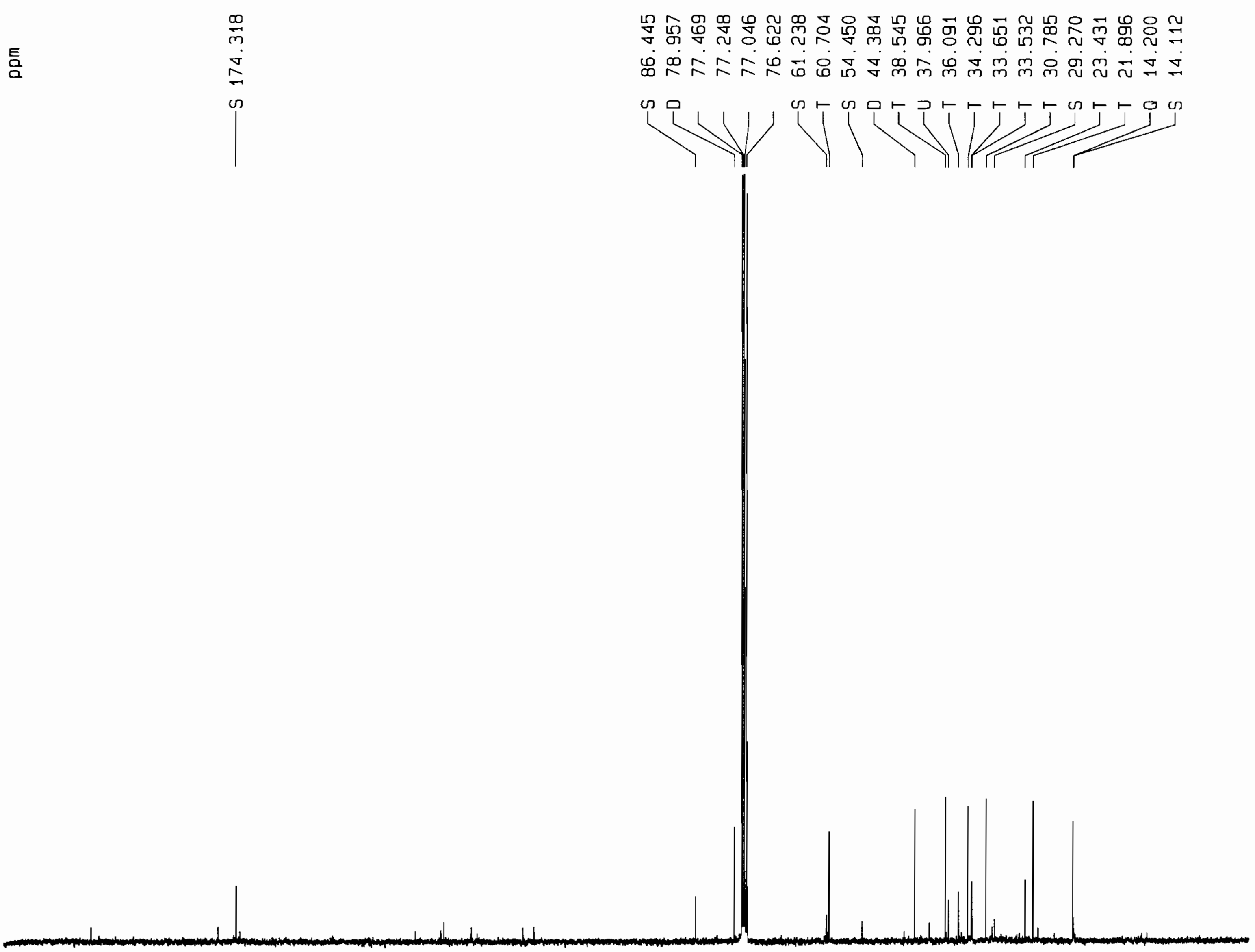
DE                     6.00 usec
TE                    300.0 K
D1               2.00000000 sec

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

F2 - Processing parameters
SI                    32768
SF              300.1300024 MHz
WDW                      no
SSB                       0
LB                     0.00 Hz
GB                        0
PC                     1.00

1D NMR plot parameters
CX                    20.00 cm
F1P                   9.935 ppm
F1                  2981.86 Hz
F2P                   0.620 ppm
F2                   186.02 Hz
PPMCM               0.46577 ppm/cm
HZCM              139.79205 Hz/cm
```

Compound 75



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Current Data Parameters
NAME        jjm-43-gp5dept
EXPNO                   10
PROCNO                   1

F2 - Acquisition Parameters
Date_             20040403
Time                  3.15
INSTRUM              spect
PROBHD        5 mm BBO BB-
PULPROG            zgpg30
TD                   65536
SOLVENT              CDCl3
NS                    3000
DS                       2
SWH             17985.611 Hz
FIDRES           0.274439 Hz
AQ              1.8219508 sec
RG                   16384
DW                  27.800 usec
DE                    6.00 usec
TE                   300.0 K
D1              2.00000000 sec
d11             0.03000000 sec
d12             0.00002000 sec

============ CHANNEL f1 ============
NUC1                   13C
P1                    7.10 usec
PL1                  -1.50 dB
SFO1           75.4752653 MHz

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

F2 - Processing parameters
SI                   32768
SF             75.4677475 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40

1D NMR plot parameters
CX                   20.00 cm
F1P                218.777 ppm
F1                16510.64 Hz
F2P                -19.544 ppm
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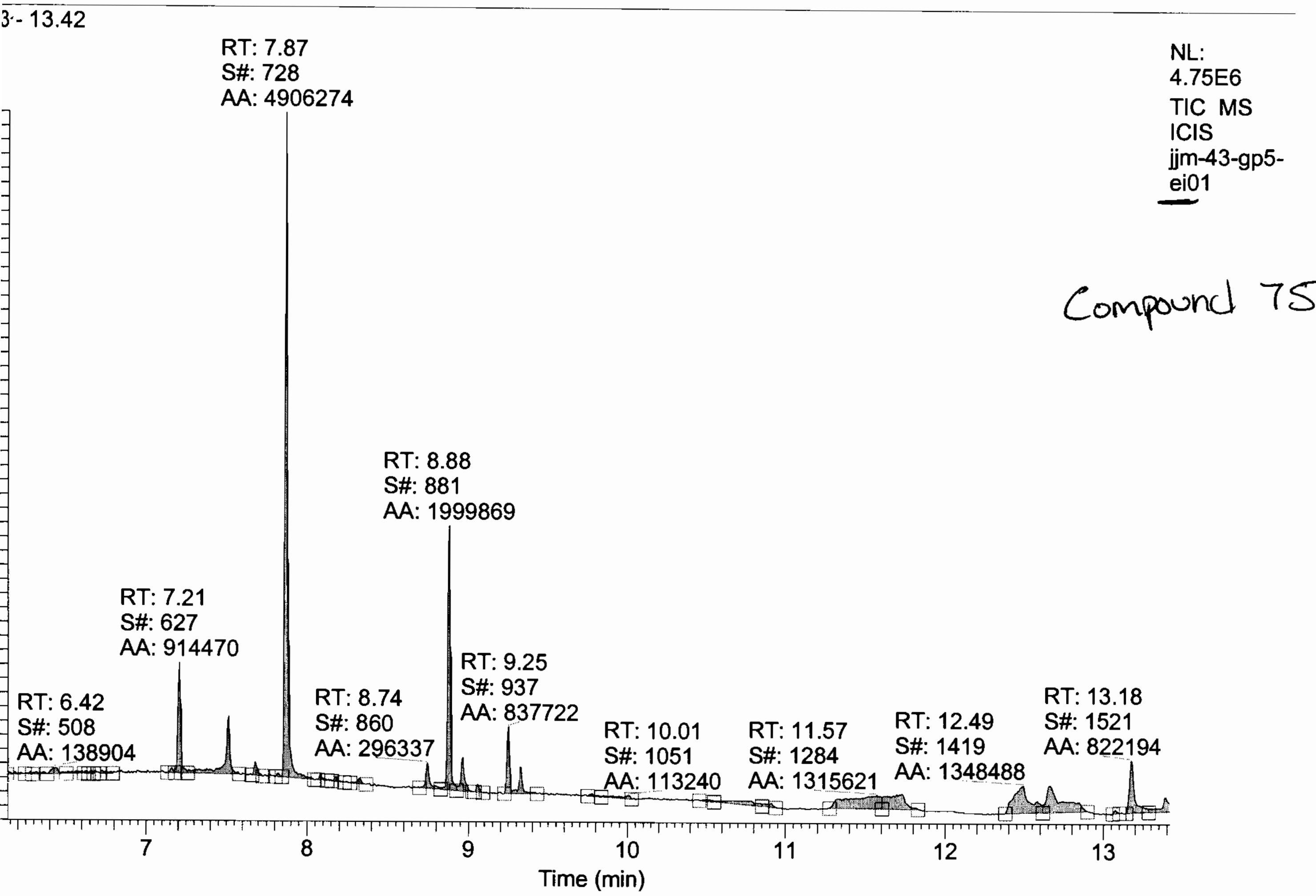
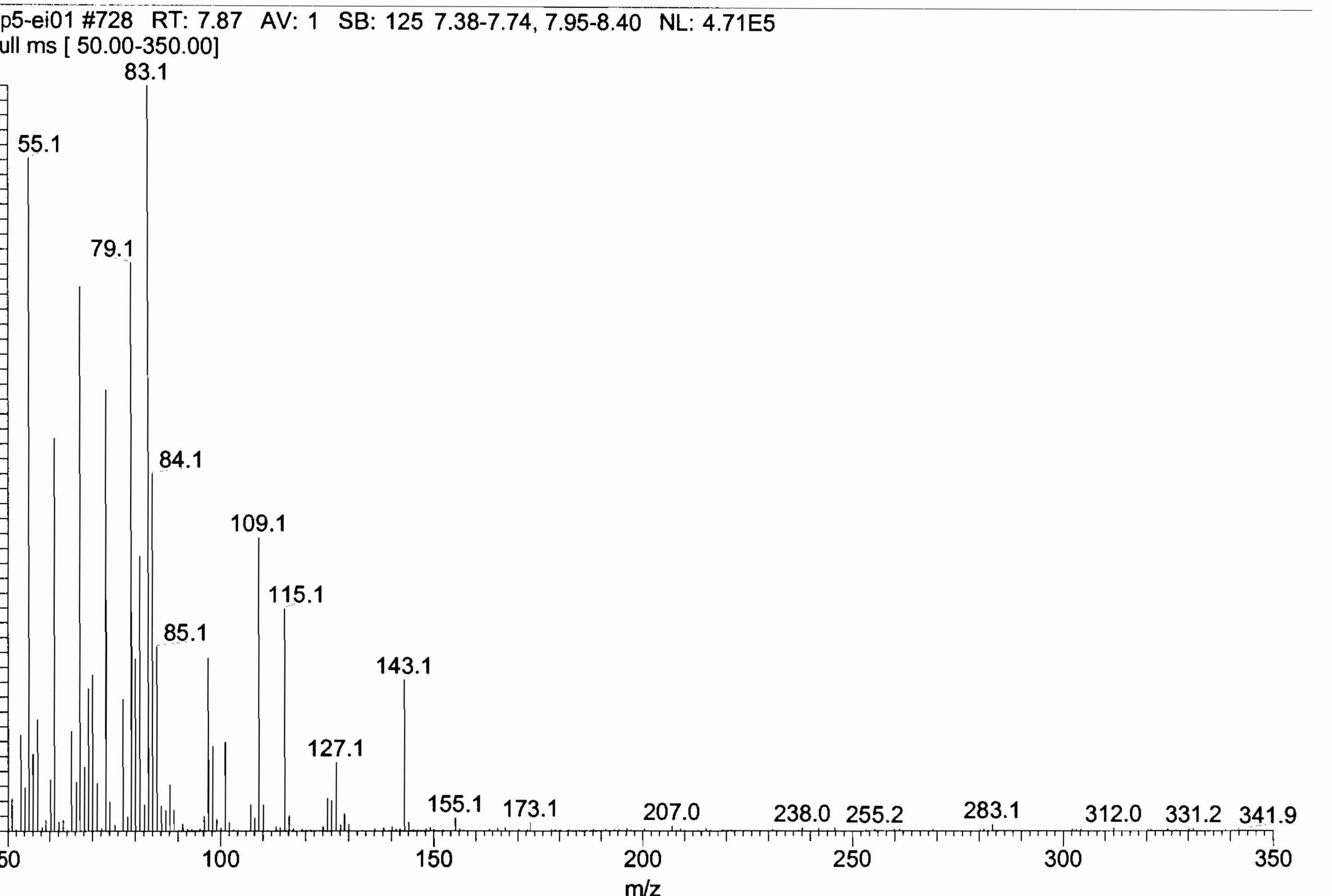
ır\data\cemrsch\jjm-43-gp5-ei01 04/05/2004 01:48:15 PM

Compound 75





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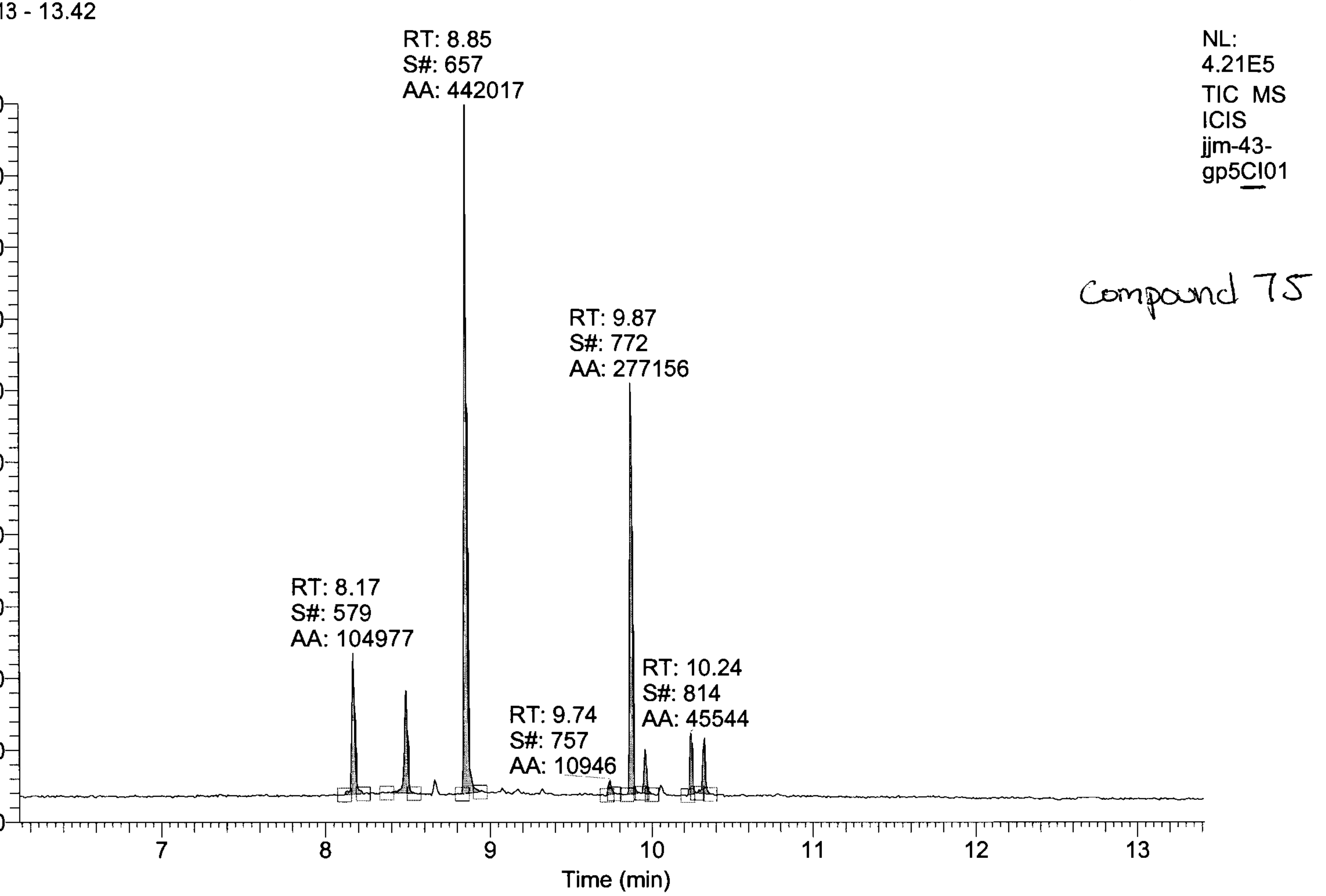

Compound 75

gp5CI01 #657 RT: 8.85 AV: 1 SB: 110 17.96-18.91 NL: 1.41E5
Full ms [70.00-450.00]