Abstract

Homer, Holly K.: Study of *N*-Acylpyridinium Salt Chemistry and Its Application in the Asymmtric Synthesis of Streptomyces SS20846A. (Under the direction of Dr. Daniel L. Comins)

The first part of this research was directed towards a study of the mechanism of *N*-acylpyridinium salt chemistry. Comparison of de's obtained from organometallic additions to the pyridinium salt versus analogous non-organometallic additions would show whether chelation of the metals plays a key role in the mechanism. The second focus of this research was on the use of chiral *N*-acylpyridinium salt chemistry in the asymmetric synthesis of Streptomyces SS20846A, a natural product isolated from a soil sample in Greece which has a restrictive action on the digestive system.

The Study of *N*-Acylpyridinium Salt Chemistry and Its Application in the Asymmetric Synthesis of Streptomyces SS20846A

By

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Approved by:

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Biography

The author, Holly K. Homer, was born in St. Mary, Ohio, on September 15, 1974 to Rev. Edwin and Margaret Homer. She grew up in Sheboygan, Wisconsin where she attended Sheboygan North High School and graduated in 1993. She studied chemistry at Evangel College in Springfield, Missouri, and graduated in 1996 with a Bachelor of Science degree. Holly attended North Carolina State University and completed her Master of Science degree in Synthetic Organic Chemistry in the spring of 2000 under the direction of Dr. Daniel L. Comins.

Table of Contents

List of Figures

List of Schemes

List of Tables

List of Symbols, Abbreviations and Terms

Abbreviation or Term	Explanation
$A^{(1,3)}$	1,3-allylic
$[\alpha]_D$	optical rotation
AcOH	acetic acid
anal.	analysis
aq	aqueous
BOC	*tert*-butoxycarbonyl
bp	boiling point
br	brine
brine	saturated aqueous sodium chloride
Bu	butyl
^oC	degree Celcius
^{13}C NMR	carbon-13 nuclear magnetic resonance spectroscopy
calcd.	calculated
CAN	ceric ammonium nitrate
CCl_4	carbon tetrachloride
$CDCl_3$	deuterated chloroform
CH_2Cl_2	methylene chloride
cm^{-1}	reciprocal centimeters
d	doublet
d	day

dd	doublet of doublets
de	diastereomeric excess
DMAP	dimethylaminopyridine
DMSO	dimethylsulfoxide
DIBAL	diisobutylaluminum hydride
ee	enantiomeric excess
equiv.	equivalent
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
g	gram
GC	gas chromatography
h	hour
H^+	proton
H_3O^+	aqueous acid
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	Hertz
i-Pr	isopropyl
IR	infrared spectroscopy
J	coupling constant
kcal	kilocalorie

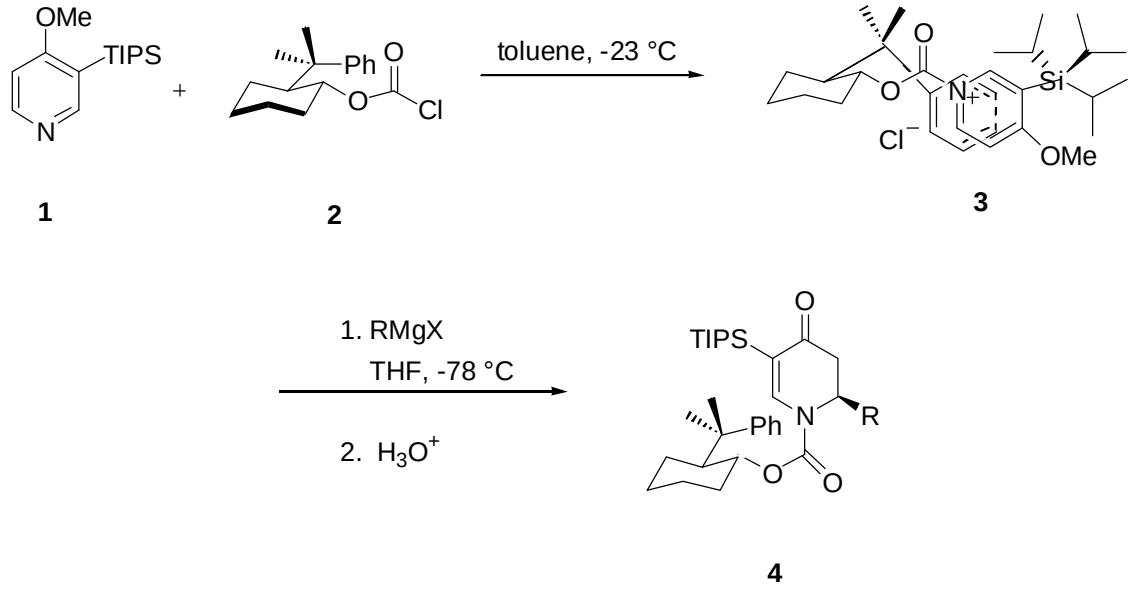
L-Selectride	lithium tri-*sec*-butylborohydride
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
lit.	literature
M	molar
m	multiplet
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram
min	minute
mL	milliliter
mmol	millimole
mol	mole
mp	melting point
NaHMDS	sodium hexamethyldisilazide
NIH	National Institutes of Health
Ph	phenyl
PMP	*p*-methoxyphenyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
q	quartet
R	alkyl group

Radial PLC	radial preparative-layer chromatography
RMgX	alkyl magnesium bromide
	alkyl Grignard
rt	room temperature
s	singlet
t	triplet
TAS	tris(diethylamino)sulfonium
TAS-F	tris(diethylamino)sulfonium
	(trimethylsilyl)difluoride
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butylsilyl
t-Bu	*tert*-butyl
TCC	*trans*-2-(α-cumyl)cyclohexanol
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMANO	trimethylamine *N*-oxide
TMEDA	tetramethylethylenediamine
Ts	*p*-toluenesulfonyl
TMS	trimethylsilyl

Chapter 1: Introduction to Chiral *N*-Acylpyridinium Salt Chemistry

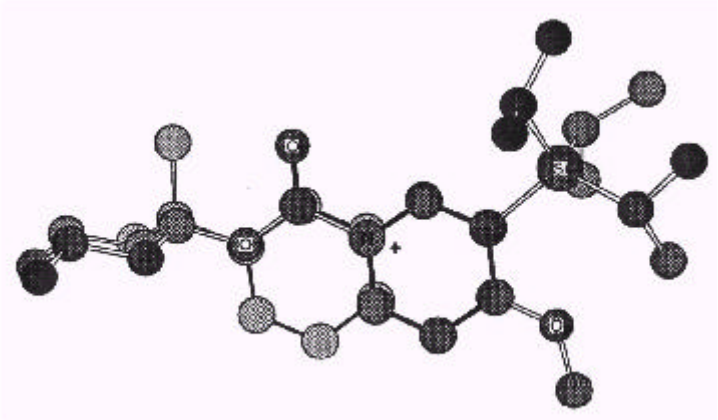
For the past several years, research in the Comins group has focused on the synthetic utility of enantiomerically pure *N*-acyldihydropyridones derived from chiral *N*-acylpyridinium salt chemistry.[1] In this chemistry, 4-methoxy-3-triisopropylsilyl-(TIPS)-pyridine **1** and the chloroformate of either enantiomer of a cyclohexyl-based chiral auxiliary such as *trans*-2-(α-cumyl)cyclohexanol[2] (TCC) **2** are stirred in toluene at –23 °C to form the intermediate *N*-acylpyridinium salt **3** shown in Scheme 1. Addition of an organometallic, such as a Grignard reagent, in THF at –78 °C, followed by acid hydrolysis gives dihydropyridones of the type **4** with yields ranging from 75-94% and de's from 85-95%.

Scheme 1: Chiral *N*-Acylpyridinium Salt Chemistry

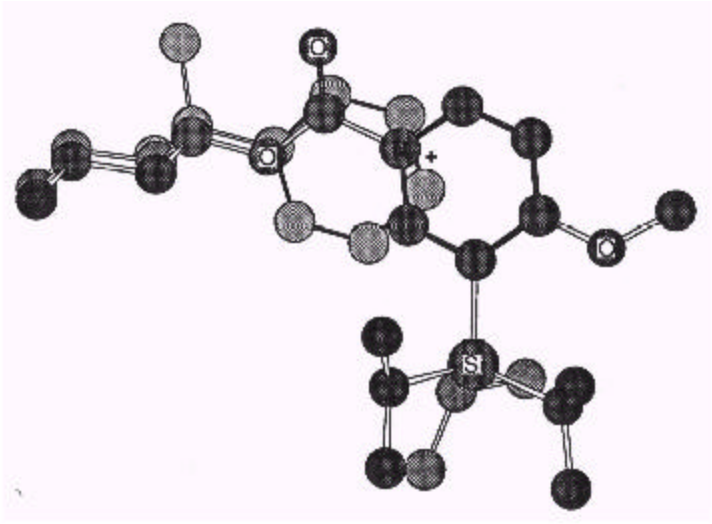


The diastereoselectivity of the reaction is affected by the use of the chiral auxiliary and the substituent at the C-3 position of the pyridine ring. As shown in Scheme 1, the aryl group of the chiral auxiliary effectively blocks one face of the nitrogen-containing ring. According to molecular mechanics calculations,[3] the two lowest energy conformations of the pyridinium salt are shown in Figure 1. Free rotation about the carbon-nitrogen bond allows the aryl group in rotamer B to come close to the TIPS group at the C-3 position. In rotamer A, this steric repulsion is eliminated, and the phenyl ring can participate in π–π interactions with the pyridine ring. Rotamer A is the more highly populated, and the energy difference between the two rotamers gives rise to the major and the minor diastereomers seen in the addition reaction.

Figure 1: MMX Pictures of Rotamers of *N*-Acylpyridinium Salt



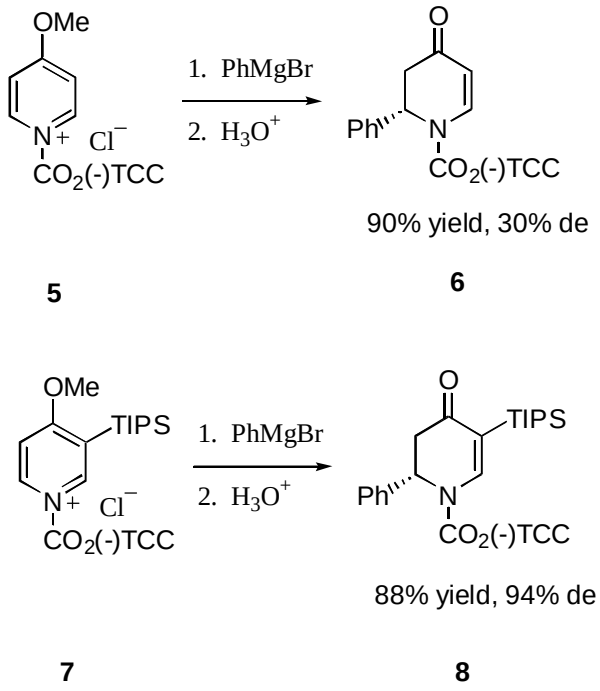
Rotamer A



Rotamer B

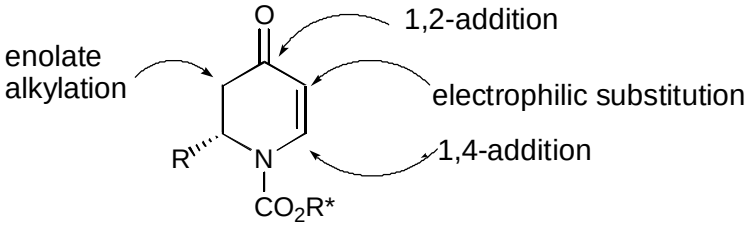
In addition to the stabilization of the above rotamers, the triisopropylsilyl group at the C-3 position of the pyridine ring plays a significant role in the addition reaction by blocking one of the positions α to the nitrogen. In the example shown in Scheme 2, addition of phenyl Grignard to the pyridinium salt formed between 4-methoxypyridine and the chloroformate of (-)TCC followed by acid hydrolysis gives a 90% yield of dihydropyridone **6** with a poor de of only 30%. The same reaction done with the TIPS group present at the C-3 position of the pyridine ring results in a comparable yield of dihydropyridone **8** with an excellent de of 94%.[4]

Scheme 2: Effect of the TIPS Group



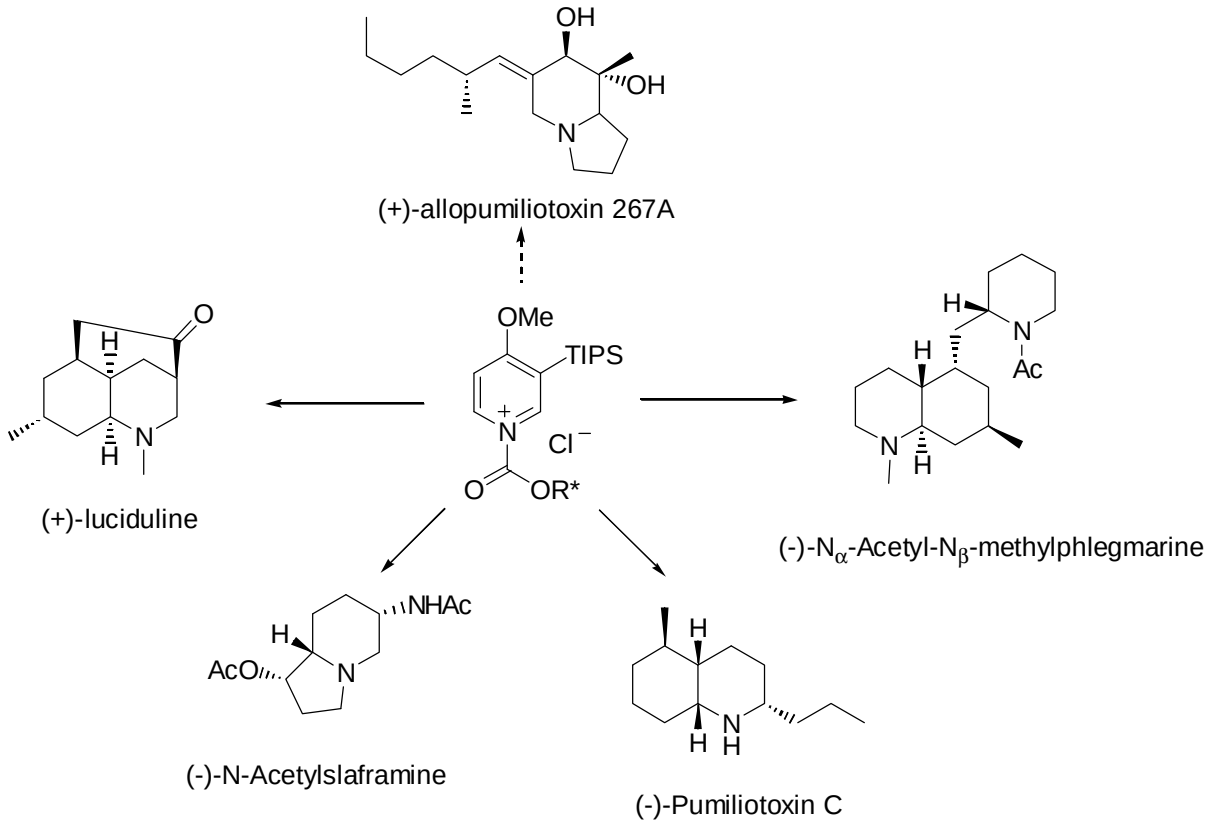
Dihydropyridones of the type shown in Figure 2 have been shown by the Comins group to be very useful intermediates in alkaloid natural product synthesis. With the presence of the carbamate, the C-2 substituent is forced into the axial position due to severe $A^{(1,3)}$ strain.[5] This conformational bias controls the stereochemistry of alkylation reactions around the ring. For example, the enone functionality can be used as a Michael acceptor[6] or a selective 1,2-addition to the carbonyl of the enone can be accomplished.[6b,7] Electrophilic substitution can be used at the C-5 position, [8] and the enolate can be used to alkylate at C-3.[9]

Figure 2: Synthetic Utility of *N*-Acyldihydropyridones



Dihydropyridones have been used as intermediates in the synthesis of indolizidinones, [10] quindizidines, [11] and piperidines.[12] Figure 3 shows a select few natural products that have recently been targeted in the Comins group.

Figure 3: Past and Present Targets Using *N*-Acylpyridinium Salt Chemistry



Chapter 2: Effect of Chelation on *N*-Acylpyridinium Salt Chemistry

Introduction

N-Acylpyridinium salt chemistry has been the focus of the Comins group research for the past several years. With the role of the chiral auxiliary and the TIPS group well understood (see Chapter One), other aspects of the pyridinium salt reaction have come under investigation. For example, the effect of temperature on additions to the pyridinium salt has been examined and optimized.[4]

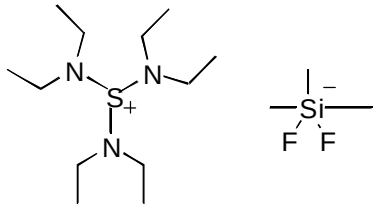
Since organometallics are typically added to the pyridinium salt, a study was to be done on the effect that possible chelation of the metals could have on the de's obtained from the reaction. This study was to be conducted by adding an organometallic to the pyridinium salt formed between 4-methoxypyridine and racemic TCC chloroformate. No TIPS group was to be used in order to keep the reaction variables to a minimum. Another reaction would then be done by adding a nucleophile analogous to the organometallic species to the same pyridinium salt. However, all metals were to be absent in order to eliminate any possibility of chelation. The de's of the two reactions would then be compared.

Utilizing the driving force of the formation of very strong silicon-fluorine bonds (139 kcal/mol),[13] reaction of a trimethylsilyl compound and a fluoride ion would be expected to yield a very nucleophilic anion and fluorotrimethylsilane. This system would effectively eliminate the need for any metals to be present in the pyridinium salt reaction.

Introduction to Tris(diethyamino)sulfonium (trimethylsilyl)difluoride (TAS-F)

In the recent literature, TAS-F (Figure 4) has been used to generate naked enolates from silyl enol ethers, [14] for the cleavage of Si-C bonds, [15] for the removal of silyl protecting groups from phenols, [16] and in the deprotection of silyl ethers.[17]

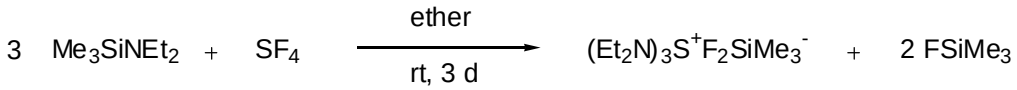
Figure 4: Tris(diethylamino)sulfonium (Trimethylsilyl)difluoride



9

An efficient synthesis of TAS-F was accomplished by William J. Middleton.[18] Condensed SF_4 is distilled into a solution of anhydrous ether. *N*,*N*-diethylamino-trimethylsilane **10** is added to the SF_4 solution at –60 °C over 30 minutes. The reaction is allowed to warm to rt and is stirred for 3 days in a closed system under constant nitrogen flow. The product **9** then separates as hydroscopic, colorless needles (Scheme 3).

Scheme 3: Synthesis of TAS-F



10 **11** **9** **12**

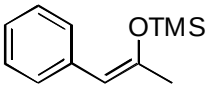
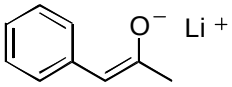
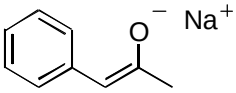
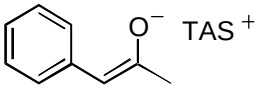
The main advantage of TAS-F is the fact that it can be prepared and is commercially available as an anhydrous solid. Quaternary ammonium fluorides have

been used in the past as fluoride sources.[19] However, the most popular quaternary fluoride source, TBAF, contains a small contamination of tetrabutylammonium hydroxide which is highly hydroscopic and notoriously difficult to dry.[20] The main disadvantages of TAS-F are its high cost and air sensitivity.

TAS anions are highly reactive species because the extremely naked anion has such little interaction with the TAS cation. Noyori and coworkers conducted a NMR study to compare TAS enolates to their analogous sodium, lithium and potassium enolates.[21] The enolate data was compared to NMR data obtained from the neutral silyl enol ether **13** studied extensively by House.[22] Observed changes in chemical shift would be due to the delocalization of the negative charge throughout the anion. The magnitude of these chemical shifts should then give some insight into the degree of nakedness of the TAS enolate compared to other studied metal enolates.

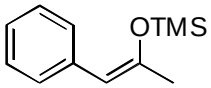
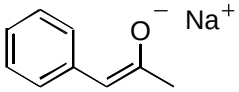
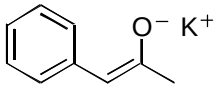
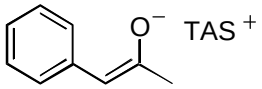
In the ^{1}H NMR data for the TAS enolate **16**, the signals of the vinyl proton and aromatic para and meta protons shift significantly upfield from the signals from the neutral silyl enol ether (Table 1). In fact, the chemical shifts are higher for the TAS enolate than those of both the lithium **14** and sodium **15** enolates.

Table 1: ^{1}H NMR Data of Enolates 14, 15, and 16 and Silyl Enol Ether 13

compound	chemical shift, δ				
	para	meta	ortho	vinyl	methyl
 **13**	7.05	7.15	7.45	5.36	1.85
 **14**[23b]				4.93	
 **15**[23b]	6.66	7.09	7.47	4.86	
 **16**	6.25	6.75	7.57	4.50	1.67

The ^{13}C NMR spectra also support these findings. In Table 2, the data for the TAS enolate **16** is compared to the silyl enol ether **13**, the sodium **15** and potassium **17** enolates, and the crown ether complexation of the sodium enolate. In comparing the TAS enolate **16** to the neutral silyl enol ether **13**, the magnitude of the chemical shift difference, which is sensitive to the nature of the ion pairing, appears to be greatest for the TAS enolate over the metal enolates shown.

Table 2: ^{13}C NMR Data of TAS and Metal Enolates and Silyl Enol Ether

compound	chemical shift, δ						
	para	meta	ortho	ipso	vinyl	C-O	CH_3
 **13**	125.5	128.3	128.1	137.5	109.2	149.0	23.8
 **15**[23b]	119.2	128.2	124.1	145.1	93.4	169.3	29.4
15 + 18-crown-6[23b]	116.4	126.7	123.1	146.0	90.7	170.3	29.7
 **17**[23b]	118.6	128.6	123.3	145.6	91.8	170.7	29.5
 **16**	116.2	127.6	123.0	149.0	88.9	174.0	29.7

Just like the TAS enolates, other TAS anions are thought to be very reactive species due to the nakedness of the negative charge. This would make various TAS anions powerful nucleophiles for use in organic synthesis.

Results and Discussion

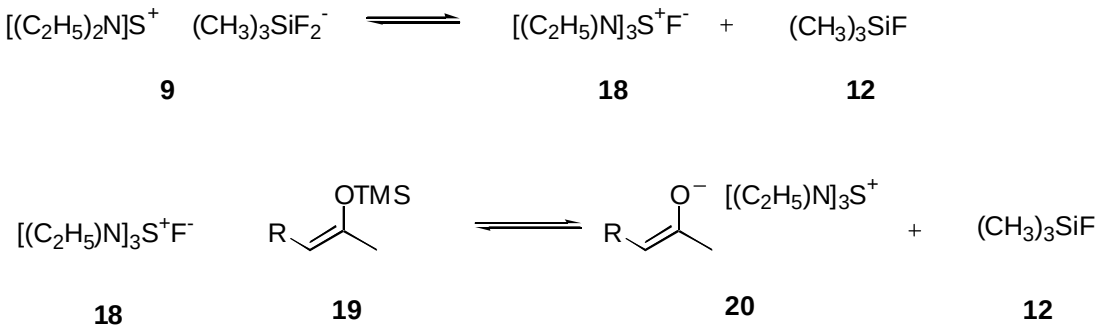
For this study, a nucleophile formed from a silated compound and a fluoride source would be added to the pyridinium salt formed between 4-methoxypyridine and the chloroformate of racemic TCC in order to determine the de. This would be compared to the de of an analogous organometallic reaction. If the de's were similar, this would

provide support that the de is not being improved by the possible chelation of the metal counterions.

A variety of classes of anions were to be used as nucleophiles in this study. These compounds had to be silated in order to form the precursor to a TAS enolate, and an analogous metal containing anion had to be easily made.

TAS enolates have been studied in the literature over the past number of years.[21,23] As discussed above, the TAS countercation greatly enhances the reactivity of the oxygen in ambident compounds such as enolates due to the nakedness of the anionic charge. The mechanism of the formation of the TAS enolates is believed to proceed through the dynamic equilibria shown in Scheme 4.[21] The TAS salt **9** is believed to exist in an equilibrium with TAS fluoride **18** and fluorotrimethylsilane **12.** The generated fluoride ion then reacts with the silyl enol ether **19** at the silicon atom to produce the TAS enolate **20** and fluorotrimethylsilane **12**.

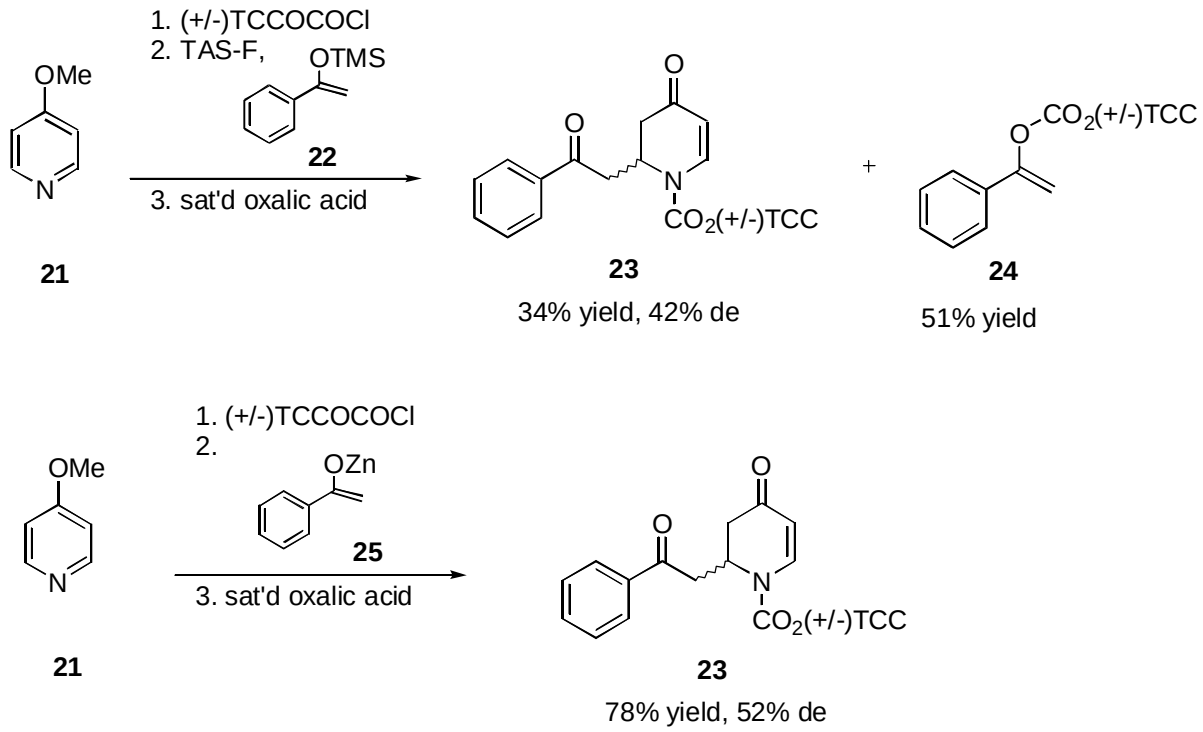
Scheme 4: Mechanism of TAS Enolate Formation



In our first set of examples, 1-phenyl-1-trimethylsiloxyethylene **22** was treated with TAS-F **9** and transferred into the pyridinium salt formed between 4-

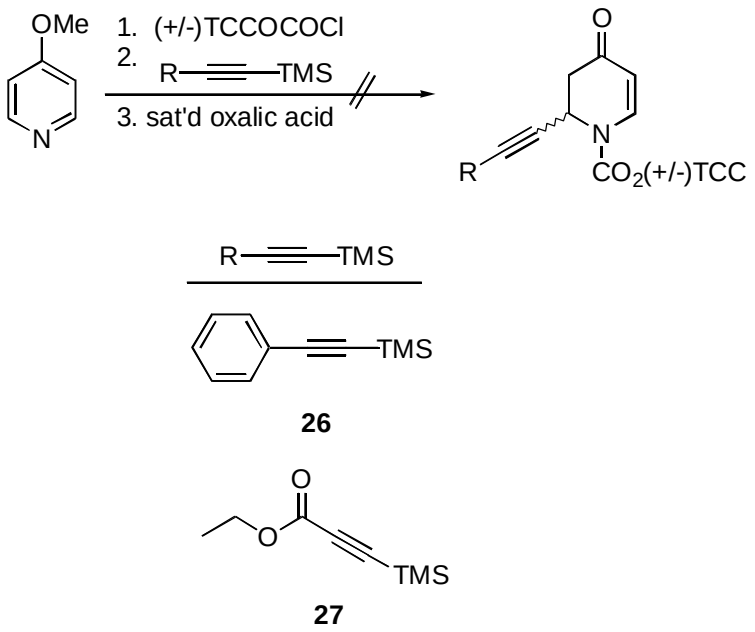
methoxypyridine **21** and the chloroformate of racemic TCC. Hydrolysis with aqueous acid gave a 34% yield of the desired dihydropyridone **23** and a 51% yield of compound **24** resulting from reaction at the oxygen of the silyl enol ether at the carbonyl of the carbamate of the pyridinium salt. The formation of compound **24** is due to the extreme hardness of the naked TAS enolate. The de of the dihydropyridone was determined by HPLC to be 42, with the ratio of diastereomers being 71 to 29. This de was compared to the de from the dihydropyridone formed by the addition of the zinc enolate **25** formed from acetophenone to the same pyidinium salt. Dihydropyridone **23** was formed in 78% yield and a de of 52 with the ratio of the diastereomers being 76 to 24 as determined by HPLC analysis of the crude reaction material.

Scheme 5: Enolate Additions to the Pyridinium Salt



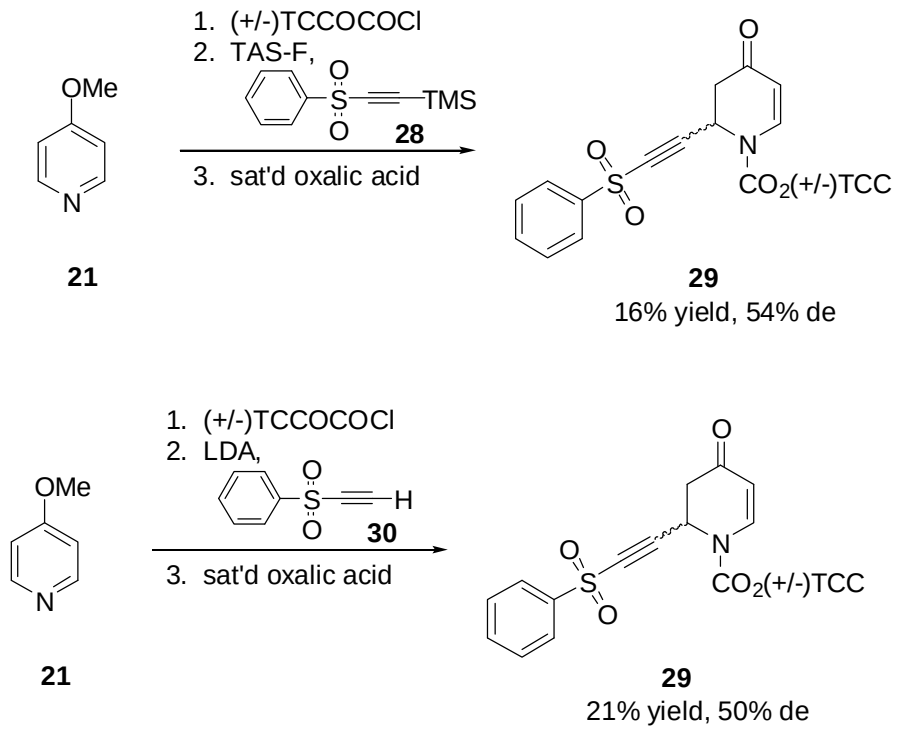
A trimethylsilyl acetylene was to be used in the second set of examples. The acetylenes had to be able to stabilize a strong negative charge in order for decomposition to not occur. 1-Phenyl-2-trimethylsilylacetylene **26** and ethyl 3-(trimethylsilyl)-propynoate[24] **27** were used in TAS-F assisted additions to the pyridinium salt. However, upon addition of the TAS-F to each of the acetylenes, decomposition occurred due to the instability of the extremely naked anion.

Scheme 6: Attempted Acetylene Additions to the Pyridinium Salt



Phenyl trimethylsilylethynylsulfone[25] **28** was chosen based on its perceived ability to stabilize a negative charge. Phenyl trimethylsilylethynylsulfone and TAS-F were added to the pyridinium salt to give a 16% yield of dihydropyridone **29** with a de of 54 (77/23). When the organolithium compound formed between lithium diisopropylamide (LDA) and phenyl ethynyl sulfone[26] **30** was added to the pyridinium salt, the desired dihydropyridone **29** was isolated in 21% yield with de of 50.

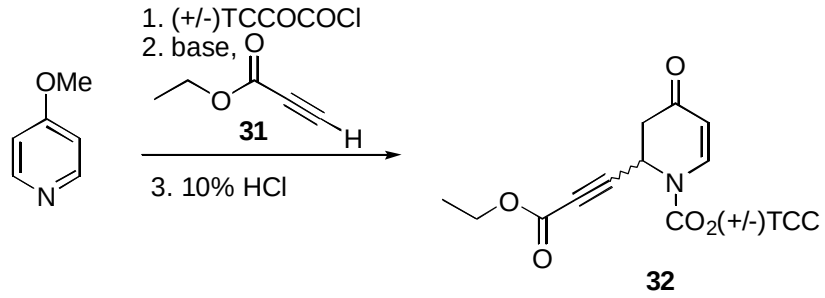
Scheme 7: Phenyl Sulfonyl Acetylene Additions to the Pyridinium Salt



Due to problems separating the diastereomers with HPLC analysis, this reaction was initially thought to give very high de's. This prompted us to study other lithium acetylide additions to the pyridinium salt. Two acetylenes which failed in the TAS-F assisted additions were examined.

Ethyl propiolate **31** was one of the acetylenes examined (Scheme 8). Deprotonation of ethyl propiolate using both *n*-BuLi and LDA, followed by addition of the lithium acetylide to the pyridinium salt gave de's of 52 and 58, respectively. These de's are very typical of compounds added in this sort of reaction.

Scheme 8: Ethyl Propiolate Addition to the Pyridinium Salt

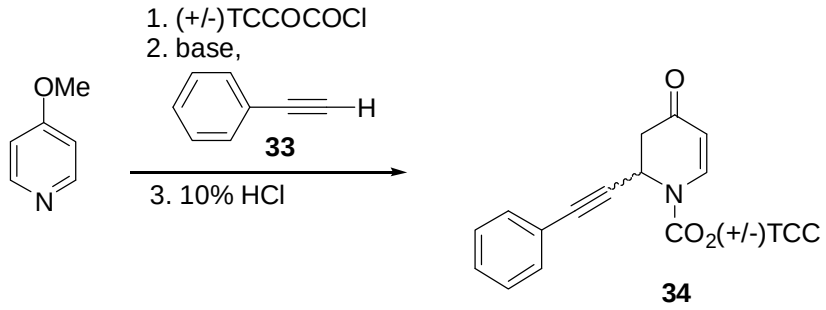


32

Base	**Yield**	**De**
n-BuLi	58%	52
LDA	65%	58

Phenyl acetylene **33** was also examined (Scheme 9). Deprotonation of phenyl acetylene with LDA followed by addition to the pyridinium salt gave a 92% yield of dihydropyridone **34**. Deprotonation using *n*-BuLi gave a 94% yield, and addition of phenyl ethynylborate[27] gave a 91%yield. These addition reactions were initially thought to give very high diastereoselectivities. However, when a 50/50 mixture of dihydropyridone **34** was made in order to prove the de, only one peak was seen by HPLC analysis. Our inability to separate the diastereomers by HPLC analysis makes it impossible for us to determine the exact de's. However, NMR analysis of the crude reaction materials may give us insight into approximate de's.

Scheme 9: Phenyl Acetylene Additions to the Pyridinium Salt



Base	**Yield**
n-BuLi	94%
LDA	92%
n-BuLi, $BF_3 \bullet OEt_2$	91%

Conclusion

Initial research into the effect of chelation on the mechanism of the *N*-acylpyridinium salt reaction shows that there are no significant improvements to the de due to a chelation controlled mechanism. The enolate additions gave quite similar diastereoselectivities as well as the acetylene additions.

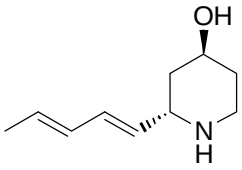
Future work could be done to analyze other classes of compounds. The TAS anion of benzyltrimethylsilane could be added and compared to the addition of benzyl Grignard, for example. Further examples could be used to support the claim that chelation is not a factor in the N-acylpyridinium salt reaction.

Chapter 3: The Asymmetric Synthesis of Streptomyces SS20846A

Literature Review of Streptomyces SS20846A

Originally isolated from the *Streptomyces* sp. S20846 strain of bacteria collected from a soil sample in Kyperissia, Greece, Streptomyces SS20846A is a 2,4-disubstituted piperidine alkaloid possessing strong biological activity. This alkaloid has a restrictive action upon the digestive system and is a biosynthetic intermediate of the well-known antibiotic Streptazoline.[29]

Figure 5: Streptomyces SS20846A and Streptazoline



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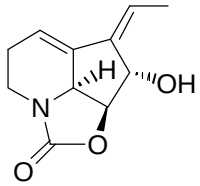
Streptomyces SS20846A



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Streptazoline

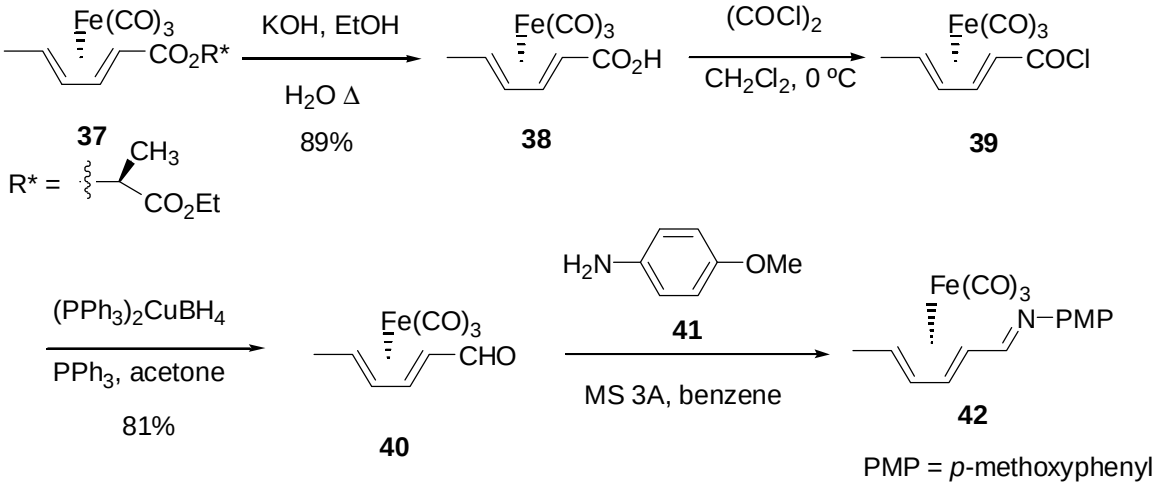
Iwata's Synthesis

The first asymmetric synthesis of Streptomyces SS20846A was accomplished by Iwata and coworkers.[29] The key step in their synthesis was a [4+2] cycloaddition reaction of a 1-azatriene iron-tricarbonyl complex **45** with Danishefsky's diene **46** to give a diastereomerically pure 2-substitued dihydropiperidone **47** which could easily be converted into the desired alkaloid.

The key azatriene iron-tricarbonyl complex **42** (Scheme 10) was prepared starting with ester **37**. Hydrolysis of the ester functionality followed by reaction with oxalyl

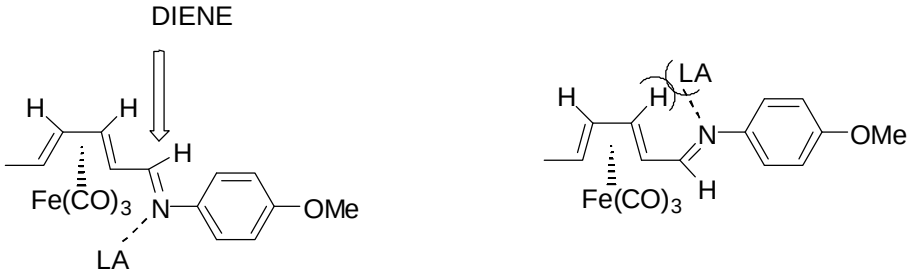
chloride gave acid chloride **39**. Reduction of **39** using $(PPh_3)_2CuBH_4$ gave chiral aldehyde **40** in 72% overall yield. The chiral aldehyde was converted to the imine complex **42** by reaction with *p*-methoxyaniline **41**.

Scheme 10: Synthesis of Key Azatriene Iron-Tricarbonyl Complex



The key step involved the catalytic lithium perchlorate ($LiClO_4$) mediated [4+2] cycloaddition reaction of the p-methoxyphenyl-imine derivative **45** with Danishefsky's diene **46**. Adduct **47** was obtained as a single isomer. This stereochemical outcome was explained by analogy to the nucleophilic addition of organometallics.[30] In the presence of Lewis acids, transoid conformation **43** in Figure 6 is favored over cisoid **44** due to the steric repulsion of the substituent on nitrogen and the vinyl proton. Due to this conformational bias, the diene should approach from the re-face of the C=N bond in conformation **43**.

Figure 6: Iwata Diene Addition Conformations

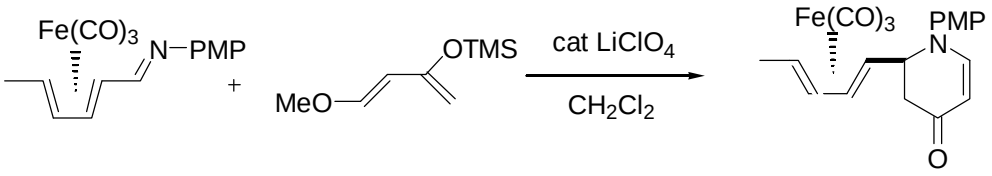


43 **44**

Conformation A Conformation B

It is not known whether the actual mechanism of this reaction proceeds through a tandem Mannich-Michael process or a Diels-Alder one.

Scheme 11: [4+2] Cycloaddition Reaction



45 **46** 93% **47**

1,4-Reduction of compound **47** with L-Selectride gave compound **51** in 80% yield (Scheme 12). The ketone reduction, however, proved to be problematic. Because the side chain occupies an axial position due to severe interaction with the protecting group on the nitrogen, the hydride was attacking the carbonyl from the upper equatorial position and yielding the undesired *cis* piperidinol **49a** as the major product (Figure 7). Both DIBAL and sodium borohydride failed to reverse the ratio of the *cis* to *trans* product

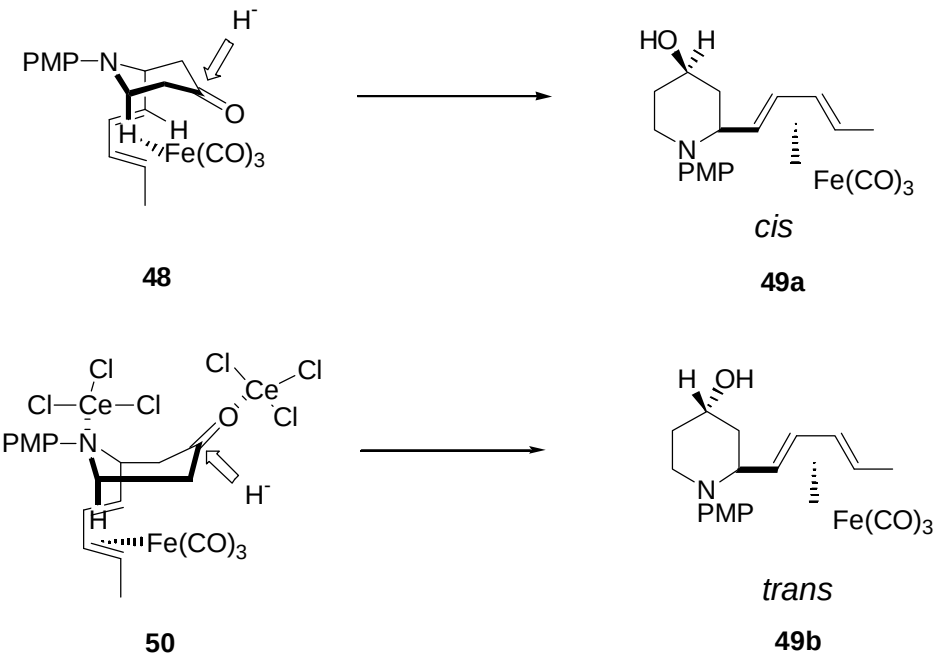
(Table 3). Finally, reduction with sodium borohydride in the presence of cerium(III) chloride yielded the *trans* isomer **49b** as the predominant product.[31]

Table 3: Ketone Reduction Conditions

Reaction Conditions	**Yield**	**Ratio (*trans*/*cis*)**
L-Selectride, THF, -78 °C	92%	11/89
DIBAL, CH_2Cl_2, -78 °C	81%	39/61
$NaBH_4$, MeOH, 0 °C	83%	29/71
$NaBH_4$, $CeCl_3$-$7H_2O$, MeOH, 0 °C	77%	70/30

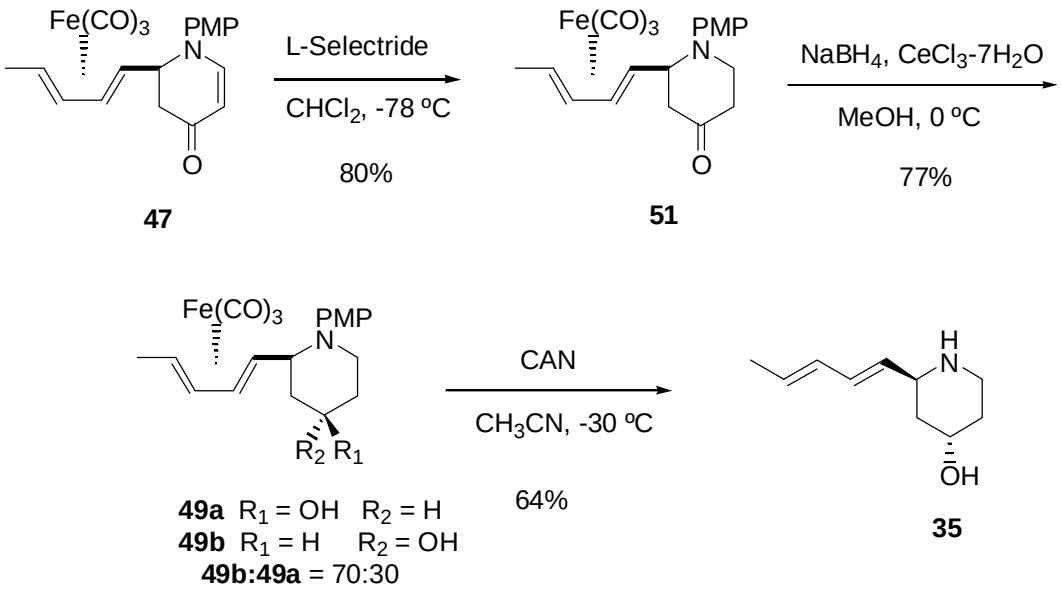
As shown in Figure 7, the coordination of cerium salts to the ketone and amine groups at the less hindered, upper side of **50** causes the hydride to change its reaction trajectory from downward to upward.

Figure 7: Effect of $CeCl_3$ Coordination on Ketone Reduction



Simultaneous deprotection of the iron-tricarbonyl and PMP groups with ceric ammonium nitrate (CAN) yielded the enantiopure product **35** in 64% yield (Scheme 12). Iwata's synthesis determined the absolute configuration of Streptomyces SS20846A.

Scheme 12: Completion of Iwata's Synthesis

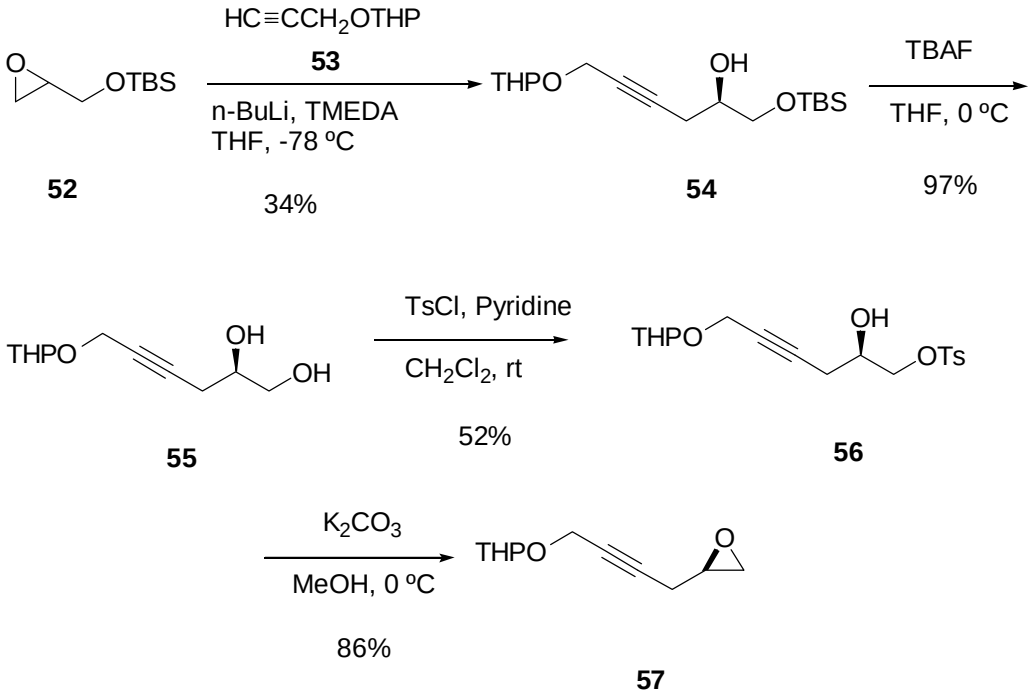


Hirai's Synthesis

Another total asymmetric synthesis of SS20846A was completed by Hirai and coworkers focusing on the construction of the *trans*-2,4-disubstitued piperidine by an intramolecular palladium(II)-catalyzed cyclization.[32] The synthesis was completed in 20 steps with starting materials taken from the chiral pool.

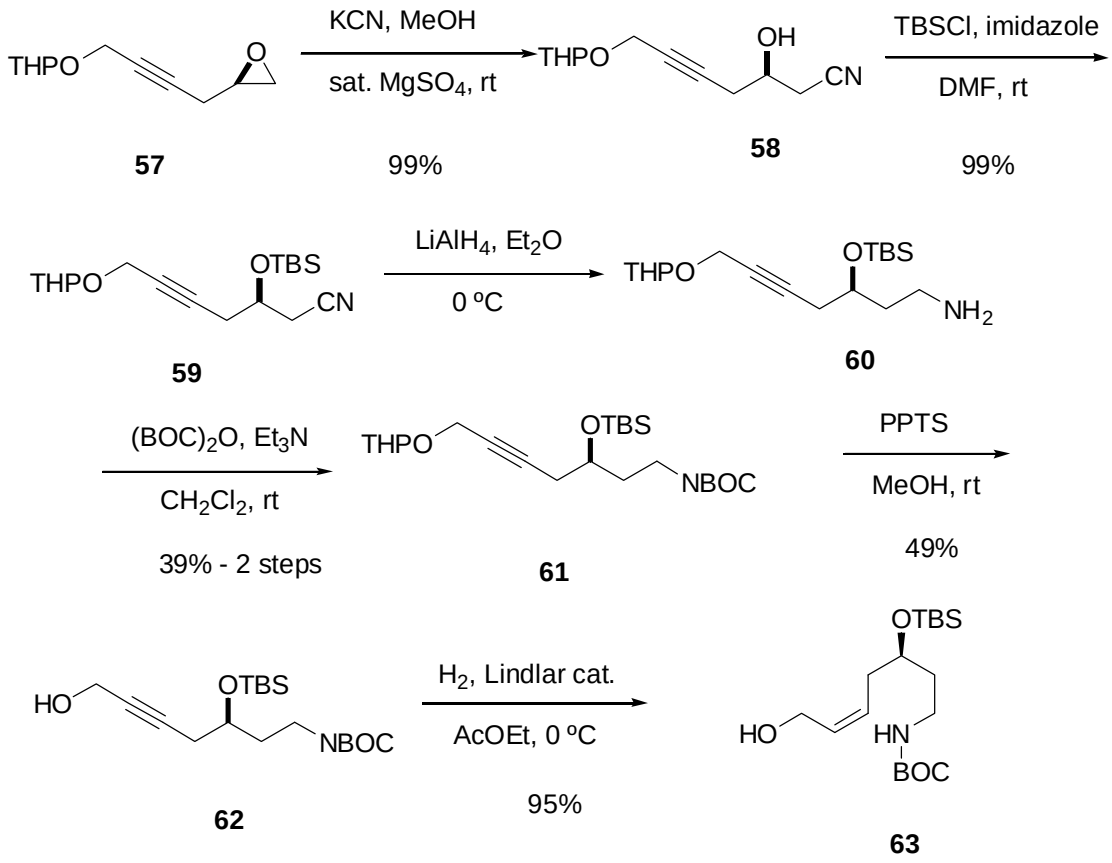
(R)-O-*Tert*-butyldimethylsilyl glycidol **52** was reacted with [tetrahydro-2-(2-proynloxy)-2H-pyran]-2-propyne **53** in the presence of *n*-butyllithium and tetramethylethylenediamine (TMEDA) to give alcohol **54** in 34% yield (Scheme 13). Deprotection of the TBS-protected alcohol with tetrabutylammonium fluoride (TBAF), selective tosylation of the primary alcohol with tosyl chloride and pyridine, and epoxidation of the tosylate using potassium carbonate gave compound **57** in 15% overall yield.

Scheme 13: Formation of Harai Key Intermediate Part I



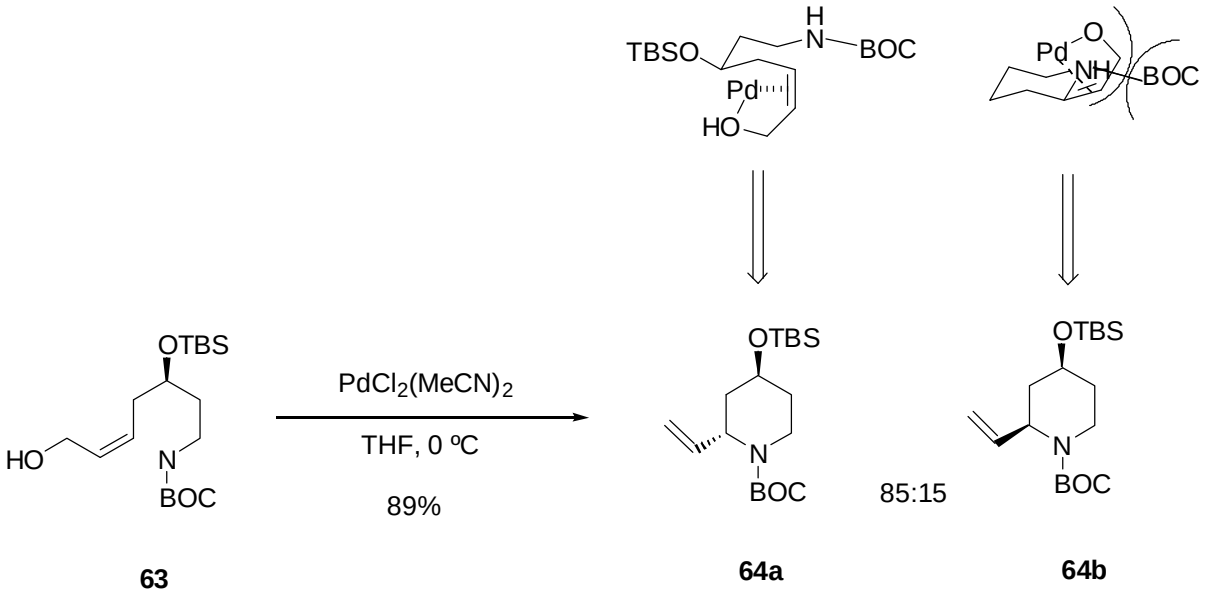
Ring opening of epoxide **57** was accomplished in 99% yield with potassium cyanide, and protection of the resulting alcohol gave nitrile **59** in 99% yield (Scheme 14). Reduction of the cyano group and protection of the amine **60** gave **61** in 39% overall yield. Deprotection of the tetrahyrdopyran (THP) group was accomplished with Pyridinium *p*-toluenesulfonate (PPTS), and hydrogenation of the resulting alcohol afforded key intermediate **63** upon which cyclization would occur.

Scheme 14: Formation of Hirai Key Intermediate Part II



The penultimate intramolecular palladium-catalyzed cyclization was performed on compound **63** to give an 85:15 mixture of the *trans* **64a** and *cis* **64b** piperidines in 89% total yield. The selectivity of the cyclization can be understood by examining the transition state of the reaction shown in Scheme 15. Of the two transition states, the one leading to **64b** is disfavored due to the nonbonding interaction between the carbamate and the palladium complex.

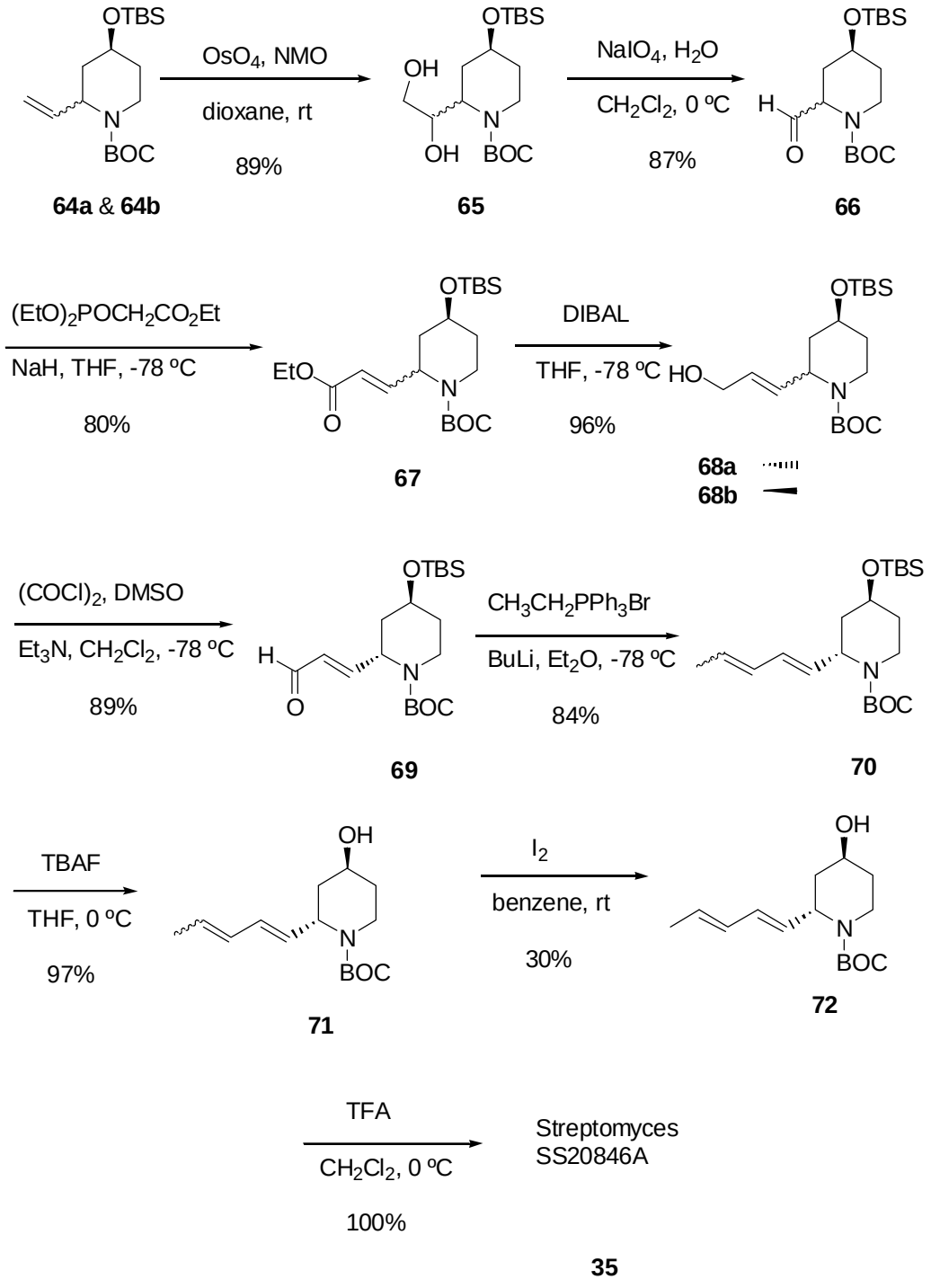
Scheme 15: Transition States of the Palladium-Catalyzed Cyclization



63 **64a** **64b**

A series of functional group manipulations were then necessary to convert the mixture of **64a** and **64b** into the target natural product (Scheme 16). Dihydroxylation of the olefin with osmium tetroxide (OsO_4), reductive degradation with sodium periodate ($NaIO_4$), followed by a Wittig reaction and DIBAL reduction gave two isomers **68a** and **68b** that could be separated by chromatography. Swern oxidation of **68a** was followed by another Wittig reaction to give piperidine **70**. Isomerization of the double bond and deprotection of the BOC group on compound **72** gave Streptomyces SS20846A **35** in 22% overall yield.

Scheme 15: Completion of the Harai Streptomyces SS20846A Synthesis

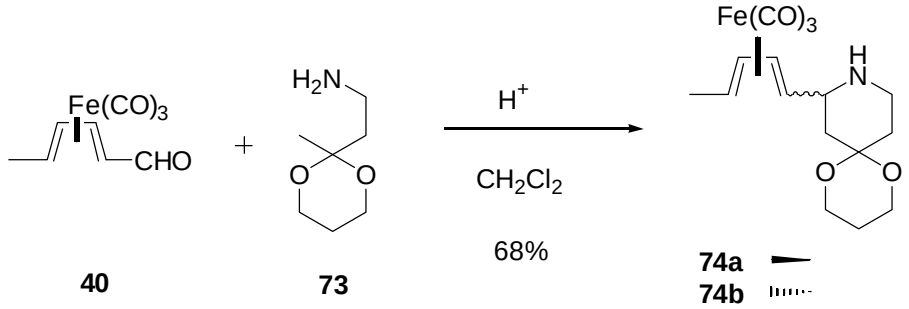


Troin's Synthesis

Troin and coworkers synthesized Streptomyces SS20846A to highlight a diastereoselective intramolecular Mannich reaction using planar chiral iron dienal complexes to form 2,4-disubstituted piperidines.[33]

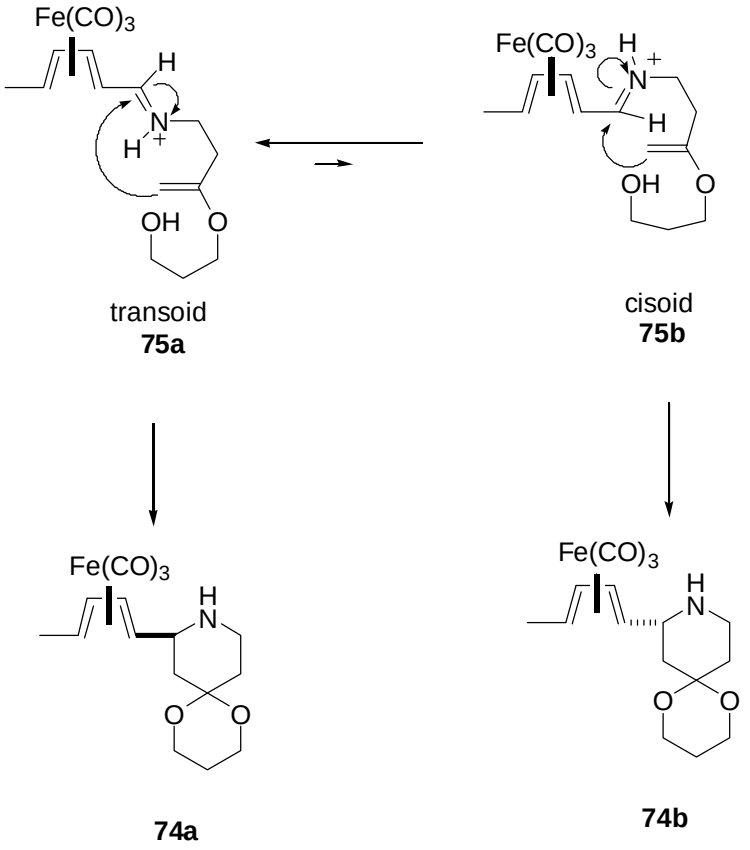
In the synthesis of Streptomyces SS20846A, treatment of chiral iron tricarbonyl complex **40** with amine **73** in anhydrous methylene chloride followed by acidic workup gave 65% of a 9:1 mixture of piperidine **74a** and **74b**, which could be separated by column chromatography (Scheme 17).

Scheme 17: Troin Intramolecular Mannich Reaction



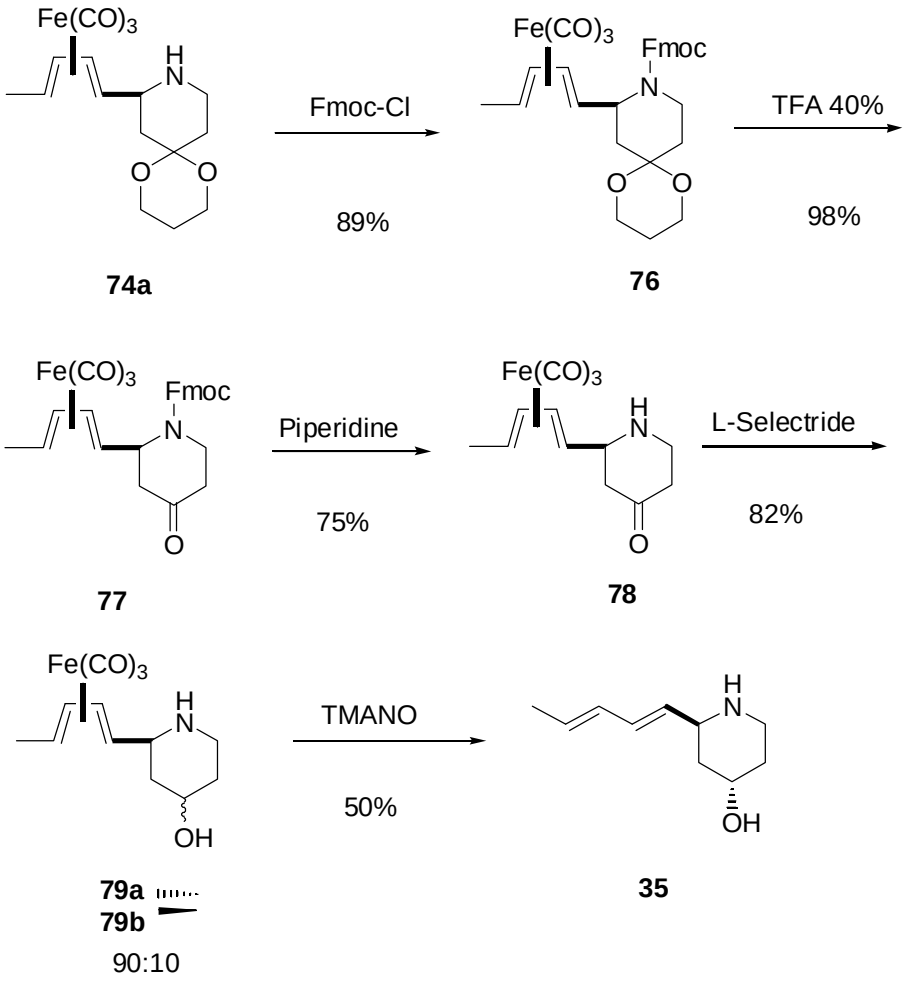
Stereoselectivity of this reaction is due to the fact that in an acidic medium, the transoid complex **75a** (Scheme 18) is more stable than cisoid complex **75b**. The intramolecular cyclization of the enol ether on the intermediate iminium ion always occurs anti to the bulky $Fe(CO)_3$.

Scheme 18: Stereoselectivity of the Troin Mannich Cyclization



The protecting group on the ketone could not be removed without protection of the amine on compound **74a**. The Fmoc group was chosen because it has orthogonal cleavage conditons to the dioxane. 9-Fluorenylmethyl chloroformate (Fmoc-Cl) was used to protect amine **74a** in 89% yield (Scheme 19). The ketone was then deprotected utilizing 40% TFA to give a 98% yield of piperidone **77**. The Fmoc group was cleaved in 75% yield using piperidine. A 1,2-reduction of **78** resulted in a 90:10 mixture of the *cis* **79b** and *trans* **79a** piperidinols with an 82% overall yield. Decomplexation of **79a** with trimethylamine N-oxide (TMANO) in acetone yielded Streptomyces SS20846A in 27% overall yield over six steps.

Scheme 19: Completion of Troin Synthesis

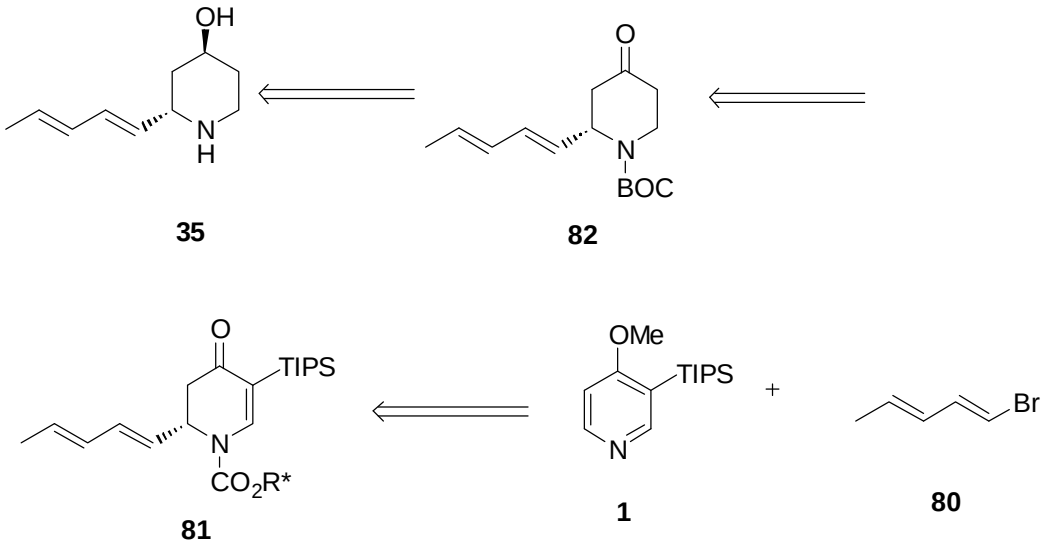


Results and Discussion

The synthesis of Streptomyces SS20846A was to be accomplished using established 1-acylpyridinium salt chemistry. Dihydropyridone **81** could be synthesized by adding the halodiene **80** via an organometallic reaction to the pyridinium salt formed between 4-methoxy-3-TIPS-pyridine **1** and the chloroformate of (-)-*trans*-(2α-cumyl)cyclohexanol ((-)TCC) followed by hydrolysis with aqueous acid (Scheme 20).

This reaction should yield the desired dihydropyridone **81** in high diastereomeric excess. The carbamate and TIPS group could be cleaved in a one-pot reaction, the vinylogous amide reprotected and 1,4-reduction done on the dihydropyridone to give compound **82**. The BOC group was chosen because it could be cleaved under mild conditions which wouldn't harm the dienyl system. After a 1,4-reduction, the BOC group would be removed. This would cause the system to flip into more of a chair conformation and a 1,2-reduction with L-Selectride should give the desired *trans* piperidinol **35** stereoselectively. This synthetic route would yield Streptomyces SS20846A in six steps.

Scheme 20: Retrosynthetic Analysis for Streptomyces SS20846A



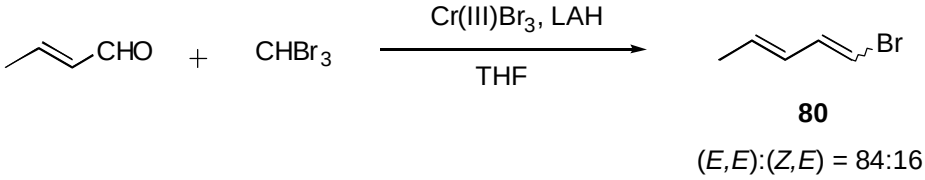
In order the prepare for the acylpyridinium salt reaction, (*E*,*E*) 1-bromo-1,3-pentadiene **80** needed to be synthesized. There are a variety of synthetic methods for the preparation of diene systems, and three of the attempted methods are described below.

The synthesis of the pentadienyl system had to fulfill two requirements. First, it had to be synthesized from inexpensive starting materials in order for large scale

reactions to be economical. Second, the purification conditions had to account for the volatility of the diene. The boiling point of the compound is reported to be 49-51 °C at 45 mmHg, [34] but its tendency to codistill with many solvents made chromatography an undesirable means of purification.

One attempted route involved the Takai olefination.[35] This reaction is a simple and selective method for converting an aldehyde to a *trans*-alkenyl halide with an organochromium reagent. Chromium (III) bromide was reduced to chromium (II) bromide with lithium aluminum hydride (LAH) (Scheme 21). A mixture of bromoform and crotonaldehyde was added to the chromium (II) bromide, and the desired diene **80** was produced in a ratio of (*E*,*E*):(*Z*,*E*) = 84:16 by GC analysis of the crude material. However, the diene could not be purified away from the excess bromoform by either distillation or chromotography. This, taken with the excessive cost of the chromium reagent, made this route undesirable.

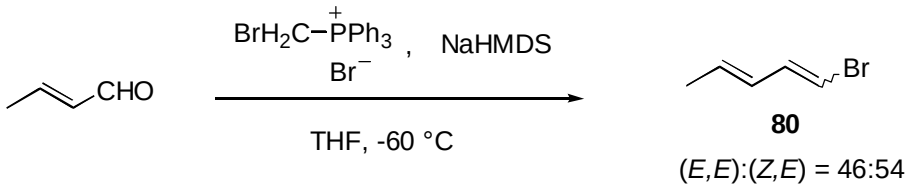
Scheme 21: Takai Olefination



A Wittig reaction between crotonaldehyde and (bromomethyl)triphenyl-phosphonium bromide was also examined (Scheme 22). Wittig reactions typically yield the *cis* over the *trans* isomers, but with an isomerization procedure available,[34] this was not seen as a problem. The ylide was formed with (bromomethyl)triphenylphosphonium

bromide and sodium hexamethyldisilazide (NaHMDS) in THF at –60 °C. The reaction was warmed to room temperature and crotonaldehyde added. GC analysis of the crude reaction mixture showed a (*E*,*E*):(*Z*,*E*) ratio of 46:54. However, it proved impossible to separate the product from the triphenylphosphonium oxide by-product, and after several attempts this route also was abandoned.

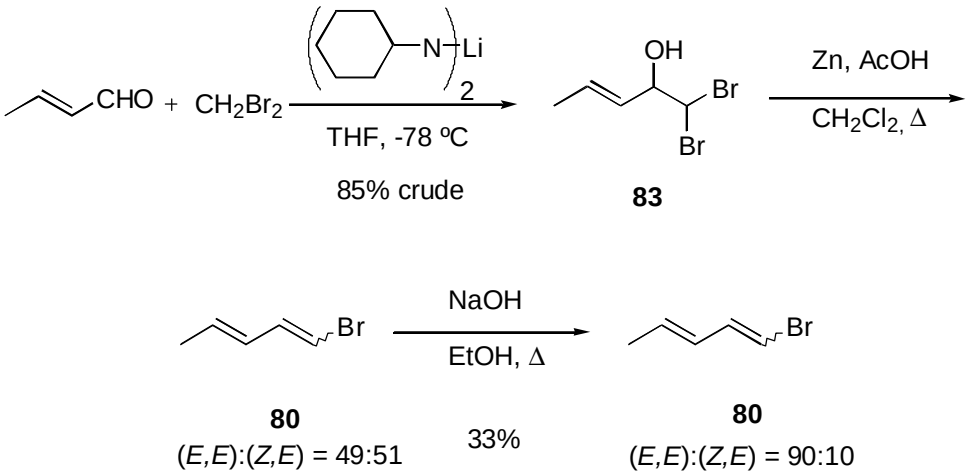
Scheme 22: Wittig Reaction to Form Diene



The final path explored was worked out by Hayashi and coworkers.[34] Crotonaldehyde was dibromomethylated with lithium dicyclohexylamide and dibromomethane (Scheme 23).[36] The crude dibromoalcohol was reductively eliminated to a 50:50 mixture of the (*E*,*E*):(*Z*,*E*) dienes **80** by zinc and glacial acetic acid in methylene chloride at reflux.[37] The mixture of dienes was purified by fractional distillation with a small fraction of the product being lost due to codistillation with the methylene chloride. Changing to a high boiling solvent such as triglyme resulted in problems retrieving all of the product from the reaction flask, and methylene chloride appeared to be the better of the choices. In agreement with Williams' findings,[37] the elimination never proceeded to completion, and the dibromoalcohol was always reisolated for a second cycle. The 50:50 mixture of dienes was isomerized with sodium

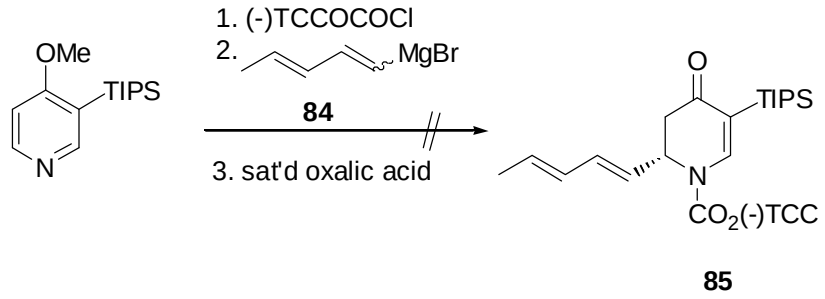
hydroxide in refluxing ethanol to yield a 90:10 (*E*,*E*):(*Z*,*E*) mixture of **80** after fractional distillation.

Scheme 23: Hayashi Pathway to 1-Bromo-penta-1,3-diene



With the vinylbromide **80** in hand, the first goal in the synthesis was to prepare dihydropyridone **81**. Dihydropyridones of this type are typically made by adding a Grignard reagent to the pyridinium salt of 4-methoxy-3-TIPS-pyridine and the chloroformate of TCC. In order to obtain the desired stereochemistry at the C2 position, (-)TCC would be employed. From previous work in the Comins group, it was known that direct metalation of the diene system with magnesium was very difficult if not impossible and would result in a loss of stereochemistry.[12a] Lithium-halogen exchange followed by transmetalation with the vinylorganolithium and magnesium bromide should yield the vinyl Grignard **84** which could be added to the acylpyridinium salt. However, numerous attempts at this route failed and gave only starting materials (Scheme 24).

Scheme 24: Attempted Grignard Addition



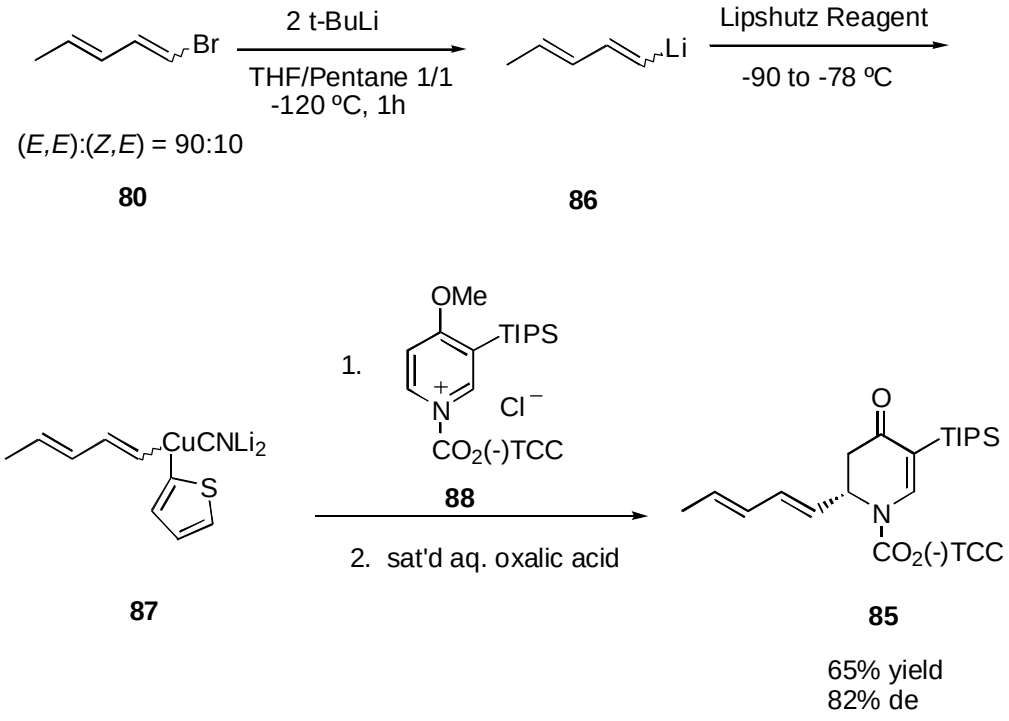
85

Next, the addition reaction using a higher order cuprate was attempted (Scheme 25). Lithium-halogen exchange was done with a mixture of (*E*,*E*):(*Z*,*E*) = 90:10 1-bromo-1,3-pentadiene **80** and *t*-BuLi at –120 °C. The low temperature is necessary because at temperatures above -120 °C acetylene formation dominates over lithium-halogen exchange.[38] The vinyl lithium was then treated with Lipshutz reagent (lithium 2-thienylcyanocuprate) to form the higher order cuprate. The pyridinium salt **88** formed with 4-methoxy-3-triisopropylsilylpyridine and the chloroformate of (-)-TCC is added to the higher order cuprate at –78 °C. Typically, the nucleophile is added to the pyridinium salts to enhance distereoselectivity, but in this case the higher order organocuprate proved to be unstable if warmed up above -78 °C, and an inverse addition was necessary. The reaction was quenched with saturated aqueous oxalic acid and hydrolyzed over 16 hours. Oxalic acid was chosen as the aqueous acid because it was mild enough to not damage the diene system. The desired diastereomer of the dihydropyridone was isolated in 65% yield.

The diastereomeric excess of the reaction was determined by HPLC analysis of the crude reaction material. A 50:50 mixture of the diastereomers was prepared in order

to detect the retention time of the minor diastereomer. The de was determined to be 82, with a ratio of diastereomers being 91 to 9 (Figure 8).

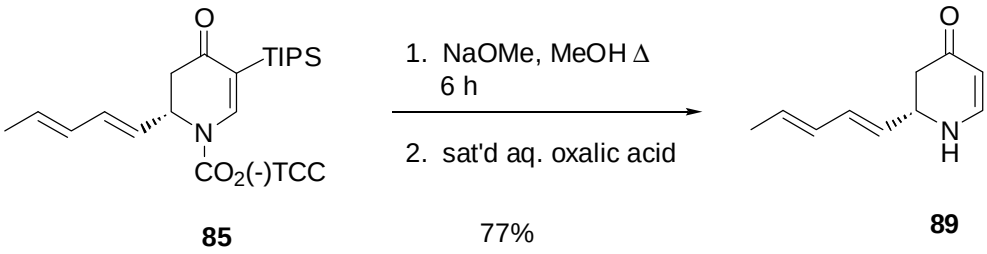
Scheme 25: Addition of Higher Order Cuprate to 1-Acylpyridinium Salt



Dihydropyridone **85** was subjected to a one-pot carbamate cleavage and protodesilation (Scheme 26).[4] Treatment with a solution of sodium methoxide in

refluxing methanol for 6 hours followed by addition of saturated aqueous oxalic acid for 16 hours yielded the unprotected dihydropyridone **56** in 77% yield.

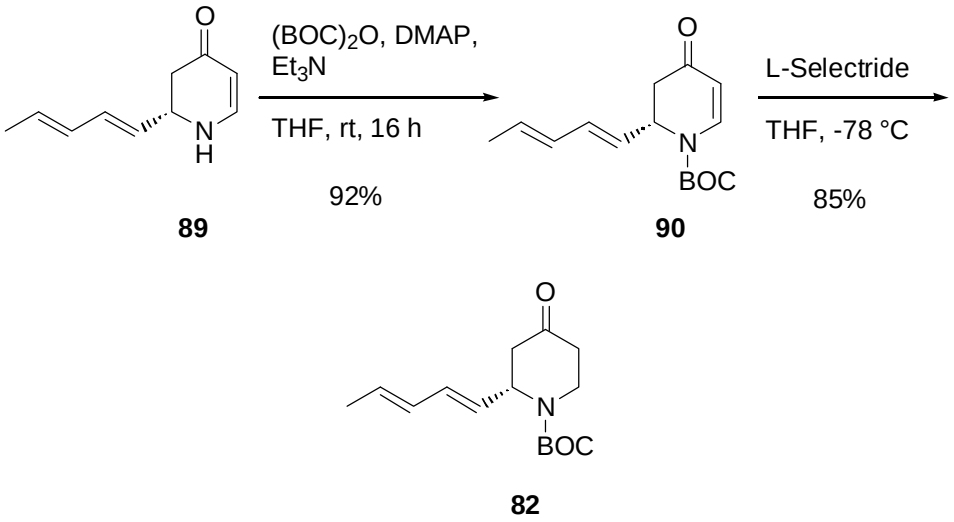
Scheme 26: Carbamate Cleavage and Protodesilation



85 77% **89**

Dihydropyridone **89** was to be reprotected as the 1-*tert*-butoxycarbamate. The BOC group was chosen because it should be simple to remove under mild conditions. Treatment with di-*tert*-butoxy-dicarbonate in the presence of triethylamine and a catalytic amount of dimethylaminopyridine (DMAP) in acetonitrile at room temperature gave the BOC protected dihydropyridone **90** in 92% yield (Scheme 27). Treatment of this compound with L-Selectride in THF at –78 °C gave piperidone **82** in 85% yield.

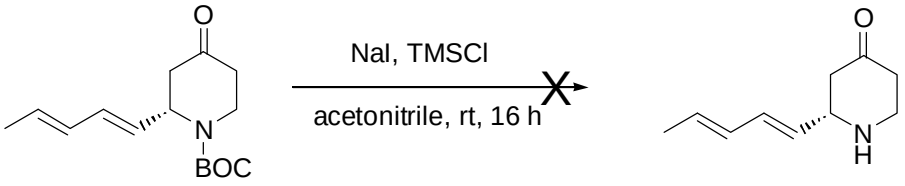
Scheme 27: Piperidone Ring Formation



In order to form the piperidinol ring system, the BOC group needed to be removed. Removal of the carbamate before the ketone reduction was desirable because this would remove the $A^{(1,3)}$ strain in the molecule, and the compound would ring-flip, allowing the C-2 substituent to move to the more stable equatorial position. Ketone reduction with a bulky reducing agent would yield the desired *trans* diastereomer with greater selectivity than if the carbamate remained.

The first attempt at cleavage of the BOC group was done with the *in situ* formation of TMSI. Reaction of compound **82** with sodium iodide (NaI) and chlorotrimethylsilane (TMSCl) in acetonitrile at room temperature for 16 hours (Scheme 28) followed by an anhydrous workup gave a very messy crude NMR spectrum. The vinyl signals and methyl group of the side chain appeared to be present, but attempts to purify the product were unsuccessful by both silica gel and basic alumina. After several attempts with similar results, this route was abandoned.

Scheme 28: Attempted BOC Cleavage with TMSI

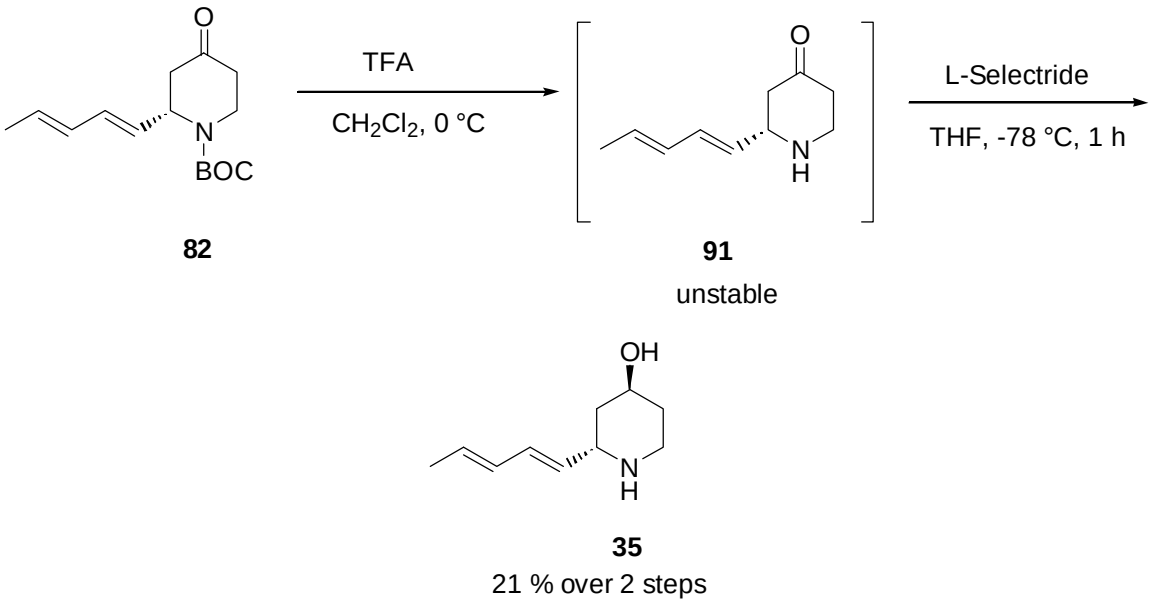


82 **91**

The BOC group was then removed with use of a strong acid. Eight equivalents of trifluoroacetic acid (TFA) was added at 0 °C to compound **51** in methylene chloride, and the reaction warmed to room temperature over 2 hours (Scheme 29). After work up of the reaction mixture, it was noticed that the material was darkening in color. By the time purification was complete, the product was virtually impossible to find. The reaction was repeated and a crude ^{1}H NMR taken immediately. The crude NMR showed that the desired compound **91** had been formed, however it appeared to be rapidly decomposing.

The crude amino ketone **91** was immediately subjected to a 1,2-reduction with L-Selectride in THF at –78 °C (Scheme 29). This reaction yielded the natural product in a 21% yield over the two steps. The *cis* isomer was not observed. The data obtained for our synthetic material compared favorably to the data reported for the natural product.[28]

Scheme 29: Initial Pathway to Streptomyces SS20846A



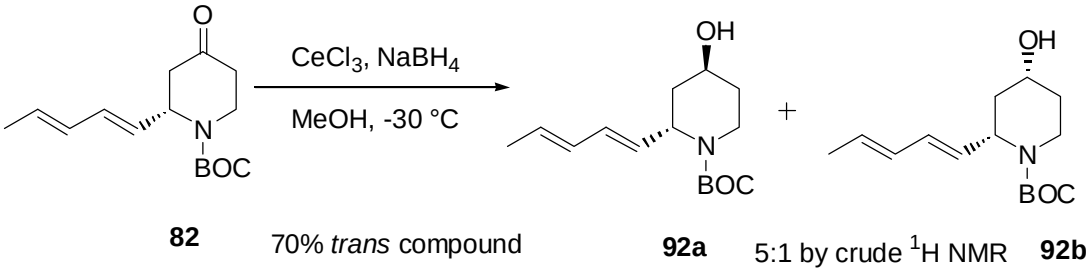
82

91
unstable

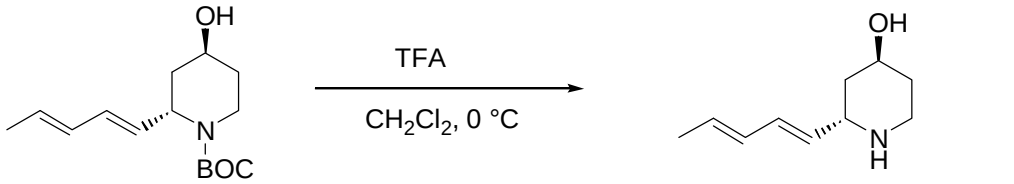
35
21 % over 2 steps

While this route was successful, it was plagued by an unstable intermediate and low yield. In order to overcome this problem, the ketone reduction would be carried out before the removal of the BOC group. With a variety of available options for 1,2-reductions, one needed to be chosen which would give a good selectivity of the *trans* **92a** over the *cis* **92b** isomer. Based on work done by Iwata and coworkers, [30] the Luche reduction was shown to give the best results. Treatment of piperidone **82** with cerium (III) chloride ($CeCl_3$) in methanol at -30 °C, followed by the addition of sodium borohydride ($NaBH_4$) yielded a 5:1 mixture of the *trans* to *cis* alcohols **92a** and **92b** (Scheme 30) by the crude ^{1}H NMR spectrum. The *trans* alcohol **92a** could be isolated in 70% yield by careful chromatography. Deprotection of the amine with TFA at 0 °C gave a 95% yield of Streptomyces SS20846A.

Scheme 30: Final Pathway to Streptomyces SS20846A



82 70% *trans* compound **92a** 5:1 by crude ^{1}H NMR **92b**



92a **35**

Streptomyces SS20846A

Spectral data for the synthesized compound compared very favorably to that reported in the isolation paper as shown in the table below.[28]

Table 4: Spectral Data for Streptomyces SS20846A

^{1}H – Isolation Paper (400 MHz)	^{1}H - Comins (300 MHz)	^{13}C - Isolation Paper (100 MHz)	^{13}C - Comins (75 Hz)
1.59 (td)		18.0	18.31
1.71 (m)		32.8	32.80
1.72 (m)	1.59 - 1.78 (m, 7H)	39.6	39.49
1.78 (d)		40.5	40.49
1.82 (dt)		52.8	52.88
2.93 (tdt)	2.92 (m, 1H)	64.8	64.91
3.13 (td)	3.10 (td, 1H, J = 11.8 and 3.0 Hz)	129.2	129.71
3.63 (t br)	3.60 (m, 1H)	130.5	131.06
4.20 (t br)	4.18 (m, 1H)	131.2	131.26
5.54 (dd)	5.53 (dd, 1H, J = 15.0 and 6.9 Hz)	133.2	132.80
5.69 (dq)	5.68 (m, 1H)		
6.04 (dd)	6.02 (m, 1H)		
6.16 (dd)	6.17 (m, 1H)		

Conclusion

This was the first chiral auxiliary mediated synthesis of Streptomyces SS20846A. This highly diastereoselective synthesis of Streptomyces SS20846A was accomplished in 6 steps with an overall yield of 26% from readily available 4-methoxy-3-TIPS-pyridine. This work clearly indicates the synthetic utility of N-acylpyridinium salt chemistry.

Experimental Section

All reactions were performed in oven-dried glassware under argon atmosphere. Tetrahydrofuran (THF) and toluene were distilled from sodium/benzophenone ketyl prior to use. Amines and pyridines were distilled from calcium hydride and stored under argon over 4 Å molecular sieves. Other solvents and reagents purchased from commercial sources were stored under argon and used directly. Melting points were obtained using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Radial preparative-layer chromatography (radial PLC) was performed on a Chromatotron (Harrison Associates, Palo Alto, CA). Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA). NMR spectra were obtained on either a Varian XL-300 or GE GN 300 spectrometer. IR spectra were collected on a Perkin-Elmer 7500 spectrometer. High resolution mass spectra were obtained using a JEOL HX11110HF mass spectrometer. Both diastereomeric and enantiomeric ratios of specific compounds were determined by HPLC analysis using either a Waters and Assoc. (Miliford, MA) 600 E multi solvent delivery system/486 tunable detector equipped with a μ-PORAIL analytical column or a Waters and Assoc. 440 absorbance detector/501 HPLC pump system equipped with either a Chiralcel OJ or OD column. Optical rotations were obtained using a Randolph Research (Flanders, NJ) Autopol III, automatic polarimeter.

(+/-)-(2S*)-[(1R*,2S*)-*trans*-(α-Cumyl)cyclohexyloxycarbonyl)-2-(2-keto-2-phenylethyl)-2,3-dihydro-4-pyridone (23):

TAS-F assisted addition

To a stirred solution of 0.025 mL (0.25 mmol) of 4-methoxypyridine in 5 mL of toluene cooled to -23 °C was added 0.25 mL (0.25 mmol) of a 1 M solution of the chloroformate of (+/-)TCC. The pyridinium salt was formed over 45 min. To 206 mg (0.75 mmol) of commercially available TAS-F in 2 mL THF cooled to -78 °C was added 0.154 mL (0.75 mmol) of 1-phenyl-1-(trimethylsilyloxy)ethylene. The orange solution was stirred for 25 min and transferred into the above pyridinium salt which was cooled to -78 °C. After 6 h, the reaction was quenched with 5 mL of sat'd aq oxalic acid, allowed to warm to rt, and stirred for 16 h. The aqueous layer was extracted with ether (3 x 5 mL). The combined organic extracts were washed with water (1 x 5 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil. Purification by radial PLC (5% EtOAc/hexanes) gave 38.7 mg (34%) of **23** as a white solid and 46.8 mg (51%) of **24** as a colorless oil: **(23)**: mp 156.5 - 157 °C ; IR(thin film) 2931, 1713, 1671, 1597, 1322, 1267, 1194 cm^{-1}; ^1H NMR (300 MHz, DMSO, 100 °C) δ 1.04 -1.26 (m, 10H), 1.63 (m, 2H), 1.80 (m, 2H), 2.15 (m, 2H), 2.64 (dd, 1H, *J* = 16.8 and 6.6 Hz), 2.95 (m, 1H), 3.20 (m, 1H), 4.37 (br s, 1H), 4.72 (m, 1H), 5.05 (d, 1H, *J* = 8.7 Hz), 6.98 (br s, 1H), 7.12 (m, 1H), 7.25 (m, 4H), 7.54 (m, 2H), 7.65 (m, 1H), 7.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 23.4, 24.7, 25.8, 28.7, 32.0, 38.3, 38.8, 39.3, 49.0, 58.6, 77.4, 105.5, 124.5, 127.5, 128.2, 132.8, 136.1, 141.2, 150.3, 151.1, 190.6, 196.5; Anal. calcd for $C_{29}H_{33}NO_4$: C, 75.79; H, 7.24; N,3.05. Found: C, 78.74; H, 7.23; N, 3.04. **(24)**: IR (thin film) 2934, 2860, 1755, 1642, 1495, 1445, 122, 1015, 765, 699; ^1H NMR (300 MHz,

$CDCl_3$) δ 1.09 (m, 4H), 1.31 (s, 3H), 1.41 (s, 3H), 1.61 (m, 3H), 2.03 (m,2H), 4.62 (dt, 1H, *J* = 10.4 and 4.3 Hz), 5.07 (d, 1H, *J* = 2.0 Hz), 5.38 (d, 1H, *J* = 2.0 Hz), 7.16 (m, 1H), 7.32 (m, 7H), 7.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 25.9, 26.0, 27.5, 28.0, 33.3, 40.5, 51.3, 80.3, 101.7, 125.2, 125.6, 128.2, 129.1, 134.5, 150.7, 152.5, 153.6;

Zn enolate addition

To a solution 0.1 mL (1 mmol) of 4-methoxypyridine in 9 mL toluene cooled to -23 °C was added 1 mL (1 mmol) of a 1 M solution of the chloroformate of (+/-)TCC. The pyridinium salt was formed over 40 min. To a freshly prepared solution of LDA (3.3 mmol) in 3 mL THF at –78 °C was slowly added 0.35 mL (3.0 mmol) of acetophenone. After 15 min, 3 mL of a 1 M solution of zinc(II) chloride was added, and the mixture was stirred for 15 min. The zinc enolate was transferred into the above pyridinium salt which was cooled to –78 °C . After 2 h the reaction was quenched with 7 mL of 10% HCl, and hydrolysis was followed by TLC. The aqueous layer was extracted with ether (3 x 10 mL). The combined organic extracts were washed with water (1 x 10 mL) and brine (1 x 10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil. Purification by radial PLC (20% EtOAc/hexanes) gave 357 mg (78%) of **23** as a white solid. mp 156-157 °C.

(+/-)-(2S*)-[(1R*,2S*)-*trans*-(α-Cumyl)cyclohexyloxycarbonyl)-2-(2-phenylsulfonylethynyl)-2,3-dihydro-4-pyridone (29):

TAS-F assisted addition

To a stirred solution of 0.035 mL (0.35 mmol) of 4-methoxypyridine in 8 mL of toluene cooled to –23 °C was added 0.35 mL (0.35 mmol) of a 1 M solution of the chloroformate

of (+/-)TCC. After 45 min, the reaction was cooled to –78 °C, and 250 mg (1.05 mmol) of 1-phenylsulfonyl-2-(trimethylsilyl)ethyne in 2.0 mL THF was added. After 2 h, the reaction mixture was quenched with sat'd oxalic acid, allowed to warm to rt, and stirred for 16 h. The reaction was neutralized by the addition of aq. sat'd $NaHCO_3$ and filtered through Celite. The aqueous layer was extracted with ether (3 x 10 mL). The combined organic extracts were washed with water (1 x 10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a brown oil. Purification by radial PLC (20% EtOAc/hexanes) gave 28 mg (16%) of **29** as a yellow oil: IR(thin film) 2927, 2351, 1726, 1680, 1600, 1325, 1163 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13-1.36 (m, 6H),1.72-1.80 (m, 3H), 2.38-2.50 (m, 2H), 2.67 (m, 1H), 3.24 (m, 1H), 4.83 (m, 2H), 5.26 (d, 1H, *J* = 7.9 Hz), 5.43 (m, 1H), 7.09-8.03 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 24.8, 26.0, 26.7, 29.9, 31.8, 33.2, 39.4, 43.9, 44.5, 51.0, 79.4, 107.3, 125.3, 127.6, 128.4, 128.9, 129.6, 134.7, 141.7, 150.8, 153.4, 189.4; HRMS Calcd. for $C_{29}H_{31}NO_3S$: 506.2001; Found: 506.1992.

Organolithium addition

To a solution of 0.04 mL (0.37 mmol) of 4-methoxypyridine in 8 mL of toluene at -23 °C was added 0.37 mL (0.37 mmol) of a 1 M solution of the chloroformate of (+/-)TCC. The reaction was stirred for 50 min. To a freshly made solution of LDA (1.12 mmol) in 4 mL of THF at -78 °C was added a solution of 186 mg (1.12 mmol) of ethynesulfonyl benzene **30** in 1 mL of THF. After 10 min, the red anion was transferred into the above pyridinium salt which was cooled to -78 °C. After 2 h, the reaction was quenched with sat'd oxalic acid, allowed to warm to rt, and stirred for 16 h. The reaction was neutralized by the addition of aq. sat'd $NaHCO_3$ and filtered through Celite. The aqueous layer was

extracted with ether (3 x 10 mL). The combined organic extracts were washed with water (1 x 10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a brown oil. Purification by radial PLC (20% EtOAc/Hexanes) gave 50 mg (27%) of **29** as a yellow oil.

(+/-)-(2S*)-[(1R*,2S*)-*trans*-(α-Cumyl)cyclohexyloxycarbonyl)-2-(2-phenylethynyl)-2,3-dihydro-4-pyridone (34): To a stirred solution of 0.04 mL of 4-methoxypyridine (0.4 mmol) in 7.5 mL of toluene cooled to –23 °C was added 0.4 mL (0.4 mmol) of a 1 M solution of the chloroformate of (+/-)TCC. The pyridinium salt was stirred for 1 h at –23 °C. To 0.13 mL of phenyl acetylene (1.2 mmol) in 2.5 ml of THF cooled to –78 °C was added either *n*-BuLi (1.2 mmol) or freshly prepared LDA (1.2 mmol). The pale yellow anion was stirred for 30 min and then transferred into the above pyridinium salt solution which had been cooled to –78 °C. After stirring for 1 h, the reaction mixture was quenched with aqueous 10% HCl, allowed to warm to rt and stirred for 30 min. The aqueous layer was extracted with ether (3 x 10 mL). The combined organic extracts were washed with brine (1 x 10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a white solid. The solid was recrystallized from MeOH to give **34** as a white solid: mp 164 – 165 °C ; IR(thin film) 2958, 2927, 2351, 1718, 1672, 1605, 1327, 1209, 1178 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (s, 3H), 1.35 (s, 3H), 1.77 (d, 2H, *J* = 11.3), 1.94 (s, 1H), 2.06 (m, 1H), 2.27 (m, 2H), 2.54 (m, 1H), 3.58 (m, 1H), 4.90 (m, 2H), 5.33 (m, 1H), 5.49 (m, 1H), 5.72 (m, 1H), 7.13-7.45 (m, 10H), 7.67 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 24.9, 26.1, 26.9, 31.3, 33.6, 39.5, 41.4, 44.8, 45.0, 45.3,

51.2, 78.7, 85.1, 107.0, 122.2, 125.2, 128.5, 128.9, 132.0, 141.9, 152.9, 191.6; Anal. calcd for $C_{29}H_{31}NO_3$: C,78.88; H, 7.08; N, 3.17. Found: C, 78.72; H, 7.06; N, 3.13.

(+/-)-(2S*)-[(1R*,2S*)-*trans*-(α-Cumyl)cyclohexyloxycarbonyl)-2-ethylpropiolate-2,3-dihydro-4-pyridone (32): To a stirred solution of 0.04 mL of 4-methoxypyridine (0.4 mmol) in 7.5 mL of toluene cooled to –23 °C was added 0.4 mL (0.4 mmol) of a 1 M solution of the chloroformate of (+/-)TCC. The pyridinium salt was stirred for 1 h at –23 °C. To 0.12 mL of ethyl propiolate (1.2 mmol) in 2.5 mL of THF cooled to –78 °C was added either *n*-BuLi (1.2 mmol in hexane) or freshly prepared LDA (1.2 mmol in THF). The pale yellow anion was stirred for 30 min and then transferred into the above pyridinium salt solution which had been cooled to –78 °C. After stirring for 1 h, the reaction mixture was quenched with aqueous 10% HCl, allowed to warm to rt, and stirred for 30 min. The aqueous layer was extracted with ether (3 x 10 mL). The combined organic extracts were washed with brine (1 x 10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil. Radial PLC (20% EtOAc/hexanes) gave an inseparable mixture of diastereomers of dihydropyridone **32** as a yellow oil: IR(thin film) 731, 1005, 1190, 1211, 1253, 1295, 1332, 1369, 1601, 1675, 1712, 1728, 2237, 2934, 2966 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16-1.33 (m, 9H), 1.52-1.98 (m, 3H), 2.11 (d, 1H, *J* = 10.2 Hz), 2.18-2.28 (m, 1H), 2.43-2.59 (m, 1H), 2.68-2.75 (m, 1H), 3.33 (m, 1H), 4.15 (m, 1H) and 4.25 (m, 1H), 4.87 (m, 1H), 5.32 (d, 1H, *J* = 7.2 Hz) and 5.38 (d, 1H, *J* = 6.0 Hz), 5.59 (m, 1H), 7.12-7.29 (m, 5H), 7.64 (d, 1H, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 20.7, 24.7, 25.9, 26.7, 31.5, 33.2, 39.3, 40.0, 43.7, 44.3, 50.9, 51.2, 62.3, 79.0, 82.5, 82.6, 106.8, 107.2, 124.8, 125.0, 125.4, 128.1,

128.2, 128.7, 141.2, 141.7, 150.5, 151.0, 152.7, 153.1, 190.1; HRMS Calcd. for $C_{26}H_{31}NO_5$: 438.2280; Found: 438.2267.

(-)-(2*S*)-1-[(2*R*,3*S*)-*trans*-2-(α-Cumyl)cyclohexyloxycarbonyl]-2-(1',3'-penta-*trans*,*trans*-dienyl)-5-triisopropylsilyl-2,3-dihydro-4-pyridone (85): To a stirred solution of 929 mg (6.3 mmol) of a 90:10 (*E*,*E*):(*Z*,*E*) mixture of 1-bromo-1,3-pentadiene[35] **80** in 40 mL of THF/pentane (1:1) cooled to -120 °C (pentane/liquid N_2) was added dropwise *t*-BuLi (7.4 mL, 12.6 mmol, 1.7 M in pentane). The solution was stirred at -120 °C for 1 h and then warmed to -90 °C. Lithium 2-thienylcyanocuprate (25.2 mL, 6.3 mmol, 0.25 M in THF) was added dropwise, and the dark orange solution was stirred for 1 h at -78 °C. To a stirred solution of 557 mg (2.1 mmol) of 4-methoxy-3-triisopropylsilylpyridine in 10 mL of toluene at -23 °C was added 2.1 mL (2.1 mmol) of a 1 M solution of the chloroformate of (-)-*trans*-(α-cumyl)cyclohexanol ((-)-TCC). The pyridinium salt was formed over 1 h, cooled to -78 °C, and transferred via cannula into the above higher order cuprate. After 2 h, the reaction was quenched with 15 mL of satd. oxalic acid, allowed to warm to rt, and stirred for 16 h. The crude reaction mixture was filtered through Celite, and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic extracts were washed with sat'd. $NaHCO_3$ (1 x 10 mL), water (1 x 10 mL), and brine (1 x 10 mL), and were dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil. Purification by radial PLC (5% EtOAc/hexanes) yielded 743 mg (63%) of **85** as a white foam: $[\alpha]_D^{23}$ -1.14 (*c* 0.35, $CHCl_3$); IR (thin film) 2934, 2852, 1715, 1658, 1572, 1380, 1323, 1290, 1241 cm^{-1}; ^1H

NMR (300 MHz, $CDCl_3$) δ 0.98 - 1.36 (m, 34H), 1.69 (d, 3H, *J* = 6.6 Hz), 2.22 (m, 2H), 2.45 (m, 1H), 3.14 (m, 1H), 4.81 (m, 1H), 5.11 (m, 1H), 5.61 (m, 2H), 5.84 (m, 1H), 7.12 (m, 1H), 7.30 (m, 4H), 7.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 11.4, 11.8, 18.1, 18.9, 18.9, 19.4, 21.3, 24.6, 24.7, 26.0, 26.9, 27.1, 27.3, 31.1, 33.5, 39.5, 41.3, 51.2, 52.9, 78.0, 110.5, 124.9, 125.2, 125.4, 127.9, 128.2, 130.3, 130.4, 131.9, 147.4, 152.3, 196.2. HRMS Calcd. for $C_{24}H_{28}NO_3$: 365.2117; Found: 365.2128.

(+)-(2*S*)-(1',3'-Penta-*trans*,*trans*-dienyl)-2,3-dihydro-4-pyridone (89): To a stirred solution of 1.6 g (2.84 mmol) of **85** in 20 mL of anhydrous methanol was added 22.8 mL (11.4 mmol) of a 0.5 M solution of sodium methoxide. The mixture was refluxed for 6.5 h. After cooling to rt, 20 mL of sat'd. aqueous oxalic acid was added, and the solution was stirred for 16 h at rt. The solution was neutralized with sat'd. $NaHCO_3$, and the crude reaction mixture was concentrated to a solid. The residue was taken up in EtOAc and filtered through a plug of Celite. The organic washings were dried over $MgSO_4$, and the solvent was removed under reduced pressure to give a yellow oil. Purification by radial PLC (5% MeOH/CH_2Cl_2) yielded 356 mg (77%) of dihydropyridone **89** as a colorless oil: $[\alpha]_D^{23}$ +277 (*c* 0.52, $CHCl_3$); IR (thin film) 3248, 3021, 1615, 1567, 1523, 1400, 1233, 1211, 990 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.74 (d, 3H, *J* = 6.8 Hz), 2.45 (d, 2H, *J* = 7.9 Hz), 4.18 (m, 1H), 4.82 (bs, 1H), 5.02 (d, 1H, *J* = 7.2 Hz), 5.57 (dd, 1H, *J* = 15.1 and 7.7 Hz), 5.75 (m, 1H), 6.02 (m, 1H), 6.21 (m, 1H), 7.15 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3, 42.9, 56.1, 99.8, 127.9, 130.3, 131.8, 133.4, 150.9, 192.6. HRMS Calcd for $C_{10}H_{13}NO$: 163.0997; Found: 163.0997.

(+)-(2*S*)-1-(*tert*-Butoxycarbonyl)-2-(1',3'-penta-*trans*,*trans*-dienyl)-2,3-dihydro-4-pyridone (90): To a solution of 44.8 mg (0.27 mmol) of **89** in 5 mL of THF was added 203 mg (0.93 mmol) of di-*tert*-butyl dicarbonate, 18 mg (0.135 mmol) of DMAP , and 58 mg (0.54 mmol) of NEt_3. The reaction mixture was stirred overnight at rt. The reaction was quenched with 10 mL of deionized water, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give a yellow oil. Purification by radial PLC (20 % EtOAc/hexanes) yielded 65.5 mg (92%) of **90** as a colorless oil: $[\alpha]_D^{23}$ +117 (*c* 2.23, $CHCl_3$); IR (thin film) 2968, 1720, 1670, 1604, 1333, 1152, 981 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 9H), 1.73 (d, 3H, *J* = 6.4 Hz), 2.49 (d, 1H, *J* = 16.5 Hz), 2.90 (dd, 1H, *J* = 16.4 and 6.9 Hz), 5.05 (m, 1H), 5.28 (d, 1H, *J* = 8.3 Hz), 5.53 (dd, 1H, *J* = 14.9 and 6.3 Hz), 5.71 (m, 1H), 5.93 – 6.13 (m, 2H), 7.75 (d, 1H, *J* = 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 28.2, 40.6, 54.3, 83.5, 106.5, 125.0, 130.3, 131.4, 132.9, 142.2, 151.3, 192.7. HRMS Calcd for $C_{15}H_{21}NO_3$: 263.1521; Found: 263.1526.

(-)-(2S)-1-(*tert*-Butoxycarbonyl)-2-(1',3'-penta-*trans*,*trans*-dienyl)-4-piperidone (82): To a stirred solution of 55 mg (0.21 mmol) of **90** in 8 mL THF cooled to -78 °C was added dropwise 0.23 mL (0.23 mmol) of a 1 M solution of L-Selectride. After stirring for 1 h, the reaction was quenched with 8 mL of brine, warmed to rt, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure to give a colorless oil. Purification by radial PLC (20% EtOAc/hexanes) yielded 47 mg (85%) of **82** as a colorless oil: $[\alpha]_D^{23}$ -58 (*c* 0.46, $CHCl_3$); IR (thin film) 2971, 1720, 1691, 1404, 1361,

1308, 1231, 1160 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H), 1.74 (d, 3H, *J* = 6.4 Hz), 2.30 - 2.72 (m, 5H), 3.30 (m, 1H), 4.15 (m, 1H), 5.16 (m, 1H), 5.44 (m, 1H), 5.71 (m, 1H), 6.01 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 18.3, 28.6, 39.1, 40.7, 44.4, 52.9, 80.7, 128.4, 130.6, 131.0, 133.0, 154.8, 207.9; HRMS Calcd for $C_{15}H_{23}NO_3$: 266.1756 $[M+H]^+$; Found: 266.1759 $[M+H]^+$.

(-)-(2S)-1-(*tert*-Butoxycarbonyl)-2-(1',3'-penta-*trans*,*trans*-dienyl)-4-piperinol (92a): To a stirred solution of 25 mg (0.094 mmol) of **82** in 2 mL of anhydrous methanol at -30 °C was added 38 mg (0.10 mmol) of $CeCl_3 \cdot 7H_2O$. After the solid dissolved, 5 mg (0.10 mmol) of $NaBH_4$ was added and reaction was stirred for 1 h. The reaction mixture was quenched with deionized water and warmed to rt. The crude material was concentrated under reduced pressure, dissolved in CH_2Cl_2, and filtered through a pipet column of $MgSO_4$ and Celite. The solvent was removed under reduced pressure to give a colorless oil. Purification by radial PLC (50% EtOAc/hexanes) yielded 17.5 mg (70%) of **92a** as a colorless oil: $[\alpha]_D^{23}$ -6.1 (*c* 0.46, $CHCl_3$); IR (thin film) 3422, 2959, 1688, 1663, 1411, 1381, 1255, 1165 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 - 1.76 (m, 12 H), 1.75 (d, 3H, *J* = 6.5 Hz), 1.89 (m, 1H), 2.04 (m, 1H), 2.87 (m, 1H), 3.87 (m, 1H), 4.05 (m, 1H), 4.96 (br s, 1H), 5.46 (dd, 1H, *J* = 14.2 and 4.7), 5.66 (m, 1H), 6.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3, 28.6, 35.3, 28.7, 52.3, 65.8, 77.4, 80.0, 129.1, 129.7, 131.0, 131.5, 155.2.

Streptomyces SS20846A (35): To a stirred solution of 6 mg (0.022 mmol) of **92a** in anhydrous CH_2Cl_2 at 0 °C was added 0.02 mL (0.25 mmol) of TFA. After 30 min, the

reaction was brought to a neutral pH with the addition of sat'd. $NaHCO_3$ and concentrated under reduced pressure to give a white solid. The crude material was dissolved in CH_2Cl_2, filtered through a pipet column of $MgSO_4$ and Celite, and concentrated under reduced pressure to provide an oil. Purification on silica gel (10% MeOH/CH_2Cl_2) afforded 2.8 mg (95%) of Streptomyces SS20846A as a colorless oil: $[\alpha]_D^{23}$ -12 (*c* 0.3, $CHCl_3$) (lit.[29] $[\alpha]_D^{20}$ -15 (*c* 1, $CHCl_3$)); IR (thin film) 3416, 2956, 1638, 1254, 799 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59 - 1.78 (m, 7H), 2.36 (br s, 2H), 2.92 (m, 1H), 3.10 (td, 1H, *J* = 11.8 and 3.0 Hz), 3.60 (m, 1H), 4.18 (m, 1H), 5.53 (dd, 1H, *J* = 15.0 and 6.9 Hz), 5.68 (m, 1H), 6.02 (m, 1H), 6.17 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3, 21.8, 39.5, 40.5, 52.9, 64.9, 129.7, 131.1, 131.3, 132.8.

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(3) Molecular modeling was performed using PCMODEL (Serena Software, Bloomington, IN) and Chem 3D (Cambridge Scientific Computing, Inc., Cambridge, MA).

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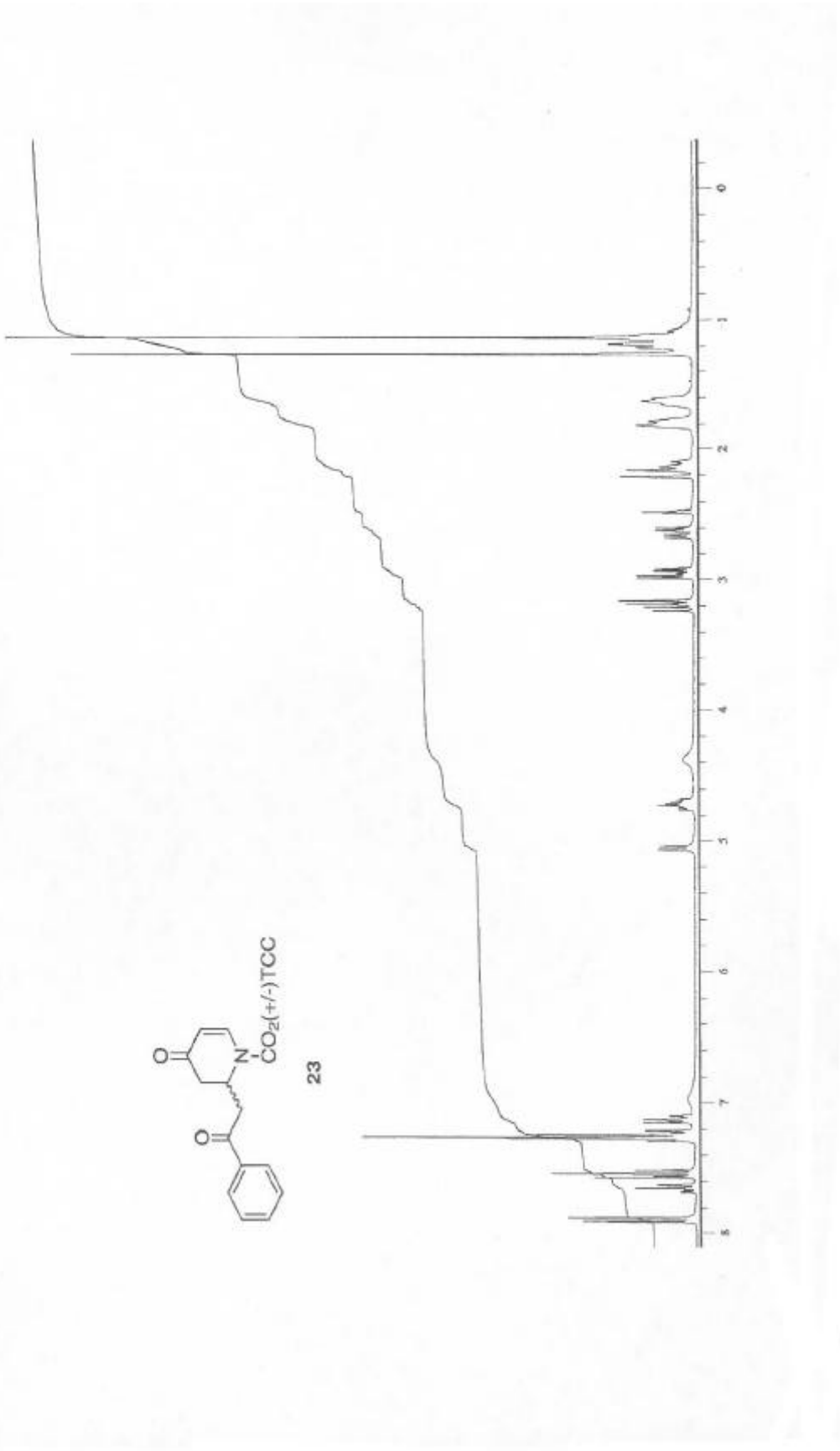
Appendix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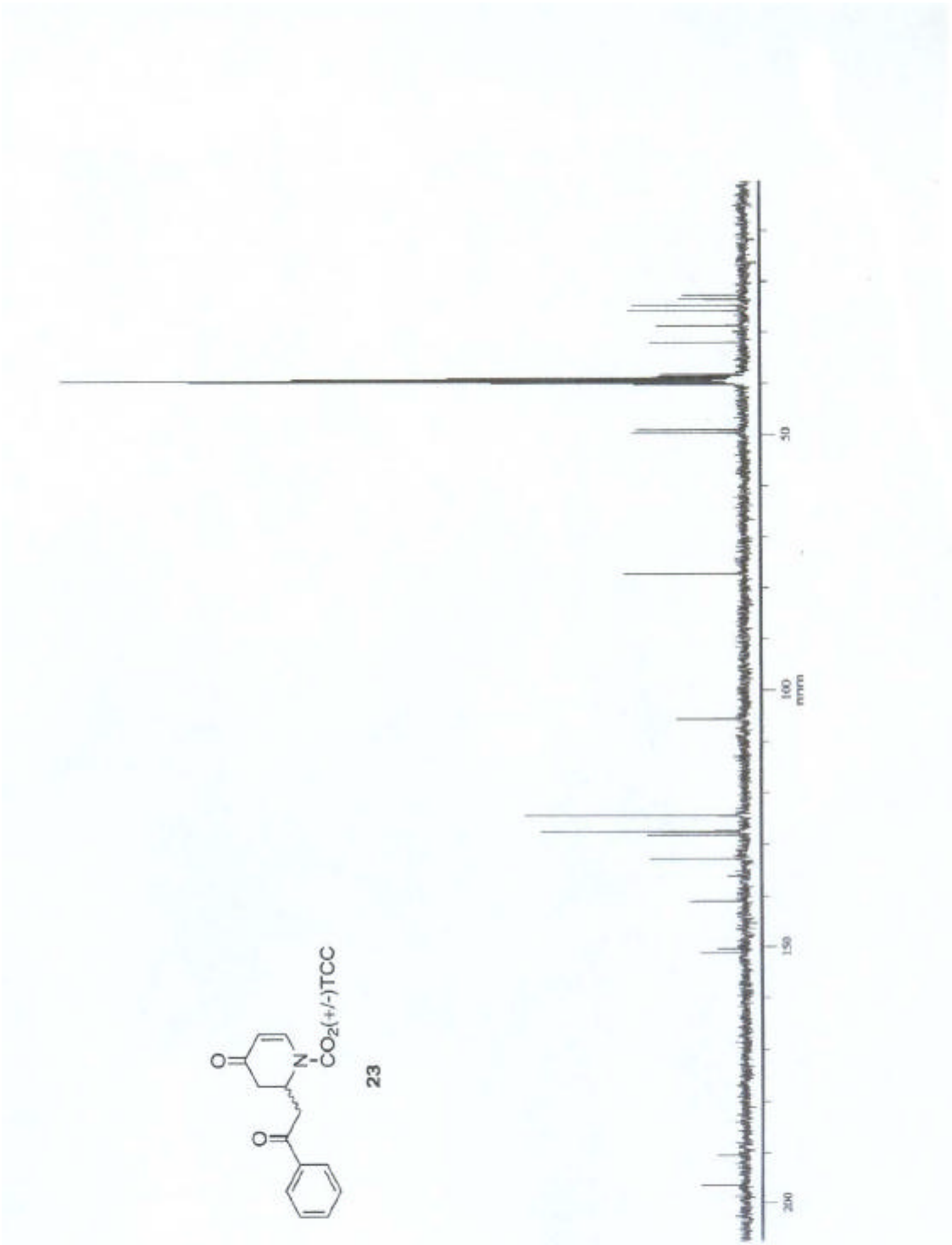
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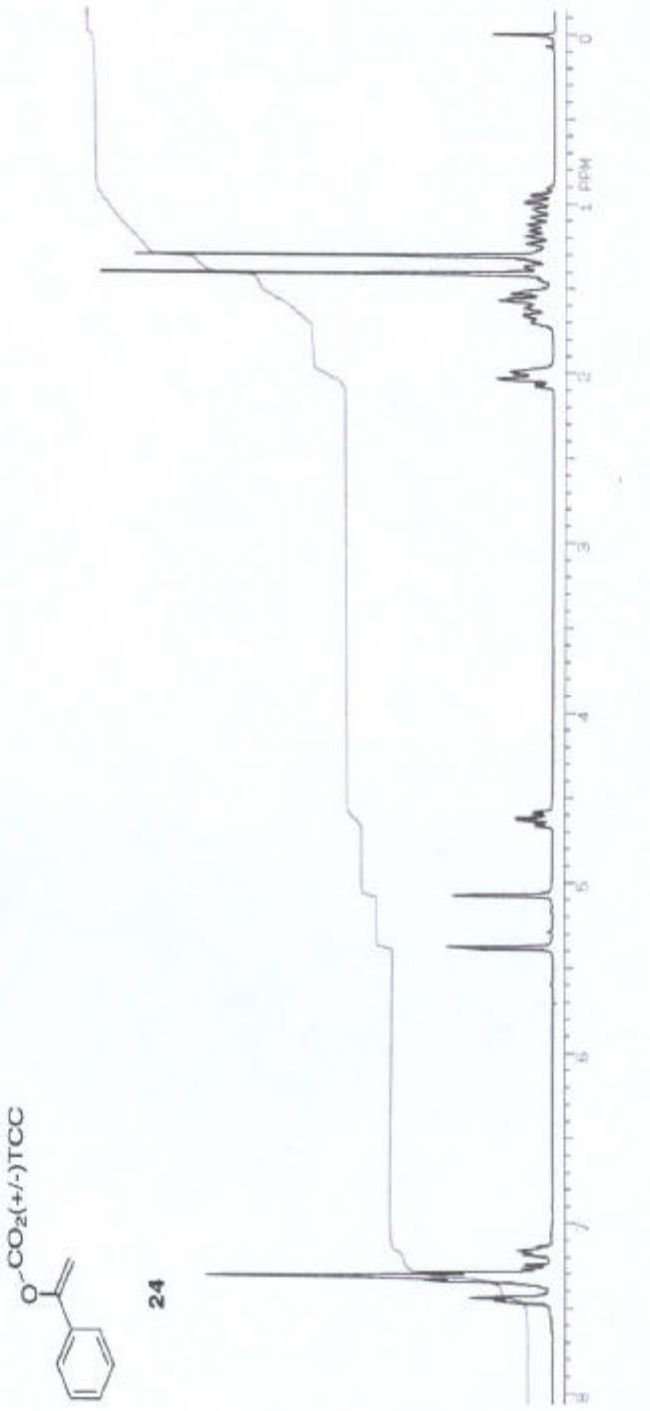

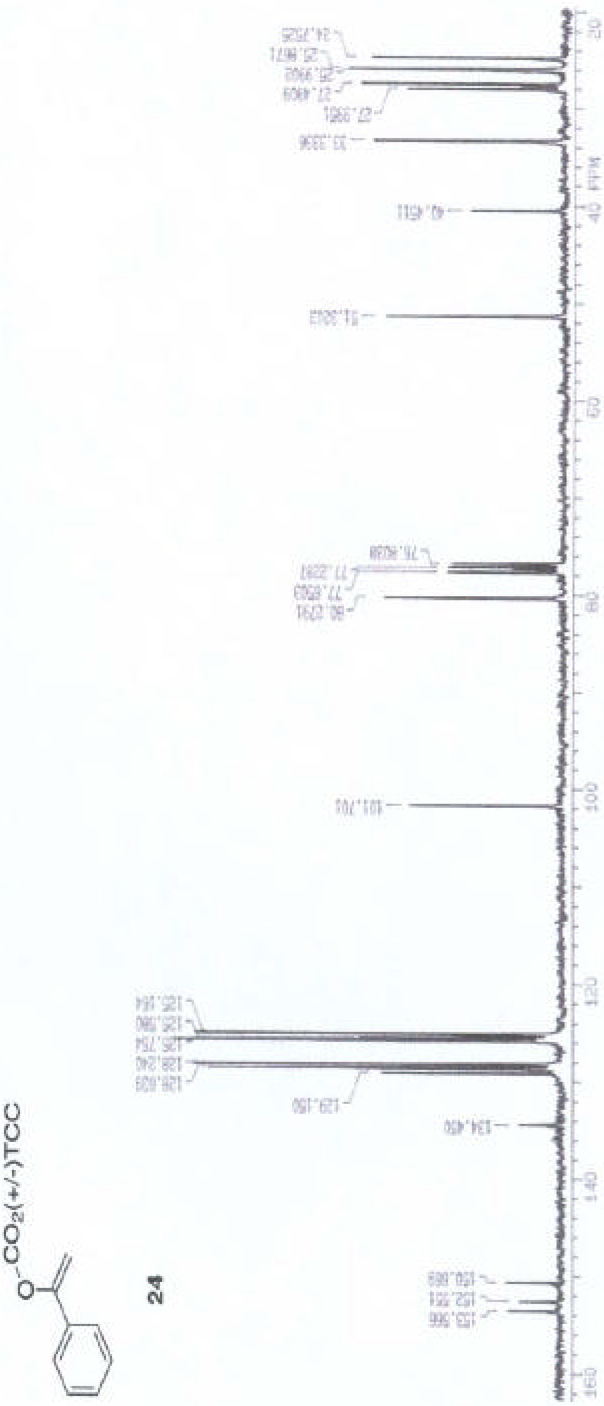

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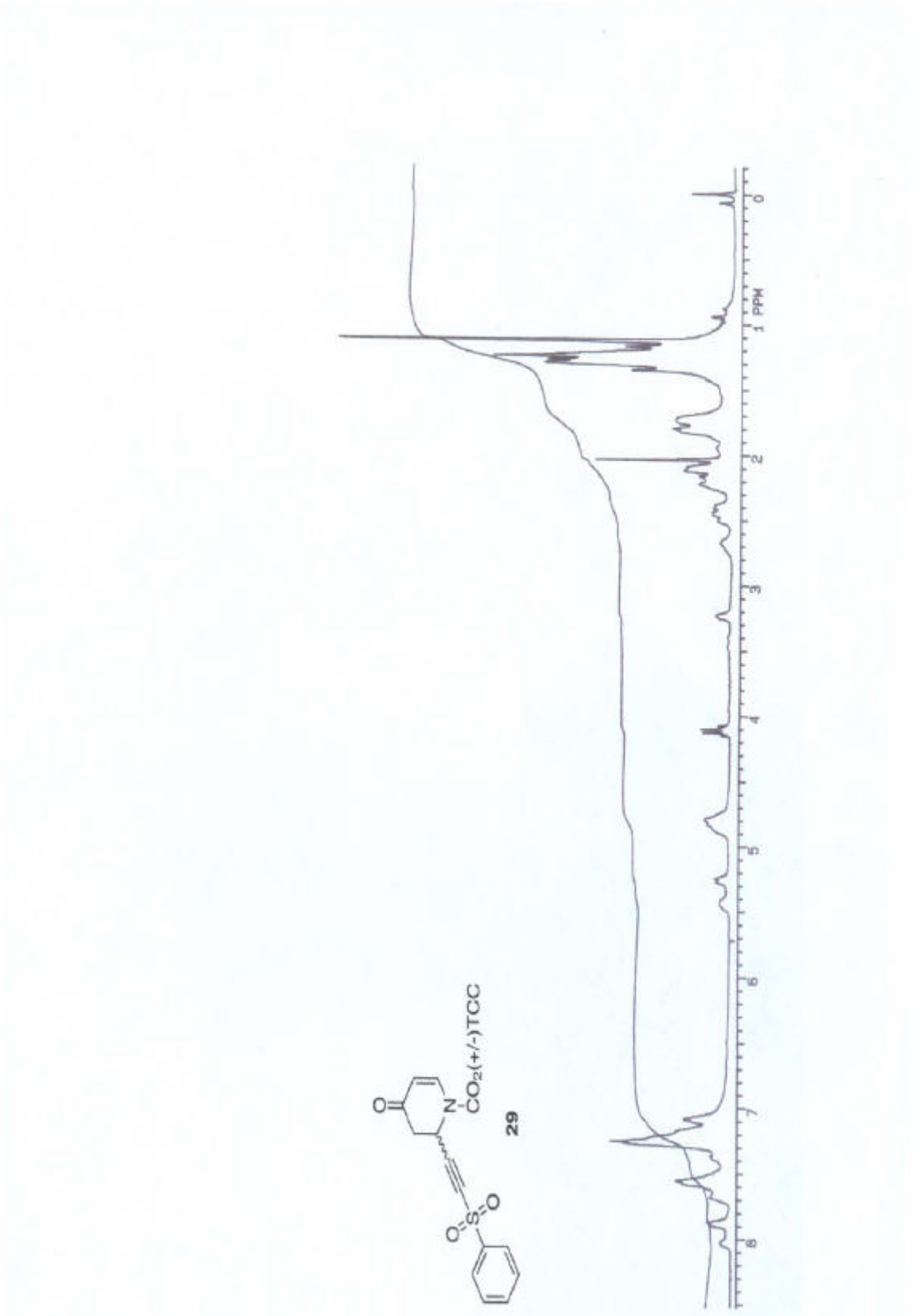
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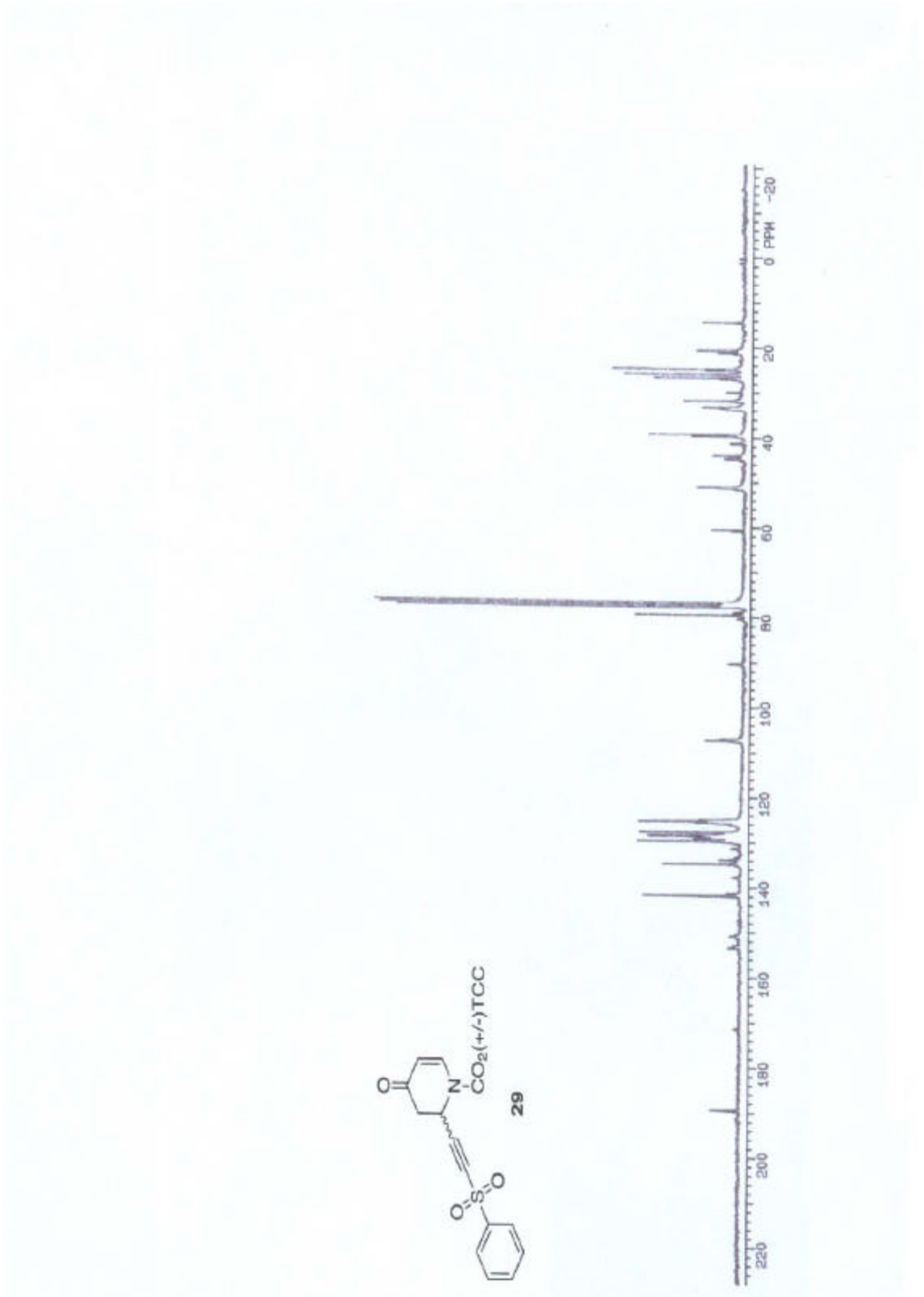
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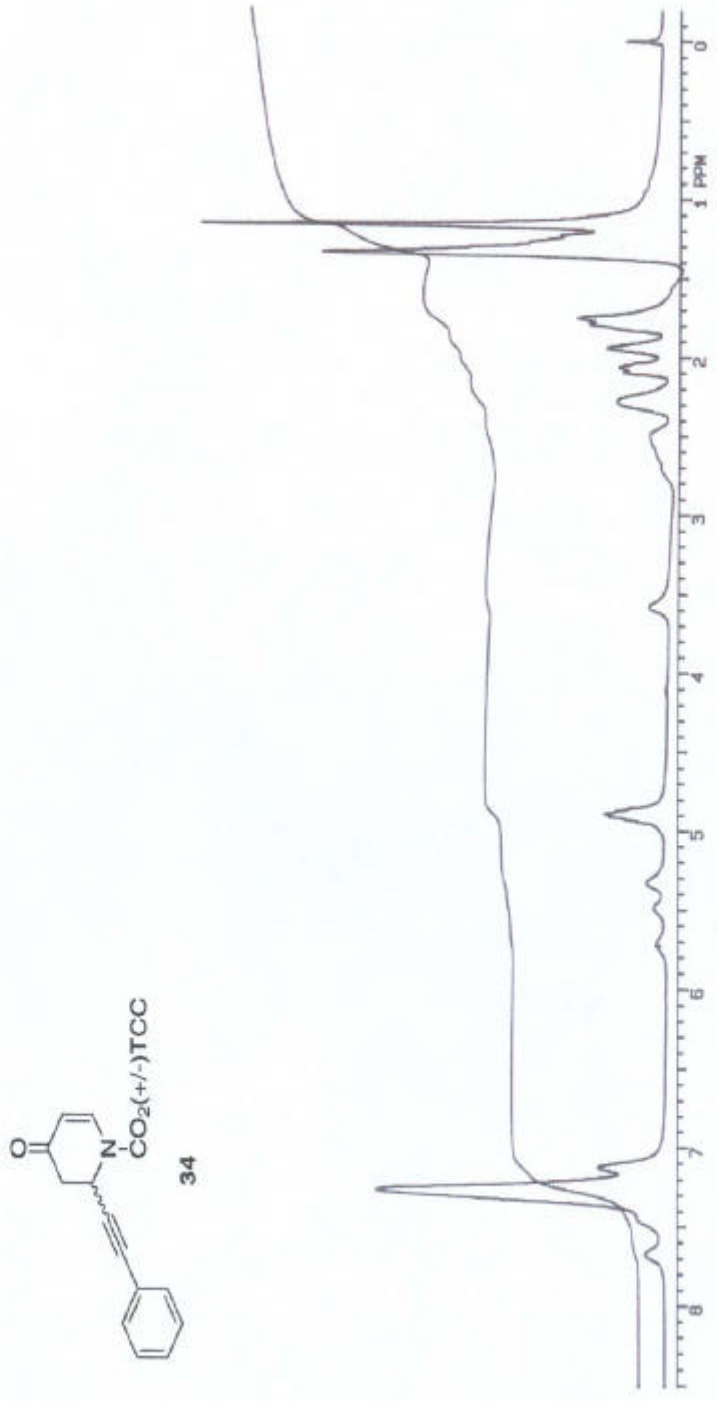
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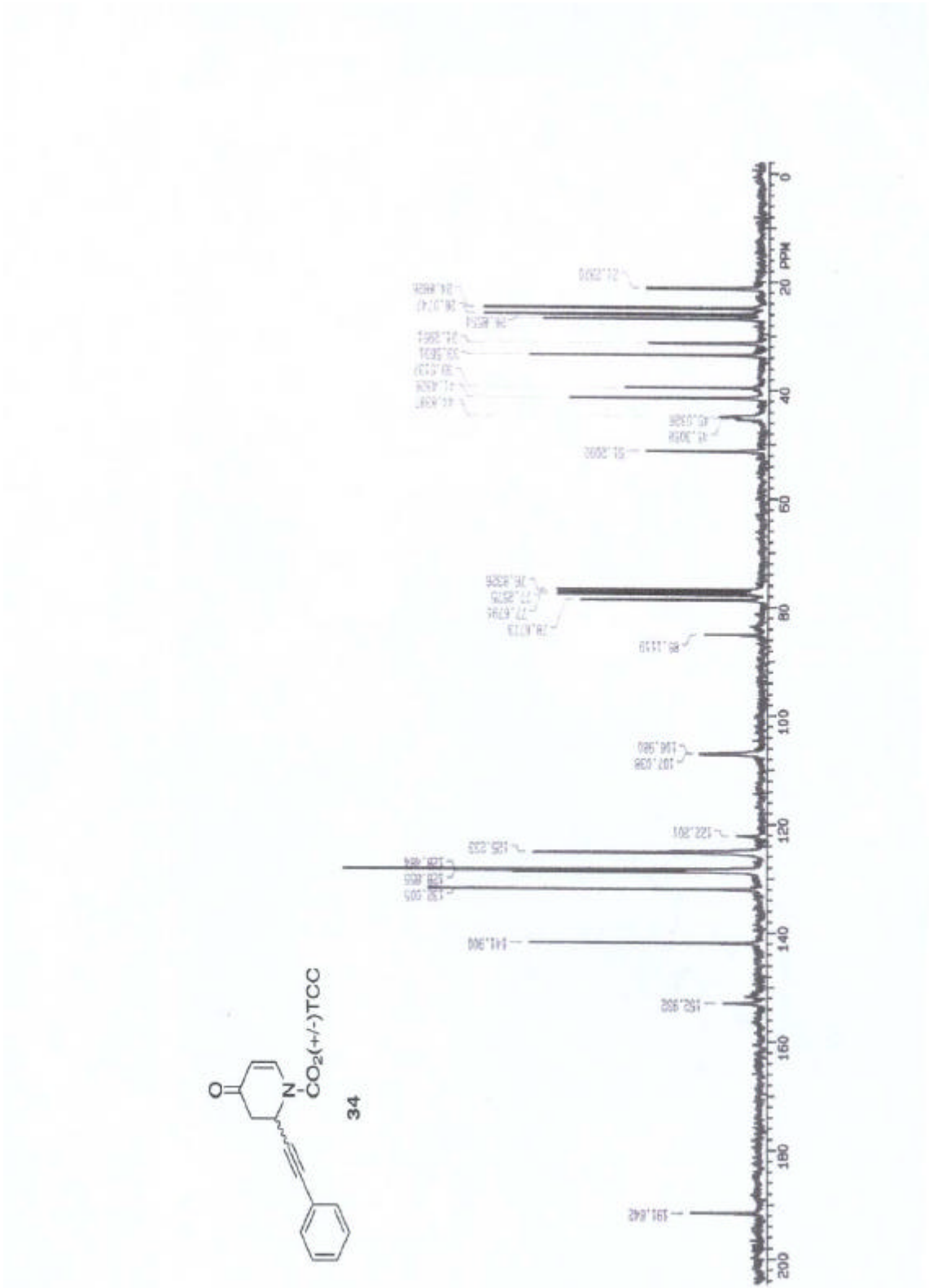
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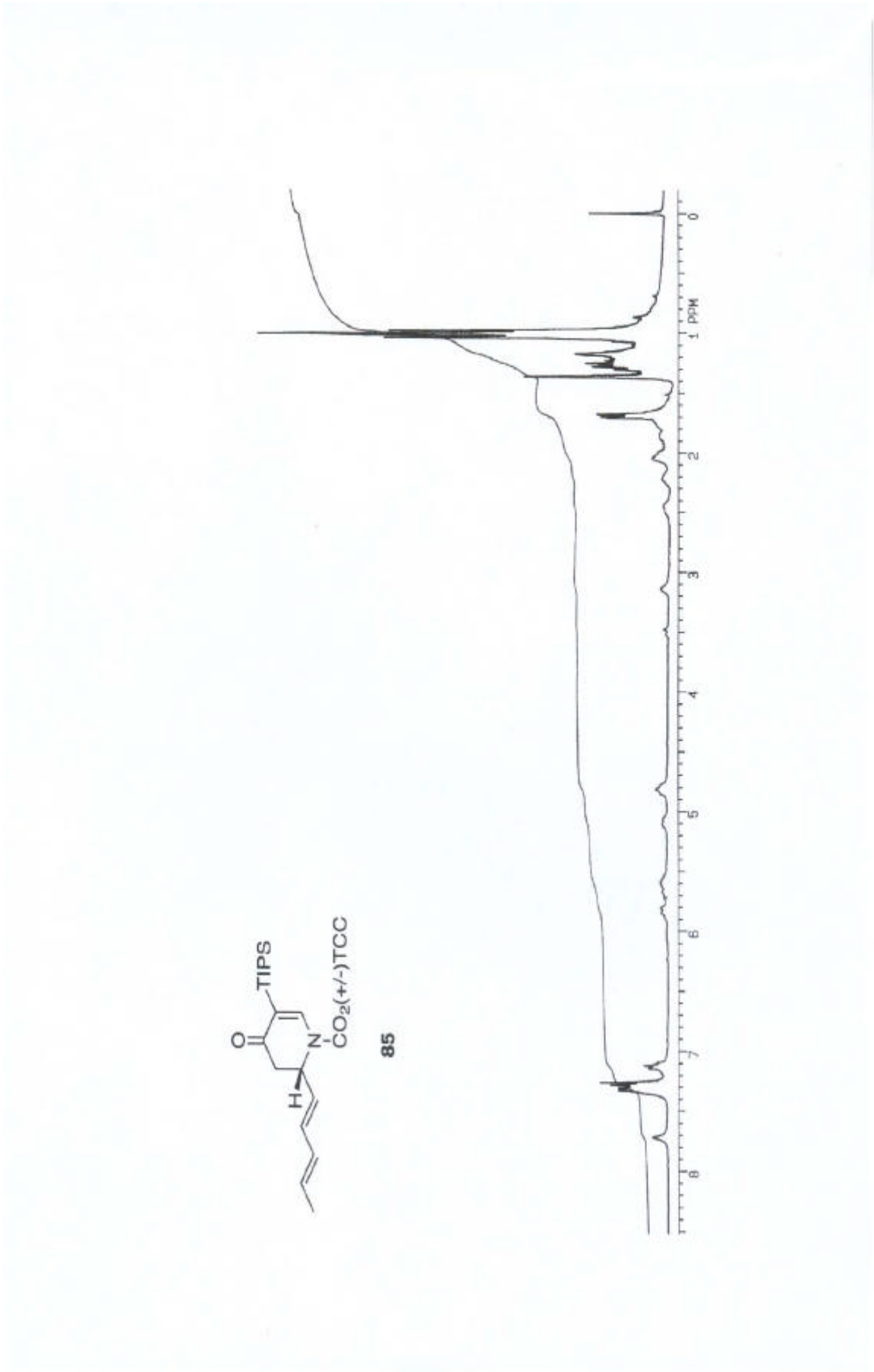
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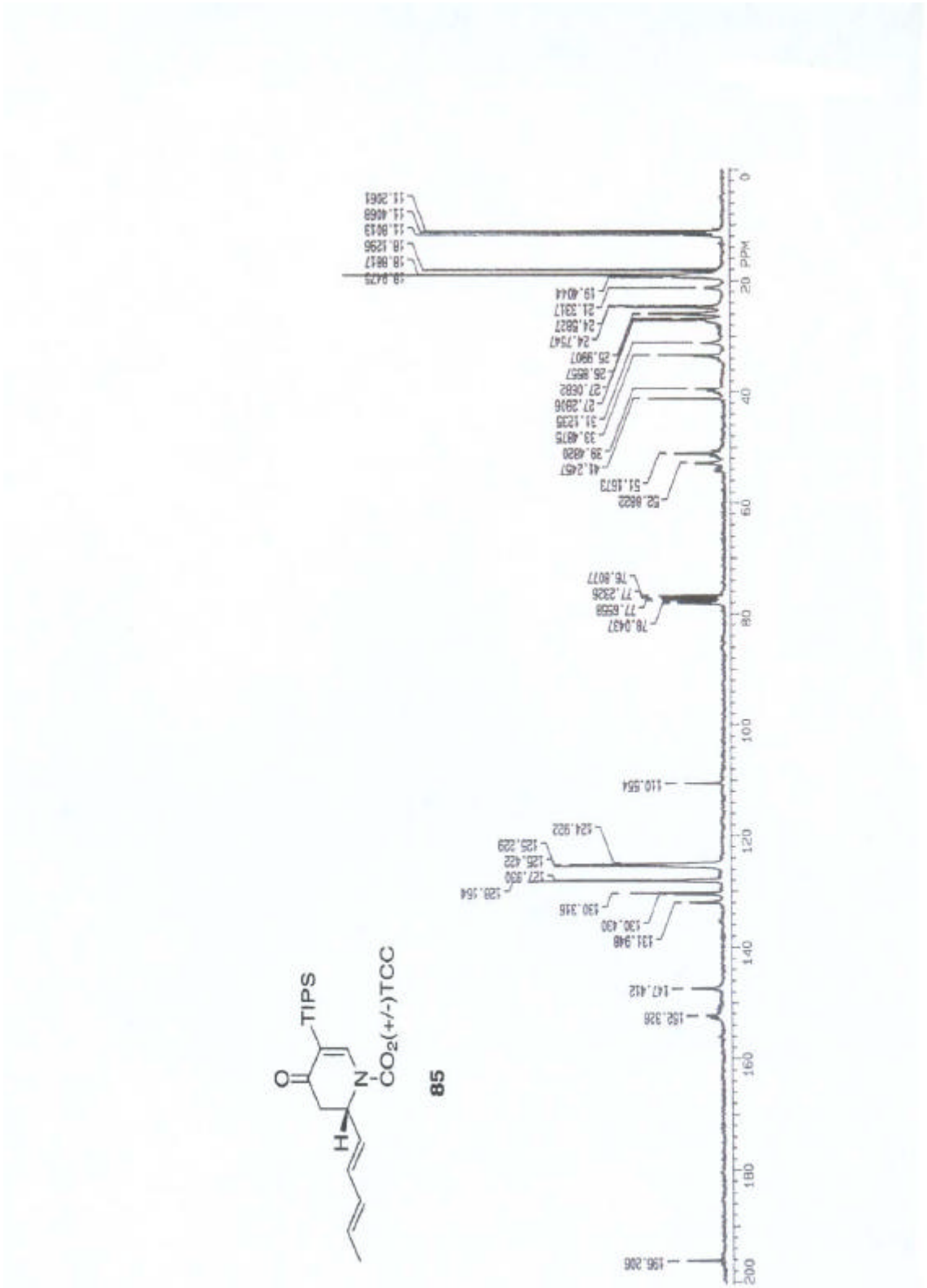
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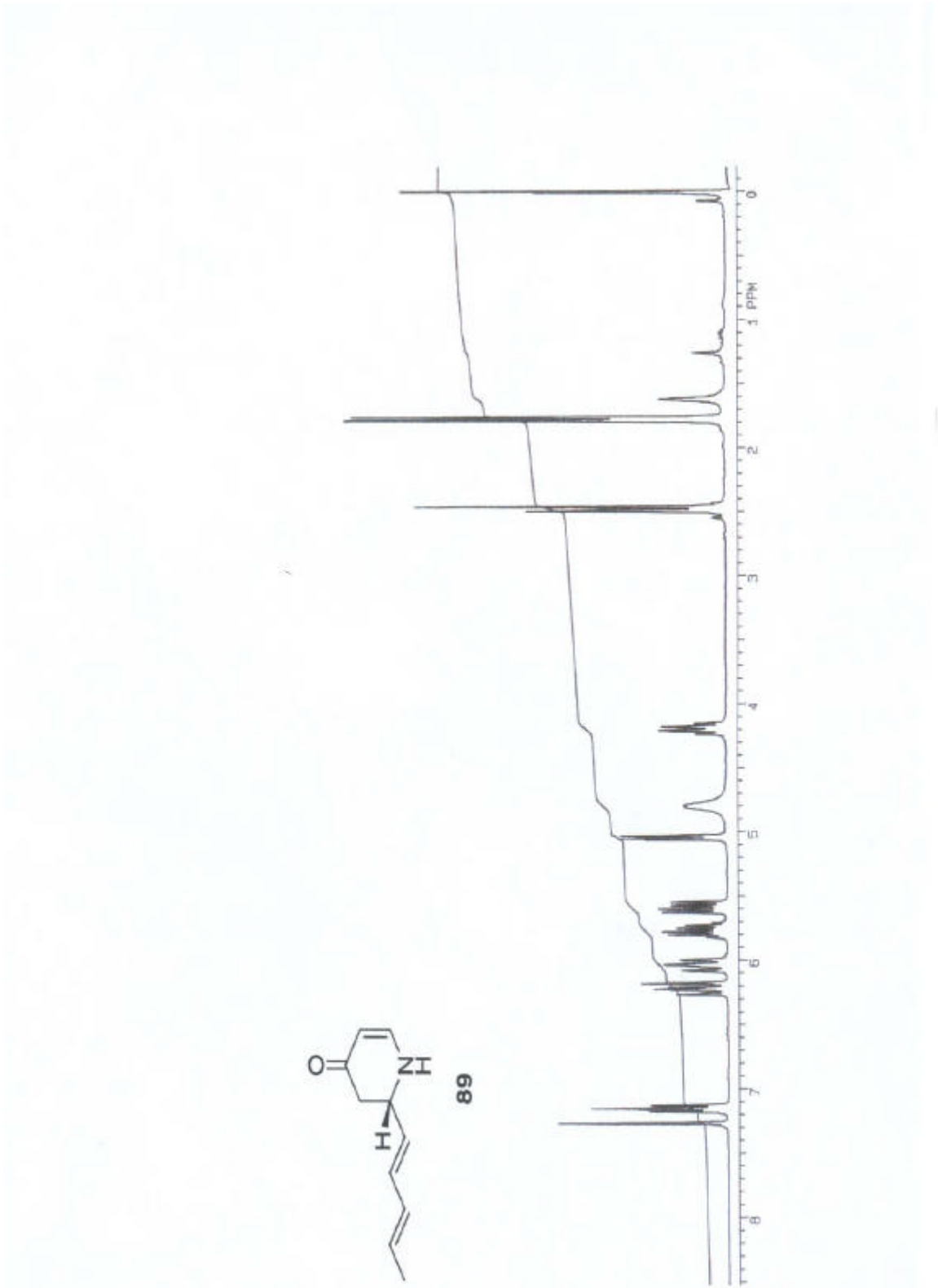
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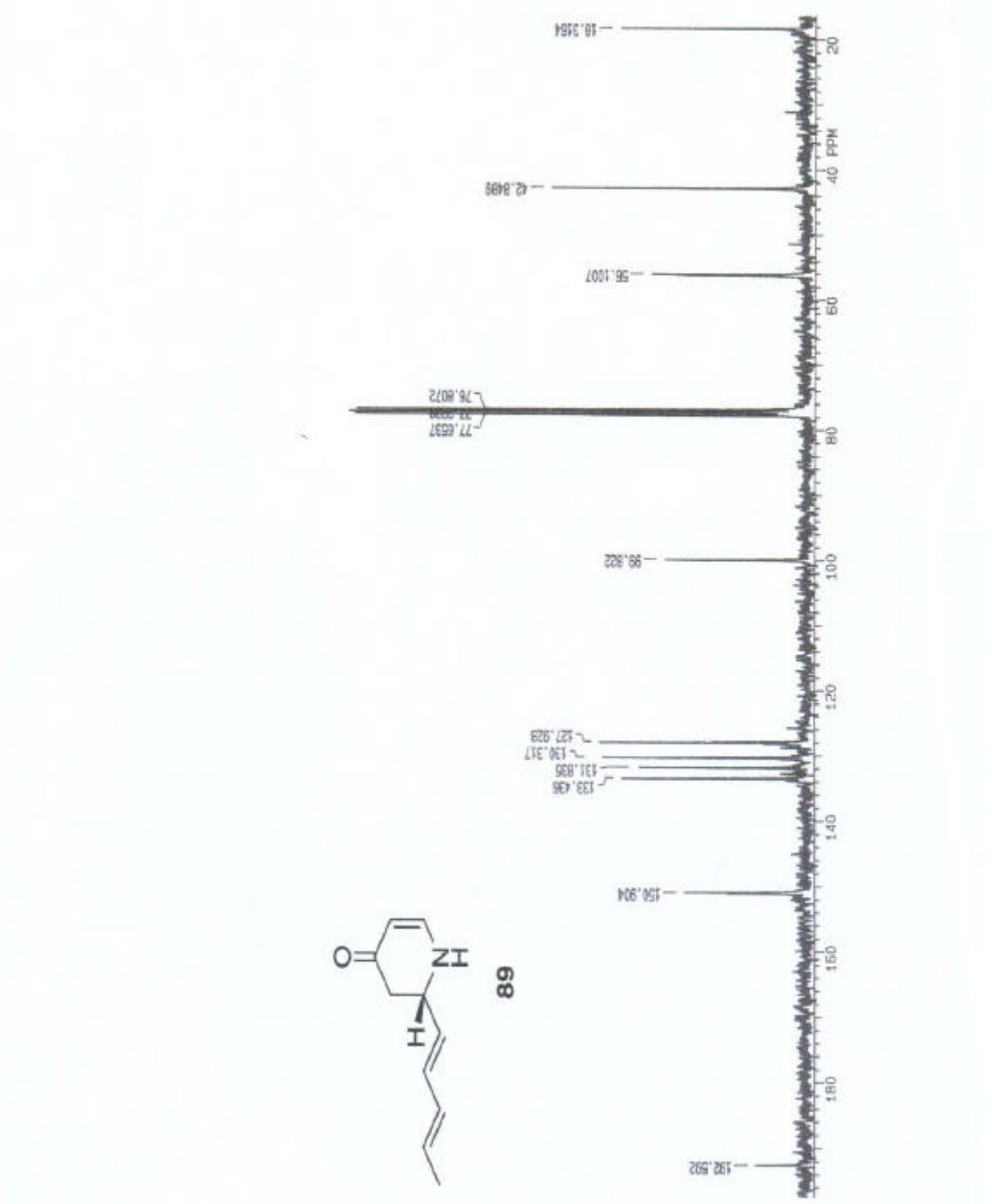
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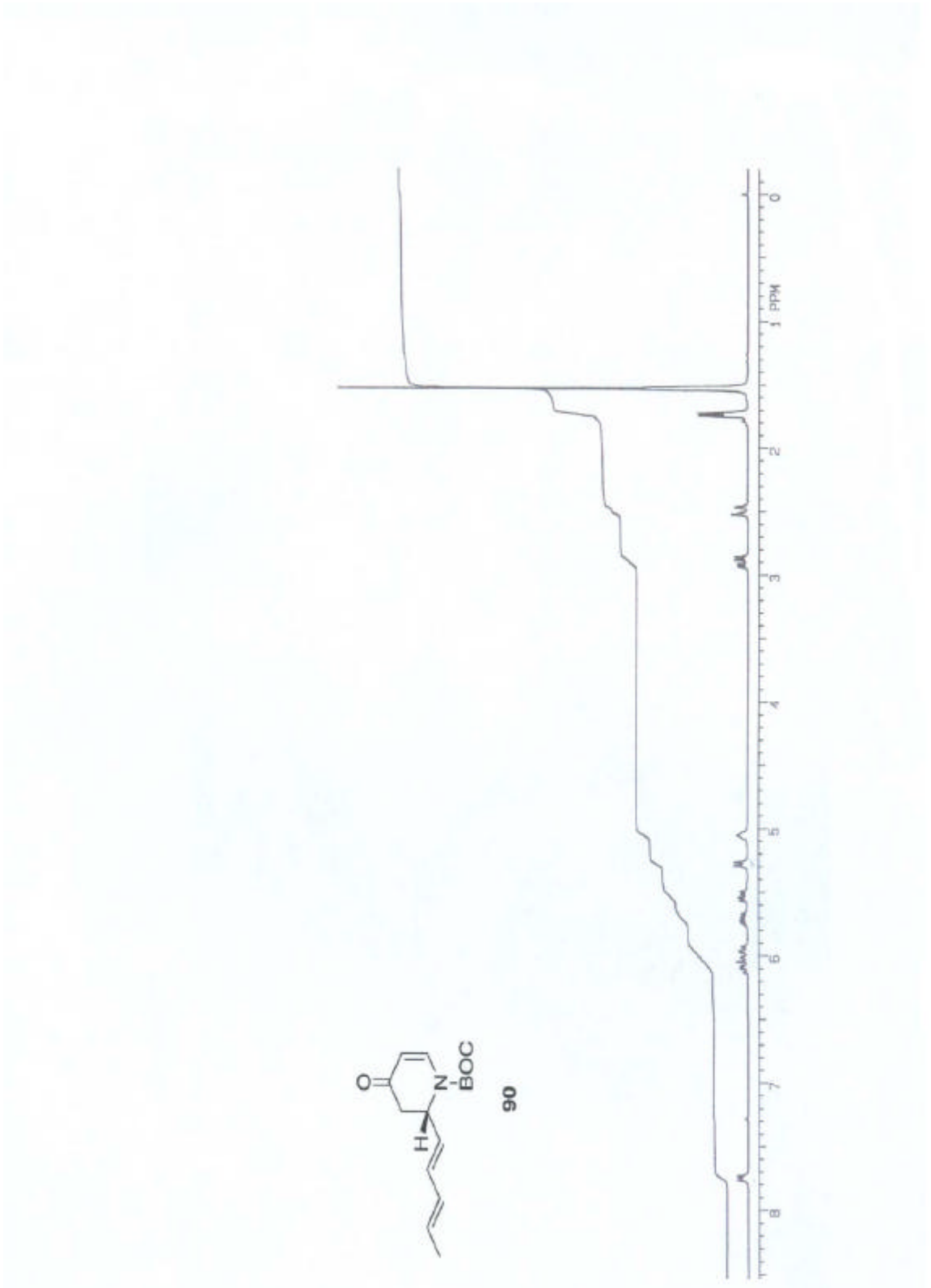
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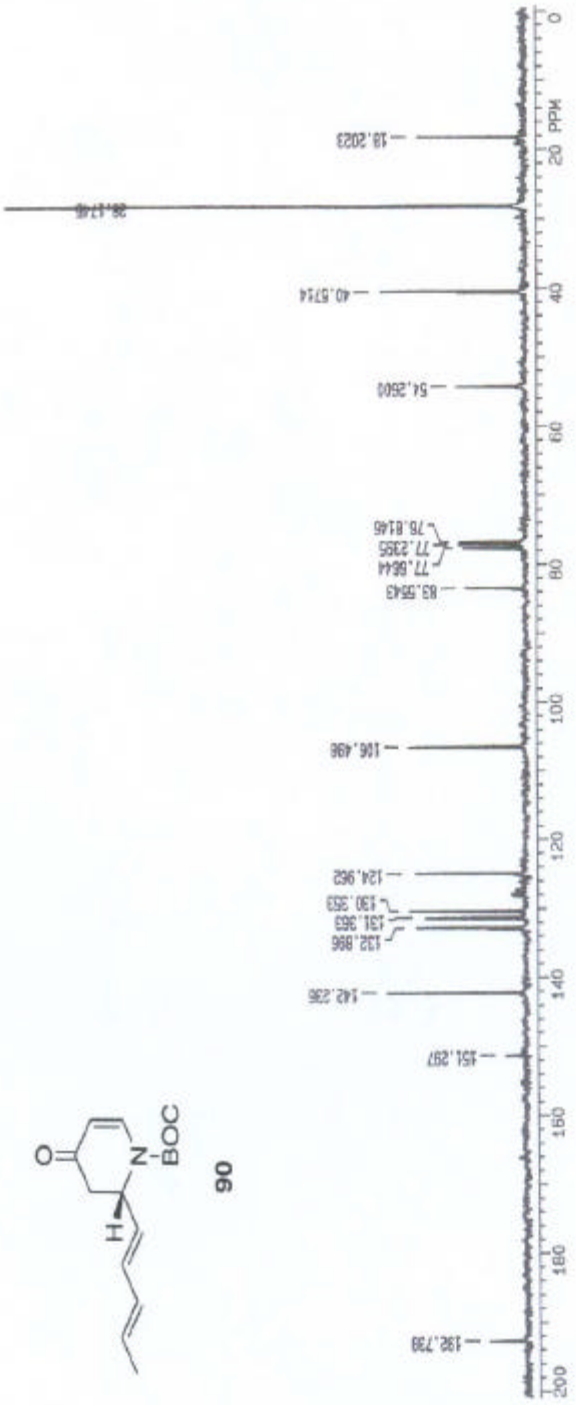
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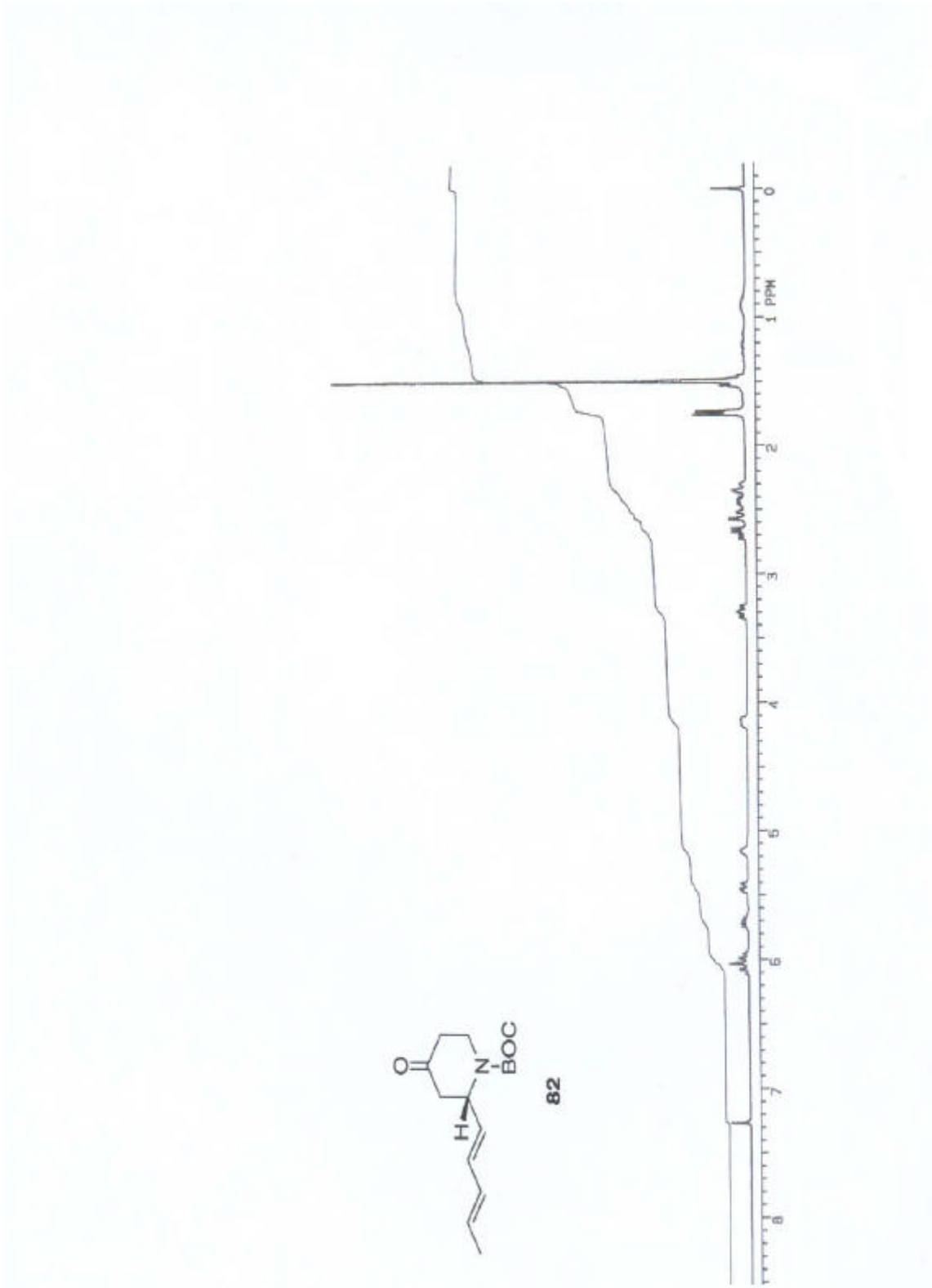
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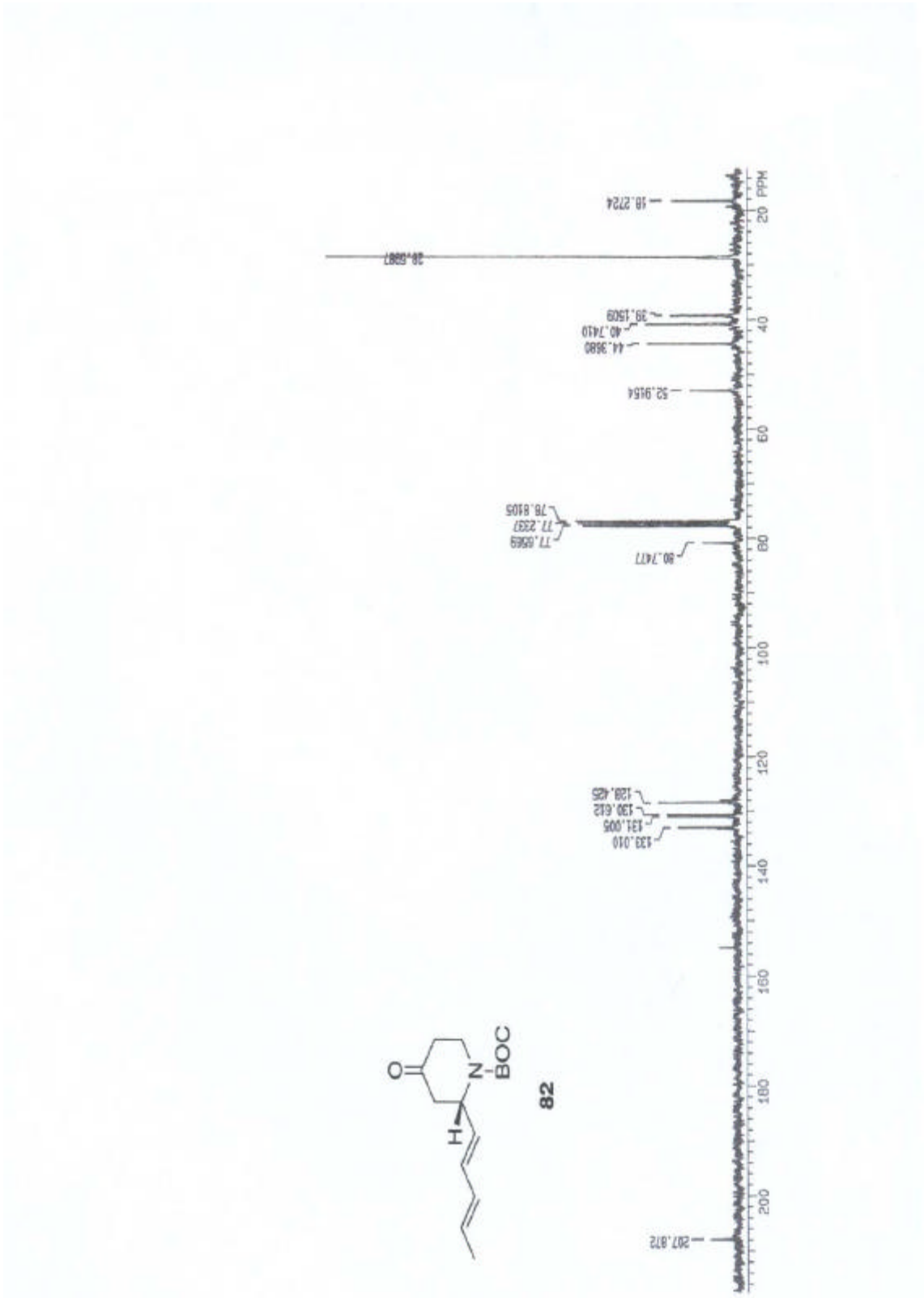
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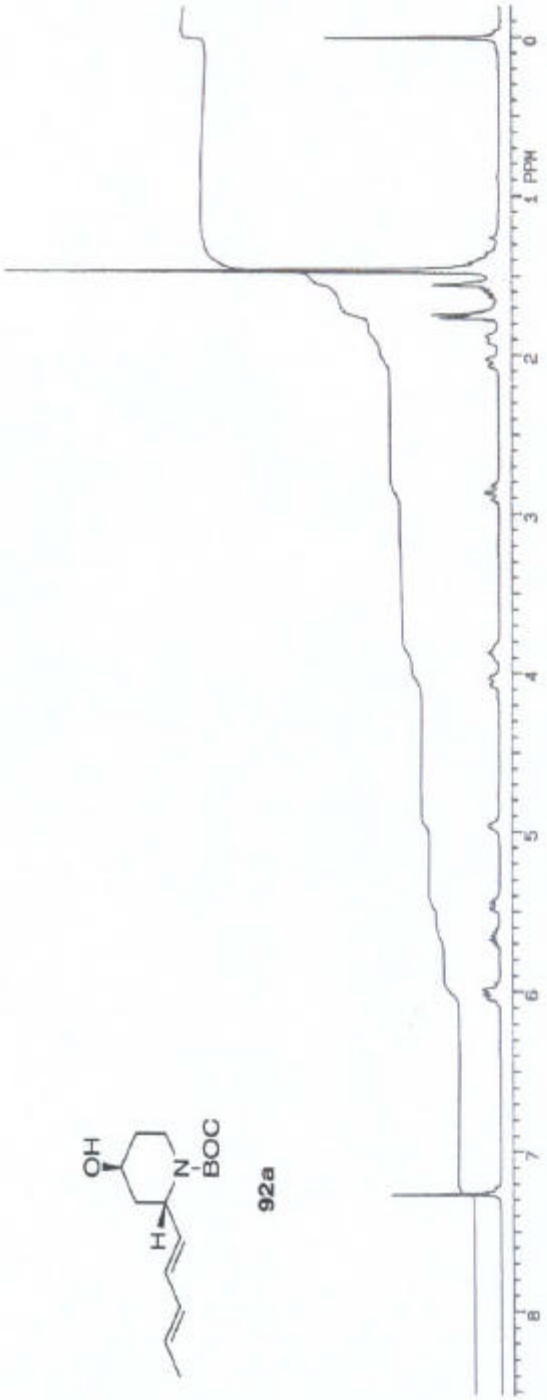
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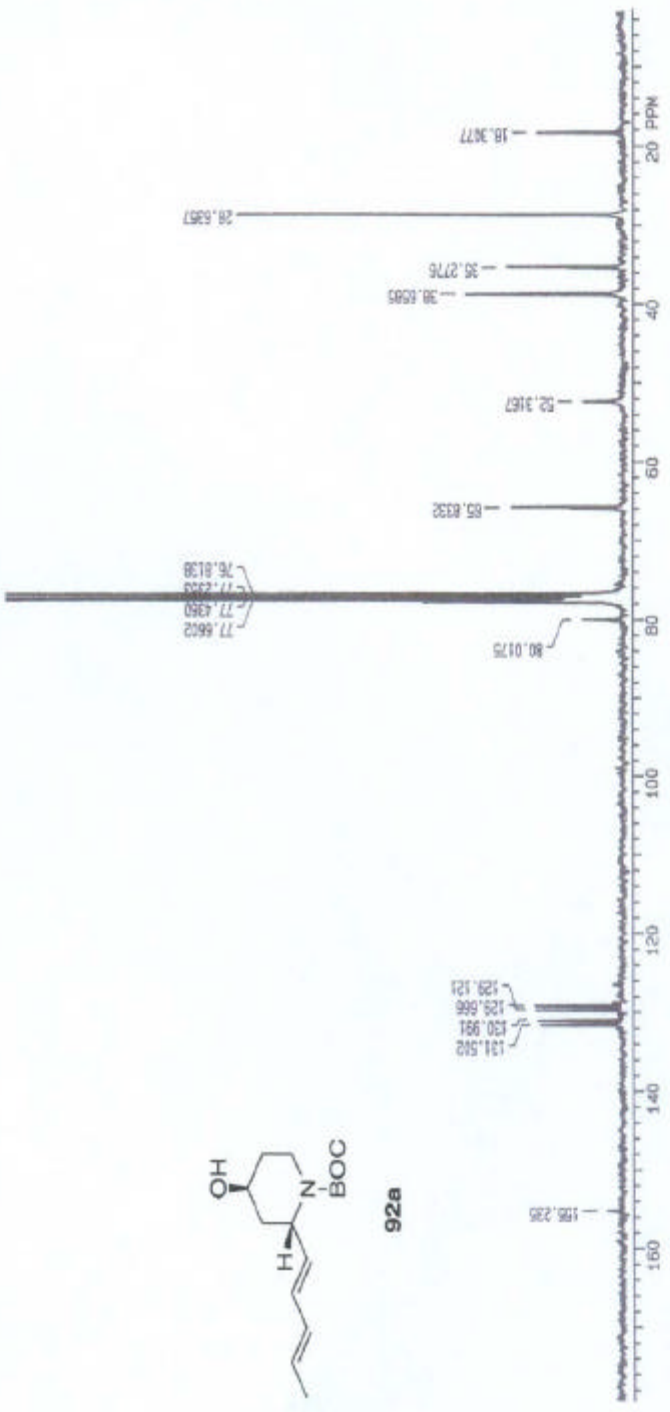
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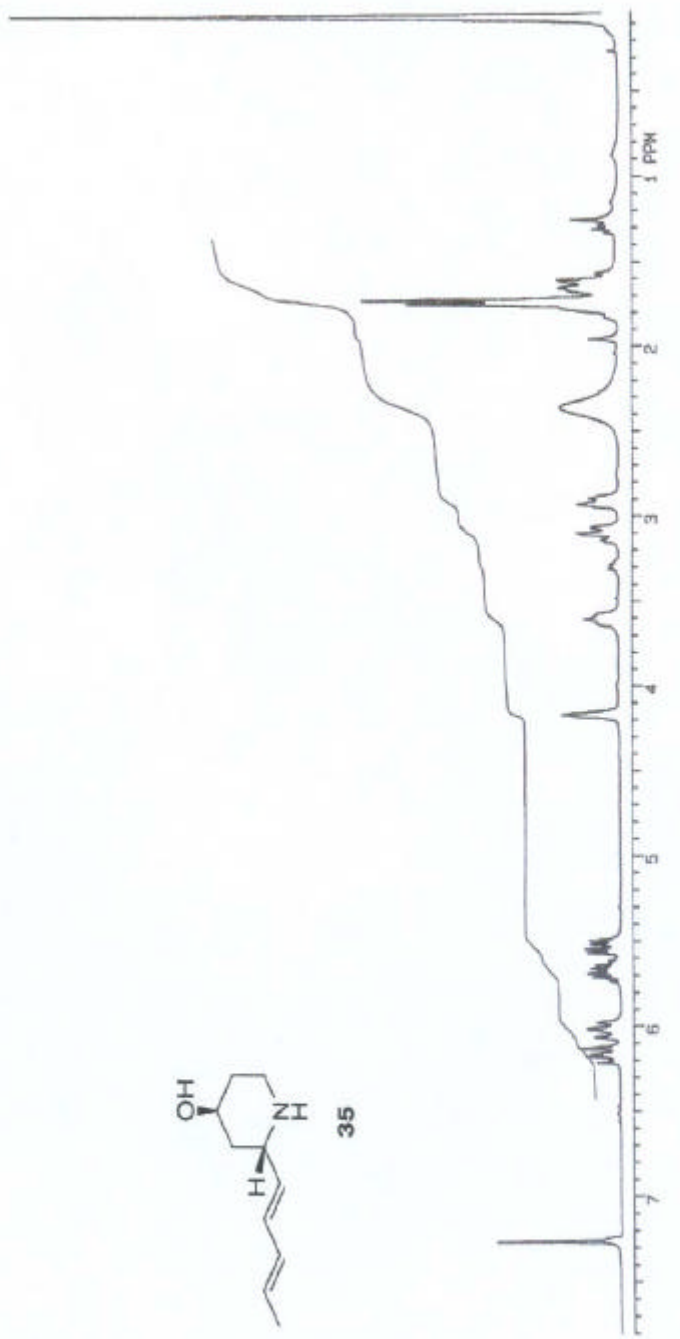
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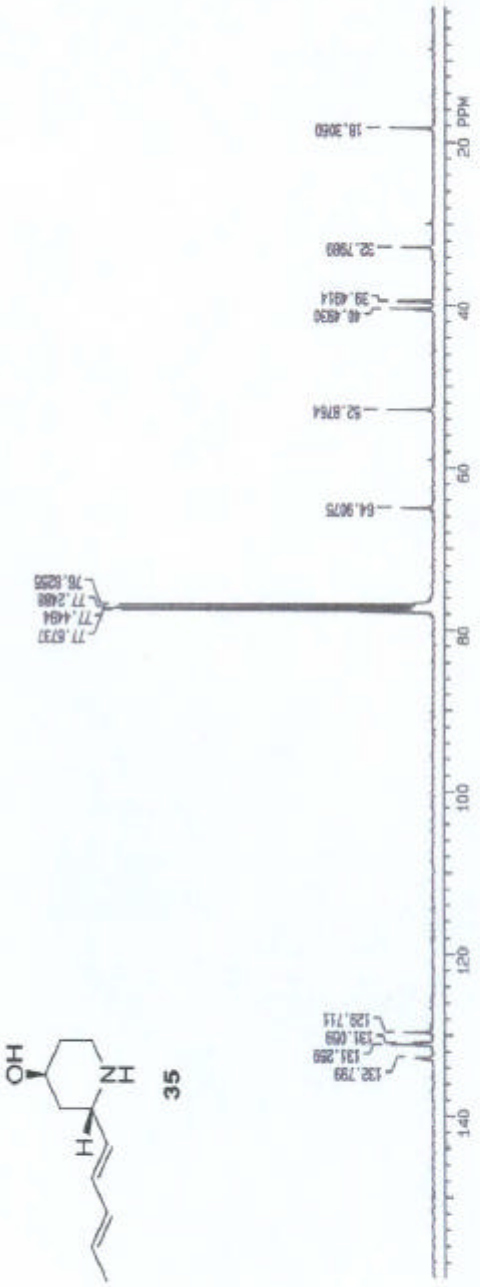
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