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Studies Toward the Total Synthesis of Eletefine

Ijaz Ahmed

July 2010

Submitted in partial fulfillment of the requirements for the degree of

Master of Science in Chemistry

Approved: _____

Professor Jeremy Alan Cody

_____

Dr. L. Paul Rosenberg

Department of Chemistry

Rochester Institute of Technology

Rochester, New York 14623 - 5603

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Acknowledgments

First of all, I would like to thank God for His grace and blessings to help me complete my thesis.

I would like to thank Dr. Jeremy A. Cody, who has pushed me to excel beyond my potential. His intellectual understanding about the core subject and most of all the encouragement he provided is something I am incredibly grateful for. I would also like to further thank my committee members: Dr. Christina Collison, Dr. Michael Coleman, and Dr. Andreas Langner; who have stimulated my research with their thoughtful questions and insight.

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for their never-ending love and attention that without, I would have never been able to attain my goals.

Abstract

A method towards the total synthesis of eletefine is described. Two related convergent syntheses are explained which divide the molecule into two fragments. Improvements towards the synthesis of a *bis*-functionalized isoquinoline fragment are explained. Expansion on the knowledge and understanding of the isoquinoline system is also described.

The synthesis illustrated entails a bromination of a triflate functionalized isoquinoline system and a regio-selective Sonogashira reaction. Suggestions towards the completion of the total synthesis are prescribed.

Table of Contents

List of Abbreviations

Ac	acetyl
AcOH	acetic acid
Cat.	catalytic
aq	aqueous
Ar	aryl
Bn	benzyl
Bu	butyl
^{13}C NMR	carbon nuclear magnetic resonance spectrometry
C	Celsius
DBDMH	1,3 dibromo-5,5-dimethyl hydantoin
DCM	dichloromethane
DIPEA	diisopropylethyl amine
DMF	N, N-dimethylforamide
DMSO	dimethylsulfoxide
Et	ethyl
EtOAc	ethyl acetate
g	gram
GC/MS	Gas chromatography/ Mass Spectrometry

^{1}H NMR	proton nuclear magnetic resonance spectrometry
IR	Infrared spectrometry
iPr	isopropyl
L	liter
Me	methyl
MeOH	methanol
MHz	megahertz
mg	milligrams
mL	milliliter
mmol	millimole
mol	mole
MS	mass spectrum
n-BuLi	*n*-Butyl lithium
NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Ph	phenyl
R	alkyl
RT	room temperature
sat	saturated

t-BuLi	*t*-Butyl lithium
Tf	trifluoromethanesulfonate
THF	tetrahydrofuran

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1. Introduction

1.1 Relevance of Natural Product Synthesis

Natural products are targets for synthetic research due to their challenging structures and potential biological activities. Natural products are naturally occurring metabolites found in animals and plants. They are often regarded as possessing some important biological activity and therefore may be possible drug candidates. Unfortunately, many desirable natural products are very scarce in nature.

Biologically relevant natural products are often found in endangered species of plants and animals. Thus, harvesting these natural products can be ecologically unsound and costly. Moreover, harvesting natural products from nature is typically a very inefficient process resulting in poor yields of the desired compound. An alternative to obtaining these natural products would be to synthesize them in the laboratory.

Natural products are particularly appealing for the synthetic chemist, due to their often challenging structures. Natural products provide the opportunity for synthetic chemists to challenge themselves and contribute new ideas and methodologies to an already growing science.

1.2 The Natural Product, eletefine (**1**)

The novel structure of eletefine (Figure 1) provides the opportunity to generate new ideas and methodologies. Eletefine has three six-membered rings, an eight-membered ring containing an oxygen bridge in the center of the molecule, and a chiral alcohol. The

structure of the molecule is intriguing because of the trapped and seemingly unreactive bridged dienol. The enols are relatively unreactive due to the poor overlap of the pi orbitals of the double bond and lone pair of electrons on the oxygen.

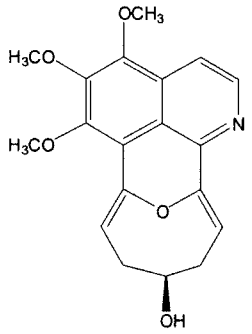


Figure 1: Molecular Structure of eletefine **(1)**

1.3 Model System Targeted

The focus of this thesis is to explore the final stages of our proposed synthetic route. To that end, model intermediates were used resulting in the new synthetic target, *des*-hydroxyeletefine (**1b**) (Figure 2). The knowledge gained through the synthesis of this molecule would provide a proof of concept toward the completion of eletefine.

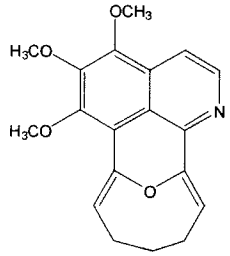


Figure 2: Molecular structure of *des*-hydroxyeletefine **(1b)**

2. Isolation and Structure Determination

Eletefine (Figure 1) is a natural product that was first isolated in 1998 from the roots of *Cissampelos glaberrima* in northeastern Brazil.[1] This species is known as "jarrinha"

and has been used for the treatment of asthma and urinary tract infections.[2] Eletefine was later isolated from *Stephania longa* in southern China.

The isolation procedure from *Cissampelos glaberrima* involved the extraction of 1 kg of dried ground root with ethanol over the course of four days. The concentrate was then dissolved in HCl and filtered through Celite. The resulting extract was then purified through vacuum liquid chromatography (VLC) while being assayed by thin layer chromatography (TLC).[3] The procedure yielded 97mg of eletefine.

Eletefine is described as a reddish brown wax. It is known to fluoresce under UV light of 360nm. The molecular structure was determined by FT-IR, electron impact mass spectroscopy, ^{1}H NMR, ^{13}C NMR, and NOESY experiments.[1]

3. Eletefine Family

Eletefine is a member of a family of alkaloids called stephaoxocanes.[4] Stephaoxocanes all bear a similar skeletal structure (Figure 3). Therefore, a total synthesis of eletefine could provide a general route to several stephaoxocanes. [1, 4, 7-10] All members of this family bear the stephaoxocane skeleton **2**. This skeleton contains an ABCD tetracyclic ring system, an oxygen bridge, and an alcohol stereocenter. This family has been conferred the name stephaoxocane, because they structurally bear an oxocane ring system.[7, 9]

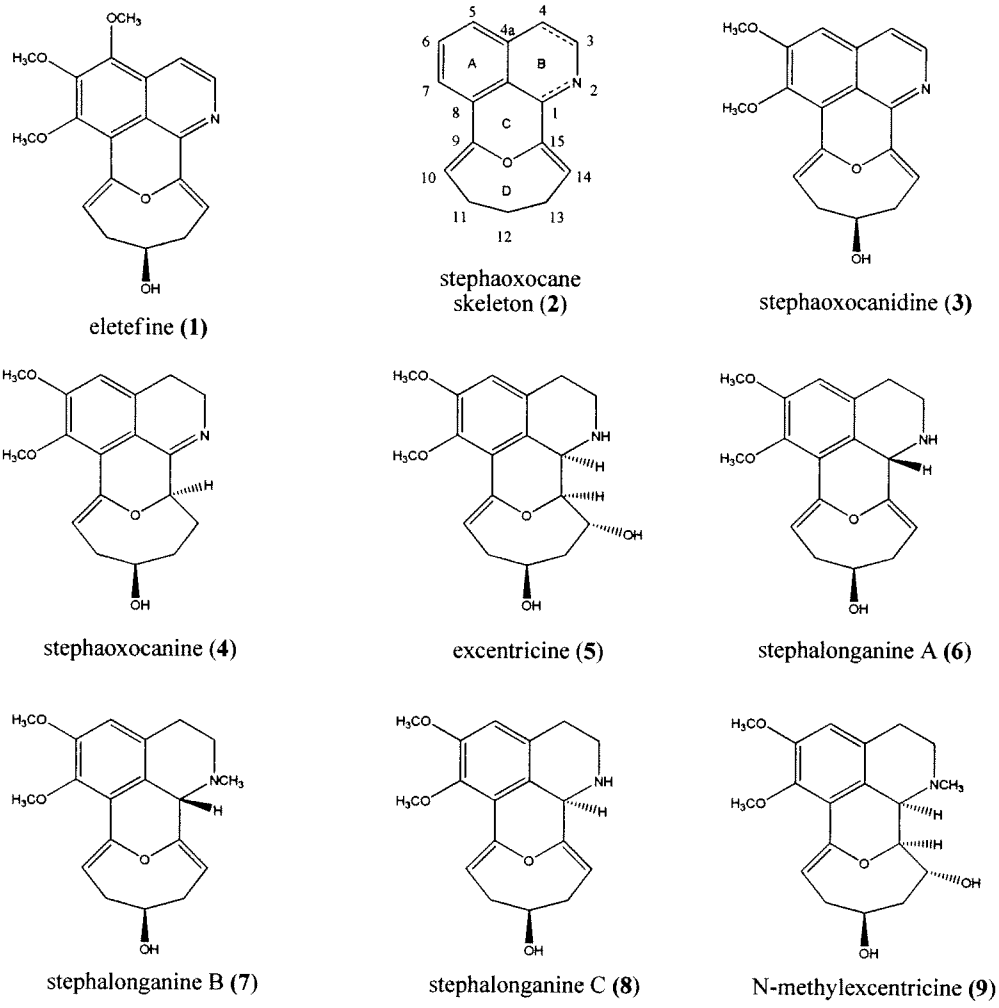


Figure 3: The stephaoxocane family of alkaloids [1, 4, 7-10]

4. Biological Activities

Both species, *Stephania longa* and *Cissamopelos glabberima*, are members of the Menispermaceae family of flowering plants. *Stephania longa* has been used to reduce fever, inflammation and to fight dysentery.[4] As stated earlier, *Cissampelos glabberima* has been used for the treatment of asthma and urinary tract infections.[2] Other members of the Menispermaceae family have been used in traditional medicine. In fact, the roots of other *Cissampelos* species have been commonly used in ancient

medicine to cure heart, genital and urinary illnesses as well as respiratory diseases.[5] The structure of the molecule closely resembles the structure of other tetracyclic isoquinoline derivatives, such as the tropoloisoquinolines, which do not contain a bridged system. Some of these derivatives have demonstrated interesting cytotoxic and antitumor activity as well as healing properties.[6]

All members of the stephaoxocane family have been isolated from plants belonging to the Menispermaceae family. Excentricine (**5**)[9] and 2-*N*-methylexcentricine (**9**)[10] have been isolated from *Stephania excentrica*. Stephaoxocanine (**4**)[8] and stephaoxocanidine (**3**)[7] have been isolated from *Stephania cepharantha*. It is important to also note that *Stephania cepharantha* is believed to possess some activity towards the herpes simplex virus. [9]

5. Previous Synthetic Work on the Stephaoxocane Skeleton

Teodoro S. Kaufmann and co-workers have engaged in studies towards the synthesis of stephaoxocanidine, one of the members of the stephaoxocane family (Figure 4).[12-14]

Kaufmann first published the successful synthesis of the ABC tricyclic ring system of stephaoxocanidine (See Figure 3, stephaoxocane skeleton **2**).[12] He then expanded on this structure in an attempt to complete the D ring of the molecule, but wasn't successful.[13] His most recent work focused on the synthesis of a tricyclic ring system containing a ten-membered ring without the chiral alcohol or oxygen bridge of the stephaoxocane skeleton.[14]

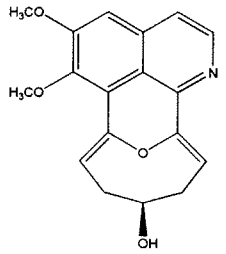
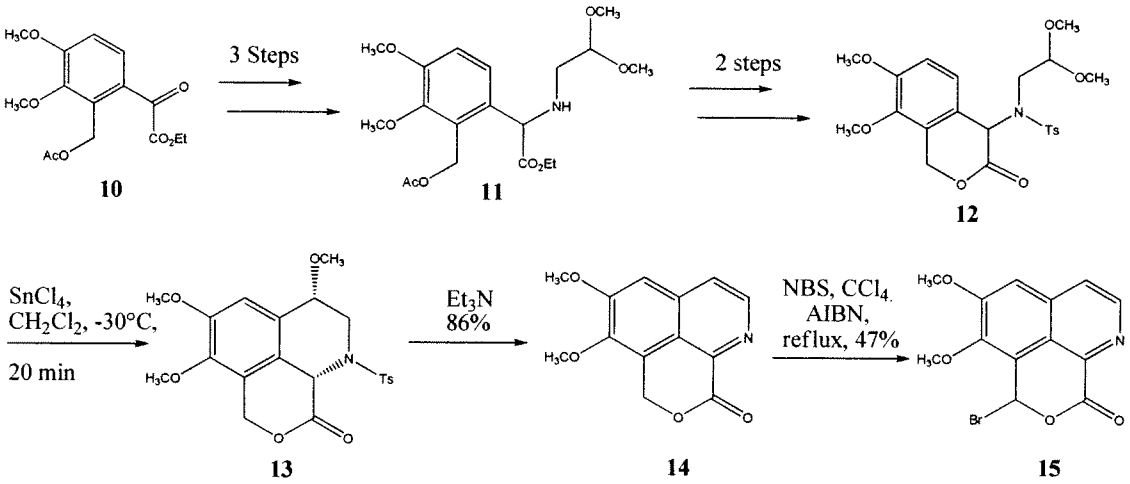


Figure 4: Molecular structure of stephaoxocanidine **(3)**.

5.1 Synthesis of ABC tricyclic ring system of stephaoxocanes

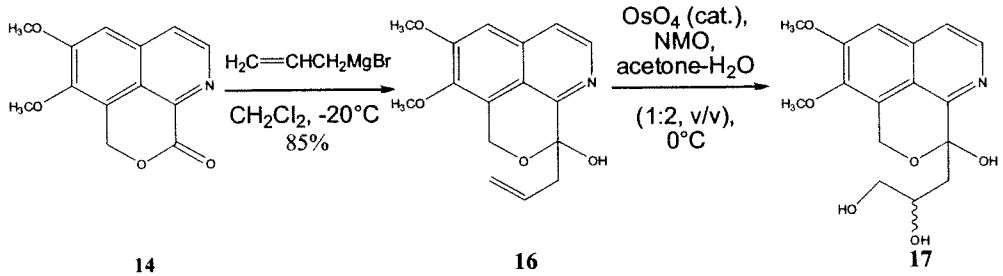
In 2003, Kaufmann published the synthesis of the ABC tricyclic ring structure (Figure 3, stephaoxocane skeleton **2**).[12] The synthesis of a tricyclic system was a challenging accomplishment. Interestingly, the cyclization reaction leading to the methyl ether **13** resulted in high relative stereochemistry. Kaufmann attributes the observed cyclization to the steric restrictions from acetal **12** to the nucleophilic attack of the activated acetal by the aromatic moiety during the cyclization.[12]



Scheme 1: Kaufmann's synthesis of the ABC tricyclic ring structure [12]

5.2 Further elaboration on ABC tricyclic ring system.

In 2005, Kaufmann built upon the ABC tricyclic structure in an attempt to create the eight-membered ring structure of the stephaoxocane skeleton (Scheme 2).[13] An allylic anion was easily attached to the carbonyl carbon of the δ-lactone **14**. This was followed by an oxidation of the alkene **16** to form a mixture of the diasteroemeric diol **17.** Although the synthesis of diol **17** is close to the final target molecule, Kaufmann has not published any further work using the advanced intermediate in Scheme 2.

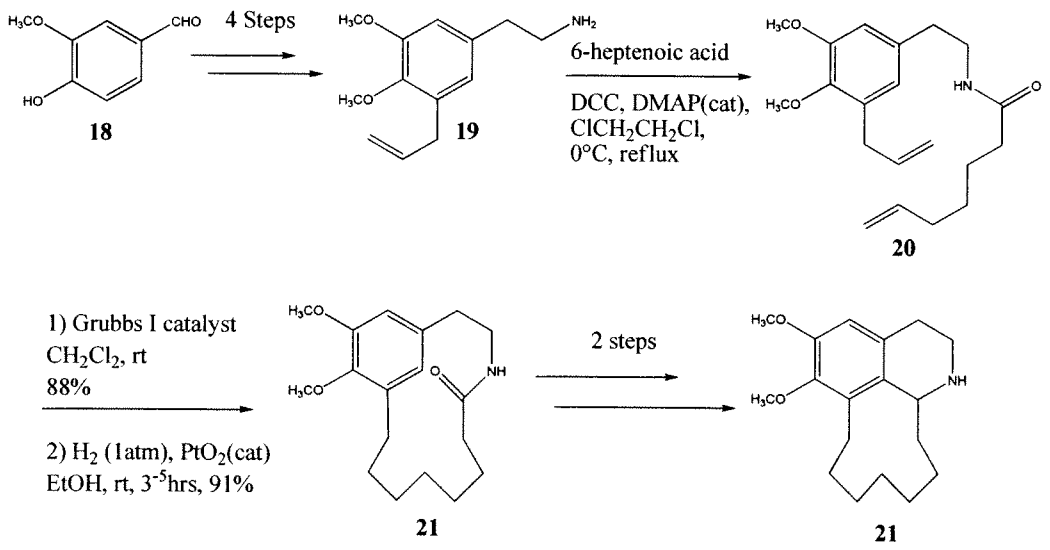


14 16 17

Scheme 2: Kaufmann's synthesis of diol **17** [13]

5.3 Synthesis of ten-membered ring of stephaoxocane skeleton

In 2009, Kaufmann utilized a ring-closing metathesis (RCM) reaction to prepare the ten-membered ring of the stephaoxocane skeleteon (Scheme 3). By applying a Grubbs' catalyst, diene **20** underwent a RCM reaction followed by a reduction to achieve macrocycle **21**. The synthesis was completed with an overall 23% yield in 8 steps without the need for protecting groups.[14] The synthesis of the ten-membered ring without the oxygen bridge or the chiral alcohol was completed.



Scheme 3: Kaufmann's synthesis of molecule **21** applying a ring closing metathesis reaction [14]

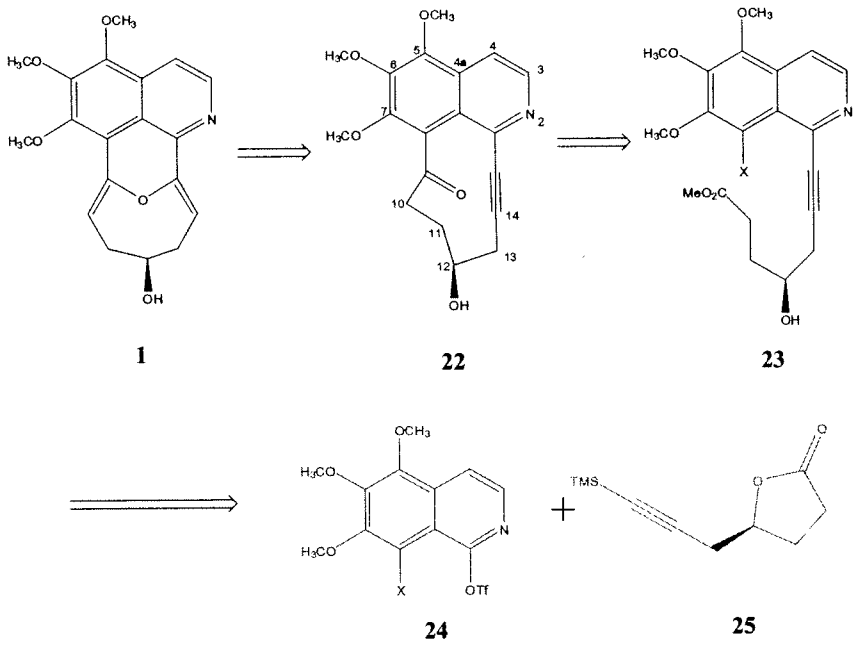
Although Kaufmann has made numerous advancements towards the synthesis of the stephaoxocane skeleton, further study and development still remains. The ten-membered ring with the chiral alcohol and an oxygen bridge is an integral part of the skeletal structure and a successful synthesis is yet to be discovered.

6. Retrosynthetic Analysis of Eletefine

The total synthesis of eletefine was envisioned to occur through two possible convergent routes. A convergent synthesis was utilized because it allows the potential to improve efficiency of a synthetic route.[15] Route A involves the formation of the ten-membered ring with two C-C bond forming reactions between a γ-lactone and an isoquinoline fragment. The order of these C-C bond forming reactions is altered in route B. Both route A and route B share intermediate **22.**

6.1 Route A towards eletefine

A convergent total synthesis of eletefine has been proposed previously by the Cody Group (Scheme 4).[15] The synthesis of eletefine is envisioned to be completed with a novel alkyne hydration reaction. The formation of the ten-membered ring is completed with a carbon-carbon bond forming reaction between C_8 and C_9, which follows a carbon-carbon bond forming reaction between C_1 and C_{15} of an isoquinoline **24** and a γ-lactone fragment **25.**

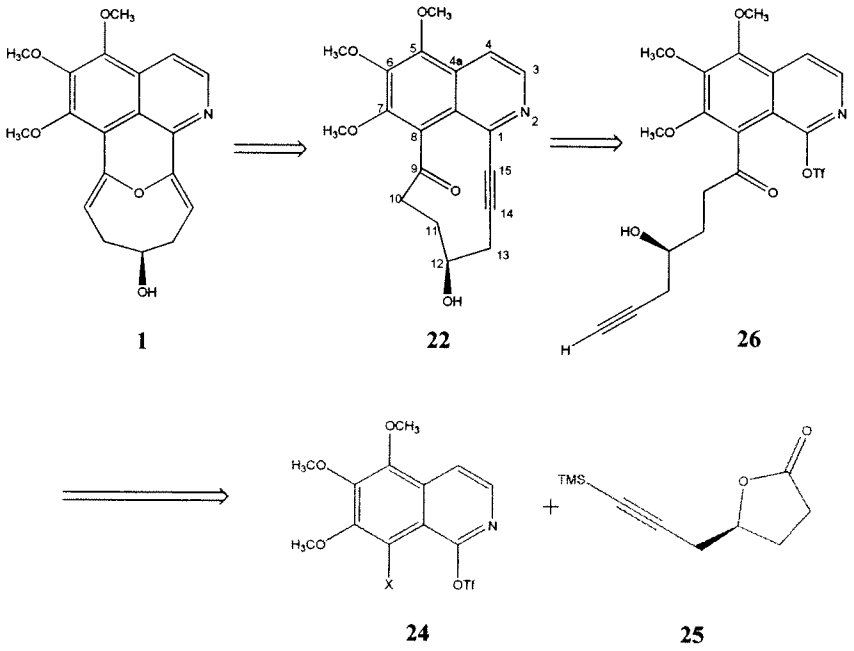


Scheme 4: Route A retrosynthetic analysis of eletefine **(1)**.

6.2 Route B Towards Eletefine

A second synthetic route to eletefine is similar to the previously proposed synthesis; however, the order of reactions is different (Scheme 5). The synthesis of eletefine is envisioned to be completed with a novel alkyne hydration reaction. This follows two carbon-carbon bond forming reactions. The formation of the ten-membered ring is

completed with a carbon-carbon bond forming reaction between C_1 and C_{15}, which follows a carbon-carbon bond forming reaction between C_8 and C_9 of an isoquinoline **24** and a γ-lactone fragment **25.** By cyclizing in this order, Route B could avoid the strain and entropy issues in forming the ten-membered ring. The Sonogashira reaction has been observed to close large macrocycles with efficient yields.[16]

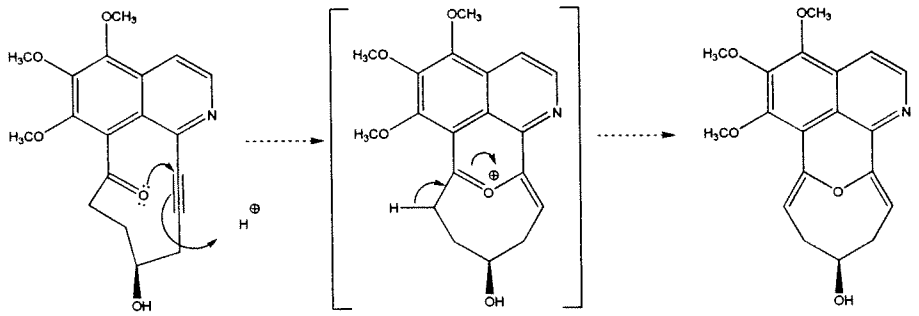


Scheme 5: Route B retrosynthetic analysis of eletefine **(1)**.

6.3 Mechanism for Alkyne hydration step

The alkyne hydration step shared by both route A and route B was envisioned to occur fairly readily due to the proximity of the carbonyl with the alkyne functionality in ten-membered isoquinolinyl **22**. The alkyne would be protonated regioselectively with assistance from the carbonyl oxygen at the benzylic position to form the alkene (Scheme 6).[17] An elimination would occur alpha to the carbonyl to give the final product

eletefine. To date, this novel alkyne hydration has not been reported in the literature. Although placing such an unexplored reaction late in the synthesis is risky, creation of the specific system intrinsically lends itself to the success of the reaction.



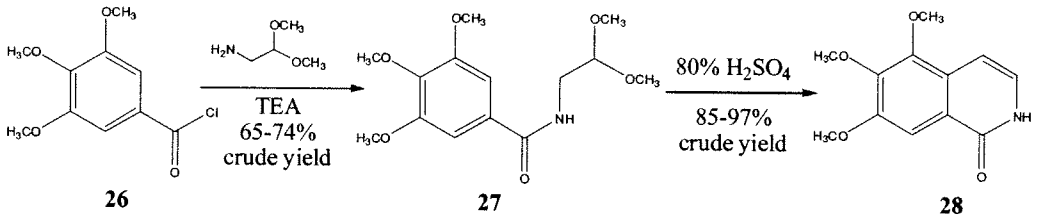
Scheme 6: Proposed mechanism for the alkyne hydration step

7. Previous synthetic work on eletefine conducted by the Cody group

Through the retrosynthetic analyses proposed, two significant fragments have been targeted for synthesis. The majority of progress before my involvement was on the isoquinoline fragment **30**.

7.1 Synthesis of Isoquinoline fragment **28** [18]

The isoquinoline fragment was synthesized from the commercially available 3,4,5-trimethoxybenzoyl chloride (**26**). The starting material was first reacted with an amine to generate the amide product **27**. The cyclization required strongly acidic or Lewis acidic conditions to form isoquinoline **28**.[18] In following classic Pomeranz-Fritsch conditions,[19] the ring closing reaction was successfully performed in good yields using 80% sulfuric acid. Both reactions were pure enough to carry through to the next step without purification.

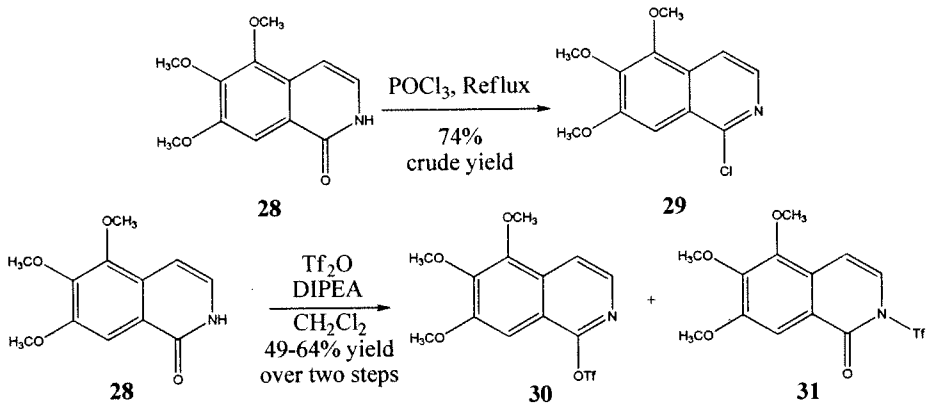


Scheme 7: Synthesis of isoquinoline fragment **28** [18]

7.2 Preparation of triflate fragment **30**

The isoquinoline fragment was then prepared for a Sonogashira coupling reaction to form the C_1-C_{15} bond. Initial work by the Cody group yielded chlorinated isoquinoline fragment **29** (Scheme 8).[18] The yields for this reaction were moderate. Eventually, further studies allowed the successful transformation of the carbonyl functional group

of isoquinoline **28** to a triflate leaving group **30,** which was purified through a silica gel column to provide a 45-64% yield from benzoyl chloride **26** (Scheme 8).[18] Triflate **30** is the first intermediate where purification was required in the three-step sequence. The triflation reaction achieved a good yield and generated an effective site for oxidative addition for the palladium-catalyzed Sonogashira coupling. In our favor, the Sonogashira reaction is known to work more efficiently during oxidative addition with a triflate leaving group than with a chlorine.[20]



Scheme 8. Synthesis of the chlorinated isoquiniline **29** and triflate **30** [18]

A by-product of the triflation reaction was observed by ^{1}H NMR and separated using silica gel chromatography. Purification using 5% MeOH/CH_2Cl_2 did not provide efficient separation of the two compounds. The by-product observed was *N*-triflate **31** (Scheme 8) with a crude ratio of product to by-product of 4:1 respectively. Optimization of the purification using 10% EtOAc/hexanes as an eluent for silica gel chromatography afforded a very reliable separation of the two compounds.

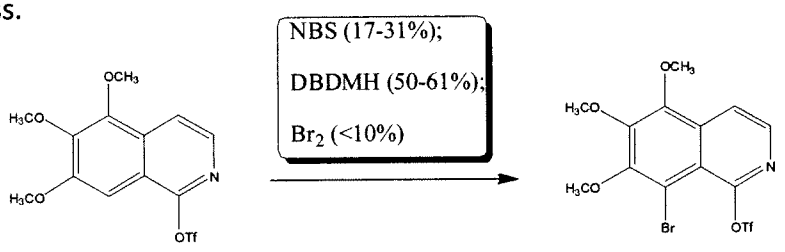
The successful attachment of a triflate to the isoquinoline system provided a functional site for forming the C_1-C_{15} bond of eletefine (Scheme 4). Further functionality at the C-8 position generates multiple options to form the C_8-C_9 bond of eletefine.

8. Results and Discussion

In developing routes A and B, a bi-functionalized isoquinoline fragment was envisioned in order to incorporate two points for attachment. In route A, the bi-functionalized isoquinoline fragment would undergo a Sonogashira reaction to form the C_1-C_{15} bond followed by a lithium-halogen exchange reaction that could be used to form the C_8-C_9 bond (Scheme 4). In route B (Scheme 5), following the lithium-halogen exchange, a Sonogashira reaction would be performed to provide the ten-membered ring followed by an alkyne hydration to yield the final product. The development of a bi-functionalized isoquinoline fragment was conducted in parallel with an exploration of route A using triflate **30** as the coupling partner for the synthesis of rings C and D.

8.1 Synthesis of the bi-functionalized isoquinoline fragment **32**

Triflated isoquinoline **30** underwent bromination to yield the brominated product **32** (Scheme 9). The bromination reaction was performed using NBS, DBDMH or Br_2 with varying success.



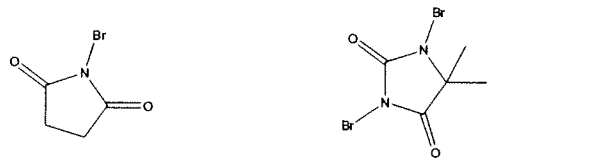
30 **32**

Scheme 9. Synthesis of brominated triflate **32**

The bromination using NBS in DMF at room temperature resulted in yields lower than 10%. However, when performing the reaction in an ice bath and allowing the

temperature to rise to room temperature overnight, the yields were improved to a range of 17-31%. The reaction was also performed with Br_2, but with very low yields.

Dibromodimethylhydantoin (DBDMH) proved to be the best reagent of the three mentioned above, providing yields in excess of 50%. One of the advantages of DBDMH over NBS is the fact that there are two sources of bromine for every molecule of DBDMH as opposed to the single source of bromine from NBS (Figure 5). This advantage allows reactions to be performed with half the equivalences of DBDMH than with NBS. Kuethe and co-workers also utilized DBDMH after experimentation with NBS and Br_2 due to its ease of use and highest yielding results.[21]



N-bromosuccinimide 1,3-dibromo-5,5-dimethylhydantoin

Figure 5: Comparison of NBS and DBDMH

Multiple reactions were performed to discover the most efficient reaction conditions for producing the brominated product **32**. Table 1 outlines the results of the bromination reaction under various conditions. Based on the results, the optimum reaction conditions were found using 1.5 eq of DBDMH at 0°C in the absence of light. At first, the reactions were performed in the presence of light. It was discovered that when the reaction was performed in the absence of light, it proceeded more effectively giving a greater yield of product. Performing the reaction in the dark is thought to minimize the production of bromine radicals as this would result in a lower yield of the desired product.[22]

It was also observed that when using DMF as a solvent, the yield was better than when using CH_2Cl_2. It is intriguing to note that larger scale reactions (≥ 1 g) had slightly higher yields (61%) of product than smaller scales (≤ 250 mg, 50% yield).

Table 1: Overview of bromination reactions to yield brominated product **32**

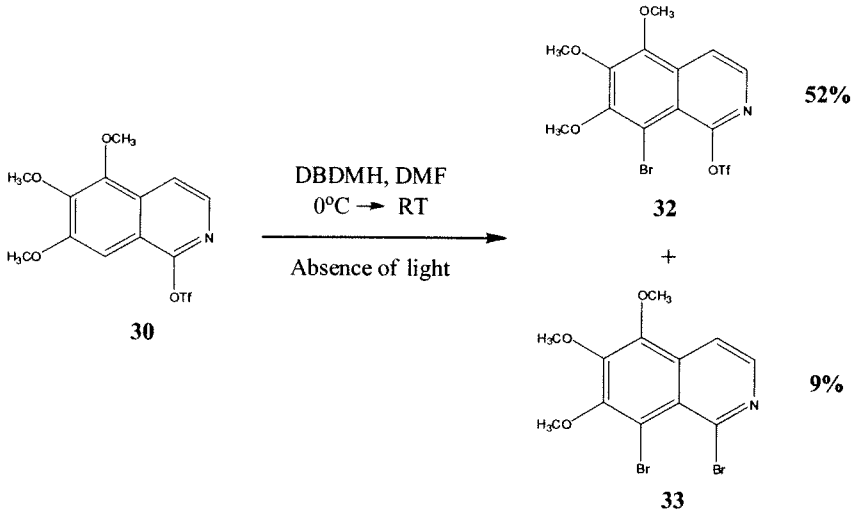
Scale	Conditions	Yield	Ratios* Brominated Triflate **32:** Triflate **30 :** *Bis*-brominated **33**
50.0 mg	0.5 eq DBDMH, CH_2Cl_2, RT, NO LIGHT	Crude = 75 mg	**1.00 : 2.31 : trace**
53.5 mg	1.0 eq DBDMH,DMF, 0 C→RT, NO LIGHT	Crude= 56.5 mg (86%)	**1.00: 0.86 : 0.02**
53.0 mg	1.25 eq DBDMH,DMF, 0 C→RT, NO LIGHT	Crude=58.4 mg (90.8%)	**1.00 : 0.77 : 0.02**
50.0 mg	1.5 eq DBDMH, DMF, 0 C→RT, NO LIGHT	Crude= 90 mg	**1.00 : 0.69 : 0.06**
60.0 mg	2.0 eq DBDMH, DMF, 0 C→RT, NO LIGHT	Crude= 116 mg	**1.00 : 1.18 : trace**
56.2 mg	2.5 eq DBDMH, DMF, 0 C→RT, NO LIGHT	Crude= 102 mg	**1.00 : 0.86 : 0.08**
49.0 mg	3.0 eq DBDMH, DMF, 0 C→RT, NO LIGHT	Crude= 71.5 mg	**1.00 : 1.68 : trace**

*Ratios were determined by TIC (Total Ion Current) obtained from GC/MS spectra

8.2 Identification of by-products from bromination reaction

The bromination reaction yielded a small portion of a byproduct that at first was not fully characterized. After careful analysis of the GC/MS data, a mass of 377 was observed with a retention time of 25.53min. The brominated product **32** had a

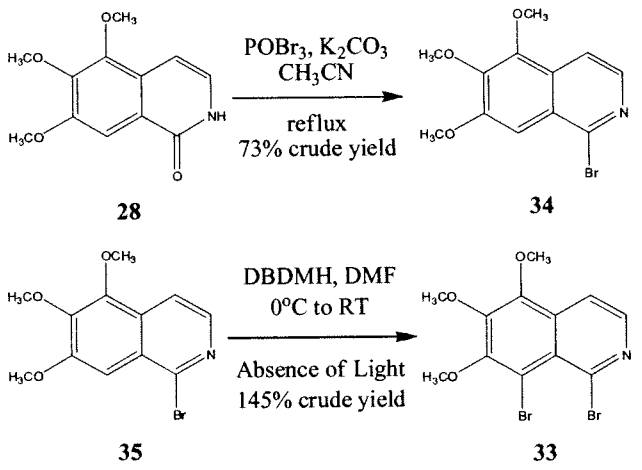
retention time of 24.98min. The by-product was believed to be *bis*-brominated isoquinoline **33** due to the observed isotope cluster on the GC/MS. Moreover, the impurity was also consistent with the ^{1}H NMR data. The aromatic protons of the brominated product **32** have chemical shifts around 6.8ppm and 7.4ppm. However another pair of chemical shifts was observed more downfield at around 7.9ppm and 8.1ppm. By ^{1}H NMR, it was determined that the by-product **33** to product **32** ratio was about 1:4 before purification and 1:6 after purification. The loss of *bis*-brominated **33** indicates that the by-product could be degrading on the silica gel.



Scheme 10. Synthesis of brominated triflate isoquinoline **32** and the by-product, *bis*-brominated isoquinoline **33**

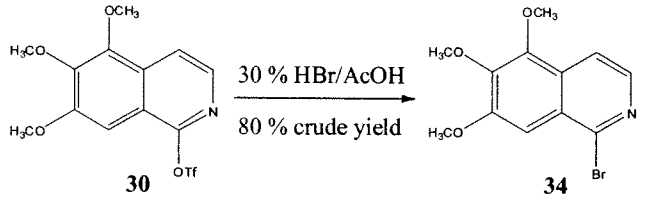
The most efficient method to prove that our structural assignment of **33** was correct would be to synthesize it using an alternative route (Scheme 11). The preparation of **33** was completed by first reacting isoquinoline **28** with $POBr_3$ under reflux in dry CH_3CN, followed by bromination with DBDMH, which yielded the desired *bis*-brominated isoquinoline **33.** Analysis of the crude product using NMR and GC/MS

supported that isoquinoline **33** was synthesized. A pure yield could not be obtained due to the production of an unknown by-product that wasn't easily separable. It is also important to note that *bis*-brominated isoquinoline **33** degrades during silica gel chromatography adding to the difficulty of purification.



Scheme 11. Synthesis of *bis*-brominated isoquiniline **33**

A reasonable explanation for the formation of *bis*-brominated **33** could be that the bromination reaction is producing HBr.[23] Once HBr is formed in the reaction, a plausible mechanism would be that the nitrogen of the isoquinoline is protonated by HBr and the bromine atom acts as a nucleophile, attacking the carbon and kicking off the triflate leaving group. To prove that the triflate could be converted to a bromide in the presence of HBr, triflate **30** was reacted with HBr to produce mono-brominated isoquinoline **34** with a good yield (Scheme 12).



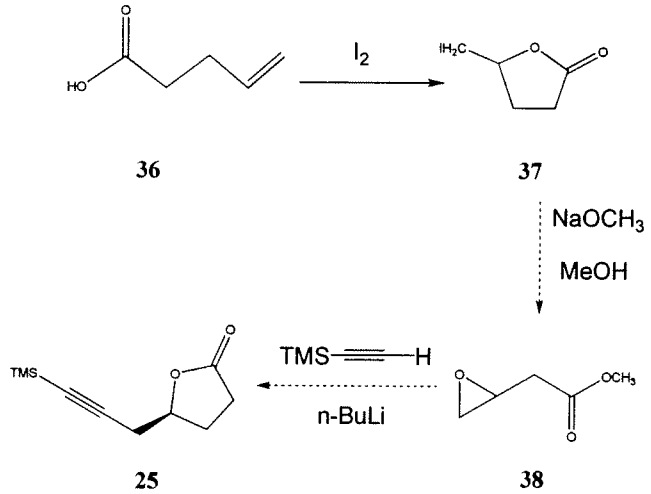
30 34

Scheme 12: Reaction of triflate **30** with HBr to give mono-brominated isoquinoline **34**

Given the completion of the bis-functionalized isoquinoline fragment, it was now our focus to construct the bottom coupling partner for forming rings C and D (Figure 3, stephaoxocane skeleton **2**).

8.3 Proposed synthesis of the γ-lactone fragment **25**

The synthesis of the enantiopure γ-lactone fragment, with the desired chirality, has been published previously by Myerson and Bartlett (Scheme 13).[24] Our achiral synthesis begins with the iodination of carboxylic acid **36** to cyclize to lactone **37**, followed by the formation of epoxide **38,** using similar reactions to Myerson and Bartlett. Reactions of epoxide **38** with the anion of a terminal alkyne should form γ-lactone **25.**



Scheme 13: Proposed synthesis of γ-lactone fragment **25** [25]

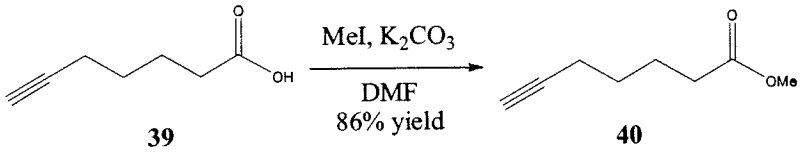
Unfortunately, the Cody group has had trouble reproducing the results for the synthesis.[25] So far, the synthesis of **37** has been successfully achieved, but epoxide **38** has proved to be unstable in our hands. The synthesis of this fragment is currently being investigated.[25] Due to the difficult synthesis of γ-lactone **25**, a model alkyne fragment has been utilized to explore the final stages of the synthetic route.

8.4 Synthesis of alternative model alkyne fragments

Some alternative alkyne fragments were synthesized to further explore the carbon-carbon bond forming reactions outlined in routes A and B. The alkynes used would ultimately allow the synthesis of the ten-membered ring, but would not provide the chiral alcohol of eletefine. A successful synthesis using these alkynes would give *des*-hydroxyeletefine (**1b**, Figure 2).

8.4.1 Preparation of methyl ester **40**

The synthesis of a methyl ester alkyne **40** was successfully achieved by reacting commercially available 6-heptynoic acid (**39**) with MeI and K_2CO_3.[26] This alkyne proved stable, making it an ideal candidate to test out certain reactions.

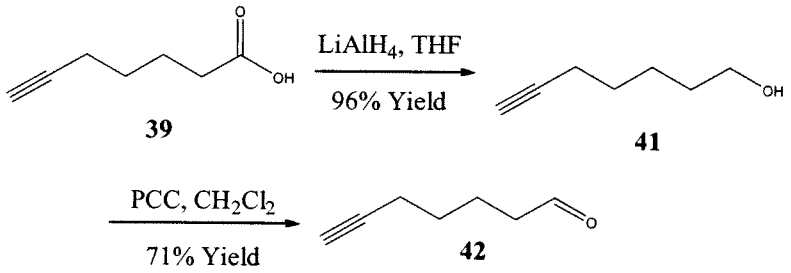


39 40

Scheme 14. Synthesis of methyl ester alkyne fragment **40** [26]

8.4.2 Preparation of aldehyde **42**

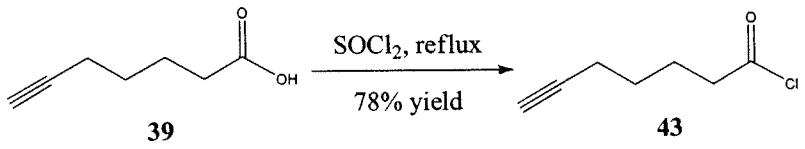
The synthesis of the aldehyde alkyne **42** was successfully attained through the reduction of 6-heptynoic acid (**39**) to the primary alcohol **41**, followed by a PCC oxidation reaction. The synthesis of aldehyde alkyne **42** was previously reported by Kolb and co-workers.[27] Aldehyde alkyne **42** was shown to be highly reactive and unstable. Any reaction with the aldehyde needed to be performed immediately after it was synthesized to ensure its purity and stability.



Scheme 15. Synthesis of the aldehyde-alkyne fragment **42** [27]

8.4.3 Preparation of acyl chloride **43**

The synthesis of the acyl chloride **43** was completed by reacting commercially available 6-heptynoic acid (**39**) with $SOCl_2$. The product was distilled under vacuum to provide a 78% pure yield.[28] Acyl chlorides are generally very reactive which makes them very useful reagents. Unfortunately, the acyl chloride was discovered to be very unstable. Therefore, like the aldehyde, the acyl chloride needed to be utilized almost immediately after its formation to ensure its purity.



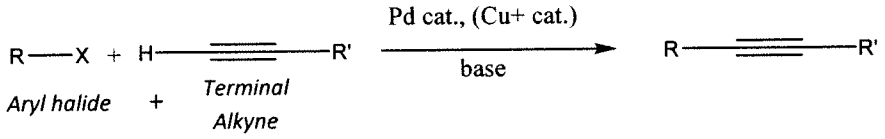
39 43

Scheme 16. Synthesis of acyl chloride **43** [28]

Model alkynes **40**, **42**, and **43** are being used to explore the final stages of the synthetic route. Specifically, these alkynes are being utilized to investigate different carbon-carbon bond forming reactions to form the C_1-C_{15} and C_8-C_9 bonds of eletefine (Scheme 4 and 5). Some of the reactions surveyed include the Sonogashira coupling reaction and the lithium-halogen exchange.

8.5 Palladium catalyzed Sonogashira coupling reaction

The use of transition metal-catalzyed cross-coupling reactions has greatly impacted the field of organic synthesis. Among these reactions, the palladium-catalyzed Sonogashira coupling reaction between aryl halides and terminal alkynes has evolved into an important method for preparing aryl alkynes.[29]



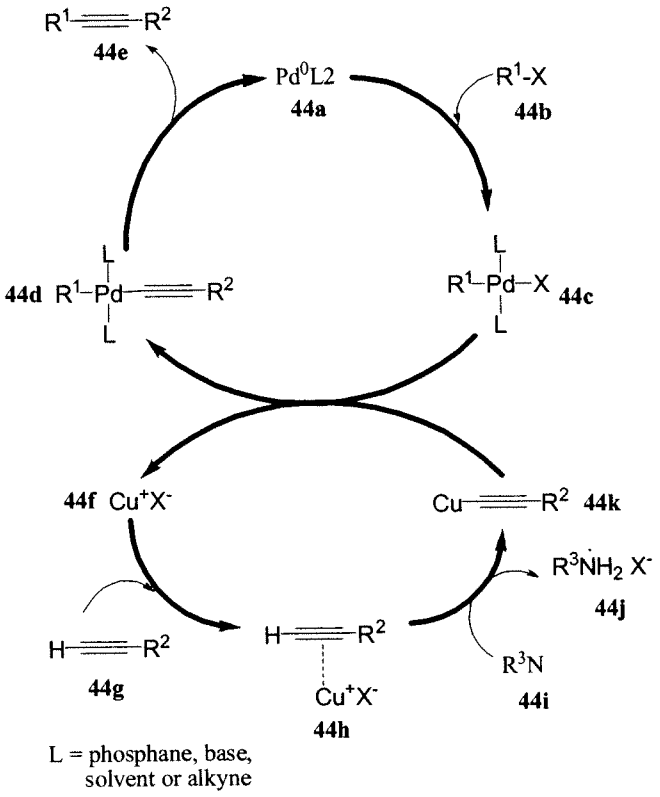
Scheme 17. Overview of Pd-catalyzed reaction to combine aryl halides with terminal alkynes [28]

Earlier studies by Heck[30] and Cassar[31] in 1975 reported the use of a palladium catalyst with a base to perform the reaction shown in Scheme 17. It was later reported by Sonogashira and Hagahira that the addition of a catalytic amount of copper (I) iodide

significantly increased the rate of the reaction to the point where the reaction could be performed at room temperature.[32] The Sonogashira coupling reaction has grown into the most popular method for the alkynylation of aryl or alkenyl halides. The Sonogashira coupling reaction would be the ideal candidate for the formation of the C_1-C_{15} bond of eletefine (Scheme 4 and 5).

8.5.1 Mechanism for the Sonogashira coupling reaction

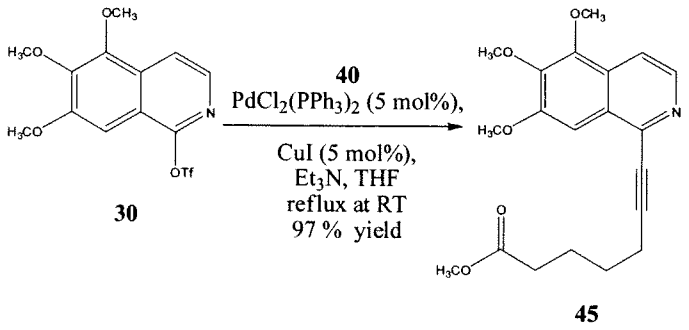
The exact mechanism for the Sonogashira coupling reaction is not fully understood; however, identification of some of the transient species suggests plausible mechanistic pathways.[33] One such mechanistic pathway takes place through two catalytic cycles: the palladium cycle and the copper cycle (Scheme 18). The palladium cycle begins with the oxidative addition of the aryl halide **44b** to the Pd(0) catalyst **44a** that is generated from the initial $PdCl_2(PPh_3)_2$ catalyst. The next step connects with the copper cycle and a rate-determining transmetallation picks up the terminal alkyne to produce intermediate **44d**. The product **44e** is then formed following reductive elimination which regenerates the catalyst to continue the cycle. The copper cycle begins with the attachment of the terminal alkyne **44g** to the copper catalyst to form the alkyne-copper complex **44h**. Exposure to base **44i** abstracts the acetylenic proton of the terminal alkyne to produce the copper acetylide **44k**. Transmetallation from the copper acetylide generates the intermediate **44d**, which further undergoes reductive elimination to yield the product.[33]



Scheme 18. Sonogashira Coupling Mechanism [33]

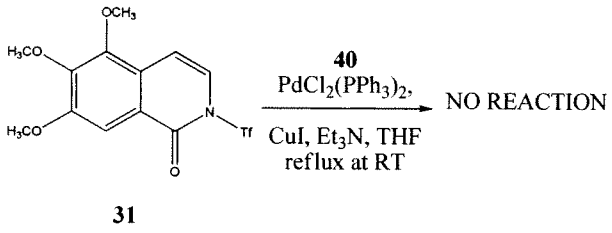
8.5.2 Sonogashira Coupling Reactions performed

The Sonogashira reaction was performed on triflate **30** with methyl ester alkyne **40** to yield isoquinolinylalkyne **45** in high yield (Scheme 19). Yields for this reaction were initially in the range of 50-60%.[18] After optimization and utilization of a recrystallized form of copper iodide, yields were greatly improved.



Scheme 19: Sonogashira reaction to produce isoquinolinylalkyne **45**

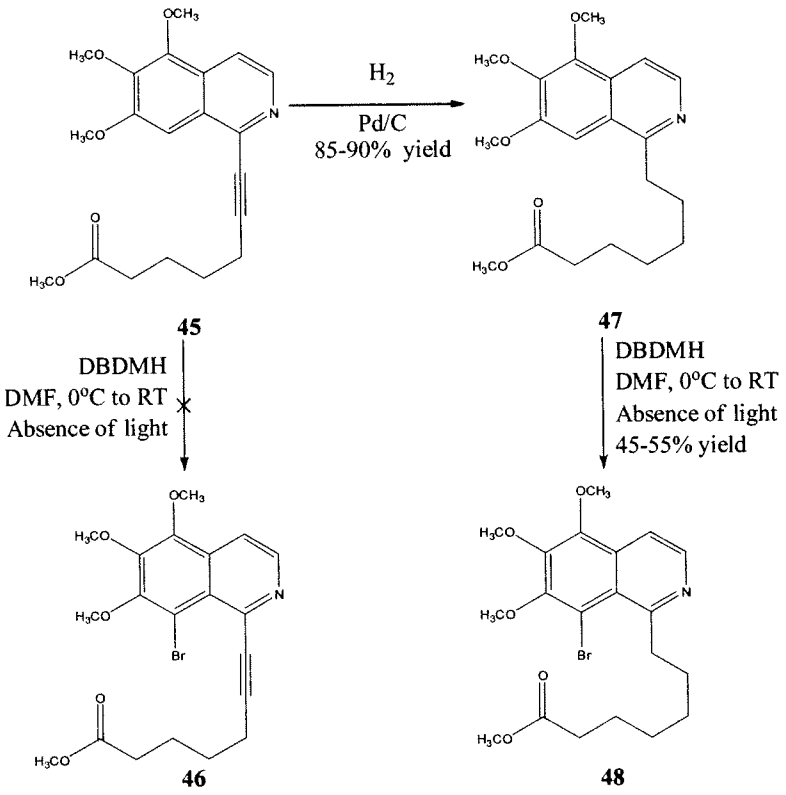
As discussed previously, an effective method for purifying triflate **30** was not initially discovered, so a mixture of triflate **30** and *N*-triflate **31** was originally subjected to the Sonogashira reaction, resulting in lower calculated yields. Since *N*-triflate **31** is unreactive to the Sonogashira reaction conditions, we did not perceive the presence of *N*-triflate **31** to be detrimental. This was further proven when a purified *N*-triflate **31** was subjected to a Sonogashira reaction (Scheme 20).



Scheme 20: Sonogashira reaction with *N*-triflate **31**

As envisioned in Route A, the Sonogashira reaction would be followed by a lithium-halogen exchange (Scheme 4). To increase the functionality and promote a lithium-halogen exchange, a halogen would need to be placed at the C_8 position of the molecule as in brominated triflate **32**. Bromination of isoquinolinylalkyne **45** with DBDMH was unsuccessful (scheme 21). Alternatively, a hydrogenation reaction was

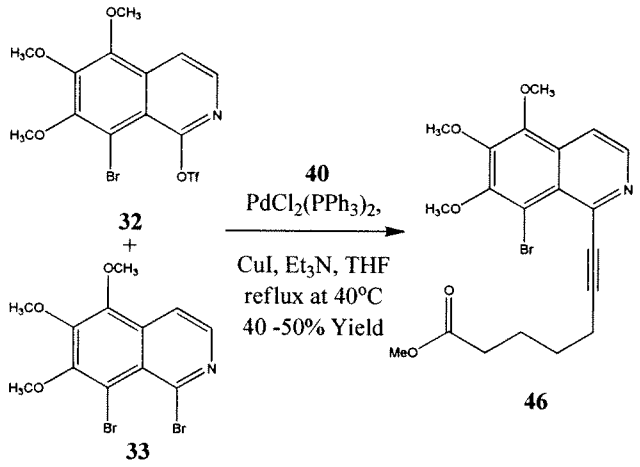
performed to reduce the alkyne before undergoing a bromination. The reduced isoquinolinylalkane **47** underwent bromination successfully to achieve bromoisoquonilinylalkane **48**.[18]



Scheme 21: Synthesis of bromoisoquinolinylalkane **48**

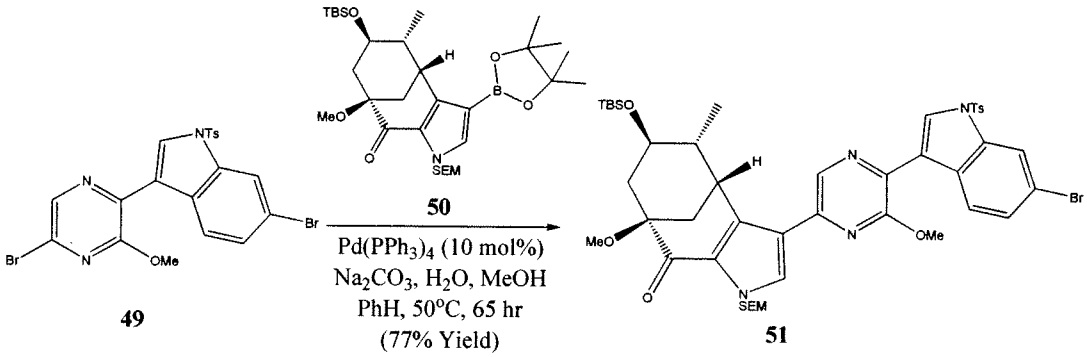
Bromoisoquinolinylalkyne **46** was a highly desirable compound because a successful ring closure would set the stage to perform the novel alkyne hydration (Scheme 4 and 5). Performing the Sonogashira reaction on brominated trfilate **32** could avoid bromination in the presence of alkyne functionality. Interestingly, when the Sonogashira reaction was performed on the 6:1 mixture of brominated triflate **32:** *bis*-brominated **33**, only a single product was observed, that being the bromoisoquinolinylalkyne **46** (Scheme 22). With brominated triflate **32,** the triflate functional group is more reactive towards oxidative addition than a bromine leading to

alkyne **46**.[34] Despite the presence of two halogenated sites on *bis*-brominated **33**, the oxidative addition of the palladium complex selectively occurred at one site over the other. Oxidative addition was preferred at the C_1 position over the C_8 position.



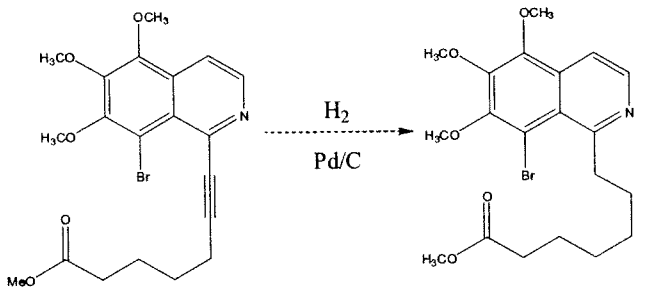
Scheme 22: Synthesis of bromoisoquinolinylalkyne **46**

Upon review of the literature, it was found that Brian Stoltz of California Technical Institute published similar results back in 2004. He reported the regioselective Suzuki coupling reaction of a pyrroloboronic ester **50** with dibromide **49** that left the indolyl bromide of the molecule intact (Scheme 23).[35]



Scheme 23: Stoltz's Suzuki coupling reaction with pyrroloboronic ester **50** and dibromide **49** [35]

To further prove the regioselectivity of the reaction, a hydrogenation could be performed on bromoisoquinolinylalkyne **46** resulting in bromoisoquinolinylalkane **48,** for which spectral data already exists (Scheme 24). By comparing the data, the correct structure of bromoisoquinolinylalkyne **46** could be determined and the regioselectivity of the Sonogashira reaction could be confirmed.



46 **48**

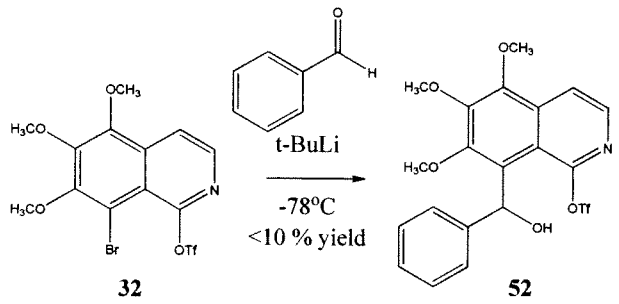
Scheme 24: Future work to confirm structure of bromoisoquinolinyl-alkyne **46**

The reactions performed to this point outline possible methods for completing route A (Scheme 4). With the presence of a bromine functional group at the C_8 position in brominated triflate **32**, a carbon-carbon bond forming reaction could take place as laid out in route B (Scheme 5). An ideal candidate for this bond formation is the lithium-halogen exchange reaction.

8.6 Lithium halogen exchange

An option for the route B synthetic plan calls for a lithium-halogen exchange reaction followed by a Sonogashira reaction. The lithium-halogen exchange was attempted on brominated triflate **32** with very little to no success. The reaction was first attempted with benzaldehyde affording a low yield of alcohol **52**, which was observed by GC/MS (Scheme 25). This strengthened our understanding of the system

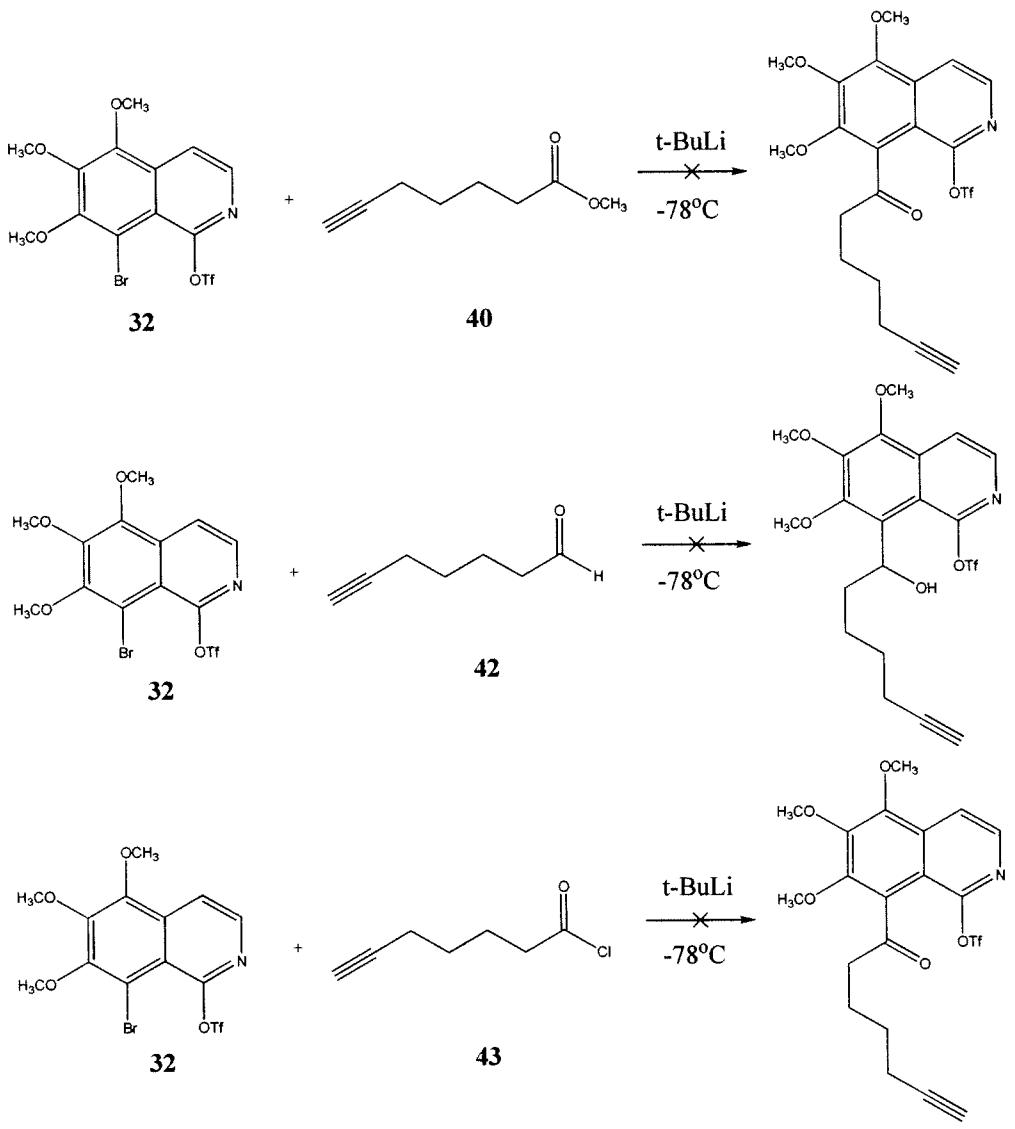
and proved that a lithium-halogen exchange could be performed on brominated triflate **32.**



32 52

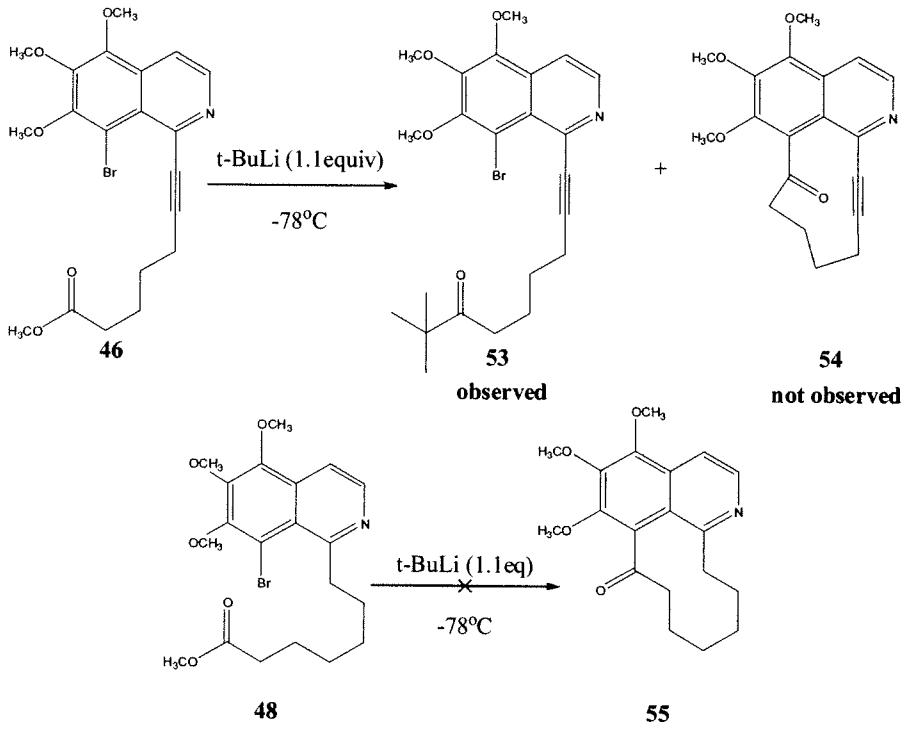
Scheme 25: Lithium halogen exchange with brominated triflate **32** and benzaldehyde

The reaction was then performed with methyl ester alkyne **40**, but no product was observed (scheme 26). Aldehyde-alkyne **42** was believed to be more reactive than the ester; however no addition product was observed in this case either. The most reactive of the alkynes mentioned was believed to be acyl chloride **43**. At first, TLC analysis indicated that the reaction of acyl chloride **43** with brominated triflate **32** was indeed generating the ketone, but no other evidence could be obtained to support product formation. All attempts were made to perform the reaction under an inert anhydrious Ar atmosphere, but the optimal reaction conditions could not be met to favor a lithium-halogen exchange.



Scheme 26: Lithium halogen exchange reactions attempted

Route A uses a lithium-halogen exchange envisioned to proceed intramolecularly with bromoisoquinolinylalkyne **46** or bromoisoquinolinylalkane **48** (Scheme 27). The reactions did not yield the products desired but reaction with bromoisoquinolinylalkane **46** yielded the by-product, t-butyl ketone **53**, that was observed using a GC/MS. The desired product **54** was not isolated. Concurrently, Lewis acid promoted cyclizations were being developed towards route A (Scheme 4).



46 **53** **54**

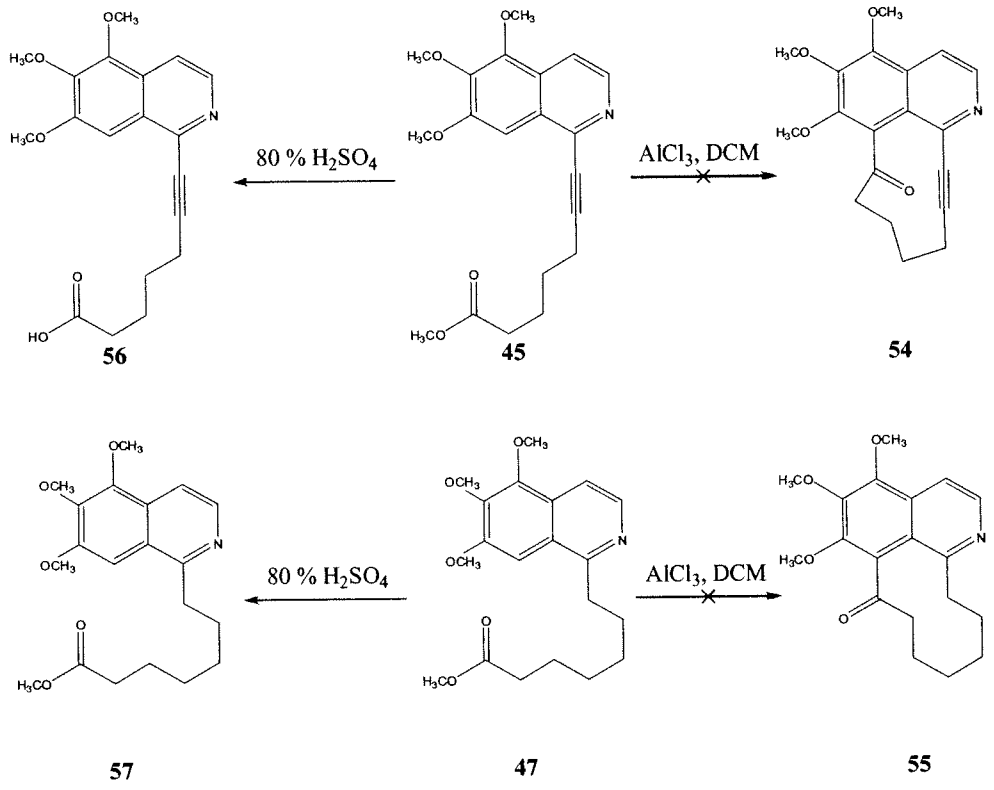
observed **not observed**

48 **55**

Scheme 27: Intramolecular lithium-halogen exchange with bromoisoquinolinylalkyne **46** and bromoisoquinolinylalkane **48**.

8.7 Lewis Acid Strategy

Attempts to cyclize on isoquinolinylalkyne **40** with Lewis acid conditions as well as strong acidic conditions did not provide the desired results (Scheme 28).[18] Treatment of alkyne-ester **45** with $AlCl_3$ resulted in no reaction at room temperature. At elevated temperatures, a complex mixture of products was observed. The formation of the ten-membered ring was also attempted using varying concentrations of sulfuric acid. Alkyne-ester **45** and alkane-ester **47** were treated with sulfuric acid to provide the hydrolysis product, carboxyilic acid **56** and **57**, respectively. Once again, when elevated temperatures were used, a complex mixture was obtained.



56 45 54

57 47 55

Scheme 28: Use of Lewis acid and acidic conditions in attempts to cyclize ten-membered ring [18]

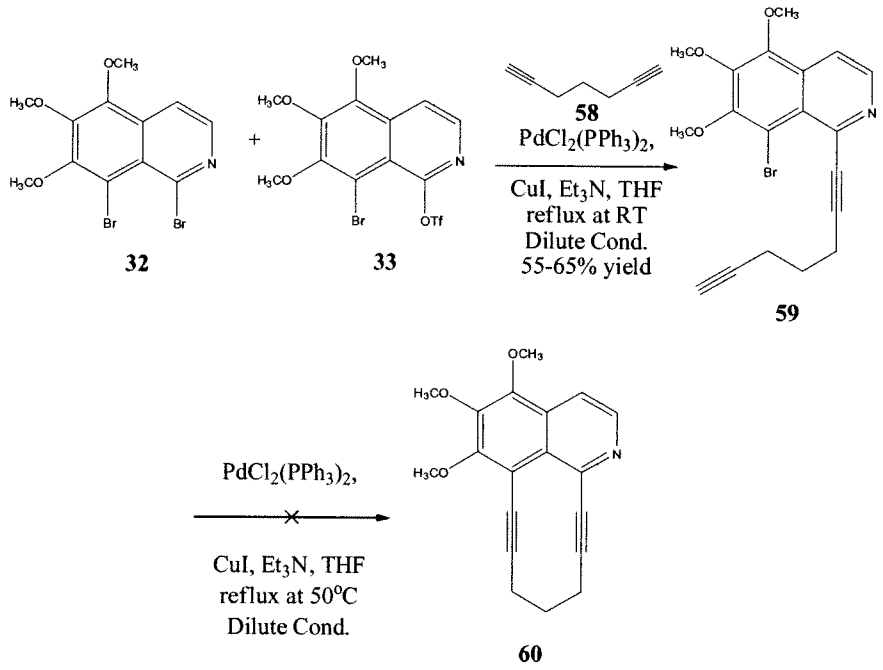
9. Current and future directions

Currently, a few areas are being explored to potentially provide a completion to the synthesis of eletefine that take advantage of the bifunctionality of brominated triflate **32**. These reactions include performing two Sonogashira reactions with dialkyne **58** or even attaching two alkyne fragments that would cyclize to form the ten-membered ring.

9.1 Use of dialkyne **58** to construct rings C and D

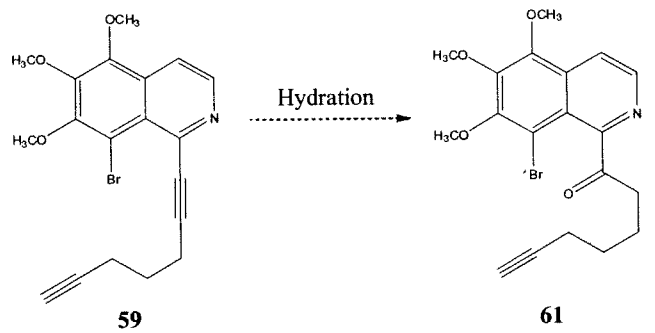
Dialkyne **58** underwent a Sonogashira reaction with a mixture of brominated triflate **32** and bis-brominated **33** to yield alkyne **59**. The product was isolated and re-subjected

to the same Sonogashira reaction under dilute conditions. Heat was applied to drive the reaction; however dialkyne **60** was not observed (Scheme 29). Instead a complex mixture was obtained.



Scheme 29: Sonogashira reaction with dialkyne **58** and brominated triflate **32**

It is believed that because of the increased strain of the two alkyne functionalities, the product made would degrade readily. To avoid the increased strain, an internal hydration could be performed on alkyne **59** to provide ketone **61** (Scheme 30). It is believed that the terminal alkyne is less reactive than the internal one towards a hydration. The difference in reactivity is because an internal hydration activation energy should be lowered due to resonance stabilization with the aromatic ring, which should also provide good regioselectivity.[36]

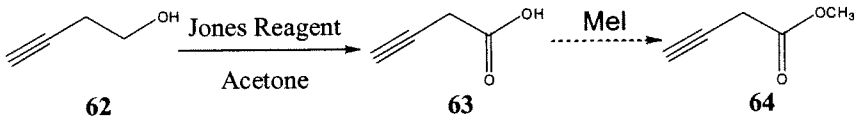


59 61

Scheme 30: Hydration of dialkyne **59**

9.2 Synthesis of C and D rings using two different alkynes

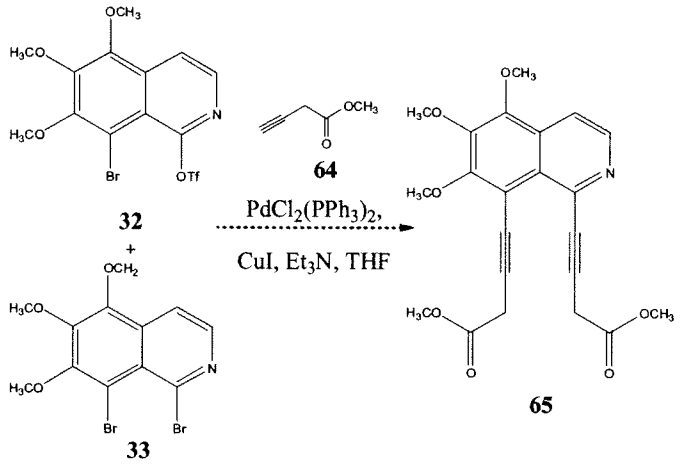
Another area being explored is a stepwise addition of two alkynes, then cyclizing to form the ten-membered ring. The alkyne fragment being used for this study is alkyne **64**, which can be easily created by reacting commercially available but-3-yn-1-ol (**62**) with a Jones Reagent and then methylating the resulting carboxylic acid **63** to give methyl ester alkyne **64** (Scheme 31).[37]



62 63 64

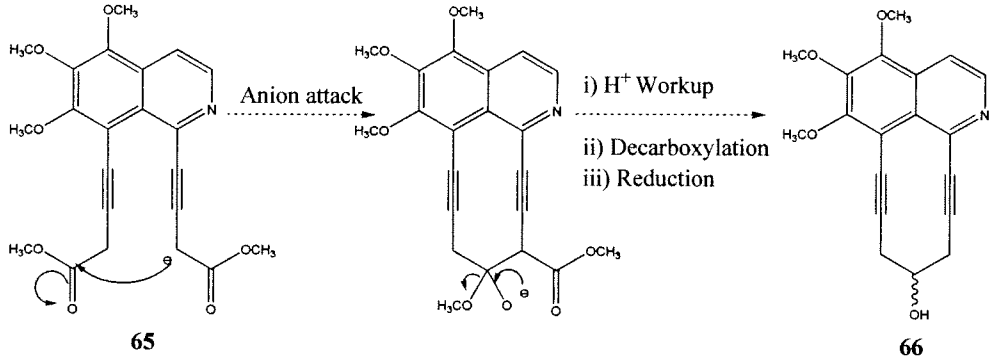
Scheme 31: Synthesis of methyl ester alkyne **64**

A Sonogashira reaction could be performed to install the methyl ester alkyne **64** twice onto brominated triflate **32** to form dialkyne **65** (Scheme 32). This method was tested with phenylacetylene, which yielded the desired product in moderate yield (45%). The advantage of putting both alkynes parallel to each other is that the pi-stacking of the alkynes would help to favor the product and even stabilize it.[38]



Scheme 32: Sonogashira reaction to form dialkyne **65**

Following the formation of dialkyne **65**, anion chemistry could be performed to cause the carbon adjacent to one of the methyl ester groups to attack the other carbonyl resulting in cyclized ketone product (Scheme 33). The ketone can then be further reduced to the alcohol **66**.

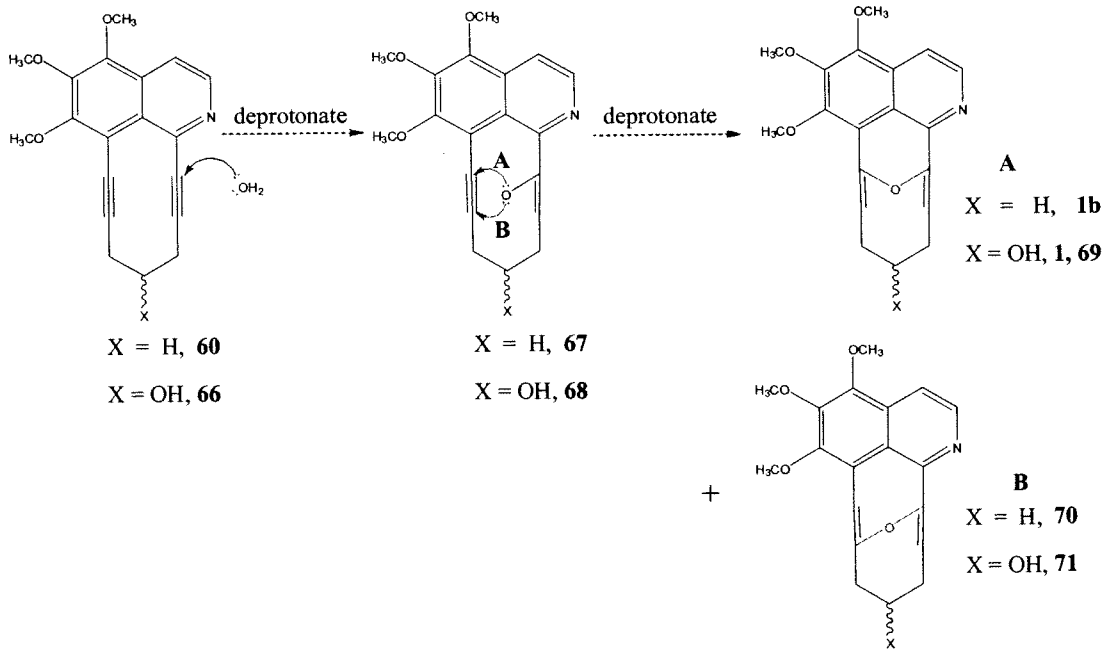


Scheme 33: Proposed intra-molecular anion attack to make the ten-membered ring **66**

9.3 Proposed oxocane formation from dialkyne's **60** and **66**

Following the formation of the 10-membered ring, a hydration reaction could be performed on the alkyne to form the oxygen bridge in the center of the molecule

(Scheme 34). Formation of the enol at the benzylic carbon is favored due to the increased stabilization caused by resonance with the aromatic ring. Furthermore, the synthesis of a six-membered ring is favored over the synthesis of a seven-membered ring. This is because a 6-*exo-dig* ring forming reaction is favored over a 7-*endo-dig* forming reaction.[17]



Scheme 34: Proposed completion of oxygen bridge

10. Conclusion

Synthetic studies performed have resulted in the successful synthesis of advanced key intermediates in our synthetic route towards eletefine. The use of *bis*-functionalized brominated triflate **32** presents some interesting opportunities to apply various methods to complete the synthesis. It sets the stage to pursue both routes A and B. Moreover, the improvements made to existing reactions have greatly improved yields towards a more efficient route. Specifically, improvements have been made towards the synthesis of triflate **30** and the Sonogashira reaction has been improved to

produce higher yields. Furthermore, the discoveries of different by-products, such as *N*-triflate **31** and bis-brominated **33**, have contributed a great deal of knowledge about the chemistry of the isoquinoline structure. A successful lithium-halogen exchange would have brought us closer to completing eletefine, but the use of the Sonogoshira reaction with the *bis*-functionalized brominated triflate **39** may prove to be an efficient alternative.

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26. **Methyl hept-6-ynoate (65)**

Rf = 0.91 (5% MeOH/DCM; stained $KMnO_4$)

IR υ_{max} (neat)/cm^{-1}: 3292, 2951, 1732, 1435, 1197, 1172, 1145, 632

^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.69 (s, 3H), 2.36 (t, *J* = 7.29 Hz, 2H), 2.23 (dt, *J* = 7.00 Hz, 2H), 1.97 (t, *J* = 2.82 Hz, 2H), 1.82 – 1.53 (m, 4H)

^{13}C-NMR (75 Hz, $CDCl_3$): δ 174.1, 84.2, 69.0, 51.8, 33.8, 28.1, 24.3, 18.4

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28. **Hept-6-ynoyl chloride (68)**

Rf = 0.66 (1 % MeOH/CH_2Cl_2; stained in ceric ammonium molybdate)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.94 (t, *J* = 7.2 Hz, 2H), 2.24 (dt, *J* = 6.9 Hz, 2H), 1.97 (t, *J* = 2.61 Hz, 1H), 1.89 – 1.54 (m, 4H)

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General Experimental Procedure

All non-aqueous reactions were conducted in flame dried apparatus under argon atmosphere. All reactions were stirred magnetically. Air- and water sensitive reagents and solutions were transferred *via* syringe (unless otherwise noted) and introduced to the apparatus through rubber septa. Reactions were heated in a sand bath encased in a heating mantle, controlling the temperature with a variable transformer. Temperatures reported refer to bath temperatures unless otherwise noted. Distillations were performed under argon atmosphere. Vacuum distillations utilized a water aspirator (> 15 mmHg).

The phrase "concentrated" or "concentrated under reduced pressure" refers to removal of solvents *via* a rotary-evaporator using a water aspirator.

Reagents and Solvents

All reagents and solvents were of commercial grade and were used as obtained from the suppliers except for the ones listed below that were purified as follows:

Distilled under argon from sodium-benzophenone ketyl: THF

Distilled under argon from calcium hydride: acetonitrile,

Recrystallized copper iodide using the following procedure: 16 g CuI was added to a saturated boiling solution of 50 mL H_2O and about 50 g NaI and boiled for 15 minutes. 1 g Norite was added and continued boiling for another 15 minutes. Filtered and then diluted cool filtrate with 50 mL water. The resulting crystals were then filtered and washed with the following in order: water (10 mL), ethanol (10 mL), ethyl acetate (10 mL), ether (10 mL) and pentane (10 mL).

Crystals were dried overnight under vacuum from an oil pump and then stored in a desiccator.

Other solvents and reagents were purified according to D. D. Perrin, W. L. Armarego, *Purification of Laboratory Chemicals* (3rd Ed.), Pergamon Press: New York, 1989.

Chromatography

"Chromatography" refers to flash column chromatography using 230-400 mesh silica gel (EMD Reagents). Analytical and preparative thin layer chromatography (TLC) was performed on EMD pre-coated silica gel 60 F-254 plastic plates (0.25 mm). Visualization was assayed by short wave UV illumination and/or by staining the plate followed by heating with a heat gun for approximately 10-15 seconds when appropriate. Ceric ammonium molybdate (CAM) stain was prepared by combining 0.2g of ceric sulfate and 4.8g of ammonium molybdate in 10mL of concentrated sulfuric acid and 90mL of water. *Para*-anisaldehyde stain was prepared by mixing 15mL of *p*-anisaldehyde, 3mL glacial acetic acid, 10mL concentrated sulfuric acid, and 260mL of 95% ethanol. Potassium permanganate ($KMnO_4$) stain was made by mixing 6g potassium permanganate with 10mL 5% sodium hydroxide and 40g potassium carbonate and diluted to 1L of water.

Physical Data and Instrumentation

Proton Nuclear Magnetic Resonance (^{1}H-NMR) spectra were obtained on a Bruker DRX-300 (300 MHz). Chemical shifts are reported in ppm downfield and are

internally referenced using $CDCl_3$ (7.26 ppm) as solvent. Proton NMR data are reported as follows: chemical shift (multiplicity, coupling constants in Hz, number of protons). Multiplicity was abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of a doublet), dt (doublet of triplets), s (br) (broad singlet).

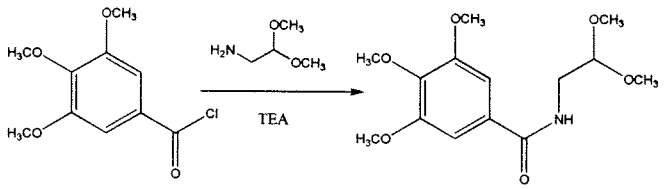
Carbon 13 Nuclear Magnetic Resonance (^{13}CNMR) spectra were obtained on a Bruker DRX-300 (75 MHz). Chemical shifts are reported in ppm downfield and are internally referenced using $CDCl_3$ (77.2 ppm) as solvent.

Infrared (IR) spectra were recorded using a **Shimadzu IR Prestige-21 with ATR** spectrophotometer and are reported in wave numbers (cm^{-1}) with polystyrene as standard.

Low-resolution mass spectra were obtained using a **Hewlett Packard Model 6890 Series gas chromatography with a 5973 Mass Selective Detector and/or an Applied Biosystems – Q Trap 3200 – LC-MS/MS**. High resolution mass spectra were obtained from the State University of New York at Buffalo. Mass spectrometry ES (electrospray).

Experimentals

The following pages contain experimental procedures for several reactions portrayed in this thesis.



N-(2,2-Dimethoxy-ethyl)-3,4,5-trimethoxy-benzamide (35)

To 20 g of 3,4,6-trimethoxy benzoyl chloride (**34**) (86.1 mmol, 1.0 eq.) in 300 mL of CH_2Cl_2 at 0°C was added 30mL triethylamine (172. mmol, 2.0 eq.) over 2 minutes using an addition funnel while magnetically stirring. The reaction was stirred for 4 minutes at 0°C before adding 10 mL of 2,2-Dimethoxy-ethylamine (92.7 mmol, 1.1 eq.) over 6 minutes using an addition funnel. The reaction was allowed to warm to room temperature and stirred for 21 hours. The reaction was washed with HCl (2 x 300 mL), water (2 x 400 mL), saturated $NaHCO_3$ (400 mL), 50 % brine (400 mL), dried over $MgSO_4$, filtered and concentrated, to give 19.17 g of *N*-(2,2-Dimethoxyethyl)-3,4,5-trimethoxybenzamide (**35**) (63.5 mmol, 74 % yield) as a white flaky solid which was carried onto the next step without purification.

Compound 35

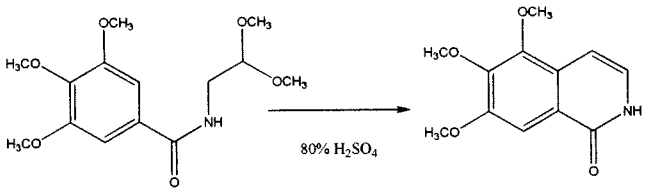
R_f = 0.6 (50 % EtOAc/Hexanes)

IR υ_{max} (neat)/cm^{-1}: 2938, 2839, 1636, 1125

^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.99 (s, 2H), 6.30 (s, 1H), 4.48 (t, *J* = 5.3Hz, 1H), 3.89 (s, 6H), 3.87 (s, 3H), 3.59 (t, *J* = 5.7 Hz, 2H), 3.43 (s, 6H,)

^{13}C-NMR (75 MHz, $CDCl_3$): δ 167.7, 153.6, 141.3, 130.2, 104.8, 103.2, 61.3, 56.7, 55.1, 42.0

HRMS (ESI+): Exact mass calculated for $C_{14}H_{21}NO_6$ [M+H^+] = 300.1442, found = 300.1438



35 36

5,6,7 trimethoxyisoquinolin-1-ol (36)

To 3.5 g of amide **35** (11.7 mmol, 1.0 eq.) was added 30 mL 80% sulfuric acid at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 22 hours. It was then poured over ice (50 g) and then quenched with saturated aqueous sodium bicarbonate. The aqueous solution was extracted with CH_2Cl_2 (3 x 100 mL), the combined organics were dried over magnesium sulfate, filtered, and concentrated to give 2.67 g (11.4 mmol, 97 % yield) of 5,6,7 trimethoxyisoquinolin-1-ol (**36**) as a white flaky solid which was used without purification.

Compound 36

R_f = 0.4 (5 % MeOH/DCM)

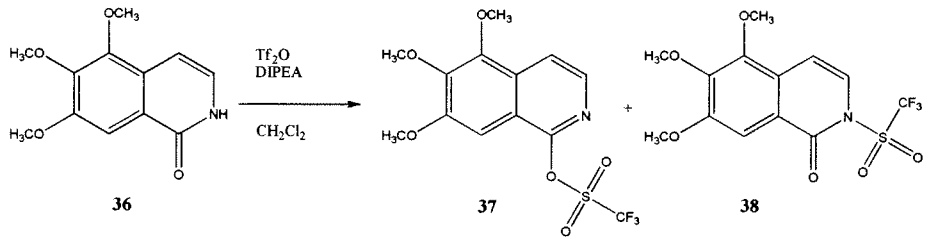
IR υ_{max} (neat)/cm^{-1}: 3154, 2835, 1672, 1117

m/z (GCMS) : 235, 220, 205, 191, 177, 106, 28

^{1}H-NMR (300 MHz, $CDCl_3$): δ 11.84 (s, 1H), 7.64 (s, 1H), 7.13 (d, *J* = 3.6 Hz, 1H), 6.80 (d, *J* = 3.6 Hz, 1H), 4.00 (s, 6H), 3.97 (s, 3H)

^{13}C-NMR (75 MHz, $CDCl_3$): δ 153.3, 147.8, 146.2, 128.4, 125.9, 122.4, 103.4, 101.2, 61.6, 61.2, 56.3

HRMS (ESI+): Exact mass calculated for $C_{12}H_{13}NO_4[M+H^+]$ = 236.0917, found = 236.0917



5,6,7-Trimethoxyisoquinolin-1-yl trifluoromethanesulfonate (37)

To 7.5 g of isoquinoline **36** (31.9 mmol, 1.0 eq.) stirring in 230 mL of DCM at 0°C was added 5.5 mL trifluormethanesulfonic anhydride (31.9 mmol, 1.0 eq.) drop-wise *via* syringe followed by addition of 9.45 mL N,N-Diisopropylethyl amine (54.2 mmol, 1.7 eq.) dropwise *via* syringe. The resulting solution was warmed to room temperature and stirred for 24 hours. To drive the reaction to completion, the solution was re-cooled to 0°C and 2.25 mL trifluoroacetic anhydride (16.0 mmol, 0.5 eq.) was added dropwise *via* syringe followed by addition of 4.73 mL N,N-Diisopropylethyl amine (27.1 mmol, 0.85 eq.) drop-wise via syringe. The reaction was then allowed to warm to room temperature and stirred for 5 hours before quenching with saturated aqueous sodium bicarbonate (200 mL). The aqueous layer was with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with water (3 x 100 mL), dried over magnesium sulfate, filtered and concentrated to yield a mixture of **37** and **38.** The crude product was purified using silica gel chromatography (3 % EtOAc/hexanes → 18 % EtOAc/ hexanes) to give 10.53g (28.6 mmol, 90 % yield) of 5,6,7-trimethoxyisoquinolin-1-yl trifluoromethanesulfonate (**37**) as yellow solid.

Compound 37

R_f = 0.5 (DCM)

IR υ_{max} (neat)/cm^{-1}: 2947, 1595, 1200, 1123

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.07 (d, *J* = 5.7 Hz, 1H), 7.87 (d, *J* = 6.6Hz, 1H), 4.06 (s, 3H), 7.12 (s, 1H), 4.03 (s, 6H)

^{13}C-NMR (75 MHz, $CDCl_3$): δ 56.3, 61.5, 61.8, 96.9, 120.9, 132.0, 137.8, 145.4, 147.2, 152.0, 155.5

HRMS (ESI+): Exact mass calculated for $C_{13}H_{12}F_3NO_6S[M+H^+]$ = 367.0414, found = 367.0413

Compound 38

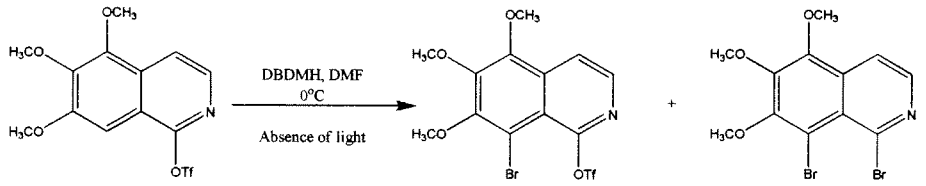
R_f = 0.5 (DCM)

IR υ_{max} (neat)/cm^{-1}: 3130, 2953, 2845, 1693, 1591, 1467, 1377, 1195, 1113, 964, 609, 578

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.60 (s, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 4.00 (s, 3H), 3.95 (s, 6H)

^{13}C-NMR (75 MHz, $CDCl_3$): δ 160.7, 154.8, 148.5, 126.2, 123.4, 121.9, 121.6, 117.6, 105.8, 104.6, 62.2, 61.6, 56.7

HRMS (ESI+): Exact mass calculated for $C_{13}H_{12}F_3NO_6S[M+H^+]$ =367.0414, found = 367.0413



37 39 27

8-bromo-5,6,7-trimethoxyisoquinolin-1-yl triflouromethanesulfonate (39)

To a stirred solution of 5,6,7-trimethoxyisoquinolin-1-yl triflouromethanesulfonate (**37**) (500 mg, 1.36 mmol, 1.0 eq) in dimethylformamide (10 mL) at 0°C in the absence of light was added 584 mg of 1,3-dibromo-5,5-dimethylhydantoin (2.04 mmol, 1.0 eq). The reaction was allowed to warm to room temperature and stirred for 24 hours. The reaction was diluted with diethyl ether (10 mL), washed with 50 % brine (3 x 10 mL), dried over magnesium sulfate, filtered, and concentrated. The crude product was purified using silica gel chromatography (2 % EtOAc/hexanes → 10 % EtOAc/hexanes) to give 326 mg (0.73 mmol, 54 % yield) of 8-bromo-5,6,7-trimethoxyisoquinolin-1-yl triflouromethanesulfonate (**39**) as a yellow viscous product.

Compound 39

R_f =0.20 (10 % EtOAc/Hex)

IR υ_{max} (neat)/cm^{-1}: 3124, 2943, 1701, 1653, 1566, 1456, 1404, 1369, 1319, 1195, 1111, 1089, 1002, 966, 613, 580

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.16 Hz, 1H), 6.89 (d, *J* = 8.07 Hz, 1H), 4.07 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H)

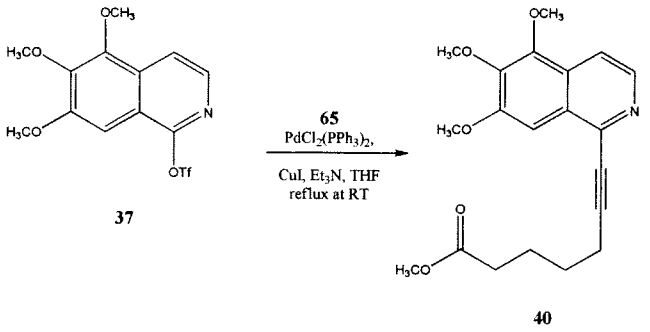
^{13}C NMR (75 Hz, $CDCl_3$): δ 159.2, 153.1, 152.3, 147.8, 130.5, 125.1, 121.9, 119.6, 115.5, 103.7, 62.2, 61.8, 61.4

HRMS (ESI+): Exact mass calculated for $C_{13}H_{11}BrF_3NO_6S[M+H^+]$ = 445.9519, found = 444.9520

Compound 27

R_f =0.20 (10 % EtOAc/Hex)

^1H NMR (300 MHz, $CDCl_3$): δ 4.07 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H)



37 40

Methyl 7-(5,6,7-trimethoxyisoquinolin-1-yl)hept-6-ynoate (40)

To 200 mg of 5,6,7-trimethoxyisoquinolin-1-yl trifluoromethanesulfonate (**38**) (545 µmols, 1.0 eq) in 6.0 ml of dry tetrahydrofuran was added 114 mg of methyl hept-6-ynoate (**65**) (817 µmols, 1.5 eq), 438 mg of diethylamine (6.00 mmols, 11 eq), followed by 26.7 mg of dichlorobis(triphenylphosphine) palladium(II) (38.1 µmols, 0.07 eq) and 8.3 mg of copper iodide (43.6 µmols, 0.08 eq). The resulting mixture was stirred at room temperature for 18 hrs when the reaction was judged complete by TLC. The mixture was then diluted with 7 mL of ethyl acetate, washed with saturated aqueous sodium bicarbonate (3 × 5 mL) and 50% aqueous brine (3 × 5 mL). The organic phase was then dried over magnesium sulfate, filtered through a plug of silica capped with Celite, and concentrated to a viscous dark brown oil. The crude product was purified with silica gel chromatography (1% MeOH/CH_2Cl_2) to give 189 mg (529 µmol, 97% yield) of methyl 7-(5,6,7-trimethoxyisoquinolin-1-yl)hept-6-ynoate (**40**) as a viscous brown oil.

Compound 40

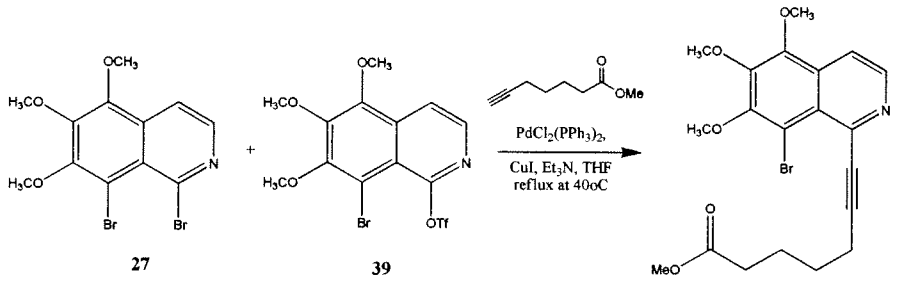
R_f = 0.3 (1% MeOH/DCM)

IR υ_{max} (neat)/cm^{-1}: 2940, 1734, 1406, 1121, 835

^{1}H-NMR (300 MHz, $CDCl_3$): 8.35 (d, *J* = 5.25 Hz, 1H), 7.76 (d, *J* = 5.25 Hz, 1H), 7.45 (s, 1H), 4.03 (s, 6H), 4.01 (s, 3H), 3.67 (s, 3H), 2.63 (t, *J* = 6.7 Hz, 2H), 2.40 (t, *J* = 7.4 Hz, 2H), 1.90 (m, 2H), 1.76 (m, 2H),

^{13}C-NMR (75 MHz, $CDCl_3$): 174.1, 154.6, 147.1, 144.5, 142.7, 141.6, 128.2, 126.9, 114.7, 101.5, 95.2, 79.6, 62.0, 61.6, 56.4, 52.0, 33.9, 28.3, 24.7, 19.8

HRMS (ESI+): Exact mass calculated for $C_{20}H_{23}NO_5[M+H^+]$ = 358.1649, found = 358.1645



Methyl 7-(8-bromo-5,6,7-trimethoxyisoquinolin-1-yl)hept-6-ynoate (41)[41]

To a stirred solution of 250 mg of brominated triflate **39** (0.48 mmol, 1.0 eq) and bisbrominated isoquinoline **24** (0.08 mmol, 0.17 eq) in THF was added 450 mg of diethylamine (6.16 mmol, 11 eq), followed by 118 mg of methyl-ester alkyne **65** (0.84 mmol, 1.5 eq), then 27.3 mg of dichlorobis(triphenylphosphine)palladium(II) (0.039 mmol, 0.07 eq) and 8.6 mg of copper(II) iodide (0.045 mmol, 0.08 eq). The reaction was stirred under reflux at 43°C in a sand bath 18 hours, at which point it was removed from the bath and cooled to room temperature. The reaction mixture was diluted with ethyl acetate (10 mL), washed with saturated sodium bicarbonate (3 x 5 mL), then 50 % brine (3 x 5 mL), dried over magnesium sulfate, filtered, and concentrated. The crude product was purified using silica gel chromatography (0.2 % MeOH/CH_2Cl_2 → 1.0 % MeOH/CH_2Cl_2) to give 106.3 mg (0.24 mmol, 43.7 % yield) of methyl 7-(8-bromo-5,6,7-trimethoxyisoquinolin-1-yl)hept-6-ynoate (41) as a dark yellow viscous product.

Compound 41

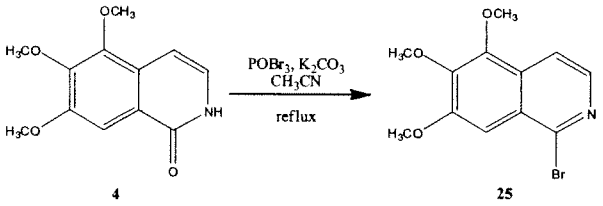
R_f = 0.017 (1 % MeOH/CH_2Cl_2)

IR υ_{max} (neat)/cm^{-1}: 2937, 2225, 1728, 1631, 1612, 1456, 1382, 1330, 1193, 1101, 1057, 1035, 1002, 966

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.42 (d, *J* = 5.67, 1H), 7.84 (d. *J* = 5.67, 1H), 4.03 (s, 1H), 4.01 (s, 3H), 4.01 (s, 3H), 3.96 (s, 3H), 3.66 (s, 3H), 2.58 (t, *J* = 6.79 Hz, 2H), 2.37 (t, *J* = 6.93, 2H), 1.87 – 1.71 (m, 4H)

^{13}C-NMR (75 Hz, $CDCl_3$): δ 174.1, 152.9, 147.4, 146.9, 142.8, 142.6, 132.1, 124.6, 114.5, 109.8, 99.7, 82.2, 62.0, 61.8, 61.3, 52.0, 34.0, 27.6, 24.9, 20.4

HRMS (ESI+): Exact mass calculated for $C_{20}H_{22}BrNO_5[M+H^+]$ = 436.0754, found = 435.0753



4 25

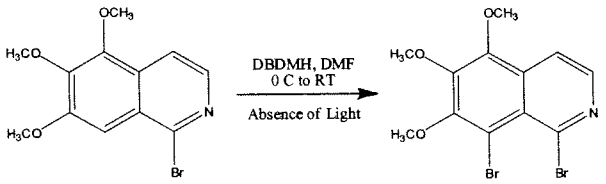
1-bromo-5,6,7-trimethoxyisoquinoline (25)

To a degassed CH_3CN was dissolved 1.0 g of 5,6,7-trimethoxyisoquinolin-1-ol (**36**) (4.25 mmol, 1.0 eq), followed by the addition of 3.65 g of $POBr_3$ (12.75 mmol, 3.0 eq) and 1.76 g of K_2CO_3 (12.75 mmol, 3.0 eq). The solution was heated under reflux at 74°C for 20 hours, then cooled to room temperature. The solvent was evaporated and the remaining solid was suspended in 150 mL of ice water, the pH was adjusted to about 8 using 5 M KOH, extracted organics with CH_2Cl_2, dried over magnesium sulfate, filtered and concentrated to yield a crude 1.33 g of 1-bromo-5,6,7-trimethoxyisoquinoline (**25**) as a dark yellow solid.

R_f = 0.19 (10% EtOAc/Hex)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.04 (d, *J* = 5.61 Hz, 1H), 7.72 (d, *J* = 5.58, 1H), 7.19 (s, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 3.94 (s, 3H)

^{13}C-NMR (75 Hz, $CDCl_3$): δ 155.0, 147.1, 145.0, 143.6, 140.7, 129.7, 126.3, 115.7, 103.4, 63.1, 61.7, 56.6



26 27

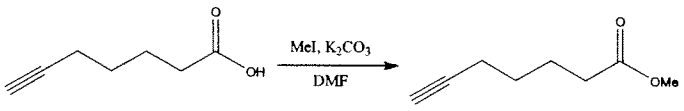
1,8-dibromo-5,6,7-trimethoxyisoquinoline (27)

To a stirred solution of 169 mg (0.57 mmol, 1.0 eq) of 1-bromo-5,6,7-trimethoxyisoquinoline (**25**) in 5 mL of DMF at 0°C in the absence of light was added 243 mg (0.85 mmol, 1.5 eq) of DBDMH and stirred for 23 hours while being warmed to room temperature. The resulting solution was diluted with 7 mL of diethyl ether, washed three times with 7 mL of 50 % brine, dried over magnesium sulfate, filterd and concentrated, then chromatographed over silica gel (2 % EtOAc/Hex → 10 % EtOAc/Hex) to yield 50 mg (0.13 mmol, 23 %) of 1,8-dibromo-5,6,7-trimethoxyisoquinoline (**27**).

Compound 27

R_f = 0.20 (10 % EtOAc/Hex)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.23 (d, *J* = 5.64 Hz, 1H), 7.94 (d, *J* = 5.64 Hz, 1H), 4.07 (s, 1H), 4.06 (s, 1H), 3.99 (s, 1H)



64 65

Methyl hept-6-ynoate (65)

To a stirred solution of 2.0 g (15.9 mmol, 1.0 eq) and 2.6 g (19.0 mmol, 1.2 eq) of K_2CO_3 in 60 mL of DMF was added 3.15 g (22.2 mmol, 1.4 eq) of iodomethane and stirred at 0°C. The solution was warmed to room temperature over three hours, diluted with 60 mL of water, extracted twice with 40 mL of EtOAc, washed three times with 40 mL of water and three times with 40 mL 50 % brine, dried over magnesium sulfate, filtered and concentrated to yield 1.94 g (13.8 mmol, 86.9 %) of methyl hept-6-ynoate (**65**).

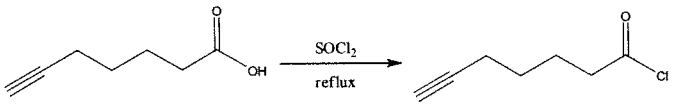
Compound 65

R_f = 0.91 (5% MeOH/DCM; stained $KMnO_4$)

IR υ_{max} (neat)/cm^{-1}: 3292, 2951, 1732, 1435, 1197, 1172, 1145, 632

^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.69 (s, 3H), 2.36 (t, *J* = 7.29 Hz, 2H), 2.23 (dt, *J* = 7.00 Hz, 2H), 1.97 (t, *J* = 2.82 Hz, 2H), 1.82 – 1.53 (m, 4H)

^{13}C-NMR (75 Hz, $CDCl_3$): δ 174.1, 84.2, 69.0, 51.8, 33.8, 28.1, 24.3, 18.4



64 68

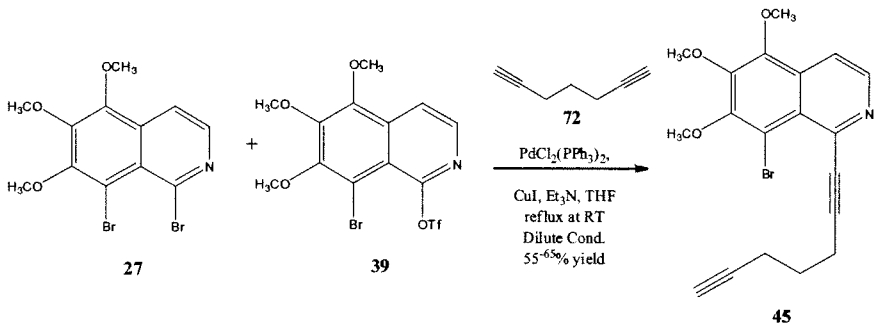
Hept-6-ynoyl chloride (68)

A solution of 1.0 g (7.92 mmol, 1.0 eq) of 6-heptynoic acid (**64**) in 10mL $SOCl_2$ was heated under reflux at 78°C for 20 hours, then cooled to room temperature. Excess $SOCl_2$ was evaporated off to yield a dark red liquid which was distilled under vacuum to yield 883 mg (6.10 mmol, 77.5 %) of hept-6-ynoyl chloride (**68**).

Compound 68

R_f = 0.66 (1 % MeOH/CH_2Cl_2; stained in ceric ammonium molybdate)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.94 (t, *J* = 7.2 Hz, 2H), 2.24 (dt, *J* = 6.9 Hz, 2H), 1.97 (t, *J* = 2.61 Hz, 1H), 1.89 – 1.54 (m, 4H)



8-bromo-1-(hepta-1,6,diynyl)-5,6,7-trimethoxyisoquinoline

To a stirred solution of 500 mg (1.12 mmol, 1.0 eq) of brominated triflate **39** in 20 mL of THF was added was added 899 mg of diethylamine (12.3 mmol, 11 eq), followed by 155 mg of dialkyne **72** (1.68 mmol, 1.5 eq), then 55 mg of dichlorobis(triphenylphosphine)palladium(II) (0.08 mmol, 0.07 eq) and 17.1 mg of copper(I) iodide (0.09 mmol, 0.08 eq). The reaction was stirred at room temperature for 18 hours, then diluted with ethyl acetate (20 mL), washed three times with 15 mL saturated sodium bicarbonate, then three times with 15 mL of 50 % brine, dried over magnesium sulfate, filtered and concentrated to yield crude 585 mg (1.51 mmol) of 8-bromo-1-(hepta-1,6,diynyl)-5,6,7-trimethoxyisoquinoline as a black viscous product.

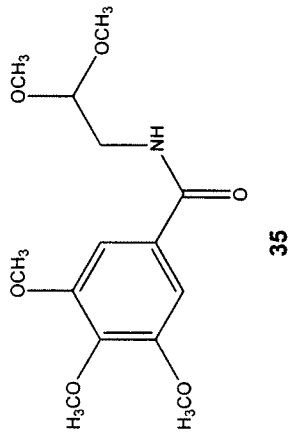
Compound 45:

^{1}H NMR: δ 8.41 (d, *J* = 5.6 Hz, 1H), 7.87 (d, *J* = 5.7 Hz, 1H), 4.04 (s, 1H), 4.03 (s, 1H), 3.97 (s, 1H), 2.71 (t, *J* = 6.93, 2H), 2.45 (dt, *J* = 6.45 Hz, 2H), 2.01 – 1.90 (m, 3H)

Appendix: NMR and IR

The following pages contain ^{1}H NMR, ^{13}C NMR and IR spectra for certain compounds.

The structures and numbers of the structures are located with each spectra.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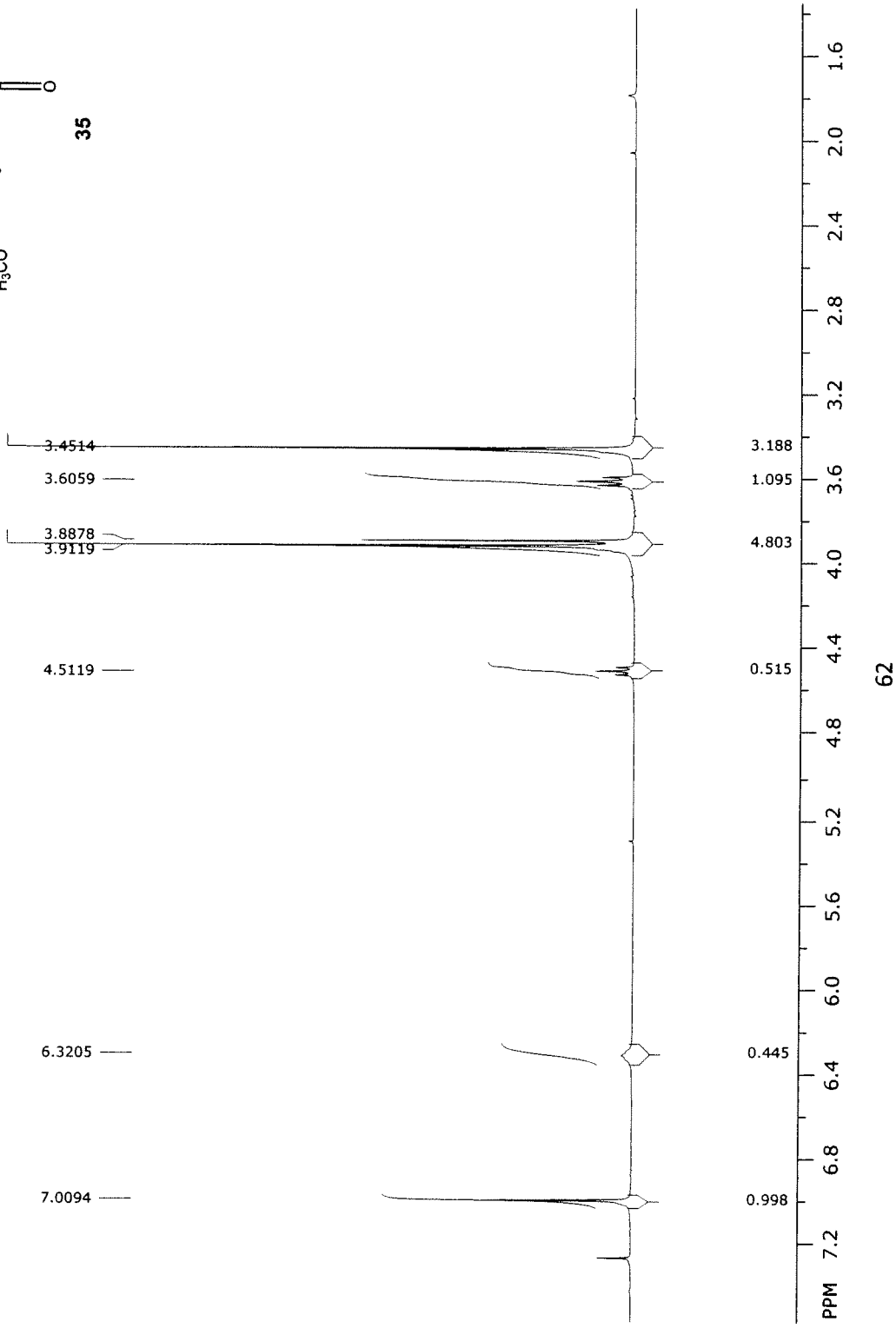
OCH3
H3CO
H3CO

35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0.998
PPM
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6.8
6.4
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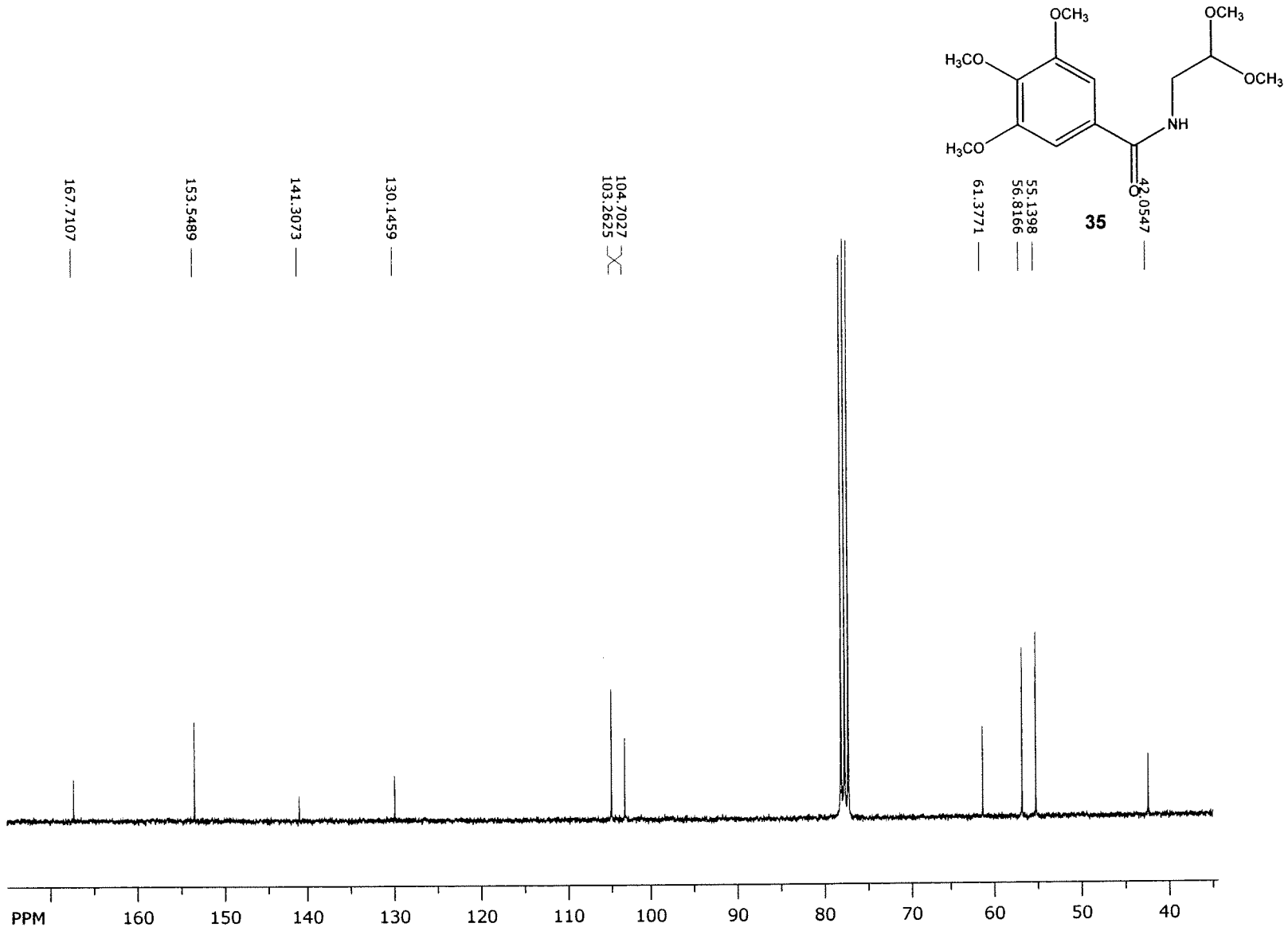
3.6
3.2
2.8
2.4
2.0
1.6

62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80
70
60
50
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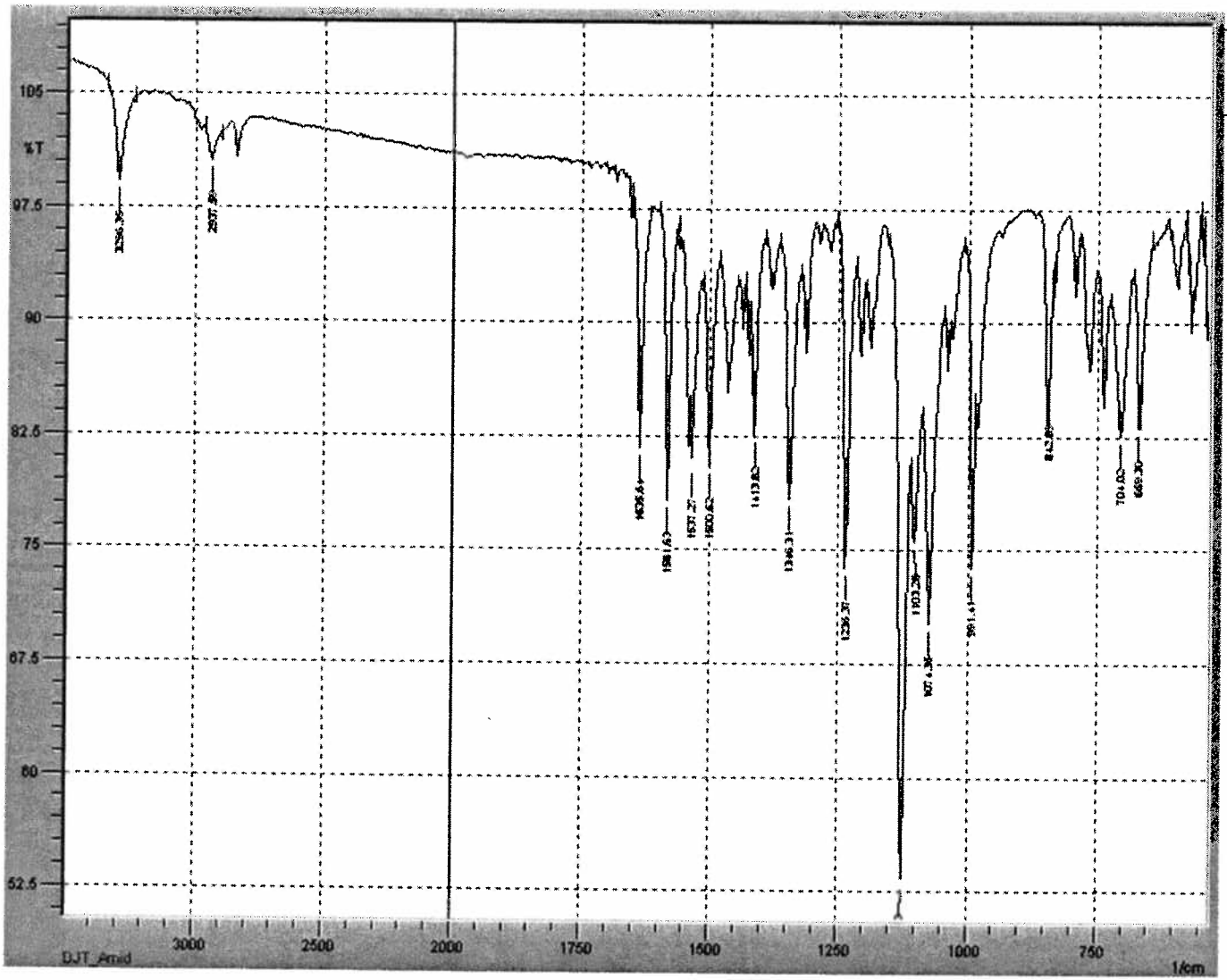
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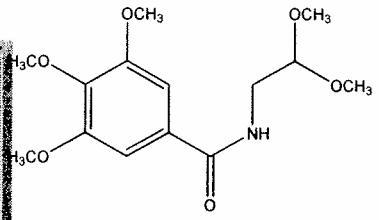
3000
2500
2000
1750
1500
1250
1000
750
1/cm
DJT_Amid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OCH3
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H3CO
NH
O

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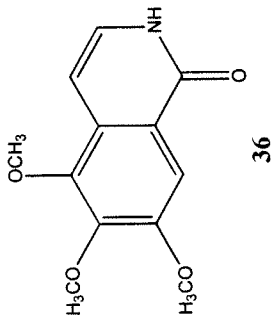
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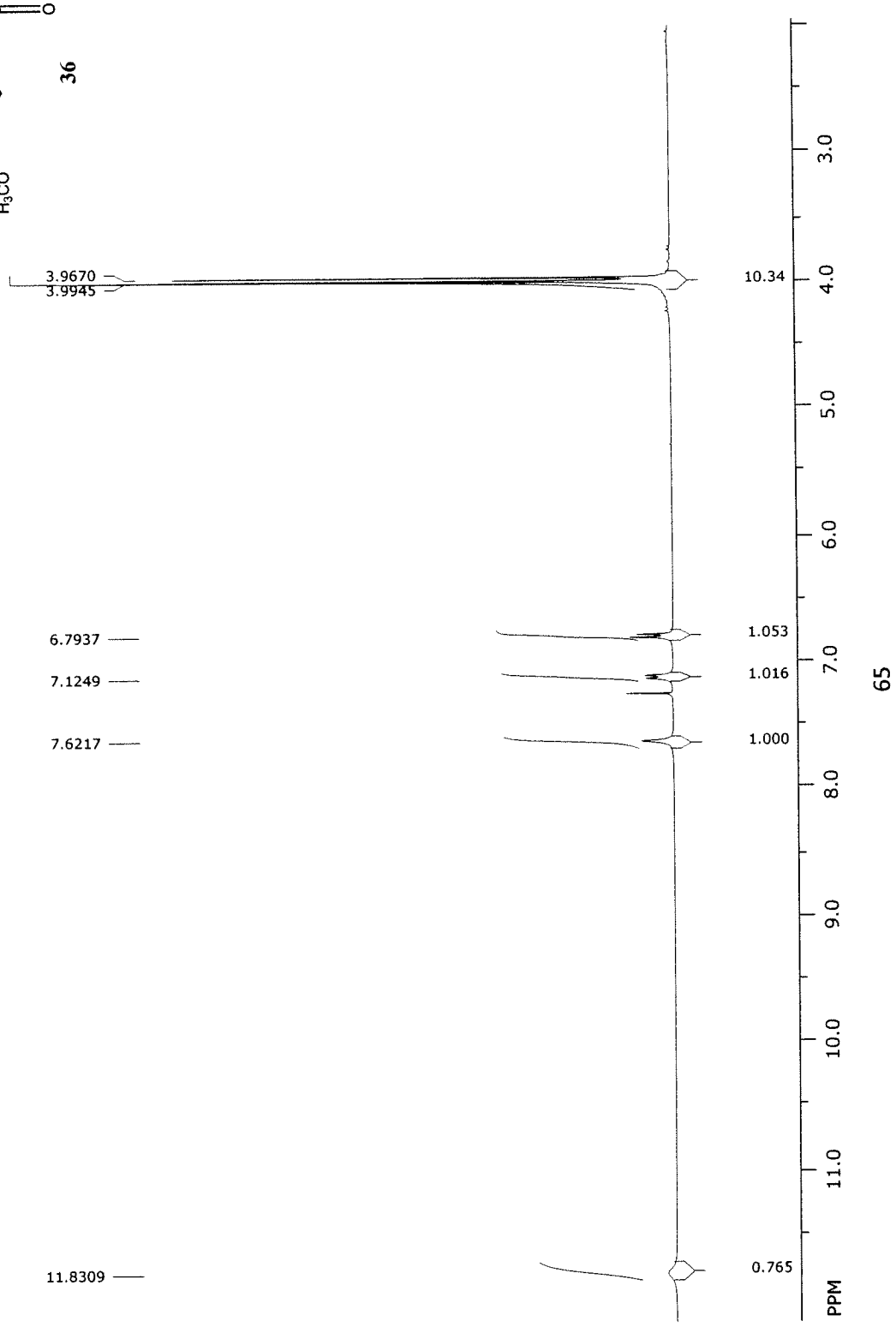
O
OCH3
H3CO
H3CO

36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1.016
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7.0
8.0
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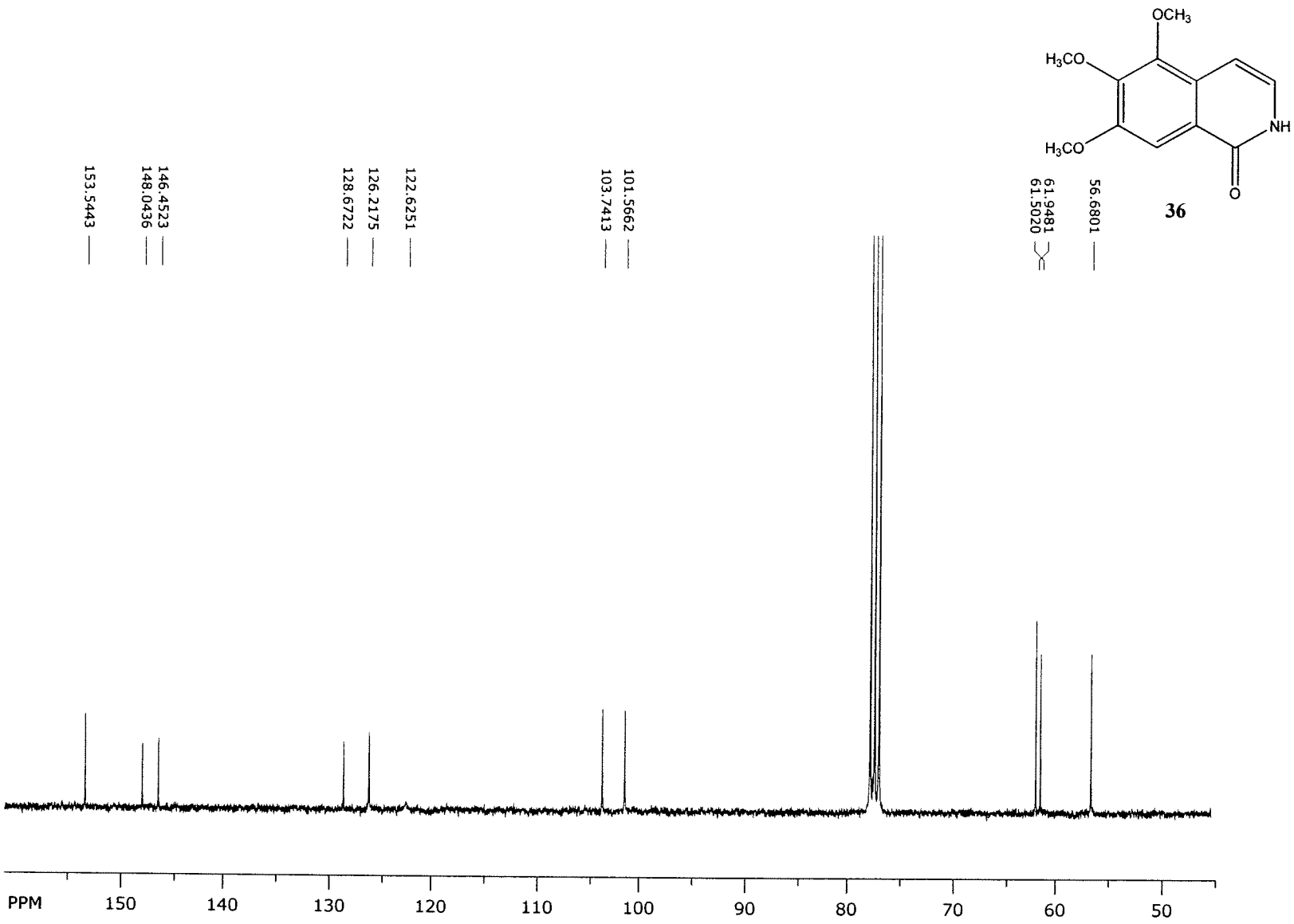
10.0
11.0
PPM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O
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122.6251
103.7413
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90
80
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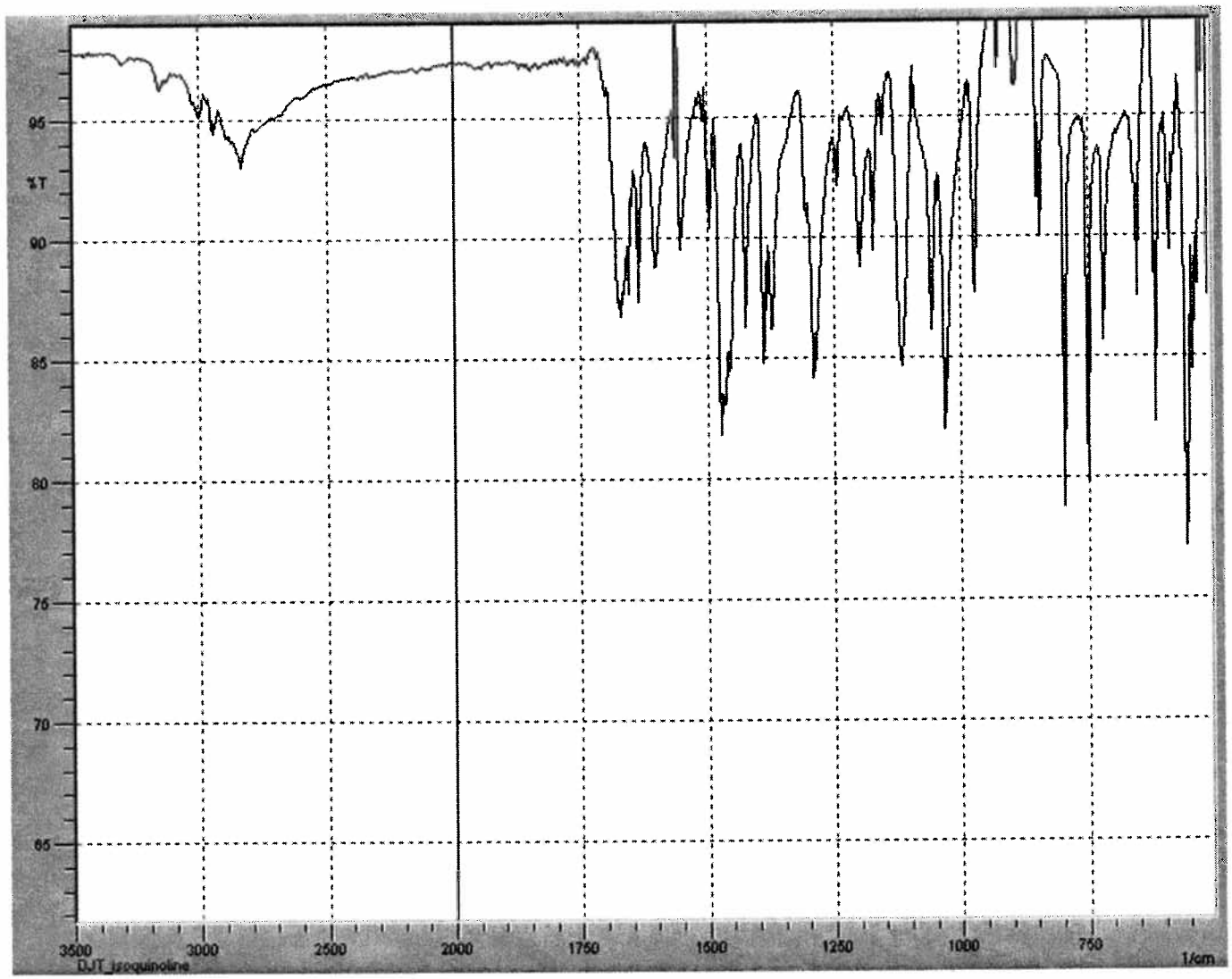
60
50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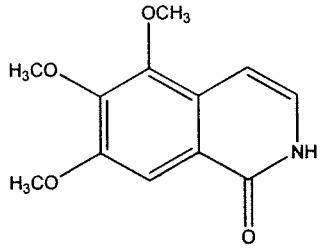
750
1/cm
DJT_isoquinoline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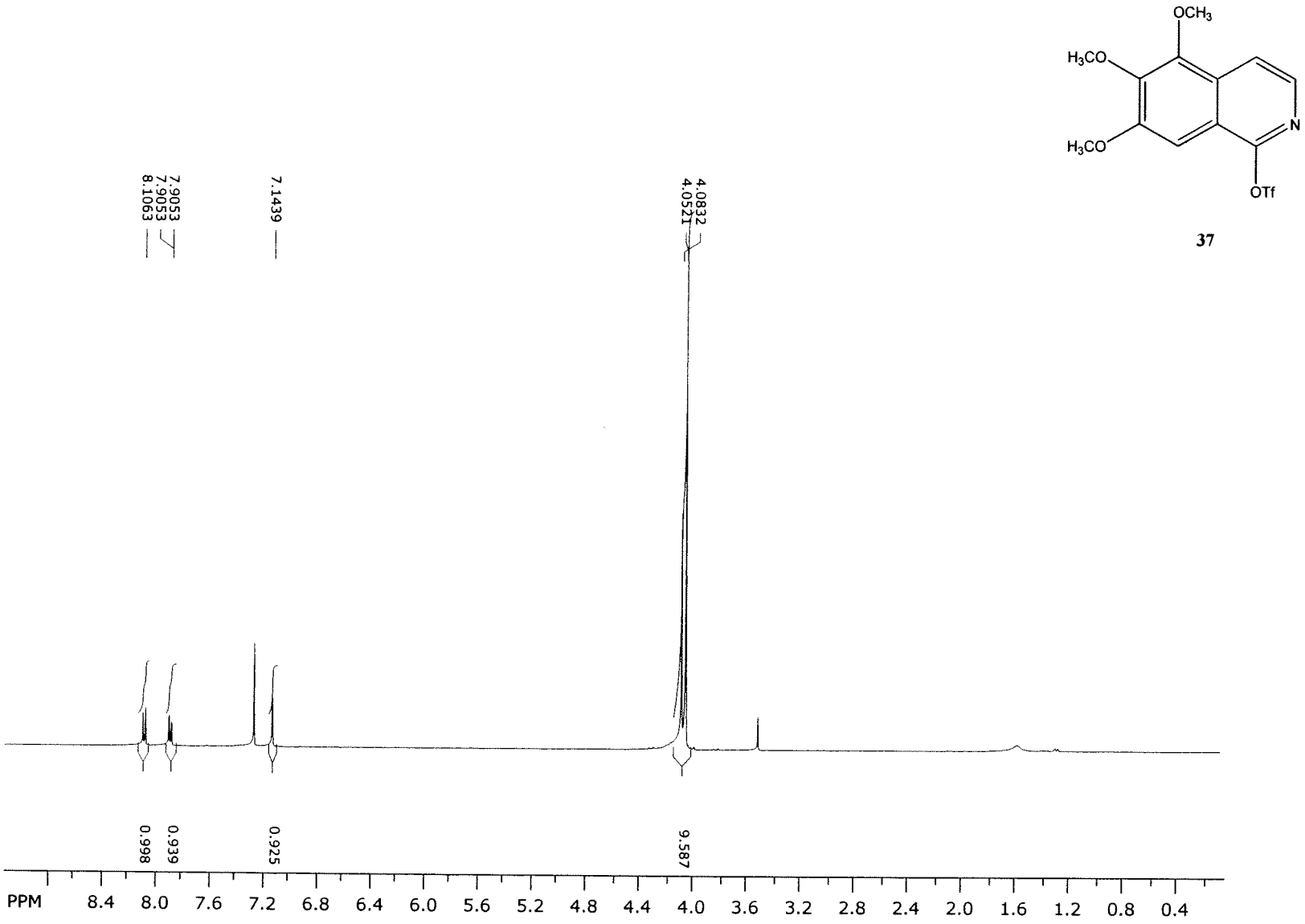
H3CO
NH
O

36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0.925
9.587
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7.6
7.2
6.8
6.4
6.0
5.6
5.2
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2.4
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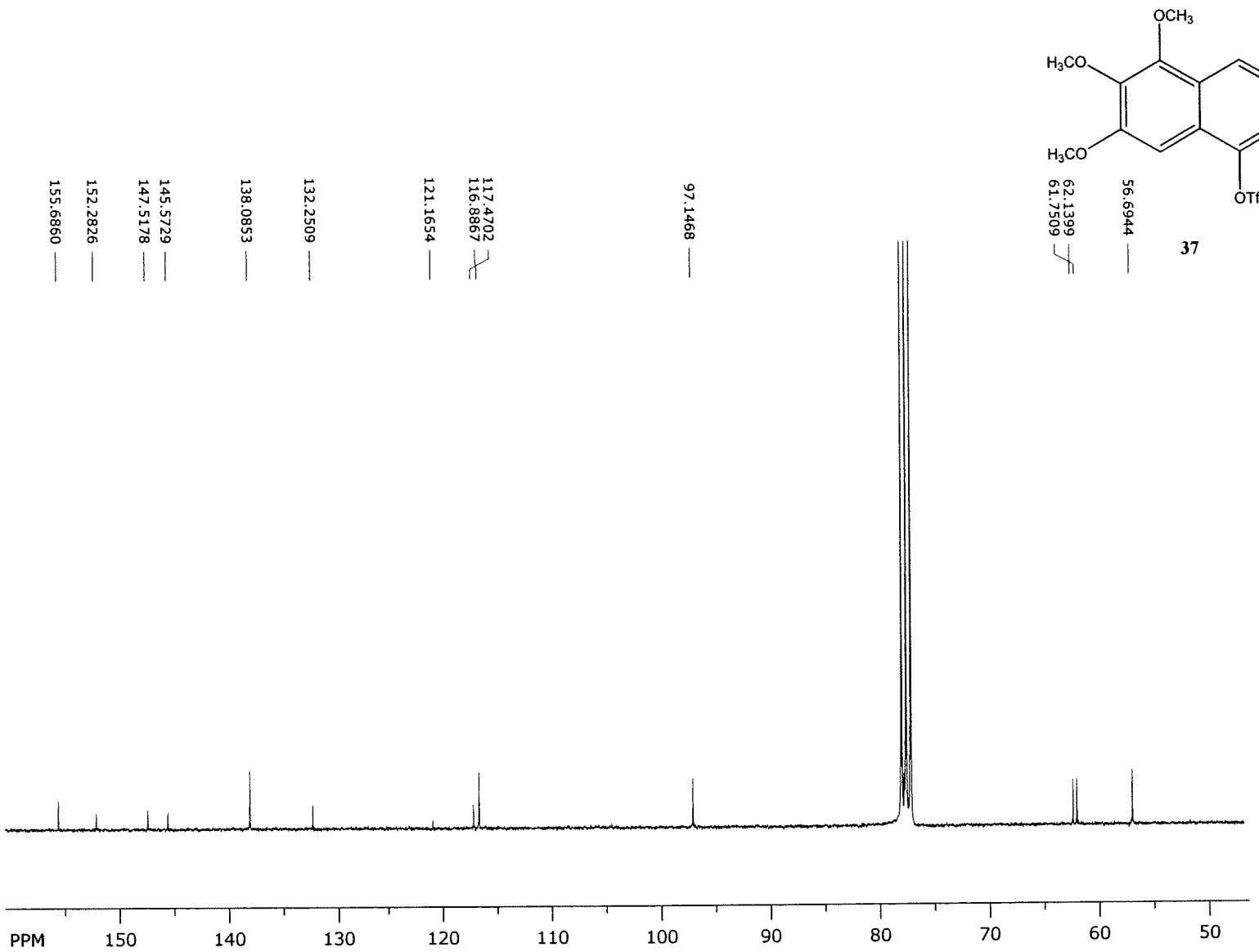
0.4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61.7509
56.6944
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N
OTf
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PPM
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120
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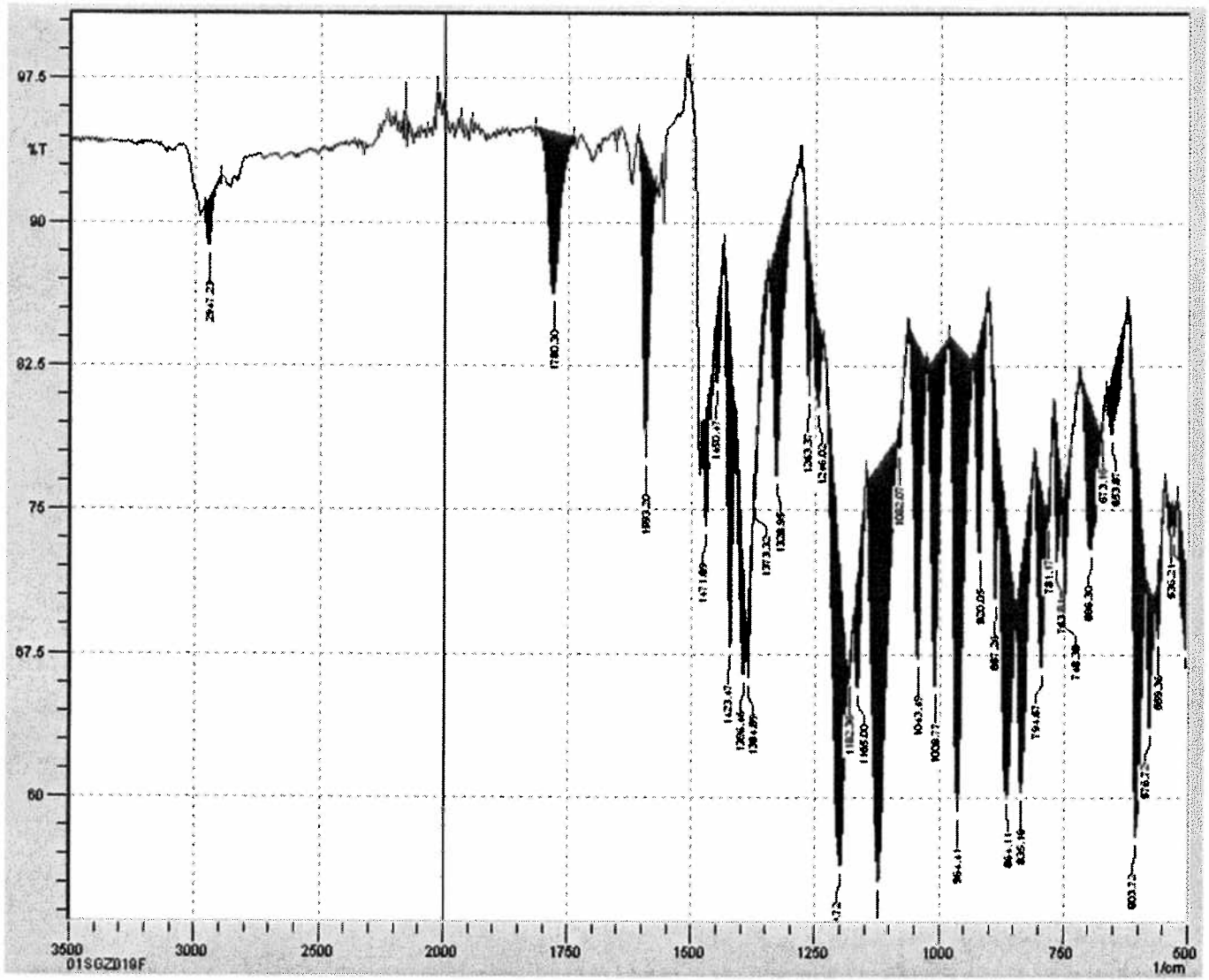
100
90
80
70
60
50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67.5
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750
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1/cm
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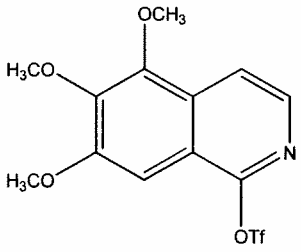
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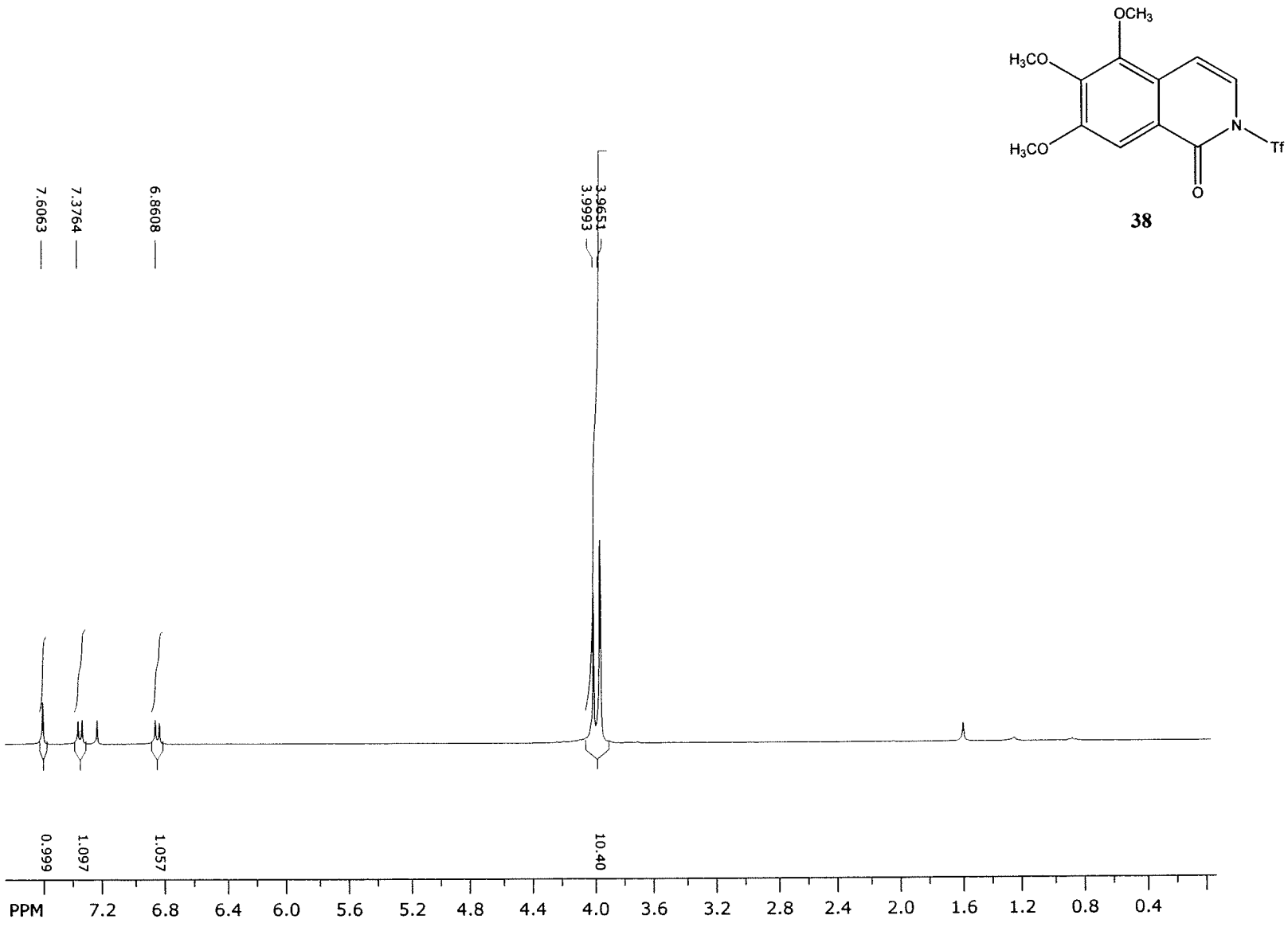
H3CO
N
OTf

37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H3CO
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Tf
O
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1.057
10.40
PPM
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6.8
6.4
6.0
5.6
5.2
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2.0
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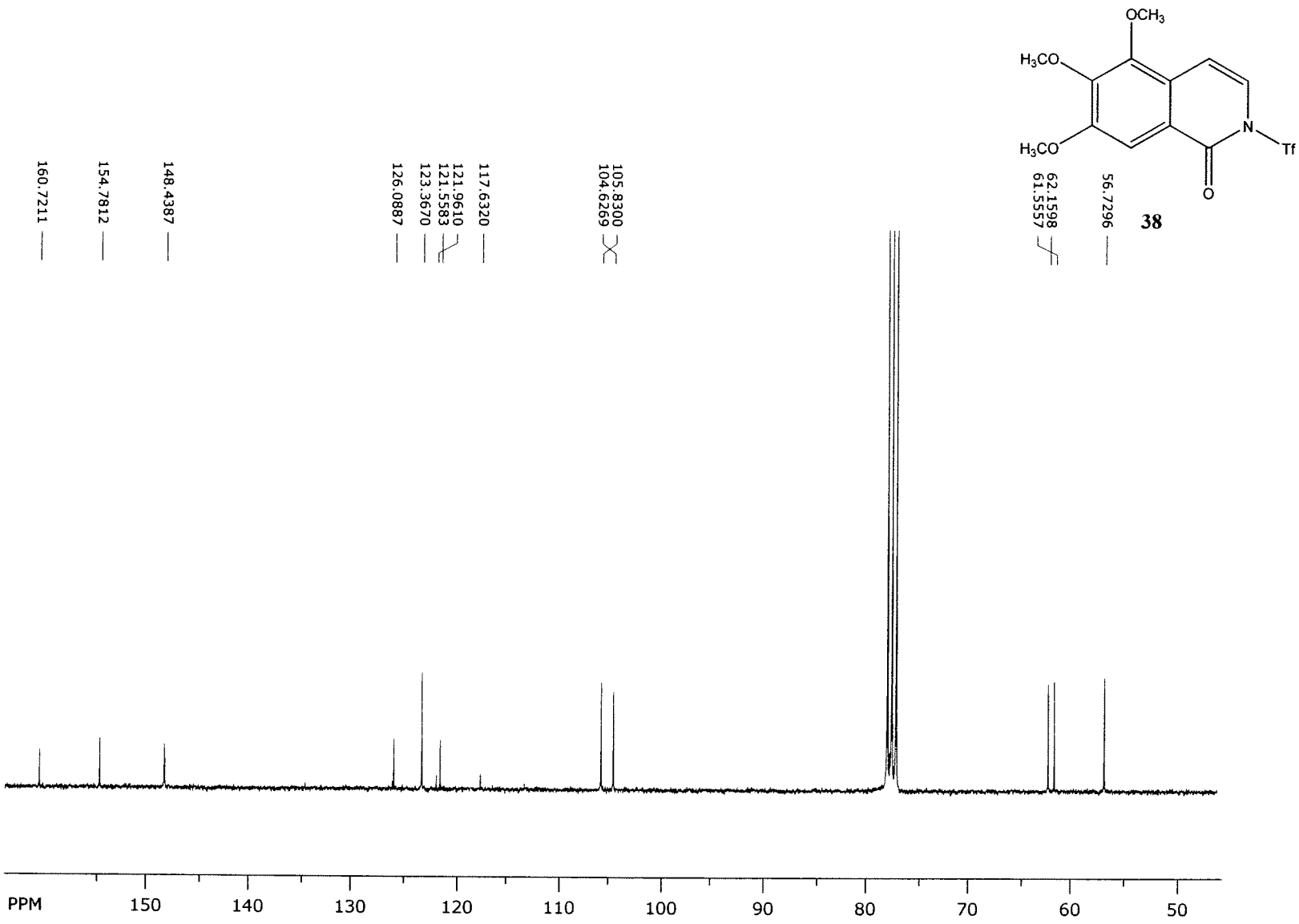
1.2
0.8
0.4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62.1598
61.5557
56.7296
OCH3
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N
Tf
O
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60
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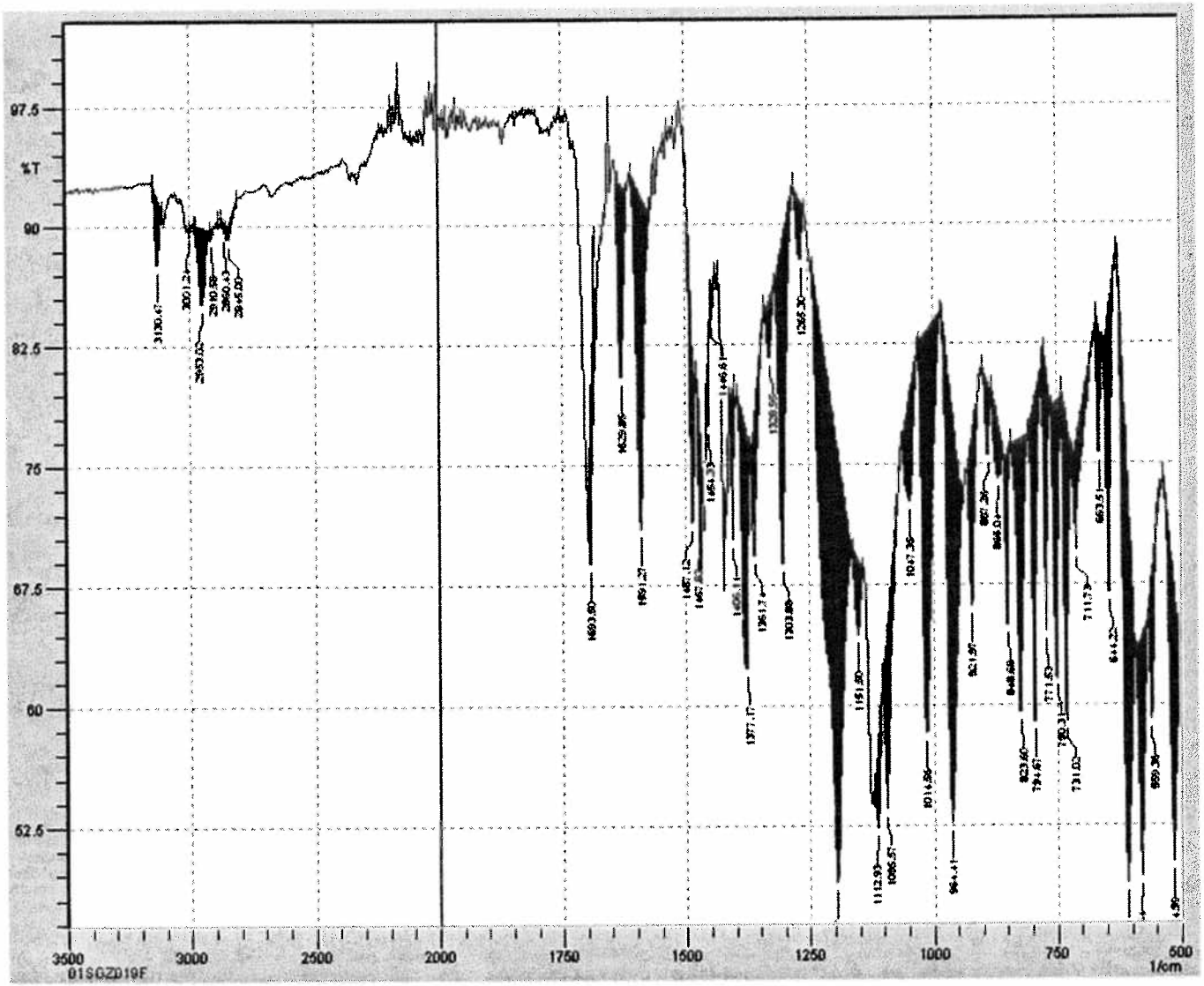
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1250
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1/cm
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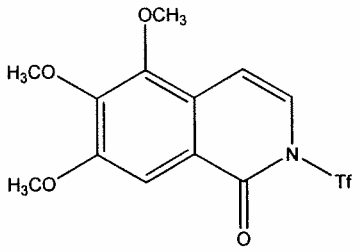
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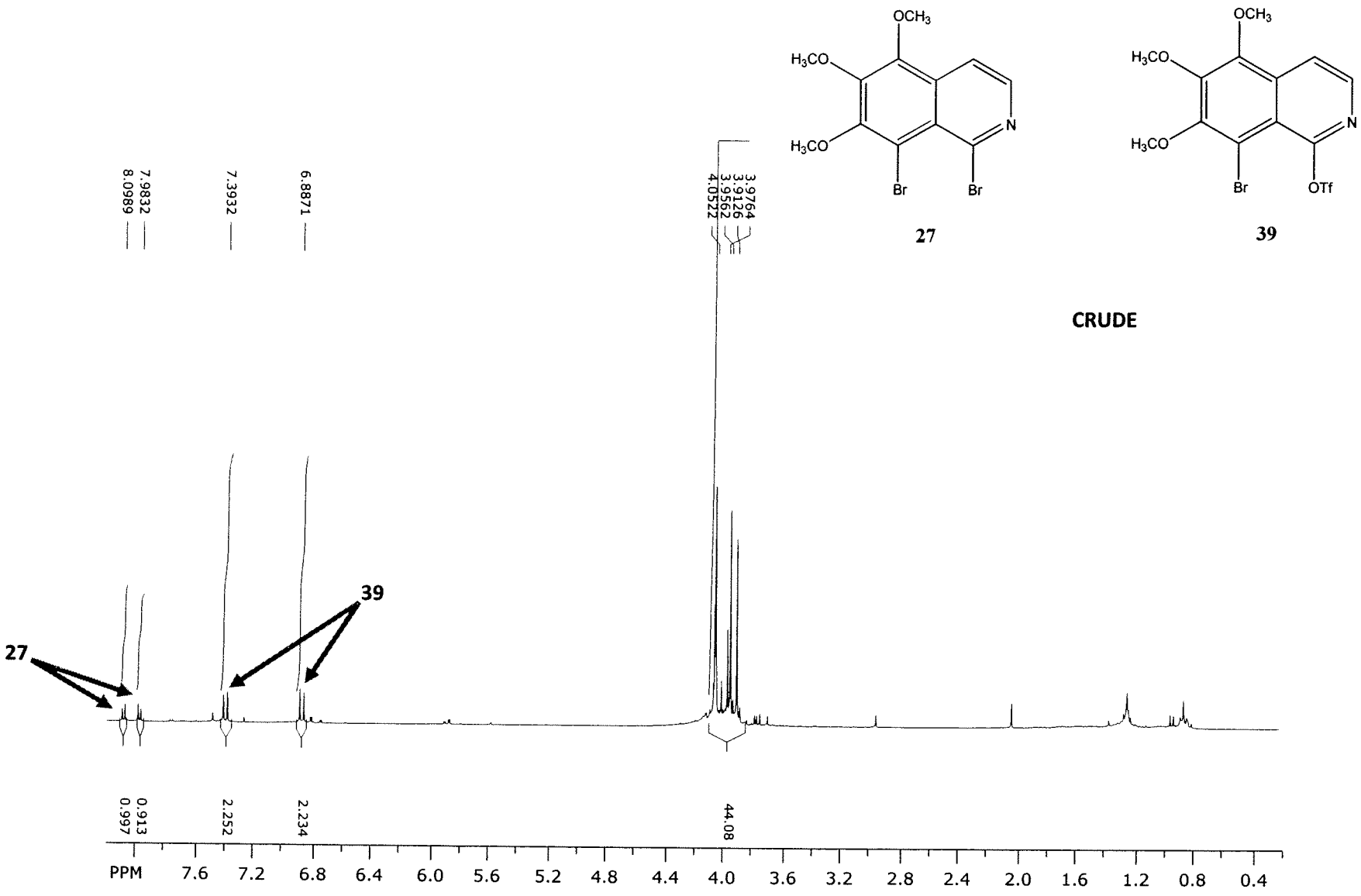
H3CO
N
Tf
O

38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Br
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7.3932
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4.0522
3.9562
3.9126
3.9764
27
39
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44.08
PPM
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7.2
6.8
6.4
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5.2
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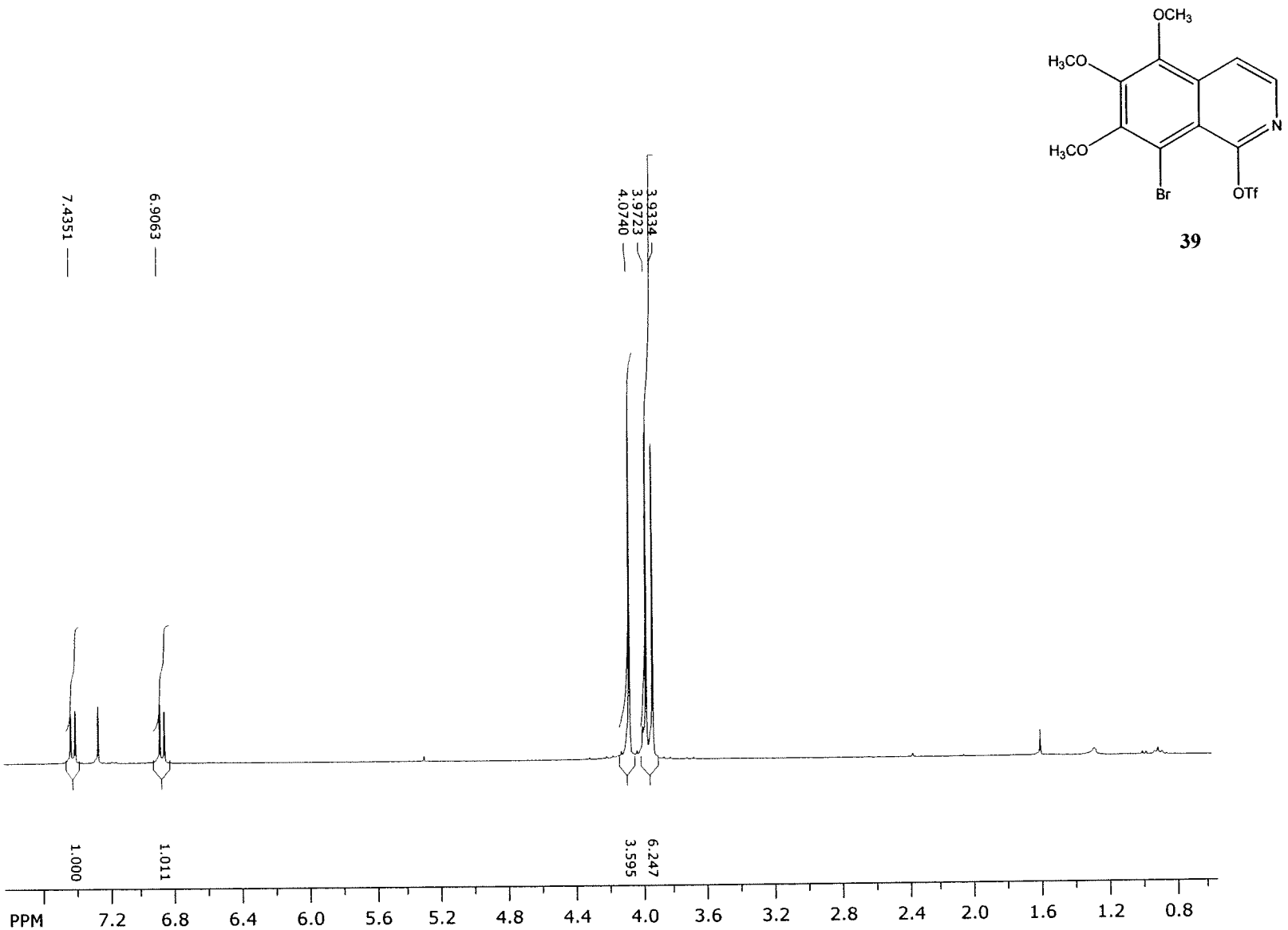
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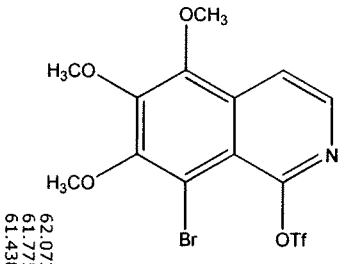
H3CO
H3CO
N
Br
OTf

39



39

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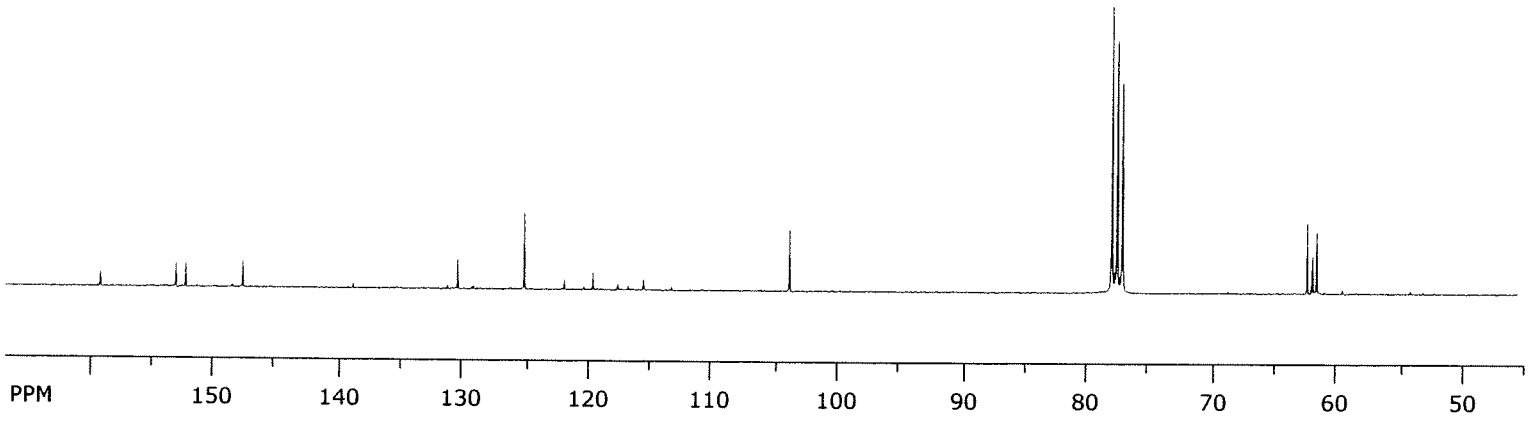

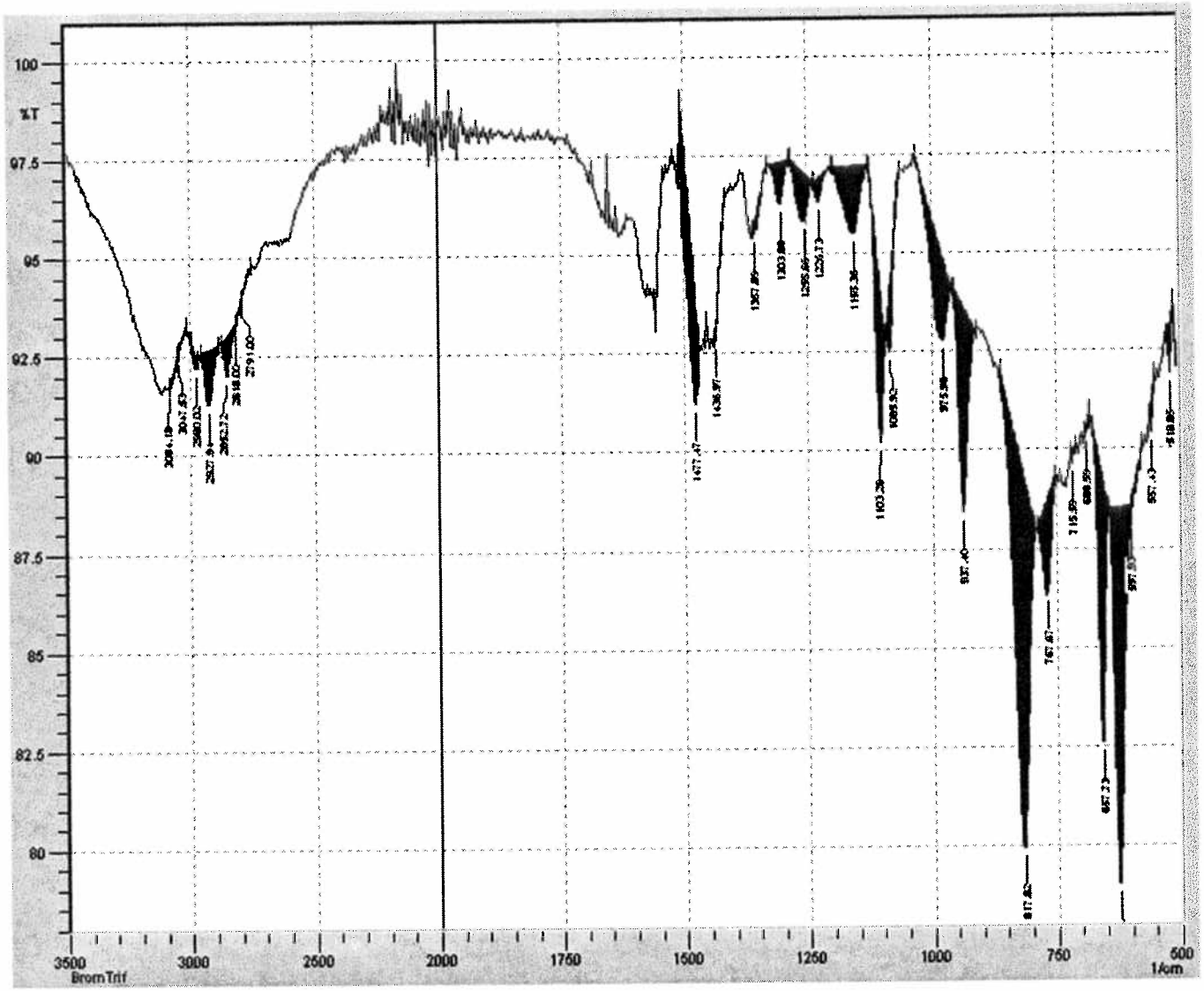
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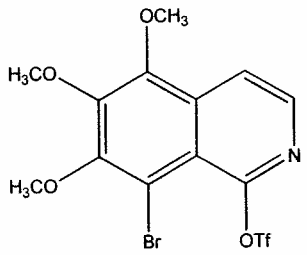
2000
1750
1500
1250
1000
750
500
BromTrif
1Aom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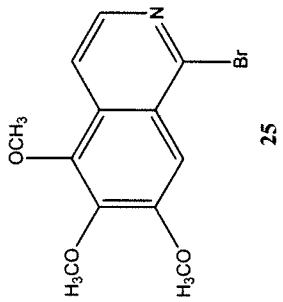
H3CO
H3CO
N
Br
OTf

39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Br
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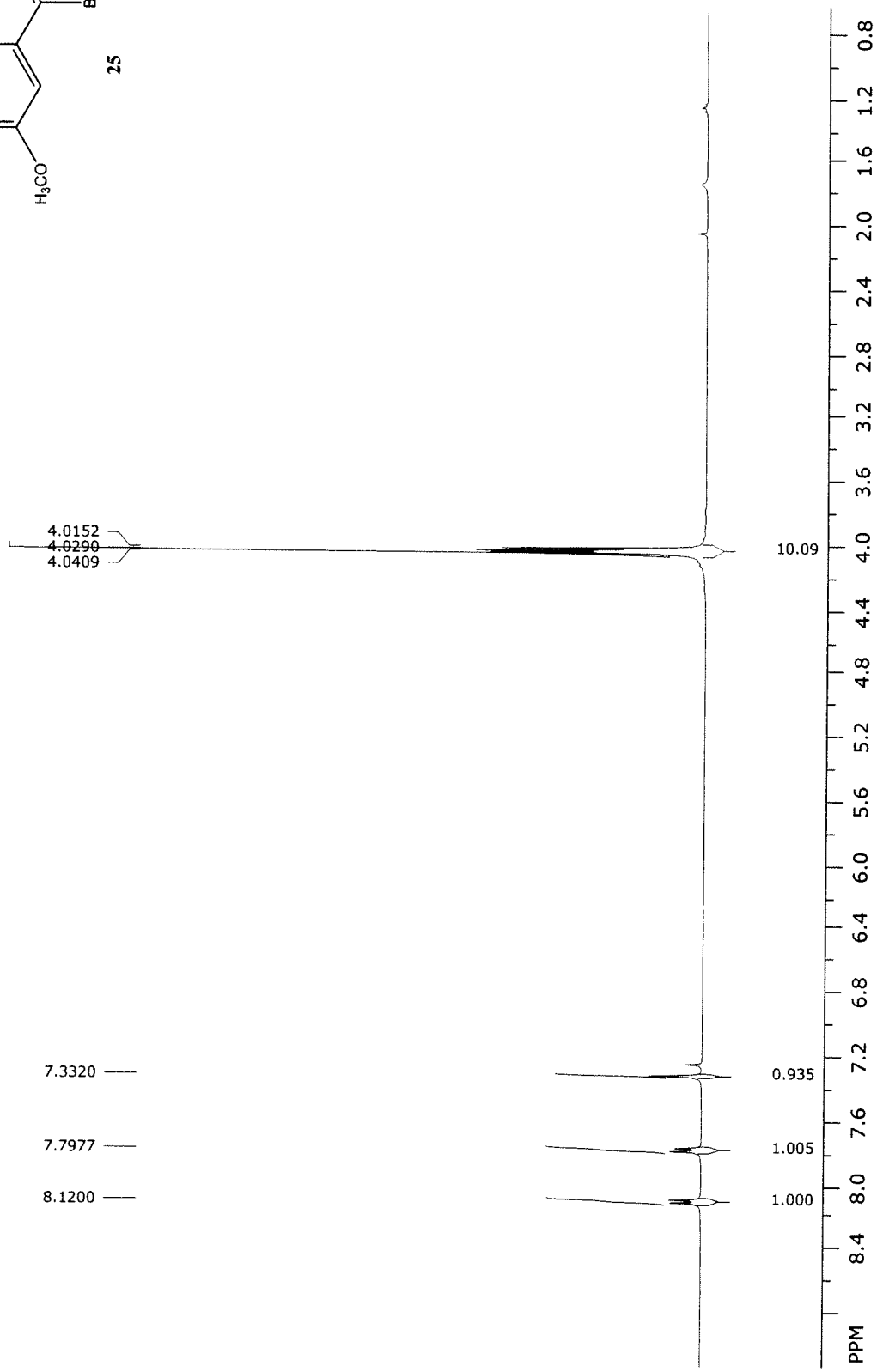
H3CO

25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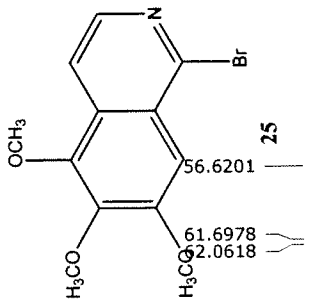
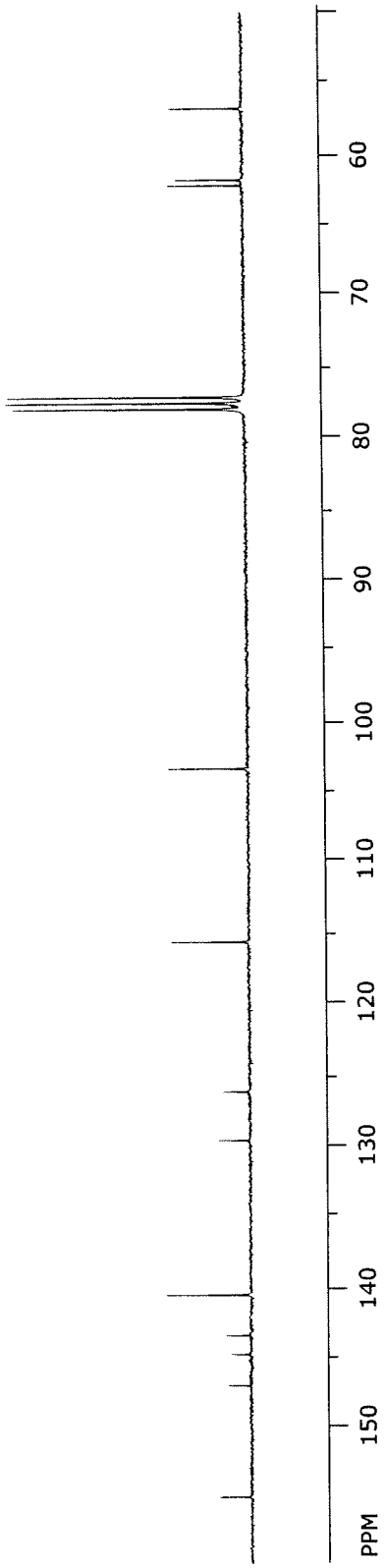
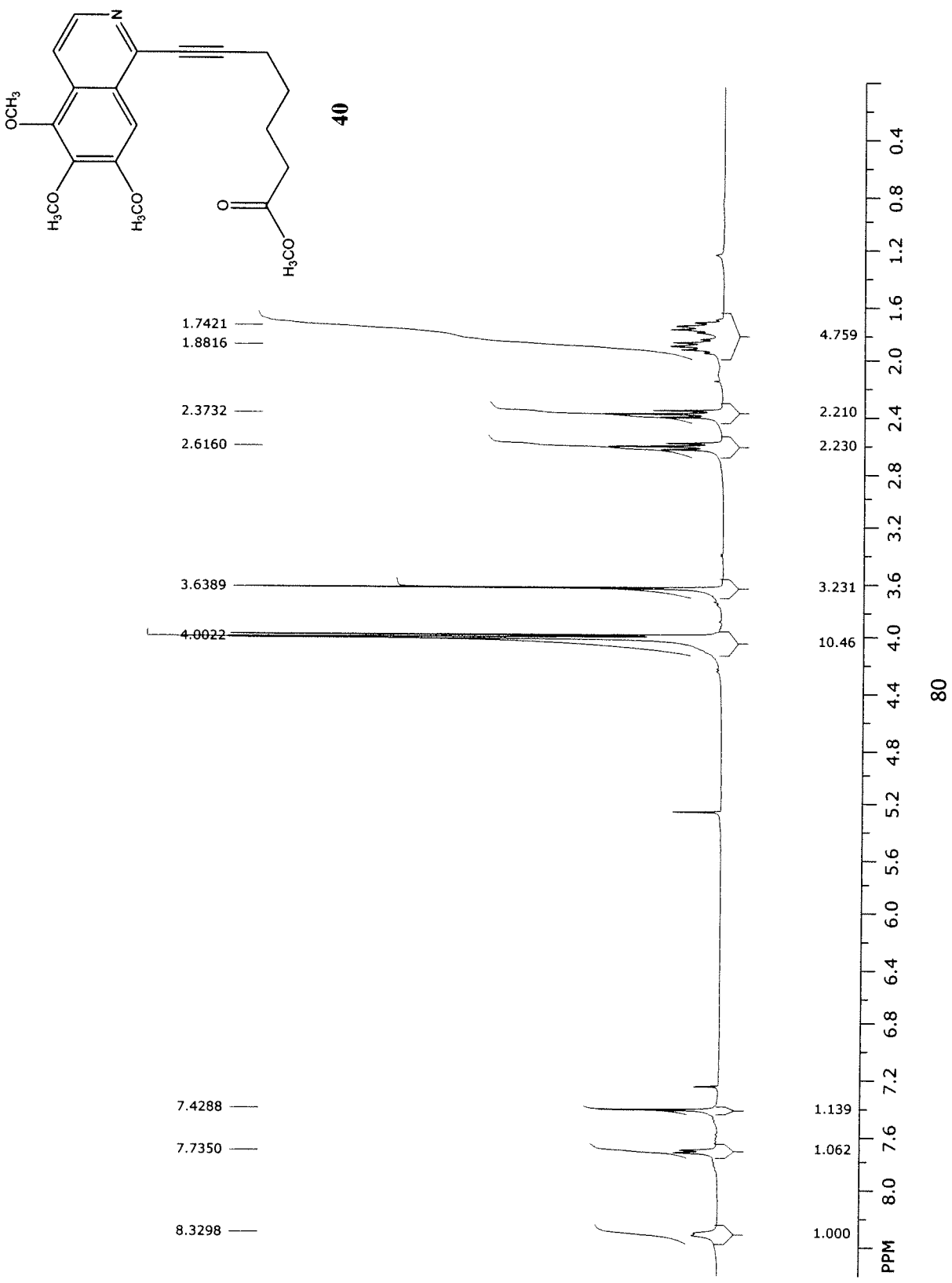
4.0290
4.0409
10.09
7.3320
0.935
7.7977
1.005
8.1200
1.000
PPM
0.8
1.2
1.6
2.0
2.4
2.8
3.2
3.6
4.0
4.4
4.8
5.2
5.6
6.0
6.4
6.8
7.2
7.6
8.0
8.4



25

56.6201
61.6978
62.0618
103.3752
115.7227
126.3251
129.7573
140.7506
143.6173
144.9403
147.1454
155.0838




OCH3
H3CO
H3CO
O
H3CO
N
40
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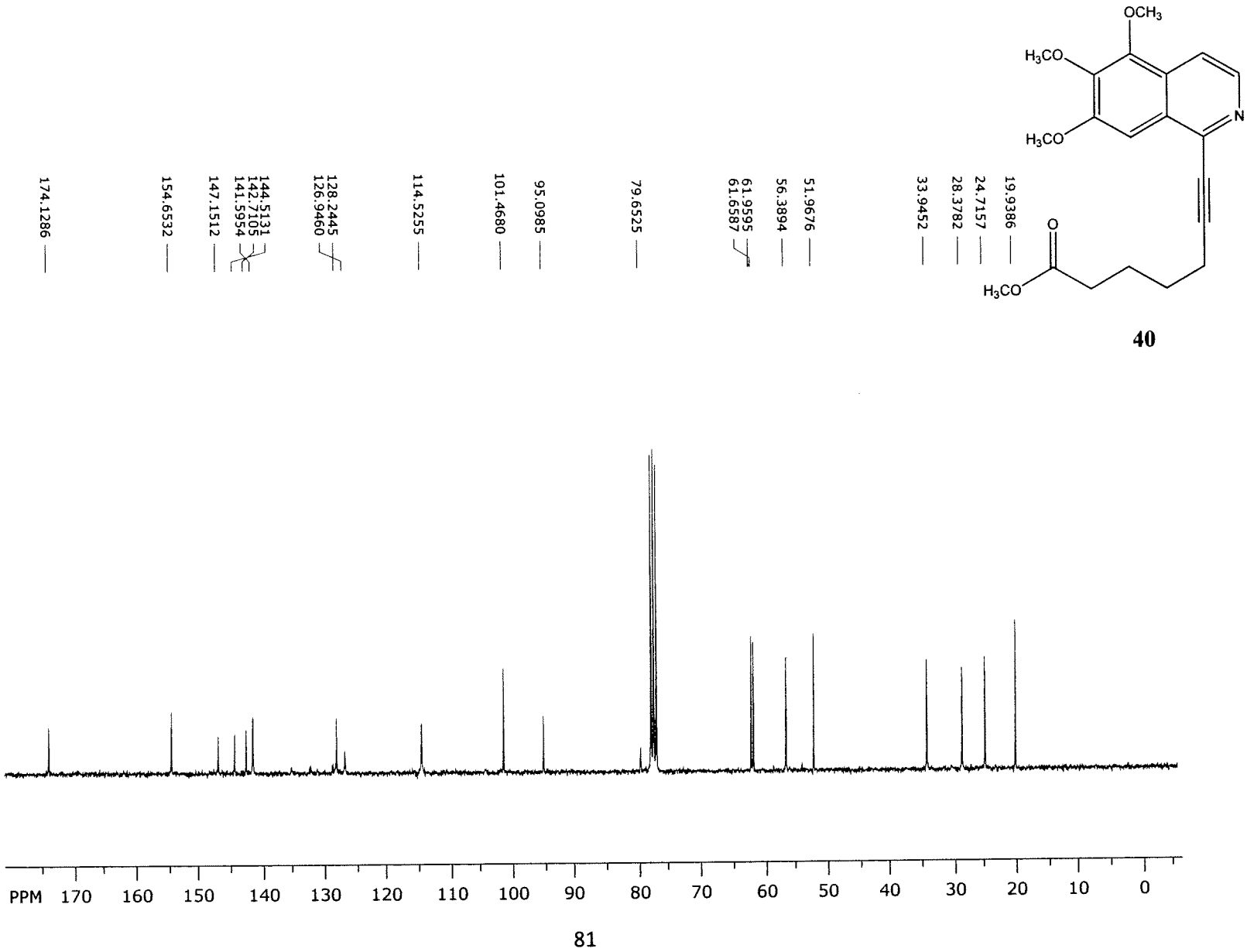
1.8816
2.3732
2.6160
3.6389
4.0022
7.4288
7.7350
8.3298
4.759
2.210
2.230
3.231
10.46
1.139
1.062
1.000
0.4
0.8
1.2
1.6
2.0
2.4
2.8
3.2
3.6
4.0
4.4
4.8
5.2
5.6
6.0
6.4
6.8
7.2
7.6
8.0
PPM
80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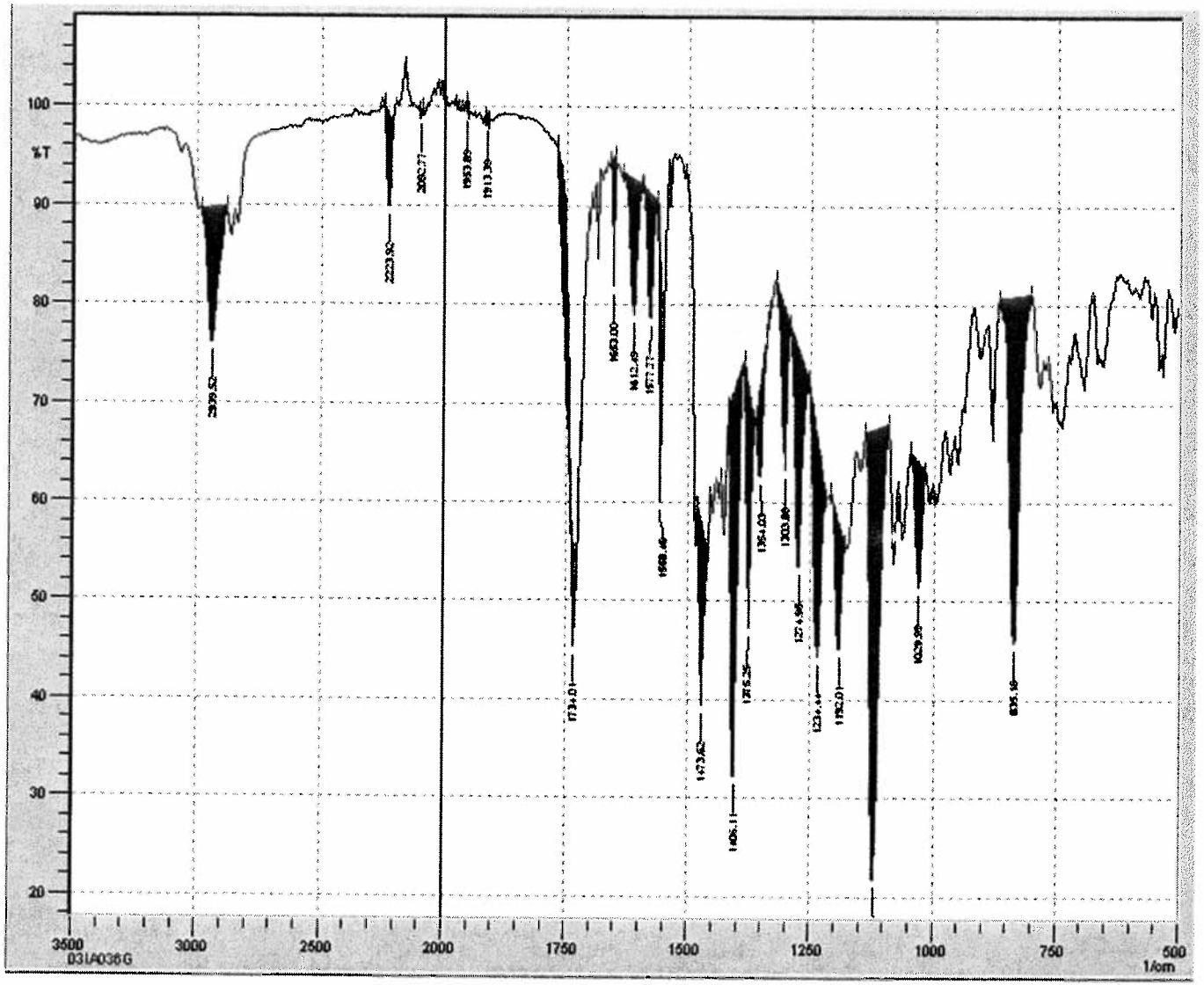
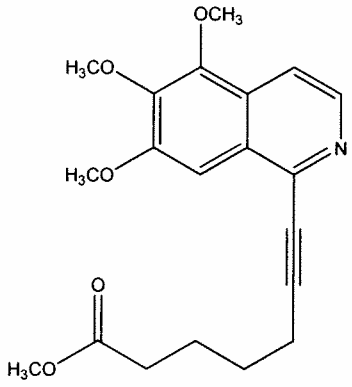
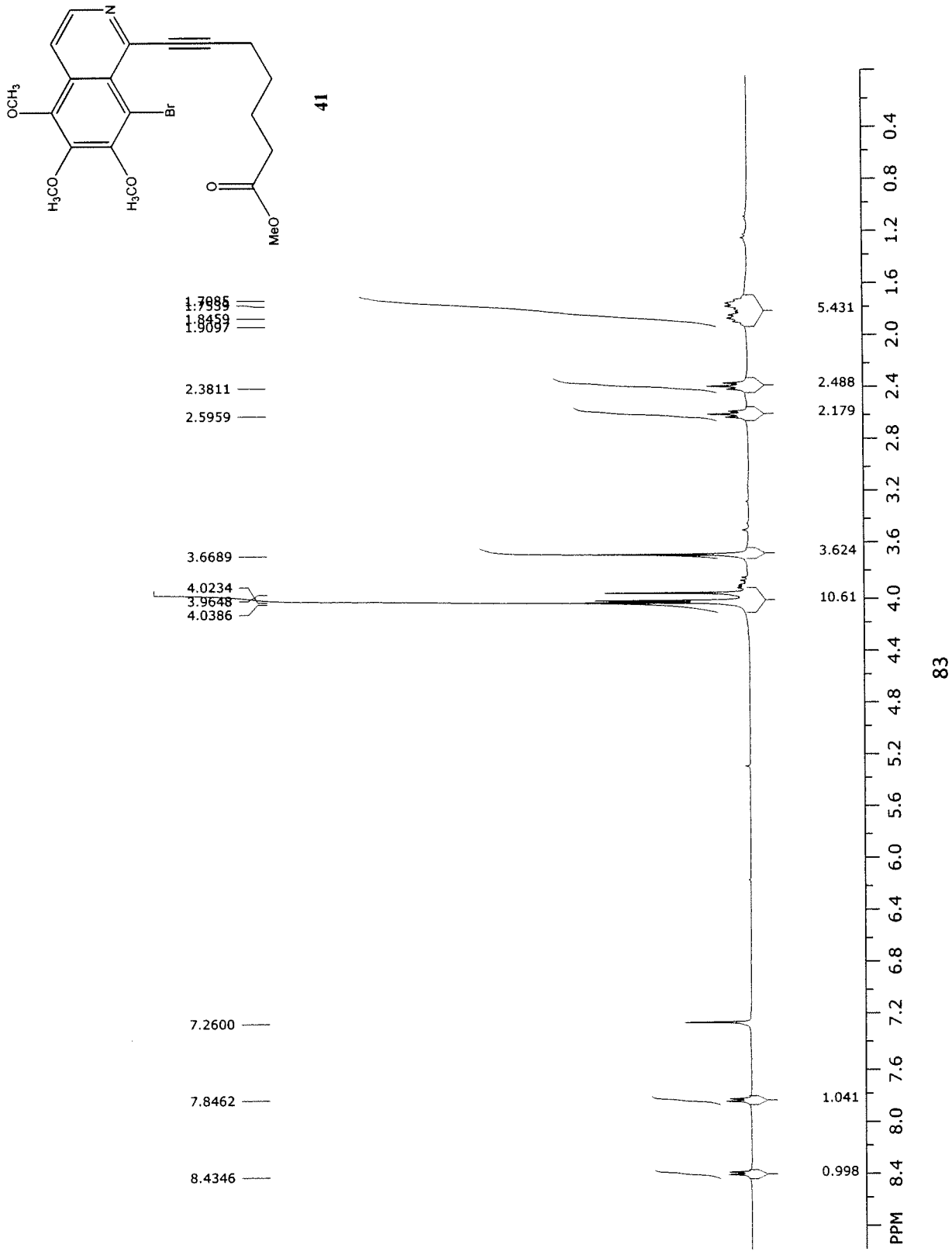
154.6532
147.1512
144.5131
142.7105
141.5954
128.2445
126.9460
114.5255
101.4680
95.0985
79.6525
61.9595
61.6587
56.3894
51.9676
33.9452
28.3782
24.7157
19.9386
OCH3
H3CO
H3CO
N
O
H3CO
PPM 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

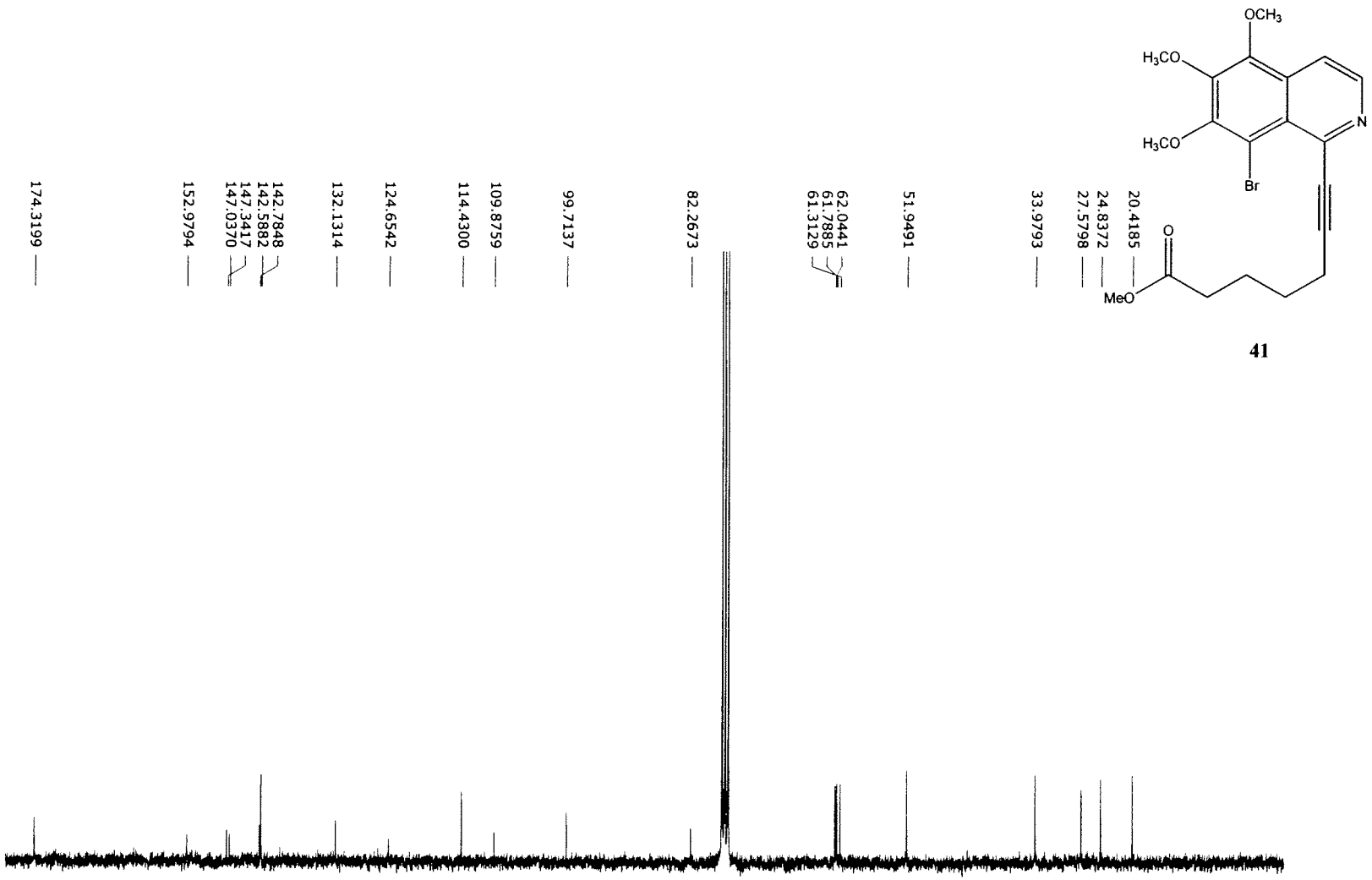
40


%T
100
90
80
70
60
50
40
30
20
3500
3000
2500
2000
1750
1500
1250
1000
750
500
1/cm
03IA036G


OCH3
H3CO
H3CO
N
O
H3CO

40


N
OCH3
Br
H3CO
H3CO
O
MeO
41
1.7085
1.7339
1.8459
1.9097
2.3811
2.5959
3.6689
4.0234
3.9648
4.0386
7.2600
7.8462
8.4346
5.431
2.488
2.179
3.624
10.61
1.041
0.998
PPM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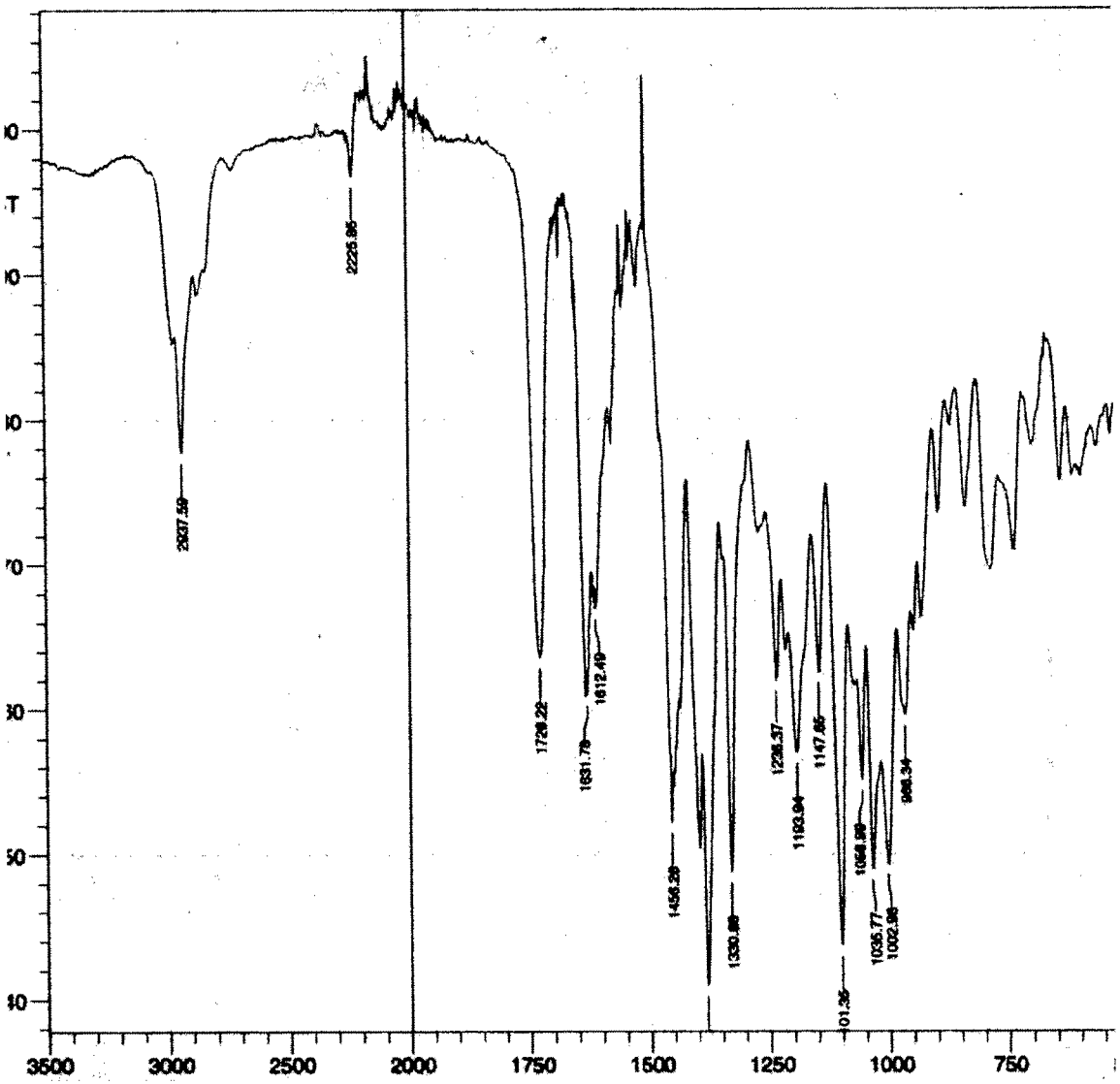
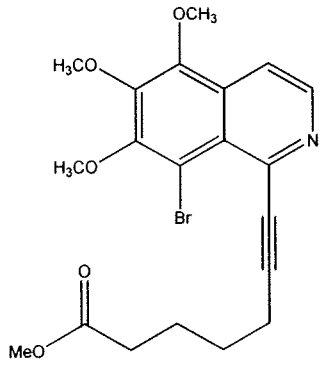
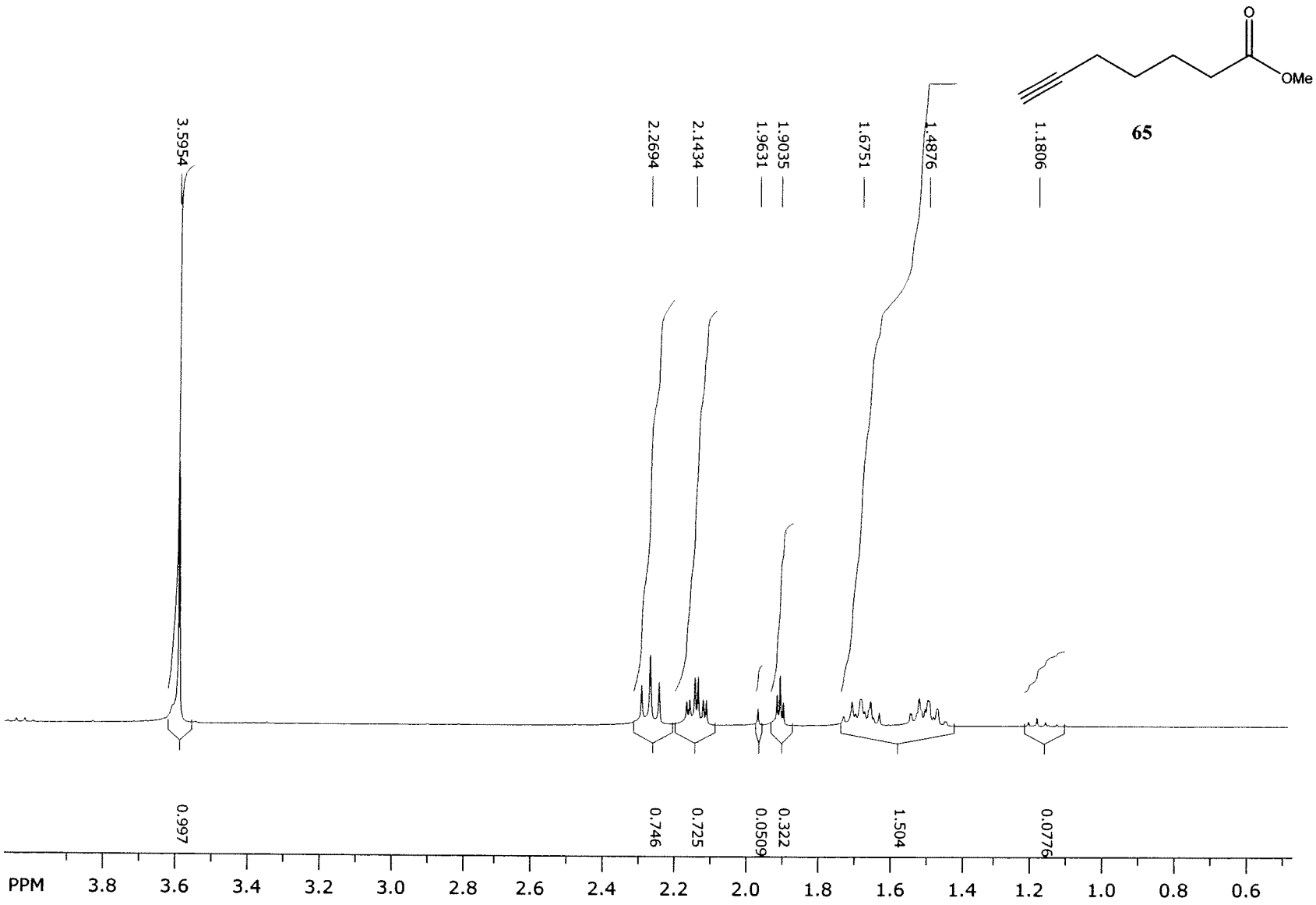
152.9794
147.0370
147.3417
142.5882
142.7848
132.1314
124.6542
114.4300
109.8759
99.7137
82.2673
62.0441
61.7885
61.3129
51.9491
33.9793
27.5798
24.8372
20.4185
OCH3
H3CO
H3CO
N
Br
O
MeO
PPM
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

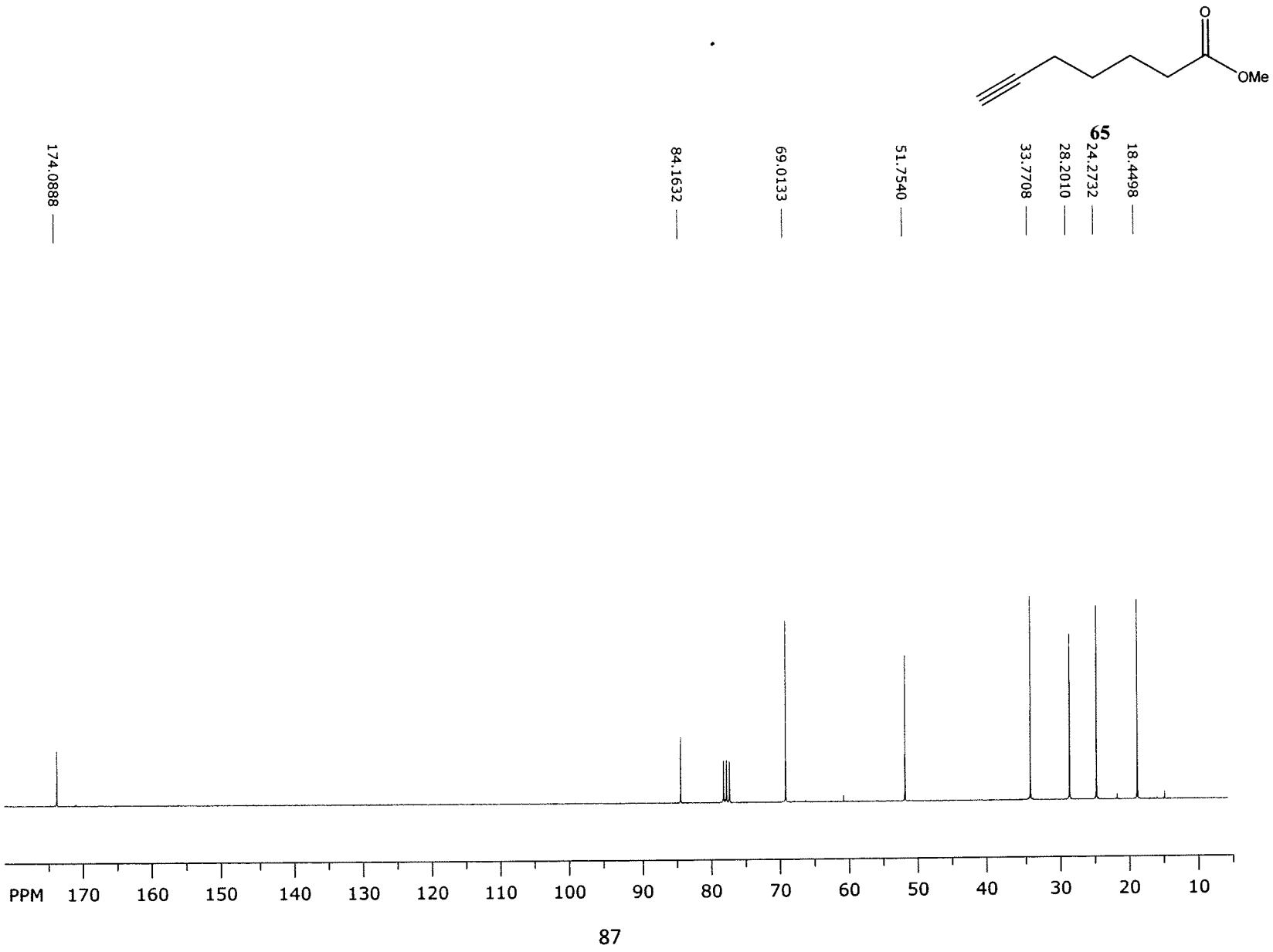
41

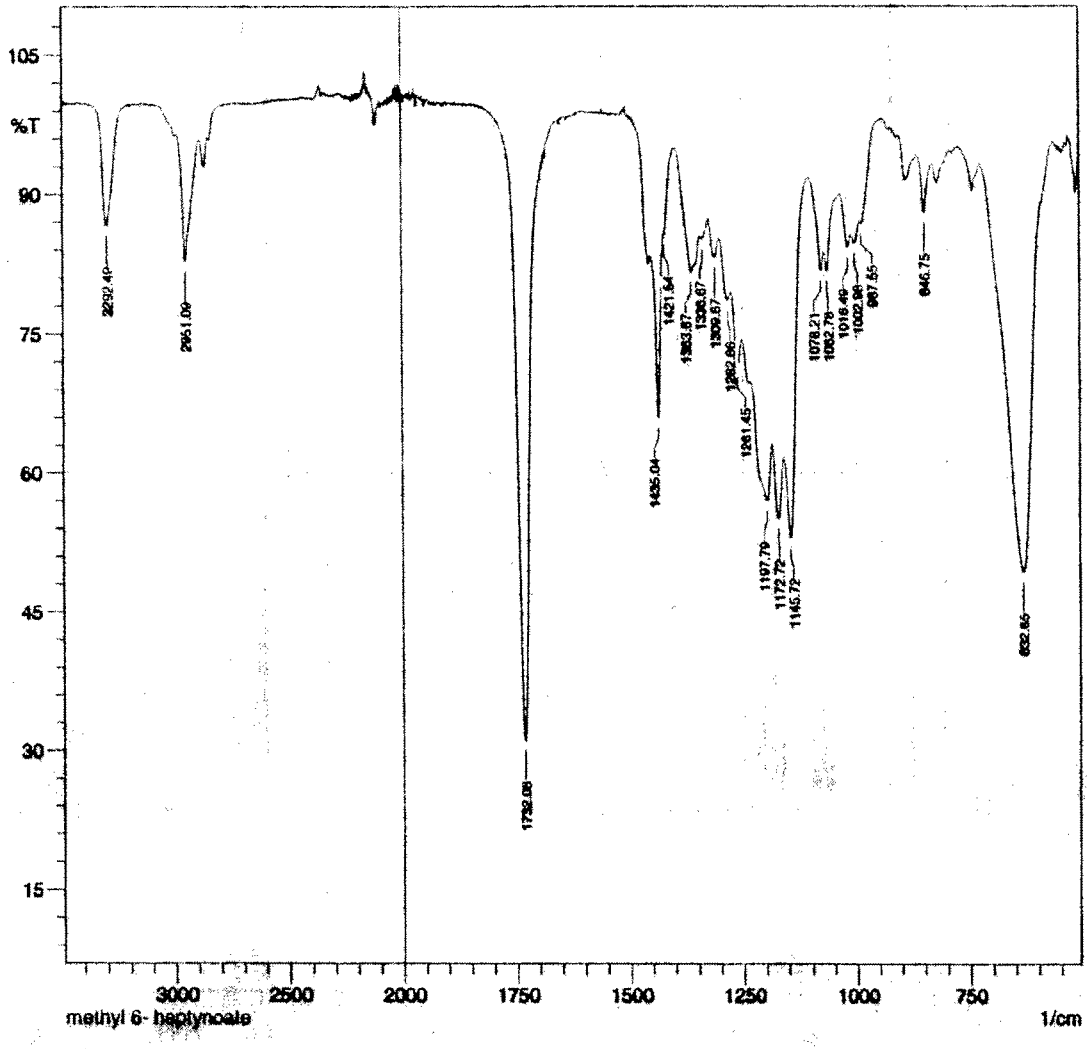

2937.59
2225.85
1726.22
1631.79
1612.49
1456.39
1330.89
1236.37
1193.04
1147.85
1101.35
1036.77
1002.98
966.34
3500
3000
2500
2000
1750
1500
1250
1000
750

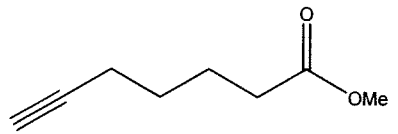

OCH3
H3CO
H3CO
N
Br
O
MeO

41

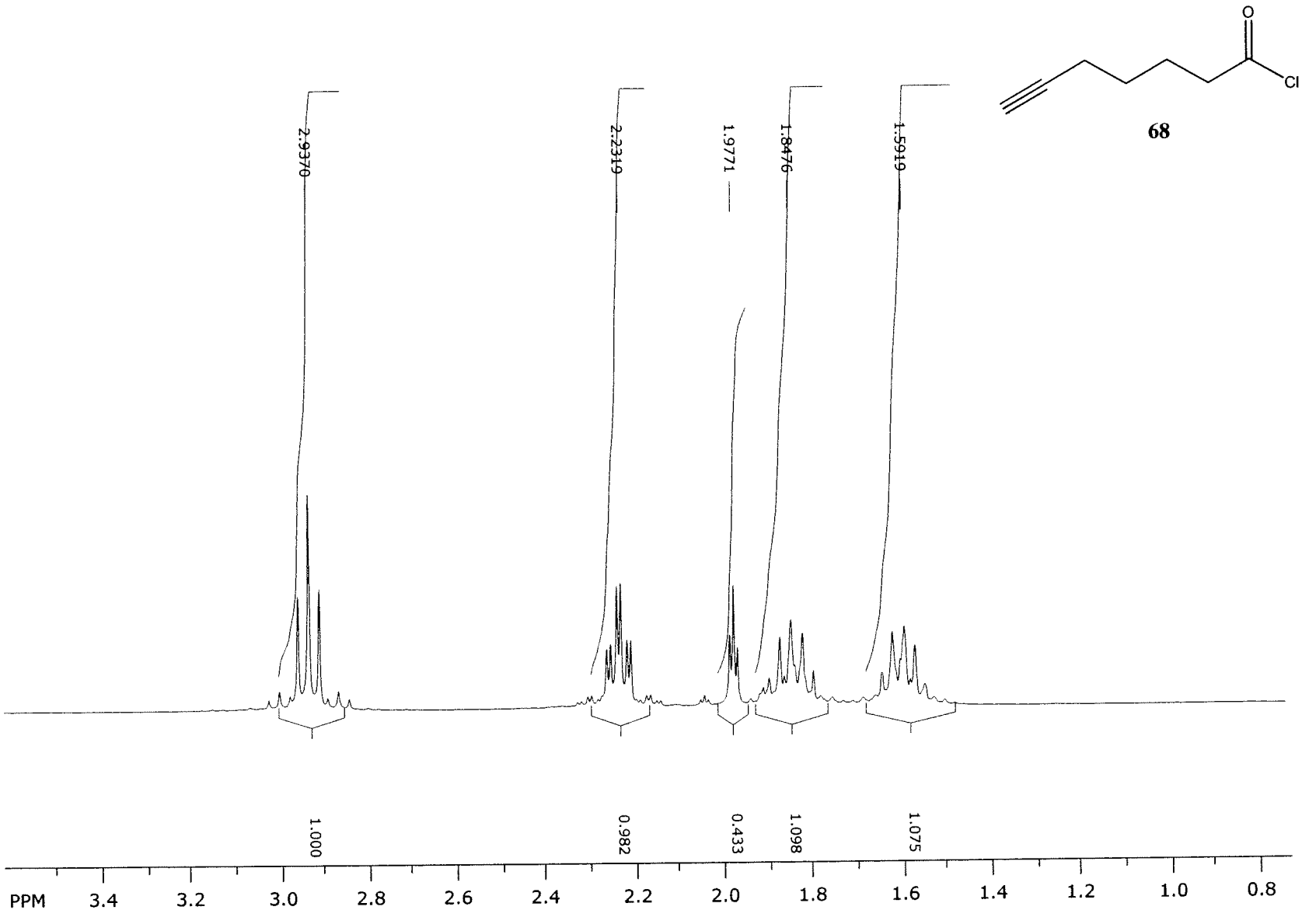

O
OMe
65
3.5954
2.2694
2.1434
1.9631
1.9035
1.6751
1.4876
1.1806
0.997
0.746
0.725
0.0509
0.322
1.504
0.0776
PPM
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6

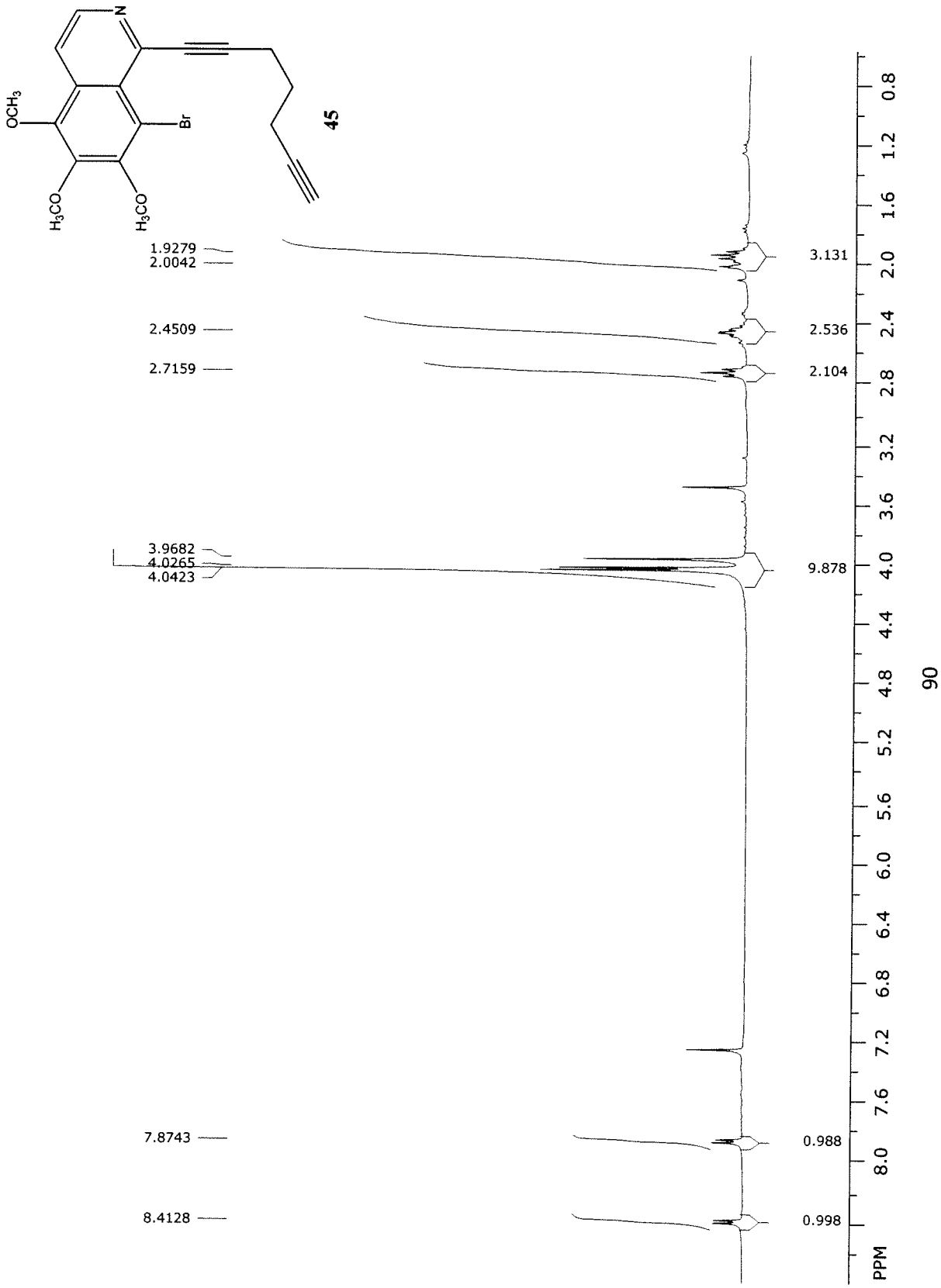

O
OMe
65
174.0888
84.1632
69.0133
51.7540
33.7708
28.2010
24.2732
18.4498
PPM 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10


105
%T
90
75
60
45
30
15
3000
2500
2000
1750
1500
1250
1000
750
1/cm
methyl 6- heptynoate
2292.49
2951.09
1732.08
1435.04
1421.64
1383.87
1366.67
1309.87
1282.86
1261.45
1197.79
1172.72
1145.72
1078.21
1062.78
1018.49
1002.98
967.55
846.75
622.85


O
OMe

65


O
Cl
68
2.9370
2.2319
1.9771
1.8476
1.5919
1.000
0.982
0.433
1.098
1.075
PPM
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8


N
OCH3
Br
H3CO
H3CO
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1.9279
2.0042
2.4509
2.7159
3.9682
4.0265
4.0423
7.8743
8.4128
3.131
2.536
2.104
9.878
0.988
0.998
PPM
0.8
1.2
1.6
2.0
2.4
2.8
3.2
3.6
4.0
4.4
4.8
5.2
5.6
6.0
6.4
6.8
7.2
7.6
8.0