Synthesis and Intermediate/By-Product Analysis of Bromo-dragonfly, a Dihydrobenzofuran Analogue of Phenethylamine Hallucinogens

By

Brittany Christine Huntington
B.S. (Northeastern University) 2007

THESIS

Submitted in partial satisfaction of the requirements for the degree of

MASTER OF SCIENCE

in

Forensic Science

in the

OFFICE OF GRADUATE STUDIES

of the

UNIVERSITY OF CALIFORNIA

DAVIS

Approved:

Marion Miller

Eric Person

Donald Land

Committee in Charge

2009

Acknowledgements

Many thanks to Lab Director Robert Jarzen and Controlled Substances Supervisor Edward "Chip" Pollock, for allowing me to do my research at the Sacramento District Attorney's Laboratory of Forensic Services. They saw value in my project, and I appreciate that they allowed me to pursue it. I am also thankful to everyone in the Controlled Substances section of the DA's lab. Their curiosity, advice, and assistance were invaluable.

Thank you to everyone who offered me technical advice on this project. I was blessed to have three brilliant and helpful scientists on my thesis committee—Marion Miller, Donald Land, and Eric Person—who helped to steer me in the right direction and kept me from veering off course. To Roger Ely, of the DEA Western Laboratory, who first recommended this idea to me, and supplied many helpful chemistry tips and suggestions as I hit difficulties. And to Jeff Borngasser, of the Central Point Oregon Crime Lab, for being so helpful and willing to discuss his lab's bromo-dragonfly finding.

I owe my biggest thank you to Brian Escamilla, Criminalist IV in the Controlled Substances section of the DA's Lab. As my technical supervisor, Brian went above and beyond in helping me with this project. I can say with all confidence that there is no way I would have completed this project without him.

Thank you to all of my friends and family for their unconditional support and interest. Especially to my husband. I would have given up a long time ago had I not had his warm support and listening ear to come home to each night.

Abstract

In 1998 and 2001, two articles were published by the Nichols lab (Purdue University) providing the synthesis for (R)-(-)-1-(8-Bromobenzo[1,2-b;4,5-b ′]difuran-4-yl)-2-aminopropane hydrochloride (bromo-dragonfly). Since that time, bromo-dragonfly has become a much discussed topic in the drug community, with both users and analysts alike. Fairly pure samples of bromo-dragonfly have been found world-wide, with the one documented sample within the United States being found in Oregon. These samples have investigators wondering when the first clandestine lab will be found. It is also possible that illicit production and use of bromo-dragonfly has been overlooked due to the lack of availability of a synthesized chemical standard for comparison purposes. There is currently no chemical library available for the intermediates, by-products, and waste accrued in the bromo-dragonfly synthesis. This paper discusses the full synthesis of bromo-dragonfly following the method published in 2001. Synthetic methods were also modified and alternate approaches used in an attempt to optimize the synthesis. A library was created at the Sacramento County District Attorney's Laboratory of Forensic Services, compiling GC-MS data for each step. This synthesis is difficult and time-consuming, requiring sophisticated equipment and knowledge as well as liters of solvent and many toxic, atmosphere sensitive reagents. It is evident that the synthesis of bromo-dragonfly is far out of the capabilities of the typical clandestine chemist and lab. From the current research it can be concluded that only experienced and sophisticated chemists would be capable of accomplishing bromo-dragonfly synthesis and that only an

established chemistry lab would be capable of producing samples of the caliber that have been documented to date.

Table of Contents

Page

Title Page…… i
Acknowledgements……..... ii
Abstract…… iii
Chapter 1. Introduction…….....… 1
1.1 A History of Bromo-dragonfly…….....2
1.1.1 Research……..….2
1.1.2 Publications……..……2
1.1.3 Bromo-dragonfly and the Drug Community…….....3
1.2 The Purpose and Significance of This Experiment……...6
1.3 Synthesis Overview…….....8
Chapter 2. Chemistry …….....9
2.1 Materials, Methods, and Results……..10
2.1.1 Reagents……...……11
2.1.2 General Reaction Conditions…….....11
2.1.3 Instrumentation…….. ..……..12
2.1.4 Results……...13
Synthesis of Intermediate A……...13
Synthesis of Intermediate B ……...16
Synthesis of Intermediate C ……...20
Synthesis of Intermediate D……...……25
Synthesis of Intermediate E…….……...28
Synthesis of Intermediate F……31
Synthesis of Intermediate G……...32
Synthesis of Intermediate H……...36
Synthesis of Bromo-dragonfly……...38
2.2 Discussion……39
2.3 Conclusion……...42
References……43
Appendix A. Figures…… 44
Appendix B. Chromatograms and Spectra—Intermediates and Prominent By-Products……... 45

Chapter 1.

Introduction

Hallucinogens are a broad group of drugs that have been used for years to alter the perception of reality. Structurally these drugs can be broken down into phenethylamines, piperidines, tryptamines, and cannabinols, of which cannabinols are by far the most common. Scientists are studying the biochemical effects of hallucinogens on the brain and developing new powerful synthetic drugs that mimic the effects of naturally occurring hallucinogenic compounds. While being researched, many of these drugs end up on the streets as drugs of abuse which causes a problem for law enforcement and the legal system. Once these drugs are illicitly distributed and become problems of abuse, it is up to the legal system and forensic scientists to identify these drugs, along with the routes of synthesis and the chemicals used in the manufacturing process.

The purpose of this project is to profile the synthesis of (*R*)-(-)-1-(8-Bromobenzo[1,2-*b*;4,5-*b*´]difuran-4-yl)-2-aminopropane hydrochloride (bromo-dragonfly) [see Figure 1] and document the by-products and intermediates during the process. The data derived from this work will assist investigators and laboratory analysts in identifying the final product (bromo-dragonfly) and relating clandestine laboratory evidence to the manufacturing process.

1.1 A History of Bromo-dragonfly

Bromo-dragonfly is classified as a hallucinogenic phenethylamine that is used for research and also found as a substance of abuse.

1.1.1 Research

Most of the research on the synthesis of bromo-dragonfly and its analogues is being conducted at the Department of Medicinal Chemistry and Molecular Pharmacology at Purdue University, in the lab of David E. Nichols, Ph.D. Dr. Nichols has been researching and working in the field of psychoactive drugs since 1969, and many consider him one of the top experts in the field of psychedelics. According to Dr. Nichols' website, the main objective of his lab is to research the activity of the 5-HT (serotonin) receptors in the brain, what role these receptors have in normal cognitive function, and how they might affect Parkinson's patients. These receptors are namely the 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors, which monitor the release of the excitatory neurotransmitters dopamine and glutamate. Dr. Nichols and his team make small structural changes to molecules already known to trigger these receptors to see if the new molecule is still neuro-reactive[1,2]. The majority of the research that has been done, both in this lab and others, concludes that the main site for hallucinogen action is the 5-HT_{2A} receptor[3].

1.1.2 Publications

The majority of published articles on the synthesis and pharmacology of bromo-dragonfly are by students in the Nichols lab at Purdue University. In 1996 and 1997,

Nichols, Aaron P. Monte, et al published two articles that alluded to the pharmacological effects of bromo-dragonfly[4,5]. The phenethylamine they derived, however, has saturated furan rings, giving it a slight structural difference from bromo-dragonfly. Still, the group discovered that this molecule {1-(8-Bromo-2,3,6,7-tetrahydrobenzo[1,2-*b*:4,5-*b*′]difuran-4-yl)-2-aminopropane Hydrochloride} [see Figure 2] is almost as potent as LSD, a result they hadn't previously achieved in phenylalkylamines[4].

Dr. Nichols, Matthew A. Parker, et al published the first article on the synthesis of bromo-dragonfly in 1998[6]. Now this hallucinogen is a hot topic on popular culture drug blogs and forums. In 2001, Dr. Nichols, James J. Chambers, et al published a shorter, higher yielding synthesis for bromo-dragonfly[7]. When users discuss online how to make bromo-dragonfly, it is Chambers' article that is referenced.

1.1.3 Bromo-dragonfly and the Drug Community

Although it started out as a research chemical, bromo-dragonfly's prominent effects on the 5-HT_{2A} receptor seems to fuel the public's interest in the use of this drug as a hallucinogen. Many of the most common and popular hallucinogens affect at least one of the thirteen 5-HT receptors. The 5-HT_{2A} receptor agonists consist of ergolines, tryptamines, and phenethylamines, leaving nearly all hallucinogens as full or partial agonists. For instance, both LSD and psilocin (the active chemical in hallucinogenic mushrooms) act upon the 5-HT_{2A} receptor. Bromo-dragonfly has the capability of over-stimulating the 5-HT_{2A} receptor leading to uncontrolled vasoconstriction in smooth muscle cells, leading to some of the side-effects that will be discussed [8].

Bromo-dragonfly has no medicinal use and very little is know about its synthesis and pharmacology in humans. Currently, only Denmark, Sweden, and Australia regulate bromo-dragonfly as a controlled substance. The Federal Analogue Act within the United States, however, makes any analogue of a Schedule I drug illegal. Bromo-dragonfly has structural similarity to two Schedule I drugs, 4-bromo-2,5-dimethoxyamphetamine (DOB) [see Figure 3] and 4-bromo-2,5-dimethoxyphenethylamine (2C-B) [see Figure 4]. While the two furan rings unique to bromo-dragonfly are not present on these controlled substances, all three do share the phenethylamine backbone.

The DEA *Microgram Bulletin*, a monthly newsletter published by the U.S. Drug Enforcement Administration's Office of Forensic Sciences, has published intelligence alerts on confiscated samples from Australia, Germany, Sweden, and the United States, exhibiting that this is not a problem unique to one country. Given its apparent global span, few samples of bromo-dragonfly have been submitted for analysis to forensic labs, raising the possibility that use of this hallucinogen is not prevalent with illicit drug users. On internet drug forums, however, such as the Vaults of Erowid and Bluelight, many people claim to have experienced this drug. Such contradictory information suggests four possibilities. First, bromo-dragonfly may be collected by authorities and tentatively identified as something else. Given the fact that several users have reported that they received their bromo-dragonfly on blotter paper, it is a possibility that authorities are assuming that it is LSD. Second, drug users are managing to elude authorities. Third, users are misinformed as to what drug they are actually taking. Since bromo-dragonfly is a drug that many users would like to try, a drug-dealer would be able to charge a

premium price for it. These dealers may successfully sell a common hallucinogen as bromo-dragonfly at a heightened price for an increased profit. Or fourth, since bromo-dragonfly is only considered illegal in three countries, it is plausible that samples are entering crime labs and being reported as a non-controlled substance or going unidentified.

Very little is known about the pharmacology of this drug. Since clinical research has only been carried out in rats, there is no guarantee that the people who claim to have taken it actually took bromo-dragonfly. It appears that bromo-dragonfly produces effects in the dose range of 800-2000 micrograms, making it comparable in potency to LSD, and potentially a very dangerous drug[9]. It has been reported that there are two different "batches" of bromo-dragonfly available, European and American, and that the European version may be more potent. This would account for the wide range of reported dosages. All of these dosages are based on the accounts of users, none of whom can we be sure actually used bromo-dragonfly versus one of the other phenethylamine derivatives. Due to the lack of knowledge and confusion as to appropriate dosage, several people have suffered severe side effects, overdoses, and even death. User accounts note that bromo-dragonfly has a very long onset time, up to six hours, which may lead people to double-dose and ingest a harmful dose level.

The only documented users are those who have suffered drastic side effects and death. In January 2009, Mette F. Andreasen published an article about one such incident; the case that led Denmark to classify bromo-dragonfly as an illegal drug in 2007[10]. Andreasen's article describes the biological identification and quantification of bromo-

dragonfly from a deceased individual, an 18-year-old woman who died after ingesting an "LSD-like liquid." Analysis of this liquid confirmed bromo-dragonfly. While the available articles are in Swedish and Norwegian, there have been at least two other documented cases of death: one in Anderstorp, Sweden, and the other in Trysil, Norway. Due to bromo-dragonfly's vasoconstrictive properties, there have also been cases of gangrene, with one victim needing the fingers of his left hand and several toes amputated.

The case that gives local value to this experiment is the finding of bromo-dragonfly in Ashland, Oregon[11]. The Ashland Police Department conducted a seizure on a minor who was suspected of selling drugs. The officers confiscated marijuana, scales, and bongs, as well as an amber dropper bottle containing a colorless liquid. The suspect claimed it was DOB, with a street name of BROMO, but analysis showed it to be bromo-dragonfly, which the suspect had been selling for $5/drop[12]. Being so close to the Oregon-California border, and adjacent to the interstate (I-5) that runs through all of California, the finding of bromo-dragonfly in this location suggests it could soon be of greater concern to the California forensic community.

1.2 The Purpose and Significance of This Experiment

Though there is not much interaction between law enforcement and bromo-dragonfly labs, the growing interest in this drug by users leads to the belief that these particular clandestine labs may increase. There is a significant amount of reference material available for other types of clandestine labs (methamphetamine, PCP, etc.). The intermediates, by-products, and routes of synthesis for many of these drugs are well

documented and profiled. However, nothing like this is currently available for bromo-dragonfly. This research seeks to fill that void.

Popular culture websites reference Chambers' article as the one to use when synthesizing bromo-dragonfly and the synthetic research in this study is predominantly based upon Chambers' methodology. This is a complicated synthesis, consisting of eight intermediates and a final product, and utilizing large volumes of solvents and many toxic reagents. When a clandestine lab is found, the precursors, reagents, intermediates, by-products, and waste are collected and analyzed. The results are then compared to known standards and reference material (spectra, chromatograms, etc.) to determine the product and its route of manufacture. Thus, the goal of this research is to assist investigators and analysts in identifying a clandestine bromo-dragonfly lab. Investigators will be able to compare the spectrums and data derived from this research to evidence collected at a clandestine laboratory. This comparison will help confirm or refute the potential clandestine synthesis of bromo-dragonfly at a particular scene.

According to both Andreasen and Forensic Scientist Jeff Borngasser from the Central Point Oregon Crime Lab, their two samples were quite pure. Borngasser's chromatogram only showed a trace impurity in the sample. Though ideal synthesis would involve producing a pure product, the benefits of this research lie in isolating and identifying the intermediates and by-products formed in the synthesis. One other point to consider from this research is that the specialty chemicals, reaction conditions, and chemical reactions required for this reaction far exceed the capabilities of the average

clandestine laboratory chemist. A clandestine bromo-dragonfly lab will likely require a complete conventional laboratory set-up, run by an educated or experienced chemist.

1.3 Synthesis Overview

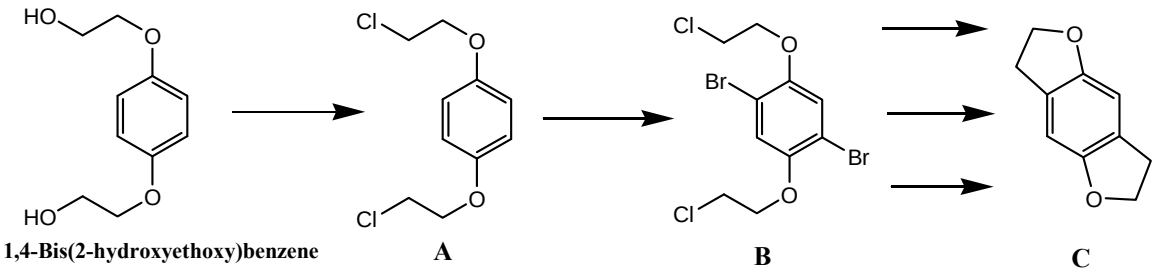
This synthesis employs two reactions: 1) synthesize the "wing" backbone [see Figure 5], and 2) build upon this structure to form bromo-dragonfly. Though only three steps, the first reaction proves to be most difficult, while the second reaction is lengthy. Since the R-enantiomer of bromo-dragonfly is more psychoactive than the S-enantiomer, the second reaction starts with D-alanine, which is inexpensive and commercially available. The D-alanine goes through a series of six chemical additions and substitutions, resulting in bromo-dragonfly. Many controlled situations are required, such as drop-wise additions and temperature maintenance. This research will analyze how altering these situations will affect the intermediates and by-products.

Chapter 2.

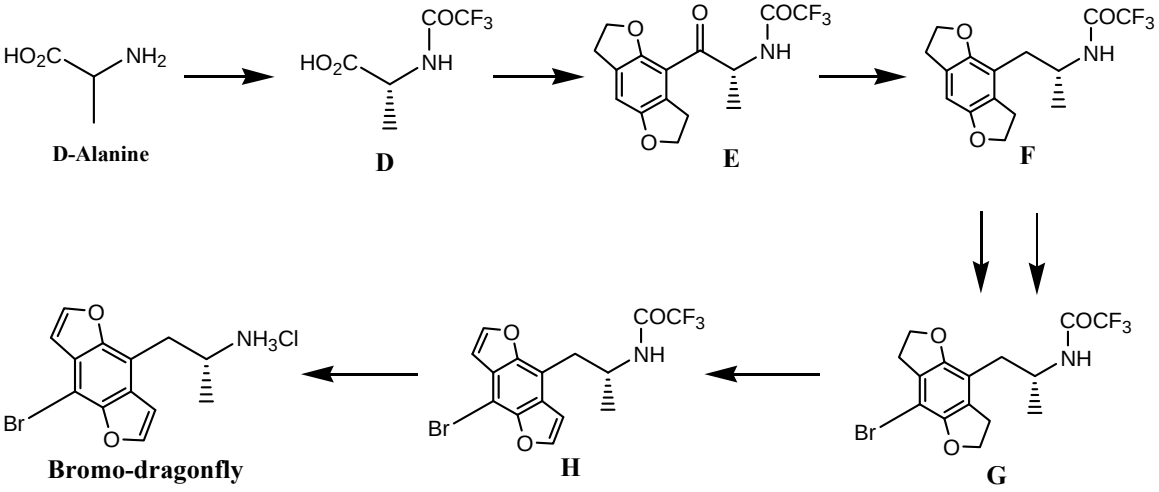
Chemistry

Bromo-dragonfly is synthesized in a multi-step reaction, converting alanine to the final product. The "wing" backbone must first be synthesized [see Reaction 1] so that it can be substituted onto Intermediate E [see Reaction 2].

Reaction 1: The synthesis of Intermediate C, used in Reaction 2 to make Intermediate E



Reaction 2: The synthesis of bromo-dragonfly



The R-enantiomer has been determined to be the more pharmacologically active version of bromo-dragonfly, so this is the only isomer made in this research (starting with D-Alanine instead of L-Alanine)[7]. The synthesis requires several specialized environments and controlled additions, many of which might be skipped in a clandestine laboratory. This experiment explores these possible alterations, documenting any differences in by-products.

2.1 Materials and Methods

The most difficult and important part of the bromo-dragonfly synthesis, 2,3,6,7-tetrahydrobenzo[1,2-*b*;4,5-*b*´]difuran (Intermediate C) is formed from 1,4-bis(2-hydroxyethoxy)benzene through a three-part synthesis. After experiencing excellent yields in the formation of Intermediates A and B, the three methods used for synthesizing Intermediate C proved inefficient. Two methods failed to yield any Intermediate C, while the third created many by-products that could not be separated.

Protection of the amine group in D-alanine is easily produced with trifluoroacetate (Intermediate D), followed by the conversion to its acid chloride with oxalyl chloride (intermediate uncharacterized). The acid chloride substitutes efficiently onto Intermediate C using a Friedel-Crafts reaction (Intermediate E), and is then reduced to afford Intermediate F. The bromination of Intermediate F into Intermediate G can be conducted one of two ways, while using bromine gives the highest yield. Oxidization of Intermediate G is achieved with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),

forming our protected bromo-dragonfly (Intermediate H). A highly basic environment removes the protection group, and a highly acidic environment produces our final hydrochloride salt (bromo-dragonfly).

2.1.1 Reagents

All reagents are commercially available through Sigma, VWR, and/or Fischer Scientific, though the Sacramento District Attorney's Laboratory of Forensic Services supplied many of the more common chemicals. All reagents used were >98% purity, except where discussed.

2.1.2 General Reaction Conditions

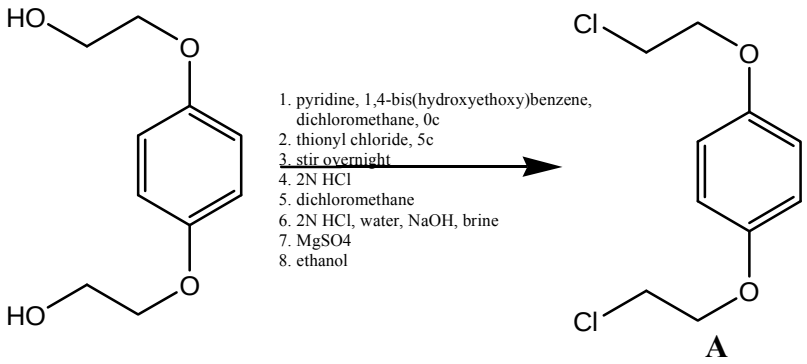
This synthesis was first conducted in normal atmosphere, followed by a full synthesis under nitrogen. There was no apparent difference between the syntheses except for yield, with normal atmosphere reactions occurring in a 0% or low yield as noted. During the nitrogen synthesis, unless otherwise stated, every mixture was first purged for five minutes by passing nitrogen through the headspace of each stirring solution. Water plays a large role in this synthesis, often keeping reactions from occurring. Therefore each solution was dried with powdered magnesium sulfate during the isolation of each intermediate, as mentioned in each experimental step. Several intermediates appear to be hygroscopic; all intermediates that weren't used immediately were stored in airtight bottles.

2.1.3 Instrumentation

Gas chromatography electron-impact mass spectrometry (GCEIMS) was used for characterization and confirmation of each intermediate and our final product, utilizing an Agilent 6890N GC with a 5973 network MS. A 15m DB-5 0.35mm ID column with 0.25µm film thickness (Agilent model 122-5012) was used with helium as the carrier gas (1.0mL/min). Conducting this research at the Sacramento County District Attorney's Laboratory of Forensic Services, their DRUG and LSD programs were utilized in all characterizations (DRUG for normal-size samples, LSD for all trace-size samples). The DRUG program starts at 90^{o}C, holds for 0.50 minutes, and then increases to 300^{o}C, ramping at 30.00^{o}C/min for ten minutes. The injection volume is 1µL, using a split mode (ratio 20.0:1). The LSD program, which was predominantly used from Intermediate G on, is exactly the same as the DRUG program except that it runs a splitless mode. All samples were prepared through a basic extraction into toluene, using methylperiline as the internal standard. The MS doesn't detect anything below m/z=43, so fragmentation analysis below this value cannot be conducted.

2.1.4 Results

Synthesis of Intermediate A {1,4-Bis(2-chloroethoxy)benzene}



Using an internal nucleophilic substitution, this step uses thionyl chloride to substitute the hydroxyl groups with chlorides. Thionyl halides are often used to convert alcohols into the corresponding alkyl halide via a SN2 reaction.

Experimental

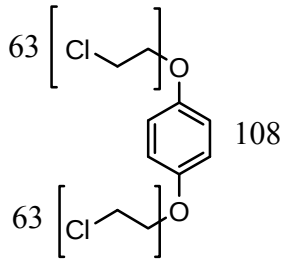
Within a 2L three-neck flask, dichloromethane (30mL) was added to 1,4-bis(2-hydroxyethoxy)benzene (30.026g, 152 mmol), followed by pyridine (29.4mL, 364 mmol). The solution's temperature was brought down to 0^{o}C by placing it into an ice bath while mechanically stirring, resulting in a thick, milky-white solution. Thionyl chloride (25.4mL, 348 mmol) was added to this solution drop-wise, ensuring that the temperature stayed around 4^{o}C. The reaction maintained a thick, cloudy, and off-white/beige appearance throughout the addition. After about an hour of addition of thionyl chloride, the precipitate present seemed to become even thicker, with the stirbar vortex no longer visible. This solution was allowed to gradually warm to room

temperature and stir overnight. Samples were taken and analyzed by GC-MS every hour to five hours to show the creation of Intermediate A. The starting products were not fully reacted until the next morning, when a clear yellow liquid was present. Aqueous 2N HCl (500mL) was added to this solution and the layers were separated. The aqueous layer was extracted with dichloromethane (3x75mL), and all organic layers combined. The dichloromethane was then washed with 2N HCl (aq) (2x200mL), water (200mL), 1N NaOH (aq) (100 mL), and brine (100mL). The organic layer was dried over magnesium sulfate and evaporated, yielding 36.875g of a white powder, Intermediate A (157 mmol).

Instrumental Analysis

Intermediate A was characterized using MS fragmentation [see Appendix B]. Appearing at retention time 4.57, the parent ion appeared at 234. The fragments and their intensities from 234-239 are consistent with what would be expected considering the two chlorines on Intermediate A (234=100%, 235=11%, 236=64%, 237=7%, 238=10.5%, 239=1%). As illustrated in Figure 6, the significant peak at 172 shows the loss of 62. This is the rearrangement of one CH2CH2Cl chain, which would have a mass of 63 (another prominent peak). The last abundant peak, at 110, appears to be a double-protonation of the benzene with two oxygens at the 1 and 4 positions, which would have a mass of 108.

Figure 6.



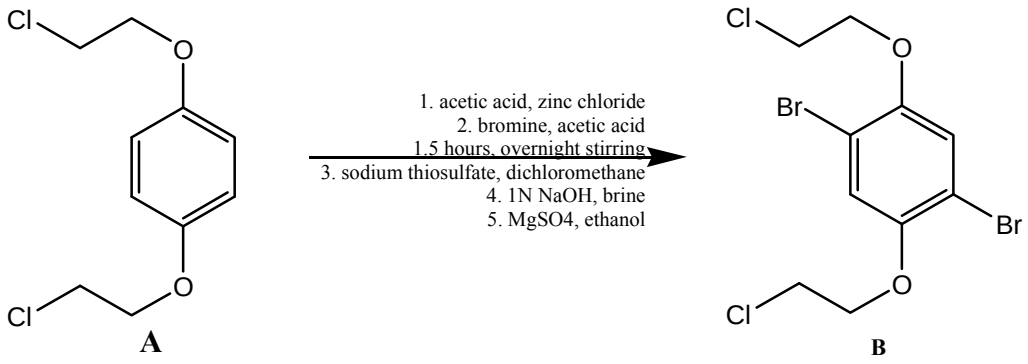
Notable Differences

After conducting this step a total of three times, we noted that the reaction looked different each time. The first time, the solution turned from yellow to tan after the addition of sodium hydroxide, with the aqueous layer appearing colored (whereas the previous aqueous washes had no color). Then, upon the addition of the brine, the aqueous layer took on a very oily appearance. The second time, there was no change in color in either the organic or aqueous layer during the washes. The third time, upon the addition of the water wash the entire solution turned into a very thick, frothy white mixture, with no separation of layers. After sitting for about 20 minutes, the emulsion did not settle. More water and dichloromethane were added to attempt to force the intermediate into the organic layer. The volume was increased to nearly 2L, but still the solvent layers could not be differentiated. The sodium hydroxide was then added, followed by brine (300mL), which forced the solution to form a bi-layered liquid. These differences wouldn't be noteworthy except all starting materials were added in the same amounts each time, and the Intermediate A chromatogram looked the same each time.

Possible Clandestine Lab Alterations

As illustrated above, there is a drop-wise addition of thionyl chloride in this reaction at 0°C. Assuming the reaction may get out of control if the thionyl chloride were added both all at once and at room temperature, this step was first attempted at room temperature with the thionyl chloride being added drop-wise, and then at zero degrees with the thionyl chloride being added quite rapidly. In both situations, there was no difference in the products forming, at least for the first few hours. But after a 24-hour stir, large by-products formed that didn't form in the controlled experiment (drop-wise addition at 0°C). Most of those by-products separated from Intermediate A during the sodium hydroxide and brine washes, but resulted in a slightly lower yield of Intermediate A. Unsure of what side-reactions may have occurred, the by-products could not be identified by fragmentation analysis alone [See Appendix B].

Synthesis of Intermediate B {1,4-Bis(2-chloroethoxy)-2,5-dibromobenzene}



The bromination of Intermediate A can be completed with just bromine and a catalyst. Zinc chloride is often used as a catalyst in the halogenation of alkyl- and polyalkylbenzenes.

Experimental

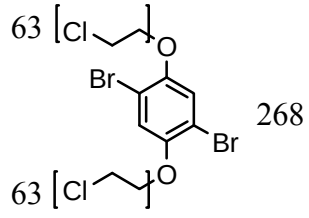
Within an aluminum foil covered flask, Intermediate A (27.55g, 117 mmol) was added to acetic acid (280mL). To this stirring solution, zinc chloride (38.8g, 285 mmol) was added, with not all of it going into solution. A solution of bromine (13 mL, 505 mmol) in acetic acid (55ml) was added drop-wise to the previous stirring solution. The reaction was monitored every hour for the rest of the day, and left to stir overnight to reach completion. When the foil was removed the next day, a transparent orange-red liquid was found stirring in the flask. This solution was diluted with saturated sodium thiosulfate (aq) (500mL) and then washed with dichloromethane (5x200mL). The organic layers were combined and washed with 1N NaOH (aq) (200mL), which picked up a yellow precipitate by-product not previously seen in the organic solution. The organic layer was washed with brine (200mL), dried with magnesium sulfate, and filtered, and the dichloromethane was evaporated down to yield a white-yellow solid. This solid was recrystallized with ethanol and filtered, resulting in a yellow ethanolic solution that contained the majority of the by-product, and 51.765g of off-white Intermediate B (132 mmol).

Instrumental Analysis

Intermediate B was characterized using MS fragmentation [see Appendix B]. Appearing at retention time 6.17, the parent ion appeared at 392. The fragments and their intensities from 390-397 are consistent with what would be expected considering the two chlorines and two bromines on Intermediate B (390=39%, 391=4.5%, 392=100%,

393=11%, 394=89%, 395=10%, 396=8%, 397=3.5%, 398=4%). As illustrated in Figure 7, the significant peak at 329 shows the loss of 63 (another prominent peak), the mass of one CH2CH2Cl chain. The last abundant peak, at 268, is the benzene ring with an alcohol group at both the 1 and 4 positions, and a bromine at both the 3 and 6 positions (these positions are assumed). This is a minor rearrangement (protonation) of Intermediate B with the two CH2CH2Cl chains cleaved off. Lastly a small peak at 79 is present, the mass of bromine.

Figure 7.



At retention time 6.41, a spectrum almost identical to that of Intermediate B is present. It is assumed that this is Intermediate B with the bromines having added in a way other than para. Though this cannot be confirmed without NMR, para should be the favored addition, and should be the more abundant peak (e.g. retention time 6.17).

Notable Differences

Intermediate B was synthesized twice, and, again, the extractions and washes looked different each time. The first time we did the five dichloromethane extractions, a thick yellow solid formed between the aqueous and organic layers, which was deemed to be waste. The first and second dichloromethane extractions were green, the third a little

less so, the fourth had a slight green tinge, and the fifth was clear. During the wash with sodium hydroxide, the aqueous layer turned a dark green/brown, while the organic layer became yellow-green. The brine didn't significantly affect the organic layer, except for making it slightly more yellow than green. The second time Intermediate B was made and the extractions were conducted, a white solid clearly formed in the first dichloromethane extraction, leaving a yellow aqueous layer. After the first dichloromethane extraction, the subsequent four stayed clear, though there was a white emulsion during the second extraction. The sodium hydroxide wash picked up a yellow precipitate, and there was no change during the brine wash. The Intermediate A used as the starting material was the same for each synthesis, other starting materials were added in the same amounts, and the Intermediate B chromatogram looked the same for both.

Possible Clandestine Lab Alterations

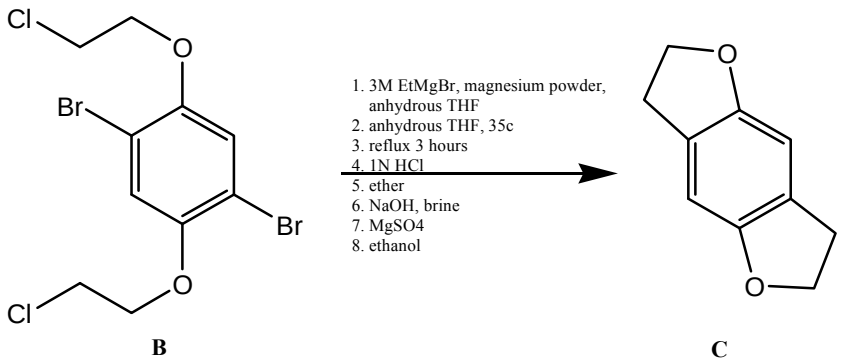
The Chambers method indicates a drop-wise addition of bromine over 1.5 hours. The speed at which the bromine is added, from 30 minutes to 2 hours, does not seem to affect the result. The experiment with a half-hour addition resulted in the quickest conversion from Intermediate A to Intermediate B, with no starting product evident after 20 hours. The other reactions required more bromine to be added after 20 hours since GC-MS spectra indicated Intermediate A and/or an intermediate between A and B (only one bromine attached) to be present. With an orange gas emitting from the separatory funnel that was holding the bromine/acetic acid mixture during the drop-wise addition, it's likely that bromine was escaping in gas form during the lengthy additions, resulting in a deficit of bromine.

Synthesis of Intermediate C {2,3,6,7-Tetrahydrobenzol[1,2-b-4,5-b']difuran}

Three different routes were used to synthesize Intermediate C. Each route varied by using a different Grignard reagent. The three Grignard reagents used were ethylmagnesium bromide, tetramethylethyldiamine with ferric chloride, and n-butyllithium.

After several attempts, the first and second routes failed to yield any Intermediate C, and the third method was successful.

Ethylmagnesium Bromide Method.



B **C**

This reaction employs a pre-made Grignard reagent, elemental magnesium, and the bromines on Intermediate B to close the two five-membered rings.

Experimental

Within a three-neck round bottom flask, magnesium -50 mesh (3.805g, 29 mmol) was suspended in THF (50mL). Ethylmagnesium bromide (3.4mL, 10 mmol, 3M in ether) was slowly added to this stirring mixture. With the solution cooled to ~10^{o}C, a solution of Intermediate B (20.192g, 51 mmol) in THF (150mL) was added drop-wise.

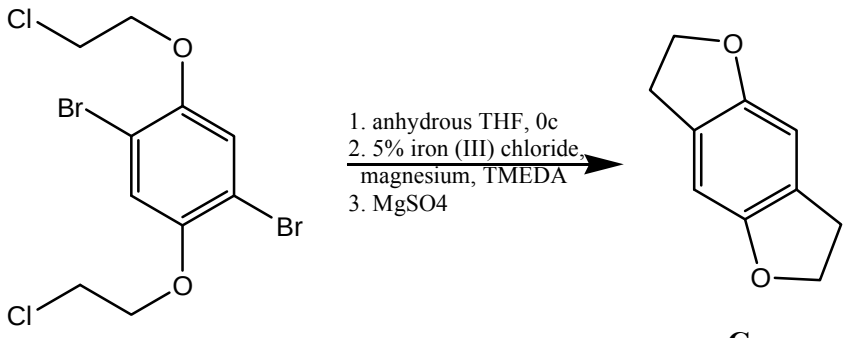
Upon addition of Intermediate B, the reaction was brought to reflux, which occurred at approximately 68^{o}C. After three hours, the heat was shut off and the reaction slowly cooled to room temperature. The entire solution was slowly poured into cold 1N HCl (aq) (200mL). The solution was extracted with ether (3x300mL), and the combined organic layers washed with 1N NaOH (aq) (4x75mL) and brine (50mL).

All four times this step was attempted, the boil was not smooth and bumped a lot, which boiling stones didn't do much to alleviate. It appears to be the magnesium mesh that causes a large release of gas, violently pushing condensation up and out of the column. Due to this, even with a large reflux column, more THF had to be added repeatedly.

Possible Clandestine Lab Alterations

Using the recipe described above, this reaction was attempted with two other types of magnesium: 30-80 mesh and turnings. The reaction utilizing 30-80 mesh magnesium had a reaction identical to the 50 mesh magnesium, again failing to make Intermediate C. The magnesium turnings, which were fresh but still scratched to ensure activation, resulted in a much smoother boil than the mesh.

Tetramethylethylenediamine (TMEDA) Method.



B **C**

On a recommendation by Dr. Andrew Allen, a chemist out of Colorado who was once a DEA forensic chemist, I researched the possibilities of using an iron catalysis direct-coupling method [13-15]. Using the bromines already present on Intermediate B, fresh magnesium turnings in THF will allow for the formation of a Grignard, catalyzed by ferric chloride and TMEDA. This step will be more active, occurring first, which will then allow for the intramolecular reaction closing the two five-membered rings. This method allows for a one-pot reaction, and avoids the highly sensitive and reactive Grignards and organolithiums.

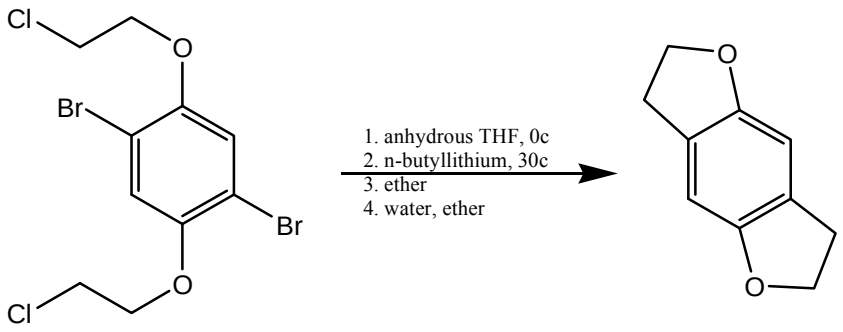
Experimental

Intermediate B (18.2 g, 46 mmol) was dissolved into THF (100mL) and cooled to 0^{o}C. Ferric chloride (13.317g, 82mmol) was added to this solution to form a 5% iron(III) chloride solution. This was quickly followed by the addition of TMEDA (5.127g, 44mmol) and fresh magnesium turnings (24.305g, 46 mmol). Though one article reported a higher yield with the addition occurring at 0^{o}C and the coupling at 20^{o}C, it was decided to keep the reaction at 0^{o}C for the entire four hours of the reaction. This decision

was predominantly made because the article was strictly discussing aryl and alkyl chlorides, not a mixture of chlorides and bromides. After four hours, the reaction was quenched with water.

This reaction failed to make Intermediate C. The reason behind this, however, cannot be determined. It was assumed that something within the reaction vessel must have been wet (the THF and/or Intermediate B), but when water was added to the reaction, the magnesium was still extremely reactive, resulting in a large amount of gas being given off. It took approximately 20 hours for this gas to finally cease.

N-Butyllithium Method.



B **C**

Comparable to a Grignard reagent, except more reactive, n-butyllithium (n-BuLi) is an organolithium reagent employed to convert Intermediate B to Intermediate C[4,16]. The n-BuLi acts as a highly reactive nucleophile to produce a halogen-lithium exchange. In THF, n-BuLi reacts with the solvent to give the reagent a fairly short half-life, which goes down in time as temperature increases.

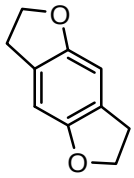
Experimental

Within a three-neck round bottom flask, Intermediate B (20.741g, 53 mmol) was dissolved into THF (500mL). This was stirred on an ice bath, bringing the temperature down to 0^{o}C, at which point n-BuLi (60mL, 637mmol) was added quickly. Full addition occurred within five seconds, causing the temperature to increase to 30^{o}C. Upon the addition, the solution turned from a light yellow color to a deep auburn/orange color. Due to the half-life of n-BuLi in these conditions, the reaction was deemed complete in ten minutes. After evaporating off the THF, ether (100mL) was added. The solution immediately turned green/blue, boiled, and off-gassed, followed by a sudden change to a dark red/brown color. Water (100mL) was added, the layers separated, and the aqueous layer was extracted with ether (2x50mL). The organic extractions were dried with magnesium sulfate, filtered, and evaporated, resulting in impure Intermediate C as a brown oil weighing 8.35g (52 mmol).

Instrumental Analysis

Intermediate C was characterized using MS fragmentation [see Appendix B]. Appearing at retention time 3.49, the parent ion is 162, consistent with the mass of Intermediate C. All of the fragments are hydrocarbon groups (77=benzene, 91=benzene + CH2, 133=loss of CH3CH2, 147=loss of CH3), while the fragment at 105 shows a loss of C2H5CO. Along with the fragmentation at the parent ion (162=100%, 163=11.5%), this is consistent with what is expected for Intermediate C [see Figure 8].

Figure 8.

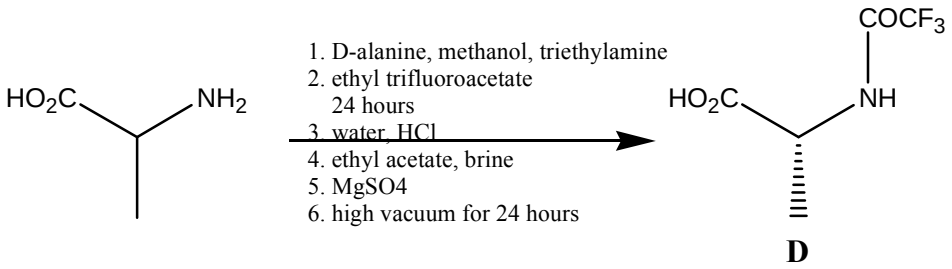


Possible Clandestine Lab Alterations

This step will fail to yield Intermediate C if conducted in normal atmosphere.

Conducting this at room temperature will also fail to produce Intermediate C; n-butyl lithium is not stable in THF at room temperature, resulting in deprotonation of the THF.

Synthesis of Intermediate D {(R)-N-Trifluoroacetylalanine}



D

Frequently used in organic chemistry, this step will utilize the ethyl trifluoroacetate as a protecting group for the amine on Intermediate D.

Experimental

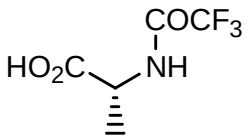
D-alanine (6.25g, 71 mmol) was dissolved into methanol (27.5mL), followed by the addition of triethylamine (7.8mL, 56 mmol). This stirred for five minutes, at which

point ethyl trifluoroacetate (8.3mL, 71mmol) was added. Upon this addition, a seemingly heavy white gas, about two inches deep, settled on top of the stirring liquid. The solution was left to stir for 24 hours. After 24 hours, the solution took on a slight yellow hue and a precipitate formed on the bottom. The solvent was removed by passing nitrogen over it, and water (90mL) was added to the residue, which dissolved immediately. This was followed by the slow addition of concentrated hydrochloric acid (10mL), which was left it to stir for 15 minutes. Extractions with ethyl acetate (4x75mL) were combined, and the organic layers washed with brine (65mL). The organic was blown down to isolate 11.61g Intermediate D (63 mmol).

Instrumental Analysis

Intermediate D could not be analyzed using the GC-MS, so IR was used for characterization [see Appendix B]. The broad peak at 2500-3500 is representative of stretching vibrations of the carboxylic acid. The moderate peak ~1100 may be the secondary amine, while the strong, broad peak at ~1200 may be a C-CO stretch, or the OH bending of the carboxylic acid. The moderate peaks ~1400-1500 are likely to be the C-C and C-H bending, particularly from the CH3 group, as are the peaks from 500-1200. The strong peak at ~1700 signifies the C=O stretch. Without GC-MS none of this can be confirmed, nor can the purity of Intermediate D, but the peaks are consistent with our intermediate [see Figure 9].

Figure 9.

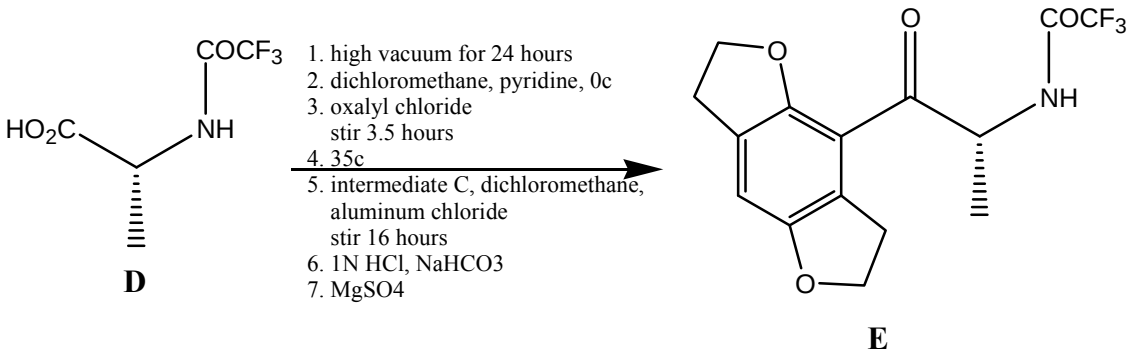


Possible Clandestine Lab Alterations

The original experiment (by Chambers) used a rotary evaporator on the final organic solution and subjected the resulting oil to high vacuum for 24 hours. For safety reasons of leaving an unattended reaction, we evaporated the ethyl acetate with nitrogen over a weekend, resulting in a white solid (with a waxy consistency). Chambers notes in his publication that Intermediate D is highly hygroscopic. Based off of the large Intermediate D yield in our experiment, our method of evaporation may allow some moisture to stay present.

Conducting this experiment in normal atmosphere resulted in an excessively large yield, indicating that exposure to air significantly increases the amount of moisture that Intermediate D absorbs.

Synthesis of Intermediate E {(R)-(+)-N-Trifluoroacetyl-2,3,6,7-tetrahydro-4-alanyl-benzo{1,2-b;4,5-b']difuran}



This reaction consists of a typical Friedel-Crafts reaction, utilizing both oxalyl chloride and aluminum chloride. The oxalyl chloride first acts upon Intermediate D, changing the carboxylic acid into an acid chloride. This acid chloride then partakes in the Friedel-Crafts by donating its chloride to the aluminum chloride, and the resulting acyl cation receiving a nucleophilic attack by the benzene ring.

Experimental

Intermediate D (11.5g, 62 mmol) was dissolved into dichloromethane (200mL), followed by the addition of pyridine (5 drops). This solution was cooled to 0^{o}C and oxalyl chloride (6.75mL, 79 mmol) was added quickly. It was allowed to warm to room temperature gradually, and then stirred for 3.5 hours. The liquid was evaporated off by applying low heat while passing nitrogen over it. The resulting pale yellow oil weighed 5.24g, but we were unable to characterize this acid chloride by the methods available to us.

A mixture of Intermediate C (1.3g, 8 mmol) in dichloromethane (40mL) was added drop-wise to a mixture of aluminum chloride (2.7g, 20 mmol) in dichloromethane (50mL). This solution started out as a dark brown, cloudy mixture, and ended up nearly black after the addition of Intermediate C. While no heat ever appeared to be given off, condensation did collect on the inside of the reaction vessel. The previous acid chloride (5.24g) was dissolved into dichloromethane (45mL) and this was added to the previous solution.

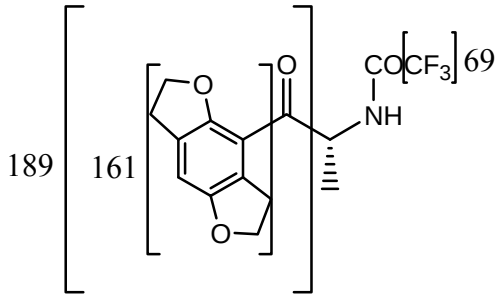
The solution was left to stir overnight, at which point analysis by GC-MS revealed an incomplete conversion of Intermediate C into Intermediate E. Knowing that there was still Intermediate C present in this solution, but being unable to determine whether there was any more of the acid chloride intermediate present, extra aluminum chloride was added to test if anything else could react. A small sample of the solution was mixed with aluminum chloride in a test tube and vortexed periodically for an hour, but the reaction failed to yield any more Intermediate E. Therefore, we moved on.

The entire solution was poured over ice and the organic layer was separated. The aqueous layer was extracted with dichloromethane (4x75mL), with the aqueous layer remaining yellow with large chunks of a brown solid floating in it. The combined organics were washed with cold 1N HCl (aq) (75mL), water (50mL), and sodium bicarbonate (2x50mL). The organics were dried with magnesium sulfate and filtered. After evaporating off all of the dichloromethane, an oil weighing 2.03g was characterized to be Intermediate E (6 mmol).

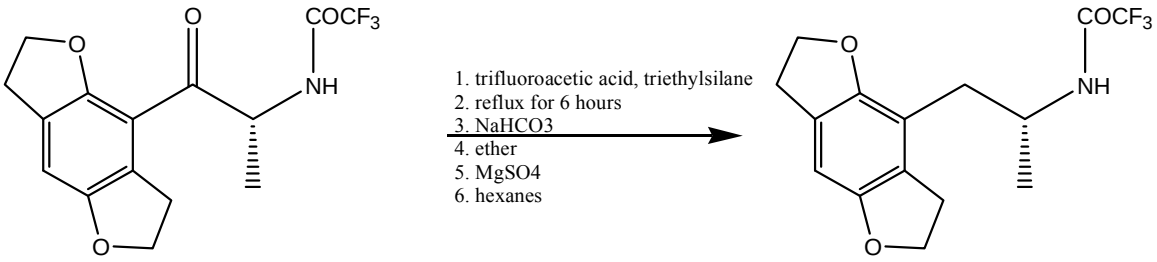
Instrumental Analysis

Intermediate E was characterized using MS fragmentation [see Appendix B]. Appearing at retention time 5.79, the parent ion appeared at 329. The fragmentation around the parent ion is consistent with what is expected (329=100%, 330=17%, 331=2%). Illustrated in Figure 10, the significant peak at 161 is representative of Intermediate C minus one hydrogen, conceivably where the chain cleaved off. The most abundant peak, at 189, indicates C with a CO chain, or Intermediate E without the CH3CH2NHCOCF3 chain (-140). Lastly, a small peak is apparent at 69, which is the CF3 group.

Figure 10.



Synthesis of Intermediate F {(R)-(+)-N-Trifluoroacetyl-1-(2,3,6,7-tetrahydrobenzo{1,2-b;4,5-b']difuran-4-yl)-2-aminopropane}



E **F**

Using the reducing agent triethylsilane, the C=O bond on Intermediate E is reduced and the oxygen removed. The trifluoroacetic acid is used to create an acidic environment, and chosen over some of the more common acids (i.e. sulfuric and hydrochloric) because it doesn't have the same oxidizing properties, and it's anhydrous.

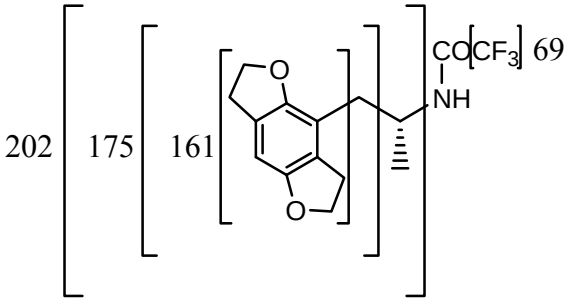
Experimental

Moving on with all of the previous intermediate, trifluoroacetic acid (9.5mL) and triethylsilane (2.3mL, 14 mmol) were added to Intermediate E (2.03g, 6mmol). This solution refluxed for six hours. It was then cooled to room temperature, and saturated sodium bicarbonate (aq) was added (250mL) until the gas ceased and the solution remained alkaline. The solution was extracted with ether (4x75mL), which was then dried with magnesium sulfate and vacuum filtered. The resulting organic solution was evaporated under nitrogen. Intermediate F presented itself as an oil, which I triturated with hexanes. This was filtered, with 1.80g of Intermediate F recovered (6 mmol).

Instrumental Analysis

Intermediate F was characterized using MS fragmentation [see Appendix B]. Appearing at retention time 5.30, the parent ion appeared at 315, with fragmentation consistent with the expected (315=100%, 316=17.5%, 317=2%). As illustrated in Figure 11, the peak at 202 represents a rearrangement of Intermediate F minus the NH-COCF3 chain, being m/z=1 less than expected for this group. The most abundant peak, at 175, is the "wing" backbone (Intermediate C) with a CH2 group attached, having lost the CH2CH3NHCOCF3 (m/z=140) chain. The minor fragment of 161 represents a negatively charged Intermediate C, having lost the entire chain. Lastly, the peak at 69 is the CF3 fragment.

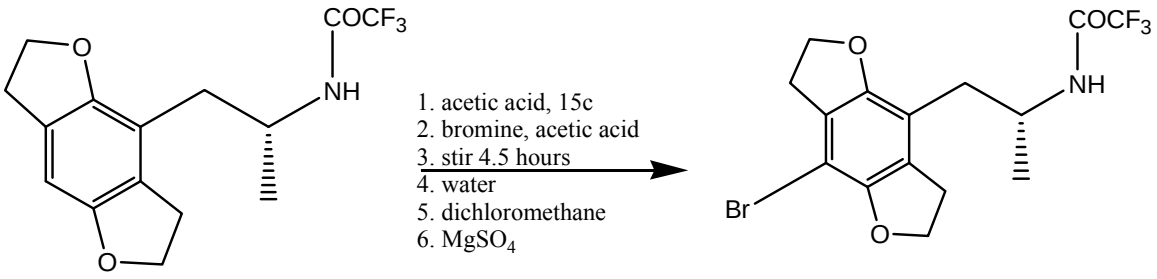
Figure 11.



Synthesis of Intermediate G {(R)-(+)-N-Trifluoroacetyl-1-(8-bromo-2,3,6,7-tetrahydrobenzo{1,2-b;4,5-b']difuran-4-yl)-2-aminopropane}

Determining a method that might work better, the bromination of Intermediate F to make Intermediate G was conducted two different ways: with bromine, and with n-bromosuccinimide (NBS).

Bromine Method.



F **G**

The bromination of Intermediate F can be achieved with bromine under acidic conditions.

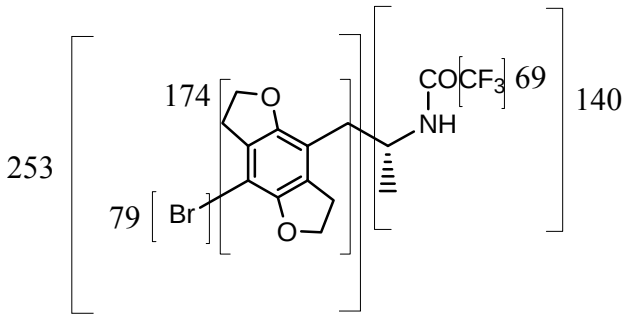
Experimental

Intermediate F (1.80g, 5.7 mmol) was dissolved into acetic acid (75mL) within a reaction flask wrapped in aluminum foil. This solution was cooled to 15^{o}C, and a solution of bromine (0.626g, 7.8 mmol) in acetic acid (12mL) was added drop-wise. The mixture warmed to room temperature and stirred for 4.5 hours, at which point it was poured into water (100mL); the solution changed from a dark brown/auburn solution to a cloudy grey/brown. The solution was extracted with dichloromethane (7x50mL), until the dichloromethane stopped picking up color. The organics were dried with magnesium sulfate and filtered, and evaporated down with nitrogen, resulting in 1.55g of Intermediate G in oil form (4.9 mmol).

Instrumental Analysis

Intermediate G was characterized using MS fragmentation [see Appendix B]. Appearing at retention time 6.19, the parent ion appeared at 393, with the surrounding fragmentation consistent with what we expect (393=100%, 394=17.5%, 395=98%, 396=16.5%). The small peak at 314 signifies a negatively charged Intermediate F, after the loss of bromine. The most abundant peak, at 253, signifies a loss of 140. This is equal to the CH3CH2NHCOCF3 chain, as illustrated in Figure 12. The last prominent peak, at 174, is an extra loss of 79 (from the structure at 253), representing the loss of bromine. This structure is negatively charged Intermediate C with a CH2 group attached.

Figure 12.

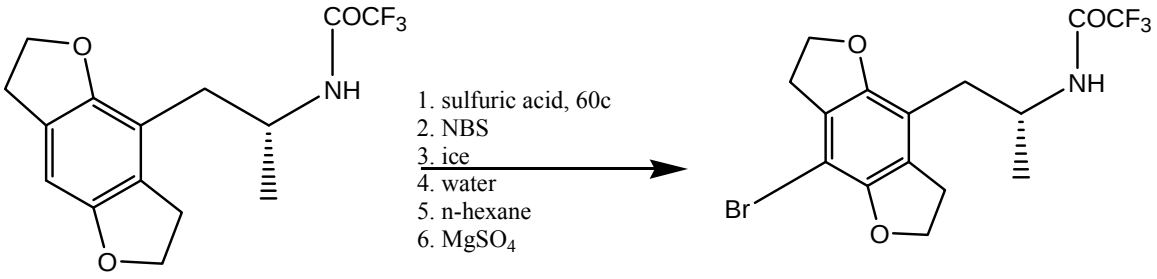


Possible Clandestine Lab Alterations

As with the synthesis of Intermediate B, a quicker addition of bromine ensured full conversion from Intermediate F to Intermediate G. Chambers warns readers in his publication to not use more than 1.0 equivalent of bromine, due to possible oxidation of the dihydrofuran moieties to furans. If bromine were to volatize and escape during the synthesis of Intermediate G, it may be nearly impossible to determine how much more

bromine need be added. Therefore, some Intermediate F will remain present if no more bromine is added. If more bromine is added to ensure a full conversion, it's likely these impurities will be present. While our Intermediate G does have impurities, we were unable to determine by GC-MS alone if these are the furans Chambers references.

N-bromosuccinimide Method.



F **G**

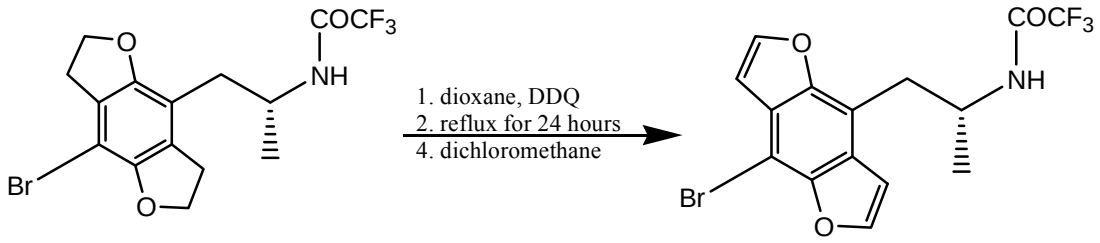
While most commonly used for the Wohl-Ziegler reaction, NBS is also safer and easier to use than bromine for the bromination of aromatic compounds.

Experimental

Following a method outlined by Rajesh et al [17], Intermediate F (0.486g, 1.5 mmol) was dissolved into concentrated sulfuric acid (10mL). This was heated to 60^{o}C, and NBS (0.600g, 3.4 mmol) was added in three equal portions every fifteen minutes (3x0.200g). The solution continued to heat for two hours, at which point the reaction was poured over ice. The solution was diluted with water (200mL), and extracted with dichloromethane (100mL). We were unable to get a full separation of layers. GC-MS analysis was attempted to confirm whether or not Intermediate G formed, but base

extraction on the highly acidic solution proved difficult. Several attempts revealed three of the by-products present in Intermediate F, but no Intermediate F nor G.

Synthesis of Intermediate H {(R)-(+)-N-Trifluoroacetyl-1-(8-bromobenzo{1,2-b;4,5-b']difuran-4-yl)-2-aminopropane}



G **H**

This reaction involves the transfer of hydride ions from a hydrocarbon to the 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ); DDQ is used for the dehydration of hydroaromatic compounds. This reaction allows for the unsaturation of our five-membered rings, leading to the two characteristic furan rings seen in bromo-dragonfly.

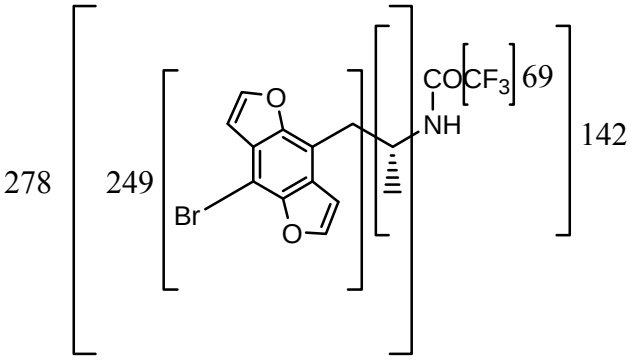
Experimental

Intermediate G (0.55g, 1.4 mmol) was dissolved into dioxane (50mL), and to this a solution of DDQ (2.150g, 9.5mmol) in dioxane (40mL) was slowly added. The solution was allowed to reflux for 24 hours, and then gradually cooled to room temperature. The solution was then filtered and the filtrate evaporated down, resulting in 0.43g of Intermediate H (1.1 mmol).

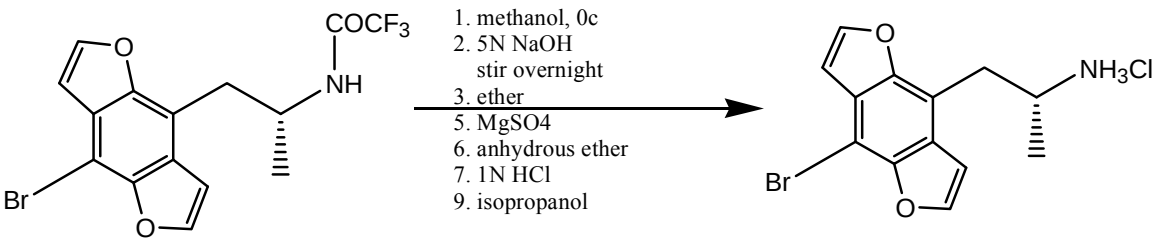
Instrumental Analysis

Intermediate H was characterized by GC-MS [see Appendix B]. Appearing at retention time 5.83, the parent ion appeared at 389, with the surrounding fragmentation consistent with what we expect (389=100%, 390=17%, 391=99%, 392=16.5%, 393=2%). As illustrated in Figure 13, the peak at 278 signifies a loss of m/z=111, likely the loss of a negatively charged NHCOCF3. The peak at 249 is a loss of m/z=140, which has been a common loss in all previous intermediates. The 249 fragment is the dehydrated Intermediate C with a bromine and CH2 group attached, while the peak at 142 is likely a rearrangement of the lost chain. Lastly, the peak at 69 is the CF3 group, revealing we haven't yet lost our protecting group.

Figure 13.



Synthesis of Bromo-dragonfly {(R)-(-)-1-(8-bromobenzo[1,2-b;4,5-b']difuran-4-yl)-2-aminopropane hydrochloride}



H **Bromo-dragonfly**

By putting Intermediate H into highly basic conditions, the protecting group is removed to reveal our product, bromo-dragonfly. Bromo-dragonfly is then salted out to become the biologically active material.

Experimental

Intermediate H (0.43g, 1.1 mmol) was dissolved into methanol (25mL) and cooled to 0^{o}C. This was followed by the addition 5N NaOH (aq) (5mL), which turned the solution a quick red and then yellow. The solution was left to warm gradually to room temperature and to stir overnight. An extraction of the aqueous solution with ether (75mL) was attempted, but the aqueous layer (bottom) was too thick to pour through the separatory funnel, leading the ether layer (top) to pour through it while pulling the aqueous waste out at the same time. Therefore, more water was added in an attempt to "thin it out," which worked. Further ether extractions were performed (3x20mL), and the organics were dried over magnesium sulfate, filtered, and evaporated down to an oil.

GC-MS analysis for the oil was consistent with bromo-dragonfly [see Appendix B], so it was turned into its salt form. The oil was dissolved into ether (15mL), and a 1N ethanolic HCl solution (30mL) was slowly added. This was left in the freezer overnight, at which point a small amount of precipitate was visible. The solution was vacuum filtered and the solid recrystallized with isopropyl alcohol. GC-MS analysis showed a highly contaminated bromo-dragonfly, which consequently could not be isolated [see Appendix B]. The contaminants seem to have come from the ethyl alcohol used to dilute the HCl.

2.2 Discussion

Before starting this project, we assumed that bromo-dragonfly could easily be made clandestinely. However, it is now clear that this synthesis requires fairly sophisticated chemistry lab equipment and knowledge. The glassware, environmental conditions, and specialty chemicals required for this reaction far exceed the capabilities of the typical clandestine laboratory chemist.

First of all, a large abundance of glassware is utilized throughout the entire reaction, from macroscale (some reactions are up to 2L in volume) to microscale (some reactions are as small as 12mL in volume) and everything in between. Often, multiple pieces are needed simultaneously. There are many large separations, requiring a 2L separatory funnel, and a few extended refluxes, requiring not only the reflux columns but a stable heat source as well. In one reflux, the reaction bumps violently throughout the entire six hours that it runs, no matter how many boiling chips/sticks are added, requiring

a very long reflux column to keep solvent from escaping. We utilized a column nearly two feet in length and solvent still escaped.

Second, every step of this reaction is air and moisture sensitive. Due to this activity, all of the reactions require an inert atmosphere to completely eliminate air and moisture. Given how long this reaction is (taking two Monday-Friday weeks working nine hour days, if no complications arise), anyone synthesizing this needs to have a proper set up and enough argon or nitrogen to run the entire time. This could be quite difficult in a typical clandestine set up. The large amount of tetrahydrofuran (THF) used throughout the experiment posed the most difficulty in regards to the moisture problem. The ease of THF to become "wet THF" leads to the need of distillation right before the THF is used, or the use of a brand new bottle each time. Also adding to the moisture problem, a few intermediates appear to be hygroscopic, gaining weight when left open to the atmosphere over night. Therefore, all intermediates must be completely dried with magnesium sulfate while in solution, the solvent evaporated off, and the completely dry intermediate placed in an airtight container within a desiccator.

The part of this reaction that seems to be most crucial to the success of this synthesis is the production of Intermediate C. Each time this synthesis was conducted, the synthesis of bromo-dragonfly depended on the success of Intermediate C. Due to the Grignard reaction that is occurring, this step is the most air and moisture sensitive. Using Chambers' method, even with dry THF and fresh ethylmagnesium bromide, we were not able to make Intermediate C any of the five times attempted. At that point, Monte's method was employed. This reaction was successful, but produced several by-products,

including one large by-product that we could not separate from Intermediate C. This by-product, at retention time 1.63 [see Appendix B], remained present in Intermediate E and Intermediate F. The reaction for Intermediate F produced another prominent by-product, at retention time 2.64 [see Appendix B], which could not be separated and carried through to the end. Based on common fragmentation, the new by-product appears to be from a side-reaction with the left over Intermediate C that remained part of Intermediate E. The impurities in Intermediate C led us to search for alternate synthesis methods, but the TMEDA method used was unsuccessful. The development of a high-yielding Intermediate C reaction would be most beneficial to the synthesis a pure bromo-dragonfly standard.

The difficulty in the production of Intermediate C is another example of how this reaction may be difficult to replicate clandestinely. At each step, instrumental analysis was vital to ensuring we had the correct intermediate to move on with, but especially so in making Intermediate C. The first few times I attempted Chambers' method I was certain that I had made Intermediate C, with crystals forming during the reflux cool-down and a final white powder after work-up. After running a sample on GC-MS, however, we found out each time that we still had Intermediate B, maintaining the same composition it had going in to the reaction. If we did not have a GC-MS, it is quite likely that we would have moved on, assuming Intermediate C had been synthesized, and would never have made bromo-dragonfly.

The purity of the chemicals used was one other aspect that largely affected the purity of the final product. This was most evident in the very last step, where ethanol

was used in the "salting out" of bromo-dragonfly. Hydrochloric acid was used to turn our product into a salt, using a 1N ethanolic HCl solution that was made with 95% ethanol. After the attempted isolation and recrystallization with isopropyl alcohol, dozens of peaks revealed themselves on the GC-MS chromatogram during the last half of the run-time, raising the baseline and drowning out our bromo-dragonfly [see Appendix B]. This typically indicates a contamination by very large hydrocarbons, as is commonly seen when plastic gets into a sample. A literature search revealed articles discussing the commercial contamination of 95% ethanol by adding industrial plasticizers, which is what we've concluded happened here[18]. Future study possibilities include using 200-proof ethanol to support this conclusion and to determine if all the by-products are otherwise removed with the isopropyl alcohol recrystallization.

2.3 Conclusion

While of great interest and moderate concern to many forensic chemists, this experiment shows that bromo-dragonfly is not likely to become one of the next big clandestine laboratory drugs. The synthesis is too complicated for the usual clandestine chemist. The amount of glassware, expense and toxicity of the chemicals, and need for very clean, controlled environments exhibits the caliber of lab needed to synthesize this hallucinogen. The multitude of steps and difficulty in making Intermediate C requires instrumentation to confirm intermediates, leading to the assumption that only industrial or university labs have the proper set-up to synthesize bromo-dragonfly successfully.

References

(1) Braden, M. R.; Parrish, J. C.; Naylor, J. C.; Nichols, D. E. Molecular Pharmacology 2006, 70, 1956-1964.
(2) McLean, T. H.; Parrish, J. C.; Braden, M. R.; Marona-Lewicka, D.; Gallardo-Godoy, A.; Nichols, D. E. Journal of Medicinal Chemistry 2006, 49, 5794-5803.
(3) Nichols, D. E. Pharmacology and Therapeutics 2004, 131-181.
(4) Monte, A. P.; Marona-Lewicka, D.; Parker, M. A.; Wainscott, D. B.; Nelson, D. L.; Nichols, D. E. Journal of Medicinal Chemistry 1996, 39, 2953-2961.
(5) Monte, A. P.; Waldman, S. R.; Marona-Lewicka, D.; Wainscott, D. B.; Nelson, D. L.; Sanders-Bush, E.; Nichols, D. E. Journal of Medicinal Chemistry 1997, 40, 2997-3008.
(6) Parker, M. A.; Marona-Lewicka, D.; Lucaites, V. L.; Nelson, D. L.; Nichols, D. E. Journal of Medicinal Chemistry 1998, 41, 5148-5149.
(7) Chambers, J. J.; Kurrasch-Orbaugh, D. M.; Parker, M. A.; Nichols, D. E. Journal of Medicinal Chemistry 2001, 44, 1003-1010.
(8) Fujita, M.; Minamino, T.; Sanada, S.; Asanuma, H.; Hirata, A.; Ogita, H.; Okada, K.-I.; Tsukamoto, O.; Takashima, S.; Tomoike, H.; Node, K.; Hori, M.; Kitakaze, M. Journal of Molecular and Cellular Cardiology 2004, 37, 1219-1223.
(9) Erowid. "Bromo-Dragonfly Dosage." Erowid. 18 Mar. 2009. 10 Apr. 2009.
(10) Andreasen, M. F.; Telving, R.; Birkler, R. I. D.; Schumacher, B.; Johannsen, M. Forensic Science International 2009, 183, 91-96.
(11) Anonymous Microgram Bulletin 2007, 40, 78.
(12) "Bromo-Dragonfly." E-mail to the author. 15 May 2009.
(13) Czaplik, W. M.; Mayer, M.; Wangelin, A. J. v. Angewandte Chemie 2009, 48, 607-610.
(14) Ritter, S. K. Chemical and Engineering News 2009, 87, 6.
(15) Sherry, B. D.; Furstner, A. Account of Chemical Research 2008, 41, 1500-1511.
(16) Parham, W. E.; Jones, L. D.; Sayed, Y. A. Journal of Organic Chemistry 1976, 41, 1184-1186.
(17) Rajesh, K.; Somasundaram, M.; Saiganesh, R.; Balasubramanian, K. K. Journal of Organic Chemistry 2007, 17, 5867-5869.
(18) Goldstein, D. B.; Feistner, G. J.; Faull, K. F.; Tomer, K. B. Alcoholism: Clinical and Experimental Research 1987, 11, 521-524.

Appendix A. Figures

Figure 1. Bromo-dragonfly

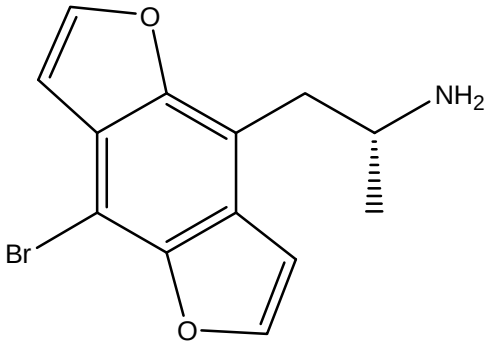


Figure 2. Monte et al's Saturated Bromo-dragonfly

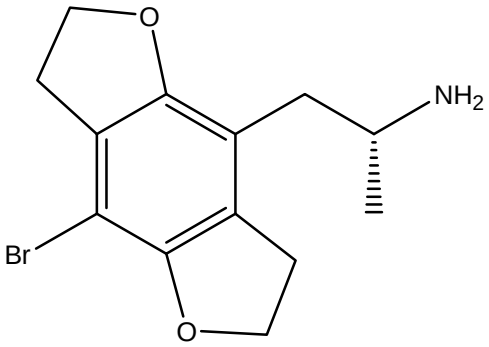


Figure 3. DOB

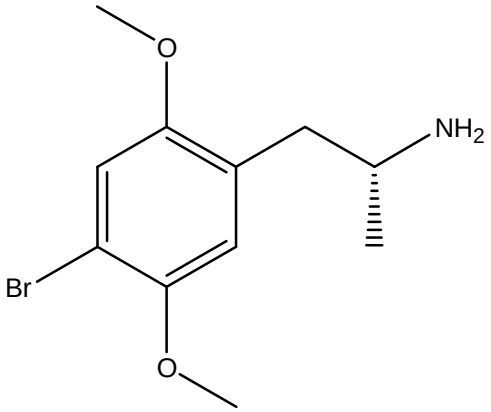


Figure 4. 2C-B

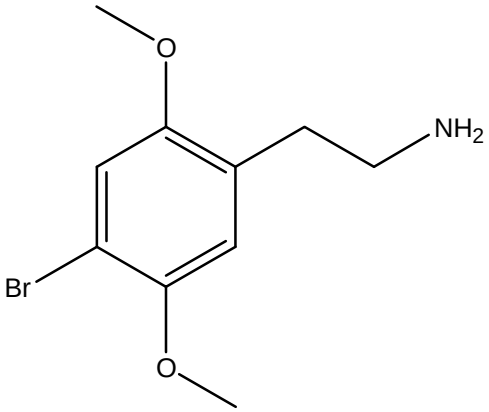
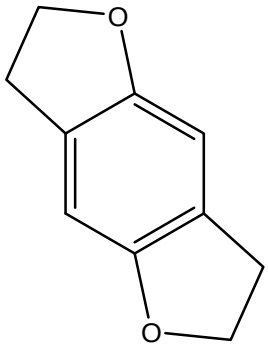
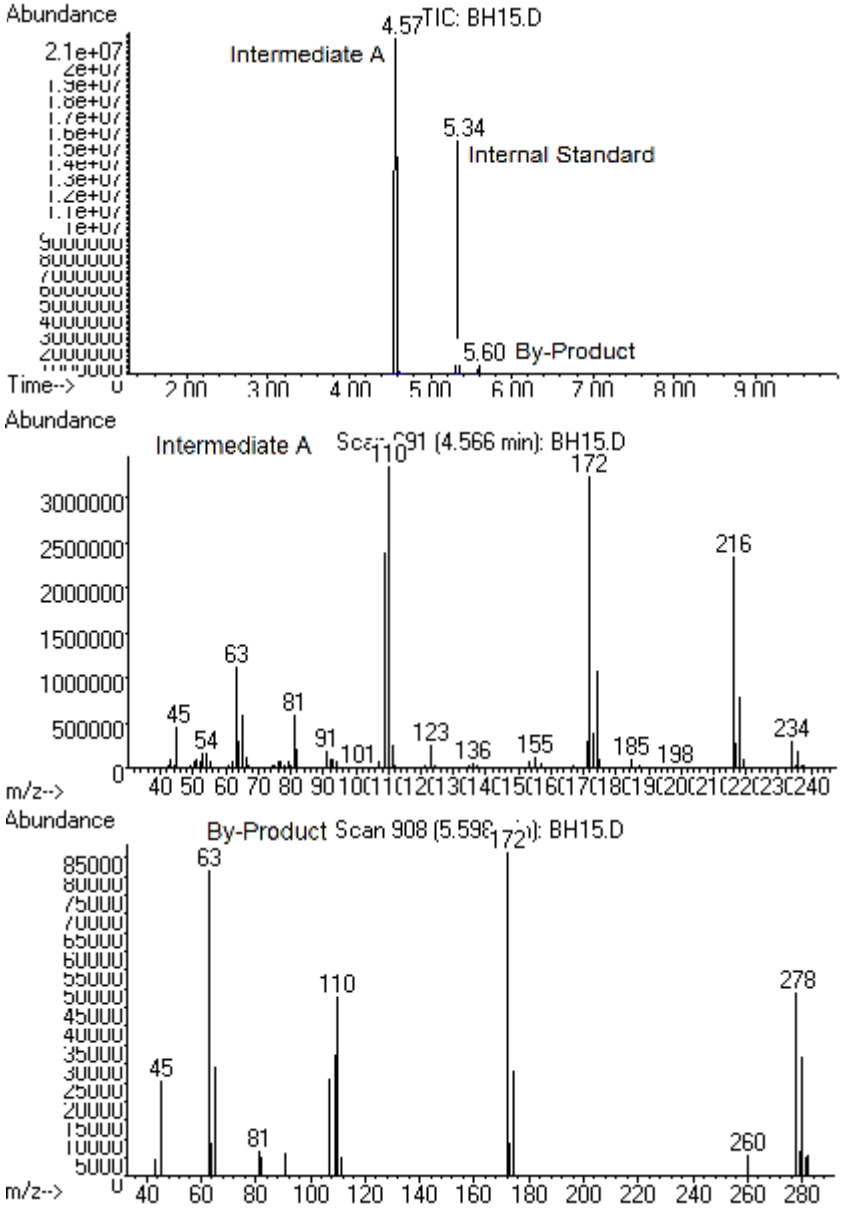


Figure 5. "Wing" Backbone

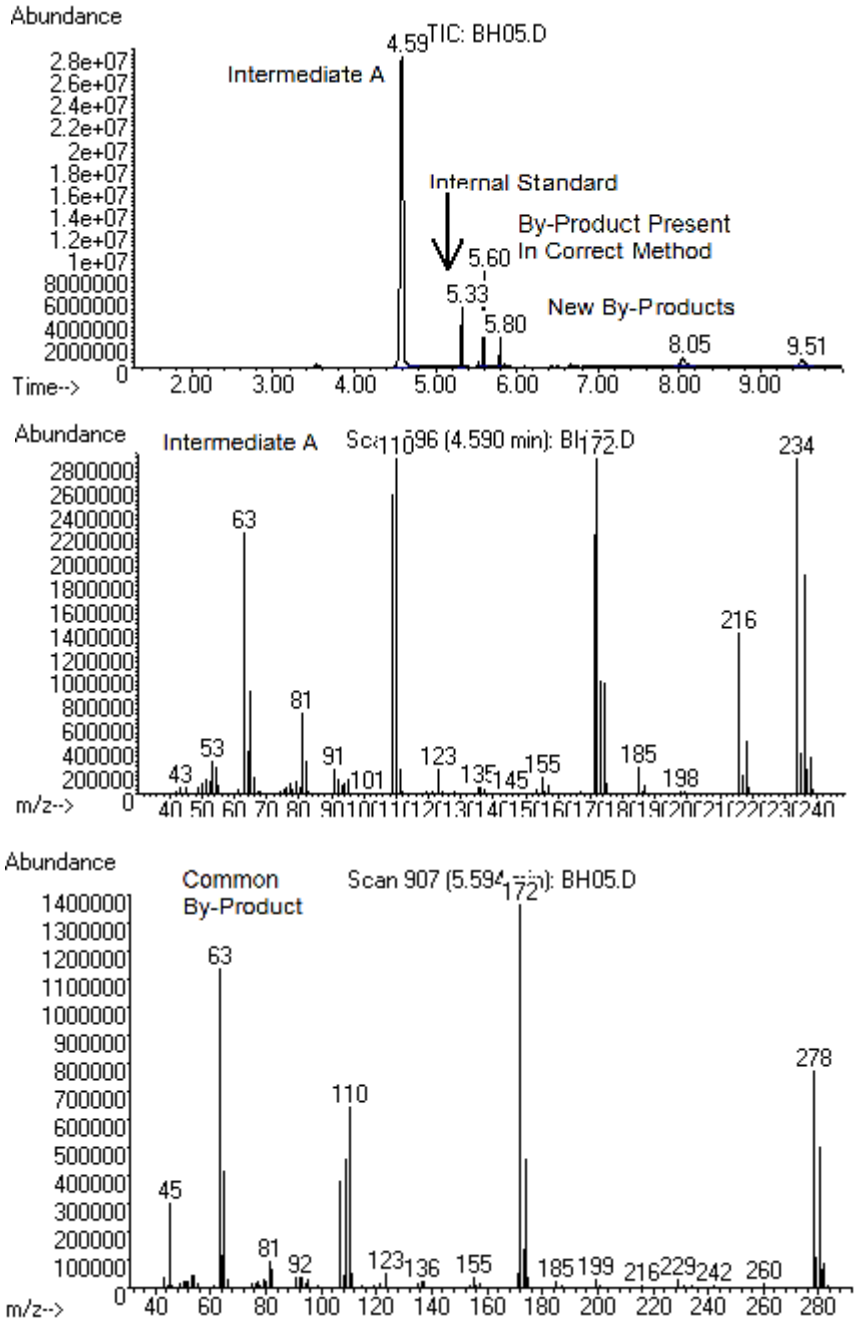


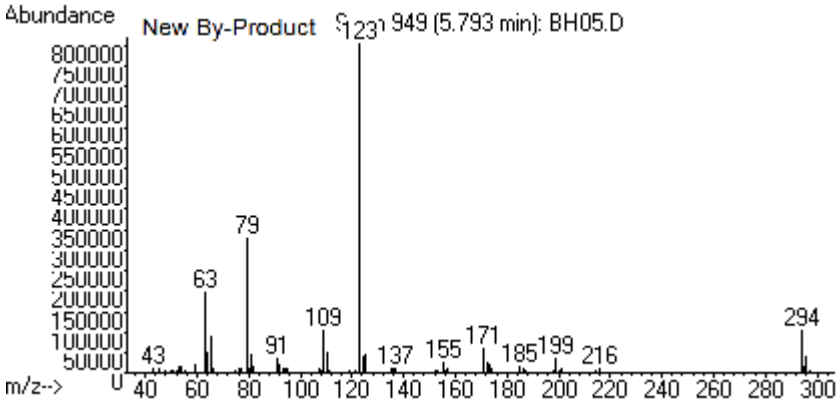
Appendix B. Intermediates and Prominent By-Products

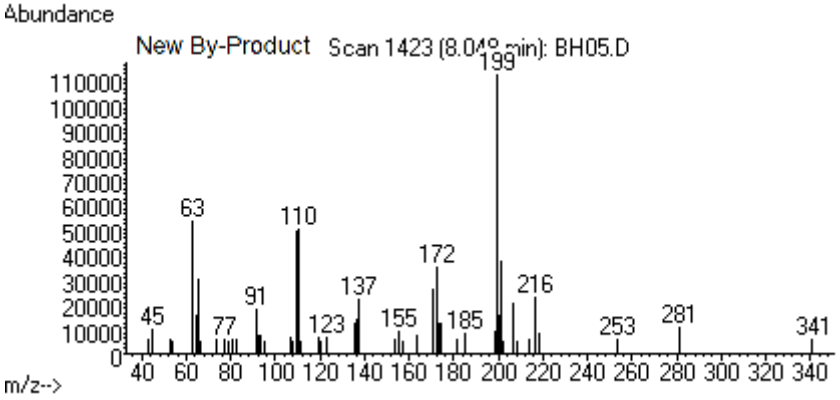
Intermediate A.

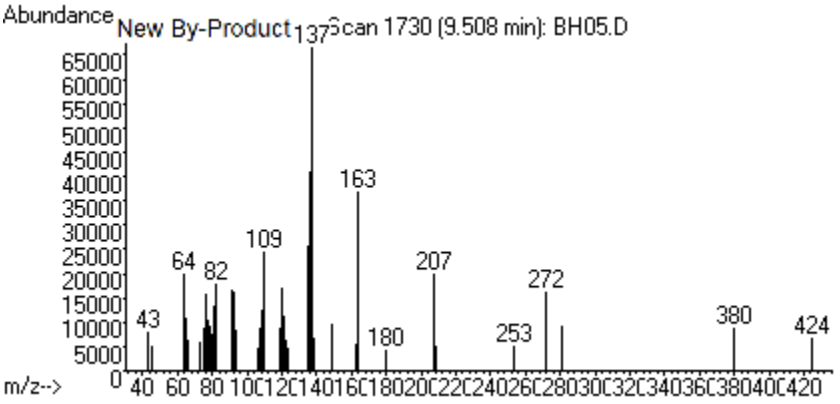


Intermediate A: Room Temperature Addition.

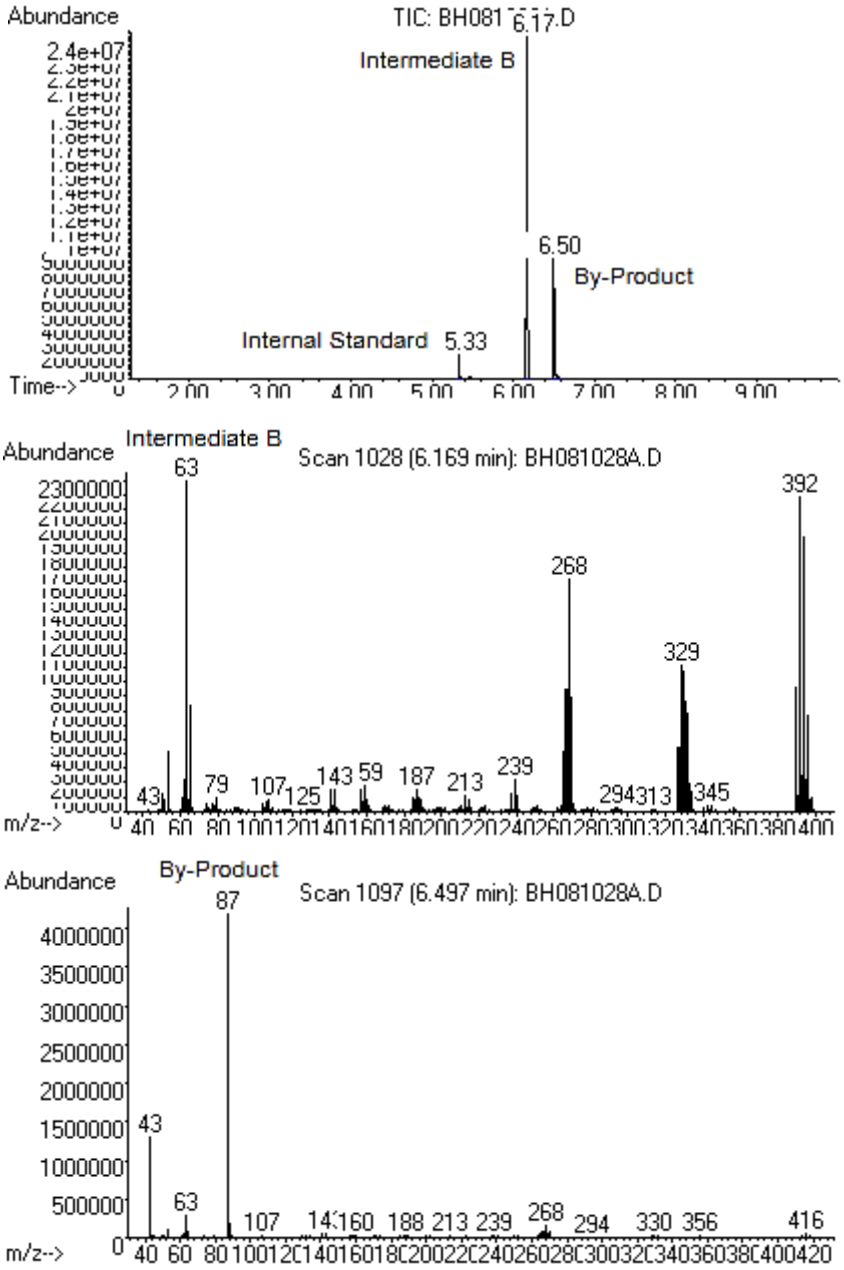



Abundance
New By-Product
949 (5.793 min): BH05.D
123
79
63
109
91
43
137
155
171
185
199
216
294
m/z-->

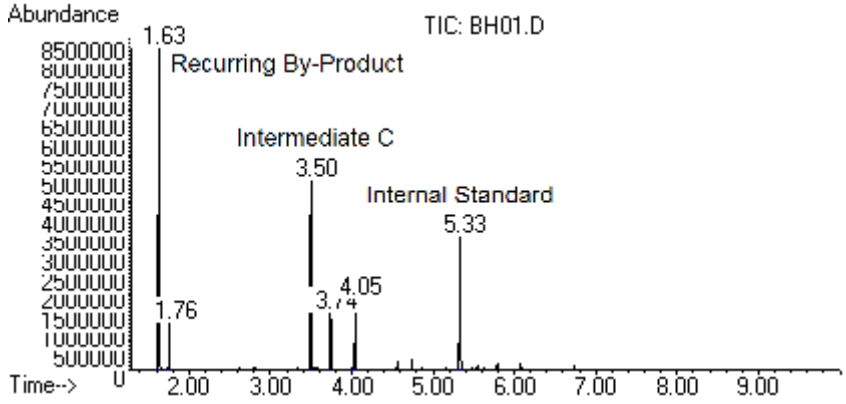

Abundance
New By-Product
Scan 1423 (8.04
199
63
110
172
137
216
91
45
77
123
155
185
253
281
341
m/z-->


Abundance
New By-Product
Scan 1730 (9.508 min): BH05.D
137
163
109
64
82
207
272
43
180
253
380
424
m/z-->

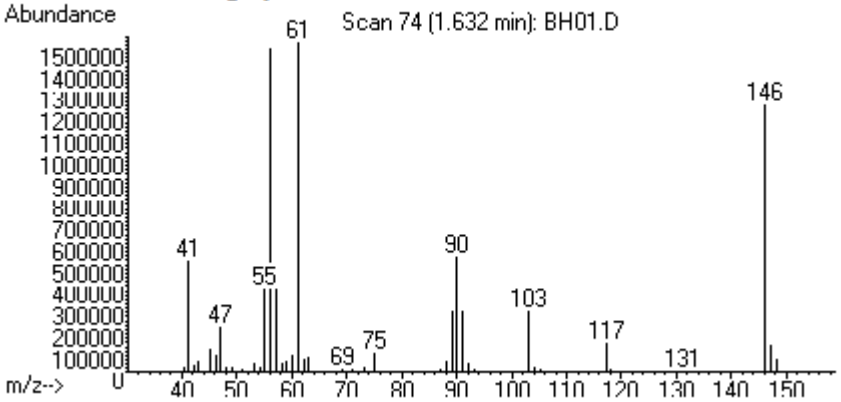
Intermediate B.

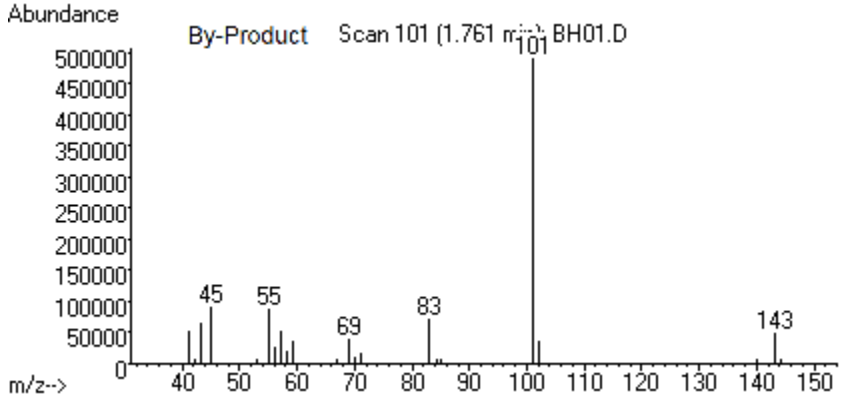


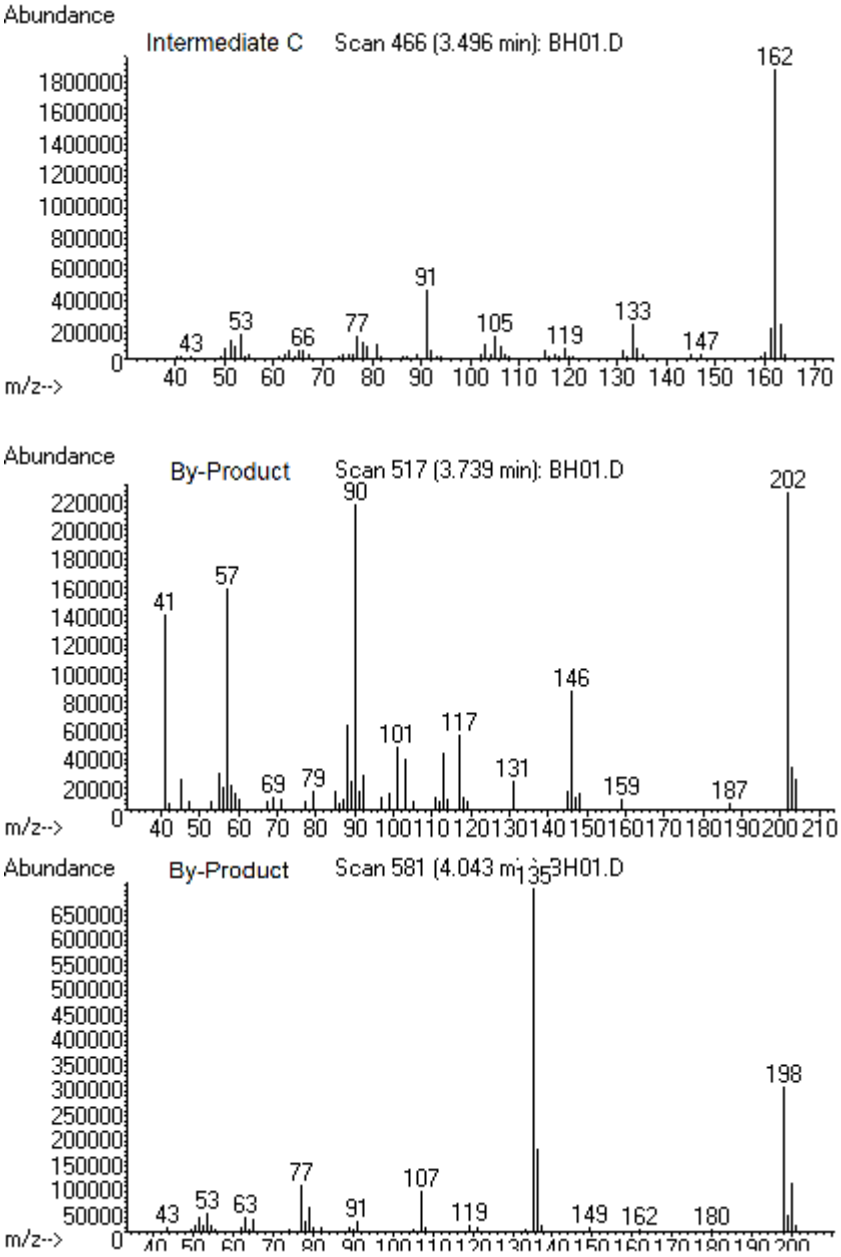
Intermediate C.



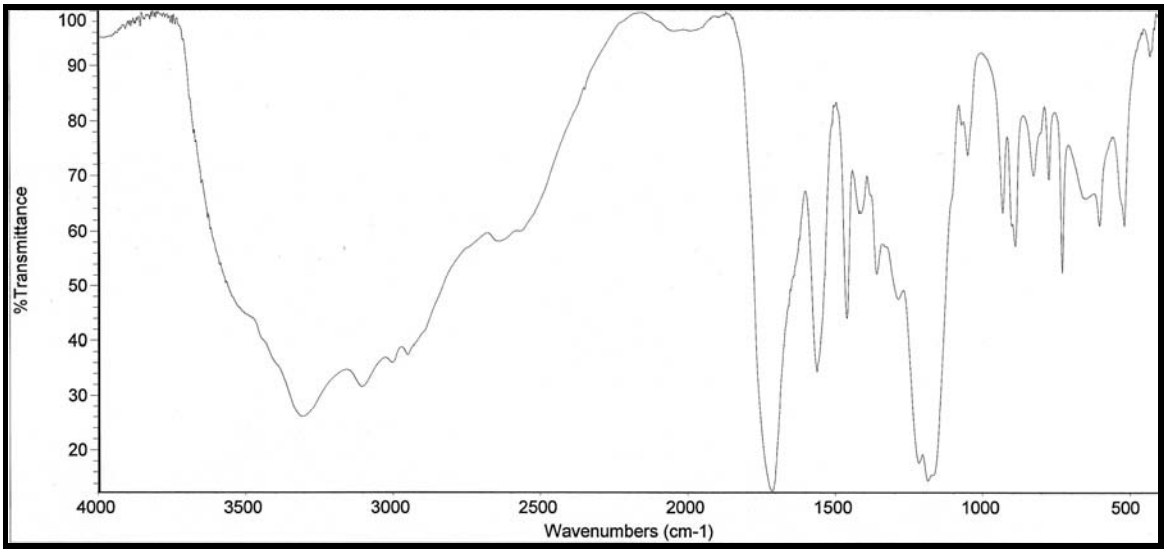
New Recurring By-Product



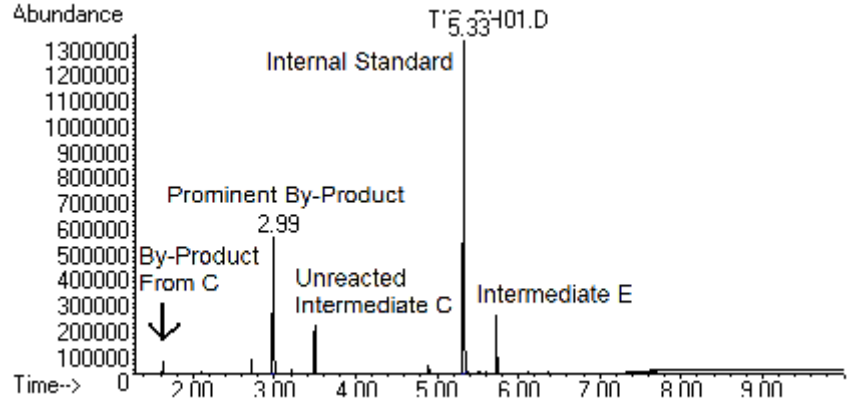


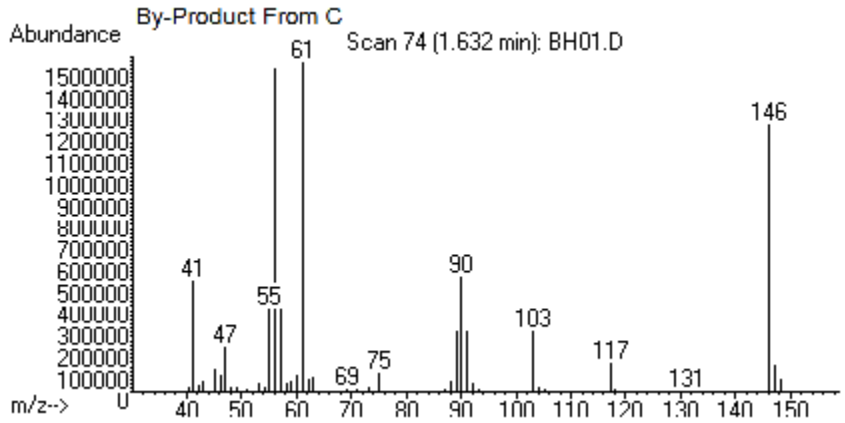

Abundance
Intermediate C Scan 466 (3.496 min): BH01.D
m/z-->
Abundance
By-Product Scan 517 (3.739 min): BH01.D
m/z-->
Abundance
By-Product Scan 581 (4.043 min): BH01.D
m/z-->

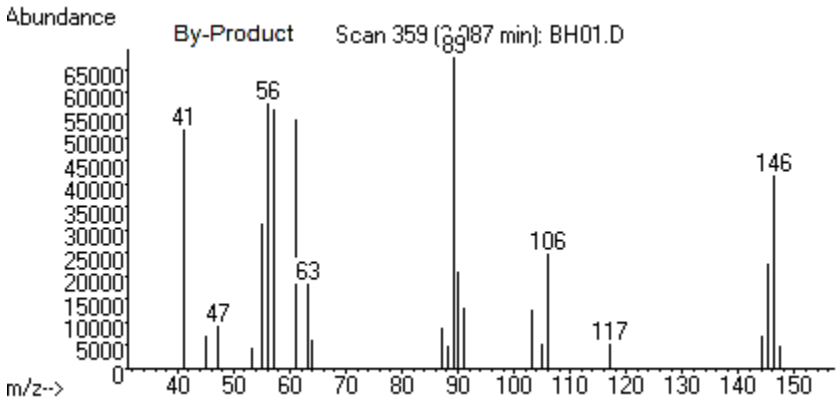
Intermediate D Infrared Spectrum.

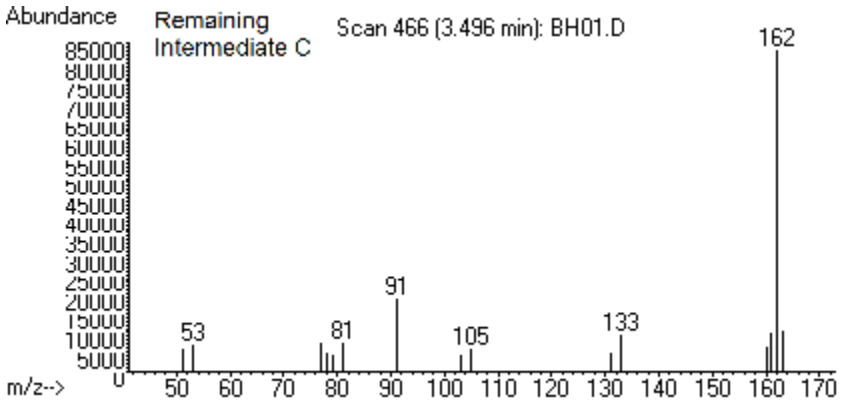


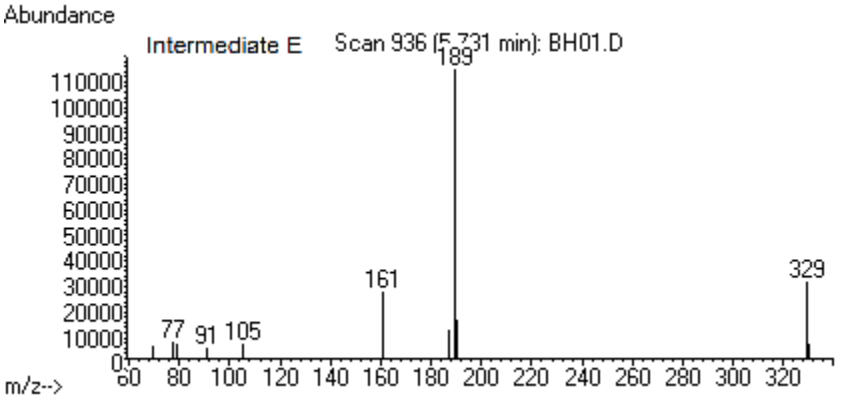
Intermediate E.



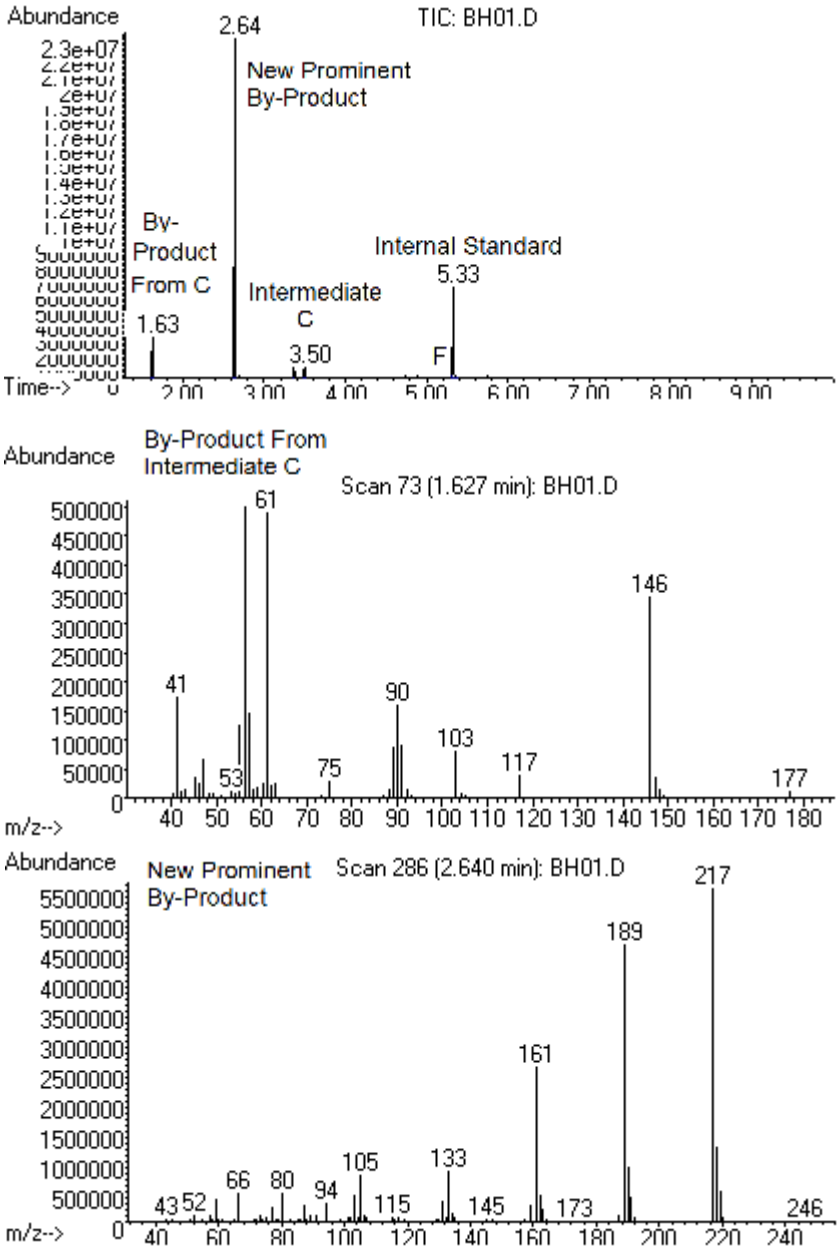


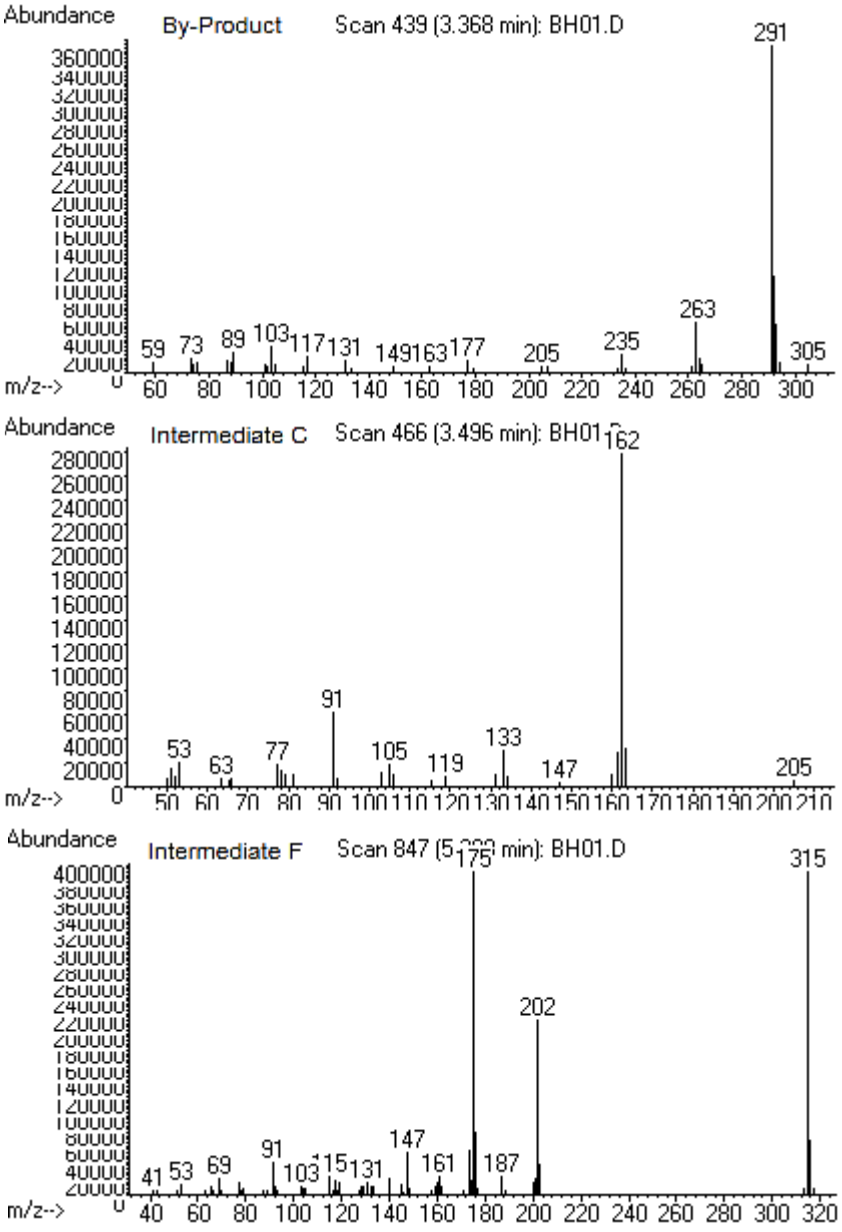



Abundance
Remaining
Intermediate C
Scan 466 (3.496 min): BH01.D
162
91
53
81
105
133
m/z-->

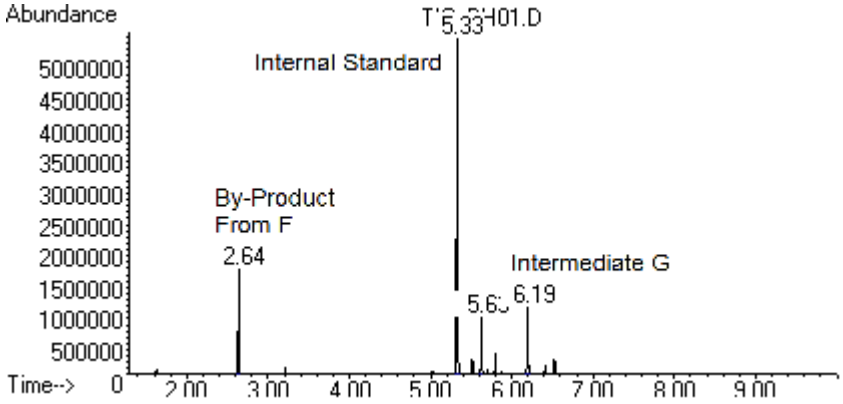

Abundance
Intermediate E
Scan 936 (5.731 min): BH01.D
189
161
329
77
91
105
m/z-->

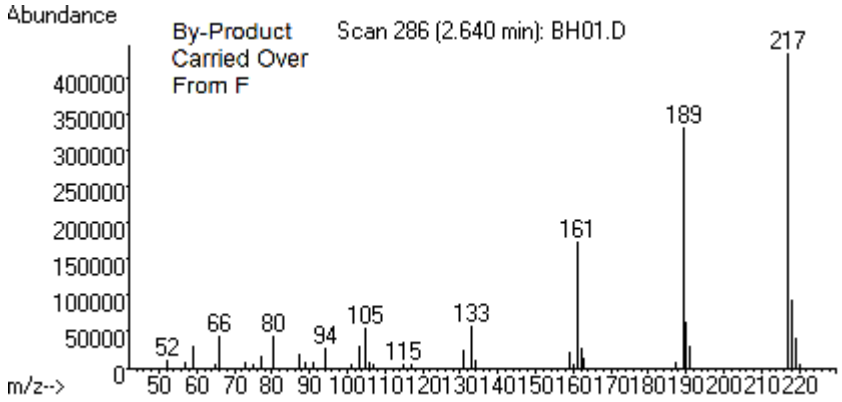
Intermediate F.

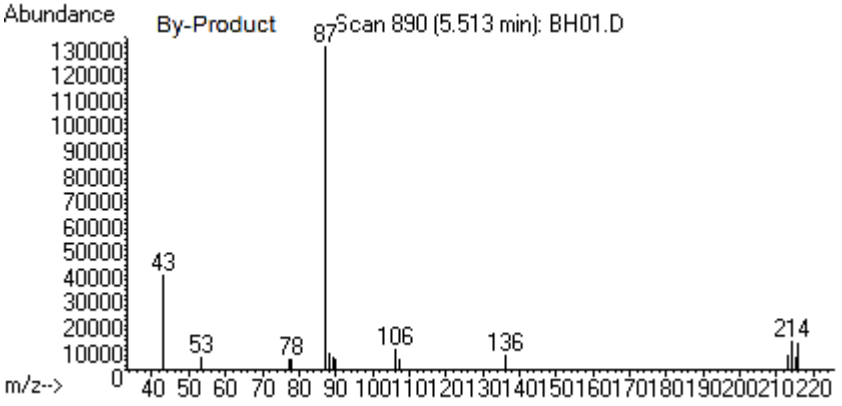


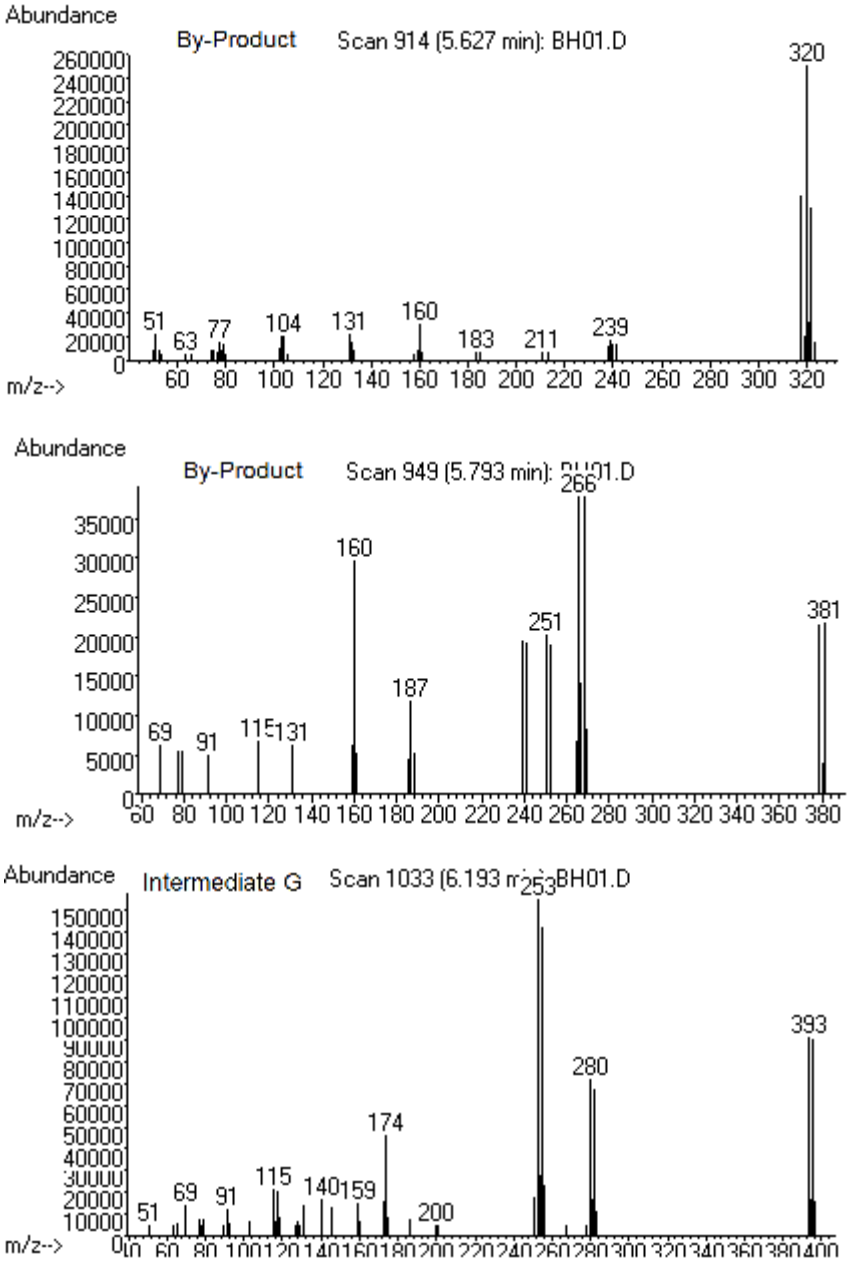

Abundance
By-Product
Scan 439 (3.368 min): BH01.D
291
263
305
235
205
177
163
149
131
117
103
89
73
59
m/z-->
Abundance
Intermediate C
Scan 466 (3.496 min): BH01.D
162
91
53
63
77
105
119
133
147
205
m/z-->
Abundance
Intermediate F
Scan 847 (5.
175
315
202
147
91
41
53
69
103
115
131
161
187
m/z-->

Intermediate G.

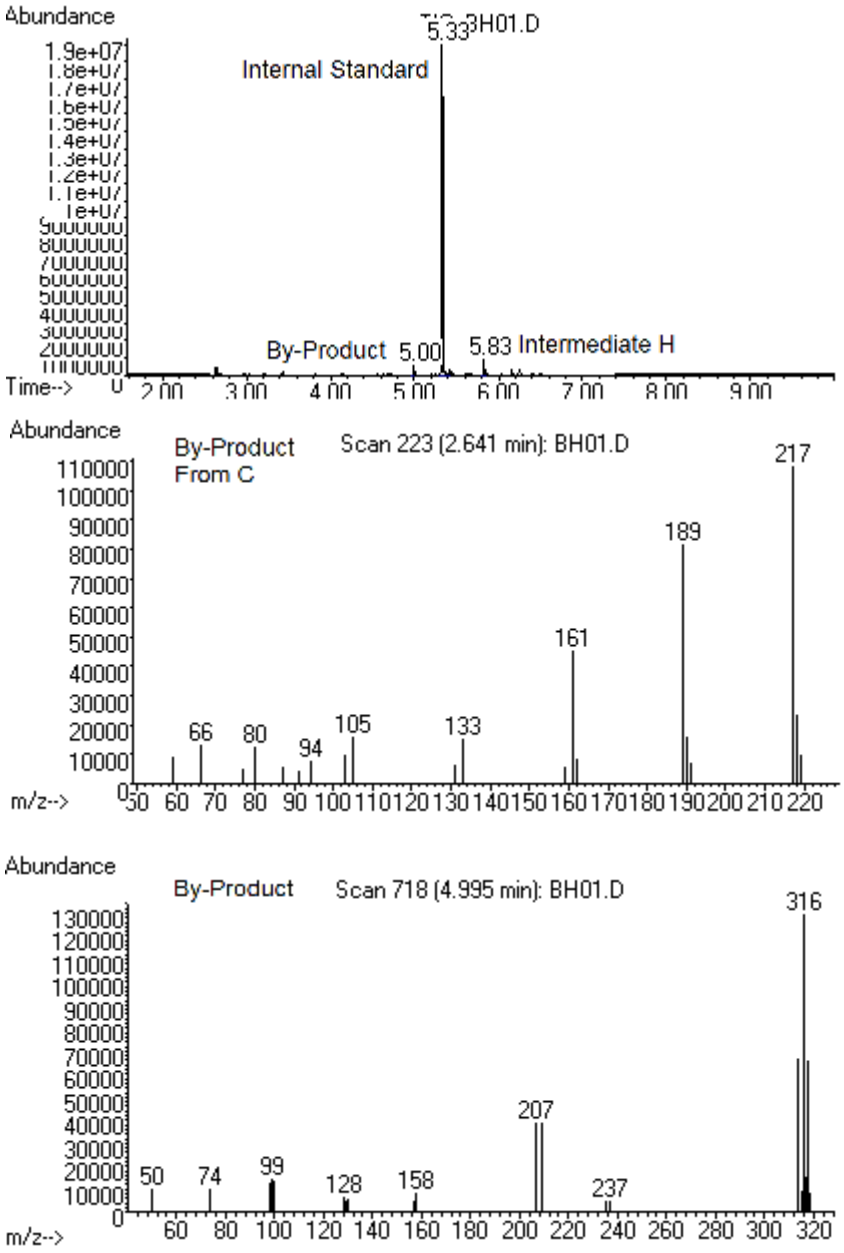


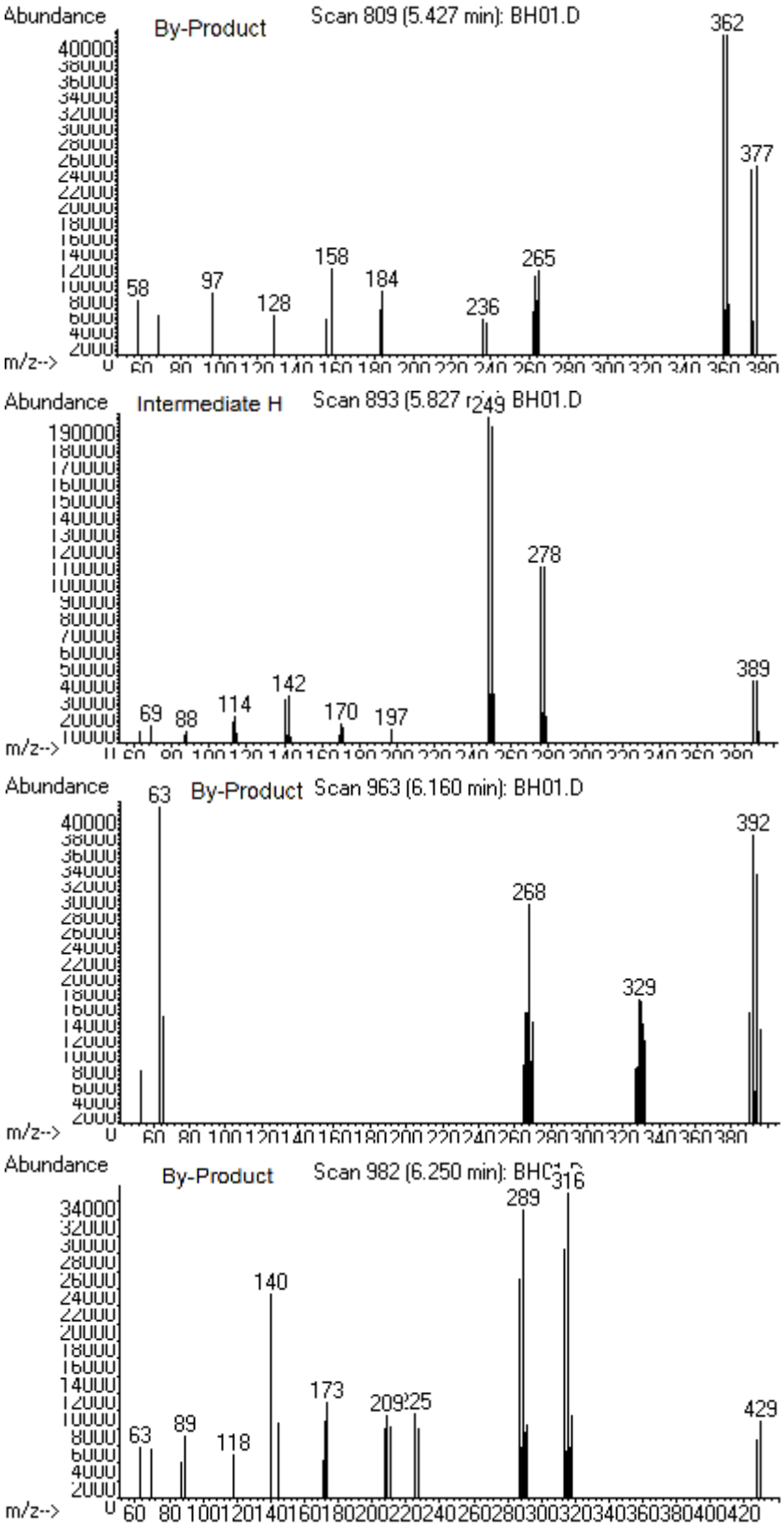




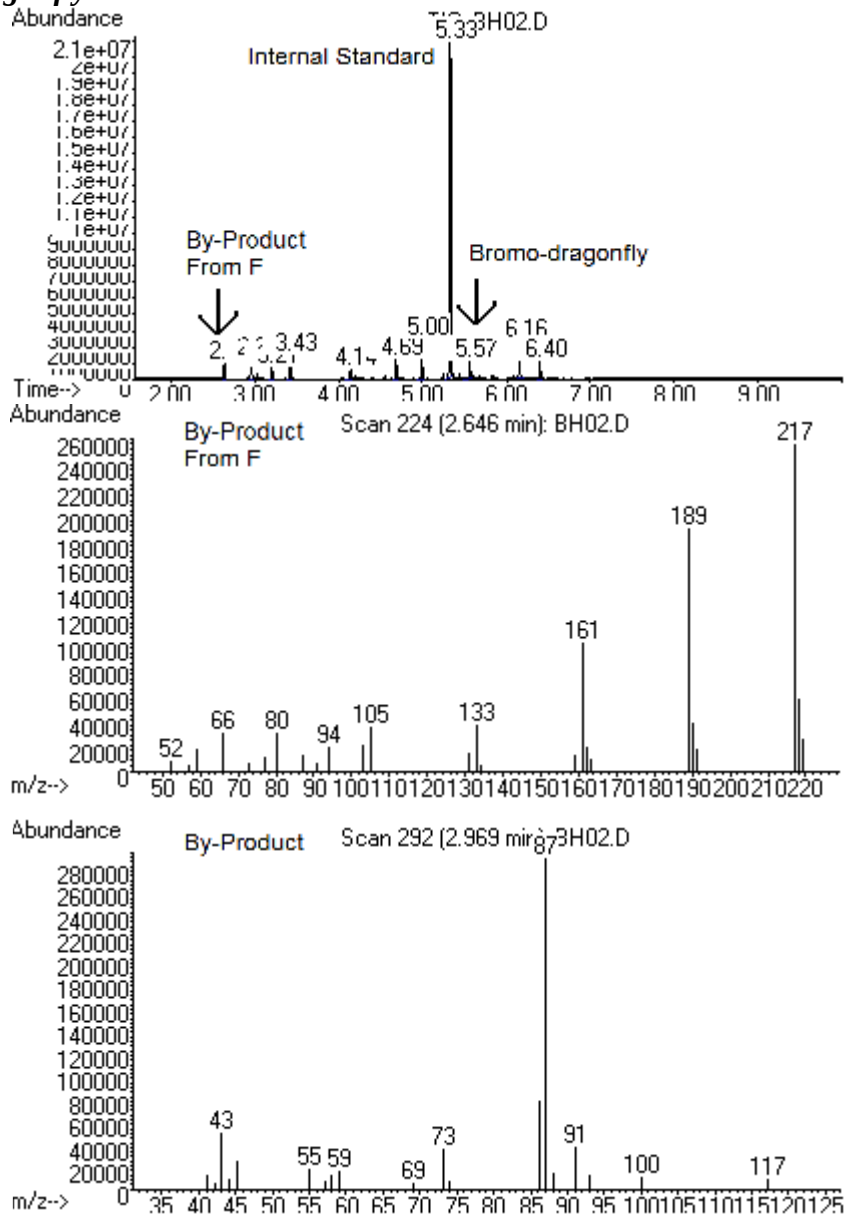

Abundance
By-Product
Scan 914 (5.627 min): BH01.D
320
160
131
104
77
63
51
183
211
239
m/z-->
Abundance
By-Product
Scan 949 (5.793 min): BH01.D
266
160
251
381
187
69
91
115
131
m/z-->
Abundance
Intermediate G
Scan 1033 (6.193 min): BH01.D
253
393
280
174
115
69
91
140
159
200
51
m/z-->

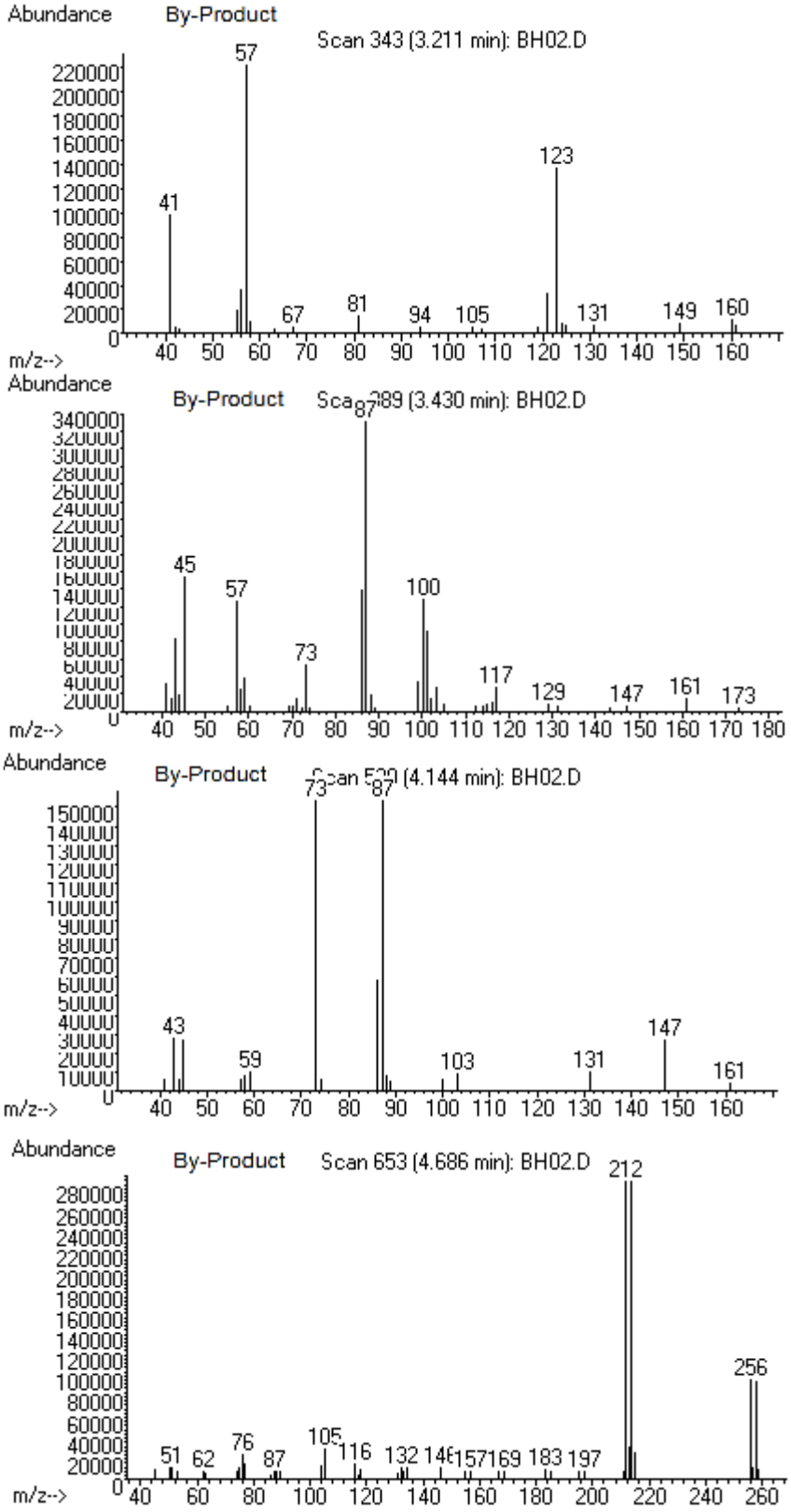
Intermediate H.

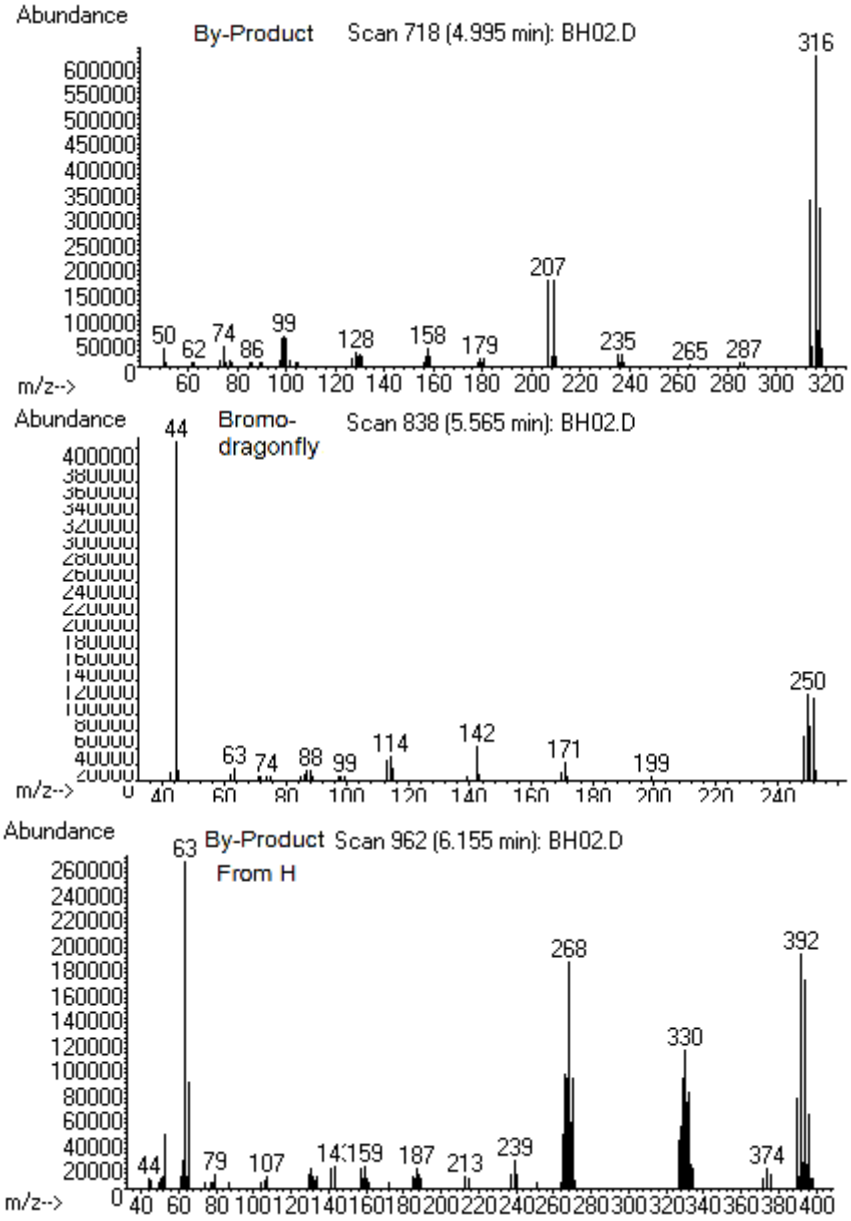


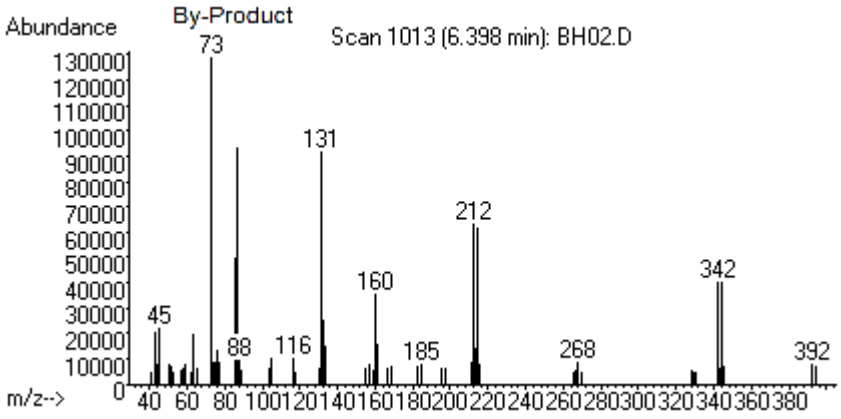

Abundance
By-Product
Scan 809 (5.427 min): BH01.D
362
377
158
265
184
97
58
128
236
m/z-->
Abundance
Intermediate H
Scan 893 (5.827 min): BH01.D
249
278
389
142
114
69
88
170
197
m/z-->
Abundance
63
By-Product
Scan 963 (6.160 min): BH01.D
392
268
329
m/z-->
Abundance
By-Product
Scan 982 (6.250 min): BH01.D
316
289
140
173
209
225
429
89
63
118
m/z-->

Bromo-dragonfly.




Abundance
By-Product
Scan 343 (3.211 min): BH02.D
57
123
41
67
81
94
105
131
149
160
m/z-->
Abundance
By-Product
Scan 389 (3.430 min): BH02.D
87
45
57
100
73
117
129
147
161
173
m/z-->
Abundance
By-Product
Scan 520 (4.144 min): BH02.D
73
87
43
59
103
131
147
161
m/z-->
Abundance
By-Product
Scan 653 (4.686 min): BH02.D
212
256
51
62
76
87
105
116
132
146
157
169
183
197
m/z-->


Abundance
By-Product
Scan 718 (4.995 min): BH02.D
316
207
99
50
62
74
86
128
158
179
235
265
287
m/z-->
Abundance
Bromo-
dragonfly
Scan 838 (5.565 min): BH02.D
44
250
63
74
88
99
114
142
171
199
m/z-->
Abundance
By-Product
From H
Scan 962 (6.155 min): BH02.D
63
268
392
330
44
79
107
159
187
213
239
374
m/z-->


By-Product
Scan 1013 (6.398 min): BH02.D
Abundance
m/z-->
73
131
212
160
342
45
88
116
185
268
392

Bromo-dragonfly: Plastics Contamination.