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Advancing The Methodology for Cyclopenta[c]thiophene Sythesis: A Step Toward Anit-Leukemia Agents and Improved Semiconductiors

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ADVANCING THE METHODOLOGY FOR CYCLOPENTA[*C*]THIOPHENE SYNTHESIS: A STEP TOWARD ANTI-LEUKEMIA AGENTS AND IMPROVED SEMICONDUCTORS.

A thesis submitted to the WKU Honors program in partial fulfillment of the requirements for the designation of honors for the degree of Bachelor of Science in the Ogden College of Sciences at Western Kentucky University.

By

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December 2006

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Abstract

Metal n5-cyclopenta[c]thienyl complexes are of significant interest in both catalysis and materials chemistry. These relatives of the low-band-gap polymer polybenzo[2,3-c]thiophene show great promise as environmentally stable conductive polymers and as energy-efficient light-emitting diodes (LEDs) due to their unique electronic properties. Recently, studies have shown that cyclopenta[c]thiophene molecules are effective as photodynamic anticancer agents which are particularly aggressive toward leukemia cells. The current method of synthesizing these compounds is lengthy, costly, and has a very low yield. Our group has developed a novel one-step method to produce precursors of these compounds. This procedure increases product yields, eliminates the use of toxic and expensive solvents such as CCl_4, and lowers the total number of synthetic steps involved in synthesis of thiapentalenes. These precursors are synthesized by C-C dialkylation using malonate esters to form fused five-membered rings. This new method is of value not only as "green" chemistry but also has the potential to lower the cost of cancer treatments and electricity bills.

Acknowledgements

There are many people to thank for making this honors thesis possible. I would like to thank the coaches in my corner: Dr.'s E. Conte, S. Burris, L. Pesterfield, C. Webb, T. Zeng, D. Dahl, T. Buthelezi, K. Williams, Alicia McDaniel, R. Salvatore, C. Henrickson, Y. Shon, N. Rice, W. Rutledge, C. Cobane, P. Minter, and D. McElroy. They nurture and encourage the independent thought and foster the expanding intellectual horizons of their students and are responsible for Western Kentucky University's widely recognized academic excellence. These individuals are much too integral to my intellectual and professional development not to be mentioned by name and deserve ovation ad infinitum.

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I would like to give special thanks to Dr. Colin David Abernethy. My gratitude for the innumerable ways in which you influenced me as a scientist and as a gentleman comes from the deepest depths of my core. I'm still not sure what it was that you saw in me, but the day you approached me as I was in the hallway struggling through homework in your intro class and invited me to join your group became the most pivotal turning point in my life. That conversation evolved into a treasured relationship and provided me with a much needed and deliberative counselor and also a trusted friend through a trying period. You lit a fire that cannot be extinguished. Thank you for helping me discover my passion for the scientific and educational odyssey.

To Dr. Chad Allen Snyder: above all else, you have had the greatest impact on me and have my sincerest respect. I owe you the most thanks for your dedication and enthusiasm which kept me on course whenever the work became frustrating. You trained me to think critically and taught me the skills necessary to answer my own questions. Under your guidance I gained a real excitement for the scientific investigation, and you showed me how to have fun in the process. Lesson number one: waiting for a reaction to run is the best time to circle the hallways and demand "tribute payments" for "protection, or else." Where others started a fire, you added fuel and created a searing blaze. Thank you again for your help, both inside and out of the classroom, as a mentor and as a great friend.

Special thanks are owed to my parents. If I ever do anything meaningful with my life it is because of my parents, Marnie C. Brindley and Travis R. Jones.

Without their guidance, sacrifice, and support I would have strayed and lost sight of my dreams long ago. Also, mention of my role model Tucker Max (the patron saint of purity and solidarity, in a sense), and the morning girls at Bread and Bagels must be made.

Thank you to all who are mentioned here. This work is not a product of my effort, but a result of your patience, diligence, and unwavering support with which you have shown me.

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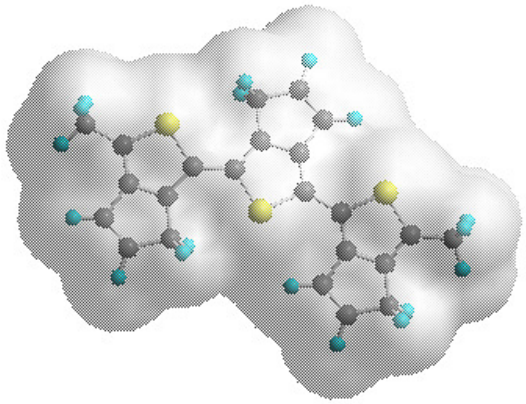
List of Abbreviatons and Symbols

c	speed of light in vacuum (3.0×10^8 m/s)
[^{o}]	degree
eV	electron volt
ΔE	energy of band gap
n-	normal or straight chain
t-	tertiary
f	frequency
g	gram
GCMS	gas chromatography-mass spectrometry
h	hour
h	Plank's constant (6.63×10^{-34} Js)
Hz	hertz, s^{-1}
J	joule
kJ	kilojoule
Λ	lambda, wavelength
M	meter
M^+	molecular ion
Me	methyl, CH_3
mg	milligram
min	minute
mL	milliliter
mmol	millimole
m.p.	melting point
MS	mass spectra
m/z	mass-to-charge ratio
Ph	phenyl
ppm	parts per million
$[\ ]_n$	monomeric unit of a polymer
s	second
S	Siemen
t	time
T	temperature
V	volt
cm^{-1}	wavenumbers
DMSO	dimethylsulfoxide (solvent)

List of Abbreviations and Symbols for Nuclear Magnetic Resonance (NMR) spectra

δ	chemical shift (in ppm)
d	doublet
J	coupling constant
m	multiplet
NMR	nuclear magnetic resonance
q	quartet
s	singlet
t	triplet
^{13}C	carbon-13 NMR
^{1}H	proton NMR

Conductivity in Conventional Materials



Semiconductors have many common applications: computer data-storage devices, digital cameras and batteries, and devices that use touchpad keys such as a computer keyboard or a telephone. Semiconductors are also widely valuable in scientific and industrial fields where the storage and transmission of energy in discrete and controlled amounts is required. Energy transmitted by semiconductors can vary, as some instruments regulate the flow of electricity across a wire while other semiconductors are used to produce certain wavelengths of light such as a tunable light emitting diode (LED). In addition, they are also used to control heat transfers in solar panels used for generating solar-powered electricity.

Semiconductors have traditionally been composed of metal alloys such as germanium arsenide (GeAs) and gold arsenide (Au_3As). To date, the most commonly used semiconductors are silicon based and incorporate the various impurities that give semiconductors different electronic properties. In 1977,

Heeger, MacDiarmid, and Shirakawa synthesized the first conducting organic polymer known as polyacetylene[1] (Figure 1.1).

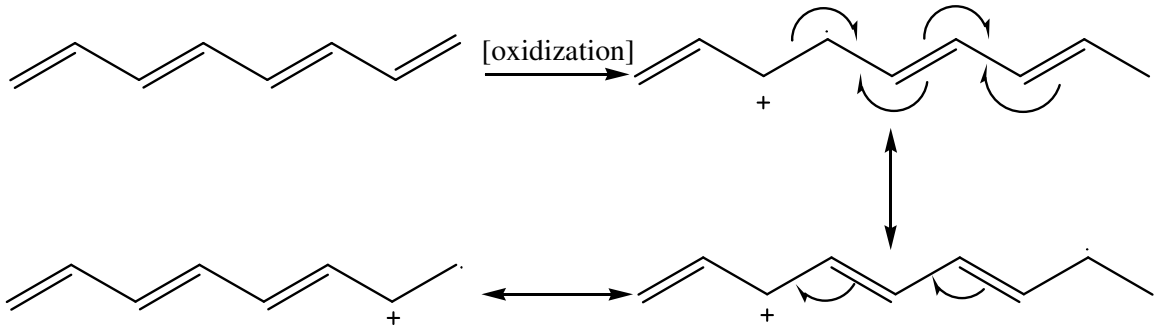


Figure 1.1 Resonance forms of Polyacetylene

Polymers, which are commonly used as plastics, demonstrate low conductivity of electricity and are generally considered good insulators. Plastics, along with other non-conductive materials such as glass, possess a high band gap between the valence and conducting energy levels (Figure 1.2). Conversely, metals have overlapping valence and conduction bands between their individual atoms in their crystalline lattice arrangement (Figure 1.3 a, b); this phenomena gives metals their high electrical conductivity[2].

The conduction and insulation properties of organic materials arise from two characteristics of a molecule: electron occupation of valence orbitals and the magnitude of the energy gap (ΔE) between quantum energy levels (bands) of the molecule.

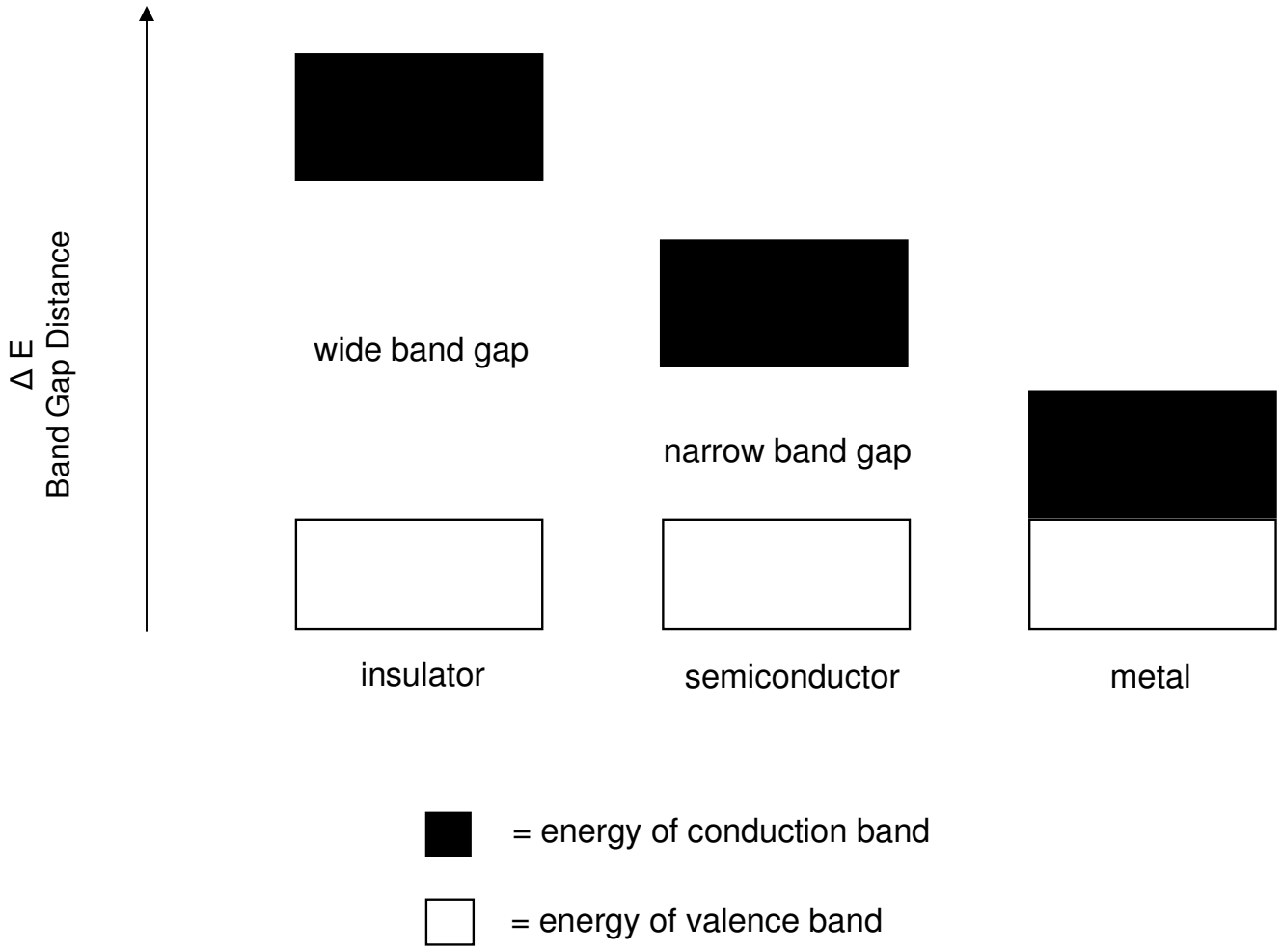


Figure 1.2 Diagram of the relative band gaps of insulators, semiconductors, and metals

Figure 3. (a)

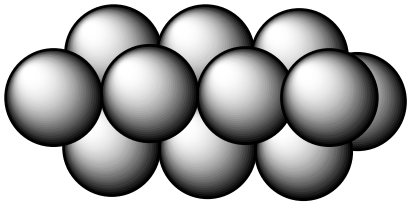


Figure 3. (b)

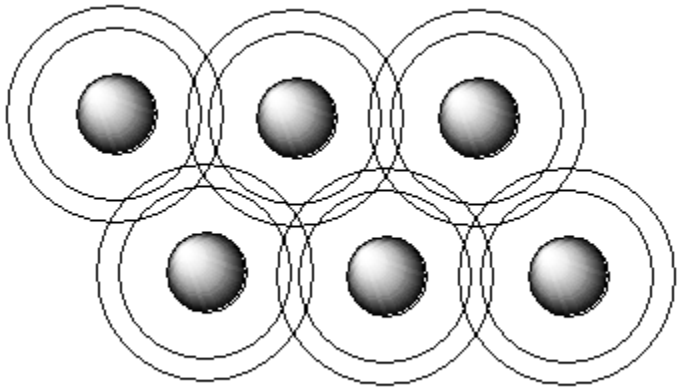


Figure 1.3 (a) Metal atoms arranged in space; (**b)** Representation of conduction band overlap of metal atoms in a crystalline lattice (two-dimensional display)

Molecular orbital occupation by electrons is one requirement of electrical conductivity for a molecular solid. Valence orbitals must be empty or partially occupied by electrons. Since a molecular orbital can only contain at most two electrons, it must contain none or one electron in at least one of its valence molecular orbitals. Completely filled molecular orbitals do not conduct, as the orbitals cannot accommodate additional electrons.

Molecular orbital band theory describes the magnitude of the energy gap between the valence and conduction bands of a molecule. As demonstrated in Figure 1.2, the more ΔE increases, the more energy is required to excite electrons from the valence band to the conduction band. As a result, conductivity decreases, and the materials behave more and more as insulators. Diamonds, the classic example of insulators, are covalent crystals possessing completely filled valence orbitals and therefore exhibit a large gap between bands[3]. Thus, too few electrons have energy sufficient enough to transition from the valence band to the conduction band. Semiconductors exhibit partially filled molecular orbitals and medium band gaps.

An example of band-gap manipulation can be found in the paint industry. Paints such as cadmium yellow (CdS) and vermilion (HgS) are examples of semiconductors used by artists for their bright colors. When white light, a relatively low-level energy form, interacts with these materials, electrons are promoted to the conduction band with ease due to their relatively low energy gap. CdS absorbs violet and blue light, while other frequencies contain less energy than is required to excite an electron above the energy gap. The frequencies

that are not absorbed are reflected, and, in the case of cadmium yellow, the color we see is yellow. Some semiconductors such as GaAs and PbS have a sufficiently small band gap that all frequencies of visible light are absorbed. There is no reflection of visible light, and the materials have a black color.

Energy gaps offer much information about the physical characteristics of semiconductors and other compounds. Visible light photons span energies from approximately 1.8 eV to 3.2 eV ($E=hf=hc/\Lambda$ where Λ=400 nm-700 nm and 1 eV=1.6x10^{-19}J). Light is absorbed by the electrons in a material. The energy gap for silicon is 1.14 eV at room temperature, while that of zinc sulfide is 3.6 eV. Zinc sulfide's energy gap is too wide to absorb visible photons, and so the light can pass through the material resulting in transparency. On the other hand, silicon's energy gap is small enough to absorb these photons (thus bumping electrons well into the conduction band), which is why silicon is opaque. Materials which possess a band gap of 1.5 eV or less are considered low band-gap materials[4]. An example of an energy gap calculation is shown in Figure 1.4.

Calculating the energy gap of zinc sulfide.

When zinc sulfide is exposed to 345 nm wavelength light or less, its conductivity increases, suggesting that electrons are being promoted from the valence band to the conduction band. The energy gap for this semiconductor can be calculated using the equation $\mathbf{E_g=hf=[hc]/\Lambda}$ where h=Plank's constant (6.63x10^{-34} J·s), c= speed of light in vacuum (3.00x10^{8}m/s), Λ=wavelength of light, and f=frequency of light.

$E_g = h \cdot c/\Lambda$

$E_g = [(6.63\text{x}10^{-34}\ \text{J}\cdot\text{s})(3.00\text{x}10^{8}\ \text{m/s})]/[(1.60\text{x}10^{-19}\ \text{J/eV})(345\text{x}10^{-9}\ \text{m})]$

$E_g = 3.6$ eV

Figure 1.4 Calculation of the energy gap for zinc sulfide (ZnS).

While these theories explain the conductivity of molecules, it is important to note that they are only theories and apply mainly to inorganic chemistry. In the field of organic chemistry, conjugation of pi bonds is the primary stipulation that predicts conductivity. As a rule, band theory and conjugation are not associated with one another; however, both are important in understanding the conductivity of organic molecules. In the realm of organic chemistry, conductive polymers require conjugation (Figure 1.5), whereas insulators do not contain an overlapping pi-bond network (Figure 1.6).

Pi-bond orbital overlap in organic molecules allows for a much more “fluid” electron cloud of the molecule as a whole (Figure 1.7, a), thus promoting the resonance of electrons about the molecule. Promotion of electrons in this manner is commonly referred to as *n*-type, or normal type, conductivity. Compounds without conjugated pi-bond orbitals do not posses this “fluidity” (Figure 1.7, b).

It is also important to note that conjugation of pi-bond orbitals not only promotes electron flow, but also allows the flow of gaps, or holes, in electron density. The conductance of electron holes along an organic polymer chain shifts electrons in the opposite direction of *n*-type conductors. As holes are promoted in one direction along a polymer chain, electrons travel in the opposite direction. Polymers conducting in this manner are considered *p*-type conductors.

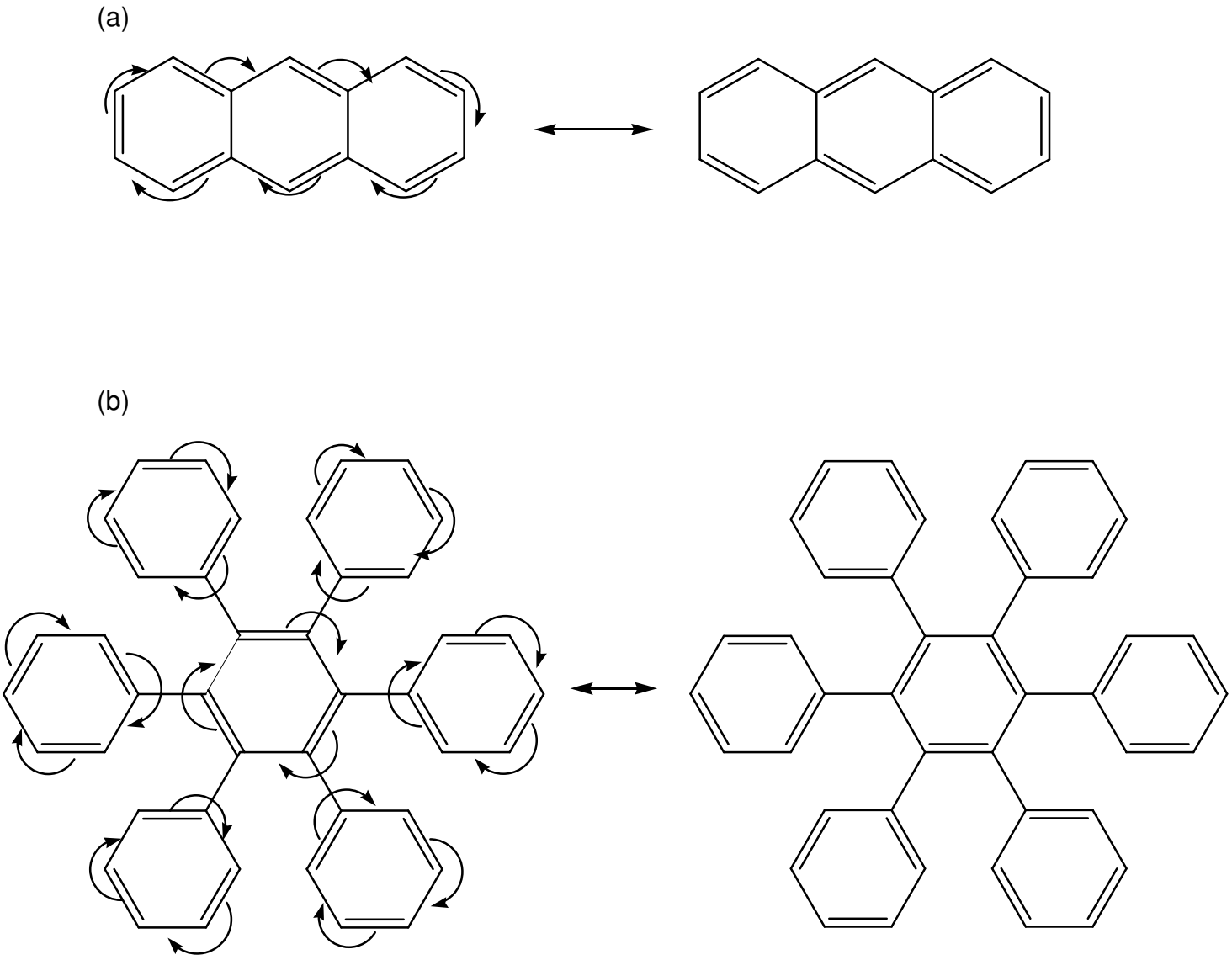
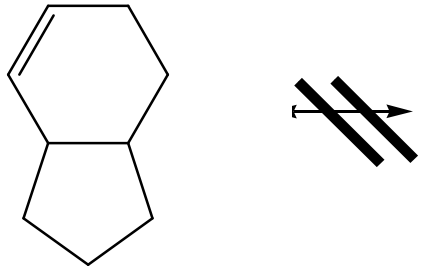


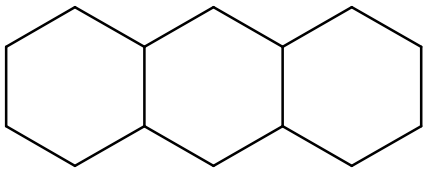
Figure 1.5 Conjugation in **(a)** Anthracene and **(b)** Hexaphenylbenzene
Electrons delocalize and constantly spin around carbon backbone.

(a)



No Possoble Alternative Resonance Forms

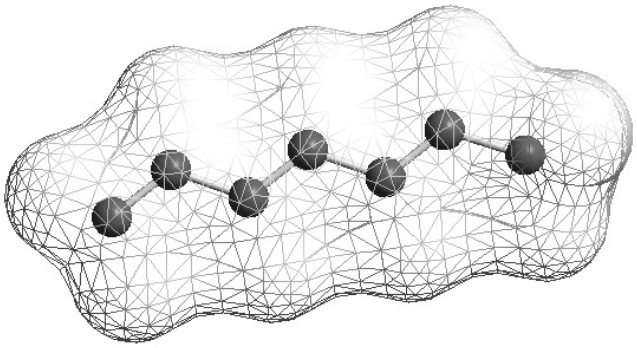
(b)



No Possible Alternative Resonance Forms

Figure 1.6 **(a)** 2,3,3a, 4,5,7a-Hexahydro-1H-indene
(b) Tetradecahydro-anthracene
Molecules representative of a typical insulator with no conjugation of pi-bond network.

(**a**)



(b)

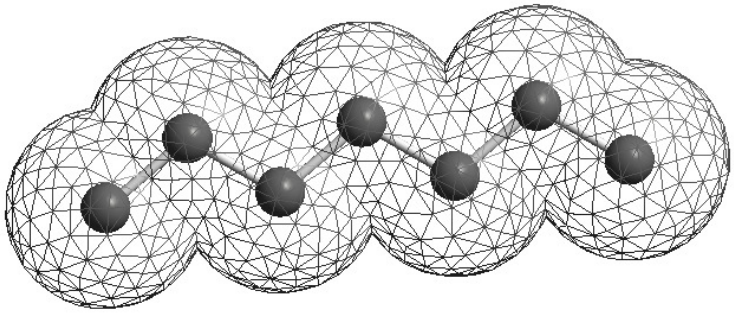


Figure 1.7 **(a)** Electrostatic cloud of a completely conjugated molecule;
(b) Electrostatic cloud of a non-conjugated molecule.

The overlap of pi-bond orbitals in organic molecules allows for a much more “fluid” electron cloud of the molecule as a whole, thus promoting the resonance of electrons about the molecule. Compounds without conjugated pi-bond orbitals do not posses this “fluidity” (Figure 1.7, a,b).

Shirakawa et. al. were awarded the Nobel prize in 1977 in chemistry for synthesizing the first conductive organic polymer polyacetylene (Figure 1.8, a). The synthesis of polyacetylene brought about the study of innumerable polymers for their conductive properties (Figure 1.9). Polythiophene and polypyrole (Figure 1.10 a, b) polymers are studied extensively because of their high conductivity and relatively high environmental stability[5-8]. To date, polybenzo[2,3-*c*]thiophene (polyisothianapthene, Figure 1.8 b), when polymerized, demonstrates the lowest known band gap of an organic polymer[9-10].

Polyisothianapthene and polyacetylene, however, are highly unstable in the presence of oxygen. The addition of oxygen to the atmosphere of polyacetylene or polybenzylthiophene quickly degrades the macromolecule as oxidation occurs and conductive quality is lost. Oxidative degradation poses a problem to researchers investigating these compounds: not only must they be studied in oxygen-free environments that require expensive tools and apparatuses, but the materials lack a commercial application due to the presence of oxygen in the environment in which they are primarily needed.

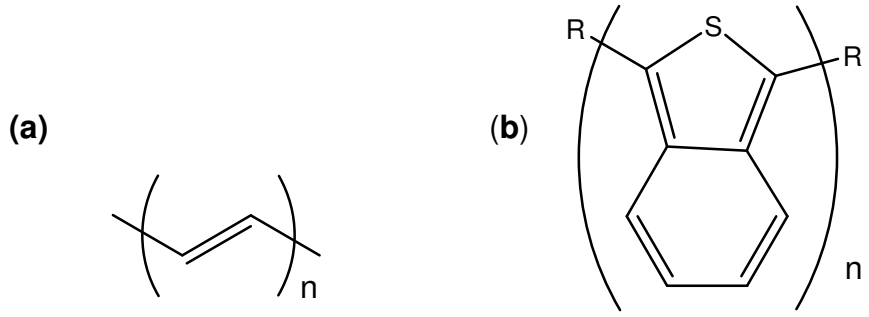


Figure 1.8 (a) Polyacetylene; **(b)** Isothianapthene

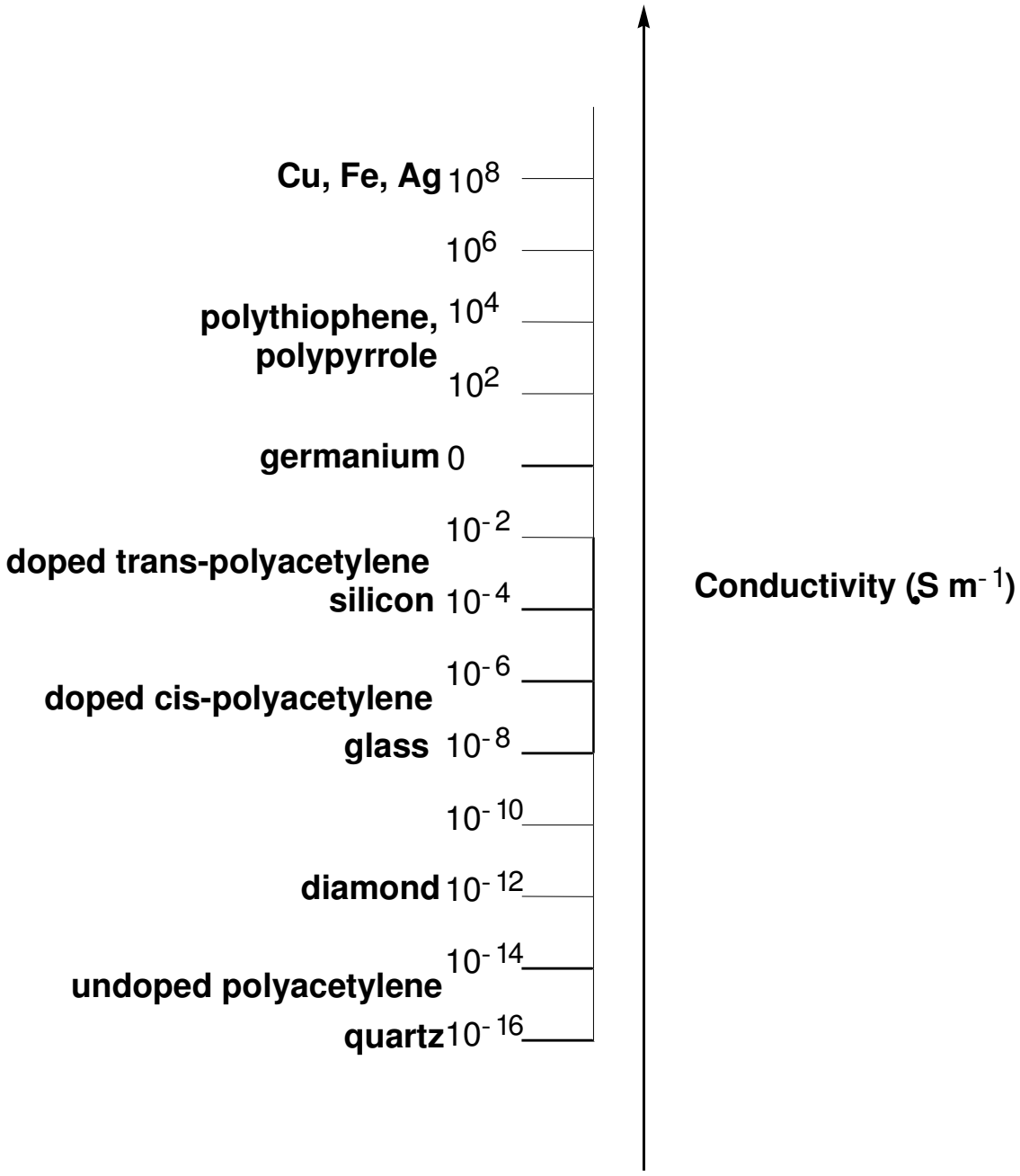


Figure 1.9 Conductivity of various materials[11].

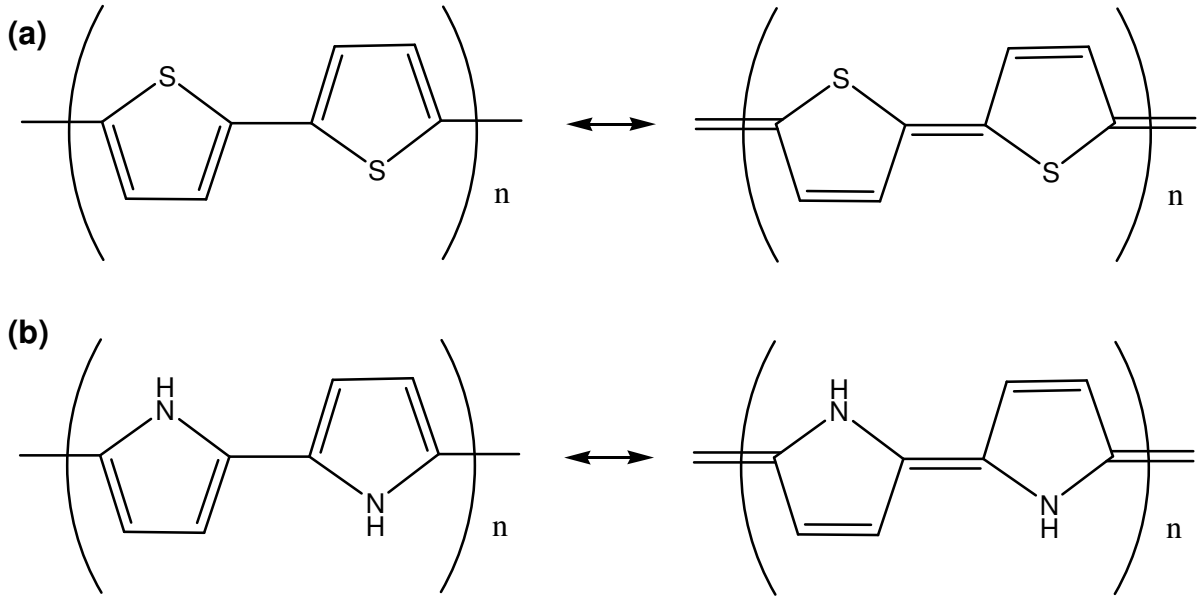


Figure 1.10 (a) Polythiophene, **(b)** Polypyrole

Because of their exceptional activity against leukemia cell (L1210) lines,[17-18] oligothiapentalenes, or trimeric thiophenes, have been investigated heavily for their apparent cytotoxicity toward human cancer cells. However, the current synthesis of these molecules follows a low-yield, hazardous, and time-consuming reaction. These limitations to thiapentalene synthesis are the motivation for the search for alternative routes to the production of cyclopenta[*c*]thiophenes.

The goals of this project are three fold: to develop a more efficient process for thiapentalene synthesis, to expand the known library of thiapentalene molecules for further scientific and medicinal study, and to investigate new methods for heterocycle ring closure in systems with high bond-angle strain.

Long term, the polymerization of the thiapentalenes developed from this research will be studied for possible commercial applications.

Our unique approach to the synthesis of a stable polythiophene derivative, polycyclopenta[*c*]thiophene, from cyclopenta[*c*]thiophene (Figure 1.11, a,b) can be optimized in future investigations.

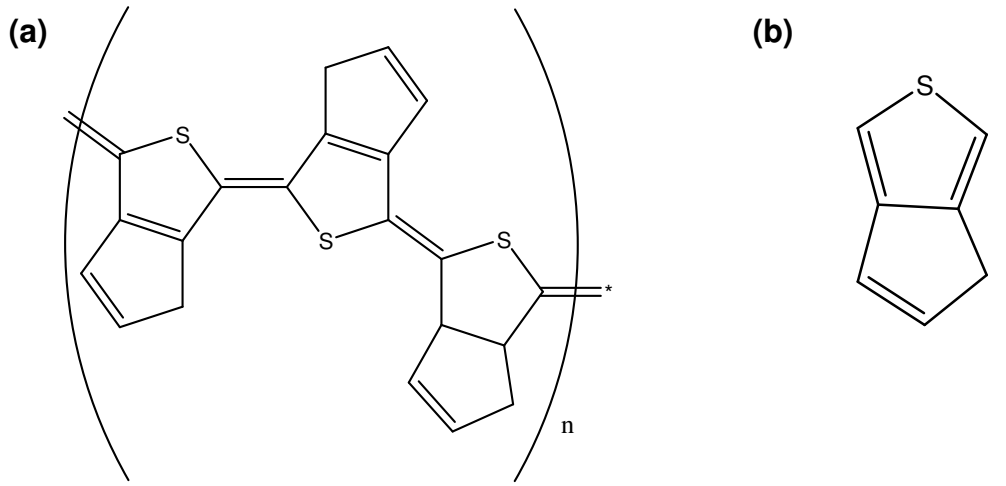
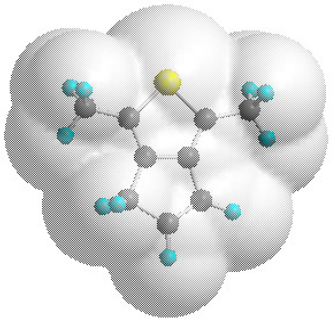


Figure 1.11 (a) Polycyclopenta[*c*]thiophene, **(b)** cyclopenta[*c*]thiophene

Attempted Synthesis of Cyclopenta[*c*]thiophene

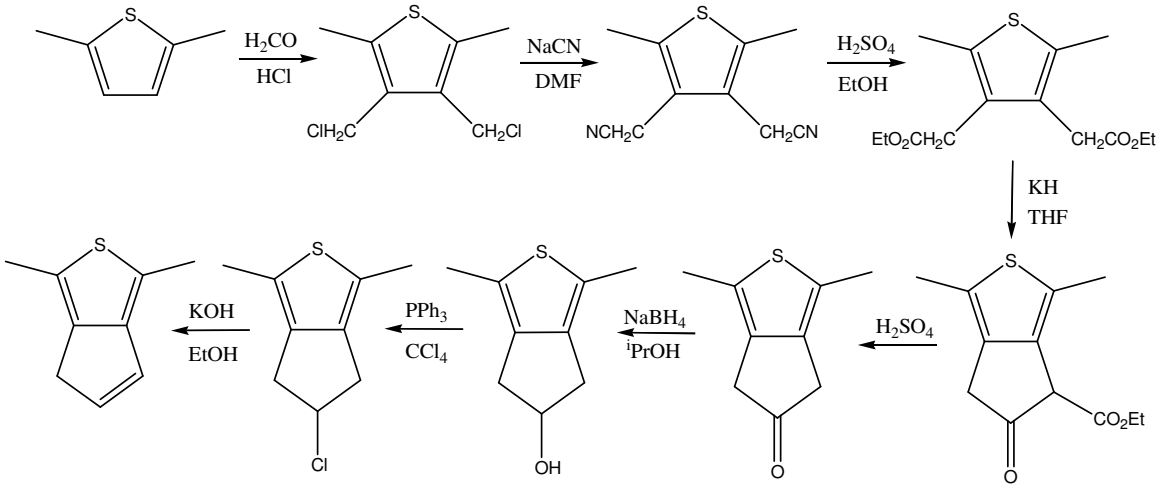


Motivation

Much investigation has accompanied the first reported preparation of conductive organic polymers. In 1984, Wudl and Heeger synthesized polyisothianapthene [poly(benzo[*c*]thiophene)], reporting the lowest known band-gap of any conductive polymer to date.[9] However, interest has shifted toward cyclopenta[*c*]thiophene, or thiapentalene, originally synthesized by Skramstad in 1969, for its relative stability in oxygen-containing environments and high-conductive capacity.[12]

A variation of polyisothianapthene, polycyclopenta[*c*]thiophenes reduce the number of aromatic carbons in the substituent aryl ring on the thiophene. Reducing the fused-ring system from a six-membered ring to a five-membered ring, it is hypothesized, will demonstrate reduced reactivity with atmospheric oxygen. To date, the most efficient method of producing cyclopenta[*c*]thiophenes

involves the Wallace-Selegue eight-step synthesis, which includes a Diekmann condensation reaction (Scheme 2.1).[13-14]

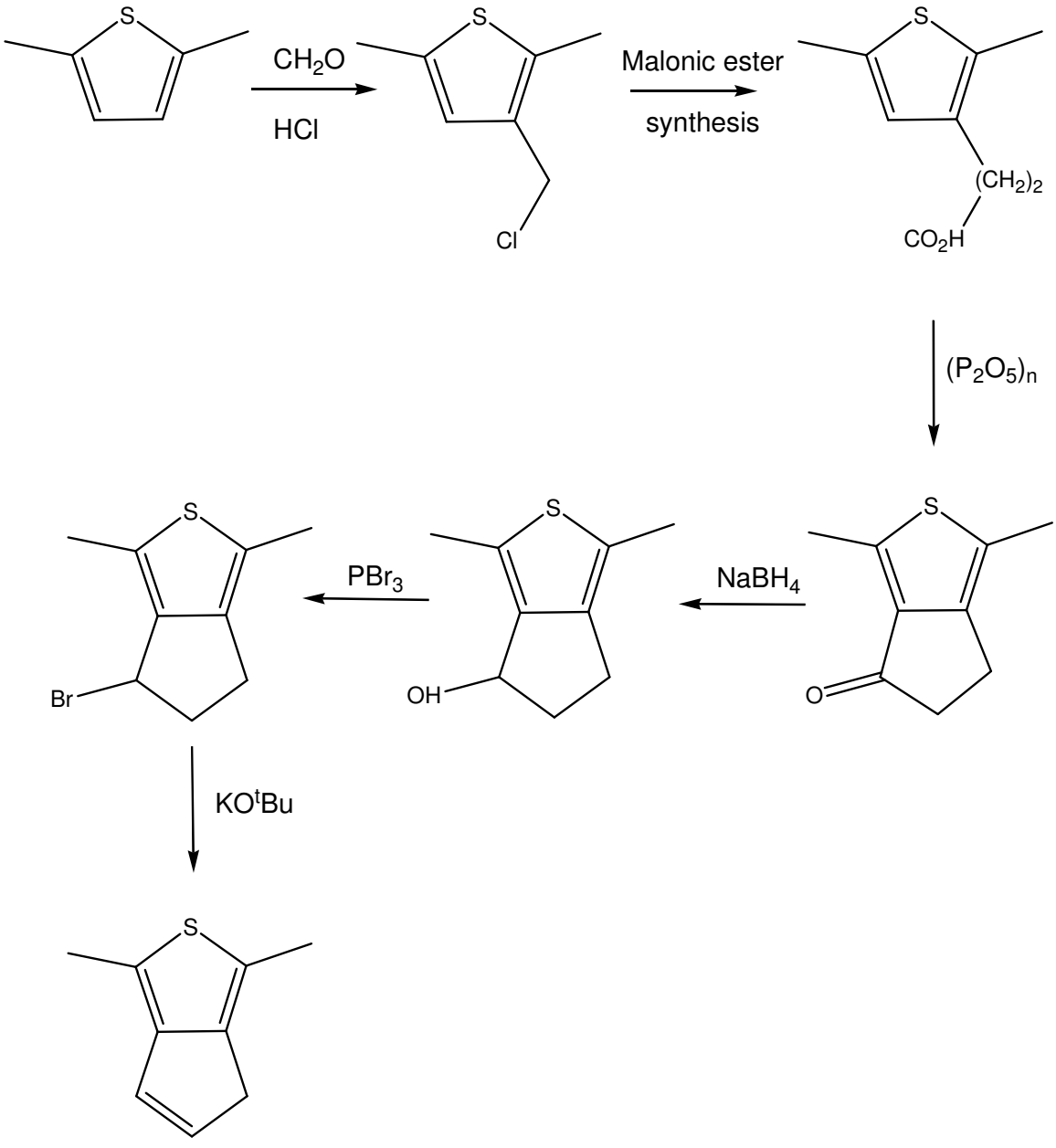


Scheme 2.1 Wallace-Selegue synthesis of 2,5-dimethylcyclopenta[*c*]thiophene[15]

While alternative synthetic routes to the production of the monomeric unit of polythiapentalene exist (Scheme 2.2)[14], new methods are under investigation because of the complications and limitations of the Wallace-Selegue route. This route, while presently the most efficient route in synthetic chemistry, has only a 3% yield of product from the starting materials. Each reaction, beginning with the chloromethylation of 2,5-dimethylthiopene, proceeds to ~85% yield of products. This loss is compounded after each step, and the total amount of product decreases significantly following each operation. Major bottlenecks in product yield are observed after the fourth and fifth steps in the sequence, producing 70% yield Dieckmann condensation and 55% yield reduction, respectively.

Other complications inherent in this reaction involve the use of sodium cyanide (NaCN) in the second step. Because this chemical is highly toxic,

extreme caution must be taken when handling the substance. Additionally, carbon tetrachloride (CCl_4) is used in the seventh step of the sequence, a



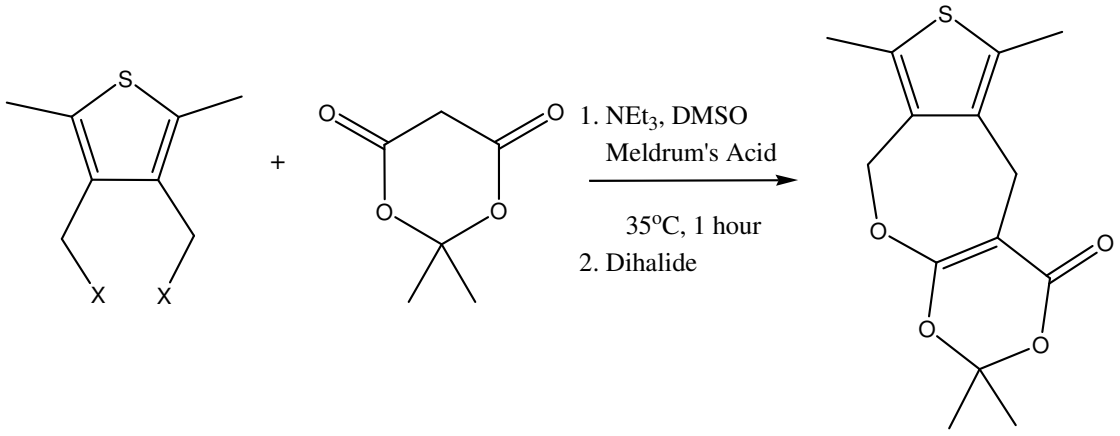
Scheme 2.2 Cantrell and Harrison synthesis of thiapentalenes.[14]

material which is highly carcinogenic to humans and is extremely hazardous in the environment-- contributing to the depletion of the ozone layer. Since the Environmental Protection Agency's restriction on the use and sale of carbon tetrachloride, it has become a very expensive solvent to use.

Approach

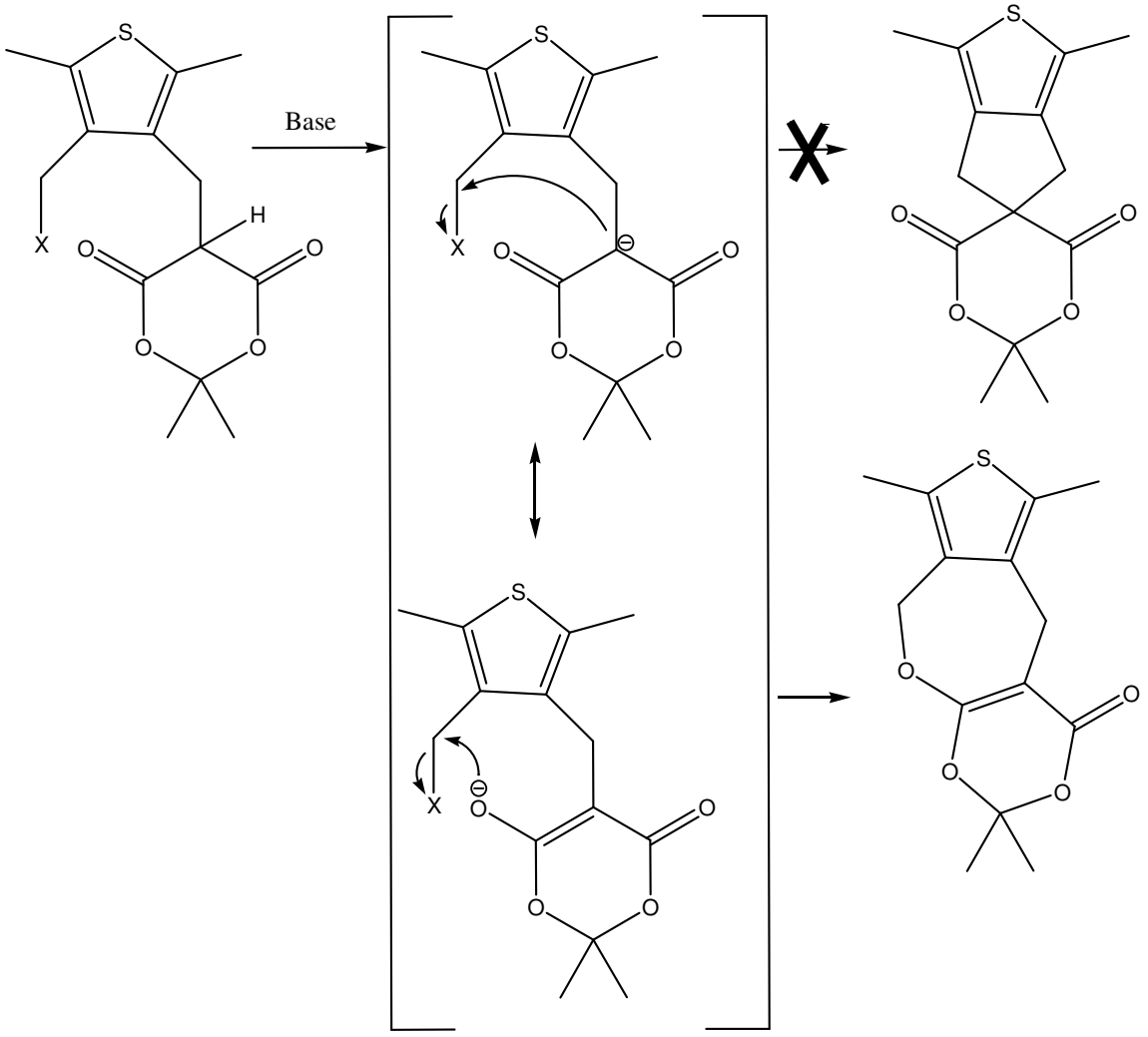
Our approach to thiapentalene synthesis utilizes both an understanding of undergraduate textbook organic chemistry and much more advanced thermodynamic calculations of enthalphy of bond formation.

In previous attempts at alternative thiapentalene synthesis by Snyder, et. al., Meldrum's acid was added to a solution of 3,4-bis(chloromethyl)-2,5-dimethylthiophene in dimethylsulfoxide (Scheme 2.3).[16] The thiapentalene product was expected to form via a C,C-alkylation of an anticipated carbanion attack mechanism. However, an unusual C,O-alkylation of Meldrum's acid was observed, which suggested an enolate attack mechanism (Scheme 2.4).[16]



Scheme 2.3 Unusual C,O-dialkylation of Meldrum's acid.[16]

Calculations of bond enthalpies of formation for the C,O- and C,C-alkylated product predicted the thermodynamically favorable C,C-alkylated product (Table 2.1, 2.2).[19]



Scheme 2.4 C,O-dialkylation of Meldrum's acid reaction mechanism.[16]

We conjecture from these observations and calculations that the C,O-alkylated product is the kinetic product and that the C,C-alkylated product may be obtained by slowing the kinetics of the reactants in three ways: by increasing the steric profiles of the reactants, investigating alternative halogen leaving-groups of the (halomethyl)thiophene substrate, and by lowering the reaction temperatures. In our study the steric hindrance of the system is increased by using the nucleophile di-*tert*-butylmalonate ester (Figure 2.1). This nucleophile is expected to impede the kinetic energy of the system enough to allow for C,C-alkylation to occur and produce the cyclopenta[c]thiophene spirocycle precursor molecule (Figure 2.2) 1,3-Dimethyl-4H,6H-cyclopenta[c]thiophene-5,5-dicarboxylic acid di-tert-butyl ester. Further studies will be performed which will investigate the decarboxylation of the spirocycle precursor (**4**) to produce the desired cyclopenta[*c*]thiophene derivative (**6**, Scheme 2.5).

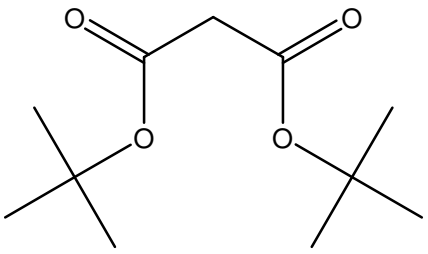


Figure 2.1 di-*tert*-Butylmalonate ester

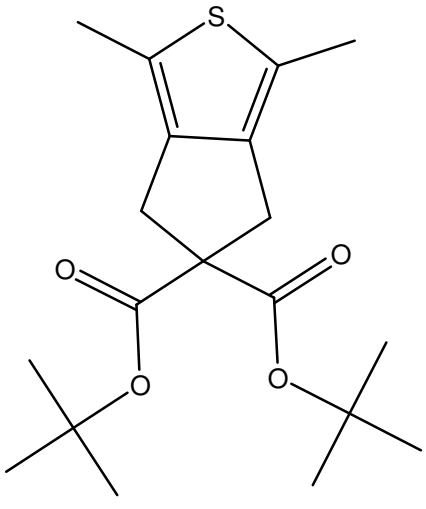
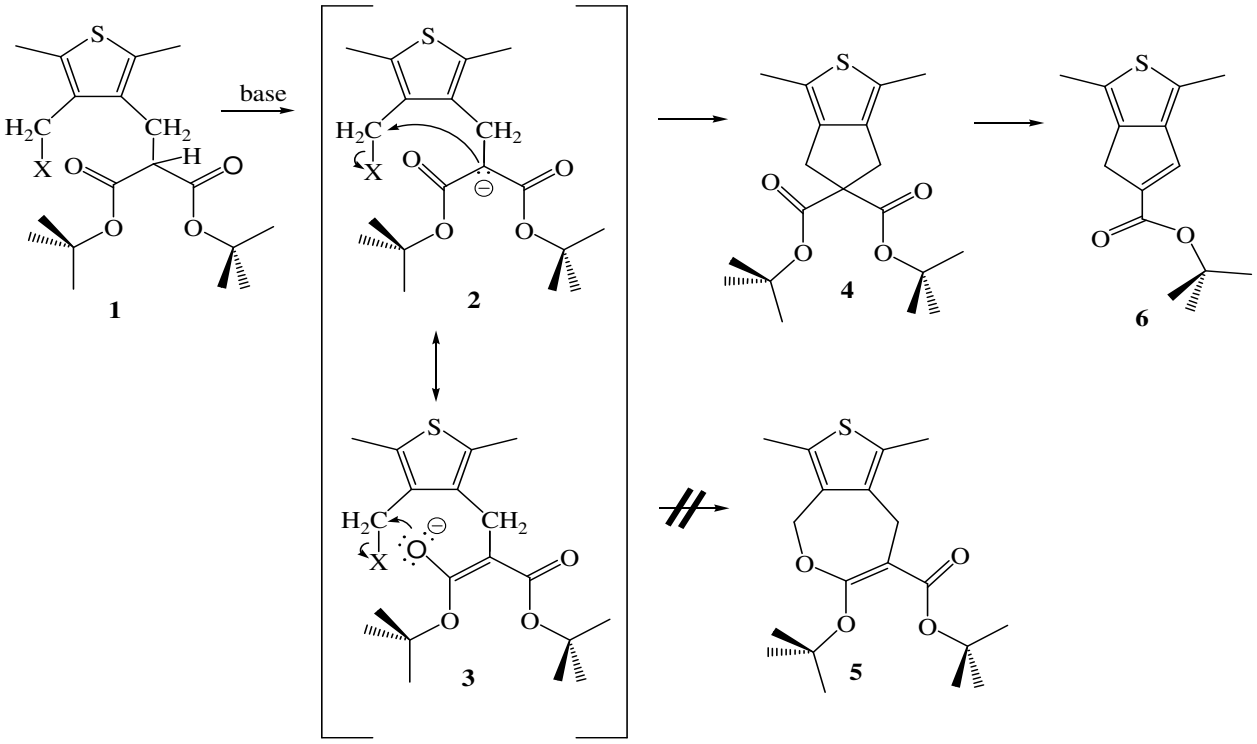
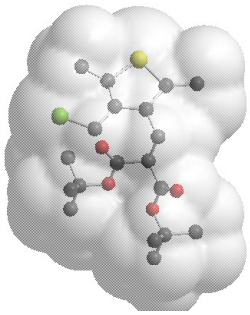


Figure 2.2 1,3-Dimethyl-4H,6H cyclopenta[c]thiophene-5,5 dicarboxylic acid di-tert-butyl ester



Scheme 2.5 Proposed C,C-dialkylation mechanism of malonate ester

Experimental Procedures



Reactions were carried out by using standard organic synthetic techniques under ambient environmental conditions. $CDCl_3$ and DMSO-d_6 (Cambridge Isotopes) were used without further purification. 3,4-bis-(bromomethyl)-2,5-dimethylthiophene was prepared according to literature methods.[16]

^1H and ^{13}C NMR spectra were recorded on a JEOL 300 MHz spectrometer at ca. 22 ^oC and were referenced to residual solvent peaks. All ^{13}C NMR spectra listed are decoupled. Infrared spectra were recorded on a PerkinElmer Spectrum One FT-IR spectrometer. Electron ionization (EI) mass spectra were recorded at 70 eV on an Agilent 5973 Mass Selective Detector at Western Kentucky University. Samples were introduced via a heated direct insertion probe. Melting points were taken on a standard MelTemp2 apparatus.

Preparation of 2,5-Dimethylthiophene, $Me_2C_4H_2S$.

A 250-mL flask with a magnetic stirrer was charged with P_4S_{10} (29.4 g, 0.133 mol). 2,5-Hexanedione (38.0 g, 0.333 mol) was added drop-wise at a rate of two milliliters per minute as reflux began. After addition, mixture was refluxed with stirring for twenty-four hours. The mixture turned dark brown and was filtered by gravity filtration. Supernatant was collected and distilled at 135 °C. A clear, colorless liquid was collected (21.5 g, 0.244 mol, 73.0% yield). **^{1}H NMR (300 MHz, $CDCl_3$, ppm)** δ 2.41 (s, 3H, Me), 6.52 (s, 1H, CH) (Appendix A). **^{1}H NMR (200 MHz, $CDCl_3$, ppm)** δ 2.44 (s, 3H, Me), 6.55 (s, 1H, CH).[15] **^{13}C NMR (300 MHz, $CDCl_3$, ppm)** δ 15.4 (Me),124.9 (*C*=CMe), 137.5 (*C*Me) (Appendix B).

Preparation of 3,4-Bis-(chloromethyl)-2,5-dimethylthiophene, $Me_2C_4H_2S(CH_2Cl)_2$.

2,5-Dimethylthiophene (10.0 g, 10.2 mL, 0.089 mol) was added to a solution of concentrated HCl (100 mL) and 37% aqueous formaldehyde solution (27.4 mL, 0.364 mol). The solution was stirred at room temperature for 14 hours and turned bright blue-green with a white solid precipitating. The solution was extracted with dichloromethane (3 x 25 mL), dried over $MgSO_4$, and the volatiles were removed. The crude black product was triturated using 95% ethanol. Volatiles were removed from solution by rotary evaporation; a pale-yellow solid was collected. The triturated product was purified using a silica plug (1:1 dichloromethane:hexane). Volatiles removed under air stream and white crystals were collected (17.4 g, 83.2 mmol, 93.2%). M.p. 68-69 °C. **^{1}H NMR (300 MHz, $CDCl_3$, ppm)** δ 2.41 (s, 3H, Me), 4.62 (s, 2H, CH) (Appendix C). **^{1}H NMR (200**

MHz, $CDCl_3$, ppm) δ 2.38 (s, 6H, Me), 4.59 (s, 2H, CH).[15] **^{13}C NMR (300 MHz, $CDCl_3$, ppm)** δ 12.9 (Me), 37.4 (*C*H_2Cl), 132.0 (*C*Me), 136.0 (*C*(CH_2Cl)) (Appendix D).

Synthesis of 1,3-Dimethyl-5,6-dihydro-4H-cyclopenta[*c*]thiophene(2-spiro-5)2,2-di-tert-butyl ester, $Me_8C_{11}H_4O_4S$ via 3,4-bis-(chloromethyl)-2,5-dimethylthiophene.

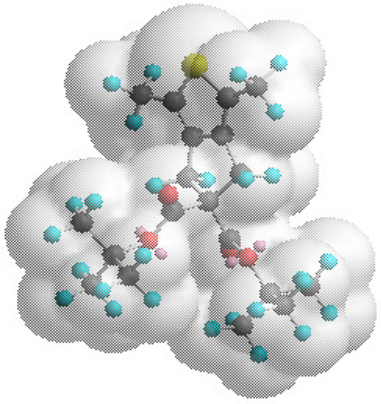
To a solution of dimethylsulfoxide (25 mL) and triethylamine (0.97 g, 1.3 mL, 9.6 mmol), *tert*-butylmalonate ester (1.0 g, 1.1 mL, 4.6 mmol) was added one hour after solution reached 110 ^{o}C. 3,4-bis-(chloromethyl)-2,5-dimethylthiophene (1.0 g, 4.5 mmol) was then added and allowed to cool to room temperature and react for one week. At the bottom of the flask, a pale yellow solution was collected, extracted using diethyl ether (3 x 20 mL), dried over $MgSO_4$, and the volatiles were removed under vacuum for ten days. The collected product was a dark orange oil (0.12 g, 0.37 mmol, 14% yield). **^{1}H NMR (300 MHz, $CDCl_3$, ppm)** δ 2.47 (s, 9H, ^{t}Bu), 2.51 (s, 3H, Me), 3.31 (s, 2H, CH_2) (Appendix E). **IR (KBr, cm^{-1}):** 1667 (CO), 2917 (C_{sp3}-H), 3002 (C_{sp2}-H) (Appendix F).

Synthesis of 1,3-Dimethyl-5,6-dihydro-4H-cyclopenta[*c*]thiophene(2-spiro-5)2,2-di-tert-butyl ester under low temperature conditions, $Me_8C_{11}H_4O_4S$, via 3,4-(bromomethyl)-2,5-dimethylthiophene.

A solution of dimethylsulfoxide (DMSO) (25 mL), triethylamine (0.97 g, 1.3 mL, 9.6 mmol), and *tert*-butylmalonate ester (1.0 g, 1.1 mL, 4.6 mmol) was prepared in a 50 mL round-bottom flask fitted with a magnetic stirrer and a reflux condenser. The solution was stirred at 40 ^{o}C for one hour and then cooled in an ice bath. 3,4-Bis-(bromomethyl)-2,5-dimethylthiophene (1.4 g, 4.8 mmol) was

added to the solution and allowed to react for one week in an ice bath. The reaction was monitored by thin-layer chromatography and the products were separated using ethyl ether. The resulting solution was dried under vacuum for ten days. The collected product was a dark, red-orange oil (0.60 g, 0.51 mmol, 36% yield). **^{1}H NMR (300 MHz, $CDCl_3$, ppm)** δ 1.38 (s, 9H, ^{t}Bu), 2.54 (s, 3H, Me), 3.58 (s, 2H, C*H*$_2$) (Appendix G). **^{13}C NMR (300 MHz, $CDCl_3$, ppm)** δ 15.2 (Me), 18.3 (*C*H$_2$), 27.9 (^{t}Bu), 57.9 (C(CO$_2$)$_2$), 65.9 (*C*Me$_3$), 166.3 (C=O) (Appendix H). **IR (NaCl, cm^{-1}):** 1679 (CO), 2930 (C_{sp3}-H), 2978 (C_{sp2}-H) (Appendix I). **GC/MS:** ***m/z*** 278 (M^+ - CHOC(CH$_3$)$_3$), 263 (M^+ - CHO(CH$_3$)$_3$, CH$_3$), 246 (M^+ - CHOC(CH$_3$)$_3$, 2CH$_3$) (Appendix J-O).

Results and Analysis of Experimental Data



The preparation of 2,5-dimethylthiophene from 2,5-hexandione and phosphorus pentasulfide initially followed prescribed literature methods and involved the use of a three-necked, one-liter, round-bottom flask with an attached reflux condenser.[15] This synthesis was improved by carrying out the reaction in a 250-mL Erlenmeyer flask. The altered reaction vessel had no effect on the previously reported product yields.

Wallace's synthesis[15] of 3,4-bis-(chloromethyl)-2,5-dimethylthiophene (dihalide) was improved by purifying the dihalide product using a silica plug apparatus. Here, a filter funnel was packed with silica (0.060-0.200 mm pore diameter) and topped off by a single layer of Whatman #2 qualitative filter paper. The crude dihalide product was then washed through the silica with a cold solution of 50% dichloromethane and 50% hexane. The product was then collected by evaporation, and the purity was determined by thin-layer chromatography, ^{1}H NMR, and melting point range determination. The percent

yield was unaffected from previously reported values[15]; however the product was more pure using this work-up method.

The reaction of 3,4-bis-(chloromethyl)-2,5-dimethylthiophene with di-*tert*-butylmalonate ester was investigated in an attempt to synthesize thiapentalene precursor molecules. Various reaction conditions were studied (Figure 4.1) in the pursuit of improving the synthesis of 1,3-dimethyl-4*H*,6*H*-cyclopenta[*c*]thiophene-5,5-dicarboxylic acid di-*tert*-butyl ester (spirocycle).

Attempted Synthesis of Thiapentalene Precursor Spirocycle			
Temperature (K)	Halogen Leaving Group	Δ Time	% Yield
423	Chloride	24 hours	N/A
383	Chloride	24 hours	14
273	Chloride	1 week	21
273	Bromide	1 week	36

Figure 4.1 Table of attempted synthesis of thiapentalene precursor spirocycles

The efficiency of the synthetic methodology of 2,5-dimethylthiophene synthesis was improved by replacing the reaction vessel from a three-necked, one-liter, round-bottom flask with a 250-mL Erlenmeyer flask. This substitution allows for much more simple reaction preparation and attention. This is largely due to the availability of Erlenmeyer flasks, expense of specialized glassware such as the former vessel, and the relative ease in which an Erlenmeyer flask is heated versus the one-liter flask.

The purification of 3,4-bis-(chloromethyl)-2,5-dimethylthiophene was previously unreported by Wallace and was necessary to maximize product yields in the synthesis of the desired spirocycle compounds. After washing the crude

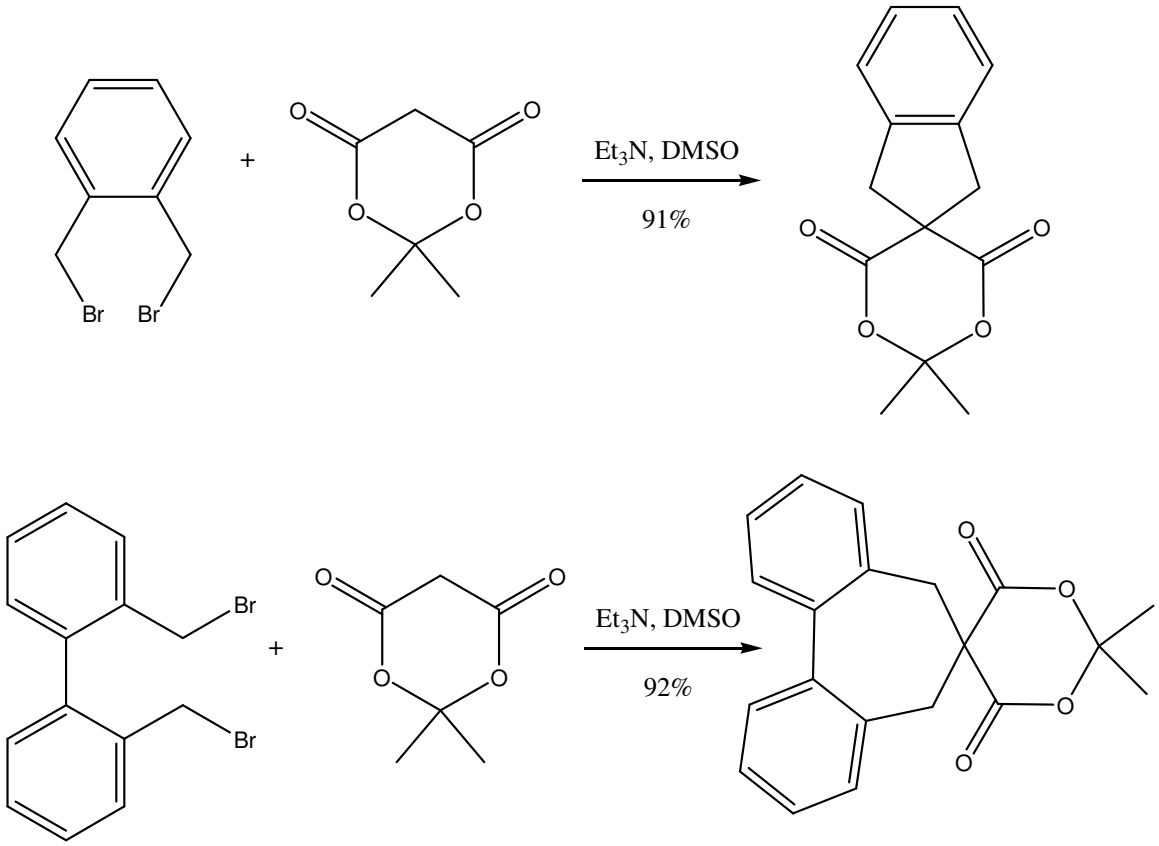
dihalide containing unidentified impurities through the silica plug, the collected product exhibited a color change from dark yellow to white. Greater purity was observed by a narrower melting point range (75-76 ^{o}C) and the absence of contamination peaks in the ^{1}H NMR spectra. This purification step was necessary to ensure that undesired side reactions were prevented.

The first successful synthesis of the spirocycle 1,3-dimethyl-4*H*,6*H*-cyclopenta[*c*]thiophene-5,5-dicarboxylic acid di-*tert*-butyl ester is reported here. The synthesis of the malonate ester spirocycle was studied by varying the halogen leaving-groups of chlorine and bromine and also varying the reaction temperatures. Analysis of the collected data indicates that longer reaction times and colder temperatures are required to achieve moderate product yields (36%).

These new compounds synthesized were characterized and their purity ascertained via FT-IR, ^{1}H and ^{13}C NMR, GC-MS, TLC, and melting point determination. While the starting compounds of the spirocycle synthesis were purified, thin-layer chromatography demonstrated that impurities were present in the collected oil product after trituration and a total of three solvent washes. These impurities were also visible in both the ^{1}H and ^{13}C NMR spectra but are relatively minor.

As part of the development of a general synthesis of cyclopenta[*c*]thiophene, the dialkylation of malonic ester yielded the cyclopenta[*c*]thiophene precursor spirocycle. Preparations of indanes via reactions of 1,2-bis-(haloalkyl)arenes with malonate anions are well known.[20-24] For instance, spiroindane derivatives were obtained by treating α,α'-dibromo-*o*

xylene and 2,2'-bis-(bromomethyl)-1,1'-biphenyl with Meldrum's acid (Scheme 4.1).[25]



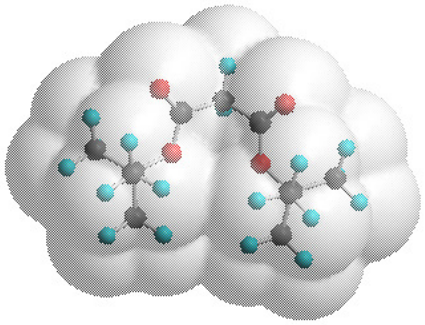
Scheme 4.1 Spirocycle derivatives of Meldrum's acid.[25]

The reaction of 3,4-bis-(bromomethyl)-2,5-dimethylthiophene with di-*tert*-butylmalonate ester in triethylamine and DMSO yielded the desired spirocycle product in moderate yield (36%). Another halogen leaving-group (X=Cl) was investigated in an effort to improve product yields but produced only 21% product yield under the same low-temperature conditions.

Identification and confirmation of the target compound was achieved with ^{1}H and ^{13}C NMR spectroscopy. The starting materials 3,4-bis-(bromomethyl)-2,5-dimethylthiophene and 3,4-bis-(chloromethyl)-2,5-dimethylthiophene have almost identical chemical shifts for both methyl (2.35 and 2.38 ppm, respectively) and methylene protons (4.89 and 4.59 ppm, respectively in their ^{1}H NMR spectra. The target compound for the C,C-dialkylation of the Malonic ester with 3,4-bis-(halomethyl)-2,5-dimethylthiophene was 1,3-Dimethyl-4*H*,6*H*-cyclopenta-[*c*]thiophene-5,5-dicarboxylic acid di-*tert*-butyl ester. This spirocycle product was confirmed when the ^{1}H NMR spectra exhibited three singlet peaks at 1.38, 2.54, and 3.58 ppm, whereas the kinetic oxepine product would have produced five singlet readings.

The amount of the thiapentalene precursor that could be obtained was limited by bond angle strain on the third and forth carbons of the thiophene ring. Additionally, the greater product yield using bromine versus chlorine can be attributed to the activity of bromine as an effective leaving group in organic synthesis.

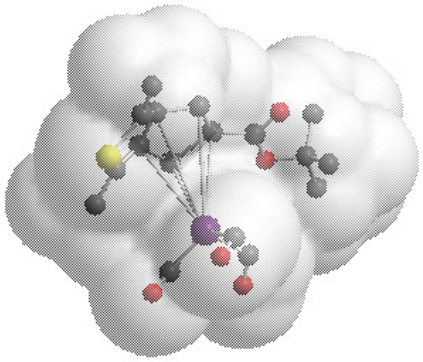
Evaluation of Research Investigation



This thesis describes a new approach to cyclopenta[*c*]thiophene synthesis that circumvents some of the limitations of high bond-angle strain systems and anomalies encountered in previous studies. This thesis also suggests an additional method for the synthesis of thiapenalenes. To this end, new 1,3-disubstituted-4*H*-cyclopenta[*c*]thiophenes were synthesized as potential precursors to thiapentalenes.

Research on organometallic heterocycles continues in the Snyder group, and extensions of the methodology developed in this thesis to various substituted cyclopenta[*c*]thienyl complexes are underway. Electrochemical studies of cyclopenta[*c*]thienyl complexes have yet to be performed to determine their suitability for semiconductor applications. This thesis has uncovered some initial steps toward those materials.

Continuing Research



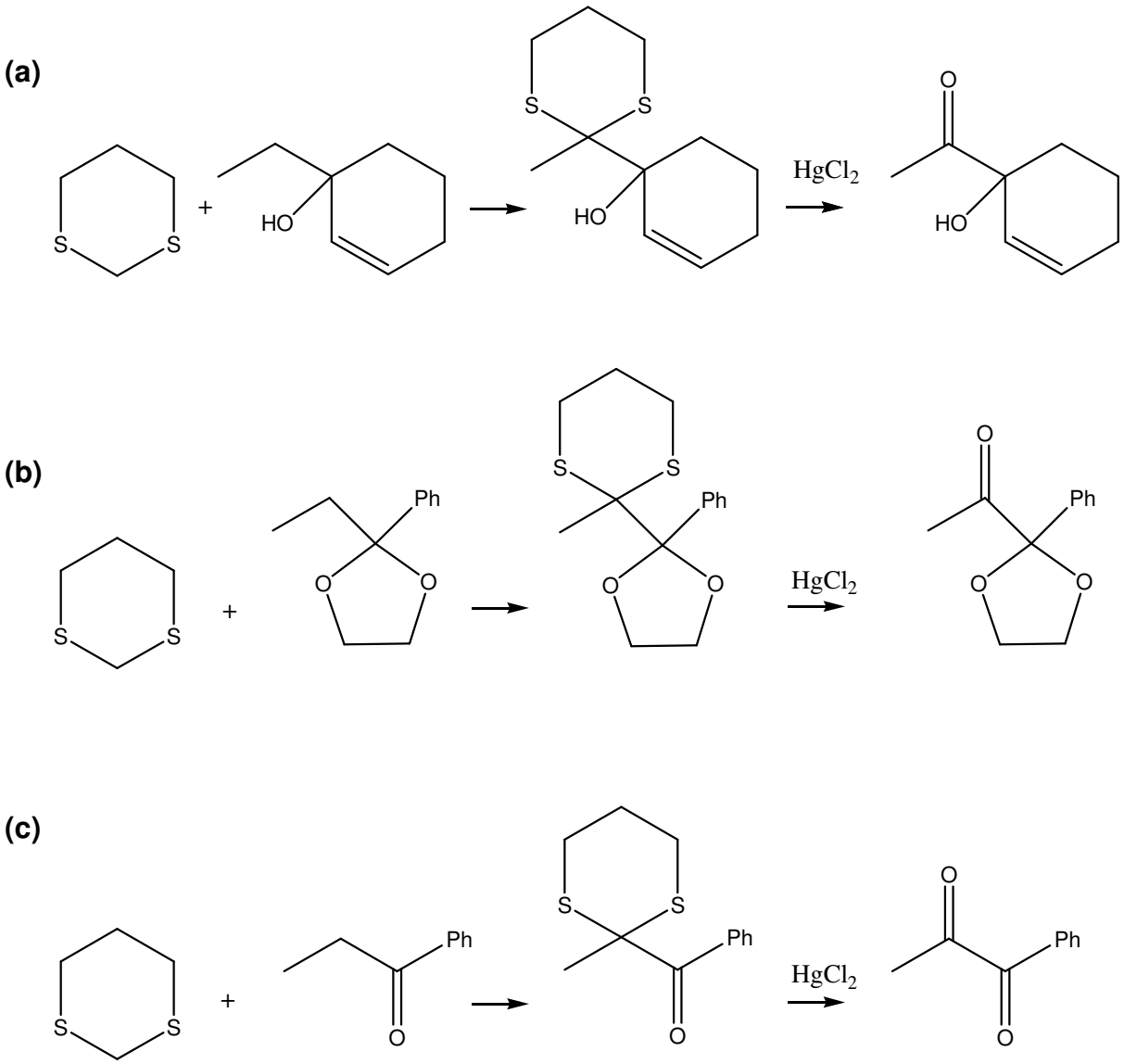
Cyclopenta[*c*]thiophenes are currently under investigation in the Snyder Group's Organic Synthesis Laboratory at Western Kentucky University. Extensions of the methodology developed in this thesis are underway. Synthesis of organometallic metal complexes to cyclopenta[*c*]thiophenes is warranted to determine electrochemical properties of thiapentalenes with the goal of developing efficient electroactive polymers. Alternative approaches to the synthesis of cyclopenta[*c*]thiophenes also deserve attention.

Proposed Thiapentalene Synthesis using 1,3-Dithiane

1,3-Dithiane should offer a convenient route to the cyclopenta[*c*]thiophene precursor 1,3-cyclopenta[*c*]thiophene-5-one (4, Scheme 6.2). 1,3-Dithiane, first reported in 1971 by Corey[26], is an effective tool used in synthetic chemistry to produce carbonyl-based functional groups [26-28] (Scheme 6.1).

Incorporating 1,3-dithiane chemistry into the Wallace-Selegue route (Scheme 2.1) reduces the number of synthetic steps by half. This synthesis

(Scheme 6.2) begins with 3,4-bis(chloromethyl)-2,5-dimethylthiophene (1, Scheme 6.2) reacting with 1,3-dithiane (2, Scheme 6.2) to produce the thiane intermediate (3, Scheme 6.2) via *n*-butyl lithium, mercuric chloride, acid, and

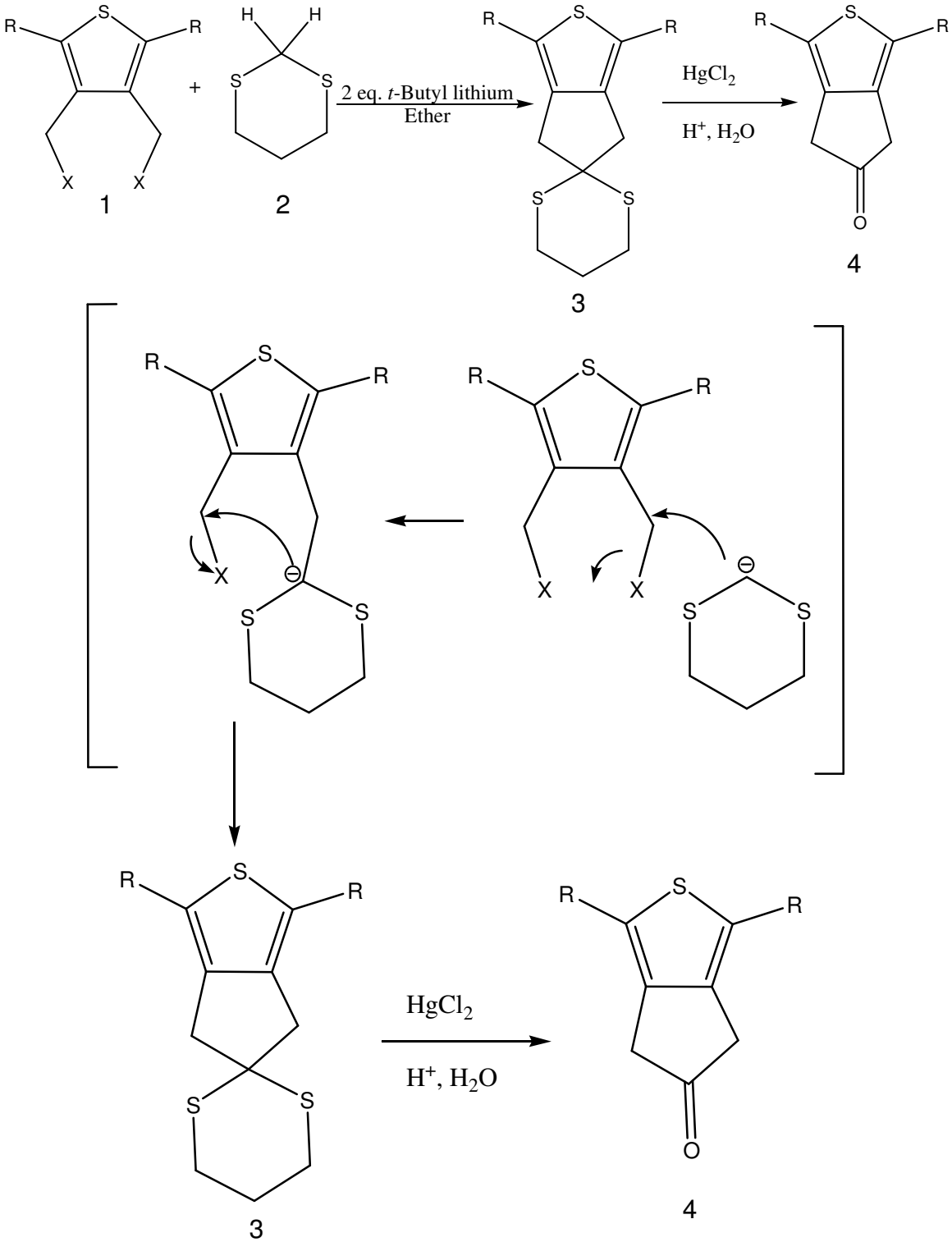


Scheme 6.1 Synthesis of various carbonyl-based functional groups via 1,3-dithiane chemistry.[26-28]

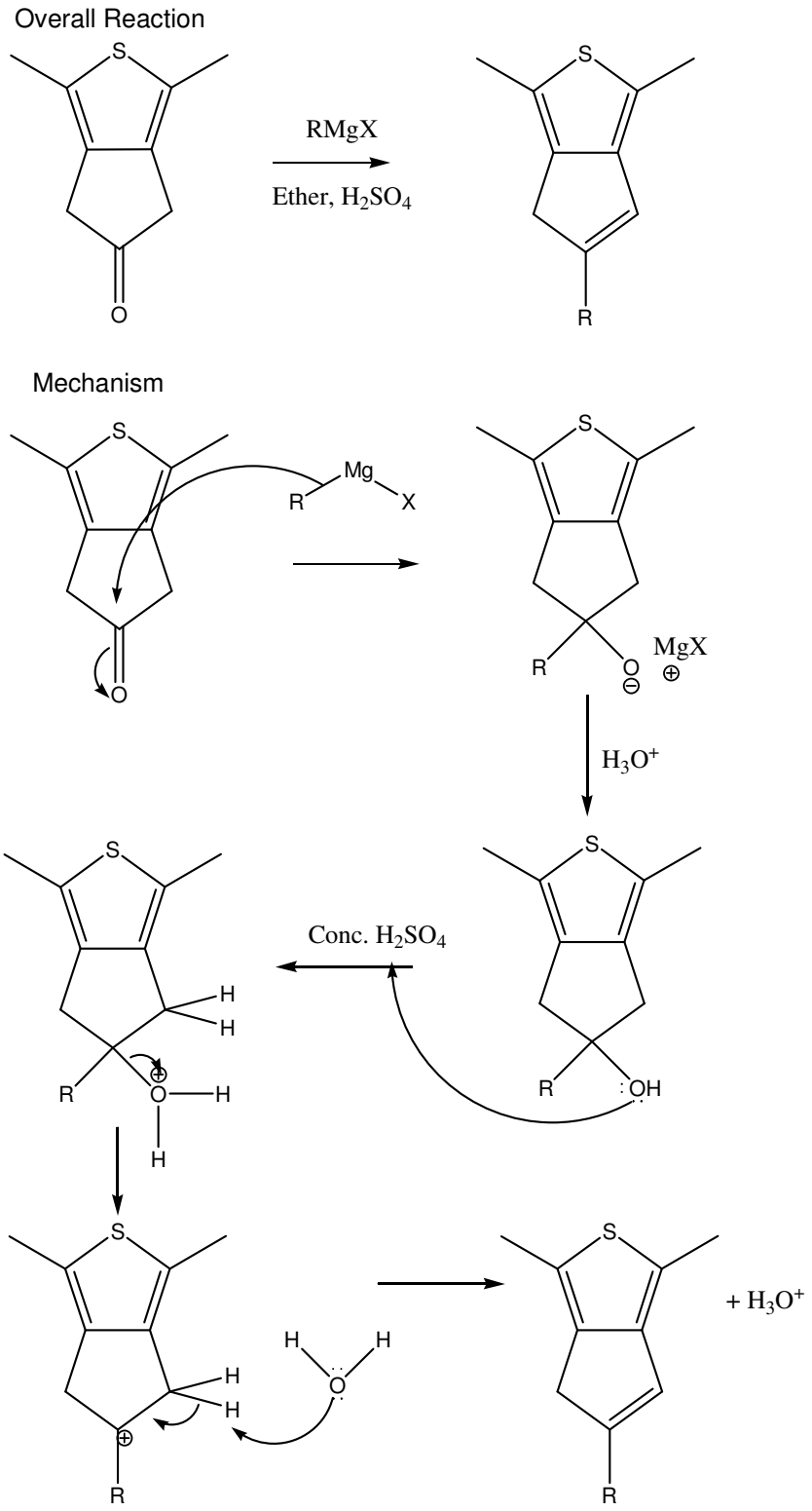
water—all of which are relatively inexpensive reagents found in most academic laboratory stockrooms. 1,3-Dithiane itself is approximately $1.00 per gram.[27-28]

A synthetic advantage of 1,3-dithiane chemistry is that it should prevent O-enolate attack, as reported by Snyder[16] in the study of Meldrum's acid producing 2,2-dimethyl-[1,3]-dioxane-4,6-dione (2, 3 Scheme 6.4). Treatment of 1,3-dimethyl-4*H*, 6*H*-cyclopenta[*c*]thiophene-5-one with Grignard reagents (Scheme 6.3) followed by decarboxylation should yield the desired cyclopenta[*c*]thiophene product.

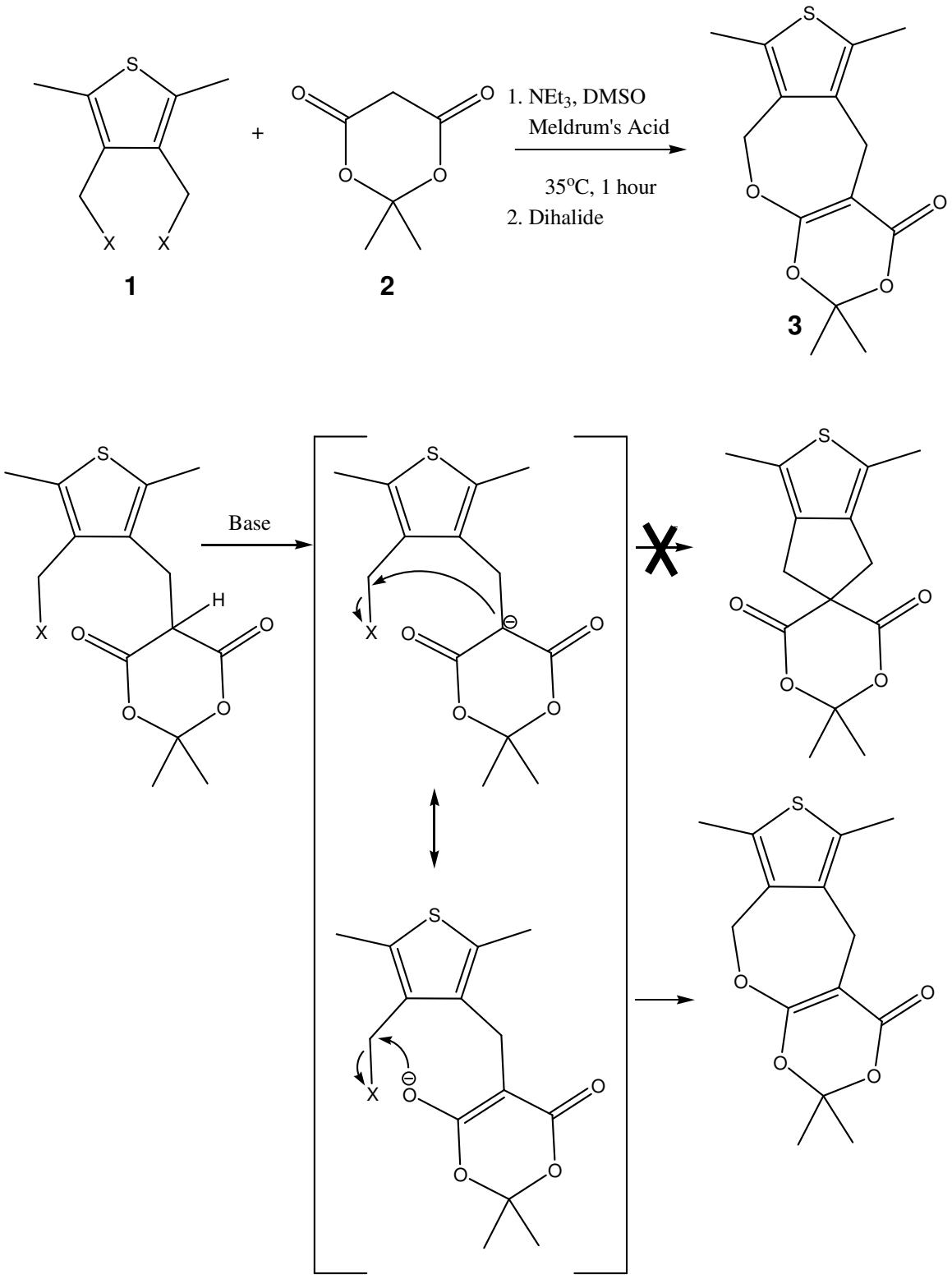
Incorporation of 1,3-dithiane chemistry into the Wallace-Selegue route should efficiently synthesize the thiapentalene 1,3-dimethyl-4*H*,6*H*-cyclopenta[*c*]thiophene-5-one (Scheme 6.2). The mechanism begins with treating 1,3-dithiane with *n*-butyl lithium (base) and adding it to a solution containing the dihalide. *n*- Butyl lithium base deprotonates 1,3-dithiane and generates a carbanion. The nucleophilic carbanion attacks the electrophilic dihalide (1, Scheme 6.2) methylene group, expelling chloride. A second equivalent of *n*-butyl lithium deprotonates the 1,3-dithiane intermediate, and an intramolecular C-C dialkylation reaction occurs which releases a second chloride. This product is oxidized to the ketone by addition of acid, water, and mercuric chloride.[26] The resulting product, 4*H*, 6*H*-cyclopenta[*c*]thiophene-5-one (4, Scheme 6.2), is then treated with Grignard reagents and dehydrated to produce the cyclopenta[*c*]thiophene product.



Scheme 6.2 Proposed mechanism for the synthesis of the cyclopenta[*c*]thiophene precursor 1,3-cyclopenta[*c*]thiophene-5-one.



Scheme 6.3 Mechanism for the treatment of 1,3-cyclopenta[*c*]thiophene-5-one with Grignard reagents and decarboxylation to thiapentalene derivative



Scheme 6.4 C,O-Dialkylation of Meldrum's Acid: Synthesis of 1,3,7,7-Tetramethyl-4*H*,10*H*-6,8,9-trioxathiabenzo[*f*]azulenone.[16]

This alternative route reduces the number of low-yield steps and uses readily available compounds. The time saved by reducing the number of operations in the synthesis is a very attractive feature of this proposed reaction. Moreover, the reduction in operations also lowers the cost associated with the number of reactants and the cost of disposal upon completion of the synthetic step. In addition to cost savings, this process leads to a “greener,” more environmentally friendly reaction.

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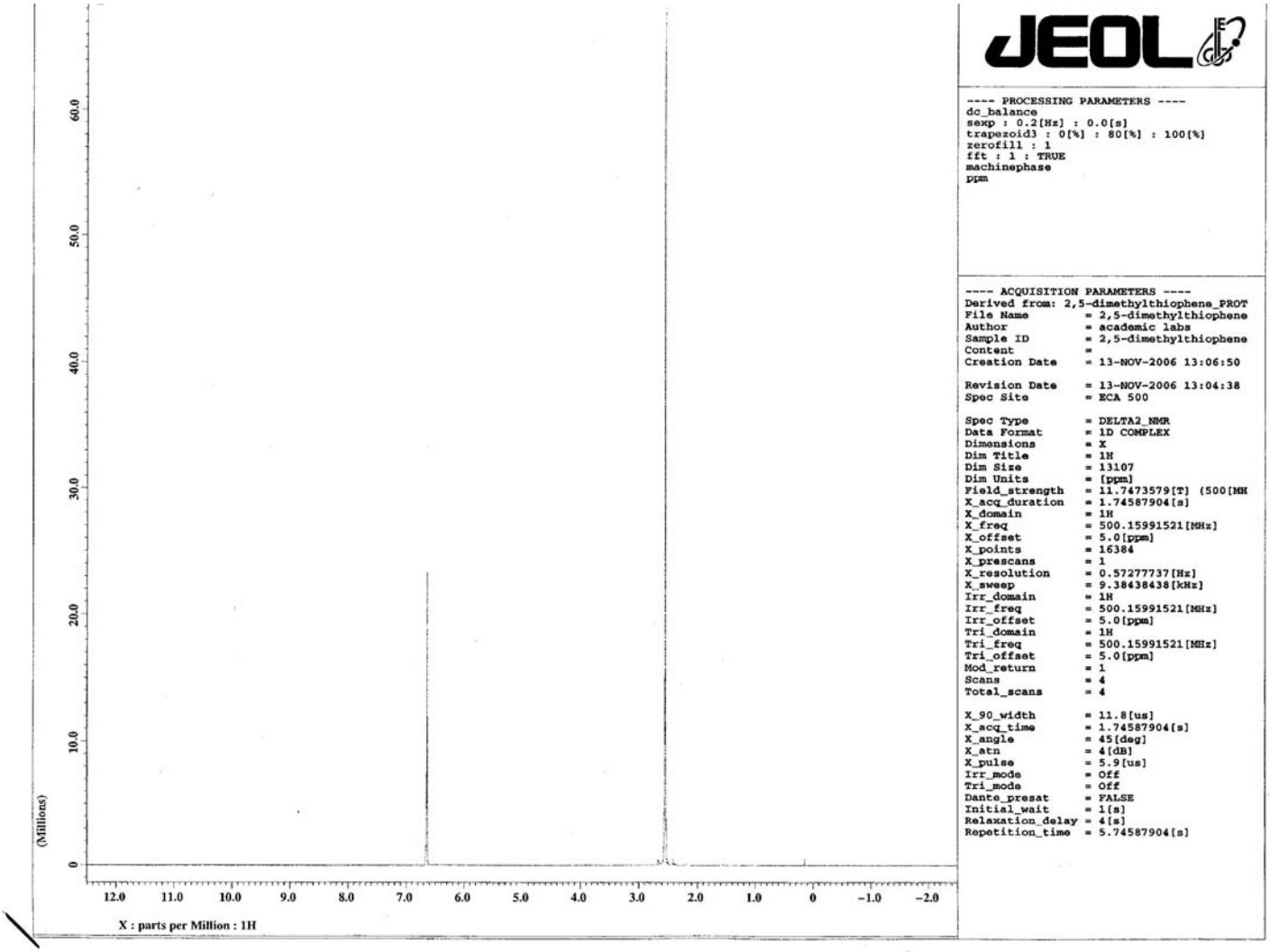
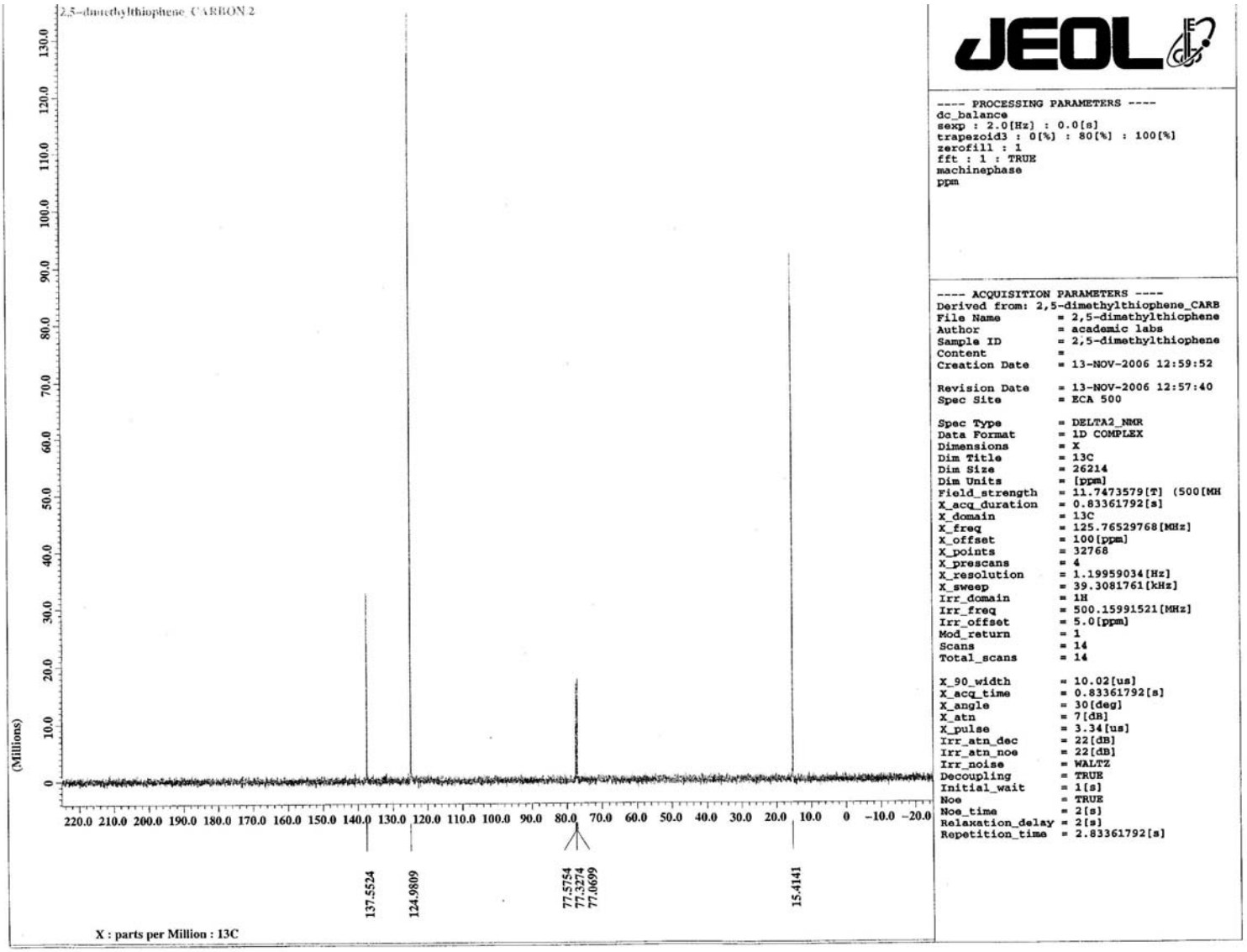
Appendix

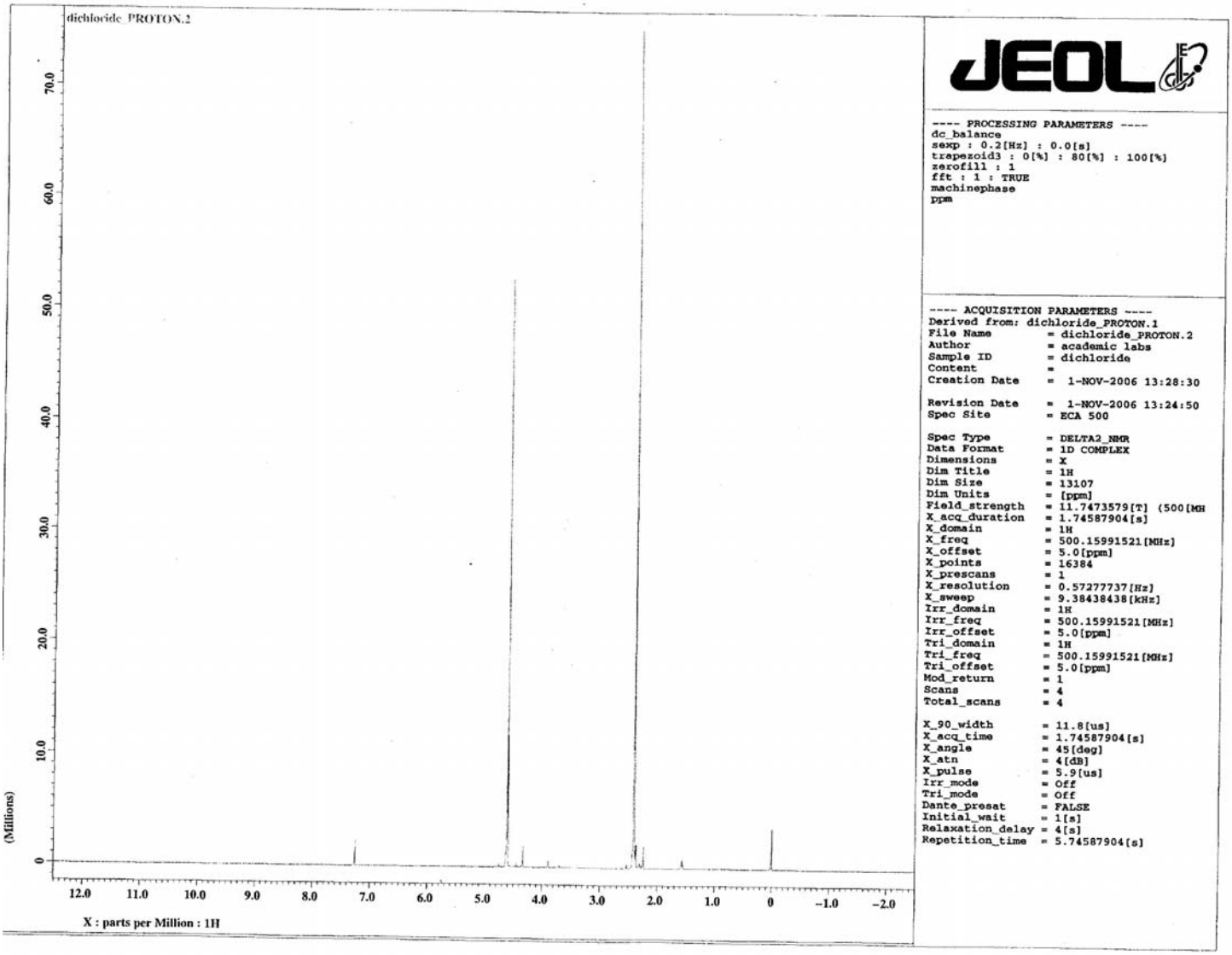
Appendix A. ^{1}H NMR Spectra of 2,5-Dimethylthiophene (300 MHz, $CDCl_3$, ppm).



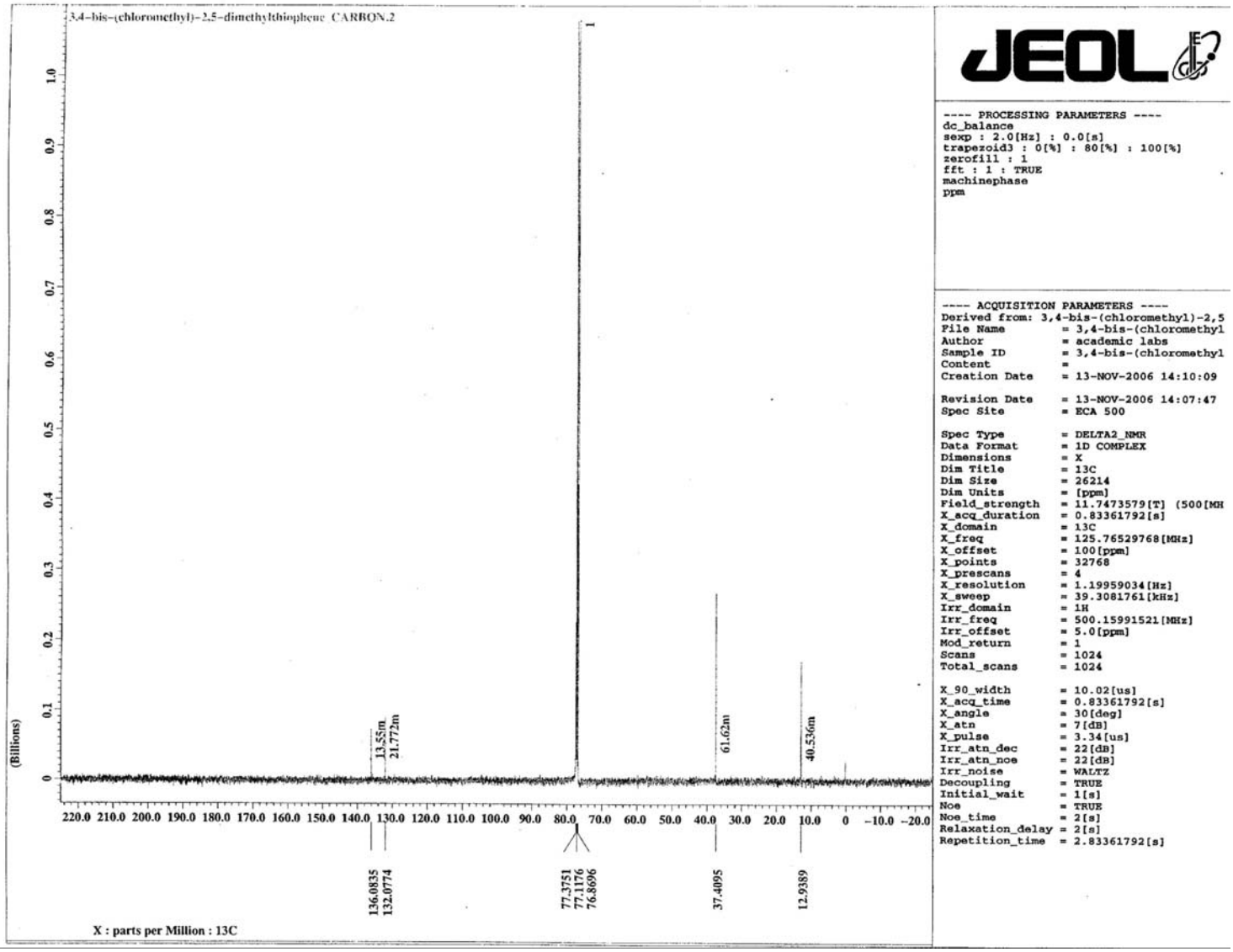
Appendix B. ^{13}C NMR Spectra of 2,5-Dimethylthiophene (300 MHz, $CDCl_3$, ppm).



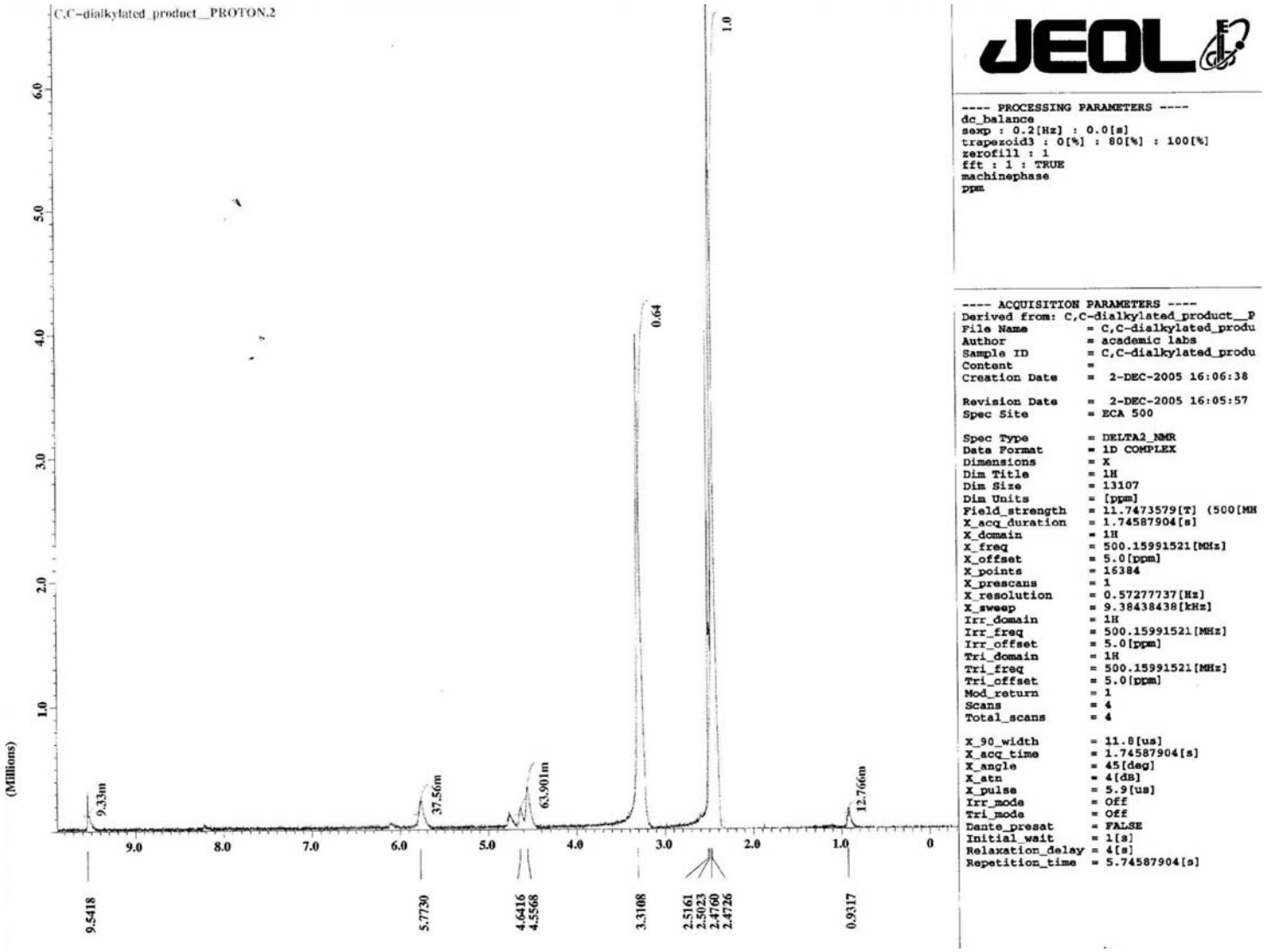
Appendix C. ^{1}H NMR Spectrum of 3,4-bis-(chloromethyl)-2,5-Dimethylthiophene (300 MHz, $CDCl_3$, ppm).



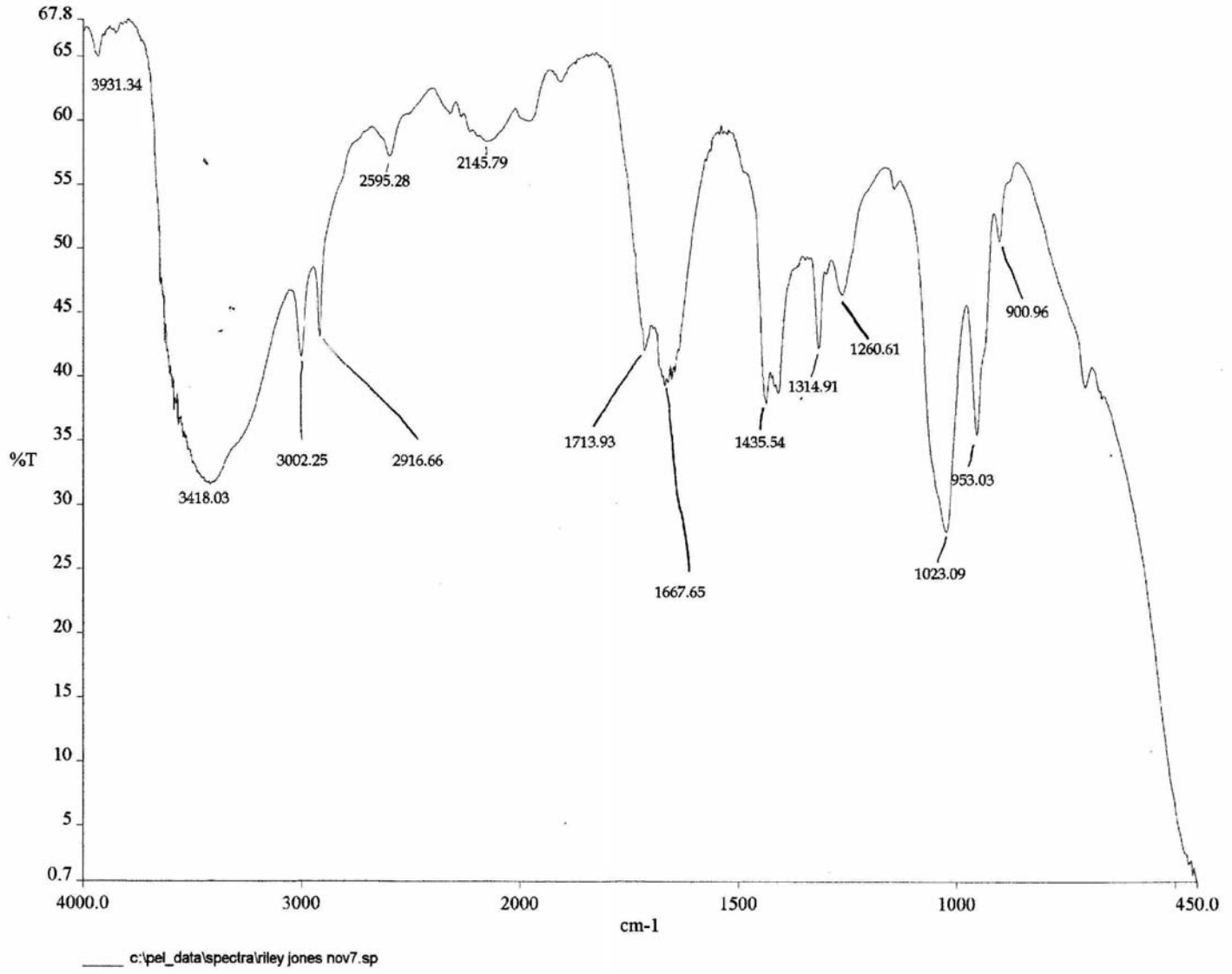
Appendix D.^{13}C NMR Spectrum of 3,4-bis-(chloromethyl)-2,5-Dimethylthiophene (300 MHz, $CDCl_3$, ppm).



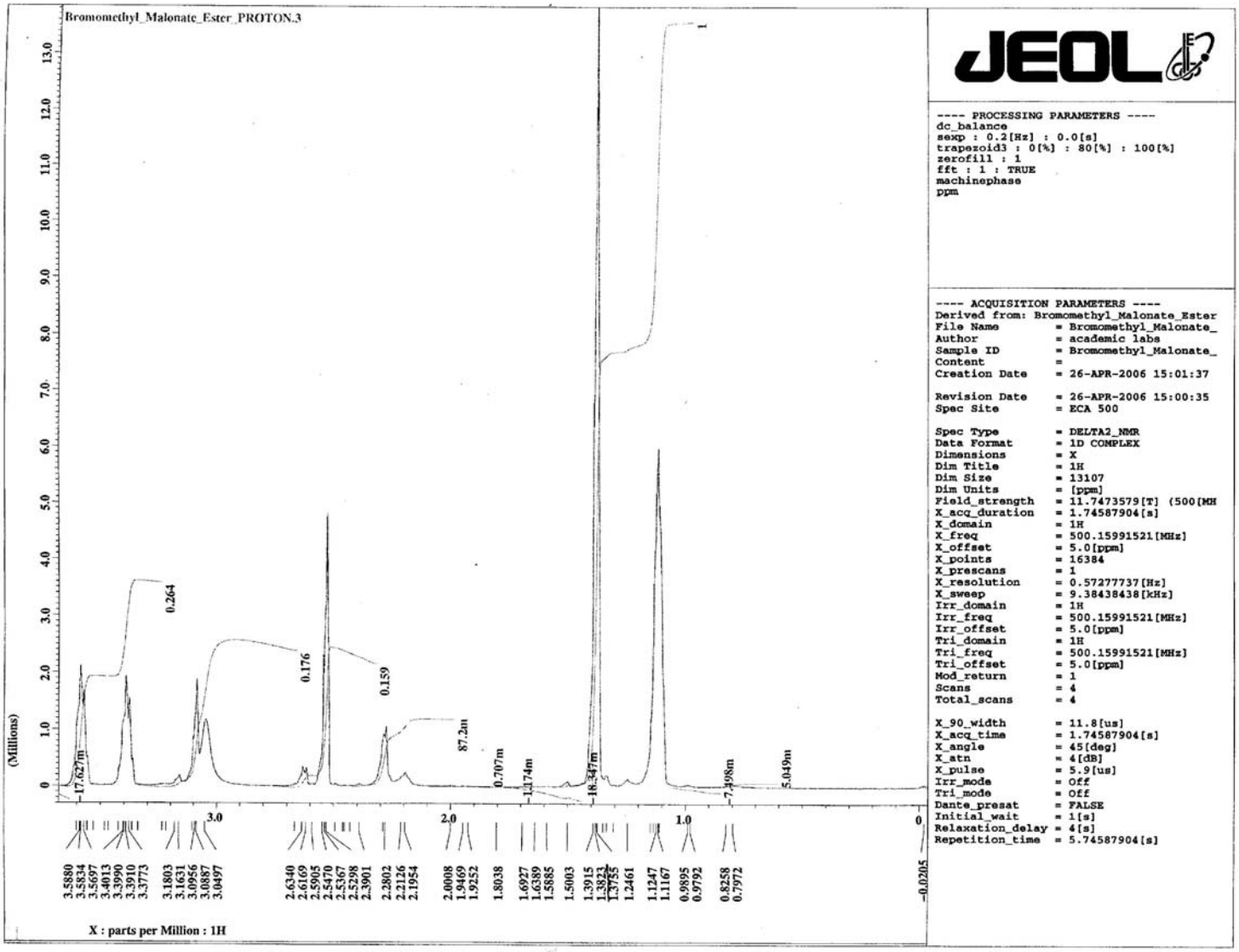
Appendix E. ^{1}H NMR Spectra of 1,3-Dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene(2Spiro-5)2,2-di-*tert*-butyl ester (300 MHz, $CDCl_3$, ppm).



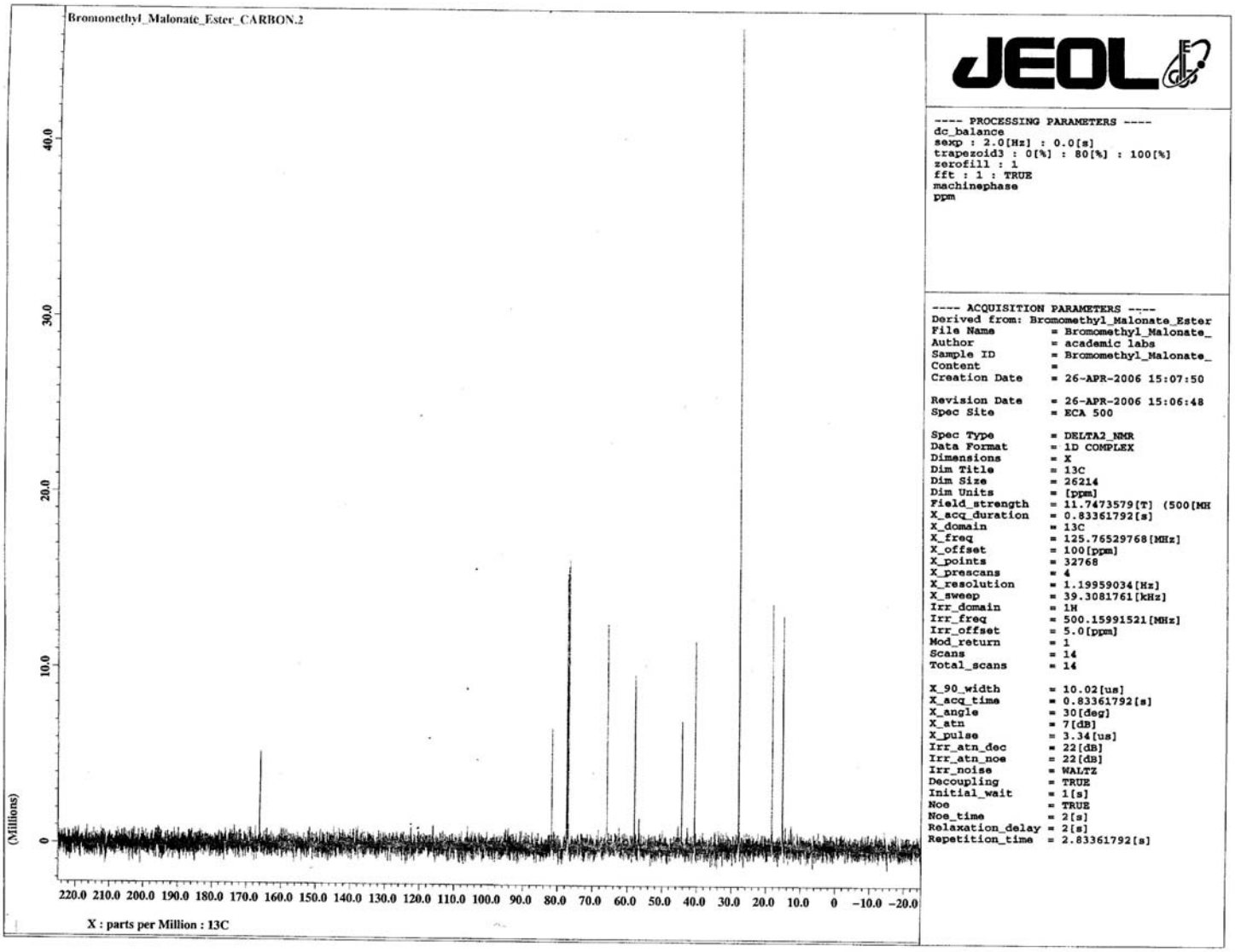
Appendix F. KBr Infrared Spectra of 1,3-Dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene(2Spiro-5)2,2-di-*tert*-butyl ester.



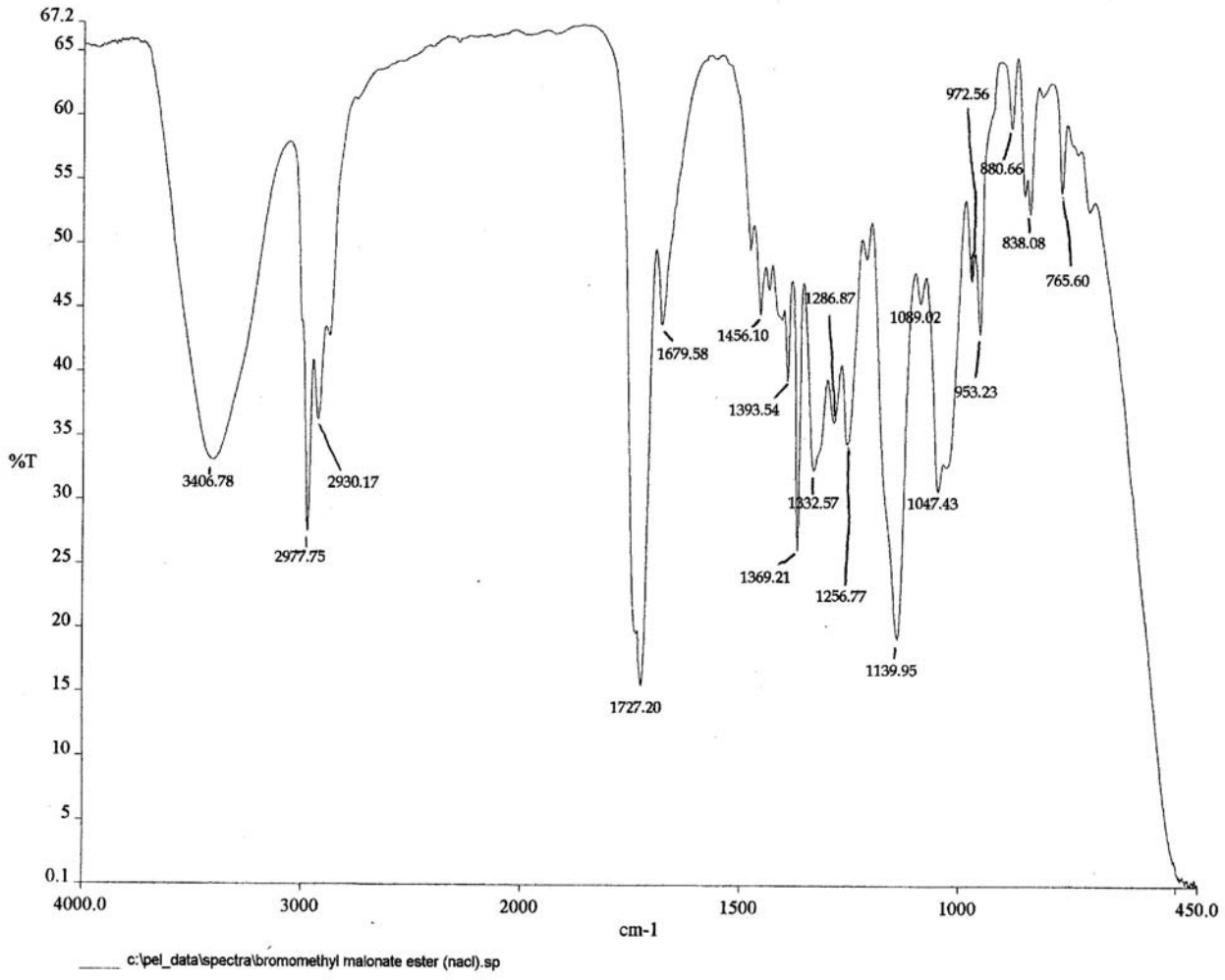
Appendix G. ^{1}H Spectra of 1,3-Dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*] thiophene(2Spiro-5)2,2-di-*tert*-butyl ester.



Appendix H. ^{13}C NMR Spectrum of 1,3-Dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene(2Spiro-5)2,2-di-*tert*-butyl ester.

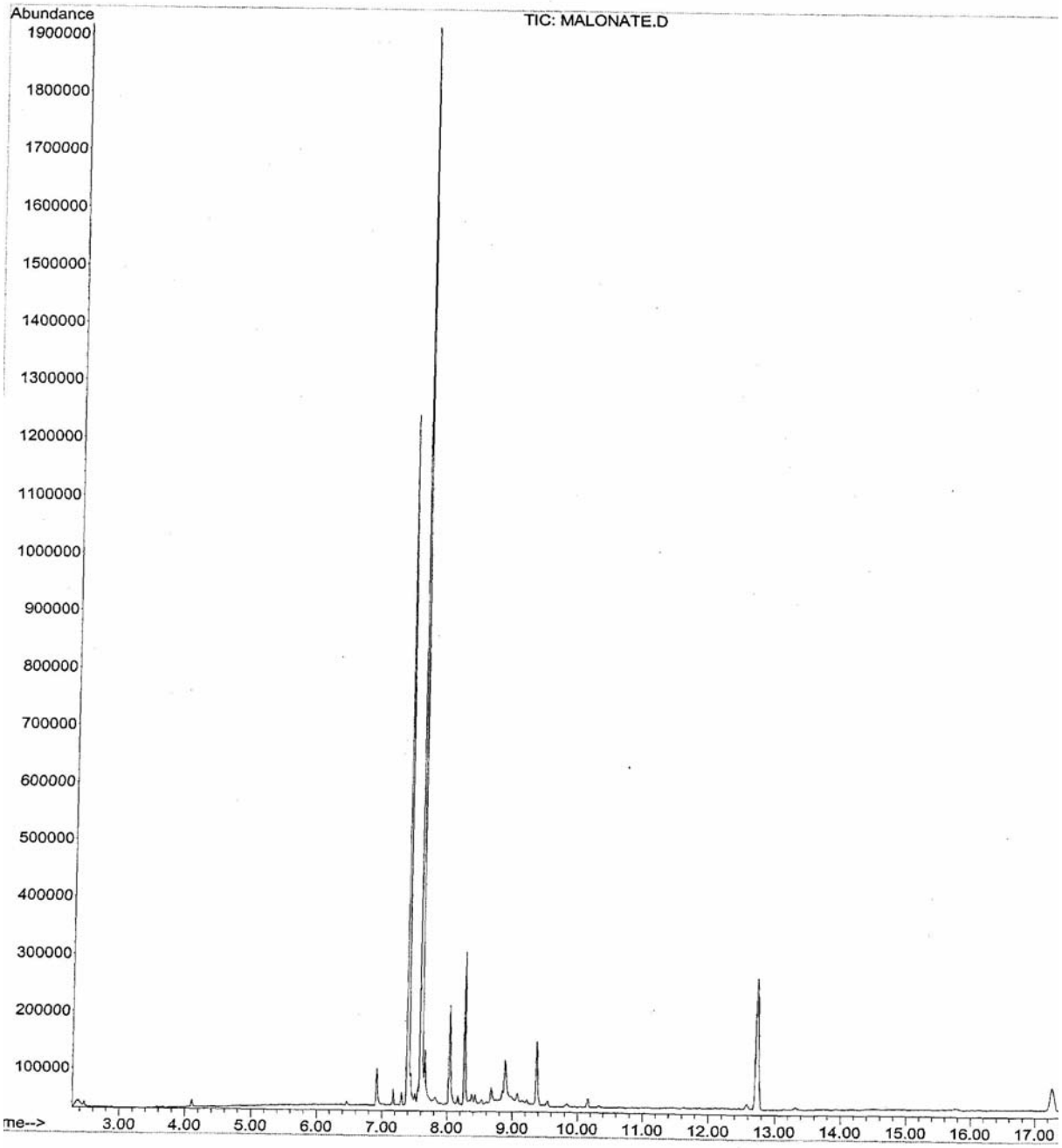


Appendix I. Infrared Spectrum of 1,3-Dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene(2Spiro-5)2,2-di-*tert*-butyl ester.



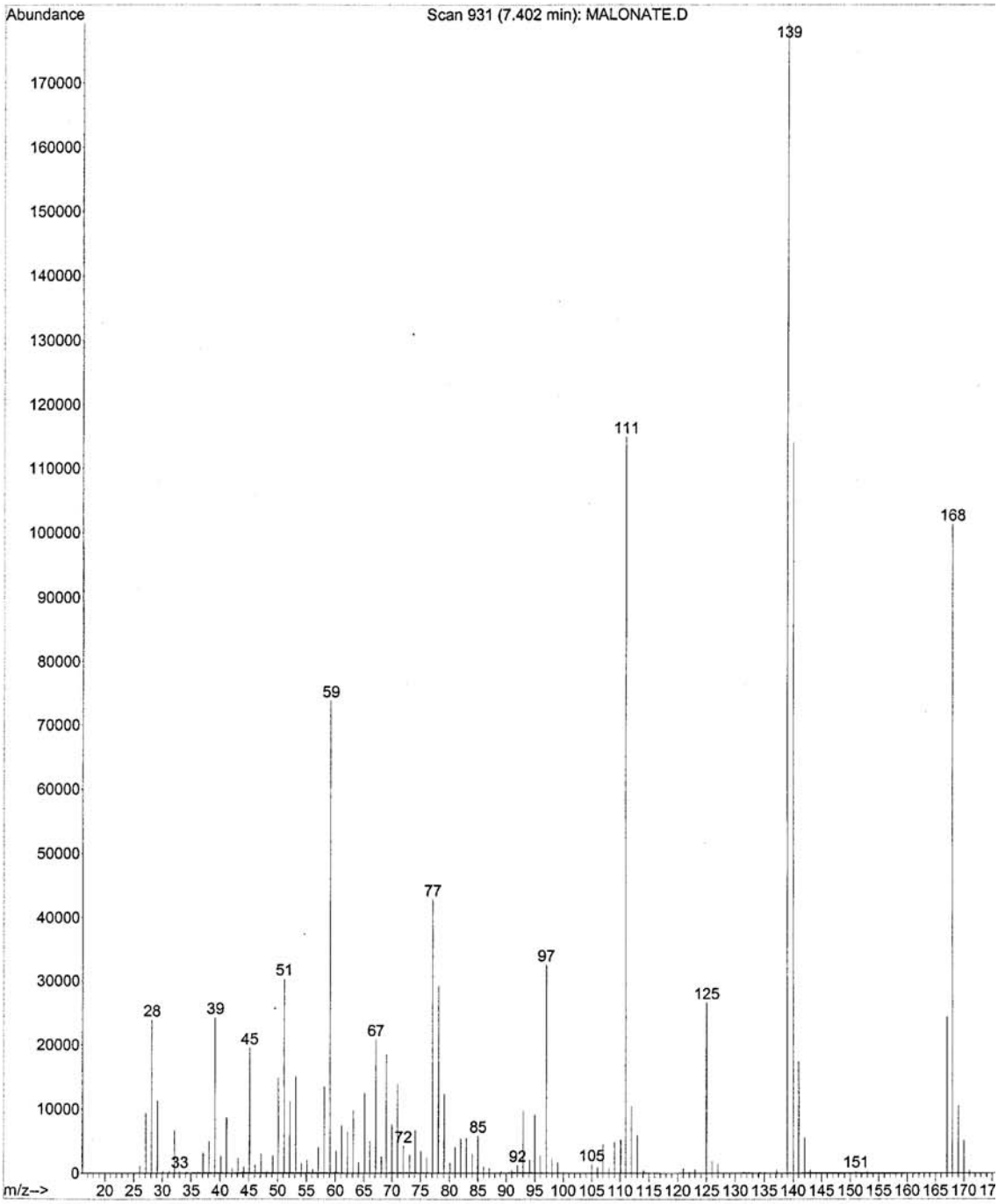
Appendix J. Gas Chromatogram of 1,3-Dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene(2Spiro-5)2,2-di-*tert*-butyl ester in Mass Spectrometer.

```
File       : D:\RILEY\MALONATE.D
Operator   : Riley
Acquired   :  9 Mar 2006  15:04      using AcqMethod JPCMS
Instrument :   5973 MSD
Sample Name: roomtemp in hcl
Misc Info  :
Vial Number: 1
```



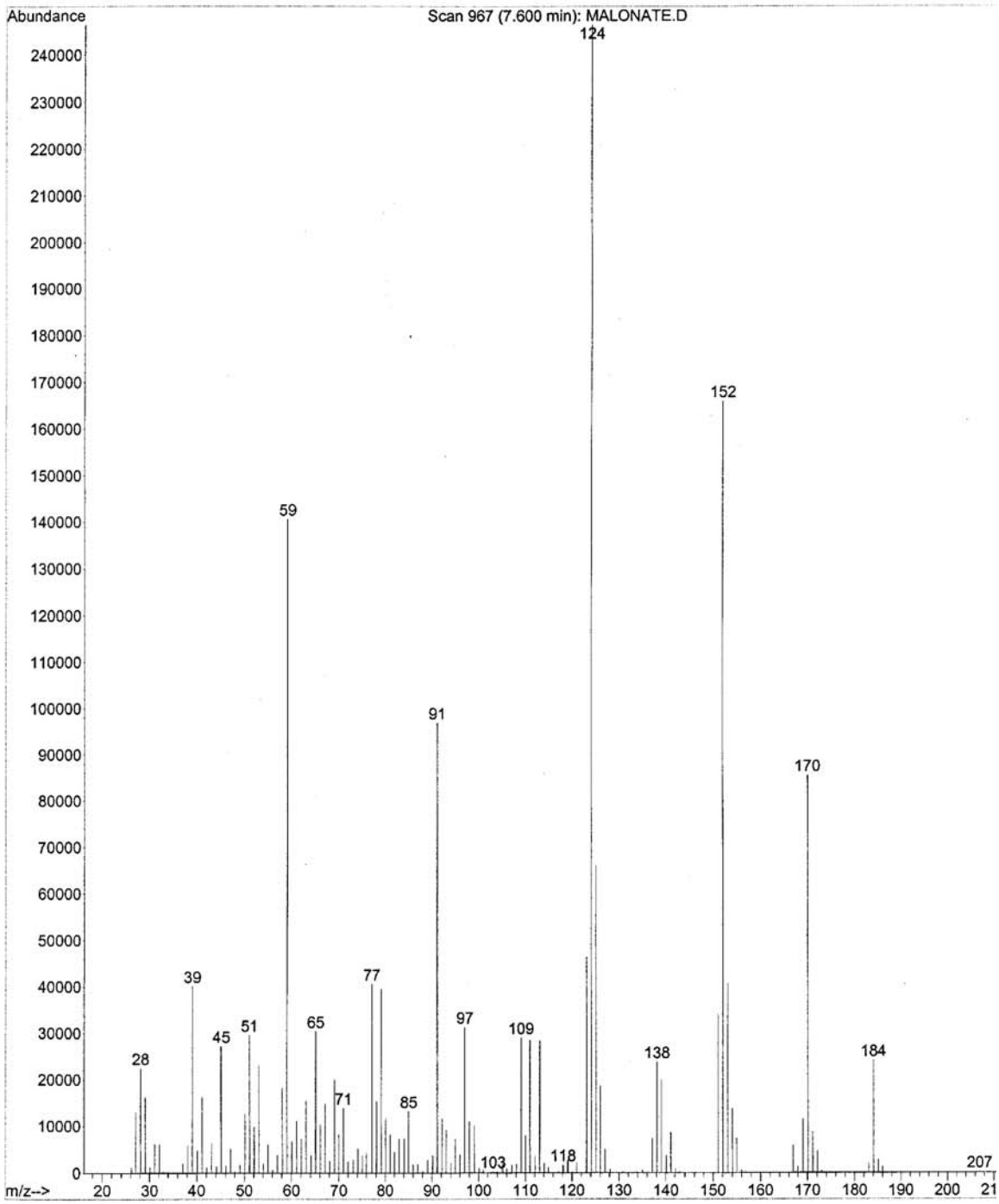
Appendix K. Mass Spectrogram (1) of 1,3-Dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene(2Spiro-5)2,2-di-*tert*-butyl ester.

```
File       : D:\RILEY\MALONATE.D
Operator   : Riley
Acquired   :  9 Mar 2006  15:04     using AcqMethod JPCMS
Instrument :   5973 MSD
Sample Name: roomtemp in hcl
Misc Info  :
Vial Number: 1
```



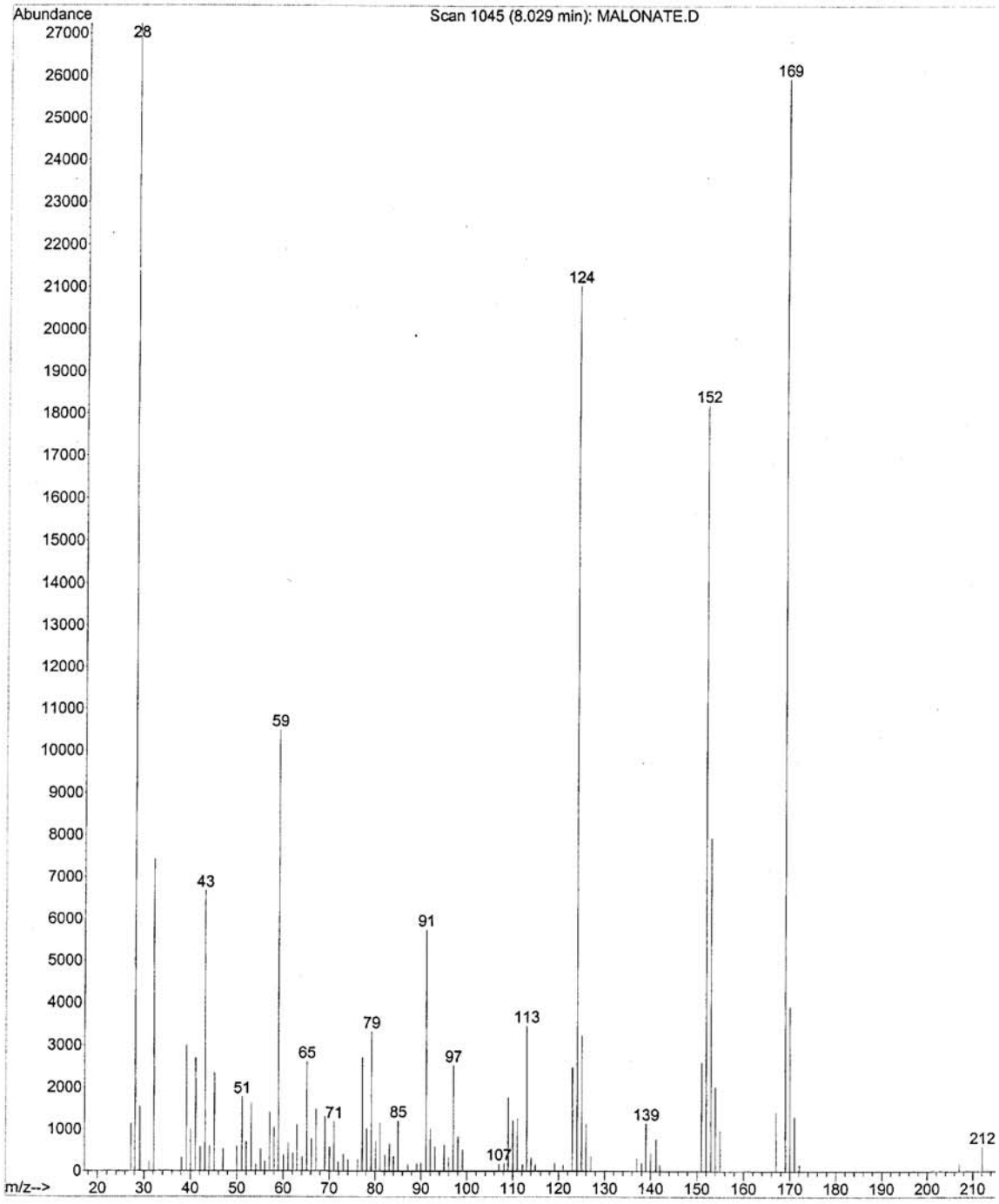
Appendix L. Mass Spectrogram (2) of 1,3-Dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene(2Spiro-5)2,2-di-*tert*-butyl ester.

```
File       : D:\RILEY\MALONATE.D
Operator   : Riley
Acquired   :  9 Mar 2006  15:04     using AcqMethod JPCMS
Instrument :   5973 MSD
Sample Name: roomtemp in hcl
Misc Info  :
Vial Number: 1
```



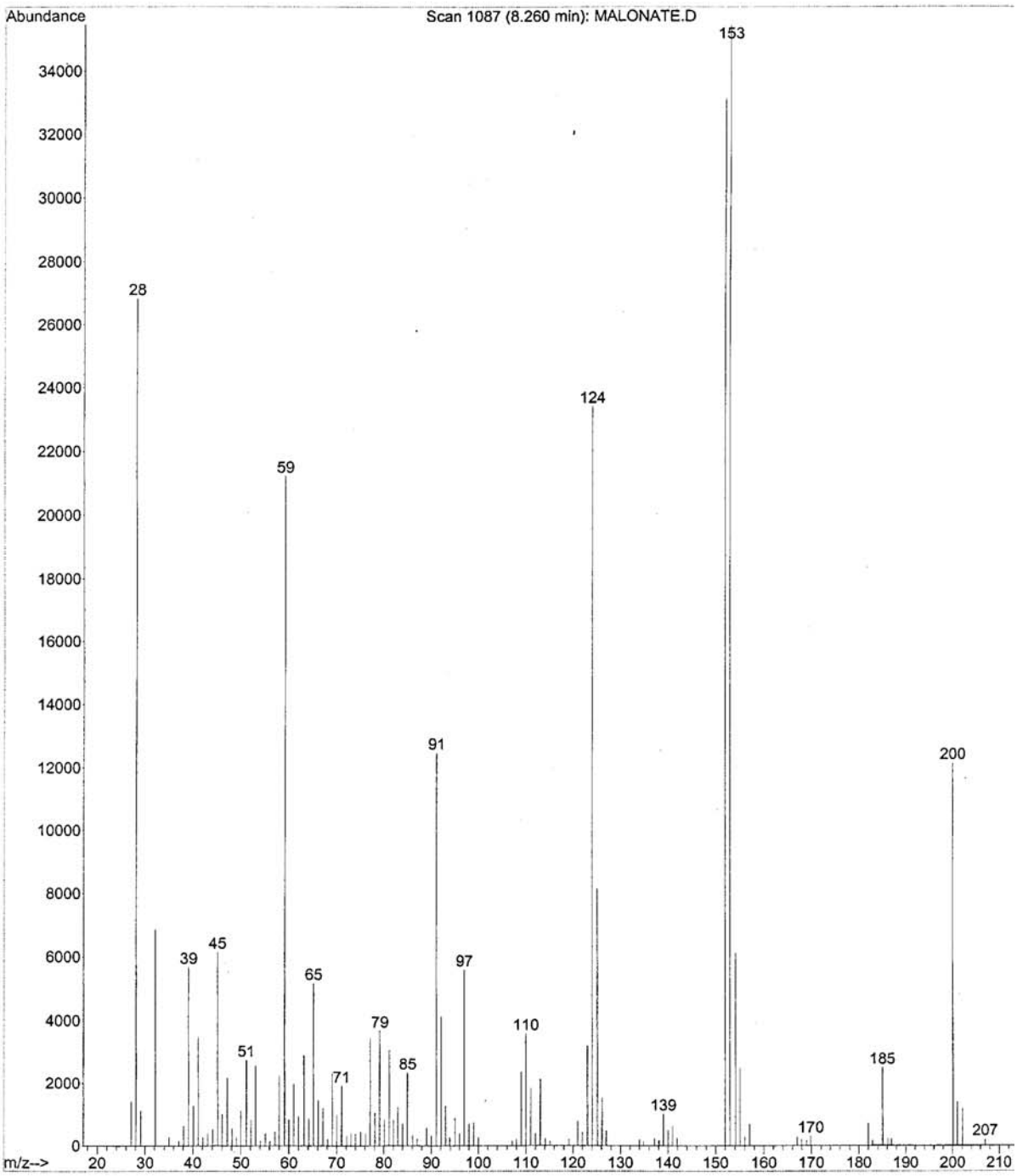
Appendix M. Mass Spectrogram (3) of 1,3-Dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene(2Spiro-5)2,2-di-*tert*-butyl ester.

```
File       : D:\RILEY\MALONATE.D
Operator   : Riley
Acquired   :  9 Mar 2006  15:04     using AcqMethod JPCMS
Instrument :   5973 MSD
Sample Name: roomtemp in hcl
Misc Info  :
Vial Number: 1
```



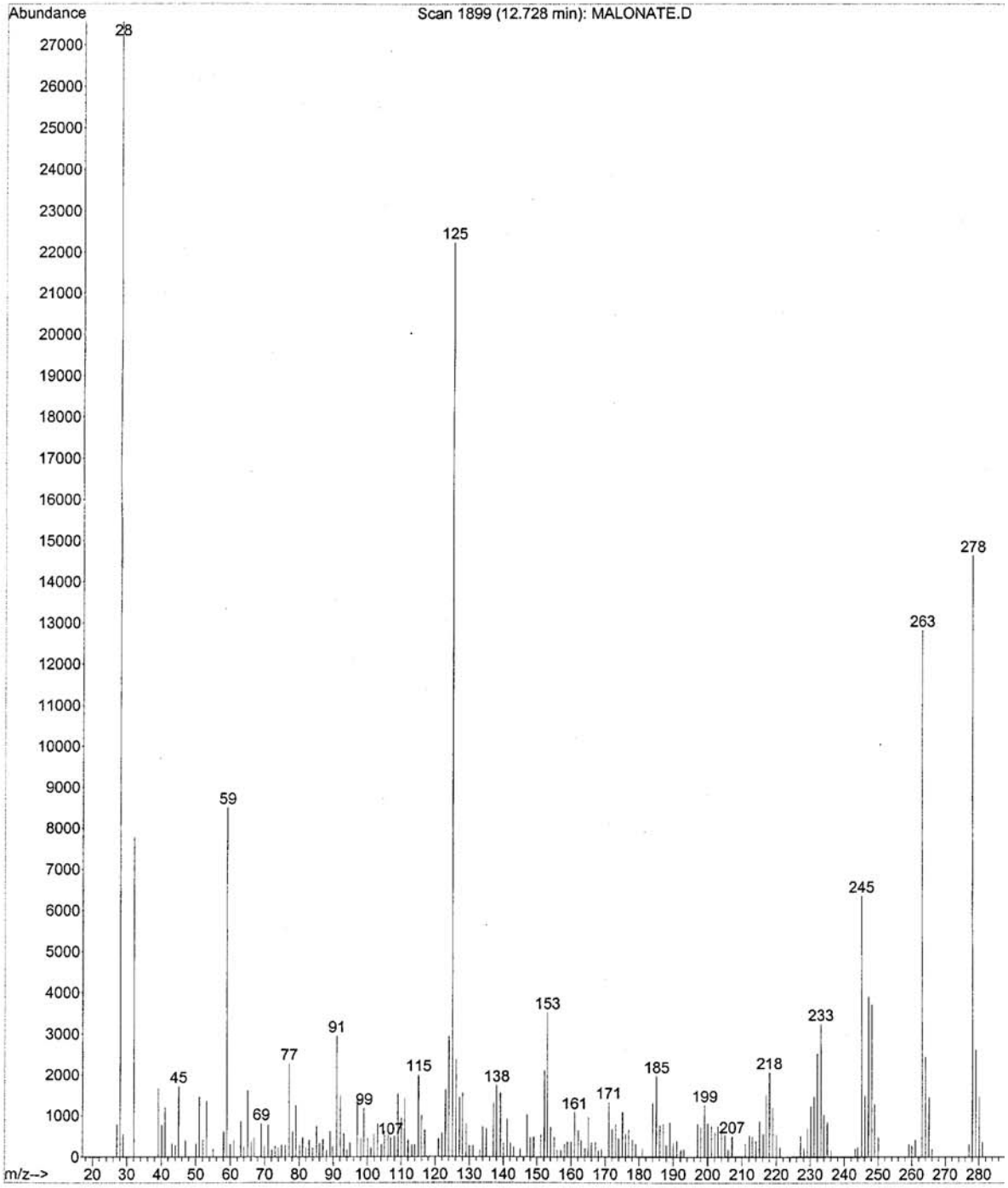
Appendix N. Mass Spectrogram (4) of 1,3-Dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene(2Spiro-5)2,2-di-*tert*-butyl ester.

```
File       : D:\RILEY\MALONATE.D
Operator   : Riley
Acquired   :  9 Mar 2006  15:04     using AcqMethod JPCMS
Instrument :   5973 MSD
Sample Name: roomtemp in hcl
Misc Info  :
Vial Number: 1
```



Appendix O. Mass Spectrogram (5) of 1,3-Dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene(2Spiro-5)2,2-di-*tert*-butyl ester.

```
File       : D:\RILEY\MALONATE.D
Operator   : Riley
Acquired   :  9 Mar 2006  15:04     using AcqMethod JPCMS
Instrument :   5973 MSD
Sample Name: roomtemp in hcl
Misc Info  :
Vial Number: 1
```



Vita

The author was born in Lake Charles, Louisiana, on August 12, 1983. He graduated from Larry A. Ryle High School in Union, Kentucky, in May of 2002. In the fall of that year he enrolled at Western Kentucky University in Bowling Green, Kentucky where he graduated with a Bachelor of Science degree in Chemistry *cum laude* with honors on December 16, 2006. While at Western Kentucky University, he was awarded numerous academic scholarships and earned several academic and professional distinctions including an internship through the American Association of Medical Colleges and the Robert Wood Johnson Foundation at Vanderbilt University's Department of Surgical Sciences. He is a member of the American Chemical Society, Golden Key International Honours Society, and the Kappa Sigma Fraternity. He is pursuing a career as a physician and hopes to specialize in orthopedic or plastic surgery.

Presentations resulting from the thesis research:

Nov. 2006 **"Alternative synthetic route to cyclopenta[*c*]thiophenes via 1,3-dithiane"** Poster presentation of a potential new synthesis of cyclopenta[*c*]thiophene precursor molecules that will provide chemists with two new approaches to fused ring closure in high bond angle strain systems. Jones, R. G., Snyder, C. A., Southeastern Regional Meeting of the American Chemical Society, Augusta, GA, November 1-4th, 2006.

Sept. 2006 "**Recent advances in cyclopenta[*c*]thiophene synthesis."** A continuation of the work presented at the Feb. 2006 honours roundtable forum, this presentation detailed data and syntheses developed in continuation of previous honours thesis work with malonate ester synthesis of thiapentalenes. Notably, the first report of the novel synthesis of the compound 3,4-(bis)hydroxymethyl-2,5-dimethylthiophene and thiapentalene synthesis using 1,3-dithiane. Morehead, KY. September 30, 2006. Jones*, Riley G., Snyder, Chad A.

Sept. 2006 "**Thiapentalene precursors via *t*-butyl malonate esters."** Poster presentation detailing research findings of new methods for leukemia fighting cyclopenta[c]thiophene molecules at the 232nd American Chemical Society national fall meeting in San Francisco, CA. September 14th, 2006. Jones*, Riley G., Snyder, Chad A.

Feb. 2006 "**Current Investigations in Cyclopenta[c]thiophene Chemistry"** Round Table forum of Kentucky Colleges Honours Researchers at the University of Kentucky, February 24, 2006. Presented the results of present research studies and also discussed future avenues of research with faculty and other honours students from around the state. Advisor: Craig T. Cobane

Nov. 2005 "**Proposed Two-Step Synthesis for Cyclopenta[*c*]thiophenes"** 91st Kentucky Academy of Sciences meeting, Eastern Kentucky University, Richmond, Ky, November 10-12, 2005. Jones*, Riley G., Sananikone, Ann P., James, Amanda L., Canty, Sarah R., Ford, Stephen C., Fielding, Cory M., Snyder**, Chad A.