SYNTHESIS OF NORDIHYDROGUAIARETIC ACID DERIVATIVES VIA SUZUKI AND STILLE CROSS-COUPLING REACTIONS AND SUBSEQUENT RANEY NICKEL DESULFURIZATION AND REDUCTION

by

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A Thesis Submitted in Partial Fulfillment
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Master of Science in Chemistry

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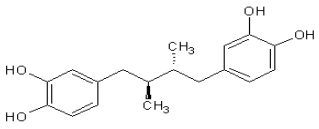
Chapter I

1.0 Introduction

Nordihydroguaiaretic acid (NDGA) is a plant hormone, more specifically a lignan type phytoestrogen, that has garnered continued interest due to its antioxidant and pharmacologic properties.



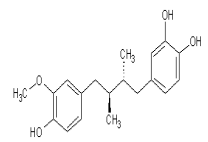
(Figure 1 – NDGA CAS # 500-38-9)

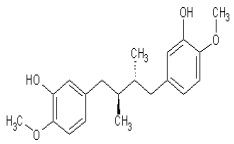
(Figure 2 – *Larrea tridentata*)

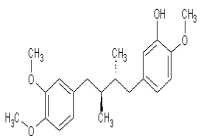
NDGA is produced naturally by *Larrea Tridentata* (i.e. creosote bush or chaparral) of the family Zygophyllaceae.[1] This resinous plant native to the south-west United States and northern Mexico is a flowering woody shrub preferring alkaline soils and arid climates. Indigenous tribes have employed the plant preparations to treat chicken pox, skin sores, diabetes, kidney and gallbladder stones, cancer, venereal disease, tuberculosis, colds, and rheumatism.[2] Early scientific publications by C. W. Waller identify NDGA as the major secondary plant metabolite comprising approximately 10-15% of the dry leaf weight and about 50% of phenolic resin extracted from external leaf surface.[1,2] During the 1950s NDGA's properties as an anti-oxidant were exploited to preserve butter and edible oils.[2] However, during the 1960s concerns over reported toxicity led to the cessation of its use in ingested products, and it was removed from the FDA's generally recognized as safe (GRAS) list in 1970. Notwithstanding it is still employed as a preservative in natural and synthetic rubber, and was used for a brief period of time as the active pharmaceutical ingredient in the anti-viral herpes medicine Actinex®.[1,2]

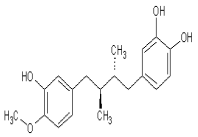
Continued interest in *Larrea* and NDGA led to extensive study by Mabry, Sakakibara, Konno, and Obermeyer that identified several structurally similar lignan extracts including guaiaretic acid and its substituted derivatives, furanoid lignans, and aryl tetralin lignans.[2-5] These molecules along with many other structurally related molecules including chalcones and catechols have been the subject of numerous research publications in the last decade mainly exploring their use as anti-oxidant, anti-inflammatory, anti-viral, or anti-neoplastic agents as well as continued exploration of their toxicological effects.[2-6]

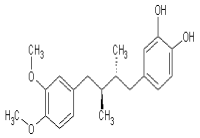
More recently some naturally derived as well as some semi-synthetic methylated derivatives of NDGA have been the subject of increased scrutiny as possible anti-viral and anti-neoplastic agents.[7-9]

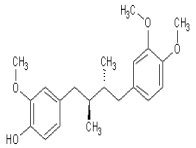
1. 

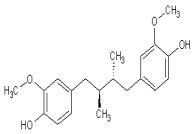
4. 

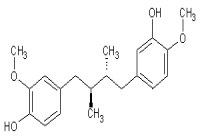
7. 

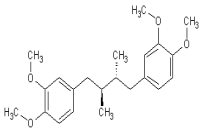
2. 

5. 

8. 

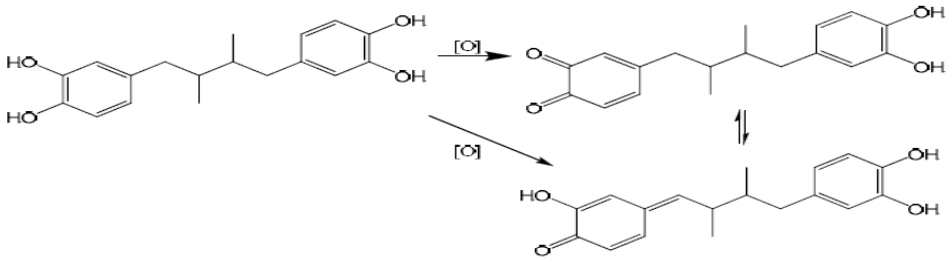
3. 

6. 

9. 

(Figure 3 – IC_{50} *tat*-regulated HIV transactivation values: (1.) 25.03 +/- 2.77 (2.) 30.81 +/- 3.88 (3.) 38.98 +/- 9.13 (4.) 29.88 +/- 7.22 (5.) 16.52 +/- 1.51 (6.) Not Enough for Test (7.)13.66 +/- 5.44 (8.) 14.31+/- 1.39 (9.) 11.09 +/- 2.14)

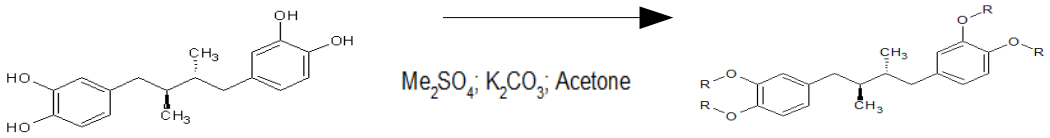
R. C. Huang et al. assayed the activity of eight semi-synthetic NDGA derivatives as possible inhibitors of tat-regulated HIV transactivation after noting that a singly methylated naturally occurring version (Figure 3 - Number 1) demonstrated inhibitory effects.[7] Several papers were published and an Investigational New Drug (IND) patent application was submitted to the FDA in the subsequent years focusing mainly on the *meso* tetra-methylated derivative (CAS # 24150-24-1, M4N, EM-1421, or Terameprocol®) as a possible pharmaceutical agent. At that time it was believed that the lipid solubility of a compound is directly related to its cell permeability (Overton's rule). Therefore M4N, not the other derivatives, demonstrated physical characteristics most compatible with lead drug candidate development. In recent years Overton's rule has been questioned and results seem to indicate that lipid solubility may not be able to accurately predict the cell permeability of a molecule.[7-9] In fact research trials indicate that formulated M4N products are absorbed into exposed tissues at a rate that is less than desirable.[9] It should be noted that M4N has proven effective in xenograft tumor models and is well tolerated as adverse events observed subsequent to administration were transient and not life threatening.[7-9] For example mice given intraperitoneal injections over a two week period at the rate of 300mg/kg body weight demonstrated no weight loss in stark contrast to results observed with NDGA where the LD_{50} is 75mg/kg intraperitoneal injection.[7-9] It has been suggested that auto-oxidative products of NDGA (Figure 4 - *ortho* and/or *para* quinones) may be the reason for increased toxicity, and that substitution of the hydroxyl moiety decreases the rate at which those species form.[2]



(Figure 4 – Oxidative Products: *Ortho* – Top, *Para* - Bottom)

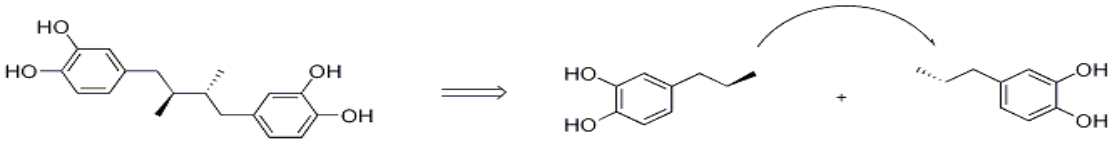
1.1 Synthetic Strategies for the Production of NDGA Derivatives

Naturally extracted NDGA has quite frequently been the substrate in substitution reactions due to its ready availability. However the products are generally a mixture of not easily separable isomers as the starting material has four relatively equally acidic hydroxyls that may be modified (Scheme 1).[7]

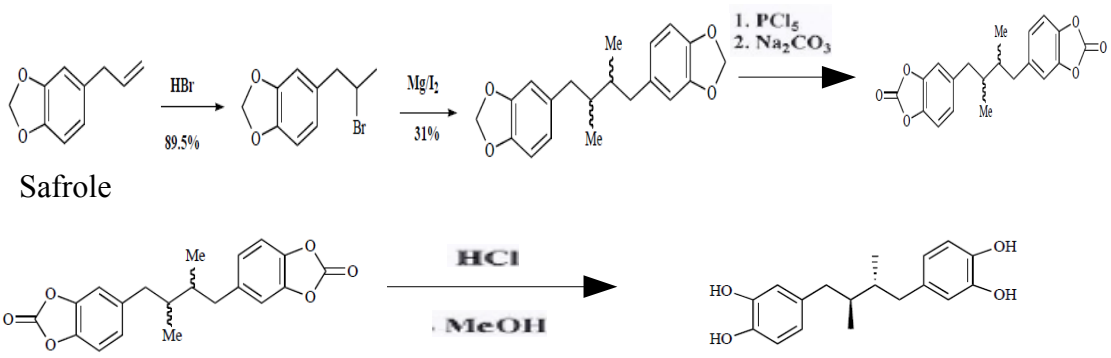


(Scheme 1 – Methylation of NDGA, Mixture of Products: R = Me or H)

This has led to the development of several synthetic protocols to generate specific NDGA derivatives that are more easily purified for biological assay. A common approach forms the desired product by coupling two nearly equivalent halves by a variety of reactions (Figure 5), and an early method couples safrole derivative 1-piperonyl-2-bromopropane using magnesium and iodine with 31% reported yield of diastereomeric dimer products

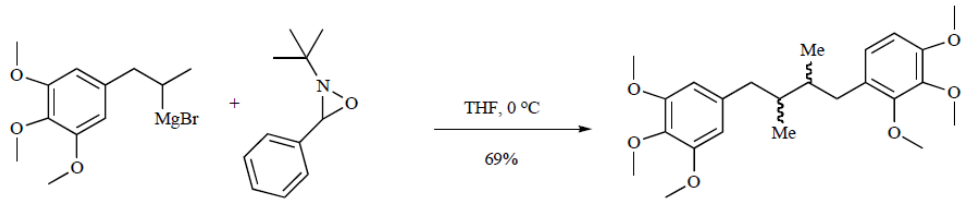


(Figure 5 – Retrosynthetic Approach 1)



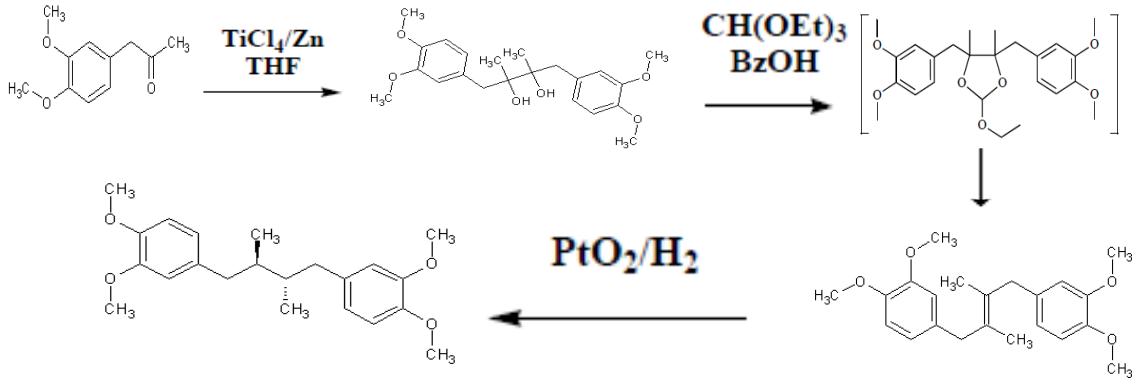
(Scheme 2 – Lieberman Synthesis of NDGA)

(Scheme 2).[10] This reaction was also attempted with sodium or zinc in benzene and copper-bronze in decalin to no avail. The dimer product was then treated with phosphorous pentachloride followed by base to produce a dicarbonate ester. Saponification with hydrochloric acid in methanol yielded NDGA however the overall process was relatively low yielding.[10] Improvements to the Grignard reagent dimerization have been made by incorporation of 2-t-butyl-3-phenyloxaziridine as a catalyst increasing yield yet still producing a diastereomeric mixture of products (Scheme 3).[10,11]



(Scheme 3 – Improved Dimerization Reaction)

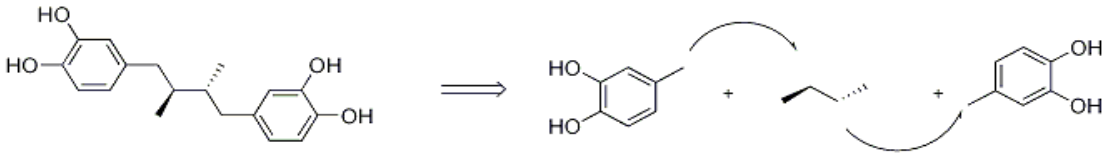
The McMurry coupling has also been utilized by Gezginci and Timmerman to effect a dimerization that ultimately yields NDGA.[10,12] The standard coupling conditions were not successful in producing the expected olefin product instead yielding a diol that was modified to an un-isolated orthoester with triethyl orthoformate and benzoic acid catalyst at 100ºC for 2 hours (Scheme 4 – Top). The reaction mixture was then heated



(Scheme 4 – McMurry Coupling)

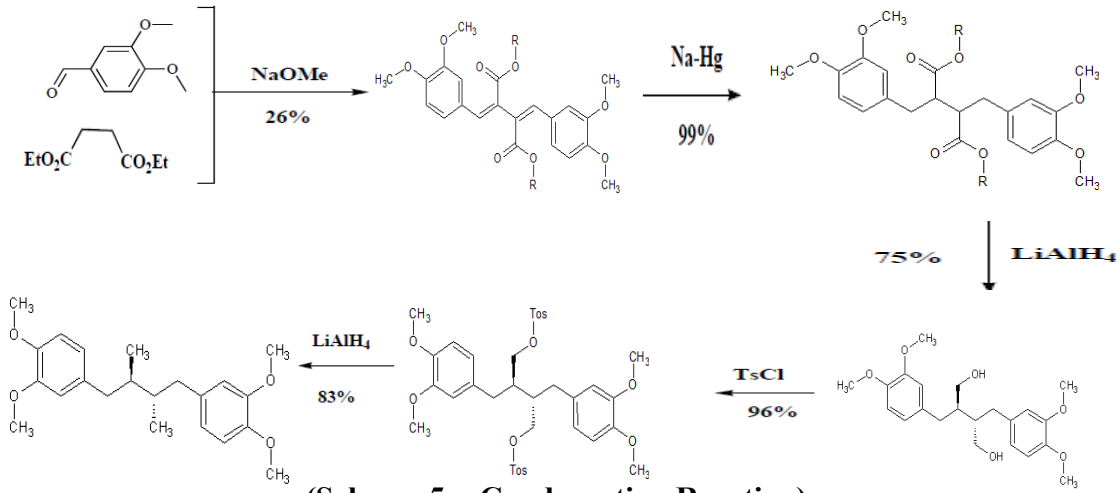
to 180ºC for 4 hours followed by chromatographic separation. Overall the reaction scheme produced a 48% yield of a 4:6 ratio of *cis* and *trans* isomers. Reports indicate the isomers were readily separated by recrystallization in ethanol, and subsequently hydrogenated with platinum black in ethyl acetate over 1 hour (Scheme 4 - bottom).[12] In this instance the hydrogenated products were de-methylated with the Lewis acid boron tribromide in methylene chloride at -78ºC by warming to room temperature to produce NDGA.[12] The McMurry type coupling scheme was also employed by Son et al. and Chang et al.[10]

A second approach to NDGA synthesis combines three separate molecules (Figure 6) and is the method first used in confirming the *meso*- configuration of the butyl chain



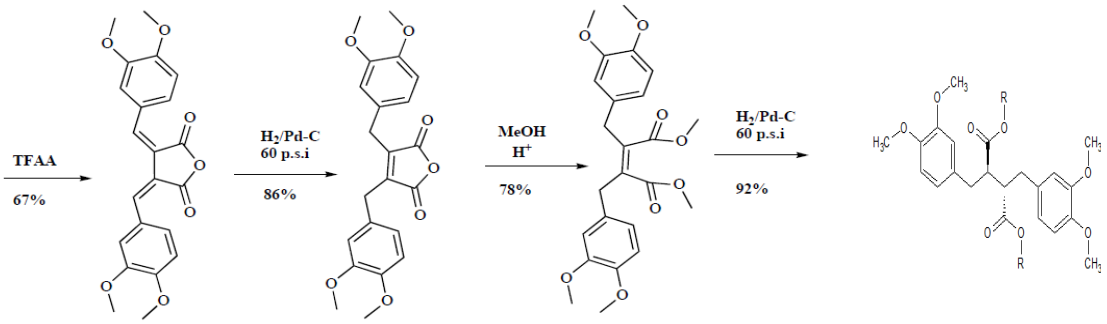
(Figure 6 – Retrosynthetic Approach 2)

tethering the two rings.[13] A condensation of two molecules of veratraldehyde and diethyl succinate with sodium methoxide base was reported by Schrecher *et al.* to produce diveratrylidenesuccinic acid in a 26% yield (Scheme 5).[14]



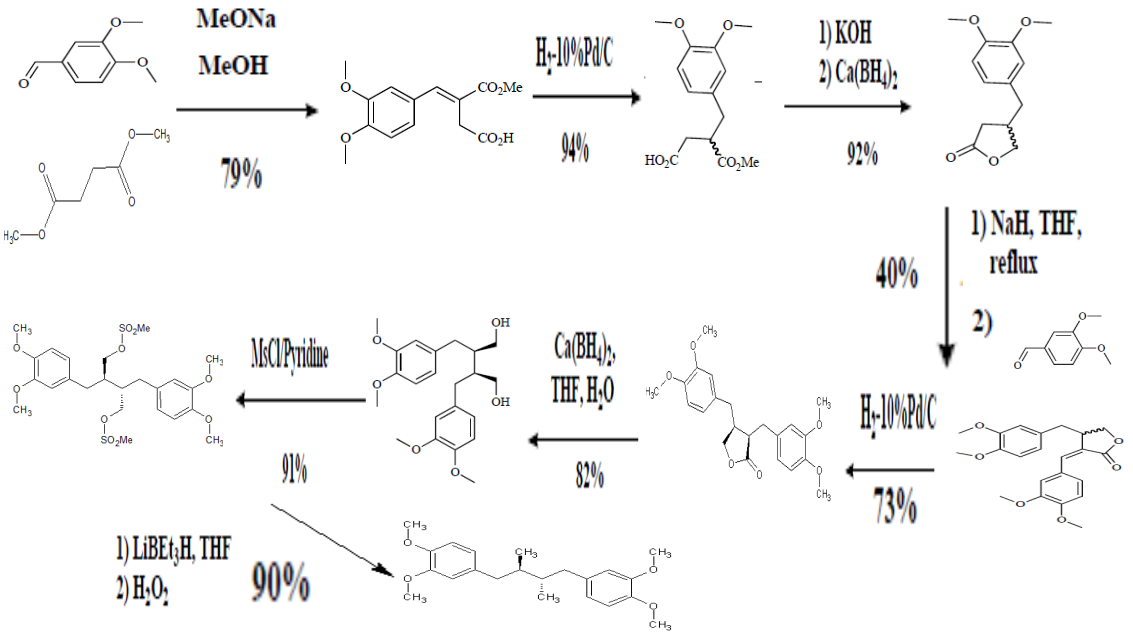
(Scheme 5 - Condensation Reaction)

The sodium-mercury amalgam mediated reduction was originally reported to produce the *meso*- form specifically, however subsequent efforts by Xia *et al* indicated that the reaction generated a 2:1 mixture of *meso*:*threo* isomers.[10] An alternative reaction sequence forms the *meso*- isomer specifically from diveratrylidenesuccinic acid by initially reacting with TFAA to create an anhydride that is then reduced in a step-wise



(Scheme 6 – Step-wise Reduction to form *meso*-diveratrylsuccinic acid)

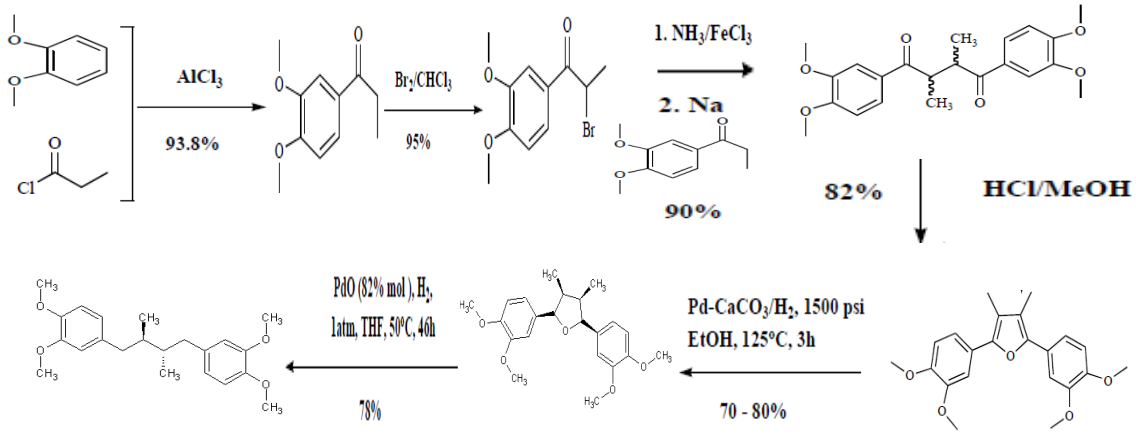
manner (Scheme 6).[15] Once the appropriate isomer has been isolated the desired product may be accessed in just a few steps by reacting with $LiAlH_4$ and tosyl chloride (Scheme 5 -bottom). A similar method that utilizes retrosynthetic approach 2 involves the Stobbe condensation of veratraldehyde and a dialkylsuccinate. The reactant ratio is 1:1 and the product is an unsaturated hemiester that is manufactured in 79% yield (Scheme 7).[16]



(Scheme 7 – Stobbe Condensation)

This reaction is then followed by reduction and cyclization generating a species that combines with veratraldehyde in a second Stobbe condensation to produce an unsaturated lactone in 40% yield. Catalytic hydrogenation over 10% Pd/C will then produce an exclusively *cis*-lactone that is readily converted to the desired product. The lactone is first reduced with $Ca(BH_4)_2$ in THF/H_2O to produce the diol substrate for a mesylation reaction. The mesylated species is then combined with $LiBEt_2H$ in THF to producing an NDGA derivative.

Another stereo-selective route to NDGA derivatives employed by Perry *et al* in 1972 makes use of retrosynthetic approach 2, and begins with a high yielding acylation of veratrol (Scheme 8).[17]

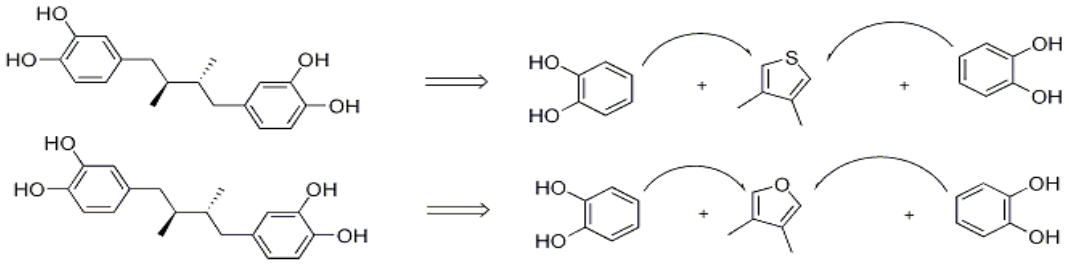


(Scheme 8 – NDGA from High Pressure Hydrogenation Reaction)

The 3,4-dimethoxy propriophenone generated from the acylation reaction is then brominated in high yield to produce an alpha halo ketone. The two ketones are subsequently coupled together by sodium amide in ammonia solvent at -33ºC using ferric chloride as a catalyst to produce a racemic mixture of products.[17] A furanoid type lignan

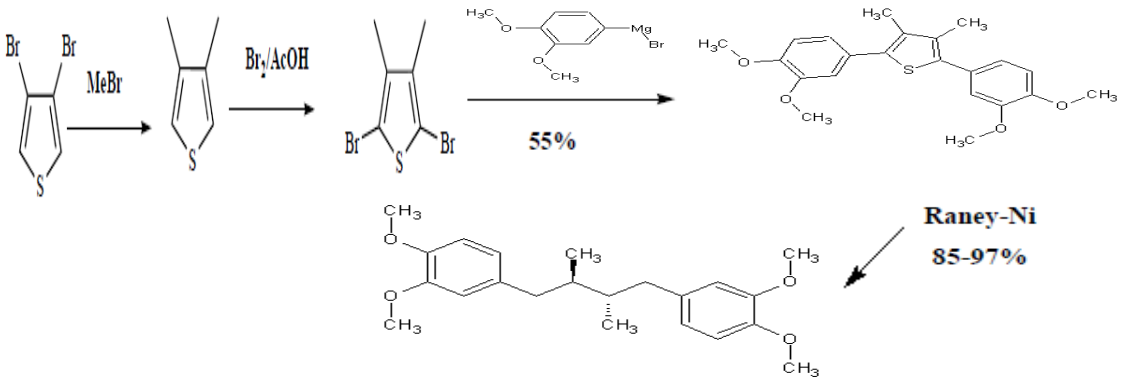
is then manufactured by refluxing in 1% HCl/MeOH to induce a cyclo-dehydration. High pressure hydrogenation over palladium catalyst transforms the furanoid species into an all *cis*-cyclic ether that will generate the desired NDGA derivative when submitted to a second catalytic hydrogenation procedure that lasts for two days.

A third retrosynthetic appoach focusing on cross-coupling reactions involving furans and thiophenes is outlined in Figure 7. This method was employed by Minato *et al* in 1980 to produce



(Figure 7 – Retrosynthetic Approach 3)

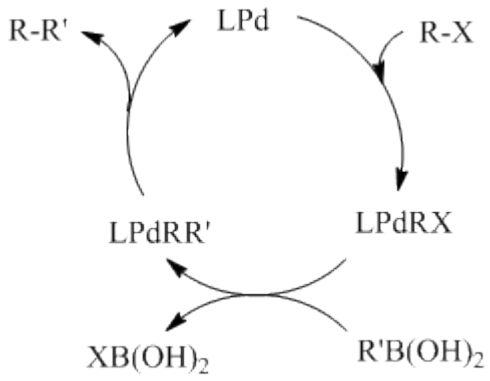
substrates for ring opening reactions similar to those previously discussed involving furanoid intermediates (Scheme 9).[18] The reaction sequence is initiated by methylating 3,4 dibromo thiophene to set the stage for a halogenation that will provide the substrate



(Scheme 9 – NDGA Derivatives from Cross-coupling Reaction)

necessary for the cross-coupling reaction. In this instance a Grignard reagent is employed to synthesize the 2,5 diaryl thiophene that will be subjected to a Raney-nickel mediated ring-opening reported to produce a mixture of isomers. Cross-coupling reactions have been extensively studied in the years following the utilization of this reaction scheme and more modern protocols may provide an improvement over the original techniques.

Palladium mediated cross-couplings have benefited from recent study in that an accepted reaction mechanism (Figure 8) has been developed along with protocols that offer high yields and predictable selectivity.[19,20] Mechanistically these palladium

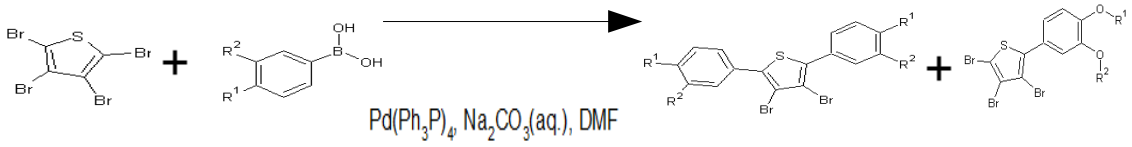


(Figure 8 – Cross-coupling Reaction Mechanism)[28]

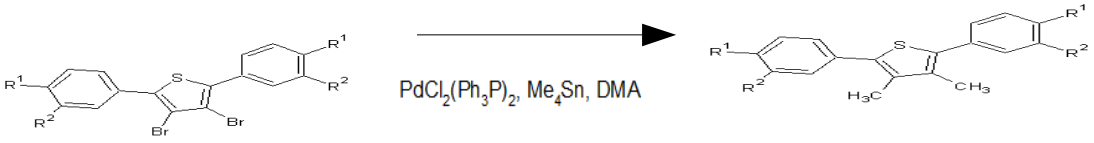
catalyzed reactions have three basic steps oxidative addition (generally the slowest step), transmetalation (sometimes the slowest step), and reductive elimination (rapid). In the final step the palladium catalyst is released so that it may undergo another round of reactions.

1.2 Current Research

The predictability of selectivity in organopalladium chemistry employed to generate carbon-carbon bonds between polyhalogenated heteroaromatic compounds and their cross-coupling partners allow for efficient production of NDGA derivatives. Suzuki couplings between tetrabromo thiophene and arylboronic acids reliably generate substrates for Stille carbon-carbon bond forming reactions (Scheme 10).[19,20] Several methods for desulfurization and reduction of tetra-substituted thiophenes



Suzuki Coupling Scheme



Stille Coupling Scheme

(Scheme 10 – Suzuki Coupling and Stille Coupling)

have been published, and a number of these methods were evaluated toward producing the desired end products. Raney nickel under an atmosphere of hydrogen gas in a Parr hydrogenator, highly activated Raney nickel in alcohol, and nickel boride generated *in-situ* from nickel chloride and sodium borohydride in a number of solvent systems were each tested en route to manufacturing substituted NDGA (Scheme 11).[21-25] The primary focus of this research is the synthesis of NDGA derivatives from tetrabromo thiophene.

(Scheme 11 – Nickel Desulfurization and Reduction)

Chapter II

2.0 Experimental

2.1 Materials

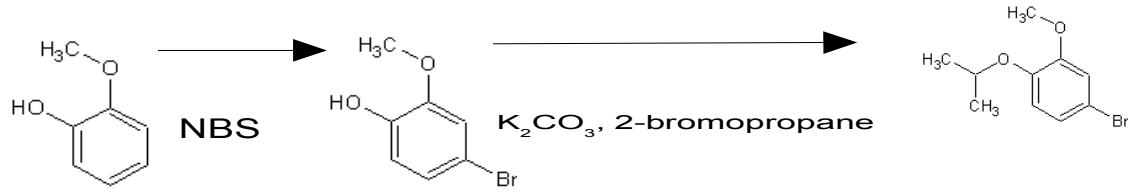
The following were obtained from Sigma-Aldrich: 99% N-bromosuccinimide (NBS), 99.8% N,N-dimethylamide (DMF), 99.9% dichloromethane, 99% tetrabromothiophene, 99% Tetrakis(triphenyl phosphine) palladium (0), 99+% N-methyl pyrrolidinone (NMP), 98% dichlorobis(triphenyl phosphine) palladium (II), 95% Tetramethyl tin, 99+% tert-butyl methyl ether, Raney 2800 nickel slurry in water, 99% sodium borohydride, chromasolv ethanol for HPLC, >99.8% chloroform, 2.5 molar butyllithium in hexanes. These materials were obtained from Fisher Scientific: laboratory grade ethyl ether, 99.0% magnesium sulfate, 99.4% sodium hydroxide, 99+% tetrahydrofuran (THF), certified A.C.S. Sodium carbonate, 100.4% nickel chloride hexahydrate. Acros Organics supplied: 99% 2-bromopropane, 99+% guaiacol, 99.7% anhydrous methyl sulfoxide (DMSO), 99.5% ammonium chloride, Whatman #1 qualitative 90mm diameter filter paper. Unless synthesized in-house all boronic acids were 97+% and sourced from Frontier Scientific. Bulk A.C.S. reagent grade hexanes, ethylacetate and methanol were obtained from Pharmco-Aaper. Silica gel (230-400 mesh) for flash chromatographic separations was purchased from Natland International Corporation. Thin layer chromatography (TLC) was performed on silica gel F coated on aluminum plates from Analytech. Nuclear magnetic resonance (NMR) analysis was performed in 99.8% deuterated chloroform sourced from Cambridge Isotope Labs without exception. Aqueous pH was tested with Phydrion pH 1 to 12 paper strips.

2.2 Equipment

All Suzuki coupling reactions were performed on a J-Kem Scientific orbital shaker at 125 oscillations per minute (o.p.m.) and 80 degrees Celsius. Solvents were evaporated on a Buchi R200 rotary evaporator under reduced pressure. Masses were recorded from a Sartorius A/C 210-S balance. All ^{1}H and ^{13}C NMR spectra were collected using a JEOL AS 500MHz NMR and chemical shifts are reported in parts per million (ppm) using tetramethylsilane (TMS) as a reference. Infrared spectrographic analysis was conducted on a Varian 800 FT-IR either neat or with deuterated chloroform as a vehicle.

2.3 Methods

2.3.1 Bromination and Protection of Guaiacol[27]



(Scheme 12 – Bromination and Protection of Guaiacol)

A solution of 5.036 g (0.041 mol) guaiacol in 25.0 mL DMF was cooled in a 0.0°C ice bath for 15 minutes, and then a solution of 7.258 g (0.041 mol) NBS in 25.0 mL DMF was added dropwise with stirring over 30 minutes turning the guaiacol solution a nice shade of red. After stirring for an additional 30 minutes the reaction was quenched with 150.0 mL of ice cold water and allowed to warm to room temperature. The desired product was then extracted with diethyl ether, dried over magnesium sulfate, filtered through a #1 filter paper, and the ether evaporated on a rotary evaporator. The purple oil produced was then separated by flash column chromatrography. The unreacted starting material has an R_f of 0.61, and the desired product material has an R_f of 0.55 in a 3:1 mixture of hexanes to ethyl acetate. After collecting the brominated product and drying by rotary evaporation a crude product weight of 6.97 g (85.00%) was observed. This product was not subjected to additional analytical testing. 6.97 g (0.034 mol) of 1-bromo-3-methoxy-4-hydroxy benzene was combined with 9.785 g (0.071 mol) potassium carbonate were combined with 100.0 mL of DMSO and mixed prior to the addition of 4.9 mL (0.052 mol) 2-bromopropane turning the 1-bromo-3-methoxy-4-hydroxy benzene solution from brown to green. The reaction was heated to 62.0 °C over 2.5 hours and

then allowed to cool to room temperature where it again obtained a brownish hue. The product mixture was diluted with water and then extracted with tert-butyl methyl ether. The ether layer was dried over magnesium sulfate and filtered through a #1 filter paper before drying on a rotary evaporator. The oil obtained was purified by flash column chromatorgraphy using 3:1 hexanes to ethyl acetate having an R_f of 0.66. Upon collection and drying by rotary evaporator 5.00 g (0.020 mol) of 1-bromo-3-methoxy-4-isopropoxy benzene was produced in 59.0% yield. The isopropoxy protecting group should easily be removed with boron tribromide although that assertion was not tested.[26]

2.3.2 Synthesis of Phenyl Boronic Acid[27]

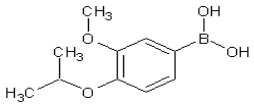
(Scheme 13 – Synthesis of Boronic Acid)

5.00 g of 1-bromo-3-methoxy-4-isopropoxy benzene was diluted with 100.0 mL of THF in a 500 mL round bottom flask, equipped with a magnetic stir bar and then purged with argon gas. The reaction vessel was then cooled in a -78°C dry ice/acetone bath prior to adding 8.5 mL of a 2.5 molar solution of n-butyl lithium in hexane dropwise. Once the addition was complete the mixture was allowed to stir for an additional 1 hour. At this point 4.5 mL tri-isopropyl borate was added by syringe, and the reaction was allowed to stir for an additional hour. The reaction was then allowed to warm to room temperature with continued stirring for another hour. 2.0 M aqueous hydrochloric acid (HCl) was

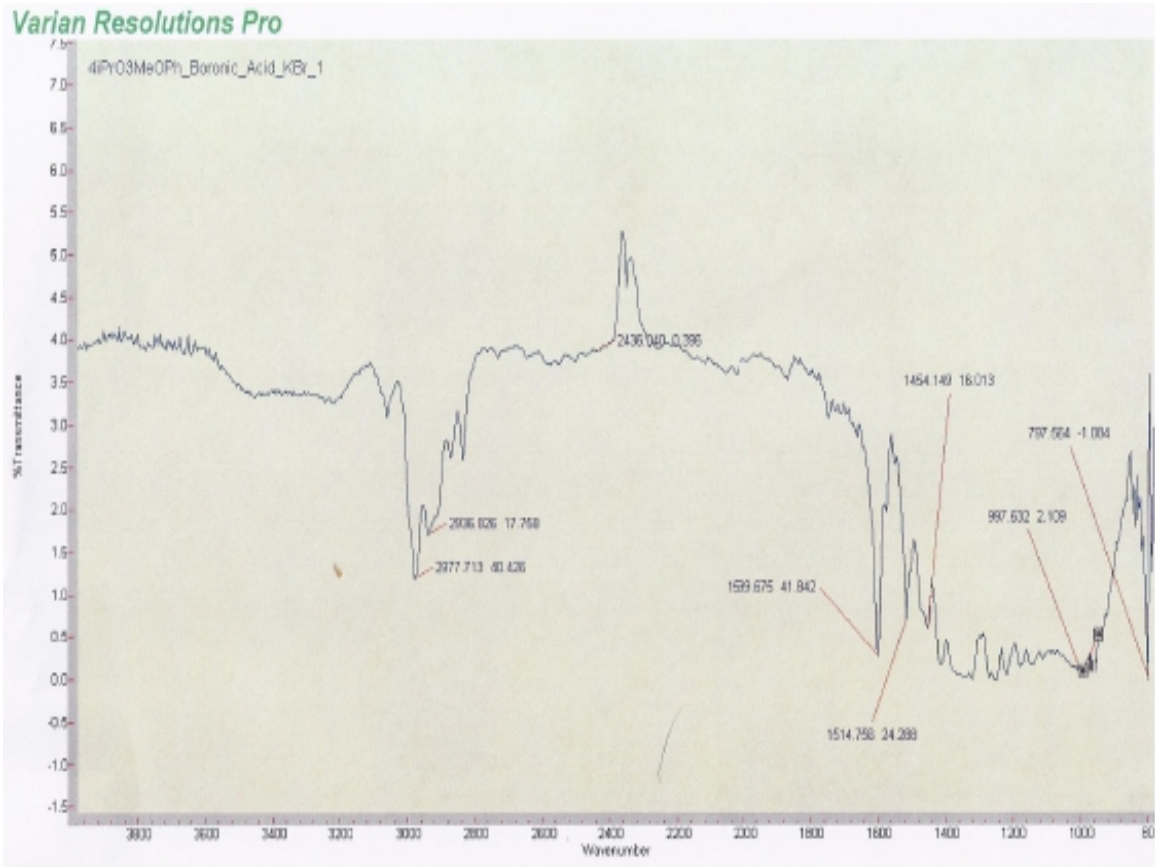
then added to adjust the pH. After the addition of 7.0 mL the solution turned from cloudy to clear. A further 8.0 mL was added and the pH was tested and recorded to be 1. The reaction was left to stir for 10 minutes during which time any precipitate dispersed.

2.3.3 Identification of 3-Methoxy-4-Isopropoxy Phenyl Boronic Acid

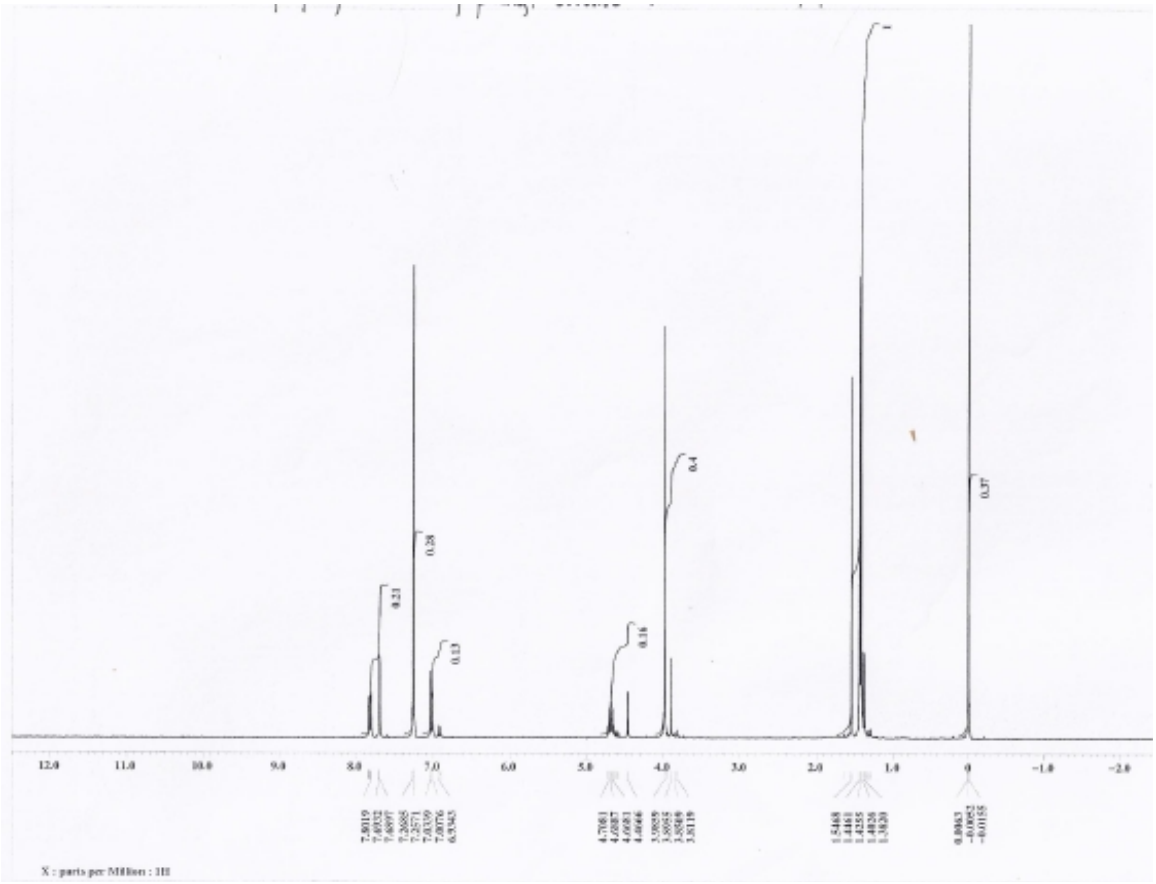
2.3.3.1 3-Methoxy-4-Isopropoxy Phenyl Boronic Acid



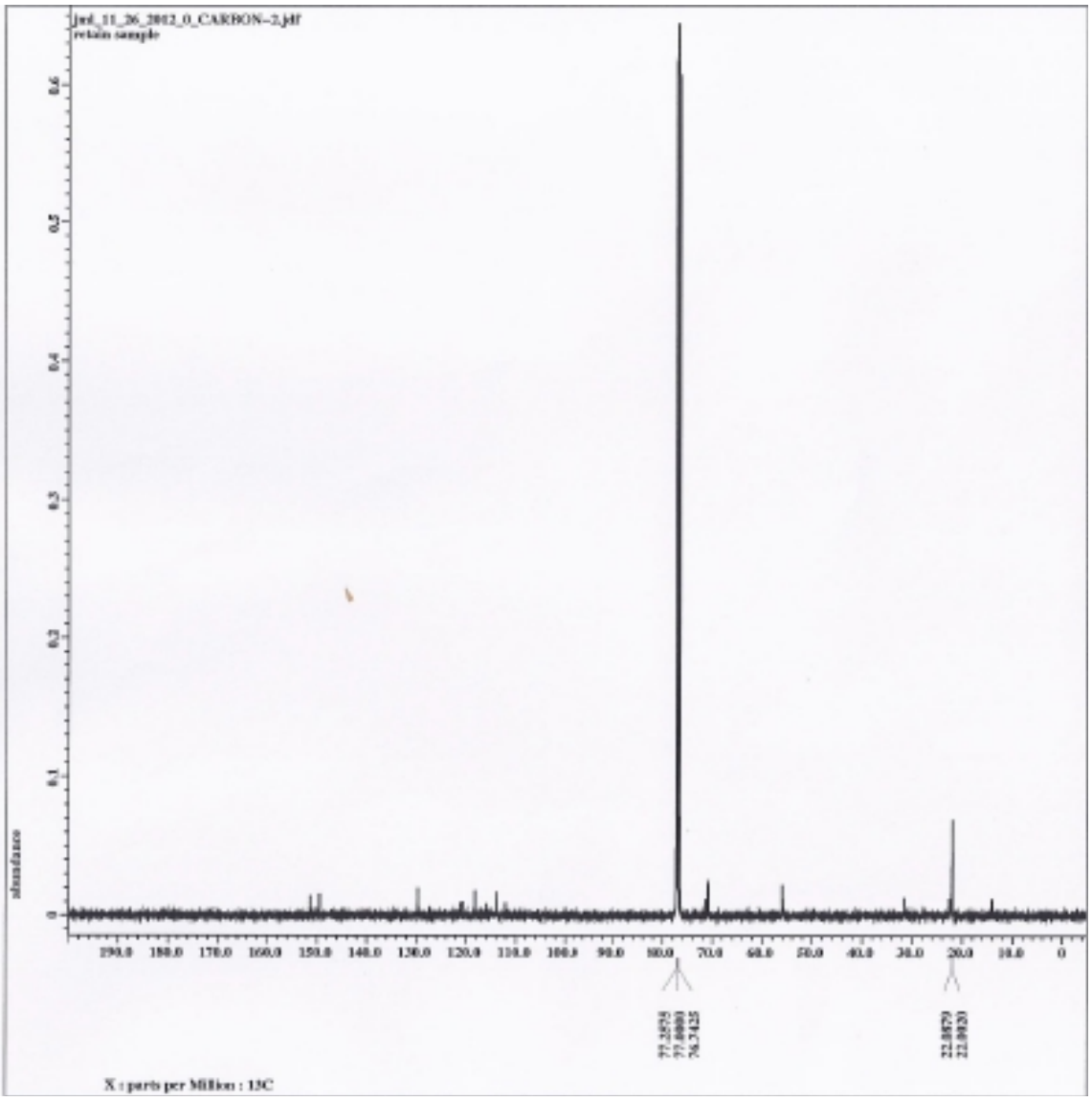
The boronic acid product was extracted into dichloromethane and collected. The solvent was then removed under negative pressure in a rotary evaporator until 1.61 g of yellow solid was recovered for a 37% yield. IR (KBr) 2978 cm^{-1}, 2937 cm^{-1}, 1600 cm^{-1}, 1515 cm^{-1}, 1454 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ 7.80 (d, 1H), 7.69 (s, 1H), 7.03 (d, 1H), 4.70 (m, 1H), 3.99 (s, 3H), 1.55 (d, 6H). ^{13}C NMR ($CDCl_3$) δ 152, 150, 130, 118, 114, 71, 55, 32, 22, 14.



(Figure 9 – IR of 3-Methoxy-4-Isopropoxy Phenyl Boronic Acid)

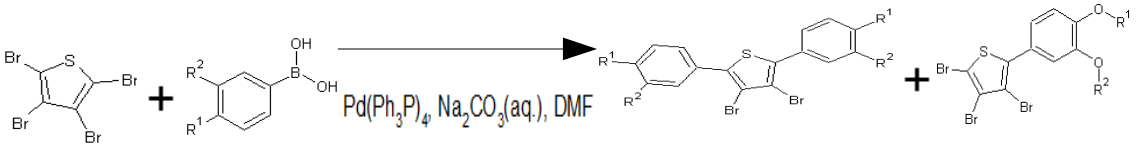


(Figure 10 – ^{1}H NMR of 3-Methoxy-4-Isopropoxy Phenyl Boronic Acid)



(Figure 11 - ^{13}C NMR of 3-Methoxy-4-Isopropoxy Phenyl Boronic Acid)

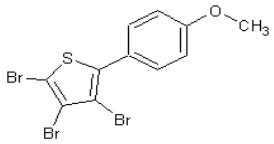
2.3.4 General Procedure for Suzuki Coupling



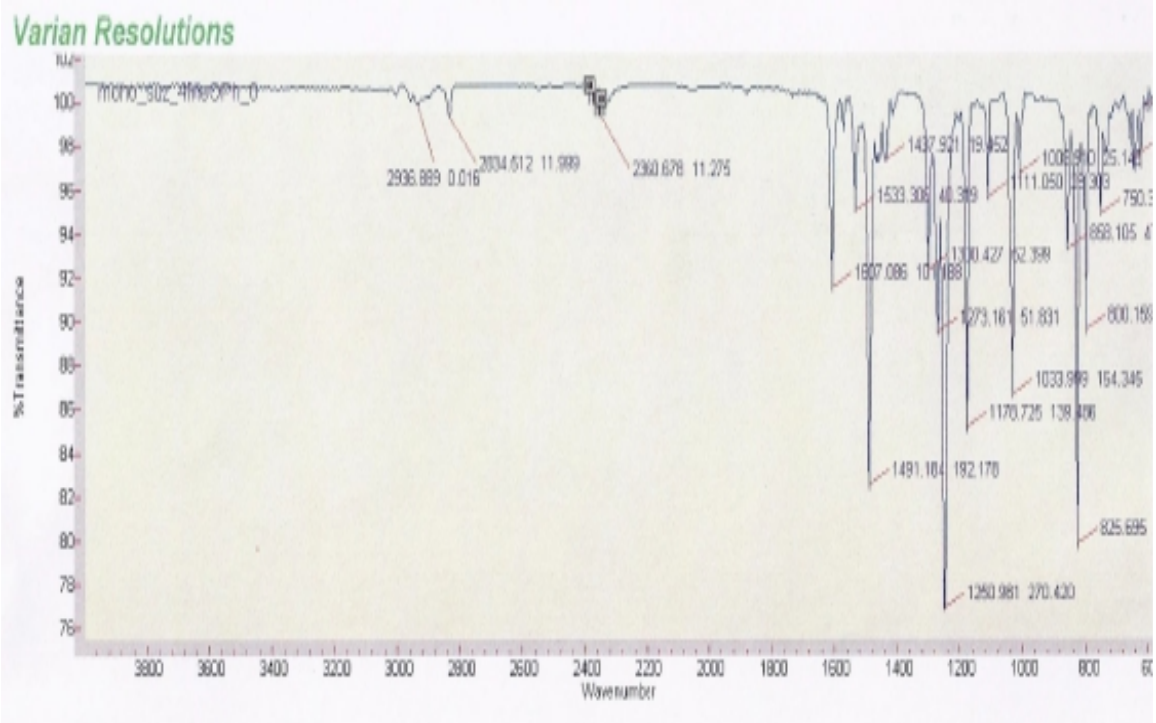
Approximately 0.240 g (0.600 mmol) tetrabromothiophene, 0.021 g (1.8 X 10^{-5} mol or 0.03 equivalents) tetrakis(triphenylphosphine)Pd^0, 1.3mmol (or 2.2 equivalents) of arylboronic acid and 8.0 mL DMF were combined in a 20 mL clear glass vial with a natural rubber lined cap. Aqueous sodium carbonate (3.6mL of 1.0 M) was added, and a white precipitate was observed to form. The reaction vessel was then transferred to a J-KEM orbital shaker set to 125 o.p.m. and 80.0° C for three hours. The reaction mixture was transferred to a separatory funnel along with three alternating washes of both water and ethyl ether. Water and ethyl ether were individually added a few milliliters at a time until any observed precipitate dispersed into solution. After mixing and separation the ether layer was collected. The aqueous layer was then extracted at least two more times, and all ether layers were collected and returned to the separatory funnel. The ether layer was then washed and collected two more times before being collected and dried over magnesium sulfate. The dried ether layer was then filtered through Whatmann #1 filter paper and the solvent removed under negative pressure on a rotary evaporator to produce the crude product. The mono- and di-aryl substituted Suzuki products were then separated over approximately 10.5 g of silica gel in a 1.25 cm diameter chromatography column product in 39% and 43% yield respectively.

2.3.5 Identification of Suzuki Coupling Products

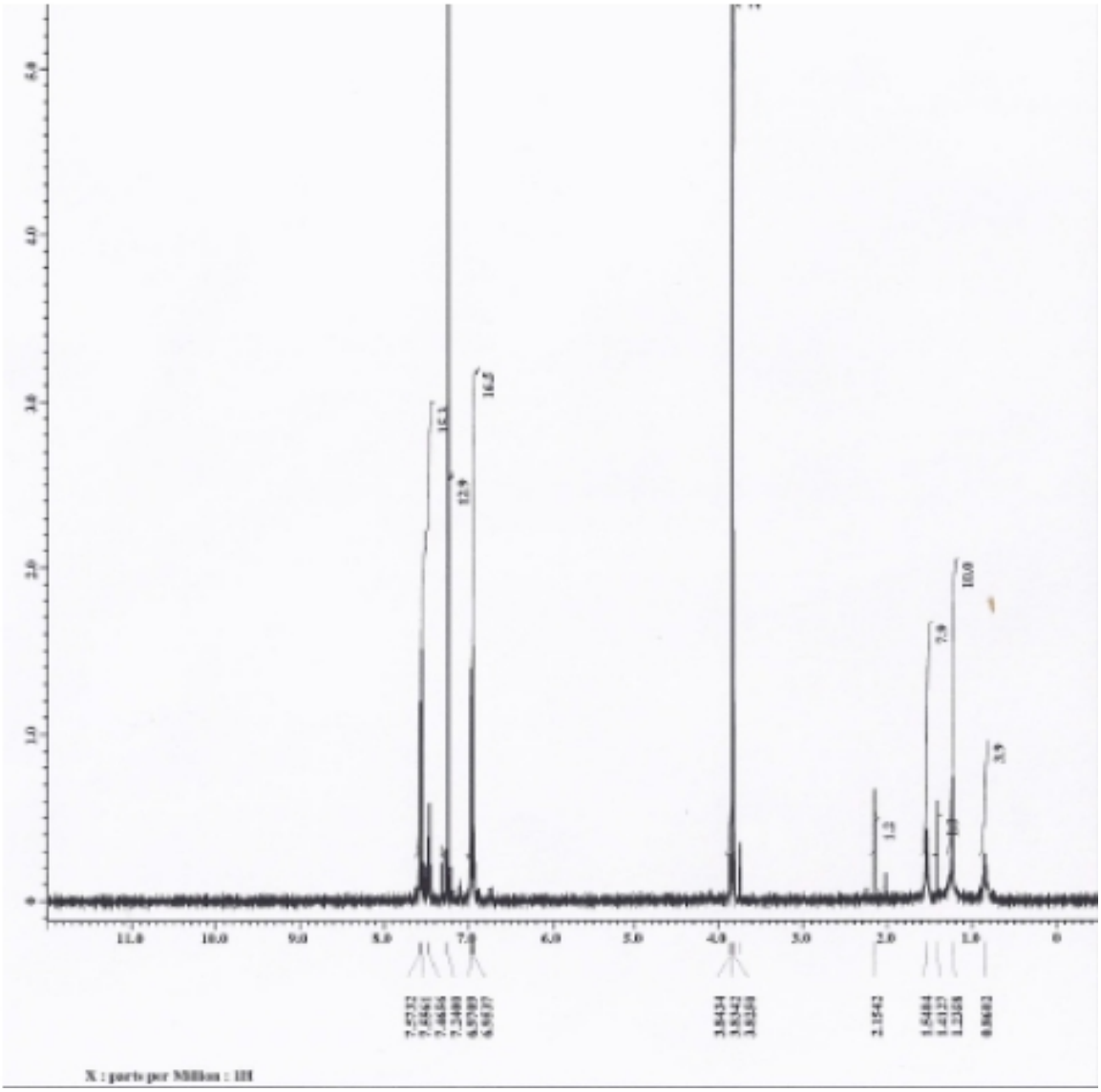
2.3.5.1 2-(4-Methoxyphenyl)-3,4,5-Tribromo Thiophene



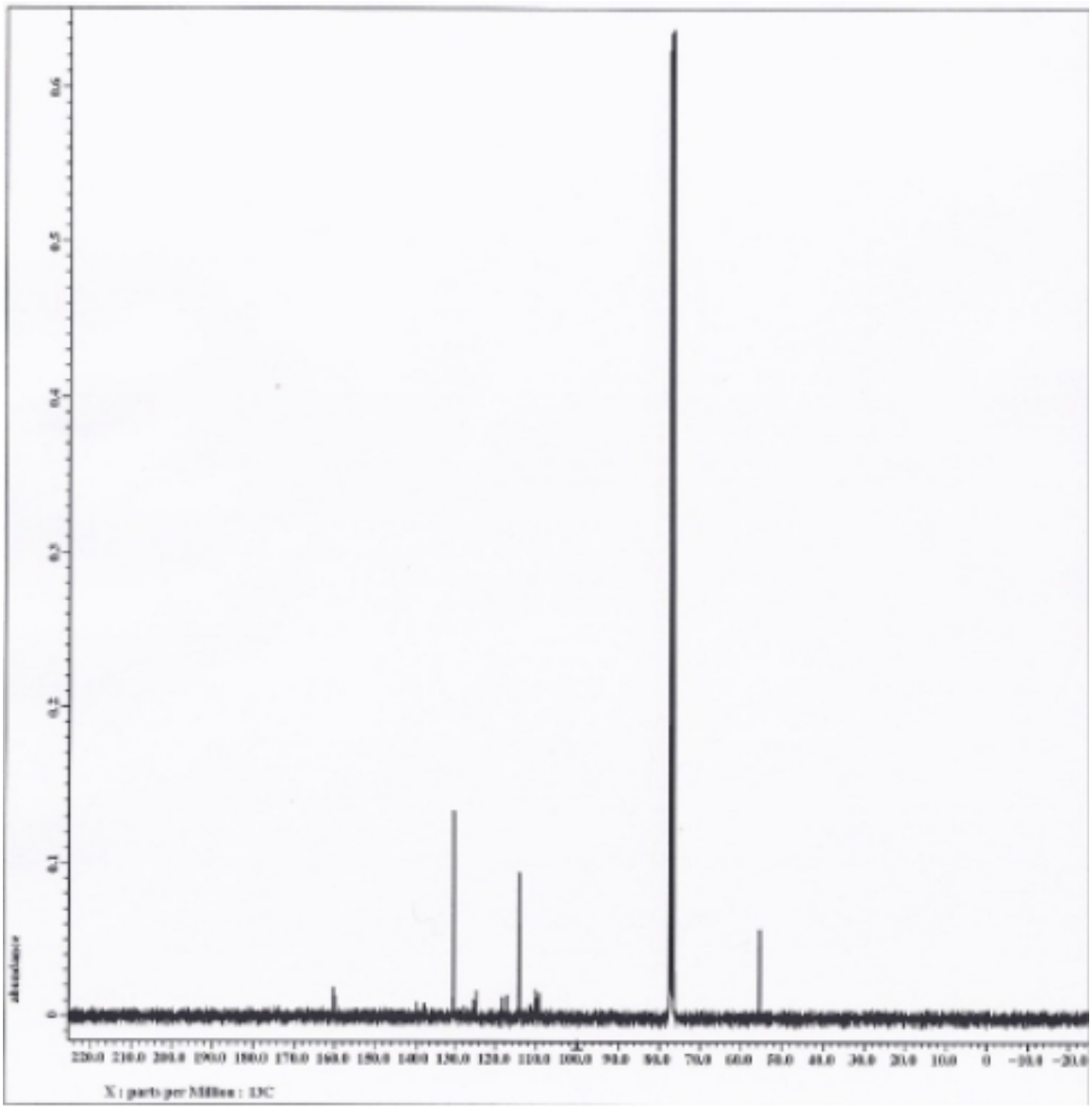
The monoaryl 2-(4-methoxyphenyl)-3,4,5-tribromo thiophene Suzuki product demonstrated an R_f of 0.58 in the eluting solvent that was a 9:1 mixture of hexanes to ethyl acetate, and was isolated with a 68% yield. IR (KBr) 2835 cm^{-1}, 1607 cm^{-1}, 1491 cm^{-1}, 1251 cm^{-1}, 1179 cm^{-1}, 1034 cm^{-1}, 826 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ 7.57 (d, 2H), 6.97 (d, 2H), 3.83 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 160, 150, 131, 126, 125, 118, 117, 114, 55.



(Figure 12 – IR of 2-(4-Methoxyphenyl)-3,4,5-Tribromo Thiophene)

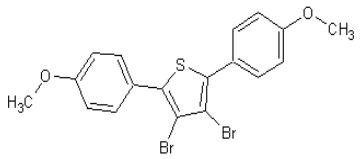


(Figure 13 – ^{1}H NMR of 2-(4-Methoxyphenyl)-3,4,5-Tribromo Thiophene)

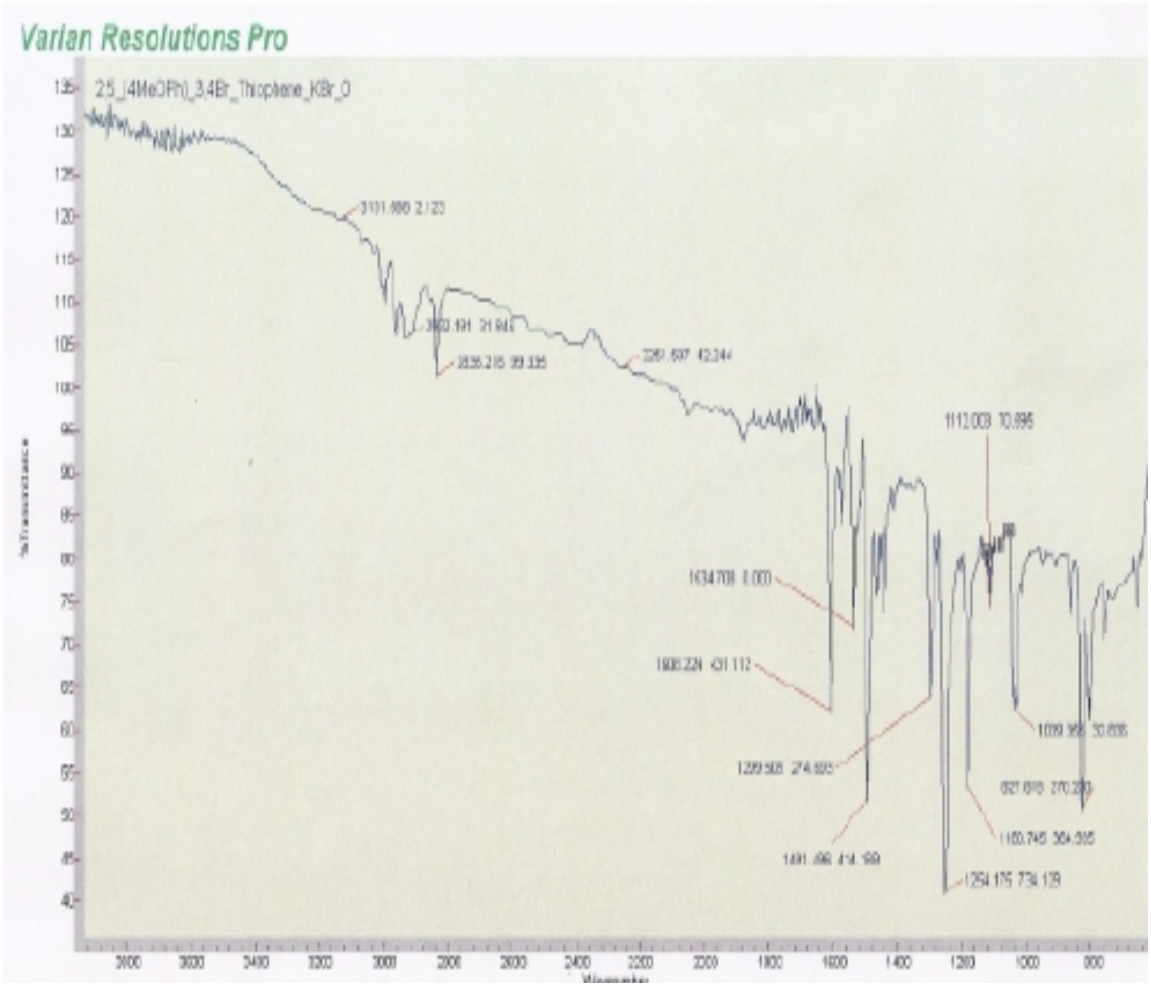


(Figure 14 – ^{13}C NMR of 2-(4-Methoxyphenyl)-3,4,5-Tribromo Thiophene)

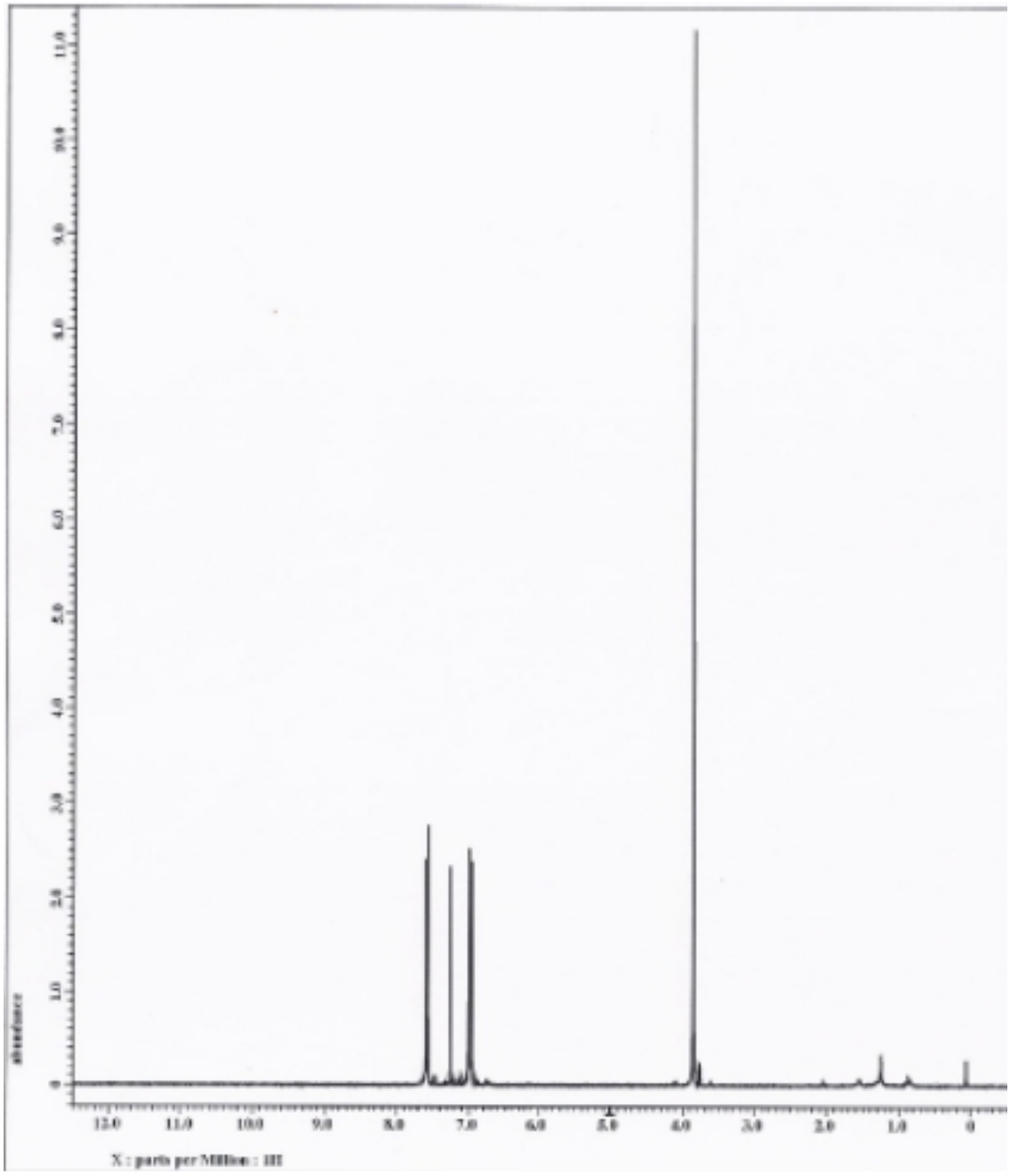
2.3.5.2 2,5-(4-Methoxyphenyl)-3,4-Dibromo Thiophene



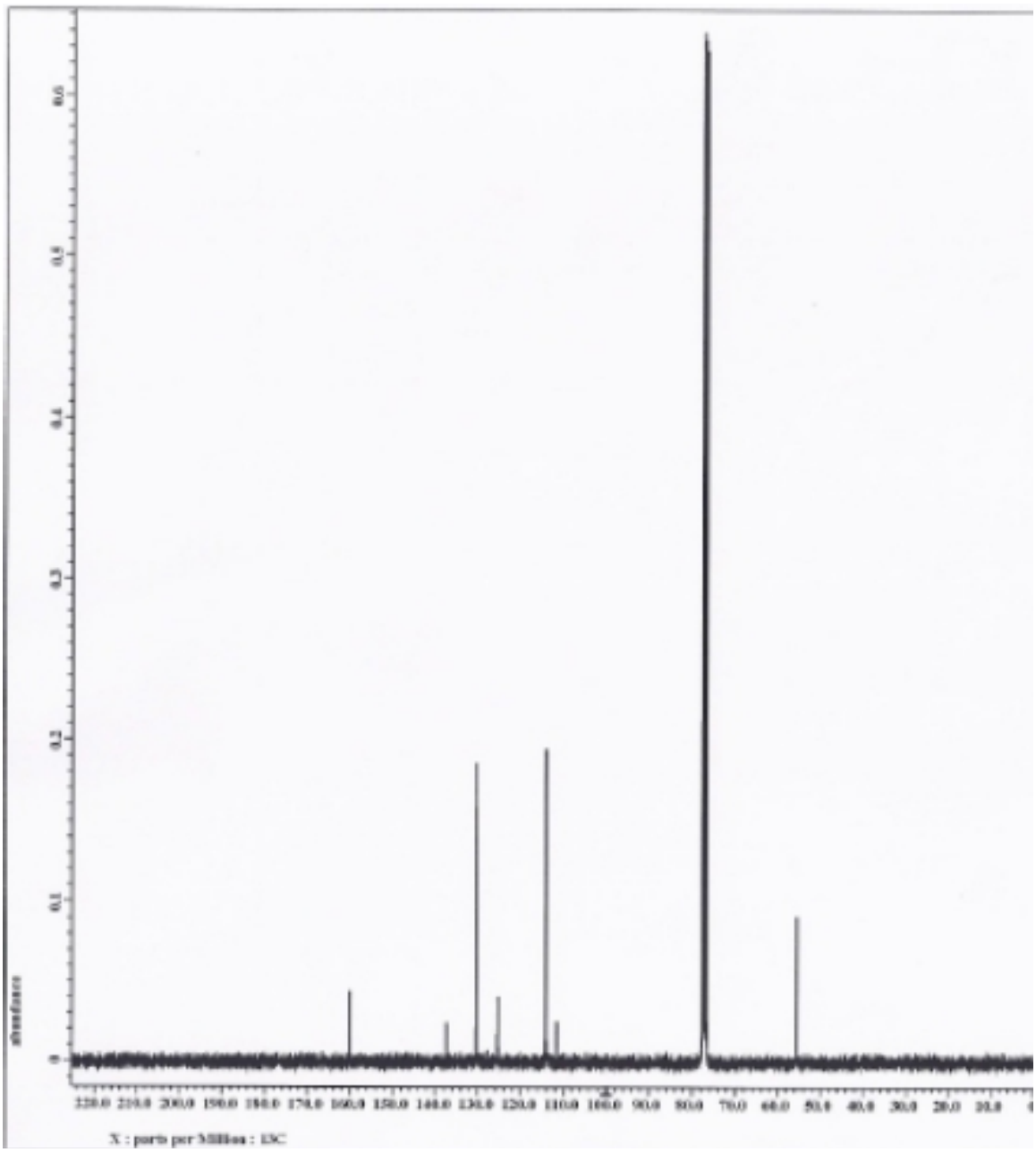
The diaryl 2,5-(4-methoxyphenyl)-3,4-tribromo thiophene Suzuki product demonstrated an R_f of 0.46 in the eluting solvent that was a 9:1 mixture of hexanes to ethyl acetate, and was isolated with a 32% yield. IR (KBr) 2835 cm^{-1}, 1608 cm^{-1}, 1491 cm^{-1}, 1254 cm^{-1}, 1181 cm^{-1}, 1039 cm^{-1}, 828 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ 7.57 (d, 4H), 6.97 (d, 4H), 3.83 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 160, 138, 131, 126, 115, 111, 56.



(Figure 15 – IR of 2,5-(4-Methoxyphenyl)-3,4-Dibromo Thiophene)

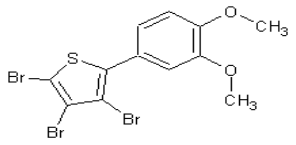


(Figure 16 – ^{1}H NMR of 2,5-(4-Methoxyphenyl)-3,4-Dibromo Thiophene)

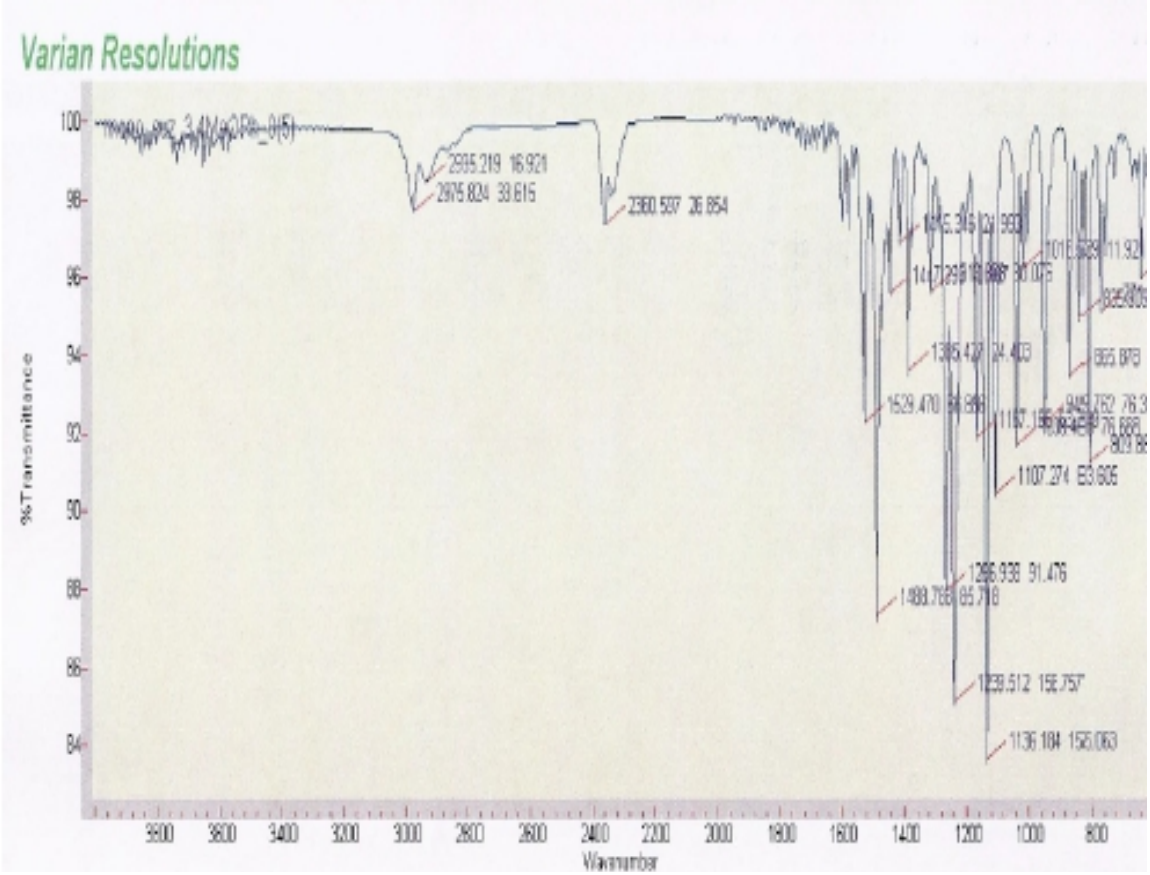


(Figure 17 – ^{13}C NMR of 2,5-(4-Methoxyphenyl)-3,4-Dibromo Thiophene)

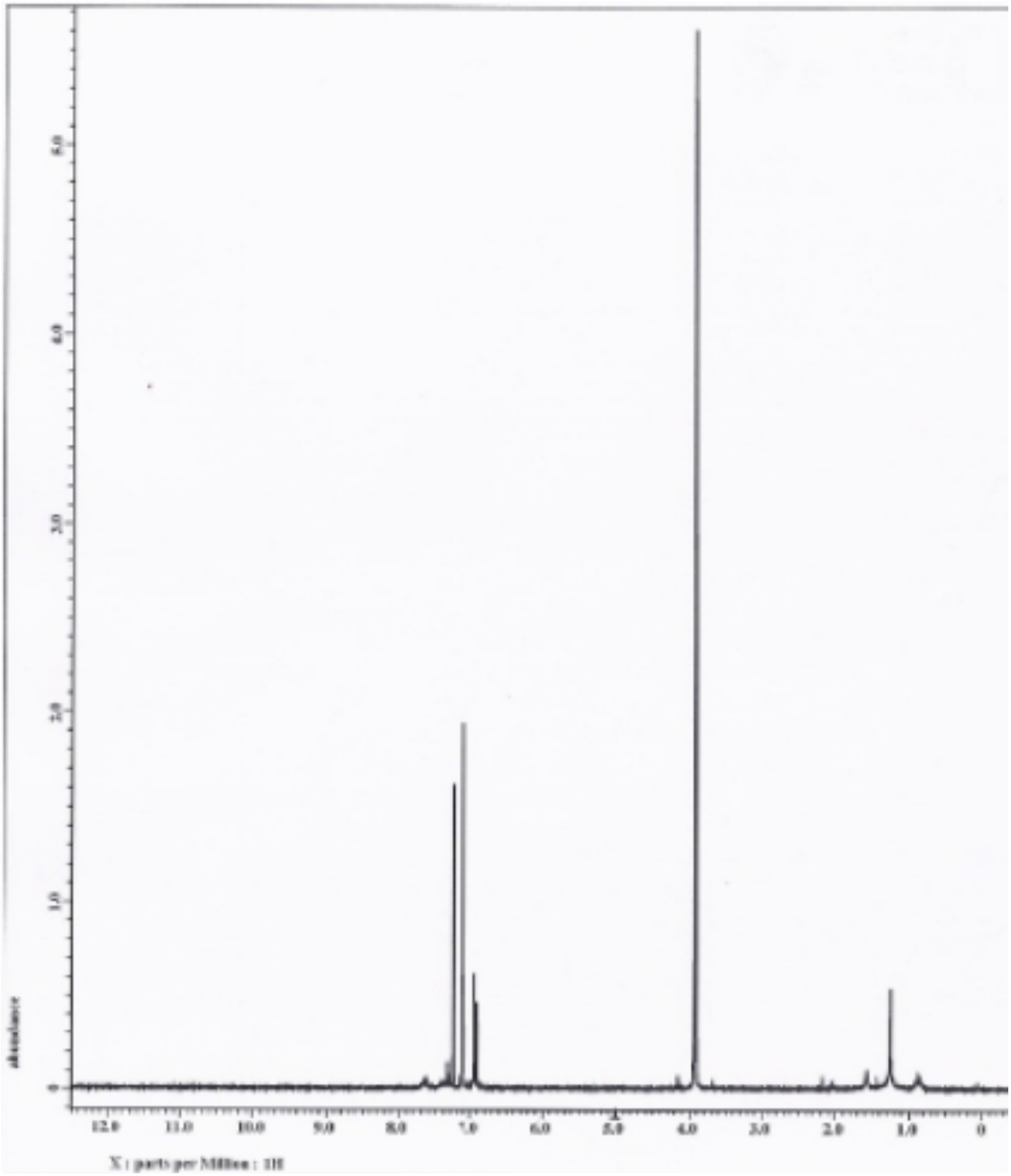
2.3.5.3 2-(3,4-Dimethoxyphenyl)-3,4,5-Tribromo Thiophene



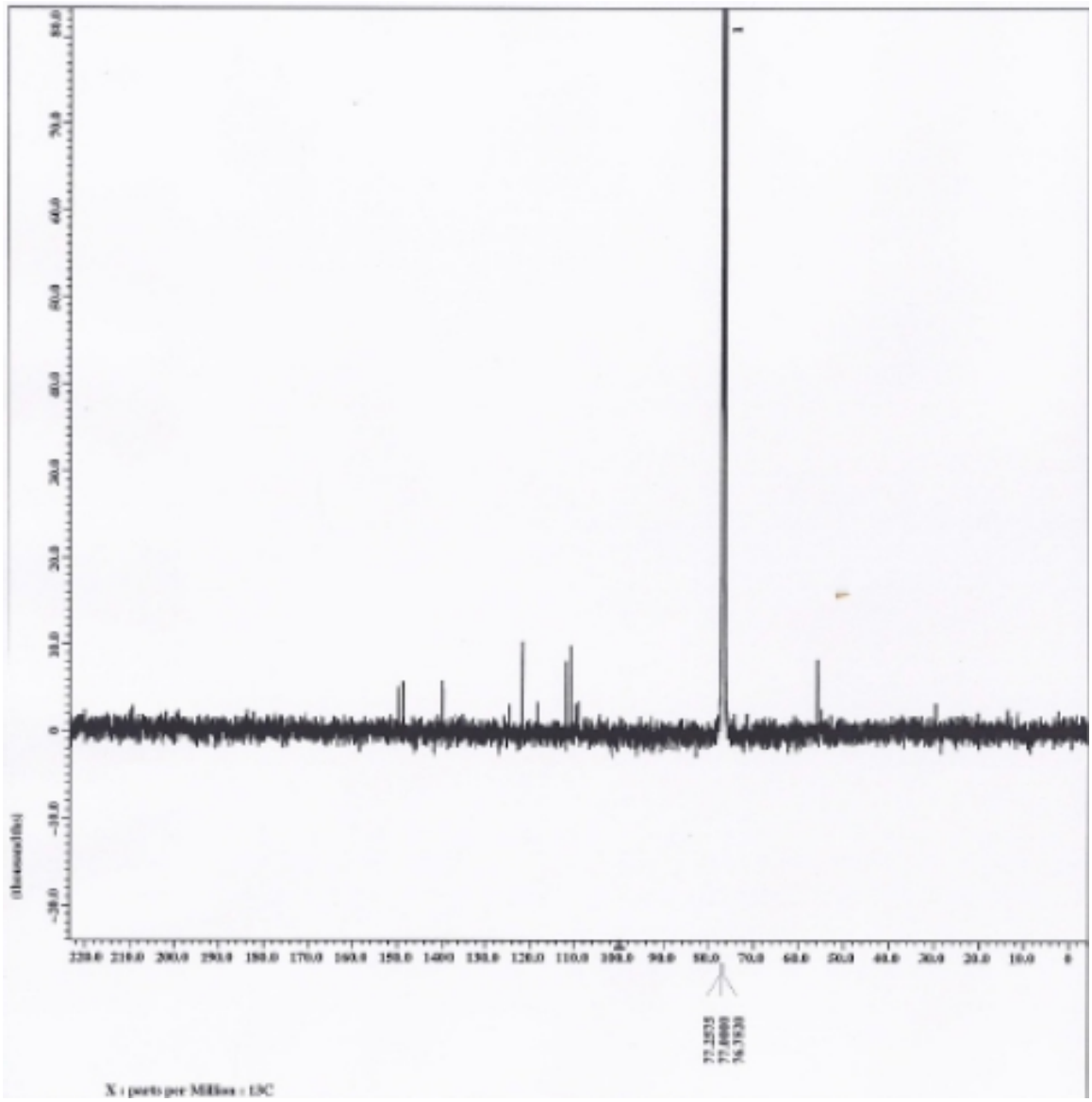
The monoaryl 2-(3,4-dimethoxyphenyl)-3,4,5-tribromo thiophene Suzuki product demonstrated an R_f of 0.58 in the eluting solvent that was a 4:1 mixture of hexanes to ethyl acetate, and was isolated with a 39% yield. IR (KBr) 2976 cm^{-1}, 2935 cm^{-1}, 1529 cm^{-1}, 1489 cm^{-1}, 1287 cm^{-1}, 1240 cm^{-1}, 1136 cm^{-1}, 1107 cm^{-1}, 950 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ 7.24 (s, 1H), 7.18 (d, 1H) 6.94 (d, 1H), 3.93 (s, 3H), 3.91 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 151, 150, 141, 125, 122, 118, 112, 111, 109, 108, 55, 54.



(Figure 18 – IR of 2-(3,4-Dimethoxyphenyl)-3,4,5-Tribromo Thiophene)

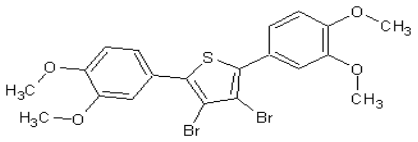


(Figure 19 – ^{1}H NMR of 2-(3,4-Dimethoxyphenyl)-3,4,5-Tribromo Thiophene)

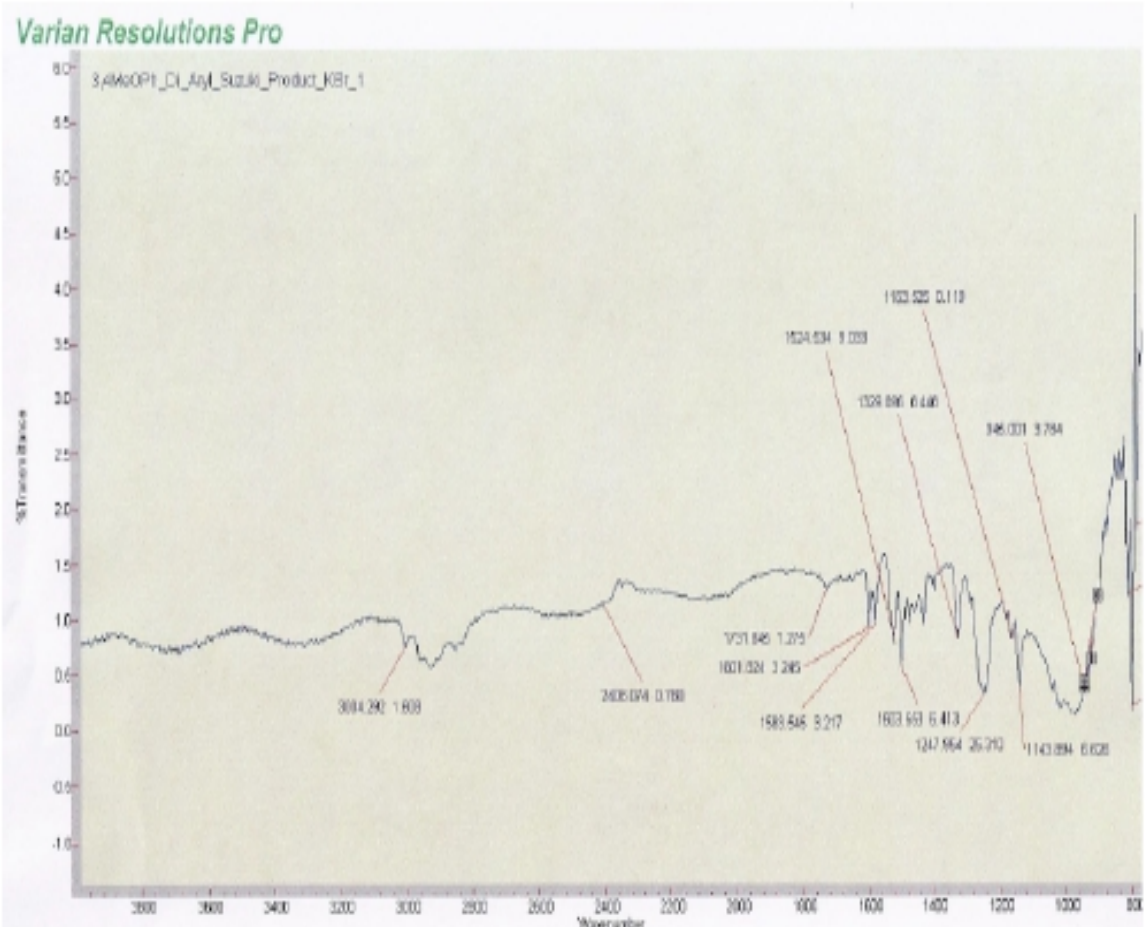


(Figure 20 – ^{13}C NMR of 2-(3,4-Dimethoxyphenyl)-3,4,5-Tribromo Thiophene)

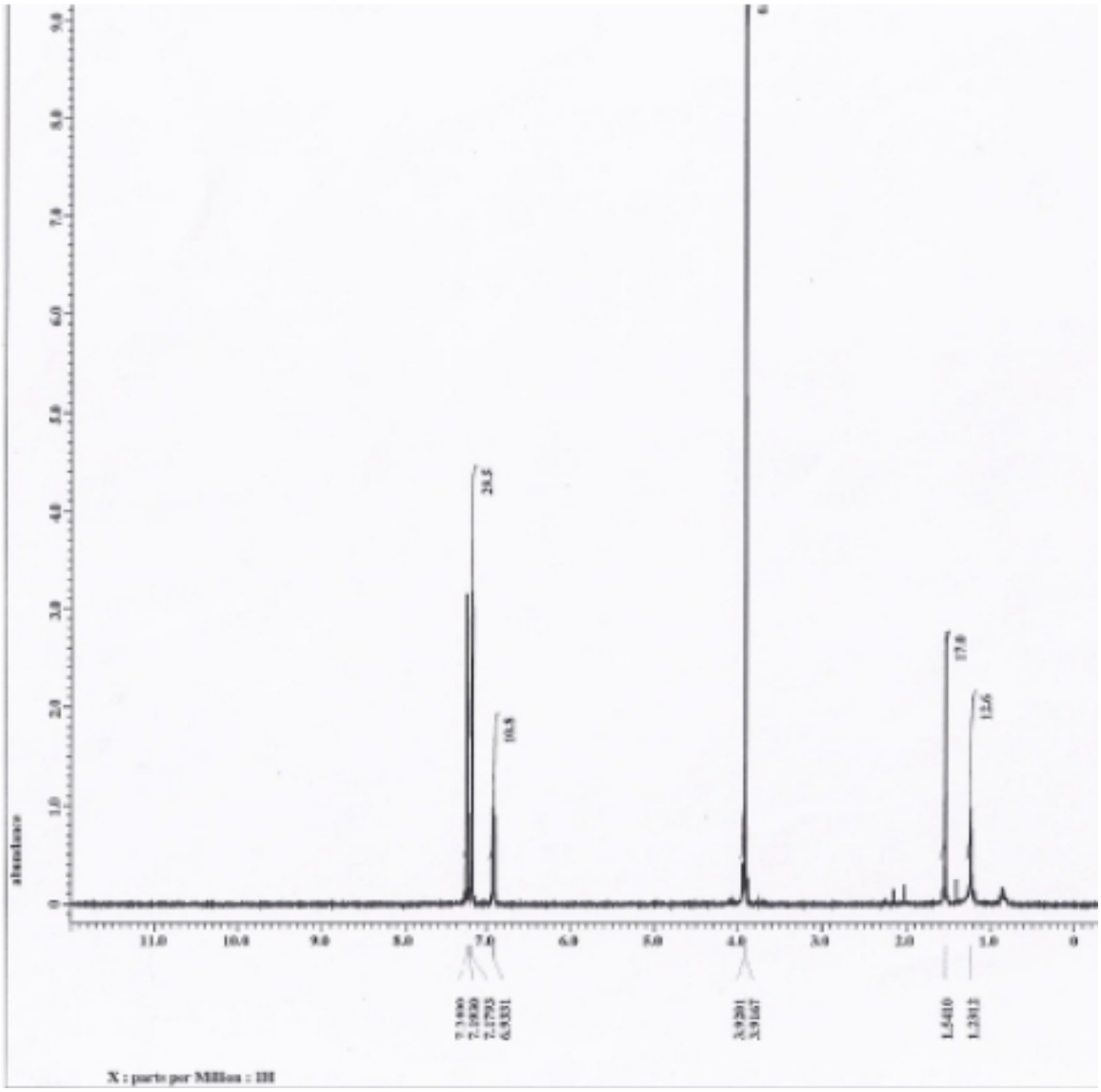
2.3.5.4 2,5-(3,4-Dimethoxyphenyl)-3,4-Dibromo Thiophene



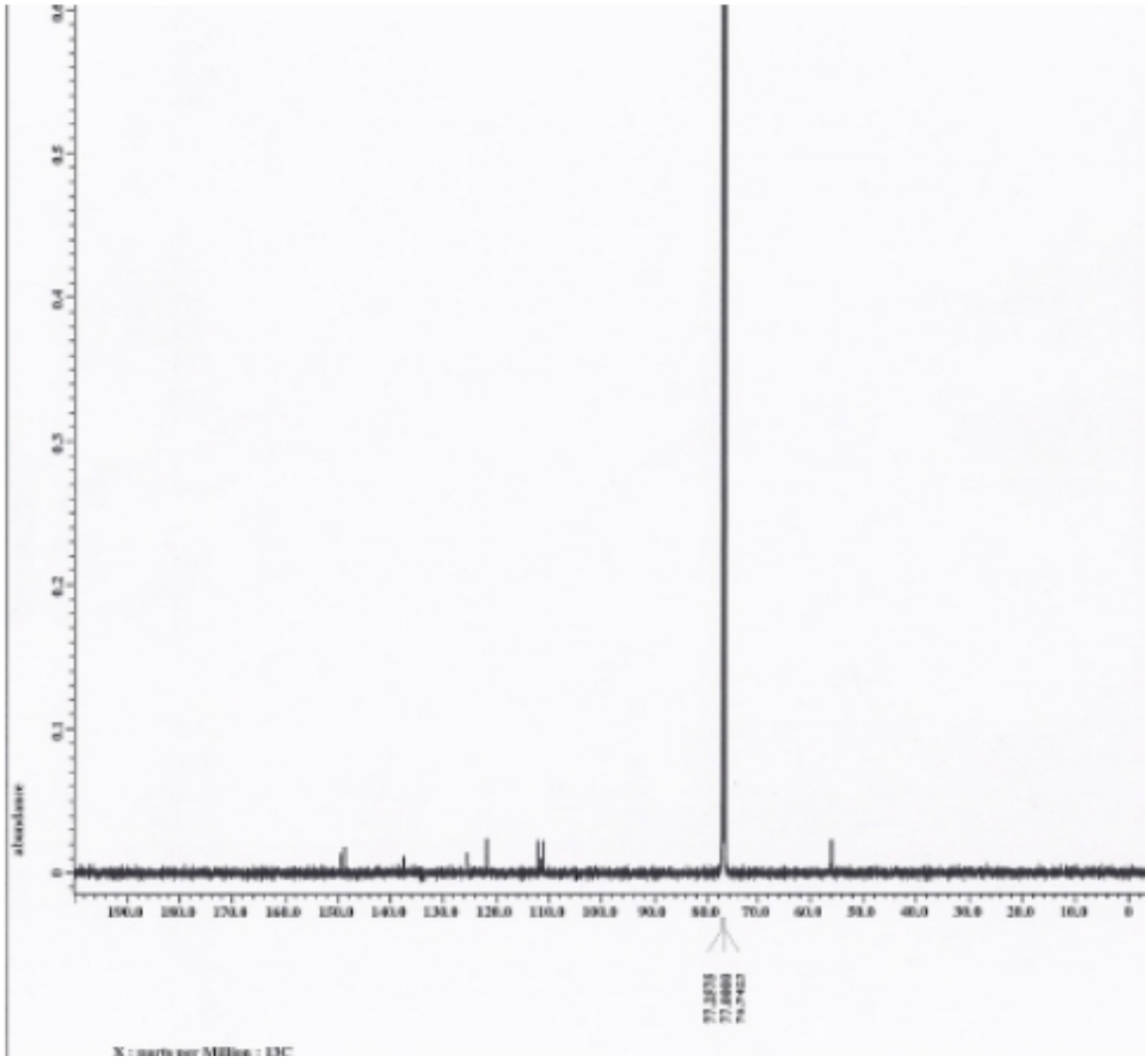
The diaryl 2,5-(3,4-dimethoxyphenyl)-3,4-dibromo thiophene Suzuki product demonstrated an R_f of 0.30 in the eluting solvent that was a 4:1 mixture of hexanes to ethyl acetate, and was isolated with a 43% yield. IR (KBr) 2976 cm^{-1}, 2935 cm^{-1}, 1602 cm^{-1}, 1583 cm^{-1}, 1525 cm^{-1}, 1504 cm^{-1}, 1330 cm^{-1}, 1248 cm^{-1}, 1144 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ 7.24 (s, 2H), 7.18 (d, 2H) 6.94 (d, 2H), 3.93 (s, 6H), 3.91 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 150, 149, 138, 125, 122, 113, 112, 111, 56.



(Figure 21 – IR of 2,5-(3,4-Dimethoxyphenyl)-3,4-Dibromo Thiophene)

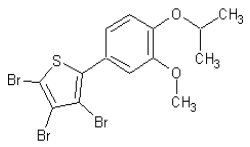


(Figure 22 – ^{1}H NMR of 2,5-(3,4-Dimethoxyphenyl)-3,4-Dibromo Thiophene)

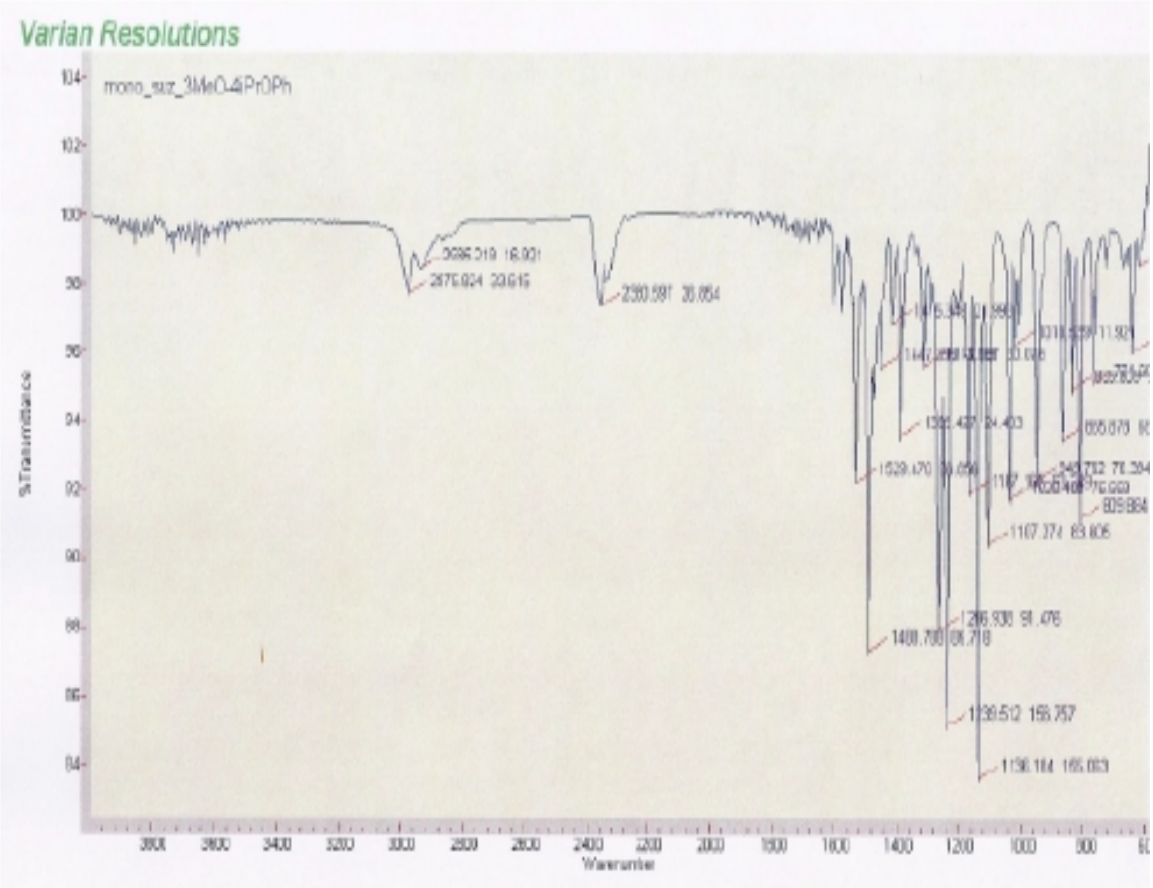


(Figure 23 – ^{13}C NMR of 2,5-(3,4-Dimethoxyphenyl)-3,4-Dibromo Thiophene)

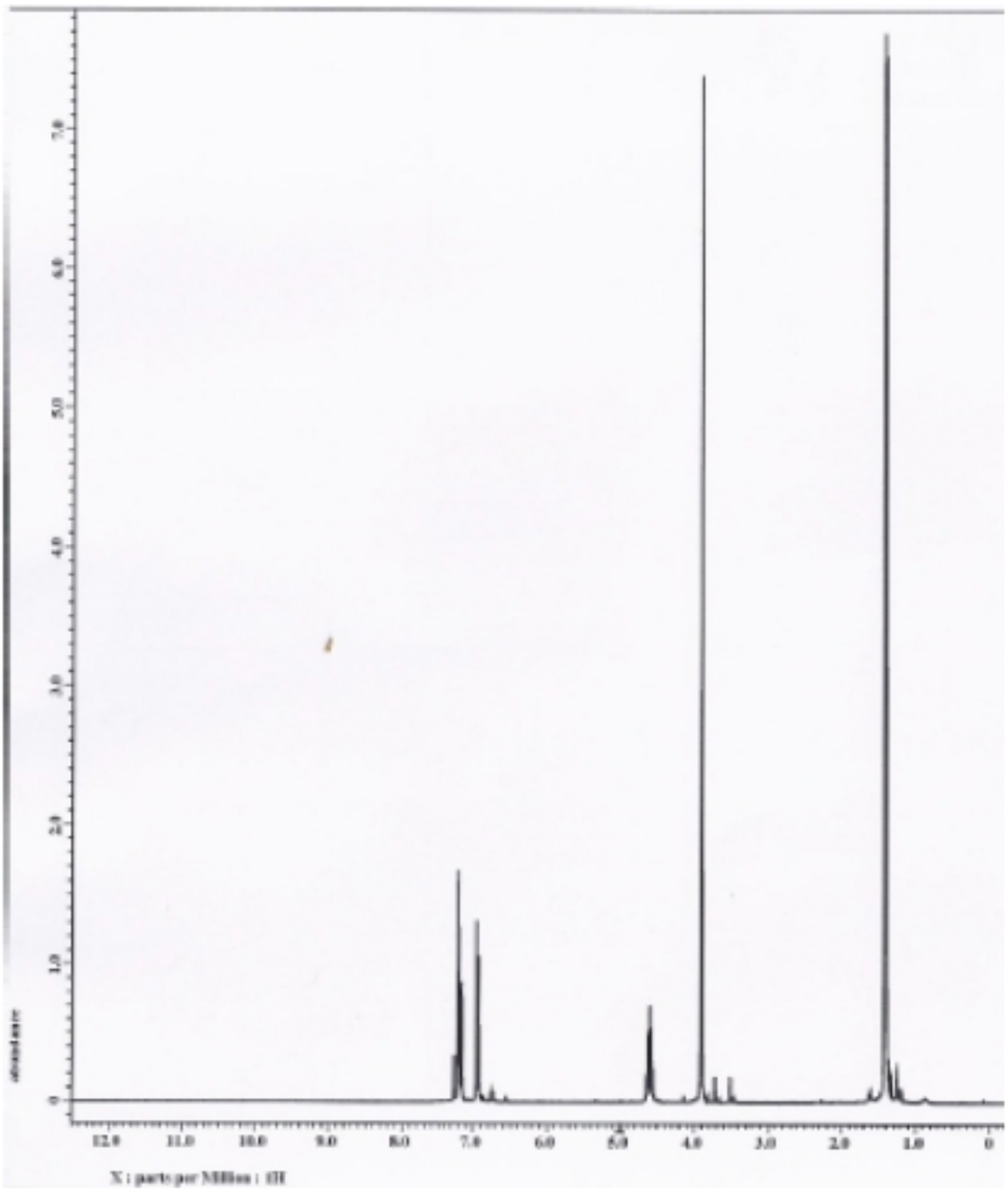
2.3.5.5 2-(3-Methoxy-4-Isopropoxyphenyl)-3,4,5-Tribromo Thiophene



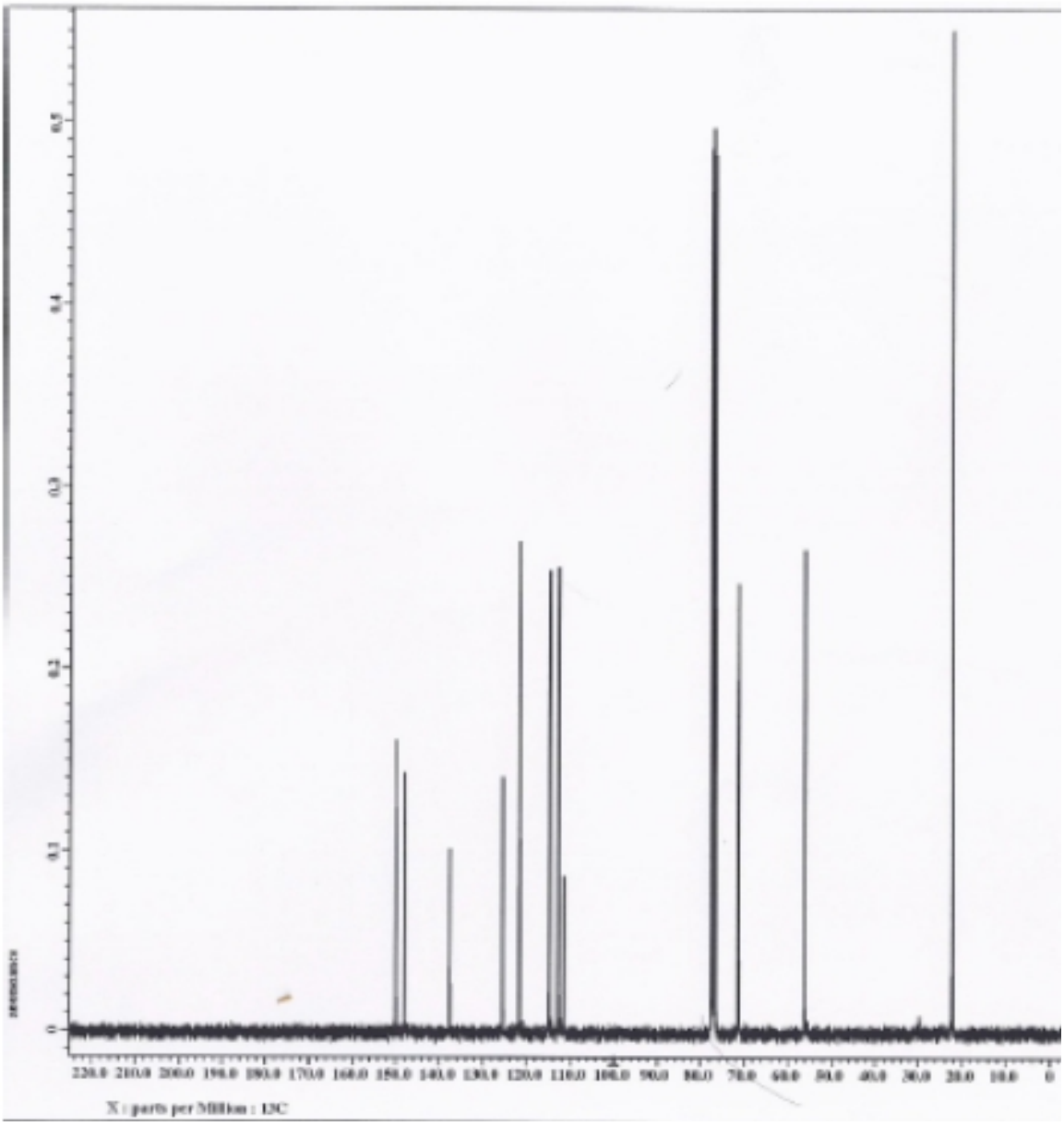
The monoaryl 2-(3-methoxy-4-isopropoxyphenyl)-3,4,5-tribromo thiophene Suzuki product demonstrated an R_f of 0.51 in the eluting solvent that was a 9:1 mixture of hexanes to ethyl acetate, and was isolated with a 24% yield. IR (KBr) 2976 cm^{-1}, 2935 cm^{-1}, 1529 cm^{-1}, 1489 cm^{-1}, 1385 cm^{-1}, 1267 cm^{-1}, 1240 cm^{-1}, 1167 cm^{-1}, 1136 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ 7.24 (s, 1H), 7.18 (d, 1H), 6.94 (d, 1H), 4.63 (m, 1H), 3.91 (s, 3H), 1.46 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 150, 149, 138, 126, 122, 115, 113, 112, 71, 56, 22.



(Figure 24 – IR of 2-(3-Methoxy-4-Isopropoxyphenyl)-3,4,5-Tribromo Thiophene)

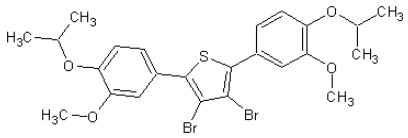


(Figure 25 – ^{1}H NMR of 2-(3-Methoxy-4-Isopropoxyphenyl)-3,4,5-Tribromo Thiophene)

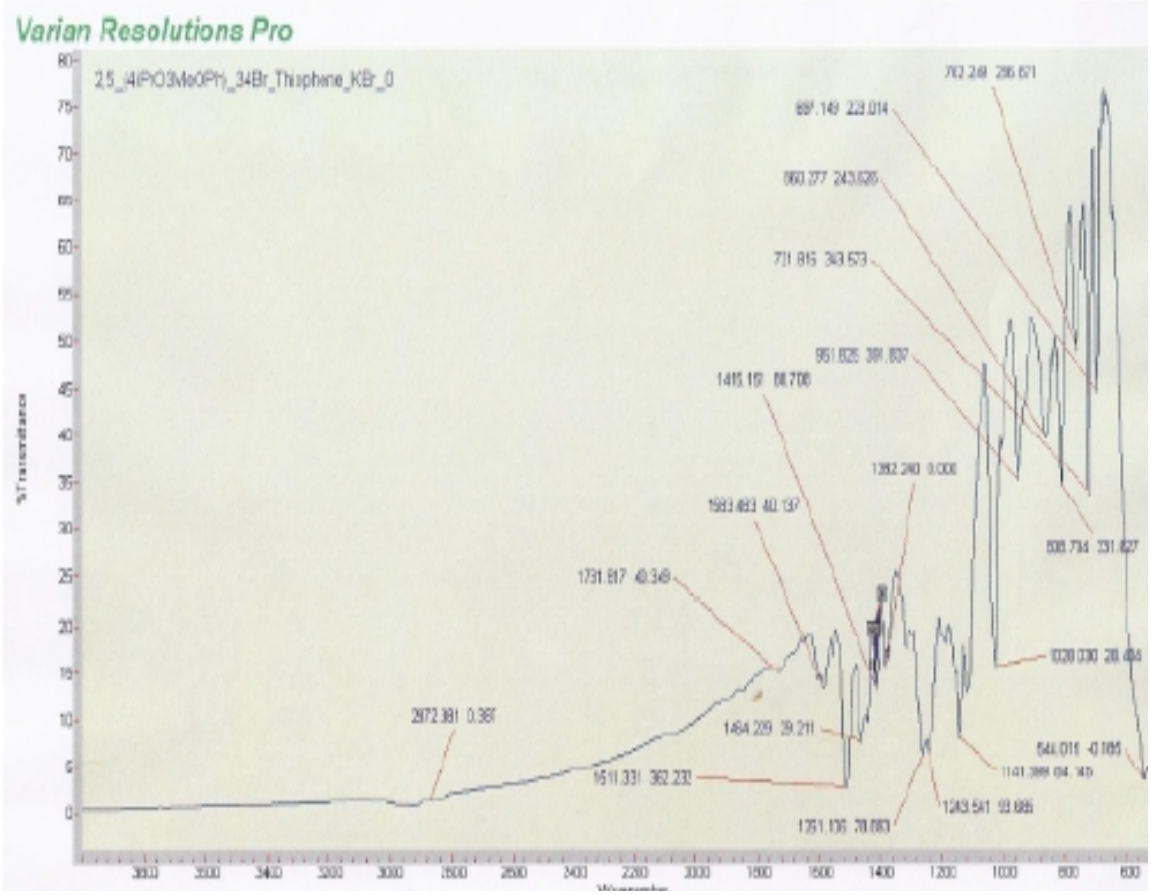


(Figure 26 – ^{13}C NMR of 2-(3-Methoxy-4-Isopropoxyphenyl)-3,4,5-Tribromo Thiophene)

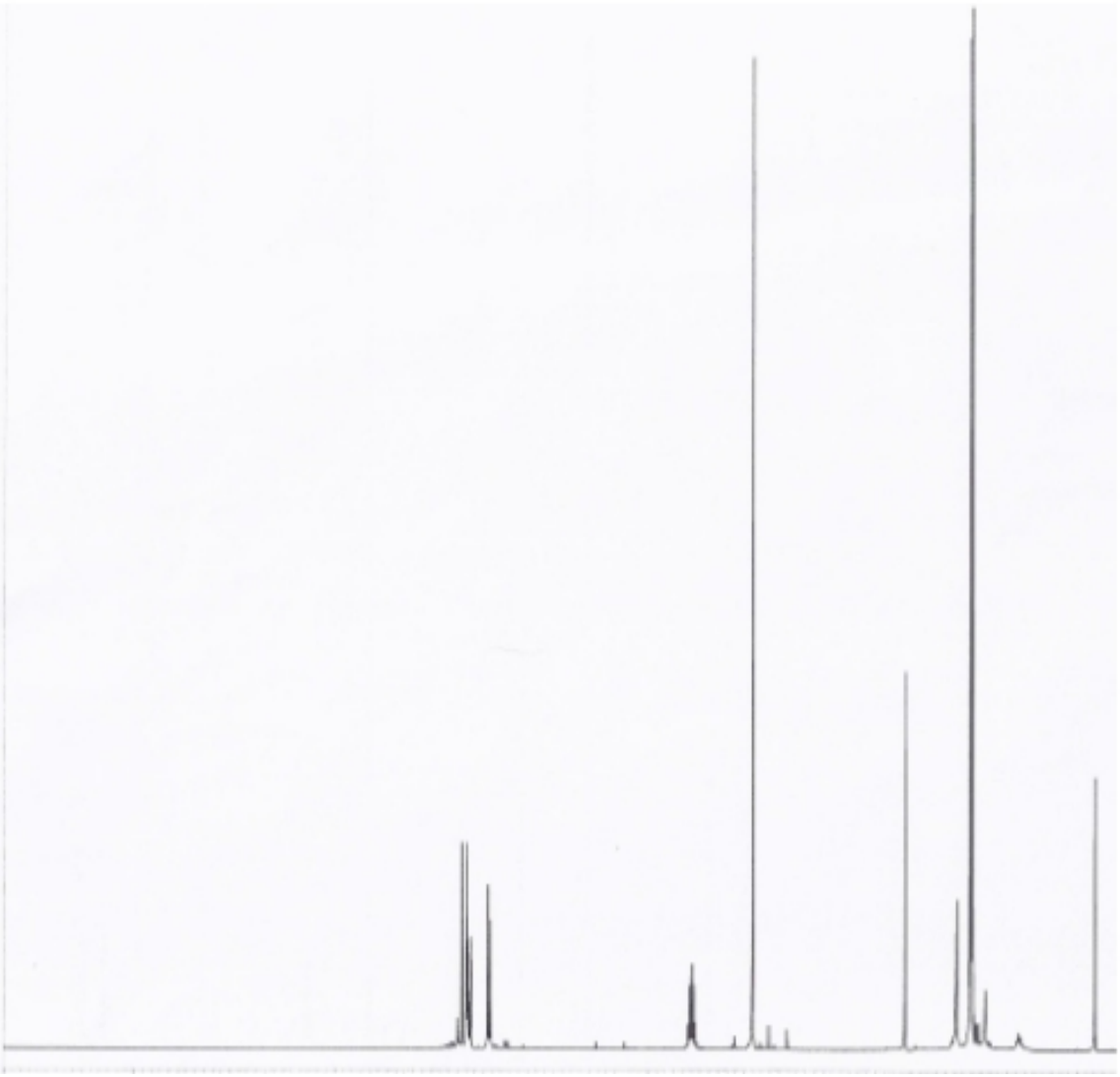
2.3.5.6 2,5-(3-Methoxy-4-Isopropoxyphenyl)-3,4-Dibromo Thiophene



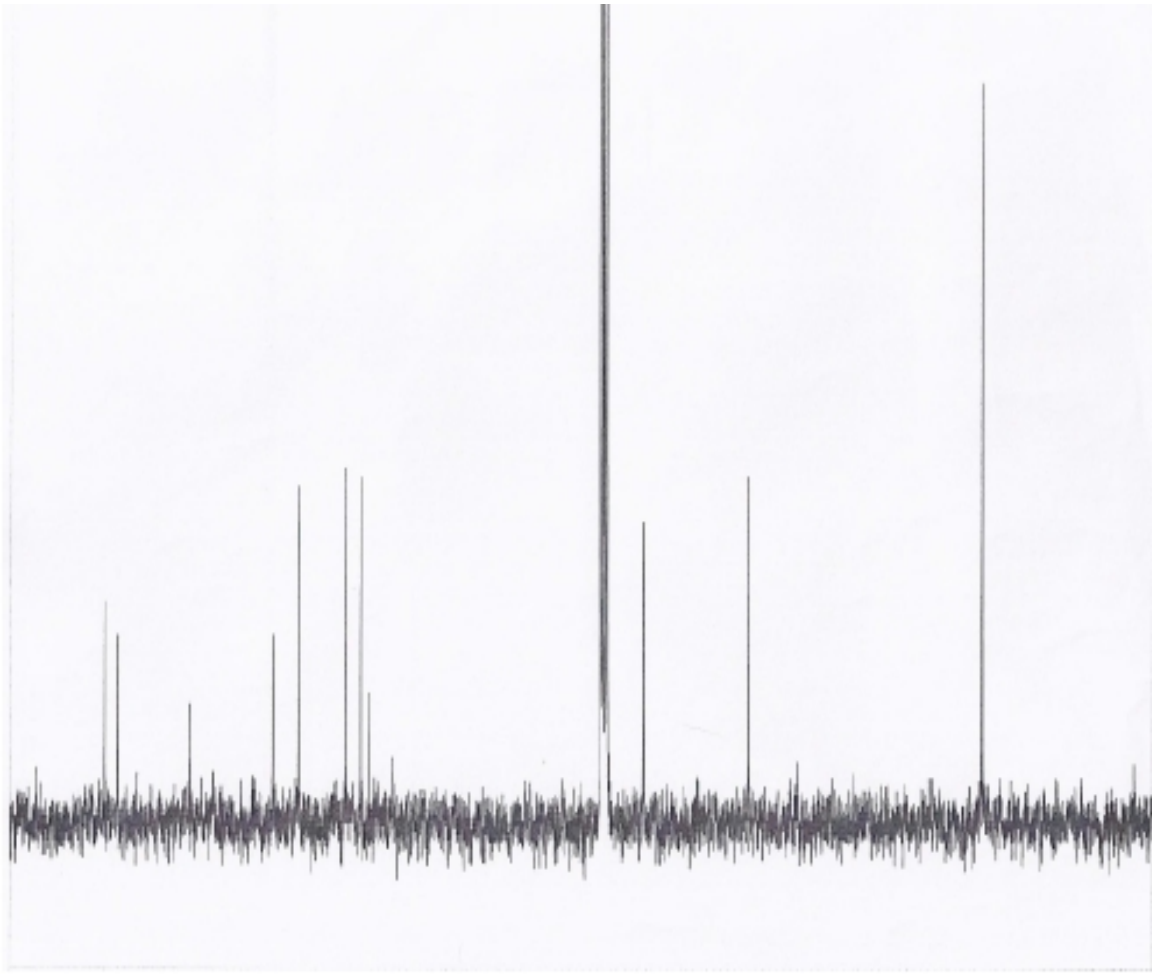
The diaryl 2,5-(3-methoxy-4-isopropoxyphenyl)-3,4-dibromo thiophene Suzuki product demonstrated an R_f of 0.25 in the eluting solvent that was a 9:1 mixture of hexanes to ethyl acetate, and was isolated with a 51% yield. IR (KBr) 2872 cm^{-1}, 1732 cm^{-1}, 1583 cm^{-1}, 1511 cm^{-1}, 1463 cm^{-1}, 1415 cm^{-1}, 1382 cm^{-1}, 1261 cm^{-1}, 1243 cm^{-1}, 1141 cm^{-1}, 1028 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ 7.24 (s, 2H), 7.18 (d, 2H) 6.94 (d, 2H), 4.63 (m, 2H), 3.91 (s, 6H), 1.46 (s, 12H). ^{13}C NMR ($CDCl_3$) δ 150, 149, 138, 126, 122, 115, 113, 112, 71, 56, 22.



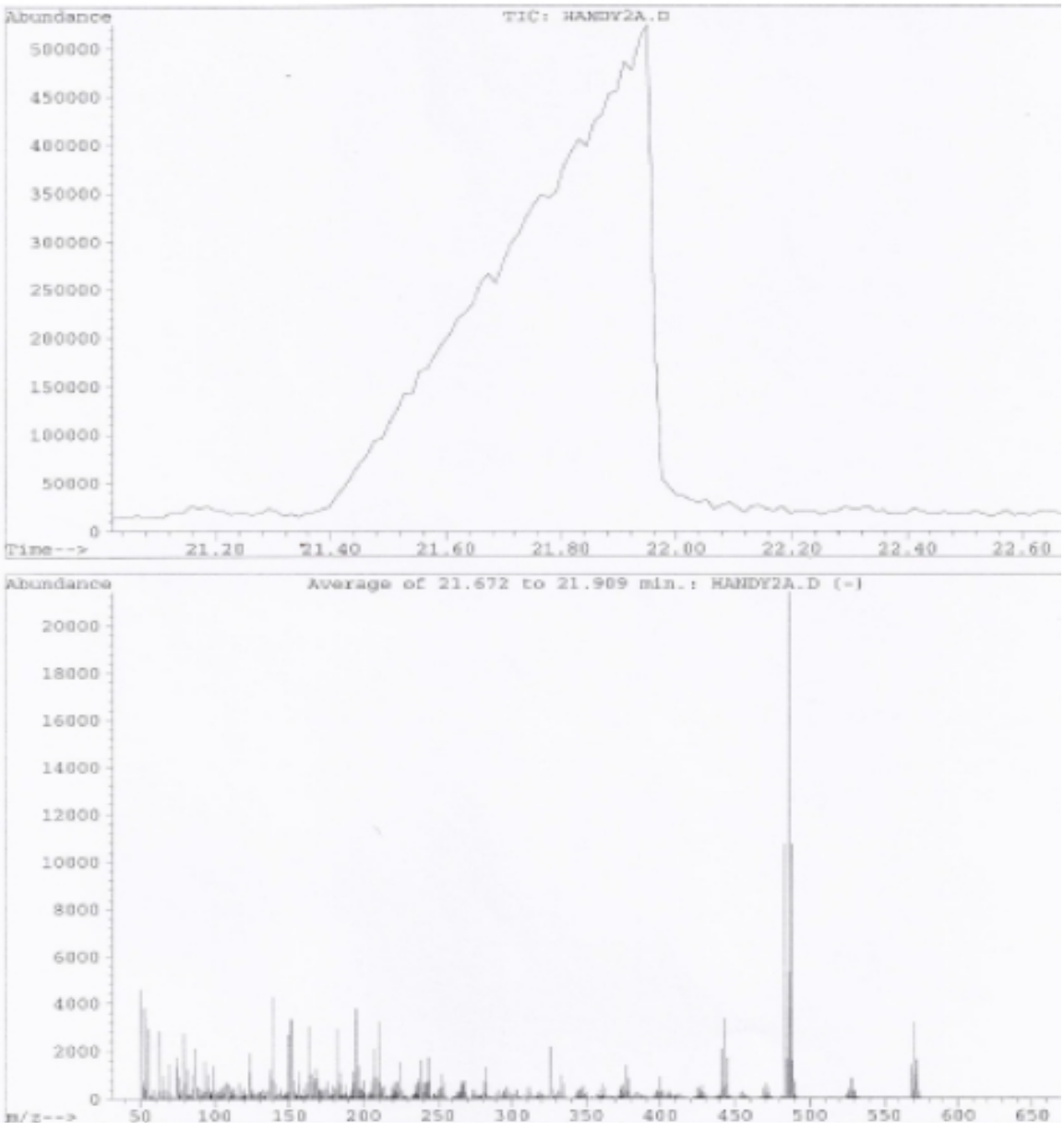
(Figure 27 – IR of 2,5-(3-Methoxy-4-Isopropoxyphenyl)-3,4-Dibromo Thiophene)



(Figure 28 – ^{1}H NMR of 2,5-(3-Methoxy-4-Isopropoxyphenyl)-3,4-Dibromo Thiophene)

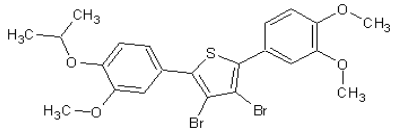


(Figure 29 – ^{13}C NMR of 2,5-(3-Methoxy-4-Isopropoxyphenyl)-3,4-Dibromo Thiophene)

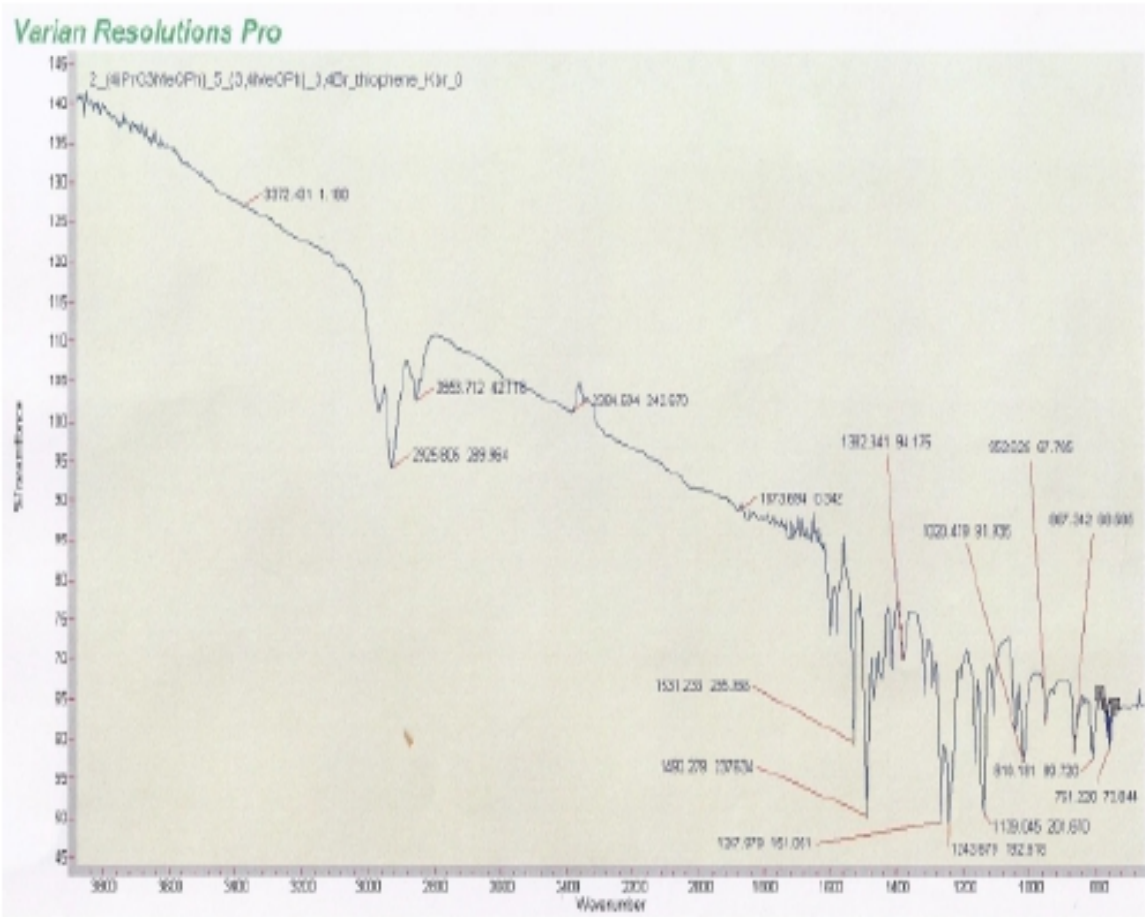


(Figure 30 – GCMS of 2,5-(3-Methoxy-4-Isopropoxyphenyl)-3,4-Dibromo Thiophene)

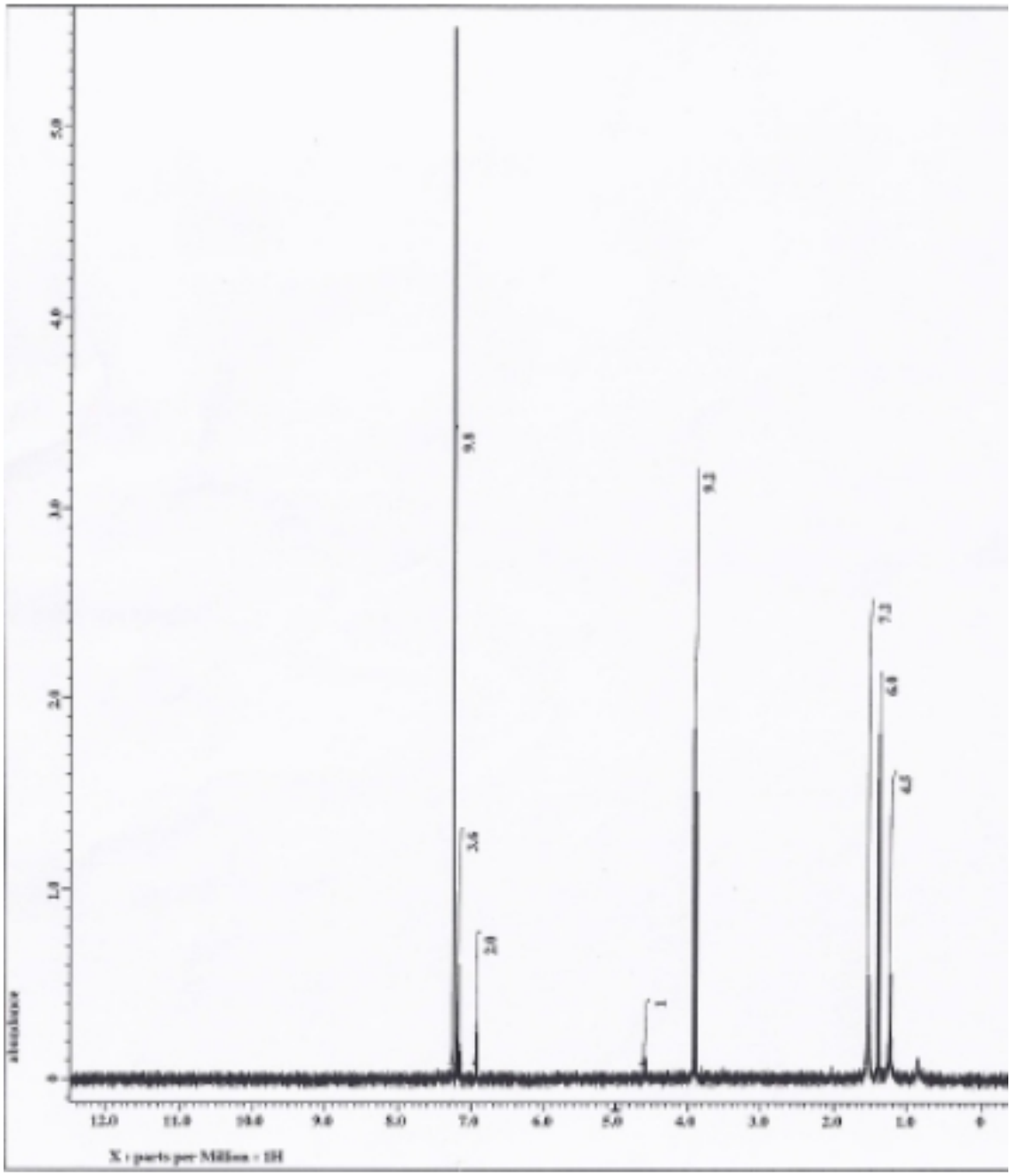
2.3.5.7 2-(3-Methoxy-4-Isopropoxyphenyl)-5-(3,4-Dimethoxyphenyl)-3,4-Dibromo Thiophene



The diaryl 2-(3-methoxy-4-isopropoxyphenyl)-5-(3,4-dimethoxyphenyl)-3,4-dibromo thiophene Suzuki product demonstrated an R_f of 0.19 in the eluting solvent that was a 9:1 mixture of hexanes to ethyl acetate, and was isolated with an average of 39% yield. IR (KBr) 2926 cm^{-1}, 2854 cm^{-1}, 1531 cm^{-1}, 1492 cm^{-1}, 1382 cm^{-1}, 1268 cm^{-1}, 1244 cm^{-1}, 1139 cm^{-1}, 1020 cm^{-1}. ^1H NMR ($CDCl_3$), δ 7.24 (s, 2H), 7.18 (d, 2H) 6.94 (d, 2H), 4.63 (m, 1H), 3.91 (s, 6H), 3.89 (s, 3H), 1.46 (s, 6H).

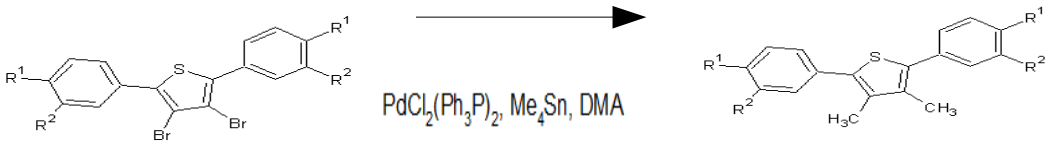


(Figure 31 – IR of 2-(3-Methoxy-4-Isopropoxyphenyl)-5-(3,4-Dimethoxyphenyl)-3,4-Dibromo Thiophene)



(Figure 32 – ^{1}H NMR of 2-(3-Methoxy-4-Isopropoxyphenyl)-5-(3,4-Dimethoxyphenyl)-3,4-Dibromo Thiophene)

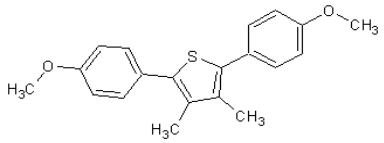
2.3.6 General Procedure for Stille Coupling Reactions



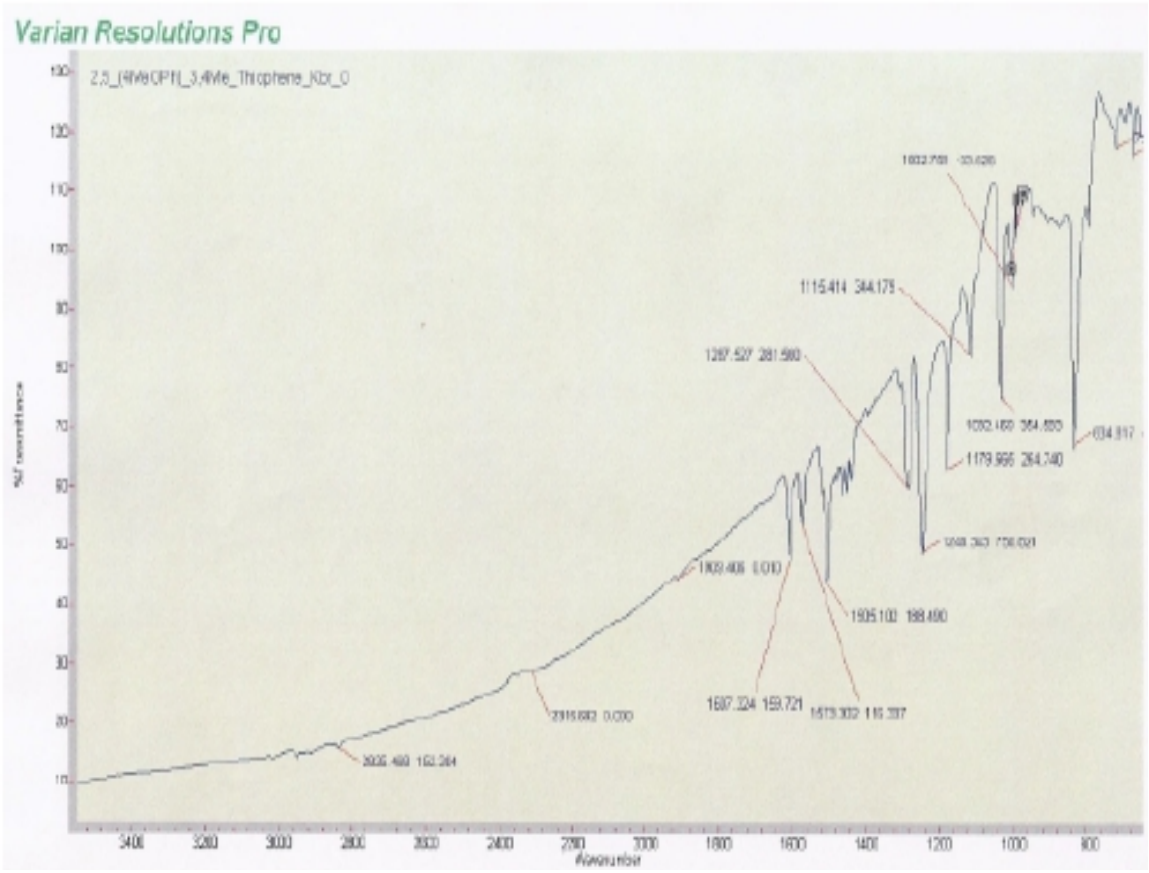
Approximately 0.180 g (or 0.36 mmol) of purified diaryl Suzuki product material, 0.012 g (or 0.05 equivalents) dichlorobis(triphenyl phosphine) Pd^{II}, and 1.0 mL NMP were combined in a 12 mL clear glass vial equipped with a magnetic stir bar. The air in the reaction vessel was replaced with ultra high purity argon gas, and 200 µL (or 4.2 equivalents) of tetramethyl tin was added by syringe. After the addition of the tin reagent the vial was sealed with a PTFE lined cap and place in a 105°C sand bath for 18 hours. If TLC of the resulting product indicated the presence of residual starting material the product would be re-submitted to the reaction conditions. The Stille coupling reaction vessel was removed from heat and allowed to equilibrate with room temperature. Once cooled to room temperature the reaction mixture was transferred to a separatory funnel and diluted with saturated aqueous ammonium chloride and ethyl ether. The aqueous layer was extracted with ether three times in total. The ether layers were collected and washed twice with purified water. The resulting ether solution was dried over magnesium sulfate and filtered through a Whatman #1 qualitative filter paper. The filtrate was then dried on a rotary evaporator under negative pressure until a white solid was produced and subsequently analyzed via GC/MS versus a starting material control. If complete transformation of the starting material was observed then no additional isolation was conducted. The desired product was produced in 98% yield.

2.3.7 Identification of Stille Products

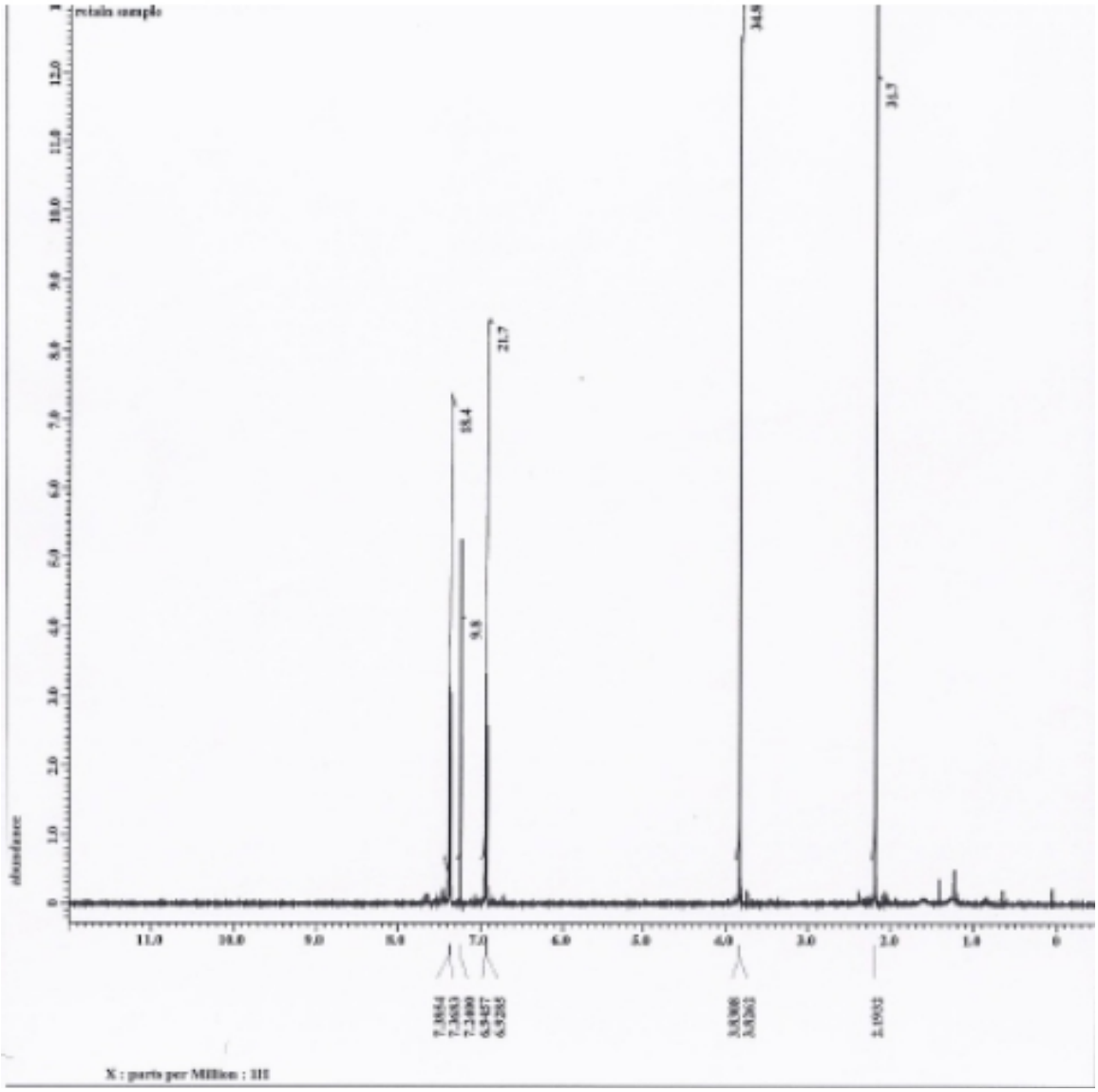
2.3.7.1 2,5-(4-Methoxyphenyl)-3,4-Dimethyl Thiophene



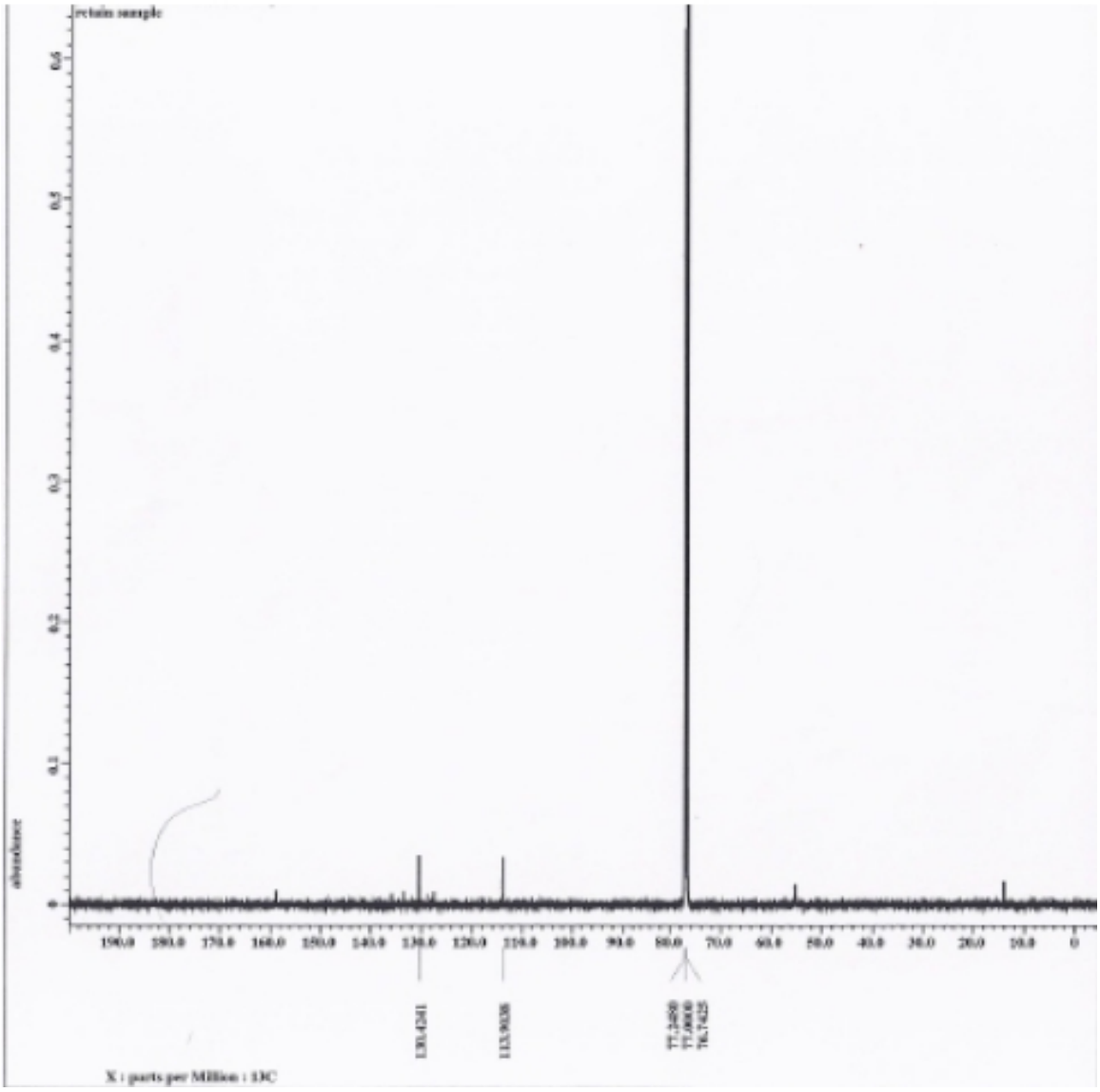
The 2,5-(4-methoxyphenyl)-3,4-dimethyl thiophene demonstrated an R_f of 0.46 in the eluting solvent that was a 9:1 mixture of hexanes to ethylacetate, and was isolated with an 85% yield. IR (KBr) 2835 cm^{-1}, 1607 cm^{-1}, 1573 cm^{-1}, 1505 cm^{-1}, 1288 cm^{-1}, 1248 cm^{-1}, 1180 cm^{-1}, 1115 cm^{-1}, 1032 cm^{-1}, 1003 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ 7.39 (d, 4H), 6.95 (d, 4H), 3.83 (s, 6H), 2.20 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 160, 138, 130, 126, 114, 111, 56, 14.



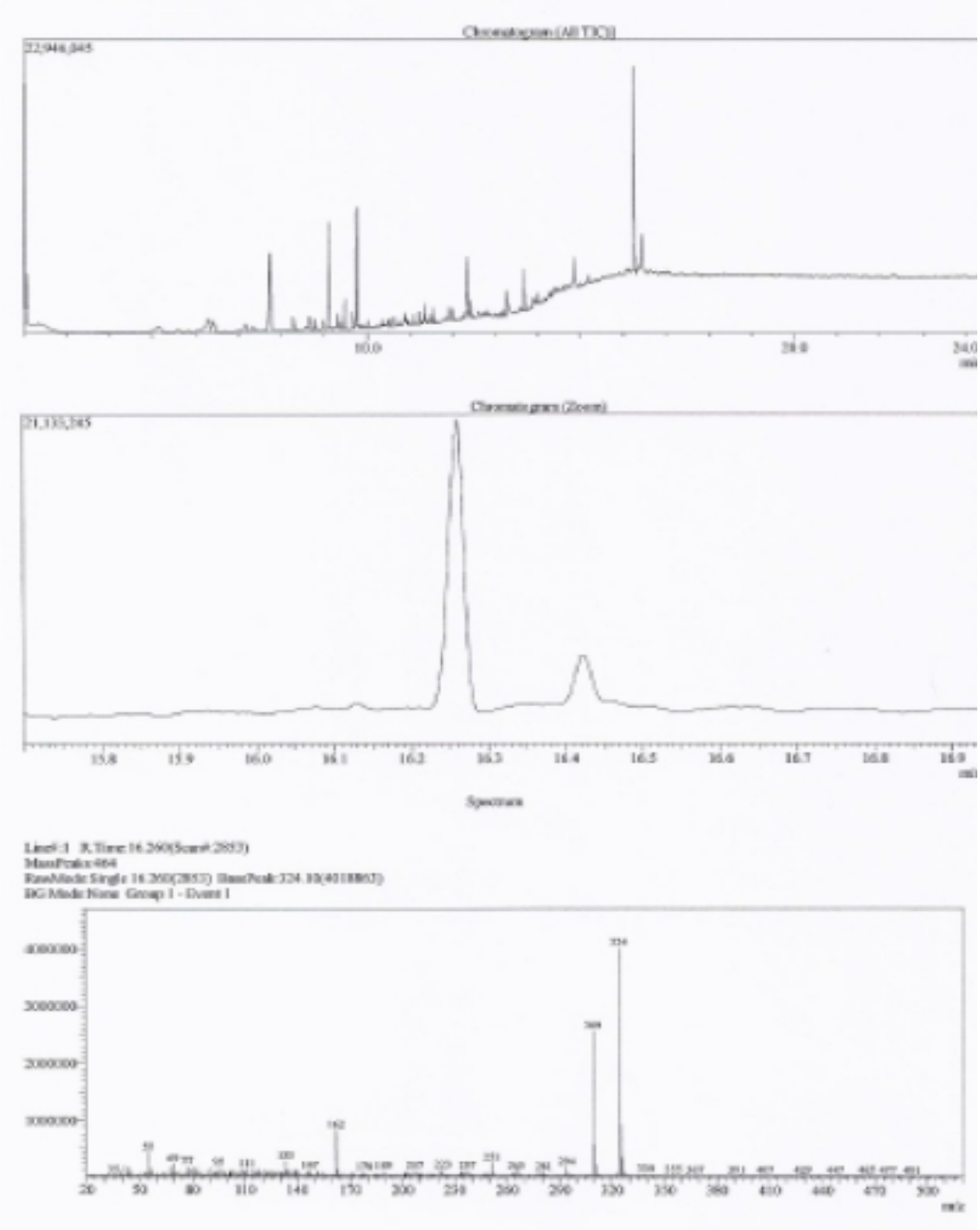
(Figure 33 – IR of 2,5-(4-Methoxyphenyl)-3,4-Dimethyl Thiophene)



(Figure 34 – ^{1}H NMR of 2,5-(4-Methoxyphenyl)-3,4-Dimethyl Thiophene)

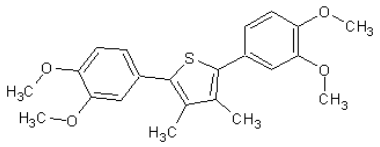


(Figure 35 – ^{13}C NMR of 2,5-(4-Methoxyphenyl)-3,4-Dimethyl Thiophene)

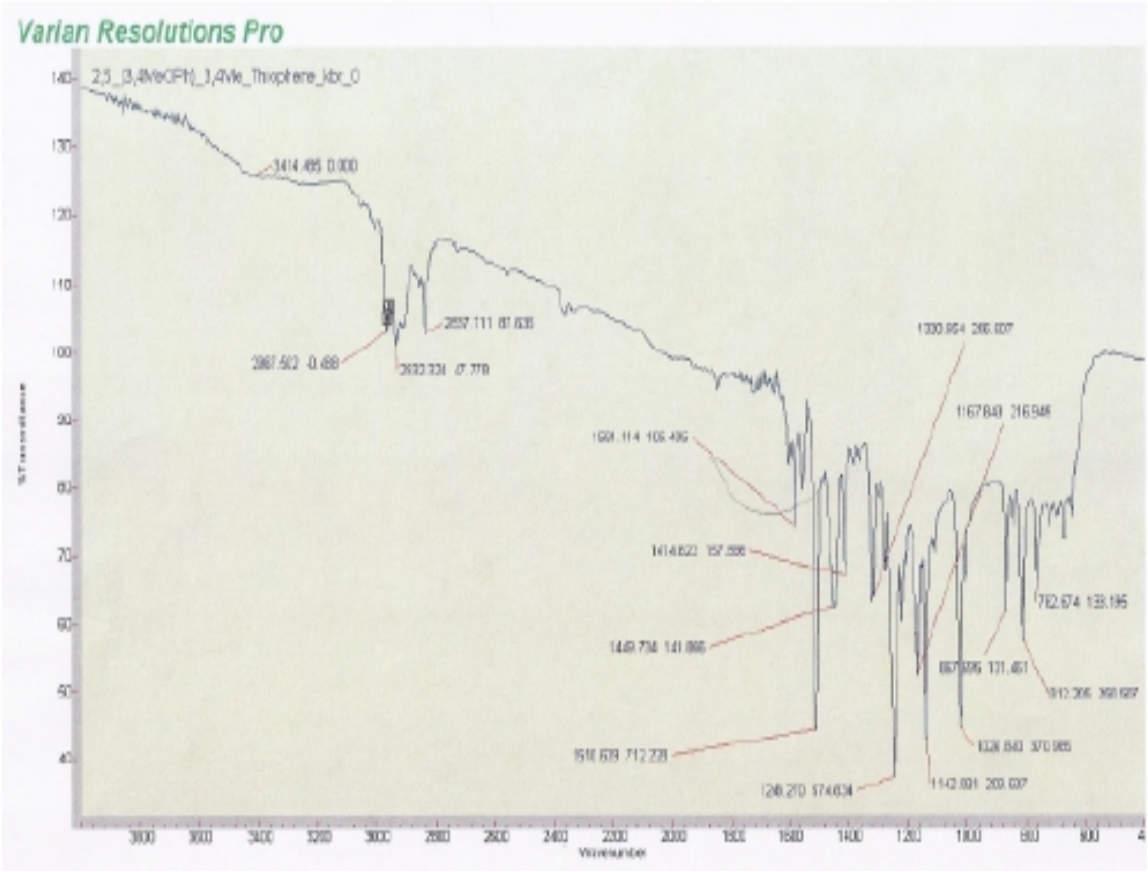


(Figure 36 – GCMS of 2,5-(4-Methoxyphenyl)-3,4-Dimethyl Thiophene)

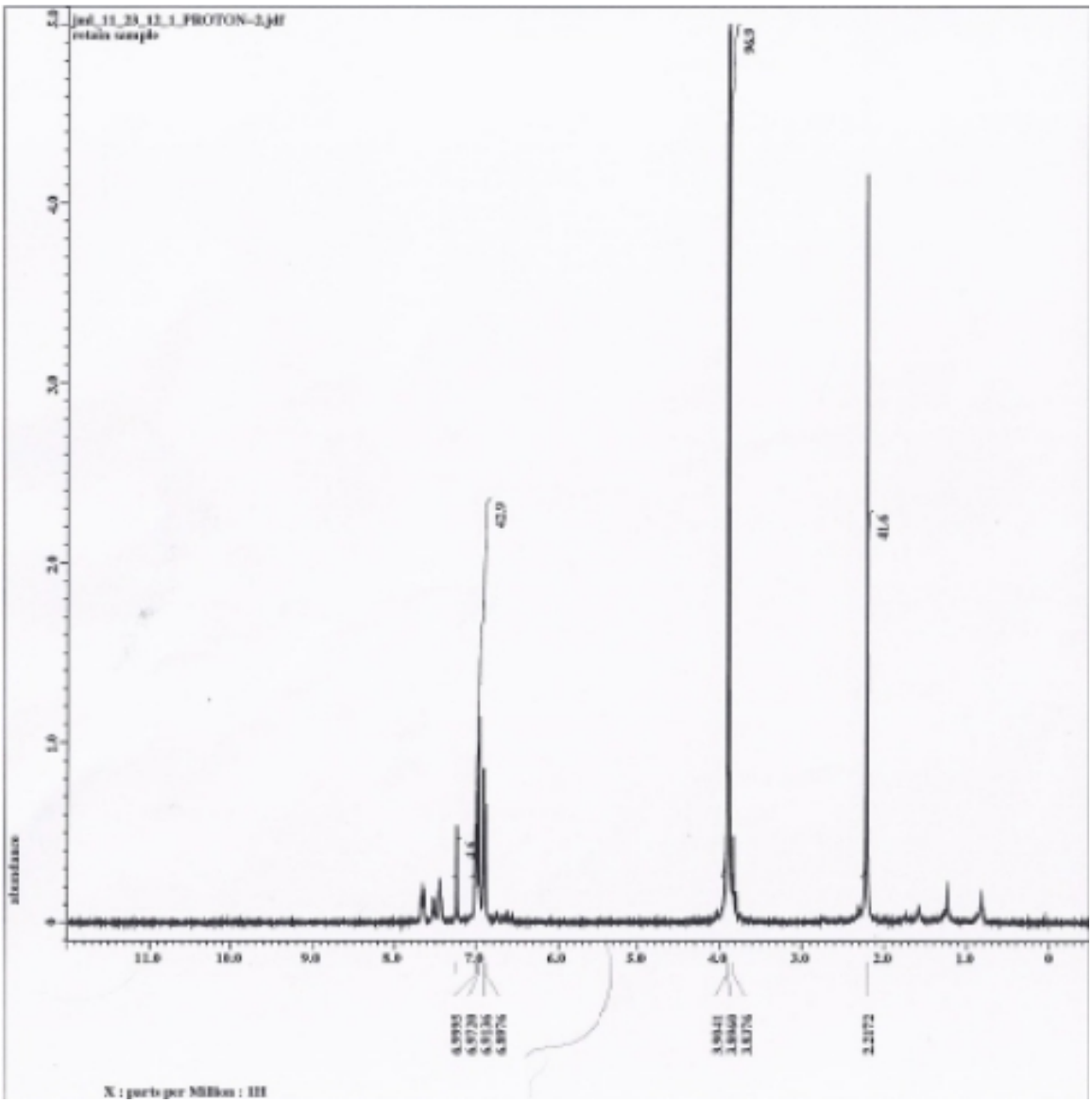
2.3.7.2 2,5-(3,4-Dimethoxyphenyl)-3,4-Dimethyl Thiophene



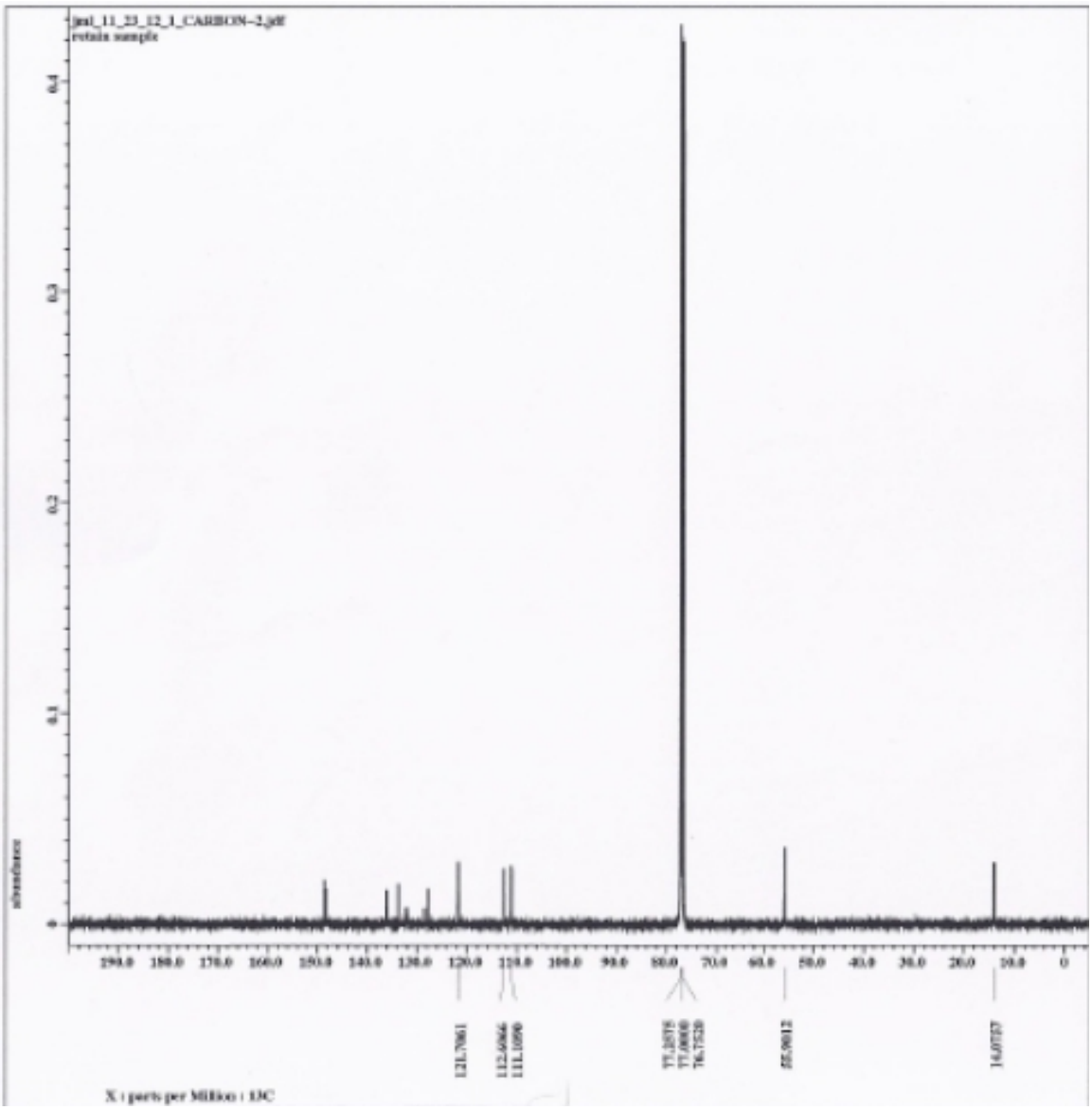
The 2,5-(3,4-dimethoxyphenyl)-3,4-dimethyl thiophene demonstrated an R_f of 0.25 in the eluting solvent that was 4:1 hexanes to ethylacetate, and was isolated with a 98% yield. IR (KBr) 2968 cm^{-1}, 2932 cm^{-1}, 2838 cm^{-1}, 1581 cm^{-1}, 1511 cm^{-1}, 1450 cm^{-1}, 1415 cm^{-1}, 1321 cm^{-1}, 1248 cm^{-1}, 1168 cm^{-1}, 1142 cm^{-1}, 1027 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ 7.24 (s, 2H), 7.00 (d, 2H) 6.91 (d, 2H), 3.91 (s, 6H), 3.90 (s, 6H), 2.22 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 149, 148, 136, 134, 128, 127, 122, 113, 111, 56, 14.



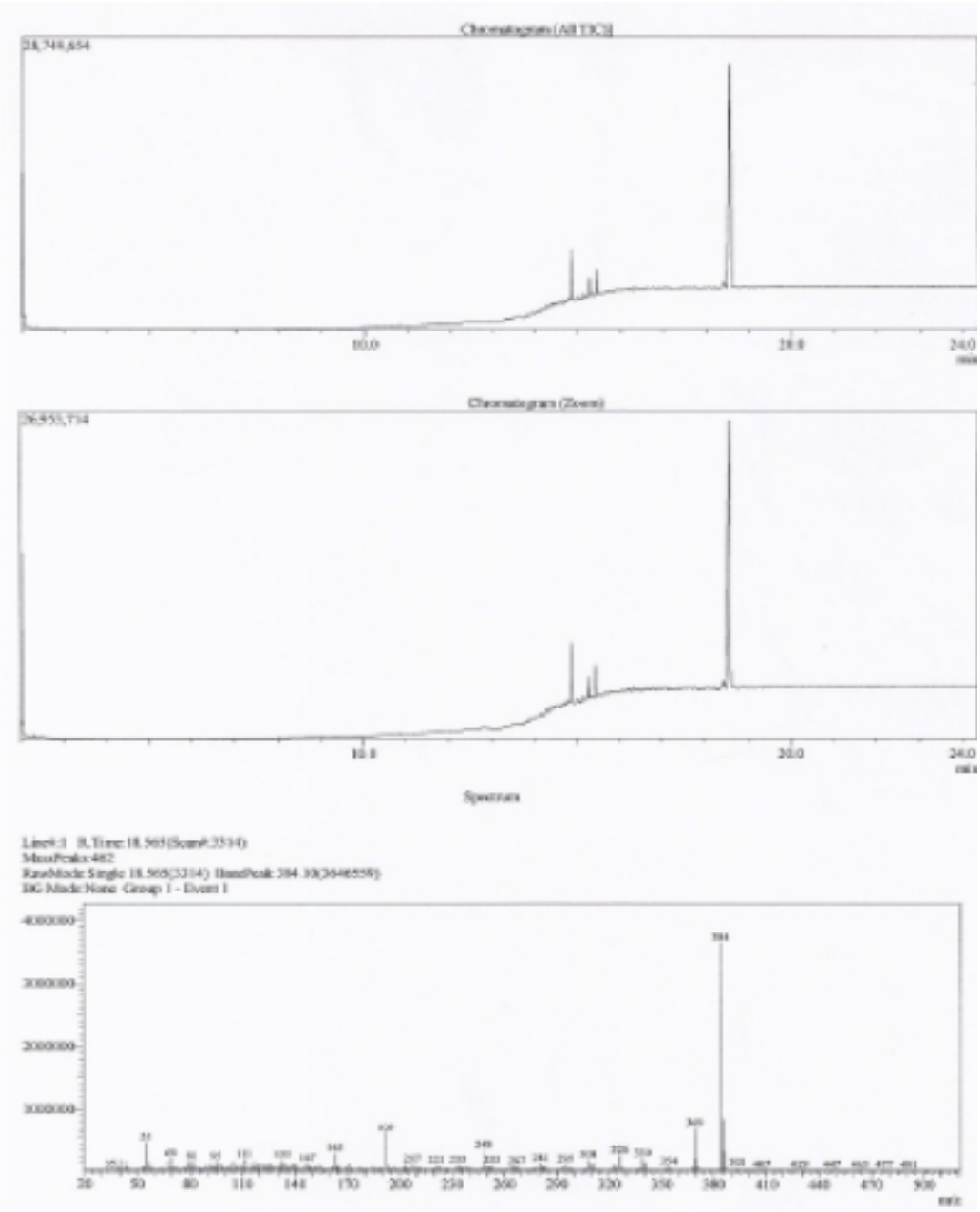
(Figure 37 – IR of 2,5-(3,4-Dimethoxyphenyl)-3,4-Dimethyl Thiophene)



(Figure 38 – ^{1}H NMR of 2,5-(3,4-Dimethoxyphenyl)-3,4-Dimethyl Thiophene)

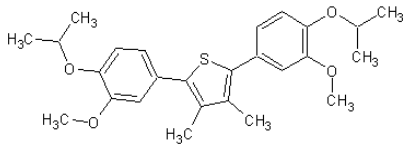


(Figure 39 – ^{13}C NMR of 2,5-(3,4-Dimethoxyphenyl)-3,4-Dimethyl Thiophene)

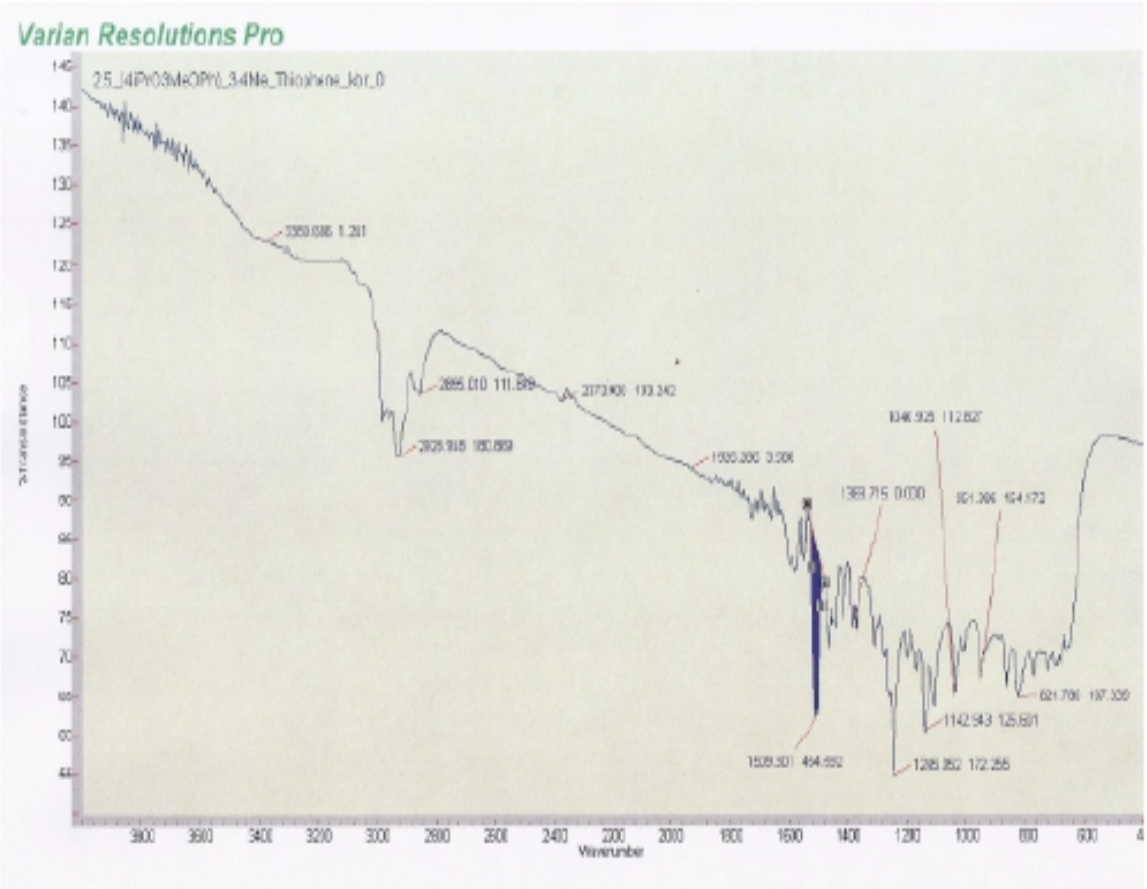


(Figure 40 – GCMS of 2,5-(3,4-Dimethoxyphenyl)-3,4-Dimethyl Thiophene)

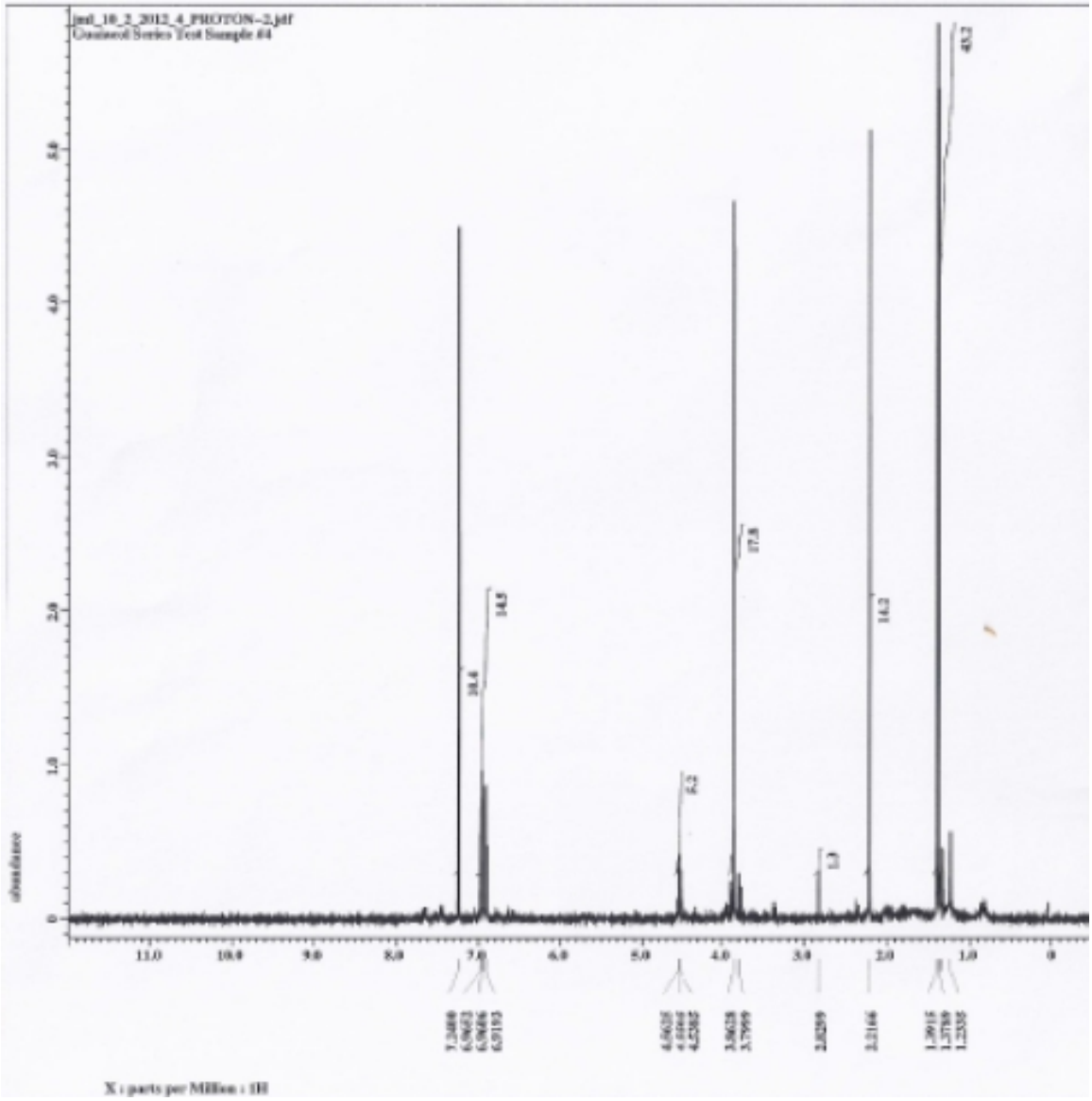
2.3.7.3 2,5-(3-Methoxy-4-Isopropoxyphenyl)-3,4-Dimethyl Thiophene



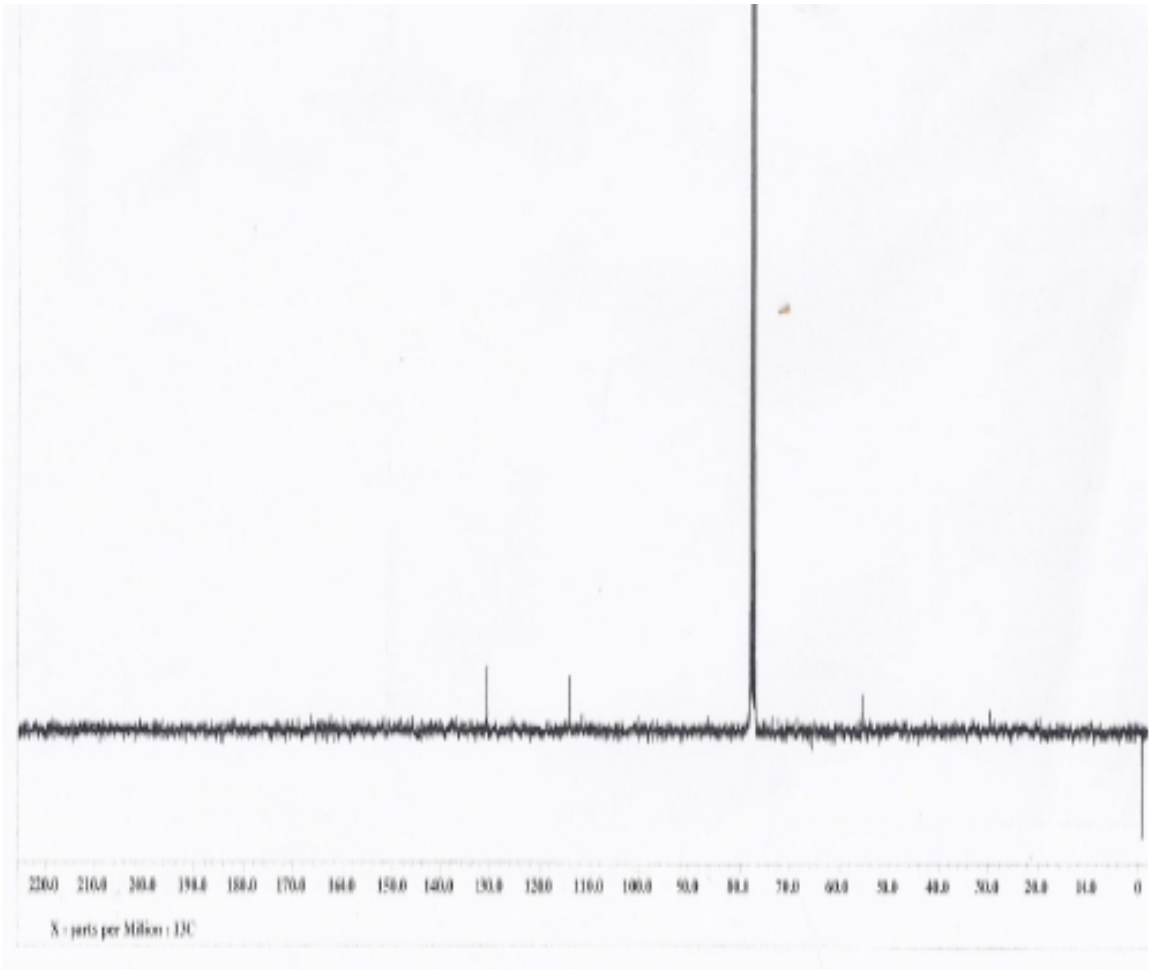
The 2,5-(3-methoxy-4-isopropoxyphenyl)-3,4-dimethyl thiophene demonstrated an R_f of 0.29 in the eluting solvent that was a 4:1 mixture of hexanes to ethylacetate, and was isolated with an 81% yield. IR (KBr) 2928 cm^{-1}, 2855 cm^{-1}, 1509 cm^{-1}, 1384 cm^{-1}, 1245 cm^{-1}, 1142 cm^{-1}, 1041 cm^{-1}, 951 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ 7.24 (s, 2H), 7.00 (d, 2H), 6.96 (d, 2H), 4.56 (m, 2H), 3.86 (s, 6H), 2.22 (s, 6H), 1.39 (s, 12H). ^{13}C NMR ($CDCl_3$) δ 150, 149, 138, 126, 122, 115, 113, 112, 71, 56, 28.



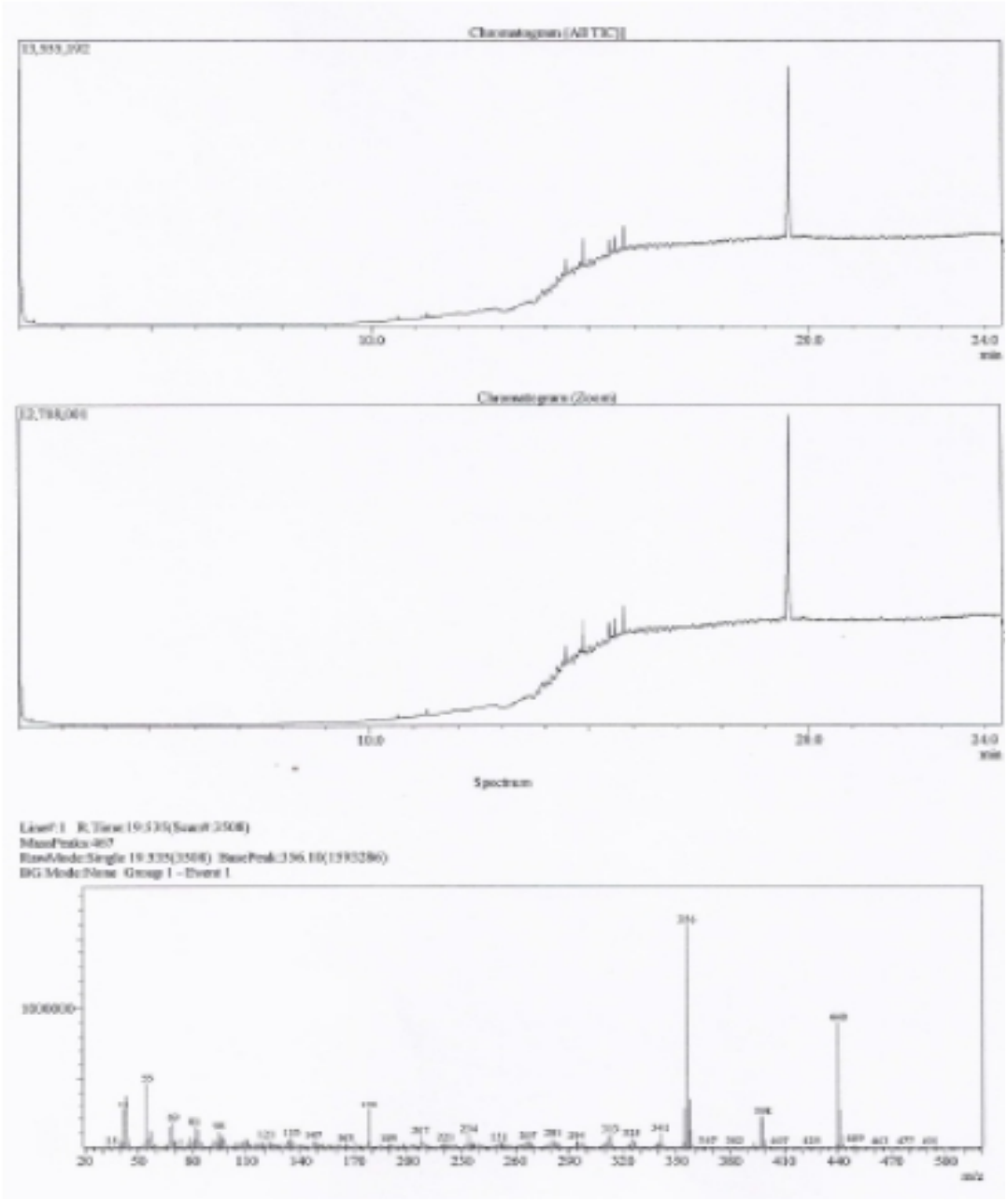
(Figure 41 – IR of 2,5-(3-Methoxy-4-Isopropoxyphenyl)-3,4-Dimethyl Thiophene)



(Figure 42 – ^{1}H NMR of 2,5-(3-Methoxy-4-Isopropoxyphenyl)-3,4-Dimethyl Thiophene)

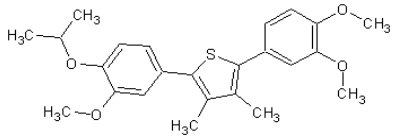


(Figure 43 – ^{13}C NMR of 2,5-(3-Methoxy-4-Isopropoxyphenyl)-3,4-Dimethyl Thiophene)

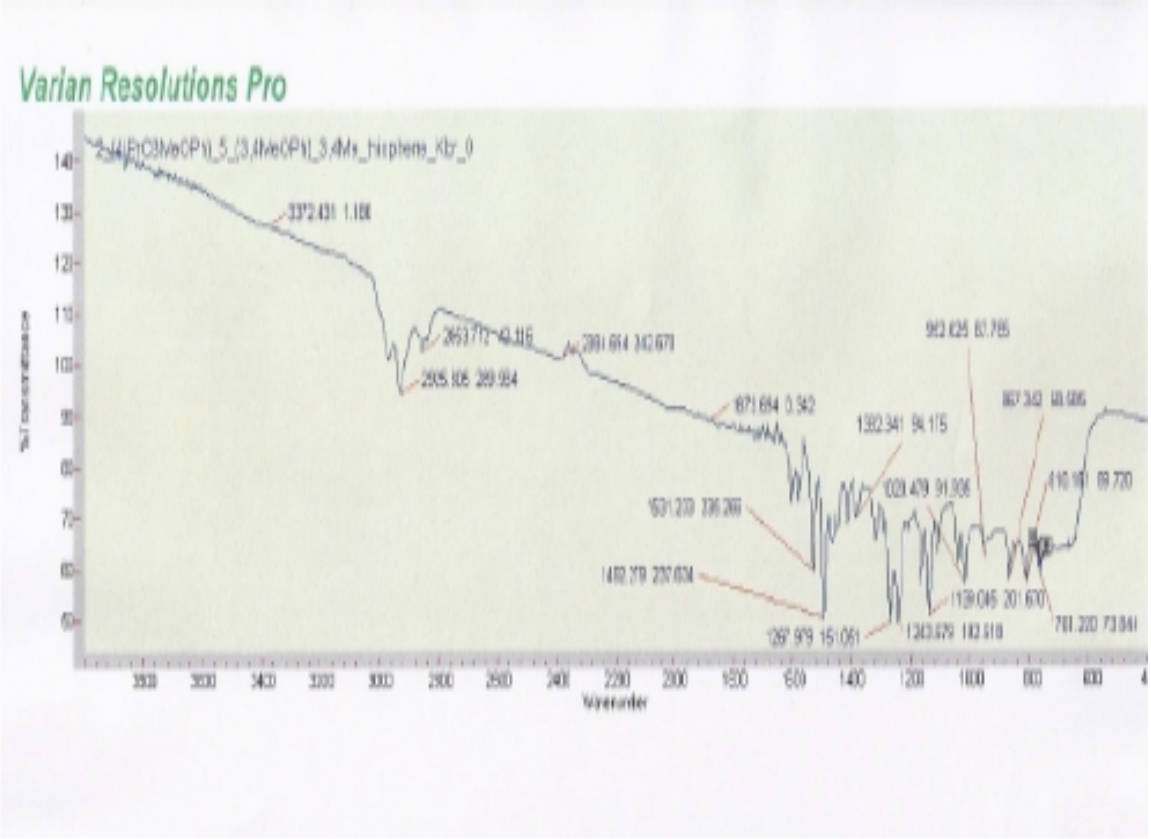


(Figure 44 – GCMS of 2,5-(3-Methoxy-4-Isopropoxyphenyl)-3,4-Dimethyl Thiophene)

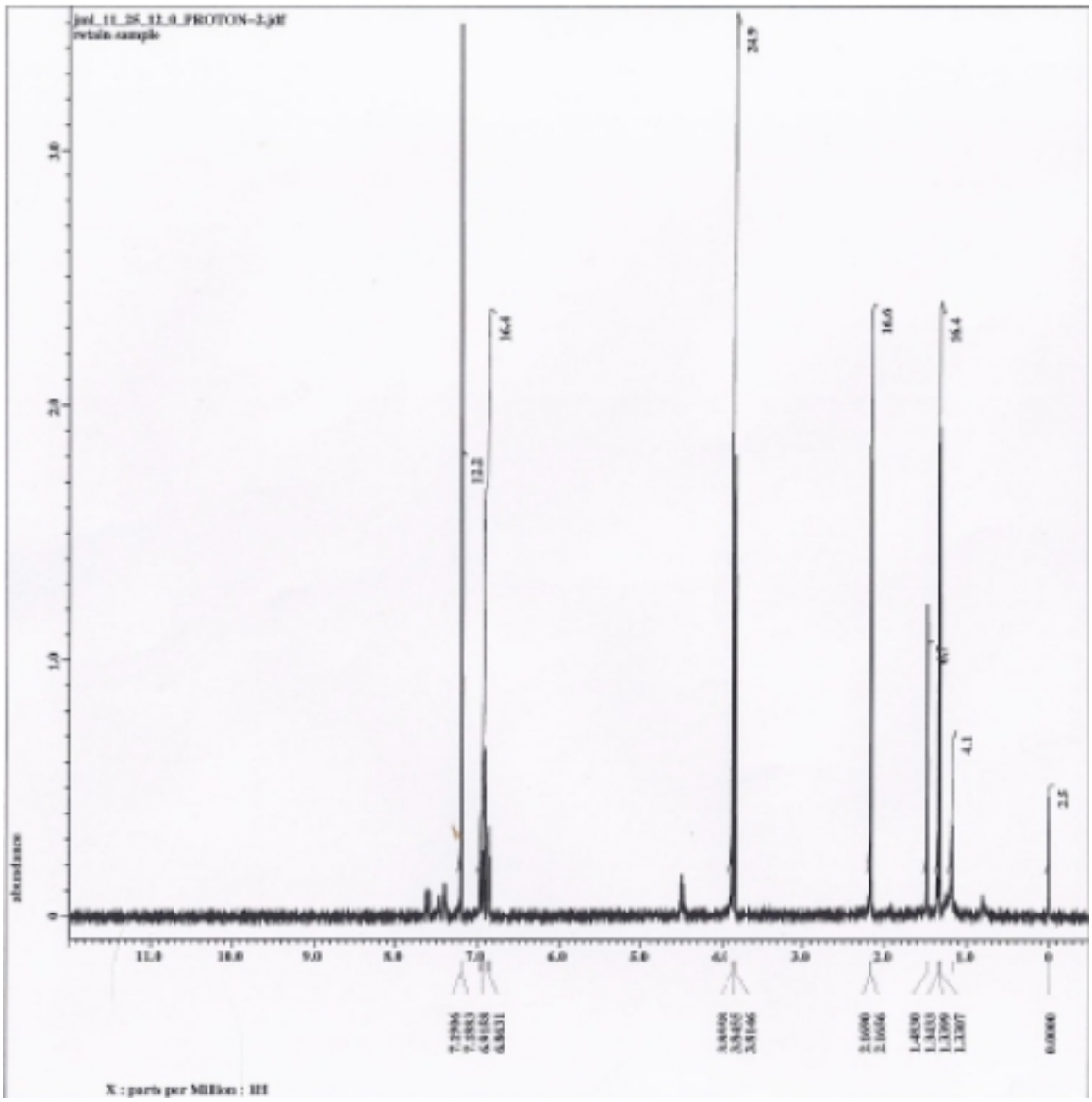
2.3.7.4 2-(3-Methoxy-4-Isopropoxyphenyl)-5-(3,4-Dimethoxyphenyl)-3,4-Dimethyl Thiophene



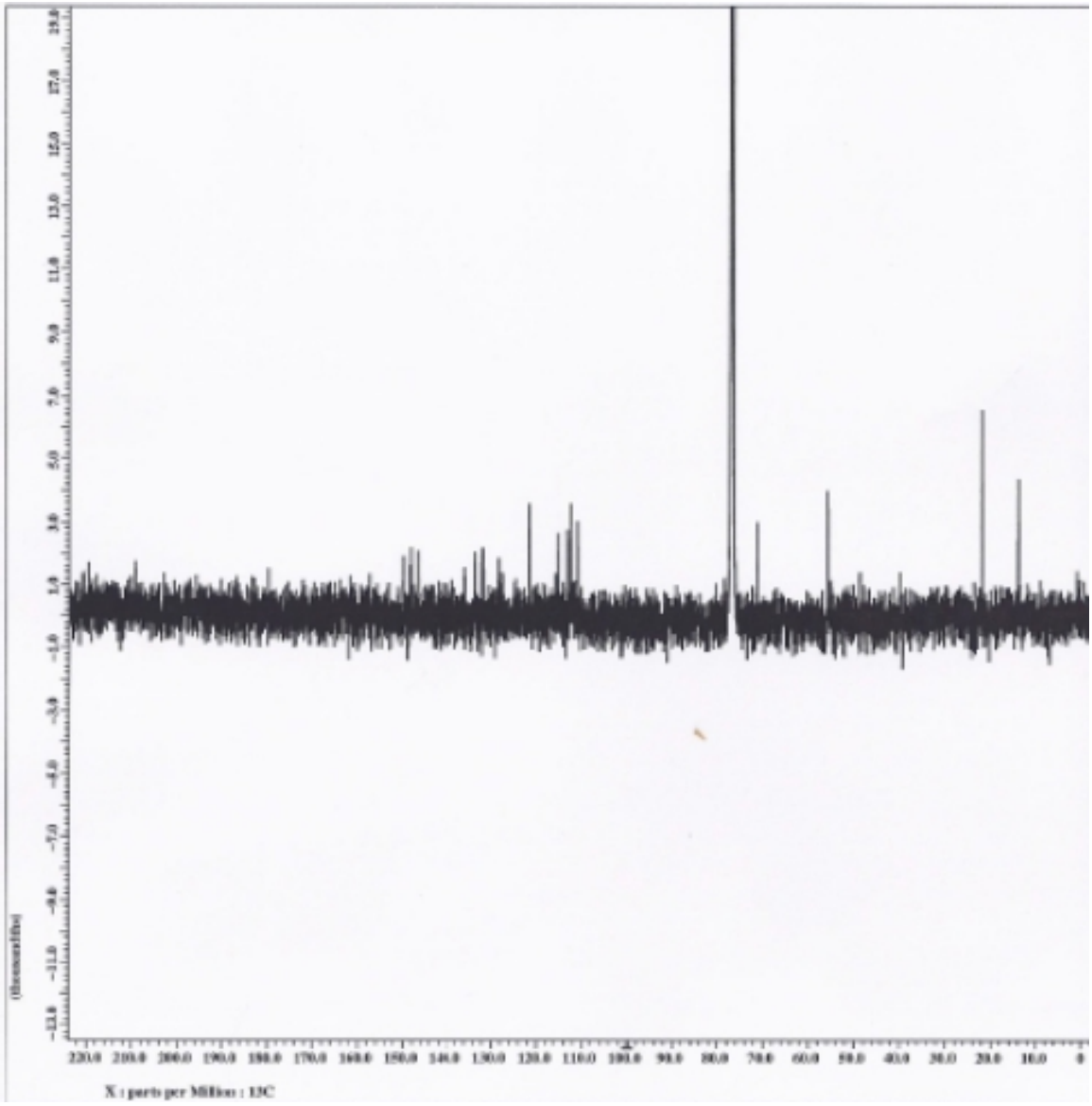
The 2-(3-methoxy-4-isopropoxyphenyl)-5-(3,4-dimethoxyphenyl)-3,4-dimethyl thiophene was obtained in 102% yield. IR (KBr) 2926 cm^{-1}, 2853 cm^{-1}, 1531 cm^{-1}, 1492 cm^{-1}, 1382 cm^{-1}, 1268 cm^{-1}, 1244 cm^{-1}, 1139 cm^{-1}, 1020 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ 7.19 (s, 2H), 6.91 (d, 2H) 6.86 (d, 2H), 4.51 (m, 1H), 3.86 (s, 6H), 3.81 (s, 3H), 2.17 (s, 6H), 1.48 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 150, 149, 138, 126, 122, 114, 113, 112, 71, 54, 22, 14.



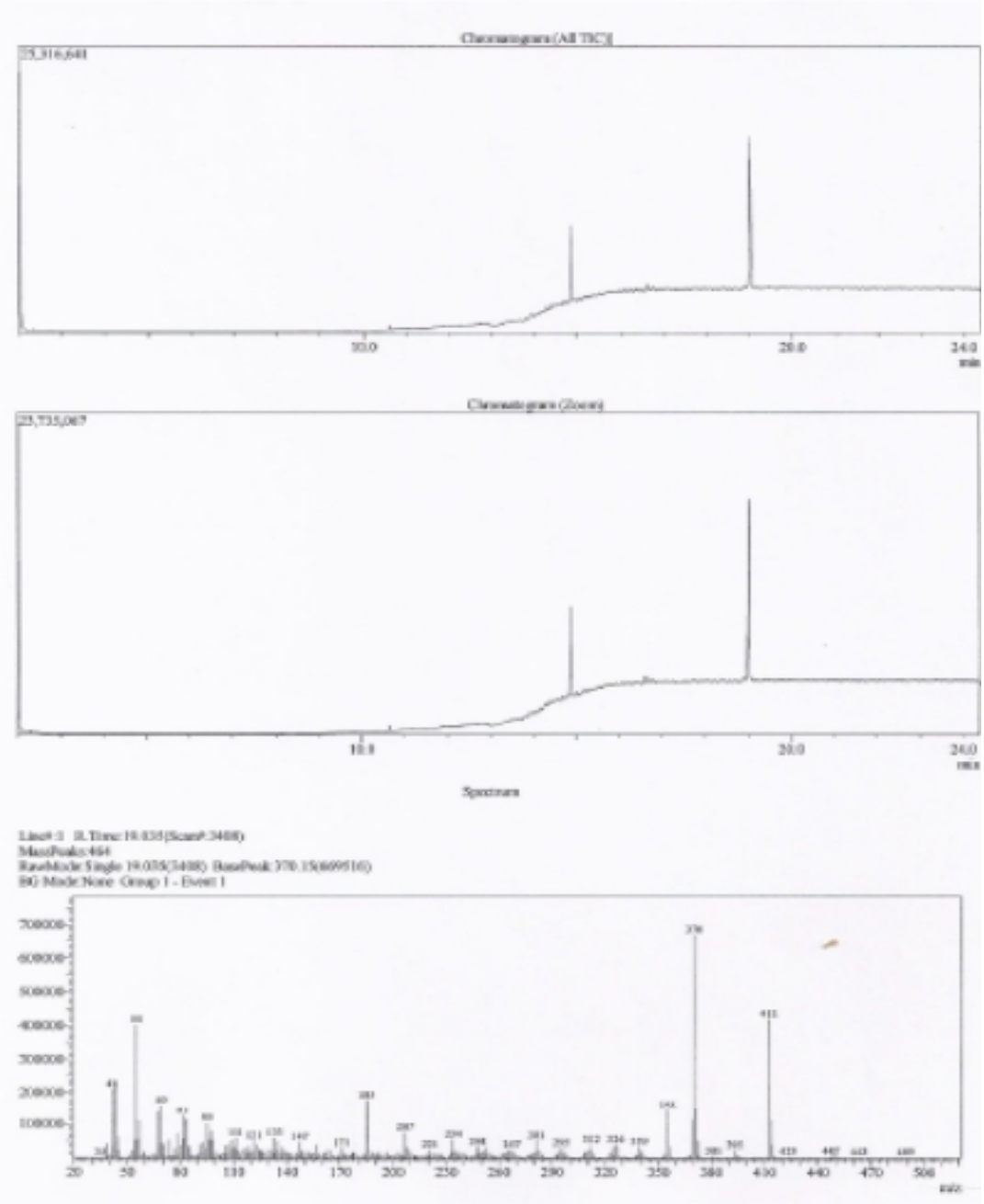
(Figure 45 – IR of 2-(3-Methoxy-4-Isopropoxyphenyl)-5-(3,4-Dimethoxyphenyl)-3,4-Dimethyl Thiophene)



(Figure 46 – ^{1}H NMR of 2-(3-Methoxy-4-Isopropoxyphenyl)-5-(3,4-Dimethoxyphenyl)-3,4-Dimethyl Thiophene)



(Figure 47 – ^{13}C NMR of 2-(3-Methoxy-4-Isopropoxyphenyl)-5-(3,4-Dimethoxyphenyl)-3,4-Dimethyl Thiophene)



(Figure 48 – GCMS of 2-(3-Methoxy-4-Isopropoxyphenyl)-5-(3,4-

Dimethoxyphenyl)-3,4-Dimethyl Thiophene)

2.3.8 General Procedure for Nickel Reagent Desulfurization and Reduction

Three different protocols were tested in an attempt to desulfurize and reduce the diaryl dimethyl thiophene species generated. Initially 0.070 g (0.16 mmol) of 2,5-diaryl-3,4-dimethyl thiophene was dispersed into 20.0 mL of methanol, combined with 0.15 g of activated Raney 2800 nickel 50% slurry in water, placed on a Parr hydrogenator, and pressurized to 30 atmospheres (atm) with hydrogen gas (H_2). The hydrogenator was then activated and the reaction was allowed to proceed for 21 hours. Additional attempts on other tetrasubstituted thiophenes with increased H_2 pressure and longer reaction times were also assayed for completeness of reaction. It has been noted that the nature of the Raney nickel reagent makes molar concentration calculations only speculative at best and possibly misleading if reported as exact values.[23]

A second method begins by dispersing approximately 0.12 g (0.28 mmol) of 2,5-diaryl-3,4-dimethyl thiophene into 30.0 mL of ethanol in round bottom flask equipped with a magnetic stir bar. Then 1.9850 g (8.35 mmol) of nickel chloride hexahydrate was added and the reaction vessel was then transferred to a 0°C icebath. At this point 0.949 g (0.0251 mol) sodium borohydride was combined with 5.0 mL purified water to produce a 5.0 molar solution. The desired ratio of reagent was 30 equivalents of nickel species and 90 equivalents of sodium borohydride for each equivalent of starting material.[22] The 5.0

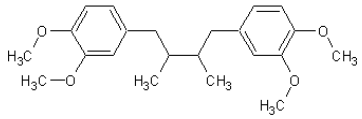
molar sodium borohydride solution was added dropwise with stirring at the rate of one drop per 3 seconds until all of the material was transferred to the reaction vessel. The addition of sodium borohydride produced a violent, exothermic response and a black precipitate was immediately observed to form. The reaction vessel remained in the icebath for 20 minutes then was transferred to a heated sand bath at 80.0°C and allowed to reflux for 30 minutes. Several protocol modifications were attempted to improve the outcome of this reaction. Of note were the attempts made employing substituted solvent solutions to disperse both the starting material and reagents. Additionally a number of reaction temperatures and durations were also tested in an attempt to improve results.

The final and most successful method for desulfurization and reduction begins by preparing the Raney 2800 nickel 50% slurry in water in a manner that makes it highly activated.[23] Raney 2800 nickel 50% slurry in water (1.5012 g) was transferred to a 50 mL beaker, diluted with approximately 20 mL of purified water, swirled to mix thoroughly, allowed to settle, and the liquid decanted. The process was repeated using 20mL aliquots of purified water until a total volume of 500 mL was decanted. After that volume each subsequently decanted solution was assayed for hydrogen ion concentration with pH test strips. The first few decanted solutions were cloudy, however by the time the solutions were tested by pH strip they were quite clear. When the decanted solution was determined to be neutral the purified water was replaced with 20 mL aliquots of ethanol. The ethanol wash process continued until approximately 100 mL total volume was used. The resulting highly activated nickel reagent was then transferred, with the help of an additional 5.0 mL ethanol, to a stirring solution of 0.0576 g (0.18mmol) 2,5-diaryl-3,4-dimethyl thiophene previously dispersed into 10.0 mL ethanol at 60.5°C.

After 30 minutes the reaction was removed from heat. Heterogeneous catalyst from desulfurization and reduction reactions was removed by filtration through Whatmann #1 filter qualitative filter paper. The filtrate was then concentrated under vacuum on a rotary evaporator until a white solid was produced. The resulting solid was transferred to a separatory funnel and diluted with purified water, and extracted with ethyl ether. The aqueous layer was extracted two additional times with ethyl ether before the organic layers were combined and dried over magnesium sulfate. The mixture was once again filtered through Whatmann #1 filter paper prior to being dried under vacuum generating the product.

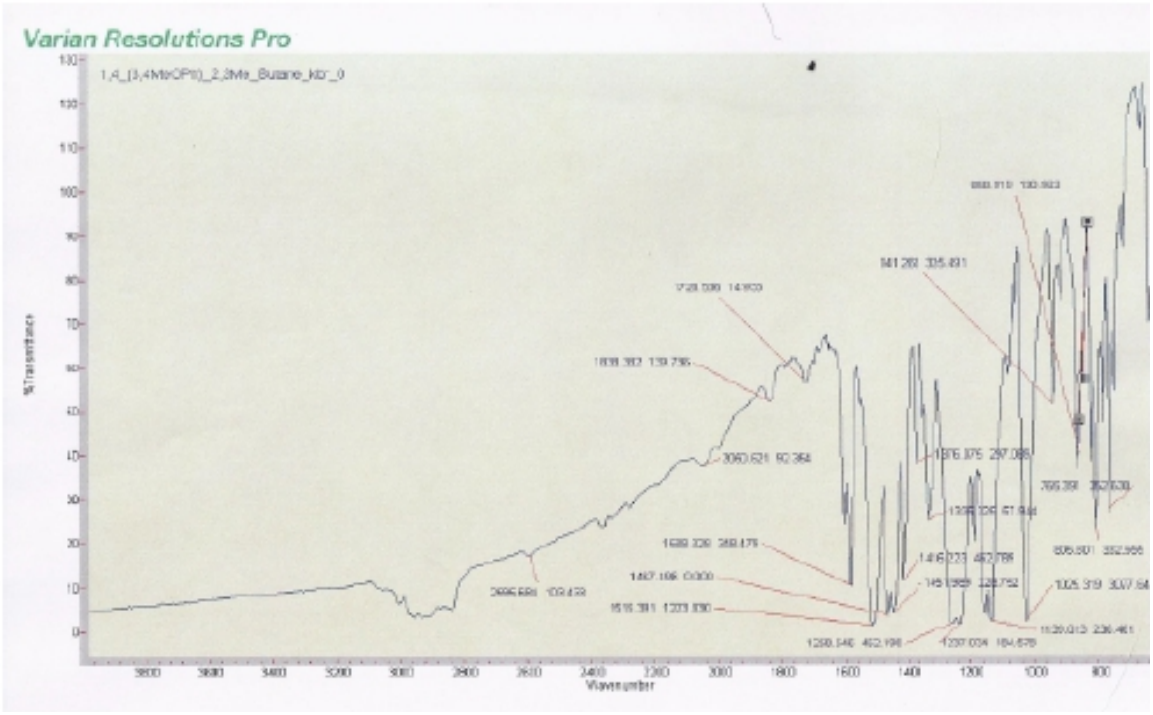
2.3.9 Identification of Raney Nickel Products

2.3.9.1 1,4-(3,4-Dimethoxyphenyl)-2,3-Dimethyl Butane

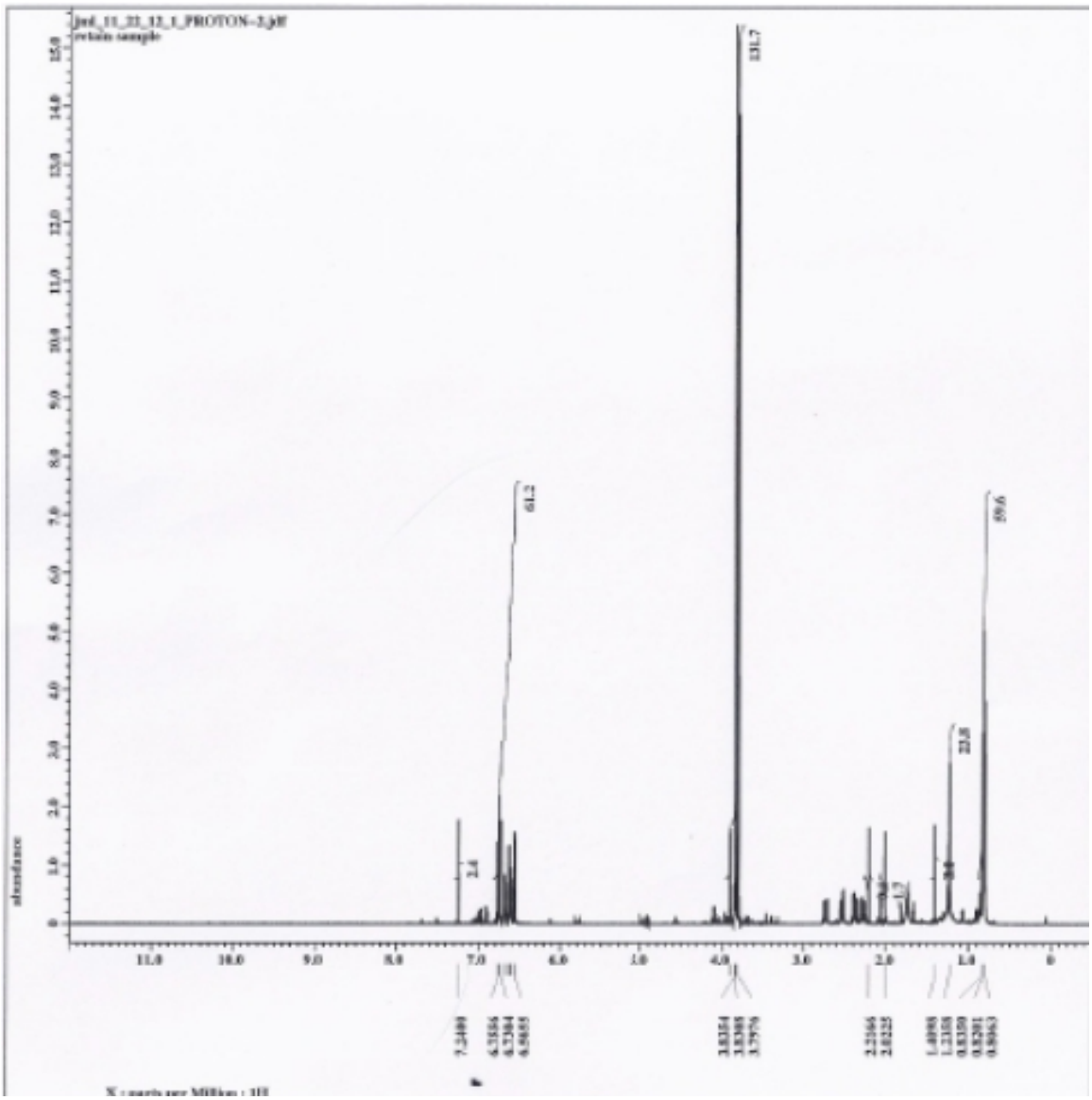


The 1,4-(3,4-dimethoxyphenyl)-2,3-dimethyl butane was obtained in 79% yield as a diastereomeric mix of the 2-(R)-3-(S) *meso* compound and the 2-(R)-3-(R)/2-(S)-3-(S) *racemate.* The products exhibited R_f values of 0.205 and 0.21 respectively in the eluting solvent that was a 4:1 mixture of hexanes to ethyl acetate. The diastereomers were observed as two distinct peaks when analyzed by Hewlett Packard 5890 gas chromatograph with a 5970 mass spectrometric detector. The retention times of the *meso* and *racemic* products were 15.01 and 14.9 minutes respectively as confirmed by x-ray

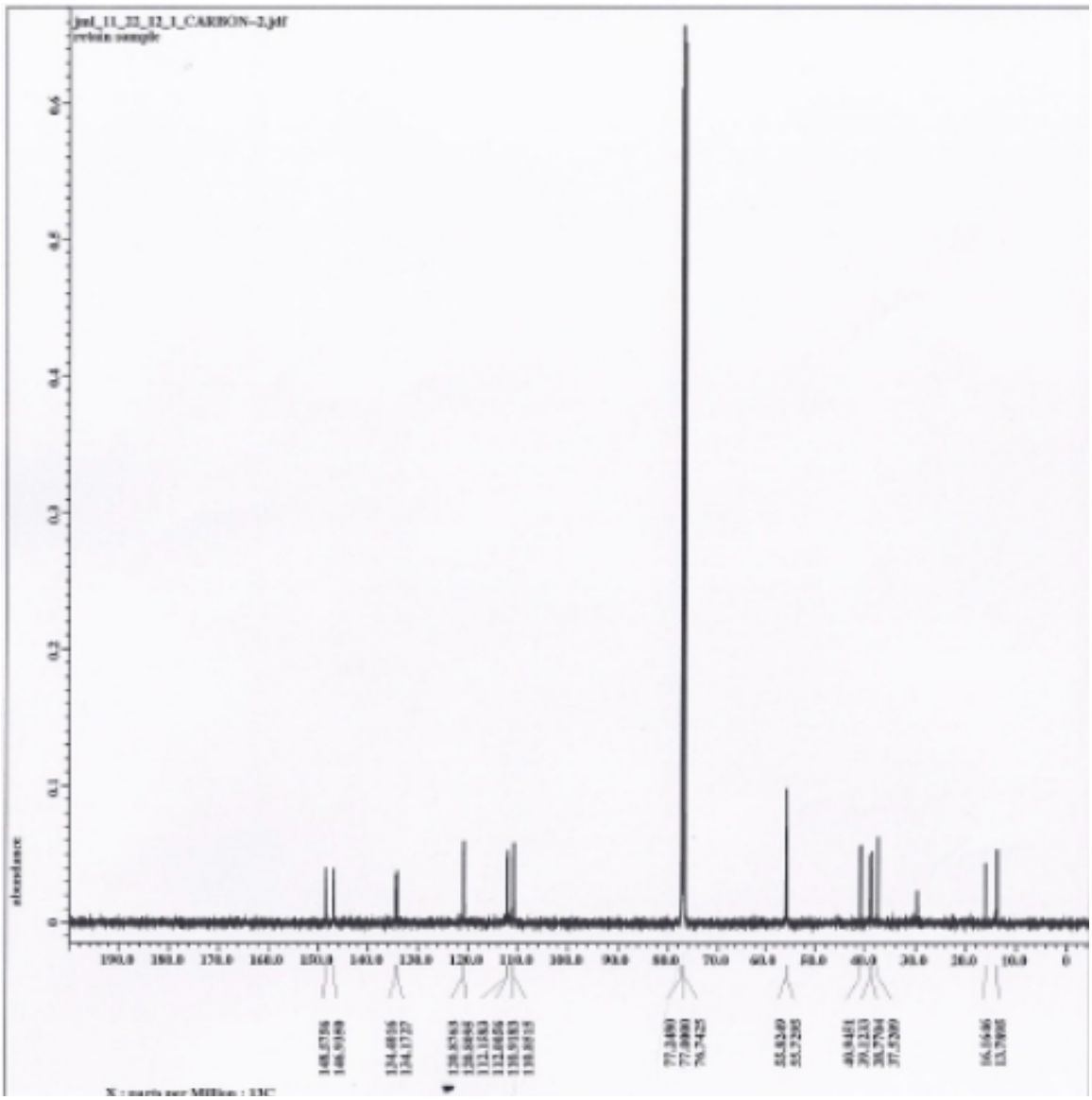
crystallography. IR (KBr) 2596 cm^{-1}, 2051 cm^{-1}, 1838 cm^{-1}, 1729 cm^{-1}, 1588 cm^{-1}, 1515 cm^{-1}, 1467 cm^{-1}, 1452 cm^{-1}, 1416 cm^{-1}, 1376 cm^{-1}, 1259 cm^{-1}, 1237 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ 7.24 (s, 2H), 6.76 (d, 2H), 6.57 (d, 2H), 3.85 (s, 6H), 3.83 (s, 6H), 2.22 (d, 6H), 1.24 (d, 4H), 0.83 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 149, 147, 135, 134, 121, 112, 110, 56, 41, 39, 38, 16, 14.



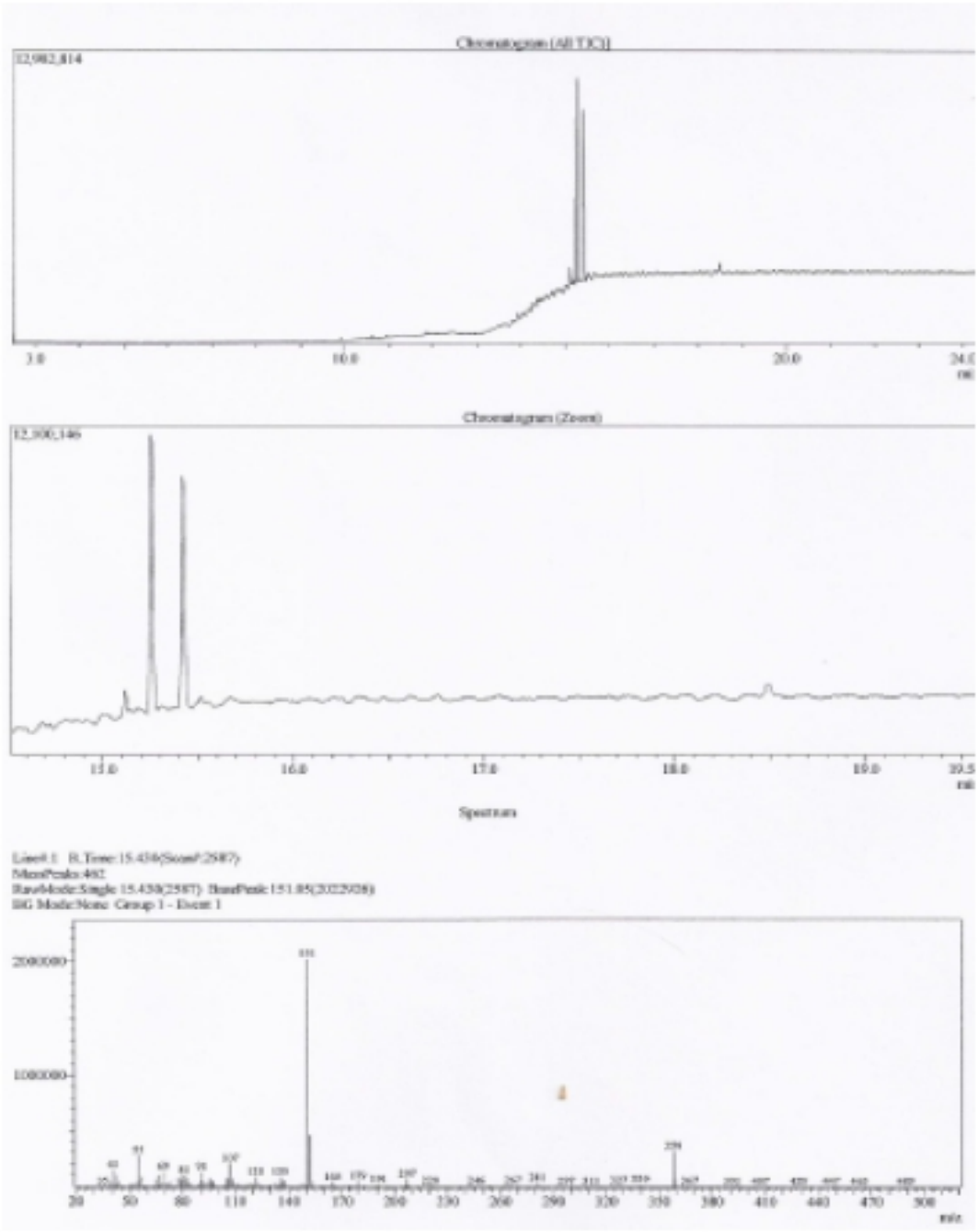
(Figure 49 – IR of 1,4-(3,4-Dimethoxyphenyl)-2,3-Dimethyl Butane)



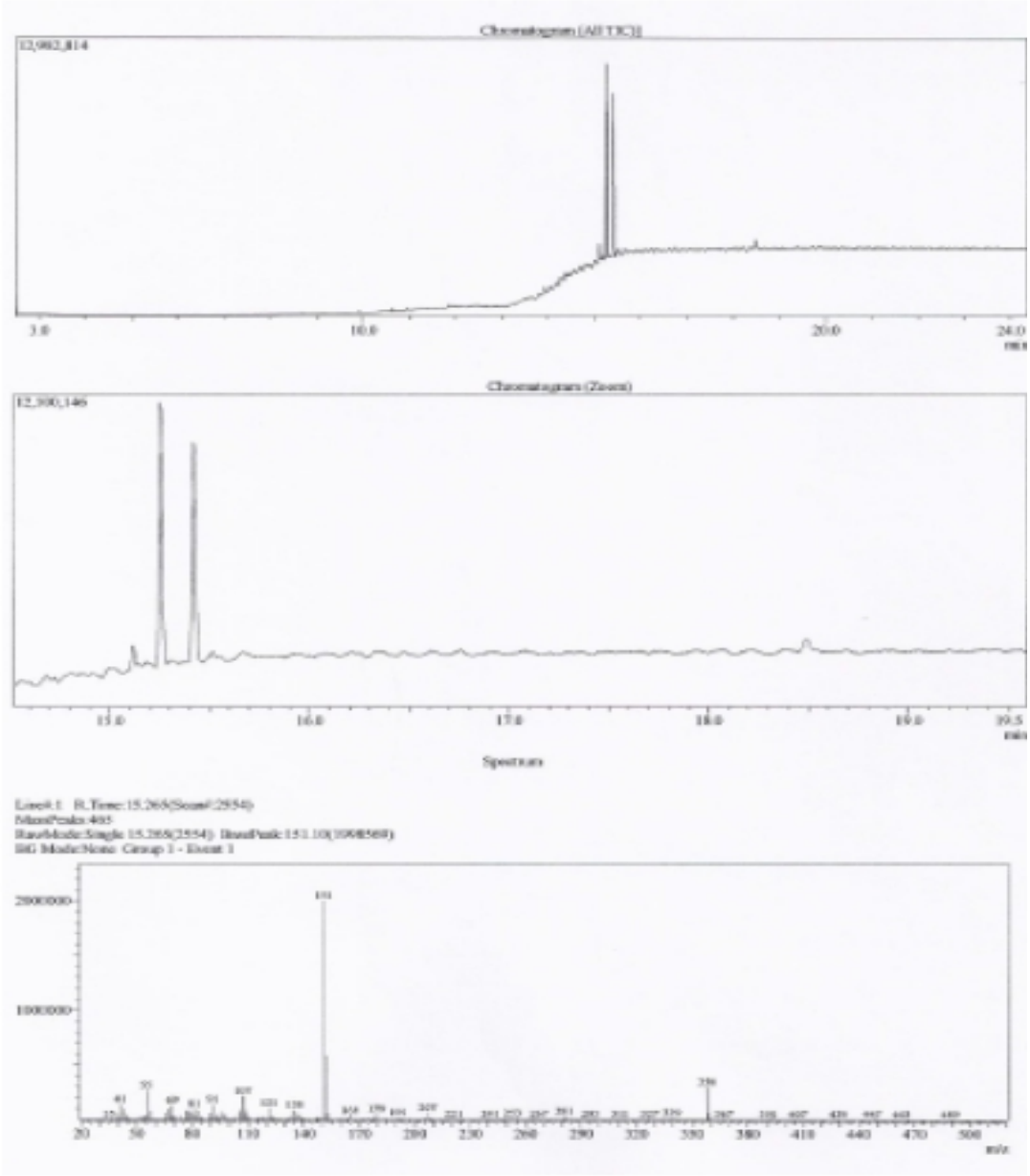
(Figure 50 – ^{1}H NMR of 1,4-(3,4-Dimethoxyphenyl)-2,3-Dimethyl Butane)



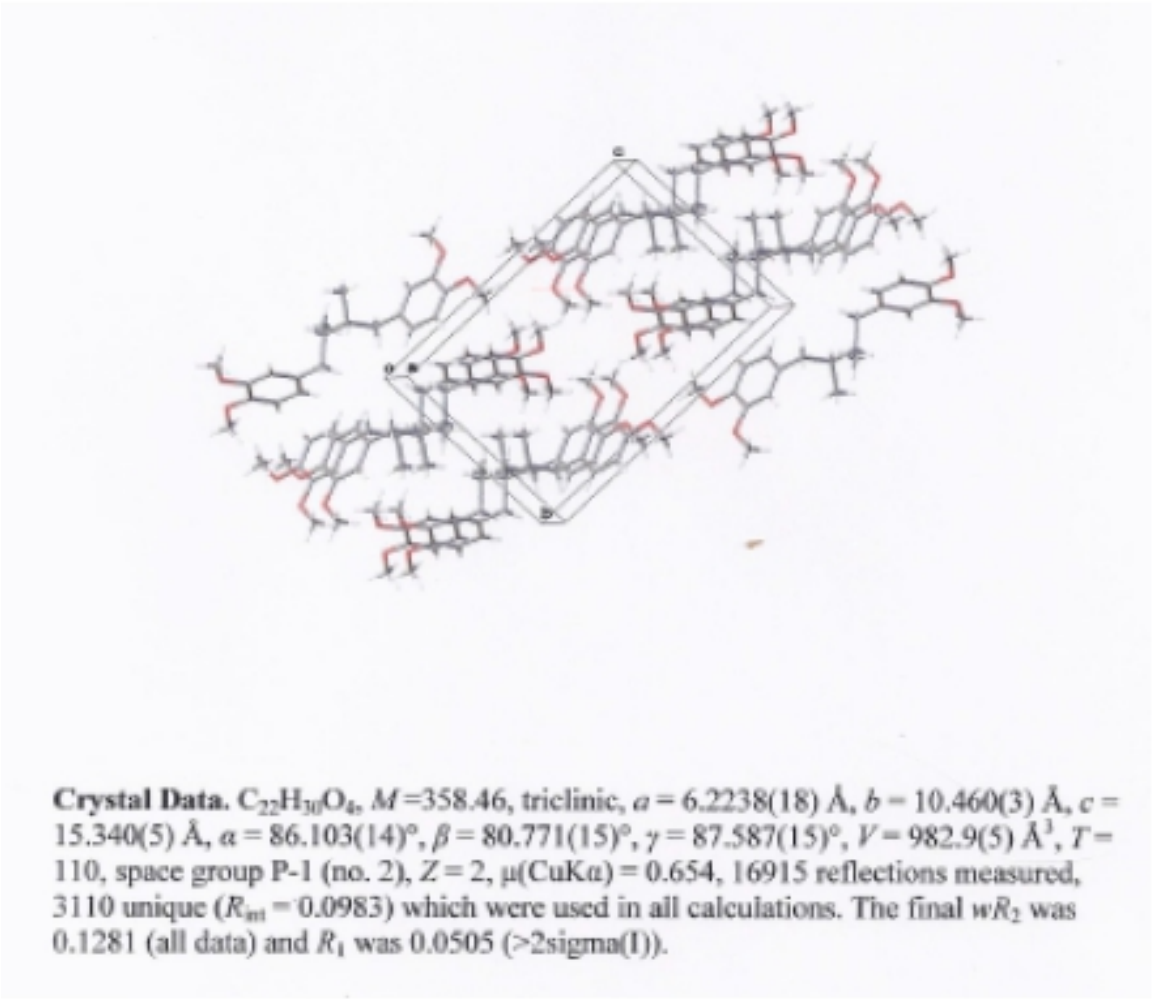
(Figure 51 – ^{13}C NMR of 1,4-(3,4-Dimethoxyphenyl)-2,3-Dimethyl Butane)



(Figure 52 – GCMS of *meso*-1,4-(3,4-Dimethoxyphenyl)-2,3-Dimethyl Butane)



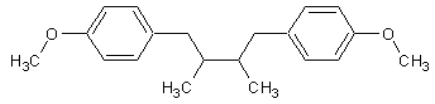
(Figure 53 – GCMS of *racemic*-1,4-(3,4-Dimethoxyphenyl)-2,3-Dimethyl Butane)



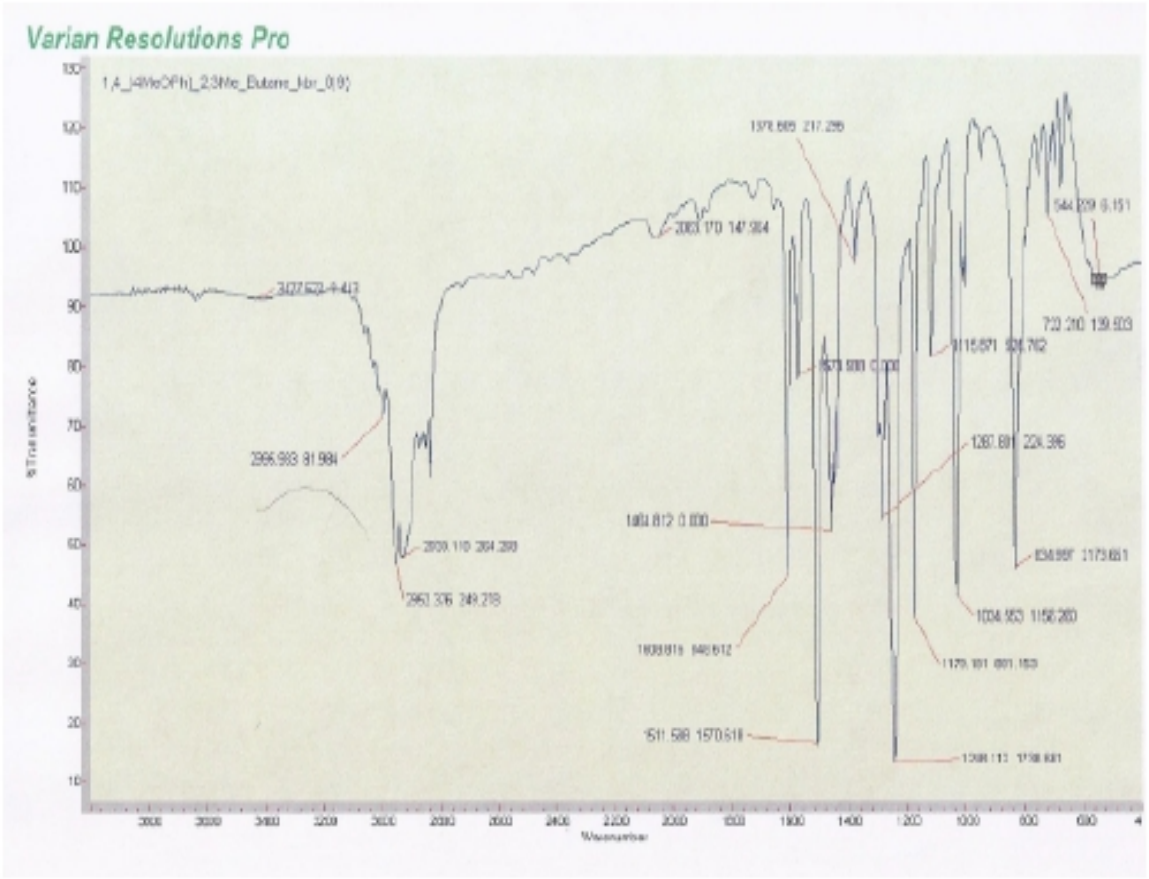
Crystal Data. $C_{22}H_{30}O_4$, M =358.46, triclinic, a = 6.2238(18) Å, b = 10.460(3) Å, c = 15.340(5) Å, α = 86.103(14)°, β = 80.771(15)°, γ = 87.587(15)°, V = 982.9(5) Å^3, T = 110, space group P-1 (no. 2), Z = 2, μ(CuKα) = 0.654, 16915 reflections measured, 3110 unique (R_{int} = 0.0983) which were used in all calculations. The final wR_2 was 0.1281 (all data) and R_1 was 0.0505 (>2sigma(I)).

(Figure 54 – X-Ray of *meso*-1,4-(3,4-Dimethoxyphenyl)-2,3-Dimethyl Butane)

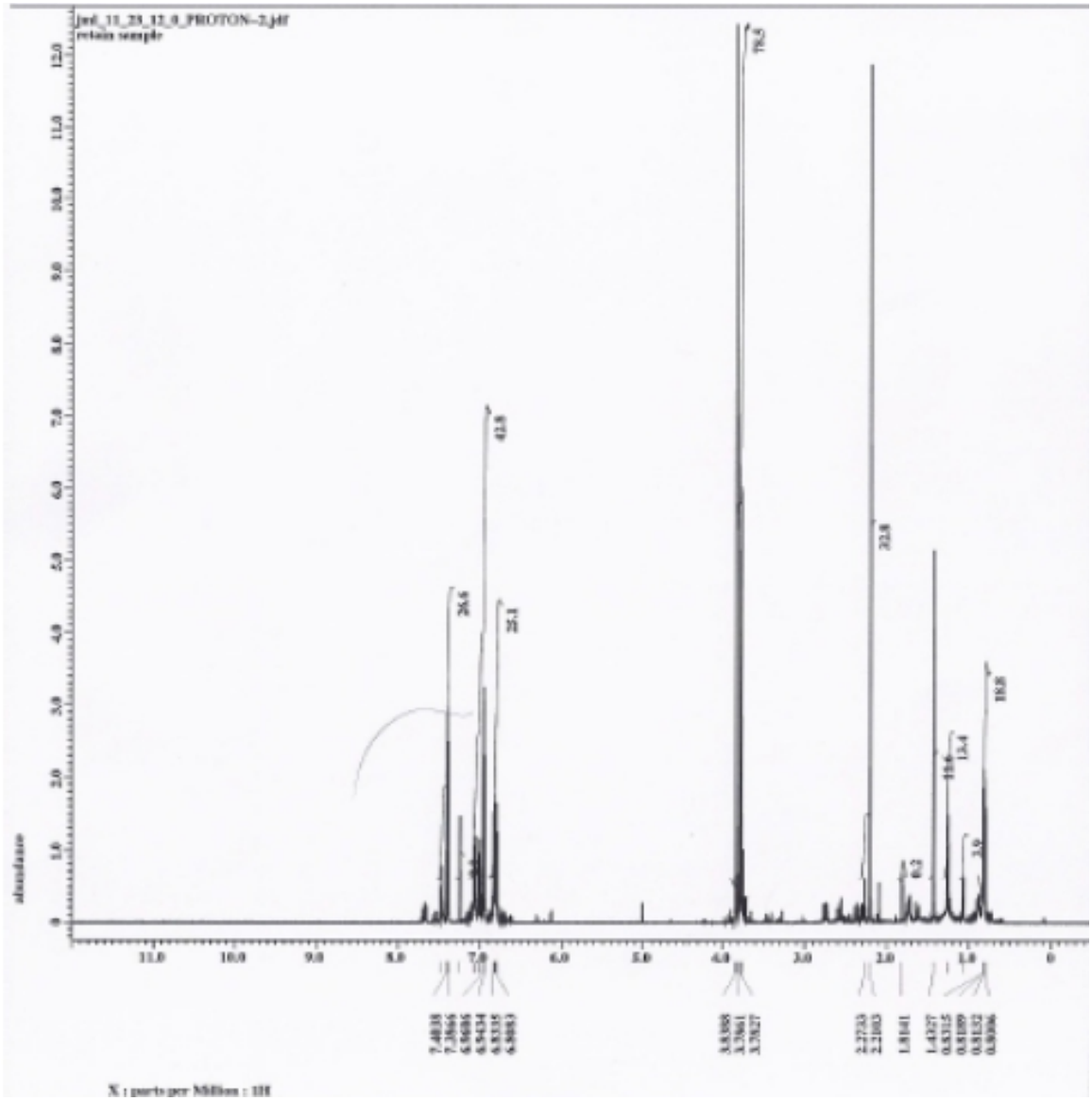
2.3.9.2 1,4-(4-Methoxyphenyl)-2,3-Dimethyl Butane



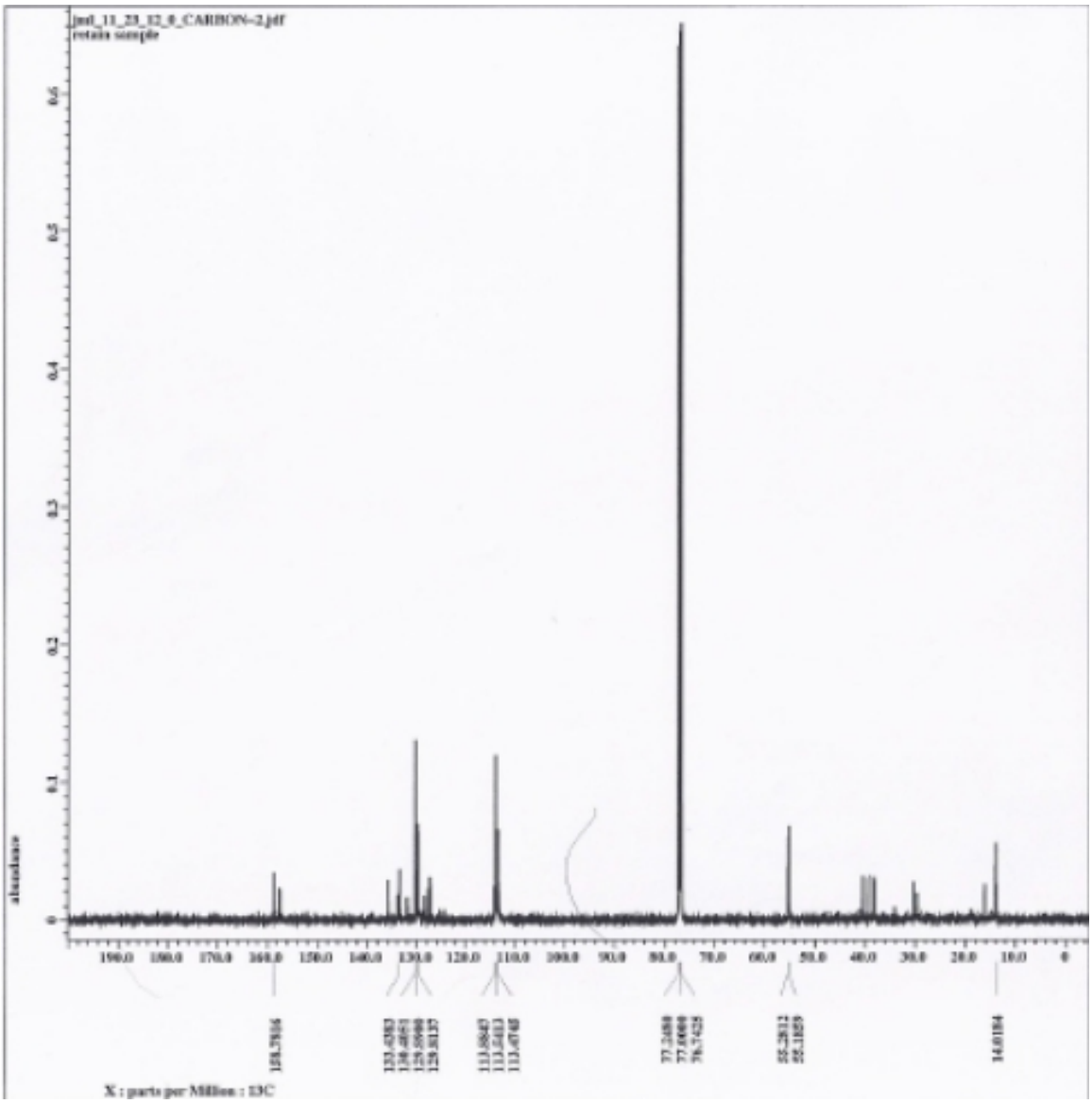
The 1,4-(4-methoxyphenyl)-2,3-dimethyl butane was obtained in 60% yield as a diastereomeric mix of the 2-(R)-3-(S) *meso* compound and the 2-(R)-3-(R)/2-(S)-3-(S) *racemate.* IR (KBr) 2952 cm^{-1}, 2930 cm^{-1}, 1609 cm^{-1}, 1574 cm^{-1}, 1512 cm^{-1}, 1288 cm^{-1}, 1248 cm^{-1}, 1179 cm^{-1}, 1035 $cm^{-1,}$ 835 cm^{-1}, ^{1}H NMR ($CDCl_3$), δ 7.40 (d, 4H), 6.95 (d, 4H), 3.84 (s, 6H), 2.21 (d, 6H), 1.43 (d, 4H), 0.83 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 159, 133, 130, 114, 113, 55, 41, 39, 38, 16, 14.



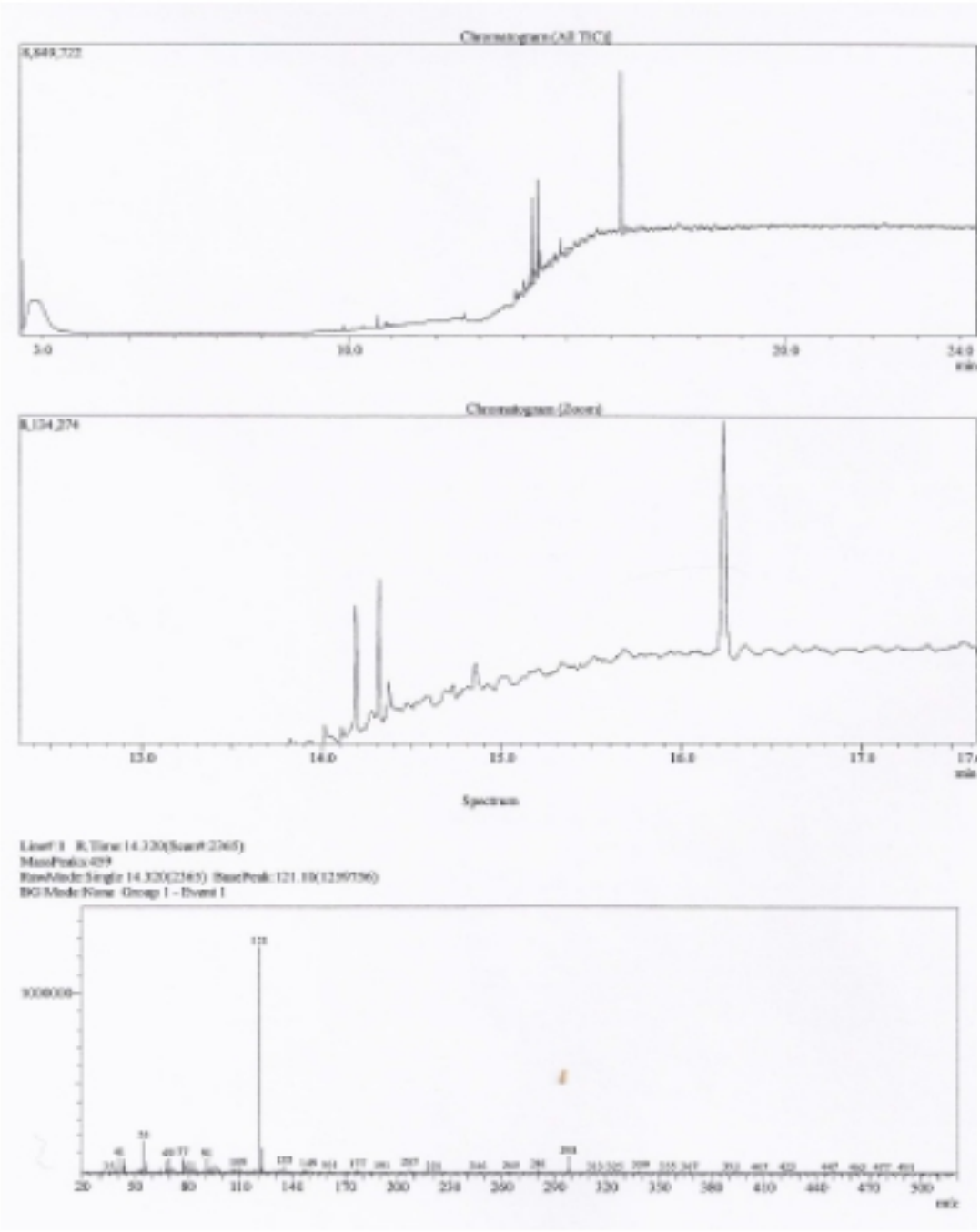
(Figure 55 – IR of 1,4-(4-Methoxyphenyl)-3,4-Dimethyl Butane)



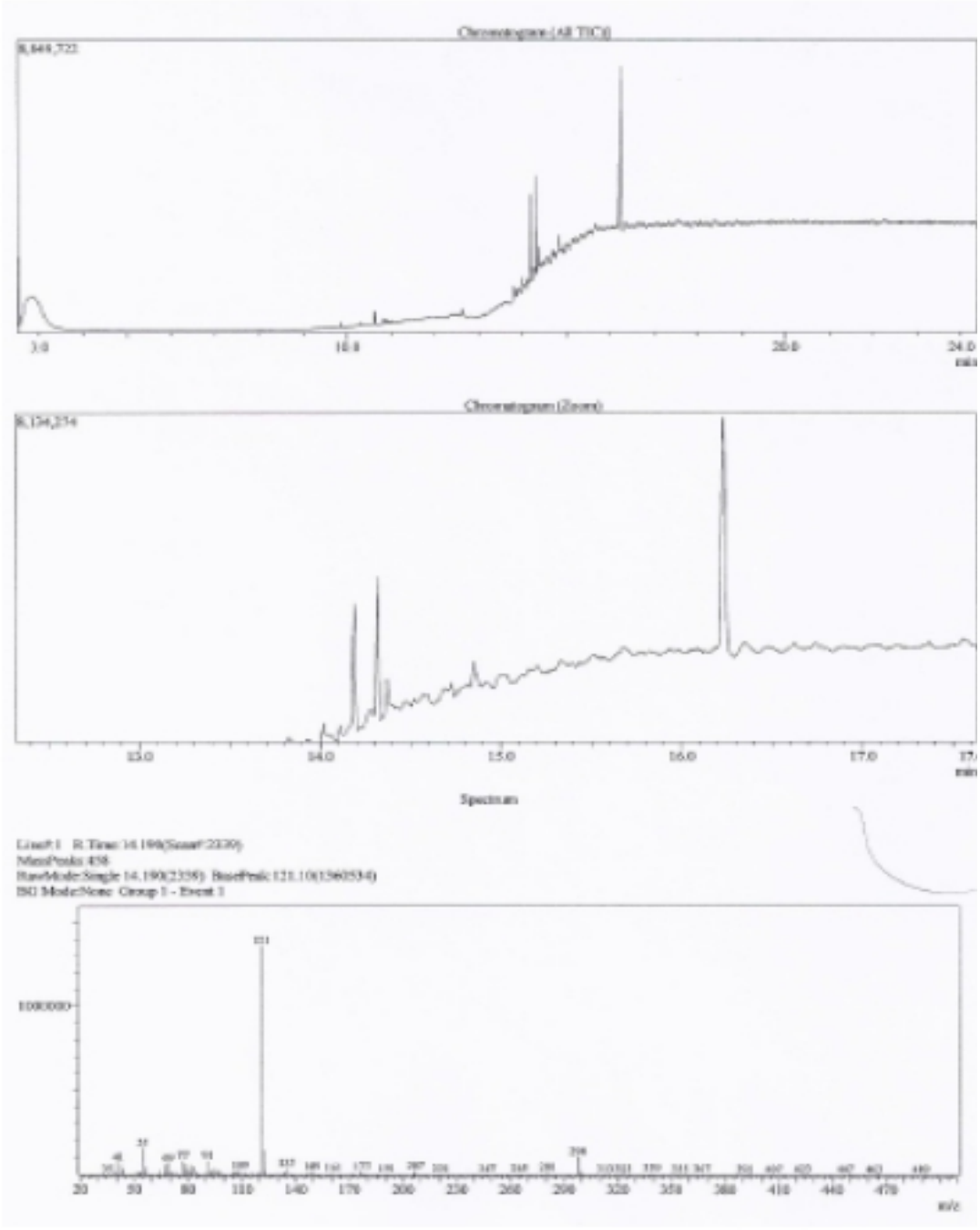
(Figure 56 – ^{1}H NMR of 1,4-(4-Methoxyphenyl)-3,4-Dimethyl Butane)



(Figure 57 – ^{13}C NMR of 1,4-(4-Methoxyphenyl)-2,3-Dimethyl Butane)

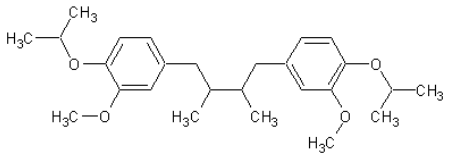


(Figure 58 – GCMS of *meso*-1,4-(4-Methoxyphenyl)-2,3-Dimethyl Butane)

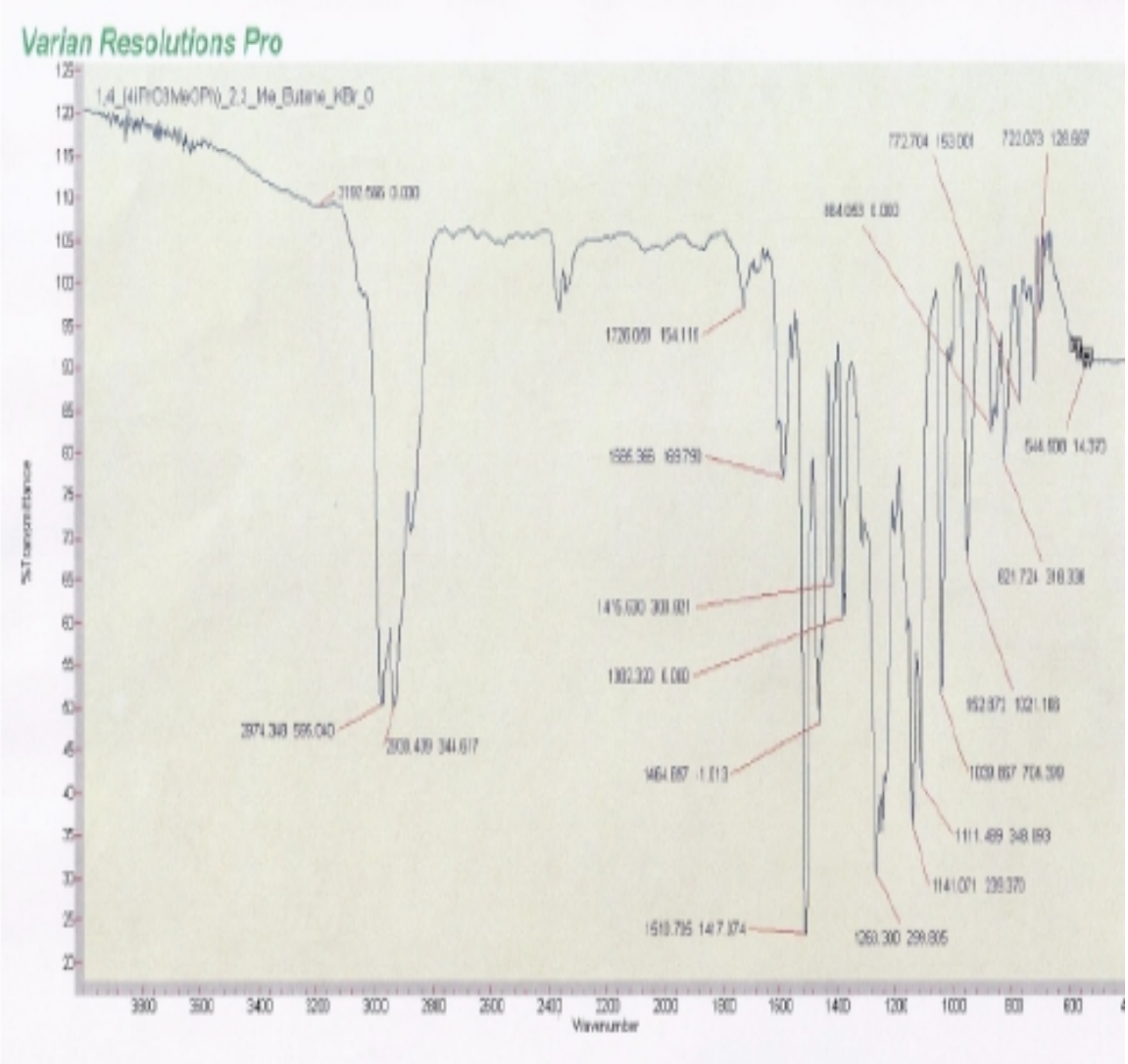


(Figure 59 – GCMS of *racemic*-1,4-(4-Methoxyphenyl)-2,3-Dimethyl Butane)

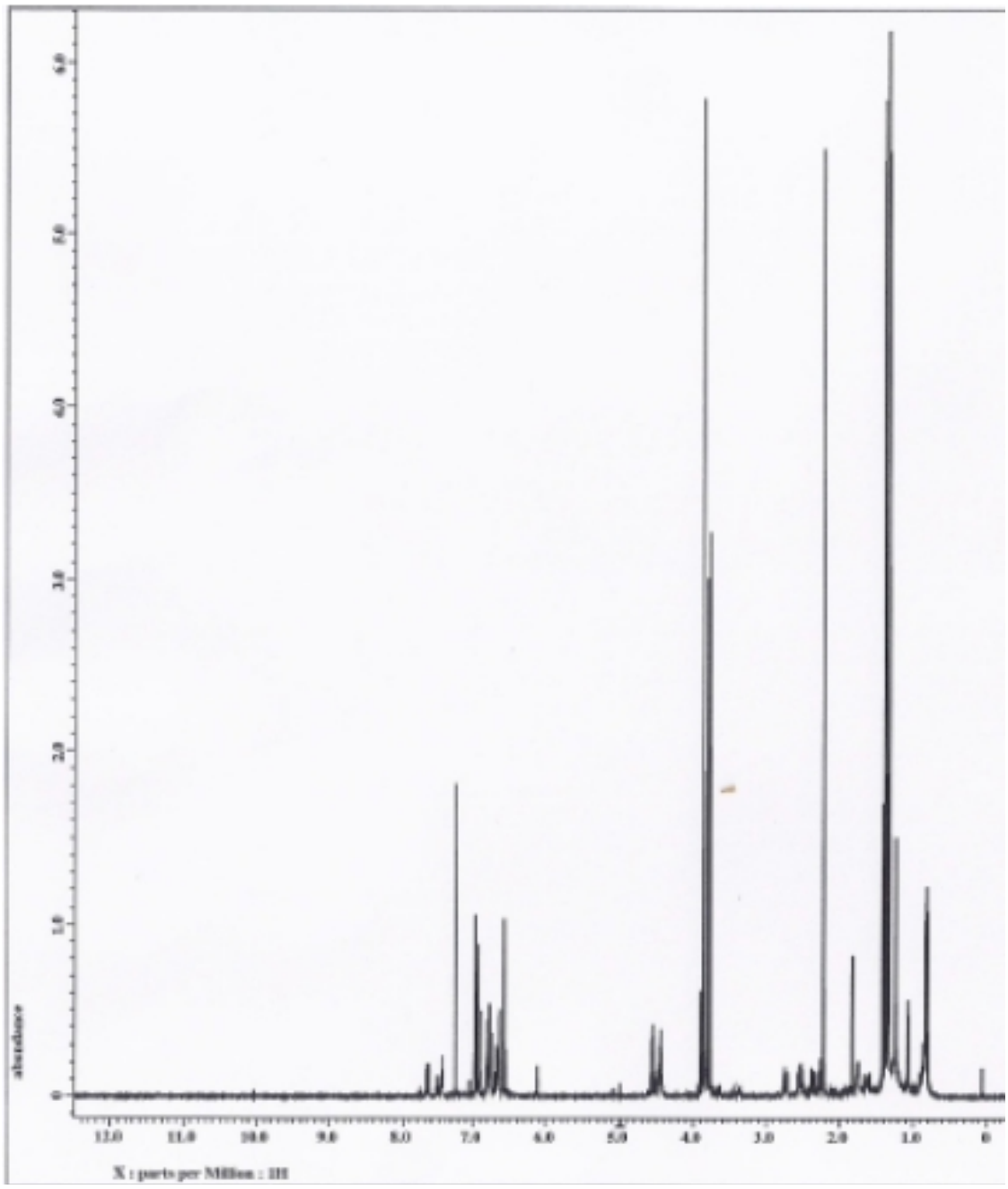
2.3.9.3 1,4-(3-Methoxy-4-Isoproxyphenyl)-2,3-Dimethyl Butane



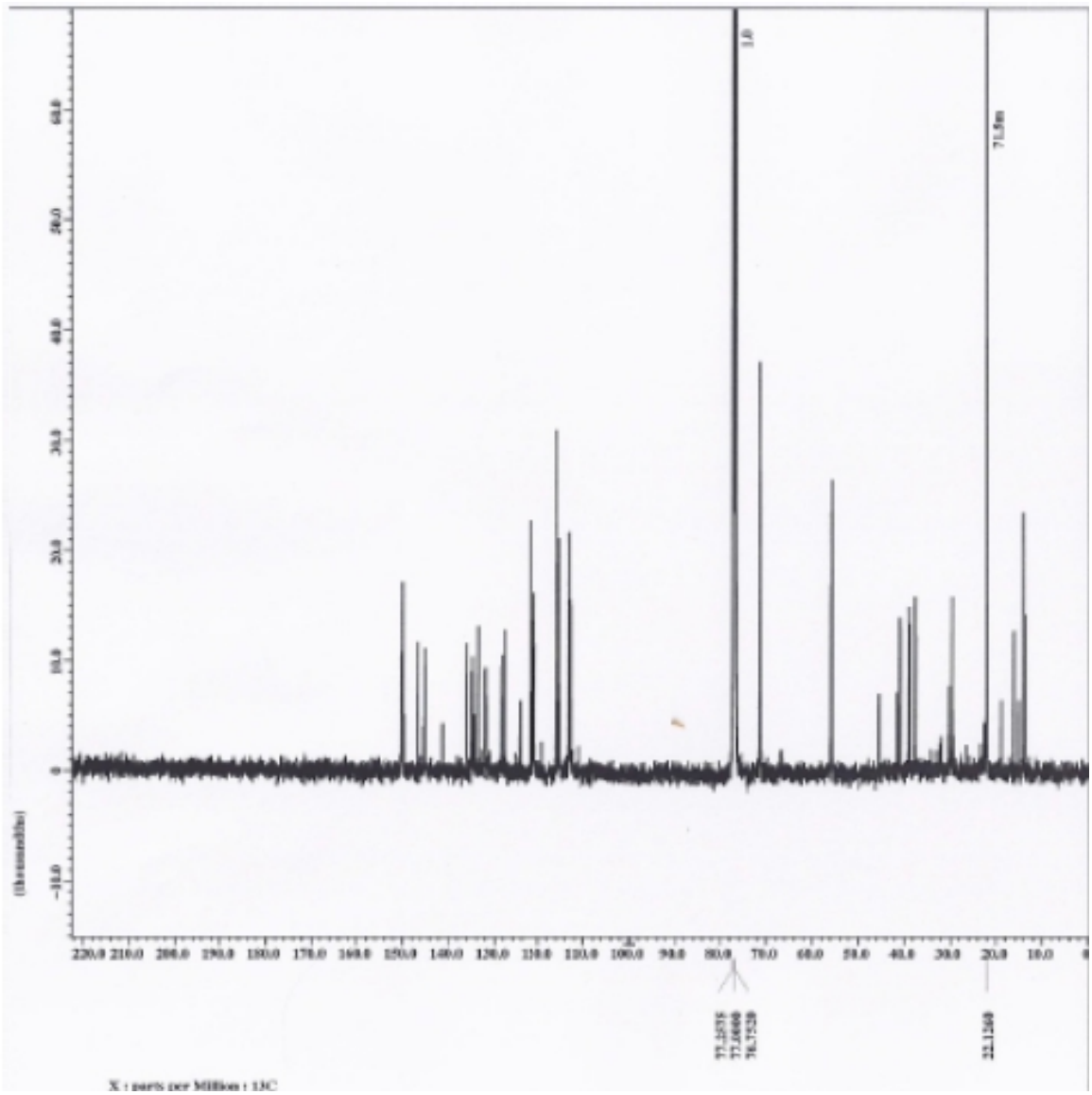
The 1,4-(3-methoxy-4-Isopropoxyphenyl)-2,3-dimethyl butane was obtained in 84% yield as a diastereomeric mix of the 2-(R)-3-(S) *meso* compound and the 2-(R)-3-(R)/2-(S)-3-(S) *racemate.* IR (KBr) 2974 cm^{-1}, 2930 cm^{-1}, 1726 cm^{-1}, 1585 cm^{-1}, 1511 cm^{-1}, 1465 cm^{-1}, 1416 cm^{-1}, 1382 cm^{-1}, 1263 cm^{-1}, 1141 cm^{-1}, 1111 cm^{-1}, 1040 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ 7.24 (s, 2H), 6.91 (d, 2H), 6.86 (d, 2H), 4.56 (m, 2H), 3.86 (s, 6H), 2.22 (s, 6H), 1.39 (s, 12H), 1.24 (d, 4H), 0.83 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 151, 150, 138, 126, 122, 115, 113, 112, 73, 56, 41, 39, 38, 22, 16, 14.



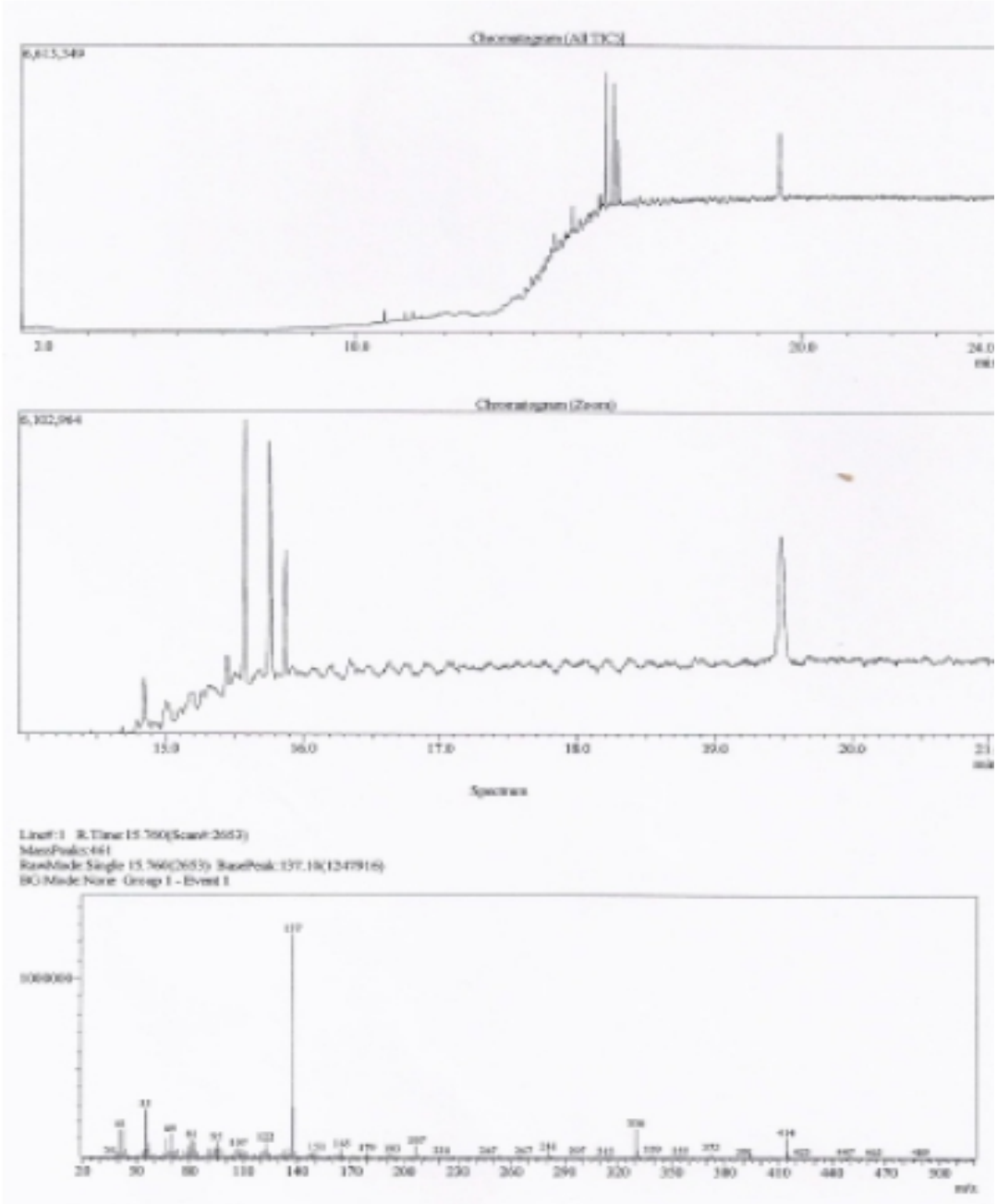
(Figure 60 – IR of 1,4-(3-Methoxy-4-Isoproxyphenyl)-2,3-Dimethyl Butane)



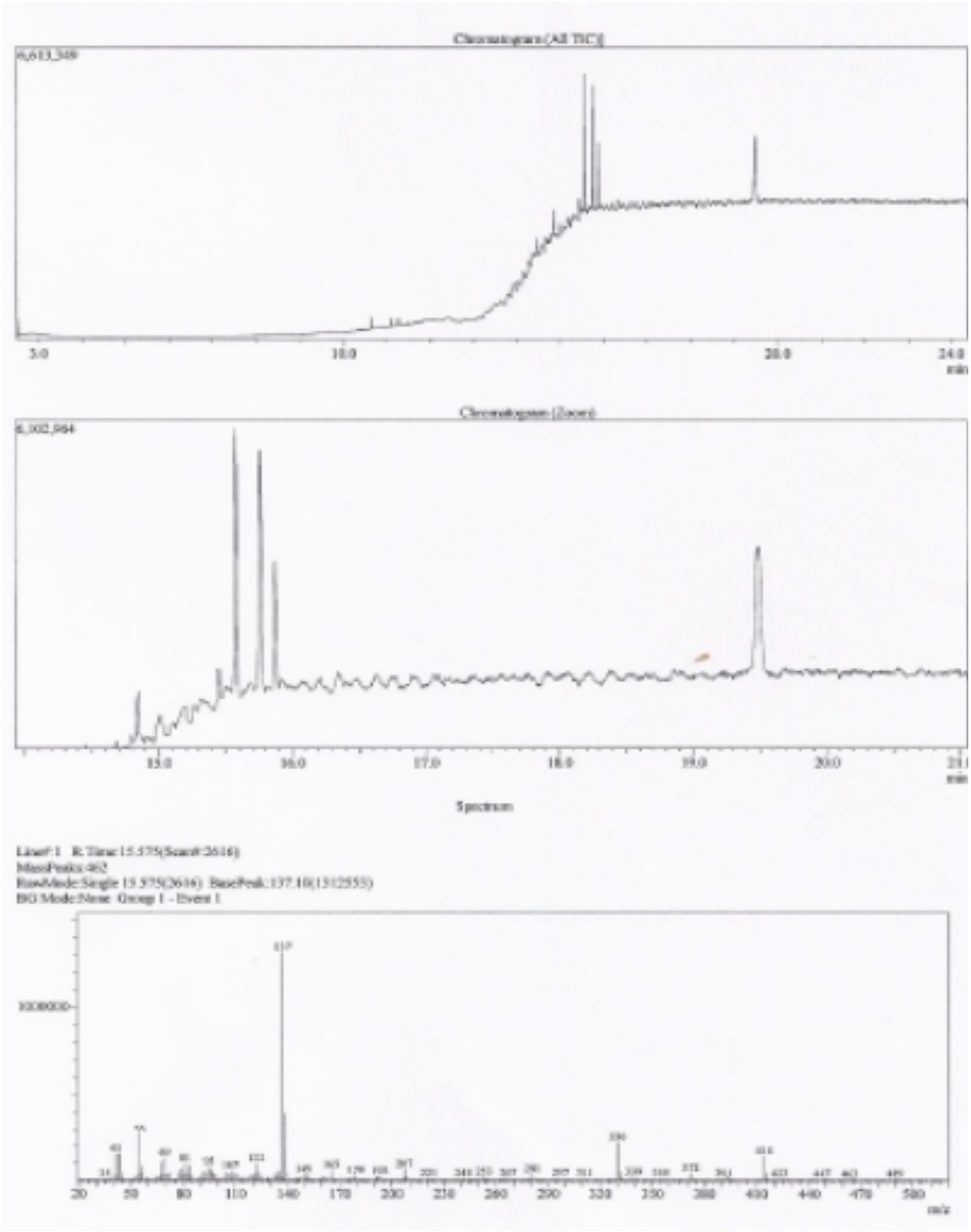
(Figure 61 – ^{1}H NMR of 1,4-(3-Methoxy-4-Isoproxyphenyl)-2,3-Dimethyl Butane)



(Figure 62 – ^{13}C NMR of 1,4-(3-Methoxy-4-Isoproxyphenyl)-2,3-Dimethyl Butane)

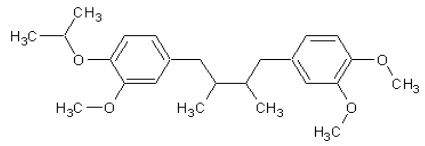


(Figure 63 – GCMS of racemic-1,4-(3-Methoxy-4-Isoproxyphenyl)-2,3-Dimethyl Butane)

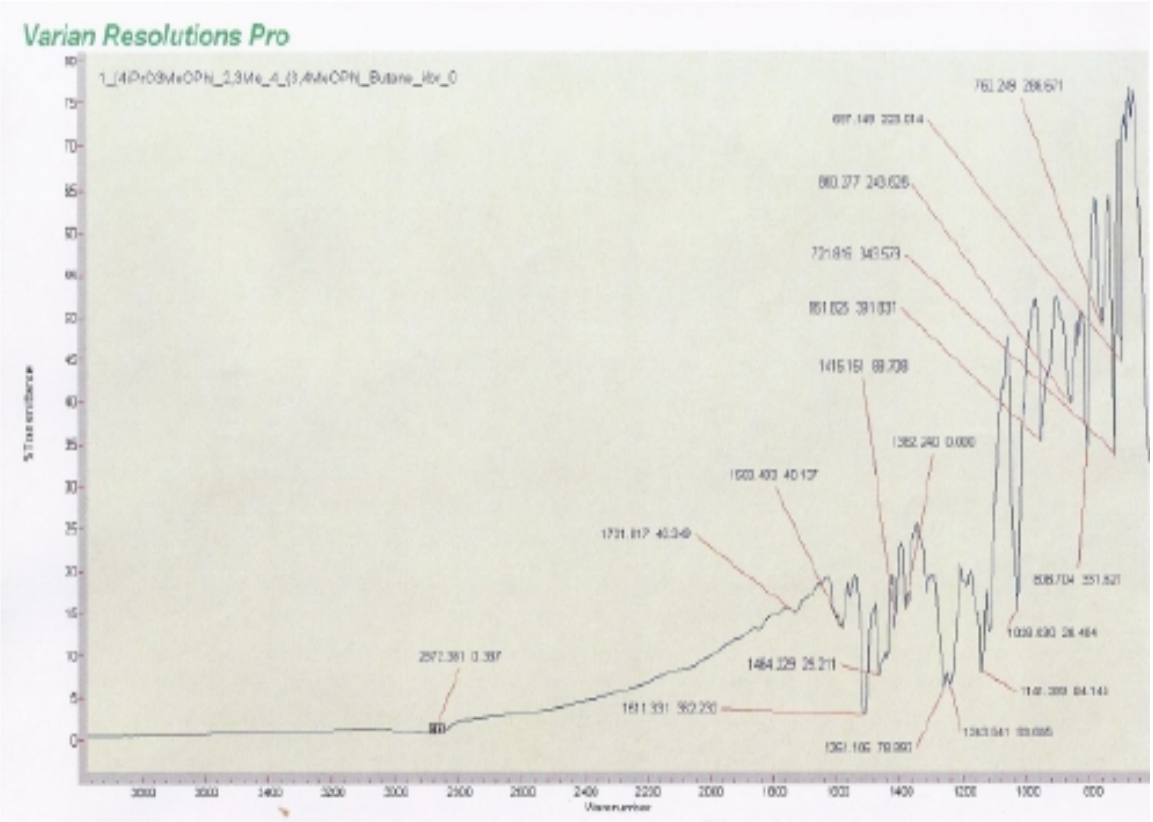


(Figure 64 – GCMS of *meso*-1,4-(3-Methoxy-4-Isoproxyphenyl)-2,3-Dimethyl Butane)

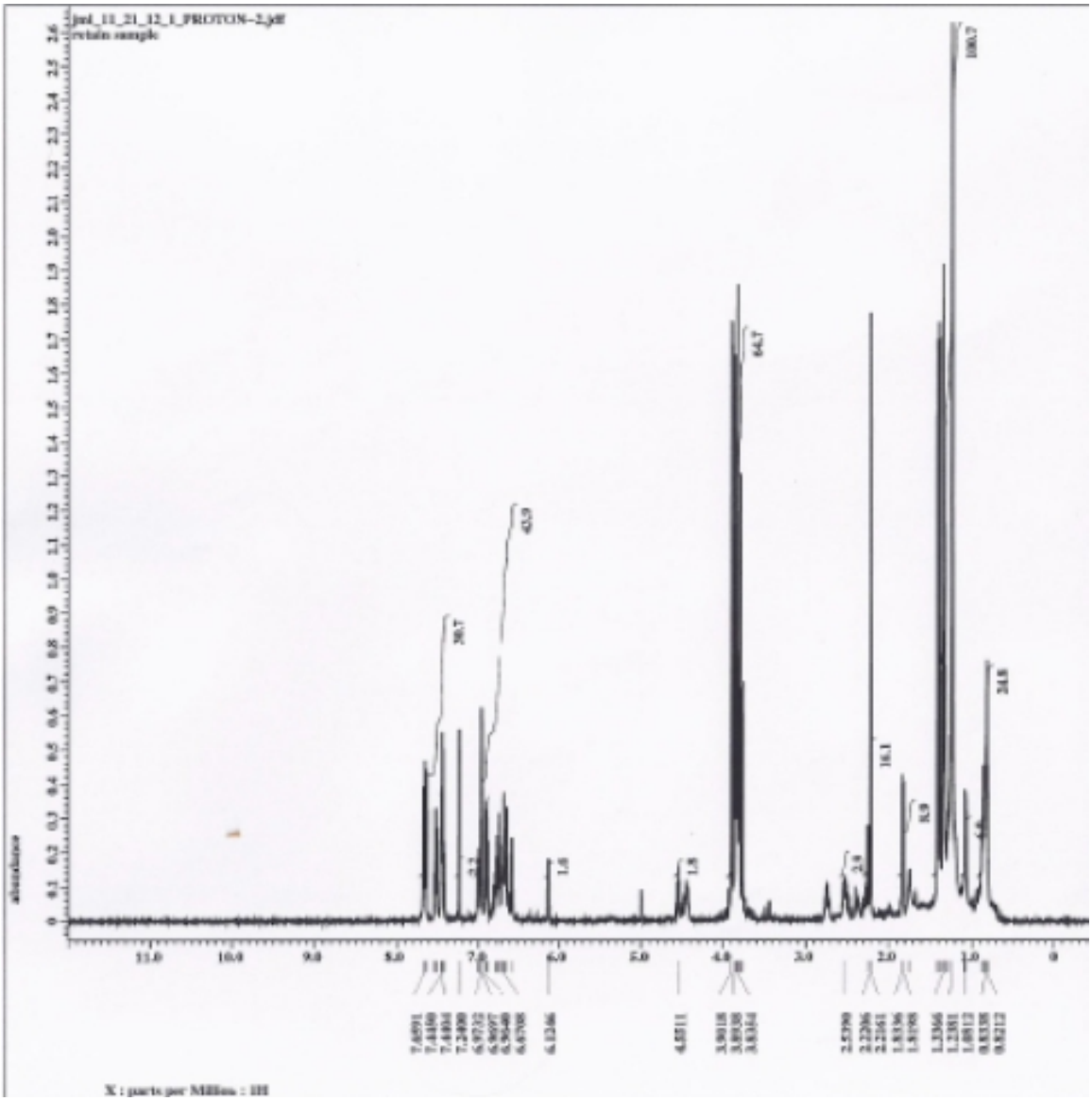
2.3.9.4 1-(3-Methoxy-4-Isopropoxyphenyl)-2,3-Dimethyl-4-(3,4-Dimethoxyphenyl) Butane



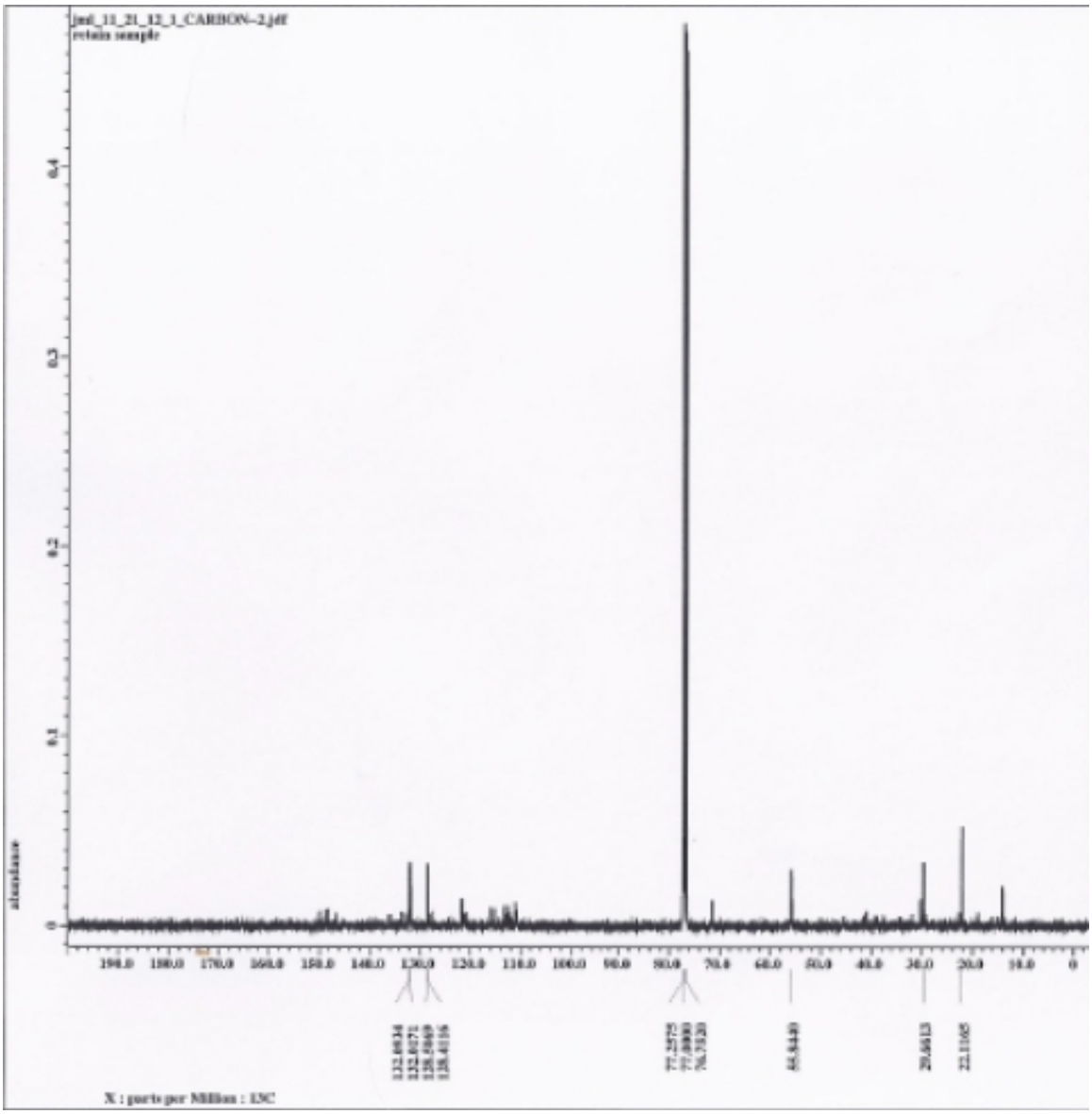
The 1-(3-methoxy-4-Isopropoxyphenyl)-2,3-dimethyl-4-(3,4-Dimethoxyphenyl) butane was obtained in 79% yield as a diastereomeric mix of all 4 possible isomers. IR (KBr) 2872 cm^{-1}, 1732 cm^{-1}, 1583 cm^{-1}, 1511 cm^{-1}, 1464 cm^{-1}, 1415 cm^{-1}, 1382 cm^{-1}, 1261 cm^{-1}, 1244 cm^{-1}, 1141 cm^{-1}, 1028 cm^{-1}, 952 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ 7.24 (s, 2H), 6.91 (d, 2H) 6.86 (d, 2H), 4.56 (m, 2H), 3.90 (s, 6H), 3.84 (s, 3H), 2.22 (s, 6H), 1.24 (d, 4H), 0.83 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 149, 147, 136, 134, 122, 112, 110, 71, 56, 41, 39, 38, 22, 16, 14.



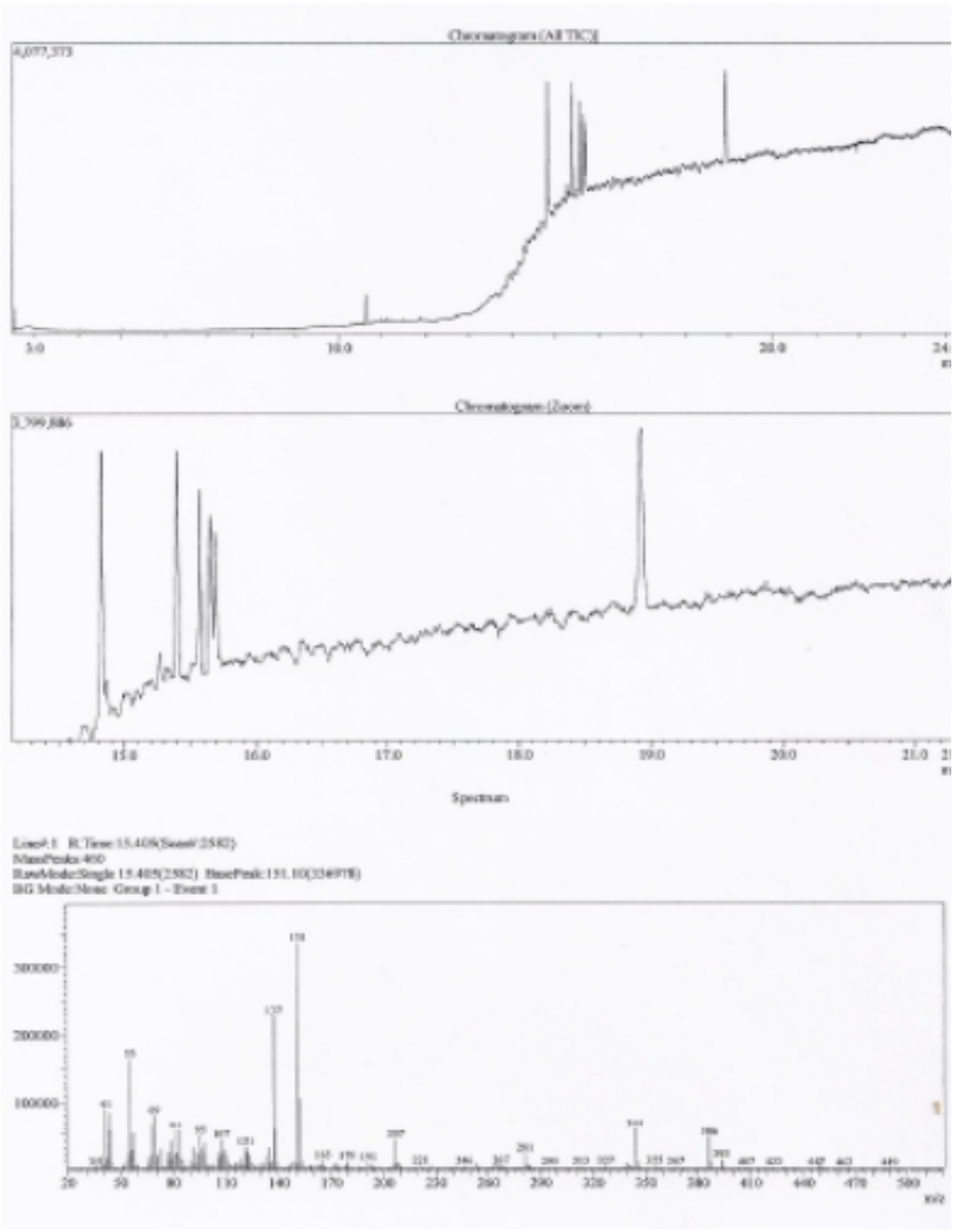
(Figure 65 – IR of 1-(3-Methoxy-4-Isopropoxyphenyl)-2,3-Dimethyl-4-(3,4-Dimethoxyphenyl) Butane)



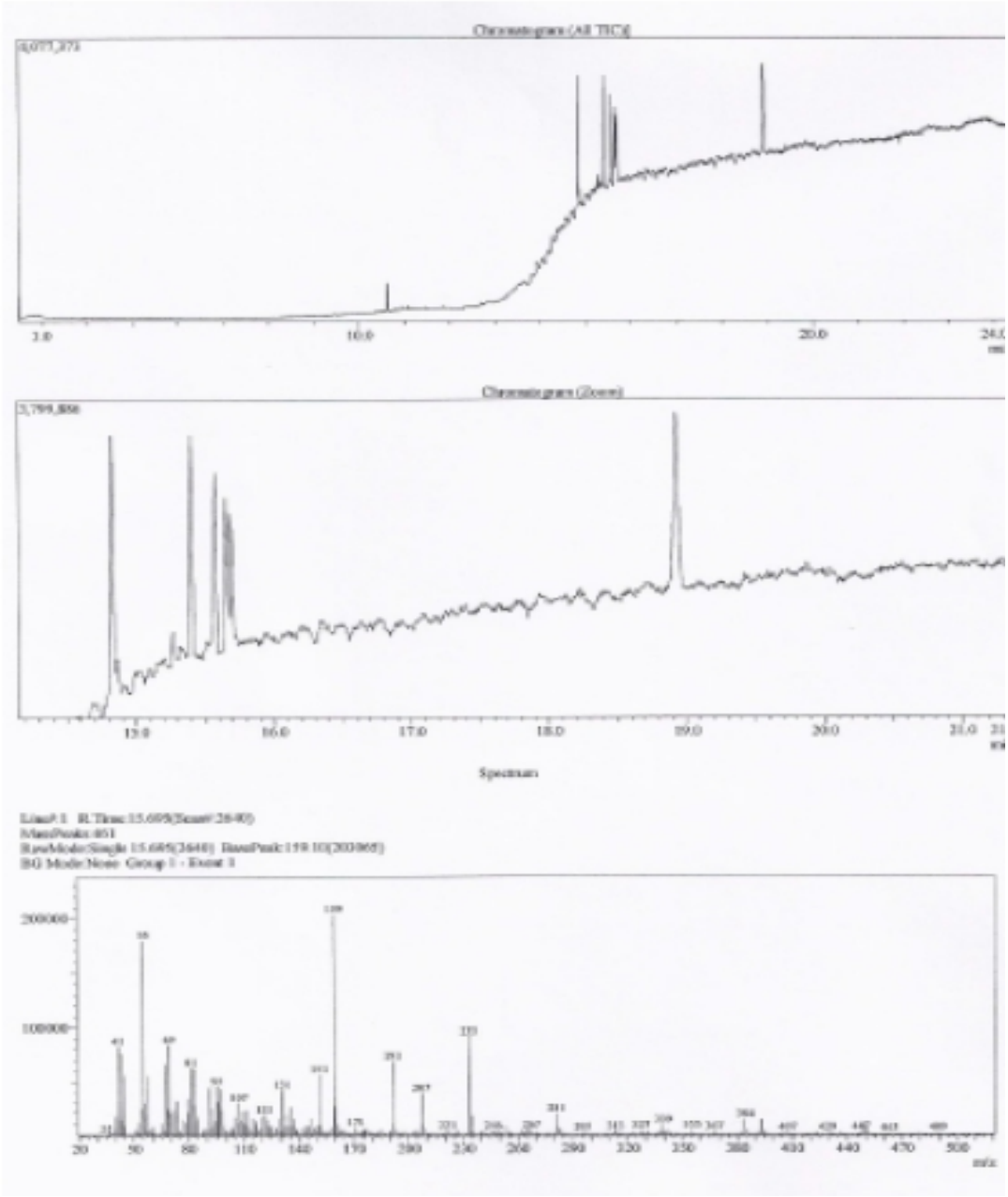
(Figure 66 – ^{1}H NMR of 1-(3-Methoxy-4-Isopropoxyphenyl)-2,3-Dimethyl-4-(3,4-Dimethoxyphenyl) Butane)



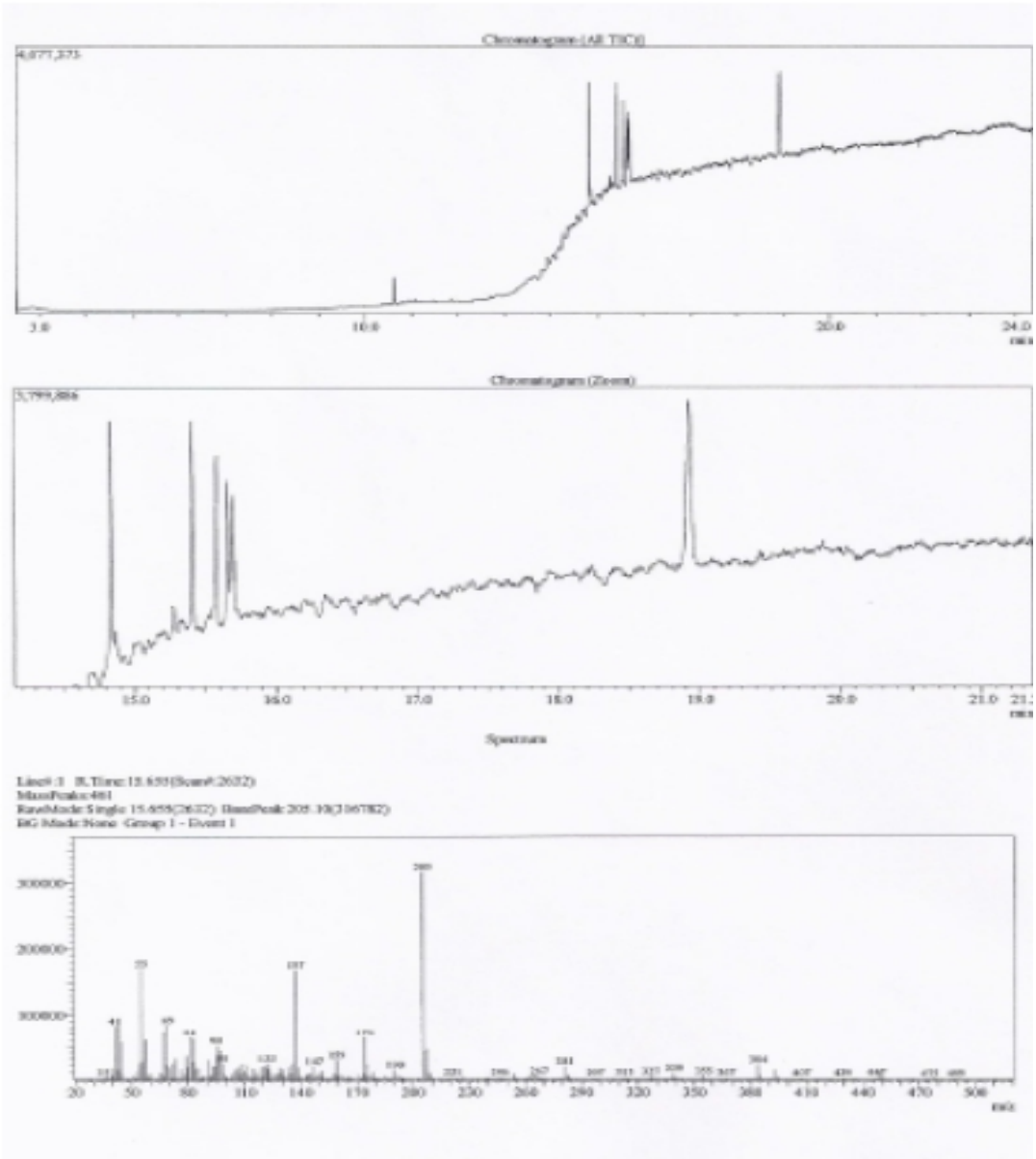
(Figure 67 – ^{13}C NMR of 1-(3-Methoxy-4-Isopropoxyphenyl)-2,3-Dimethyl-4-(3,4-Dimethoxyphenyl) Butane)



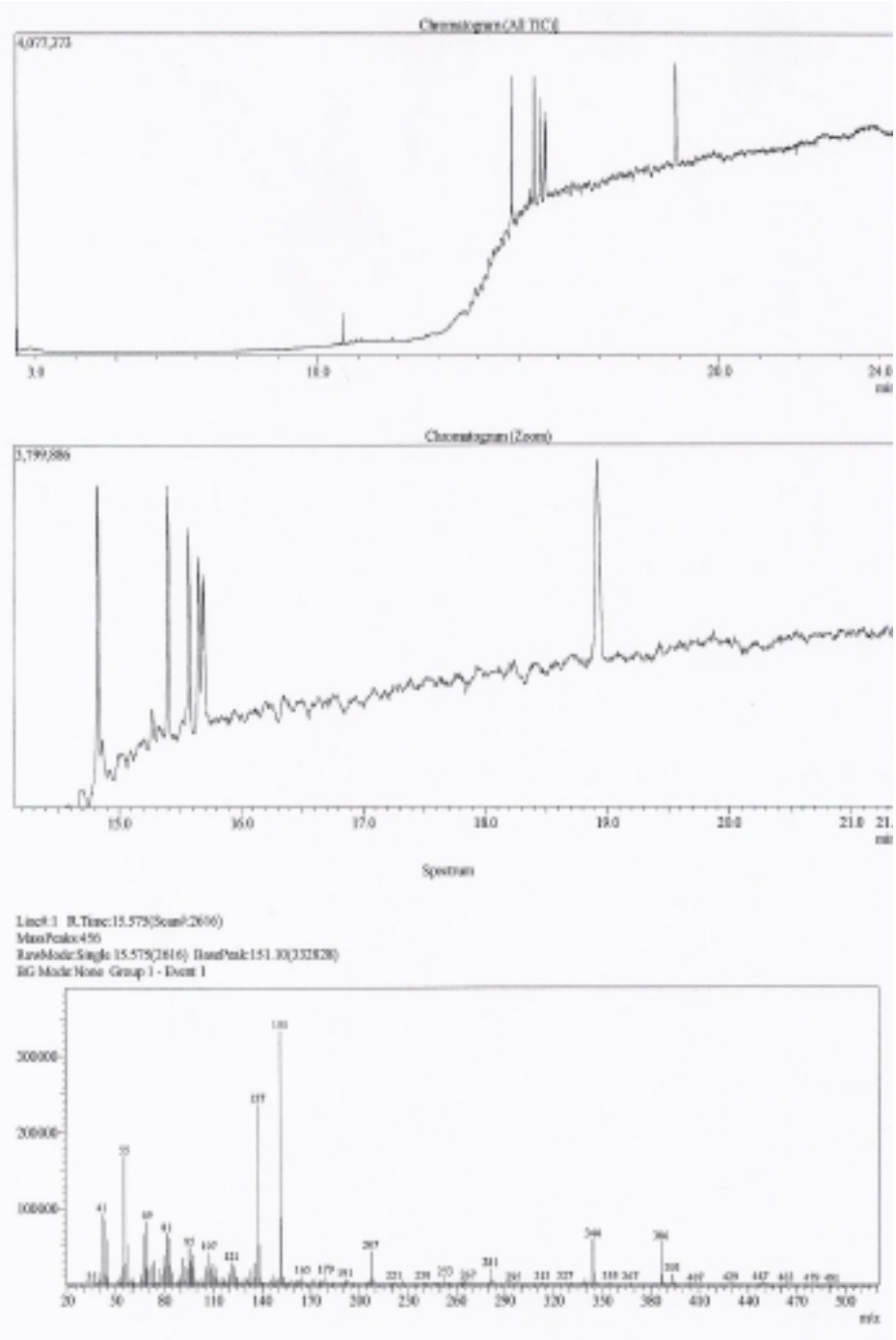
(Figure 68 – GCMS of primary isomer of 1-(3-Methoxy-4-Isopropoxyphenyl)-2,3-Dimethyl-4-(3,4-Dimethoxyphenyl) Butane)



(Figure 69 – GCMS of secondary isomer of 1-(3-Methoxy-4-Isopropoxyphenyl)-2,3-Dimethyl-4-(3,4-Dimethoxyphenyl) Butane)



(Figure 70 – GCMS of tertiary isomer of 1-(3-Methoxy-4-Isopropoxyphenyl)-2,3-Dimethyl-4-(3,4-Dimethoxyphenyl) Butane)



(Figure 71 – GCMS of quaternary isomer of 1-(3-Methoxy-4-Isopropoxyphenyl)-2,3-Dimethyl-4-(3,4-Dimethoxyphenyl) Butane)

Chapter III

3.0 Results and Discussion

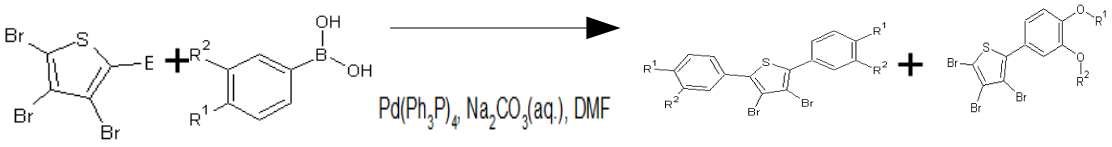
The preparation of NDGA derivatives in this study was accomplished with consecutive palladium catalyzed cross-coupling reactions followed by a nickel mediated desulfurization and reduction. The palladium reactions allowed for the introduction of alkyl and differentially substituted aryl moieties such that a range of target molecules were easily accessible. The aryl boronic acid not obtained from a commercial source was synthesized from the natural product guaiacol. A single series of transformations was productive enough to supply all the needed material for the palladium catalyzed cross-couplings.

Both the Suzuki and Stille reactions effected consecutive couplings during a single attempt. The Suzuki couplings in particular were highly proficient and predictable, and therefore did not require any form of systematic optimization to produce the desired products (Table 1&2). The 2 and 5 positions, alpha to the thiophene sulfur atom, were understood to be the most active with respect to cross-coupling and were easily manipulated.[19] The positions beta to the sulfur remained unmodified during all of the Suzuki reactions studied herein as confirmed by ^{1}H NMR and TLC. The NMR displayed signals indicative of the incorporation of the employed aryl moieties in both mono and di substituted products although TLC analysis of the products generated disparate R_f values. These characteristics made product separation and identification convenient. Another positive attribute associated with the Suzuki couplings was that the boronic acids pose minimal health and safety risks in stark contrast to the organostannane of the Stille

coupling. The tin reagent is both highly volatile and toxic, and was therefore always handled in a fume hood, transferred by syringe, and added to cool reaction vessels that remained sealed throughout the coupling.

Upon examination the initial Stille protocol was observed to generate unmodified starting material (disubstituted thiophenes), singly modified (trisubstituted thiophenes), as well as the desired tetrasubstituted species as confirmed by GC/MS and ^{1}H NMR. The newly added methyl groups were easily identified, and upon integration of the signals the appropriate ratios were observed. No degradation products were detected, and as only the brominated 3 and 4 positions of the thiophene ring remained reactive to the cross-coupling the products were resubmitted to the reaction conditions.

Table 1 - Symmetric Product Suzuki Reaction (3 hours @ 80°C)



Boronic Acid	Boronic Acid (eq.)	Thiophene Conc. (mol)	Palladium Reagent (eq.)	Sodium Carbonate (eq.)	Crude Yield (%)	Diaryl Species Purified Yield (%)
4-Methoxy Phenyl Boronic Acid	2.277	0.000622	0.031	5.79	98.7	31.7
3,4-Dimethoxy Phenyl Boronic Acid	2.197	0.000636	0.032	5.66	82.0	43.3
4-Isopropoxy-3-Methoxy Phenyl Boronic Acid	2.213	0.000602	0.030	5.98	111.6	50.8

Table 2 - Asymmetric Product Suzuki Reaction (3 hours @ 80°C)

Thiophene (Starting Material)	Starting Material (mol)	Boronic Acid	Boronic Acid (eq.)	Palladium Reagent (eq.)	Na_2CO_3 (eq.)	Product	Purified Yield (%)
Tetrabromo Thiophene	0.000601	4-Isopropoxy-3-Methoxy Phenyl Boronic Acid	2.265	0.035	5.99	2-(3-Methoxy-4-Isopropoxy Phenyl)-3,4,5-Tribromo Thiophene	24.5
Tetrabromo Thiophene	0.000636	3,4-Dimethoxy Phenyl Boronic Acid	2.197	0.032	5.66	2-(3,4-Dimethoxy Phenyl)-3,4,5-Tribromo Thiophene	38.8
2-(3,4-Dimethoxy Phenyl)-3,4,5-Tribromo Thiophene	0.000173	4-Isopropoxy-3-Methoxy Phenyl Boronic Acid	1.132	0.041	3.47	2-(4-Isolpropoxy-3-Methoxy Phenyl)-3,4-Dibromo-5-(3,4-Methoxy Phenyl) Thiophene	30.1
2-(3-Methoxy-4-Isopropoxy Phenyl)-3,4,5-Tribromo Thiophene	0.000147	3,4-Dimethoxy Phenyl Boronic Acid	1.125	0.033	3.40	2-(4-Isopropoxy-3-Methoxy Phenyl)-3,4-Dibromo-5-(3,4-Methoxy Phenyl) Thiophene	77.6

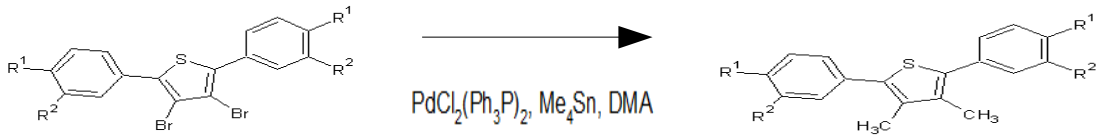
When the products of the second Stille coupling were examined by GC/MS and ^{1}H NMR only the tetrasubstituted thiophene remained. Therefore the final protocol for Stille couplings entailed back to back reactions with no attempt at isolation of the intermediate products. It was also noted that separation or isolation of these intermediate products would introduce additional cost in terms of both time and material. However attempts were made to optimize the overall sequence such that waste was reduced to a minimum and that product of interest was ultimately obtained in high yield. The overall best scheme with respect to both cost and yield employed 0.05 equivalents of palladium reagent and 2.1 equivalents of tin reagent for each attempt. That determination was made after a series of tests. All modifications were assayed by GC/MS, and the effect of more thoroughly removing reactive gasses from the reaction mixture with inert argon was analyzed first. Ultimately argon was transferred to the reaction vessel through a tube equipped with a 25 gauge needle at 3 psi (pounds per square inch) for at least 15 minutes per liter of vessel. As the degassing time increased it was noted that the appearance of black precipitate in the reaction mixture was delayed from approximately 5 to approximately 30 minutes. Unfortunately that did not translate into a more complete initial cross-coupling, and the precipitate was always observed after 30 minutes.

The next parameter to face optimization was the quantity of palladium catalyst needed. The number of equivalents was varied from 0.04 to 0.075 yet complete transformation of the starting material to the tetrasubstituted speicies of interest remained elusive. The molar ratio of organotin to starting material was yet another parameter varied in an attempt to obtain a more complete transformation with only a single

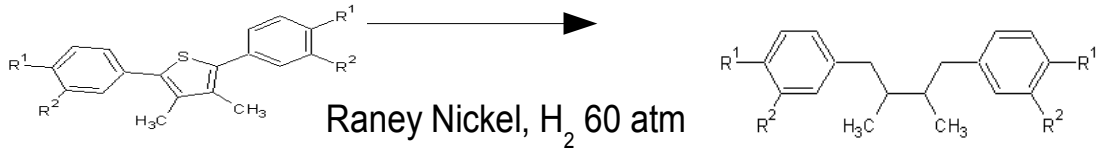
coupling. That optimization process was also to no avail. At that point the necessity of subsequent Stille couplings was accepted, and the final protocol therefore always included a reintroduction of intermediate products to the original reaction conditions. Reduction of cost was also important. In the ultimately accepted route necessary reagent concentrations were calculated as if the reactions were intended as consecutive single replacements. After the initial cross-coupling a mixture of all three possible products was nearly always detected, and at no time was the initial Stille coupling successful in generating the desired tetrasubstituted thiophene completely. In fact the author speculated that any modest increase in overall yield derived from using the larger quantities of reagents may likely be due to an increase in low percentage impurity isolated with the species of interest. The back to back Stille process was able to produce substrates for the desulfurization and reduction process in acceptable yields ranging from 81% to 102% (Table 3). The desulfurization and reduction of tetrasubstituted thiophenes required a considerable number of attempts to identify a protocol that reliably produced the species of interest. In the beginning it was believed that combining the alcohol solubilized tetrasubstituted thiophene and the active as purchased Raney nickel catalyst under an atmosphere of hydrogen gas would be sufficient to produce NDGA derivatives. That belief proved unwarranted in that subsequent H^1 NMR analysis of the product material revealed only unreacted starting material and no new signals in either the olefinic or aliphatic region. The Parr hydrogenator reaction vessel was rated for up to 60 atmospheres of pressure so subsequent attempts on that apparatus were conducted under that pressure of H_2 gas. The reaction times for desulfurization and reduction attempts on

the Parr hydrogenator were also systematically increased to approximately 4 days. In each case only starting material remained (Scheme 14 - Top).

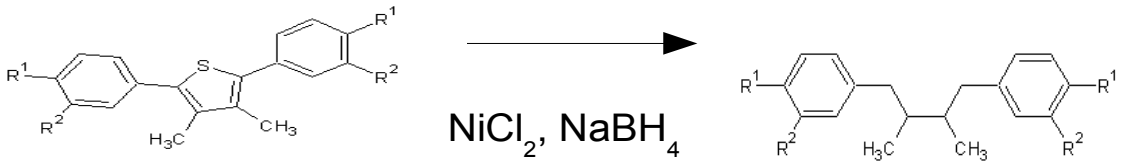
Table 3 - Stille Reaction



Substrate	Substrate Concentration (mol)	Pd Reagent (1st/2nd) (equivalents)	Tin Reagent (1st/2nd) (equivalents)	Temperature (1st/2nd) (°C)	Time (1st/2nd) (hours)	Crude Yield (%)
2,5-(3,4-Methoxy Phenyl)-2,3-Bromo Thiophene	0.000189	0.05/0.04	2.1/1.9	105/105	21/21	98
2,5-(4-Methoxy Phenyl)-2,3-Bromo Thiophene	0.000242	0.04/0.03	3.1/2.7	105/107	19/22.5	85
2,5-(4-Isopropoxy-3-Methoxy Phenyl)-2,3-Bromo Thiophene	0.000306	0.05/0.06	4.7/2.7	105/100	22.5/21	81
2-(4-Isopropoxy-3-Methoxy Phenyl)-3,4-Bromo-5-(3,4-Methoxy Phenyl) Thiophene	0.000098	0.08/0.06	7.4/5.2	105/105	21.5/22	102



Desulfurization Method 1: Raney Nickel and Hydrogen Gas 60 atm.



Desulfurization Method 2: $NiCl_2$, $NaBH_4$

(Scheme 14 – Low Yield Desulfuruizations)

The second method for desulfurization and concomitant reduction of thiophenes was a slight improvement on the initial procedure in that disappearingly small quantities of the desired product were later determined to have indeed been produced (Scheme 14 - Bottom). Several factors complicated accurate assessment of the nickel boride reaction. The first encountered problem was that TLC analysis of both product and starting material was identical in all solvent systems tested. Although both starting material and product had similar R_f values it was hoped that NMR analysis would display results indicating successful reactions. Unfortunately H^1 NMR analysis of nickel boride products proved extremely misleading in that even after extraction the starting material was exhibiting two large peaks in the olefinic region. The false positive might have

never been discovered without additional testing by a gas chromatorgraph equipped with a mass spectrometric detector. The initial thought was that the nickel boride reaction had been successful in desulfurizing the starting material, but that the reduction process remained incomplete. The gas chromatrograph testing was intended to determine the extent of the reaction, however when compared to control injections of starting material the main product was observed to have the same retention time and mass to charge ratio for the molecular ion peaks. That information was disconcerting. The large NMR peaks in the alkene region and the GC/MS analysis of the product seemed to be at odds with each other. Those results precipitated efforts to purify the reaction mixture by flash column chromatography that subsequently succeeded in demonstrating that the major product peak from the GC/MS was indeed unreacted starting material. The author speculated that the starting material may have been acting as a ligand or chelator for one of the reagents possibly the nickel species. The gas chromatorgraphic analysis was also useful in another respect in that injections of product mixture did produce minute peaks whose molecular ion mass to charge ratios were inline with the desired desulfurized and reduced starting material.

At this point a concerted effort was initiated to optimize reaction conditions for the nickel boride reaction. Experimental observation precipitated solubility studies of the tetrasubstituted thiophene substrate and the nickel chloride reagent. It was believed that if fully solubilized these materials would increase their activity toward the sodium borohydride reagent. Unfortunately that was not the case, and results were similar to the initial attempt. Research into other similar reactions generated an idea for using a solvent

other than ethanol for the substrate and nickel reagent.[24] The increased volume of ethanol used in the previous attempt was thought to possibly have diluted the reaction mixture such that any gain associated with solubilization was ameliorated by the dilution effect. A limited solubility study was conducted where in ethanol, methanol, and a 3:1 mixture of methanol to THF were compared. The 3:1 mixture was employed in publications of similar thiophene desulfurization reactions, and did produce the most concentrated solutions.[24] When no improvement in experimental yield was observed the decision was made to focus optimization attempts on the reactivity of the other reagent. When the sodium borohydride was prepared as an aqueous solution a significant volume of gas was released, and this was believed to possibly be associated with spontaneous decomposition of the reagent. Therefore methanol was employed as the solvent for all species in the next attempt at desulfurization and reduction. Methanol had produced intermediate results with respect to solubility of the reaction substrate thiophenes and the nickel chloride reagent, and the decision to use the same solvent for all species to avoid any possible issues with mixing. Research had indicated that actual desulfurization and reduction may occur very rapidly and the idea was to reduce any impediment to that process.[24] Once again the effort was to no avail, and yields would best be described as dismal at best. Further complicating matters were the concerns of possible miss-identification of a truly desulfurized product that had plagued the initial attempt. None the less deterred to reach the ultimate goal of successfully synthesizing a NDGA derivative, reseach efforts continued. A final nickel boride reaction modification was attempted. The final protocol involved adding the sodium borohydride neat to the 3:1

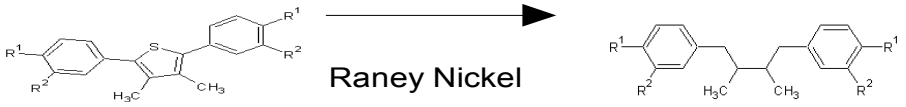
methanol to THF solubilized nickel chloride and tetrasubstituted thiophene solution. Once again the reaction failed to bare fruit, and additional research was conducted on the original Raney nickel slurry reagent. Two references were consulted that indicated the Raney nickel reagent, although active as the slurry in water form, could be made even more reactive with a wash process that removed any contaminates associated with the original preparation of the reagent.[23,25]

Incorporation of the wash process led to the first successful desulfurization and reduction reactions. The nickel reagent was not through demonstrating its esoteric nature, and another obstacle was soon encountered. References related that once washed the highly activated reagent could successfully be stored completely submerged in alcohol at 2 -8 °C at the very least overnight and possibly up to one week.[23] Unfortunately any attempts at desulfurization and reduction with previously prepared and stored reagent met with failure. The author speculated that completely drying the alcohol solutions to thoroughly degas and remove any reactive oxygen may allow for storage. No attempts were made to test that hypothesis, and any reaction subsequent to that determination were conducted with freshly washed reagent. The highly activated species was extremely efficient at generating the desired products, and GC/MS analysis of reaction time points revealed that after 30 minutes of incubation the starting material was completely removed. The control injection of starting material exhibited a retention time of 21 minutes, and by the 30 minute time point only two large closely associated peaks were observed at 14.9 and 15.0 minutes for the reaction where the tetramethyl nordihydroguaiaretic acid species was produced. TLC of the purified product mixture

revealed that chromatographic separation of those species may not be as straightforward and convenient as desired. However an attempt was made to separate those species with flash chromatrography in 9:1 hexanes to ethyl acetate by collecting 1mL fractions throughout the experimentally determined chromatographic product elution fractions. An early eluting fraction was analyzed by GC/MS and found to contain the peak with the 15.0 retention time and the molecular ion of 358 m/z. Based upon the isomer's phase change temperatures it was believed that material would be the meso tetramethyl nordihydroguaiaretic acid (CAS # 24150-24-1) and subsequent X-ray crystallography at Texas A & M confirmed that determination. Therefore the material with the 14.9 minute retention time and the 358 m/z molecular ion peak was the racemic mixture of (R,R)/ (S,S) products, and that determination was applied to subsequent Raney nickel reaction product analysis (Table 4).

The isomeric ratio of products produced by the reductive desulfurization are indicative of a mechanistic sequence that removes the sulfur atom as the initial step. Desulfurization allows for free rotation about the internal bonds of the butane tether leading to a 50:50 mixture of isomers following the reduction step. If reduction were the initial step a single isomer would be expected as attack would be limited to a single face of the thiophene species.

Table 4 - Highly Activated Raney Nickel Reaction



Substate	Substrate Conc. (mol)	Raney Nickel (g)	Ethanol (mL)	Time (min)	Temperatrue (°C)	Yield (%)
2,5-(3,4-Methoxy Phenyl)-2,3-Methyl Thiophene	0.000185	1.87	25	35	80.0	79*
2,5-(4-Meoxy Phenyl)-2,3-Methyl Thiophene	0.000178	1.50	20	35	60.5	60
2,5-(4-Isopropoxy-3-Methoxy Phenyl)-2,3-Methyl Thiophene	0.000075	0.69	15	35	52.0	84
2-(4-Isopropoxy-3-Methoxy Phenyl)-3,4-Methyl-5-(3,4-Methoxy Phenyl) Thiophene	0.000084	0.88	15	35	50.5	79[!]

[!] **Additional Non-*Meso* & Non-*Racemate* Isomers also produced**

***Purified yield.**

In conclusion several nordihydroguaiaretic acid derivatives were produced, and some very specific reaction conditions were identified to effect the necessary transformations. The conditions ultimately employed for the synthesis of these species all proceeded in high yield with excellent selectivity (Table 5). The documented synthesis should be amenable toward production of interesting species for assessment of biological activity. Possible future work may also include rearrangement of the reaction sequence such that all of the palladium mediated reactions may be conducted as a handy single pot synthesis to reduce waste and increase overall yield.

Table 5 – Percentage overall Yield

Product	Overall Yield (%)
1,4-(3,4-Methoxy Phenyl)-2,3-Methyl Butane	41.9*
1,4-(4-Methoxy Phenyl)-2,3-Methyl Butane	16.0
1,4-(3-Methoxy-4-Isopropoxy Phenyl)-2,3-Methyl Butane	34.2
1-(3-Methoxy-4-Isopropoxy Phenyl)-2,3-Methyl-4-(3,4-Methoxy Phenyl) Butane	9.9[!]

[!] **Average of individual suzuki couplings used to generate this value**

***Purified yield**

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