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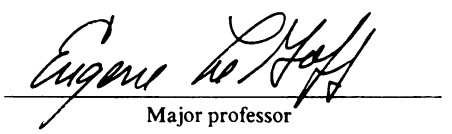
Synthesis of Thiophene Oligomers Containing 3,4-Dibutylthiophenes and Synthesis of Related Mixed Oligomers

presented by

Michael E. Benz

has been accepted towards fulfillment of the requirements for

Ph.D. degree in Chemistry



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SYNTHESIS OF THIOPHENE OLIGOMERS CONTAINING 3,4-DIBUTYLTHIOPHENES AND SYNTHESIS OF RELATED MIXED OLIGOMERS

By

Michael Eric Benz

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

1992

ABSTRACT

SYNTHESIS OF THIOPHENE OLIGOMERS CONTAINING 3,4-DIBUTYLTHIOPHENES AND SYNTHESIS OF RELATED MIXED OLIGOMERS

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Michael Eric Benz

Alkyl-substituted thiophene oligomers are of interest both as precursors to electrically conducting polythiophenes and as models of these polymers. Efficient routes to oligomers containing dibutyl substituted thiophenes separated by unsubstituted thiophenes were developed. The key compound, 3',4'-dibutyl-2,2':5',2''-terthiophene **12**, was synthesized in 49% net yield from tetrabromothiophene. The principal reactions used were transition metal-catalyzed couplings of Grignard reagents with arylbromides. Repetition of the coupling procedure resulted in the synthesis of 3'',4''-dibutyl-2,2':5',2'':5'',2''':5''',2''''-quinquethiophene **27**. Dimerization of terthiophene **12** by treatment with n-butyllithium followed with cupric chloride was also achieved. The X-ray structures of all three compounds have been determined.

Another route, using a 1,4-diketone intermediate, allowed synthesis of terthiophene **12** in 22% net yield, and additionally, allowed

synthesis of 3,4-dibutyl-2,5-dithienylpyrrole **25** and 3,4-dibutyl-2,5-dithienylfuran **24**.

The UV spectra of all oligomers were taken and compared with that of the corresponding unsubstituted and monosubstituted oligomer (when available). This comparison indicated that the terthiophene, quinquethiophene, and sexithiophene had a moderate decrease in conjugation. The pyrrole **25** and the furan **24** showed little effect due to substitution.

A new reagent for converting 1,4-diketones to pyrroles (the Paal-Knorr reaction) was found: methylchloroaluminum amide. This reagent converts aryl 1,4-diketones to pyrroles efficiently. In most cases, the reaction is run at room temperature for a few hours. Use of this reagent allows the synthesis of pyrroles by a method which is rapid, employs mild conditions, and allows synthesis of pyrroles not available using tradition Paal-Knorr conditions.

This dissertation is dedicated with love to my family

and especially

to Nancy.

Acknowledgments

It is a pleasure to thank Professor LeGoff for his support and enthusiasm throughout my studies at Michigan State University, and especially, for always taking my ideas and suggestions seriously. His deep knowledge of his field combined with a far-ranging imagination are the essence of creativity.

I greatly appreciate the interest shown in this work by Professors Blanchard and Kanatzidis. It is always good to feel that your work has application. Thanks also go to Professor Kanatzidis and J. H. Liao for providing the X-ray data used in this dissertation.

I am indebted to Dave Gale and Evaldo de Armas for teaching me the basics of electrochemistry and for investigating my compounds. Thanks also go to Paul Weipert for teaching me about his research, some of which was applied to this work.

I am grateful to Eric Lind for getting me started in the lab, and to Bryon Merrill, for his friendship and for teaching me so much chemistry. His thoroughness and thoughtful approach to chemistry are the models I strive to emulate. My interactions with the other graduate students greatly enlivened my experiences here ("can you name a reagent that won't work for that reaction?"), and I would especially like to thank Michael Waldo for his friendship, humor, and for helping me out in various times of need.

Special thanks go to my family for their support throughout my studies, and especially to my wife, Nancy Tomboulian, for her love, understanding, and unending support.

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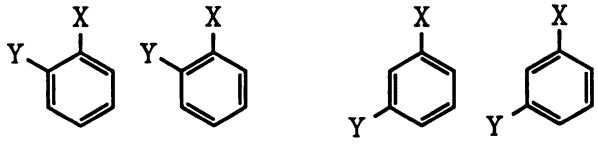
INTRODUCTION

1. Synthesis of Thiophene-based Annulenes

Investigation of the concept of aromaticity has been a source of inspiration to chemists since the early nineteenth century. The prototypical aromatic molecule, benzene, has been known since its isolation by Faraday in 1825. Benzene was an intriguing molecule to nineteenth century chemists. It contained four units of unsaturation, yet did not show the reactivity usually associated with olefins. Kekulé[1] proposed that the structure of benzene was a hexagonal ring containing three double bonds. It was soon observed that his proposed structure implied isomers should be found for the *ortho* and *meta* disubstituted benzenes, because of the arrangement of bonds and substituents (Figure 1).

Figure 1: Isomers Implied by Kekulé's Proposed Structure for Benzene

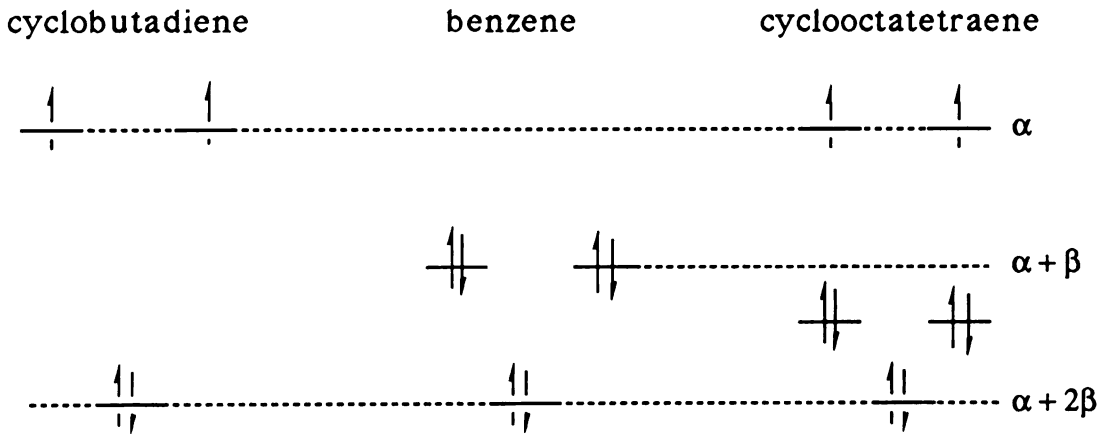


Subsequent investigations determined that no such isomerization existed, and that in fact, the six bonds connecting the carbon atoms were equivalent. Kekulé then suggested that the three double bonds could be interconverted by 'mechanical motion', giving equivalent structures. This early suggestion of resonance, which was derided at the time as an expedient designed to save the

proposed structure, has developed into one of the most important concepts in organic chemistry.

The concept of resonance was first suggested by Kekulé to explain the structure of benzene. The explanation for its surprising stability was developed in the theoretical work of Hückel.[2] Hückel's approach considered the π-electrons of benzene separately from the other electrons of the molecule, which greatly simplified calculations. This separate consideration of π-electrons is known as the *Hückel approximation.* The resulting molecular orbital calculations using this method gave a straight-forward explanation of its stability: benzene has all of its electrons in filled bonding orbitals, and these orbitals are of lower energy than the equivalent acyclic compound, hexatriene. Application of the Hückel method to cyclobutadiene and cyclooctatetraene shows that these molecules would not be expected to be as stable, because they have unpaired electrons in nonbonding orbitals. These orbitals are shown in Fig. 2.

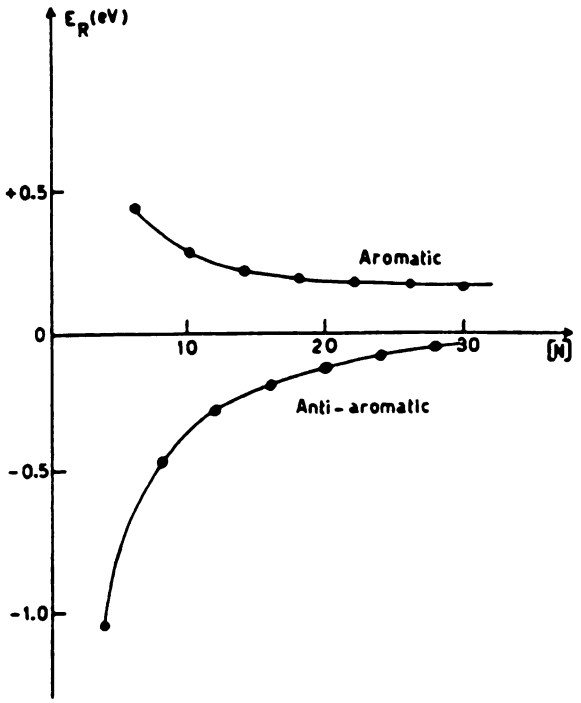
Figure 2: Relative Energies of π Electrons by the Hückel Method



Hückel further generalized this approach to state that molecules containing 4n+2 conjugated, out-of-plane π-electrons would show additional stability. He also stated that molecules with a 4n π–electron system would not be as stable. Both theoretical and experimental investigations have confirmed these statements. Hückel's method has several drawbacks, however, the most serious being a large overestimation of resonance energy for all 4n and 4n+2 systems larger than benzene.

The next major step[3] in quantifying resonance stabilization was made by Dewar and Gleicher. They improved on Hückel's method by introducing two elements: (i) use of the semiempirical Pople-Pariser-Parr (PPP) molecular orbital approach to calculate the energy of the delocalized structure, and (ii) calculation of the net resonance stabilization by comparison to an acyclic polyene with the same number of single and double bonds. This change in the reference structure was the more important innovation, and resonance energies calculated using it are referred to as 'Dewar resonance energies', regardless of the molecular orbital approach used. Dewar determined by his method that as the size of a conjugated system increases, the resonance stabilization (or destabilization) of an aromatic (or antiaromatic) compound decreases, eventually tailing toward zero (Figure 3).

Figure 3. Calculated Resonance Energies of [N]-Annulenes

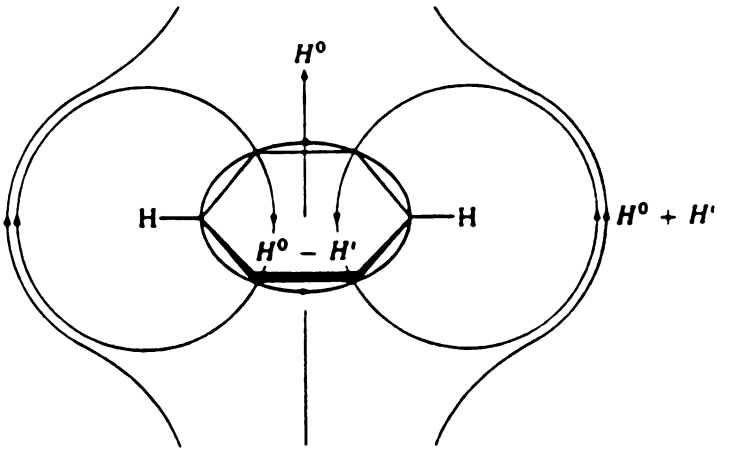


The concept of aromaticity had, as developed by Kekulé and Hückel, come to embrace two different properties. These are bond delocalization, as suggested by Kekulé, and thermodynamic stability, as shown by Hückel. Other criteria for determining aromaticity have been suggested, including lack of reactivity and reaction by electrophilic substitution. Of these criteria, thermodynamic stability and bond delocalizaton are most generally accepted as evidence of aromaticity.

Direct evaluation of the additional thermodynamic stability attributible to aromatic character has often proven to be an elusive target for experimentalists. An investigator must determine the heat of formation, and then compare it to that of the equivalent

bond-localized molecule. While good estimates of the energy of this hypothetical bond-localized molecule may be made from thermodynamic cycles, exact solutions are unavailable. Furthermore, determining the heat of formation involves the destruction of the compound. Qualitative experimental evidence of aromatic character, in the form of a diamagnetic ring current effect in the proton nuclear magnetic resonance (^{1}H-NMR) spectra[4], is more accessible. This diamagnetic ring current arises from precession of the π electrons in the presence of an external magnetic field (Figure 4). The precession produces a small magnetic field in the opposite direction of the external field. The effect of the induced field is to deshield the protons outside the aromatic ring and shield the protons on the interior of the ring. Conversely, antiaromatic character is determined by the presence of a paramagnetic ring current. Protons which are deshielded appear in the spectrum at a lower field than expected, and the shielded protons at a relatively higher field.

Figure 4: Ring Current Induced by External Field



Since both properties are functions of the number of electrons in the π system, the resonance energy of simple annulenes may be calculated to close approximation using the ring current, and this relationship has been developed by Haddon[5]. Thus, examination of the ring current gives qualitative evidence of π electron delocalization for all 4n and 4n+2 systems and allows an approximate determination of the resonance energy for simple annulenes by a method which is readily available, nondestructive, and requires only a small amount of material.

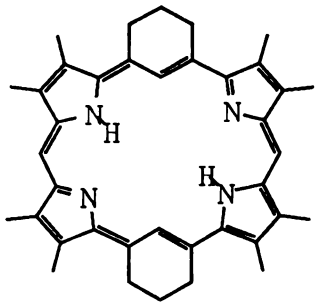
Attempts to investigate and explore the limits of 'aromatic character' have inspired many syntheses. Synthesis of annulenes was led by Sondheimer[6], who found that annulenes containing 14, 18, and 22 carbons showed diamagnetic ring current shielding in their NMR spectra, indicating they are aromatic. Analogously, annulenes containing 12, 16, 20, and 24 carbons showed paramagnetic ring current shielding in their NMR spectra, indicating they are antiaromatic.

All of these annulenes are fluxional molecules at room temperature, and transpose inner and outer protons in a manner similar to the flexing of cyclooctatetraene. This property is thought to contribute to tendency of the larger annulenes to give spectra similar to that of polyenes. The desire to eliminate this fluxional character and to ensure a rigid, planar molecule led to the synthesis of dehydroannulenes. Dehydroannulenes use triple bonds to help fix

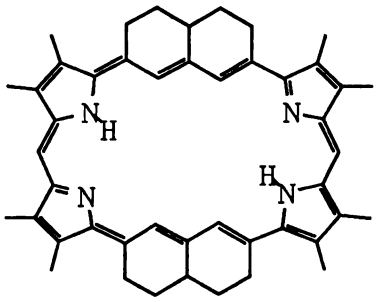
the geometry of the molecule. Dehydro[26]- and [30]annulenes have been synthesized which show a diamagnetic ring current[7].

Another method of ensuring planarity has been to incorporate heterocyclic rings into the annulene structure. An ongoing project in this laboratory has been the synthesis of macrocycles based on expansion of the porphyrin system by extending the bridging units between pyrrole rings[8]. Two examples of this type of expansion are shown in Figure 5. These compounds have been named [1,3,1,3]platyrin and [1,5,1,5]platyrin.

Figure 5. [1,3,1,3]Platyrin and [1,5,1,5]Platyrin



[1,3,1,3]Platyrin



[1,5,1,5]Platyrin

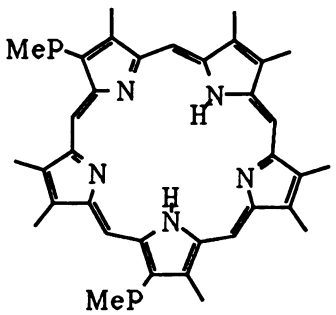
These compounds (22 and 26 π electron systems, respectively) both show strong evidence of a diamagnetic ring current, as indicated by the proton shifts shown in Table 1.

Table 1: ^{1}H-NMR of [1,3,1,3]Platyrin and [1,5,1,5]Platyrin

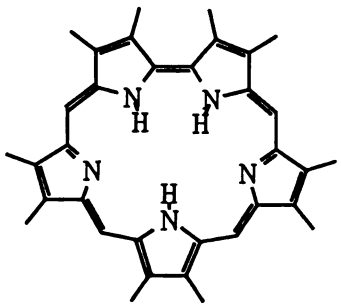
	[1,3,1,3]Platyrin	[1,5,1,5]Platyrin
internal C-H(δ)	-8.97	-14.26
N-H(δ)	-5.6	-10.58
ext. methine(δ)	11.64	11.75

Other investigations devoted to the synthesis of hetero-bridged annulenes include the 22 π-electron systems pentaphyrin[9a] 1, decamethylsapphyrin[9b] 2, texaphyrin[9c] 3, and the 26 π-electron system, hexaphyrin[9d] 4 (Figure 6). All show strong diamagnetic ring current shielding in their ^{1}H-NMR.

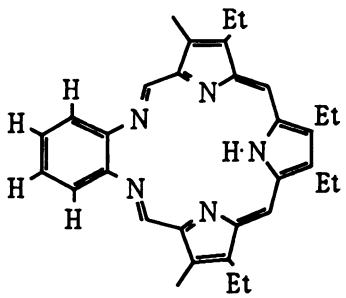
Figure 6: Expanded Porphyrin-type Molecules



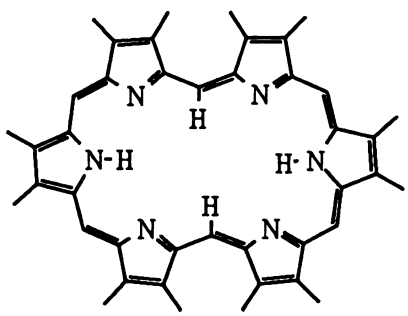
Pentaphyrin (1)
(PMe=$CH_2CH_2CO_2Me$)



Decamethylsapphyrin (2)



Texaphyrin (3)



Hexaphyrin (4)

The largest heteroannulene synthesized[10] to date is shown in Figure 7. It has a conjugated ring containing 34 π electrons. The ^{1}H-NMR spectrum (Table 2) shows evidence of a strong diamagnetic ring current, clearly demonstrating that the limit for showing electron delocalization has not yet been reached.

Figure 7: [34]Porphyrin

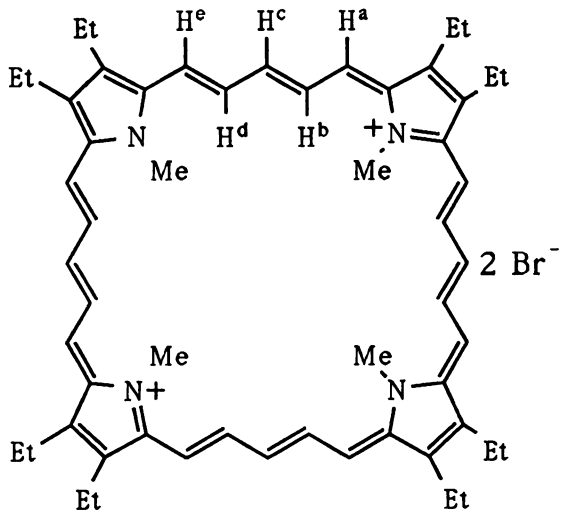
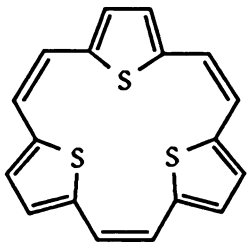


Table 2: ^{1}H-NMR of [34]Porphyrin

	(δ)
H^a, H^e	16.18
H^b, H^d	-14.27
H^c	17.19

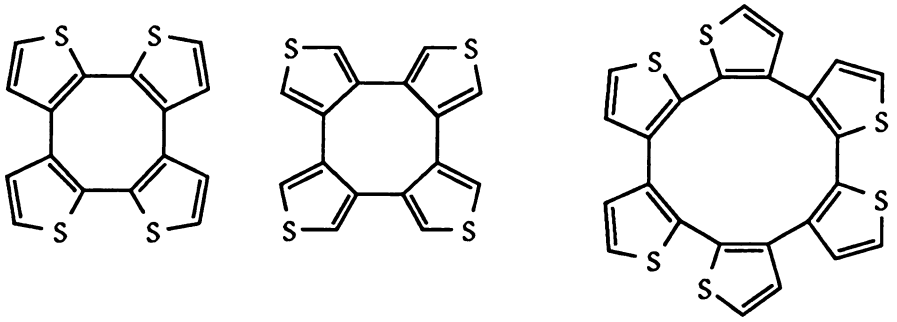
Relatively few heteroannulenes containing thiophene have been synthesized. One, synthesized by Badger[11] and coworkers, is shown in Figure 8. Because of the large sulfur atoms, this molecule is not planar, and its aromaticity is only that of its three component thiophenes acting independently.

Figure 8: Badger's Thiophene-containing Heteroannulene



The compounds shown in Figure 9 were synthesized by Kauffmann[12] and coworkers. These compounds are also nonplanar. The X-ray structure determination of the center compound shows it to have adopted a saddle conformation, with opposing pairs of thiophenes tipped toward each other. The ^{1}H-NMR spectra show only signals normally expected for disubstituted thiophenes.

Figure 9: Kauffmann's Cyclopolythiophenes

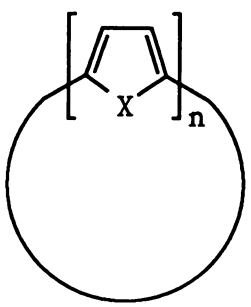


Thus, it seems that conjugated ring systems that (i) contain 4n+2 π-electrons, and (ii) have a rigid planar structure, generally show evidence of aromatic character in the form of a diamagnetic ring current, up to the limits so far obtained for n. Synthesis and investigation of larger ring systems must both meet the challenge of

guaranteeing the desired planarity of the ring system and cope with the highly reactive nature of large π-electron systems.

Our conceptual approach to such a macrocyclic system is shown in Figure 10. The system is created by linking heteroaromatic molecules (such as furan, pyrrole, or thiophene) in a consecutive 2:2' fashion.

Figure 10: Representation of a Generalized Epicycle Made of α-Linked Heteroaromatic Units



This macrocycle (or 'epicycle', as it has been named in this laboratory), with proper selection of X and n, will be planar. We investigated various epicycles using the MM2 modeling system[13] and found that for n=8 or 10, furan and pyrrole give a planar structure. For thiophene, n=10 gives an interesting bowl-shaped epicycle (Figure 11) and n=12 gives a planar epicycle (Figure 12). The chemical robustness of thiophene relative to that of furan or pyrrole[14] indicates that it would be the best starting material for synthesis of such an epicycle.

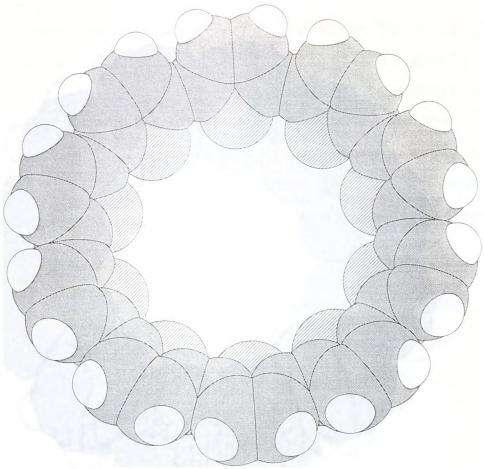


Figure 11: Space Filling Representation of 10-Epicycle

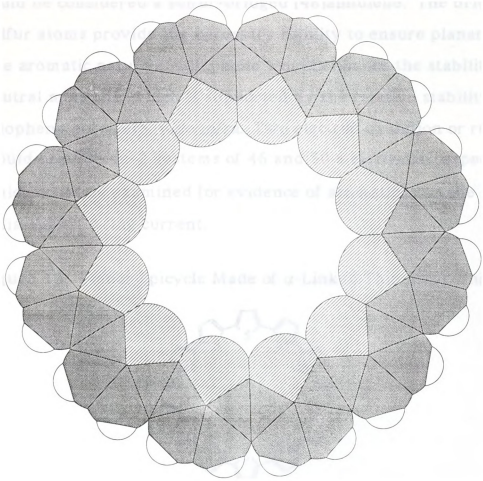
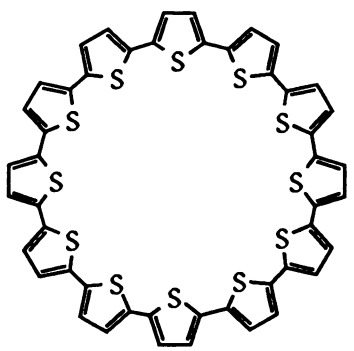


Figure 12: Space Filling Representation of 12-Epicycle

The epicycle containing twelve thiophenes (Figures 12 and 13) could be considered a sulfur-bridged [48]annulene. The bridging sulfur atoms provide the necessary rigidity to ensure planarity. The aromatic nature of thiophene would enhance the stability of the neutral molecule, which is supported by the relative stability of thiophene polymers, *vide infra*. Two electron oxidation or reduction would provide 4n+2 systems of 46 and 50 π electrons, respectively, which could be examined for evidence of aromaticity in the form of a diamagnetic ring current.

Figure 13: Planar Epicycle Made of α-Linked Thiophene Units

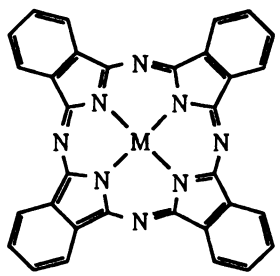


5

In addition to the study of aromaticity, this compound would also be of interest as a potential electric conductor because of its similarity to known molecular organic conductors. It has been found that metallophthalocyanines[15] (Figure 14) form crystals which conduct electricity upon partial oxidation (doping). These crystals have phthalocyanine molecules arranged in stacks, allowing interaction between the π-orbitals of adjacent molecules. Since this feature may also be found in crystals of the macrocycle **5**, its electrical conductivity could be investigated. The thiophene

macrocycle would also represent an 'ideal' polythiophene model, because it is defect free, all α-linked, and has no end effects. The space between sulfur atoms across the molecule, which we calculate by MM2 to be 12.2 Å, opens the possibility of using it as a complexant.

Figure 14: Metallophthalocyanine



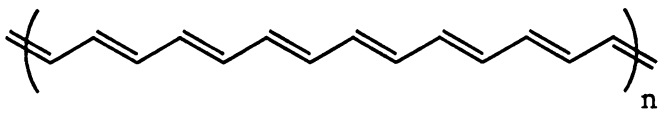
2. Synthesis of 3,4-Dialkylsubstituted Thiophene Oligomers

Thiophene oligomers have attracted interest due to their biological activity and electronic properties. Terthiophene, a compound found in some species of marigolds[16], has a phototoxic effect on nematodes[17] and the larvae of the mosquito and blackfly[18]. Longer oligomers have been investigated for their potential to be incorporated into electronic devices[19] and as models for higher polymers[20]. High molecular weight thiophene polymers have been shown to be relatively good organic conductors, with conductivities in excess of 1000 $S \bullet cm^{-1}$ after doping[21]. Thiophene-based polymers have been investigated for use in many applications. Among these are batteries[22], solar cells[23], and electronically controlled drug delivery systems[24].

Polymers which contain a conjugated π-electron system are found to conduct electricity upon partial oxidation, or "doping". This property was discovered by Shirakawa and coworkers in 1977[25]. They found that polyacetylene (Figure 15) doped with iodine, bromine, or chlorine vapor showed an improvement in conductivity of some seven orders of magnitude. Polyacetylene is highly labile in the presence in oxygen, limiting its possibilities as a raw material

for devices. Indeed, it has been suggested that polyactetylene may be useful as an oxygen scavenger.

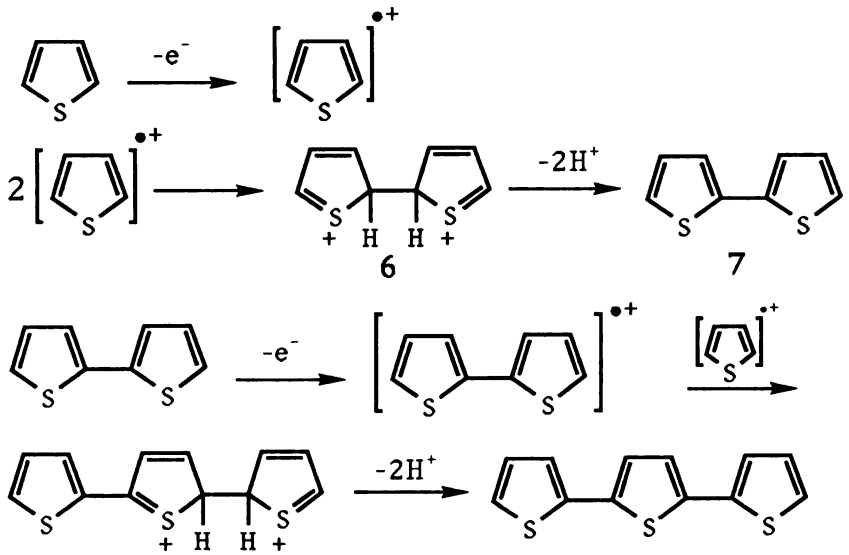
Figure 15: Polyacetylene



Other organic compounds that could be converted to conjugated polymers were investigated, and many found to conduct electricity upon doping. Thiophene was found to be readily chemically or electrochemically polymerized, and to form polymers of good conductivity[26]. It also proved to be air and moisture stable in both the doped and neutral form. These properties have made thiophene and especially β-substituted thiophenes among the most interesting and most widely investigated building blocks for conducting polymer synthesis. The use of electrochemical synthesis gives a polymer which is free of impurities and has relatively few interruptions of conjugation[27].

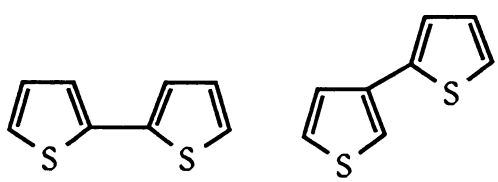
The electropolymerization[27,28] of thiophene (Figure 16) starts with electrochemical generation of radical cations. These couple to give the dihydrobithiophene dication **6**, which forms bithiophene upon elimination of a pair of protons. Rearomatization has been suggested to be the driving force for the reaction. The newly formed oligomers (in Figure 16, bithiophene, **7**), have lower oxidation potentials than the starting monomer.

Figure 16: Proposed Mechanism of Polymerization of Thiophene



The coupling of the radical cations can also occur in an α-β', rather than the α-α' fashion, as shown in Figure 17. Initially, α-α' coupling is favored, because the singlet electron density resides primarily on the α-carbon. As polymerization procedes, α-α' coupling is not as strongly favored over α–β' coupling, because as oligomer length increases, π-delocalization of the radical over the chain decreases the relative probability of α–α' coupling[29].

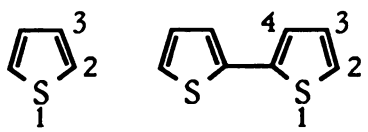
Figure 17: Two Modes of Coupling in Thiophene Polymers



α–α' coupling α–β' coupling

Molecular orbital calculations[29] indicate that the spin density of the thiophene radical cation (Figure 18) strongly favors the α-position. The bithiophene radical cation, while still having the greatest spin density at the α-position, also has high spin density at the internal β-position. Steric interactions disfavor coupling at this site, but it may still make an appreciable contribution. These α-β' couplings are thought to decrease the conductivity of polymers because the interruption of conjugation prevents the transport of charge carriers such as bipolarons. While up to one third[30] of the linkages in polypyrrole are α-β', spectroscopic evidence indicates that this defect occurs rarely in polythiophene.[31, 39d,g]

Figure 18: Spin Density of Thiophene and Bithiophene by Position



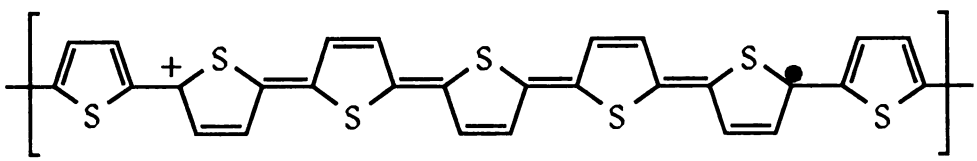
Spin density

position	thiophene	bithiophene
1	-.20	-.14
2	.67	.67
3	-.01	-.50
4	----	.57

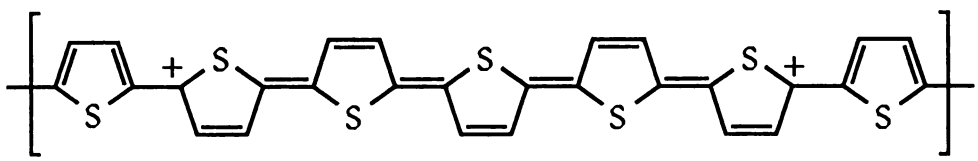
Neutral polythiophene is an insulator. To convert it to the conducting phase, it must be oxidized. Removing electrons from the π system creates vacant p orbitals, which act as charge carriers. Low levels of doping cause the formation of polarons (radical-cations). At higher levels of doping (approximately seven percent

or greater), bipolarons (dications) are formed, which are thought to be the major charge carriers in conjugated polymers[32] (Figure 19). Maximum doping levels[33] for polythiophenes are typically on the order of 30-50 %.

Figure 19: Polarons and Bipolarons in Polythiophene



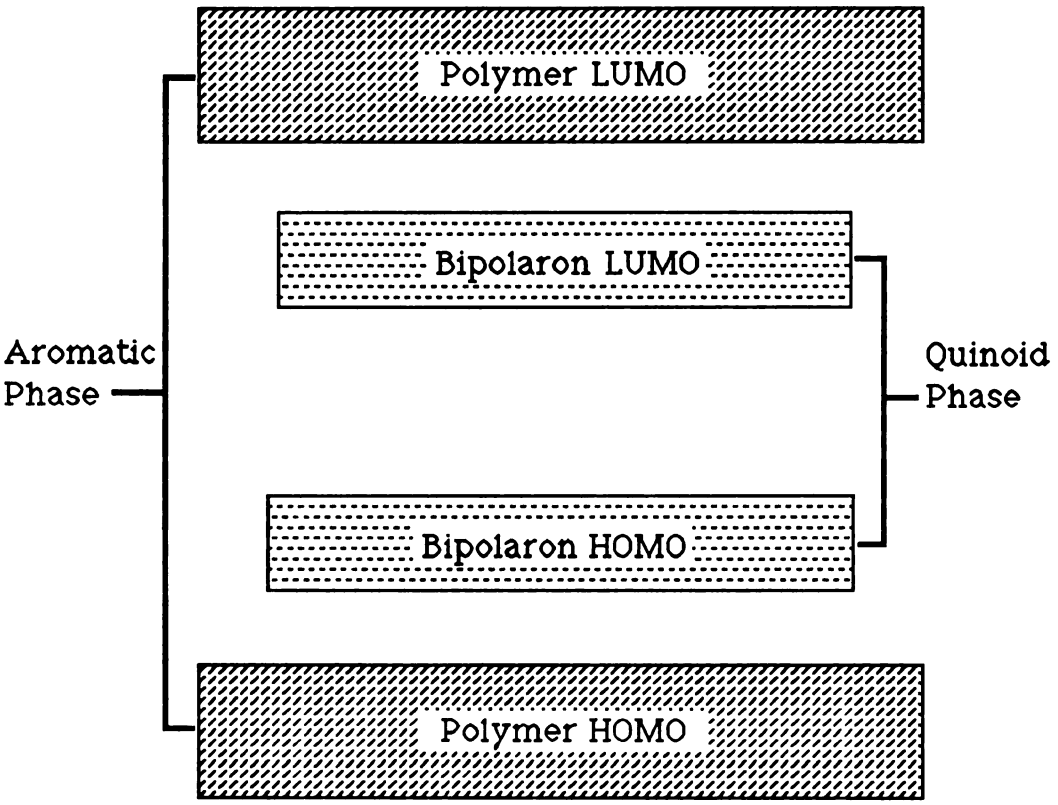
polaron



bipolaron

As can be seen in figure 19, the creation of bipolarons forms a "quinoidal" phase. The reorganization of the polymer to form this quinoidal phase raises the energy of the highest occupied molecular orbital (HOMO), with a corresponding decrease in the energy of the lowest unoccupied molecular orbital (LUMO) (figure 20). Brédas[34] has shown that the band gap decreases as a function of increasing quinoidal character and that the conductivity of the polymer is proportional to the degree of doping.

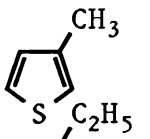
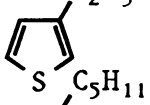
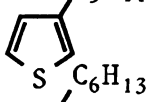
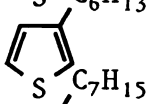
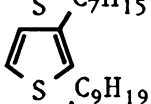
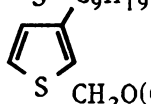
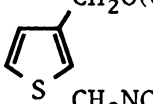
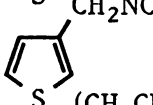
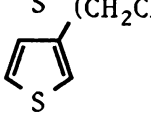
Figure 20: Energy Level Diagram Showing the Smaller Band Gap of the Bipolaron Phase of Doped Polythiophene



Much research has been directed toward investigating the changes in physical and electrical properties of conducting polythiophenes caused by modifying their structure. It is desirable to develop the ability to 'tune' the properties of the polymer by appropriate selection of the reaction conditions and monomer. These properties include conductivity, environmental stability, solubility, melting point (for melt processing), and optical response. Synthetic chemists may contribute to this effort by synthesizing monomers to be incorporated into conducting polymers. Initial efforts in this area were directed toward synthesis of 3-substituted thiophenes. It was shown that use of 3-substituted thiophenes gave improved

electronic conductivities in the resulting polymers (Table 3). 3-Methyl thiophene gave a polymer which has higher conductivity than thiophene. Many of these substituents have the additional advantage of improving the physical properties of the resulting polymer.

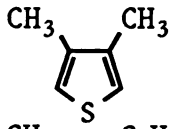
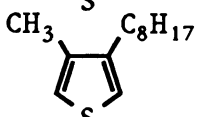
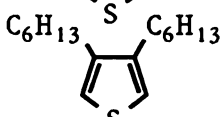
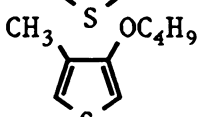
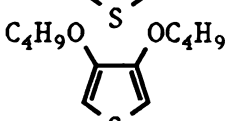
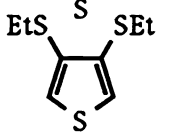
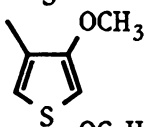
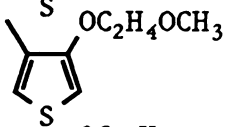
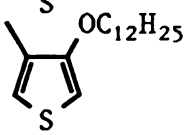
Table 3: Conductivities of Some 3-Substituted Polythiophenes

Monomer	Conductivity ($S \bullet cm^{-1}$)	Reference
	1975	35(a)
	270	35(b)
	140	35(c)
	95	35(d)
	110	35(c)
	100	35(c)
	1050	35(e)
	200	35(e)
	250	35(f)

Polymers of 3,4-disubstituted thiophenes have also been studied, but they were generally found to be poorer conductors than monosubstituted polythiophenes (Table 4). This relative lack of

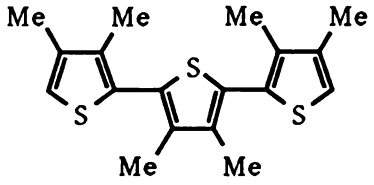
conductivity is thought to be caused by poor π-orbital overlap due to the inability of the rings to adopt a coplanar conformation.

Table 4: Conductivities of Some 3,4-Disubstituted Polythiophenes

Monomer	Conductivity ($S \bullet cm^{-1}$)	Reference
	0.5	36(a)
	1×10^{-5}	36(b)
	$< 1 \times 10^{-5}$	36(b)
	2.0	36(b)
	1×10^{-5}	36(b)
	Does not electrochemically polymerize.	29
	10-20	36(c)
	Does not electrochemically polymerize.	36(c)
	220	36(d)
	30	36(d)
	5	36(d)

We have tested this proposal by using MM2 calculations to investigate the effect of adding β-methyl groups to terthiophene (Figure 21). The calculations performed on this oligomeric model of the polymer (Figure 22) gave torsional angles of 47°. The degree of π-orbital overlap follows the cosine of the angle between rings, so a small degree of nonplanarity will not have a great effect on the conductivity[37]. It has been proposed that torsional angles less than 40° permit sufficient overlap for good conductivity[37].

Figure 21: Model Segment of Poly(3,4-dimethylthiophene)



The relatively higher conductivities of the fused cyclopentyl- and dialkoxythiophene polymers in Table four have inspired the synthesis of several related systems[38], but the 3,4-disubstituted systems so far synthesized have conductivities typically an order of magnitude less than that of polythiophene or the polymers of 3-substituted thiophenes.

Other studies devoted to exploring the properties of polythiophenes have focused on the effect of coupling longer oligomer units to form the polymer. Electropolymerization of thiophene, bithiophene, terthiophene, and quaterthiophene has given different results in the hands of different investigators[39]. It has been suggested that the

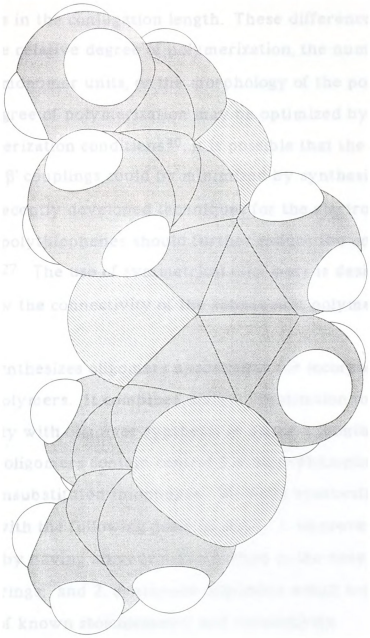


Figure 22: Space Filling Representation of 3,4,3',4',3'',4''-Hexamethyl-2,2':5',2''-terthiophene

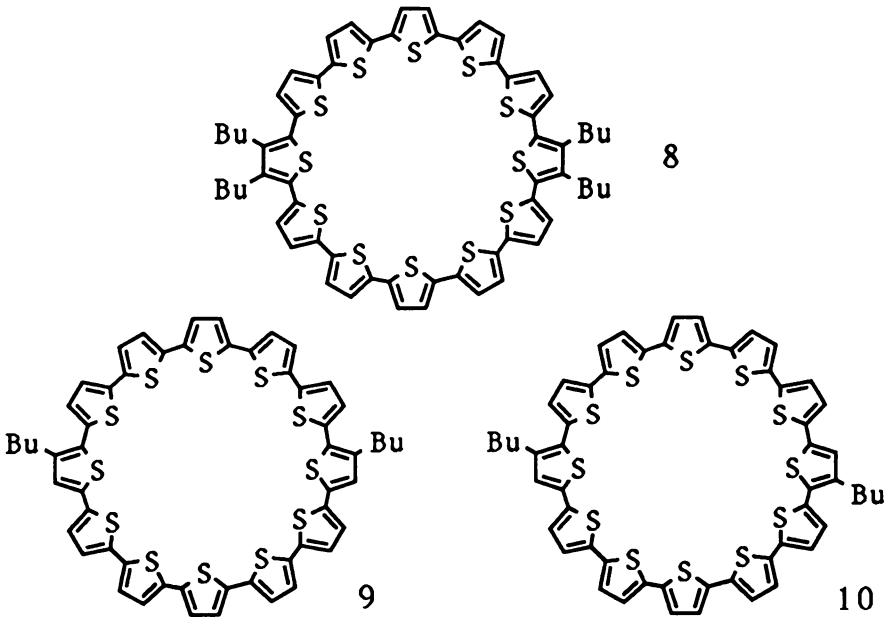
basis for the differences observed in these materials is a reflection of differences in the conjugation length. These differences could be caused by the relative degree of polymerization, the number of α-β' couplings of monomer units, or the morphology of the polymer. While the degree of polymerization may be optimized by changes in electropolymerization conditions[40], it is possible that the relative number of α-β' couplings could be minimized by synthesizing longer oligomers. Recently developed techniques for the electrochemical synthesis of polythiophenes should further reduce the occurence of α–β' linkages[27]. The use of symmetrical oligomers is desirable in order to know the connectivity of the subsequent polymer.

This study synthesizes oligomers appropriate for incorporation into conducting polymers. It combines dialkyl substitution to provide good solubility with oligomer synthesis in discrete lengths. These symmetrical oligomers contain central 3,4-dibutylthiophenes flanked by unsubstituted thiophenes. We have synthesized compounds with the following goals in mind: 1. improve solubility of oligomers by having alkyl groups attached to the beta position of heterocyclic rings; and 2. synthesize oligomers which would give copolymers of known stoichiometry and connectivity.

1. Progress Toward the Synthesis of Thiophene-based Annulenes

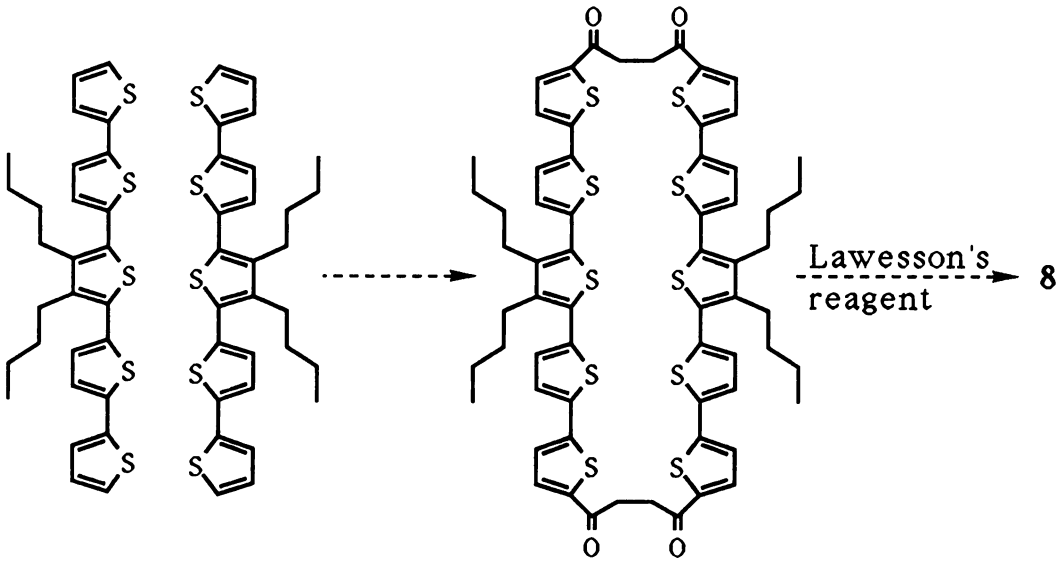
Any strategy for the synthesis of a macrocycle such as **5** must address the insolubility of thiophene oligomers. Previous work in this laboratory[14(c)] has shown that the solubility of thiophene oligomers drops sharply as the number of thiophenes in the oligomer increases. As described in the introduction, β-alkyl groups are commonly used to improve the solubility of thiophene oligomers and polymers. We chose to use butyl groups to improve solubility. The use of 3,4-dibutylthiophenes in the target macrocycle **8**, as shown in Figure 23, has the additional advantage of eliminating the possibility of forming isomers such as **9** and **10** due to unsymmetrical incorporation of oligomers.

Figure 23: Symmetrical Epicycle Compared to Isomeric Pair of Epicycles Generated by Use of Single Substituents

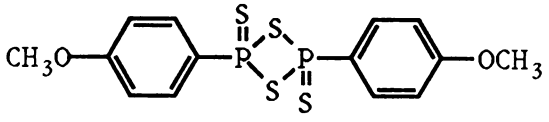


Synthesis of such an epicycle called for soluble, symmetrical oligomers containing dibutyl-substituted thiophenes. We planned to synthesize these oligomers, functionalize them, and then cyclize through formation of 1,4-diketones to give compound **11**. Conversion of the 1,4-diketones to thiophenes would be carried out by treatment with Lawesson's reagent (Scheme 1). This strategy has an additional advantage, because it can also be used to generate other macrocycles by converting the 1,4-diketones in **11** to furan or pyrrole.

Scheme 1: Synthetic Plan for Synthesis of Thiophene Macrocycle



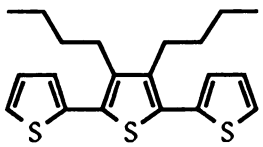
11



Lawesson's Reagent

Accordingly, compound **12** (Figure 24) was seen as a key intermediate in the synthesis of macrocycle **8**. Although many terthiophenes have been synthesized,[41] none of them contain a 3,4-disubstituted central thiophene with alkyl substituents larger than methyl. Of the possible methods available to prepare **12**, the most direct method was considered to be the use of the transition metal-

Figure 24: 3',4'-Dibutyl-2,2':5',2''-terthiophene

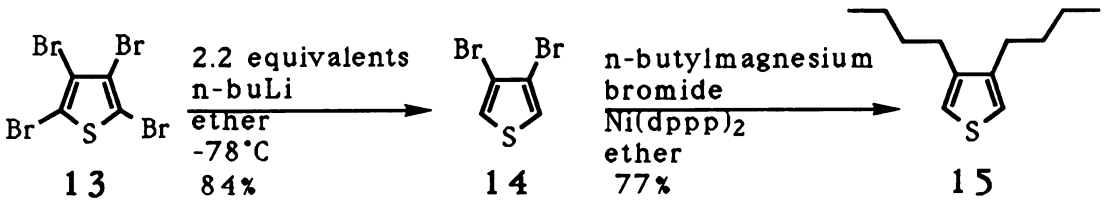


12

mediated coupling reactions developed by Kumada. Kumada[41b] has used this strategy to perform aryl-aryl and aryl-alkyl couplings in high yield, and in fact had synthesized 3,4-dibutylthiophene and 2,2':5',2''-terthiophene.

3,4-Dibutylthiophene was synthesized as shown in Scheme 2, starting with selective debromination of tetrabromothiophene with n-buLi. Although the original publication[42] called for running the reaction at 0°C, running the reaction at -78°C improved the yield from 74% to 84%. The 3,4-dibromothiophene was converted to 3,4-dibutylthiophene by coupling with n-butylmagnesium bromide in the presence of a catalytic amount of [1,3-bis(diphenylphosphino)-propane]Ni(II) chloride ($Ni(dppp)Cl_2$). 3,4-Dibutylthiophene **12** was produced in 77% yield upon distillation.

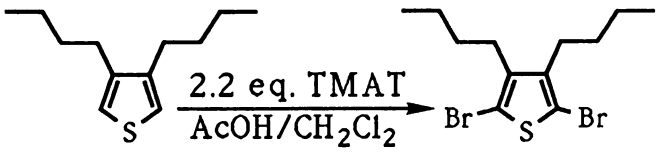
Scheme 2: Synthesis of 3,4-Dibutylthiophene



13 84% 14 77% 15

Compound **15** was treated with tetramethylammonium tribromide (TMAT) in a 1:1 mixture of acetic acid and dichloromethane (Scheme 3). This resulted in the formation of 2,5-dibromo-3,4-dibutylthiophene **16** in 92% yield.

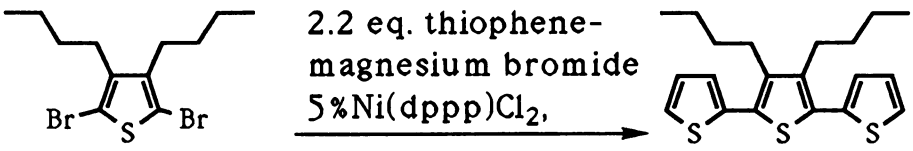
Scheme 3: Bromination of 3,4-Dibutylthiophene



15 92% 16

Initial attempts to couple **16** with thiophenemagnesium bromide using $Ni(dppp)Cl_2$ as catalyst resulted in the formation of **12** in 11% yield (Scheme 4). Although the desired product was obtained, the reaction did not go to completion and resulted in the formation of undesired side products, with starting material remaining. Since it has been reported that lithioalkenes may be coupled with alkyl and aryl bromides using $Ni(dppp)Cl_2$, the analogous reaction using 2-lithiothiophene was attempted. This gave the desired terthiophene **12** in 20% yield. Use of bis(triphenylphosphino)nickel(II) chloride as the coupling catalyst produced only trace amounts of **12**.

Scheme 4: Initial Attempt to Synthesize Terthiophene **12**



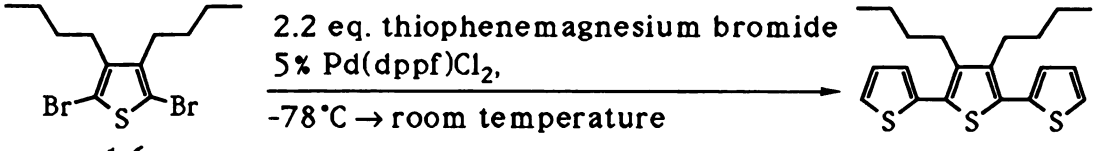
16 11% **12**

Examination of other coupling catalysts showed that [1,3-bis(diphenylphosphino)ferrocene]Pd(II) chloride (Pd(dppf)Cl2) has been used by Kumada[43] to couple aryl bromides with sterically crowded alkyl magnesium halides. Using this catalyst gave an immediate improvement in yield to 31%. More vigorous conditions were tried using the higher boiling solvents tetrahydrofuran and *t*-butyl-methyl ether. These attempts to push the reaction to completion were not successful. Use of tetrahydrofuran resulted in no formation of the desired product. It was found that thiophenemagnesium bromide was not soluble in *t*-butyl-methyl ether.

In previous reactions, I had observed that when the addition of thiophenemagnesium bromide to the flask containing $Ni(dppp)Cl_2$ and **16** was made at 0°C, a clearer solution resulted (although the yield did not increase). Based on this observation, I attempted the reaction (Scheme 5) using $Pd(dppf)Cl_2$ as catalyst and adding the Grignard reagent to the solution of **16** at -78°C. The cold bath was removed after one hour and the reaction allowed to continue an additional twelve hours. The reaction went to completion and **12** was isolated in 83% yield after flash chromatography. The only side

product observed was bithiophene, which is necessarily formed in the initial activation of the catalyst. It appears that using a catalyst with a more highly hindered catalytic site eliminates the side reactions observed using $Ni(dppp)Cl_2$. This, combined with the low initial temperature of the reaction, prevented subsequent deactivation of the catalyst.

Scheme 5: Optimized Synthesis of **12**



16 83% **12**

Terthiophene **12** forms pale green crystals with a melting point of 36.0-36.5°C. It is extremely soluble in chloroform, dichloromethane, and ether. It is moderately soluble in most other organic solvents. The isolation of high quality crystals resulted in the determination by M.G. Kanatzidis and J.H. Liao of the structure by X-ray diffraction (Figure 25). This structure is very similar to that of the unsubstituted terthiophene,[44] whose thiophene rings are in a similar antiplanar conformation with a torsional angle of about 6-9°. The UV spectrum of terthiophene **12** showed a maximum at 331 nm. Comparison with nonsubstituted terthiophene **17** (364 nm) and the mono-alkyl terthiophenes of Ferraris[41e] (**18**, 350 nm; **19**, 342 nm) and Delabouglise[41d] (**20**, 347 nm) shows a regular hypsochromic shift of approximately 16 nm associated with each alkyl group (Figure 26). According to the Woodward-Fieser rules

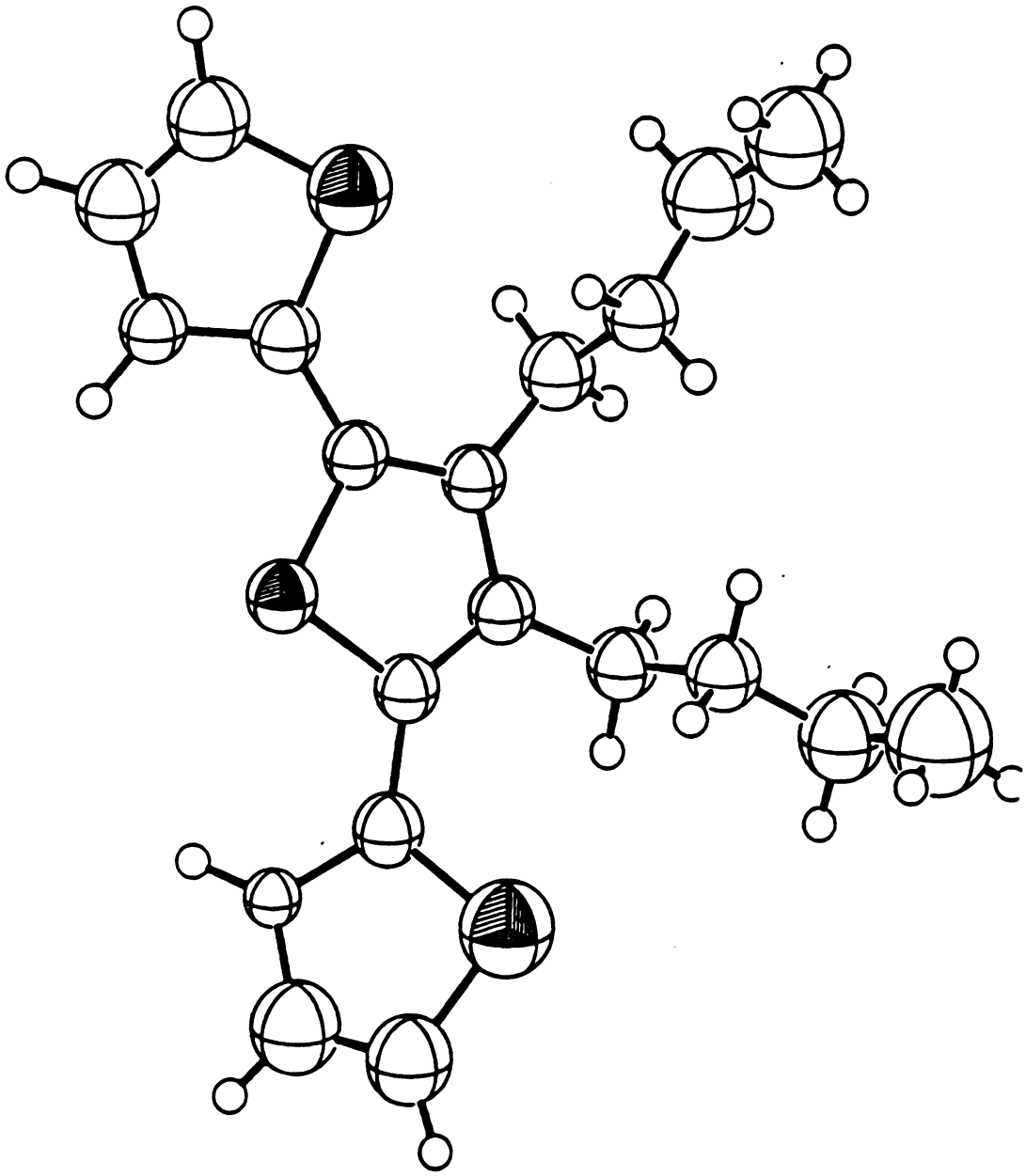
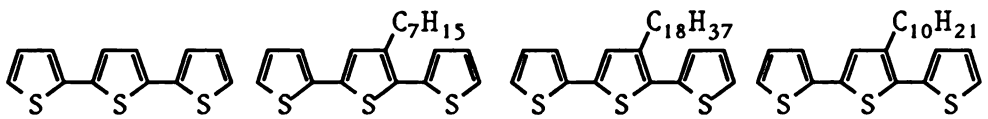


Figure 25: X-ray Structure of Terthiophene **12**

for calculating the λ_{max} of conjugated polyenes, addition of alkyl substituents should produce a bathochromic shift of 5 nm per substituent. Apparently, the alkyl groups prevent maximum coplanarity from being achieved. A test for this proposal would be to synthesize the 2,5"-dialkyl-2,2':5',2"-terthiophene, since alkyl groups on the end positions should not adversely affect conjugation. Uhlenbroek and Bijloo[17b] have synthesized the 2,5"-dimethyl-2,2':5',2"-terthiophene, which shows a bathochromic shift of 9 nm. This corresponds well with the prediction of the Woodward-Fieser rules.

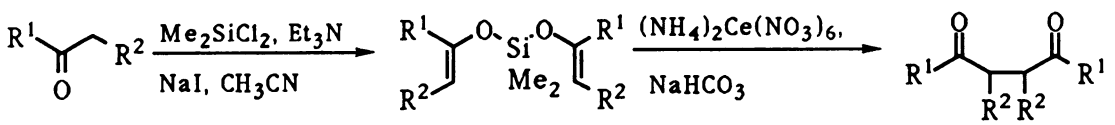
Figure 26: UV Spectra of Various Terthiophenes



	17	18	19	20
UV (λ_{max})	364	350	342	347

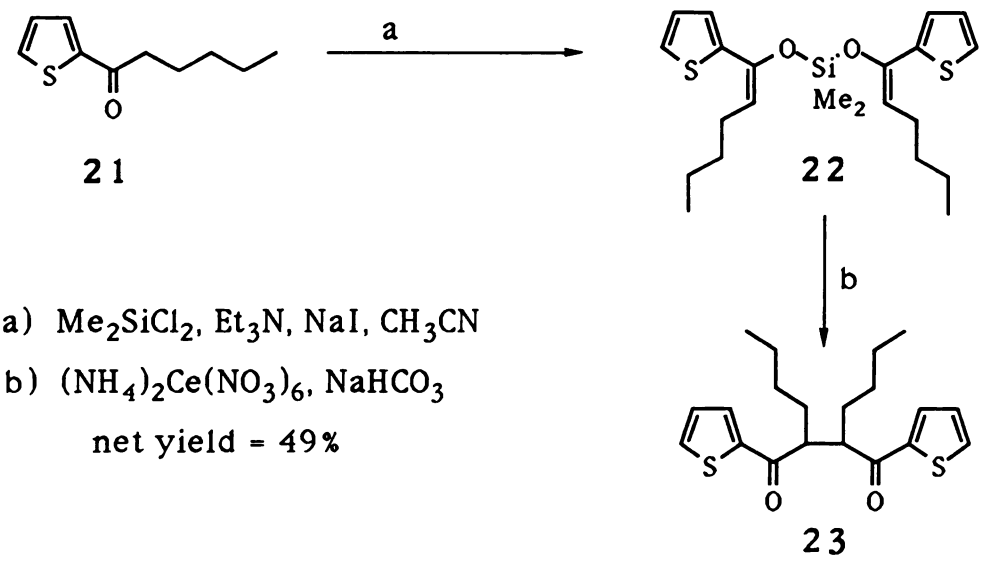
Another route to terthiophene **12** was opened by the efforts of Rathke and Weipert[45] (Scheme 6). They have developed a new method to couple ketones *via* an intermediate bis-silyl enol ether. The bis-silyl enol ether is oxidized by the action of cerric ammonium nitrate to form the 1,4-diketone.

Scheme 6: The Rathke-Weipert Reaction



This route is unique in that it works only for alkyl ketones larger than methyl (R^2 cannot be H). Use of this method gives the coupled product diketone **23** in 49% yield from the starting 2-hexanoylthiophene **21** (Scheme 7).

Scheme 7: Coupling of 2-Hexanoylthiophene by the Method of Rathke and Weipert



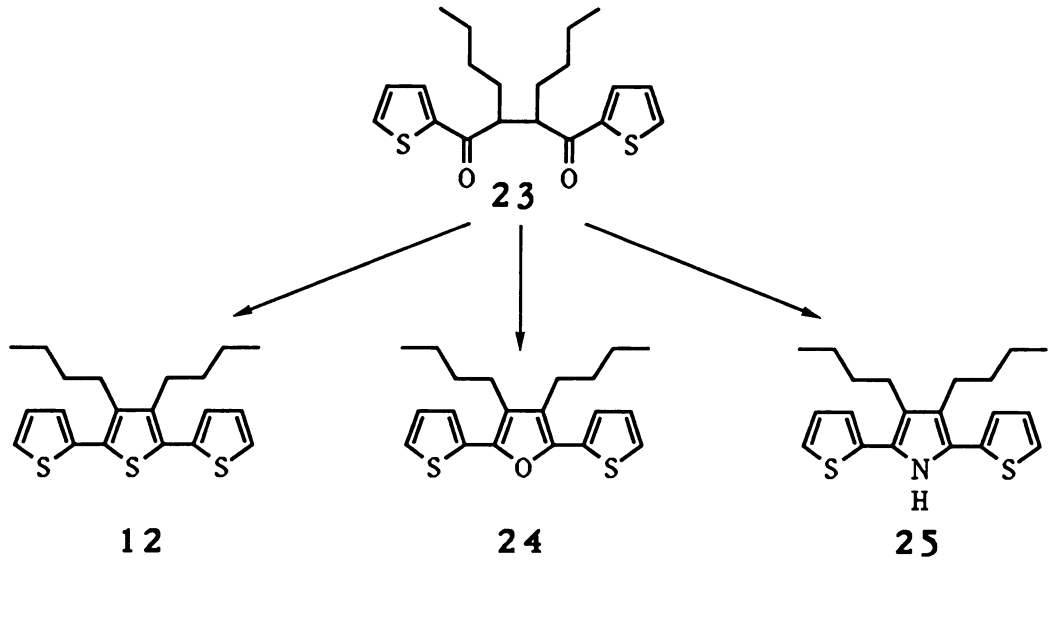
a) Me_2SiCl_2, Et_3N, NaI, CH_3CN

b) $(NH_4)_2Ce(NO_3)_6$, $NaHCO_3$

net yield = 49%

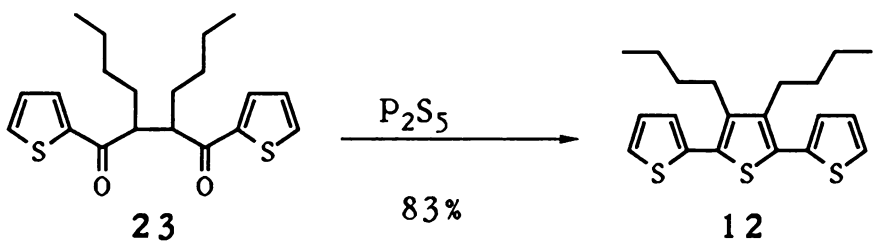
This route to **12** also opened the possibility of forming mixed oligomers, by converting the 1,4-diketone **23** to furan **24**, or pyrrole **25** (Scheme 8). These mixed heterocyclic systems would allow comparison of the properties within the trio of **12**, **24**, and **25**.

Scheme 8: Mixed Systems Available From Diketone **23**



Conversion of **23** to **12** was achieved in 83% by treatment with phosphorous pentasulfide in refluxing toluene (Scheme 9).

Scheme 9: Synthesis of Terthiophene **12** from Diketone **23**

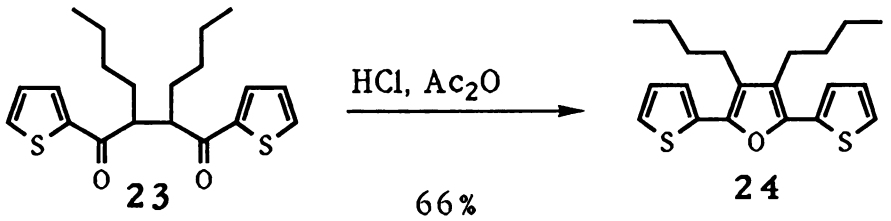


Comparison of the two routes to **12** show them to be quite similar in the amount of work required. Both take four steps and three purification operations. The higher yield (49% versus 22%) obtained using the transition metal-catalyzed coupling reaction make it the preferred route to **12**. The other route has the advantages of not requiring expensive coupling catalysts and of providing the

diketone **23**, which can be used to synthesize the corresponding furyl and pyrryl compounds.

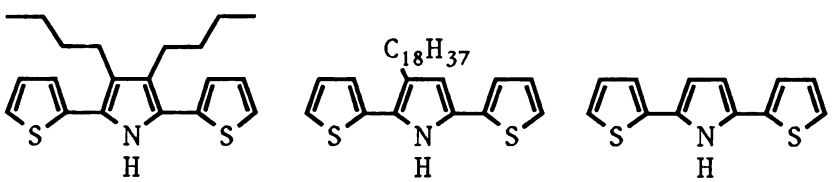
Initial attempts to dehydrate the diketone **23** by treating with hydrochloric acid in acetic anhydride gave the furan **24** in yields of less than 10%. Although the reaction was run for up to four days, TLC showed a large amount of unreacted starting material. However, a later attempt gave a yield of 66% after a reaction time of 24 h (Scheme 10). Comparison of these results led to the realization that the intial attempts, giving the poorer yields, were made using the easily purified higher melting isomer of **23**. The latter attempt was made using a mixture consisting mainly of the lower melting isomer. This difference in rate of reaction of 2,3-dialkyl-1,4-diketones has been previously noted[46] in studies of the Paal-Knorr reaction, with the *d,l* isomers reacting 4-40 times the rate of the *meso*. Since the dehydration of 1,4-diketones to form furans has some similarities to the Paal-Knorr reaction, it is not surprising that it shows a similar difference in rates. Compound **24** is a green oil (λ_{max} = 351 nm). This value for the UV absorption is almost unchanged from that of the unsubstituted oligomer (l_{max} = 352 nm), perhaps indicating less steric crowding by the butyl groups with the smaller furan ring.

Scheme 10: Synthesis of 3,4-Dibutyl-2,5-bis-(2'-thienyl)-furan



Conversion of diketone **23** to the pyrrole **25** was not achieved by standard methods. The method developed for converting this and other 1,4-diketones to pyrrole is described in part two of this section. Pyrrole **25** (Figure 27) is a pale green solid (m.p. = 45.5-46.5°C) with λ_{max} = 342 nm, which again, is little changed from the unsubstituted trimer. Ferraris[41e] has also synthesized a similar mono-alkyl pyrrole **26**, with λ_{max} = 315 nm.

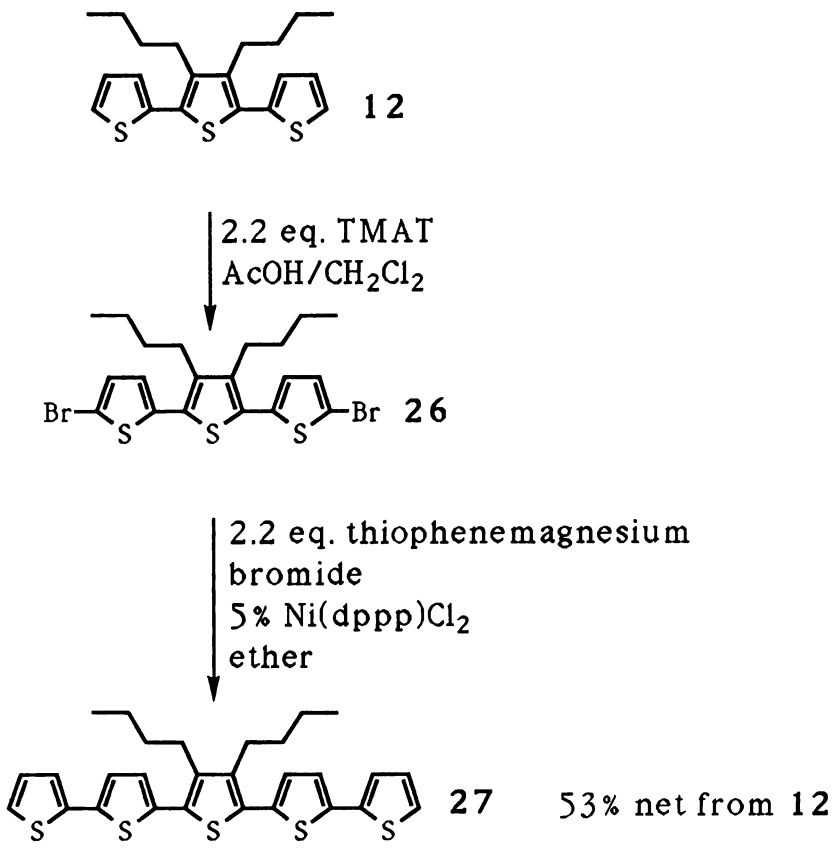
Figure 27: UV Spectra of Thiophene-Pyrrole-Thiophene Trimers



	25	**26**	**27**
UV (λ_{max})	342	315	349

In continuing with the plan for the synthesis of **8**, **12** was dibrominated using TMAT and the nickel-catalyzed coupling reaction was repeated (Scheme 11). This produced the bright golden-yellow quinquethiopohene **27** in 53% yield.

Scheme 11: Synthesis of Quinquethiophene **27**



Quinquethiophene **27** forms golden yellow needles with a melting point of 102°C. It has good solubility in common organic solvents. In fact, in one case where a modification of the synthetic procedure resulted in contamination of the product with quaterthiophene, **27** was easily purified by dissolving the mixture in hot hexanes, cooling, and filtering off the solid quaterthiophene from the solution of **27**. Slow recrystallization of **27** from hexanes gave crystals suitable for X-ray structure determination by M.G. Kanatzidis and J.H. Liao (Figure 28). Quinquethiophene **27** displays a UV absorbtion at 389 nm. The λ_{max} of the nonsubstituted quinquethiophene **29** and Wynberg's[47] butylsubstituted thiophene

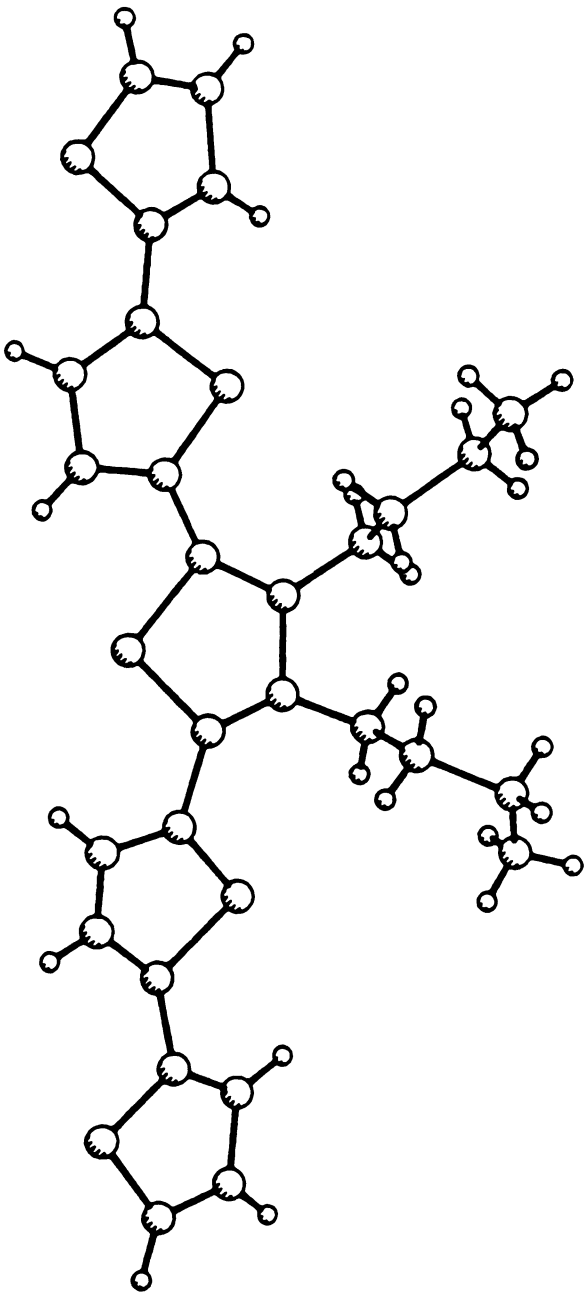
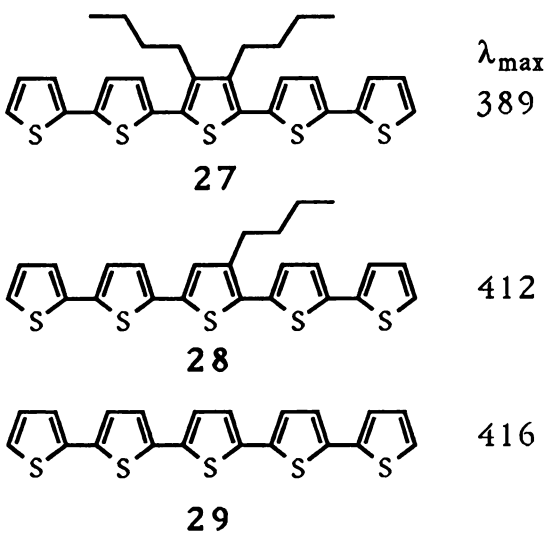


Figure 28: X-ray Structure of Quinquethiophene 27

28 are shown below in Figure 29. This series follows the trend of the di- and monosubstituted terthiophenes in showing a regular hypsochromic shift in the UV absorbance with increasing alkyl substitution.

Figure 29: UV Spectra of Quinquethiophenes

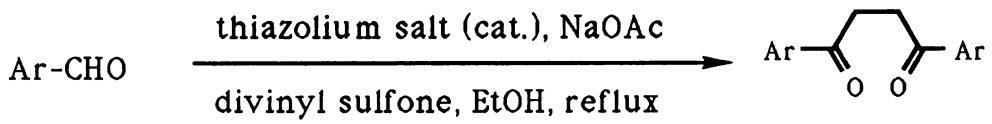


An alternative route to **27**, using $Pd(dppf)Cl_2$ as catalyst and the conditions shown in Scheme **5**, gave the quinquethiophene in 39% yield. Although this method results in a slightly lower yield, it gives more consistent results, and is the preferred method for synthesizing quinquethiophene **27**.

The initial strategy for cyclization was to diformylate **27** and join two molecules of the resulting dialdehyde using the Michael-Stetter[48] reaction, which would give **11**. This reaction (Scheme 12)

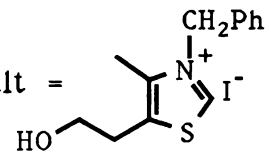
has been used with great success in this laboratory in the synthesis of numerous oligomers of pyrrole, thiophene, and furan[14].

Scheme 12: The Michael-Stetter Reaction



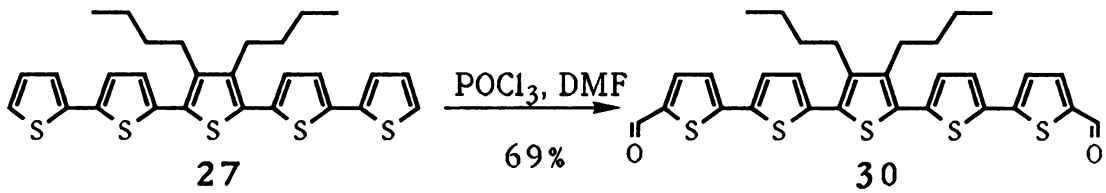
Ar	Yield (%)
phenyl	46
2-thienyl	48
2-furyl	75
2-pyrryl	70

thiazolium salt =



Treating quinquethiophene **27** with excess phosphorous oxychloride in dimethylformamide (DMF) resulted in formation of the dialdehyde **28** in 69% yield (Scheme 13). This brick red compound had much lower solubility than **27**.

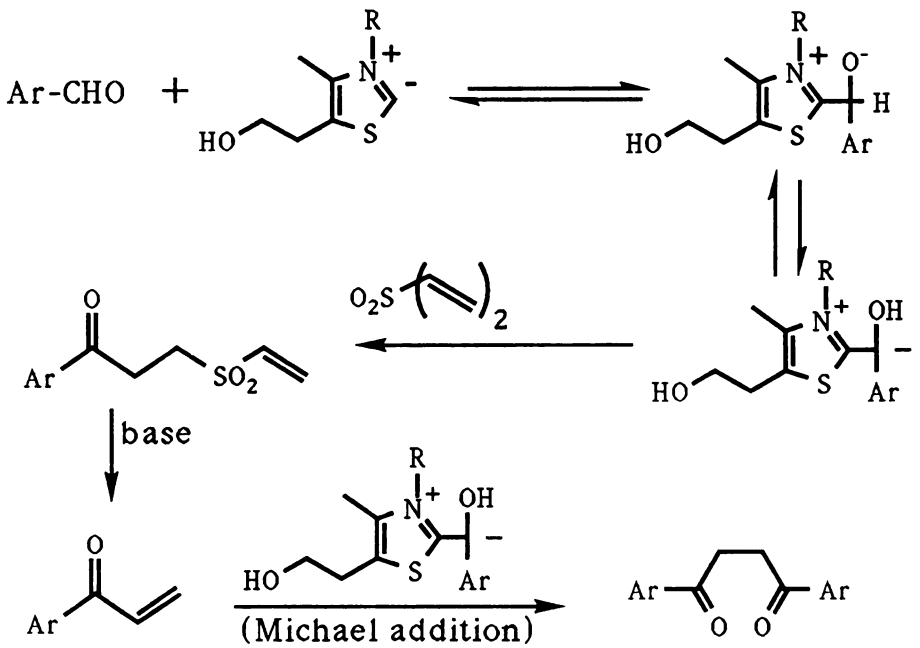
Scheme 13: Vilsmeier Formylation of Quinquethiophene 27



Subjecting **30** to Michael-Stetter conditions resulted in recovery of starting material. An examination of the proposed mechanism for the Michael-Stetter reaction (Scheme 14) shows it to have several equilibria which are concentration dependant. The dilute solution necessitated by the low solubility of **30** appeared to be the source of the lack of reactivity.

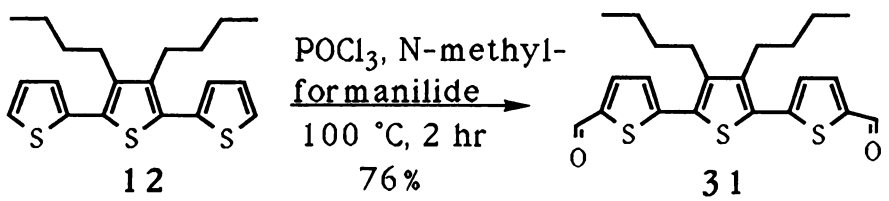
necessitated by the low solubility of **30** appeared to be the source of the lack of reactivity.

Scheme 14: Proposed Mechanism for the Michael-Stetter Reaction



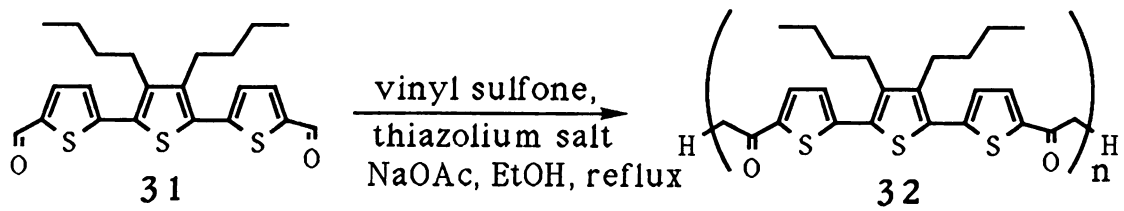
This possibility was investigated by synthesizing the dialdehyde **31** and subjecting it to Michael-Stetter conditions. Treating **12** with $POCl_3$ and N-methylformanilide produced **31** in 76% yield (Scheme 15). This golden yellow solid was much more soluble than **30**.

Scheme 15: Vilsmeier Formylation of Terthiophene **12**



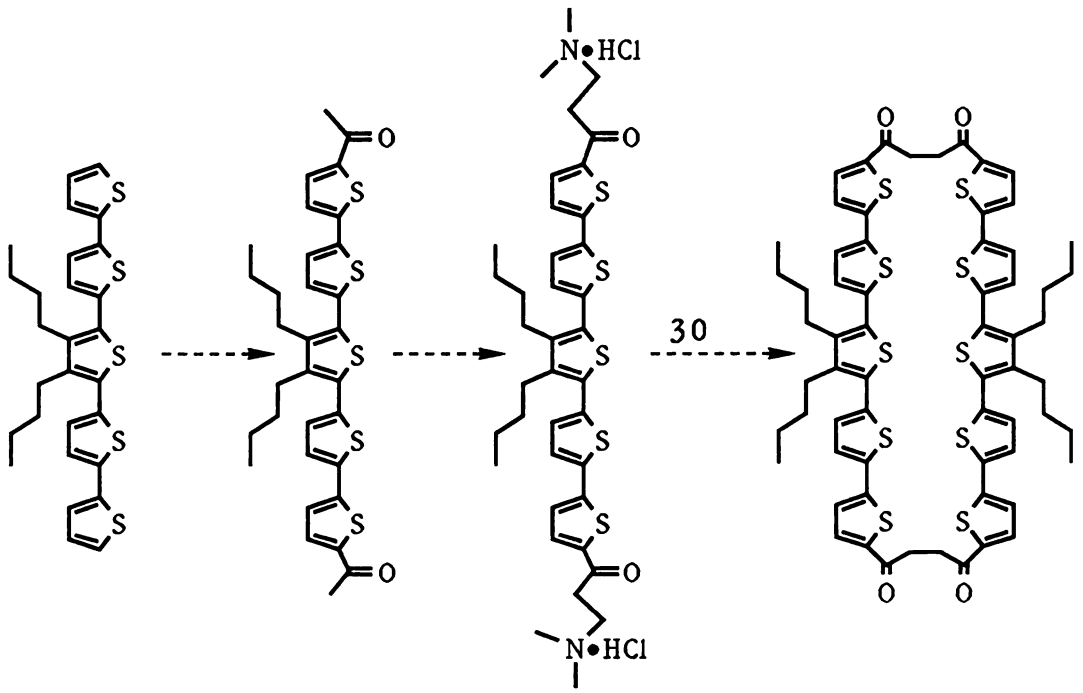
When compound **31** was subjected to Michael-Stetter conditions at 0.0012 **M** (1 gram **31** in 2 L anhydrous ethanol), no reaction occured after 15 days. When the same reaction was attempted at 0.012 **M**, reaction was swift and complete in a few hours (Scheme 16). This great difference in reactivity seems to indicate that the Michael-Stetter reaction is strongly concentration dependent. The reaction produced 890 mg of an orange solid and a small soluble fraction (100 mg), which contained a plethora of products. The solid fraction was insoluble in all solvents. Separation of the soluble compounds was attempted by both flash chromatography and preparative thin layer chromatography, neither of which was successful. Treating the solid, presumably the polymer shown in Scheme **16**, with Lawesson's reagent resulted in the formation of a glossy black material, which was equally intractable.

Scheme 16: Application of the Michael-Stetter Reaction to Compound **31**



An alternative method[49] for performing the Michael-Stetter reaction is to use the addition of aldehydes to Mannich bases. Applying this methodology to the synthesis of **11** could be done as shown in Scheme 17.

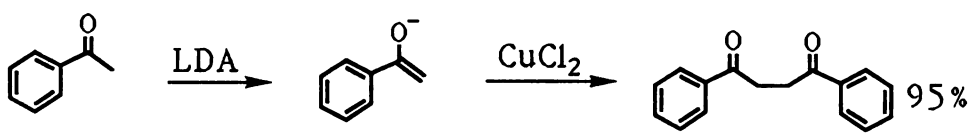
Scheme 17: Plan for Synthesis of Bis-1,4-diketone **8** Through the Mannich Base



27 33 34 11

Synthesizing the bisacetylquinquethiophene **33** would also open another route to **11** (Scheme 18). This is the oxidative coupling of methyl ketones *via* their enolates, which is a procedure[50] known to proceed in good yields.

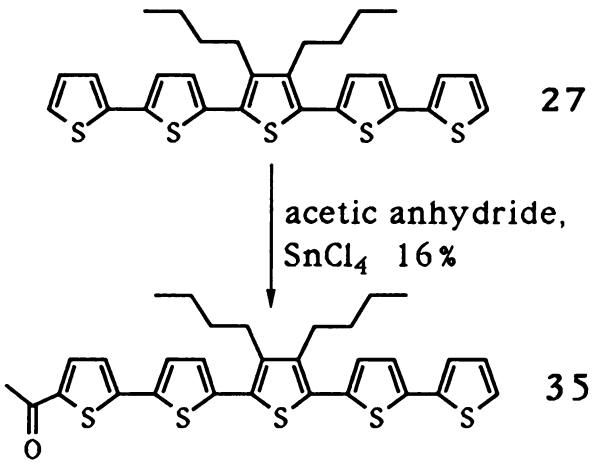
Scheme 18: Coupling of Methyl Ketones



Attempts to synthesize the bisacetylquinquethiophene **33** were undertaken using several standard methods of Friedel-Crafts

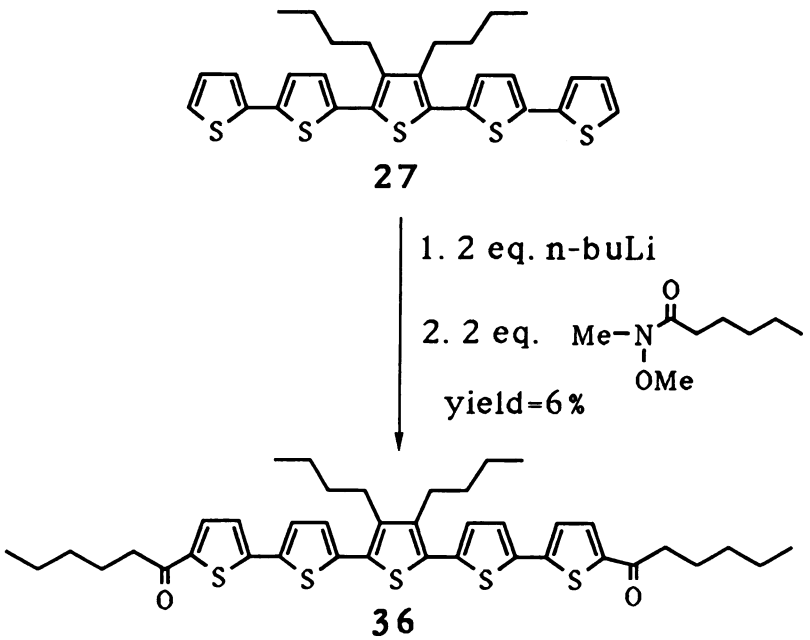
acylation. Treating **27** with acetic anhydride and phosphoric acid as catalyst resulted in no reaction. Treating **27** with acetyl chloride using tin chloride as catalyst at room temperature resulted in no reaction, but warming caused reaction to occur, quickly followed by the formation of black material. Quenching the reaction at the moment it started to throw down black material allowed the isolation of 2-acetylquinquethiophene **35** in 16% (Scheme 19).

Scheme 19: Acetylation of Quinquethiophene **27**



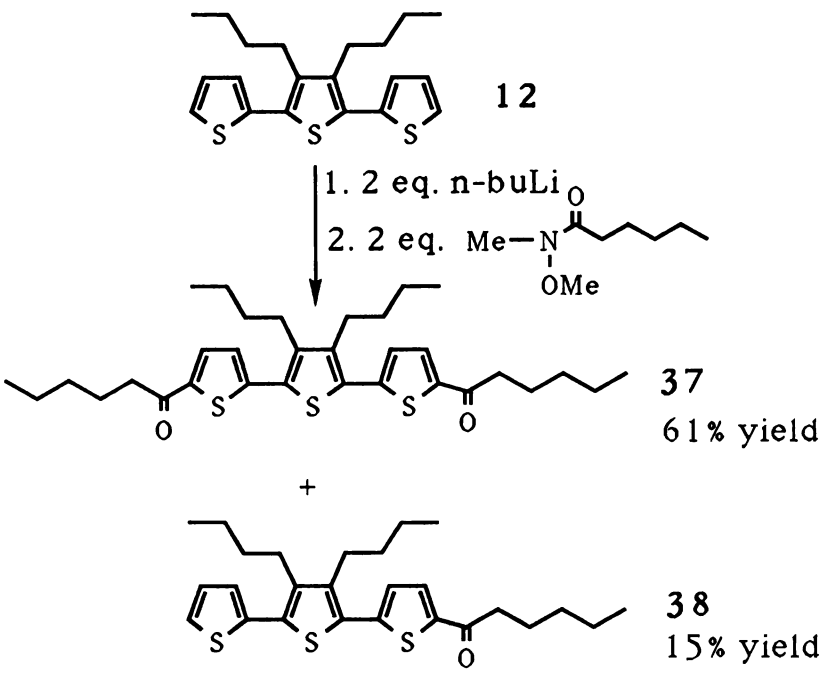
The ketone coupling reaction developed by Rathke and Weipert was also considered for its potential to generate an intermediate similar to **11**. In addition to the methods used in the attempted synthesis of **25**, which were unsuccessful, Weinreb's ketone synthesis[51] through use of N,N-methoxymethylamides, which does not subject the substrate to acid conditions, was attempted (scheme 20).

Scheme 20: Acylation of Quinquethiophene **27**



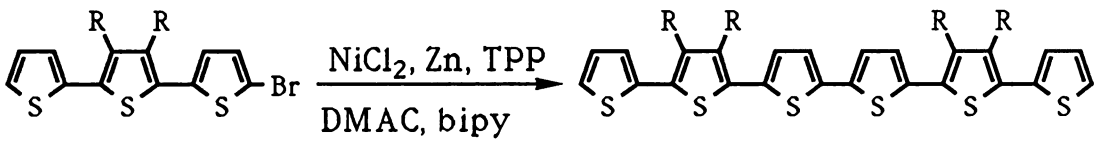
This method gave the dihexanoylquinquethiophene **36** in very poor yield. Upon addition of N-methoxy-N-methylhexanamide, the solution quickly turned dark red. Flash chromatography resulted in significant decomposition of material on the column, with the result that diketone **36** was isolated in 6% as an impure sample. The inability of Weinreb's method to generate more than milligram quantities of the desired compound was surprising. I therefore subjected **12** to these conditions (Scheme 21), resulting in the formation of **37** in good yield.

Scheme 21: Acylation of Terthiophene **12**



The lack of success obtained by the routes examined above led to attempts to create an epicycle by sequential oxidative coupling of **12**. Two methods were examined. The first was developed by Colon and Kelsey,[52] which reductively couples aryl chlorides using Ni^0 catalyst and Zn as the reducing agent. This method has been used by Luo[14c] in this laboratory to synthesize two sexithiophenes in good yield (Scheme 22).

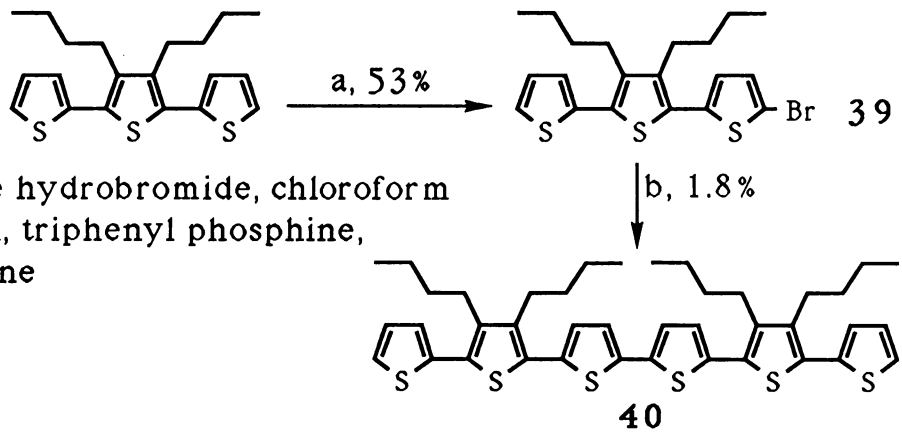
Scheme 22: Luo's Synthesis of Sexithiophenes by the Method of Colon



R=H, 54%;
R=Methyl, 41%

2-Bromoterthiophene **38** was synthesized by treating **12** with pyridinium hydrobromide in 53% yield. Subjecting it to the conditions of Colon (Scheme 23) resulted in the formation on sexithiophene **39** in 1.8% yield.

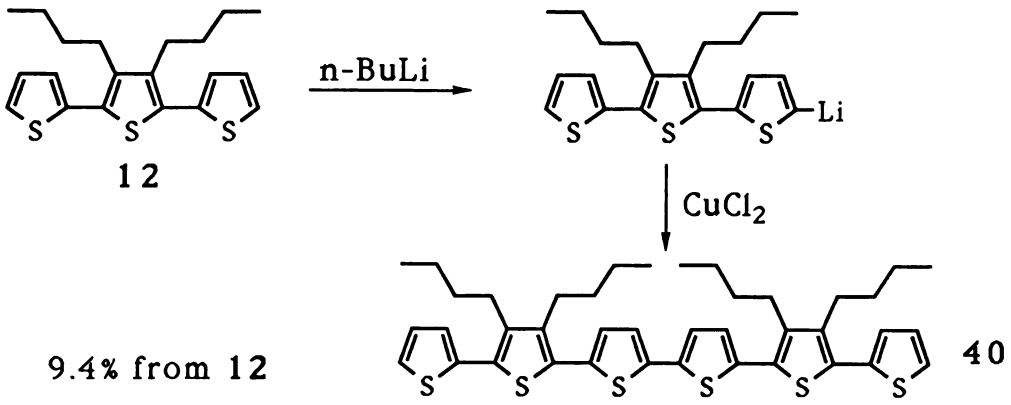
Scheme 23: Coupling of Terthiophene **12** by the Method of Colon



a) pyridine hydrobromide, chloroform
b) $NiCl_2$, Zn, triphenyl phosphine, bipyridine

Although the reaction was very clean, the poor yield and inability to consistently generate the catalyst system prompted us to switch to Kagon's method[53] of making symmetrical thiophene oligomers. Accordingly, compound **12** was treated sequentially with n-buLi and $CuCl_2$ (Scheme 24).

Scheme 24: Synthesis of Sexithiophene **40**



This method generated the sexithiophene **40** in 9.4% yield. The sexithiophene is a bright orange solid, m.p.= 118-118.5°C. Recrystallization from hexanes gave orange crystals suitable for X-ray structure determination by M.G. Kanatzidis and J.H. Liao , Figure 30. It shows the almost planar arrangement of the central four thiophenes, in an antiparallel orientation similar that shown in terthiophene **12**. The outer thiophenes are variably tilted, lying parallel in 11% of the molecules and antiparallel in 89% of the molecules. Sexithiophene **40** is the longest oligomer yet characterized by single crystal X-ray. The three X-ray structures made available through the compounds synthesized in this work doubles the number of oligothiophene structures known.

Sexithiophene **40** shows a long wavelength maximum in its UV spectrum at 406 nm. The UV spectra of **40** and other sexithiophenes are given in Table 5. The first four examples demonstrate a correspondence of UV absorbence with alkyl substitution that is similar to that found in terthiophene **12** and

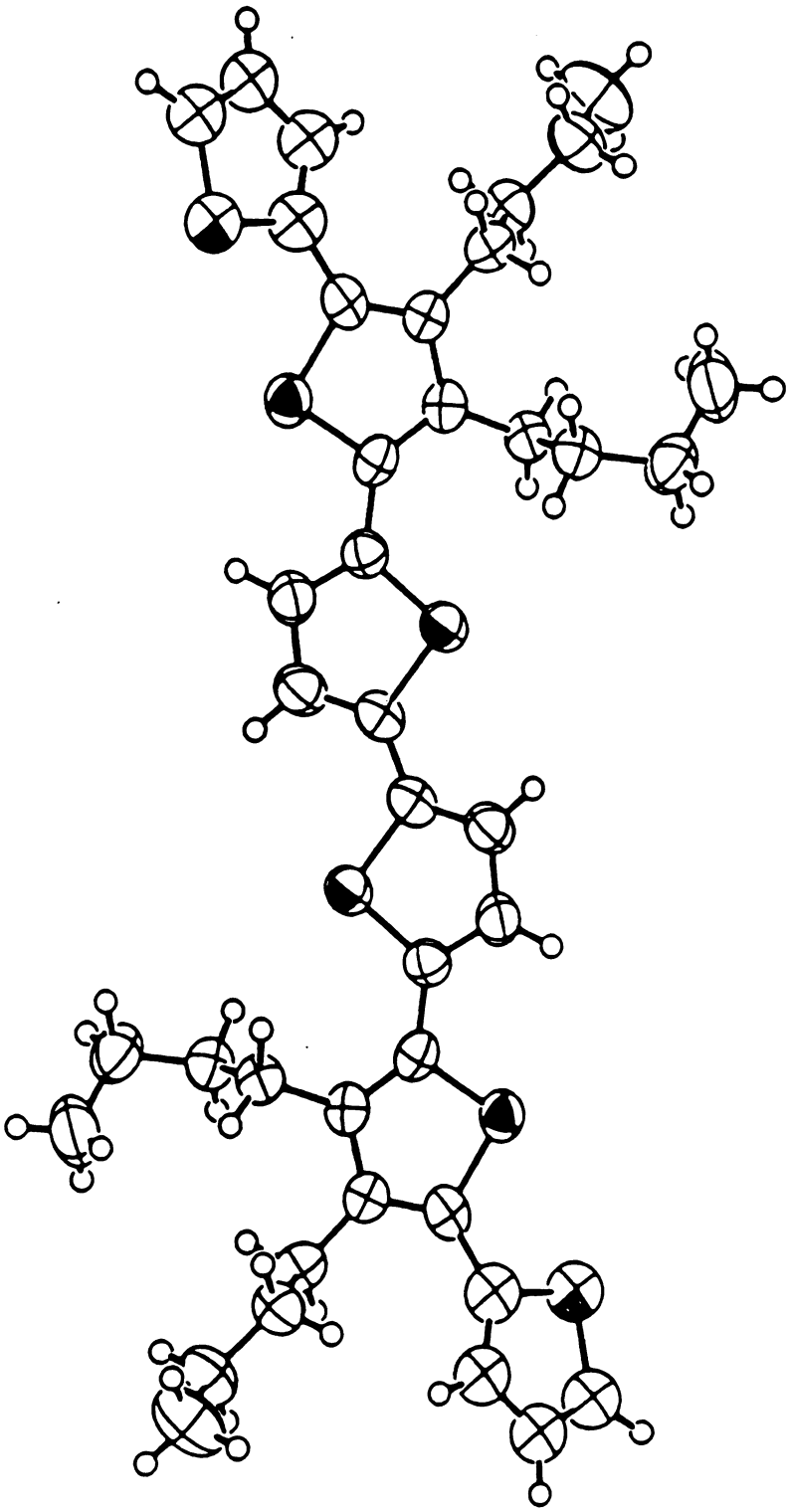
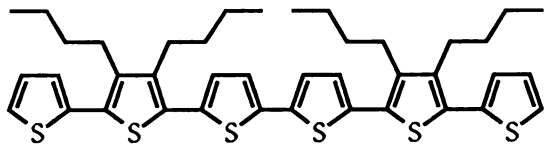
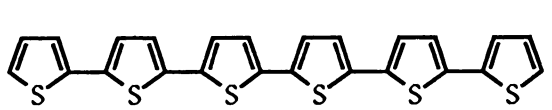
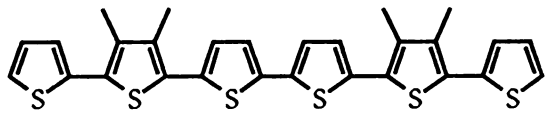
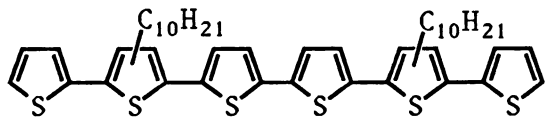
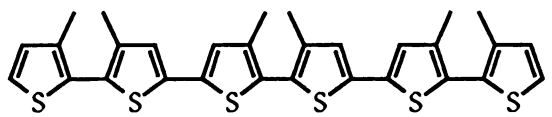
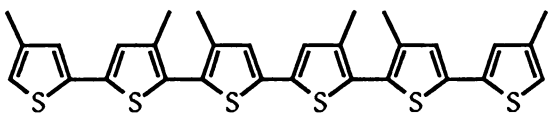


Figure 30: X-ray Structure of Sexithiophene 40

quinquethiophene **27**. The UV spectra of the last two examples indicate that conjugation is interrupted by the opposing pairs of methyl groups, and shows the value of using unsubstituted thiophenes as spacers between substituted thiophenes.

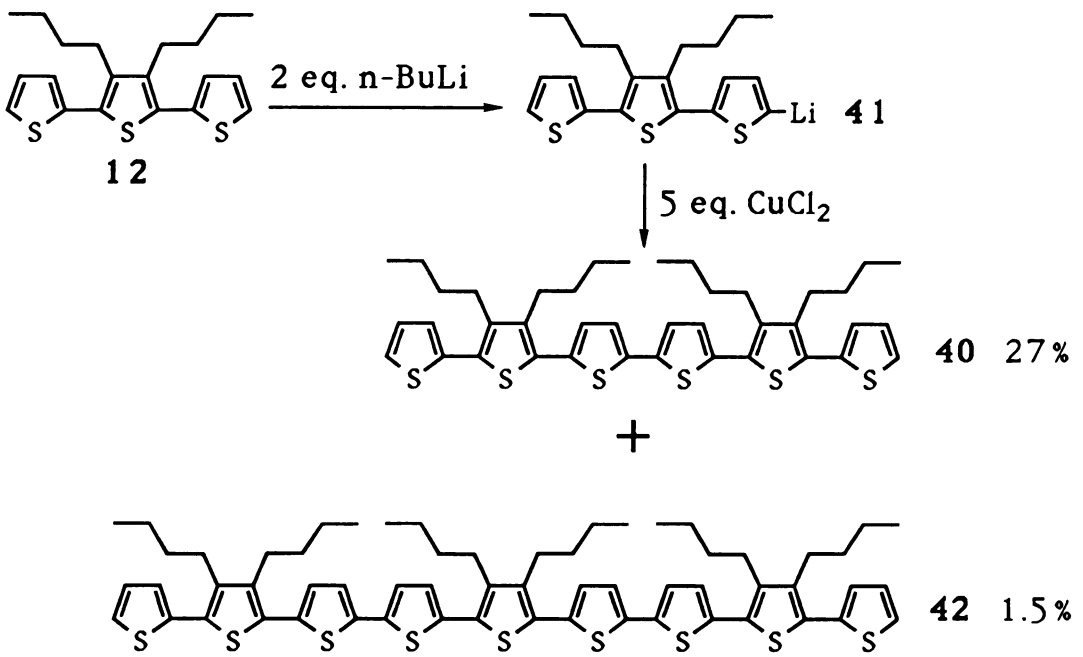
Table 5: UV spectra of Various Sexithiophenes

	λ_{max}	reference
	406	
	434	14(c)
	409	14(c)
	424	54
	368	55
	368	55

Synthesizing sexithiophene **40** by forming the dilithioterthiophene **41** and coupling with cupric chloride (Scheme 25) not only improved the yield to 27%, it also generated 27 mg (1.5%) of a light and acid sensitive brick red powder. Integrating the β and α peaks in its proton NMR spectrum gave a ratio of 6:1. Examination of its UV spectrum showed peak absorbances at 426 and 690 nm. This

information indicated that the compound was the nonathiophene **42**. FAB-MS provided confirming evidence, showing a peak at 1076 daltons. Features around 700 nm in the UV spectrum of polythiophene made by polymerization of terthiophene have been observed.[39m]

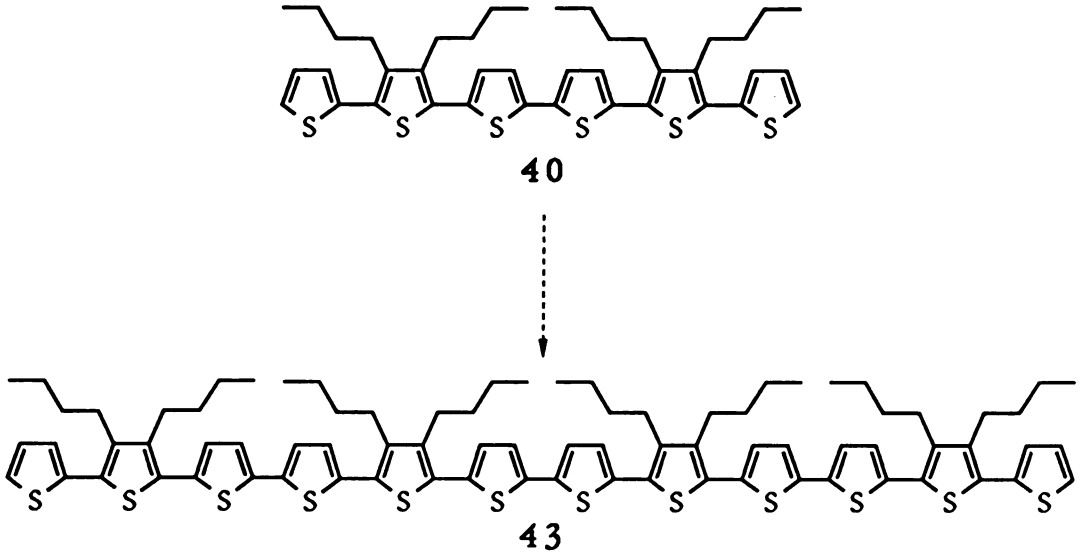
Scheme 25: Further Oligomerization of **12** to Give **42**



The successful synthesis of **40** in useful yields using these couplings led to the attempt to use this method to synthesize the duodecithiophene **43** (Scheme 26). Using 1 equivalent n-buLi and 4 equivalents $CuCl_2$ gave 87% recovered **40** and 41 mg of a dark red material. TLC analysis indicated that this material contained several components. These fractions could not be separated by flash chromatography or preparative thin layer chromatography. The UV spectrum of this material showed a maximum at 435 nm,

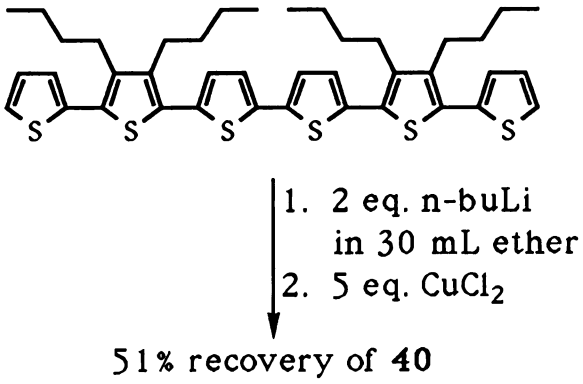
which does not correspond well with Horowitz'[54] duodecithiophene, which has λ_{max} = 465 nm.

Scheme 26: Attempted Synthesis of Duodecithiophene **43**



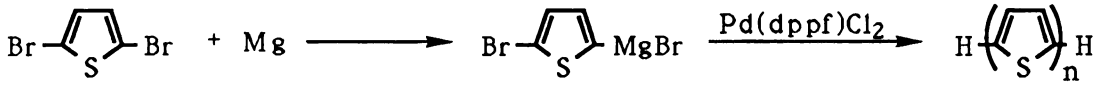
Since $CuCl_2$ is sparingly soluble in ether, such a small amount of $CuCl_2$ may have dissolved before reacting. (Additional evidence for this possibility is the lack of reaction when attempting to make **40** using THF as solvent. $CuCl_2$ is relatively soluble in THF.) To investigate this possibility, the reaction was attempted using fifty equivalents $CuCl_2$. This method gave identical results. Horowitz' report[54] of such a coupling being done in very concentrated solution led to an attempt to replicate their results with sexithiophene **40**. This method gave none of the desired product, with extensive decomposition of starting material (Scheme 27).

Scheme 27: Attempted Synthesis of **43** by the Method of Horowitz



The coupling of 2,5-dibromothiophenes by forming the Grignard and coupling with a transition metal catalyst[56] (Scheme 28) showed potential as a way to produce higher oligomers, and perhaps provide the epicycle directly.

Scheme 28: Transition Metal-catalyzed Polymerization of Thiophene



This methodology was attempted using 2,5"-dibromoterthiophene **26** (Scheme 29). When **26** was added to 1.1 equivalents Mg and stirred overnight, TLC showed decomposition products, but no trace of terthiophene **12** or bromoterthiophene **39**. The presence of these products on the TLC plate would have provided evidence that the Grignard was being formed. Bringing the mixture to reflux only accelerated decomposition.

2. Conclusions

A variety of oligomers containing 3,4-disubstituted thiophenes have been synthesized, resulting in the thiophene, pyrrole, furan series **12**, **24**, **25**. These syntheses complement the existing series of unsubstituted and monosubstituted oligomers. Also, they have paved the way for the doubling the number of known X-ray crystal structures.

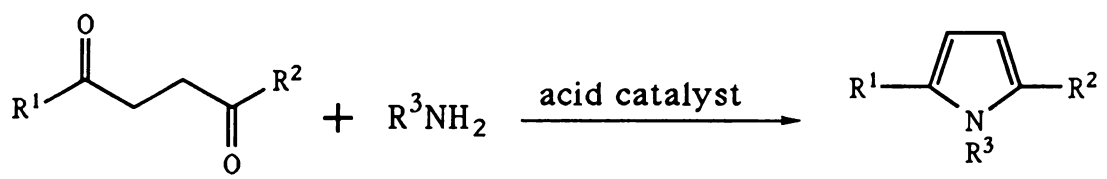
Attempts aimed toward the synthesis of an epicycle based on **5** probed the outer limits of solubility, stability, and separability. Use of the Michael-Stetter reaction was prohibited by the low solubility of **30**. It was found that conditions strong enough to initiate a reaction often were strong enough to initiate polymerization, as shown in attempts to functionalize **27**. Many separations were hampered by the poor resolution of these compounds by flash chromatography.

Any future work on the synthesis of epicycles should attempt to make use of shorter oligomers which are functionalized and reacted in a manner which would maximize differences in the chromatographic properties of the reactants and expected products.

Conversion of 1,4-Diketones to Pyrroles

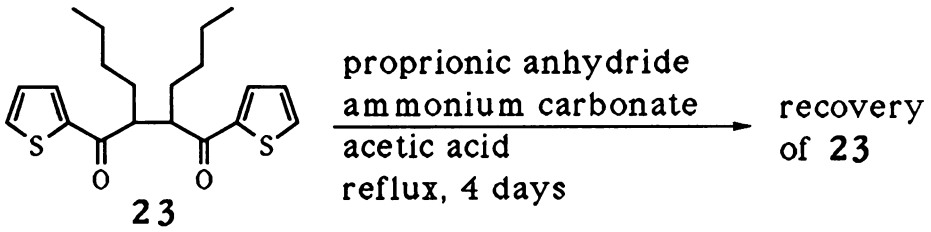
Treating 1,4-diketones with an amine source in the presence of an acid catalyst, known as the Paal-Knorr reaction, is the most widely reported method for producing pyrroles[57] (Scheme 30). The reaction is commonly run using acetic acid as catalyst and ammonium carbonate or ammonium acetate as the amine source. Primary amines may be used to form N-substituted pyrroles.

Scheme 29: The Paal-Knorr Reaction



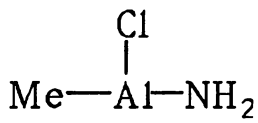
When these conditions were applied to diketone **23** (Scheme 31), no reaction was observed using acetic acid or tin(IV) chloride as catalyst. Even refluxing four days in propionic acid with propionic anhydride to act as water scavenger resulted in complete recovery of starting material. Since we desired to have the pyrrole **25** to complement the thiophene **12** and furan **24**, and since other attempts[14(b)] in this group to convert 1,4-diketones to pyrroles had proceeded only with difficulty, a more effective route to pyrroles was desired, preferably one more mild than refluxing in acid for several days.

Scheme 30: Attempted Conversion of Diketone **23** to the Pyrrole



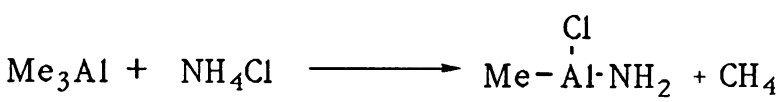
Methylchloroaluminum amide, **44**, has been used by Weinreb[58] and coworkers to convert esters to amides with good result. The reagent appeared to contain all elements desired in the Paal-Knorr synthesis: it provided an amine source, it could function as a Lewis acid catalyst, and it could also function as a dehydrating agent.

Figure 31: Methylchloroaluminum Amide



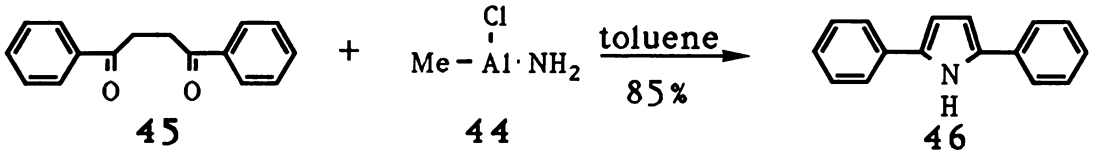
This reagent is made by treating an amine hydrochloride with trimethylaluminum (Scheme 32). Although trimethylaluminum is extremely pyrophoric, it is available as less dangerous solutions in hexanes and toluene.

Scheme 31: Formation of the Methylchloroaluminum Amide Reagent



Treating 1,4-diphenyl-1,4-butanedione **45** with four equivalents of methylchloroaluminum amide in toluene at room temperature (Scheme 33) resulted in conversion to 2,5-diphenylpyrrole **46** in 85% yield .

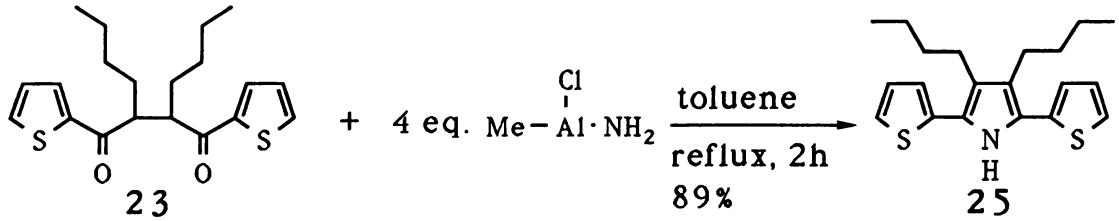
Scheme 32: Synthesis of 2,5-Diphenylpyrrole



45 44 46

Heartened by this result, diketone **23** was submitted to the same conditions. After 17 hours at room temperature, TLC indicated partial conversion to the pyrrole. Heating to reflux for 2 hours pushed the reaction to completion. The pyrrole **25** was isolated in 73% yield after flash chromatography. Bringing the reaction to reflux immediately after addition of the amide **44** resulted in an isolated yield of 89% (Scheme 34).

Scheme 33: Synthesis of 2,5-Bis-(2'-thienyl)-3,4-dibutylpyrrole

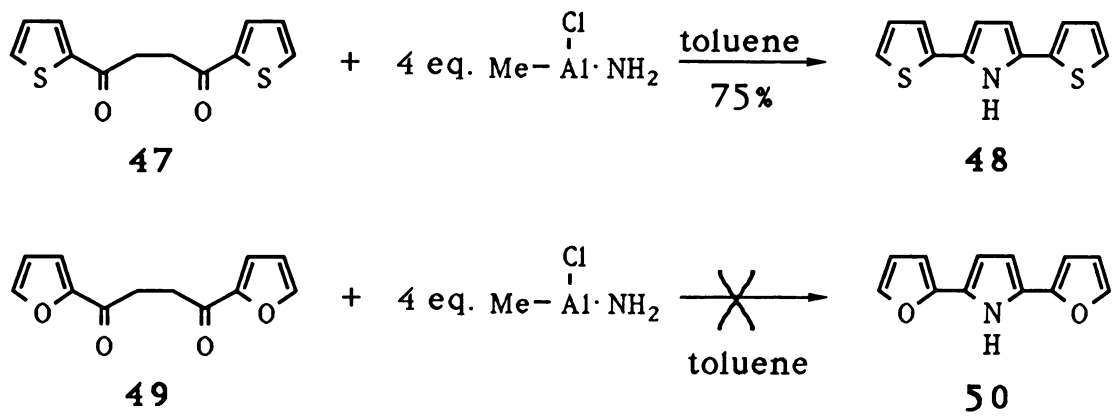


23 25

Similar results were obtained for 1,4-bis-(2'-thienyl)-1,4-butanedione **47** when treated with 4 equivalents of amide **44** and stirred two hours at room temperature. The 2,5-bis-(2'-thienyl)-

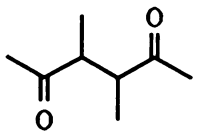
pyrrole **48** isolated in 75% (Scheme 35). Application of this method to 1,4-bis-(2'-furyl)-1,4-butanedione **49** resulted in decomposition of starting material upon addition of the amide.

Scheme 34: Synthesis of the Trimer **48** and the Attempted Synthesis of **50**

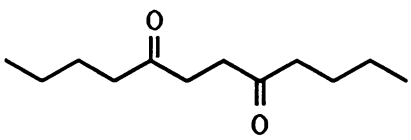


Attempts were also made to convert alkyl-substituted 1,4-diketones by the same method. 3,4-Dimethyl-2,5-hexanedione **51** and 5,8-dodecanedione **52** were submitted to the conditions above (Figure 32). One product was formed in each case, as indicated by TLC, but the products could not be seperated from the toulene solvent. The 1,4-(2-pyrryl)-1,4-butanedione **53** did not react under these conditions. Previous work by Merrill[14b] directed toward converting this compound to the terpyrrole, and observation of the reaction mixture in this particular case, indicate that low solubility was responsible for the lack of reactivity.

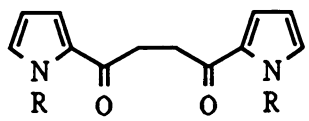
Figure 32: Substrates Not Successfully Converted to Pyrroles



51



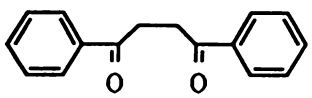
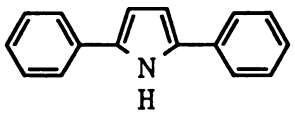
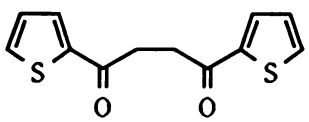
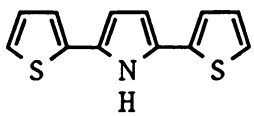
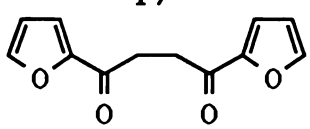
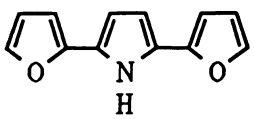
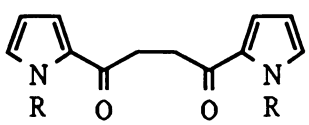
52



53

Since the use of toluene made solvent removal unwieldy, the reactions were attempted using trimethyl aluminum in hexanes solution and dichloromethane as solvent. These reactions were run at room temperature overnight, with the results summarized in Figure 33.

Figure 33: Room Temperature Synthesis of Pyrroles with Dichloromethane

1,4-diketone	pyrrole	yield
 45	 46	81%
 47	 48	34%
 49	 50	52%
 53	———	recovered starting material

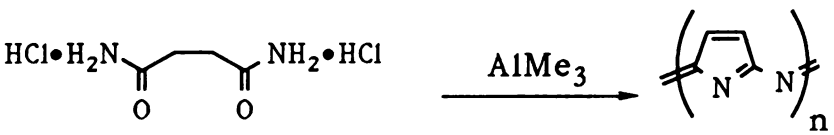
All 1,4-diketones treated with 4 equivalents methylchloroaluminum amide in dichloromethane

Again, the 1,4-bis(2'-pyrryl)-1,4-butanedione **52** failed to react, probably due to its insolubility in dichloromethane. Applying the reaction to alkyl-substituted 1,4-diketones failed to produce alkyl-substituted pyrroles, for when 3,4-dimethyl-2,5-hexanedione **51** and 5,8-dodecanedione **52** were treated with 4 equivalents methylchloroaluminum amide in dichloromethane, no reaction was observed. It is interesting to note that **49**, which decomposed when toluene was the solvent, gave a yield which is more than twice that obtained (52% versus 22%) when more traditional Paal-Knorr conditions are used.[14a]

Conclusions

Methylchloroaluminum amide is an efficient reagent for converting aryl 1,4-diketones to pyrroles. Its advantages over the traditional Paal-Knorr reaction are its rapid rate of conversion, good yield, mild conditions, and ability to generate pyrroles such as **25**, which cannot otherwise be synthesized. It is possible that further investigation will allow its application to the conversion of alkyl-substituted 1,4-diketones to pyrroles. While this reagent should be examined for its applicability to all transformations Paal-Knorr conditions are used for, its use in the reaction below may provide a new conducting polymer in one step from easily obtainable reagents.

Scheme 36: One Step Synthesis of Poly(2-aminopyrrole)



Experimental

General: Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) were obtained using either a Bruker WM-250 (250 MHz) or Varian Gemini (300 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) using either the residual solvent proton resonance (chloroform, δ 7.24), or tetramethyl silane as internal standard (δ 0.00). ^{1}H-NMR data are reported as the chemical shift, chemical shift multiplicity (s for singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet) and number of hydrogens. ^{13}C nuclear magnetic resonance (^{13}C-NMR) spectra were obtained using either a Bruker WM-250 (62.9 MHz) or Varian Gemini (75.4 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) using the residual solvent resonance as internal reference (chloroform, δ 77.0). Ultraviolet (UV) spectra were obtained using a Beckman DU-64 spectrometer. Electron impact mass spectra (EI-MS) were obtained using either a Finnegan 400 mass spectrometer or a VG Instruments Trio-1 mass spectrometer. Fast atom bombardment mass spectra (FAB-MS) were obtained by the MSU-NIH Mass Spectrometry Facility, Biochemistry Building, Michigan State University. Flash chromatography was performed according to the method of Still,[59] Kahn, and Mitra. Trimethyl aluminum solutions,

n-butyllithium solutions, anhydrous tetrahydrofuran, diethyl ether, dimethyl acetimide, and dimethyl formamide were purchased from the Aldrich Chemical Company, Milwaukee, WI and used as received. Dichloromethane and triethyl amine were distilled from calcium hydride. Toluene was distilled from sodium-benzophenone ketyl. Tetramethyl ammonium tribromide was prepared according to the method of Chattaway and Hoyle[60] and used without recrystallization. Ethanol was dried by distillation from magnesium. Cupric chloride was dried in an oven at 150°C overnight, ground to a fine powder, and replaced in the oven until used. Sodium iodide was dried in an Abder-Halder apparatus under vacuum with refluxing toluene. Chloroform was washed with water, predried with magnesium sulfate, and distilled from phosphorous pentoxide. All reactions were performed under an argon or nitrogen atmosphere unless otherwise mentioned.

3,4-Dibromothiophene 14: A dry 1000 ml flask containing 47 g (0.117 mole) of tetrabromothiophene in 300 ml dry ether was placed in a dry ice/acetone bath. One hundred mL 0.25 M n-butyl lithium (in hexanes) in 150 mL dry ether was added dropwise over a period of one hour. Twenty minutes after the addition was complete, the cold bath was removed and 50 mL ice was added to quench. The solution was allowed to come to room temperature and placed in a 1000 mL separatory funnel. The organic layer was washed with water, dried with $MgSO_4$, and concentrated under reduced pressure. The product was distilled (74 °C at 2.75 mm Hg)

through a twelve inch vacuum-jacketed Vigreux column, yielding 23.83 gm (84%) of 3,4-dibromothiophene as a clear liquid. ^{1}H-NMR ($CDCl_3$): δ 7.3 (s); ^{13}C-NMR (chloroform-d): δ 123.5, 113.6; EI-MS *m/z* (relative intensity) 242 (m^+, 52.9), 241 (43.7), 162 (52.4), 160 (44.2), 82 (51.0), 81 (87.9), 40 (base).

3,4-Dibutylthiophene 15: A dropping funnel containing 22 mL (0.205 mole) of n-butyl bromide and 80 mL dry ether was attached to a 500 mL flask containing 6 gm (0.25 g.atom) Mg. Dry ether was added to cover the Mg. The flask was placed in an ice-water bath. The solution was slowly dripped in with vigorous stirring. After the addition was complete, the ice bath was removed and the mixture refluxed for one hour. A 1000 mL flask was charged with 23.4 grams 3,4-dibromothiophene, 500 mg Ni(dppp)Cl_2 and 300 ml dry ether. This flask was placed in an ice-water bath. The Grignard solution was then transferred to the well stirred mixture by double ended needle. The ice bath was removed after addition was complete and the solution was refluxed for 16 h. The reaction was quenched with 50 mL ice, washed with water, dried with $MgSO_4$, and concentrated under reduced pressure. The product was distilled (99.5-101°C) through a twelve inch vacuum-jacketed Vigreux column, yielding 14.6 g (77%) of 3,4-dibutylthiophene. ^{1}H-NMR (chloroform-d) 7.0 (s, 2H), 2.6 (t, 4H), 1.7 (quintet, 4H), 1.5 (sextet, 4H), 1.0 (t,6H); ^{13}C-NMR (chloroform-d) δ 141.7, 119.5, 31.2, 27.8, 22.0, 13.3; EI-MS m/z (relative intensity) 196 (m^+, 7.62), 179, 167 (2.65), 154 (31.54), 139 (34.01), 125 (21.99), 111 (base); UV(acetonitrile) 241 nm (ε 11,500).

2,5-Dibromo-3,4-dibutylthiophene 16: To 18.7 g (0.0954 mol) 3,4-dibutylthiophene was added to 66 g (.21 mmol) tetramethyl ammonium tribromide (TMAT) in 100 ml of 1:1 acetic acid/dichloromethane. The reaction was monitored by TLC and complete in 25 minutes. The mixture was diluted to 200 mL with dichloromethane and filtered to remove the tetramethyl ammonium bromide. The filtrate was washed with water (3x50 ml) and then with saturated $NaHCO_3$ solution until all acetic acid odor was gone. It was dried with $MgSO_4$, the solvent removed under reduced pressure. Purification of the crude product by flash chromatography gave 31.1 g (92%) as a clear liquid. ^{1}H-NMR ($CDCL_3$) δ 2.5 (t, 4H), 1.1-1.3 (m, 8H) 0.95 (t, 6H); ^{13}C-NMR ($CDCL_3$) δ 141.4, 107.8, 31.7, 28.7, 22.6, 13.9; EI-MS *m/z* (relative intensity) 356 (m+2, 9.6), 354 (m^+, 18.9), 352 (9.1), 269 (49.6), 233 (31.8), 191 (92.8), 189 (base).

3',4'-Dibutyl-2,2':5',2"-terthiophene 12: Three grams 3,4-dibutylthiophene (0.0325 mol) was brominated with 20.1 g (0.064 mol) TMAT as described above. A dry 100 mL flask containing 2.0 g Mg was placed in an ice bath and dry ether was added to cover. To it was added dropwise 6.1 mL 2-bromothiophene (0.063 mol) in 20 mL ether. After addition was complete, 100 mL dry ether was added and the solution refluxed for one hour. A dry 500 ml flask containing the 2,5-dibromo-3,4-dibutylthiophene, 100 mg $Pd(dppf)Cl_2$ (0.4 mol %) and 300 mL dry ether was placed in a Dry Ice/acetone bath. The Grignard solution was transferred to this

flask by double ended needle. The Grignard solution must be added with care to ensure that vigorous stirring continues. The cold bath was removed and the mixture was stirred for 72 h at room temperature. It was then quenched and washed with water. The organic layer was dried with $MgSO_4$ and the solvent removed under reduced pressure. The product was purified by flash chromatography using hexanes as eluent. Yield was 4.58 g (83%) of the pale green terthienyl **12** (m.p.=36.0-36.5°C). ^{1}H-NMR ($CDCL_3$) δ 7.35 (d, 2H), 7.19 (d, 2H), 7.10 (dd, 2H), 2.77 (t, 4H), 1.61 (quintet, 4H), 1.50 (sextet, 4H), 1.00 (t,6H); ^{13}C-NMR ($CDCL_3$) δ 139.7, 135.9, 127.0, 124.5, 124.9, 123.4, 32.3, 27.1, 22.3, 13.1; EI-MS *m/z* (relative intensity) 360 (m^+, 3.63), 317 (6.41), 303 (2.56), 275 (32.40), 166 (18.79), 127 (22.74); UV (acetonitrile) 331 nm (ε 15,000). *anal.* Calcd. for $C_{20}H_{24}S_3$: C, 66.62; H, 6.71
Found: C, 67.04; H, 6.83

Alternate procedure for **12**: To 200 mg 1,4-diketone **23**, in 100 mL dry toluene, was added 123 mg phosphorous pentasulfide. The reaction was heated to 80°C for one hour. The solution was cooled, washed with water, and dried with $MgSO_4$. The solvent was removed under reduced pressure and the crude product purified by flash chromatography (hexanes eluent). The product **12** was obtained (165 mg) in 83% yield, identical to above.

2,5"-Dibromo-3',4'-dibutyl-2,2':5',2"-terthiophene 26: Terthienyl **12** (2.00 g) was brominated with 2.1 equivalents (3.66 g) TMAT in 20 ml 1:1 acetic acid/dichloromethane. After 25

minutes, 50 mL dichloromethane was added. The solution was then filtered, washed with water (3x200 mL), and then saturated sodium bicarbonate solution. Flash chromatography (hexanes eluent) gave the product, 2.724 g, (m.p.=40.0-41.0°C) as a pale green solid (95%). ^{1}H-NMR ($CDCL_3$) δ 6.99 (d, 2H), 6.85 (d, 2H), 2.63 (t, 4H), 1.25-1.6 (m, 8H), 0.93 (t, 6H); ^{13}C-NMR ($CDCL_3$) δ 140.4, 137.3, 130.1, 129.2, 126.1, 111.9, 32.8, 27.7, 22.9, 13.7; EI-MS *m/z* (relative intensity) 520 (m+2, 55.1), 518 (m^+, base), 516 (47.6), 396 (37.9), 352 (26.5), 286 (5.8), 272 (12.2); UV (acetonitrile) 342 nm (ε 20,000).

2-Bromo-3',4'-dibutyl-2,2':5',2"-terthiophene 39: One g terthiophene **12** was placed in a 250 mL flask and 100 mL dry chloroform added. 890 mg pyridinium bromide was added. The reaction was quenched after stirring for 40 minutes. The chloroform solution was washed with water, and the solvent removed under reduced pressure. Flash chromatography (hexanes) gave 651 mg (53.3%) of **39**, 233 mg (16.1%) of the dibrominated product **26**, and 274 mg (27.4%) recovered **12**.
^{1}H-NMR ($CDCL_3$): δ 6.8-7.3 (m, 5H), 2.32 (m, 4H), 1.35-1.6 (m, 8H), 0.90 (m, 6H); ^{13}C-NMR ($CDCL_3$): δ 140.1, 139.6, 137.2, 135.5, 129.9, 129.7, 128.3, 125.6, 125.5, 125.0, 111.2; EI-MS m/z (relative intensity) 440 (m+1, 91.2), 439 (m^+, 19.4),438 (base), 397 (20.7), 383 (7.0), 355 (20.0), 316 (59.0), 274 (73.7).

3",4"-Dibutyl-2,2':5',2":5",2"':5"',2"":5"",2""'-quinquethiophene 27: Dibromoterthiophene **26** (597 mg, 1.15 mmol) was placed in a flask with 100 mg Ni(dppp)Cl_2 and 50 mL dry ether. Five

equivalents of 2-thienyl magnesium bromide were added by cannula. The reaction was refluxed for four hours. The mixture turned yellow-green after 45 minutes. The reaction was quenched with ice, washed with water and dried with $MgSO_4$. The product was purified by flash chromatography (hexanes eluent) to give 324 mg (53.7%) of **3**, m.p.=102°C.

^{1}H-NMR ($CDCL_3$): δ 7.0-7.3 (m, 10H), 2.75 (t, 4H), 1.4-1.6 (m, 8H), .9 (t, 6H); ^{13}C-NMR ($CDCL_3$): δ 140.2, 137.1, 137.0, 135.0, 129.7, 127.9, 126.3, 124.4, 124.0, 123.8, 32.8, 27.8, 23.0, 13.8; EI-MS *m/z* (relative intensity) 524 (m^+, 53.15), 481 (9.20), 439 (8.15), 424 (1.48), 262 (2.01), 207 (3.27), 179 (1.53), 149 (2.29), 127 (3.68), 101 (5.74), 85 (base); UV (heptane) 389 nm (ε 33,000).

anal. Calcd. for $C_{28}H_{28}S_5$: C, 64.01; H, 5.38

Found: C, 64.58; H, 5.40

Alternate procedure for **27**: One gram terthiophene **12** (0.00278 mol) is brominated with 1.83 g TMAT (0.00584 mol, 2.1 equivalents) as above. The product is placed in a flask with 100 mg $Pd(dppf)Cl_2$ and 300 mL dry ether. The flask is placed in a Dry Ice/acetone bath and 2.1 equivalents thiophenemagnesium bromide in 100 mL ether is added by double ended needle. The cold bath is remove one hour after addition is complete and the reaction stirred 18 h. The reaction is quenched and washed with water, dried, and the ether removed under reduced pressure. Flash chromatography (hexanes eluent) gave 420 mg (29%) of **27**, identical to above. Although the yield is lower, this reaction is more consistant than using $Ni(dppp)Cl_2$.

3",4"-Dibutyl-2,5""-diformyl-2,2':5',2":5",2"':5"',2""-quinquethiophene 30: Quinquethiophene **27** (324 mg, 0.00061 mol) was treated with 1.5 g $POCl_3$ in 10 ml DMF and heated on a steam bath for one hour. The material was decomposed by cautious addition of sodium bicarbonate solution. The product was a brick red solid (286 mg) that was obtained in 69% after flash chromatography (hexanes eluent).
^{1}H-NMR ($CDCL_3$): δ 9.9 (s, 2H), 7.7 (d, 2H), 7.35 (d, 2H), 7.26 (d, 2H), 7.1 (d, 2H), 2.75 (t, 2H), 1.4-1.6 (m, 8H), 0.9 (t, 6H); EI-MS m/z 580, 495, 277, 238, 211, 185, 139.

Bis(2-thienoyl)-5,6-decane 23: A dry flask containing 7.5 g (50 mmol) dry NaI was charged with Ar and purged. Three mL (25 mmol) dichlorodimethyl silane in 100 mL freshly distilled acteonitrile were added to produce an opaque yellow mixture. After stirring for ten minutes, the flask was placed in a water bath and 7.0 mL (50 mmol) freshly distilled triethyl amine followed by 9.0 g (25 mmol) 2-hexanoylthiophene were added dropwise. The reaction was allowed to run for 18.5 hr at room temperature and was then quenched by addition of 200 mL 1:1 ice/saturated $NaHCO_3$ solution. It was extracted with pentane (2x50mL) and dried over sodium sulfate. ^{1}H-NMR showed a 3:1 ratio of the bis-silyl enol ether to starting the ketone. This crude product was used without further purification. A dry flask containing 27.41 g (50 mmol) cerium ammonium nitrate and 8.4 g (100 mmol) sodium

bicarbonate was charged with Ar and purged. One hundred mL dry acetonitrile were added to the flask. The bis-silyl enol ether in 150 mL dry acetonitrile were added over 2.5 h. The reaction was worked up 24 h after the addition was complete by addition of 500 mL saturated sodium bicarbonate solution, followed by extraction with ether (2x100mL). The organic phase was washed with 50 mL brine and then dried over sodium sulfate. The product was purified by flash chromatography (9:1 hexanes/ether eluent) to give 4.325 g (48% from 2-hexanoylthiophene) of the coupled dione as a diastereomeric mixture. One of the diastereomers was easily isolated by recrystallization from hexanes (M.P.=162-163°C) and was used to obtain the analytical data.
^{1}H-NMR ($CDCL_3$): δ 7.82 (d, 2H), 7.68 (d, 2H), 7.16 (dd, 2H), 3.95 (m, 2H), 1.7 (m, 2H), 1.1 (m, 2H), 1.0-1.2 (m, 8H), 0.65 (t, 6H); ^{13}C-NMR ($CDCL_3$): δ 196.5, 146.4, 134.7, 132.5, 128.4, 50.7, 32.2, 29.7, 22.6, 13.6. IR (CCl4) 2970, 2940, 2840, 2820, 1654, 1410; EI-MS *m/z* (relative intensity) 362 (m^+, 8.5), 345 (2.6), 306 (31.0), 251 (19.2), 195 (95.3), 182 (88.2), 168 (56.5), 139 (77.7), 111 (base).

3,4-Dibutyl-2,5-(2-thienyl)-furan 24: One hundred milligrams diketone **23** (lower melting diastereomer) was placed in a flask to which 100 mL acetic anhydride and 2 mL hydrochloric acid were added. The reaction was stirred for 24 h in the absence of light. The solution was poured over 50 g ice and stirred for one hour, transferred to a separatory funnel and extracted with carbon tetrachloride. The carbon tetrachloride solution was washed with sodium bicarbonate solution and dried with magnesium sulfate.

The solvent was removed under reduced pressure and the crude product purified by flash chromatography (hexanes eleunt), giving 63 mg **24** (66%) as a pale green oil.
^{1}H-NMR ($CDCL_3$): δ 7.09-7.31 (m, 6H), 2.62 (t, 4H), 1.47-1.75 (m, 8H), 1.00 (t, 6H); ^{13}C-NMR ($CDCL_3$): δ 143.8, 133.8, 127.4, 123.7, 123.4, 122.5, 32.0, 24.0, 23.1, 14.0; EI-MS *m/z* (relative intensity) 344 (m^+, base), 301 (16.9), 273 (9.2), 259 (23.1), 231 (11.5), 111 (79.8); UV (acetonitrile) 351 (ε 29,000).

3,4-Dibutyl-2,5-(2-thienyl)-pyrrole 25: Fifty mL toluene was placed in a dry 100 mL flask with 1.773 mg ammonium chloride. To this was added 16.5 mL of 2.0 M trimethyl aluminum in toluene solution by syringe. The reaction was stirred for one hour, and transferred to a dry 250 mL flask containing 3.00 g diketone **23** in 100 mL toluene *via* double-ended needle. The reaction was heated to reflux and complete in two hours. The reaction was quenched by *cautiously* adding water dropwise. The toluene solution was filtered, dried, and the toluene removed under reduced pressure. Purification by flash chromatography gave the product (2.541 g, 89%) as a green solid (mp=45.5-46.5°C).
^{1}H-NMR ($CDCL_3$): δ 8.0 (br s, 1H), 7.0-7.24 (m, 6H), 2.66 (t, 4H), 1.4-1.65 (m, 8H), 0.97 (t,6H); ^{13}C-NMR ($CDCL_3$): δ 127.0,122.9, 122.8 (2C), 122.4, 121.8, 33.1, 24.3, 22.6, 13.5; EI-MS *m/z* (relative intensity) 345 (m+2, 10.5), 344 (m+1, 23.1), 343 (m^+, base), 300 (62.8) 258 (96.3), 129 (17.0); UV (acetonitrile) 342 nm (ε 25,000).

2,5-Diphenylpyrrole 46: Ninety milligrams ammonium chloride were placed in a dry 100 mL flask to with 50 mL toluene. To this was added 0.84 mL of 2.0 **M** trimethylaluminum in toluene solution by syringe. The reaction was stirred for one hour, and transferred to a dry 250 mL flask containing 100 mg 1,4-diphenyl-1,4-butanedione **45** in 100 mL toluene. The reaction was stirred at room temperature 2 h, cooled, quenched (*carefully*) with water and filtered. The solution was washed with water, dried with magnesium sulfate, and the solvent removed under reduced pressure. Flash chromatography of the crude product gave 78 mg (85%) of **46** as a white solid (m.p.=139.8-140.0°C). ^{1}H-NMR ($CDCL_3$): δ 8.6 (br s, 1H), 7.55 (d, 2H), 7.41 (dd, 4H), 7.25 (m, 4H), 6.60 (s, 2H); ^{13}C-NMR ($CDCL_3$): δ 133.1, 132.5, 129.0, 126.4, 123.8, 107.9; EI-MS *m/z* (relative intensity) 220 (m+1, 18.6), 219 (m^+, base), 217 (9.5), 191 (4.1), 165 (3.1), 140 (2.1), 115 (43.3).

Alternatively, the reaction may be performed using dichloromethane as solvent and trimethylaluminum in hexanes solution. The reaction was run at room temperature overnight and worked up as above, yielding 81%.

2,5-Di-(2-thienyl)-pyrrole 48: One gram 1,4-di-(2-thienyl)-1,4-butanedione **48** was treated according to the toluene procedure above, yielding 690 mg **48** (75%) as a white solid (mp=81.0-81.5°C). ^{1}H-NMR ($CDCL_3$): δ 8.3 (br s, 1H), 7.00-7.20 (m, 6H), 6.4 (s, 2H); ^{13}C-NMR ($CDCL_3$): δ 135.6, 127.7, 127.4, 122.9, 121.1, 108.5; EI-MS *m/z*

(relative intensity) 233 (m+2, 10.7), 232 (m+1, 16.5), 231 (m^+, base), 199 (6.0), 186 (17.4), 171 (3.7), 154 (3.8), 122 (29.5), 115 (24.7).

2,5-Di-(2-furyl)-pyrrole 50: One gram 1,4-di-(2-furyl)-1,4-butanedione **47** is treated using the dichloromethane procedure, yielding 444 mg **50** (52%) as a white solid, m.p.=80.5-81.0°C. ^{1}H-NMR ($CDCL_3$): δ 8.78 (br s, 1H), 7.39 (s, 2H), 6.4-6.7 (m, 6H); ^{13}C-NMR ($CDCL_3$): δ 147.8, 140.5, 124.2, 111.6, 108.8, 102.7; EI-MS m/z (relative intensity) 200 (m+1, 14.4), 199 (m^+, base), 170 (24.6), 142 (36.3), 115 (10.6), 100 (12.6).

3',4'-Dibutyl-2,5"-diformyl-2,2':5',2"-terthiophene 31: To 2 g terthiophene **12** in a dry 50 mL flask was added 4.54 g N-methylformanilide and 5.2 g phosphorous oxychloride. The mixture was heated on a steam bath for two hours, forming a bright red solution. This was cooled and decomposed by cautious addition of sodium bicarbonate solution. The material was extracted with ether, washed with water, dried with magnesium sulfate, and the ether removed under reduced pressure. Recrystallization from hexanes gave 1.78 g (76%) **31**.
^{1}H-NMR ($CDCL_3$): δ 9.88 (s, 2H), 7.70 (d, 2H), 7.25 (d, 2H), 2.75 (t, 4H), 1.40-1.56 (m, 8H), 0.94 (t, 6H); ^{13}C-NMR ($CDCL_3$): δ 181.2, 147.6, 142.9, 136.8, 130.8, 127.1, 111.1, 32.8, 28.0, 14.0; MS-EI m/z (relative intensity) 418 (m+2, 16.7), 417 (m+1, 25.1), 416 (m^+, base), 359 (5.2), 345 (27.6), 331 (7.7), 303 (51.1), 275 (7.0), 240 (9.1).

3',4'-Dibutyl-2,5"-dihexanoyl-2,2':5',2"-terthiophene 37:
Two grams **12** were placed in a flask with 200 mL dry ether. The flask was placed in an ice/water bath and 2.1 equivalents n-buLi (2.5 M in hexanes) was added. The cold bath was removed and the solution stirred for 2 h. Then 2.0 g (2.2 equivalents) N-methyl-N-methoxyhexanoic amide was added. The reaction was stirred for one hour and then quenched and washed with dilute HCl. The ethereal solution was dried with magnesium sulfate and the solvent removed under reduced pressure. Flash chromatography (hexanes eluent) gave 1.88 g **37** (61%) as deep green plates (m.p.=93.5-94.5°C) and 388 mg **38** (15%) as a dark green oil.
For Compound **37**: ^{1}H-NMR ($CDCL_3$): δ 7.61 (d, 2H), 7.13 (d, 2H), 2.88 (t, 4H), 2.76 (t, 4.4), 1.77 (quintet, 4H), 1.1-1.6 (m, 16H), 0.86-1.00 (m, 12H); ^{13}C-NMR ($CDCL_3$): δ 193.7, 143.9, 143.3, 142.1, 132.0, 130.6, 126.5, 39.2, 32.8, 31.6, 24.7, 21.6, 21.4 (2C), 13.9 (2C); EI-MS *m/z* (relative intensity) 557 (m+1, 30), 556 (m^+, 99.1), 500 (58.1), 485 (18.8), 444 (11.2), 415 (19.3), 373 (9.5), 222 (53.6), 43 (base).

For Compound **38**: ^{1}H-NMR ($CDCL_3$): δ 7.62 (d, 1H), 7.32 (dd, 1H), 7.06-7.15 (m, 3H), 2.88 (t, 2H), 2.70 (m, 4H), 1.88 (quintet, 2H), 1.2-1.7 (m, 12H), 0.90-1.00 (m, 9H); ^{13}C-NMR ($CDCL_3$): δ 193.3, 144.5, 142.8, 141.7, 140.5, 135.7, 132.0, 131.5, 129.1, 127.4, 126.2, 126.0, 125.7, 39.0, 32.8, 32.6, 31.5, 28.0, 27.7, 24.8, 23.0, 22.9, 22.5, 13.9, 13.8 (2C); EI-MS *m/z* (relative intensity) 460 (m+2, 16.4), 459 (m+1, 29.4), 458 (m^+, base), 415 (9.9), 402 (54.0), 387 (12.8), 360 (13.0), 317 (14.1), 275 (11.6).

3',3'''',4',4''''-Tetrabutyl-2,2':5',2'':5'',2''':5''',2'''':5'''',2'''''-sexithiophene 40:

Method one: Two grams terthiophene **12** were placed in a 500 mL flask with 250 mL dry ether. 2.5 mL (1.0 equivalent) n-buLi solution (2.5 **M** in hexanes) was added by syringe and the reaction stirred for one hour. The flask was placed in a Dry Ice/acetone bath and 1.882 g (2.5 equivalents) anhydrous cupric chloride were added. The cold bath was removed and the reaction stirred overnight. The resulting greenish-brown solution was quenched by addition of five mL water and filtered. The filtrate was washed, dried with magnesium sulfate, and the solvent removed under reduced pressure. Flash chromatography (hexanes eluent) gave 47 mg sexithienyl (9.4%) and 1.623 g (81%) recovered **12**. The bright orange product formed prismatic crystals, m.p.=118.0-118.5°C. ^{1}H-NMR ($CDCL_3$): δ 7.33 (dd, 2H), 7.05-7.18 (m, 6H), 2.68-2.82 (m, 8H), 1.4-1.7 (m, 16H), 0.95-1.06 (m, 12H); ^{13}C-NMR ($CDCL_3$): δ 140.2, 136.7, 136.1, 135.2, 130.0, 129.6, 127.3, 126.3, 125.9, 125.3, 123.8, 32.9, 32.8, 27.9, 27.8, 23.0, 22.0, 13.8; EI-MS *m/z* (relative intensity) 721 (m+3, 9.5), 719 (m+1, 39.0), 718 (m^+, base), 675 (11.2), 633 (6.7), 360 (48.5), 295 (16.5), 274 (33.8); UV (heptane) 406 nm (ε 25,000). *anal.* Calcd. for $C_{40}H_{46}S_6$: C, 66.80; H, 6.45

Found: C, 66.86; H, 6.50

Method two: The above procedure was followed, except that 2.0 equivalents n-buLi (4.0 mL solution) and five equivalents cupric chloride (3.36 g) were used. Accordingly, 1.75 g terthiophene **12** (0.00486 mol) gave 478 mg sexithiophene **40** (27%) and 27 mg

nonathiophene **42** (1.5%). Nonathiophene **42** was isolated as a light and acid sensitive brick red powder, m.p.=128°C (dec.).
For compound **42**: ^{1}H-NMR ($CDCL_3$): δ 7.3 (d, 2H), 7.0-7.2 (m, 12H), 2.6-2.95 (m, 12H), 1.4-1.7 (m, 12H), 0.90-1.05 (m, 18H); FAB-MS: 1076.4 (m^+), 993.3, 882.3, 800.3, 765.3, 749.3, 679.2, 636.3, 596.3, 485.2, 443.2, 403.2, 371.3, 341.3; UV (acetonitrile) λ_2 710 nm (ε 3,400) λ_{max} 426 nm (ε 36,000).

N-Methoxy-N-methylhexanamide: Ten grams hexanoyl chloride and 7.4 g N-methoxy-N-methylamine hydrochloride were placed in a dry flask with 100 mL dichloromethane. The flask was placed in an ice/water bath and 12.2 mL (.15 mol) pyridine was added dropwise. The cold bath was removed and the reaction stirred overnight. The solution was washed with water and dried with magnesium sulfate. The compound was distilled (79°C at 2.25 mm Hg) to give 9.77 g product.
^{1}H-NMR ($CDCL_3$): δ 3.6 (s, 3H), 3.08 (s, 3H), 2.34 (t, 2H), 1.56 (quintet, 2H), 1.22 (m, 4H), 0.8 (t, 3H); ^{13}C-NMR ($CDCL_3$): δ 61.0, 33.8, 31.7, 31.5, 24.2, 22.1, 13.8; EI-MS m/z (relative intensity) 160 (m+1, 2.3), 159 (m^+, 2.0), 130 (3.1), 116 (2.7), 103 (30.5), 99 (base), 71 (85.6).

2-Hexanoylthiophene 21: Ten gram thiophene (0.119 mol) and 13.5 hexanoyl chloride (0.1 mol) were placed in a dry flask with 100 mL dichloromethane. Tin(IV) chloride (26 g, 0.1 mol) in 100 mL dichloromethane was added dropwise. The reaction turned bright red as the first few drops entered the solution. The reaction

was stirred 24 h. The mixture was quenched and washed with water, dried with magnesium sulfate, and the solvent removed under reduced pressure. The crude product was distilled (79°C at 0.5 mm Hg) to give 11.94 g (55%) 2-hexanoylthiophene. ^{1}H-NMR ($CDCL_3$): δ 7.7 (d, 1H), 7.68 (d, 1H), 7.13 (dd, 1H), 2.91 (T, 2H), 1.78 (quintet, 2H), 1.37 (m, 4H), 0.91 (t, 3H); ^{13}C-NMR ($CDCL_3$): δ 193.4, 144.5, 133.2, 131.5, 127.9, 39.3, 31.4, 24.4, 22.4, 13.8; EI-MS *m/z* (relative intensity) 183 (m+1, 45.2), 182 (m^+, 8.7), 165 (1.9), 139 (4.1), 126 (56.6), 111 (base).

2-Acetyl-3",4"-dibutyl-2,2':5',2":5",2"':5"',2"":5"",2""'-quinquethiophene 35: One hundred milligrams quinquethiophene **27** was placed in a dry flask with 50 mL dry toluene. Acetic anhydride (0.06 mL) and 0.15 mL tin(IV) chloride were added and the reaction stirred at room temperature until it started to deposit black material at the meniscus, about one hour. The reaction was immediately stopped and the crude product purified by flash chromatography (hexanes eluent) to give 34 mg **35** (16%) (m.p.=116-117°C).
^{1}H-NMR ($CDCL_3$): δ 7.54 (d, 1H), 6.95-7.25 (m, 8H), 2.68 (m, 4H), 2.50 (s, 3H), 1.25-1.65 (m, 8H), 0.93 (m, 6H); ^{13}C-NMR ($CDCL_3$): δ 190.3, 145.5, 142.3, 140.8, 140.4, 137.5, 137.2, 135.6, 134.8, 133.4, 130.4, 129.2, 127.9, 126.5, 126.0, 124.5, 124.1, 124.0, 123.9, 123.8, 123.7, 32.8, 32.7, 27.93, 27.86, 26.5, 26.4, 23.0, 13.8 (2C); EI-MS *m/z* (relative intensity) 569 (m+3, 6.4), 568 (m+2, 20.8), 567 (m+1, 28.3), 566 (m^+, base), 523 (16.8), 481 (15.9), 433 (3.5), 405 (2.6), 283 (21.6).

Attempted synthesis of duodecithiophene 43:

Method 1: A flask containing 500 mg **40** (0.0007 mol) and 300 mL dry ether was placed in an ice/water bath. One equivalent (0.3 mL) n-buLi (2.5 M in hexanes) was added by syringe. It was then placed in a Dry Ice/acetone bath and 376 mg (4 equivalents) anhydrous cupric chloride . The cold bath was immediately removed and the reaction stirred 14 h. The reaction was quenched by adding 2 mL water, stirred 15 minutes, and decanted. The ethereal solution was washed with water, dried with magnesium sulfate, and the solvent removed under reduced pressure. Flash chromatography (1% ethyl acetate in hexanes) gave 436 mg **40** (87% recovery) and 41 mg of a dark reddish material. TLC of this material showed it to contain five bands. Prepartive TLC was attempted, whith no resolution of the material. Resubmission of the material to flash chromatography using a 10 mm column showed that most of the material had polymerized, and no pure products were obtained.

Method 2: The technique described in method 1, above, was applied to 333 mg **40** , with the exception that 50 equivalents cupric chloride were used. Flash chromatography gave no pure products, excepting 300 mg **40** (90% recovery). ^{1}H-NMR of the crude product showed peaks (δ 4.2-4.6) indicative of chlorination of the benzylic carbons of the side chains. Preparative TLC was attempted without the isolation of pure product.

Method 3: To 300 mg **40** in 30 mL THF, 2 equivalents n-buLi were added and the reaction stirred 30 minutes. Anhydrous cupric chloride (5 equivalents, 280 mg) was added and the resulting slurry stirred 2h. After one hour, the mixture started to turn dark. TLC prior to workup showed no material other than **40**. Flash chromatography gave 153 mg (51%) recovered **40**.

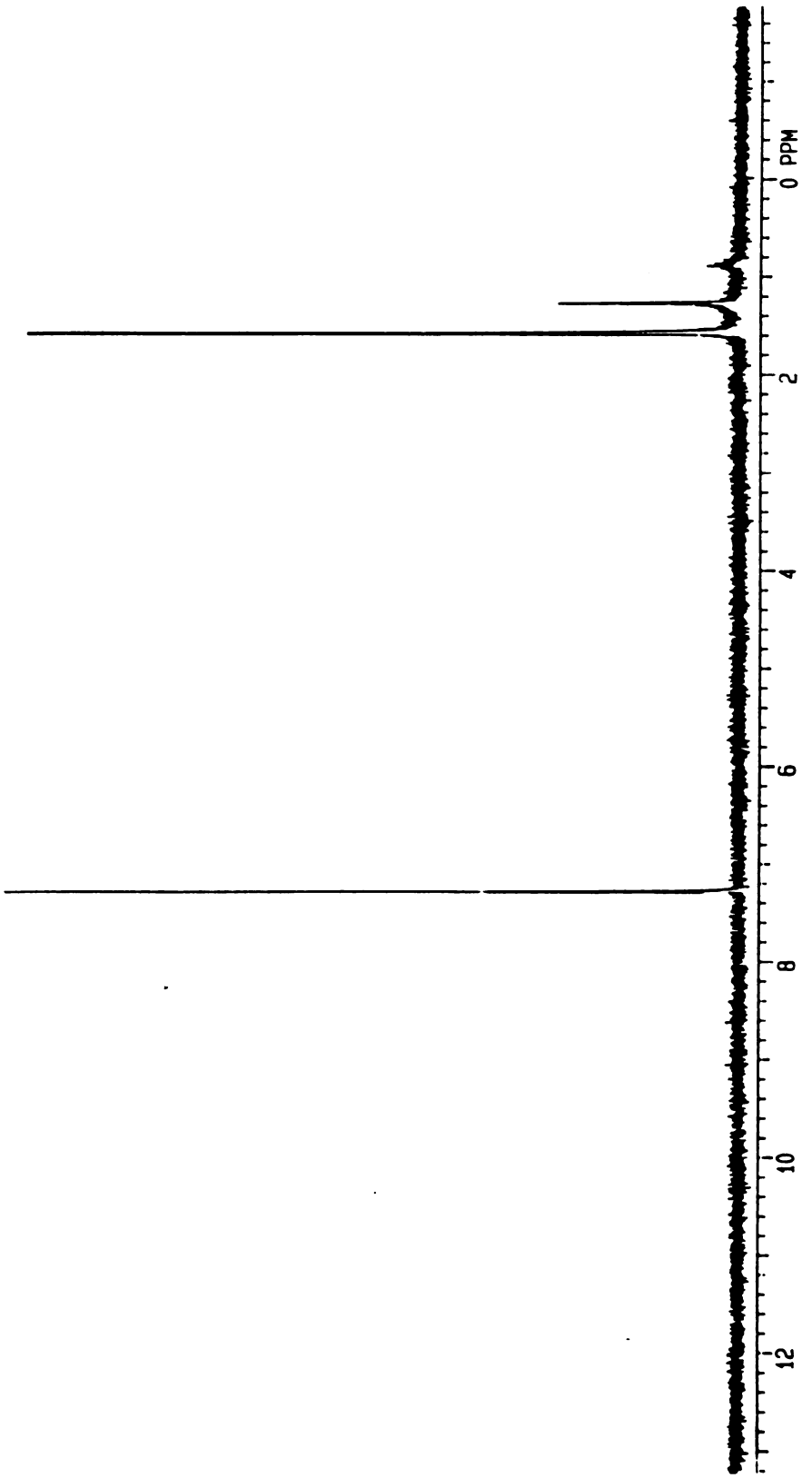


Figure A1: 300 MHz ^{1}H-NMR spectrum of Cambridge 99%+ $CDCl_3$

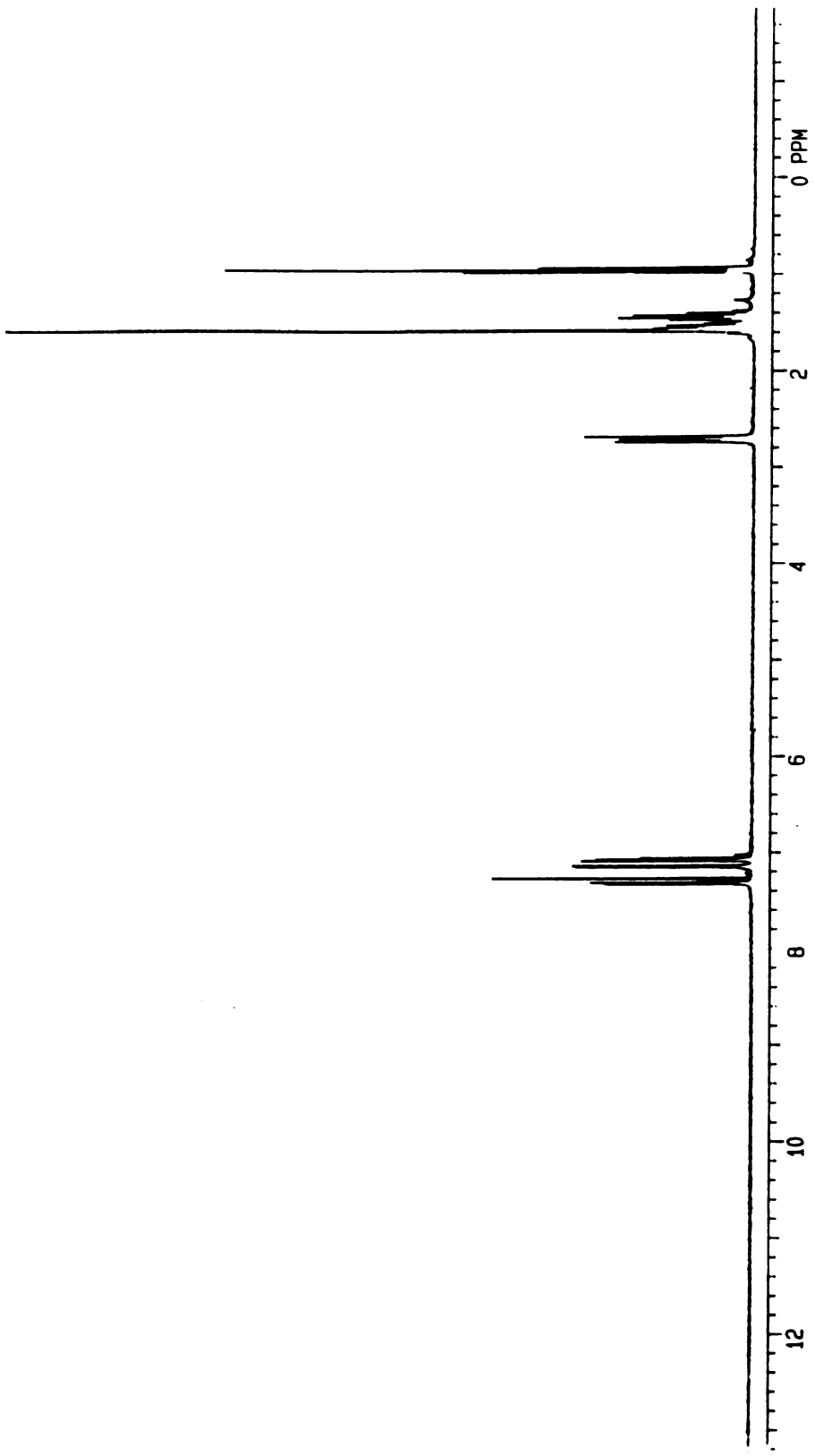


Figure A2: 300 MHz ^{1}H-NMR spectrum of terthiophene 12

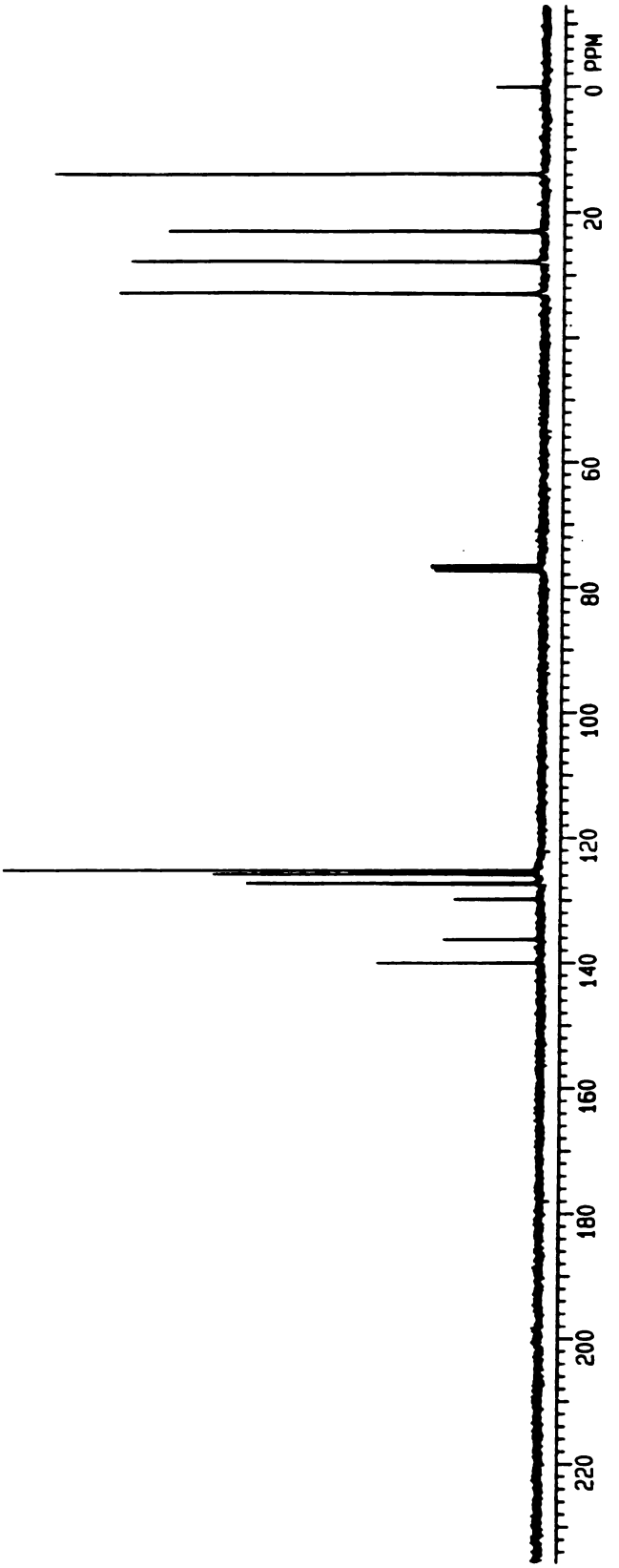


Figure A3: 75.4 MHz ^{13}C-NMR spectrum of terthiophene **12**

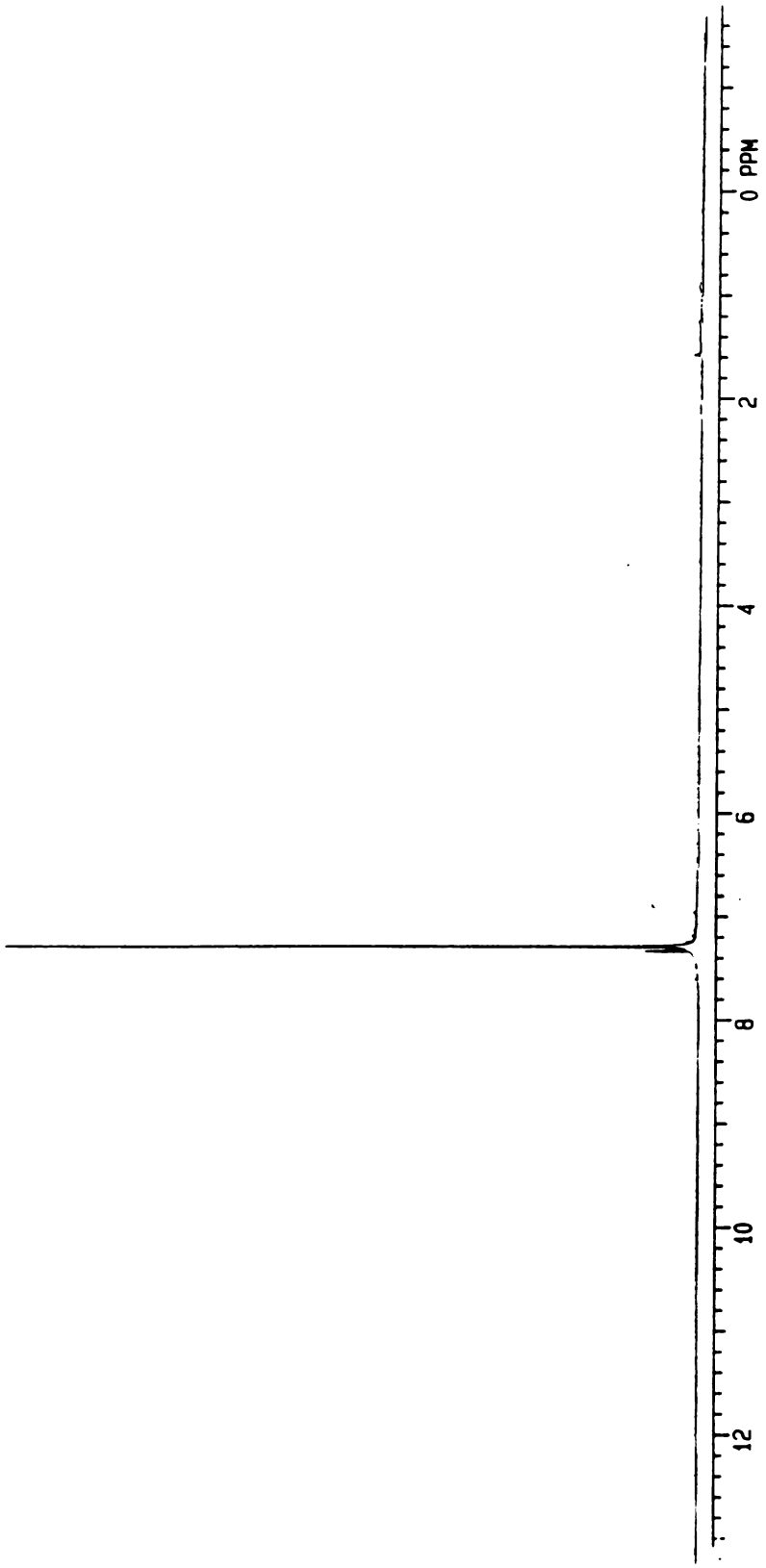


Figure A4: 300 MHz ^{1}H-NMR spectrum of 3,4-dibromothiophene **14**

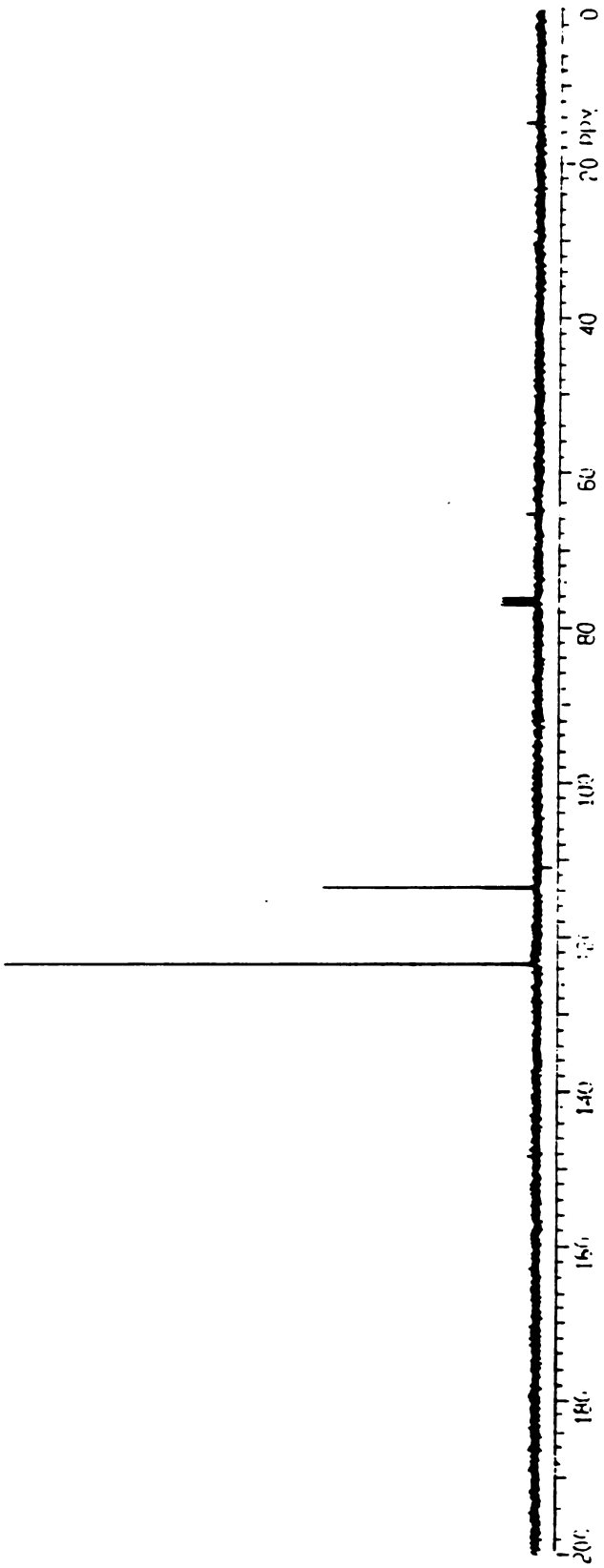


Figure A5: 75.4 MHz ^{13}C-NMR spectrum of 3,4-dibromothiophene **14**

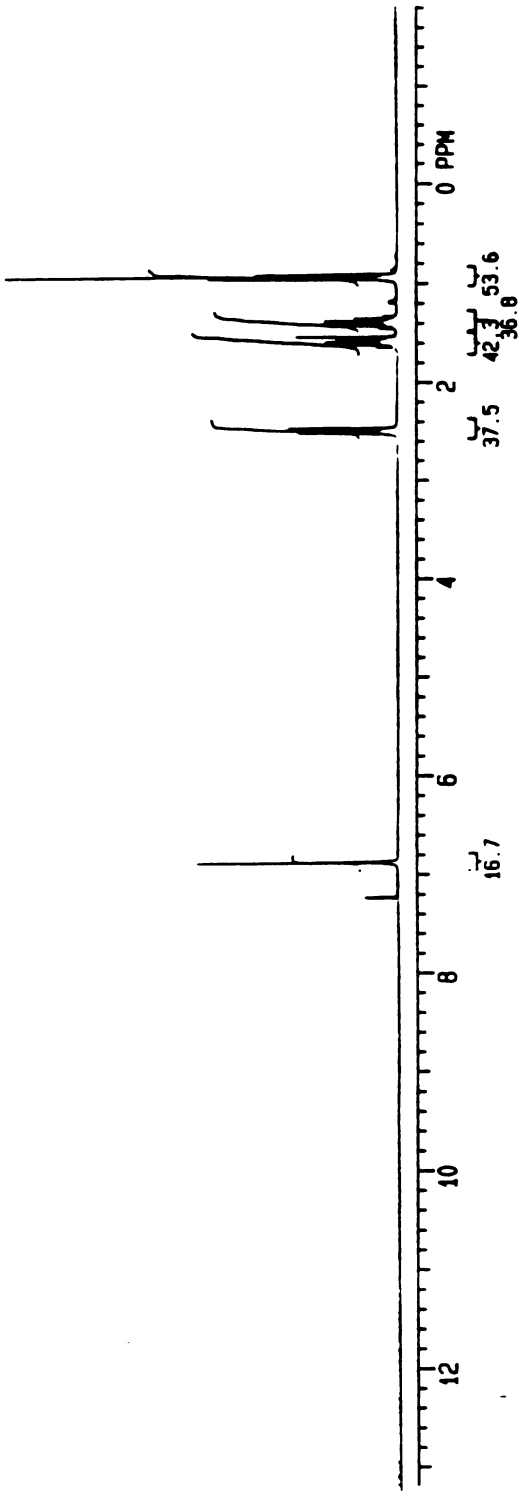


Figure A6: 300 MHz ^{1}H-NMR spectrum of 3,4-dibutylthiophene **15**

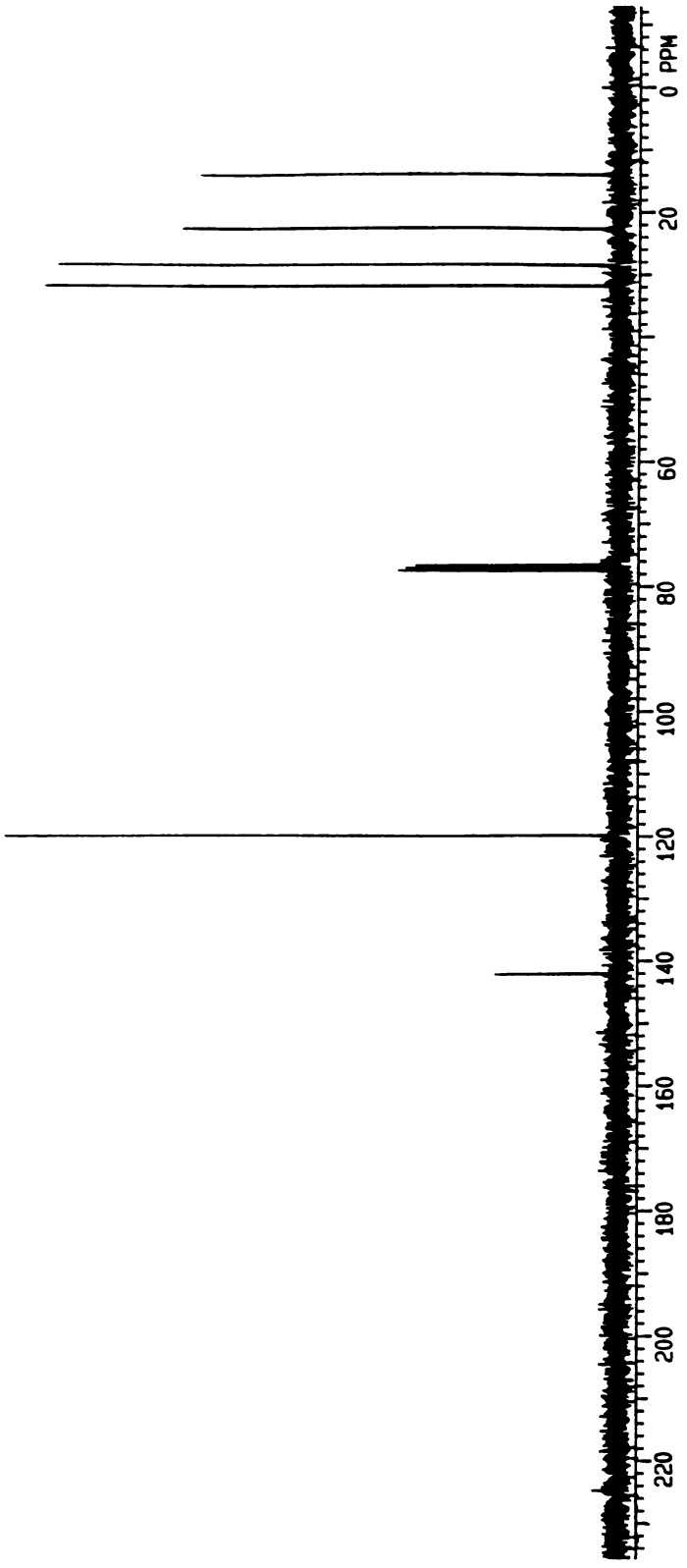


Figure A7: 75.4 MHz ^{13}C-NMR spectrum of 3,4-dibutylthiophene **15**

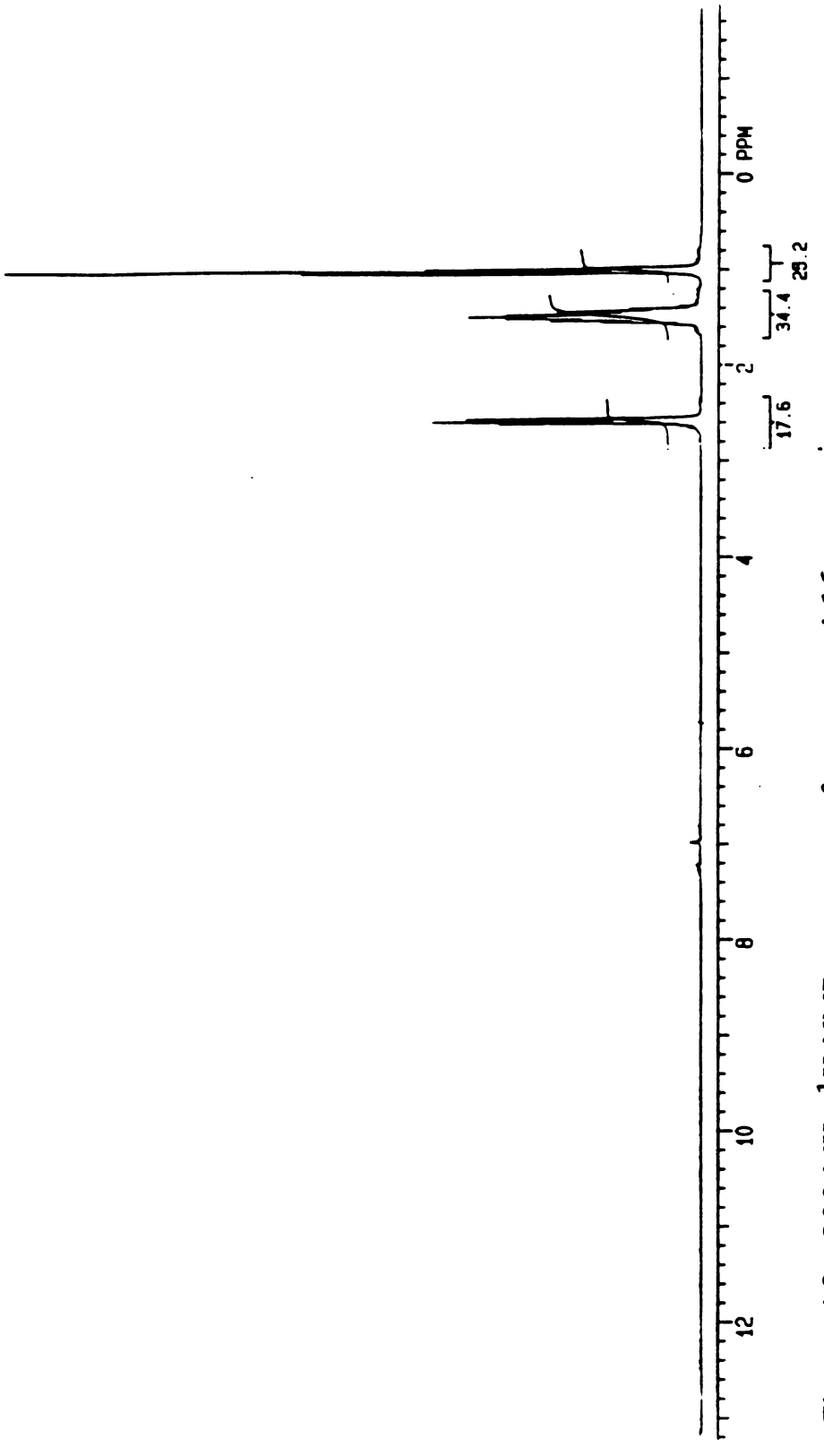


Figure A8: 300 MHz ^{1}H-NMR spectrum of compound **16**

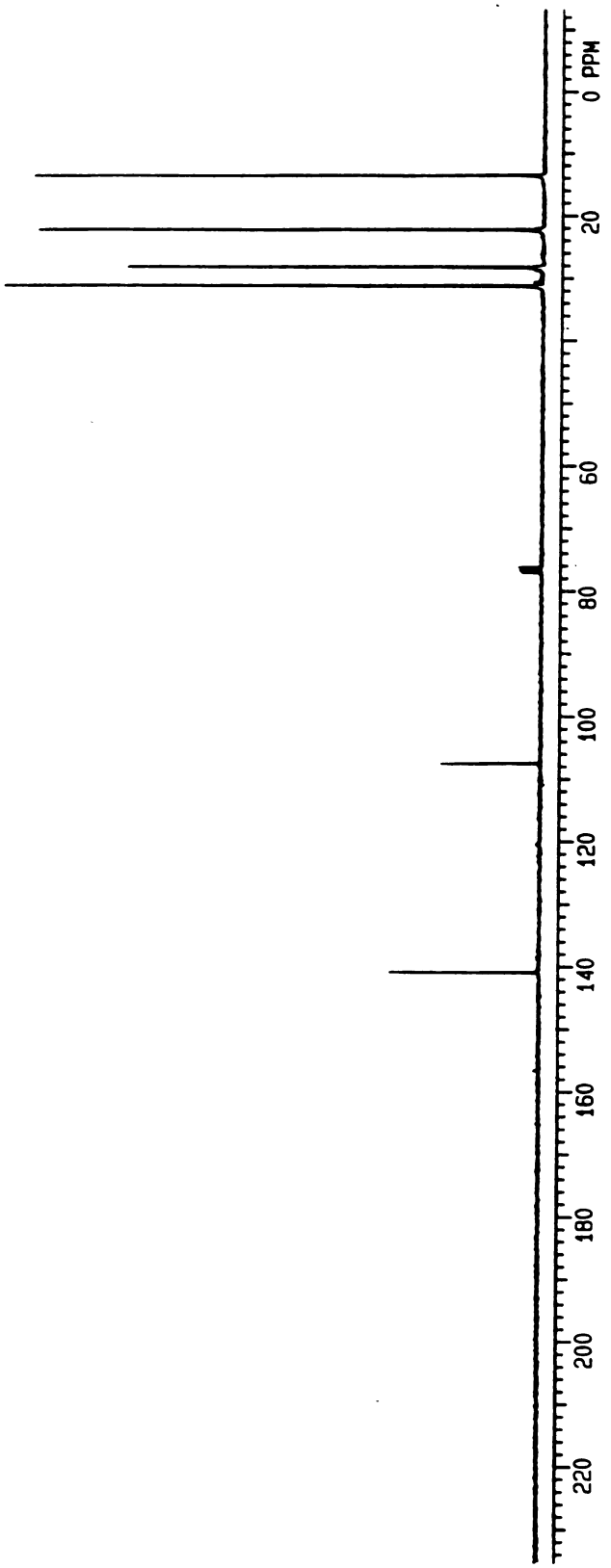


Figure A9: 75.4 MHz ^{13}C-NMR spectrum of compound **16**

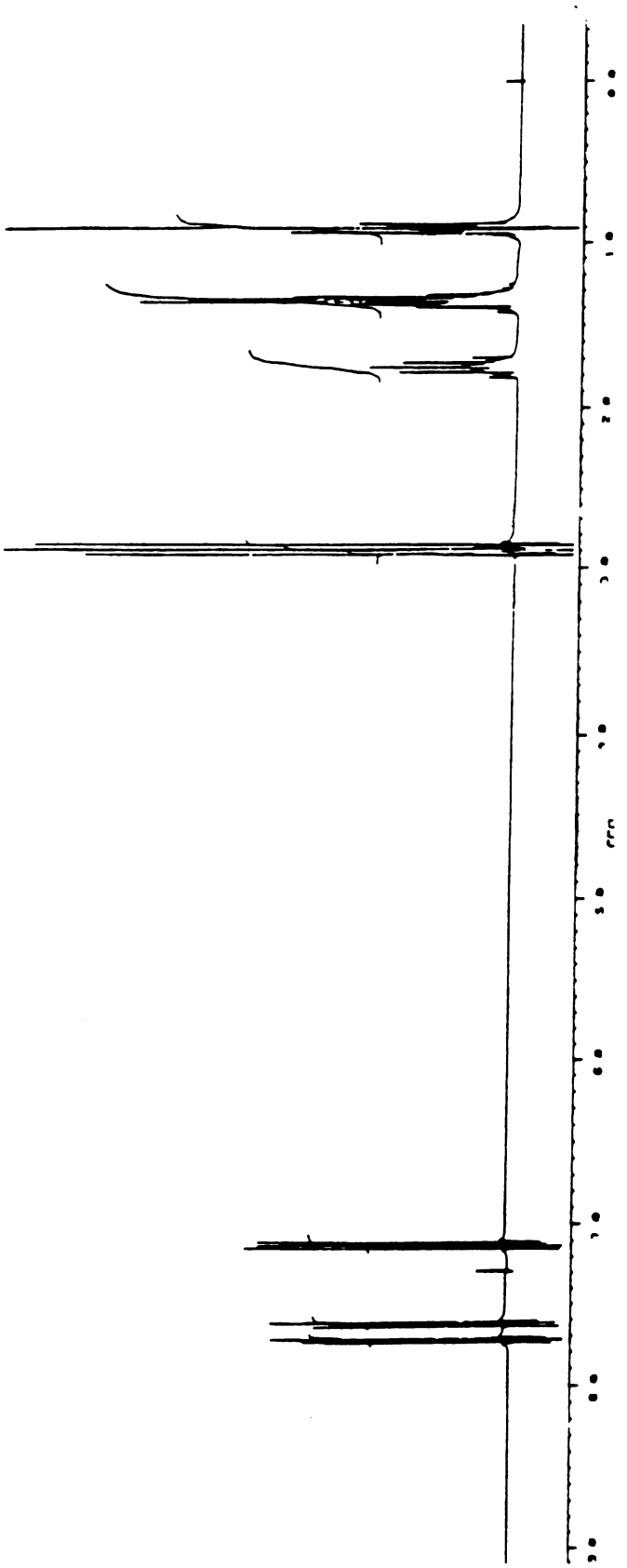


Figure A10: 250 MHz ^{1}H-NMR spectrum of compound 21

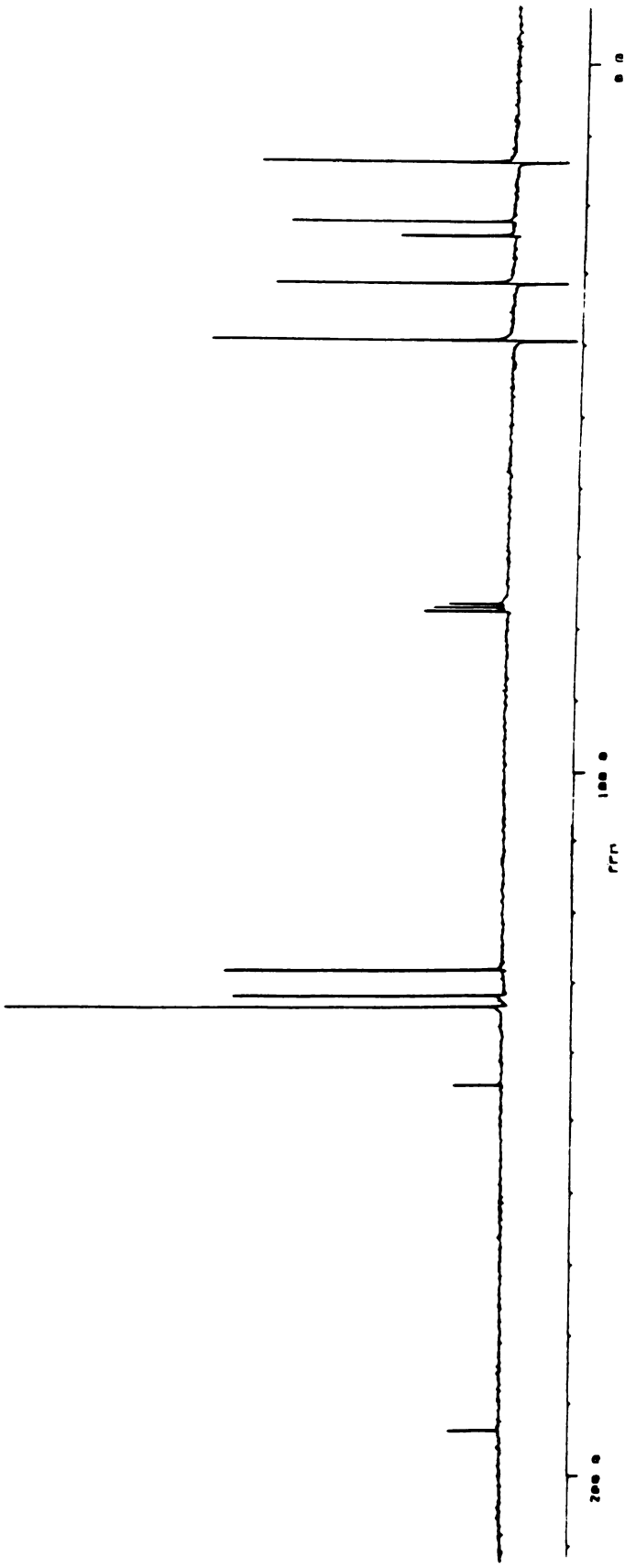


Figure A11: 62.9 MHz ^{13}C-NMR spectrum of compound 21

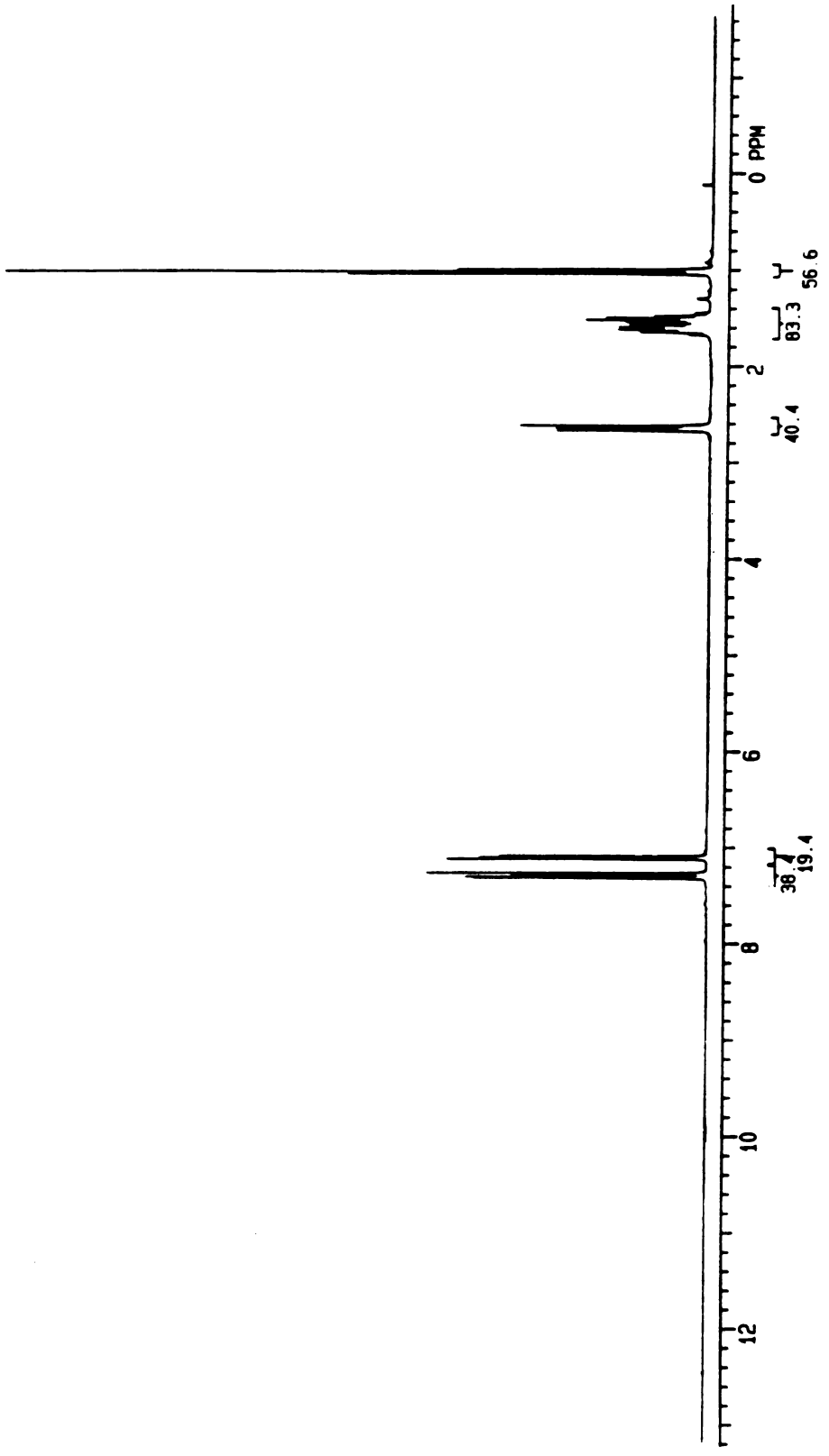


Figure A12: 300 MHz ^{1}H-NMR spectrum of compound 24

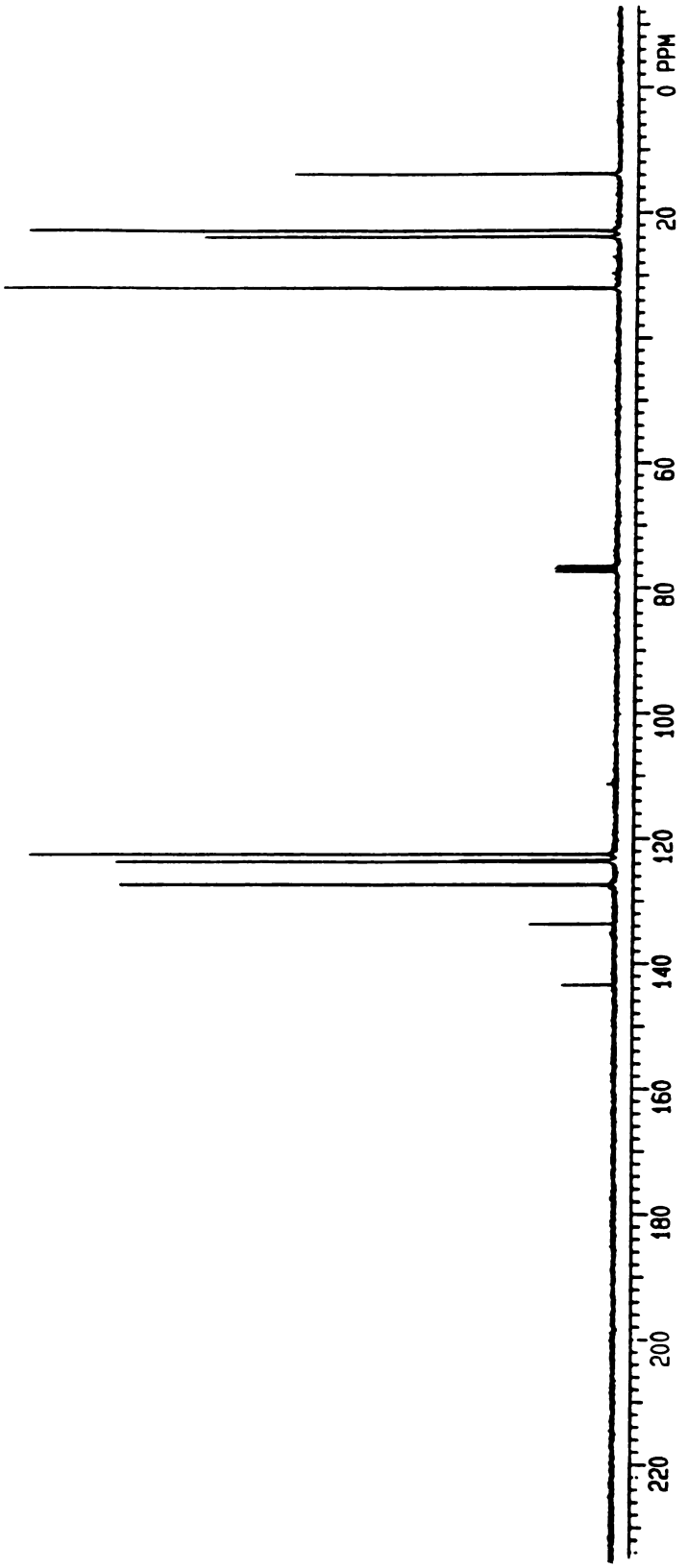


Figure A13: 75.4 MHz ^{13}C-NMR spectrum of compound **24**

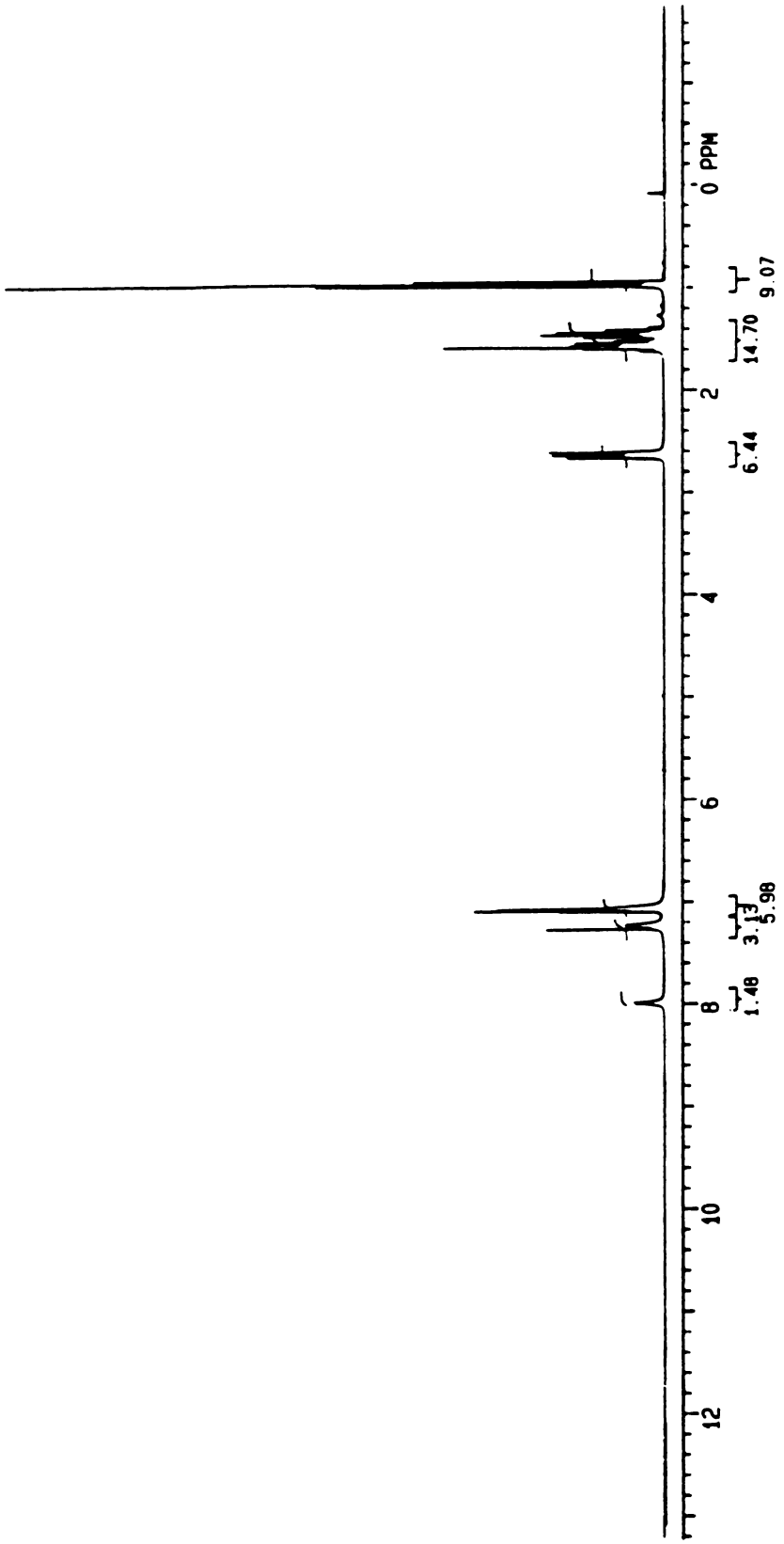


Figure A14: 300 MHz ^{1}H-NMR spectrum of compound **25**

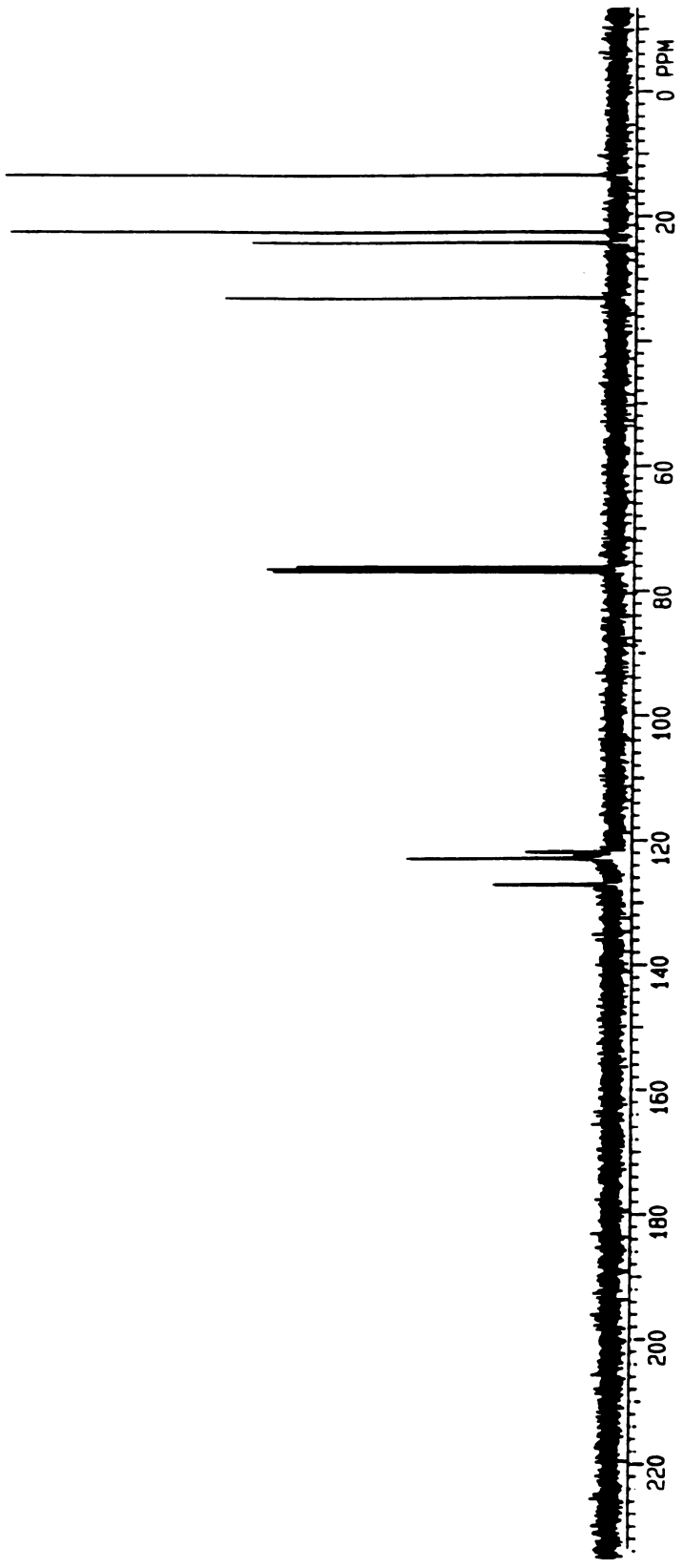


Figure A15: 75.4 MHz ^{13}C-NMR spectrum of compound 25

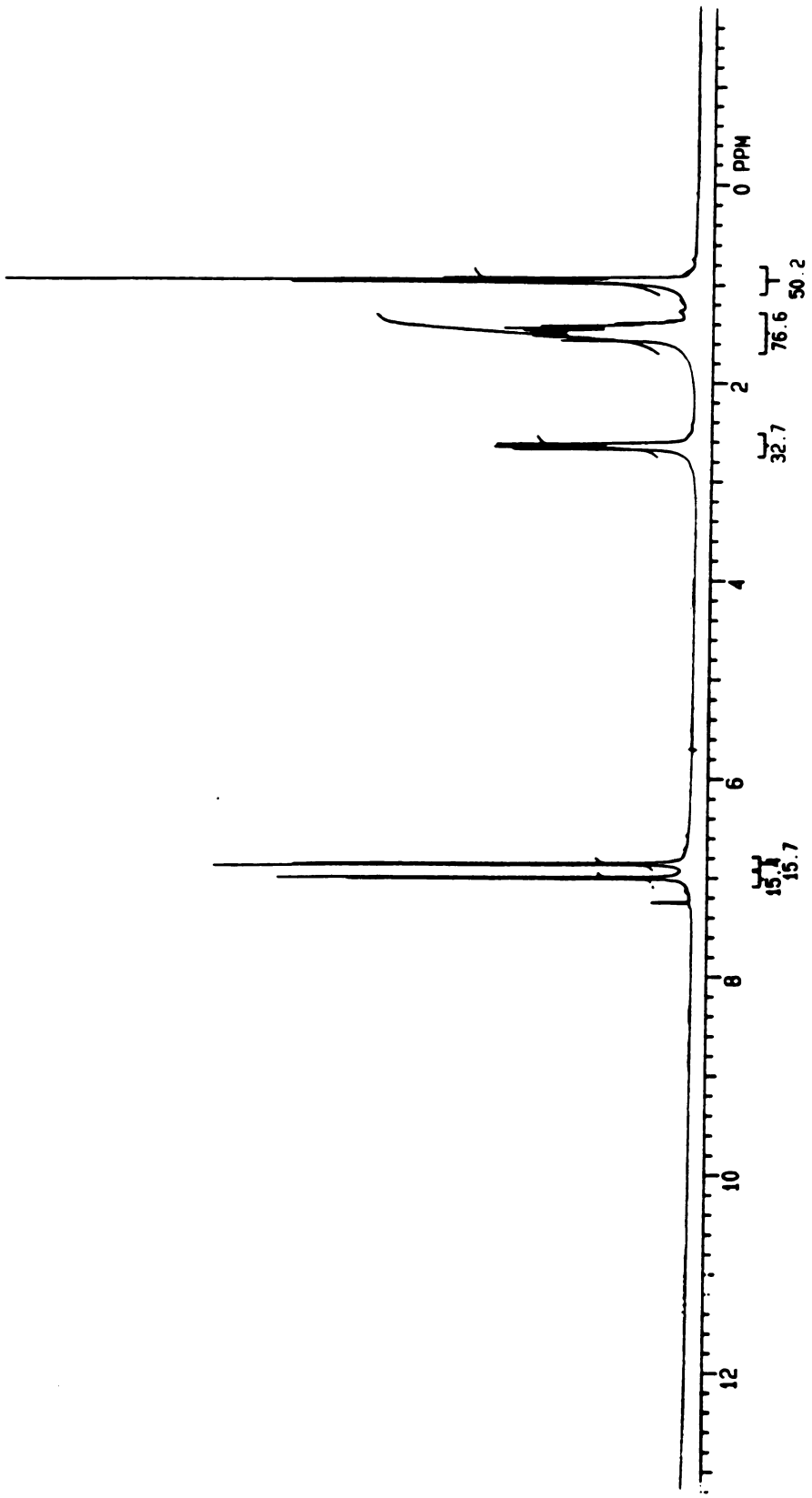


Figure A16: 300 MHz ^{1}H-NMR spectrum of compound **26**

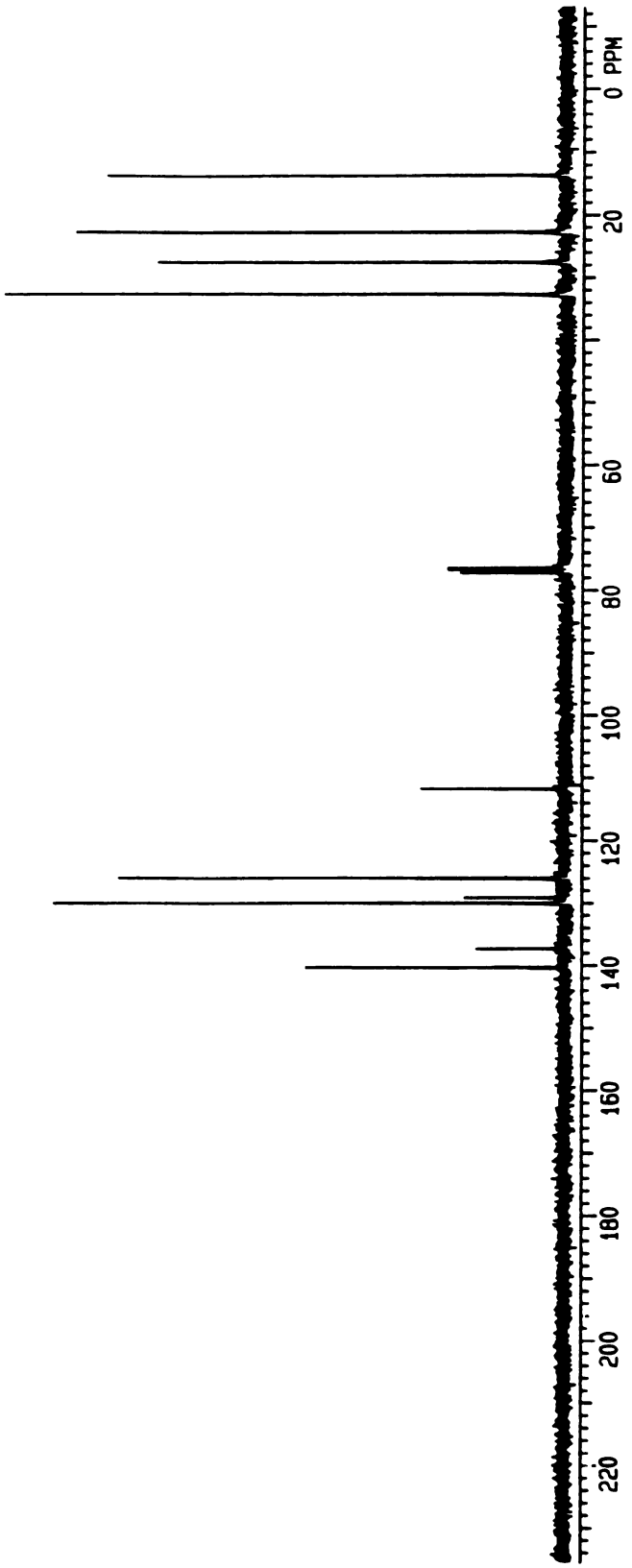


Figure A17: 75.4 MHz ^{13}C-NMR spectrum of compound 26

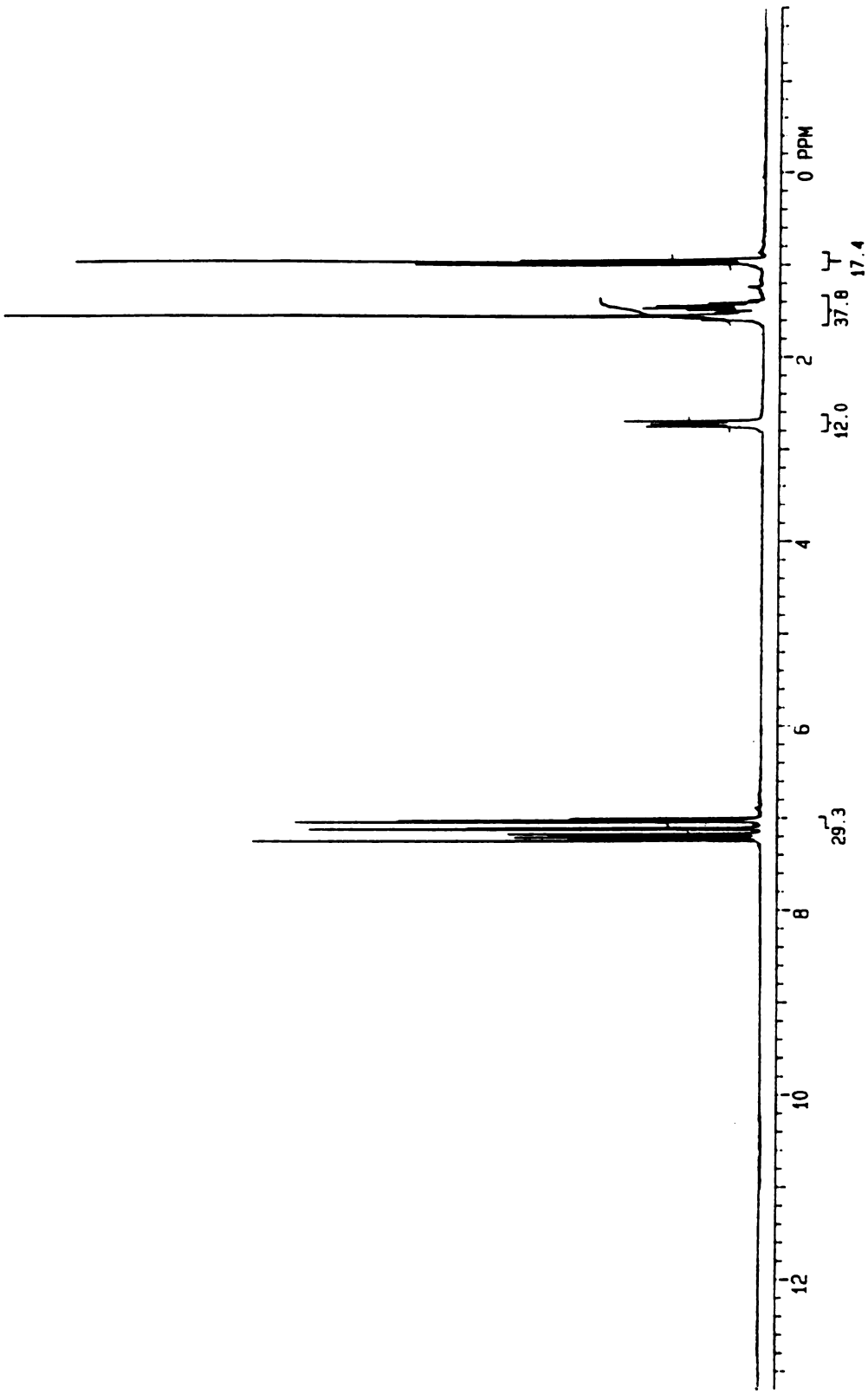


Figure A18: 300 MHz ^{1}H-NMR spectrum of compound **27**

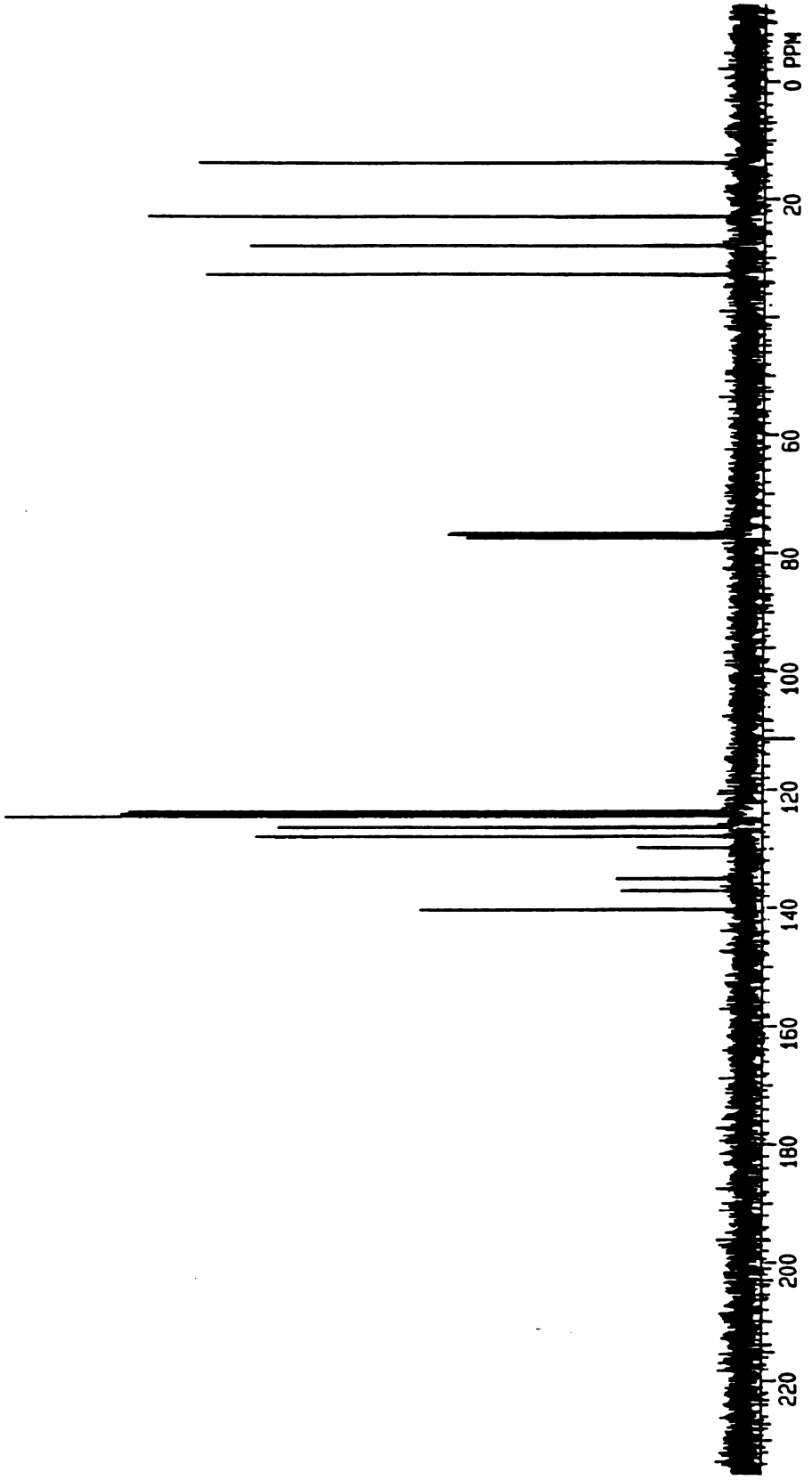


Figure A19: 75.4 MHz ^{13}C-NMR spectrum of compound 27

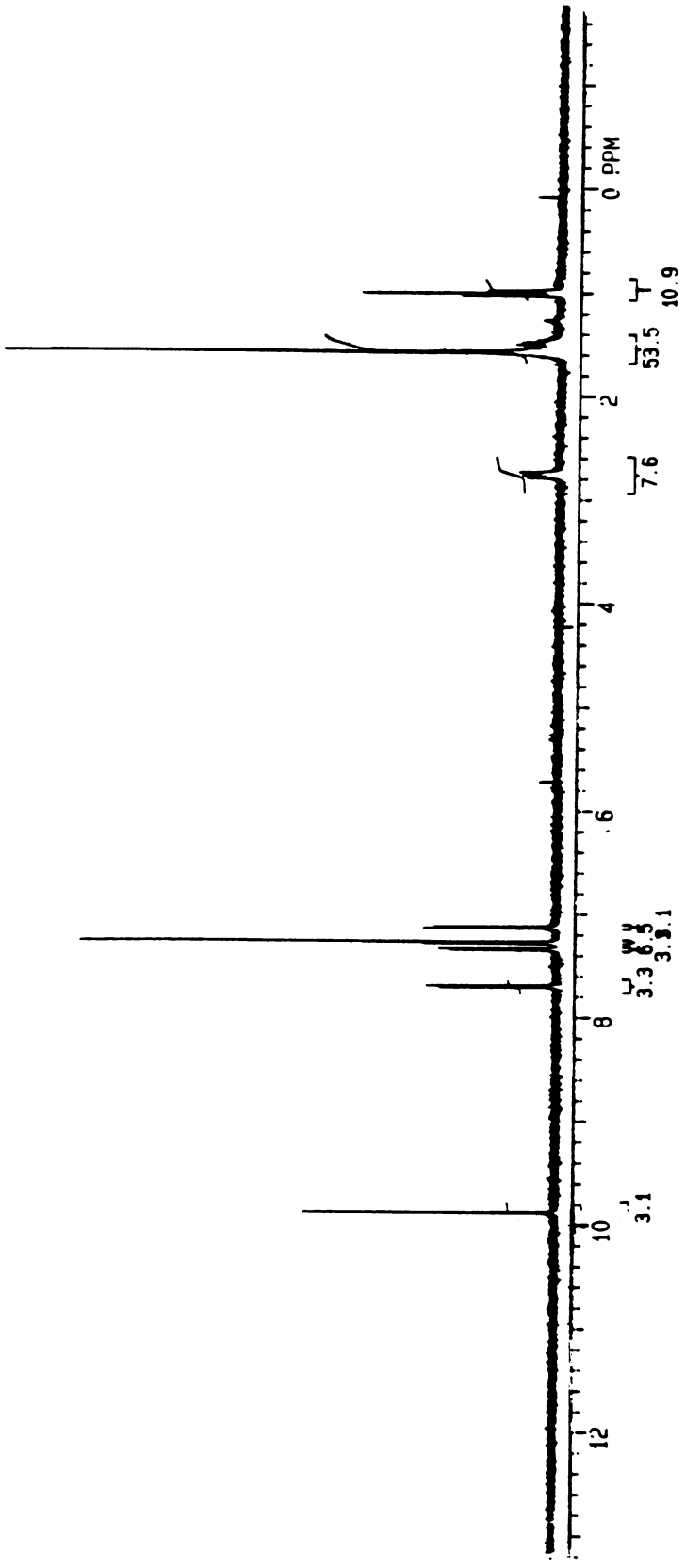


Figure A20: 300 MHz ^{1}H-NMR spectrum of compound **30**

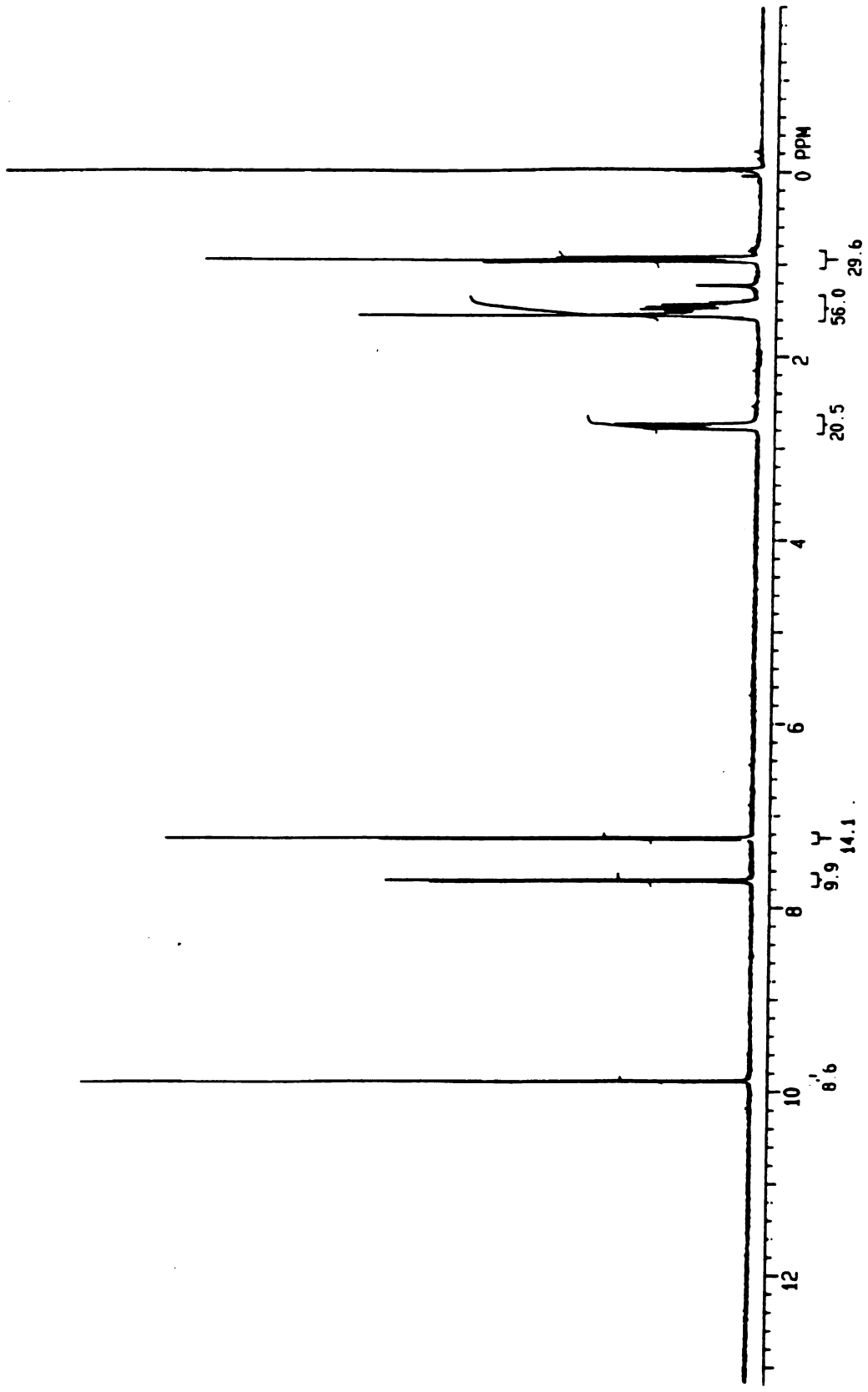


Figure A21: 300 MHz ^{1}H-NMR spectrum of compound **31**

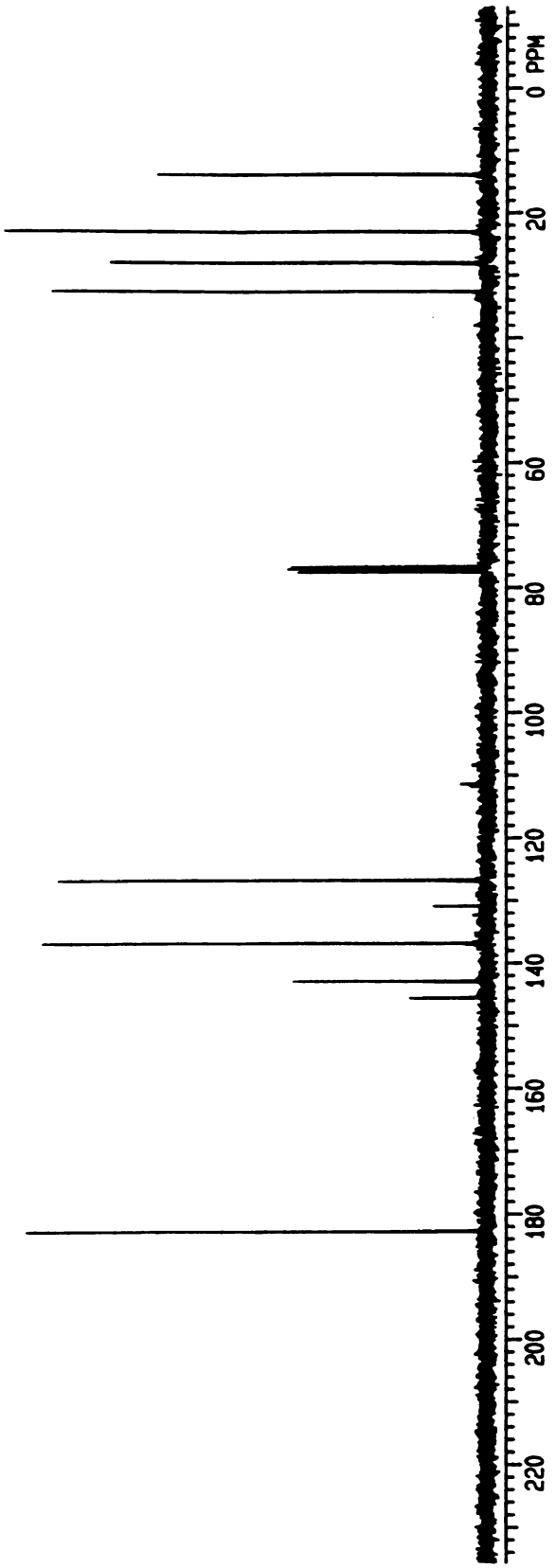


Figure A22: 75.4 MHz ^{13}C-NMR spectrum of compound **31**

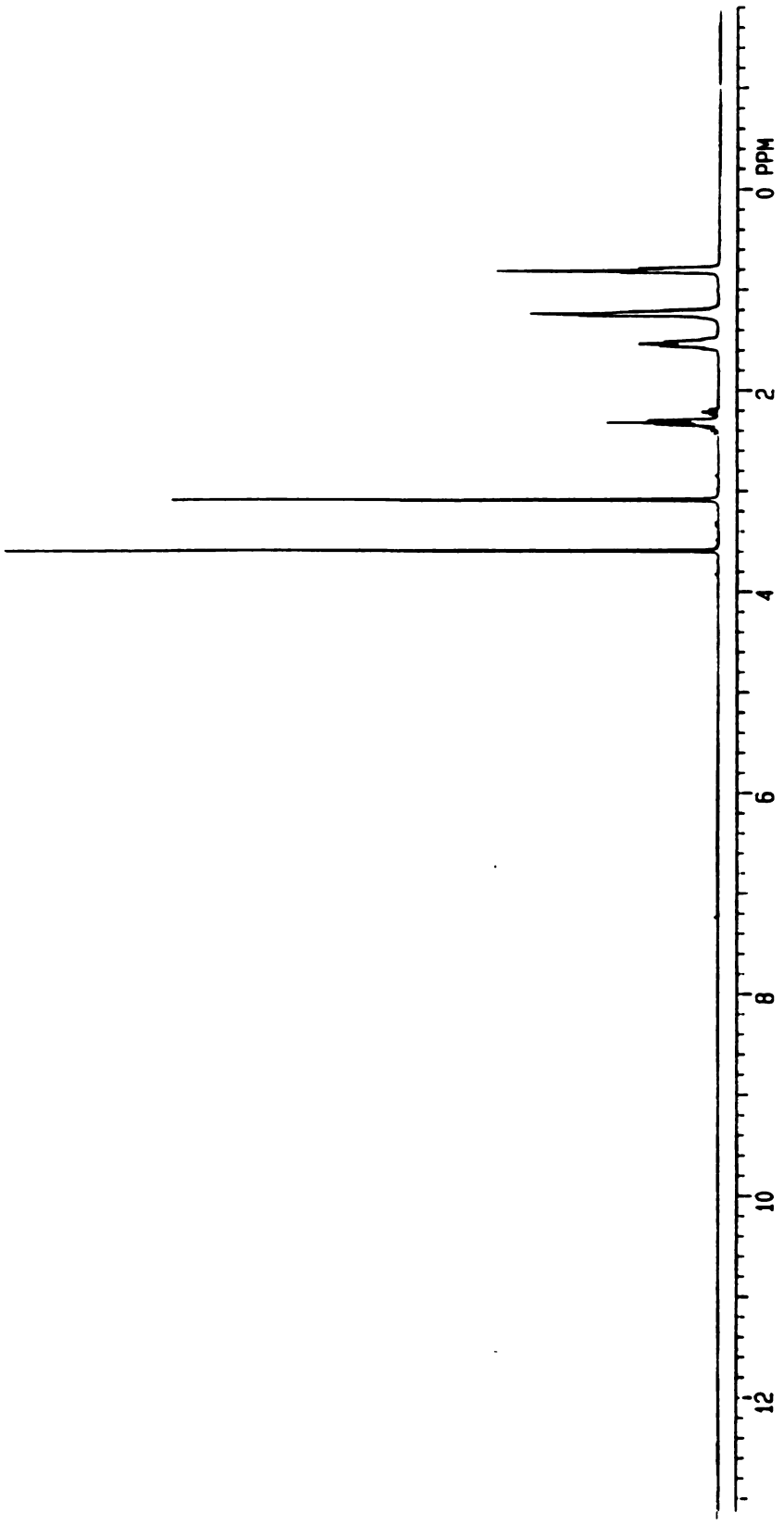


Figure A23: 300 MHz ^{1}H-NMR spectrum of N-methoxy-N- methylhexanamide

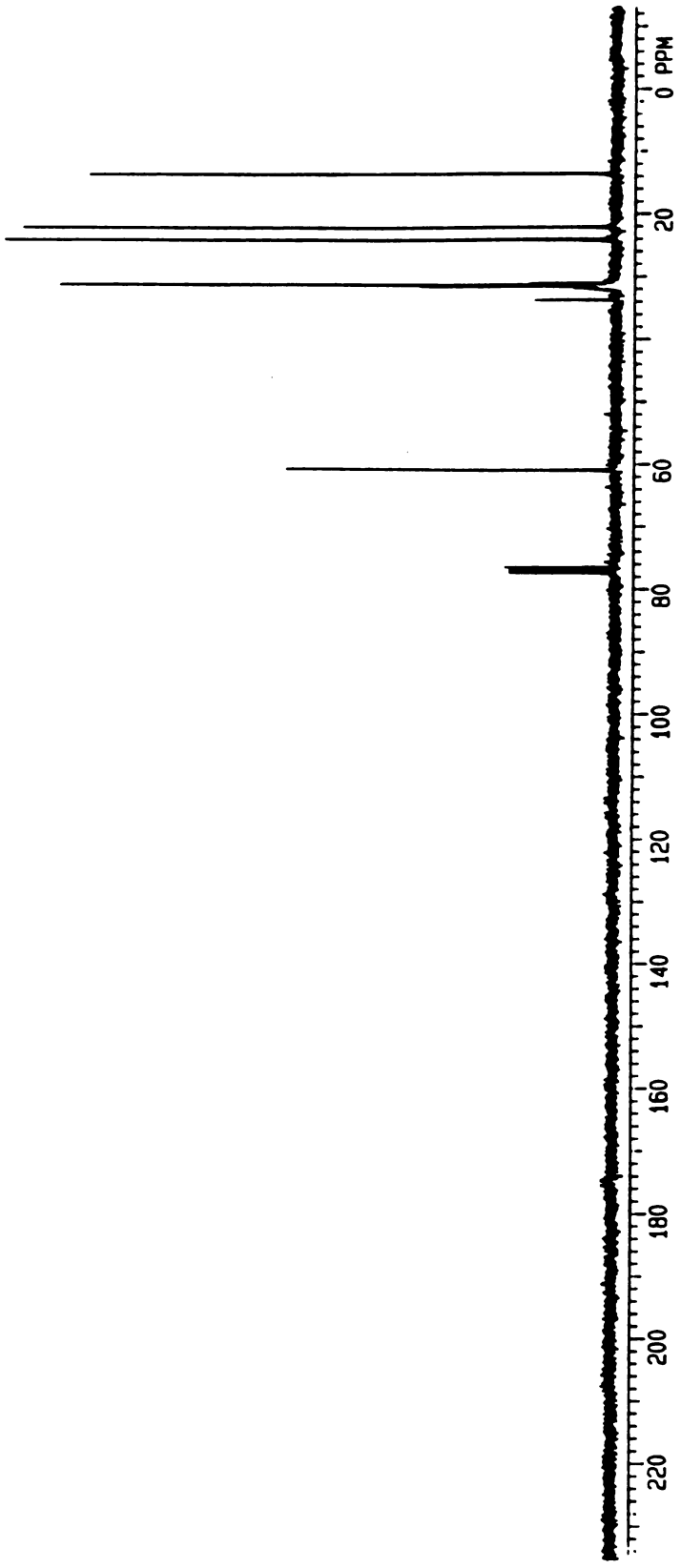


Figure A24: 75.4 MHz ^{13}C-NMR spectrum of N-methoxy-N-methylhexanamide

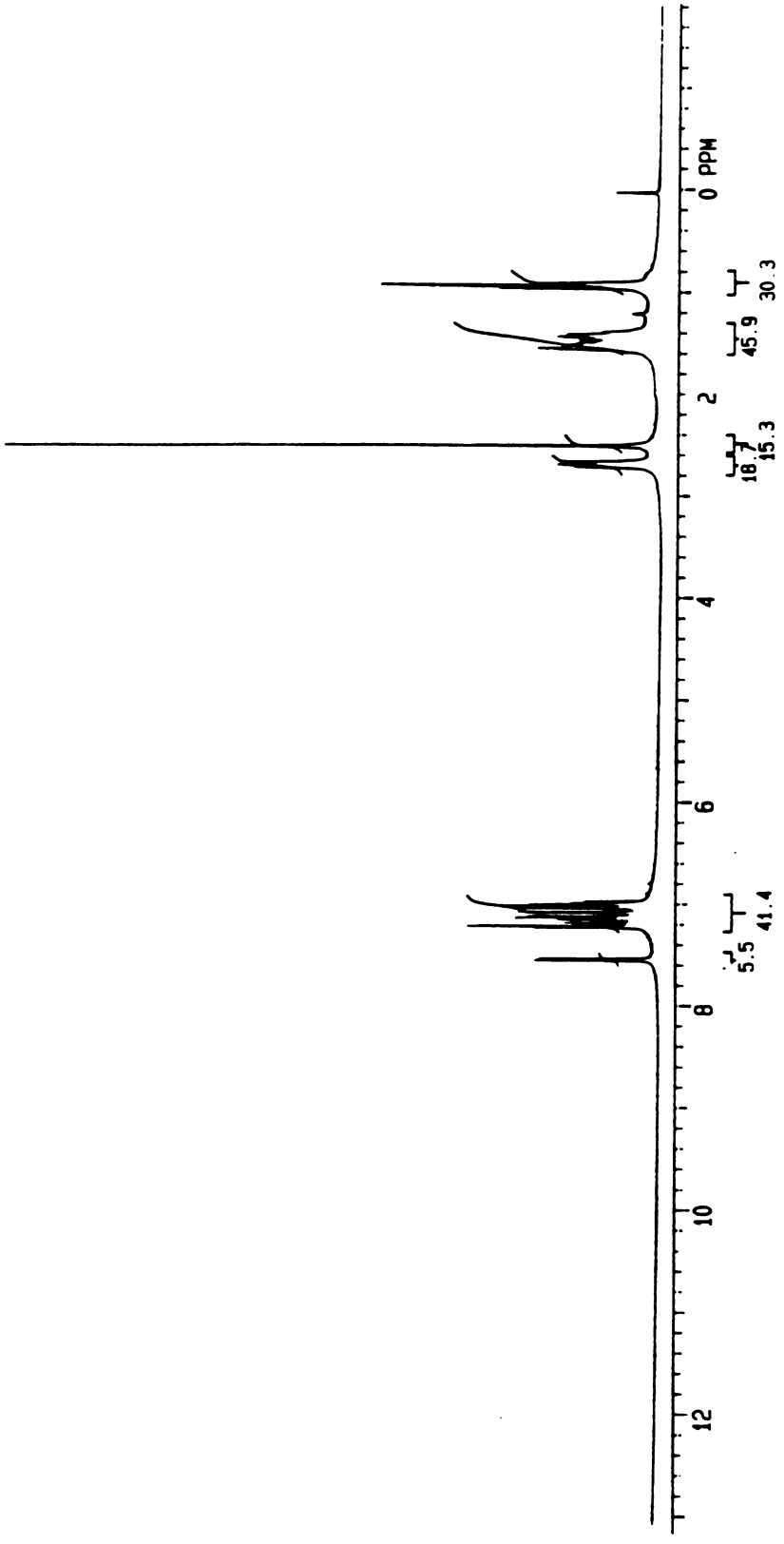


Figure A25: 300 MHz ^{1}H-NMR spectrum of compound **35**

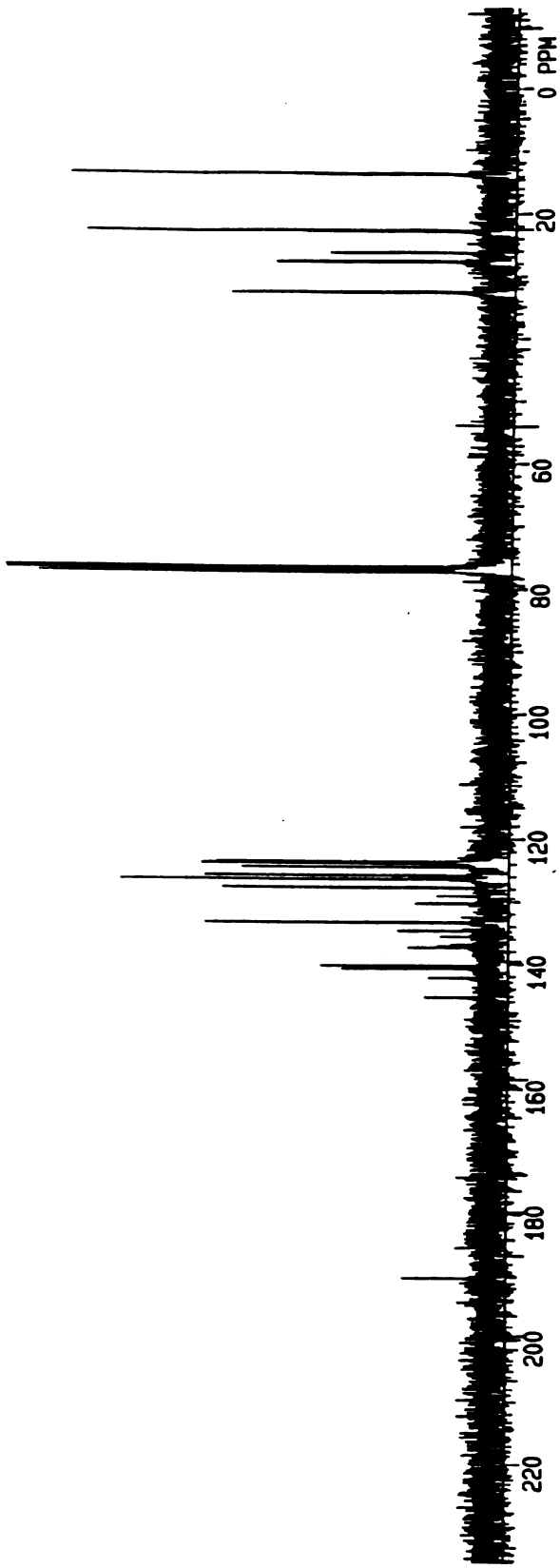


Figure A26: 75.4 MHz ^{13}C-NMR spectrum of compound **35**

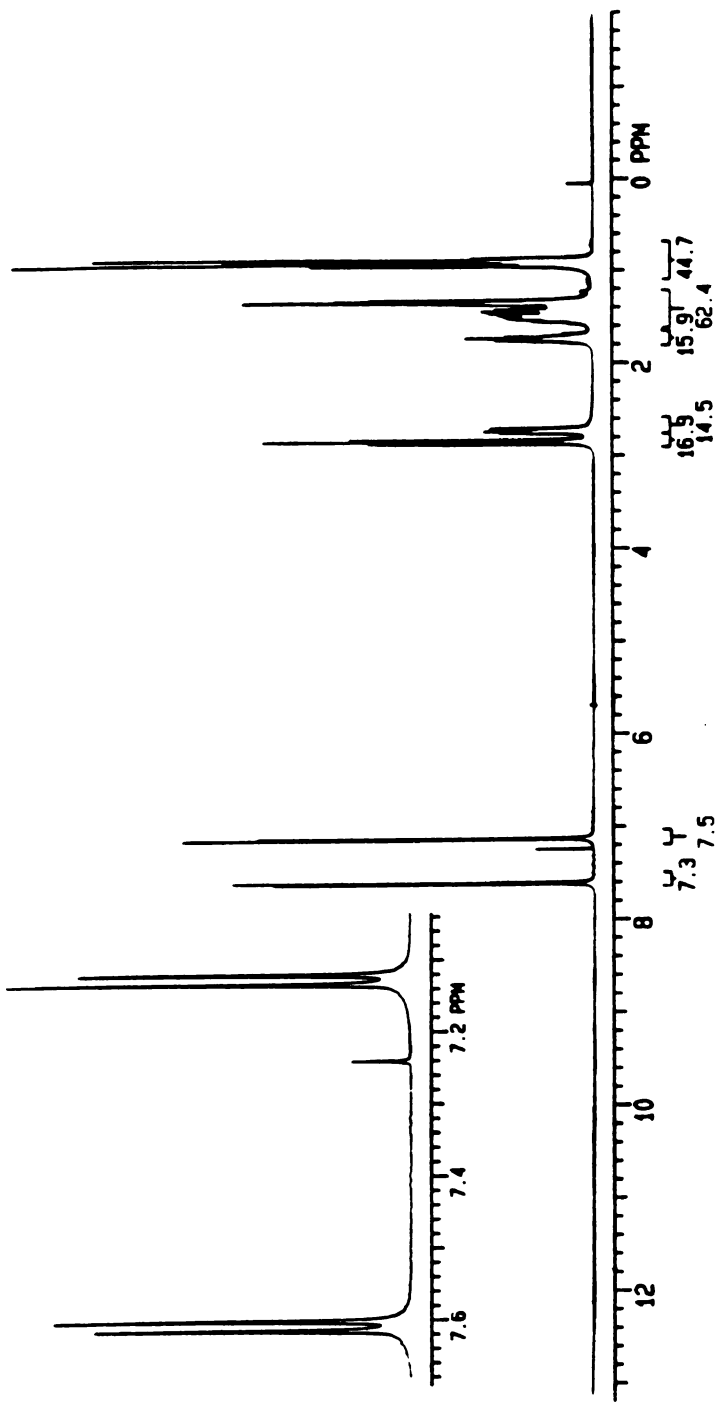


Figure A27: 300 MHz ^{1}H-NMR spectrum of compound **37**

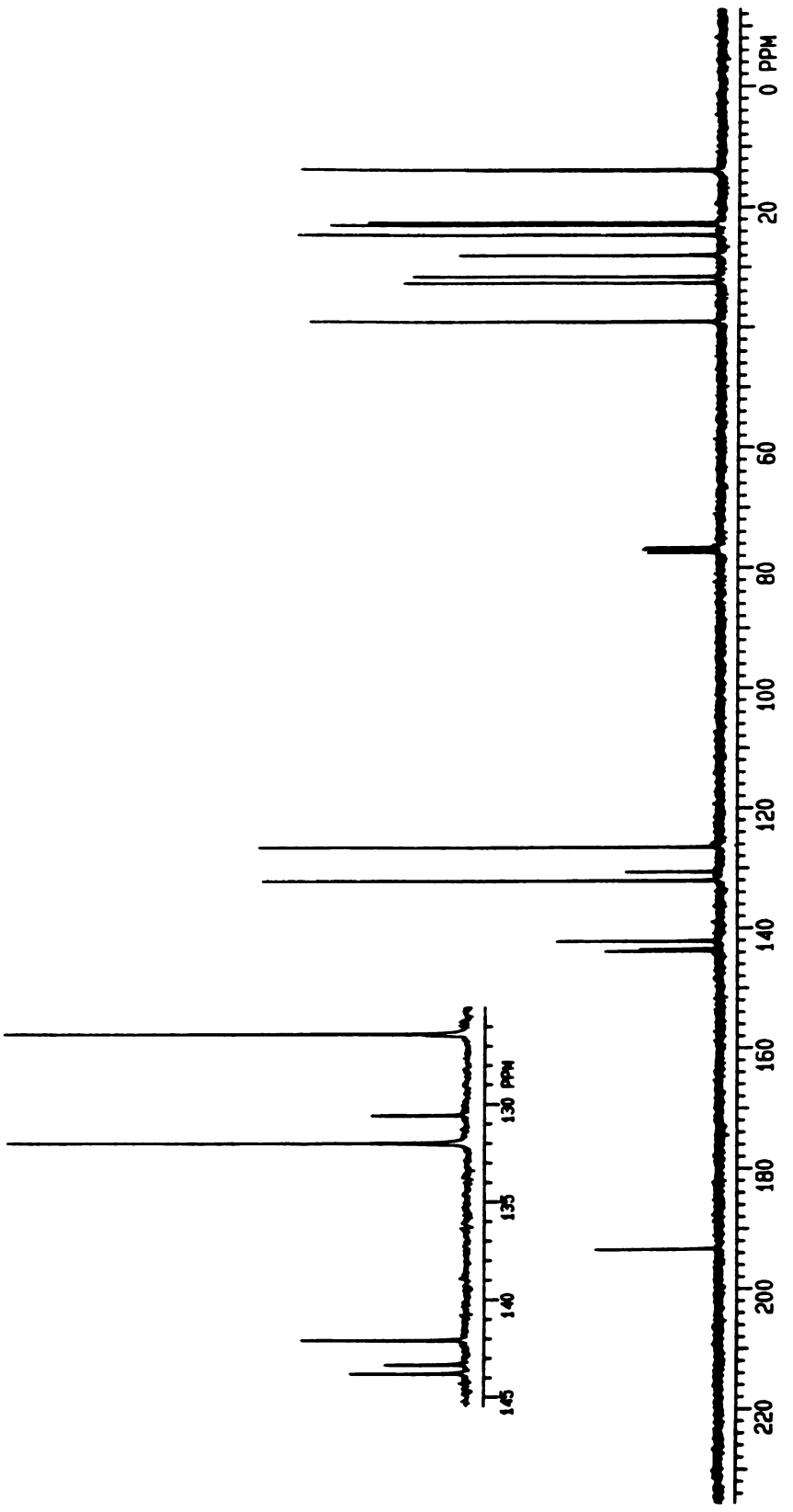


Figure A28: 75.4 MHz ^{13}C-NMR spectrum of compound **37**

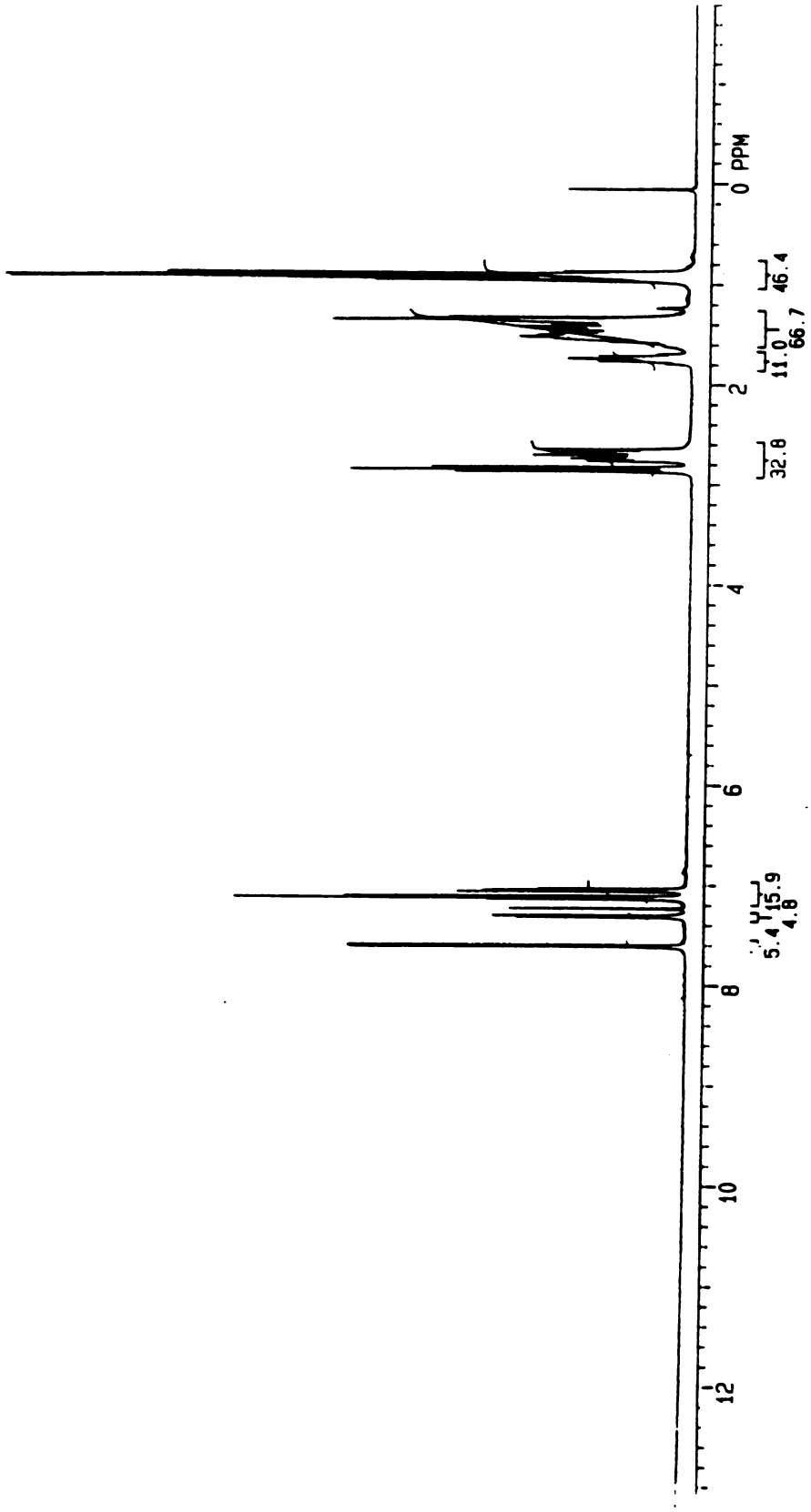


Figure A29: 300 MHz ^{1}H-NMR spectrum of compound **38**

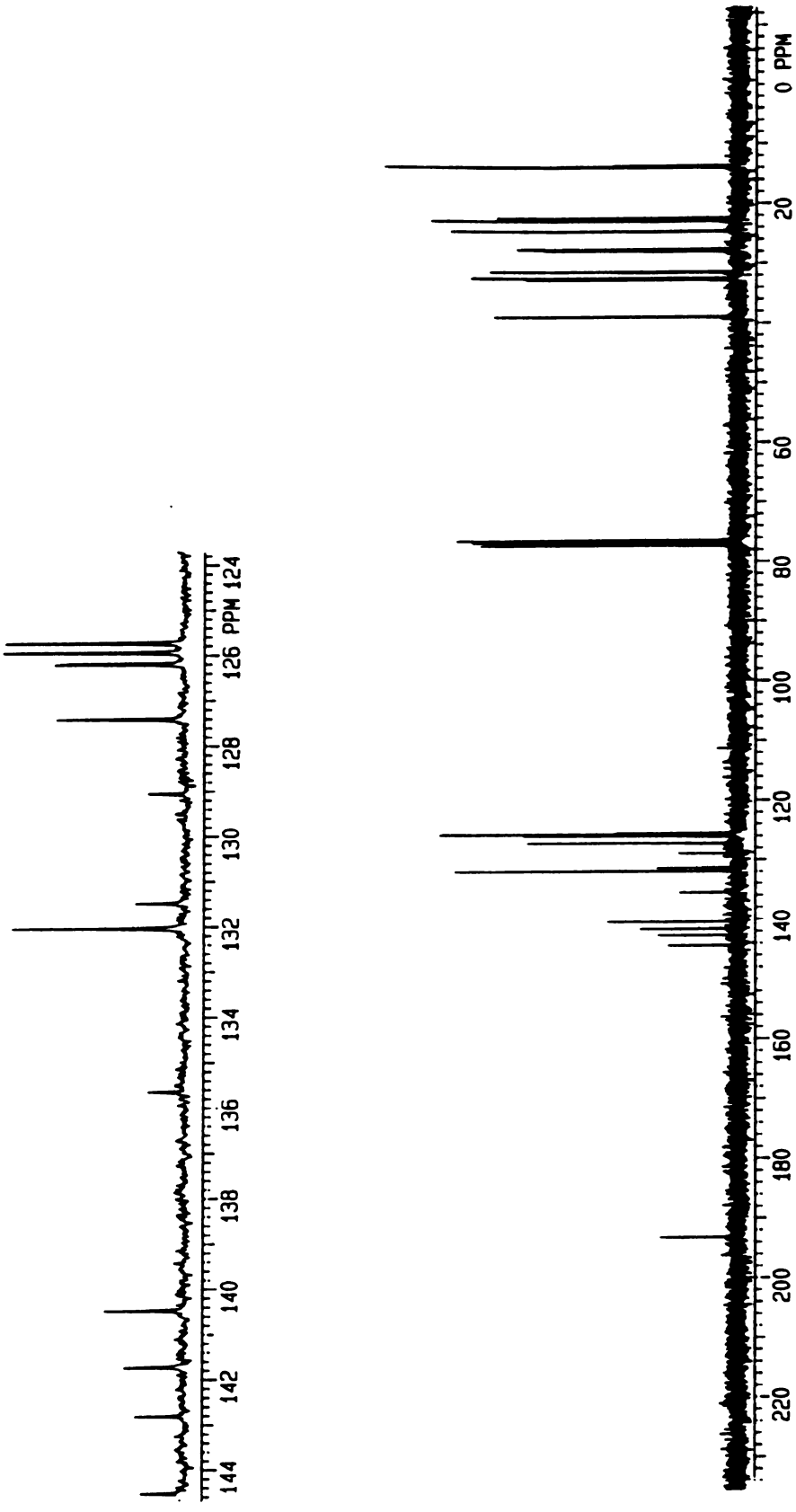


Figure A30: 75.4 MHz ^{13}C-NMR spectrum of compound **38**

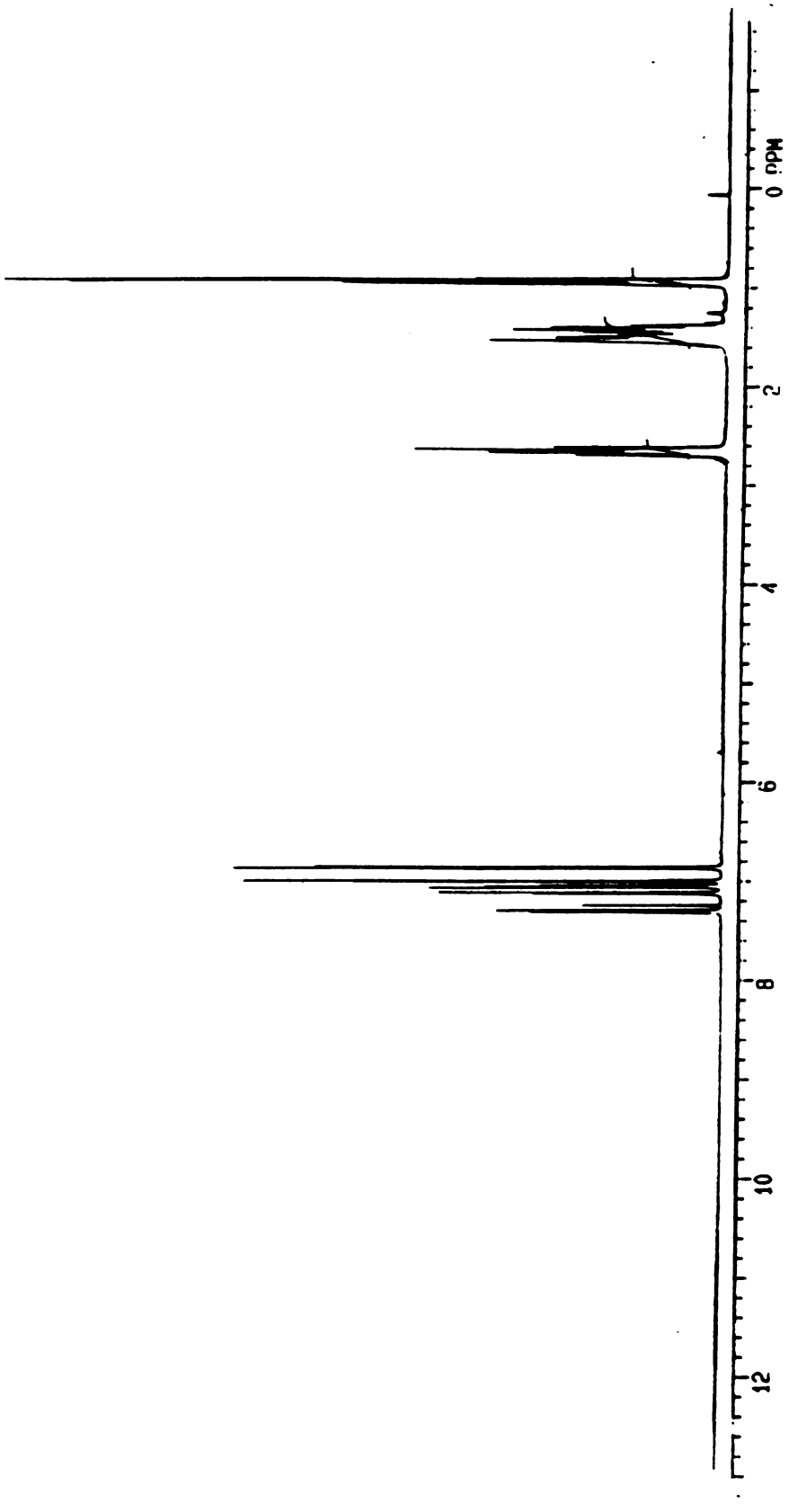


Figure A31: 300 MHz ^{1}H-NMR spectrum of compound **39**

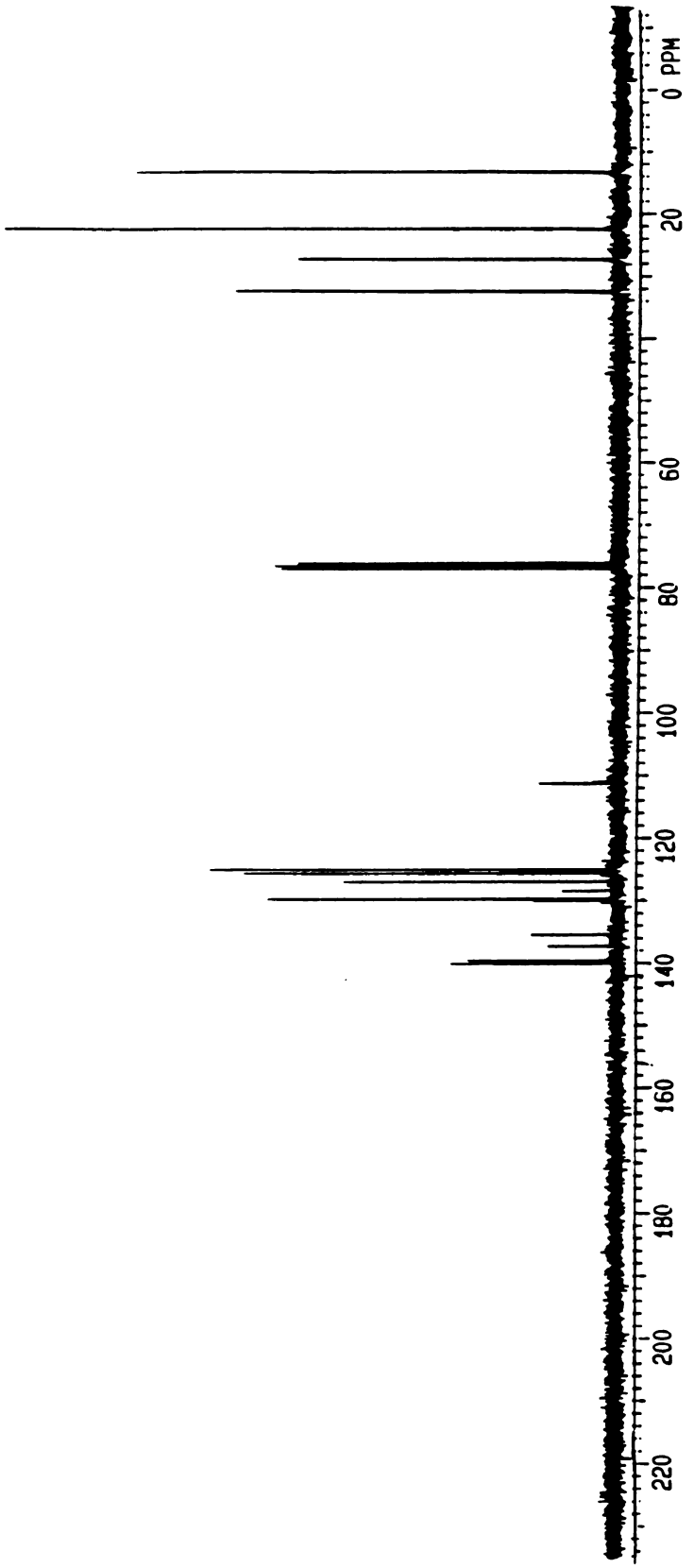


Figure A32: 75.4 MHz ^{13}C-NMR spectrum of compound **39**

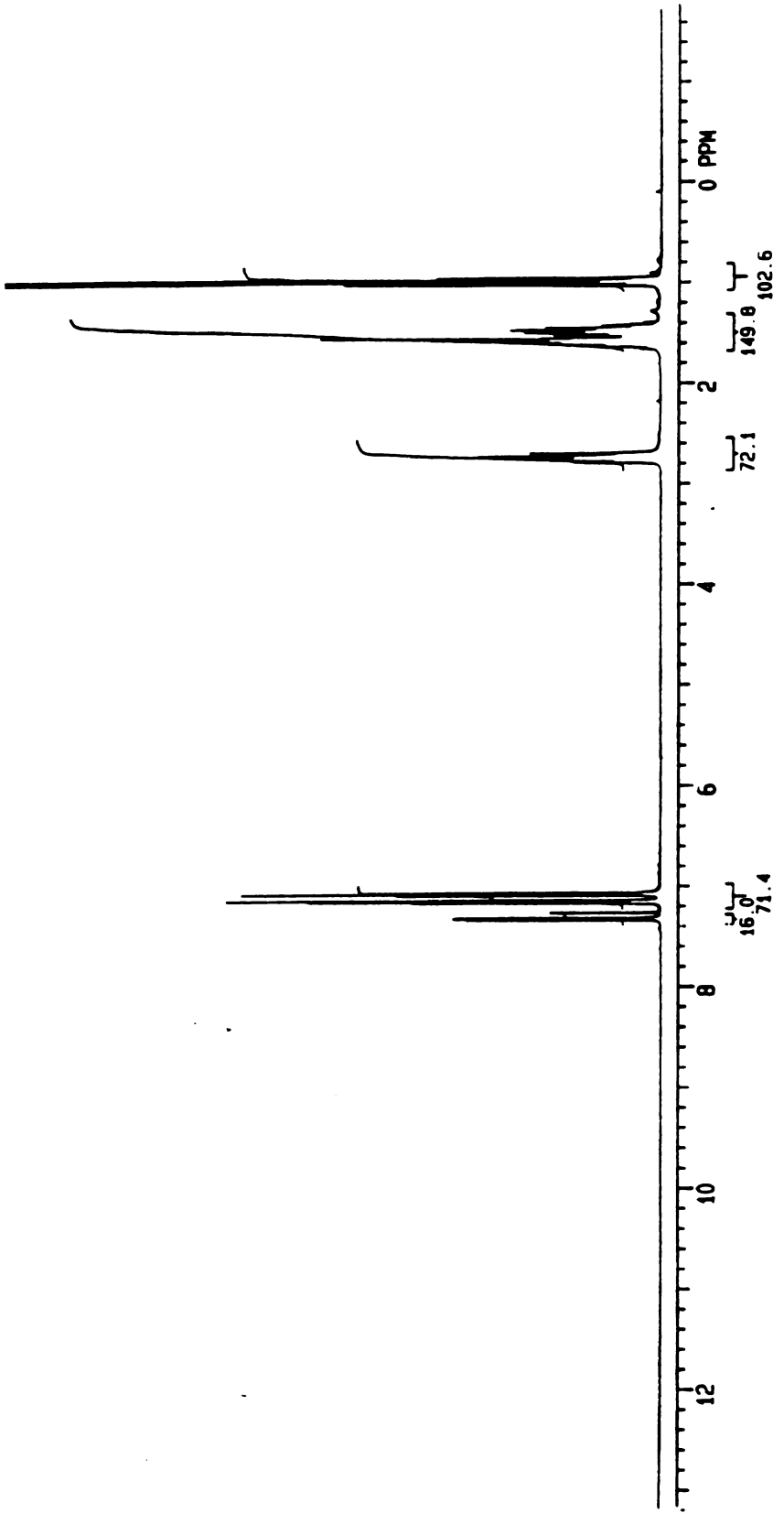


Figure A33: 300 MHz ^{1}H-NMR spectrum of compound 40

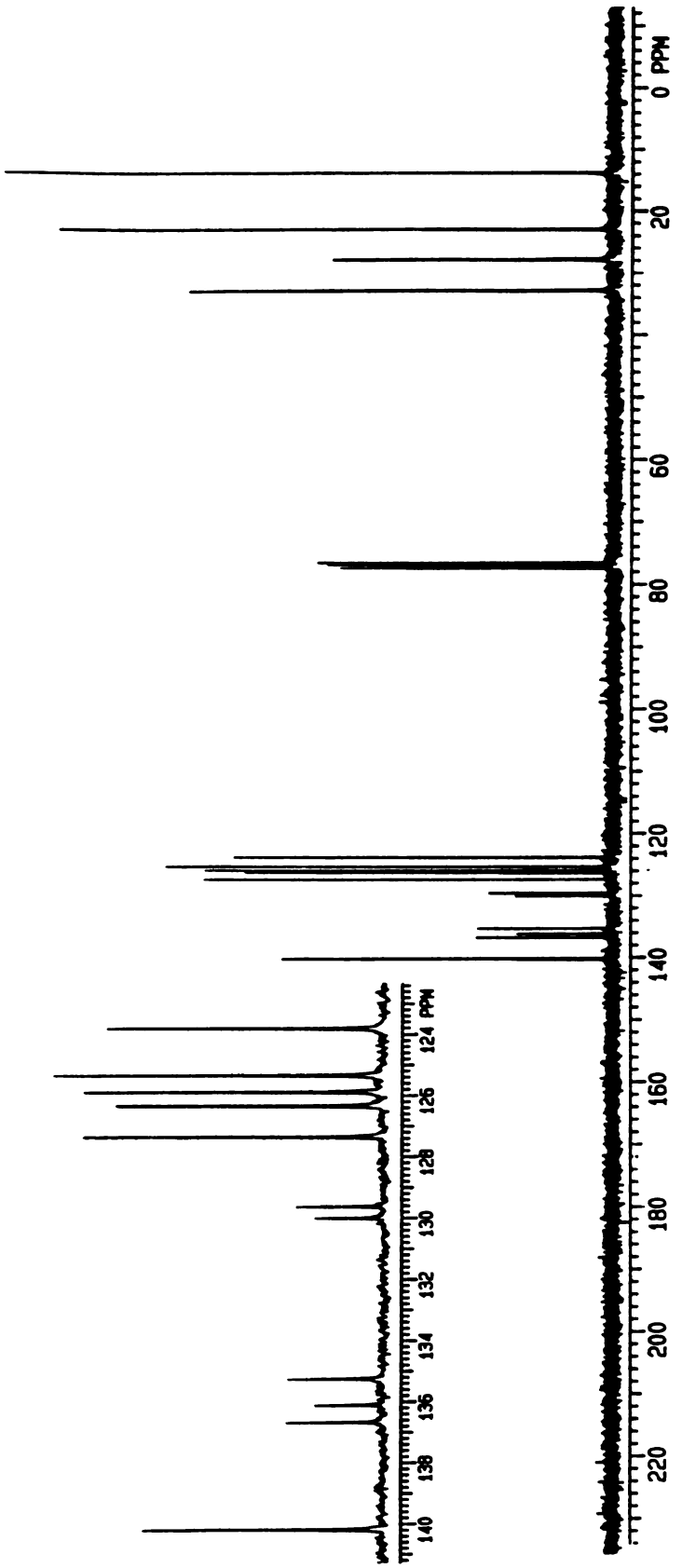


Figure A34: 75.4 MHz ^{13}C-NMR spectrum of compound **40**

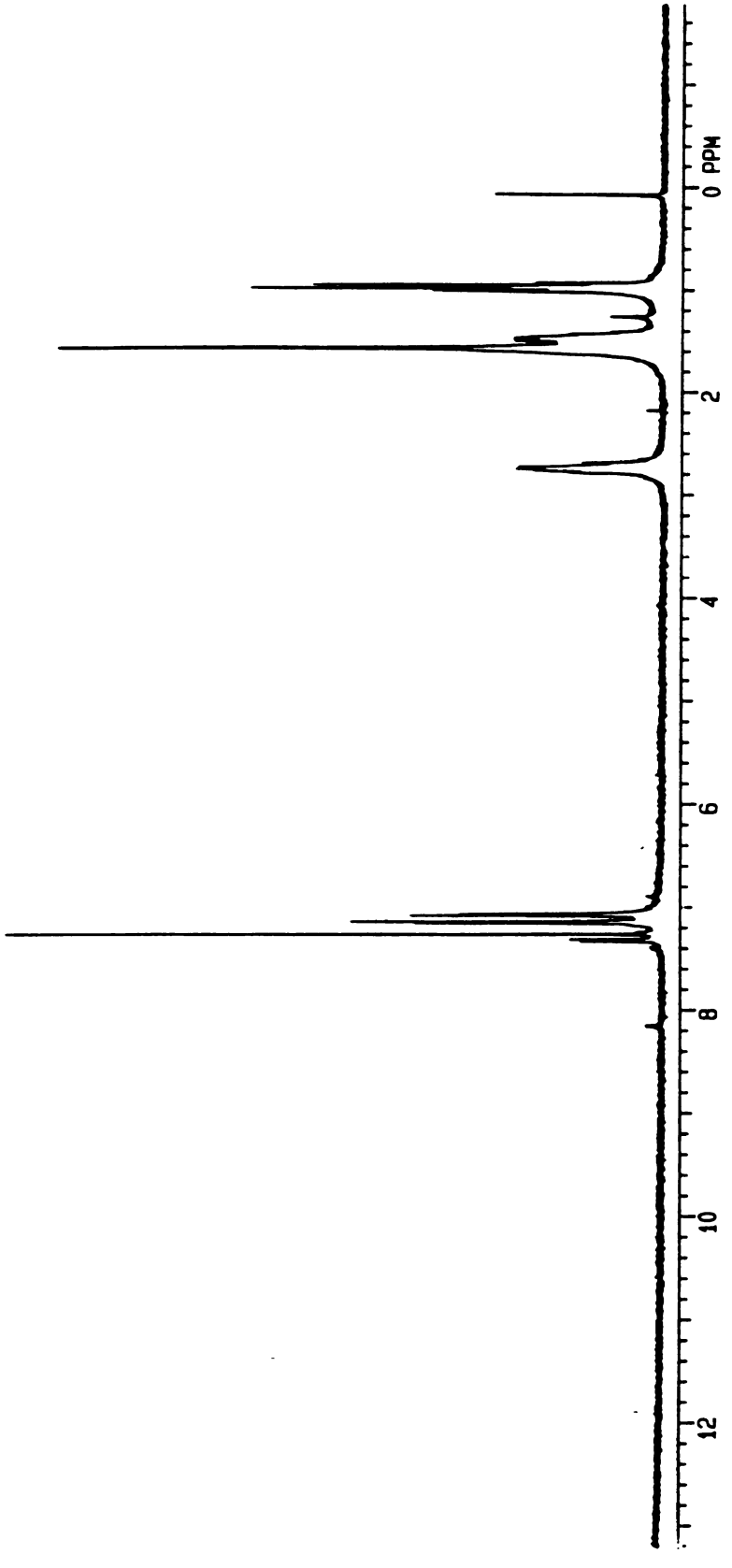


Figure A35: 300 MHz ^{1}H-NMR spectrum of compound **42**

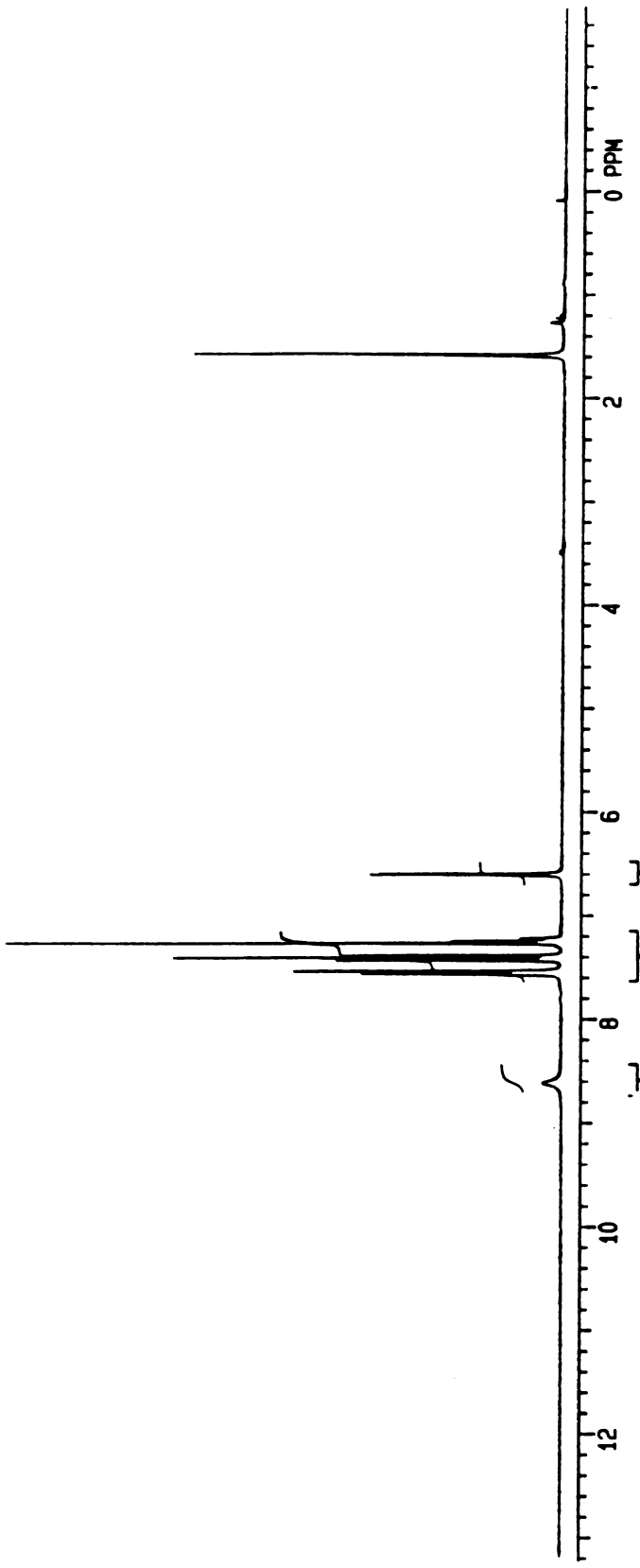


Figure A36: 300 MHz ^{1}H-NMR spectrum of compound **46**

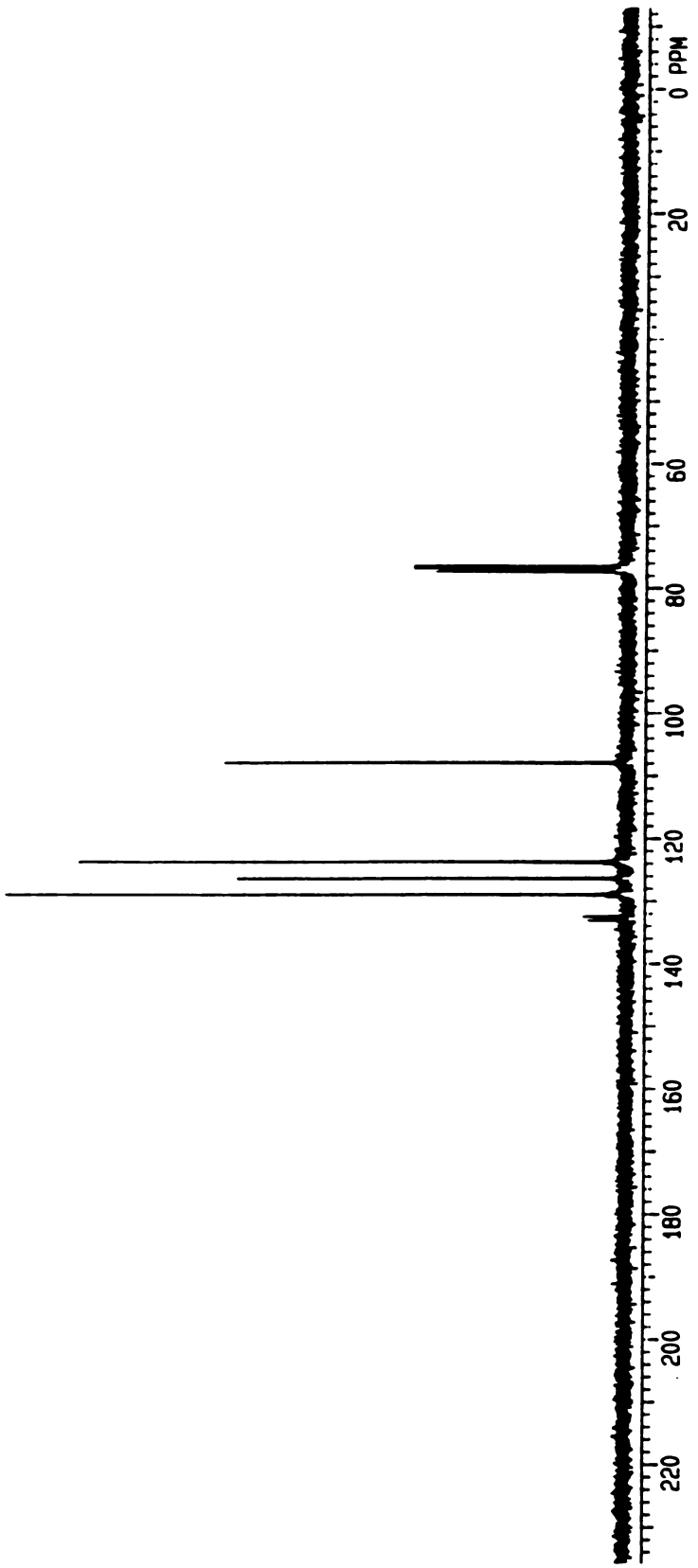


Figure A37: 75.4 MHz ^{13}C-NMR spectrum of compound **46**

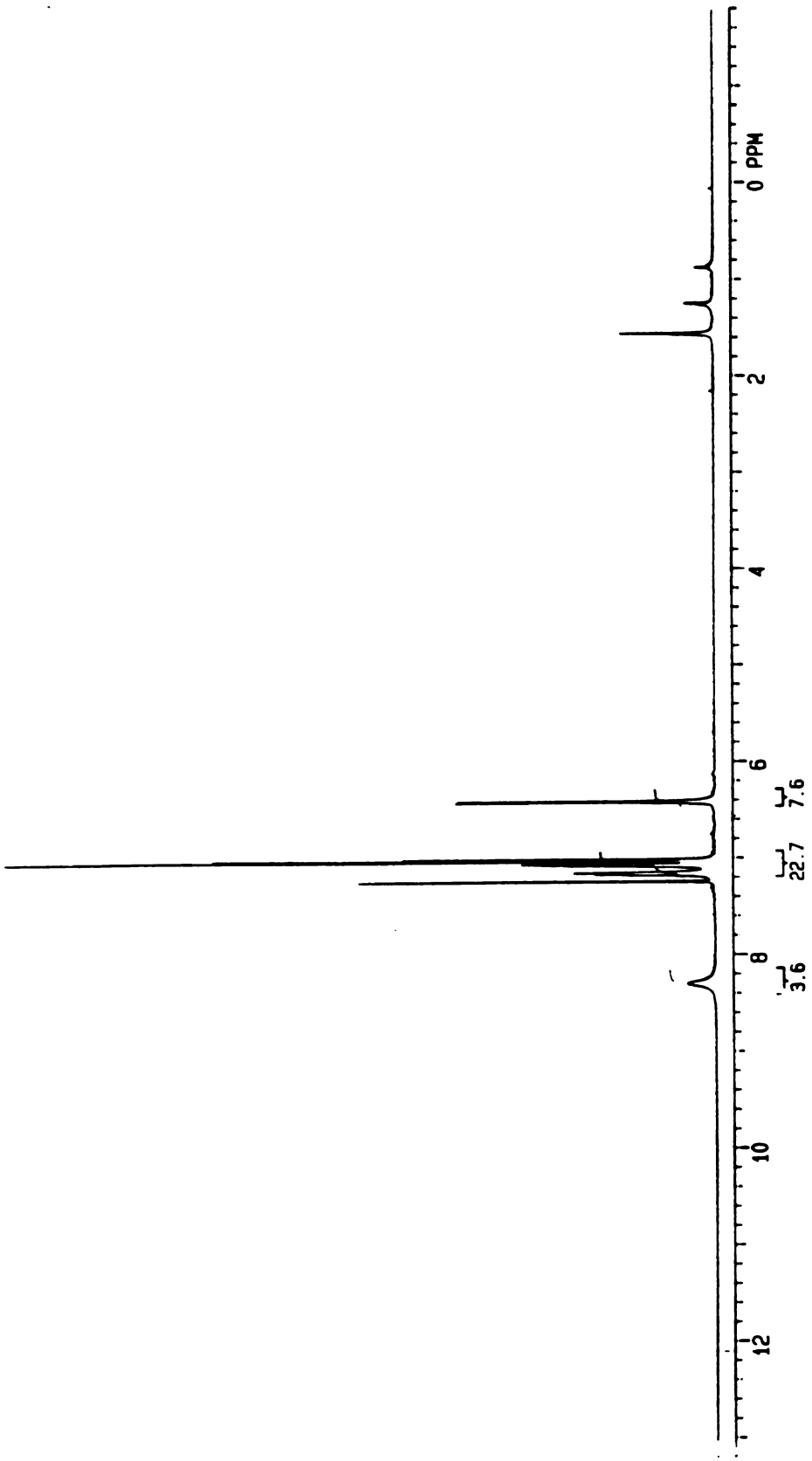


Figure A38: 300 MHz ^{1}H-NMR spectrum of compound **48**

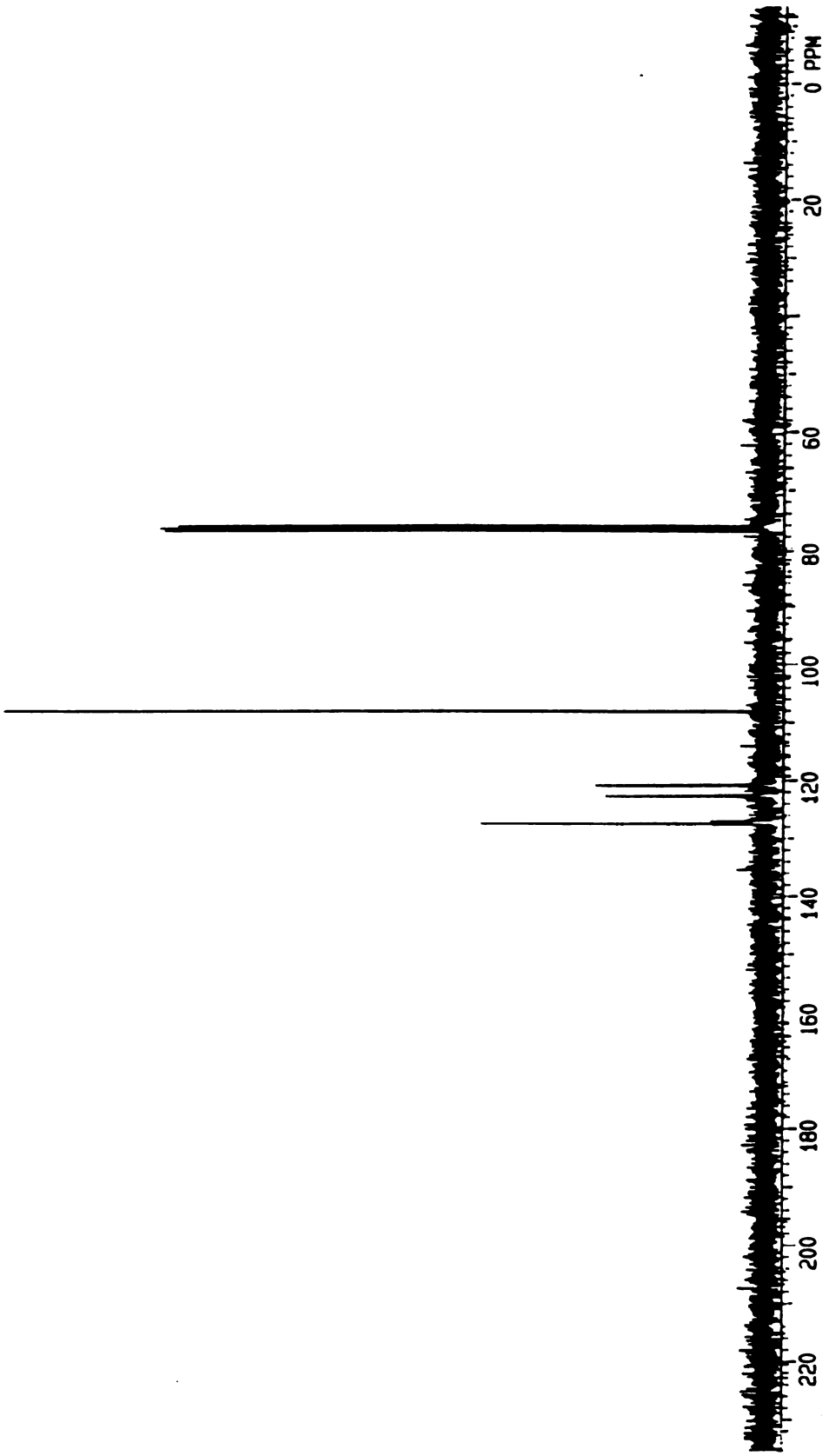


Figure A39: 75.4 MHz ^{13}C-NMR spectrum of compound **48**

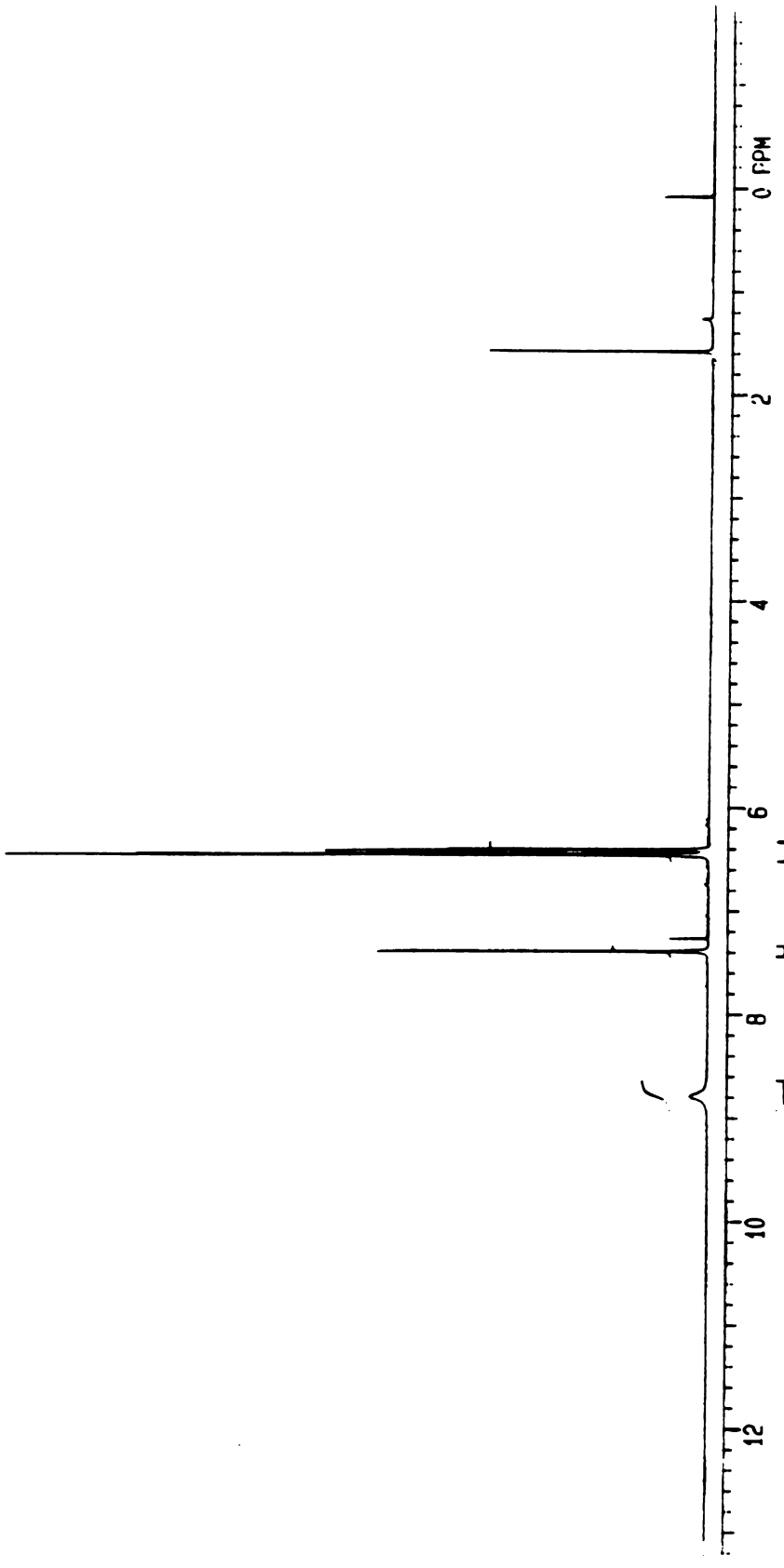


Figure A40: 300 MHz ^{1}H-NMR spectrum of compound **50**

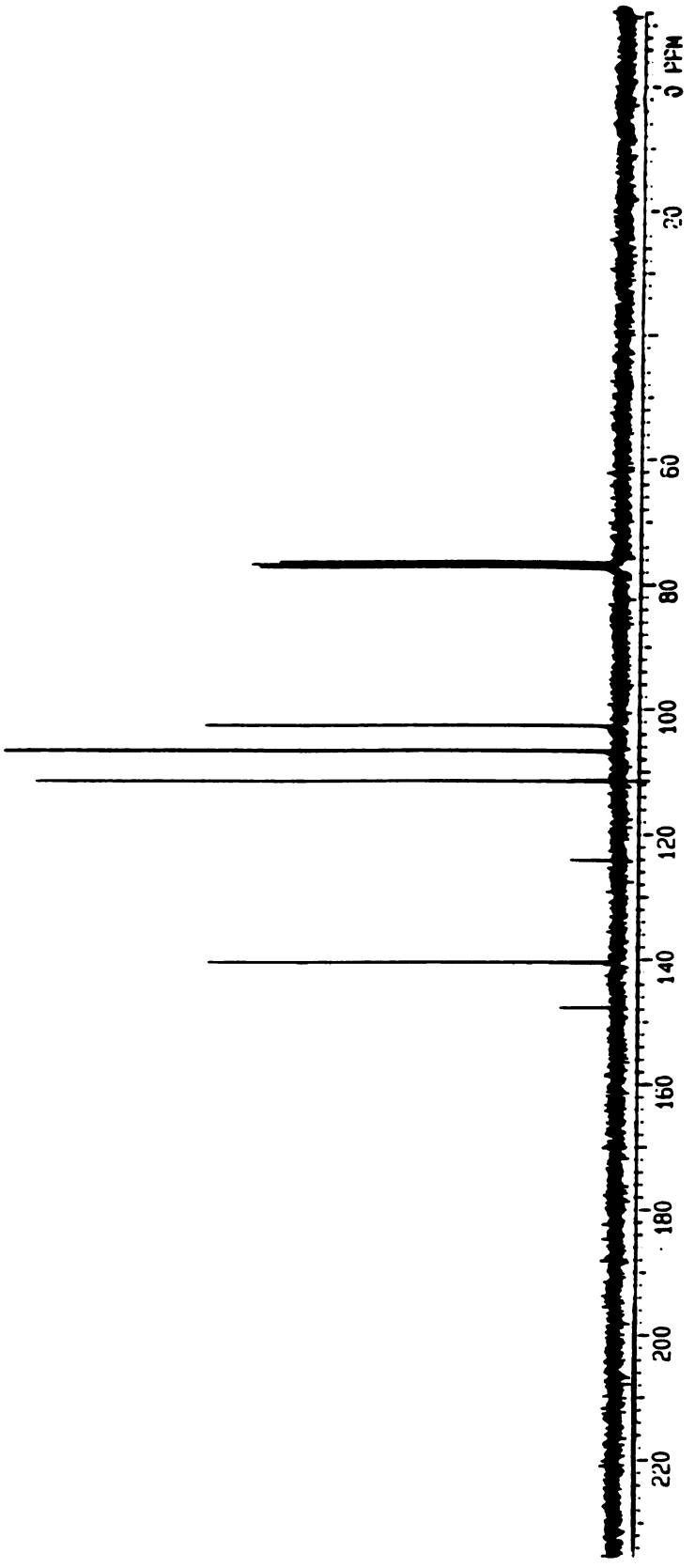


Figure A41: 75.4 MHz ^{13}C-NMR spectrum of compound 50

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