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The intramolecular cyclization of bis-2,5-dimethylene-2,5-dihydrofurans and bis-2,5-dimethylene-2,5-dihydrothiophenes: an approach to macrocycles

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by

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1993

In memory of my father, Nelson William Klumpp

TABLE OF CONTENTS

LIST OF FIGURES

PAPER 2

PAPER 3

LIST OF TABLES

GENERAL INTRODUCTION

Over the past several years, the Trahanovsky research group has been involved with the investigation of reactive organic molecules. The goal of this research has been to explore the properties and chemistry of these reactive species. A considerable amount of work has been done investigating classes of compounds known as *o*-quinodimethanes and *p*-quinodimethanes. These compounds have been of general interest to organic chemists from a theoretic stand point and for their application in synthetic chemistry. Much is known regarding the intermolecular reactions of these compounds, but little is known of possible intramolecular reactions of these compounds. Our purpose has been to explore the intramolecular chemistry of these reactive species.

The first two papers of this dissertation present our work with the intramolecular cyclizations of a pair of *p*-quinodimethanes. The *p*-quinodimethanes were generated by flash vacuum pyrolysis (FVP) and were linked by a bridging chain. The third paper of this dissertation presents our work in the synthetic manipulation of the products formed from the intramolecular reactions of the *p*-quinodimethanes.

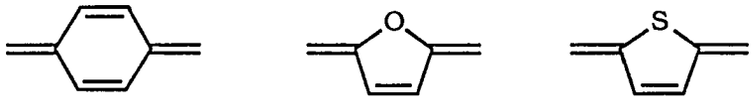
EXPLANATION OF DISSERTATION FORMAT

This dissertation is composed of three separate papers written in the style suitable for publication in the professional journals published by the American Chemical Society. Each paper has its own numbering system, detailed experimental section, reference section, and appendix. A general summary follows the third paper of this dissertation.

PAPER 1. THE INTRAMOLECULAR CYCLIZATION OF BIS-2,5-DIMETHYLENE-2,5-DIHYDROFURANS: AN APPROACH TO MACROCYCLES

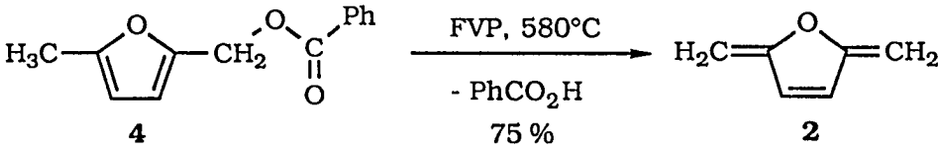
INTRODUCTION

The *p*-quinodimethanes form an important class of reactive molecules that has been of considerable interest in recent years. These reactive molecules have been exploited as monomers in polymerization reactions,[1] have been used in organic synthesis,[2] and are thought to be primary products in coal pyrolysis.[3] Representative *p*-quinomethanes include: *p*-xylylene (**1**), 2,5-dimethylene-2,5-dihydrofuran (**2**), and 2,5-dimethylene-2,5-dihydrothiophene (**3**).

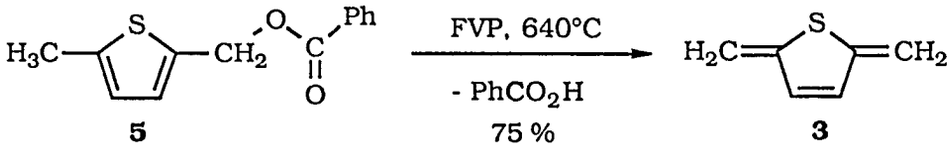


1 **2** **3**

The *p*-quinodimethanes have been prepared by various routes including Hoffman elimination,[4] fluoride-induced 1,6-elimination,[5] and others.[6] Compounds **2** and **3** may also be prepared in good yield by the flash vacuum pyrolysis (FVP) of **4** and **5**, respectively.[7] The transformations below most likely occur by a three-step mechanism. The benzoate group undergoes a pair of reversible [3,3] sigmatropic bond shifts followed

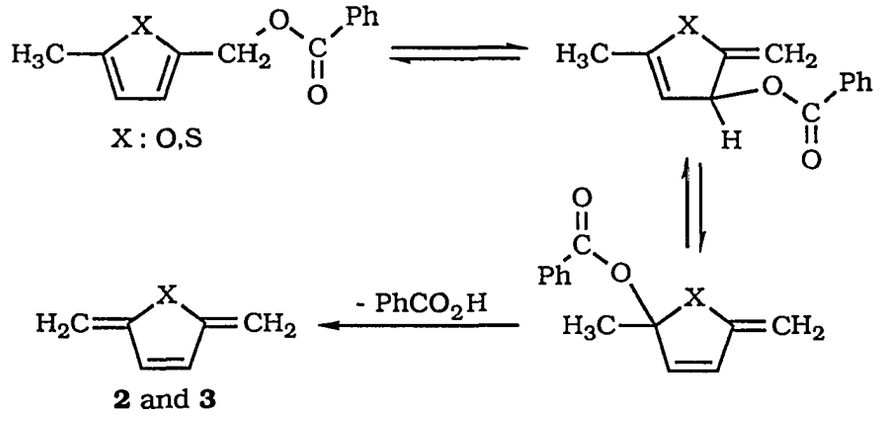


4 **2** (1)



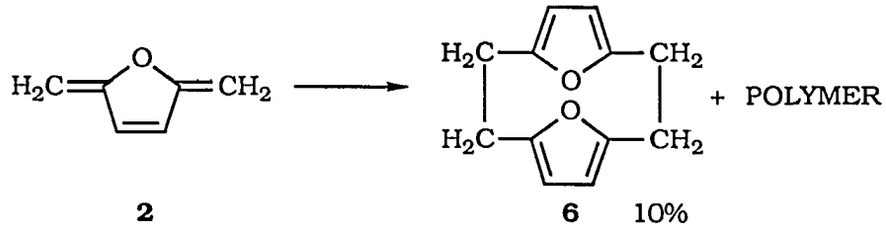
5 **3** (2)

Scheme I



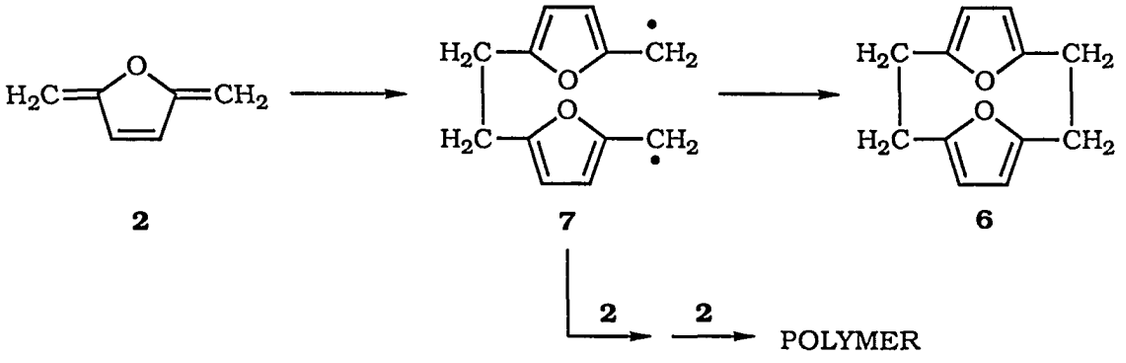
by irreversible elimination of benzoic acid by β-hydrogen abstraction to produce *p*-quinodimethanes **2** and **3**.[7] Although FVP of **4** and **5** provides good yields of the furan-based and thiophene-based *p*-quinodimethanes (eqs 2 and 3), the FVP of *p*-methylbenzyl benzoate gives only minor amounts of the benzene-based *p*-quinodimethane (**1**).[8]

The *p*-quinodimethanes are relatively reactive molecules, and when in solution these molecules slowly form dimers, trimers, and polymers. For example, compound **2** is known to fully react within 4 hr at 110 °C in solution.[5] In the absence of radical-chain inhibitors, reaction of **2** yields about 10% dimer (**6**) and the remaining



material balance is polymer. Addition of a radical-chain inhibitor increases yield of dimer (**6**) to 73% from the starting material.[4a]

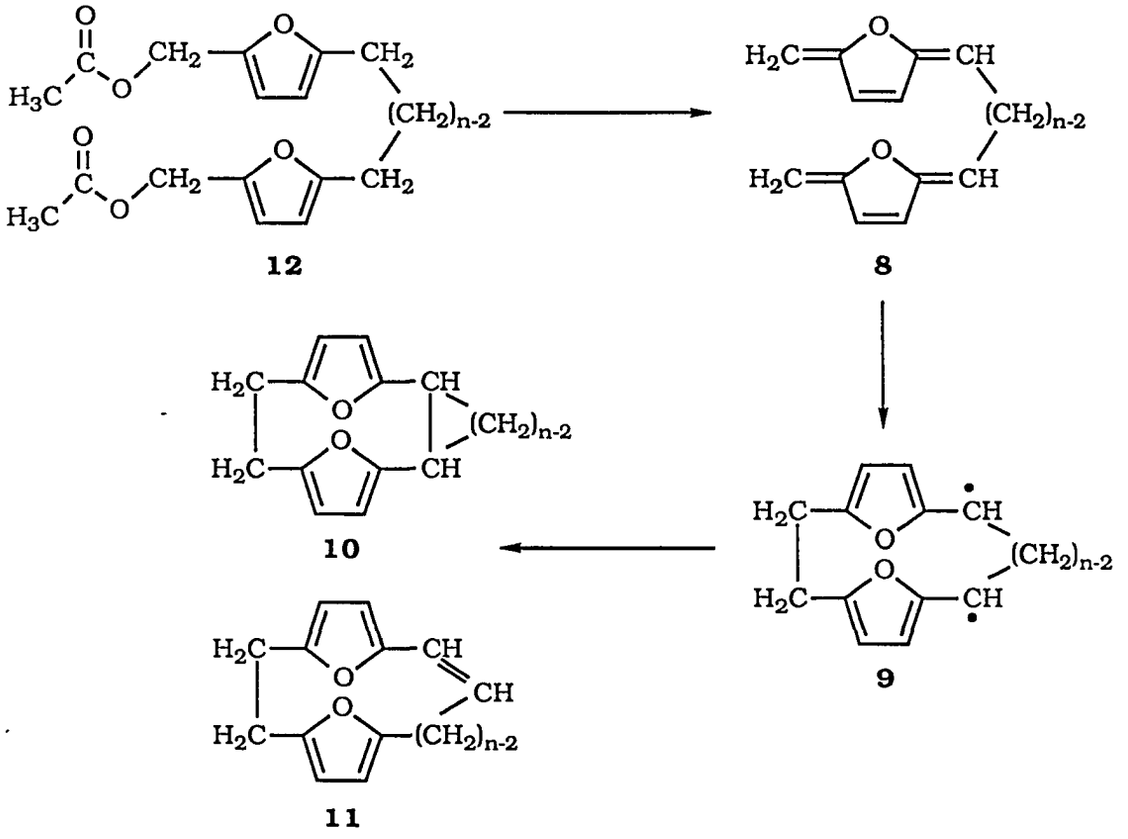
It has been proposed that the reactions of the *p*-quinodimethanes proceed through diradical intermediates enroute to the dimers, trimers, and polymers.[9] For example, compound **2** would dimerize to give diradical **7**. Closure of diradical **7** gives the dimer [2.2](2,5)furanophane (**6**), while further reaction of **7** with **2** results in polymer. Although the existence of diradical intermediates has yet to be



rigorously established in the reactions of *p*-quinodimethanes, the closely related *o*-quinodimethanes have been studied more thoroughly and been found to dimerize through diradicals.[10]

Based on the chemistry of the *p*-quinodimethanes, we postulated that an intramolecular reaction of two *p*-quinodimethanes would be possible if the two *p*-quinodimethanes were linked by an alkyl chain or other suitable bridging unit. Thus for *p*-quinodimethane **2**, we proposed that bis-2,5-dimethylene-2,5-dihydrofuran **8** (Scheme II) would cyclize to form diradical **9** and that this cyclic diradical would undergo intramolecular radical coupling to form the ring-fused cyclophane **10** or intramolecular radical disproportionation to form macrocycle **11**. It also seemed likely to us that the bis-2,5-dimethylene-2,5-dihydrofuran **8** could be conveniently prepared by the FVP of the bis-furfuryl acetate **12**, since the furfuryl esters are known to be effective precursors

Scheme II



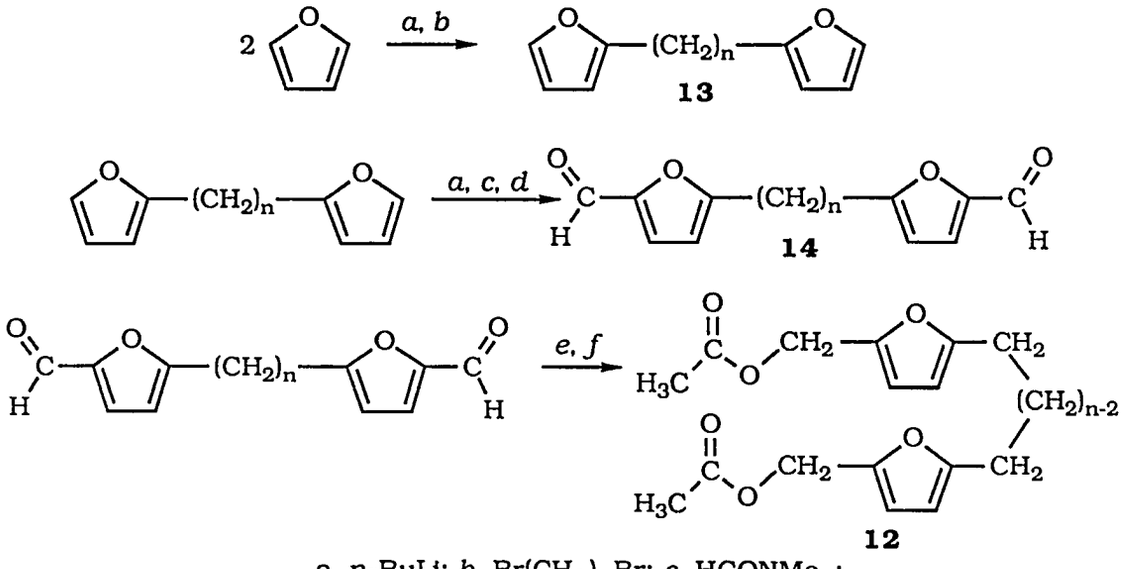
of the furan-based *p*-quinodimethane.[7] Furthermore, acetate groups were deemed best for the bis-furfuryl ester because benzoate groups would greatly reduce the volatility of the bis-furfuryl ester which could cause problems in the FVP experiments. In this chapter, our results from the experiments involving the synthesis and FVP of compounds of general structure **12** are presented and discussed.

RESULTS

Preparation of the α,ω-Di(2-acetoxymethyl-furyl-5)alkanes (12)

The preparation of compounds of general structure **12** was accomplished in four steps as outlined in Scheme III. In the first step, the furyl anion was generated by reacting furan with *n*-BuLi in THF/HMPA and addition of a α,ω-dibromoalkane gave the α,ω-difurylalkane (**13**).[11] For the α,ω-dibromoalkanes of n = 3 to 16, this reaction

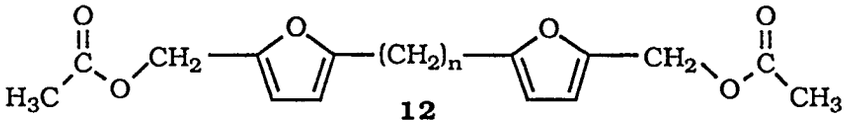
Scheme III



a, n-BuLi; *b*, $Br(CH_2)_nBr$; *c*, $HCONMe_2$;
d, H_2O; *e*, $LiAlH_4$; *f*, Et_3N, CH_3COCl

proceeded in good yields (70-90%). Next, the furan rings were formylated by reaction with *n*-BuLi , DMF, and then water.[12] Formylation provided compounds of general structure **14** in moderate yields (50-80%). Finally, compound **14** was reduced to the diol and acylated to give the bis-furfuryl acetate **12**.[13] The combined steps of reduction and acylation were nearly quantitative in all cases. The above series of reactions allowed

gram quantities of **12** to be prepared for FVP experiments. Compounds **12a** to **12g** were all prepared according to the route described above.



12

a: n = 3; **b**: n = 4; **c**: n = 5; **d**: n = 6;
e: n = 7; **f**: n = 12; **g**: n = 16

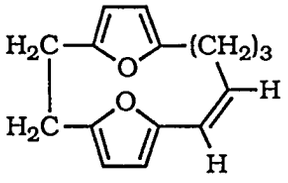
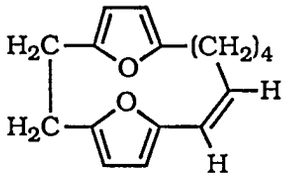
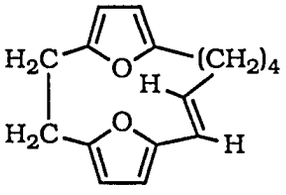
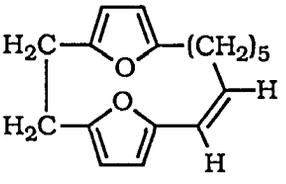
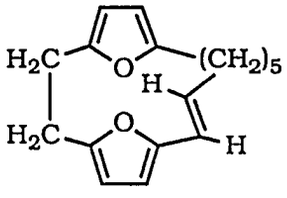
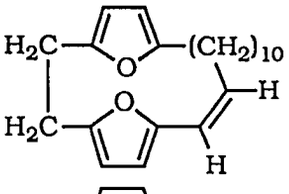
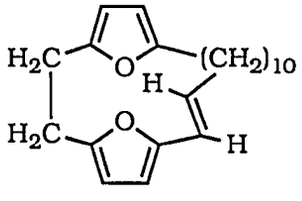
Flash vacuum pyrolysis of α,ω-di(2-acetoxymethyl-furyl-5)alkanes 12a to 12g

Compounds **12a** to **12g** were pyrolysed using a FVP apparatus and methods previously described.[14] FVP experiments were conducted with the apparatus evacuated to about 10^{-5} torr and the hot zone at 580°C . To effect transfer of the starting material through the hot zone, the samples required some heating to effect volatilization of the starting material. Typically, 10 to 100 mg of starting material was pyrolysed. The products of the FVP were condensed in a liquid N_2 cooled trap and isolated using flash chromatography.

FVP of compounds **12c** to **12f** provided reasonably good yields of the macrocyclic alkenes **11c** to **11f** (Table I). FVP of compounds **12a**, **12b**, and **12g** gave unexpected products which will be described below.

As shown in Table I, FVP of **12c** gave the macrocyclic olefin **11c (cis)** in 46% yield. The double bond of **11c (cis)** was established to be the cis conformation on the basis of the coupling constant (J = 11.60 Hz) of the olefinic hydrogens. By comparing the ^{1}H NMR spectrum of the crude product mixture (Figure 1) and the spectrum of the purified **11c (cis)** (Figure 2), it can be seen that **11c (cis)** was the major product of the

Table I. Macrocyclic Pyrolysis Products from 12c to 12f

starting material	product	structure	yield[a], %
12c	**11c (cis)**		46
12d	**11d (cis)**		47
	11d (trans)		11
12e	**11e (cis)**		22
	11e (trans)		17
12f	**11f (cis)**		4
	11f (trans)		19

[a] Absolute yields were determined by GC analysis using an internal standard (phenyl ether); the GC response factor was determined for **11c (cis)** and used for all products.

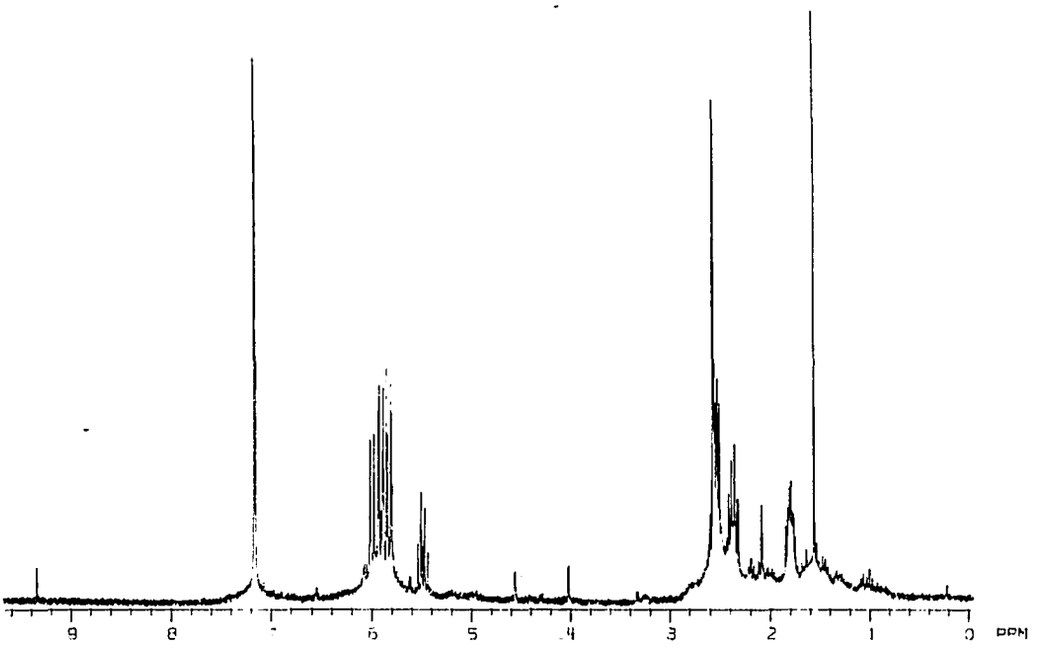


Figure 1. ^{1}H NMR spectrum of crude pyrolysis products from **12c**

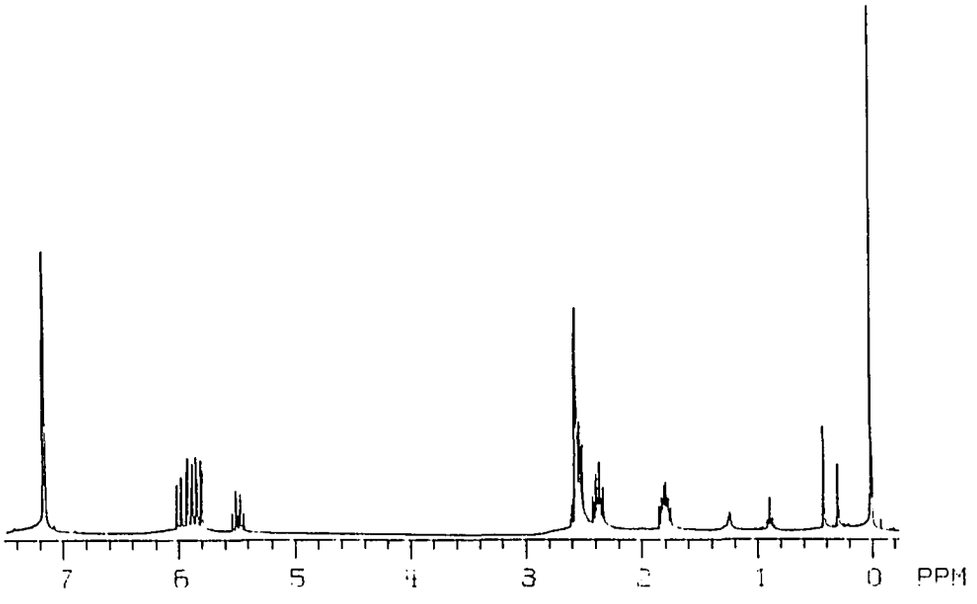
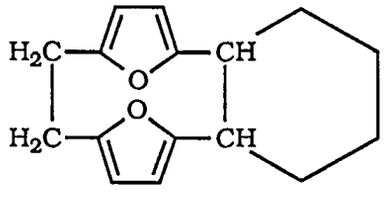


Figure 2. ^{1}H NMR spectrum of macrocyclic product **11c (cis)**

FVP of **12c.** The remaining material balance from this conversion was unreacted starting material, polymeric film in the FVP apparatus, and char in the hot zone of the FVP apparatus.

When diacetate **12d** was pyrolyzed, **11d (cis)** was formed in 47% yield, while **11d (trans)** was formed in 11% yield. Again, the stereochemistry of the double bond was established by the olefinic hydrogen coupling constants in products **11d (cis)** and **11d (trans).** In addition to the macrocyclic products, product **10d** was also isolated. The ring-fused cyclophane **10d** was formed in 4% yield from FVP of **12d.** Spectroscopic data and GC analysis confirmed that **10d** was isolated as a single stereoisomer, however the stereochemistry of the ring junction could not be definitively assigned.



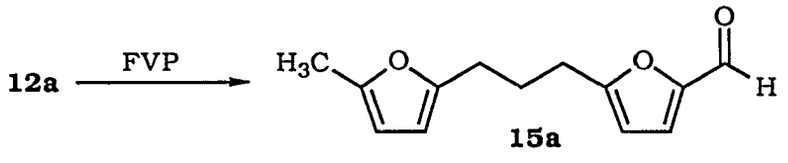
10d

Pyrolysis of the bis-furfuryl acetate **12e** generated the macrocyclic products **11e (cis)** and **11e (trans)** as the major products. The cis isomer was produced in 22% yield and the trans isomer was produced in 17% yield. The double bond stereochemistry of **11e (cis)** could was assigned by examination of the olefinic hydrogen coupling constant. Data from the ^{13}C NMR spectra, high-resolution mass spectra, and IR spectra are also consistent with the structures **11e (cis)** and **11e (trans).**

FVP of bis-furfuryl acetate **12f** also produced macrocyclic products. Although formed in just 19% yield, macrocycle **11f (trans)** was isolated from the FVP of **12f** (Table I). This product contains a macrocyclic ring of 22 carbons. Again, the analytical

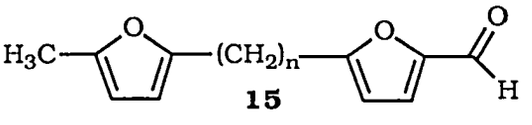
data are consistant with the structure of **11f (trans)**. Product **11f (cis)** was also obtained, but only in 4% yield. The low yield of **11f (cis)** allowed only partial characterization of this product. The ^1H NMR and low-resolution mass spectra support the structure proposed for **11f (cis)**. When **12f** was pyrolyzed, a significant amount of the starting material decomposed in the sample head, formed polymeric deposits within the FVP apparatus, and produced char in the hot zone. These undesirable by-products were produced in greater quantities from **12f** than from **12c** to **12e**.

Pyrolysis of bis-furfuryl acetates **12a**, **12b**, and **12g** gave little or no macrocyclic product **11**. FVP of **12a** gave the unexpected product **15a** in 33% yield as the only



15a

major product. The structure assignment of **15a** was made on the basis of ^1H NMR (1-D and COSY), ^{13}C NMR, IR, and mass spectra. Examination of the crude product mixtures from FVP of bis-furfuryl acetates **12b** to **12f** revealed that a similar product was formed in low yield in all cases. FVP pyrolysis of **12b** to **12f** gave the products **15b**

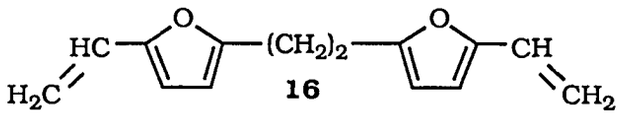


15

a: n = 3; **b**: n = 4; **c**: n = 5; **d**: n = 6;
e: n = 7; **f**: n = 12

to **15f** in less than 2% yield. The low yields of products **15b** to **15f** did not allow full characterization of these products, but their identity was inferred by mass spectral and

^{1}H NMR analysis of the crude FVP product mixtures. When **12b** was pyrolysed, the



16

most abundant product was isolated and identified as the vinyl-substituted product **16**. This product was formed in 10% yield and the structure was assigned based on the ^{1}H NMR, ^{13}C NMR, IR, and high resolution mass spectra. The bis-furfuryl acetate **12g** was also pyrolysed, however no products could be identified or isolated. It appeared that only polymerization and undesirable decomposition reactions were the result when **12g** was pyrolysed.

Estimation of the thermodynamic ratio of macrocycles 11e (cis) and 11e (trans)

Examination of Table I reveals that the macrocyclic products were formed with a preference for the cis double bond for product **11c** and **11d**, but as the macrocycles got larger, a preference for the trans double bond was seen. This observation suggested that a kinetic effect was controlling the product stereochemistry. To test for such an effect, we established the approximate thermodynamic ratio of products **11e (cis)** and **11e (trans)** to see if this ratio differed from that produced by pyrolysis of the starting material **(12e)**.

Compounds **11e (cis)** and **11e (trans)** were purified by flash chromatography and the purified macrocycles were then pyrolysed. To effect isomerization of the double bond, the pyrolysis temperature was raised to about 750°C. As shown in Table II, the

Table II. Equilibration of Macrocycles 11e (cis) and 11e (trans)

starting material			product mixture	
11e (cis)	**11e (trans)**	FVP temperature	**11e (cis)**	**11e (trans)**
98.0	2.0	753°C	74.7	25.3
99.4	0.6	766°C	74.6	25.4
6.2	93.8	753°C	70.5	29.5
14.0	86.0	740°C	76.8	23.2

FVP of purified **11e (cis)** gave a ratio of 75 : 25 for **11e (cis)** : **11e (trans)**, and a similar ratio was obtained from the FVP of purified **11e (trans)**. The equilibration of both **11e (cis)** and **11 (trans)** established that the thermodynamic ratio of these isomers is about 3 to 1, respectively.

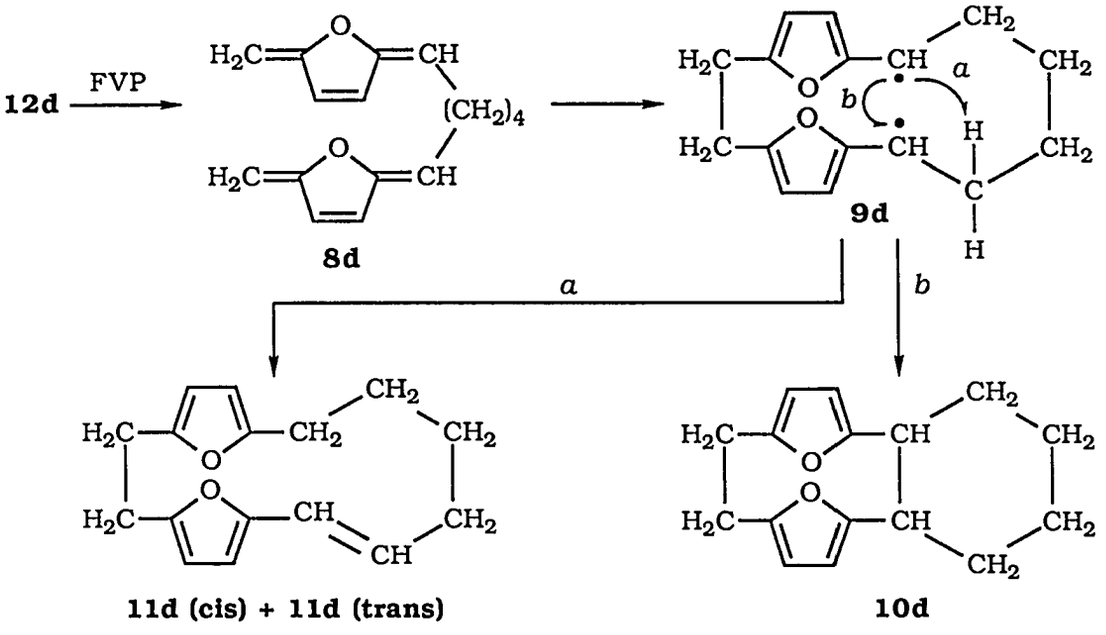
DISCUSSION

Formation of Bis-2,5-dimethylene-2,5-dihydrofurans 8b to 8f by FVP

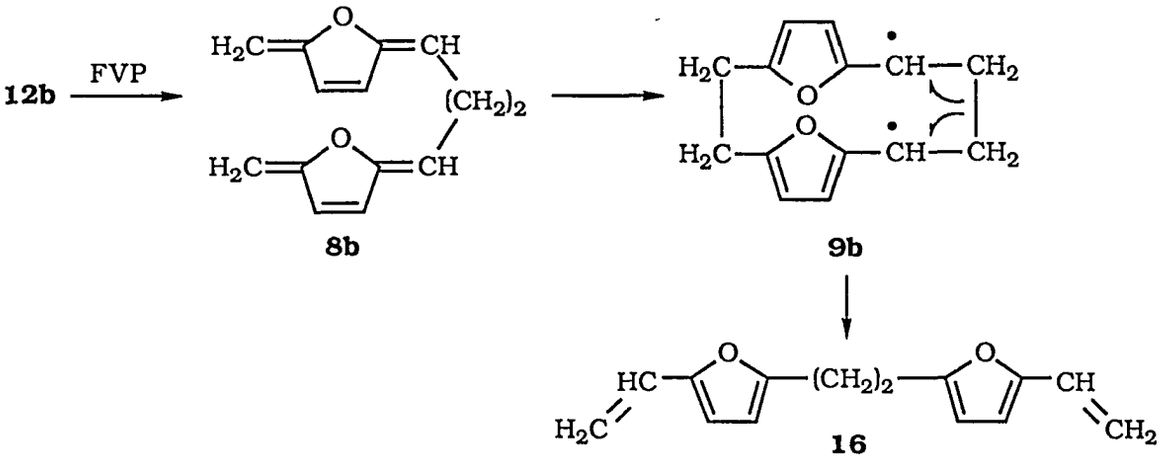
Our results indicate that the bis-furfuryl acetates **12b** to **12f** effectively produce the bis-2,5-dimethylene-2,5-dihydrofurans **8b** to **8f** by FVP. The macrocyclic products (**11c** to **11f**), the ring-fused cyclophane **10d**, and the vinyl-substituted product **16** are all consistent with the formation of the bis-2,5-dimethylene-2,5-dihydrofurans. Thus,

we propose that FVP of **12d** provides **8d** which closes to give diradical **9d** (Scheme IV).

Scheme IV



Formation of **11d (cis)** and **11d (trans)** is explained by an intramolecular radical disproportionation of diradical **9d**, route *a*, and formation of **10d** is explained by intramolecular coupling of diradical **9d**, route *b*. The formation of diradical **9d** is consistent with the postulated intermediacy of diradicals in p-quinodimethane dimerizations. The structure of product **16** is suggestive of the formation of cyclic diradical **9b**, which is a 1,4-diradical. There is ample evidence for the tendency of 1,4-diradicals to cleave and yield a pair of vinyl groups.[15] Diradical **9b** could be formed by the bis-2,5-dimethylene-2,5-dihydrofuran **8b**. Product **16** provides evidence for the



intermediacy of the cyclic diradical (**9b**), and ultimately to the intermediacy of the bis-2,5-dimethylene-2,5-dihydrofuran. Therefore, the bis-2,5-dimethylene-2,5-dihydrofurans (**8**) appear to be generally accessible by FVP of the bis-furfuryl acetates (**12**) (Scheme I).

Macrocycles 11c to 11f by the Intramolecular Cyclization of the Bis-2,5-dimethylene-2,5-dihydrofurans 8c to 8f

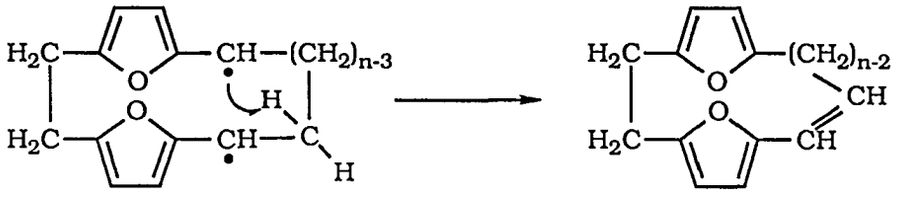
We postulate that the FVP of bis-furfuryl acetates **12c** to **12f** generates the bis-2,5-dimethylene-2,-5-dihydrofurans **8c** to **8f** and by resulting intramolecular cyclizations, fair yields of macrocycles **11c** to **11f** were produced. The reaction of the bis-2,5-dimethylene-2,5-dihydrofurans has been found to be an effective way to generate macrocycles between 15 and 22 carbons. Furthermore, the intramolecular radical disproportionation of intermediate **9** introduces a specifically oriented double bond into these macrocyclic products. Although there are a number of routes to cyclophanes and macrocycles containing furan rings, the generation of **8c** to **8f** is likely the most direct route to macrocycles **11c** to **11f**. Intramolecular reactions of

intermediates believed to contain a pair of *o*-quinodimethanes have been used as an elegant route to multibridged cyclophane products.[16] Thus, reactive *o*-quinodimethanes and *p*-quinodimethanes may be expoited through intramolecular reactions to provide novel products.

Experimental observations suggest that the formation of macrocycles is occurring in the gas-phase. We examined the FVP product mixture ^{1}H NMR shortly after the products were collected (Figure 1) and there was no evidence for the bis-2,5-dimethylene-2,5-dihydrofuran (**8**) in the product mixture. In contrast, 2,5-dimethylene-2,5-dihydrofuran (**2**) persists in solution and may be observed by ^{1}H NMR for several hr at room temperature.[7] Although it is conceivable that the bis-2,5-dimethylene-2,5-dihydrofuran (**8**) is part of our solution-phase product mixture and that macrocycle formation occurs too rapidly to detect **8** by ^{1}H NMR, this does not appear to be the case. If the bis-2,5-dimethylene-2,5-dihydrofuran (**8**) is in our solution-phase product mixture, then one would expect to see at least some polymer formation in our product mixture. No evidence for polymer formation was seen in our FVP apparatus trap or NMR samples. These observations suggest that formation of the macrocyclic products occurs primarily in the gas phase.

The preparation of macrocycles is generally not associated with high temperature, gas-phase chemistry. The forming of macrocycles from acyclic precursors involves considerable loss of entropy and high temperature reactions favor products of increased entropy.[17] Yet, we have prepared macrocycles **11c** to **11f** in reasonably good yields from the acyclic precursors **12c** to **12f**. Product **11f** is even a macrocycle of 22 carbons. The rigidity of the furan-based *p*-quinodimethanes in **8** probably aids in the closure of this acyclic intermediate.

Our results also demonstrate that the double bond of macrocycle **11** is produced by kinetic control of the stereochemistry. As seen in Table 1, the double bond stereochemistry goes from mostly cis to mostly trans as the ring size increases. Although this may partially reflect that the cis conformation is thermodynamically much more stable in the smaller rings , a kinetic effect seems to be a major factor in product stereochemistry. This is shown by our study of the thermodynamic ratio of **11e (cis)** and **11e (trans)**. The thermodynamic ratio of **11e (cis)** and **11e (trans)** was determined to be about 3 to 1, respectively. This ratio differs considerably from the ratio which was observed from FVP of the starting material **12e**. Therefore, the isomeric macrocycles **11e (cis)** and **11e (trans)** are produced in a ratio that reflects their relative rates of formation and not their relative thermodynamic stability. This kinetic effect may result from the conformation of the cyclic diradical **9** during the intramolecular radical disproportionation step which yields the final macrocyclic product.



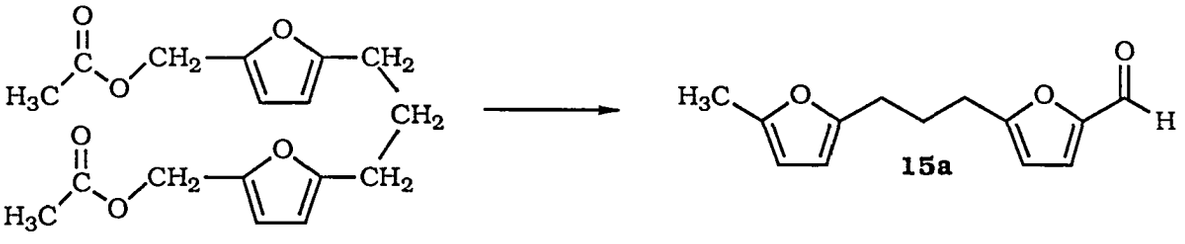
9 **11**

The intramolecular radical disproportionation of **9** is a relatively rare type of reaction. Although known, there are only a few examples of transannular hydrogen abstractions across macrocycles.[18] The largest macrocycle we produced was **11f**, which was generated by a transannular hydrogen abstraction across a 22 carbon ring and through a 12-center transition state. To our knowledge, this is the largest ring across which hydrogen atom abstraction has been observed.

Other than product **10d**, the bis-2,5-dimethylene-2,5-di-hydrofurans (**8**) gave little or none of the ring-fused cyclophanes (**10**) and instead gave macrocyclic products. This might not be what one would expect considering that 2,5-dimethylene-2,5-di-hydrofuran (**2**) forms the dimer [2.2](2,5)furanophane (**6**). However, crystallographic data indicate significant bending of the furan rings in **6** due to repulsive interaction of the aromatic systems.[19] This suggests that reaction of the cyclic diradical **9** (Scheme II) to give the ring-fused cyclophane **10** would require the molecule to overcome the repulsive interaction of the two furan rings.

Although this route to macrocycles is novel and gives products that are not easily accessible by other routes[20], this chemistry has obvious limitations. The starting material **12** must be sufficiently volatile for FVP. When **12f** was pyrolysed, macrocycle **11f** was produced, but **12f** required forcing conditions to effect FVP. Starting material **12g** did not provide macrocyclic products, presumably due to its lack of volatility. Another limitation were unpredicted side reactions in the FVP of **12a** and **12b**.

FVP of **12a** gave product **15a** as the predominant product. It is not clear how this product is formed, but possible routes would be the elimination of acetic



12a **15a**

anhydride from **12a** with a hydrogen migration, or decomposition of the acetate groups by CO_2, CO, and methyl radical loss with a hydrogen migration. No acetic anhydride was observed in the crude product mixture, however, this may be due to the fact that

acetic anhydride itself decomposes under FVP conditions.[21] Whatever the mechanism of formation of product **15a**, it results in the oxidation of one end and reduction of the other end of the acyclic starting material **12a**. This unexpected reaction also occurs to some extent during FVP of the bis-furfuryl acetates **12b** to **12f**.

CONCLUSION

In summary, FVP of **12b** to **12f** provided macrocycles **11c** to **11f** in fair yields (20 to 60%). We propose that the bis-2,5-dimethylene-2,5-dihydrofurans **8b** to **8f** were formed from **12b** to **12f** by elimination of two molecules of acetic acid and that an intramolecular cyclization gave a cyclic diradical intermediate (**9b** to **9f**). By an intramolecular radical disproportionation reaction, the cyclic diradical then gave macrocycles **11c** to **11f**. The intramolecular radical disproportionation is a kinetically controlled process that determines the stereoisomeric ratio of the double bonds in macrocycles **11c** to **11f**. Experimental observations also suggest that the formation of macrocycles is occurring in the gas phase. Our experimental results verify that two *p*-quinodimethanes are capable of intramolecular reaction if linked by an alkyl chain. In addition to the macrocyclic products, a ring-fused cyclophane (**10d**) was produced when **12d** was pyrolysed. Other unexpected products include the vinyl-substituted product **16** from FVP of **12b**, and the rearrangement products **15a** to **15f**.

EXPERIMENTAL SECTION

Methods and materials

Some general methods have been described previously.[21] Gas chromatographic analysis was performed on a Hewlett-Packard 5890 Series II gas chromatograph (GC), employing a 30 meter DB-1 capillary column, helium carrier gas, and flame ionization detector. Infrared spectra (IR) were obtained from an IBM IR/98 fourier transform infrared spectrometer (FT-IR). Combustion analysis was done by Spang Microanalytical Laboratory of Eagle Harbor, MI. For the FVP product mixtures, yield percentages were calculated from GC integration by comparison to an internal standard. Phenyl ether was used as the internal standard, and the detector response factor was determined by preparing a solution of measured amounts of phenyl ether and **11c (cis)**. For the preparation of diacetates **12**, the yield percentages represent purified, isolated yields of products. When flash chromatography was used to purify products, standard methods were used[23] with Merck grade 60, 230-400 mesh silica gel, which was purchased from Aldrich.

General procedure for the preparation of α,ω-di(2-acetoxymethylfuryl-5)-alkanes (12)

α,ω-Di(furyl-2)-alkanes (**13**) were prepared by a procedure based on a published procedure[11] for the alkylation of furans. To a stirred solution at -78 °C containing furan (2.0 g, 29 mmol) in THF (18 mL) and HMPA (2 mL), 11.6 mL BuLi (2.5 M, 29 mmol) was added slowly. The solution was stirred at -78 °C for 1 h, then the α,ω-dibromoalkane (13 mmol, in 5 mL THF) was added and the mixture was allowed to warm (3 h, -78 to 20 °C). The dark solution was then quenched with 20 mL 1.0 M HCl, and this mixture was poured into a separatory funnel containing 50 mL of diethyl ether

and 30 mL of 1.0 M HCl. Acidic extraction was followed by washes with saturated $NaHCO_3$, brine, and drying with anhydrous $MgSO_4$. Filtration and removal of ether provides the α,ω-difuryl-2-alkane which may be purified by distillation or by flash chromatography using 9:1 hexanes:ethyl acetate. Typical yields for this step were 60 to 90%.

α,ω-*Di(2-formylfuryl-5)alkanes* (**14**) were prepared by a procedure based on a published procedure[12] for the formylation of furans. To a solution at -78 °C containing the α,ω-difuryl-2-alkane (10 mmol) in THF (9 mL) and HMPA (1 mL), 8.4 mL of butyllithium (2.5 M, 21 mmol) was added slowly. The solution was stirred at -78 °C for 1 h, DMF (0.73 g, 0.1 mol) was then added and it was allowed to warm (3 h, -78 °C to 20 °C). This solution was stirred for 12 h, then quenched with enough 10% HCl to produce a solution of about pH 7, and added to a separatory funnel containing 50 mL of diethyl ether and 30 mL of 10% HCl. Acidic extraction was followed by washes with saturated $NaHCO_3$, brine, and drying with anhydrous $MgSO_4$. Filtration and removal of the ether provided the α,ω-di(2-formylfuryl-5)alkanes which were purified by flash chromatography using 3:2 hexanes:ethyl acetate. The α,ω-di(2-formylfuryl-5)alkanes were yellow solids obtained in 50-70% yields.

The procedure used to convert the dialdehydes to the diacetates is based on published procedures.[13] Typical yields were 80-90% for the preparation of diacetates **12** from the α,ω-di(2-formylfuryl-5)alkane.

1,3-Di(2-acetoxymethylfuryl-5)propane (12a): *1,3-di(furyl-2)-propane* (**13a**): oil, bp 60 °C (1 mm Hg); ^1H NMR, see Table III; MS m/e (EI) 176 (36, M^+), 94 (100), 81 (57). *1,3-Di(2-formyl-furyl-5)propane* (**14a**): yellow solid, mp 77-79°C; ^1H NMR, see Table IV; MS m/e (EI) 232 (4, M^+), 204 (26), 123 (100), 110 (52), 95 (15), 94 (23), 81 (56), 53 (68).

Table III. ^{1}H NMR data for α,ω-Di(furyl-2)-alkanes (13a to 13g)[a]

compound	resonance signals, ppm[b]
13a	7.27 (s, 2H), 6.24 (d, *J* = 2.9 Hz, 2H), 5.97 (d, *J* = 2.9 Hz, 2H), 2.63 (t, *J* = 7.5 Hz, 4H), 1.93 (quin, *J* = 7.4, 2 H)
13b	7.28 (s, 2H), 6.26 (dd, *J* = 2.9, 1.9 Hz, 2H), 5.96 (dd, *J* = 2.9, 0.7 Hz, 2H), 2.66-2.62 (m, 4 H), 1.71-1.67 (m, 4 H)
13c	7.28 (s, 2H), 6.26 (d, *J* = 2.6 Hz, 2H), 5.97 (d, *J* = 2.6 Hz, 2H), 2.61 (t, *J* = 7.6 Hz, 4H), 1.71-1.59 (m, 4 H), 1.44-1.37 (m, 2 H)
13d	7.28 (s, 2H), 6.24 (d, *J* = 2.6 Hz, 2H), 5.97 (d, *J* = 2.6 Hz, 2H), 2.60 (t, *J* = 7.5 Hz, 4H), 1.72-1.60 (m, 4 H), 1.39-1.33 (s, 4 H)
13e	7.28 (s, 2H), 6.26 (d, *J* = 2.6 Hz, 2H), 5.95 (d, *J* = 2.5 Hz, 2H), 2.60 (t, *J* = 7.5 Hz, 4H), 1.66-1.58 (m, 4 H), 1.33 (s, 6 H)
13f	7.25 (d, *J* = 1.9, 2H), 6.24 (dd, *J* = 2.9, 2.0 Hz, 2H), 5.92 (d, *J* = 2.9 Hz, 2H), 2.59 (t, *J* = 7.6 Hz, 4H), 1.62-1.57 (m, 4 H), 1.27-1.20 (m, 16 H)
13g	7.25 (d, *J* = 1.8, 2H), 6.23 (dd, *J* = 3.0, 2.0 Hz, 2H), 5.92 (d, *J* = 3.0 Hz, 2H), 2.57 (t, *J* = 8.0 Hz, 4H), 1.62-1.52 (m, 4 H), 1.30-1.20 (m, 24 H)

[a] ^{1}H NMR data obtained in $CDCl_3$ and 300 MHz field strength. [b] Chemical shifts measured relative to $Si(CH_3)_4$ or $CHCl_3$.

Table IV. ^{1}H NMR data for α,ω-Di(2-formylfuryl-5)alkanes (14a to 14g)[a]

compound	resonance signals, ppm[b]
14a	9.52 (s, 2H), 7.16 (d, *J* = 3.4 Hz, 2H), 6.26 (d, *J* = 3.4 Hz, 2H), 2.80 (t, *J* = 7.4 Hz, 4H), 2.14 (quin, *J* = 7.4 Hz, 2H)
14b	9.51 (s, 2H), 7.14 (d, *J* = 3.4 Hz, 2H), 6.24 (d, *J* = 3.4 Hz, 2H), 2.80-2.71 (m, 4H), 1.82-1,75 (m, 4H)
14c	9.51 (s, 2H), 7.16 (d, *J* = 3.4 Hz, 2H), 6.23 (d, *J* = 3.4 Hz, 2H), 2.74 (t, *J* = 7.5 Hz, 4H), 1.77-1.69 (m, 4H), 1.47-1.39 (m, 2H)
14d	9.47 (s, 2H), 7.13 (d, *J* = 3.5 Hz, 2H), 6.19 (d, *J* = 3.4 Hz, 2H), 2.68 (t, *J* = 7.6 Hz, 4H), 1.69-1.65 (m, 4H), 1.34 (bs, 4H)
14e	9.47 (s, 2H), 7.13 (d, *J* = 3.5 Hz, 2H), 6.18 (d, *J* = 3.4 Hz, 2H), 2.67 (t, *J* = 7.6 Hz, 4H), 1.70-1.58 (m, 4H), 1.31 (s, 6H)
14f	9.47 (s, 2H), 7.13 (d, *J* = 3.5 Hz, 2H), 6.19 (d, *J* = 3.5 Hz, 2H), 2.68 (t, *J* = 7.6 Hz, 4H), 1.68-1.61 (m, 4H), 1.36-1.16 (m, 16H)
14g	9.47 (s, 2H), 7.13 (d, *J* = 3.4 Hz, 2H), 6.19 (d, *J* = 3.4 Hz, 2H), 2.68 (t, *J* = 7.6 Hz, 4H), 1.68-1.63 (m, 4H), 1.35-1.15 (m, 24H)

[a] ^{1}H NMR data obtained in $CDCl_3$ and 300 MHz field strength. [b] Chemical shifts measured relative to $Si(CH_3)_4$ or $CHCl_3$.

12a: Clear oil; ^{1}H NMR, see Table V; ^{13}C NMR, see Table VI; IR, see Table VII;EIHRMS *m/e* 320.12537 ($C_{17}H_{20}O_6$ requires 320.12599).

1,4-Di(2-acetoxymethylfuryl-5)butane (12b): *1,4-di(furyl-2)-butane* (**13b**): oil, bp 89 °C (1 mm Hg); ^{1}H NMR, see Table III; MS m/e (EI) 190 (40, M^+), 81 (100), 53 (45). *1,4-Di(2-formylfuryl-5)butane* (**14b**): yellow solid, mp 65-67°C; ^{1}H NMR, see Table IV; MS m/e (EI) 246 (26, M^+), 123 (100), 109 (50), 95 (21), 81 (43), 53 (56). **12b:** White solid, mp 99-101°C; ^{1}H NMR, see Table V; ^{13}C NMR , see Table VI; IR, see Table VII; Anal. Calcd. for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63. Found: C, 64.70; H, 6.56.

1,5-Di(2-acetoxymethylfuryl-5)pentane (12c): *1,5-di(furyl-2)-pentane* (**13c**): oil, bp 107 °C (1 mm Hg); ^{1}H NMR, see Table III; MS m/e (EI) 204 (25, M^+), 95 (38), 81 (100), 53 (31). *1,5-Di(2-formylfuryl-5)pentane* (**14c**): yellow solid, mp 71-72 °C; ^{1}H NMR, see Table IV. **12c:** Clear oil; ; ^{1}H NMR, see Table V; ^{13}C NMR , see Table VI; IR, see Table VII.

1,6-Di(2-acetoxymethylfuryl-5)hexane (12d): *1,6-di(furyl-2)-hexane* (**13d**): oil, bp 130 °C (3 mm Hg), ^{1}H NMR, see Table III; *1,6-Di(2-formylfuryl-5)hexane* (**14d**): yellow solid, mp 69-70 °C; ^{1}H NMR, see Table IV. **12d:** Clear oil; ^{1}H NMR, see Table V; ^{13}C NMR, see Table VI; IR, see Table VII.

1,7-Di(2-acetoxymethylfuryl-5)heptane (12e): *1,7-di(furyl-2)-heptane* (**12e**): oil, bp 130 °C (1 mm Hg); ^{1}H NMR, see Table III; MS m/e (EI) 232 (12, M^+), 95 (50), 94 (32), 81 (100), 53 (25). *1,7-Di(2-formylfuryl-5)heptane* (**14e**): yellow solid, mp 73-74°C; ^{1}H NMR, see Table IV; MS m/e (EI) 288 (24, M^+), 179 (30), 123 (100), 110 (64), 109 (55), 81 (49), 53 (53). **12e:** Clear oil; ^{1}H NMR, see Table V; ^{13}C NMR, see Table VI; IR, see Table VII.

1,12-Di(2-acetoxymethylfuryl-5)dodecane (12f): *1,12-di(furyl-2)-dodecane* (**13f**): white solid; mp 35-36 °C; ^{1}H NMR, see Table III; MS m/e (EI) 302 (14, M^+), 95 (45),

Table V. ^{1}H NMR data for α,ω-Di(2-acetoxymethylfuryl-5)alkanes (12a to 12g)[a]

compound	resonance signals, ppm[b]
12a	6.28 (d, *J* = 3.1 Hz, 2H), 5.96 (d, *J* = 3.0 Hz, 2H), 4.98 (s, 4H), 2.65 (t, *J* = 7.5 Hz, 4H), 2.06 (s, 6H), 1.99 (p, *J* = 7.4 Hz, 2H)
12b	6.29 (d, *J* = 3.1 Hz, 2H), 5.95 (d, *J* = 3.1 Hz, 2H), 4.99 (s, 4H), 2.69-2.60 (m, 4H), 2.08 (s, 6H), 1.73-1.67 (m, 4H)
12c[c]	6.15 (d, *J* = 3.1 Hz, 2H), 5.74 (d, *J* = 3.1 Hz, 2H), 4.94 (s, 4H), 2.34 (t, *J* = 7.5 Hz, 4H), 1.59 (s, 6H), 1.41-1.32 (m, 4H), 1.12-1.07 (m, 2H)
12d	6.25 (d, *J* = 3.0 Hz, 2H), 5.90 (d, *J* = 3.0 Hz, 2H), 4.95 (s, 4H), 2.56 (t, *J* = 7.6 Hz, 4H), 2.03 (s, 6H), 1.62-1.55 (m, 4H), 1.37-1.30 (m, 4H)
12e	6.24 (d, *J* = 3.1 Hz, 2H), 5.89 (d, *J* = 3.1 Hz, 2H), 4.95 (s, 4H), 2.56 (t, *J* = 7.6 Hz, 4H), 2.03 (s, 6H), 1.64-1.52 (m, 4H), 1.30 (s, 6H)
12f	6.29 (d, *J* = 3.1 Hz, 2H), 5.93 (d, *J* = 3.1 Hz, 2H), 4.99 (s, 4H), 2.60 (t, *J* = 7.7 Hz, 4H), 2.07 (s, 6H), 1.67-1.59 (m, 4H), 1.39-1.23 (m, 16H)
12g	6.25 (d, *J* = 3.1 Hz, 2H), 5.90 (d, *J* = 3.1 Hz, 2H), 4.90 (s, 4H), 2.56 (t, *J* = 7.6 Hz, 4H), 2.04 (s, 6H), 1.63-1.54 (m, 4H), 1.34-1.20 (m, 24H)

[a] ^{1}H NMR data obtained in $CDCl_3$ and 300 MHz field strength. [b] Chemical shifts measured relative to $Si(CH_3)_4$ or $CHCl_3$. [c] ^{1}H NMR data obtained in C_6D_6.

Table VI. ^{13}C NMR data for α,ω-Di(2-acetoxymethylfuryl-5)alkanes (12a to 12g)[a]

compound	resonance signals, ppm[b]
12a	170.08, 156.94, 147.14, 110.89, 105.62, 57.73, 26.89, 25.90, 20.40
12b	170.64, 157.04, 147.60, 111.45, 105.88, 58.29, 27.77, 27.36, 20.93
12c	170.75, 157.37, 147.53, 111.48, 105.79, 58.38, 28.71, 27.98, 27.59, 21.01
12d	170.70, 157.48, 147.46, 111.46, 105.71, 58.34, 28.82, 28.00, 27.73, 20.95
12e	170.68, 157.57, 147.44, 111.43, 105.66, 58.34, 29.04, 28.99, 28.04, 27.81, 20.95
12f	171.71, 157.72, 147.40, 111.43, 105.61, 58.37, 29.59, 29.53, 29.34, 29.20, 28.09, 27.88
12g	171.70, 157.71, 147.36, 111.43, 105.61, 58.38, 29.67, 29.58, 29.36, 29.23, 28.11, 27.90 (3 magnetically equal carbons)

[a] ^{1}H NMR data obtained in $CDCl_3$ and 300 MHz field strength. [b] Chemical shifts measured relative to $Si(CH_3)_4$ or $CHCl_3$.

Table VII. IR data for α,ω-Di(2-acetoxymethylfuryl-5)alkanes (12a to 12g)[a]

compound	absorbance frequencies, cm^{-1}
12a	2949, 2872, 1732, 1560, 1437, 1375, 1227, 1022, 972, 791, 752
12b	2941, 2864, 1734, 1560, 1437, 1375, 1215, 1018, 974, 957, 791
12c	2937, 2862, 1742, 1560, 1435, 1375, 1236, 1018, 974, 795
12d	2934, 2860, 1745, 1560, 1437, 1375, 1360, 1238, 1018, 974, 798
12e	2932, 2858, 1744, 1560, 1437, 1375, 1360, 1236, 1018, 972, 798
12f	2920, 2853, 1736, 1562, 1472, 1379, 1246, 1204, 1028, 937, 798
12g	2916, 2851, 1730, 1558, 1472, 1377, 1236, 1207, 1020, 966, 800

[a] IR data obtained from thin films on NaCl .

94 (17), 81 (100), 53 (22). *1,12-Di(2-formylfuryl-5)dodecane* (**14f**): yellow solid, mp 76-77°C; ^{1}H NMR, see Table IV; MS m/e (EI) 358 (22, M^+), 147 (30), 123 (100), 110 (38), 109 (62), 95 (37), 81 (53), 53 (45). **12f:** White solid, mp 43-46 °C; ^{1}H NMR, see Table V; ^{13}C NMR, see Table VI; IR, see Table VII. Anal. Calcd. for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 70.02; H, 8.66.

1,16-Di(2-acetoxymethylfuryl-5)hexadecane (12g): *1,16-di(furyl-2)-hexadecane* (**13g**): white solid, mp 35-36 °C; ^{1}H NMR, see Table III; *1,16-Di(2-formylfuryl-5)hexadecane* (**14g**): yellow solid, mp 77-80 °C; ^{1}H NMR, see Table IV. **12g:** White solid, mp 56-57°C; ^{1}H NMR, see Table V; ^{13}C NMR, see Table VI; IR, see Table VII. Anal. Calcd. for $C_{30}H_{46}O_6$: C, 71.68; H, 9.22. Found: C, 71.61; H, 9.32.

FVP of 12a

FVP required heating the starting material to 70 °C for volatilization. Product composition was somewhat variable, but one major product was observed by GCMS to have *m/e* of 218. This product was isolated and identified as **15a**. **1-(2-Methylthienyl-5)-3-(2-formylthienyl-5)propane (15a):** clear oil, 33% yield; IR (neat, NaCl) 2950, 1677, 1516, 1020, 784 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.50 (s, 1H), 7.15 (d, J = 3.5, 1H), 6.23 (d, J = 3.5 Hz, 1H), 5.85 (s, 1H), 5.82 (s, 1H), 2.75 (t, J = 7.6, 2H), 2.62 (t, J = 7.3, 2H), 2.23 (s, 3H), 2.01 (p, J = 7.5, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 176.84, 163.17, 152.86, 151.74, 150.42, 123.22, 108.79, 105.90, 105.70, 27.52, 27.21, 25.98, 13.38; MS m/e (EI) 218 (19, M^+), 123 (36), 122 (8), 109 (9), 108 (24), 107 (8), 96 (42), 95 (100), 81 (10), 53 (14); EIHRMS *m/e* 218.09428 ($C_{13}H_{14}O_3$ requires 218.09429).

FVP of 12b

FVP required heating the starting material to 90 °C for volatilization. The crude mixture contained four products in a 43:10:4:1 ratio and GCMS indicated respective *m/e* values of 214, 232, 214, and 214. The most abundant product was isolated and

identified as 1,2-di(2-vinylfuryl-5)ethane (**16**), the second most abundant product was thought to be **15b**, and the two minor products could not be identified. **1,2-Di-(2-vinylfuryl-5)ethane (16):** clear oil, 10% yield; IR (neat, NaCl) 2918, 1678, 1639, 1585, 1528, 1254, 1032, 1018, 897, 785 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.40 (dd, J = 11.3, 17.5 Hz, 2H), 6.10 (d, J = 3.2, 2H), 5.96 (d, J = 3.2 Hz, 2H), 5.54 (dd, J = 1.2, 17.5 Hz, 2H), 5.04 (dd, J = 1.3, 11.3 Hz, 2H), 2.95 (s, 4H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 154.52, 151.83, 125.04, 110.88, 108.97, 108.90, 107.08, 26.91; MS m/e (EI) 214 (12, M^+), 108 (7), 107 (100), 77 (14), 55 (6); EIHRMS m/e 214.09969 ($C_{14}H_{14}O_2$ requires 214.09938). **1-(2-Methylthienyl-5)-4-(2-formylthienyl-5)butane (15b):** ^1H NMR (C_6D_6, 300 MHz) δ 9.32 (s, 1H), 6.51 (d, J = 3.4 Hz, 1H), 5.78 (s, 2H), 5.58 (d, J = 3.4 Hz, 1H), 2.37 (t, J = 7.1 Hz, 2H), 2.18 (t, J = 7.2 Hz, 2H), 2.05 (s, 3H), 1.41-1.23 (m, 4H); MS m/e (EI) 232 (22, M^+), 189 (13), 123 (8), 110 (8), 95 (100), 53 (10), 43 (30).

FVP of 12c

FVP required heating the starting material to 100°C for volatilization. The crude mixture contained three products in a 17:2:1 ratio and GCMS indicated respective m/e values of 228, 228, and 246. The most abundant product was isolated and identified as **11c (cis)**, the product of m/e 246 was thought to be **15c**, while the other product could not be identified. **cis-1,2-Dehydro[5,2](2,5)furanophane (11c (cis)):** white solid, mp 96-97°C, 46% yield; IR (neat, NaCl) 2924, 2854, 1560, 1456, 1423, 1396, 1169, 1018, 789 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.99 (d, J = 11.6 Hz, 1H), 5.92 (d, J = 3.1 Hz, 1H), 5.88 (d, J = 2.9, 1H), 5.84 (d, J = 2.9 Hz, 1H), 5.79 (d, J = 3.2 Hz, 1H), 5.48 (dt, J = 8.8, 11.6 Hz, 1H), 2.60-2.51 (m, 6H), 2.42-2.35 (m, 2H), 1.87-1.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 155.65, 154.65, 153.82, 153.39, 129.11, 118.18, 110.43, 107.87, 107.17, 105.93, 30.17, 28.65, 28.50, 27.71, 27.64; MS m/e (EI) 228 (100, M^+), 134 (57), 133 (95), 121 (58), 107 (51); EIHRMS m/e 228.11479 ($C_{15}H_{16}O_2$ requires 228.11503). **1-(2-Methylthien-**

yl-5)-5-(2-formylthienyl-5)pentane (15): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.5 (s), 7.1 (d), 6.2 (d), 5.8 (s), 2.7 (t), 2.5 (t), 2.2 (s), 1.8-1.6 (m); MS m/e (EI) 246 (21, M^+), 228 (5), 203 (9), 123 (11), 109 (9), 95 (100), 43 (26).

FVP of 12d

FVP required heating the starting material to 105°C for volatilization. The crude mixture contained four products in a 18:4:2:1 ratio and GCMS indicated respective *m/e* values of 242, 242, 242, and 260. The three most abundant products were isolated and identified as **12d (cis)**, **12d (trans)**, and **10d**, while one product could not be isolated but presumably was product **15d**. **cis-1,2-Dehydro[6.2](2,5)furanophane (12d (cis)):** clear oil, 47% yield; IR (neat, NaCl) 2930, 2860, 1568, 1435, 1213, 1132, 1015, 984, 783 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.99 (d, *J* = 3.3 Hz, 1H), 5.97 (d, *J* = 3.2 Hz, 1H), 5.89 (d, *J* = 11.7, 1H), 5.80 (d, *J* = 2.9 Hz, 1H), 5.75 (d, *J* = 2.9 Hz, 1H), 5.42 (dt, *J* = 8.3, 11.6 Hz, 1H), 3.07-2.98 (m, 2H), 2.81-2.75 (m, 2H), 2.62 (t, *J* = 6.3, 2H), 2.30-2.20 (m, 2H), 1.78-1.65 (m, 2H), 1.28-1.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 155.20, 154.10, 152.42, 152.09, 129.75, 116.98, 110.26, 106.88, 106.85, 106.38, 29.32, 28.89, 27.86, 27.45, 27.44, 26.95; MS m/e (EI) 242 (84, M^+), 135 (50), 120 (72), 107 (100), 94 (51); EIHRMS *m/e* 242.13086 ($C_{16}H_{18}O_2$ requires 242.13068). **trans-1,2-Dehydro[6.2](2,5)furanophane (12d (trans)):** clear oil, 11% yield; IR (neat, NaCl) 2930, 2858, 1555, 1431, 1340, 1250, 1173, 1034, 986, 781 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.02 (d, *J* = 3.0 Hz, 1H), 5.97 (d, *J* = 15.9 Hz, 1H), 5.96 (d, *J* = 3.0, 1H), 5.91 (d, *J* = 3.0 Hz, 1H), 5.84 (d, *J* = 2.9 Hz, 1H), 5.56 (dt, *J* = 7.1, 15.9 Hz, 1H), 2.84 (s, 4H), 2.57-2.50 (m, 2H), 2.12-2.03 (m, 2H), 1.67-1.50 (m, 4H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 155.09, 154.02, 153.04, 149.49, 132.16, 118.27, 107.51, 106.22, 105.41, 105.40, 31.01, 29.17, 28.66, 28.09, 25.77, 23.51; MS m/e (EI) 242 (87, M^+), 135 (46), 120 (56), 107 (100), 77 (45); EIHRMS *m/e* 242.13060 ($C_{16}H_{18}O_2$ requires 242.13068). **[1:2]Butano[2.2](2,5)furanophane (10d):** clear oil, 4% yield; IR

(neat, NaCl) 2918, 2853, 1547, 1447, 1190, 1157, 1016, 1007, 787 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.10 (d, J = 3.0 Hz, 2H), 6.03 (d, J = 3.0 Hz, 2H), 2.82 (d, J = 9.4, 2H), 2.61 (d, J = 9.6, 2H), 2.43-2.37 (m, 2H), 1.95-1.84 (m, 2H), 1.70-1.55 (m, 2H), 1.43-1.33 (m, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 161.16, 156.00, 107.90, 105.28, 48.72, 30.65, 28.37, 26.03; MS m/e (EI) 242 (94, M^+), 135 (51), 120 (76), 107 (100), 94 (52); EIHRMS *m/e* 242.13112 ($C_{16}H_{18}O_2$ requires 242.13068). **1-(2-Methylthienyl-5)-6-(2'-formylthienyl-5')hexane (15d):** ^1H NMR ($CDCl_3$, 300 MHz) δ 9.47 (s), 7.13 (d, J = 3.5 Hz, 1H), 6.18 (d, J = 3.4 Hz, 1H), 5.8 (s, 2H), 2.68 (t, J = 7.6 Hz, 2H), 2.51 (t, J = 7.5 Hz, 2H), 2.21 (s, 3H), 1.8-1.6 (m, 4H); MS m/e (EI) 246 (12, M^+), 123 (11), 109 (11), 95 (100), 81 (5), 53 (8), 43 (21).

FVP of 12e

FVP required heating the starting material to 105 °C for volatilization. The crude mixture contained three products in a 25:18:1 ratio and GCMS indicated respective *m/e* values of 256, 256, and 274. The two most abundant products were isolated and identified as **11e (trans)**, and **11e (cis)**, while the minor product could not be isolated, but was likely **15e**. **cis-1,2-Dehydro[7.2](2,5)furanophane (11e (cis)):** clear oil, 22% yield; IR (neat, NaCl) 2920, 2857, 1585, 1429, 1013, 980, 779 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.02 (d, J = 3.1 Hz, 1H), 6.00 (d, J = 3.1 Hz, 1H), 5.92 (d, J = 11.7 Hz, 1H), 5.89 (d, J = 11.7, 1H), 5.76 (d, J = 2.9 Hz, 1H), 5.71 (d, J = 2.8 Hz, 1H), 5.29 (dt, J = 8.1, 11.7 Hz, 1H), 3.01-2.93 (m, 2H), 2.85-2.79 (m, 2H), 2.56 (t, J = 6.0 Hz, 2H), 2.32 (dd, J = 6.9, 6.9, 2H), 1.69-1.57 (m, 2H), 1.42-1.31 (m, 4H); ^{13}C NMR ($CDCl_3$, 300 MHz) d 155.04, 152.42, 151.98, 129.96, 116.86, 110.32, 106.40, 106.32, 105.73, 29.26, 28.17, 28.02, 28.00, 27.83, 27.25, 26.95; MS m/e (EI) 256 (75, M^+), 120 (82), 107 (100), 94 (68), 91 (44); EIHRMS *m/e* 256.14629 ($C_{17}H_{20}O_2$ requires 256.14633). **trans-1,2-Dehydro[7.2](2,5)furanophane (11e (trans)):** clear oil, 17% yield; IR (neat, NaCl) 2920, 2857, 1585, 1429, 1013, 980, 779 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.96 to 5.87 (m, 5H), 5.83 (d, J = 3.0 Hz, 1H), 2.94-

2.83 (m, 4H), 2.54 (t, J = 6.1 Hz, 2H), 2.10 (dd, J = 6.0, 5.7 Hz, 2H), 1.70-1.61 (m, 2H), 1.49-1.41 (m, 4H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 154.09. 153.85, 129.94, 117.92, 106.53, 106.11, 105.82, 105.53, 31.13, 27.92, 27.68, 27.17, 27.03, 26.48, 24.60; MS m/e (EI) 256 (93, M^+), 120 (86), 107 (100), 94 (69), 91 (46); EIHRMS *m/e* 256.14669 ($C_{17}H_{20}O_2$ requires 256.14633). **1-(2-methylthienyl-5)-7-(2'-formylthienyl-5')heptane (15e):** MS m/e (EI) 246 (11, M^+), 123 (8), 109 (13), 95 (100), 81 (6), 53 (9), 43 (24).

FVP of 12f

FVP required heating the starting material to 130 °C for volatilization. The crude mixture contained two major products in a 4:1 ratio and GCMS indicated respective *m/e* values of 326 and 326. The most abundant product was isolated and identified as **11f (trans)**, while a partitial characterization of the other product suggested its identity as **11f (eis)**. In addition, a minor product was observed by GCMS which had a *m/e* value of 344. This product was thought to be **15f. trans-1,2-Dehydro[12.2](2,5)-furanophane (11f (trans)):** clear oil, 19% yield; IR (neat, NaCl) 2926, 2854, 1568, 1533, 1460, 1437, 1281, 1092, 1015, 960, 800, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.05 (d, J = 16.1, 1H), 5.96-5.86 (m, 3H), 5.80 (d, J = 3.0 Hz, 1H), 5.75 (d, J = 2.9 Hz, 1H), 2.99-2.84 (m, 4H), 2.47 (t, J = 7.1 Hz, 2H), 2.14 (dd, J = 6.0, 5.7 Hz, 2H), 1.53-1.12 (m, 16H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 154.62, 153.68, 152.64, 151.67, 128.57, 119.19, 106.83, 106.45, 105.67, 105.07, 31.13, 27.97, 27.62, 27.54, 27.23, 27.17, 26.60, 26.10; MS m/e (EI) 326(100, M^+), 121 (52), 108 (42), 107 (87), 95 (58); EIHRMS *m/e* 326.22470 ($C_{22}H_{30}O_2$ requires 326.22459). **cis-1,2-Dehydro[12.2](2,5)furanophane (11f (cis)):** ~4% yield; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.05-5.95 (m), 5.86 (d), 5.86-5.75 (m), 2.92 (s), 2.55 (t), 2.23 (d), 1.30 (s); MS m/e (EI) 326 (88, M^+), 133 (42), 121 (64), 108 (51), 107 (100), 95 (68), 94 (55), 55 (45). **1-(2-Methylthienyl-5)-12-(2'-formylthienyl-5')dodecane (15e):** MS m/e (EI) 246 (7, M^+), 123 (5), 109 (17), 96 (11), 95 (100), 81 (8), 53 (7), 43 (20).

FVP of 12g

FVP required heating the starting material to 150°C for volatilization. The crude mixture contained no products such as **11g** or **10g**. The GCMS data ssuggested that considerable fragmentation occurred during FVP.

Equilibration study of 11e (cis) and 11e (trans)

Following a pyrolysis of **12e**, the two isomers **11e (cis)** and **11e (trans)** were isolated and checked by GC to establish the purity of each sample. Each isomer (~10 mg of **11e (cis)** and **11e (trans)**) was then subjected to FVP at about 750°C and $1x10^{-5}$ torr. The products were then dissolved in diethyl ether and analyzed by GC.

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APPENDIX

Supplementary Procedure

General procedure for the reduction and acylation of the α,ω-di(2-formylfuryl-5)alkanes (**14**) to prepare the α,ω-di(2-acetoxymethylfuryl-5)alkanes (**12**):

A stirred mixture of $LiAlH_4$ (0.57 g, 15 mmol) in THF (25 mL) was cooled to 0 °C, and to it was added slowly a solution of the α,ω-di-(2-formylfuryl-5)alkane (10 mmol) in THF (10 mL). The ice bath was then removed and the mixture was stirred for 1 h at 25 °C. The reaction was worked up by first cooling the solution to 0 °C and then slowly adding 0.6 mL of H_20, 0.6 mL of 15% NaOH, and then 1.8 mL of H_2O. The mixture was stirred at 25 °C for an additional 20 min. and ~2 g of $MgSO_4$ then was added to the solution. Vacuum filtration removed the precipitated salts, and the reaction flask was then rinsed with 20 mL of ethyl acetate and this solution was poured through the filtered salts. The resulting diol was not isolated, but dissolved in THF (20 mL). To the diol (10 mmol) solution, triethyl amine (3.5 mL, 25 mmol) and acetyl chloride (1.8 mL, 25 mmol) was added and the solution stirred at 25 °C. The mixture was allowed to react for at least 5 h, during which the triethylammonium chloride precipitated. The progress of the reaction was monitored by thin layer chromatography (eluent, 4:1 hexanes:ethyl acetate). Upon completion of the reaction, the product mixture was poured into a separatory funnel containing 50 mL of 1.0 M HCl and 25 mL of ethyl ether. The acidic extraction was then followed by extraction with saturated $NaHCO_3$ and saturated NaCl. Drying with $MgSO_4$ and removal of the solvent gave the crude diacetate **12**. The diacetate was then purified by flash chromatography using 9:1 hexanes:ethyl acetate as the eluent.

Supplementary Figures

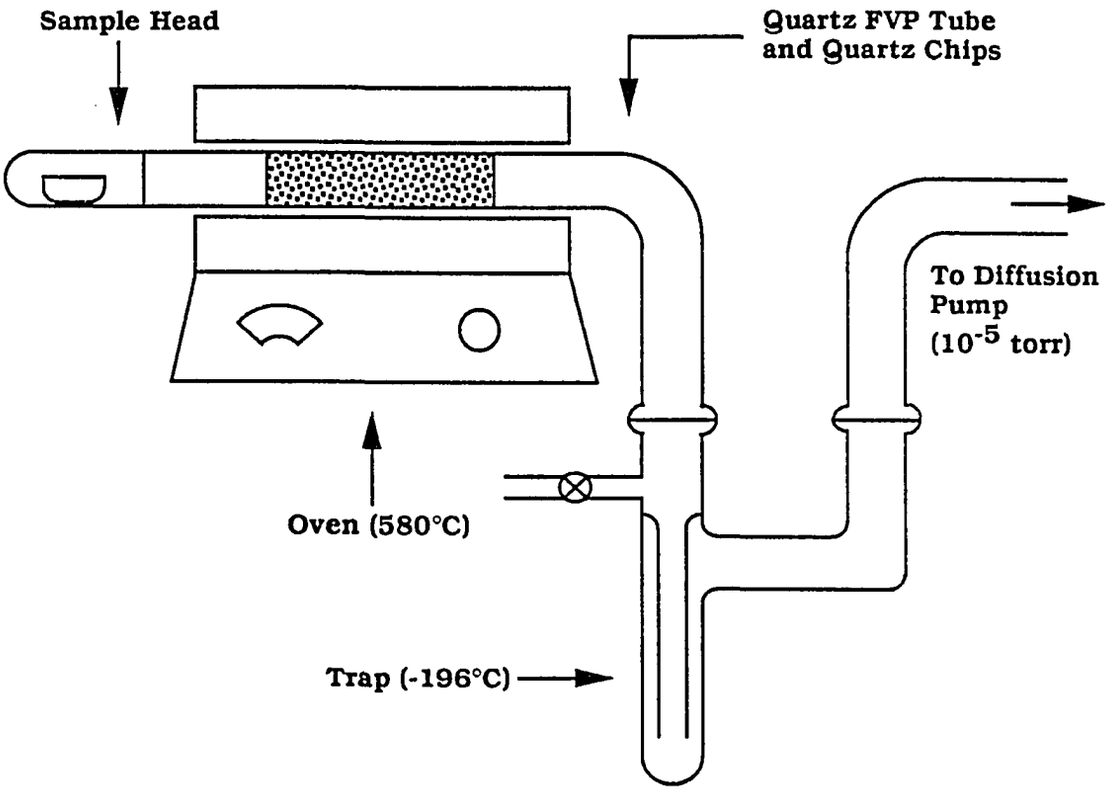


Figure A-1. Schematic diagram of the flash vacuum pyrolysis apparatus.

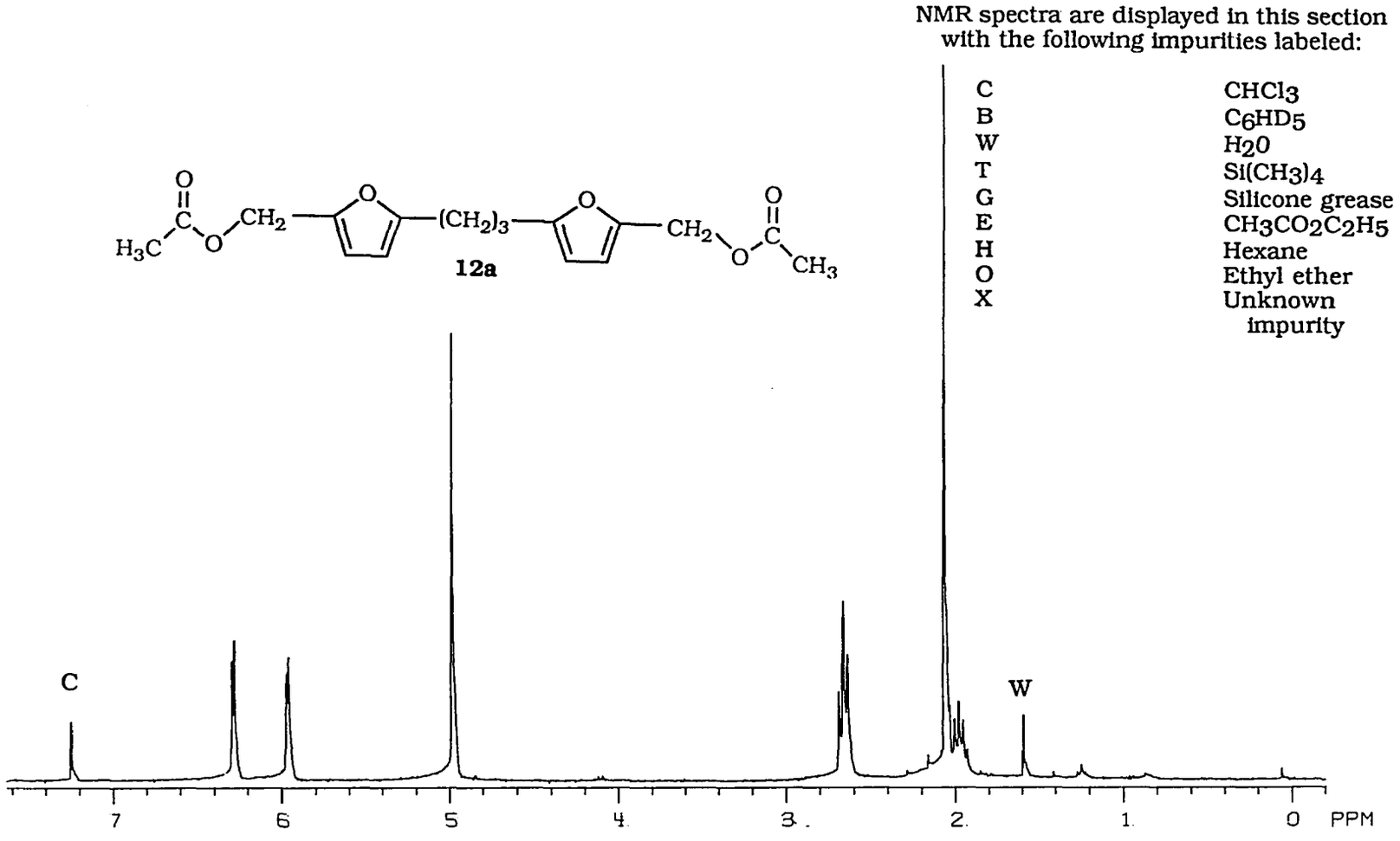
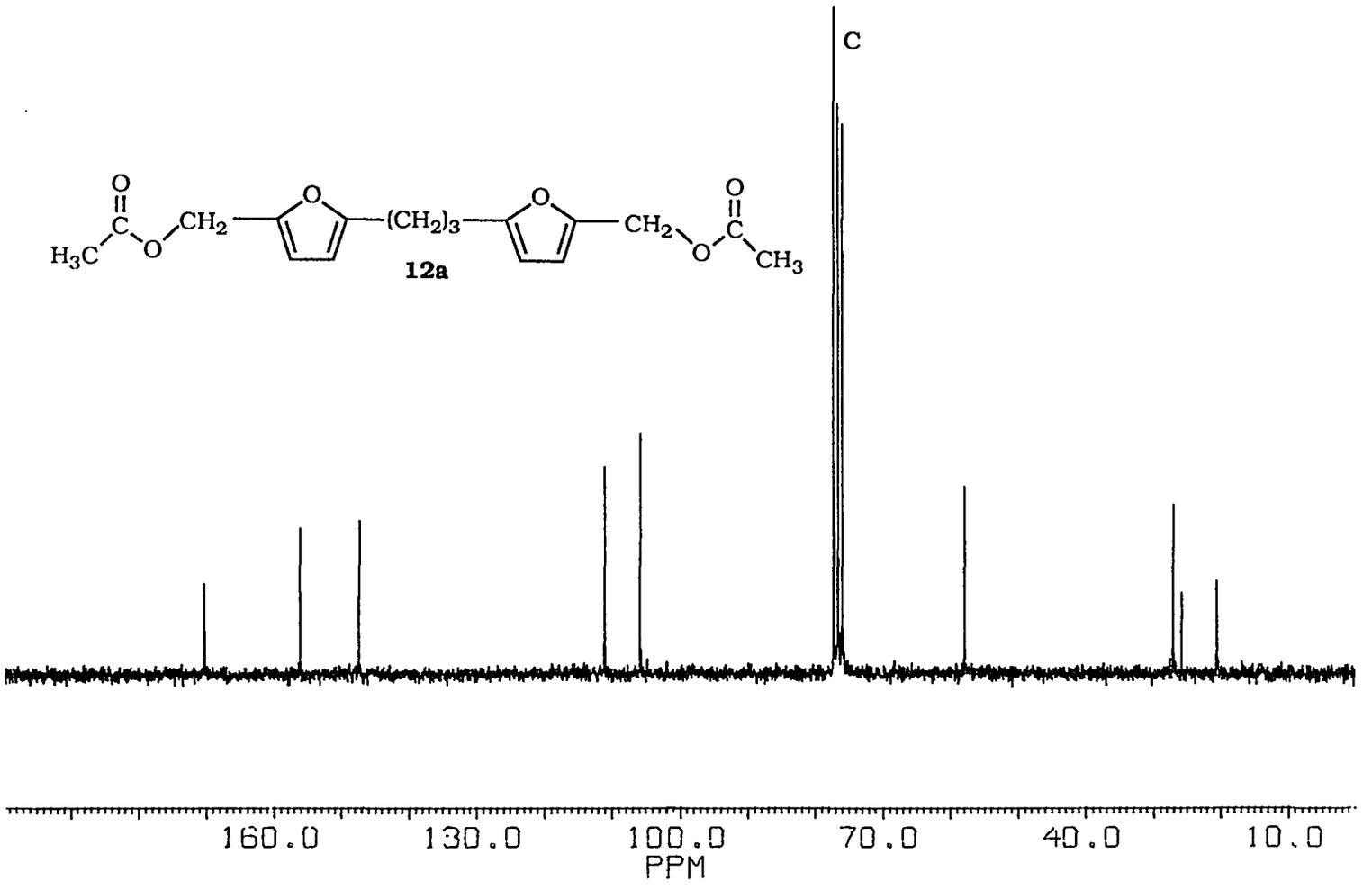


Figure A-2. ^{1}H NMR spectrum of bis-furfuryl acetate **12a**.



12a

Figure A-3. ^{13}C NMR spectrum of bis-furfuryl acetate **12a**.

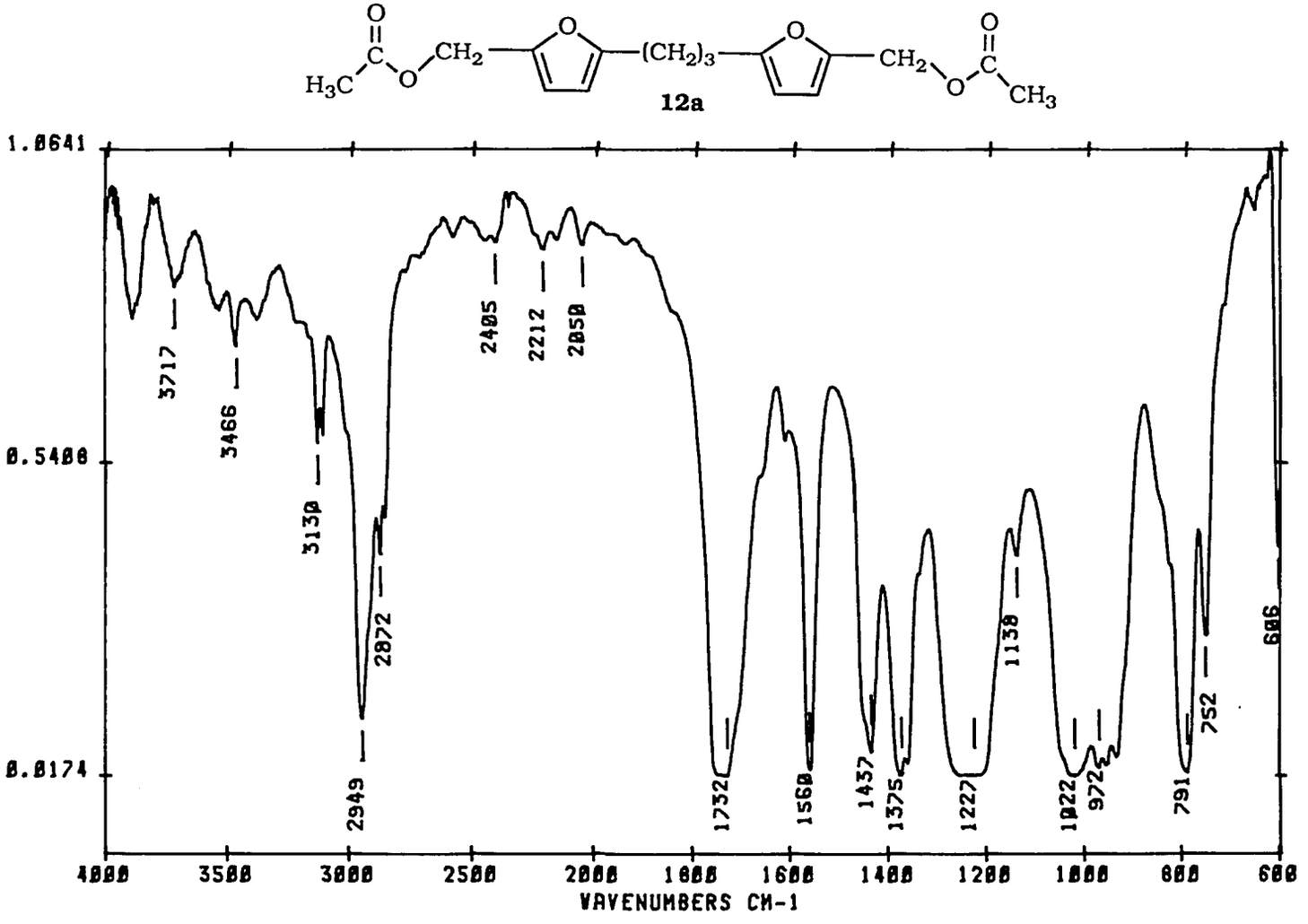


Figure A-4. IR spectrum of bis-furfuryl acetate **12a**.

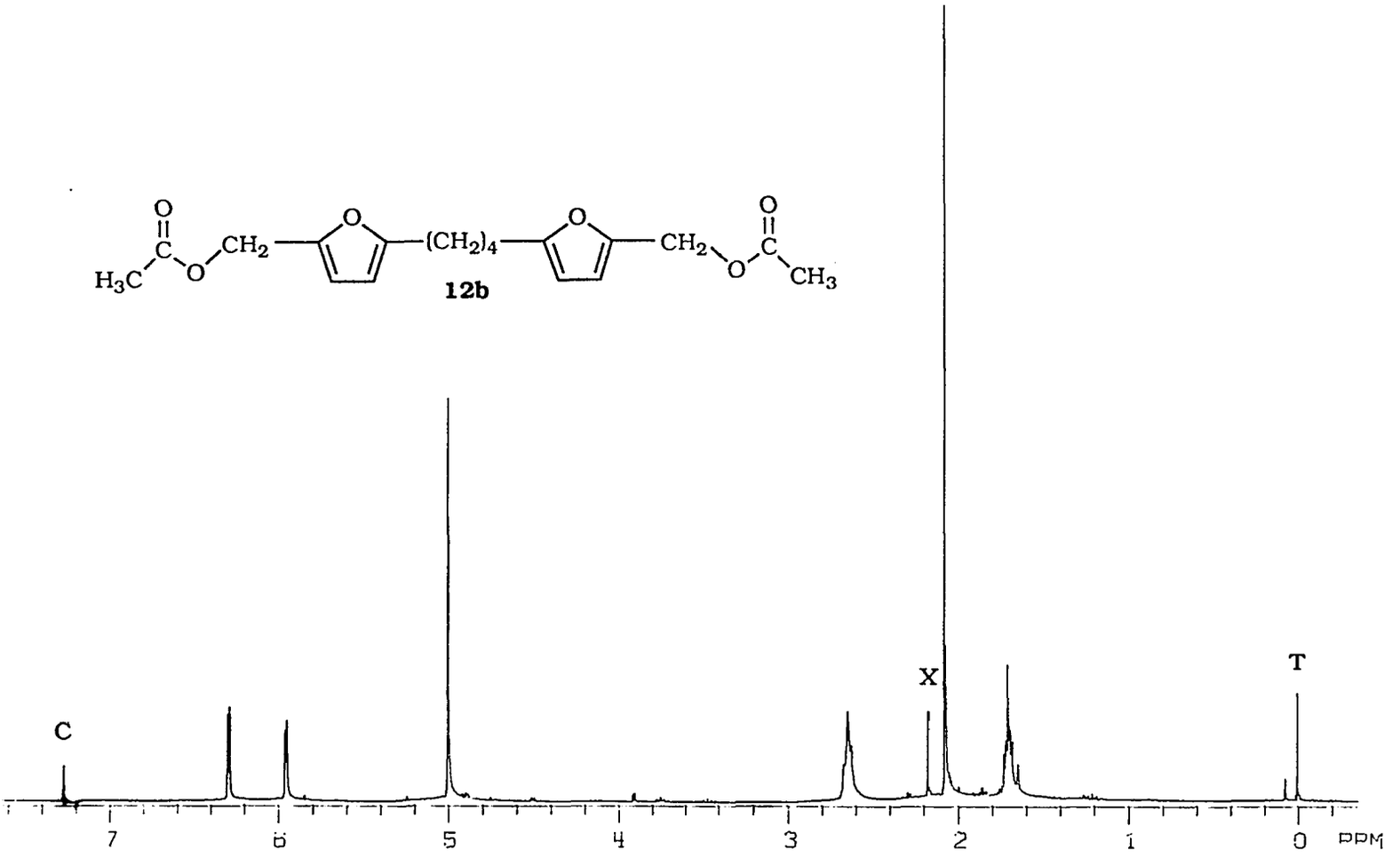


Figure A-5. ^{1}H NMR spectrum of bis-furfuryl acetate **12b**.

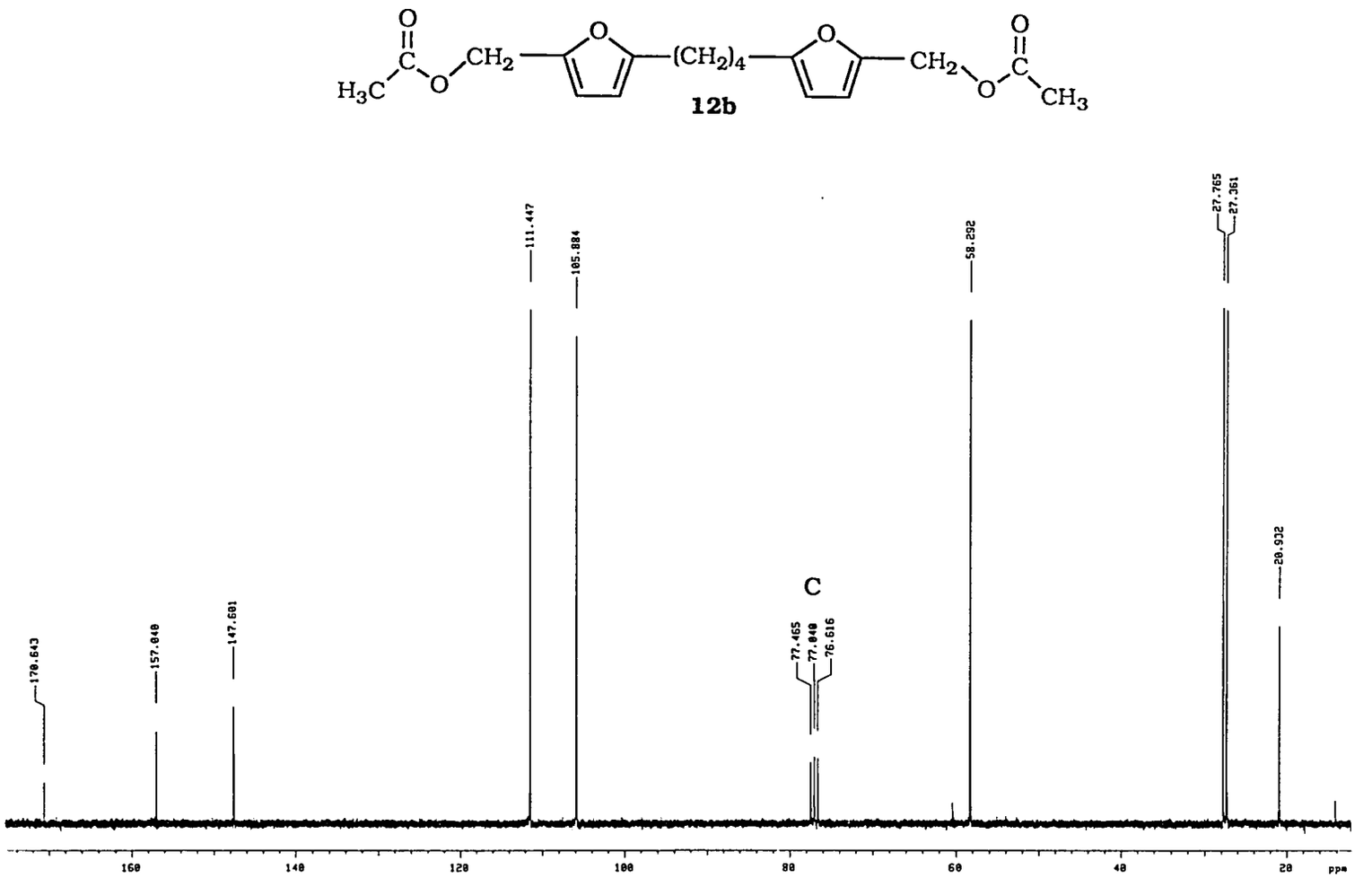


Figure A-6. ^{13}C NMR spectrum of bis-furfuryl acetate **12b**.

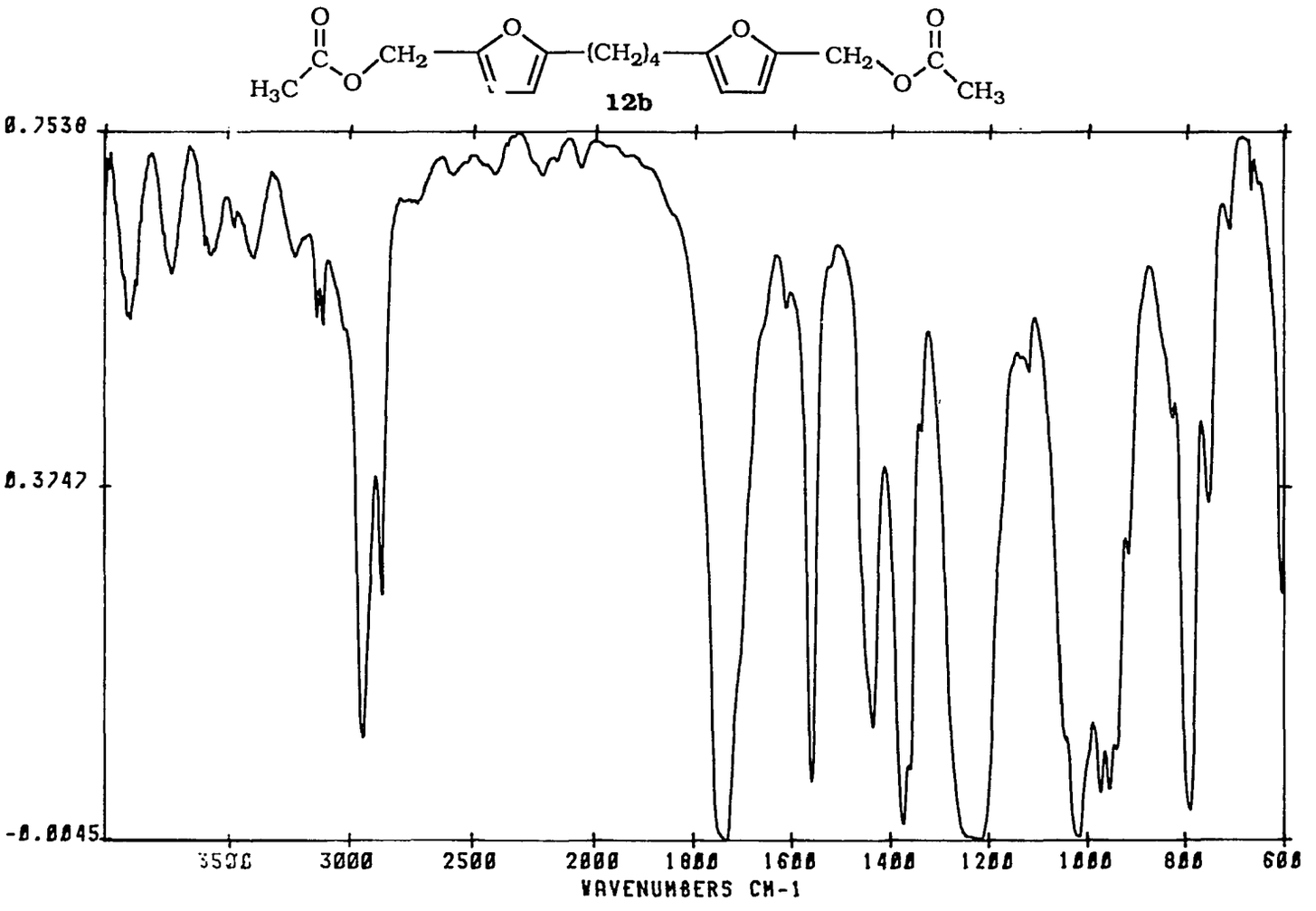


Figure A-7. IR spectrum of bis-furfuryl acetate **12b**.

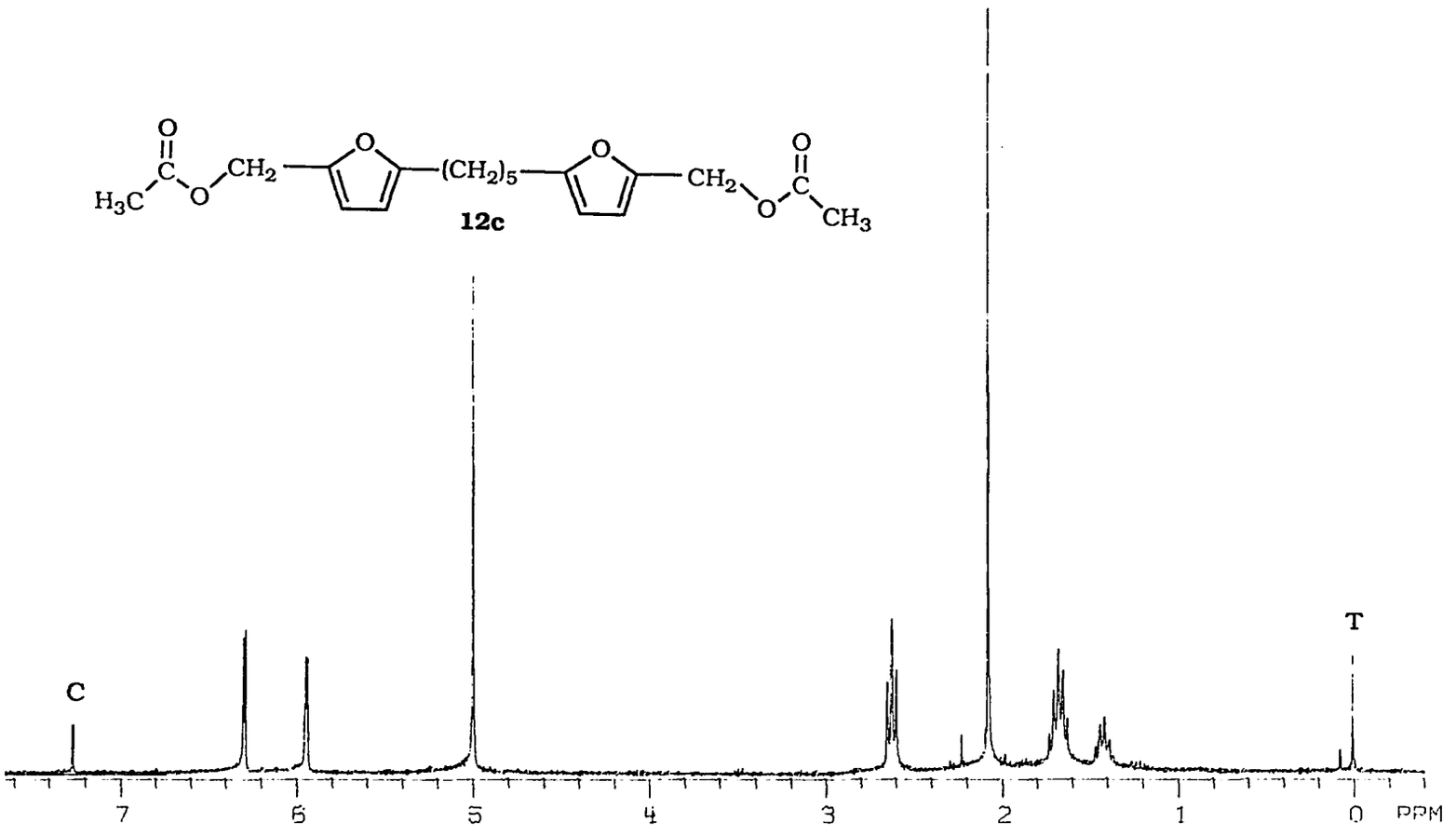


Figure A-8. ^{1}H NMR spectrum of bis-furfuryl acetate **12c**.

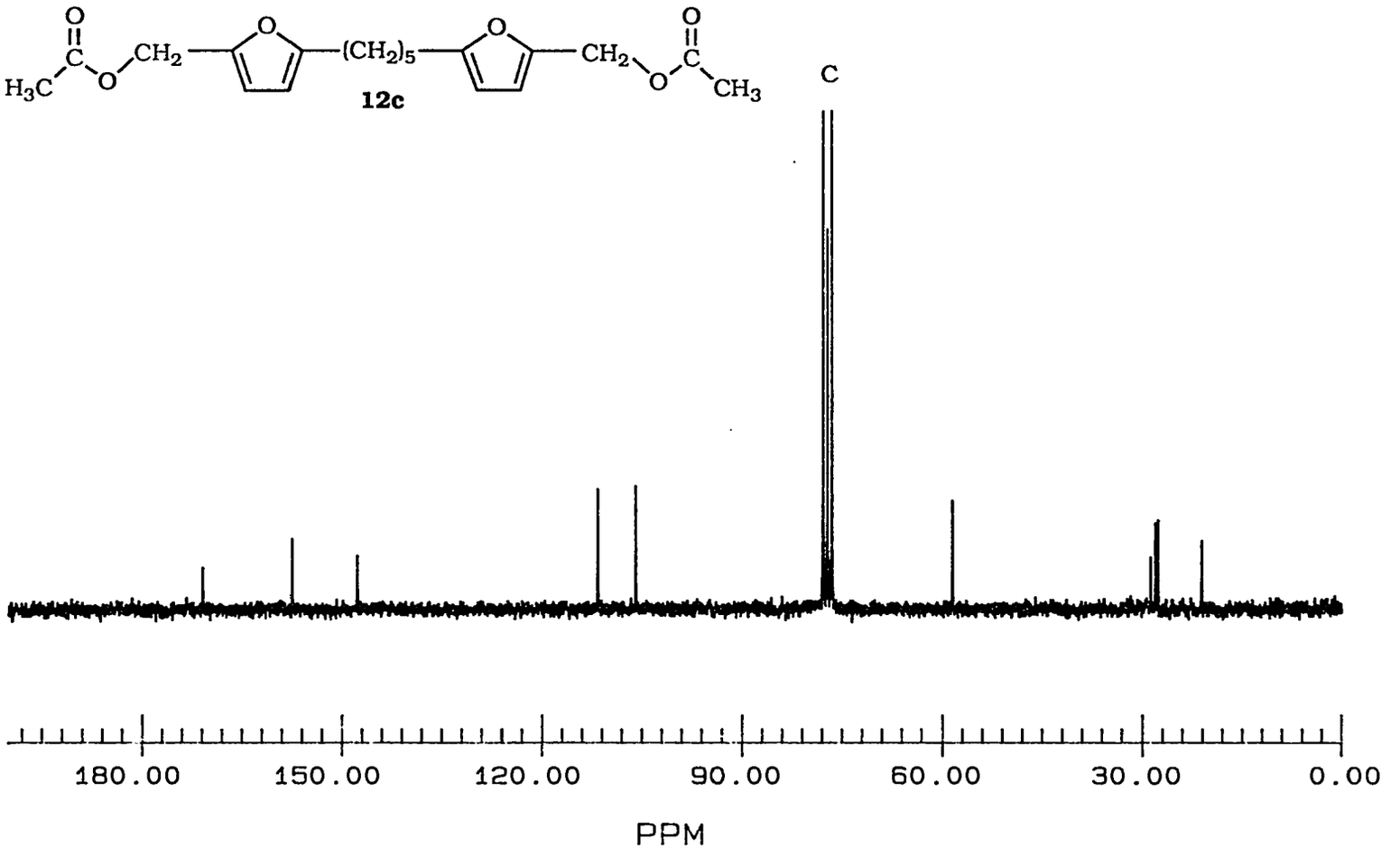


Figure A-9. ^{13}C NMR spectrum of bis-furfuryl acetate **12c**.

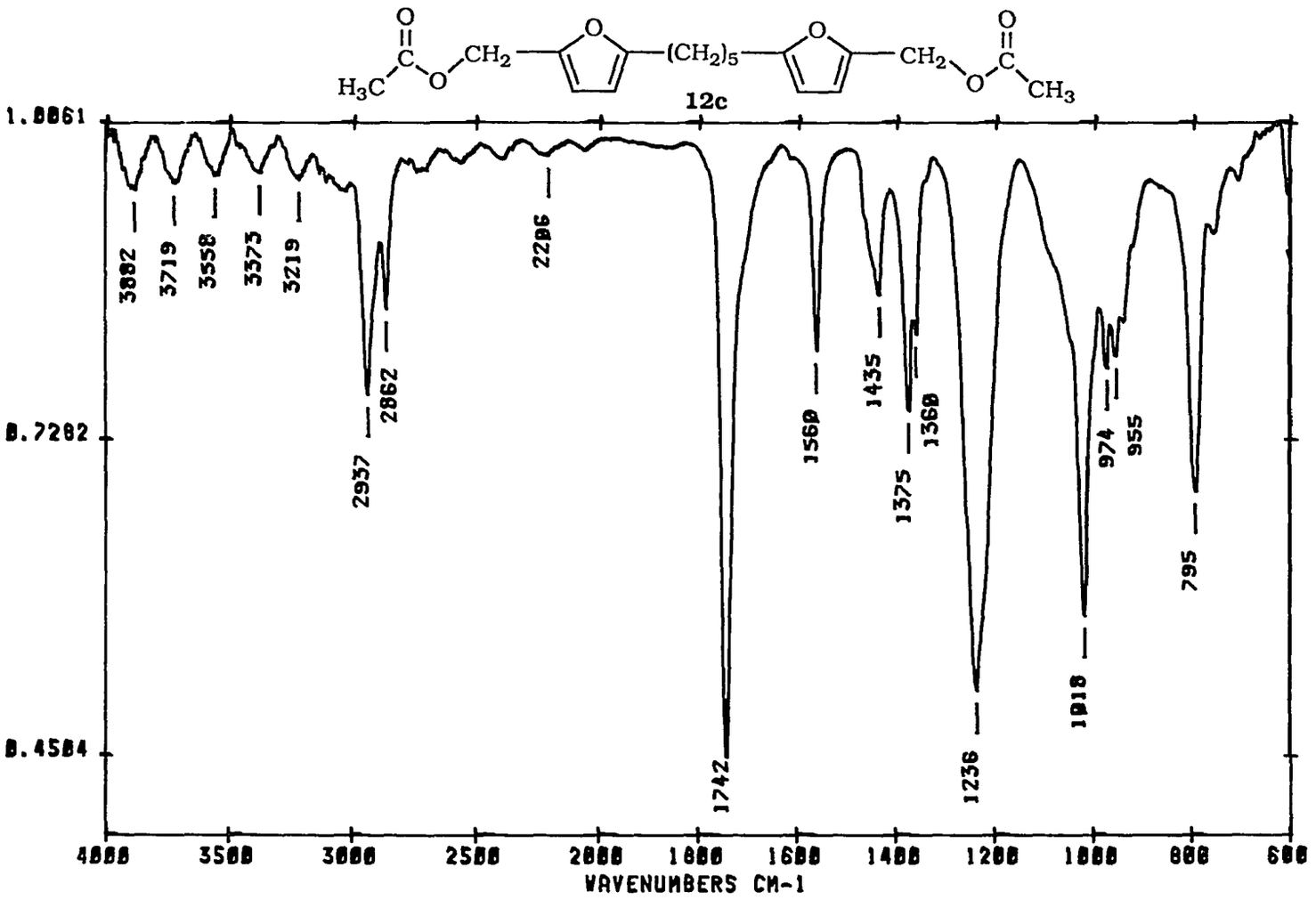


Figure A-10. IR spectrum of bis-furfuryl acetate **12c**.

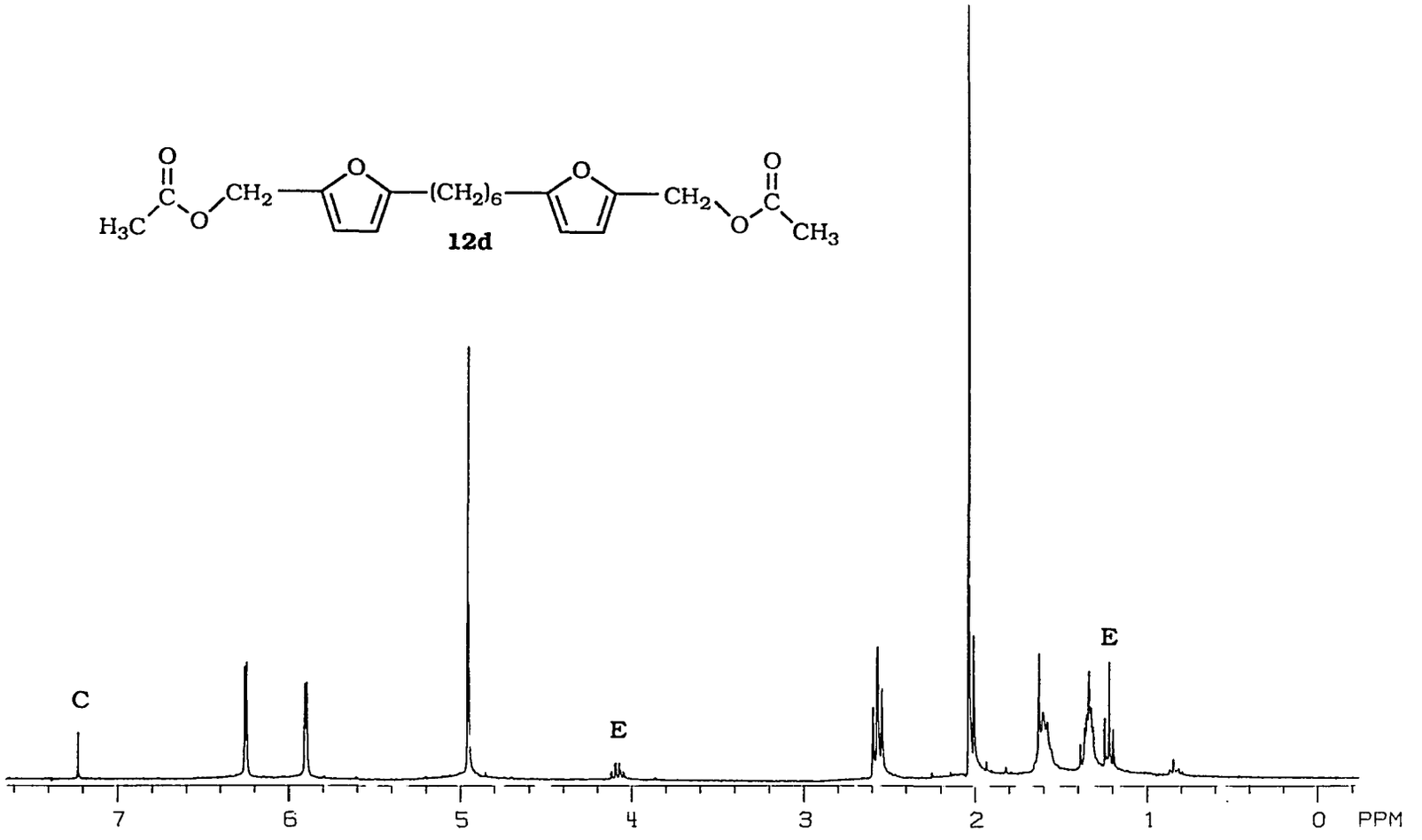


Figure A-11. ^{1}H NMR spectrum of bis-furfuryl acetate **12d**.

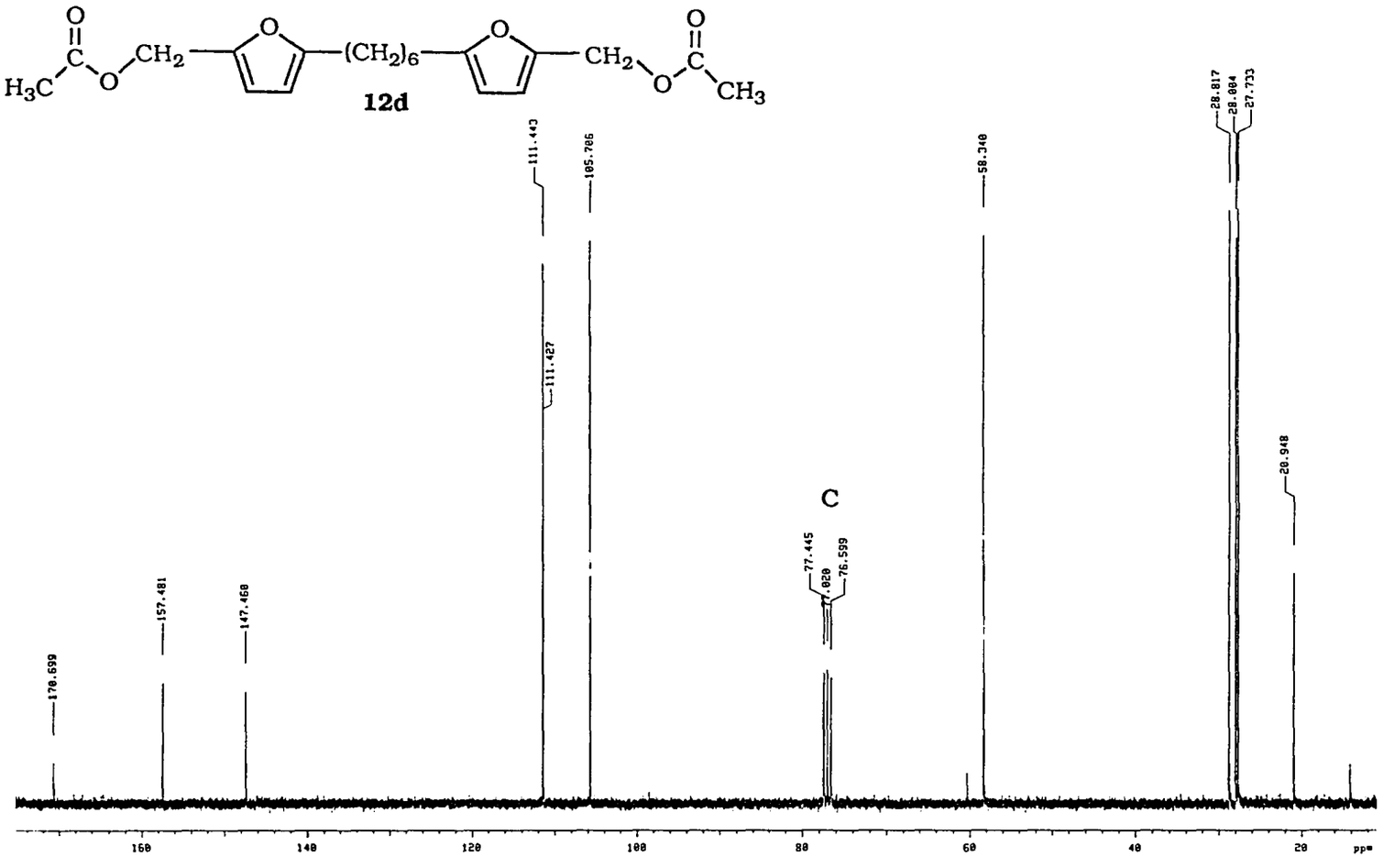


Figure A-12. ^{13}C NMR spectrum of bis-furfuryl acetate **12d**.

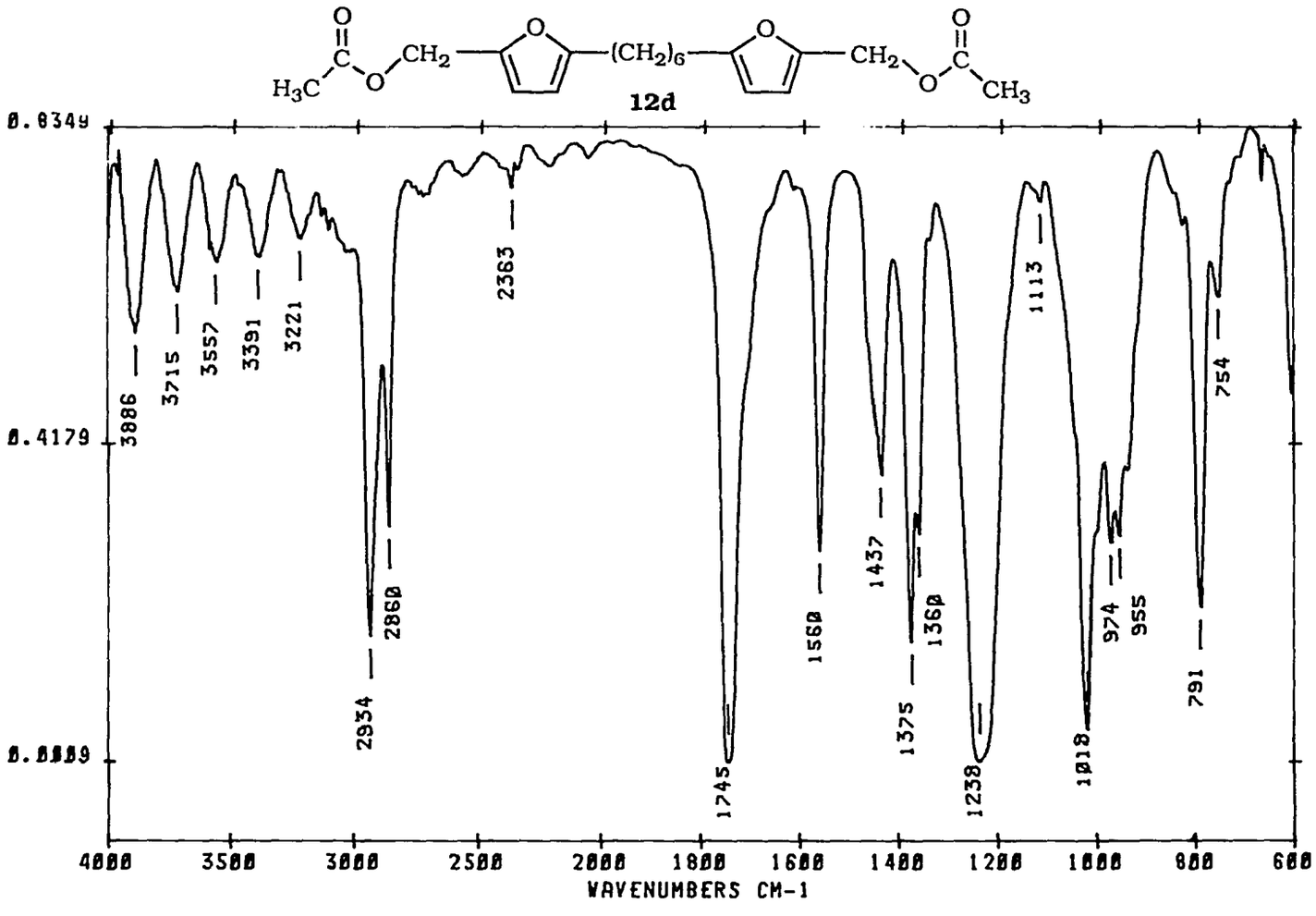


Figure A-13. IR spectrum of bis-furfuryl acetate **12d**.

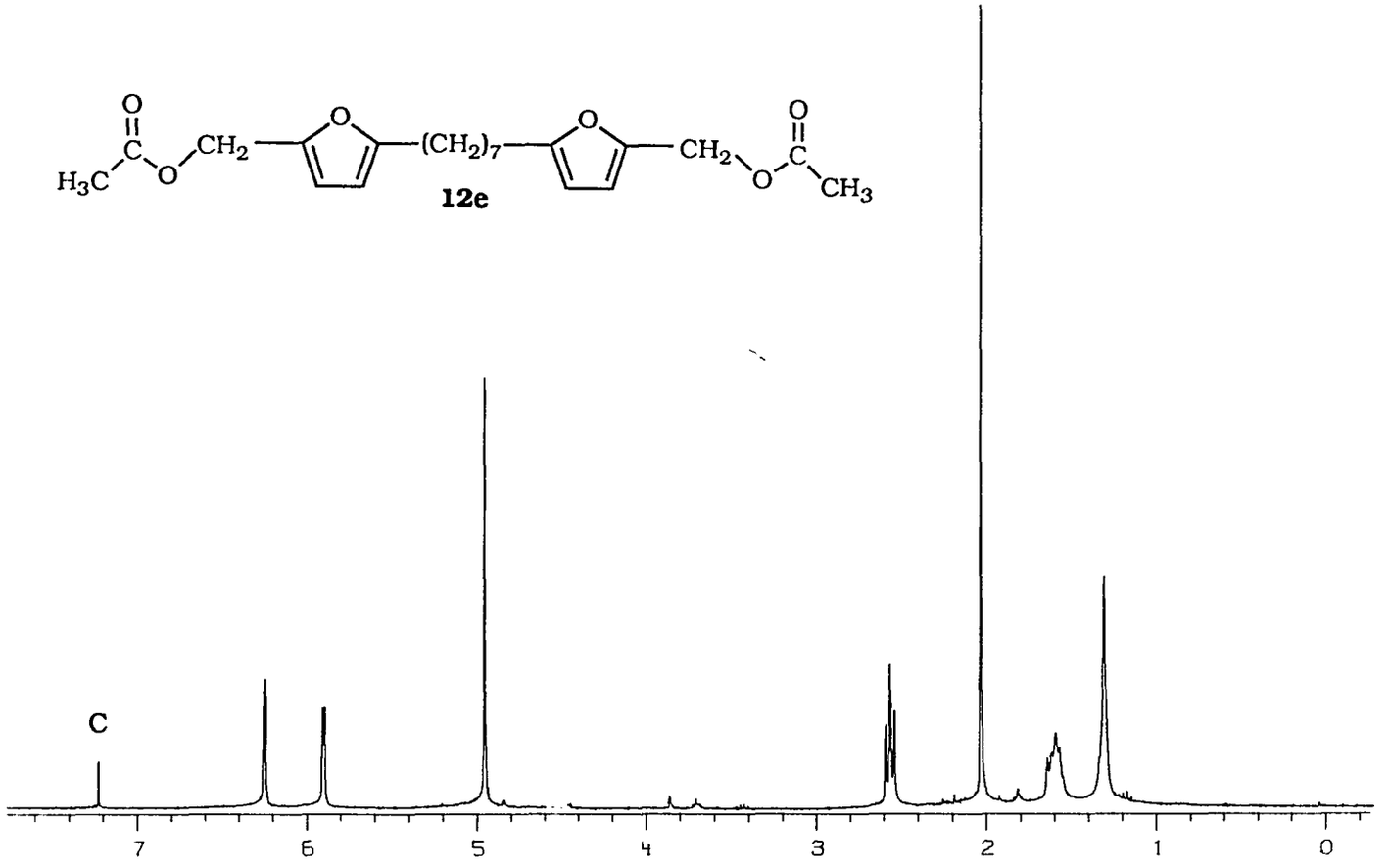


Figure A-14. ^{1}H NMR spectrum of bis-furfuryl acetate **12e**.

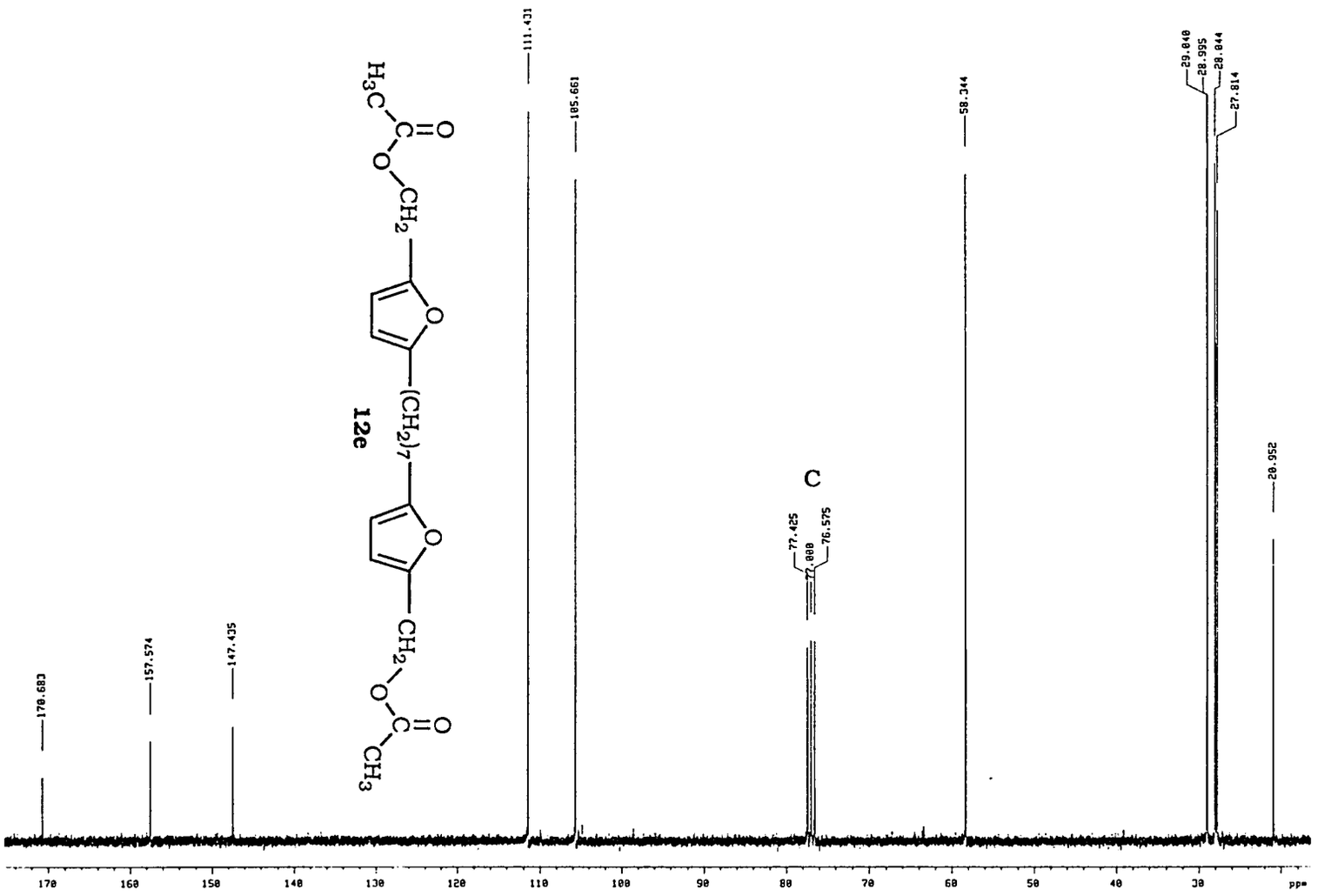


Figure A-15. ^{13}C NMR spectrum of bis-furfuryl acetate **12e**.

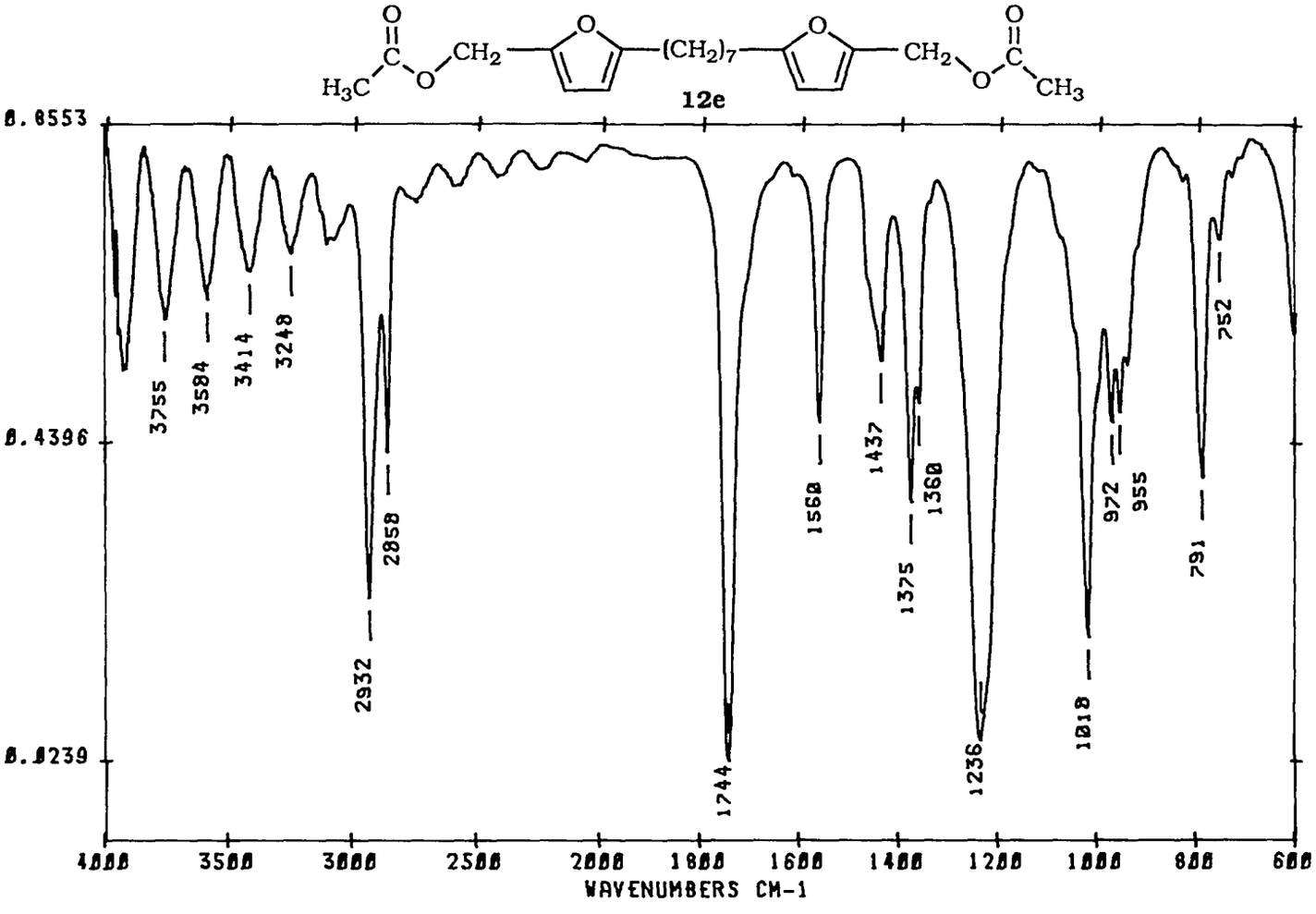


Figure A-16. IR spectrum of bis-furfuryl acetate **12e**.

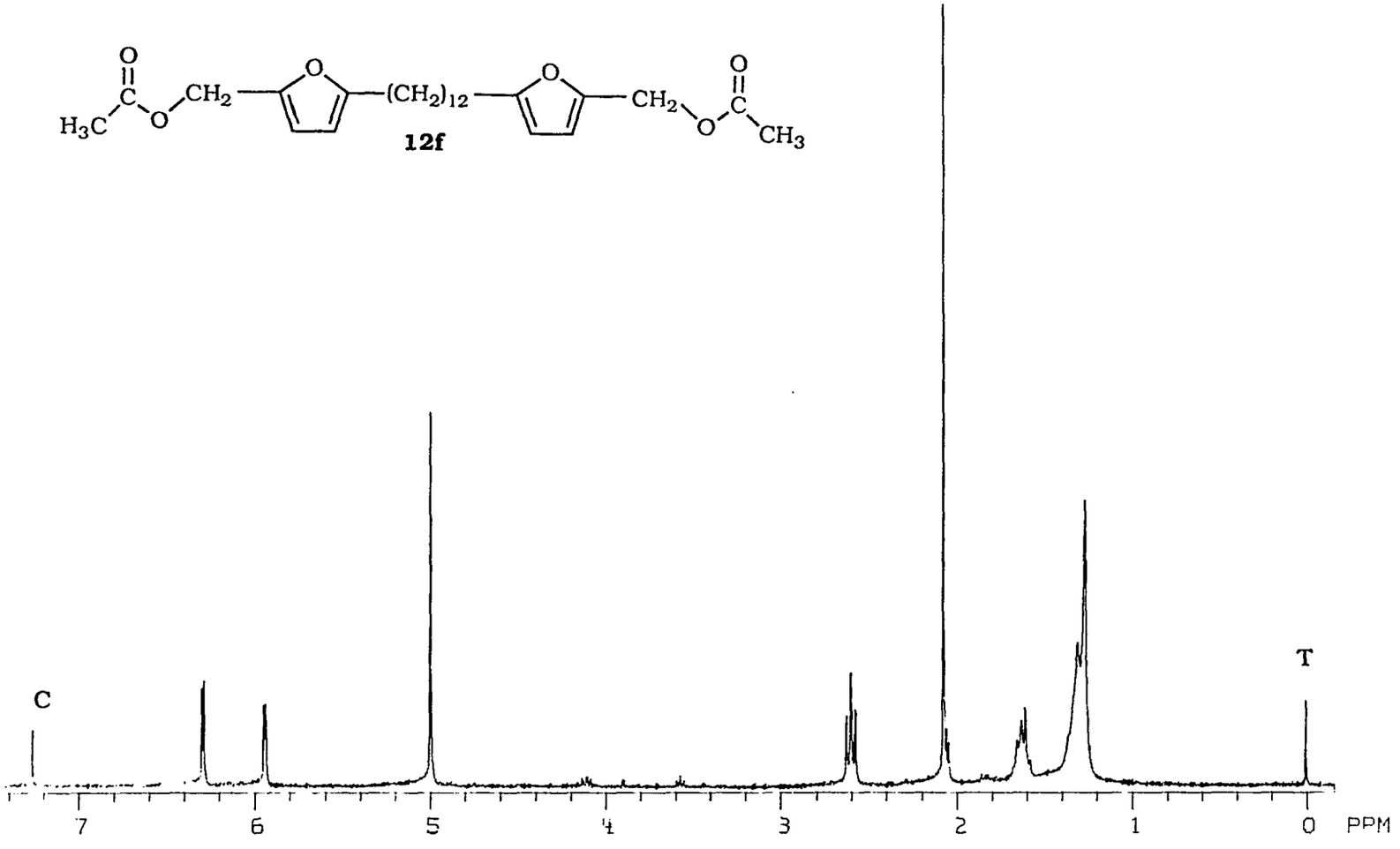
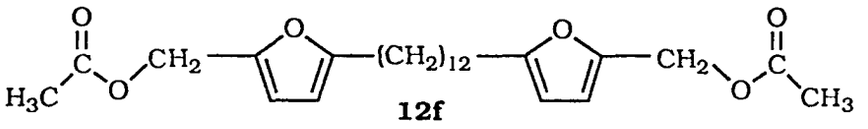


Figure A-17. ^{1}H NMR spectrum of bis-furfuryl acetate **12f**.



12f

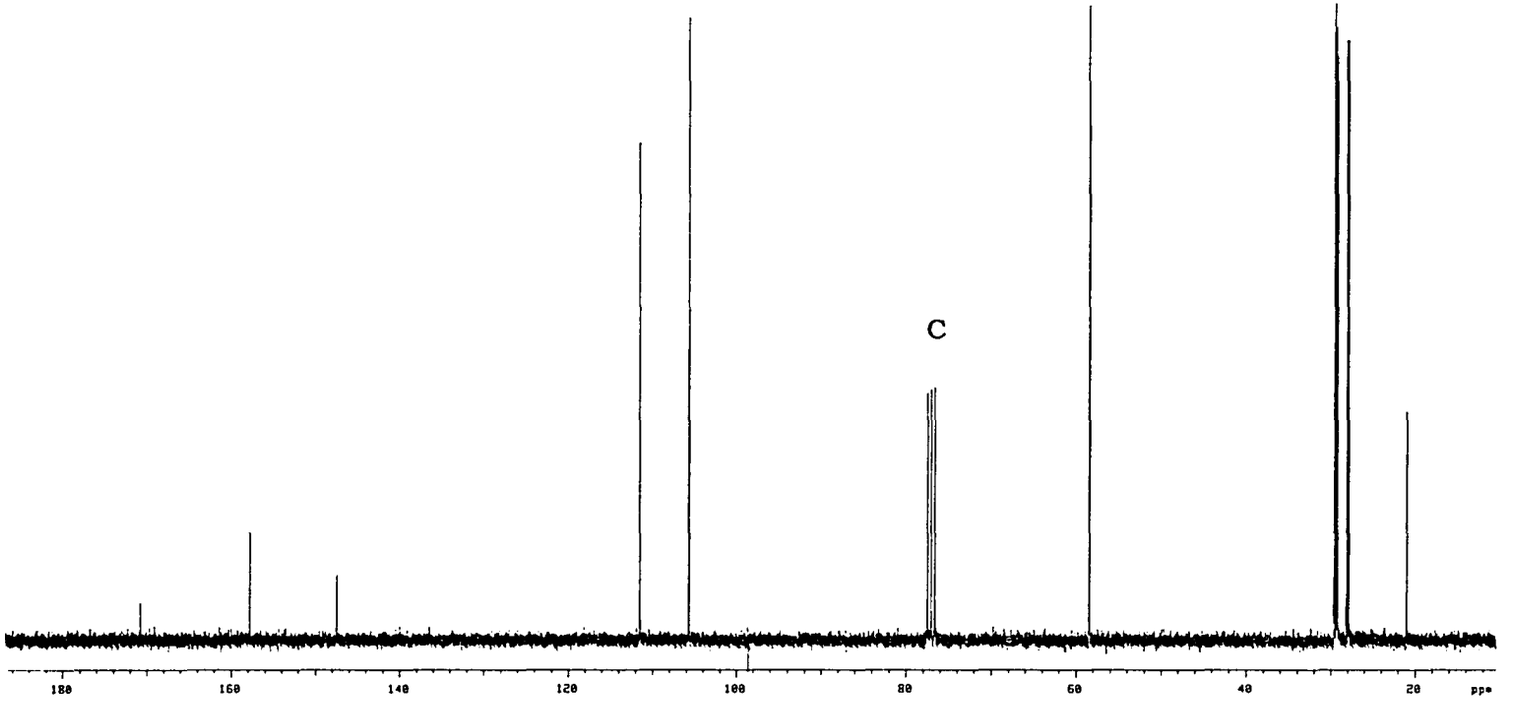


Figure A-18. ^{13}C NMR spectrum of bis-furfuryl acetate **12f**.

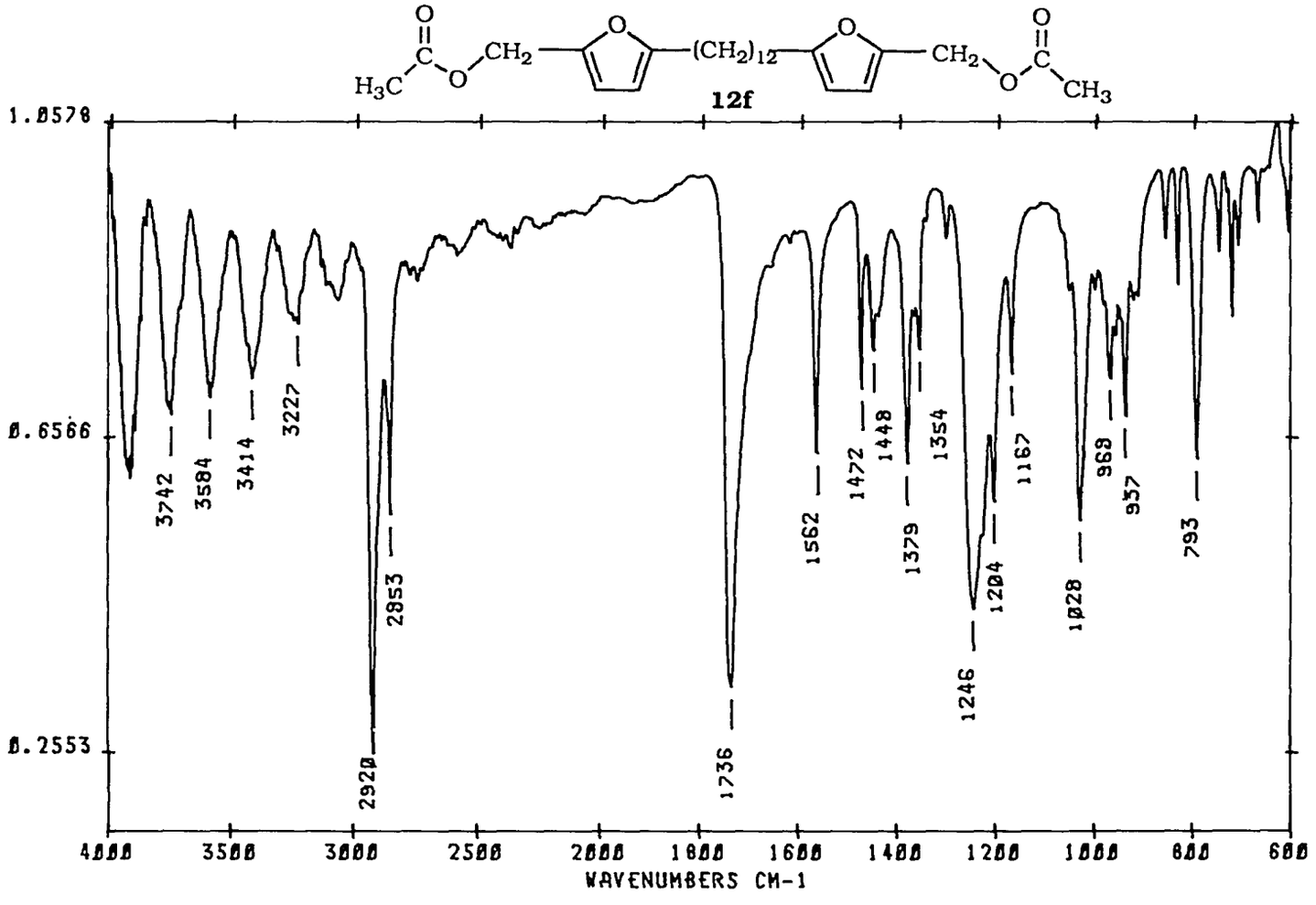
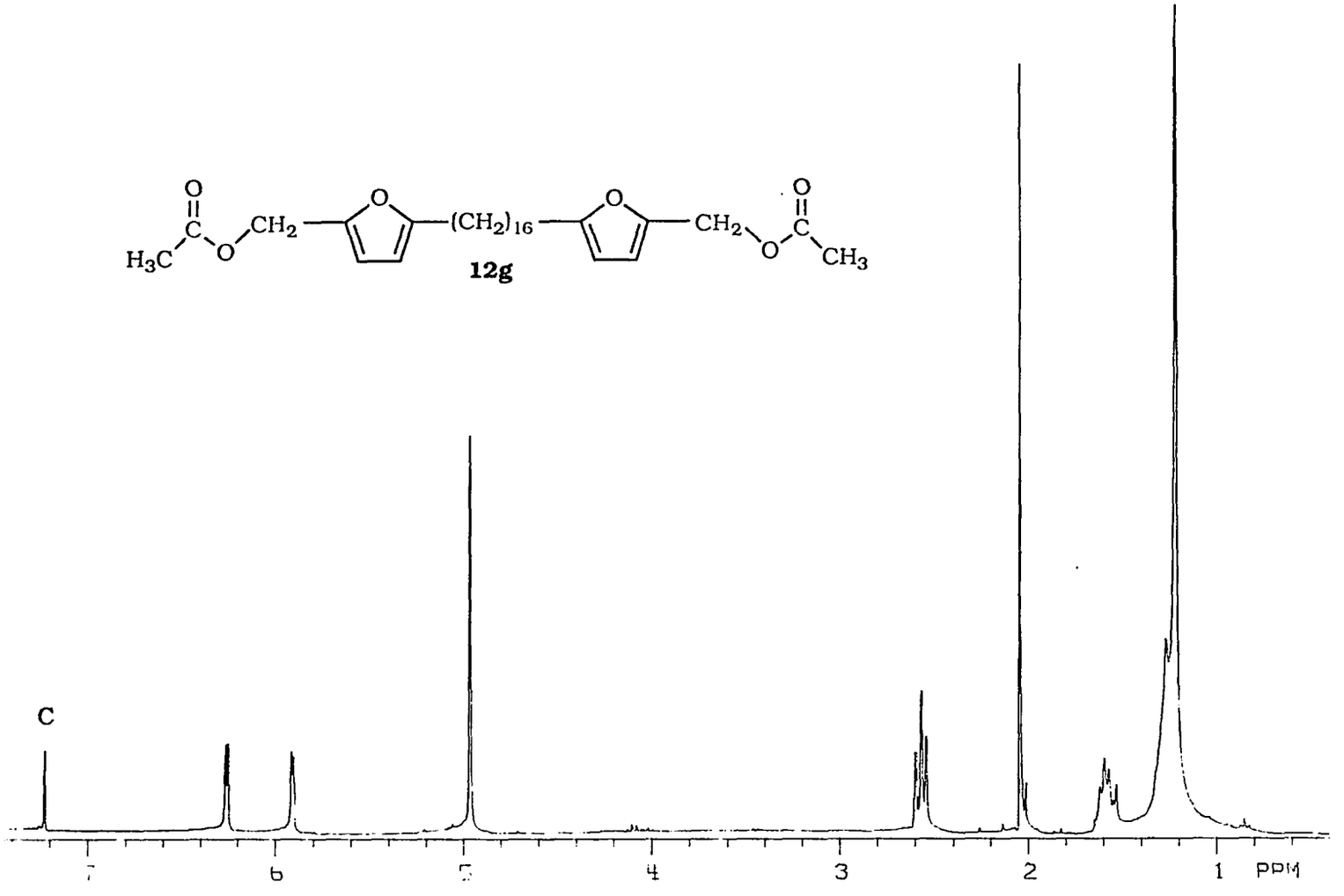
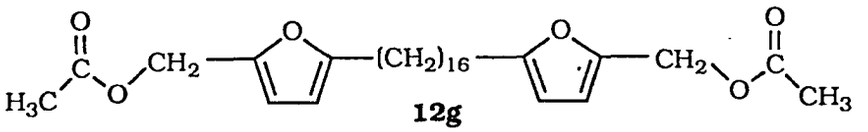


Figure A-19. IR spectrum of bis-furfuryl acetate **12f**.



12g

Figure A-20. ^{1}H NMR spectrum of bis-furfuryl acetate **12g**.



12g

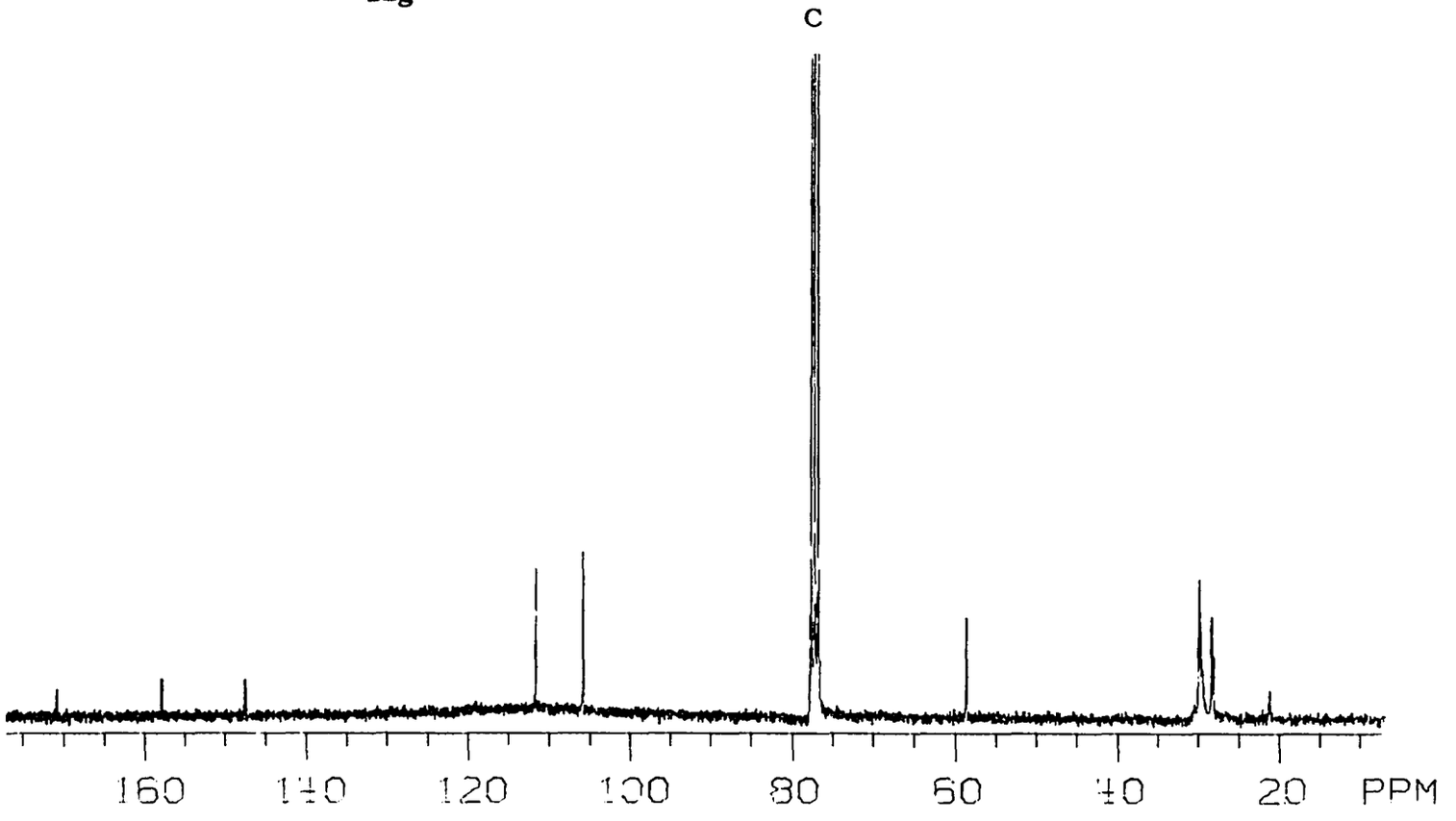


Figure A-21. ^{13}C NMR spectrum of bis-furfuryl acetate **12g**.

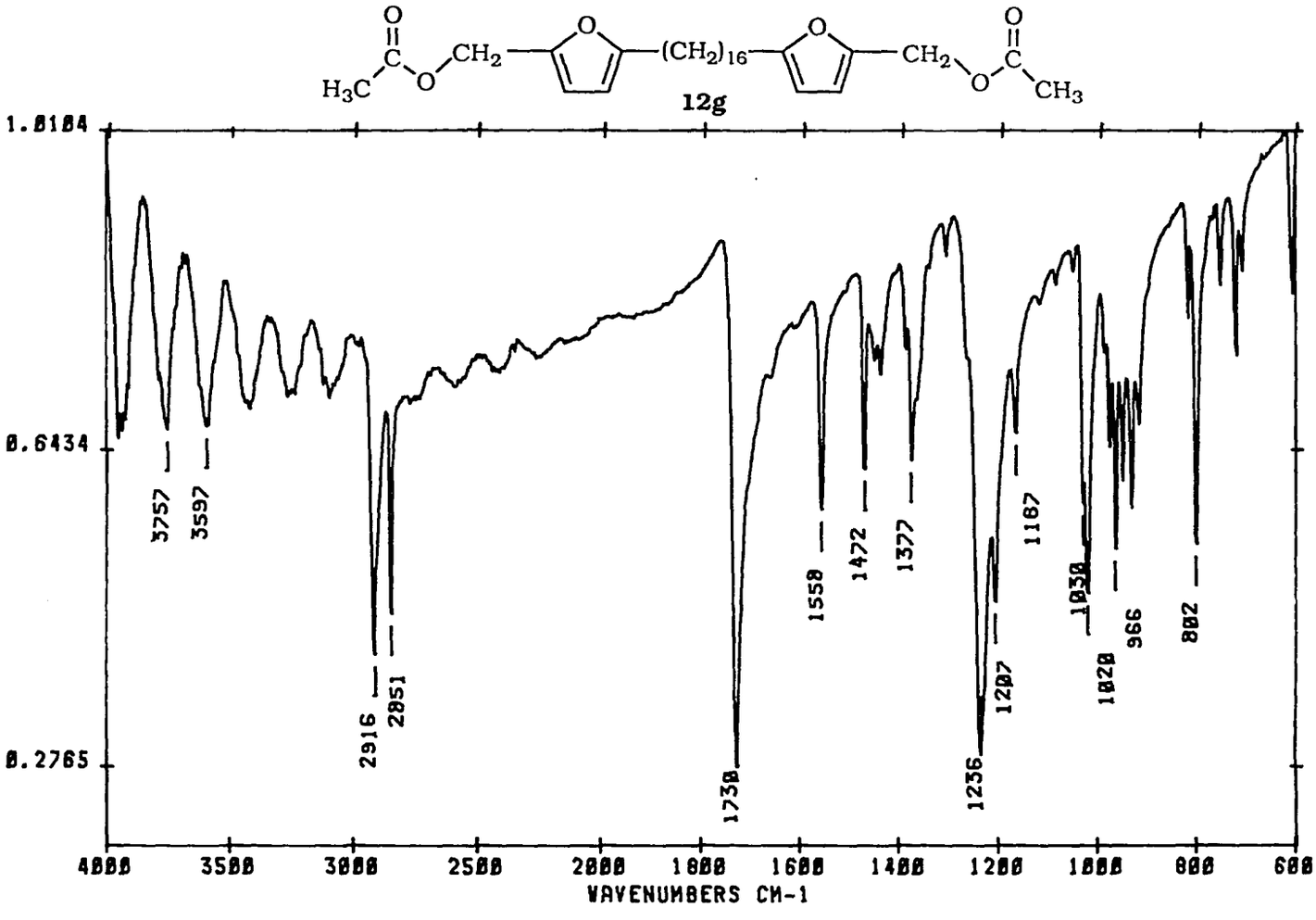
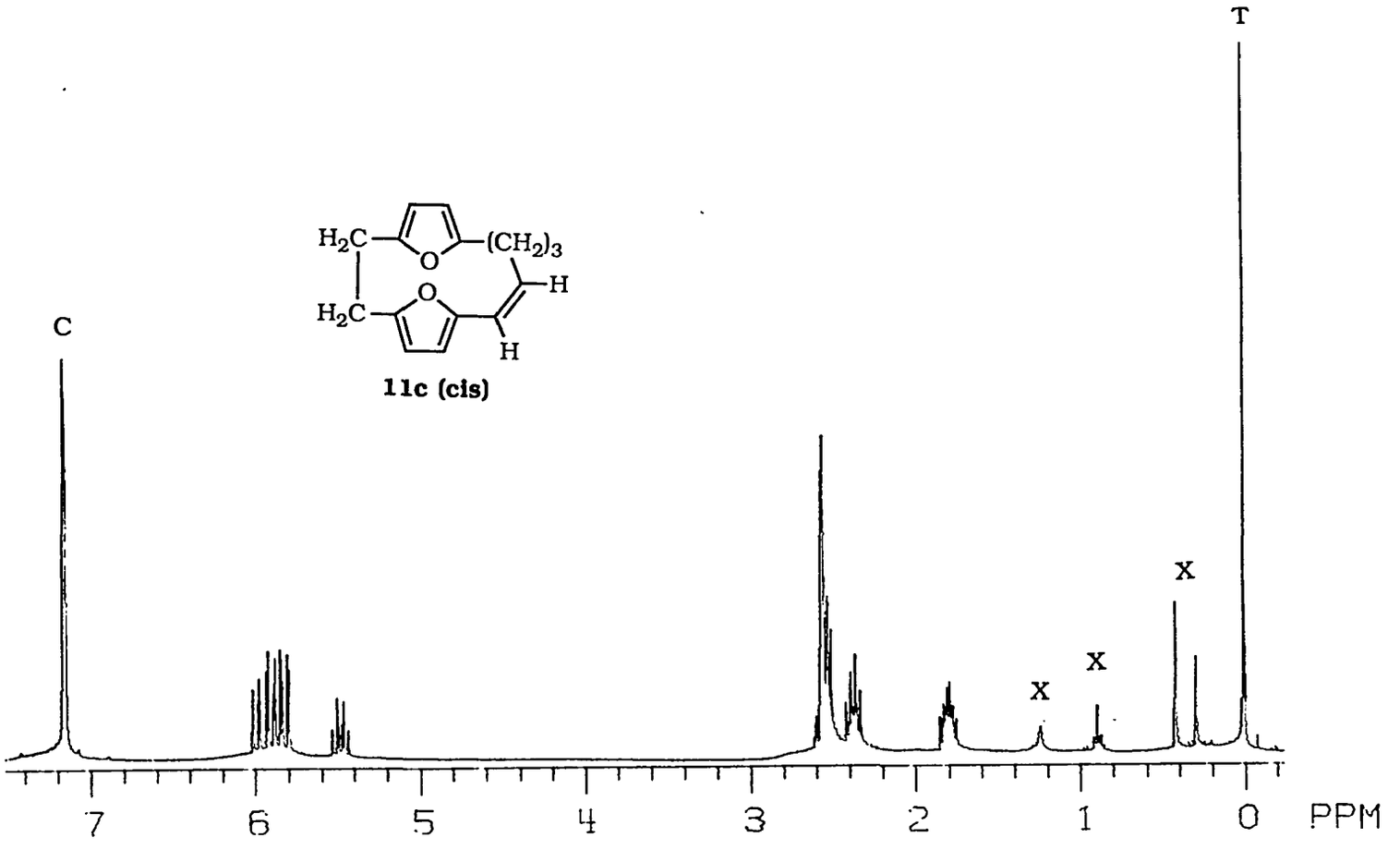


Figure A-22. IR spectrum of bis-furfuryl acetate **12g**.



11c (cis)

Figure A-23. ^{1}H NMR spectrum of macrocycle **11c (cis)**.

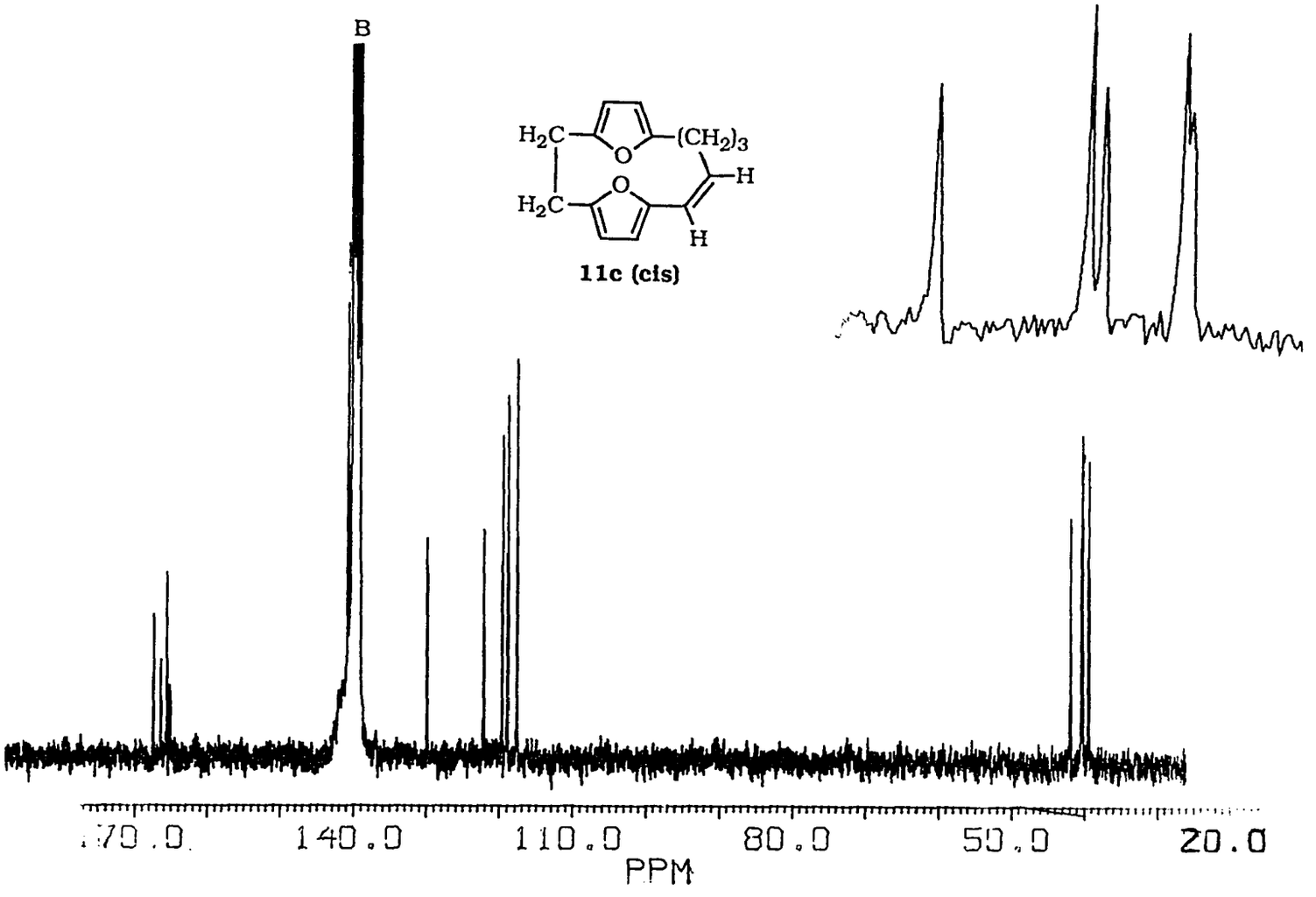


Figure A-24. ^{13}C NMR spectrum of macrocycle **11c (cis)**.

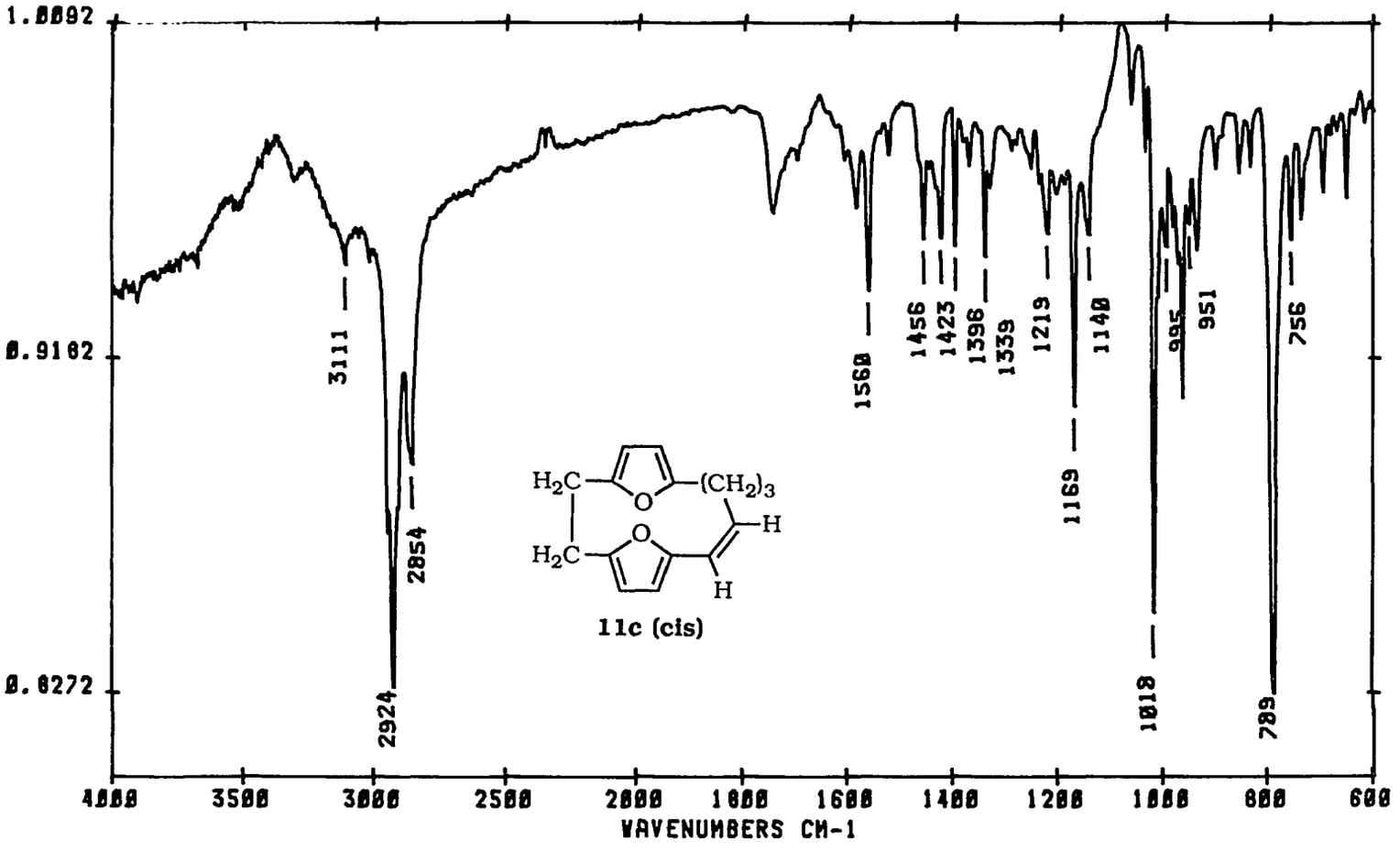


Figure A-25. IR spectrum of macrocycle **11c (cis)**.

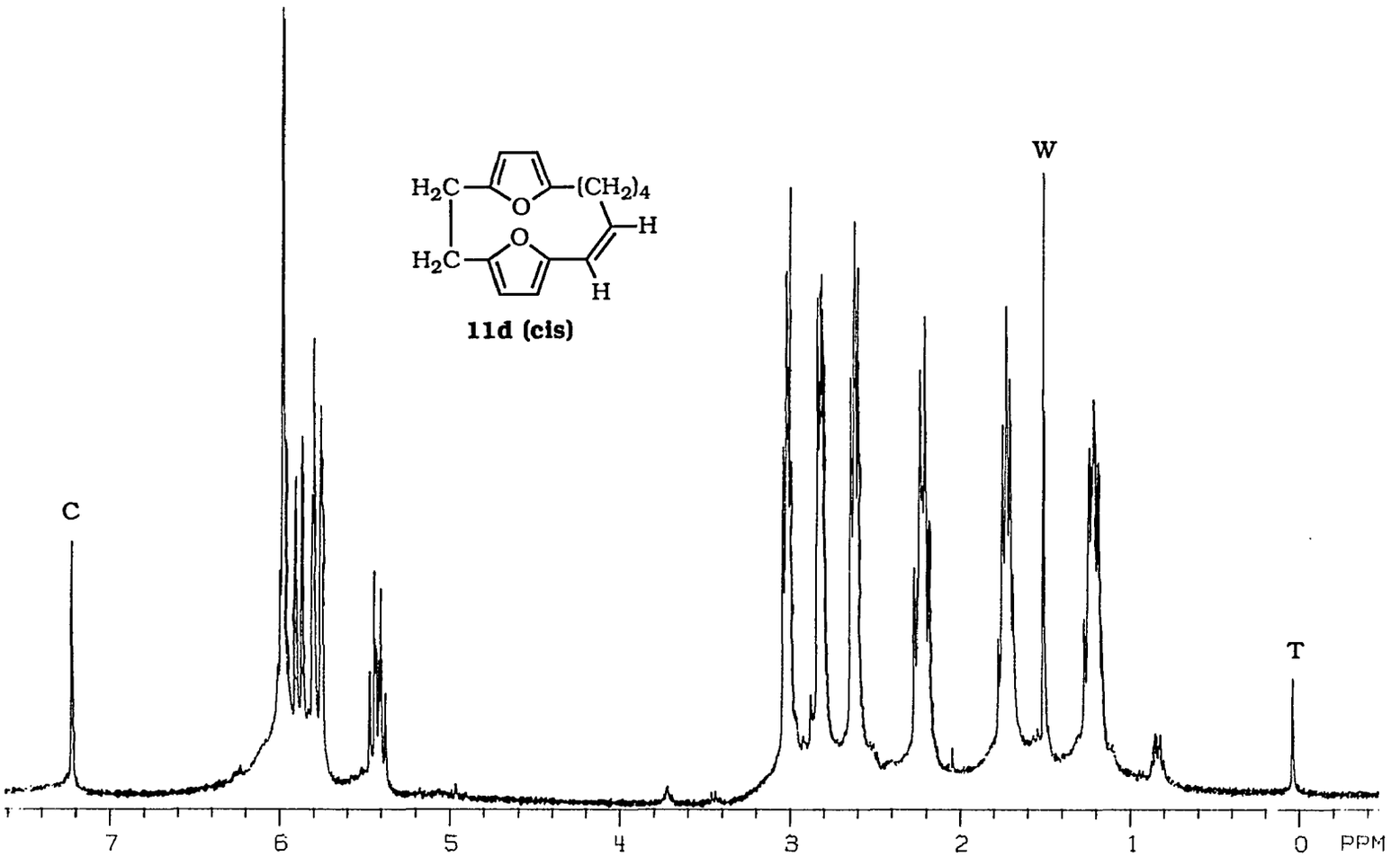
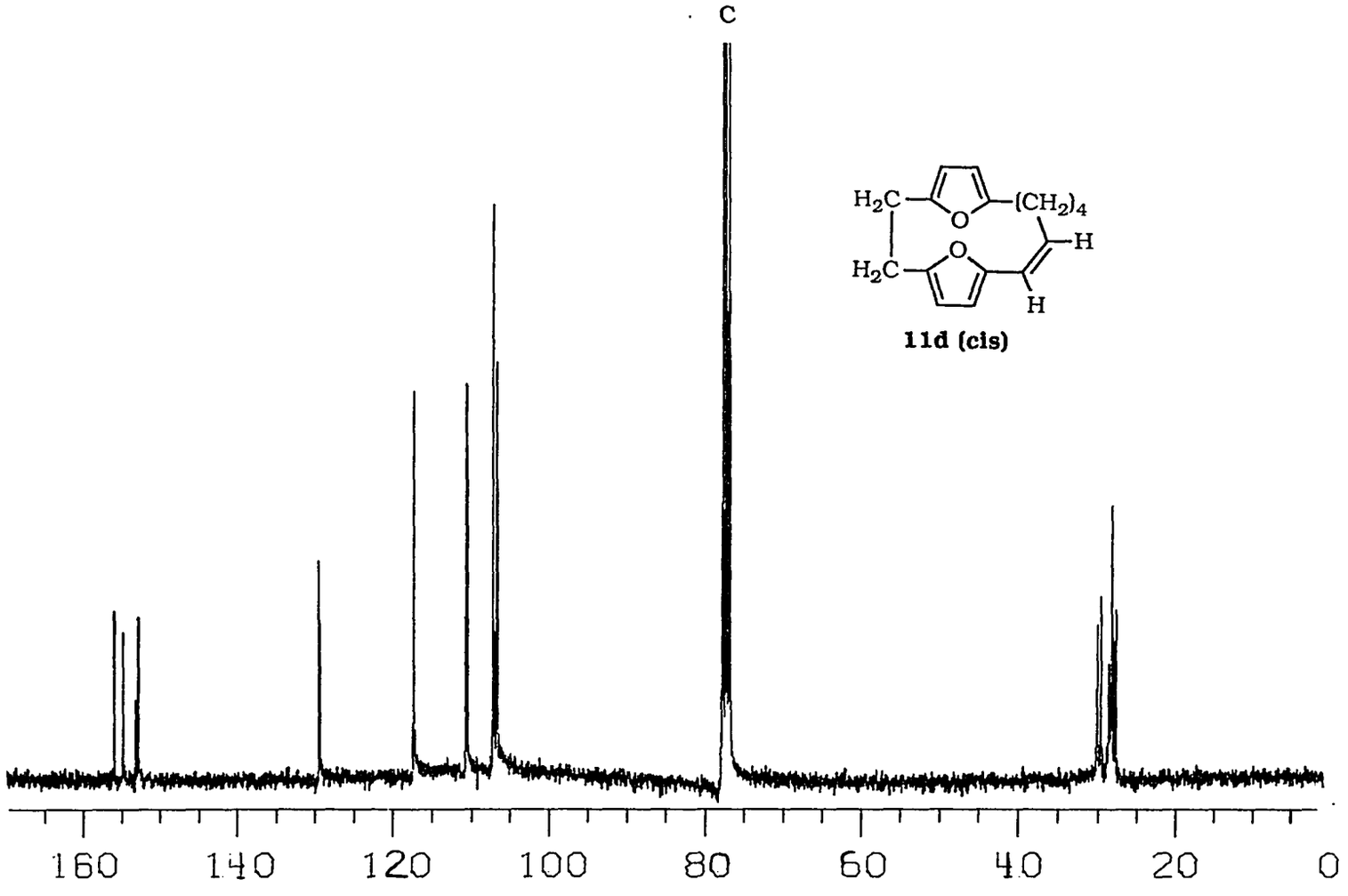


Figure A-26. ^{1}H NMR spectrum of macrocycle **11d (cis)**.



11d (cis)

Figure A-27. ^{13}C NMR spectrum of macrocycle **11d (cis)**.

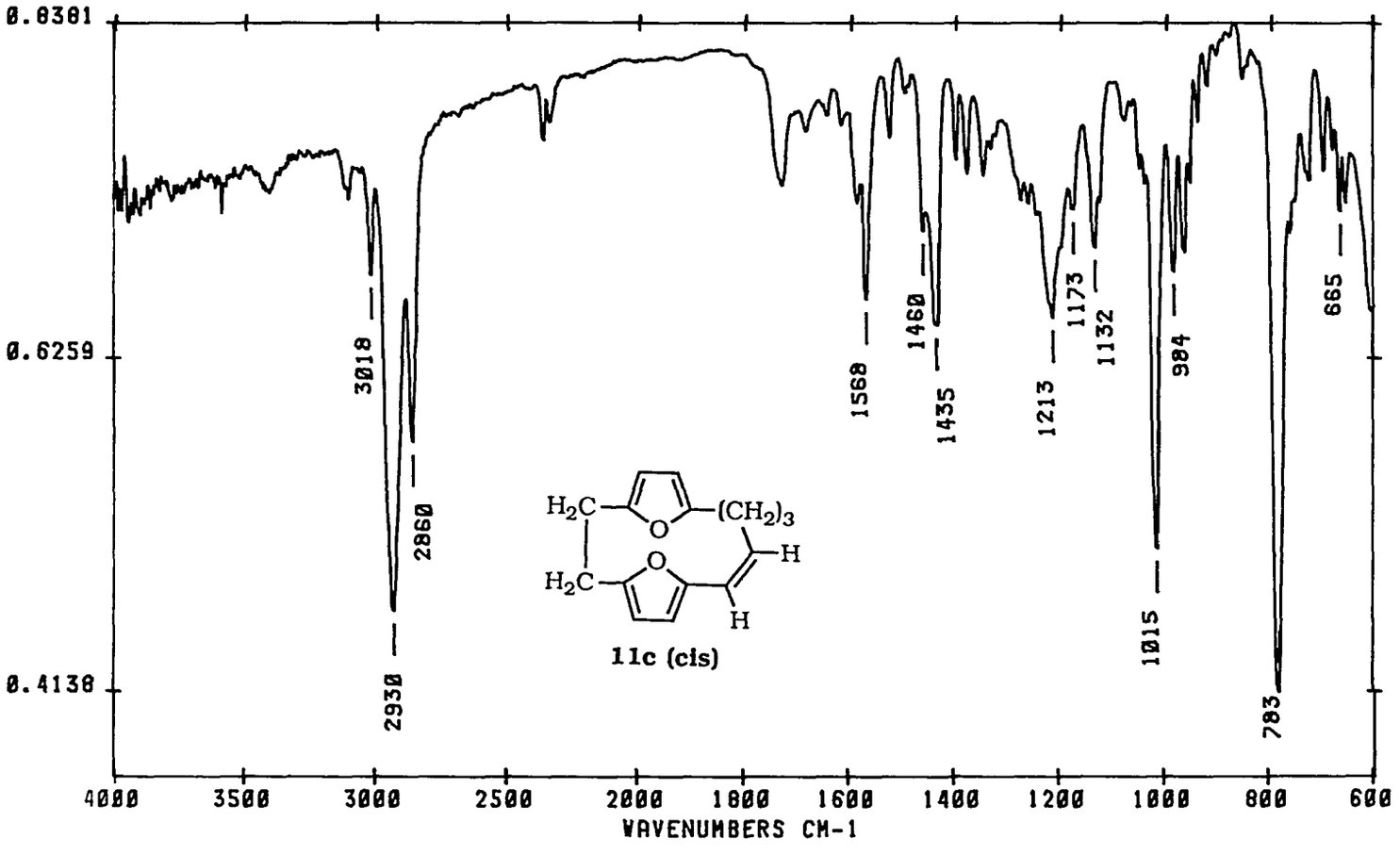


Figure A-28. IR spectrum of macrocycle **11d (cis)**.

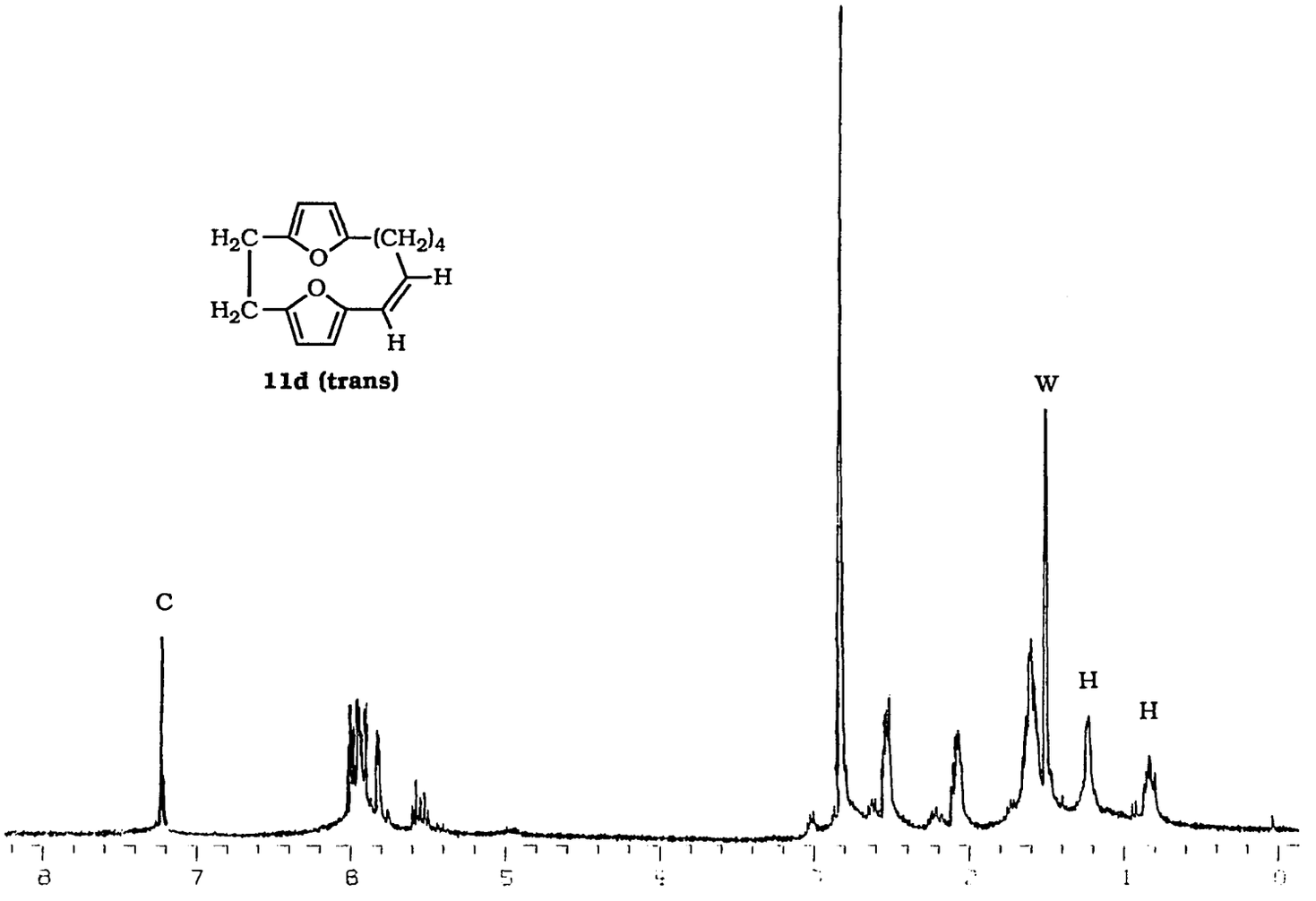
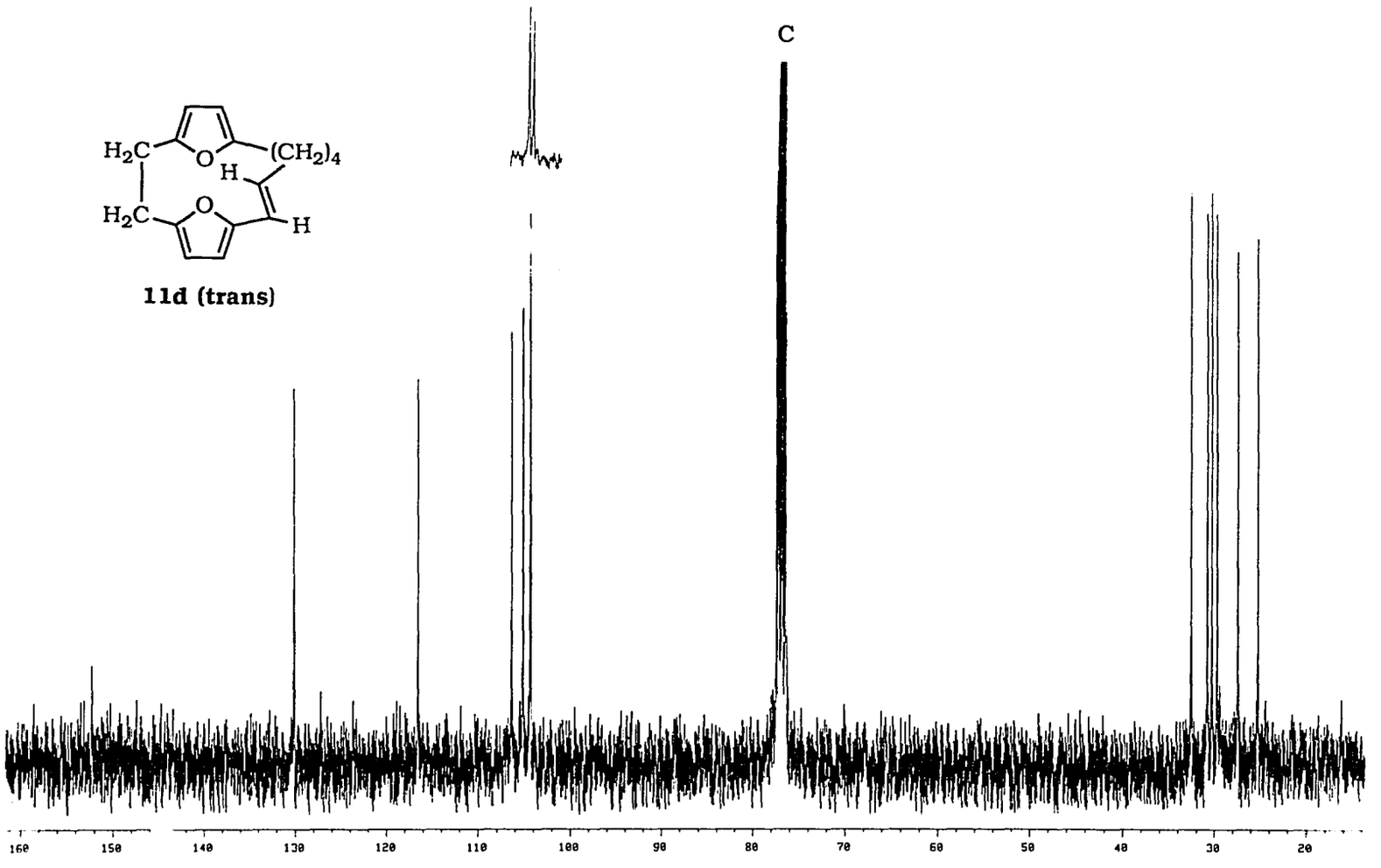


Figure A-29. ^{1}H NMR spectrum of macrocycle **11d (trans)**.



11d (trans)

Figure A-30. ^{13}C NMR spectrum of macrocycle **11d (trans)**.

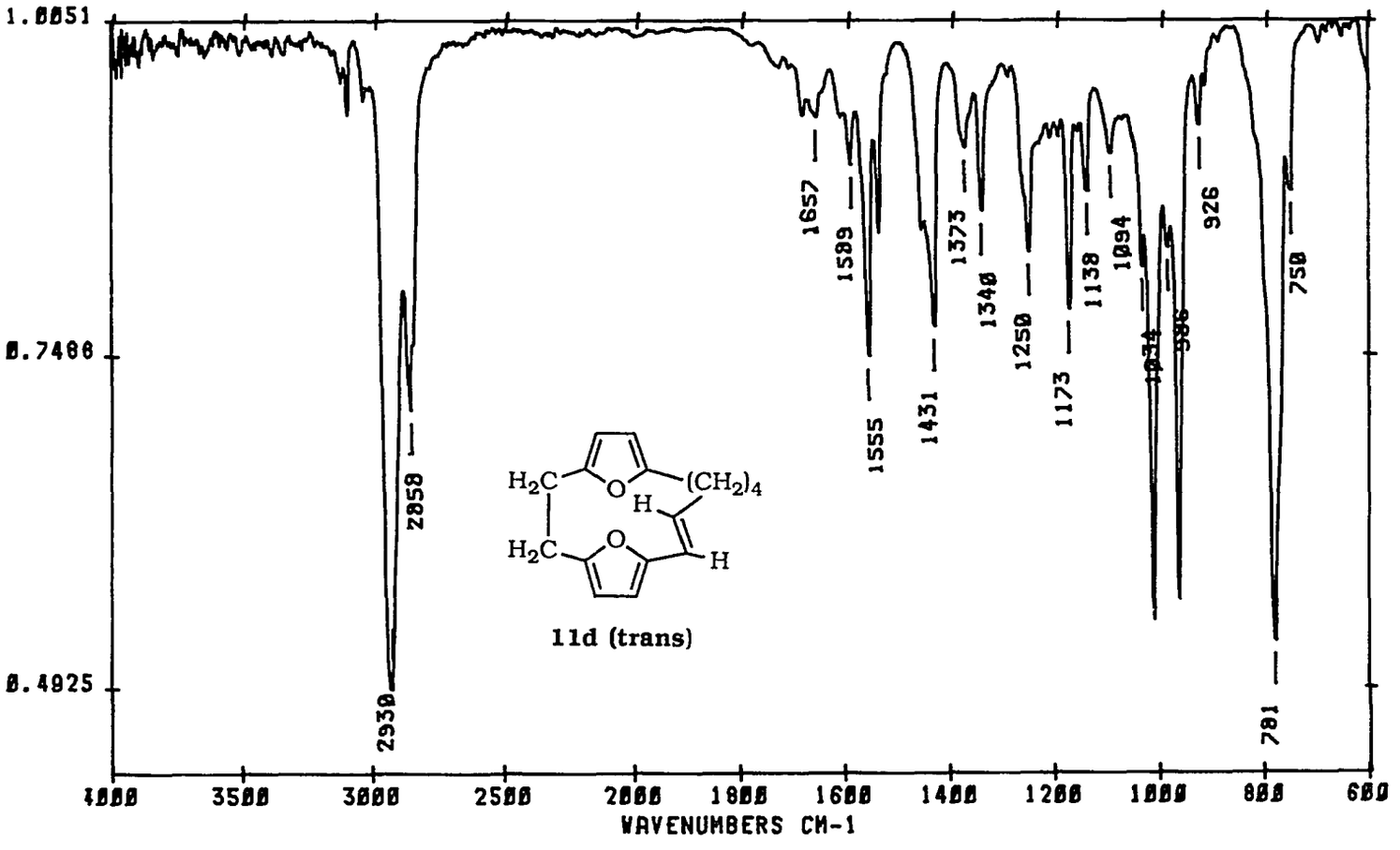
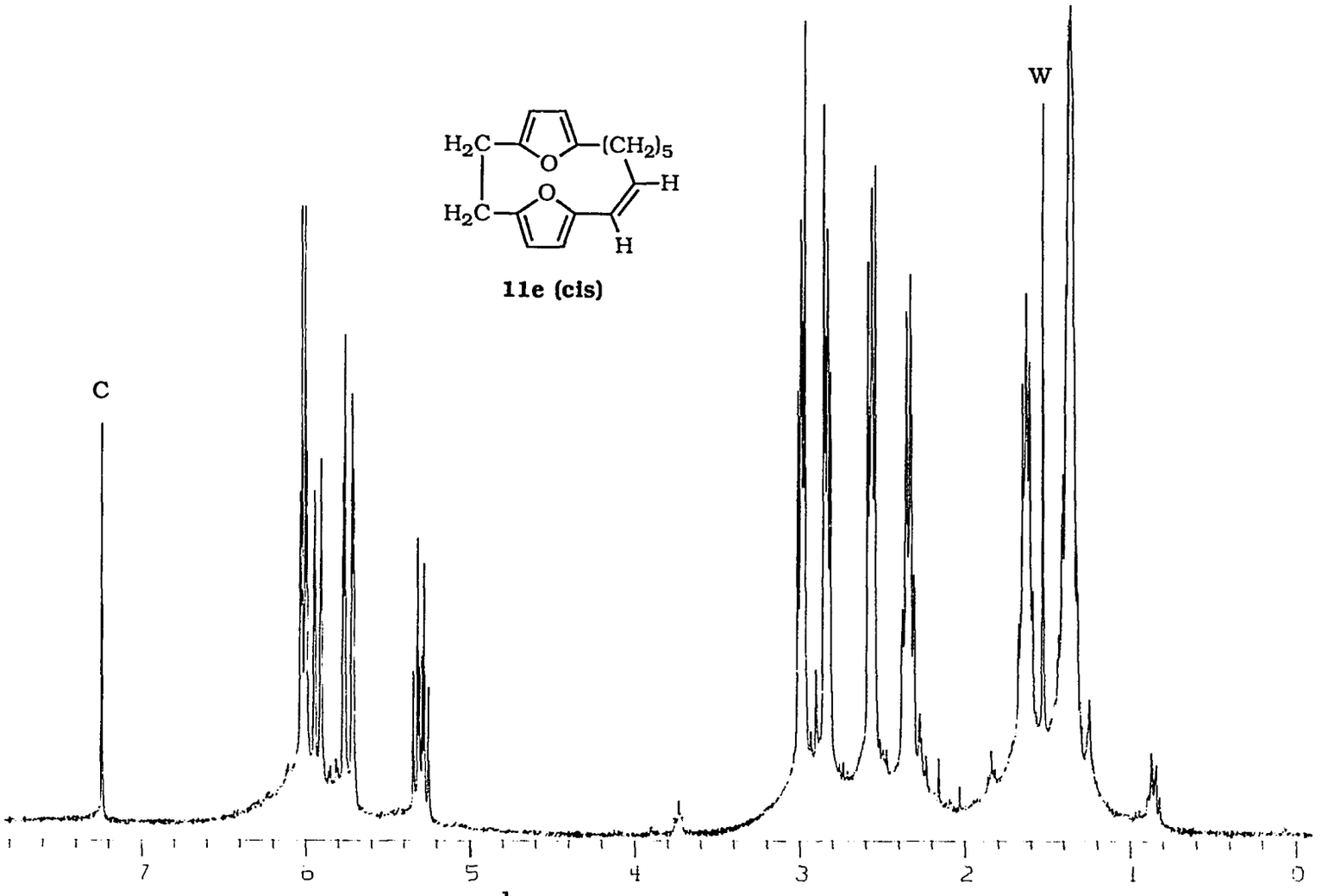
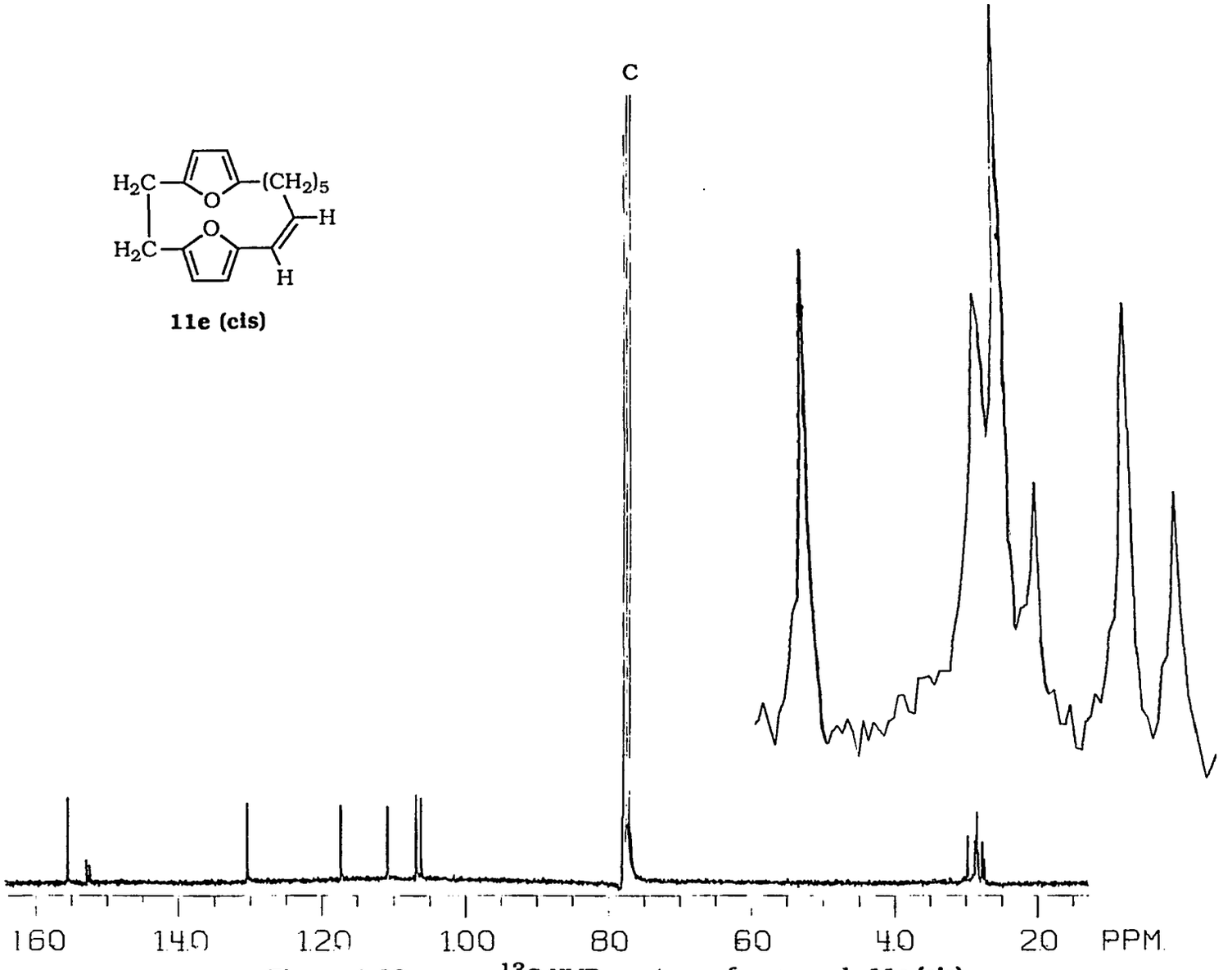


Figure A-31. IR spectrum of macrocycle **11d (trans)**.



11e (cis)

Figure A-32. ^{1}H NMR spectrum of macrocycle **11e (cis)**.



11e (cis)

Figure A-33. ^{13}C NMR spectrum of macrocycle **11e (cis)**.

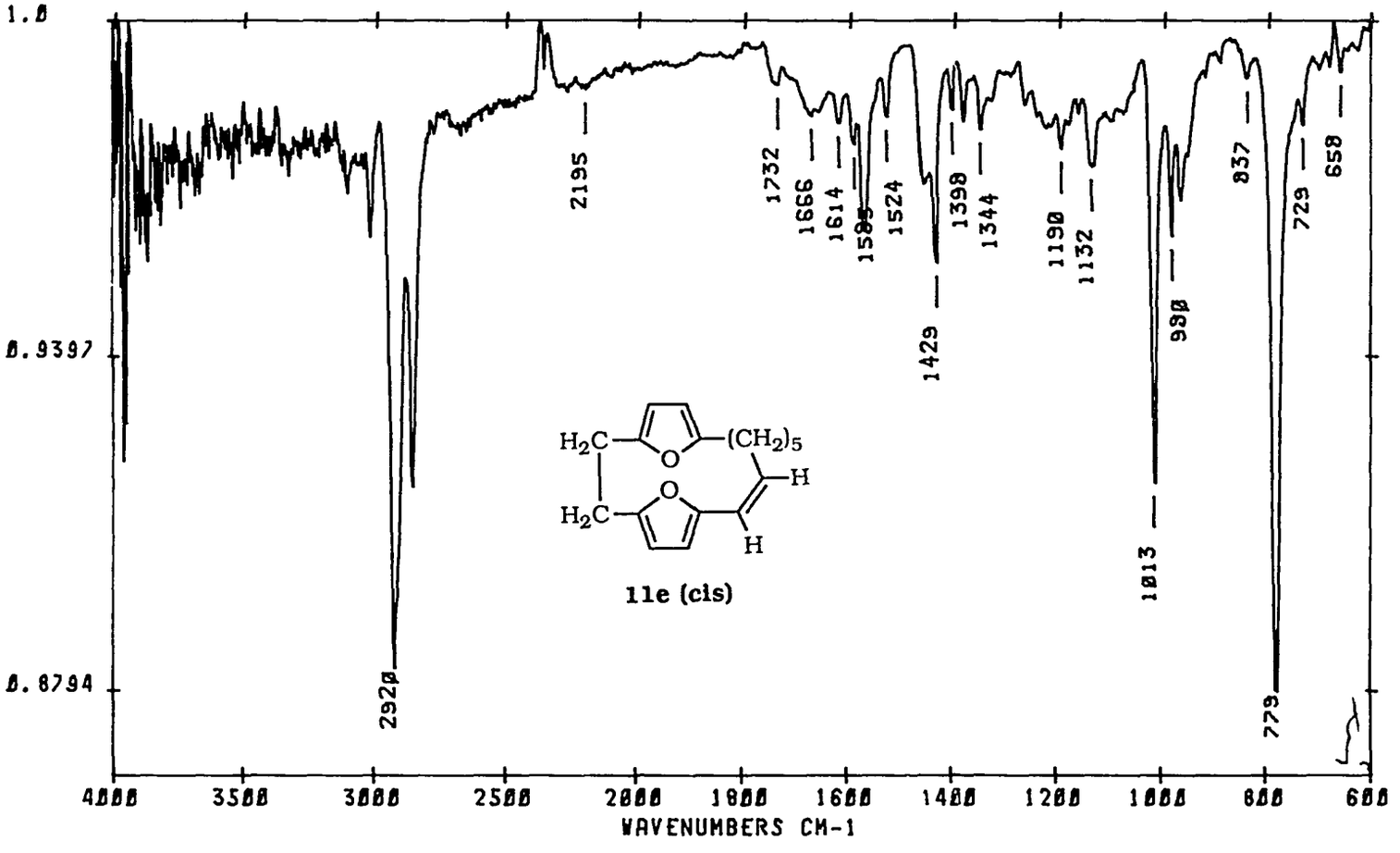
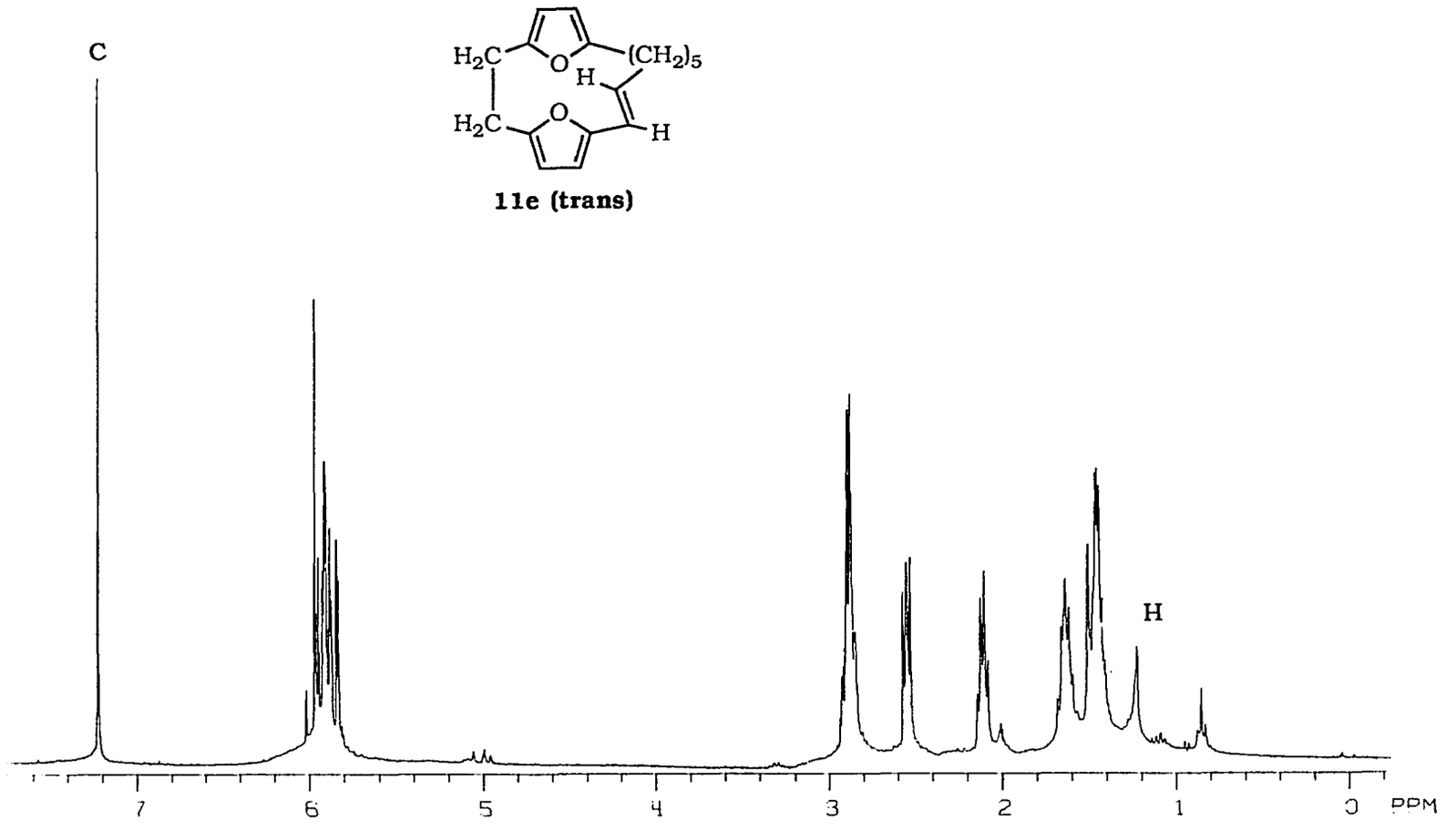


Figure A-34. IR spectrum of macrocycle **11e (cis)**.



11e (trans)

Figure A-35. ^{1}H NMR spectrum of macrocycle **11e (trans)**.

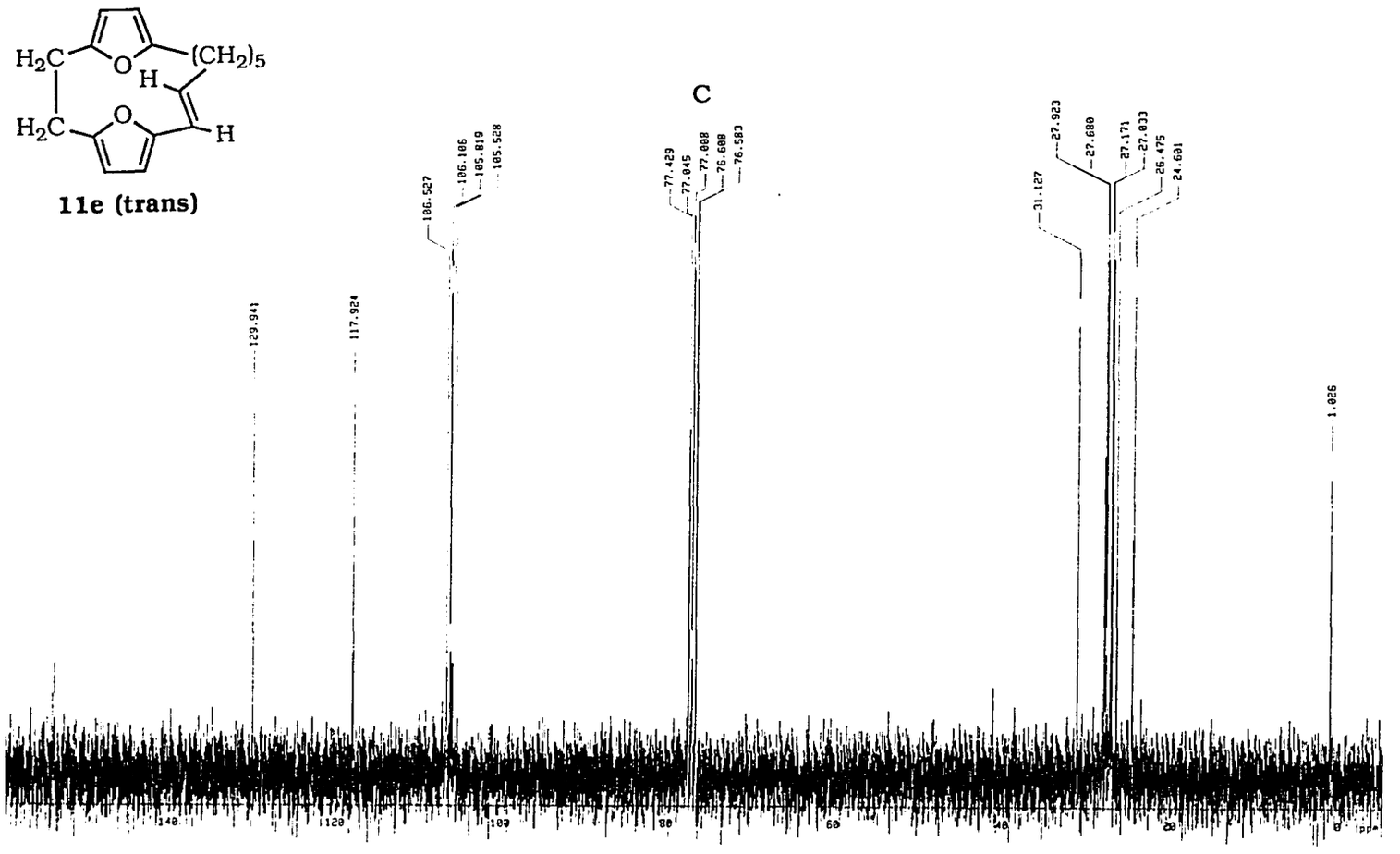


Figure A-36. ^{13}C NMR spectrum of macrocycle **11e (trans)**.

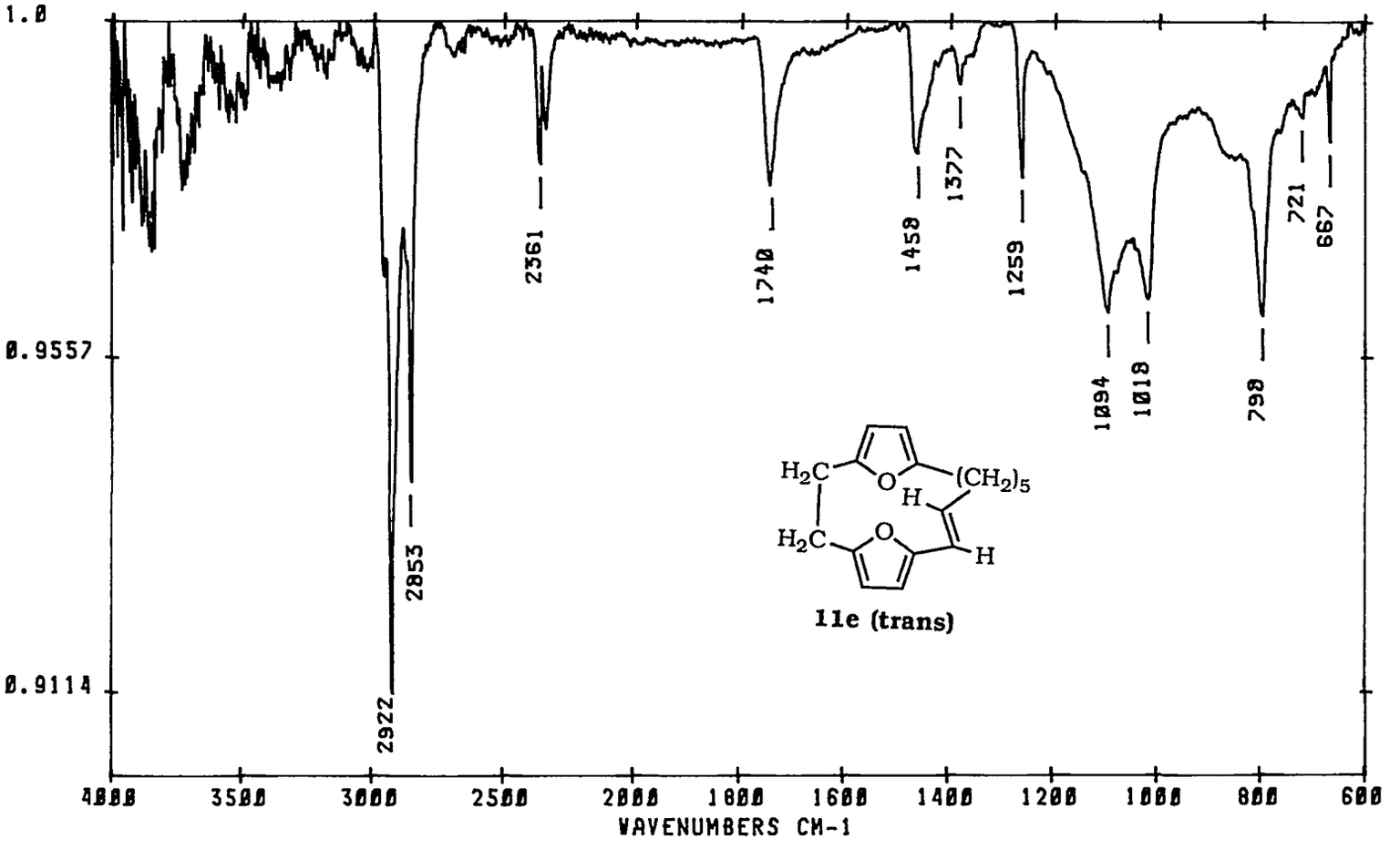
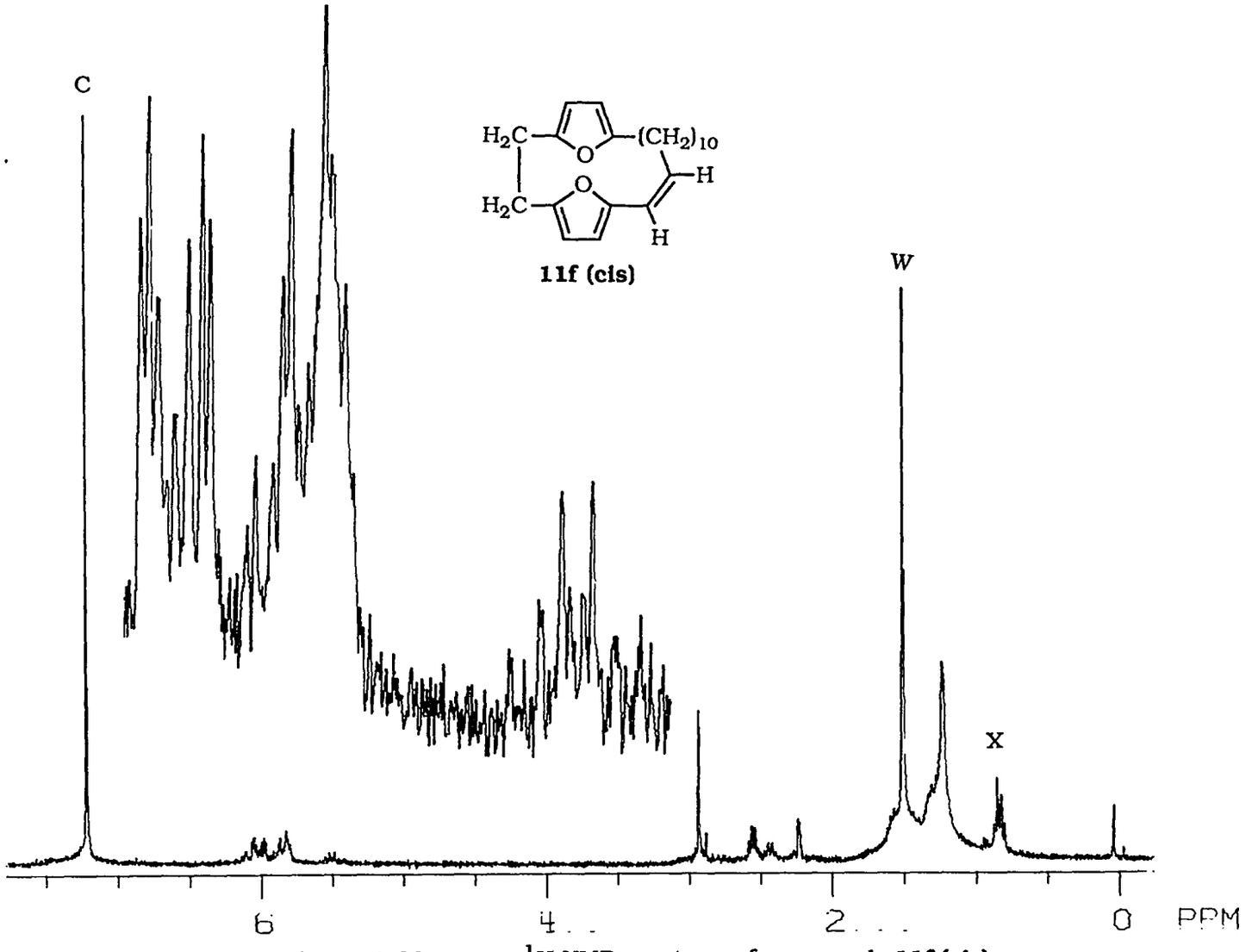


Figure A-37. IR spectrum of macrocycle **11e (trans)**.



11f (cis)

Figure A-38. ^{1}H NMR spectrum of macrocycle **11f (cis)**.

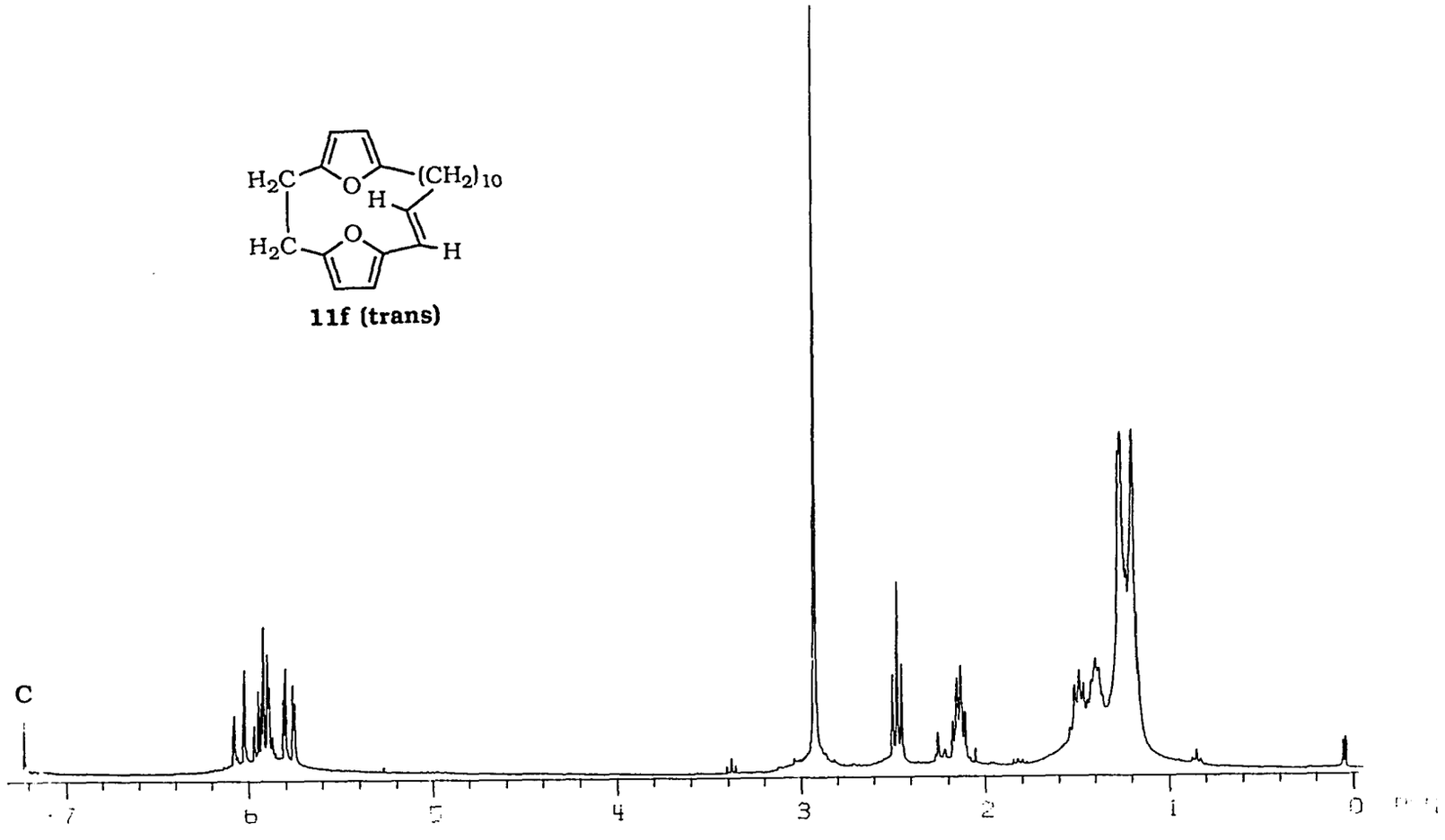
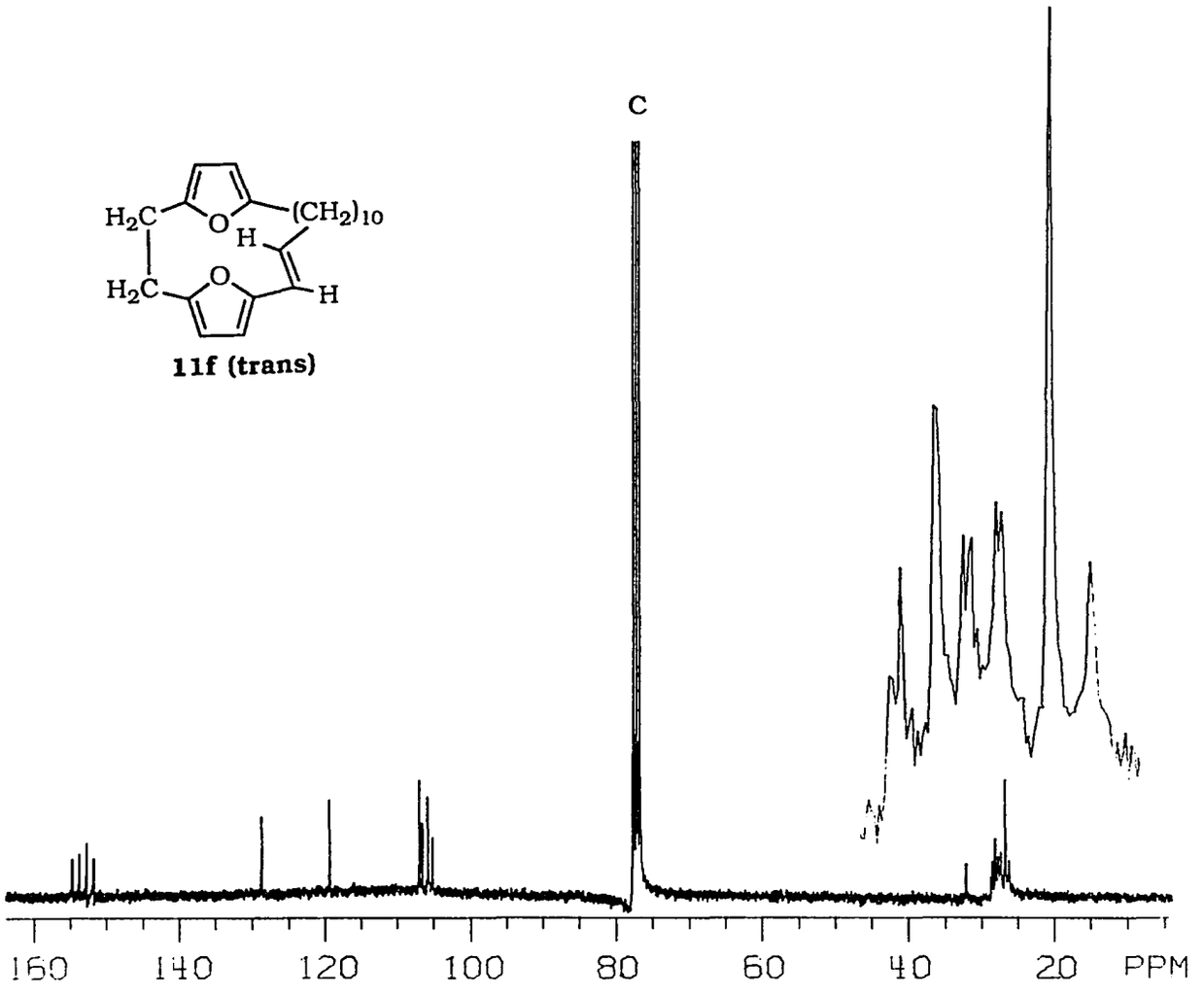


Figure A-39. ^{1}H NMR spectrum of macrocycle **11f (trans)**.



11f (trans)

Figure A-40. ^{13}C NMR spectrum of macrocycle **11f (trans)**.

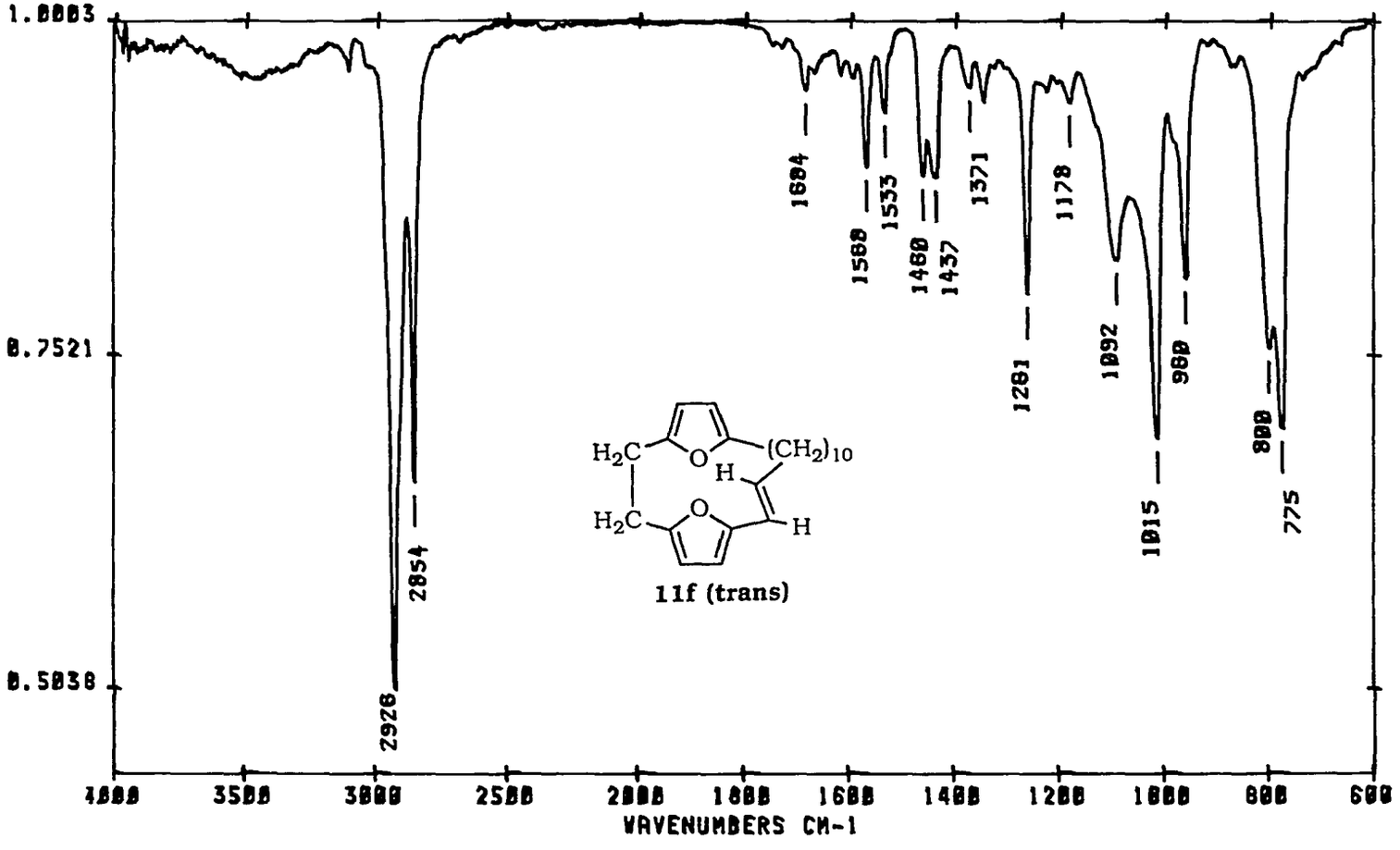


Figure A-41. IR spectrum of macrocycle **11f (trans)**.

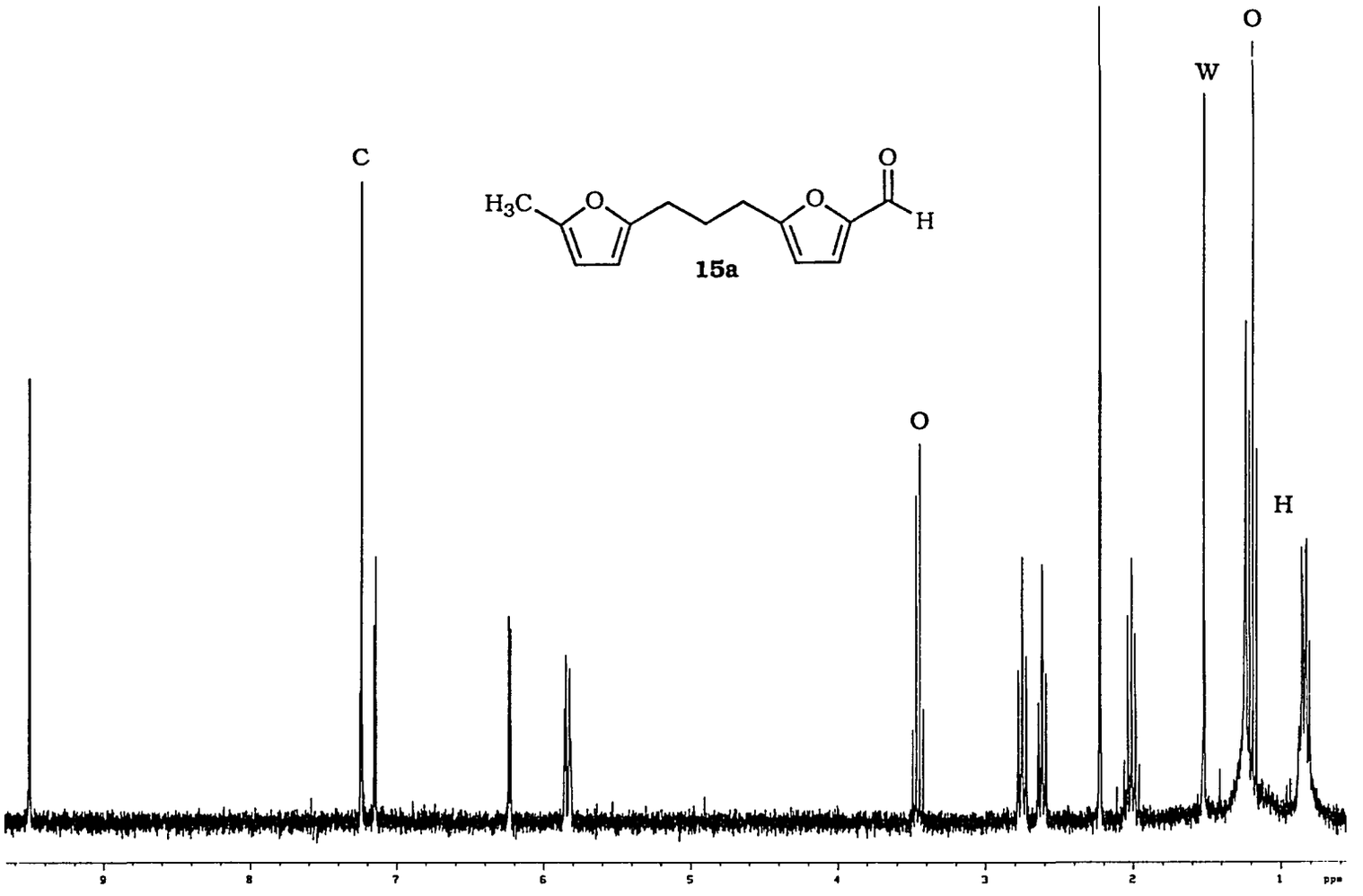


Figure A-42. ^{1}H NMR spectrum of product **15a**.

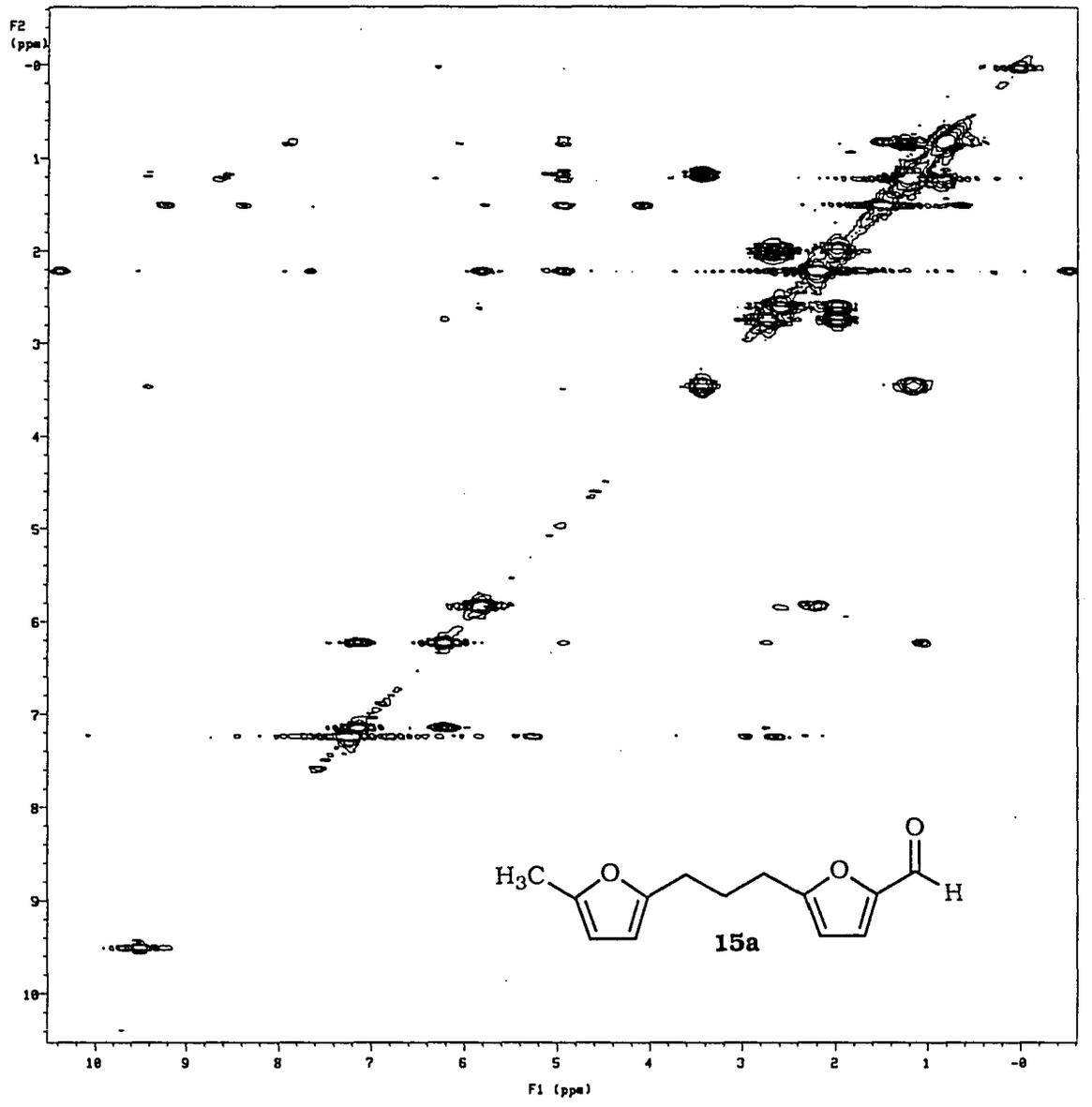


Figure A-43. COSY ^{1}H NMR spectrum of product **15a**.

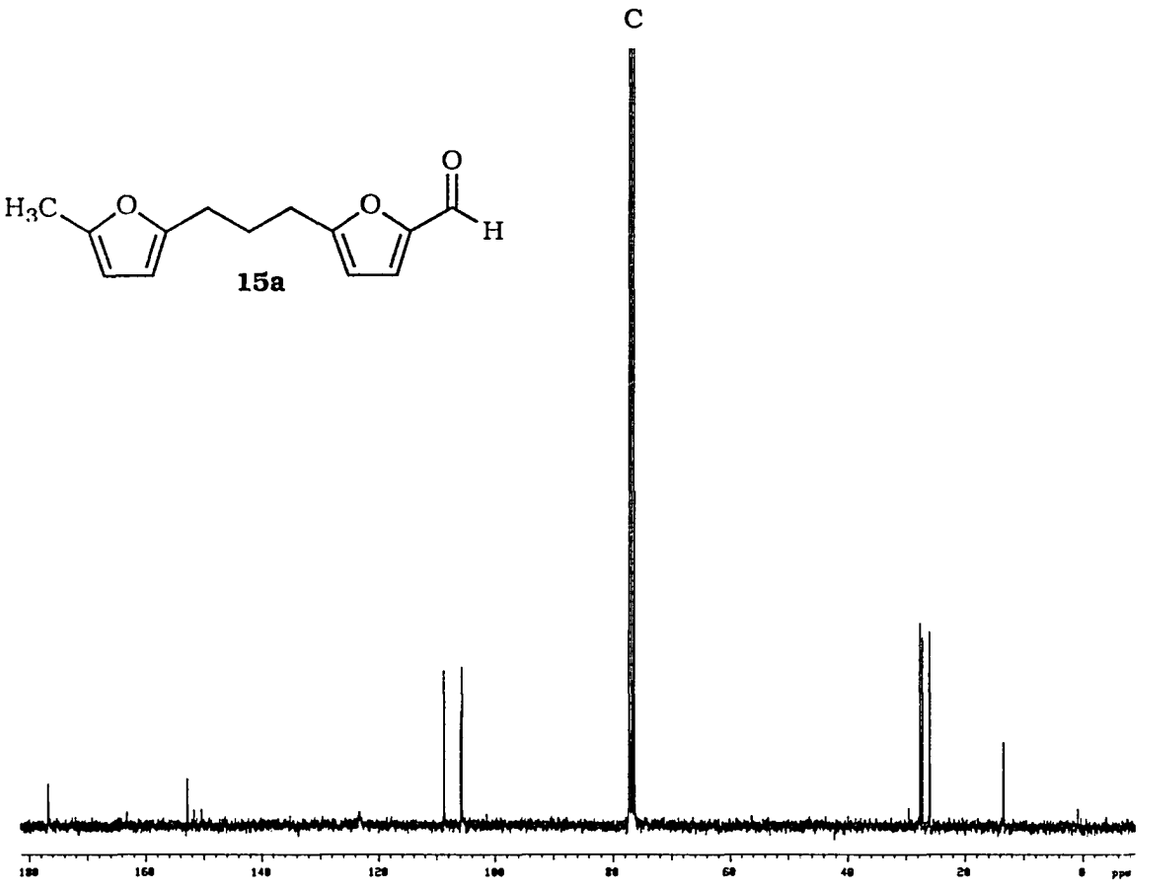


Figure A-44. ^{13}C NMR spectrum of product **15a**.

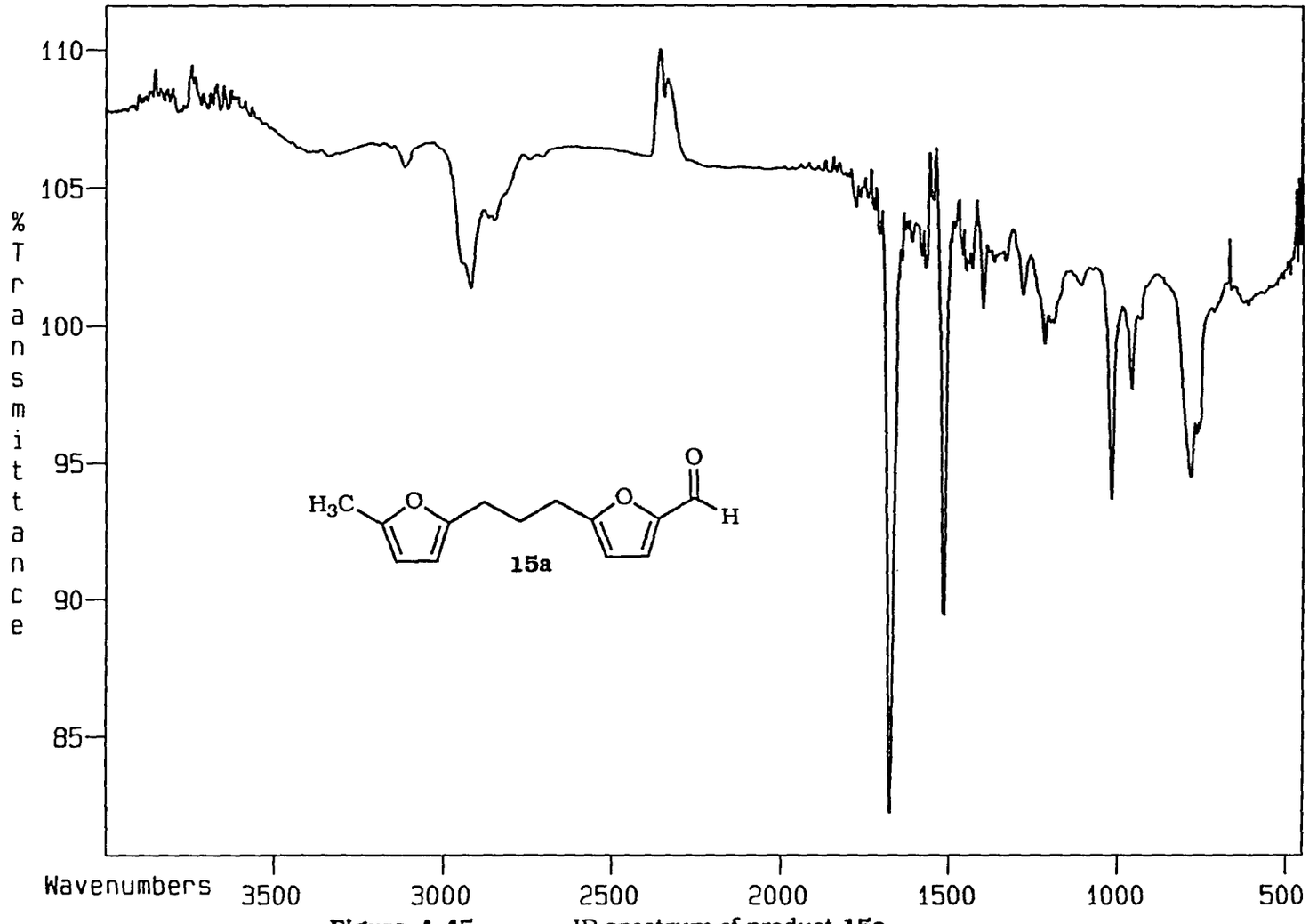


Figure A-45. IR spectrum of product **15a**.

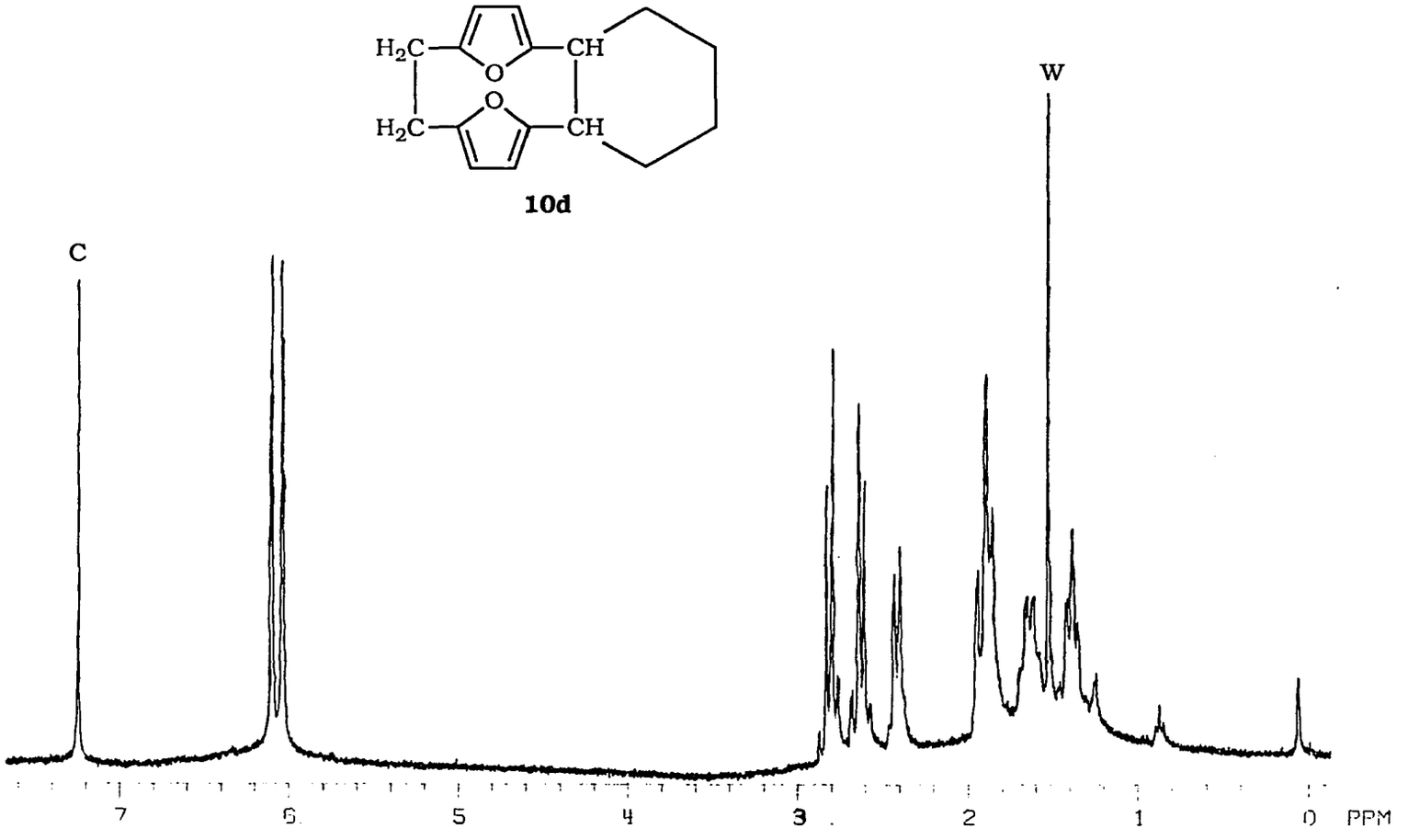


Figure A-46. ^{1}H NMR spectrum of product **10d**.

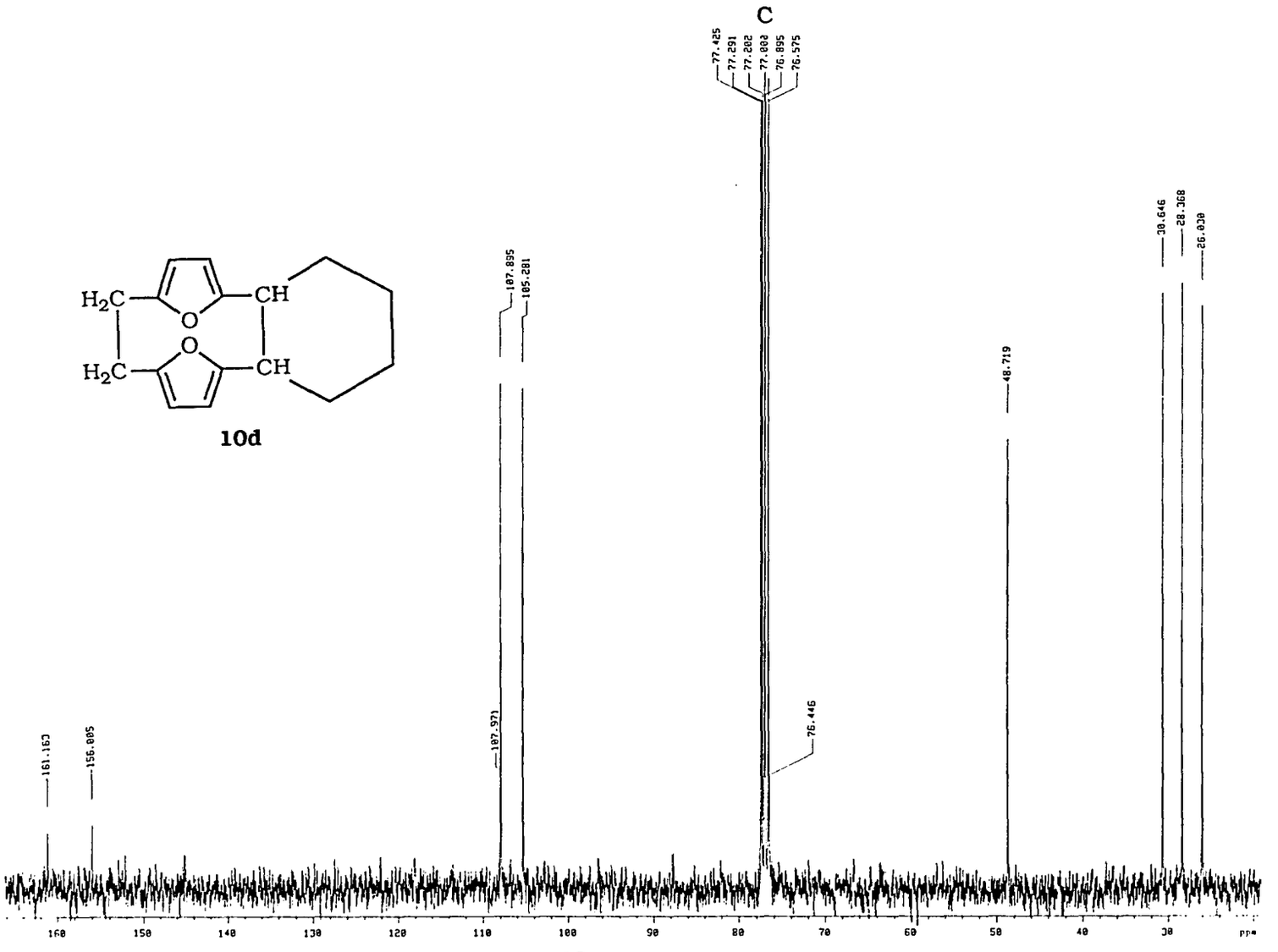


Figure A-47. ^{13}C NMR spectrum of product **10d**.

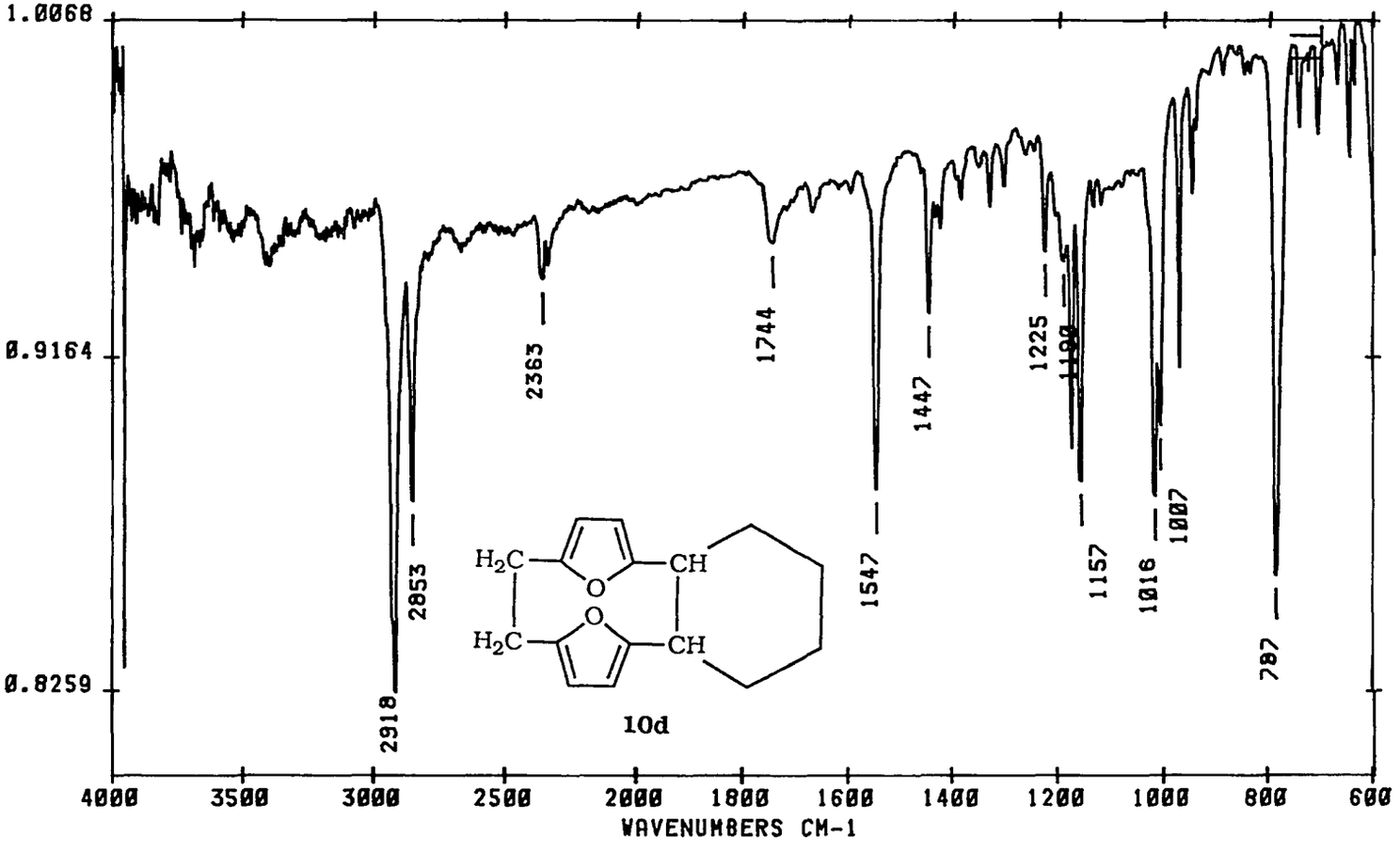


Figure A-48. IR spectrum of product **10d**.

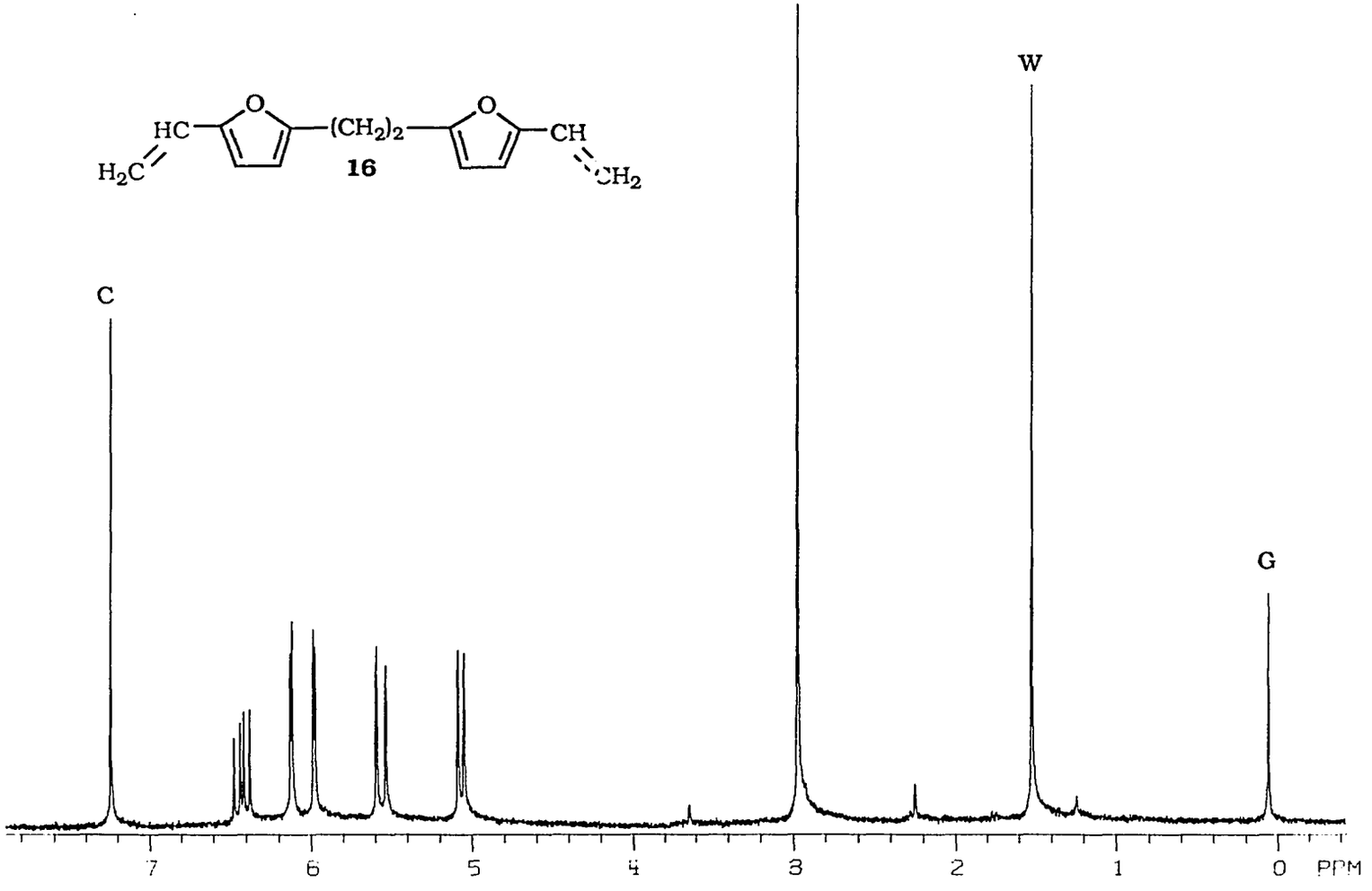


Figure A-49. ^{1}H NMR spectrum of product **16**.

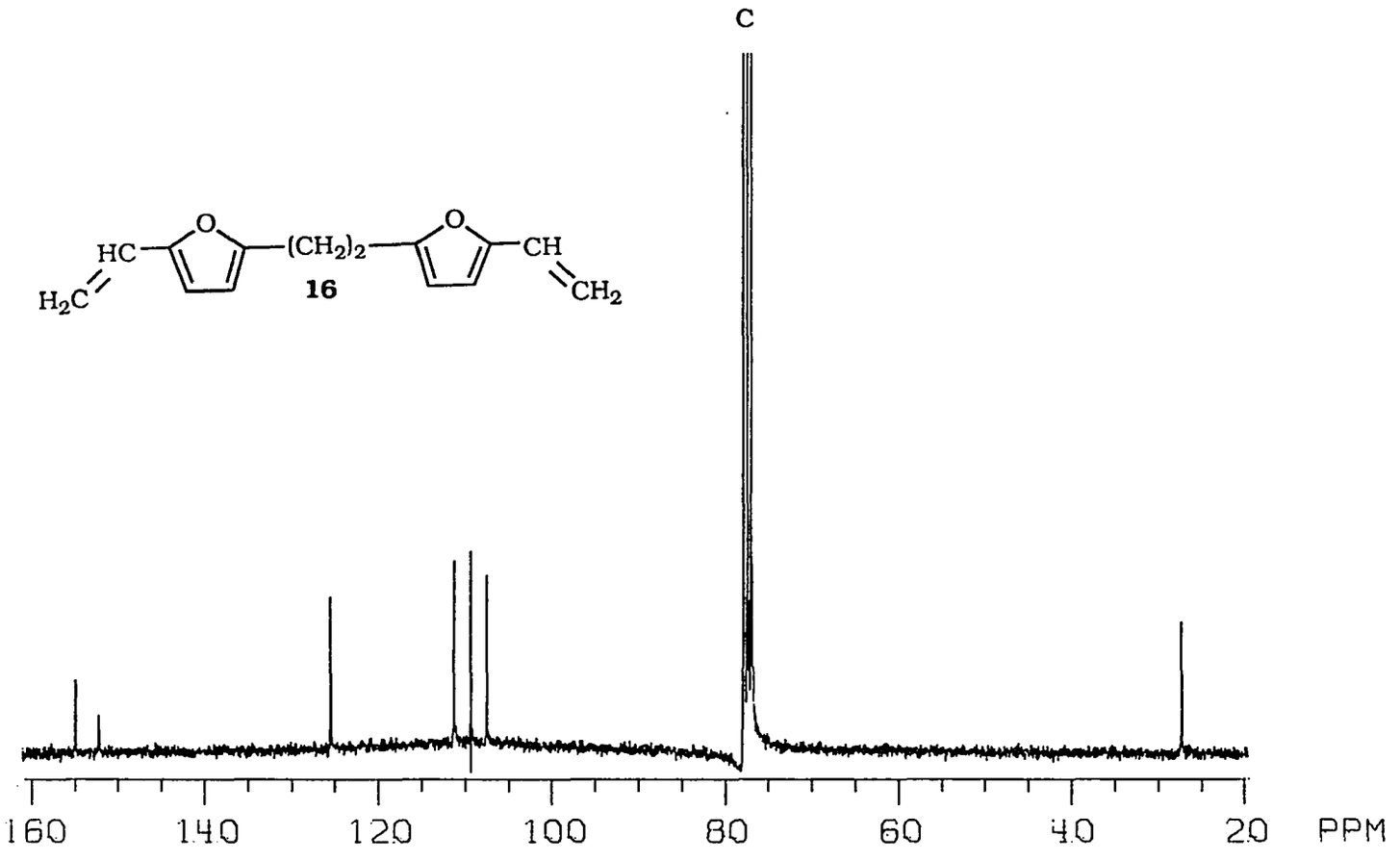


Figure A-50. ^{13}C NMR spectrum of product **16**.

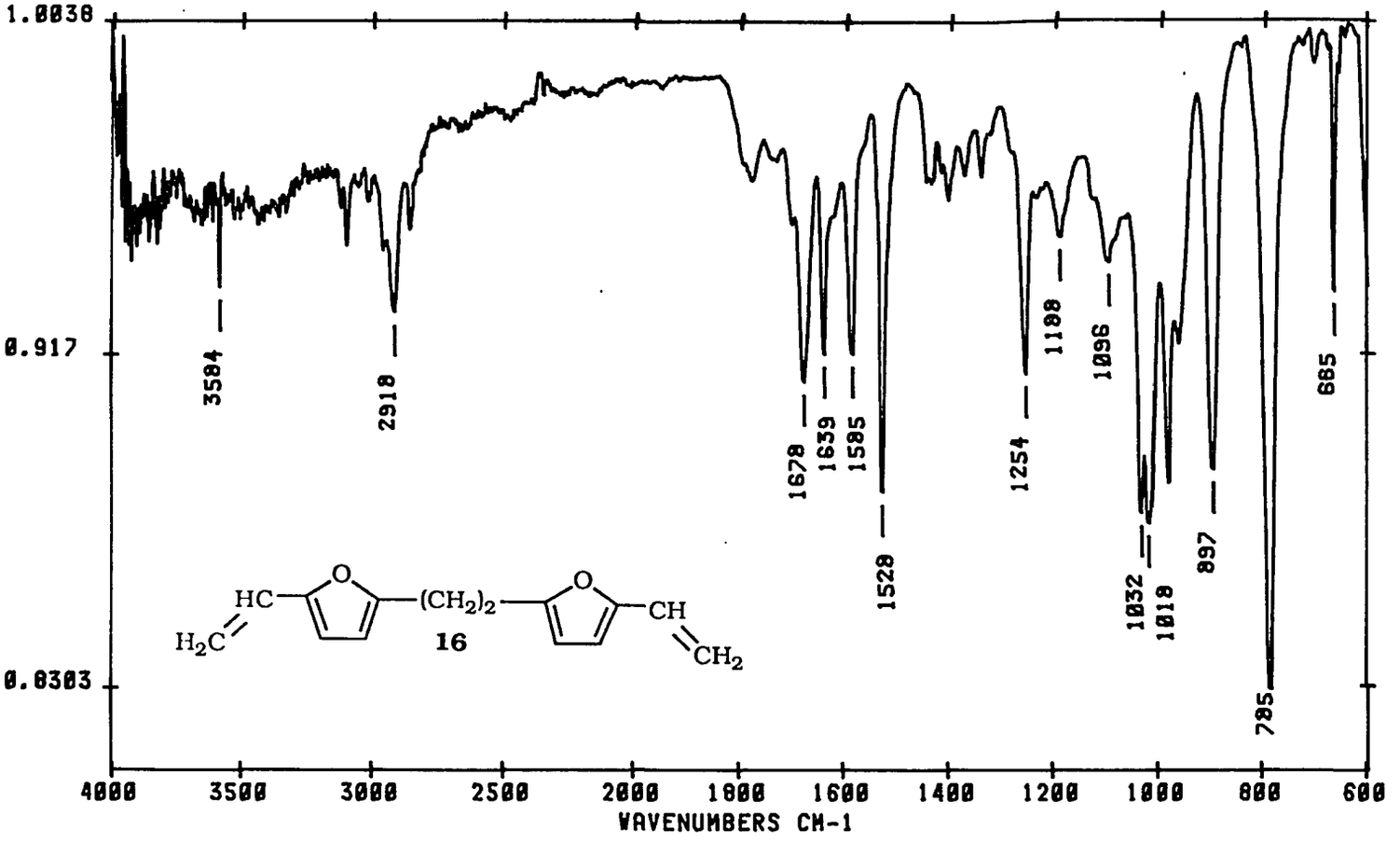


Figure A-51. IR spectrum of product **16**.

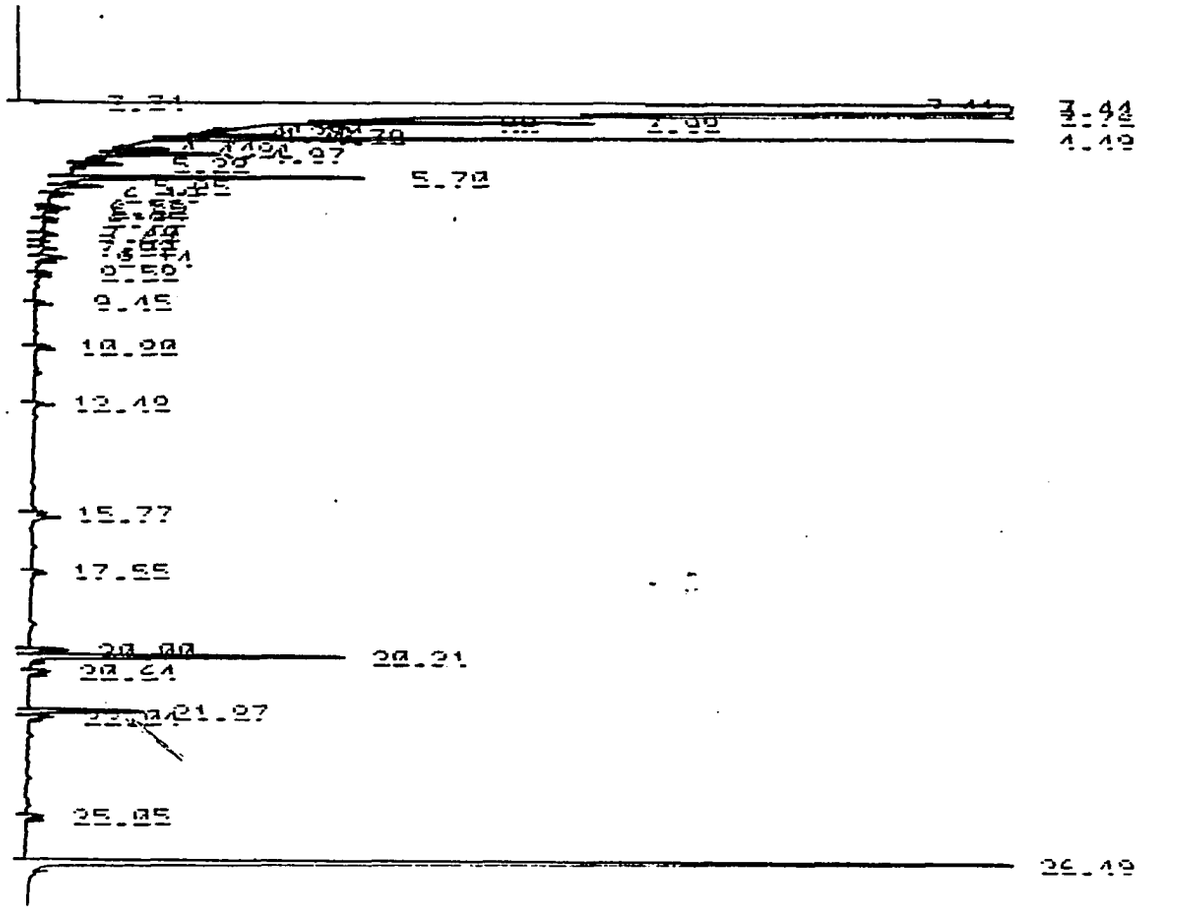
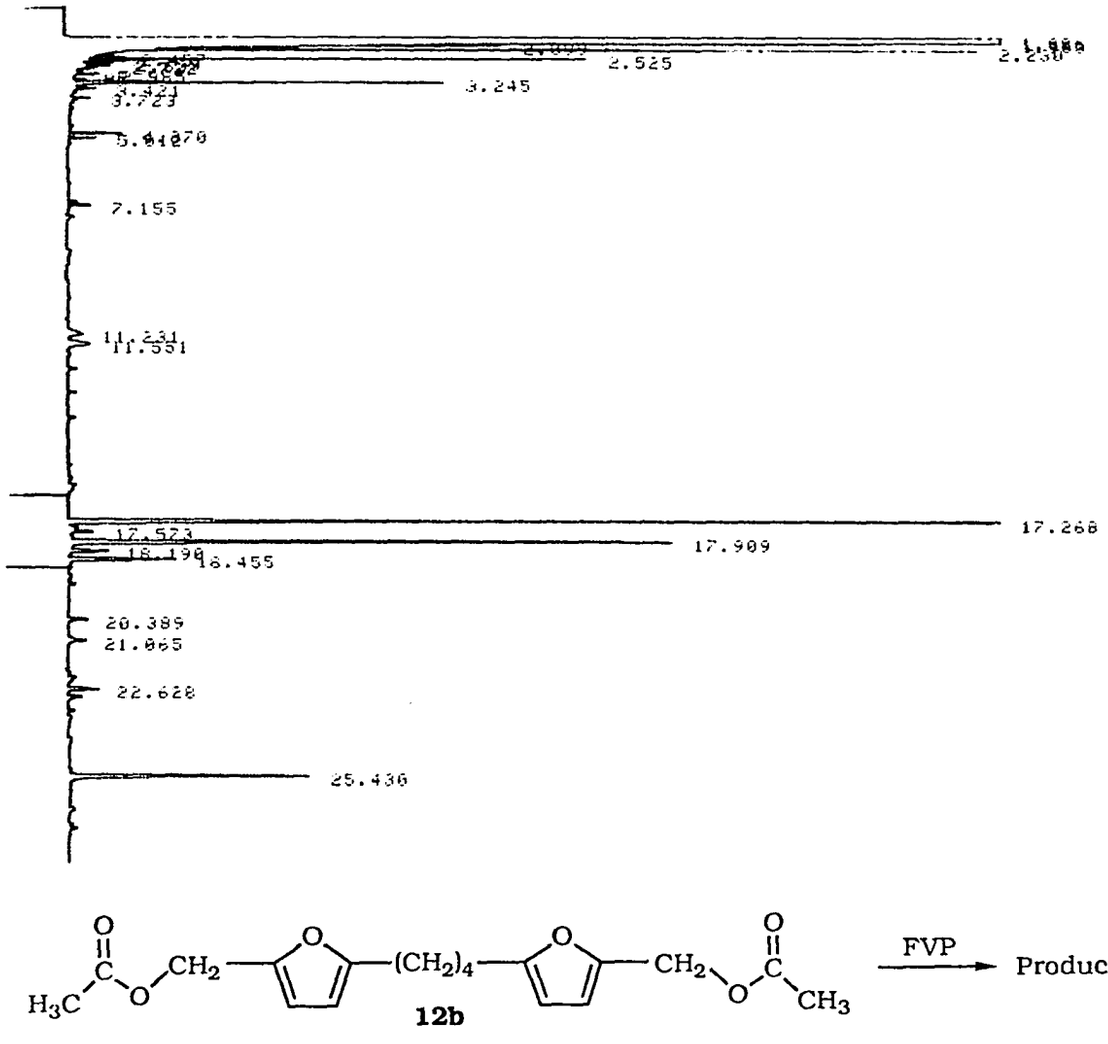


Figure A-52. GC trace of FVP products from **12a**.



12b

Figure A-53. GC trace of products from FVP of **12b**.

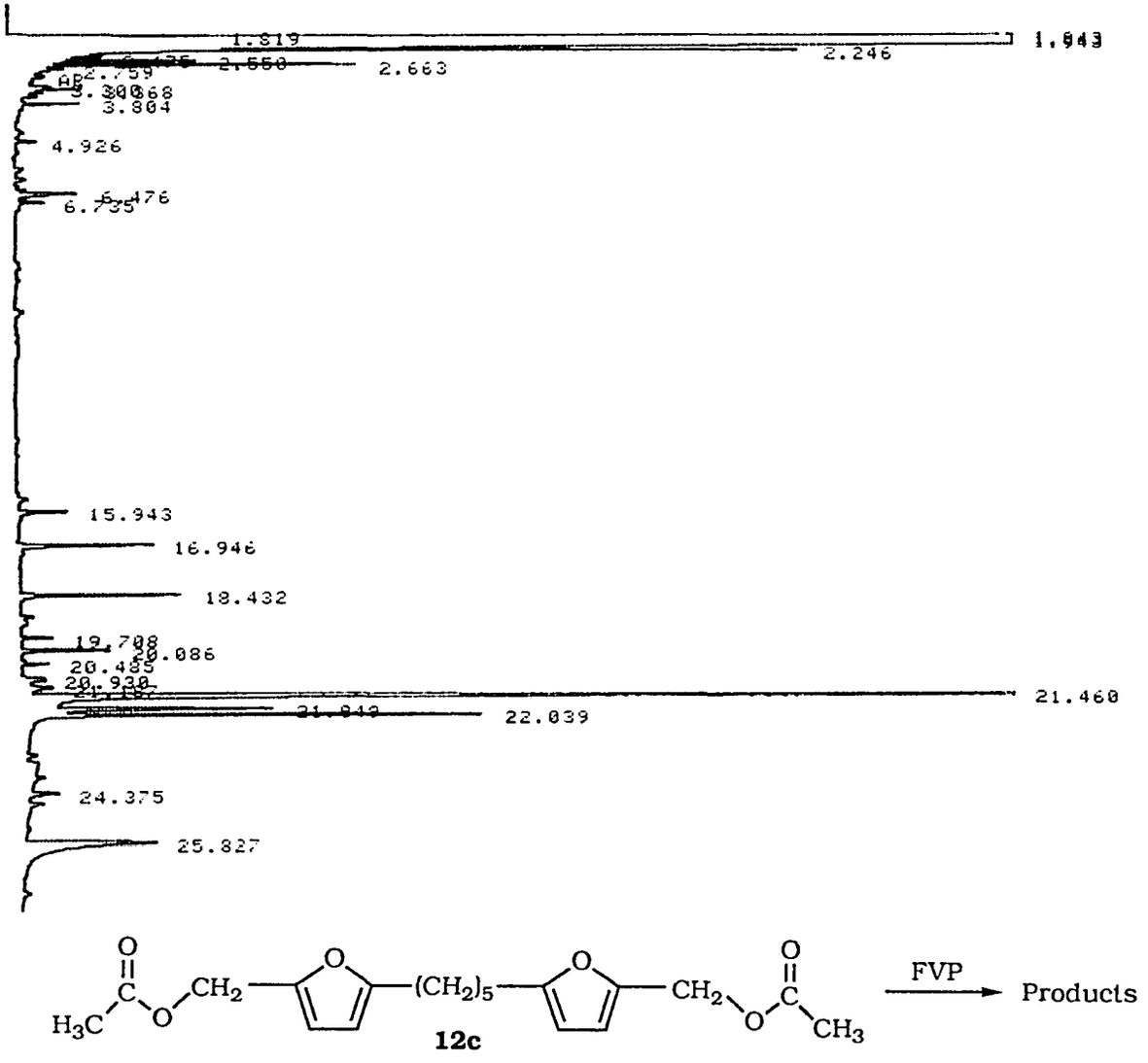


Figure A-54. GC trace of products from FVP of **12c**.

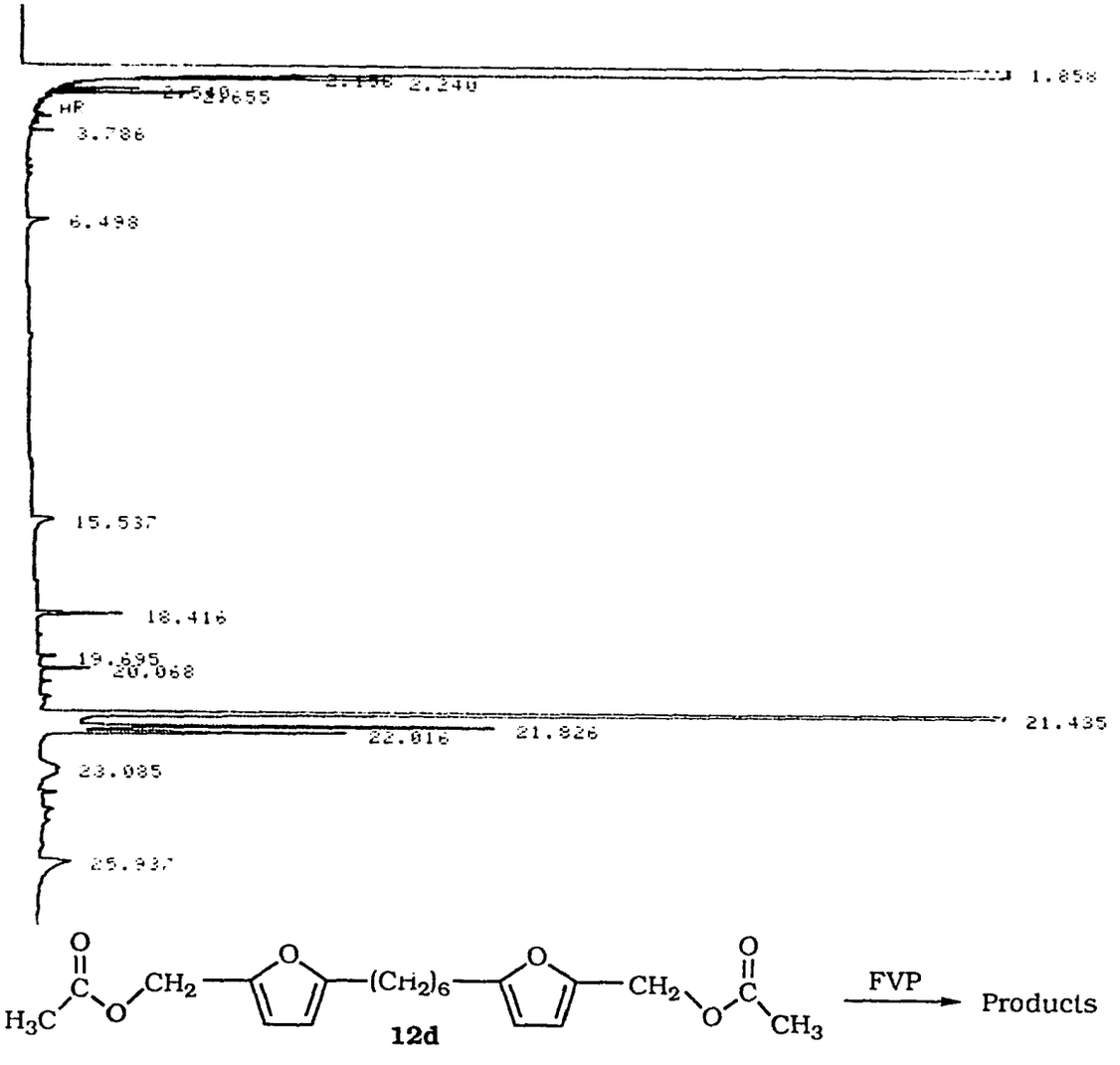
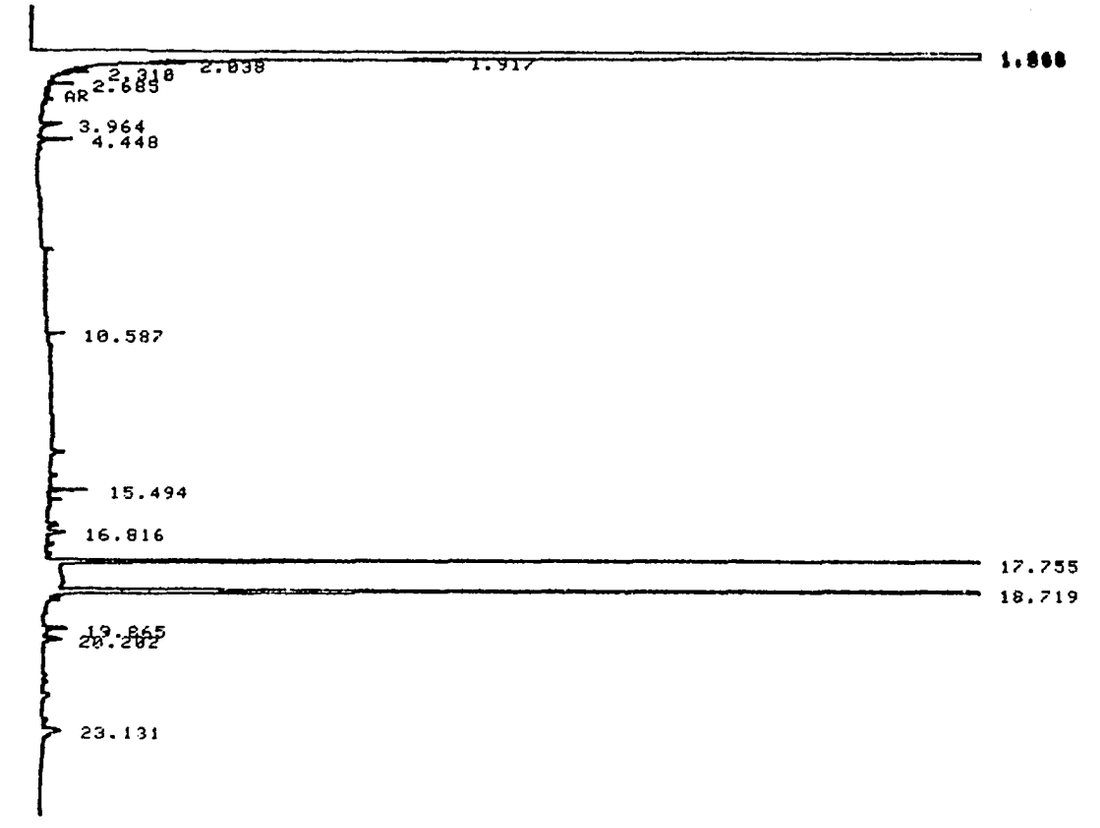
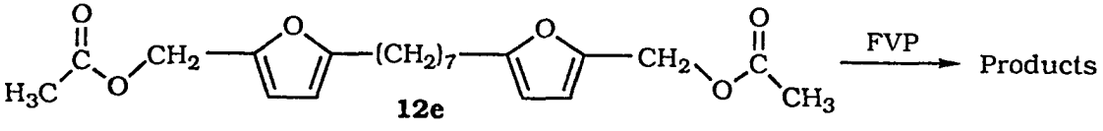


Figure A-55. GC trace of products from FVP of **12d**.





12e

Figure A-56. GC trace of products from FVP of **12e**.

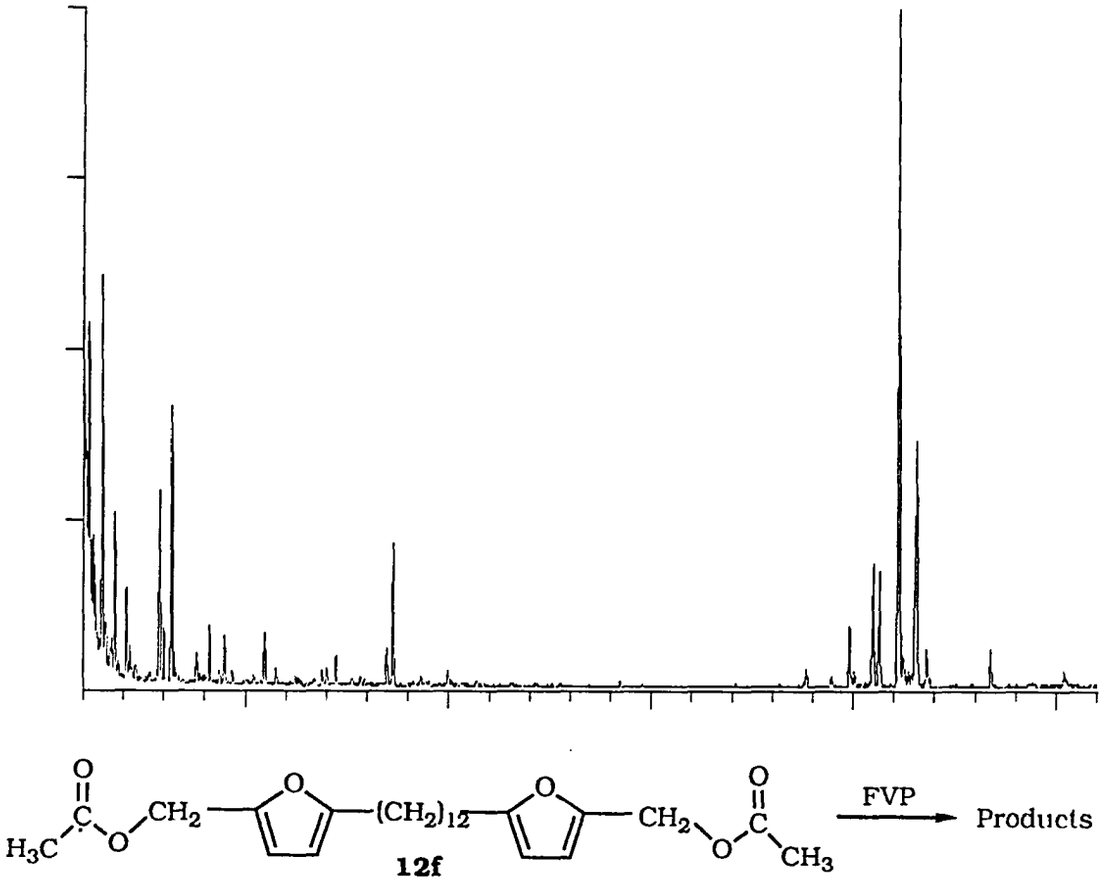
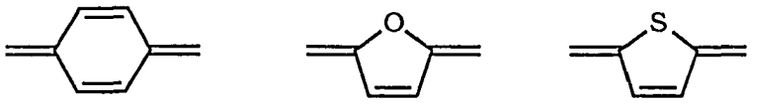


Figure A-57. GC trace of products from FVP of **12f** .

PAPER 2. THE INTRAMOLECULAR CYCLIZATION OF BIS-2,5-DIMETHYLENE-2,5-DIHYDROTHIOPHENES AND THE GENERATION OF FUNCTIONALIZED MACROCYCLES

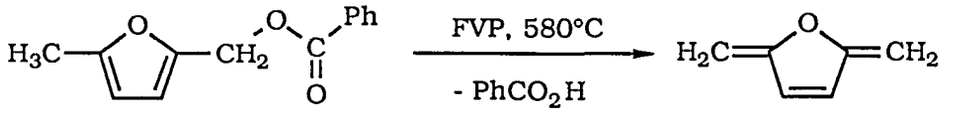
INTRODUCTION

The *p*-quinodimethanes form a class of reactive molecules that has been of considerable interest in recent years. These reactive molecules have been exploited as monomers in polymerization reactions,[1] have been used in organic synthesis,[2] and are thought to be primary products in coal pyrolysis.[3] Representative *p*-quinomethanes include: *p*-xylylene (**1**), 2,5-dimethylene-2,5-dihydrofuran (**2**), and 2,5-dimethylene-2,5-dihydrothiophene (**3**).

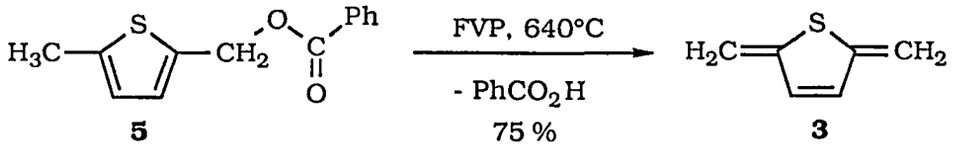


1 **2** **3**

As part of our research efforts investigating the properties of reactive molecules, we found that *p*-quinomethanes **2** and **3** could readily prepared by flash vacuum pyrolysis (FVP) of heterocycles **4**[4a] and **5**.[4b] We believe that the formation of **2** and **3** occurs by a pair of reversible, [3,3] sigmatropic bond shifts followed by irreversible elimination of benzoic acid to yield **2** and **3** from **4** and **5**, respectively. More recently, we found that



4 **2** (1)

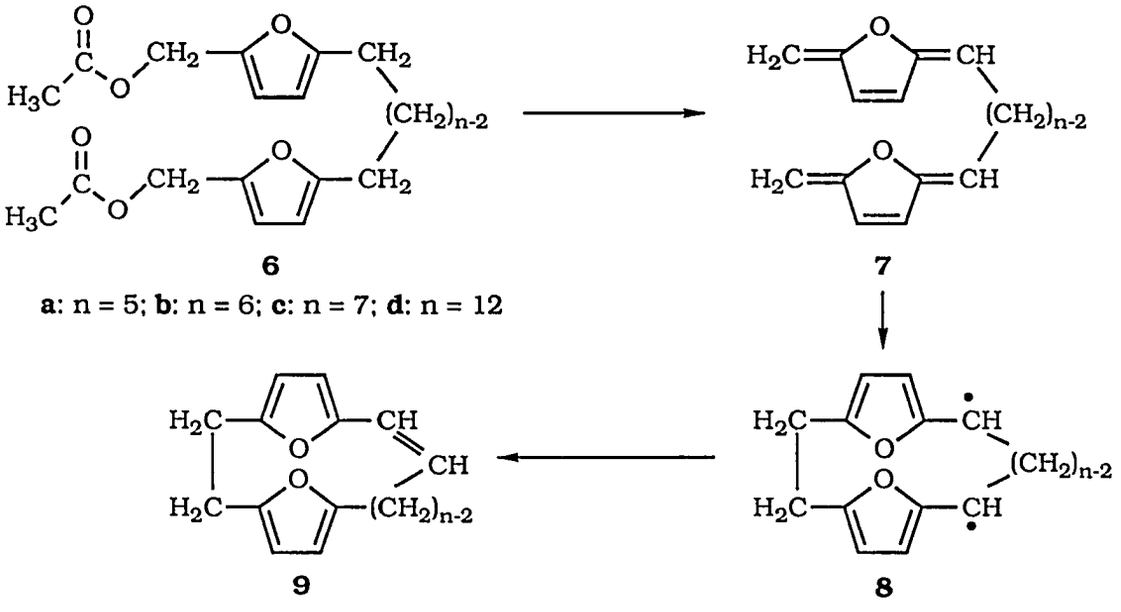


5 **3** (2)

two of the furan-based *p*-quinodimethanes could be simultaneously generated by FVP if two furfuryl acetate groups were linked by an alkyl chain (Scheme I).[5] Pyrolysis of the bis-furfuryl acetates (**6a** to **6d**) was found to give macrocycles **9a** to **9d** in up to 60% yield. We believe that macrocycles **9a** to **9d** were formed by the generation of the bis-2,-5-dimethylene-2,5-dihydrofuran (**7**) followed by a cyclization to give diradical intermediate **8** which then the cyclic diradical **8** undergoes an intramolecular radical disproportionation step to provide the macrocyclic products. FVP of **6a** gave a 46% yield of 9a (cis olefin), **6b** gave a 47% yield of **9b** (cis olefin) and 11% yield of **9b** (trans olefin), **6c** gave a 22% yield of **9c** (cis olefin) and 17% yield of **9c** (trans olefin), and **6d** gave a 4% yield of **9d** (cis olefin) and 19% yield of **9d** (trans olefin). By this chemistry, macrocycles between 15 and 22 carbons in size were prepared in reasonable yield.

Our results above indicate that two *p*-quinodimethanes are capable of intramolecular reaction if joined by an alkyl chain. The *p*-quinodimethanes are fairly

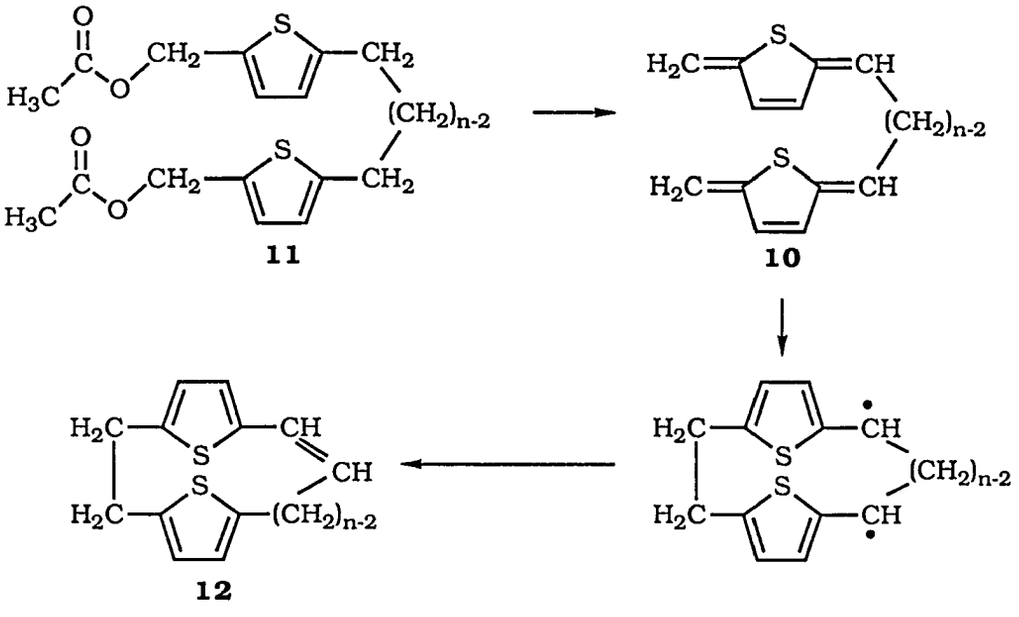
Scheme I



reactive molecules and are known for their tendency to dimerize, trimerize, and polymerize through intermolecular reactions.[6] These new findings demonstrate that an intramolecular reaction can occur between *p*-quinodimethanes and that macrocycles can be produced by this reaction.

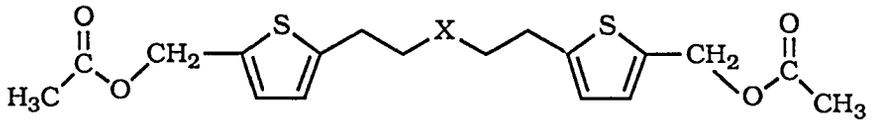
Because of the similarities of the chemistry of furan- and thiophene-based *p*-quinodimethanes (**2** and **3**), we proposed that bis-2,5-dimethylene-2,5-dihydrothiophene (**10**) could also be produced by FVP of **11** and that macrocycle **12**, which contains thiophene rings would result (Scheme II).

Scheme II



As our initial entry into the preparation bis-2,5-dimethylene-2,5-dihydrothiophenes (**10**), we planned to generate the bis-2,5-dimethylene-2,5-dihydrothiophene which would produce the 15 carbon macrocycle of general structure **12** (n=5). Since the analogous furan-based cyclization (**6a** → **9a**) was particularly well behaved, we felt that

this would be the most convenient entry into the thiophene-based cyclization. In the following chapter, our results are presented for the synthesis and FVP of compound **13**. We also report the synthesis and FVP of compounds (**18** and **27**) which have a functionalized chain between the thiophene groups.



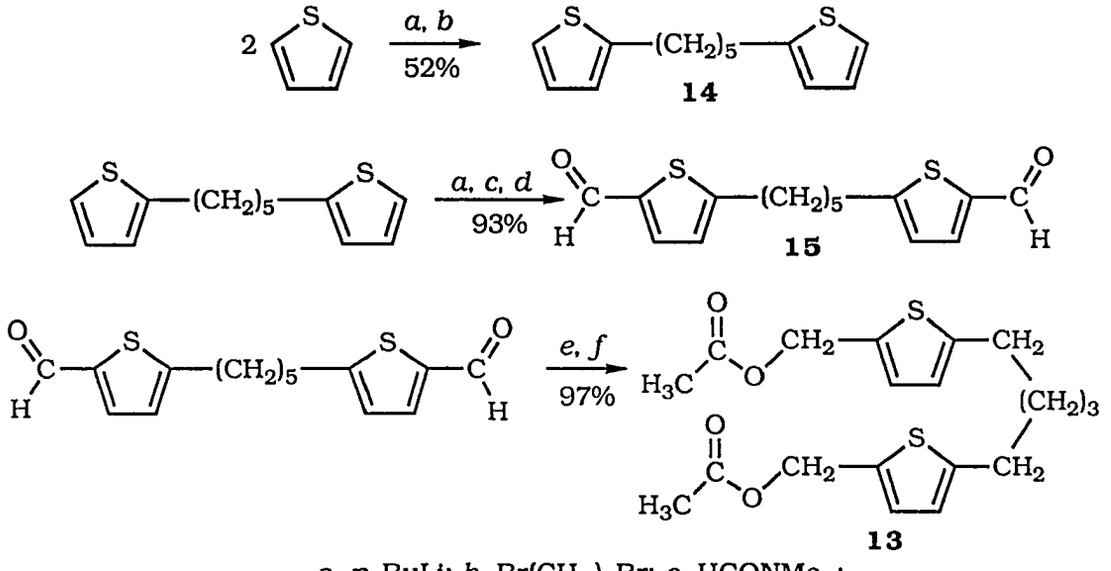
13: X = CH_2; **18**: X = CHOH; **27**: X = CO

RESULTS

Preparation of 1,5-di(2-acetoxymethylthienyl-5)pentane (13)

An efficient 4-step synthetic route was developed for the preparation of **13** (Scheme III). Thiophene was reacted with nBuLi in THF/HMPA and the resulting 2-thienyl anion was reacted with 1,5-dibromopentane[7] to produce 1,5-di(thienyl-2)-pentane (**14**) in 86% isolated yield. Formylation[8] provided compound **15** in about 80% yield. Reduction of **15** and acylation[9] of the diol gave the desired product **13**. The last step of this synthesis was nearly quantitative. This synthetic route provides gram quantities of **13**.

Scheme III



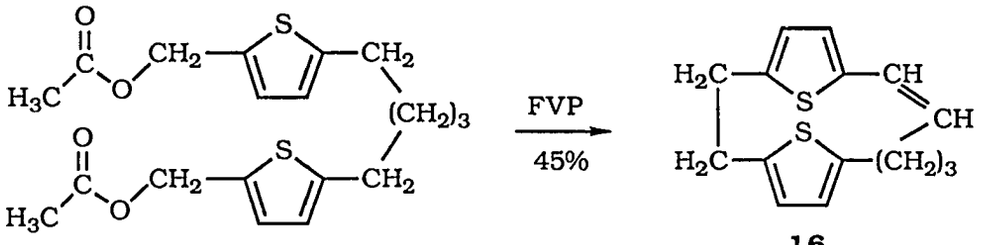
a, n-BuLi; *b*, $Br(CH_2)_5Br$; *c*, $HCONMe_2$;
d, H_2O; *e*, $LiAlH_4$; *f*, Et_3N, CH_3COCl

Flash vacuum pyrolysis of 1,5-di(2-acetoxymethylthienyl-5)pentane (13)

Compound **13** was pyrolyzed using a flash vacuum pyrolysis apparatus and methods that have been previously described.[10] FVP experiments were conducted at 640°C with the apparatus being evacuated to 10^{-5} torr. Compound **13** required heating

to 120°C to make it sufficiently volatile to traverse the hot zone of the FVP apparatus. Typically, 50 to 100 mg of **13** was pyrolyzed.

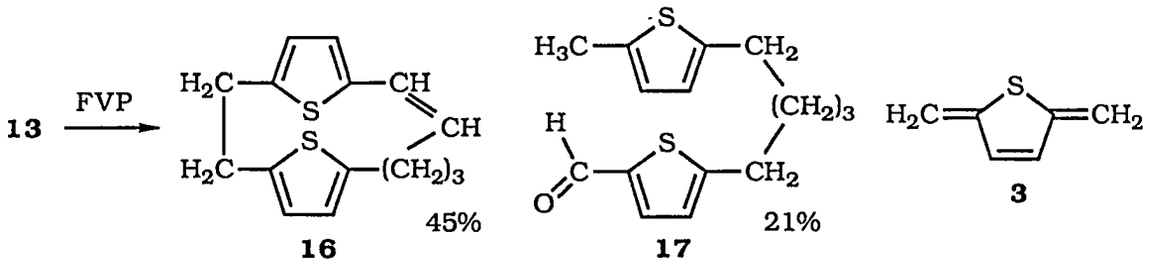
When diacetate **13** was pyrolyzed, macrocycle **16** was produced. Macrocycle **16** was purified by flash chromatography and isolated in up to 45% yield.



13 **16**

The stereochemistry of the double bond in **16** was established to be of cis conformation on the basis of the olefinic coupling constant (J = 11.4 Hz) in the ^{1}H NMR spectrum. In addition, the ^{1}H NMR spectrum of **16** was very similar to that of the furan-containing macrocycle **9a** (Scheme I). Like related macrocyclic ring systems,[11] compound **16** appears to exist in at least two equilibrating conformations in solution. Inspection of the ^{1}H NMR at room temperature reveals broad resonance signals for the up field methylene protons and warming of the sample to 60°C, dramatically sharpened these signals.

In addition to macrocycle **16**, two other major products were observed from the pyrolysis of **13**, products **17** and **3**. Product **17** could be isolated by flash chromatography and its structure was thoroughly established by characterization using ^{1}H NMR (1-D and COSY), ^{13}C NMR (decoupled, ^{1}H-^{13}C coupled, and HETCOR), IR, and mass spectroscopy. While product **17** could be isolated in as high as 21%



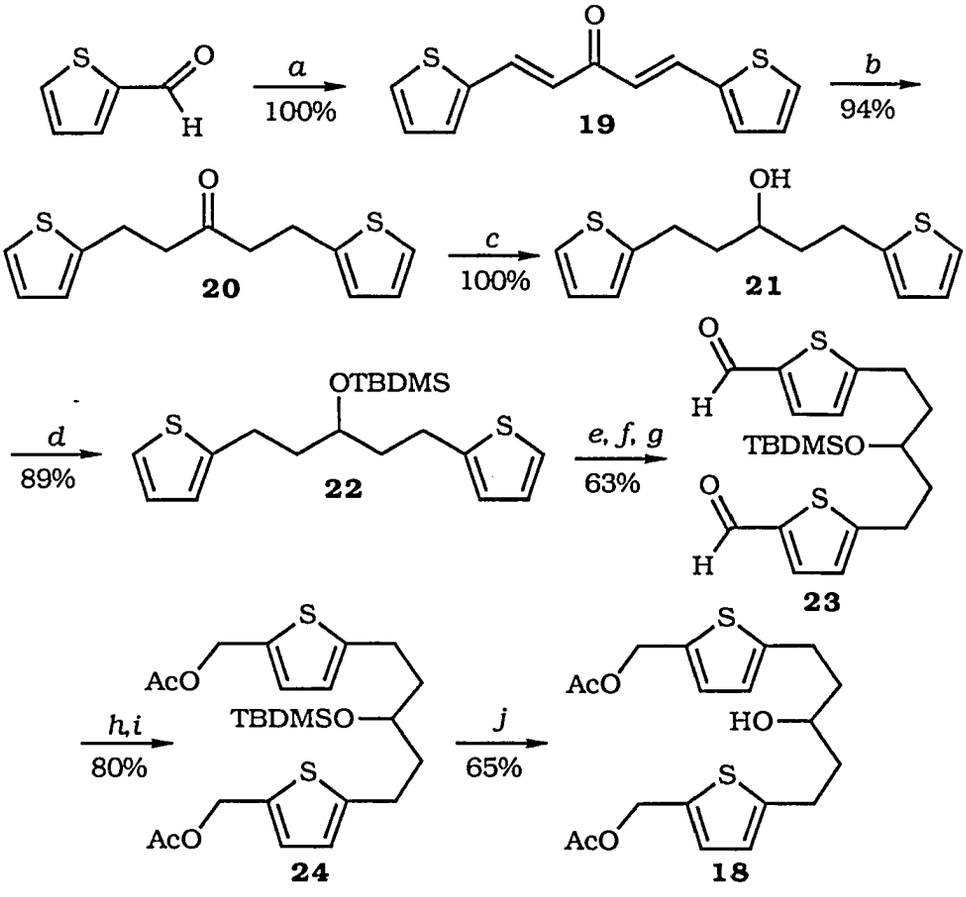
yield, the yield varied between 3-20%. The average ratio of products **16** and **17** was about 8 to 1, respectively.

The observation of product **17** was suprising, but even more so was the detection of product **3**. The thiophene-based *p*-quinodimethane (**3**) could be observed in the ^{1}H NMR spectrum of crude product mixture. With time, the proton signals arising from **3** disappeared. A subtracted ^{1}H NMR spectrum was obtained by subtracting two spectra of the crude product mixture, one spectrum taken immediately after the pyrolysis and one spectrum taken 24 hr later. The subtracted ^{1}H NMR spectrum clearly shows resonance peaks at 6.5, 5.3 and 5.0 ppm, which matches closely the published ^{1}H NMR spectrum for **3**.[4b]

Preparation of 1,5-di(2-acetoxymethylthienyl-5)-3-pentanol (18)

The synthesis of 1,5-di(2-acetoxymethylthienyl-5)-3-pentanol (**18**) was accomplished in seven steps beginning with 2-thiophenecarboxaldehyde (Scheme IV). When reacted with acetone, 2-thiophenecarboxaldehyde produced compound **19** in quantitative yield.[12] Reduction of **19** with H_2 and Pd-C catalyst[13] gave 1,5-di(thienyl-2)-3-pentanone (**20**) in good yield (80%), and further reduction[9] of the ketone with $LiAlH_4$ (100% yield) gave **21**. The hydroxy group was then protected[14] to give **22** (89%) and the thiophene rings were formylated[8] (63%) via the thienyl anion and reaction with dimethylformamide. Compound **23** was then reduced and acylated[9] in 80% yield to give

Scheme IV



a, acetone, KOH; *b*, H_2, Pd-C; *c*, $LiAlH_4$;
d, TBDMS-Cl; *e*, n-BuLi $LiAlH_4$; *f*,Me_2NCHO;
g, H_2O; *h*,$LiAlH_4$; *i*, Et_3N, CH_3COCl;
j, NBu_4F

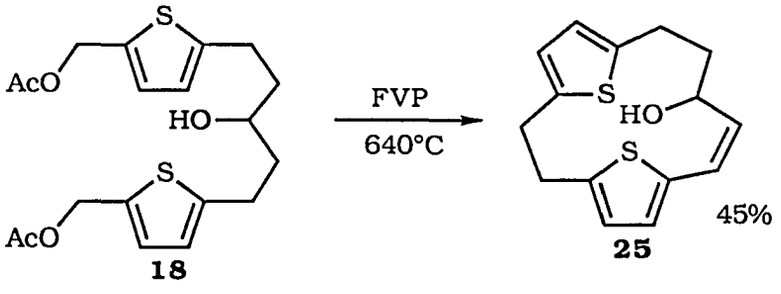
24. Deprotection of **24** with fluoride[14] gave **18** in 65% yield. By this route, 100 milligram quantities of **18** could be prepared.

Flash vacuum pyrolysis of 1,5-di(2-acetoxymethylthienyl-5)-3-pentanol (18)

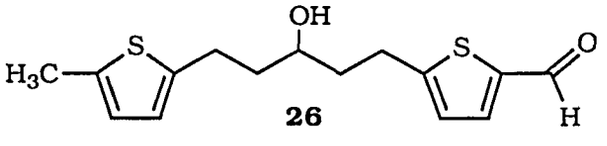
Compound **18** was pyrolyzed using the same methods as those used for FVP of compound **13**. Typically 20 to 50 mg of **18** was pyrolyzed, and FVP was done at 640°C

and 10^{-5} torr;. Compound **18** was noticeably less volatile than **13**, and FVP required heating **18** to about 140°C to effect volatilization.

It was found that FVP of **18** gave the macrocyclic allylic alcohol **25** as the major product. Compound **25** was produced along with several minor products. Macrocycle **25** could be isolated in as high as 45% yield. However, **25** was not easily handled due to the instability of this functionalized macrocycle. Conventional flash chromatography with silica gel was always accompanied by some decomposition of **25**. Like macrocycle **16**, the ^{1}H NMR revealed a cis double bond. Unlike the FVP of **13**, none



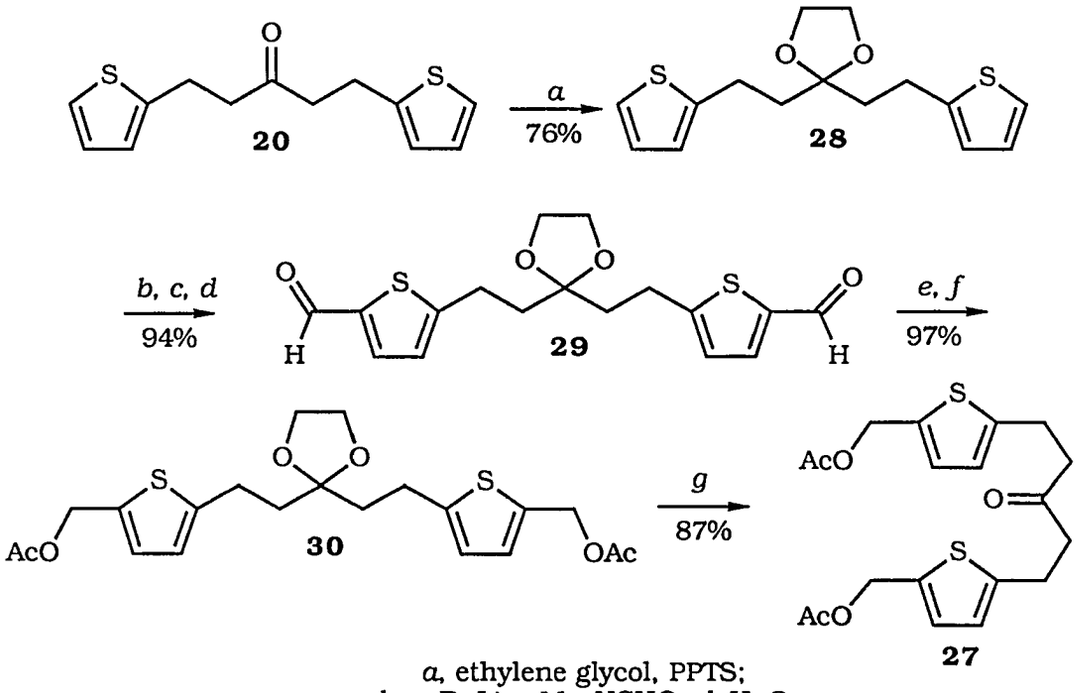
of the 2,5-dimethylene-2,5-dihydrothiophene (**3**) was observed in the ^{1}H NMR of the crude product mixture from **18**. NMR and GCMS analysis suggested that product **26** was a minor product, but **26** could not be isolated from the FVP product mixture.



Preparation of 1,5-di(2-acetoxymethylthienyl-5)-3-pentanone (27)

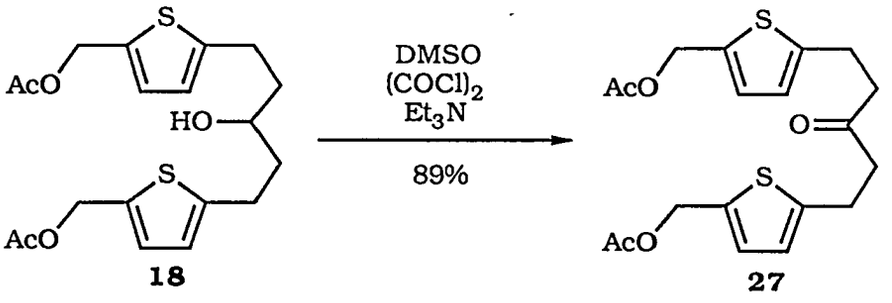
To extend the scope of this route to functionalized macrocycles, 1,5-di(2-acetoxymethylthienyl-5)-3-pentanone (**27**) was also prepared and pyrolyzed. Compound

Scheme V



a, ethylene glycol, PPTS;
b, n-BuLi; *c*,Me_2NCHO; *d*, H_2O;
e,$LiAlH_4$; *f*, Et_3N, CH_3COCl;
g, acetone, PPTS

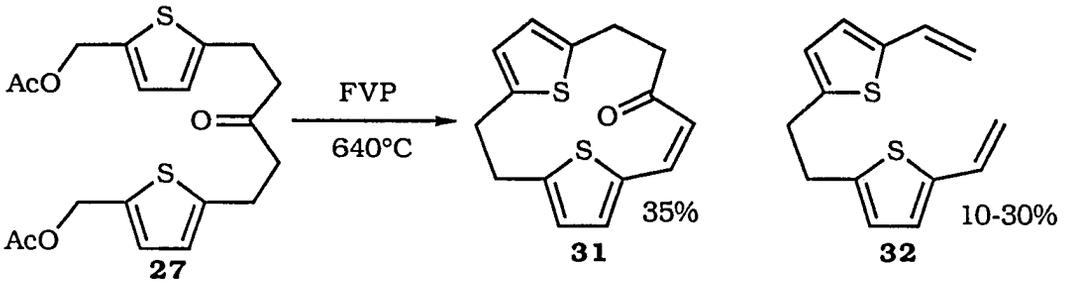
27 was prepared in four steps from 1,5-di(thienyl-2)-3-pentanone (**20**) (Scheme V). Protection of the ketone[15] was accomplished in 76% yield to give ketal **28**. Formylation[8] of the thiophene rings was done in 94% yield to give **29**, and **29** was reduced and acylated[9] in high yield to provide ketal **30**. Deprotection[15] of ketal **30** was done in as high as 87% yield, but deprotection was usually accompanied by hydrolysis of the ester groups. If the product mixture was found to contain significant hydrolysis of the acyl groups, the crude product mixture could be reacted with acetyl chloride to give **27**. Ketone **27** could also be obtained from Swern oxidation[16] of **18** in 89% yield.



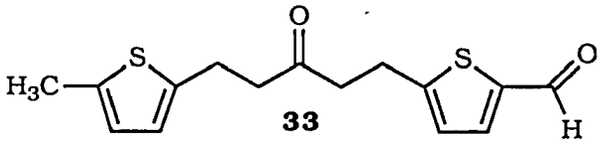
Flash vacuum pyrolysis of 1,5-di(2-acetoxymethylthienyl-5)-3-pentanone (27)

Compound **27** was pyrolyzed using conditions similar to those of the FVP of compounds **13** and **18**, the hot zone was 640°C and the vacuum was 10^{-5} torr in the FVP apparatus. Compound **27** also required heating to 140°C to effect volatilization for FVP.

When compound **27** was pyrolyzed, two major products were obtained. As we



had hoped, the macrocyclic enone **31** was produced. Product **31** was usually the most abundant product formed in 35% yield from FVP of **27**, but **32** was also produced as a major product. The yield of product **32** varied between 10 to 30% and in a few experiments **32** was the dominant product. In addition to products **31** and **32**, a minor amount of the acyclic aldehyde **33** was also produced. Although we were unable to



33

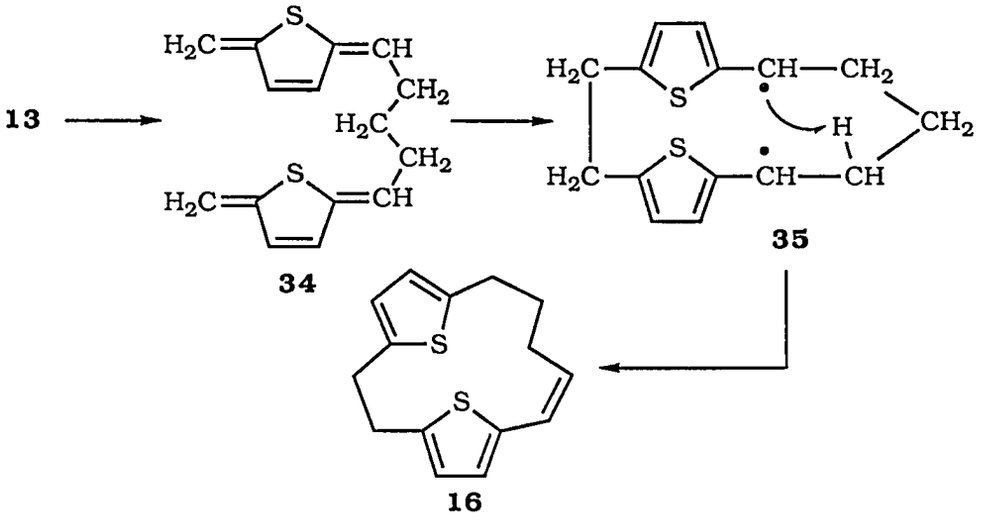
isolate **33**, its presence was suggested based on the GCMS and ^{1}H NMR of the crude product mixture. Like the FVP of **18**, FVP of **27** did not produce any of the 2,5-dimethylene-2,5-dihydrothiophene (**3**).

DISCUSSION

Formation of bis-2,5-dimethylene-2,5-dihydrothiophenes and the resulting macrocycles by FVP of 13, 18, and 27

Our results provide firm evidence that bis-2,5-dimethylene-2,5-dihydrothiophenes are generated by the pyrolysis of **13**, **18**, and **27**. The macrocyclic products **16**, **25**, and **31**, as well as product **32**, are all consistent with the formation of the bis-2,5-dimethylene-2,5-dihydrothiophenes. Thus, FVP of **13** would have produced the bis-2,5-dimethylene-2,5-dihydrothiophene (**34**) in the gas-phase by elimination of two molecules of acetic acid (Scheme VI). Further reaction of intermediate **34** would then have provided the cyclic diradical **35**. Given the tendency of *p*-quinodimethanes to dimerize through diradical intermediates, the formation of **35** is quite reasonable. Intramolecular radical disproportionation of **35** then gave macrocycle **16**.

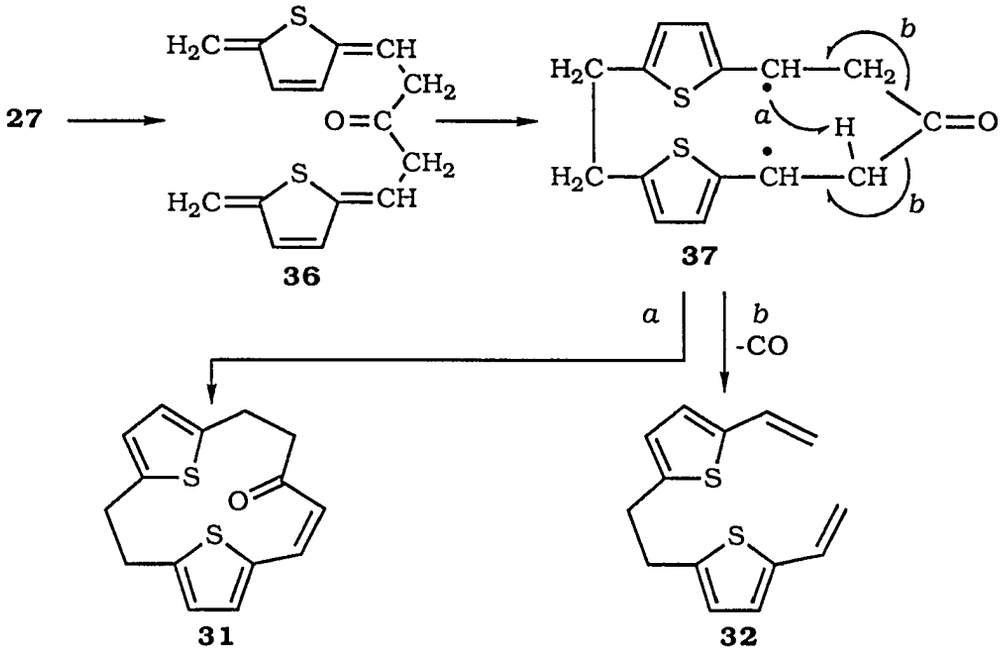
Scheme VI



When **27** was pyrolyzed, macrocycle **31** was produced along with the acyclic product **32**. Both products support the postulated intermediacy of the bis-2,5-dimethylene-2,5-dihydrothiophene, as well as the intermediacy of the cyclic diradical (Scheme VII). FVP of **27** would have initially produced the bis-2,5-dimethylene-2,5-dihydrothiophene (**36**) and an intramolecular reaction of the thiophene-based *p*-quinodimethanes produced the cyclic diradical **37**. Intermediate **37** then reacted by one of two routes: route *a* produced macrocycle **31** by an intramolecular hydrogen abstraction, while route *b* gave **32** by extrusion of carbon monoxide. Therefore, the bis-2,5-dimethylene-2,5-dihydrothiophenes appear to be generally accessible by the FVP of the appropriate precursors.

The results we report confirm that intramolecular reactions are capable of occurring between two thiophene-based *p*-quinodimethanes if linked by a bridging chain. The intramolecular cyclization of the bis-2,5-dimethylene-2,5-di-

Scheme VII



hydrothiophenes produced functionalized macrocycles of 15 carbons in fair yield. Presumably larger macrocycles could also be prepared, simply by employing a longer bridging chain between the thiophene rings of the precursor. Furthermore, the intramolecular radical disproportionation of the cyclic diradical introduces an regiospecific double bond into these macrocyclic products. Because similar results were seen with the bis-2,5-dimethylene-2,5-dihydrofurans, we feel that this chemistry is a somewhat general route to macrocycles and cyclophanes. Although there are a number of routes to macrocycles containing furan and thiophene rings,[2a,17] the FVP of the acyclic precursors gives these functionalized macrocycles in a single, direct step.

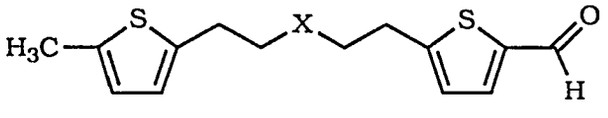
It was also found that the bridging chain may be substituted to produce more highly functionalized macrocycles. Substituted with a hydroxy group, starting material **18** gave the macrocyclic allylic alcohol (**25**) in 45% yield, and substitution with a ketone in **27** provided the macrocyclic enone (**31**) in 35% yield. It was observed that functionalization of the acyclic precursors reduced the volatility of these starting materials, and for FVP of **27** the carbonyl group allowed the extrusion of carbon monoxide. Thus as a general route to macrocycles, this route to macrocycles may be limited by the size, number, and thermal stability, of the functional groups on the bridging chain.

Experimental observations in the furan-based cyclizations (Scheme I), suggested that the formation of the macrocycles occurs primarily in the gas-phase. The thiophene-based cyclization also appears to be a gas-phase reaction. We examined the FVP product mixtures shortly after the products were collected. The macrocyclic products were clearly present in these mixtures, while the bis-2,5-dimethylene-2,5-dihydrothiophenes were not visible. In contrast, 2,5-dimethylene-2,5-dihydrothiophene (**3**) persists in solution for several hr at room temperature[4b] and may be observed by ^1H

NMR, so one would also expect to observe the bis-2,5-dimethylene-2,5-dihydrothiophene if it were condensed as a product from FVP.

The *p*-quinodimethanes **1**, **2**, and **3**, are known to react by intermolecular reactions to give the ethano-bridged cyclophanes.[6] Diradical intermediates have been postulated for these reactions, however the existence of these intermediates has yet to be rigorously established.[6a,i,j,18] We have produced macrocycles from the bis-2,-5-dimethylene-2,5-dihydrothiophenes and bis-2,5-dimethylene-2,5-dihydrofurans. The formation of these macrocycles suggests that the thiophene- and furan-based *p*-quinodimethanes are reacting to give a cyclic diradical, which disproportionates intramolecularly to yield macrocyclic products. Given that the cyclic diradicals are formed by the intramolecular "dimerization" of two *p*-quinodimethanes, these results provide further evidence to suggest that *p*-quinodimethanes form products through diradical intermediates.

Clearly the macrocycles **16**, **25**, and **31**, as well as product **32**, are consistent with the formation of the bis-2,5-dimethylene-2,5-dihydrothiophenes, but our results also indicate that the starting materials **13**, **18**, and **27**, are decomposing by some other routes, too. The unexpected products **17**, **26**, and **33**, were probably all formed by



17: X = CH_2; **26**: X = CHOH;
33: X = CO

the same decomposition mechanism. It is not clear how these products are formed, but possible routes would be the elimination of acetic anhydride from the starting materials with a hydrogen migration, or decomposition of the acetate groups by CO_2, CO, and

methyl radical loss, with a hydrogen migration. Products **17**, **26**, and **33**, are formed from **13**, **18**, and **27**, respectively, by a reaction or sequence of reactions that result in the oxidation of one end and reduction of the other end of the acyclic starting materials.

Neither is it clear how 2,5-dimethylene-2,5-dihydrothiophene (**3**) is produced when **13** is pyrolyzed. It may be that **3** is produced from either the starting material **11** or by fragmentation of polymeric deposits formed in the hot zone of the FVP apparatus. The decomposition of **13** to produce **17** may have occurred by the decomposition of the acetate groups and the formation of **3** may be related to this decomposition. The ^{1}H NMR spectrum of the product mixture from **13** revealed the presence of **3**. It is certain that the NMR signals we observed were not due to the presence of the acyclic intermediate bis-2,5-dimethylene-2,5-dihydrothiophene (**34**). If the transient ^{1}H NMR signals were due to intermediate **34**, then one would expect to see ^{1}H-^{1}H coupling between the methylene group and the olefinic hydrogen, but this was not observed.

In summary, bis-2,5-dimethylene-2,5-dihydrothiophenes have been generated by FVP of **13**, **18**, and **27**. From the bis-2,5-dimethylene-2,5-dihydrothiophenes, macrocycles (**16**, **25**, and **31**) were formed in fair yield (35 to 45%). This chemistry was also found to tolerate some functionalization of the bridging chain between the thiophene-based *p*-quinodimethanes. Both the furan- and thiophene-based cyclizations work reasonably well, so we believe that this is a general and novel route to macrocycles.

EXPERIMENTAL SECTION

Methods and materials

Some general methods have been described previously.[19] Gas chromatographic analysis was performed on a Hewlett-Packard 5890 Series II gas chromatograph (GC), employing a 30 meter DB-1 capillary column, helium carrier gas, and flame ionization detector. Infrared spectra (IR) were obtained from an IBM IR/98 fourier transform infrared spectrometer (FT-IR). Combustion analysis was done by Galbraith Laboratories of Knoxville, TN. For the synthesis of FVP precursors and products, yield percentages represent purified, isolated yields. The 2-thiophene-carboxaldehyde , 1,5-dibromopentane, n-butyllithium, tert-butyldimethylsilyl chloride, lithium aluminum hydride, and tetrabutylammonium fluoride were obtained from Aldrich Chemical and used as received. Thiophene was purchased from Aldrich Chemical and purified according to published procedures.[20] The N,N-dimethyl-formamide and HMPA were obtained from Fisher Scientific and distilled from CaH_2 prior to use. The triethylamine was obtained from Fisher Scientific and distilled from KOH prior to use. The acetone, ethylene glycol, and acetylchloride were obtained from Fisher Scientific and used as received. Pyridinium p-tosylate was prepared by reacting pyridine with p-toluene-sulfonic acid, filtering off the resulting precipitate, and recrystallizing the solids from acetone. When flash chromatography was used to purify products, standard methods were used[21] with Merck grade 60, 230-400 mesh silica gel, which was purchased from Aldrich. Distillation and flash chromatography were used to purify compounds for combustion analysis.

Preparation of 1,5-di(acetoxymethylthienyl-5)pentane (13)

1,5-Di(thienyl-2)-pentane (**14**) was prepared by a procedure based on a published procedure[7] for the alkylation of thiophene. To a stirred solution at -60 °C containing thiophene (3.6 g, 43 mmol) in THF (9 mL) and HMPA (1 mL), 18 mL BuLi (2.1 M, 38 mmol) was added slowly. The solution was stirred at -60 °C for 0.5 h as the thienyl anion was produced. A solution of the 1,5-dibromopentane (2.0 mL, 14 mmol, in 5 mL THF) was then slowly added to the thienyl anion. This solution was allowed to slowly warm to room temperature (4 h, -60 to 20 °C). The dark solution was then quenched with 20 mL 1.0 M HCl, and this mixture was poured into a separatory funnel containing 50 mL of diethyl ether and 30 mL of 1.0 M HCl. After extraction with acid, the organic phase was then extracted once with saturated $NaHCO_3$ solution, three times with brine, and dried with anhydrous $MgSO_4$. Filtration and concentration provides crude (**14**). Compound **14** was then purified by vacuum distillation (1.79 g, 7.6 mmol, 52%). **14**: oil, bp 110 °C (2 mm Hg); IR (neat, NaCl) 2927, 2851, 1457, 1234, 849, 819, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.13 (dd, J = 5.1, 1.2 Hz, 2H), 6.95 (dd, J = 5.1, 3.3 Hz, 2H), 6.83-2.81 (m, 2H), 2.87 (t, J = 7.8 Hz, 4H), 1.76 (pent, J = 7.8, 4H), 1.54-1.44 (m, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 145.4, 126.6, 123.9, 122.7, 31.5, 29.7, 28.5; MS m/e (EI) 236 (13, M^+), 139 (9), 111 (19), 98 (19), 97 (100), 53 (13), 45 (23).

1,5-Di(2-formyl-thienyl-5)pentane (**15**) was prepared based on a published procedure for the formylation of thiophene.[8] To a solution at -78 °C containing **14** (1.65 g, 5 mmol) in THF (40 mL) and HMPA (4 mL), 6.0 mL of butyllithium (2.1 M, 13 mmol) was added slowly. The solution was stirred at -78 °C for 1 h as the deep red thienyl anion was produced. DMF (5.0 mL, 65 mmol) was then added to the solution and it was allowed to warm slowly to room temperature (3 h, -78 °C to 20 °C). This solution was then stirred for 8 h. The resulting solution was then quenched with

enough 10% HCl to produce a solution of about pH 7, and added to a separatory funnel containing 50 mL of diethyl ether and 30 mL of 10% HCl. Following the acidic extraction, the organic phase was then extracted once with saturated $NaHCO_3$ solution, three times with brine, and dried with anhydrous $MgSO_4$. Filtration and removal of the ether provided (**15**) which was purified by flash chromatography using 3:2 hexanes:ethyl acetate (1.80 g, 46 mmol, 93%). **15**: yellow oil; IR (neat, NaCl) 2931, 2851, 1666, 1454, 1228, 810 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.78 (s, 2H), 7.57 (d, J = 3.9 Hz, 2H), 6.86 (d, J = 3.6 Hz, 2H), 2.84 (t, J = 7.5 Hz, 4H), 1.71 (pent, J = 7.5 Hz, 4H), 1.46-1.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 182.5, 156.9, 141.6, 137.0, 125.9, 30.7, 30.5, 28.1. MS m/e (EI) 292 (7, M^+), 264 (21), 167 (13), 139 (51), 137 (12). 126 (39), 125 (58), 111 (12), 98 (12), 97 (100), 53 (20), 45 (32).

1,5-di(2-acetoxymethylthienyl-5)pentane (**13**) was prepared from **15** (1.35 g, 4.6 mmol) using published procedures for the reduction and acylation of a formyl group.[9] The crude product **13** was purified by flash chromatography using 4:1 hexanes:ethyl acetate as the eluent (1.71 g, 4.5 mmol, 97%). **13**: oil, bp 140 °C (0.01 mm Hg); IR (neat, NaCl) 2934, 2856, 1740, 1485, 1441, 1377, 1362, 1229, 1022, 991, 955, 804 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.87 (d, J = 3.4 Hz, 2H), 6.50 (d, J = 3.4 Hz, 2H), 5.17 (s, 4H), 2.76 (t, J = 7.6 Hz, 4H), 2.06 (s, 6H), 1.68 (p, J = 7.6 Hz, 4H), 1.49-1.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 170.6, 147.3, 135.1, 128.0, 123.7, 60.7, 31.2, 29.9, 28.3, 20.9; Anal. Cacld. for $C_{19}H_{24}O_4S_2$: C, 59.97; H, 6.36; S,16.85. Found: C, 60.14; H, 6.40; S, 17.18.

Preparation of 1,5-di(2-acetoxymethylthienyl-5)-3-pentanol (18)

1,5-Di(2-thienyl)-1,4-pentadien-3-one (**19**) was prepared by a procedure based on a published procedure[12] for the condensation of benzaldehyde with acetone. Acetone (0.93 mL, 12.5 mmol) was added to 2.34 mL of 2-carboxaldehyde thiophene (25 mol) and about 1/2 of this mixture was added to a stirred solution at 20 °C containing 2.5 g

NaOH (62.5 mmol) in 25 mL H_2O and 20 mL ethanol. The resulting mixture was stirred 15 min during which time the solution turned yellow/green with a granular precipitate. The remaining acetone/aldehyde solution was then added to the stirring product mixture. After an additional 30 min, the product mixture was filtered and the precipitate was washed with about 5 mL of ice cold water. The bright yellow solid was then dried and identified as pure **19** (3.04 g, 12.4 mmol, 99%). **19**: yellow solid, mp 113-115 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.99 (d, J = 15 Hz, 2H), 7.40 (d, J = 5.1Hz, 2H), 7.32 (d, J = 3.4 Hz, 2H), 7.18-7.01 (m, 2H), 6.81 (d, J = 15 Hz, 2H); UV-Vis λ_{max} 370 nm (CH_3OH); MS m/e (EI) 248 (5, M+2), 247 (9, M+1), 246 (50, M^+), 217 (24), 185 (24), 184 (21), 162 (39), 137 (54), 134 (31), 109 (100), 97 (50), 69 (39), 65 (93), 39 (75).

1,5-Di(2-thienyl)-3-pentanone (**20**) was prepared by Pd catalyzed reduction[13] of **19**. 0.2 g of 5% Pd-C and 100 mL absolute ethanol:ethyl acetate (1:1) were placed in a 200 mL hydrogenation bottle and the sealed bottle was filled with 30 psi of H_2. The solution was then shaken on a Parr Hydrogenation Apparatus for 30 min. The hydrogenation bottle was then opened and a solution was added containing 2.5 g (10 mmol) of **19** in 50 mL absolute ethanol:ethyl acetate (1:1). The bottle was again sealed and pressurized to 30 psi of H_2. The progress of the reaction was monitored by GC, and after 40 hr of shaking, the reaction was stopped. The product mixture was then filtered through celite. The crude product mixture was concentrated and **20** was isolated by flash chromatography using hexane:ethyl acetate (9:1) as the eluent (2.34 g, 9.4 mmol, 94%). **20**: clear oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.10 (dd, J = 5.3, 1.0 Hz, 2H), 6.87 (dd, J = 5.1, 3.4 Hz, 2H), 6.76-6.75 (m, 2H), 3.10 (t, J = 7.5 Hz, 4H), 2.77 (t, J = 7.5 Hz, 4H); MS m/e (EI) 252 (1, M+2), 251 (2, M+1), 250 (14, M^+), 153 (7), 152 (11), 139 (11), 135 (15), 111 (46), 98 (15), 97 (100), 84 (10), 53 (18), 45 (35), 39 (18).

1,5-Di(2-thienyl)-3-pentanol (**21**) was prepared using standard methods for the reduction of ketones.[9] To a suspension of $LiAlH_4$ (0.35 g, 9 mmol) in 100 mL THF at 0 °C was slowly added 3.1 g (12.4 mmol) of **20** in 100 mL THF. After three hr of stirring at room temperature, the gray suspension was quenched by addition of 0.5 mL H_2O, 0.5 mL 15% NaOH, and then 1.5 mL H_2O. The resulting solution was stirred 20 min and 0.5 g of anhydrous $MgSO_4$ was added the stirring mixture. After filtration and removal of the solvent, 3.1 g (12.3 mmol, 99%) of **21** was obtained. **21**: clear oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.10 (d, J = 4.8 Hz, 2H), 6.91-6.86 (m, 2H), 6.78 (d, J = 3.0 Hz, 2H), 3.77-3.65 (m, 1H), 3.08-2.83 (m, 4H), 1.93-1.76 (m, 4H), 1.51 (s, 1H); MS m/e (EI) 253 (1, M+1), 252 (4, M^+), 234 (3, m-18), 138 (4), 137 (20), 136 (45), 123 (11), 111 (12), 110 (13), 98 (44), 97 (100), 53 (16), 45 (32).

1,5-Di(2-thienyl)-3-(tert-butyldimethylsiloxy)pentane (**22**) was prepared using a standard method[14] for the protection of an alcohol. To a solution of **21** (0.91 g, 3.6 mmol) in 40 mL of DMF, was added 0.64 g of imidazole (9.4 mmol) followed by addition of 0.67 g of *tert*-butyldimethylsilyl chloride (4.3 mmol). The mixture was stirred at 20 °C for 12 hr and then the extracted with 100 mL diethyl ether and 30 mL sat. $NaHCO_3$. The organic phase was extracted three times with brine, dried with anhydrous $MgSO_4$, and filtered. Removal of the solvent and purification by flash chromatography using hexanes:ethyl acetate (9:1) as the eluent provide 1.18 g of pure **22**. **22**: clear oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.09 (dd, J = 4.1, 0.8 Hz, 2H), 6.89 (dd, J = 5.1, 3.5 Hz, 2H), 6.77-6.73 (m, 2H), 3.81 (p, J = 5.6, 1H), 2.92-2.82 (m, 4H), 1.91-1.81 (m, 4H), 0.90 (s, 9H), 0.85 (s, 6H); MS m/e (EI) 351 (0.2, M-15), 309 (17, M-57), 136 (12), 98 (11), 97 (100), 75 (80), 73 (19).

1,5-Di(2-formyl-thienyl-5)-3-(tert-butyldimethylsiloxy)pentane (**23**) was prepared using an identical procedure to that employed in the preparation of **15**. Compound **22**

(0.80 g, 2.2 mmol) was formylated[8] to give 0.581 g (1.4 mmol, 63%) of purified **23**. **23**: yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.80 (s, 2H), 7.59 (d, J = 3.7 Hz, 2H), 6.89 (d, J = 3.7 Hz, 2H), 3.83 (p, J = 5.6 Hz, 1H), 2.98-2.87 (m, 4H), 1.94-1.83 (m, 4H), 0.93 (s, 9H), 0.53 (s, 6H); MS m/e (EI) 407 (0.3, M-15), 365 (30, M-57), 227 (9), 200 (9),197 (9), 125 (39), 97 (24), 75 (100), 73 (31).

1,5-di(2-acetoxymethylthienyl-5)-3-(tert-butyldimethylsiloxy)pentane (**24**) was prepared using an identical procedure to that employed in the preparation of **13**. Compound **24** (0.40 g, 0.95 mmol) was reduced, acylated,[9] and purified to give 0.40 g of **22** (0.79 mmol, 83%). **24**: clear oil; IR (neat, NaCl) 2952, 2856, 1741, 1231, 1081, 836 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.87 (d, J = 3.4 Hz, 2H), 6.62 (d, J = 3.4 Hz, 2H), 5.17 (s, 4H), 3.79 (s,1H), 2.90-2.78 (m, 4H), 2.06 (s, 6H), 1.87-1.80 (m, 4H), 0.89 (s, 9H), 0.42 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 170.8, 147.4, 135.3, 128.2, 123.8, 70.6, 60.8, 38.7, 25.9, 21.0, 18.1, -4.4 (2 magnetically equal carbons).

1,5-di(acetoxymethylthienyl-5)-3-pentanol (**18**) was prepared using a general method for the deprotection of a silyl-protected alcohol.[14] To a stirred solution of **24** (1.14 g, 2.3 mmol) in 50 mL of dry THF, was added 1.8 g of tetrabutylammonium fluoride (7.8 mmol). The solution was stirred for 3 hr and the product mixture was poured into a separatory funnel containing 50 mL diethyl ether and 30 mL 1.0 M HCl. Following acidic extraction, the product mixture was washed with brine, dried with anhydrous $MgSO_4$, and purified with flash chromatography using hexane:ethyl acetate (3:2). 0.5854 g of pure **18** was isolated (1.5 mmol, 65%). **18**: white solid, mp 44-45 °C; IR (neat, NaCl) 3408, 2937, 1740, 1232, 1022, 806 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.87 (d, J = 3.4 Hz, 2H), 6.63 (d, J = 3.4 Hz, 2H), 5.15 (s, 4H), 3.75-3.65 (m, 1H), 2.99-2.79 (m, 4H), 2.05 (s, 6H), 1.87-1.76 (m, 4H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 170.6, 146.6, 135.4,

128.1, 123.9, 69.9, 60.7, 39.0, 26.3, 20.9; Anal. Cacld. for $C_{19}H_{24}O_5S_2$: C, 57.55; H, 6.10; S, 16.17. Found: C, 57.35; H, 6.28; S, 16.86.

Preparation of 1,5-di(2-acetoxymethylthienyl-5)-3-pentanone (27)

1,5-di(2-thienyl)-3,3-ethylenedioxypentane (**28**) was prepared by standard methods for the protection of a ketone.[15] Compound **20** (2.34 g, 0.94 mmol) was dissolved in a solution of 150 mL benzene:toluene (1:1), 10 mL ethylene glycol (180 mmol), and 0.4 g of pyridinium *p*-toluenesulfonate (1.6 mmol). The flask containing this solution was then fitted with a Dean-Stark trap and condenser, and the mixture was heated to reflux at 110 °C. After refluxing 5 hr, the product mixture was extracted with brine, dried with $MgSO_4$, and concentrated. The crude ketal (**28**) was purified by flash chromatography using hexane:ethyl ether (4:1) as the eluent and 2.09 g of **28** was isolated (7.1 mmol, 76%). **28**: white solid, mp 49-50 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.98 (d, J = 3.0 Hz, 2H), 6.78 (dd, J = 5.1, 4.5 Hz, 2H), 6.68-6.63 (m, 2H), 3.89 (s, 4H), 2.86-2.76 (m, 4H), 1.99-1.89 (m, 4H); MS m/e (EI) 294 (1, M^+), 232 (2), 183 (48), 135 (4), 97 (100), 53 (7), 45 (12).

1,5-Di(2-formyl-thienyl-5)-3,3-ethylenedioxypentane (**29**) was prepared using the same procedure[8] employed in the formylation of **14** and **22**. From 0.89 g of **28** (3.0 mmol), 0.99 g of **29** was isolated (2.8 mmol, 94%). **29**: yellow oil; δ 9.79 (s, 2H), 7.58 (d, J = 3.7 Hz, 2H), 6.89 (d, J = 3.7 Hz, 2H), 4.00 (s, 4H), 3.03-2.84 (m, 4H), 1.98-1.79 (m, 4H); MS m/e (EI) 350 (6, M^+), 212 (12), 211(100), 139 (11), 126 (10), 125 (90), 97 (34), 45 (20).

1,5-di(2-acetoxymethylthienyl-5)-3,3-ethylenedioxypentane (**30**) was prepared using an identical procedure to that employed in the preparation of **16** and **24**. Compound **29** (1.1491 g, 3.3 mmol) was reduced, acylated,[9] and purified to give 1.40 g of **30** (1.40 g, 3.2 mmol, 97%). **30**: clear oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.87 (d, J = 3.4 Hz, 2H), 6.64 (d, J = 3.4 Hz, 2H), 5.15 (s, 4H), 3.99 (s,4H), 2.90-2.82 (m, 4H), 2.05 (s, 6H),

2.07-1.96 (m, 4H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 170.8, 147.4, 135.3, 128.2, 123.8, 70.6, 60.8, 38.7, 25.9, 21.0, 18.1.

1,5-di(2-acetoxymethylthienyl-5)-3-pentanone (**27**) Method A: **27** was prepared from **30** by a general method for the deprotection of a ketal protecting group.[15] A solution containing 0.1077 g of **30** (0.25 mmol), 10 mL acetone, 0.5 mL H_2O, and 0.075 g pyridinium *p*-toluenesulfonate was heated to reflux at 80 °C. The progress of the reaction was monitored by HPLC (C_{18} reverse phase column, CH_3OH:H_2O (80:20) mobile phase) and after 72 hr the ratio of **27** to **30** was 9:1. The product mixture was then poured into a separatory funnel containing 50 mL diethyl ether and 20 mL 1.0 M HCl. After acidic extraction, the organic phase was washed with sat. $NaHCO_3$, and then brine. Product **24** (0.0846 g, 0.21 mmol, 84%) was then isolated by flash chromatography using hexane:diethyl ether (3:2) as the eluent. In some cases, analysis of the crude product mixture by HPLC indicated that deacylation had occurred. If so, the products were reacted with acetyl chloride and triethylamine prior to the purification of **27**. Method B: Product **27** was also prepared by oxidation of **18** using a general method for the oxidation of 2° alcohols.[16] To a solution at -70 °C containing 0.36 mL oxalyl chloride (2.0 M in CH_2Cl_2, 0.72 mmol) in 1 mL CH_2Cl_2, was added 0.1 mL DMSO (1.4 mmol). This solution was stirred 10 min, and then **18** (0.0833 g, 0.21 mmol) in 1.5 mL of CH_2Cl_2 was added. After stirring 25 min, 0.36 mL (2.6 mmol) of triethylamine was added to the mixture. The solution was stirred an additional 30 min at -70 °C, and then allowed to warm (-70 °C → 20 °C, 30 min). To the product mixture was added 10 mL H_2O, 10 mL CH_2Cl_2, and the mixture was extracted. The aqueous phase was then washed with 10 mL CH_2Cl_2 and the organic solutions were combined. Compound **27** was dried with $MgSO_4$ and isolated (0.071 g, 0.18 mmol, 86%) by flash chromatography with hexane:ethyl acetate (4:1) as the eluent. **27**: clear oil; IR (neat,

NaCl) 2955, 2850, 1738, 1710, 1441, 1410, 1229; 1022, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.85 (d, J = 3.3 Hz, 2H), 6.62 (d, J = 3.4 Hz, 2H), 5.14 (s, 4H), 3.06 (t, J = 7.3 Hz, 4H), 2.76 (t, J = 7.3 Hz, 4H), 2.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 207.5, 170.8, 145.5, 135.9, 128.3, 124.5, 60.8, 44.3, 24.0, 21.0; Anal. Cacld. for $C_{19}H_{22}O_5S_2$: C, 57.85; H, 5.62; S,16.25. Found: C, 57.74; H, 5.78; S, 16.30.

Flash vacuum pyrolysis of 1,5-di(acetoxymethylthienyl-5)pentane (13)

Compound **13** was pyrolyzed (187 mg, 0.49 mmol) using standard FVP methods[10]. The hot zone of the FVP apparatus was maintained at 650 °C under a vacuum of about 10^{-5} torr and **13** was heated to 120 °C. The FVP products were collected in a liquid N_2 cooled trap. The crude product mixture was analyzed by GCMS and found to contain two major products in an 8:1 ratio with respective *m/e* values of 260 and 278. These products were identified as **16** and **17**. By flash chromatography using hexanes as the eluent, macrocycle **16** was isolated (58 mg, 0.22 mmol, 45%). In another FVP experiment, 0.102 g (0.27 mmol) of **13** was pyrolyzed and 0.015 g (0.054 mmol, 20%) of **17** was isolated. ^1H NMR analysis of the crude FVP pyrolysis mixture also revealed the presence of a transient intermediate, 2,5-dimethylene-2,-5-dihydrothiophene (**3**). An NMR spectrum of the crude products in C_6D_6 was taken within 30 min of the completion of the FVP and another spectrum was taken 24 hr later. The two NMR spectra were subtracted and the observed NMR signals suggested the presence of **3**. The yield of **3** was not established.

cis-1,2-Dehydro[5,2](2,5)thienophane (**16**): clear oil; IR (neat, NaCl) 2930, 2849, 1454, 1032, 804, 781 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.60 (d, J = 3.6 Hz, 1H), 6.67 (s, 2H), 6.59 (dd, J = 3.6, 0.9 Hz, 1H), 6.35 (dd, J = 11.1, 0.6 Hz, 1H), 5.57 (dt, J = 11.4, 8.4 Hz, 1H), 2.96 (s, 4H), 2.70-2.61 (m, 2H), 2.40-2.29 (m, 2H), 1.60-1.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 144.9, 142.4, 142.2, 138.1, 133.5, 126.0, 125.1, 123.8 (2 peaks

superimposed), 122.4, 33.3, 32.3, 32.1, 29.7, 24.9; MS m/e (EI) 262 (6, M+2), 261 (12, M+1), 260 (55, M^+), 163 (23), 150 (100), 149 (67), 137 (37), 136 (33), 135 (38), 123 (62), 117 (29), 110 (24), 97 (29), 91 (30), 45 (40); EIHRMS *m/e* 260.06955 ($C_{15}H_{16}S_2$ requires 260.06935).

1-(2-methylthienyl-5)-5-(2'-formylthienyl-5')pentane (**17**): clear oil; IR (neat, NaCl) 2932, 2856, 1668, 1460, 1229, 1036, 798 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.82 (s, 1H), 7.60 (d, J = 3.8 Hz, 1H), 6.88 (d, J = 3.8 Hz, 1H), 6.53 (s, 2H), 2.87 (t, J = 7.7 Hz, 2H), 2.74 (t, J = 7.7 Hz, 2H), 2.43 (s, 3H), 1.79-1.62 (m, 4H), 1.50-1.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz, ^1H decoupled) δ 182.5, 157.3, 142.9, 141.5, 137.1, 136.9, 125.7, 124.4, 123.6, 31.2, 30.9, 30.6, 29.8, 28.2, 15.2; ^{13}C NMR ($CDCl_3$, 300 MHz, ^1H-^{13}C coupled) δ 182.5 (d, J_{C-H} = 702 Hz), 136.9 (d, J_{C-H} = 665 Hz), 125.7 (d, J_{C-H} = 649 Hz), 124.4 (d, J_{C-H} = 654 Hz), 123.6 (d, J_{C-H} = 646 Hz), 31.2 (t, J_{C-H} = 494 Hz), 30.9 (t, J_{C-H} = 502 Hz), 30.6 (t, J_{C-H} = 515 Hz), 29.8 (t, J_{C-H} = 500 Hz), 28.2 (t, J_{C-H} = 491 Hz), 15.2 (t, J_{C-H} = 445 Hz), 4° carbons not visible; MS m/e (EI) 280 (3, M+2), 279 (5, M+1), 278 (30, M^+), 249 (1), 167 (4), 152 (7), 139 (8), 113 (5), 112 (11), 111 (100), 97 (10); EIHRMS *m/e* 278.07991 ($C_{15}H_{18}OS_2$ requires 278.07938).

2,5-dimethylene-2,5-dihydrothiophene (**3**): ^1H NMR (C_6D_6, 300 MHz) δ 6.56 (s), 5.26 (s), 5.07 (s) [lit.[4b] 6.52 (s), 5.24 (s), 5.02 (s) (1:1 $CS_2/CDCl_3$)].

Flash vacuum pyrolysis of 1,5-di(2-acetoxymethylthienyl-5)-3-pentanol (18)

Compound **18** was pyrolyzed (20 mg, 0.05 mmol) using the same methods as FVP of **13**. To effect volatilization of **18**, the sample required heating to 145 °C. The crude product mixture was analyzed by GCMS and found to contain two major products in an 5:1 ratio with respective *m/e* values of 276 and 294. The most abundant product was identified as **25**, while the other product was assumed to be **26** based on GCMS and ^1H NMR analysis of the crude product mixture. By flash chromatography

using hexanes:ethyl ether (4:1) as the eluent, macrocycle **25** was isolated (8 mg, 0.02 mmol, 45%).

cis-1,2-Dehydro-3-hydroxy[5,2](2,5)thienophane (**25**): clear oil; IR (neat, NaCl) 3393, 2918, 2849, 1433, 1261, 1107, 1040, 816, 795 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 60 °C) δ 6.57 (d, J = 2.7 Hz, 1H), 6.4 (m, 3H), 6.11 (d, J = 11.5 Hz, 1H), 5.53 (dd, J = 11.4, 7.9 Hz, 1H), 5.14 (broad m, 1H), 2.75-2.45 (m, 6H), 1.70-1.40 (m, 3H); MS m/e (EI) 278 (7, M+2), 277 (13, M+1), 276 (65, M^+), 166 (19), 165 (51), 153 (45), 152 (32), 125 (30), 124 (35), 123 (100), 111 (43), 110 (58), 97 (42), 91 (25), 45 (55); EIHRMS *m/e* 276.06454 ($C_{15}H_{16}OS_2$ requires 276.06426).

1-(2-methylthienyl-5)-5-(2'-formylthienyl-5')-3-pentanol (**26**: MS m/e (EI) 296 (1.6, M+2), 295 (1.4, M+1), 294 (11, M^+), 276 (2, M-18), 137 (26), 126 (59), 125 (18), 110 (41), 111 (100), 97 (36), 53 (20), 45 (34).

Flash vacuum pyrolysis of 1,5-di(2-acetoxymethylthienyl-5)-3-pentanone (27)

Compound **27** was pyrolyzed (87 mg, 0.21 mmol) using the same methods as FVP of **18**. The crude product mixture was analyzed by GCMS and found to contain three major products in a 1:5:2 ratio with respective *m/e* values of 246, 274, and 292. Two of these products were isolated and identified as **31** and **32** (*m/e* 274 and 246), while the other product was assumed to be **33** based on GCMS and ^1H NMR analysis of the crude product mixture. By flash chromatography using hexanes:ethyl ether (19:1) as the eluent, macrocycle **31**(18 mg, 0.07 mmol, 33%) and product **32** (6 mg, 0.02 mmol, 11%) were isolated.

cis-1,2-Dehydro-3-oxo[5,2](2,5)thienophane (**31**): clear oil; IR (neat, NaCl) 2963, 2926, 1745, 1699, 1670, 1460, 1379, 1231, 1026, 847 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 70 °C) δ 6.89 (d, J = 3.6 Hz, 1H), 6.79-6.70 (m, 3H), 6.66 (d, J = 3.3 Hz, 1H), 5.90 (d, J = 12.3 Hz,

1H), 3.10-2.99 (m, 2H), 2.92 (s, 4H), 2.79-2.75 (m, 2H); ^{1}H NMR ($CDCl_3$, 300 MHz, -50 °C) δ 6.89 (d, J = 3.6 Hz, 1H), 6.79-6.70 (m, 3H), 6.66 (d, J = 3.3 Hz, 1H), 5.90 (d, J = 12.3 Hz, 1H), 3.42-2.94 (m, 6H), 2.74-2.58 (m, 2H); MS m/e (EI) 276 (3, M+2), 275 (5, M+1), 274 (28, M^+), 150 (8), 135 (11), 124 (9), 123 (100), 121 (15), 110 (8), 97 (7), 91 (8), 45 (20); EIHRMS *m/e* 274.04855 ($C_{15}H_{14}OS_2$ requires 276.04861).

1,2-di(2-vinylthienyl-5)ethane (**32**): clear oil; IR (neat, NaCl) 2963, 2928, 1261, 1092, 1022, 998, 798 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz,) δ 6.76 (d, J = 3.3 Hz, 2H), 6.72 (dd, J = 17.4, 10.8 Hz, 2H), 5.45 (d, J = 17.4 Hz, 2H), 5.06 (d, J = 10.8 Hz, 2H), 3.12 (s, 4H); MS m/e (EI) 248 (0.4, M+2), 247 (2, M+1), 246 (14, M^+), 125 (6), 124 (9), 123 (100), 97 (4), 79 (12), 77 (13), 45 (30); EIHRMS *m/e* 246.05408 ($C_{14}H_{14}S_2$ requires 246.05370).

1-(2-methylthienyl-5)-5-(2'-formylthienyl-5')-3-pentanone (**33**): MS m/e (EI) 294 (3, M+2), 293 (4, M+1), 292 (25, M^+), 140 (8), 139 (24), 126 (59), 126 (8), 125 (30), 112 (12), 111 (100), 110 (10), 97 (25), 77 (15), 67 (11), 65 (10), 53 (17), 45 (29).

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APPENDIX

Supplementary Procedures

Purification of compounds **13**, **18**, and **27**, for combustion analysis:

Compound **13** was obtained in highly pure form by initially purifying it by flash chromatography using silica gel and 3:2 pentane:ethyl ether as the eluent. After removal of the solvent using a rotary evaporator, about 300 mg of **13**was placed in a clean and thoroughly dry Hickman still. Preparation of the Hickman still was done within an argon-filled glove bag. The Hickman still was equipped with 10 mL flask which contained a clean, dry 1/2 dram vial. Distillation of **13** was accomplished at 140 °C and 0.01 torr. Within 4 hr, several drops of pure **13** had fallen into the vial. The Hickman still was allowed to cool and it was disassembled within the glove bag. The open vial containing **13** was then transfered (within the glove bag) into the interior chamber of a clean, dry Abderhalden drying apparatus. The Abderhalden flask was filled with hexane and the apparatus evacuated to 0.1 torr. The hexane was heated to reflux and the sample of **13** was allowed to remain in the apparatus for 12 hr. Following the drying period, the apparatus was cooled, it was disassebled in the glove bag, and the vial was capped with teflon tape and a screw cap.

Compounds **18** and **27** were both obtained in highly pure form by flash chromatography followed by drying within the Abderhalden apparatus. Both substances were purified using silica gel chromatograpy and 3:2 pentane:ethyl ether as the eluent. Care was taken to only combine and concentrate the chromatography fractions which were of high purity. Following concentrating on a rotary evaporator, the purified oil (40 mg) was transfered by syringe into a clean, dry vial and placed in the

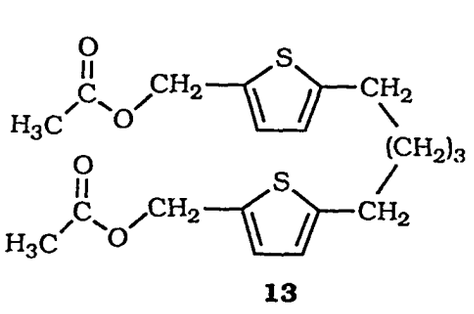
Abderhalden apparatus (all within the glove bag). As with **13**, the samples were then dried and sealed.

General procedure for the reduction and acylation to give **13**, **18**, and **27**:

A stirred mixture of $LiAlH_4$ (15 mmol) in THF (25 mL) was cooled to 0 °C, and to it was added slowly a solution of the aldehyde (**13**, **18**, or **27**) (10 mmol) in THF (10 mL). The ice bath was then removed and the mixture was stirred for 1 h at 25 °C. The reaction was worked up by first cooling the solution to 0 °C and then slowly adding 0.6 mL of H_20, 0.6 mL of 15% NaOH, and then 1.8 mL of H_2O. The mixture was stirred at 25 °C for an additional 20 min. and ~2 g of $MgSO_4$ then was added to the solution. Vacuum filtration removed the precipitated salts, and the reaction flask was then rinsed with 20 mL of ethyl acetate and this solution was poured through the filtered salts. The resulting diol was not isolated, but dissolved in THF (20 mL). To the diol (10 mmol) solution, triethyl amine (3.5 mL, 25 mmol) and acetyl chloride (1.8 mL, 25 mmol) was added and the solution stirred at 25 °C. The mixture was allowed to react for at least 5 h, during which the triethylammonium chloride precipitated. The progress of the reaction was monitored by thin layer chromatography (eluent, 4:1 hexanes:ethyl acetate). Upon completion of the reaction, the product mixture was poured into a separatory funnel containing 50 mL of 1.0 M HCl and 25 mL of ethyl ether. The acidic extraction was then followed by extraction with saturated $NaHCO_3$ and saturated NaCl. Drying with $MgSO_4$ and removal of the solvent gave the crude diacetate **13**. The diacetate was then purified by flash chromatography using 9:1 hexanes:ethyl acetate as the eluent.

NMR spectra are displayed in this section with the following impurities labeled:

C	$CHCl_3$
B	C_6HD_5
W	H_2O
T	$Si(CH_3)_4$
G	Silicone grease
E	$CH_3CO_2C_2H_5$
H	Hexane
O	Ethyl ether
X	Unknown impurity



13

Figure A-1. ^1H NMR spectrum of **13** ($CDCl_3$, 300 MHz).

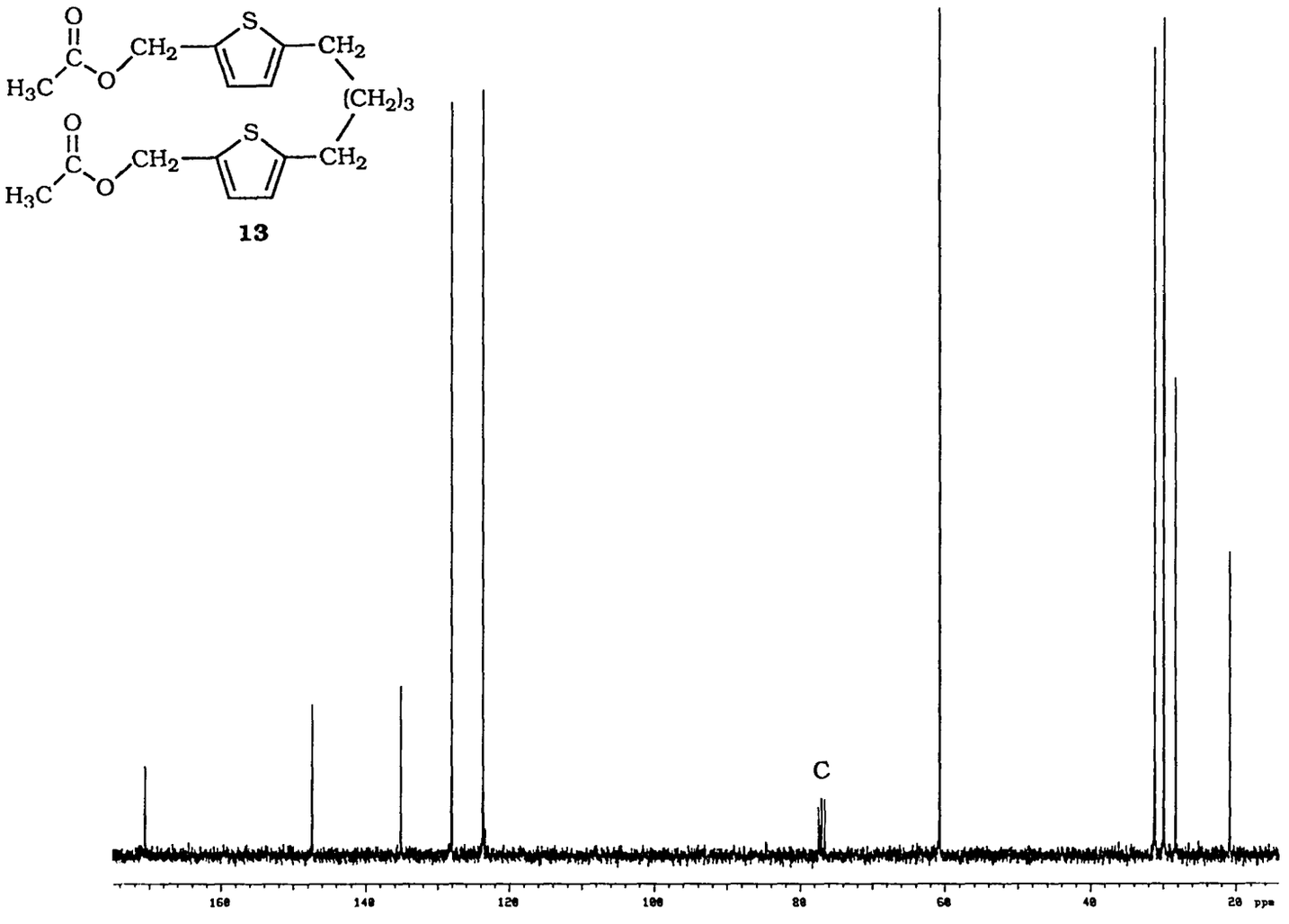
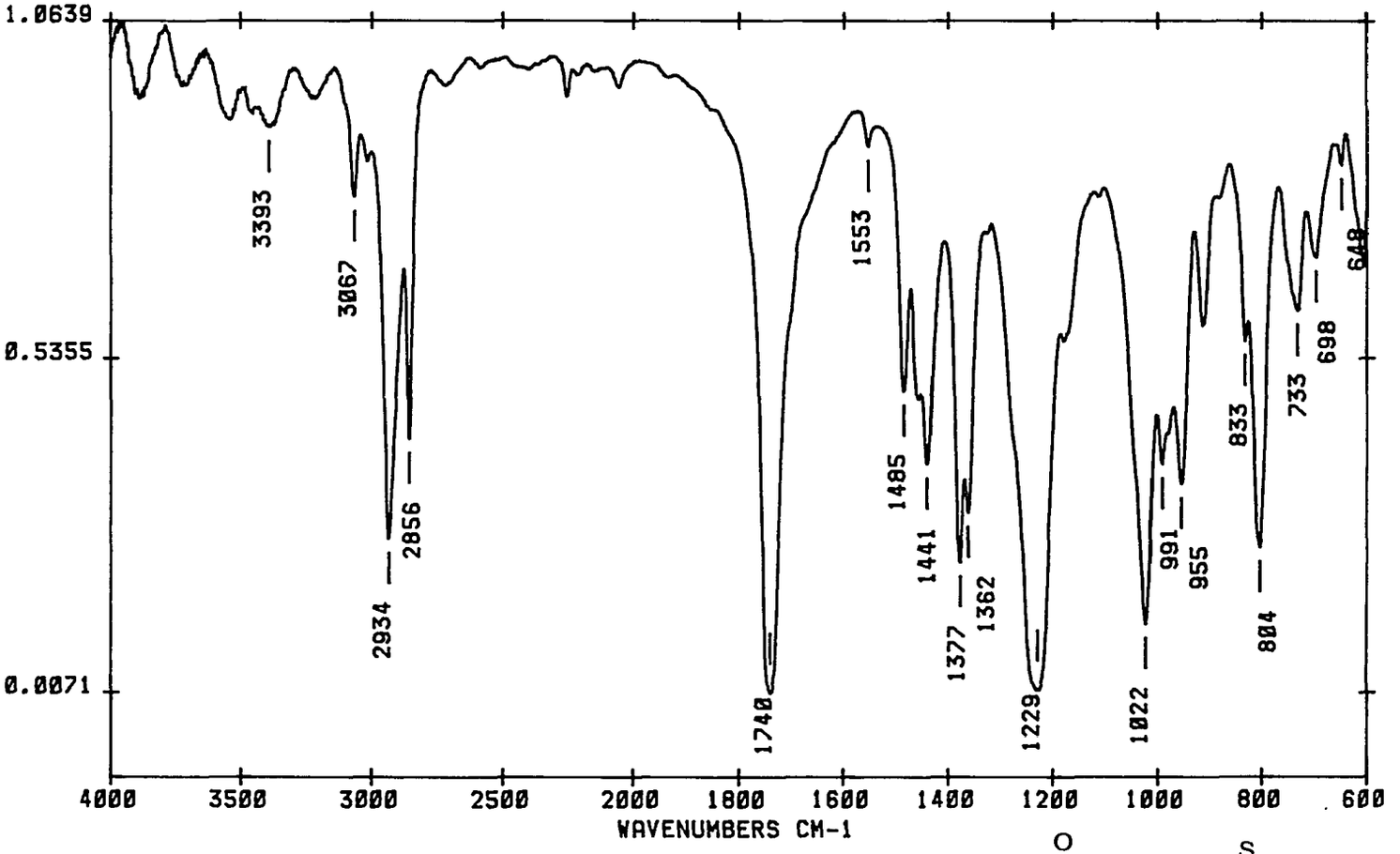


Figure A-2. ^{13}C NMR spectrum of **13** ($CDCl_3$, 300 MHz).



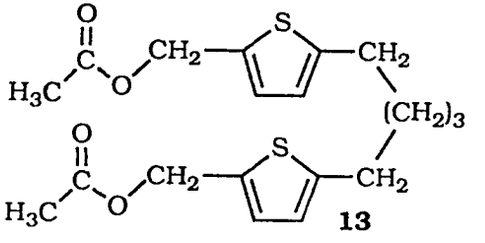


Figure A-3. IR spectrum of **13** (NaCl, thin film).

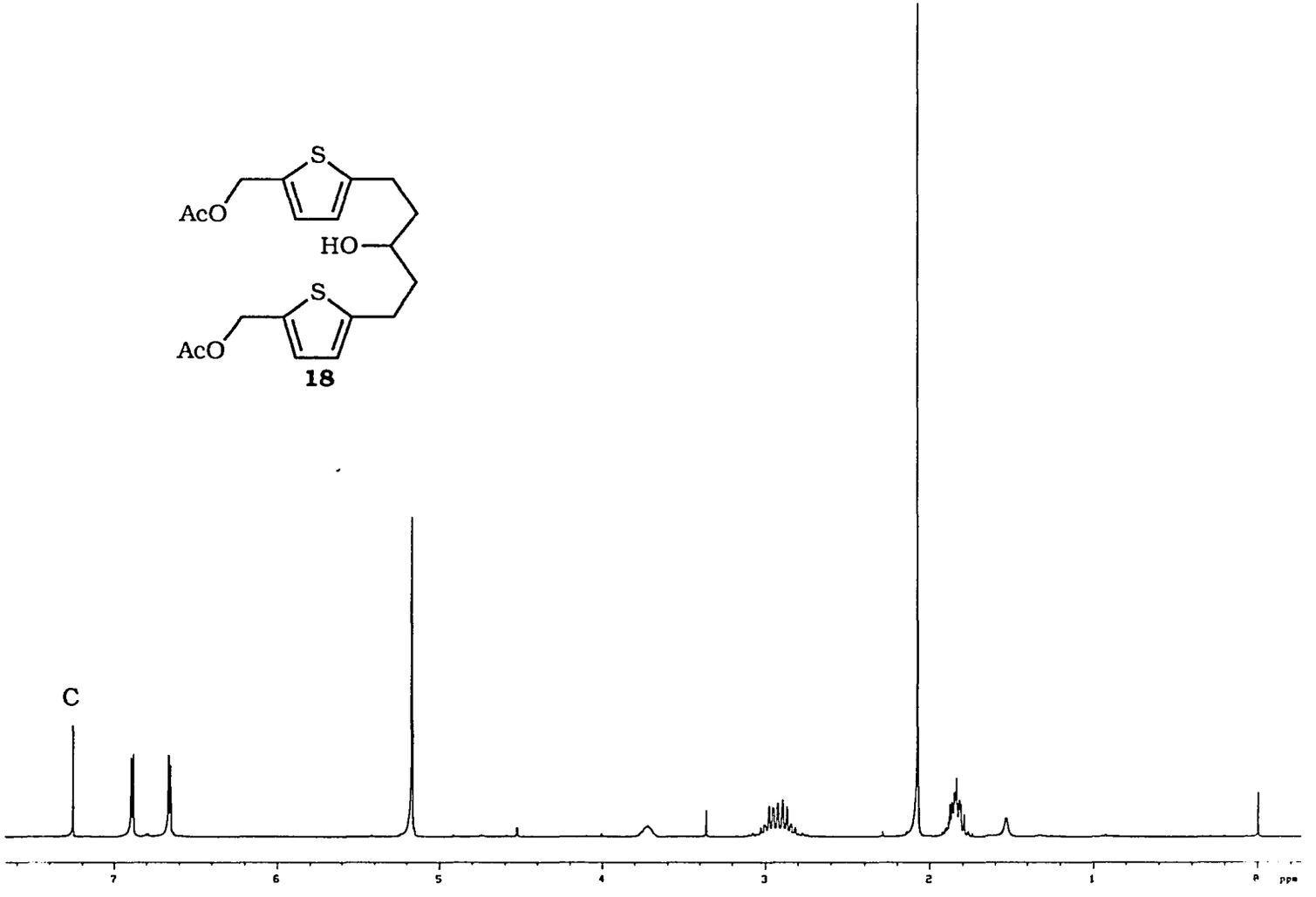


Figure A-4. ^{1}H NMR spectrum of **18** ($CDCl_3$, 300 MHz).

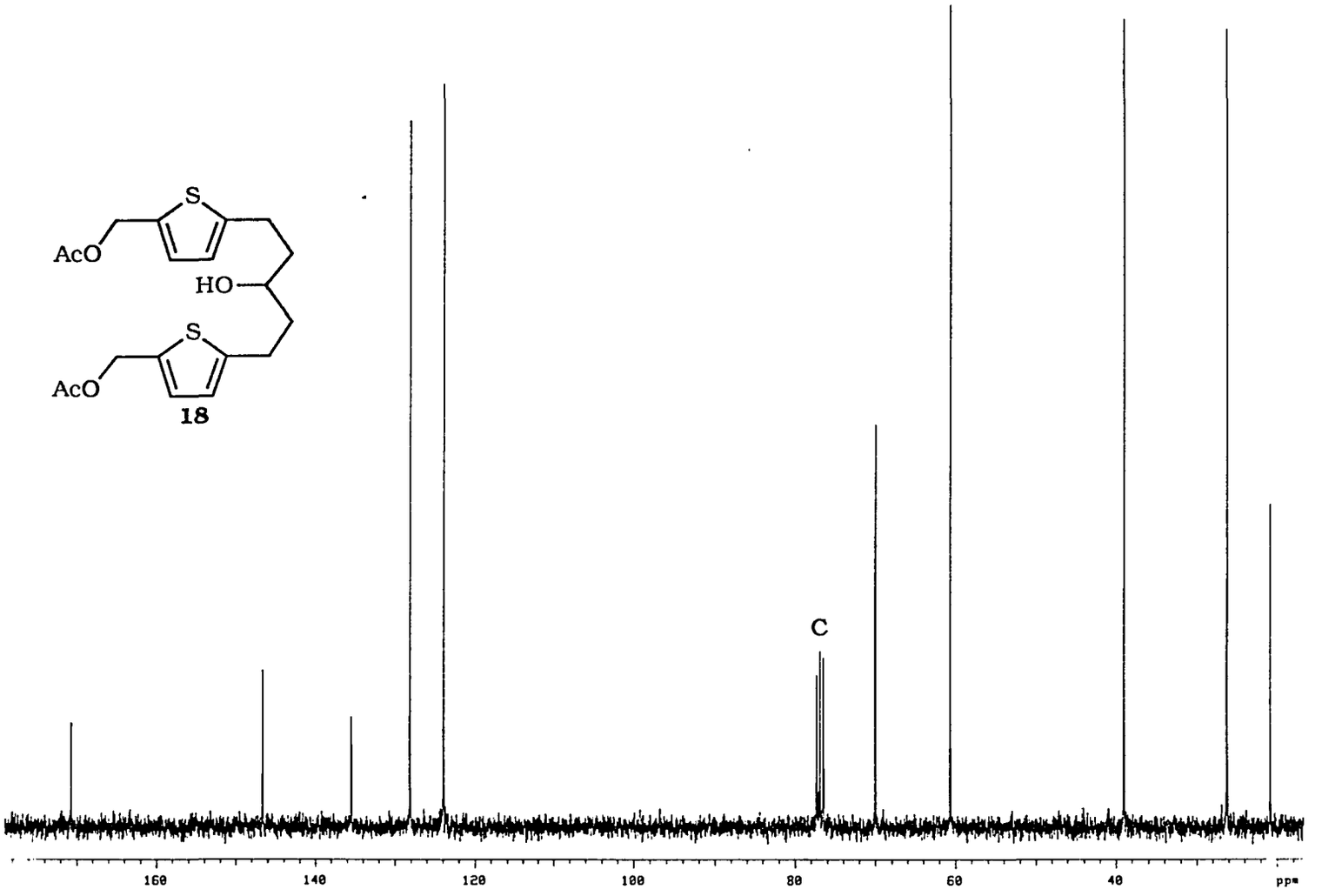


Figure A-5. ^{13}C NMR spectrum of **18** ($CDCl_3$, 300 MHz).

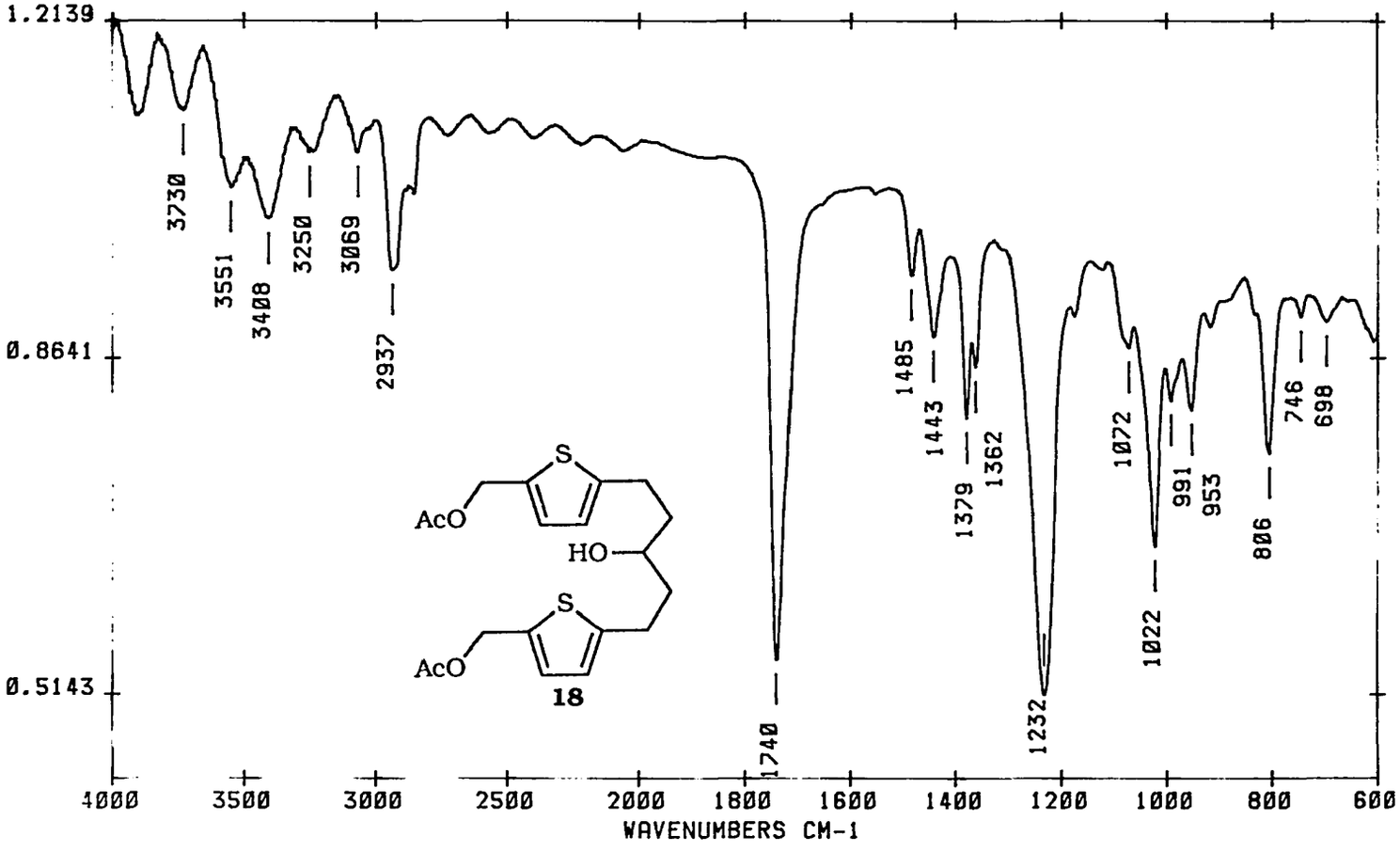


Figure A-6. IR spectrum of **18** (NaCl, thin film).

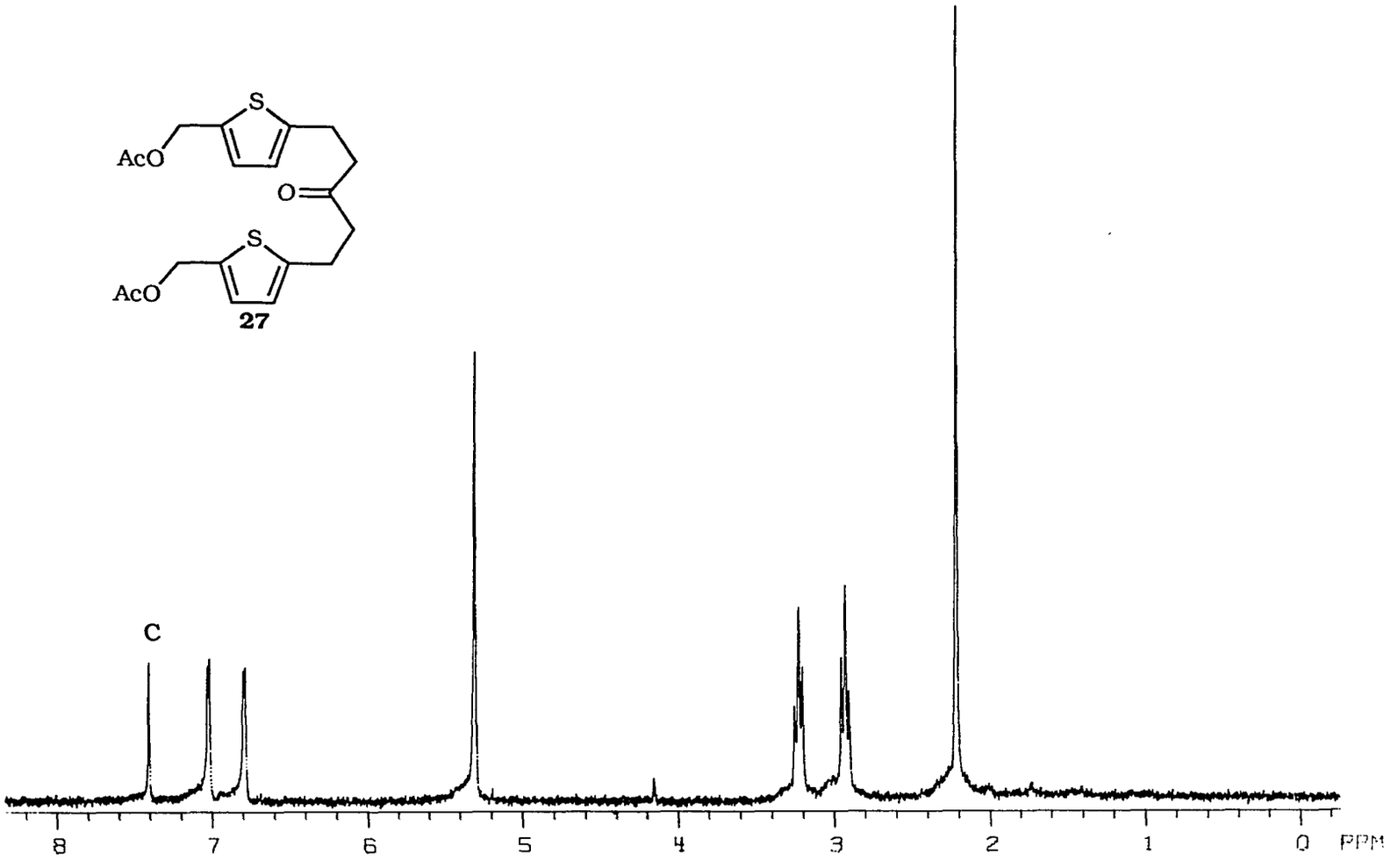


Figure A-7. ^{1}H NMR spectrum of **27** ($CDCl_3$, 300 MHz).

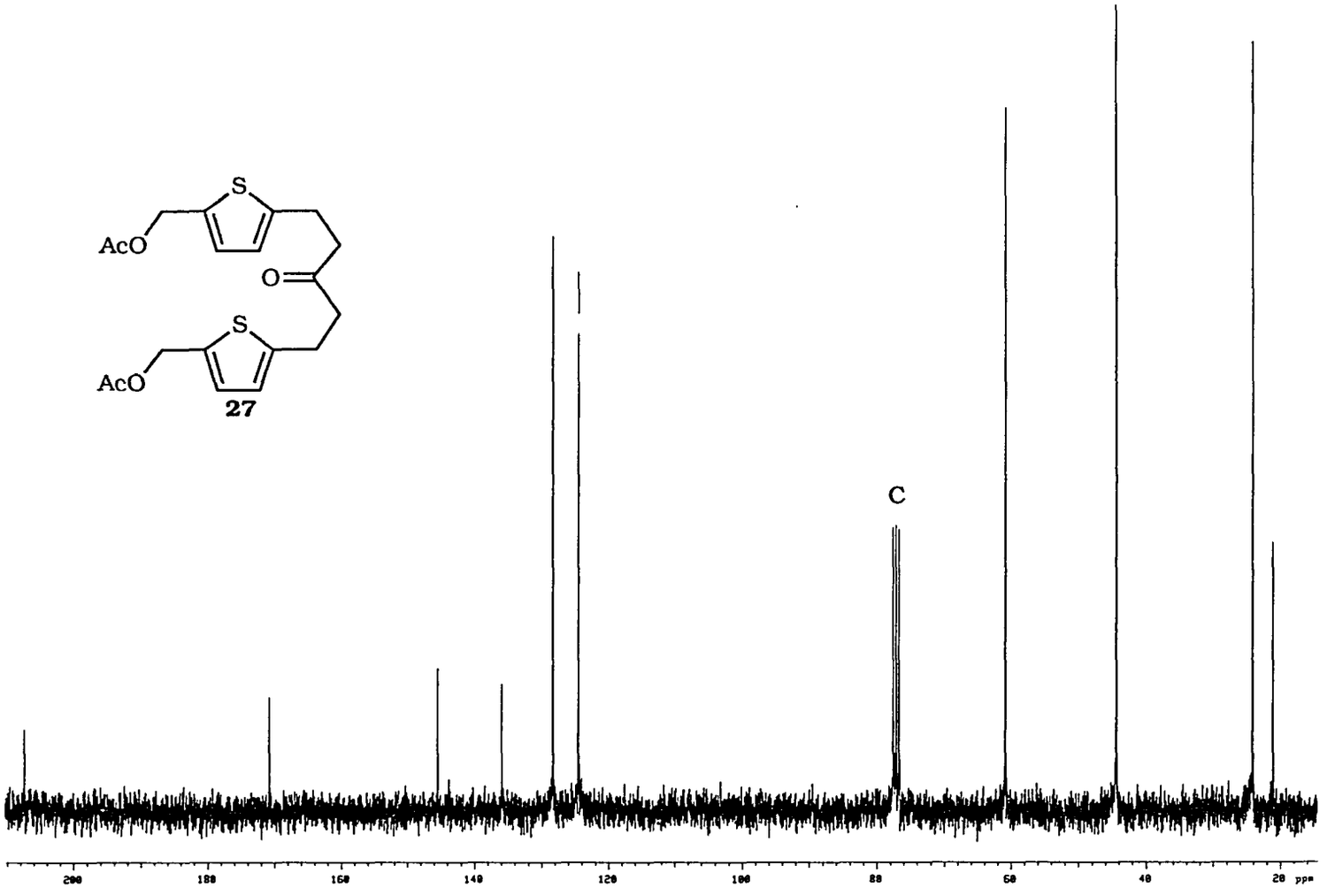


Figure A-8. ^{13}C spectrum of **27** ($CDCl_3$, 300 MHz).

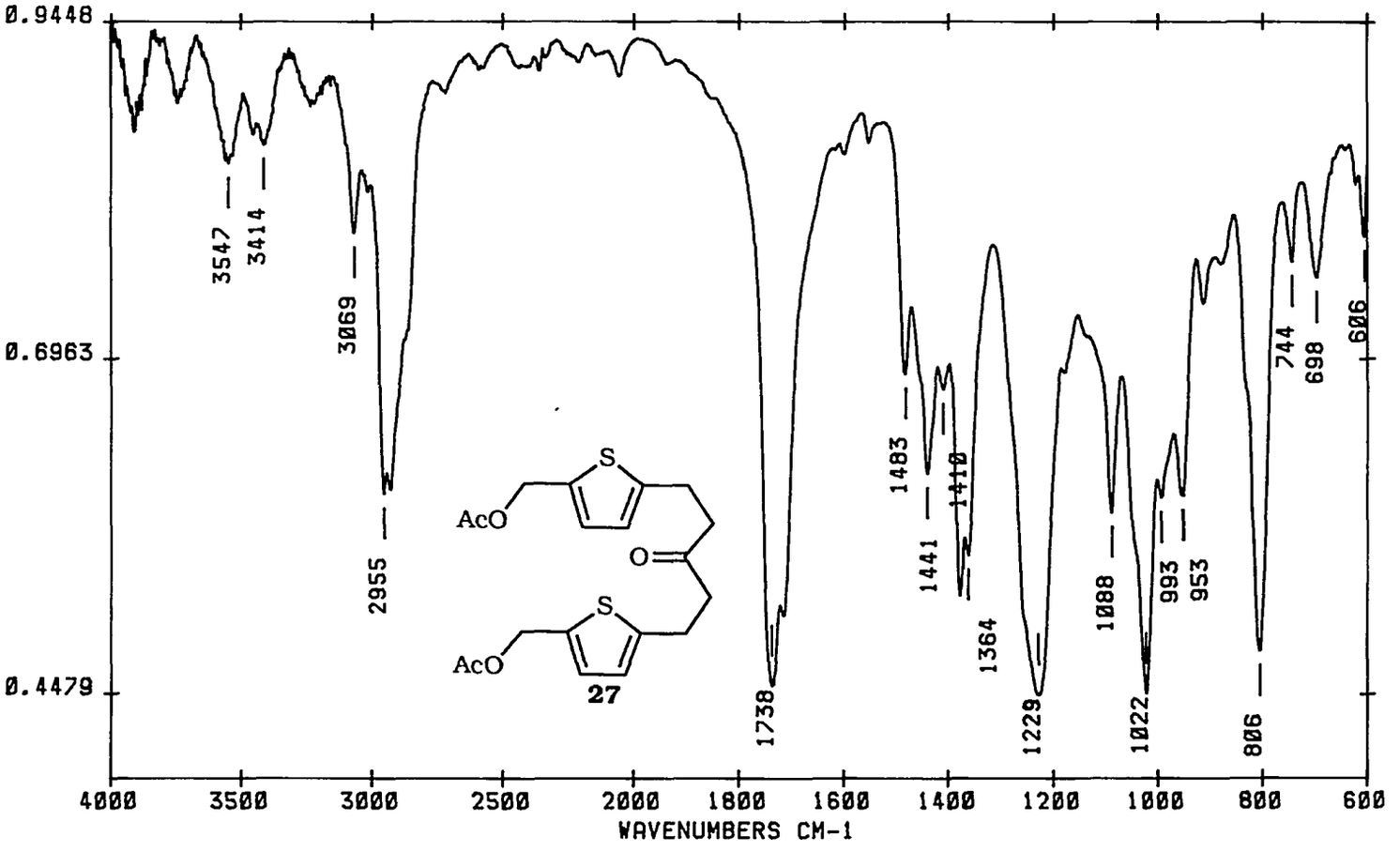
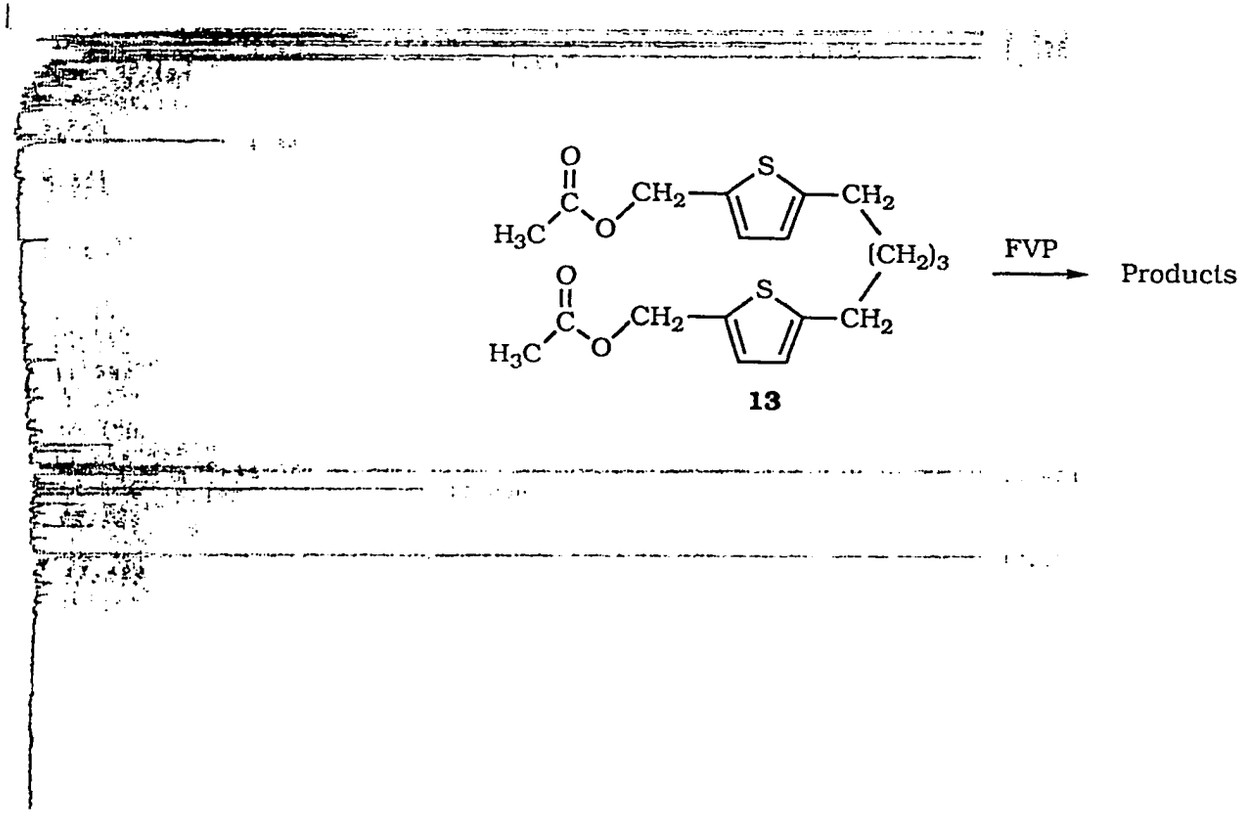


Figure A-9. IR spectrum of **27** (NaCl, thin film).



13

Figure A-10. GC trace of the crude products from FVP of **13**.

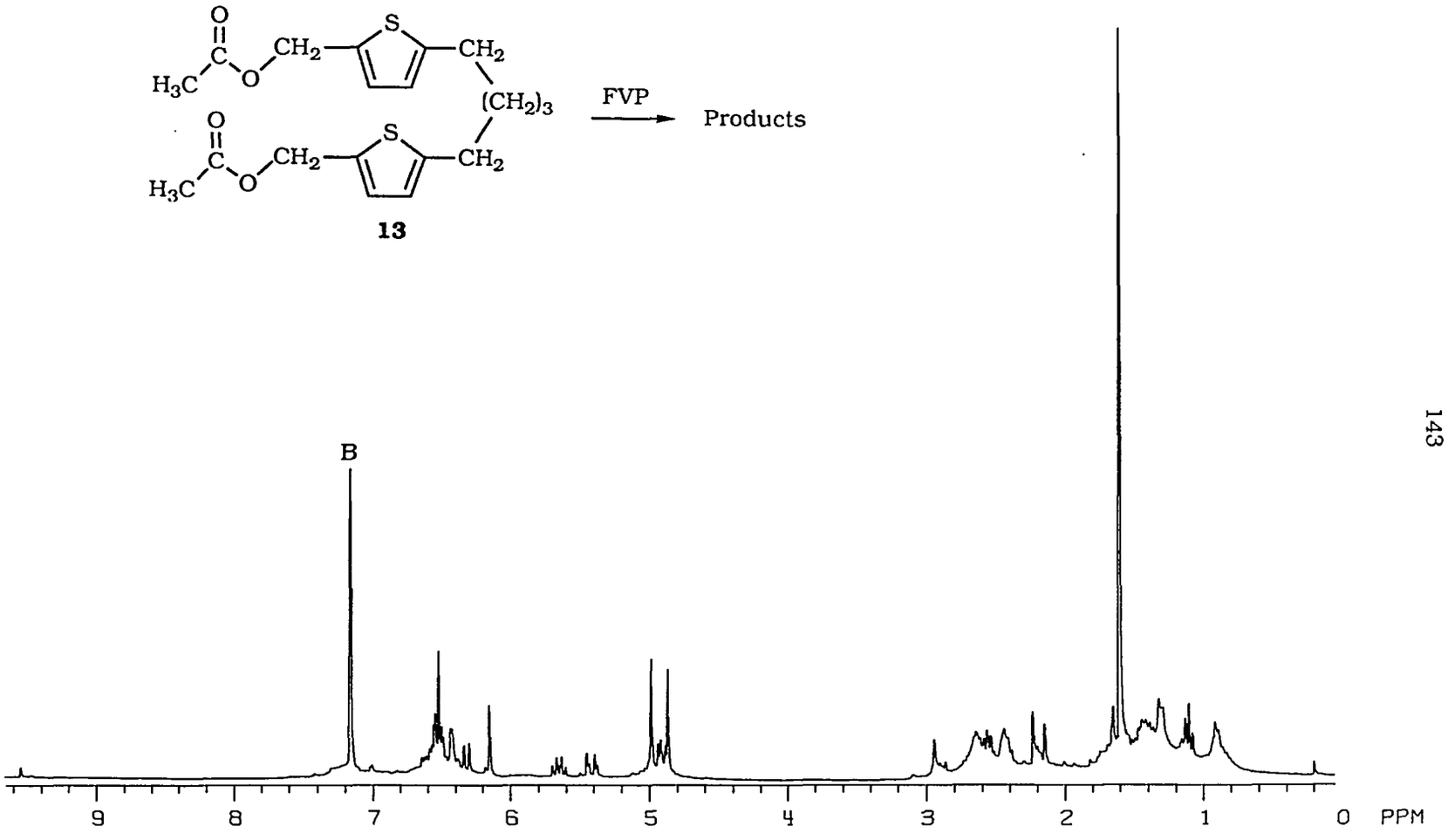
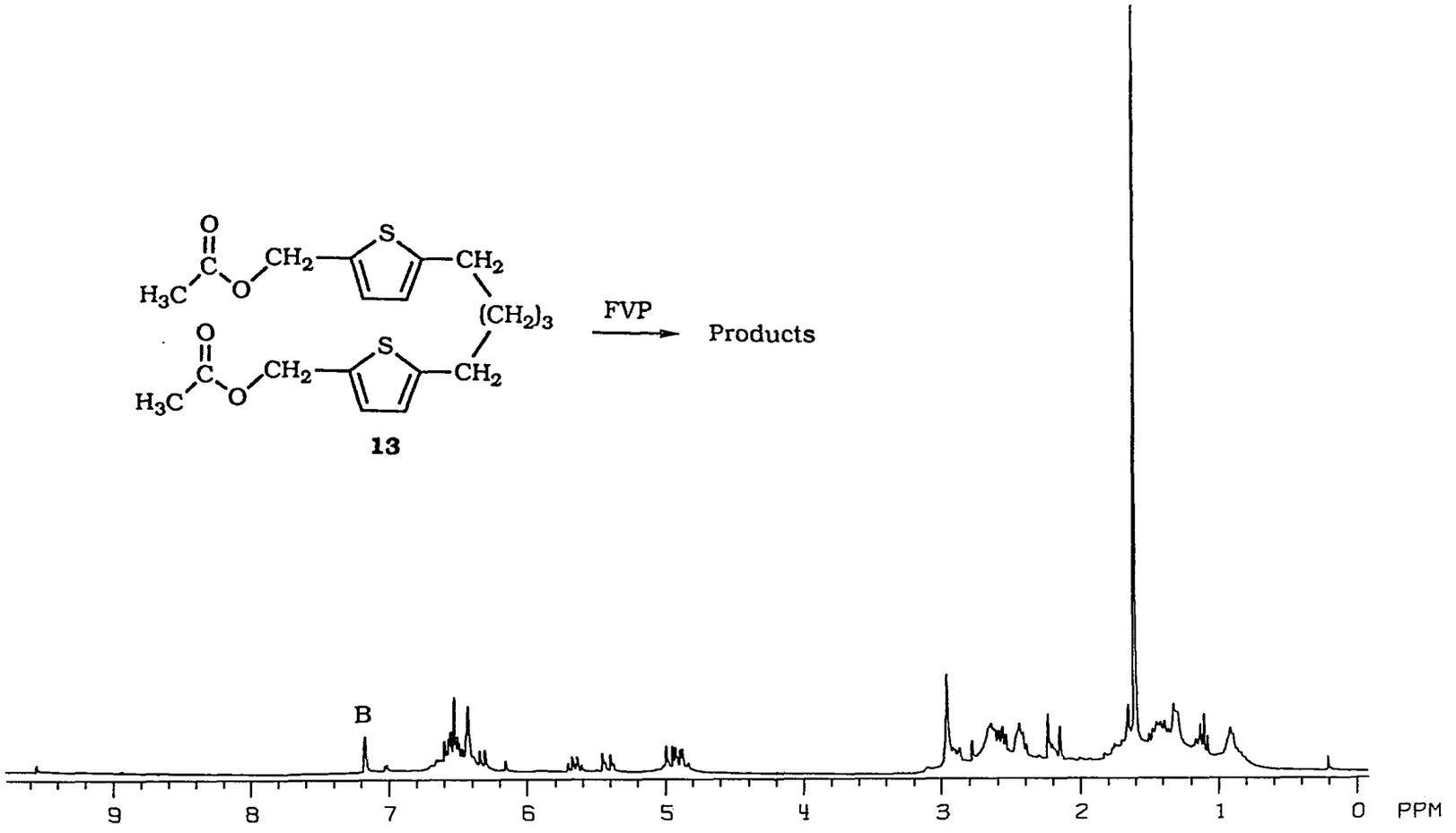


Figure A-11. ^{1}H NMR spectrum taken of the crude products from FVP of **13** (C_6D_6, 300 MHz); spectrum taken within 30 minutes of completion of the FVP experiment.



13

Figure A-12. ^{1}H NMR spectrum taken of the crude products from FVP of **13** (C_6D_6, 300 MHz); spectrum taken 24 hours after of completion of the FVP experiment.

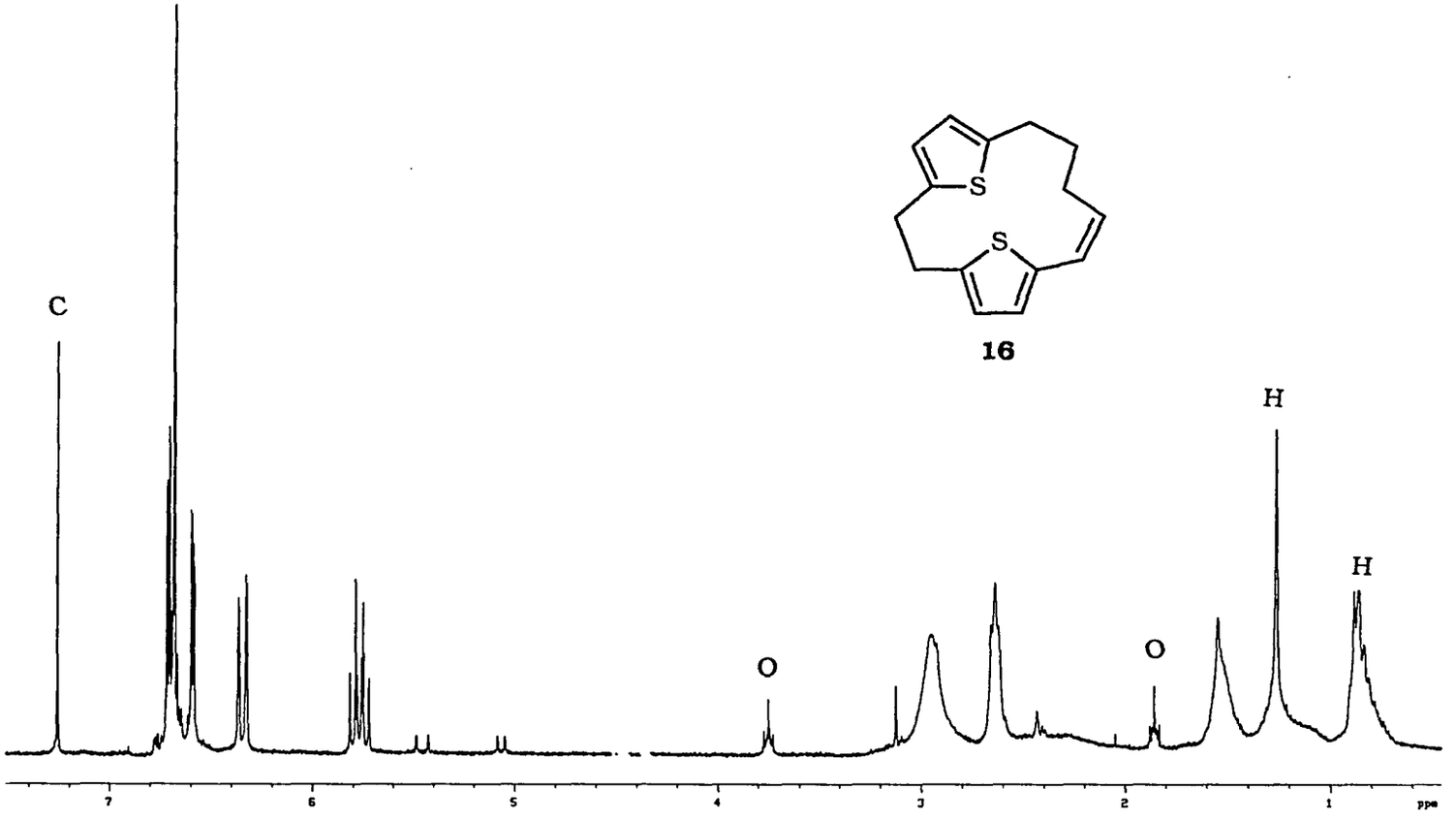


Figure A-13. ^{1}H NMR spectrum of macrocycle **16** (22 °C, $CDCl_3$, 300 MHz).

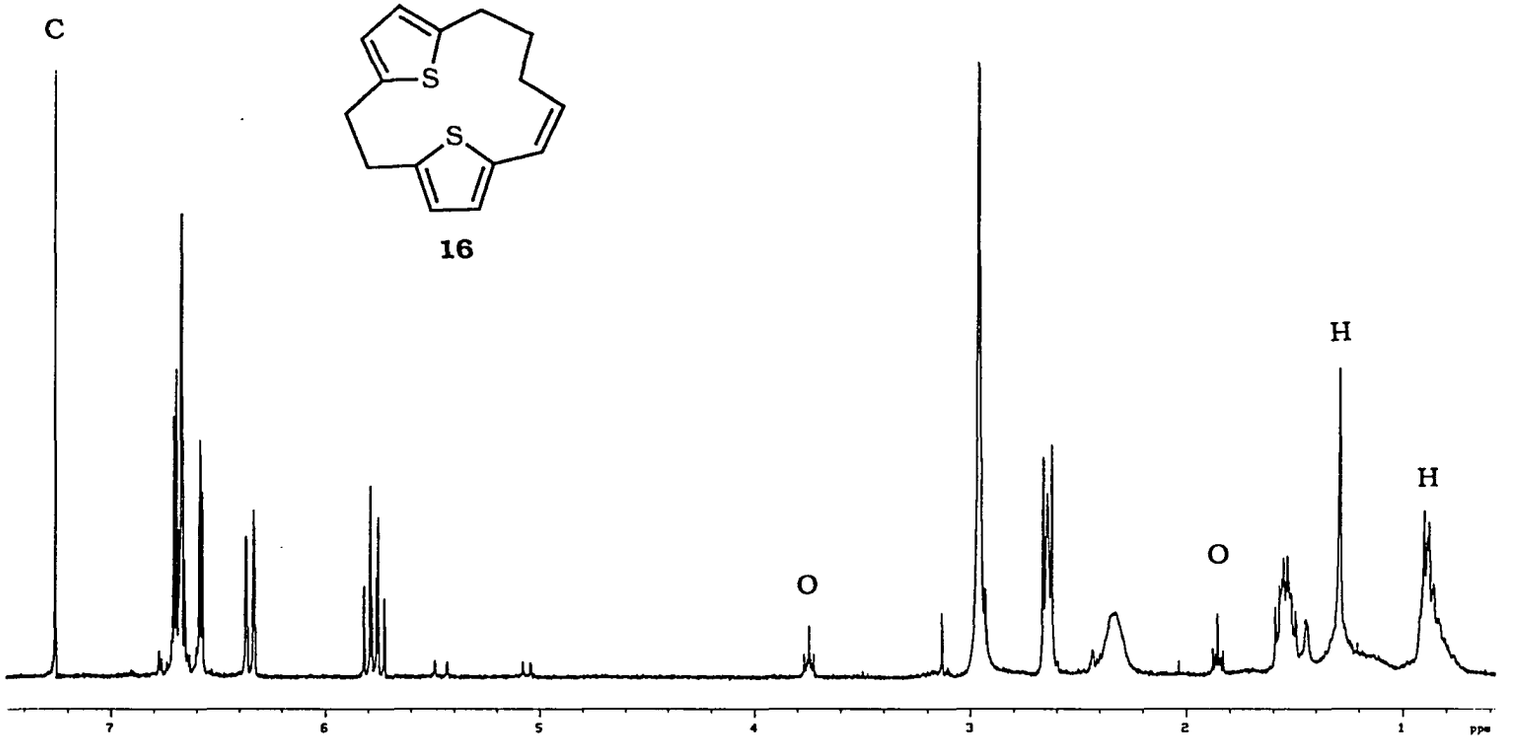


Figure A-14. ^{1}H NMR spectrum of compound **16** (60 °C, $CDCl_3$, 300 MHz).

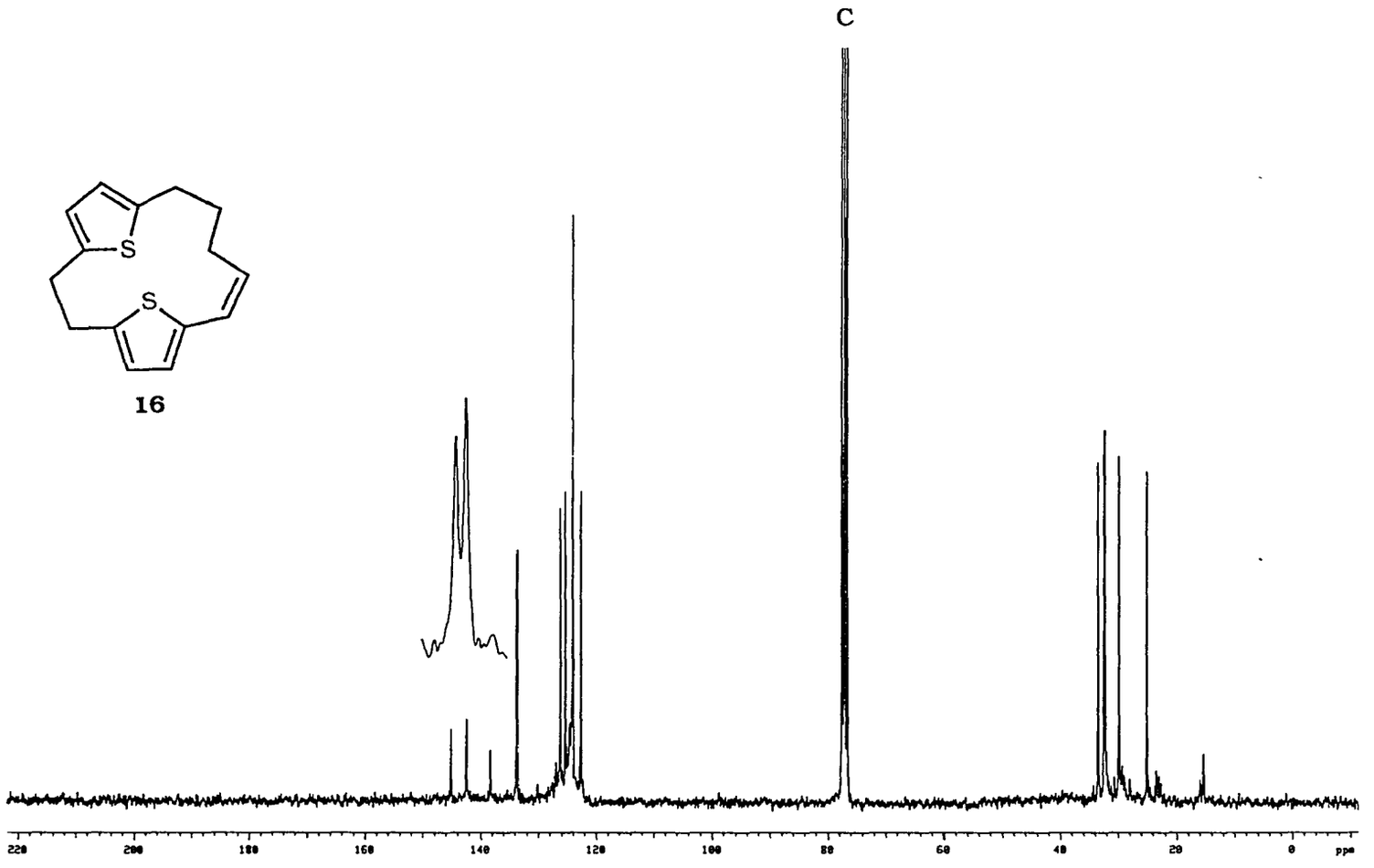


Figure A-15. ^{13}C NMR spectrum of compound **16** ($CDCl_3$, 300 MHz).

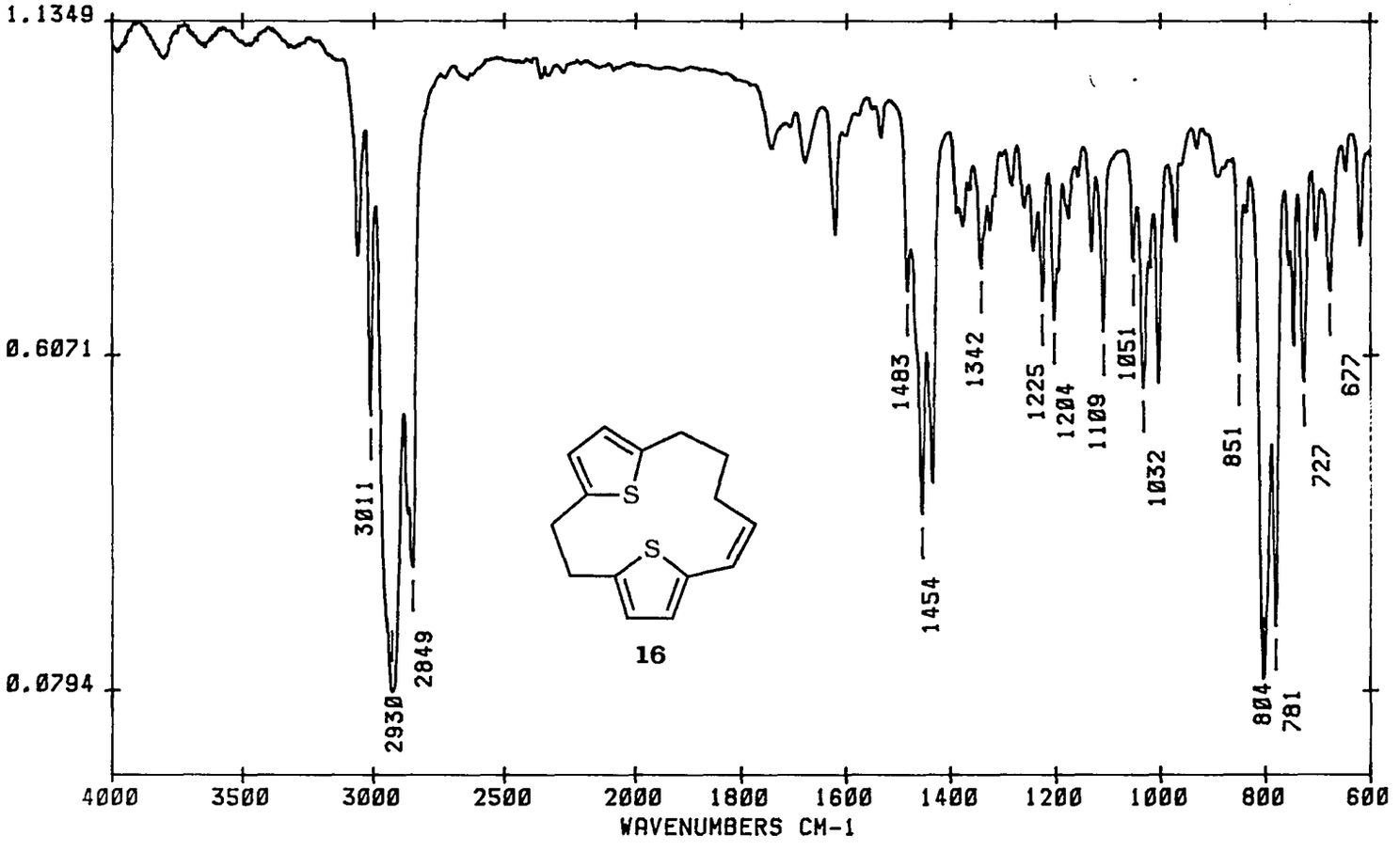


Figure A-16. IR spectrum of compound **16** (NaCl, thin film).

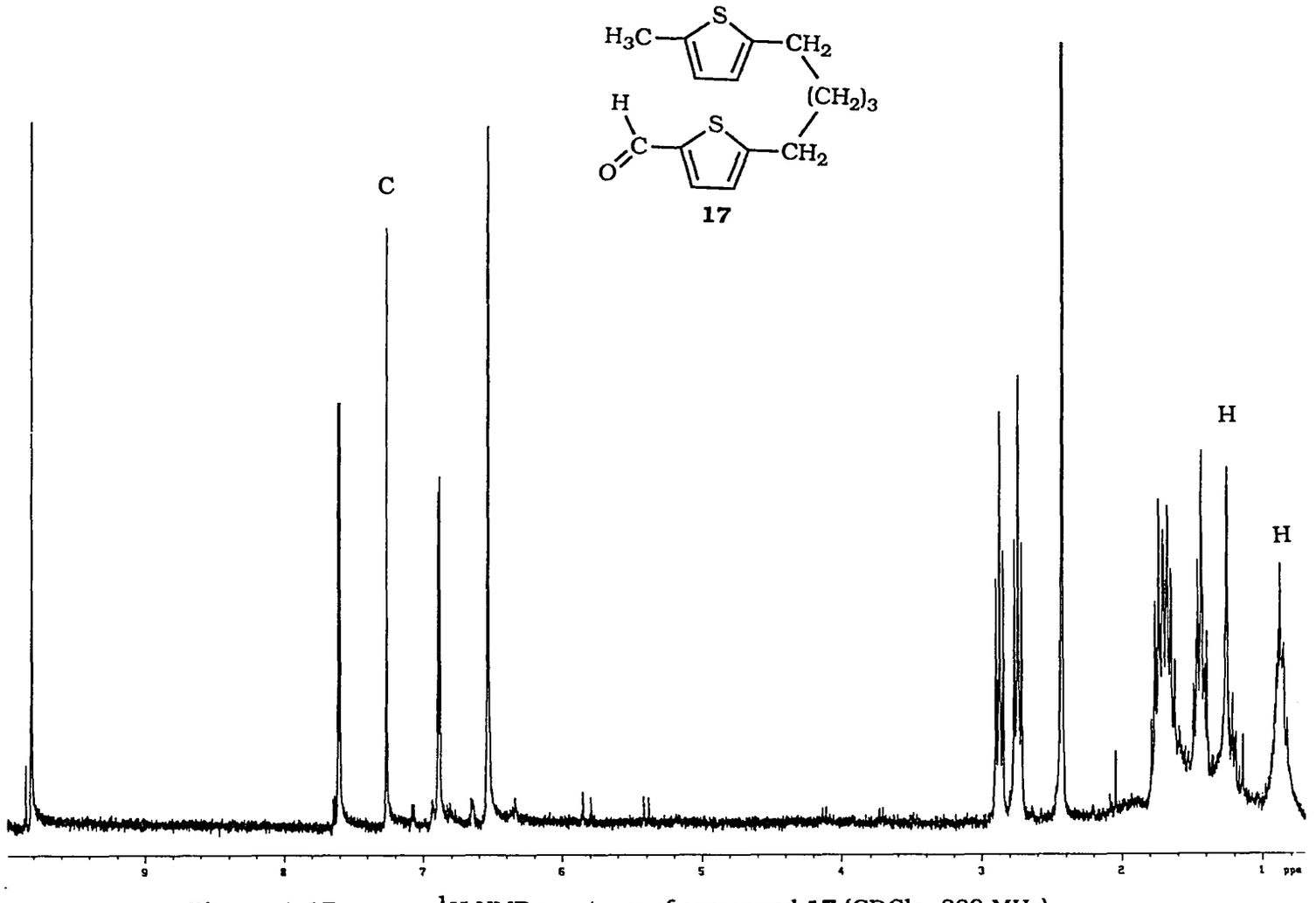


Figure A-17. ^{1}H NMR spectrum of compound **17** ($CDCl_3$, 300 MHz).

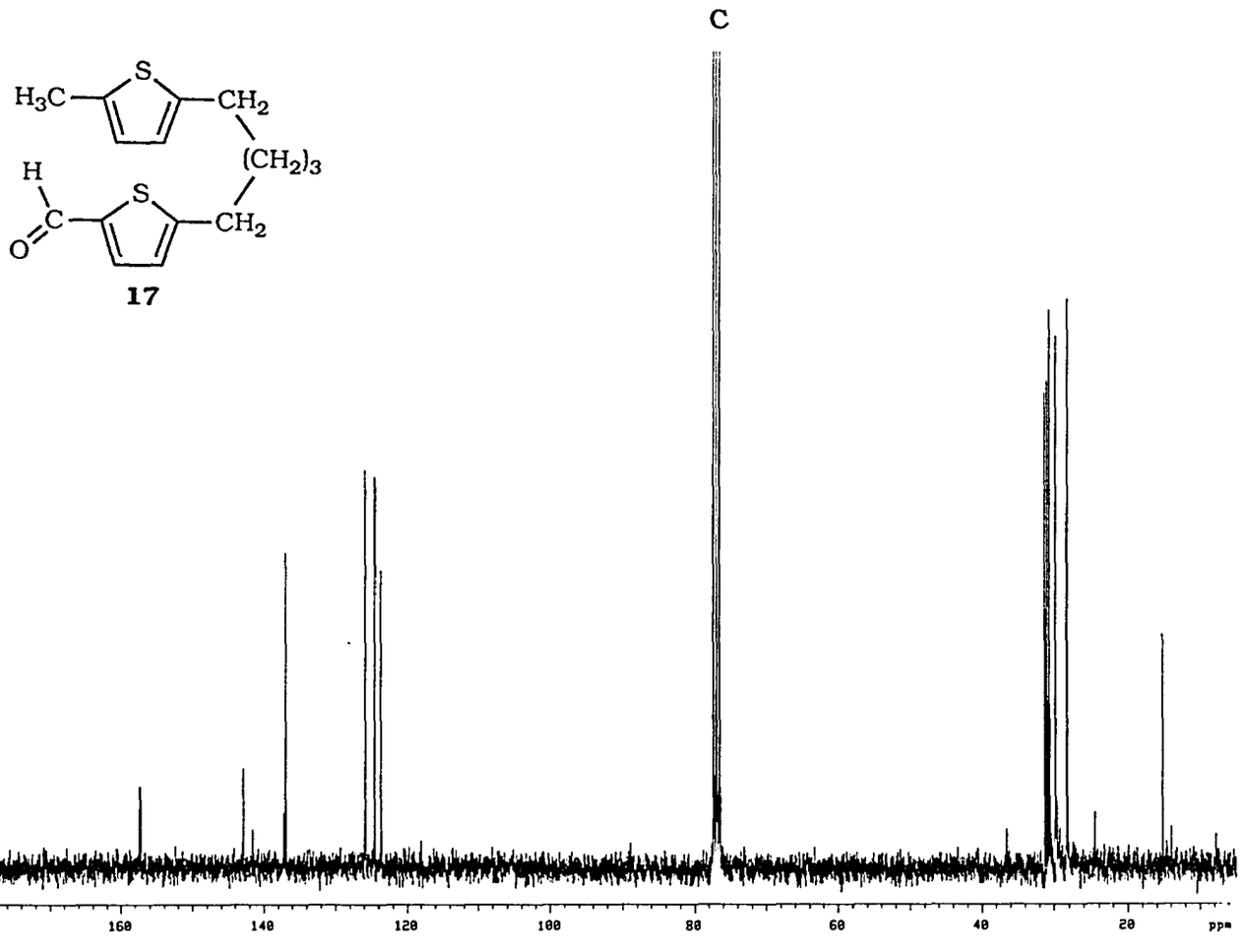


Figure A-18. Decoupled ^{13}C NMR spectrum of compound **17** ($CDCl_3$, 300 MHz).

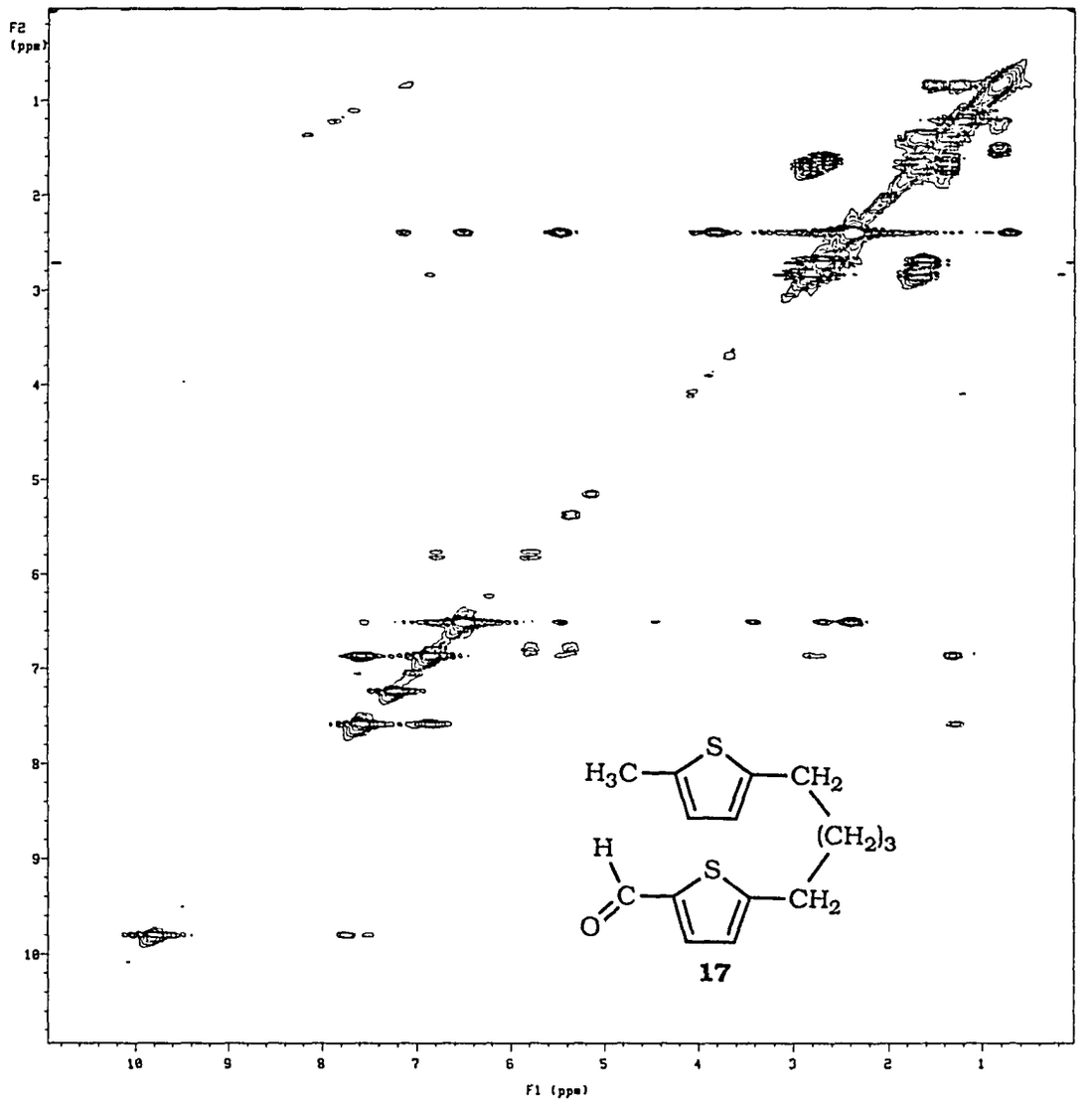


Figure A-19. ^{1}H NMR COSY spectrum of compound **17** ($CDCl_3$, 300 MHz).

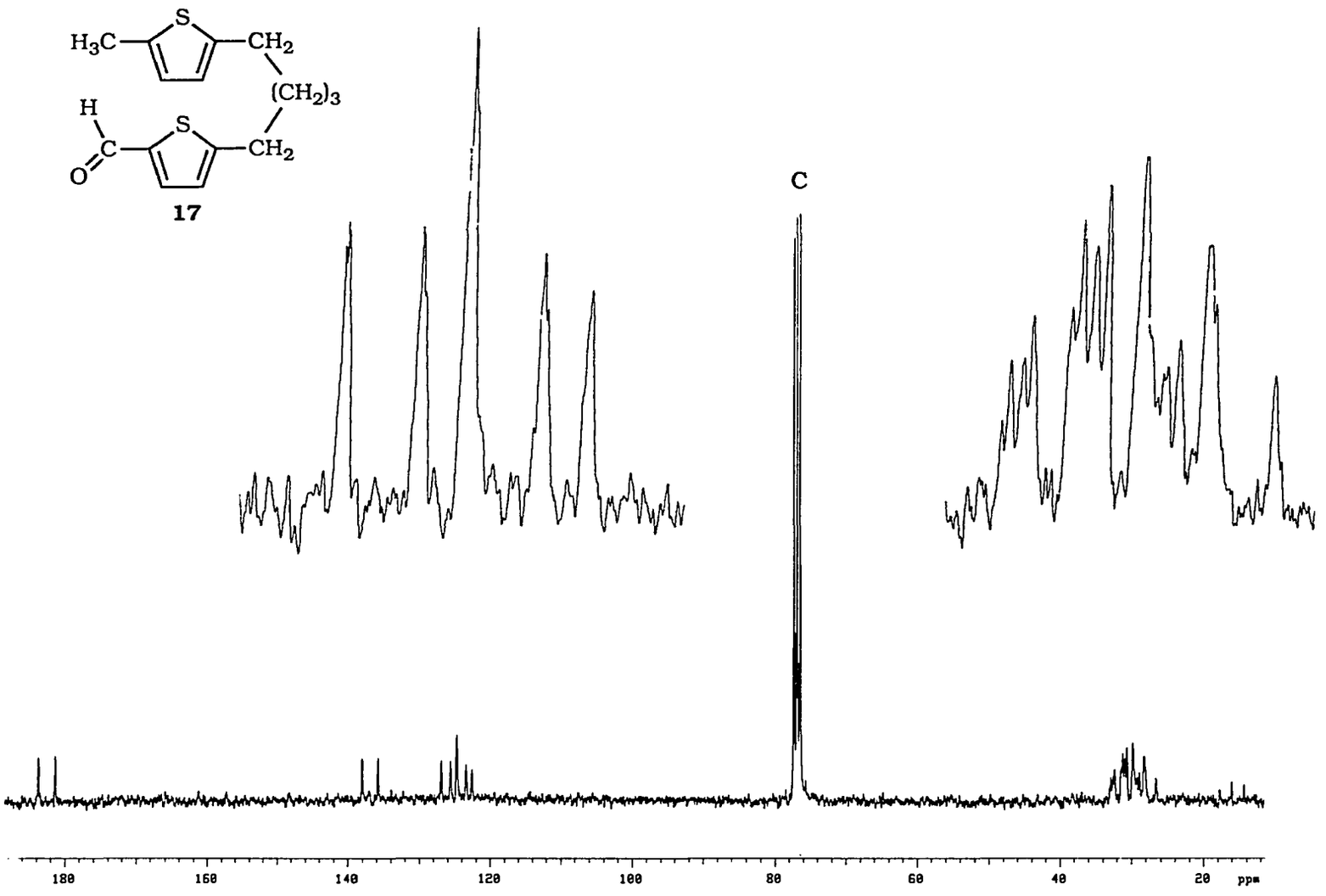


Figure A-20. ^{13}C NMR spectrum with ^{1}H-^{13}C coupling of compound **17** ($CDCl_3$, 300 MHz).

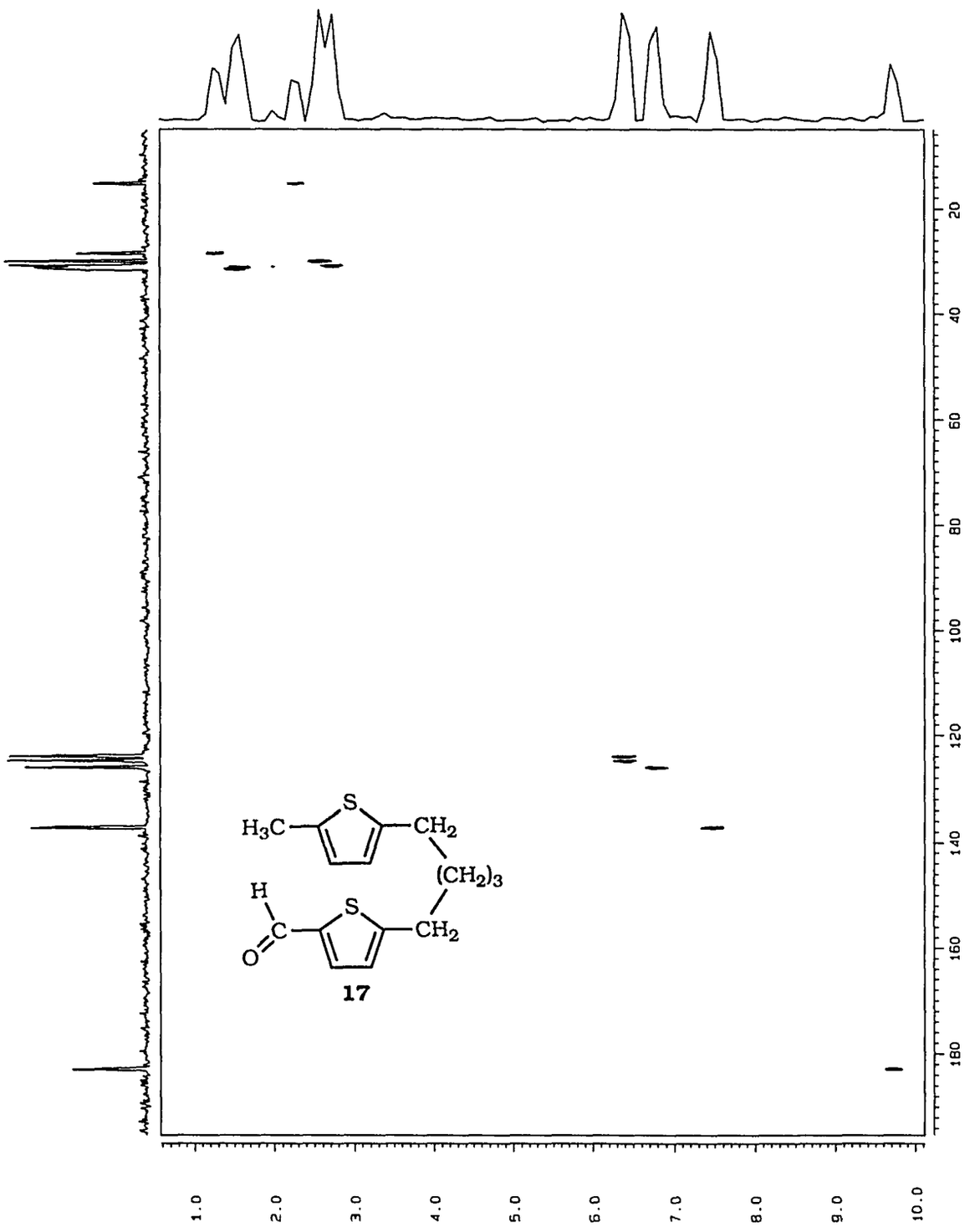


Figure A-21. HETCOR NMR spectrum of compound **17** ($CDCl_3$, 300 MHz).

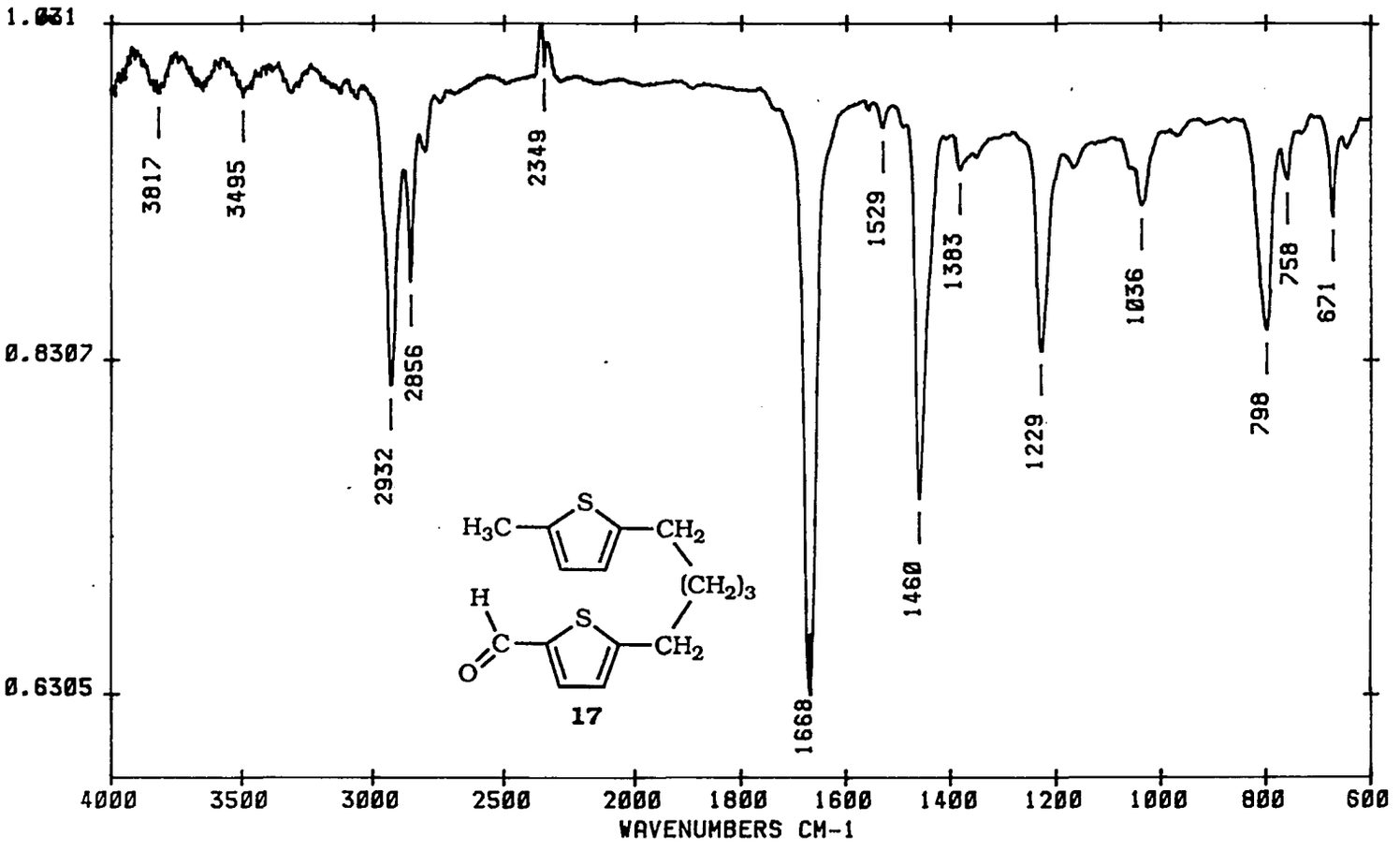


Figure A-22. IR spectrum of compound **17** ($CDCl_3$, 300 MHz).

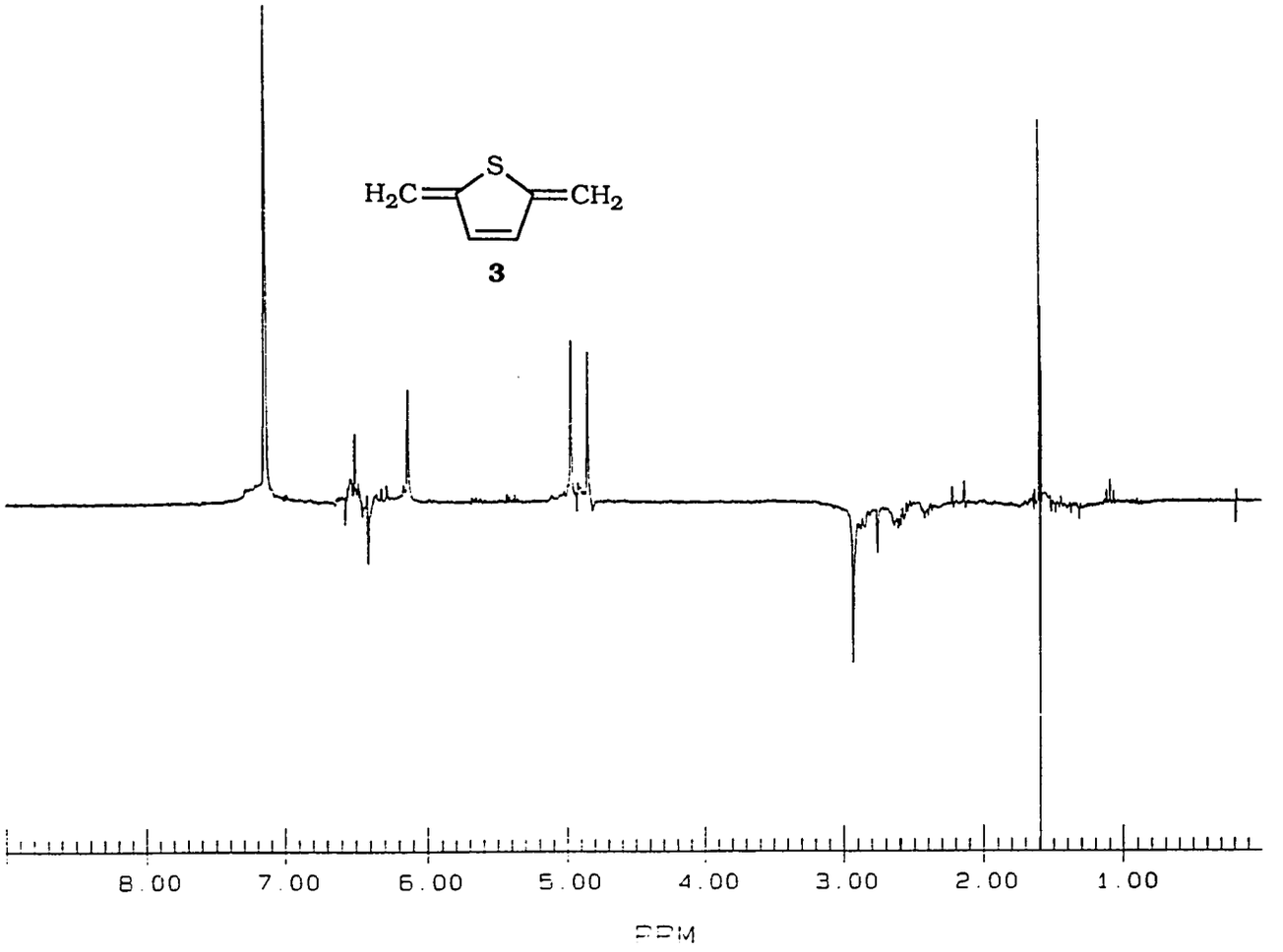


Figure A-23. Subtracted ^{1}H NMR spectrum of crude FVP products from **13** (C_6D_6, 300 MHz); spectrum obtained from Figures A-11 and A-12 by computer subtraction; ^{1}H NMR spectrum of **3**.

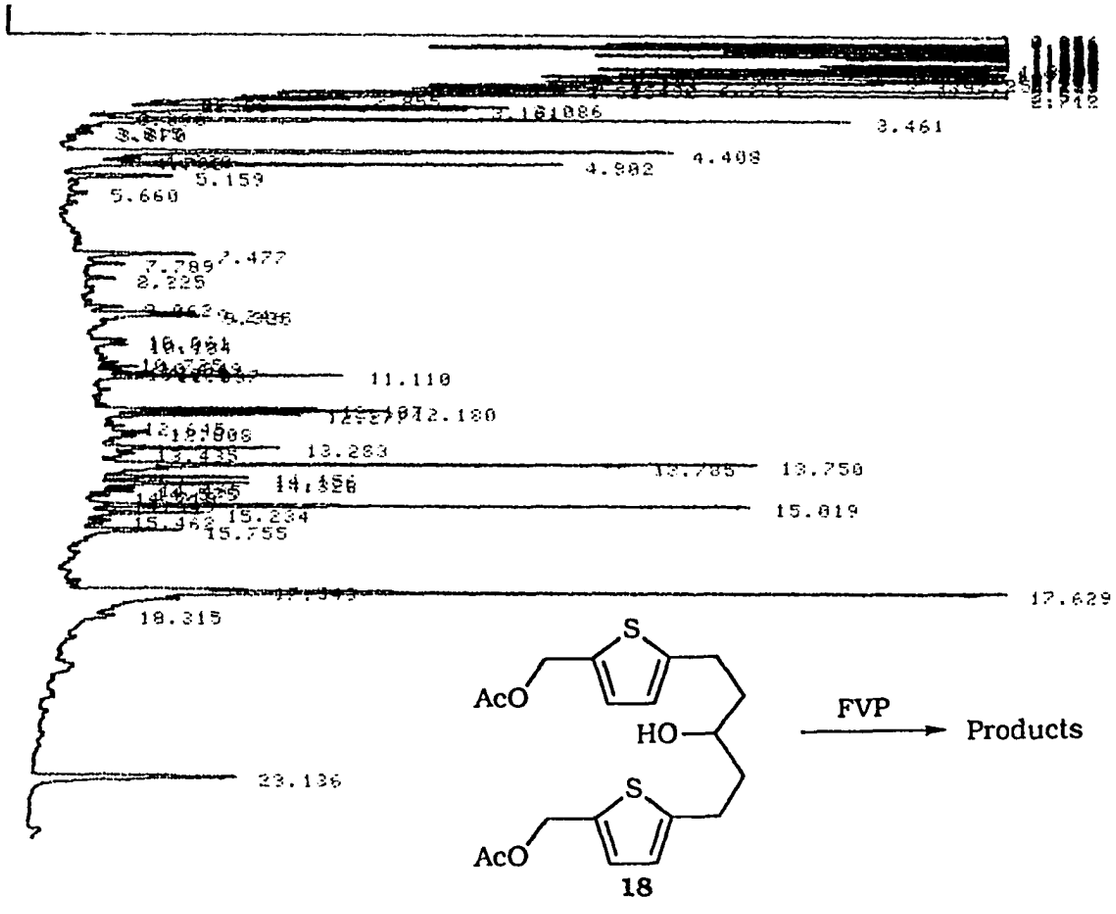


Figure A-24. GC trace of crude products from FVP of compound **18.**

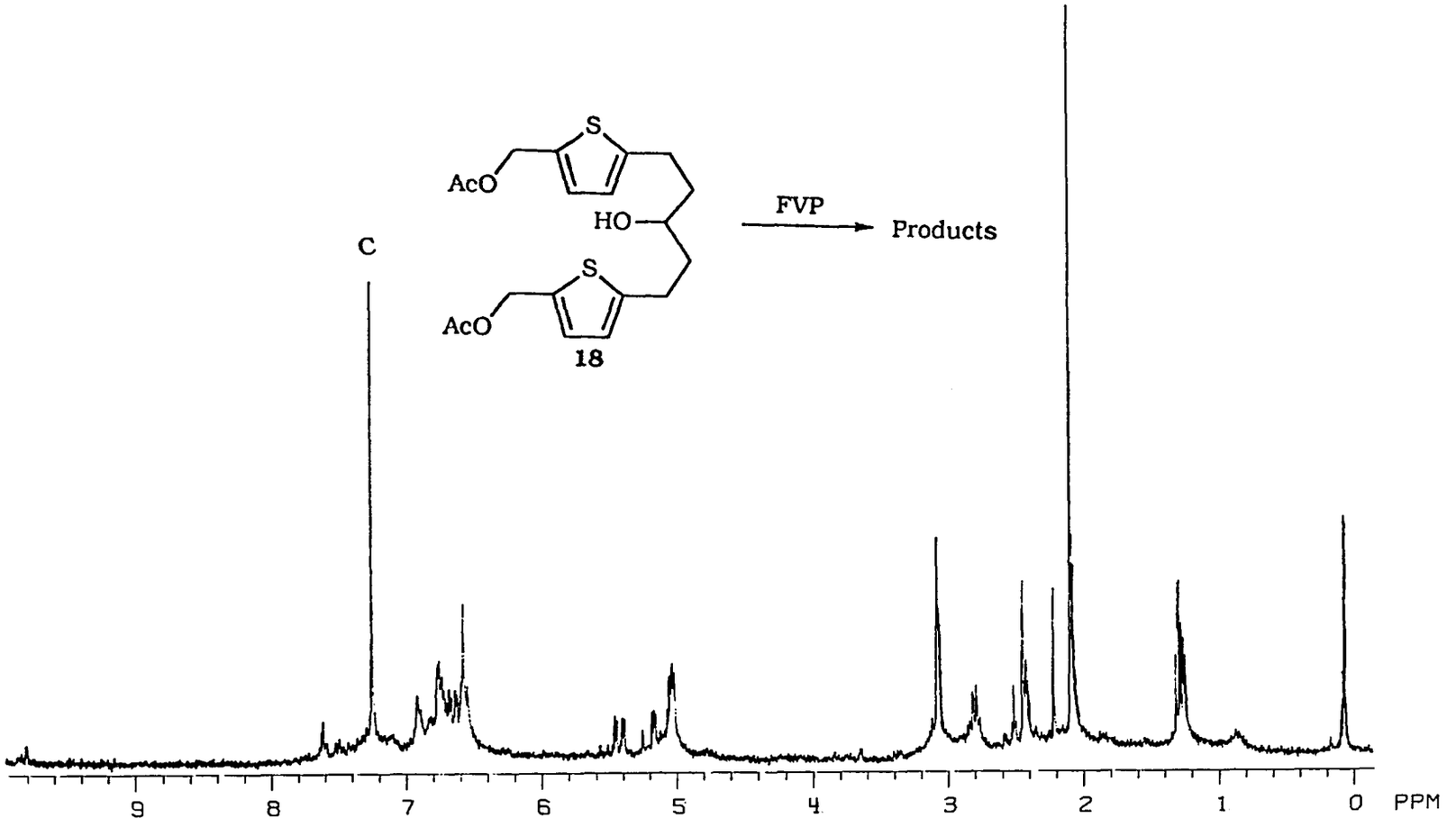


Figure A-25. ^1H NMR spectrum of the crude products from FVP of **18** ($CDCl_3$, 300 MHz).

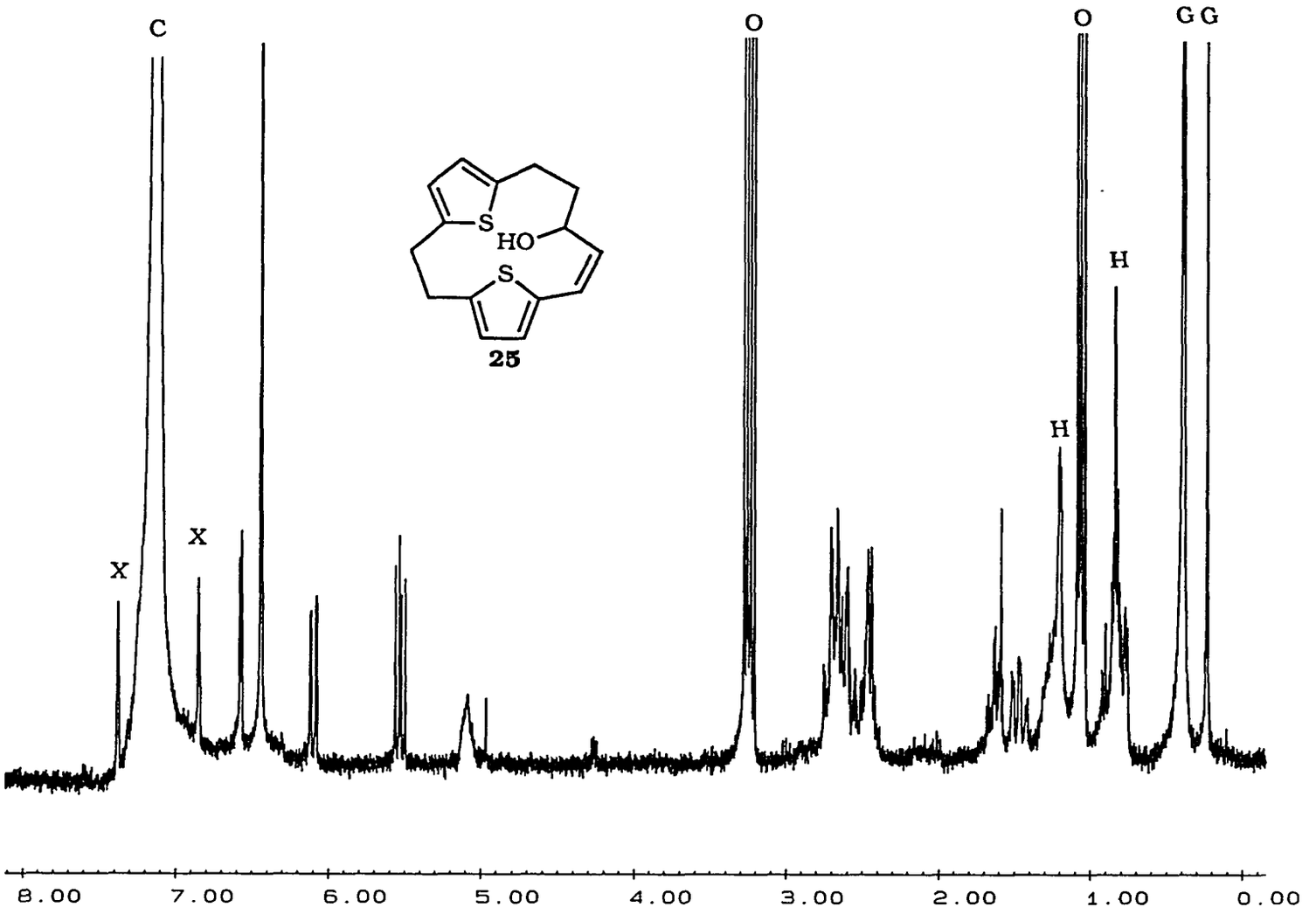
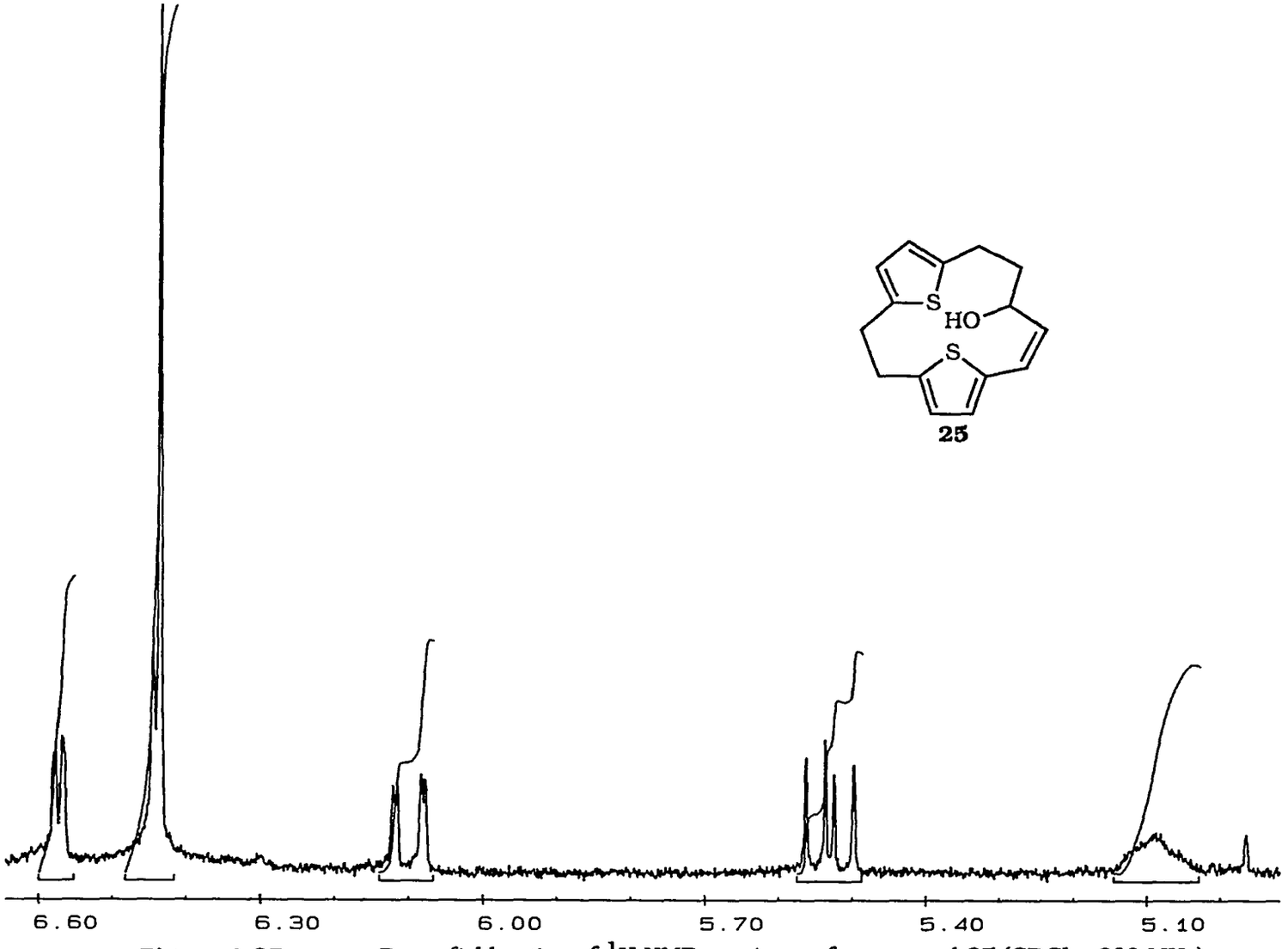


Figure A-26. ^{1}H NMR spectrum of macrocycle **25** ($CDCl_3$, 300 MHz).



25

Figure A-27. Down field region of ^{1}H NMR spectrum of compound **25** ($CDCl_3$, 300 MHz).

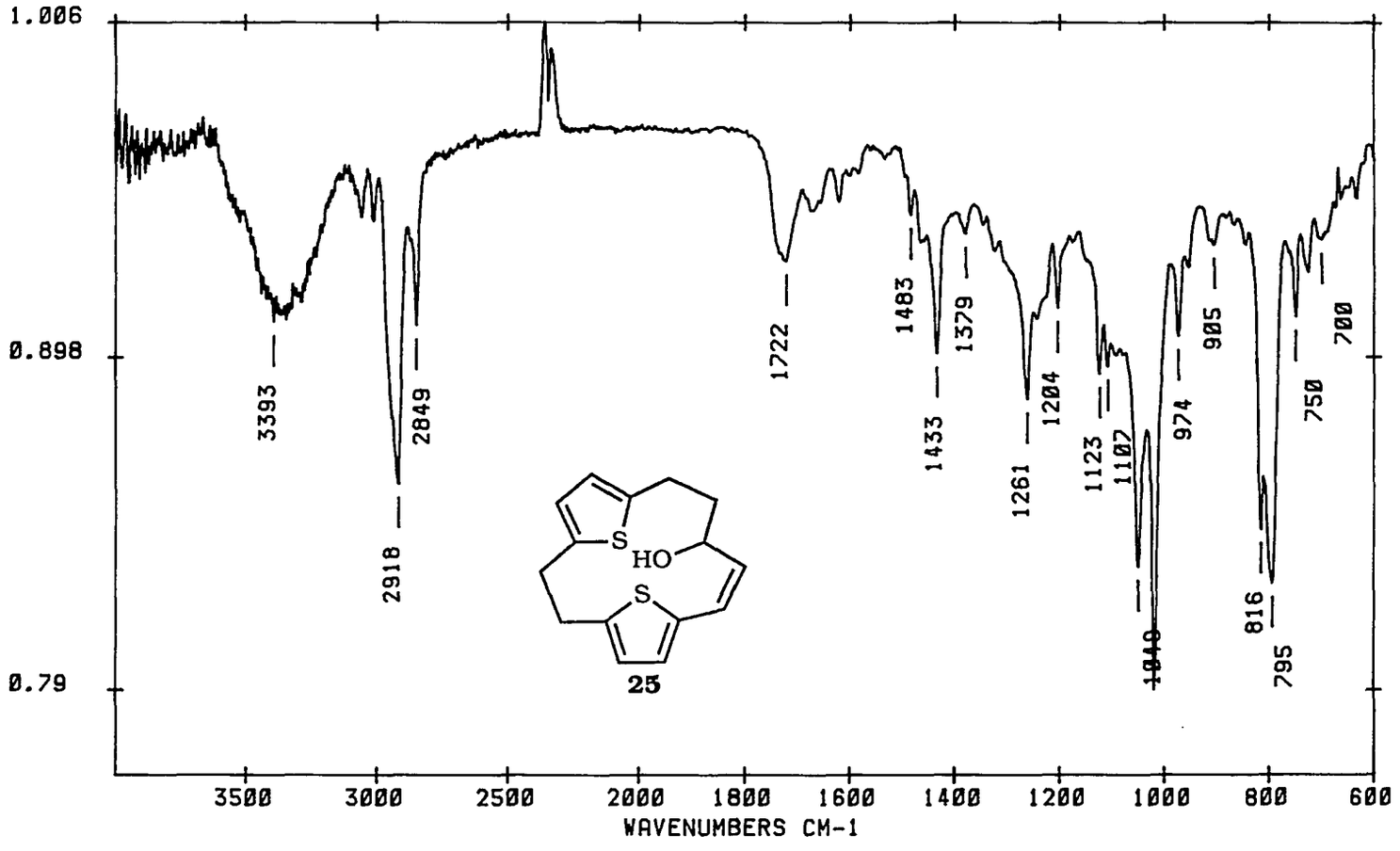


Figure A-28. IR spectrum of macrocycle **25** (NaCl, thin film).

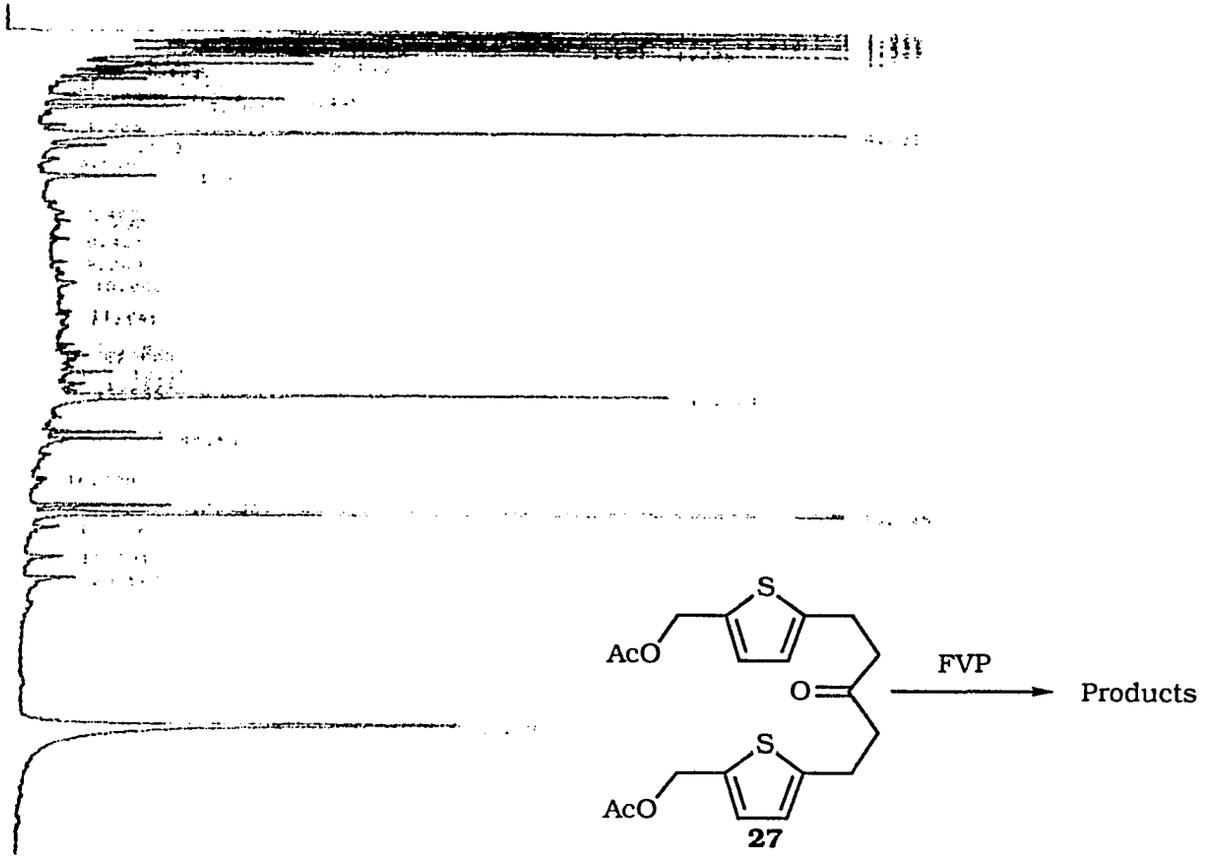


Figure A-29. GC trace of crude products from FVP of compound **27**.

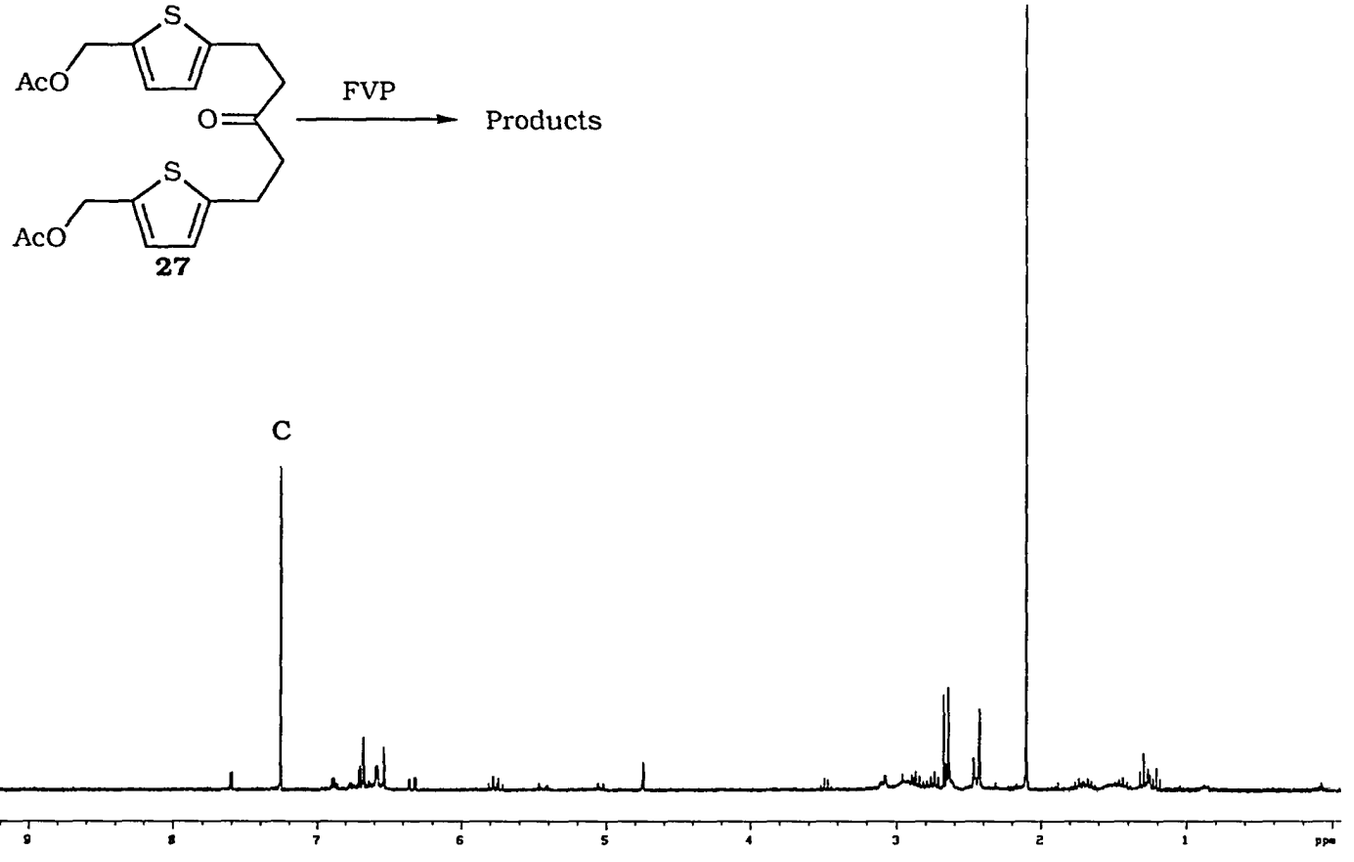


Figure A-30. ^{1}H NMR spectrum of crude products from FVP of **27** ($CDCl_3$, 300 MHz).

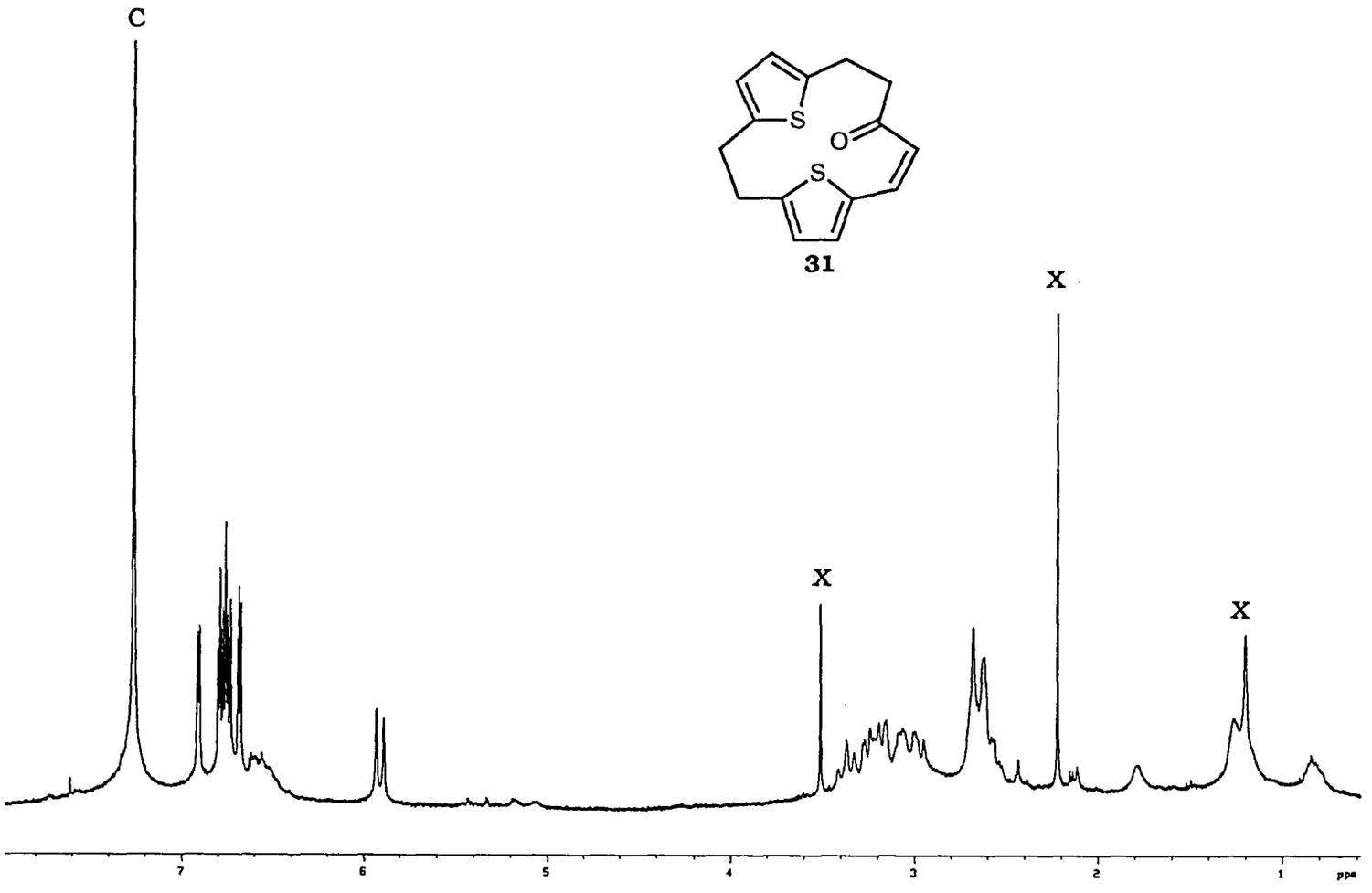


Figure A-31. ^{1}H NMR spectrum of macrocycle **31** (-50 °C, $CDCl_3$, 300 MHz).

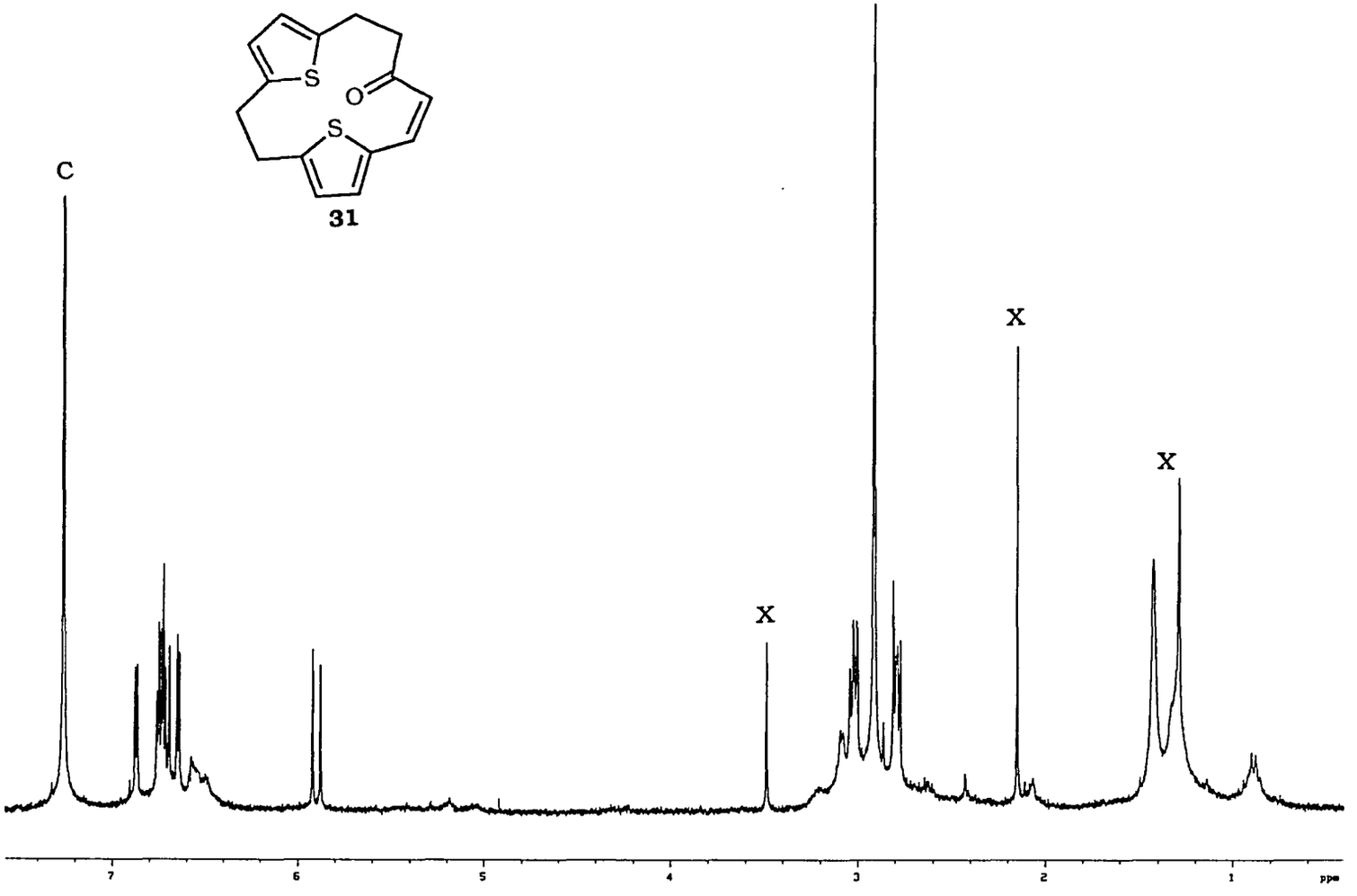


Figure A-32. ^{1}H NMR spectrum of macrocycle **31** (60 °C, $CDCl_3$, 300 MHz).

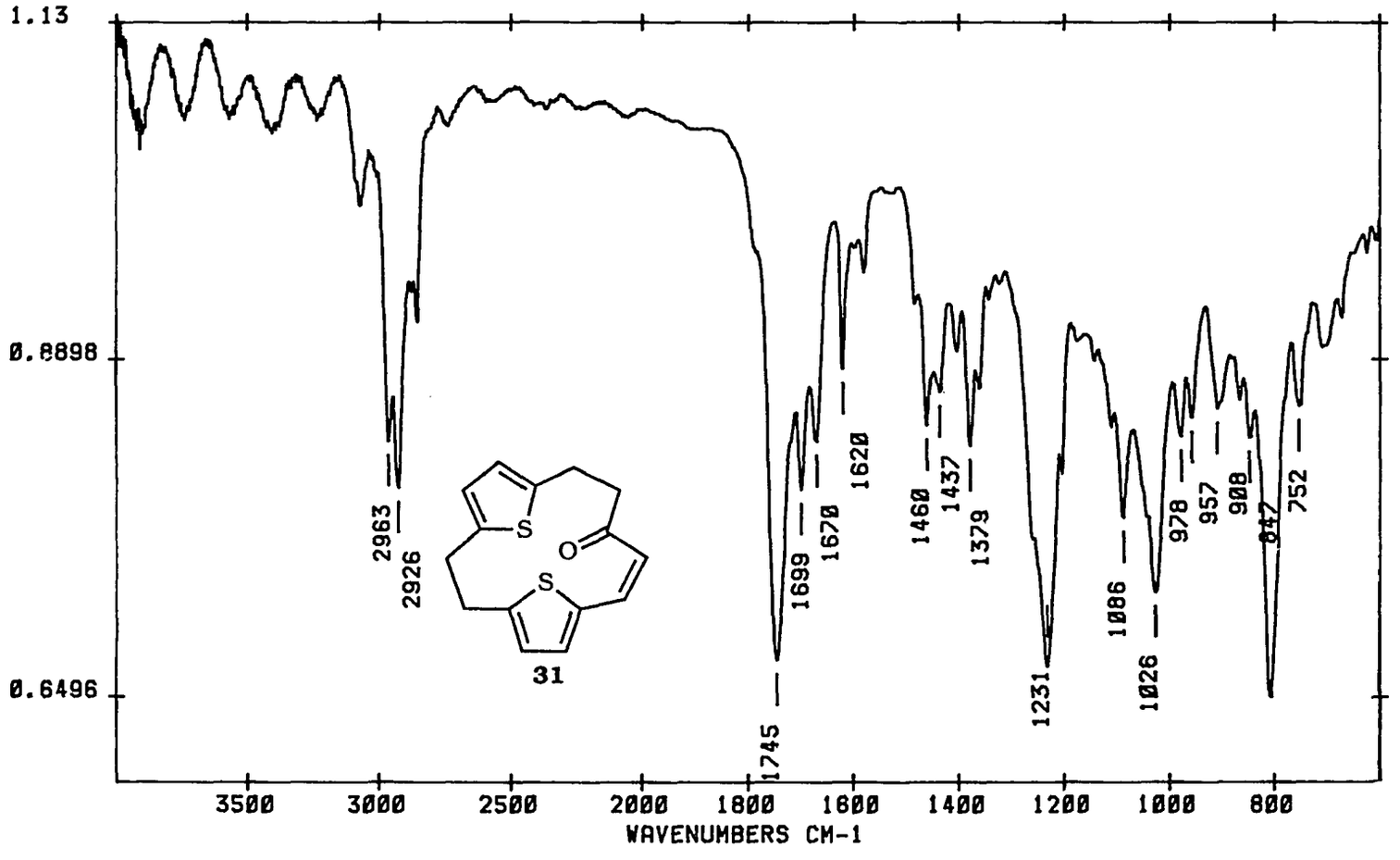


Figure A-33. IR spectrum of compound **31** (NaCl, thin film).

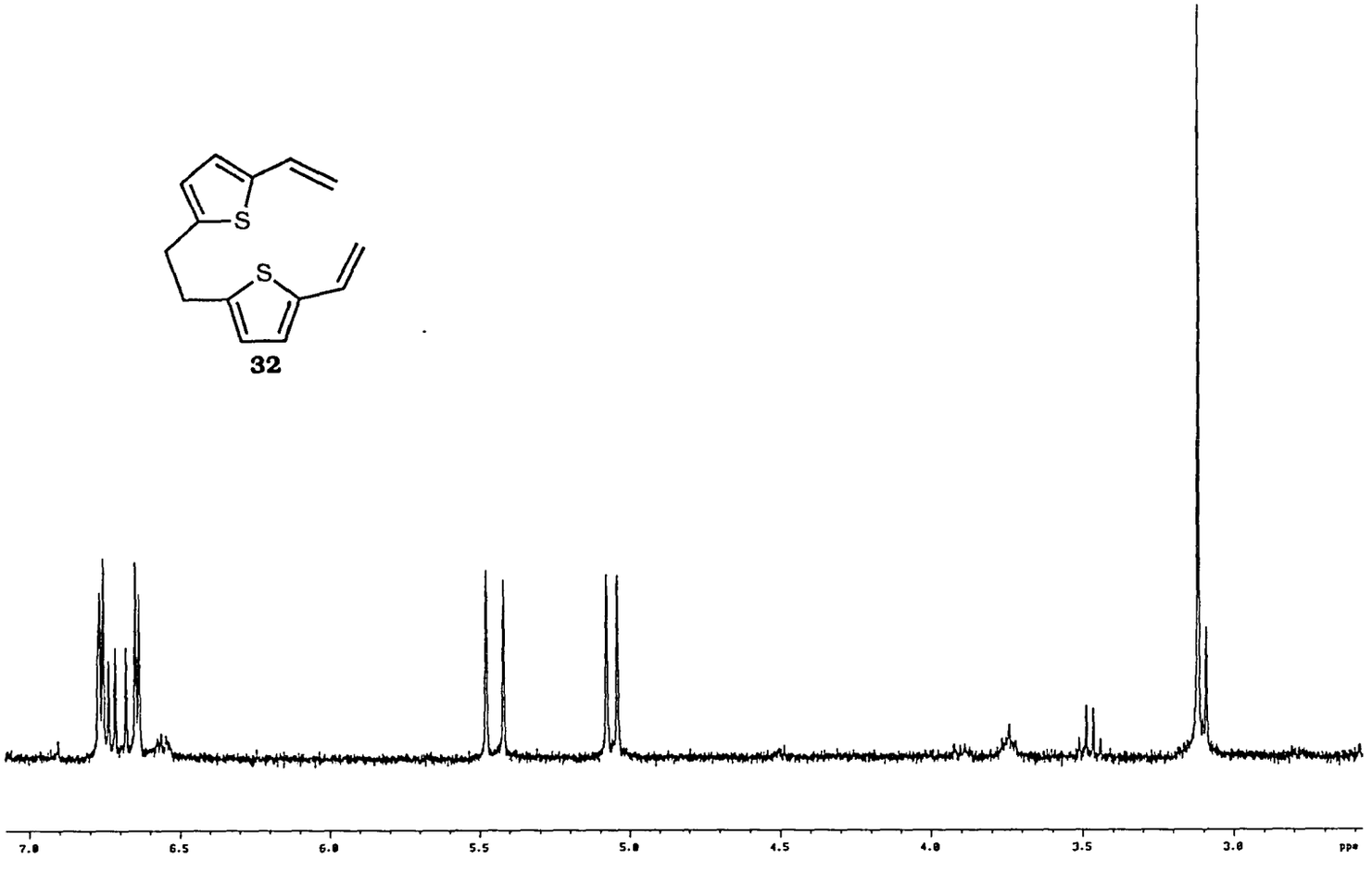


Figure A-34. ^{1}H NMR spectrum of compound **32** ($CDCl_3$, 300 MHz).

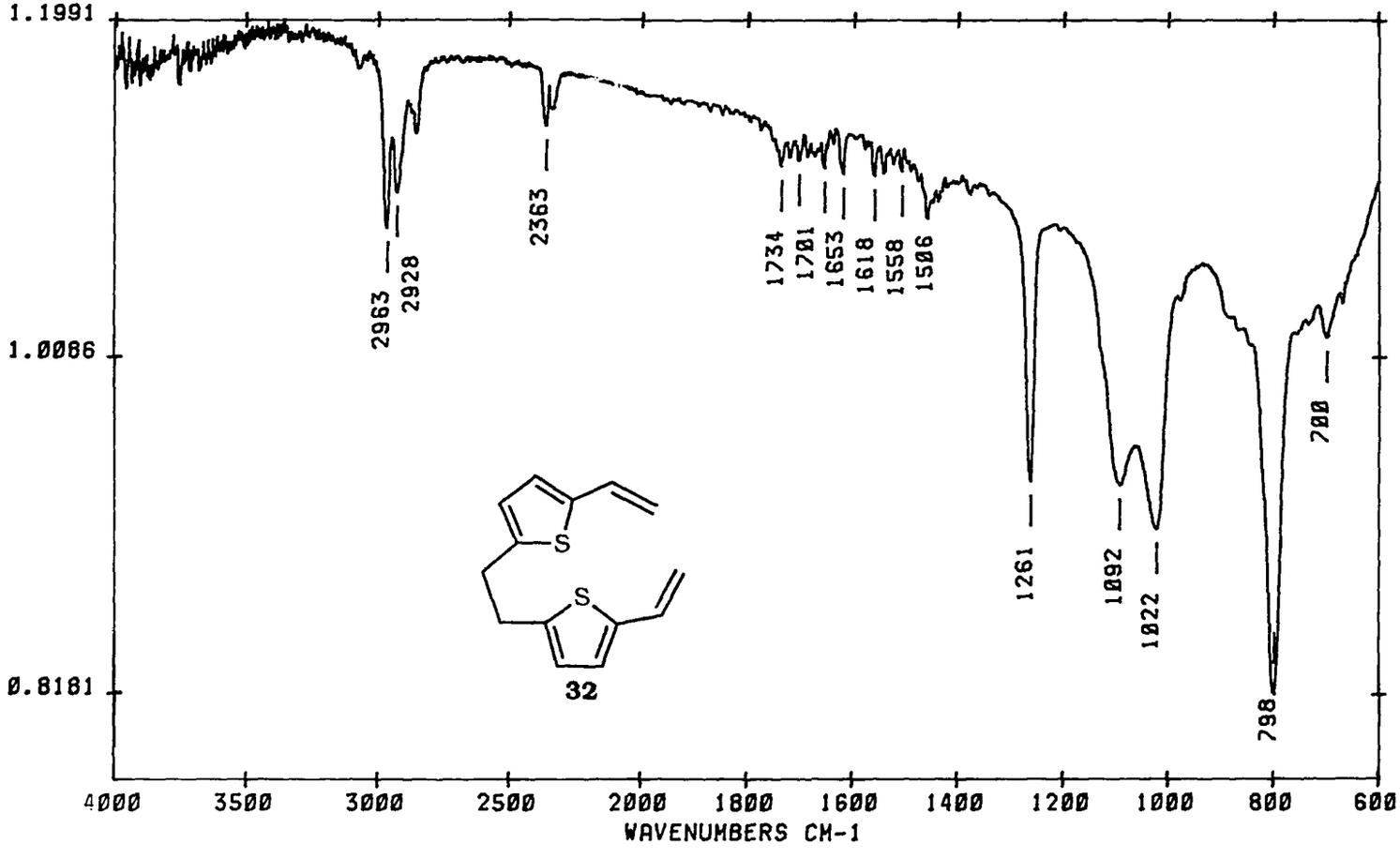
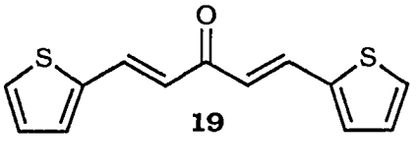


Figure A-35. IR spectrum of compound **29** (NaCl, thin film).



19

λ_{max}, CH_3OH = 370 nm
Et_2O = 360 nm
Hexane = 358 nm

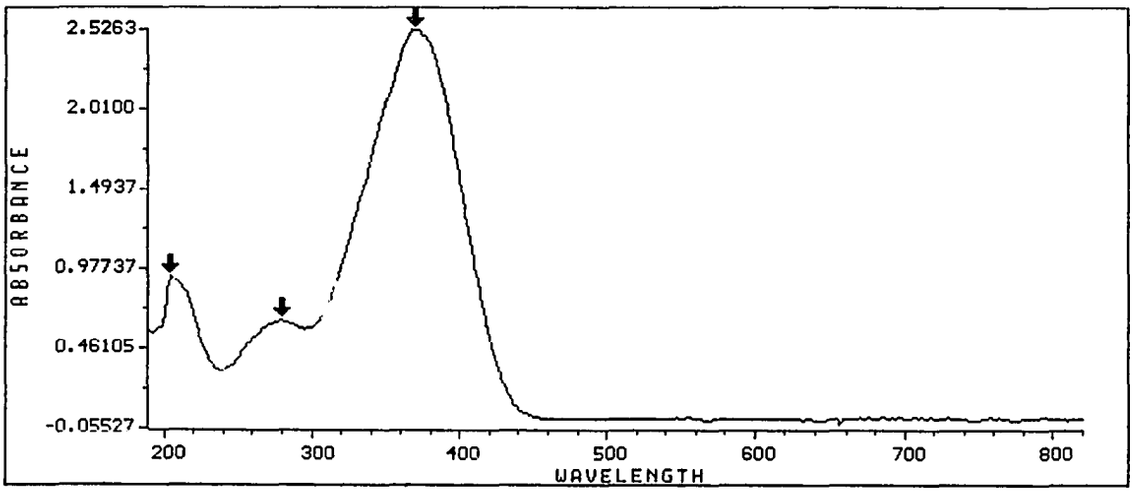


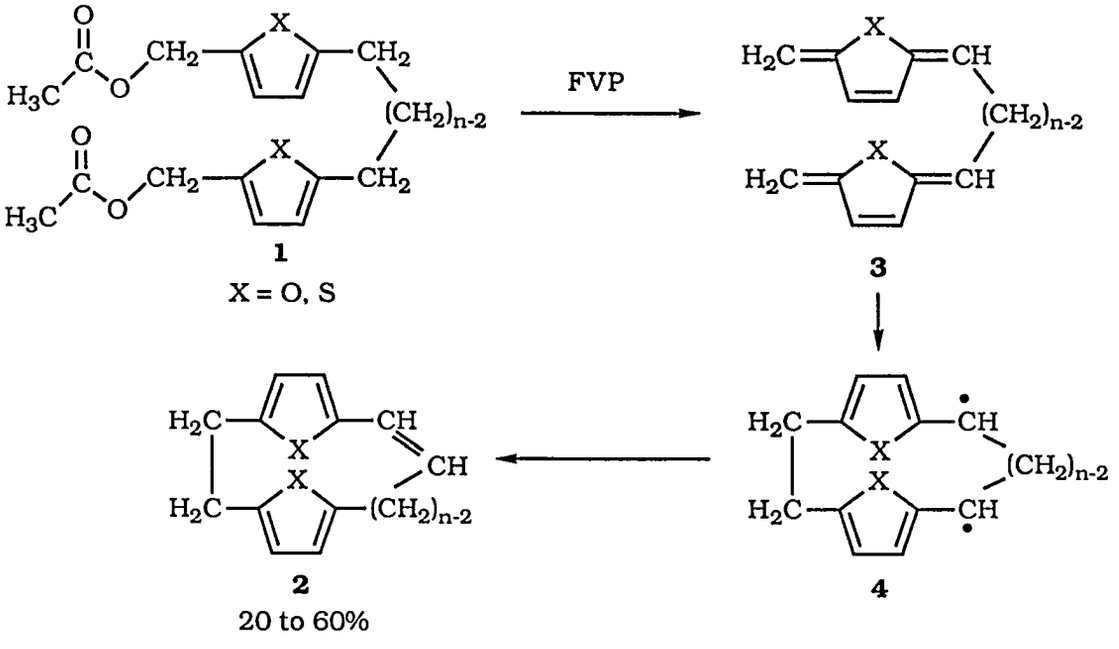
Figure A-36. UV-Vis spectrum of **19** in CH_3OH.

PAPER 3. THE SYNTHETIC MANIPULATION OF FUNCTIONALIZED MACROCYCLES PRODUCED BY THE INTRAMOLECULAR CYCLIZATION OF BIS-2,5-DIMETHYLENE-2,5-DIHYDROTHIOPHENES; SYNTHESIS OF *dl*-MUSCONE

INTRODUCTION

The synthesis of macrocycles and cyclophanes has been an active area of research for many years.[1] These classes of compounds have important application in host-guest chemistry, natural products synthesis, and other areas.[2] We have recently described a new route to functionalized macrocycles by the intramolecular cyclization of a two *p*-quinodimethanes linked by a bridging chain (Scheme I).[3] Flash vacuum pyrolysis (FVP) of compounds of general structure **1** provide macrocycles

Scheme I



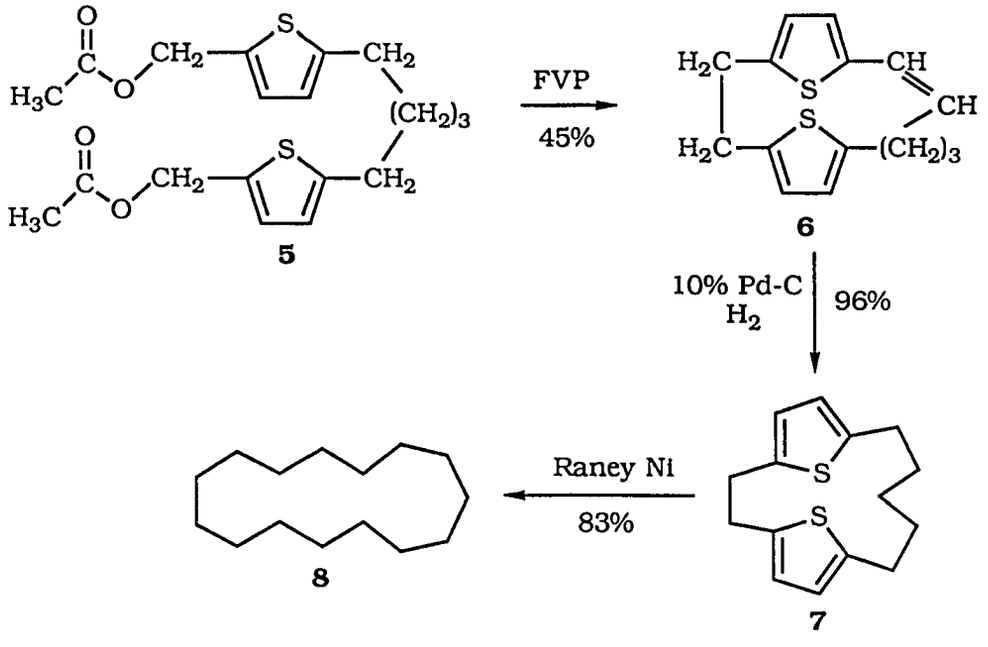
(**2**) in fair yields. These products are consistant with the initial formation of intermediate **3**, which consists of two furan-based or two thiophene-based *p*-quinodimethanes linked by a bridging chain. An intramolecular cyclization of **3** would result in the formation of the cyclic diradical **4**, and an intramolecular radical disproportionation would give the macrocyclic products (**2**). Macrocycles have been

produced which contain rings from 15 to 22 carbons.[3a] Furthermore, we found that the bridging chain in **1** may be substituted with either a ketone or hydroxy group to give more highly functionalized macrocyclic products.[3b] In this chapter, results are presented from the synthetic manipulation of the functionalized macrocycles **2**, including the synthesis of [5,2](2,5)thienophane, cyclopentadecane, 1-Methyl-3-oxo-[5,2](2,5)thienophane, and *dl*-muscone.

RESULTS

We have reported that FVP of compound **5** gave cis-1,2-dehydro[5,2](2,5)thienophane (**6**) in 45% yield (Scheme 2).[3b] When hydrogenated[4] with 10% Pd-C, the previously unknown cyclophane **7** was produced in good yield. Reductive desulfurization of **7** with an excess of Raney nickel[5] produced cyclopentadecane (**8**) in 83% isolated yield.

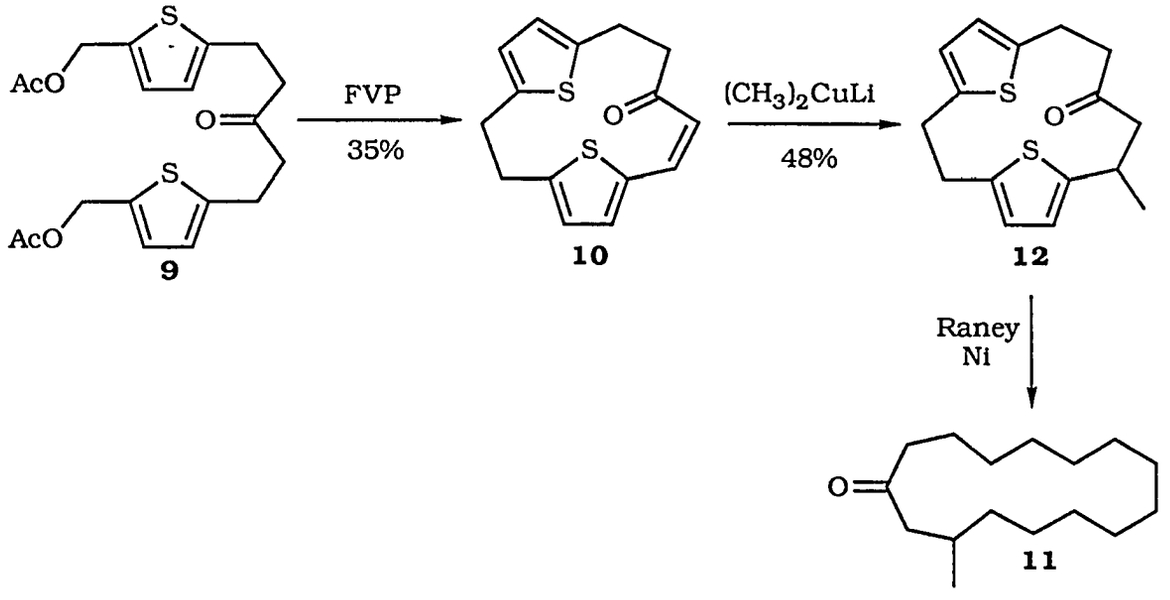
Scheme 2



We have also reported that FVP of the acyclic ketone **9** produced the macrocyclic enone **10** in 35% yield (Scheme 3).[3b] Realizing that compound **10** was just two synthetic steps from the racemate of the natural product muscone (**11**), we examined the chemistry of the enone **10**. Reaction of **10** with methyl cuprate[6] provided the methyl substituted product **12** in fair yield. Reductive desulfurization of the thiophene rings in **12** was attempted using an excess of Raney nickel. Although obtained in only small quantities, GCMS analysis indicated that *dl*-muscone (**11**) was the predominant

product from the reduction of **12**. Even in small quantities, product **11** was found to possess the characteristic strong musk odor. *dl*-Muscone has been the target of numerous synthetic efforts in recent years due to its potential as a fragrant component in perfume formulations.[5c, 7]

Scheme 3



In summary, we have produced macrocycles by FVP, and these macrocycles (**2**, **6**, and **10**) may be useful precursors to a variety of other cyclophanes and macrocycles. Although we have explored only a few of the potential conversions of macrocycles **2**, **6**, and **10**, this work demonstrates that these macrocycles may be converted to other cyclophanes and macrocyclic products.

EXPERIMENTAL

Methods and materials

Some general methods have been previously described.[3] For products **7**, **8**, and **12**, yield percentages represent calculated values from the weight of isolated, pure material. The 10% Pd-C and methyl lithium were purchased from Aldrich Chemical and used as recieved. The CuI was purchased from Aldrich Chemical and purified[6] prior to use. The Raney Ni was also purchased from Aldrich Chemical and washed immediately prior to use.[8]

[5,2](2,5)Thienophane (**7**). To a solution of cis-1,2-dehydro[5,2](2,5)thienophane (**6**)[3b] (7.5 mg, 0.029 mmol) in 10 mL of distilled absolute ethanol contained in a 25-mL flask, was added 5 mg of 10% Pd-C. The flask was then flushed thoroughly with H_2. The solution was stirred for 3 h at room temperature under slightly more than 1 atmosphere of H_2. GC analysis revealed that starting material **6** had been consumed and that a new product had been formed. Isolation of the product was accomplished by filtration of the product mixture through celite, extraction between hexane and brine, and drying with $MgSO_4$. Concentration of the organic phase gave the product identified as **7** (7.2 mg, 0.027 mmol, 93%): clear oil; IR (neat, NaCl) 2961, 1260, 1093, 1019, 799 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.64 (d, J = 3.3 Hz, 2H), 6.59 (d, J = 3.0 Hz, 2H), 2.91 (s, 4H), 2.63-2.54 (m, 4H), 1.50-1.42 (m, 4H), 1.38-1.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 144.1, 140.8, 124.5, 124.1, 32.1, 31.9, 29.1, 22.7; MS m/e (EI) 262 (100, M^+), 165 (10), 153 (10), 152 (88), 151 (28), 124 (16), 123 (43), 110 (52), 97 (16); EIHRMS *m/e* 262.08503 ($C_{15}H_{18}S_2$ requires 262.08500).

Cyclopentadecane (**8**). Immeadiately prior to the reduction of **7**, a sample of commercial Raney nickel (RaNi) was washed following a published procedure.[8] About 0.5 g of RaNi in 0.25 mL ethanol was then placed in a vial and sealed under Ar. The vial was then heated to 60 °C and a solution of **7** (1.8 mg, 0.0065 mmol, in 0.25 mL acetone) was added. After stirring at 60 °C for 1 h, product **8** was isolated by extraction of the product mixture into pentane and water. Drying of the organic phase with $MgSO_4$ and removal of the solvent gave crude **8** (1.1 mg, 0.0052 mmol, 80%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (s) [lit.[9] 1.33, CS_2]; MS m/e (EI) 210 (16, M^+), 139 (4), 125 (12), 111 (29), 83 (69), 69 (65), 55 (86), 41 (93), 39 (100).

1-Methyl-3-oxo[5,2](2,5)thienophane (**12**). MeLi (0.22 mL, 0.29 mmol) was added to a stirred solution of CuI (0.026 g, 0.14 mmol) in ether (2.0 mL) at 0 °C. After 5 min, a solution of enone **10**[3b] (0.011g, 0.042 mmol) in 2.0 mL of ether was added. The mixture was stirred for an additional 3 h after which it was poured into a rapidly stirred solution of saturated NH_4Cl (15 mL). The resulting product mixture was then extracted twice with 20 mL portions of ether, and the organic phase was washed with brine. The crude product mixture was dried with $MgSO_4$, and compound **12** (0.0058 g, 48%) was isolated by flash chromatography (hexane:ethyl acetate, 9:1). **12**: clear oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.74 (d, J = 3.3 Hz, 1H), 6.67 (d, J = 3.3 Hz, 1H), 6.61 (d, J = 3.3 Hz, 1H), 6.58 (d, J = 3.3 Hz, 1H), 3.55-3.45 (m, 1H), 3.17-3.08 (m, 2H), 2.92-2.75 (m, 6H), 2.74-2.46 (m, 4H), 1.28 (d, J = 6.0 Hz, 3H); MS m/e (EI) 292 (9, M+2), 291 (15, M+1), 290 (81, M^+), 276 (4), 275 (2), 274 (4), 180 (14), 167 (23), 166 (21), 153 (21), 145 (6), 137 (28), 125 (21), 124 (100), 123 (49), 110 (39), 97 (12); EIHRMS *m/e* 290.07957 ($C_{16}H_{18}OS_2$ requires 290.07991).

dl-Muscone (**11**). Freshly washed Raney Ni (0.5 g) in 0.25 mL of ethanol was warmed to 60 °C. A solution containing ketone **12** (about 1 mg) in 0.25 mL of acetone was then added to the Raney Ni. The solution was stirred for 1 h at 60 °C and then dissolved in

pentane and extracted with 10 mL of water. Compound **11** was then isolated in trace quantities by flash chromatography using pentane:ether (19:1). **11**: fragrant oil; Rf 0.57, silica gel, pentane:ether (9:1); MS m/e (EI) 238 (10, M^+), 223 (4, M - CH_3), 180 (8), 142 (7), 125 (31), 124 (10), 112 (13), 111 (21), 110 (14), 98 (20), 97 (34), 85 (81), 71 (53), 69 (59), 55 (100), 41 (100) [lit.[10] MS m/e (EI) 238 (34), 223 (12), 180 (12), 125 (30), 111 (33), 97 (45), 85 (93), 69 (67), 55 (100), 41 (83)].

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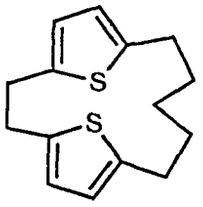
APPENDIX

Supplementary Procedure

Preparation of Raney nickel for reductive desulfurization:

About 2 g of Raney nickel slurry was placed in a 50-mL vacuum flask fitted with inlet and outlet tubes. Through the inlet tube, 250 mL of deionized water was allowed to flow over the Raney nickel solids , and the wash was collected in a waste bottle from the outlet tube. The water wash was then followed by washes of 95% ethanol (250 mL) and 100% ethanol (500 mL).



7

NMR spectra are displayed in this section with the following impurities labeled:

C	$CHCl_3$
B	C_6HD_5
W	H_2O
X	Unknown impurity

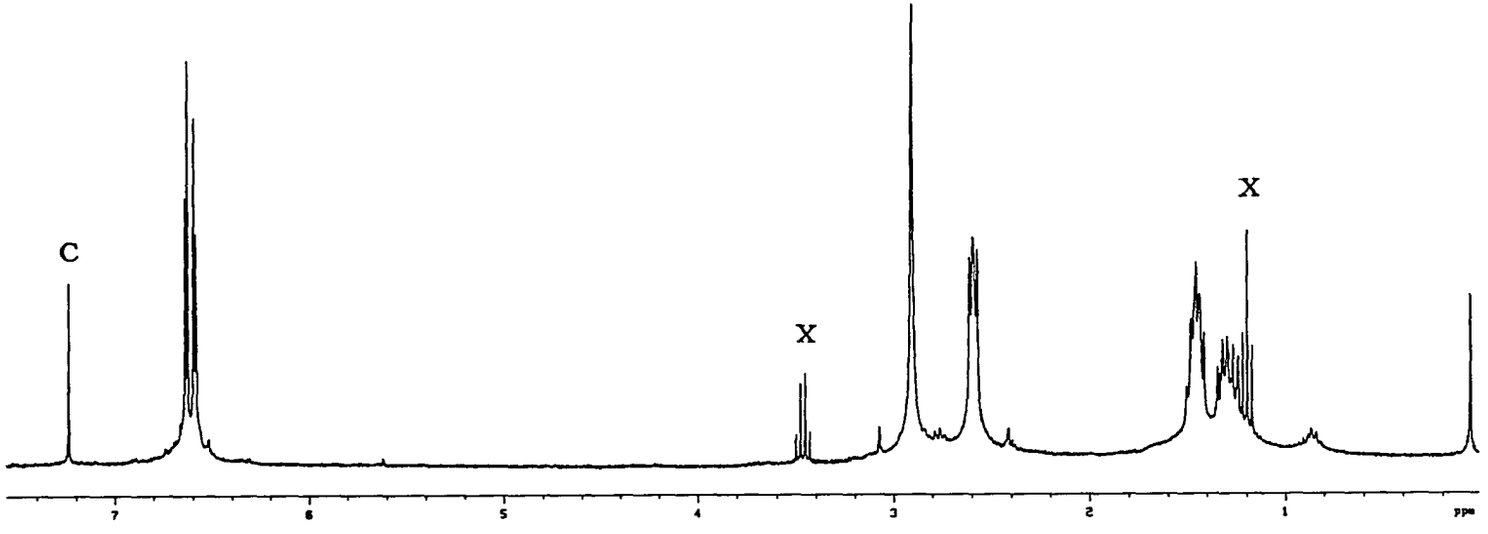


Figure A-1. ^1H NMR spectrum of **7** ($CDCl_3$, 300 MHz).

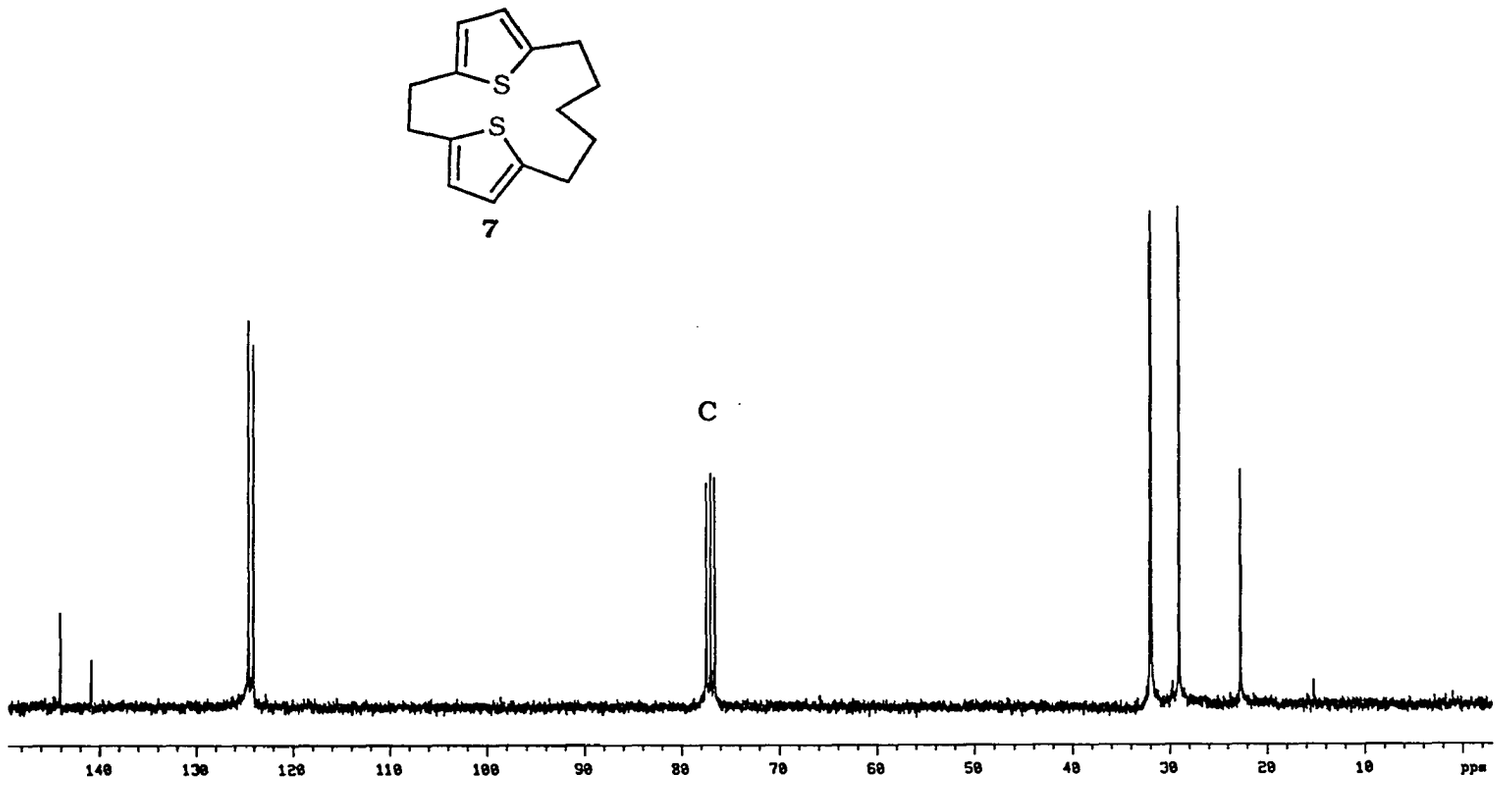


Figure A-2. ^{13}C NMR spectrum of **7** ($CDCl_3$, 300 MHz).

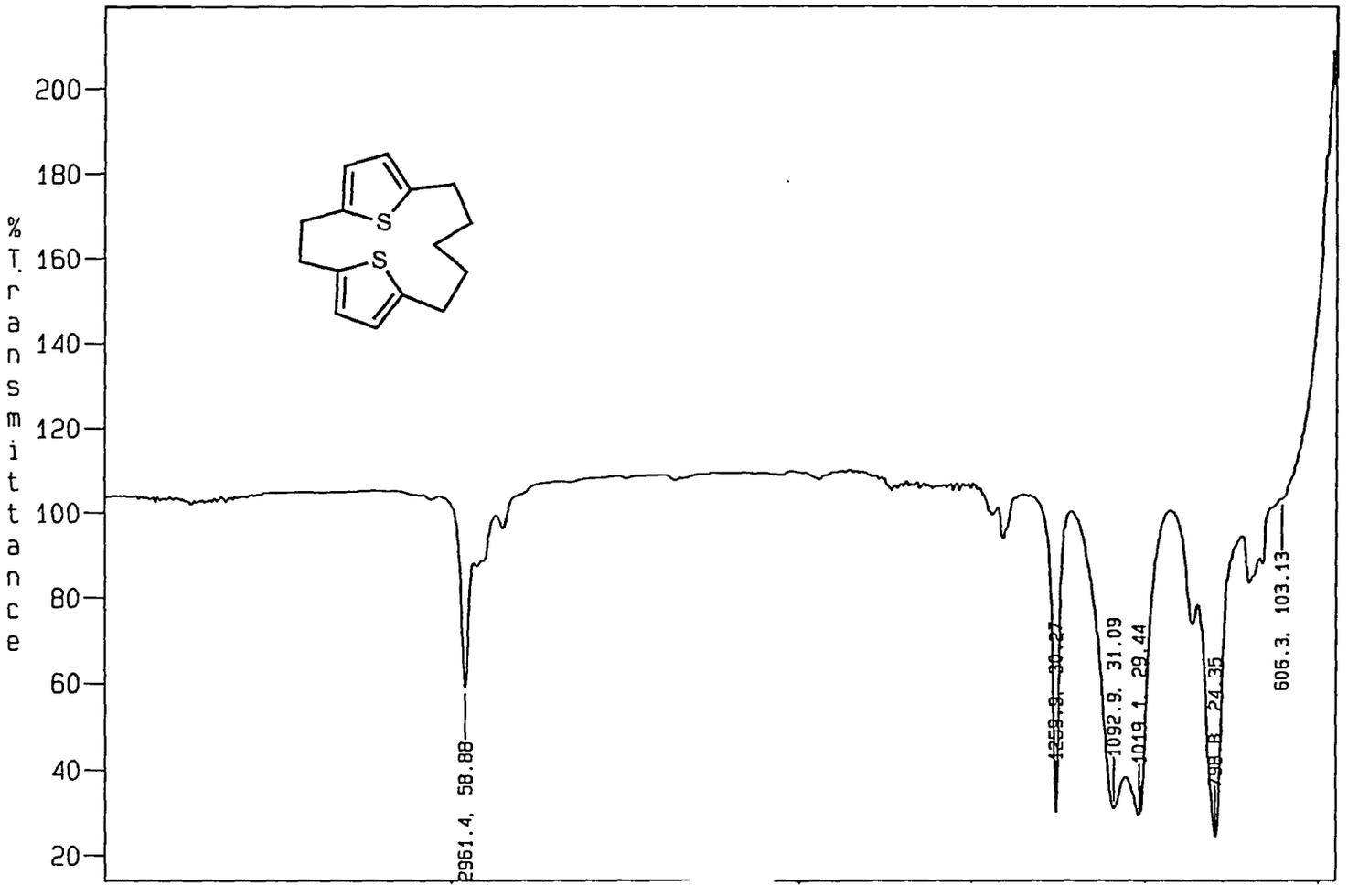
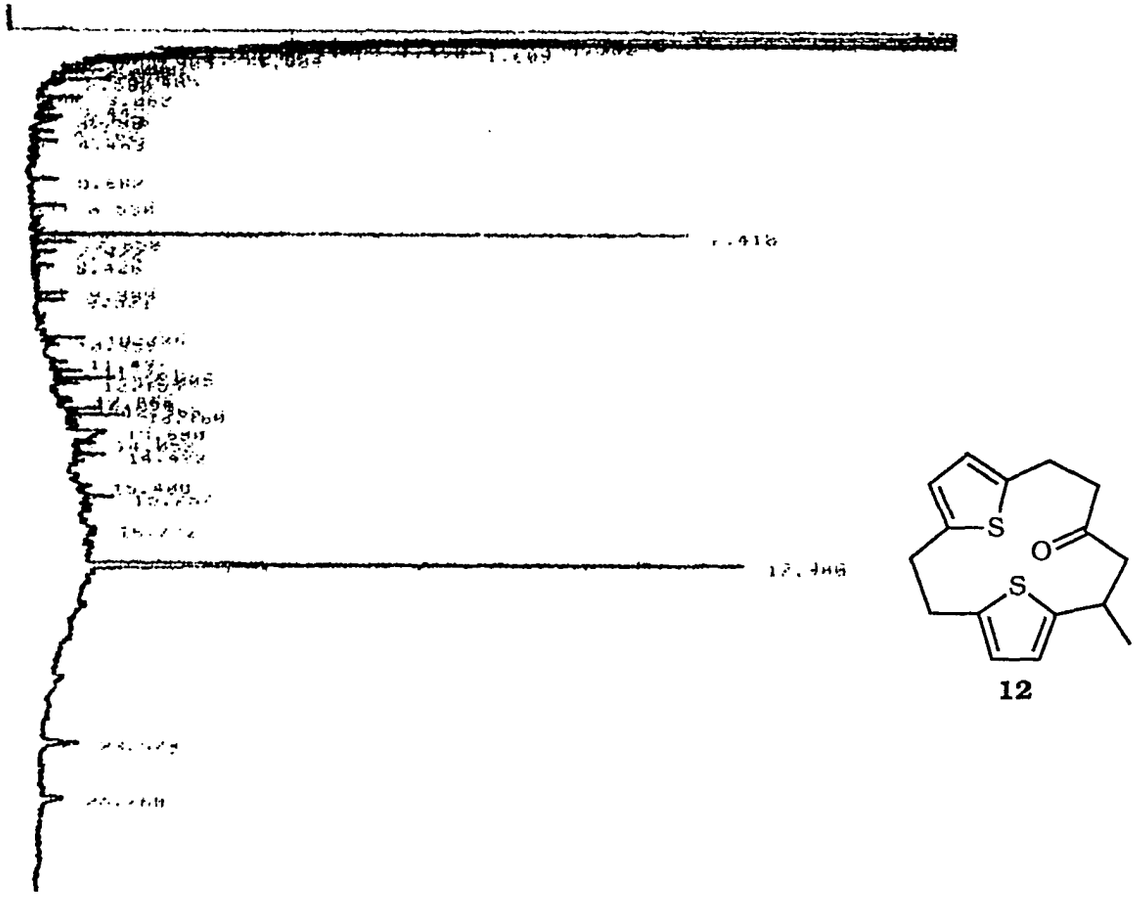


Figure A-3. IR spectrum of **7** (NaCl, thin film).



12

Figure A-4. GC trace of product mixture from the preparation of **12**.

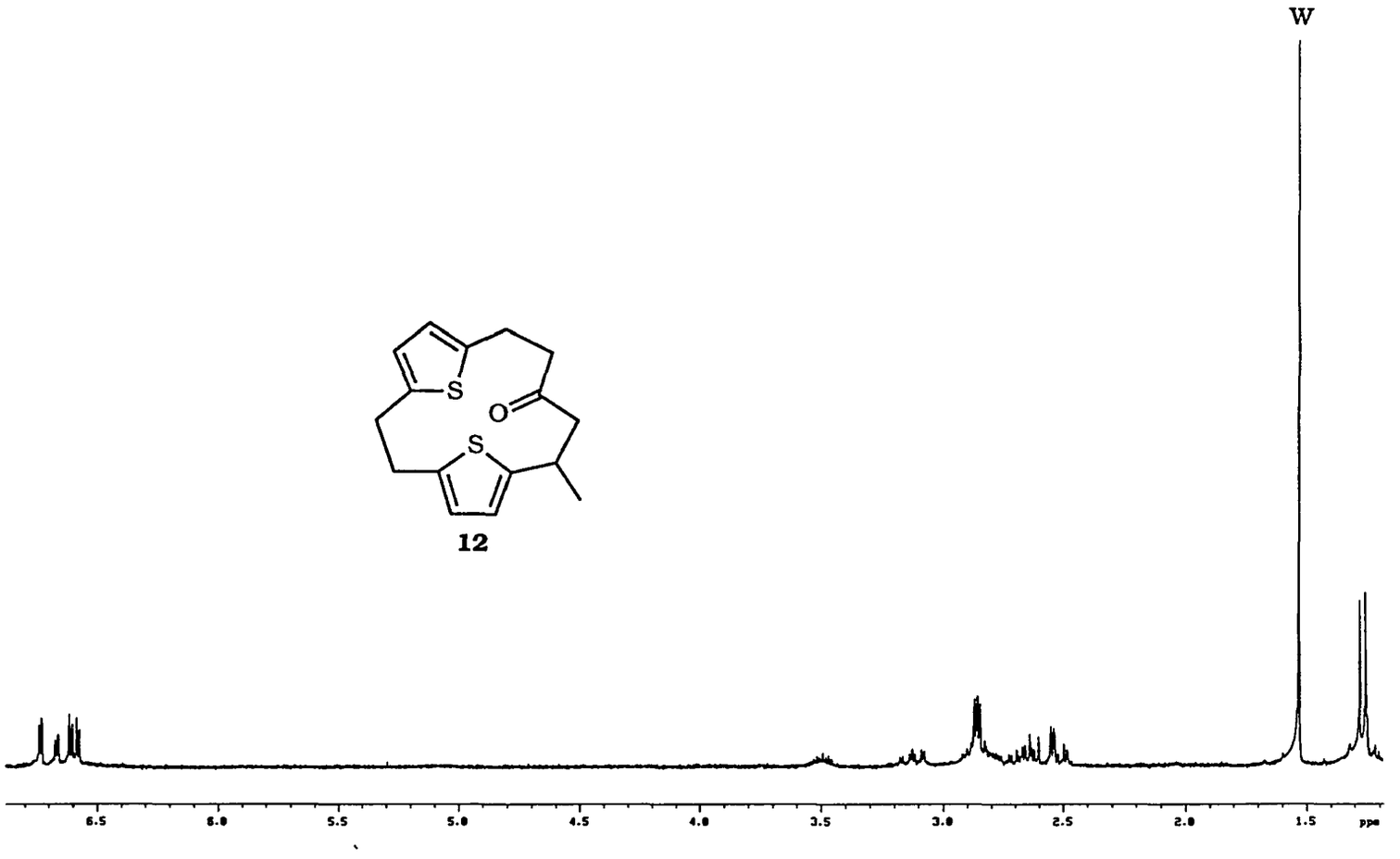


Figure A-5. ^{1}H NMR spectrum of **12**($CDCl_3$, 300 MHz).

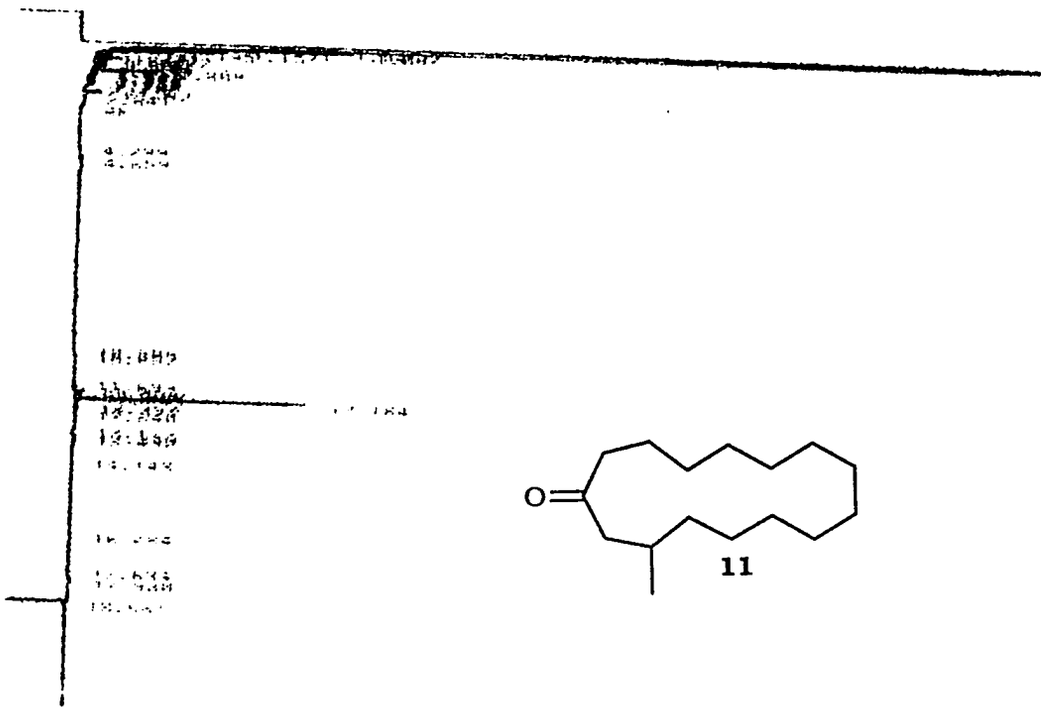


Figure A-6. GC trace of the product mixture from the preparation of **11**.

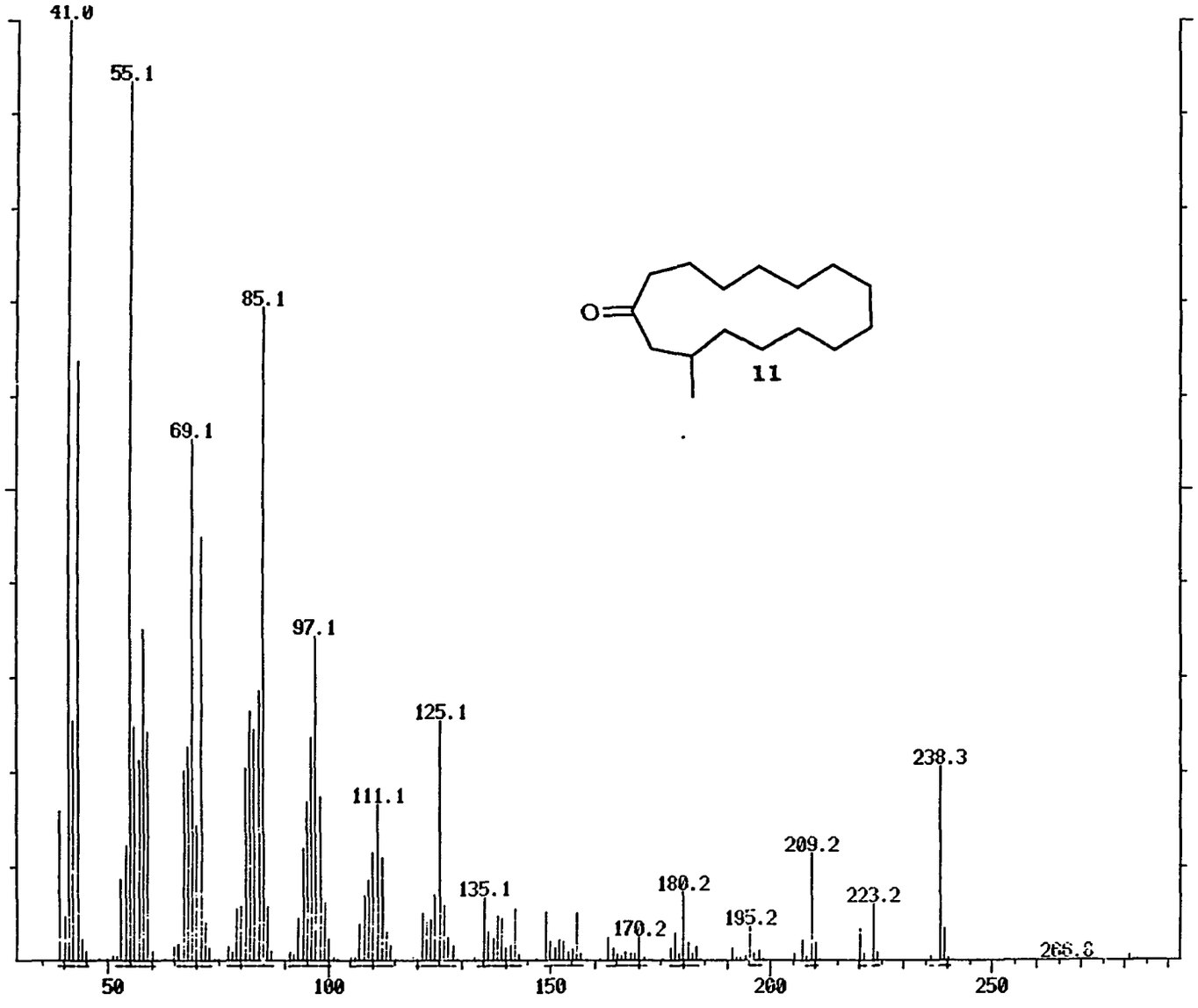


Figure A-7. EI mass spectrum of **11** (70 eV).

GENERAL SUMMARY

Flash vacuum pyrolysis (FVP) has been used to prepare macrocycles from 15 to 22 carbons by the pyrolysis of a general series of compounds, α,ω-di(2-acetoxymethyl-furyl-5)alkanes (**12**). The formation of these macrocyclic products is consistent with the generation of bis-2,5-dimethylene-2,5-dihydrofurans (**8**), which each of which contains two furan-based *p*-quinodimethanes linked by alkyl chains. We propose that the products are produced from intermediates **8** by an intramolecular cyclization of the furan-based *p*-quino-dimethanes to give cyclic diradical intermediates which undergo an intramolecular radical disproportionation to yield the macrocycles. The yields of the macrocyclic products are 20 to 60%. Experimental evidence suggests that formation of the macrocycles occurs in the gas phase.

FVP has also been used to prepare macrocycles which contain thiophene rings. The thiophene-based cyclizations resulting from the FVP of 1,5-di(2-acetoxy-methylthienyl-5)pentane (**13'**), 1,5-di(2-acetoxymethyl-thienyl-5)-3-pentanol (**18'**), and 1,5-di(2-acetoxymethylthienyl-5)-3-pentanone (**27'**) are similar to the furan-based cyclizations by FVP of compounds **12**. Pyrolysis of **13'** gives *cis*-1,2-dehydro[5.2]-(2,5)thienophane (**16'**) in 45% yield and 1-(2-methylthienyl-5)-5-(2'-formylthienyl-5')-pentane in 21% yield. FVP of **18'** provides a 45% yield of the *cis*-1,2-dehydro-3-hydroxy-[5.2](2,5)thienophane (**25'**) and **27'** gives a 35% yield of *cis*-1,2-dehydro-3-oxo[5.2]-(2,5)thienophane (**31'**) and a 10% yield of 1,2-di(2-vinylthienyl-5)ethane (**16'**).

Macrocycle **25'** is reduced with H_2 and 10% Pd-C to give [5,2](2,5)thienophane (**7"**) in 93% yield. Cyclophane **7"** is then further reduced with Raney nickel to give cyclopentadecane in 83% yield. Treatment of macrocyclic enone **31'** with $(CH_3)_2CuLi$ provides a 48% yield of 1-methyl-3-oxo[5,2](2,5)thienophane (**12"**). Compound **12"** can be reduced with Raney nickel to produce *dl*-muscone.

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