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

Douglas Allen Klumpp
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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

Klumpp, Douglas Allen, Ph.D.

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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

by

Douglas Allen Klumpp

A Dissertation Submitted to the Graduate Faculty in Partial Fulfillment of the Requirements for the Degree of DOCTOR OF PHILOSOPHY

Department: Chemistry
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Approved:
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For the Major Department
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For the Graduate College

Iowa State University
Ames, Iowa
1993
In memory of my father, Nelson William Klumpp
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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).

\[ \begin{align*}
\text{PhCO}_2\text{H} \\
\text{H}_3\text{C} & \quad \text{O} \\
\text{C} & \quad \text{Ph} \\
\text{O} & \quad \text{CH}_2 \\
\text{O} & \quad \text{CO}_2\text{H} \\
\end{align*} \]

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 by

\[ \begin{align*}
\text{FVP}, 580^\circ\text{C} & \quad \text{H}_3\text{C} & \quad \text{O} \\
- \text{PhCO}_2\text{H} & \quad \text{75\%} \\
\text{PhCO}_2\text{H} & \quad \text{75\%} \\
\text{H}_3\text{C} & \quad \text{O} \\
\text{C} & \quad \text{Ph} \\
\text{O} & \quad \text{CH}_2 \\
\text{O} & \quad \text{CO}_2\text{H} \\
\end{align*} \]
by irreversible elimination of benzoic acid by β-hydrogen abstraction to produce $p$-quinodimethanes 2 and 3. 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).

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. 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.
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.
of the furan-based \( p \)-quinodimethane. 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 an α,ω-dibromoalkane gave the α,ω-difurylalkane (13). For the α,ω-dibromoalkanes of n = 3 to 16, this reaction proceeded in good yields (70-90%). Next, the furan rings were formylated by reaction with n-BuLi, DMF, and then water. 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. 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.

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.\textsuperscript{14} FVP experiments were conducted with the apparatus evacuated to about 10\textsuperscript{-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\textsubscript{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
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<tr>
<td>12c</td>
<td>11c (cis)</td>
<td><img src="https://example.com/structure1.png" alt="Structure" /></td>
<td>46</td>
</tr>
<tr>
<td>12d</td>
<td>11d (cis)</td>
<td><img src="https://example.com/structure2.png" alt="Structure" /></td>
<td>47</td>
</tr>
<tr>
<td>12e</td>
<td>11e (cis)</td>
<td><img src="https://example.com/structure3.png" alt="Structure" /></td>
<td>22</td>
</tr>
<tr>
<td>12f</td>
<td>11f (cis)</td>
<td><img src="https://example.com/structure4.png" alt="Structure" /></td>
<td>4</td>
</tr>
</tbody>
</table>

$^a$ 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.

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 be 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 consistent 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 $^1$H 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 major product. The structure assignment of 15a was made on the basis of $^1$H 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 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 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 11e 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)

<table>
<thead>
<tr>
<th>starting material</th>
<th>product mixture</th>
</tr>
</thead>
<tbody>
<tr>
<td>11e (cis)</td>
<td>11e (trans)</td>
</tr>
<tr>
<td>98.0</td>
<td>2.0</td>
</tr>
<tr>
<td>99.4</td>
<td>0.6</td>
</tr>
<tr>
<td>6.2</td>
<td>93.8</td>
</tr>
<tr>
<td>14.0</td>
<td>86.0</td>
</tr>
</tbody>
</table>

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 (11e 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).

\[
\begin{align*}
\text{Scheme IV} \\
12d \xrightarrow{\text{FVP}} & \quad 8d \\
& \quad 9d \\
& \quad a \quad b \\
& \quad 11d \text{ (cis)} + 11d \text{ (trans)} \\
& \quad 10d
\end{align*}
\]

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. 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 cyclopane products. Thus, reactive o-quinodimethanes and p-quinodimethanes may be exploited 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. 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. 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.

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. 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.\textsuperscript{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\textsuperscript{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 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

![Diagram of chemical structures](image-url)
acetic anhydride itself decomposes under FVP conditions. 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.\textsuperscript{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 11\textsuperscript{c} (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\textsuperscript{23} with Merck grade 60, 230-400 mesh silica gel, which was purchased from Aldrich.

General procedure for the preparation of $\alpha,\omega$-dl(2-acetoxy methyl furl-5)-alkanes (12)

$\alpha,\omega$-Dil(furl-2)-alkanes (13) were prepared by a procedure based on a published procedure\textsuperscript{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 $\alpha,\omega$-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 NaHCO₃, brine, and drying with anhydrous MgSO₄. 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 procedure¹² 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 NaHCO₃, brine, and drying with anhydrous MgSO₄. 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 (El) 176 (36, M⁺), 94 (100), 81 (57). 1,3-Di(2-formylfuryl-5)propane (14a): yellow solid, mp 77-79°C; ¹H NMR, see Table IV; MS m/e (El) 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)$^a$

<table>
<thead>
<tr>
<th>compound</th>
<th>resonance signals, ppm$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>13a</td>
<td>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)</td>
</tr>
<tr>
<td>13b</td>
<td>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)</td>
</tr>
<tr>
<td>13c</td>
<td>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)</td>
</tr>
<tr>
<td>13d</td>
<td>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)</td>
</tr>
<tr>
<td>13e</td>
<td>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)</td>
</tr>
<tr>
<td>13f</td>
<td>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)</td>
</tr>
<tr>
<td>13g</td>
<td>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)</td>
</tr>
</tbody>
</table>

$^a$ $^1$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)$^a$

<table>
<thead>
<tr>
<th>compound</th>
<th>resonance signals, ppm$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>14a</td>
<td>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)</td>
</tr>
<tr>
<td>14b</td>
<td>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)</td>
</tr>
<tr>
<td>14c</td>
<td>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)</td>
</tr>
<tr>
<td>14d</td>
<td>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)</td>
</tr>
<tr>
<td>14e</td>
<td>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)</td>
</tr>
<tr>
<td>14f</td>
<td>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)</td>
</tr>
<tr>
<td>14g</td>
<td>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)</td>
</tr>
</tbody>
</table>

$^a$ $^1$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 ($^{13}$C$_{17}$H$_{20}$O$_6$ requires 320.12599).

1,4-Di(2-acetoxymethylfuryl-5)-butane (12b): 1,4-di(furfuryl-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).

1,5-Di(2-acetoxymethylfuryl-5)-pentane (12c): 1,5-di(furfuryl-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).

1,6-Di(2-acetoxymethylfuryl-5)-hexane (12d): 1,6-di(furfuryl-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.

1,7-Di(2-acetoxymethylfuryl-5)-heptane (12e): 1,7-di(furfuryl-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).

1,12-Di(2-acetoxymethylfuryl-5)dodecane (12f): 1,12-di(furfuryl-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 $\alpha,\omega$-Di(2-acetoxymethylfuryl-5)alkanes (12a to 12g)$^a$

<table>
<thead>
<tr>
<th>compound</th>
<th>resonance signals, ppm$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>12a</td>
<td>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)</td>
</tr>
<tr>
<td>12b</td>
<td>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)</td>
</tr>
<tr>
<td>12c$^c$</td>
<td>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)</td>
</tr>
<tr>
<td>12d</td>
<td>6.25 (d, $J = 3.0$ Hz, 2H), 5.90 (d, $J = 3.0$ Hz, 2H), 4.95 (s, 4H), 2.68-2.69 (m, 4H), 2.03 (s, 6H), 1.62-1.55 (m, 4H), 1.37-1.30 (m, 4H)</td>
</tr>
<tr>
<td>12e</td>
<td>6.24 (d, $J = 3.1$ Hz, 2H), 5.89 (d, $J = 3.1$ Hz, 2H), 4.95 (s, 4H), 2.68-2.69 (m, 4H), 2.03 (s, 6H), 1.64-1.52 (m, 4H), 1.30 (s, 6H)</td>
</tr>
<tr>
<td>12f</td>
<td>6.29 (d, $J = 3.1$ Hz, 2H), 5.93 (d, $J = 3.1$ Hz, 2H), 4.99 (s, 4H), 2.68-2.69 (m, 4H), 2.07 (s, 6H), 1.67-1.59 (m, 4H), 1.39-1.23 (m, 16H)</td>
</tr>
<tr>
<td>12g</td>
<td>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)</td>
</tr>
</tbody>
</table>

$^a$ $^1$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$_6$D$_6$. 

Table VI. $^{13}$C NMR data for $\alpha,\omega$-Di(2-acetoxyethylfuryl-5)alkanes (12a to 12g)$^a$

<table>
<thead>
<tr>
<th>compound</th>
<th>resonance signals, ppm$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>12a</td>
<td>170.08, 156.94, 147.14, 110.89, 105.62, 57.73, 26.89, 25.90, 20.40</td>
</tr>
<tr>
<td>12b</td>
<td>170.64, 157.04, 147.60, 111.45, 105.88, 58.29, 27.77, 27.36, 20.93</td>
</tr>
<tr>
<td>12c</td>
<td>170.75, 157.37, 147.53, 111.48, 105.79, 58.38, 28.71, 27.98, 27.59, 21.01</td>
</tr>
<tr>
<td>12d</td>
<td>170.70, 157.48, 147.46, 111.46, 105.71, 58.34, 28.82, 28.00, 27.73, 20.95</td>
</tr>
<tr>
<td>12e</td>
<td>170.68, 157.57, 147.44, 111.43, 105.66, 58.34, 29.04, 28.99, 28.04, 27.81, 20.95</td>
</tr>
<tr>
<td>12f</td>
<td>171.71, 157.72, 147.40, 111.43, 105.61, 58.37, 29.59, 29.53, 29.34, 29.20, 28.09, 27.88</td>
</tr>
<tr>
<td>12g</td>
<td>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)</td>
</tr>
</tbody>
</table>

$^a$ $^1$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 \( \alpha,\omega \)-Di(2-acetoxymethylfuryl-5)alkanes (12a to 12g)\(^{a}\)

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

\(^{a}\) IR data obtained from thin films on NaCl.
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) $\delta$ 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) $\delta$ 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 (CDCl₃, 300 MHz) δ 6.40 (dd, J = 11.3, 17.5 Hz, 2H), 6.10 (d, J = 3.2 Hz, 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); ¹³C NMR (CDCl₃, 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 (C₁₄H₁₄O₂ requires 214.09938).

**l-(2-Methylthienyl-5)-4-(2-formylthienyl-5)butane (15b):** ¹H NMR (CDCl₃, 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 (cls),** 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 (cls)):** white solid, mp 96-97°C, 46% yield; IR (neat, NaCl) 2924, 2854, 1560, 1456, 1423, 1396, 1169, 1018, 789 cm⁻¹; ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (C₁₅H₁₆O₂ requires 228.11503). **1-(2-Methylthienyl-5)-...**
yl-5)-5-(2-formylthienyl-5)pentane (15): $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 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 (El) 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) $\delta$ 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) $\delta$ 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 (El) 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) $\delta$ 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) $\delta$ 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 (El) 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, 1190, 1157, 1016, 1007, 787 cm⁻¹; ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (C₁₆H₁₈O₂ requires 242.13068).

1-(2-Methylthienyl-5)-6-(2'-formylthienyl-5')hexane (15d): ¹H NMR (CDCl₃, 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 (CDCl₃, 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 Hz, 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); ¹³C NMR (CDCl₃, 300 MHz) δ 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 (C₁₇H₂₀O₂ 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 (CDCl₃, 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); 13C NMR (CDCl3, 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 (El) 256 (93, M+), 120 (86), 107 (100), 94 (69), 91 (46); EIHRMS m/e 256.14699 [C17H20O2 requires 256.14633].

l-(2-methylthienyl-5)-7-(2'-formylthienyl-5')heptane (15c): MS m/e (El) 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 partial characterization of the other product suggested its identity as 11f (cis). 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 (CDCl3, 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); 13C NMR (CDCl3, 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 (El) 326(100, M+), 121 (52), 108 (42), 107 (87), 95 (58); EIHRMS m/e 326.22470 [C22H30O2 requires 326.22459].

**cis-1,2-Dehydro[12.2](2,5)-furanophane (11f (cis))**: ~4% yield; 1H NMR (CDCl3, 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 (El) 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 (El) 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 suggested 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.
REFERENCES


(3) Poutsma, M. A Review of Thermal Studies of Model Compounds Relevant to the Processing of Coal; ORNL/TM-10673, Oak Ridge National Laboratory, Oak Ridge, TN 37831. This review is available from National Technical Information Service, U. S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161.


APPENDIX

Supplementary Procedure

General procedure for the reduction and acylation of the \(\alpha,\omega\)-di(2-formylfuryl-5)alkanes (14) to prepare the \(\alpha,\omega\)-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 \(\alpha,\omega\)-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 \(\text{H}_2\text{O}\), 0.6 mL of 15% NaOH, and then 1.8 mL of \(\text{H}_2\text{O}\). 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.
Figure A-1. Schematic diagram of the flash vacuum pyrolysis apparatus.
Figure A-2. $^1$H NMR spectrum of bis-furfuryl acetate 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. $^1\text{H}$ 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.
Figure A-18. $^{13}$C NMR spectrum of bis-furfuryl acetate 12f.
Figure A.19.
IR spectrum of bis-furfuryl acetate 12f.

H₃C
O
CH₂
O
CH₂

1736
1562
1472
1448
1379
1354
1246
1204
1167
1028
969
937
793

3742
3684
3414
3227
2920
2853

69
Figure A-20. $^1$H NMR spectrum of bis-furfuryl acetate 12g.
Figure A-21. $^{13}$C NMR spectrum of bis-furfuryl acetate 12g.
Figure A-22. IR spectrum of bis-furfuryl acetate 12g.
Figure A-23. \(^1H\) NMR spectrum of macrocycle 11c (cis).
Figure A-24. $^{13}$C NMR spectrum of macrocycle 11c (cis).
Figure A-25. IR spectrum of macrocycle 11e (cls).
Figure A-26. $^1$H NMR spectrum of macrocycle 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).
Figure A-30. $^{13}$C NMR spectrum of macrocycle 11d (trans).
Figure A-31. IR spectrum of macrocycle 11d (trans).
Figure A-32. $^1$H NMR spectrum of macrocycle 11e (cis).
Figure A-33. $^{13}$C NMR spectrum of macrocycle 11e (cis).
Figure A-34. IR spectrum of macrocycle 11e (cis).
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).
Figure A-38. $^{1}$H NMR spectrum of macrocycle 11f (cis).
Figure A-39. $^1$H NMR spectrum of macrocycle 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. \( ^1H \) 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.
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.
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).

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

\[
\begin{align*}
\text{H}_3\text{C} & \text{O} \text{C} \text{Ph} \; \text{O} \text{C} \text{Ph} \text{H}_2C & \text{O} \text{C} \text{Ph} \text{H}_2C \\
\text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} \\
\text{H}_3C & \text{O} \text{C} \text{Ph} \text{H}_2C & \text{O} \text{C} \text{Ph} \text{H}_2C \\
\text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} \\
\text{H}_3C & \text{O} \text{C} \text{Ph} \text{H}_2C & \text{O} \text{C} \text{Ph} \text{H}_2C \\
\text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} \\
\text{H}_3C & \text{O} \text{C} \text{Ph} \text{H}_2C & \text{O} \text{C} \text{Ph} \text{H}_2C \\
\text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} \\
\text{H}_3C & \text{O} \text{C} \text{Ph} \text{H}_2C & \text{O} \text{C} \text{Ph} \text{H}_2C \\
\text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} \\
\text{H}_3C & \text{O} \text{C} \text{Ph} \text{H}_2C & \text{O} \text{C} \text{Ph} \text{H}_2C
\end{align*}
\]

\[
\begin{align*}
\text{H}_3C & \text{O} \text{C} \text{Ph} \text{H}_2C & \text{O} \text{C} \text{Ph} \text{H}_2C \\
\text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} \\
\text{H}_3C & \text{O} \text{C} \text{Ph} \text{H}_2C & \text{O} \text{C} \text{Ph} \text{H}_2C \\
\text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} \\
\text{H}_3C & \text{O} \text{C} \text{Ph} \text{H}_2C & \text{O} \text{C} \text{Ph} \text{H}_2C \\
\text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} \\
\text{H}_3C & \text{O} \text{C} \text{Ph} \text{H}_2C & \text{O} \text{C} \text{Ph} \text{H}_2C
\end{align*}
\]

(1) FVP, 580°C
- PhCO₂H
75%

(2) FVP, 640°C
- PhCO₂H
75%
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**

\[O \quad (CH_2)_{n-2} \quad O \]

6

\[O \quad (CH_2)_{n-2} \quad O \]

7

9

8

a: \(n = 5\); b: \(n = 6\); c: \(n = 7\); d: \(n = 12\)
reactive molecules and are known for their tendency to dimerize, trimerize, and polymerize through intermolecular reactions. 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).

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: $X = \text{CH}_2$; 18: $X = \text{CHOH}$; 27: $X = \text{CO}$
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.

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.

![reaction scheme]

The stereochemistry of the double bond in 16 was established to be of cis conformation on the basis of the olefinic coupling constant \( J = 11.4 \text{ Hz} \) in the \(^1\text{H} \) NMR spectrum. In addition, the \(^1\text{H} \) NMR spectrum of 16 was very similar to that of the furan-containing macrocycle 9a (Scheme I). Like related macrocyclic ring systems,\(^\text{11} \) compound 16 appears to exist in at least two equilibrating conformations in solution. Inspection of the \(^1\text{H} \) 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 \(^1\text{H} \) NMR (1-D and COSY), \(^{13}\text{C} \) NMR (decoupled, \(^1\text{H}-^{13}\text{C} \) 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 surprising, 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.\textsuperscript{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.\textsuperscript{12} Reduction of 19 with H$_2$ and Pd-C catalyst\textsuperscript{13} gave 1,5-di(thienyl-2)-3-pentanone (20) in good yield (80%), and further reduction\textsuperscript{9} of the ketone with LiAlH$_4$ (100% yield) gave 21. The hydroxy group was then protected\textsuperscript{14} to give 22 (89%) and the thiophene rings were formylated\textsuperscript{8} (63%) via the thienyl anion and reaction with dimethylformamide. Compound 23 was then reduced and acylated\textsuperscript{9} in 80% yield to give
24. Deprotection of 24 with fluoride\textsuperscript{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-acetoxyethylthienyl-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.

\[
\begin{align*}
\text{20} & \xrightarrow{\text{a, ethylene glycol, PPTS;}} 76\% \text{ ketal } 28 \\
\text{b, c, d, n-BuLi; c, Me_2NCHO; d, H_2O; e, LiAIH}_4; f, Et_3N, CH_2COCl; g, acetone, PPTS & \text{ 94\% formylation } \rightarrow 29 \\
\text{29} & \xrightarrow{g, acetone, PPTS} 87\% \text{ acetone derivative } 30 \\
\text{30} & \xrightarrow{\text{g, acetone, PPTS}} 87\% \text{ deprotection } \rightarrow 27
\end{align*}
\]

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-acetoxyethylthienyl-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
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).
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.
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-
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, 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 and may be observed by $^1$H
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. Diradical intermediates have been postulated for these reactions, however the existence of these intermediates has yet to be rigorously established. 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 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 CO2, 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.\textsuperscript{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.\textsuperscript{20} The N,N-dimethyl-formamide and HMPA were obtained from Fisher Scientific and distilled from CaH\textsubscript{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\textsuperscript{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\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) 6 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) 6 145.4, 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 NaHCO₃ solution, three times with brine, and dried with anhydrous MgSO₄. 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 (CDCl₃, 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); ¹³C NMR (CDCl₃, 300 MHz) δ 182.5, 156.9, 141.6, 137.0, 125.9, 30.7, 30.5, 28.1. MS m/e (El) 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. 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 (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₁₉H₂₄O₄S₂: 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 procedure¹² 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$_2$O 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) $\delta$ 7.99 (d, $J = 15$ Hz, 2H), 7.40 (d, $J = 5.1$ Hz, 2H), 7.32 (d, $J = 3.4$ Hz, 2H), 7.18-7.01 (m, 2H), 6.81 (d, $J = 15$ Hz, 2H); UV-Vis $\lambda_{\text{max}}$ 370 nm (CH$_3$OH); 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) $\delta$ 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. To a suspension of LiAlH₄ (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 H₂O, 0.5 mL 15% NaOH, and then 1.5 mL H₂O. The resulting solution was stirred 20 min and 0.5 g of anhydrous MgSO₄ 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 (CDCl₃, 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+), 231 (1), 211 (2.5), 195 (3), 138 (14), 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 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. NaHCO₃. The organic phase was extracted three times with brine, dried with anhydrous MgSO₄, 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 (CDCl₃, 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), 308 (17, M-57), 231 (1), 195 (2), 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 to give 0.581 g (1.4 mmol, 63%) of purified 23. 23: yellow oil; \( ^1H \) NMR (CDCl\(_3\), 300 MHz) \( \delta \) 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, 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\(^{-1}\); \( ^1H \) NMR (CDCl\(_3\), 300 MHz) \( \delta \) 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); \( ^13C \) NMR (CDCl\(_3\), 300 MHz) \( \delta \) 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. 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\(^{-1}\); \( ^1H \) NMR (CDCl\(_3\), 300 MHz) \( \delta \) 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); \( ^13C \) NMR (CDCl\(_3\), 300 MHz) \( \delta \) 170.6, 146.6, 135.4.
Preparation of 1,5-di(2-acetoxymethylthienyl-5)-3-pentanone (27)

1,5-di(2-thienyl)-3,3-ethylenedioxyptane (28) was prepared by standard methods for the protection of a ketone. 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 MgSO₄, 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; ¹H NMR (CDCl₃, 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-ethylenedioxyptane (29) was prepared using the same procedure as 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; ¹H NMR (CDCl₃, 300 MHz) 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-ethylenedioxyptane (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, and purified to give 1.40 g of 30 (1.40 g, 3.2 mmol, 97%). 30: clear oil; ¹H NMR (CDCl₃, 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-acetoxyethylthien-5)-3-pentanone (27) Method A: 27 was prepared from 30 by a general method for the deprotection of a ketal protecting group. A solution containing 0.1077 g of 30 (0.25 mmol), 10 mL acetone, 0.5 mL H$_2$O, 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$_3$OH:H$_2$O (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. To a solution at -70 °C containing 0.36 mL oxalyl chloride (2.0 M in CH$_2$Cl$_2$, 0.72 mmol) in 1 mL CH$_2$Cl$_2$, 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$_2$Cl$_2$ 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$_2$O, 10 mL CH$_2$Cl$_2$, and the mixture was extracted. The aqueous phase was then washed with 10 mL CH$_2$Cl$_2$ 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,
Flash vacuum pyrolysis of 1,5-di(acetoxymethylthienyl-5)pentane (13)

Compound 13 was pyrolyzed (187 mg, 0.49 mmol) using standard FVP methods. 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 N2 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. ^H 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 C6D6 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; ^H NMR (CDCl₃, 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); ^13C NMR (CDCl₃, 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 (C15H16S2 requires 260.06935).

1-(2-methylthienyl-5)-5-(2'-formylthienyl-5')pentane (17): clear oil; IR (neat, NaCl) 2932, 2856, 1668, 1460, 1036, 798 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 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, \(^1\)H decoupled) \(\delta\) 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, \(^1\)H,\(^13\)C coupled) \(\delta\) 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 (4), 167 (4), 152 (7), 139 (8), 113 (5), 112 (11), 111 (100), 97 (10); EIHRMS m/e 278.07991 (C15H18OS2 requires 278.07938).

2,5-dimethylene-2,5-dihydrothiophene (3): \(^1\)H NMR (C6D\(_6\), 300 MHz) \(\delta\) 6.56 (s), 5.26 (s), 5.07 (s) [lit.\(^2\) 6.52 (s), 5.24 (s), 5.02 (s) (1:1 CS\(_2_2\)/CDCl\(_3\))].

**Flash vacuum pyrolysis of 1,5-di(2-acetoxyethythieryl-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 \(^1\)H 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 (CDCl₃, 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 (C₁₅H₁₆O₃S₂ 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-acetoxythienyl-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 (CDCl₃, 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): ¹H NMR (CDCl₃, 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 (El) 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 (C₁₅H₁₁₄O₂S₂ requires 276.04861).

1,2-di(2-vinylthieryl-5)ethane (32): clear oil; IR (neat, NaCl) 2963, 2928, 1261, 1092, 1022, 998, 798 cm⁻¹; ¹H NMR (CDCl₃, 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 (El) 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 (C₁₄H₁₄S₂ requires 246.05370).

1-(2-methylthieryl-5)-5-(2'-formylthieryl-5')-3-pentanone (33): MS m/e (El) 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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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 transferred (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 disassembled 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 chromatography 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 transferred 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 LiAlH₄ (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 H₂O, 0.6 mL of 15% NaOH, and then 1.8 mL of H₂O. The mixture was stirred at 25 °C for an additional 20 min. and ~2 g of MgSO₄ 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 NaHCO₃ and saturated NaCl. Drying with MgSO₄ 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: CHCl₃
- B: C₆H₅D₅
- W: H₂O
- T: Si(CH₃)₄
- G: Silicone grease
- E: CH₃CO₂C₂H₅
- H: Hexane
- O: Ethyl ether
- X: Unknown impurity

Figure A-1. ¹H NMR spectrum of 13 (CDCl₃, 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).
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$_6$D$_6$, 300 MHz); spectrum taken within 30 minutes of completion of the FVP experiment.
Figure A-12. $^1$H NMR spectrum taken of the crude products from FVP of 13 (C$_6$D$_6$, 300 MHz); spectrum taken 24 hours after completion of the FVP experiment.
Figure A-13. $^1$H NMR spectrum of macrocycle 16 (22 °C, CDCl₃, 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 (CDCl₃, 300 MHz).
Figure A-21. HETCOR NMR spectrum of compound 17 (CDCl₃, 300 MHz).
Figure A-22. IR spectrum of compound 17 (CDCl₃, 300 MHz).
Figure A-23. Subtracted $^1$H NMR spectrum of crude FVP products from 13 (C$_6$D$_6$, 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. $^1$H NMR spectrum of the crude products from FVP of 18 (CDCl₃, 300 MHz).
Figure A-26. $^1$H NMR spectrum of macrocycle 25 (CDCl$_3$, 300 MHz).
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).
Figure A-36. UV-Vis spectrum of 19 in CH$_3$OH.
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. These classes of compounds have important application in host-guest chemistry, natural products synthesis, and other areas. 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). Flash vacuum pyrolysis (FVP) of compounds of general structure 1 provide macrocycles (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.\textsuperscript{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.\textsuperscript{3b} In this chapter, results are presented from the synthetic manipulation of the functionalized macrocycles 2, including the synthesis of \([5,2][2,5]\text{thienophane}, \text{cyclopentadecane, 1-Methyl-3-oxo-}[5,2][2,5]\text{thienophane, and dl-muscone.}
RESULTS

We have reported that FVP of compound 5 gave cis-1,2-dihydro[5,2][2,5]thienophane (6) in 45% yield (Scheme 2).\textsuperscript{3b} When hydrogenated\textsuperscript{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\textsuperscript{5} produced cyclopentadecane (8) in 83% isolated yield.

We have also reported that FVP of the acyclic ketone 9 produced the macrocyclic enone 10 in 35% yield (Scheme 3).\textsuperscript{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\textsuperscript{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

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. 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 received. The Cul was purchased from Aldrich Chemical and purified prior to use. The Raney Ni was also purchased from Aldrich Chemical and washed immediately prior to use.

[5,2](2,5)Thienophane (7). To a solution of cis-1,2-dehydro[5,2](2,5)thienophane (6) (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 H2. The solution was stirred for 3 h at room temperature under slightly more than 1 atmosphere of H2. 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 MgSO4. 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 (CDCl3, 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); ¹³C NMR (CDCl3, 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 (C₁₅H₁₈S₂ requires 262.08500).
Cyclopentadecane (8). Immediately prior to the reduction of 7, a sample of commercial Raney nickel (RaNi) was washed following a published procedure. 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 MgSO₄ and removal of the solvent gave crude 8 (1.1 mg, 0.0052 mmol, 80%): ¹H NMR (CDCl₃, 300 MHz) δ 1.23 (s, 11), 1.33, CS₂; MS m/e (El) 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 (0.01 g, 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 NH₄Cl (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 MgSO₄, and compound 12 (0.0058 g, 48%) was isolated by flash chromatography (hexane:ethyl acetate, 9:1). 12: clear oil; ¹H NMR (CDCl₃, 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 (El) 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 (C₁₆H₁₈OS₂ 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 - CH3), 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)].
REFERENCES


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

- C  \( \text{CHCl}_3 \)
- B  \( \text{C}_{6}\text{H}_5 \)
- W  \( \text{H}_2\text{O} \)
- X  Unknown impurity

Figure A-1. \( ^1\text{H} \) NMR spectrum of 7 (CDCl₃, 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).
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, \( \alpha, \alpha \text{-dil}(2\text{-acetoxymethyl-furyl-5}) \text{alkanes (12).} \) 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 \( p \)-quinodimethanes 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-acetoxymethylthienyl-5)-pentane (13'), 1,5-di(2-acetoxymethylthienyl-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 \( \text{H}_2 \) 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 \( \text{(CH}_3\text{)}_2\text{CuLi} \) 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 \( \text{dl-muscone.} \)
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