STUDIES AND APPLICATIONS OF FURAN OXIDATIONS

By

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ABSTRACT

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The oxidation of alkylfurans using *m*-chloroperoxybenzoic acid (MCPBA) was investigated. In methylene chloride solution, 2,5-dialkylfurans were oxidized by one equivalent of MCPBA to give *cis*-1,4-enediones in high yield. The initial enedione product derived from 2-*n*-butylfuran rearranged in the presence of acid to give 5-*n*-butyl-2-(3H)furanone in good yield. Further oxidation occurred with more highly substituted alkylfurans. For example, 2,3,5-trimethylfuran consumed two equivalents of MCPBA to give (Z)-4-acetoxy-3-methyl-3-buten-2-one, along with a minor amount of 3,4-epoxy-3-methylhexane-2,5-dione. The mono-oxidation product, (Z)-3-methyl-3-hexene-2,5-dione, gave the same product mixture upon treatment with MCPBA, suggesting that the second oxidation occurs *via* a regioselective Baeyer-Villiger mechanism. Oxidation of alkylfurans using MCPBA in methanol gave 2,5-dimethoxy-2,5-dihydrofuran derivatives in high yield.

Furan oxidation methodology was employed as the key step in a model study for the construction of the

2,9-dioxabicyclo[3.3.1]nonane ring system of the antibiotic, tirandamycin. Thus, oxidation of 2-(1,3-dihydroxypropyl)-3,5-dimethylfuran with MCPBA followed by the addition of a catalytic amount of aqueous *p*-toluenesulfonic acid gave 1,7-dimethyl-2,9-dioxabicyclo[3.3.1]non-7-en-6-one in high yield.

Selective oxidation of the furan nucleus in substrates possessing a 3,5-hexadienyl side chain enabled the synthesis of several 3,8,10-undecatriene-2,5-diones, whose thermal chemistry provided hydrindenone products *via* intramolecular Diels-Alder cyclization. The effect of enedione (dienophile) double bond geometry and substitution upon the *exo/endo* cyclization selectivity was examined.

The synthesis of macrocyclic polyketones was realized by oxidation of furan-containing macrocycles.[1] Thus, the cyclic tetramer obtained from the condensation of furan and acetone was oxidized by bromine in acetic acid or MCPBA to give *trans*- and *cis*-enedione-functionalized macrocycles. The cyclic furan-acetone hexamer was oxidized using MCPBA to the fully ring-opened dodecaketone derivative. A new furan macrocycle, 1,1,15,15-tetramethyl[1.3.1.3](2,5)-furanophane, was synthesized and then oxidized by MCPBA to the corresponding 24-membered macrocyclic octaketone.

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1. Williams, P.D.; LeGoff, E. J. Org. Chem. (1981) 46, 4143.

To my parents; without their love and support this work could never have begun,

and

to my wife, Theresa; without her love and companionship this work could never have been so happily ended.

ACKNOWLEGEMENT

It is with great pleasure that I acknowledge the guidance, support, and friendship of Professor Eugene LeGoff. His willingness to share chemical insight at both the blackboard and bench levels has made the art of chemical research infinitely more comprehensible, and the interest and support he has shown for me has made my experience as a graduate student infinitely more meaningful.

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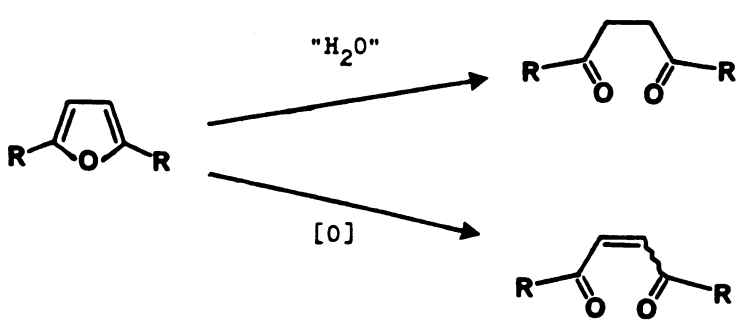
INTRODUCTION

The use of furan compounds in organic synthesis has been extensive.[1-3] Owing to the enol-like structure of furan, an important aspect of its chemistry has been concerned with transformations to 1,4-dicarbonyl compounds. As shown in Scheme 1, both hydrolytic and oxidative pathways are conceptually available, from which saturated and unsaturated 1,4-dicarbonyl products, respectively, may be obtained. Direct hydrolysis of the furan ring has

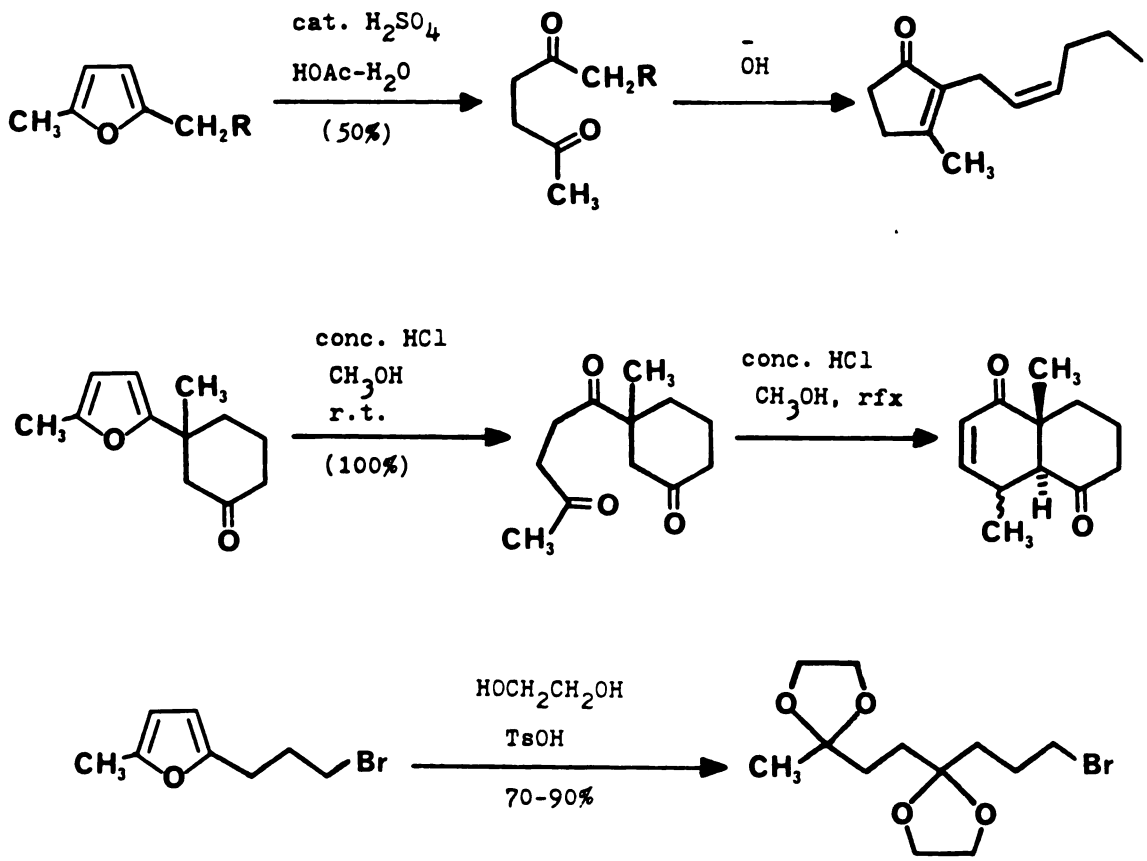
Scheme 1



met with varied success because of the limited stability of the product to the reaction conditions. In many cases, however, this method has been successfully applied. For example, the first two equations in Scheme 2 illustrate the use of furans as masked 1,4-diketones in annulation

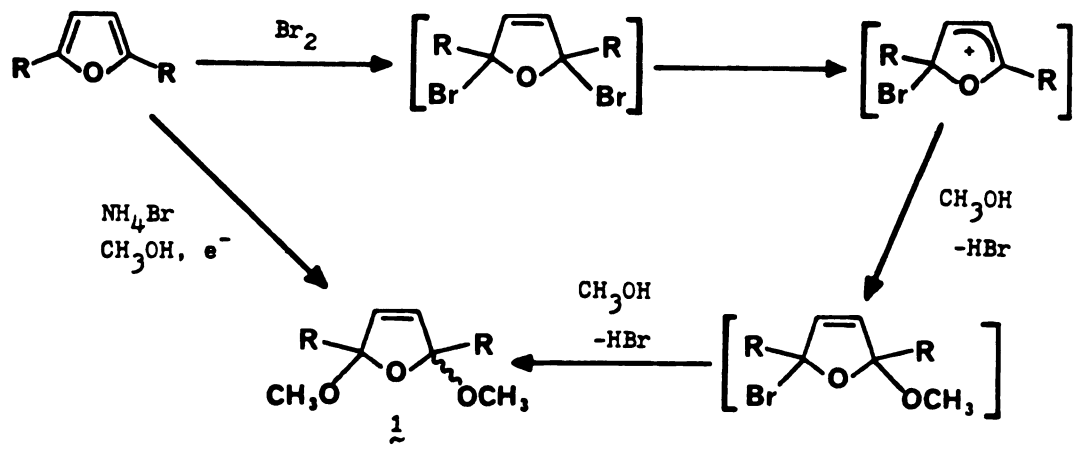
sequences.[3b,4,5] The third equation is an interesting example of a "glycolytic" method which produces the 1,4-diketone in protected form as a *bis*-ketal.[6]

Scheme 2



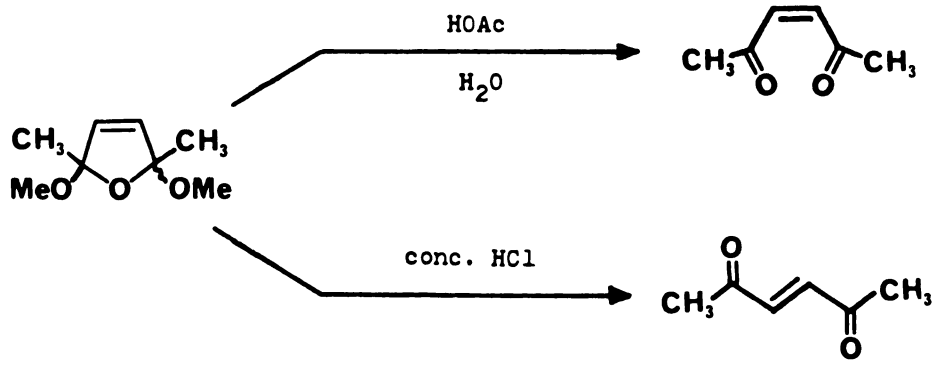
Perhaps the most widely employed method for the oxidation of furans is that of Clauson-Kaas,[1,7] in which the furan is treated with bromine in a buffered methanolic solution. The product 2,5-dimethoxy-2,5-dihydrofuran 1 (see Scheme 3) is thought to arise from 1,4 addition of bromine to the furan nucleus, followed by methanolysis. This transformation can also be accomplished electrochemically, and reviews of these two

Scheme 3

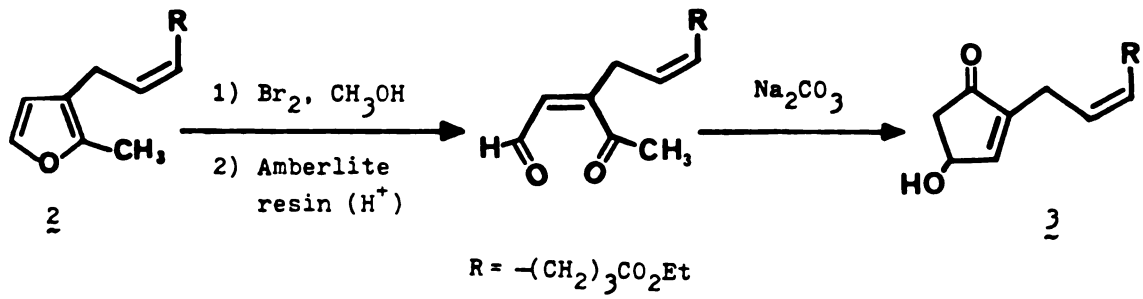


methods have appeared.[1,8] The oxidation products 1 serve as a convenient source of *cis*- and *trans*-enediones, depending on the conditions of hydrolysis (see Scheme 4).[9]

Scheme 4

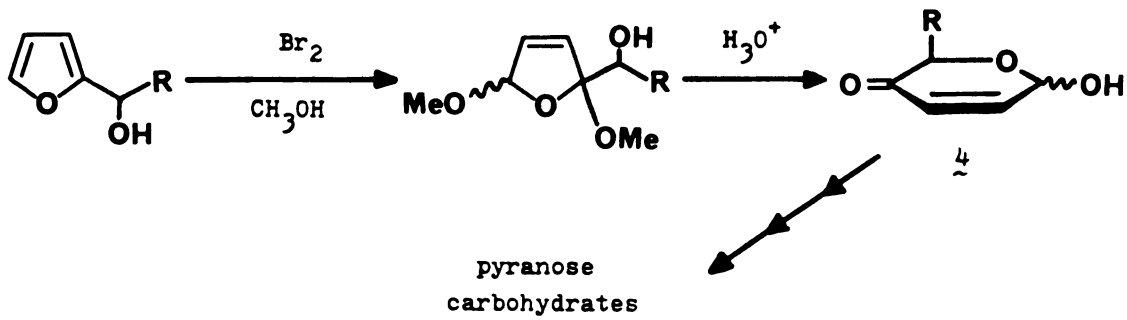


cis-Enediones have been employed in hydroxycyclopentenone annulation sequences[10] as illustrated by the transformation of furan 2 to the useful intermediate for prostaglandin synthesis, 3.[10a] Achmatowicz and associates have developed a very convenient entry to pyranose carbohydrates and higher-carbon sugars using a furan oxidation/hydrolysis



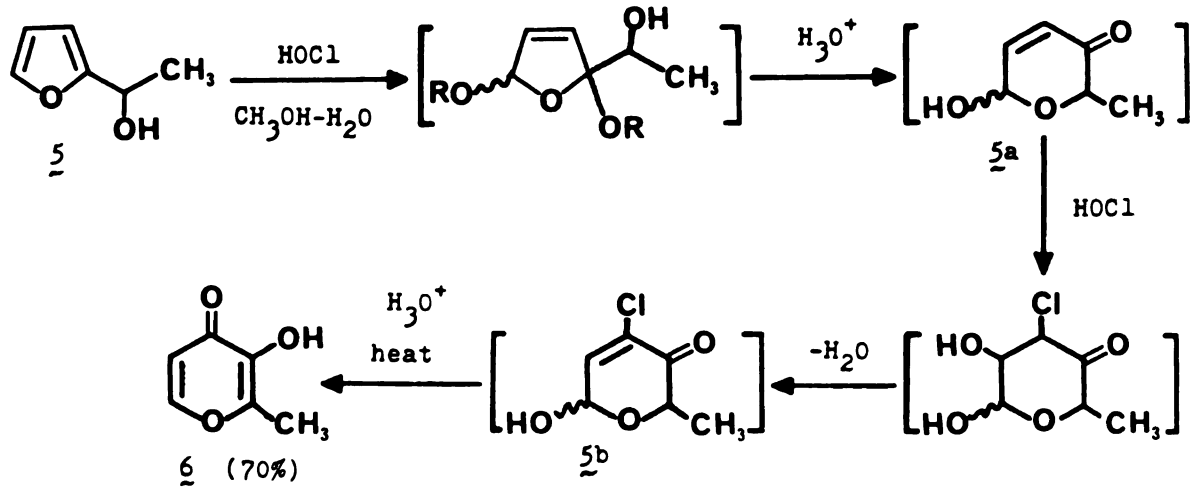
sequence.[11] The 2,5-dialkoxy-2,5-dihydrofurans derived from furfuryl alcohols give upon mild acid hydrolysis pyranone hemiacetals 4,[11a] which have been elaborated in a stereocontrolled manner to numerous sugar derivatives (see Scheme 5). Oxidation of furfuryl alcohols to γ-pyrones

Scheme 5



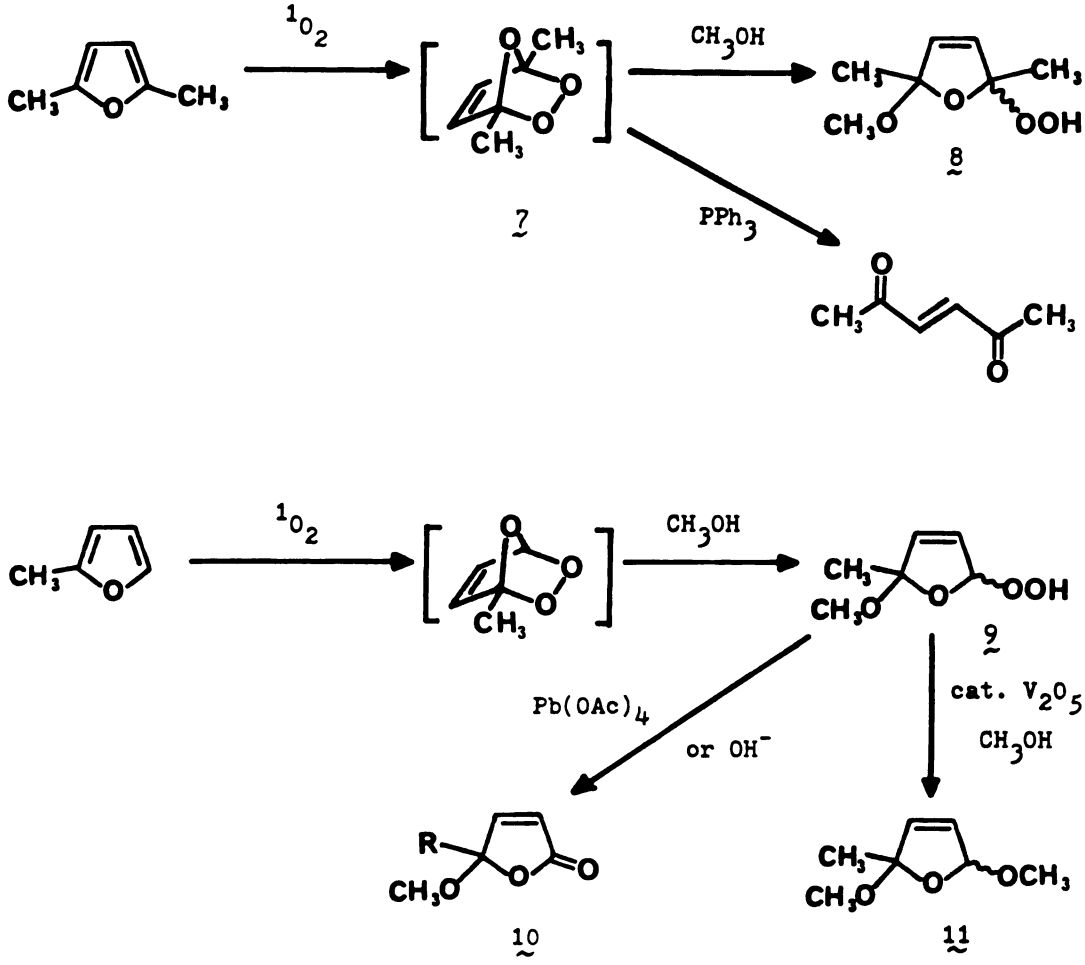
has also been reported.[12] Thus, an efficient, one-pot synthesis of maltol 6 was realized by the oxidation of 5 using two equivalents of aqueous chlorine (see Scheme 6).[12c] The first oxidation occurs on the furan ring to give, after *in situ* hydrolysis, pyranone hemiacetal 5a. Consumption of the remaining equivalent of hypohalous acid and dehydration gives chloro-enone 5b, from which maltol is obtained upon heating.

Scheme 6



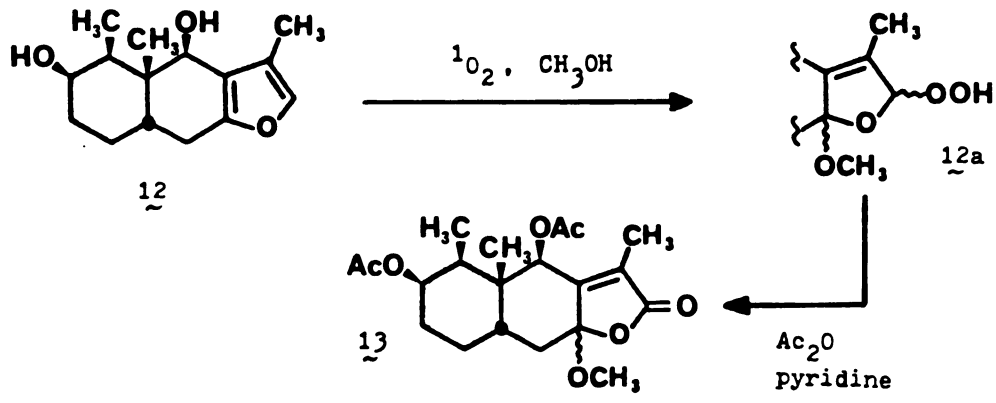
Another method for the oxidation of furans which has received considerable attention uses singlet oxygen. Thus, photochemically[13] or chemically[14] generated singlet oxygen adds to furans in a [4+2] cycloaddition process to give endoperoxides (*e.g.* 7, Scheme 7), the thermal and chemical transformations of which have provided a number of interesting products. For example, the endoperoxide derived from 2,5-dimethylfuran undergoes nucleophilic ring opening in methanol solution to hydroperoxide 8, and deoxygenation by triphenylphosphine to give *trans*-3-hexene-2,5-dione (see Scheme 7).[15] The endoperoxides of unsymmetrically substituted alkylfurans undergo regiospecific ring opening in alcoholic media as exemplified by hydroperoxide 9, which is derived from the endoperoxide of 2-methylfuran.[15a] Treatment of hydroperoxides which possess an α-hydrogen with base or lead tetraacetate gives γ-alkoxybutenolides such as 10.[16] Replacement of the hydroperoxy group to

Scheme 7



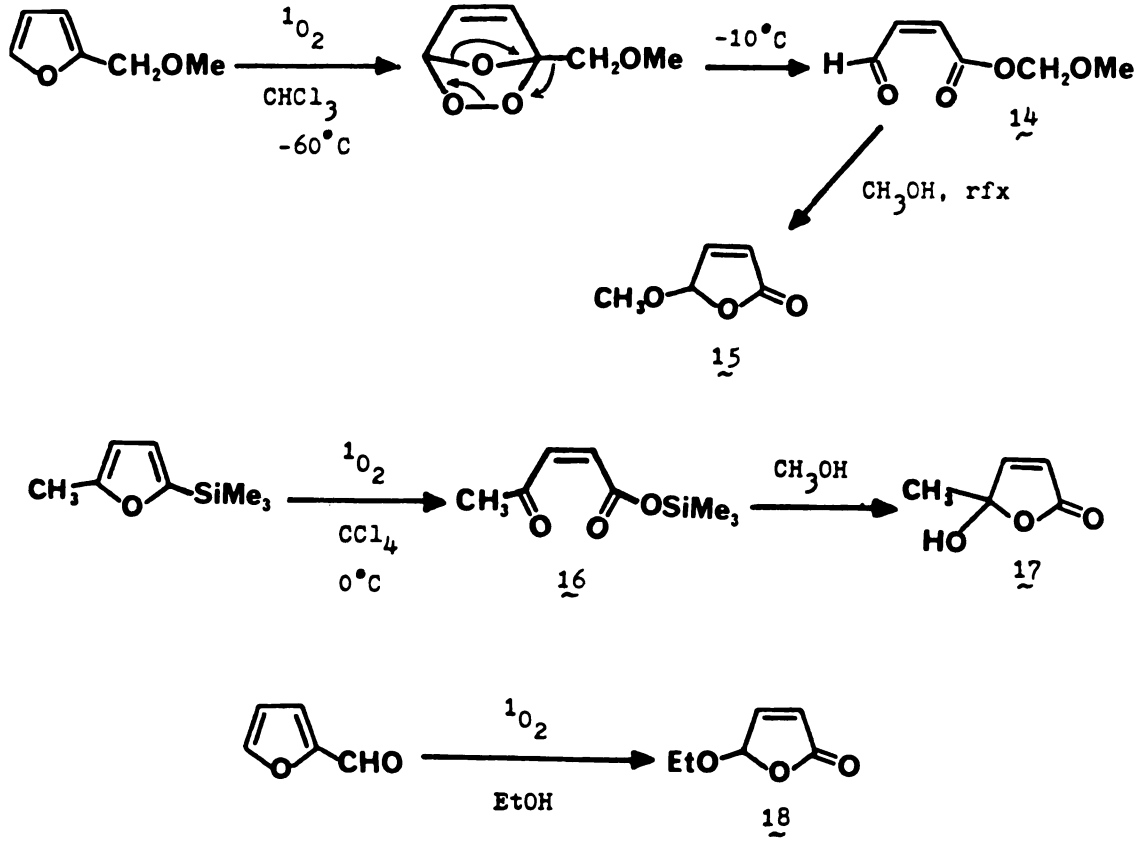
give Clauson-Kaas-type products (*e.g.*, 11) occurs readily in methanol solution containing catalytic quantities of vanadium pentoxide.[17] The former transformation has found application in the conversion of certain furanoeremophilanes to the corresponding butenolides (*e.g.*, 12 → 13).[18]

In certain cases, depending on the nature of the the substitutents on the furan ring, the endoperoxides undergo a Baeyer-Villiger-like rearrangement in non-nucleophilic solvents to give γ-oxo-α,β-unsaturated



esters (*e.g.*, 14 and 16, Scheme 8).[19] Butenolides 15 and 17

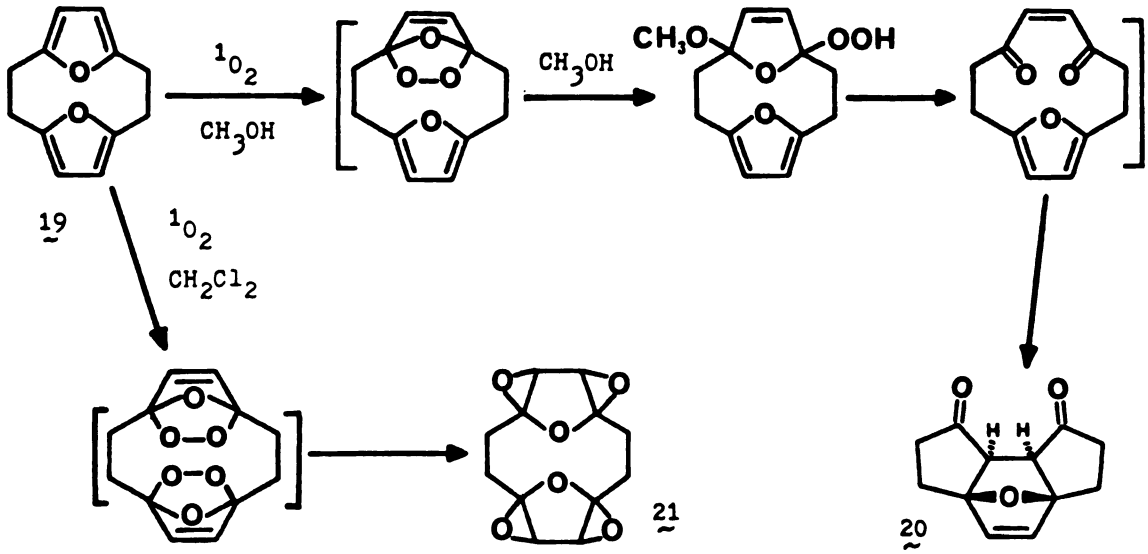
Scheme 8



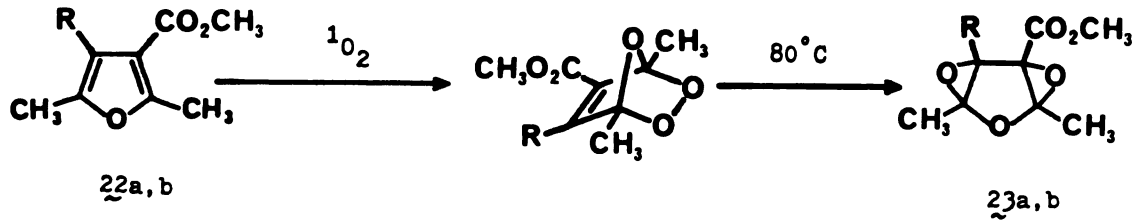
were formed upon exposure of the primary photoproducts to methanol. Analogous γ-alkoxybutenolides, *e.g.*, 18, can be obtained directly from the photosensitized

oxygenation of several furan derivatives in alcoholic solvents.[20] The reaction of furanocyclophane 19 with singlet oxygen was found to be solvent dependent (see Scheme 9). In methanol,[21a,b] polycyclic dione 20 was obtained (presumably *via* the intramolecular Diels-Alder

Scheme 9



pathway shown), whereas in methylene chloride,[21c] the *bis*-endoperoxide 19a rearranged thermally to give the novel tetra-epoxide 21. Analogous to this latter rearrangement, the endoperoxides derived from furans 22a and 22b undergo



22a,b

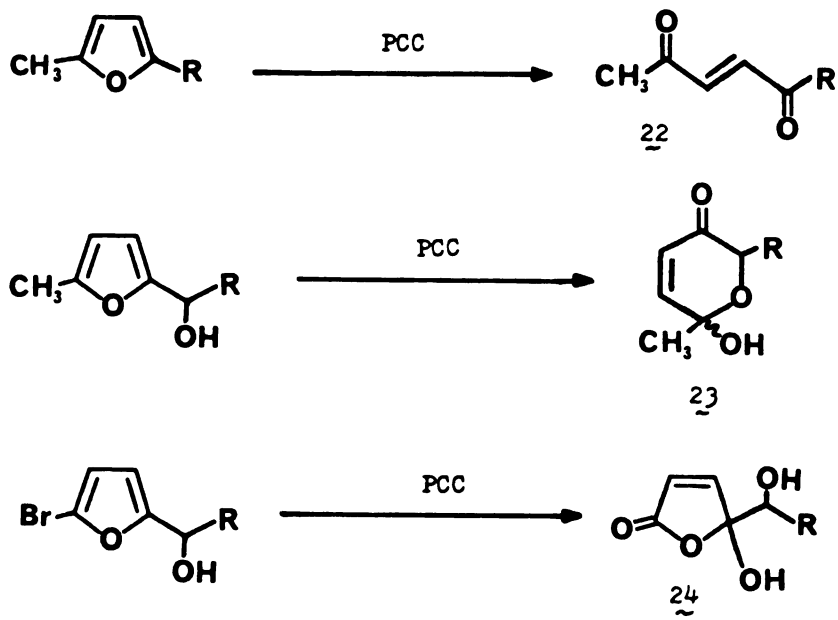
23a,b

a, R = H
b, R = CO_2CH_3

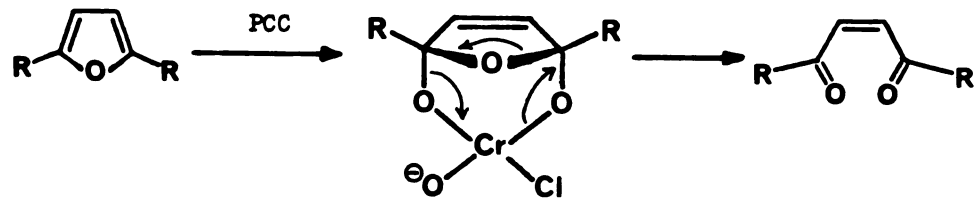
valence isomerization to the *bis*-epoxides 23a,b in high yield.[22]

Recently, the use of chromium(VI) reagents for furan oxidations has been investigated. Thus, as shown in Scheme 10, pyridinium chlorochromate (PCC) oxidizes 2,5-dialkylfurans to *trans*-enediones 22,[23a] 5-methyl-2-furyl-carbinols to pyranone hemiacetals 23,[23b] and 5-bromo-2-furyl-carbinols to hydroxybutenolides 24.[23c] These

Scheme 10



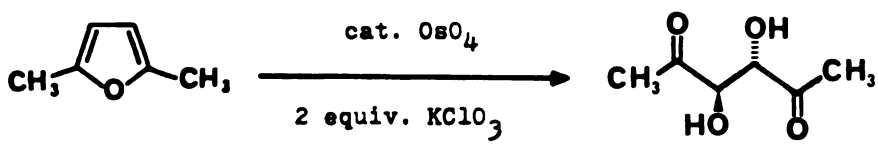
reactions are thought to proceed *via* 1,4-addition of the active Cr(VI) species to give a cyclic chromate ester such as 25. Heterolytic reorganization then affords a *cis*-enedicarbonyl compound which is subject to intramolecular capture in the case of 23 and 24, or isomerization in the case of 22. It is interesting to note that using



25

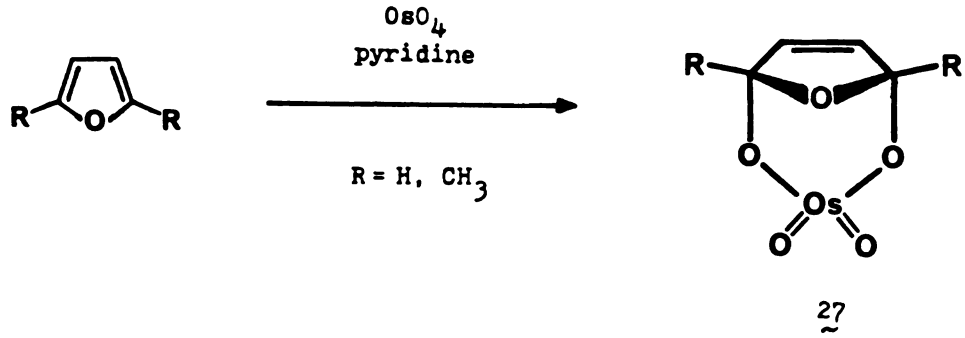
PCC supported on alumina, furfuryl alcohol was oxidized to furfural in high yield.[24] It is not known whether this difference in oxidation selectivity is a result of the modified reagent, or if there is a particular requirement within the substrate, *e.g.*, alkyl substitution, which facilitates ring cleavage.

Oxidation of furans with osmium tetroxide has recently been investigated using a catalytic procedure in which potassium chlorate is used to regenerate the oxidant. 2-5-Dimethylfuran was oxidized to the *meso* form of 3,4-dihydroxyhexane-2,5-dione 26,[25] in accordance with earlier findings by Clauson-Kaas.[26] The structure of



26

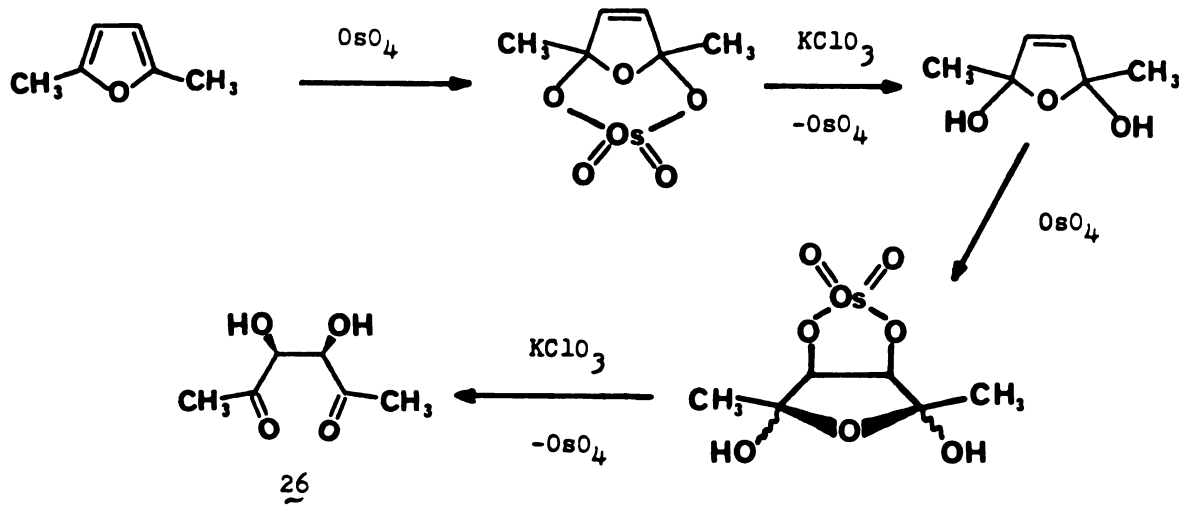
osmium tetroxide-furan adducts in pyridine solution have recently been elucidated by proton NMR.[27] These findings indicate that furan, 2-methylfuran, and 2,5-dimethylfuran form cyclic osmate esters 27, the result of 1,4-addition.



27

In pyridine, 2:1 osmium-furan adducts were not observed for these substrates. Thus, from these and other[28] observations, it is likely that the formation of *meso*-26 is the result of sequential oxidations by osmium tetroxide in which the second equivalent acts upon the double bond of dihydrofuran 26a (see Scheme 11).

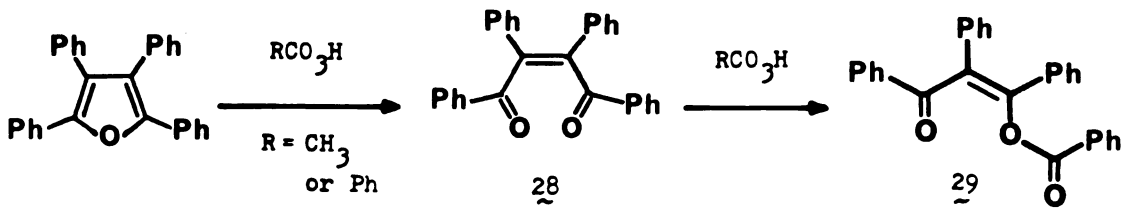
Scheme 11



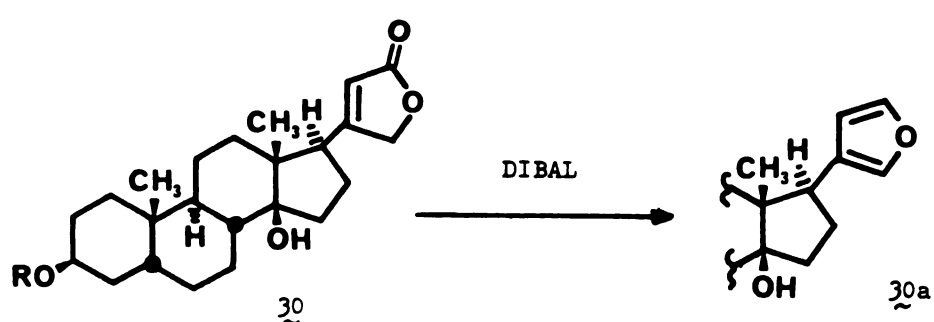
26

Until recently, the reactions of furans with peroxy-acids had not been extensively investigated. Clauson-Kaas

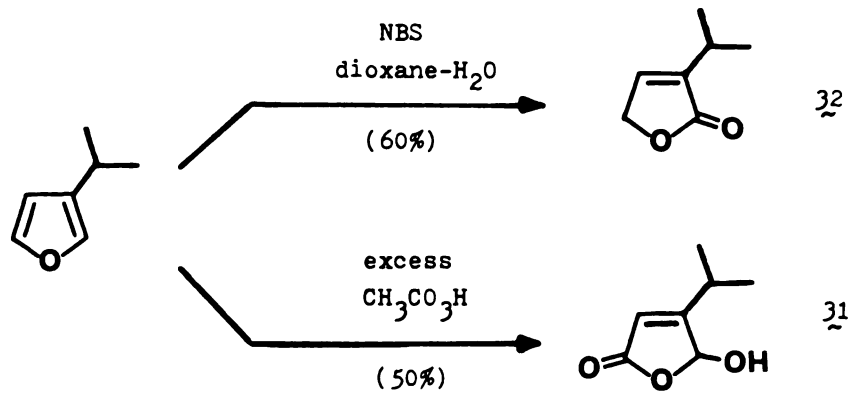
examined the oxidation of furan with peracetic and perbenzoic acids[29] and isolated the *bis*-phenylhydrazone of malealdehyde in yields never exceeding 20%. Other products from these reactions were not reported. In a series of papers, Lutz and co-workers studied oxidations of tetraarylfurans and noted unusual "*cis* effects" in *cis*-diaroylstilbenes. Tetraphenylfuran, for example, was reported to give *cis*-enedione 28 upon oxidation with



peracetic or perbenzoic acid (among other oxidizing agents).[30] Further oxidation of *cis*-28 (but not *trans*-28) gave enol benzoate 29. More recently, a Canadian research group at Ayerest has been interested in synthesizing new cardiotonic agents related to the cardenolide family of steroids (*e.g.*, digitoxigenin 30, R=H) in which the

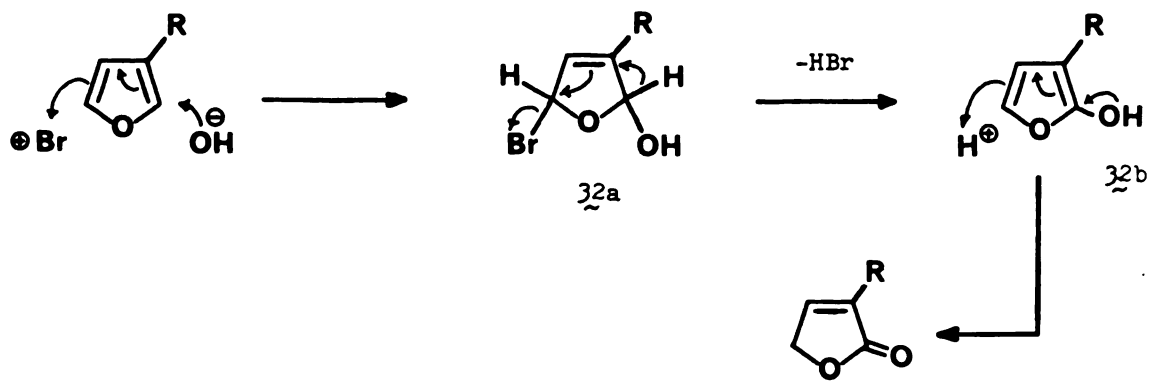


C_{17} butenolide moiety has been modified.[31] Their approach involved oxidation reactions of furyl steroid 30a. Oxidation of a model compound, 3-isopropylfuran,[31b] with peracetic acid gave hydroxybutenolide 31, whereas oxidation with aqueous N-bromosuccinimide (NBS) gave a different butenolide, 32. Analogous results were obtained with steroid 30a, although the peracid procedure gave a poor



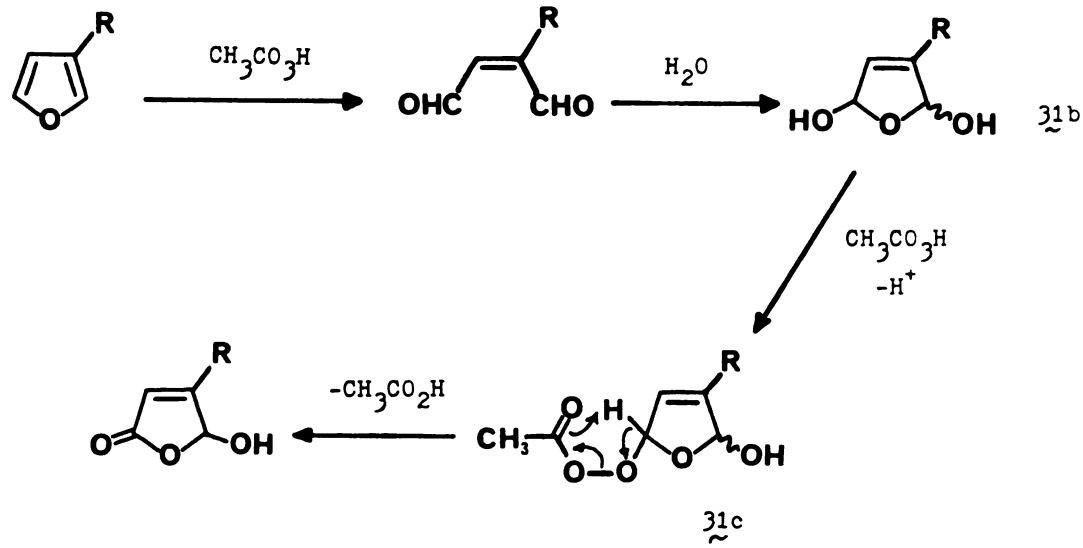
yield (16%). A mechanistic interpretation was not given for the peracid oxidation; however, comment was made on the NBS oxidation (see Scheme 12).[31a] Attack of electrophilic bromine at the less hindered C_5 α-position (and

Scheme 12



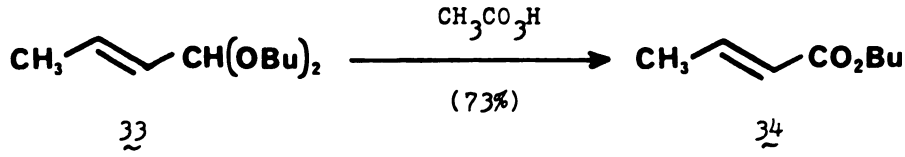
electronically less nucleophilic[32]) produces bromohydrin 32a, which loses HBr to give enol 32b. Protonation at the C_5 α-position produces the observed butenolide. A plausible mechanism for the peracetic acid oxidation is given in Scheme 13. As will become apparent from the

Scheme 13



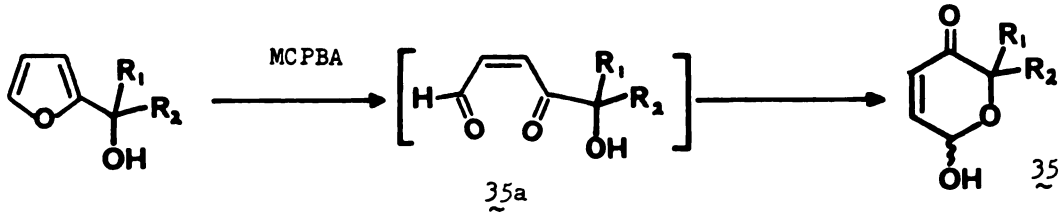
results in the first section of this thesis, the initial products from the peracid oxidation of furans are *cis*-enediones. Thus, it is likely that malealdehyde derivative 31a is an unstable intermediate which, under the aqueous acidic reaction conditions, can exist as hydrate 31b. Solvolysis at the less hindered and more electrophilic C_5 α-position using a second equivalent of peracid gives peroxyester 31c which can eliminate acetic acid as shown to provide the hydroxybutenolide product. The mechanism

of the second oxidation in this sequence finds analogy with a known procedure in which aldehyde acetals are oxidized to esters (*e.g.*, 33 → 34).[33] The Ayerest group



33 34

has also investigated the oxidation of furfuryl alcohols with *m*-chloroperoxybenzoic acid (MCPBA) and obtained pyranone hemiacetals 35 in good yield,[34] certain derivatives of which were found to possess significant antimicrobial activity.[34b] In these reactions, the intermediate



35a 35

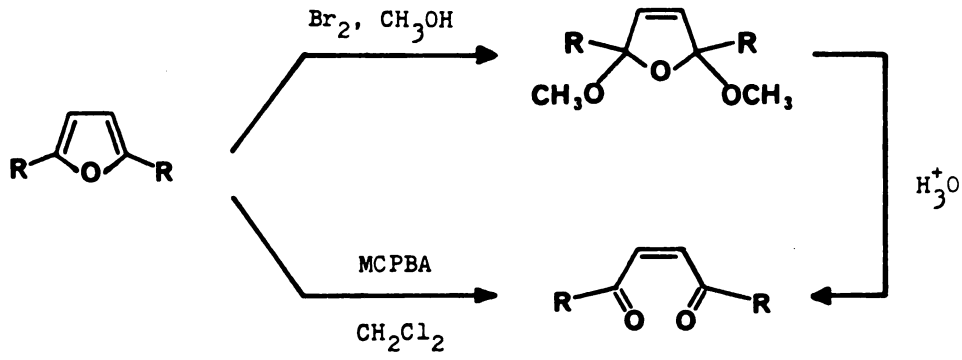
cis-enedione 35a undergoes rapid cyclization to give exclusively hemiacetal products.

In this thesis, the oxidation of alkylfurans with MCPBA is examined. In the first section, the scope of the reaction is explored using simple furan substrates and various reaction conditions. The subsequent sections deal with specific applications of furan oxidations which demonstrate the utility of this method in organic synthesis.

A. OXIDATION OF SIMPLE FURANS: GENERAL CONSIDERATIONS

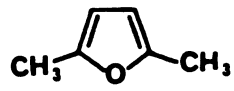
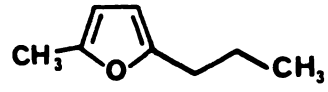
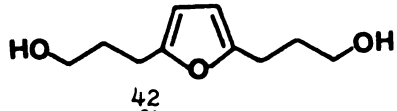
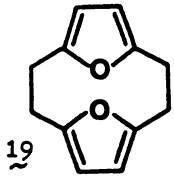
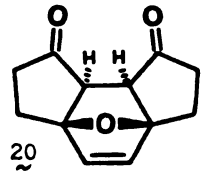
Although a number of methods have been developed for the oxidation of furan compounds, a direct, high yield route to geometrically pure *cis*-enediones from 2,5-dialkylfurans has not been reported.[35] The most commonly employed method for this transformation is a two-step procedure in which the furan is first oxidized to the 2,5-dialkoxy-2,5-dihydrofuran derivative and then hydrolyzed under mildly acidic conditions (see Scheme 14).[9,10,36] We have found that this transformation can be accomplished directly using *m*-chloroperoxybenzoic acid (hereafter abbreviated as MCPBA).

Scheme 14



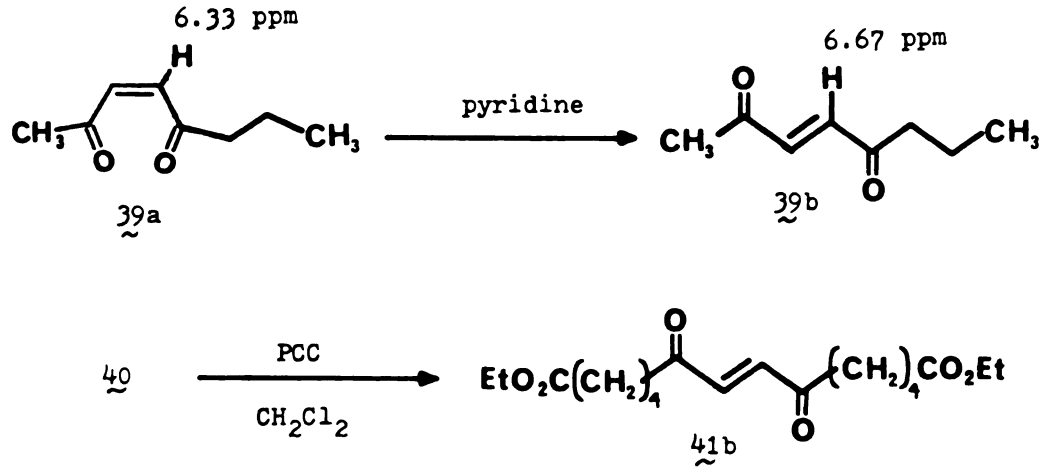
The reaction is simple, rapid, and provides exclusively *cis*-enediones in high yield. Examples are given in Table 1. In the first three entries, the *cis*-enedione double bond geometry was assigned on the basis of the upfield chemical shift of the olefinic protons (*ca.* 6.1-6.3 ppm). For

Table 1. Results from the oxidation of 2,5-dialkylfurans using MCPBA.

substrate	product	yield
 36	 37	99%
 38	 39a	96%
 40	 41a	97%
 42	 43	87%
 19	 20	88%

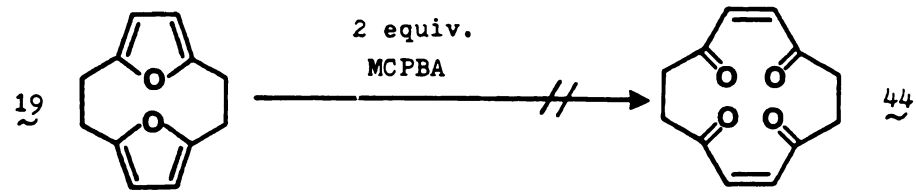
instance, the olefinic proton resonances of *cis*-3-hexene-2,5-dione (37) and its *trans* isomer fall at 6.18 and 6.72 ppm, respectively.[9b] Conclusive evidence for the *cis* configuration in 39a and 41a was obtained by preparation of their respective *trans* isomers. Thus, isomerization of 39a in pyridine (presumably *via* an addition-elimination mechanism in which the more thermodynamically stable *trans*

isomer dominates the equilibrium) gave 39b in nearly quantitative yield. Diester 40 was oxidized using pyridinium chlorochromate[23a] to the *trans*-enedione 41b in 60% yield.



Facile intramolecular ketalization occurs upon MCPBA oxidation of diol 42, giving *bis*-spiroketal 43 as a 1:1 mixture of diasteriomers.[37] No open chain products were observed. Furanocyclophane 19 was smoothly oxidized by one equivalent of MCPBA to give the intramolecular Diels-Alder adduct 20, identical in all respects with the physical properties reported by Wasserman[21a] and Katz[21b] (mp, ^1H and ^{13}C NMR, IR) for the product obtained upon photosensitized oxygenation of 19 in methanol (*cf.* Scheme 9). Attempts at preparation of the unsaturated tetraketone 44 from 19 using two equivalents of peracid failed, and gave instead low yields of an uncharacterized mixture.

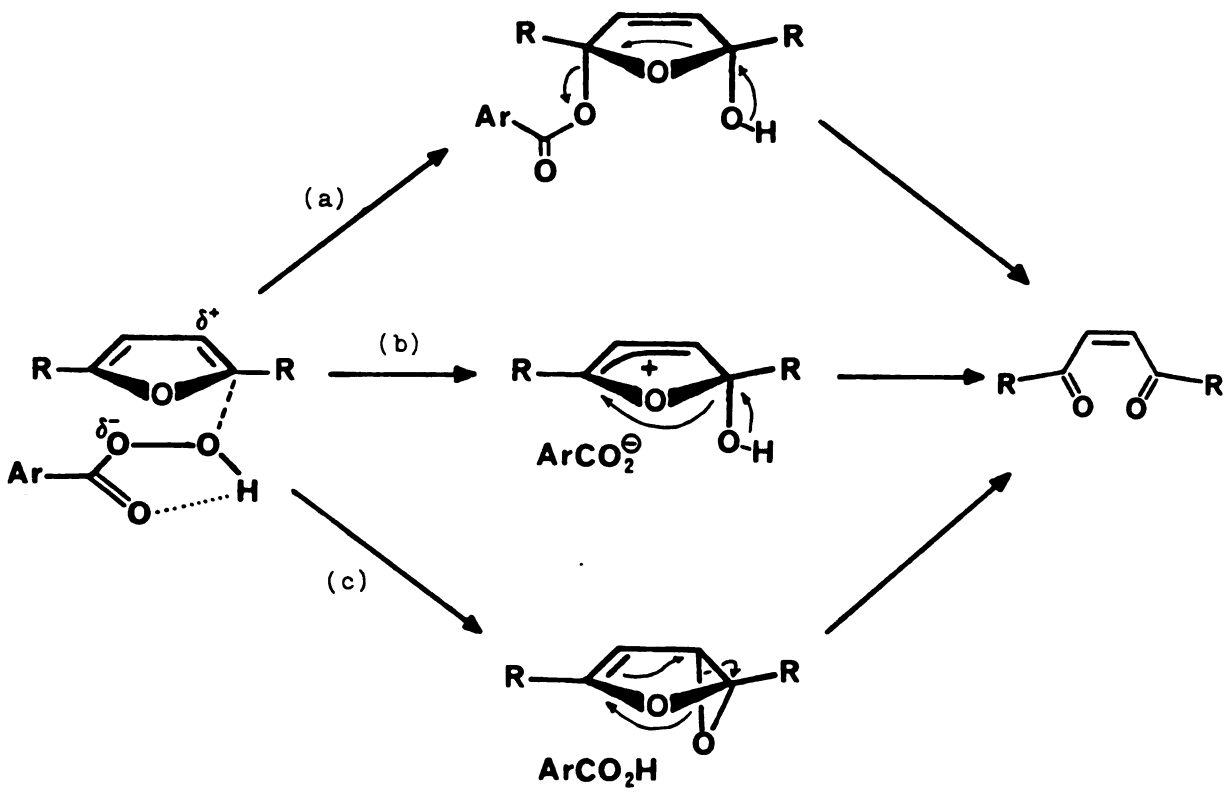
The mechanism of the MCPBA oxidation is thought to occur *via* initial attack of the electrophilic peracid



19 44

oxygen at an α-position on the furan ring as shown in Scheme 15. The precise electronic events which follow are not clear; possibilities are as follows. The

Scheme 15

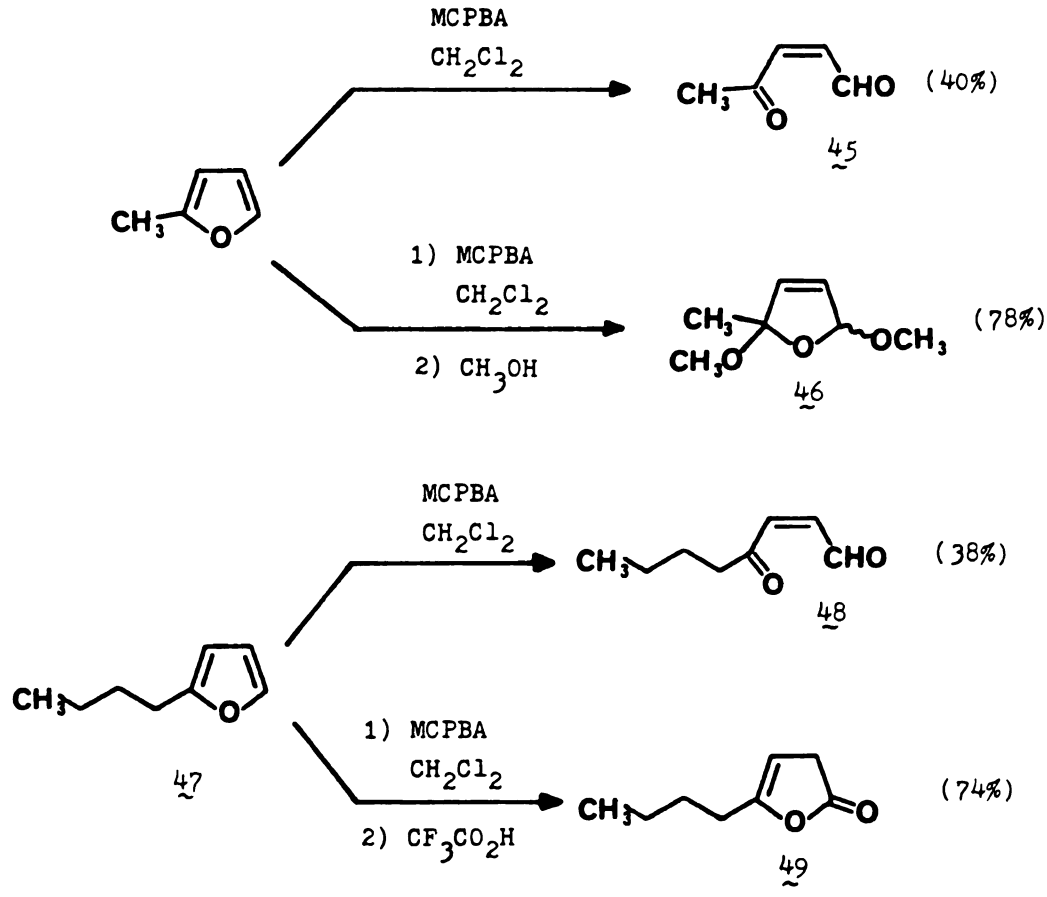


developing positive charge in the furan ring might be stabilized by the incipient carboxylate anion to the extent that 1,4-addition is achieved (path a). Alternatively, covalent attachment of the carboxylate may never occur, resulting in the formation of an ion pair (path b).

The peracid might function as in the oxidation of alkenes to give a furan epoxide (path c). While the studies performed here do not conclusively distinguish between these alternatives, it is clear that all of the intermediates in Scheme 15 can produce the observed *cis*-enedione product by the appropriate reorganization of electrons.

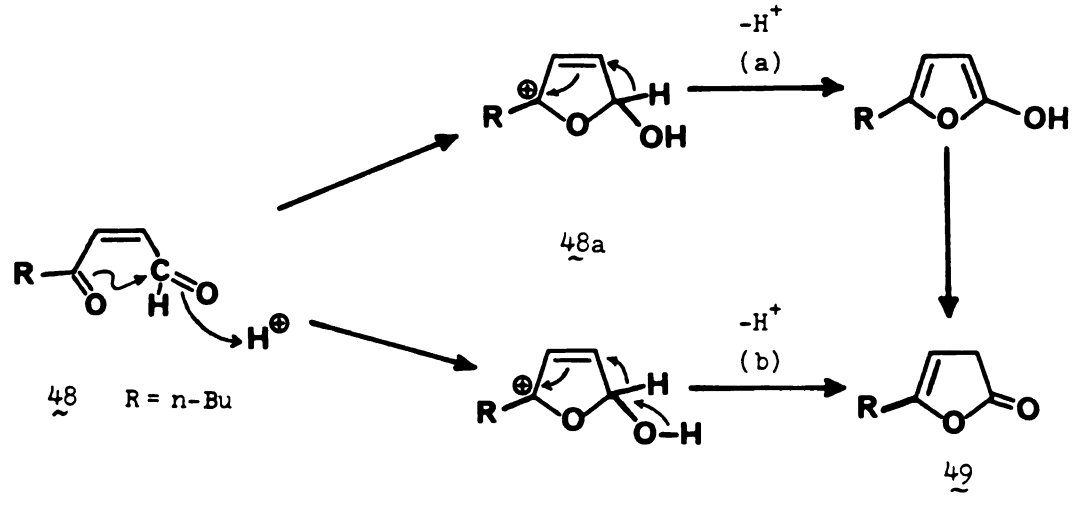
Oxidation of 2-substituted furans with MCPBA gave the anticipated *cis*-γ-oxo-α,β-unsaturated enals 45 and 48 (see Scheme 16), albeit in rather low yields. The *cis* olefin geometry was established by comparison of the proton NMR spectral data with literature values.[9b,36]

Scheme 16



Loss of product in these reactions had evidently occurred during the aqueous bicarbonate workup as concluded from the following observations. *cis*-Enal 45 could be "trapped" upon methanolic quench to give the ketalized derivative 46 in 78% isolated yield. The crude reaction mixture from the oxidation of 2-*n*-butylfuran (47) with MCPBA in chloroform-d_1 solution was examined by 250 MHz ^{1}H NMR and revealed the presence of *cis*-enal 48 and *m*-chlorobenzoic acid as the only products. Upon standing at room temperature for 24 hours, however, a second product began to appear at the expense of 48. This new product exhibited narrow multiplets at 5.11 and 3.18 ppm, in addition to butyl group resonances at higher field, data consistent with 2(3H)-furanone 49. Lactone formation is thought to occur *via* the protonated species 48a (see Scheme 17), which

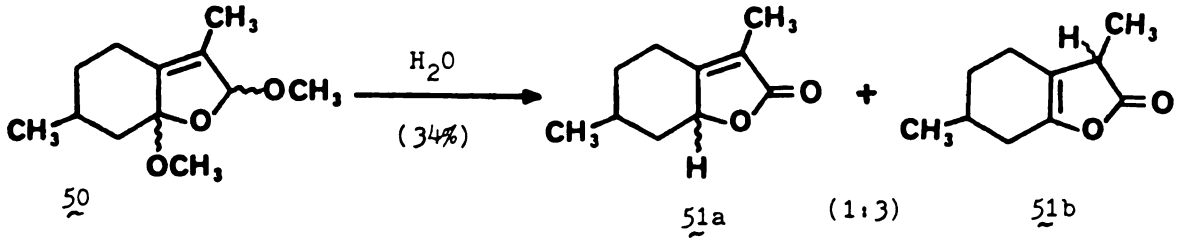
Scheme 17



can either lose a ring proton and tautomerize (path a), or undergo a 1,2-hydride shift with concomitant loss of

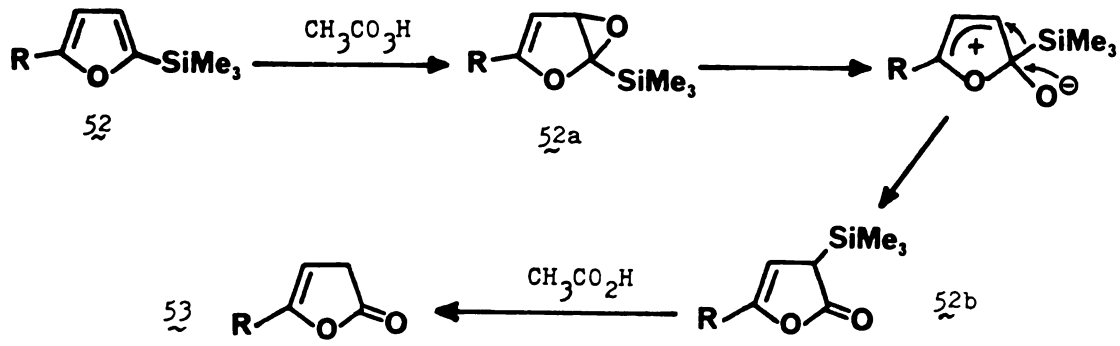
the OH proton (path b). The rate of butenolide formation was greatly enhanced by the addition of a catalytic amount of trifluoroacetic acid to the crude reaction mixture. Thus, in a one-pot procedure, 2-*n*-butylfuran was oxidized to β,γ-unsaturated butenolide 49 in 74% yield after flash column chromatography.

Lactonic products have been observed previously from the hydrolysis of 2,5-dialkoxy-2,5-dihydrofurans which are unsubstituted at one α-position.[9b,36,38] For instance, Hirsch and Eastman[38] were unable to isolate enedione products from the hydrolysis of 50, the Clauson-Kaas oxidation product of menthofuran. Instead there was



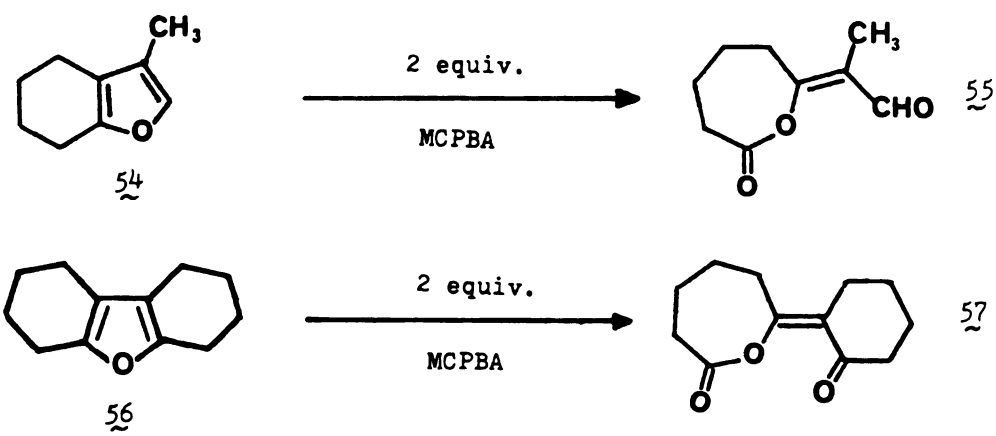
50 51a (1:3) 51b

obtained a 1:3 mixture of butenolides 51a and 51b, respectively, presumably *via* a mechanism similar to the one given in Scheme 17. Recently, it has been reported that 2-trimethylsilylfurans are oxidized by peracetic acid to β,γ-unsaturated lactones.[39] This is thought to occur *via* rearrangement of an intermediate silylepoxide 52a as shown below. Protiodesilation of the resulting α-trimethylsilyl lactone 52b under the mildly acidic conditions produces the observed product. This method does not seem to offer

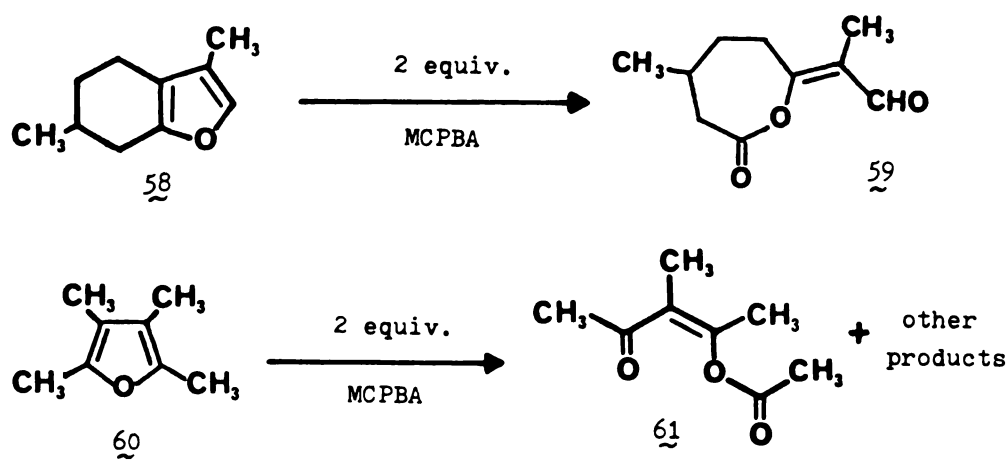


much advantage for the synthesis of butenolides 53 where R=alkyl, compared to the more direct method reported here. However, the use of trimethylsilylfurans 52 would appear to be useful when acid sensitive side chains are present. These authors also maintained that oxidation of 2-*n*-hexylfuran with MCPBA or peracetic acid gave intractable mixtures.[39]

Concurrent with the work in this thesis, the MCPBA oxidation of two more highly substituted furans was reported. Thus, tri- and tetrasubstituted furans 54 and 56 rapidly consumed two equivalents of MCPBA to give di-oxidized products 55 and 57, respectively.[40] The kinetics of these reactions are such that the products of



mono-oxidation could not be isolated; use of only one equivalent of MCPBA gave a 50:50 mixture of starting material and di-oxidized product. These findings are in agreement with the results obtained here using similarly substituted substrates. Thus, menthofuran (58), prepared by the method of Morel and Verkade,[41] gave enol lactone 59 in high yield. The *cis* arrangement about the enol double bond in 59 was not rigorously established,



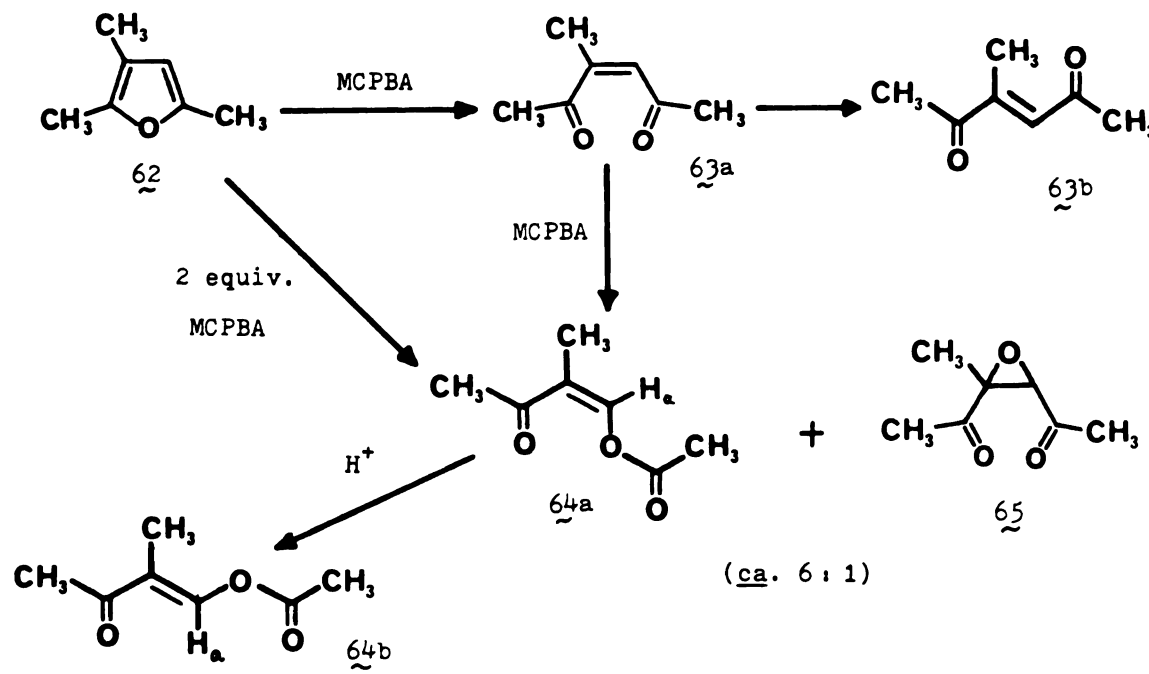
58 59 60 61

but was inferred on the basis of enol lactone 57, whose structure was established by single-crystal X-ray analysis,[40] and from the observations in subsequent oxidation experiments (*vide infra*). Tetramethylfuran (60), on the other hand, was not oxidized cleanly to only one product. Spectroscopic evidence (^{1}H and ^{13}C NMR, IR, MS) suggests that the major product from this reaction is enol acetate 61, although the inability to obtain this material in reasonably pure form precluded definitive characterization. As noted before, use of only one equivalent of MCPBA with

58 and 60 generated mixtures of starting material and di-oxidized products, indicating that the second equivalent of peracid is consumed more rapidly than the first.

As shown in Scheme 18, the kinetics of oxidation of 2,3,5-trimethylfuran (62) are such that *cis*-enedione 63a was obtained in nearly quantitative yield in the reaction with one equivalent of MCPBA. The *cis* configuration of 63a was confirmed by its partial isomerization to

Scheme 18

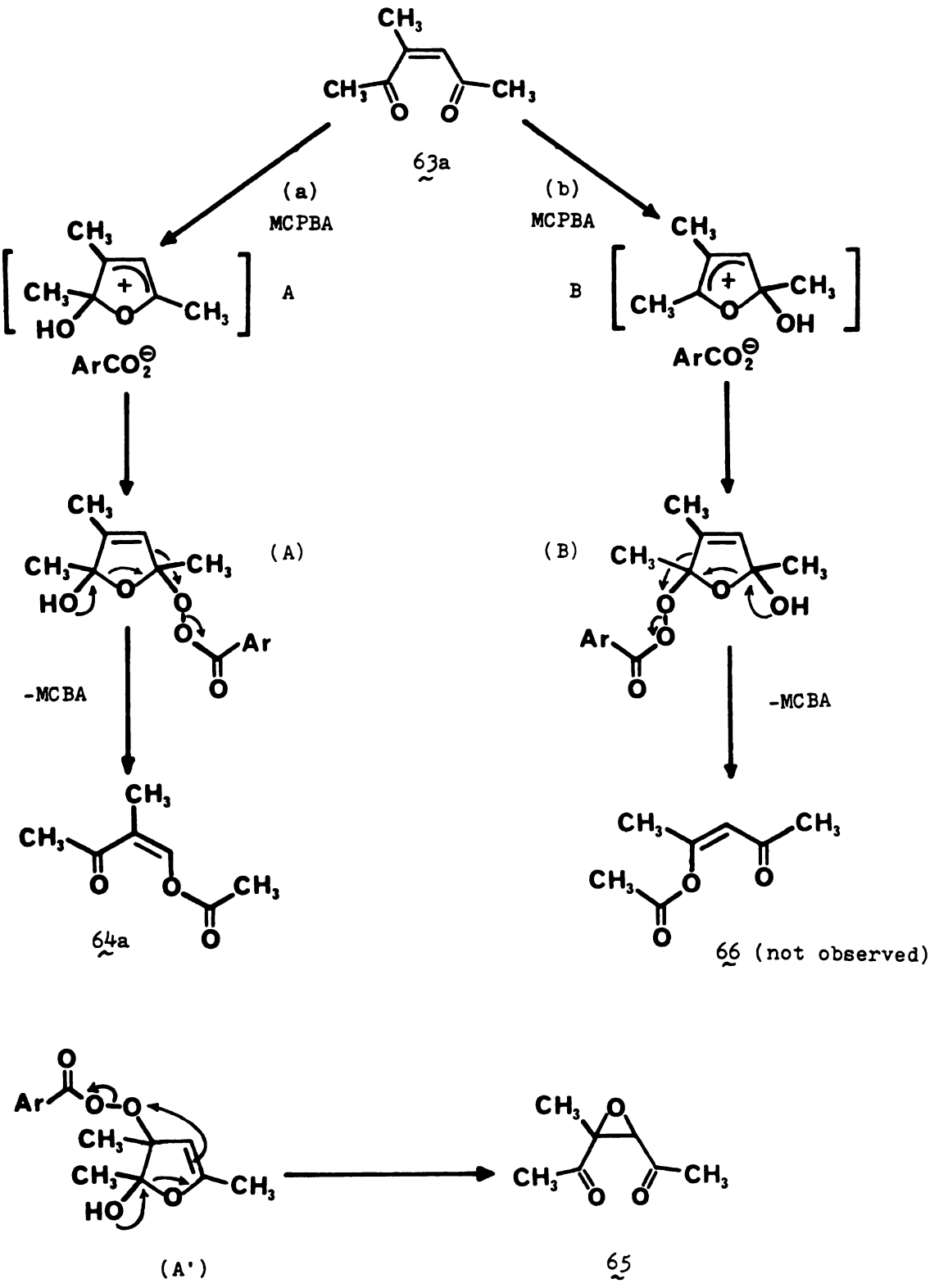


trans-enedione 63b after standing in $CDCl_3$ solution at room temperature for *ca.* 2 months. Using two equivalents of MCPBA, 62 was oxidized to enol acetate 64a and a minor amount of epoxyketone 65. The *cis* arrangement in 64a was demonstrated by acid-catalyzed equilibration, which gave 64a and its *trans* isomer 64b as a 1:1 mixture. These

isomers were distinguished on the basis of the chemical shift of vinyl proton H_a (7.71 and 8.24 ppm, respectively). The di-oxidized product mixture 64a/65 was also obtained upon oxidation of enedione 63a with one equivalent of MCPBA, thus implicating the intermediacy of enediones in the oxidation of substrates 54, 56, 58, and 60. This conclusion is supported by the observation that oxygen-labelled 56 gives enol lactone 57 having the label equally distributed between the ketone and lactone carbonyl oxygens.[42]

The second oxidation which occurs in the higher substituted substrates is thought to occur *via* a Baeyer-Villiger rearrangement. Also, because of the regiospecificity observed in the case of the unsymmetrical substrates 58 and 62, it is clear that peracid addition to the intermediate enedione must be subject to some sort of steric and/or electronic control. In Scheme 19, two possible peracid adducts A and B are shown. It is postulated that addition of the peracid to the intermediate enedione 63a is the rate-limiting step[43] with respect to the second oxidation process, and that the energy of the transition state for peracid addition is sensitive to electronic factors as depicted in the charge-separated transition states $A^{\ddagger}$ and $B^{\ddagger}$. Thus, path a in Scheme 19 is favored because of the increased electronic stability of the cation (protonated enedione) in transition state $A^{\ddagger}$ relative to the cation in transition state $B^{\ddagger}$. Notice, too,

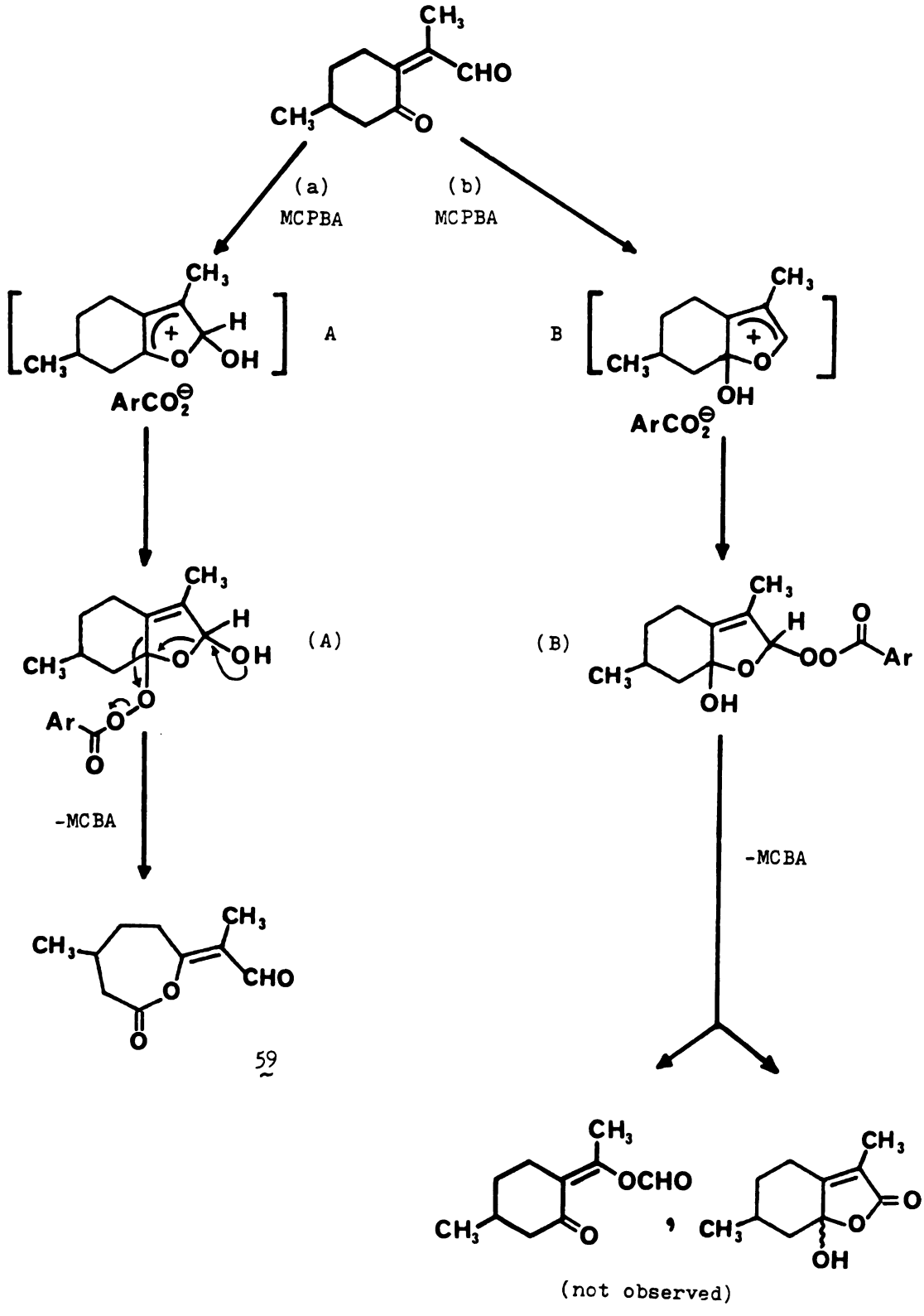
Scheme 19



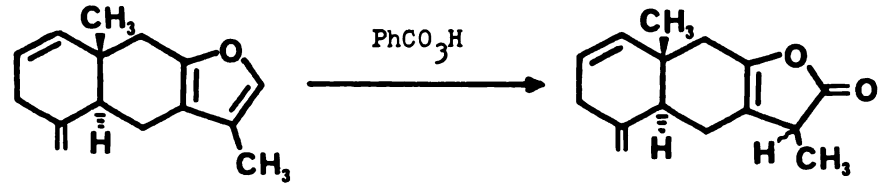
that the unfavorable eclipsing interaction of the vicinal methyl groups in $B^{\ddagger}$ is absent in $A^{\ddagger}$. Peroxyester A can then rearrange with preferential migration of the sp^2 carbon to the electron-deficient oxygen, thereby producing enol acetate 64a. Close examination of the 250 MHz ^1H NMR spectrum of crude 64a did not reveal the presence of the regioisomeric enol acetate 66,[44] which would have resulted from oxidation path b. The minor product, 65, might result from a Michael addition of the peracid to the intermediate enedione to give peroxyester A' (see Scheme 19). Displacement at the electrophilic oxygen center using the enol π bond would then produce the observed product.

That electronic effects dominate in the addition of the peracid to the intermediate enedione may readily be inferred from the oxidation of 58 (see Scheme 20). Thus, oxidation products derived from peroxyester B, the adduct which should be preferred on steric grounds, were not observed. Rather, the increased electronic stability associated with transition state $A^{\ddagger}$ lowers the energy of this pathway such that enol lactone 59 is the only observed product. This mode of addition might be likened to the regiospecific ring opening of unsymmetrical furan endoperoxides by methanol (*cf.* 12 → 12a in the Introduction).

Scheme 20



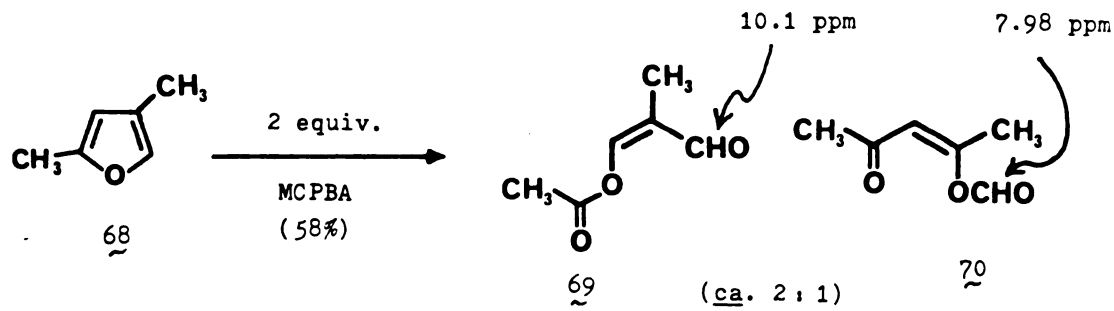
An interesting deviation from this reactivity pattern should be noted in the oxidation of lindestrene (66) to β,γ-unsaturated lactone 67 using perbenzoic acid.[45]



66 67

Evidently, this peracid is not effective at bringing about the facile Baeyer-Villiger oxidation as observed in the MCPBA oxidation of similarly substituted menthofuran (58). Although these authors had no comment on the oxidation, it is suggested here that lactone 67 is the result of a very facile acid-catalyzed rearrangement of an intermediate enedione as described previously in Scheme 17.

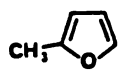
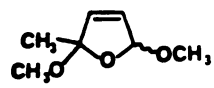
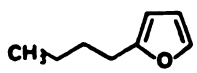
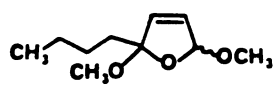
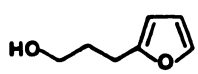
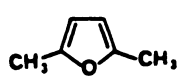
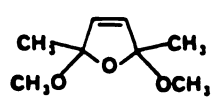
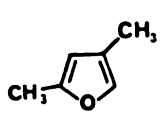
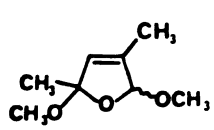
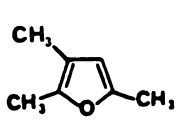
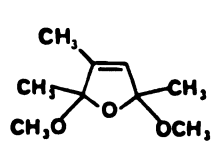
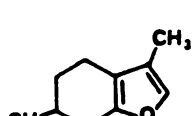
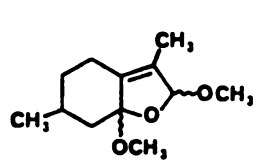
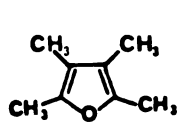
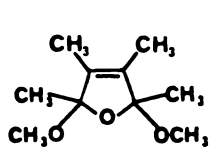
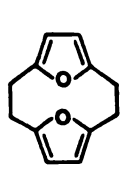
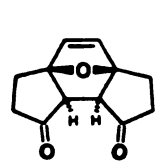
2,4-Dimethylfuran 68 was oxidized using one and two equivalents of MCPBA, and in both cases a rather complex product mixture was obtained in comparatively low isolated yield. From the reaction using two equivalents of peracid, the major products appeared to be enol acetate 69 and enol formate 70 by ^{1}H NMR analysis of the crude mixture. These results indicate that the Baeyer-Villiger oxidation had not occurred with the regiospecificity observed earlier. Separation of this reaction mixture was not attempted, so the structural assignments should be considered tentative. The reaction mixture obtained using one equivalent of



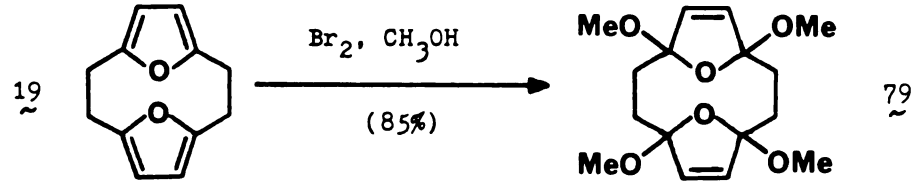
MCPBA proved even more complex as evidenced by ^{1}H NMR; in addition to a multitude of other products (*e.g.*, the proton-decoupled ^{13}C NMR spectrum of this mixture exhibited in excess of 70 signals!), varying amounts of the apparently di-oxidized 69 were detected, indicating that a second oxidation must proceed at a comparable rate. In contrast, 2,5-dimethylfuran (36) did not undergo a second, Baeyer-Villiger oxidation in the presence of excess peracid, even when more forcing conditions were used (*e.g.*, heating and/or addition of acid catalysts). These experiments demonstrate the sensitivity of the reaction to differences in furan substitution, a factor which seems to play a major role in determining the mode, regioselectivity, and velocity of oxidation.

The oxidation of furans using MCPBA in methanol was also examined. As can be seen from the results in Table 2, all of the substrates tested, with the exception of 19, underwent smooth oxidation to give 2,5-dimethoxy-2,5-dihydrofuran derivatives. Further oxidation did not occur

Table 2. Oxidation of furans by MCPBA in methanol.

substrate	product	yield
	46 	95%
 47	73 	92%
 71	72 	82%
 36	74 	97%
 68	75 	89%
 62	76 	90%
 58	77 	94%
 60	78 	93%
 19	20 	90%

in the more highly substituted furans as observed previously in methylene chloride. The formation of intramolecular Diels-Alder adduct 20 from furanocyclophane 19 is noteworthy, as oxidation using the methanolic bromine method provided the expected methoxylated product 79 in 85% yield.[46] These observations suggest that in



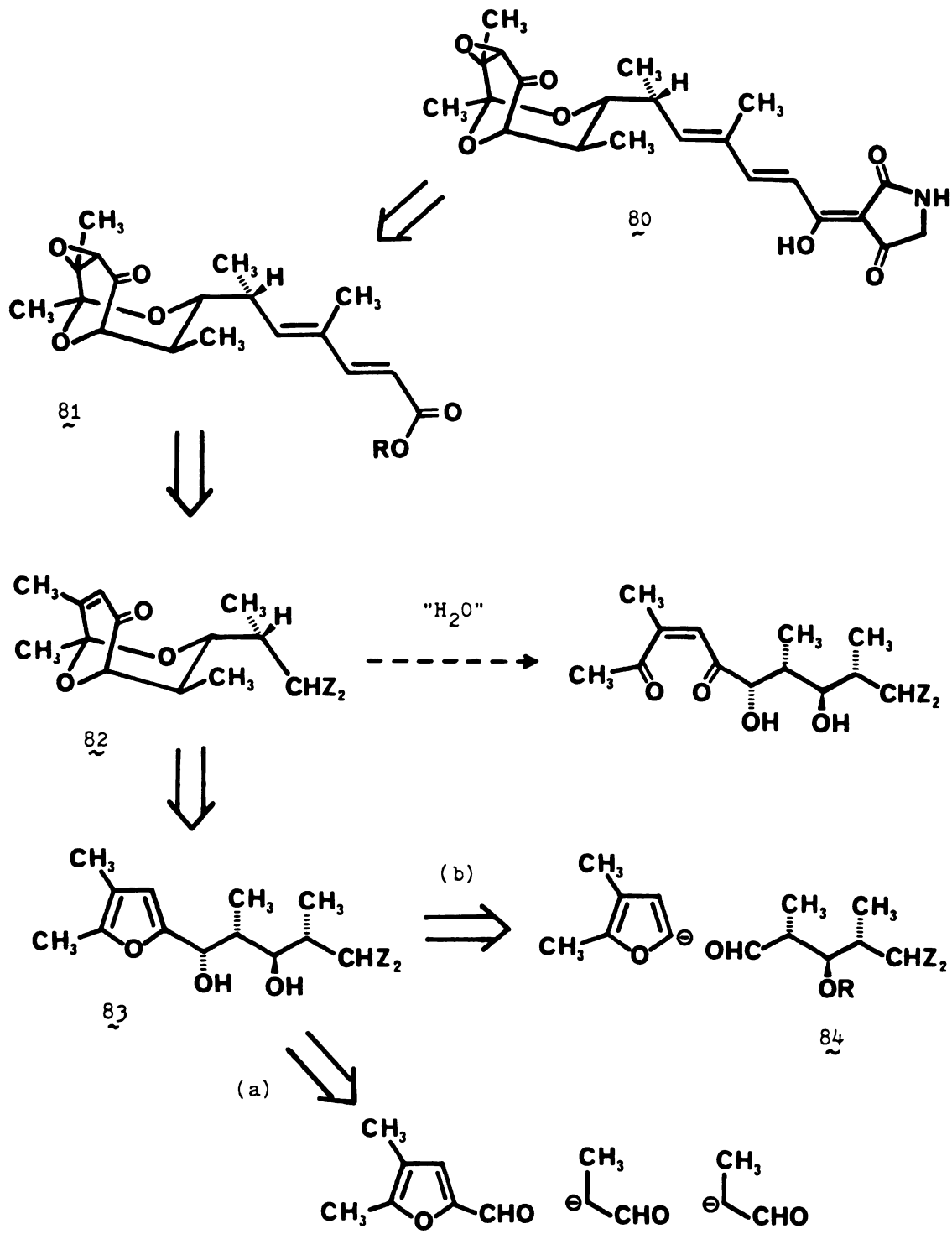
the MCPBA-CH_3OH oxidations, the immediate precursor to the 2,5-dimethoxy-2,5-dihydrofuran product is a *cis*-enedione. In the case of 19, intramolecular Diels-Alder reaction occurs faster than ketalization. This interpretation is supported by the result that *cis*-3-hexene-2,5-dione (37) gives 2,5-dimethyl-2,5-dimethoxy-2,5-dihydrofuran (72) in nearly quantitative yield when treated with *m*-chlorobenzoic acid in methanol. The MCPBA-CH_3OH oxidation method seems to be of synthetic importance in view of the poor yields obtained from the oxidation of the more highly substituted furans (*e.g.*, tetramethylfuran, 77) using methanolic bromine.[9a]

B. TIRANDAMYCIN MODEL STUDY

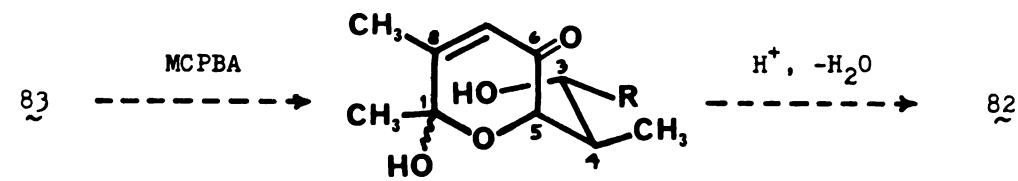
The occurrence of a 2,9-dioxabicyclo[3.3.1]nonane ring system in the antibiotic tirandamycin (80),[47] presents an excellent opportunity to employ furan oxidation methodology (see Retrosynthetic Scheme 1). Tirandamycin belongs to the 3-acyl tetramic acid family of antibiotics and displays, in addition to antibiotic activity, inhibitory activity against bacterial DNA-directed RNA polymerase.[48] This latter activity contrasts sharply with that of the simpler 3-acyl tetramic acids, and it has been suggested that the presence of the 2,9-dioxabicyclo[3.3.1]nonane moiety in 80 might be responsible for the additional activity.[49]

Recently, tirandamycic acid (81, R=H), a degradation product of tirandamycin, has been synthesized in optically active form by Ireland and co-workers.[50] The bicyclic portion of 81 was constructed in a multistep sequence starting from a glycal derived from D-glucose, and the dienoate side chain was subsequently elaborated by consecutive Wittig condensations from enone aldehyde 82 (Z_2=O). Importantly, the Ireland synthesis established that base-catalyzed epoxidation of the bicyclic enone proceeds in a selective fashion to give the desired epoxyketone diasteriomer. The latter stages of the synthetic plan depicted in Retrosynthetic Scheme 1 thus parallel the Ireland approach.

Retrosynthetic Scheme 1



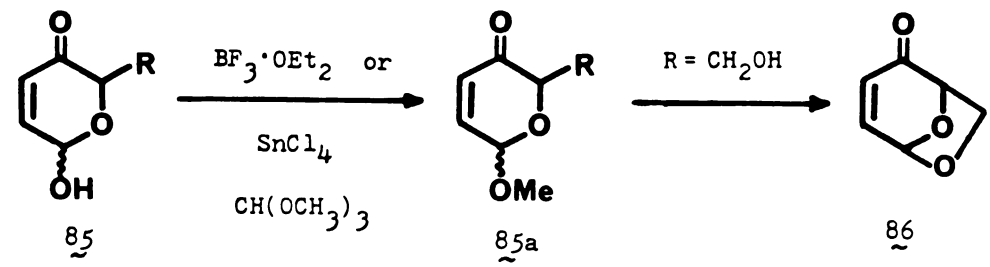
The formal hydrolysis product of 82, however, reveals the presence of an enedione moiety and thus suggests the furan precursor, 83. It is known through the work of Lefebvre,[34a] Achmatowicz,[11a] and Piancatelli[23a] that furfuryl alcohols upon oxidation yield pyranone hemiacetals (*i.e.*, cyclization of an intermediate hydroxyenedione occurs spontaneously) and thus it is anticipated that MCPBA oxidation of furan 83 would provide pyranone 82a.



82a

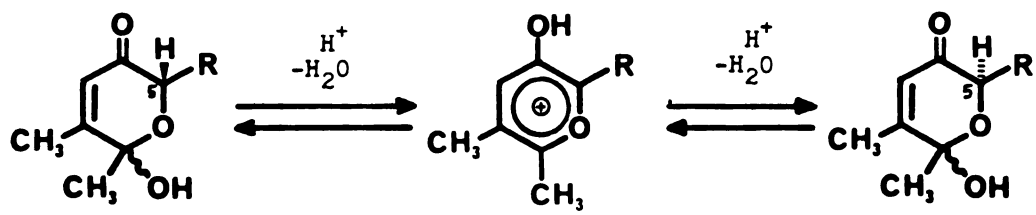
Participation of the C_3 hydroxyl, then, in an acid (or Lewis acid) catalyzed closure at C_1 would produce the bicyclic enone 82. Electronic considerations for the moment notwithstanding, closure at C_1 should be facilitated from a conformational standpoint, as the substituents at C_3 and C_4 would occupy pseudo-equatorial positions in the transition state leading to the desired dioxane ring formation. Other modes of ring closure, *i.e.*, Michael addition at C_8 or hemiketal formation at C_6, might be competitive, especially when one considers the electronic consequences of carbonium ion formation at C_1 relative to C_8 and C_6 of the enone moiety. In this regard, it should be noted that Achmatowicz and co-workers[11a] have been successful in the preparation of methyl glycosides 6a

from the corresponding pyranosuloses 85. The above-mentioned problems, however, were encountered to varying degrees when other more standard glycosidation methods were employed. Noteworthy to this discussion, too, is the



85 85a 86

intramolecular cyclization observed for substrate 85 (R=CH_2OH) to bicyclic enone 86 (*ca.* 25% yield) under the indicated reaction conditions. Finally, there exists the possibility that the acidic conditions required for ring closure might induce epimerization at C_5 *via* pyrylium salt 87.[51]



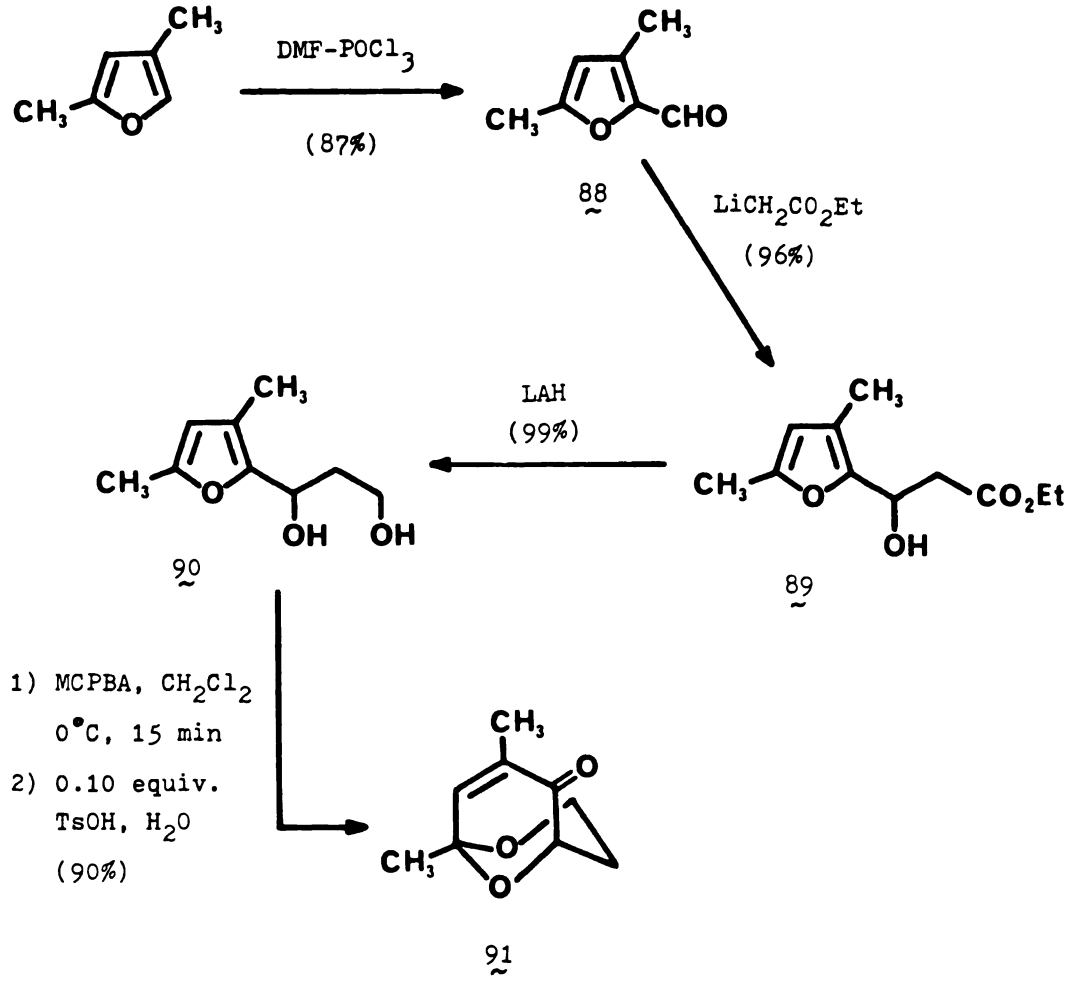
87

The oxygenated side chain of furan 83 in Retrosynthetic Scheme 1 might be constructed by either of two pathways. The more linear route depicted in path a utilizes a sequential, stereoselective aldol approach, an area in which there has recently been great progress.[52]

The desired stereochemistry in 83 requires that the first condensation between the furyl aldehyde and propanal enolate equivalent proceeds with *erythro* selectivity,[53] and that the second propanal enolate equivalent must add in a Cram's rule sense (chelation controlled) with *threo* selectivity.[53] An added feature of path A is that optically active 83 might be prepared using the recently devised chiral enolate methodology of Evans[54] or Masamune.[55] Path b, the more convergent approach, necessitates a Cram's rule addition (steric) of an α-metallated furan to (optically active) aldehyde 84.

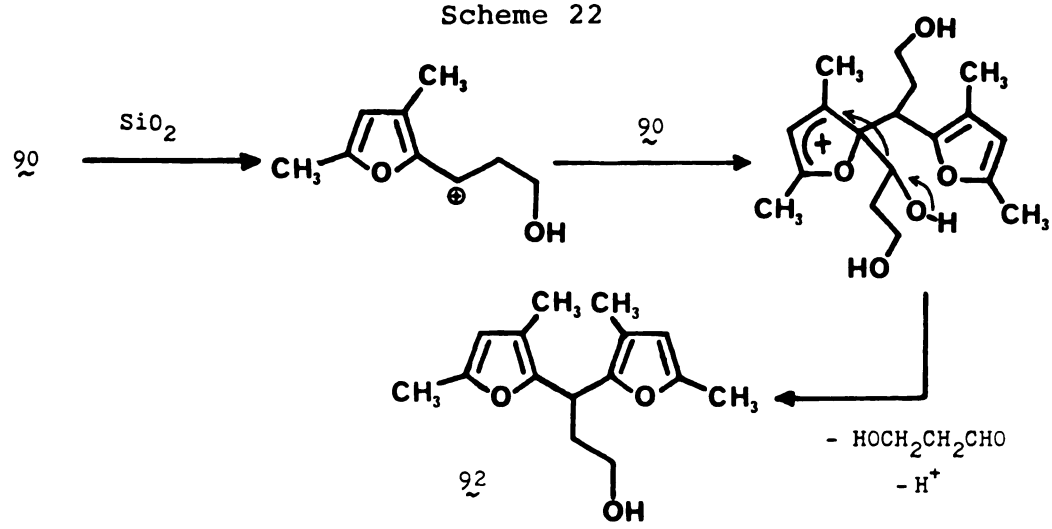
With an approach to tirandamycin as described above, one which differs significantly from the Ireland strategy in the method for construction of the 2,9-dioxabicyclo-[3.3.1]nonane portion of the molecule, a model system was sought in order to assess the feasibility of a furan oxidation approach. 3,5-Dimethylfuran-2-carboxaldehyde 88 (see Scheme 21) was already available from previous work, and can be prepared in multigram quantities by Vilsmeier-Haak formylation of 2,4-dimethylfuran. Condensation of the lithium enolate of ethyl acetate, prepared by deprotonation using lithium diisopropylamide, with aldehyde 88 at -78°C provided aldol 89 in excellent yield. Used directly in the next step, crude 89 was reduced by lithium aluminum hydride to diol 90 in nearly quantitative yield. From its NMR spectra, crude 90

Scheme 21



appeared to be at least 95% pure and gave only one spot on TLC. Additionally, Diol 90, proved to be quite sensitive to acidic conditions and decomposed when subjected to flash column chromatography. The major decomposition product thus obtained was identified as 92 from its spectral properties. A likely mechanism for the formation of 92 is given in Scheme 22. Although well known in pyrrole chemistry for the formation of dipyrrylmethanes,[56]

Scheme 22



it is only recently that this type of self-condensation has been reported using furan compounds.[57]

It was realized from the outset that the methyl substitution in model compound 90 is incorrect; tirandamycin requires a 4,5-dimethyl substitition pattern on the furan ring. However, because of the ease with which certain trisubstituted furans undergo a second, more rapid Baeyer-Villiger oxidation,[40] it was at this stage deemed more important to determine the effect, if any, of trisubstitution *per se* on the course of the peracid oxidation.

Initial attempts at oxidation of 90 (1.1 equiv. MCPBA, CH_2Cl_2, 0°C → RT) in which the reaction was worked up after relatively short time periods (1-2 h) were discouraging in that low yields of complex product mixtures were obtained. However, when the reaction progress was monitored by TLC (SiO_2, ether), it was found that within

10 minutes after addition of the peracid, all of the starting material had been consumed and converted to a single, less polar product. After 1-2 hours, when the reaction mixture had warmed to room temperature, TLC analysis indicated the presence of several less polar intermediates. After stirring at room temperature overnight, virtually all of these intermediates had disappeared, leaving only one UV-active component at high R_f. The reaction progress could also be conveniently monitored by ^1H NMR, and the spectra of the product mixtures which resulted after reaction times of 15 minutes, 2 hours, and 12 hours are shown in Figures 1, 2, and 3, respectively. The spectrum in Figure 1, during which time there was observed only one spot by TLC, is consistent with the anticipated pyranone hemiketal 93 (see Scheme 23). It is suggested that the occurrence of 93 as only one diasteriomer (inferred from ^1H NMR and TLC) is due to an anomeric effect described by Achmatowicz and co-workers in their studies of related pyranosulose systems;[11a] hence 93 is tentatively formulated here as the α anomer. The spectrum in Figure 2 exhibits a plethora of methyl group resonances at high field, as well as regions of uninterpretable overlapping multiplets in the alkene and alcohol α-CH regions. To account for this complexity, one might assume that pyranone hemiacetal 93 after standing at room temperature in the presence of the

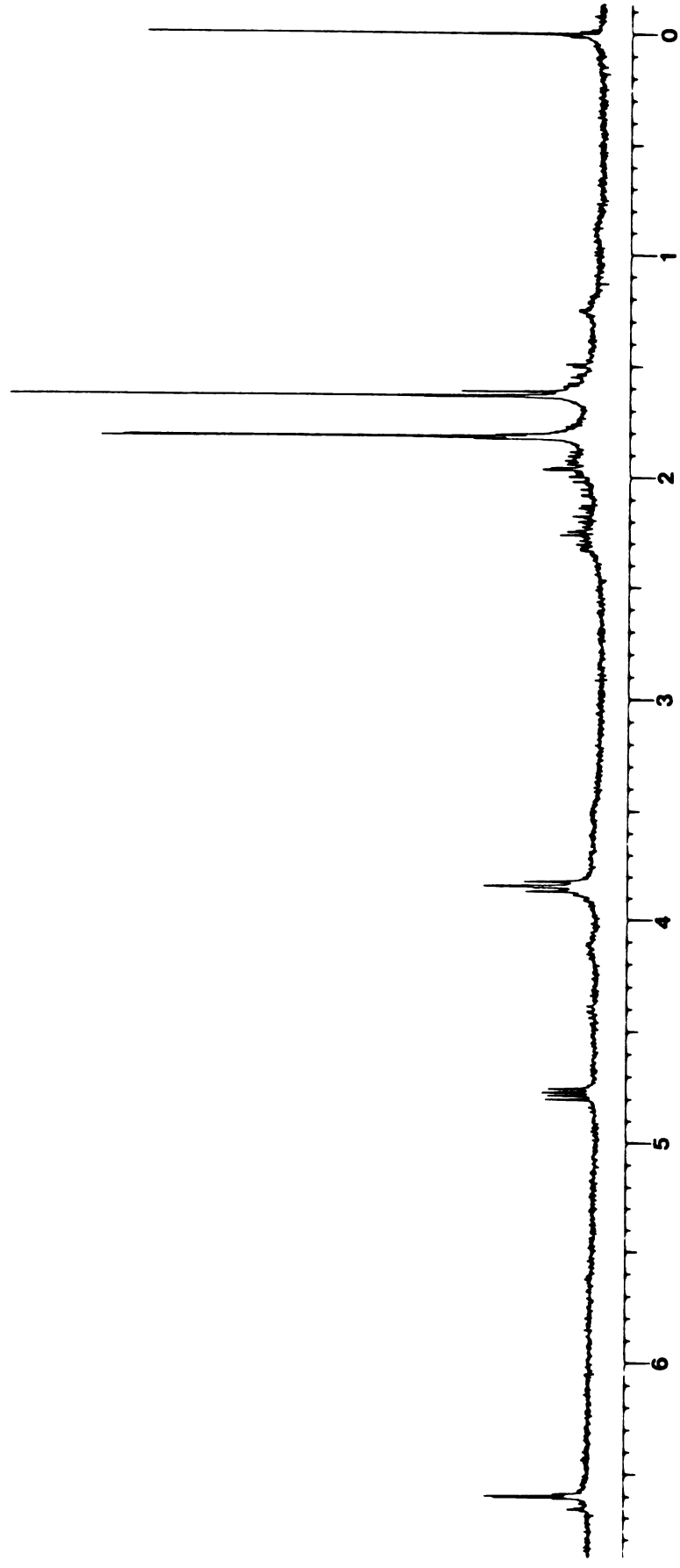


Figure 1. Oxidation of diol 90 with MCPBA; 250 MHz ^{1}H NMR spectrum after 15 minutes.

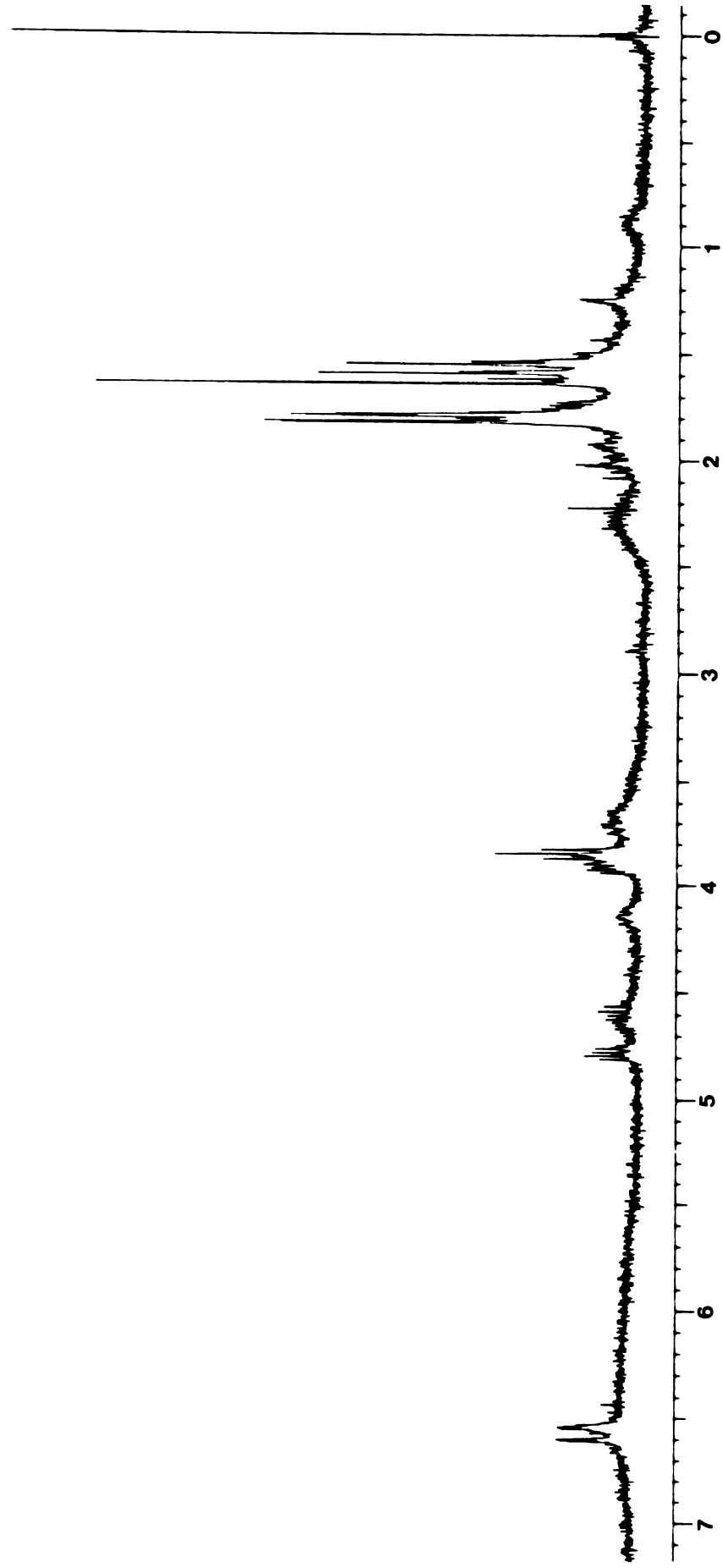


Figure 2. Oxidation of diol 90 with MCPBA; 250 MHz ^{1}H NMR spectrum after 2 hours.

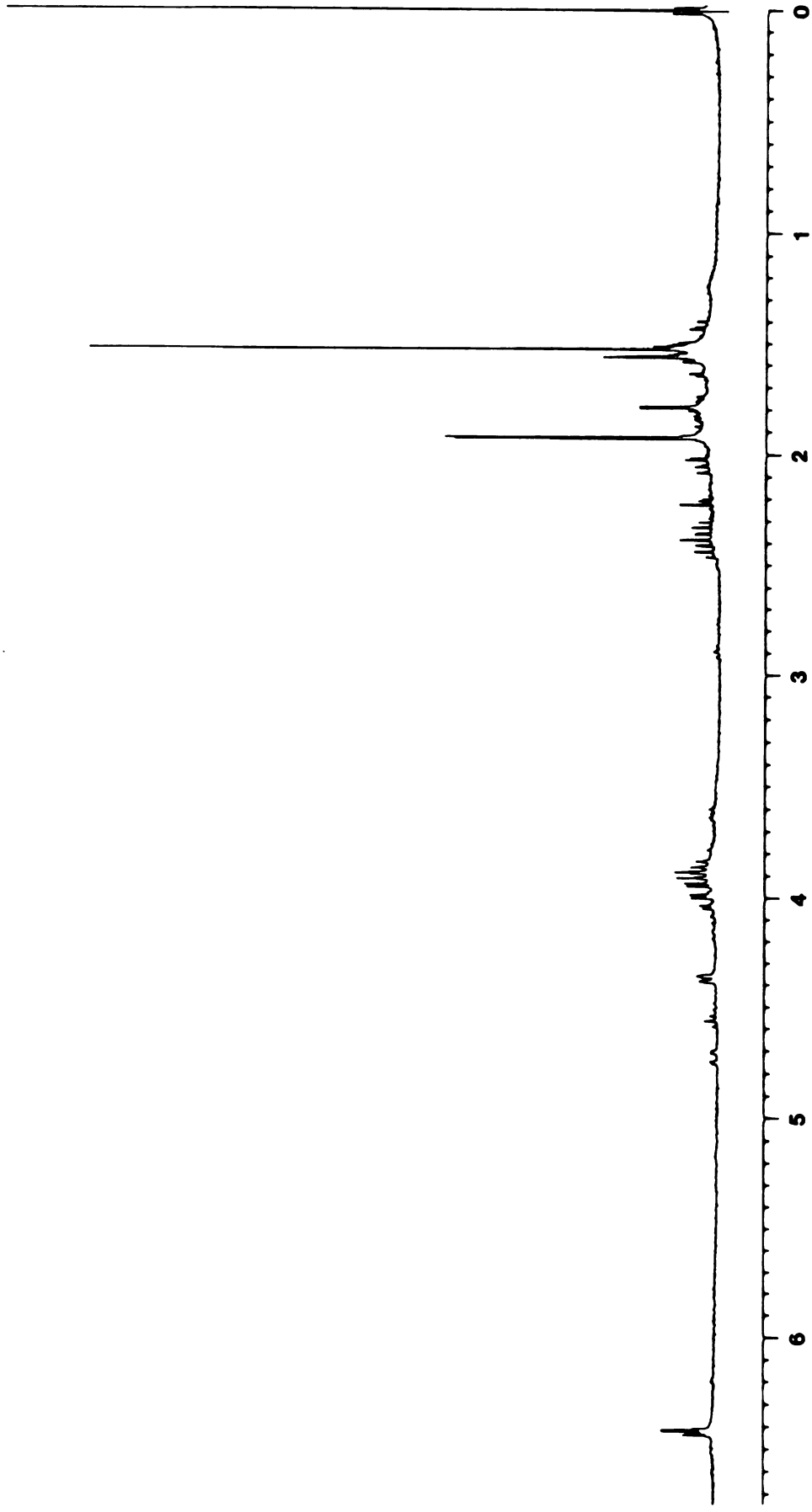
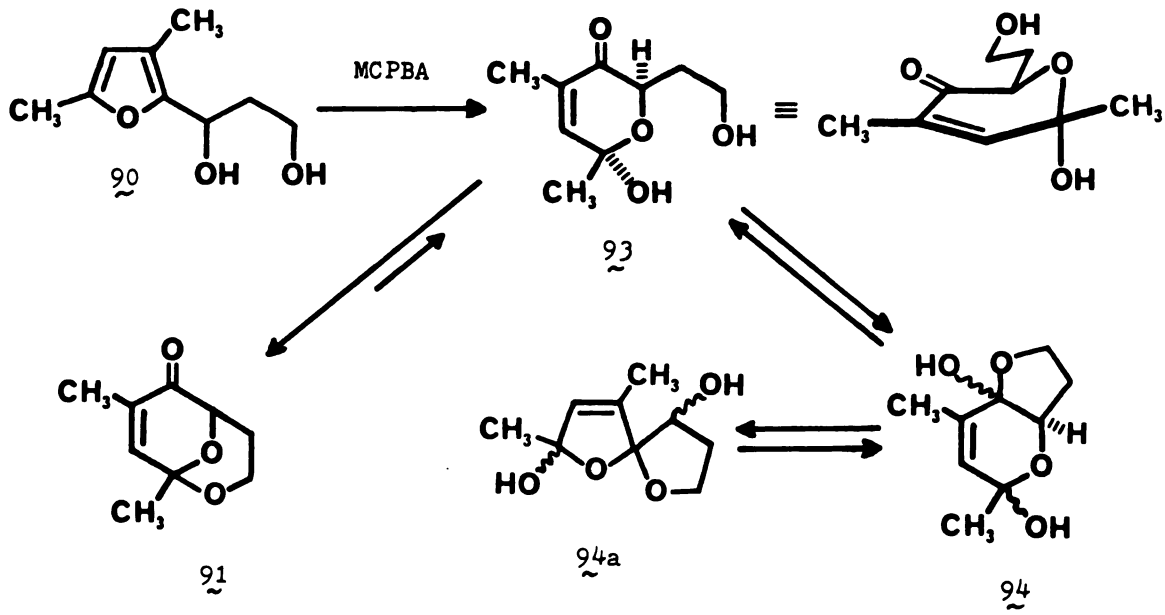


Figure 3. Oxidation of diol 90 with MCPBA; 250 MHz ^{1}H NMR spectrum after 12 hours.

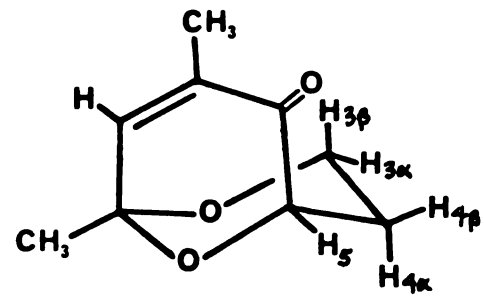
Scheme 23



m-chlorobenzoic acid by-product has undergone several ketal reorganizations, giving rise to intermediates such as 94 and 94a. The possibility, then, for the existence of these intermediates in several diasteriomeric forms would produce the complexity observed in the ^{1}H NMR spectrum of this mixture. As the spectrum in Figure 3 reveals, the equilibrium channels most of the intermediates to one major product, the desired bicyclic enone 91, which appears to constitute approximately 70% of the crude product mixture. Purification of this mixture by flash column chromatography did not enable separation of the major impurity having methyl resonances at 1.79 and 1.56 ppm (see Figure 3), nor did treatment of a chloroform solution of this mixture with aqueous *p*-toluenesulfonic

acid convert the impurity to the major component (*vide infra*).

Using a slightly different set of reaction conditions, conversion of 90 to the desired bicyclic enone 91 could be accomplished in high yield (Scheme 22). Oxidation of diol 90 with MCPBA in methylene chloride at 0°C for 15 minutes, followed by the addition of 0.10 equivalents of aqueous *p*-toluenesulfonic acid and stirring for 6 hours at room temperature furnished 91 in 90-96% yield, accompanied by only traces of by-products. The structure of 91 is fully supported by its spectral properties (^{1}H and ^{13}C NMR, IR, MS). An analysis of the 250 MHz ^{1}H NMR spectrum is given in Figure 4 and Table 3. Use of the stronger acid increases the rate of product formation and evidently bypasses the pathway which produced the impurity observed in the previous experiment. Interesting, too, is the fact that ketalization occurs readily using *aqueous* conditions. Concurrent to this work, Ziegler and Thottathil[58] published a conceptually related approach to the 2,9-dioxabicyclo[3.3.1]nonane skeleton of tirandamycin (see Figure 5) in which they also noted the effectiveness with which aqueous acidic conditions brought about cyclization. During the writing of this thesis, a second furan oxidation model study by DeShong and



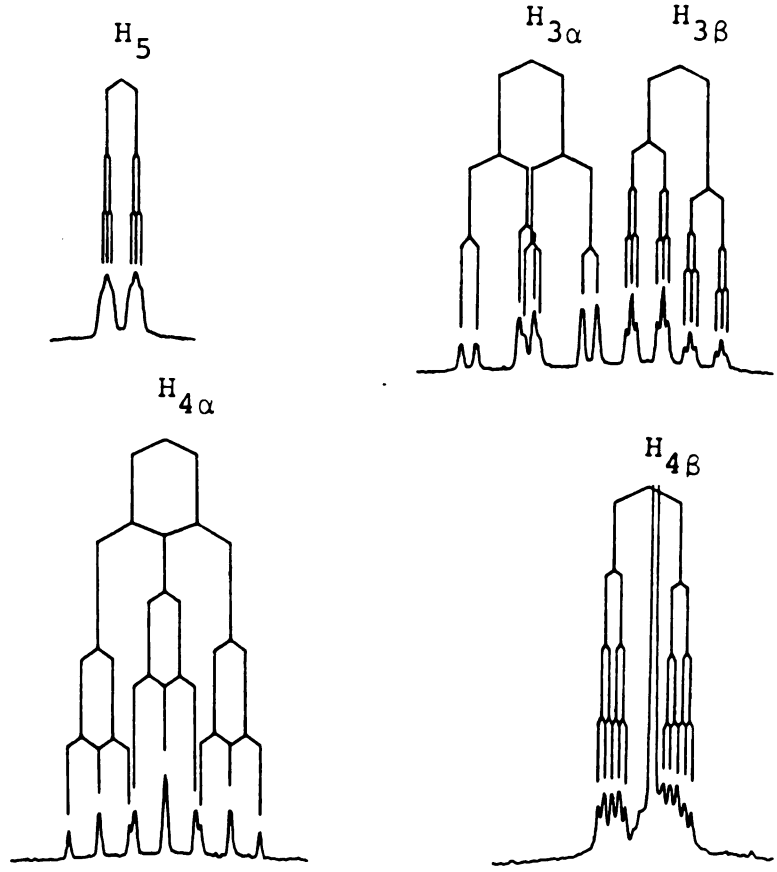


Figure 4. Expanded regions in the 250 MHz ^{1}H NMR spectrum of 91. Methyl and enone resonances have been omitted. See Table 3 for accompanying chemical shifts and coupling constants.

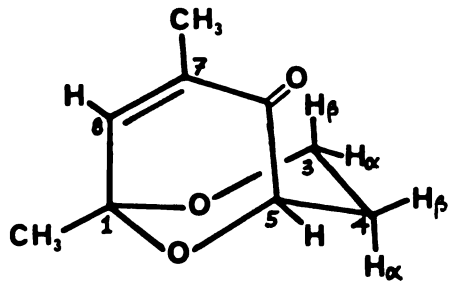


Table 3. High field ^1H NMR assignments for 9l.

proton	chemical shift (ppm)	mutiplicity and coupling constants (Hz)		
$CH_3(C_1)$	1.52	s		
$CH_3(C_7)$	1.92	d;	$J_{CH_3,8} = 1.5$	
$H_{3\alpha}$	3.86	dddd;	$J_{3\alpha,3\beta} = 12.1$	$J_{3\alpha,4\beta} = 1.1$
			$J_{3\alpha,4\alpha} = 6.2$	$J_{3\alpha,5} = 1.1$
$H_{3\beta}$	3.99	ddd;	$J_{3\beta,3\alpha} = 12.1$	$J_{3\beta,4\alpha} = 13.3$
			$J_{3\beta,4\beta} = 3.0$	
$H_{4\alpha}$	2.38	dddd;	$J_{4\alpha,4\beta} = 13.3$	$J_{4\alpha,3\beta} = 13.3$
			$J_{4\alpha,3\alpha} = 6.2$	$J_{4\alpha,5} = 6.2$
$H_{4\beta}$	1.53	dddd;	$J_{4\beta,4\alpha} = 13.2$	$J_{4\beta,3\beta} = 3.0$
			$J_{4\beta,3\alpha} = 1.1$	$J_{4\beta,5} = 1.1$
H_5	4.36	ddd:	$J_{5,4\alpha} = 6.2$	$J_{5,4\beta} = 1.1$
			$J_{5,3\alpha} = 1.1$	
H_8	5.41	q;	$J_{8,CH_3(C_7)} = 1.5$	

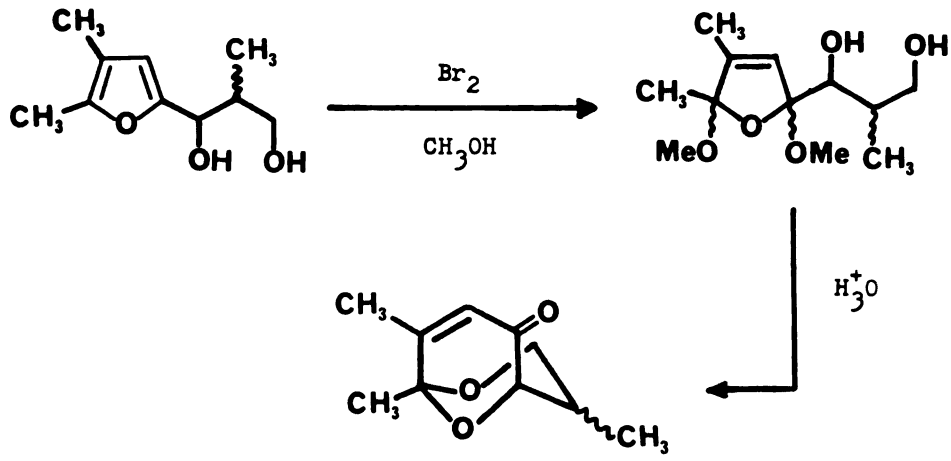


Figure 5. Ziegler's tirandamycin model.

and co-workers[59] appeared (see Figure 6) in which an interesting observation was made concerning the effect of the configuration at C_3 on the ring closure. Namely, closure to the bicyclic enone does not occur when the

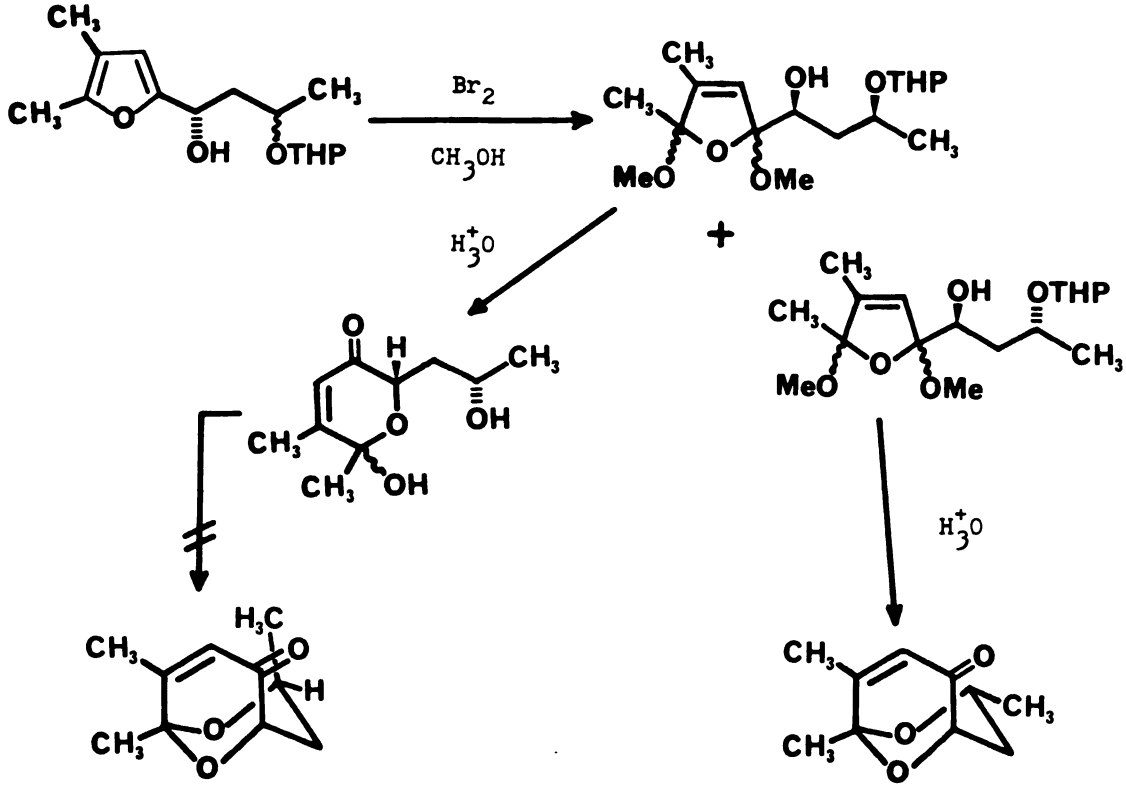


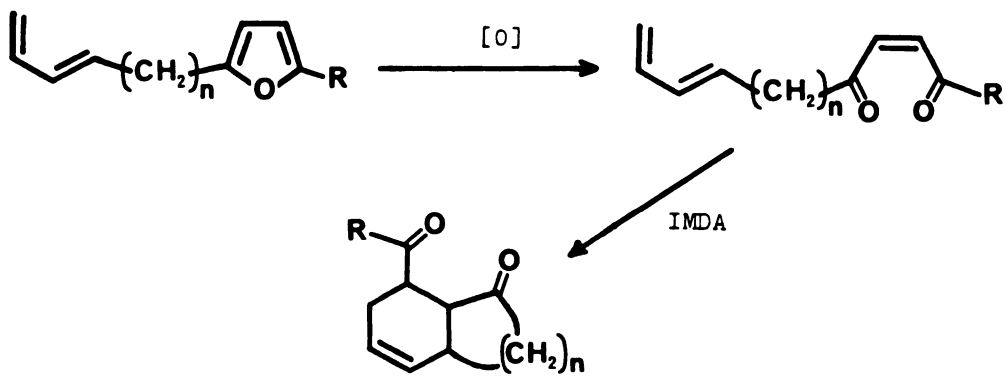
Figure 6. DeShong's tirandamycin model.

configuration at C_3 is such that a substituent at this position must occupy an axial position in the product, a point touched upon earlier in the discussion of the retrosynthetic analysis.

Thus, from the work described in this thesis, in addition to the two published works by Ziegler and DeShong, the furan oxidation approach to tirandamycin seems to hold much promise.

C. INTRAMOLECULAR DIELS-ALDER REACTIONS

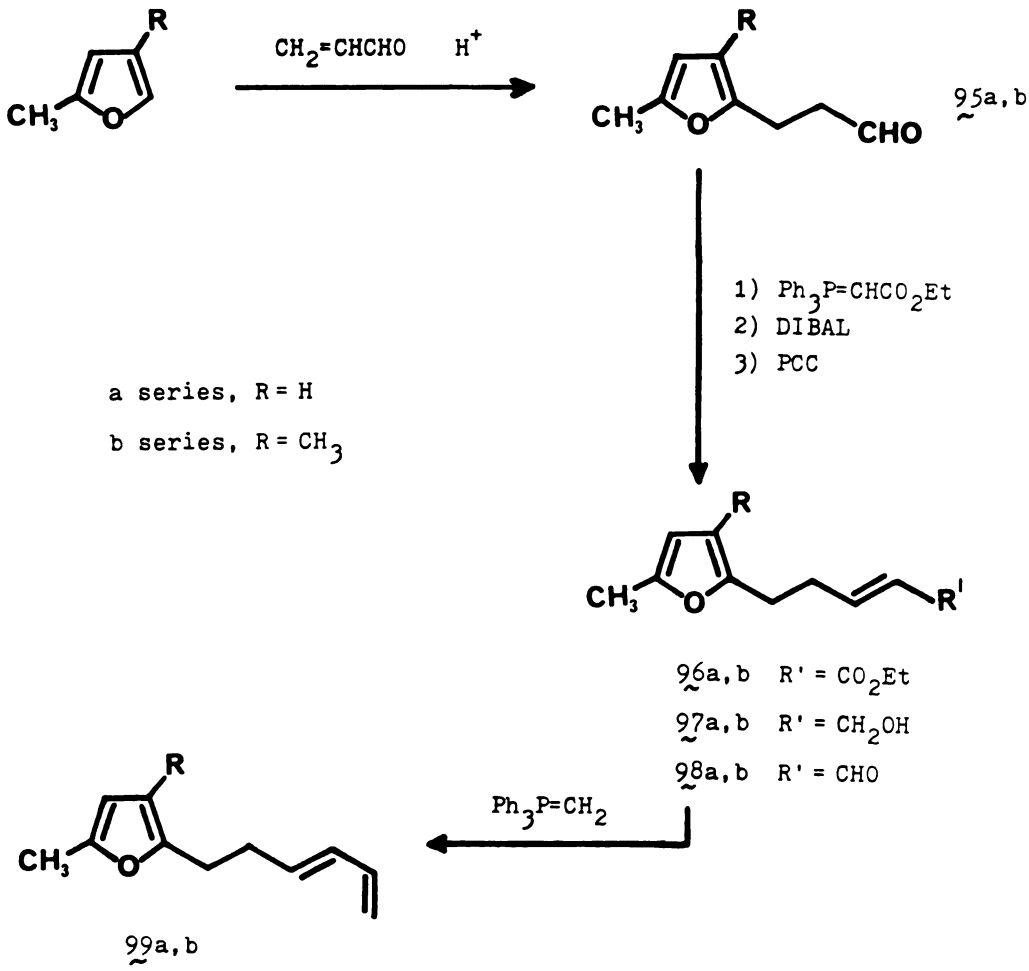
An interesting and potentially useful application of furan oxidation methodology is shown in the equation below, wherein the furan nucleus of an appropriately substituted



alkadienylfuran serves as a masked dienophile in an intramolecular Diels-Alder (IMDA) reaction.[60] The feasibility of this overall transformation from a synthetic standpoint requires that 1) the furan can be oxidized selectively in the presence of the diene moiety and 2) cycloaddition occurs at temperatures which do not affect the enedione (dienophile) double bond geometry.

As an entry to akladienylfurans required for this study, furylpropionaldehydes 95a and 95b were prepared by the acid-catalyzed addition of acrolein[97] to 2-methylfuran and 2,4-dimethylfuran, respectively (see Scheme 24). Wittig condensation of 95a,b with carbethoxymethylenetriphenylphosphorane (1.1 equiv., THF, r.t., 8 h) gave the

Scheme 24



unsaturated esters 96a,b in nearly quantitative yield. The corresponding unsaturated aldehydes 98a,b were

prepared from the esters by diisobutylaluminum hydride (DIBAL) reduction (2.2 equiv., ether-toluene, 0°C to r.t., 1.5 h; 1 N HCl; 92-96%) to allylic alcohols 97a,b followed by pyridinium chlorochromate (PCC) oxidation (2 equiv., CH_2Cl_2, 0°C to r.t., 1.5 h; 58-68%). In this last operation, it is noteworthy that the allylic alcohol moieties in 97a,b were oxidized selectively in the presence of the furan ring which can also undergo oxidation by Cr(VI) species. The selectivity was anticipated on the basis of the somewhat more vigorous conditions employed by Piancatelli and co-workers[23a] (5-6 equiv. PCC, CH_2Cl_2, r.t. for 24 h, then reflux for 9 h) in their oxidations of 2,5-dialkylfurans to *trans*-enediones. Close examination of the 250 MHz ^1H NMR spectra of 98a,b revealed that they were obtained as geometrically pure E unsaturated aldehydes. Olefination of 98a,b with methylenetriphenylphosphorane (1.1 equiv., THF-hexane, -10°C to r.t., 2 h; 81-88%) furnished hexadienylfurans 99a,b, also obtained as exclusively E isomers.

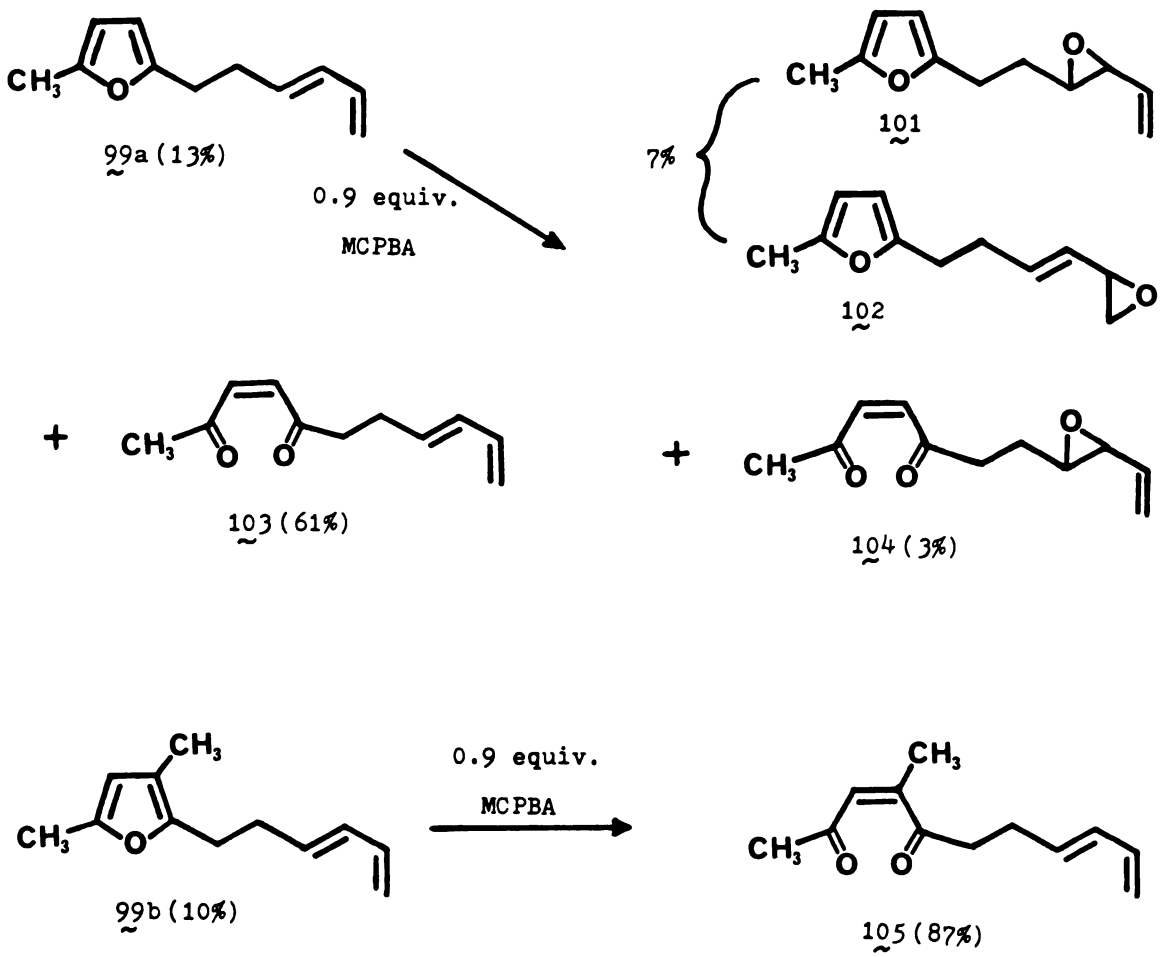
It should be noted at this point that a more general method for the preparation of alkadienylfurans might be envisioned wherein an α-lithiofuran is coupled with an appropriate alkadienyl halide 100 (n=1, X=Br[61]; n=2,

100

x=OMs[70]). The route employed in the present work, however, illustrates the ability of the furan nucleus to serve as "latent functionality" during the course of a multistep sequence, an especially desirable feature in the construction of more complex target compounds.

With 99a and 99b on hand, the oxidation chemoselectivity was examined using MCPBA (see Scheme 25). Thus, oxidation of 99a using a slight deficiency of peracid (0.9 equiv., CH_2Cl_2, -10°C to r.t., 1 h) gave a complex mixture which was separated by flash column chromatography.

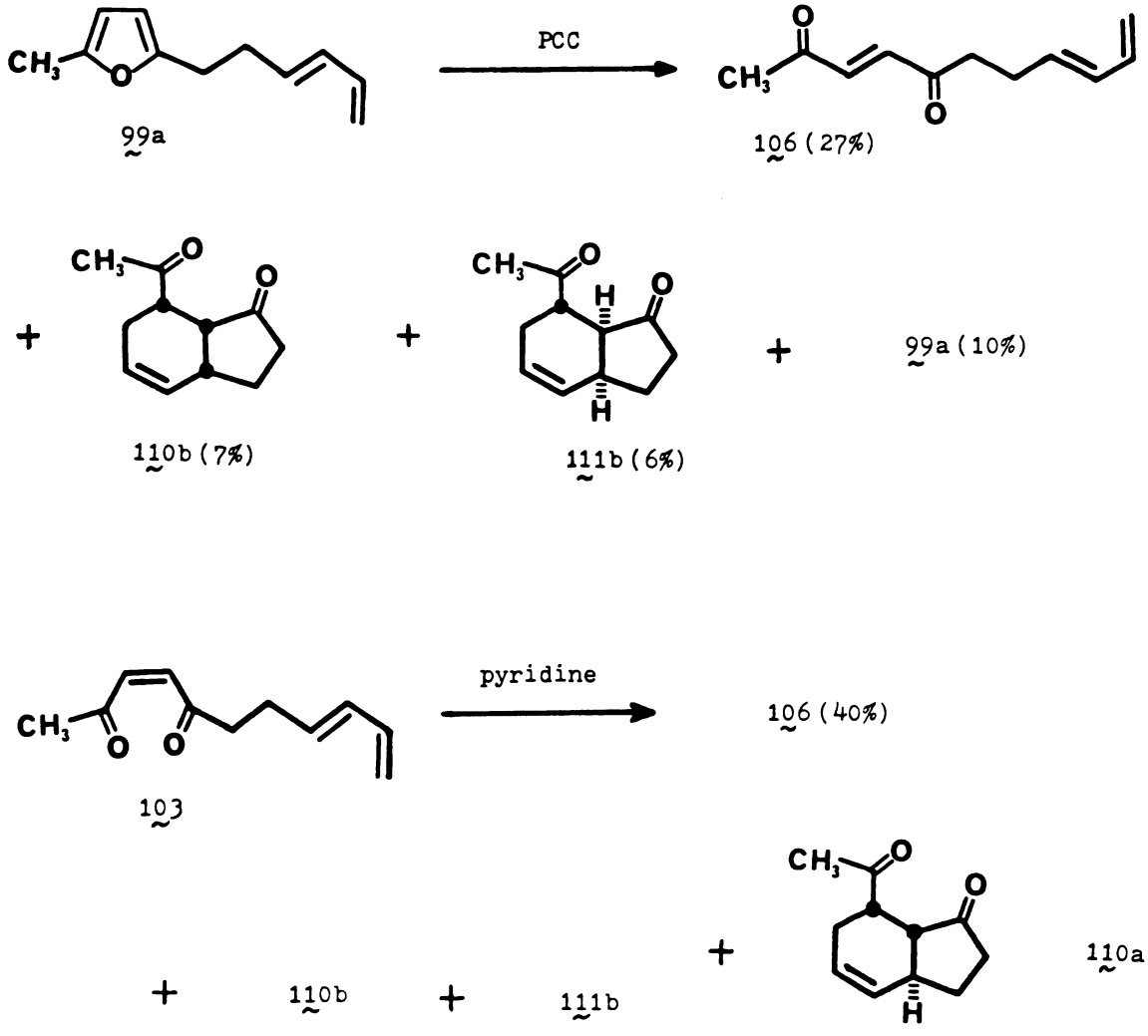
Scheme 25



The products were readily identified from their 250 MHz ^{1}H NMR spectra. From the isolated yields indicated in Scheme 25, it is clear that a furan-selective oxidation is operative. The yield of the desired triene 103 was 70% based on consumed starting material, and the relative rate of furan *vs.* diene oxidation for 99a was *ca.* 9.5:1. Oxidation of 99b under the same reaction conditions (Scheme 25) gave only two products, recovered starting material (10%) and triene 105 (96% yield based on consumed starting material). No products resulting from diene oxidation were isolated. Evidently the additional methyl group in 99b increases the electron density on the furan nucleus such that an even more selective reaction by the electrophilic peracid takes place.

To examine the influence of the dienophile double bond geometry on the *exo/endo* cyclization selectivity of the ensuing IMDA reactions, the *trans*-enedione isomers of 103 and 105 were sought. The previously mentioned oxidation procedure of Piancatelli was thus applied to 99a (see Scheme 26). Oxidation with PCC (5-6 equiv., CH_2Cl_2, r.t. for 20 h, then reflux for 6 h) gave a multi-component product mixture which was separated by flash column chromatography. In this manner, only a moderate yield of the desired *trans*-enedione 106 was obtained (30% based on consumed starting material). Other products identified from this mixture were the hydrindenones 110b and 111b.

Scheme 26



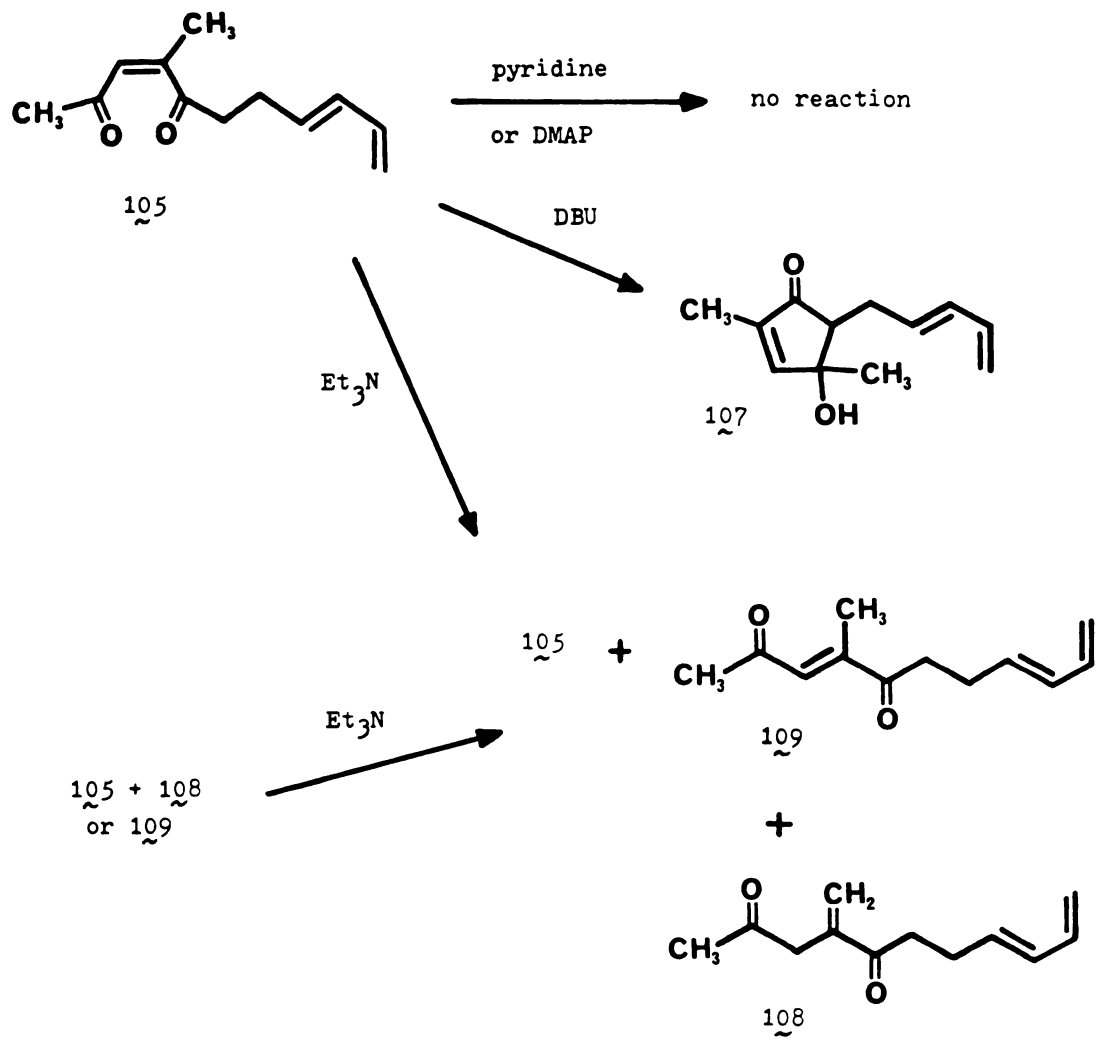
The presence of the latter two products was detected by TLC early in the reaction, concurrent with the formation of *trans*-enedione 106. This observation, in addition to the much faster rate of cyclization of 103 compared to 106 (*vide infra*) leads to the conclusion that hydrindenones 110b and 111b are derived from the initially formed *cis*-enedione 103, which undergoes IMDA cyclization (and epimerization in the case of 111b) competitive with

isomerization to *trans*-106.

The experiment in which *cis*-enedione 39a was cleanly isomerized to *trans*-enedione 39b by pyridine (see Section A) suggested that 103 might be isomerized in an analogous fashion (see Scheme 26). Treatment of 103 with a large excess of pyridine ($CHCl_3$, r.t., 18 h) gave *trans*-enedione 106 in *ca.* 40% yield after flash column chromatography. The presence of hydrindenones 18a, 18b, and 19b (2:1:1, respectively), which constituted *ca.* 40% of the reaction mixture, indicated that this procedure also suffers from competetitve IMDA cyclization.

The isomerization of *cis*-enedione 105 was also investigated; however, neither pyridine nor 4-N,N-dimethylaminopyridine (DMAP) were effective in bringing about this transformation (see Scheme 27). On the other hand, the more basic amine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), catalyzed a rapid internal condensation (1.2 equiv. DBU, $CHCl_3$, r.t., 3-5 min) to give cyclopentenone 107 in good yield. Satisfactory results could only be obtained using triethylamine. Thus, reaction of 105 with a large excess of triethylamine ($CHCl_3$, r.t., 8 h) gave an equilibrium mixture of three compounds, 105, 108, and 109 in a ratio of 1:1.8:1.2, respectively. Fortuitously, the desired *trans*-enedione 109 was easily separated by flash column chromatography from the more polar *cis*-enedione 105 and deconjugated isomer 108, which eluted as a completely inseparable mixture. The latter mixture, however, could be

Scheme 27



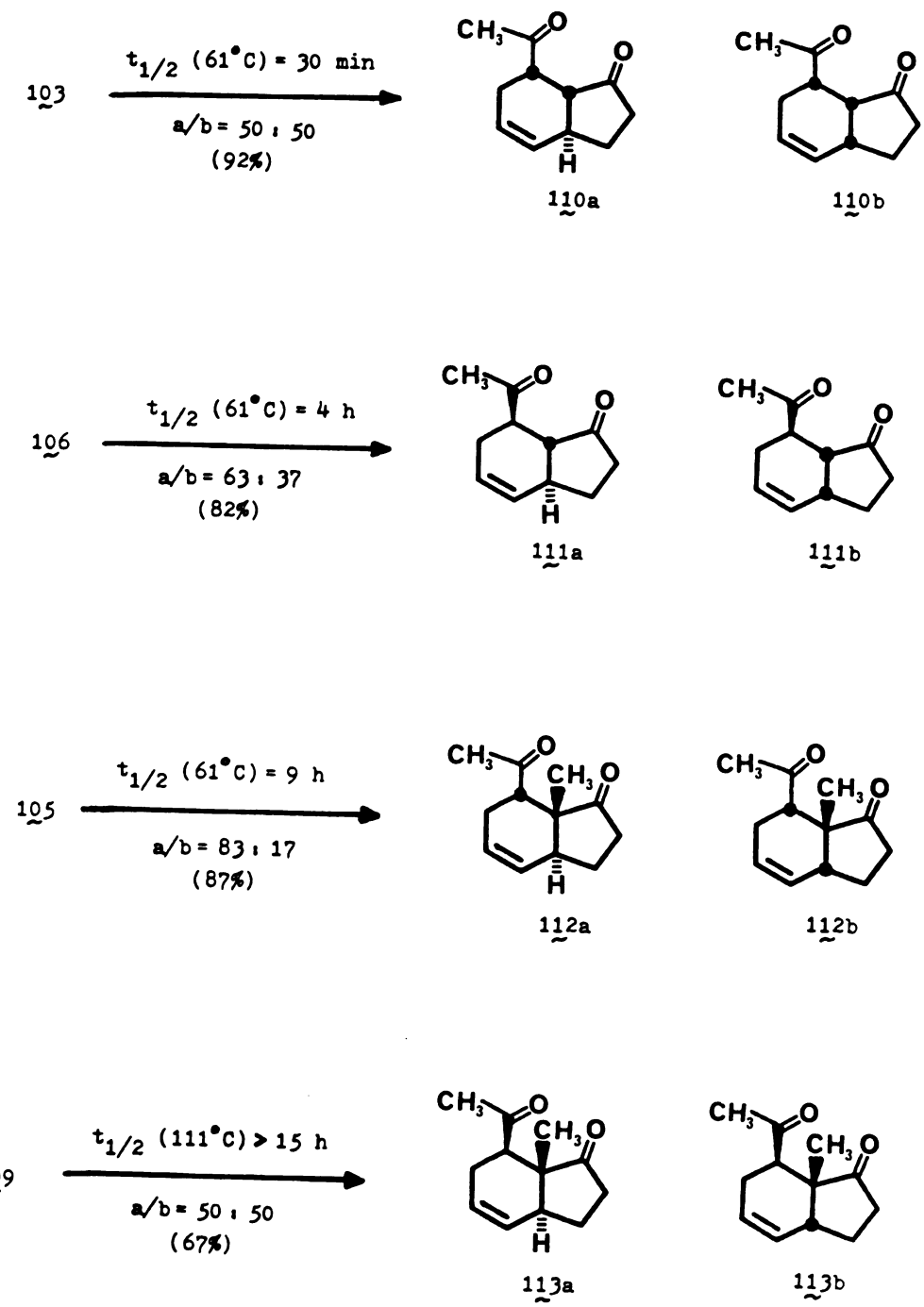
recycled by treatment with triethylamine as before to provide more 109. That 109 is the product of an equilibrium-controlled process was demonstrated by re-establishment of the original three-component mixture upon exposure to triethylamine (see Scheme 27).

With the two pairs of *cis*- and *trans*-enedione IMDA precursors on hand, investigations were then set forth to determine their relative rates of cyclization and

exo/endo cyclization selectivities. Cyclizations were performed in refluxing chloroform-d_1 (bp=61°C) or toluene-d_8 (bp=111°C) and the reaction progress was monitored by 250 MHz ^{1}H NMR. Integration of appropriately resolved product and starting material resonances from aliquots withdrawn at measured intervals provided half-life data. The cyclizations of trienes 10~3, 10~5, and 10~6 proceded at convenient rates in refluxing chloroform-d_1, whereas negligible cyclization had occurred with substrate 10~9 after 6 hours in this solvent, and therefore the higher boiling toluene-d_8 was used instead. The half-life data given in Scheme 28 indicate that the methyl substituted trienes undergo cyclization more slowly than their unsubstituted counterparts, not a surprising result in terms of steric considerations. Also, the half-life data indicate that, for a given dienophile substitution, the *cis*-enediones cyclize faster than the corresponding *trans* isomers. A similar rate effect has been observed by White and Sheldon[62] in their studies on the IMDA reactions of trienes which also possess dienophile 1,2-diactivation (see Figure 7).

Stereochemical assignments for the product hydrindenones shown in Scheme 28 were made on spectroscopic considerations (250 MHz ^{1}H NMR and 62.9 MHz ^{13}C NMR), using as a guide the growing body of data available from related studies. Thus, triene 10~3, which undergoes facile cyclization (ether, r.t., 3 days; or $CHCl_3$, reflux, 4.5 h), gave

Scheme 28


103
t1/2 (61°C) = 30 min
a/b = 50 : 50
(92%)
110a
110b
106
t1/2 (61°C) = 4 h
a/b = 63 : 37
(82%)
111a
111b
105
t1/2 (61°C) = 9 h
a/b = 83 : 17
(87%)
112a
112b
109
t1/2 (111°C) > 15 h
a/b = 50 : 50
(67%)
113a
113b

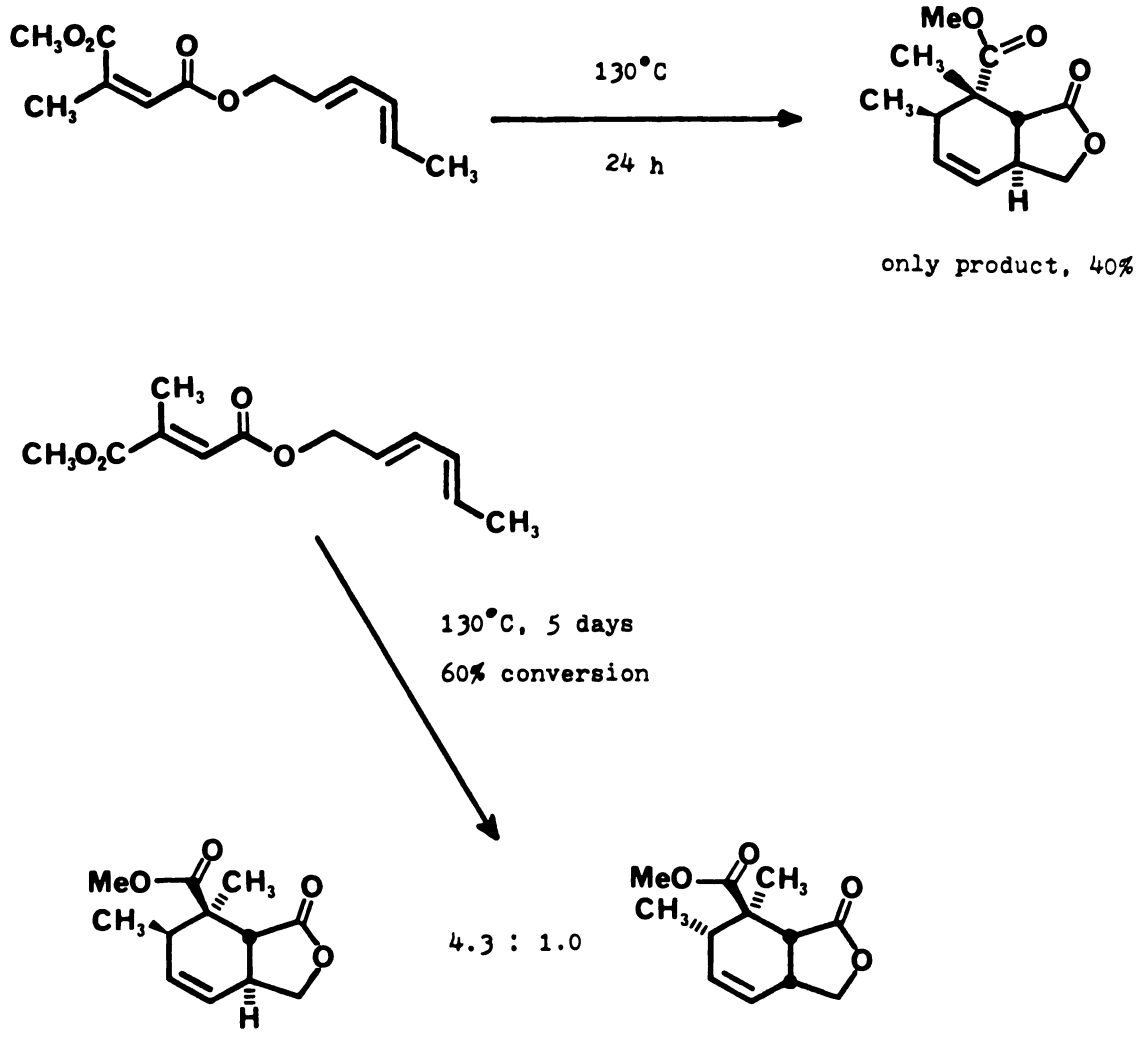


Figure 7. Studies by White and Sheldon on the IMDA reactions of sorbyl mesaconates and citraconates.

two hydrindenones in equal amounts as determined by integration in the ^{1}H NMR spectrum of the crude product mixture. Separation of the two products was effected by flash column chromatography, thus enabling unambiguous assignment of the resonances peculiar to each. Assignment of the less polar isomer as *trans*-fused 110a and the more polar, crystalline product as the *cis*-fused isomer 110b rests upon the following spectroscopic observations. The J_{7a-3a} values for 110a and 110b, as determined by decoupling experiments in which H-7 was selectively irradiated, are 13.6 and 7.7 Hz, respectively (see Figure 8). On the basis of dihedral angle considerations, the *trans*-diaxial arrangement of H-7a and H-3a in the conformationally restricted *trans*-fused isomer 110a is expected to give rise to greater coupling compared to *cis*-fused 110b, which has available to it conformations in which the H-C_{7a}-C_{3a}-H dihedral angle ranges from 0° to *ca.* 40°. Diagnostic, too, is the 1.2 ppm upfield chemical shift of H-7a in 110a compared with the same proton in 110b. Examination of molecular models of 110a indicates that H-7a, by virtue of the *trans* ring fusion, is rather rigidly held in a pseudo-axial position, which places it nearly perpendicular to the C_1 carbonyl C-O bond axis and hence out of the strongly deshielding region associated with this functional group.[63] Additionally, the *trans* ring fusion in 110a holds H-7a in a region of moderate

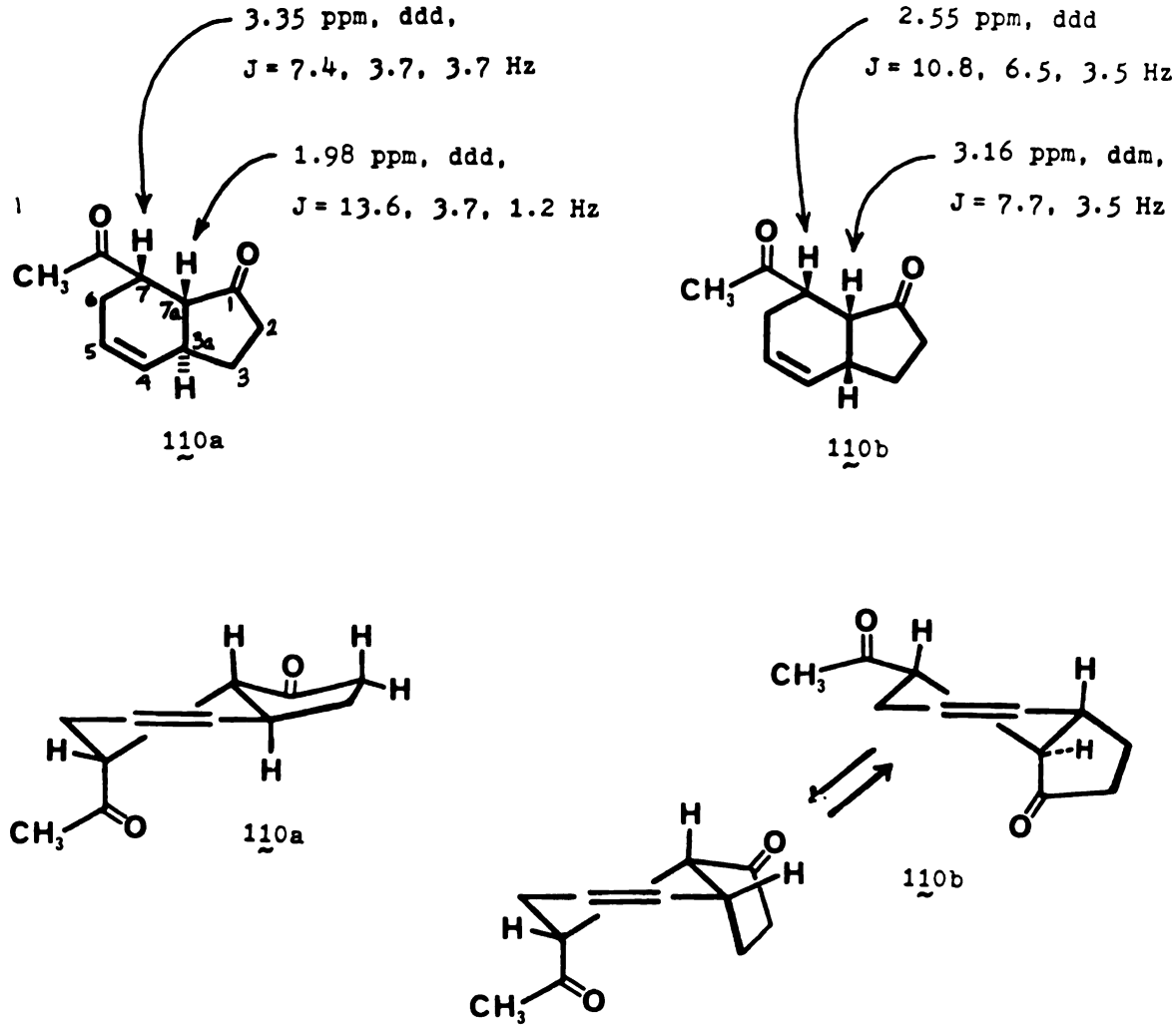


Figure 8. Chemical shifts, coupling constants, and conformations of hydrindenones 110a and 110b.

shielding over the C_4-C_5 double bond.[64] The *cis*-fused isomer 11̲0b, on the other hand, has conformations available to it in which H-7a is nearly coplanar with the C_1 carbonyl C-O bond axis and well away from the shielding region of the C_4-C_5 double bond. Consistent with the presumed *cis* arrangement of H-7 and H-7a in cycloadducts 11̲0a and 11̲0b (which requires a gauche-like arrangement of these protons in the various conformers) are the J_{7-7a} values of 3.7 and 3.5 Hz, respectively. The origin of the additional 1.2 Hz splitting of H-7a in 11̲0a could not be conclusively determined by decoupling experiments. Long range coupling *via* the well known "W conformation" is not possible in the *trans*-fused hydrindenone ring system; however, it does seem possible as judged by examination of molecular models that splitting of H-7a by the pseudo-axial proton at C_2 (see Figure 8) could occur by a mechanism in which long range coupling takes place *via* mutual overlap of the C-H σ bonds with the π p orbital of the C_1 carbonyl carbon.[65]

Chemical evidence for the *trans* fusion in 11̲0a was provided by its slow epimerization at room temperature in the absence of acid or base to give a new hydrindenone (as an inseparable mixture with 11̲0a), whose structure was determined to be *cis*-fused 11̲1b based on the following spectroscopic evidence. The new J_{7a-3a} value as determined by irradiation of H-7 was found to be 7.3 Hz (see Figure 9) and, consistent with previous observations, H-7a in the new isomer resonates at 0.8 ppm downfield of the

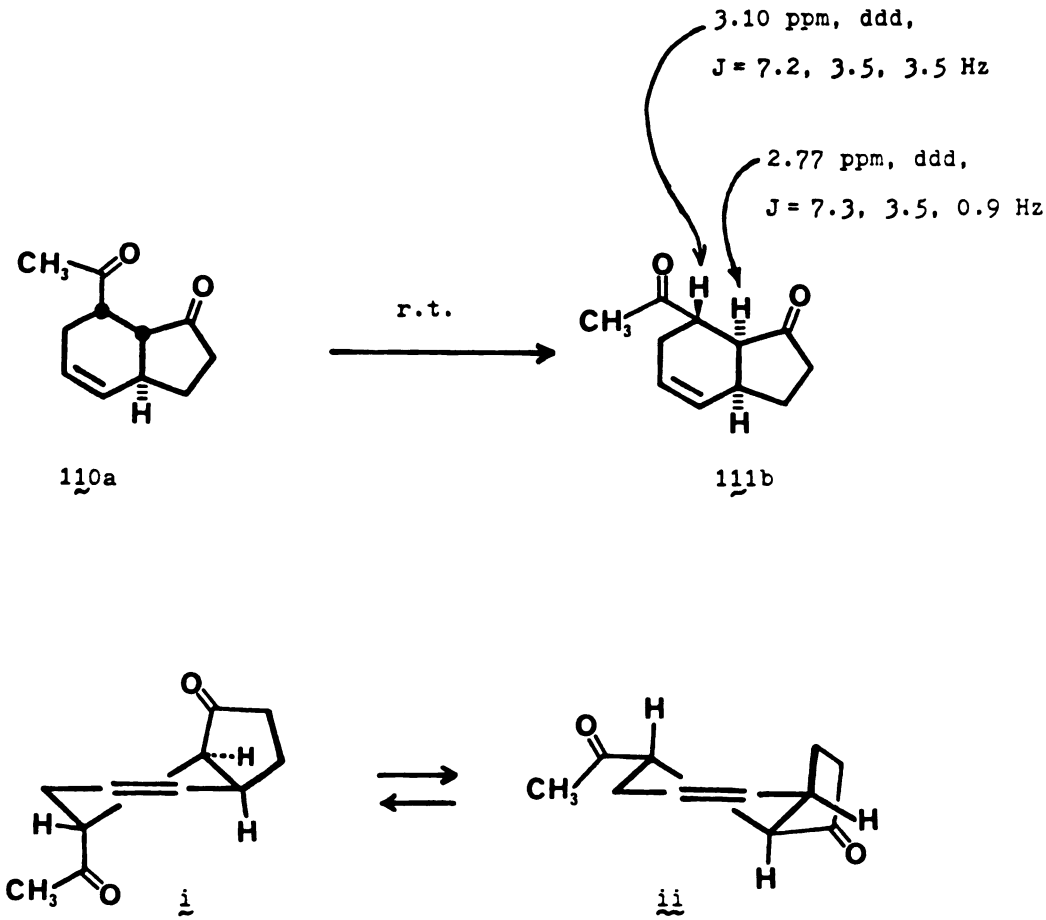


Figure 9. Epimerization of 110a. Chemical shifts, coupling constants, and conformations of hydrindenone 111b.

corresponding proton in the original epimer. The rather small J_{7-7a} value of 3.5 Hz suggests that the conformation of 111b in solution does not resemble ii (see Figure 9) because of the *trans*-diaxial arrangement of H-7 and H-7a in the latter.

The slow epimerization of 110a to its *cis*-fused epimer is not surprising in light of similar observations by other workers. For example, in the base-catalyzed equilibration of 1-hydrindanone using triethylamine, House and Rasmusson[66] found a *ca.* 3:1 preference for the *cis*-fused isomer. Ichihara and co-workers described the acid[67a] and base[67b] catalyzed epimerization of *trans*-coronafacic acid 114a to the *cis*-fused isomer 114b, the latter being the naturally occurring stereoisomer found in the phytotoxin, coronatine 115 (see Figure 10). Lactone 116a, a product of IMDA cyclization from a study by White and Sheldon,[62] was epimerized to its *cis*-fused epimer, 116b (see Figure 10). The spectral data shown in Figure 10 for the 116a,b epimeric pair concur nicely with the spectroscopic arguments in the foregoing discussion.

Cyclization of triene 106 required longer reaction times than 103 (see Scheme 28), and examination of the crude product mixture by ^{1}H NMR indicated the presence of two cycloadducts in a ratio of 63:37. A small amount of diene polymerization had occurred as inferred from a broad singlet at 6.8 ppm (the chemical shift region for *trans*-enedione vinyl protons) and a somewhat lower yield of

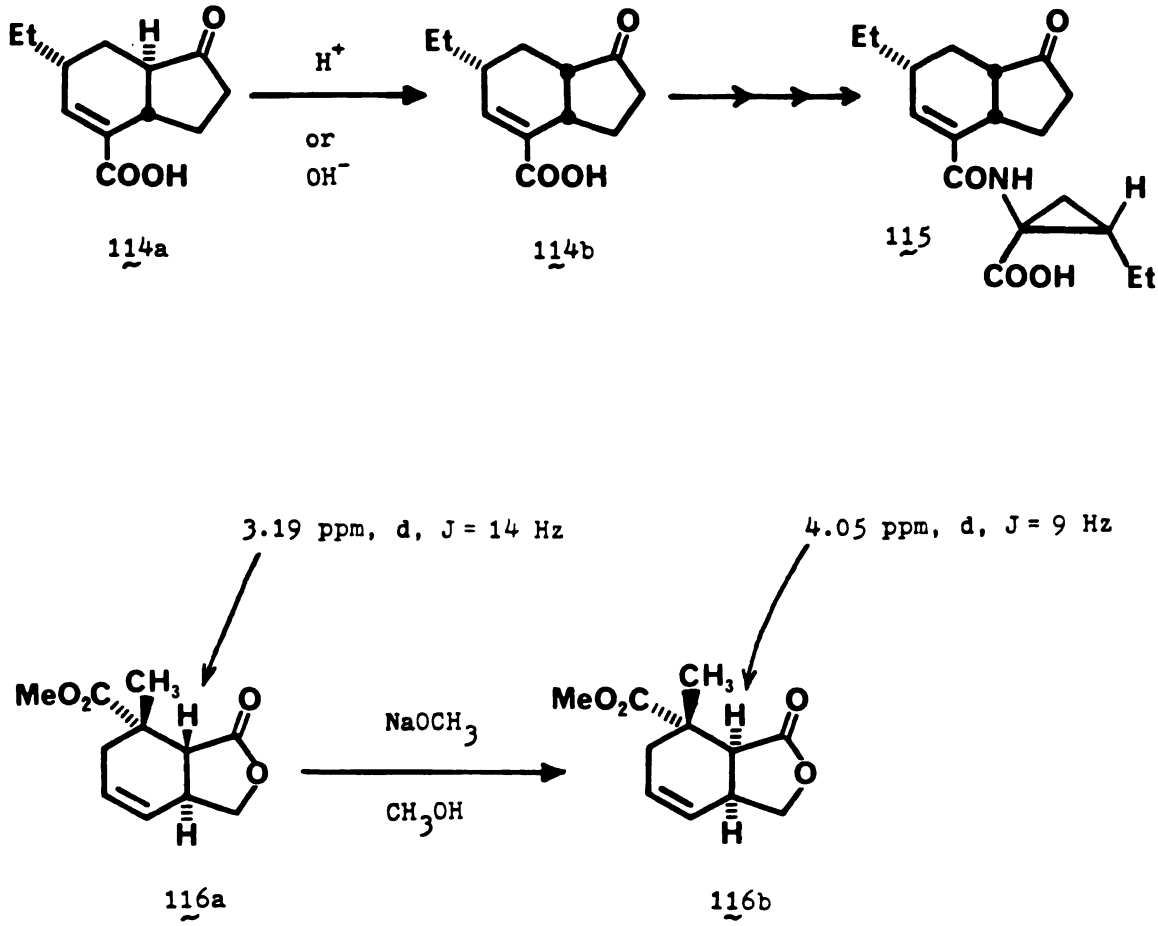


Figure 10. Epimerizations of *trans*-fused bicyclo[4.3.0] systems to *cis*-fused isomers.

chromatographed cycloadducts. The mixture of hydrindenones proved to be inseparable by flash column chromatography, and therefore structural assignments had to be made using the mixture. The minor isomer showed resonances in the proton and ^{13}C NMR identical to those of 111b, the epimerization product of 110a described above. By default, then, the structure of the new hydrindenone must be *trans*-fused 111a (see Figure 11). The diagnostic J_{7a-3a} value for 111a, however, could not be assessed in this case

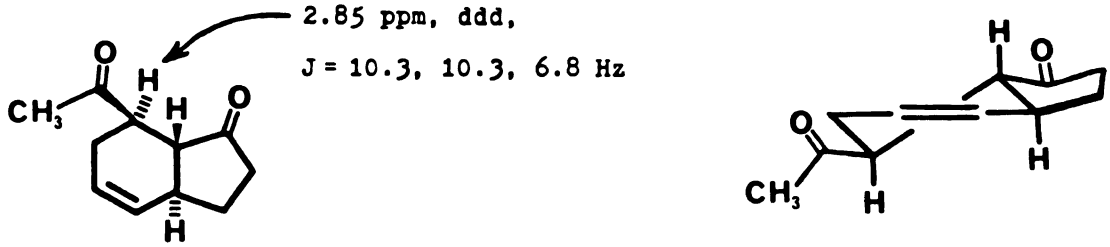


Figure 11. Chemical shift and coupling constant data for hydrindenone 111a.

because the upfield-shifted H-7a was obscured by other high field resonances. Supportive of the stereochemical assignment, though, is the J_{7-7a} value of 10.3 Hz (which could not be verified by decoupling experiments since the positions of H-7a and the protons at C_6 were unknown), consistent with a *trans*-diaxial arrangement of these protons. Also, the upfield chemical shift of H-7 in 111a (2.85 ppm) relative to the same proton in *trans*-fused 110a (3.35 ppm) is a demonstration that H-7 in the former occupies a pseudo-axial position and is out of the

strongly deshielding region of the nearby C_1 carbonyl group.

The ^{13}C NMR spectra of the two *trans*-fused hydrindenones 110a and 111a show striking similarities, as do the spectra of the two *cis*-fused epimers 110b and 111b (see Table 4). Although it is still quite early to be making generalizations, it appears that the chemical shift of the C_1 carbonyl carbon might be of diagnostic value to aid in the differentiation between *cis*- and *trans*-fused hydrindenones. Of the two carbonyl resonances for each compound, the upfield signal is ascribed to the acetyl carbonyl carbon (cyclohexyl methyl ketone exhibits a resonance at 210.7 ppm[68]). Thus, from the values given in Table 4, it can be seen that the C_1 carbonyl carbons of the *trans*-fused hydrindenones exhibit chemical shifts upfield of those in the *cis*-fused isomers. It is tempting to speculate that the difference in chemical shift is strain related; construction of molecular models clearly indicates that the *trans*-fused ring system is more strained. If the strain is manifested as a deformation of bond angles in the cyclopentanone portion of the molecule, then a slight change in hybridization at C_1 might be responsible for the chemical shift differences.

Triene 105 cyclized cleanly to give an inseparable mixture of two products in the ratio of 83:17 as determined from the crude product mixture by integration of the

Table 4. ^{13}C NMR chemical shifts of hydrindenones 110a, 110b, 111a, and 111b.

compound	C=O	C=C	other						
110a	214.25	129.91	54.61	44.11	38.32	35.96	29.49	27.94	26.47
	208.25	126.91							
111a	214.10	129.50	55.28	46.46	39.76	37.17	30.26	29.76	26.29
	210.87	127.21							
110b	217.95	129.44	49.99	45.49	37.64	34.73	27.67	27.17	23.08
	208.75	128.03							
111b	219.51	129.50	48.52	44.87	35.26	34.35	27.67	27.05	22.82
	209.43	126.44							

angular methyl group signals. The major product was assigned a *trans* ring fusion based on the upfield chemical shift of its angular methyl group (0.89 ppm), a characteristic feature for *trans*-hydrindenones which has been noted by several other workers.[69,71] Values of 8.5 and 1.8 Hz for the coupling of H-7 with the vicinal C_6 protons imply a pseudo-axial orientation of the acetyl group at C_7, and thus the major product was formulated as 20a (see Figure 12). The minor product was therefore assigned structure 112b, the product of *endo* cyclization. Comparison of the spectral data for 112a and 112b with the related compounds 117a,b[69] shown in Figure 12 lends further credence to these structural assignments.

Cyclization of triene 109 required much higher temperatures as noted previously. After 15 hours at 111°C, the reaction was only 35-40% complete as judged by ^{1}H NMR. The mixture was therefore transferred to a re-sealable tube and heated at 195°C in the presence of methylene blue for an additional 8 hours. The ^{1}H NMR spectrum of the crude product mixture thus obtained revealed the presence of a 1:1 mixture of two new hydrindenones as the major products, *ca.* 10% of a 5:1 mixture of hydrindenones 112a and 112b (the same relative ratio as obtained from 105), and less than 5% of the deconjugated triene 108. The presence of the latter three products suggests that 109 had undergone thermal isomerization to give 105 and 108, the same products

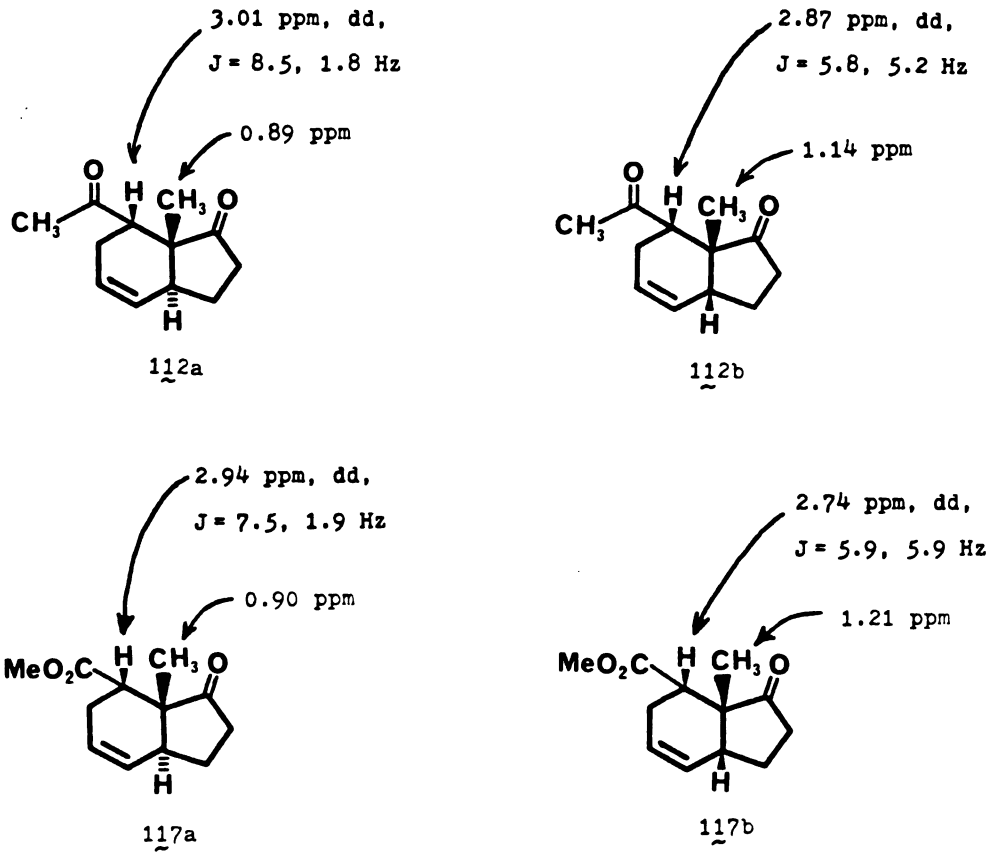


Figure 12. Comparison of selected spectral properties of hydrindenones 112a and 112b with related compounds.

obtained from base-catalyzed isomerization (see Scheme 27). At the temperature required for isomerization, 105 should undergo relatively rapid IMDA cyclization to give the 112a,b mixture (*vide supra*). Triene 108, on the other hand, appears to be unreactive under these conditions.

A partial separation of the two new hydrindenone isomers was achieved by flash column chromatography, providing the less polar 113a in greater than 90% purity and 113b as a *ca.* 3:1 mixture with 113a. The similarity in chemical shift of the angular methyl groups in these isomers prevented an unambiguous assessment of their ring fusion stereochemistries, and hence H-7 was used as a stereochemical probe. *Trans*-fused 113a exhibited coupling constants for this proton of 10.7 and 6.6 Hz, values consistent with a pseudo-axial orientation of H-7 (see Figure 13). The conformationally more flexible *cis*-fused 113b, on the other hand, exhibited values of 6.4 and 4.0 Hz. Roush[69] has reported similar values (9.7, 7.8 Hz and 5.5, 5.5 Hz) for hydrindenones analogous to 113a and 113b wherein the acetyl group at C_7 is replaced by carbomethoxyl.

As noted previously in the "nor" series, the C_1 carbonyl carbon resonances of the *trans*-fused hydrindenones 112a and 113a appear upfield of the C_1 resonances of the *cis*-fused isomers 112b and 113b (see Table 5). From these data, it would appear that the C_1 resonance is

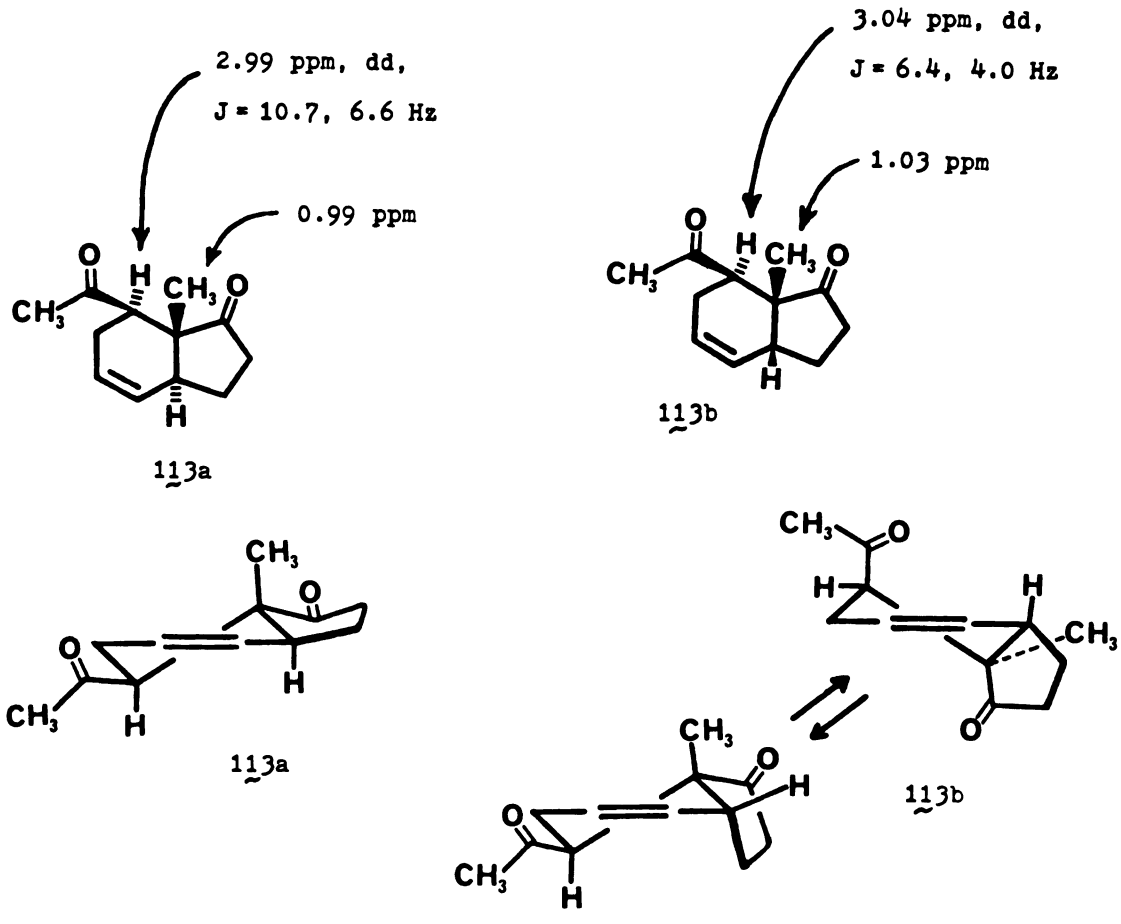


Figure 13. Chemical shifts, coupling constants, and conformations for hydrindenones 113a and 113b.

Table 5. Chemical shifts of the C_1 carbonyl carbon in the *cis*- and *trans*-fused hydrindenone pairs 110a,b-113a,b.

compound	*trans*-fused (a series)	*cis*-fused (b series)
110	214.25 ppm	217.95 ppm
111	214.10 ppm	219.51 ppm
112	217.92 ppm	222.51 ppm
113	217.45 ppm	221.45 ppm

indeed of diagnostic value in the assignment of *cis*- and *trans*-hydrind-4-en-1-ones of similar constitution.

The *exo/endo* cyclization selectivities observed for the trienes in this investigation (see Scheme 28) are not easily rationalized using the generalizations and conclusions put forth in related IMDA studies. From the work of Roush[69,70] and others,[62,71-73] it has become apparent that the *exo/endo* selectivities in the thermal cyclization of trienes which give hydrindene products (*i.e.*, three atoms in the chain connecting the diene and dienophile) are not dominated by classical secondary orbital overlap. Instead, rather subtle non-bonded interactions which develop along the reaction coordinate, as the diene and dienophile approach one another, have helped to rationalize the results in many cases. For example, Roush[70] studied the cyclization of trienes 118a and 118b (see Figure 14) and found that the geometry of the dienophile did not alter to significant extent the ratio of *cis*- and *trans*-fused

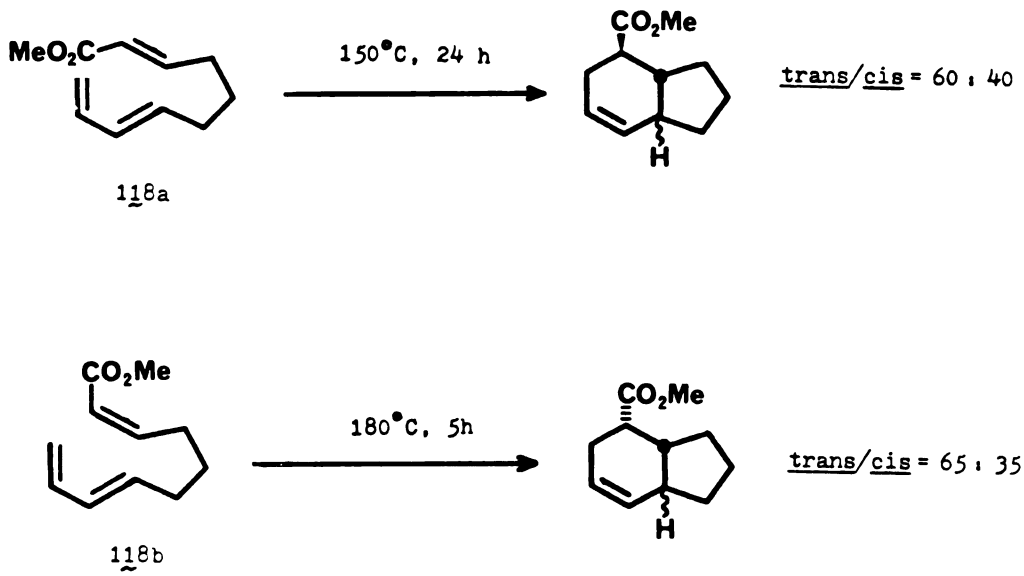


Figure 14. Observations on the cyclization of *cis*- and *trans*-decatrienoates.

products as might have been expected on the basis of secondary orbital effects. Rather, from these and many other examples it has been demonstrated that trienes which possess terminally activated dienophiles cyclize selectively to give *trans*-hydrindenes as major products. On the other hand, trienes which contain internally placed activating groups have been found to give predominantly *cis*-hydrindene products (see Figure 15). Thus, terminally activated trienes prefer transition state A in which the connecting chain adopts an *exo* orientation with respect to the diene (see Figure 16), while internally activated trienes prefer transition state B in which the connecting chain is *endo*. It has been proposed by several groups[62,69,70,72,73] that these selectivities are the

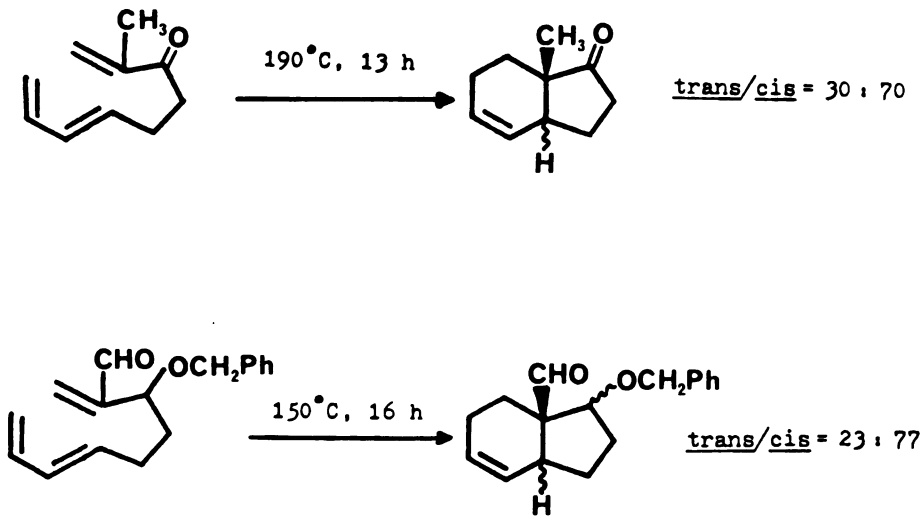


Figure 15. IMDA reactions of internally activated trienes which give predominantly *cis* hydrindenes.

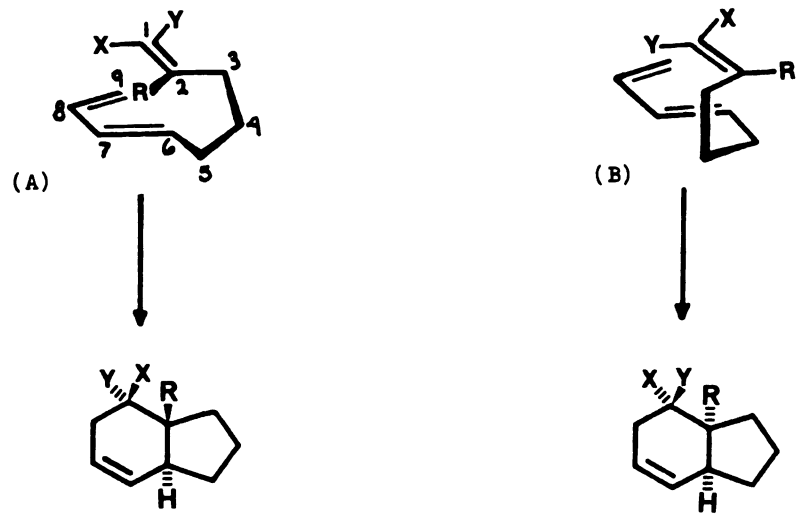


Figure 16. *Exo* and *endo* transition states for the IMDA reactions of 1,6,8-nonatrienes.

result of a "concerted but non-synchronous" mechanism wherein bond formation between one pair of carbon atoms precedes bond formation at the other termini. Using frontier molecular orbital theory as a guide,[74,75] the following conclusions regarding the observed selectivities were formulated. For the IMDA cyclizations involving terminally activated dienophiles, the LUMO coefficient at C_2 should be greater in magnitude than the coefficient at C_1,[75,76] and therefore bonding between C_2 and C_6 should be initiated first. In this situation, the steric interactions involving the chain linking the diene and dienophile develop at an early stage of the reaction, as the five-membered ring is forming, and become a dominant factor in the course of the reaction. The *exo* transition state A is thus favored under these circumstances because of the non-bonded interactions which develop in transition state B between the C_7 hydrogen and the C_3 methylene group in the connecting chain. For trienes which possess internally activated dienophiles, C_1 bears the larger LUMO coefficient and thus bond formation between C_1 and C_9 precedes bond formation between C_2 and C_6. In this case, the steric and/or electronic features which disfavor transition state A relative to transition state B are not as clear, although Roush[69] has suggested that close approach between C_1 and C_9 is best accomodated in a skewed, *cis*-fused transition state. On the basis of the foregoing discussion, one might anticipate that the *exo/endo*

cyclization selectivity for substrates possessing dienophile 1,2-diactivation, as in the present study, should be governed by an even more complex interplay of steric and electronic effects.

As a general remark concerning both *exo* and *endo* cyclization modes for the substrates studied here, it is apparent from molecular models that when a product-like boat arrangement of diene and dienophile is attained, the internal C_5 carbonyl group is tilted out of planarity with the dienophile double bond by about 30-40° due to torsional forces within the connecting chain. The restricted π orbial overlap is expected to cause a slight decrease in magnitude of the LUMO coefficient at C_3 (for numbering, see Figure 17). Thus, in the absence of other steric factors, it is presumed that there would exist a moderate polarization of the dienophile double bond such that the substrates might behave as weak terminally activated trienes.

Also, it is anticipated that the presence of an sp^2 hybridized center in the connecting chain (*i.e.*, the C_5 carbonyl group) is going to considerably lessen the previously noted unfavorable non-bonded interactions associated with the *endo* transition state. Molecular models indicate that the position of the C_5 carbonyl group in an *endo* transition state is not well-suited for effective secondary orbital overlap and hence, stabilization of the

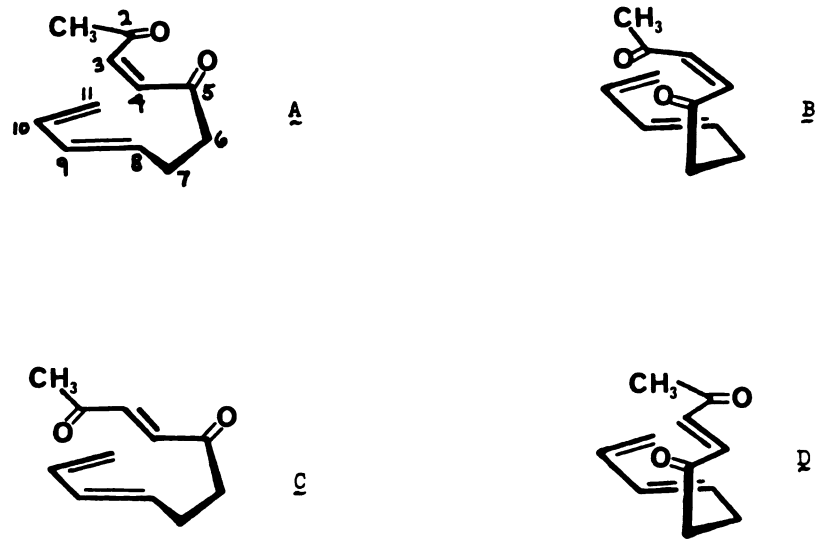


Figure 17. *Exo* and *endo* transition states for trienes 10~3 and 10~6.

endo transition state by this interaction is not expected to be a dominating feature.

Noteworthy for substrate 10~3 in Scheme 28 is the comparatively low temperature at which cyclization takes place. Other examples in the literature which exhibit this rapid a cyclization rate to give bicyclic[4.3.0] systems all employ an activated alkyne as the dienophile.[62,69] In the absence of steric factors, *i.e.*, diene and/or dienophile substitution, *cis*-1,2-diactivation as in 10~3 seems to contribute strongly towards lowering the dienophile LUMO energy, a situation not unlike that in the potent dienophile, maleic anhydride.

The lack of selectivity in the cyclization of 103 is thought to be the result of competetive stabilizing and destabilizing forces present in *endo* transition state B (see Figure 17) which contribute towards its total energy in such a way as to make the two cyclization modes comparable in energy. Thus, relative to *exo* transition state A, the *endo* transition state is destabilized because of non-bonded interactions experienced between the diene and connecting chain. But because the destabilization is attenuated due to the presence of the C_5 carbonyl group, secondary orbital overlap using the terminal acetyl group becomes a competetive factor in determining transition state energy, and thus stabilization is also experienced in this cyclization mode. Compatible with these arguments is the moderate selectivity observed in the cyclization of *trans*-enedione 106. In this case, secondary orbital overlap by the terminal acetyl group would serve to stabilize transition state C, while non-bonded interactions due to an *endo* orientation of the connecting chain destabilize transition state D. The stabilizing and destabilzing forces thus conspire to create a selectivity for the *trans*-fused product 111a, as observed. The magnitude of the forces under consideration must be quite small, though, as the energy difference between transition states C and D is only *ca.* 0.35 kcal/mole.

The presence of the methyl group in *cis*-enedione 105 noticeably perturbs the relative energies of the *exo* and

endo transition states as evidenced by the reasonably high selectivity for the *trans*-fused product 112a (see Scheme 28). Electronically, substitution of a methyl group at C_4 should serve to further polarize the dienophile double bond in such a way as to increase the LUMO coefficient at C_4.[75,76] Thus, it is expected that cycloaddition might occur in a comparatively less synchronous manner, with bond formation between C_4 and C_8 significantly preceding bond formation between C_3 and C_{11}. Representations of non-synchronous transition states for 105 are given in Figure 18. From a comparison of the top views A and B, it appears that the incipient angular methyl group experiences an additional non-bonded interaction in

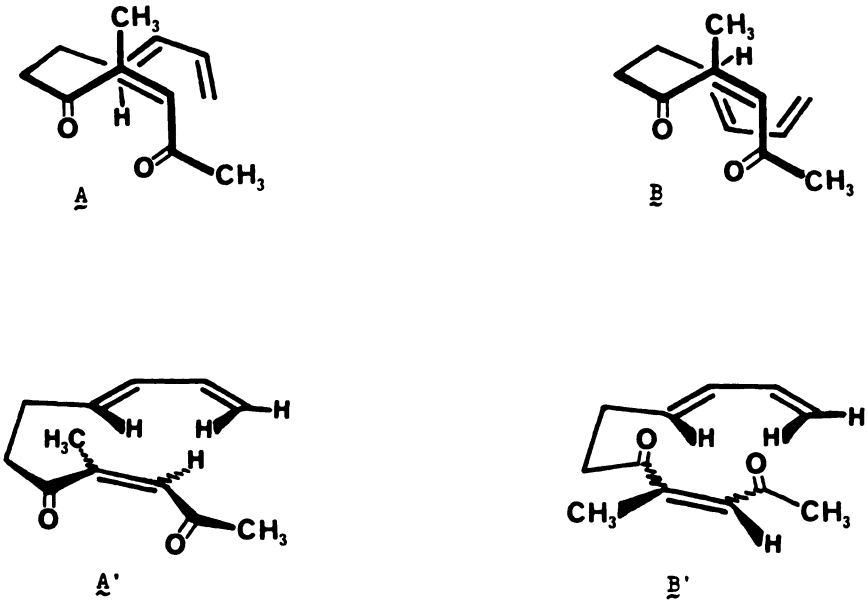
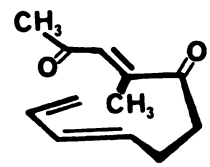


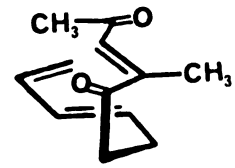
Figure 18. Non-synchronous *exo* and *endo* transition states for triene 105.

transition state A (the one which leads to the major product) due to its proximal approach with H-9 of the diene. However, in transition state B, the terminal acetyl group lies over the diene, and it is suspected that because of the larger distance separating C_3 and C_{11} in this presumedly non-synchronous transition state (depicted by A' and B'), secondary orbital overlap between the C_2 carbonyl group and diene in *endo* transition state B' is going to be severely weakened. Therefore the diene will perceive the terminal acetyl group only in a steric sense, an interaction of considerably less importance in *exo* transition state A'.

The effect of the methyl group in *trans*-enedione 109 should not be one which further polarizes the dienophile double bond. Rather, it is expected that $A^{1,3}$ strain produced by the *peri* arrangement of the methyl group and C_2 carbonyl oxygen would result in a slight disruption of π orbital overlap between the latter and the dienophile double bond. Therefore, it is expected that the LUMO coefficient at C_4 should not differ significantly from the unsubstituted dienophile double bond of 106. Presumably it is the inhibition of conjugation of <u>both</u> carbonyl groups with the dienophile double bond during IMDA cyclization which accounts for the much higher cyclization temperatures in this case. The lack of cyclization selectivity is thought to be the result of opposing forces in both *exo* and *endo* transition states. Thus, transition



A



B

Figure 19. *Exo* and *endo* transition states for triene 109.

state A in Figure 19 is destabilized by steric interactions between the methyl group and C_9 hydrogen, but lacks the less favorable *endo* orientation of the connecting chain. In transition state B, these steric consequences are reversed. The contribution of the terminal acetyl group towards the total energy of each transition state is less clear; *i.e.*, the terminal acetyl group does not seem to exert a dominating steric effect to destabilize transition state A nor does secondary orbital overlap strongly stabilize it.

In retrospect, it is apparent that the cyclizations of the four trienes in this study are not dominated by one strong steric or electronic effect. In order to examine more clearly the effect of dienophile 1,2-diactivation, it would be necessary to "insulate" the electronics of the dienophile from the torsional effects which develop in the connecting chain as the transition state geometry is reached. It might therefore be

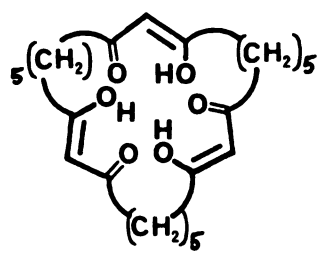
informative to examine IMDA cyclizations of substrates in which the diene and dienophile are separated by a greater number of atoms. As mentioned earlier, flexibility in the alkadienylfuran synthesis would enable an easy entry to these other systems. Finally, it should be noted that the cyclization selectivities observed in the present study contrast sharply with the results of White and Sheldon,[62] who examined the IMDA reactions of trienes possessing dienophile 1,2-diester activation (see Figure 7, for example) and found a high selectivity for *trans*-fused products in all cases. It is speculated that the lower reaction temperature employed in the present study (with the exception of 109) allows secondary orbital effects to compete with the steric factors which seem to dominate in the IMDA reactions performed at higher temperatures.[77]

D. SYNTHESIS OF MACROCYCLIC POLYKETONES

Macrocyclic chemistry has grown enormously since the pioneering studies of large-ring hydrocarbons, ketones, and lactones conducted by Ruzicka[78] during the first half of this century. Since then, macrocyclic compounds have attracted an interdisciplinary range of interest owing to their diverse physical and chemical properties.[79,80] Spawned by the discovery of the crown ethers in 1967 by Petersen,[81] there has been a great deal of interest in the design and synthesis of macrocyclic polydentate

ligands which can selectively complex metal ions, a phenomenon of considerable importance from both a chemical and biological point of view (*e.g.* phase transfer catalysis[82a] and ion transport across lipid membranes[82b]). Most of the synthetic efforts to date have focused on the incorporation of polyether functionality in the various topological arrangements (*e.g.*, coronands, cryptands, podands, and spherands[83]). The incorporation of a donor oxygen atom in the form of a carbonyl group, however, has received much less attention, even though it is known that ester carbonyl oxygens can ligate effectively as in the K^+ ion complex of the dodecadepsipeptide, valinomycin.[84]

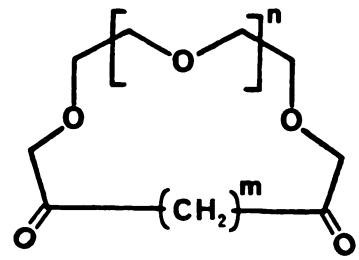
Several groups have reported synthesis of macrocycles containing 1,3-diketone units,[85-87] and it is not surprising that the β-diketonates derived therefrom have shown good metal ion binding properties. Hexaketone 119, for example, has been shown to be a specific host for UO_2^{2+}, an ion whose coordination sphere is *quasi*-



119, enol form

planar hexacoordinate. Other complexes have been observed for oxo-crown ethers of the type 120 (m = 6,8,9; n = 3) with K^+ (Zeise's salt) in chloroform solution,[88] although

it was not mentioned in this communication what effect, if any, the carbonyl groups had upon the complexing ability of these compounds.

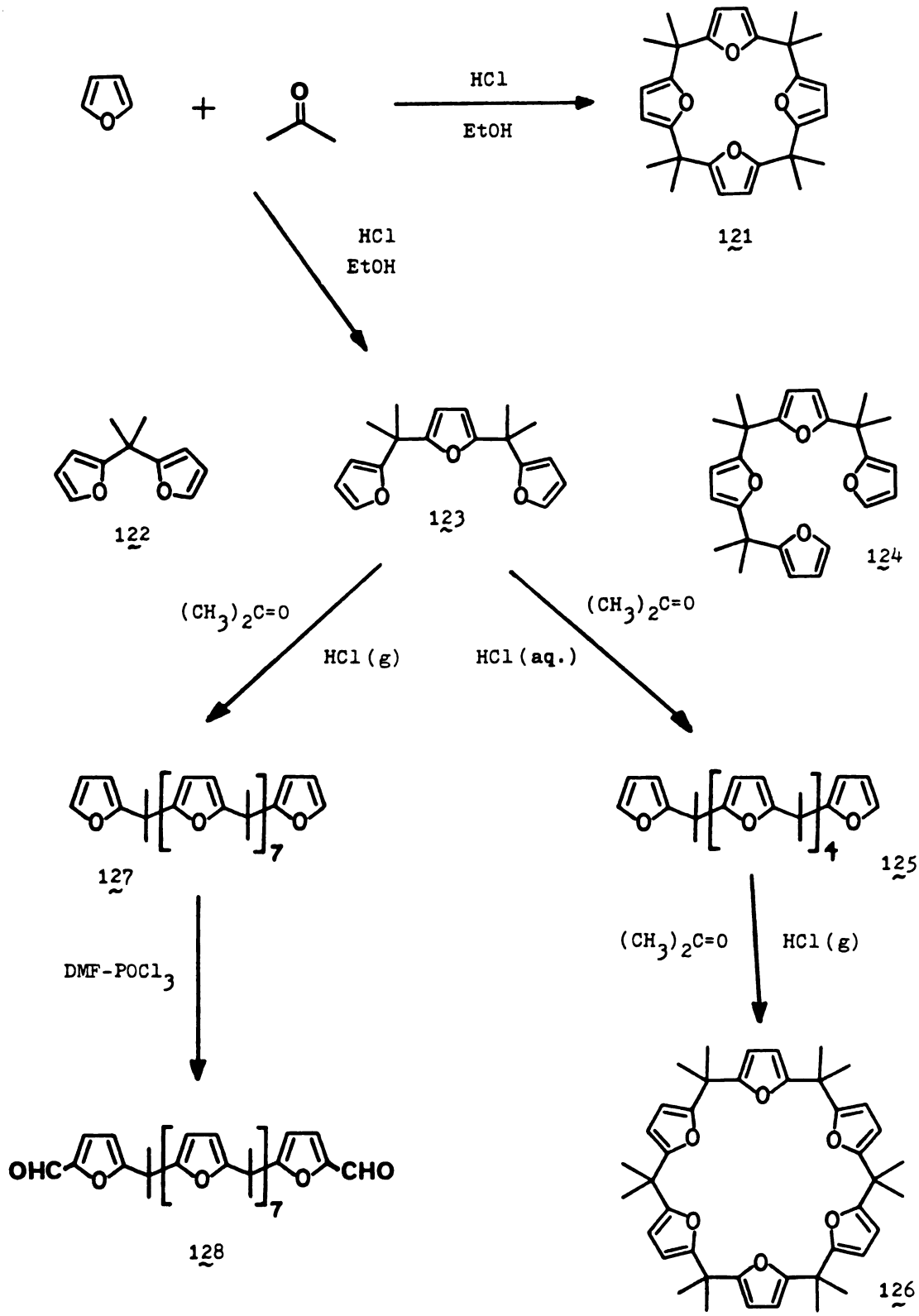


120 m = 6,8,9
n = 3

Because of the limited number of methods available for the synthesis of macrocyclic polyketones,[89] we wanted to explore the chemistry of the known furan macrocycles 121 and 126 (see Scheme 29), with the hope that furan ring-opening reactions would enable the production of polyketone derivatives. Thus, condensation of furan with excess acetone in ethanolic aqueous HCl produces the cyclic furan-acetone cyclic tetramer 121[90] in 22-29% yield. The survival of this product under the strongly acidic reaction conditions can be attributed to the fact that 121 precipitates from the reaction medium as it is formed, thereby minimizing side reactions such as hydrolysis and/or polymerization. The ease of preparation and ready availability of starting materials enables the production of 121 in relatively large quantities (up to 70 grams per run), an attractive feature for the starting point in an exploratory project!

Under a different set of reaction conditions in which furan is used in excess,[90a] condensation with acetone

Scheme 29

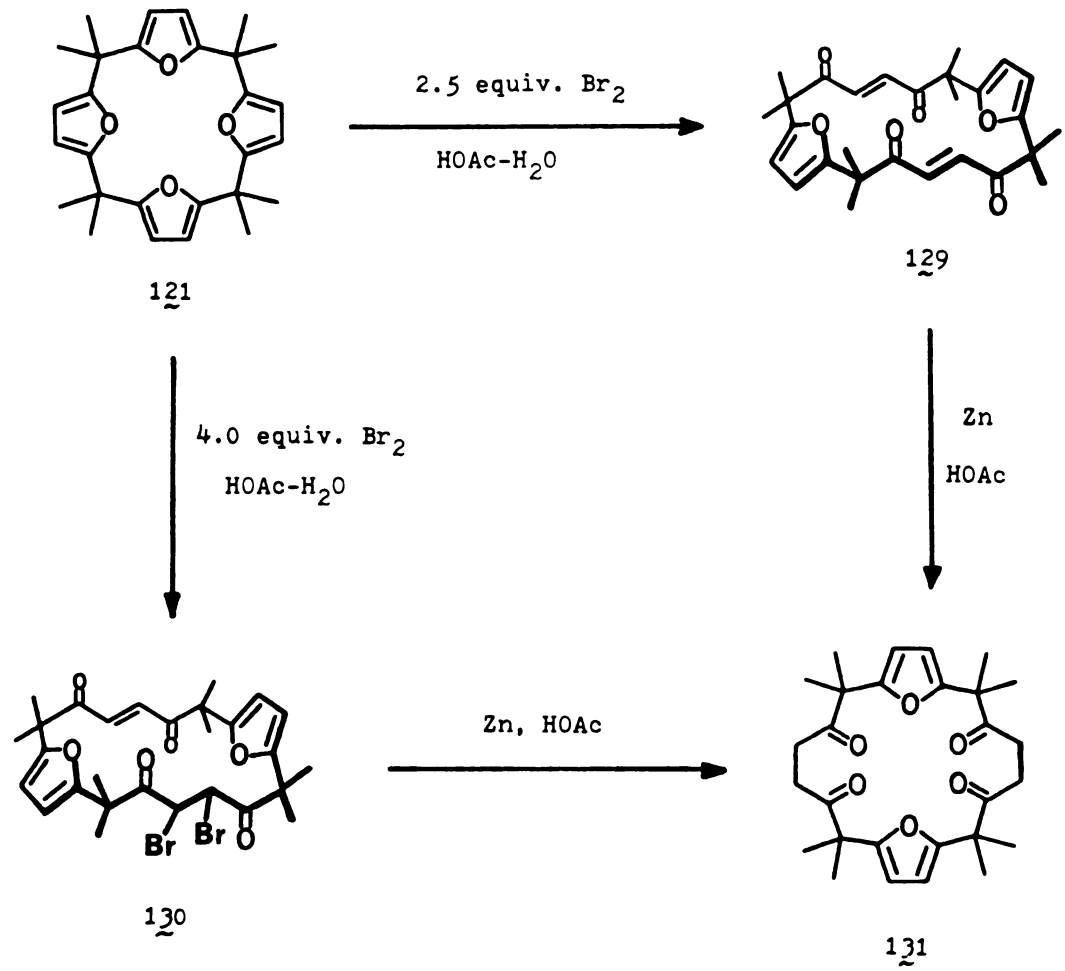

HCl
EtOH
121
HCl
EtOH
122
123
124
$(CH_3)_2C=O$
HCl(g)
$(CH_3)_2C=O$
HCl(aq.)
127
125
DMF-$POCl_3$
$(CH_3)_2C=O$
HCl(g)
OHC
CHO
128
126

gives the linear products 122, 123, and 124 (see Scheme 29). Using the two-step procedure worked out by Kobuke and co-workers,[91] linear "trimer" 123 can be converted to the cyclic hexamer 126. The successful condensation of two molecules of 123 with acetone to give linear hexamer 125, with no further oligimerization, relies on the insolubility of 125 in the aqueous ethanolic medium. In an attempt to simplify the two-step conversion of 123 to 126, anhydrous reaction conditions were employed (*i.e.*, HCl gas was used instead of aqueous HCl) with the hope that cyclization to 126 would occur *via* a soluble linear hexamer. After stirring for several hours, the reaction mixture yielded a thick precipitate. Analysis of this material by proton NMR indicated the presence of furan α-protons, a clear indication that cyclization had not occurred. Formylation of this linear oligimer gave a dialdehyde whose 250 MHz ^{1}H NMR spectrum exhibited four different methyl group signals of equal intensity, data consistent with an oligiomeric structure containing nine furan rings. The products from the condensation and subsequent formylation reaction are thus formulated as 127 and 128, respectively (see Scheme 29). Although the anhydrous reaction conditions employed in the condensation did not meet the requirements for a "one-pot" conversion of 123 to 126, the procedure does constitute a relatively efficient method for the controlled oligimerization of 123.

Initial attempts at oxidizing cyclic tetramer 12̃1 were performed using the methanolic bromine method of Clauson-Kaas.[7] Thus, a suspension of 12̃1 and sodium acetate in methanol decolorized a solution of methanolic bromine (2.5 equivalents) which was added dropwise to 12̃1 over a period of about three hours. The methoxylated derivative of 12̃1 was isolated and then hydrolyzed using a variety of acidic conditions to give large amounts of a viscous yellow oil, and a small amount of a bright yellow crystalline product whose yield was never much greater than 10%. A more efficient method for the production of this compound was found which involves the dropwise addition of 2.5 equivalents of bromine to a well-stirred suspension of finely divided 12̃1 in moist acetic acid. In this way, yields ranging from 65-74% were obtained. The presence of a carbonyl stretching frequency in the infrared spectrum at 1695 cm^{-1} and a molecular ion peak at *m/e* 464 in the mass spectrum indicated that this material must be a di-ring-opened derivative of 12̃1, and from the ^{1}H and ^{13}C NMR spectra, it was clear that the more symmetrical of the two possible di-ring-opened regioisomers was obtained. Because of the downfield chemical shift of the olefinic protons (6.95 ppm) in the proton NMR spectrum, it was concluded that oxidative ring-opening had proceeded to give *trans*-enedione functionalization, not a surprising result in view of the rather acidic conditions of the reaction.[96]

Thus, the structure of this compound was formulated as di-ring-opened *trans*-enedione 129 (see Scheme 30). Verification of the *trans*-enedione configuration in 129 was provided by single-crystal X-ray analysis (see Figure 20).[92] An inclusion compound was formed upon

Scheme 30



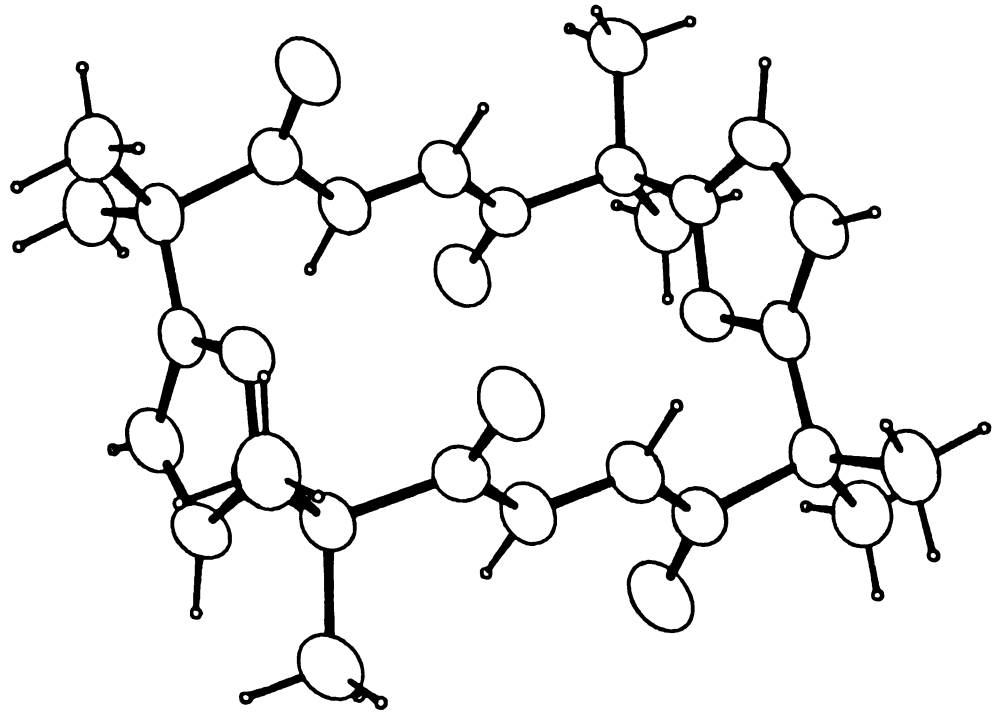


Figure 20. ORTEP representation of di-ring-opened *trans*-enedione 129 with the acetic acid dimers omitted for clarity.

recrystallization of 129 from acetic acid, with a host-guest ratio of 1:4 as determined by integration in the proton NMR spectrum of the adduct. From the X-ray analysis, it was found that acetic acid dimers[93] were located in the intermolecular cavities of the host lattice, with the mean plane of each acetic acid dimer being perpendicular to the mean plane of host 129 (see Figure 21).

Isolation of only the more symmetrical of the two possible di-ring-opened regioisomers from the bromine-acetic acid oxidation procedure is attributed to the fact that 129 is rather insoluble in acetic acid and precipitates from the reaction mixture as it is formed, thus protecting it from further oxidation and/or degradation. It is suspected that a lesser amount of the "1,2" di-ring-opened regioisomer is also produced, but is destroyed because it does not precipitate from the strongly acidic reaction medium. Attempts at effecting further ring-opening of 121 using 4.0 equivalents of bromine in acetic acid failed, and gave instead the dibromo-*trans*-enedione 120 (see Scheme 30), in addition to greatly diminished yields of 129. The bromine adduct 130 and *trans*-enedione 129 were shown to be related by the reduction of each using zinc in acetic acid to the same product, saturated tetraketone.[131]

Attention was then turned to oxidations using MCPBA. Treatment of cyclic tetramer 121 in hot chloroform with 4.2 equivalents of MCPBA gave excellent yields of the

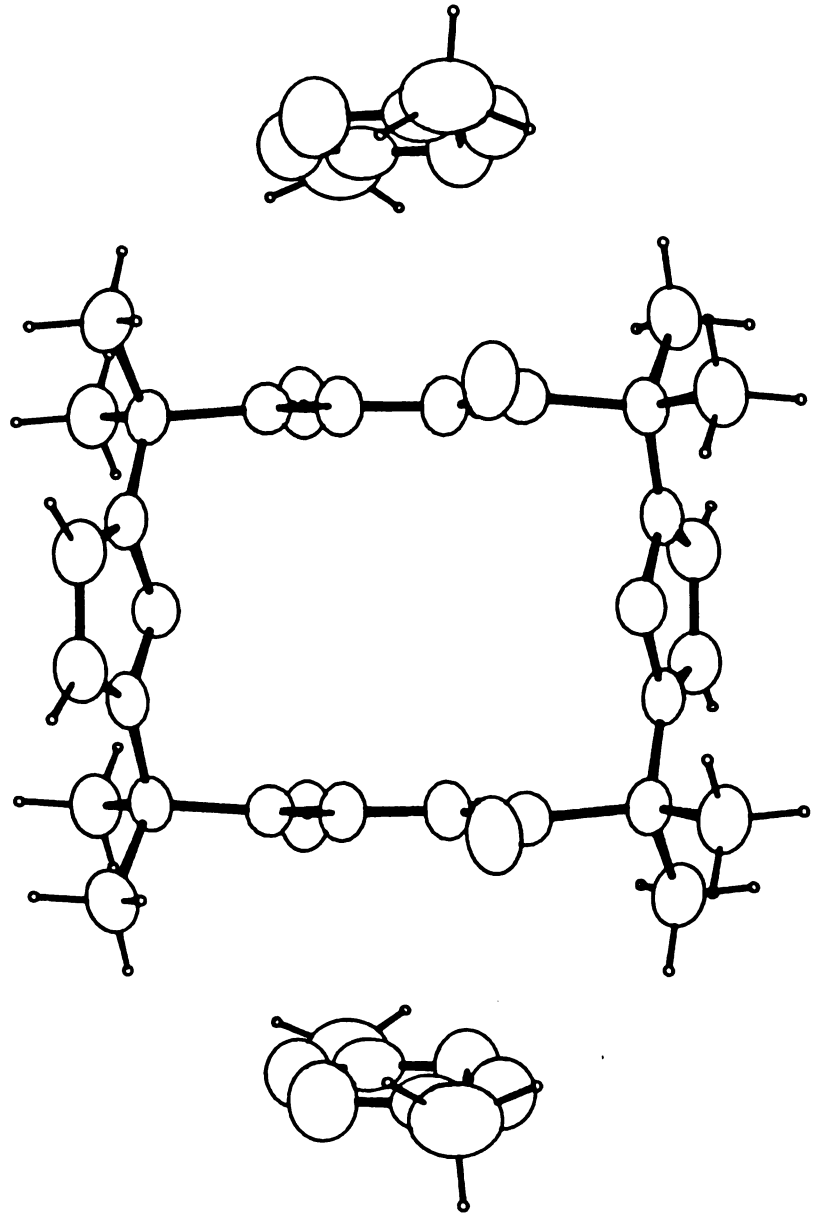
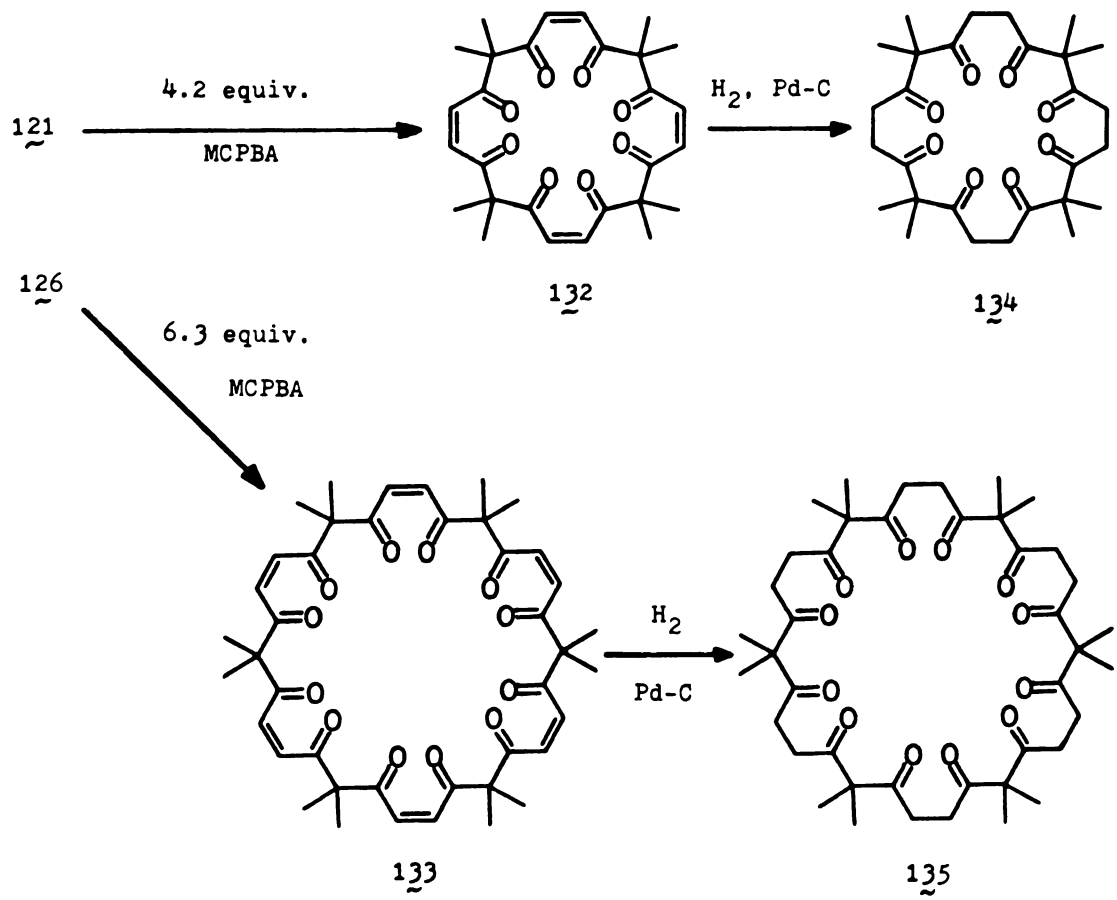


Figure 21. "Top view" of di-ring-opened *trans*-enedione 129 showing the orientation of the acetic acid dimers.

fully ring-opened octaketone 132 (see Scheme 31). The symmetry of this product is evident from its uncomplicated ^{1}H and ^{13}C NMR spectra (2 and 4 signals, respectively). In accordance with the *cis*-enedione double bond configuration in 132, the olefinic protons resonate 0.47 ppm upfield of those in the macrocyclic *trans*-enedione 129.

Scheme 31



Likewise, treatment of the cyclic furan-acetone hexamer 126 with 6.3 equivalents of MCPBA resulted in oxidation of all six furans to give the dodecaketone 133 in good yield. Once again, the high degree of symmetry and *cis*-enedione functionalization in 133 is evident from the ^{1}H and ^{13}C NMR spectra. Single-crystal X-ray analysis of tetra-ring-opened octaketone 132 was performed (see Figure 22),[92] verifying the degree of oxidation and configuration of enedione double bonds. An interesting conformational feature depicted in the stereostructure of 132 (see Figure 22) is the significant deviation from planarity of one of the carbonyl groups with the remainder of the enone grouping in each of the *cis*-enedione moieties, a situation which must arise because of unfavorable non-bonded interactions between the carbonyl oxygens in a coplanar arrangement. In contrast, the stereostructure of di-ring-opened *trans*-enedione 129 (see Figures 21 and 22) reveals an entirely coplanar arrangement of the atoms which comprise each of the *trans*-enedione units. The difference in geometry, and hence degree of π orbital overlap, of the *cis*- and *trans*-enedione moieties results in markedly different UV-vis spectra for 129 and 132 in that the more extended *trans*-enedione chromophore in 129 absorbs at longer wavelengths than the twisted *cis*-enedione chromophore in 132. This tendency has also been noted for simple *cis*- and *trans*-enediones[9b] (see Table 6). Hydrogenation of the enedione double bonds in 132 and 133

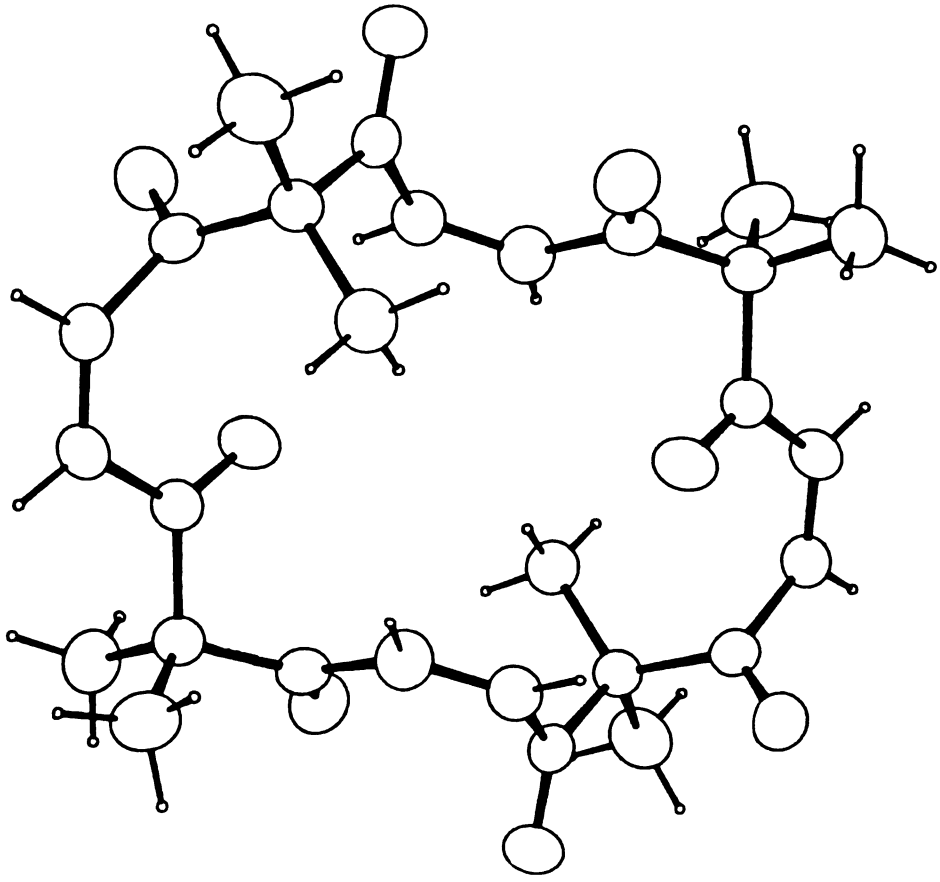


Figure 22. ORTEP representation of tetra-ring-opened octaketone 132.

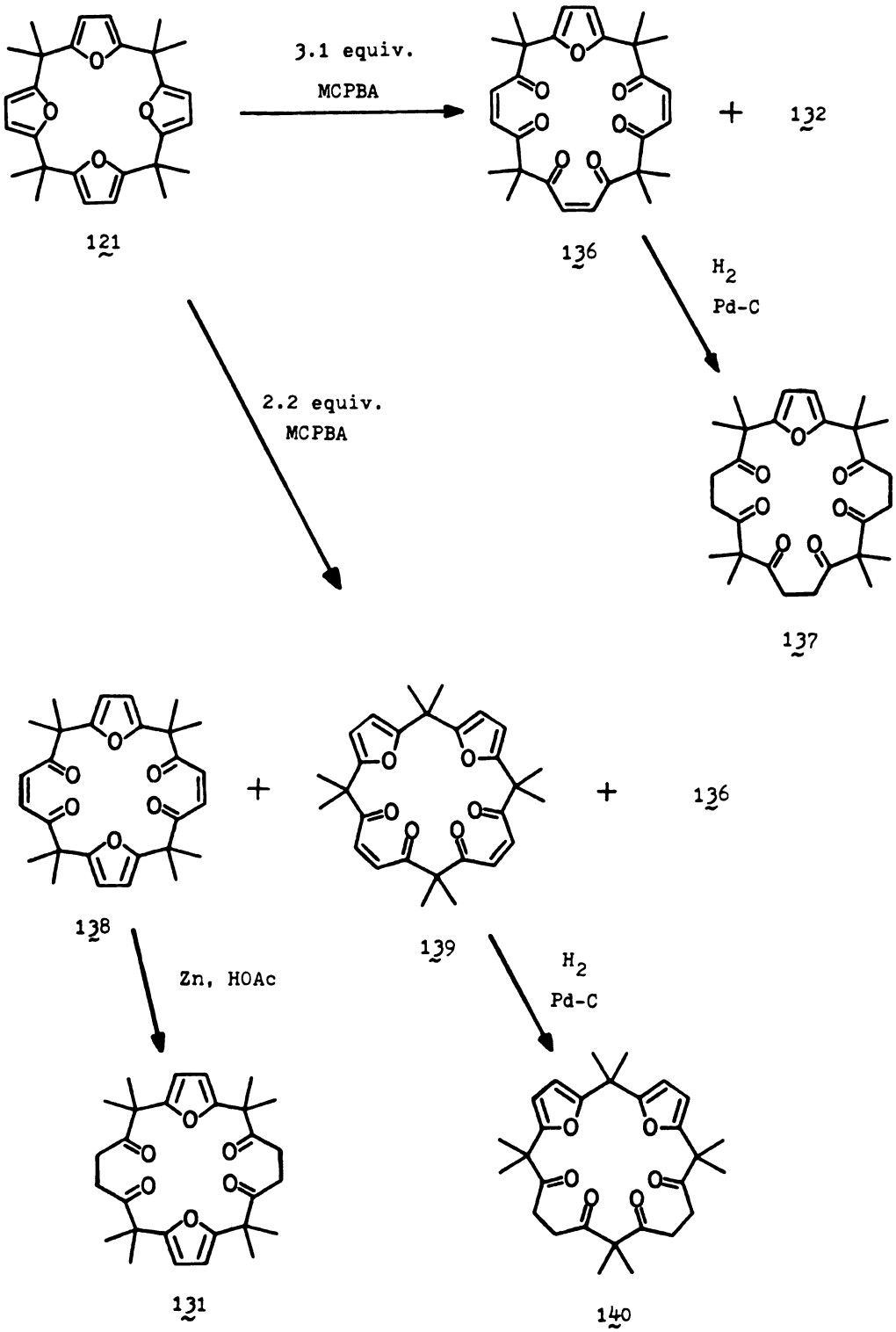
Table 6. Electronic absorption spectra for *cis*- and *trans*-enediones.

compound (solvent)	UV-vis ; λ_{max}, nm(log ε)
di-ring-opened *trans*-enedione 129 (CH_3CN)	382(3.25), 304(3.67), 232(4.52)
tetra-ring-opened *cis*-enedione 132 (CH_3CN)	shoulder at ~290(2.9), 212(4.4)
cis-3-hexene-2,5-dione[9b] (ethanol)	284(2.00), 221(3.58)
trans-3-hexene-2,5-dione[9b] (ethanol)	328(1.8), 227(4.15)

gave the crystalline macrocyclic polyketones 134 and 135, respectively.

By varying the stoichiometry of MCPBA in the oxidation of tetramer 121, several other enedione-functionalized macrocycles were obtained (see Scheme 32). Thus, treatment of 121 with 3.1 equivalents of MCPBA gave a mixture of tri-ring-opened hexaketone 136 and a small amount of tetra-ring-opened 132, which were readily separated by flash column chromatography to give pure 136 in 60% yield. Hydrogenation of the enedione double bonds in 136 gave the saturated hexaketone 137 in good yield. Using 2.2 equivalents of MCPBA, a three-component mixture resulted which, after separation by flash column chromatography, gave the di-ring-opened regioisomers 138 and 139 in yields of 32%

Scheme 32

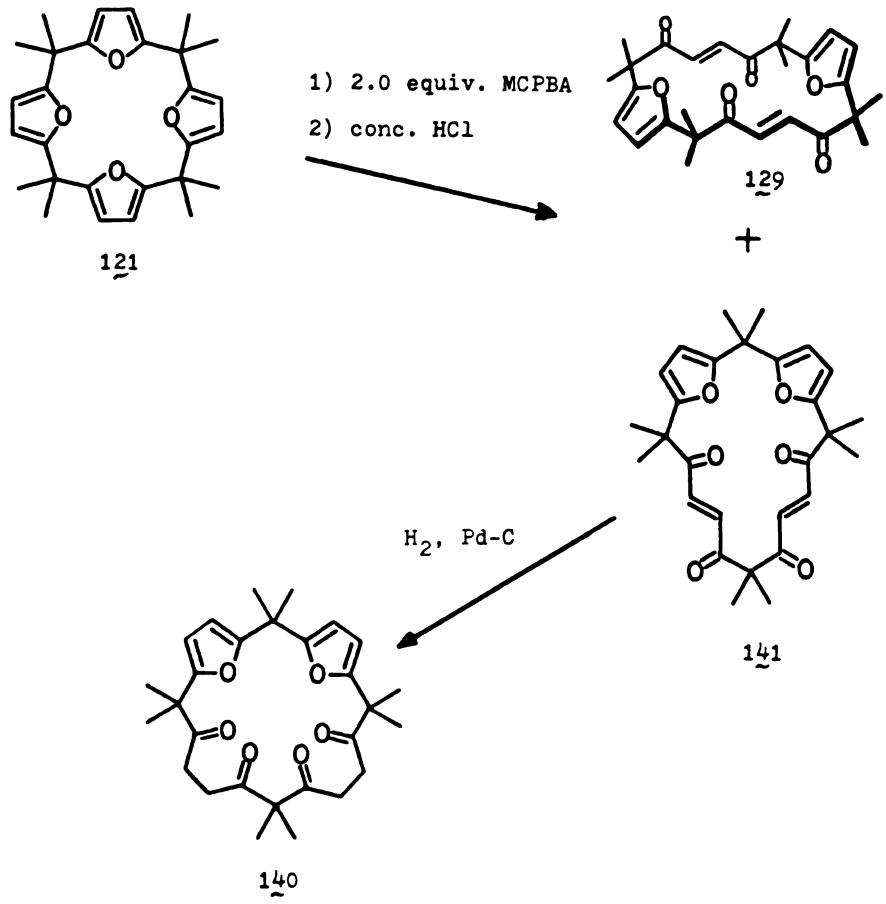

3.1 equiv.
MCPBA
+
132
121
136
H2
Pd-C
2.2 equiv.
MCPBA
137
+
+
136
138
139
Zn, HOAc
H2
Pd-C
131
140

and 36%, respectively, in addition to 17% of tri-ring-opened 136. In accordance with the anticipated *cis*-enedione configuration, the olefinic protons in di-ring-opened 138 resonate at 0.95 ppm upfield from those in *trans*-enedione 129; moreover, reduction of the enedione double bonds in 138 using zinc in acetic acid gave 131, the same product as obtained from 129. Hydrogenation of the regioisomeric di-ring-opened 139 gave a different saturated tetraketone derivative, 140.

In another experiment using 2.0 equivalents of MCPBA, a small amount of concentrated aqueous HCl was added to the crude reaction mixture, causing isomerization of the initially formed *cis*-enedione products. The two products which survived the acidic conditions were the regioisomeric di-ring-opened *trans*-enediones 129 and 141, isolated in 41% and 19% yield, respectively (see Scheme 33). That 141 differs from 139 only in the configuration about the enedione double bonds was demonstrated by catalytic hydrogenation of the former to give saturated tetraketone 140, the same product as obtained from 139. Attempts at isomerization of *cis*-enediones 132 and 136 using either acids (*e.g.*, conc. HCl in chloroform, conc. HCl in acetic acid, acetic acid and heating) or base (*e.g.*, pyridine, triethylamine in chloroform) gave complex mixtures of intractable products.

The results from these studies leave little doubt that furan-containing macrocycles can serve as a convenient

Scheme 33



source of polyketo macrocycles *via* oxidative transformations using MCPBA.[94] Attack of the peracid does not seem to be particularly sensitive to the rather hindered environment of the furan rings in 121 and 126 as evidenced by the efficacy of peracid ring-opening to give the fully oxidized polyketo derivatives 132 and 133.

Preliminary investigations on the ability of several of the polyketo macrocycles prepared here (129, 131, 132, 134, and 135) to complex cesium ion have given

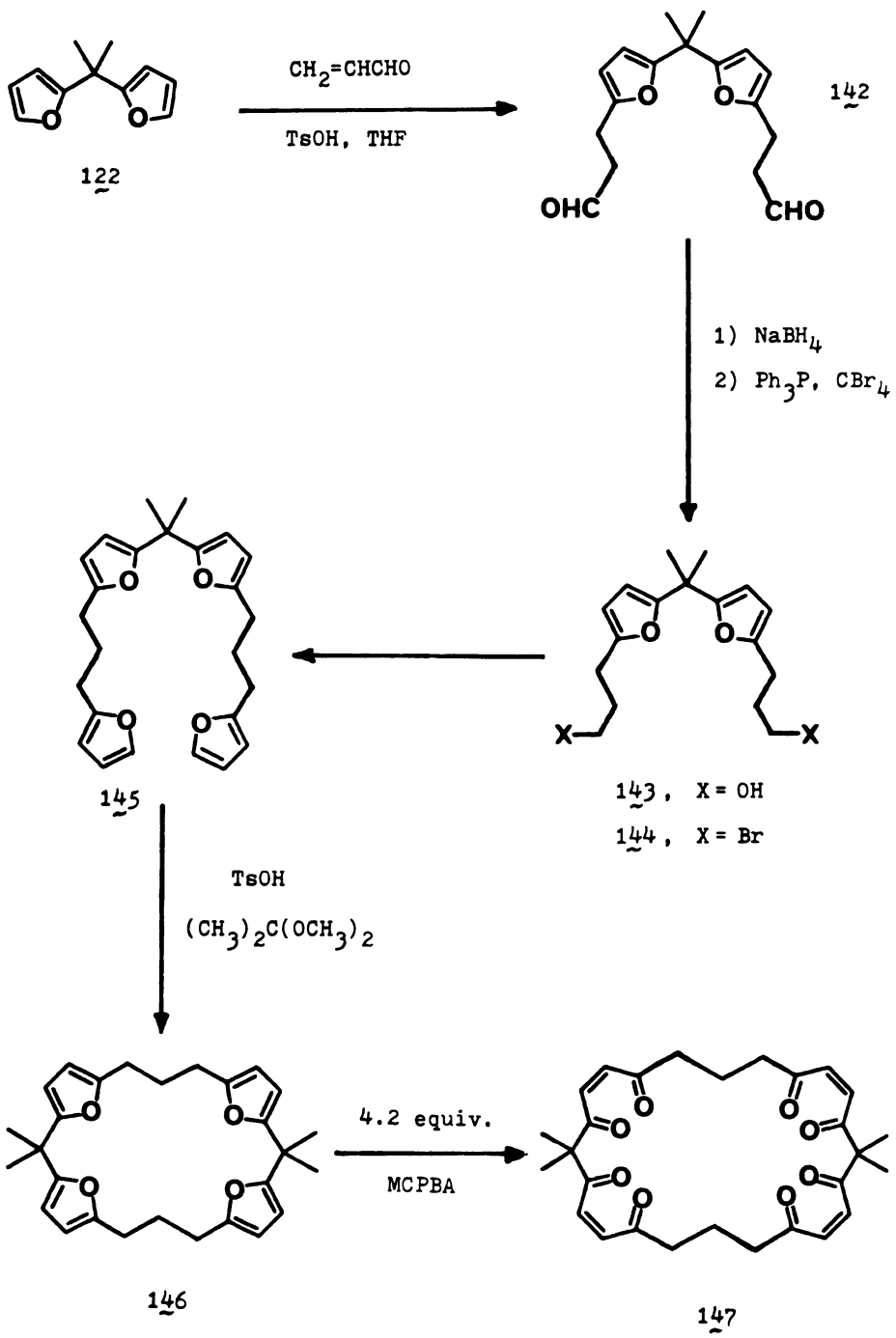
negative results.[95] Problems were encountered with the reactivity of several of these compounds when tetrahydrofuran solutions containing cesium octanoate were made up. It seems likely that the carboxylate anion might function as a relatively strong base under the anhydrous conditions with the highly electropositive cesium counterion. Thus, the saturated polyketones 131, 134, and 135 would be subject to intra- and intermolecular condensation reactions, and the unsaturated polyketones 129 and 132 could add the carboxylate anion in a Michael fashion. Investigations of the complexation of polyketo macrocycles with other metal ions have not yet been pursued.

One of the major concerns regarding the macrocyclic polyketones discussed thus far is the presence of a tertiary center adjacent to each carbonyl group. If the carbonyl oxygen is to function as a ligand, then it is anticipated that an adjacent *gem*-dimethyl group would only serve to destabilize complex formation in a steric sense as the metal ion approaches the ligand (on the other hand, one might argue that an adjacent tertiary center would also retard undesired addition reactions to the carbonyl group, as well as preclude enolization in that direction). Also, it is possible that conformational mobility in the polyketo macrocycles discussed above is somewhat restricted because of the many *gem*-dimethyl groups,[96] and thus, it might be difficult

for the molecule to assume a conformation required for complexation. In order to overcome some of these inherent problems, synthesis of the extended furan macrocycle 146 was undertaken (see Scheme 34).

Acid-catalyzed addition of acrolein[97] to 2,2-difurylpropane[90a] (excess acrolein, catalytic *p*-touluenesulfonic acid, THF, reflux, 6 h) gave dialdehyde 142 in 43% yield after column chromatography. Reduction to diol 143 (excess $NaBH_4$, methanol, -10°C to 0°C, 1 h; 98%) followed by bromination[98] (4.4 equiv. CBr_4, 4.6 equiv. Ph_3P, ether, r.t., 4 h; 81%) gave dibromide 144 in 79% yield from 142. Treatment of 144 with 4 equivalents of 2-lithiofuran[99] (THF-hexane, -78°C to r.t., 12 h; 85%) gave the linear furan compound 145 which was cyclized in dilute solution (6.3 equiv. 2,2-dimethoxypropane, 4.2 equiv. *p*-toluenesulfonic acid, benzene, 60°C, 20 h) to give 1,1,15,15-tetramethyl-[1.3.1.3]furanophane 146 in 47% yield after column chromatography. Incorporation of the trimethylene bridges is expected to endow 146 with much more conformational mobility as compared to the isomeric tetramer 121. Additionally, relief of steric impedance about the furan rings in 146 might enable the production of other large-ring compounds *via* cycloaddition reactions.[100] For the present, however, 146 was oxidized with 4.2 equivalents of MCPBA to give the 24-membered ring octaketone 147 in 48% yield. The chemistry of this compound, including possibilities for metal ion complexation, have not yet been investigated.

Scheme 34


CH2=CHCHO
TsOH, THF
122
142
OHC
CHO
1) NaBH4
2) Ph3P, CBr4
143, X = OH
144, X = Br
145
TsOH
(CH3)2C(OCH3)2
146
4.2 equiv.
MCPBA
147

EXPERIMENTAL

General Methods

All melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Unless otherwise noted, all NMR spectra were obtained in chloroform-d_1 solution with the chemical shifts reported in parts per million downfield from tetramethylsilane internal standard. Proton NMR spectra were obtained on Varian T-60 and Bruker WM-250 spectrometers at 60 MHz and 250 MHz, respectively. Carbon-13 NMR spectra (proton-decoupled) were obtained on Varian CFT-20 and Bruker WM-250 spectrometers at 20 MHz and 62.9 MHz, respectively. Unless otherwise noted, NMR data are reported at 60 MHz for proton spectra and 20 MHz for carbon-13 spectra. Infrared spectra (IR) were obtained on a Perkin-Elmer 237 grating spectrophotometer and were calibrated using the polystyrene 1601 cm^{-1} peak. Ultraviolet and visible spectra (UV-vis) were recorded on a Cary 219 spectrophotometer in acetonitrile solution (MCB-Omni Solv spectral grade) using matched quartz cells. Mass spectra (MS) were obtained on a Finnigan 4000 instrument at 70 eV or, when noted, using ionized methane (CI). Combustion analyses were performed at Guelph Chemical Laboratories, Ltd., Spang Microanalytical Laboratory, and Galbraith

Laboratories, Inc. Flash column chromatography refers to the method of Still, Kahn, and Mitra,[101] using Whatman LPS-2 silica gel (37-53 μm). For regular column chromatography, "Silica Gel 60" (EM cat. #7734, 70-230 mesh) was employed. Thin layer chromatography (TLC) was performed using Machery-Nagel "Polygram SIL N-HR/UV_{254}" 0.2 mm pre-coated silica gel plates. Technical grade *m*-chloroperoxybenzoic acid (MCPBA) was used as obtained from Aldrich Chemical Company (80-90%; the amounts used were calculated assuming 85% by weight peroxy acid). Dry ether, benzene, and tetrahydrofuran (THF) were obtained by distillation from potassium-benzophenone under an atmosphere of nitrogen. Dry methylene chloride was obtained by passage through a column of alumina (Woelm B, Akt. I).

cis-3-Hexene-2,5-dione (37), *cis*-3-octene-2,5-dione (39a), *cis*-enedionediester 41a, *bis*-spiroketal 43, and tetracyclic dione 20

General Procedure:

To a magnetically stirred solution of the furan compound (10 mmol) in methylene chloride or chloroform (50 mL) at 0°C was added MCPBA (11 mmol) in one portion. The reaction mixture was stirred at 0°C for 1-2 h and then at room temperature for an additional 1-3 h. The resulting milky-white suspension was extracted with saturated aqueous $NaHCO_3$ (3 × 75 mL), dried over anhydrous Na_2SO_4, filtered,

and the solvent was removed under reduced pressure. The products thus obtained were essentially pure as evidenced by TLC (SiO_2, ether) and NMR. Purification methods (if any), yields, and spectral data are given below.

cis-3-Hexene-2,5-dione (37)[9a,b]

Obtained as a very pale yellow liquid, 99%. ^{1}H NMR: δ6.18 (s, 2H), 2.18 (s, 6H); ^{13}C NMR: 200.11, 135.32, 29.27 ppm; IR (neat): 1698, 1616 cm^{-1}.

cis-3-Octene-2,5-dione (39a)

Obtained as a very pale yellow liquid, 96%. 250 MHz ^{1}H NMR: δ6.33 (AB quartet, J = 11.9 Hz, 2H), 2.54 (t, J = 7.0 Hz, 2H), 2.30 (s, 3H), 1.66 (sextet, J = 7.0 Hz, 2H), 0.95 (t, J = 7.0 Hz, 3H); 62.9 MHz ^{13}C NMR: 202.72, 200.72, 136.12, 135.32, 44.46, 29.73, 16.97, 13.61 ppm; IR (neat): 1695, 1615 cm^{-1}; MS (CI): m/e = 141 (M+1, base peak).

cis-Enedionediester 41a

Obtained as a very pale yellow oil which was passed through a short column of silica gel (ether eluent) to remove the last traces of MCPBA. Yield = 97%. 250 MHz ^{1}H NMR: δ6.34 (s, 2H), 4.12 (q, J = 7 Hz, 4H), 2.58

(br t, J = 7 Hz, 4H), 2.32 (br t, J = 7 Hz, 4H), 1.67 (m, 8H), 1.26 (t, J = 7 Hz, 6H); 62.9 MHz ^{13}C NMR: 202.25, 173.35, 135.71, 60.25, 42.08, 34.08, 24.38, 22.91, 14.26 ppm; IR (neat): 1725, 1690 cm^{-1}; MS: m/e = 340 (parent), 165 (base peak).

bis-Spiroketal 43[37]

Obtained as a colorless liquid which was passed through a short alumina column (Woelm N, Akt. 1; methylene chloride eluent) to remove last traces of MCPBA. Yield = 87%. An analytical sample was prepared by distillation using a molecular still; bp = 110-120°C (bath temp.), *ca.* 20 mm Hg (lit.[37] bp = 89-90°C, 2 mm). 250 MHz ^{1}H NMR: δ5.93, 5.92 (2s, 4H), 4.08 (m, 4H), 3.85 (q of m, J = 6.7 Hz, 4H), 2.2-1.9 (m, 16H); 62.9 MHz ^{13}C NMR: 132.94, 132.64, 117.15, 116.26, 68.63, 68.36, 36.84, 36.46, 24.99, 24.88 ppm; IR (neat): broad, intense bands at 1075 and 980 cm^{-1}; MS: m/e = 182 (parent), 110 (base peak).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.19
Found: C, 65.42; H, 7.60

Tetracyclic dione 20[21a,b]

Obtained as a white crystalline solid. Yield = 88%. Recrystallized from ethanol, mp = 188-189°C (lit.[21a]

mp = 186-187°C). 250 MHz ^{1}H NMR: δ6.52 (s, 2H), 2.52 (s, 2H), 2.75-2.35 (m, 8H); ^{13}C NMR: 211.62, 136.89, 95.94, 56.24, 38.19, 24.58 ppm; IR (Nujol): 1745 cm^{-1}; MS: m/e = 204 (parent), 108 (base peak).

Isomerization of 39a to *trans*-3-octene-2,5-dione (39b)

To a 5 mm NMR tube containing a solution of 39a (*ca.* 50 mg) in $CDCl_3$ (*ca.* 0.5 mL) was added 2 drops of pyridine-d_5. The progress of the reaction was monitored by 250 MHz ^{1}H NMR, and after 8 h, 39a had completely isomerized. The *trans*-enedione product was not isolated. 250 MHz ^{1}H NMR (*ca.* 10% pyridine-d_5 in $CDCl_3$): δ6.67 (AB quartet, J = 16.5 Hz, 2H), 2.48 (t, J = 7.3 Hz, 2H), 2.20 (s, 3H), 1.50 (sextet, J = 7.3 Hz, 2H), 0.78 (t, J = 7.3 Hz, 3H).

trans-Enedionediester 41b

To a solution of 1.0 g of furandiester 40 (3.1 mmol) in dry methylene chloride (30 mL) at 0°C under an atmosphere of nitrogen was added 4.0 g of pyridinium chlorochromate (18 mmol) in one portion. The mixture was stirred for 1 h at 0°C and then for 24 h at room temperature. A condenser was attached and the dark mixture was refluxed for 8 h. Ether (60 mL) was added to the cooled reaction mixture and the resulting suspension was filtered through a

glass frit packed with Florisil. The gummy black residue remaining in the flask was rinsed several times with ether and filtered. The filtrate solvents were removed under reduced pressure and the semi-solid residue was flash chromatographed using 30% ether-hexane to give 0.63 g of 41b (60%) as shiny white flakes, mp = 54-56°C. 250 MHz ^{1}H NMR: δ6.88 (s, 2H), 4.13 (q, J = 7.2 Hz, 4H), 2.68 (t, J = 7.1 Hz, 4H), 2.32 (t, J = 7.1 Hz, 4H), 1.65 (m, 8H), 1.26 (t, J = 7.2 Hz, 6H); IR (Nujol): 1725, *ca.* 1690 (shoulder) cm^{-1}; MS: m/e = 340 (parent), 226 (base peak).

cis-4-Oxo-2-pentenal (45)[9b]

To a solution of 1.00 g of 2-methylfuran (12.2 mmol) in 45 mL of methylene chloride at 0°C was added 2.7 g of MCPBA (13 mmol) in one portion. The mixture was stirred for 2 h at 0°C and then for 1 h at room temperature. The resulting bright yellow suspension was extracted with saturated aqueous $NaHCO_3$ (3 × 50 mL). The aqueous washings were combined, saturated with NaCl, and extracted with methylene chloride (2 × 35 mL). The organic phases were combined, dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure to give 0.48 g of the title compound (40%) as a bright yellow liquid. The product decomposed over a period of days when stored at room temperature as a neat liquid or in

solution. ^{1}H NMR: δ10.08 (d, J = 7 Hz, 1H), 7.0 (d, J = 12 Hz, 1H), 6.12 (dd, J = 7, 12 Hz, 1H), 2.38 (s, 3h).

cis-4-Oxo-2-octenal (48)[36]

The procedure was followed as in 45 above; 0.50 g of 2-*n*-butylfuran (47) gave 0.21 g of the title compound (38%) as a bright yellow liquid, which decomposed as noted for 45 above. 250 MHz ^{1}H NMR: δ10.23 (d, J = 7 Hz, 1H), 7.96 (d, J = 12 Hz, 1H), 6.19 (dd, J = 7, 12 Hz, 1H), 2.62 (t, J = 7.2 Hz, 2H), 1.65 (pentet, J = 7.2 Hz, 2H), 1.37 (sextet, J = 7.2 Hz, 2H), 0.94 (t, J = 7.2 Hz, 3H).

5-*n*-Butyl-2(3H)-furanone (49)

To a solution of 752 mg of 2-*n*-butyl-furan (6.06 mmol) in 60 mL of methylene chloride at 0°C was added 1.35 g of MCPBA (6.6 mmol) in one portion. The mixture was stirred for 2 h at 0°C, and then for 1 h at room temperature. After adding 30 mL more methylene chloride (which dissolved all of the *m*-chlorobenzoic acid precipitate), the solution was cooled to 0°C and 2 drops of trifluoroacetic acid were added, causing a noticeable lightening of the bright yellow solution. After 8 h at 0°C, the solution was extracted with saturated aqueous $NaHCO_3$ (3 × 50 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure to give 0.72 g of a very pale

yellow oil. Examination of this material by proton NMR indicated that butenolide 49 was the major product. Purification by flash column chromatography (40% ether-hexane) gave 627 mg of the title compound as a colorless liquid. Upon standing at room temperature as a neat liquid under an atmosphere of nitrogen, 49 decomposed to a viscous oil after *ca.* two weeks. 250 MHz ^{1}H NMR: δ5.11 (tt, J = 2.4, 1.2 Hz, 1H), 3-18 (dt, J = 2.4, 2.4 Hz, 2H), 2.30 (tm, J = 7.3 Hz, 2H), 1.54 (pentet of m, J ~ 7.3 Hz, 2H), 1.37 (sextet of m, J ~ 7.3 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H); 62.9 MHz ^{13}C NMR: 176.93, 157.47, 98.16, 33.96, 27.99, 27.91, 22.14, 13.70 ppm; IR (neat): 1795, 1680 cm^{-1}; MS: m/e = 140 (parent), 96 (base peak).

Oxidation of menthofuran (58) to enol lactone 59

Freshly distilled menthofuran[41] (1.00 g; 6.67 mmol) dissolved in 65 mL of methylene chloride was cooled to 0°C. To this solution was added 2.84 g of MCPBA (14.0 mmol) in one portion. After stirring at 0°C for 1 h, the white suspension was extracted with saturated aqueous $NaHCO_3$ (3 × 75 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure to give 1.18 g of 59 (97%) as a colorless oil. ^{1}H NMR: δ10.00 (s, 1H), 1.75 (s, 3H), 1.10 (d, J = 7 Hz, 3H), 1.2-3.0 (m, 7H); ^{13}C NMR: 191.05, 170.79, 165.49, 124.93, 42.12, 34.45, 31.27, 31.01, 23.05, 10.42 ppm; IR (neat): 1770,

1680, 1645 cm^{-1}; MS: m/e = 182 (parent), 85 (base peak).

Oxidation of tetramethylfuran (60) to enol acetate 61

Tetramethylfuran (520 mg; 4.19 mmol) dissolved in chloroform (30 mL) was cooled to 0°C. To this solution was added 1.79 g of MCPBA (8.8 mmol) in one portion. After stirring at 0°C for 3 h and then at room temperature for and additional 9 h, the white suspension was extracted with saturated aqueous $NaHCO_3$ (3 × 50 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure to give 652 mg of a colorless liquid (99%). Spectral data and TLC analysis (SiO_2, 1:1 ether-hexane) indicated the presence of more than one product. The major component, as analyzed in the crude product mixture, exhibited spectral properties consistent with enol acetate 61. ^{1}H NMR: δ2.17 (s, ~6 H), 1.83 (s, ~3H), 1.53 (s, ~3h); ^{13}C NMR: 205.04, 168.14, 133.13(?), 124.13, 26.59, 20.71, 14.59, 13.51 ppm; IR (neat): 1760, 1720, 1655 cm^{-1}; MS: m/e = 156 (parent, rel. intensity = 1.2%), 114 (M-42, rel. intensity = 25.2%), 99 (rel. intensity = 49.5%), 43 (base peak).

Oxidation of 2,3,5-trimethylfuran (62) using 1 equivalent of MCPBA to (Z)-3-methyl-3-hexene-2,5-dione (63a)

A solution of 2,3,5-trimethylfuran (503 mg; 4.57 mmol) in methylene chloride (30 mL) was cooled to 0°C, when

0.97 g of MCPBA (4.8 mmol) was added in one portion. The solution was stirred at 0°C for 1 h, and then at room temperature for 0.5 h. The resulting white suspension was extracted with saturated aqueous $NaHCO_3$ containing a small amount of $Na_2S_2O_3$ (2 × 50 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure to give 570 mg of the title compound (99%) as a colorless liquid. In several runs, a small amount (*ca.* 5%) of di-oxidized product 64a was also observed. Separation of this minor by-product by flash column chromatography (40% ether-hexanes) was not possible. 250 MHz ^{1}H NMR: δ6.11 (q, J = 1.5 Hz, 1H), 2.28 (s, 3H), 2.22 (s, 3H), 1.98 (d, J = 1.5 Hz, 3H); 62.9 MHz ^{13}C NMR: 206.84, 196.75, 155.67, 124.36, 29.99, 28.02, 20.11 ppm; IR (neat) 1695, 1620 cm^{-1}; MS: m/e = 126 (parent), 111 (base peak).

Isomerization of 63a to (E)-3-methyl-3-hexene-2,5-dione (63b)

A solution of 63a (*ca.* 150 mg) in $CDCl_3$ (*ca.* 2 mL) was allowed to stand at room temperature for approximately 2 months. After this time period, the proton NMR spectrum was run again, showing 63a as a mixture with a second compound in a ratio of *ca.* 2:1, respectively. The new compound was not isolated, but exhibited the following in the 250 MHz ^{1}H NMR: δ6.91 (q, J = 1.5 Hz, 1H), 2.40 (s, 3H), 2.36 (s, 3H), 2.13 (d, J = 1.5 Hz, 3H).

Oxidation of 2,3,5-trimethylfuran (62) using 2 equivalents of MCPBA to (Z)-4-acetoxy-3-methyl-3-buten-2-one 64a and epoxyketone 65

To a solution of 600 mg of 2,3,5-trimethylfuran 62 (5.45 mmol) in 45 mL of methylene chloride at 0°C was added 2.41 g of MCPBA (11.9 mmol) in one portion. The mixture was stirred for 12 h, allowing the cooling bath to warm to room temperature. The resulting white suspension was extracted with saturated aqueous $NaHCO_3$ containing a small amount of $Na_2S_2O_3$ (3 × 40 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure to give 689 mg of a clear, colorless liquid (89%). Analysis of the proton NMR spectrum of this mixture indicated the presence of the 64a as the major product, along with a second componet whose relative abundance varied from run to run, ranging from 0-15%. Flash column chromatography (40% ether-hexanes) enabled purification of 64a, although the minor component could not be isolated (presumably because of decomposition on the column). The chromatographed major product was distilled using a molecular still, bp = 85-95°C (bath temp.) at *ca.* 20 mm Hg to give pure 64a. 250 MHz ^{1}H NMR: δ7.71 (q, J = 1.5 Hz, 1H), 2.48 (s, 3H), 2.27 (s, 3H), 1.75 (d, J = 1.5 Hz, 3H); 62.9 MHz ^{13}C NMR: 198.08, 166.49, 139.91, 124.39, 31.73, 18.73, 14.50 ppm; IR (neat): 1775, 1720, 1670, 1650 cm^{-1}; MS (CI): m/e = 143 (M+1, base peak). The minor component,

analyzed as a mixture with 64a, had spectral characteristics consistent with epoxyketone 65. 250 MHz ^{1}H NMR: δ3.65 (s, 1H), 2.26 (s, 3H), 2.24 (s, 3H), 1.59 (s, 3H), 62.9 MHz ^{13}C NMR: 204.84, 201.81, 66.93, 64.84, 28.23, 27.41, 20.85 ppm.

Isomerization of 64a to *trans*-enol acetate 64b

A solution of crude 64a (*ca.* 150 mg) in $CDCl_3$ (*ca.* 2 mL) containing *m*-chlorobenzoic acid (*ca.* 20 mol% by ^{1}H NMR) was allowed to stand at room temperature for approximately 1 month. After this time period, the proton NMR spectrum was run again, showing 64a as a *ca.* 1:1 mixture with 64b (a moderate amount of decomposition had also occurred, as evidenced by the rather complex absorptions in the methyl group region). The *trans* isomer was not isolated, but exhibited the following resonances in the 250 MHz ^{1}H NMR: δ8.24 (q, J = 1.5 Hz, 1H), 2.33 (s, 3H), 2.29 (s, 3H), 1.81 (d, J = 1.5 Hz, 3H).

Oxidation of (Z)-3-methyl-3-hexene-2,5-dione (63a) using MCPBA to 64a and 65

To a solution of chromatographed 63a (110 mg; 0.87 mmol) in chloroform-d_1 (10 mL) at 0°C was added 195 mg of MCPBA (0.97 mmol) in one portion. The mixture was

stirred for 13 h, allowing the cooling bath to warm to room temperature. An aliquot was withdrawn (*ca.* 0.5 mL) and diluted with enough $CDCl_3$ such that the *m*-chlorobenzoic acid precipitate had completely dissolved. Analysis by 250 MHz ^1H NMR revealed the presence of the di-oxidized products 64a and 65 in a ratio of *ca.* 4:1. The aliquot was combined with the reaction mixture and the resulting solution was extracted with saturated aqueous $NaHCO_3$ containing a small amount of $Na_2S_2O_3$ (3 × 25 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure to give 92 mg of a colorless liquid (74%). Analysis of the product mixture by 250 MHz ^1H NMR showed 64a as the major component, with less than 5% of 65 present (loss of the latter product had evidently occurred during the aqueous work-up).

Oxidation of 2,4-dimethylfuran (68) using 2 equivalents of MCPBA

To a solution of 1.50 g of 2,4-dimethylfuran[41] (15.6 mmol) in 75 mL of methylene chloride at 0°C was added 6.66 g of MCPBA (32.8 mmol) in one portion. The mixture was stirred for 2 h at 0°C, and then for 0.5 h at room temperature. The white suspension was extracted with saturated aqueous $NaHCO_3$ (3 × 100 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure to give 0.85 g of a colorless

liquid (43%). Analysis of this material by proton NMR indicated the presence of several products. The major component appeared to be (Z)-3-acetoxy-2-methylpropenal (69) based on the following resonances in the ^{1}H NMR: δ10.1 (s, 1H), 7.83 (q, J = 1.5 Hz, 1H), 2.25 (s, ~3H), 1.67 (d, J = 1.5 Hz, ~3H). Suggestive of the regioisomeric Baeyer-Villiger product, 70, was another set of resonances; δ7.98 (s, 1H), 6.85 (q, J = 1.5 Hz, 1H), 2.10 (s, ~3H), 1.87 (d, J = 1.5 Hz, ~3 H). Separation of this mixture was not attempted, and therefore the structural assignments presented here must be considered tentative.

2-Methyl-2,5-dimethoxy-2,5-dihydrofuran (46), 2-*n*-butyl-2,5-dimethoxy-2,5-dihydrofuran (73), spiroketal 72, 2,5-dimethyl-2,5-dimethoxy-2,5-dihydrofuran (74), 2,4-dimethyl-2,5-dimethoxy-2,5-dihydrofuran (75), 2,3,5-trimethyl-2,5-dimethoxy-2,5-dihydrofuran (76), 2,5-dimethoxy-2,5-dihydro-menthofuran (77), 2,3,4,5-tetramethyl-2,5-dimethoxy-2,5-dihydrofuran (78), and tetracyclic dione 20

General Procedure:

The furan compound (10 mmol) was dissolved in reagent grade methanol (50-75 mL) and cooled to 0°C in an ice bath, when MCPBA (12 mmol) was added in one portion. Stirring was continued at 0°C for 1-2 h, and then at room temperature for an additional 1 h. The volume was condensed under reduced pressure at room temperature to *ca.* one-half the

original volume, chloroform (50-75 mL) was added, followed by extraction using saturated aqueous $NaHCO_3$ (100 mL), 5% aqueous $Na_2S_2O_3$ (50 mL), again with $NaHCO_3$ (75 mL), and then with saturated aqueous NaCl. The organic phase was dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Yields, purification methods (if any), and spectral properties are given below.

2-Methyl-2,5-dimethoxy-2,5-dihydrofuran (46)[9,a,b]

Obtained as a colorless liquid in 95% yield. ^{1}H NMR: δ5.83 (br s, 2H), 5.65, 5.37 (2s, 1H), 3.43, 3.33 (2s, 3H), 3.13, 3.08 (2s, 3H), 1.53, 1.47 (2s, 3H); IR (neat): broad, intense bands between 1095-960 cm^{-1}; MS (CI): m/e = 113 (M-31, base peak).

2-*n*-Butyl-2,5-dimethoxy-2,5-dihydrofuran (73)[36]

Obtained as a very pale yellow liquid in 92% yield. ^{1}H NMR: δ5.83 (AB quartet, J = 6 Hz, 2H), 5.63, 5.35 (2 br s, 1H), 3.43, 3.37 (2s, 3H), 3.13, 3.05 (2s, 3H), 1.77 (m, 2H), 1.33 (m, 4H), 0.89 (t, 3H); IR (neat): broad, intense bands between 1100-980 cm^{-1}; MS (CI): m/e = 155 (M-31, base peak).

Spiroketal 72[102]

Obtained as a colorless liquid after passage through a short column of alumina (Woelm N, Akt. 1; chloroform eluent) in 82% yield. ^{1}H NMR: δ5.87 (s, 2H), 5.66, 5.50 (2s, 1H), 4.00 (m, 2H), 3.30 (s, 3H), 2.00 (m, 4H); 62.9 MHz ^{13}C NMR: 134.11, 134.02, 130.64, 130.08, 118.32, 116.66, 107.62, 106.38, 68.66, 68.54, 54.34, 53.19, 36.93, 36.17, 24.88 ppm; IR (neat): broad, intense bands between 1100-950 cm^{-1}; MS: m/e = 155 (M-1), 125 (M-31, base peak).

2,5-Dimethyl-2,5-dimethoxy-2,5-dihydrofuran (74)[9a,b]

Obtained as a colorless liquid in 97% yield. ^{1}H NMR: δ5.78 (s, 2H), 3.25, 3.15 (2s, 6H), 1.55, 1.47 (2s, 6H); IR (neat): broad, intense bands between 1070-1010 cm^{-1}; MS (CI): m/e = 127 (M-31, base peak).

2,4-Dimethyl-2,5-dimethoxy-2,5-dihydrofuran (75)[9b]

Yields and purity were variable. A persistent by-product appeared to be 2-methoxy-3,5-dimethylfuran from the peaks in the proton NMR at δ5.57 (br s, 1H), 3.75 (s, 3H), and 2.08 (d, J ~ 1 Hz, 3H). The other methyl resonance was obscured (lit.[9b] values: δ5.62, 3.78, 2.12, 1.79). The formation of this product has been observed previously in the electrochemical oxidation of 2,4-dimethylfuran.[9b]

The best yield obtained was 89%, in which case the purity of 75 was *ca.* 88% as judged by the proton NMR spectrum of the crude product. ^{1}H NMR: δ5.40 (br s, 1H), 5.13 (br s, 1H), 3.43, 3.32 (2s, 3H), 3.12, 3.05 (2s, 3H), 1.77 (2 overlapping narrow doublets, 3H), 1.50, 1.47 (2s, 3H); ^{13}C NMR: 139.5, 128.0, 127.6, 111.0, 109.1, 108.8, 108.3, 55.6, 49.9, 26.03, 11.5, 11.3 ppm.

2,3,5-Trimethyl-2,5-dimethoxy-2,5-dihydrofuran (76)

Obtained as a colorless liquid in 90% yield. ^{1}H NMR: δ5.50 (q, J ~ 1.5 Hz, 1H), 3.27, 3.23, 3.18, 3.12 (4s, 6H), 1.73 (d, J ~ 1.5 Hz, 3H), 1.53, 1.50 (2s, 3H), 1.43, 1.40 (2s, 3H); 62.9 MHz ^{13}C NMR: 141.62, 141.47, 127.86, 127.80, 112.21, 111.01, 109.92, 49.99, 49.90, 49.64, 24.47, 24.32, 23.47, 23.35, 11.23 ppm; MS: m/e = 141 (M-31, base peak), 157 (M-15).

2,5-Dimethoxy-2,5-dihydromenthofuran (77)[38]

Obtained as a colorless liquid in 94% yield. ^{1}H NMR: δ5.52, 5.07 (2 br s, 1H), 3.43, 3.33 (2s, 3H), 3.05, 2.98 (2s, 3H), 1.67 (s, 3H), 0.88 (d, J = 6 Hz, 3H), 2.5-1.0 (m); ^{13}C NMR: 135.88, 135.35, 128.63, 128.17, 112.14, 110.46, 109.52, 108.54, 55.75, 53.89, 49.11, 48.62, 46.86, 46.58, 34.67, 29.41, 22.89, 21.31, 9.27, 8.90 ppm; IR (neat):

strong, broad bands between 1175-925 cm^{-1}; MS (CI): m/e = 212 (parent), 181 (M-31), 153 (base peak).

2,3,4,5-Tetramethyl-2,5-dimethoxy-2,5-dihydrofuran (78)

Obtained as a colorless liquid in 93% yield. ^{1}H NMR: δ3.18, 3.05 (2s, 6H), 1.62 (s, 6H), 1.48, 1.37 (2s, 6H); ^{13}C NMR: 132.21, 111.19, 109.88, 49.34, 49.14, 22.93, 22.76, 8.78 ppm; IR (neat): strong, broad bands between 1200-880 cm^{-1}; MS: m/e = 171 (M-15, base peak), 155 (M-31).

Tetracyclic dione 20[21a,b]

Obtained as a white crystalline solid in 90% yield. After recrystallization from ethanol, 20 had mp = 188-189°C (lit.[21a] mp = 186-187°C). Spectral data appeared earlier in this section.

3,5-Dimethylfuran-2-carboxaldehyde (88)

To a flame-dried 250 mL three-necked round-bottomed flask equipped with a nitrogen inlet/bubbler atop a reflux condenser, a mechanical stirrer, and a 50 mL pressure-equalized addition funnel was added 9.7 mL of dry dimethylformamide (d = 0.994 g/mL; 125 mmol). After cooling to -10°C using an ice-salt bath, 10.7 mL of phosphorus oxychloride (115 mmol) was added dropwise over a period

of 10 min. A small amount of dimethylformamide (*ca.* 2 mL) was used to rinse the residual phosphorus oxychloride from the addition funnel into the flask, and the resulting solution was stirred at -10°C to 0°C for 1.5 h, during which time the imminium salt precipitated as a heavy white solid. Dry methylene chloride (30 mL) was added, the cooling bath was removed, and the mixture was stirred until the solid had dissolved. After cooling the solution to 0°C, 10.00 g of 2,4-dimethylfuran[41] (104 mmol) in 20 mL of dry methylene chloride was added over a period of 45 min, during which time the reaction took on a reddish-brown color. Stirring was continued for 4 h, allowing the cooling bath to warm to room temperature, followed by heating at reflux for 3 h. A solution of 20 g of sodium acetate (240 mmol) in 100 mL of water was then added to the cooled (0°C) reaction mixture, and stirring was continued at room temperature for 18 h. The two-phase mixture was poured into a separatory funnel, the layers were separated, and the aqueous phase was saturated with NaCl and extracted with chloroform (4 × 40 mL). The organic extracts and mother liquor were combined and washed with saturated aqueous $NaHCO_3$ (2 × 50 mL; caution, foaming!), saturated aqueous NaCl (1 × 50 mL), dried over anhydrous Na_2SO_4, and filtered. The solvents were removed under reduced pressure, giving 12.4 g of a dark liquid which was distilled under vacuum using a short path distillation apparatus. The title compound was obtained as a very pale

yellow liquid (11.2 g; 87%), bp = 34-37°C at 0.10 mm Hg. ^{1}H NMR: δ9.53 (s, 1H), 6.05 (s, 1H), 2.33 (s, 6H).

Ethyl 3-(3,5-dimethyl-2-furyl)-3-hydroxypropanoate (89)

To an ice cold solution of 2.73 mL of diisopropylamine (d = 0.722 g/mL; 19.5 mmol) in 20 mL of anhydrous THF under a nitrogen atmosphere was added 12.0 mL of *n*-butyllithium in hexane (1.55 M; 18.6 mmol). The resulting solution was stirred for 15 min at 0°C and then cooled to -78°C. Ethyl acetate (1.73 mL, d = 0.902 g/mL; 17.7 mmol) was introduced dropwise *via* syringe over a period of 3 min, and stirring at -78°C was continued for 30 min. A solution of 2.00 g of 3,5-dimethylfuran-2-carboxaldehyde, 88, (16.1 mmol) in 10 mL of anhydrous THF was added through an addition funnel as rapidly as possible and stirring at -78°C was continued for 2 min. The reaction was quenched at -78°C by the rapid addition of 10 mL of water. The cooling bath was removed, and after warming to room temperature, the mixture was transferred to a separatory funnel and the reaction flash was rinsed with ether (2 × 20 mL). The layers were separated and the organic phase was washed with 1% HCl (2 × 20 mL). The combined aqueous washings were extracted with ether (2 × 20 mL) and the organic phases were combined and washed with saturated aqueous $NaHCO_3$ (2 × 30 mL), saturated aqueous NaCl (1 × 30 mL), dried over anhydrous $MgSO_4$, and filtered.

Removal of the solvents under reduced pressure gave 3.28 g of the title aldol (96%) as a very pale yellow oil. This material was sufficiently pure as evidenced by TLC (SiO_2, ether), ^1H and ^{13}C NMR for use in the next step without further purification. 250 MHz ^1H NMR: δ5.77 (s, 1H), 5.10 (dd, J = 4.3, 8.9 Hz, 1H), 4.17 (q, J = 7.0 Hz, 2H), 3.2 (v br s, 1H; OH), 3.00 (dd, J = 8.9, 16.2 Hz, 1H), 2.69 (dd, J = 4.3, 16.2 Hz, 1H), 2.21 (s, 3H), 1.99 (s, 3H), 1.26 (t, J = 7.0 Hz, 3H); 62.9 MHz ^{13}C NMR: 172.09, 150.86, 147.54, 117.61, 109.28, 62.23, 60.73, 40.21, 14.15, 13.39, 9.66 ppm; IR (neat): 3450, 1730, 1630, 1575 cm^{-1}; MS: m/e = 212 (parent), 125 (base peak).

2-(1,3-Dihydroxypropyl)-3,5-dimethylfuran (90)

To a suspension of 0.61 g of lithium aluminum hydride (15.9 mmol) in 25 mL of anhydrous THF at 0°C under an atmosphere of nitrogen was added dropwise over a period of 30 min a solution of 3.00 g of aldol 89 (14.2 mmol) in 10 mL of anhydrous THF. The cooling bath was allowed to warm to room temperature and stirring was continued for 24 h. After cooling to 0°C, the reaction was quenched by the successive dropwise addition of 0.60 mL of water, 0.60 mL of 15% aqueous NaOH, and 2.4 mL of water. After stirring at room temperature for 3 h, the granular grey suspension was suction filtered through Celite and washed with ether (3 × 15 mL). The filtrate was dried over

anhydrous Na_2SO_4, filtered, and the solvents were removed under reduced pressure to give 2.42 g of the title diol (99%) as a dense, colorless oil. Analysis of the product by TLC (SiO_2, ether; $R_f = 0.22$, I_2 visualiztion), ^1H NMR, and ^{13}C NMR indicated the presence of only one component. Purification by silica gel column chromatography was accompanied by decomposition and loss of material (see below). Accordingly, the crude product was used directly in the next step. Storage of diol 90 for extended periods of time without decomposition was best accomplished in ether solution at -20°C. 250 MHz ^1H NMR ($CDCl_3$ + D_2O): δ5.78, (s, 1H), 4.89 (dd, J = 4.5, 9.0 Hz, 1H), 3.9-3.7 (m, 2H), 2.22 (d, J = 0.9 Hz, 3H), ~2.2 (m, 1H), ~1.95 (m, 1H), 1.98 (s, 3H); 62.9 MHz ^{13}C NMR: 150.62, 148.88, 117.00, 109.21, 64.78, 60.63, 37.46, 13.41, 9.67 ppm; IR (neat): 3350, 1635, 1575 cm^{-1}; MS (CI): m/e = 153 (M-17, base peak).

3,3-*bis*(3,5-Dimethyl-2-furyl)-1-propanol (92)

In an attempted purification of diol 90 by flash column chromatography (ether eluent), a second, less polar component co-eluted with the desired diol product. The new product was obtained in pure form by re-chromatographing the fractions containing the mixture. In this way, 320 mg of 92 was obtained as a white crystalline solid (mp = 86-87°C) from 1.08 g of diol 90 originally

chromatographed. 250 MHz ^{1}H NMR: δ5.72 (m, 1H), 4.22 (t, J = 7.9 Hz, 1H), 3.58 (t, J = 6.1 Hz, 2H), 2.25 (dt, J = 7.9, 6.1 Hz, 2H), 2.21 (d, J = 0.9 Hz, 3H), 1.86 (s, 3H); IR (Nujol): 3250, 1635, 1575 cm^{-1}; MS: m/e = 248 (parent), 203 (base peak).

1,7-Dimethyl-2,9-dioxabicyclo[3.3.1]non-7-en-6-one (91)

To a magnetically stirred solution of 1.00 g of 2-(1,3-dihydroxypropyl)-3,5-dimethylfuran 90 (5.88 mmol) in 60 mL of methylene chloride at 0°C was added 1.31 g of MCPBA (6.47 mmol) in one portion. Stirring at 0°C was continued for 15 min, after which time 5.9 mL of 0.10 N aqueous *p*-toluenesulfonic acid solution (0.59 mmol) was added. The cooling bath was removed and the reaction progress was monitored by TLC (SiO_2, ether, anisaldehyde-sulfuric acid visualization) for disappearance of the more polar intermediates at R_f = 0.18 and 0.24, and appearance of the product (UV-active) at R_f = 0.69. After 6 h, the reaction was complete, and work-up involved washing the organic solution with saturated aqueous $NaHCO_3$ containing *ca.* 1% $Na_2S_2O_3$ (3 × 30 mL), drying over anhydrous Na_2SO_4, and filtering. Removal of the solvent under reduced pressure gave 0.95 g of bicyclic enone 91 (96%) as a colorless liquid. Examination of the crude material by TLC (SiO_2, ether, anisaldehyde-sulfuric acid visualization) indicated the presence of trace impurities at low R_f,

and in the 250 MHz ^{1}H NMR spectrum, the impurities were observed as several very small methyl resonances in the region from 1.0-1.8 ppm. After passage through a short column of silica gel (50% ether-hexane eluent) and evaporation of the solvents under reduced pressure, 0.89 g of the title compound (90%) was obtained as a colorless liquid. An analytical sample was prepared by distillation using a molecular still, bp = 85-90°C (bath temp.) at *ca.* 20 mm Hg. 250 MHz ^{1}H NMR: δ5.41 (q, J = 1.5 Hz, 1H), 4.36 (ddd, J = 6.2, 1.1, 1.1 Hz, 1H), 3.99 (ddd, J = 12.1, 13.3, 3.0 Hz, 1H), 3.86 (dddd, J = 12.1, 6.2, 1.1, 1.1 Hz, 1H), 2.38 (dddd, J = 13.3, 13.3, 6.2, 6.2 Hz, 1H), 1.92 (d, J = 1.5 Hz, 3H), 1.53 (dddd, J = 13.2, 3.0, 1.1, 1.1 Hz, 1H), 1.52 (s, 3H); 62.9 MHz ^{13}C NMR: 197.69, 140.47, 137.12, 94.45, 74.95, 58.55, 27.61, 26.96, 13.85 ppm; IR (neat): 1690, 1640 cm^{-1}; MS m/e = 168 (parent), 43 (base peak).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27 H, 7.19
Found: C, 63.56 H, 7.04

3-(5-Methyl-2-furyl)propanal (95a)

A solution containing 19.0 g of 2-methylfuran (232 mmol), 20.7 g of acrolein (371 mmol), and 30 mL of glacial acetic acid in 120 mL of THF was refluxed for 6.5 h under an atmosphere of nitrogen. The cooled reaction mixture was filtered with suction through Celite (to remove the

particulate acrolein stabilizer which causes emulsions during the aqueous washings) and the filtrate was transferred to a separatory funnel along with 100 mL of ether. After successive washings with water (2 × 75 mL), saturated aqueous $NaHCO_3$ (2 × 75 mL; caution, foaming!), and saturated aqueous NaCl (1 × 50 mL), the organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvents were removed under reduced pressure to give an orange-brown oil. Vacuum distillation of this material gave 21.8 g (68%) of the title compound, bp = 34-36°C (0.10 mm Hg). ^{1}H NMR: δ9.67 (t, J = 1 Hz, 1H), 5.78 (br s, 2H), 2.80 (m, 4H), 2.20 (s, 3H); 62.9 MHz ^{13}C NMR: 201.08, 152.09, 150.82, 106.18, 106.07, 42.05, 20.91, 13.41 ppm; IR (neat): 1725, 1610, 1565 cm^{-1}; MS: m/e = 138 (parent), 95 (base peak).

Ethyl 5-(5-methyl-2-furyl)-2-pentenoate (96a)

A solution containing 6.00 g of aldehyde 95a (43.4 mmol) and 16.64 g of carbethoxymethylenetriphenylphosphorane (47.8 mmol) in 150 mL of THF was stirred at room temperature for 12 h. The semi-solid which was obtained after evaporating the solvent under reduced pressure was suspended in 125 mL of ice-cold 1:1 ether-hexanes and suction filtered. The filtrate solvents were then removed under reduced pressure affording a pale yellow liquid,

from which the last traces of triphenylphosphine oxide were removed by passage through a short column (silica gel, ether). In this way, 8.86 g (99%) of the title compound was obtained. ^{1}H NMR: δ6.88 (dt, J = 16.6 Hz, 1H), 5.92 (dt, J = 16.1 Hz, 1H), 5.93 (br s, 2H), 4.12 (q, J = 7 Hz, 2H), 2.60 (m, 4H), 2.22 (s, 3H), 1.25 (t, J = 7 Hz, 3H); 62.9 MHz ^{13}C NMR: 166.44, 152.59, 150.59, 147.59, 122.09, 106.07, 105.98, 60.13, 30.76, 26.73, 14.26, 13.41 ppm; MS: m/e = 208 (parent), 95 (base peak).

5-Methyl-2-(5-hydroxy-3-pentenyl)furan (97a)

A solution of 8.40 g of ester 96a (40.4 mmol) in 35 mL of anhydrous ether was added dropwise to a solution of 60 mL of 25% diisobutylaluminum hydride in toluene (1.5 M, 89.8 mmol) at 0°C under an atmosphere of nitrogen. After the addition was complete (10 min), the cooling bath was removed and stirring was continued for 1.5 h. Excess hydride was destroyed by the cautious dropwise addition of methanol (5 mL), and the reaction mixture was slowly poured into 200 mL of ice-cold 2N HCl. The organic phase was separated and the aqueous phase extracted with ether (2 × 60 mL). The organic phases were combined and washed successively with 1N HCL (1 × 50 mL), saturated aqueous $NaHCO_3$ (1 × 50 mL), saturated aqueous NaCl (1 × 50 mL), dried over anhydrous $MgSO_4$, and filtered. Removal of the solvents under reduced pressure gave 6.23 g (94%) of

the title compound. The purity of this material was sufficient for use in the next step. ^{1}H NMR: δ5.77 (s, 2H), 5.60 (m, 2H), 3.98 (br d, J = 3 Hz, 2H), 2.5-2.8 (m, 4H), 2.21 (s, 3H); 62.9 MHz ^{13}C NMR: 153.61, 150.32, 131.74, 129.91, 105.83, 105.62, 63.52, 30.76, 27.82, 13.44 ppm; MS: m/e = 166 (parent), 95 (base peak).

5-(5-Methyl-2-furyl)-2(E)-pentenal (98a)

A solution of 6.00 g of allylic alcohol 97a (36.1 mmol) in 15 mL of dry methylene chloride was added to a suspension of 14.15 g of pyridinium chlorochromate (65.8 mmol) in 45 mL of dry methylene chloride at 0°C under an atmosphere of nitrogen. After the addition was complete (3 min), the cooling bath was removed and the progress of the reaction was monitored by TLC (SiO_2, 1:1 ether-hexane) for disappearance of starting material (R_f alcohol = 0.28, R_f aldehyde = 0.46). When the reaction was complete (1.5-2.0 h), the dark mixture was diluted with 200 mL of ether and filtered through a fritted funnel packed with Florisil (bottom layer) and Celite (top layer). The remaining black salts were broken up, slurried in ether, and filtered. The filtrate solvents were removed under reduced pressure leaving a pale yellow-green liquid (4.45 g) which was purified by column chromatography (silica gel, 25% ether-hexanes) to give 4.04 g (68%) of the title compound as a very pale yellow

liquid. 250 MHz ^{1}H NMR: δ9.52 (d, J = 7.8 Hz, 1H), 6.86 (dt, J = 15.4, 6.4 Hz, 1H), 6.15 (ddt, J = 15.4, 7.8, 1.3 Hz, 1H), 5.88 (AB q, J = 3.0 Hz, 2H), 2.80 (br t, J = 6.8 Hz, 2H), 2.68 (m, 2H), 2.24 (d, J = 1.0 Hz, 3H); 62.9 MHz ^{13}C NMR: 193.78, 156.79, 152.06, 150.88, 133.50, 106.36, 105.98, 31.20, 26.49, 13.47 ppm; IR (neat): 1690, 1635, 1565 cm^{-1}; MS: m/e = 164 (parent), 95 (base peak).

2-(3(E),5-Hexadienyl)-5-methylfuran (99a)

To a rapidly stirred suspension of 10.45 g of (methyl)triphenylphosphonium bromide (29.2 mmol) in 85 mL of anhydrous THF at 0°C under a nitrogen atmosphere was added 17.3 mL of *n*-butyllithium in hexane (1.55 M, 26.8 mmol) dropwise over a period of 5 min, and the resulting yellow-orange solution was stirred for 2 h, allowing the cooling bath to warm to room temperature. The solution was then re-cooled to -10°C using an ice-salt bath, when a solution of 4.00 g of enal 98a (24.4 mmol) in 25 mL of anhydrous THF was introduced dropwise over a period of 15 min. Stirring was continued at -10°C for 45 min and then, after removing the cooling bath, at room temperature for an additional 45 min. Excess ylid was destroyed by the dropwise addition of glacial acetic acid, until the color of the ylid had dissipated. Pentane (125 mL) was added, and the supernatant liquid was decanted from the gummy precipitate into a 1000-mL

Erlenmeyer flask containing 300 mL of pentane. The gummy residue was washed twice with 1:1 pentane-ether (75 mL) and the combined organic phases were cooled at -20°C overnight. The resulting cloudy suspension was filtered through Celite into a 1000-mL round-bottomed flask and the solvents were distilled at atmospheric pressure through a 30 cm Vigreaux column until the volume had been reduced to *ca.* 20 mL. The remaining liquid was then passed through a short column of silica gel using 10% ether-pentane. The product was collected in one large fraction (250 mL) and the solvents were removed by distillation at atmospheric pressure. The remaining pale yellow liquid was vacuum distilled to give 3.20 g (81%) of diene 99a as a colorless liquid, bp = 34-37°C (0.18 mm Hg). 250 MHz ^{1}H NMR: δ6.29 (dt, J = 16.9, 10.3 Hz, 1H), 6.08 (ddm, J = 15.0, 10.3 Hz, 1H), 5.83 (AB q, J = 2.9 Hz, 2H), 5.71, (dt, J = 15.0, 7.0 Hz, 1H), 5.09 (dm, J = 16.9 Hz, 1H), 4.96 (dm, J = 10.3 Hz, 1H), 2.67 (t, J = 7.2 Hz, 2H), 2.41 (q, J = 7.1 Hz, 2H), 2.24 (d, J = 0.8 Hz, 3H); 62.9 MHz ^{13}C NMR: 153.64, 150.26, 137.18, 133.77, 131.74, 115.18, 105.89, 105.65, 31.17, 27.91, 13.44 ppm; IR (neat): 1640, 1600, 1560 cm^{-1}; MS: m/e = 162 (parent), 95 (base peak).

3-(3,5-Dimethyl-2-furyl)propanal (95b)

The procedure was followed as for 95a, using 6.00 g of 2,4-dimethylfuran. There was obtained 5.89 g (62%) of the title compound after distillation, bp = 45-47°C (0.10 mm Hg). ^{1}H NMR: δ9.67 (t, J = 1 Hz, 1H), 5.65 (s, 1H), 2.75 (m, 4H), 2.17 (s, 3H), 1.88 (s, 3H); 62.9 MHz ^{13}C NMR: 201.61, 149.73, 146.79, 115.21, 108.96, 42.52, 18.76, 13.38, 9.76 ppm; IR (neat); 1720, 1635, 1575 cm^{-1}; MS: m/e = 152 (parent), 109 (base peak).

Ethyl 5-(3,5-dimethyl-2-furyl)-2-pentenoate (96b)

The procedure was followed as for 96a, using 5.50 g of aldehyde 95b. There was obtained 7.88 g (98%) of the title compound as a colorless liquid. ^{1}H NMR: δ6.88 (dt, J = 15.5, 6.5 Hz, 1H), 5.75 (dm, J = 15.5 Hz, 1H), 5.65 (s, 1H), 4.15 (q, J = 7 Hz, 2H), 2.58 (m, 4H), 2.17 (s, 3H), 1.87 (s, 3H), 1.25 (t, J = 7 Hz, 3H); 62.9 MHz ^{13}C NMR: 166.58, 147.94, 149.53, 147.44, 121.89, 115.09, 108.77, 60.16, 14.29, 31.35, 24.70, 13.41, 9.82 ppm; IR (neat): 1720, 1650, 1575 cm^{-1}; MS: m/e = 222 (parent), 109 (base peak).

3,5-Dimethyl-2-(5-hydroxy-3-pentenyl)furan (97b)

The procedure was followed as for 97a, using 7.50 g of ester 96b. There was obtained 5.83 g (96%) of the title compound as a colorless oil. ^{1}H NMR: δ5.63 (s, 1H), 5.56 (m, 2H), 3.98 (br d, J = 3 Hz, 2H), 2.7-2.3 (m, 5H, including OH), 2.17 (s, 3H), 1.87 (s, 3H); 62.9 MHz ^{13}C NMR: 149.20, 148.47, 131.94, 129.77, 114.62, 108.71, 63.52, 31.41, 25.82, 13.41, 9.82 ppm; IR (neat): 3300, 1665, 1635, 1575 cm^{-1}; MS: m/e = 180 (parent), 109 (base peak).

5-(3,5-Dimethyl-2-furyl)-2(E)-pentenal (98b)

The procedure was followed as for 98a, using 5.50 g of allylic alcohol 97b. There was obtained 3.15 g (58%) of the title compound as a pale yellow oil. 250 MHz ^{1}H NMR: δ9.49 (d, J = 8.1 Hz, 1H), 6.84 (dt, J = 15.8, 6.7 Hz, 1H), 6.12 (ddt, J = 15.8, 8.1, 1.4 Hz, 1H), 5.74 (s, 1H), 2.75-2.6 (m, 4H), 2.20 (d, J = 0.9 Hz, 3H), 1.89 (s, 3H); 62.9 MHz ^{13}C NMR: 193.75, 157.17, 149.65, 146.97, 133.38, 115.33, 115.33, 108.86, 31.76, 24.41, 13.38, 9.79 ppm; IR (neat): 1685, 1635, 1575 cm^{-1}; MS: m/e = 178 (parent), 109 (base peak).

3,5-Dimethyl-2-(3(E),5-hexadienyl)furan (99b)

The procedure was followed as for 99a, using 3.00 g of enal 98b. There was obtained 2.61 g (88%) of the title compound, bp = 47-50°C (0.10 mm Hg). 250 MHz ^{1}H NMR: δ6.28 (dt, J = 17.1, 10.1 Hz, 1H), 6.06 (ddm, J = 10.2, 15.0 Hz, 1H), 5.71 (s, 1H), 5.69 (dt, J = 15.0, 7.0 Hz, 1H) 5.07 (dm, J = 17.1 Hz, 1H), 4.95 (dm, J = 10.1 Hz, 1H), 2.59 (br t, J = 6.7 Hz, 2H), 2.35 (br q, J = 7.0 Hz, 2H), 2.19 (d, J = 0.9 Hz, 3H), 1.87 (s, 3H); 62.9 MHz ^{13}C NMR: 149.20, 148.44, 137.24, 134.09, 131.50, 115.06, 114.62, 108.68, 31.79, 25.88, 13.41, 9.79 ppm; IR (neat): 1650, 1595, 1575 cm^{-1}; MS: m/e = 176 (parent), 109 (base peak).

3(Z),8(E),10-Undecatriene-2,5-dione (103)

To a solution of 720 mg of furyl diene 99a (4.44 mmol) in 30 mL of methylene chloride at -10°C (ice-salt bath) was added 811 mg of MCPBA (4.00 mmol) in one portion. After being stirred 1.5 h at -10°C, and then for 0.5 h at room temperature, the mixture was extracted with saturated aqueous $NaHCO_3$ (3 × 40 mL), dried over anhydrous Na_2SO_4, and filtered. The solvent was removed under reduced pressure to give 740 mg of a light yellow oil. Analysis of this material by TLC (SiO_2, 40% ether-hexane, anisaldehyde-sulfuric acid spray visualization) indicated the presence of at

least five components (R_f = 0.68, 0.54, 0.48, 0.21, 0.11). Separation of this mixture was accomplished by flash column chromatography (40% ether-hexane eluent) to give the following products, in order of their elution: starting furan 99a (96 mg, 13%); epoxyfurans 101 and 102 (only partially separated; combined mass = 26 mg, 3.8% based on consumed starting material); the title compound 103 (478 mg, 70% based on consumed starting material); and di-oxidized epoxyenedione 104 (29 mg; 3.9% based on recovered starting material). The desired enedione product 103 was obtained as a pale yellow liquid which underwent intramolecular Diels-Alder cyclization upon storage at room temperature as a neat liquid or in solution. 250 MHz ^{1}H NMR: δ6.32 (s, 2H), 6.29 (ddd, J = 16.8, 10.6, 10.6 Hz, 1H), 6.09 (ddm, J = 14.9, 10.6 Hz, 1H), 5.70 (dt, J = 14.9, 7.2 Hz, 1H), 5.11 (dm, J = 16.8 Hz, 1H), 4.99 (dm, J = 10.6 Hz, 1H), 2.65 (t, J = 7.4 Hz, 2H), 2.43 (br q, J ~ 7.2 Hz, 2H), 2.39 (s, 3H); 62.9 MHz ^{13}C NMR: 201.84, 200.28, 136.91, 135.91, 135.53, 132.80, 131.97, 115.59, 41.84, 29.73, 26.41 ppm; IR (neat): 1690, 1600 cm^{-1}; MS: m/e 178 (parent), 98 (base peak).

Spectral data for epoxyfuran 101. 250 MHz ^{1}H NMR: δ5.87 (AB q, J = 3.2 Hz, 2H), 5.57 (ddd, J = 17.1, 9.6, 7.2 Hz, 1H), 5.43 (dd, J = 17.1, 2.1 Hz, 1H), 5.25 (ddm, J = 9.6, 2.1 Hz, 1H), 3.09 (dd, J = 7.2, 2.1 Hz, 1H), 2.90 (ddd, J = 6.0, 5.3, 2.1 Hz, 1H), 2.78-2.70 (m, 2H), 2.25 (br s, 3H), 1.95-1.85 (m, 2H).

Spectral data for epoxyfuran 102. 250 MHz ^{1}H NMR: δ5.99 (dt, J = 15.7, 6.8 Hz, 1H), 5.85 (AB q, J = 2.9 Hz, 2H), 5.20 (ddt, J = 15.7, 8.2, 1.5 Hz, 1H), 3.32 (ddd, J = 8.2, 4.1, 2.8 Hz, 1H), 2.94 (dd, J = 5.1, 4.1 Hz, 1H), 2.67 (t, J = 7.2 Hz, 2H), 2.64 (dd, J = 5.1, 2.7 Hz, 1H), 2.40 (qm, J ~ 7.2 Hz, 2H), 2.25 (br s, 3H).

Spectral data for epoxyenedione 104. 250 MHz ^{1}H NMR: δ6.34 (s, 2H), 5.58 (ddd, J = 16.9, 9.5, 6.9 Hz, 1H), 5.46 (dd, J = 16.9, 2.3 Hz, 1H), 5.27 (ddm, J = 9.5, 2.3 Hz, 1H), 3.15 (dd, J = 6.9, 2.1 Hz, 1H), 2.94 (ddd, J = 7.0, 4.4, 2.1 Hz), 2.71 (t, J = 7.1 Hz, 2H), 2.30 (s, 3H), 2.11 (dtd, J = 14.6, 7.1, 4.4 Hz, 1H), 1.88 (dq, J = 14.6, 7.1 Hz, 1H); 62.9 MHz ^{13}C NMR: 201.63 (second carbonyl resonance not observed), 135.82, 135.68, 135.47, 119.21, 59.25, 58.87, 38.26, 29.76, 25.73 ppm; IR (neat): 1690, 1605 cm^{-1}; MS: m/e = 194 (parent), 82 (base peak).

4-Methyl-3(Z),8(E),10-undecatriene-2,5-dione (105)

To a solution of 750 mg of furyl diene 99b (4.26 mmol) in 35 mL of methylene chloride at 0°C was added 779 mg MCPBA (3.84 mmol) in one portion. After being stirred for 1 h at 0°C, and then for 0.5 h at room temperature, the mixture was extracted with saturated aqueous $NaHCO_3$ (3 × 40 mL), dried over anhydrous Na_2SO_4, and filtered. Evaporation of the solvent under reduced pressure gave

787 mg of a colorless oil. Analysis of this material by TLC (SiO_2, 50% ether-hexane, anisaldehyde-sulfuric acid spray visualization) indicated the presence of only two components, $R_f = 0.69$ and 0.31. Separation of this mixture by flash column chromatography (30% ethyl acetate-hexane eluent) gave 74 mg of starting furan 99b (10%), and 710 mg of the title compound (95% based on consumed starting material) as a pale yellow liquid. 250 MHz ^{1}H NMR: δ6.29 (ddd, J = 16.8, 10.1, 10.1 Hz), 6.10 (q, J = 1.8 Hz, 1H), 6.08 (splitting obscured, 1H), 5.74 (dt, J = 15.0, 6.8 Hz, 1H), 5.09 (dm, J = 16.8 Hz, 1H), 4.96 (dm, J = 10.1 Hz, 1H), 2.61 (m, 2H), 2.48 (br q, J ~ 6.8 Hz, 2H), 2.19 (s, 3H), 1.96 (d, J = 1.8 Hz, 3H); 62.9 MHz ^{13}C NMR: 208.10, 196.64, 155.79, 137.03, 133.32, 131.77, 124.68, 115.33, 39.93, 29.96, 26.35, 20.44 ppm; IR (neat): 1690, 1615 cm^{-1}; MS: parent ion not observed, m/e = 112 (M-80, base peak).

3(E),8(E),10-Undecatriene-2,5-dione (105) *via* PCC oxidation

A solution of furyl diene 99a (1.00 g; 6.17 mmol) in 3 mL of dry methylene chloride was added dropwise over a period of *ca.* 1 min to a suspension of pyridinium chlorochromate (7.95 g; 37 mmol) in 20 mL of dry methylene chloride at 0°C under an atmosphere of nitrogen. After 15 min, the cooling bath was removed and the mixture was stirred for 20 h at room temperature, and then for 6 h at

reflux. Ether (75 mL) was added to the cooled reaction mixture, and the resulting suspension was suction filtered through a glass frit packed with Florisil. The black salts remaining in the reaction flask were broken up in ether and filtered. The filtrate solvents were removed under reduced pressure to give 632 mg of a pale yellow oil. Analysis of this material by TLC (SiO_2, 1:1 ether-hexane, anisaldehyde-sulfuric acid spray visualization) indicated the presence of at least four components (R_f = 0.70, 0.37, 0.31, 0.26). Separation of this mixture by flash column chromatography (30% ethyl acetate-hexane eluent) gave the following products, in order of their elution: starting furan 99a (100 mg, 10%); the title compound 106 (296 mg, 30% based on consumed starting material); hydrindenone 111b (84 mg, 8.5% based on consumed starting material); and hydrindenone 110b (89 mg, 9% based on consumed starting material). The desired triene 106 was obtained as a pale greenish-yellow waxy solid (mp ~30°C). 250 MHz ^{1}H NMR: δ6.83 (s, 2H), 6.29 (ddd, J = 16.9, 10.2, 10.2 Hz, 1H), 6.09 (ddm J = 15.4, 10.2 Hz, 1H), 5.69 (dt, J = 15.4, 7.1 Hz, 1H), 5.12 (dm, J = 16.9 Hz, 1H), 5.00 (dm, J = 10.2 Hz, 1H), 2.78 (t, J = 7.6 Hz, 2H), 2.44 (br q, J ~ 7.2 Hz, 2H), 2.37 (s, 3H); 62.9 MHz ^{13}C NMR: 199.52, 198.22, 137.06, 136.97, 136.77, 132.35, 132.24, 115.89, 40.76, 28.20, 26.47 ppm; IR (neat): 1685, 1620 cm^{-1}; MS: parent ion not observed, m/e = 135 (M-43), 43 (base peak).

3(E),8(E),10-Undecatriene-2,5-dione (105) *via* pyridine isomerization of *cis*-enedione (103)

To a solution of freshly chromtographed *cis*-enedione 103 (212 mg; 1.19 mmol) in chloroform (3 mL) was added an equal volume of pyridine. The mixture was checked periodically by TLC (SiO_2, 1:1 ether-hexane) for disappearance of starting material (R_f = 0.27) and appearance of product (R_f = 0.38). After 18 h, the solvents were removed *in vacuo* and the residue was flash chromatographed (30% ethyl acetate-hexane eluent) to give, in order of elution: 84 mg of the title compound (40%); hydrindenones 110a and 111b as an inseparable mixture (43 mg, 20%); and hydrindenone 110b (41 mg, 19%).

Attempted isomerization of *cis*-enedione 105 using DBU: 2,4-dimethyl-4-hydroxy-5-(2,4-pentadienyl)-2-cyclopentenone (107)

To a solution of *cis*-enediones 105 (192 mg; 1.00 mmol) in chloroform-d_1 (5 mL) was added 1,8-diazabicyclo-[5.4.0]undec-7-ene (0.15 g; 1.0 mmol). The reaction progress was followed by proton NMR, and after 5 min, all of the starting material had been consumed. The reaction mixture was diluted with methylene chloride (20 mL) and extracted with 1% aqueous HCl (2 × 20 mL), saturated aqueous $NaHCO_3$ (1 × 20 mL), dried over anhydrous Na_2SO_4, and filtered.

Evaporation of the solvents under reduced pressure gave a pale brown oil which was passed through a short column of silica gel (40% ether-hexane eluent) to give 138 mg of the title compound (72%) as a colorless oil. 250 MHz ^{1}H NMR: δ7.03 (q, J = 1.5 Hz, 1H), 6.33 (ddd, J = 16.8, 10.1, 10.1 Hz, 1H), 6.19 (ddm, J = 15.0, 10.1 Hz, 1H), 5.85 (ddd, J = 15.0, 7.6, 5.8 Hz, 1H), 5.12 (dm, J = 16.8 Hz, 1H), 5.00 (dm, J = 10.1 Hz, 1H), 2.67 (ddd, J = 15.3, 5.8, 4.6 Hz, 1H), 2.62 (br s, 1H; OH), 2.54 (dd, J = 9.5, 4.6 Hz, 1H), 2.19 (ddd, J = 15.3, 9.5, 7.6 Hz, 1H), 1.76 (d, J = 1.5 Hz, 3H), 1.36 (s, 3H); 62.9 MHz ^{13}C NMR: 206.28, 159.55, 139.85, 136.94, 132.77, 132.47, 115.62, 58.75, 28.91, 24.58, 9.82 ppm.

Isomerization of *cis*-enedione 105 using triethylamine: 4-methyl-3(E),8(E),10-undecatriene-2,5-dione (109) and 4-methylidene-8,10(E)-undecadiene-2,5-dione (108)

To a solution of 405 mg of *cis*-enedione 105 (2.11 mmol) in 6 mL of chloroform was added 3 mL of triethylamine. After 8 h at room temperature, the solvents were removed under reduced pressure to give a pale brown oil. Analysis of this mixture by proton NMR (250 MHz) revealed the presence of the starting *cis*-enedione 105 along with the *trans* isomer 109 and deconjugated isomer 108 in a ratio of 1:1.2:1.8, respectively. Analysis of this mixture by TLC (SiO_2, 40% ether-hexane) showed two UV-active spots at

R_f = 0.38 and 0.26. Flash column chromatography (40% ether-hexane eluent) provided 118 mg of *trans*-enedione 109 (29%) and 277 mg of a 1:1.8 mixture of *cis*-enedione 105 and deconjugated isomer 108. The latter two compounds were totally inseparable by column chromatography. The desired *trans*-enedione 109 was obtained as a colorless liquid and exhibited the following spectral properties. 250 MHz ^{1}H NMR: δ6.84 (q, J = 1.5 Hz, 1H), 6.29 (ddd, J = 17.1, 10.3, 10.3 Hz, 1H), 6.09 (ddm, J = 15.0, 10.3 Hz, 1H), 5.70 (dt, J = 15.0, 7.0 Hz, 1H), 5.12 (dm, J = 17.1 Hz, 1H), 5.00 (dm, J = 10.3 Hz, 1H), 2.82 (t, J = 7.0 Hz, 2H), 2.42 (br q, J ~ 7.0 Hz, 1H), 2.34 (s, 3H), 2.16 (d, J = 1.5 Hz, 3H); 62.9 MHz ^{13}C NMR: 201.93, 199.63, 147.26, 136.82, 132.77, 132.15, 130.83, 115.80, 37.96, 32.05, 26.94, 13.64 ppm; IR (neat): 1685, 1615 cm^{-1}; MS m/e = 192 (parent), 43 (base peak).

Spectral data for 108 (analyzed as a mixture with 105). 250 MHz ^{1}H NMR: δ6.18 (s, 1H) and 5.86 (t, J = 1.1 Hz, 1H) are due to the methylidene group (the diene resonances were obscured by similar resonances in 105), 3.38 (s, $W_{\frac{1}{2}}$ = 2.1 Hz, 2H), 2.83 (t, J = 7.3 Hz, 2H), 2.39 (br q, J ~ 7.1 Hz, 2H), 2.18 (s, 3H); 62.9 MHz ^{13}C NMR: 205.25, 199.90, 142.79, 136.94, 133.21, 131.80, 127.33, 115.48, 45.90, 36.61, 29.82, 27.02 ppm.

Intramolecular Diels-Alder cyclization of 103 to hydrindenones 110a and 110b

A solution of triene 103 (425 mg; 2.39 mmol) in chloroform (20 mL) was refluxed for 4.5 h, after which time TLC analysis (SiO_2, 30% ethyl acetate-hexane, anisaldehyde-sulfuric acid spray visualization) indicated that all of the starting material ($R_f = 0.47$) had been consumed, leaving two closely spaced spots at $R_f = 0.23$ and 0.30. The solvent was removed under reduced pressure and the residue was flash chromatographed (25% ethyl acetate-hexane eluent) to give, in order of their elution, 197 mg of *trans*-fused hydrindeone 110a (46%) and 194 mg of *cis*-fused hydrindenone 110b (46%). The latter product solidified upon removal of the solvent, and was recrystallized from methylene chloride-hexane (1:10) to give 110b as white needles, mp = 84-85°C.

Spectral data for *cis*-fused hydrindenone 110b: 250 MHz ^{1}H NMR: δ5.80 (doublet of pentets (dddd), J = 10.0, ~2.5 Hz, 1H), 5.60 (dm, J = 10.0 Hz, 1H), 3.16 (ddm, J = 7.7, 3.5 Hz, 1H), ~3.12 (m, overlaps with signal at δ3.16, 1H), 2.55 (ddd, J = 10.8, 6.1, 3.5 Hz, 1H), 2.26 (s, 3H), 1.95 (m); 62.9 MHz ^{13}C NMR: 217.95, 208.75, 129.44, 128.03, 49.99, 45.49, 37.64, 34.73, 27.67, 27.17, 23.08 ppm; IR (Nujol): 1725, 1700 cm^{-1}; MS: m/e = 178 (parent), 43 (base peak).

Spectral data for *trans*-fused hydrindenone 110a: 250 MHz ^{1}H NMR: δ5.88 (dq (dddd), J = 10.2, ~2.0 Hz, 1H), 5.66 (dddd, J = 10.2, 3.9, 3.2, 3.2 Hz, 1H), 3.35 (ddd, J = 7.4, 3.7, 3.7 Hz, 1H), 2.16 (s, 3H), 1.98 (ddd, J = 13.6, 3.7, 1.2 Hz, 1H), 1.50 (m); 62.9 MHz ^{13}C NMR: 214.25, 208.25, 129.91, 126.91, 54.61, 44.11, 38.32, 35. 96, 29.49, 27.94, 26.47 ppm.

Epimerization of *trans*-fused hydrindenone 110a to *cis*-fused 111b

Upon standing at room temperature for two weeks in methylene chloride, a sample of 110a epimerized to give a *ca*. 1:1 mixture of 110a and *trans*-fused 111b. These two products could not be separated by flash column chromatography. Spectral data for 111b, as analyzed from the mixture, are as follows. 250 MHz ^{1}H NMR: δ5.73 (doublet of pentets (dddd), J = 10.2, ~2.4 Hz 1H), 5.59 (dm, J = 10.2 Hz, 1H), 3.10 (ddd, J = 7.2, 3.5, 3.5 Hz, 1H), 3.02 (m, 1H), 2.77 (ddd, J = 7.3, 3.5, 0.9 Hz, 1H), 2.20 (s, 3H); 62.9 MHz ^{13}C NMR: 219.51, 209.43, 129.50, 126.44, 48.52, 44.87, 35.26, 34.35, 27.67, 27.05, 22.82 ppm.

Intramolecular Diels-Alder cyclization of 106 to hydrindenones 111a and 111b

A solution of triene 106 (110 mg; 0.62 mmol) in chloroform (6 mL) was refluxed for 36 h, after which time

TLC analysis (SiO_2, 1:1 ether-hexane, anisaldehyde-sulfuric acid spray visualization) indicated that the starting material ($R_f = 0.44$) had been completely consumed. The solvent was removed under reduced pressure, and the residue was flash chromatographed (35% ether-hexane eluent) to give 90 mg of hydrindenones 111a and 111b (82%) as an inseparable mixture. From integration in the proton NMR, these products were obtained in a ratio of 1.7:1, respectively. Spectral data for *cis*-fused 111b were given in the previous experiment. Spectral data for *trans*-fused hydrindenone 111a, as analyzed from the mixture, are as follows. 250 MHz ^{1}H NMR: δ5.89 (dm, J = 10.3 Hz, 1H), 5.69 (dm, J = 10.3 Hz, 1H), 2.85 (ddd, J = 10.3, 10.3, 6.8 Hz, 1H), 2.32 (s, 3H), 1.63 (m); 62.9 MHz ^{13}C NMR: 214.10, 210.87, 55.28, 46.46, 39.76, 37.17, 30.26, 29.76, 26.29 ppm.

Intramolecular Diels-Alder cyclization of 105 to hydrindenones 112a and 112b

A solution of triene 105 (183 mg; 0.95 mmol) in chloroform (8 mL) was refluxed for 54 h, after which time TLC analysis (SiO_2, 40% ether-hexane, anisaldehyde-sulfuric acid spray visualization) indicated that the starting material had been completely consumed. The solvent was removed under reduced pressure and the residue was flash chromatographed (30% ether-hexane eluent) to give 159 mg

of hydrindenones 112a and 112b (87%) as an inseparable mixture. As determined from integration of the angular methyl groups in the proton NMR spectrum, 112a and 112b were obtained in a ratio of 4.9:1, respectively. The difference in relative abundance of the two products made possible assignments in the ^{13}C NMR spectrum on the basis of signal intensities, except where noted by an asterisk (*).

Spectral data for *trans*-fused hydrindenone 112a. 250 MHz ^{1}H NMR: δ5.75 (d q (dddd), J = 10.0, ~2.4 Hz, 1H), 5.61 (d q (dddd), J = 10.0, ~3.3 Hz, 1H), 3.01 (dd, J = 8.5, 1.8 Hz, 1H), 3.10 (m, 1H), 2.18 (s, 3H), 0.89 (s, 3H); 62.9 MHz ^{13}C NMR: 217.92, 209.31, 127.56, 125.15, 50.93, 49.11*, 38.40, 36.58, 30.26, 26.02, 22.52, 15.70 ppm.

Spectral data for *cis*-fused hydrindenone 112b. 250 MHz ^{1}H NMR: the olefinic resonances are obscured by those of 112a, δ2.87 (dd, J = 5.8, 5.2 Hz, 1H), 2.13 (s, 3H), 1.14 (s, 3H); 62.9 MHz ^{13}C NMR: 222.51, 209.19, 131.24, 122.65, 55.19*, 47.34, 44.73*, 37.51, 28.05, 26.20, 24.90, 24.20 ppm.

Intramolecular Diels-Alder cyclization of 109 to hydrindenones 113a and 113b

A solution of triene 109 (212 mg; 1.10 mmol) in chloroform-d_1 (8 mL) was refluxed for 6 h, when an aliquot

was withdrawn and examined by 250 MHz ^{1}H NMR. The spectrum revealed that no reaction had taken place. The aliquot was combined with the reaction mixture and the solvent was removed *in vacuo*. Toluene-d_8 (5 mL) was added, and the mixture was refluxed. Aliquots were removed after 4 h and 15 h, the latter indicating that cyclization was only *ca.* 35% complete. Small resonances at 0.89 and 1.14 ppm (relative ratio = 5:1, respectively) indicated the presence of the hydrindenone mixture 112a,b derived from *cis*-enedione 105. The reaction mixture was allowed to cool and then transferred to a re-sealable high pressure reaction vessel along with 15 mg of methylene blue as a radical inhibitor.[72] After flushing the system with nitrogen, the vessel was sealed and immersed into a silicon oil bath at 195°C for 8 h. After cooling to room temperature, the vessel was opened, the contents transferred to a round-bottomed flask, and the solvent was removed under reduced pressure. The residue was analyzed by 250 MHz ^{1}H NMR, which indicated the presence of a 50:50 mixture of hydrindenones 113a and 113b, *ca.* 10% of the 112a,b hydrindenone pair, less than 5% of the deconjugated triene 108, and a small amount of starting material. Separation of these products was effected by flash column chromatography (35% ether-hexane eluent) to give, in order of their elution, 7 mg of starting material 109 (3.3%), 43 mg of a *ca.* 10:1 mixture of 113a-113b (20%), 99 mg of a *ca.* 1:2.5 mixture of 113a-113b (47%), and 18 mg

of a mixture of triene 10̲8 and hydrindenones 11̲2a,b (8.5% combined yield).

Spectral data for *trans*-fused hydrindenone 11̲3a. 250 MHz ^{1}H NMR: δ5.69 (m, 2H), 2.99 (dd, J = 10.7, 6.6 Hz, 1H), 2.36 (s, 3H), 0.99 (s, 3H); 62.9 MHz ^{13}C NMR: 217.28, 210.75, 127.94, 126.18, 51.25, 50.81, 45.46, 35.70, 32.85, 28.17, 22.38, 9.15 ppm.

Spectral data for *cis*-fused hydrindenone 11̲3b. 250 MHz ^{1}H NMR: δ5.69 (m, 2H), 3.04 (dd, J = 6.4, 4.0 Hz, 1H), 2.88 (m, 1H), 2.17 (s, 3H), 1.03 (s, 3H); 62.9 MHz ^{13}C NMR: 221.45, 209.13, 130.59, 124.36, 49.55, 48.28, 42.43, 34.17, 30.64, 25.38, 24.49, 19.41 ppm.

Condensation of 123 with acetone to give linear nonamer 127

Trimer 123 (15.0 g; 52.8 mmol) was suspended in 125 mL of absolute ethanol. Gaseous HCl was bubbled into the mixture for *ca.* 6 min, which generated enough heat to dissolve all of the starting material. Then, with mechanical stirring, a solution of acetone (4.0 g; 68 mmol) in 20 mL of absolute ethanol was added dropwise over a period of *ca.* 10 min. After being stirred at room temperature for another 10 min, a white precipitate began to form. Stirring was continued for 15 h, and then the mixture was allowed to stand for 20 h at room temperature, during which time the suspension had become very thick. The precipitate was collected by suction filtration, dissolved in methylene chloride (200 mL), and washed with saturated aqueous $NaHCO_3$ (2 × 100 mL) and saturated aqueous NaCl (1 × 100 mL). The resulting greenish solution was dried over anhydrous Na_2SO_4, filtered, and condensed *in vacuo* to *ca.* 30 mL, with precipitation. Ethanol (100 mL) was added and the suspension was cooled at -30°C for 2 h. Suction filtration gave 10.2 g of the title compound as an off-white amorphous solid (83%), mp = 107-112°C. This material was not purified further. A second crop (1.7 g) of a white crystalline material was obtained. Proton NMR analysis indicated that it was the cyclic hexamer 126 (10%), mp = 179-181°C (lit.[91] mp = 182°C). Spectral properties of nonamer 127. ^{1}H NMR: δ7.17

(m, 2H), 6.12 (m, 2H), 5.82 (dm, J = 3 Hz, 2H), 5.68 (m, 14H), 15.5 (s, 48H).

Formylation of linear nonamer 127 to dialdehyde 128

To 1.0 mL of dry dimethylformamide at 0°C was added 0.88 mL of phosphorus oxychloride (d = 1.645 g/mL; 9.4 mmol) dropwise over a period of *ca*. 3 min. The mixture was stirred at 0°C for 1 h, during which time the solution had solidified. Dry 1,2-dichloroethane (10 mL) was added and the mixture was stirred at room temperature until all of the iminium salt had dissolved. The colorless solution was cooled to 0°C, when a solution of 127 (4.0 g; 4.3 mmol) in 20 mL of dry 1,2-dichloroethane was added dropwise over a period of 0.5 h. After the reddish brown reaction mixture had been stirred at room temperature for 8 h, a solution of 10 g of sodium acetate in 50 mL of water was added, and the resulting two-phase mixture was stirred at room temperature overnight. The layers were separated and the aqueous phase was extracted with chloroform (2 × 25 mL). The combined organic phases were washed with water (1 × 25 mL), saturated aqueous $NaHCO_3$ (2 × 25 mL), saturated aqueous NaCl (1 × 25 mL), dried over anhydrous Na_2SO_4, and filtered. Removal of the solvent under reduced pressure gave 3.94 g of a pale yellow solid which was recrystallized from a minimum amount of ethanol to give 3.41 g of dialdehyde 128 (80%) as a very pale yellow amorphous solid, mp = 123-125°C.

250 MHz ^{1}H NMR: δ9.53 (s, 2H), 7.10 (d, J = 3.4 Hz, 2H), 6.07 (d, J = 3.4 Hz, 2H), 5.98 (d, J = 3.4 Hz, 2H), 5.86 (d, J = 3.4 Hz, 2H), 5.79 (m, 10H), 1.66 (s, 3H), 1.57 (s, 3H), 1.56 (s, 3H), 1.55 (s, 3H); IR (Nujol): 1680, 1550, 1510 cm^{-1}; MS: m/e = 988 (parent), 245 (base peak).

Di-ring-opened *trans*-enedione 129

A magnetically stirred, 1000-mL round-bottomed flask was charged with 5.00 g of finely powdered tetramer 121 (11.6 mmol), 650 mL of glacial acetic acid and 20 mL of distilled water. Added dropwise to the vigorously stirred suspension was a solution of 4.64 g of bromine (29.0 mmol) in 100 mL of glacial acetic acid over a period of 3 h, during which time the suspension had taken on a bright yellow color. Stirring was continued for an additional hour, and the crude product was collected by suction filtration and washed with methanol. Recrystallization from chloroform to remove the acetic acid from the crude product gave 3.97 g of 129 as small bright yellow cubes, mp = 276-278°C (dec). ^{1}H NMR: δ6.95 (s, 4H), 6.10 (s, 4H), 1.40 (s, 24H); ^{13}C NMR: 194.39, 156.43, 132.47, 107.51, 48.53, 22.03 ppm; IR (Nujol): 1698, 1540 cm^{-1}; UV-vis: 382 nm (log ε = 3.25), 304 (3.67), 232 (4.52); MS: m/e = 464 (parent), 150 (base peak).

Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94
Found: C, 72.88; H, 6.90

Dibromo-*trans*-enedione 130

The procedure was followed as for 129 above, except that 7.42 g of bromine (4.0 equivalents) were used. The addition took 2.5 h, and the reaction mixture was allowed to stand overnight. The crude product was collected by suction filtration, and the proton NMR spectrum of this material showed a mixture of 129, 130, and acetic acid. The bright yellow solid was suspended in 50 mL of ethyl acetate with warming on a steam bath to dissolve 130 (129 is insoluble). The remaining solids were removed by filtration, and the filtrate was taken to dryness *in vacuo*. The resulting oily yellow solid was cooled in ethanol at -30°C overnight and the product was collected by suction filtration to give 2.90 g of 130 (40%). Recrystallization from chloroform-ethanol (1:4) gave 130 as long, fine yellow needles, mp = 247-248°C (dec.). ^{1}H NMR: δ7.08 (s, 2H), 6.13 (s, 4H), 4.87 (s, 2H), 1.53 (s, 6H), 1.48 (s, 6H), 1.43 (s, 12H); ^{13}C NMR: 199.79, 196.56, 155.27, 155.06, 133.02, 108.71, 108.35, 48.97, 48.49, 39.85, 22.68, 22.40, 22.14, 22.03 ppm; IR (Nujol): 1710, 1675, 1530 cm^{-1}; UV-vis: 388 nm (log ε = 3.03), 311 (3.47), 224 (4.32); MS (CI): m/e = 625 (M+1; base peak).

Anal. Calcd for $C_{28}H_{32}Br_2O_6$: C, 53.86; H, 5.17

Found: C, 52.89; H, 5.11

Saturated tetraketone 131

Reduction of 129, 131, and 138 using zinc in acetic acid gave a nearly quantitative yield of 131. A typical procedure is as follows. In a 250-mL Erlenmeyer flask was placed 1.00 g of di-ring-opened *trans*-enedione 129 (2.16 mmol) and 75 mL of glacial acetic acid. The mixture was brought to a boil on a hot plate to dissolve 129, removed from the heat for *ca.* 1 min, and with swirling, 2.0 g of zinc dust was added. The bright yellow solution was decolorized within seconds after addition of the zinc, indicating that the reaction was complete. After cooling to room temperature, the excess zinc and zinc salts were removed by suction filtration through celite and washed thoroughly with chloroform. The colorless filtrate was poured into two volumes of water, the layers were separated, and the aqueous phase was extracted with chloroform (2 × 30 mL). The combined organic phases were washed with water (1 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), saturated aqueous NaCl (1 × 50 mL), dried over anhydrous Na_2SO_4, and filtered. Removal of the solvent under reduced pressure left a white crystalline solid. Cold ethanol was added and the crystals were collected by suction filtration to give 1.00 g of saturated tetraketone 131 (99%). Recrystallization from chloroform-ethanol (1:3) gave 131 as small white cubes, mp = 269-270°C. ^{1}H NMR: δ6.03 (s, 4H), 2.40 (s, 8H), 1.40 (s, 24H); ^{13}C NMR:

209.26, 157.44, 106.38, 48.70, 30.88, 22.94 ppm; IR (Nujol): 1706, 1600, 1550 cm^{-1}; MS: m/e = 468 (parent), 135 (base peak).

Anal. Cacd for $C_{28}H_{36}O_6$: C, 71.77; H, 7.74
Found: C, 72.20; H, 7.79

Tetra-ring-opened octaketone 132

Tetramer 121 (1.00 g; 2.31 mmol) in 75 mL of chloroform was brought to a boil. The solution was removed from the heat and allowed to cool to 55-60°C, when 1.97 g of MCPBA (9.70 mmol) was added in one portion. After being stirred overnight at room temperature, the pale greenish yellow solution was extracted with saturated aqueous $NaHCO_3$ (3 × 50 mL), dried over anhydrous Na_2SO_4, and filtered. The solution was concentrated *in vacuo* to *ca.* 15 mL, when ethanol (40 mL) was added. Cooling for several hours at 0°C gave white crystals which were collected by suction filtration to afford 0.99 g of the product (87%), mp = 208-210°C (dec.). ^{1}H NMR: δ6.48 (s, 8H), 1.40 (s, 24H); ^{13}C NMR: 200.50, 133.91, 59.77, 21.79 ppm; IR (Nujol): 1711, 1698, 1684, 1615, 1600 cm^{-1}; UV-vis: shoulder at 290 nm (log ε = 2.9), 212 (4.4); MS (CI): m/e = 497 (M+1), 125 (base peak).

Anal. Calcd for $C_{28}H_{32}O_8$: C, 67.73; H, 6.50
Found: C, 68.18; H, 6.47

Hexa-ring-opened dodecaketone 133

To a solution of 0.50 g of cyclic hexamer 126 (0.77 mmol) in 35 mL of chloroform was added 0.99 g of MCPBA (4.9 mmol) in one portion. After being stirred at room temperature overnight, the pale greenish yellow solution was extracted with saturated aqueous $NaHCO_3$ (3 × 40 mL), dried over anhydrous Na_2SO_4, and filtered. Removal of the solvent under reduced pressure gave a pale greenish yellow solid which was broken up in ethanol and cooled at -30°C for several hours. Collection of the crude product by suction filtration gave 0.49 g (85%). Recrystallization from chloroform-ethanol (1:4) gave 0.43 g of 133 as fluffy pale greenish yellow needles, mp = 173-174°C. ^{1}H NMR: δ6.47 (s, 12H), 1.40 (s, 36H); ^{13}C NMR: 201.08, 135.17, 60.44, 20.93 ppm; IR (Nujol): 1685, 1630 cm^{-1}; UV-vis: shoulder at 295 nm (log ε = 3.0), 223 (4.42); MS (CI): m/e = 745 (M+1; base peak).

Anal.[102] Calcd for $(C_{42}H_{48}O_{12})_2 \cdot CHCl_3$: C, 63.45; H, 6.08
Found: C, 63.16; H, 6.13

Saturated octaketone 134

A suspension of 0.50 g of tetra-ring-opened octaketone 132 (1.0 mmol), 60 mg of 10% palladium on carbon, and 60 mL of ethyl acetate was shaken under 50 psi of hydrogen in a Parr apparatus for 3 h. The catalyst was removed by

filtration and washed with chloroform. The filtrate was evaporated under reduced pressure, and the resulting oily solid was suspended in 20 mL of ethanol and cooled to -30°C overnight. Collection of the product by suction filtration gave 0.40 g of the product (78%) as a white crystalline solid. Recrystallization from chloroform-ethanol (1:4) gave 134 as long white needles, mp = 187-188°C. ^{1}H NMR: δ2.70 (s, 16H), 1.35 (s, 24H); ^{13}C NMR: 207.78, 62.71, 32.72, 20.79 ppm; IR (Nujol): 1702 cm^{-1}; MS (CI): m/e = 501 (M+1), 126 (base peak).

Anal. Calcd for $C_{28}H_{40}O_8$: C, 66.65; H, 7.99
Found: C, 66.21; H, 8.05

Saturated dodecaketone 135

The procedure was used as in 134 above; 0.20 g of hexa-ring-opened 133 (0.27 mmol) and 10 mg of catalyst in 25 mL of ethyl acetate gave 0.13 g of 135 (65%) after recrystallization from chloroform-ethanol (1:4) as white needles, mp = 186-187°C. ^{1}H NMR: δ2.65 (s, 24H), 1.37 (s, 36H); ^{13}C NMR: 208.12, 61.74, 32.20, 21.45 ppm; IR (Nujol): 1698 cm^{-1}; MS: a molecular ion could not be detected using electron impact or chemical ionization; m/e = 126 (base peak).

Anal. Calcd for $C_{42}H_{60}O_{12}$: C, 66.65; H, 7.99
Found: C, 66.40; H, 8.11

Tri-ring-opened hexaketone 136

To a solution of 1.00 g of tetramer 121 (2.31 mmol) dissolved in 45 mL of chloroform was added 1.45 g of MCPBA (7.14 mmol) in one portion. After being stirred for 4.5 h at room temperature, the mixture was washed with saturated aqueous $NaHCO_3$ (3 × 50 mL), dried over anhydrous Na_2SO_4, and filtered. Removal of the solvent under reduced pressure gave an oily greenish yellow solid whose proton NMR spectrum showed a mixture of 136 and tetra-ring opened 132. TLC analysis (SiO_2, 4:1 chloroform-ethyl acetate, UV visualization) gave two spots at $R_f = 45$ and 0.35. Separation of this mixture by flash column chromatography (4:1 chloroform-ethyl acetate eluent) gave 0.67 g of pure tri-ring-opened hexaketone 136. The tetra-ring-opened product 132 had evidently decomposed on the column. Recrystallization of 136 from chloroform-ethanol (1:5) gave the product as small, pale greenish yellow prisms, mp = 186-187°C (dec.). ^{1}H NMR: δ6.22 (AB quartet, J = 11.5 Hz, 4H), 6.53 (s, 2H), 6.12 (s, 2H), 1.43 (s, 12H), 1.38 (s, 12H); ^{13}C NMR: 203.11, 202.33, 199.53, 157.15, 139.82, 134.81, 128.80, 106.81, 60.78, 47.86, 22.33, 22.01 ppm; IR (Nujol): 1685, 1600, 1550 cm^{-1}; MS: m/e = 480 (parent), 149 (base peak).

Anal. Calcd for $C_{28}H_{32}O_7$: C, 69.98; H, 6.71
Found: C, 69.93; H, 6.85

Saturated hexaketone 137

The procedure was used as for 134 above, using 165 mg of tri-ring-opened 136 (0.344 mmol), 10 mg of palladium on carbon, and 20 mL of ethyl acetate. After removing the solvent under reduced pressure, the colorless oil was crystallized by cooling in hexane-benzene (3:1) at -30°C for 24 h. The product was collected by suction filtration to give 117 mg of 137 (70%) as very small white prisms, mp - 143-144°C. ^{1}H NMR: δ5.97 (s, 2H), 2.55 (s, 4H), 2.48 (s, 8H), 1.38 (s, 12H), 1.33 (s, 12H); IR (Nujol): 1700, 1540 cm^{-1}; MS: m/e = 486 (parent), 135 (base peak).

Anal. Calcd for $C_{28}H_{38}O_7$: C, 69.11; H, 7.87
Found: C, 68.78; H, 8.02

Di-ring-opened *cis*-enediones 138 and 139

To a solution of tetramer 121 (0.70 g; 1.6 mmol) in 45 mL of chloroform at 0°C was added 0.73 g of MCPBA (3.6 mmol) in one portion. After being stirred for 1 h at 0°C and 2 h at room temperature, the mixture was washed with saturated aqueous $NaHCO_3$ (3 × 50 mL), dried over anhydrous Na_2SO_4, and filtered. Removal of the solvent under reduced pressure gave a pale greenish yellow solid which was broken up in ethanol (10 mL) and cooled to 0°C for 1 h. Suction filtration afforded 0.64 g of a solid

which, by TLC analysis (SiO_2, 8:1 chloroform-ethyl acetate, UV visualization), consisted of three components, R_f = 0.62, 0.52, and 0.37. Separation of the mixture by flash column chromatography (10% ethyl acetate-chloroform eluent) gave, in order of thier elution, 0.24 g of di-ring-opened 13~8 (32%), 0.26g of di-ring-opened 13~9 (36%) and 0.15 g of tri-ring-opened 13~6 (19%). The di-ring-opened tetraketones were each recrystallized from chloroform-ethanol (1:6), giving 0.19 g of 13~8 as tiny pale yellow prisms, mp = 211-212°C, and 0.20 g of 13~9 as pale greenish yellow plates, mp = 165-166°C.

Spectral data for 13~8. ^{1}H NMR: δ6.00 (s, 4H), 5.97 (s, 4H), 1.45 (s, 24H); ^{13}C NMR: 202.26, 156.88, 134.13, 106.95, 48.19, 23.08 ppm; IR (Nujol): 1700, 1610, 1600, 1550 cm^{-1}; UV-vis: shoulder at 333 nm (log ε = 3.0), 277 (3.53), 221 (4.41); MS: m/e = 464 (parent), 150 (base peak).

Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94
Found: C, 72.29; H, 6.98

Spectral data for 13~9. ^{1}H NMR: δ5.95 (AB quartet, J = 12 Hz, 4H), 5.87 (AB quartet, J = 3 Hz, 4H), 1.58 (s, 6H), 1.52 (s, 12H), 1.18 (s, 6H); IR (Nujol): 1695, 1680, 1605, 1540 cm^{-1}; UV-vis: shoulder at 332 nm (log ε = 2.8), shoulder at 290 (3.1), 221 (4.32); MS: m/e = 464 (parent), 150 base peak).

Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94
Found: C, 72.50; H, 7.04

Di-ring-opened *trans*-enediones 129 and 141

To a solution of tetramer 121 (2.00 g; 4.63 mmol) in 150 mL of chloroform was added 1.88 g of MCPBA (9.26 mmol) in one portion. After being stirred for 45 min at room temperature, 1 mL of concentrated HCl was added, causing a deepening of the initially pale greenish yellow solution. After being stirred for an additional 2 h, the solution was washed with saturated aqueous $NaHCO_3$ (3 × 100 mL), dried over anhydrous Na_2SO_4, and filtered. The volume was concentrated to *ca.* 20 mL under reduced pressure, when 50 mL of ethanol was added. After cooling at 0°C for several hours, the bright yellow precipitate which resulted was collected by suction filtration to give 0.88 g of 129 (41%), identified by its proton NMR spectrum and melting point. The orange-yellow filtrate was taken to dryness *in vacuo*, leaving an oil. Ethanol (25 mL) was added, and the solution was cooled to -30°C for 12 h to give a second crop of crystals. Suction filtration gave 0.41 g of 141 (19%) as yellow-orange prisms, mp = 159-160°C. ^{1}H NMR: δ6.72 (AB quartet, J = 16 Hz, 4H), 6.00 (AB quartet, J = 3.2 Hz, 4H), 1.52 (s, 6H), 1.40 (s, 12H), 1.33 (s, 6H); ^{13}C NMR: 197.95, 197.41, 159.93, 153.98, 133.84, 132.91, 107.36, 105.09, 61.34, 48.38, 36.81, 25.31, 22.18, 20.71 ppm; IR (Nujol): 1700, 1680, 1615, 1600, 1550 cm^{-1}; UV-vis: 382 nm (log ε = 303), 306 (3.38), 233 (4.47); MS: m/e = 464 (parent),

150 (base peak).

Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94
Found: C, 72.22; H, 6.91

Saturated tetraketone 140

The procedure was used as for 134 above, using either 139 or 141. *trans*-Enedione 141 (150 mg; 0.323 mmol) in 25 mL of ethyl acetate with 10 mg of palladium on carbon gave 111 mg of the title compound (74%) as white needles from ethanol, mp = 162-163°C. ^{1}H NMR: δ5.88 (s, 4H), 2.45 (m, 8H), 1.52 (s, 6H), 1.40 (s, 12H), 1.27 (s, 6H); IR (Nujol): 1695, 1550 cm^{-1}; MS: m/e = 468 (parent), 150 (base peak).

Anal. Calcd for $C_{28}H_{36}O_6$: C, 71.77; H, 7.74
Found: C, 71.32; H, 7.79

2,2-*bis*[5-(3-Oxopropyl)-2-furyl]propane (142)

A solution containing 4.00 g of 2,2-*bis*(2-furyl)-propane 122 (22.7 mmol), 6.36 g of acrolein (114 mmol), and 0.15 g of *p*-toluenesulfonic acid hydrate (0.79 mmol) in 50 mL of THF was refluxed under an atmosphere of nitrogen. The reaction was monitored by TLC (SiO_2; 20% ether-hexanes, anisaldehyde-sulfuric acid spray visualization) until the starting material (R_f = 0.79) had disappeared (6-7 h). The cooled reaction mixture

was filtered through Celite to remove the acrolein stabilizer, transferred to a separatory funnel containing an equal volume of ether, and then washed successively with saturated aqueous $NaHCO_3$ (2 × 75 mL) and saturated aqueous NaCl (1 × 50 mL). After drying the organic phase over anhydrous $MgSO_4$ and filtering, the organic solvents were removed under reduced pressure and the resulting thick brown oil was chromatographed (SiO_2; 50% ether-hexane eluent) to give 2.82 g of the title compound (43%) as a viscous, pale orange oil. ^1H NMR: δ9.70 (t, J ~ 1.5 Hz, 2H), 5.88 (s, 4H), 3.0-2.5 (m, 8H), 1.60 (s, 6H); MS: m/e = 288 (parent), 273 (base peak).

2,2-*bis*[5-(3-Hydroxypropyl)-2-furyl]propane (143)

A solution of 2.50 g of dialdehyde 142 (8.68 mmol) in 35 mL of methanol was cooled to -10°C using an ice-salt bath, and 0.75 g of $NaBH_4$ (20 mmol) was added in small portions over a period of 5 min. After being stirred at -10°C for 1 h, the reaction mixture was poured into water (100 mL) and extracted with methylene chloride (4 × 30 mL). The extracts were dried over anhydrous $NaSO_4$, filtered, and the solvents were removed under reduced pressure to give 2.48 g of the crude diol (98%) as a viscous oil which was used without purification in the next step. ^1H NMR: δ5.82 (s, 4H), 3.53 (t, J = 7 Hz, 4H), ~3.15 (br s, 2H; OH), 2.62 (t, J = 7 Hz, 4H), 1.80

(pentet, J = 7 Hz, 4H), 1.57 (s, 6H); MS: m/e = 292 (parent), 277 (base peak).

2,2-*bis*[5-(3-Bromopropyl)-2-furyl]propane (144)

To a well-stirred solution of 2.00 g of the crude diol 143 (6.85 mmol) and 10.0 g of carbon tetrabromide (30.1 mmol) in 150 mL of anhydrous ether at room temperature was added 8.25 g of triphenylphosphine (31.5 mmol) in one portion. The progress of the reaction was monitored by TLC (SiO_2; 30% ether-hexanes, anisaldehyde-sulfuric acid spray visualization) for the disappearance of starting material (R_f = 0.20) and intermediate monobromide (R_f = 0.40), and appearance of product (R_f = 0.6), which required 3-4 h. An equal volume of hexane was added to the reaction mixture and the flocculent white precipitate was removed by suction filtration and washed with hexane. The filtrate solvents were removed under reduced pressure and the resulting oil was chromatographed (SiO_2; 15% ether-hexane eluent) to give 2.30 g of the title compound (81%) as a colorless liquid. ^{1}H NMR: δ5.87 (br s, 4H), 3.38 (t, J = 7 Hz, 4H), 2.73 (t, J = 7 Hz, 4H), 2.12 (pentet, J = 7 Hz, 4H), 1.57 (s, 6H); MS: m/e = 418 (parent), 403 (base peak).

2,2-*bis*{5-[3-(2-Furyl)propyl]-2-furyl}propane (145)

To a solution of 1.46 mL of distilled, dry furan (20.1 mmol) in 35 mL of anhydrous THF at -78°C under nitrogen atmosphere was added 20.6 mL of *n*-butyllithium in hexane (0.95 M; 19.6 mmol). The solution was stirred at -78°C for 2 h, warmed to -20° to -30°C for 1 h, and then re-cooled to -78°C. Dibromide 144 (2.00 g; 4.78 mmol) in 15 mL of anhydrous THF was added dropwise over a period of 15 min. The cooling bath was allowed to warm to room temperature (*ca.* 4 h) and stirring was continued overnight. The reaction mixture was poured into an equal volume of water, the layers were separated, and the aqueous phase was extracted with ether (2 × 30 mL). The combined organic phases were then washed with 1% HCl, (1 × 30 mL), saturated aqueous $NaHCO_3$ (1 × 50 mL), and saturated aqueous NaCl (1 × 50 mL), dried over anhydrous $MgSO_4$, and filtered. Removal of the solvents under reduced pressure gave 1.72 g of a pale orange-brown oil which was purified by flash column chromatography (10% ether-hexane eluent) to give 1.57 g of the title compound (85%) as a colorless oil. 250 MHz ^{1}H NMR: δ7.29 (dd, J = 1.8, 0.9 Hz, 2H), 6.27 (dd, J = 3.1, 1.8 Hz, 2H), 5.98 (dd, J = 3.1, 0.9 Hz, 2H), 5.87 (AB quartet, J = 3.1 Hz, 4H), 2.65 (t, J = 7.6 Hz, 4H), 2.61 (t, J = 7.6 Hz, 4H), 1.94 (pentet, J = 7.6 Hz, 4H), 1.59 (s, 6H); 62.9 MHz ^{13}C NMR: 158.73, 155.85, 154.14, 140.85, 110.09, 105.36, 105.04,

104.33, 37.43, 27.44, 27.35, 26.61, 26.47 ppm; MS: m/e = 392 (parent), 377 (base peak).

1,1,15,15-Tetramethyl-[1.3.1.3](2,5)furanophane (146)

A solution containing 150 mg of the open-chain substrate 145 (0.383 mmol), 0.25 g of 2,2-dimethoxypropane (2.4 mmol), 0.30 g of *p*-toluenesulfonic acid hydrate (1.6 mmol), and 70 mL of anhydrous benzene was stirred at 60°C (bath temperature) under a nitrogen atmosphere for 20 h. An equal volume of ether was added and the solution was washed with saturated aqueous $NaHCO_3$ (2 × 30 mL) and saturated aqueous NaCl (1 × 30 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvents were removed under reduced pressure, leaving a dark brown oil. Flash column chromatography (20% benzene-hexane eluent) gave 78 mg of the title compound (47%) as a white solid. Recrystallization from benzene-hexane (1:4) gave 146 as white flakes, mp = 113-114°C. 250 MHz ^{1}H NMR: δ5.96 (d, J = 3.2 Hz, 4H), 5.82 (dt, J = 3.2, ~0.5 Hz, 4H), 2.46 (t, J = 7.6 Hz, 8H), 1.73 (pentet of multiplets, J = 7.6 Hz, 4H), 1.56 (s, 12H); 62.9 MHz ^{13}C NMR: 158.82, 154.59, 104.86, 103.54, (quaternary carbon signal not observed), 27.64, 26.96, 26.26 ppm; MS: m/e = 432 (parent), 417 (base peak).

Tetra-ring-opened *cis*-enedione 147

To a solution of 65 mg of furanophane 146 (0.150 mmol) in 15 mL of chloroform was added 128 mg of MCPBA (0.632 mmol in one portion. After being stirred for 3 h at room temperature, the solution was washed with saturated aqueous $NaHCO_3$ (3 × 30 mL), dried over anhydrous Na_2SO_4, and filtered. Removal of the solvent under reduced pressure gave 74 mg of a solid which was recrystallized from chloroform-ethanol (1:5) to give 36 mg of 146 (48%) as tiny neeldes, mp = 172-173°C. 250 MHz ^{1}H NMR: δ6.48 (AB quartet, J = 11.9 Hz, 8H), 2.67 (t, J = 6.4 Hz, 8H), 1.95 (pentet, J = 6.4 Hz, 4H), 1.38 (s, 12H); IR (Nujol): 1685, 1600 cm^{-1}; MS: m/e = 496 (parent), 107 (base peak).

APPENDIX

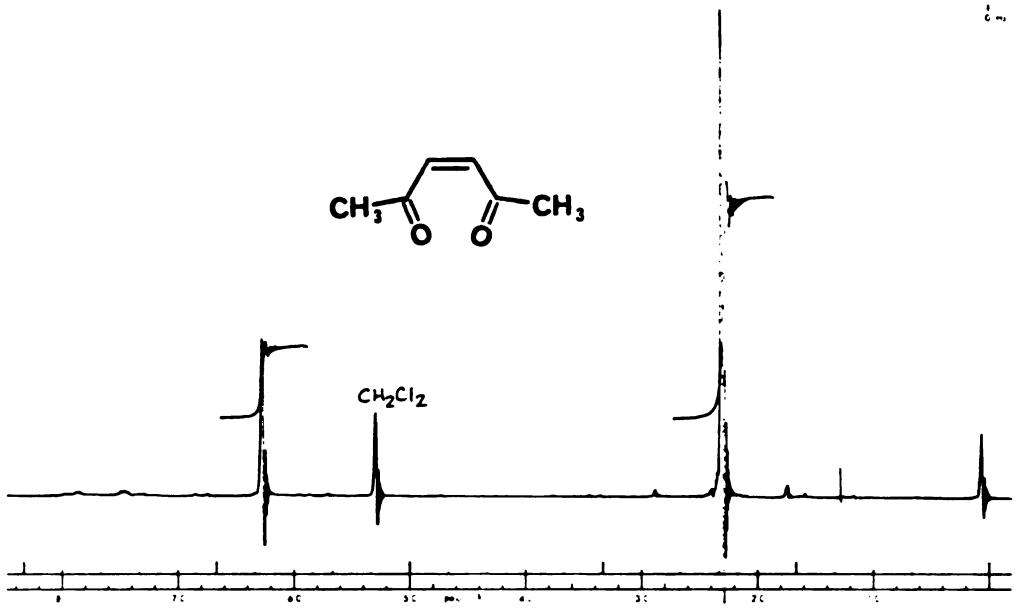


Figure A1. 60 MHz ^{1}H NMR spectrum of *cis*-3-hexene-2,5-dione (37).

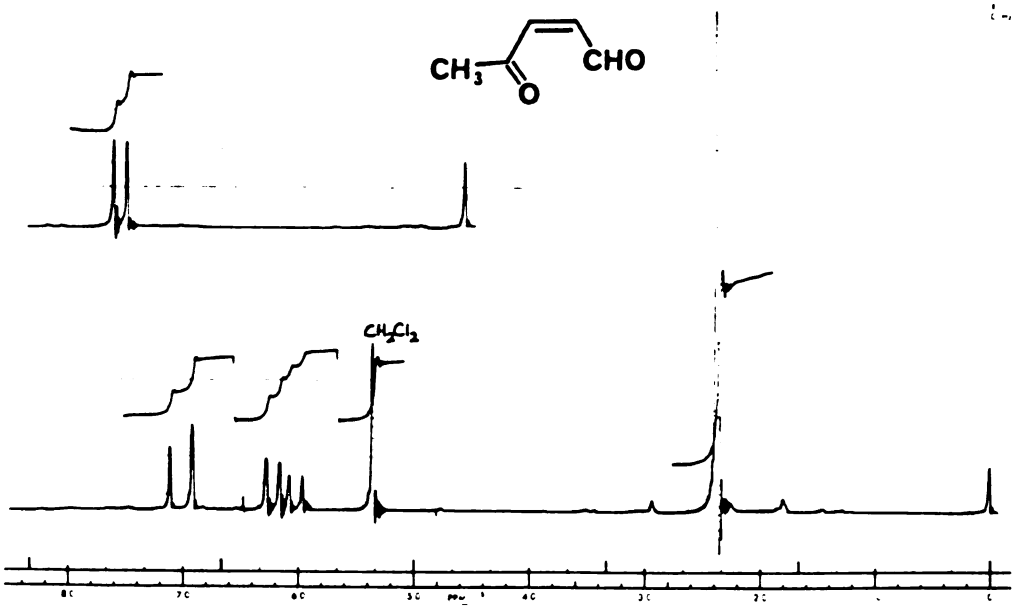


Figure A2. 60 MHz ^{1}H NMR spectrum of *cis*-4-oxo-2-pentenal (45).

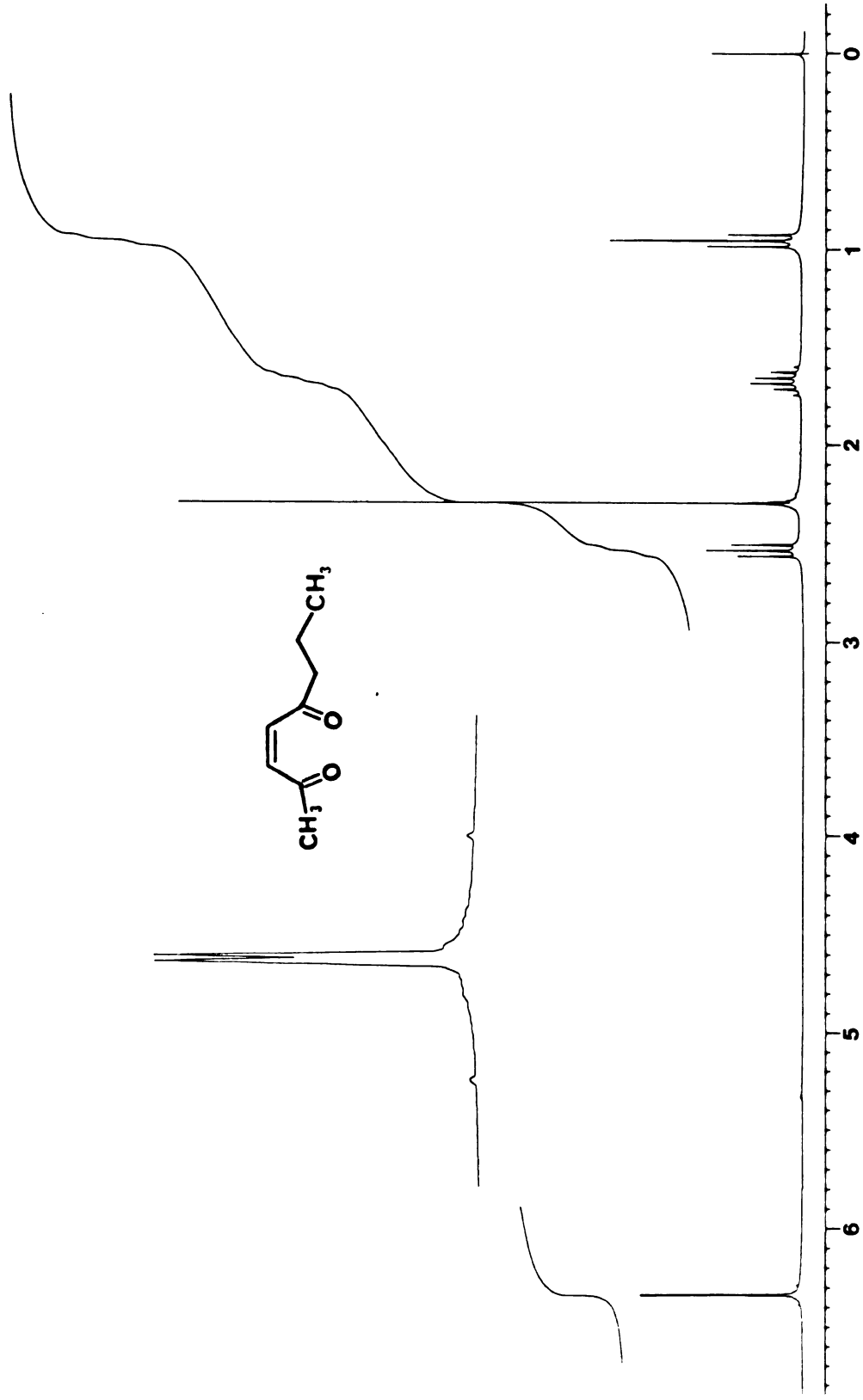


Figure A3. 250 MHz ^{1}H NMR spectrum of *cis*-3-octene-2,5-dione (39a).

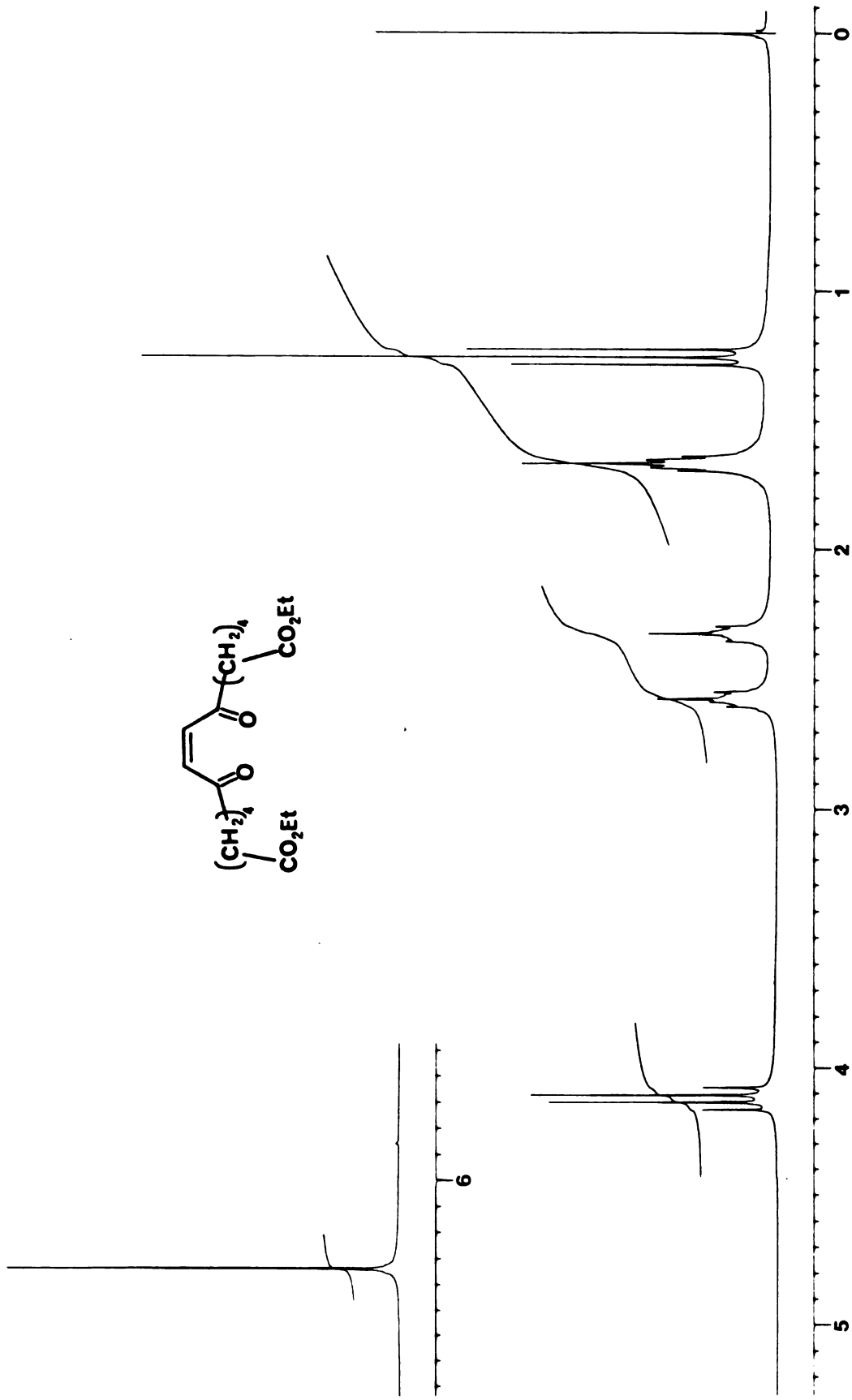


Figure A4. 250 MHz ^{1}H NMR spectrum of *cis*-enedionediester 41a.

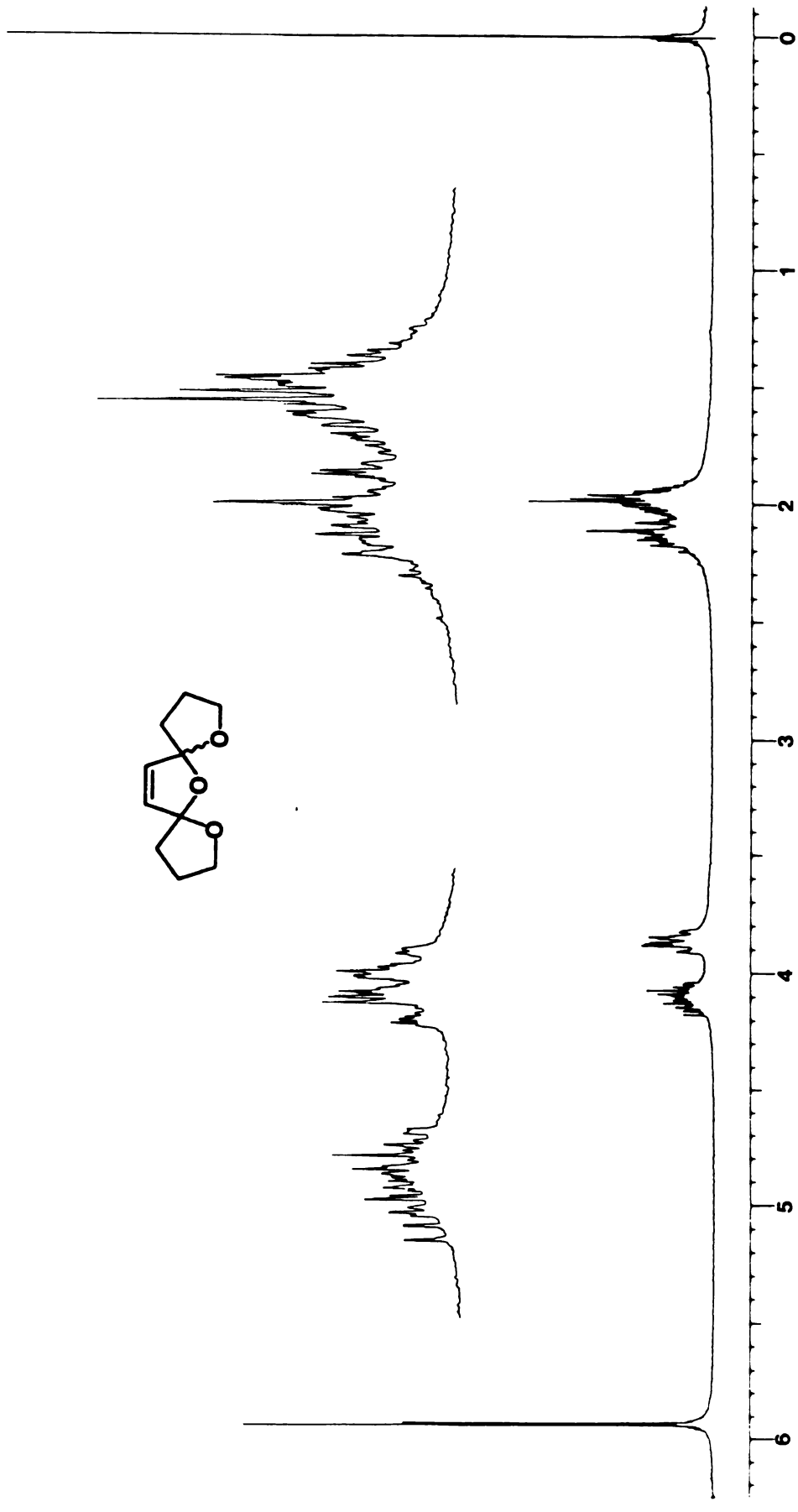


Figure A5. 250 MHz ^{1}H NMR spectrum of *bis*-spiroketal 43.

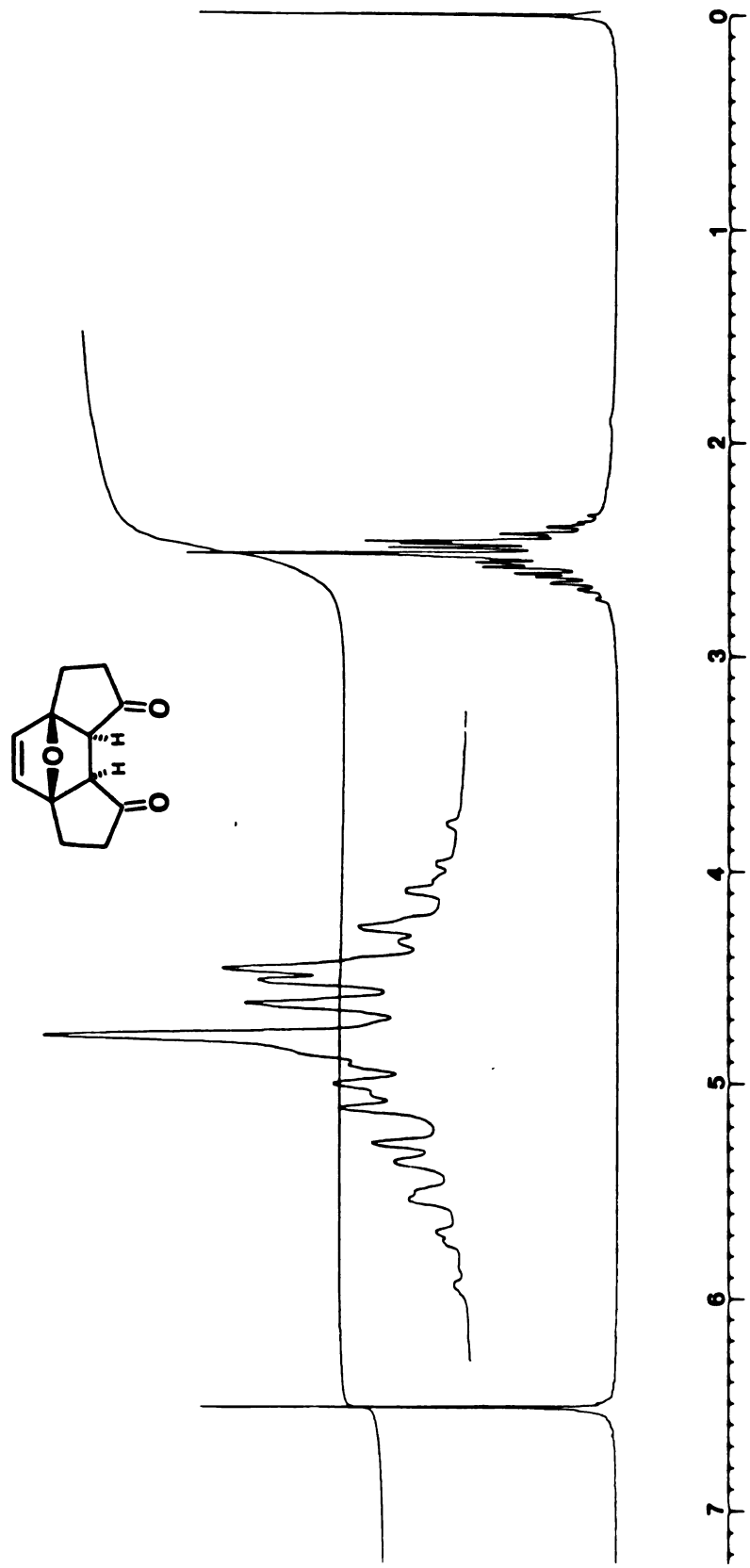


Figure A6. 250 MHz ^{1}H NMR spectrum of tetracyclic dione 20.

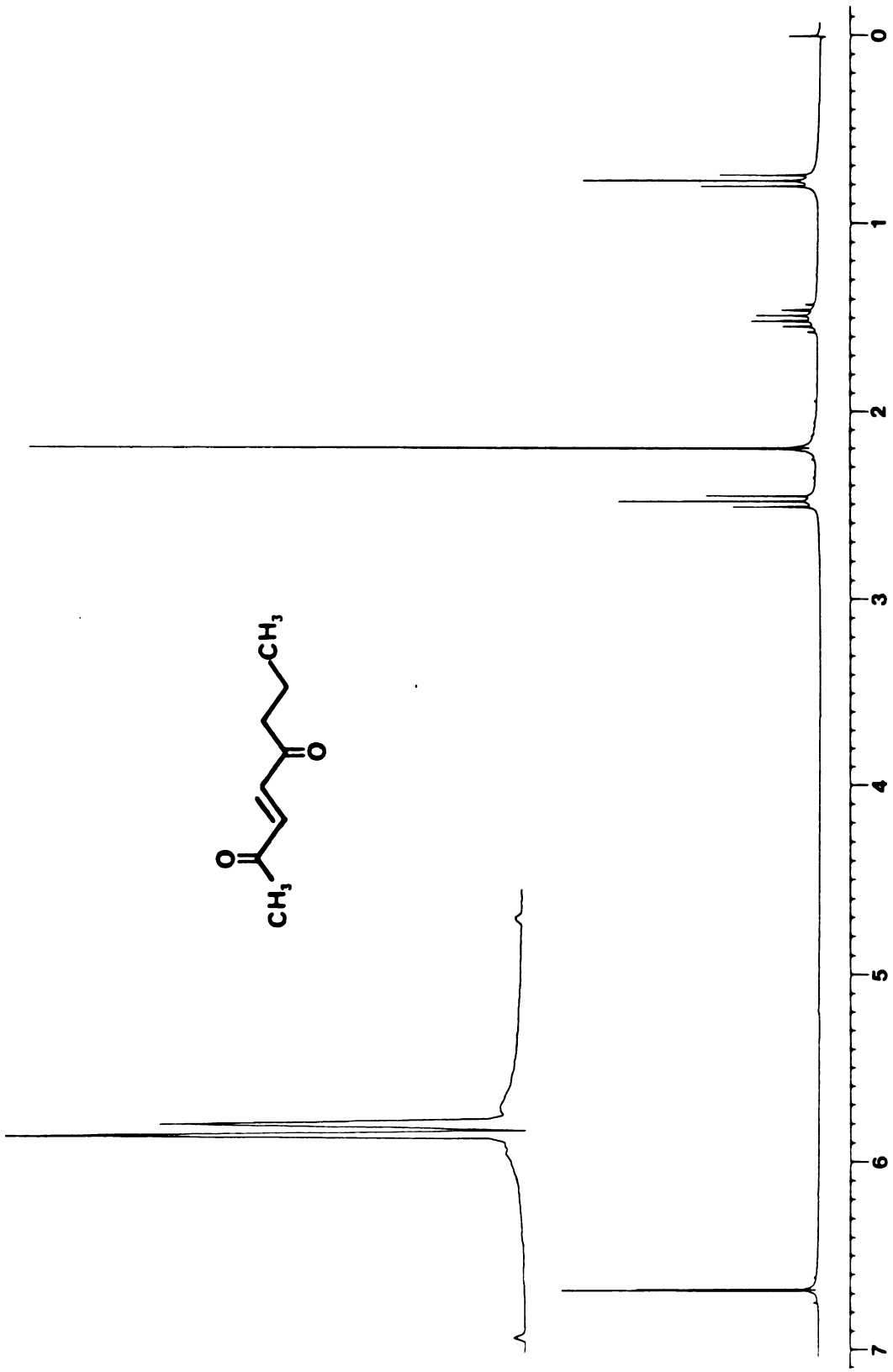


Figure A7. 250 MHz ^{1}H NMR spectrum of *trans*-3-octene-2,5-dione (39b).

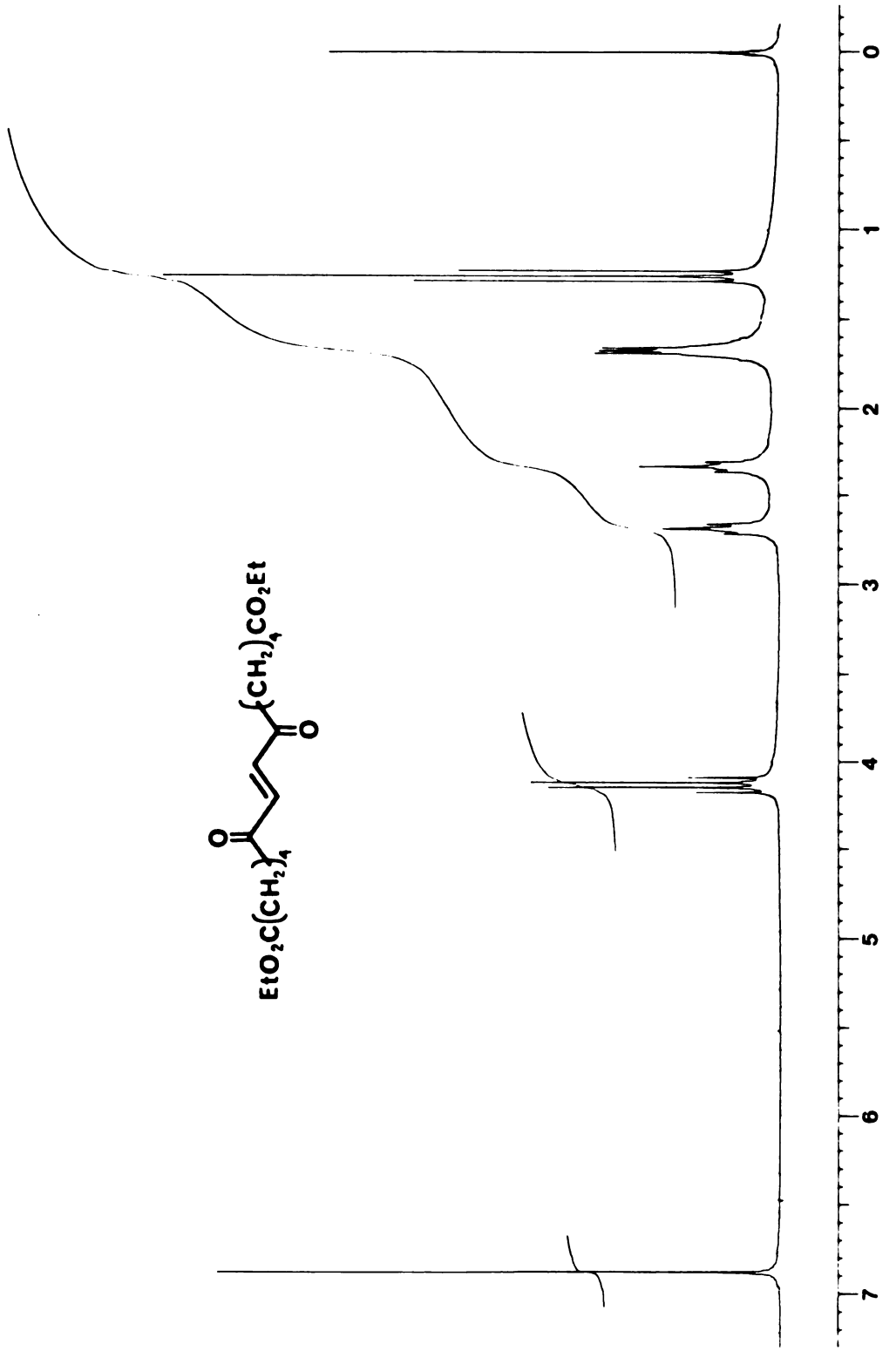


Figure A8. 250 MHz ^{1}H NMR spectrum of *trans*-enedionediester 41b.

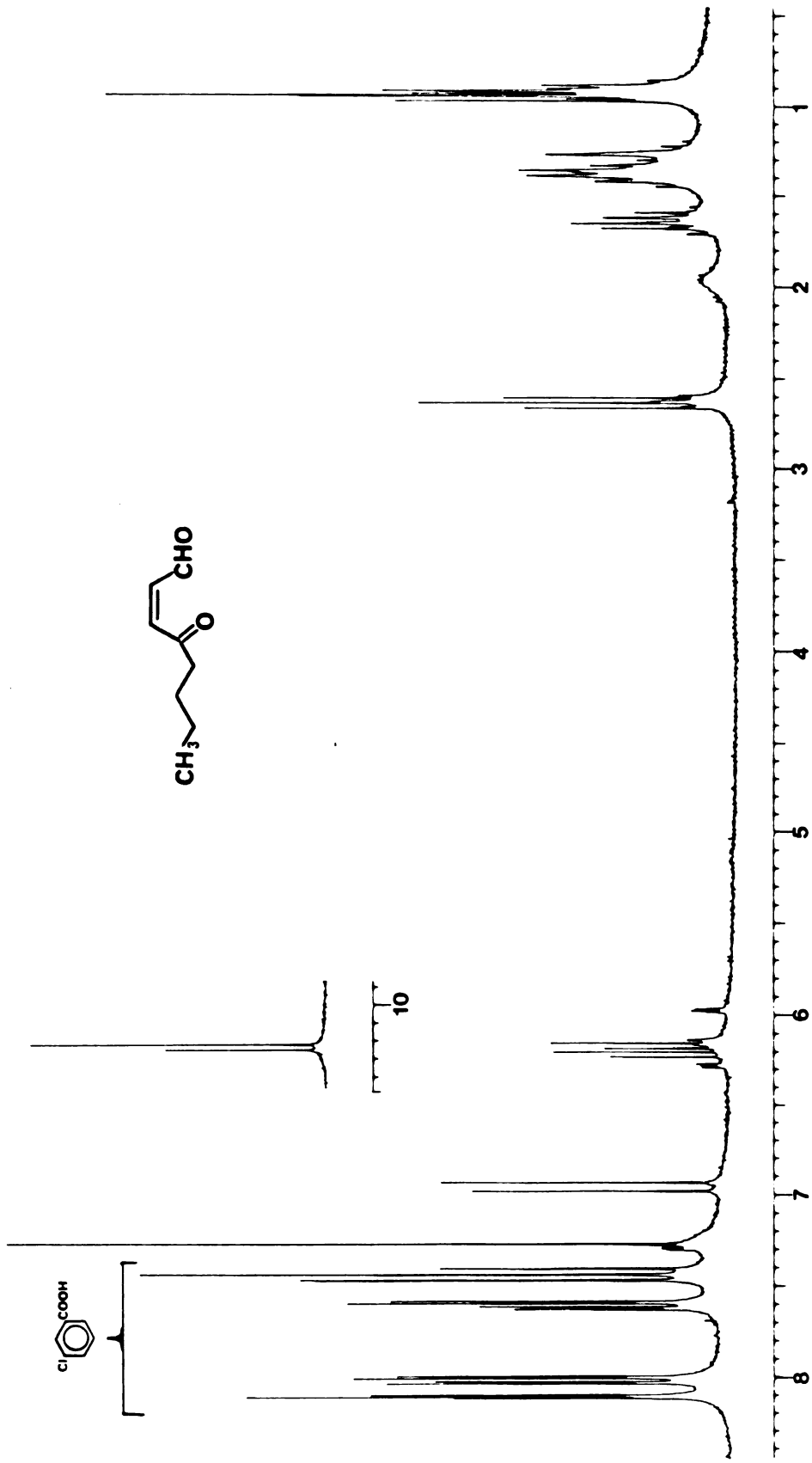


Figure A9. 250 MHz ^{1}H NMR spectrum of *cis*-4-oxo-2-octenal (48).

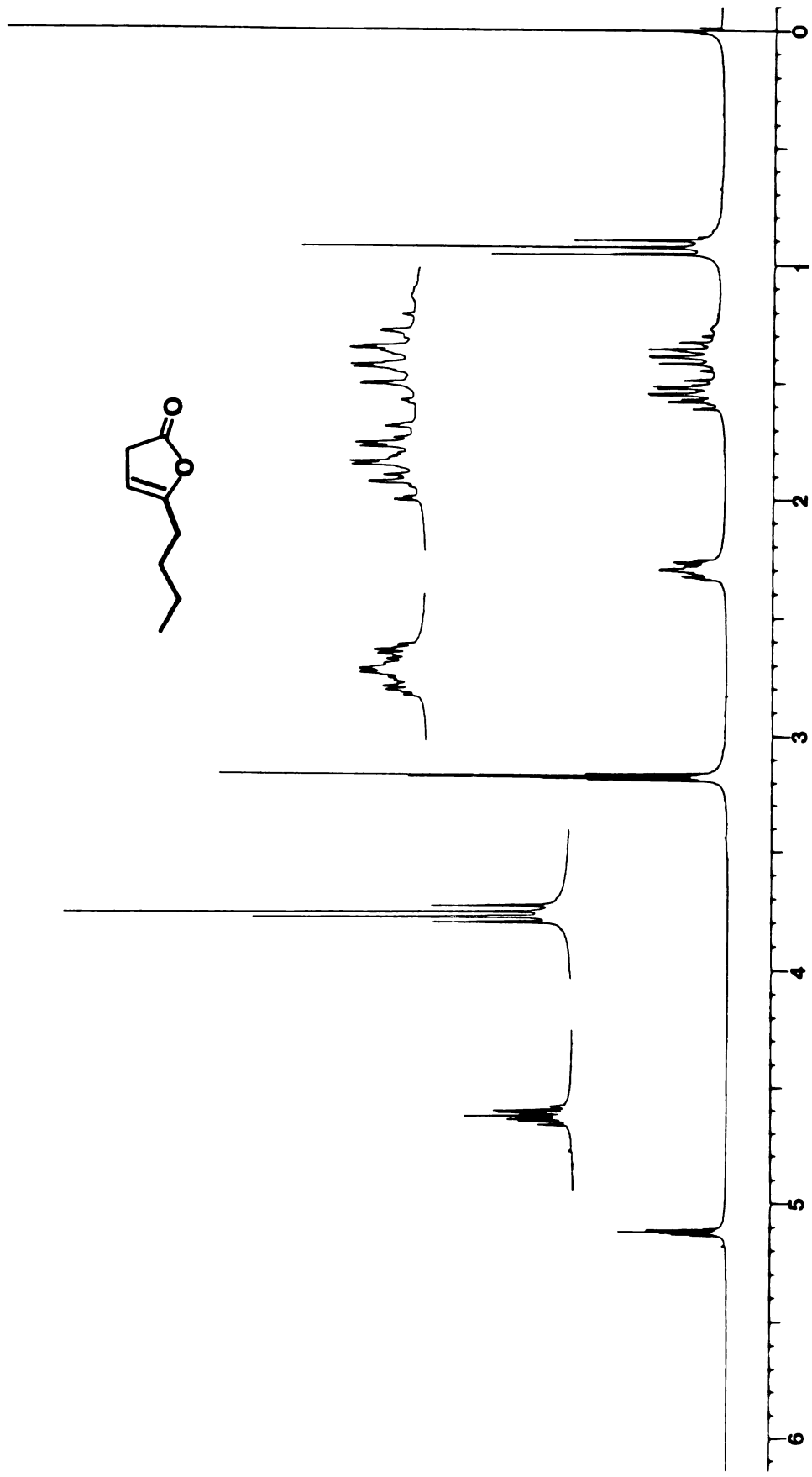


Figure A10. 250 MHz ^{1}H NMR spectrum of 5-*n*-butyl-2(3H)furanone (49).

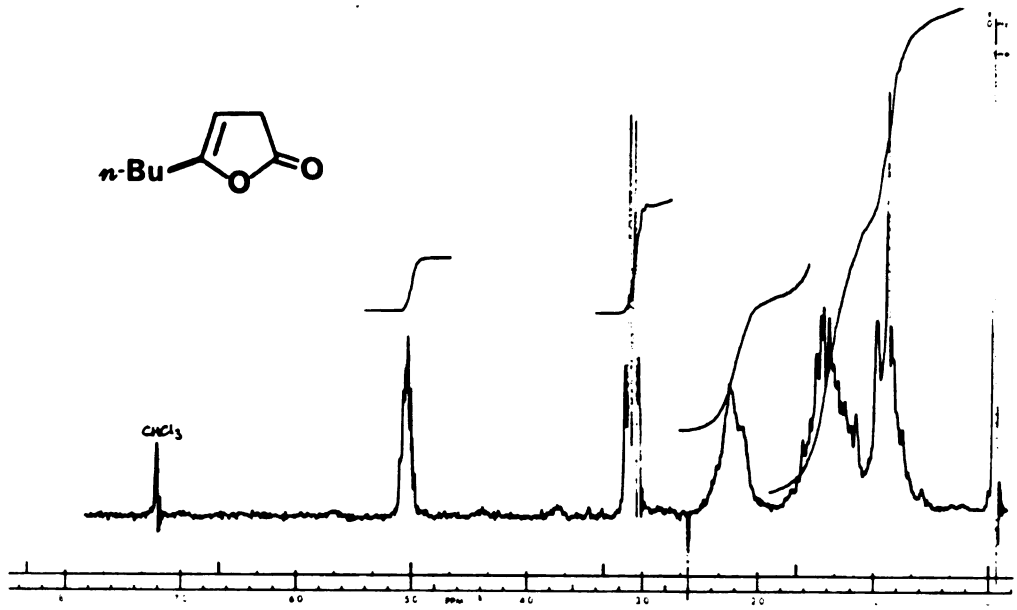


Figure A11. 60 MHz ^{1}H NMR spectrum of 5-*n*-butyl-2(3H)furanone (49).

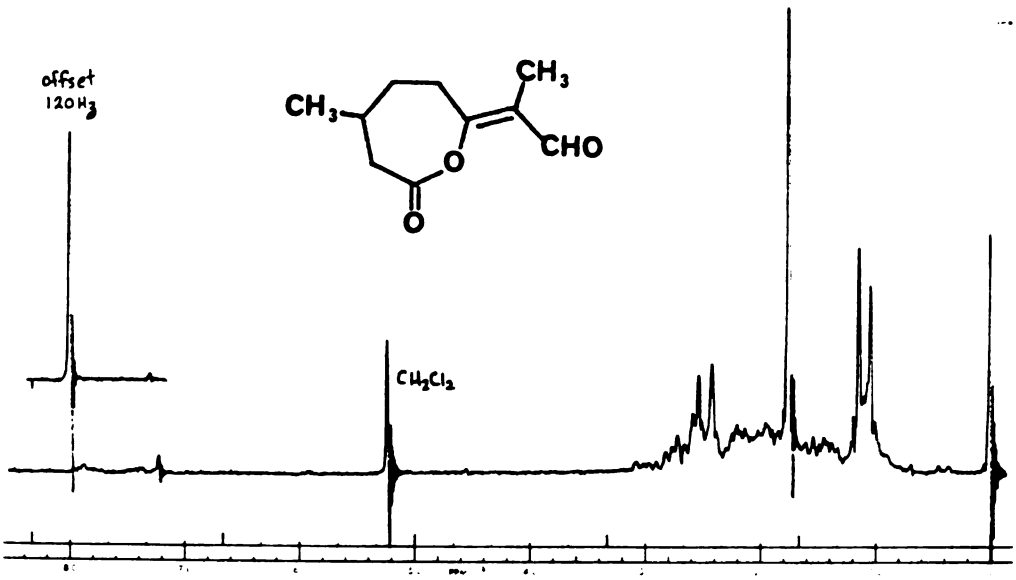


Figure A12. 60 MHz ^{1}H NMR spectrum of enol lactone 59.

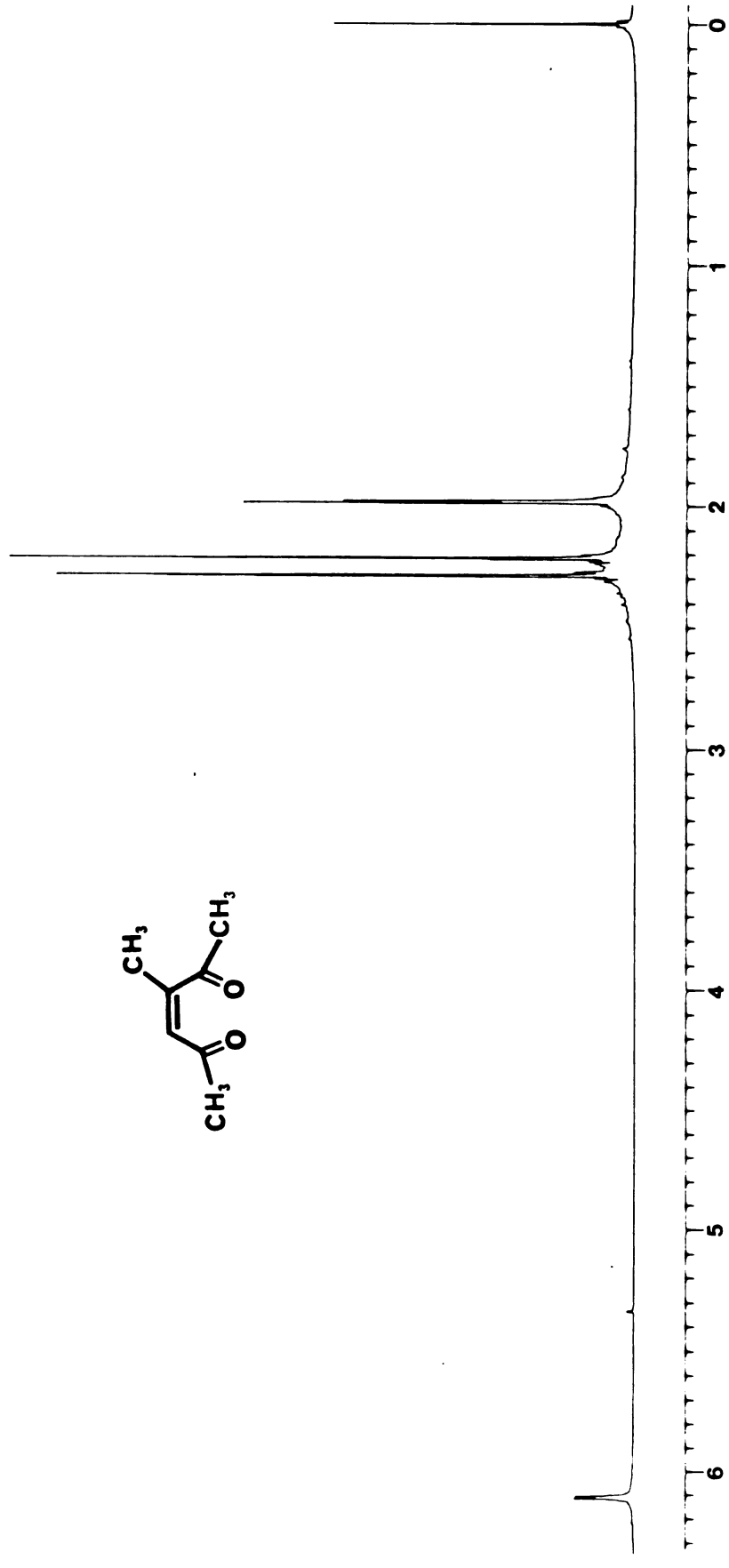


Figure A13. 250 MHz ^{1}H NMR spectrum of (Z)-3-methyl-3-hexene-2,5-dione (63a).

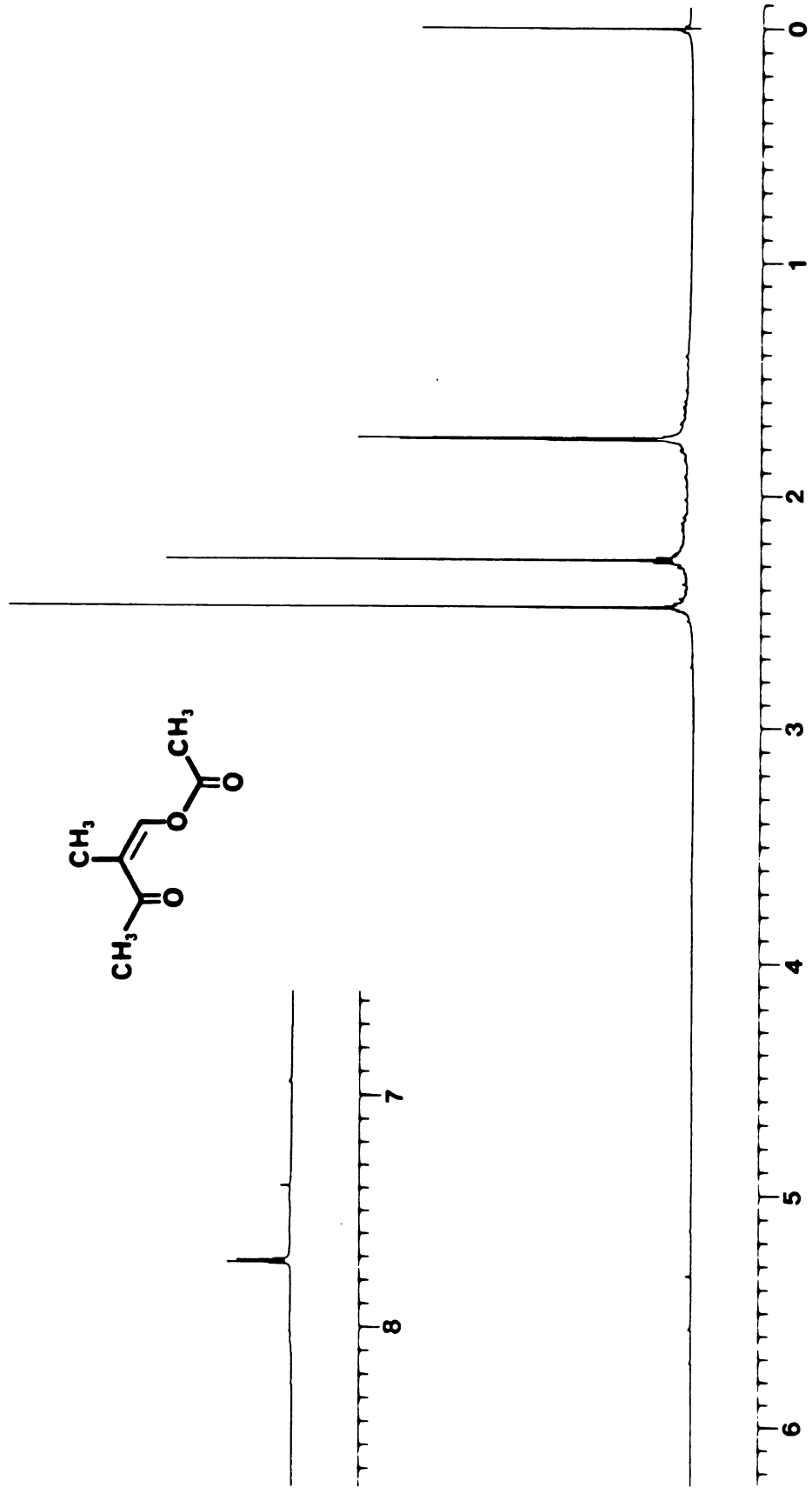


Figure A14. 250 MHz ^{1}H NMR spectrum of (Z)-4-acetoxy-3-methyl-3-butene-2-one (64a).

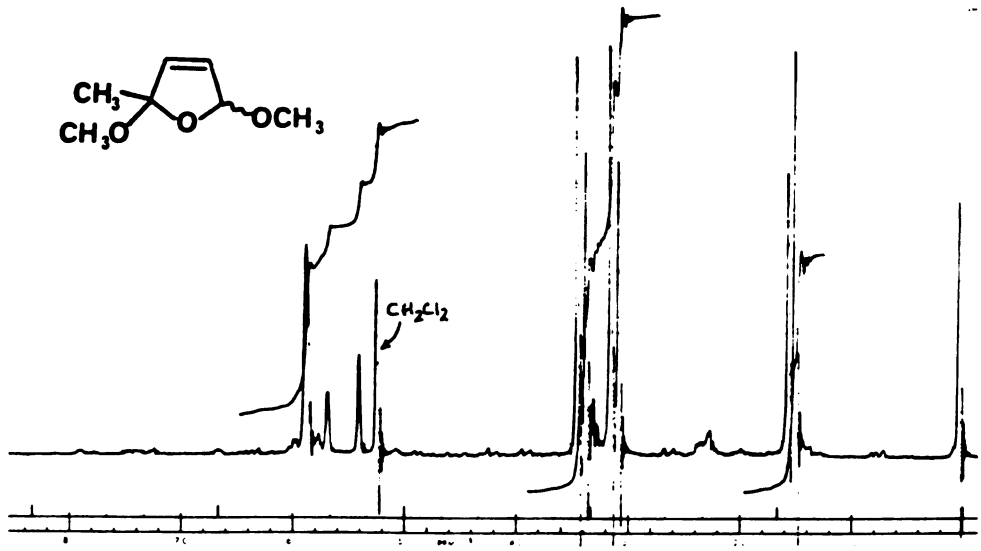


Figure A15. 60 MHz ^{1}H NMR spectrum of 2-methyl-2,5-dimethoxy-2,5-dihydrofuran (46).

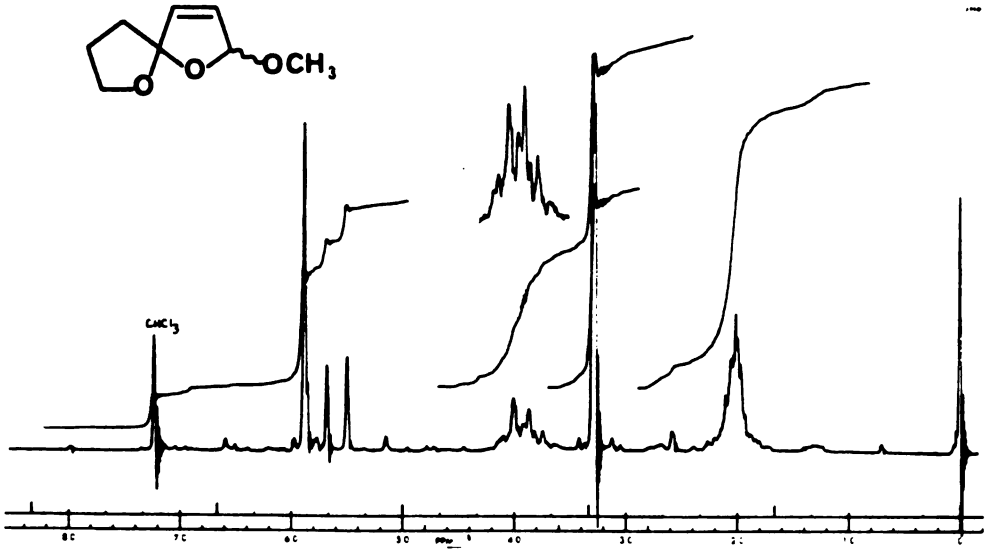


Figure A16. 60 MHz ^{1}H NMR spectrum of spiroketal 72.

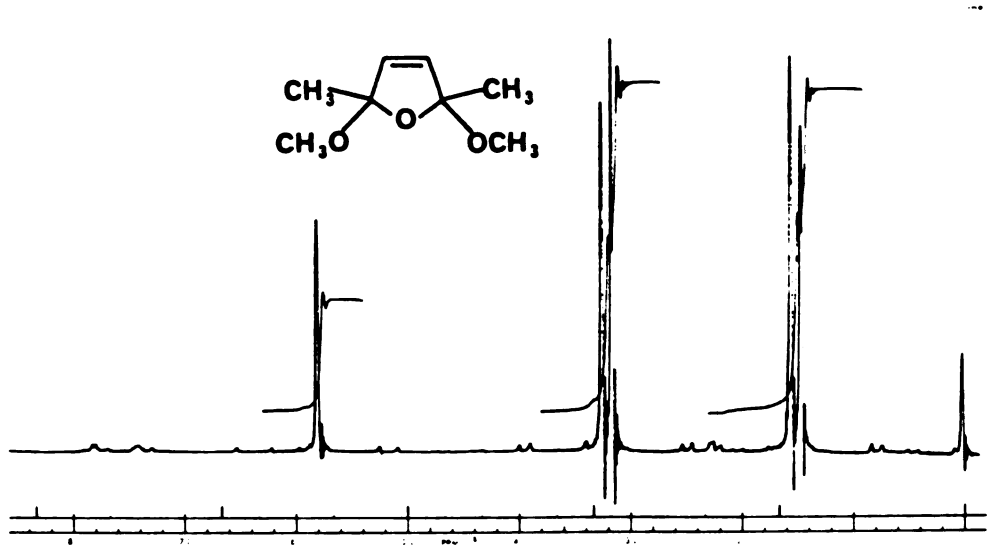


Figure A17. 60 MHz ^{1}H NMR spectrum of 2,5-dimethyl-2,5-dimethoxy-2,5-dihydrofuran (74).

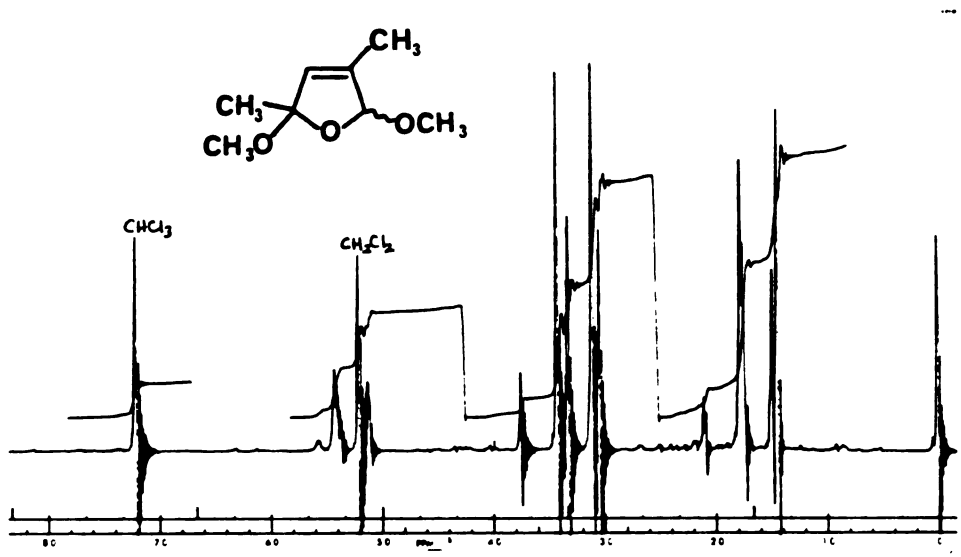


Figure A18. 60 MHz ^{1}H NMR spectrum of 2,4-dimethyl-2,5-dimethoxy-2,5-dihydrofuran (75).

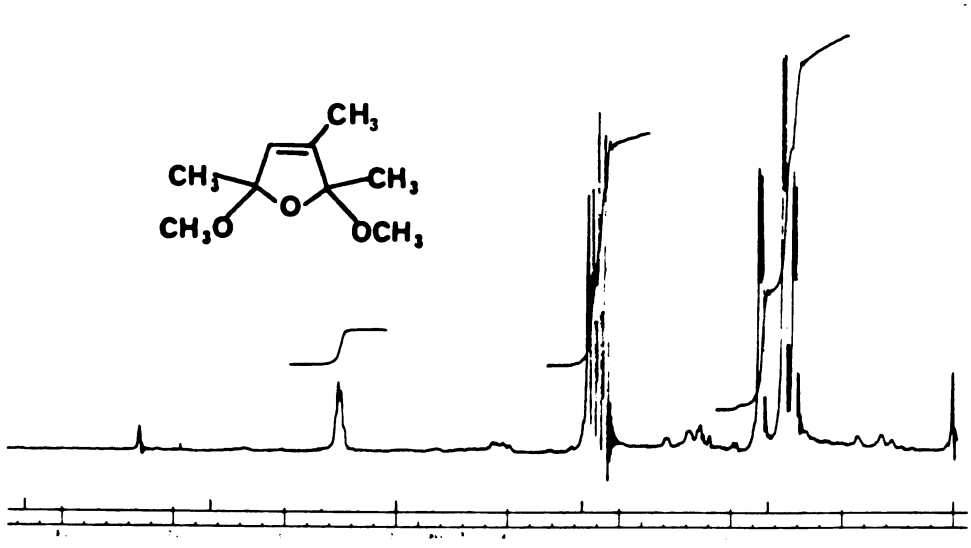


Figure A19. 60 MHz ^{1}H NMR spectrum of 2,3,5-trimethyl-2,5-dimethoxy-2,5-dihydrofuran (76).

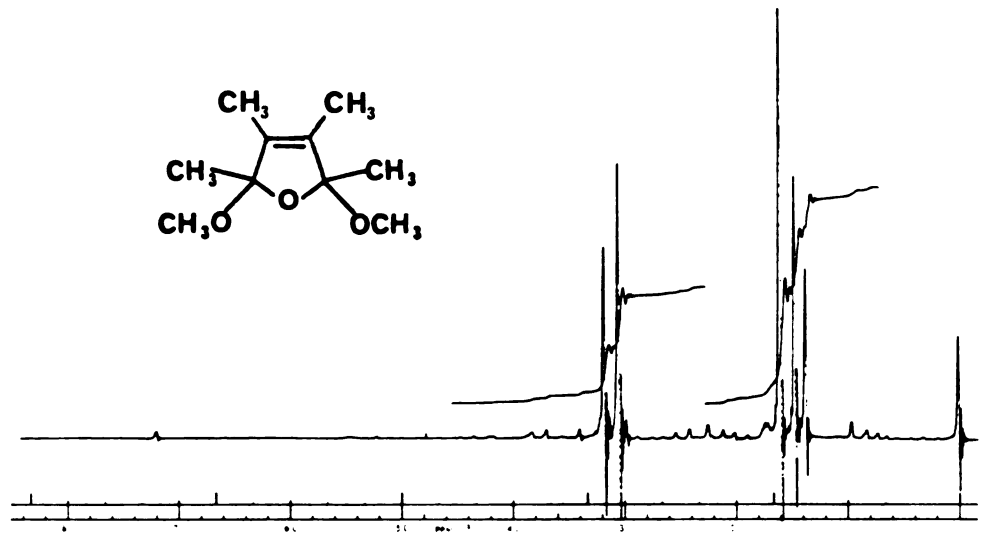


Figure A20. 60 MHz ^{1}H NMR spectrum of 2,3,4,5-tetramethyl-2,5-dimethoxy-2,5-dihydofuran (78).

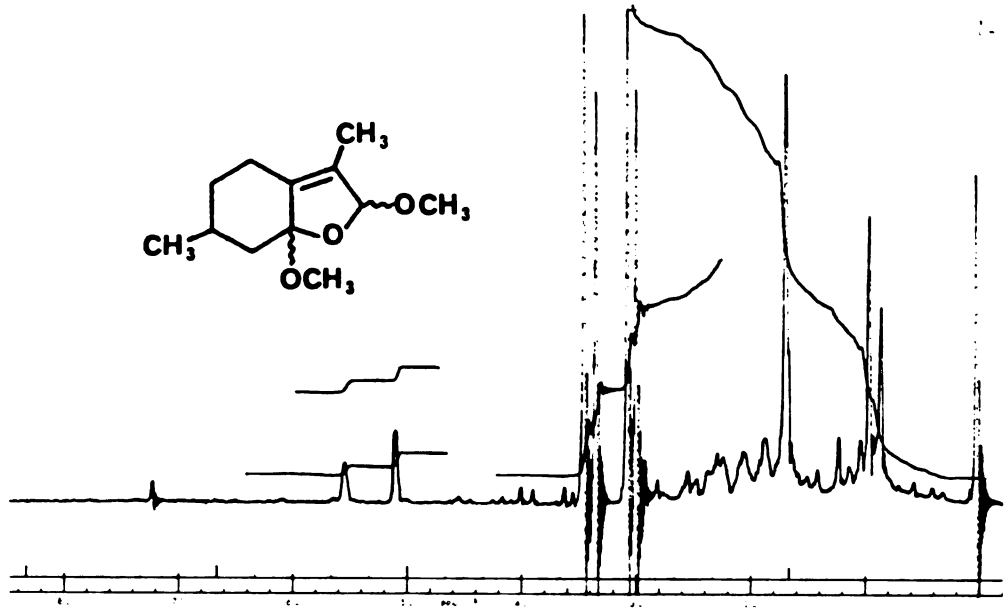


Figure A21. 60 MHz ^{1}H NMR spectrum of 2,5-dimethoxy-2,5-dihydromenthofuran (77).

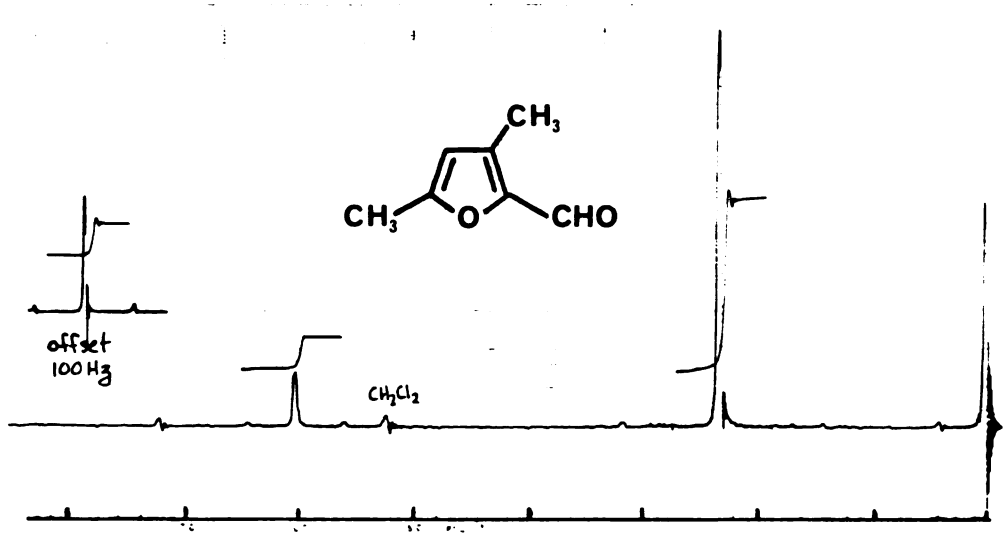


Figure A22. 60 MHz ^{1}H NMR spectrum of 3,5-dimethylfuran-2-carboxaldehyde (88).

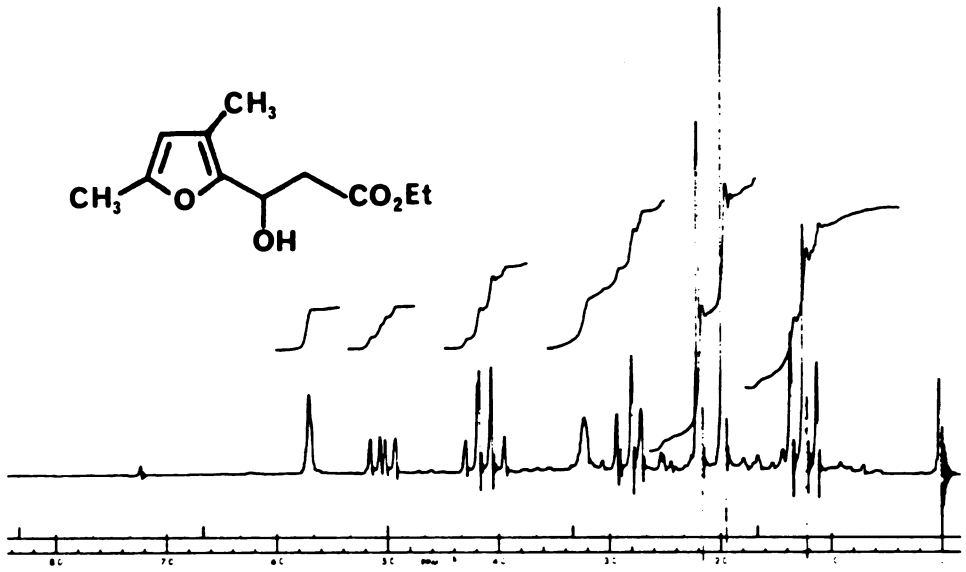


Figure A23. 60 MHz ^{1}H NMR spectrum of ethyl 3-(3,5-dimethyl-2-furyl)-3-hydroxypropanoate (89).

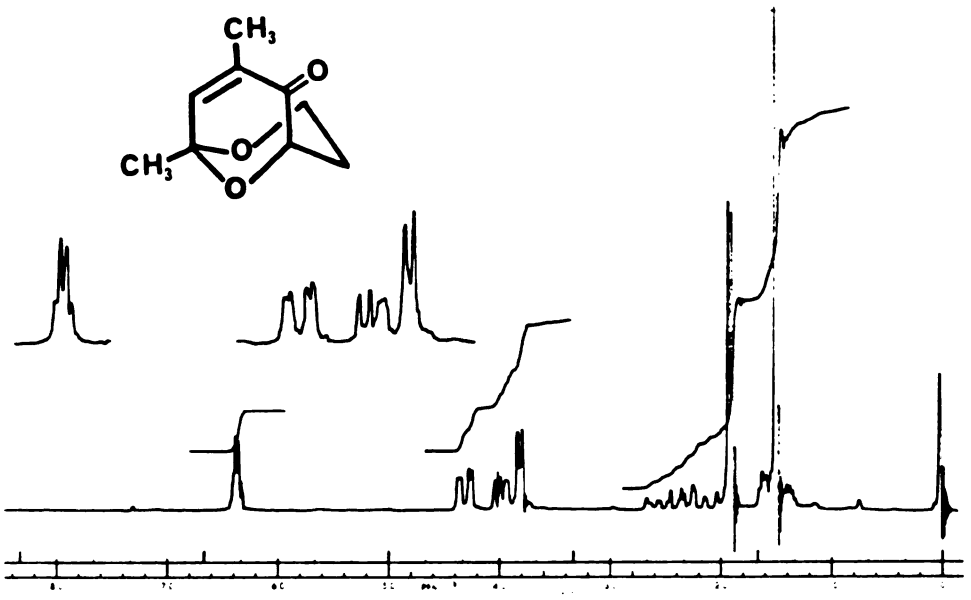


Figure A24. 60 MHz ^{1}H NMR spectrum of 1,7-dimethyl-2,9-dioxabicyclo[3.3.1]non-7-ene-6-one (91).

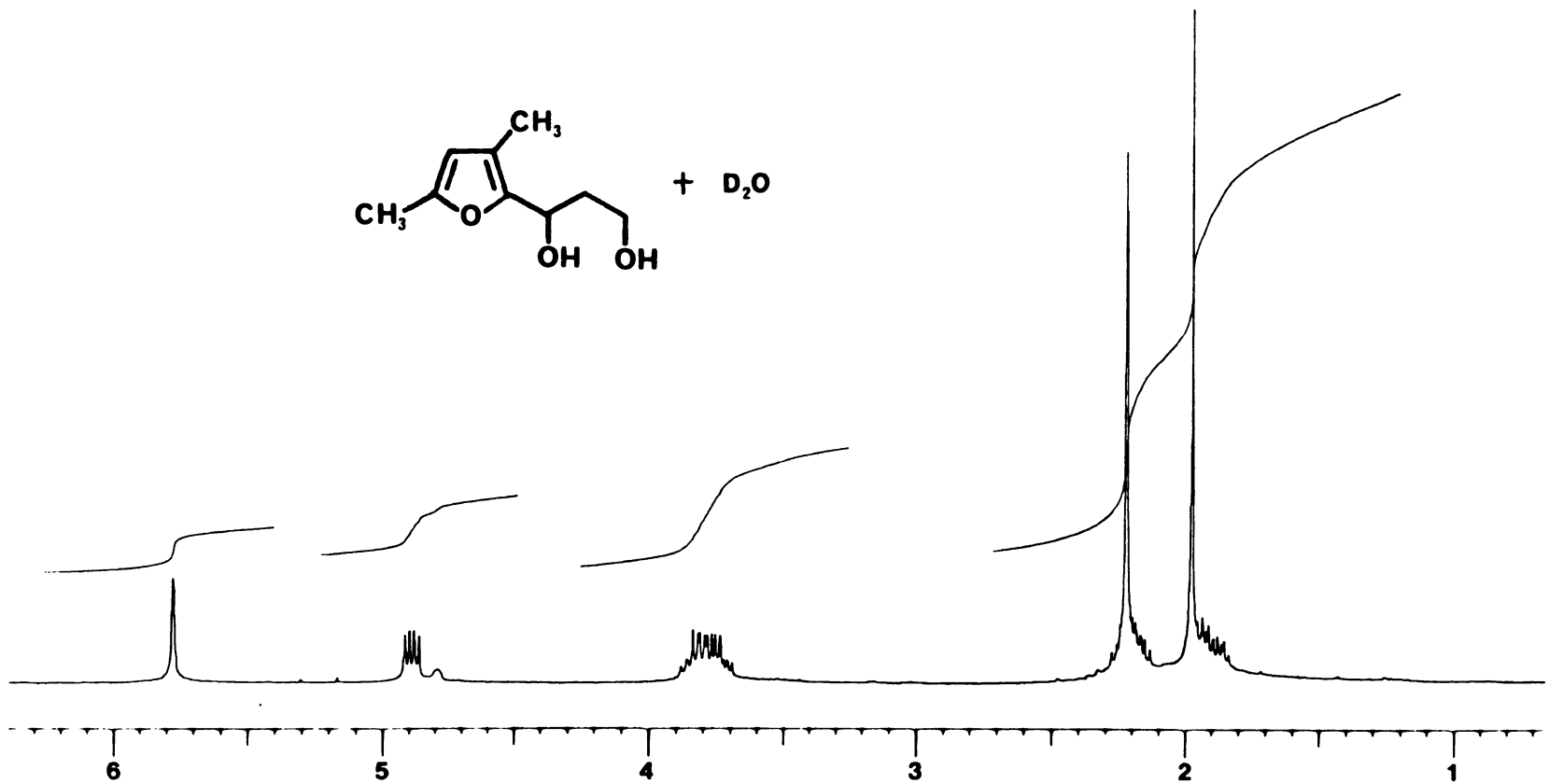


Figure A25. 250 MHz ^{1}H NMR spectrum of 2-(1,3-dihydroxypropyl)-3,5-dimethylfuran (90).

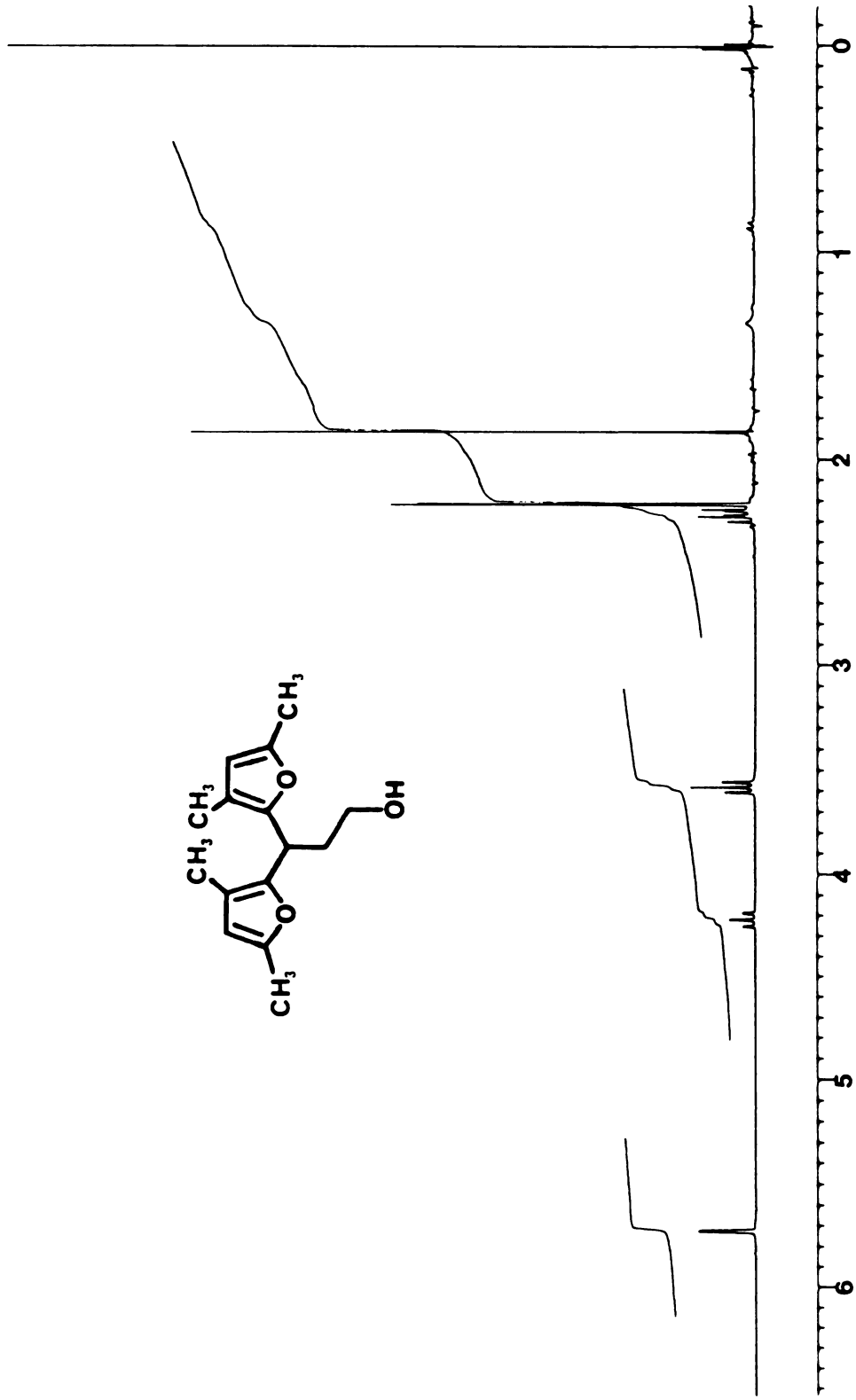


Figure A26. 250 MHz ^{1}H NMR spectrum of 3,3-*bis*(3,5-dimethyl-2-furyl)-1-propanol (92).

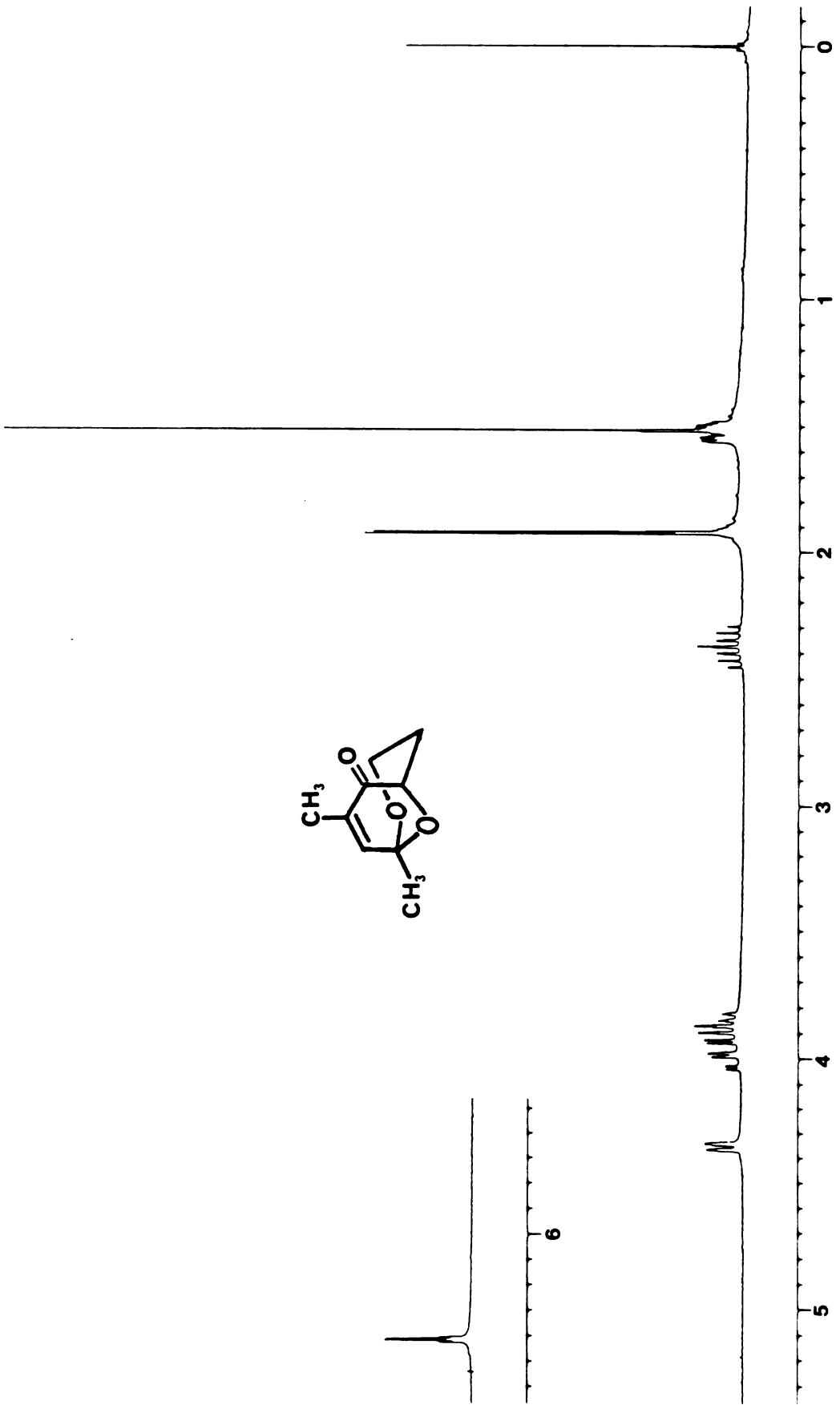


Figure A27. 250 MHz ^{1}H NMR spectrum of 1,7-dimethyl-2,9-dioxabicyclo[3.3.1]-non-7-en-6-one (91).

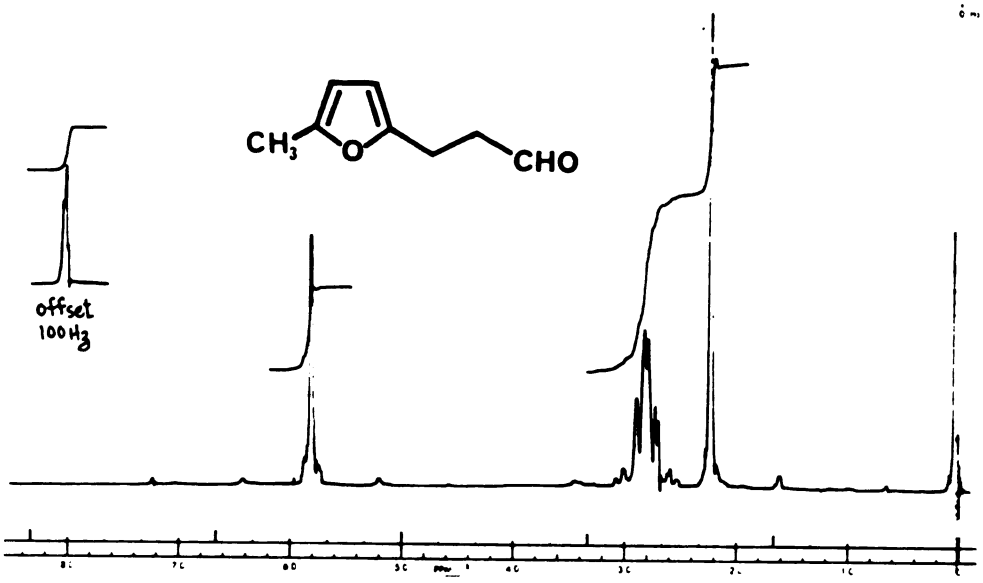


Figure A28. 60 MHz ^{1}H NMR spectrum of 3-(5-methyl-2-furyl)propanal (95a).

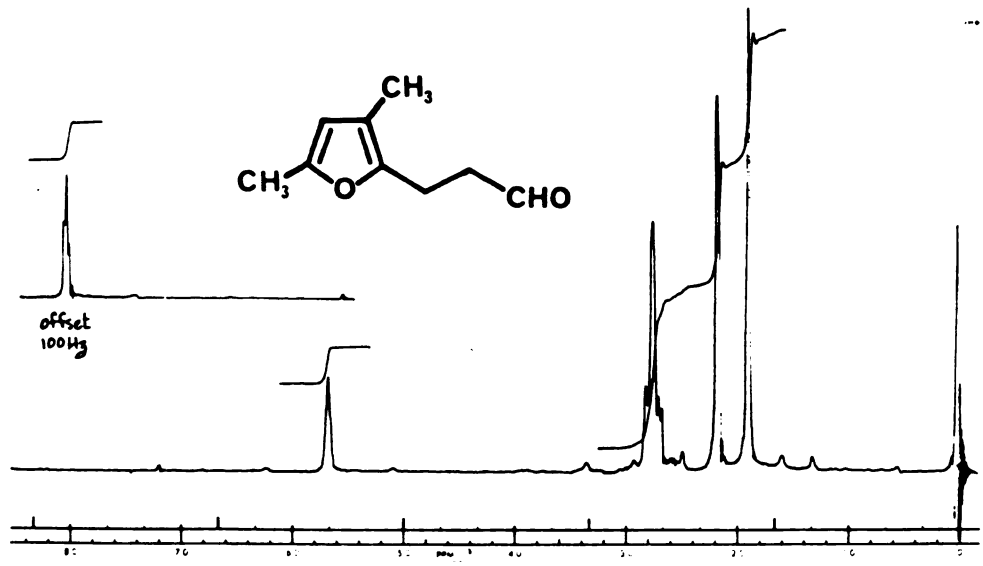


Figure A29. 60 MHz ^{1}H NMR spectrum of 3-(3,5-dimethyl-2-furyl)propanal (95b).

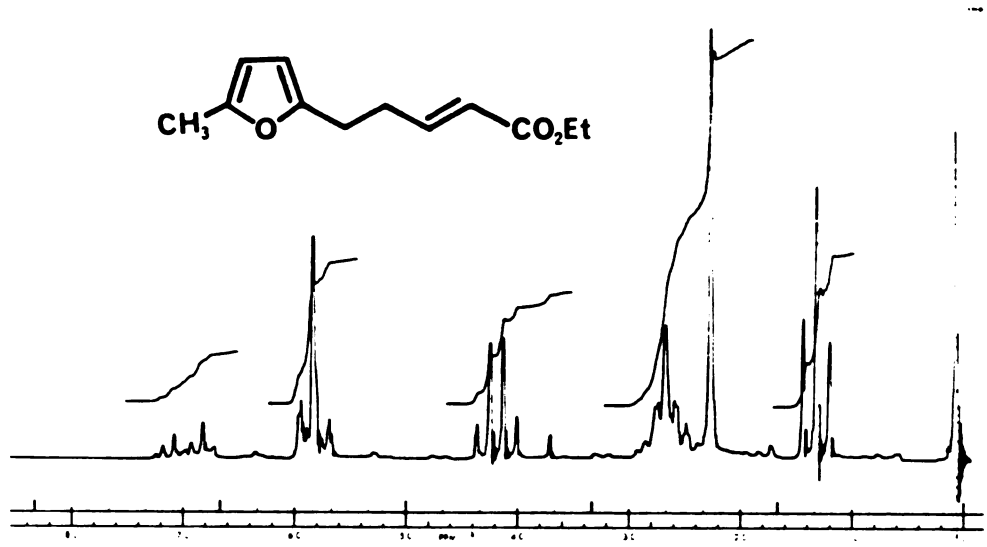


Figure A30. 60 MHz ^{1}H NMR spectrum of ethyl 5-(5-methyl-2-furyl)-2-pentenoate (96a).

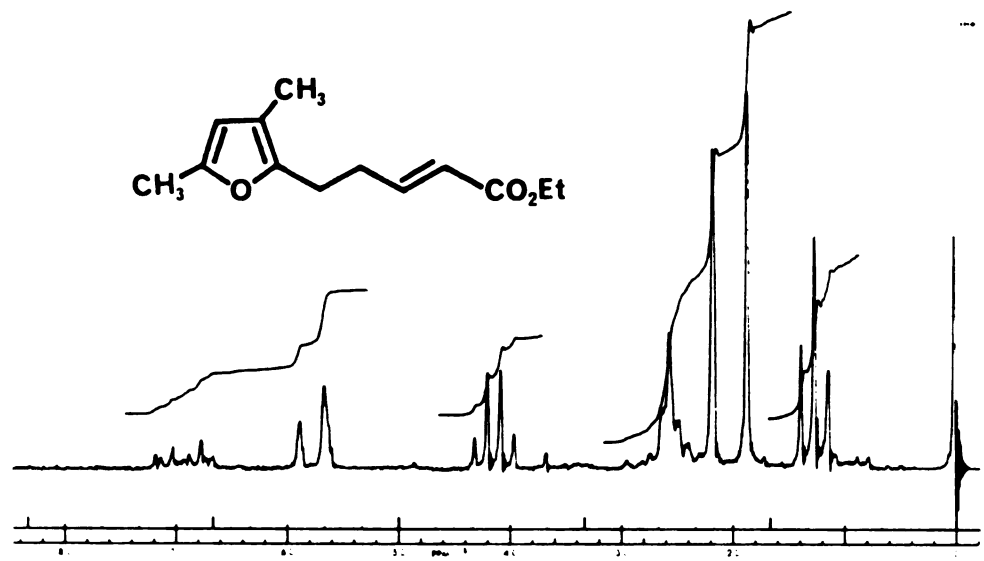


Figure A31. 60 MHz ^{1}H NMR spectrum of ethyl 5-(3,5-dimethyl-2-furyl)-2-pentenoate (96b).

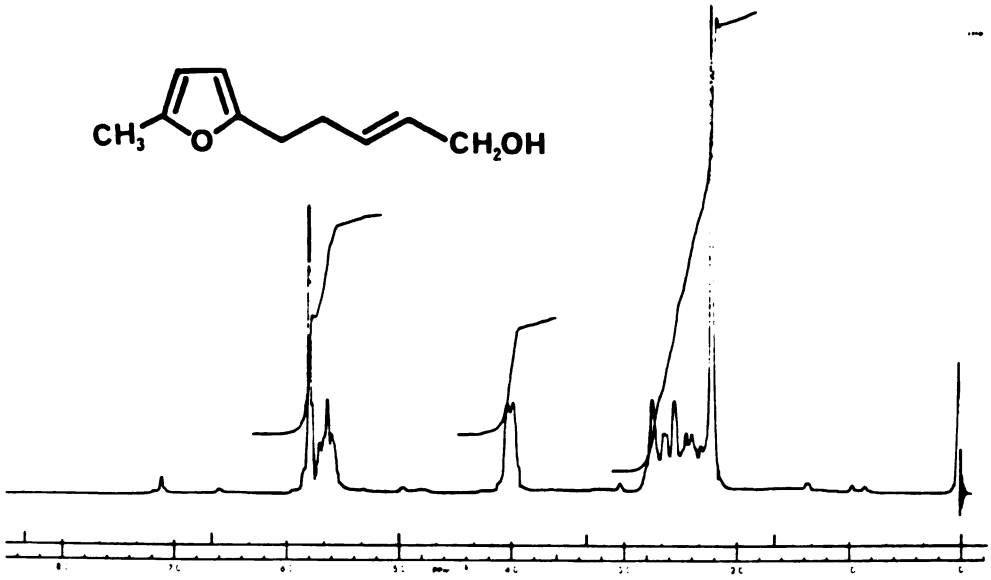


Figure A32. 60 MHz ^{1}H NMR spectrum of 5-methyl-2-(5-hydroxy-3-pentenyl)furan (97a).

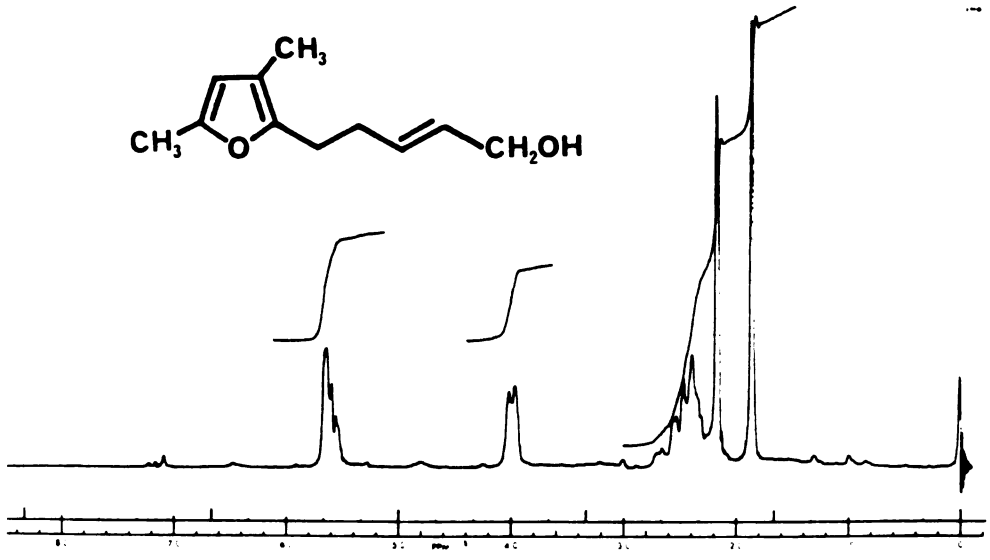


Figure A33. 60 MHz ^{1}H NMR spectrum of 3,5-dimethyl-2-(5-hydroxy-3-pentenyl)furan (97b).

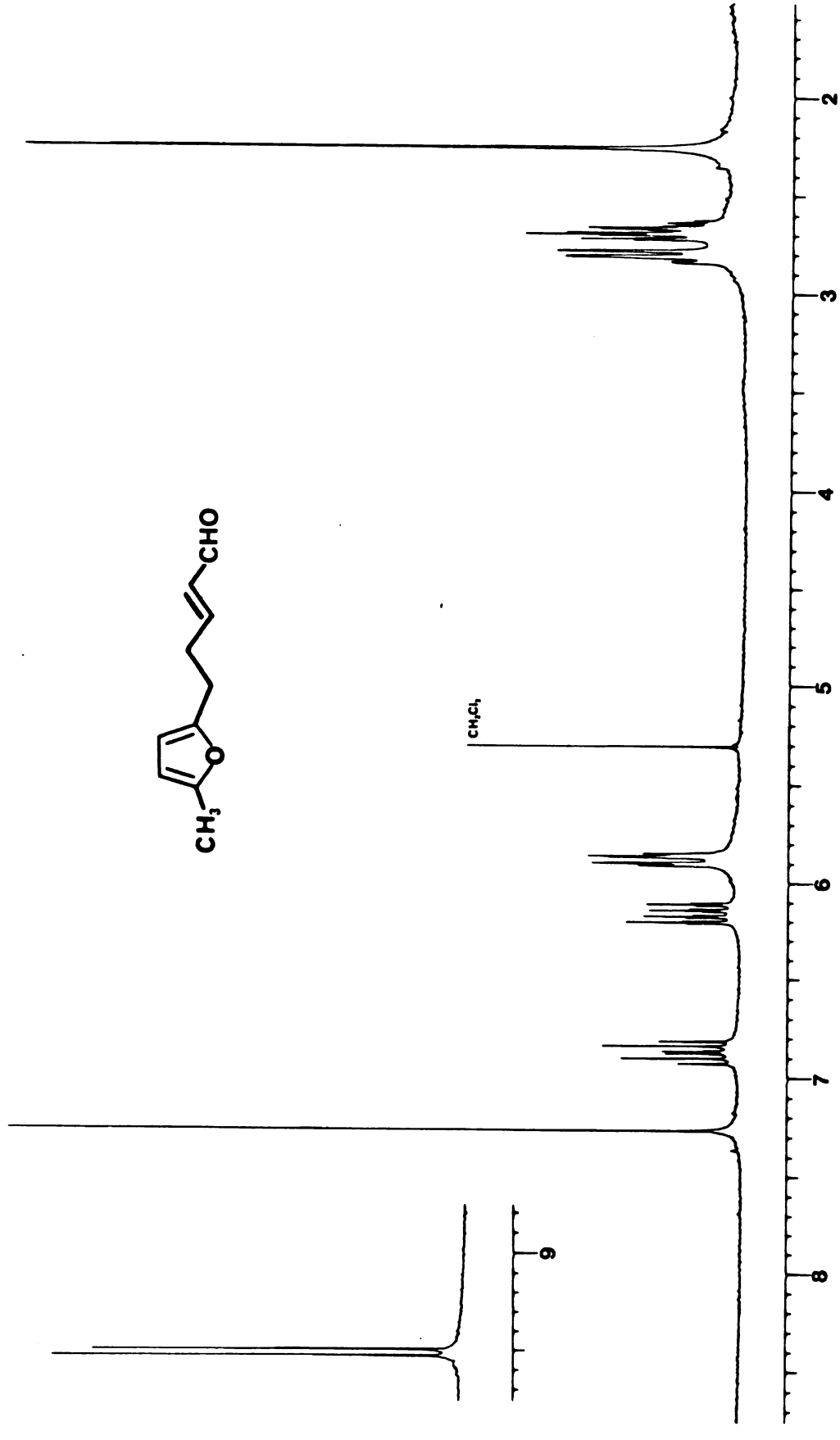


Figure A34. 250 MHz $^{1}_{H}$ NMR spectrum of 5-(5-methyl-2-furyl)-2(E)-pentenal (98a).

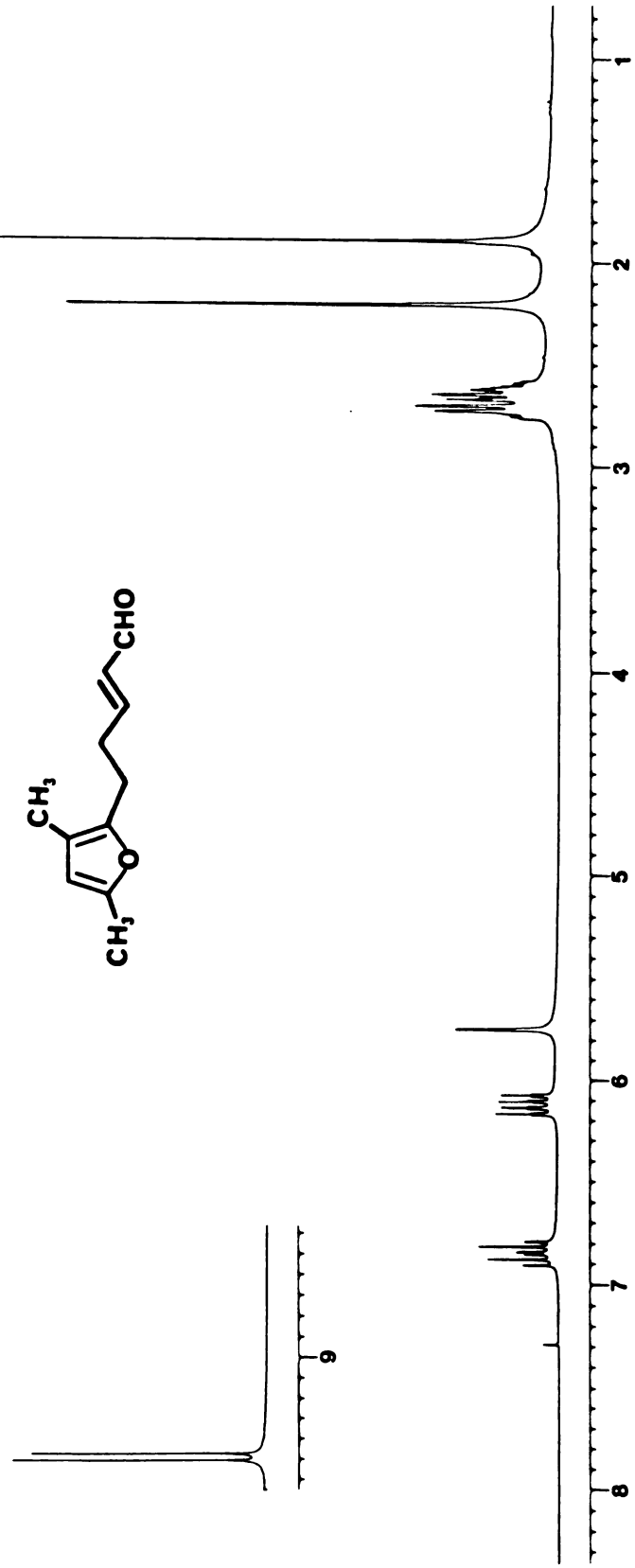


Figure A35. 250 MHz ^{1}H NMR spectrum of 5-(3,5-dimethyl-2-furyl)-2(E)-pentenal (98b).

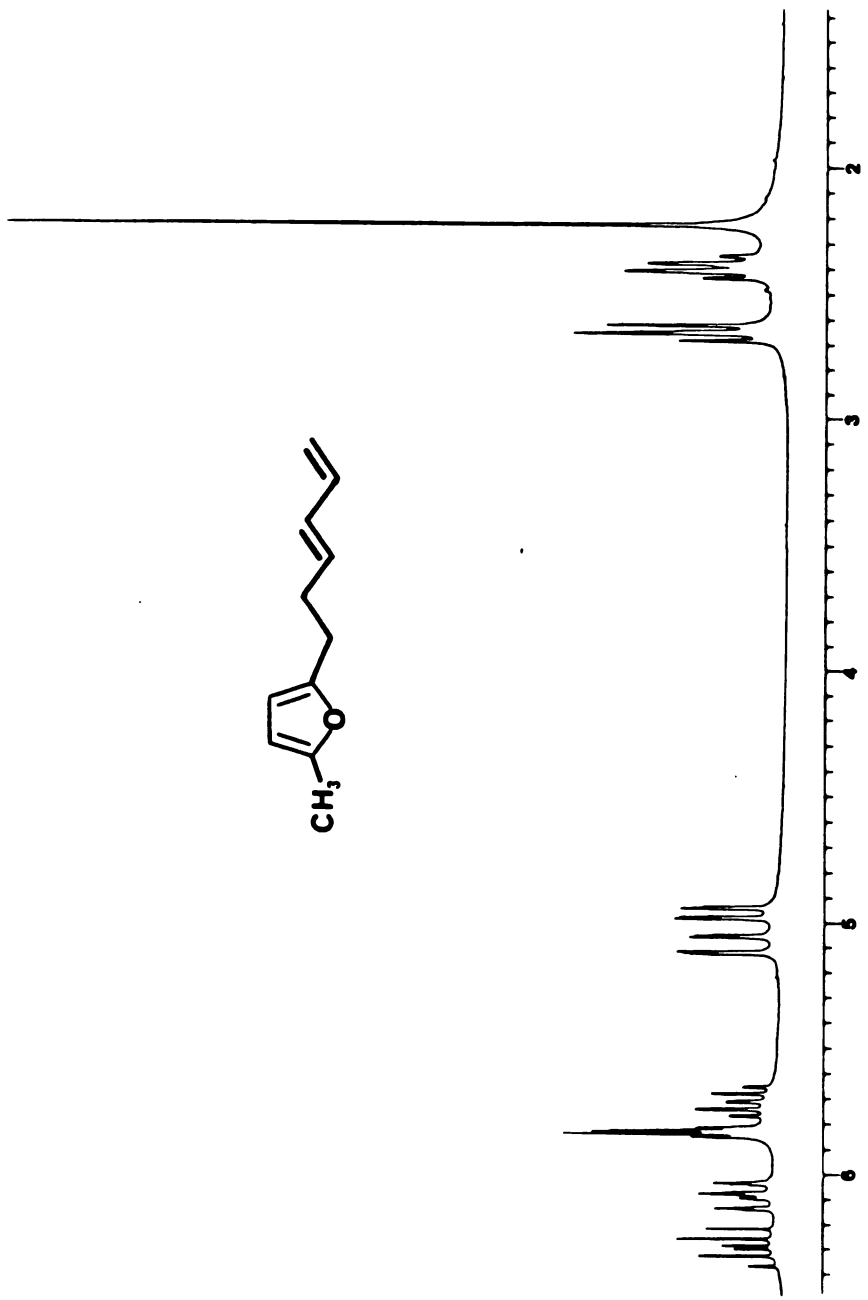


Figure A36. 250 MHz ^{1}H NMR spectrum of 2-(3(E),5-hexadienyl)-5-methylfuran (99a).

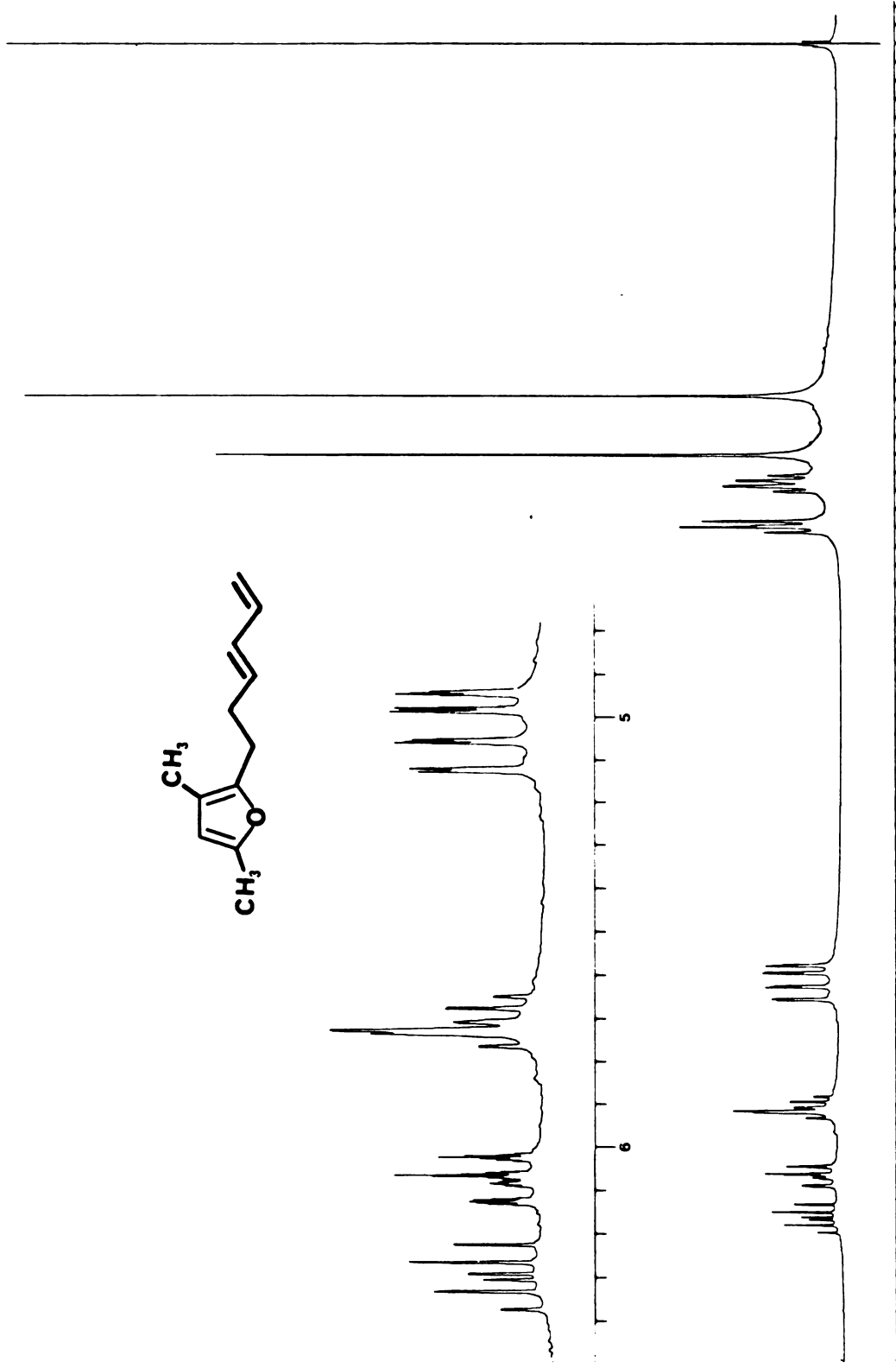


Figure A37. 250 MHz ^{1}H NMR spectrum of 3,5-dimethyl-2-(3(E),5-hexadienyl)furan (99b).

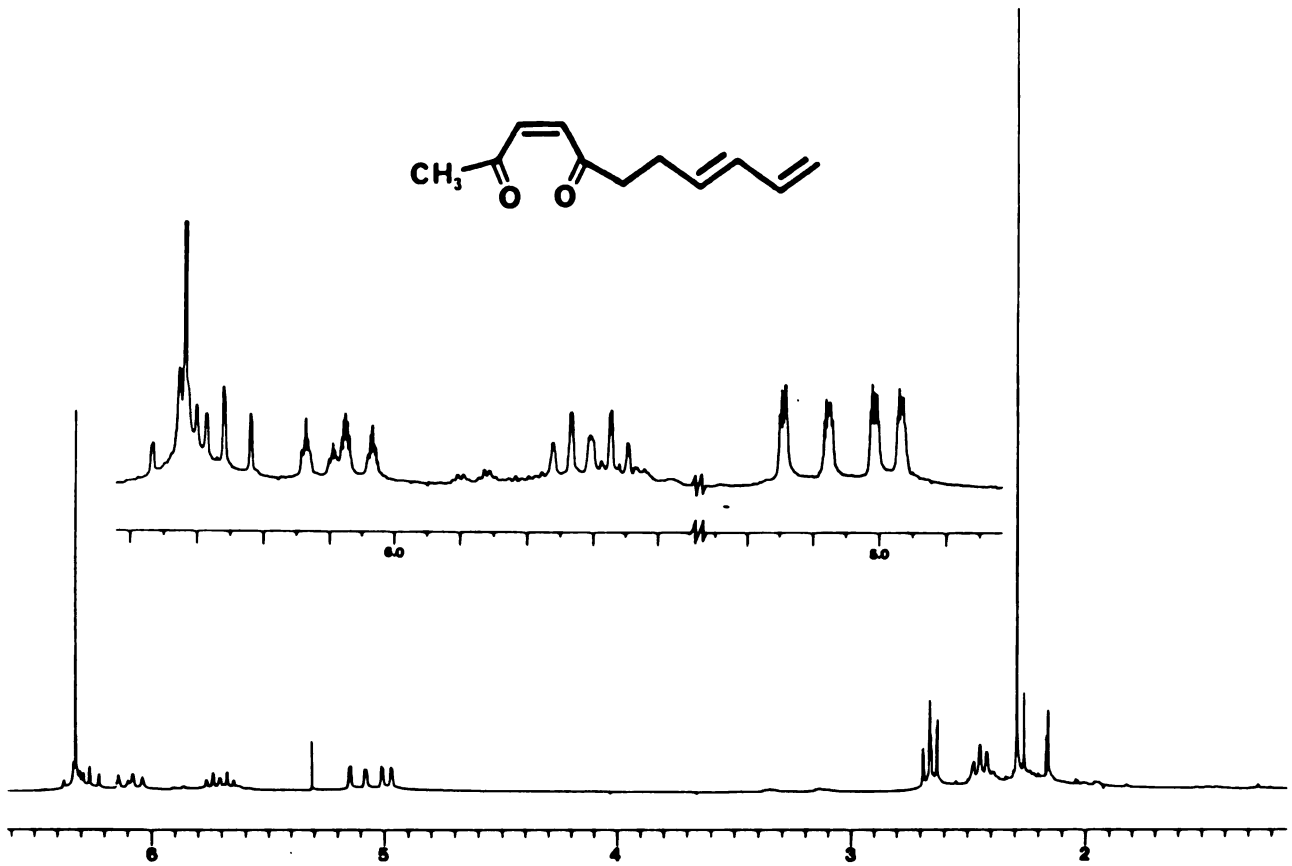


Figure A38. 250 MHz ^{1}H NMR spectrum of 3(Z),8(E),10-undecatriene-2,5-dione (103).

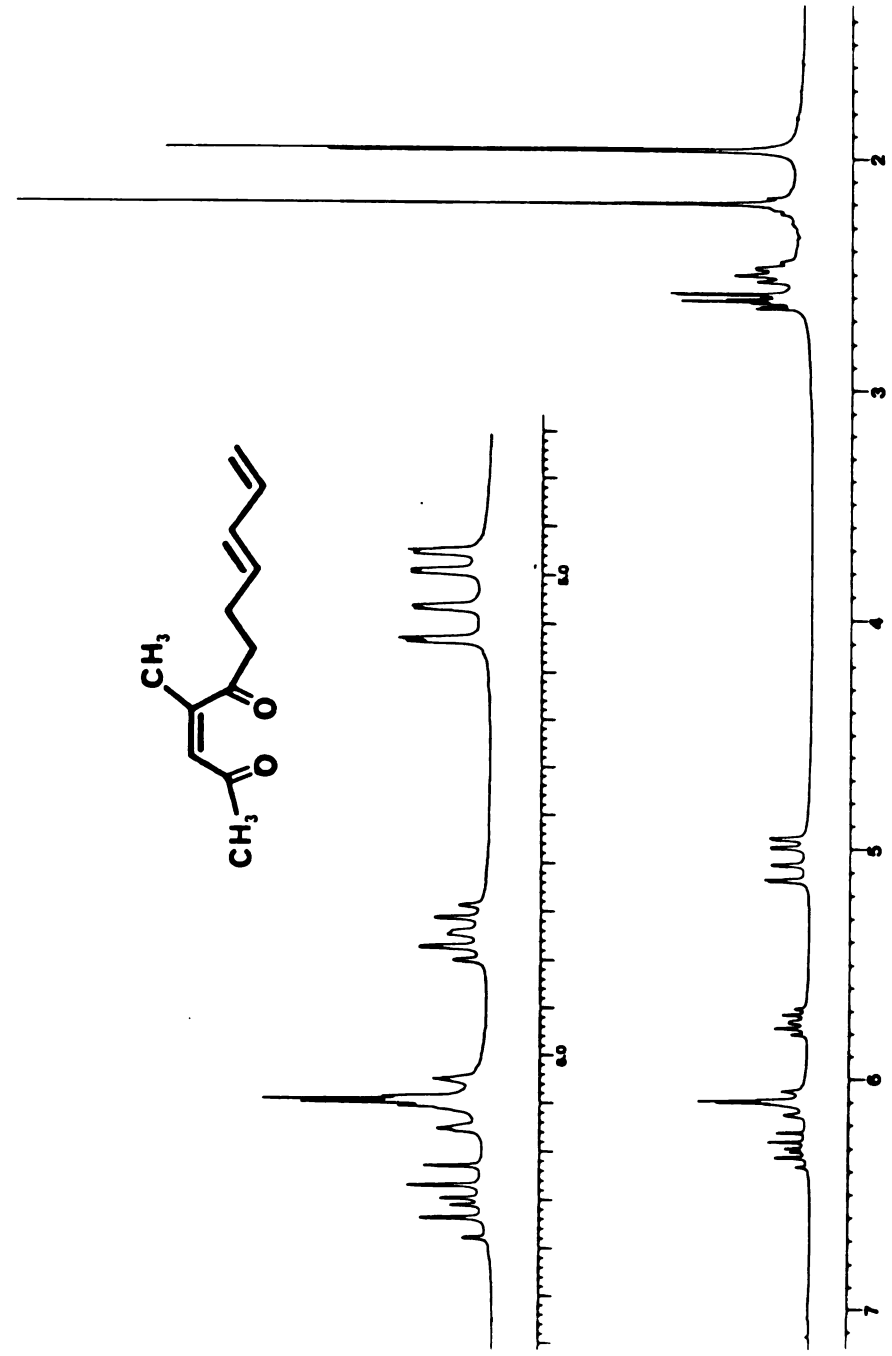


Figure A39. 250 MHz ^{1}H NMR spectrum of 4-methyl-3(Z),8(E),10-undecatriene-2,5-dione (105).

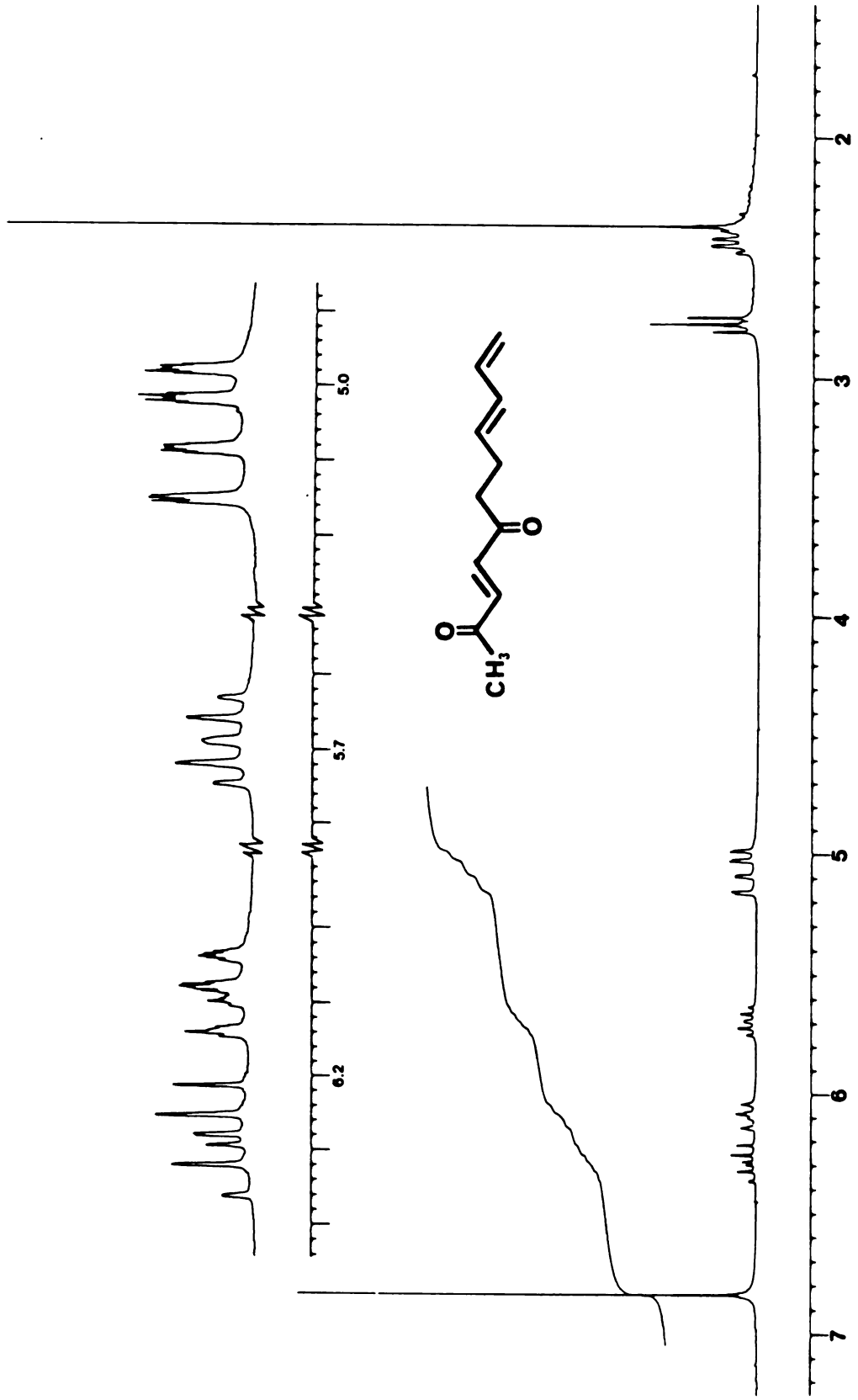


Figure A40. 250 MHz ^{1}H NMR spectrum of 3(E),8(E),10-undecatriene-2,5-dione (106).

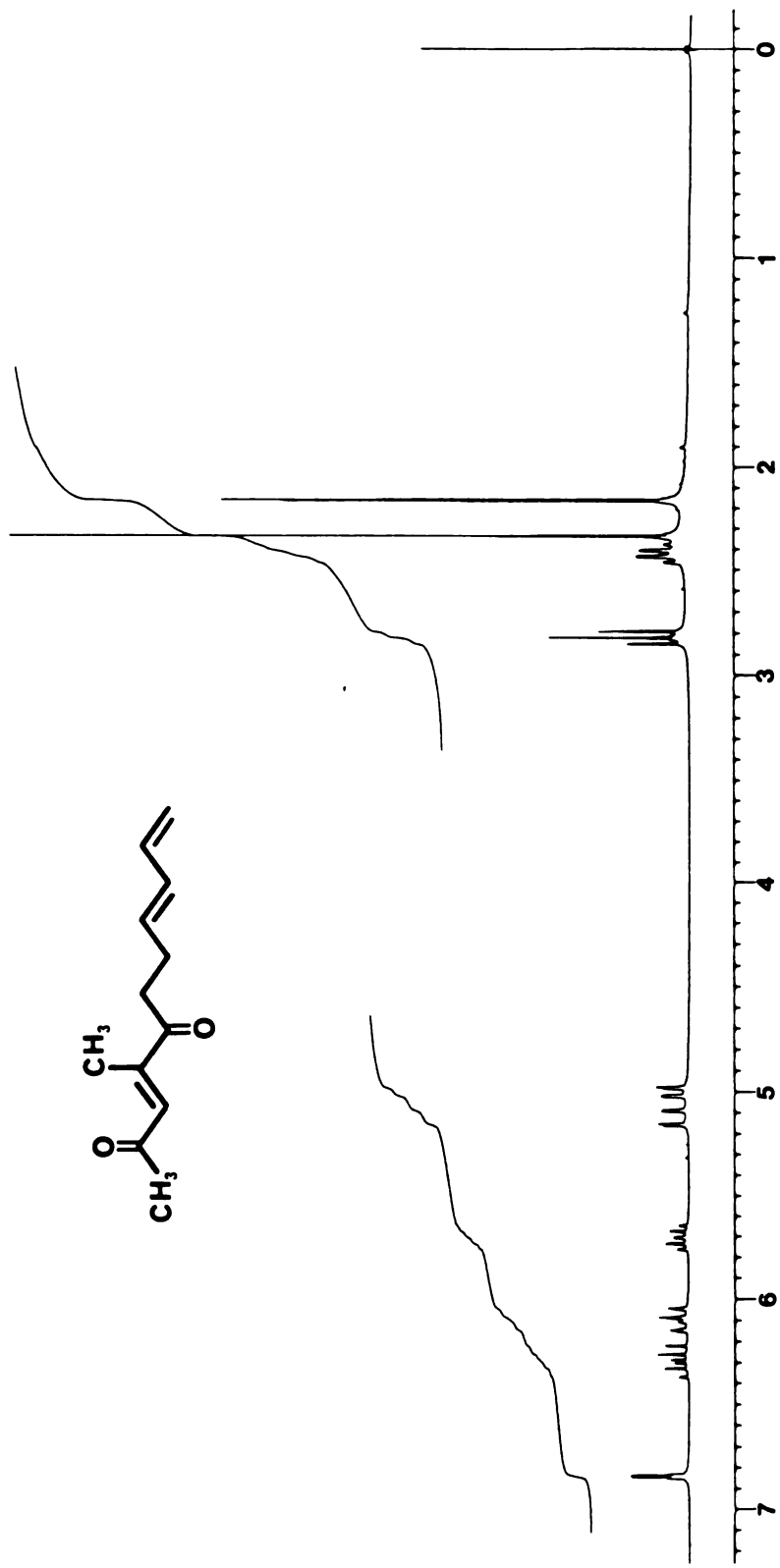


Figure A41. 250 MHz ^{1}H NMR spectrum of 4-methyl-3(E),8(E),10-undecatriene-2,5-dione (109)

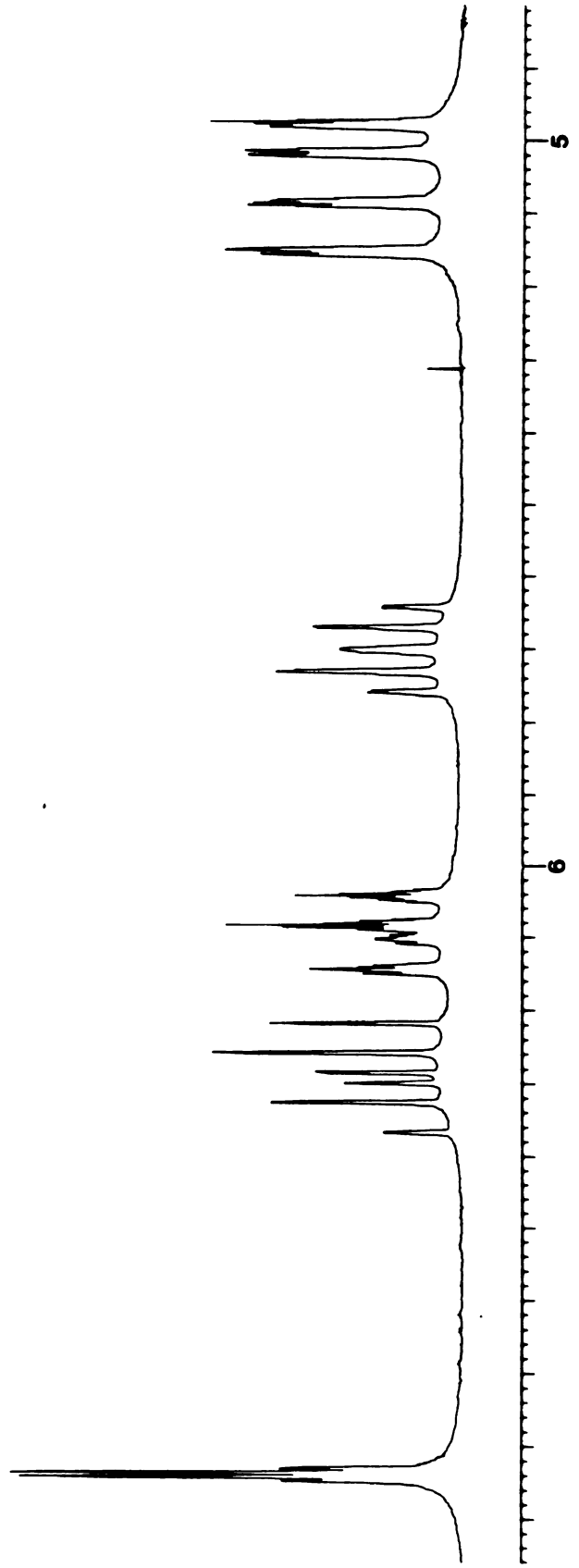


Figure A42. Expansion in the 250 MHz ^{1}H NMR spectrum of 109 (see Figure A41).

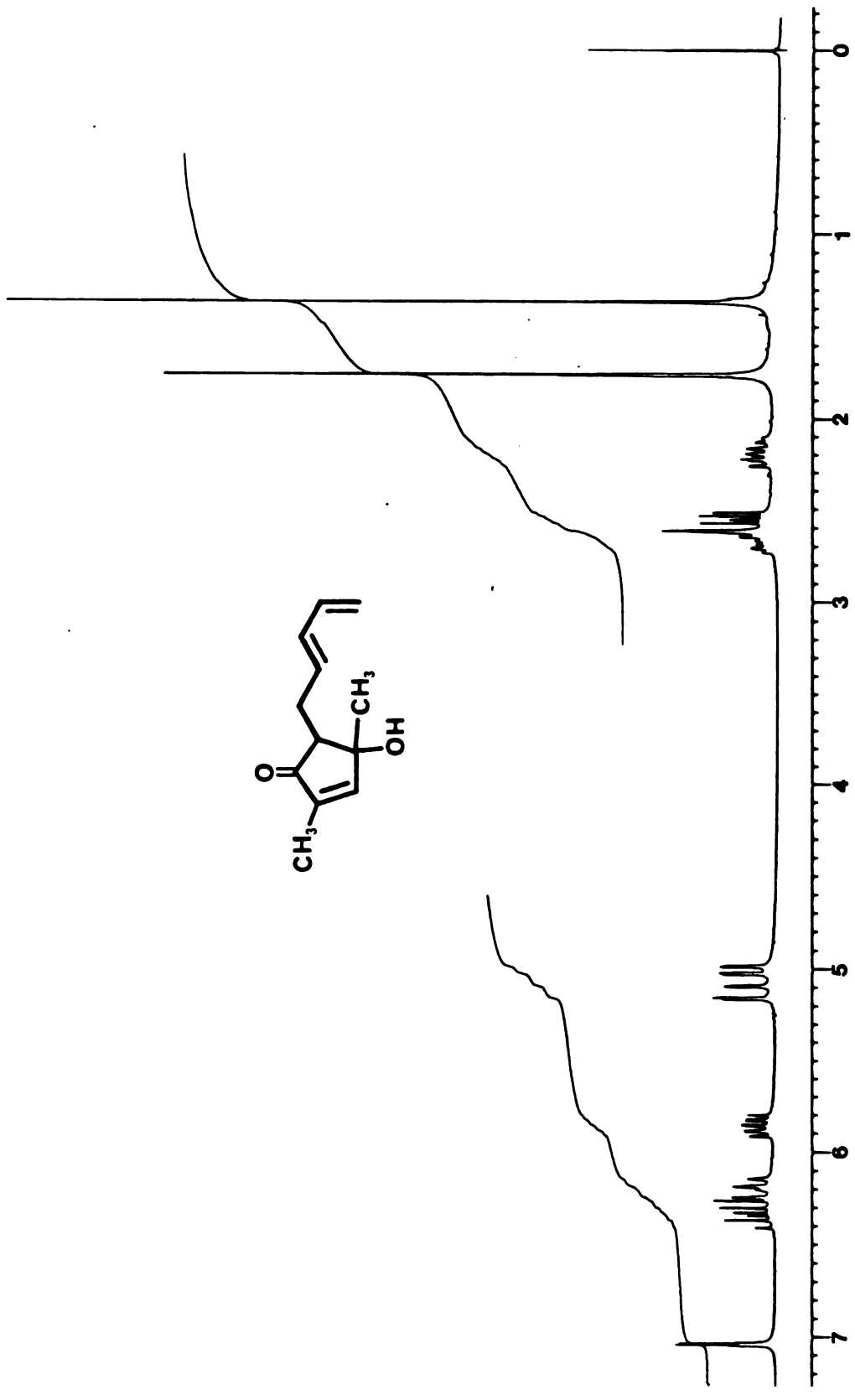


Figure A43. 250 MHz ^{1}H NMR spectrum of 2,4-dimethyl-4-hydroxy-5-(2,4-pentadienyl)-2-cyclopentenone (107).

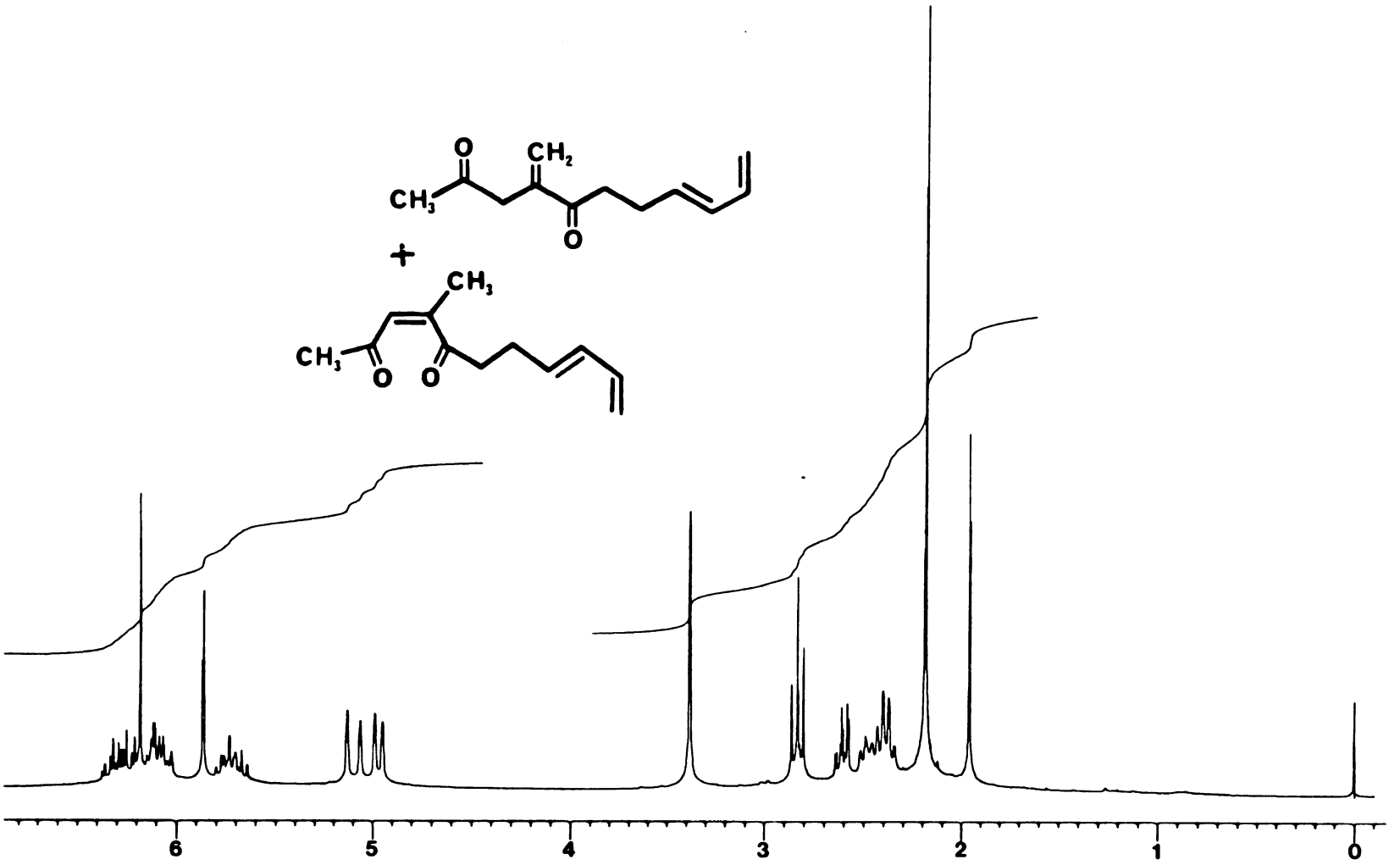


Figure A44. 250 MHz ^{1}H NMR spectrum of 4-methylidene-8(E),10-undecadiene-2,5-dione (108) as a mixture with triene 105 (see Figure A39).

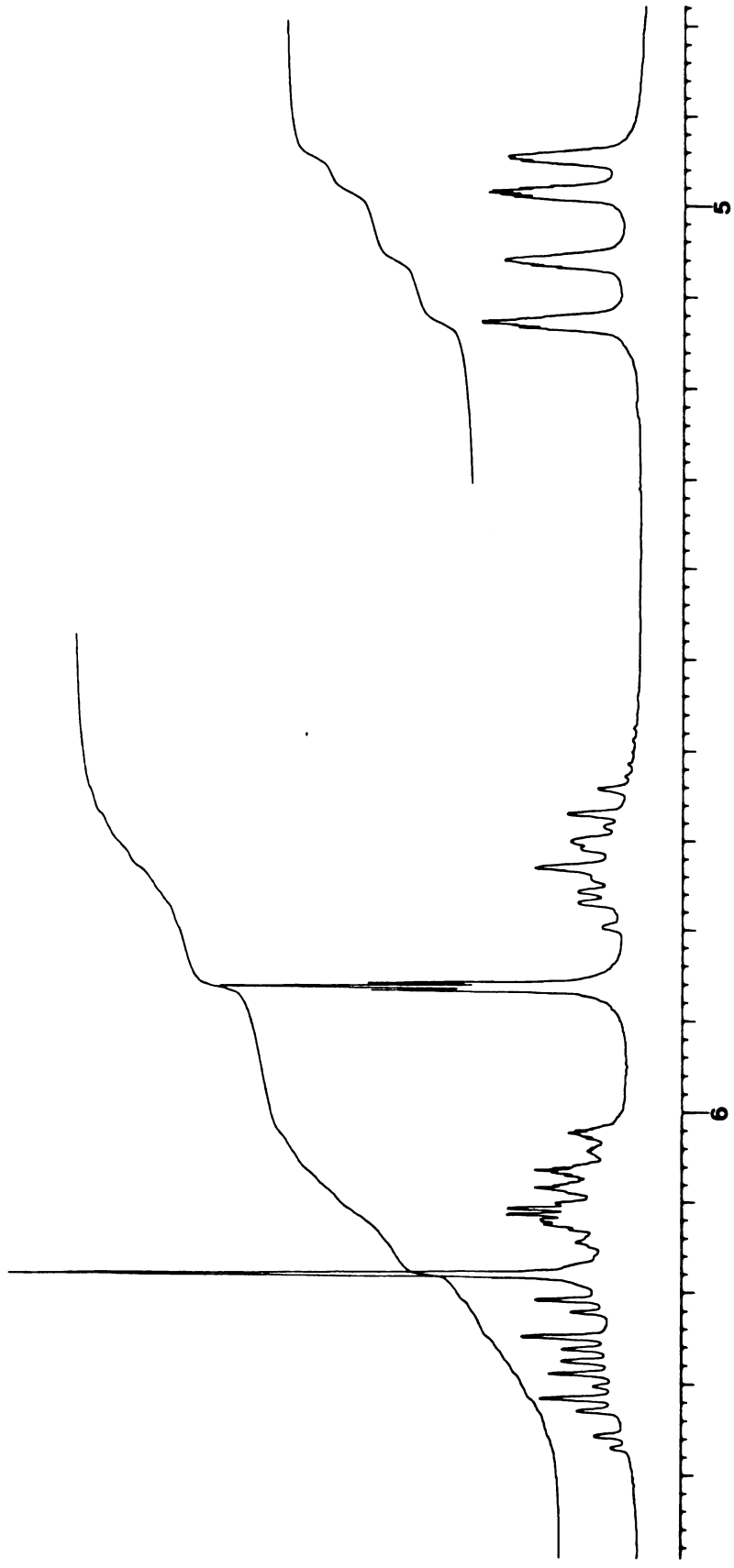


Figure A45. Expansion in the 250 MHz ^{1}H NMR spectrum of 108 (see Figure A44).

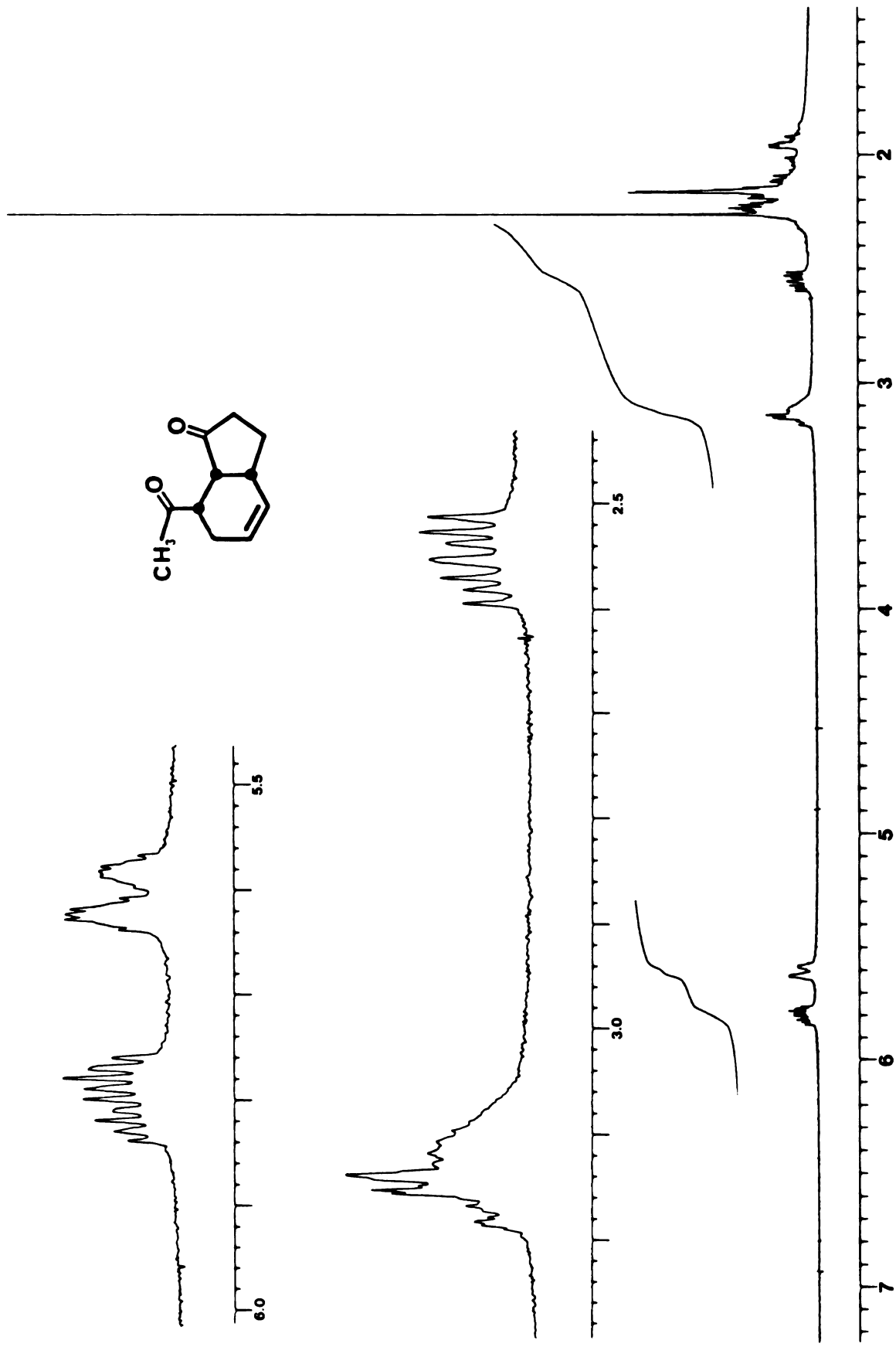


Figure A46. 250 MHz ^{1}H NMR spectrum of *cis*-fused hydrindenone 110b.

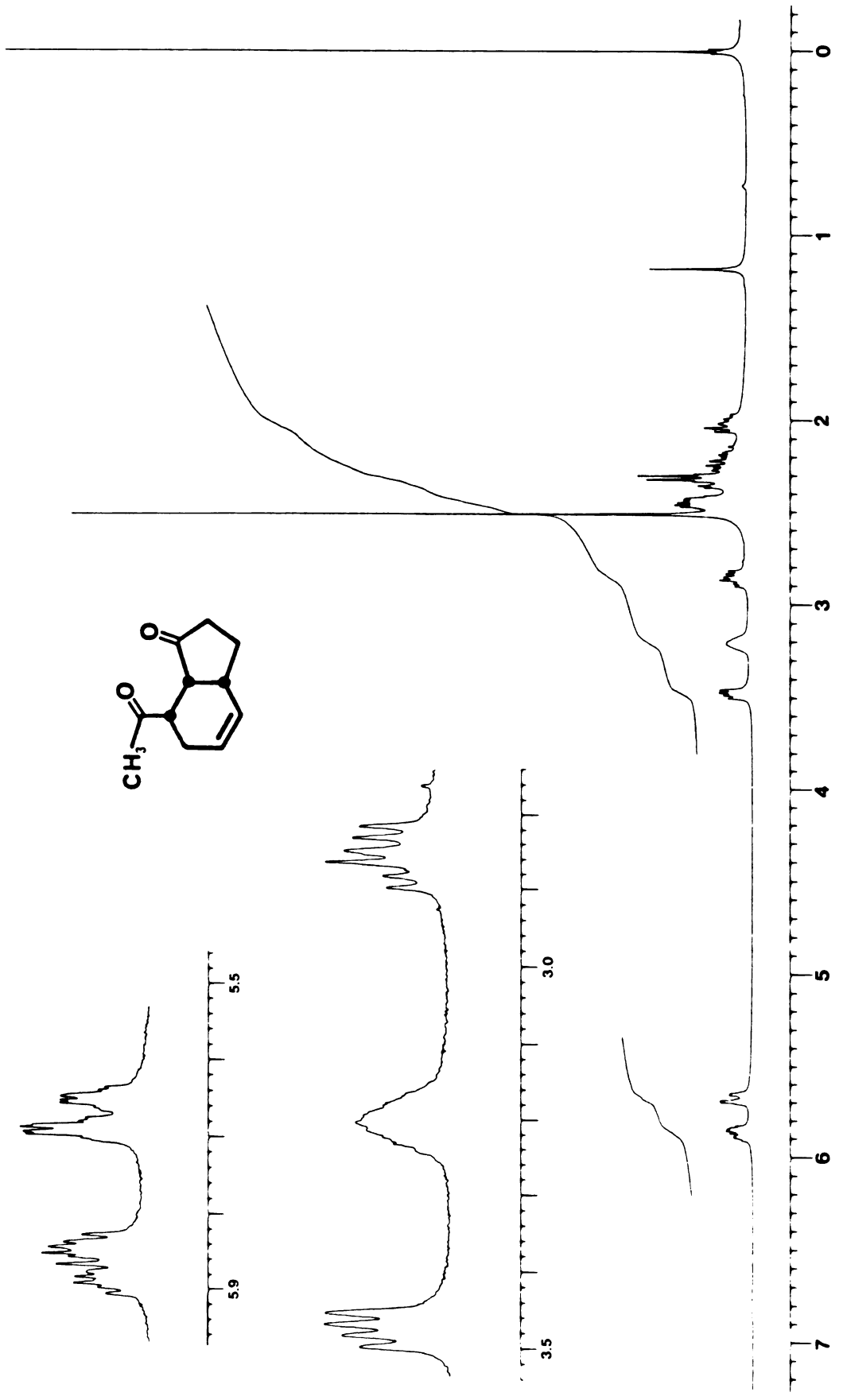


Figure A47. 250 MHz ^{1}H NMR spectrum of 110b (see Figure A46) plus Eu(fod)$_3$.

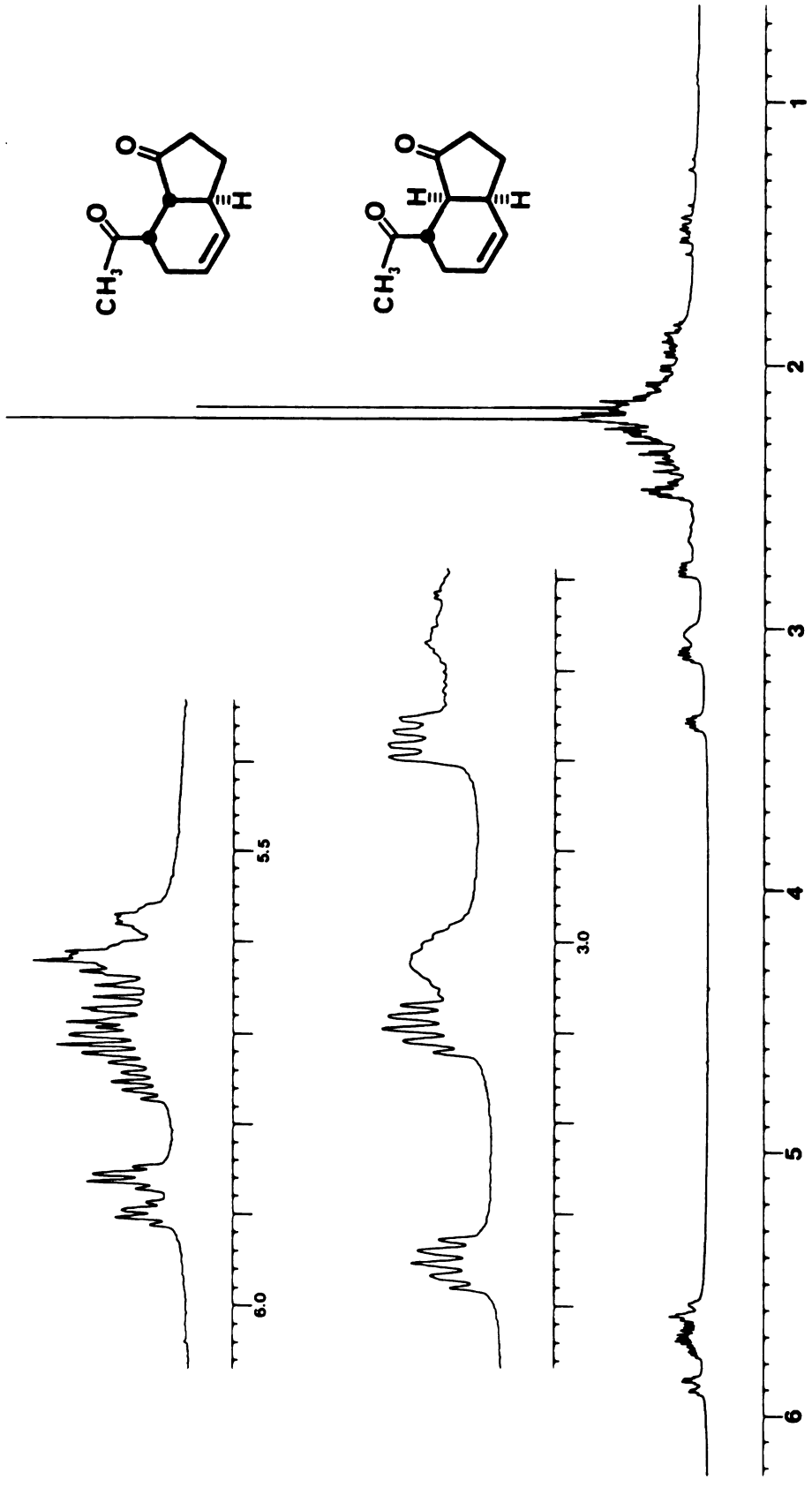


Figure A48. 250 MHz ^{1}H NMR spectrum of *trans*-fused hydrindenone 110a and epimer, *cis*-fused hydrindenone 111b.

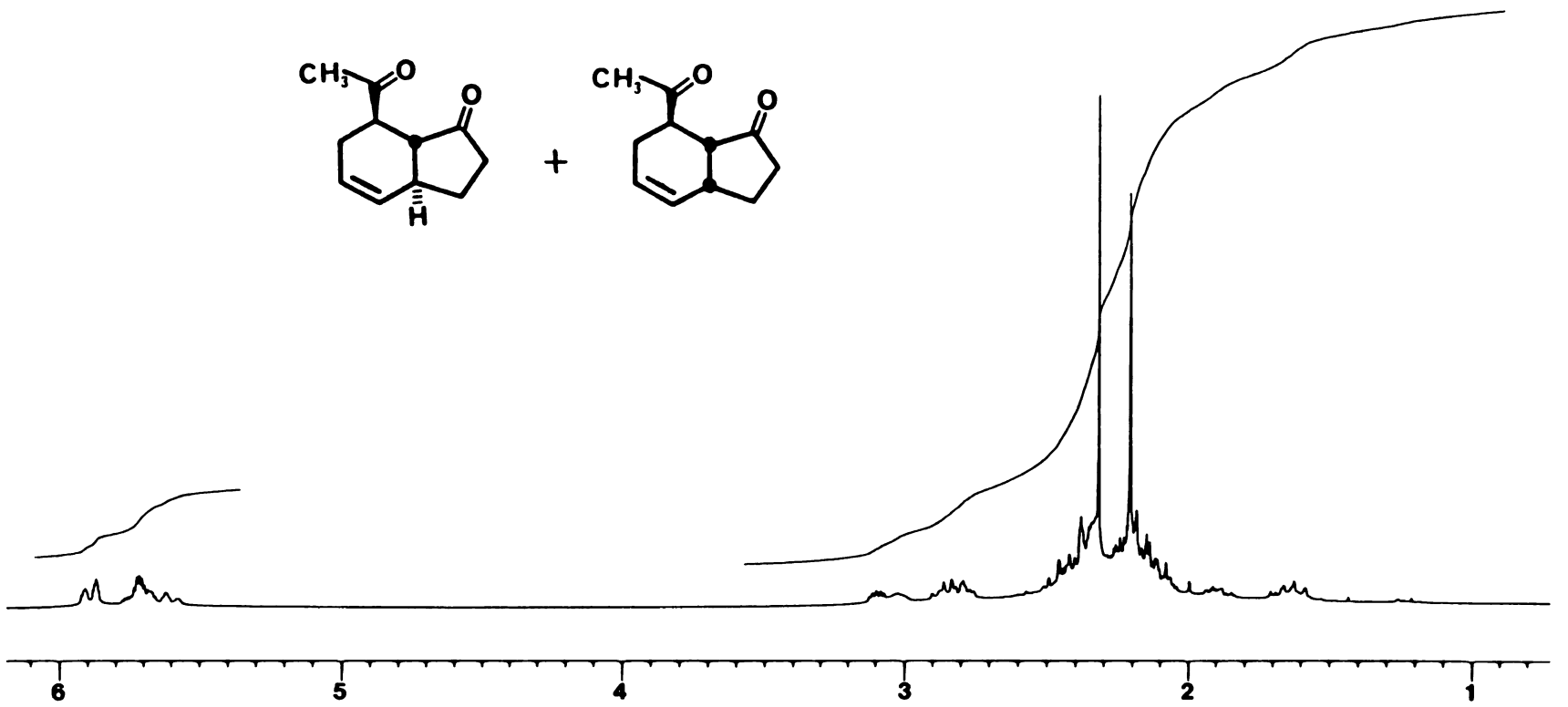


Figure A49. 250 MHz ^{1}H NMR spectrum of *trans*- and *cis*-fused hydrindenones 111a and 111b.

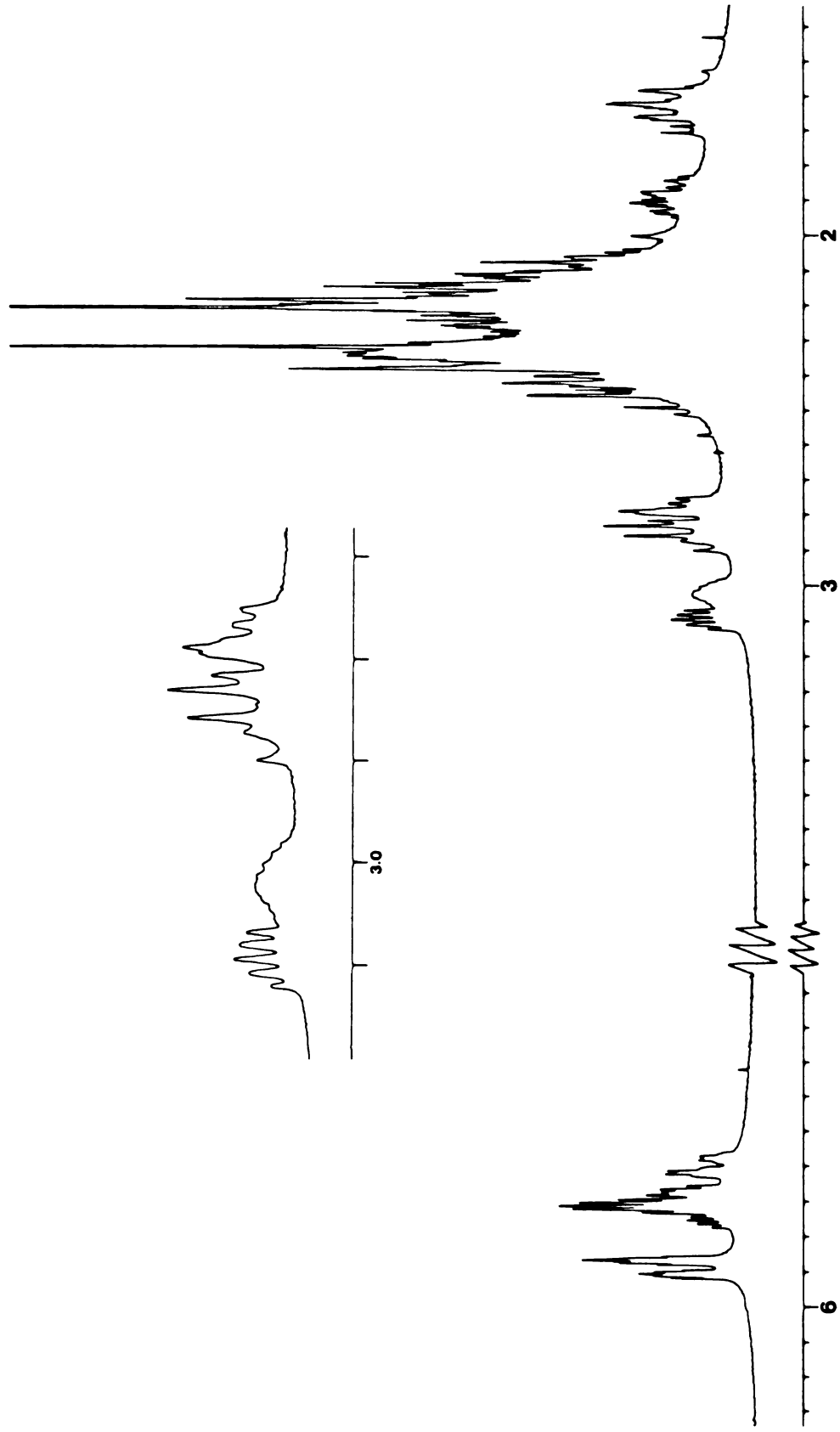


Figure A50. Expansion in the 250 MHz ^{1}H NMR spectrum of hydrindenones 111a and 111b (see Figure A49).

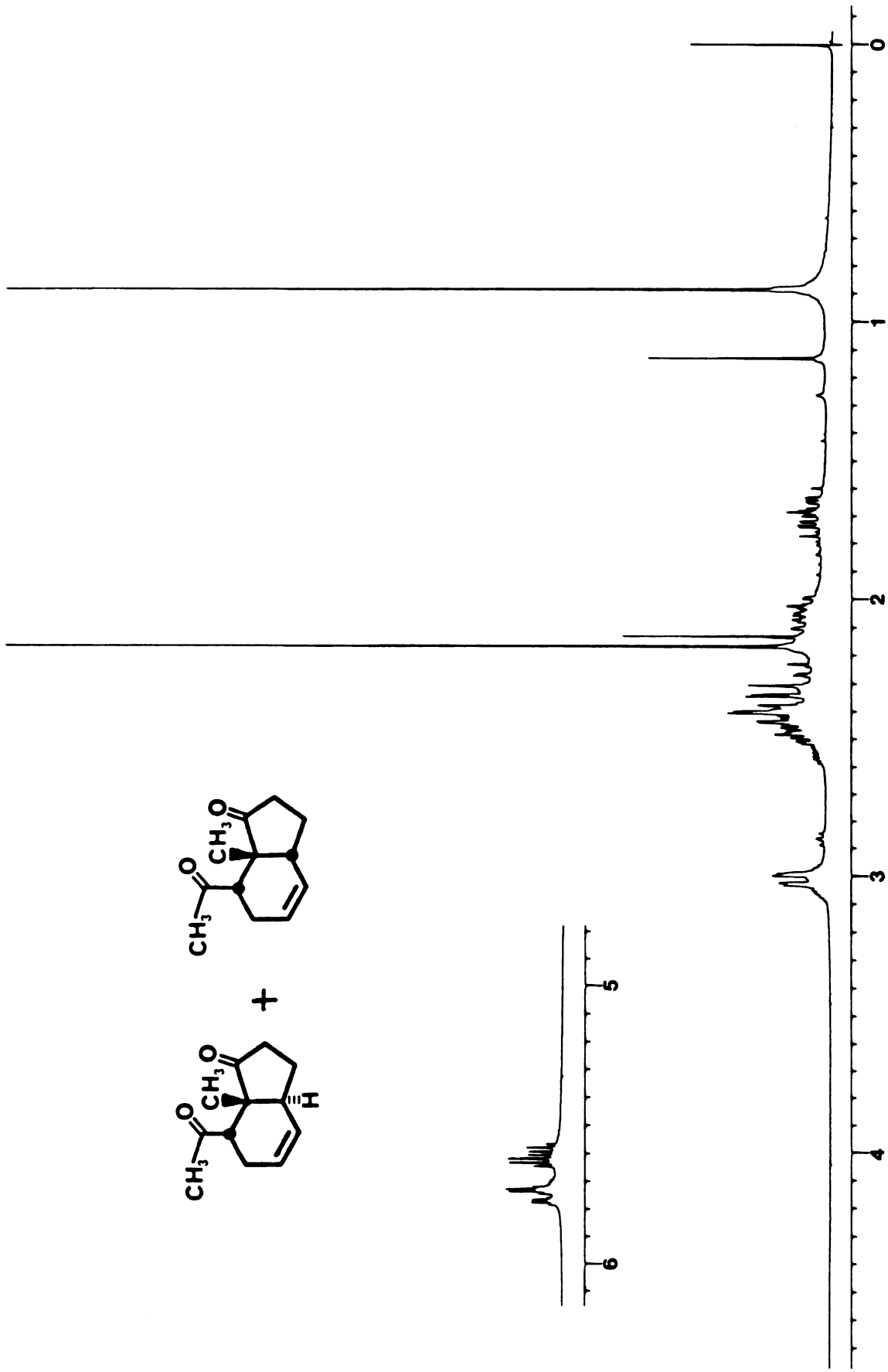


Figure A51. 250 MHz ^{1}H NMR spectrum of *trans*- and *cis*-fused hydrindenones 112a and 112b.

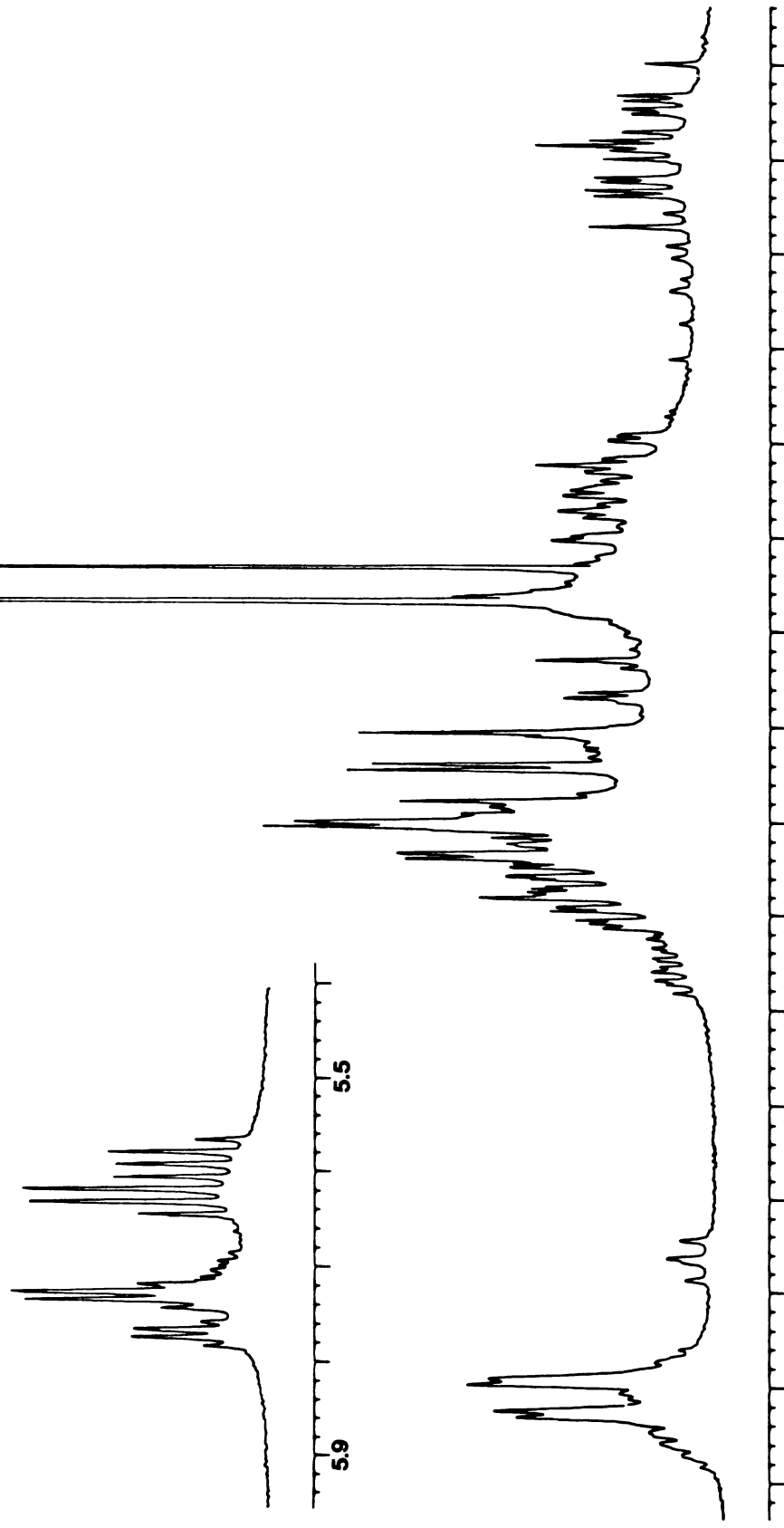


Figure A52. Expansion in the 250 MHz ^{1}H NMR spectrum of hydrindenones 112a and 112b (see Figure A51).

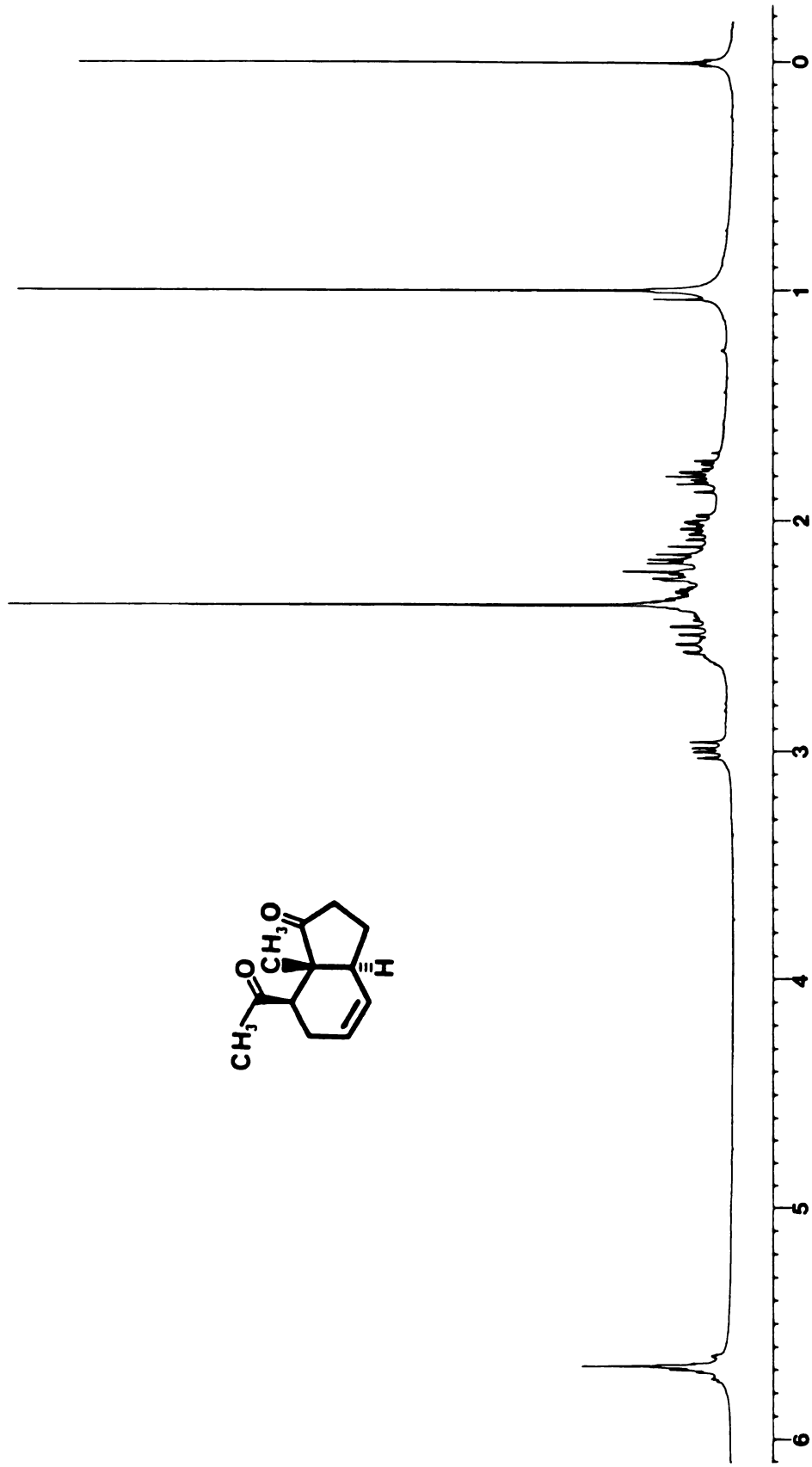


Figure A53. 250 MHz ^{1}H NMR spectrum of *trans*-fused hydrindenone 113a (contains a minor amount of *cis*-fused 113b).

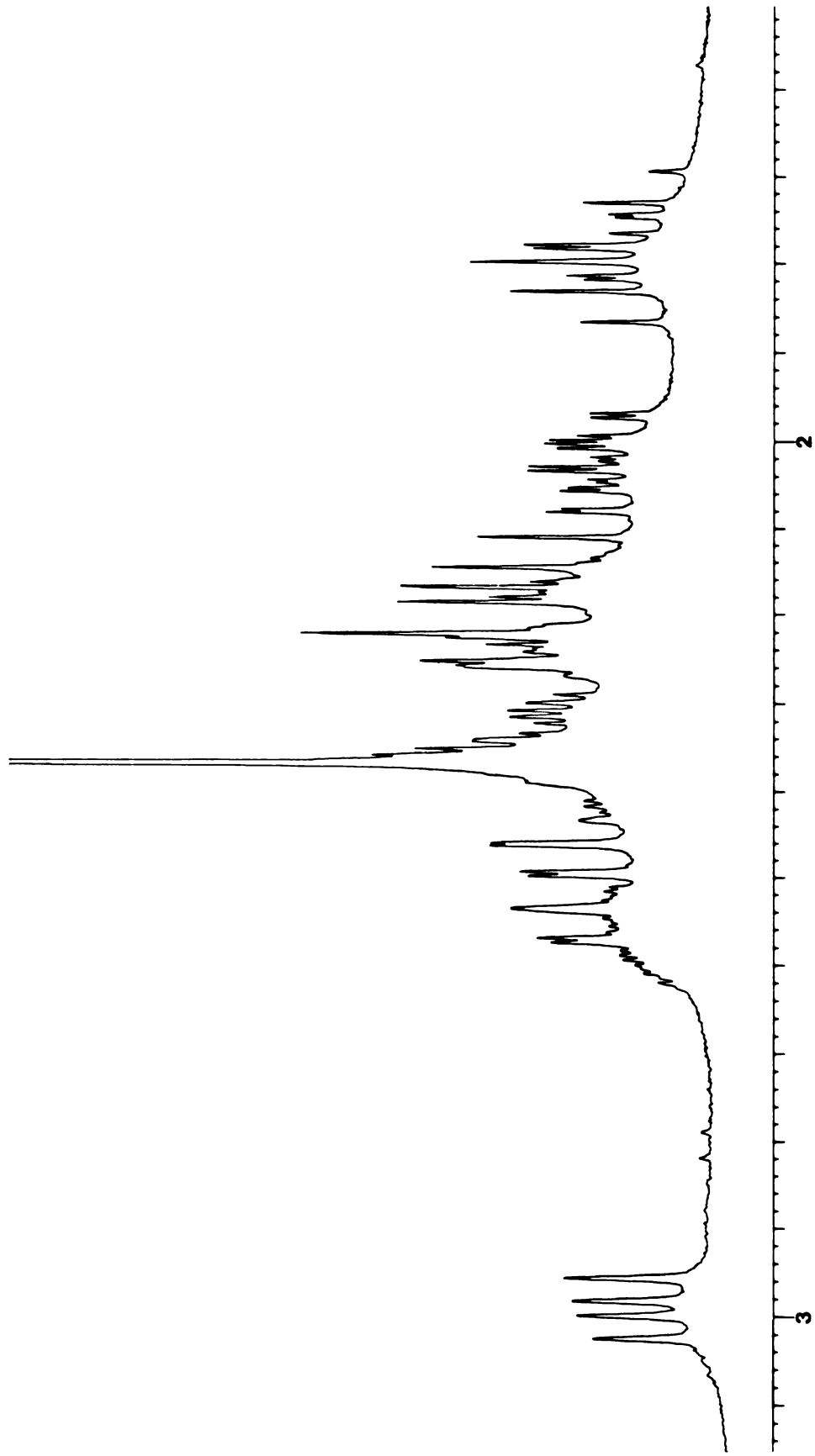


Figure A54. Expansion in the 250 MHz ^{1}H NMR spectrum of hydrindenone 113a (see Figure A53).

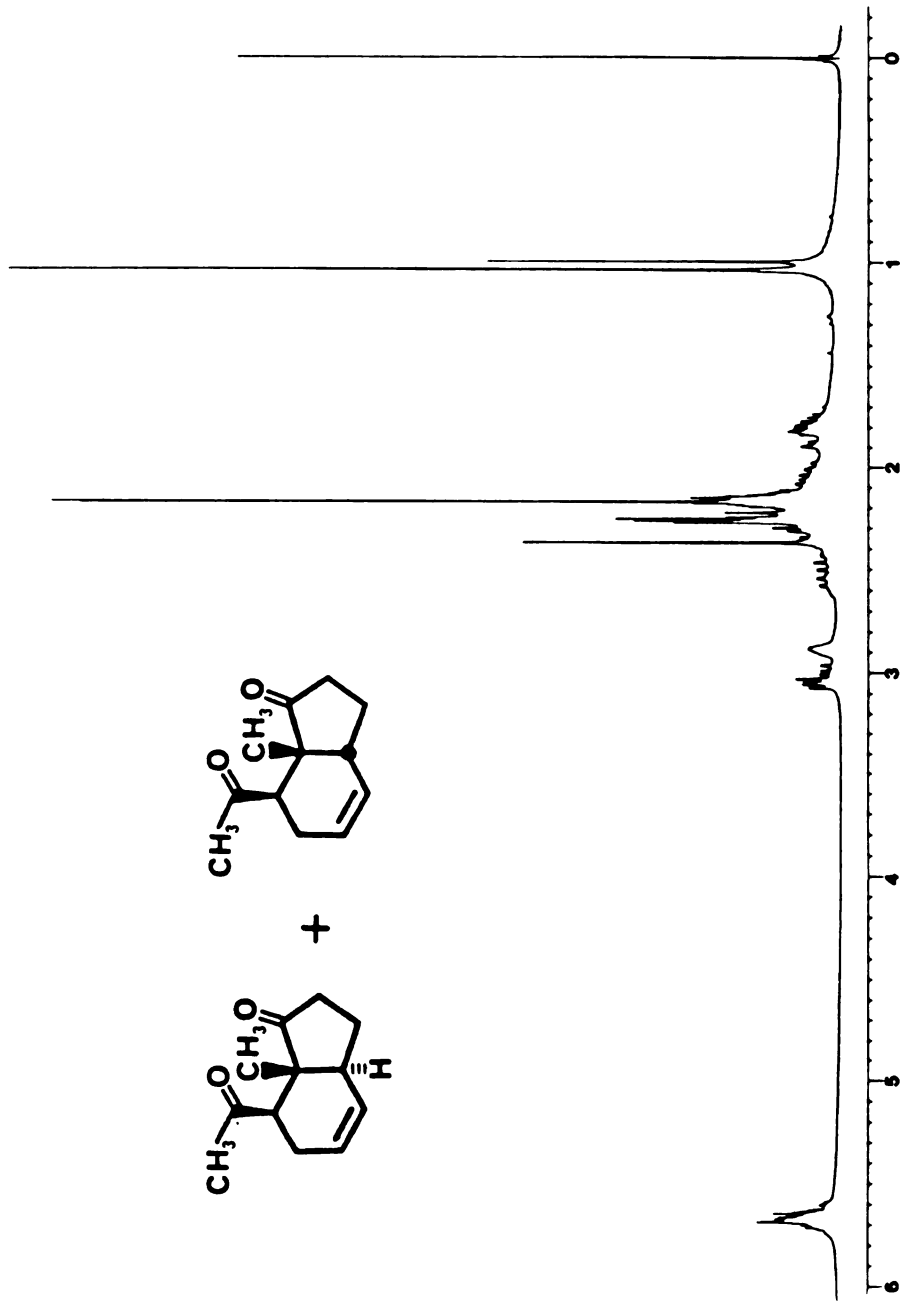


Figure A55. 250 MHz ^{1}H NMR spectrum of *trans*- and *cis*-fused hydrindenones 113a and 113b.

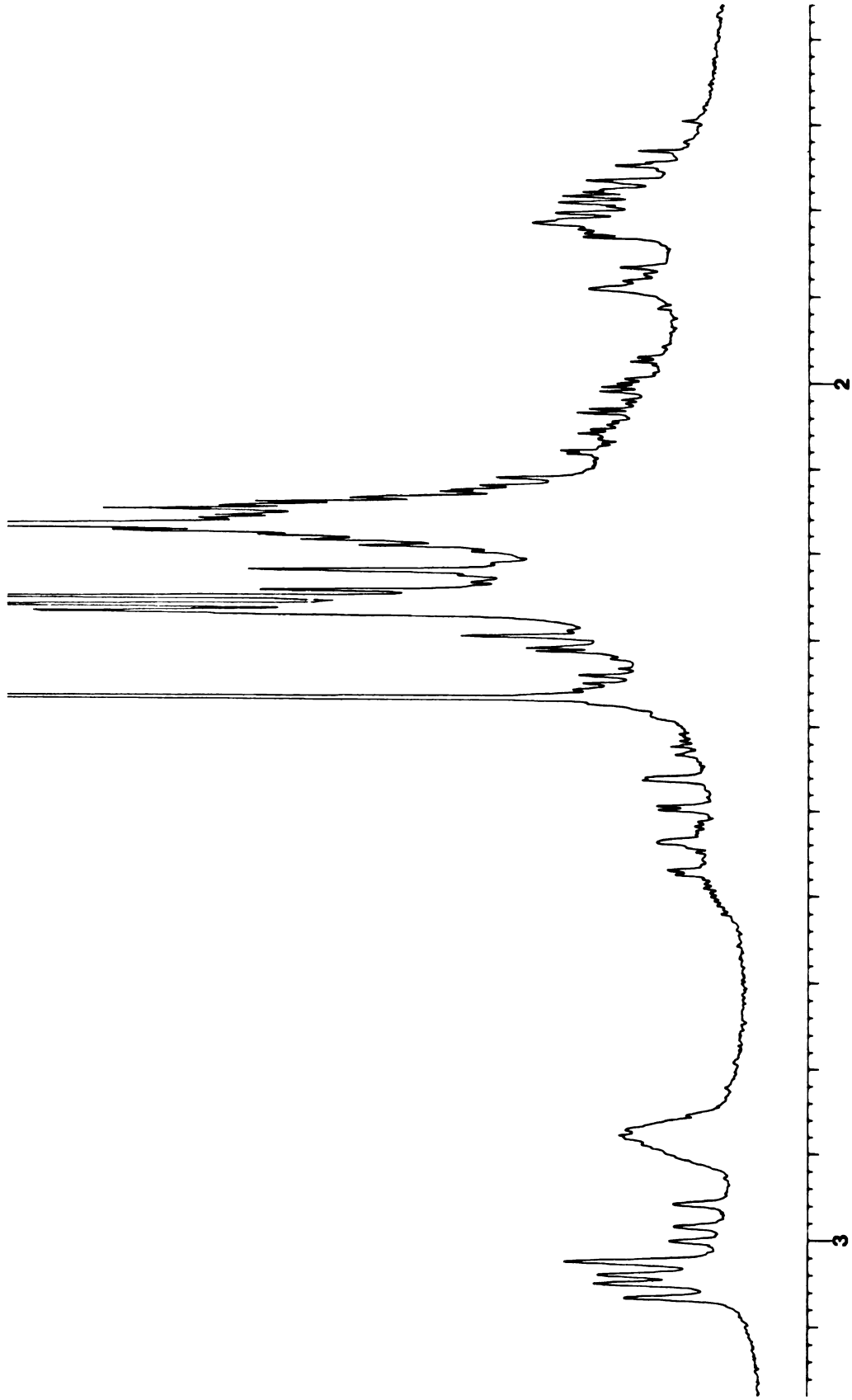


Figure A56. Expansion in the 250 MHz ^{1}H NMR spectrum of hydrindenones 113a and 113b (see Figure A55).

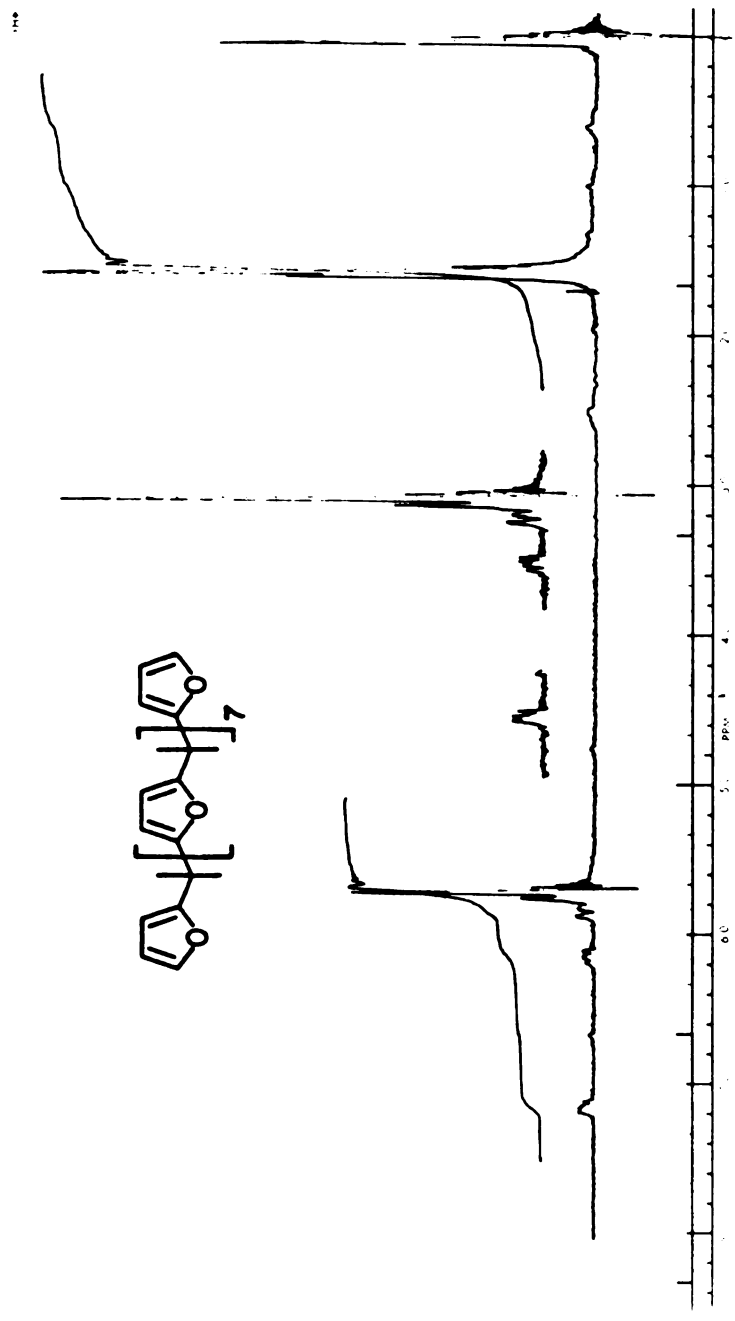


Figure A57. 60 MHz ^{1}H NMR spectrum of linear furan-acetone nonamer 127.

Figure A58. 250 MHz ^{1}H NMR spectrum of linear furan-acetone nonamer dialdehyde 128.

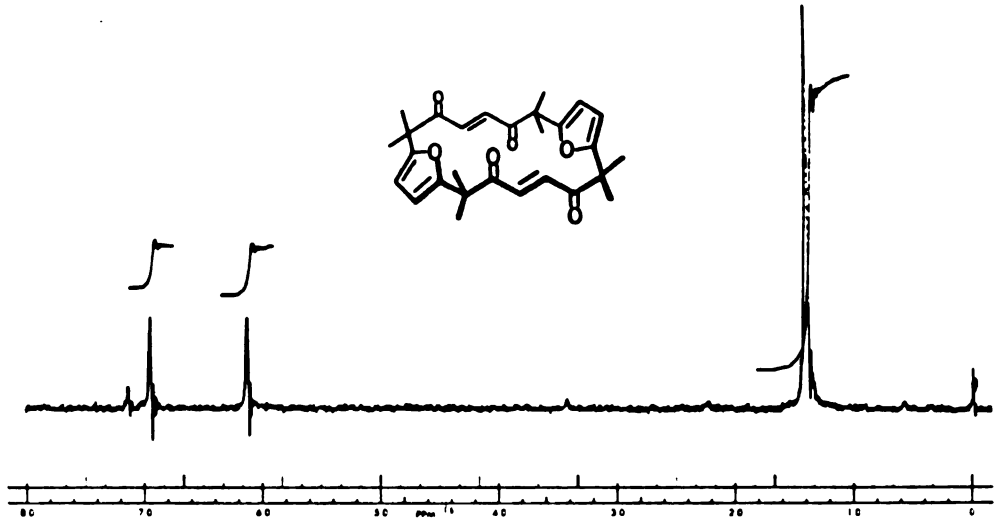


Figure A59. 60 MHz ^{1}H NMR spectrum of di-ring-opened *trans*-enedione 129.

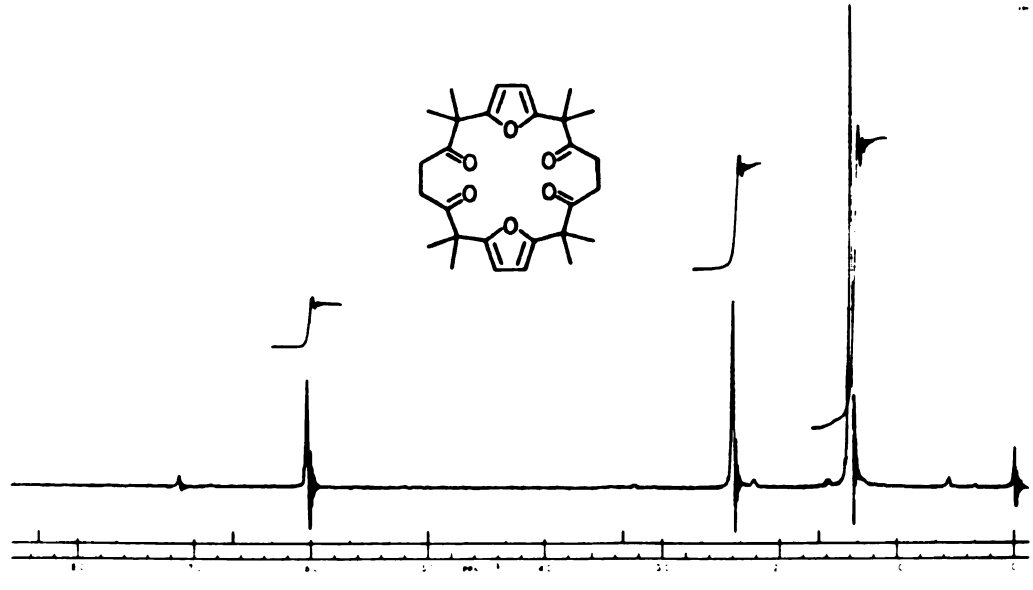


Figure A60. 60 MHz ^{1}H NMR spectrum of saturated tetraketone 131.

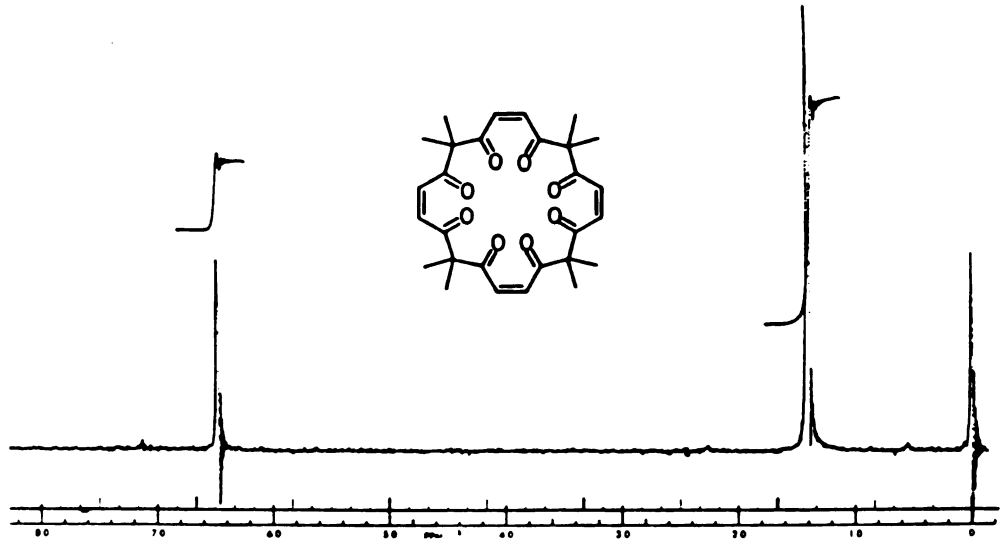


Figure A61. 60 MHz ^{1}H NMR spectrum of tetra-ring-opened octaketone 132.

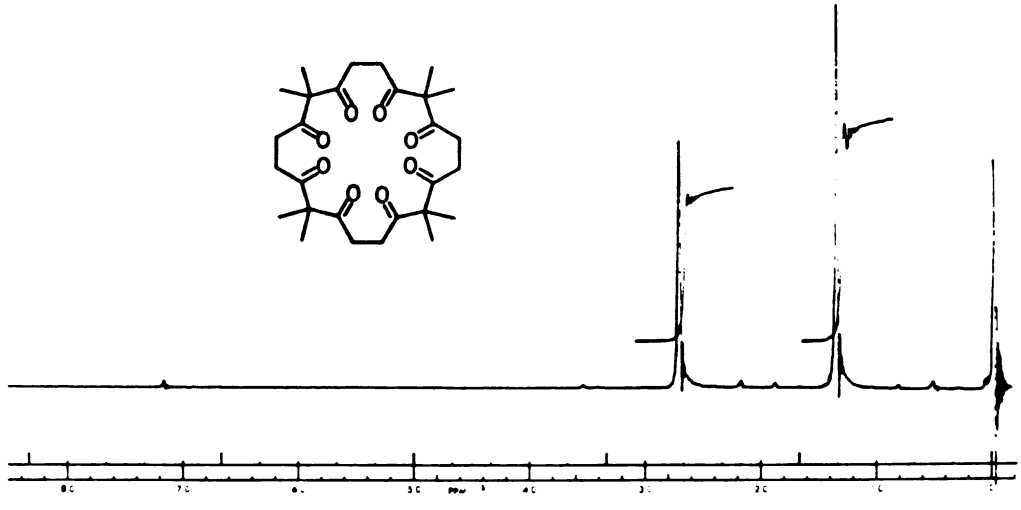


Figure A62. 60 MHz ^{1}H NMR spectrum of saturated octaketone 134.

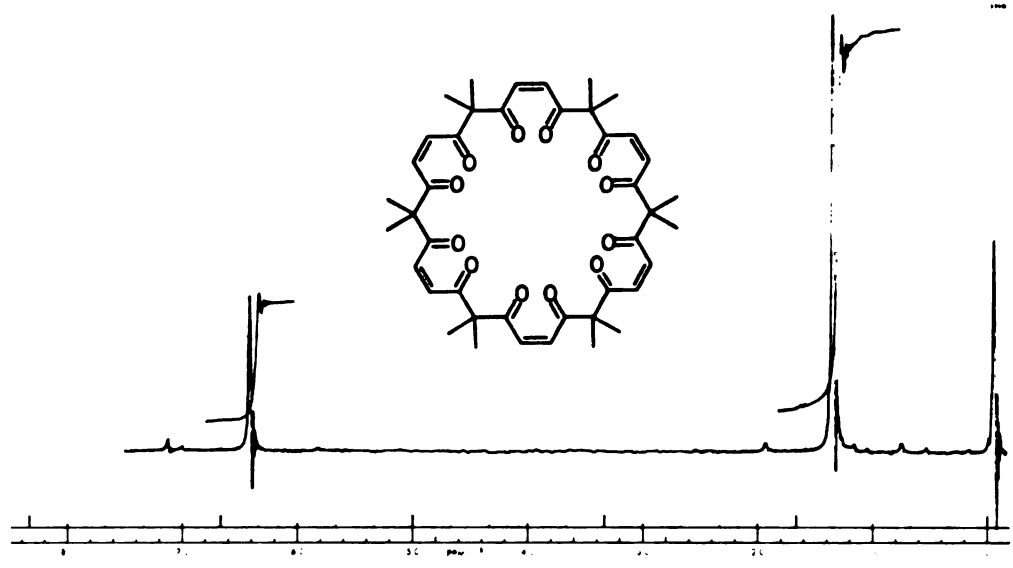


Figure A63. 60 MHz ^{1}H NMR spectrum of hexa-ring-opened dodecaketone 133.

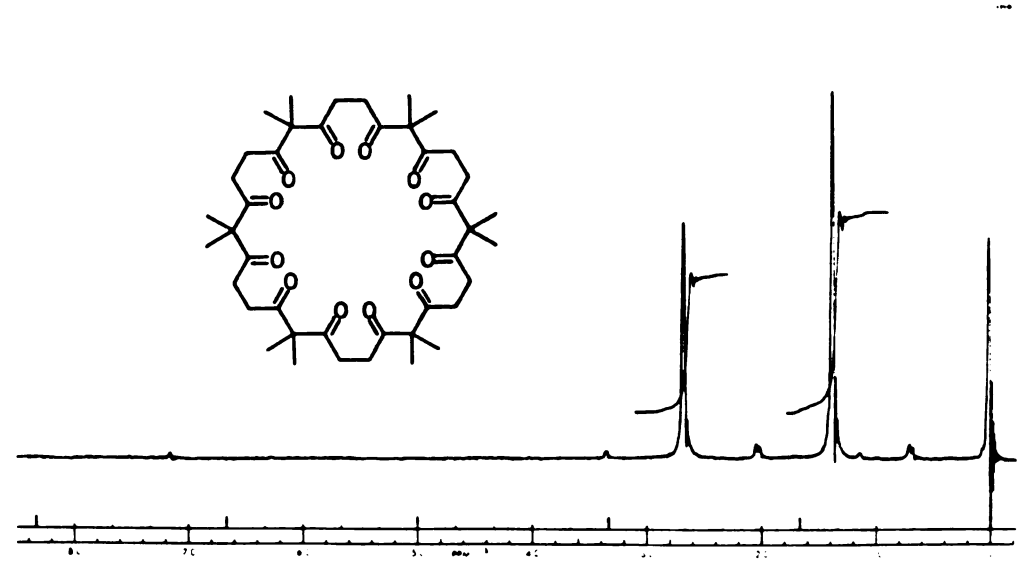


Figure 64. 60 MHz ^{1}H NMR spectrum of saturated dodecaketone 135.

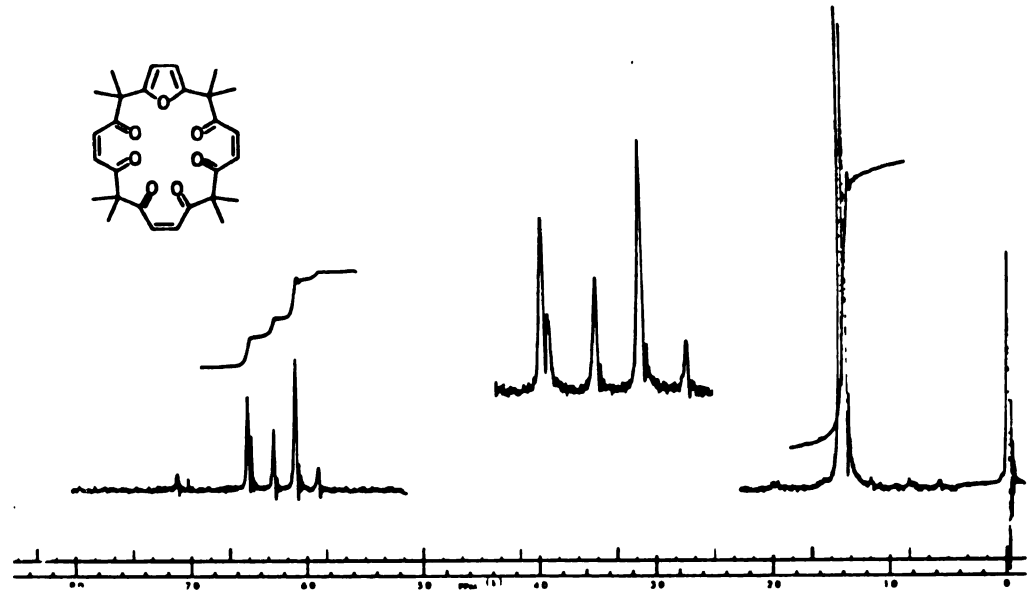


Figure A65. 60 MHz ^{1}H NMR spectrum of tri-ring-opened hexaketone 136.

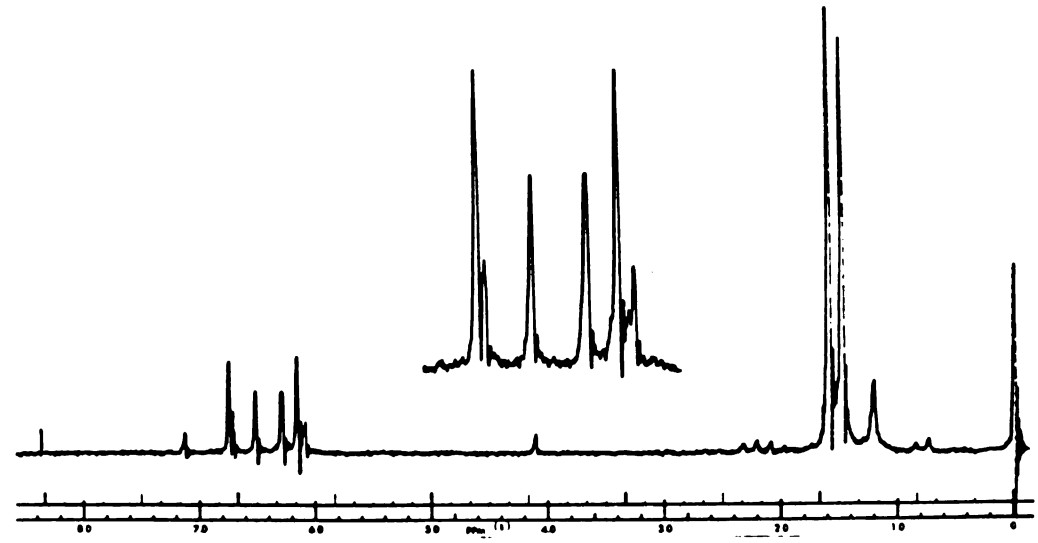


Figure A66. 60 MHz ^{1}H NMR spectrum of tri-ring-opened hexaketone 136 plus $Eu(fod)_3$.

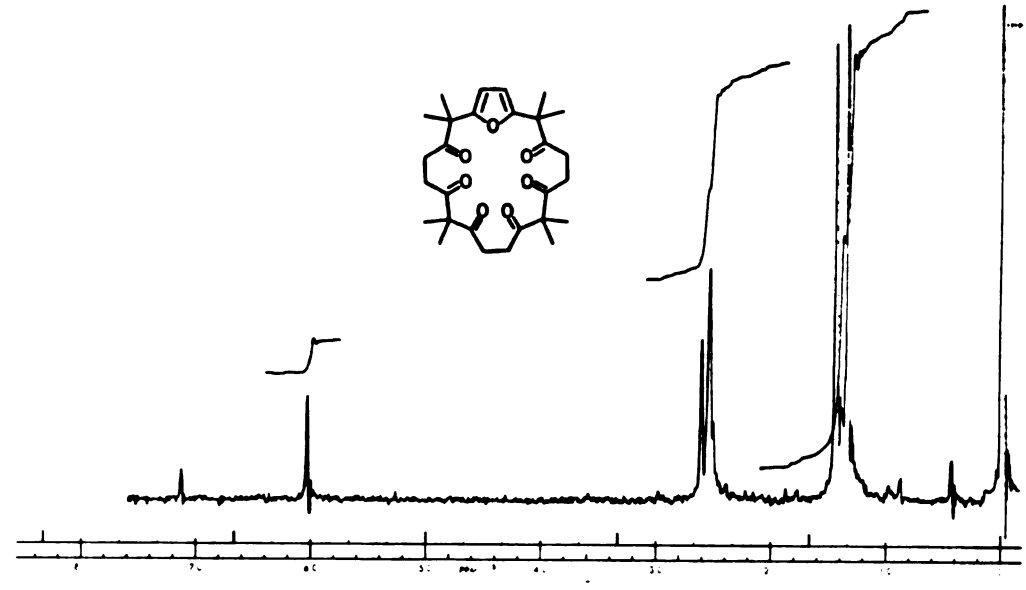


Figure A67. 60 MHz ^{1}H NMR spectrum of saturated hexaketone 137.

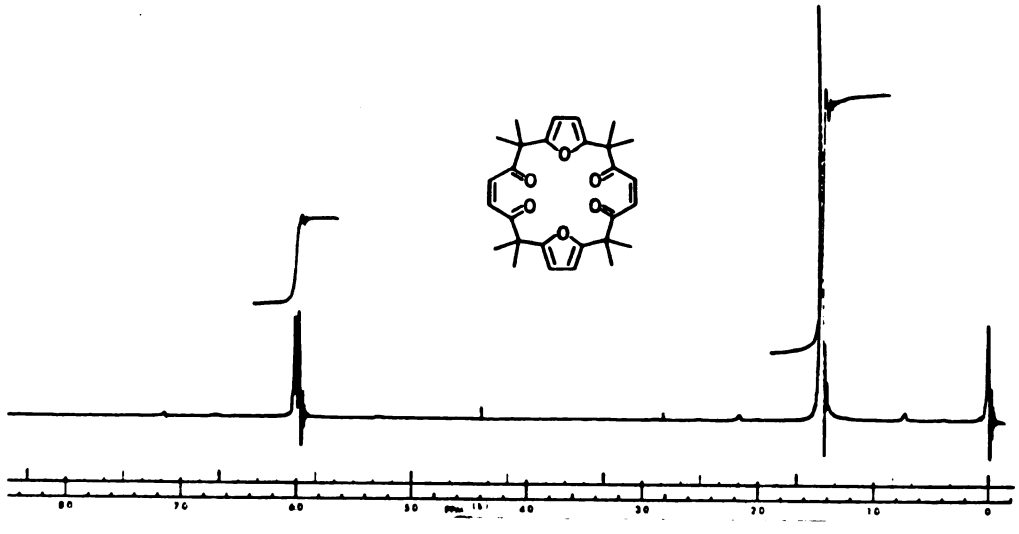


Figure A68. 60 MHz ^{1}H NMR spectrum of di-ring-opened *cis*-enedione 138.

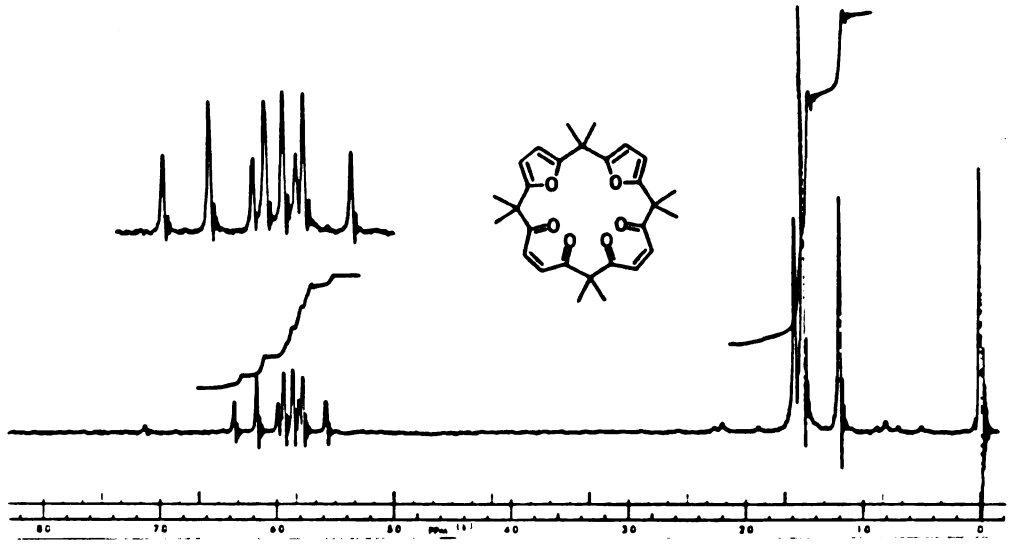


Figure A69. 60 MHz ^{1}H NMR spectrum of di-ring-opened *cis*-enedione 139.

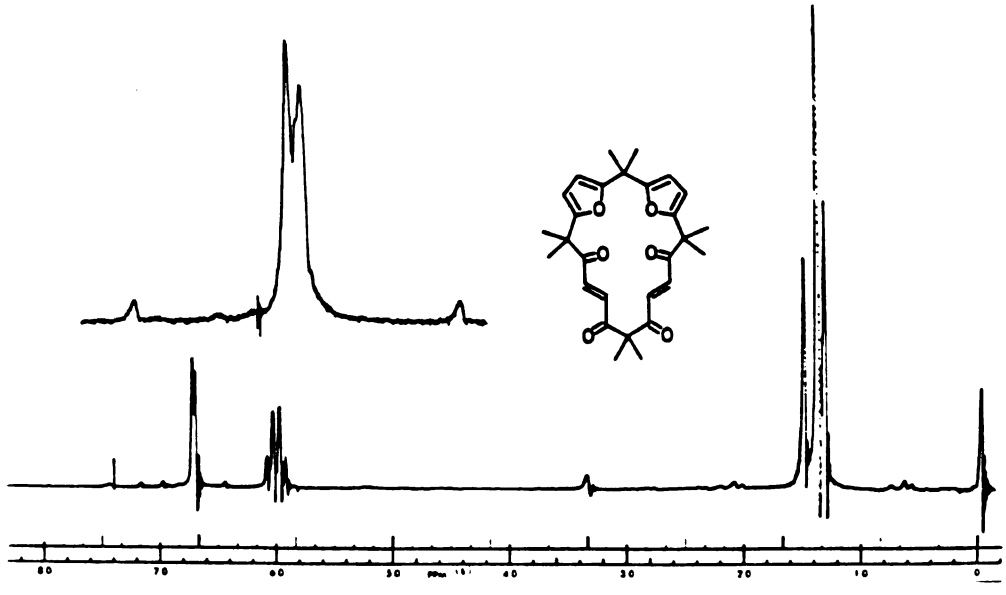


Figure A70. 60 MHz ^{1}H NMR spectrum of di-ring-opened *trans*-enedione 141.

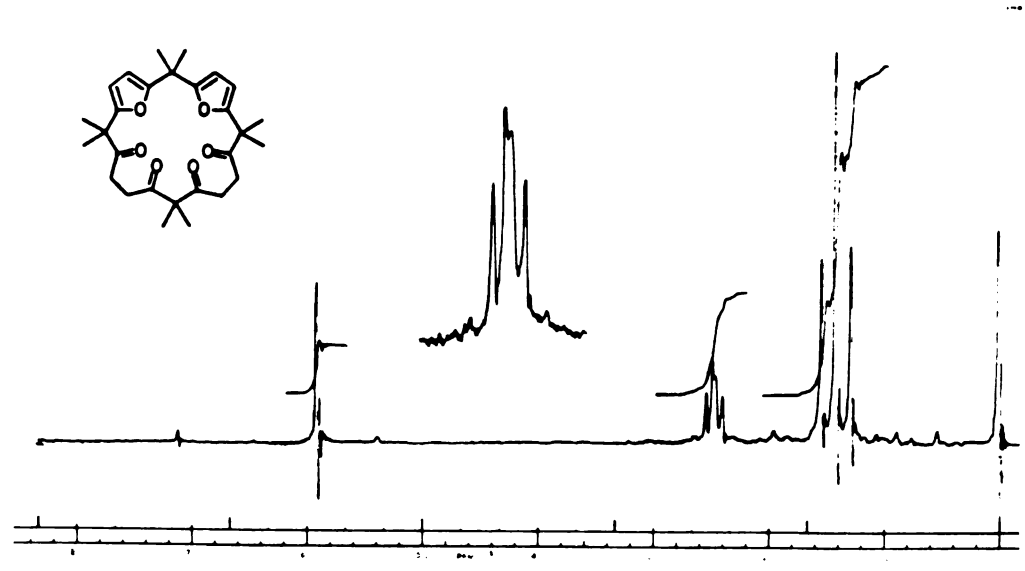


Figure A71. 60 MHz ^{1}H NMR spectrum of saturated tetraketone 140.

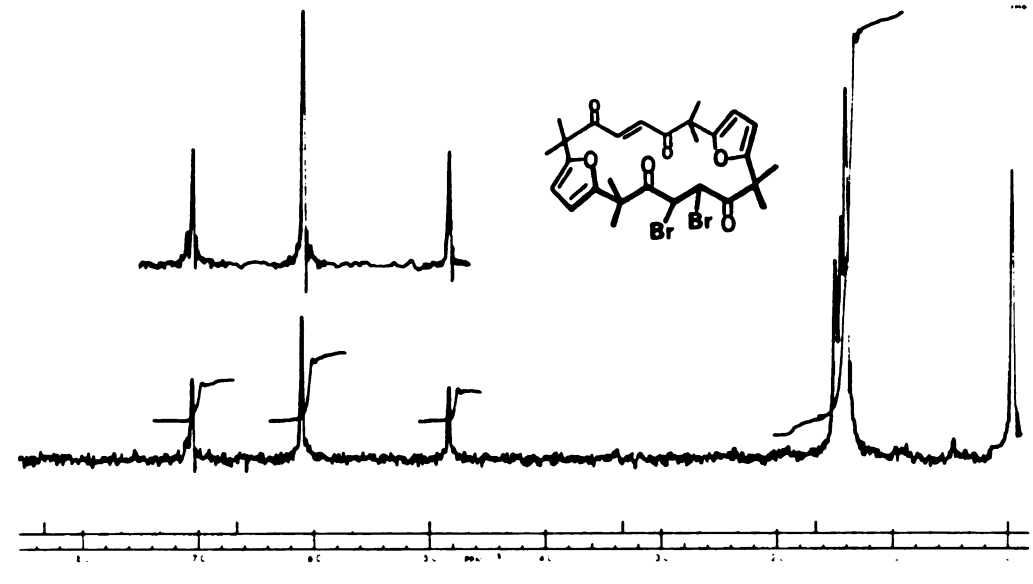


Figure A72. 60 MHz ^{1}H NMR spectrum of dibromo-*trans*-enedione 130.

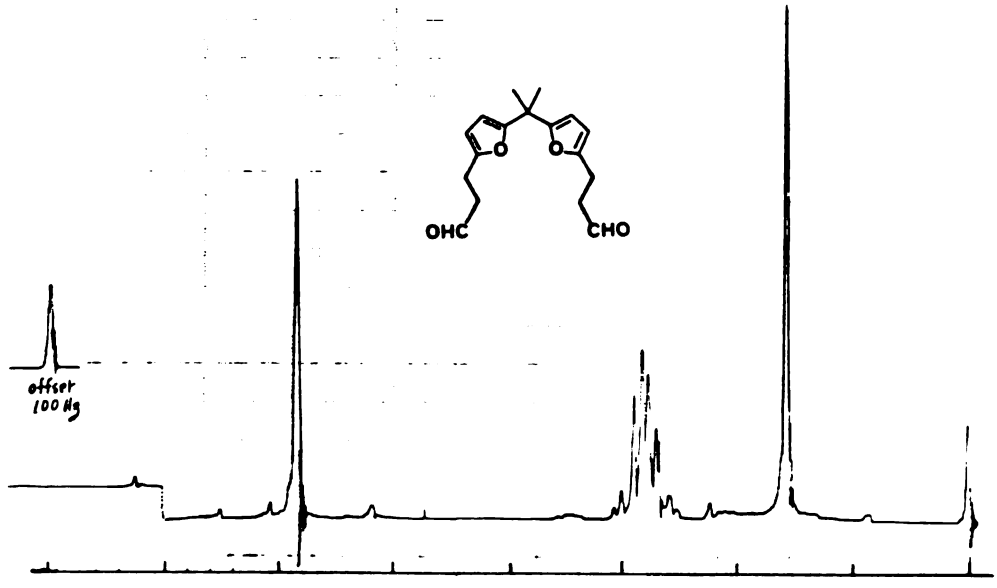


Figure A73. 60 MHz ^{1}H NMR spectrum of 2,2-*bis*[5-(3-oxopropyl)-2-furyl]propane (142).

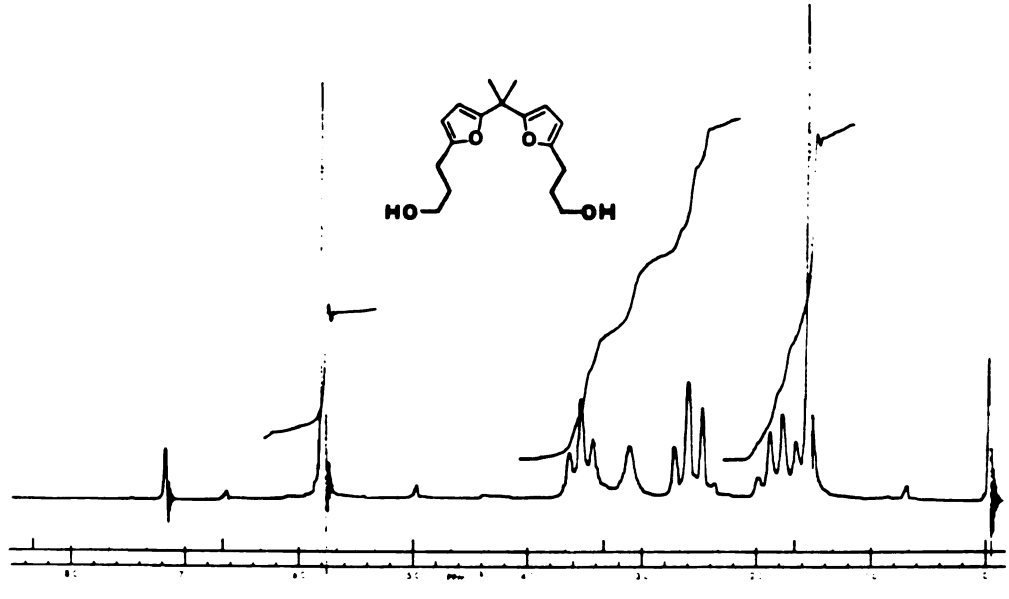


Figure A74. 60 MHz ^{1}H NMR spectrum of 2,2-*bis*[5-(3-hydroxypropyl)-2-furyl]propane (143).

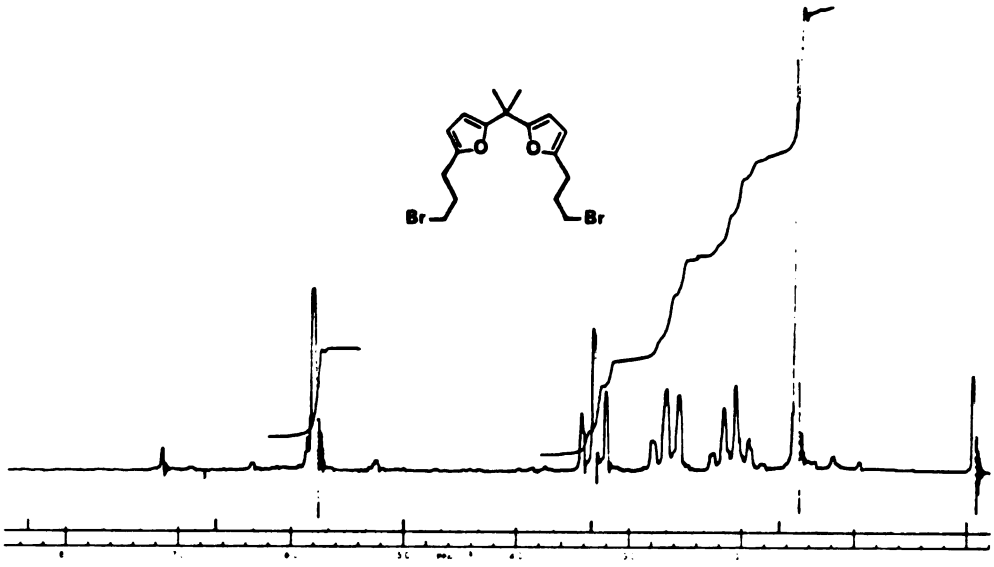


Figure A75. 60 MHz ^{1}H NMR spectrum of 2,2-*bis*[5-(3-bromopropyl)-2-furyl]propane (144).

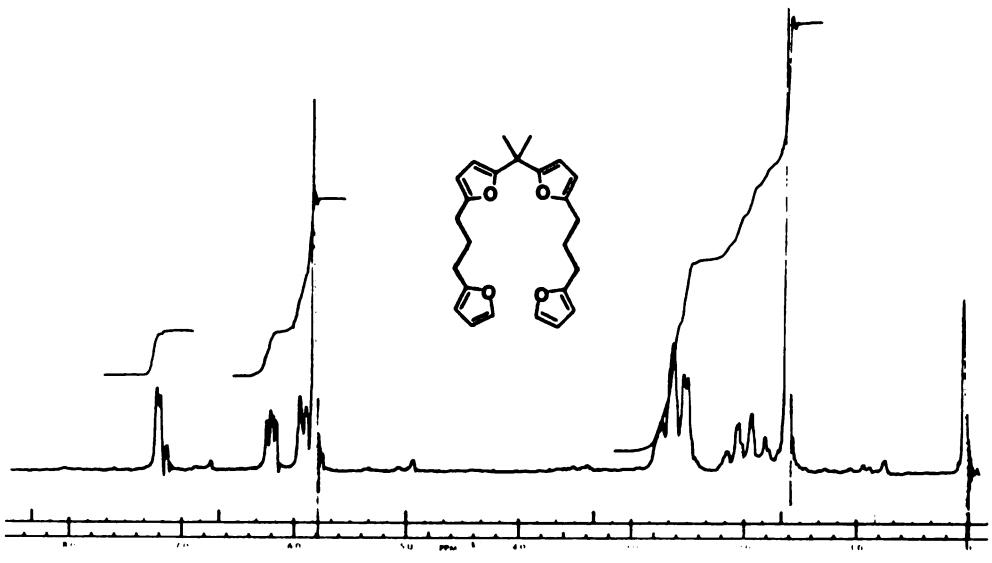


Figure A76. 60 MHz ^{1}H NMR spectrum of 2,2-*bis*{5-[3-(2-furyl)propyl]-2-furyl}propane (145).

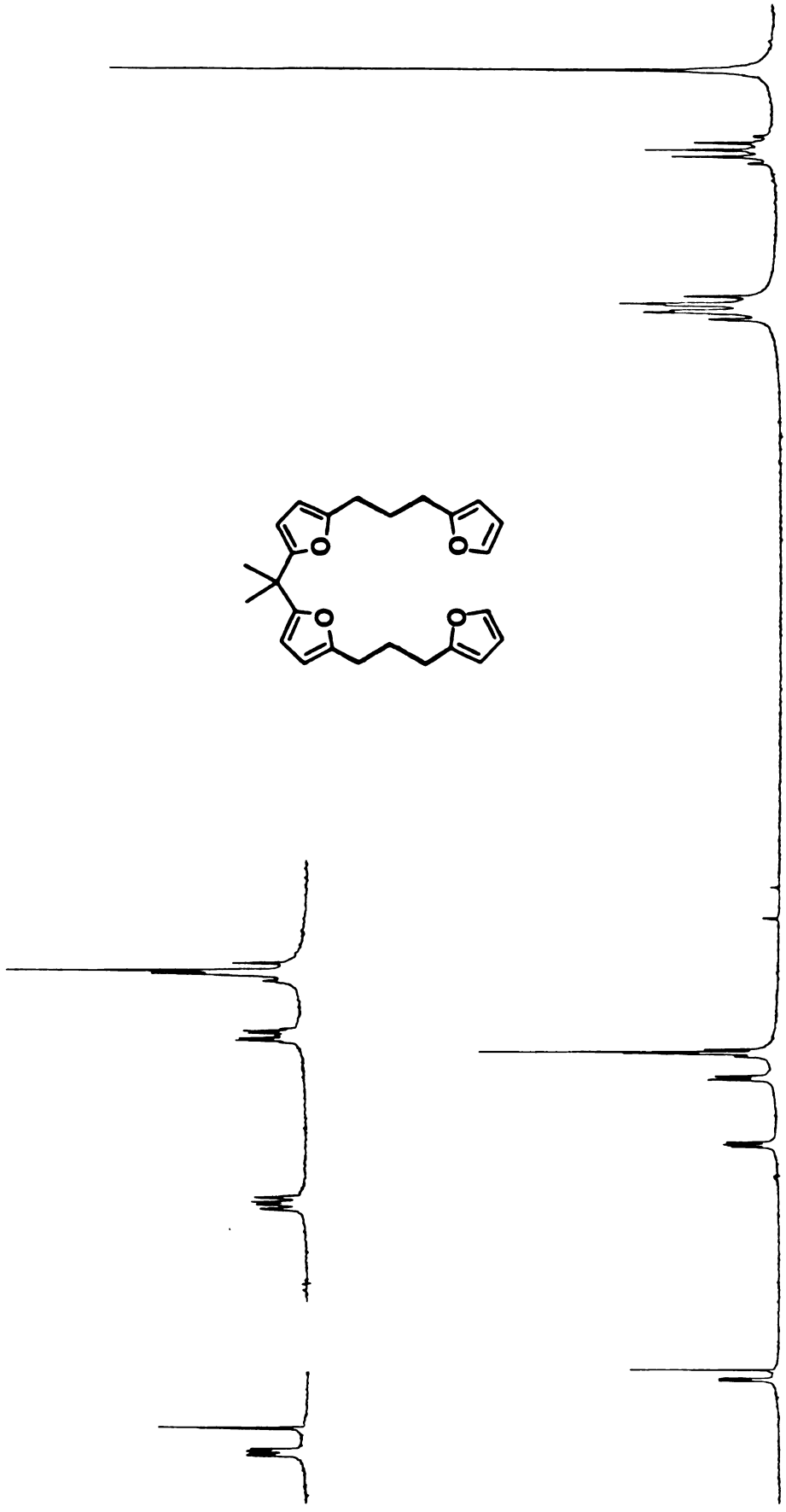


Figure A77. 250 MHz ^{1}H NMR spectrum of 2,2-*bis*{5-[3-(2-furyl)propyl]-2-furyl}-propane (145).

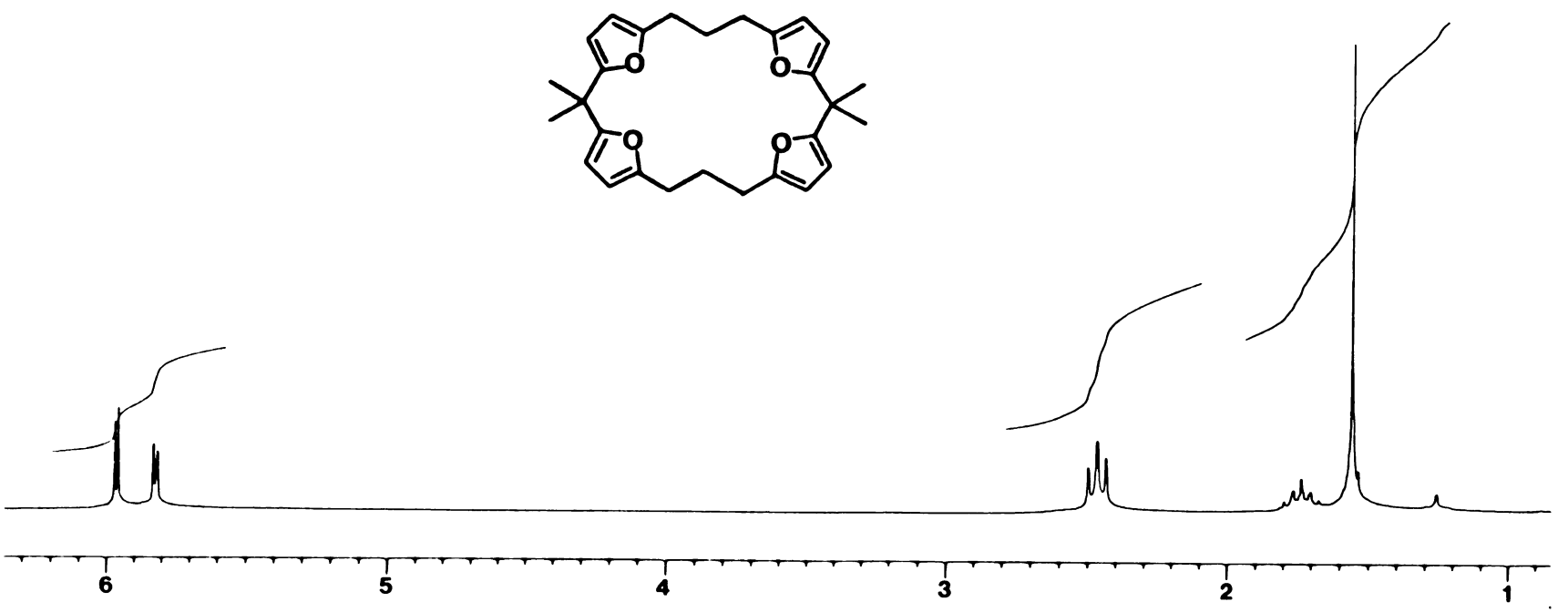


Figure A78. 250 MHz ^{1}H NMR spectrum of 1,1,15,15-tetramethyl-[1.3.1.3](2,5)-furanophane (146).

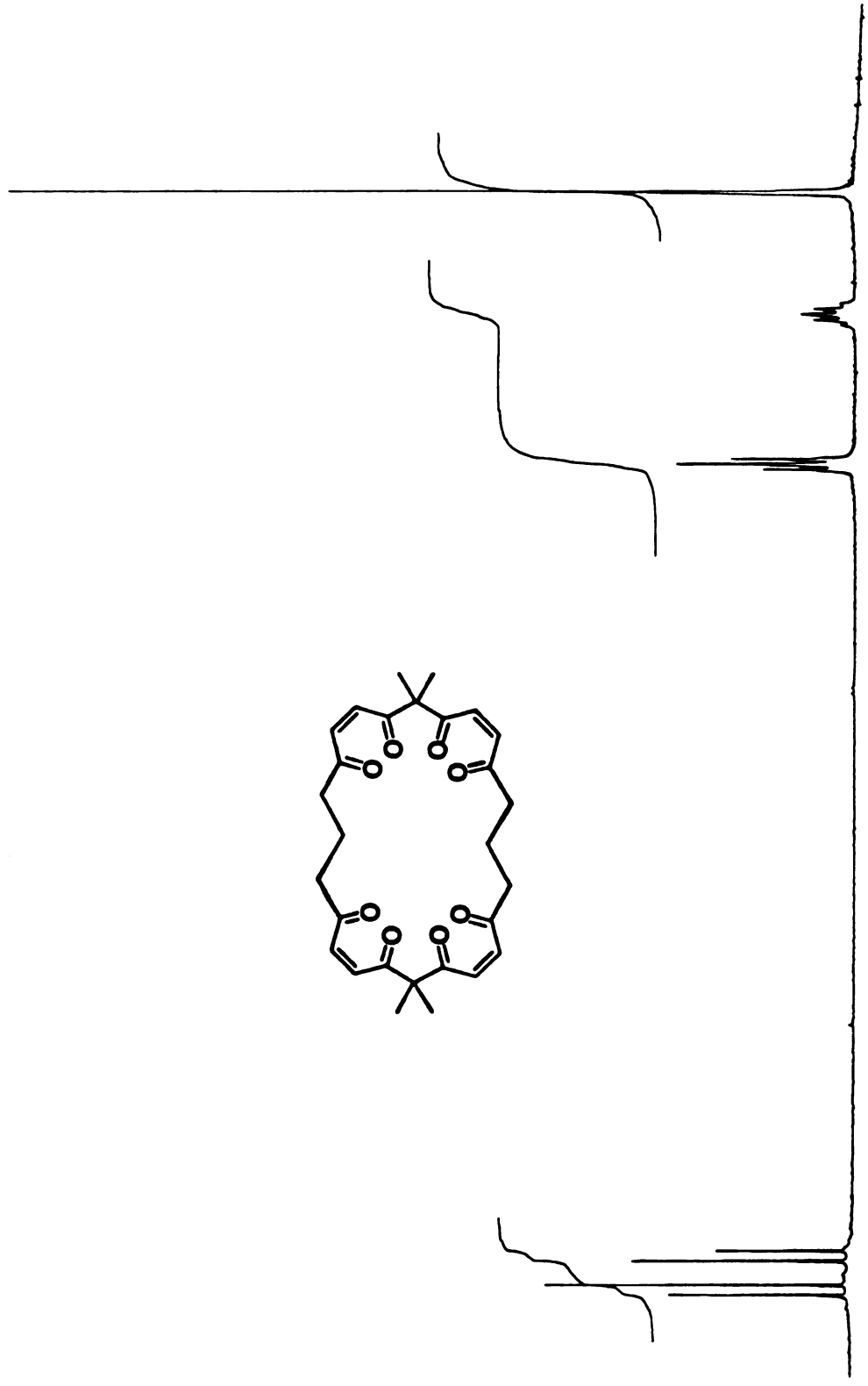


Figure A79. 250 MHz ^{1}H NMR spectrum of tetra-ring-opened *cis*-enedione (147).

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LIST OF REFERENCES

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