ABSTRACT

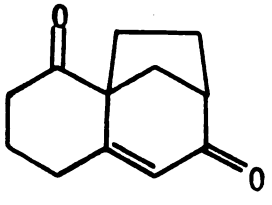
SYNTHETIC APPROACHES TO THE
TRICYCLO[7.2.1.$0^{1,6}$]DODECANE
PING SYSTEM

By

John W. Patterson, Jr.

The ascending importance of the tricyclo[6.2.1.$0^{1,5}$]undecane and the spiro[4.5]decane ring systems in sesquiterpene chemistry motivated this study in which tricyclo[7.2.1.$0^{1,6}$]dodec-6,7-ene-2,8-dione (1) is proposed as a potential intermediate for the synthesis of several naturally occurring derivatives of these two ring systems.

Three synthetic routes to the tricyclo[7.2.1.$0^{1,6}$]dodecanes were investigated. The first involved the preparation of decalone 2, which could undergo an intramolecular alkylation to give the desired skeleton. The second approach was similar in that an internal alkylation of decalone 3 was proposed for the formation of the tricyclododecane. Attempts to synthesize decalones 2 and 3 were however unsuccessful.



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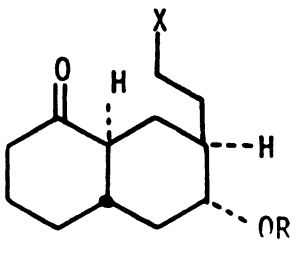

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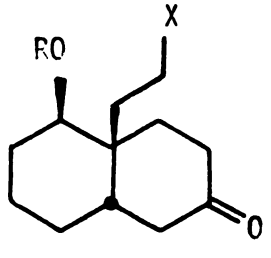

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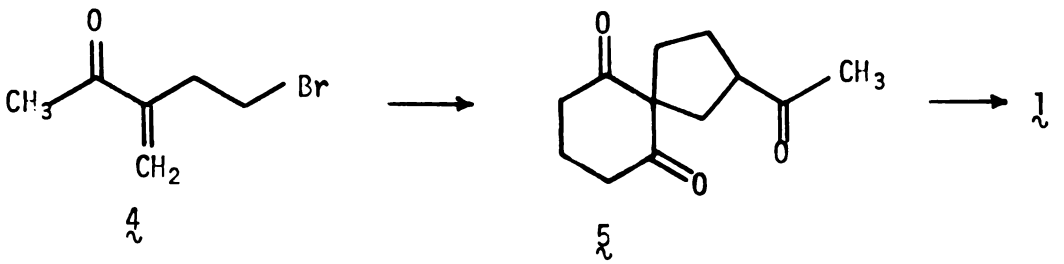
In the third route to the tricyclododecane skeleton, a bis-alkylation of cyclohexane-1,3-dione was effected with bromo-3-methylene-4-oxopentane (4) giving 2-acetylspiro[4.5]deca-6,10-dione (5). The The relatively straightforward preparation of bromo enone 4 and the conjecture that only an aldol condensation and dehydration is required to convert 5 into 1, makes this route to the tricyclo[7.2.1.$0^{1,6}$]-dodecane 1 the most promising of those investigated.



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SYNTHETIC APPROACHES TO THE TRICYCLO[7.2.1.$0^{1,6}$]DODECANE RING SYSTEM

By

John W. Patterson, Jr.

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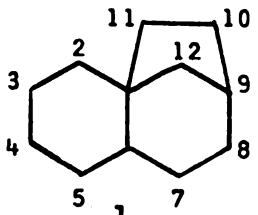
INTRODUCTION

This investigation concerns the preparation of a suitably functionalized derivative of tricyclo[7.2.1.$0^{1,6}$]dodecane (1) as a potential intermediate in the synthesis of two classes of sesquiterpenes: the spiro[4.5]decanes (2) and the tricyclo[6.2.1.$0^{1,5}$]undecanes (3). However, before discussing the synthetic methods, it is useful to survey some recent developments in the sesquiterpene field. These remarks will illustrate the type of substitution and stereochemistry present in the naturally occurring derivatives of ring systems 2 and 3.



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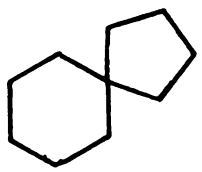

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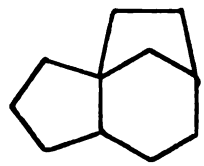

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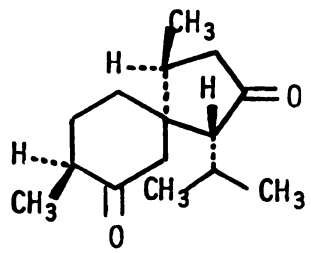
During the past several years the spiro[4.5]decane ring system has assumed a prominent place in sesquiterpene chemistry. The first example of this ring system to be reported was acorone (4)[1].



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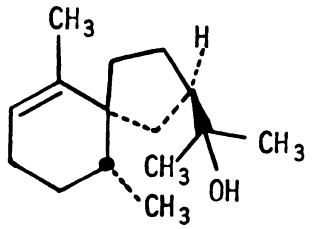
In 1965 S.C. Bhattacharyya reported[2] the isolation of agarospirol and assigned structure 5 to this compound. Classical degradation and spectroscopic analysis were used to establish the gross structure of agarospirol. Independent synthesis of the spiro ketone 6 and comparison of this with the same compound derived from agarospirol revealed only

minor differences attributable to the stereochemical nonhomogenity of the synthetic material. However the stereochemistry shown in structure 5 was deduced on tenuous arguments concerning the nmr spectra of agarospirol



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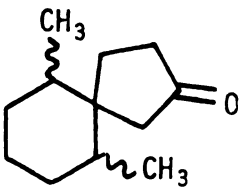

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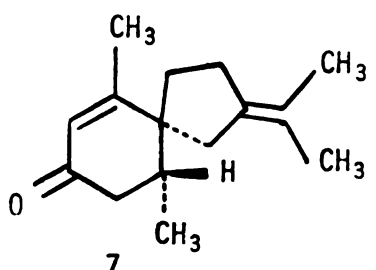
and the reactivity of its hydroxyl group.

In addition to these two new sesquiterpenes, Marshall and co-workers have demonstrated that β-vetivone (7) possesses the spiro[4.5]decane skeleton. This was accomplished by first synthesizing[3] the three epimeric 6,10-dimethyl-cis-decahydroazulene-8-ones (8) and observing each to be different from desisopropylidenedihydro-β-vetivone. Revision of the azu-



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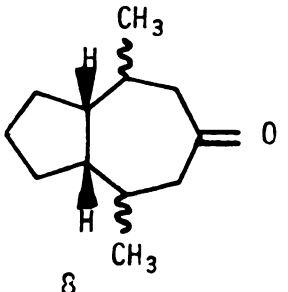

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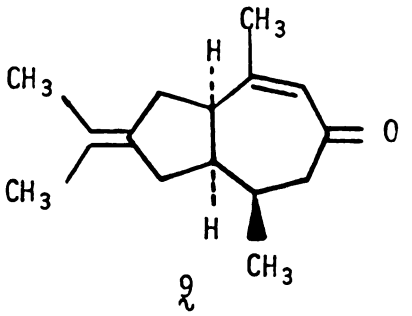

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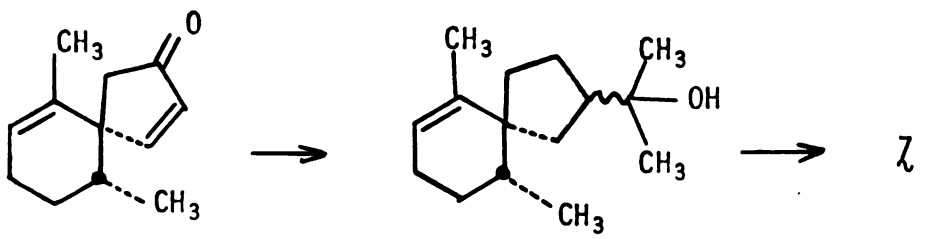
lenic structure 9 previously assigned to β-vetivone is therefore required. The original degradative studies on β-vetivone were also consistent with structure 7, proposed by Marshall, and this structure was confirmed by correlation of β-vetivone with a synthetic spiro[4.5]decane of known stereochemistry[4].

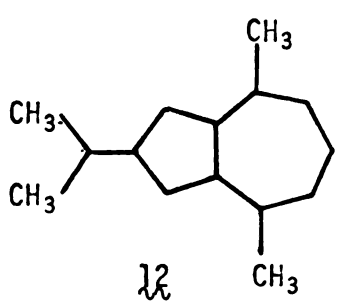
A total synthesis of β-vetivone has been reported[5], beginning with the known spiro[4.5]decadienone 10. Several rather obvious steps transformed this into compound 11 (mixture of C_2 epimers). One of the epimers

is hinesol and the other may have been agarospirol. Marshall and his co-workers were, however, unable to determine the stereochemistry at C_2. This mixture was converted to β-vetivone by a known procedure, involving oxidation of the allylic methylene group and dehydration of the alcohol.



10 11

A significant feature of this work on β-vetivone is that it requires revision of the structures of all the sesquiterpenes correlated to isovetivane (12). Among these are hinesol (13)[6], bicyclovetivenol[7], the isovetivenenes (14)[8], and acorenone (15)[9].



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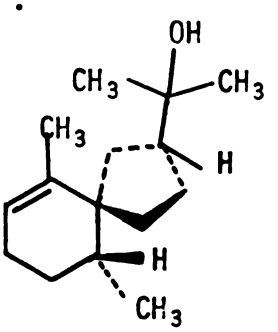

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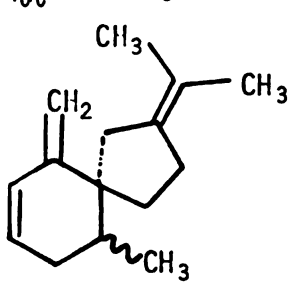

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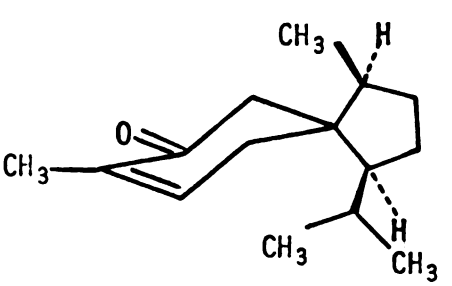

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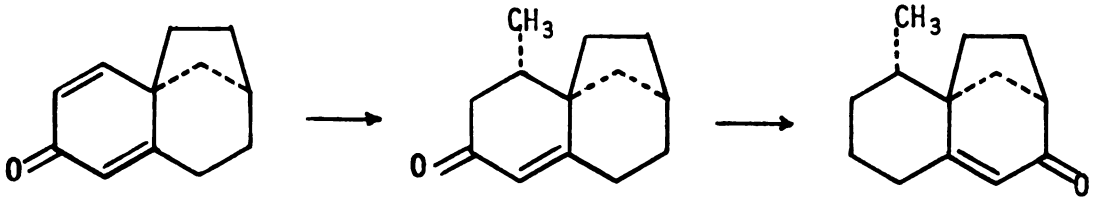
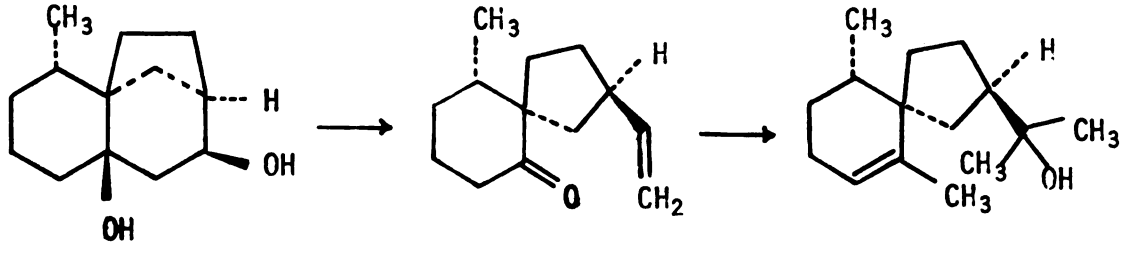
As mentioned above, during the course of the β-vetivone synthesis a stereoisomeric mixture of alcohols 11 was obtained. One of these must

have been hinesol. Very recently Marshall and Brady have synthesized hinesol (13) by an unambiguous route[10]. Reaction of the known tricyclic



16 17 18

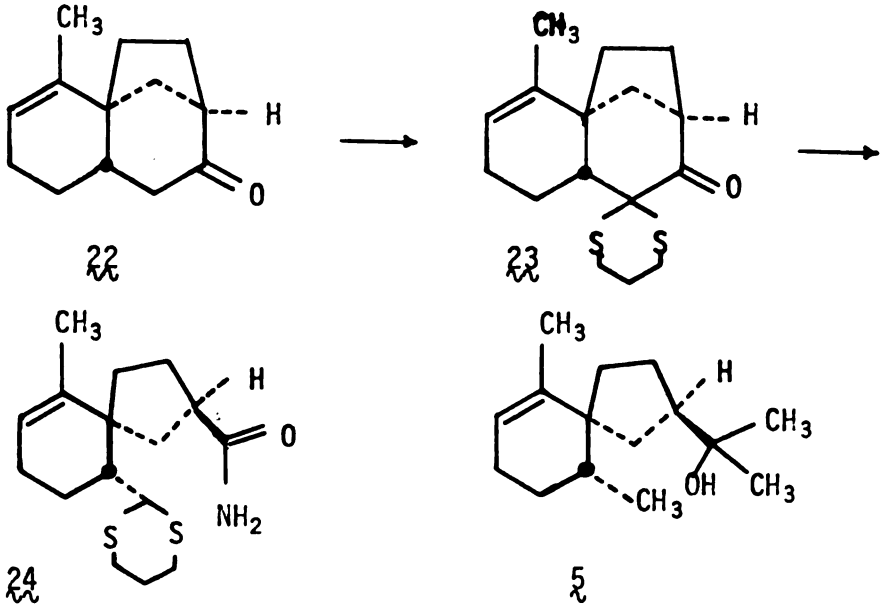


19 20 21

dienone (16) with dimethyl copper lithium introduced the C_2 methyl group, but the desired epimer (17) constituted only 20 percent of the mixture. In several steps the carbonyl was transposed to C_8 and the enone was converted to diol 19. The secondary hydroxyl was converted to a methane sulfonyl ester and fragmentation gave the unsaturated ketone 20 which was converted to hinesol. X-ray crystallographic analysis was used to establish the stereochemistry of 17, and that in conjunction with the synthetic route requires hinesol to have configuration 13.

Although Marshall's work on hinesol was successful, it has several imperfections: introduction of the C_2 methyl in 17 gave predominantly the wrong isomer, and the ketone carbonyl was in the wrong position necessitating a tedious transposition to C_8. Scheme 1 outlines a possible route to agarospirol (and hinesol) employing a suitably functionalized tricyclo[7.2.1.$0^{1,6}$]dodecane intermediate.

Scheme 1:

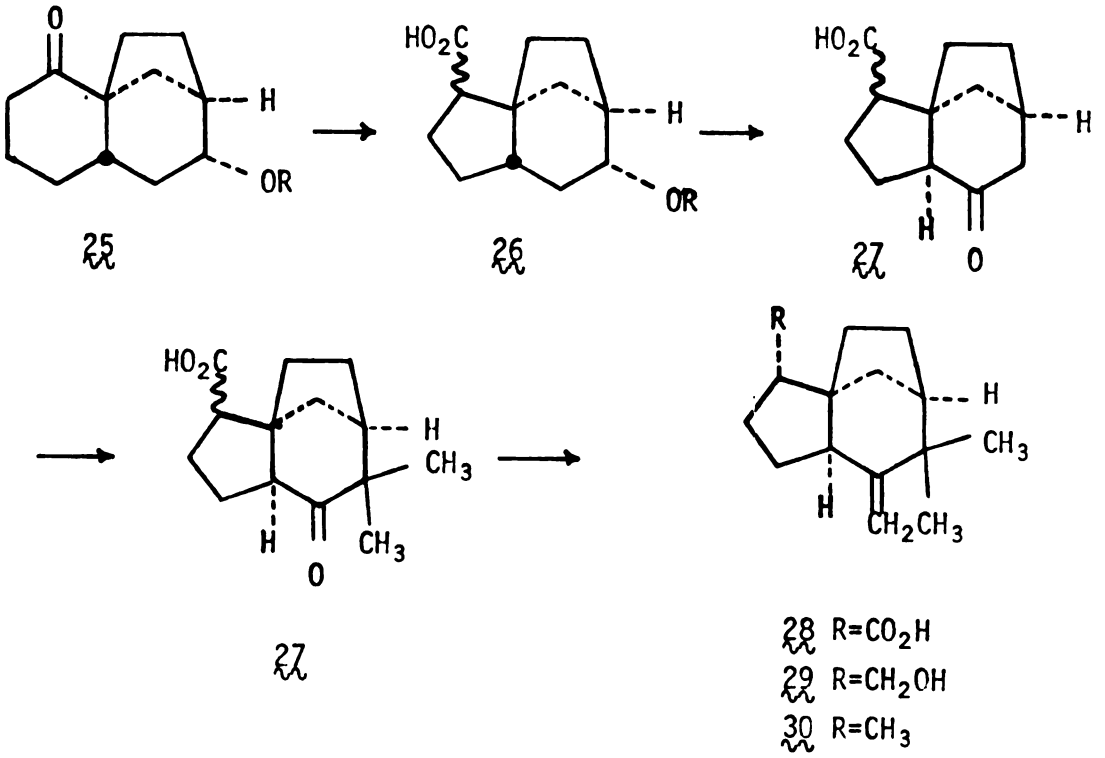


The essential features of this approach are: introduction of a thioketal α to the carbonyl of 22, Haller-Bauer type cleavage yielding 24, desulfurization of the resulting thioacetal and finally introduction of the two remaining methyl groups.

The second class of sesquiterpenes for which the tricyclo[7.2.1.$0^{1,6}$]-dodecanes serve as potential precursors possess the tricyclo[6.2.1.$0^{1,5}$]-undecane ring system. The first three members of this group have recently been reported: zizanoic acid (28),[11] zizaene (29)[12] and khusimol (30)[11]

Scheme 2 outlines a short reaction sequence by which 25 could be transformed into zizanoic acid. Bromination α to the carbonyl followed by Favorskii rearrangemnt should give the carboxylic acid 26. Transposition of the carbonyl and α-dimethylation generates 27 and introduction of the methylene group via a Wittig-type reaction forms zizanoic acid.

Scheme 2:



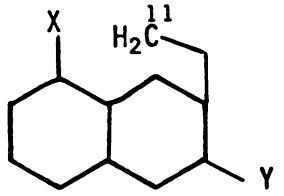
25 26 27

27

28 R=CO_2H
29 R=CH_2OH
30 R=CH_3

Having established the potential synthetic usefulness of 2,8-difunctionalized tricyclo[7.2.1.$0^{1,6}$]dodecanes , let us now consider some synthetic approaches to these intermediates. A useful technique in planning the synthesis of a polycyclic compound is to consider the structures formed by breaking bonds in such a way as to reduce the number of rings. Hopefully these structures with fewer rings can be synthesized in such a manner as to permit subsequent closure of the ruptured bond. This technique leads to many different approaches to the tricyclo[7.2.1.$0^{1,6}$]dodecane ring system. For example, cleavage of the C_1-C_{11}, C_9-C_{10} or C_6-C_7 bonds generates the bicyclic systems 31, 32 and 33. In order to reform the broken bonds, it will be necessary to introduce appropriate sites of reactivity (i.e. functional groups) into these bicyclic ring systems.

Two general and widely used methods of forming carbon-carbon bonds are the alkylation of ambident enolate ions and aldol type condensations. If C_{11} of structure 31 is bonded to a



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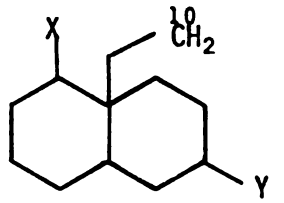

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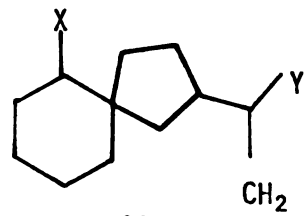

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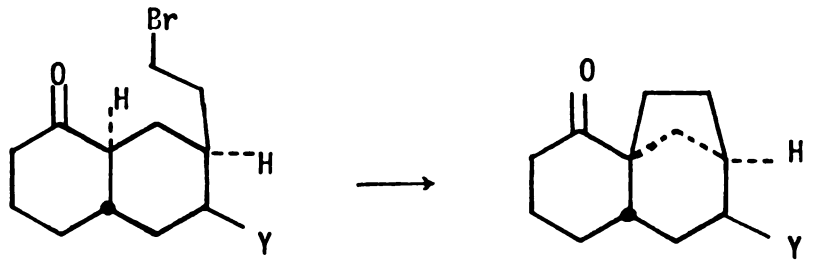
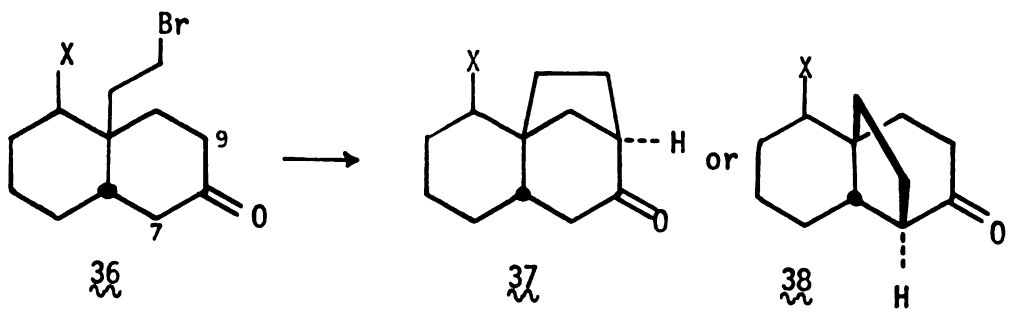
nucleophilic leaving group and the group X is a carbonyl group then an intramolecular alkylation could be used to close the broken bond as shown in equation 1. Synthesis of intermediate 34 having the C_6 hydrogen cis



34 35 (Eqn 1)

to the C_9 side chain insures that the stereochemistry of the alkylation product will be that shown in structure 35.

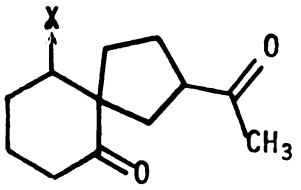
Similarly, the ruptured bond of 32 can conceivably be closed via alkylation. The necessary intermediate in this case is compound 36, which could cyclize to either 37 or 38. A considerable body of literature



36 37 38

suggests that cis-decalones such as 36 preferably enolize to C_9 rather than C_7, thus 37 is a reasonable product from internal alkylation.

In the case of the spirodecane 33 an aldol condensation could provide a convenient means of closing the final bond. Thus, an intermediate of type 39 should give the desired tricyclic product.



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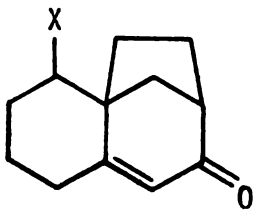

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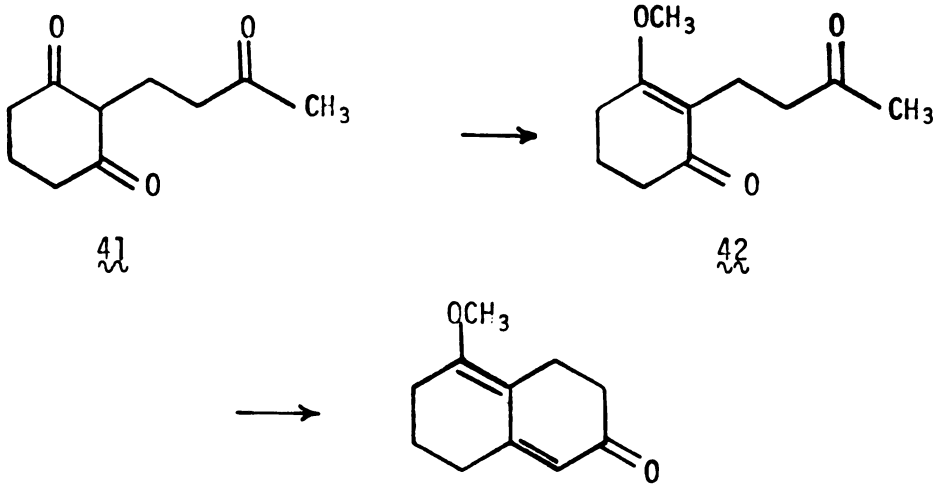
Synthetic routes to the intermediates 34, 36 and 39 have been investigated in detail and are the subject of this dissertation.

RESULTS AND DISCUSSION

The first approach to the tricyclo[7.2.1.$0^{1,6}$]dodecane ring system is based on the work of I.N. Nazarov[13] depicted in Scheme 3. According to the Russian workers, condensation of cyclohexane-1,3-dione with methyl vinyl ketone in the presence of potassium carbonate gave the triketone 41. Since the β-diketone moiety existed primarily in the enol form, reaction with diazomethane produced the enol ether 42. On treatment with potassium t-butoxide this enol ether underwent an intramolecular aldol condensation, followed,by dehydration generating the methoxy dienone 43.

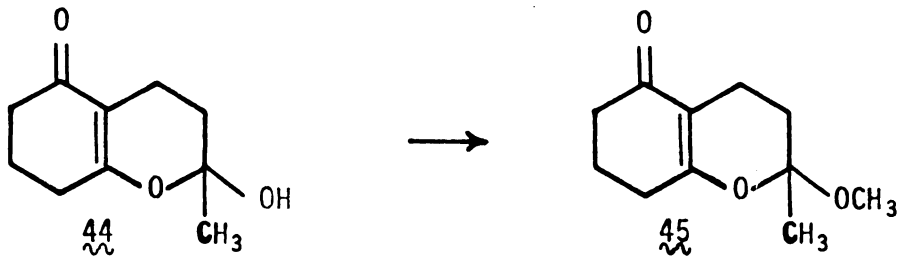
Scheme 3:



41 42 43

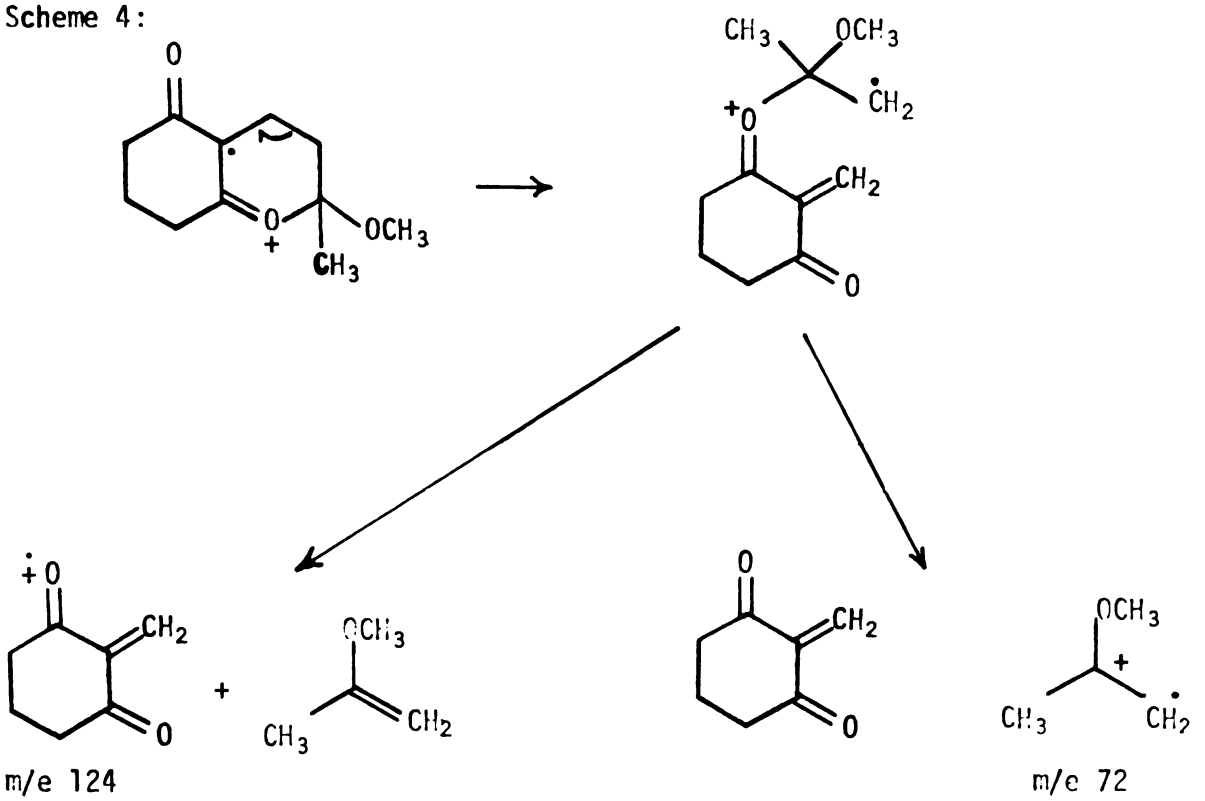
A repetition of Nazarov's work gave in one experiment an isomeric product, hemiketal 44. This hemiketal was acidic, i.e. soluble in aqueous sodium bicarbonate, and reacted with diazomethane to give the bicyclic ketal 45. The structure of the bicyclic ketal followed from its spectral

properties. The nmr spectrum exhibits two singlet methyl groups at τ 6.77 and 8.56; the ultraviolet spectrum has a maximum at 257 mμ (ε=15,400); and the infrared spectrum shows strong absorption at 1650 and 1625 cm^{-1},



indicative of an αβ-unsaturated carbonyl group, but lacks any absorption attributable to a methyl ketone. In addition, the mass spectrum of 45 has ions at m/e 196, 124 and 72. These are consistent with the fragmentation of the parent ion as shown in Scheme 4.

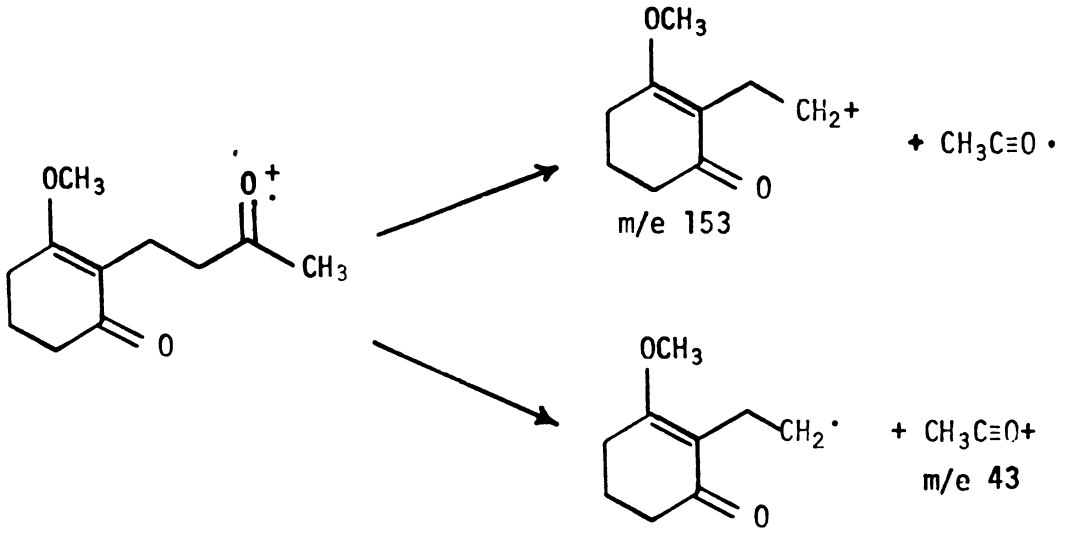
Scheme 4:



m/e 124 m/e 72

In contrast to these observations, the enol ether 42 shows a saturated methyl ketone in the infrared spectrum and has mass spectral

ions at m/e 196, 153 and 43, which are consistent with simple α-cleavage of the methyl ketone as shown in Scheme 5. In this case m/e 43 is the base peak, a common feature in many methyl ketones. This fragmentation Scheme 5:



is supported by a metastable peak at m/e 119.5, which corresponds to a m/e 196 → m/e 153 ion decomposition. The nmr spectrum of the monocyclic enol ether 42 showed an interesting solvent effect. In CCl_4 or d_6-dimethyl sulfoxide the methylene groups in the 3-oxobutyl side chain appeared as a four-proton singlet at τ 7.67; however, in pyridine these methylene groups were split into a complex multiplet.

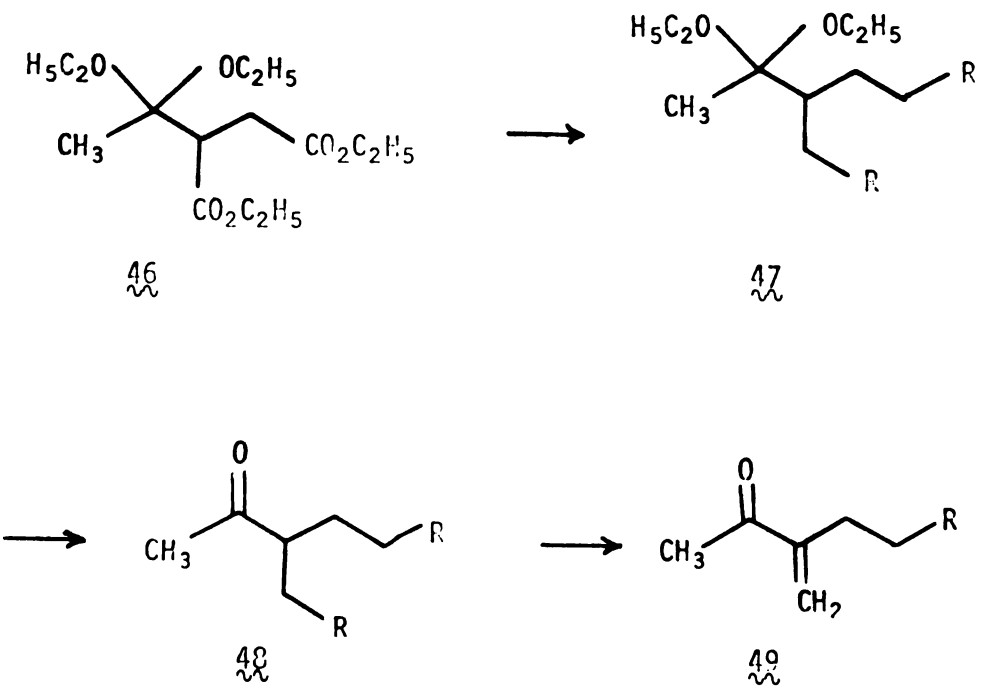
These two isomeric enol ethers possess chemical behavior which is in agreement with the assigned structures. Compound 42 undergoes an aldol condensation and dehydration to yield 43 on treatment with potassium t-butoxide as reported by Nazarov, whereas 45 is inert to this reagent.

In general, glpc analysis of the enol ether mixture obtained by Nazarov's procedure indicated 5-10 percent of the bicyclic ether 45,

and the high yield of 45 observed in the first experiment could not be reproduced.

The application of Nazarov's work to the synthesis of the desired tricyclododecane requires a substituted methyl vinyl ketone such as 49, R=$OCOCH_3$. This has been prepared by the route shown in Scheme 6.

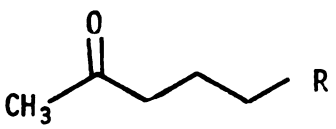
Scheme 6:



Ketal diester 46 was prepared[14] from acetyl diethyl succinate. Reduction with lithium aluminum hydride gave the ketal diol 47, R=OH. On treatment with acetic anhydride in pyridine the diol was converted to the diacetate 47, R=$OCOCH_3$, which could be hydrolysed to the keto diacetate 48, R=$OCOCH_3$, by shaking a chloroform solution of the ketal with 10 percent hydrochloric acid. Distillation of this keto diacetate from triethanolamine (at 2 mm pressure) occurred with elimination of the acetoxy group β to the carbonyl function, giving the acetoxy enone 49,

R=$OCOCH_3$. Without purification of the intermediates, acetyl diethyl succinate can be converted to the unsaturated ketone 49, R=$OCOCH_3$, in 65 percent overall yield.

It should be pointed out that a more obvious route to enones of type 49, namely synthesis of ketones of type 50 followed by introduction of the C_3 methylene, was also investigated. A classical method for



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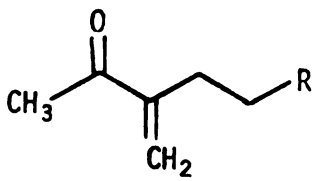


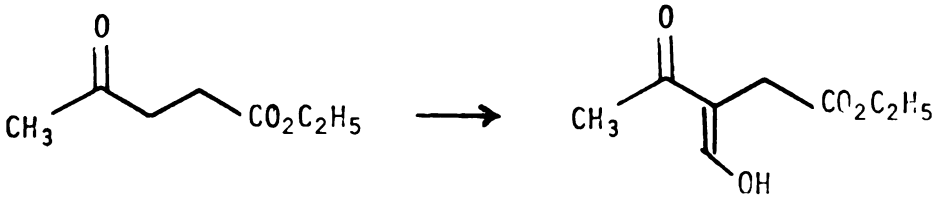
49

introduction of a methylene α to a carbonyl is the aldol condensation with formaldehyde followed by dehydration. Many examples of this type of reaction have been reported and suggest that condensation usually occurs on the methylene side of a methyl ketone. However, examination of the experimental procedures reveals the majority of them to involve commercially available ketones which reacted with only 0.1 - 0.3 equivalents of formaldehyde. This is necessary to avoid multiple condensations but severely limits the yield. Landon[15] in a detailed study of the condensation of 2-butanone and formaldehyde found use of 0.2 equivalents of formaldehyde resulted in the maximum yield of 2-methyl-1-butene-3-one.

Another common means of introducing a methylene group is the Mannich condensation. As reported by Hagermeyer[16], this condensation proceeded at C_3 of 2-butanone in good yield. Unfortunately, pyrolysis of the hydrochloride salt of the β-amino ketone under a variety of conditions gave considerable 2-butanone in addition to the desired

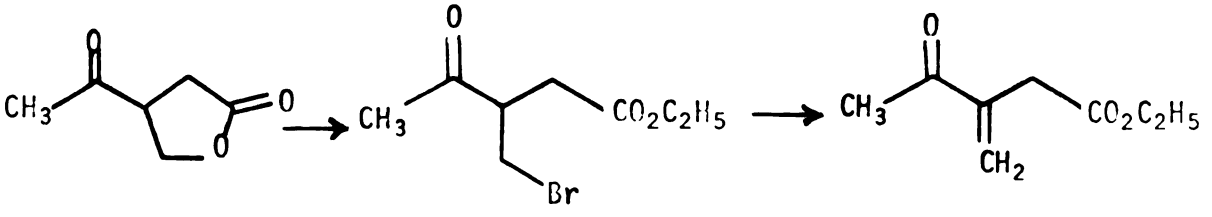
2-methyl-1-buten-2-one. Since these two products were difficult to separate by distillation, it was concluded that the Mannich condensation would be of little use in the synthesis of 49.

Several promising condensations with levulinic acid have been described. For example, the Claisen condensation between ethyl formate and ethyl levulinate is reported[17] to occur at the methylene group α to the ketone carbonyl; however, several attempts to repeat this reaction have failed. The Mannich reaction with levulinic acid gave condensation



at both sides of the ketone carbonyl[18], the two products being separable by crystallization. In the present study several repetitions of this experiment gave primarily condensation at the methyl group.

The enone ester 51 has been prepared[19] by a circuitous route beginning with acetyl diethyl succinate and proceeding thru 3-acetyl butyrolactone[20].



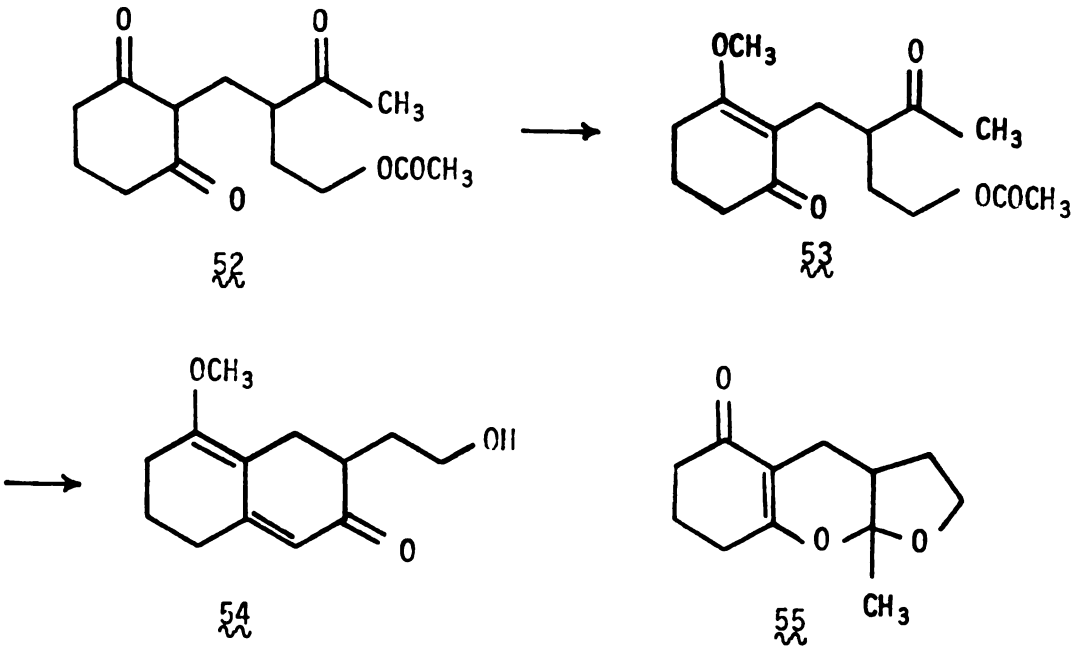
51

In view of the fact that the enones sought here are to be used in a Michael condensation requiring base catalysis, enone 51 is of questionable utility because of the possibility of isomerization to the fully conjugated isomer. For this reason the Michael condensation of 51 with cyclohexane-1,3-dione was not investigated.

The acetoxy enone 49, R=$OCOCH_3$, reacted with cyclohexane-1,3-dione

and a catalytic amount of potassium carbonate to give the mono Michael addition product 52 in higher yield than the corresponding product from methyl vinyl ketone. This can be attributed to the steric hindrance of the β-acetoxyethyl side chain of 52 which inhibits the formation of the bis-adduct. As in the model system, treatment of the Michael adduct 52 with diazomethane gave the enol ether 53. However aldol condensation dehydration of 53 with potassium t-butoxide led to approximately equal amounts of two products.

Scheme 7:

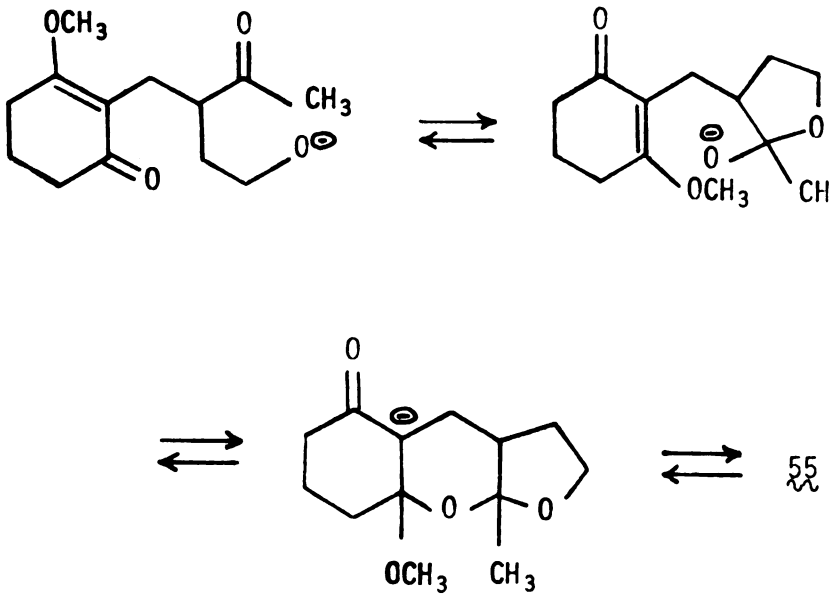


One of the products (54) is analogous to that obtained in the model system. The other product was assigned structure 55 on the basis of its spectral properties and elemental analysis. The infrared spectrum showed that no hydroxyl was present and absorptions at 1665 and 1635 cm^{-1} were characteristic of an enone system. This chromophore was further identified by its absorption maximum at 259 mμ (ε=16,800) in the ultraviolet spectrum. A singlet methyl signal at τ 1.88 and a two-proton multiplet

at τ 5.9-6.3 in the nmr spectrum (the remainder of the protons being an unresolved multiplet at τ 7.5-8.2) agree with structure 55. A strong parent ion appears in the mass spectrum at m/e 208 and two rearrangement ions are observed at m/e 124 and 84 (base peak). The latter two ions could arise via the same type of fragmentation observed for enol ether 45, shown in Scheme 4.

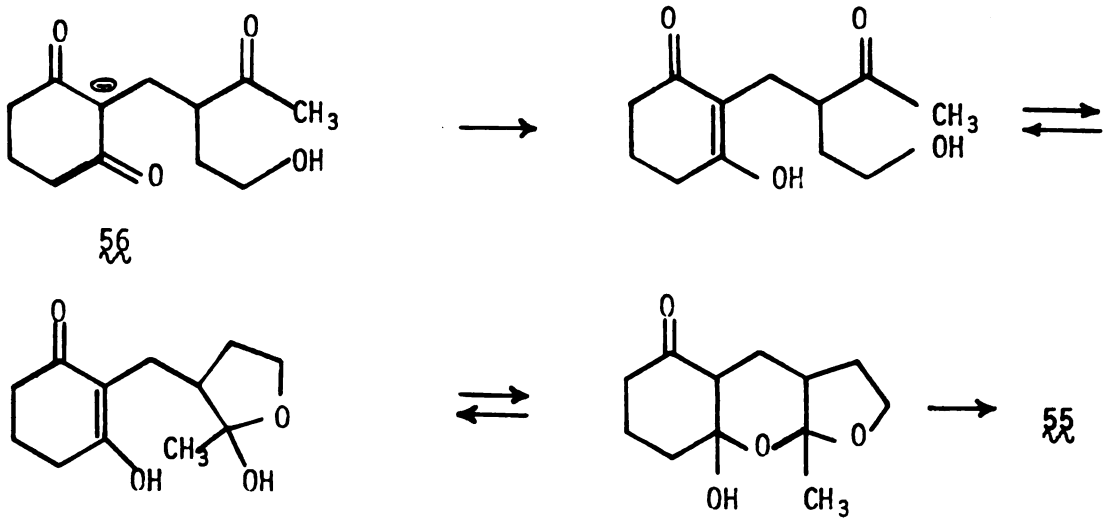
A reasonable mechanism for the formation of 55 is illustrated in Scheme 8. This mechanism involves solvolysis of the acetate and cyclization of an intermediate hemiketal.

Scheme 8:



Indeed, tricyclic ether 55 could be prepared in good yield by basic hydrolysis of the acetate of 52 to give an aqueous solution of anion 56, which on acidification gave 55. Scheme 9 illustrates a a reasonable mechanism for the formation of 55 under acid catalysis.

Scheme 9:



56

55

If this mechanism for the formation of 55 is valid, then this undesireable side reaction can be blocked by replacement of the acetate with a protecting group which is inert to nucleophilic bases.

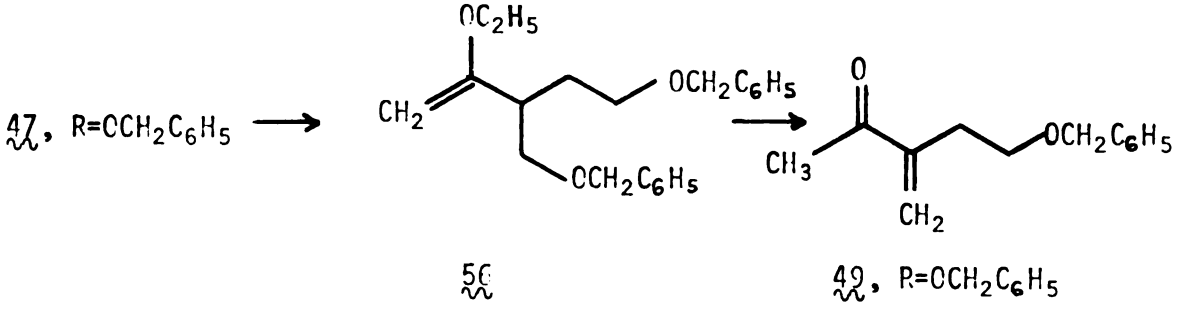
To this end the pivalic ester 49, R=$OCOC(CH_3)_3$, was prepared by a procedure completely analogous to that for preparation of acetate 49, R=$OCOCH_3$. This enone was used to synthesize the pivalic ester anologue of 53. Unfortunately, the aldol condensation again gave a mixture of 54 and 55.

Ethers are known to be resistent to basic reaction conditions and the benzyl ether protecting group was next investigated. Ketal diol 47, R=OH, reacted with benzyl chloride in the presence of sodium hydride in dimethyl sulfoxide to give the ketal dibenzyl ether 47, R=$OCH_2C_6H_5$. The keto dibenzyl ether 48, R=$OCH_2C_6H_5$, was then obtained by mild acidic hydrolysis of the diethyl ketal. Unfortunately compound 48,R=$OCH_2C_6H_5$, failed to eliminate the benzyloxy group β to the carbonyl group to yield 49, R=$OCH_2C_6H_5$, on distillation from triethanolamine.

An attempt to generate the benzyloxy enone 49, R=$OCH_2C_6H_5$, <u>in situ</u>

and to trap it by Michael addition to cyclohexane-1,3-dione was then made[21]. In this experiment a mixture of the dibenzyl ether 48, R=$OCH_2C_6H_5$, and cyclohexane-1,3-dione were treated with potassium t-butoxide, however the dibenzyloxy ketone merely decomposed giving an intractable black oil as the neutral product along with a nearly complete recovery of the cyclohexane-1,3-dione as the sole acidic product.

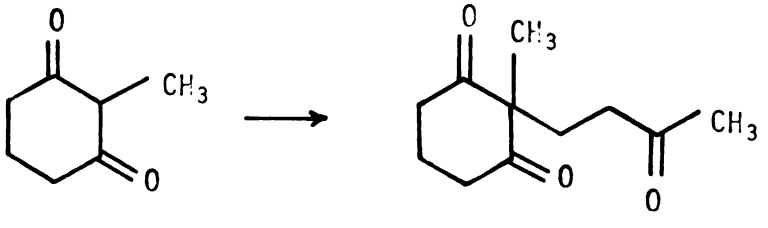
In one experiment, distillation of the ketal dibenzyl ether 47, R=$OCH_2C_6H_5$, resulted in elimination of ethanol, producing the enol ether 56. Mild acidic hydrolysis of the enol ether function resulted in concomitant elimination of benzyl alcohol giving the enone 49, R=$OCH_2C_6H_5$.

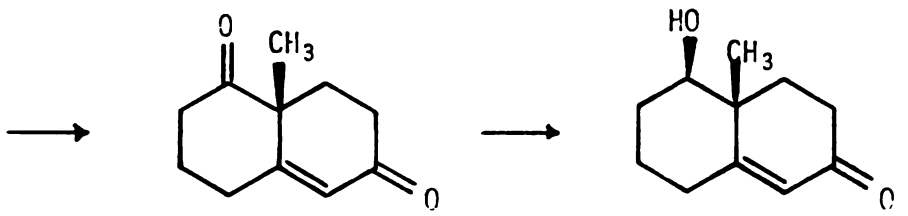


56 49, R=$OCH_2C_6H_5$

This later success was obtained only recently and other approaches to the tricyclododecanes have been investigated.

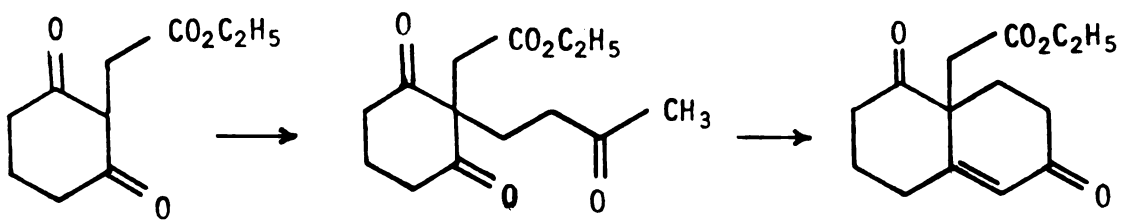
The second approach to the tricyclo[7.2.1.$0^{1,6}$]dodecane ring system to be described here is based on the synthesis[22] of 4a-methyl-4,4a,7,8-tetrahydronaphthalene-2,5(3H,6H)-dione (57) and its selective reduction to 4aβ-methyl-4,4a,5,6,7,8-hexahydronaphth-5β-ol-2(3H)-one (58)[23].





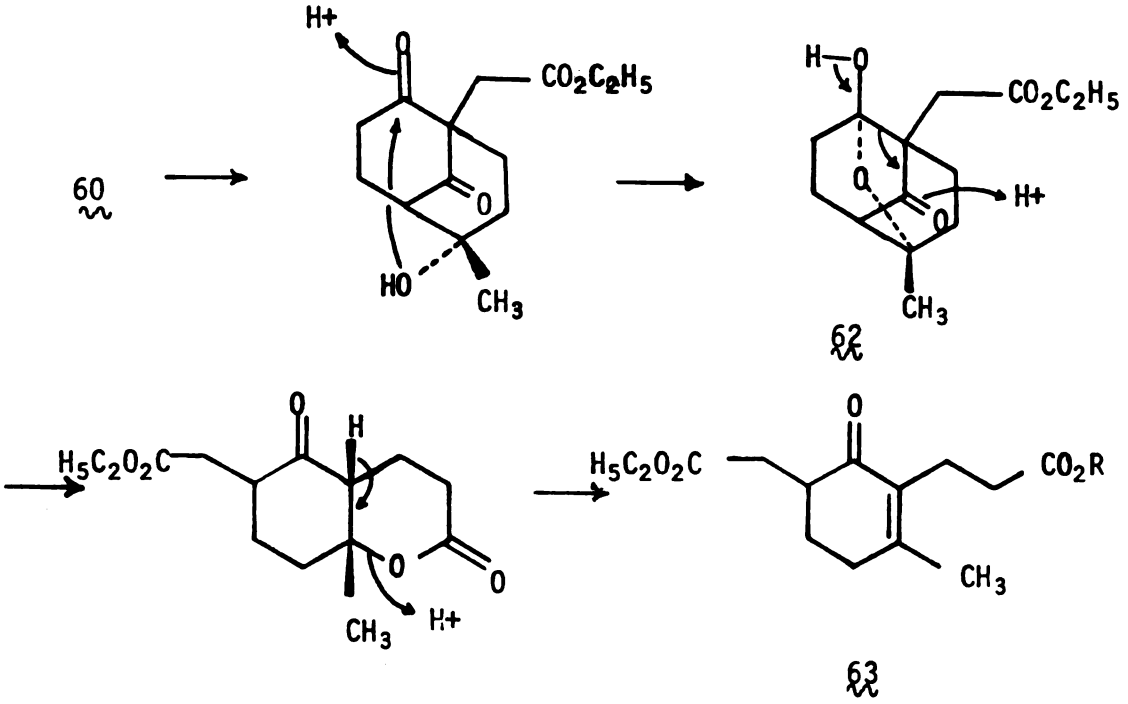
57 58

This reaction sequence was applied to the synthesis of decalin 36 by effecting a base catalysed Michael addition of the readily available 2-(2'-cyclohexane-1',3'-dione)-acetic acid ethyl ester (59)[24] to methyl vinyl ketone.



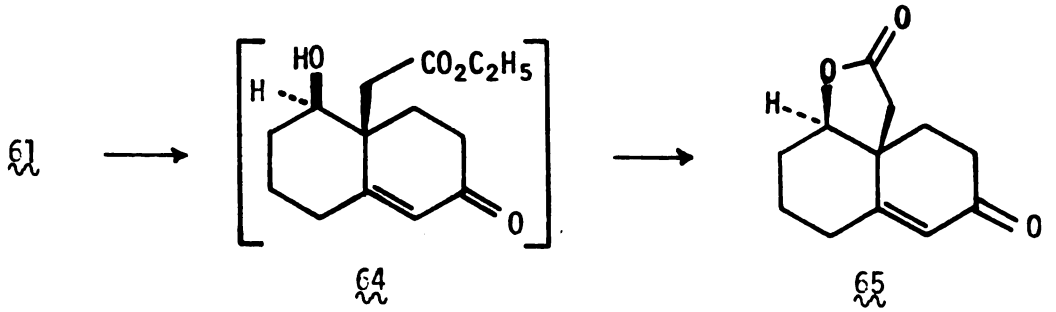
59 60 61

The desired intramolecular aldol condensation-dehydration of the adduct 60 proved to be elusive, since 60 gave a variety of products depending on the catalyst employed. Thus, a catalytic amount of pyrrolidine in refluxing benzene (the conditions used in the preparation of 57) gave only recovered starting material, while p-toluenesulfonic acid in refluxing benzene gave enone 63, R=H. The bicyclo-[3.3.1]nonane ketol 62 is thought to be a reasonable intermediate in this latter reaction, as acid catalysed aldol condensations of 2-(3'-oxobutyl)cyclohexanones frequently yield 2-hydroxy-9-oxo-2-methylbicyclo[3.3.1]nonanes as the isolated product[25].

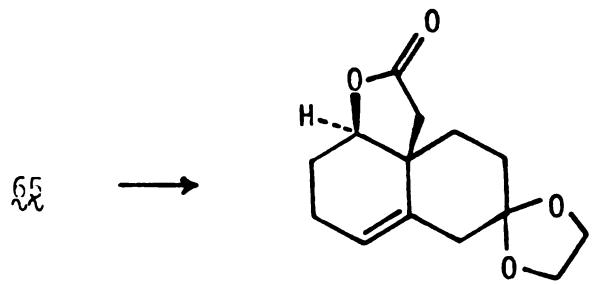


The desired aldol condensation and dehydration to the enedione 61 was ultimately achieved in 60 percent yield by using 1.1 equivalents of a 1:1 mixture of pyrrolidine and acetic acid at room temperature. Due to the instablity of 61 toward oxygen, the structure assignment was based on its spectroscopic properies and the characteristic reactions discussed below.

Reduction with a 10 percent excess of sodium borohydride converted enedione 61 to the enone lactone 65. The cis relationship of the hydroxyl and methylcarbethoxy groups in structure 64 was inferred from the spontaneous lactonization of this intermediate hydroxy ester 64.

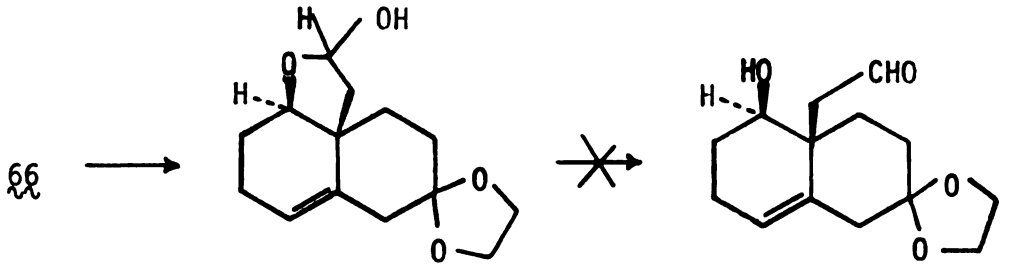


The enone lactone 65 was transformed in high yield to an ethylene ketal derivative 66. The migration of the double bond to the 8,8a-position is normal and is supported by spectroscopic evidence. In the nmr spectrum of the enone 65 the vinyl proton is a singlet with a half-height width of 3 cps, whereas in the ethylene ketal the vinyl proton is a very broad signal with a width of 10 cps. This large increase in the spin-spin coupling suggests that the double bond moves to the $\Delta^{4,4a}$ position. In addition the infrared stretching frequency of the lactone carbonyl in the ketal is 25 cm^{-1} higher than in the enone. Examination of molecular models reveals that shifting the double bond increases the strain in the five-membered lactone ring and therefore increases the carbonyl stretching frequency.



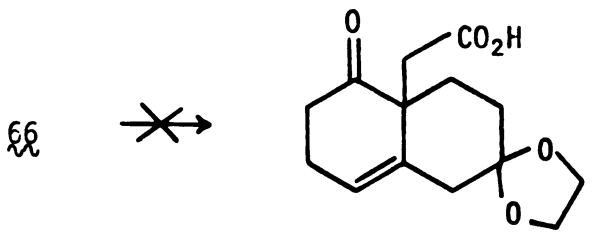
65 → 66

In order for lactone 66 to be a useful intermediate in this synthesis, the lactone ring must be opened in such a way that the terminal carbon atoms can be chemically distinguished. An ideal solution would leave the terminal carbons in different oxidation states, and to this end two methods were investigated. The first was founded on the report[26] that disiamylborane reduces γ-lactones to hydroxy aldehydes. However, when ketal lactone 66 was reduced with this reagent, the intermediate cyclic hemiacetal could not be induced to open to the hydroxy aldehyde 67.



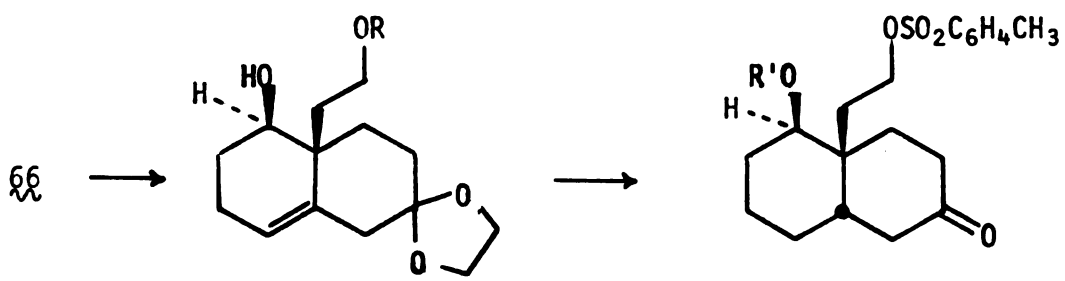
66 67

In the second approach, oxidation of the ketal lactone with Sarett's reagent did not generate the keto acid 68, but gave instead recovered starting material at room temperature and intractable tars at higher temperatures.



66 68

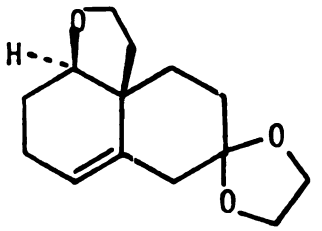
Although these attempts at selective lactone opening were unsuccessful, reduction of 66 to diol 69, R=H, was accomplished in good yield by action of lithium aluminum hydride. Since primary alcohols are generally more reactive than secondary alcohols, the prospect of selective esterification of the former appeared promising. In particular, conversion of the diol into a mono-tosylate derivative (69, R= $SO_2C_6H_4CH_3$) would set the stage for further development of this system.



66 69 70

However, the two hydroxyl groups in diol 69, R=H, are close together; consequently the hydroxy tosylate 69, R=$SO_2C_6H_4CH_3$, could not be isolated, but was rapidly transformed to the ether 71.

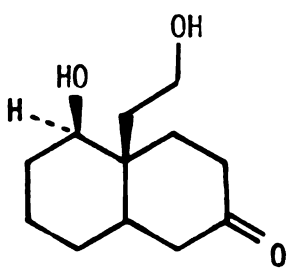
69, R=H ⟶ 69, R=$SO_2C_6H_4CH_3$ ⟶



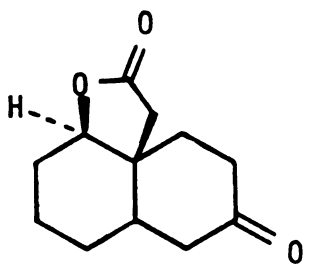
71

This interference by the secondary hydroxyl group necessitated a lengthy subterfuge beginning with protection of the primary hydroxyl as a less reactive ester. Although 69, R=H, reacted with 1.1 equivalents of p-nitrobenzoyl chloride to give the mono ester 69, R=$COC_6H_4NO_2$, the yield was a disappointing 47 percent and hence this route was not pursued.

Another possible method for opening the lactone ring is the Birch reduction, which should simultaneously reduce the enone moiety producing keto diol 72. However in the case of enone lactone 65 it was found that



72



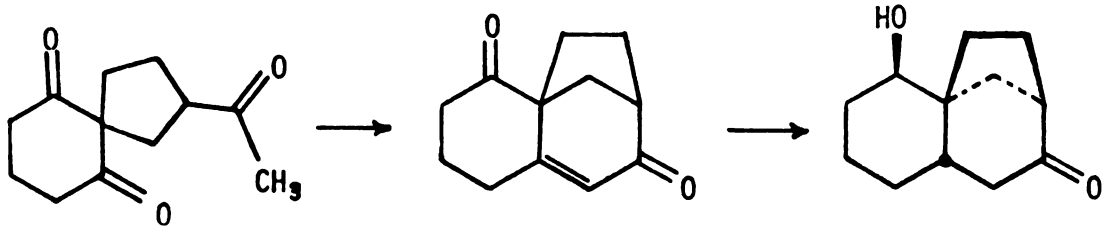
73

although the enone system was rapidly reduced, the lactone ring opened very slowly. Thus, it was possible to obtain keto lactone 73 in 61 percent yield by employing a short reaction period; however, the keto diol 72

could not be obtained as a pure crystalline compound even after extended reaction times.

The difficulties experienced in differentiating the two hydroxyl groups in conjunction with the growing length of this route raised serious doubts with respect to its usefulness in the preparation of the desired tricyclododecane intermediate.

The third general route to the tricyclo[7.2.1.$0^{1,6}$]dodecane ring system involves initial formation of the spiro[4.5]decane 75 followed by aldol condensation and dehydration to 76. In this approach the aldol condensation—dehydration sequence serves two purposes: first, it removes one of the cyclohexanone carbonyls, permitting reduction of the other; second, reduction of the enone moiety of 76

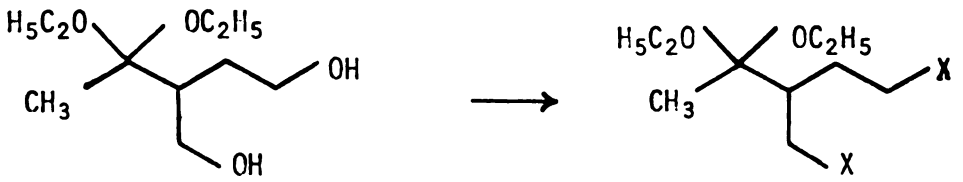


75 76 77

allows control of the stereochemistry at C_6 in 77 which becomes C_{10} in agarospirol. The directness of this approach justifies the detailed investigation of the various bis-alkylations of cyclohexane-1,3-dione described below.

The diol 47, R=OH, which was described in an earlier section, appeared to be a suitable precursor for dihalides of type 78. However, the usual reagents for converting alcohols to halides, e.g. thionyl chloride and phosphorous tribromide, transformed 47 into dark oily products which contained no volatile compounds. Consequently, the

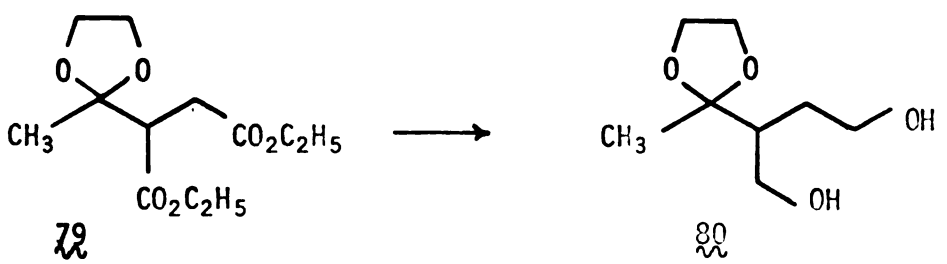
reaction of butane-1,4-diol with thionyl chloride was examined as a model. In contrast to the vigorous conditions reported for the conver-



47 78

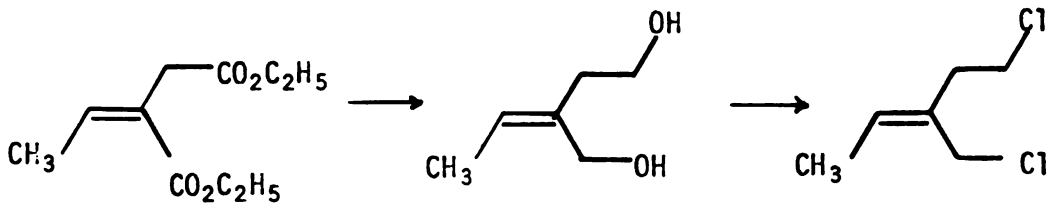
sion of this diol to 1,4-dichlorobutane[27], it was possible to obtain an 80 percent yield of the dichloride under very mild conditions. Even these mild conditions, however, failed to effect a similar transformation with diol 47, P=OH, suggesting that the acidic reaction conditions resulted in hydrolysis of the labile diethyl ketal protecting group and subsequent decomposition of the β-halo ketone. Since 1,3-dioxolanes are considerably more stable to acid treatment, this protective group was investigated next.

Acetyl diethyl succinate was converted to its 1,3-dioxolane derivative (79) by the usual procedure, but in only 55-60 percent yield (presumably due to transesterification). Reduction of the ketal diester was accomplished by treatment with lithium aluminum hydride; however, the resulting diol (80) failed to give the corresponding dihalide when treated with the customary halogenation reagents.



79 80

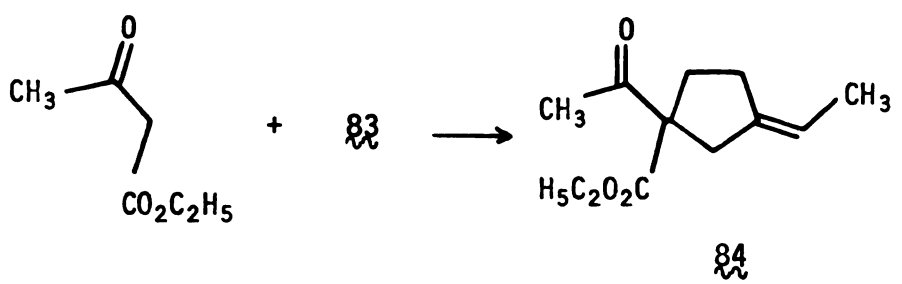
Because the ketal function in diols 47 and 80 proved to be so troublesome, the synthesis of dihalides not having this function was considered. To this end, compound 83 was prepared from ethylidine diethyl succinate[28] (81) by lithium aluminum hydride reduction to diol



81 82 83

82 followed by reaction with thionyl chloride under very mild conditions. The unstable dichloride 83 was obtained in 45 percent yield after distillation at reduced pressure and could be stored at -10° for several days. Another mild reagent for the conversion of primary alcohols to chlorides, tri-n-octyl phosphine in carbontetrachloride[29], gave a slightly lower yield of 83 from diol 82 than was obtained with thionyl chloride.

The dichloride (83) reacted with ethyl acetoacetate in the presence of two equivalents of sodium ethoxide in ethanol to give the desired bis-alkylation product 84. Although 84 was a mixture of

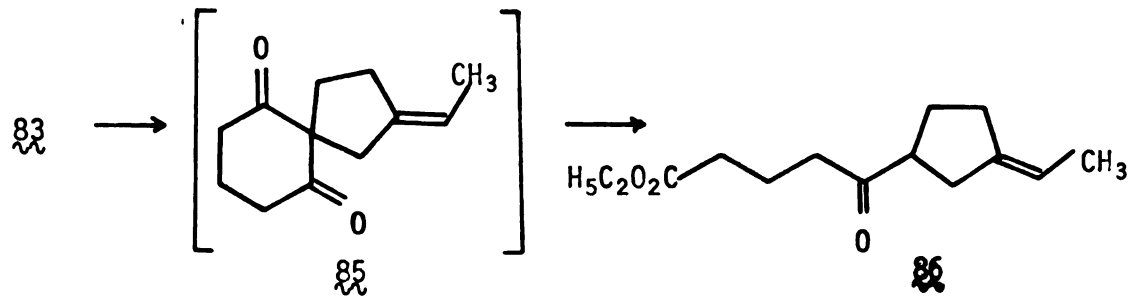


84

double bond isomers and consequently failed to give a solid derivative suitable for elemental analysis, its spectral properties were in

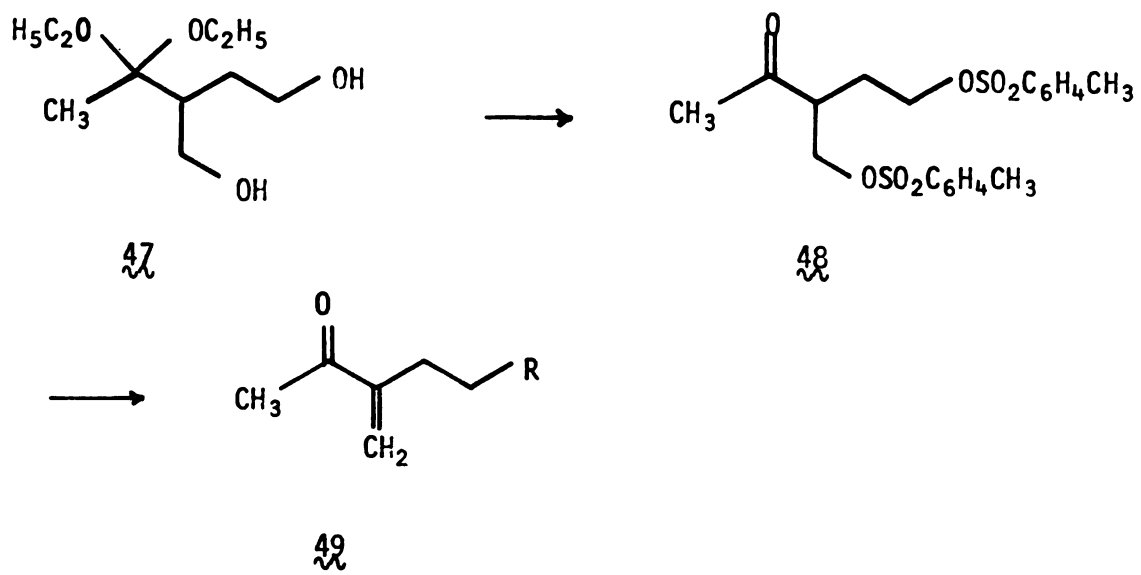
good agreement with the assigned structure.

When this bis-alkylation procedure was applied to cyclohexane-1,3-dione, the keto ester 86 was obtained as a mixture of isomers. This difficulty was not unexpected in view of the known lability of



2,2-disubstituted cyclohexane-1,3-diones toward nucleophilic cleavage. Unfortunately, the dichloride proved unreactive toward the conjugate base of cyclohexane-1,3-dione in non-nucleophilic solvents.

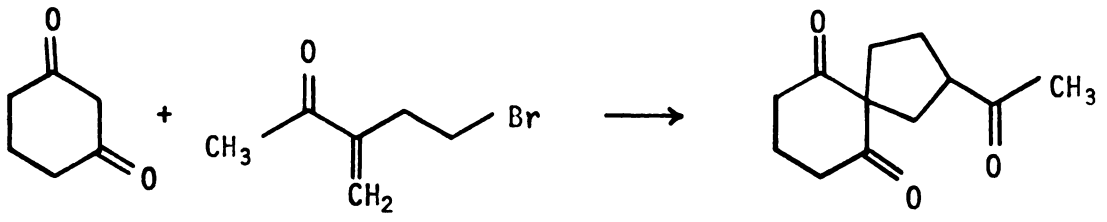
A successful bis-alkylation of cyclohexane-1,3-dione was finally accomplished with the bromo enone 49, R=Br, which was prepared from diol 47, R=OH. Thus, treatment of 47, R=OH, with p-toluenesulfonyl



chloride in pyridine followed by an acidic workup gave the unstable

keto ditosylate 48. R=$OSO_2C_6H_4CH_3$, Triethylamine at room temperature catalysed the elimination of the tosyloxy group which is β to the carbonyl function, yielding the enone tosylate 49, R=$OSO_2C_6H_4CH_3$, and the tosylate group in 49 was replaced with a bromine atom by reaction with anhydrous lithium bromide in acetone[30]. By this sequence the bromo enone 49, R=Br, was obtained in 29 percent overall yield from diol 47. Although the bromo enone was unstable , it could be distilled at reduced pressure and its spectral properties were in good agreement with structure 49, R=Br. In particular the infrared spectrum revealed an αβ-unsaturated ketone, and the nmr spectrum yielded to simple first order analysis.

The enone 49, R=Br, reacted with one equivalent of cyclohexane-1,3-dione and 1.1 equivalents of sodium hydride in 1,2-dimethoxyethane giving the spiro triketone 75. The nmr spectrum of 75 consists of a singlet at τ 7.30 for the methyl ketone and a four-proton triplet at τ 7.36 due to the two nearly equivalent methylene groups α to the carbonyl functions on the six-membered ring. The mass spectrum shows a molecular ion at m/e 208 and fragment ions at m/e 193 and 165 corresponding to loss of CH_3 and $COCH_3$ via α-cleavage of the methyl ketone. The infrared spectrum has a broad carbonyl absorption between 1715 and 1700 cm^{-1}.

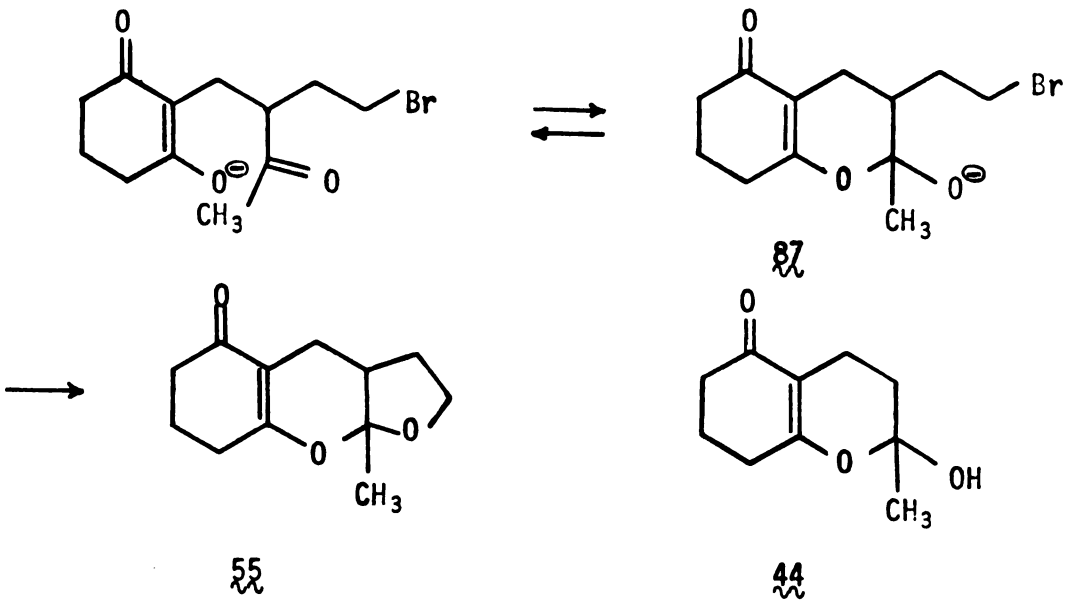


49 75

The more direct route to 75, namely using one of the three intermediate tosylates in the preparation of the brome enone 49 as a bis-alkylation reagent, was not attempted because sulfonic acid esters are known to give exclusive O-alkylation of cyclohexane-1,3-dione[31].

A minor product of this reaction between 49, R=Br, and the conjugate base of cyclohexane-1,3-dione in dimethoxyethane, and the major product when the reaction was conducted in dioxane was the tricyclic ketal 55. A plausible mechanism for the formation of 55 is shown in Scheme 10. In view of the previous study of the Michael addition

Scheme 10:



of the conjugate base of cyclohexane-1,3-dione to methyl vinyl ketone, which showed that the hemiketal 44 was soluble in aqueous sodium bicarbonate, anion 87 appears to be a reasonable intermediate in this transformation.

The relatively straightforward preparation of bromo enone 49, R=Br, and the conjucture that only an aldol condensation and dehydration is required to convert 75 into the desired tricyclododecane

76, makes this synthetic route the most promising of those investigated.

EXPERIMENTAL

General. Melting points were taken in capillary tubes on the Hoover Thomas apparatus. Infrared spectra were recorded on a Perkin-Elmer 327 B spectrophotometer in carbon tetrachloride solution, with the exception of Figure 16. Nuclear magnetic reasonance spectra were taken on a Varian A-60 spectrometer. Tetramethylsilane was used as an internal standard in all cases. The ultraviolet spectra were recorded on a Unicam SP 800 spectrophotometer. An Hitachi RM-60 spectrometer was used to obtain the mass spectra.

Absolute ethanol refers to commercial absolute ethanol further purified by distillation from magnesium ethoxide.

3-methoxy-2-(3'-oxobutyl)cyclohex-2-enone (42) and 3-methoxy-3-methyl-bicyclo[4.4.0]-2-oxadec-1,6-en-7-one (45). Repetition of Nazarov's procedure[13] for the preparation of 42 gave a mixture containing 85-90 percent of 42 and 10-15 percent of 45. A pure sample of each was obtained by preparative glpc using a 6'x1/4", 4% QF-1 column (175°). The infrared spectra are in Figures 1 and 2 (p 51), the nmr spectra in Figure 23-25 (pp 62-4) and the mass spectra in Figures 45 and 46 (pp 84, 85). As previously discussed, these spectra are in good agreement with the assigned structures.

Acetyl diethyl succinate diethyl ketal (46). This compound was prepared from the readily available acetyl diethyl succinate by the method of E. C. Kornfield[14] using the modified workup described below.

A solution of 90 g of acetyl diethyl succinate, 85 g of triethylorthoformate, 25 g of absolute ethanol and 10 drops of concentrated sulfuric acid was allowed to stand at room temperature for three days in a closed flask. The reaction mixture was cooled in an icebath and 5 ml of triethanolamine and 300 ml of methylene chloride were added. The organic phase was separated and washed twice with 100 ml of water and dried over sodium sulfate. Removal of the solvent under reduced pressure gave ketal 46 of sufficient purity for use in the next reaction, a glpc analysis (10'x1/8", 20% SE-30 column at 185°) indicated this crude product to be at least 90 percent ketal 46.

2-acetylbutane-1,4-diol diethyl ketal (47, R=OH). To a 2 l, three-necked flask equiped with a Hirshberg stirrer, calcium sulfate drying tube, condenser, addition funnel and heating mantle was added 300 ml of dry ether, 1200 ml of dry tetrahydrofuran and 22 g of lithium aluminum hydride. The crude ketal diester prepared from 90 g of acetyl diethyl succinate was dissolved in 75 ml of tetrahydrofuran and added dropwise over 90 minutes and the reaction mixture was then refluxed for two days. After cooling to room temperature, 40 ml of water and 40 ml of 5 percent aqueous sodium hydroxide were slowly added with caution to the rapidly stirred mixture. The insoluble salts were filtered, the filtrate was dried over sodium sulfate and the solvent was evaporated to give 64.2 g of diol 47, R=OH. The aluminum salts were agitated with 300 ml of methanol for one hour and filtered again. The methanol was evaporated and the residue treated with 200 ml of

ether and 5 g of sodium sulfate. Filtration and evaporation of the solvent gave another 13.0 g of diol (89 percent total yield).

The infrared spectrum (neat) of 47, R=OH, showed strong bands at 3600-3200, 3000-2875, 1448, 1380, 1230, 1130 and 1045 cm^{-1}; the nmr spectrum consisted of a two-proton singlet at τ 5.10 (hydroxyl protons), an eight-proton multiplet at τ 6.2-6.9 (protons α to oxygen atoms), a three-proton multiplet at τ 7.9-8.5 (aliphatic protons) and a nine-proton multiplet at τ 8.7-9.1 (methyl groups).

This diol could not be distilled without decomposition, but proved to be satisfactory for use in the various transformations described below.

2-acetylbutane-1,4-diol diacetate (48, R=$OCOCH_3$). To a cold solution of 77.2 g of diol 47, R=OH, in 400 ml of pyridine (ice bath) were added with stirring three 40 ml portions of acetic anhydride at 10 minute intervals. The ice bath was removed and, after standing for two hours at room temperature, the pyridine was removed by evaporation at reduced pressure. The residue was dissolved in 500 ml of chloroform and this solution was washed with 200 ml of water, 125 ml of cold 10 percent hydrochloric acid, shaken for five minutes with 125 ml of 10 percent hydrochloric acid, and finally washed with 200 ml of saturated aqueous sodium bicarbonate. After drying with sodium sulfate, the solvent was evaporated leaving 68.8 g of keto diacetate 48, R=$OCOCH_3$ (86 percent).

A pure sample of 48, R=$OCOCH_3$, was obtained for analytical purposes by glpc. The infrared spectrum (Figure 3, p 52) showed carbonyl absorptions at 1745 and 1720 cm^{-1}. The nmr spectrum (Figure 26, p 65)

displays a six-proton singlet at τ 8.02 (acetate methyls), a three-proton singlet at τ 7.85 (acetyl methyl), a one-proton pentet at τ 7.15 (methine proton, J=6.5 cps), a two-proton doublet at τ 5.91 (α acetoxy protons, J=6.0 cps), a two-proton triplet at τ 6.04 (α acetoxy protons, J=6.0 cps) and a multiplet at τ 8.2 which is partially obscured by the methyl groups.

3-methylene-4-oxopentanol acetate (49, R=$OCOCH_3$). A mixture of 68.8 g of keto diacetate 48, R=$OCOCH_3$, and 9 ml of triethanolamine was slowly distilled at 2 mm pressure thru a six inch wire gauze heated column, and the distillate (54 g) was dissolved in 300 ml of ether and washed with excess aqueous sodium carbonate to remove any acetic acid. After evaporating the ether solvent the residue was distilled and gave 34.6 g of enone 49, R=$OCOCH_3$, bp 84-6°/4.5 mm. This represents an overall yield of 55 percent for the five steps beginning with acetyl diethyl succinate.

It was possible to prepare[32] a 2,4-dinitrophenylhydrazone of 49, mp 113.7-114.7°, without concomitant isomerization of the double bond to the trisubstituted position.

Anal. Calc for $C_{14}H_{16}O_6N_4$: C, 50.00; H, 4.80; N, 16.66. Found: C, 50.08; H, 4.81; N, 16.64.

The infrared spectrum (Figure 4, p 52) shows absorption at 1735, 1670 and 1625 cm^{-1}, as anticipated for the ester and unsaturated ketone carbonyls and the double bond. The nmr spectrum (Figure 27, p 66) shows two three-proton singlets at τ 8.10 (acetate methyl) and τ 7.70 (acetyl methyl), two-proton triplets at τ 7.50 (protons α to the acetoxy group, J=6.0 cps) and τ 5.95 (allylic protons, J=6.0 cps) and two one-proton singlets at τ 4.15 and 3.85 (vinyl protons).

Methoxy-2-(2'-ethyl acetoxy-3'-oxobutyl)-cyclohexen-3-one (53). A solution of 8.7 g of cyclohexane-1,3-dione, 12.0 g of enone 49, R=$OCOCH_3$, 50 ml of methanol, 35 ml of water and 1.3 g of potassium carbonate was heated at 70-80° for 100 minutes. The reaction mixture was cooled to room temperature, poured into a slurry of 200 ml of chloroform and 200 g of ice, and treated with concentrated hydrochloric acid (added dropwise with stirring) until pH 4 was reached. The organic layer was separated and the aqueous phase was washed with 50 ml of chloroform. The combined organic layers were dried with magnesium sulfate and the solvent was removed leaving the crude Michael adduct 52.

A solution of the crude triketo ester 52 in 75 ml of ether was treated overnight with excess ethereal diazomethane at room temperature. Evaporation of the ether and distillation of the remaining oil thru a short-path apparatus gave 2.74 g of recovered 49 and 1-methoxycyclohexen-3-one, bp 60-70°/0.07 mm and 15.12 g (67 percent yield based on enone 49) of enol ether 53, bp 187-92°/0.07 mm.

The infrared spectrum of 53 (Figure 5, p 53) shows strong bands at 1740, 1715, 1655 and 1620 cm^{-1} characteristic of the ester, methyl ketone and methoxycyclohexen-3-one carbonyl groups present in this molecule. The nmr spectrum (Figure 28, p 67) consists of a partially obscured two-proton triplet at τ 6.00 (protons α to the acetoxy group) and three-proton singlets at τ 6.10 (methoxyl group), 7.80 (acetate methyl) and 7.95 (acetyl methyl).

3-methyltricyclo[7.4.0.$0^{3,7}$]-2,4-dioxatridec-1,9-en-10-one (55). A solution of 10.0 g of acetoxy enone 49, R=$OCOCH_3$, 7.2 g of cyclohexane-1,3-dione, 1.2 g of potassium carbonate, 30 ml of water and 45 ml of

methanol was heated for 1 hour at 80°. The reaction mixture was cooled to 50°, a solution of 7.2 g of potassium hydroxide in 20 ml of water was added, and this mixture was stirred for 40 minutes at 50°. After cooling to room temperature, the solution was diluted with 150 ml of water, and extracted twice with 70 ml of chloroform. The aqueous solution was then cooled in an ice bath and acidified with hydrochloric acid. Extraction of this aqueous mixture with three 75 ml portions of chloroform gave a mixture of tricyclic ketal 55 and unreacted cyclohexane-1,3-dione. This mixture was then treated with excess ethereal diazomethane in order to convert the cyclohexane-1,3-dione to its methyl enol ether and distillation of this product mixture thru a short-path apparatus gave 8.0 g of 55 (60 percent yield based on enone 49), bp 120-25°/0.1 mm as a colorless oil which solidified on standing. Recrystallization from ethanol followed by sublimation gave an analytical sample, mp 42-3°.

Anal. Calc for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.62; H, 7.73.

The infrared spectrum of 55 (Figure 6, p 53) shows strong absorption at 1665 and 1635 cm^{-1}. The nmr spectrum (Figure 29, p 68) exhibits a two-proton multiplet at τ 6.00-6.30 (C_5 methylene protons) and a three-proton singlet at τ 8.62 (methyl protons).

3-methylene-4-oxopentanol pivalate (49, R=OCOC$(CH_3)_3$). To a cold solution of 40 g of diol 47, R=OH, in 200 ml of pyridine (ice bath) was slowly added 56 g of pivaloyl chloride. This mixture was stirred for two hours at room temperature and then worked up in the same manner as the preparation of the corresponding diacetate. Distillation thru

a short vigreaux column gave 32.5 g of keto diester 48, R=OCOC$(CH_3)_3$, bp 130-32°/0.2 mm.

A 2,4-dinitrophenylhydrazone was prepared[32], mp 101-2° after three recrystallizations from 90 percent ethanol.

Anal. Calc for $C_{22}H_{32}O_8N_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.09; H, 6.76; N, 11.76.

The infrared spectrum of 48, R=OCOC$(CH_3)_3$, (Figure 7, p 54) shows a broad carbonyl absorption at 1735-15 cm^{-1}. The nmr spectrum (Figure 30, p 69) has a peak assignment similar to that discussed for the keto diacetate 48, R=$OCOCH_3$.

Distillation of 48, R=OCOC$(CH_3)_3$, from triethanolamine at 2 mm pressure gave the enone 49, R=OCOC$(CH_3)_3$, bp 98-100°/5 mm. A 2,4-dinitrophenylhydrazone was prepared[32], mp 119-20°.

Anal. Calc for $C_{17}H_{22}O_6N_4$: C, 53.96; H, 5.86; N, 14.81. Found: C, 53.82; H, 5.98; N, 14.79.

The infrared spectrum of 49, R=OCOC$(CH_3)_3$, (Figure 8, p 54) shows the ester and enone carbonyls at 1735 and 1670 cm^{-1} and the double bond at 1625 cm^{-1}. The nmr spectrum (Figure 31, p 70) shows the two vinyl protons as singlets at τ 3.85 and 4.17, the two methylene triplets at τ 5.85 and 7.42 (J=6 cps), the acetyl methyl at τ 7.70 and the t-butyl group at τ 8.90.

2-acetylbutane-1,4-diol dibenzyl ether (48, R=$OCH_2C_6H_5$). A solution of 16 g of ketal diol 47, R=OH, in 50 ml of dimethyl sulfoxide was added to 10.5 g of sodium hydride (52%, washed with pentane to remove the mineral oil) in 250 ml of dimethyl sulfoxide under a nitrogen atmosphere and then 35 ml of benzyl chloride was added over a 45 minute

period with stirring and cooling (20° water bath). After stirring for 10 hours at room temperature the reaction mixture was poured onto 1 kg of ice and the dibenzyl ether was extracted with ether. Removal of the solvent and distillation of the residue gave 18.0 g of ketal dibenzyl ether 47, R=$OCH_2C_6H_5$, bp 130-40°/0.02 mm (61 percent yield).

A solution of 17 g of 47, R=$OCH_2C_6H_5$, in 70 ml of acetone was treated with 20 ml of 3 percent hydrochloric acid at room temperature for 20 minutes. The ketone was then extracted with ether and evaporation of the solvent gave 13.5 g of 48, R=$OCH_2C_6H_5$ (95 percent). The infrared spectrum of 48 (Figure 9, p 55) displays a saturated ketone carbonyl absorption at 1710 cm^{-1}.

3-methylene-4-oxopentanol benzyl ether (49, R=$OCH_2C_6H_5$). In one experiment, distillation of the crude 2-acetylbutane-1,4-diol dibenzyl ether diethyl ketal resulted in elimination of ethanol, giving an impure product which appeared from the nmr spectrum to be the enol ether 56.

A solution of 9.0 g of this crude enol ether in 100 ml of methylene chloride was shaken with 50 ml of 5 percent hydrochloric acid for 5 minutes. The organic phase was separated, washed with water, dried and after evaporation of the solvent yielded 6.13 g of fairly pure enone 49, R=$OCH_2C_6H_5$. A 2,4-dinitrophenylhydrazone, mp 98-99°, was prepared[32].

Anal. Calc for $C_{19}H_{20}O_5N_4$: C, 59.37; H, 5.24; N, 14.58. Found: C, 59.38; H, 5.26; N, 14.67.

A sample of 49 was purified by distillation, bp 110°/0.04 mm, for spectral analysis. The infrared spectrum (Figure 10, p 55) shows absorption characteristics of an unsaturated carbonyl (1680 cm^{-1}).

a double bond (1625 cm^{-1}), aromatic substitution bands (1945, 1875 and 1800 cm^{-1}) and aromatic hydrogen absorptions (3100-3000 cm^{-1}). The nmr spectrum (Figure 32, p 71) is similar to that of related enones (structure 49) discussed above.

2-(2'-cyclohexane-1',3'-dione)acetic acid ethyl ester (59). The synthesis described by H. Stetter[24] was modified to permit facile preparation of large quantities of 59.

Under a nitrogen atmosphere, cyclohexane-1,3-dione (110 g) was added in one portion to a solution of 23 g of sodium in 500 ml of absolute ethanol. A solution of 120 ml of ethyl bromoacetate in 100 ml of ethanol was then added dropwise over a period of 45 minutes, and this reaction mixture was stirred at room temperature for 12 hours. The ethanol was removed by distillation (beginning at atmospheric pressure and finishing ar reduced pressure) and the resulting semi-solid was dissolved in 75 ml of water and 500 ml of methylene chloride. The organic phase was separated and extracted with ice cold 5N sodium hydroxide solution until the pH of the aqueous layer reached 10. The combined aqueous layers were cooled in an ice bath and neutralized by dropwise addition of concentrated hydrochloric acid to the vigorously stirred mixture. Although the alkylated diketone (59) began to precipitate during the addition of acid, a characteristic color change from orange to white occurred when neutralization was complete. After stirring the aqueous slurry an additional hour a 0° to insure complete precipitation, the product was filtered and washed with ice water. Drying the crude product overnight gave 86-110 g (44-55 percent) of 59 sufficiently pure for use in the next reaction.

2-(2'-cyclohexane-1',3'-dione-2'-(3"-oxobutyl))acetic acid ethyl ester(60). 40 g of diketo ester 59 and 20 ml (15 percent excess) of freshly distilled methyl vinyl ketone were added to a solution of 0.2 g of sodium in 150 ml of absolute ethanol, and this mixture was refluxed two hours under nitrogen. Following evaporation of the ethanol and excess methyl vinyl ketone under reduced pressure, the residue was dissolved in 250 ml of methylene chloride and washed three times with 100 ml of water. The methylene chloride solution was dried with sodium sulfate and evaporated. Crystallization of the crude solid residue from 1:1 ethyl acetate-pentane gave two crops of Michael adduct 60 totalling 39 g (73 percent). An analytical sample, mp 95.5-96.5°, was obtained by further recrystallization from ethyl acetate-pentane.

Anal. Calc for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 62.87; H, 6.87.

The infrared spectrum of 60 (Figure 11, p 56) shows strong absorptions at 1725 and 1695 cm^{-1}. The nmr spectrum (Figure 33, p 72) includes signals a τ 5.96 (two-proton quartet, J=7 cps, methylene protons of the ethyl group), τ 7.03 (two-proton singlet, protons α to the ester carbonyl), τ 7.90 (three-proton singlet, acetyl methyl) and τ 8.76 (three-proton triplet, J=7 cps, methyl group of the ethyl ester).

2-(β-carboxymethyl)-6-carbethoxymethyl-3-methylcyclohex-2-enone (63, R=H). A mixture of 3.1 g of Michael adduct 60, 0.28 g of p-toluenesulfonic acid mono hydrate and 50 ml of dry benzene was refluxed for three hours. After cooling this solution was siluted with 100 ml of methylene chloride and washed with 20 ml of water to remove the sulfonic acid. The acidic product, carboxylic acid 63, R=H, was then extracted by

shaking with 100 ml of 2 percent aqueous sodium carbonate. Acidification of the basic water layer with hydrochloric acid followed by extraction with 25 ml of methylene chloride, gave after evaporation of the solvent 1.6 g (55 percent)yield) of 63. The nmr spectrum of 63 (Figure 34, p 73) shows the presence of an ethyl ester (triplet at τ 8.77 and a quartet at τ 5.93, J=7 cps), a vinyl methyl (singlet at τ 8.05) and the absence of any vinyl protons. The infrared spectrum (Figure 12, p 56) displays absorptions at 1735, 1710, 1665 and 1625 cm^{-1} characterisitic of the ester, acid and enone carbonyl groups and the double bond.

On treatment with excess ethereal diazomethane at room temperature for 20 minutes, 63, R=H, was converted to its methyl ester, which proved to be homogeneous by glpc analysis on 20 percent SE-30 (6'x1/8" column at 240°).

4a-carbethoxymethyl-4,4a,7,8-tetrahydronaphthalene-2,5(3H,6H)-dione (61). To an ice cold solution of 1.60 ml of glacial acetic acid and 2.2 ml of pyrrolidine in 75 ml of benzene was added under nitrogen 6.0 g of triketo ester 60, and after stirring the reaction mixture for 30 minutes the cooling bath was removed. The reaction mixture was stirred for 10 hours at room temperature and then poured into 100 ml of water and 100 ml of chloroform. The organic layer was separated, washed successively with 50 ml of 5 percent hydrochloric acid and 50 ml of saturated sodium bicarbonate and dried over sodium sulfate. Removal of the solvent by evaporation at reduced pressure gave 3.90 g of 61 as a tan oil.

This enedione could be purified by preparative glpc of 4 percent

QF-1 at 200° or by distillation a 175°/0.002 mm. The infrared spectrum (Figure 13, p 57) shows absorptions at 1735, 1715, 1675 and 1620 cm^{-1} for the ester, ketone and enone carbonyls and the double bond. The nmr spectrum (Figure 35, p 74) exhibits a vinyl proton (singlet at τ 4.22) and an ethyl group (quartet at τ 6.96 and triplet at τ 8.92, J=7 cps). The ultraviolet spectrum (methanol) contains a maximum at 243 mμ (ε=11,900).

4aβ-carboxymethyl-4,4a,5,6,7-hexahydronaphth-5β-ol-2(3H)-one lactone (65). A solution of 3.48 g of the crude enedione 61 in 20 ml of 95 percent ethanol was cooled in an ice bath under a nitrogen atmosphere while 0.140 g (1.1 equivalents) of sodium borohydride in 80 ml of ethanol was added dropwise and with stirring over a two hour period. The reaction mixture was stirred for an additional half hour and then 1 ml of acetic acid was added to destroy any excess hydride. The precipitated lactone was filtered and the filtrate concentrated for a second crop. A total of 1.68 g (36 percent yield for the two steps from 60) of lactone 65 was obtained. Two recrystallizations from ethanol gave an analytical sample, mp 149-50°.

Anal. Calc for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.82; H, 6.90.

The infrared spectrum (Figure 14, p 57) shows bands at 1785, 1675 and 1625 cm^{-1}. The ultraviolet spectrum contains a maximum at 236 mμ (ε=12,700). The nmr spectrum (Figure 36, p 75) displays a one-proton singlet at τ 4.13 (vinyl proton), a one-proton multiplet at τ 5.71 (C_5 hydrogen) and a two-proton singlet at τ 7.30 (protons α to the lactone carbonyl).

4aβ-carboxymethyl-2-(1',3'-dioxolane)-1,4,4a,5,6,7-hexahydronaphth-5β-ol lactone (66). A solution of 1.34 g of the enone lactone (65) in 40 ml of benzene containing 1.5 ml of ethylene glycol and a few crystals of p-toluenesulfonic acid was refluxed in a Dean-Stark apparatus for 90 minutes. The reaction mixture was cooled, dissolved in 100 ml of chloroform, washed twice with 25 ml of water, dried over sodium sulfate and concentrated at reduced pressure. An unsaturated carbonyl absorption was barely perceptible in the infrared spectrum of the crude product, and recrystallization from ethyl acetate gave 1.28 g (79 percent yield) of ketal 66. An analytical sample, mp 151-52°, was obtained by further recrystallization from ethyl acetate.

Anal. Calc for $C_{14}H_{18}O_4$: C, 67.18; H, 6.84. Found: C, 66.81; H, 6.90.

The infrared spectrum of 66 (Figure 15, p 58) shows a strong absorption at 1760 cm^{-1} for the lactone carbonyl. The nmr spectrum (Figure 37, p 76) includes one-proton multiplets at τ 4.4 and 5.6 (vinyl and C_5 protons), a four-proton singlet at τ 6.05 (dioxolane protons) and two-proton singlets at τ 7.40 and 7.68 (protons α to the carbonyl and the C_1 protons).

2-(1',3'-dioxolane)-1,4,4a,5,6,7-hexahydro-4aβ-(2"-hydroxyethyl)naphth-5β-ol (69, R=H). A solution of 1.27 g of ketal lactone 69, R=H, in 25 ml of tetrahydrofuran was added dropwise over a 15 minute period to 0.160 g of lithium aluminum hydride and 25 ml of ether in a three-necked flask fitted with a condenser and drying tube. The mixture was then refluxed for three hours, cooled and 1 ml of water and 1 ml of 5 percent aqueous sodium hydroxide were carefully added. The salts

were filtered and thoroughly washed with ether. Evaporation of the solvent gave a white solid product, the infrared spectrum of which was devoid of carbonyl absorption. Recrystallization from ethyl acetate gave 1.04 g (81 percent yield) of the diol. An analytical sample, mp 127-28°, was obtained by further recrystallization from ethyl acetate.

Anal. Calc for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.13; H, 8.65.

The infrared spectrum (Figure 16, p 58) shows a strong O-H stretching absorption between 3600 and 3100 cm^{-1}. The nmr spectrum (Figure 38, p 77) displays a broad one-proton singlet at τ 4.65 (vinyl proton), a two-proton singlet at τ 5.05 (hydroxyl protons), a four=proton singlet at τ 6.10 (dioxolane protons), and a three-proton multiplet at τ6.35 (protons α to the hydroxyls).

2-(1',3'-dioxolane)-1,4,4a,5,6,7-hexahydro-4aβ-(2"-hydroxyethyl)naphth-5β-ol mono p-nitrobenzoate (69, R=$COC_6H_4NO_2$). To an ice cold solution of 0.400 g of ketal diol 69, R=H, in 10 ml of pyridine was slowly added a solution of 0.340 g of p-nitrobenzoylchloride in 5 ml of chloroform. The reaction mixture was stirred in an ice bath for 1 hour followed by 3 hours at room temperature, and the poured onto ice. The product was extracted with methylene chloride and the organic phase was washed with cold 10 percent hydrochloric acid. Removal of the solvent gave an oily product which, after two recrystallizations from ethyl acetate pentane, yielded 0.301 g (47 percent) of a mono ester, mp 119-22°. Further recrystallization gave a sample, mp 130.5-131.5°, suitable for elemental analysis.

Anal. Calc for $C_{21}H_{25}O_7N$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.77; H, 6.22; N, 3.55.

The infrared spectrum of this substance (Figure 17, p 59) shows hydroxyl absorption at 3610 and 3500 cm^{-1}, and appropriate bands for the p-nitrobenzoate function at 1725 and 1525 cm^{-1}. The most interesting feature of the nmr spectrum (Figure 39, p 78) is the downfield shift (from τ 6.27 to 5.40) of the triplet signal due to the protons α to the primary hydroxyl, clearly indicating that esterification of this group has occurred.

4aβ-carboxymethyl-3,4,4a,5,6,7,8,8a-octahydronaphth-5β-ol-2(1H)-one lactone (73). A slurry of 2.85 g of enone lactone 65 in 50 ml of tetrahydrofuran was added to a solution of 0.445 g of lithium in a liquid ammonia (200 ml) - tetrahydrofuran (70 ml) mixture. The addition required 5 minutes, following which the reaction was allowed to reflux (dry ice condenser) with mechanical stirring for 80 minutes. After cooling the flask in a dry ice - acetone bath for 10 minutes, ammonium chloride was added to destroy the excess lithium and the ammonia was evaporated. Water was added to the residue and the aqueous solution was extracted eight times with 50 ml portions of methylene chloride. The combined organic washes were dried with sodium sulfate and the solvent was removed under reduced pressure to give 2.95 g of crude keto lactone 73.

This crude product was chromatographed on 40 g of silica gel. The first fractions were eluted with methylene chloride (100 ml) and contained hydrocarbons (from the lithium coating); the fourth thru tenth fractions (eluted with 1:9 ether - methylene chloride) contained a total of 1.75 g (61 percent yield) of keto lactone 73.

Recrystallization from ethyl acetate, followed by sublimation at 0.005 mm gave an analytical sample, mp 100-101.5°.

Anal. Calc for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.36; H, 7.83.

The infrared spectrum (Figure 18, p 59) of the keto lactone shows a lactone carbonyl (1890 cm^{-1}) and a saturated ketone carbonyl (1723 cm^{-1}). The nmr spectrum (Figure 40, p 79) shows the C_5 proton as a multiplet at τ 5.7-6.0.

3-hydroxymethylpent-3-enol (81). 80 g of ethylidine diethyl succinate[28] in 100 ml of tetrahydrofuran was added slowly (two hours) to 20 g of lithium aluminum hydride dispersed in 1100 ml of tetrahydrofuran and 300 ml of ether in a 2 l three-necked flask fitted with a mechanical stirrer, condenser and calcium sulfate drying tube. On completion of the addition, the reaction mixture was refluxed 16 hours and, when worked up in the same manner as the reduction of acetyl diethyl succinate diethyl ketal, yielded 39 g of crude diol. Distillation thru a six inch vigreaux column gave 29.2 g (64 percent yield) of diol 81, bp 88-94°/0.5 mm.

A sample, bp 87-89°/0.5 mm, obtained by distillation thru a apinning band column, was used for spectral analysis. This was judged to be a mixture of double bond isomers from the fact that the bis-p-nitrobenzoate melted over a wide range even after repeated recrystallization. The infrared spectrum (Figure 19, p 60) shows O-H absorption at 3600-3100 cm^{-1}. The nmr spectrum (Figure 41, p 80) yields to simple first order analysis. Thus, the C_1 and C_2 methylene hydrogens appear as triplets (τ 6.40 and 7.68, J=6 cps), the allylic protons α to the other hydroxyl group as a singlet (τ 6.08), the

hydroxyl protons as a singlet (τ 4.93) and the vinyl hydrogen as a quartet (τ 4.45) coupled to the methyl group (doublet, τ 8.38, J=6 cps).

Chloro-3-chloromethyl-3-pentene (82). A solution of 25.9 g of diol 81 in 115 ml of chloroform and 62 ml of triethyl amine in a three-necked flask, equiped with a mechanical stirrer, drying tube, thermometer and addition funnel, was cooled to -30° and 37 ml of thionyl chloride[33] in 50 ml of chloroform was added at a rate which allowed the reaction mixture temperature to be maintained below -15°. After being kept at 5° for 12 hours, the dark reaction mixture was poured onto ice and the organic layer was separated and washed twice with 100 ml of saturated aqueous sodium carbonate. Evaporation of the solvent gave 39.2 g of crude dichloride, which on distillation thru a six inch vigreaux column gave 16.6 g (43 percent) of materail bp 53-70°/5mm. glpc analysis (4% OF-1 column, 6'x1/4", 102°) indicated this to be a three component mixture with the major product (85 percent) having nmr and infrared spectra consistent with structure 82.

The infrared spectrum (Figure 20, p 60) shows the absence of O-H stretching and the presence of a double bond (1660 cm^{-1}). The nmr spectrum (Figure 42, p 81) can be interpreted in the same manner as that for diol 81.

Bromo-3-methylene-4-oxopentane (49, R=Br). A solution of 20.0 g of ketal diol 47, R=OH, in 100 ml of pyridine was cooled in an ice bath and 50 g of p-toluenesulfonylchloride dissolved in 100 ml of pyridine was added dropwise over a 1 hour period. After stirring the reaction mixture an additional 2 hours at 0° followed by 45 minutes at room

temperature, it was poured into 500 ml of ice water and extracted with methylene chloride (150-100 ml). The combined organic extracts were washed twice with 400 ml of cold 10 percent hydrochloric acid, once with 100 ml of water and then dried over sodium sulfate.

The resulting solution of keto ditosylate 48, $R=OSO_2C_6H_4CH_3$, was cooled in an ice bath and 150 ml of triethylamine added. After 1 hour the ice bath was removed and the solution stirred 3 hours at room temperature. The triethylamine was removed by washing twice with 300 ml of cold 10 percent hydrochloric acid. Removal of the solvent under reduced pressure at 35° gave the enone tosylate 49, $R=OSO_2C_6H_4CH_3$.

The crude enone tosylate in 50 ml of dry acetone was added over a 30 minute period to an ice cooled mixture of 30 g of anhydrous lithium bromide (dried at 110°/0.1 mm for 10 hours) and 250 ml of acetone. The ice bath was removed after 1 hour and the reaction mixture was stirred for 11 hours at room temperature. Two thirds of the acetone was removed under reduced pressure at 35°, the residue poured onto 500 g of ice and the product was extracted with methylene chloride. Removal of the solvent at 35° gave 10 g of crude bromo enone 49, R=Br. Distillation thru a short path apparatus gave 5.0 g (29 percent yield for the four steps from 47, R=OH) of 49, R=Br, bp 62-67°/4.5 mm, which glpc analysis on 4% QF-1 (6'x1/4" at 110°) indicated to be about 90 percent pure. Samples of this purity could be stored several days at -10° without decomposition.

The infrared spectrum (Figure 21, p 61) shows an unsaturated carbonyl at 1677 cm^{-1} and a double bond at 1625 cm^{-1}. The nmr spectrum (Figure 43, p 82) is similar to that of the other enones of structure 49. The mass spectrum (Figure 48, p 87) displays parent ions at

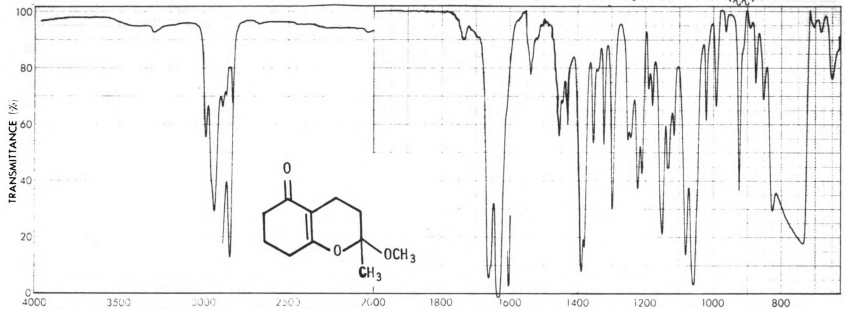
m/e 178 and 176, the two possible α cleavages of the methyl ketone at m/e 163, 161 and 135, 133 and loss of bromine at m/e 97.

2-acetylspiro[4.5]deca-6,10-dione (75). To a slurry of 0.600 g of sodium hydride (52 percent, washed with pentane to remove the mineral oil) and 150 ml of dimethoxyethane was added a solution of 1.51 g of cyclohexane-1,3-dione in 50 ml of dimethoxyethane. The reaction mixture was stirred at room temperature for 45 minutes under nitrogen and then a solution of 1.77 g of enone 49, R=Br, in 20 ml of dimethoxyethane was added and the reaction mixture refluxed for 100 minutes. Filtration of the sodium bromide and evaporation of the solvent then gave 2.2 g of crude 75, which on distillation thru a short path apparatus gave 1.5 g of a fraction bp 133-38°/0.05 mm. glpc analysis of this fraction indicated it to be a 4:1 mixture of 75 and 55. Chromatography of this material on 55 g of silica gel (eluting 25 ml fractions with 9:1 methylene chloride - ether) gave 0.80 g of pure 75 in fractions 6 thru 8.

A sample of 75 was collected by preparative glpc on a 4% OF-1 column (210°) for spectral analysis. The infrared spectrum (Figure 22, p 61) shows carbonyl absorption at 1730, 1715 and 1705 cm^{-1}. The nmr spectrum (Figure 44, p 83) contains a four-proton triplet at τ 7.35 (J=7 cps) for the protons α to the carbonyls in the six-membered ring and a three-proton singlet at τ 7.90 for the acetyl methyl. The mass spectrum (Figure 49, p 88) has a parent ion at m/e 208 and fragment ions at m/e 193 and 165 for the two possible α cleavages of the methyl ketone.

FIGURES

Figure 1. Infrared spectrum of 3-methoxy-3-methylbicyclo[4.4.0]-2-oxadec-1,6-en-7-one (45).



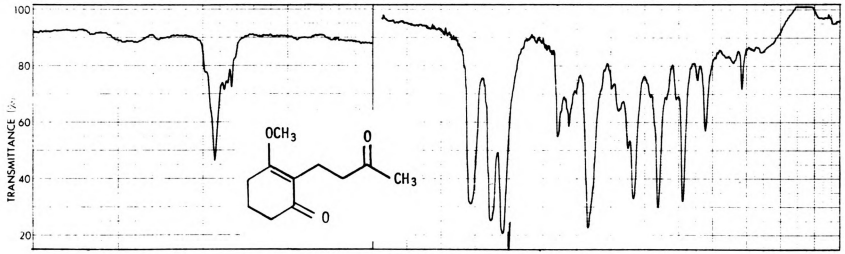


Figure 2. Infrared spectrum of methoxy-2-(3'-oxobutyl)cyclohexen-3-one (42).

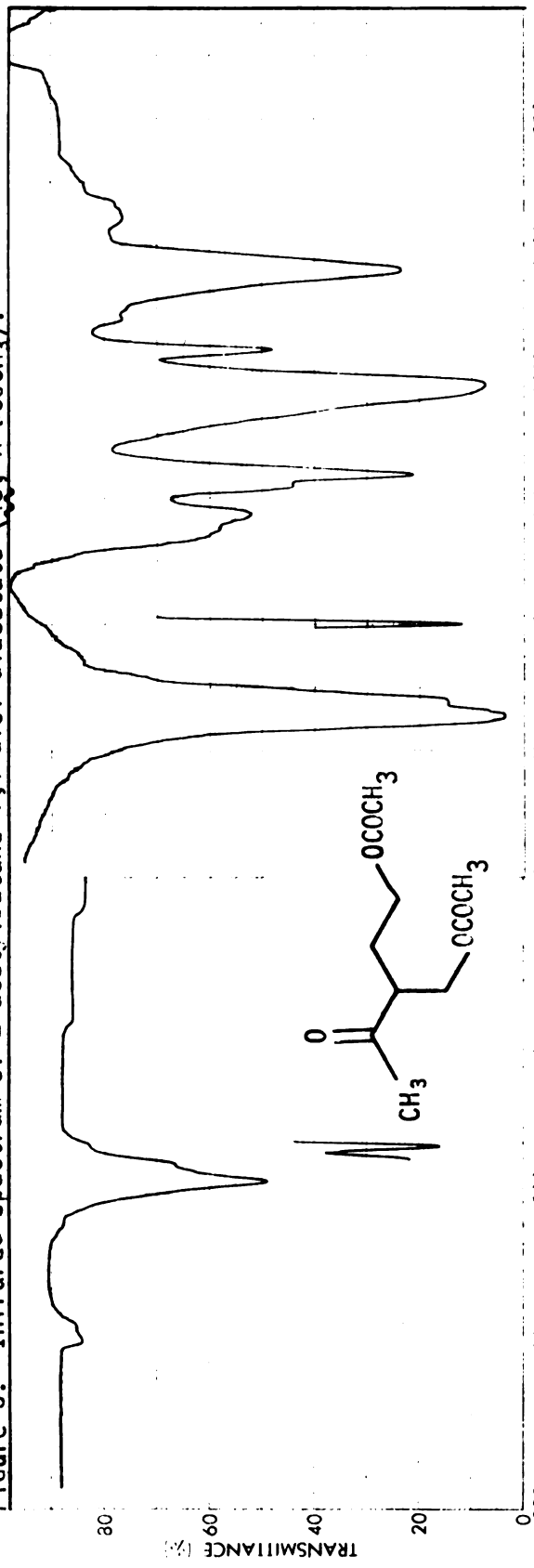


Figure 3. Infrared spectrum of 2-acetylbutane-1,4-diol diacetate (48, R=$OCOCH_3$).

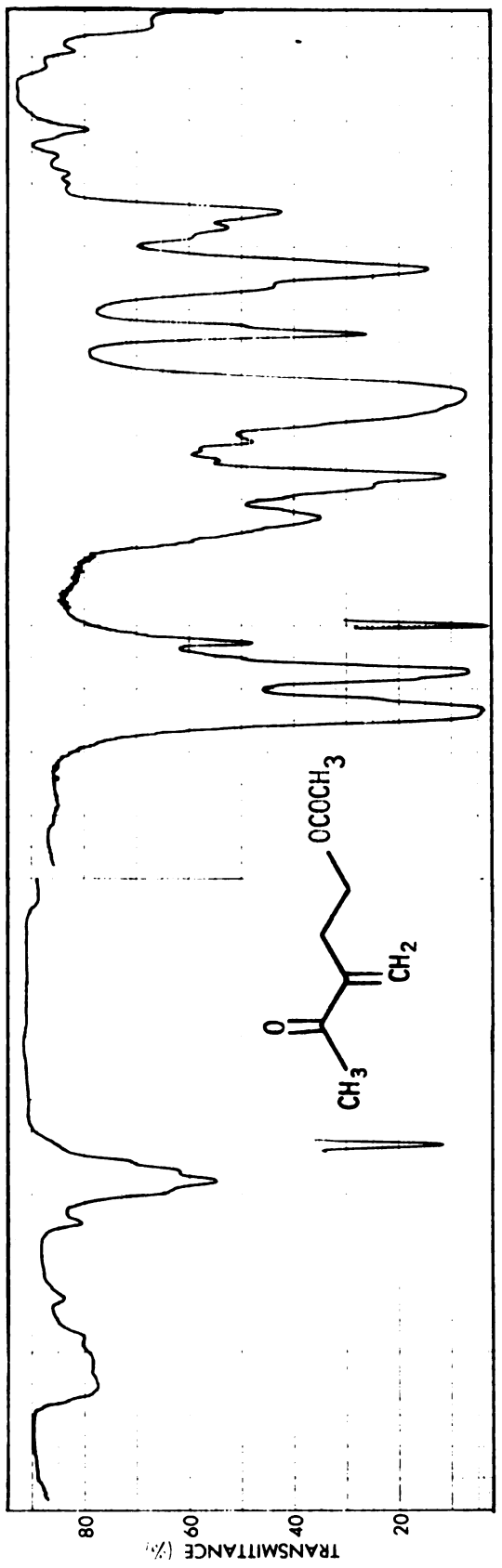


Figure 4. Infrared spectrum of 3-methylene-4-oxopentanol acetate (49, R=$OCOCH_3$).

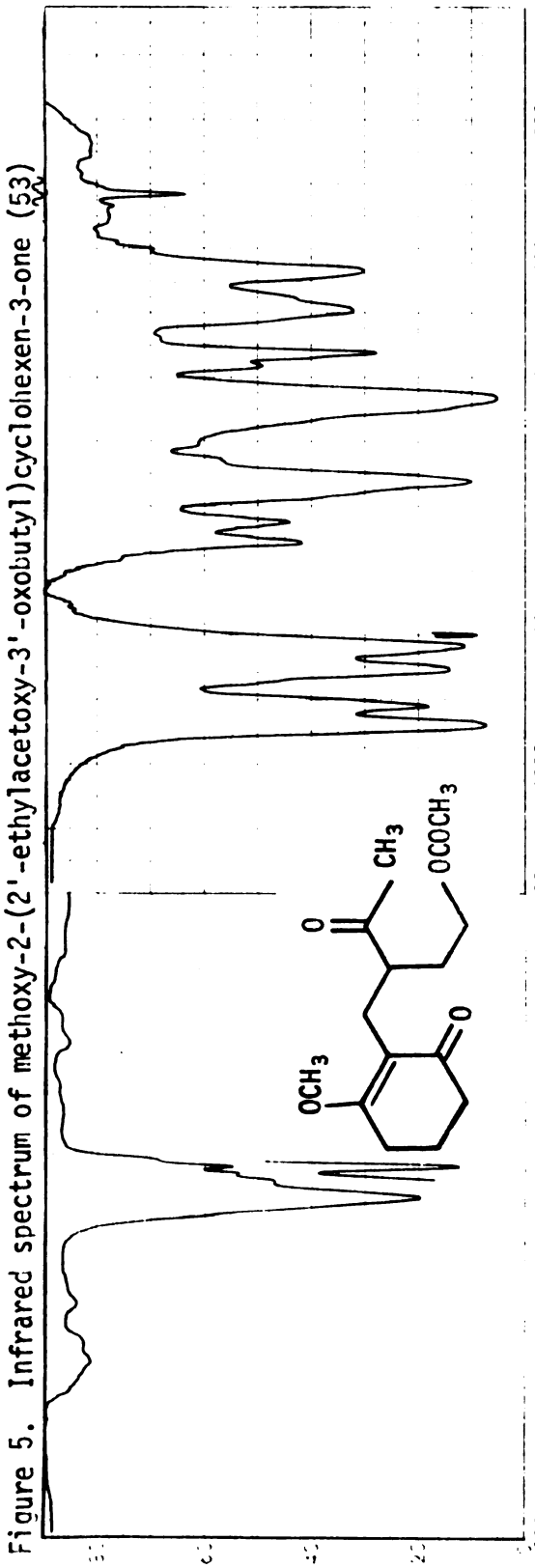


Figure 5. Infrared spectrum of methoxy-2-(2'-ethylacetoxy-3'-oxobutyl)cyclohexen-3-one (53)

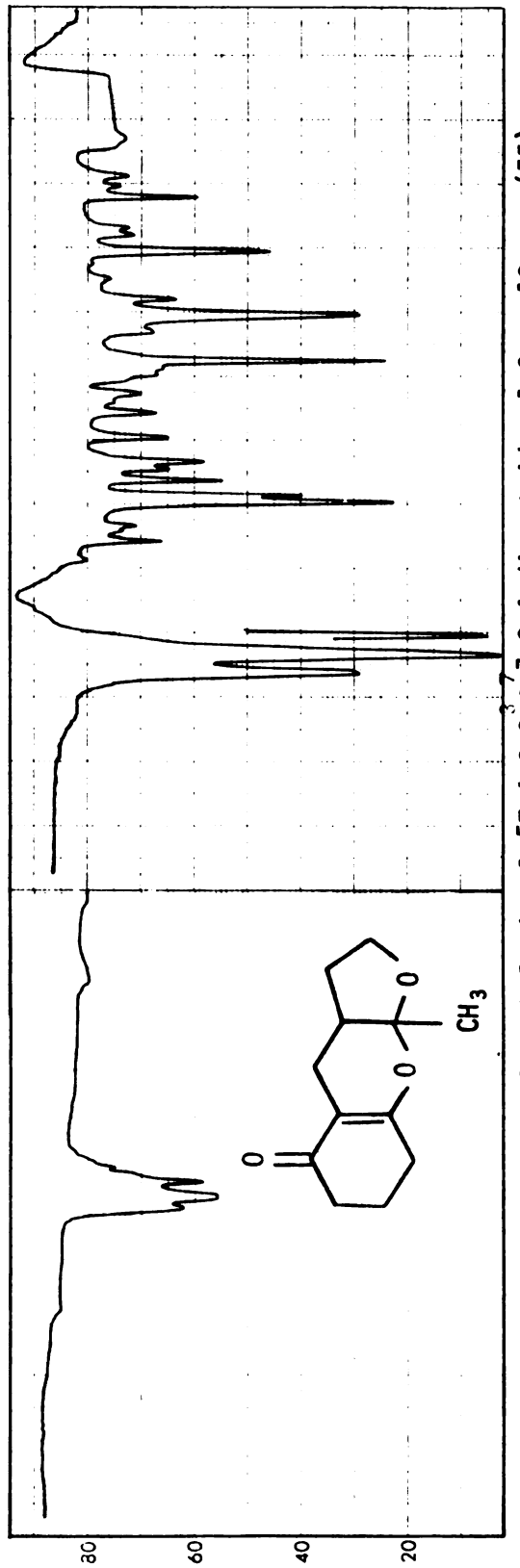
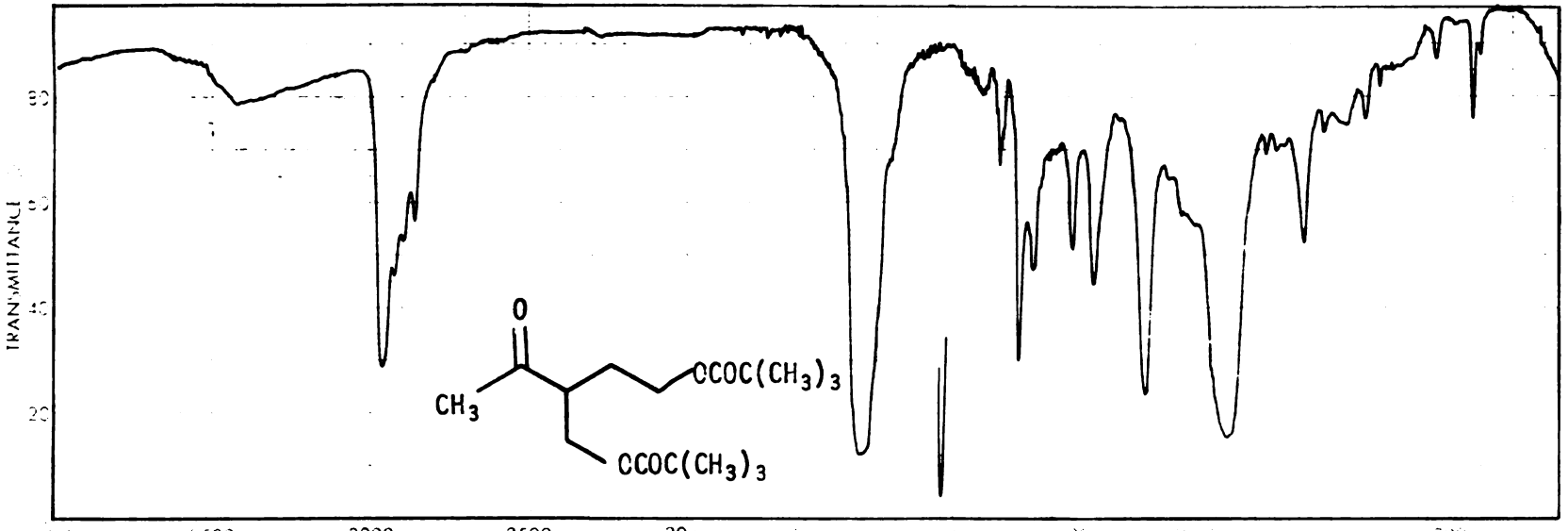


Figure 6. Infrared spectrum of 3-methyltricyclo[7.4.0.0^{3,7}]-2,4-dioxatridec-1,9-en-10-one (55).

Figure 7. Infrared spectrum of 2-acetylbutane-1,4-diol dipivalate (48, R=OCOC$(CH_3)_3$).



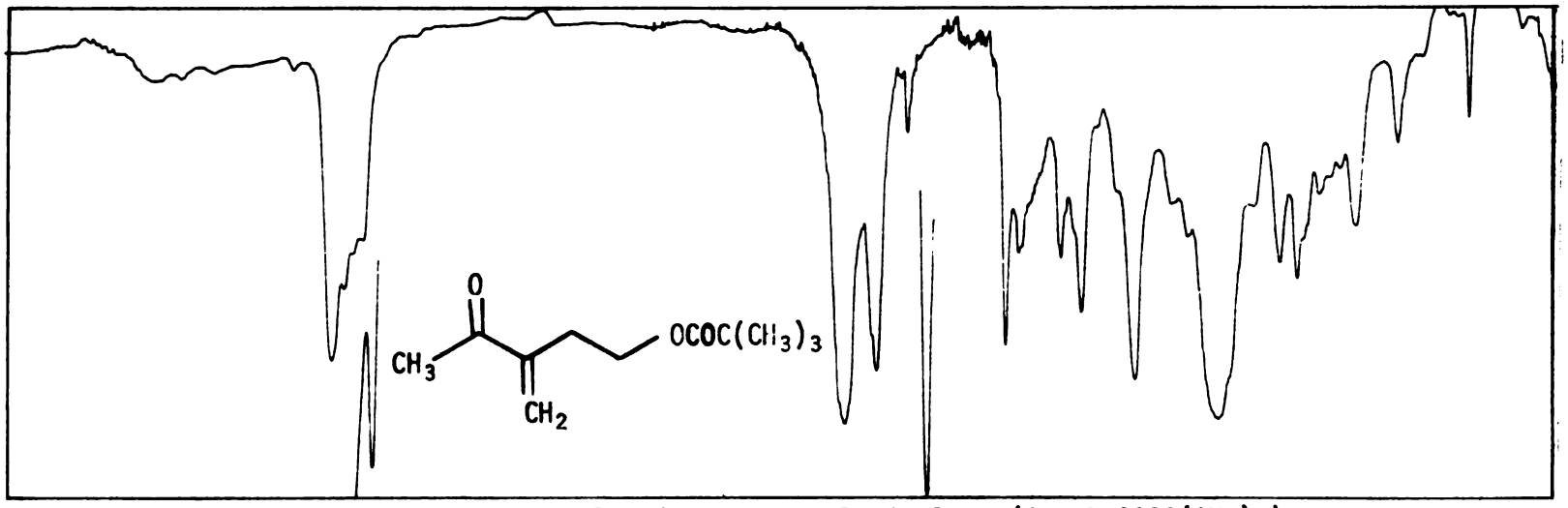


Figure 8. Infrared spectrum of 3-methylen-4-oxopentanol pivalate (49, R=OCOC$(CH_3)_3$).

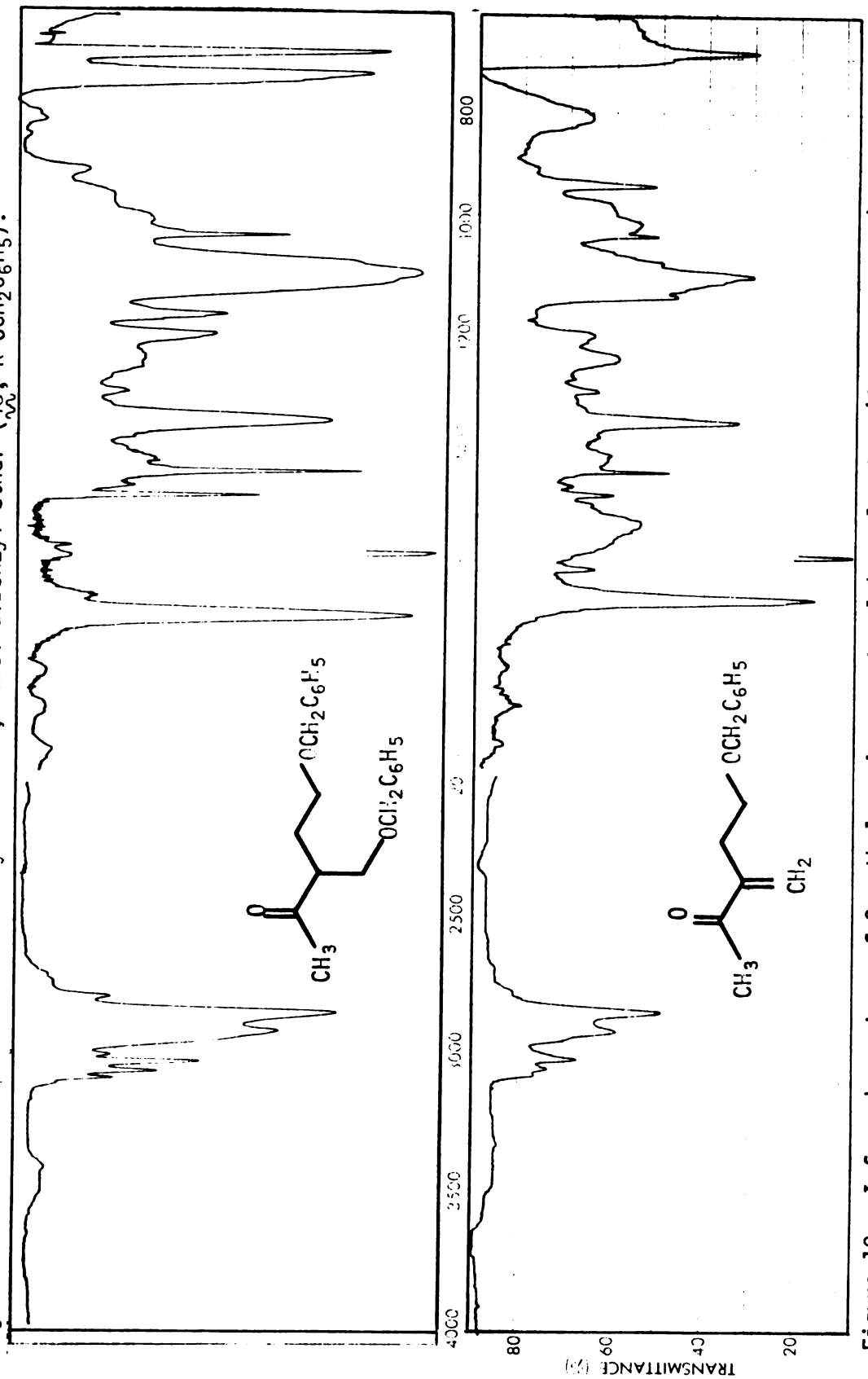
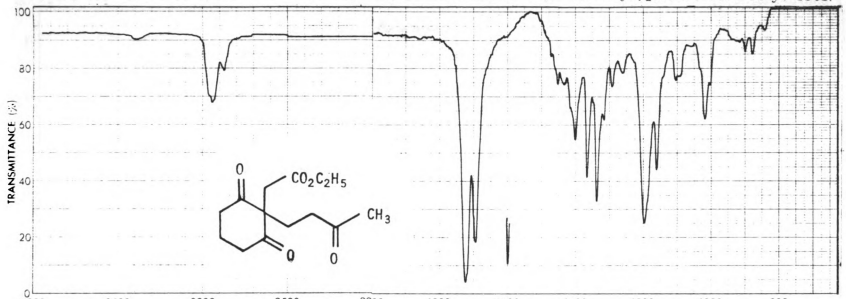


Figure 9. Infrared spectrum of 2-acetylbutane-1,4-diol dibenzyl ether (48, R=OCH$_2$C$_6$H$_5$).

Figure 10. Infrared spectrum of 3-methylene-4-oxopentanol benzyl ether (49, R=OCH$_2$C$_6$H$_5$).

Figure 11. Infrared spectrum of 2-[2'-cyclohexane-1',3'-dione-2-(3"-oxobutyl)]acetic acid ethyl ester (60).



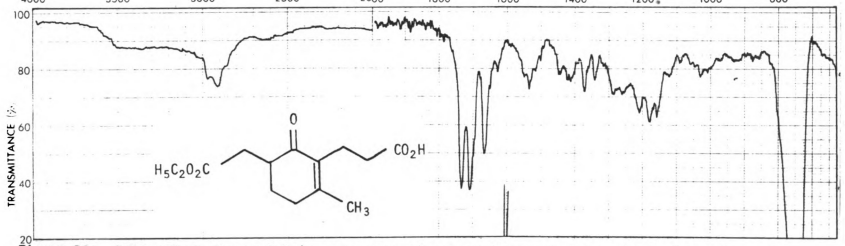
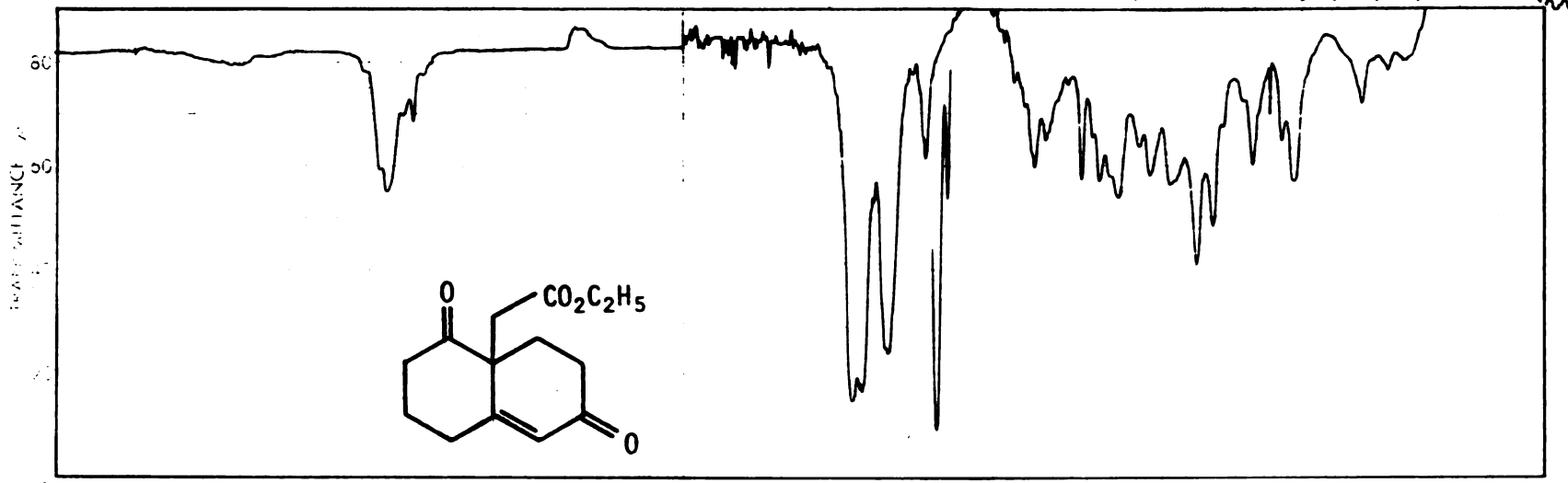


Figure 12. Infrared spectrum of 2-(β-carboxyethyl)-6-carbethoxymethyl-3-methylcyclohex-2-enone (63, R=H).

Figure 13. Infrared spectrum of 4a-carbethoxymethyl-4,4a,7,8-tetrahydronaphthalene-2,5(3H,6H)-dione (61).



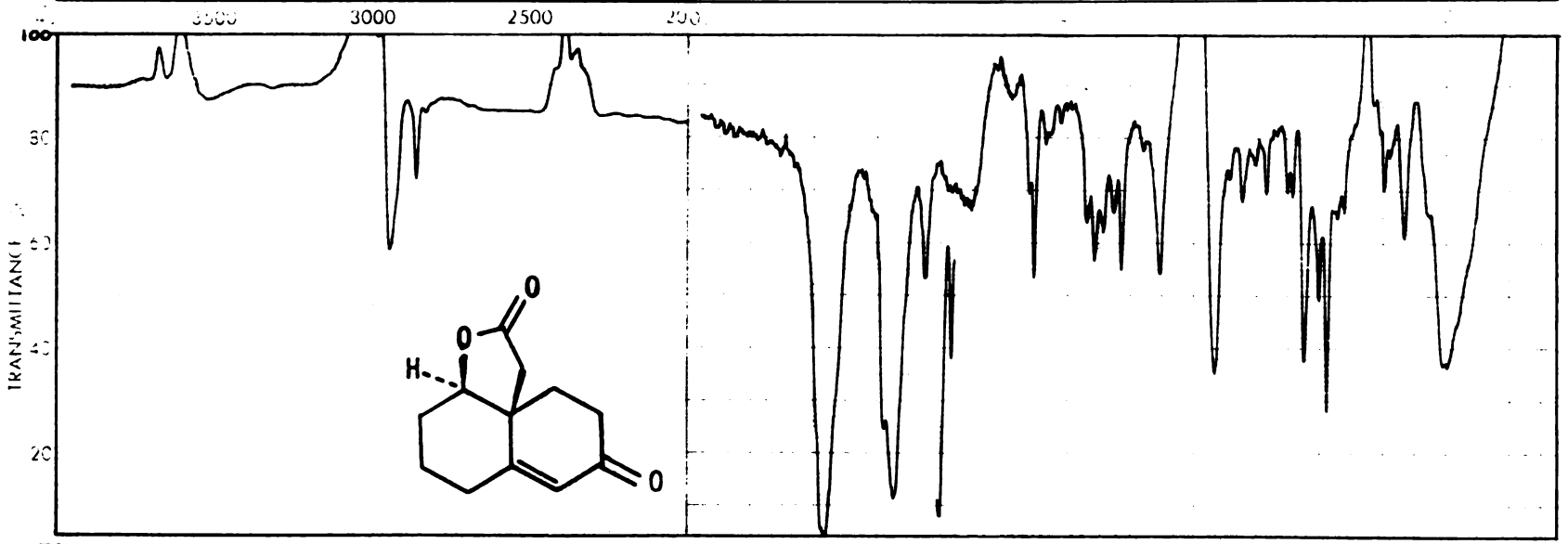
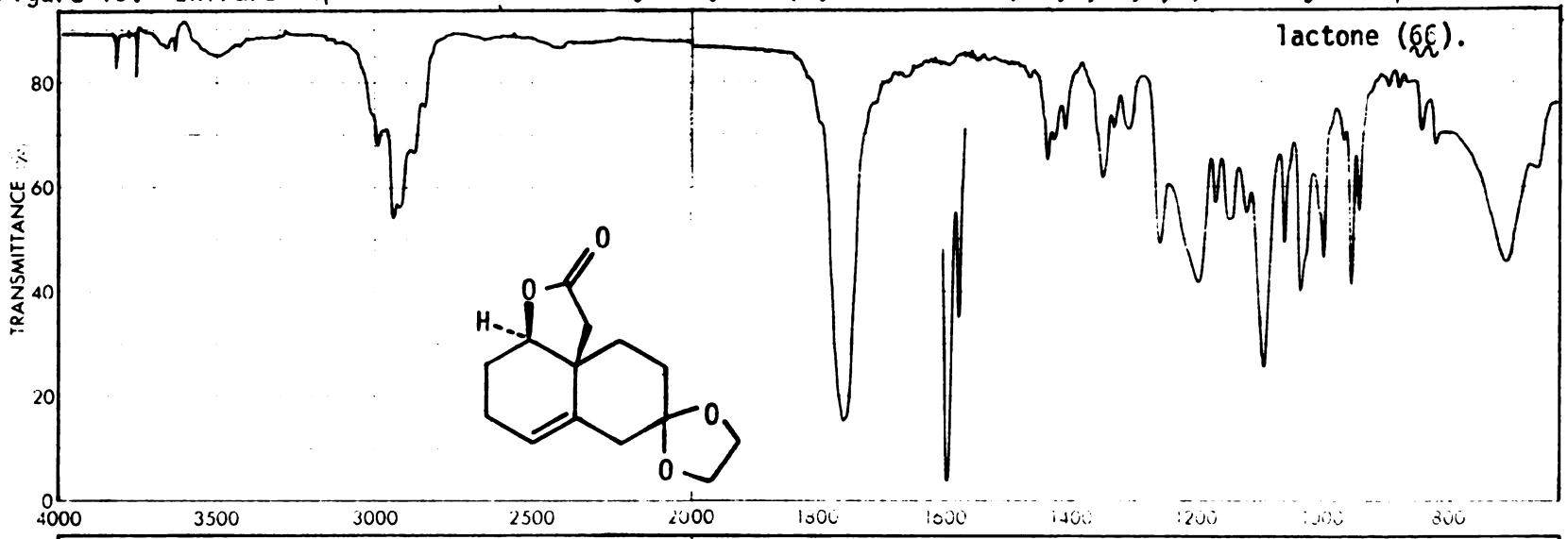


Figure 14. Infrared spectrum of 4aβ-carboxymethyl-4,4a,5,6,7,8-hexahydronaphth-5β-ol-2(3H)-one lactone (65).

Figure 15. Infrared spectrum of 4aβ-carboxymethyl-2-(1',3'-dioxolane)-1,4,4a,5,6,7-hexahydronaphth-5β-ol lactone (66).



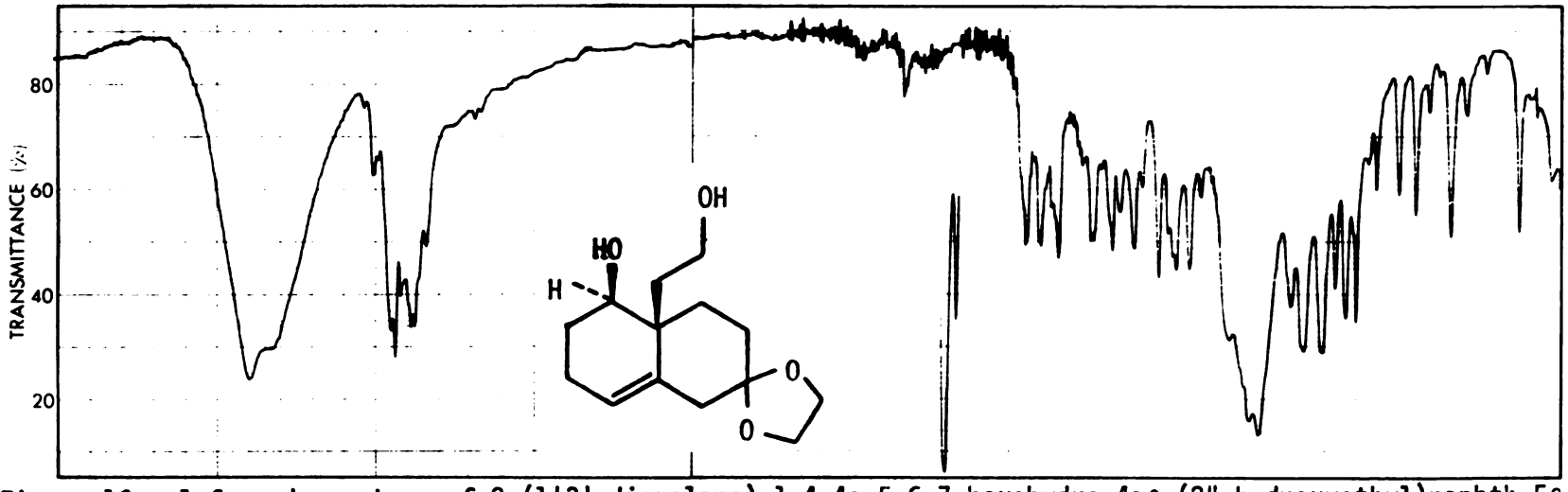
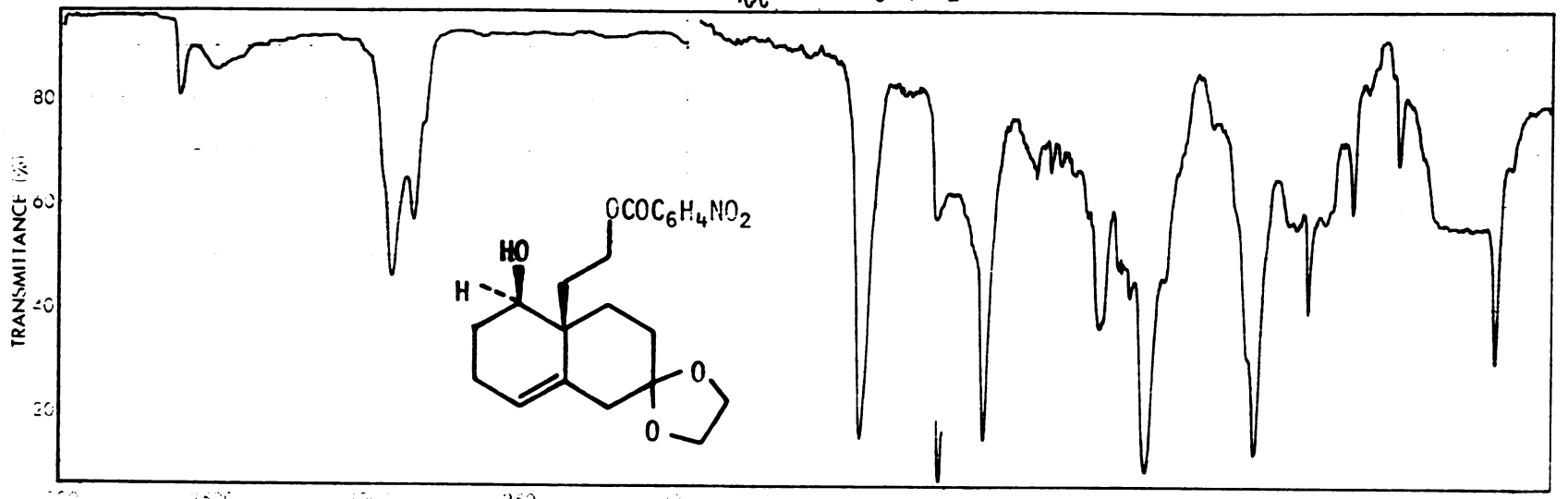


Figure 16. Infrared spectrum of 2-(1',3'-dioxolane)-1,4,4a,5,6,7-hexahydro-4aβ-(2"-hydroxyethyl)naphth-5β-ol (69, R=H). (KBr)

Figure 17. Infrared spectrum of 2-(1',3'-dioxolane)-1,4,4a,5,6,7-hexahydro-4aβ-(2''-hydroxyethyl) naphth-5β-ol mono p-nitrobenzoate (69, R=$COC_6H_4NO_2$).



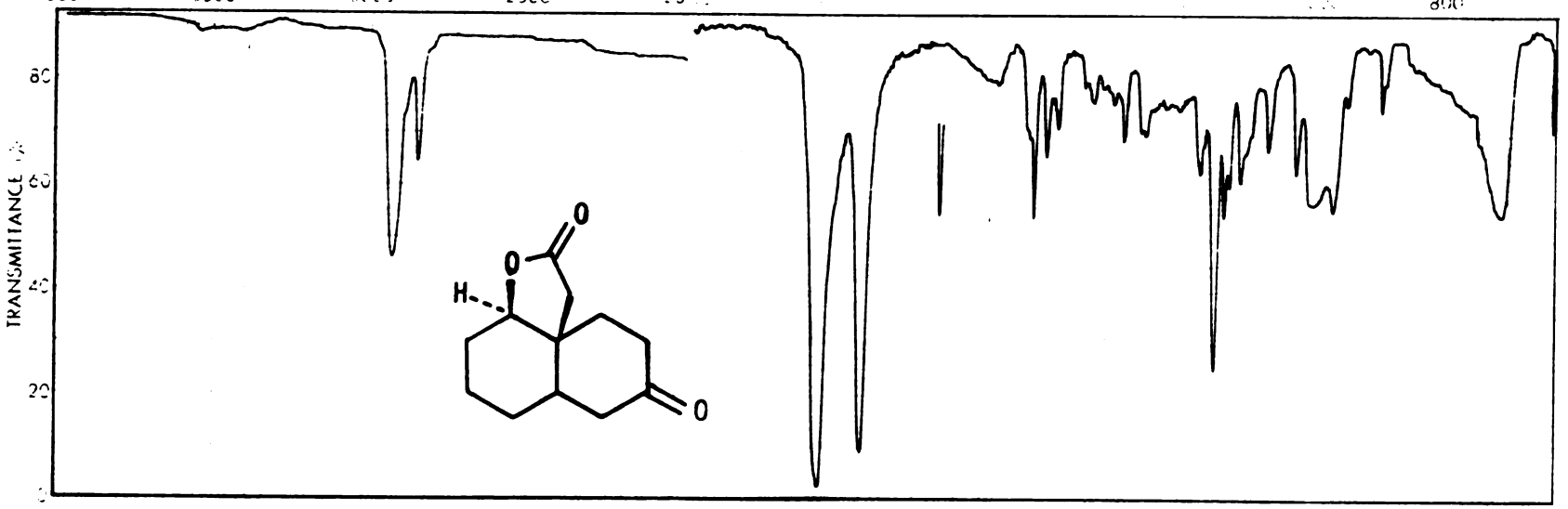


Figure 18. Infrared spectrum of 4aβ-carboxymethyl-3,4,4a,5,6,7,8,8a-octahydronaphth-5β-ol-2(1H)-one lactone (73).

Figure 19. Infrared spectrum of 3-hydroxymethylpent-3-enol (81).

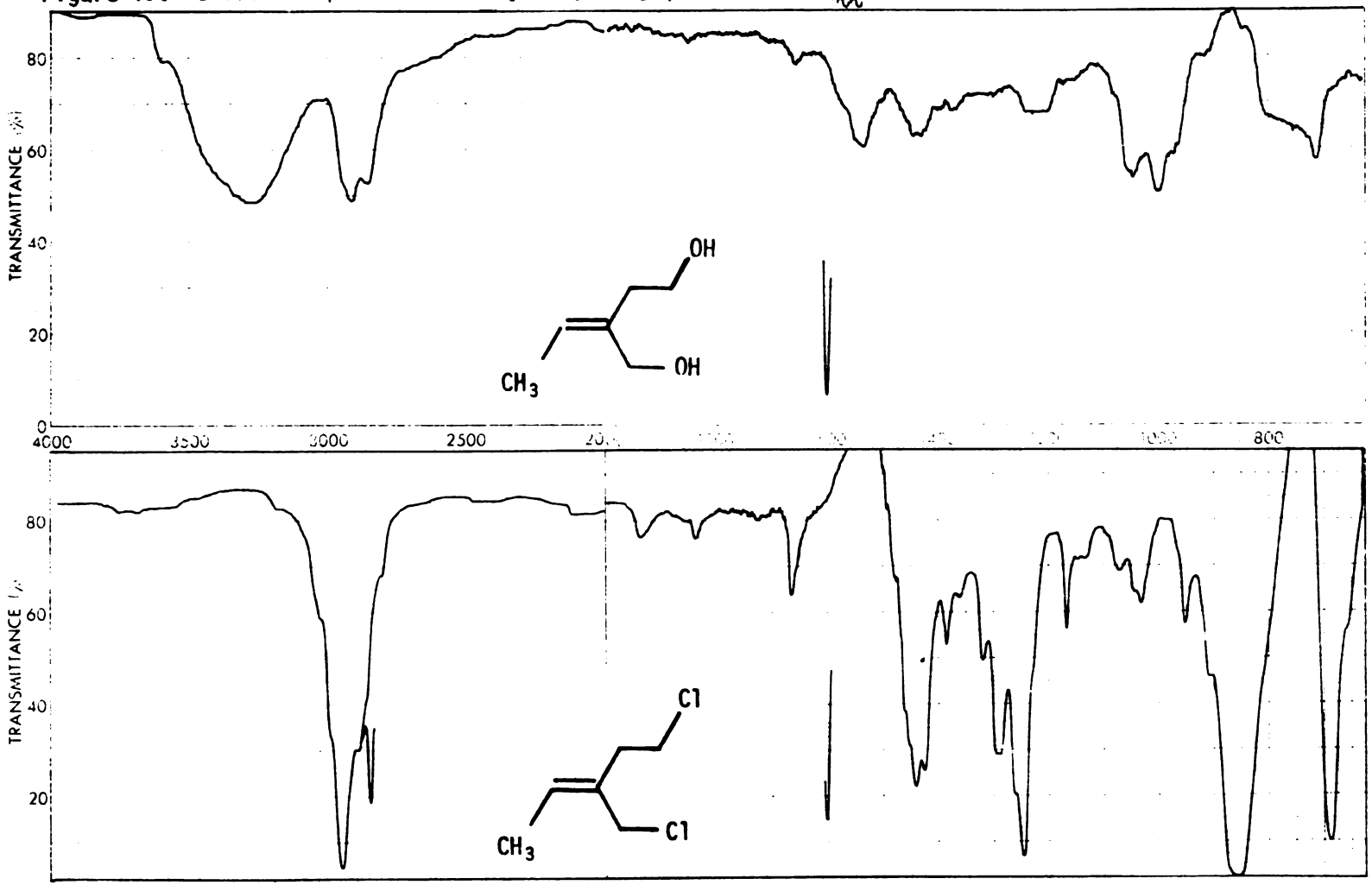


Figure 20. Infrared spectrum of chloro-3-chloroomethylpent-3-ene (82).

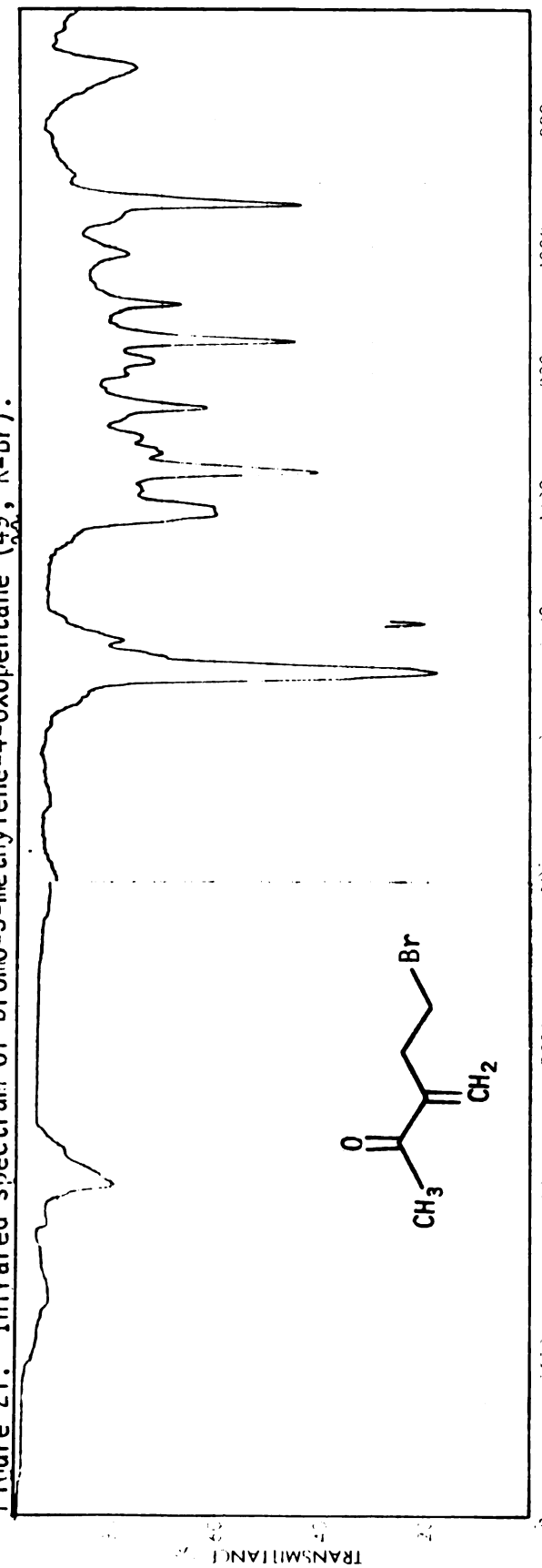


Figure 21. Infrared spectrum of bromo-3-methylene-4-oxopentane (49, R=Br).

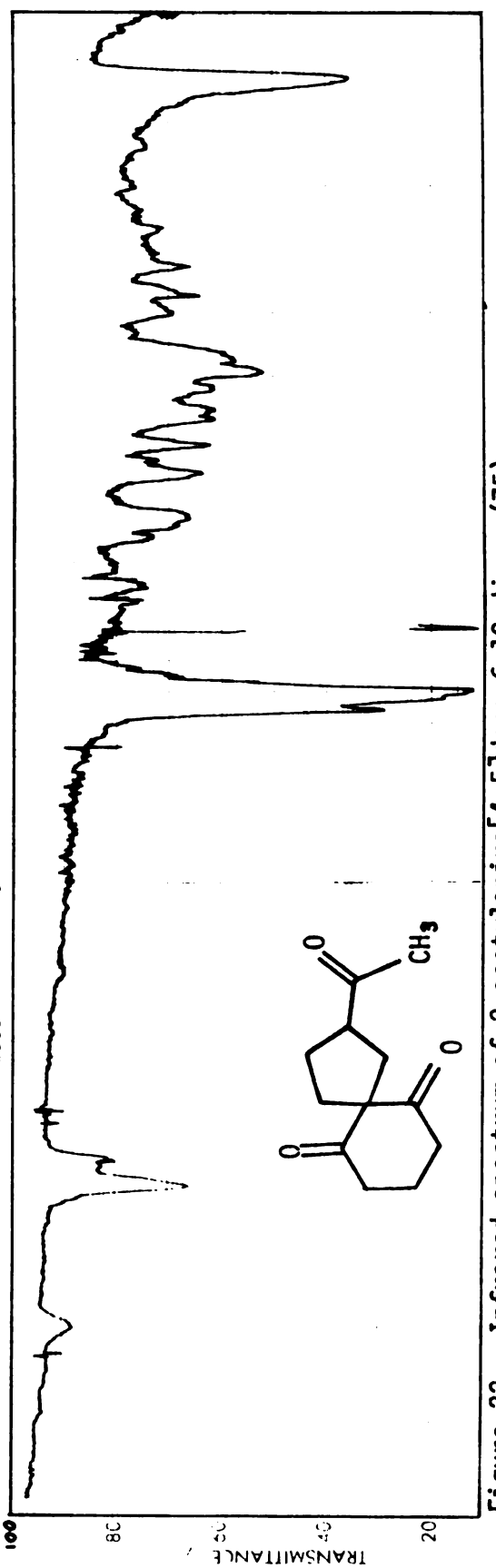


Figure 22. Infrared spectrum of 2-acetylspiro[4.5]deca-6,10-dione (75).

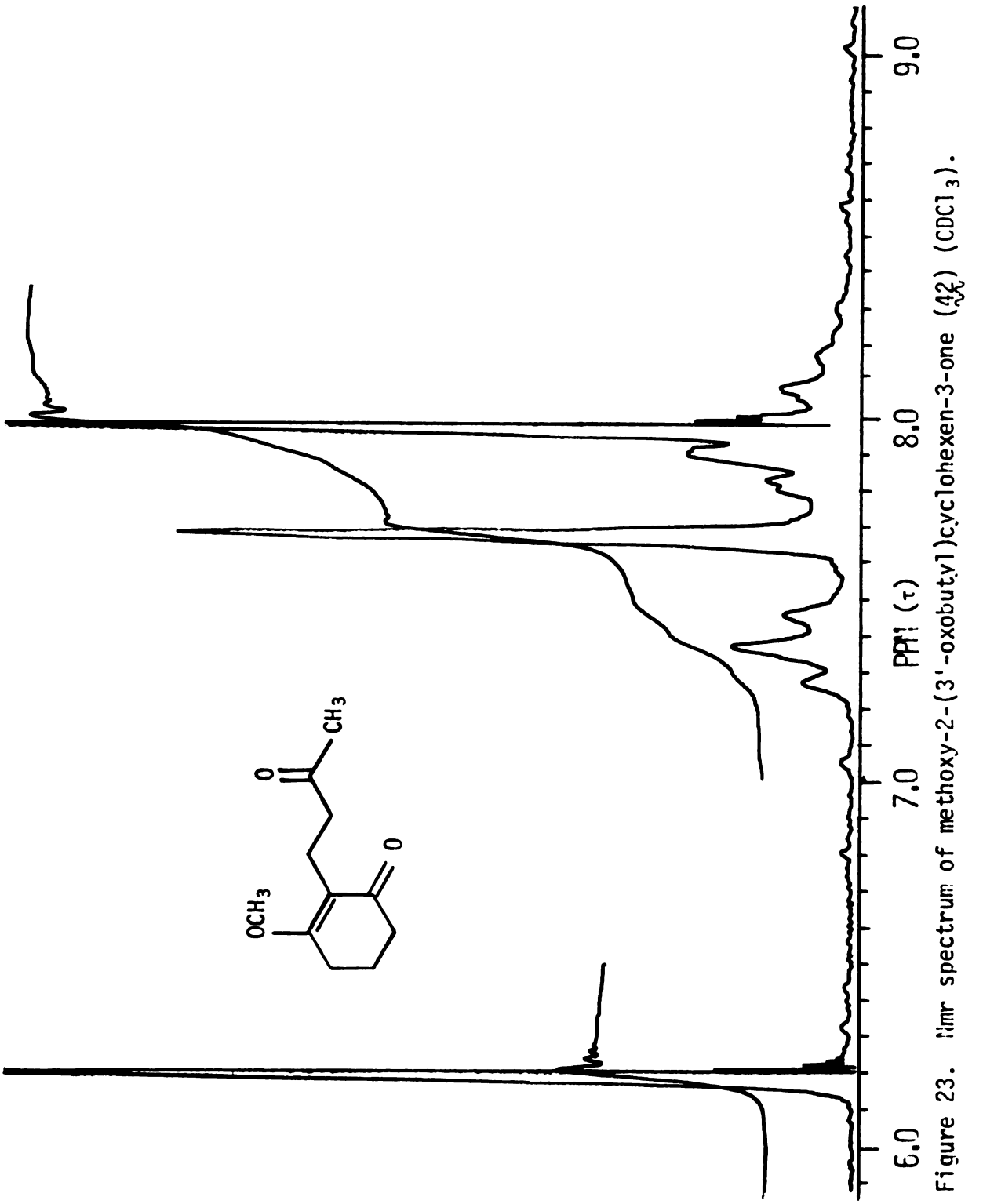


Figure 23. Nmr spectrum of methoxy-2-(3'-oxobutyl)cyclohexen-3-one (42) ($CDCl_3$).

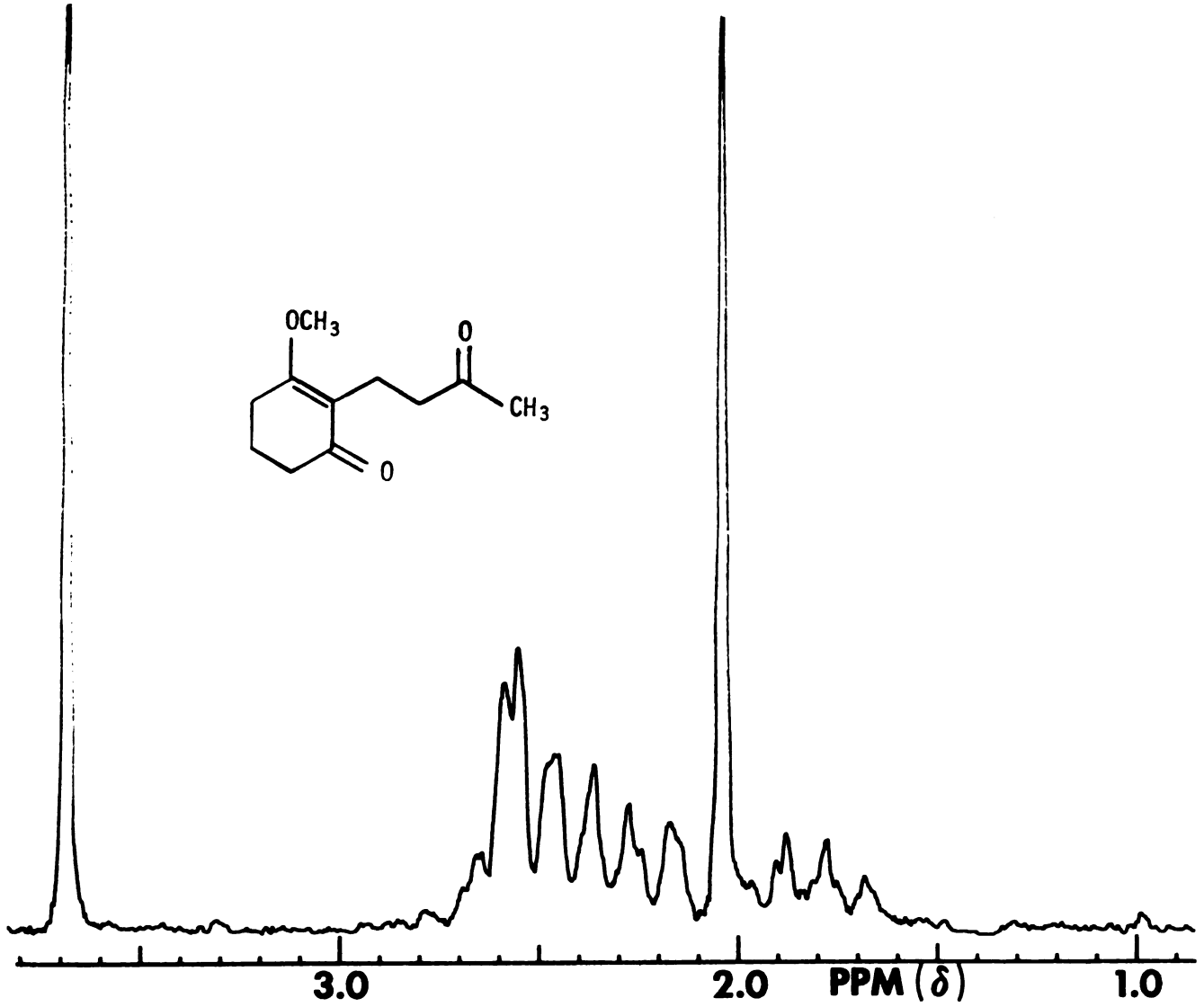


Figure 24. Nmr spectrum of methoxy-2-(3'-oxobutyl)cyclohexen-3-one (42) (pyridine).

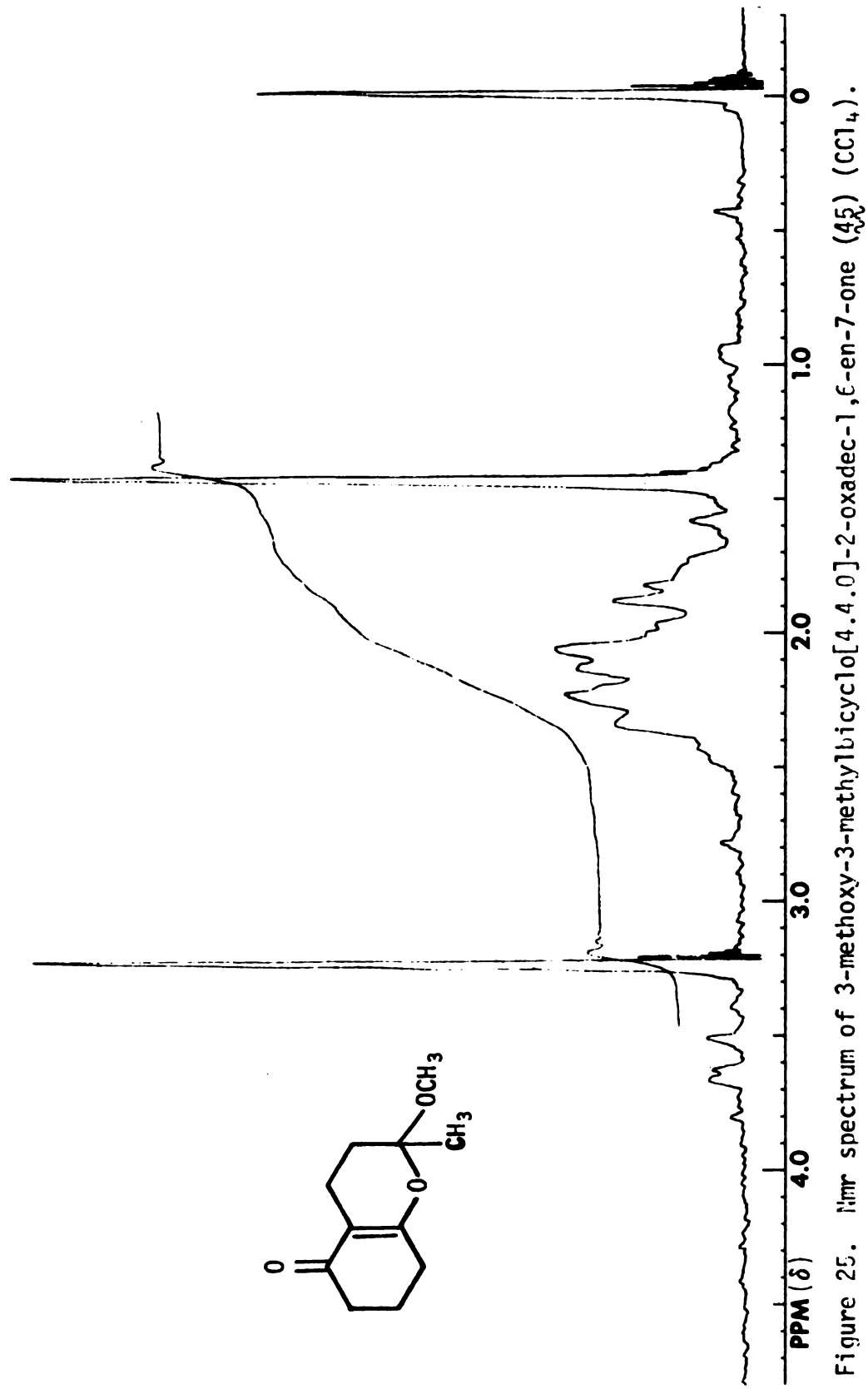


Figure 25. Nmr spectrum of 3-methoxy-3-methylbicyclo[4.4.0]-2-oxadec-1,5-en-7-one (45) (CCl_4).

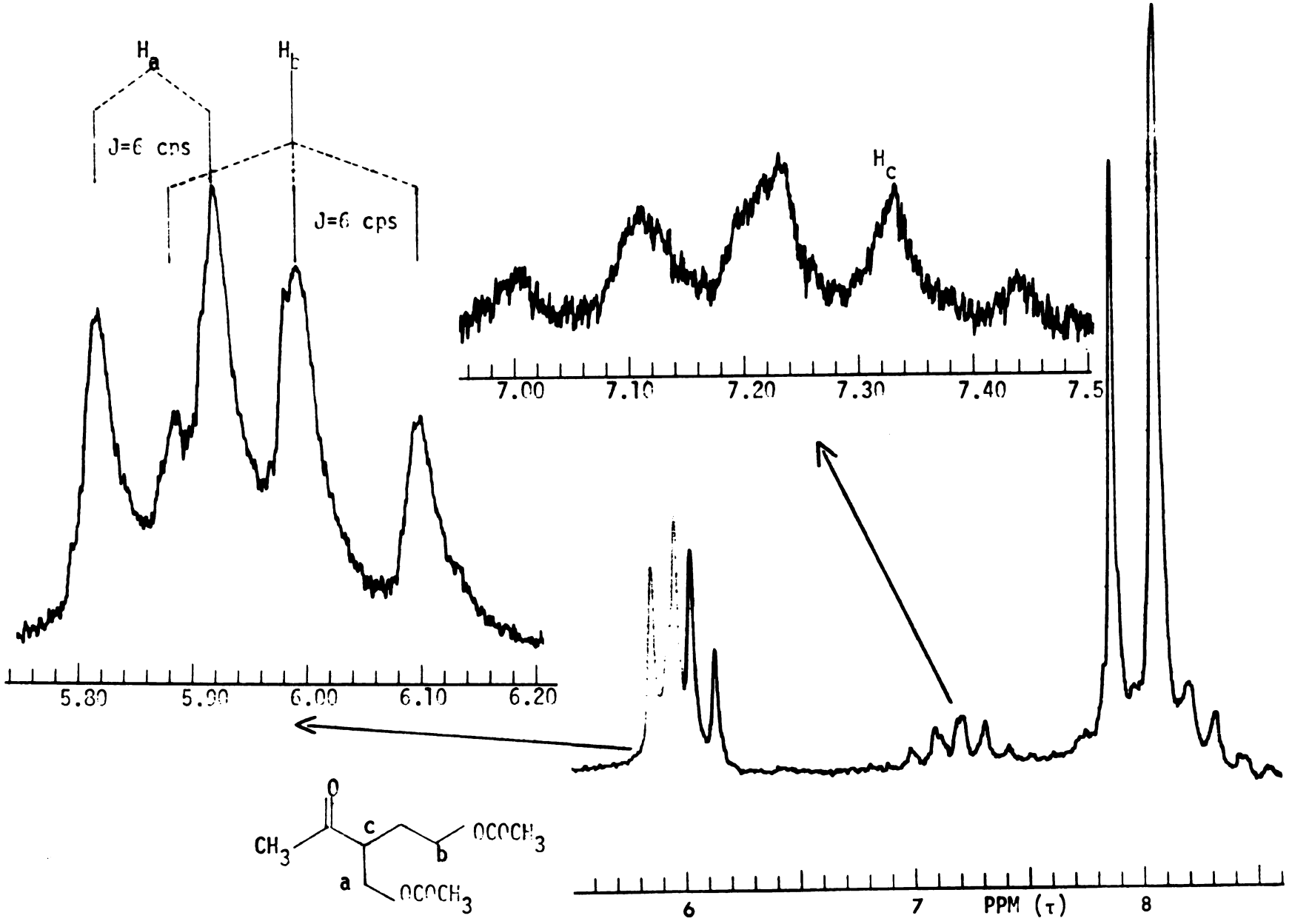


Figure 26. Nmr spectrum of 2-acetylbutane-1,4-diol diacetate (48, R=$OCOCH_3$) (CCl_4).

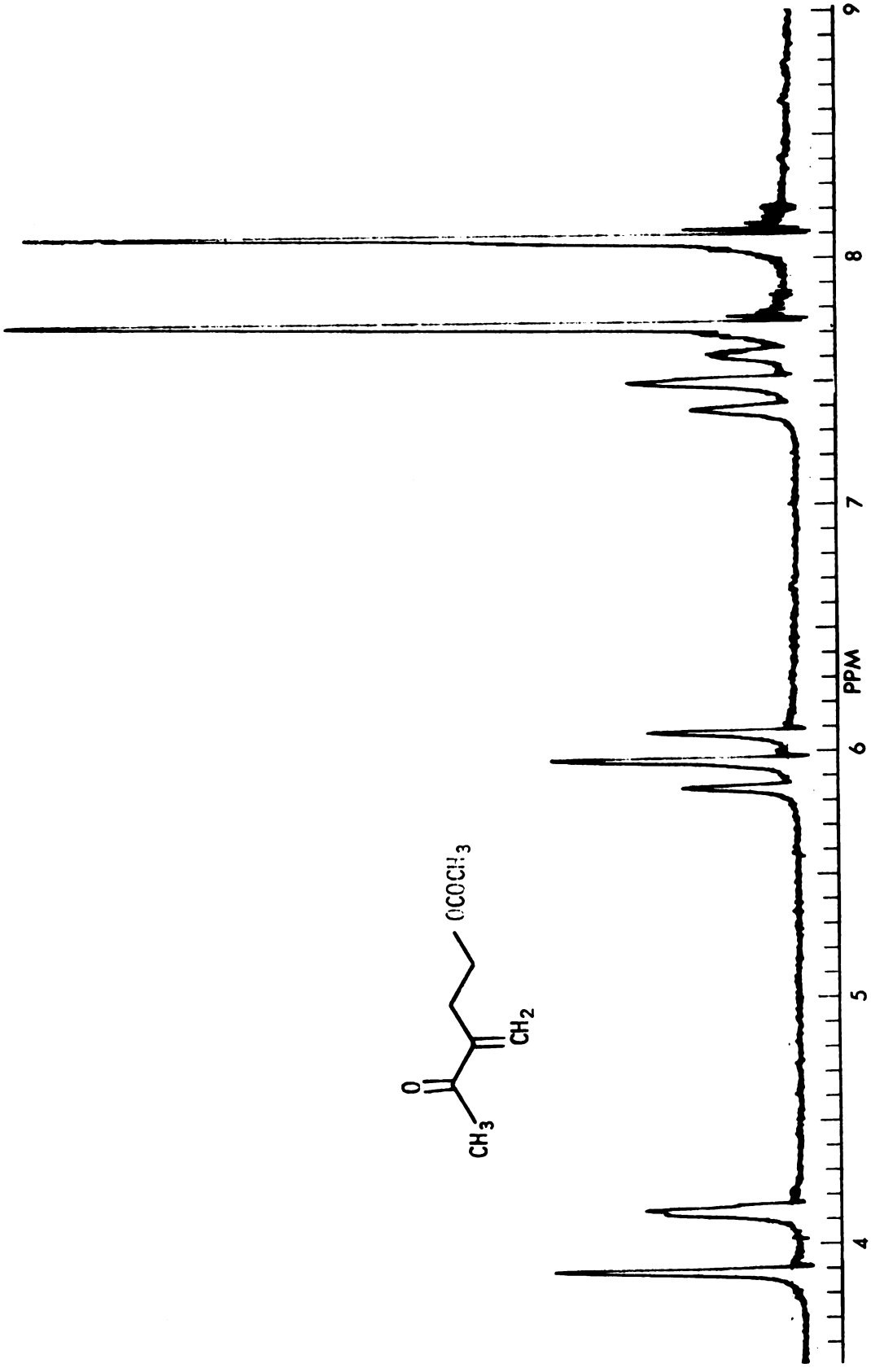


Figure 27. Nmr spectrum of 3-methylene-4-oxopentanol acetate (40, R=OCOCH$_3$) (neat).

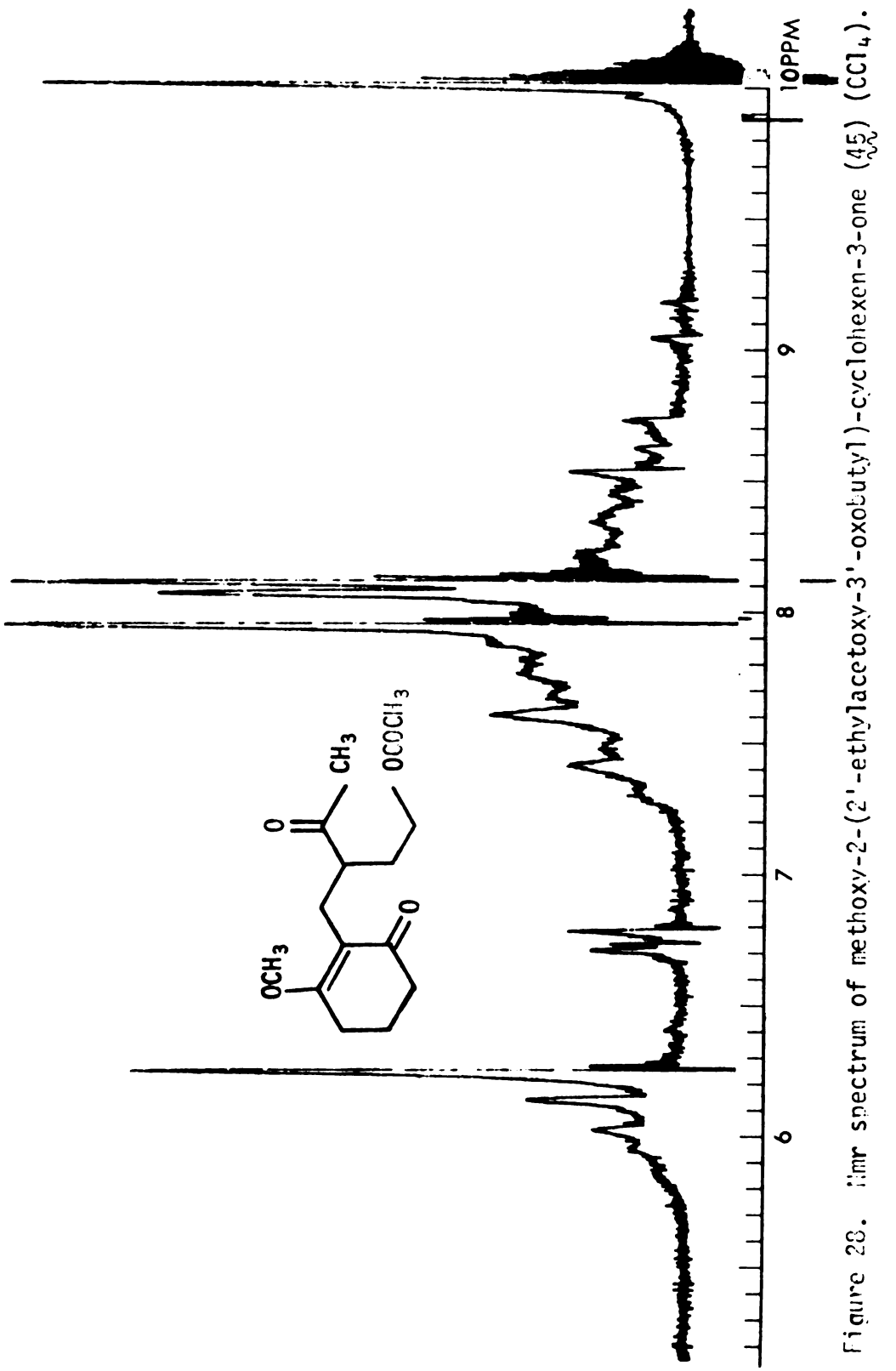


Figure 28. Nmr spectrum of methoxy-2-(2'-ethylacetoxy-3'-oxobutyl)-cyclohexen-3-one (45) (CCl_4).

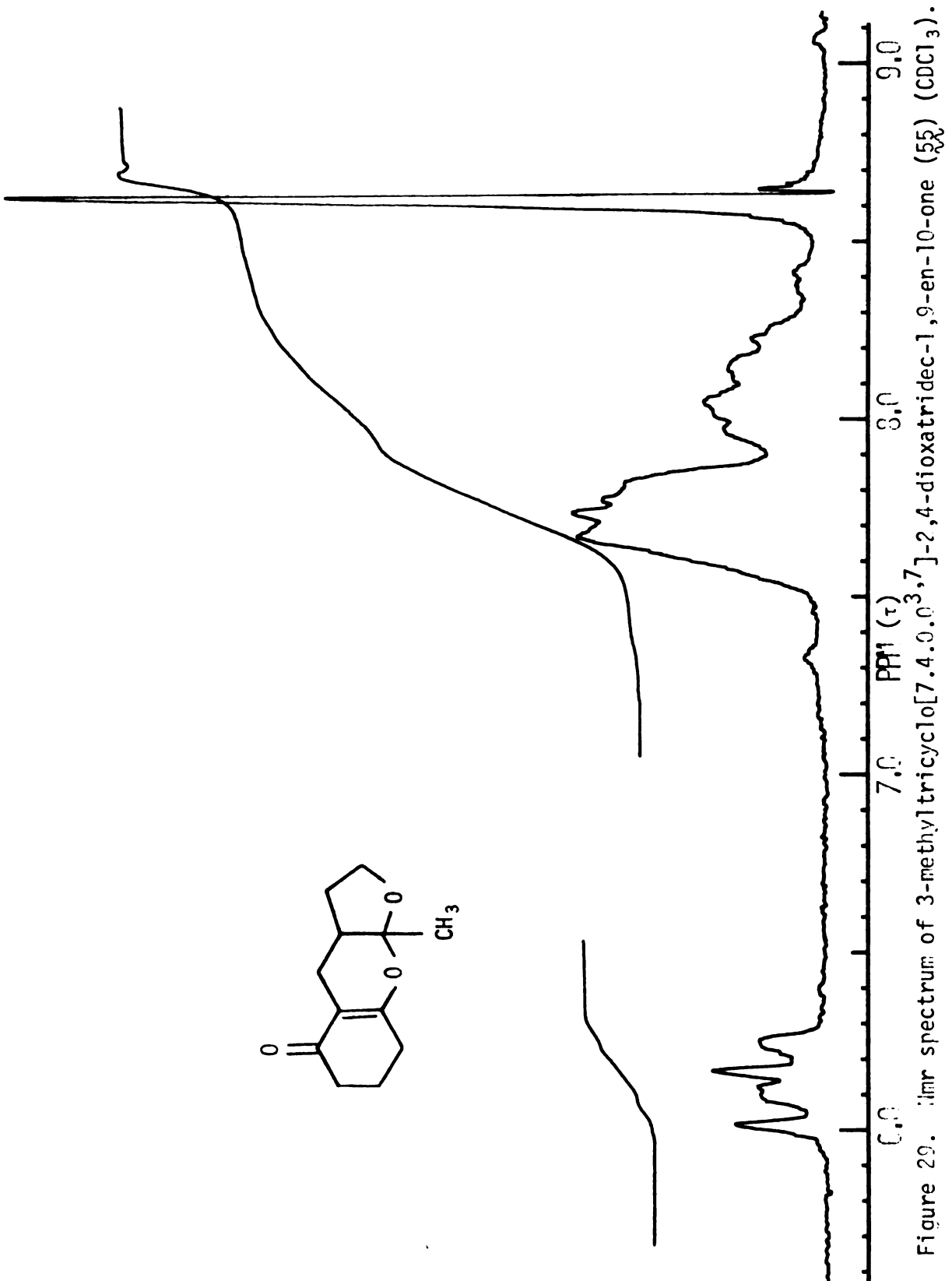


Figure 29. Nmr spectrum of 3-methyltricyclo[7.4.0.0^{3,7}]-2,4-dioxatridec-1,9-en-10-one (55) ($CDCl_3$).

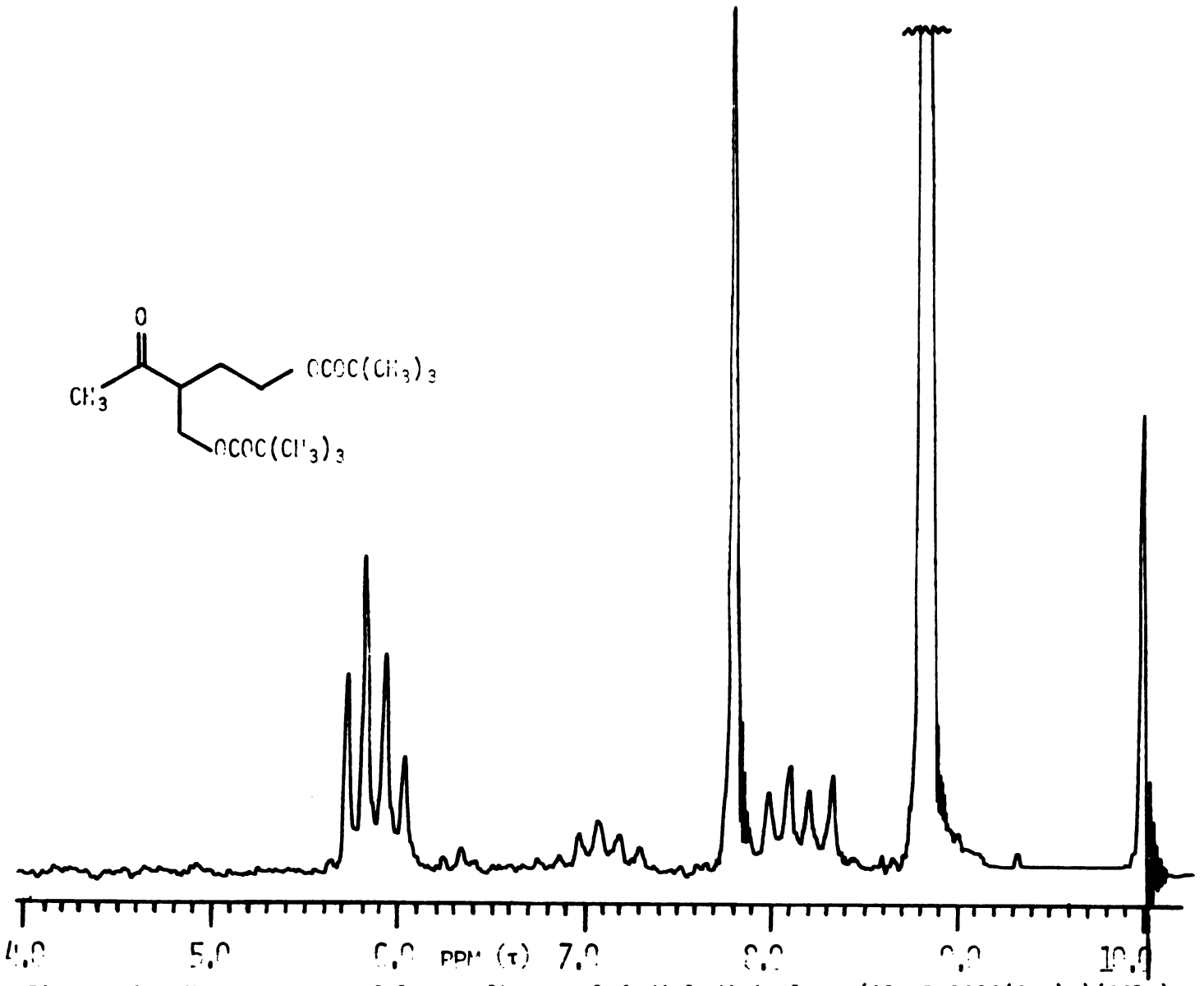


Figure 30. Nmr spectrum of 2-acetylbutane-1,4-diol dipivalate (48, R=$OCOC(CH_3)_3$)(CCl_4).

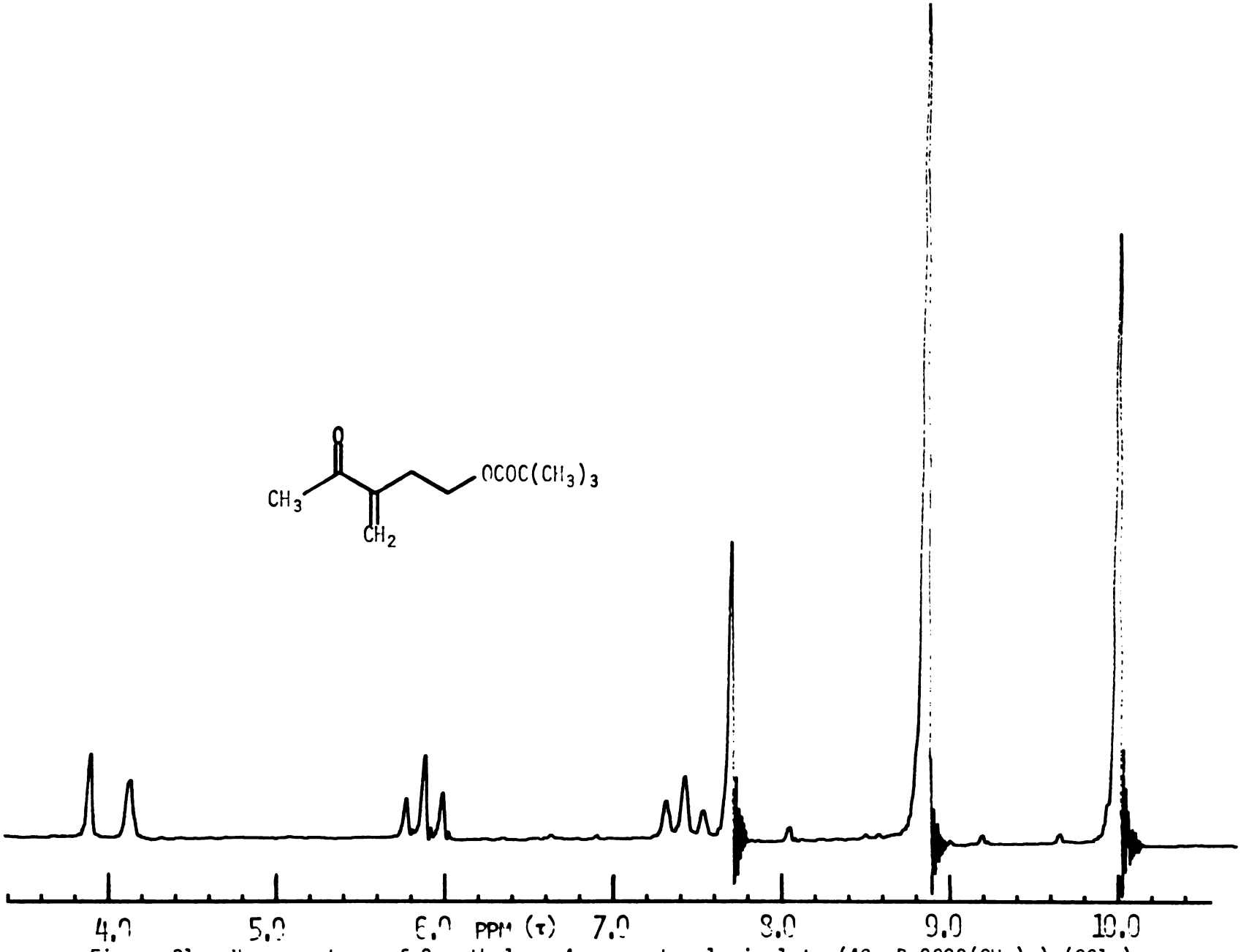


Figure 31. Nmr spectrum of 3-methylene-4-oxopentanol pivalate (49, R=OCOC$(CH_3)_3$) (CCl_4).

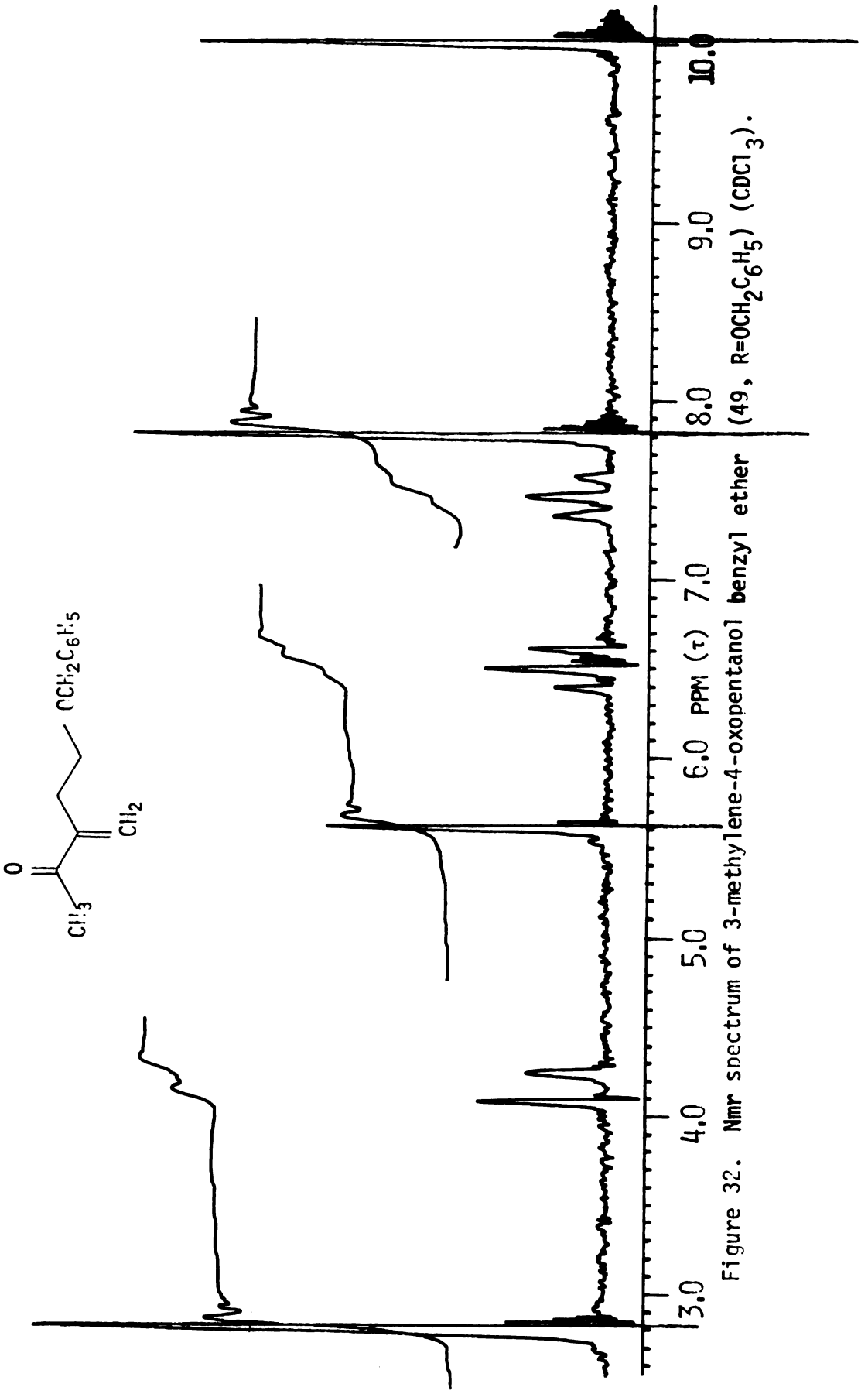


Figure 32. Nmr spectrum of 3-methylene-4-oxopentanol benzyl ether (49, R=$OCH_2C_6H_5$) ($CDCl_3$).

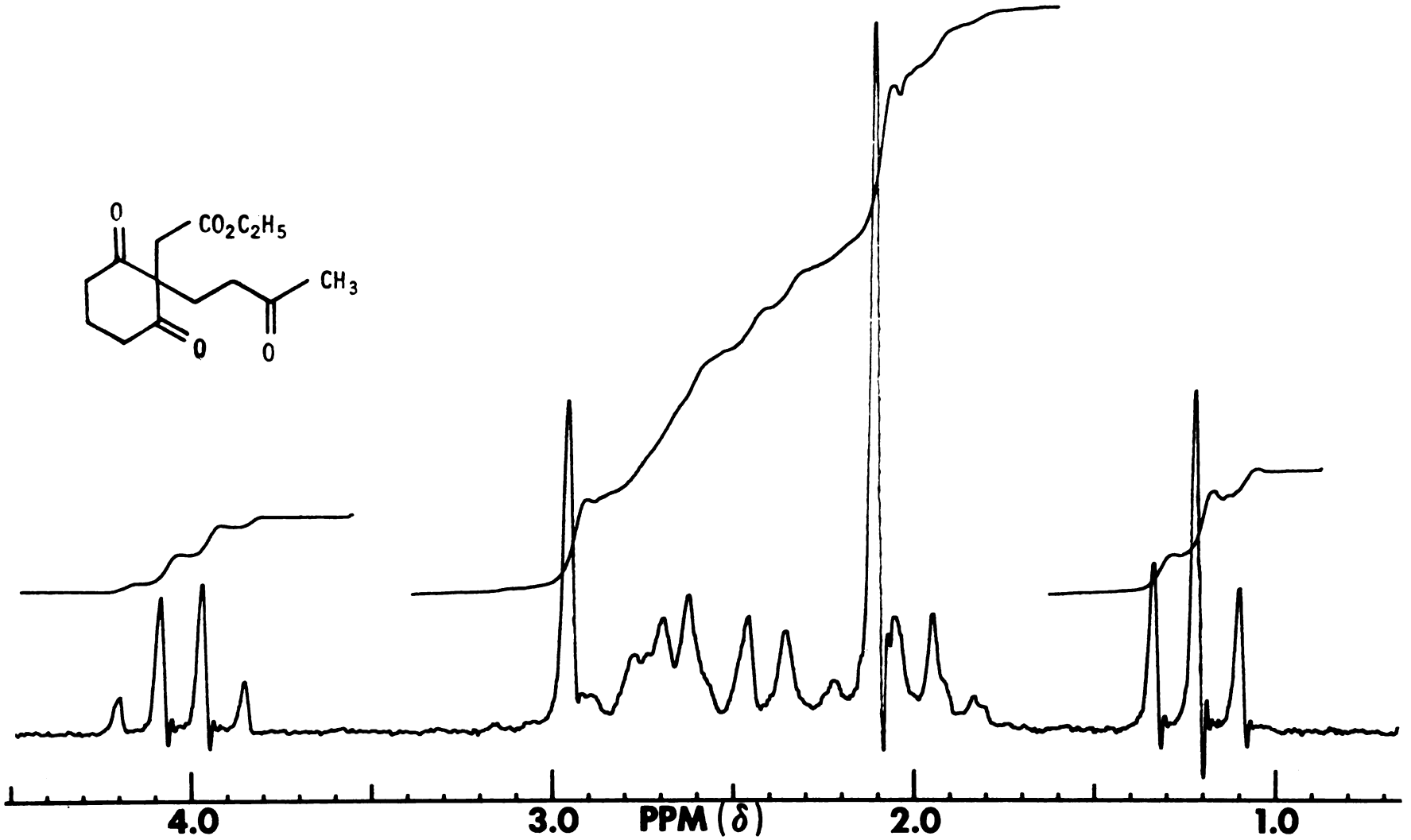


Figure 33. Nmr spectrum of 2-[2'-cyclohexane-1',3'-dione-2-(3"-oxobutyl)]acetic acid ethyl ester (60)($CDCl_3$).

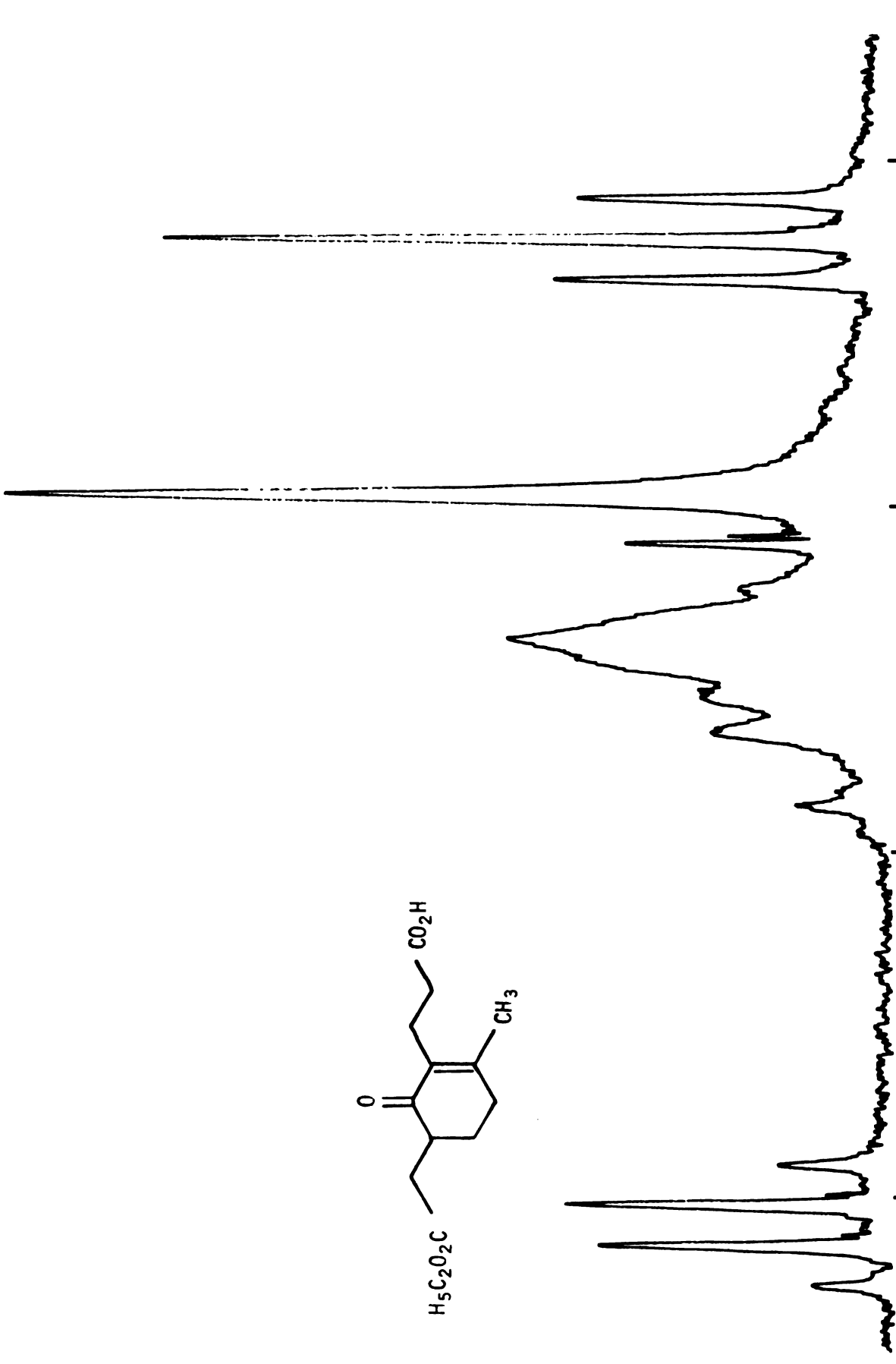


Figure 34. Nmr spectrum of 2-(β-carboxyethyl)-6-carbethoxymethyl-3-methylcyclohex-2-enone (63,R=H)(CCl_4).

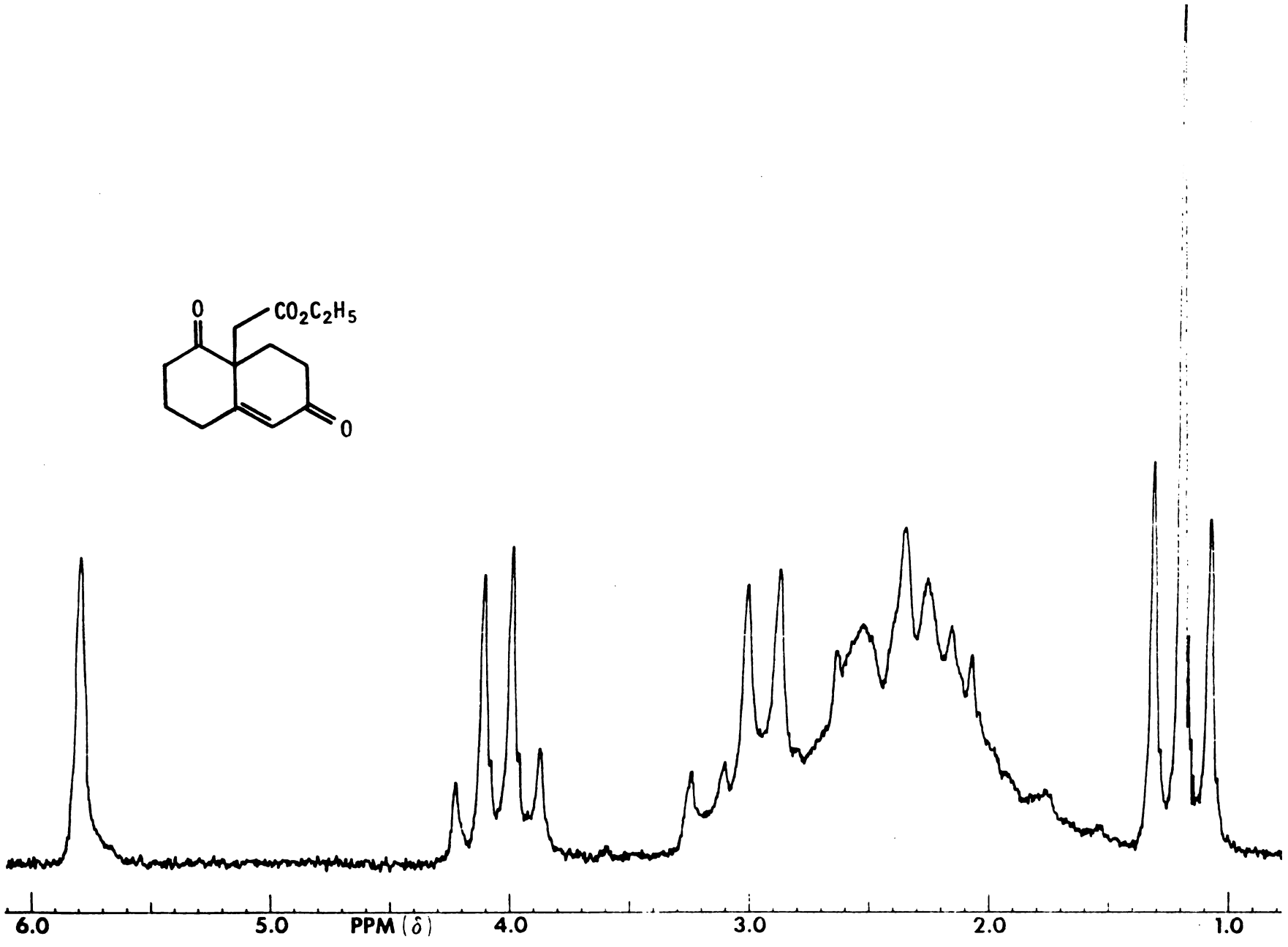


Figure 35. Nmr spectrum of 4a-carbethoxymethyl-4,4a,7,8-tetrahydronaphthalene-2,5(3H,6H)-dione (61)($CDCl_3$).

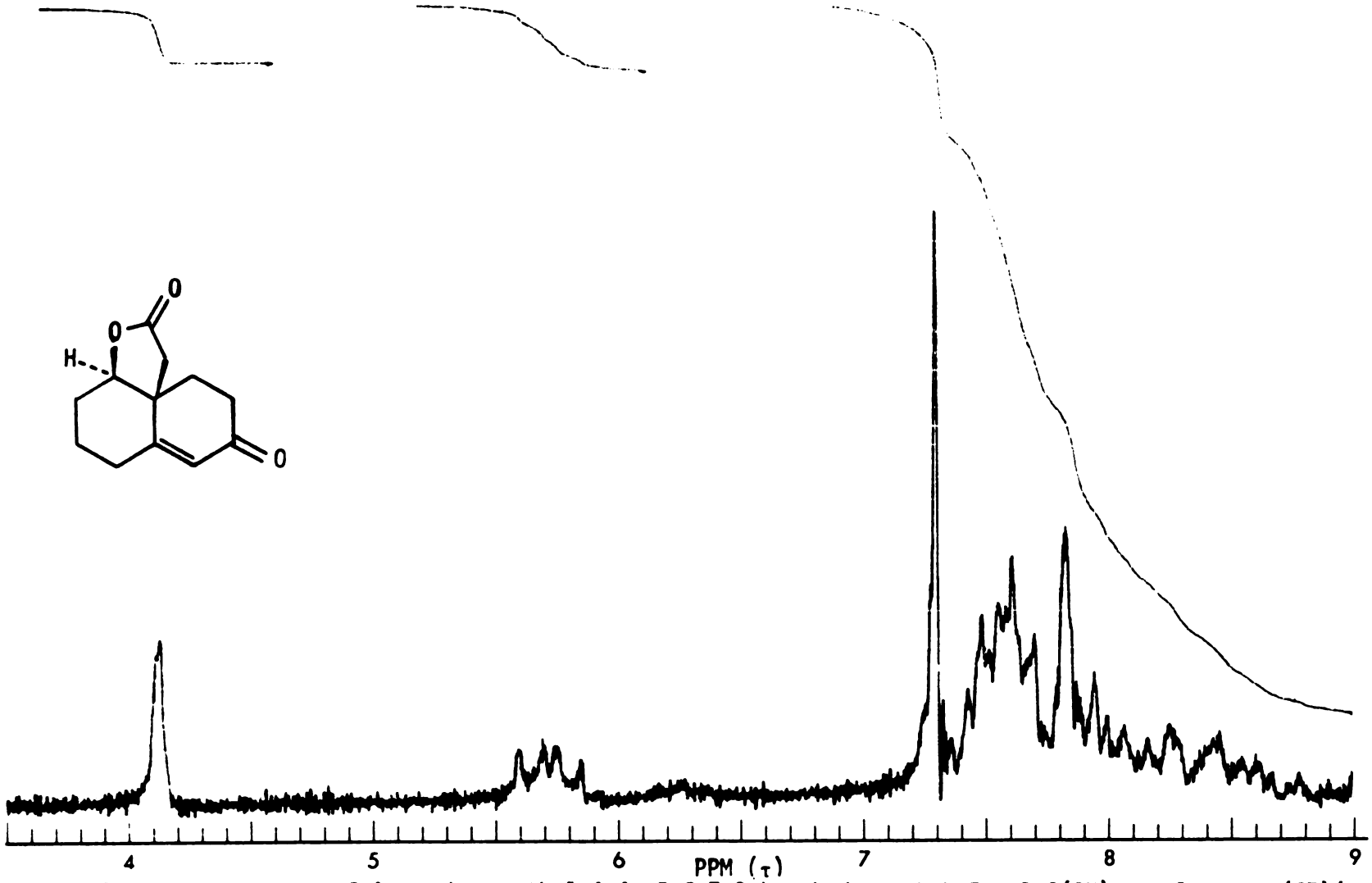


Figure 3C. Nmr spectrum of 4aβ-caboxymethyl-4,4a,5,6,7,8-hexahydronaphth-5β-ol-2(3H)-one lactone (65)($CDCl_3$).

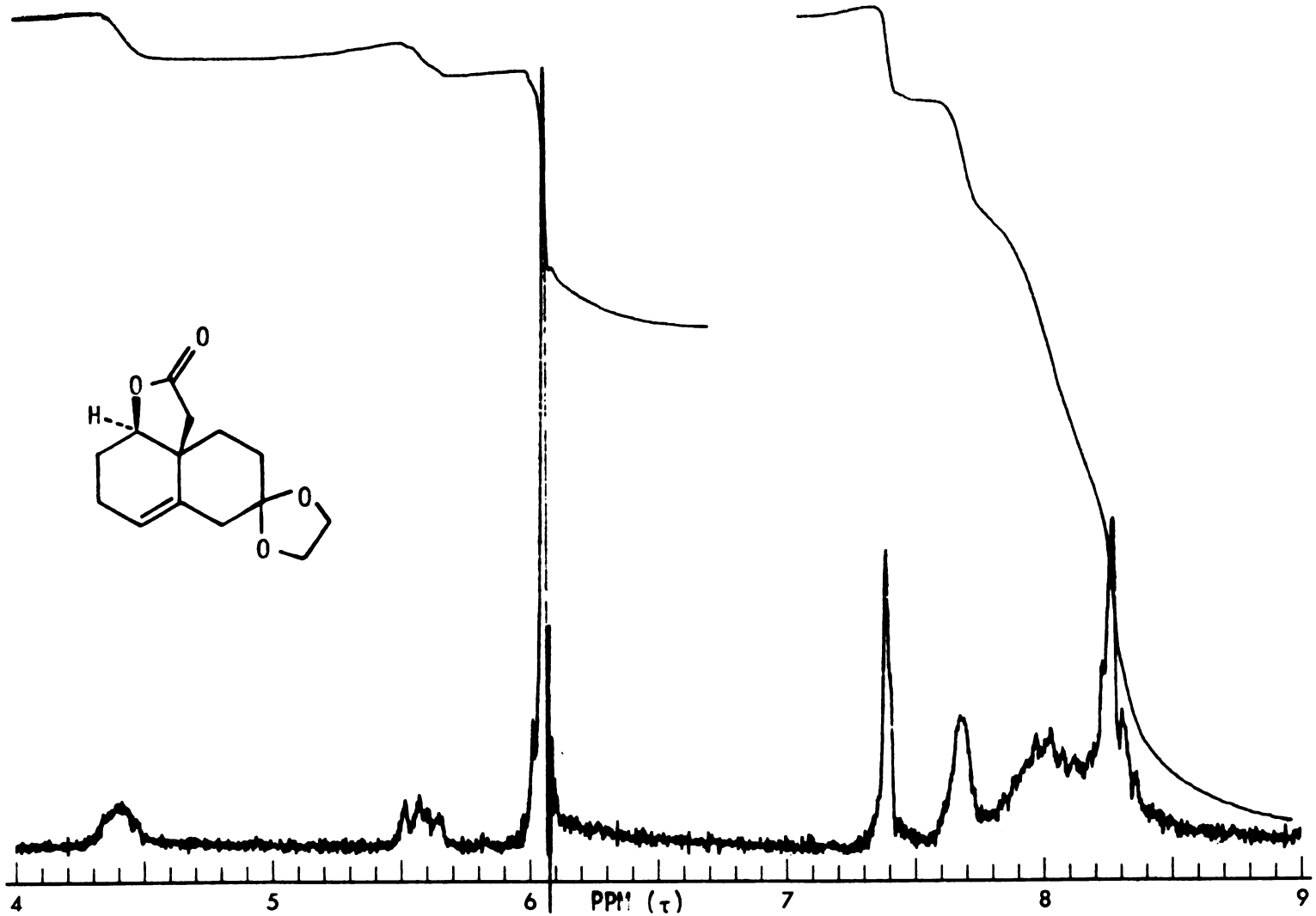


Figure 37. Nmr spectrum of 4aβ-carboxymethyl-2-(1',3'-dioxolane)-1,4,4a,5,6,7-hexahydronaphth-5β-ol lactone (66) ($CDCl_3$).

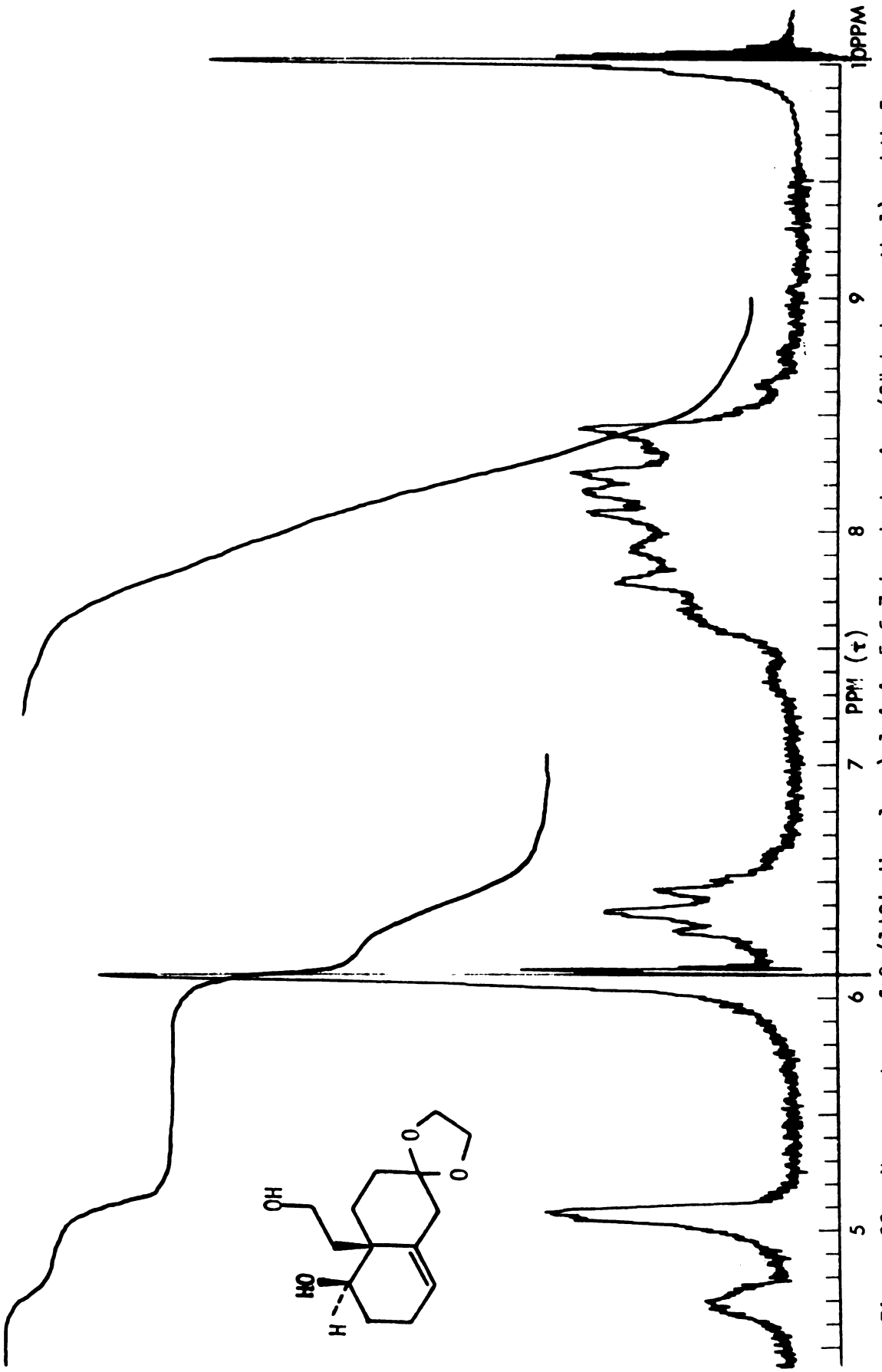


Figure 38. Nmr spectrum of 2-(1';3'-dioxolane)-1,4,4a,5,6,7-hexahydro-4aβ-(2"-hydroxyethyl)naphth-5-ol (62, R=H) ($CDCl_3$).

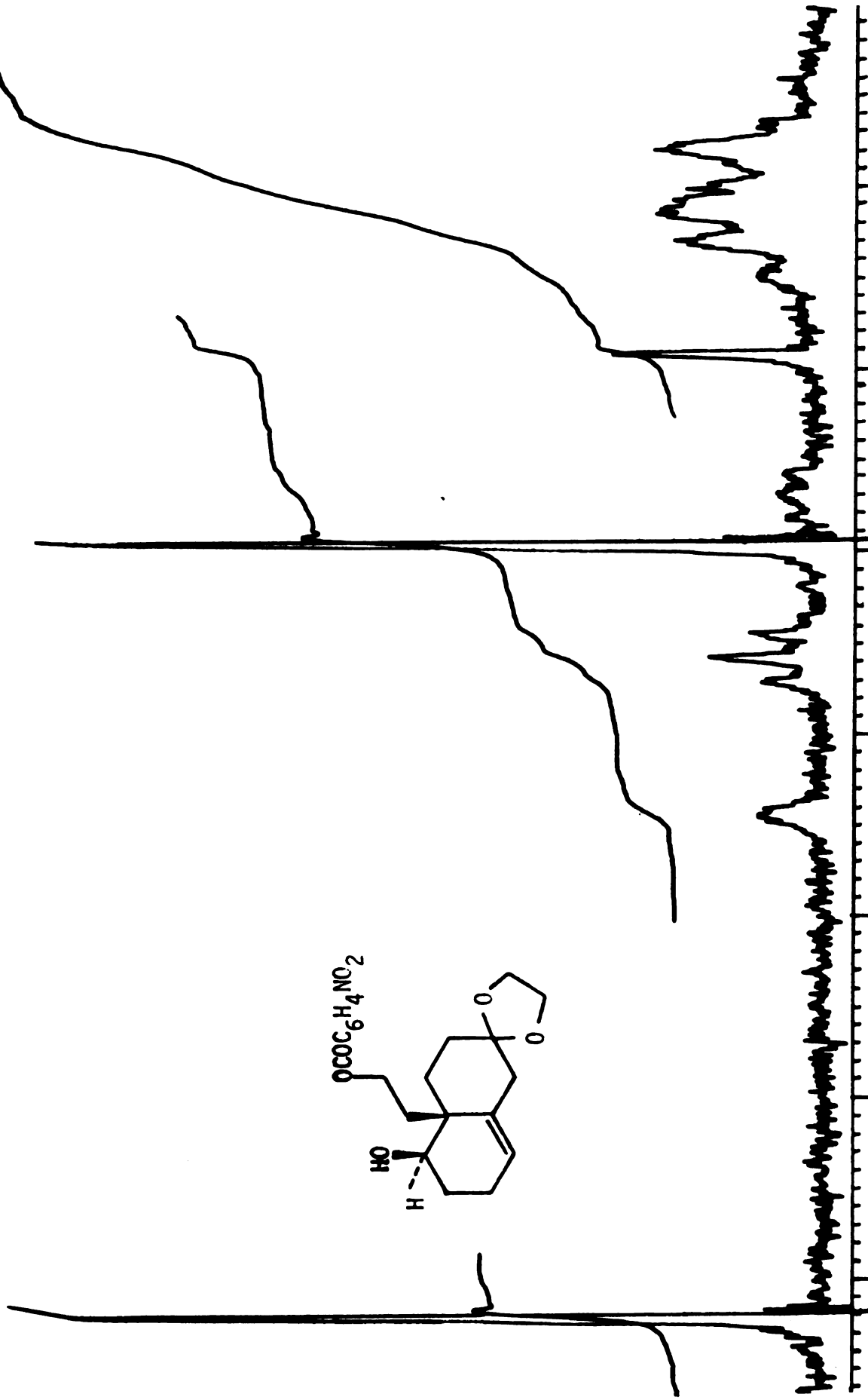


Figure 39. Nmr spectrum of 2-(1';3'-dioxolane)-1,4,4a,5,6,7-hexahydro-4aβ-(2''-hydroxyethyl)naphth-5β-ol mono p-nitrobenzoate (62, R=$COC_6H_4NO_2$) ($CDCl_3$).

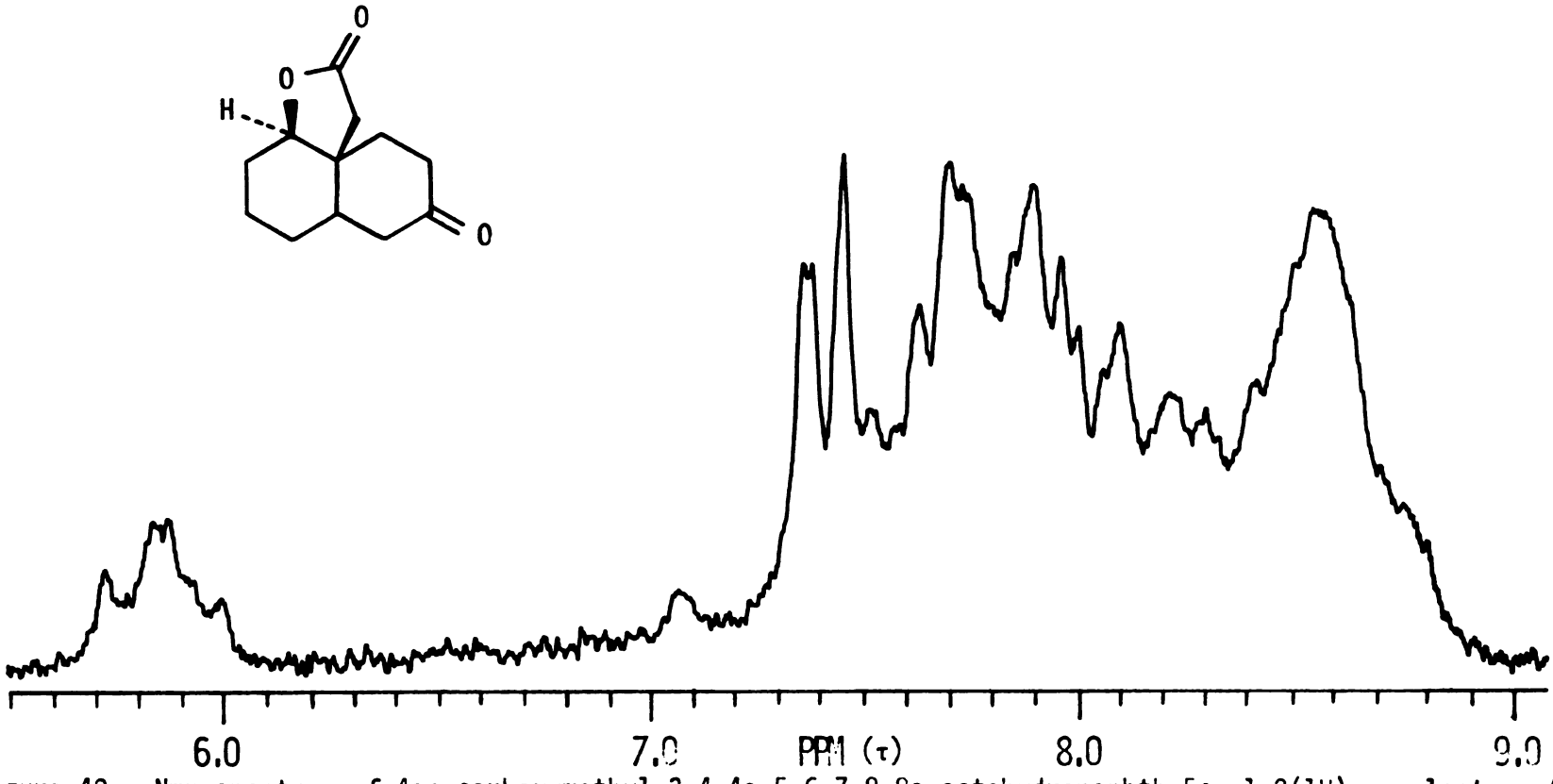


Figure 40. Nmr spectrum of 4aβ-carboxymethyl-3,4,4a,5,6,7,8,8a-octahydronaphth-5β-ol-2(1H)-one lactone (73) ($CDCl_3$).

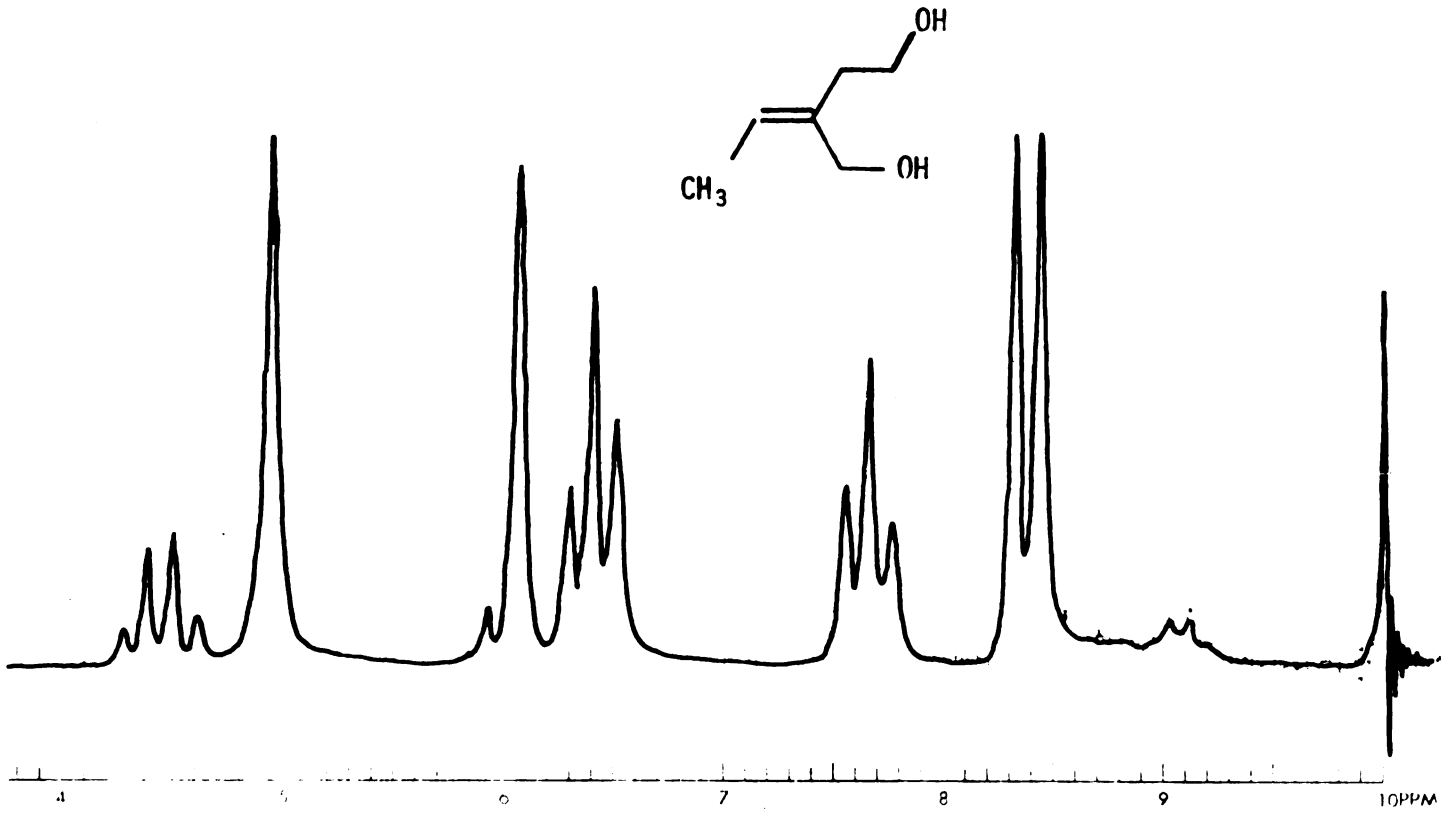


Figure 41. ¹Hmr spectrum of 3-hydroxymethylpent-3-enol (81) ($CDCl_3$).

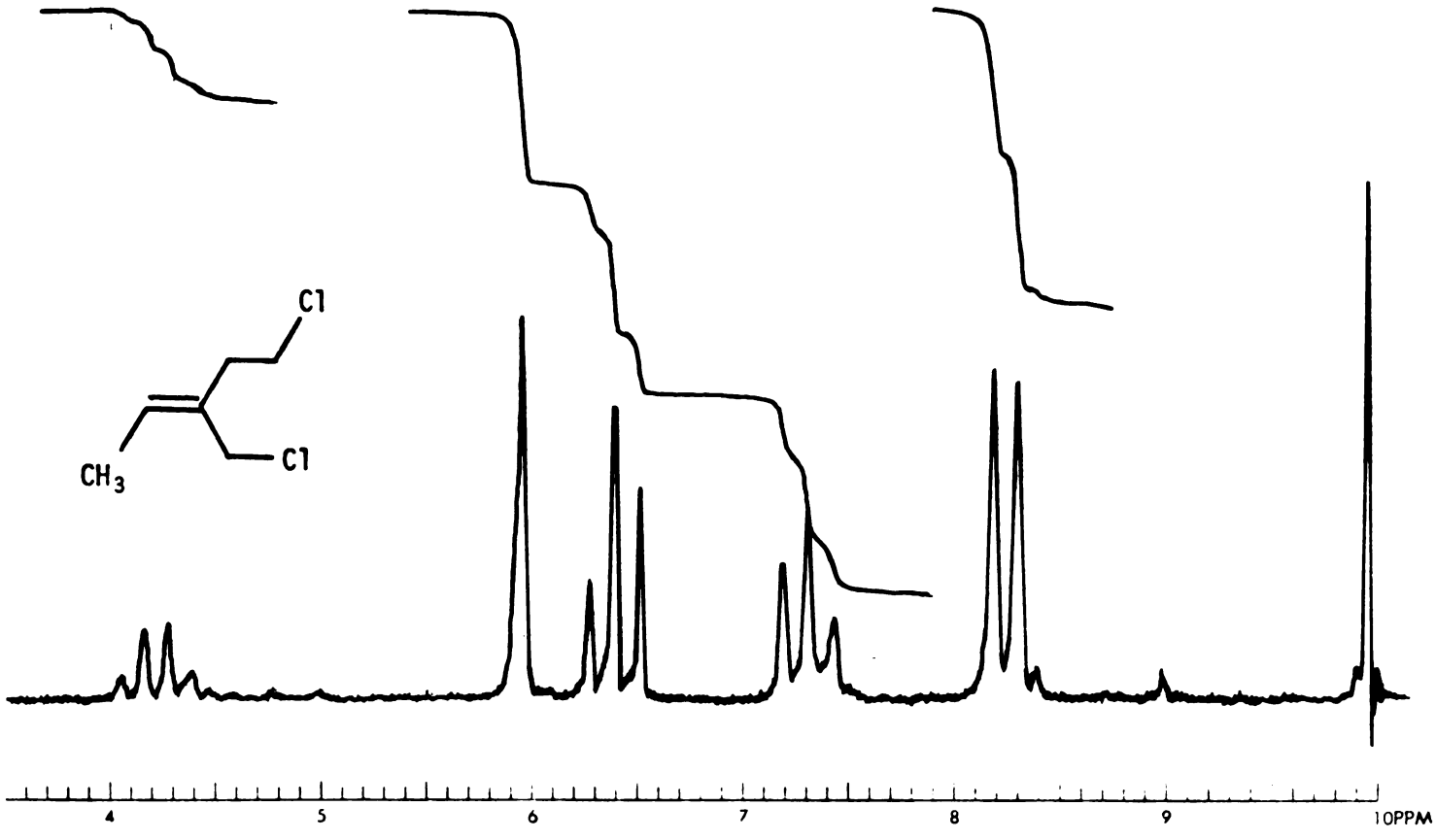


Figure 42. Nmr spectrum of chloro-3-chloromethylpent-3-ene (82) (CCl_4).

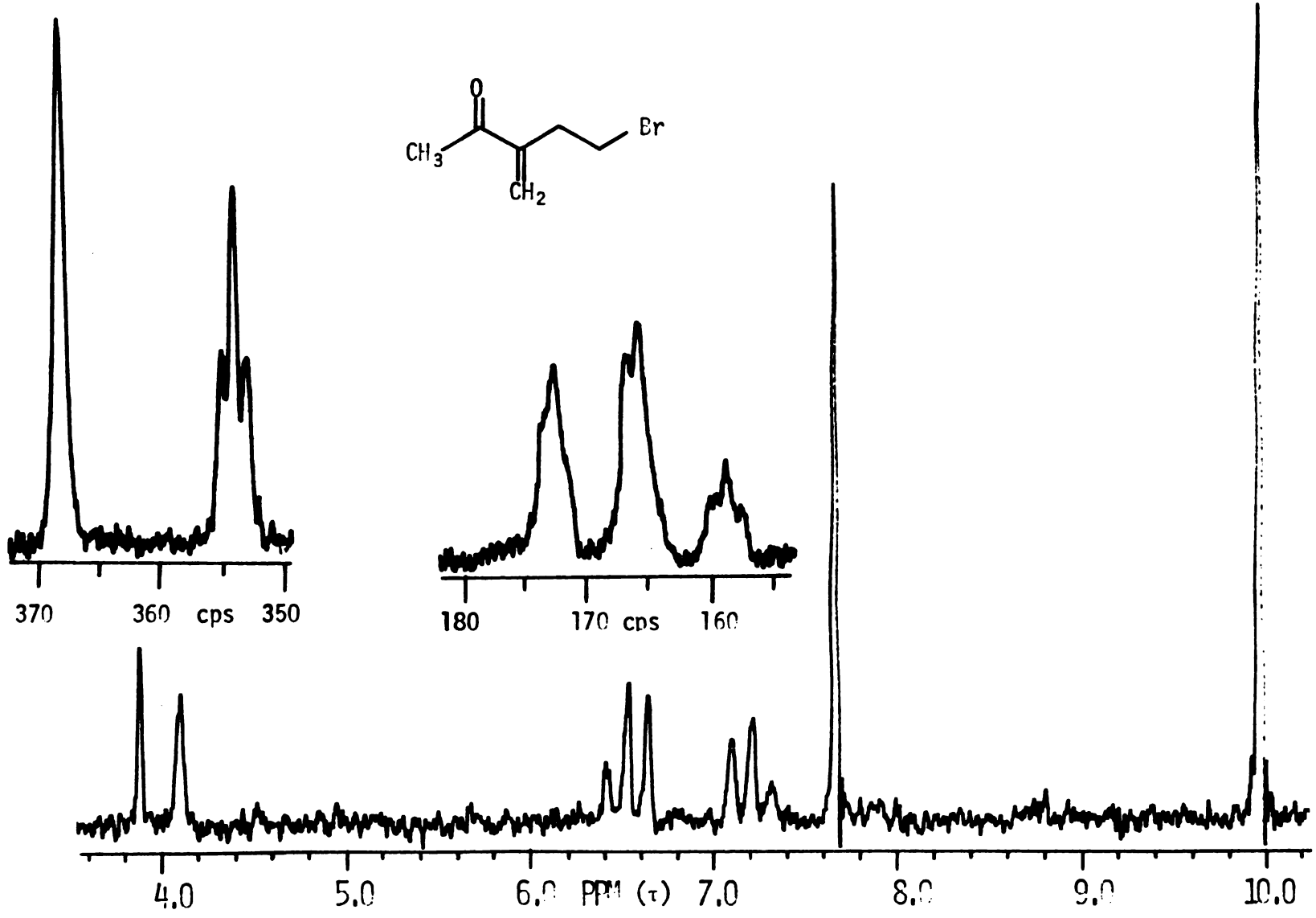


Figure 43. Nmr spectrum of bromo-3-methylene-4-oxopentane (48, R=Br) (CCl_4).

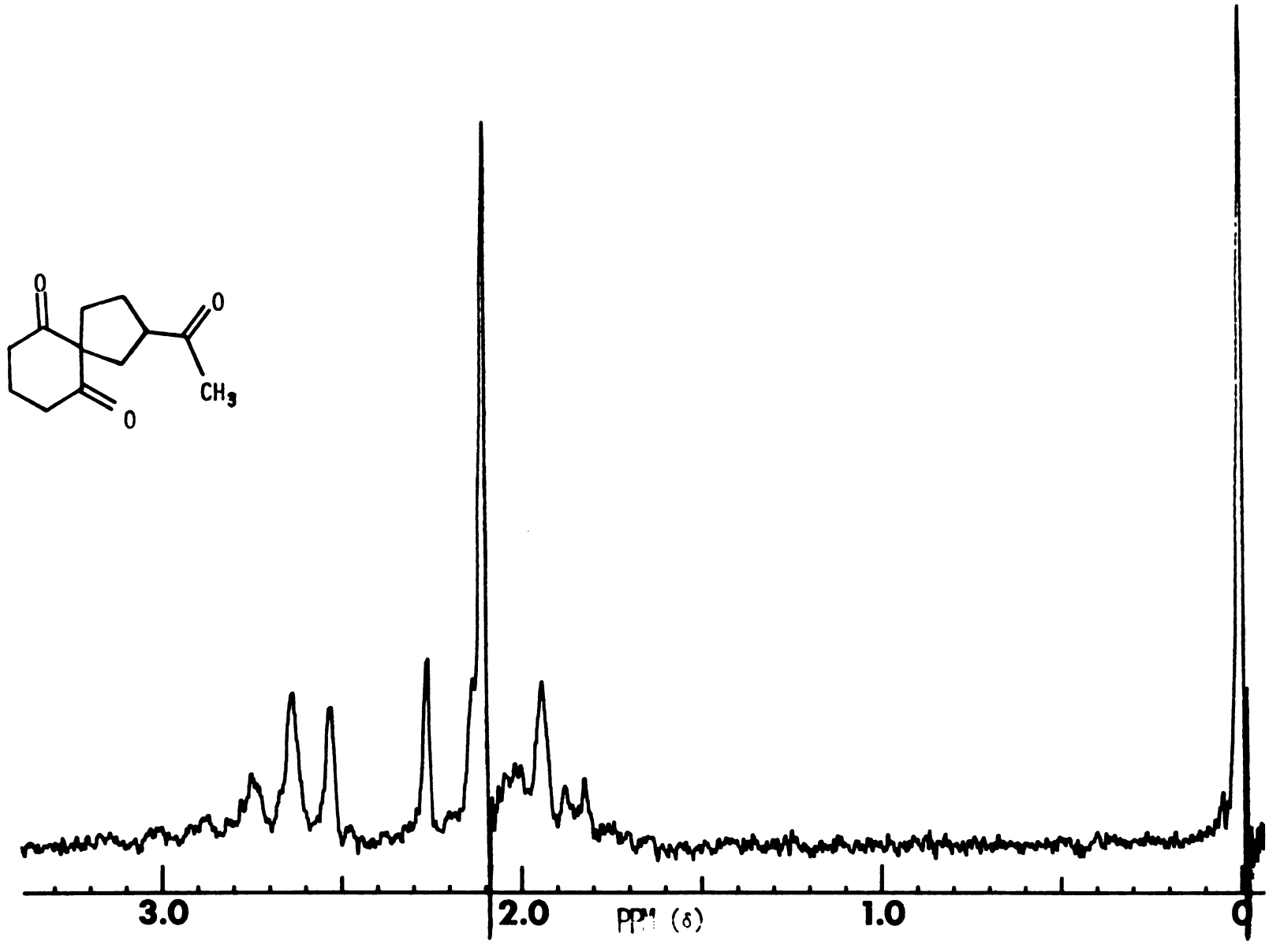


Figure 44. Nmr spectrum of 2-acetylspiro[4.5]deca-6,10-dione (75) (CCl_3).

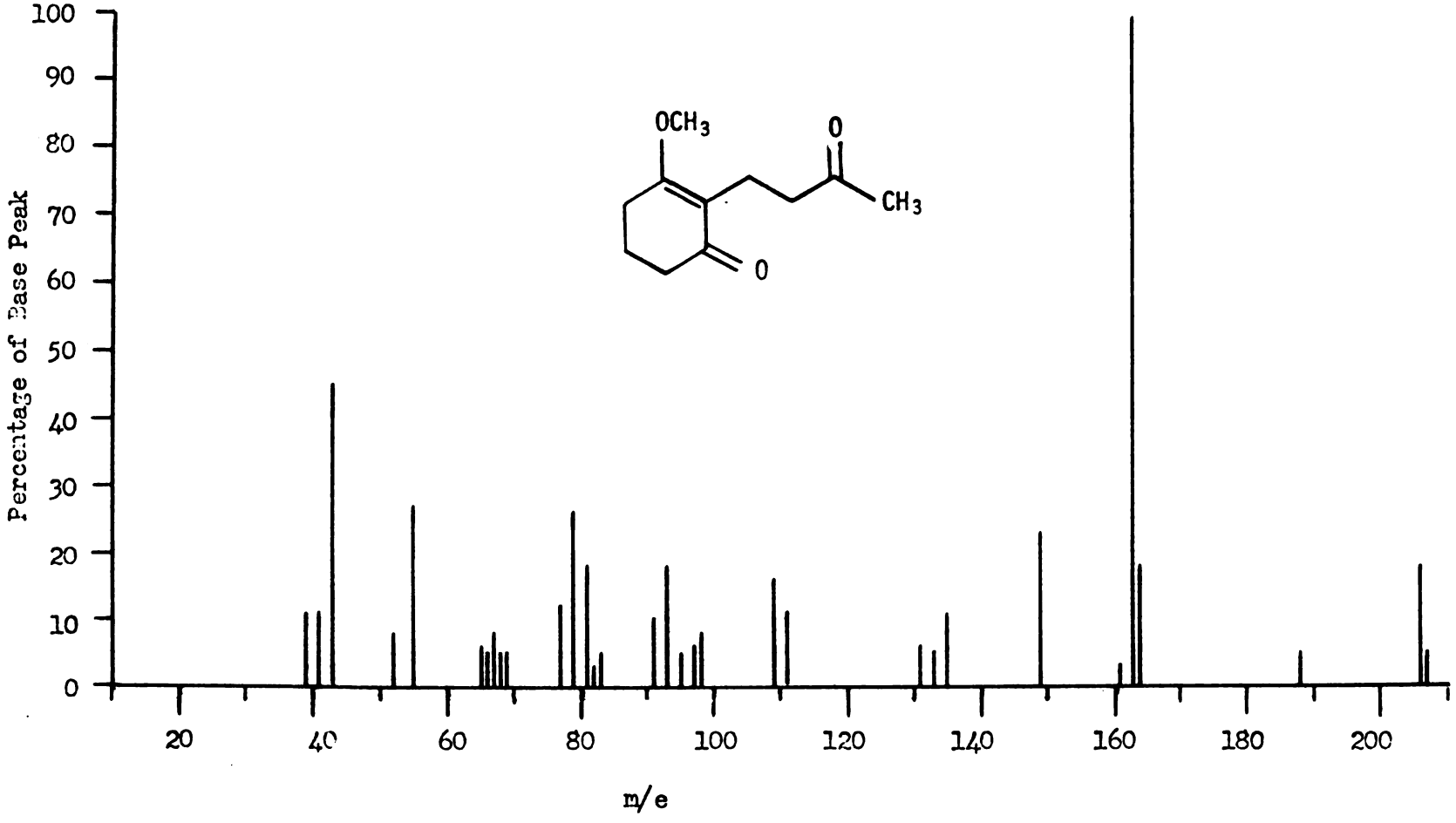


Figure 45. Mass spectrum of methoxy-2-(3'-oxobutyl)cyclohexen-3-one (42).

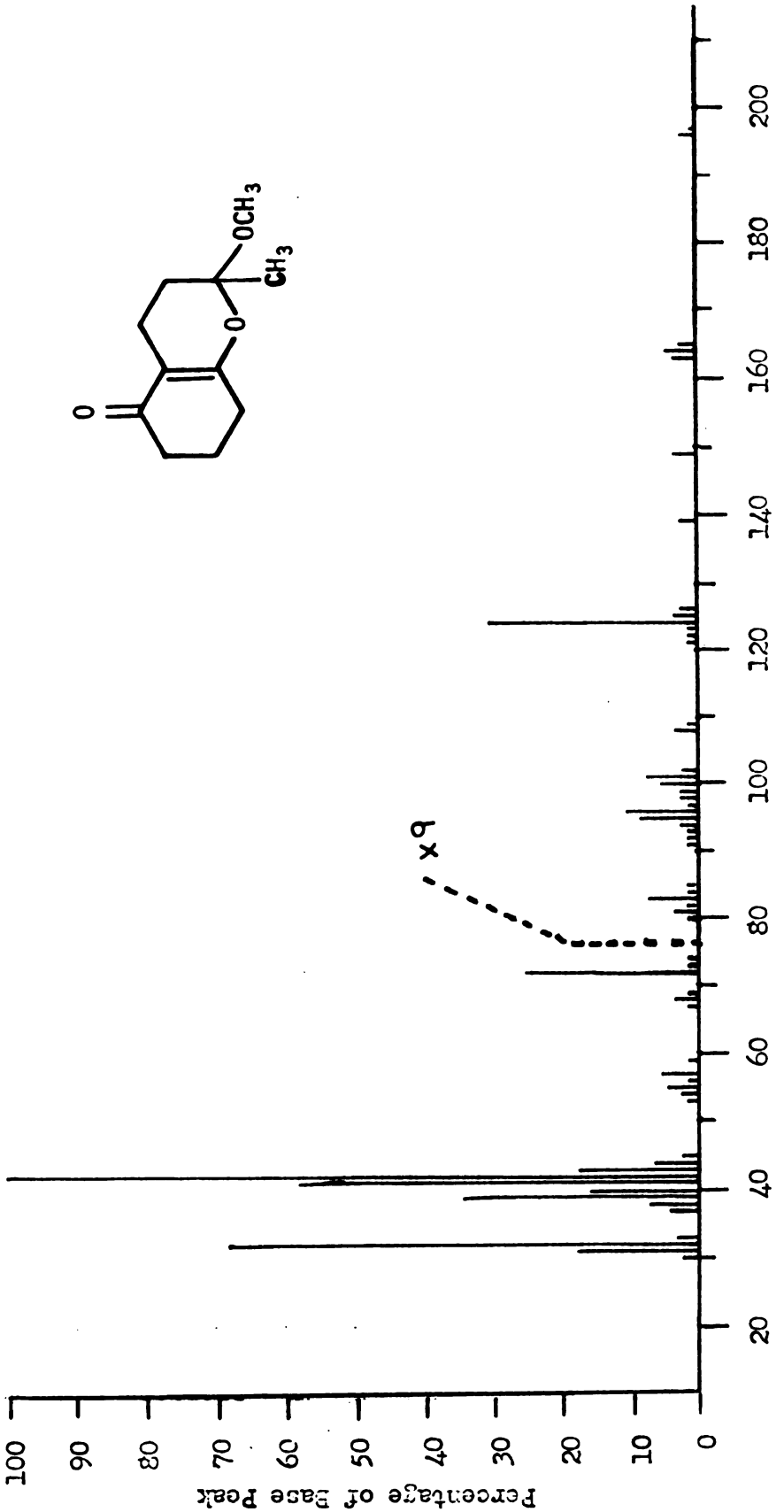


Figure 46. Mass spectrum of 3-methoxy-3-methylbicyclo[4.4.0]-2-oxadec-1,6-en-7-one (45).

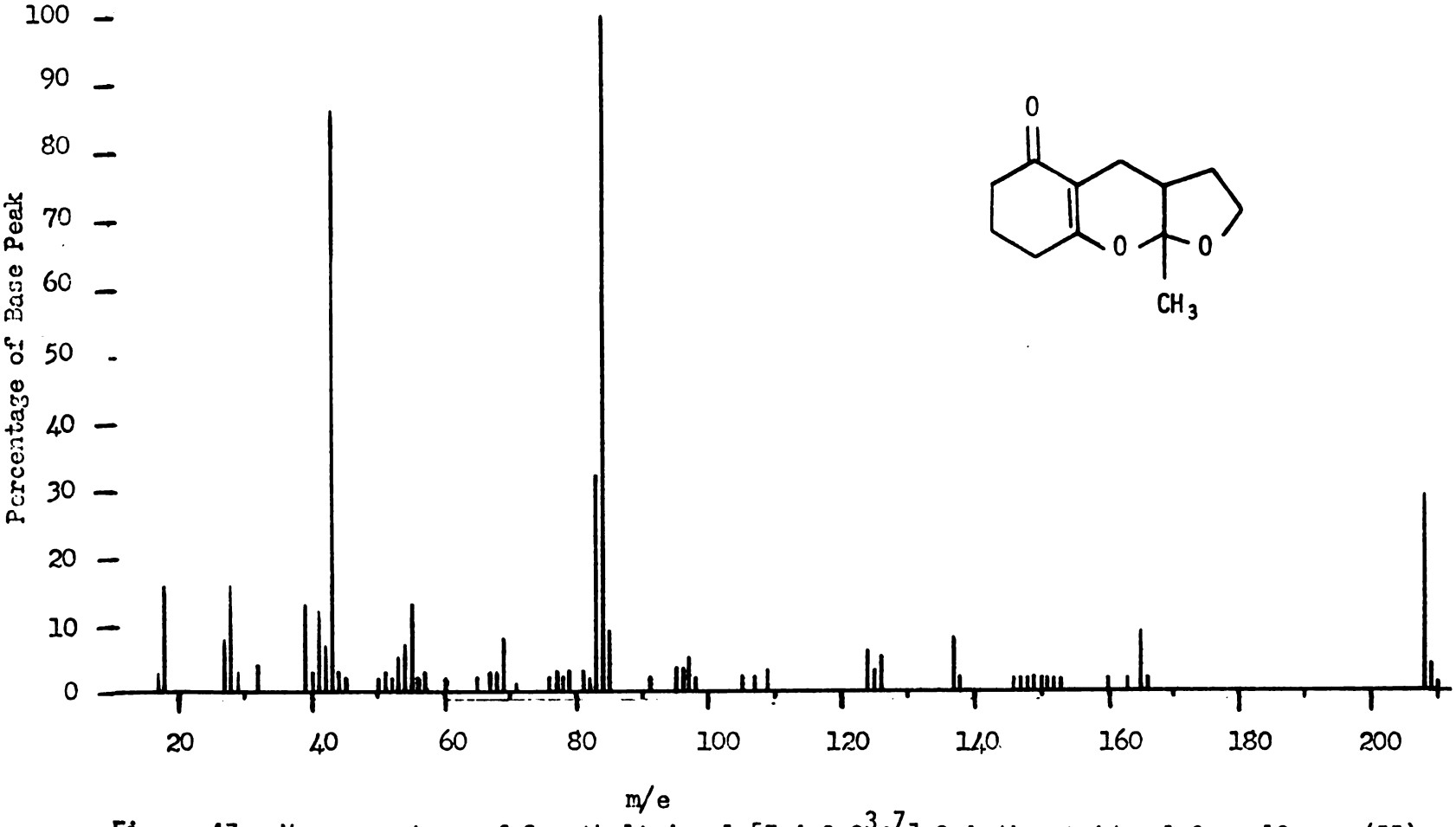


Figure 47. Mass spectrum of 3-methyltricyclo[7.4.0.$0^{3,7}$]-2,4-dioxatridec-1,9-en-10-one (55).

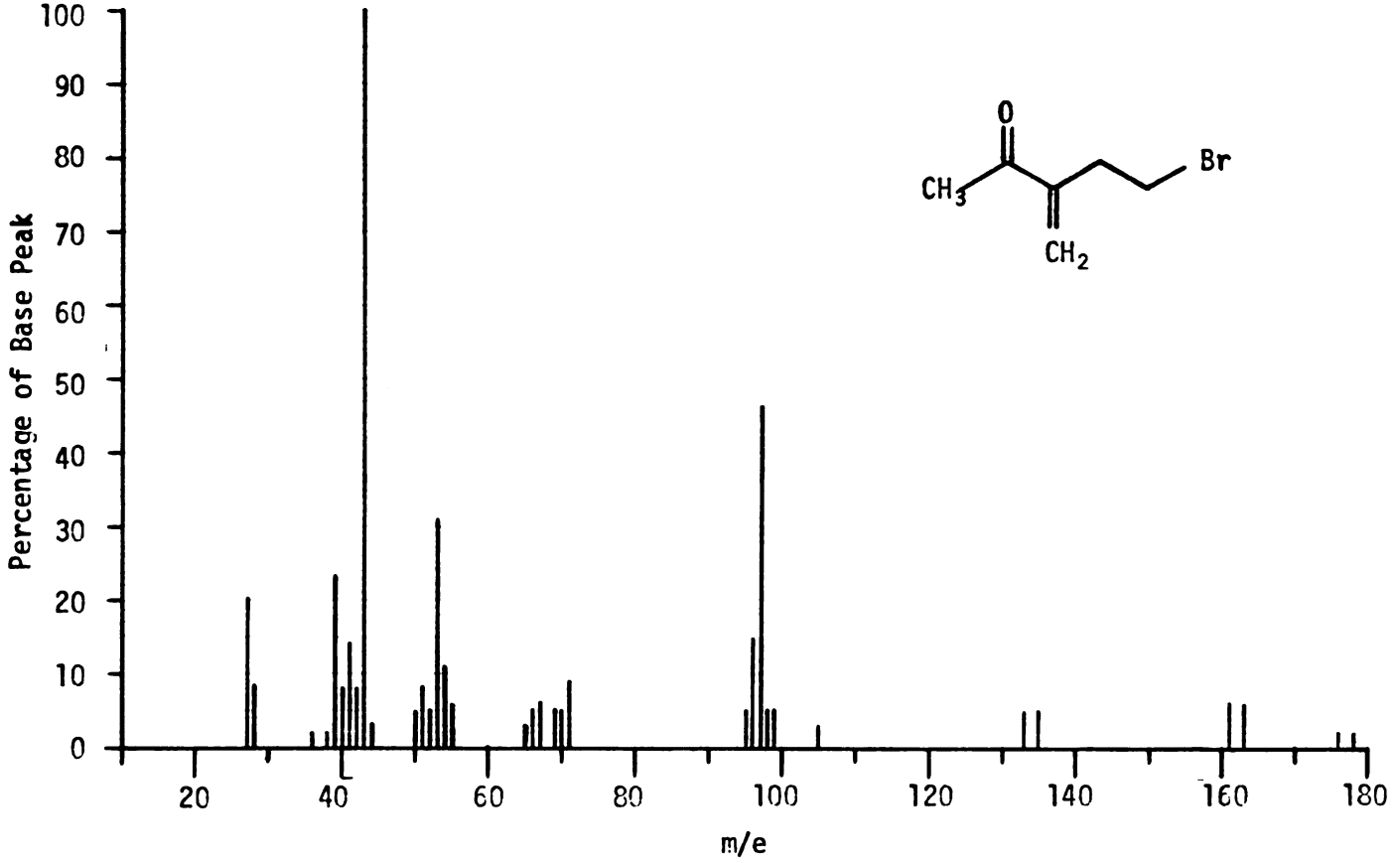


Figure 48. Mass spectrum of bromo-3-methylene-4-oxopentane (48, R=Br).

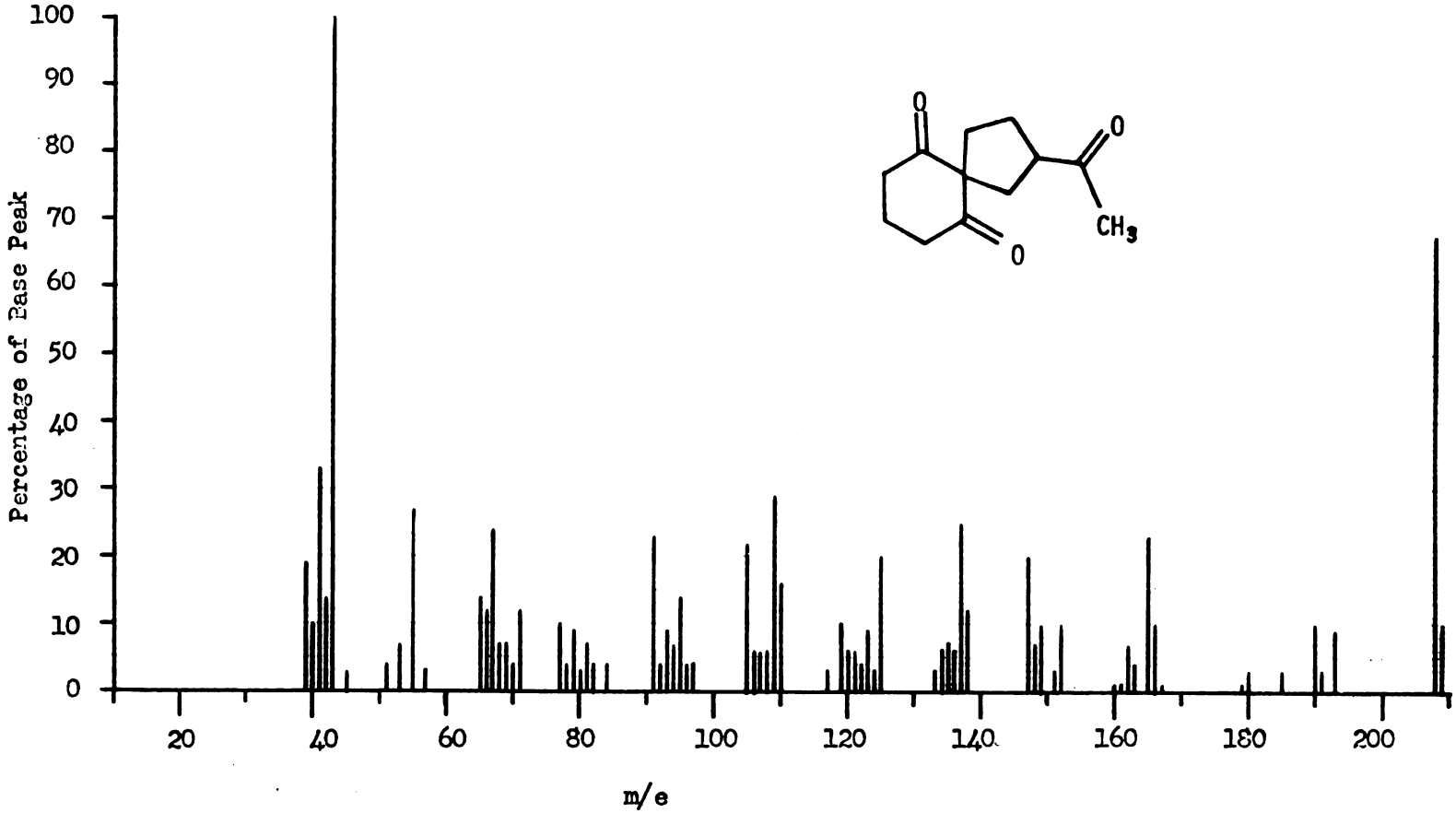


Figure 49. Mass spectrum of 2-acetylspiro[4.5]deca-6,10-dione (75).

REFERENCES

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1. J. Vrkot, J. Jonas, V. Herout and F. Sorm, Coll.Czech. Chem. Comm., 29, 539 (1964).

2. K. R. Varma, M. L. Maheshwari and S. C. Bhattacharyya, Tetrahedron, 21, 115 (1965).

3. J. A. Marshall, N. H. Anderson and P. C. Johnson, J. Am. Chem. Soc., 89, 2748 (1967).

4. J. A. Marshall and P. C. Johnson, J. Am. Chem. Soc., 89, 2750 (1967).

5. J. A. Marshall and P. C. Johnson, Chem. Comm., 391 (1968).

6. W. Z. Chow, O. Moth and F. Sorm, Coll. Czech. Chem. Comm., 27, 1914 (1962).

7. G.Chiurdoglu and J. Decot, Tetrahedron, 4, 1 (1958).

8. M. Romanuk and V. Herout, Coll. Czech. Chem. Comm., 25, 2540 (1960).

9. J. Vrkoc, V. Herout and F. Sorm, ibid., 26, 3183 (1961). R. J. Mc Clure et al, Chem. Comm., 1135 (1968) give an X-ray structure determination.

10. J. A. Marshall and S. F. Brady, Tetrahedron Letters, 1387 (1967).

11. F. Kido, H. Uda and A. Yoshikoshi, Tetrahedron Letters, 2815 (1967) and 1247 (1968).

12. R. Sakuma and A. Yoshikoshi, Chem. Comm., 41 (1968). An X-ray crystal analysis has recently confirmed these structures, see R. M. Coates, F. Farney, S. Johnson and I. C. Paul, Chem. Comm., 999 (1969).

13. I. N. Nazarov and S. I. Zavyalov, Izvest. Akad. Nauk. SSSR, Otdel. Khim. Nauk., 207 (1957).

14. E. C. Kornfield, J. Org. Chem., 19, 1671 (1954).

15. E. F. Landon and E. P. Irany, J. Org. Chem., 12, 422 (1946).

16. H. J. Hagermeyer, Jr., J. Am. Chem. Soc., 71, 1117 (1949).

17. D. R. Gupta and H. D. Pathak, Ind. J. Chem., 2, 373 (1964).

18. H. Kataoka, Chemical Abstracts, 59, P451a.

19. V. B. Piskov, Zh. Obschch. Khim., 30, 1390 (1960).

20. The aldol condensation between levulinic acid and formaldehyde provides a more direct route to 3-acetyl butyrolactone, but the yield is only 8 percent, cf. J. Rothe and H. Zimmer, J. Org. Chem., 24, 586 (1959).

21. For a recent example of in situ generation of an unsaturated ketone from a β-keto ether see E. Wenkert and D. A. Berges, J. Am. Chem. Soc., 89, 2507 (1967).

22. P. Wieland and K. Miescher, Helv. Chim. Acta., 33, 2215 (1950). S. Ramachandram and M. S. Newman, Org. Syn., 41, 38 (1961).

23. C. B. C. Boyce and J. S. Whitehurst, J. Chem. Soc., 2680 (1960).

24. H. Stetter and W. Dierichs, Chem. Ber., 85, 61 (1952).

25. For several examples of this see: E. J. Corey and S. Nozoe, J. Am. Chem. Soc., 87, 5728 (1965) and the references cited therein.

26. H. C. Brown and D. B. Bigley, J. Am. Chem. Soc., 83, 486 (1961).

27. For example E. Oka, Chemical Abstracts, 52,P15568i suggests heating the diol wtih excess thionyl chloride in benzene and pyridine at 50° for three hours.

28. M. C. Kloetzel, J. Am. Chem. Soc., 70, 3571 (1948).

29. J. Hooz and S. S. H. Gilani, Can. J. Chem., 46, 86 (1968).

30. This lithium bromide acetone of converting tosylates to bromides is due to S. F. Brady, M. A. Ilton and W. S. Johnson, J. Am. Chem. Soc., 90, 2883 (1968).

31. H. Stetter, "Newer Preparative Methods of Organic Chemistry", Vol. 2, Academic Press, New York, N. Y., 1963 , pp 51-100.

32. N. Cheronis and J. Entrikin, "Semimicro Qualitative Organic Analysis", 2nd Ed., Interscience Publishers, New York, N. Y., 1957, p 393.

33. Purificarion of the thionyl chloride is essential to the success of the reaction, for a simple procedure see L. F. Fieser, "Experiments in Organic Chemistry", D. C. Heath and Company, Boston, 1957, p 345.