A TOTAL SYNTHESIS OF APHIDICOLIN

by

Robert M. Kennedy

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APPROVED:

R.A. Holton, Chairman

H.C. Dorn

J.G. Mason

D.G.I. Kingston

B.E. Hanson

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Robert Michael Kennedy

Committee Chairman: Robert A. Holton
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(ABSTRACT)

A formal total synthesis of aphidicolin, an important antitumor agent, has been accomplished. Completion of this synthesis required the development of novel methodology. Virtually all of the previous syntheses of aphidicolin share a common difficulty in the construction of the C-9 and C-10 vicinal quaternary centers. In order to solve this problem an investigation into the Michael reaction was launched.

This study has revealed that steric encumbrance may be overcome by electronic activation of the acceptor. In fact, two withdrawing substituents were found to make possible the addition of the kinetic enolates of cyclohexenones to β,β-disubstituted acceptors. Several combinations of carboethoxy, cyano, and sulfinyl substituents were utilized. Also, use of sulfinyl butenolides as acceptors demonstrated that considerable stereochemical control may be exercised over the Michael reaction.

In addition to work on the Michael reaction, the utility of a novel annulation procedure was demonstrated in the one-pot construction of the

AB rings of aphidicolin. The required desulfurization of an α-sulfinyl lactone in the presence of an enone resulted in the development of a new, mild desulfurization agent. Some difficulty was encountered in the dissolving metal reduction of the A ring enone to provide the required trans decalin stereochemistry of the AB ring system of aphidicolin. However, this problem was solved by the construction of the D ring of aphidicolin prior to the dissolving metal reduction.

This work resulted in the synthesis of an intermediate in Corey's total synthesis of aphidicolin. This synthesis is approximately 15 steps long, which is competitive with the shortest reported synthesis of aphidicolin. Furthermore, this synthesis is the most efficient reported to date, providing the natural product in approximately 10% overall yield.

ACKNOWLEDGMENTS

I would first like to thank my parents for their support and encouragement throughout my education. I would like to express my deepest appreciation of Prof. R.A. Holton's advice, guidance, and support during my years at VPI&SU. I wish to thank Prof. H.C. Dorn for his assistance and advice in a variety of NMR experiments, without which this work would have been much more uncertain and difficult. Finally, I would like to thank Prof. M.E. Krafft whose initial work on this project provided fertile ground for an efficient synthesis of aphidicolin.

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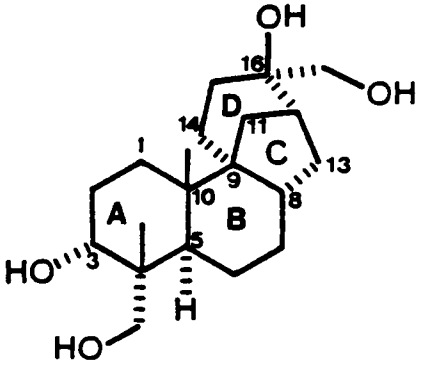
INTRODUCTION

I. Background

Aphidicolin (1) is a tetracyclic diterpenoid tetraol isolated from the culture filtrates of the fungus Cephalosporium aphidicola Petch.[1] Its structure was elucidated by chemical and spectroscopic means and was then confirmed by X-ray crystal structure.[1a] The absolute configuration of 1 was determined by anomalous dispersion of Cu-K_α radiation by oxygen and circular dichroism spectra of degradation products.



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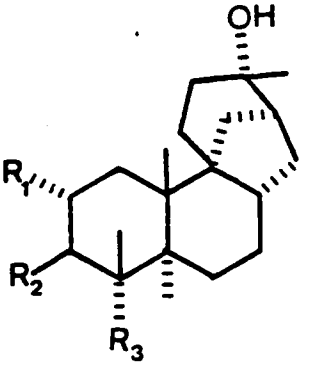


2

2a R_1=H, R_2=OH, R_3=CH_3

b R_1=R_2=H, R_3=CH_2OH

c R_1=OH, R_2=H, R_3=CH_3

Aphidicolin embodies a unique ring system but is similar to maritimol (2a)[2] and other stemodia components 2b-d,[3] which occur in the

plant stemodia maritima L. (Scrophulariaceae) obtained from the Palisadoes peninsula of Jamaica.

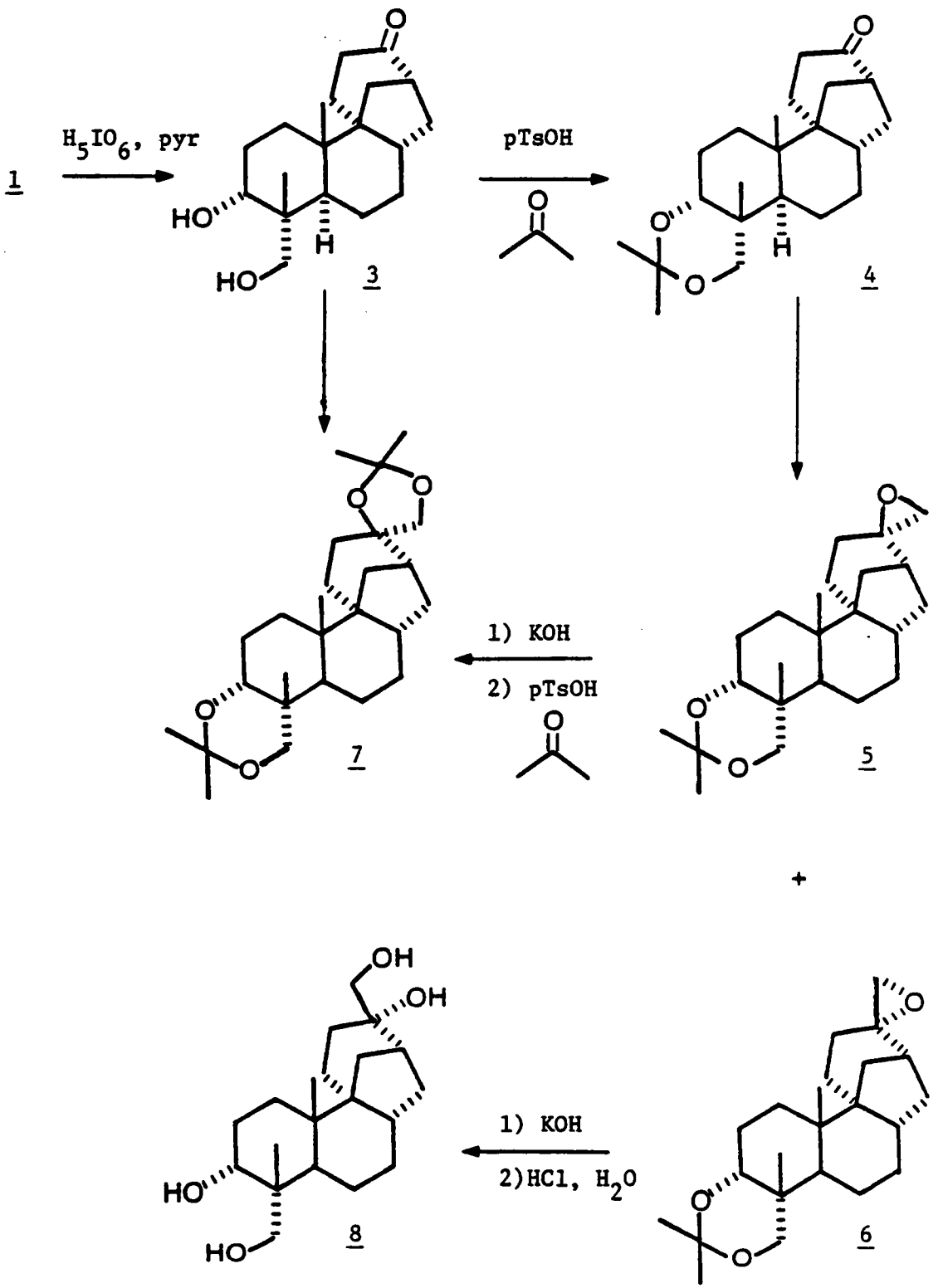
Both aphidicolin and stemodane diterpenes exhibit biomedical and pharmacological properties. The stemodane diterpenes occur in a plant used in the Caribbean for treatment of venereal disease.[2]

Aphidicolin has been found to reduce the mitotic rate of mouse L cells growing in tissue culture and also to inhibit the growth of Herpes simplex type I, both in cultures of human embryonic lung cells and in the rabbit cornea.[4] The strong in vitro activity of aphidicolin against herpes virus presumably arises through an inhibition of viral DNA synthesis.[5]

Aphidicolin exhibits striking biological activity despite rather simple functionality. Models of aphidicolin reveal that all four hydroxyls can very nearly touch the same flat surface.[6] Although this observation may have some connection with the biological activity of 1, structure activity studies[4] indicate that the non-rigid hydroxyls at C-17 and C-18 are less important than the two rigid hydroxyls at C-3 and C-16.

As part of a structure activity investigation[1b] that becomes particularly relevant to the synthesis of aphidicolin, aphidicolin was treated with periodic acid in pyridine, resulting in the loss of formaldehyde and formation of ketone 3. The acetonide 4 reacted with dimethyl sulfoxonium methylide to provide a mixture of epoxides 5 and 6, epimeric at C-16 (Scheme I). Alkaline hydrolysis of the major diastereomer 5 gave a diol which was converted to bis acetonide 7, which was identical to the bis acetonide formed from aphidicolin. Alkaline

Scheme I.



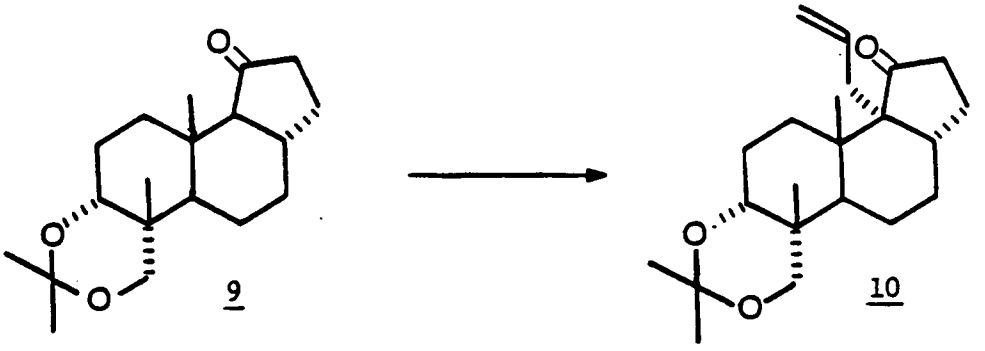
hydrolysis of the minor epoxide 6 followed by hydrolysis of the acetonide produced tetraol 8. Periodate cleavage of 8 gave ketone 3, confirming the relationship of 8 to aphidicolin. Tetraol 8 was found to be almost two orders of magnitude less active against Herpes simplex type I in cultures of human embryonic lung cells.[4]

The challenges to synthesis offered by aphidicolin are several. The previously mentioned structure activity study revealed that aphidicolin is accessible from ketone 4. It also demonstrated that reagents may approach either side of this ketone. There is also the problem presented by the A ring stereochemistry. The 3α-hydroxyl-4α-hydroxymethyl-4β-methyl substitution pattern is unique to aphidicolin. Finally, the most severe stereochemical problem is that posed by spiro center C-9 which is also adjacent to quaternary center C-10. The presence of these vicinal quaternary centers makes this region of aphidicolin quite crowded and a source of potential trouble for any projected synthesis.[7]

Eight synthetic routes to aphidicolin have been described.[6,8,9] Six of these have resulted in the total synthesis of 1.[6,9] Despite the elegance of some of these approaches, even the most efficient produces 1 in ca 5% overall yield. Virtually all of the syntheses share a common difficulty in the construction of the C-9, C-10 quaternary centers. For example, Trost and coworkers[9a] attempted to alkylate the more substituted enolate of 9 only to find that, even under a variety of conditions, only a 35% yield of 10 could be realized.

In the McMurry synthesis[9b,6] a similar problem was encountered in the attempted conjugate addition to enone 11. Since the conjugate

Trost Synthesis



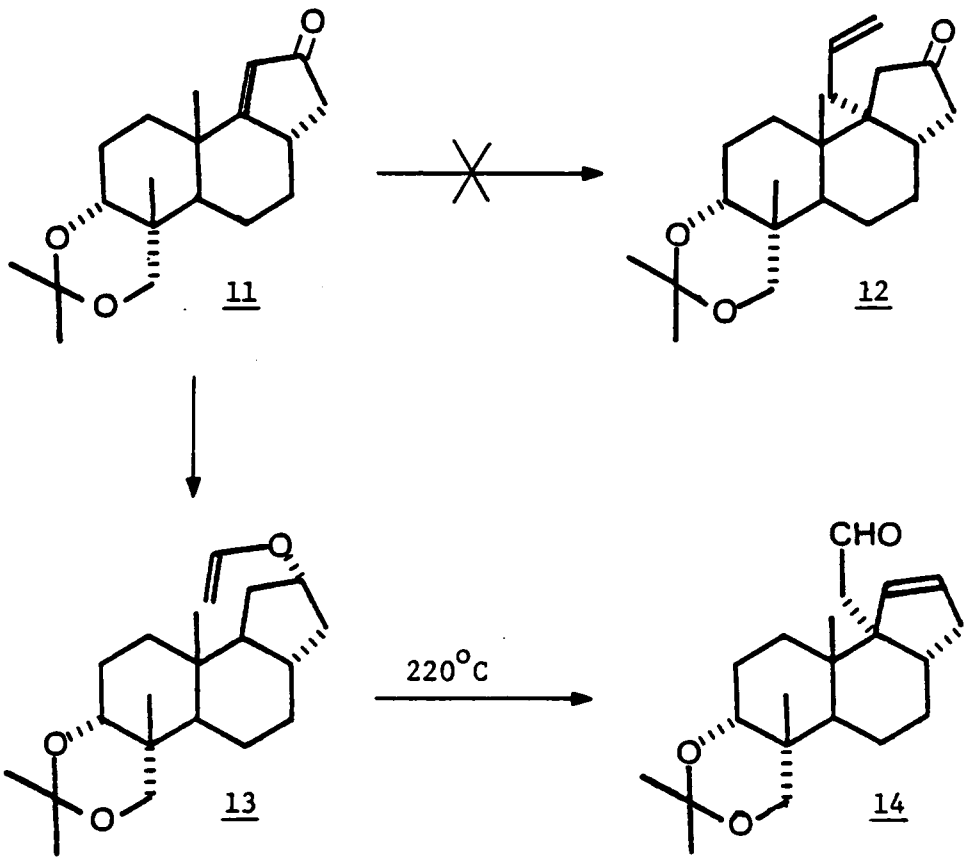
9 10

addition approach was entirely unsuccessful, the McMurry group then resorted to the Claisen rearrangement (13 ➤ 14). This rearrangement was initially reported to proceed in 20% yield. Presumably this low yield resulted from competing elimination of the allyl ether under the forcing conditions required for the Claisen rearrangement. Subsequent work has shown that addition of strong base effectively suppresses this side reaction and increases the yield of the Claisen rearrangement to 60%.

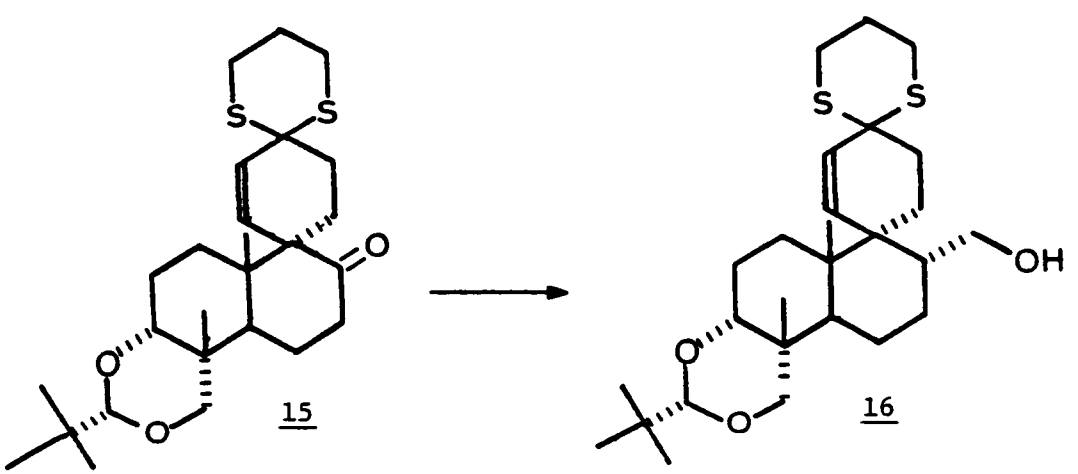
Corey's synthesis[9c] required a one-carbon homologation of ketone 15 to alcohol 16. This, however, proved unexpectedly difficult, owing to steric inhibition of carbonyl addition relative to α-deprotonation. This time the mere proximity of stereocenters C-9, C-10 had become a source of difficulty. Ultimately, a five-step sequence was devised to overcome this problem.

van Tamelen's synthesis[9e] suffered a variety of problems. The Diels-Alder reaction of diene 17 with maleic anhydride provided adduct 18 in 84% yield. However, the choice of this acetylene equivalent proved costly, since oxidative decarboxylation with lead tetraacetate to give olefin 19 proceeded in only 21% yield.

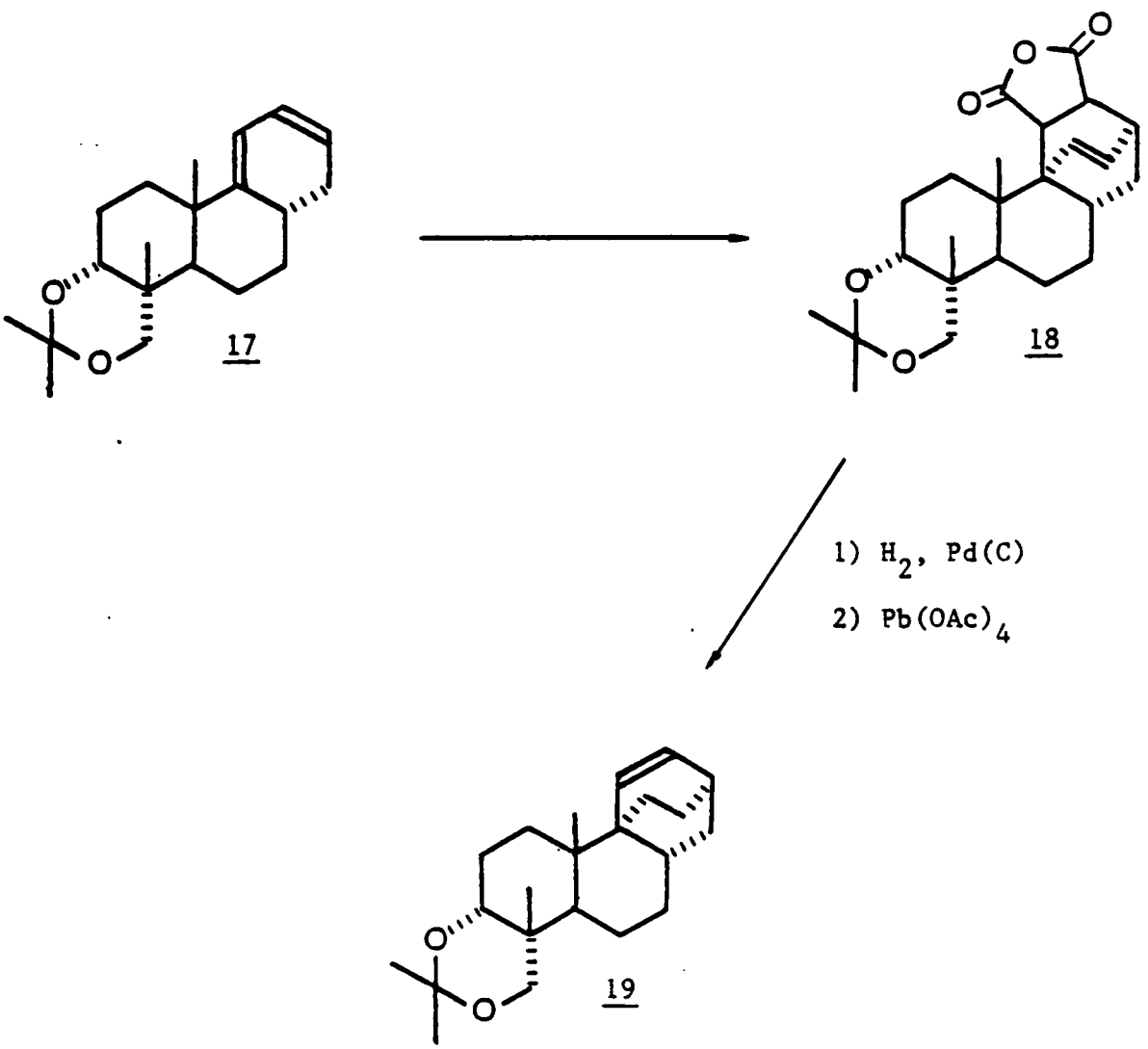
McMurry Synthesis



Corey Synthesis



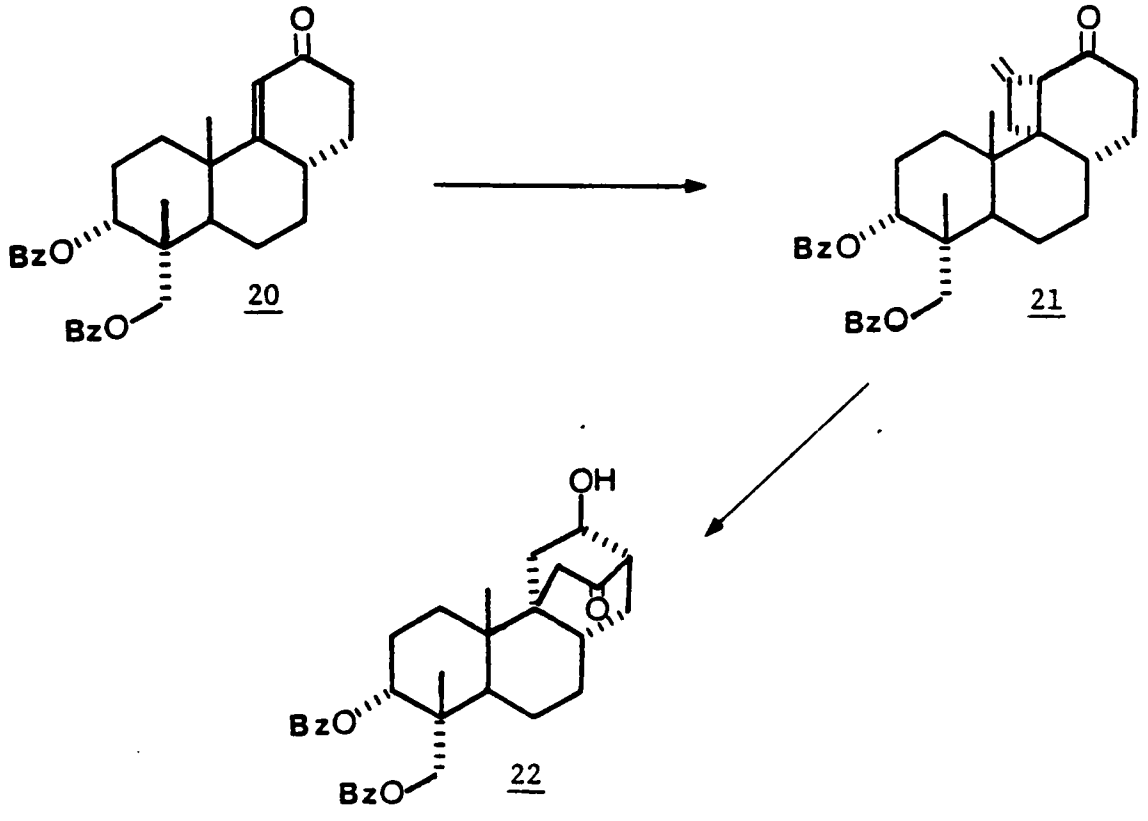
van Tamelen Synthesis



A far more efficient construction of the bicyclo[2.2.2] ring system as a precursor for a biomimetic synthesis of the bicyclo[3.2.1] rings of aphidicolin was accomplished in Bettollo's synthesis.[9f] Photoaddition of allene to 20 gave 21 stereospecifically in 86% yield. Ketalization, ozonolysis, and reductive work-up provided the desired bicyclo[2.2.2] aldol product 22 in 61% overall yield from photoaddition adduct 21.

Bettollo's synthesis is the most efficient (5.2% overall yield) of those reported.

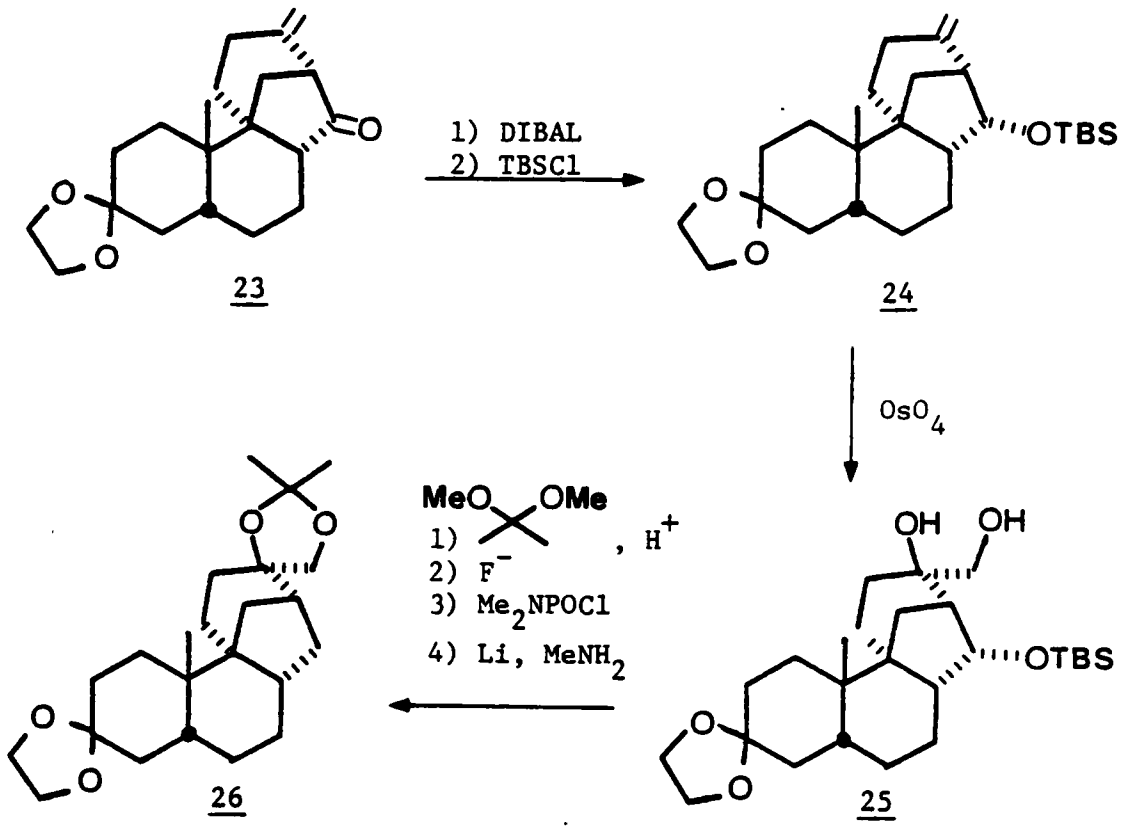
Bettollo Synthesis



Ireland's synthesis[9d] is lengthy, but, in having to remove a ketone at C-13 in 23, his group was able to demonstrate stereochemical control at C-16. Reduction of ketone 23 with diisobutylaluminum hydride (DIBAL) produced the α-alcohol. This was protected as the bulky TBS ether 24. Osmylation of the exocyclic olefin gave 25 in high yield. In the absence of functionality at C-13 (ketone removed) osmylation of the exocyclic olefin produced a 60:40 mixture of diastereomers (the major

being the desired diastereomer). Clearly, the TBS ether blocks attack from the α-face of the olefin. Unfortunately, four additional steps were required for subsequent removal of the -OTBS group to give 26.

Ireland Synthesis

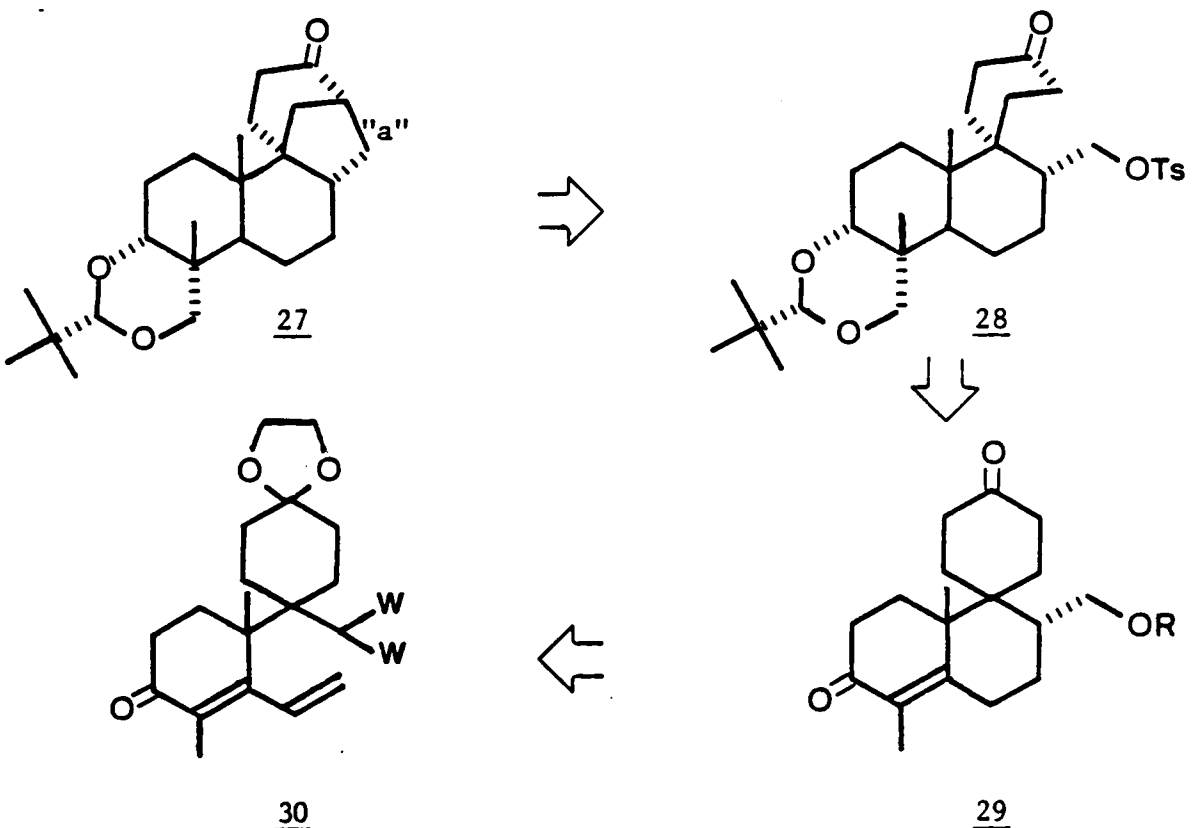


II. Retrosynthetic Analysis

In our synthesis of aphidicolin we planned to address the most serious problem, construction of contiguous quaternary centers C-9 and C-10, at the beginning of the synthesis. We also planned to take

advantage of the more successful elements of previous syntheses. Our retrosynthetic analysis of aphidicolin proceeded as follows.

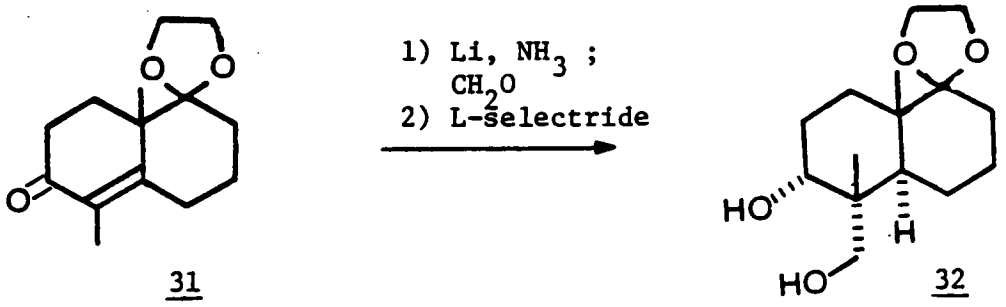
It was our plan to construct the bicyclo[3.2.1] CD ring system in the later stages of the synthesis. We hoped to accomplish this via ketone 27, which has been converted to aphidicolin,[9c] and whose analogue (4) has been the target of several total syntheses. Disconnection of 27 by cleavage of bond "a" leads to precursor 28. Corey has converted 28 to aphidicolin via intermediate 27. Thus, spiro ketone 28 became the target of our synthesis.



27 28 29 30

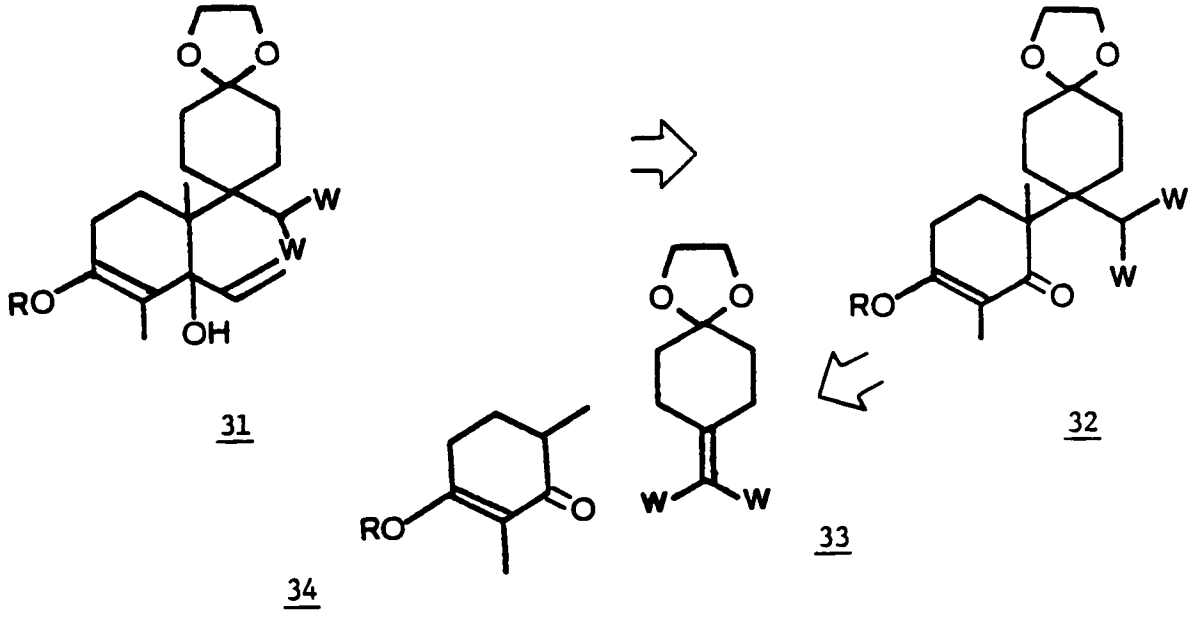
Trost, McMurry, and others have amply demonstrated that the stereochemistry of the A ring of aphidicolin may be established from an

enone such as 29. For example, the conversion of 31 to 32 may be carried out in 82% overall yield.



31 32

We hoped to construct the B ring via an intramolecular Michael addition to a vinyl enone such as 30. Dienone 30 was envisioned to arise via an acid-catalyzed rearrangement of 31, the product of addition of vinyllithium to 32. The formation of 32 was imagined to arise most easily via Michael reaction of the kinetic enolate of 34 with 33.

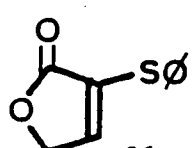


31 32

33

34

Preliminary studies[10] focused on verification of the viability of this annulation sequence. Incorporation of C-9, C-10 quaternary centers was postponed. Deprotonation of enone 35 with lithium diisopropylamide in THF at -78°C provided the kinetic enolate which reacted rapidly with thiophenyl butenolide 36[11] at -95°C. The adduct 37 was obtained as a single diastereomer in 96% yield. Addition of vinyllithium to 37 (3 eq, THF, 0°C, 30 min) provided a bis allylic alcohol, which upon treatment with 3% H_2SO_4 (THF, 0°C, 30 min) gave dienone 38 in 70% yield. Under basic conditions ($NaOCH_3$, CH_3OH/THF, 0°C, 1 h) 38 cyclized to the tricyclic enone 39 as a single diastereomer in 93% yield.



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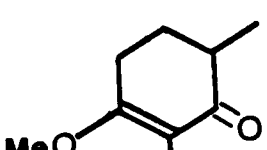

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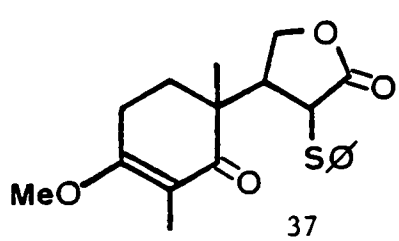

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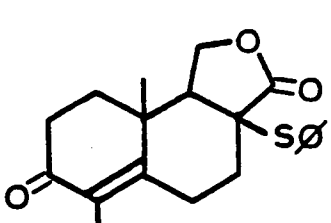
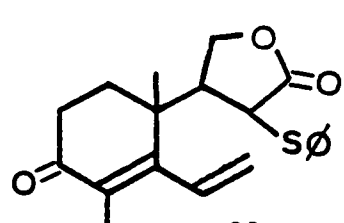


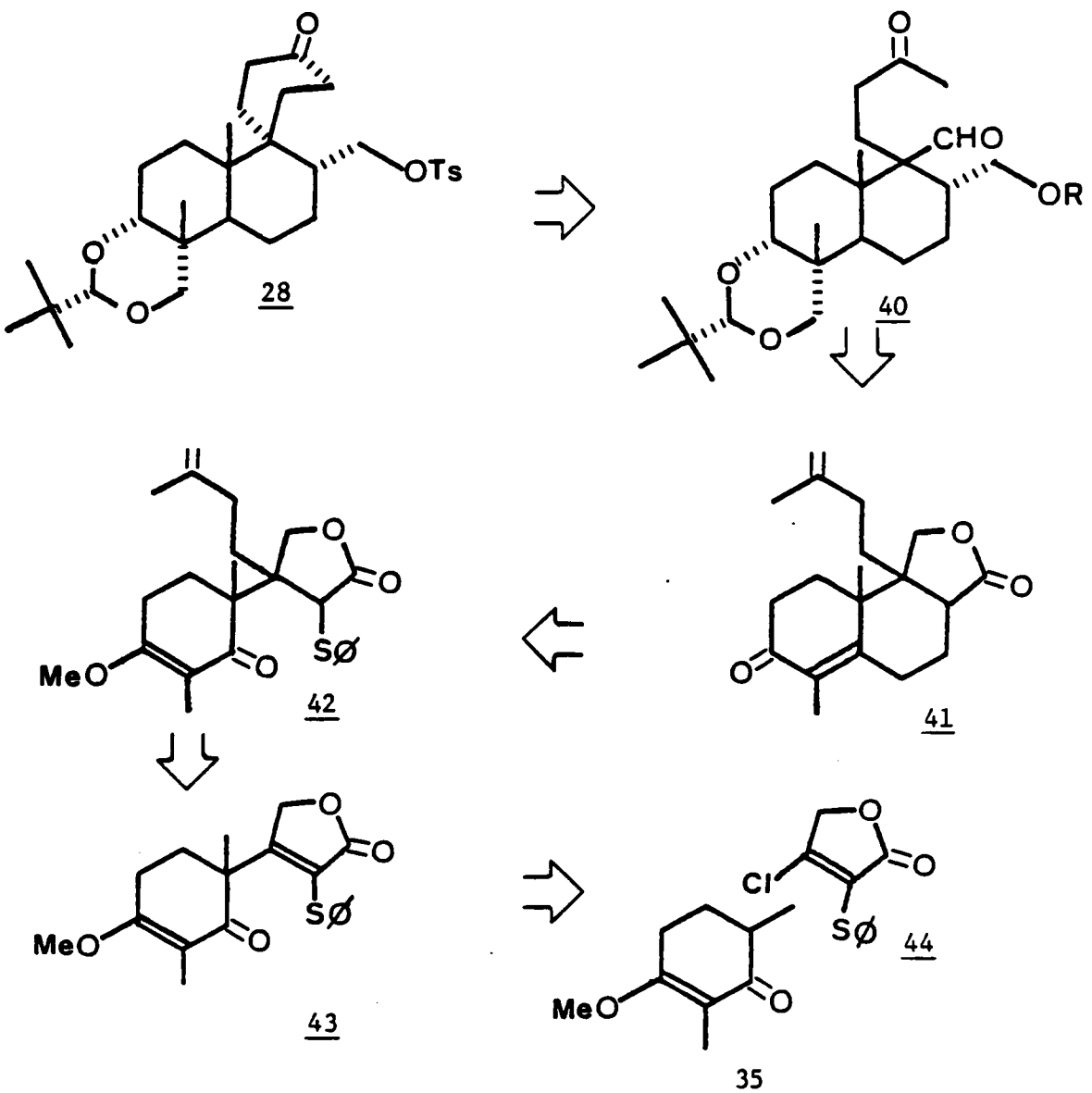
39



38

Successful completion of this work provided the following additional opportunities. Instead of Michael addition to a doubly activated

cyclohexylidene, Michael addition to a β-butenylbutenolide could be employed. In such a scheme the D ring of aphidicolin would be closed after completion of the AB ring system. The retrosynthetic analysis for this plan proceeded as follows.



Intramolecular aldol condensation of 40 and hydrogenation of the resulting spiroenone had precedent in Corey's synthesis. Aldehyde 40 was envisioned to be available from tricyclic lactone 41 via elaboration

of the A ring as previously described, followed by reduction of the lactone to a diol, selective protection, and oxidation to the aldehyde. Oxidative cleavage of the side chain would then expose the desired ketone 40. We anticipated no additional problems would be posed by the C-9 butenyl fragment in the previously described annulation.

We envisioned two possible routes to adduct 42. Michael addition of the kinetic enolate of 34 to a β-butenylbutenolide was expected to be the most efficient approach. A less elegant, but potentially more successful route involved Michael addition of the kinetic enolate of 34 to β-chlorobutenolide 44. This was expected to afford, after elimination of chloride, the unsaturated Michael adduct 43. This Michael adduct could then undergo conjugate addition of butenyl cuprate to afford 42.

In conclusion, three routes to aphidicolin were considered viable. The first involved the preformed D ring in which a cyclohexylidene acted as an acceptor in the initial Michael reaction. The second would utilize a β-butenyl butenolide as an acceptor. In this plan the D ring would have to be closed at a later stage of the synthesis. Finally, the third would complete the C-9 quaternary center after the initial Michael reaction. The D ring would, again, have to be closed at some point later in the synthesis.

RESULTS AND DISCUSSION

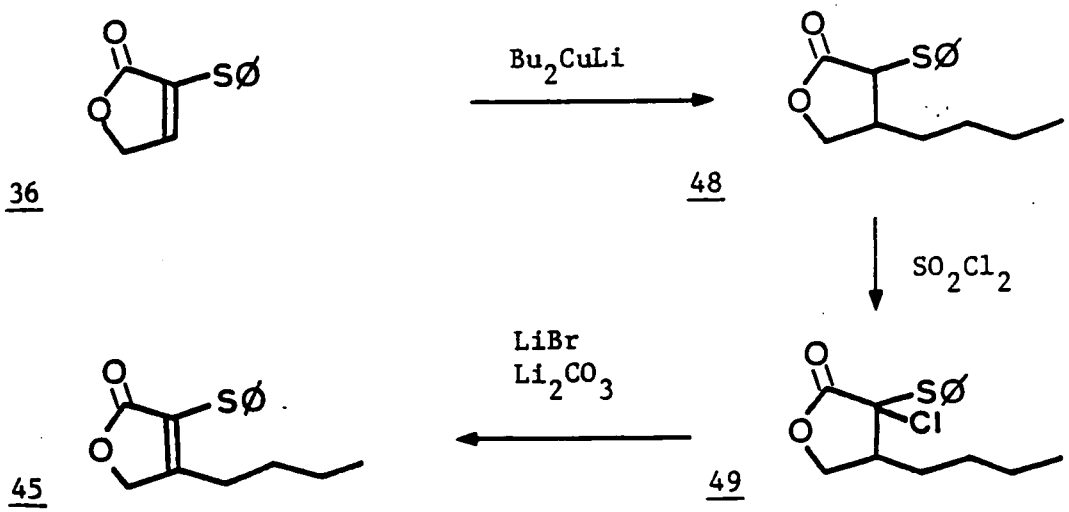
I. Attempted Construction of the C-9 Quaternary Center via Cuprate Addition

Of the three approaches to aphidicolin that we have outlined, we chose to initially pursue the last route. In this approach we intended to establish the C-9 quaternary center via a cuprate addition. It was felt that this strategy for the construction of vicinal quaternary centers C-9 and C-10 stood the greatest chance of success.

Prior to attempts to establish the C-9 quaternary center via conjugate addition to an acceptor like Michael adduct 43, it was decided to demonstrate the viability of cuprate addition to simple β-substituted butenolides. To this end butenolides 45, 46, and 47 were prepared.

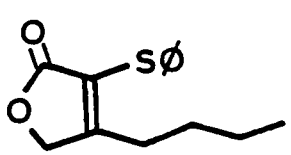
Addition of lithium dibutyl cuprate to butenolide 36[12] afforded the β-butyl butyrolactone 48. Chlorination of 48 with sulfuryl chloride with subsequent elimination of hydrogen chloride from the resulting crude α-chloride 49 afforded the desired β-butyl butenolide 45. The sulfoxide 46 and the sulfone 47 were obtained by oxidation with one and two equivalents of mCPBA,[13] respectively.

Attempted conjugate addition of lithium dibutyl cuprate[14] to the sulfide 45 resulted only in returned starting material. However, conjugate addition was found to be possible utilizing either the sulfoxide 46 or the sulfone 47. These results were sufficiently



36 48 49 45

encouraging to warrant preparation of the requisite β-chlorobutenolide 44 for the construction of the key Michael adduct 53.

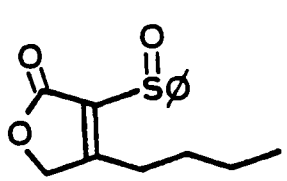


45

5 eq Bu_2CuLi

Et_2O

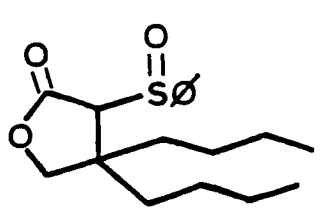
N.R.



46

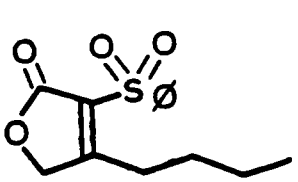
5 eq Bu_2CuLi

Et_2O



50

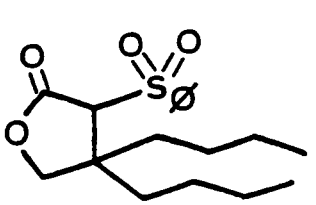
65%



47

5 eq Bu_2CuLi

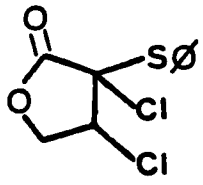
Et_2O



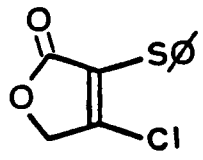
51

50%

After several unsuccessful approaches to 44 had been explored, its successful preparation was finally accomplished in the following manner. Addition of chlorine to butenolide 36 produced a mixture of diastereomeric dichlorides 52. Upon treatment of 52 with silver nitrate in refluxing acetonitrile, hydrogen chloride was eliminated to afford the desired β-chlorobutenolide in 35% overall yield from 36.

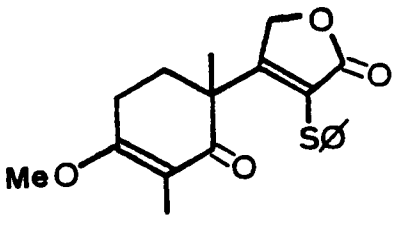


52



44

The Michael reaction of the kinetic enolate of 35 (LDA, THF, -78°C) with butenolide 44 afforded Michael adduct 53 in a disappointingly low yield of 57%. Furthermore, our initial attempts at cuprate addition to 53 or the corresponding sulfoxide 54 (mCPBA, CH_2Cl_2) were unsuccessful. Oxidation of 54 to the corresponding sulfone proved impossible in the presence of the 3-methoxyenone functionality.



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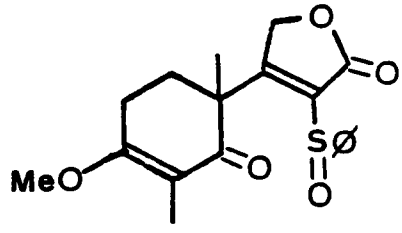


54

II. Hindered Michael Reactions

The failure of our initial attempts to construct the C-9 quaternary center after the initial Michael reaction caused us to consider the possibility of its construction in the Michael reaction. If successful this would shorten the proposed synthesis considerably. However, the Michael reaction has earned a reputation for sensitivity to steric encumbrance.

It has only recently been found that sterically demanding substrates can be forced to undergo reaction under conditions of extreme pressure.[15] Traditionally, Michael reactions have been conducted in protic media under conditions which permit rapid proton transfer.[16] Elegant pioneering studies conducted by Stork[17a] demonstrated that the Michael reaction may be carried out under aprotic conditions, provided that the enolate formed in the addition is more stabilized than that which acts as the nucleophilic addend. These observations have been fully verified in numerous subsequent studies.[17b-x]

We anticipated that compensation for steric bulk at the β-terminus of the Michael acceptor could be provided by the attachment of two electron-withdrawing substituents. We viewed the results of cuprate addition to the model butenolides 45, 46, and 47 as a preliminary indication that electronic effects might overcome steric encumbrance in Michael additions. The ready availability of doubly activated cyclohexylidenes, and the fact that use of a pre-formed D ring in the Michael reaction would further simplify our synthesis of aphidicolin, caused us

to investigate the viability of diethyl cyclohexylidene malonate[10] 55, ethyl cyclohexylidene cyanoacetate[18] 56, and cyclohexylidene malononitrile[19] as acceptors in the Michael reaction with the kinetic enolate of enone 35.

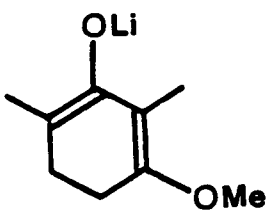
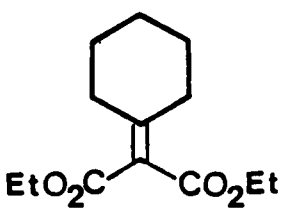
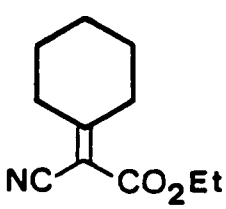
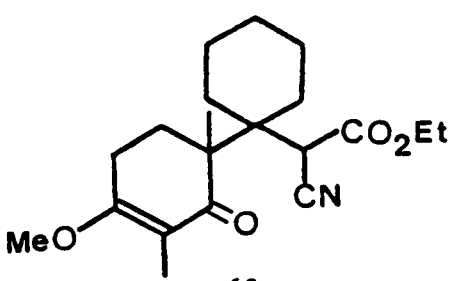
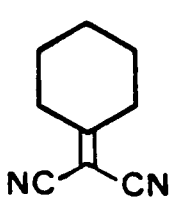
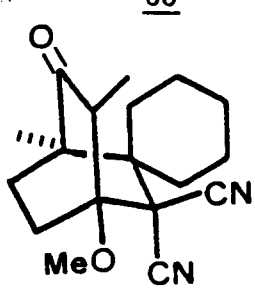
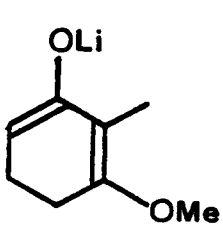
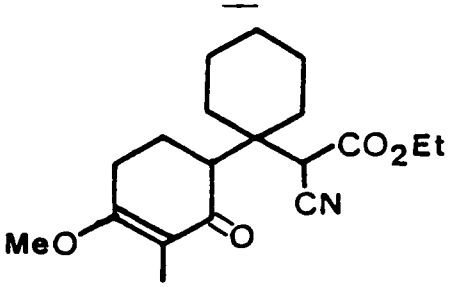
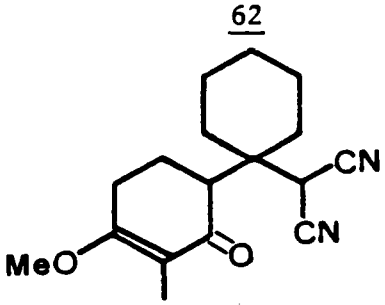
In all cases the kinetic enolate was formed by either (a) addition of the corresponding ketone to a THF solution of LDA[20] at -78°C or (b) treatment of the corresponding TMS enol ether[21] with MeLi[22] in THF. The reactions were quenched at -78°C by rapid addition to a large excess of saturated sodium bicarbonate solution. The results of this work are listed in Table I.

Diethyl cyclohexylidene malonate 55 failed to react with 58 under these conditions, but the use of either cyano and carboethoxy or two cyano groups resulted in the formation of the long sought contiguous quaternary centers. While reactions with cyclohexylidene cyanoacetate 56 were found to proceed to completion within 15 min at -78°C, cyclohexylidene malononitrile 57 required longer reaction times (12 h, -78°C).

Only one example (58→61) was observed in which a "double" or sequential Michael reaction[23] occurred. This product was not observed when the C-6 methyl substituent was removed. A "buttressing" effect by this methyl group may be responsible for closure to the bicyclo[2.2.2] octanone.

Our success with the cyano group as a second activating substituent prompted us to explore the utility of a sulfoxide group in this role. The desired sulfinyl cyclohexylidenes[24] 64 and 65 were prepared in the

Table I. Michael Additions to Cyclohexylidenes: Cyano and Carboethoxy Activating Substituents

Enolate	Acceptor	Product	Isolated Yield
 58	 55	N.R.	
58	 56	 60	100%
58	 57	 61	78%
 59	56	 62	89%
59	57	 63	91%

following manner (see Scheme II). The lithium enolate of ethyl thiophenyl acetate (or thiophenylacetonitrile) with cyclohexanone provided an aldol product (66, 67) which was acetylated (N-methyl imidazole (NMI), acetic anhydride (Ac_2O), pyridine). The resulting acetates eliminated under basic conditions to provide the respective sulfides 68 and 69. The corresponding sulfoxides 64 and 65 were obtained by oxidation with mCPBA.

Michael addition of enolate 72 to sulfoxides 64 and 65 proceeded in high yield (Table II). However, in both cases a mixture of three diastereomers was obtained. The stereochemical relationship of these three diastereomers could not be determined. Michael addition to sulfide 68 did not proceed, which was consistent with the results of attempted cuprate addition. Michael addition to the corresponding sulfone 70 proceeded in low yield, perhaps due to its insolubility in THF at low temperatures.

Although the preceding work provided a variety of Michael adducts, all potentially applicable to our synthesis of aphidicolin, we were intrigued by the stereospecific Michael reaction in the model study. We hoped that it might be possible to incorporate an appropriately substituted butyl fragment into this stereospecific reaction. This would demonstrate the generality of this stereospecific Michael reaction as well as preserve our options at this stage of the synthesis.

We were pleased to find that butenolide 46 underwent Michael addition with the kinetic enolate of 35. With careful attention to purity of the unstable butenolide 46, the yield of Michael adduct 74 was 85-92%, obtained as a 12:1 mixture of diastereomers.

Scheme II.

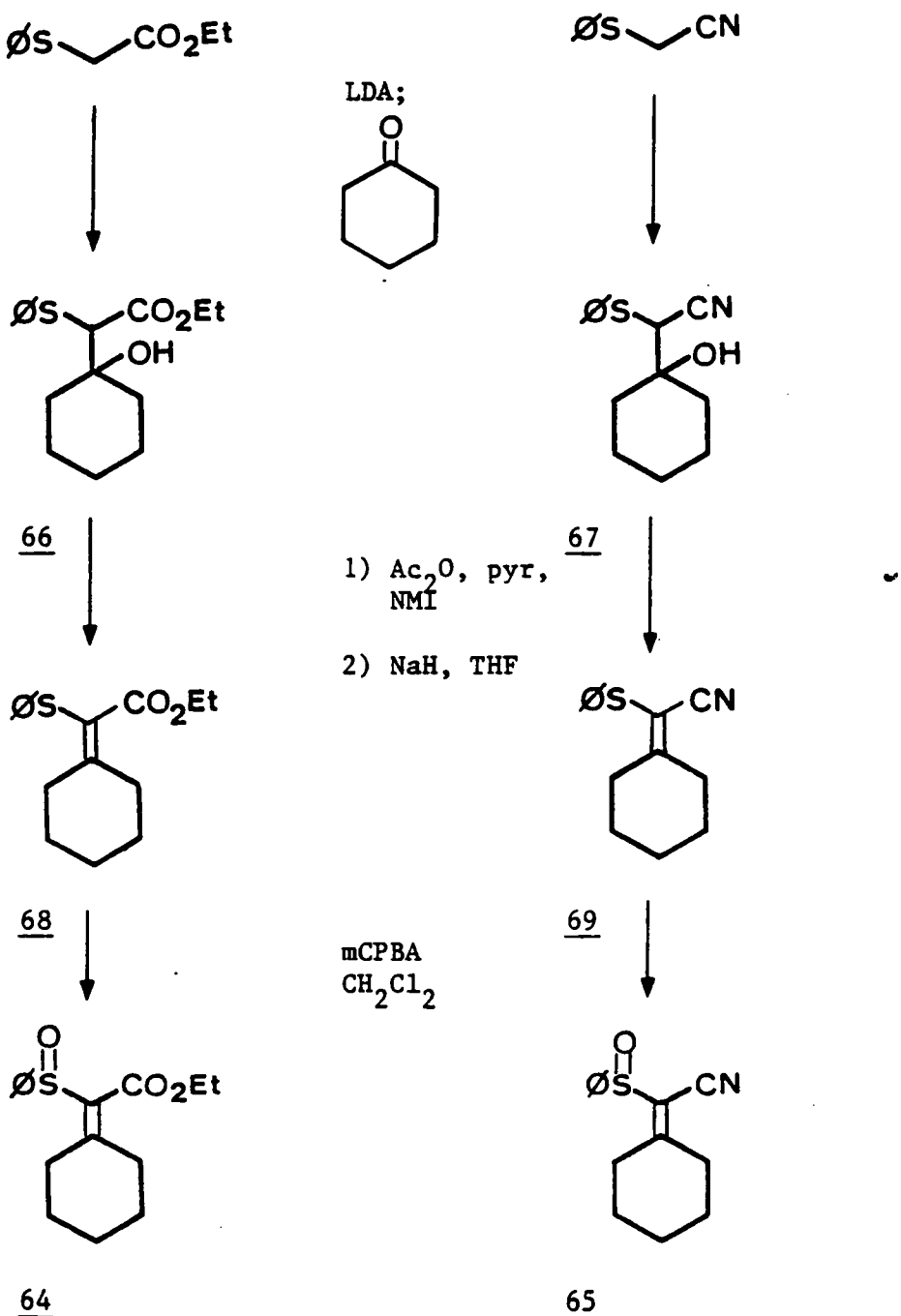
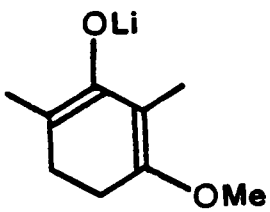
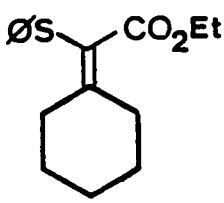
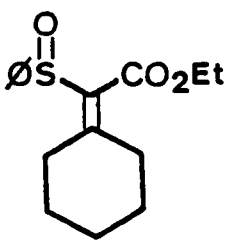
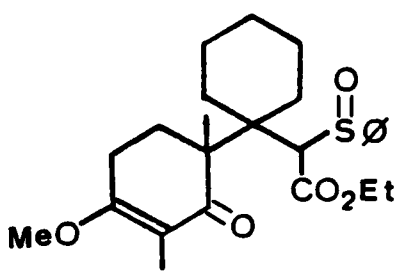
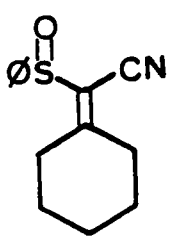
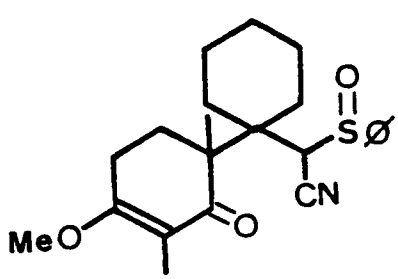
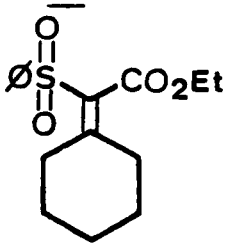
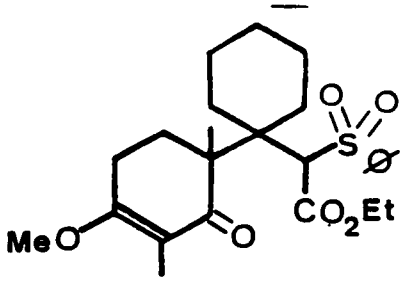
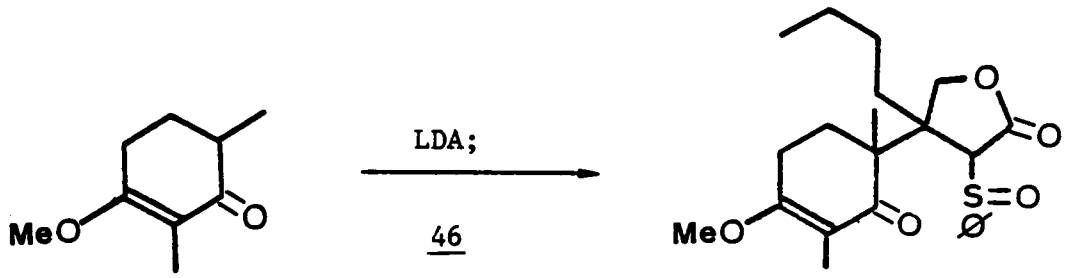

ØS CO2Et
ØS CN
LDA;
O
ØS CO2Et
OH
ØS CN
OH
66
67
1) Ac2O, pyr, NMI
2) NaH, THF
ØS CO2Et
ØS CN
68
69
mCPBA
CH2Cl2
O
ØS CO2Et
O
ØS CN
64
65

Table II. Michael Addition to Cyclohexylidenes: Use of Sulfoxide as an Activating Substituent.

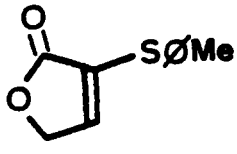
Enolate	Acceptor	Product	Isolated Yield
		N.R.	
58	68		
58			89%
	64	71	
58			95%
	65	72	
58			50%
	70	73	



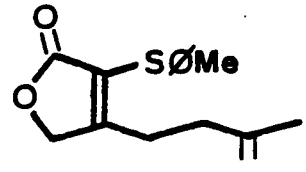
35 74

At this point a latent C-16 carbonyl had to be incorporated into the Michael acceptors. Syntheses of the mono ketal of 1,4-cyclohexanediones[25] had already appeared in the literature. However, a 2-methyl-1-butene side chain was chosen for incorporation of the desired latent functionality in the butenolide route. A further modification was also made (use of a tolyl sulfinyl butenolide) in order to coincide with ongoing efforts to prepare optically active sulfinyl butenolide.

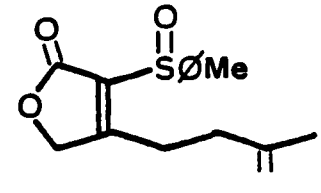
Tolyl sulfinyl β-butenyl butenolide 75 was prepared in racemic form in the following manner. Thiotolyl butenolide 76 was prepared in a manner similar to that for thiophenyl butenolide[12] 36. The Grignard reagent prepared from 4-bromo-2-methyl-1-butene[26] underwent conjugate addition to 76 in the presence of a catalytic amount of copper iodide. The resulting enolate was trapped in situ with N-bromosuccinimide to



76



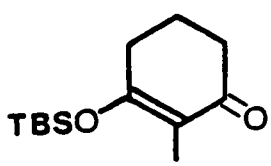
77



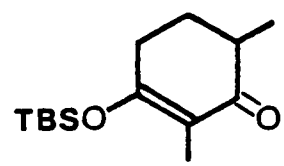
75

provide an α-bromobutyrolactone which eliminated hydrogen bromide under basic conditions to provide the desired sulfide 77 in 50% yield. The unstable sulfoxide 75 was obtained in 99% yield via oxidation with mCPBA.

Additionally, a derivative of enone 35 was prepared in order to improve the yield of subsequent reactions in the synthesis. t-Butyldimethylsilyl ether 78 was prepared via silylation of 2-methyl-1,3-cyclohexanedione. Alkylation of the kinetic enolate (LDA, THF, -78°C) of 78 with methyl iodide provide the desired enone 79.[27]

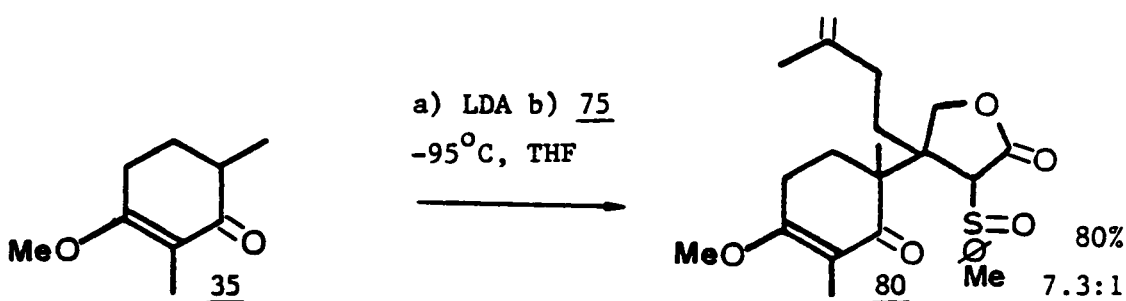


78

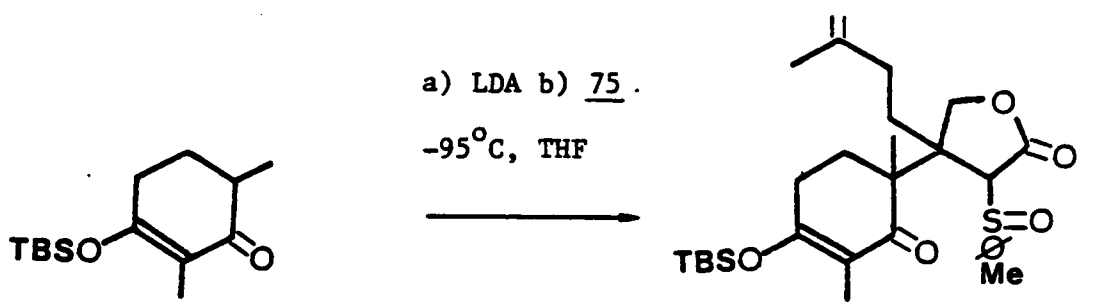


79

Michael additions of the kinetic enolates of 79 and 35 to 75 resulted in a disappointing loss in stereoselectivity. At present, we do not have an explanation for this result.



The major and minor diastereomers of 81 were separable by careful column chromatography. Equilibration of these two diastereomers under basic conditions provided two new, different diastereomers. This result implied that these two products resulted from competing transition states in the Michael reaction. We felt that it would be better to address these stereochemical questions when the B ring of aphidicolin had been constructed. It was sufficient, at this point, to know that a single diastereomer predominated, and that, therefore, use of optically active sulfoxide would result in the enantiospecific construction of C-9 and C-10.

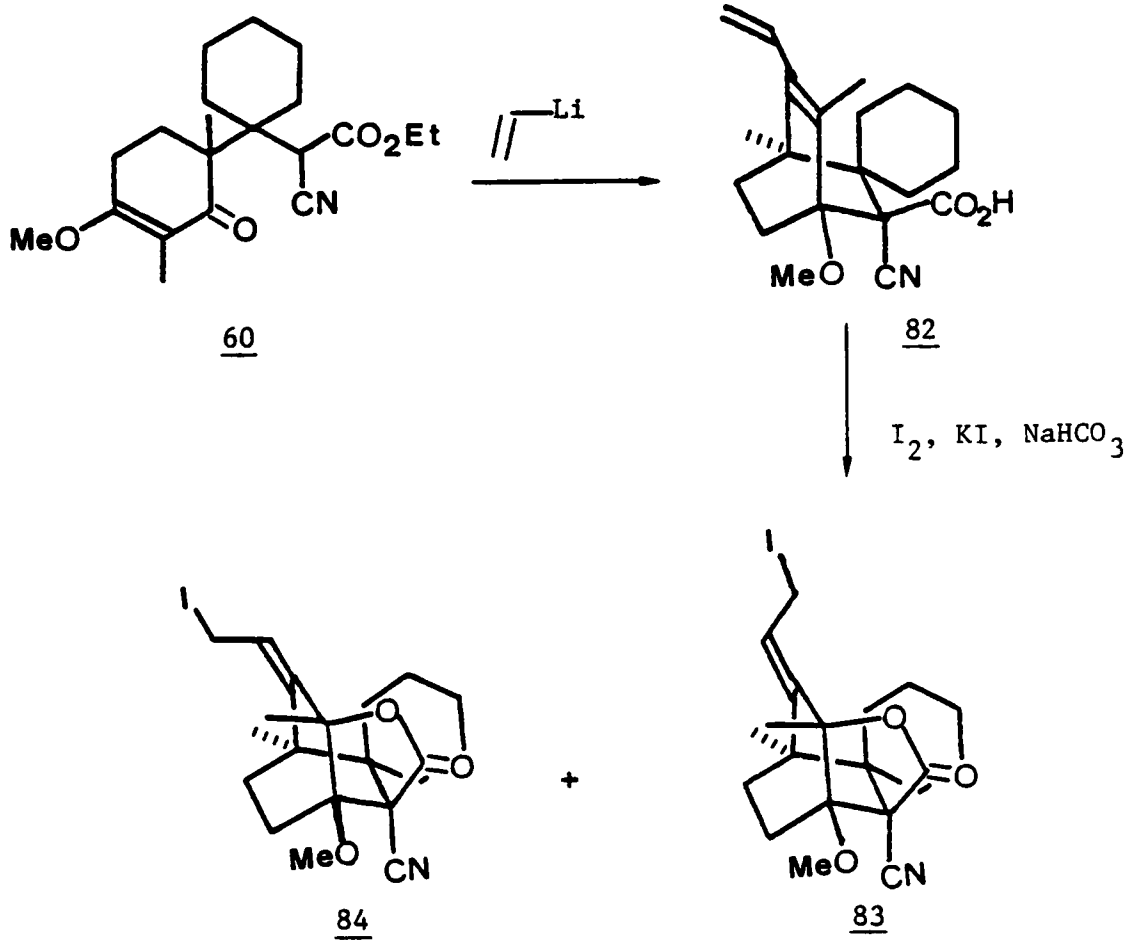


79 81 76% 7:1

III. Annulation of the AB Ring System

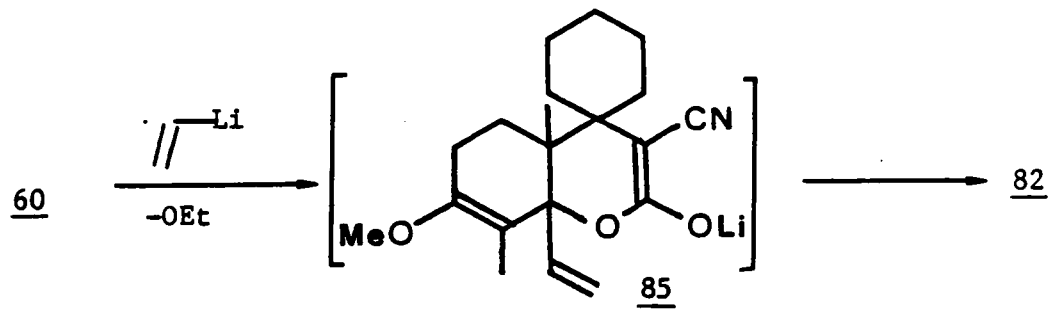
Since cyclohexylidene substrates would provide the most efficient solution to the construction of the C-9 and C-10 centers of aphidicolin, we embarked upon a study of the addition of vinyllithium to cyclohexylidene adducts 60 and 61. Vinyllithium was prepared via metal-halogen exchange with vinyl bromide.[28] Vinyllithium obtained in this manner was a slurry of insoluble vinyllithium and lithium bromide in pentane.

Vinyllithium addition to cyanoester 60 in THF resulted in non-polar unidentifiable products. However, vinyllithium addition of 60 in ether resulted in a 19% yield of carboxylic acid 82. The structure and stereochemistry of 82 was verified by iodolactonization, which produced isomeric allylic iodides 83 and 84.

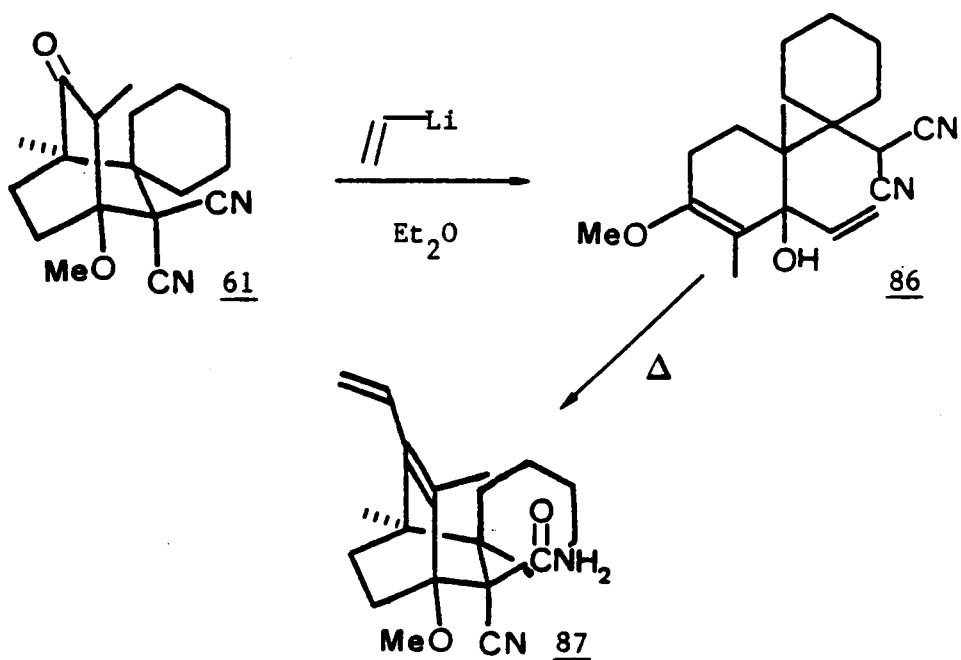


60 82 84 83

Carboxylic acid 82 was the sole carboxylic acid isolated from the reaction of vinyllithium with 60. The stereospecific formation of this product may be rationalized as follows. Saponification of the ester may proceed through lactone 85. Subsequent ester enolate Claisen[29] rearrangement of lactone 85 would stereospecifically provide 82.



Vinyllithium addition to cyano ketone 61 was explored next. Once again, in THF (or DME) unidentifiable products were obtained. However, in ether an acid labile and heat sensitive product was obtained. This labile product 86 when stirred with silica gel in chloroform lost the methoxy group (^{1}H NMR). When warmed, the labile product 86 changed to a stable substance 87, whose ^{1}H NMR spectrum bore striking similarity to that of 82. The yield of 87 from 61 was 31%. The loss of the methoxy



group under mildly acidic conditions is indicative of 1,2 addition of vinyllithium. Again, the presence of an amide in 87 supported the proposal that a Claisen rearrangement had taken place.

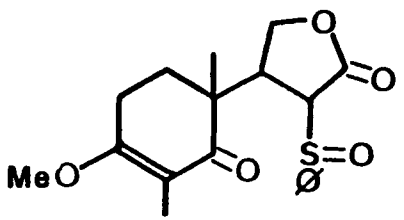
Despite the intriguing aspects of these vinyllithium addition reactions we were concerned about the viability of cyclohexylidene adducts as synthetic intermediates. Most of the reaction mixture could not be identified. Furthermore, these products could not be rearranged to the recognizable vinyl enones under acidic conditions. The formation of bicyclo[2.2.2] ring systems was thought to be irreversible and, therefore, even the identified products would be synthetically useless.

The addition of vinyllithium to the model compound 37 had proceeded in 70% yield, but a number of differences exist between the butenolide Michael adduct 37 and the cyclohexylidene adducts. It was therefore decided to incorporate changes in a stepwise fashion from adduct 37 to synthetically relevant intermediates in order to more fully understand this crucial reaction.

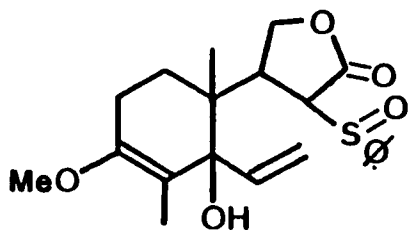
As a first step in this strategy, 37 was oxidized to the sulfoxide 88. Several conditions for vinyllithium addition to 88 were tried and are shown in Table III. These results demonstrated that a sulfinyl substituent could be accommodated by a change in solvent, albeit, with some loss in conversion.

The effect of a quaternary center at C-9 on the vinyllithium addition was then explored, and the results are listed in Table IV. Michael adduct 74 was utilized for this study. Once again, a change of solvent proved necessary. Interestingly, vinyllithium is not soluble in toluene, the solvent of choice. Also, lower yields (up to 10%

Table III Vinyllithium Addition to Enone 88.



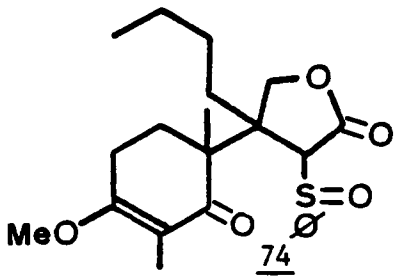
88



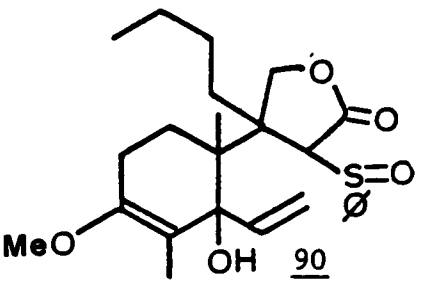
89

Solvent	eq( )	T, °C	Time (min)	Ratio 88:89
THF	5	0	15	95:5
THF	5	25	5	66:33
DME	5	25	5	37:63
DME/Et_2O	5	25	5	45:55

Table IV. Vinyllithium Addition to Enone 74.



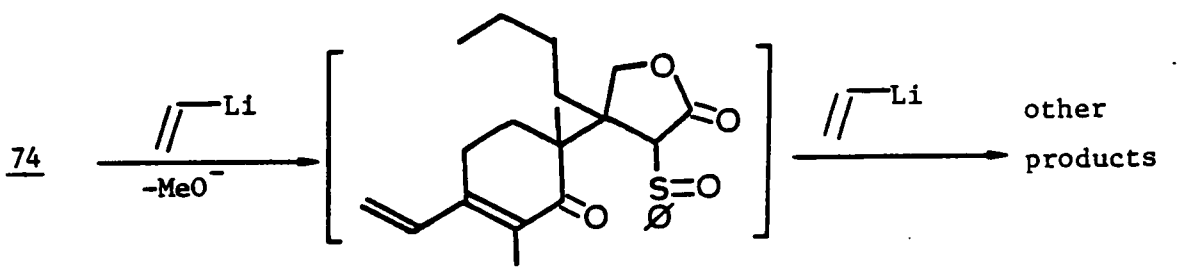
74



90

Solvent	eq( )	T, °C	Time (min)	Isolated Yield
DME	6	25	15	-
$ØCH_3/Et_2O$ (2:1)	6	25	15	35%
$ØCH_3$	6	0	15	33%
$ØCH_3$	6	0	14h	43%
ØH	6	25	15	53%
$ØCH_3$	6	25	15	56%
$ØCH_3$	10	25	15	46%
$ØCH_3$	6	reflux	2	47%
Et_2O/THF	6(MgBr)	25	15	-
$ØCH_3$	6(Sn, nBuLi)	25	15	35%

lower) were often observed from different individual preparations of vinyllithium. Starting enone 74 (15-20%) was recovered from these reactions. The only other isolated products from this reaction were non-polar substances whose ^1H NMR showed no methoxy resonance. This led to the assumption that this material resulted from 1,4 addition to the A ring. Addition of vinylmagnesium bromide resulted in the

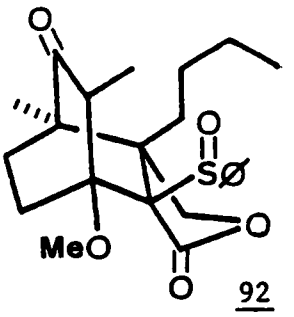


91

exclusive formation of 1,4 addition products. Generation of vinyllithium via metal exchange of tetravinyltin and n-butyllithium[30] was utilized in an attempt to remove lithium bromide from the reaction mixture. However, the reversibility of the exchange probably accounts for the lowered yield observed in this case.

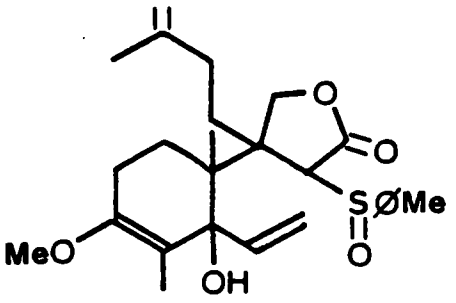
When Michael adduct 74 was deprotonated with 1 eq of n-butyllithium in toluene at -78°C, allowed to warm to 25°C, and poured into an excess of aqueous sodium bicarbonate, a 1:1 mixture of 74 and labile bicyclo[2.2.2] octanone 92 was obtained. Higher temperatures for retro-Michael of 92 to the enolate of 74 may offer an explanation for the high temperature required in the vinyllithium addition.

Under the optimum conditions found for vinyllithium addition to 74, Michael adduct 80 gave 93 in 63% yield, and 81 gave 94 in 74%

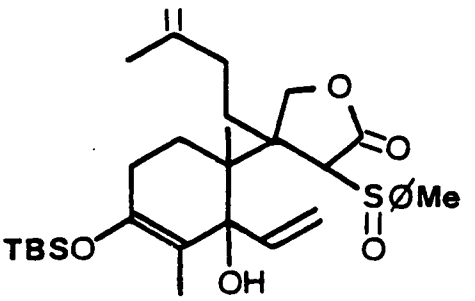


92

yield. The reason for the dramatically higher yield of 94 is obscure. Fewer 1,4 addition products were detected and this could be the result of increased bulk at the β-position of the enone. Also, the lowered amount of recovered starting material may reflect increased solubility of the substrate in the toluene/pentane reaction solvent.



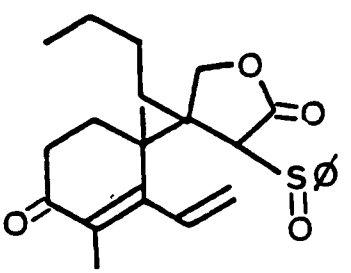
93



94

Treatment of bis allylic alcohol 90 with 2% sulfuric acid provided a 1:1 mixture of vinyl enone 95 and aldol product 96 in 68% yield. Similar results were obtained for alcohol 93. No migration of the isopropenyl olefin was observed under these conditions but the low yield was disturbing. Alcohol 94 rearranged to a mixture of 95 and 96 in 97% yield.

Bis allylic alcohols 90, 93, and 94 were obtained as a mixture of two diastereomers (at C-5?). The major diastereomer of 93 could be isolated by crystallization. The yield for acid-catalyzed rearrangement of crystalline 93 was 87%. This observation led to the conclusion that either the minor diastereomer underwent rearrangement in lower yield or that an impurity was present in the diastereomeric mixture 93. The only detected by-product of rearrangement of 93 was alcohol 99, isolated in only 4.7% yield, whose structure was assigned on the basis of ^{1}H NMR and IR data.



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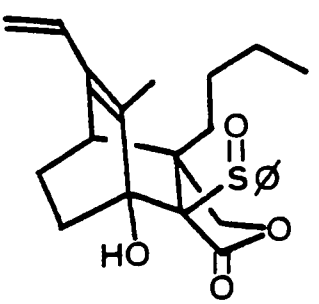

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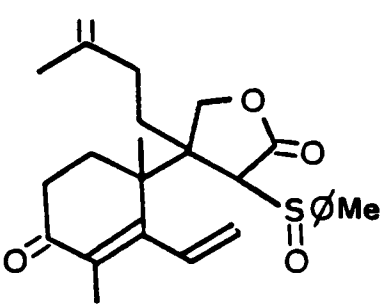

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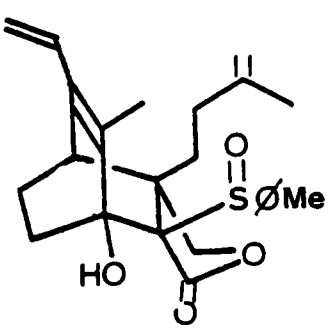
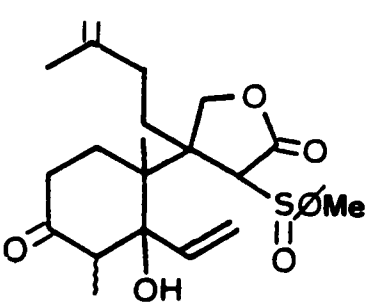
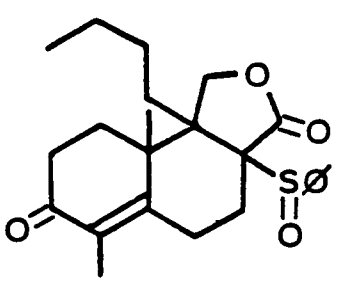


98

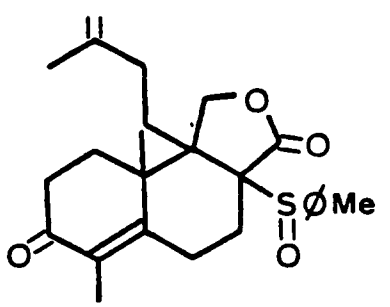


99

The mixture of vinyl enone 95 and aldol product 96 were converted almost completely to 96 upon treatment with sodium methoxide at 0°C for 1 min (THF/MeOH). However, this process was shown to be reversible since these conditions over a longer period of time led to the desired enone 100. Similarly, under these conditions (NaOMe, MeOH/THF, 2.5 h, 0°C) 97 and 98 were converted to enone 101 in 68% yield. It was later found that the presence of a small amount of water increased this yield to 100%. Apparently, a more acidic proton donor than methanol is required to efficiently protonate the dienolate resulting from closure of the B ring.



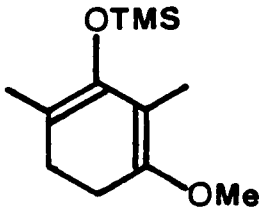
100



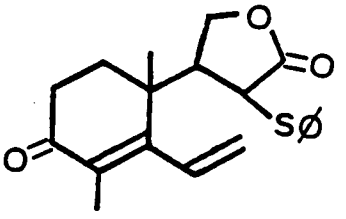
101

A long range objective of this work was to incorporate the steps of this annulation into a single synthetic operation. In partial fulfillment of this goal the first three steps of the model annulation were performed in "one pot." The enolate 58 was prepared via regeneration of the lithium enolate from the corresponding TMS enol ether 102. The Michael addition of 58 to butenolide 36 proceeded in the expected manner, and, upon warming to room temperature, three equivalents of vinyllithium were added to the solution of the stabilized enolate of the Michael product. To the resulting bis allylic alcohol

was added a 2% sulfuric acid solution and the vinyl enone 38 was obtained in 76% yield.



102



38

Despite this success, incorporation of these three steps of the annulation into a single synthetic operation for the β-butenyl sulfinyl butenolide 75 was problematic. The solvent utilized for the Michael reaction was known to be incompatible with the vinyllithium addition. Amazingly, when the Michael reaction of the kinetic enolate (LDA, 0°C) of 79 with butenolide 75 was conducted in toluene at -78°C, little or no effect was observed on either the yield or diastereomer ratio. This development made possible direct addition of vinyllithium to the Michael reaction mixture. Hydrogen fluoride in methanol was added to the mixture to increase the rate of rearrangement of the alcohol 94. Since water had previously been demonstrated to be beneficial to the intramolecular Michael closure of the B ring, sodium methoxide was added directly to the vinyl enone and aldol mixture. This one-pot sequence provided the tricyclic enone 101 in 44% overall yield. A minor diastereomer of 101 was also isolated in 5.3% yield.

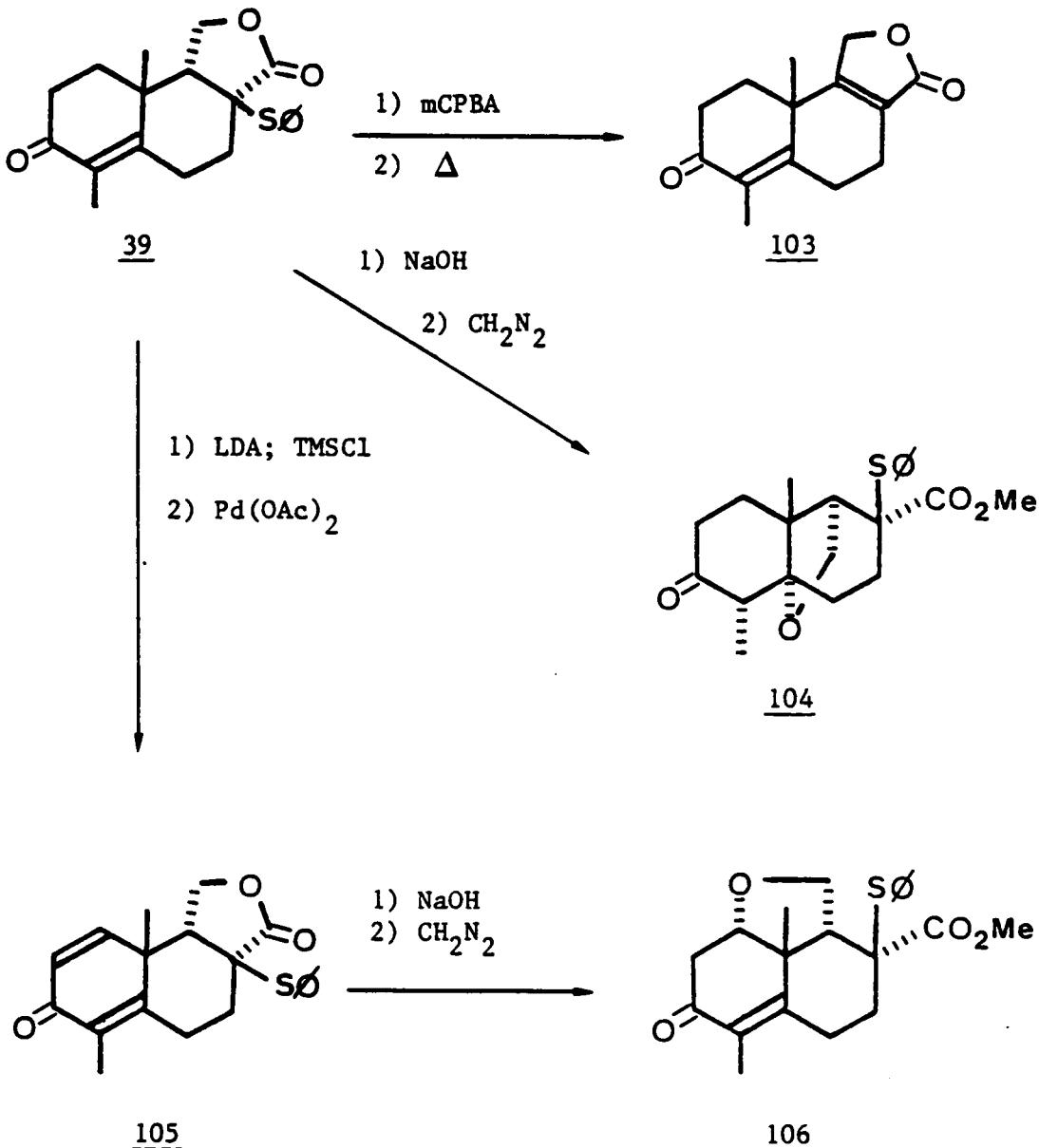
IV. Stereochemistry of Michael Adducts

Having completed synthesis of tricycle 101 we felt that it was now possible to address the question of stereochemistry of C-8, C-9, and C-10. The relative stereochemistry of these centers had essentially been established in the Michael reaction but it was only now in 101 that free rotation about the C-9, C-10 bond had been eliminated. However, we decided to first determine the stereochemistry of the model tricycle 39.

The relative stereochemistry of centers C-8 through C-10 in 39 were revealed as shown in Scheme III. Oxidation of sulfide 39 to the corresponding sulfoxide was followed by thermal elimination[10] to provide butenolide 103 as the sole product. This sequence unambiguously establishes the cis relationship between C-8 thiophenyl and C-9 hydrogen in tricycle 39.

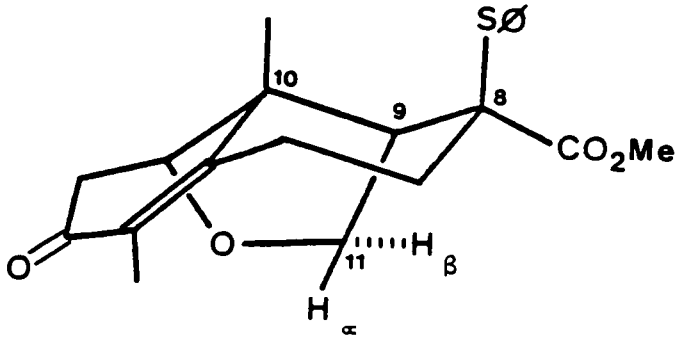
Furthermore, hydrolysis of the butyrolactone moiety of 39 followed by esterification with diazomethane[31] provided the cyclic ether 104, suggesting a cis relationship between the C-9 hydrogen and C-10 methyl in tricycle 39. This suggestion was confirmed by the following results. Conversion of 39 to the corresponding dienol TMS ether (LDA, THF, -78°C, TMSCl) was followed by treatment with palladium acetate[32] to afford the dienone 105. Hydrolysis of 105 as before and subsequent esterification then gave cyclic ether 106 in high yield. Formation of 106 (equatorial H at C-1) can only be possible when C-10 methyl and C-9 hydrogen are cis to one another.

Scheme III.



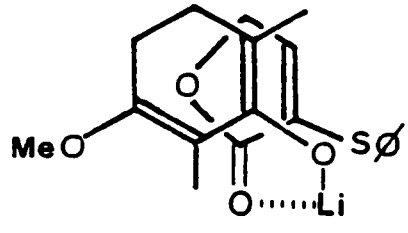
39 103 104 105 106

The 100 MHz ^1H NMR spectrum of 106 in benzene-d_6 confirmed this postulate. The C-1 proton appeared as an AB triplet (2.5 Hz, 2.5 Hz), as expected for an equatorial proton at 3.6 ppm. However, the C-11 α proton (3.3 ppm, 8 Hz, 10 Hz) appeared 0.7 ppm upfield of the C-11 β proton (4.0 ppm, 8 Hz, 8 Hz). This apparently is a result of the fact that the α-proton sits very nearly underneath the carbon-carbon double bond of the A ring enone and is therefore shielded.



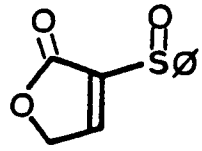
106

We had rationalized the stereochemistry of tricycle 39 at centers C-9, C-10 as arising through transition state 107 in the Michael reaction.[10] We have dubbed this mode of approach of butenolide to dienolate as "endo" approach, since the butenolide oxygen sits under the diene system in this model.

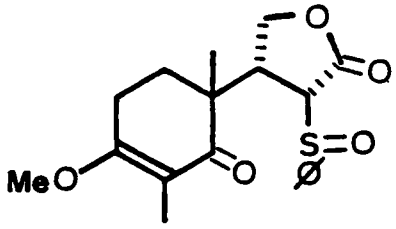


107

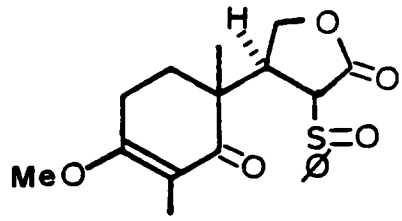
It was our expectation that the same transition state would be operative for Michael addition of the dienolates of 35 and 79 to butenolide 75. There are two major differences between butenolides 36 and 75. The first is the β-alkyl substituent and the second is the oxidation state of sulfur. In order to bridge this gap, sulfoxide 108 was prepared by oxidation of butenolide 36 with peracetic acid. Michael addition of the kinetic enolate of 35 to butenolide 108 provided a 78% yield of a 2:1 mixture of diastereomers 109a and 109b. Desulfurization (Ra-Ni) of this mixture, again, produced a 2:1 mixture of 110 and 111. Examination of the 200 MHz ^1H NMR spectrum of this mixture revealed that the major diastereomer 110 was identical to that produced from desulfurization of Michael adduct 37.



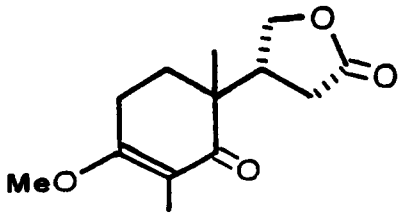
108



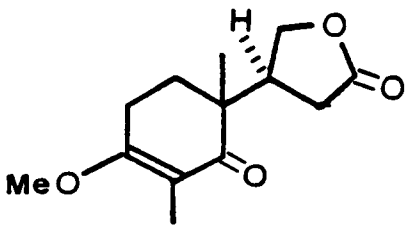
109a



109b

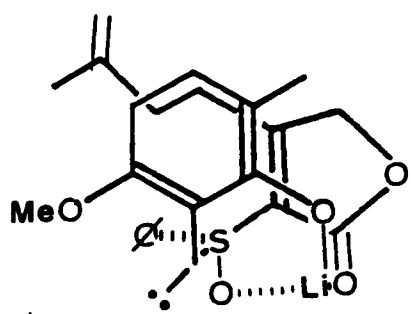


110



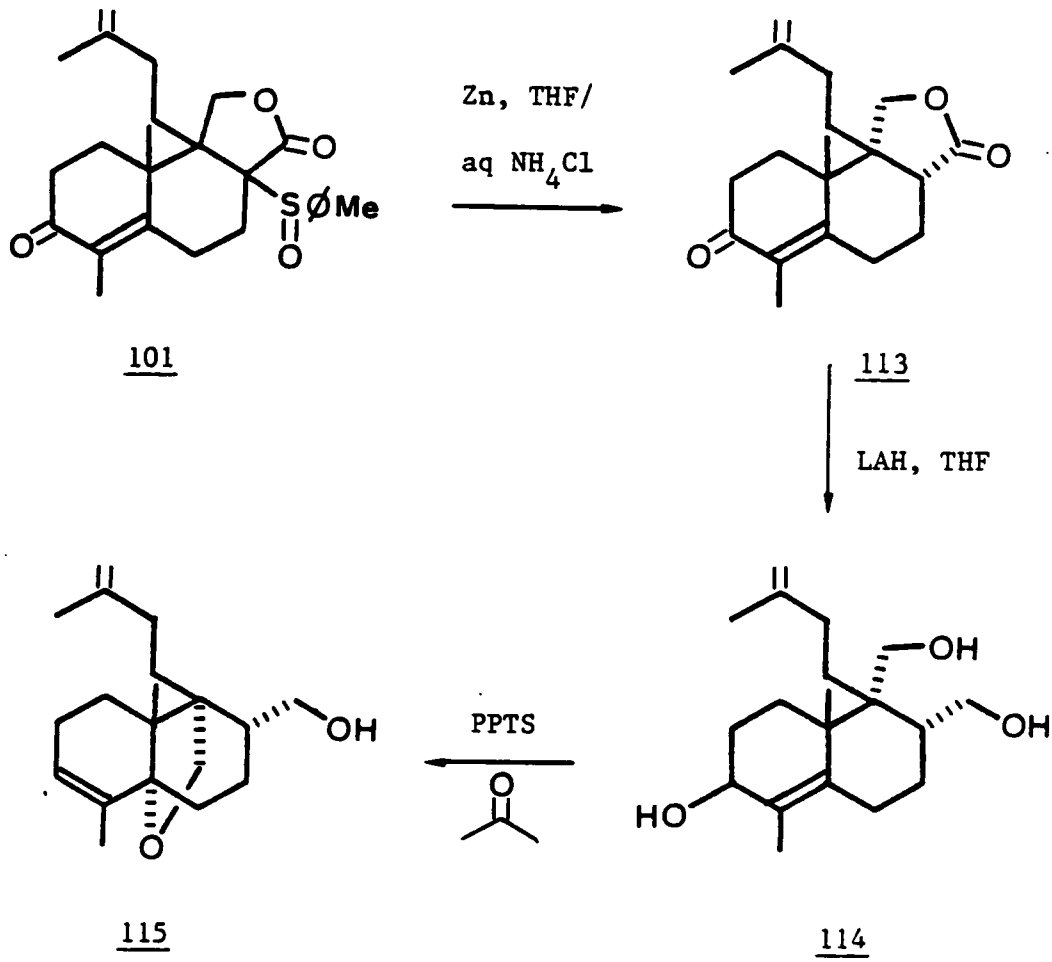
111

This result was not as conclusive as we had hoped. It appears that the sulfoxide may provide some relative stabilization of the "exo" transition state. The improvement of this 2:1 ratio of adducts for acceptor 108 to 7:1 for butenyl butenolide 75 may be a result of the β-alkyl substituent's interaction with the enone in the "exo" transition state 112.



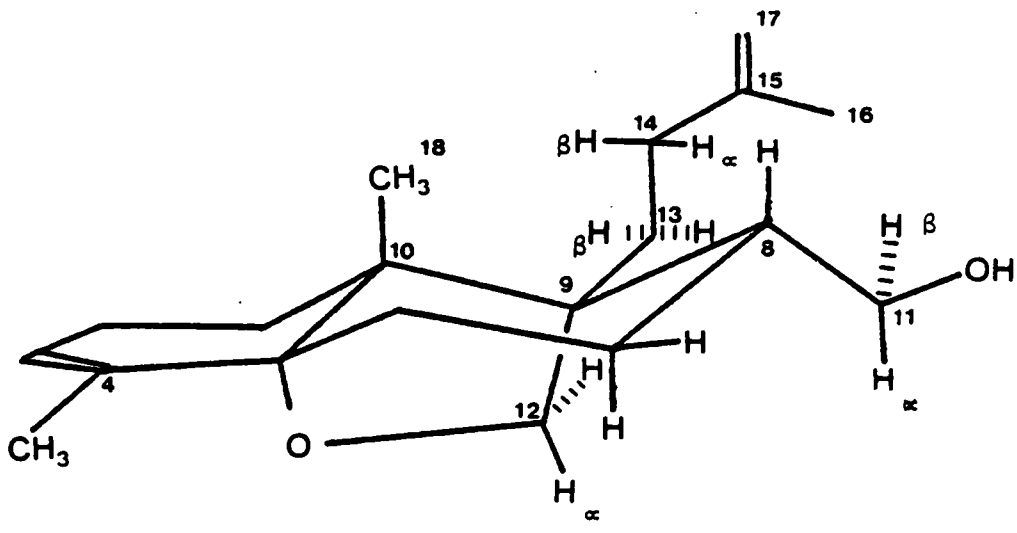
112

In order to confirm that the C-9 and C-10 stereocenters of Michael adduct 81 had arisen from an "endo" transition state, tricycle 101 was subjected to the following reactions. Desulfurization with Raney Nickel provided a mixture of products resulting from hydrogenation and isomerization of the isopentenyl side chain. Desulfurization with zinc dust in THF/saturated aqueous NH_4Cl afforded tricycle 113 in 94% yield. Reduction of enone 113 with LAH in THF gave triol 114, which, under mildly acidic conditions (pyridinium p-toluenesulfonate (PPTS), acetone, 25°C), afforded furan 115. Once again, formation of this furan was, in and of itself, indicative of the trans relationship of the C-9 hydroxymethyl and C-10 methyl substituents.



101 113 115 114

Analysis of the ^1H NMR spectrum in combination with europium shift reagent and irradiation techniques allowed us to determine the stereochemistry of 115 and therefore 101. The most important resonance was that of the proton at C-8. This proton was identified by its coupling constants to H-11α and H-11β (10 Hz, 5 Hz). These constants also gave the conformation of the C-8, C-11 bond. The C-8 proton had a small W-coupling constant to H-12β, establishing an anti relationship of H-8 and C-12. This was further confirmed when irradiation of H-12α produced an NOE enhancement of the H-11α resonance. Finally, irradiation of the C-10 methyl group (H-18) produced an NOE enhancement of the H-8 resonance.

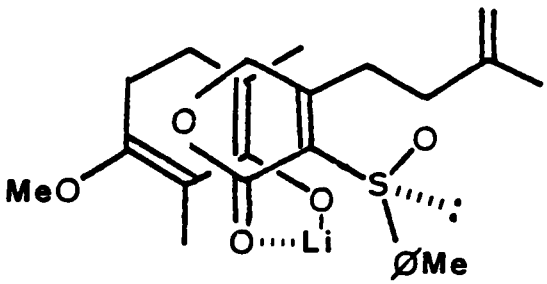


115

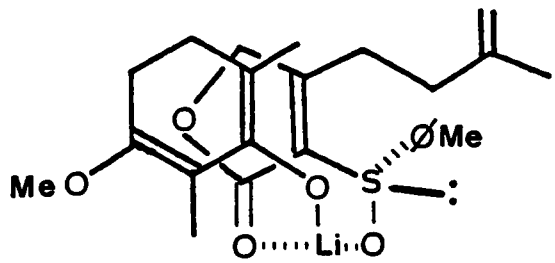
This result established a 1,3 diaxial relationship of the C-10 methyl and C-8 proton and, therefore, an anti relationship of the C-10 methyl and the C-9 hydroxymethylene group. Furthermore, the conformation of the side chain was determined by the proximity of H-8 and H-14α, H-11β, and H-13α from NOE measurements.

These results confirmed that an "endo" transition state was responsible for the formation of Michael adduct 81. However, the predominant formation of one diastereomer in 81 indicated that the stereochemistry at sulfur had in some way determined which face of the butenolide had been attacked by the dienolate. This observation could be explained in one of two ways.

The first explanation postulates coordination of the sulfoxide oxygen as well as lactone oxygen and enolate oxygen to lithium. Given the "endo" approach of butenolide to dienolate, only transition state 116 avoids severe methyl-phenyl interactions.



117



116

The second presumes no such complexation of sulfoxide oxygen but, instead, postulates that the sulfoxide will adopt a conformation in which the oxygen has rotated 180° to minimize dipole-dipole interactions, as in 117. In this conformation the dienolate must approach from the opposite face of the butenolide in order to avoid interaction with the phenyl substituent.

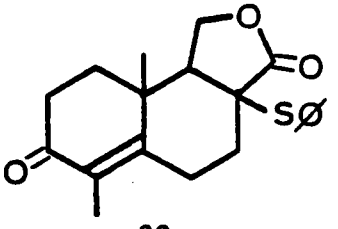
At present, we have no method to determine the stereochemistry at sulfur and its relationship to the stereochemistry at C-9, C-10. Thus, we cannot determine whether transition state 116 or 117 is operative in the formation of the Michael adduct. Regardless, use of an optically active butenolide will provide an optically active Michael adduct. Although there are reported examples of asymmetric induction in Michael additions to vinyl sulfoxides,[33] our findings will constitute, to our knowledge, the first observation of asymmetric induction at enolate carbon. Efforts are currently underway to prepare optically active 75. Completion of the synthesis of aphidicolin and comparison of the optically active synthetic sample from the known enantiomer of 75 and the known enantiomer of the natural product will provide the stereochemical relationship of C-9, C-10 and sulfur in the Michael

adduct. This may complete the information necessary to postulate the transition state of the Michael reaction.

V. Dissolving Metal Reduction

According to our plan, we embarked upon functionalization of the A ring of tricycle 101. This was to involve dissolving metal reduction of the enone to afford an enolate which would be alkylated *in situ* to provide an aldol adduct. This adduct would be reduced stereospecifically with a hindered hydride to give the desired 1,3 diol. Furthermore, it was expected that the dissolving metal reduction would also desulfurize the C-8 position of the tricycle to form the lactone enolate, and, as such, the lactone would be protected from over-reduction.

In order to test the viability of this scheme, enone 39 was subjected to dissolving metal conditions (Li, NH_3/THF, -78°C).[34] Ammonia was removed and the bis-enolate was silylated (TMSCl/THF, -78° 25°C).[35] The isolated silyl enol ether 118 apparently resulted from selective hydrolysis of the labile silyl ketene acetal of the lactone enolate in the work-up of the reaction. Treatment of silyl enol ether 118 with dry tetrabutylammonium fluoride[36] in THF in the presence of formaldehyde provided aldol product 119 in 45% yield. On the other hand, treatment of 118 with $TiCl_4$[37] in methylene chloride in the presence of s-trioxane gave a diastereomeric aldol product 120 in 60% yield. This unusual result prompted us to investigate the stereochemistry of 119 and 120.



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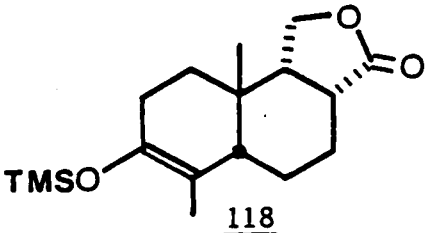
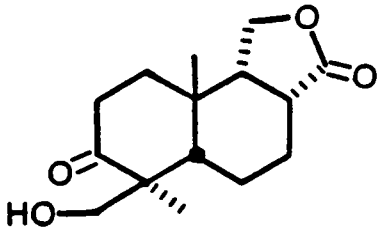


118



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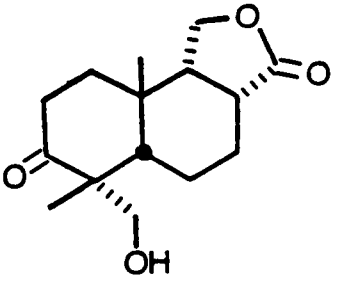
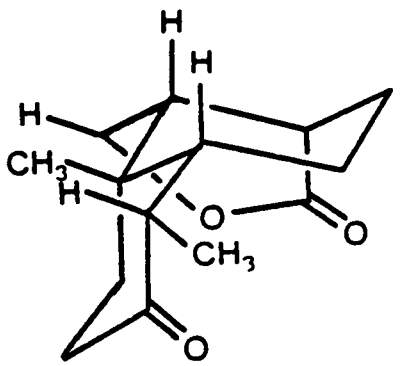


120

Dissolving metal reduction of enone 39 and protonation of the resulting bis-enolate with ammonium chloride gave keto lactone 121. Irradiation of the C-4 methyl resonance gave the C-4 proton as a 4 Hz doublet. This small coupling constant to the C-5 proton suggested a cis fused decalin. This was confirmed when the C-10 angular methyl group was irradiated and an NOE enhancement of the C-12α proton was observed. This could only be possible for an equatorial C-10 methyl group, which indicated that we had obtained the cis fused decalin. Further determination of the stereochemistry of 119 and 120 rests on a weak NOE observed between the 1,3 diaxial methyl groups of 120.

Formation of a cis fused decalin from enones such as 39 is quite rare.[34] However, in those rare instances the B ring had been constrained to be in a boat conformation.[38] We therefore rationalized that the reductive desulfurization at C-8 to produce enolate 122 in the

dissolving metal reduction had occurred prior to reduction of the enone. Examination of molecular models indicated that the exocyclic enolate would force the B ring into a boat conformation.



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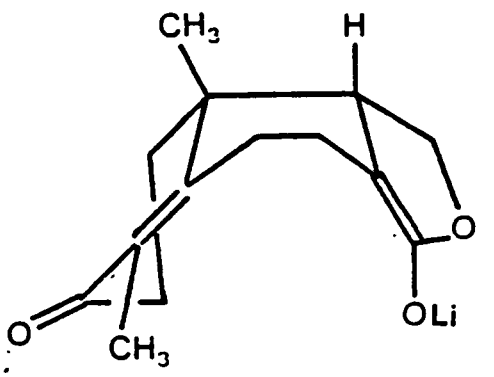
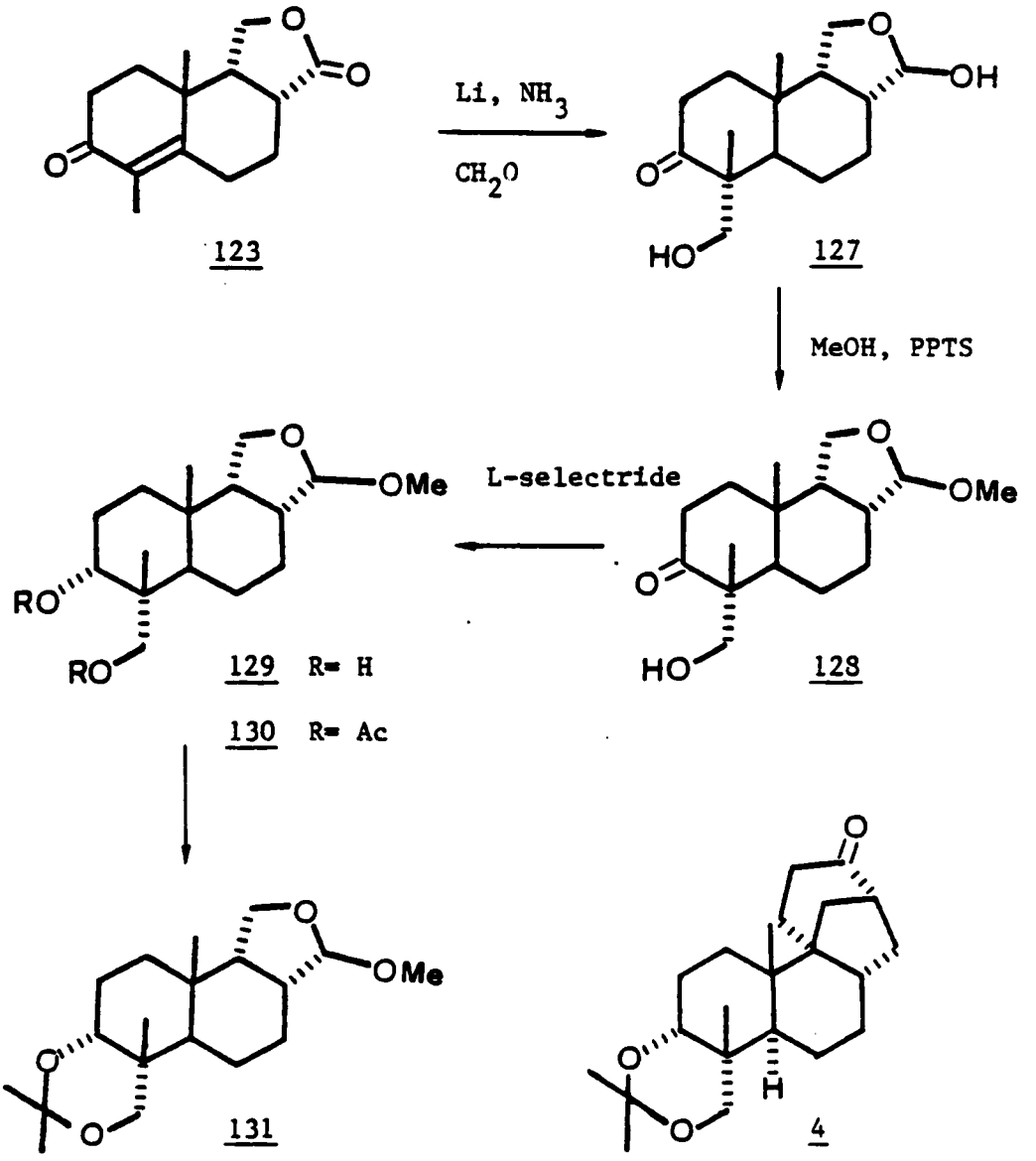


122

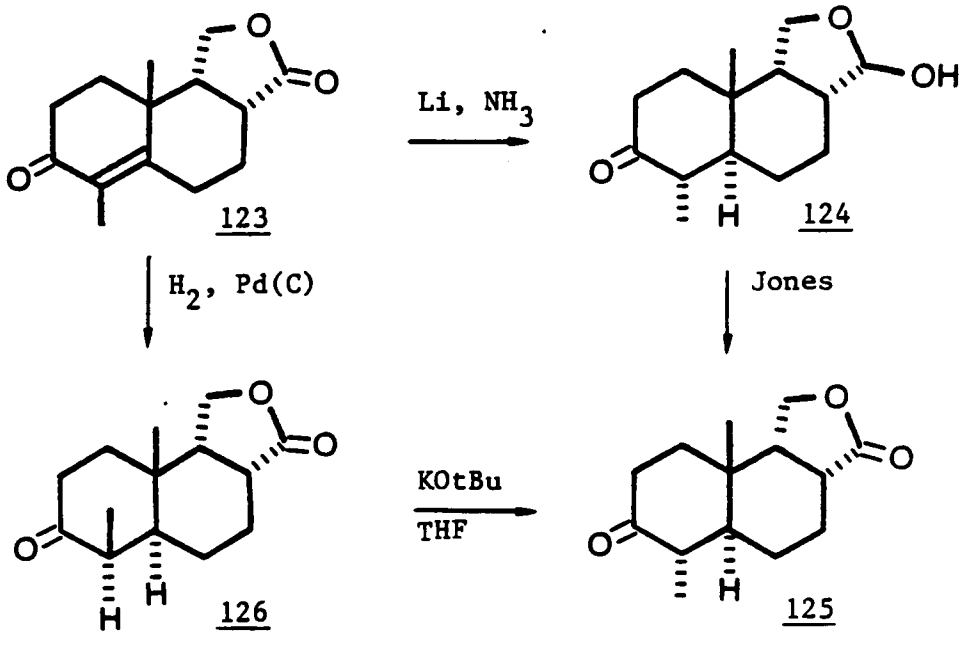
Therefore, we attempted to avoid this problem by removal of the sulfur substituent prior to the dissolving metal reduction. Desulfurization of enone 39 with Raney nickel provided enone 123 in 88% yield. Dissolving metal reduction of 123 gave keto lactol 124 which was oxidized to lactone 125 for comparison to the previous dissolving metal product 122. The C-4, C-5 proton-proton coupling constant in 125 was shown to be 11 Hz, which is compatible with that expected for a trans fused decalin. Chemical confirmation of this assignment was obtained by hydrogenation of enone 123 to provide a third keto lactone 126. This ketone was epimerized under basic conditions to give lactone 125. This is consistent only with hydrogenation from the α face of the enone to give the trans decalin with an axial methyl group.

Greatly encouraged by this result, we completed introduction of substituents of the A ring of aphidicolin (Scheme IV). In situ

Scheme IV.



123 127 128 129 R= H 130 R= Ac 131 4

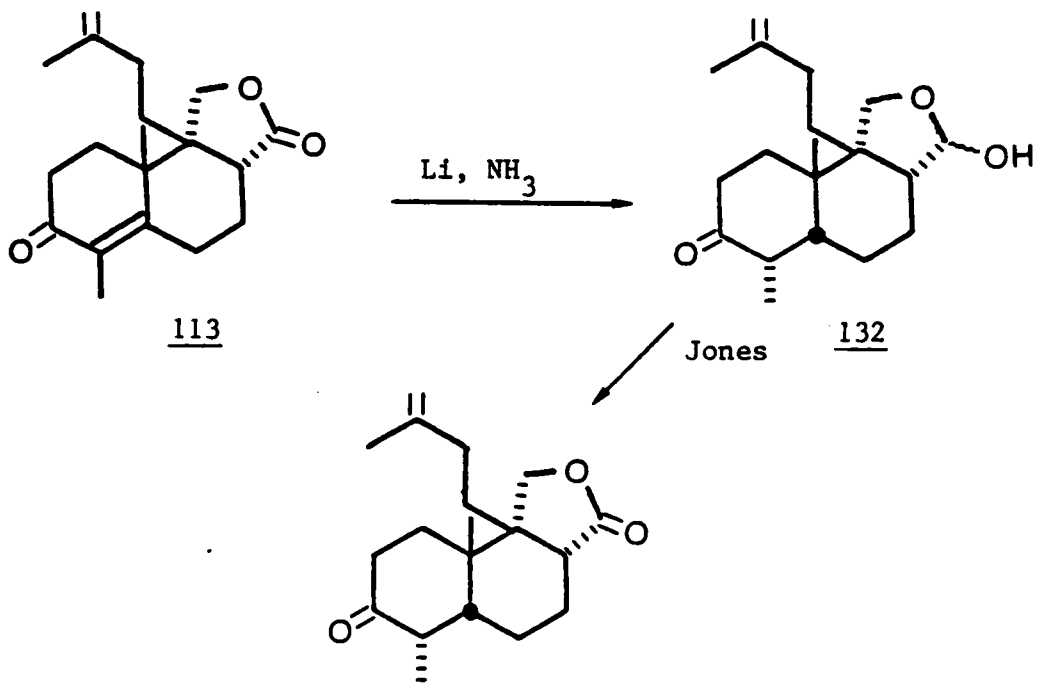


123 124 126 125

alkylation of the enolate formed from the dissolving metal reduction of 123 provided aldol product 127 in 60% yield.[35] The lactol was protected by formation of the methoxy acetal 128 in acidic methanol. Reduction of 128 with L-selectride[39] provided the axial alcohol 129 as indicated by the ^{1}H NMR spectrum of the bis acetate 130 (C-3 hydrogen triplet). The diol 129 was treated with acetone and p-toluenesulfonic acid to afford the acetonide[40] 131 whose ^{1}H NMR spectrum was similar to that of authentic acetonide 4.

Upon completion of our investigation of the model system, we subjected tricycle 113 to the dissolving metal reduction. The lactol obtained from this reduction was, again, oxidized with Jones reagent to lactone 133. The stereochemistry of 133 was elucidated by decoupling

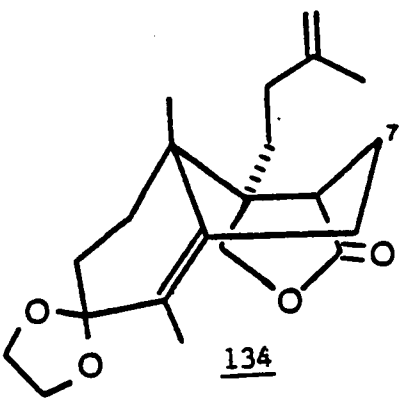
the C-4 methyl group to reveal the C-4 proton as a doublet with a 4 Hz coupling constant. We suspected that, once again, the B ring had adopted a boat conformation.



113 132 133

The boat conformation of the B ring in 113 could only be indirectly confirmed. Enone 113 was ketalized[41] (PPTS, ØH, 2-ethoxy-dioxolane, 8 h, reflux) to afford ketal 134 in 89% yield. This transformation simplified our NMR spectroscopic investigation in the following way. It shifted the C-2 proton resonances back upfield so that the C-8 and C-7 proton resonances could be better observed. Also, it ensured that $Eu(fod)_3$ would complex the lactone oxygen and not the enone oxygen.

The important C-8 proton resonance was identified by its downfield shift and the fact that irradiation of this resonance collapsed the only methine doublet in the C-13 proton coupled spectrum. That 134 was



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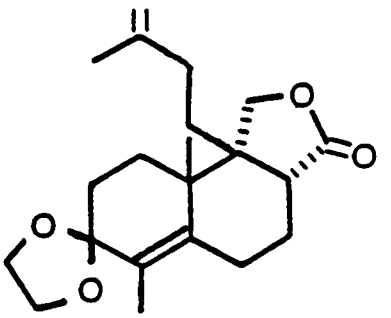
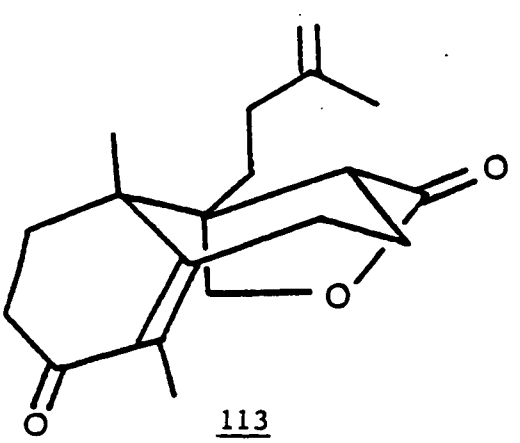


134

in a boat conformation was indicated by the C-8 proton coupling constants to the C-7 protons. This was confirmed by an NOE enhancement of the C-7β proton resonance upon irradiation of the C-10 methyl group.

The only difference between tricycle 39 and 113 is the C-9 alkyl substituent. Presumably, this substituent is responsible for the boat conformation of 113. The mechanism by which this occurs is most certainly subtle, but might be explained in the following manner.

When the B ring is in the chair conformation the C-11 lactone carbon is equatorial and might interact with the C-9 alkyl substituent.

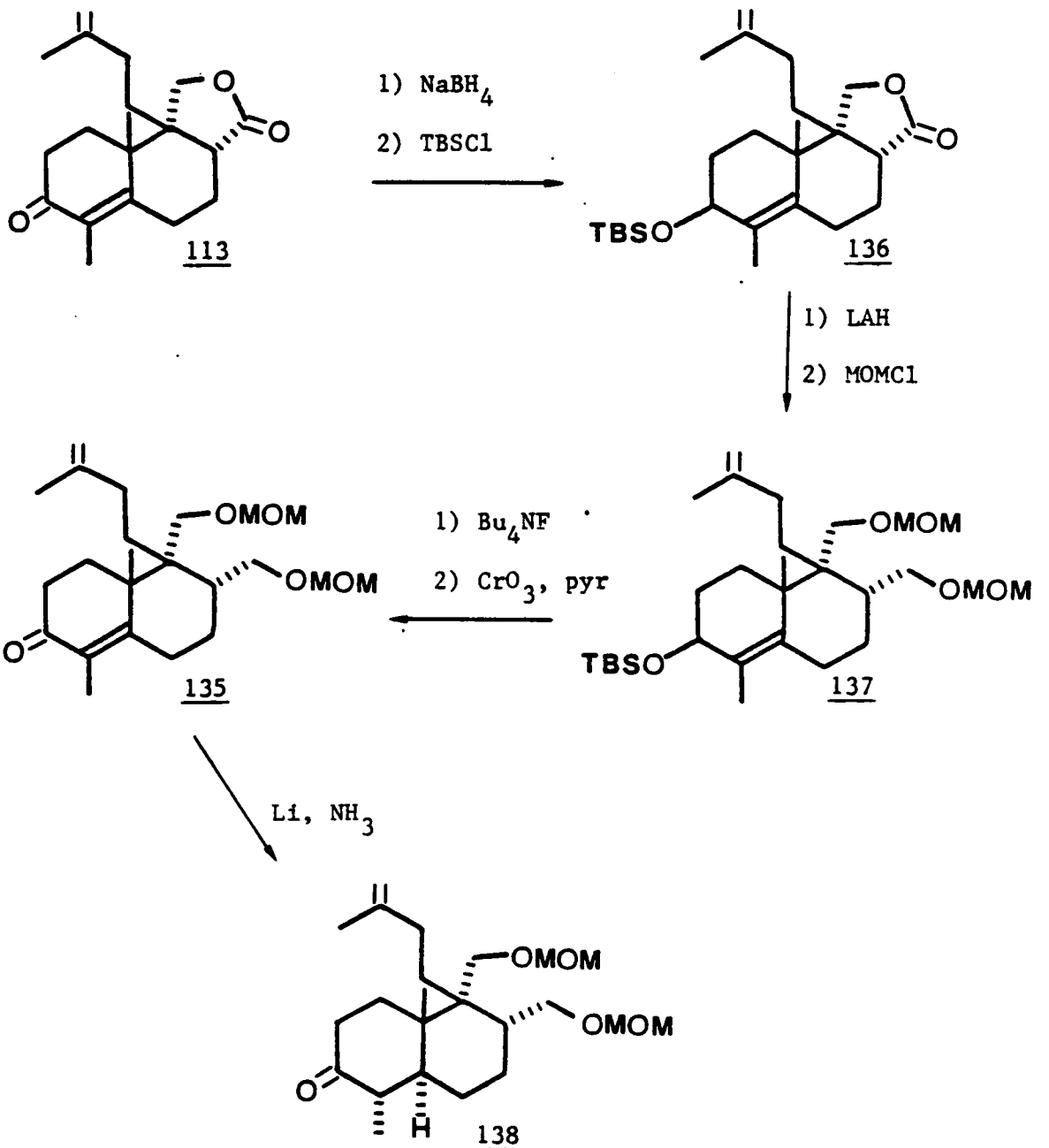


113

Relief of this interaction would be provided by downward movement of C-11 to an axial position, which places the B ring in a boat. This movement is also presumably encouraged by a "pull" from the axial hydroxymethylene group of the lactone moiety. We, therefore, rationalized that the B ring might, once again, adopt a chair conformation if the lactone could be opened. Indirect confirmation of this postulate was provided by the dissolving metal reduction of bis-methoxymethyl ether 135. Enone 135 was prepared via a six step sequence (Scheme V). Enone 113 was protected by reduction and silylation to provide the t-butyldimethylsilyl ether[42] 136. The lactone was opened by reduction with LAH and protected as the bis-methoxymethyl ether[43] 137. The enone functionality was regenerated by cleavage of the silyl ether[42] and oxidation with chromium trioxide in pyridine.

Dissolving metal reduction of 135 gave ketone 138. Trans decalin stereochemistry was indicated by the 11 Hz C-4, C-5 proton-proton coupling constant. These results confirmed that the lactone ring had played a role in forcing the B ring into a boat conformation. Therefore, it was decided that with ketal 134 in hand, it would be best to form the C,D rings first, and to address dissolving metal reduction of the A ring enone later. After formation of the C ring the B ring would be constrained to adopt a chair conformation. Furthermore, Ireland's[9d] results indicated that once the C,D ring system of aphidicolin is complete the dissolving metal reduction proceeds to provide a trans fused decalin.

Scheme V.



113 136 135 137 138

VI. The C,D Ring System

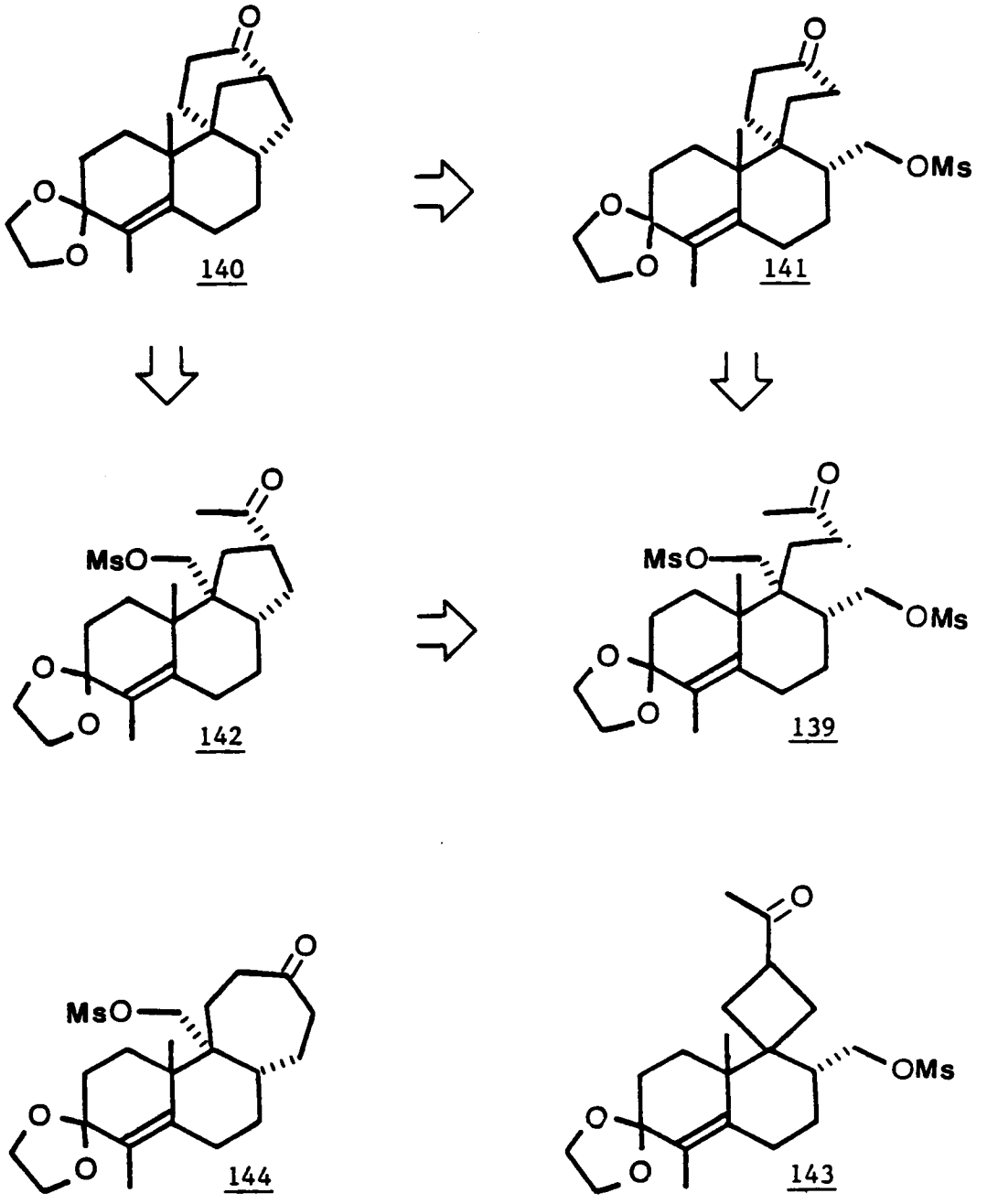
Our plan for the construction of the C,D ring system of aphidicolin involved two possible approaches. We believed that the lactone moiety could easily be reduced to a diol and mesylated. We then envisioned that the methyl ketone would be exposed via oxidative cleavage of the less substituted olefin to afford the keto bis-mesylate 139. This substrate has two electrophilic sites and two nucleophilic sites. There are, therefore, four possible bonds that may be formed (141, 142, 143, 144). Formation of the four- and seven-membered rings (143, 144) were considered unlikely on the basis of ring strain and entropic considerations respectively (see Scheme VI).

The first plan involved generation of the kinetic enolate (less substituted) of the methyl ketone. This enolate would then undergo alkylation to form the six-membered (D) ring[44] (141). It would then be possible to form the C ring as in Corey's synthesis[9c] of aphidicolin.

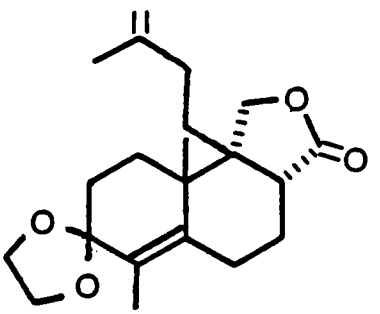
The second plan was to form the C ring first (142) under protic conditions in which the thermodynamic enolate would be alkylated to form the five (142) in preference to the four-membered ring. At this point it should be possible to form the six-membered D ring (140) utilizing kinetic conditions if necessary.

The keto bis-mesylate 139 was prepared in the following manner. Reduction of lactone 134 with LAH in THF at 25°C gave the acid labile diol 145. As previously described, the axial hydroxymethylene group is conveniently disposed for allylic displacement of the allylic ether function. This reaction and the general lability of the unsaturated

Scheme VI.



ketal moiety required the use of base-washed glassware for manipulation of all subsequent intermediates containing this functionality. Hydrolysis of 145 resulted in formation of the furan 146.



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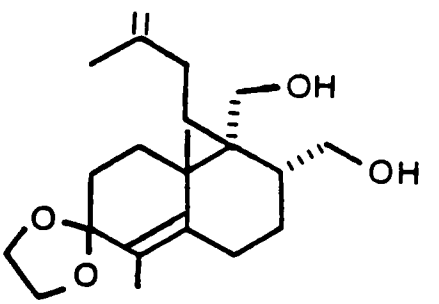
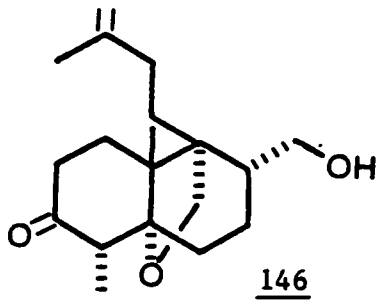


145

Mesylation[45] of the diol 145 was performed at -78°C (MsCl, Et_3N) in methylene chloride to give bis mesylate 148. At higher temperatures formation of the furan 147 from the mono mesylate was competitive with the second mesylation to afford 148. The use of the corresponding bis tosylate was, therefore, precluded on the basis of its slow rate of formation.

Oxidative cleavage of the disubstituted olefin was accomplished with osmium tetroxide and sodium metaperiodate in a biphasic solvent system (Et_2O/H_2O)[46] to give 139. Triethylamine was added because sodium metaperiodate is acidic enough in water (pH 3.5) to hydrolyze the sensitive ketal moiety. Under these conditions 139 was generated in an 84% overall yield from 134.



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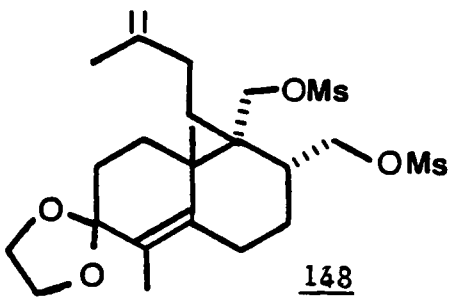

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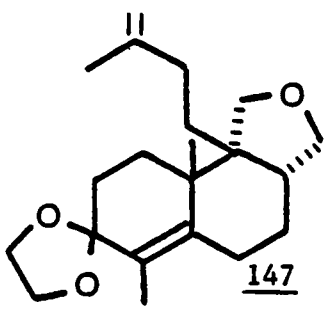

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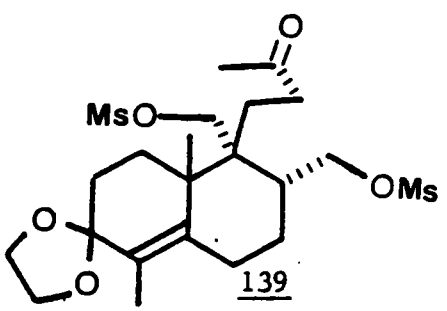
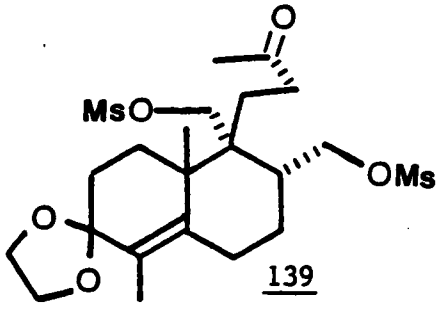


139

Because the first plan involving formation of the kinetic enolate offered the potential for constructing the C,D ring in one synthetic operation, it was the first approach tried. Deprotonation of 139 with KOtBu in THF provided cycloheptanone 144. This structure was assigned on the basis of its ^{1}H NMR spectrum, which showed only one mesylate methyl resonance, an AB quartet for mesyloxymethylene protons, and the loss of acetyl methyl.

Under protic conditions, however, 139 cyclized to cyclopentane 142 (^{1}H NMR: 1 mesylate methyl, ABX for mesyloxymethylene, acetyl methyl).



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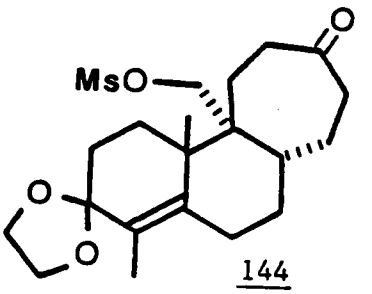

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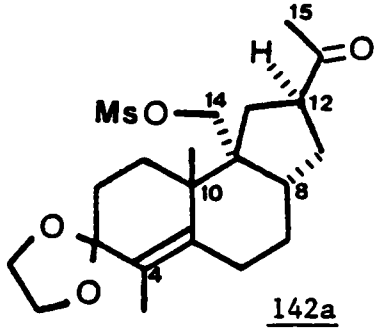
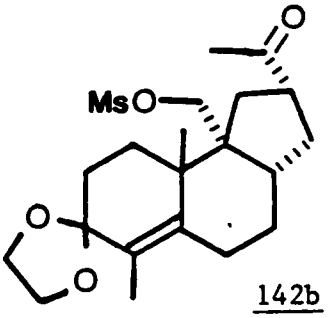


142a



142b

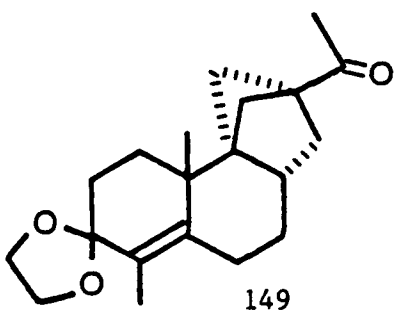
The acetyl cyclopentane 142 was obtained as a mixture (5.5:1) of two diastereomers 142a and 142b. Deprotonation of the mixture with KOtBu (0°C, THF) and reprotonation with a saturated aqueous solution of sodium bicarbonate provided the minor diastereomer 142b in 80% yield. Also, a 1:1 mixture of the two diastereomers could be equilibrated (DBU, ØH, reflux) to the major diastereomer 142a.

The major diastereomer 142a was expected to have the acetyl group in the less crowded β-position. The diastereomer resulting from kinetic protonation of the more substituted enolate was expected to have

the acetyl group in the α-position. This was based upon the presumption that the mesyloxymethylene group is proximate to the α-side of the C-12 position of the cyclopentane.

These assignments were verified by ^{1}H NMR. An NOE enhancement of one of the C-14 proton resonances was observed upon irradiation of the C-12 proton of the major diastereomer 142a. Furthermore, in a europium shift reagent study, the C-14 proton resonances were the fastest downfield moving resonances in 142b. This was clearly not the case in 142a.

With the C-ring closed, we turned our efforts to closure of the D ring. Treatment of 142 with sodium methoxide at reflux resulted in no reaction. However, treatment of 142 with KOtBu in THF at reflux provided a 1:1 mixture of 149 and 150. The latter compound, 150, was



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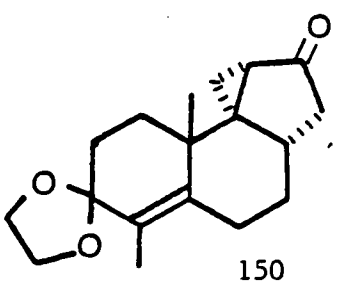

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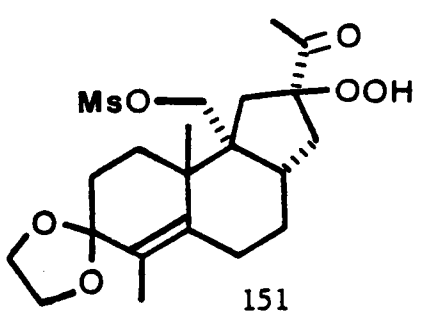

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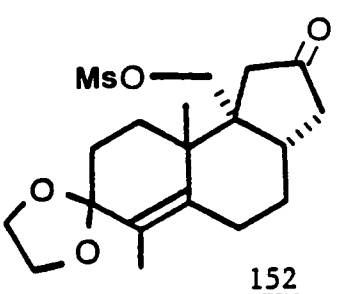
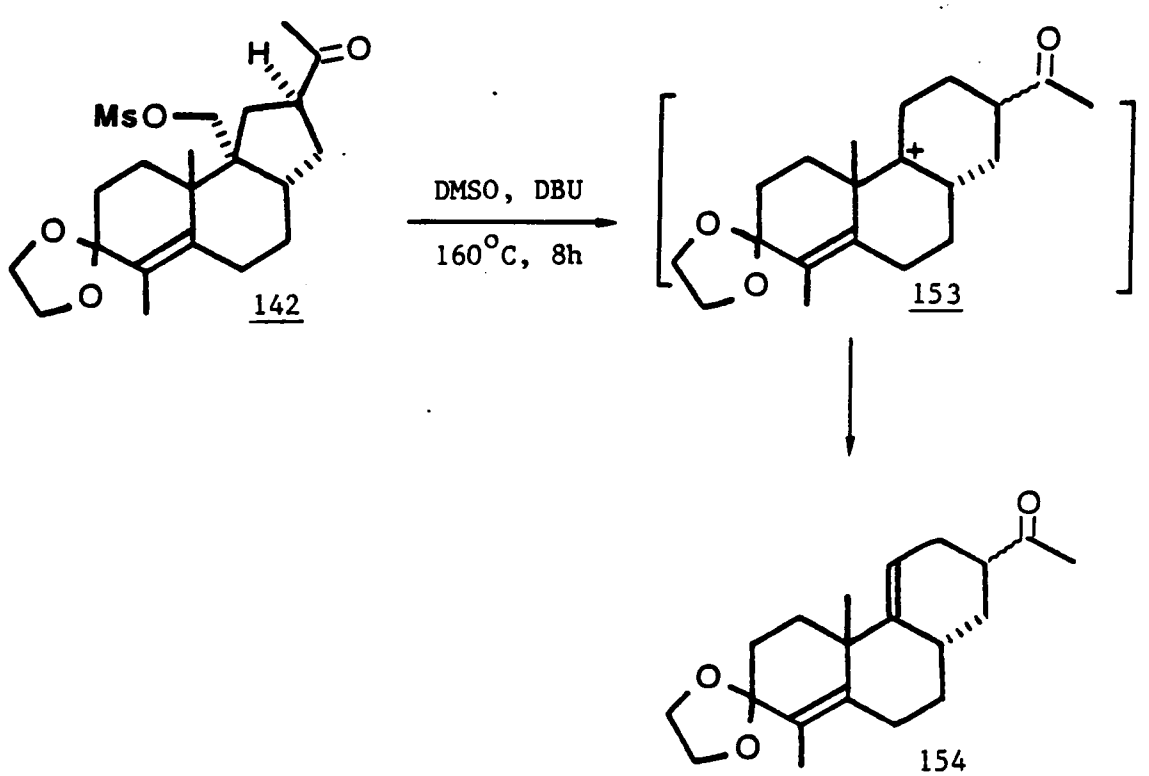


152

initially mistaken for 140. However, it was found that when O_2 was carefully excluded from the reaction only 149 was observed. If O_2 was not carefully excluded, at 0°C a more polar compound, 151, was isolated which showed a positive test for hydroperoxides (Fe^{++}, SCN^-).[47]

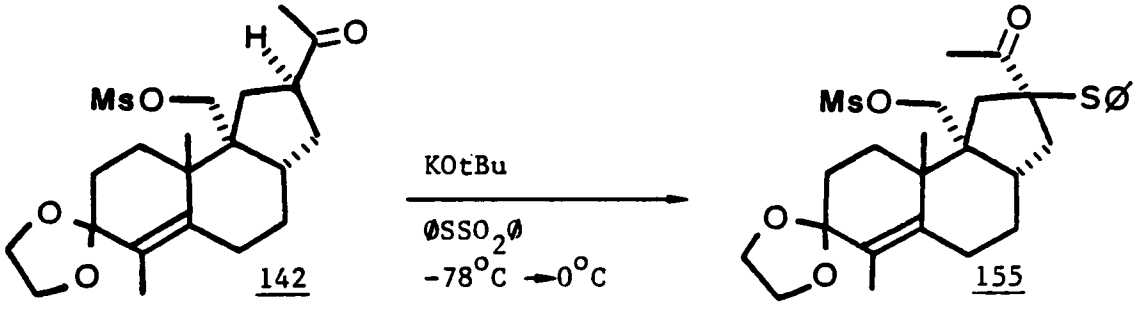
Cleavage of 151 to 152 is likely under the conditions employed for formation of 149.[48] Displacement of the mesylate to form the cyclopropane 150 is tentatively postulated to explain the second product observed in this reaction.

When 142a was heated in DMSO in the presence of DBU (160°C, 8 h) a single new product was formed. This product had an olefinic proton resonance and was tentatively assigned the structure 154. ^1H NMR data



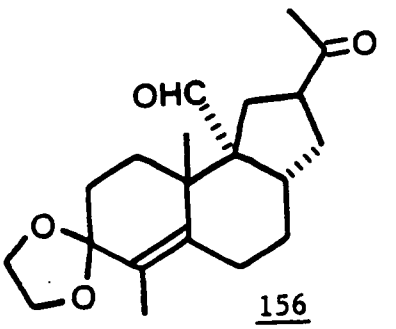
of 142a indicates that the C-O bond of C-14 is oriented 180° with respect to the C-9, C-11 bond. This is supportive of the suggested skeletal rearrangement.

Since all attempts to close the D ring under equilibrating conditions had failed, the minor isomer 142b was deprotonated (1 eq, LDA, THF, -78°C 25°C) under kinetic conditions. This resulted, once again, in a mixture of unidentifiable products. Finally, it was decided to take advantage of the enolate produced by deprotonation with KOtBu. Sulfenylation ($\emptyset SSO_2\emptyset$)[13] of this enolate gave sulfide 155. We believed that use of this sulfide would overcome two difficulties. First, sulfenylation (like protonation) placed the acetyl group on the side of the cyclopentane required for closure of the D ring, and second, since the C-12 position was now quaternary the four-membered ring could no longer form. However, repeated attempts to close the D ring utilizing 155 under a variety of conditions (KOtBu, LDA, DBU, ...) all met with failure.



These results led to concern, not about the nucleophile, but about the electrophile in the closure of the D ring. Mesylate 142 did not

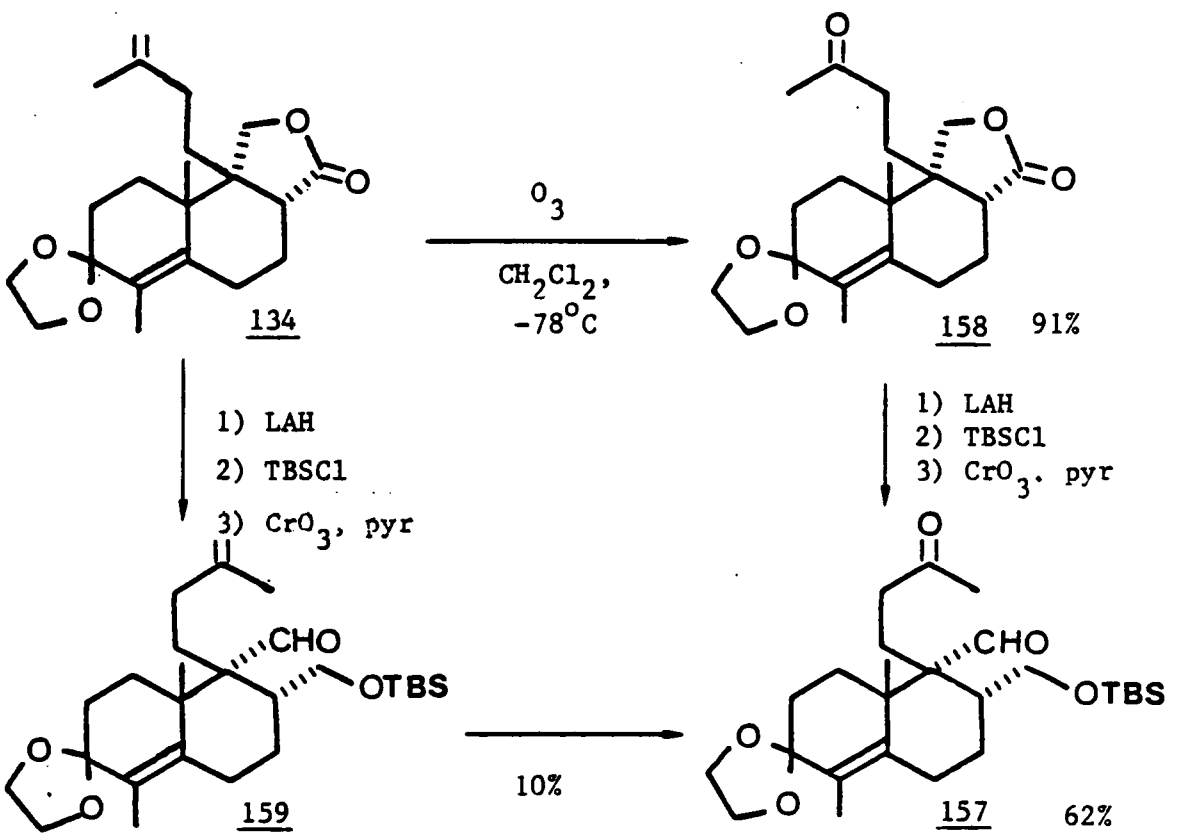
react with sodium iodide in acetone at reflux for 3 days. Therefore, we attempted to prepare aldehyde 156 from mesylate 142. It was our rationale that attack on an sp^2 hybridized center would be more facile than attack on an sp^3 hybridized center. Furthermore, such a closure had precedent in Stork's cedrol synthesis.[49] However, cleavage of the sulfur-oxygen bond of mesylate 142 utilizing the few literature methods[50] met, again, with failure.



156

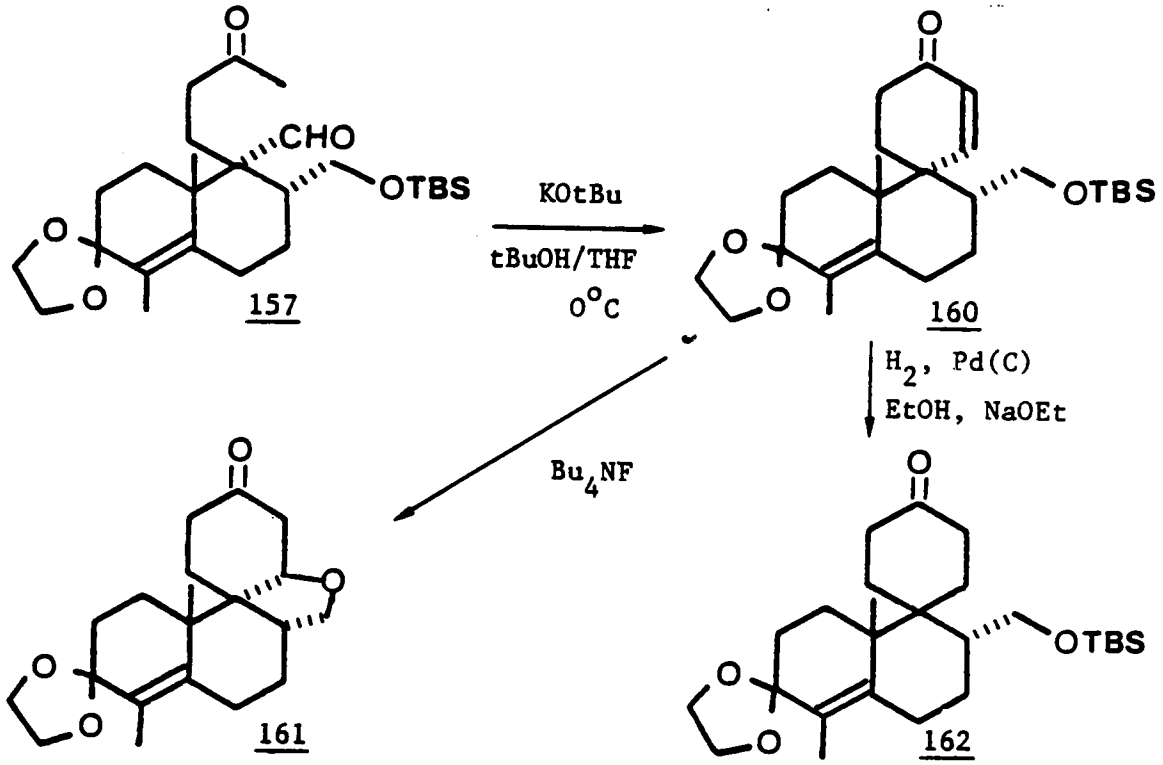
It was at this point clear that the D ring would not only have to be formed from an aldol condensation to the C-14 aldehyde, but that the D ring would have to be formed first. Therefore, we directed our efforts toward the preparation of the key intermediate 157. Keto-aldehyde 157 was finally prepared in the following manner. The disubstituted olefin was oxidatively cleaved in 91% yield by titration of 134 with a saturated solution of ozone (CH_2Cl_2, -78°C). The resulting ketone 158 was reduced to a mixture of diastereomeric triols, which were selectively silylated[51] (TBSCl, DMAP, Et_3N, CH_2Cl_2, -78°C, 6 h) and the mixture of diols oxidized to the keto aldehyde 157 in 62% overall yield from 158.

The major by-product from this reaction resulted from hydrolysis of the ketal functionality during oxidation of the secondary alcohol to the methyl ketone (CrO_3, pyr, 25°C, 2.5 h). Aldehyde 159 was prepared by the same sequence (80% overall yield). But, our attempts to oxidatively cleave the disubstituted olefin 159 (OsO_4, $NaIO_4$, or O_3) produced the desired aldehyde 157 only in very low yield.



Finally, the closure of the D ring of aphidicolin was accomplished from aldehyde 157 (KOtBu, t-BuOH, 0°C, 1 h), quantitatively providing spiro enone 160. We had hoped that desilylation and tosylation of 160

would provide a substrate that would undergo stereochemically unambiguous alkylation. However, treatment of 160 with Bu_4NF in THF resulted in the formation of furan 161. To avoid this Michael reaction, 160 was hydrogenated (H_2, 5% Pd(C), EtOH, NaOEt) to give spiro ketone 162 quantitatively. Addition of strong base (NaOEt) was necessary to suppress hydrogenolysis of the labile unsaturated ketal.

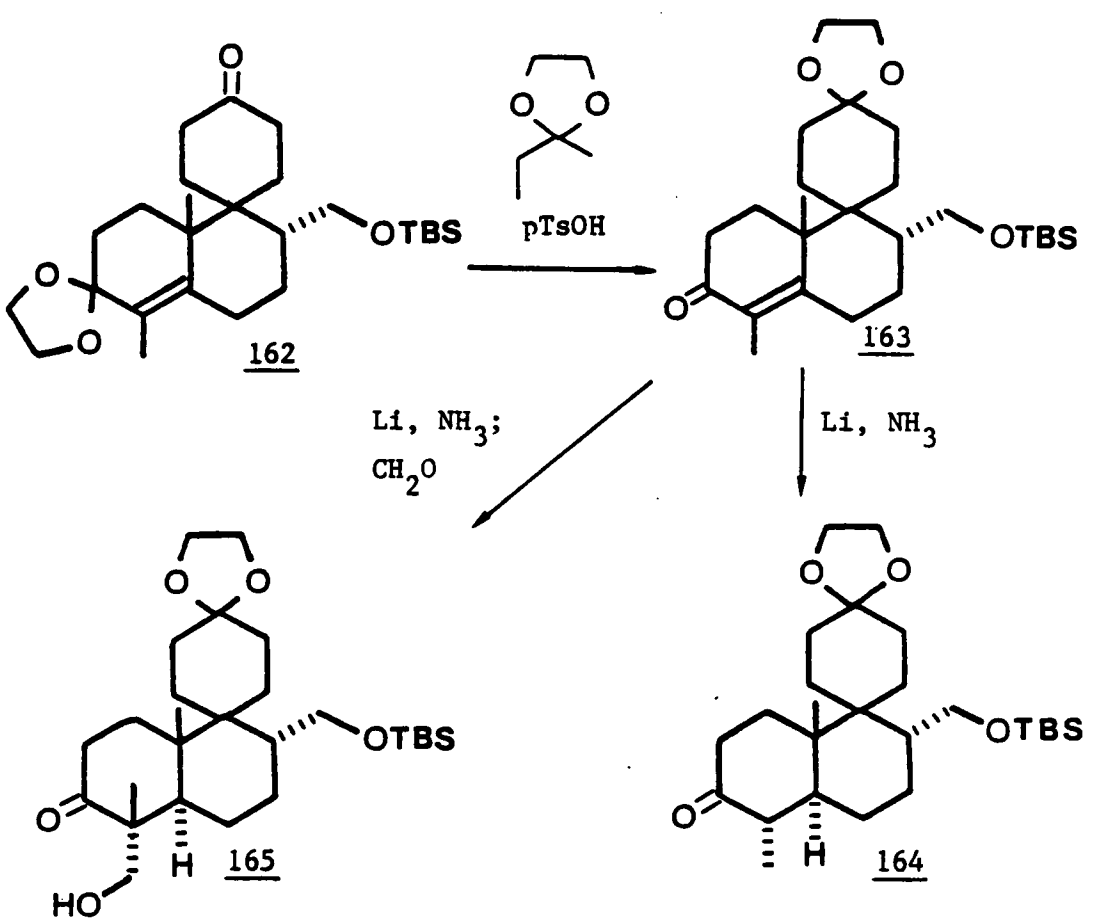


VII. Completion of the A Ring

At intermediate 162 a decision whether to complete the C,D ring system or to complete the A ring had to be made. The latter course was

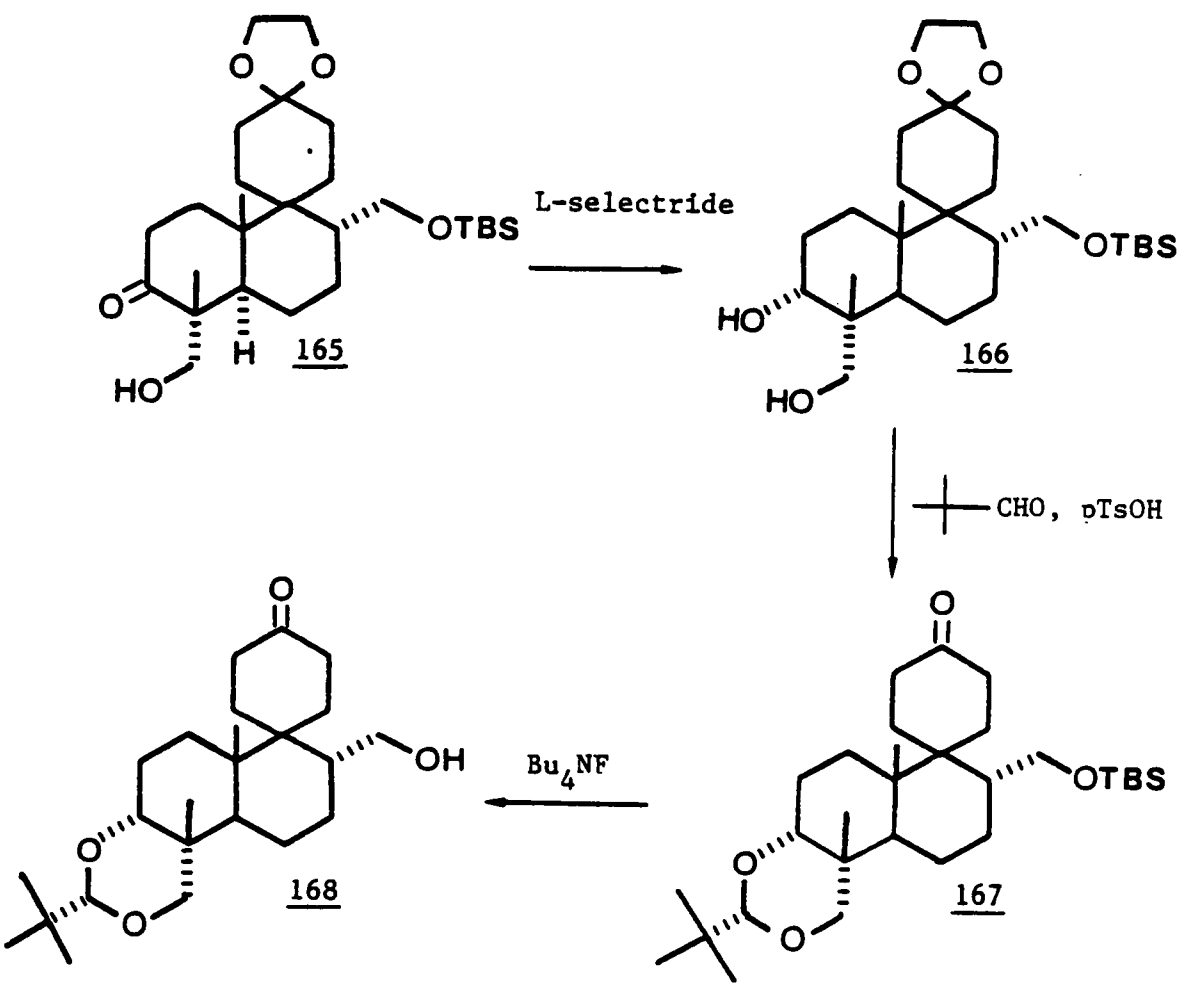
chosen. Determination of the site of alkylation (C-12 or C-15) by the tosylate of 162 might have been quite difficult. On the other hand, completion of the A ring was expected to be relatively straightforward and a comparison to Corey's intermediate[9c] could then be made prior to closure of the C ring.

Therefore, ketal 162 was transketalized with 2-methyl-2-ethyl dioxolane[52] under acidic conditions to afford ketal 163 in 88% yield. While it may appear that an extra step was added in this approach it really was not. The same synthetic operation would have to be performed on 140 if the C ring had been closed prior to elaboration of the A ring.



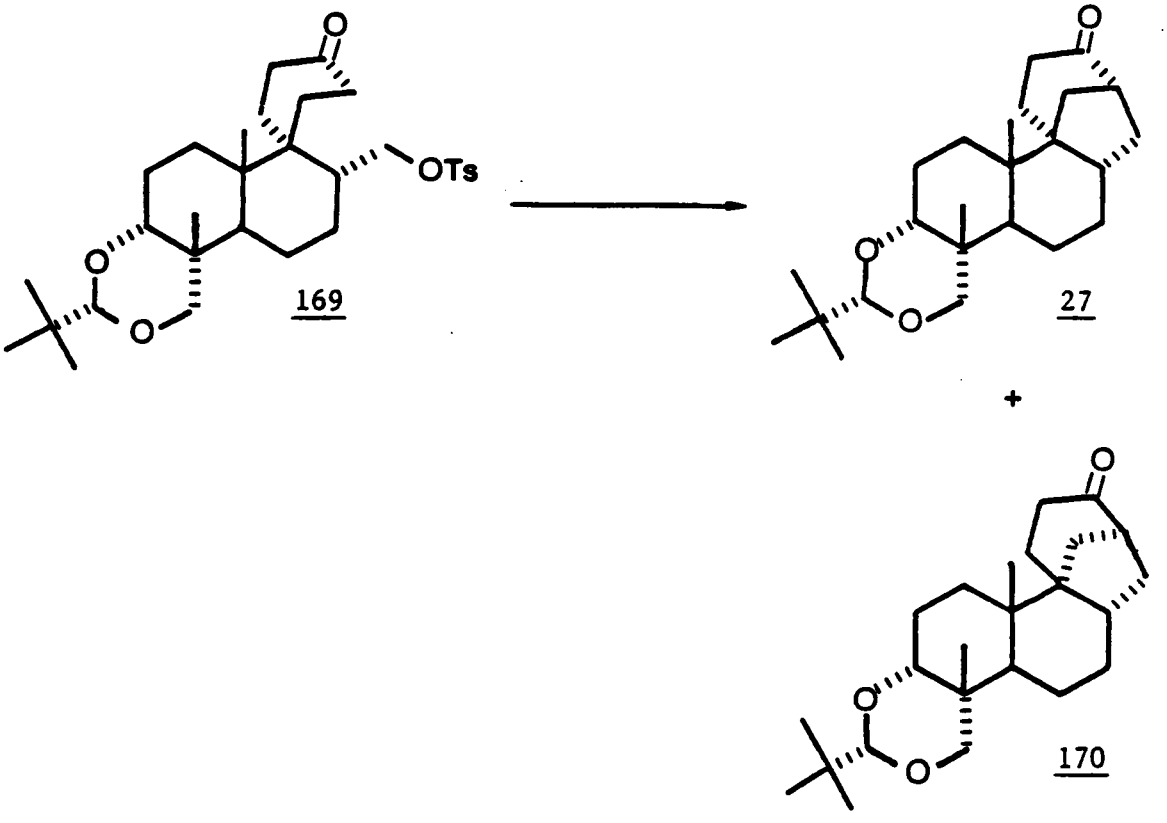
Enone 163, when subjected to the dissolving metal reduction conditions, provided ketone 164. The long-sought trans decalin stereochemistry was indicated by a C-4, C-5 proton-proton coupling constant of 11 Hz. Direct alkylation of the enolate generated in the dissolving metal reduction of 163 with formaldehyde produced aldol product 165. Equatorial alkylation was indicated by a proton-proton NOE observed between the 1,3 diaxial methyl groups at C-10, C-4.

Aldol product 165 was reduced to the axial alcohol with L-selectride to provide 1,3 diol 166. This diol was protected as the



pivalyl acetal 167. Disilylation of 167 with Bu_4NF gave Corey's intermediate, alcohol 168.

Although this completed a formal total synthesis of aphidicolin, we were not satisfied with comparison of the 80 MHz ^1H NMR spectrum of Corey's intermediate and that of our alcohol 168. Therefore, the tosylate 169 was prepared according to Corey's procedure. Comparison of the 80 MHz ^1H NMR spectra of the corresponding tosylates was, again, satisfactory but inconclusive. The tosylate 169 underwent intramolecular alkylation (LiTMP, THF, -95°C) to afford a 60:40 mixture of diastereomers 27 and 170 respectively. Corey obtained a 90:10 ratio of 27:170 under other conditions (LDTBA, 2 M THF, -130°C).[53] The major



isomer 27 was separated from 170 by preparative TLC (multiple elution, benzene). The 270 MHz ^{1}H NMR spectrum of 27 was indistinguishable from that of authentic 27.

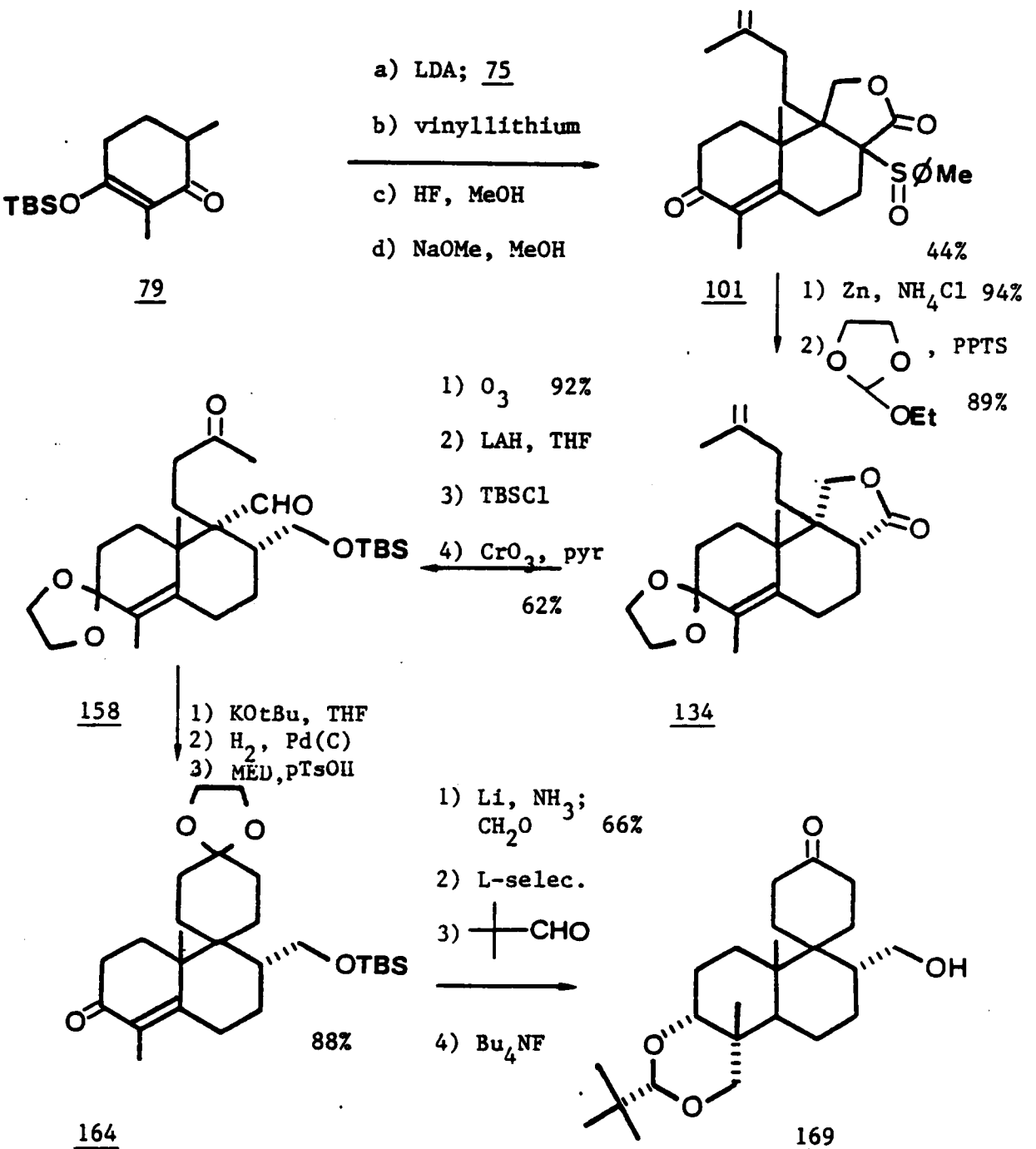
VIII. Summary of the Formal Total Synthesis

The entire formal total synthesis of aphidicolin is summarized in Scheme VII. This synthesis is approximately 15 steps long from enone 79 and butenolide 75. This is competitive with the shortest reported total synthesis of aphidicolin. Furthermore, this synthesis is twice as efficient in overall yield.

Completion of this total synthesis required the development of novel methodology. Work on the Michael reaction has revealed that steric encumbrance may be overcome by electronic activation of the acceptor. Use of sulfinyl butenolides as acceptors demonstrated that considerable stereochemical control may be exercised over the aprotic Michael reaction. The utility of a novel annulation method was demonstrated by the one-pot construction of the AB rings of aphidicolin. Desulfurization of tricycle 101 required the development of a new, mild desulfurization agent, zinc dust in aqueous ammonium chloride.

Difficulties were encountered in elaboration of the A ring functionality of aphidicolin from enone 113. Ultimately, the source of this problem was recognized as conformational distortion of the B ring of the enone 113 by the lactone. This problem was solved by cleavage of the lactone and construction of the D ring of aphidicolin prior to dissolving metal reduction of the A ring enone.

Scheme VII.


TBSO
79
a) LDA; 75
b) vinyllithium
c) HF, MeOH
d) NaOMe, MeOH
SØMe
44%
101
1) Zn, NH4Cl 94%
2) , PPTS
OEt
89%
1) O3 92%
2) LAH, THF
3) TBSCl
4) CrO3, pyr
62%
CHO
OTBS
158
134
1) KOtBu, THF
2) H2, Pd(C)
3) MED, pTsOH
1) Li, NH3;
CH2O 66%
2) L-selec.
3) CHO
4) Bu4NF
88%
OTBS
OH
164
169

Although this work represents the most efficient total synthesis of aphidicolin to date, further work on this project is expected to be fruitful. Preparation of optically active butenolide 75 will result in the first enantioselective synthesis of aphidicolin and will also provide an answer to the question of the role that sulfoxide plays in the transition state of the Michael reaction. Also, application of the double Michael annulation strategy to acceptors in which the D ring is already formed may result in an even more efficient synthesis. Finally, further study of methods for the construction of the CD ring system of aphidicolin may provide a shorter, yet still enantioselective, route to the natural product.

EXPERIMENTAL

General. Melting points were taken on a hot stage and are uncorrected. Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer model 710B spectrometer and were referenced to the 1601.4 cm^{-1} absorption of polystyrene. Proton magnetic resonance spectra were recorded at 90 MHz on a Varian EM-390 spectrometer, at 100 MHz on a JEOL PS-100 Fourier transform spectrometer, or at 270 MHz on an IBM SY-270 spectrometer. All chemical shifts are reported in δ units, relative to tetramethylsilane. Carbon magnetic resonance spectra were recorded on either an IBM NR80 spectrometer at 80 MHz or an IBM SY-270 spectrometer at 67.5 MHz. Analytical thin layer chromatography was performed using silica gel 60 PF-254 (E. Merck). Flash chromatography was performed using 40-63 μm (400-300 mesh) silica gel 60 (E. Merck no. 9385) as the stationary phase. All reactions were carried out under a blanket of nitrogen unless otherwise noted.

Tetrahydrofuran (THF), ether, and 1,2-dimethoxyethane (DME) were refluxed (ca 1 week) over lithium aluminum hydride (LAH) in a continuous still under a blanket of nitrogen. Methylene chloride (CH_2Cl_2) was refluxed in a continuous still over calcium hydride. Potassium t-butoxide (KOtBu) was sublimed in vacuo before use. Diisopropylamine was distilled from calcium hydride before use. Toluene was refluxed in a continuous still over LAH. Trimethylsilyl chloride (TMSCl), triethylamine (Et_3N), and hexamethylphosphonic triamide (HMPA) were all

distilled from calcium hydride less than 1 month before use. Anhydrous methanol and ethanol were distilled from the corresponding magnesium alkoxide and stored over 3 A molecular sieves. Spectral data are recorded in the appendix.

Butyrolactone **48**. To a suspension of 15.24 g (83.5 mmol, 2.08 eq) of copper (I) iodide in 10 mL of dry ether at 0°C under nitrogen was added 100 mL (160 mmol, 4 eq) of a 1.6 M solution of n-butyllithium in hexane. The black suspension was stirred for 5 min and then cooled to -78°C. A solution of 7.68 g (40 mmol, 1 eq) of butenolide 36 in 40 mL of dry THF was slowly added via syringe down the side of the flask. The mixture was stirred for 4 h, then allowed to warm to 25°C. The mixture was partitioned between 400 mL of saturated aqueous sodium bicarbonate and 200 mL of 40% ethyl acetate/hexane. The aqueous layer was extracted with an additional 200 mL of 40% ethyl acetate/hexane. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford 9.7 g (38.7 mmol, 96.8%) of butyrolactone 48 as a colorless oil.

Butyrolactone **45**. To a solution of 20 g (80 mmol, 1 eq) of butyrolactone 48 in 160 mL of carbon tetrachloride at 0°C was added dropwise a solution of 12.96 g (96 mmol, 1.2 eq) of sulfuryl chloride in 80 mL of carbon tetrachloride. After the addition was complete the mixture was allowed to warm to 25°C and was then carefully poured into 200 mL of saturated aqueous sodium bicarbonate. The layers were separated and the aqueous layer was extracted twice with 100 mL of methylene chloride. The combined organic layers were dried over sodium

sulfate, filtered, and concentrated to afford crude chloride 49 as an oil.

To a solution of crude chloride 49 in 200 mL of THF were added 20.9 g (240 mmol, 3 eq) of lithium bromide and 16 g (217 mmol, 2.7 eq) of lithium carbonate. The mixture was refluxed for 10 h, cooled, and partitioned between 400 mL of saturated aqueous sodium bicarbonate and 200 mL of hexane. The aqueous layer was extracted twice with 200 mL of 40% ethyl acetate/hexane. The combined organic layers were filtered through a plug of silica gel and concentrated to afford 19 g of a yellow oil. Crystallization from ethyl acetate/hexane gave 15.22 g of white crystals. Flash chromatography of the mother liquor and crystallization from ethyl acetate/hexane produced another 1.34 g of butenolide 45. The overall yield of butenolide 45 from sulfide 48 was 16.56 g (67 mmol, 83%).

Sulfoxide 46. To a solution of 100 mg (0.403 mmol, 1 eq) of sulfide 45 in 5 mL of dry methylene chloride at -78°C was added a solution of 82 mg (0.4 mmol, 1 eq) of 85% mCPBA in 4 mL of dry methylene chloride. The mixture was allowed to warm to 25°C, stirred for 15 min, washed with 10% aqueous sodium sulfite, dried over sodium sulfate, filtered, and concentrated to afford 110 mg (0.41 mmol) of sulfoxide 46 as an unstable oil which was used directly.

Sulfone 47. To a solution of 100 mg (0.4 mmol, 1 eq) of sulfide 45 in 5 mL of dry methylene chloride at -78°C was added a solution of 200 mg (0.98 mmol, 2.4 eq) of 85% mCPBA in 4 mL of methylene chloride. The mixture was allowed to warm to 25°C, stirred for 3 h, washed with 10% aqueous sodium sulfite, dried over sodium sulfate, and concentrated

to afford 115 mg (0.41 mmol) of sulfone 47 as an oil which was used directly.

Sulfoxide 50. To a suspension of 477 mg (2.61 mmol, 6.5 eq) of copper (I) iodide in 12.5 mL of dry ether at 0°C was added 3.12 mL (4.37 mmol, 11 eq) of a 1.4 M solution of n-butyllithium in hexane. The black suspension was stirred for 2 min and cooled rapidly to -78°C. A solution of 110 mg (0.4 mmol, 1 eq) of sulfoxide 46 in 2 mL of dry THF was added dropwise via syringe. After stirring for 1 h at -78°C, the mixture was allowed to warm to 0°C, stirred for 1 h, and was then warmed to 25°C and stirred for 1 h. The mixture was washed with a saturated aqueous ammonium chloride solution, dried over sodium sulfate, and concentrated to afford 122 mg of an oil. Column chromatography (30% ethyl acetate/hexane) afforded 84 mg (0.26 mmol, 65%) of sulfoxide 50.

Sulfone 51. To a suspension of 477 mg (2.61 mmol, 6.5 eq) of copper (I) iodide in 12.5 mL of dry ether at 0°C was added 3.12 mL (4.37 mmol, 11 eq) of a 1.4 M solution of n-butyllithium in hexane. The black suspension was stirred for 2 min and cooled rapidly to -78°C. A solution of 115 mg (0.4 mmol, 1 eq) of sulfone 47 in 2 mL of dry THF was added dropwise via syringe. After stirring for 1 h at -78°C the mixture was warmed to 0°C, stirred for 1 h, warmed to 25°C, and stirred for 1 h. The mixture was diluted with ether, washed with saturated aqueous ammonium chloride, dried over sodium sulfate, and concentrated to afford 133 mg of an oil. Column chromatography (30% ethyl acetate/hexane) yielded 68 mg (0.2 mmol, 50%) of sulfone 51.

Butenolide 44. Chlorine gas was bubbled into a solution of 1.37 g (7.13 mmol) of butenolide 36 in 70 mL of dry methylene chloride at

25°C. Progress of the reaction was monitored by TLC (40% ethyl acetate/hexane). After ca 1 h the solution was concentrated to afford 1.97 g of a colorless oil.

To a solution of this crude dichloride in 70 mL of freshly distilled acetonitrile was added 1.2 g (7.1 mmol) of silver nitrate crystals. The mixture was refluxed for 24 h, an additional 1.2 g (7.1 mmol) portion of crystalline silver nitrate was added, and the mixture was refluxed for 14 h. The mixture was cooled, filtered, and concentrated. The resulting oil was dissolved in 40% ethyl acetate/hexane, filtered through a plug of silica gel, and concentrated to afford 1.1 g of an oil. Column chromatography (40% ethyl acetate/hexane) provided 0.55 g (2.4 mmol, 34%) of butenolide 44 which crystallized on concentration. Recrystallization from ethyl acetate/hexane gave fine pale yellow needles, Mp 54-54.5°C.

Michael Adduct 53. To a solution of 0.3 mL (4.1 mmol, 2.7 eq) of diisopropylamine in 10 mL of dry THF at -78°C was added 1.3 mL (2.08 mmol, 1.4 eq) of a 1.6 M solution of n-butyllithium in hexane. The mixture was stirred for 5 min, warmed to 0°C, and stirred for 45 min. The mixture was cooled to -78°C and a solution of 231 mg (1.5 mmol, 1 eq) of enone 35 in 3 mL of THF was added dropwise. The mixture was stirred for 15 min, warmed to 0°C, stirred for 1 h, then cooled to -95°C (CH_2Cl_2 slush bath), and a solution of 343 mg (1.5 mmol, 1.5 eq) of butenolide 44 in 3 mL of dry THF was added via syringe down the side of the flask. The mixture was stirred for 1 h, allowed to slowly warm to 0°C, and poured quickly into 50 mL of saturated aqueous sodium bicarbonate. The aqueous solution was extracted with three 25 mL

portions of ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford 551 mg of an oil. Column chromatography (80% ethyl acetate/hexane) gave 294 mg (0.84 mmol, 57%) of Michael adduct 53.

Michael Adduct **60**. To a solution of 0.735 mL (5.25 mmol, 1.05 eq) of diisopropylamine in 40 mL of THF at -78°C was added 3.28 mL (5.25 mmol, 1.05 eq) of a 1.6 M solution of n-butyllithium in hexane. The mixture was stirred for 15 min, and a solution of 770 mg (5 mmol, 1 eq) of enone 35 in 5 mL of THF was added via syringe down the side of the flask. The mixture was stirred for 1 h, and a solution of 730 mg (5 mmol, 1 eq) of acceptor 56 in 5 mL of THF was added via syringe down the side of the flask. The mixture was stirred for 1 h and poured quickly into 50 mL of saturated aqueous sodium bicarbonate. The aqueous solution was extracted with three 25 mL portions of 40% ethyl acetate/hexane. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford 1.74 g (5 mmol, 100%) of Michael adduct 60 which was homogeneous by TLC and ^{1}H NMR analysis.

Michael Adduct **61**. To a solution of 0.735 mL (5.25 mmol, 1.05 eq) of diisopropylamine in 40 mL of THF at -78°C was added 3.28 mL (5.25 mmol, 1.05 eq) of a 1.6 M solution of n-butyllithium in hexane. The mixture was stirred for 15 min, and a solution of 770 mg (5 mmol, 1 eq) of enone 35 in 5 mL of THF was added via syringe down the side of the flask. The mixture was stirred for 1 h and a solution of 730 mg (5 mmol, 1 eq) of acceptor 57 in 5 mL of THF was added slowly down the side of the flask. The mixture was stirred for 12 h and poured quickly into 50 mL of saturated aqueous sodium bicarbonate. The aqueous

solution was extracted with three 25 mL portions of 40% ethyl acetate/hexane. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford 1.6 g of a semi-crystalline solid. Crystallization from ethyl acetate/hexane gave 1.15 g (3.83 mmol, 76.6%) of adduct 61, Mp 166.5-168°C.

Michael Adduct **62**. To a solution of 0.077 mL (0.55 mmol, 1.1 eq) of diisopropylamine in 3 mL of THF at -78°C was added 0.32 mL (0.55 mmol, 1.1 eq) of a 1.7 M solution of n-butyllithium in hexane. The mixture was stirred for 15 min and a solution of 70 mg (0.5 mmol, 1 eq) of 2-methyl-3-methoxycyclohexenone in 1 mL of THF was added slowly down the side of the flask. The mixture was stirred for 15 min and a solution of 96.6 mg (0.5 mmol, 1 eq) of acceptor 56 in 1 mL of THF was added via syringe down the side of the flask. The mixture was stirred overnight at -78°C then poured quickly into 50 mL of saturated aqueous sodium bicarbonate. The aqueous solution was extracted with three 25 mL portions of 40% ethyl acetate/hexane. The combined organic layers were dried over sodium sulfate and concentrated to afford 155.3 mg (0.47 mmol, 93%) of adduct 62 as an oil, homogeneous by TLC and ^{1}H NMR analysis.

Michael Adduct **63**. To a solution of 0.077 mL (0.55 mmol, 1.1 eq) of diisopropylamine in 3 mL of THF at -78°C was added 0.32 mL (0.55 mmol, 1.1 eq) of a 1.7 M solution of n-butyllithium in hexane. The mixture was stirred for 15 min and a solution of 70 mg (0.5 mmol, 1 eq) of 2-methyl-3-methoxycyclohexenone in 1 mL of THF was added via syringe down the side of the flask. The mixture was stirred overnight at -78°C then poured quickly into 50 mL of saturated aqueous sodium bicarbonate. The aqueous solution was extracted with three 25 mL

portions of 40% ethyl acetate/hexane. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford 135 mg (0.47 mmol, 94%) of adduct 63 as an oil, homogeneous by TLC and ^{1}H NMR analysis.

Aldol **66**. To a solution of 6.16 mL (44 mmol, 1.1 eq) of diisopropylamine in 400 mL of THF at -78°C was added 27.5 mL (44 mmol, 1.1 eq) of a 1.6 M solution of n-butyllithium in hexane. The mixture was stirred for 1 h and a solution of 7.84 g (40 mmol, 1 eq) of ethyl phenylthioacetate in 30 mL of THF was added dropwise. The mixture was stirred for 2 h and a solution of 4.7 g (48 mmol, 1.2 eq) of cyclohexanone in 30 mL of THF was added. The mixture was stirred for 2 h at -78°C then poured rapidly into 500 mL of saturated aqueous ammonium chloride. The aqueous solution was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered, and concentrated. The resulting crude oil was dissolved in 40% ethyl acetate/hexane and filtered through a plug of silica gel. Concentration produced 11.8 g (40 mmol, 100%) of aldol 66 as an oil.

Sulfide **68**. To a solution of 3.18 mL (0.04 mol, 1 eq) of N-methylimidazole and 11.8 g (0.04 mol, 1 eq) of aldol 66 in 32 mL of pyridine at 25°C was added 19 mL (0.2 mol, 5 eq) of acetic anhydride. The mixture was stirred for 24 h then warmed to 57°C and stirred for 48 h. The mixture was cooled, and poured into cold 1 N HCl. The aqueous solution was extracted with ethyl acetate. The organic layer was washed with cold 1 N NaOH and saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated to afford 11.1 g of the acetate as a crude oil.

To a solution of the crude acetate in 300 mL of THF at 25°C was added 1.6 g (0.042 mol, 1.2 eq) of 60% sodium hydride as a dispersion in oil. The mixture was refluxed for 30 h then poured into 500 mL of saturated aqueous sodium bicarbonate. The aqueous solution was extracted with hexane and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield 10.2 g of an oil. Column chromatography (10% ethyl acetate/hexane) afforded 8.2 g (29 mmol, 73%) of sulfide 68.

Sulfoxide 64. To a solution of 2.76 g (9.4 mmol, 1 eq) of sulfide 68 in 75 mL of methylene chloride at -78°C was added a solution of 2.06 g (11 mmol, 1.3 eq) of 85% m-chloroperbenzoic acid in 25 mL of methylene chloride. The mixture was allowed to warm to 25°C, stirred for 2 h, washed with 10% aqueous sodium sulfite and saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated. Column chromatography (40% ethyl acetate/hexane) of the resulting unstable oil afforded 2.0 g (6.8 mmol, 72%) of sulfoxide 64.

Aldol 67. To a solution of 0.31 mL (22 mmol, 1.1 eq) of diisopropylamine in 20 mL of THF at -78°C was added 1.38 mL (2.2 mmol, 1.1 eq) of a 1.6 M solution of n-butyllithium in hexane. The mixture was stirred for 45 min and a solution of 289 mg (2 mmol, 1 eq) of phenylthioacetonitrile in 1 mL of THF was then added dropwise. The mixture was stirred for 60 min and a solution of 196 mg (2 mmol, 1 eq) of cyclohexanone in 1 mL of THF was added dropwise. The mixture was stirred 90 min and 2 mL of saturated aqueous ammonium chloride was added rapidly. The resulting slurry was warmed to 0°C and the mixture was partitioned between ethyl acetate and 100 mL of saturated aqueous

ammonium chloride. The organic layer was dried over sodium sulfate, filtered, and concentrated to afford 526 mg (2.13 mmol) of aldol 67 as an oil.

Sulfide **69**. To a solution of 261.8 mg (1 mmol, 1 eq) of aldol 67 and 1 mL of N-methylimidazole in 4 mL of pyridine at 25°C was added 2 mL of acetic anhydride. The mixture was stirred overnight and poured into 6 N HCl. The aqueous solution was extracted with ether and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford 225 mg of a mixture of the acetate and sulfide 69 as an oil. The crude oil was dissolved in 5 mL of THF, and 36.2 mg (1 mmol, 1 eq) of 60% sodium hydride as a dispersion in oil was added. The mixture was refluxed for 2 h, cooled, and poured into saturated aqueous sodium bicarbonate. The aqueous solution was extracted with hexane and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to give 250 mg of an oil. Column chromatography (20% ethyl acetate/hexane) afforded 138 mg (0.6 mmol, 60%) of sulfide 69 as an oil.

Sulfoxide **65**. To a solution of 138 mg (0.6 mmol, 1 eq) of sulfide 69 in 10 mL of methylene chloride was slowly added a solution of 122 mg (0.6 mmol, 1 eq) of mCPBA in 1 mL of methylene chloride. The mixture was allowed to warm to 0°C, stirred for 30 min, washed with 10% aqueous sodium sulfite, dried over sodium sulfate, filtered, and concentrated to afford 145 mg (0.59 mmol, 98%) of sulfoxide 65 as an oil, homogeneous by TLC and ^{1}H NMR analysis.

Silyl Enol Ether **102**. To a solution of 0.7 mL (5 mmol, 1.25 eq) of diisopropylamine in 40 mL of THF at -78°C was added 3.12 mL (5 mmol,

1.25 eq) of a 1.6 M solution of n-butyllithium in hexane. The mixture was stirred for 45 min and a solution of 616 mg (4 mmol, 1 eq) of enone 35 in 4 mL of THF was added dropwise via syringe. The mixture was stirred for 15 min and 0.71 mL (5.6 mmol, 1.4 eq) of trimethylsilyl chloride and 0.84 mL (6 mmol, 1.5 eq) of triethylamine were added dropwise via syringe. The mixture was allowed to warm to 25°C and poured into 100 mL of hexane. The white suspension was filtered through a plug of silica gel, washed with 20% ethyl acetate/hexane, and concentrated to afford 917 mg (4 mmol, 100%) of silyl enol ether 102 as a colorless oil.

Michael Adduct 71. To a solution of 226 mg (1 mmol, 1 eq) of silyl enol ether 102 in 9 mL of THF at 0°C was added 1 mL (1.05 mmol, 1.05 eq) of a 1.05 M solution of methyllithium in ether. The mixture was stirred for 30 min, cooled to -78°C, and a solution of 292 mg (1 mmol, 1 eq) of sulfoxide 64 in 1 mL of THF was added slowly via syringe down the side of the flask. The mixture was stirred for 12 h and 2 mL of saturated aqueous ammonium chloride was quickly added. The resulting slurry was warmed to -20°C and 1 mL of pyridine was added. The mixture was warmed to 25°C, stirred 1 h, poured into 50 mL of 1 M HCl overlayed with 20 mL of ether, and shaken. The organic layer was separated, washed with 50 mL of saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated to yield 452 mg of an oil. Column chromatography (35% ethyl acetate/hexane) afforded 396 mg (0.89 mmol, 89%) of adduct 71. ^{1}H NMR analysis indicated three diastereomers in the ratio 3.3:2.7:1.

Michael Adduct 72. To a solution of 226 mg (1 mmol, 1 eq) of silyl enol ether 102 in 9 mL of THF at 0°C was added 1 mL (1.05 mmol, 1.05 eq) of a 1.05 M solution of methyllithium in ether. The mixture was stirred for 30 min, cooled to -78°C, and a solution of 229 mg (1 mmol, 1 eq) of sulfoxide 65 in 1 mL of THF was slowly added via syringe down the side of the flask. The mixture was stirred for 15 h and poured quickly into saturated aqueous ammonium chloride. The aqueous solution was extracted with ether and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford 392 mg (1.02 mmol) of adduct 72 as an unstable oil. TLC and ^{1}H NMR analysis indicated the presence of three diastereomers in the ratio 2:1:1.

Michael Adduct 74. To a solution of 1.54 mL (11 mmol, 1.1 eq) of diisopropylamine in 70 mL of THF at -78°C was added 6.47 mL (11 mmol, 1.1 eq of a 1.7 M solution of n-butyllithium in hexane. The mixture was stirred 15 min and a solution of 1.54 g (10 mmol, 1 eq) of enone 35 in 15 mL of THF was added dropwise. The mixture was stirred 15 min and a solution of 2.64 g (10 mmol, 1 eq) of freshly crystallized butenolide 46 in 15 mL of THF was added slowly via syringe down the side of the flask. The mixture was stirred 2 h and poured rapidly into 100 mL of saturated aqueous sodium bicarbonate. The aqueous solution was extracted with three 50 mL portions of 40% ethyl acetate/hexane and the combined organic layers were dried over sodium sulfate, filtered, and concentrated. Crystallization from ethyl acetate/hexane produced 2.96 g of adduct 74. Concentration and column chromatography (25% ethyl acetate/hexane) of the mother liquor provided 540 mg of adduct 74 as a

1:1 mixture of two diastereomers. The total yield of adduct 74 was 3.5 g (8.37 mmol, 83.7%, 12:1 diastereomer ratio). Anal. Calcd. for $C_{23}H_{30}SO_5$: C, 66.00; H, 7.22. Found: C, 66.01; H, 7.31.

Butenolide **76**. To 400 mL of methanol in a flask equipped with a reflux condenser and mechanical stirrer was added 11.5 g (0.5 mol, 1 eq) of sodium metal in small portions. After the sodium had completely dissolved a solution of 68.2 g (0.55 mol, 1.1 eq) of thiocresol in 40 mL of benzene was added dropwise. The mixture was cooled to 0°C and a solution of 82 g (0.5 mol, 1 eq) of α-bromobutyrolactone in 30 mL of methanol was added dropwise over a period of 15 min. The mixture was stirred for 15 min and poured into 1 L of cold benzene, which was then washed with 500 mL of cold 1 N NaOH, and 500 mL of saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated to afford 100 g of the crude sulfide as an oil.

To a solution of the crude sulfide in 500 mL of carbon tetrachloride at 0°C was added dropwise a solution of 81 g (0.61 mol, 1.2 eq) of sulfuryl chloride in 20 mL of carbon tetrachloride. The mixture was stirred for 2 h, warmed to 25°C, and poured into 1 L of half-saturated aqueous sodium chloride. The organic layer was dried over sodium sulfate, filtered, and concentrated to afford the crude α-chloride as an oil.

To a solution of the crude α-chloride in 1 L of THF was added with rapid stirring 130 g (1.5 mol, 3 eq) of lithium bromide powder and 100 g (1.3 mol, 2.6 eq) of lithium carbonate powder. The slurry was stirred 2 h at 25°C, diluted with 1 L of ethyl acetate, filtered, washed with saturated aqueous sodium bicarbonate, dried over sodium

sulfate, filtered, and concentrated to yield 44 g (0.21 mol, 43%) of butenolide 76 as a semi-crystalline yellow solid. Recrystallization from ethyl acetate/hexane afforded pink crystals, Mp 86-87°C.

Butenolide 77. To a 1 L round bottom flask containing 760 mg (4 mmol, 0.1 eq) of cuprous iodide (extracted with refluxing THF) under nitrogen was added 400 mL of ether. The suspension was cooled to 0°C and 49.4 mL (47.8 mmol, 1.2 eq) of a 0.97 M solution of 3-methyl-3-butenylmagnesium bromide in ether was added dropwise. The heterogeneous mixture was stirred for 5 min. To the black suspension was added a solution of 7.24 g (35 mmol, 1 eq) of sulfide 76 in 80 mL of THF, maintaining the black color. The mixture was stirred 15 min and a solution of 8.52 g (48 mmol, 1.2 eq) of N-bromosuccinimide (recrystallized from water) in 80 mL of THF was added with rapid stirring. The mixture was stirred for exactly 15 min. The cold slurry was poured into 500 mL of saturated aqueous sodium bicarbonate and the aqueous solution was extracted with 40% ethyl acetate/hexane. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford the crude α-bromobutyrolactone.

To a solution of the crude α-bromobutyrolactone in 200 mL of THF at 25°C was added 7.3 g (100 mmol, 2.5 eq) of solid lithium carbonate and stirred for 16 h. The mixture was poured into 500 mL of saturated aqueous sodium bicarbonate and the aqueous solution was extracted with 40% ethyl acetate/hexane. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford 12 g of a crude oil. Column chromatography (25% ethyl acetate/hexane) yielded 6.2 g (22.6 mmol, 65%) of butenolide 77 as an orange oil. Crystallization

from ethyl acetate/hexane produced 4.77 g (17.4 mmol, 50%) of slightly yellow crystals, Mp 64-65°C. Anal. Calcd. for $C_{16}H_{18}SO_2$: C, 70.03; H, 6.61. Found: C, 70.15; H, 6.73.

Sulfoxide **75**. To a solution of 8.1 g (29.6 mmol, 1 eq) of sulfide 77 in 150 mL of methylene chloride at 0°C was added a solution of 6.38 g (32.2 mmol, 1.1 eq) of 85% mCPBA in 120 mL of methylene chloride. After 30 min, the slurry was poured into 400 mL of 3:1 saturated aqueous sodium bicarbonate and 10% aqueous sodium sulfite. The layers were separated and the organic layer was dried over sodium sulfate, filtered, and concentrated to yield 8.6 g of sulfoxide 75. The crude sulfoxide was dissolved in 10 mL of ethyl acetate, diluted with 17 mL of hexane, and cooled to -20°C. After 2 h, 8.09 g of crystals were obtained. Subsequent crystallization of the mother liquor produced 0.39 g (8.48 g total, 29 mmol, 98.6%) of crystalline 75, Mp 61.5-63°C.

Silyl Enol Ether **78**. To a solution of 10 g (79 mmol, 1 eq) of 2-methylcyclohexane-1,3-dione in 40 mL of dry DMF was added 12 mL (86 mmol, 1.1 eq) of triethylamine and 12.6 g (84 mmol, 1.06 eq) of solid t-butyldimethylsilyl chloride. The slurry was stirred overnight at 25°C, diluted with hexane, washed with 300 mL of saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated to yield 20 g of the crude silyl enol ether which was distilled from base-washed glassware (5 mm Hg, 160°C) to afford 18.3 g (76 mmol, 97%) of the silyl enol ether 78.

Enone **78**. To a freshly prepared solution of LDA (86 mmol, 1.13 eq) in 42 mL of THF at -78°C was added a solution of 18.38 g (76 mmol, 1 eq)

of the silyl enol ether 78 in 20 mL of THF. The mixture was stirred for 1 h and 5.8 mL (93.8 mmol, 1.2 eq) of methyl iodide was added. The mixture was stirred for 30 min, allowed to warm to 25°C, then partitioned between 300 mL of hexane and 300 mL of saturated aqueous sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered, and concentrated. The crude oil was redissolved in 15% ethyl acetate/hexane, filtered through a plug of silica gel, and concentrated. Crystallization from pentane (-78°C) yielded 15.5 g (61 mmol, 77%) of 79 as white crystals, Mp 36.5-37.5°C.

Michael Adduct **80**. To a solution of 3.08 g (2.2 mmol, 1.1 eq) of diisopropylamine in 120 mL of THF at -78°C was added 13.4 mL (22 mmol, 1.1 eq) of a 1.64 M solution of n-butyllithium in hexane. The mixture was stirred 15 min and a solution of 3.08 g (20 mmol, 1.2 eq) of enone 35 in 18 mL of THF was added dropwise. The mixture was stirred 15 min, cooled to -95°C (CH_2Cl_2 slush bath), and a solution of 4.88 g (16.8 mmol, 1 eq) of butenolide 75 in 18 mL of THF was slowly added via syringe down the side of the flask. The mixture was stirred 1 h, warmed to -78°C, stirred 1 h, and poured into 500 mL of saturated aqueous sodium bicarbonate. The aqueous solution was extracted with 40% ethyl acetate/hexane and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield 8.5 g of an oil. Column chromatography (30% ethyl acetate/hexane) afforded 6.1 g (14 mmol, 82%) of adduct 80 as a 7.3:1 ratio of diastereomers. Crystallization from ethyl acetate/hexane gave white crystals, Mp 145-146°C. Anal. Calcd. for $C_{25}H_{32}SO_5$: C, 67.54; H, 7.25. Found: C, 67.42; H, 7.32.

Michael Adduct **81**. To a solution of 0.154 mL (1.1 mmol, 1.1 eq) of diisopropylamine in 10 mL of THF at -78°C was added 0.67 mL (1.1 mmol, 1.1 eq) of a 1.64 M solution of n-butyllithium in hexane. The mixture was stirred 15 min and a solution of 254 mg (1 mmol, 1 eq) of enone 79 in 2 mL of THF was added dropwise. The mixture was stirred 15 min, was cooled to -95°C (CH_2Cl_2 slush bath), and a solution of 290 mg (1 mmol, 1 eq) of sulfoxide 75 in 2 mL of THF was slowly added via syringe down the side of the flask. The mixture was stirred 1 h, warmed to -78°C, stirred 1 h, then poured into 30 mL of saturated aqueous sodium bicarbonate. The aqueous solution was extracted with hexane and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield 410 mg of an oil. Column chromatography (10% ethyl acetate/hexane) yielded 381 mg (0.7 mmol, 70%) of 81 as a 7:1 mixture of diastereomers. Crystallization from pentane gave white crystals, Mp 138-140°C.

Preparation of Vinyllithium. A 500 mL round bottomed flask equipped with a dry-ice/acetone cold finger condenser and an oversized magnetic stir bar was charged with 24 mL of ether and 16.8 mL (238 mmol, 1.2 eq) of vinyl bromide. The mixture was cooled to -78°C and with rapid stirring 247 mL (395 mmol, 2 eq) of a 1.6 M solution of t-butyllithium in pentane was added via syringe. The last 100 mL of t-butyllithium had to be added slowly to avoid an exotherm. The white slurry was stirred for 5 h at -78°C then allowed to warm to 25°C over several hours. Vinyllithium prepared in this manner was stable indefinitely at -20°C.

Titration of Vinyllithium. To a solution of 373 mg (2 mmol) of anisaldehyde in 10 mL of THF at -78°C was added 2 mL of a suspension of vinyllithium in pentane. Care had to be taken to ensure that the suspension was stirred rapidly and that the aliquot was taken with a wide bore needle so that the sample was representative of the entire solution. The solution was warmed to 0°C and poured into saturated aqueous sodium bicarbonate. The aqueous solution was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield 318 mg of a crude oil. ^{1}H NMR analysis indicated a 66% conversion (0.66 M) to the allylic alcohol.

Carboxylic Acid **82**. To a solution of 1.74 g (5 mmol, 1 eq) of adduct 60 in 60 mL of ether at 0°C was added 20 mL (13.4 mmol, 2.7 eq) of a 0.67 M solution of vinyllithium in pentane. The slurry was stirred for 1 h at 25°C and poured into 100 mL of saturated aqueous sodium bicarbonate. The layers were separated. The aqueous layer was then acidified with 6 N HCl to ca pH 1. The aqueous solution was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford 352 mg (1.08 mmol, 21.6%) of acid 82 as an oil.

Allylic Iodides **83**, **84**. To a solution of 48.5 mg (0.15 mmol, 1 eq) of carboxylic acid 82 in 2 mL of saturated aqueous sodium bicarbonate was added 32.5 mg (0.13 mmol, 0.85 eq) of iodine crystals and 129 mg (0.77 mmol, 5 eq) of potassium iodide crystals. The mixture was stirred for 1 h and the solution became cloudy. The aqueous solution was extracted with methylene chloride which was then washed

with 10% aqueous sodium sulfite, dried over sodium sulfate, filtered, and concentrated to afford 55 mg (0.12 mmol, 81%) of a mixture of 83 and 84 (6:7) as an oil. These two labile allylic iodides were partially resolved by preparative TLC (30% ethyl acetate/hexane).

Allylic Alcohol **86**. To a solution of 150 mg (0.5 mmol, 1 eq) of ketone 61 in 20 mL of ether at 0°C was added 3 mL (2 mmol, 4 eq) of a 0.67 M solution of vinyllithium in pentane. The slurry was warmed to 25°C, stirred for 30 min, poured into 50 mL of saturated aqueous sodium bicarbonate, and extracted with 40% ethyl acetate/hexane. The combined organic layers were dried over sodium sulfate, filtered, and carefully concentrated (at 25°C) to afford 170 mg of a crude oil. Column chromatography (30% ethyl acetate/hexane) gave ca 50 mg (0.15 mmol, 30%) of allylic alcohol 86 as a labile semi-solid.

Diene **87**. To a solution of 605 mg (2 mmol, 1 eq) of ketone 61 in 60 mL of ether at 0°C was added 11.5 mL (7.7 mmol, 3.9 eq) of a 0.67 M solution of vinyllithium in pentane. The slurry was warmed to 25°C and stirred for 2 h. The mixture was poured into saturated aqueous sodium bicarbonate and the aqueous solution was extracted with 40% ethyl acetate/hexane. TLC analysis of the organic layers indicated the presence of allylic alcohol 86. The combined organic layers were dried over sodium sulfate, filtered, and concentrated (during concentration the oil was allowed to reach 40°C for ca 10 min), yielding 607 mg of an oil. Column chromatography (40% ethyl acetate/hexane) afforded 187 mg (0.57 mmol, 28%) of diene 87 as an oil.

Allylic Alcohol **90**. To a solution of 105 mg (0.25 mmol, 1 eq) of adduct 74 in 2.5 mL of toluene at -78°C was added 0.83 mL (0.55 mmol,

2 eq) of a 0.66 M solution of vinyllithium in pentane. The solution was warmed to 0°C and 1.66 mL (1.1 mmol, 4.4 eq) of the vinyllithium solution in pentane was added. After 15 min the slurry was warmed to 25°C and stirred 15 min. The yellow slurry was poured into 50 mL of saturated aqueous sodium bicarbonate and the aqueous solution was extracted with 40% ethyl acetate/hexane. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford 138 mg of an oil. Column chromatography (40% ethyl acetate/hexane) yielded 56 mg (0.125 mmol, 50%) of allylic alcohol 90 as an oil and 21 mg (0.005 mmol, 19%) of returned adduct 74. Crystallization from ethyl acetate/hexane gave white crystals, Mp 126-129.5°C.

Allylic Alcohol 93. To a solution of 1.02 g (2.3 mmol, 1 eq) of crystalline enone 80 in 30 mL of toluene at -78°C was added 20 mL (13.2 mmol, 5.7 eq) of a 0.66 M solution of vinyllithium in pentane. The mixture was allowed to slowly warm to 25°C, stirred 15 min, and poured into 100 mL of saturated aqueous sodium bicarbonate. The aqueous mixture was extracted with 40% ethyl acetate/hexane, and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield 1.4 g of an oil. Column chromatography afforded 682 mg (1.44 mmol, 63%) of bis allylic alcohol 93 and 214 mg (0.48 mmol, 21%) of enone 86.

Allylic Alcohol 94. To a solution of 50 mg (0.092 mmol, 1 eq) of enone 81 in 1.5 mL of toluene at -78°C was added 1 mL (0.66 mmol, 7 eq) of a 0.66 M solution of vinyllithium in pentane. The mixture was allowed to warm to 25°C, stirred for 20 min, and poured into 25 mL of saturated aqueous sodium bicarbonate. The aqueous solution was

extracted with 40% ethyl acetate/hexane, and the combined organic layers were dried over sodium sulfate, filtered, and concentrated. Column chromatography (10% ethyl acetate/hexane) afforded 39 mg (0.068 mmol, 74%) of allylic alcohol 94.

Acid Catalyzed Rearrangement of 90: **95, 96.** To a solution of 907 mg (2 mmol, 1 eq) of alcohol 90 in 20 mL of THF was added 0.7 mL of a 2-3% solution of sulfuric acid. After 20 min the mixture was poured into 50 mL of saturated aqueous sodium bicarbonate. The aqueous solution was extracted with 40% ethyl acetate/hexane and the combined organic layers were dried over sodium sulfate, filtered, and concentrated. Column chromatography (20% ethyl acetate/hexane) yielded 570 mg (1.37 mmol, 68%) of a mixture of 95 and 96.

Acid Catalyzed Rearrangement of 93: **97, 98.** To a solution of 552 mg (1.1 mmol, 1 eq) of alcohol 93 in 11 mL of THF and 0.55 mL of water was added 108 mg (0.43 mmol, 0.4 eq) of pyridinium p-toluenesulfonate. The mixture was stirred 14 h and poured into 50 mL of saturated aqueous sodium bicarbonate. The aqueous solution was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford 485 mg of an oil. Column chromatography (25% ethyl acetate/hexane) yielded 323 mg (0.73 mmol, 66%) of a mixture of 97 and 98 as an oil.

Acid Catalyzed Rearrangement of 94: **97, 98.** To a solution of 39 mg (0.068 mmol, 1 eq) of alcohol 94 in 1.1 mL of THF and 0.06 mL of water was added 11 mg (0.05 mmol, 1.3 eq) of pyridinium p-toluenesulfonate. The mixture was stirred 7 da and poured into 25 mL of saturated aqueous sodium bicarbonate. The aqueous solution was

extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered, and concentrated. Column chromatography (25% ethyl acetate/hexane) afforded 29 mg (0.066 mmol, 97%) of a mixture of 97 and 98 as an oil.

Enone 100. To a solution of 25 mg (0.06 mmol, 1 eq) of 95 and 96 in 1.3 mL of THF at 0°C was added 0.45 mL (0.45 mmol, 7.5 eq) of a 1 M solution of sodium methoxide in methanol. The mixture was stirred for 75 min then poured into 25 mL of saturated aqueous sodium bicarbonate. The aqueous solution was extracted with 40% ethyl acetate/hexane and the combined organic layers were dried over sodium sulfate, filtered, and concentrated. Column chromatography (30% ethyl acetate/hexane) yielded 18 mg (0.043 mmol, 72%) of enone 100. Crystallization from ethyl acetate/hexane gave white crystals, Mp 108-111°C.

Enone 101. To a solution of 46 mg (0.104 mmol, 1 eq) of a mixture of 97 and 98 in 1.3 mL of THF and 0.45 mL of "wet" methanol at 0°C was added 0.15 mL (1.5 mmol, 1.4 eq) of a 1 M solution of sodium methoxide in methanol. The solution was stirred for 2.5 h and poured into saturated aqueous sodium bicarbonate. The aqueous solution was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered, and concentrated. Column chromatography (30% ethyl acetate/hexane) afforded 46 mg (0.104 mmol, 100%) of enone 101.

Vinyl Enone 38. To a solution of 9.54 g (42.2 mmol, 1 eq) of silyl enol ether 102 in 300 mL of THF at 0°C was added 53.5 mL (44 mmol, 1.05 eq) of a 0.84 M solution of methyllithium in ether. The mixture was stirred for 30 min, cooled to -78°C, and a solution of 8.1 g

(42.2 mmol, 1 eq) of butenolide 36 in 40 mL of THF was added slowly. The mixture was warmed to 0°C and 120 mL (80.0 mmol, 2 eq) of 0.67 M solution of vinyllithium in pentane was added. After 15 min at 25°C the solution was poured into 500 mL of 2-3% solution of sulfuric acid. The mixture was stirred 2 h, poured carefully into saturated aqueous sodium bicarbonate, and the aqueous solution was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. Column chromatography (40% ethyl acetate/hexane) and crystallization from ethyl acetate/hexane yielded 11 g (32.1 mmol, 76%) of crystalline enone 38, Mp 144-146°C.

One Pot Annulation: Enone **101**. To a solution of 2.4 mL (17 mmol, 1.1 eq) of diisopropylamine in 120 mL of toluene at 0°C was added 10.17 mL (16.48 mmol, 1.06 eq) of a 1.62 M solution of n-butyllithium in hexane. The mixture was stirred 10 min and a solution of 4.2 g (16.5 mmol, 1.06 eq) of enone 79 in 10 mL of toluene was added dropwise. The yellow solution was cooled to -78°C, stirred 10 min, and a solution of 4.5 g (15.5 mmol, 1 eq) of freshly crystallized sulfoxide 75 in 27 mL of toluene was added via syringe down the side of the flask. The orange solution was stirred 10 min, allowed to slowly warm to 0°C, and 150 mL (100 mmol, 6.3 eq) of a 0.66 M solution of vinyllithium in pentane was added. The heterogeneous yellow solution was stirred for 1 h and carefully poured into 180 mL of a 1 M solution of HF in methanol. The flask was rinsed with 30 mL of methanol. The mixture was stirred 20 min, cooled to 0°C, and 150 mL of a 1 M solution of methoxide in methanol was added. The mixture was stirred 90 min and 27 mL of acetic acid was added. The mixture was concentrated, triturated with

60% ethyl acetate/hexane, and filtered through a plug of silica gel. Column chromatography (30% ethyl acetate/hexane) yielded 2.97 g (6.7 mmol, 43%) of enone 101 and 0.45 g (1 mmol, 6.6%) of its diastereomer. Crystallization of 101 from ethyl acetate/hexane afforded white crystals, Mp 133-134°C. Anal. Calcd. for $C_{26}H_{32}SO_4$: C, 70.88; H, 7.32. Found: C, 70.76; H, 7.34.

Ester **104**. To a solution of 25 mg (0.07 mmol) of enone 39 in 2 mL of 95% ethanol was added 4 drops of 15% sodium hydroxide. After 30 min the solution was carefully acidified to pH 7 with glacial acetic acid and extracted with methylene chloride. The aqueous layer was then acidified to pH 4 with acetic acid and extracted with methylene chloride. This organic layer was dried over sodium sulfate, filtered, and concentrated to afford the crude carboxylic acid which was redissolved in 1 mL of THF and titrated with ethereal diazomethane. The solution was concentrated, and column chromatography (40% ethyl acetate/hexane) afforded 11 mg (0.03 mmol, 40%) of ester 104.

Dienone **105**. To a freshly prepared solution of 1 mmol of LDA in 10 mL of THF at -78°C was added a solution of 100 mg (0.29 mmol) enone 39 in 2 mL of THF. The mixture was stirred 15 min and 0.25 mL (2 mmol) of trimethylsilyl chloride was added followed by 0.42 mL (3 mmol) of triethylamine. The mixture was allowed to warm to 25°C and poured into 50 mL of hexane. The cloudy solution was washed with 50 mL of saturated aqueous sodium bicarbonate, dried over sodium sulfate, and concentrated.

To a solution of the silyl enol ether in 3 mL of freshly distilled acetonitrile was added 67 mg (0.3 mmol, 1 eq) of palladium (II) acetate and the resulting mixture was stirred for 6 h. The mixture was diluted

with 40% ethyl acetate/hexane, filtered through a plug of silica gel, and concentrated to afford 112 mg of an oil. Column chromatography (40% ethyl acetate/hexane) afforded 30 mg of a 1:1 mixture of enone 39 and dienone 105, and 30 mg of the silyl enol ether of enone 39. Separation of dienone 105 and enone 39 was accomplished by preparative TLC (2% THF/methylene chloride). The yield of clean dienone 105 was 10 mg (10% yield overall from 39).

Ester **106.** To a solution of dienone 105 (10 mg, 0.03 mmol) in 2 mL of 95% ethanol was added 4 drops of 15% aqueous sodium hydroxide. The mixture was stirred 30 min and 3 drops of glacial acetic acid was added to titrate the mixture to ca pH 4. The mixture was partitioned between saturated aqueous sodium chloride and methylene chloride. The organic layer was dried over sodium sulfate, filtered, and concentrated to yield 10 mg of an oil. The crude carboxylic acid was dissolved in 1 mL of THF, and cooled to 0°C. Titration with ethereal diazomethane and concentration produced 10 mg of methyl ester 106. Crystallization from ethyl acetate/hexane produced white crystals, Mp 148.5-149.5°C.

Sulfoxide **108.** To a solution of 637 mg (3.31 mmol) of sulfide 36 in 30 mL of methylene chloride at 0°C was added 0.5 mL (3.75 mmol, 1.1 eq) of a 7.5 M solution of peracetic acid. The mixture was stirred 15 min and anhydrous sodium sulfite was added. The mixture was filtered, concentrated, and placed under vacuum. Crystallization from ethyl acetate/hexane afforded 552 mg (2.6 mmol, 80%) of yellow crystals, Mp 84-86.5°C.

Michael Adduct **109a, 109b.** To a freshly prepared solution of 0.7 mmol (1.4 eq) of LDA in 3 mL of THF at -78°C was added a solution of

77 mg (0.5 mmol, 1 eq) of enone 35 in 1 mL of THF. The mixture was stirred 1 h, warmed to 0°C, stirred 1 h, and recooled to -95°C (CH_2Cl_2 slush bath). A solution of 104 mg (0.5 mmol, 1 eq) of sulfoxide 81 in 1 mL of THF was added slowly down the side of the flask. The mixture was allowed to warm to -10°C then poured into saturated aqueous sodium bicarbonate. The aqueous solution was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered, and carefully concentrated to afford 170 mg of an oil. Column chromatography gave 142 mg (0.39 mmol, 78%) of Michael adducts 109a and 109b as a 2:1 mixture.

Lactone 110, 111. To a solution of 10 mg (0.028 mmol) of the mixture of Michael adducts (109a, 109b) in 3 mL of absolute ethanol was added Raney nickel (Aldrich) with rapid stirring until the reaction was shown to be complete by TLC analysis (3 elutions, 40% ethyl acetate/hexane). The solution was diluted with ethyl acetate and filtered through celite. Concentration afforded 3 mg (0.013 mmol, 45%) of a 2:1 mixture of lactones 110 and 111.

Enone 113. A suspension of 1 g of freshly activated zinc dust (washed: 2% HCl, H_2O, MeOH, Et_2O, and dried under vacuum) in 5 mL of saturated aqueous ammonium chloride was stirred vigorously for 10 min at 25°C. To this suspension 4 mL of THF was added followed by 104 mg (0.24 mmol) of crystalline enone 101. The mixture was stirred 2.5 h, filtered through celite, diluted with ethyl acetate, and the layers separated. The organic layer was dried over sodium sulfate, filtered, and concentrated. Column chromatography (7% ethyl acetate/methylene chloride) of the resulting oil afforded 67 mg of enone 113 (0.22 mmol,

94%) as a crystalline solid. Crystallization from ethyl acetate gave white crystals, Mp 146-147°C.

Triol 114. To a solution of 50 mg of lithium aluminum hydride in 2 mL of THF was added a solution of 6 mg (0.02 mmol) of enone 113 in 1 mL of THF. The solution was stirred 15 min and 0.1 mL of water, 0.1 mL of 15% sodium hydroxide, and 0.3 mL of water was added carefully in that order. The solution was diluted with ether, filtered, and concentrated to afford 5 mg (0.017 mmol, 83%) of triol 114 as an oil.

Furan 115. To a solution of 5 mg of alcohol 114 in 2 mL of acetone was added 5 mg of pyridinium p-toluenesulfonate. The mixture was stirred 1 h, poured into saturated aqueous sodium bicarbonate, and the aqueous solution was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford 5 mg of furan 115 as an oil.

Silyl Enol Ether 118. To a solution of 14 mg (2 mmol, 4 eq) of lithium in ca 10 mL of ammonia at -78°C was added a solution of 171 mg (0.5 mmol, 1 eq) of enone 39 and 0.04 mL (0.42 mmol, 0.85 eq) of t-butanol in 2 mL of THF. The mixture was stirred 15 min, warmed to reflux, stirred 15 min, and dry isoprene was added to discharge the blue color. Ammonia was removed by warming the flask under nitrogen. THF was removed under vacuum, followed by heating to 40°C under vacuum (50 μ Hg) for 10 min. The flask was flushed with N_2 and cooled to -78°C. THF (5 mL) was added to dissolve the salts and 0.38 mL (3 mmol, 6 eq) of trimethylsilyl chloride was added. The solution was warmed to 25°C and stirred for 20 min. THF and excess trimethylsilyl chloride were removed under vacuum. The residue was triturated with pentane

which was filtered and concentrated to afford 248 mg of an oil. Column chromatography (10% ethyl acetate/hexane) yielded 139 mg (0.45 mmol, 90%) of silyl enol ether 118.

Aldol Product 119. To a solution of 10 mg (0.032 mmol, 1 eq) of silyl enol ether 118 in 0.3 mL of THF at -20°C was added 0.12 mL (0.12 mmol, 3.8 eq) of a ca 1 M solution of formaldehyde in THF. This was rapidly followed by the addition of 0.016 mL (0.0032 mmol, 0.1 eq) of a 0.2 M solution of tetrabutylammonium fluoride (dried over P_2O_5, 40°C, 10 da, 50 μ Hg). The mixture was stirred 15 min, 2 mL of hexane was added, and the cloudy solution was poured onto a plug of silica gel, eluted with 80% ethyl acetate/hexane, and concentrated. Column chromatography (75% ethyl acetate/hexane) yielded 4.6 mg (0.017 mmol, 54%) of aldol 119 as an oil.

Aldol Product 120. To a solution of 50 mg (0.16 mmol, 1 eq) of silyl enol ether 118 and 14 mg (0.16 mmol, 1 eq) of trioxane in 2 mL of methylene chloride at -78°C was added 0.05 mL (0.46 mmol, 2.28 eq) of titanium tetrachloride. The solution was warmed to -20°C for 7 min, and 0.5 mL of THF was added to clarify the red solution. The mixture was stirred 10 min then was poured onto a plug of silica gel and eluted with methylene chloride, followed by ethyl acetate. The combined eluents were concentrated to afford 60 mg of a colorless oil. Column chromatography (75% ethyl acetate/hexane) yielded 30 mg (0.11 mmol, 70%) of aldol 120 as an oil.

Ketone 121. Into a 15 mL flask equipped with a dry ice/acetone condenser containing 7 mg (1 mmol, 4 eq) of lithium was distilled ca 5 mL of NH_3 from lithium wire. The blue solution of lithium was cooled

to -78°C and a solution of 85.5 mg (0.25 mmol, 1 eq) of enone 39 and 0.02 mL (0.21 mmol, 0.85 eq) of t-butanol in 1 mL of THF was added dropwise to the blue solution. After 15 min the solution was brought to reflux (-33°C) and isoprene was added to discharge the blue color. The ammonia was removed upon warming and the resulting solution was diluted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated to afford 86 mg (100%) of ketone 121 as an oil. Crystallization from ethyl acetate yielded crystals, Mp 200-202°C.

Enone 123. To a rapidly stirred solution of 684 mg (2 mmol, 1 eq) of sulfide 39 in 8 mL of THF and 12 mL of 95% ethanol at 25°C was added, in portions, Raney nickel (deactivated by refluxing 2 h in acetone). The reaction was monitored by TLC analysis. After ca 40 min the solution was filtered through celite and washed with an additional 20 mL of ethanol. The eluent was concentrated, dissolved in chloroform, filtered through glass wool, and concentrated again to afford 452 mg of a semi-solid. Crystallization from ethyl acetate/hexane produced 414 mg (1.77 mmol, 88%) of crystalline enone 123, Mp 128-129.5°C.

Ketone 125. To a solution of 7 mg (1 mmol, 3.1 eq) of lithium in ca 10 mL of NH_3 at -78°C was added 75 mg (0.32 mmol, 1 eq) of enone 123 and 19.2 mg (0.26 mmol, 0.8 eq) of t-butanol in 1.2 mL of THF. The blue mixture turned white and the flask was warmed to remove the ammonia. THF (5 mL) was added and the mixture was poured into saturated aqueous sodium bicarbonate. The aqueous solution was extracted with 40% ethyl acetate/hexane and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield 75.3 mg of an

oil. The crude keto-lactol 124 was dissolved in 10 mL of acetone at 25°C and 2 mL of Jones reagent was added. After 30 min isopropanol was added to consume excess oxidant and stirring was continued for 30 min. The solution was diluted with hexane, filtered through a plug of silica gel, and concentrated to afford 75.6 mg of an oil. Column chromatography (40% ethyl acetate/hexane) yielded 54.3 mg (0.23 mmol, 72%) of ketone 125.

Ketone 125. To a solution of 5 mg (0.045 mmol, 2.1 eq) of potassium t-butoxide in 1 mL of THF at 0°C was added 5 mg (0.021 mmol, 1 eq) of ketone 126 in 0.5 mL of THF. After several hours the solution was diluted with saturated aqueous sodium bicarbonate and extracted with 40% ethyl acetate/hexane. The aqueous portion was acidified with 6 N HCl and reextracted with 40% ethyl acetate/hexane. The organic layer was dried over sodium sulfate, filtered, and concentrated to yield 125 as an oil, homogeneous by TLC and ^{1}H NMR analysis.

Ketone 126. Into a solution of 50 mg of 5% palladium on carbon in 20 mL of 95% ethanol at 25°C was bubbled hydrogen gas. After 15 min a solution of 42 mg (0.18 mmol) of enone 123 in 2 mL of ethanol was added. After ca 1 h, the mixture was filtered through celite and concentrated to yield 43 mg of an oil. Column chromatography (50% ethyl acetate/hexane) afforded 19.4 mg (0.082 mmol, 45%) of ketone 126.

Aldol Product 127. To a solution of 14 mg (2 mmol, 4 eq) of lithium in 10 mL of NH_3 and 5 mL of THF at -78°C was added a solution of 107 mg (0.46 mmol, 1 eq) of enone 123 and 0.08 mL (0.84 mmol, 1.8 eq) of t-butanol in 2 mL of THF. The mixture was brought to reflux for 15 min and isoprene was added to discharge the blue color. The mixture

was warmed under N_2 to remove the ammonia, then the flask was placed under vacuum to remove THF, and finally, warmed to 40°C for 10 min at 50 μ Hg. The flask was cooled to -78°C, flushed with nitrogen and charged with 4 mL of THF. The mixture was stirred for 15 min to dissolve the salts, 4 mL (4 mmol, 8 eq) of a 1 M solution of formaldehyde in THF was added, and the mixture was warmed to 0°C and stirred for 5 min. The mixture was poured into saturated aqueous sodium bicarbonate, and the aqueous solution was extracted with 40% ethyl acetate/hexane. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield 98 mg of an oil. Column chromatography (40% ethyl acetate/hexane) afforded 64 mg (0.24 mmol, 51%) of aldol 127 and 27 mg of the unalkylated lactol 124.

Preparation of an Anhydrous Solution of Formaldehyde in THF. Paraformaldehyde was dried under vacuum over P_2O_5 for 10 days prior to use. In a 50 mL two-neck, round-bottom flask was placed 3 g of the dried formaldehyde. A slow stream of dry nitrogen was passed through the flask and into a trap cooled to -78°C, then into a 100 mL two-neck flask, and finally out through a bubbler to monitor the rate of flow of nitrogen (ca 2 bubbles/sec). The 100 mL flask containing a large magnetic stir bar was charged with 50 mL of dry THF and the 50 mL flask was heated to 140°C with rapid stirring. After 30 min the paraformaldehyde had almost completely disappeared from the 50 mL flask and heating was discontinued. When the 50 mL flask had cooled to ambient temperature the cold bath was removed from the trap and the flask was allowed to slowly warm to 0°C. The clear solution in the trap (ca 2 mL) slowly distilled into the rapidly stirred 100 mL flask containing

the THF. After 15 min the distillation was complete and the 100 mL flask was disconnected from the trap and placed under nitrogen. The colorless and clear formaldehyde solution thus obtained is usually 1 M as determined by the dimedone method. This solution maintained its titer at -78°C for more than a week.

Acetal **128.** To a solution of 4 mg (0.03 mmol, 1 eq) of aldol product 127 in 0.4 mL of methanol at 25°C was added 5 mg (0.1 mmol, 3.3 eq) of pyridinium p-toluenesulfonate. The mixture was stirred 14 h and poured into saturated aqueous sodium bicarbonate. The aqueous solution was extracted with ethyl acetate, and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield ca 5 mg of acetal 128 as an oil.

Diol **129.** To a solution of 5 mg (0.018 mmol, 1 eq) of aldol product 128 in 0.2 mL of THF at -78°C was added 2 drops of 1 M L-selectride in THF via syringe. The mixture was stirred 1 h and warmed to 0°C, stirred 2 min, and 0.5 mL of 2:1 15% aqueous sodium hydroxide/30% aqueous hydrogen peroxide was carefully added. The mixture was stirred 1 h and poured into saturated aqueous sodium bicarbonate. The aqueous solution was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford 6 mg of diol 129 as an oil.

Diacetate **130.** The mixture (2 mg) from the L-selectride reduction of the aldol product 129 was dissolved in 2:1 pyridine/acetic anhydride at 25°C and stirred for 6 h. The mixture was poured into saturated aqueous sodium bicarbonate and extracted with 40% ethyl acetate/hexane. The combined organic layers were dried over sodium sulfate, filtered,

and concentrated. Column chromatography (40% ethyl acetate/hexane) afforded the pure diacetate 130 as an oil.

Acetonide 131. To a solution of 6 mg (0.021 mmol, 1 eq) of diol 129 in 2 mL of THF and 0.1 mL of 2,2-dimethoxypropane at 25°C was added 10 mg of pyridinium p-toluene sulfonate (0.04 mmol, 2 eq). The mixture was stirred for 15 min and poured into saturated aqueous sodium bicarbonate. The aqueous solution was extracted with 40% ethyl acetate/hexane and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield 7 mg of acetonide 131 as an oil.

Ketone 133. To a solution of 3 mg (0.43 mmol, 4.3 eq) of lithium in ca 10 mL of NH_3 and 5 mL of THF at -78°C was slowly added 30 mg (0.1 mmol, 1 eq) of enone 113 and 13 mg (0.18 mmol, 1.8 eq) of t-butanol in 1 mL of THF. To the white mixture was added solid ammonium chloride and the solution was allowed to warm to remove the ammonia. The solution was diluted with ethyl acetate, washed with saturated sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated to afford 35 mg of an oil. Column chromatography (60% ethyl acetate/hexane) yielded 12 mg (0.04 mmol, 40%) of the keto lactol 132.

The crude lactol was redissolved in 5 mL of acetone and 10 drops of Jones reagent were added. The mixture was stirred 10 min and 1 mL of isopropanol was added. The mixture was stirred for 30 min, diluted with hexane, and filtered through silica gel. Concentration afforded 10 mg (0.033 mmol, 33%) of keto lactone 133.

Ketal 134. To a solution of 414 mg (1.37 mmol, 1 eq) of enone 113 in 14 mL of benzene, 1.4 mL of 2-ethoxydioxolane, and 0.7 mL of ethylene

glycol was added 140 mg (0.56 mmol, 0.4 eq) of pyridinium p-toluenesulfonate. The mixture was refluxed for 5 h, cooled, and poured into saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield 510 mg of an oil. Column chromatography (30% ethyl acetate/hexane) afforded 421 mg (1.22 mmol, 89%) of ketal 134 as a semi-solid. Recrystallization from ethyl acetate/hexane afforded flakes, Mp 139.5-142°C. Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.8; H, 8.73. Found: C, 72.62; H, 8.71.

Ether **136**. To a solution of 20 mg (0.066 mmol) of enone 113 in methanol at 0°C was added ca 20 mg of solid sodium borohydride. The mixture was stirred 15 min and poured into saturated aqueous sodium bicarbonate. The aqueous solution was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered, and concentrated. The resulting oil was redissolved in N,N-dimethylformamide. Triethylamine, t-butyldimethylsilyl chloride, and a catalytic amount of DMAP were added, and the solution was stirred overnight at 25°C. The solution was poured into saturated aqueous sodium bicarbonate overlayed with hexane. The layers were separated and the organic layer was dried over sodium sulfate, filtered, and concentrated to afford 30 mg (0.7 mmol, 107%) of crude ether 136.

Bis-MOM Ether **137**. To a solution of 50 mg of LAH in ether at 0°C was added a solution of 50 mg (0.12 mmol) of ether 136 in ethyl ether. The mixture was stirred 30 min and 0.05 mL of water, 0.05 mL of 15% aqueous sodium hydroxide, and 0.15 mL of water were carefully added in that order. The mixture was stirred 15 min at 25°C, filtered, and

concentrated. The resulting oil was dissolved in methylene chloride and cooled to 0°C. An excess of methoxymethyl chloride and triethylamine was added and the solution was stirred overnight, during which the mixture was allowed to come slowly to 25°C. The mixture was poured into saturated aqueous sodium bicarbonate and the aqueous solution was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. Column chromatography (5% ethyl acetate/hexane) afforded 30 mg (0.058 mmol, 49%) of bis-MOM ether 137.

Enone 135. To a solution of 30 mg (0.058 mmol) of bis-MOM ether 137 in THF at 25°C was added a 1 M solution of tetrabutylammonium fluoride in THF. The solution was stirred for 48 h, then poured into saturated aqueous sodium bicarbonate. The aqueous solution was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered, and concentrated. The resulting oil (15 mg, 0.038 mmol, 65%) was dissolved in 0.5 mL of methylene chloride and added to a 25°C solution of 30 mg of chromium trioxide in 0.3 mL of pyridine. After 10 min the mixture was diluted with 40% ethyl acetate/hexane and filtered through a plug of silica gel. Concentration afforded 12 mg of an oil. Column chromatography (20% ethyl acetate/hexane) afforded 9 mg (0.023 mmol, 40% overall) of pure enone 135.

Ketone 138. To a solution of 5 mg (0.71 mmol) of lithium in ca 2 mL of ammonia and 2 mL of THF at -78°C was added a solution of 2.2 mg (0.006 mmol) of enone 135 in 1 mL of THF. The mixture was stirred 20 min and isoprene was added to discharge the blue color. The solution was brought to reflux and solid ammonium chloride was added. The

mixture was diluted with saturated ammonium chloride and the aqueous solution was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. Column chromatography (20% ethyl acetate/hexane) yielded 2.8 mg of ketone 138 as an oil.

Ketone 146. A solution of 5 mg of diol 145 in chloroform was concentrated in a 10 mL round bottom flask which had not previously been washed with base. ^{1}H NMR and TLC analysis indicated that ketal cleavage had occurred. The oil was redissolved in wet THF and a crystal of p-toluenesulfonic acid was added. The mixture was stirred for 15 min at 25°C and poured into saturated aqueous sodium bicarbonate. The aqueous solution was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield furan 146 as an oil.

Bis Mesylate 139. To a solution of 300 mg of lithium aluminum hydride in 9 mL of THF at 20°C was added a solution of 143 mg (0.413 mmol) of ketal 134 in 6 mL of THF. The mixture was stirred 15 min and 0.3 mL of water, 0.3 mL of 15% aqueous sodium hydroxide, and 0.9 mL of water was carefully added in that order via syringe. Ether (9 mL) was added to facilitate stirring, and after 15 min the mixture was filtered into a base-washed flask containing 1 mL of pyridine and concentrated. The resulting oil was dissolved in 30 mL of methylene chloride and 0.84 mL (6 mmol, 15 eq) of triethylamine. The mixture was cooled to -78°C and a solution of 0.24 mL (3 mmol, 8 eq) of methanesulfonyl chloride in 6 mL of methylene chloride was added dropwise. The mixture was stirred 4 h, warmed to 0°C, and poured into

saturated aqueous sodium bicarbonate. The aqueous solution was extracted with methylene chloride and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield 192 mg of an oil. The crude bis mesylate was dissolved in 9 mL of ether, 1.2 mL (8.6 mmol) of triethylamine, and 9 mL of water. To the rapidly stirred mixture was added 0.75 mL of a 2% aqueous solution of osmium tetroxide (0.06 mmol, 0.14 eq). Solid sodium meta-periodate (900 mg, 4.2 mmol, 10.5 eq) was added in 6 equal portions over 1 h. The brown mixture was poured into saturated aqueous sodium bicarbonate and the aqueous solution was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford 208 mg of a brown oil. Column chromatography (75% ethyl acetate/hexane) yielded 190 mg (0.37 mmol, 91%) of keto bis mesylate 139.

Cyclopentane 142. To a solution of 190 mg (0.37 mmol, 1 eq) of bis mesylate 139 in 6 mL of THF at 25°C was added 3 mL (3.0 mmol, 8.1 eq) of a 1 M solution of sodium methoxide in methanol. The mixture was stirred 80 min, poured into saturated aqueous sodium bicarbonate, and the aqueous solution was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield 140 mg of an oil. Column chromatography (60% ethyl acetate/hexane) afforded 120 mg (0.29 mmol, 79%) of cyclopentane 142 as an oil. Crystallization from ethyl acetate/hexane yielded crystals, Mp 103-106°C.

Cyclopentane 142a. A 1:1 mixture (5 mg) of 142a and 142b was dissolved in 1 mL of benzene. The solution was brought to reflux and 0.05 mL of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added. The

mixture was refluxed for 4 h, cooled, filtered through a plug of silica gel (70% ethyl acetate/hexane), and concentrated to afford ca 3 mg of a 4.6:1 mixture of 142a and 142b respectively.

Cyclopentane **142b**. To a solution of 5 mg (0.012 mmol) of ketone 142a in 2 mL of THF at 0°C was added a solution of 5 mg (0.045 mmol, 3.7 eq) of oxygen-free potassium t-butoxide in 0.1 mL of THF. The mixture was stirred 10 min and 1 mL of saturated aqueous sodium bicarbonate was added. The mixture was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield 5 mg of an oil. Column chromatography (50% ethyl acetate/hexane) afforded pure ketone 142b as an oil.

Attempted cyclization of **142**: **149, 150**. To a solution of 5 mg of ketone 143 in 2 mL of THF was added 15 mg (0.13 mmol) of potassium t-butoxide at 25°C. The mixture was brought to reflux for 30 min, cooled, and 1 mL of saturated aqueous sodium bicarbonate was added. The aqueous solution was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered, and concentrated. Column chromatography (40% ethyl acetate/hexane) provided a 1:1 mixture of pure ketones 149 and 150.

Hydroperoxide **151**. To a solution of 5 mg (0.012 mmol) of ketone 142 in 2 mL of THF at 0°C was added a solution of 15 mg (0.135 mmol, 11 eq) of potassium t-butoxide in 0.3 mL of THF. The mixture was stirred 10 min and 1 mL of saturated aqueous sodium bicarbonate was added. The mixture was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered, and

concentrated. Column chromatography (60% ethyl acetate/hexane) afforded hydroperoxide 151 as an oil.

Olefin 154. To a solution of 7 mg (0.017 mmol) of mesylate 142 in 1 mL of DMSO at 25°C was added 0.05 mL of DBU. The mixture was warmed to 160°C, stirred 8 h, cooled, diluted with 40% ethyl acetate/hexane, and filtered through a plug of silica gel. Concentration afforded 5 mg of an oil.

Sulfide 155. To a solution of 5 mg (0.012 mmol) of ketone 142 in 0.1 mL of THF at 0°C was added 2 mg (0.018 mmol, 1.5 eq) of potassium t-butoxide in 0.04 mL of THF. The mixture was stirred 10 min, cooled to -78°C, and a solution of 3.7 mg (0.014 mmol, 1.2 eq) of phenylthio benzenesulfonate in 0.1 mL of THF was added dropwise. The mixture was warmed to 0°C, stirred 30 min, and 1 mL of saturated aqueous sodium bicarbonate was added. The aqueous solution was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield 7 mg of an oil. Crystallization from ethyl acetate/hexane afforded 3.4 mg (0.006 mmol, 54%) of crystalline 155, Mp 79-86°C.

Ketone 158. To a solution of 55 mg (0.16 mmol) of ketal 134 in 4 mL of methylene chloride at -78°C was slowly added a saturated solution (ca 0.04 M) of ozone in methylene chloride at -78°C. The reaction was monitored by TLC (70% ethyl acetate/hexane), and upon completion 0.2 mL of triethylamine and 2 mL of 5% dimethylsulfide in methanol was added. The mixture was warmed to reflux momentarily, then cooled and concentrated to yield ketone 158 as a semi-solid. Column chromatography (75% ethyl acetate/hexane) afforded 50 mg (0.14 mmol,

91%) of crystalline ketone 158. Recrystallization from ethyl acetate/hexane yielded crystals, Mp 146-147.5°C.

Aldehyde **159.** To a solution of 250 mg of LAH in 8 mL of ethyl ether at 25°C was added 200 mg (0.58 mmol) of ketal 134 in 3 mL of THF. The mixture was stirred for 30 min and the addition of 10 mL of ether was followed by the careful addition of 0.25 mL of water, 0.25 mL of 15% aqueous sodium hydroxide, and 0.75 mL of water. The mixture was stirred for 15 min, filtered, and concentrated to afford 202 mg of an oil. The oil was dissolved with 30 mg of DMAP and 0.2 mL of triethylamine in 3 mL of methylene chloride. The mixture was cooled to -78°C and a solution of 97 mg (0.65 mmol, 1.12 eq) of t-butyldimethylsilyl chloride in 2 mL of methylene chloride was added slowly down the side of the flask. The mixture was stirred for 6 h and 1 mL of methanol was added. The mixture was allowed to warm to 25°C and 2 mL of saturated aqueous sodium bicarbonate was added. The mixture was poured into 50 mL of saturated sodium bicarbonate and the aqueous solution was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford 290 mg of the crude silyl ether as an oil.

To 16 mL of pyridine was slowly added 1.6 g of solid chromium trioxide, and the mixture was vigorously stirred until homogeneous (ca 15 min). The solution was cooled to 10°C and a solution of 290 mg of the crude silyl ether in 8 mL of pyridine was slowly added. The mixture was stirred 3 h, diluted with 30% ethyl acetate/hexane, filtered through a plug of silica gel, and concentrated to afford 260 mg of a

crude oil. Column chromatography (15% ethyl acetate/hexane) afforded 214 mg (0.46 mmol, 79%) of aldehyde 159 as an oil.

Aldehyde 157. To a suspension of 500 mg of lithium aluminum hydride in 8 mL of THF at 25°C was added a solution of 500 mg (1.43 mmol) of lactone 158 in 6 mL of THF. The mixture was stirred 30 min, diluted with 10 mL of ether followed by the careful addition of 0.5 mL of water, 0.5 mL of 15% aqueous sodium hydroxide, and 1.5 mL of water in that order. The mixture was stirred for 1 h and filtered. The solids were dissolved in water and extracted with ether. The combined ethereal extracts were concentrated to yield 493 mg (1.39 mmol, 97%) of the triol as a semi-solid.

To a solution of 453 mg (1.28 mmol, 1 eq) of the triol, 60 mg (0.49 mmol, 0.38 eq) of DMAP and 0.4 mL (2.9 mmol, 2.2 eq) of triethylamine in 10 mL of methylene chloride at -78°C was added a solution of 210 mg of TBSCl in 2 mL of methylene chloride. The mixture was stirred and 2 mL of methanol was added. The solution was poured into saturated aqueous sodium bicarbonate and the aqueous solution was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield 740 mg of crude silyl ether as an oil.

To a solution of 4 g of chromium trioxide in 40 mL of pyridine at 25°C was added the crude silyl ether in 20 mL of pyridine. The mixture was stirred 2.5 h and the solution was poured into 250 mL of 40% ethyl acetate/hexane, filtered through a plug of silica gel, and concentrated to afford 580 mg of an oil. Column chromatography (35% ethyl

acetate/hexane) afforded 380 mg (0.81 mmol, 63%) of aldehyde 157 as an oil. Crystallization from hexane afforded crystals, Mp 108-110°C.

Spiro Enone 160. To a solution of 93 mg (0.2 mmol, 1 eq) of aldehyde 157 in 2 mL of THF at 0°C was added 0.26 mL (0.23 mmol, 1.16 eq) of a 0.89 M solution of potassium t-butoxide in t-butanol. The mixture was stirred for 1 h and 2 mL of saturated aqueous sodium bicarbonate was added. The mixture was poured into 9 mL of saturated aqueous sodium bicarbonate and the aqueous solution was extracted with hexane. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford 93.5 mg (0.21 mmol, 104%) of enone 160 as an oil. Crystallization from methanol produced crystals, Mp 106-111°C.

Spiro Ketone 162. To a suspension of 20 mg of 5% palladium on carbon in 0.4 mL of anhydrous ethanol under an atmosphere of hydrogen was added 0.2 mL of a 2 M solution of sodium ethoxide in ethanol. The mixture was stirred 10 min and a solution of 45 mg (0.10 mmol) of enone 160 in 0.4 mL of anhydrous ethanol was added. After ca 30 min TLC analysis indicated loss of UV activity and the solution was diluted with ether and filtered through celite into 2 mL of saturated aqueous sodium bicarbonate. The aqueous solution was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield 47 mg (0.104 mmol, 104%) of ketone 162. Crystallization from methanol produced crystals, Mp 99.5-100.5°C.

Enone 163. A solution of 40 mg (0.089 mmol) of ketone 162 in 0.08 mL of 2-methyl-2-ethyldioxolane was added to 0.02 mL of ethylene glycol and 4 mg of p-toluenesulfonic acid at 0°C. The mixture was

stirred 1 h and 0.05 mL of triethylamine was added. The mixture was poured into saturated aqueous sodium bicarbonate and the aqueous solution was extracted with 40% ethyl acetate/hexane. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield 46 mg of an oil. Column chromatography (40% ethyl acetate/hexane) afforded 35.2 mg (0.078 mmol, 88%) of enone 163 as an oil.

Ketone 164. To a solution of 6 mg (0.86 mmol) of lithium in ca 4 mL of ammonia and 2 mL of THF at -78°C was added a solution of 5 mg of enone 163 in 0.5 mL of THF. The mixture was stirred 2 min and isoprene was added to discharge the blue color. Solid ammonium chloride was added and the flask was warmed to remove the ammonia. The mixture was diluted with 1 mL of saturated aqueous sodium bicarbonate and the aqueous solution was extracted with hexane. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield 7 mg of an oil. Column chromatography (30% ethyl acetate/hexane) afforded 5 mg of ketone 164 as an oil.

Aldol Product 165. To a solution of 4.8 mg (0.69 mmol) of lithium in ca 5 mL of ammonia and 2.5 mL of THF at -78°C was added a solution of 19 mg (0.042 mmol) of enone 163 in 1 mL of THF. The mixture was stirred 3 min and isoprene (distilled, 3 drops) was added to discharge the blue color. The mixture was warmed to remove ammonia and then placed under vacuum to remove THF, and finally heated to 40°C (50 μ Hg) for 10 min. The flask was cooled to 0°C, flushed with nitrogen, and 4 mL of THF was added. The mixture was stirred for 5 min then cooled to -78°C, and 4 mL (1.72 mmol) of a 0.43 M solution of formaldehyde in

THF was added via syringe. The mixture was stirred for 20 min and 1 mL of 10% acetic acid in THF was added. The mixture was stirred for 2 min and 0.4 mL of triethylamine was added. The mixture was poured into 15 mL of saturated aqueous sodium bicarbonate and the aqueous solution was extracted with 40% ethyl acetate/hexane. The combined organic layers were dried over sodium sulfate, filtered through celite, and concentrated to yield 24.7 mg of an oil. Column chromatography (50% ethyl acetate/hexane) afforded 13.4 mg (0.028 mmol, 66%) of the aldol product 165.

Diol 166. To a solution of 13.5 mg (0.028 mmol) of alcohol 165 in 1 mL of THF at -78°C was added 0.2 mL (0.2 mmol, 7.1 eq) of a 1 M solution of L-selectride in THF. The mixture was stirred for 1 h, allowed to warm to 25°C, stirred 15 min, and 0.15 mL of 95% ethanol was carefully added, followed by 0.3 mL of a 1:1 mixture of 15% sodium hydroxide/30% hydrogen peroxide aqueous solution. The mixture was stirred 2 h at 25°C and poured into 15 mL of saturated aqueous sodium bicarbonate. The aqueous solution was extracted with 40% ethyl acetate/hexane and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield ca 11 mg of an oil. To a solution of the oil in 2 mL of THF at 0°C, 10 drops of 15% sodium hydroxide and 20 drops of 30% hydrogen peroxide were added. The mixture was stirred 24 h at 25°C and poured into saturated aqueous sodium bicarbonate. The aqueous solution was extracted with 40% ethyl acetate/hexane, and the combined organic layers were dried over sodium sulfate, filtered, and concentrated. Column chromatography (80% ethyl acetate/hexane) yielded 7.4 mg (0.015 mmol, 55%) of diol 166 as an oil.

Acetal 167. To a solution of 5 mg of diol 166 in 0.2 mL of methylene chloride and 0.2 mL of pivaldehyde at 0°C was added 2.5 mg of p-toluenesulfonic acid. The mixture was stirred 20 min and 0.05 mL of triethylamine was added. The mixture was poured into saturated aqueous sodium bicarbonate and the aqueous solution was extracted with hexane. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield ca 7 mg of acetal 167 as an oil.

Alcohol 168. To a solution of ca 7 mg of acetal 167 in 0.5 mL of THF at 25°C was added 0.1 mL of a 1 M solution of tetrabutylammonium fluoride in THF. The mixture was stirred 1 h and was poured into saturated aqueous sodium bicarbonate. The aqueous solution was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield 5 mg of crude alcohol 168 as an oil. Column chromatography (80% ethyl acetate/hexane) provided pure alcohol 168.

Tosylate 169. A solution of 5 mg of alcohol 168 in 0.5 mL of methylene chloride was added to a mixture of 0.06 mL of triethylamine, 6 mg of p-toluenesulfonyl chloride, and 1 mg of N,N-dimethylamino-pyridine. The mixture was stirred 4 h at 25°C and 0.05 mL of triethylamine and 0.05 mL of water were added. The mixture was stirred 20 min and poured into saturated aqueous sodium bicarbonate. The aqueous solution was extracted with 40% ethyl acetate/hexane and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to yield 10 mg of an oil. Column chromatography (40% ethyl acetate/hexane) afforded 4.5 mg of still impure tosylate 169.

Preparative TLC (25% ethyl acetate/hexane) afforded 2.5 mg of pure tosylate 169.

Norketone 27. To a solution of 0.2 mL (1.1 mmol) of 2,2,6,6-tetramethylpiperidine in 10 mL of THF at 25°C was added 1.02 mL (1.02 mmol, 1.2 eq) of a 1 M solution of methyllithium in ether. The mixture was stirred 15 min and 2.0 mL of this solution was added slowly down the side of a flask at -95°C containing a solution of 5 mg of tosylate 169 in 4 mL of THF. The mixture was allowed to slowly warm to 0°C, and then poured into saturated aqueous sodium bicarbonate. The aqueous solution was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered, and concentrated. Column chromatography (15% ethyl acetate/hexane) afforded 3 mg of a mixture of 27 and 170. Preparative TLC (8 times, benzene) afforded pure ketone 27.

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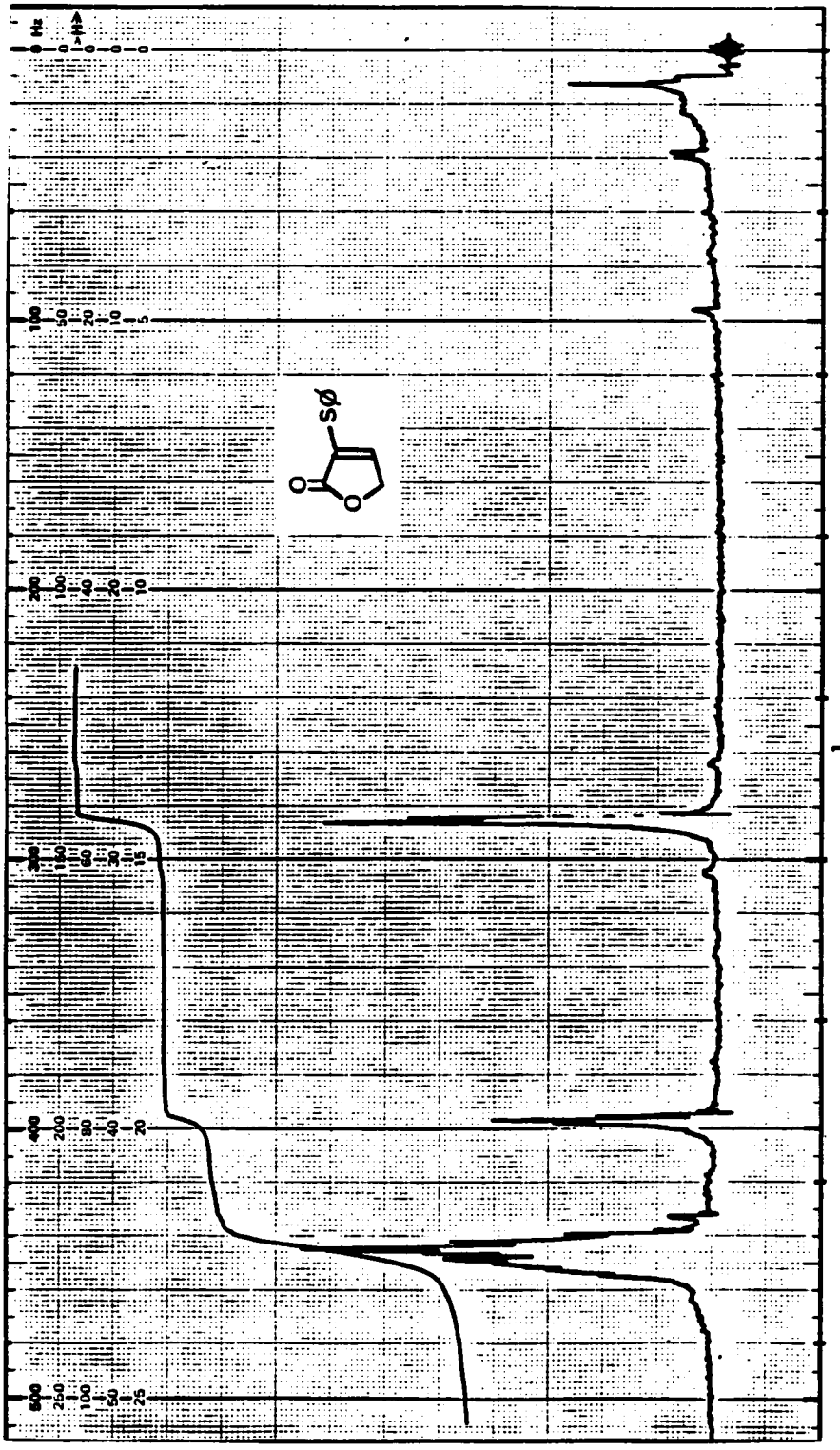
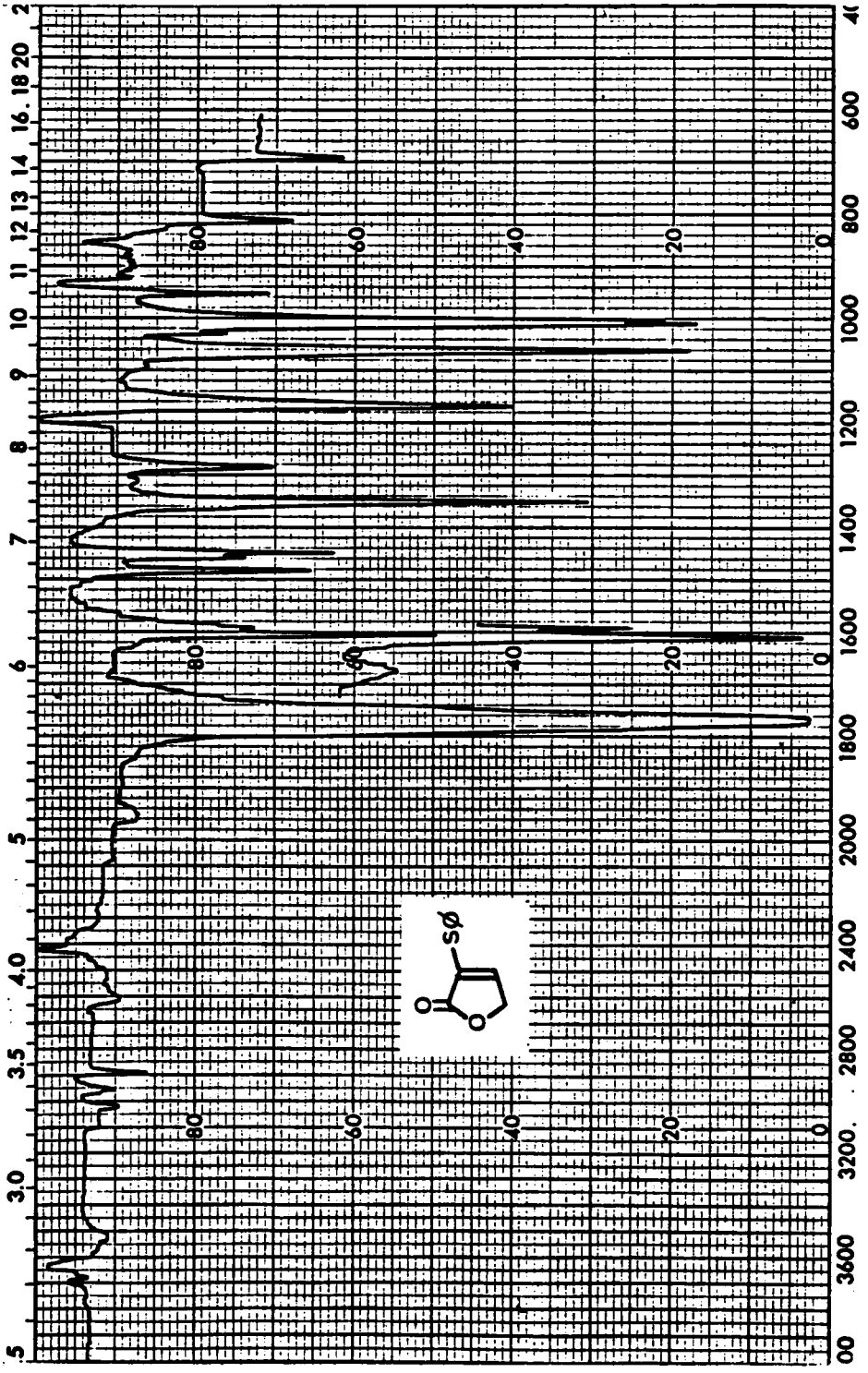
APPENDIX

Table of Contents



90 MHz ^{1}H NMR spectrum of butenolide 36



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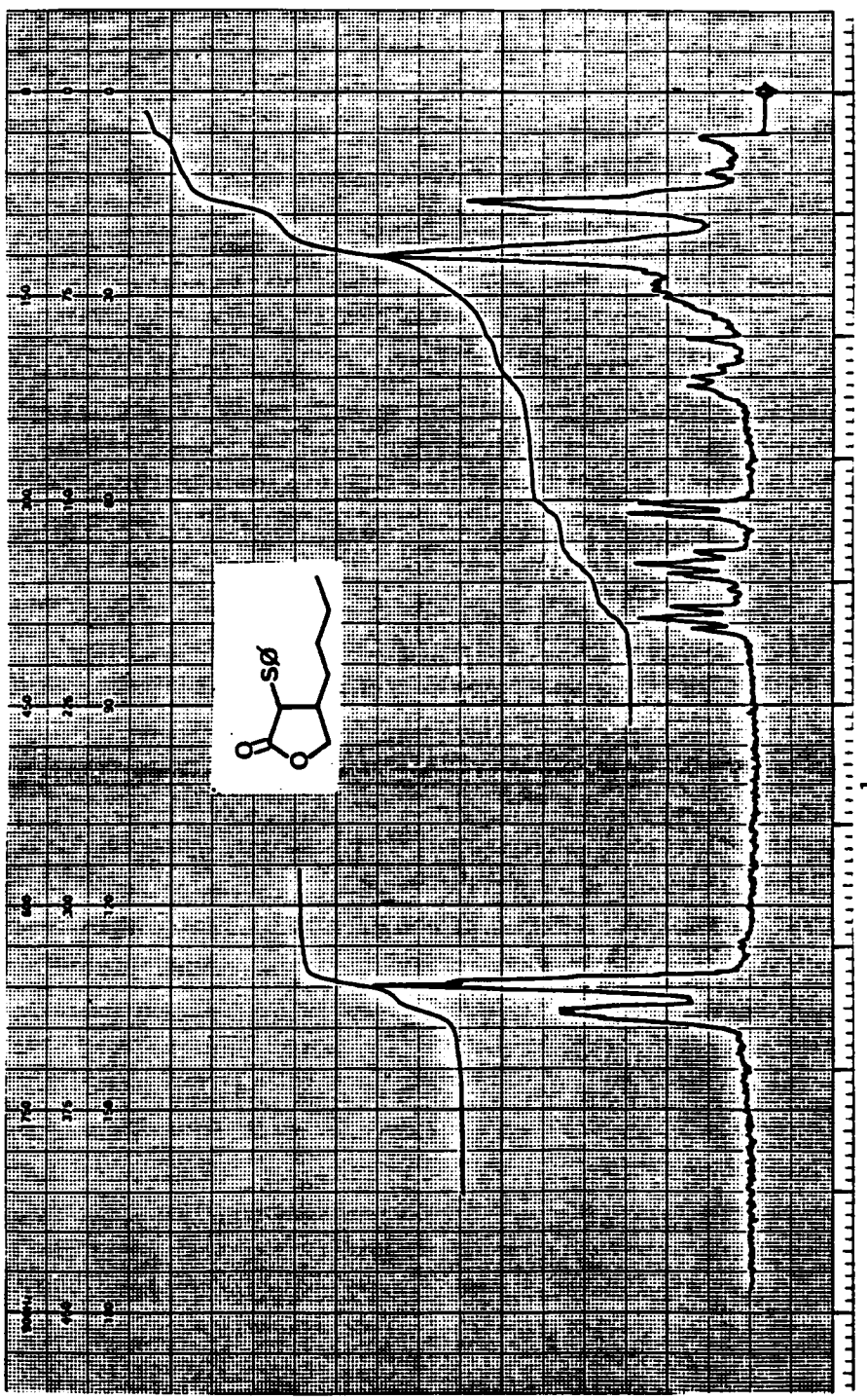

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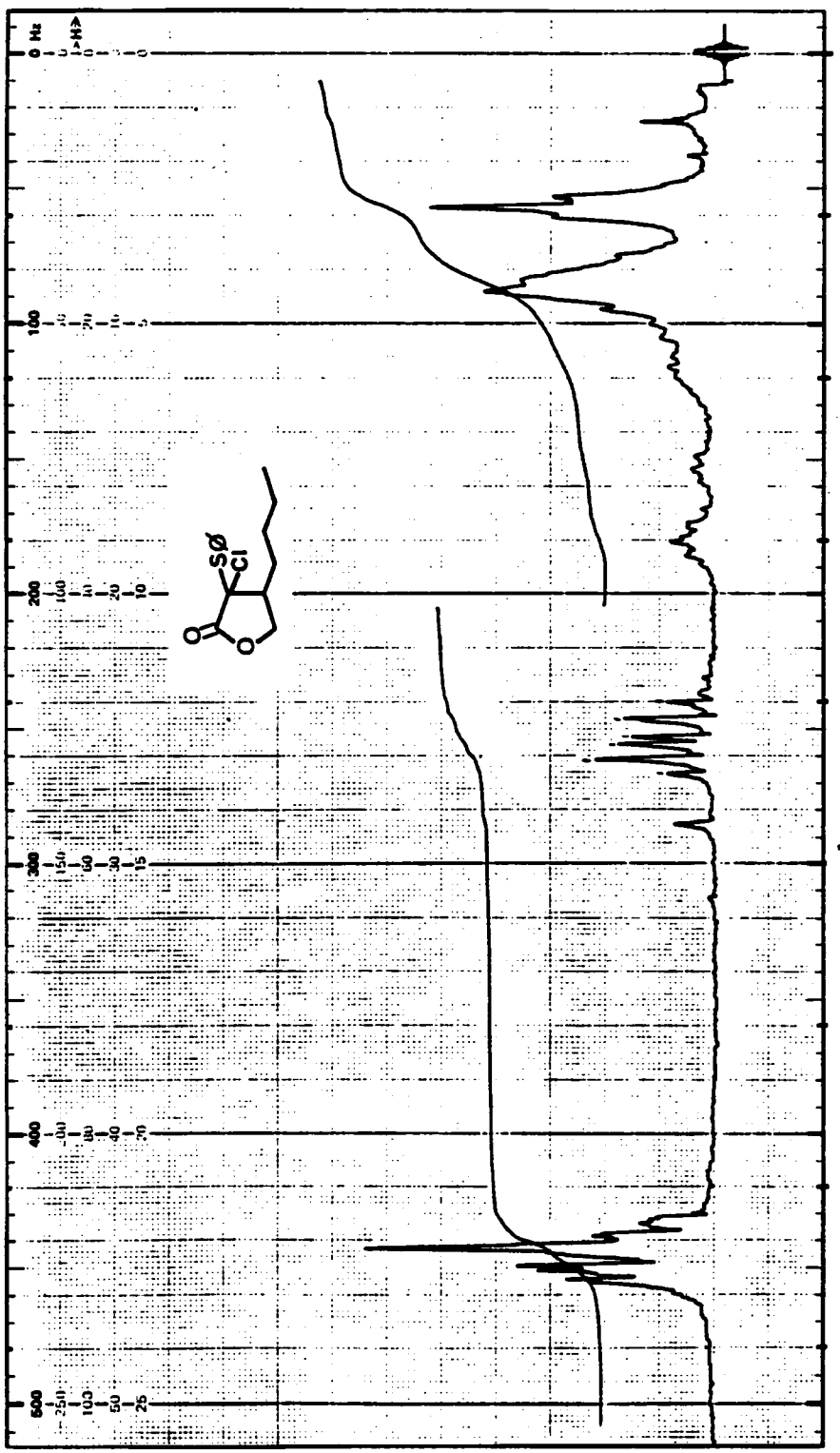

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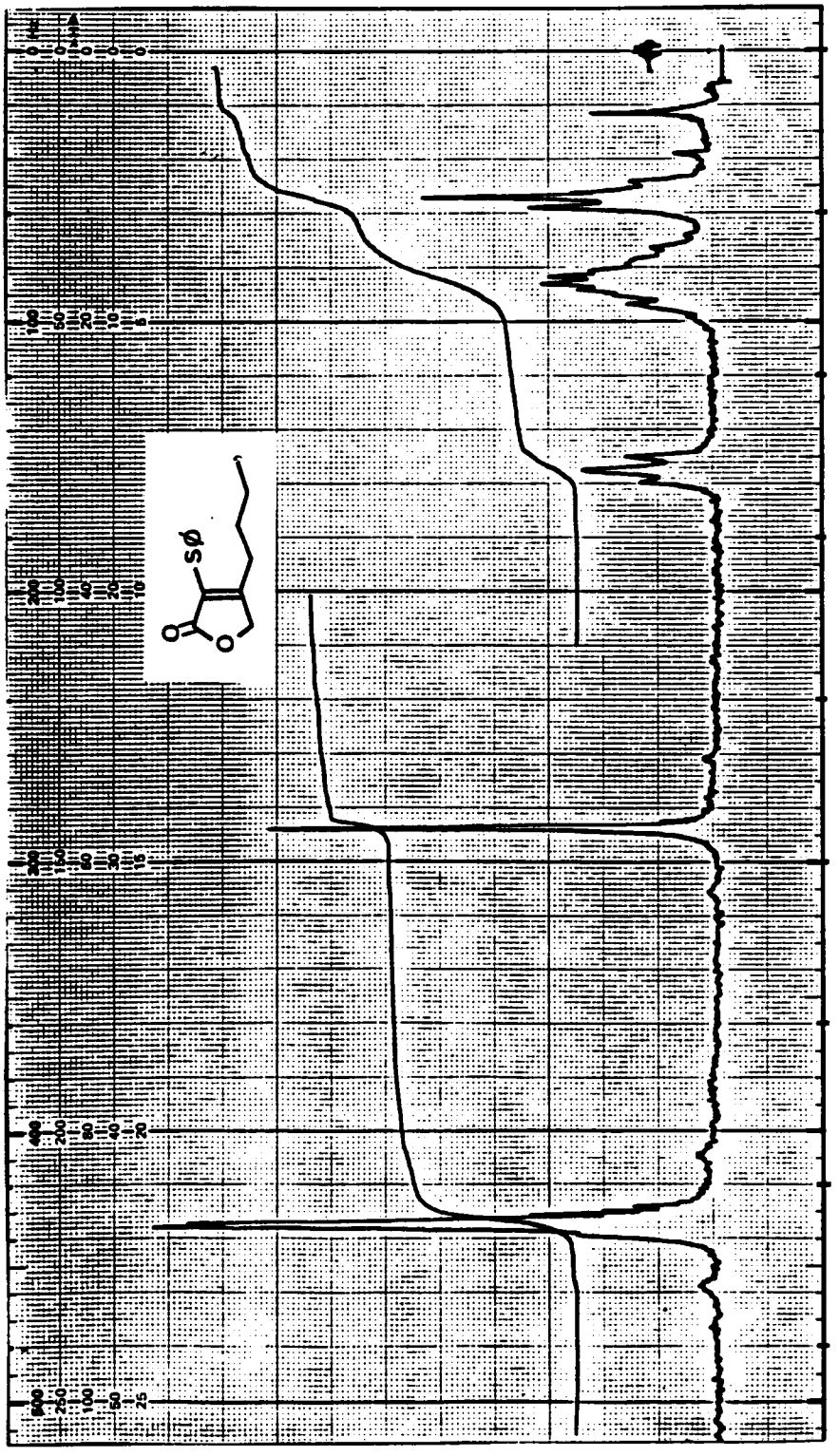

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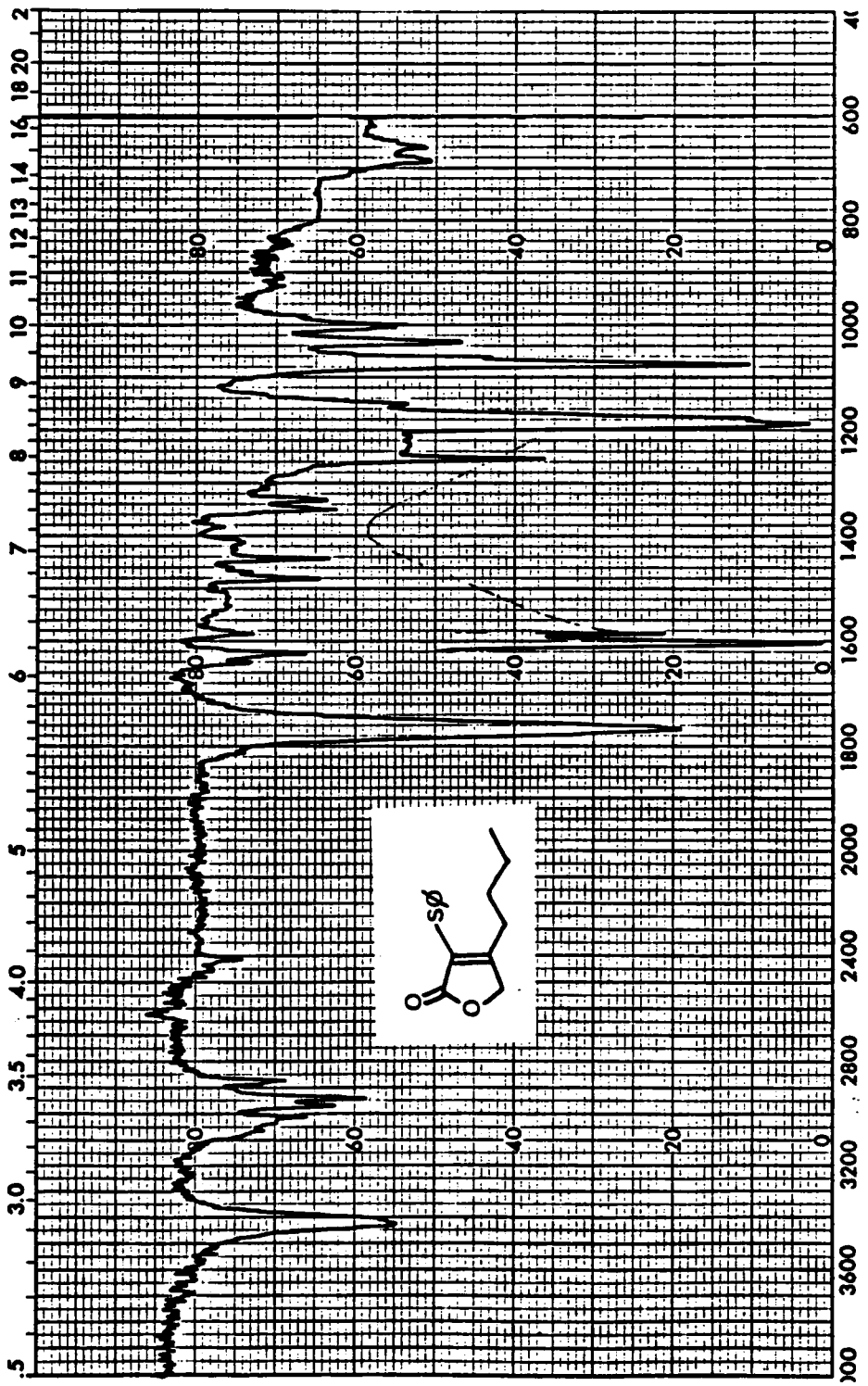
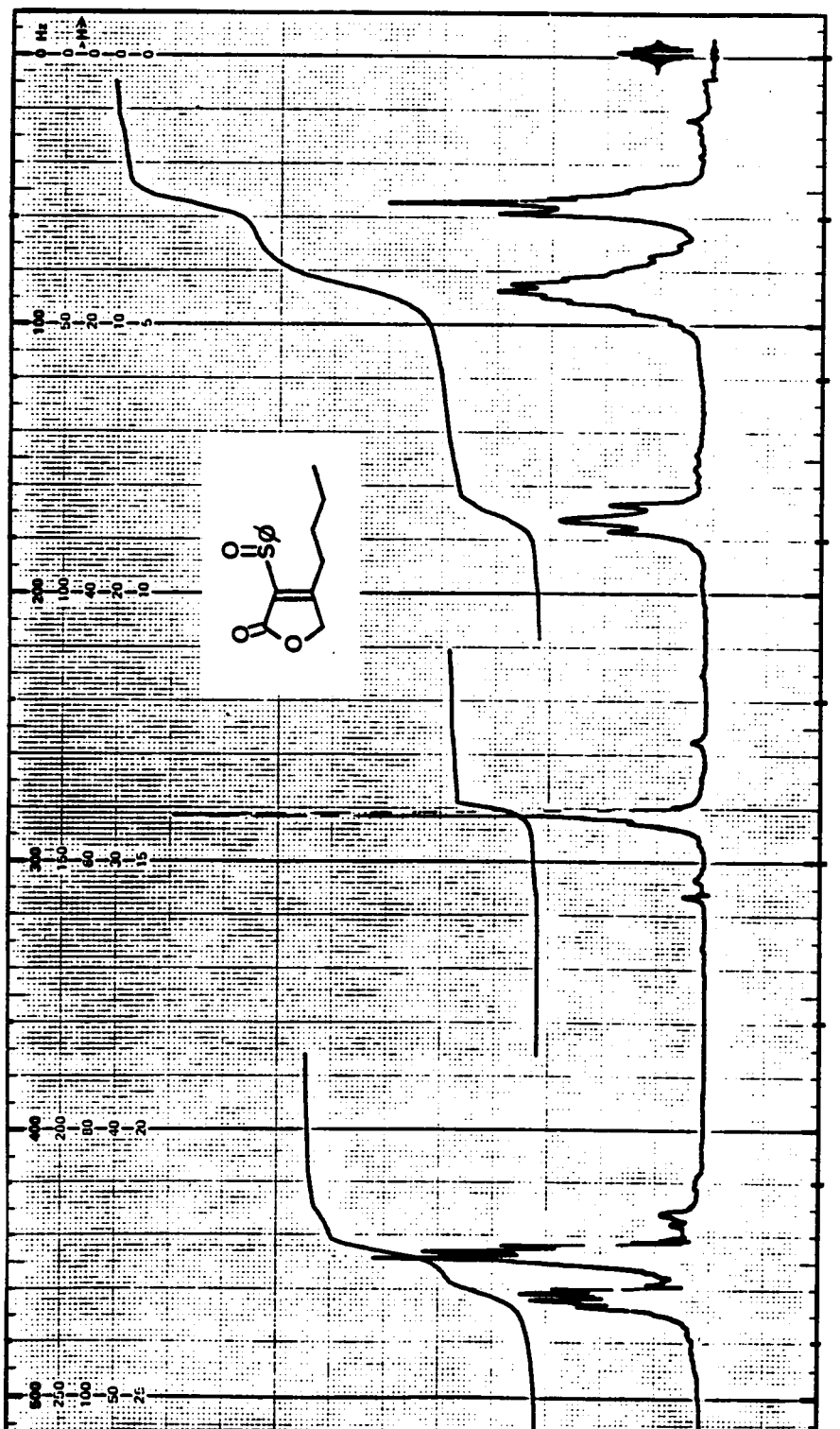


IR spectrum of sulfide 45



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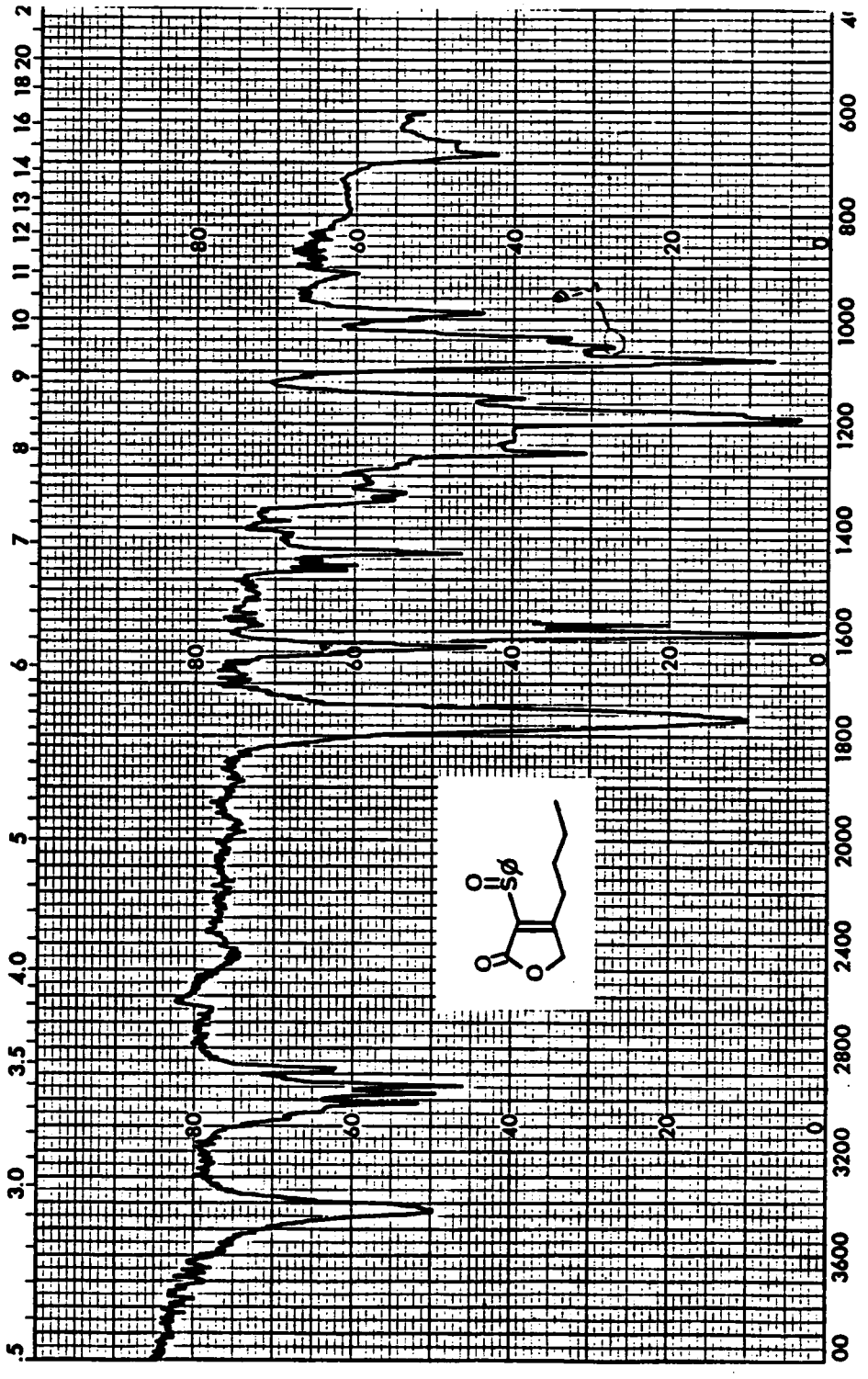

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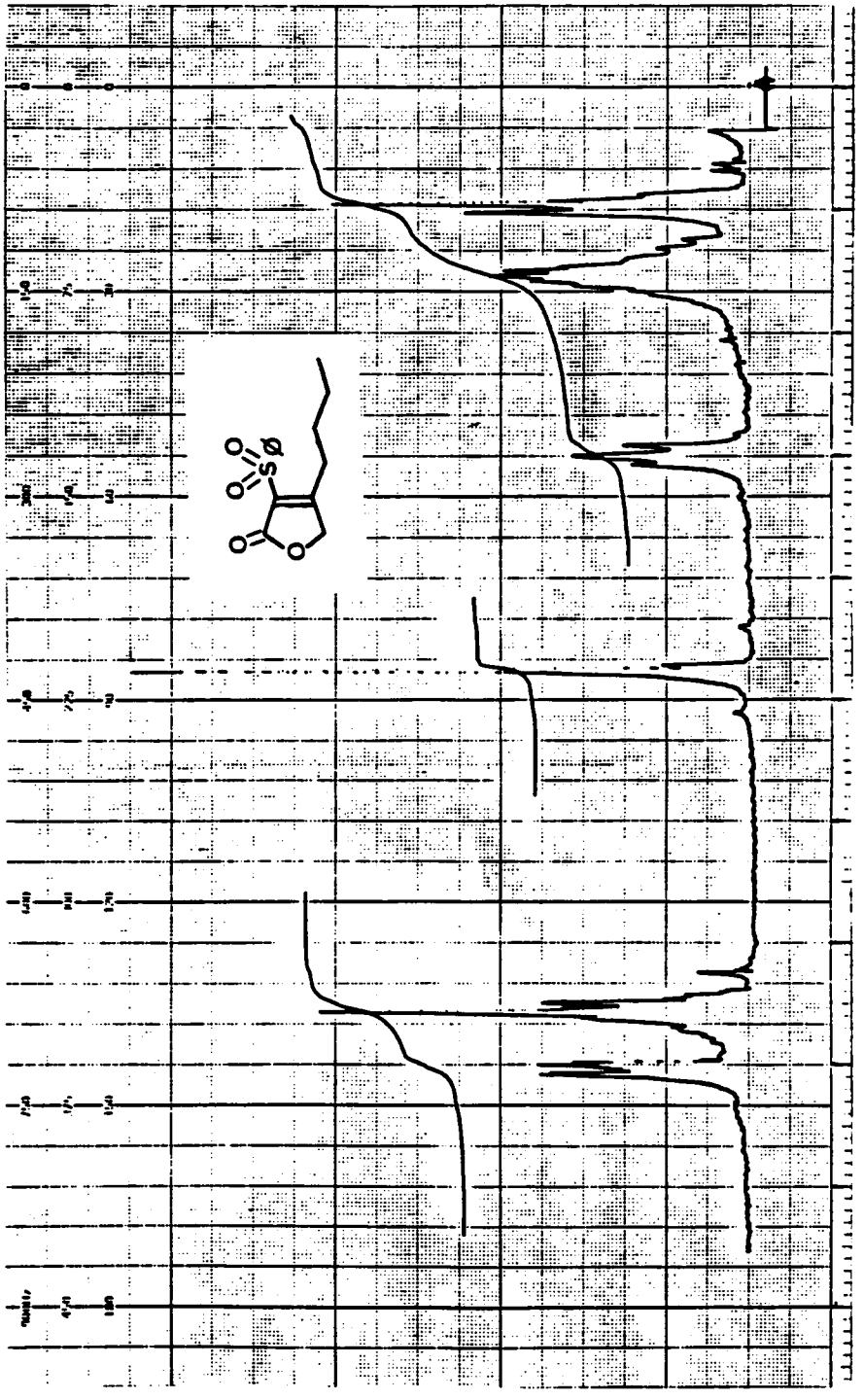

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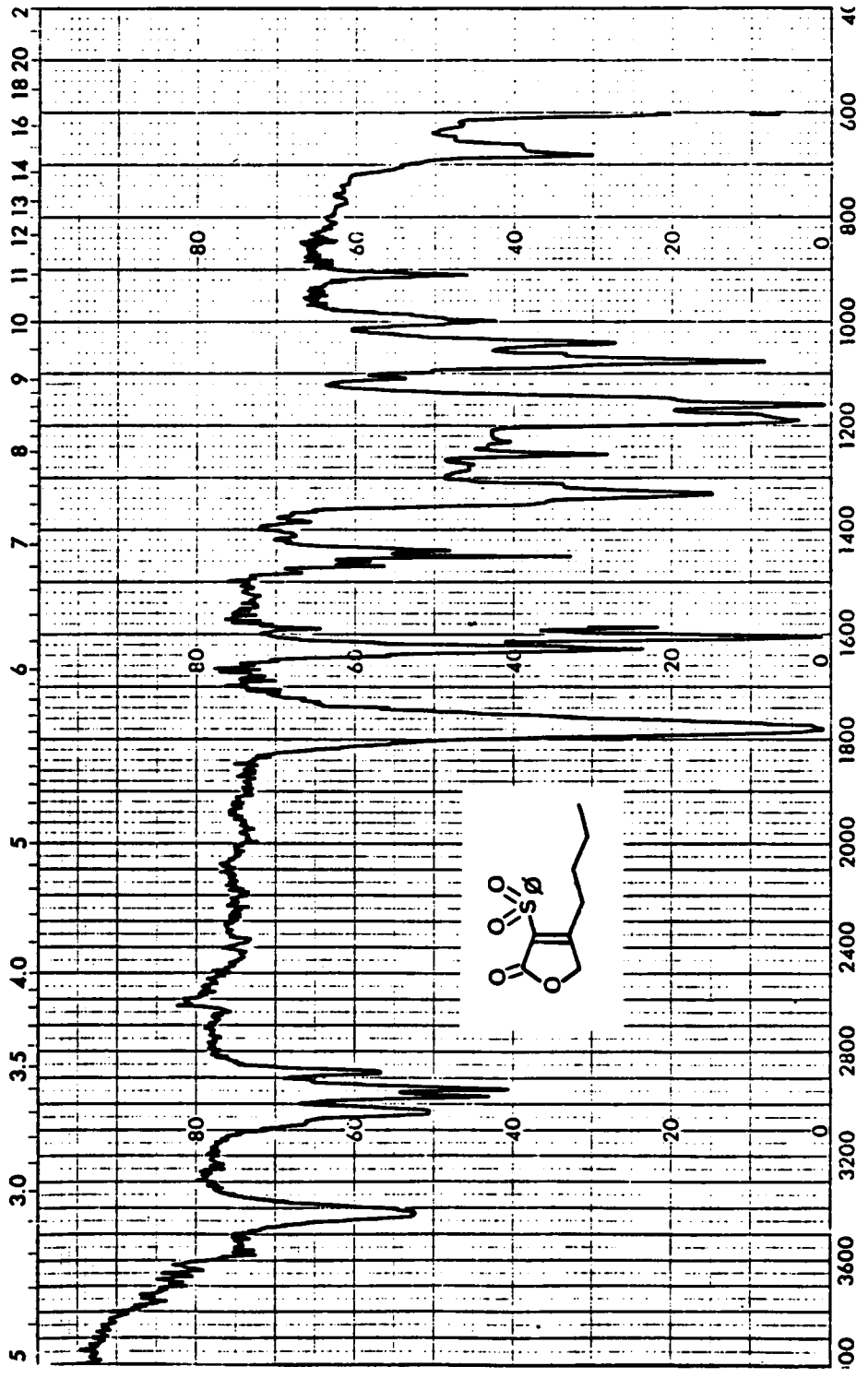

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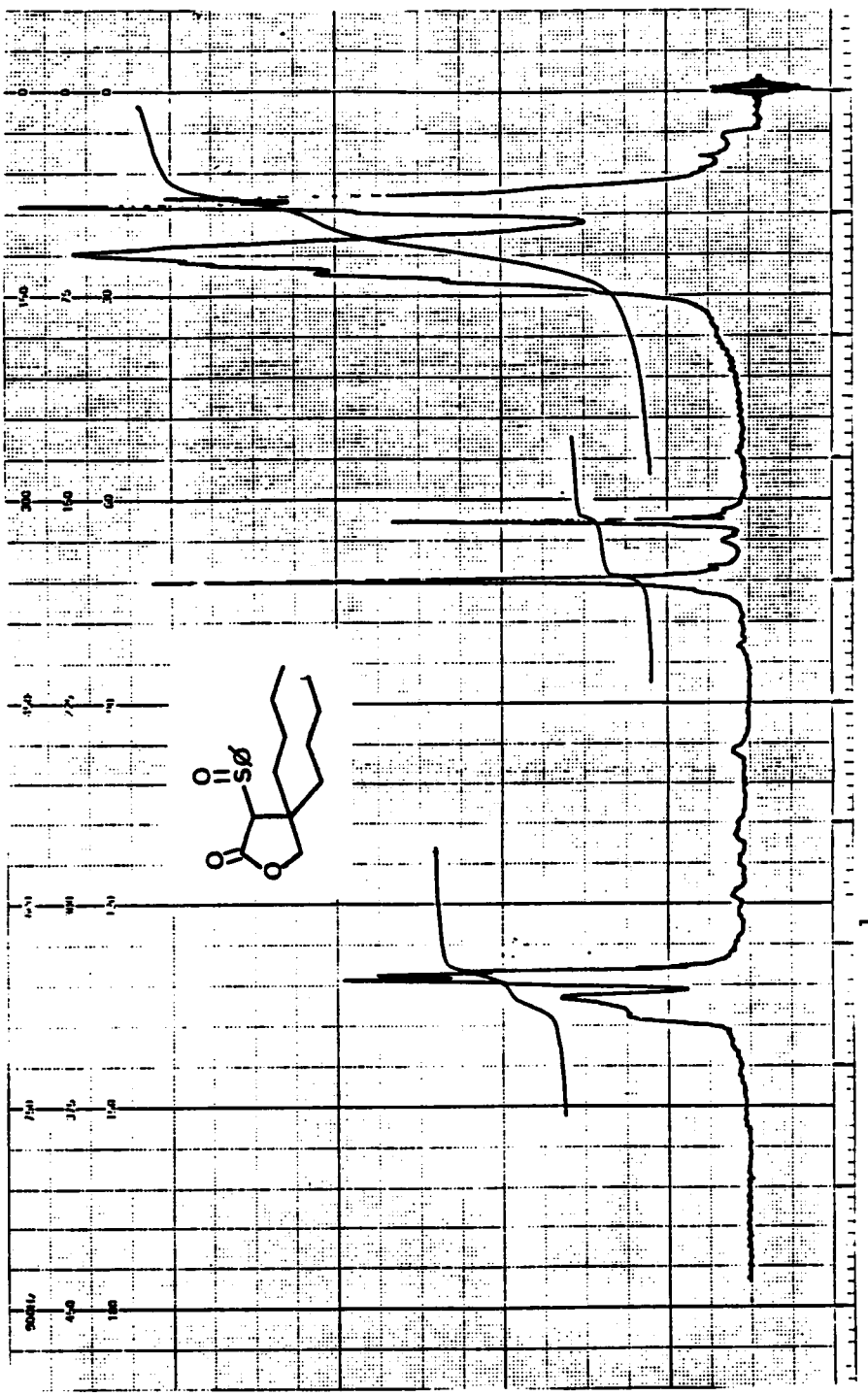

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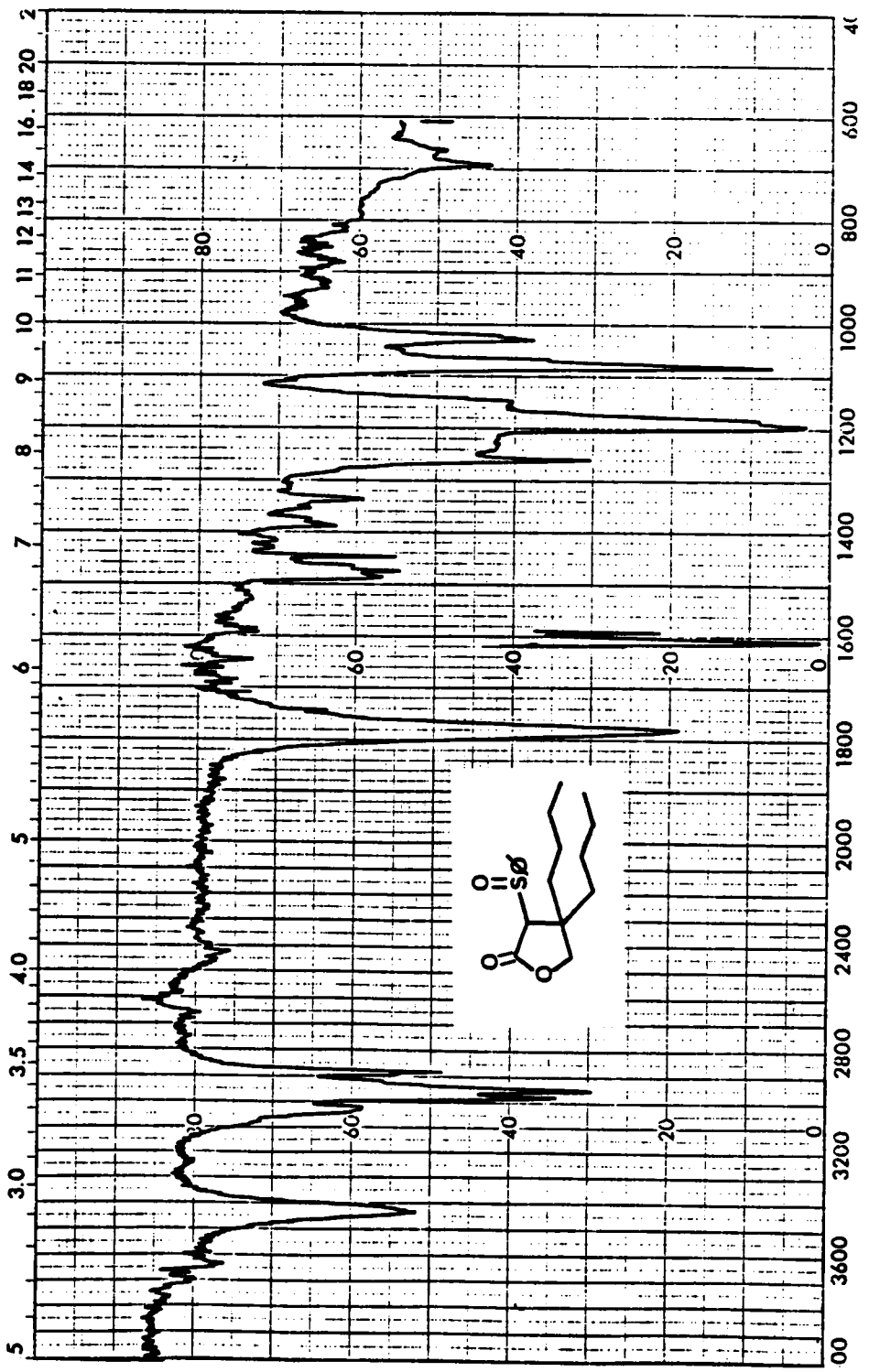

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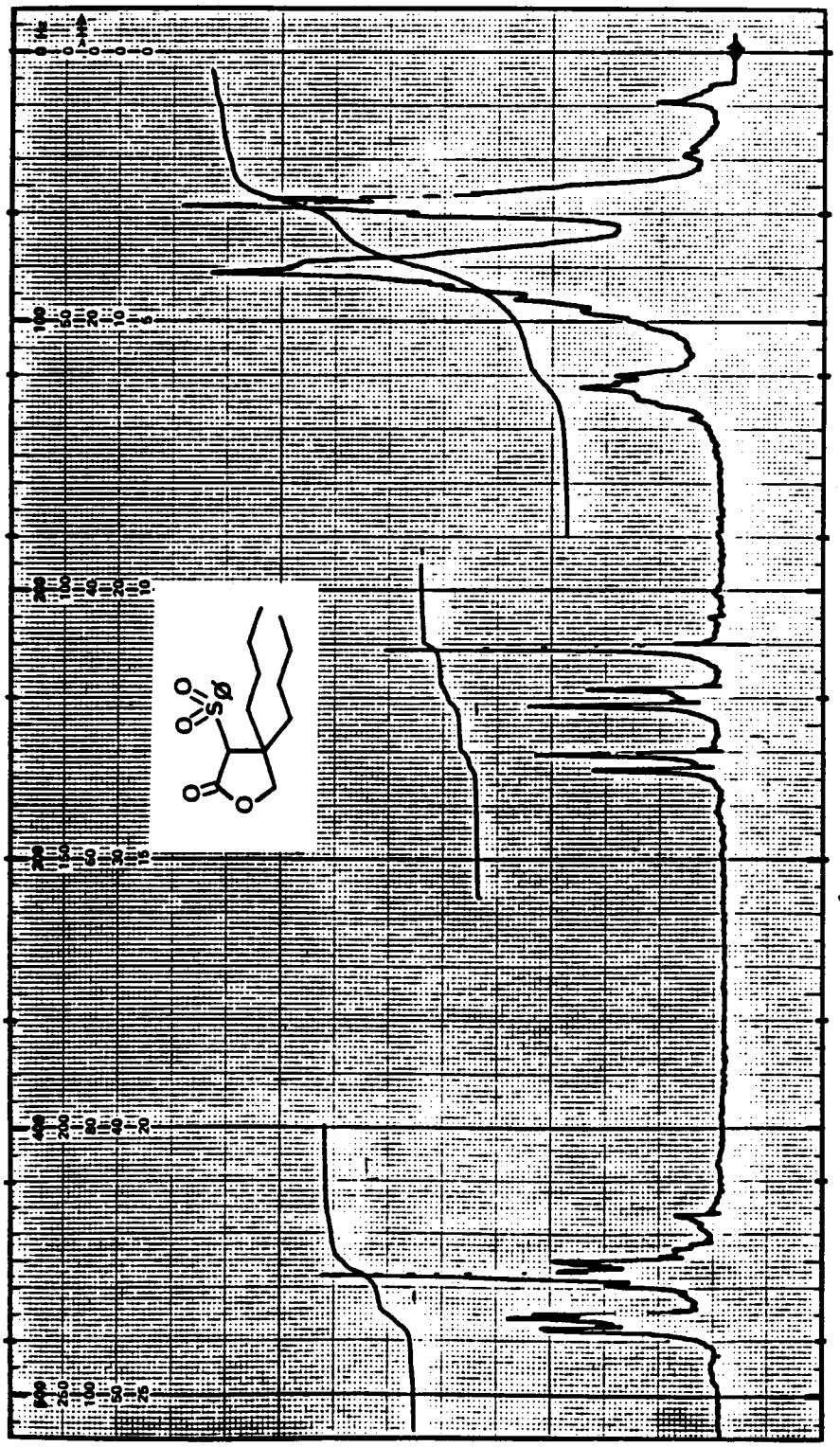

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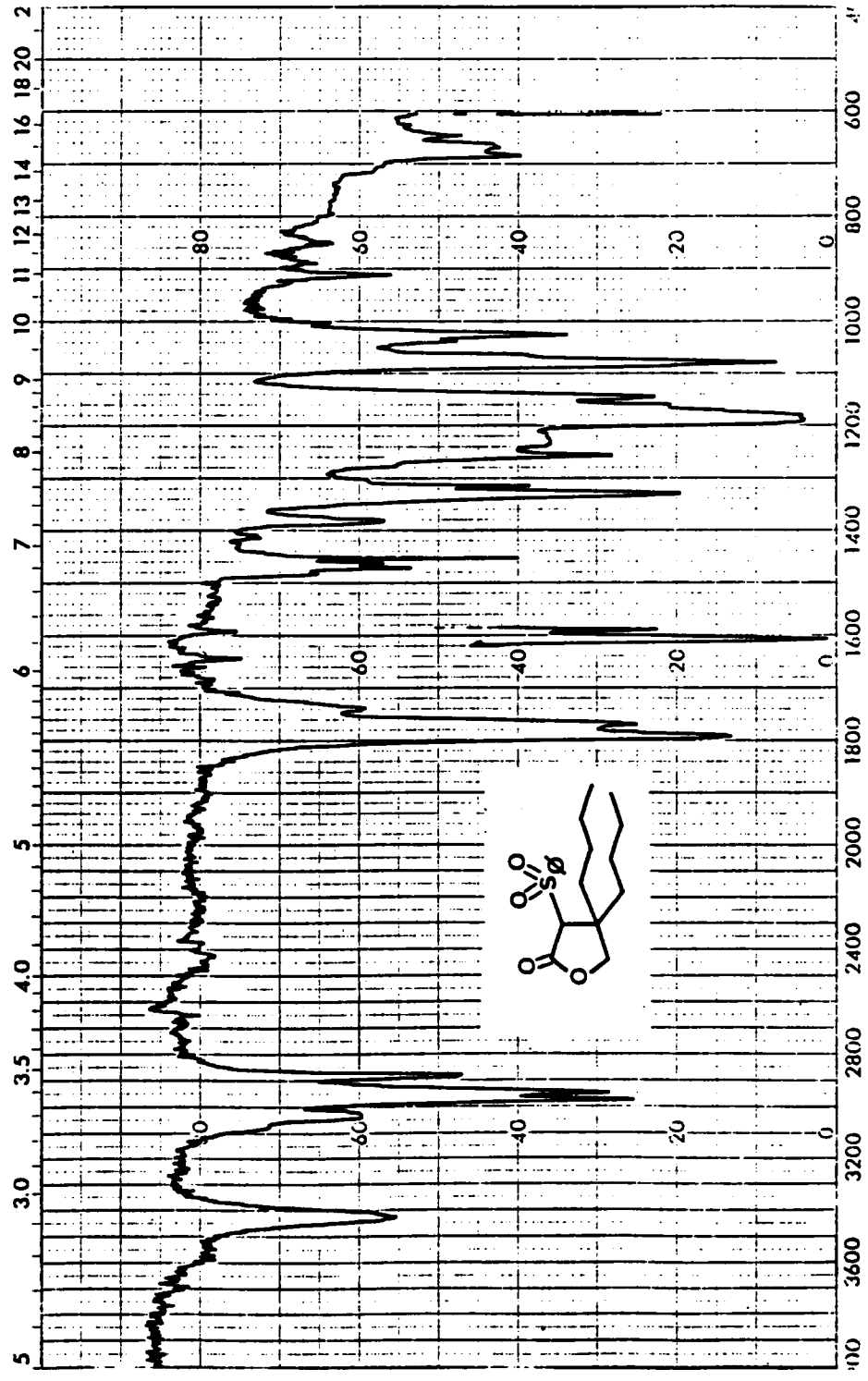
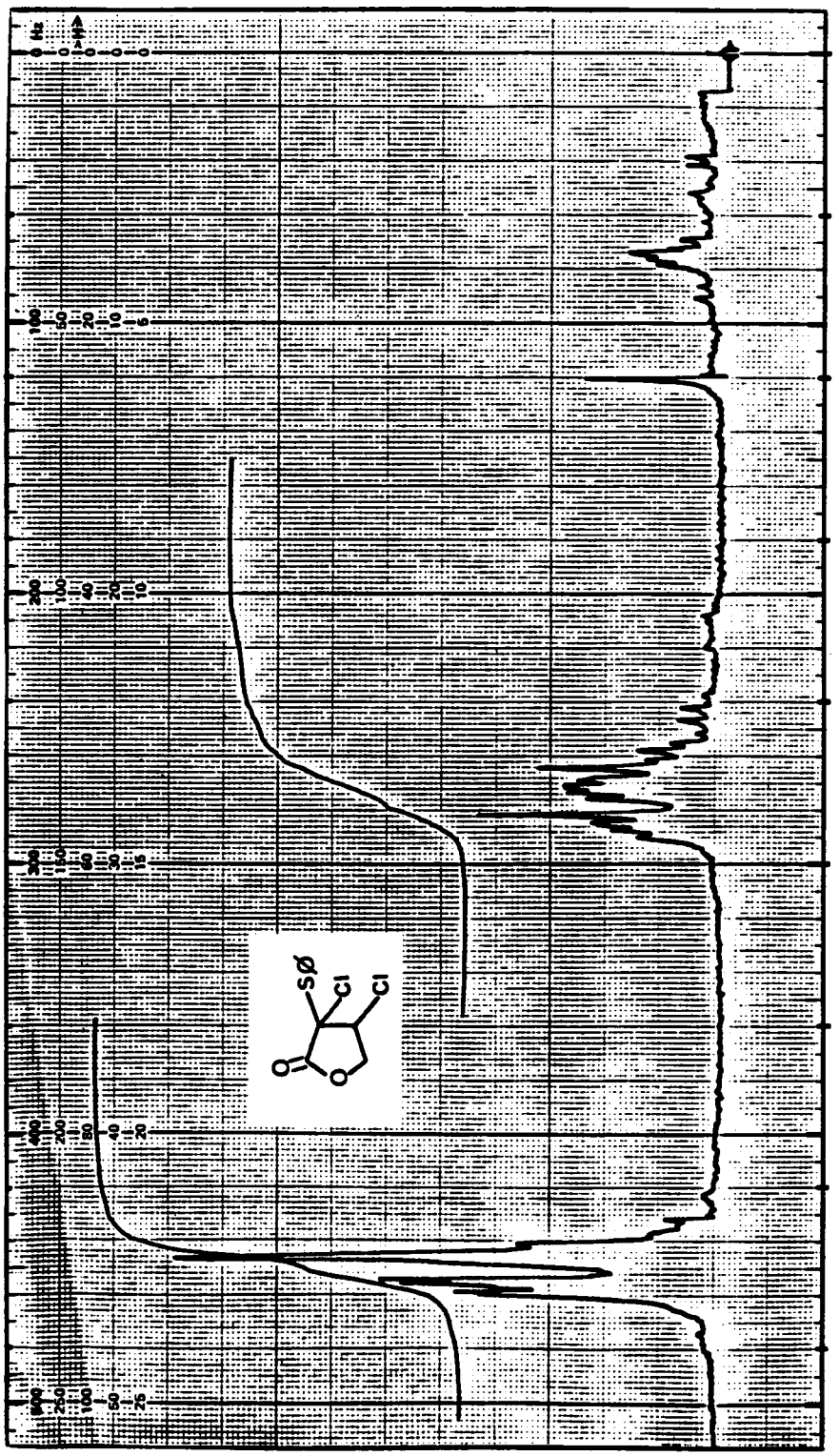
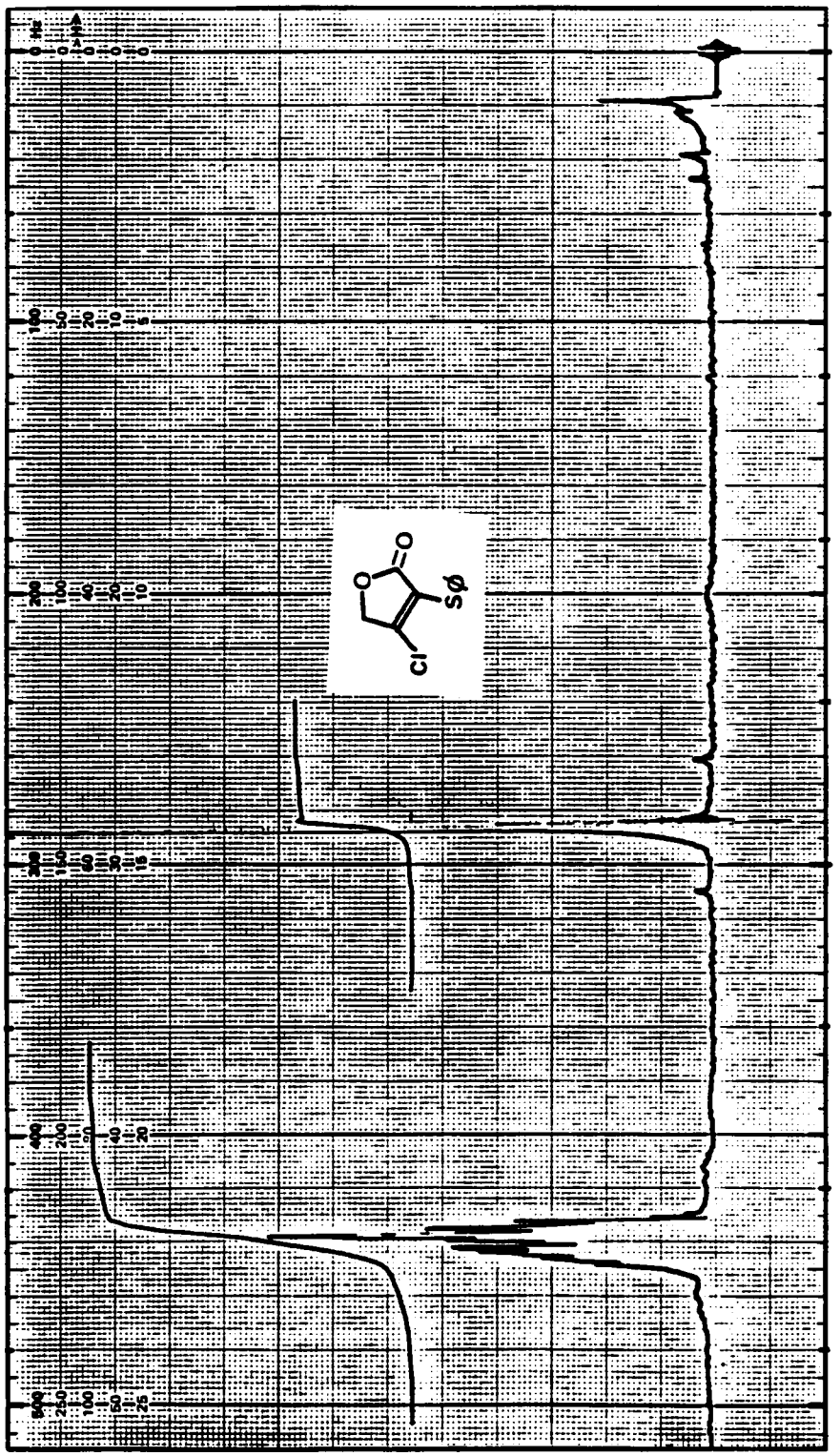


IR spectrum of sulfone 51



90 MHz ^{1}H NMR spectrum of dichloride 52



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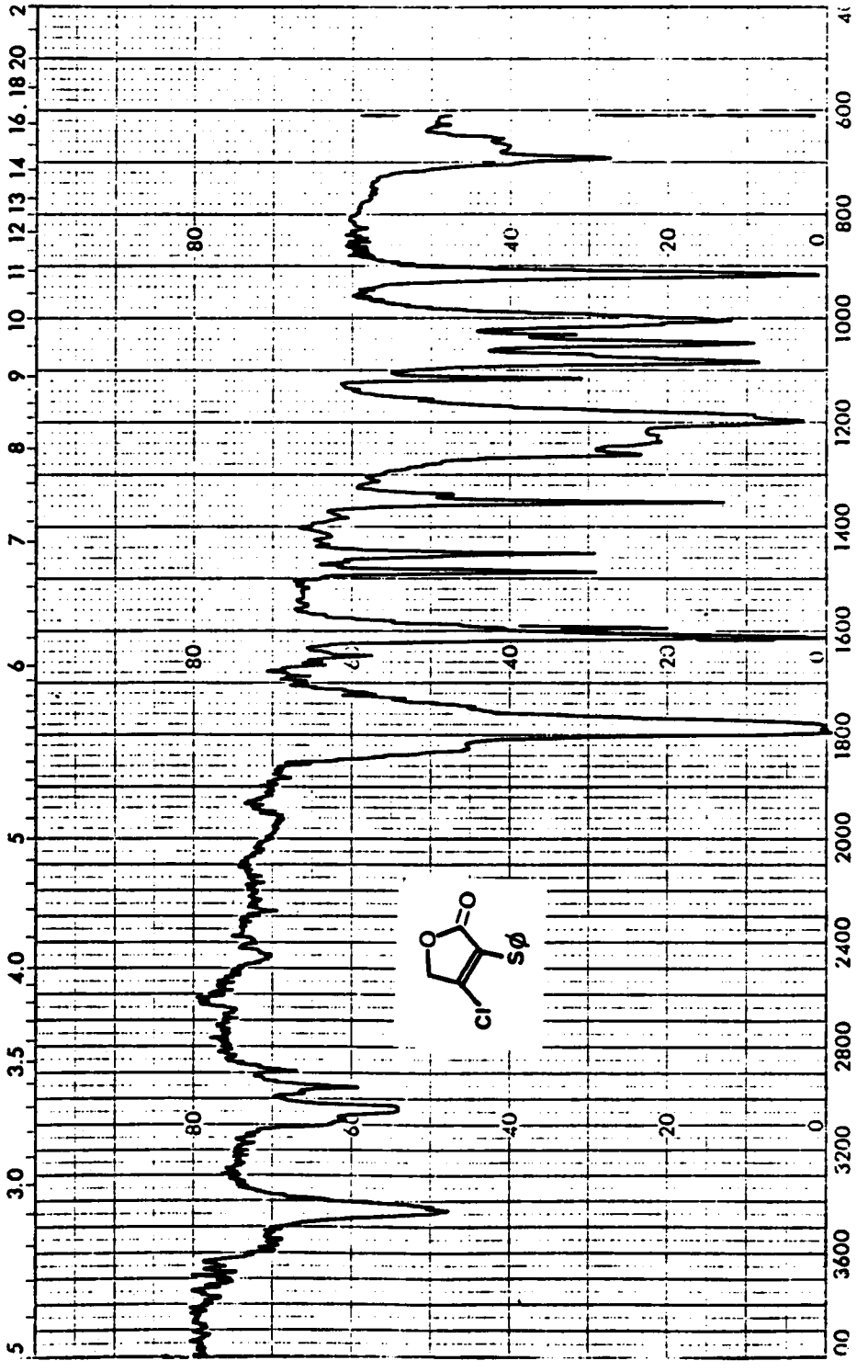
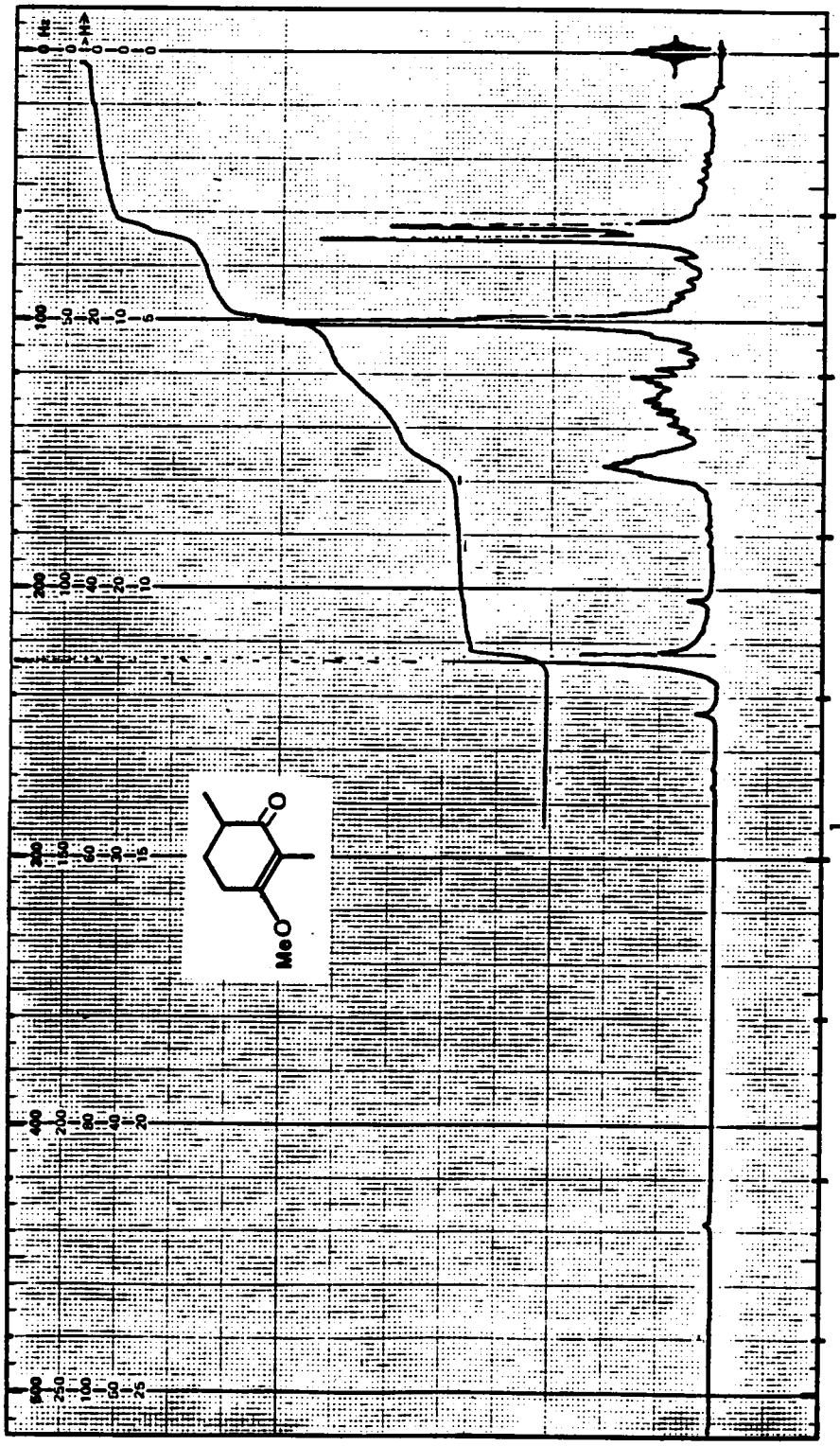
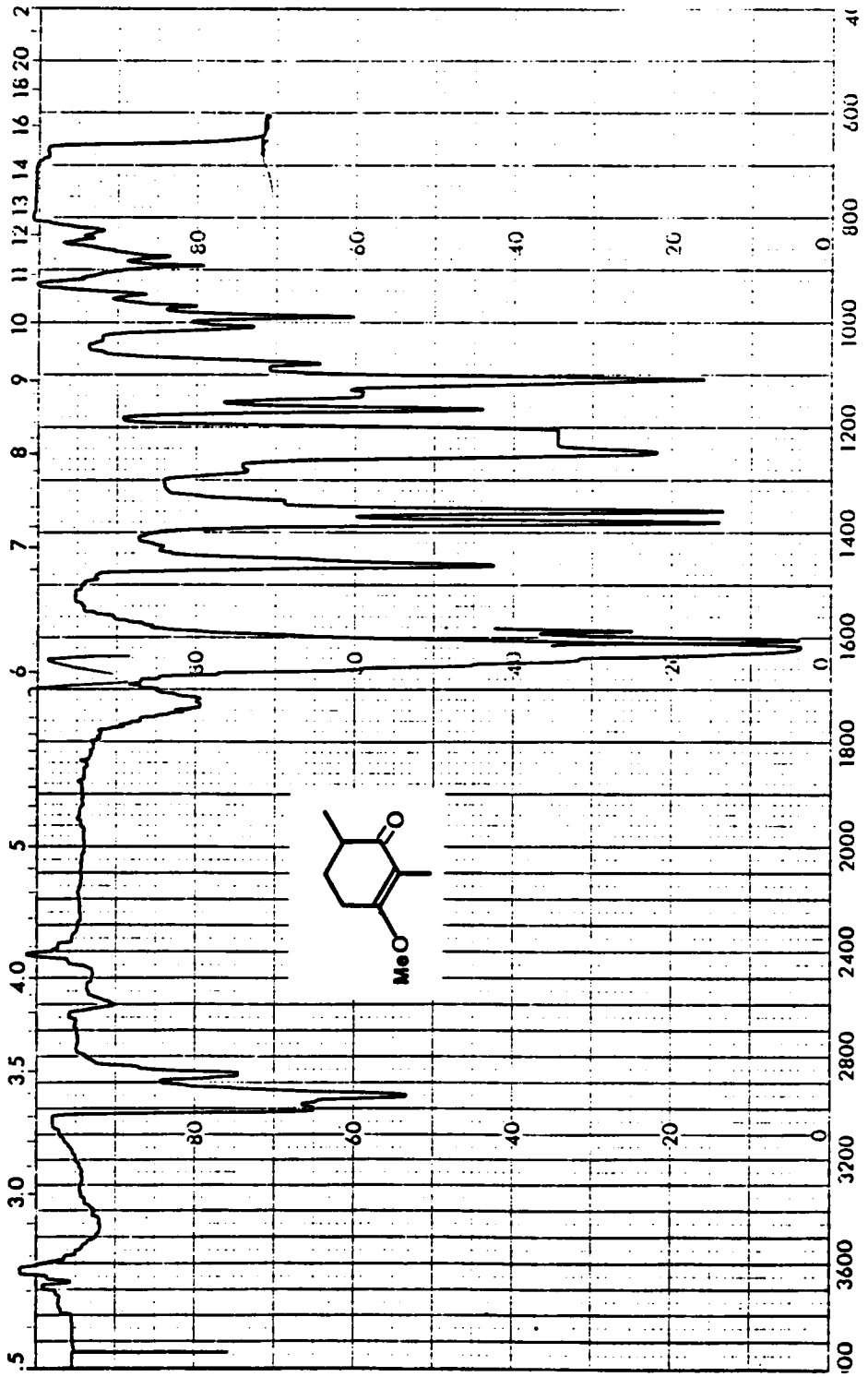


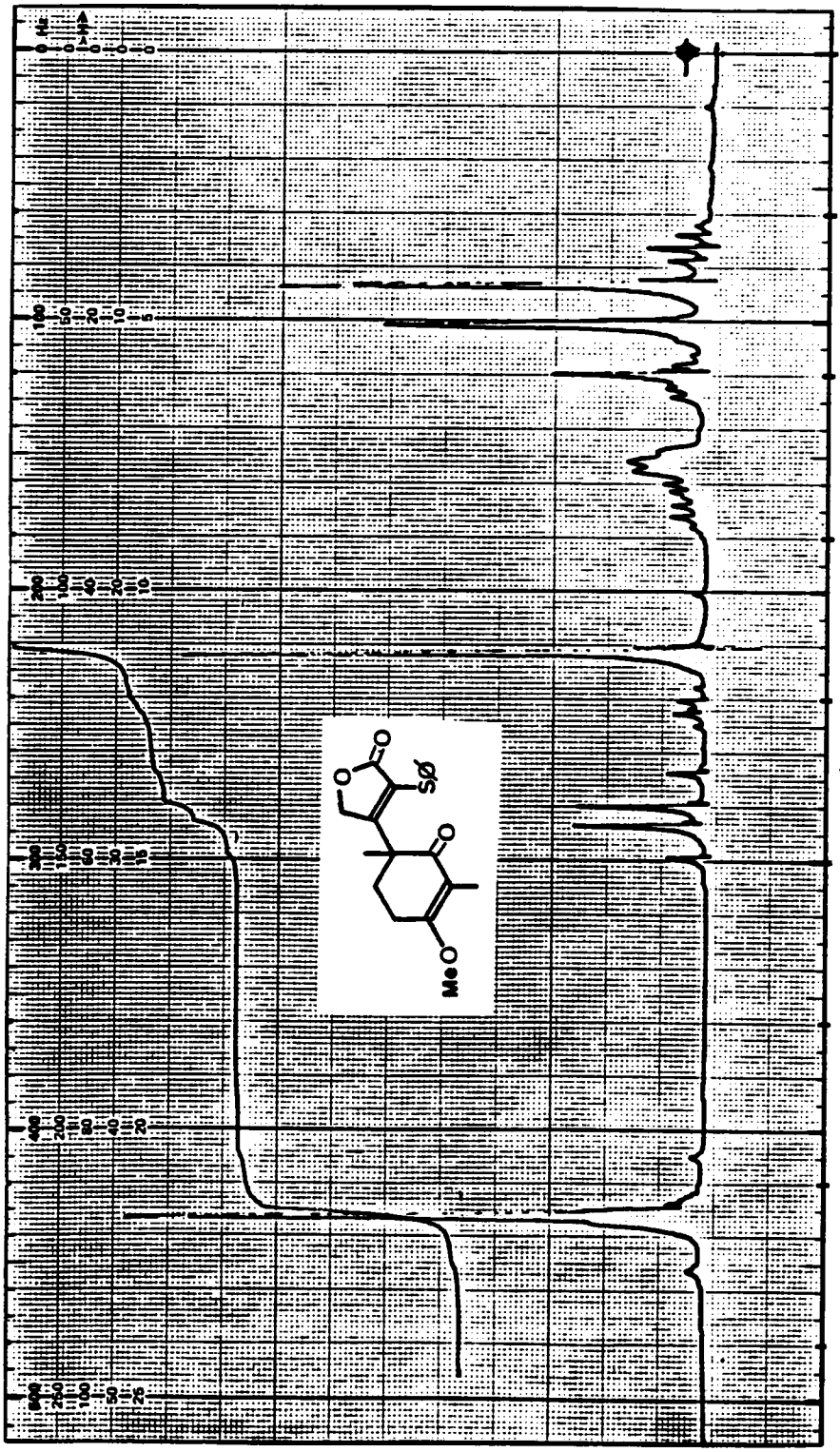
IR spectrum of butenolide 44



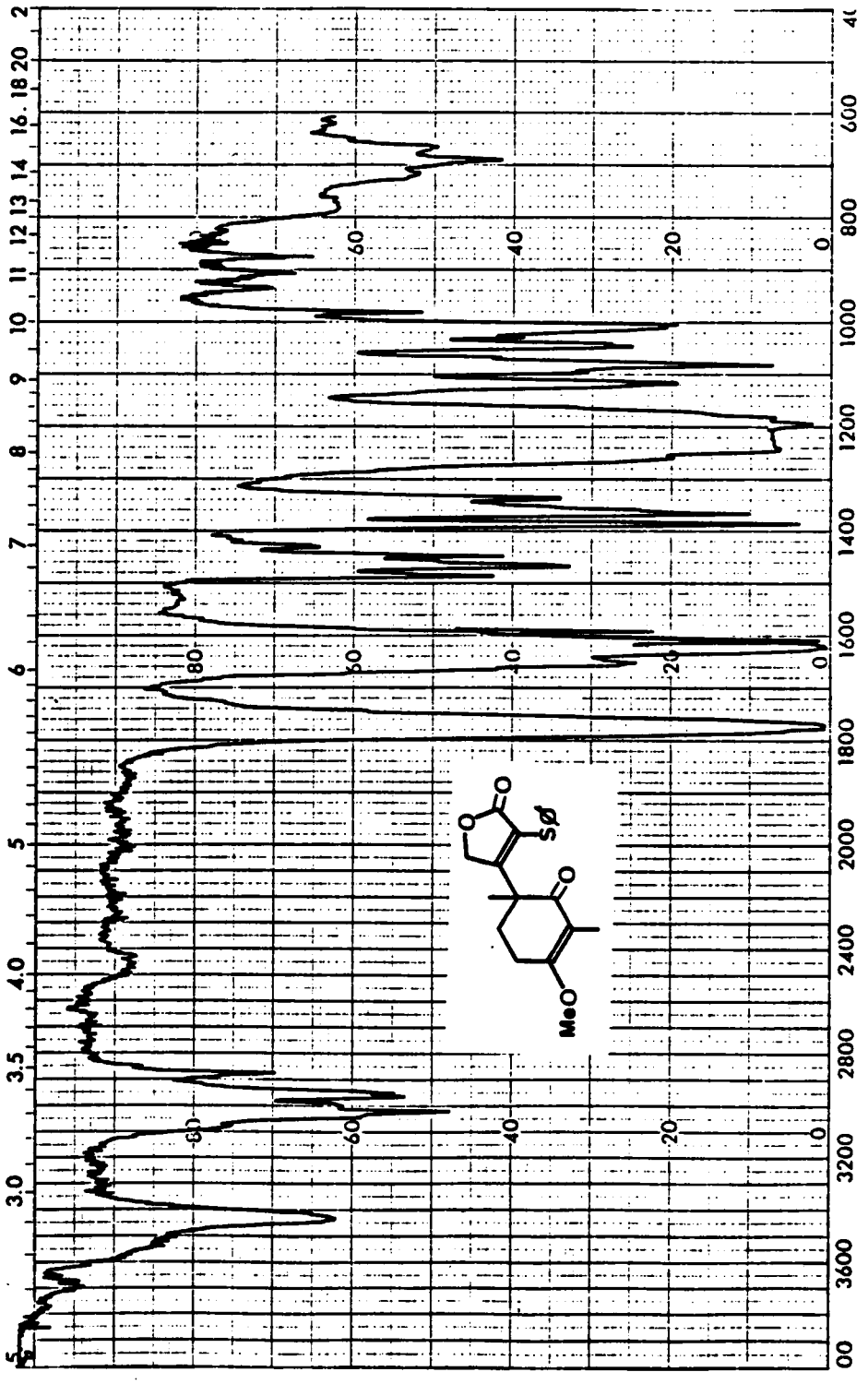
90 MHz ^{1}H NMR spectrum of enone 35



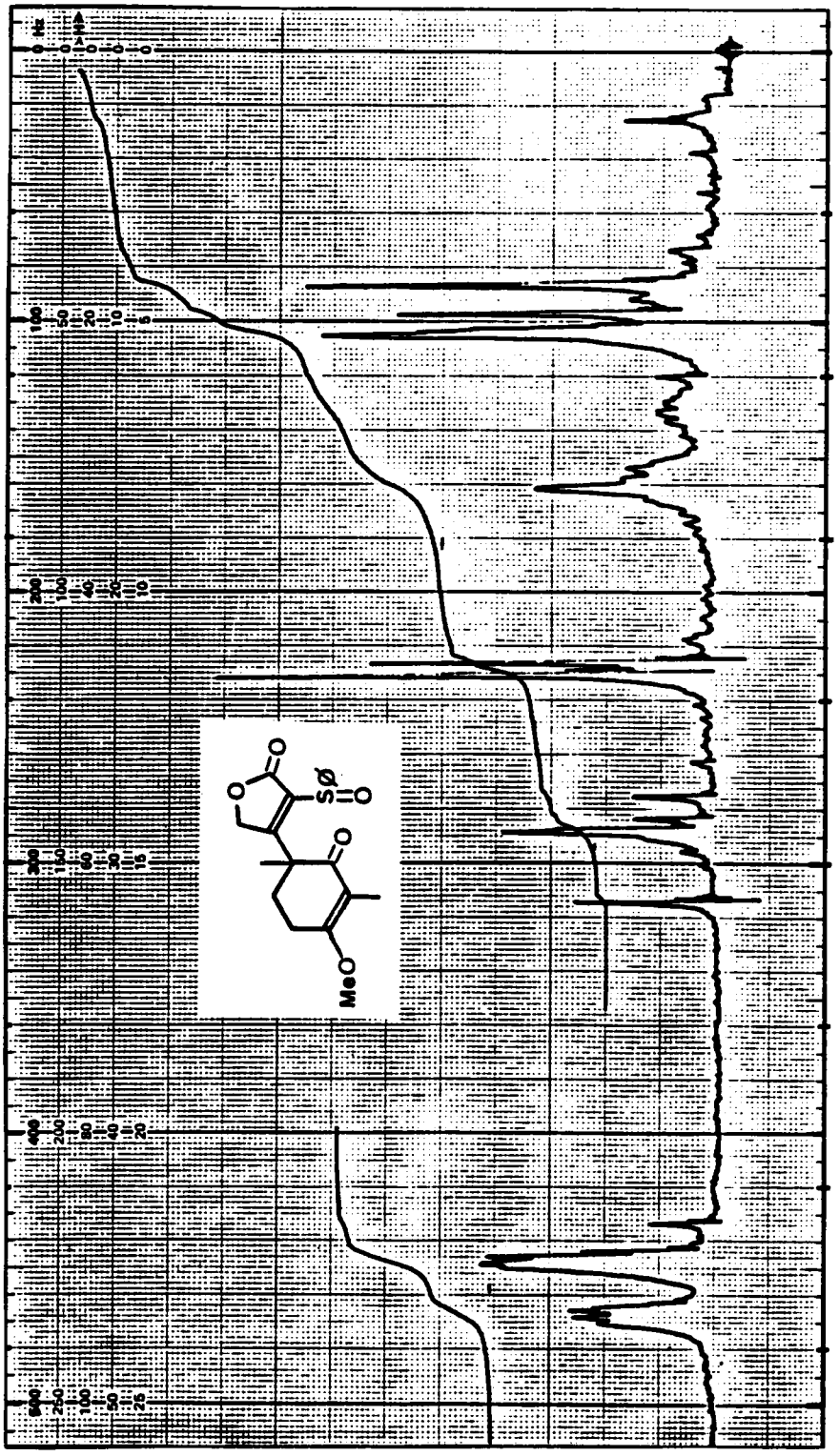
IR spectrum of enone 35



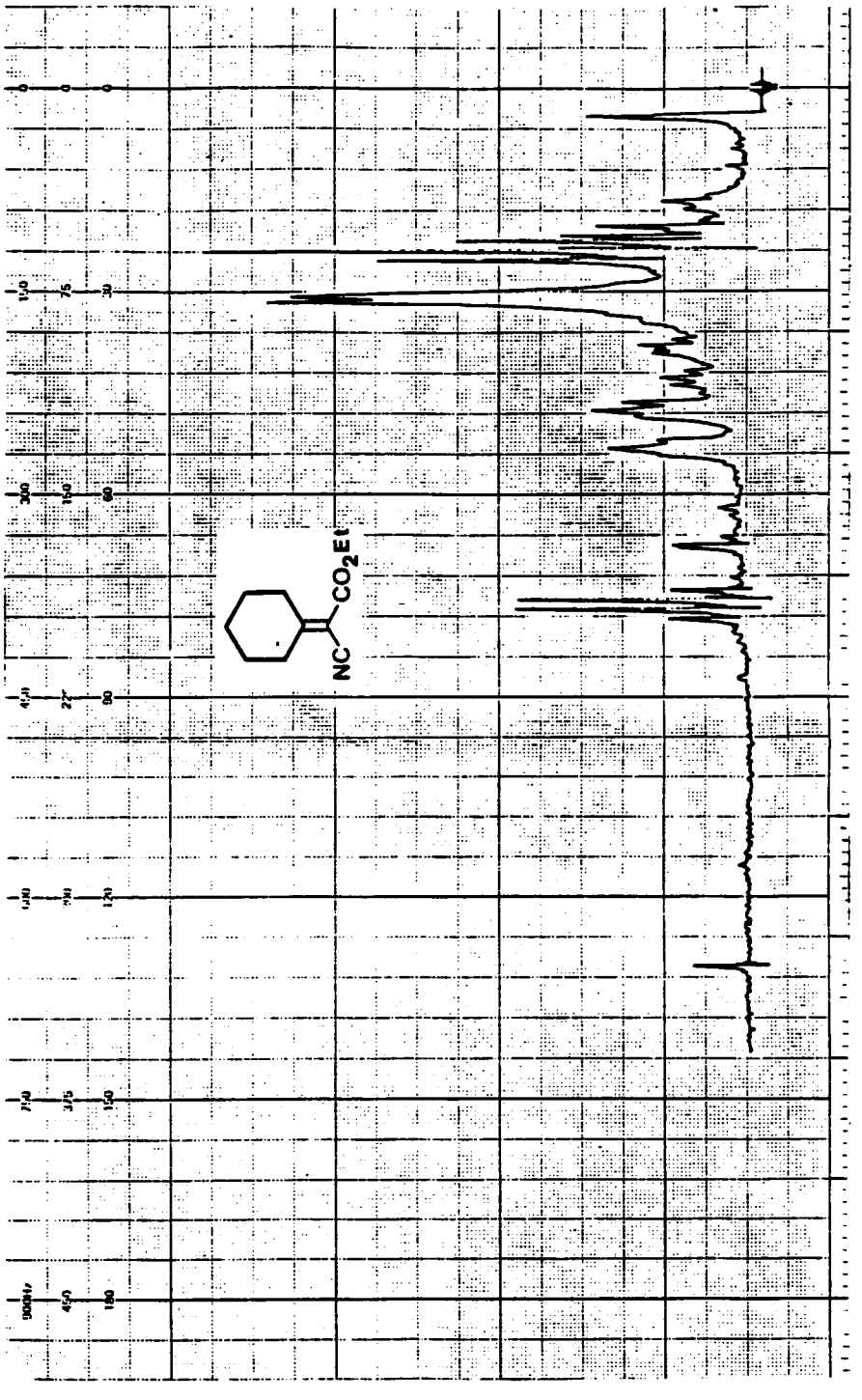
90 MHz ^{1}H NMR spectrum of Michael adduct 53



IR spectrum of Michael adduct 53



90 MHz ^{1}H NMR spectrum of sulfoxide 54



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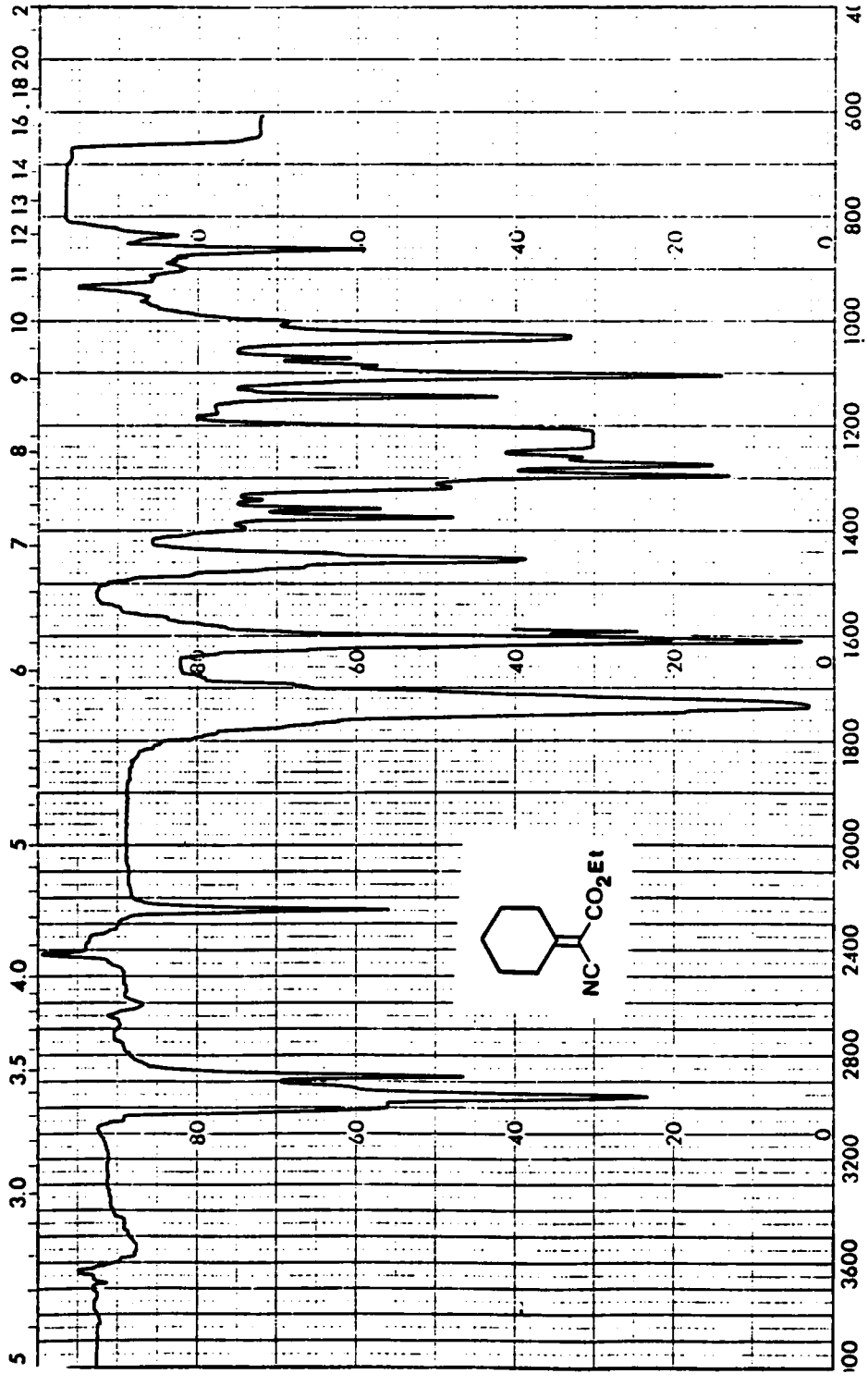

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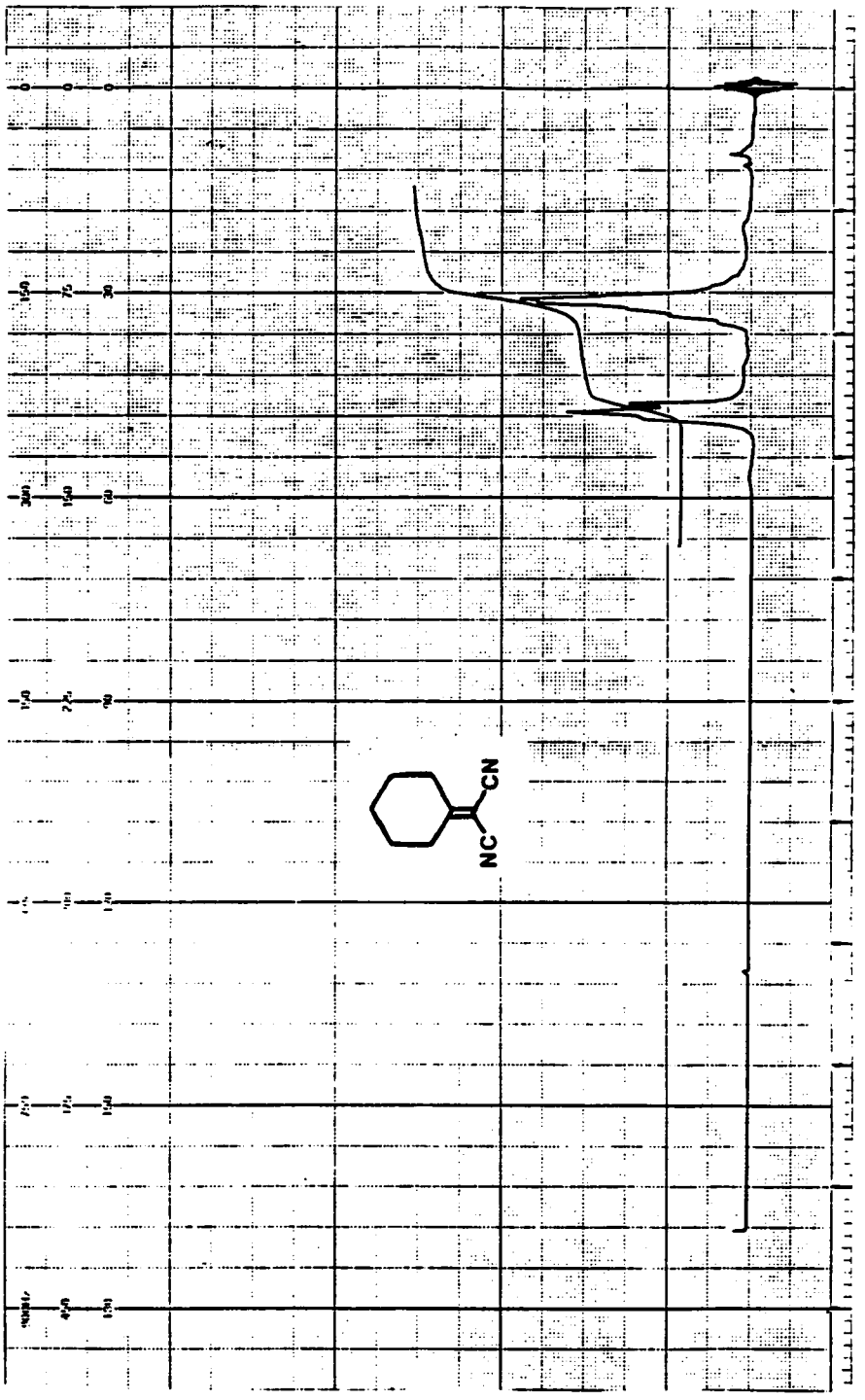

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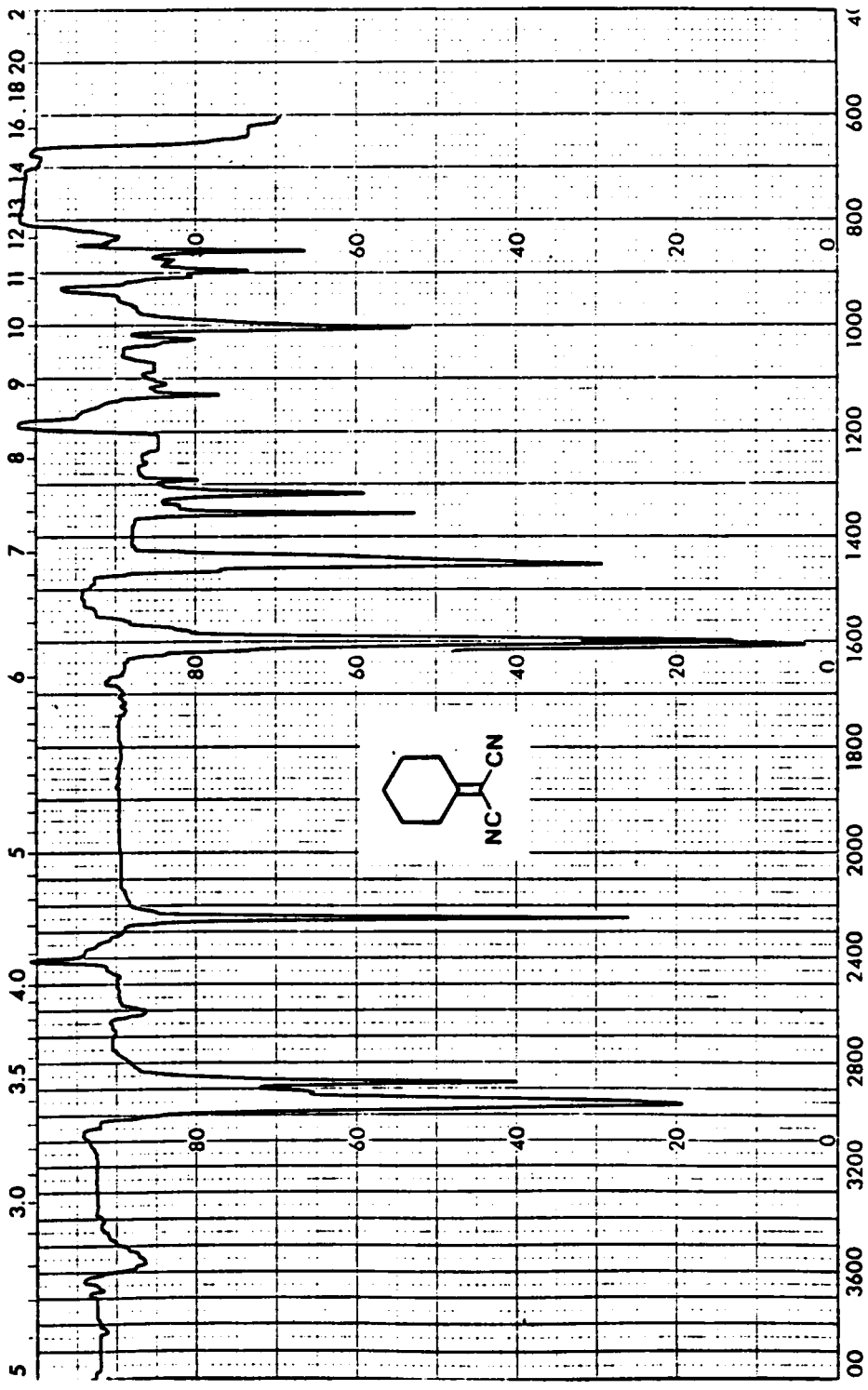

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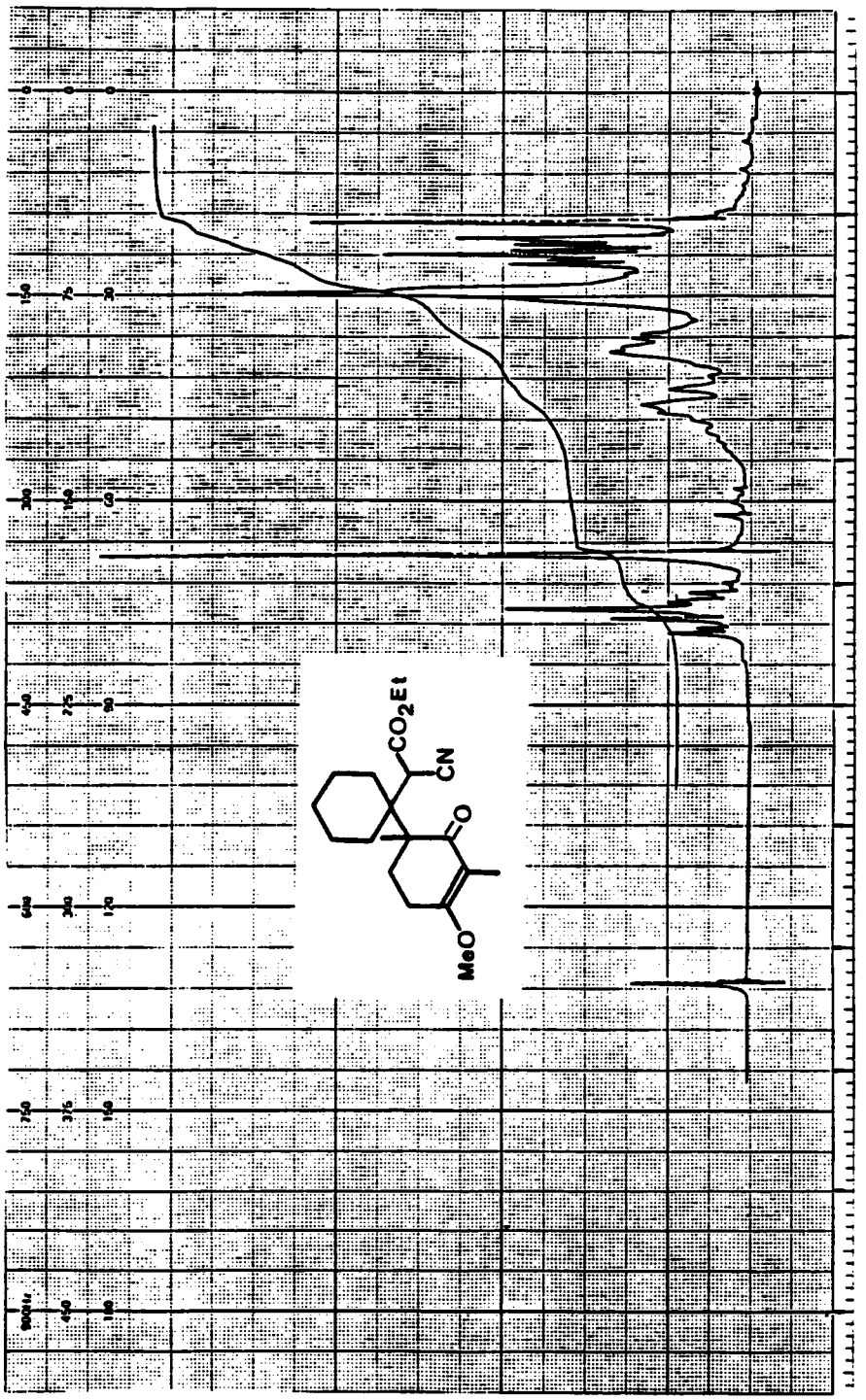

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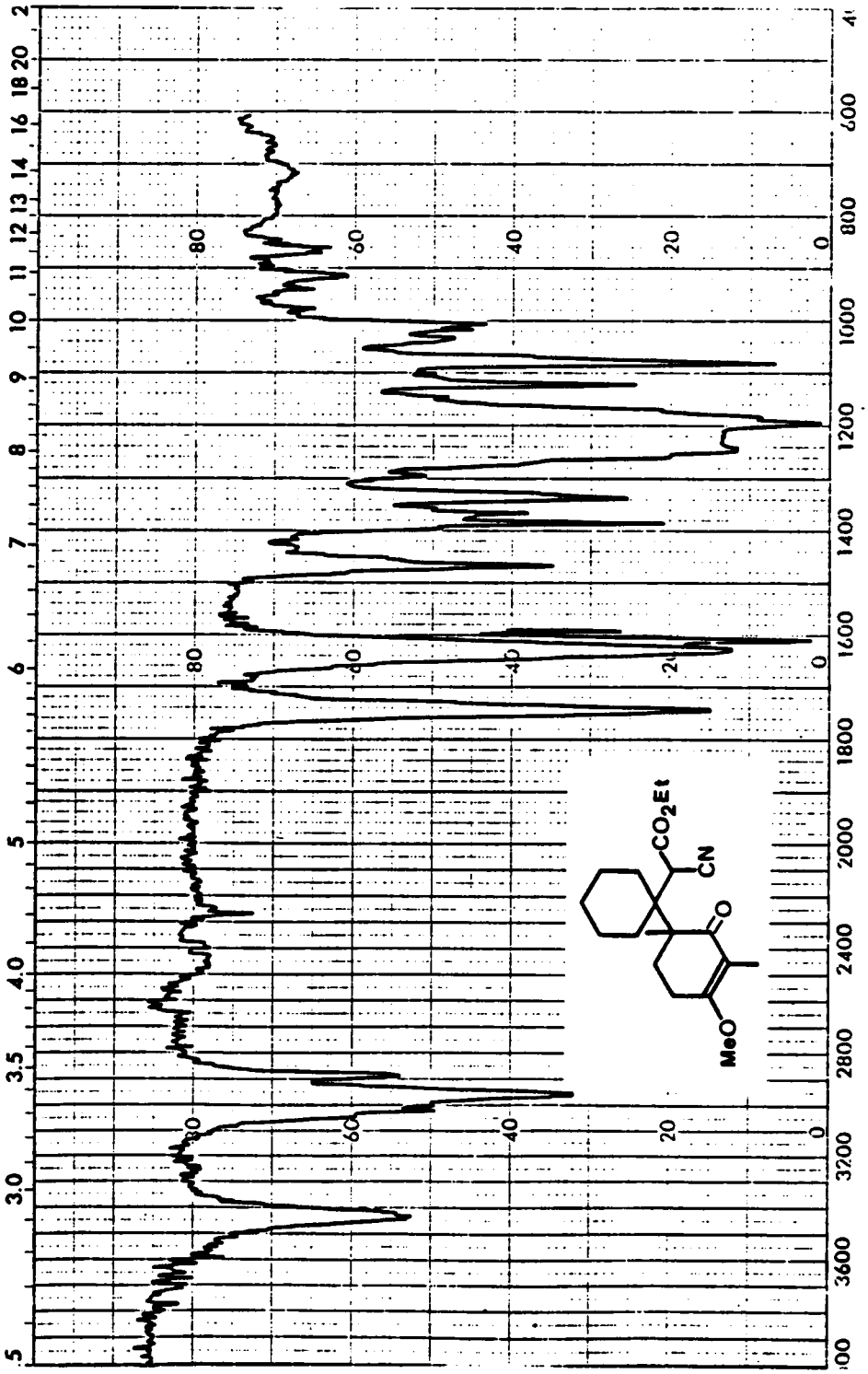
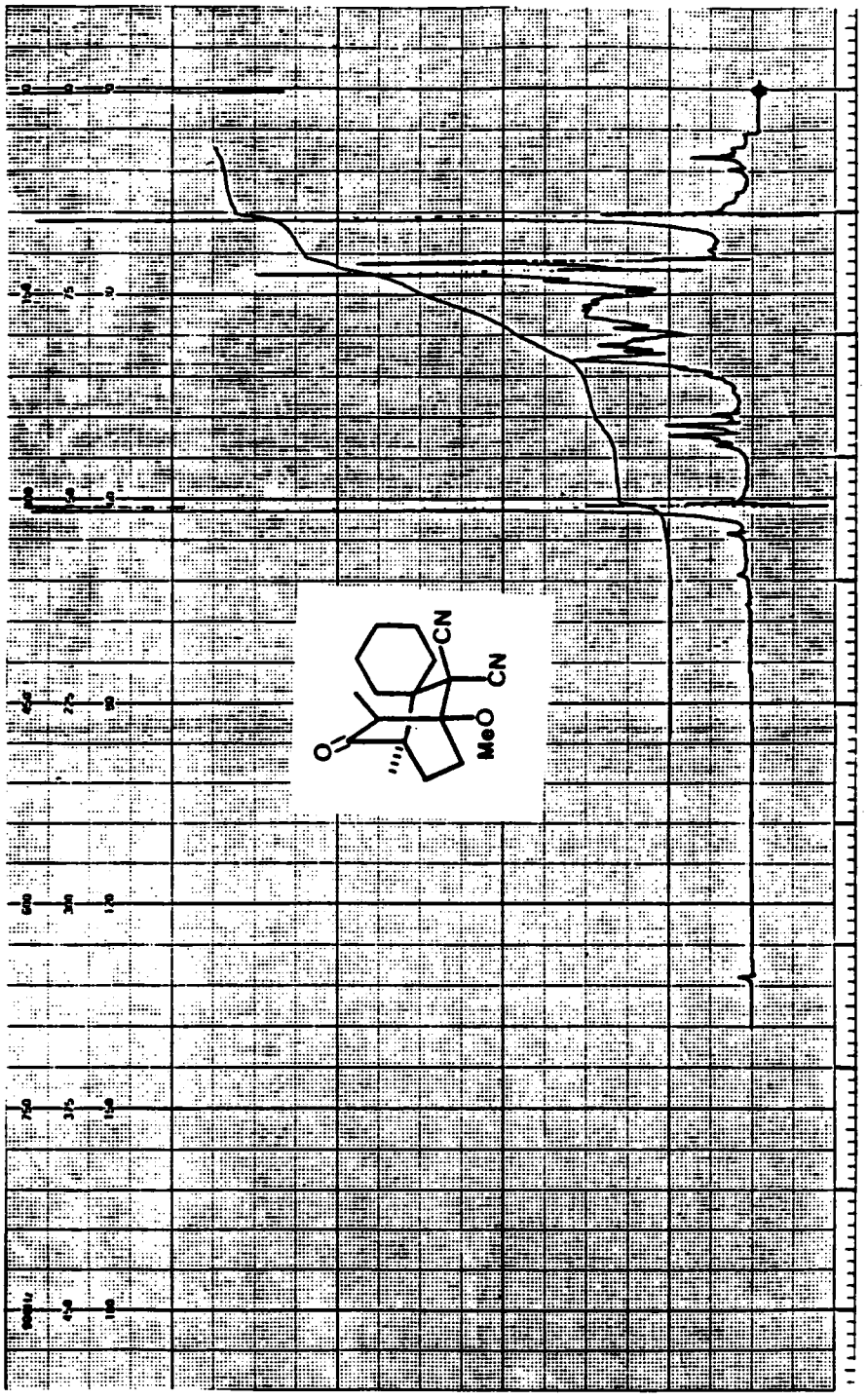


IR spectrum of Michael adduct 60



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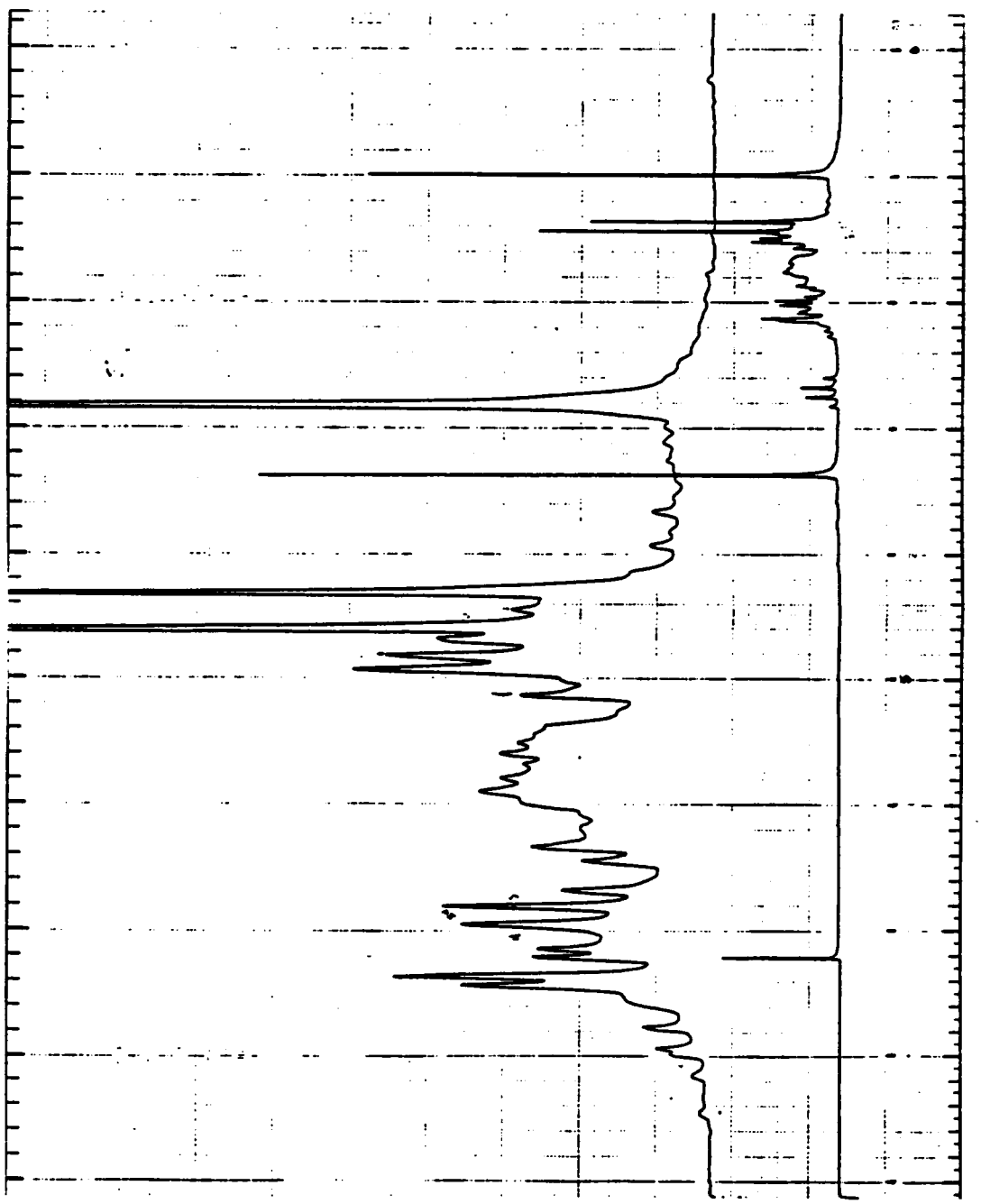

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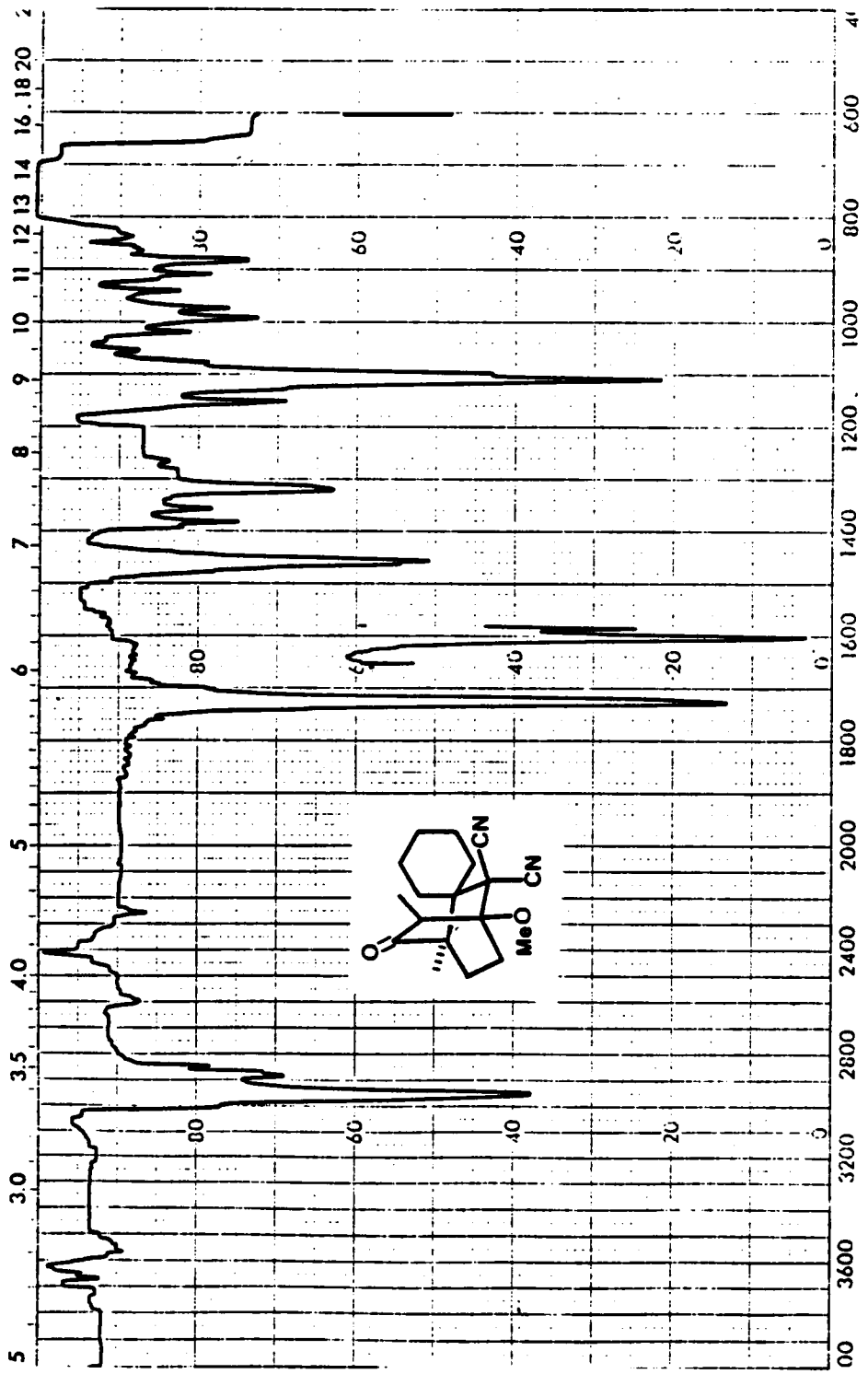

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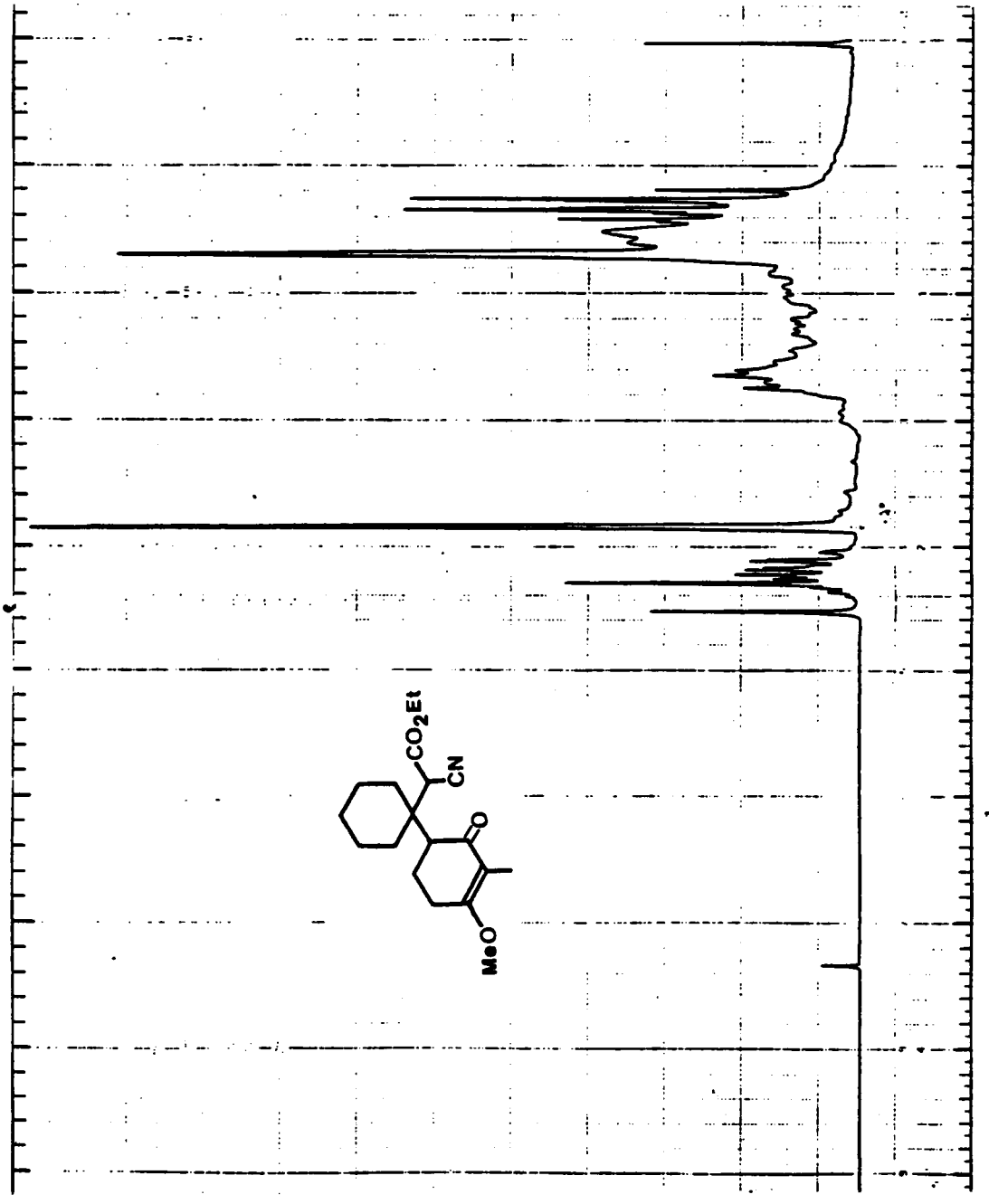
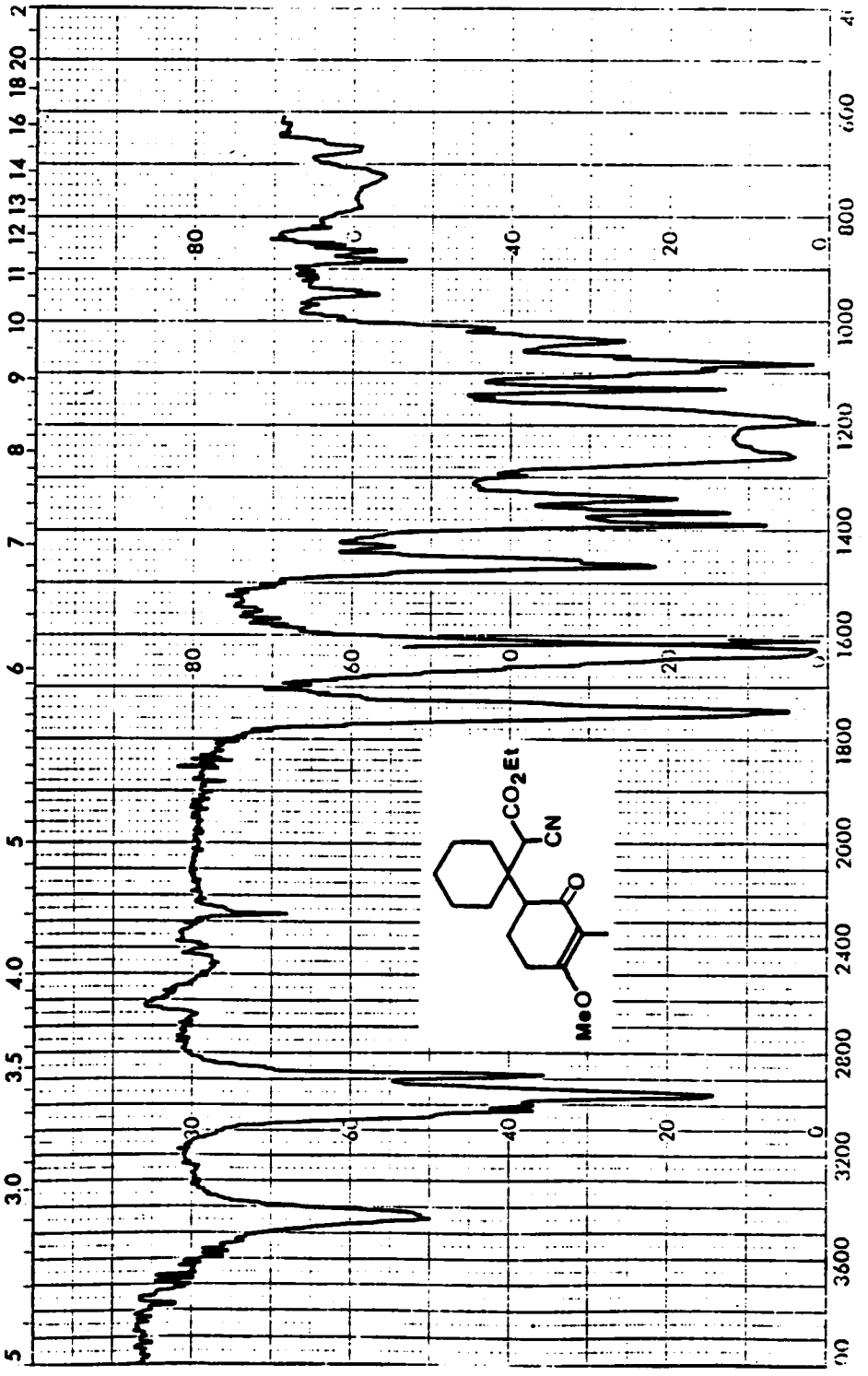
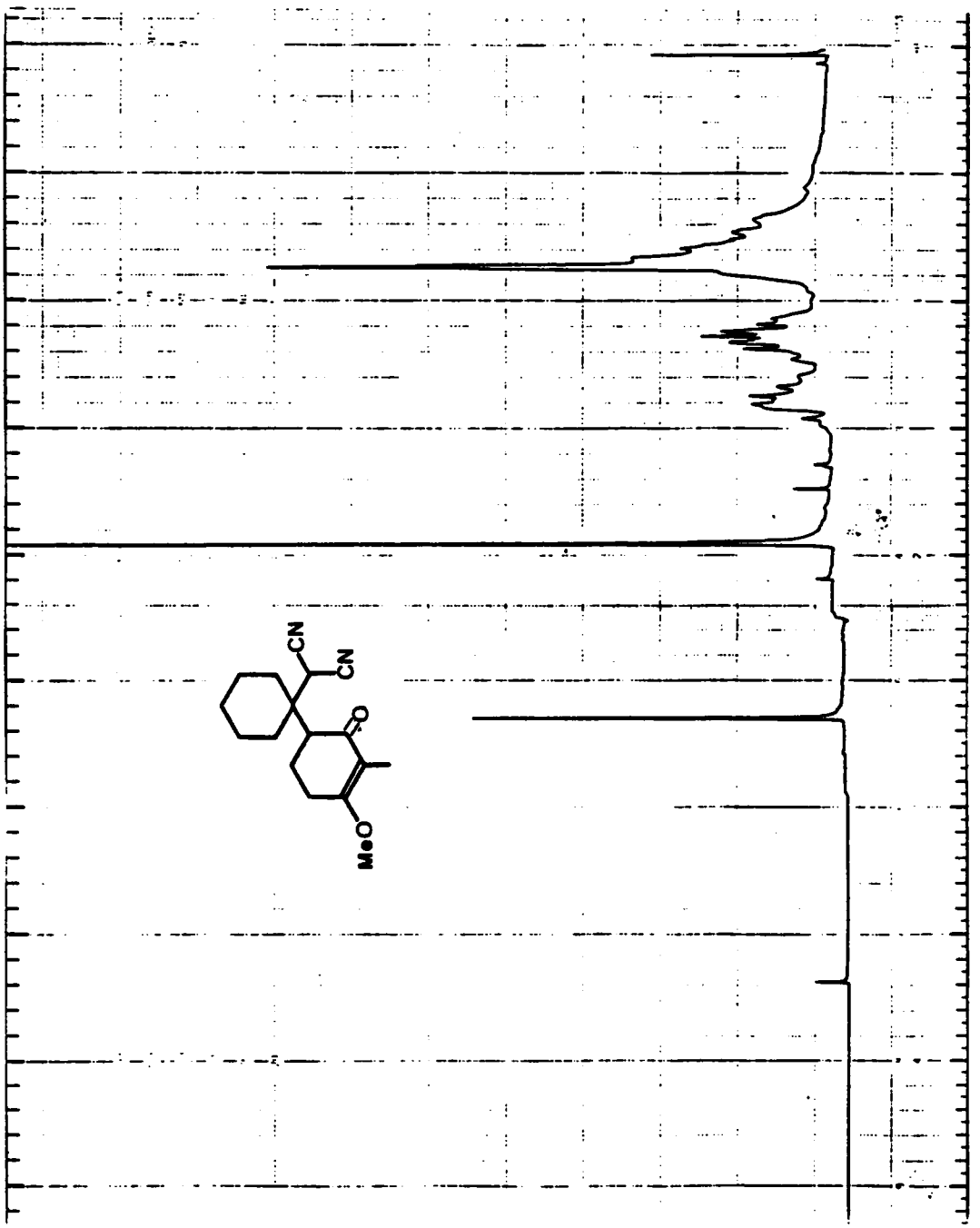


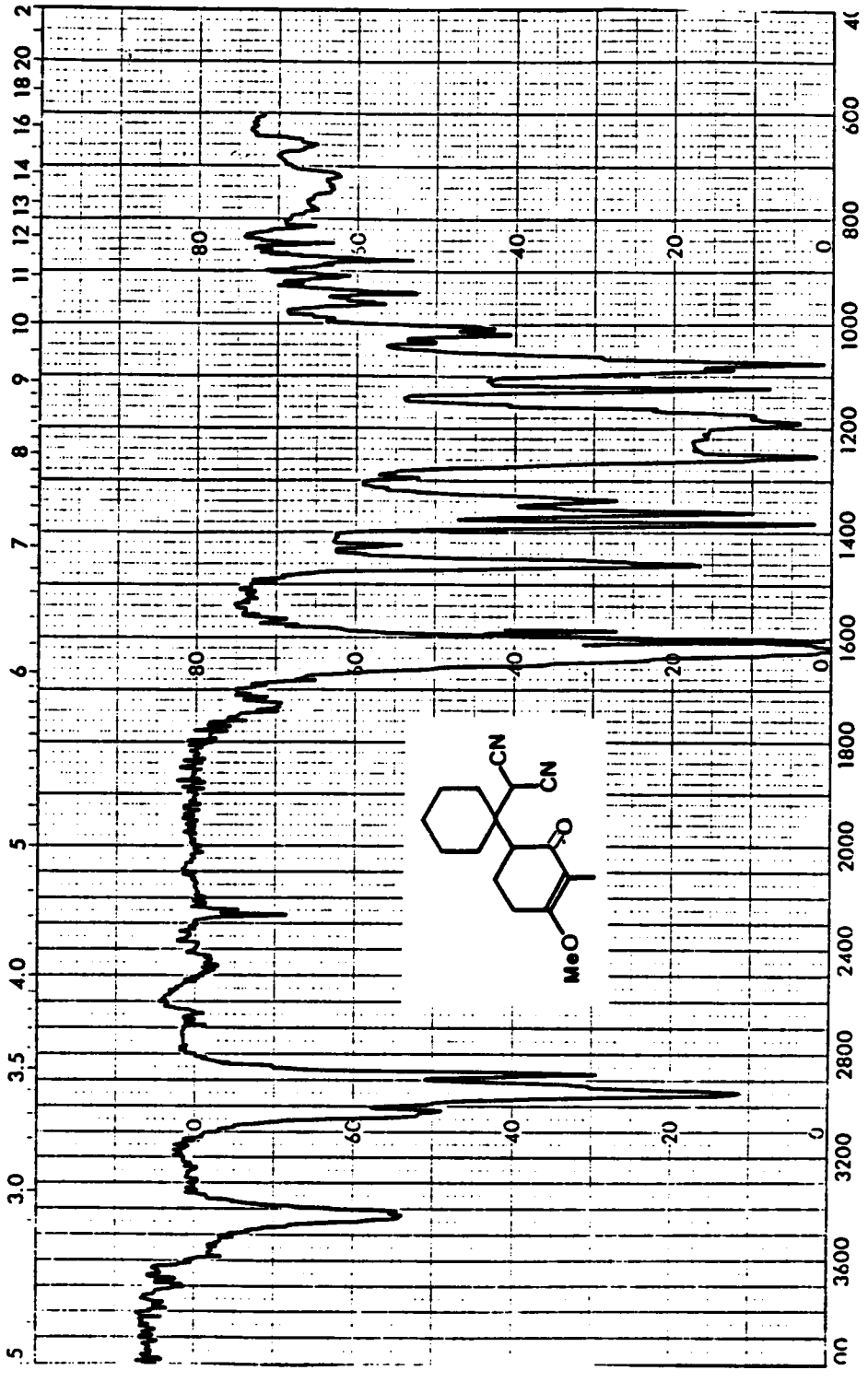
100 MHz ^{1}H NMR spectrum of Michael adduct 62



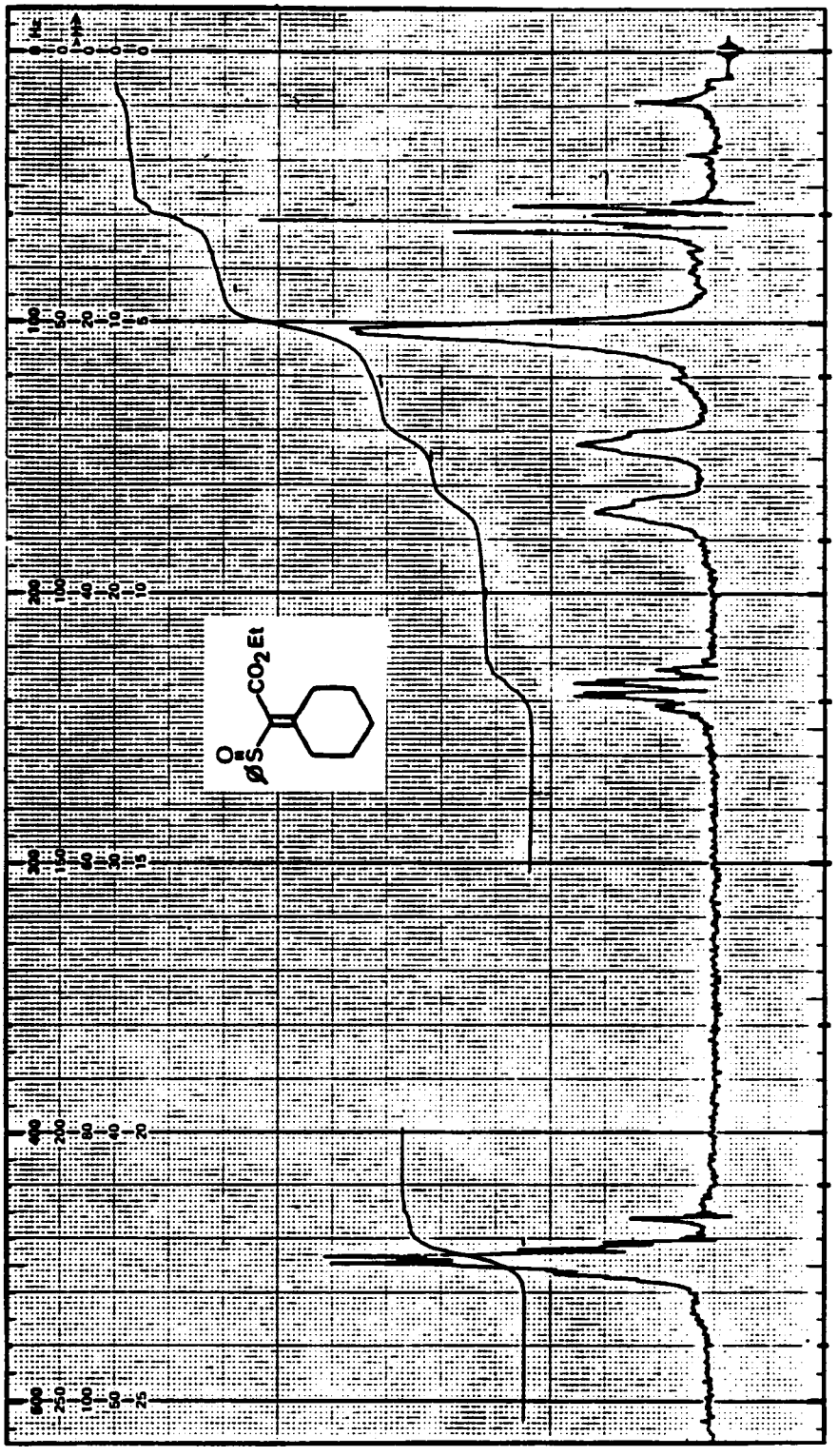
IR spectrum of Michael adduct 62



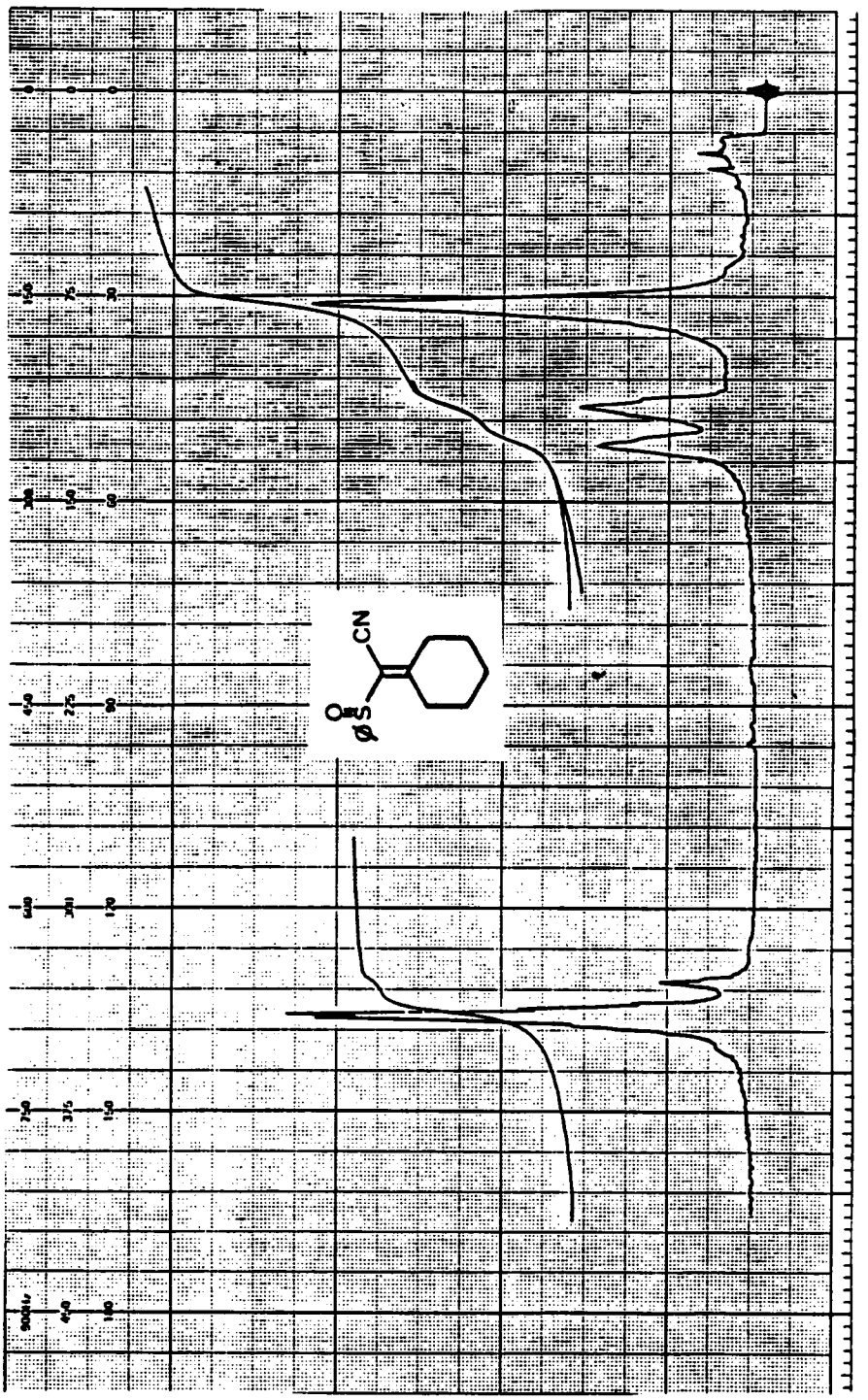
100 MHz ^{1}H NMR spectrum of Michael adduct 63



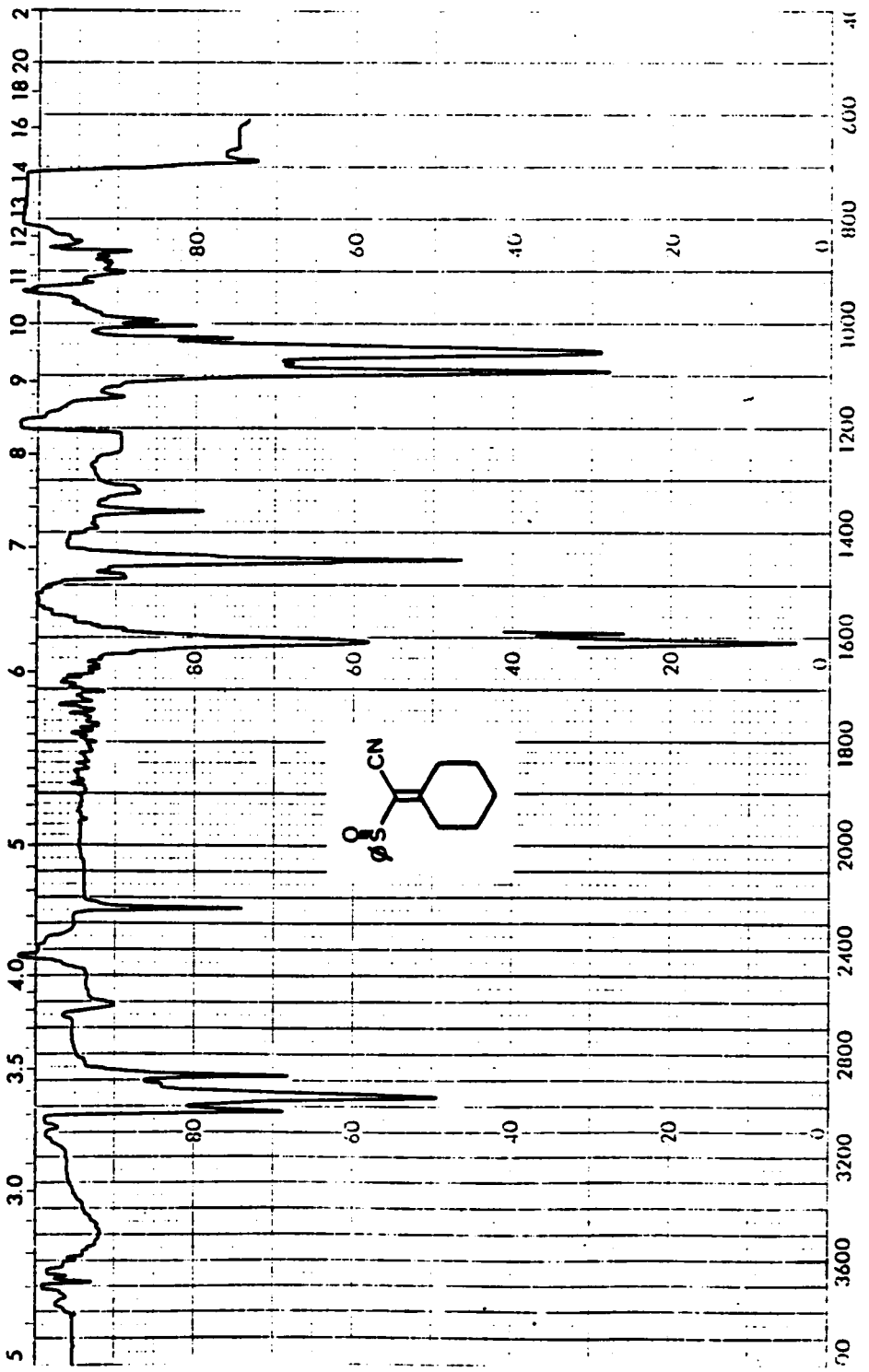
IR spectrum of Michael adduct 63



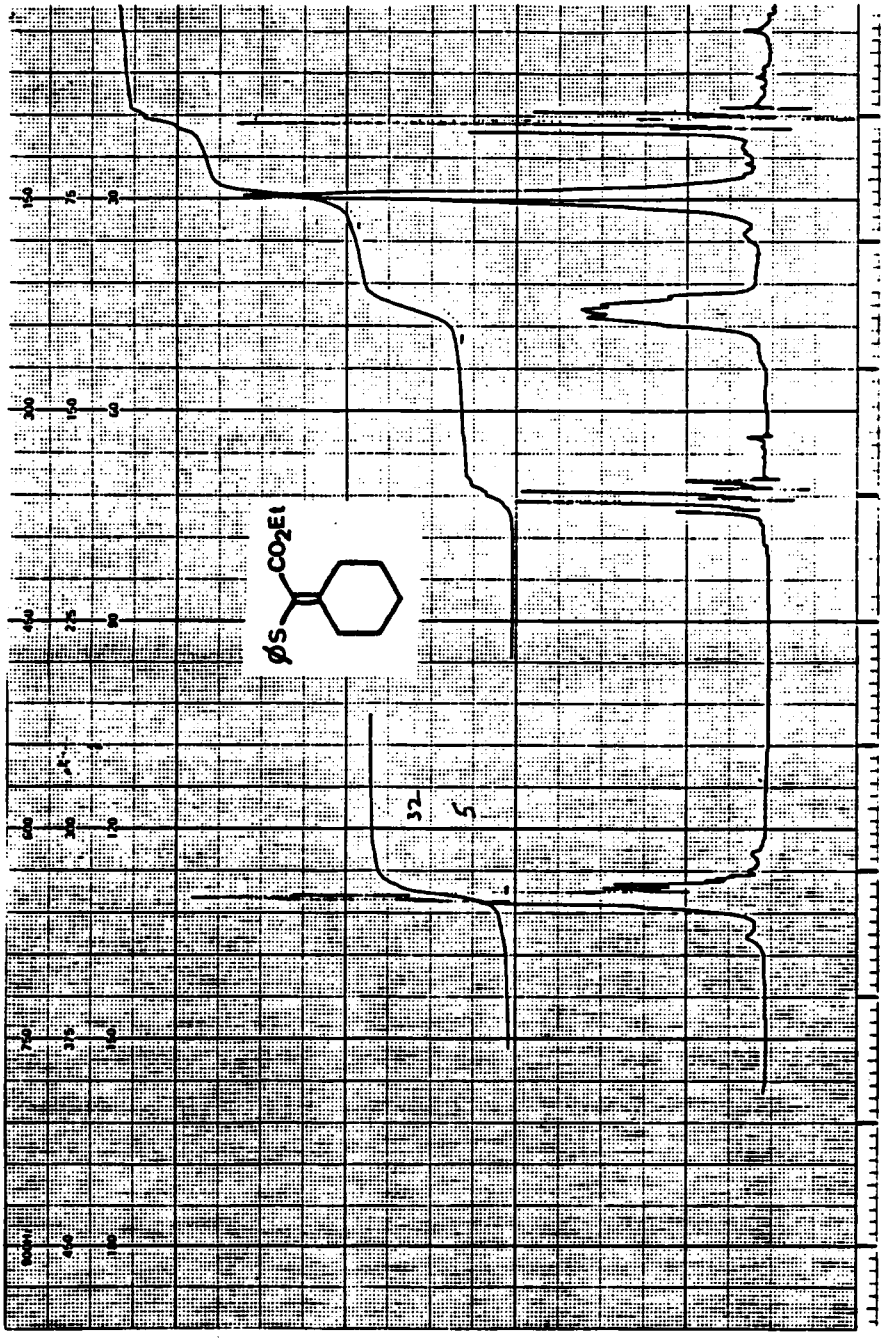
90 MHz ^{1}H NMR spectrum of sulfoxide 64



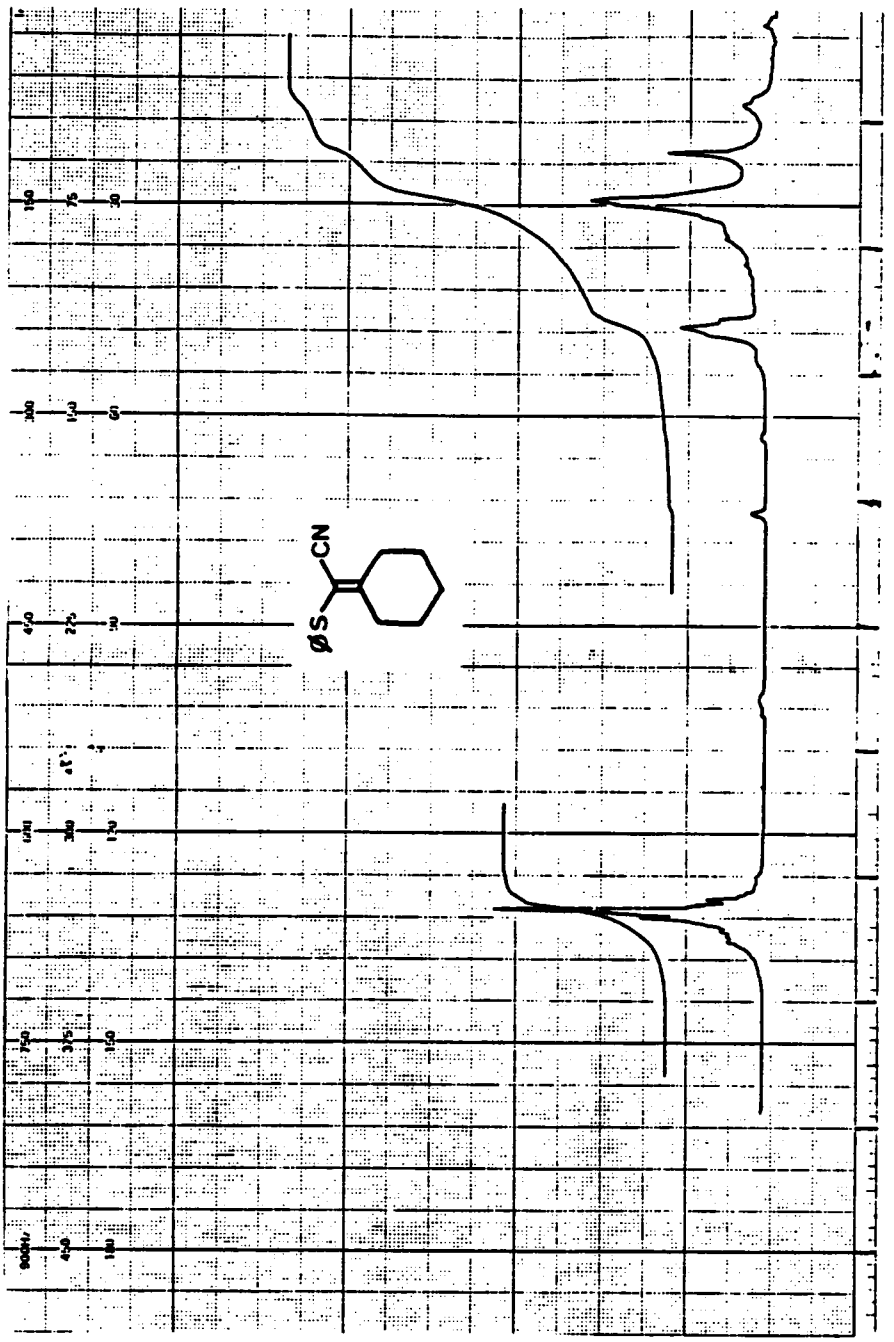
90 MHz ^{1}H NMR spectrum of sulfoxide 65



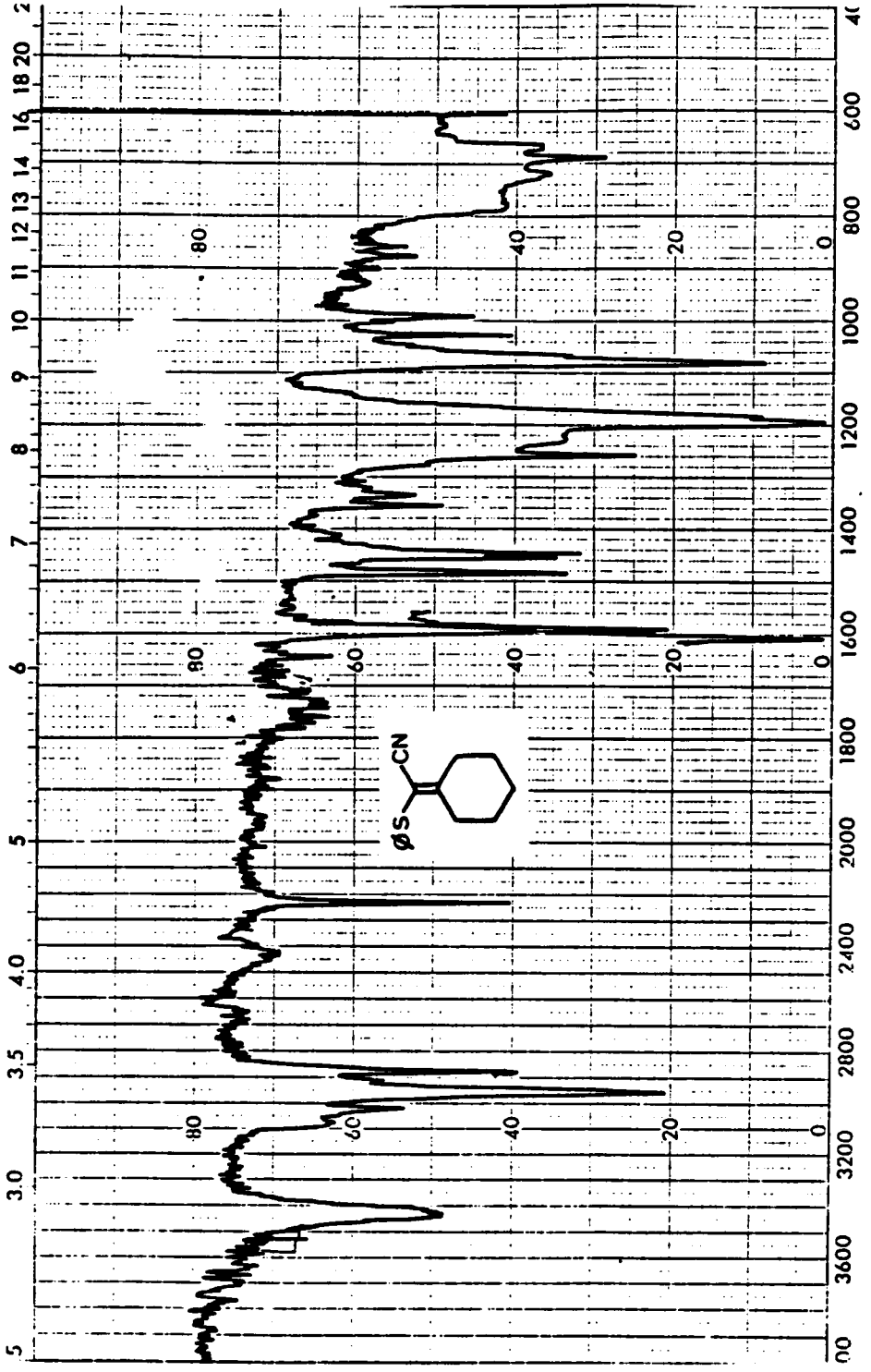
IR spectrum of sulfoxide 65



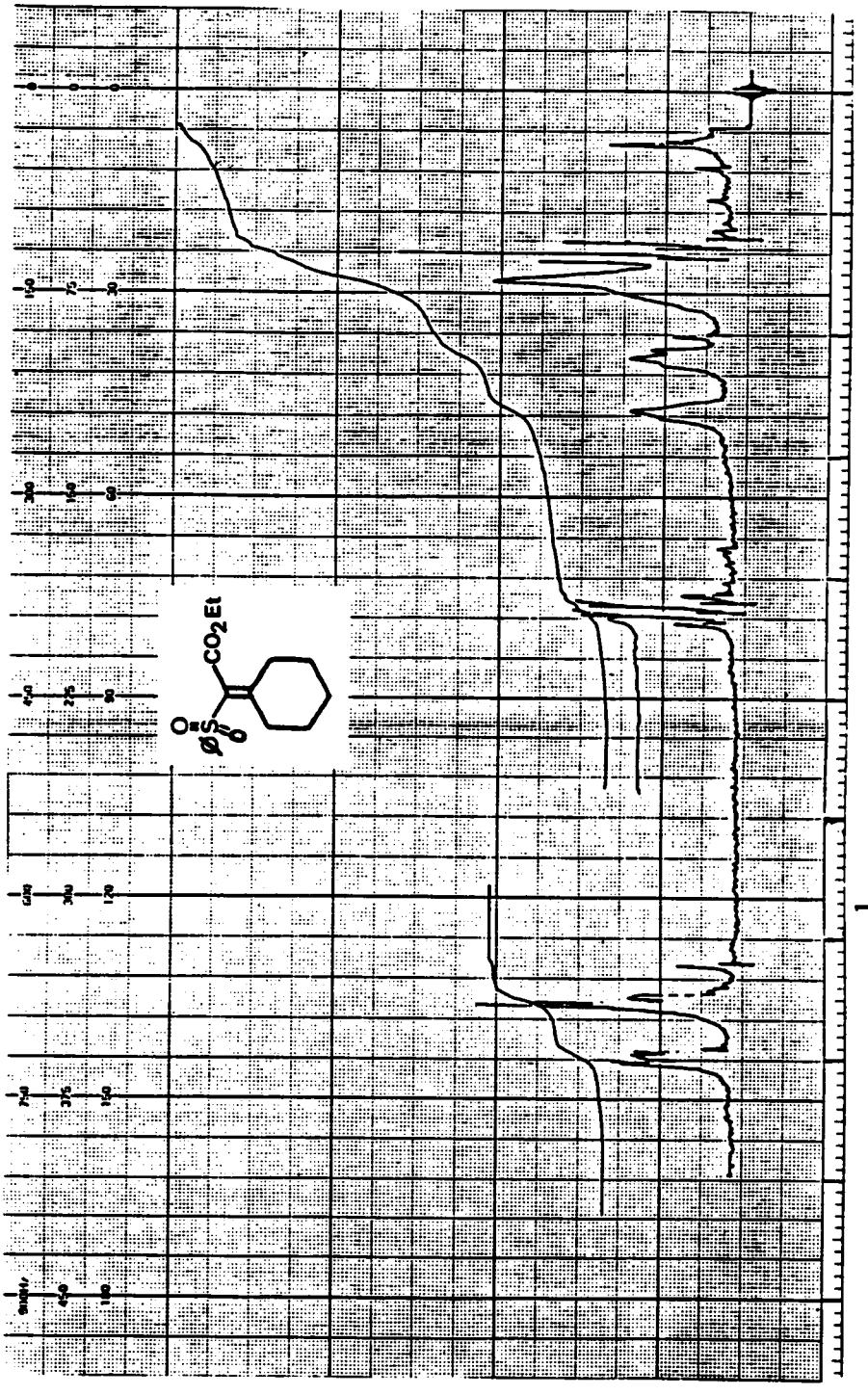
90 MHz ^{1}H NMR spectrum of sulfide 68



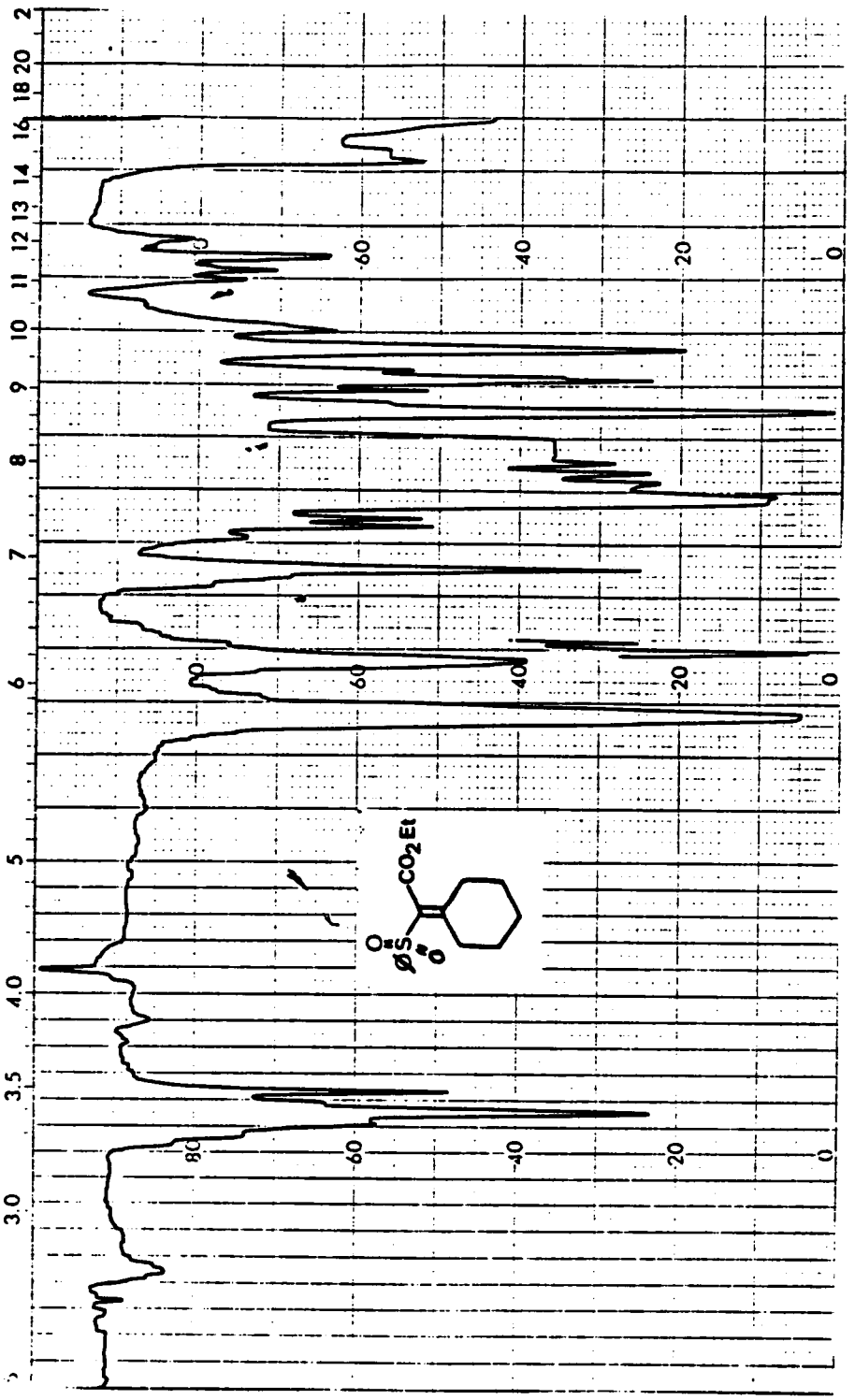
90 MHz ^{1}H NMR spectrum of sulfide 69



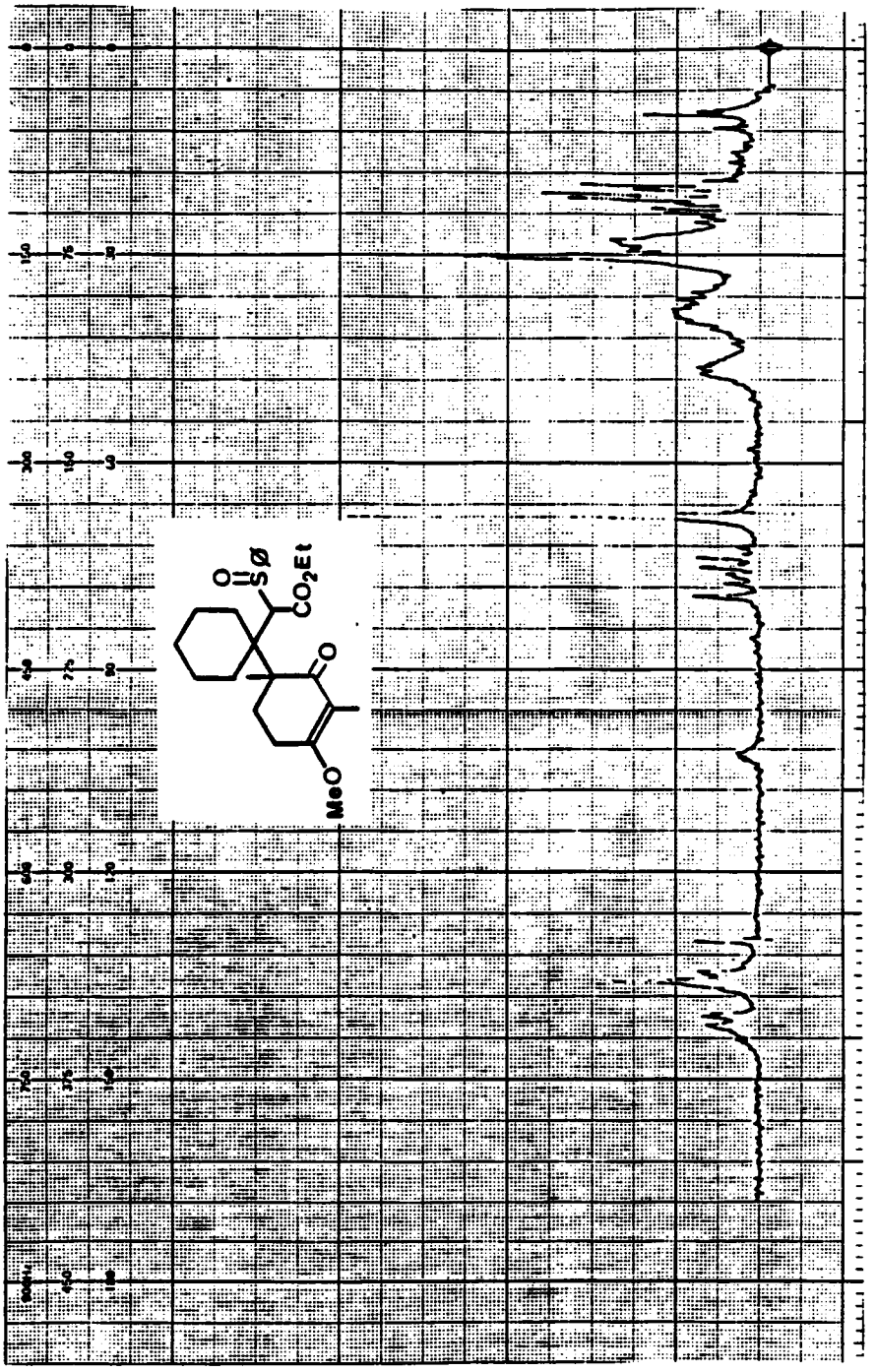
IR spectrum of sulfide 69



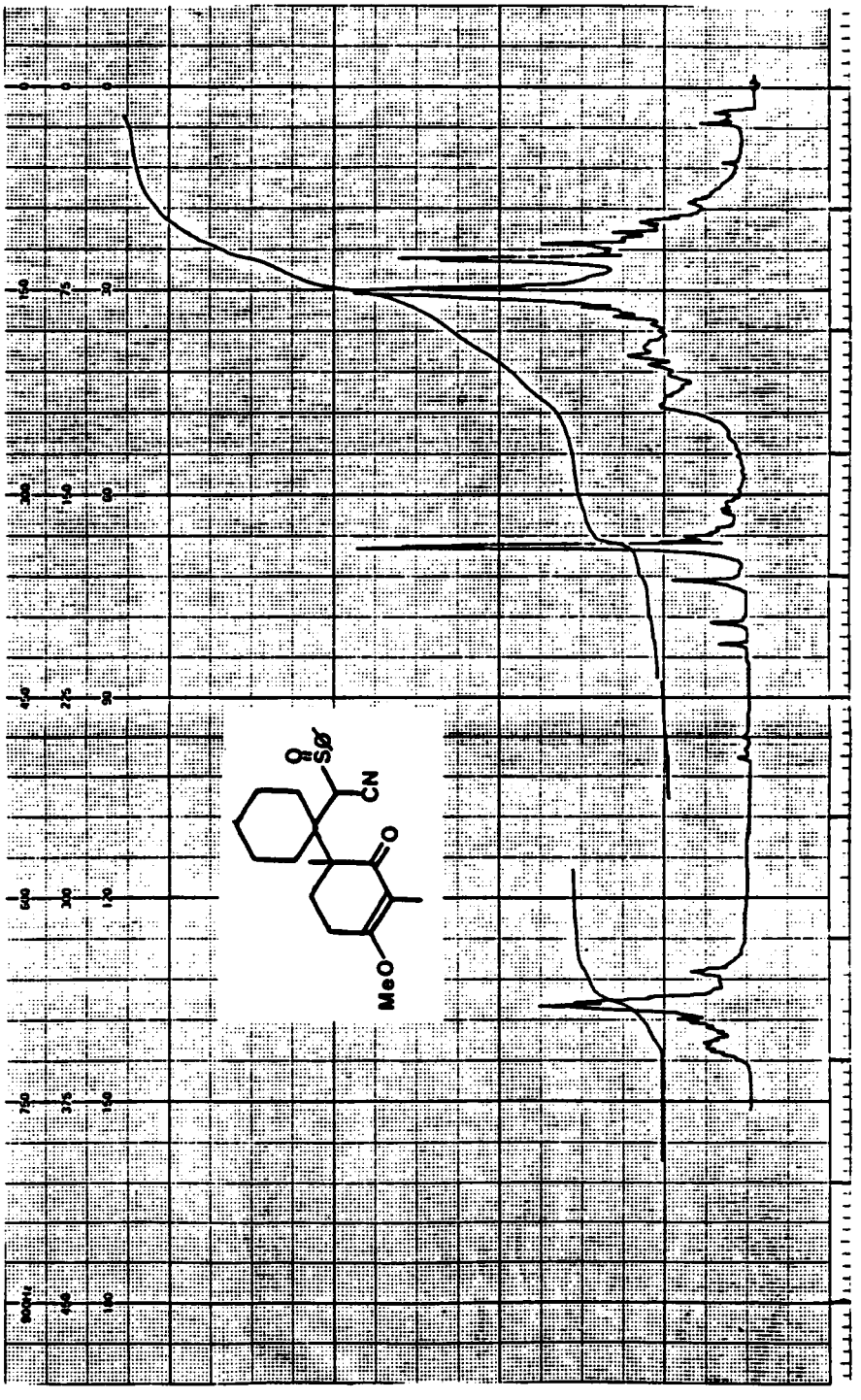
90 MHz ^{1}H NMR spectrum of sulfone 70



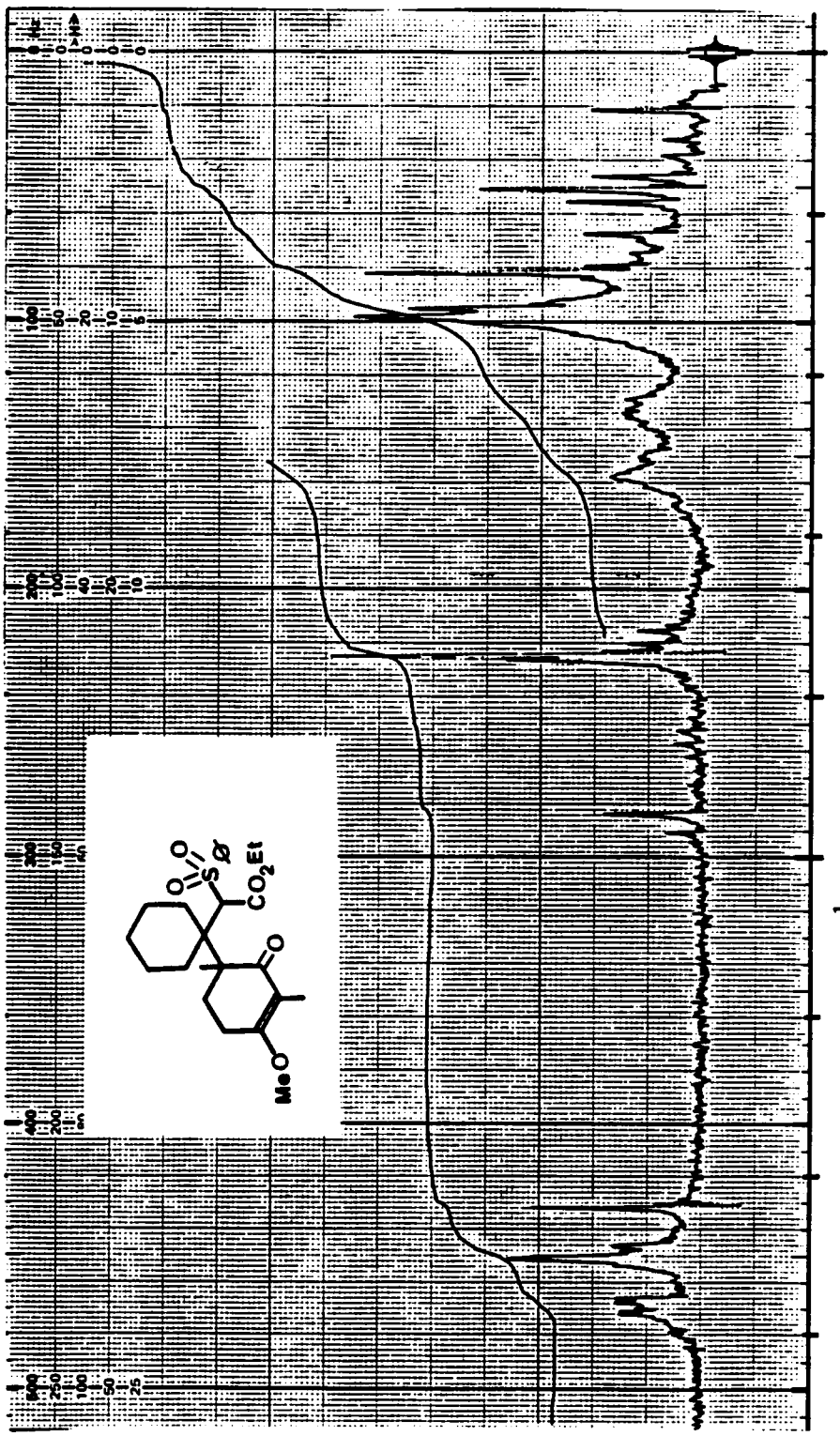
IR spectrum of sulfone 70



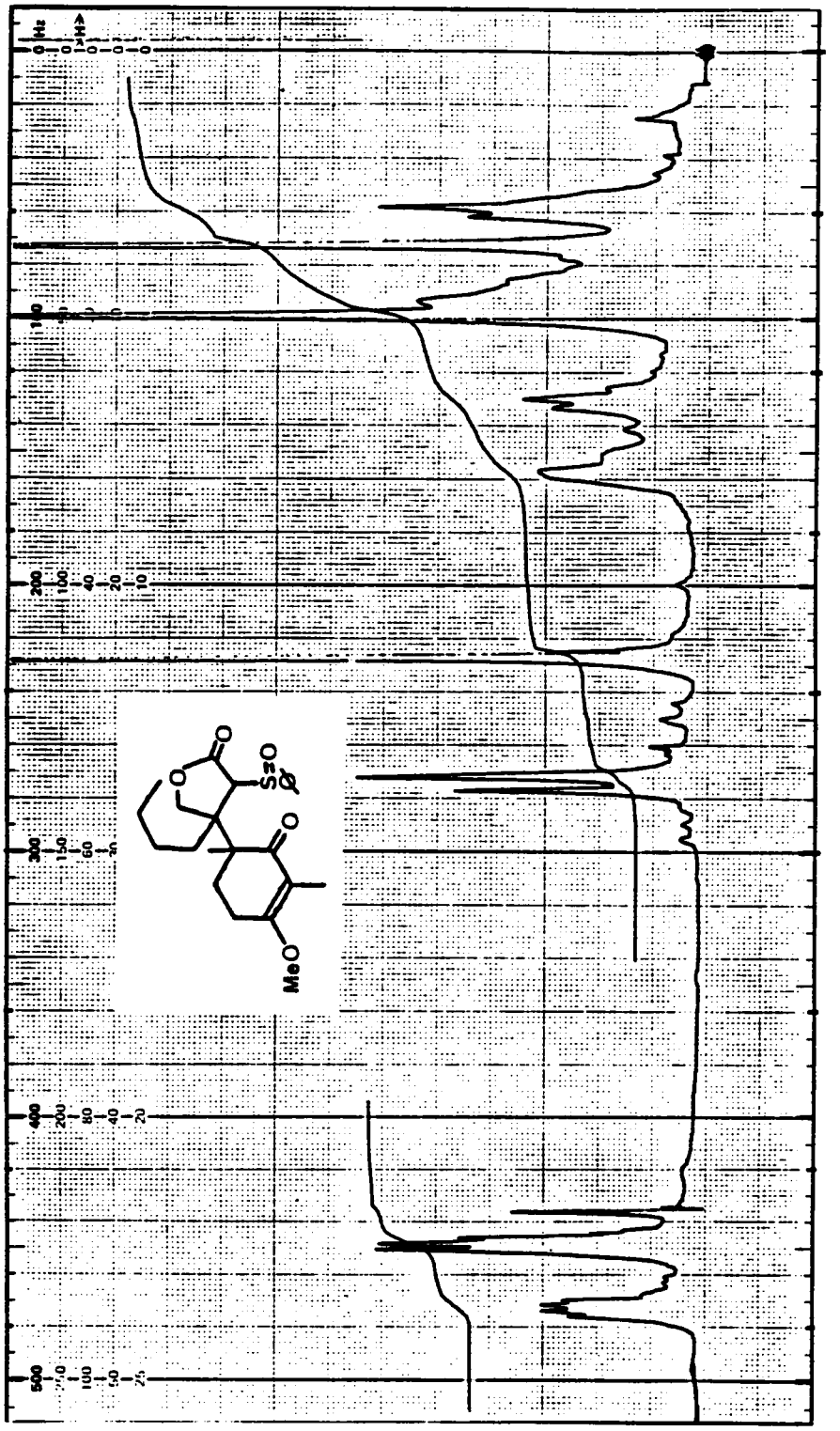
90 MHz ^{1}H NMR spectrum of Michael adduct 71



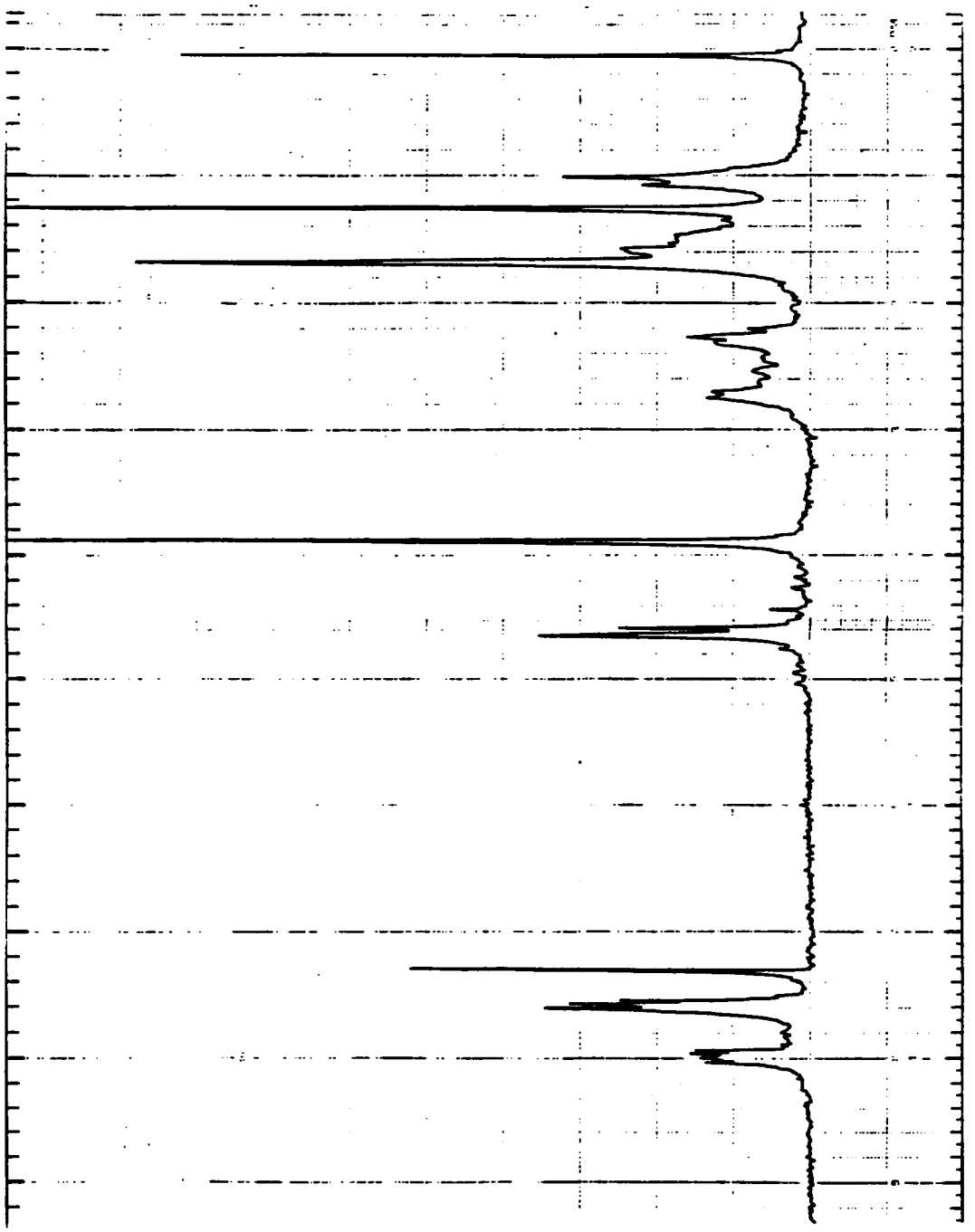
90 MHz ^{1}H NMR spectrum of Michael adduct 72



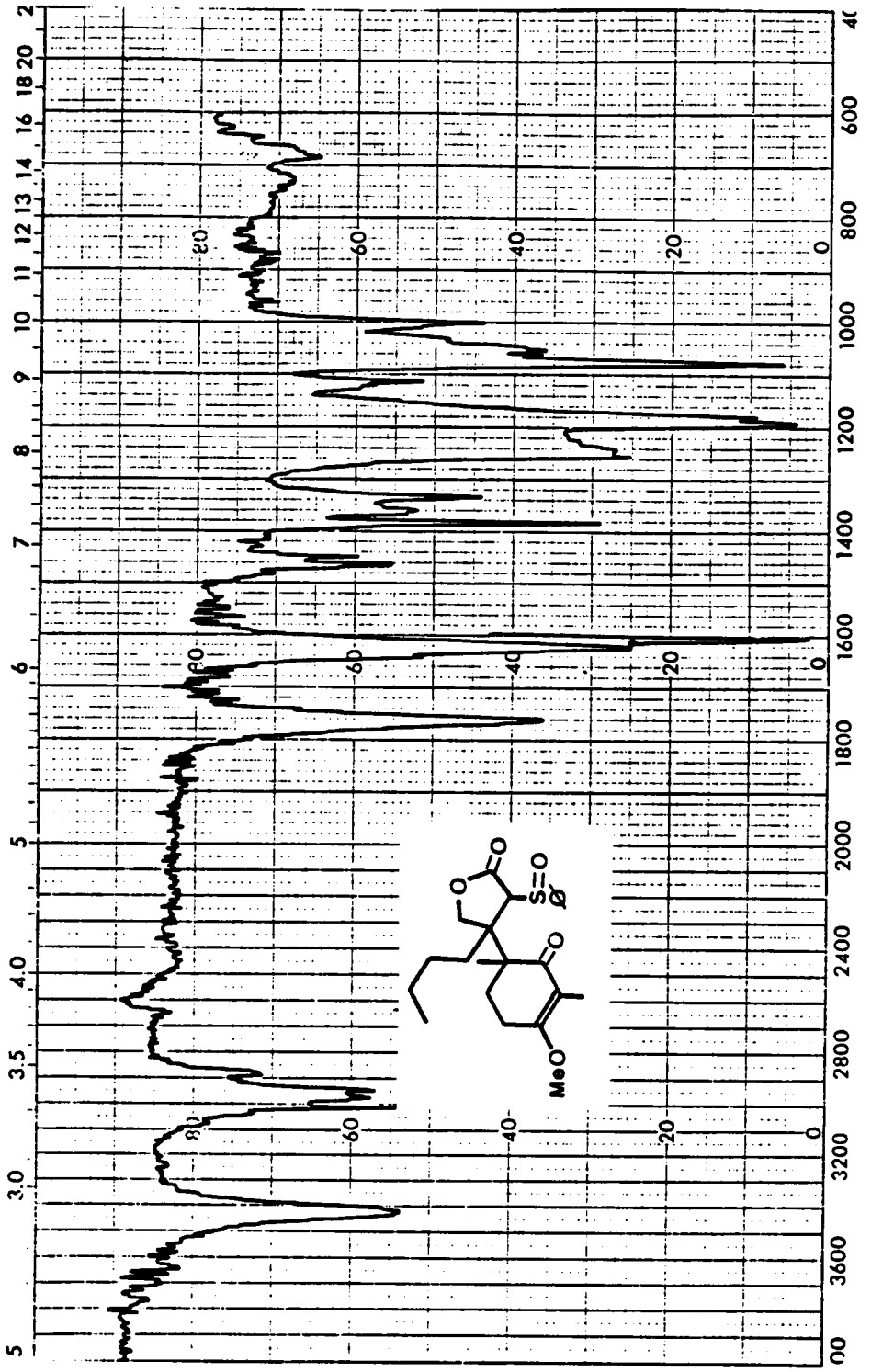
90 MHz ^{1}H NMR spectrum of Michael adduct 73



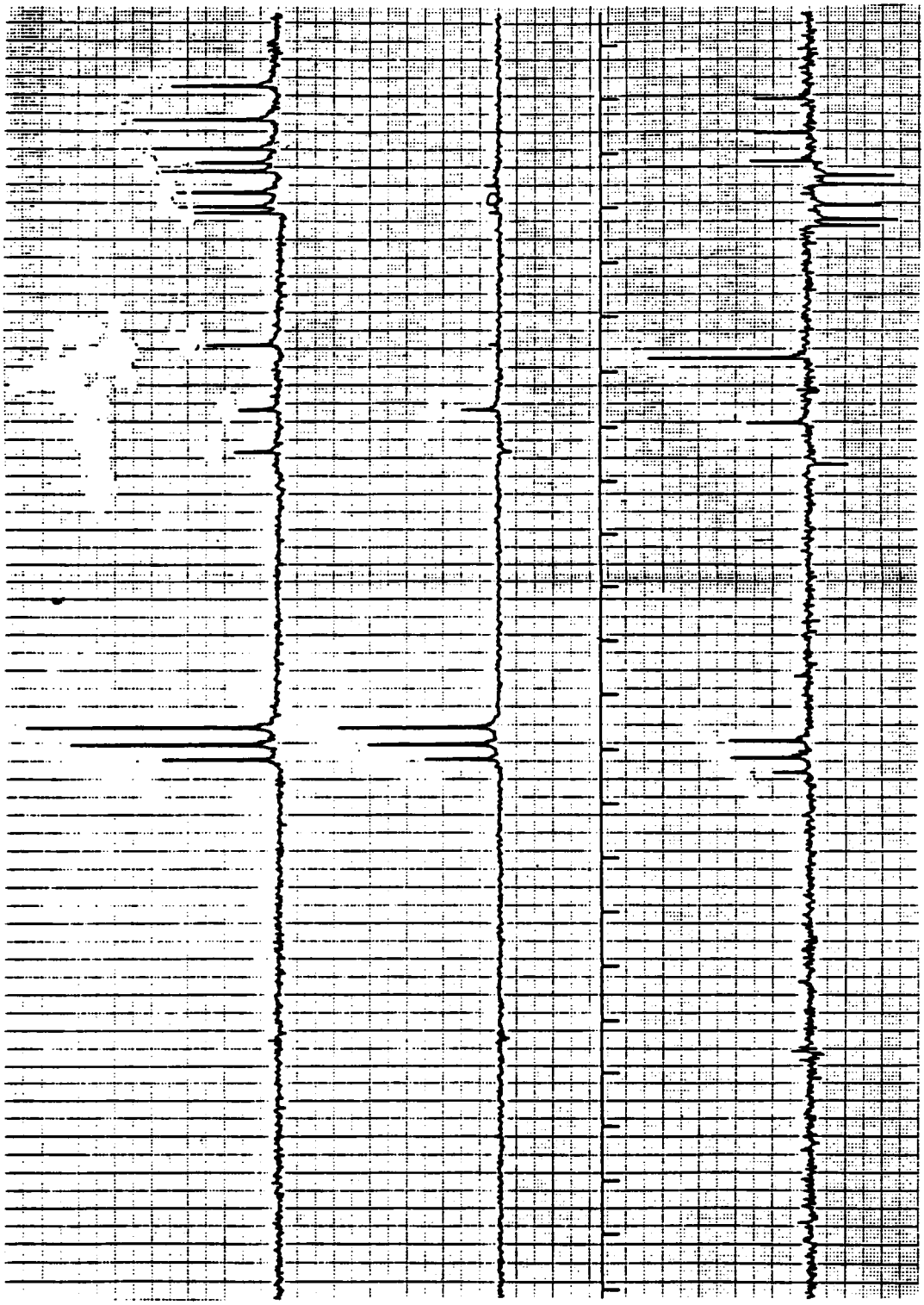
90 MHz ^{1}H NMR spectrum of Michael adduct 74



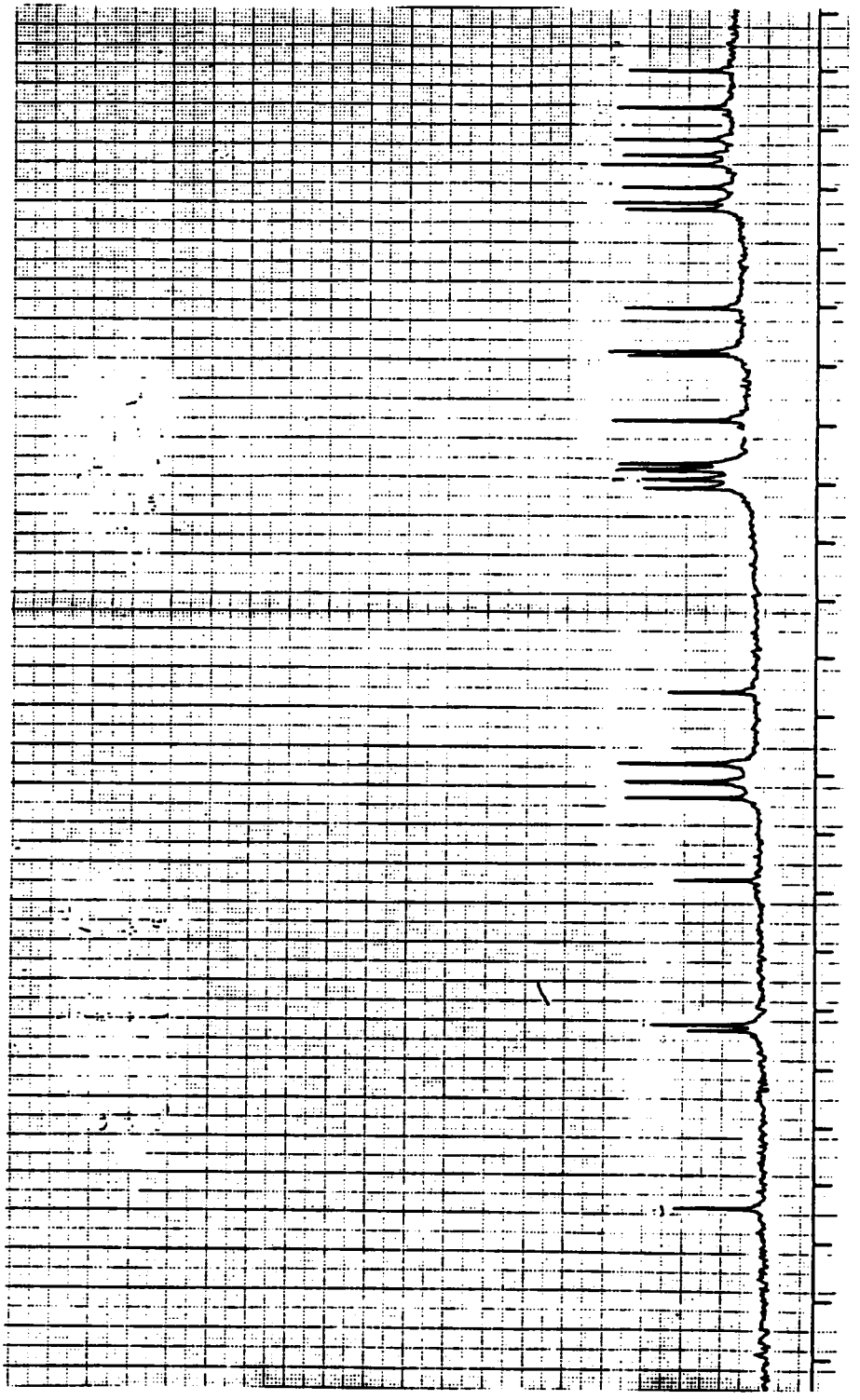
100 MHz ^{1}H NMR spectrum of Michael adduct 74



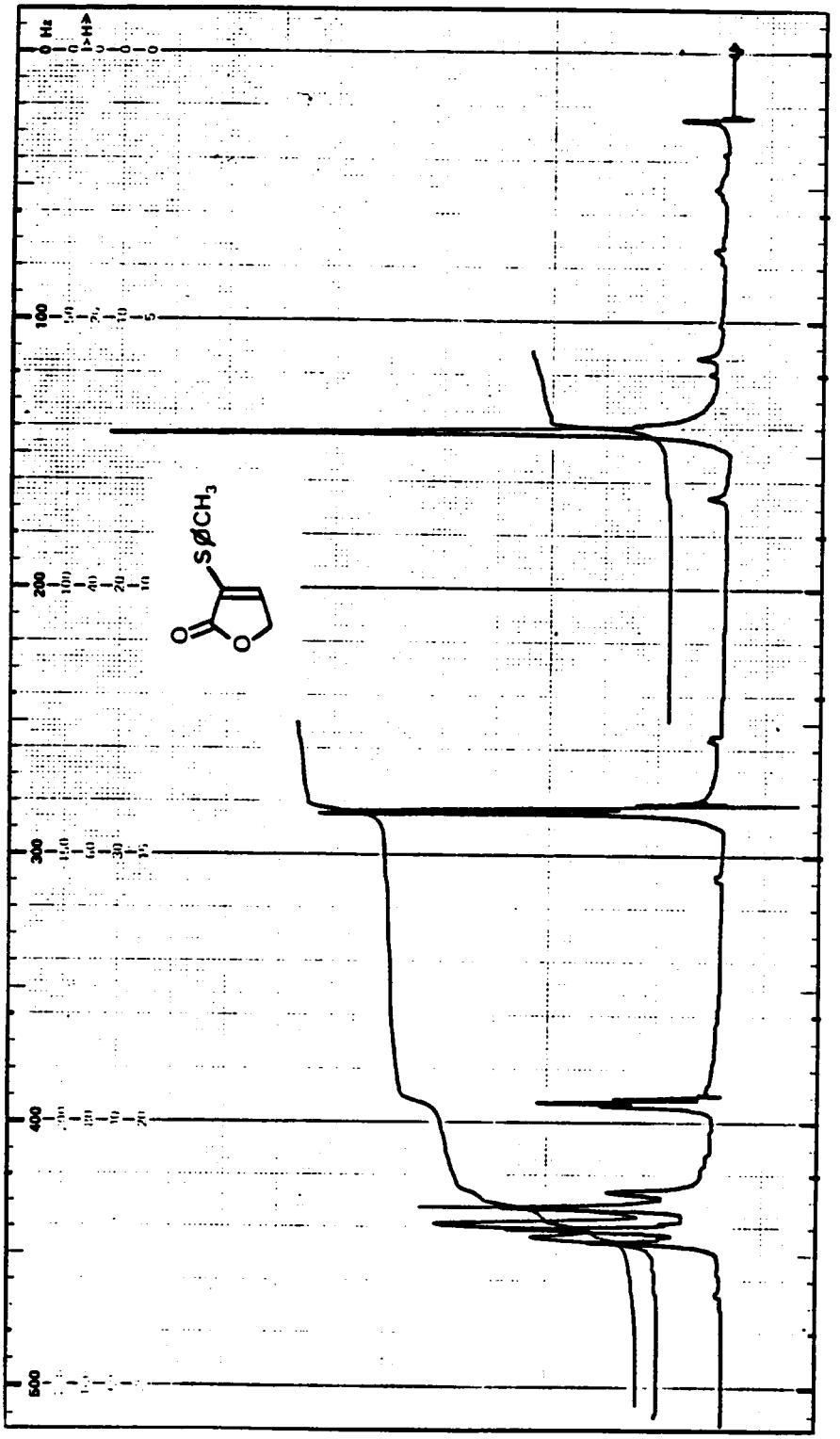
IR spectrum of Michael adduct 74



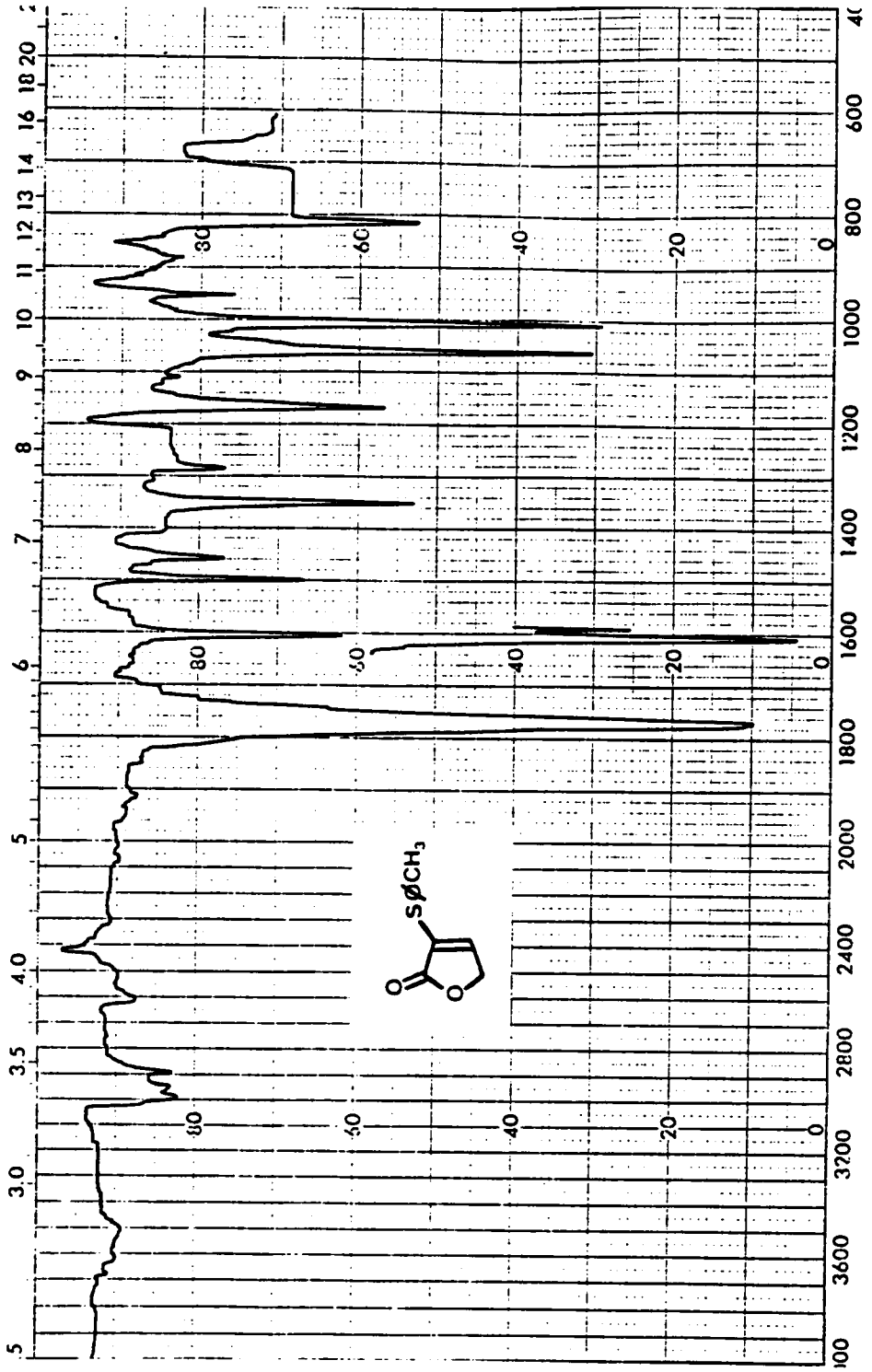
80 MHz ^{13}C INEPT spectra of Michael adduct 74



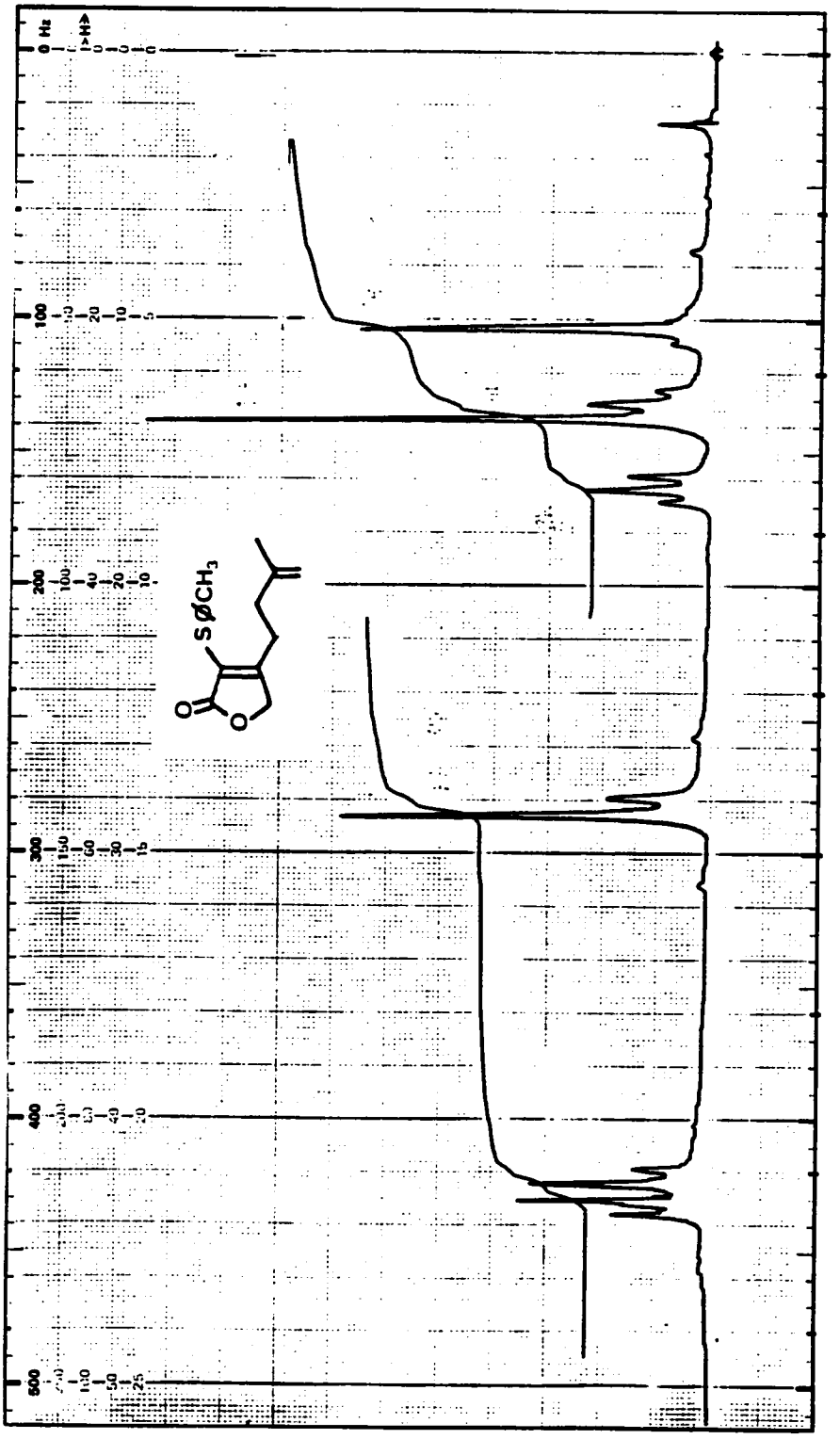
80 MHz ^{13}C decoupled NMR spectrum of Michael adduct 74



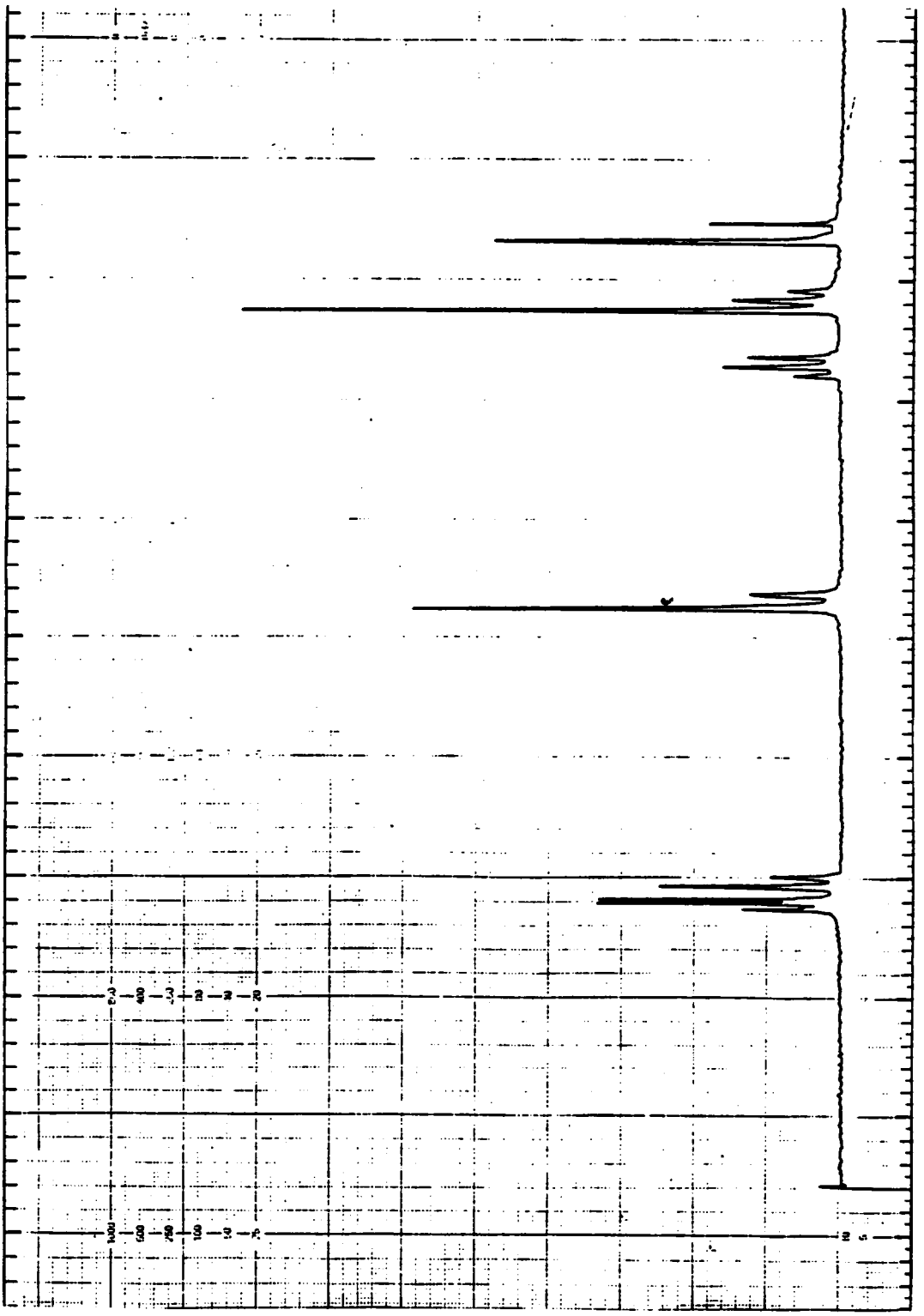
90 MHz ^{1}H NMR spectrum of butenolide 76



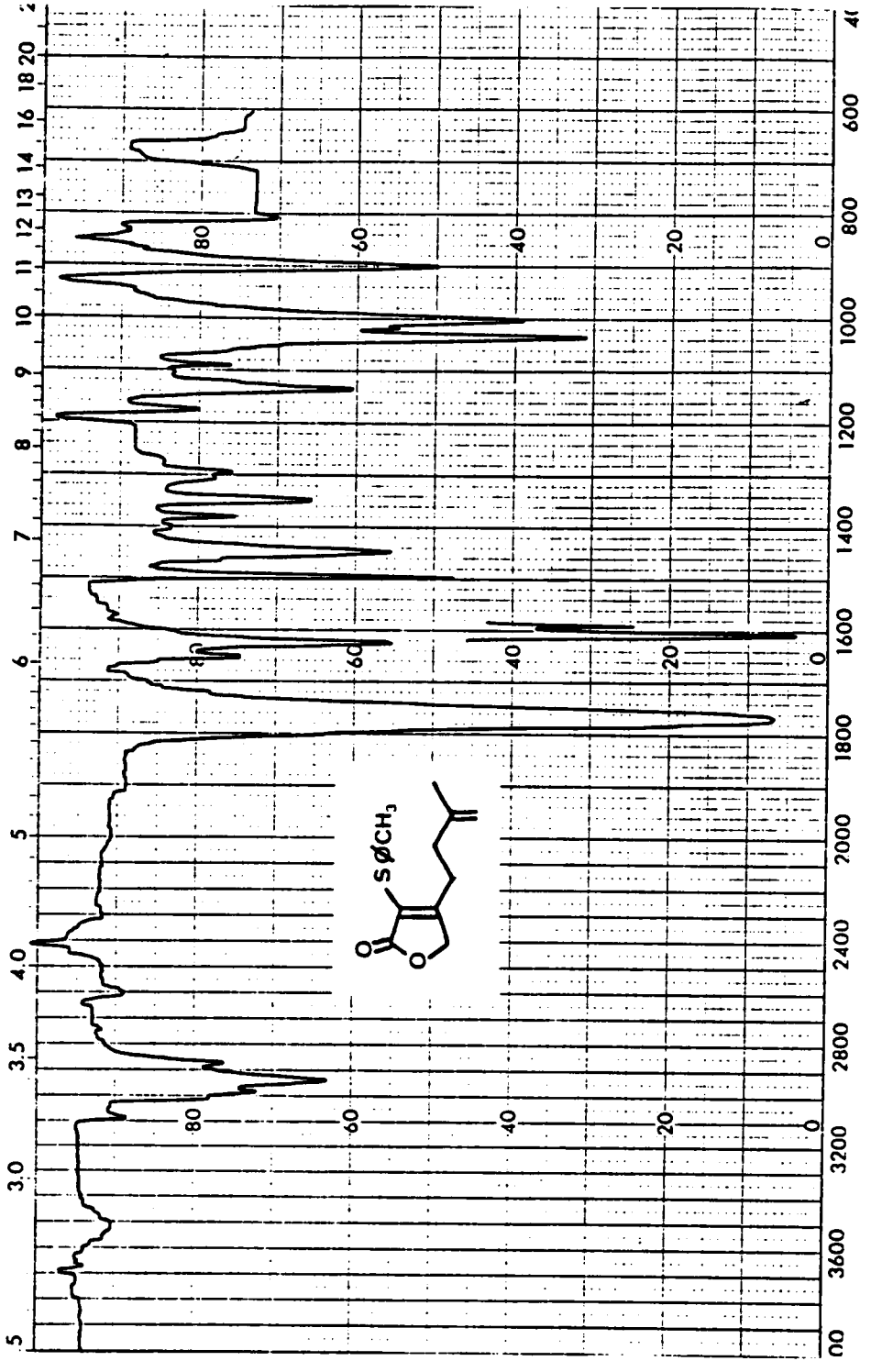
IR spectrum of butenolide 76



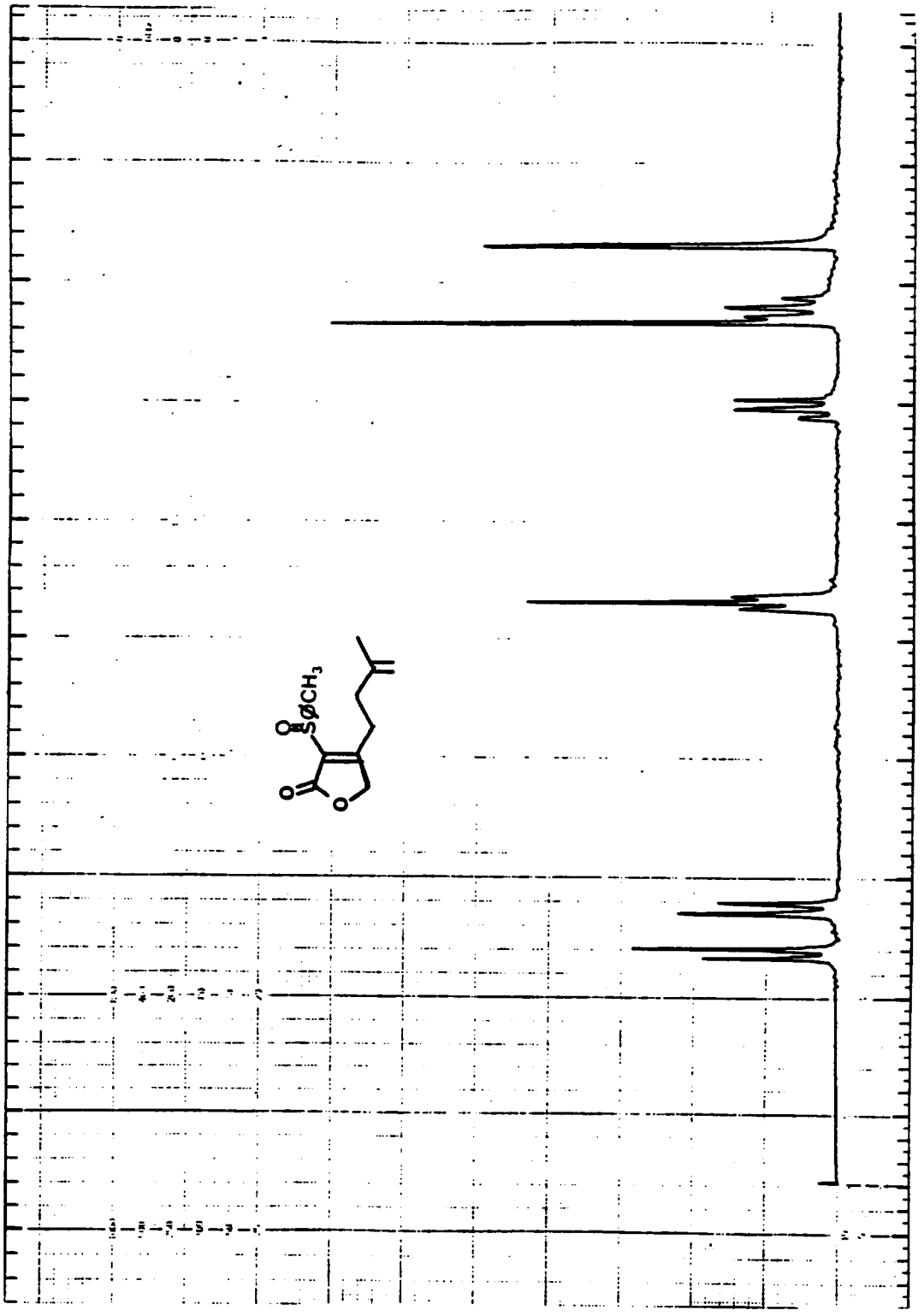
90 MHz ^{1}H NMR spectrum of butenolide 77



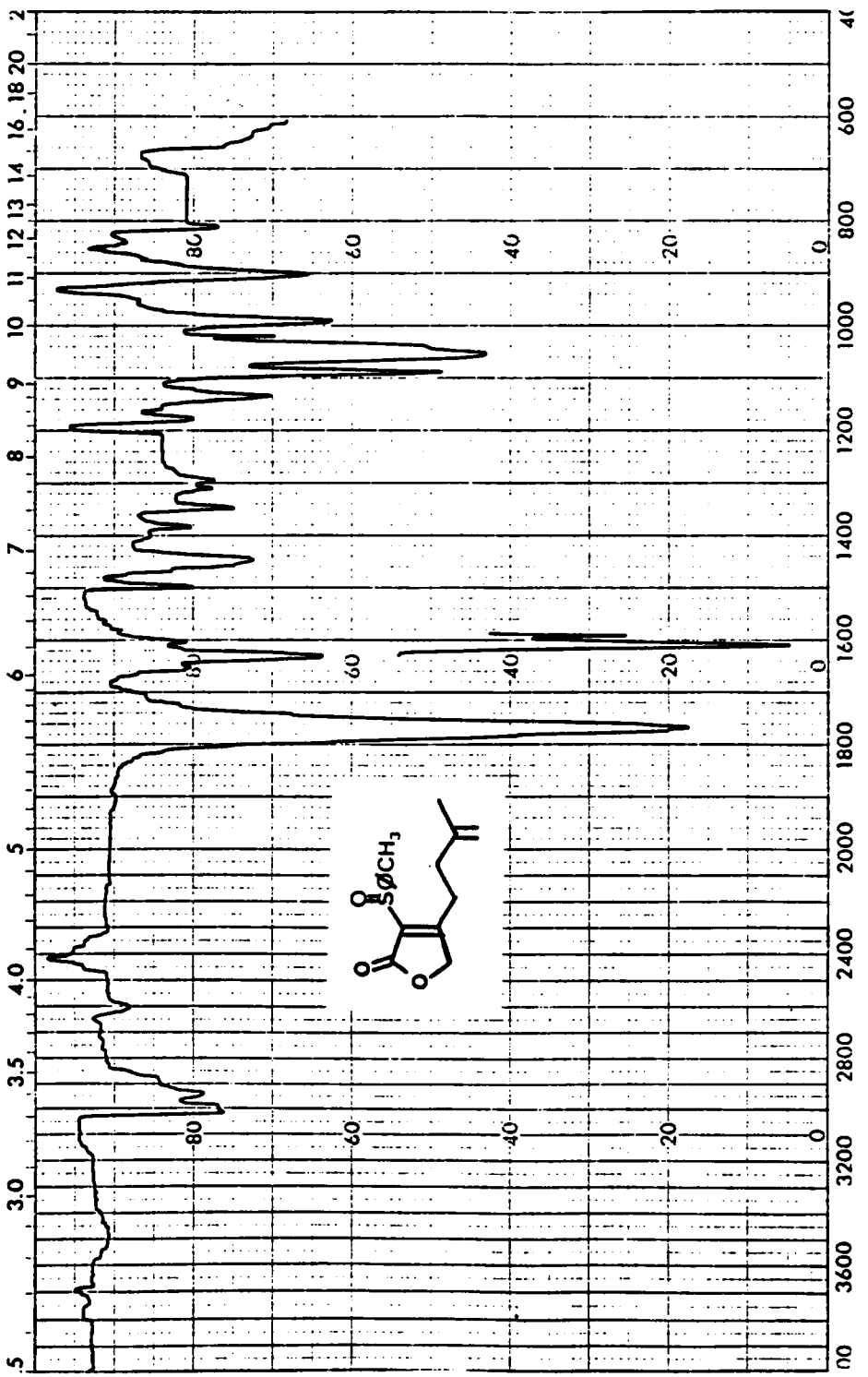
100 MHz ^{1}H NMR spectrum of butenolide *77*



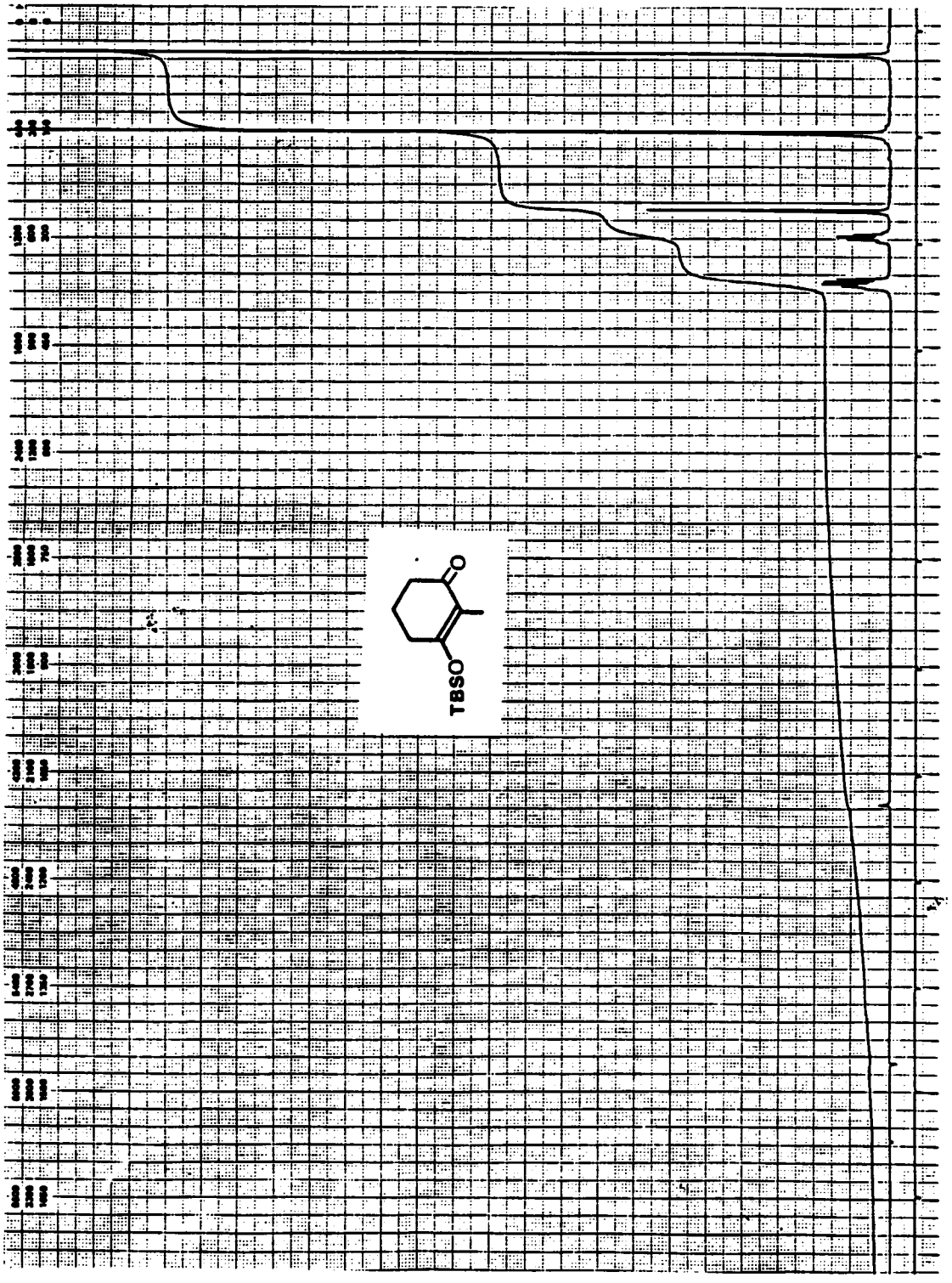
IR spectrum of butenolide 77



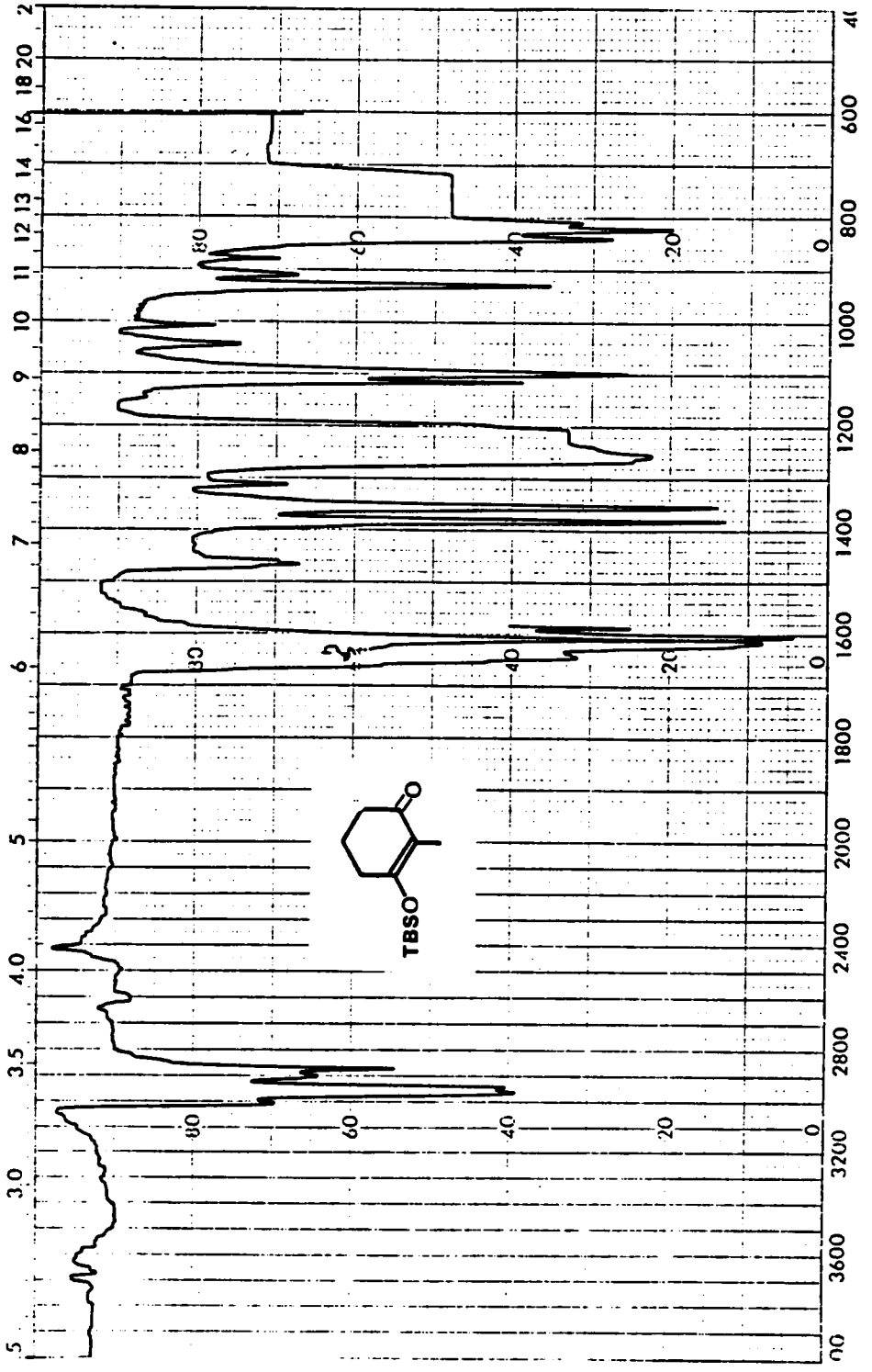
100 MHz ^{1}H NMR spectrum of butenolide 75



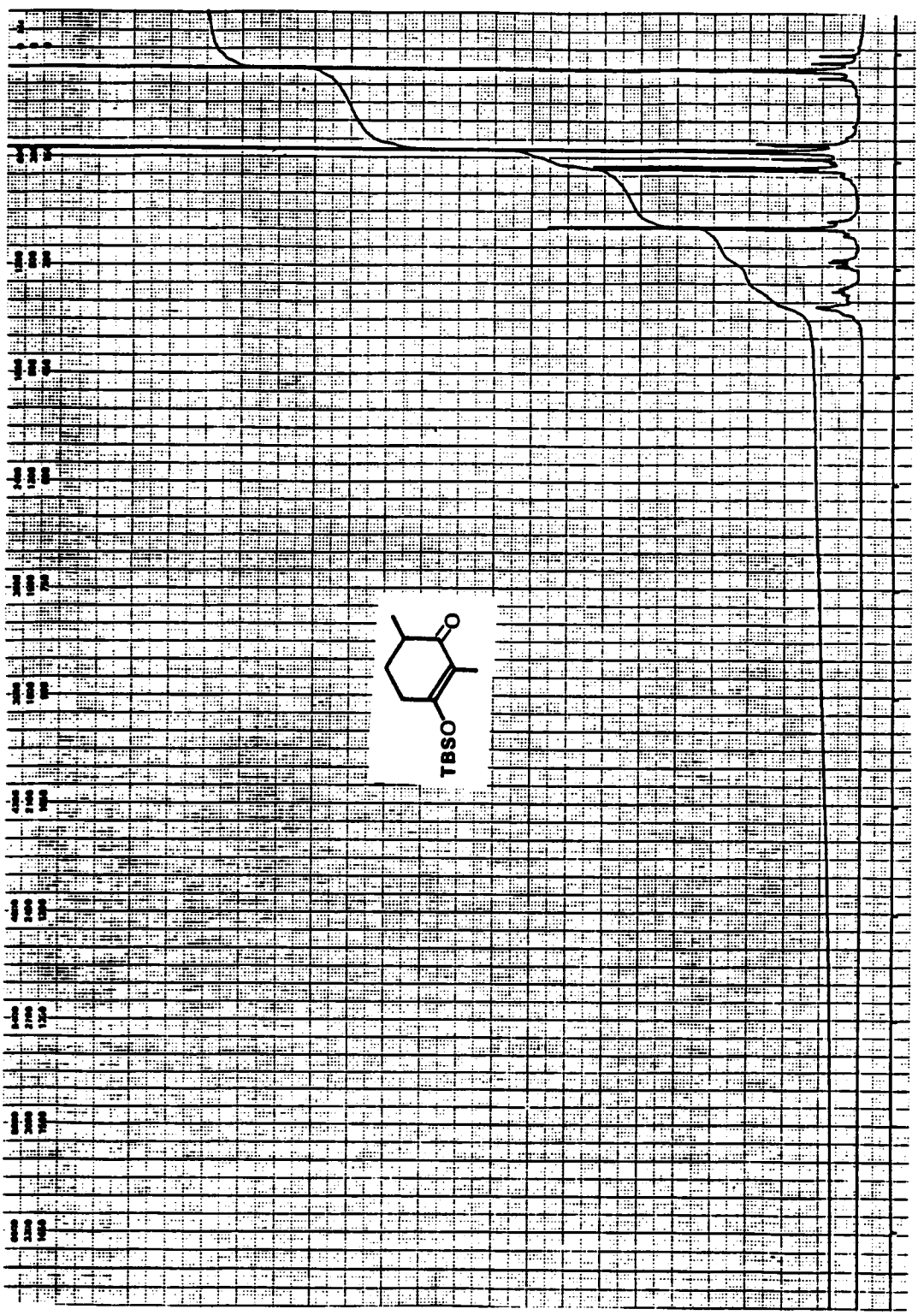
IR spectrum of butenolide 75



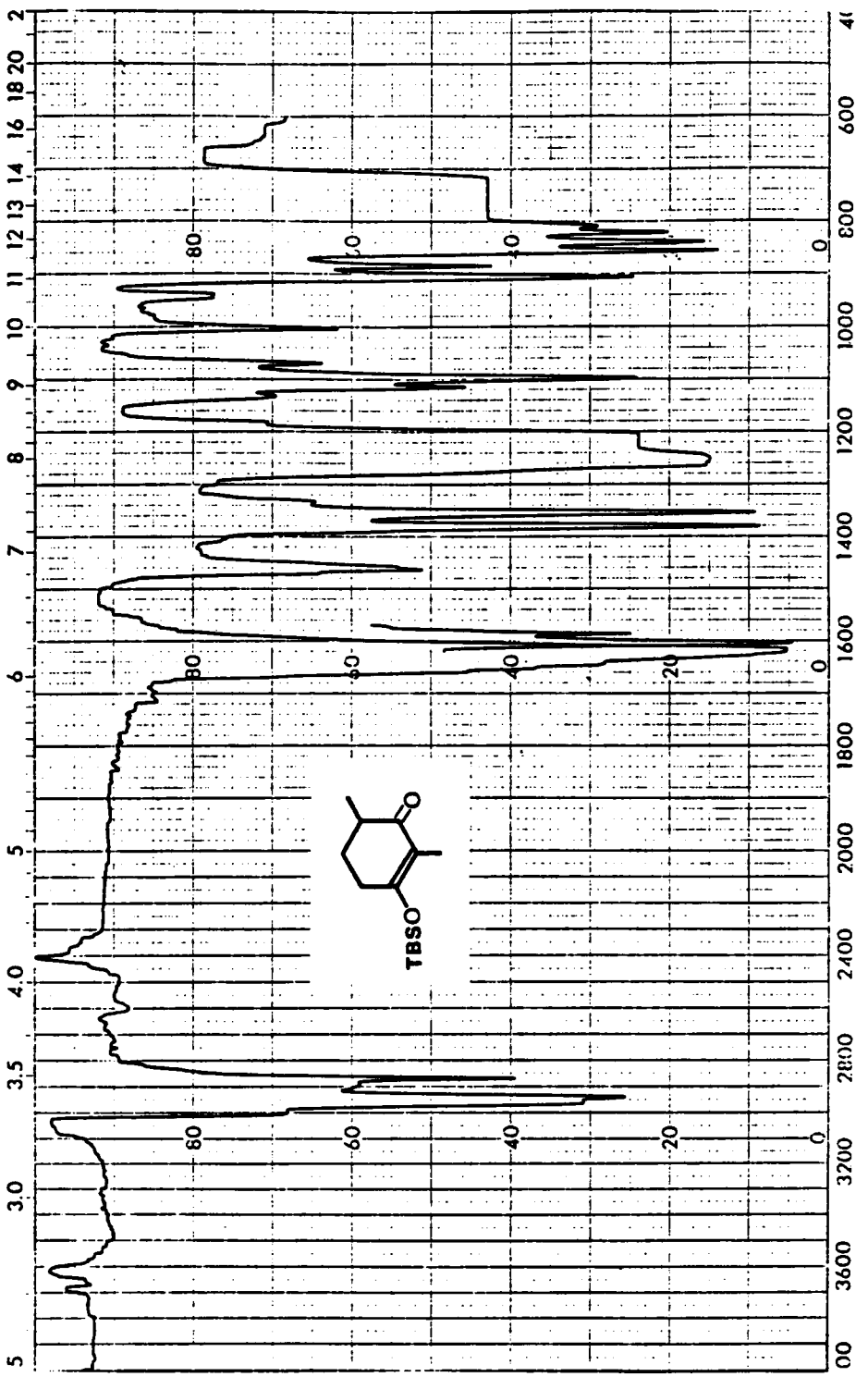
270 MHz ^{1}H NMR spectrum of enone 78



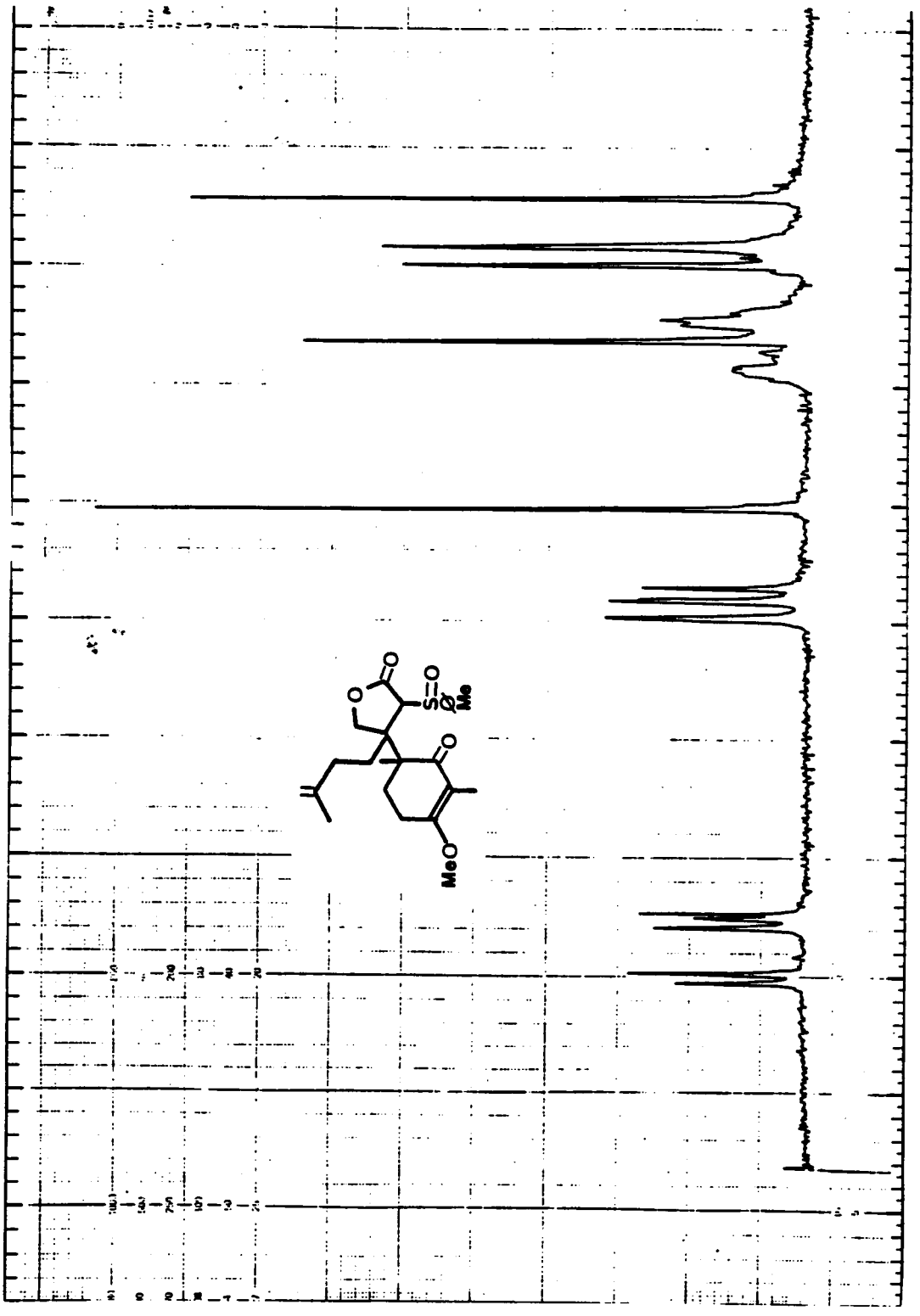
IR spectrum of enone 78



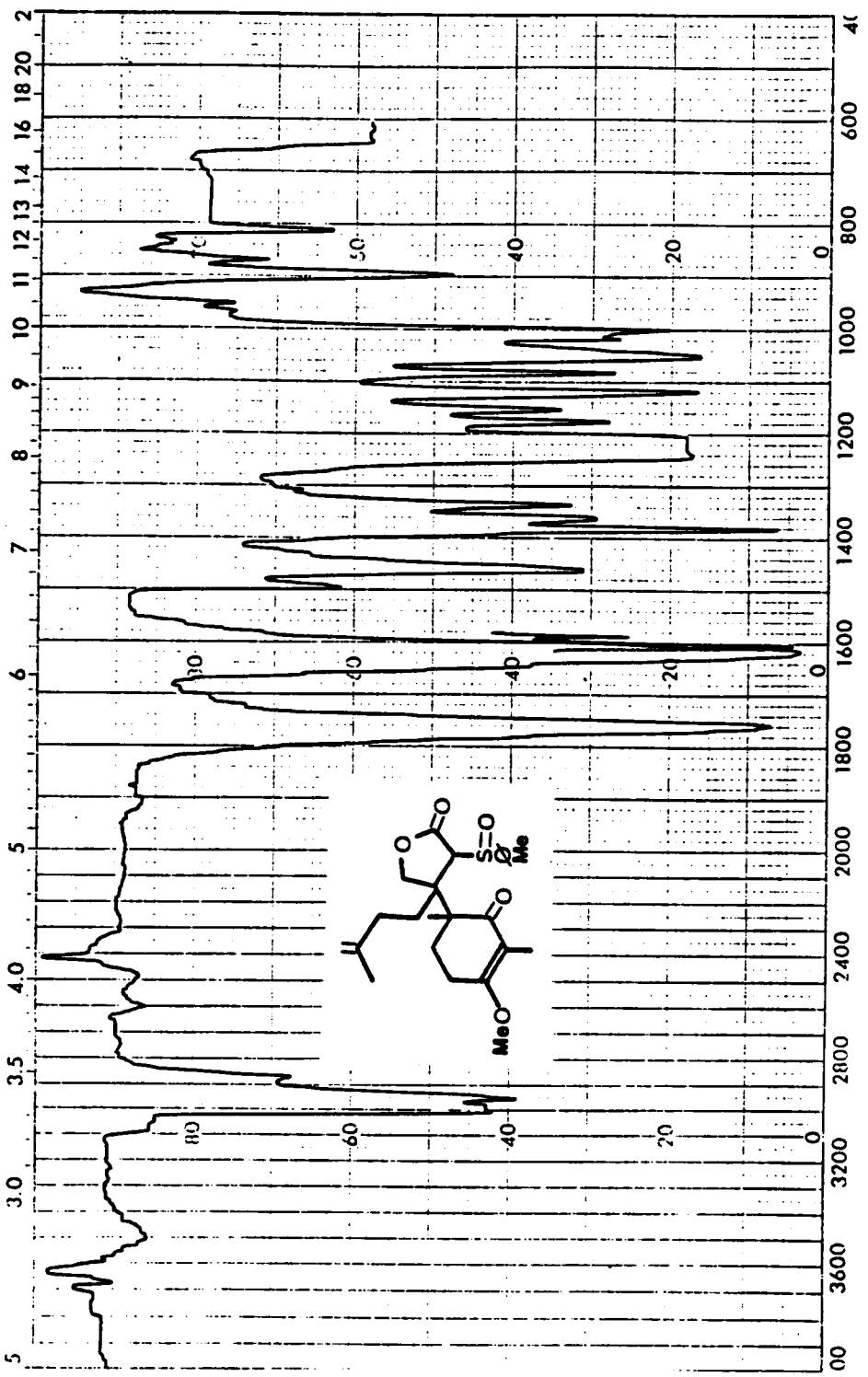
270 MHz ^{1}H NMR spectrum of enone 79



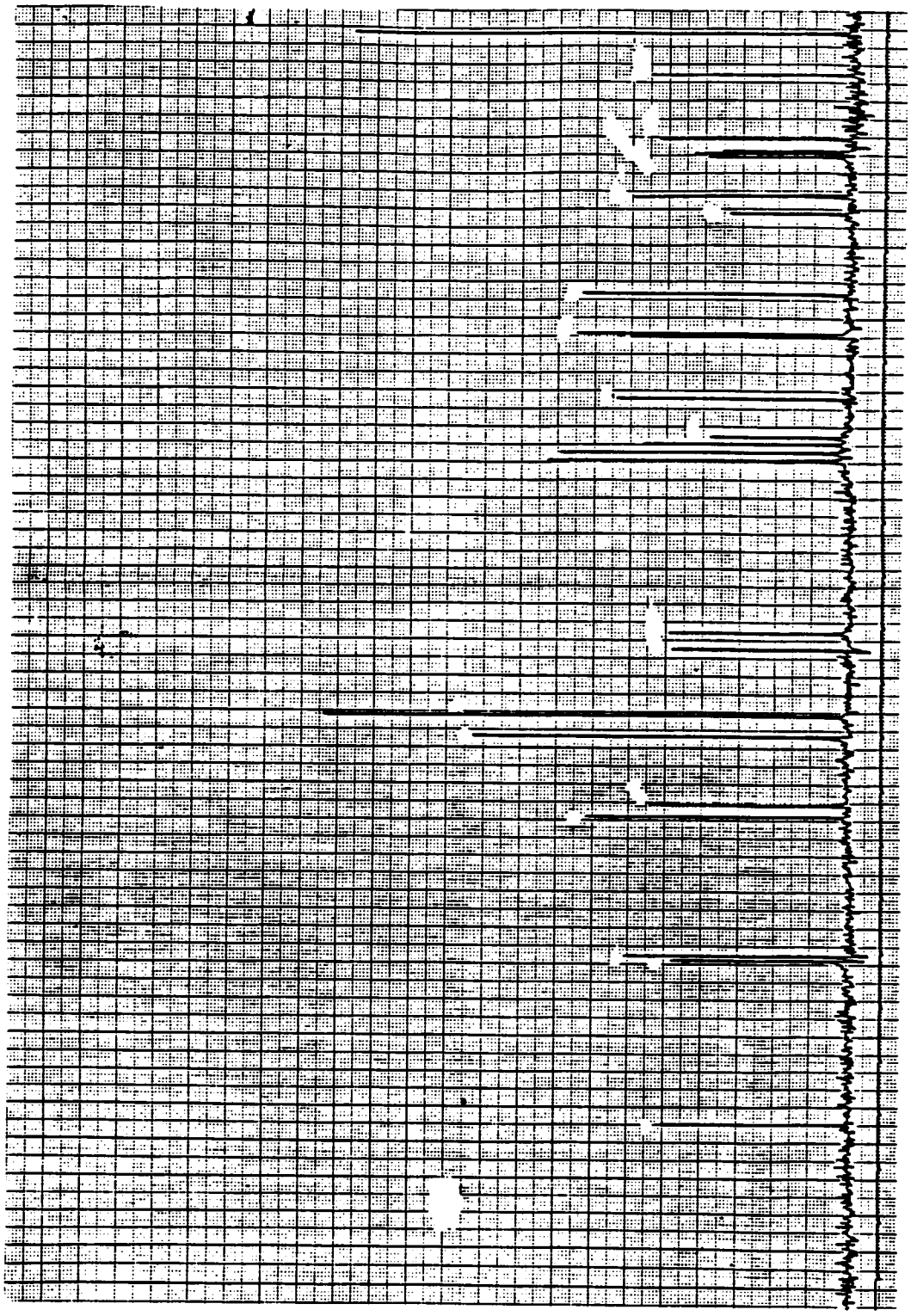
IR spectrum of enone 79



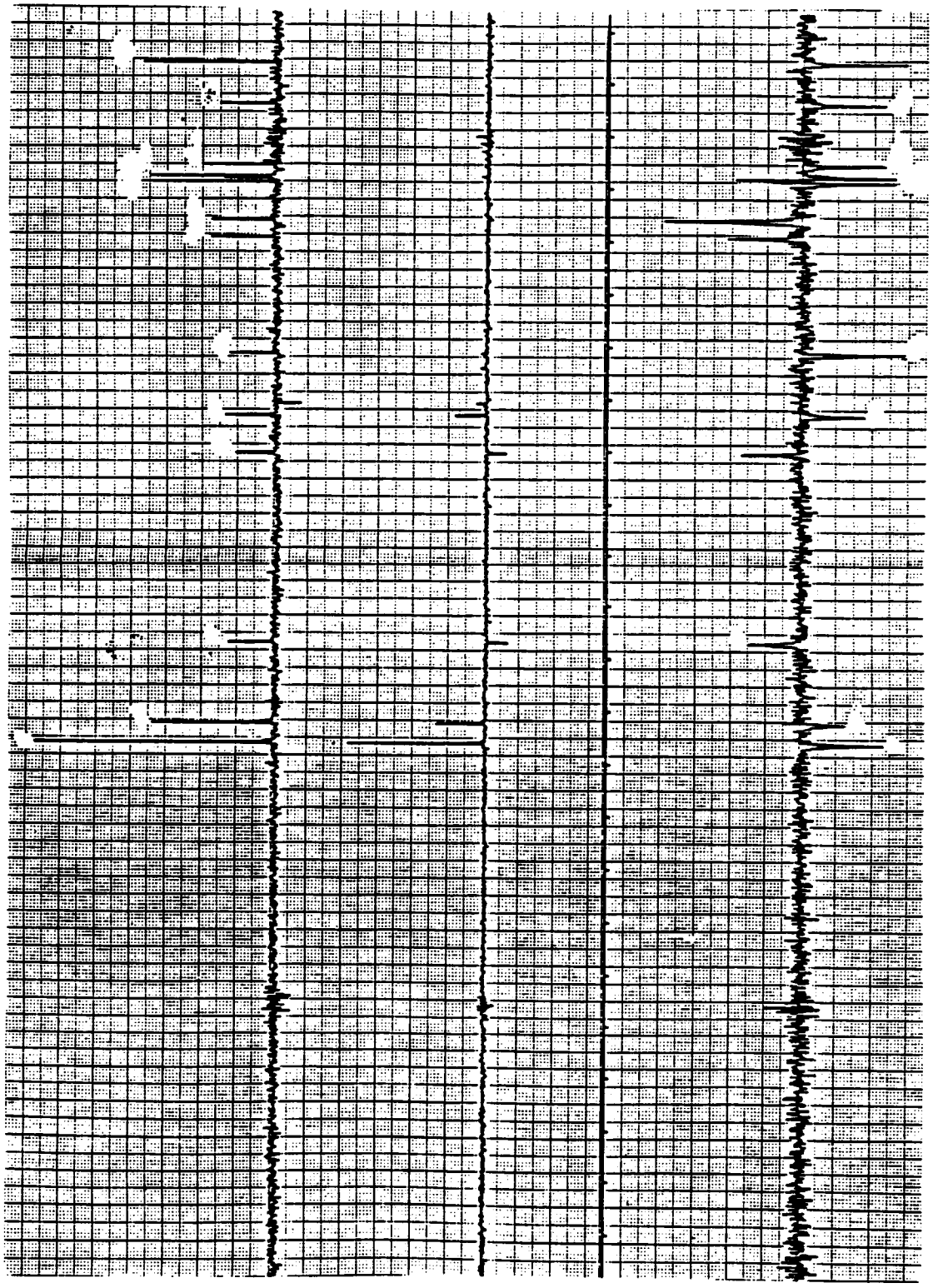
100 MHz ^{1}H NMR spectrum of Michael adduct 80



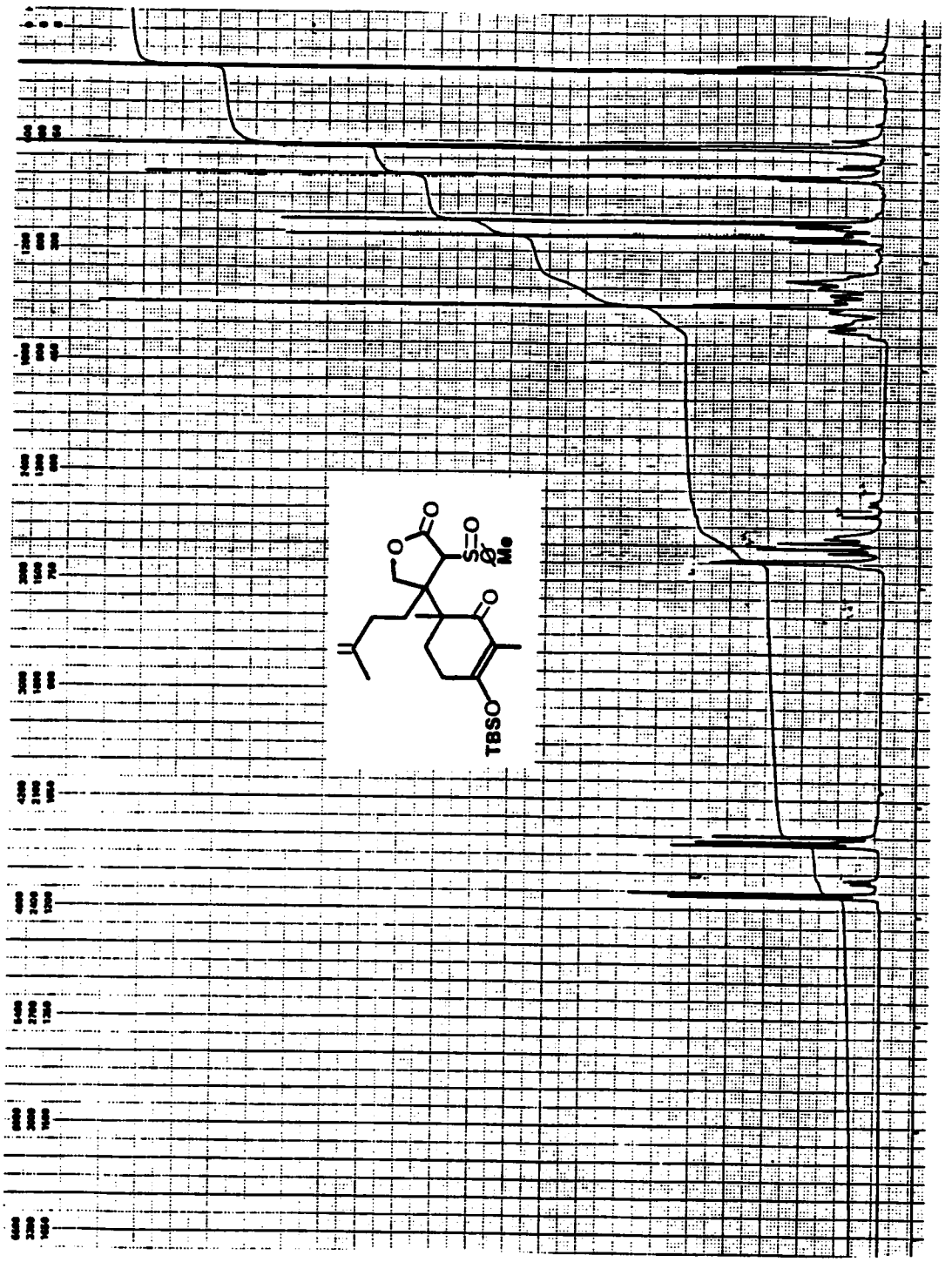
IR spectrum of Michael adduct 80



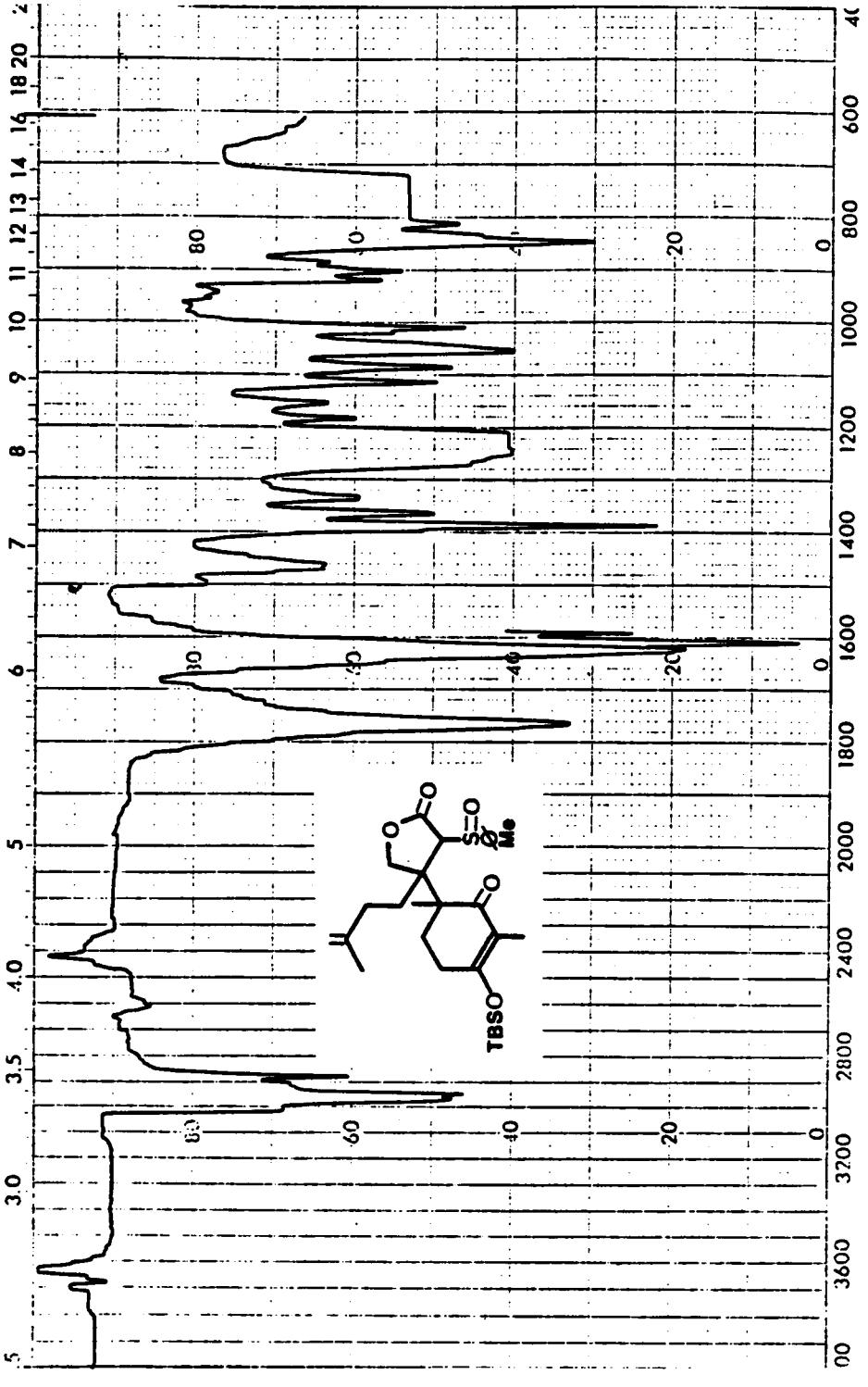
80 MHz ^{13}C decoupled NMR spectrum of Michael adduct 80



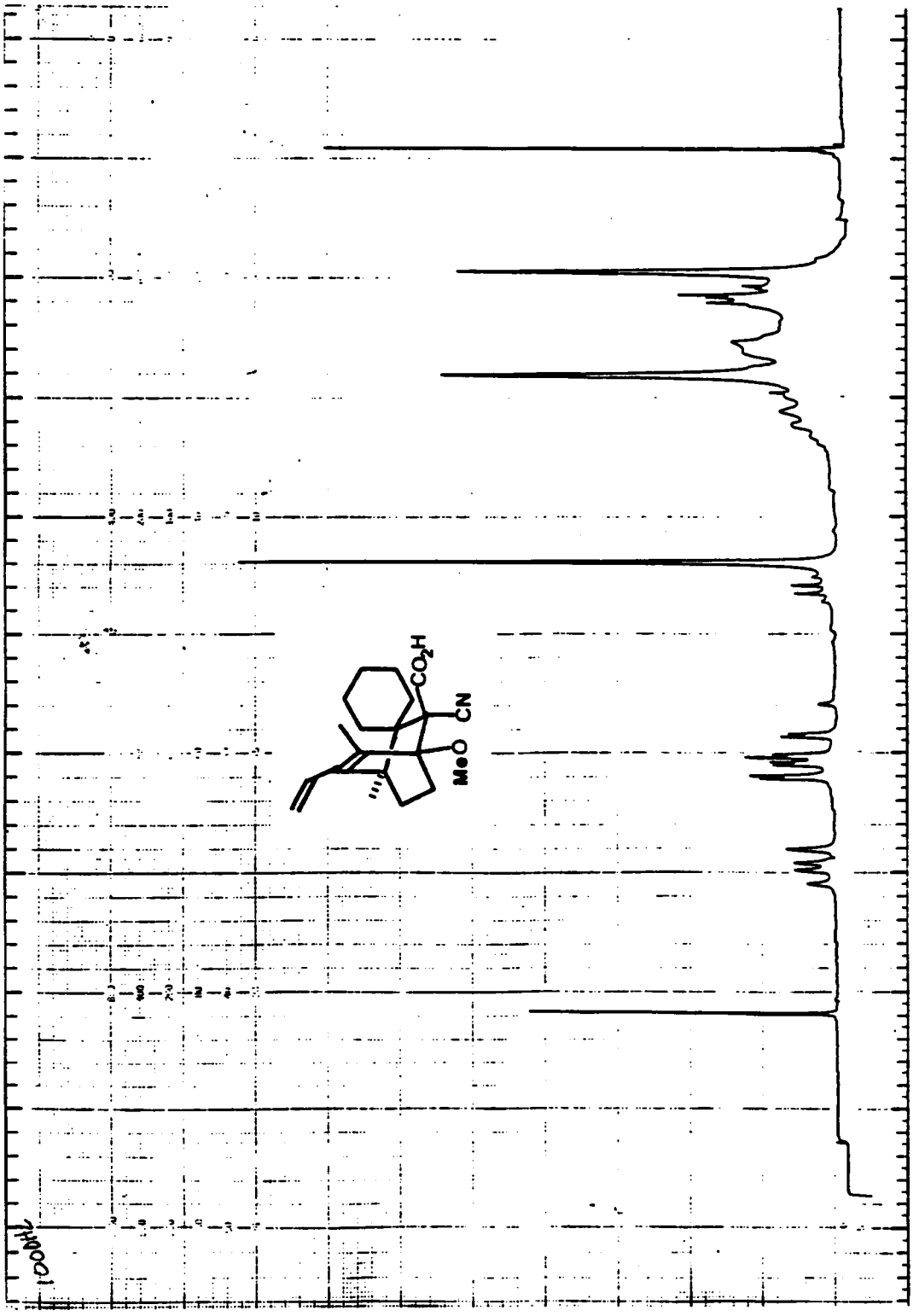
80 MHz ^{13}C INEPT spectra of Michael adduct 80



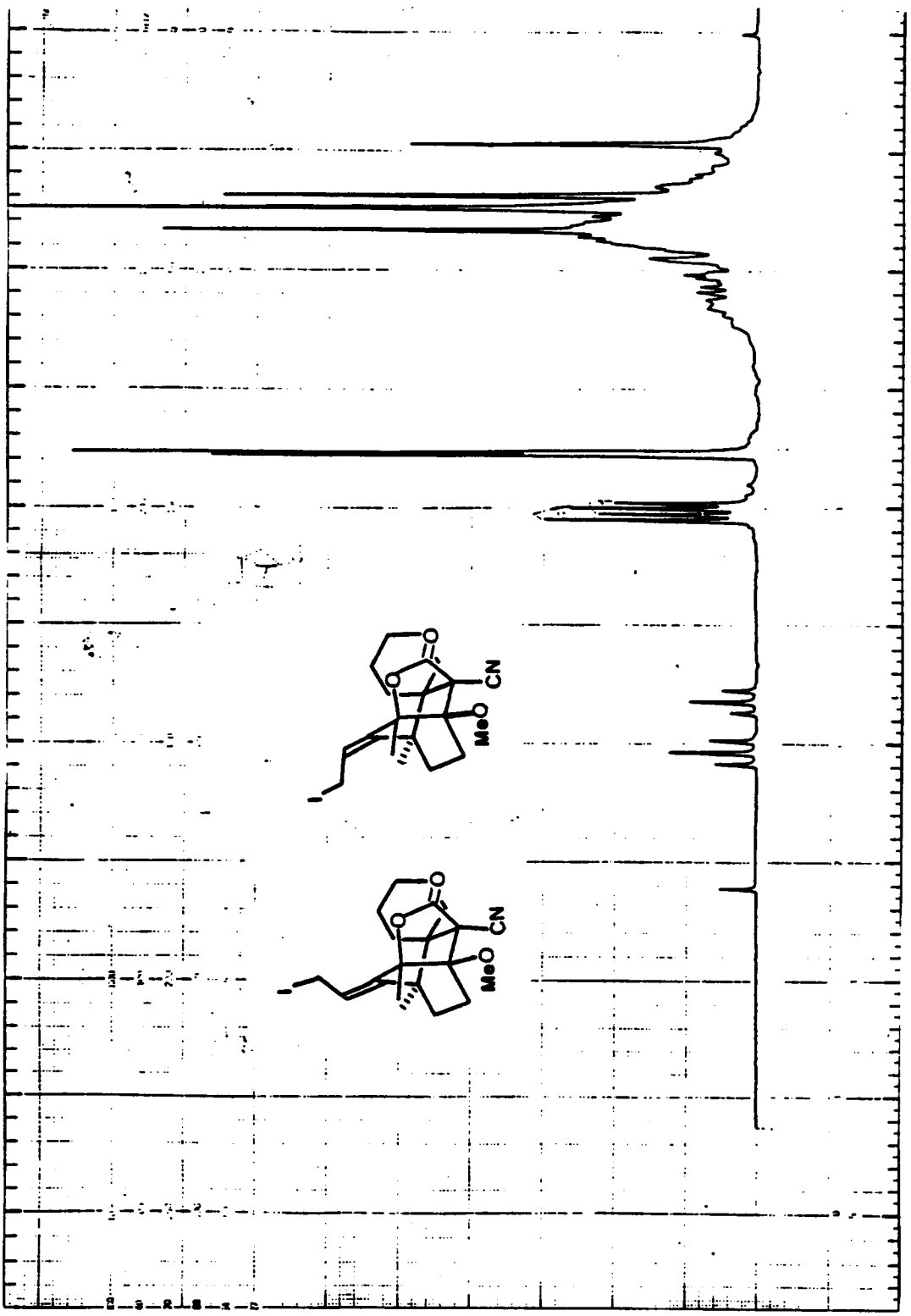
270 MHz ^{1}H NMR spectrum of Michael adduct 81



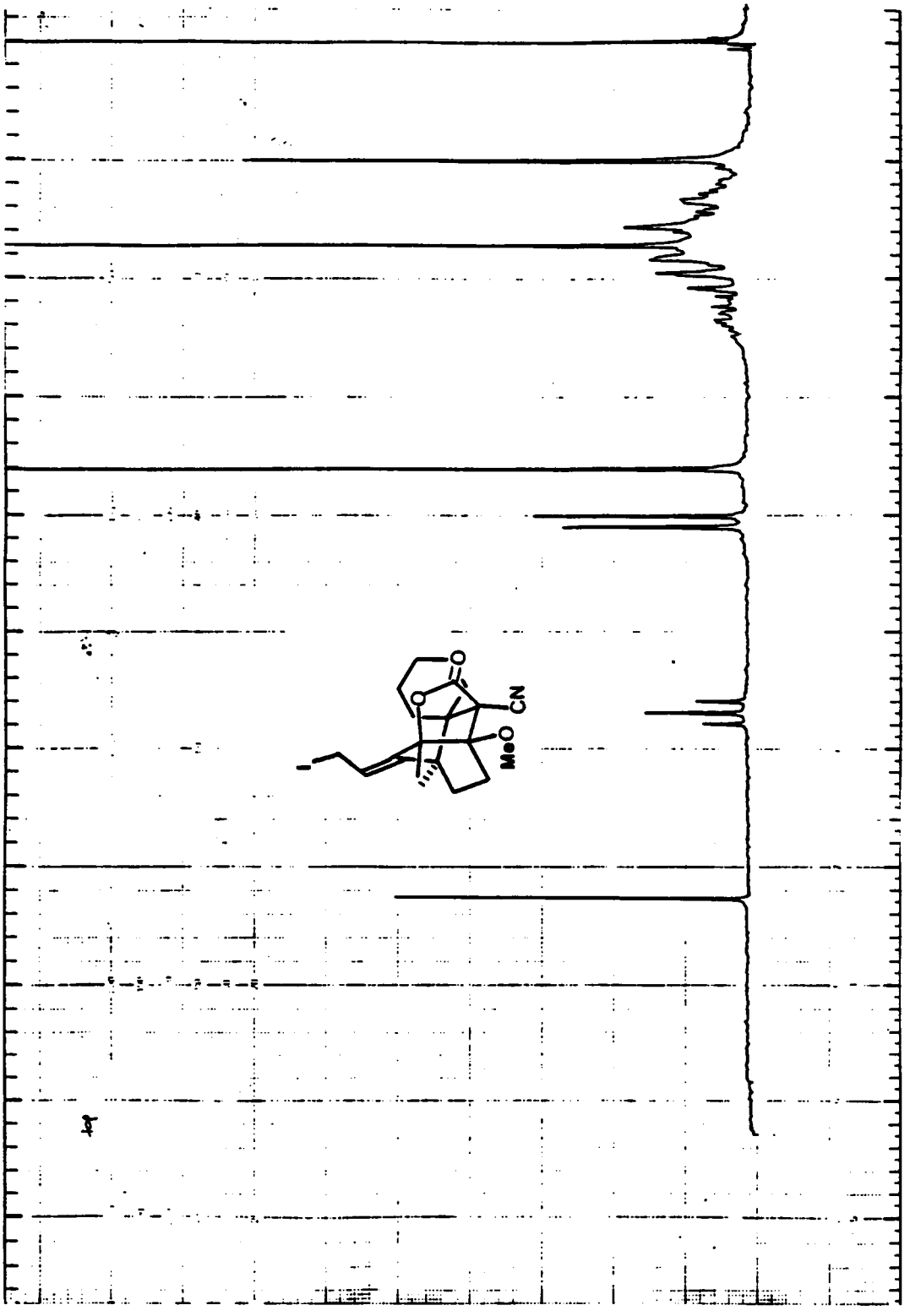
IR spectrum of Michael adduct 81



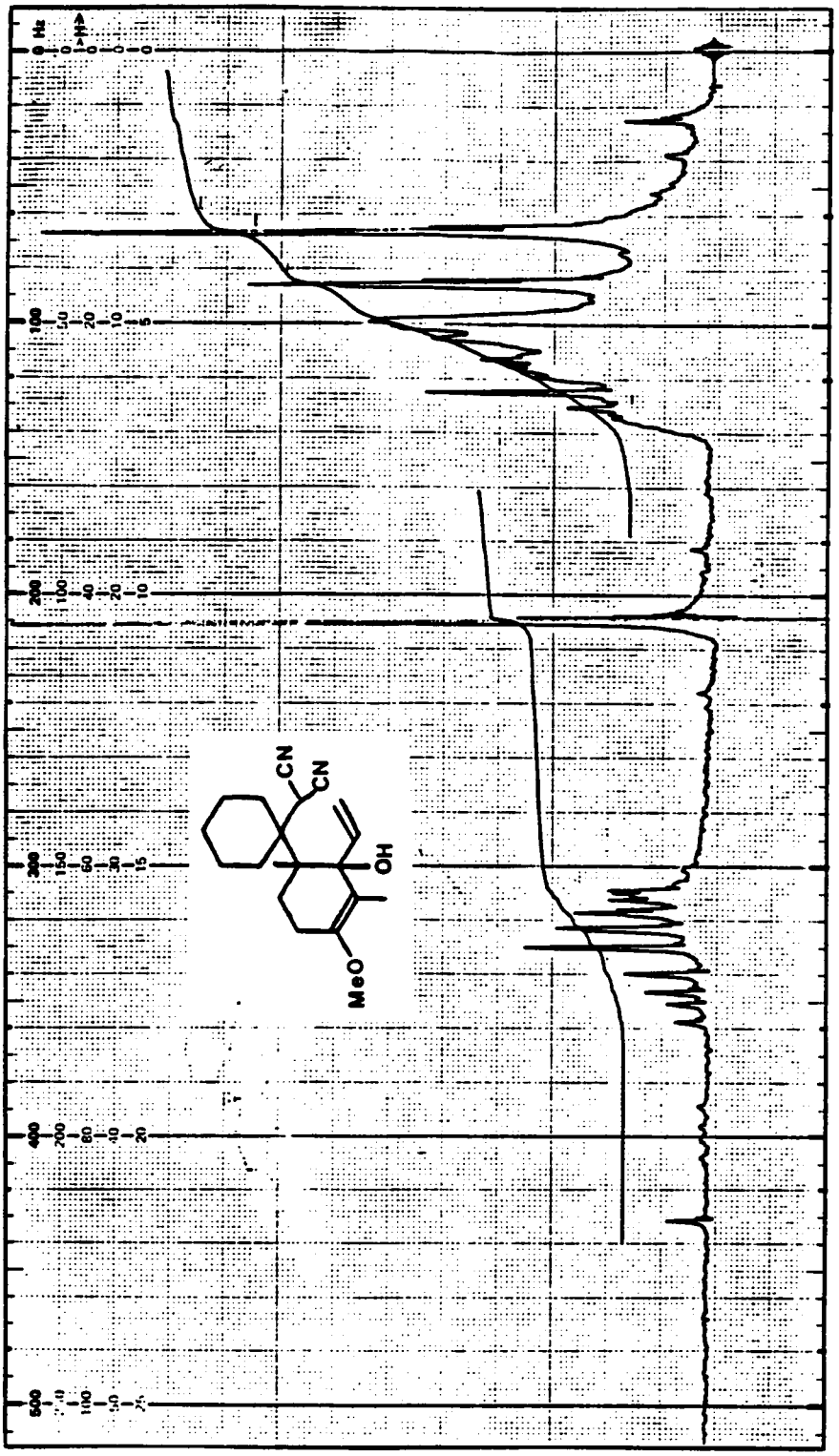
100 MHz ^{1}H NMR spectrum of carboxylic acid 82



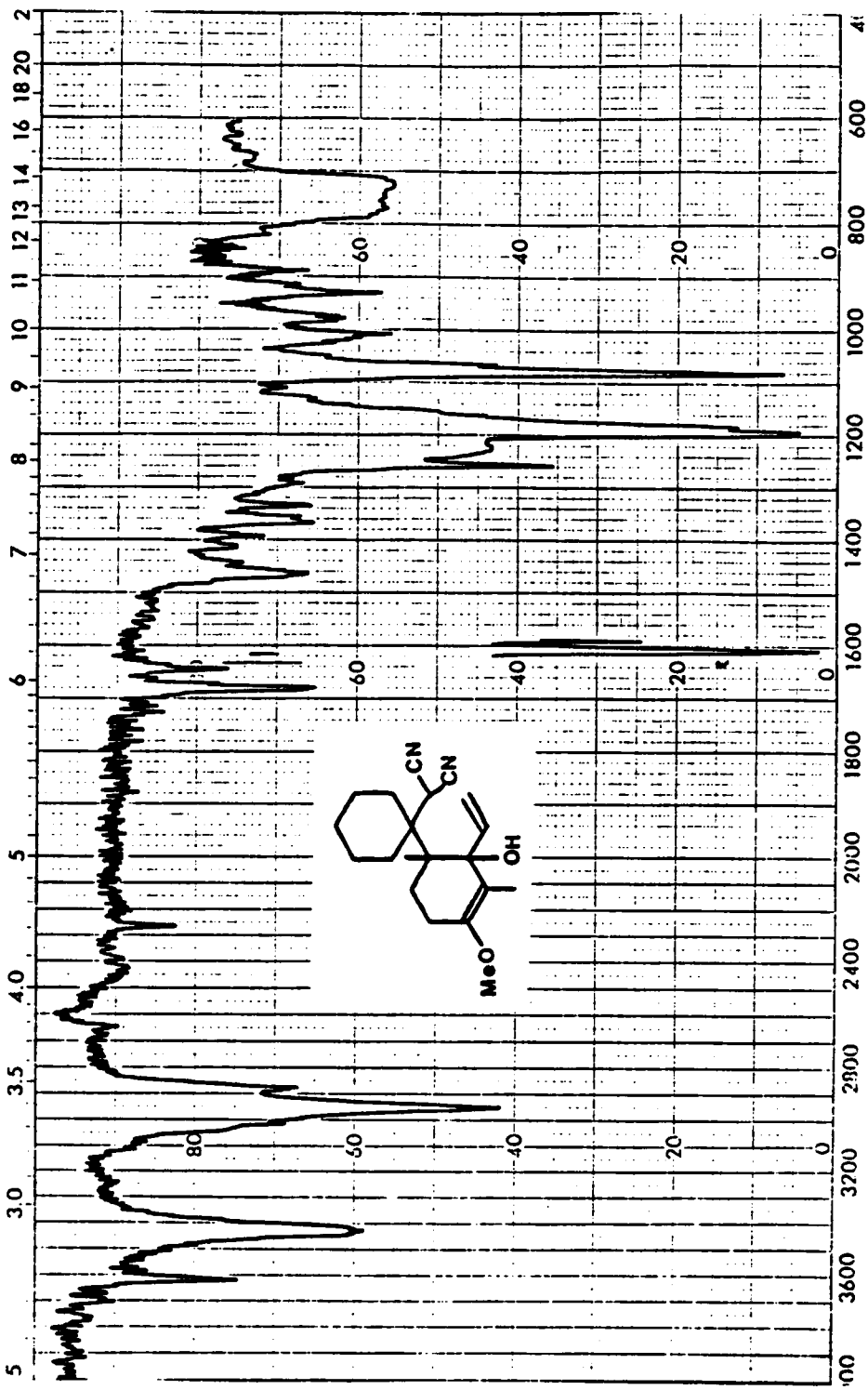
100 MHz ^{1}H NMR spectrum of allylic iodides 83 and 84



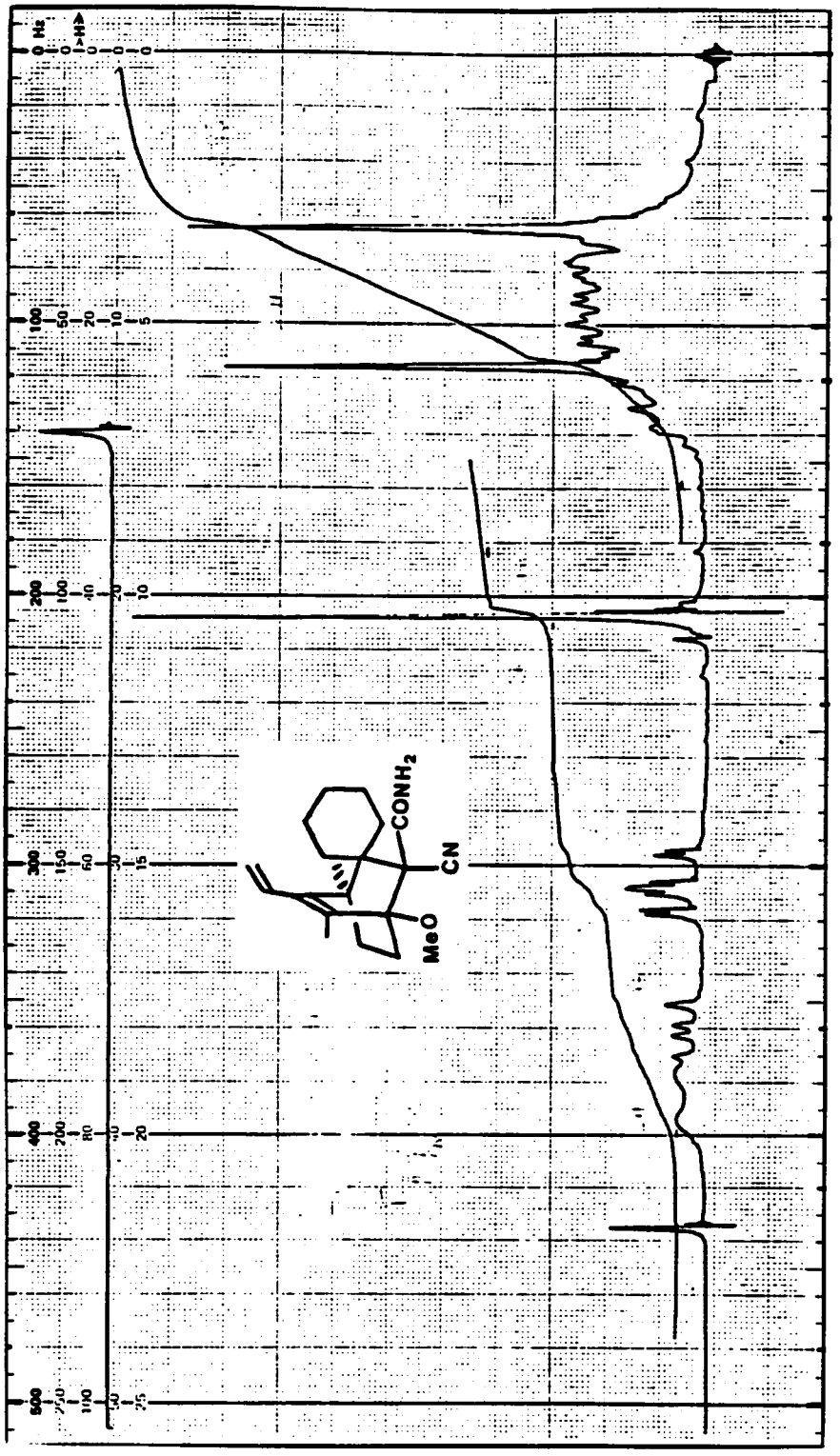
100 MHz ^{1}H NMR spectrum of allylic iodide 83



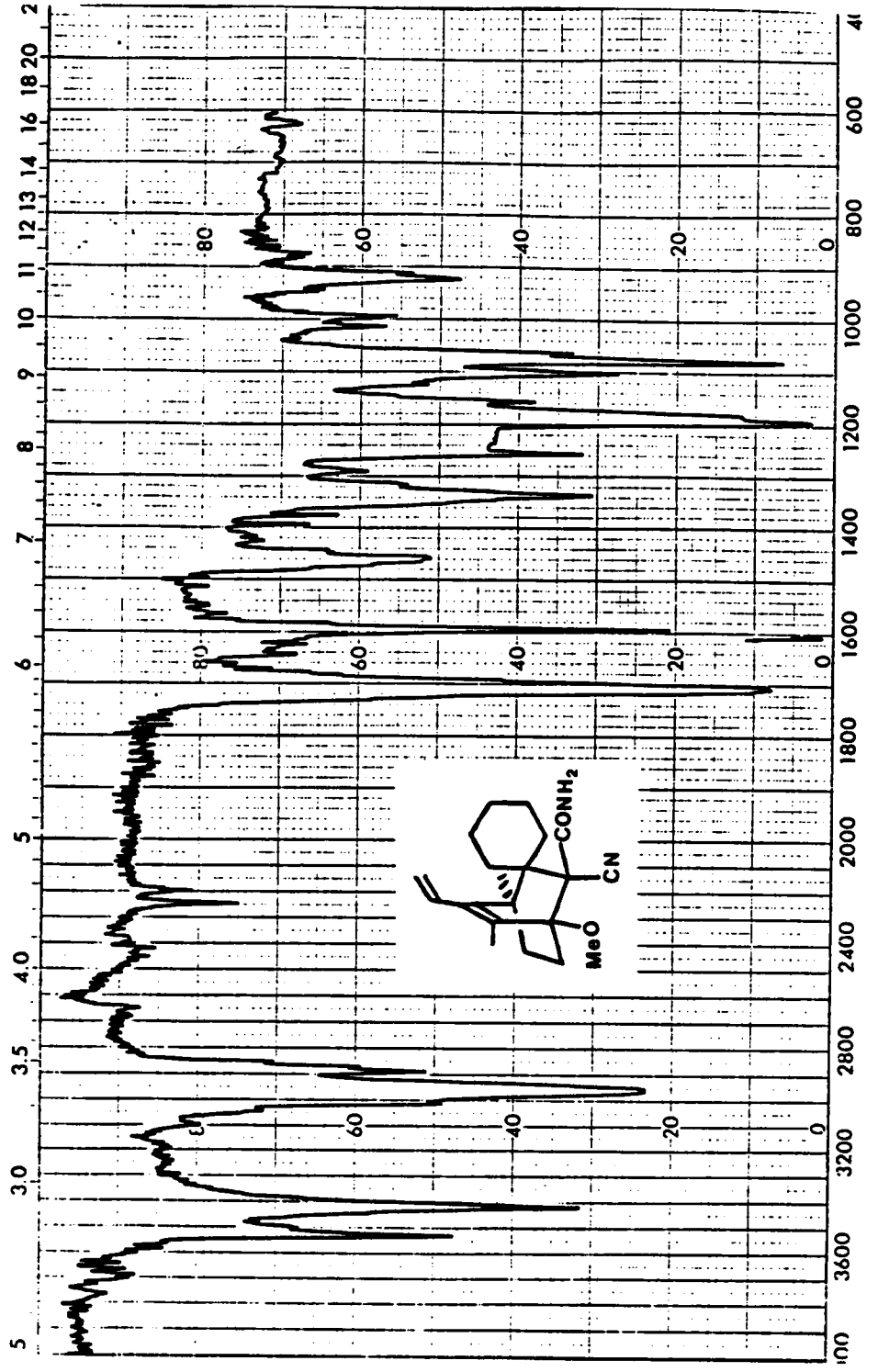
90 MHz ^{1}H NMR spectrum of alcohol 86



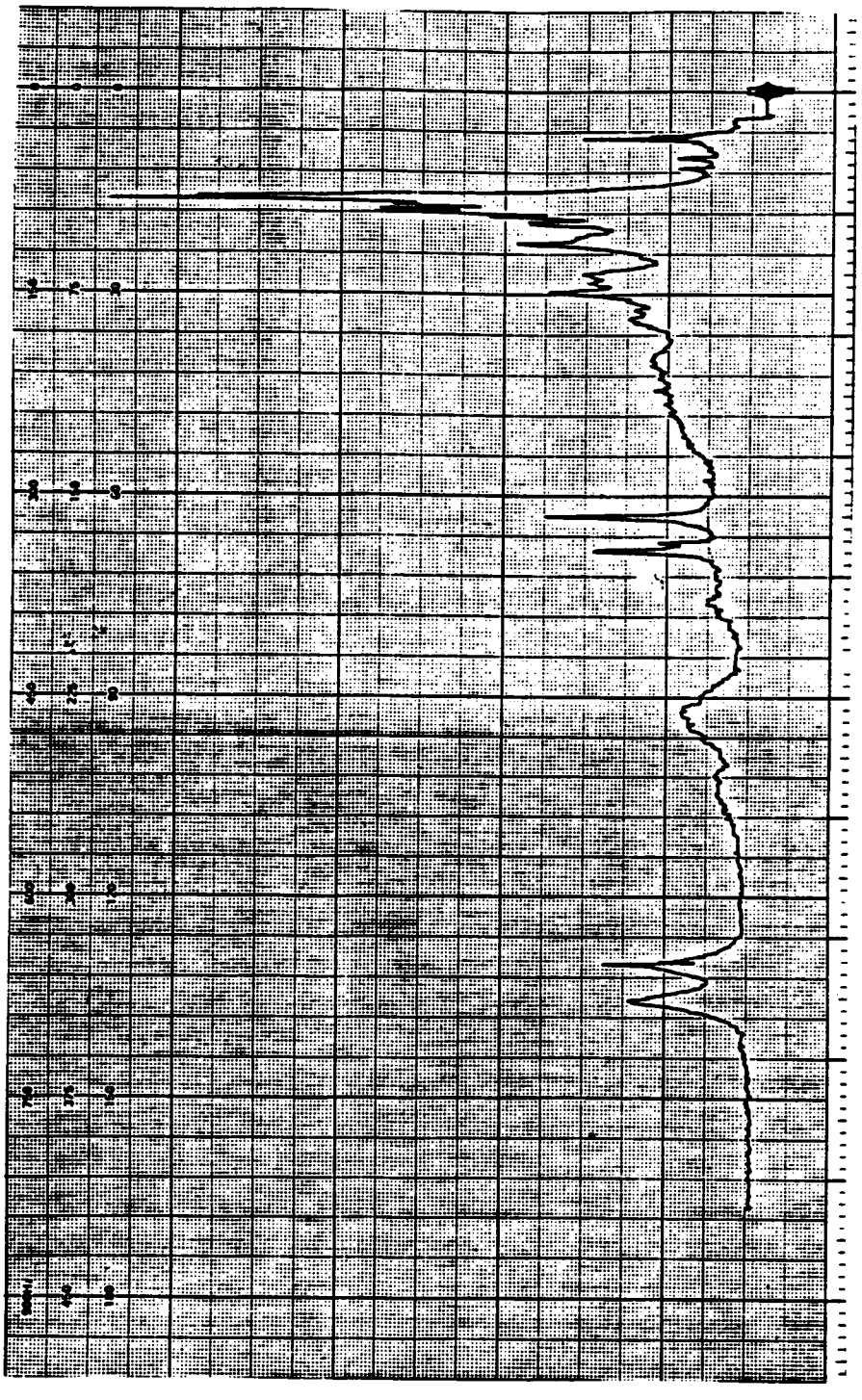
IR spectrum of alcohol 86



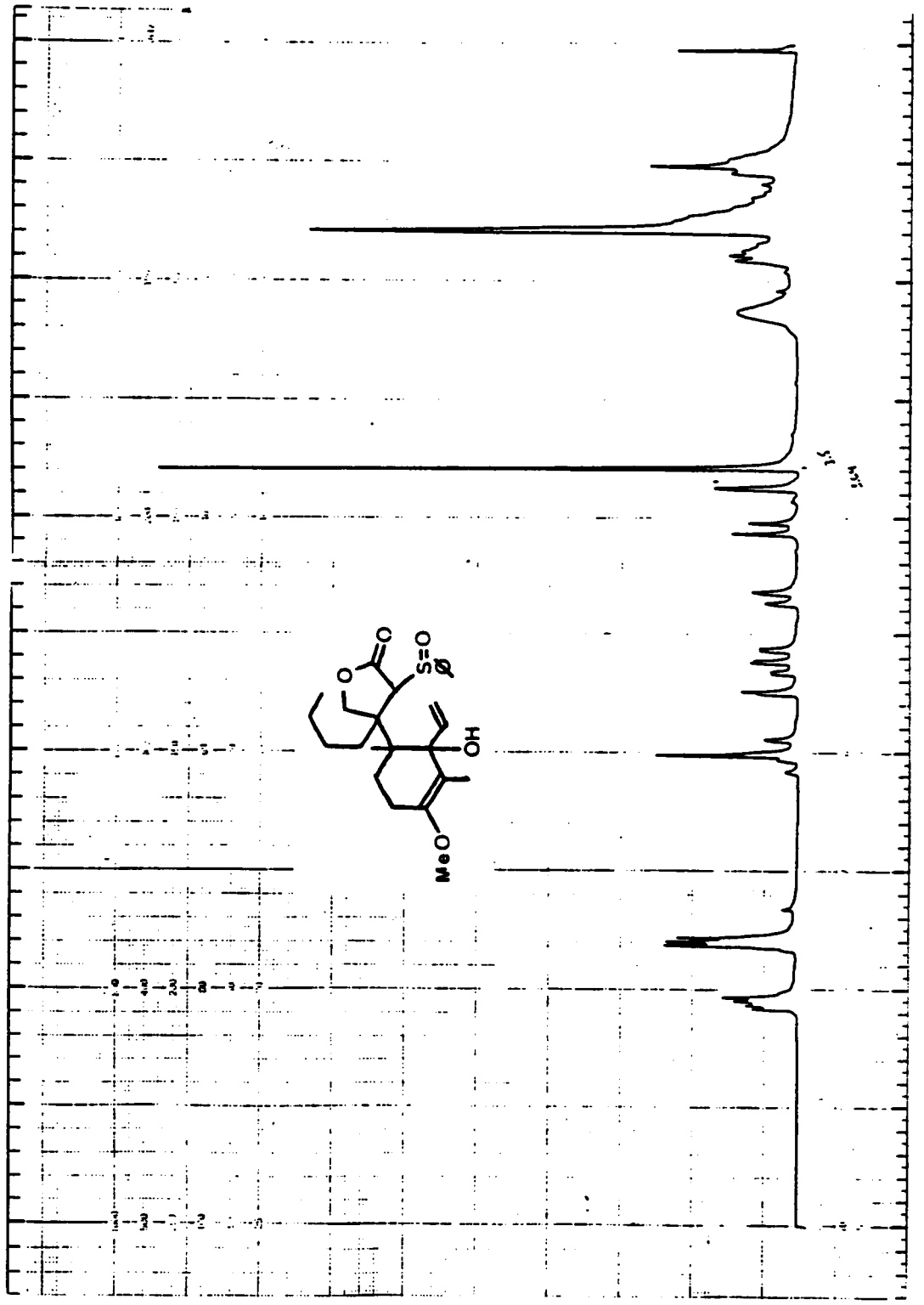
90 MHz ^{1}H NMR spectrum of diene 87



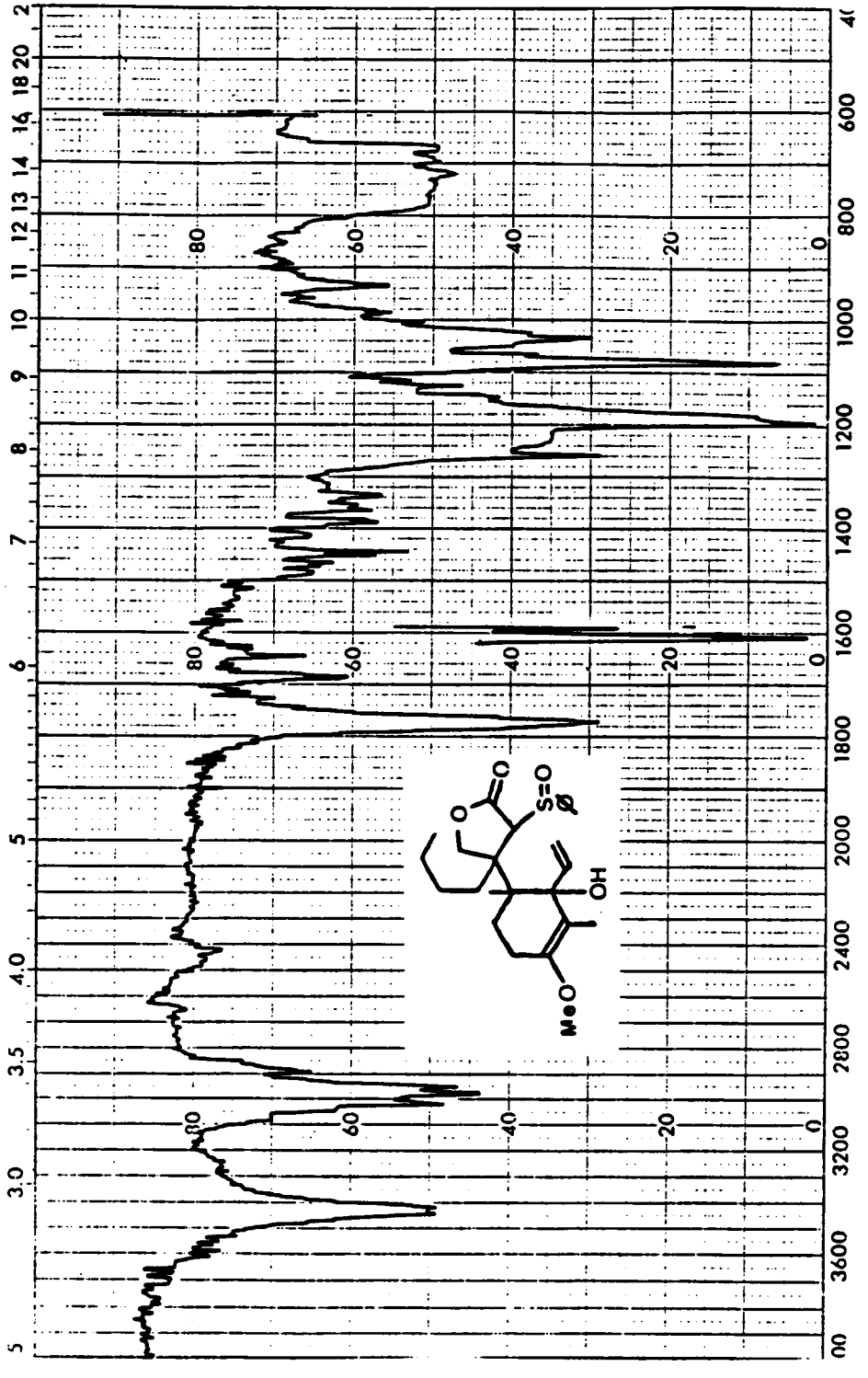
IR spectrum of diene 87



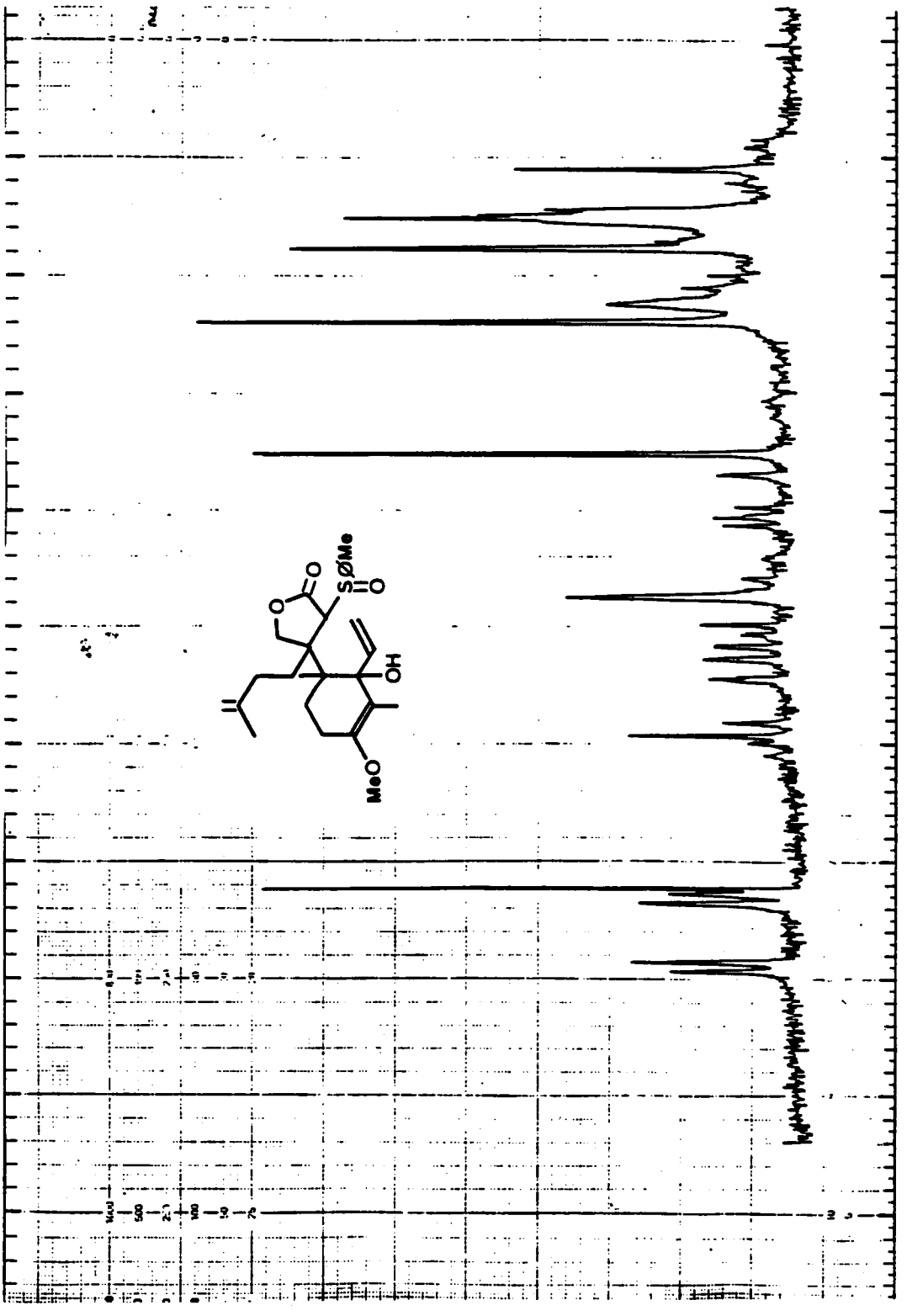
90 MHz ^{1}H NMR spectrum of vinyllithium addition to sulfoxide 88



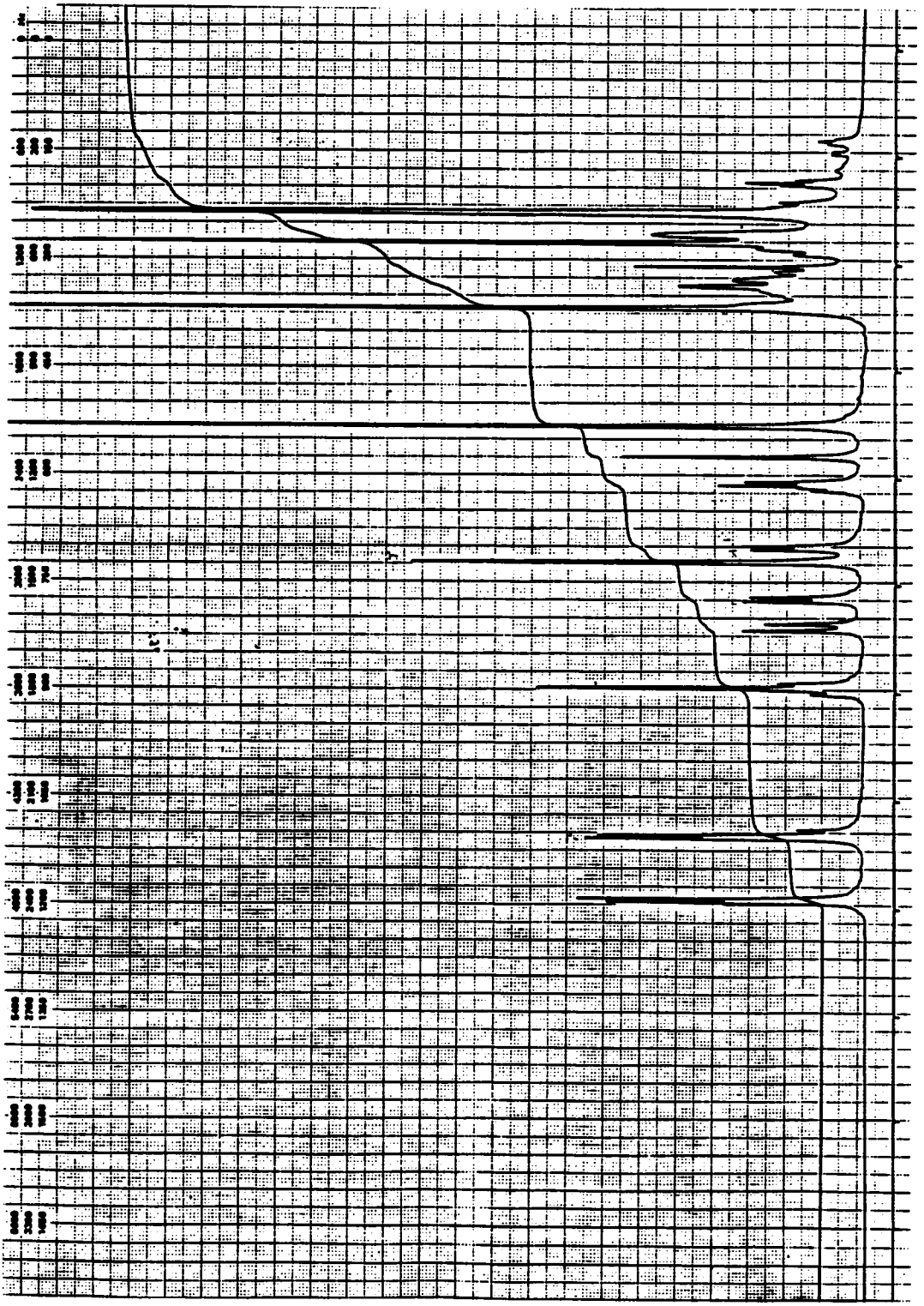
100 MHz ^{1}H NMR spectrum of alcohol 90



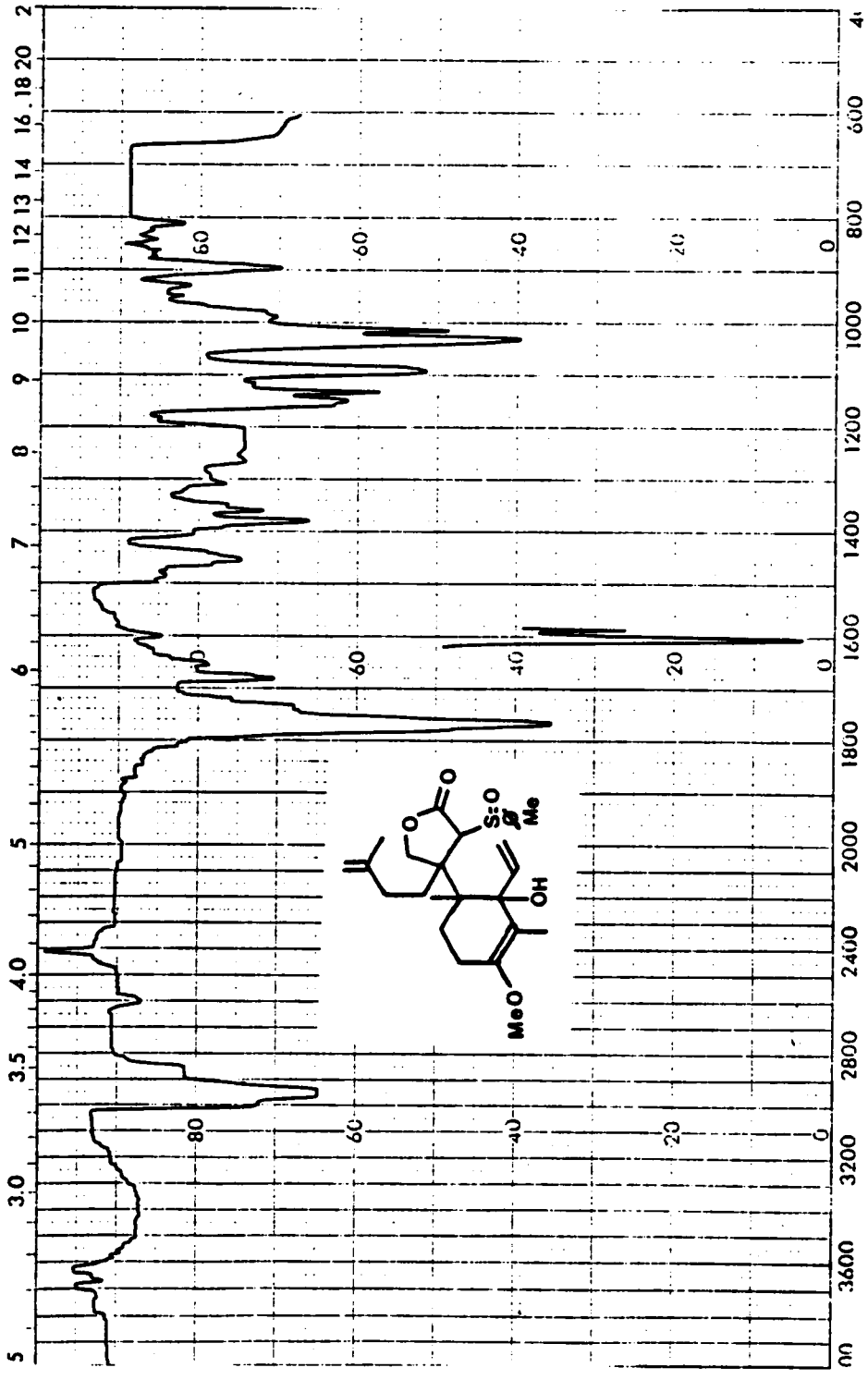
IR spectrum of alcohol 90



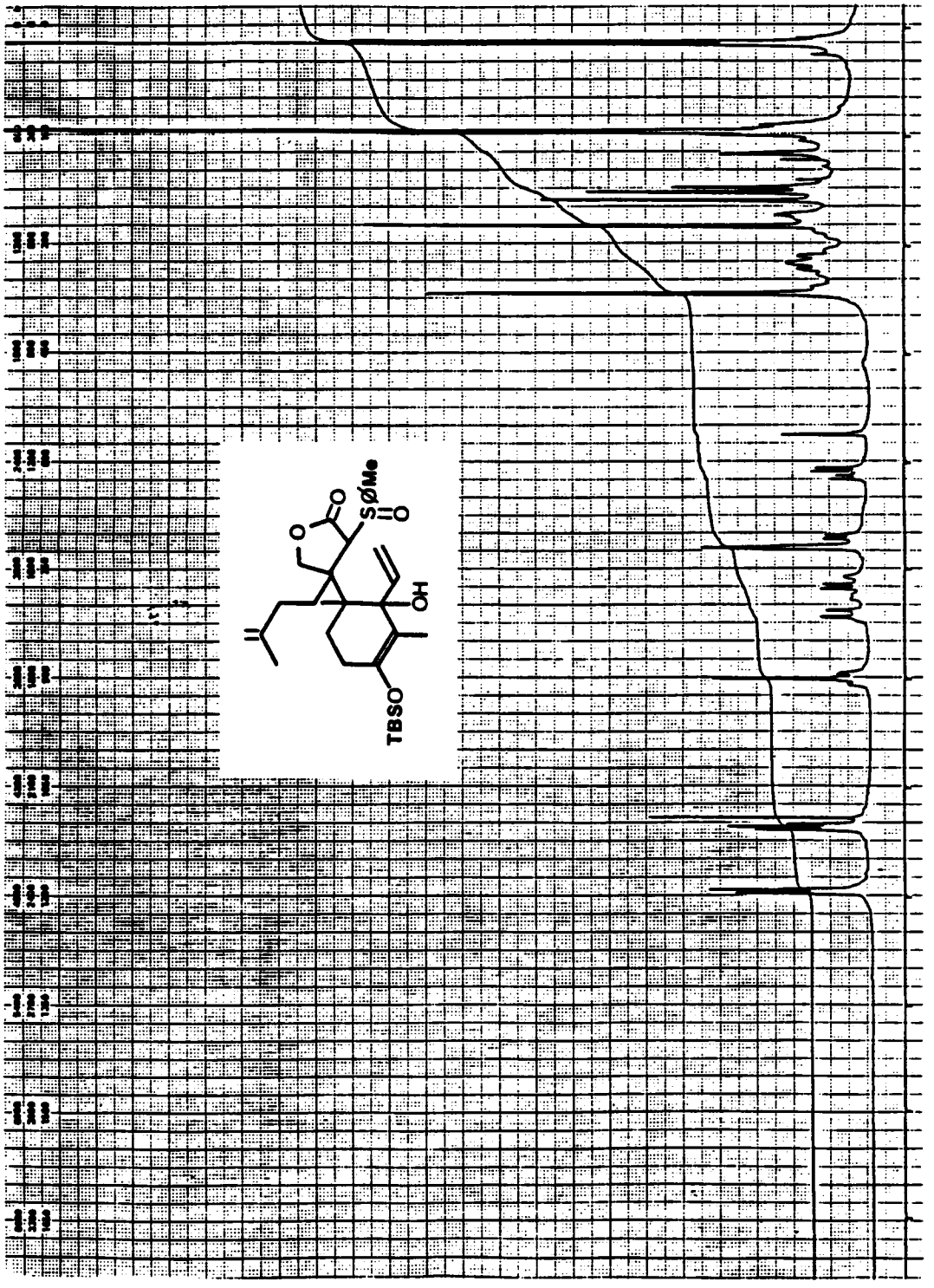
100 MHz ^{1}H NMR spectrum of alcohol 93



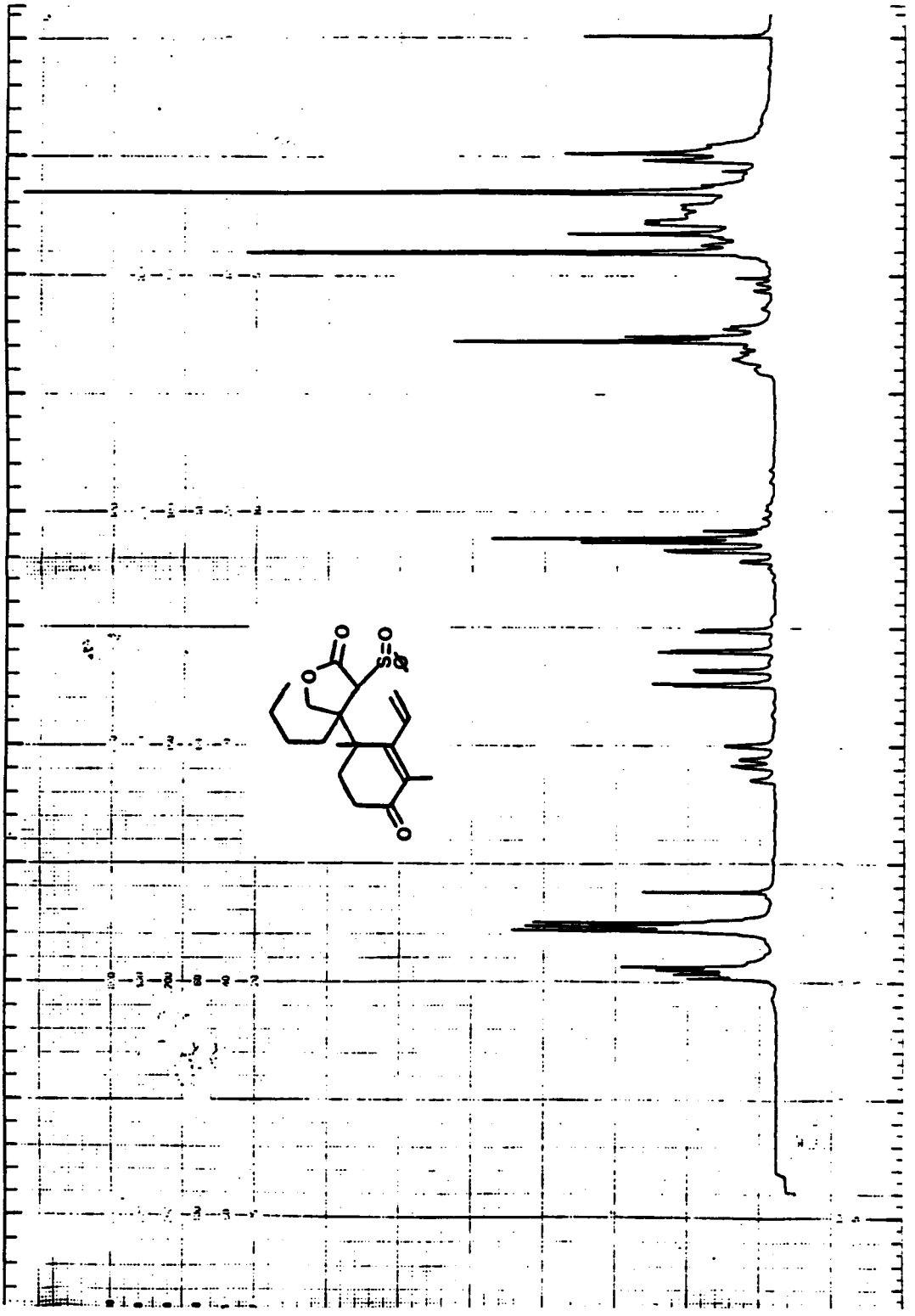
270 MHz ^{1}H NMR spectrum of alcohol 93



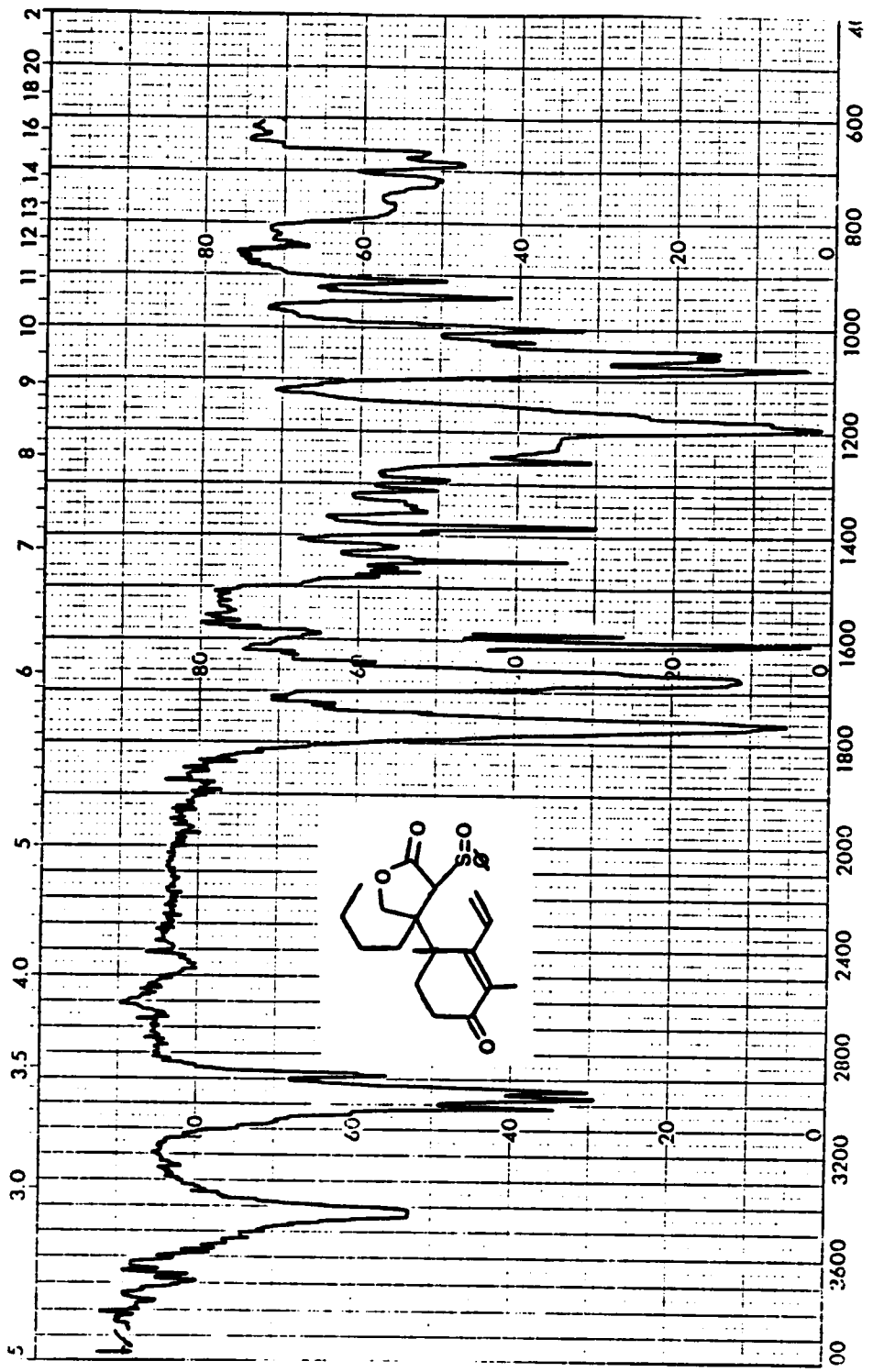
IR spectrum of alcohol 93



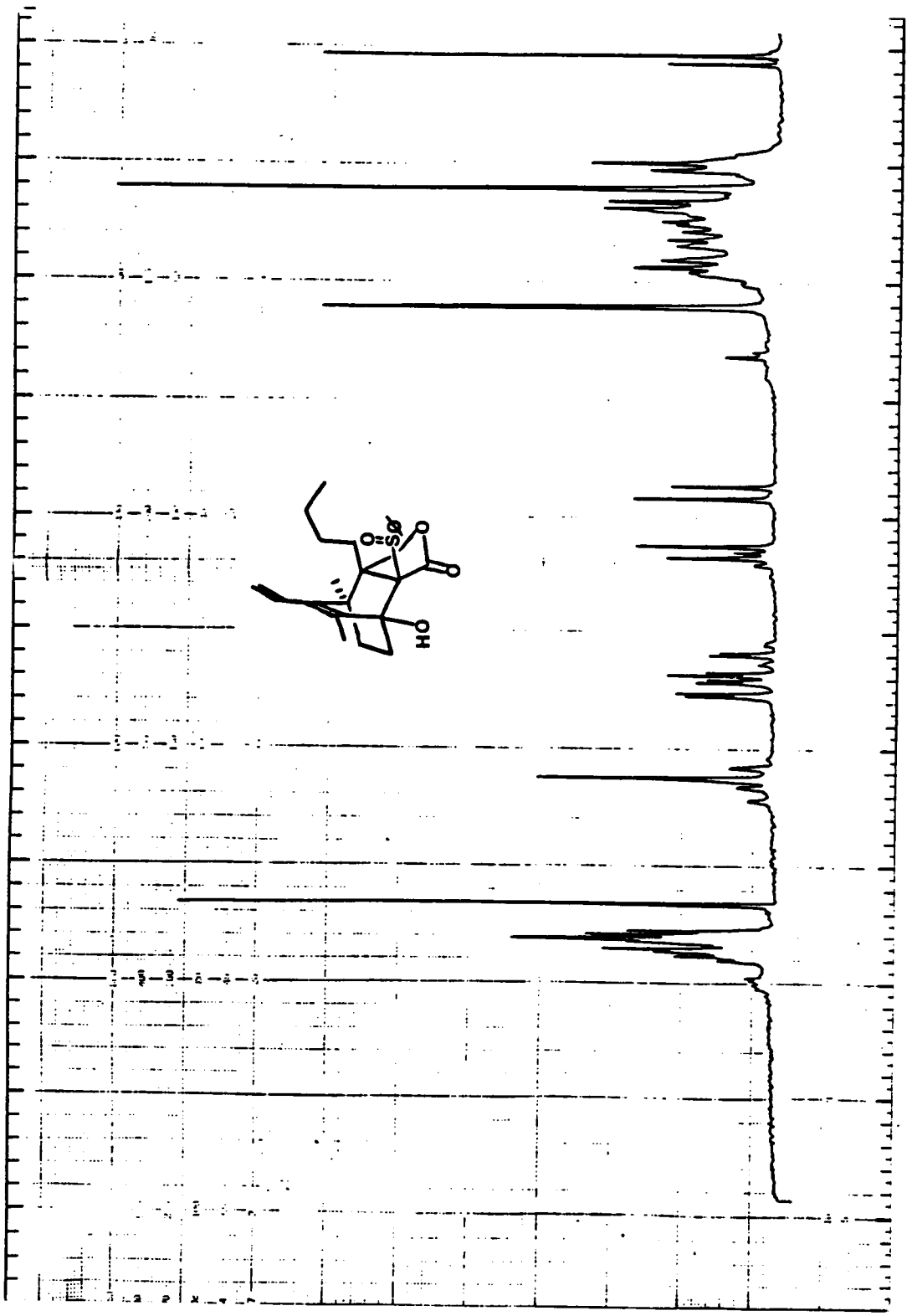
270 MHz ^{1}NMR spectrum of alcohol 94



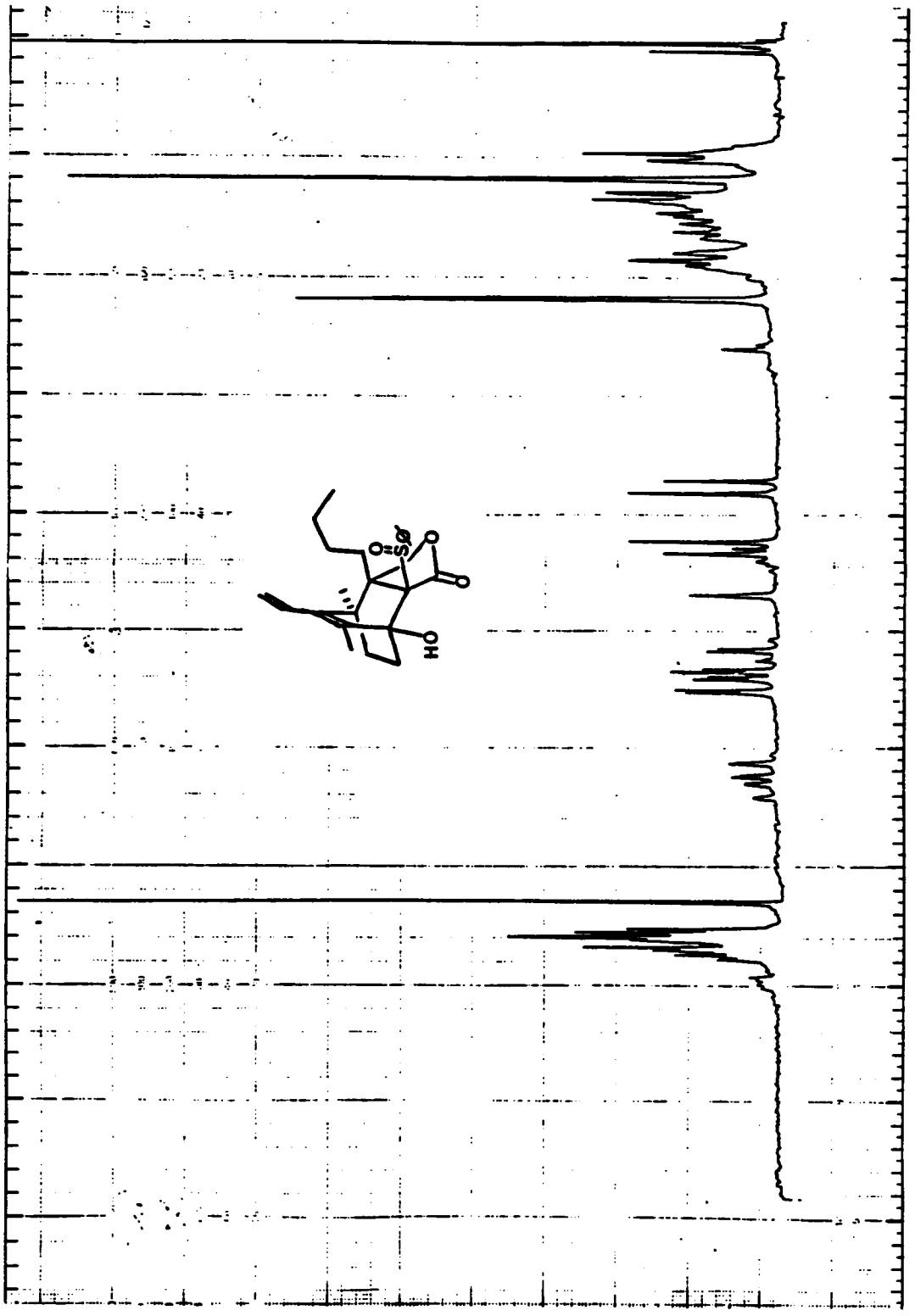
100 MHz ^{1}H NMR spectrum of vinyl enone 95



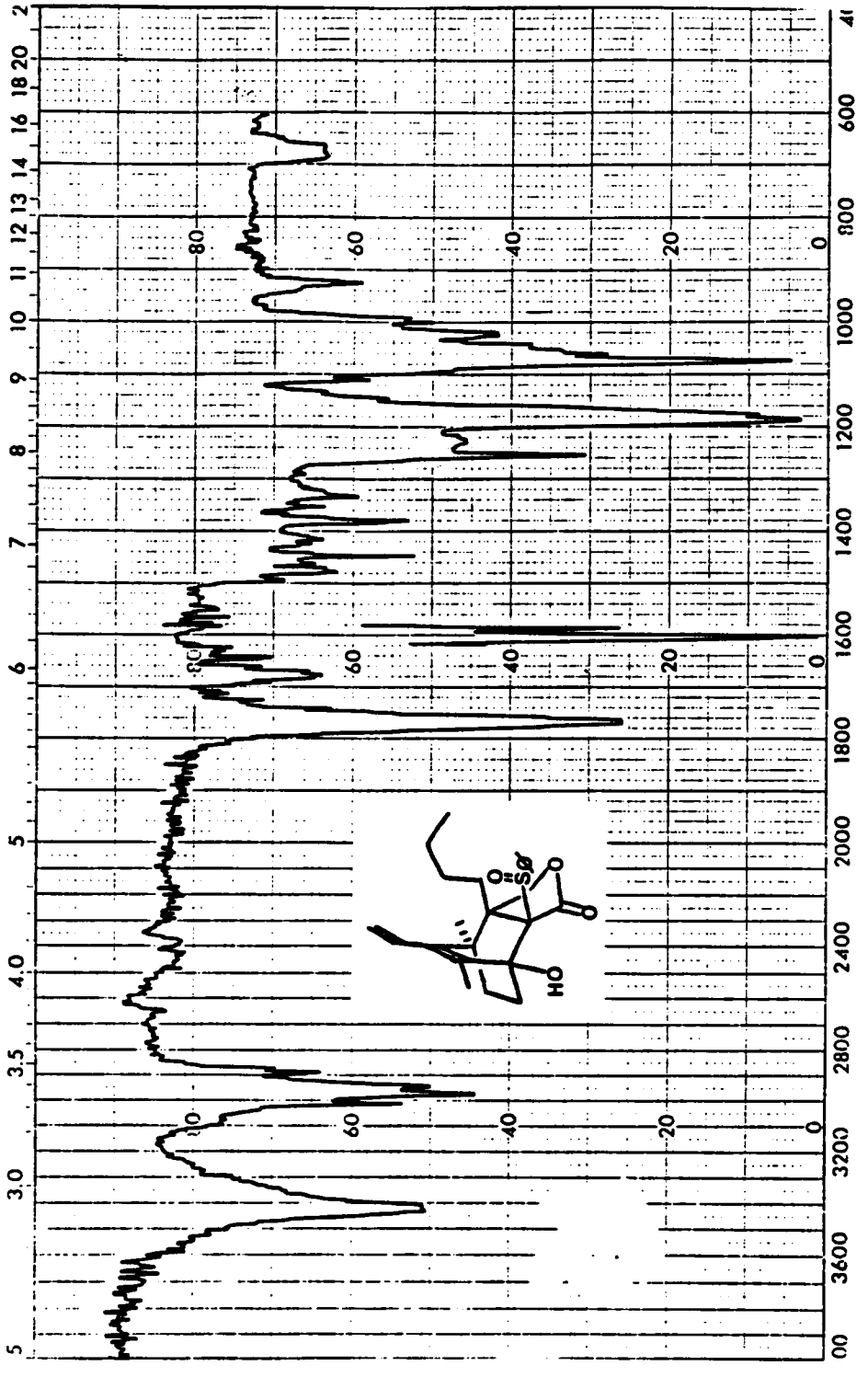
IR spectrum of vinyl enone 95



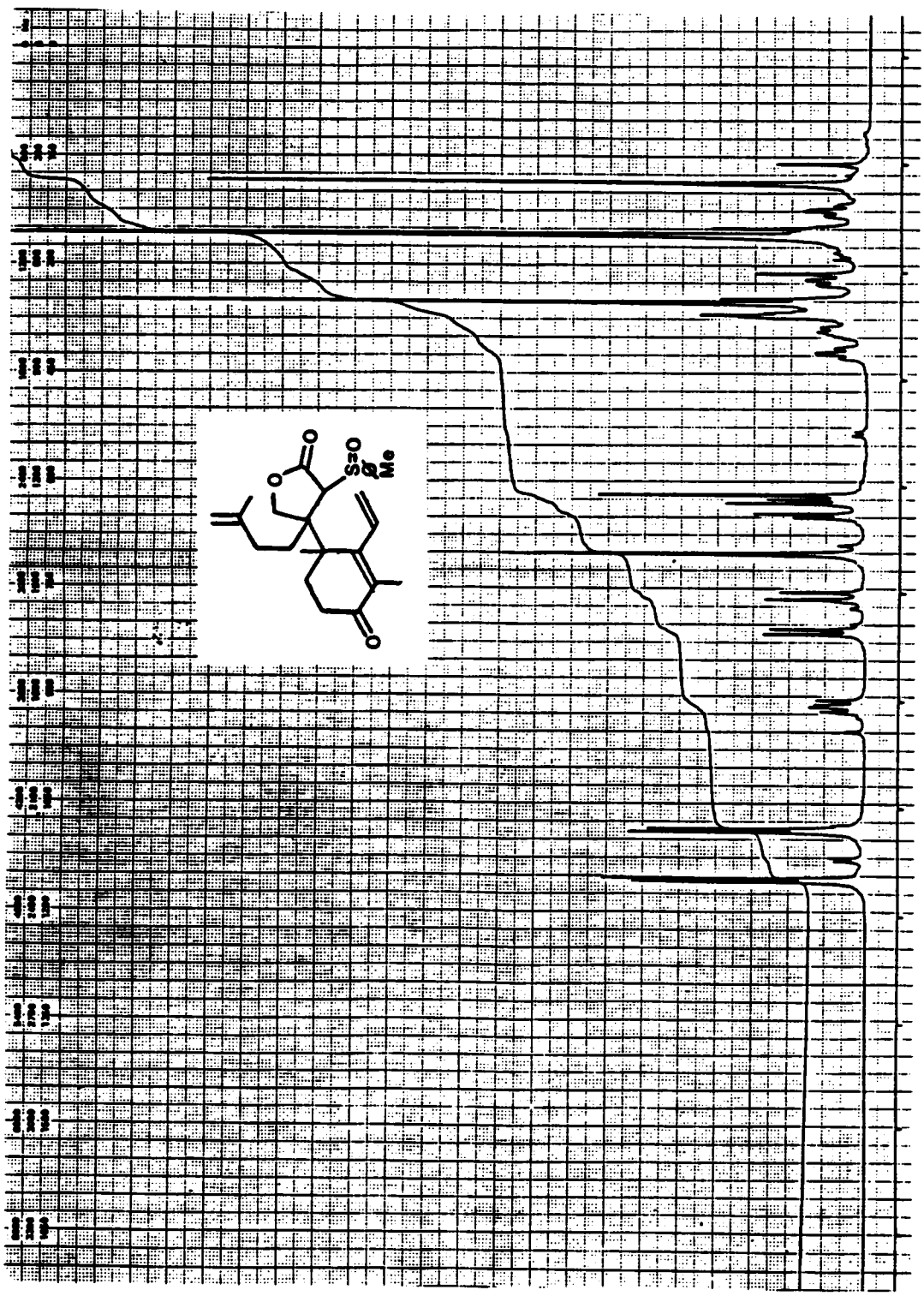
100 MHz ^{1}H NMR spectrum of alcohol 96



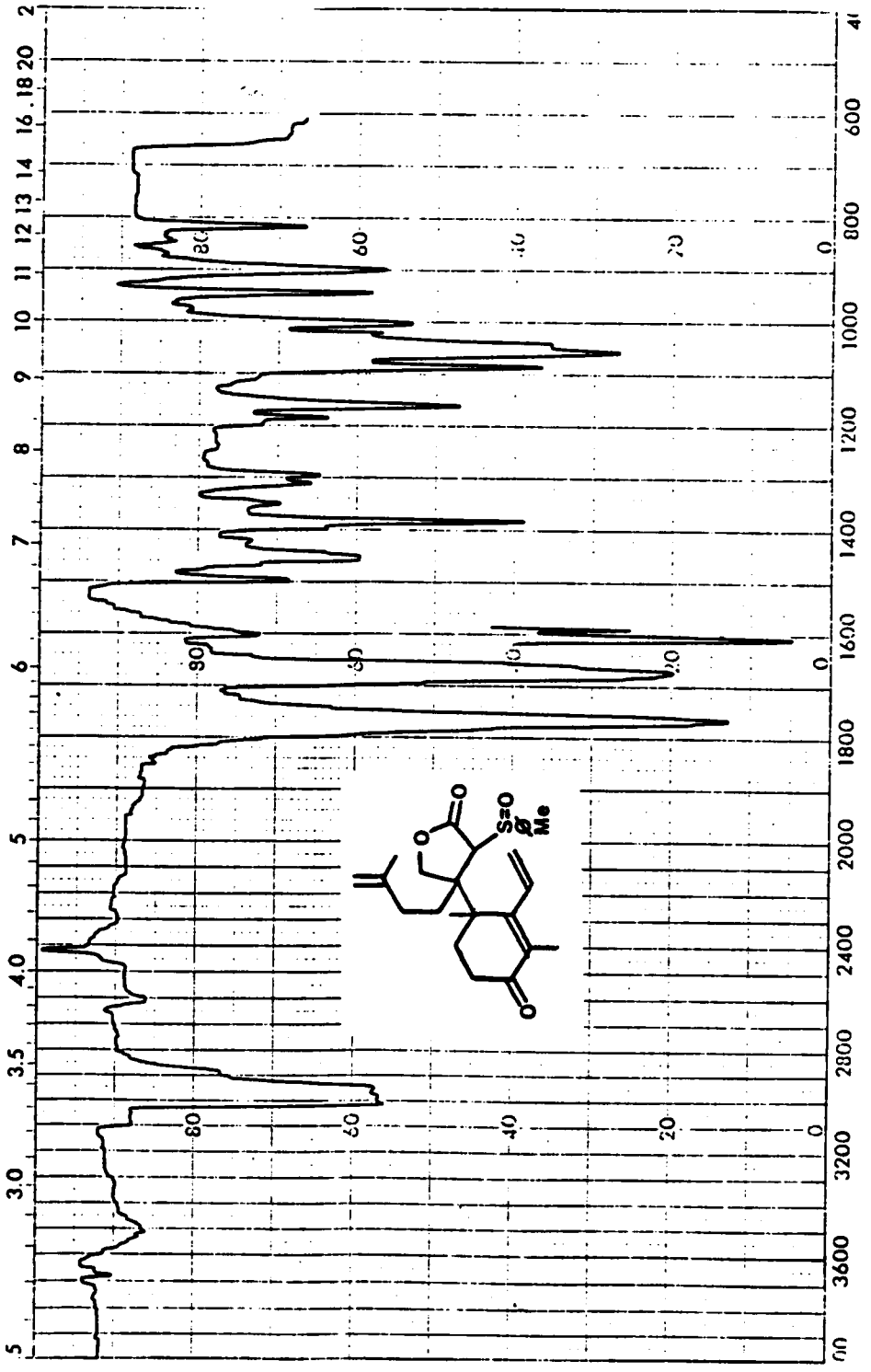
100 MHz ^{1}H NMR spectrum of alcohol 96; D_2O exchanged



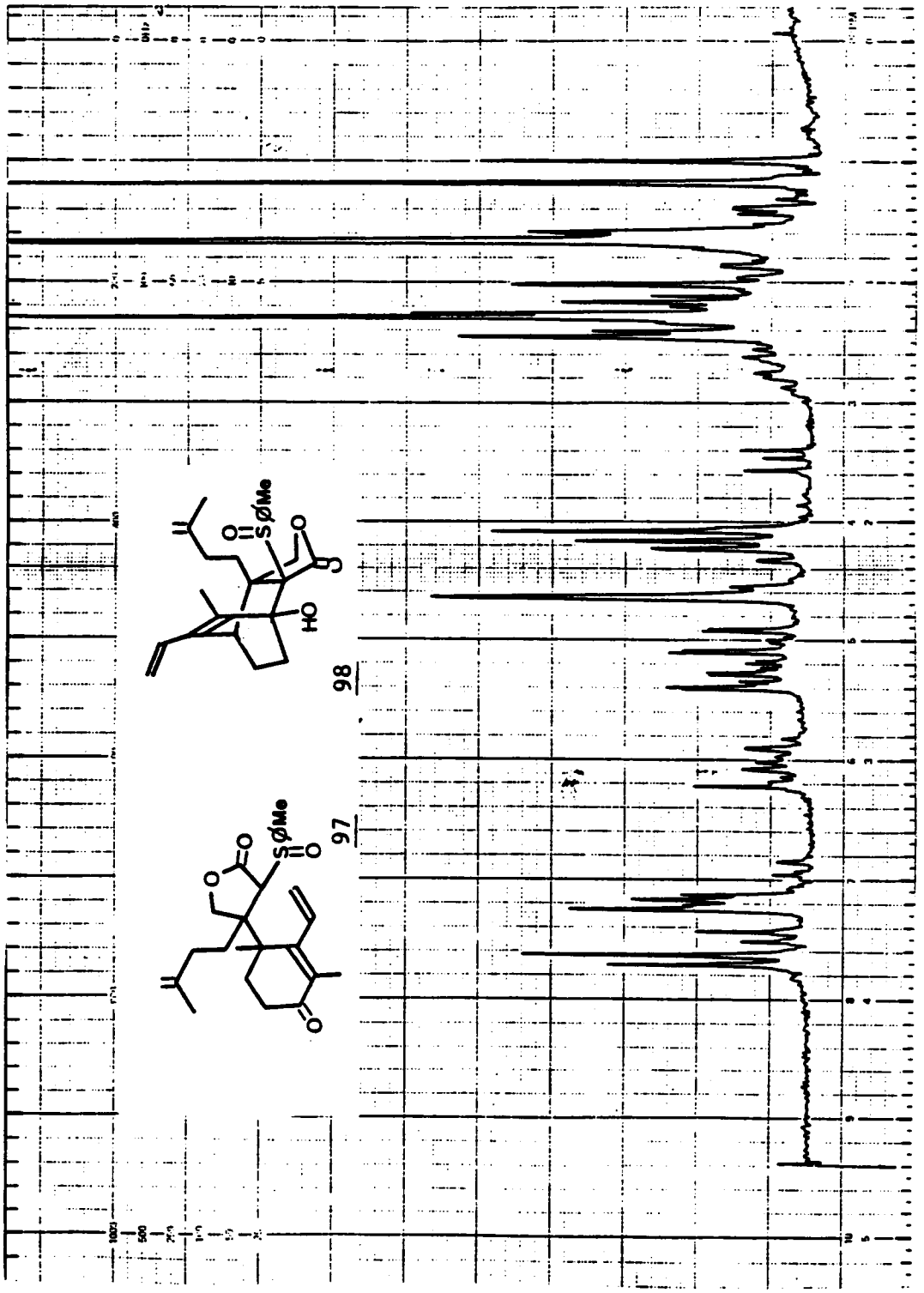
IR spectrum of alcohol 96



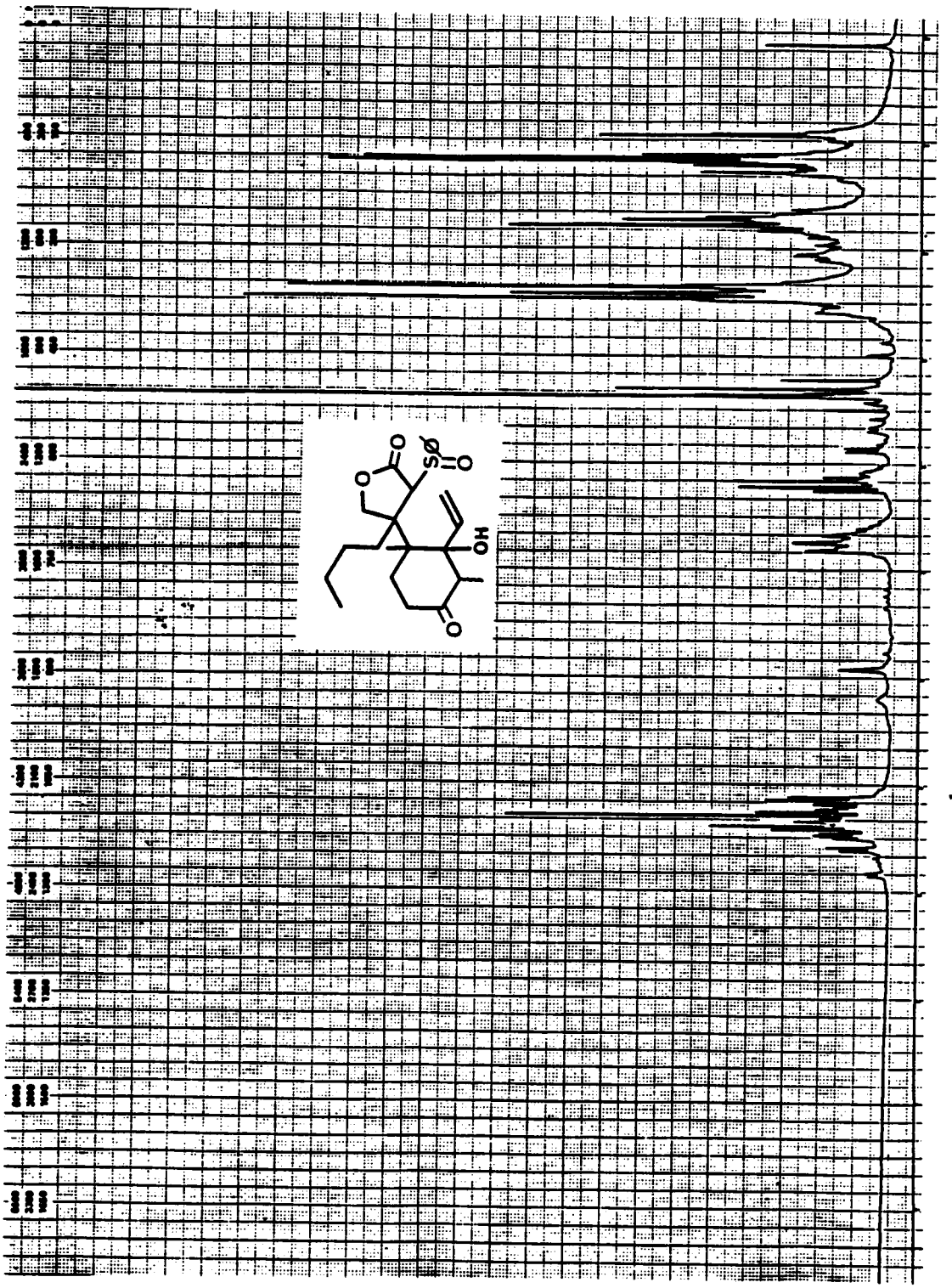
270 MHz ^{1}H NMR spectrum of vinyl enone 97



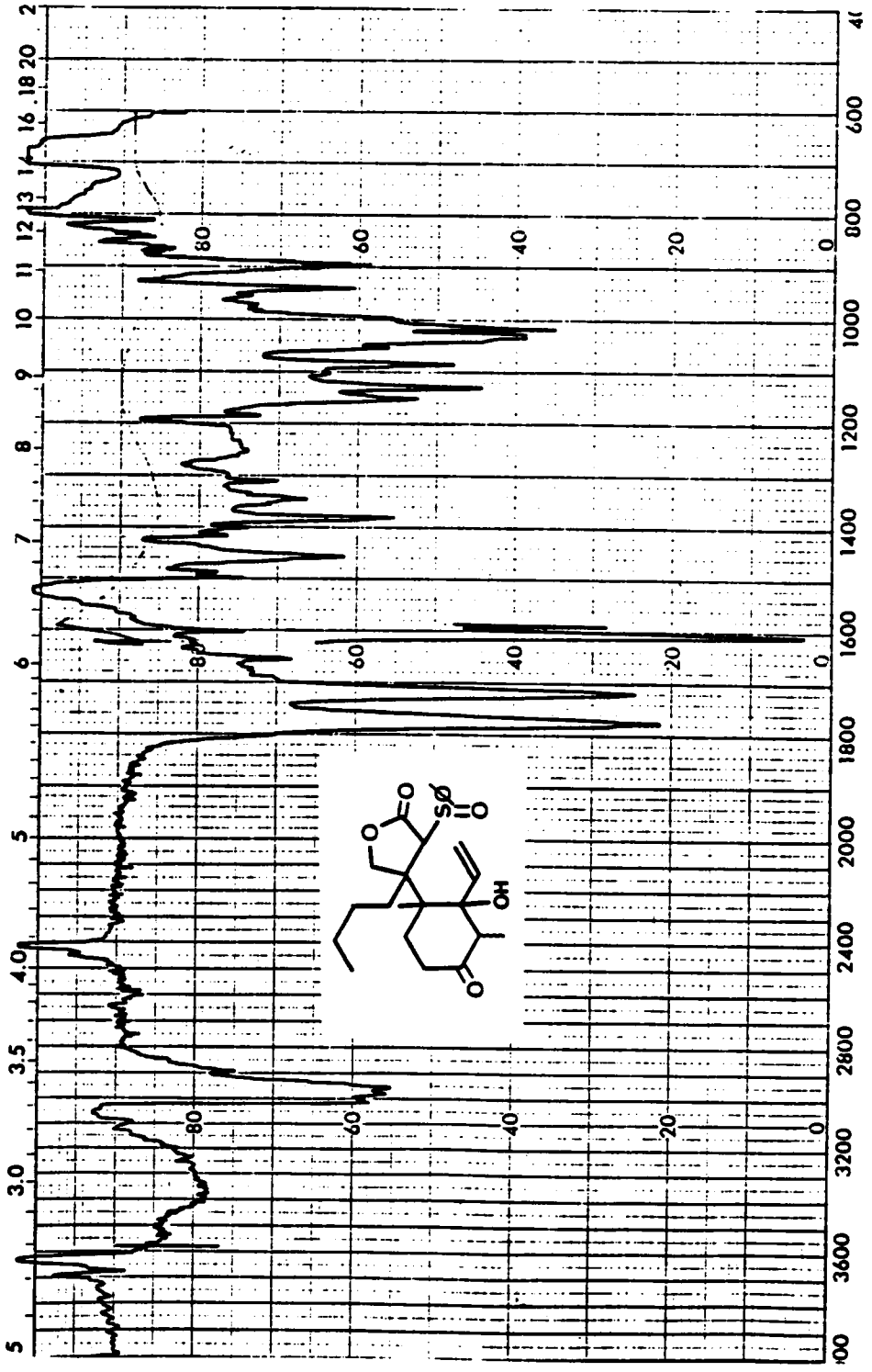
IR spectrum of vinyl enone 97



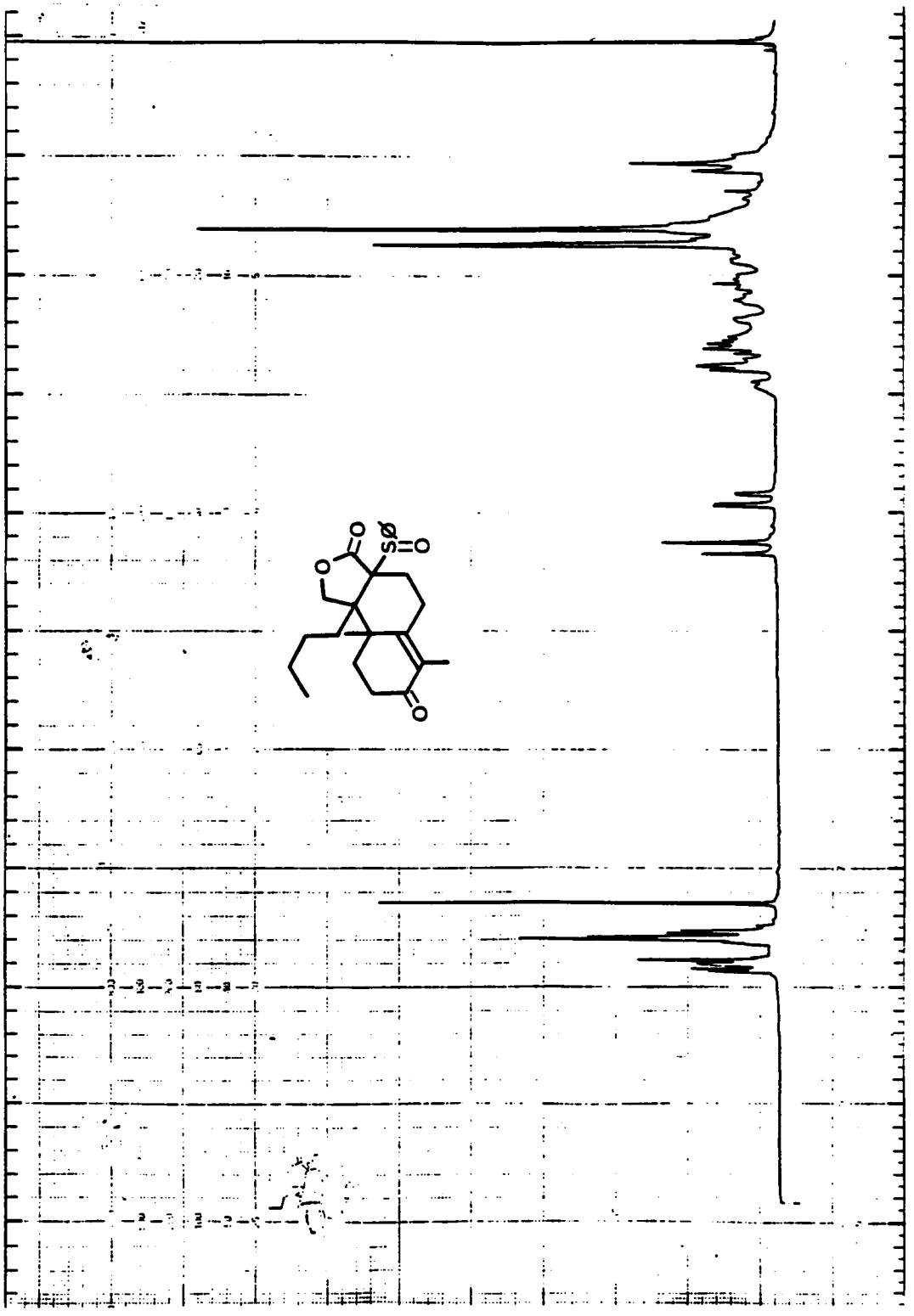
100 MHz ^{1}H NMR spectrum of a mixture of 97 and 98



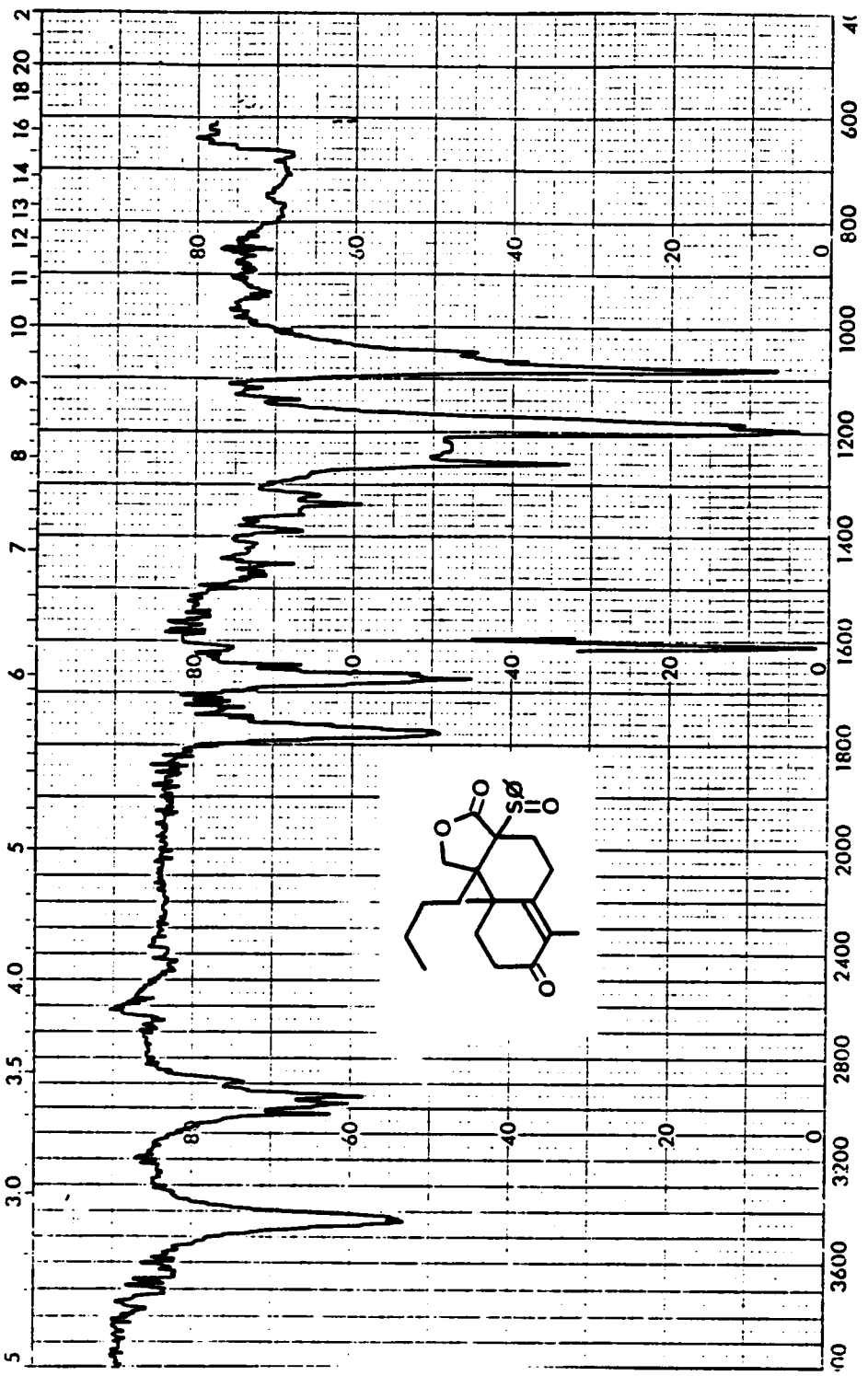
270 MHz ^{1}H NMR spectrum of ketone 99



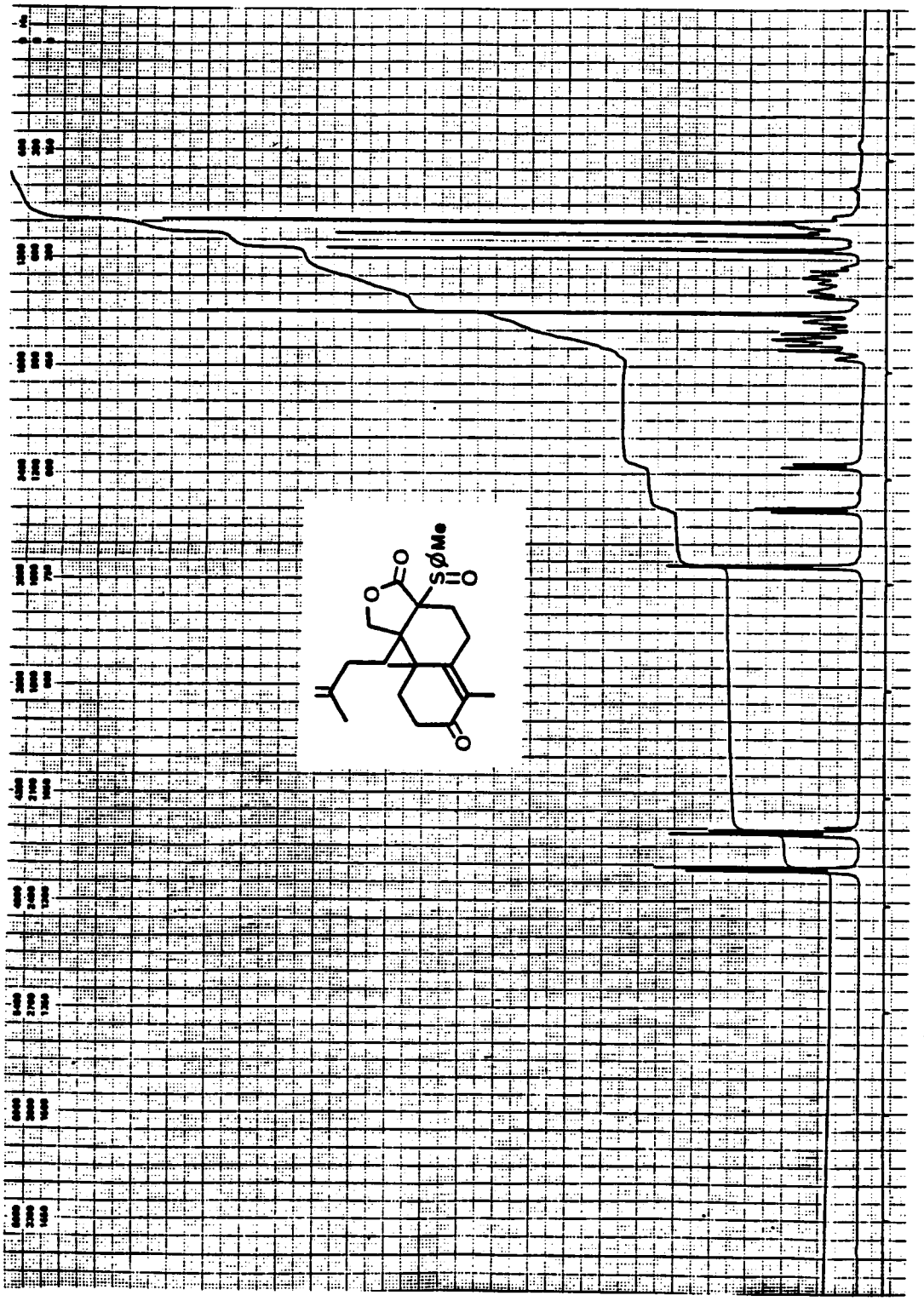
IR spectrum of ketone 99



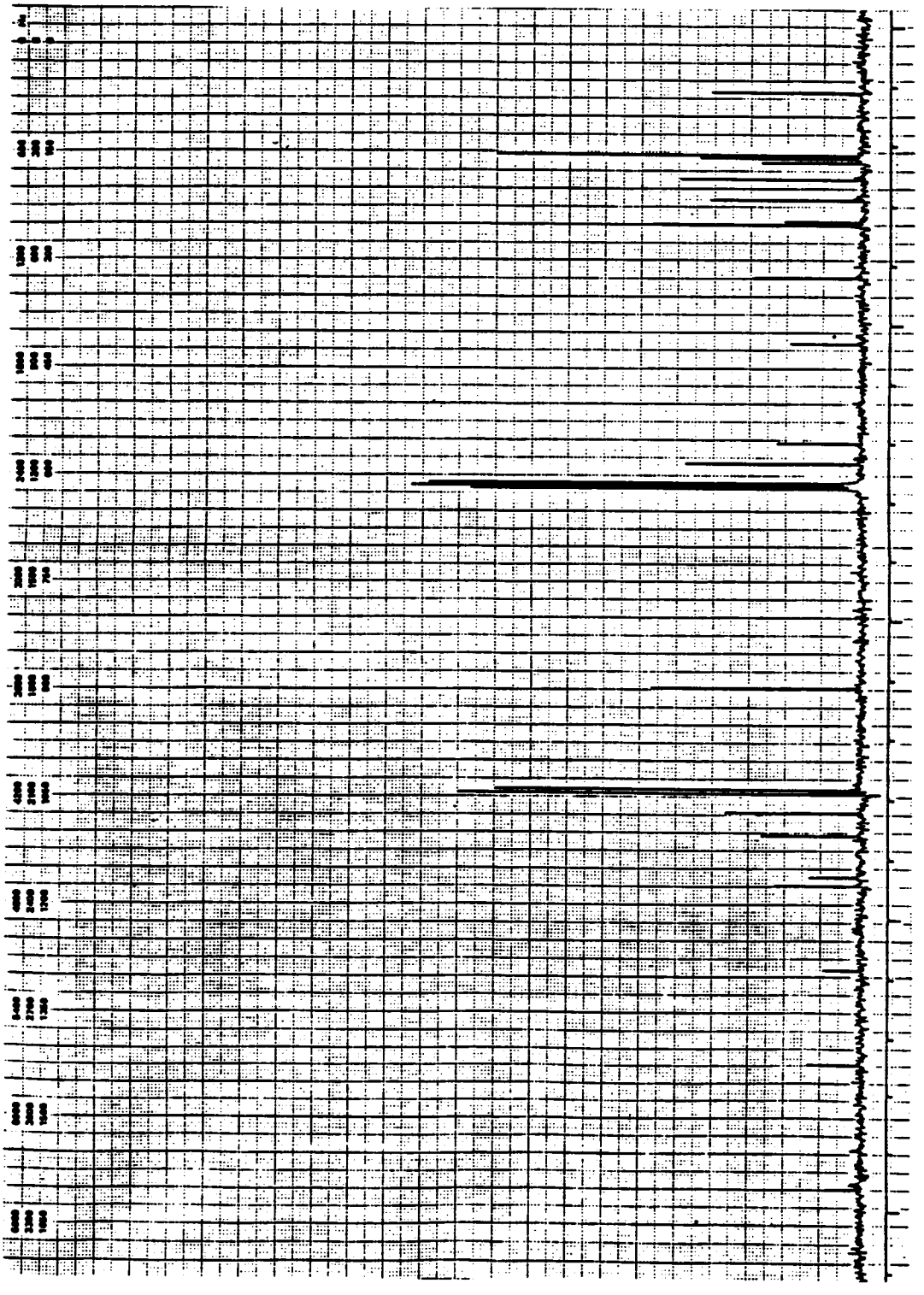
100 MHz ^{1}H NMR spectrum of enone 100



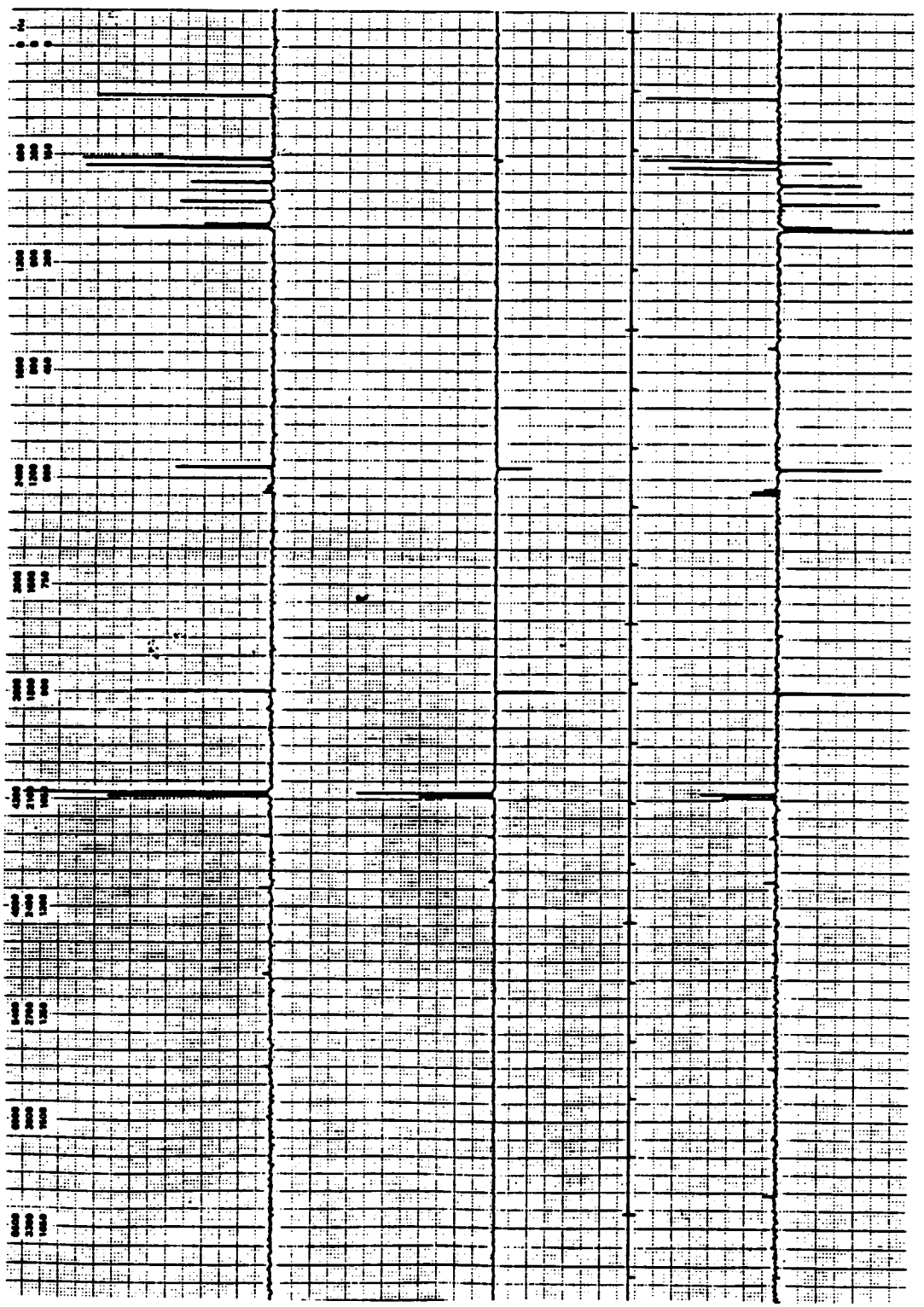
IR spectrum of enone 100



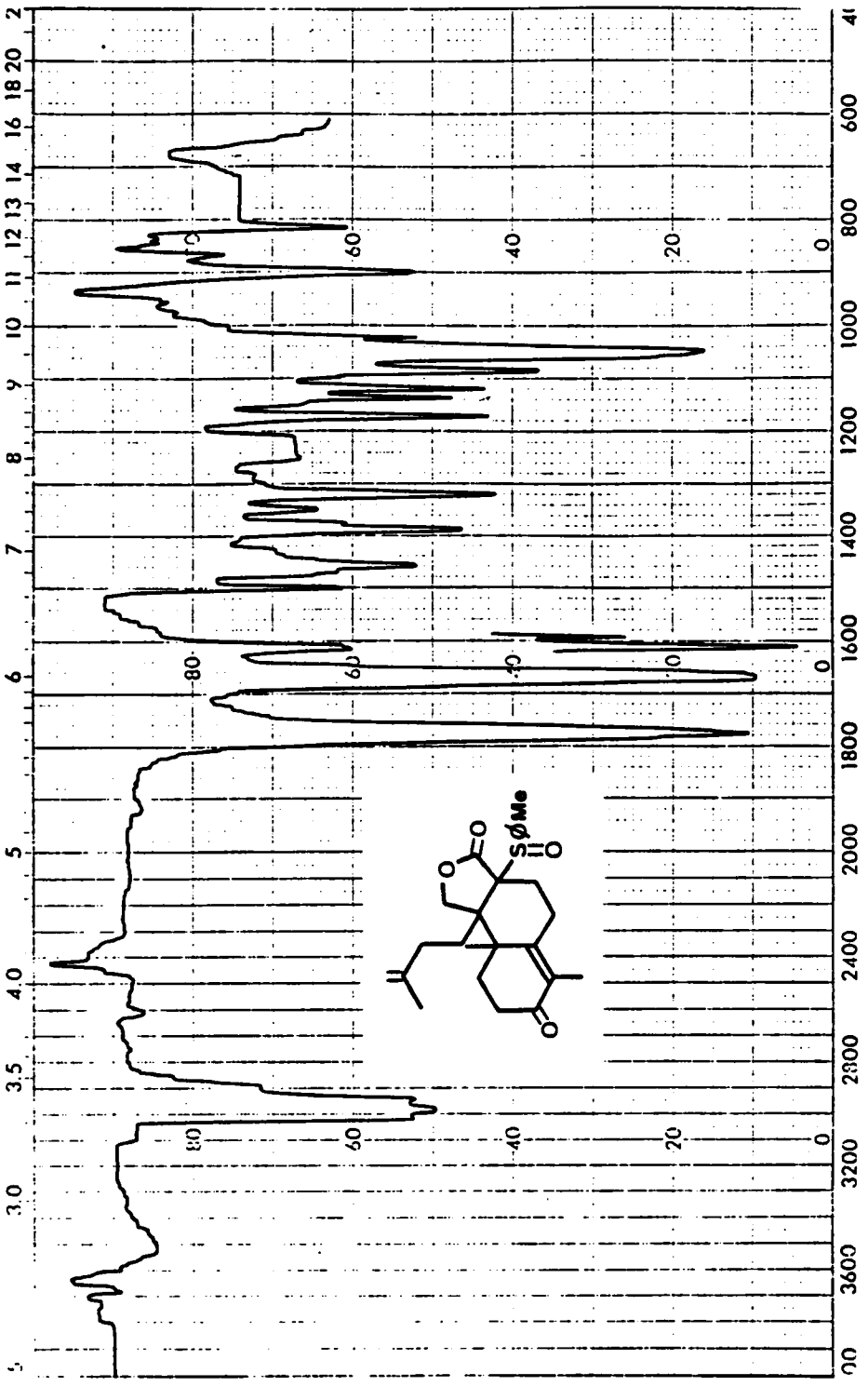
270 MHz ^{1}H NMR spectrum of enone 101



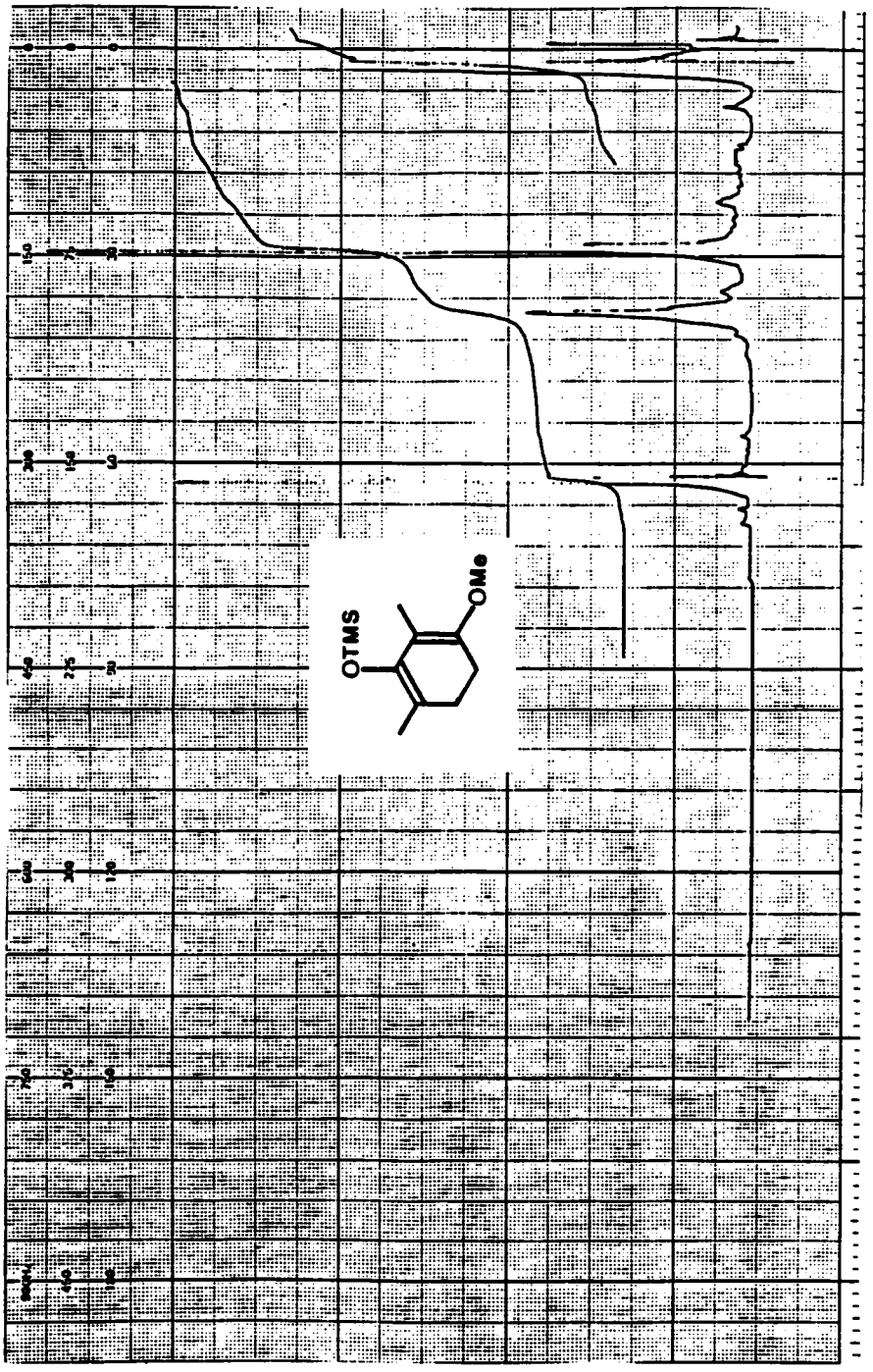
270 MHz ^{13}C NMR spectrum of enone 101



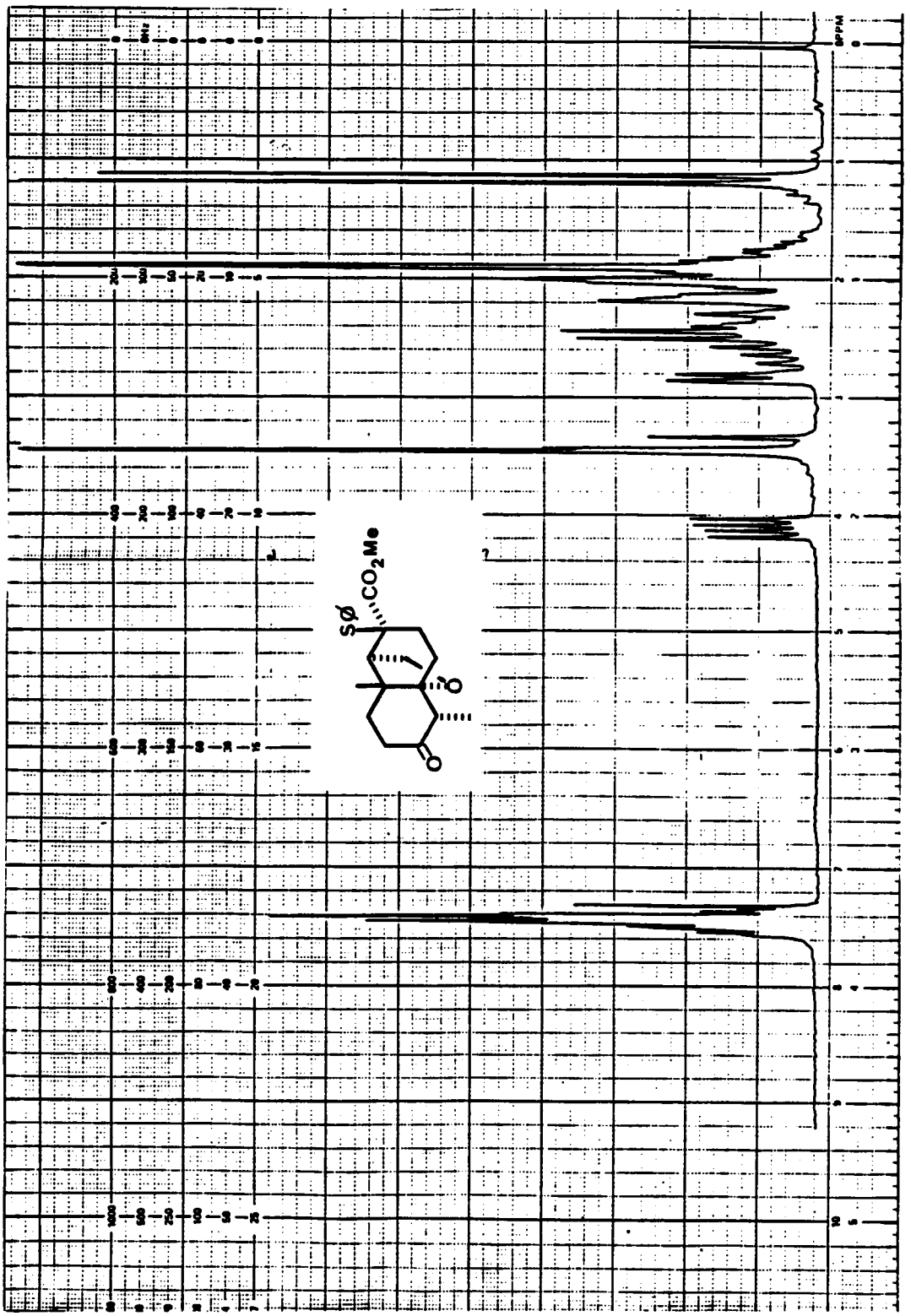
270 MHz ^{13}C INEPT spectra of enone 101



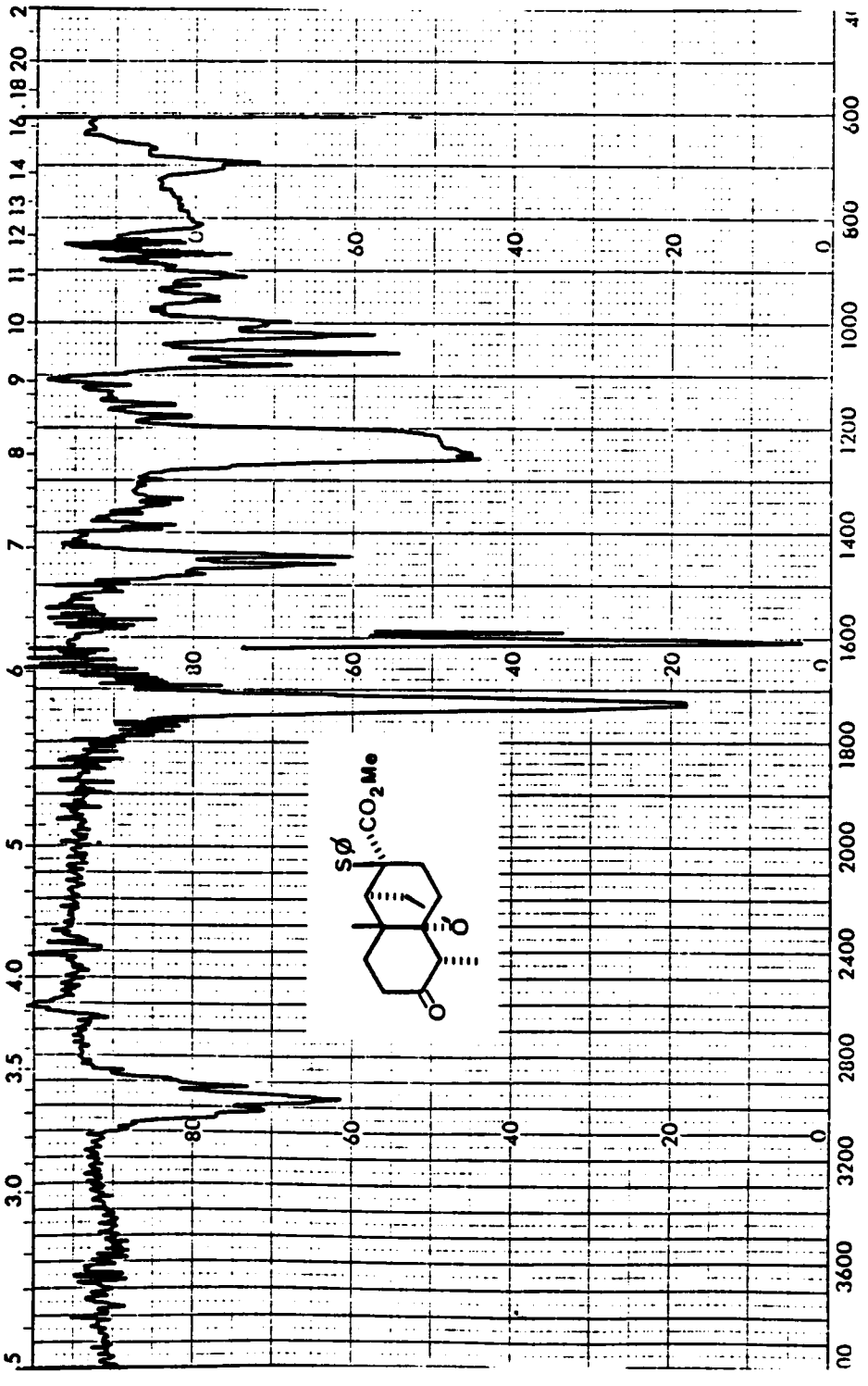
IR spectrum of enone 101



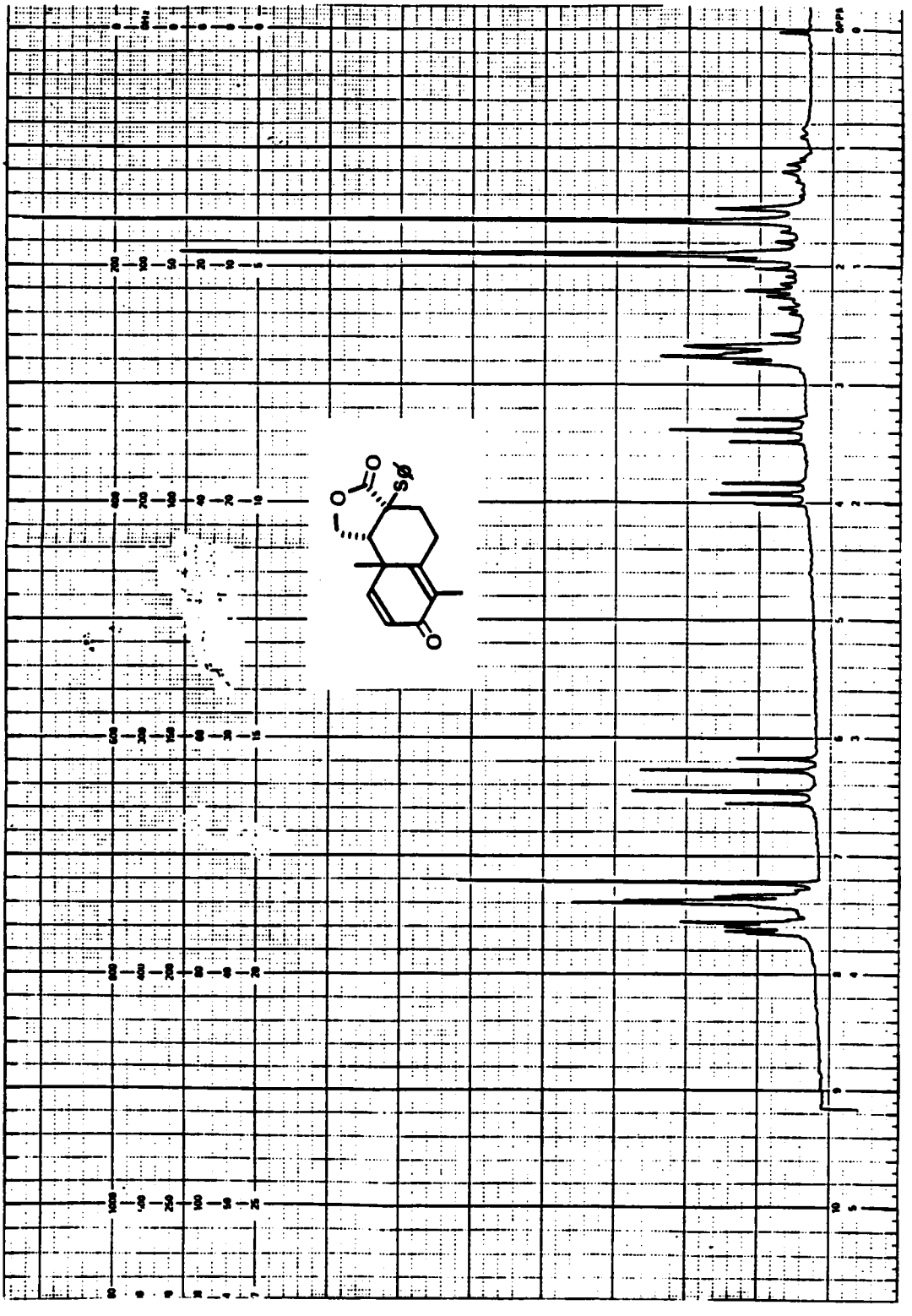
90 MHz ^{1}H NMR spectrum of silyl enol ether 102



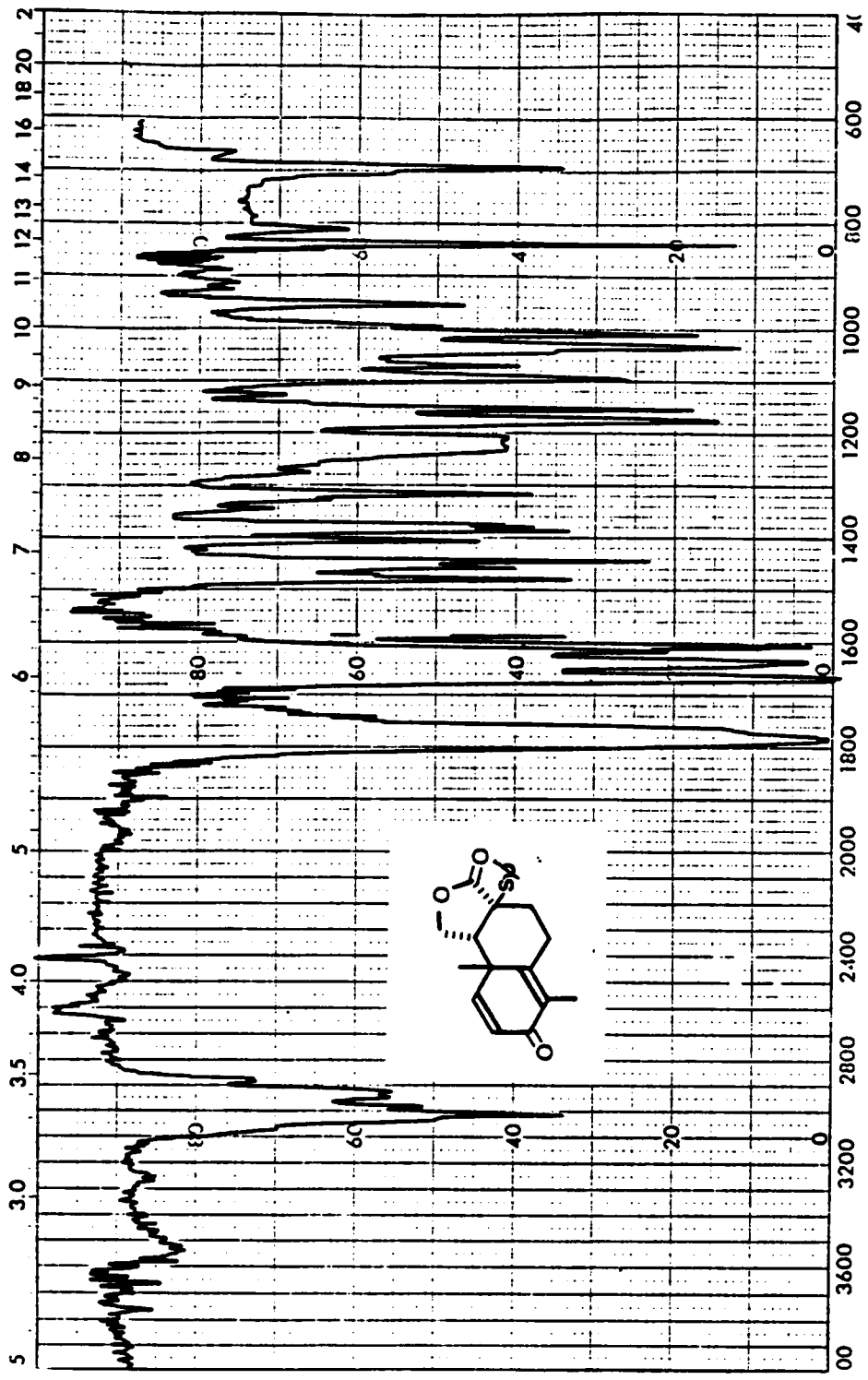
100 MHz ^1H NMR spectrum of furan 104



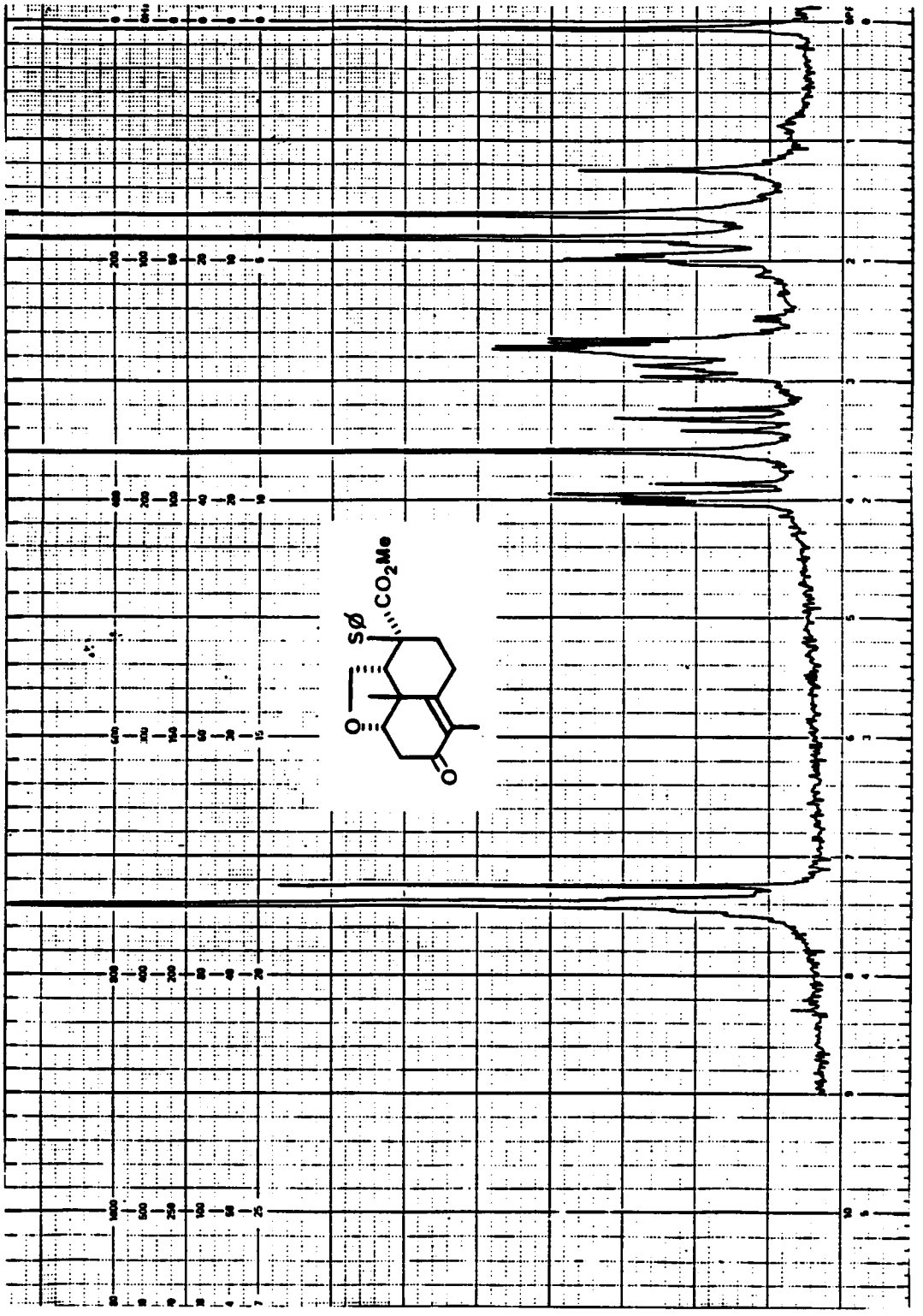
IR spectrum of furan 104



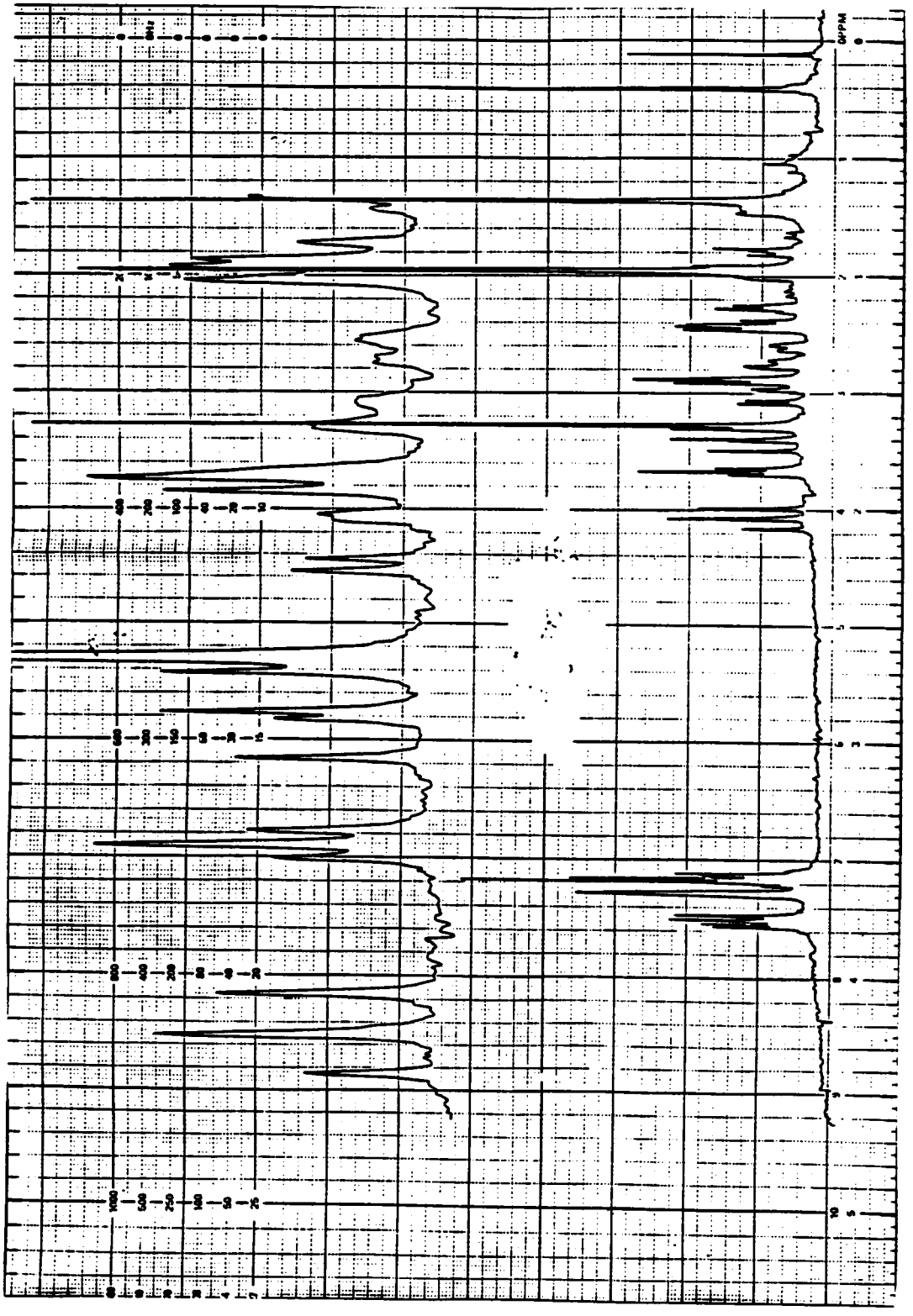
100 MHz ^{1}H NMR spectrum of dienone 105



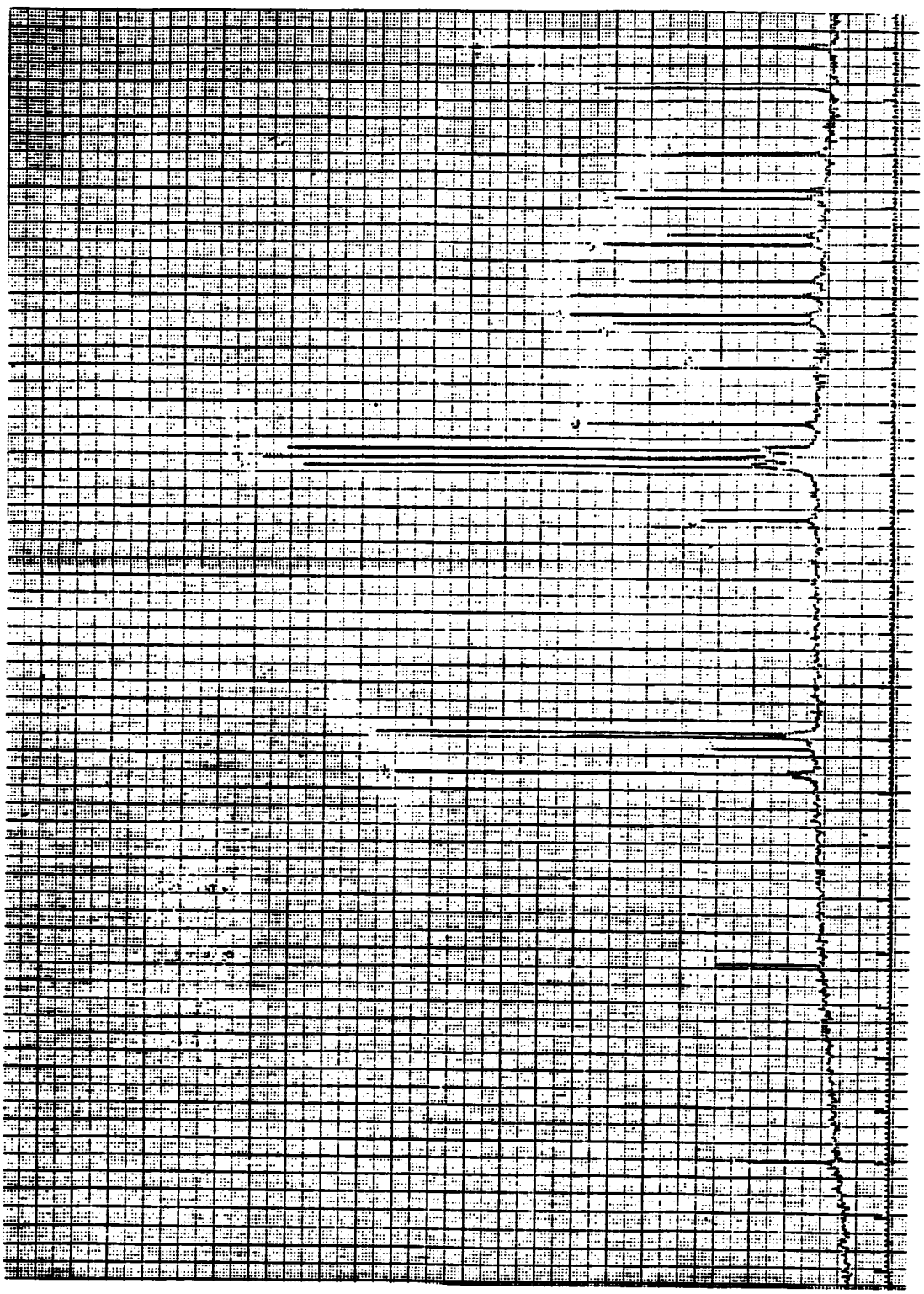
IR spectrum of dienone 105



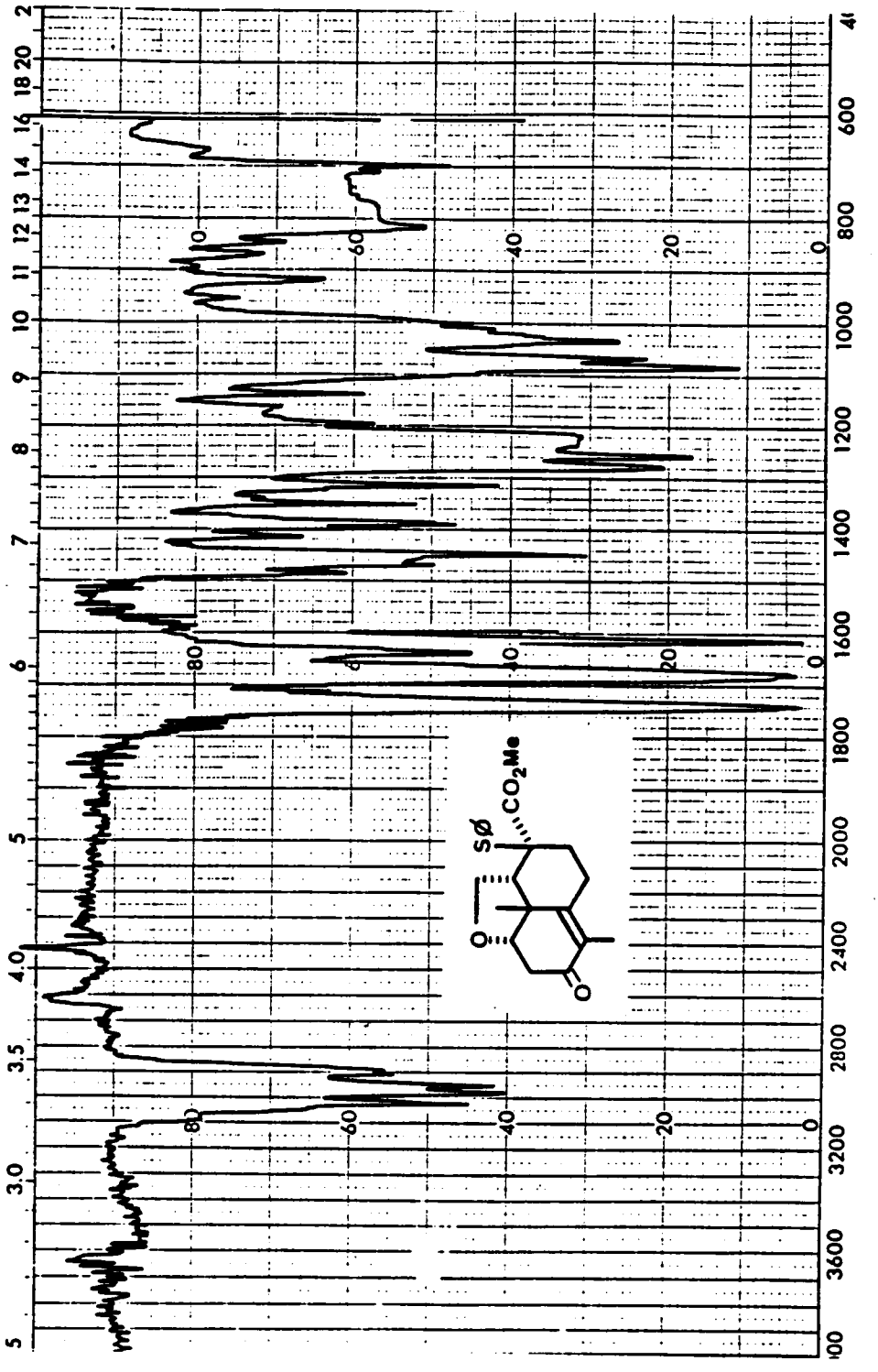
100 MHz ^{1}H NMR spectrum of enone 106



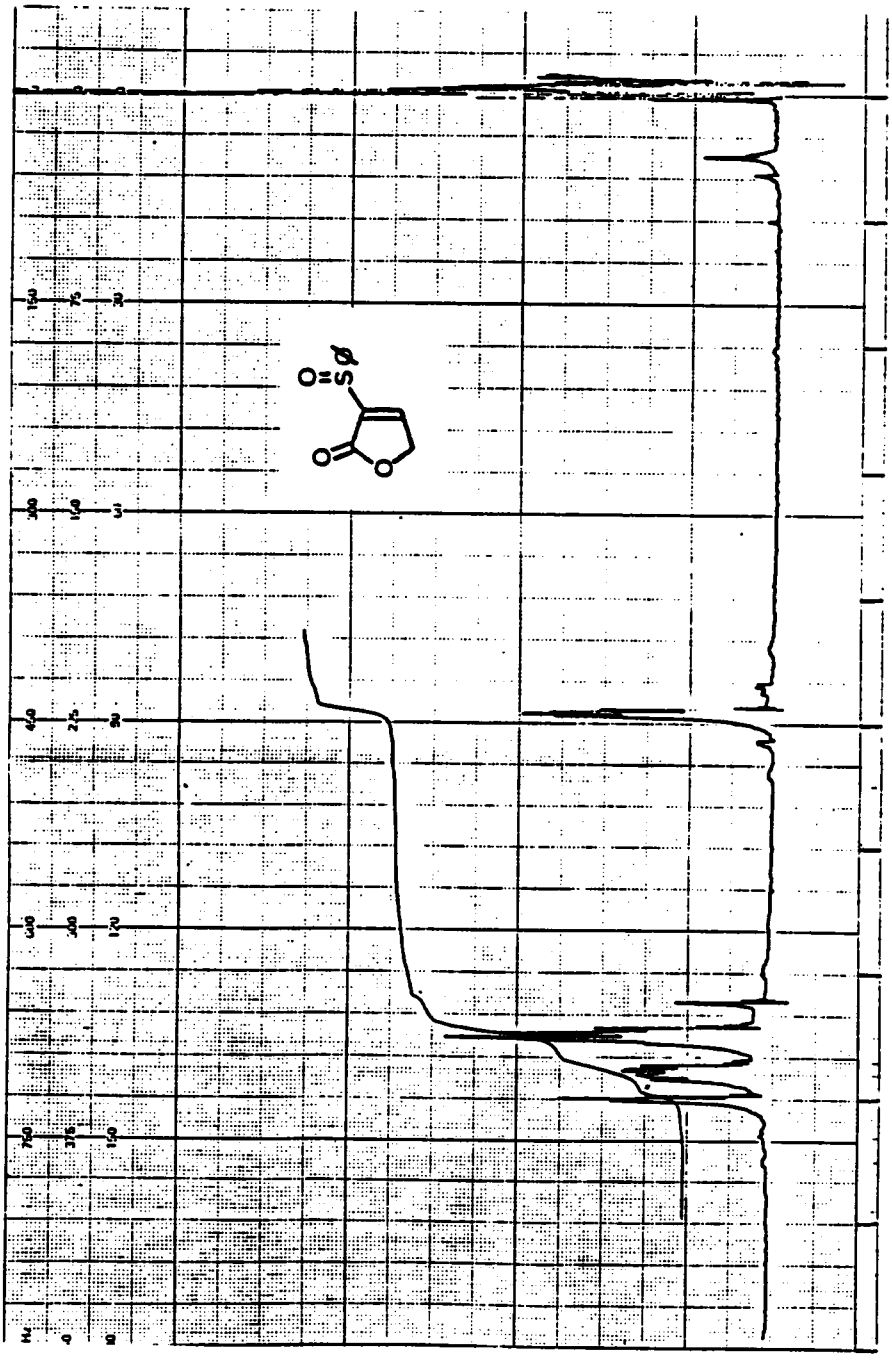
100 MHz ^{1}H NMR spectrum of enone 106; in benzene-d_6



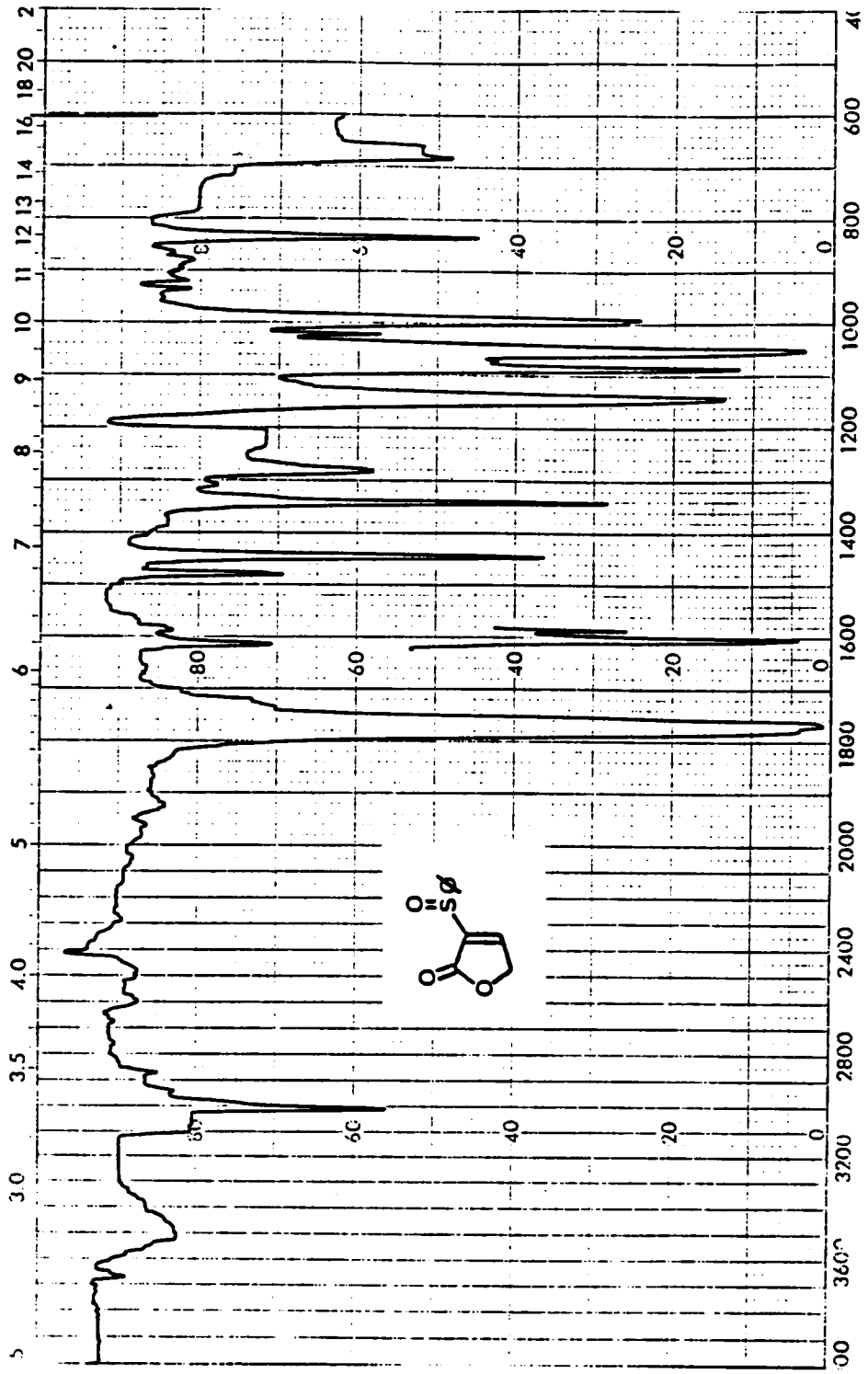
80 MHz ^{13}C NMR decoupled spectrum of enone 106



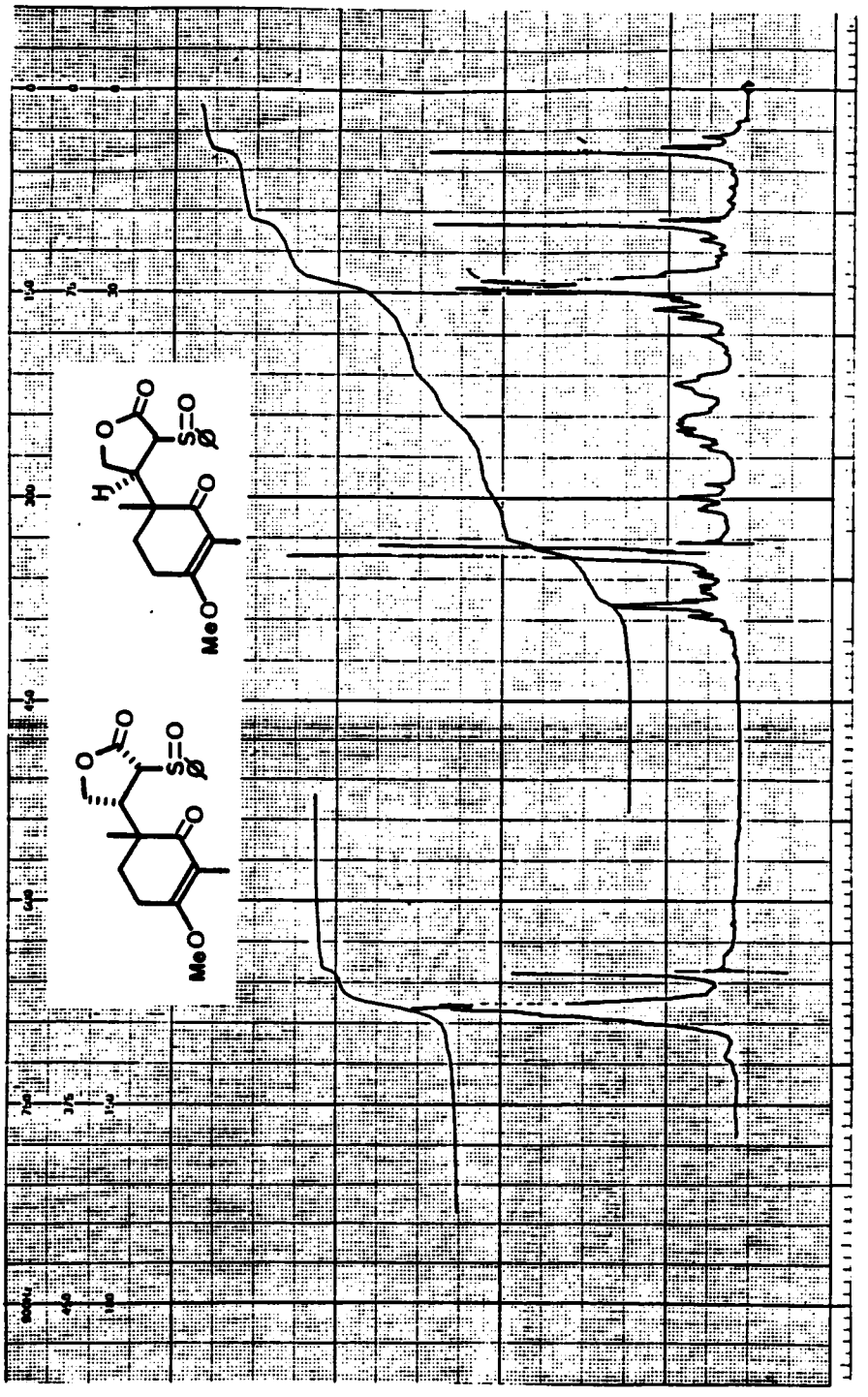
IR spectrum of enone 106



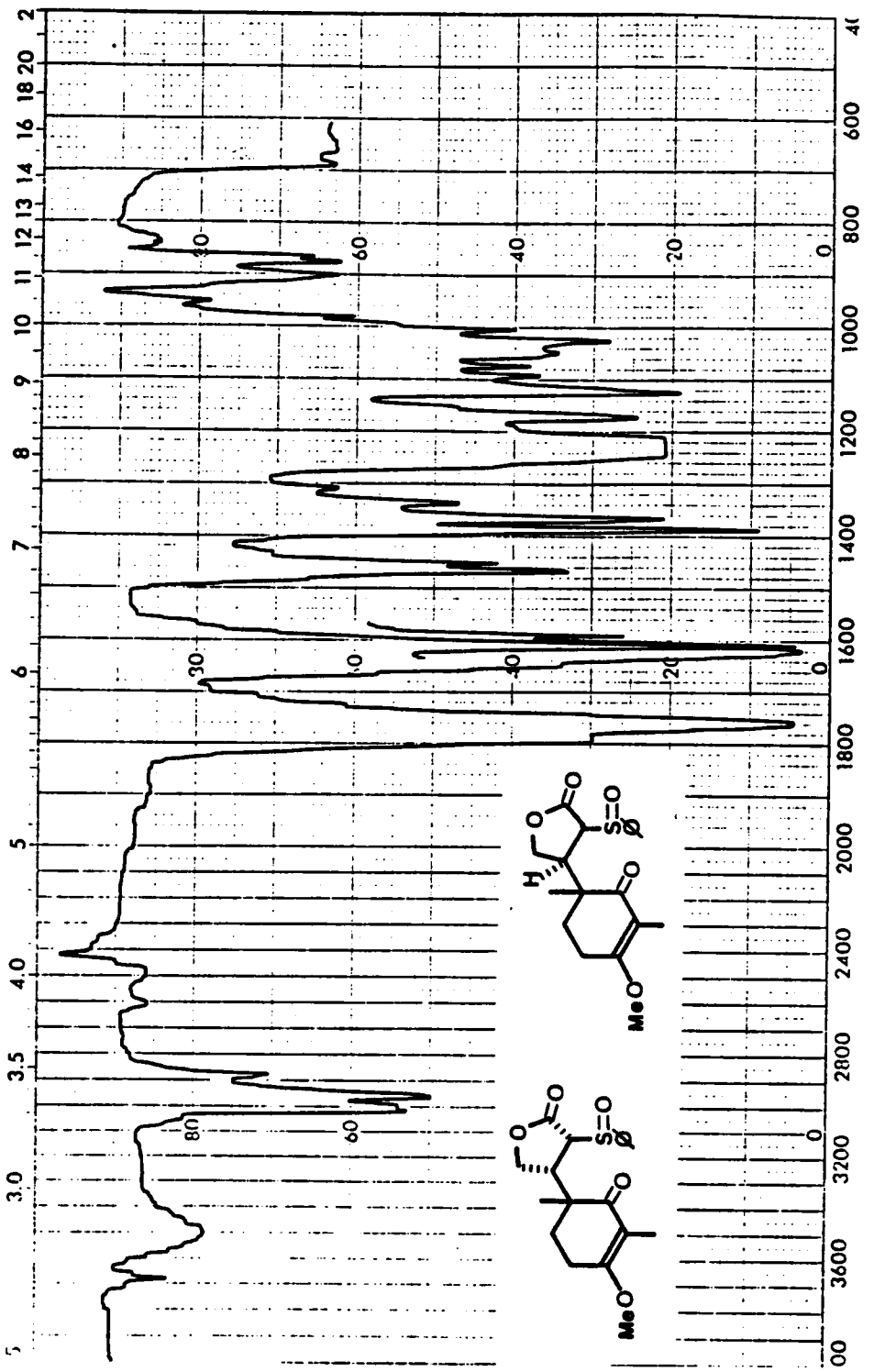
90 MHz ^{1}H NMR spectrum of butenolide 108



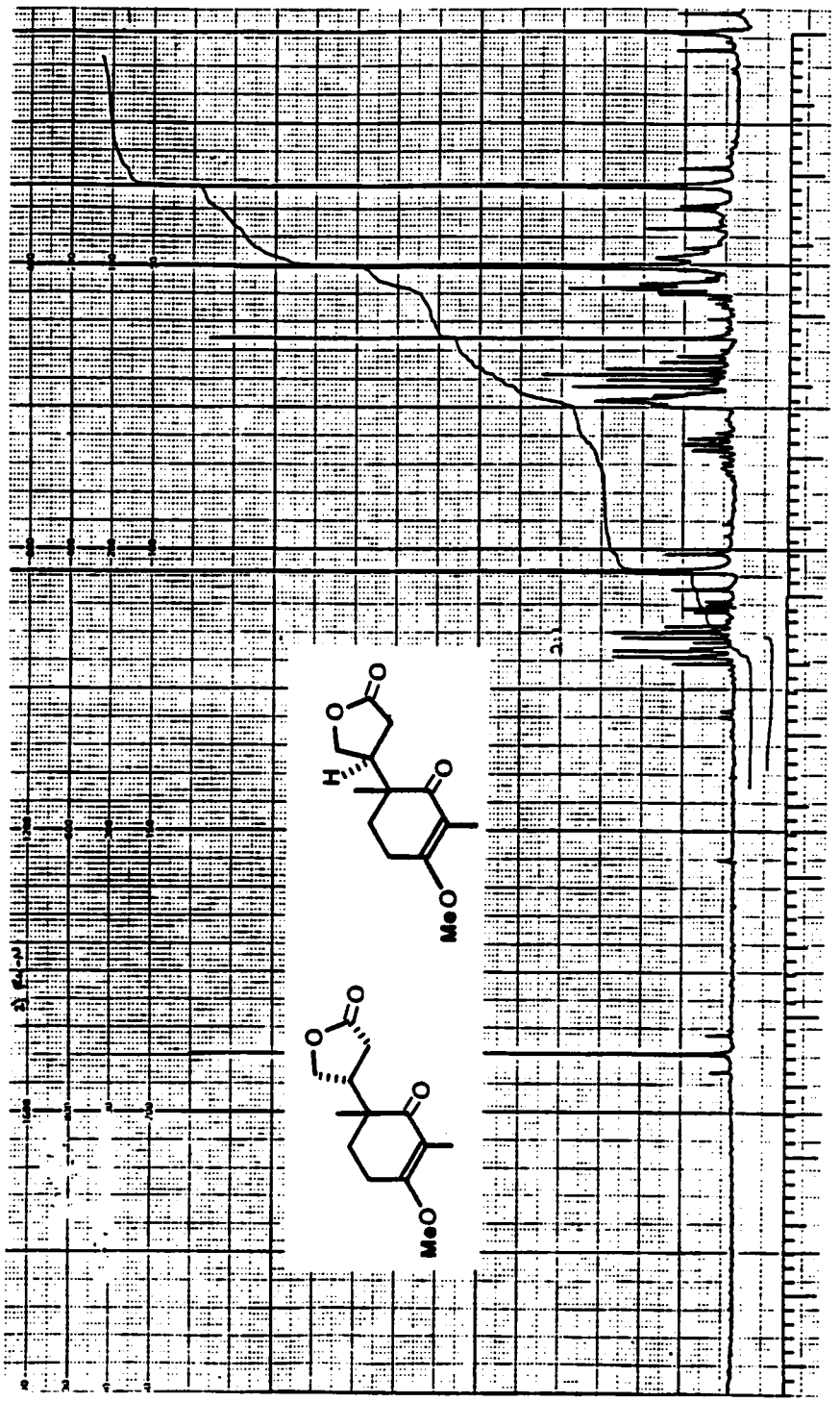
IR spectrum of butenolide 108



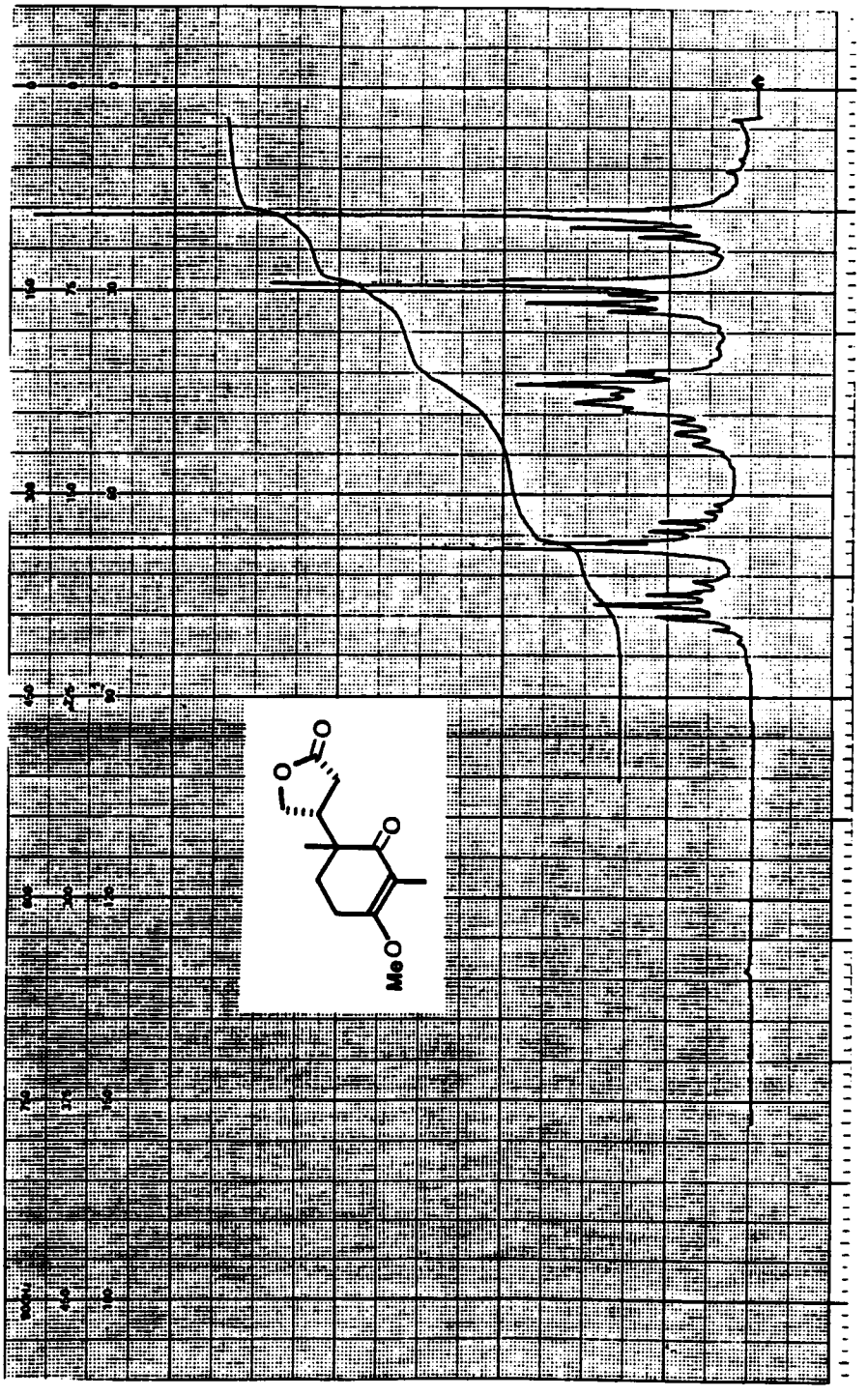
90 MHz ^{1}H NMR spectrum of Michael adducts 109a,b



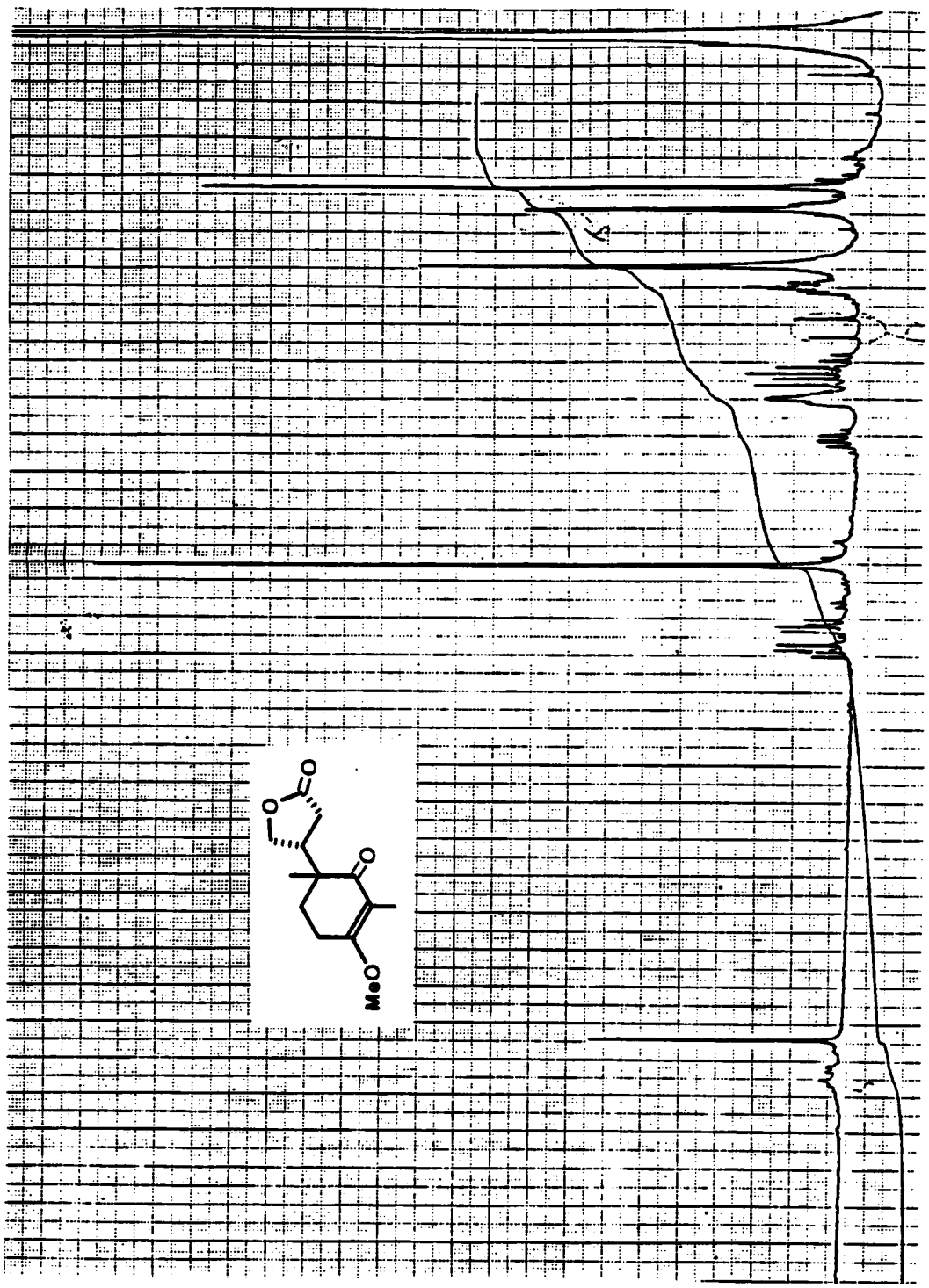
IR spectrum of Michael adducts 109a,b



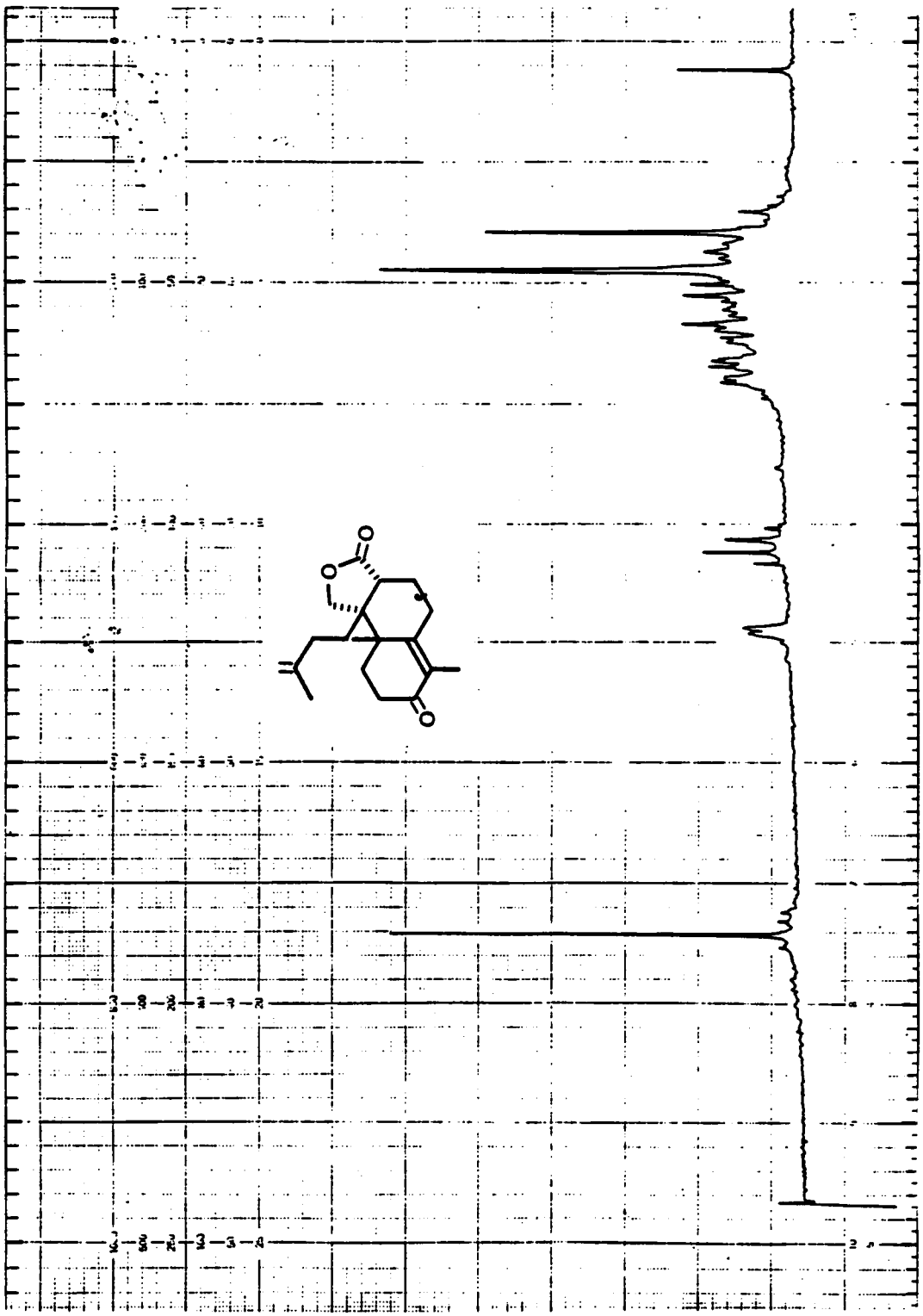
200 MHz ^{1}H NMR spectrum of Michael adduct 110 and 111



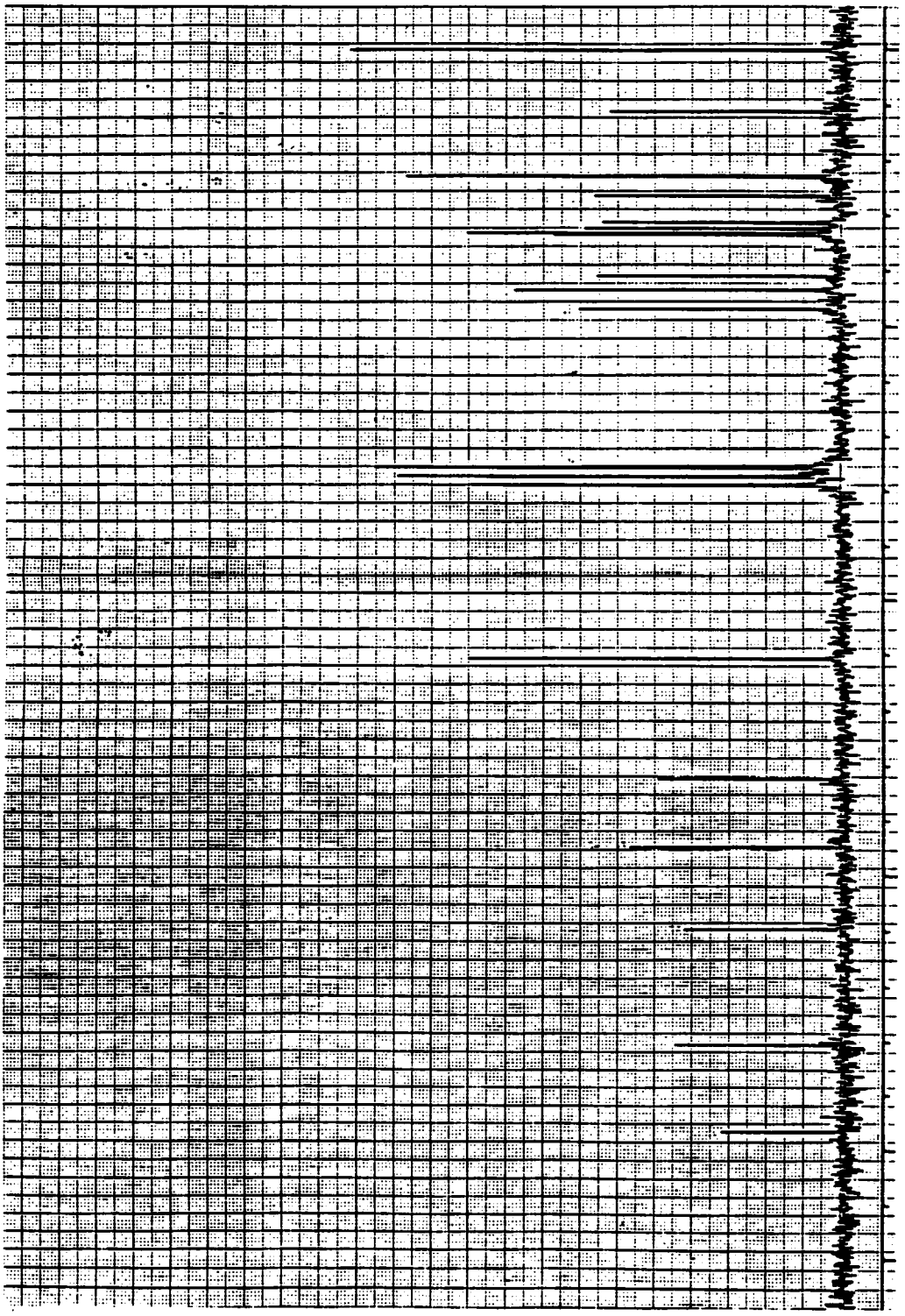
90 MHz ^{1}H NMR spectrum of Michael adduct 110



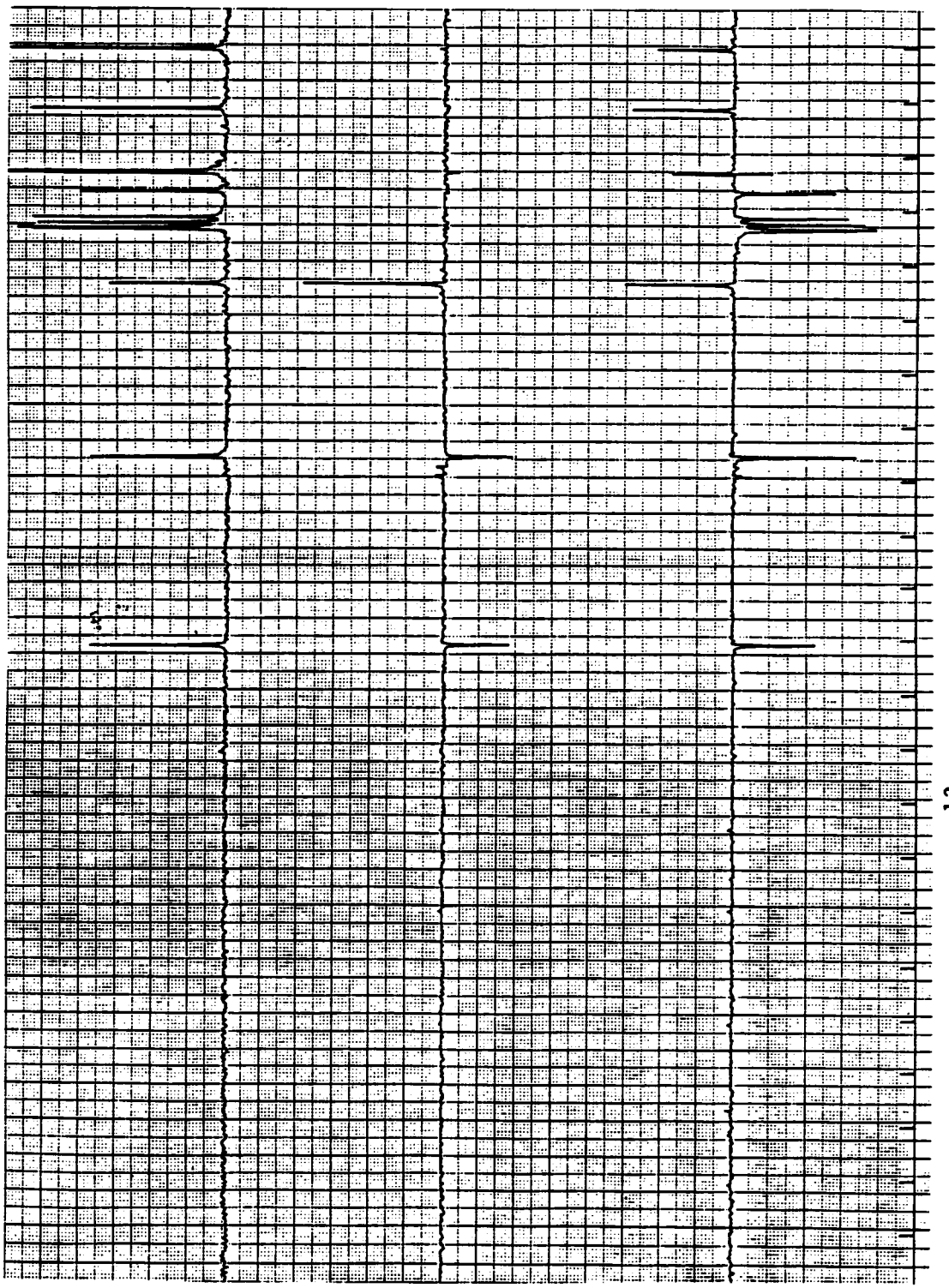
200 MHz ^{1}H NMR spectrum of Michael adduct 110



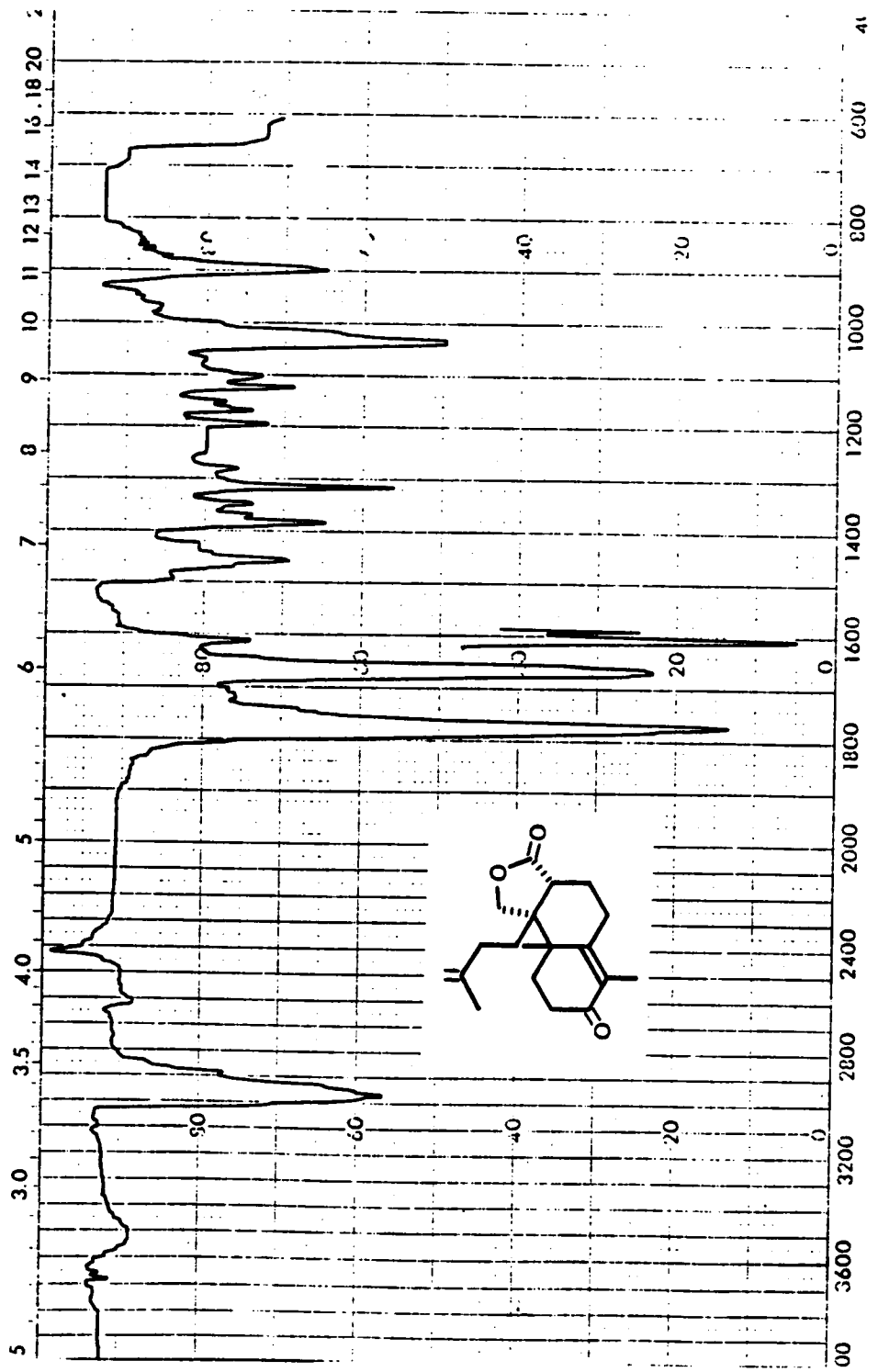
100 MHz ^{1}H NMR spectrum of enone 113



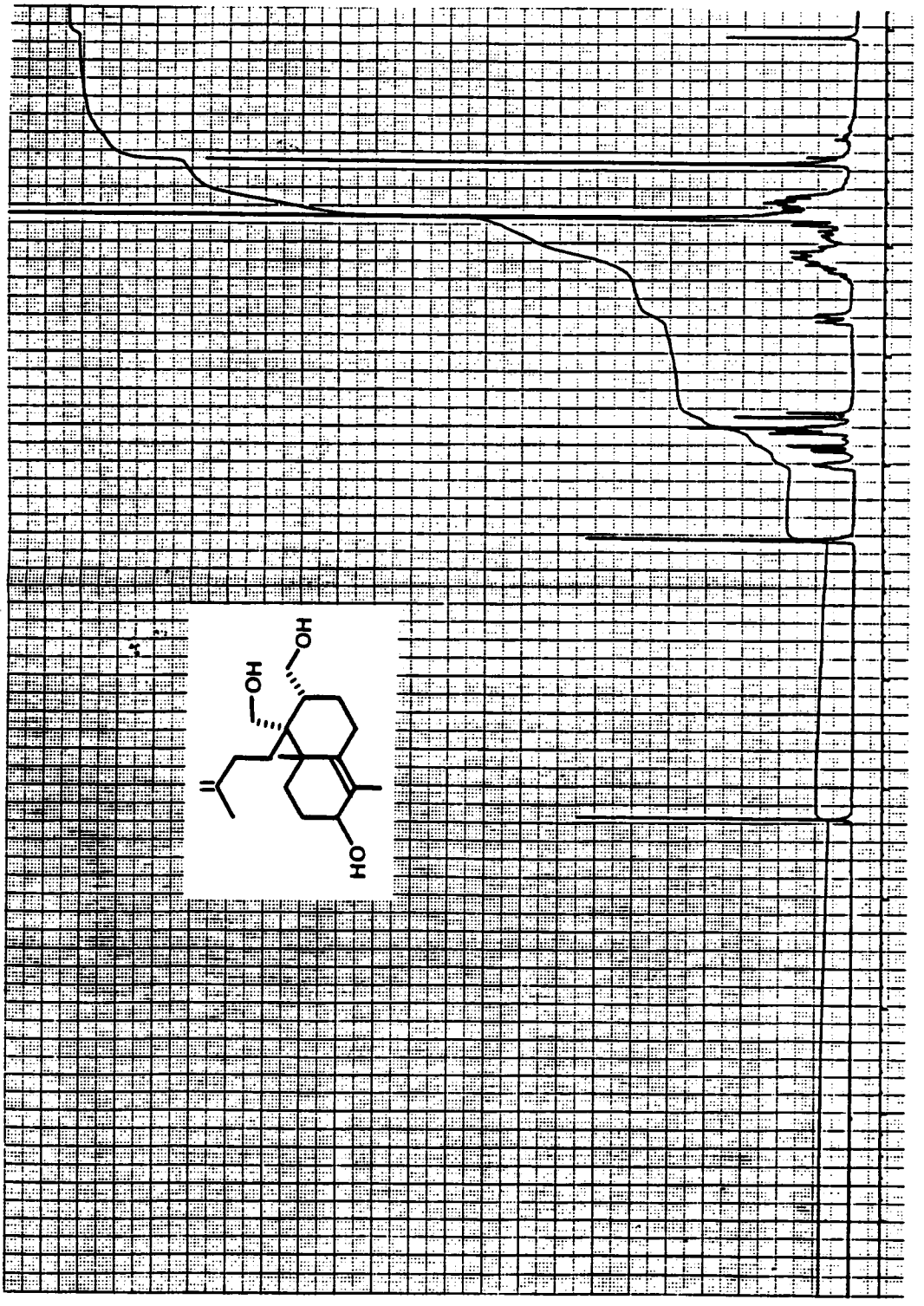
80 MHz ^{13}C decoupled NMR spectrum of enone 113



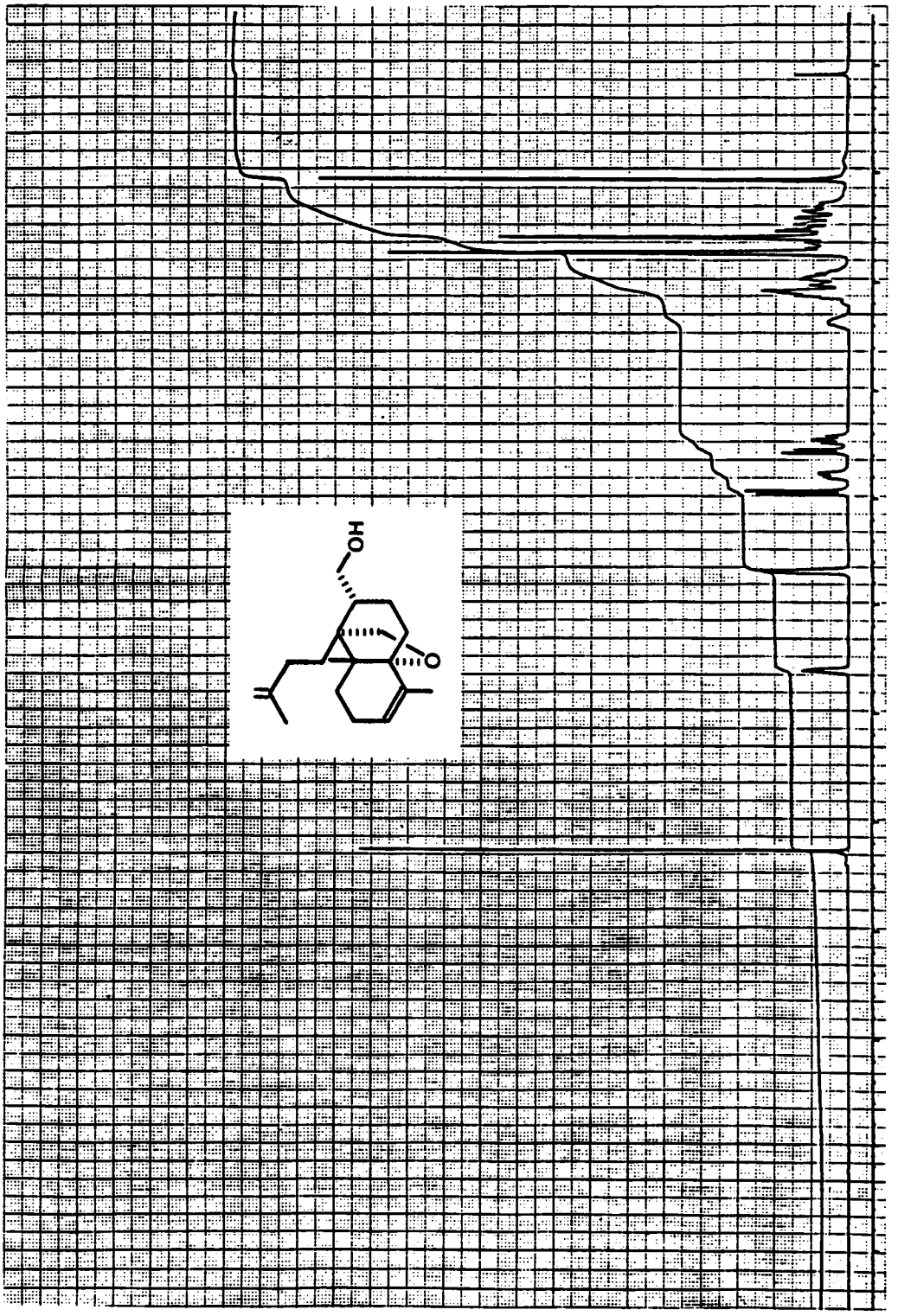
80 MHz ^{13}C INEPT spectra of enone 113



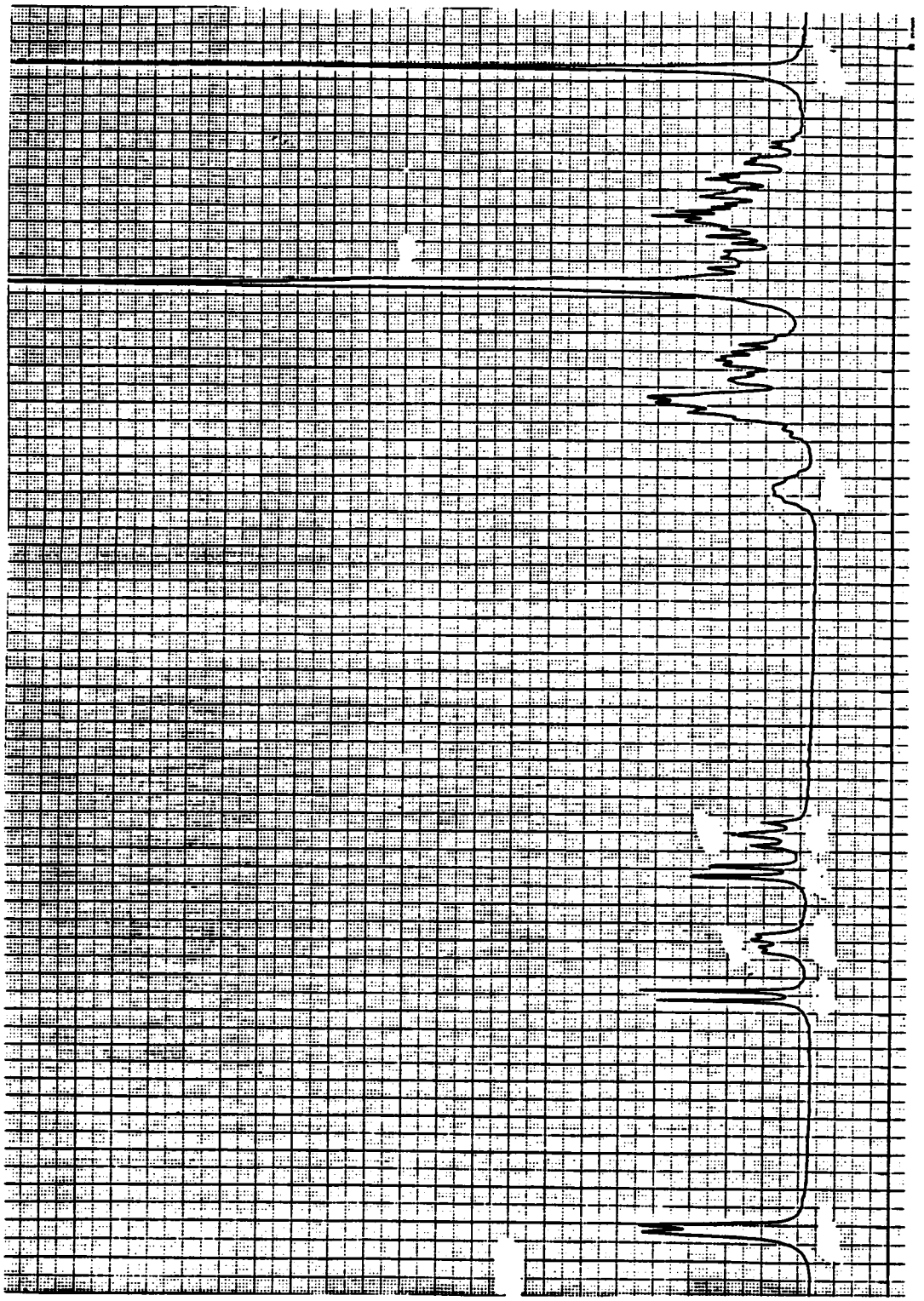
IR spectrum of enone 113



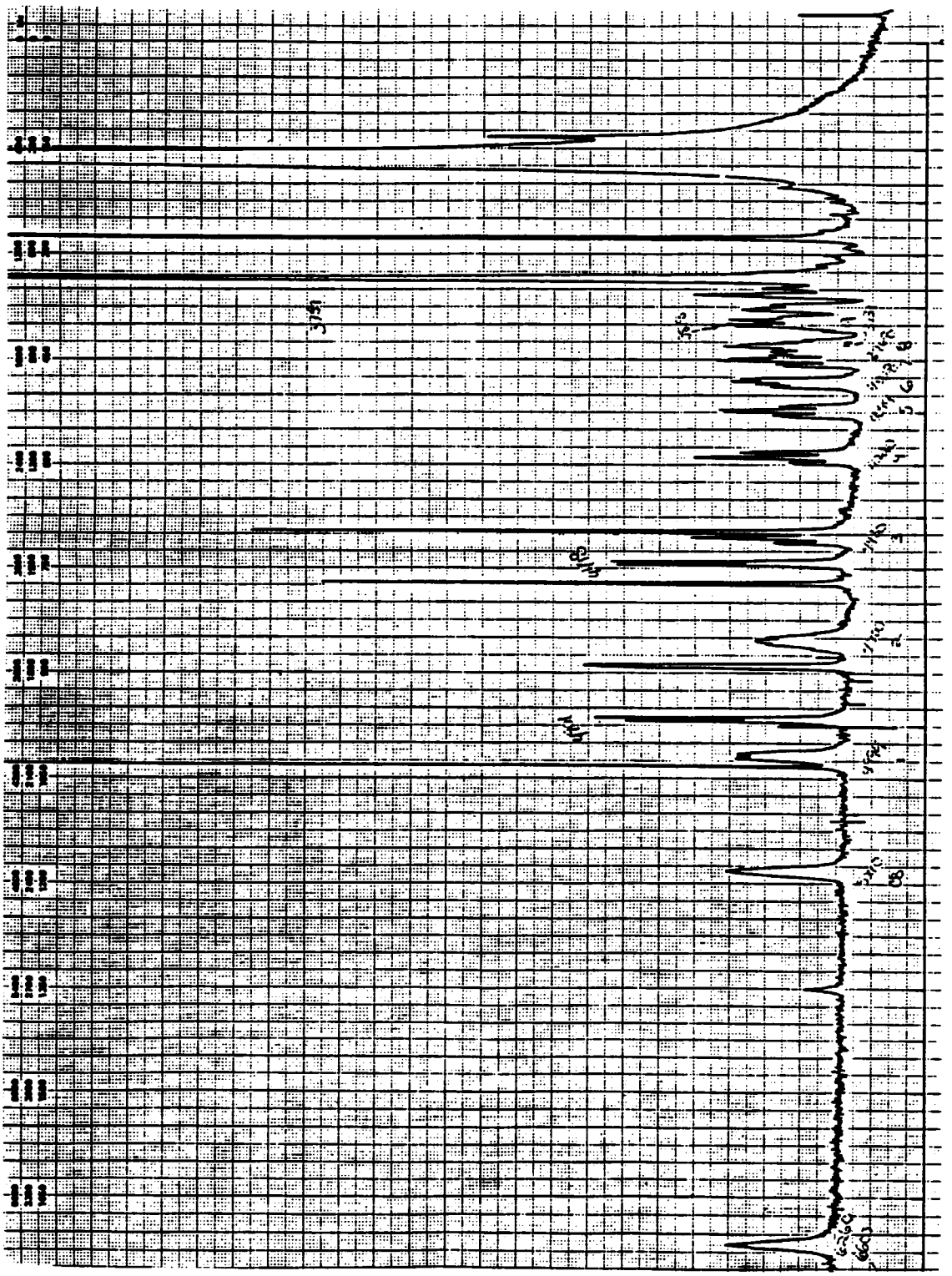
270 MHz ^{1}H NMR spectrum of triol 114



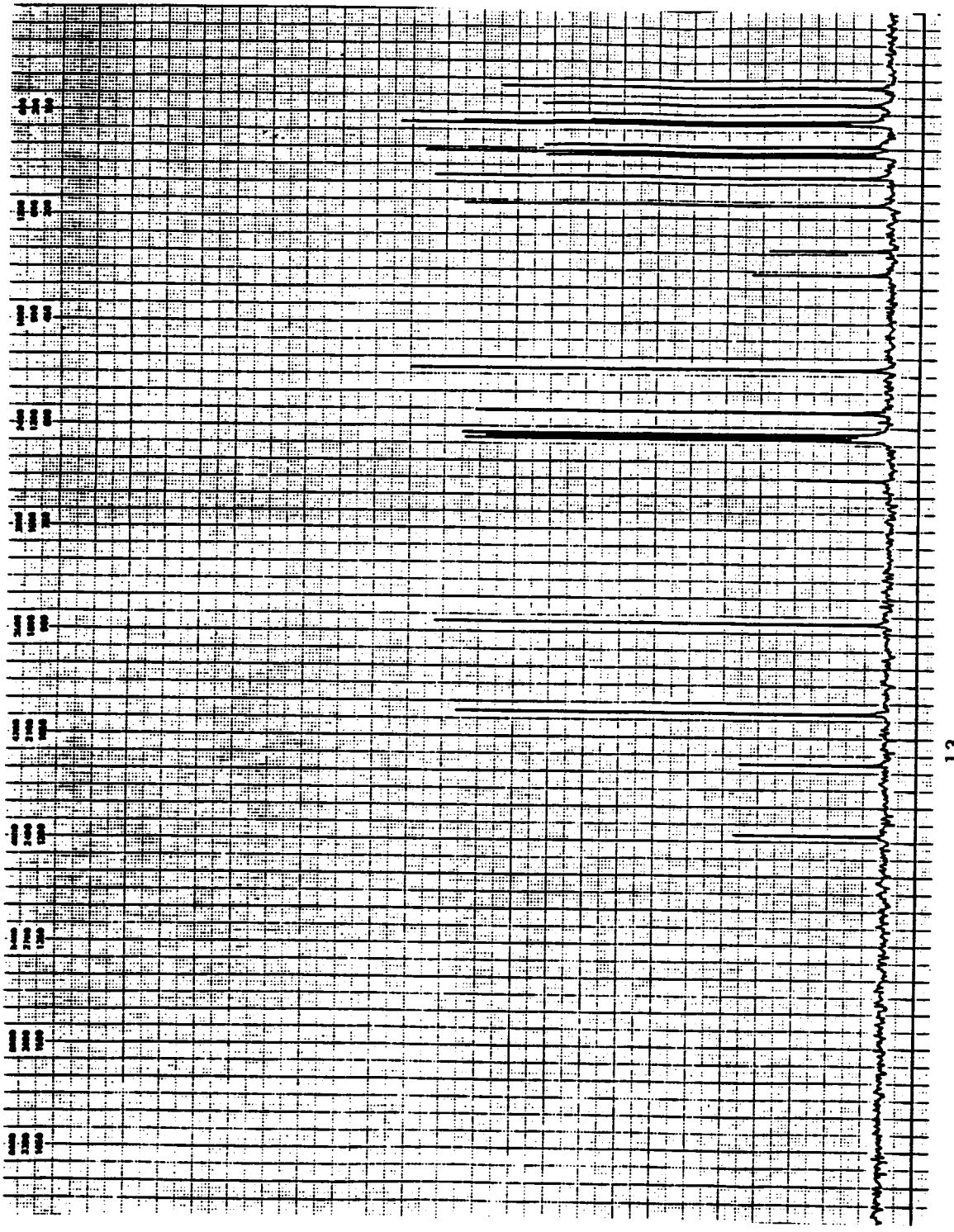
270 MHz ^{1}H NMR spectrum of furan 115



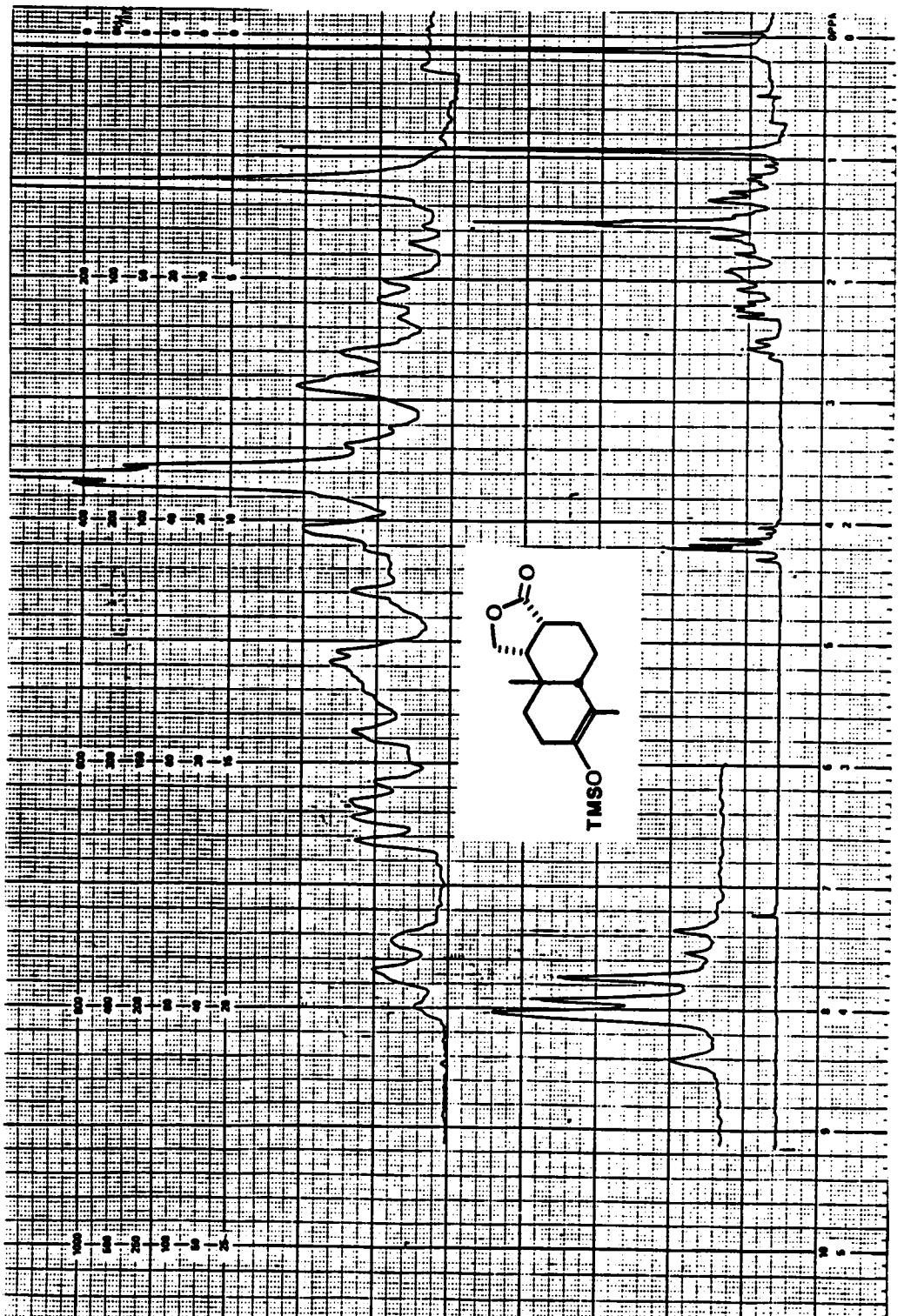
expanded 270 MHz ^{1}H NMR spectrum of furan 115



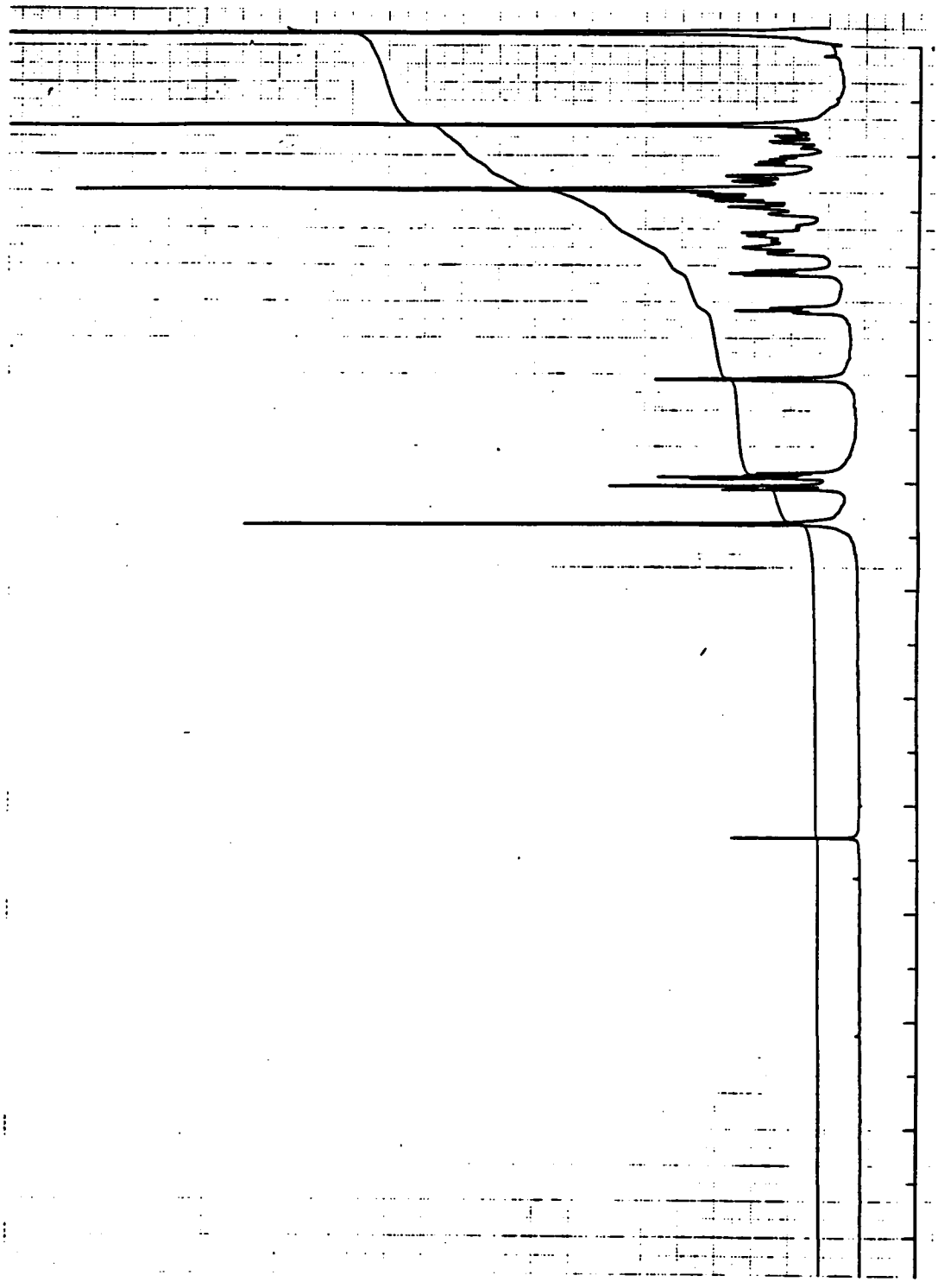
270 MHz ^{1}H NMR spectrum of furan 115; addition of Eufod



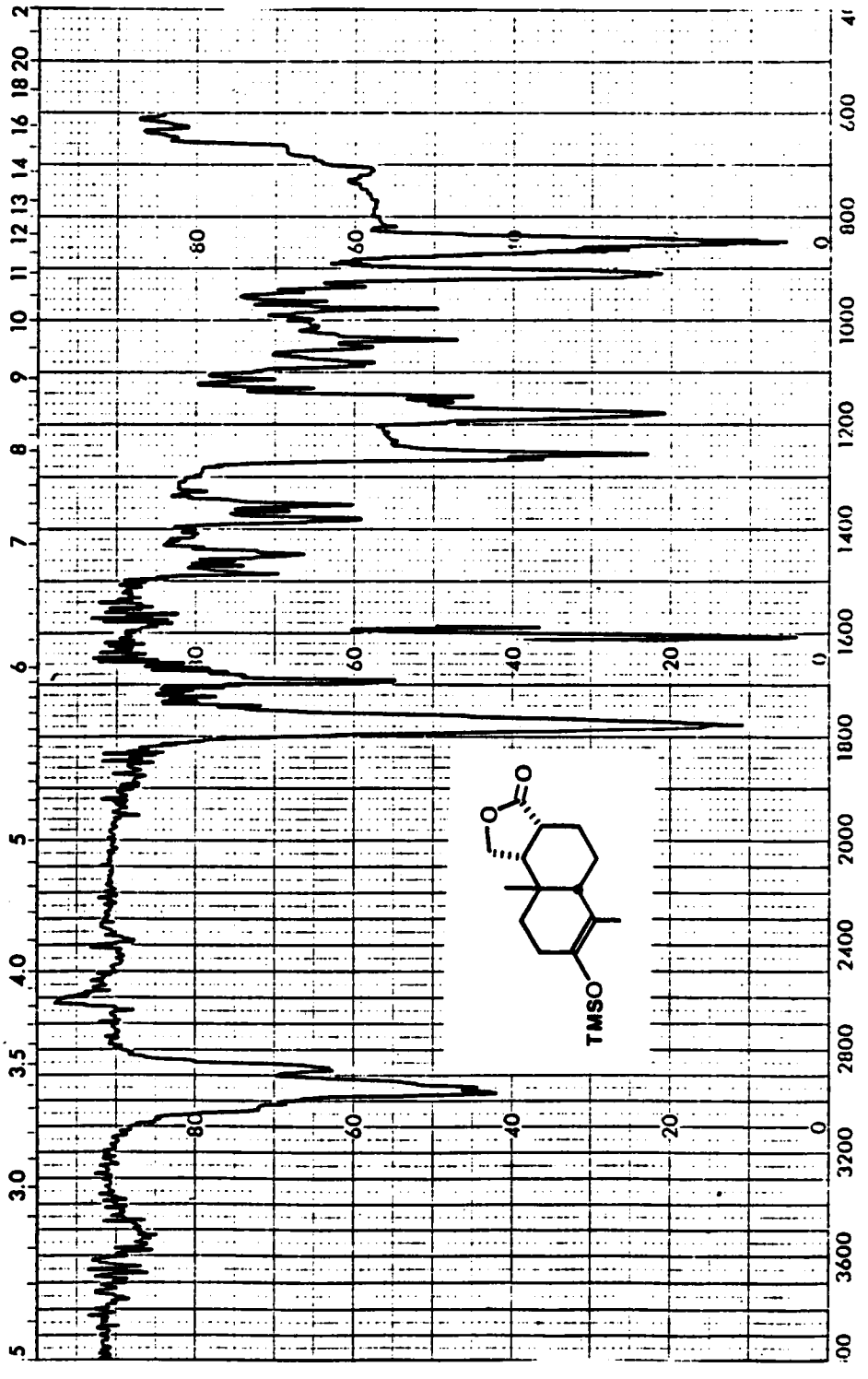
270 MHz ^{13}C NMR decoupled spectrum of furan 115



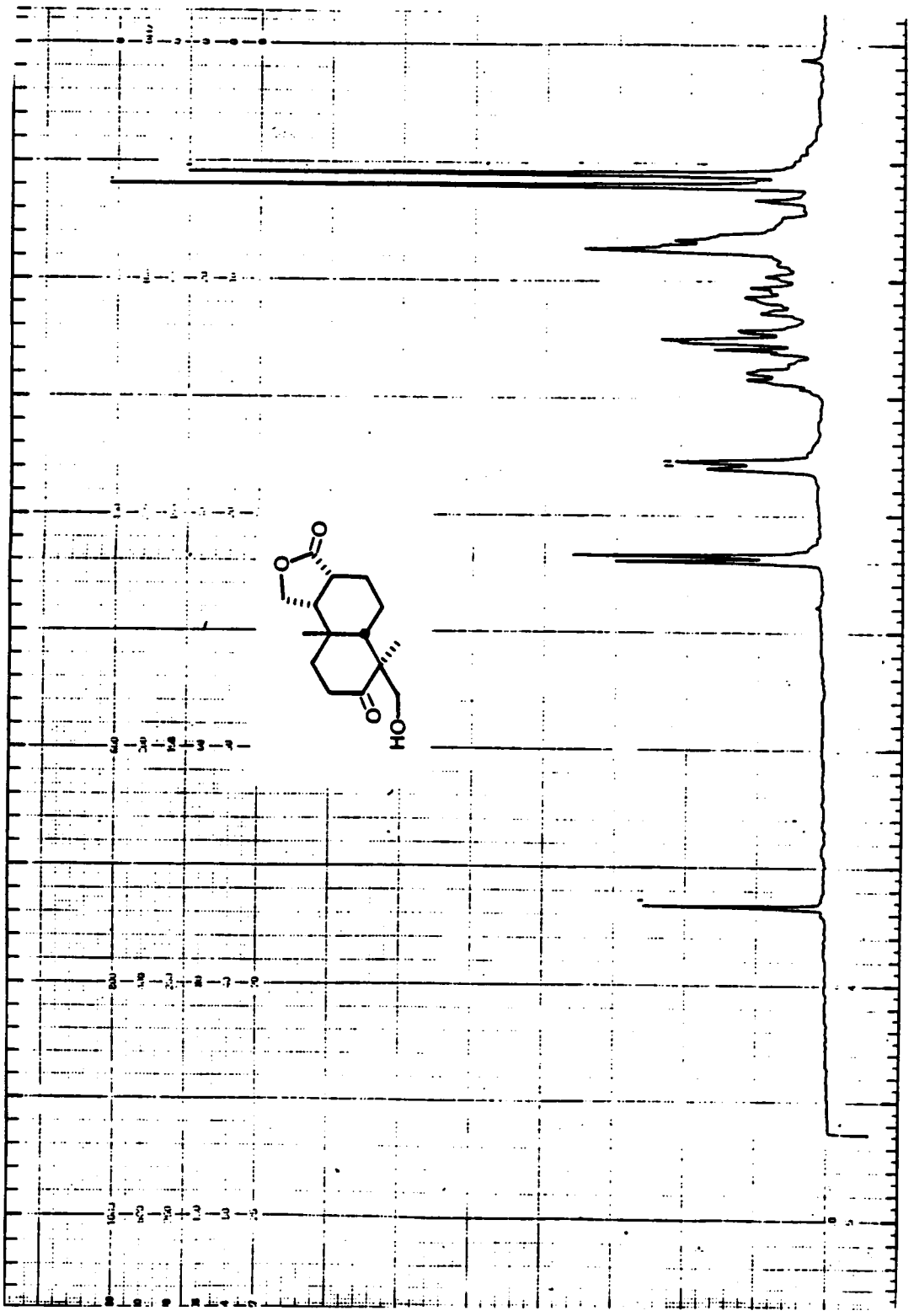
100 MHz ^{1}H NMR spectrum of silyl ether 118



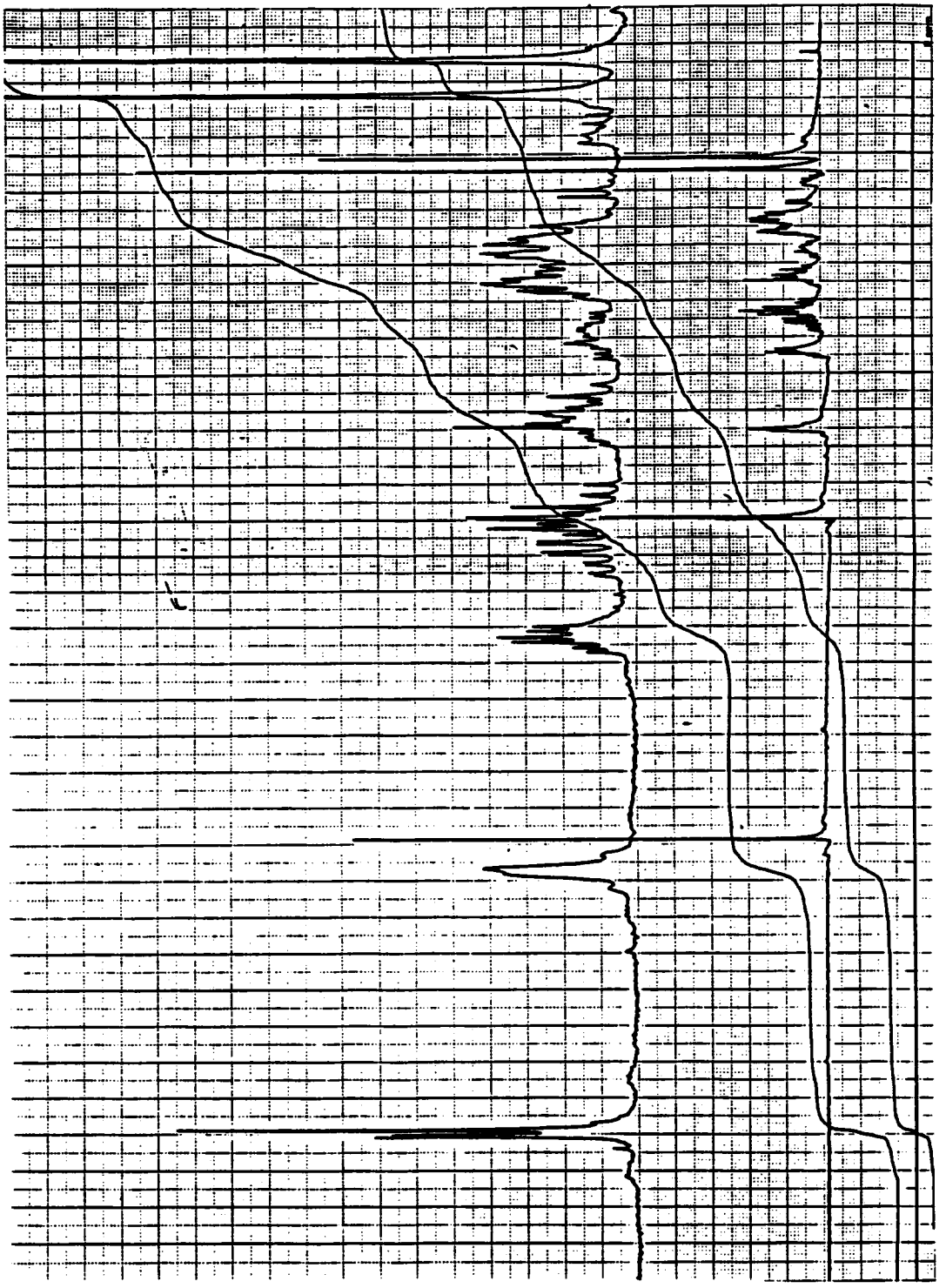
270 MHz ^{1}H NMR spectrum of silyl ether 118 in CD_3OD



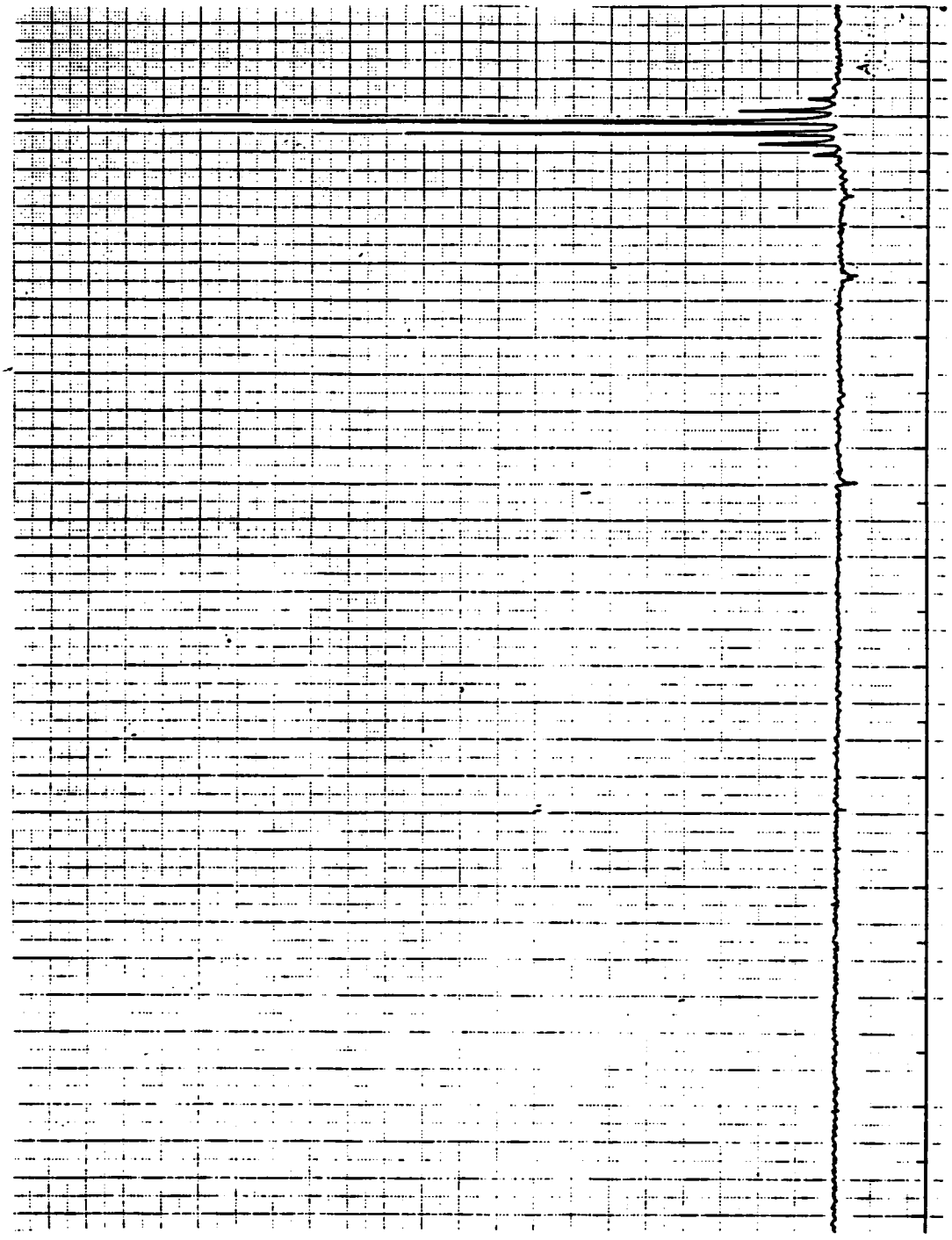
IR spectrum of silyl ether 118



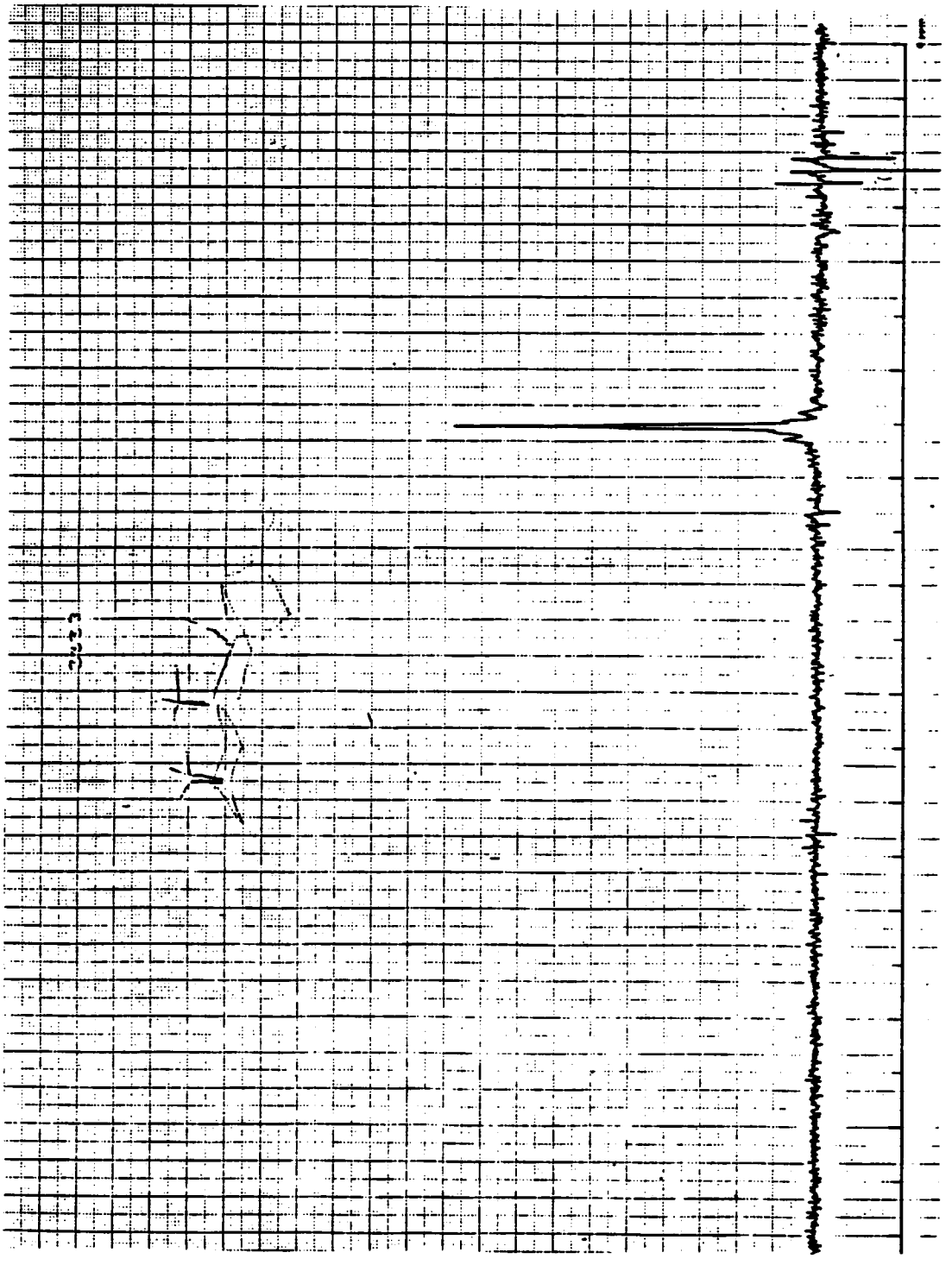
100 MHz ^{1}H NMR spectrum of alcohol 119



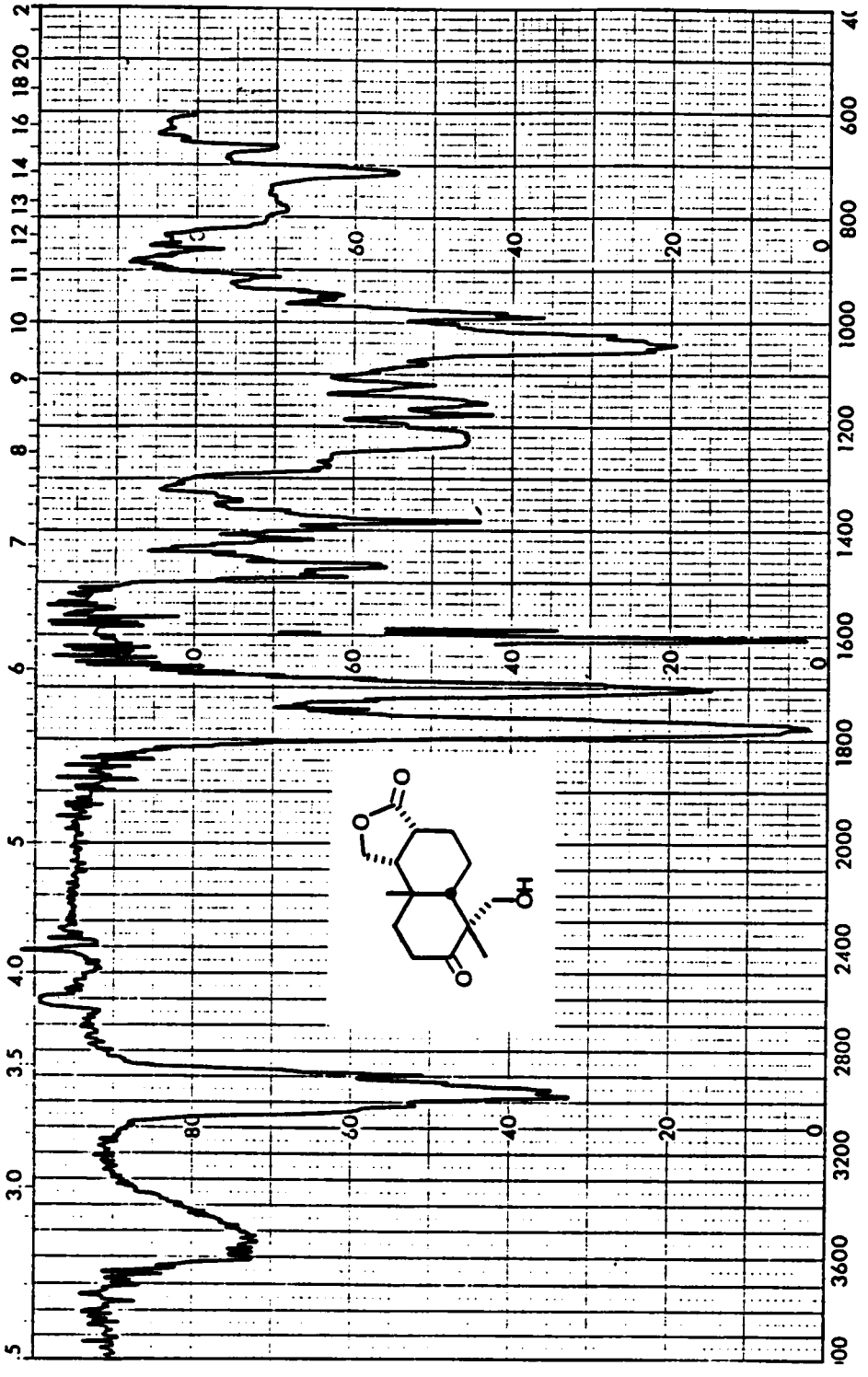
270 MHz ^{1}H NMR spectrum of alcohol 119



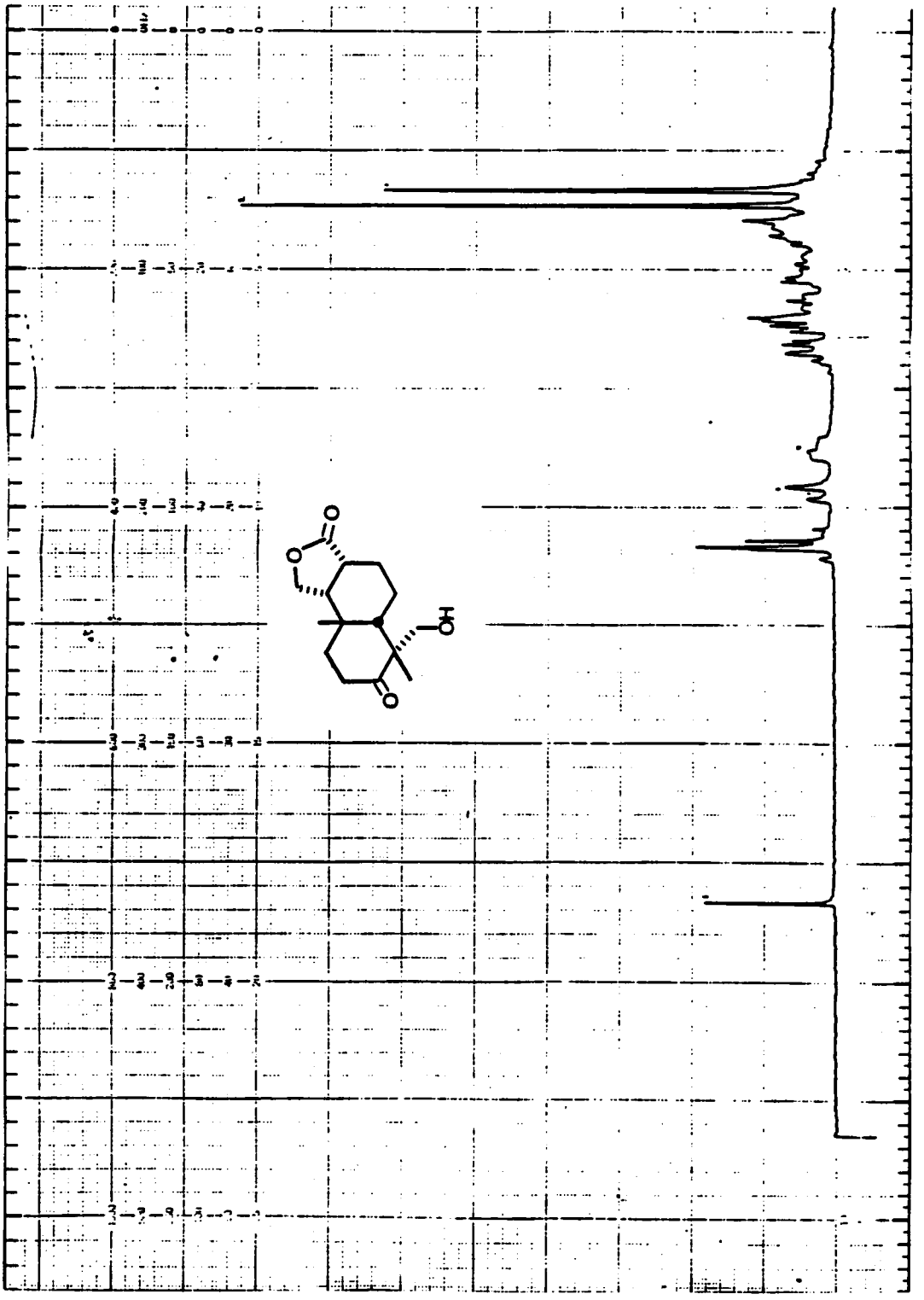
270 MHz ^{1}H NOE difference NMR spectrum of alcohol 119; irradiation of the C-4 methyl group



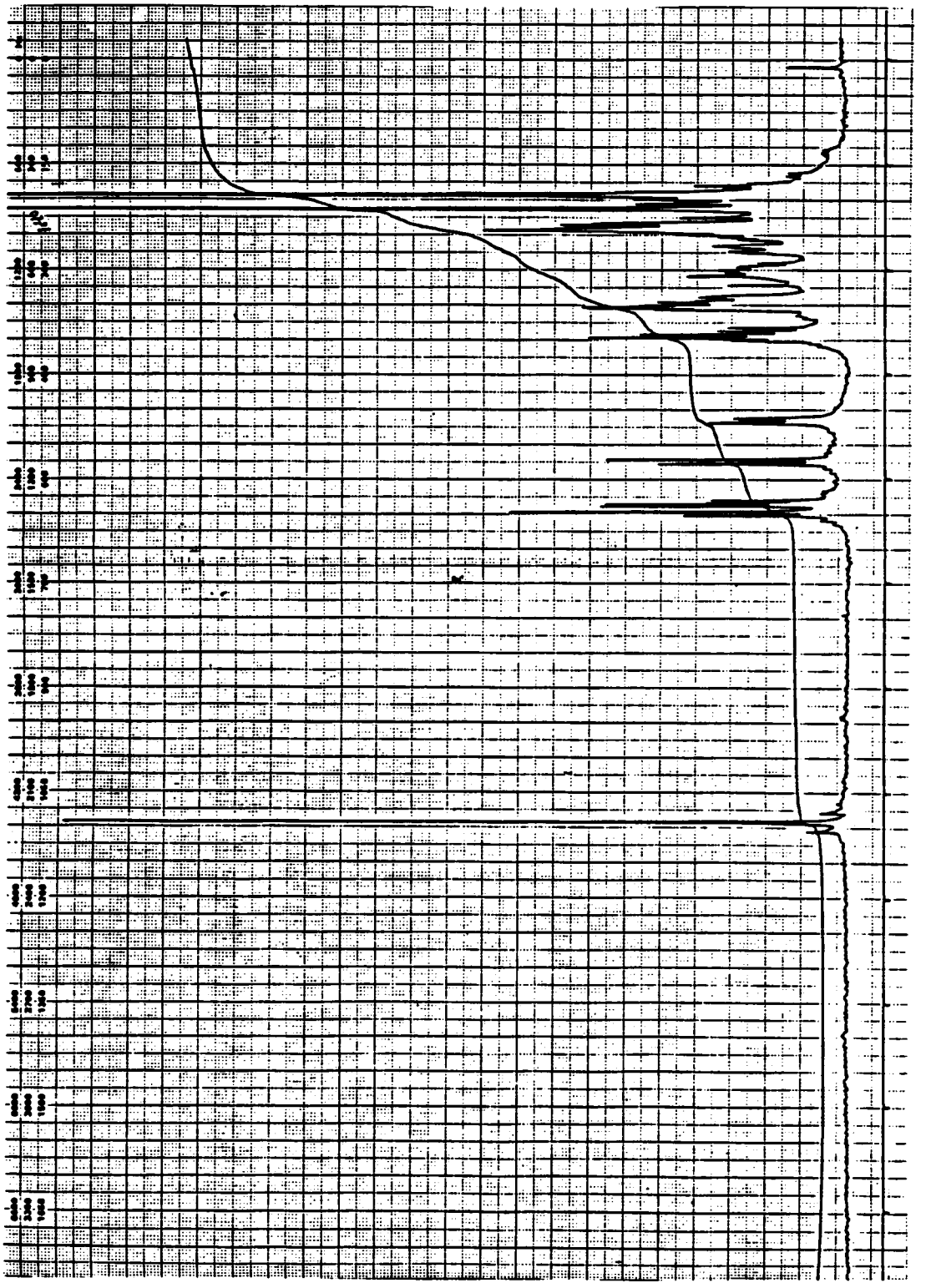
270 MHz ^{1}H NOE difference spectrum of alcohol 119; irradiation of hydroxymethyl group



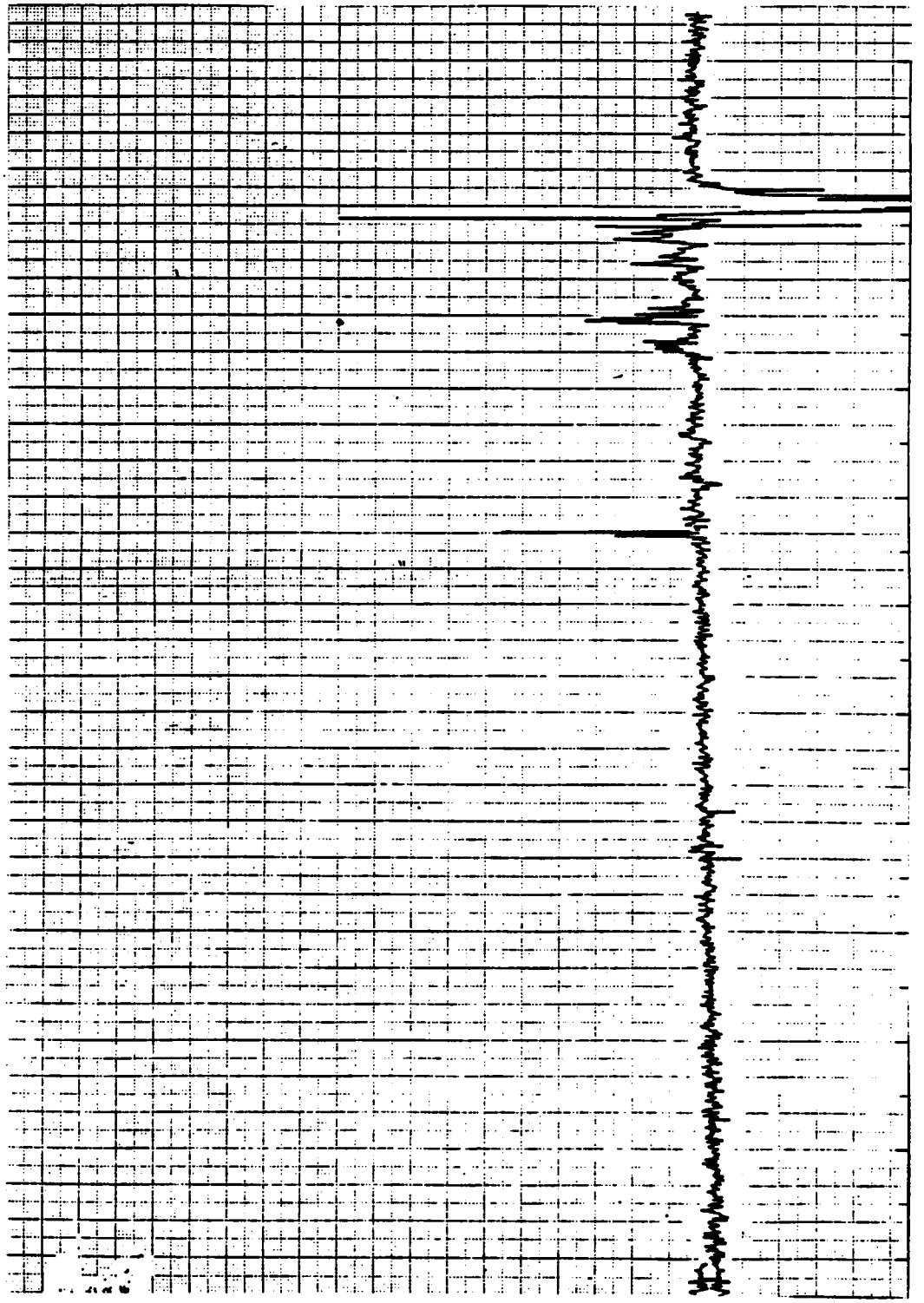
IR spectrum of alcohol 119



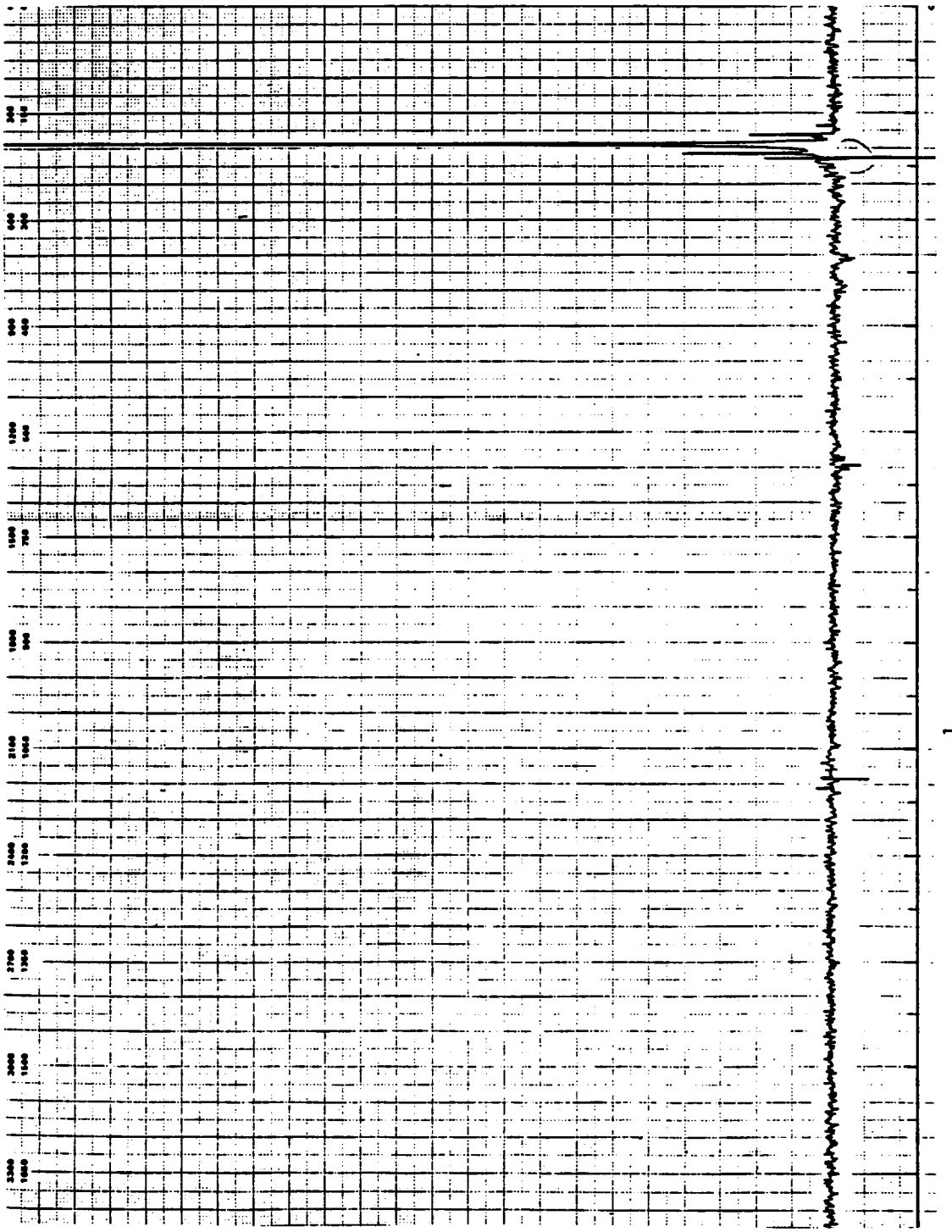
100 MHz ^{1}H NMR spectrum of alcohol 120



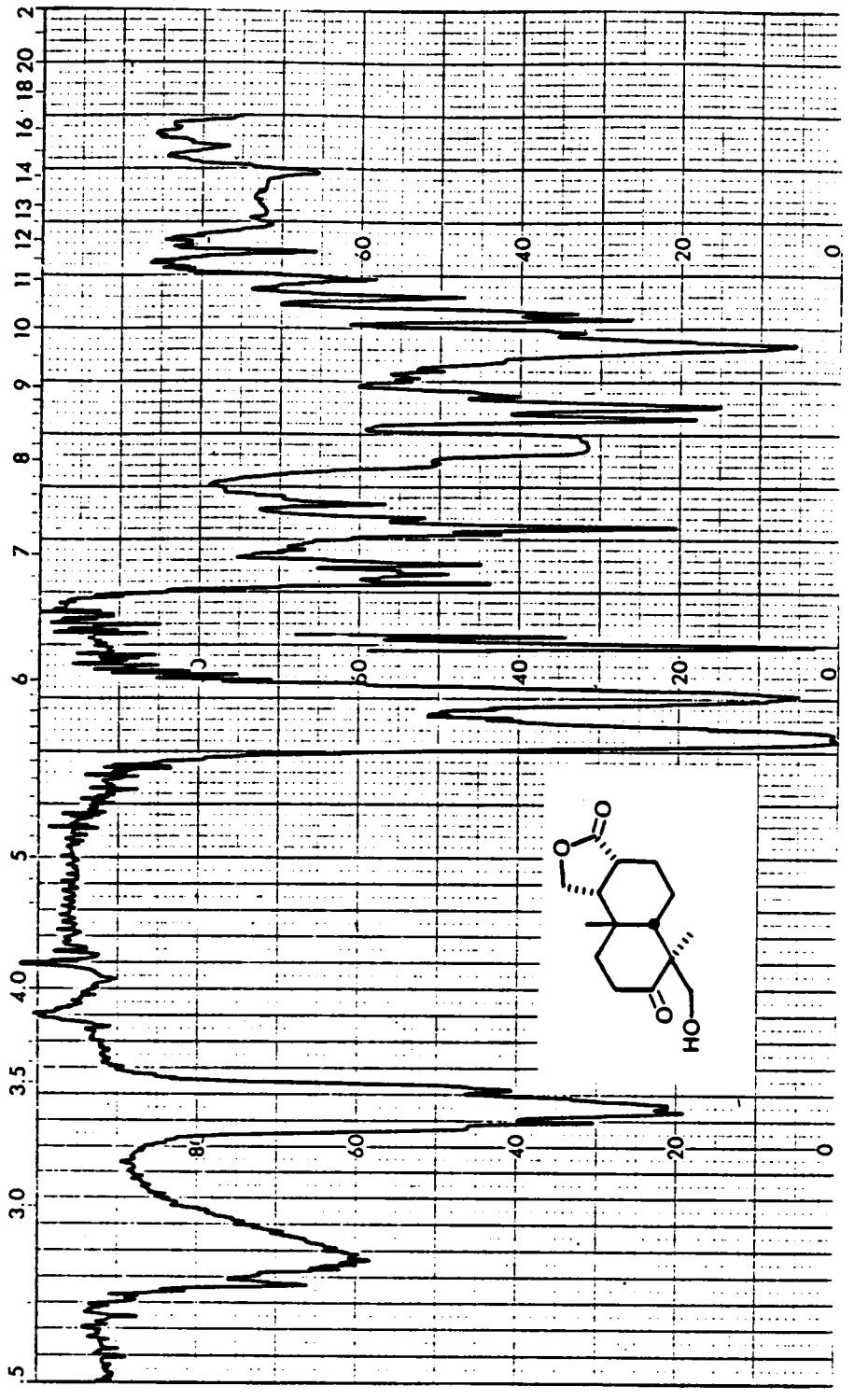
270 MHz ^{1}H NMR spectrum of alcohol 120



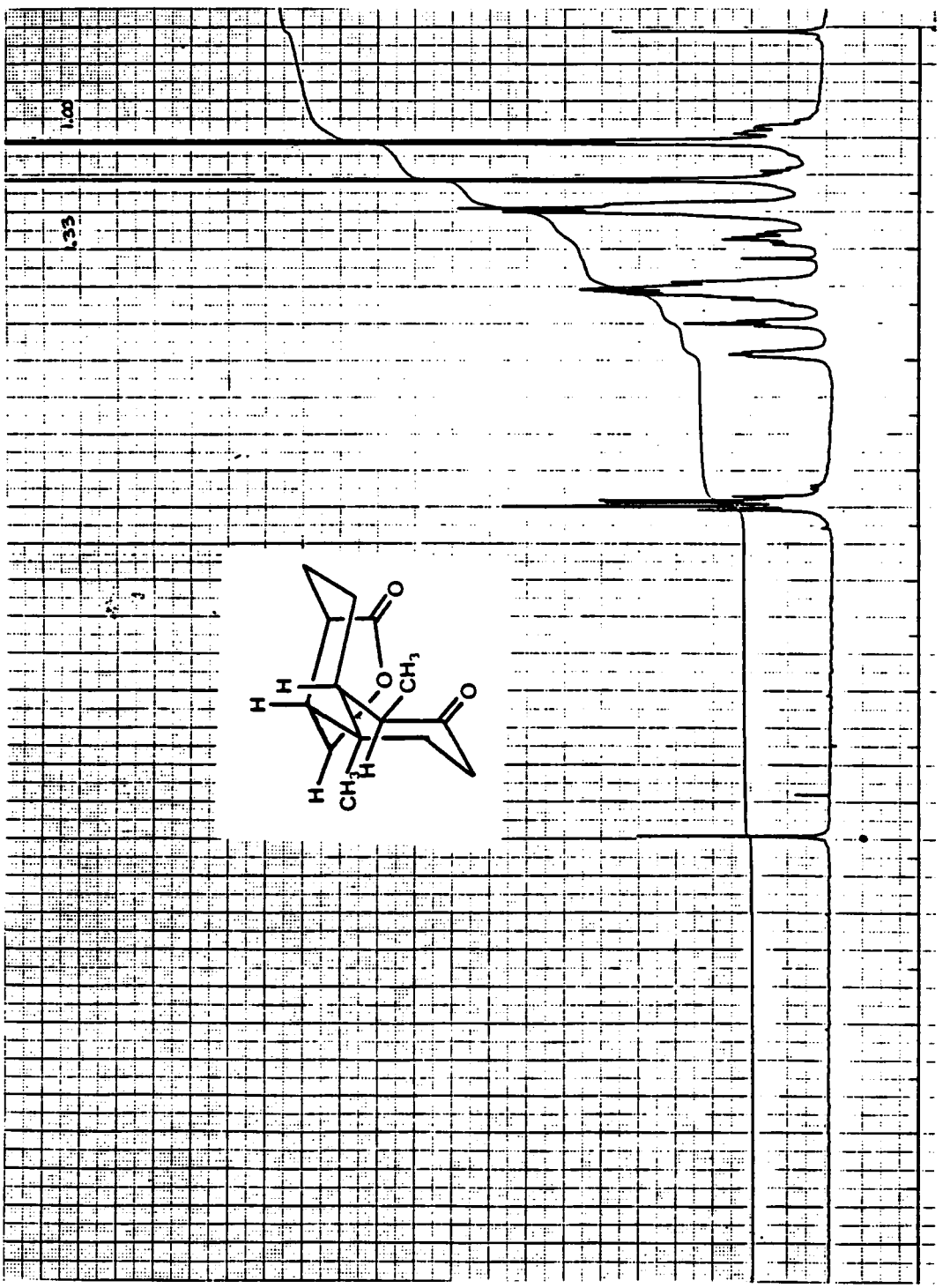
270 MHz ^{1}H NOE difference NMR spectrum of alcohol 120; irradiation of the C-10 methyl group



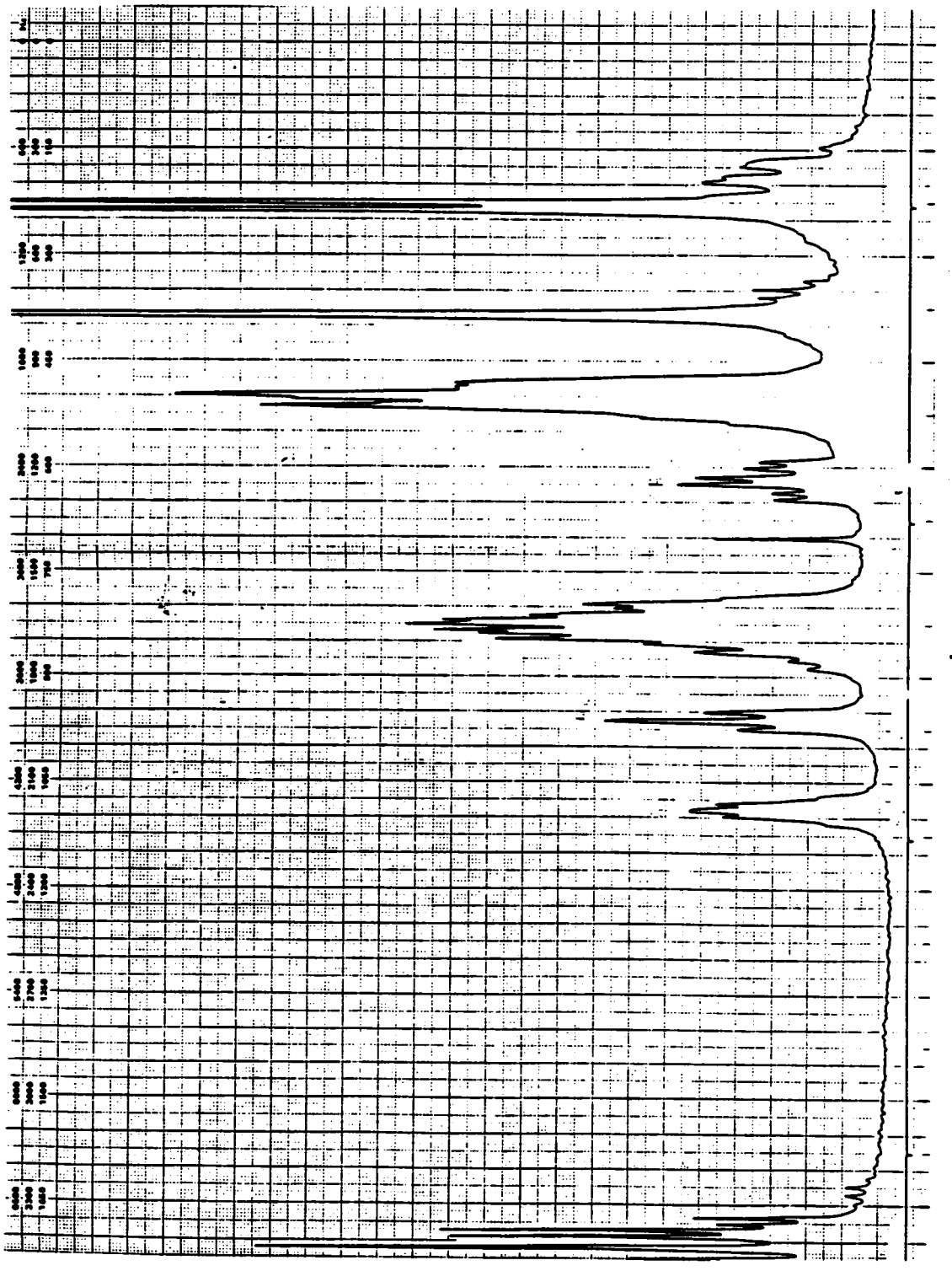
270 MHz ^{1}H NOE difference NMR spectrum of alcohol 120; irradiation of the C-4 methyl group



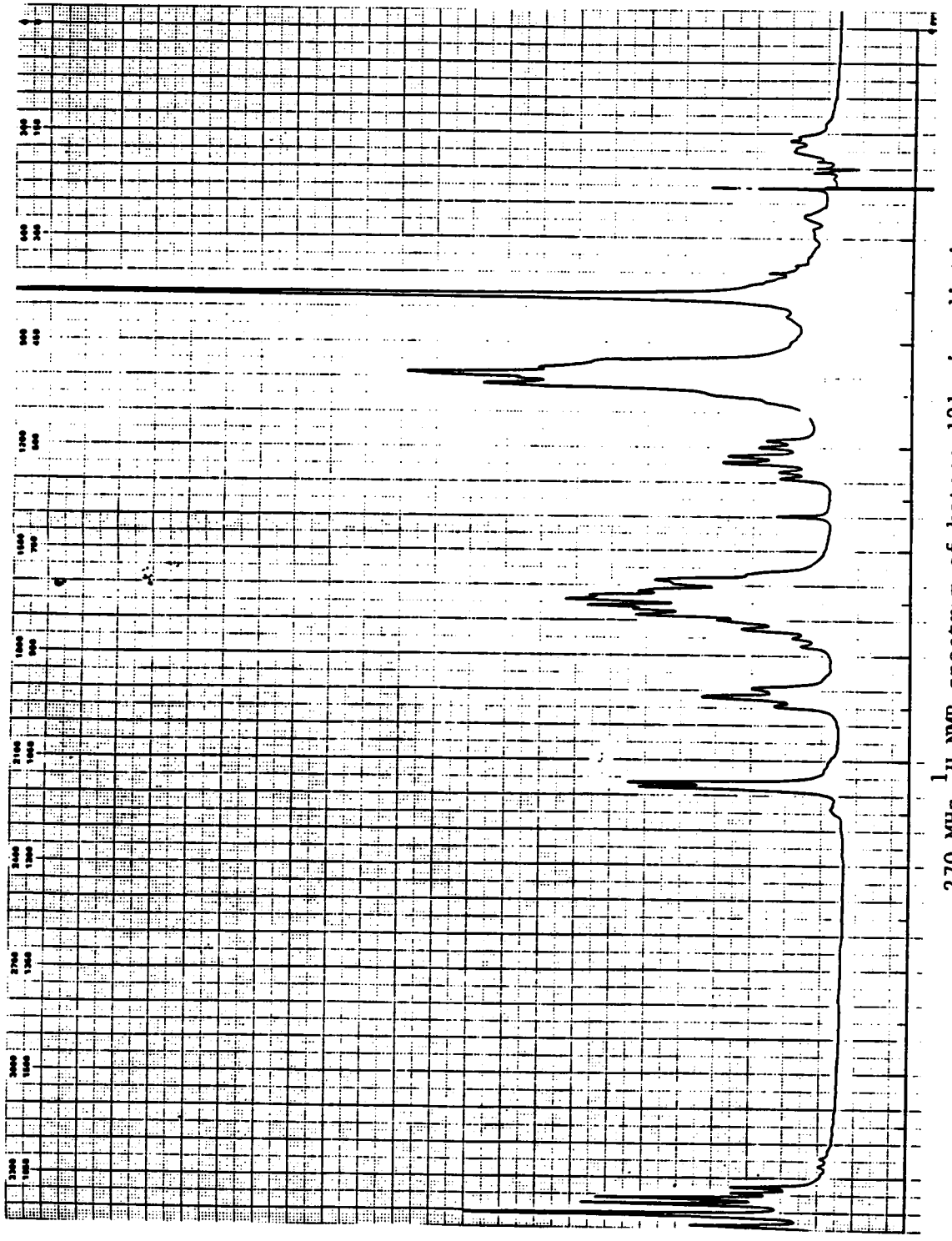
IR spectrum of alcohol 120



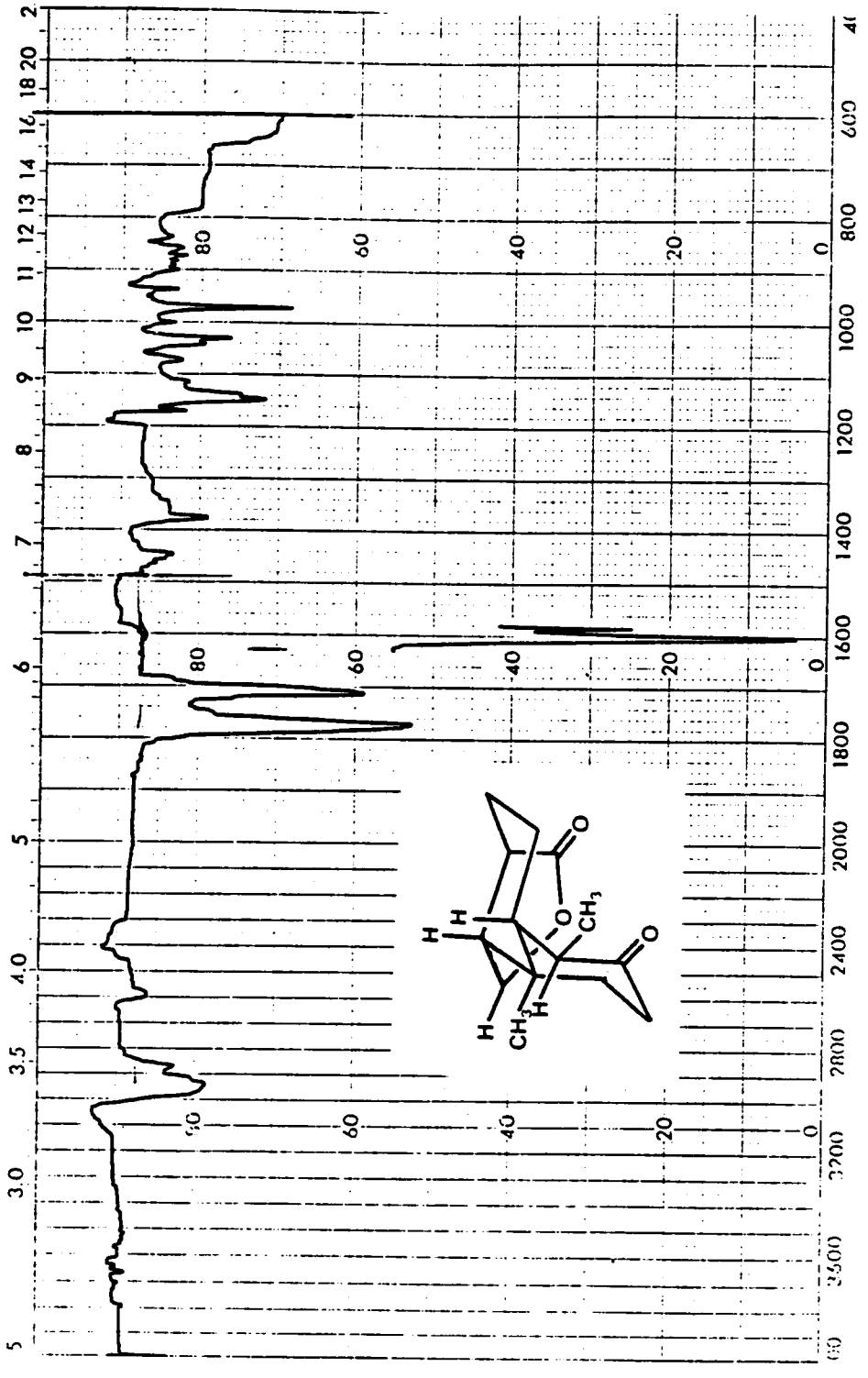
270 MHz ^{1}H NMR spectrum of ketone 121



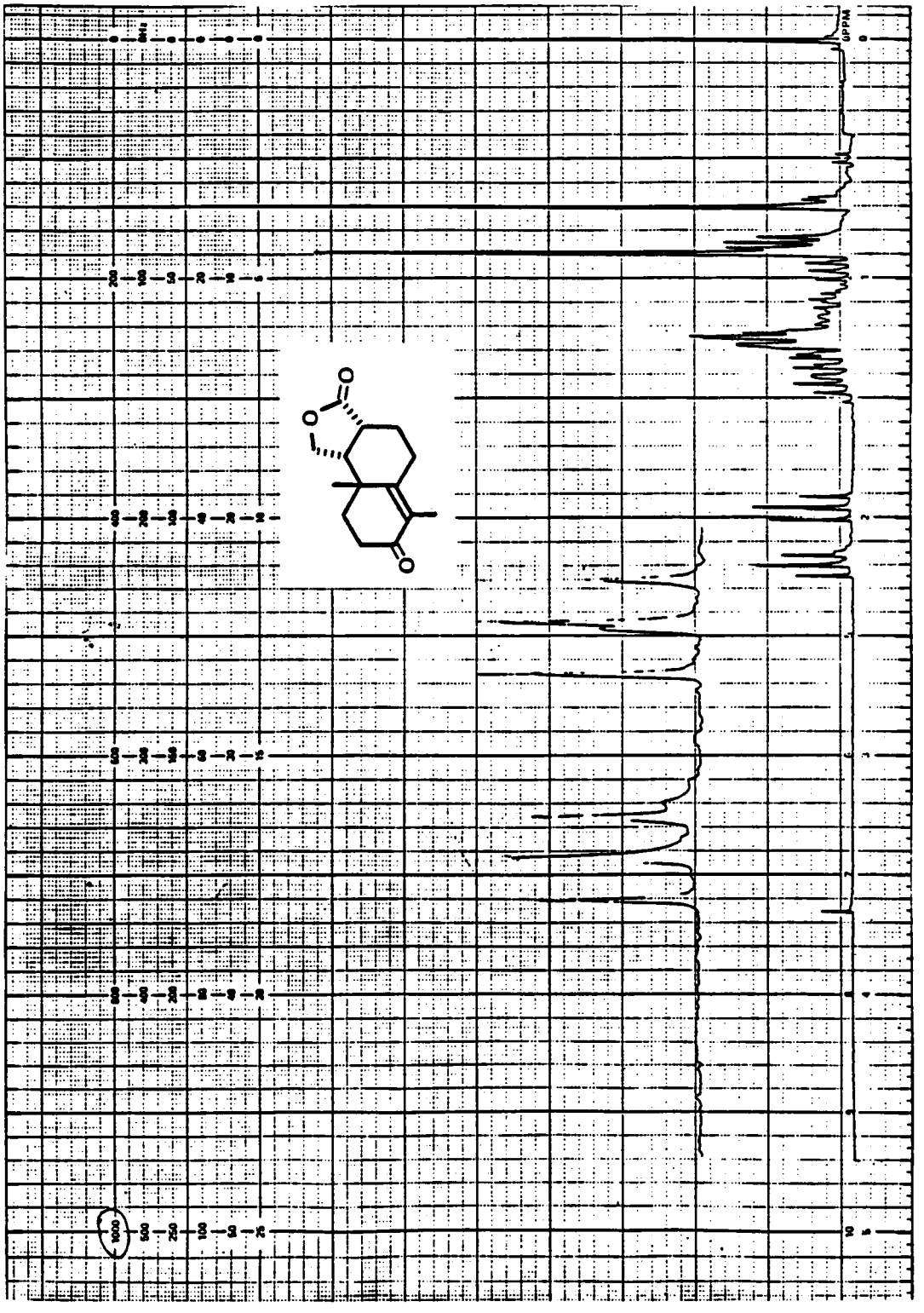
expanded 270 MHz ^{1}H NMR spectrum of ketone 121



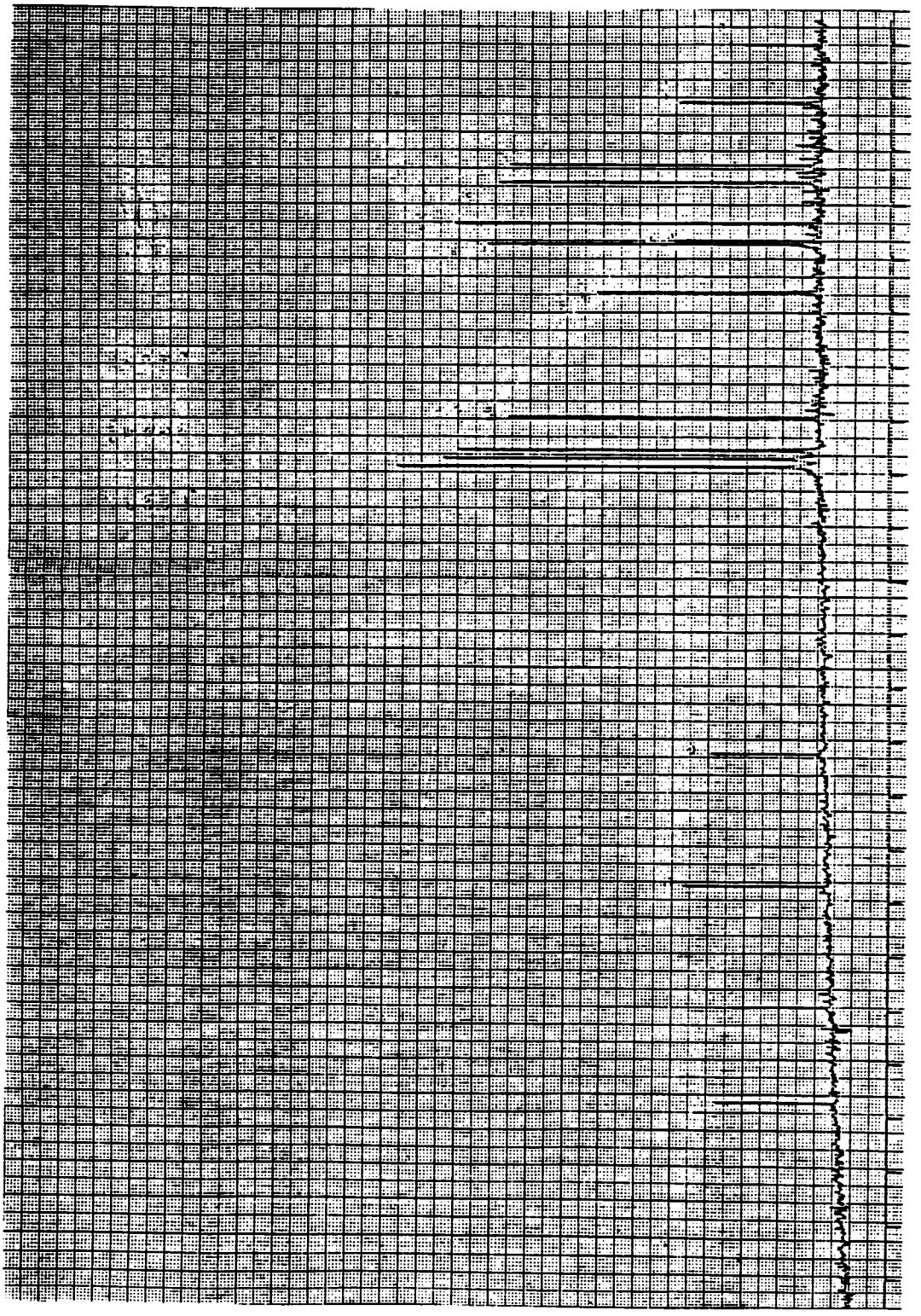
270 MHz ^{1}H NMR spectrum of ketone 121; irradiation of the C-4 methyl group



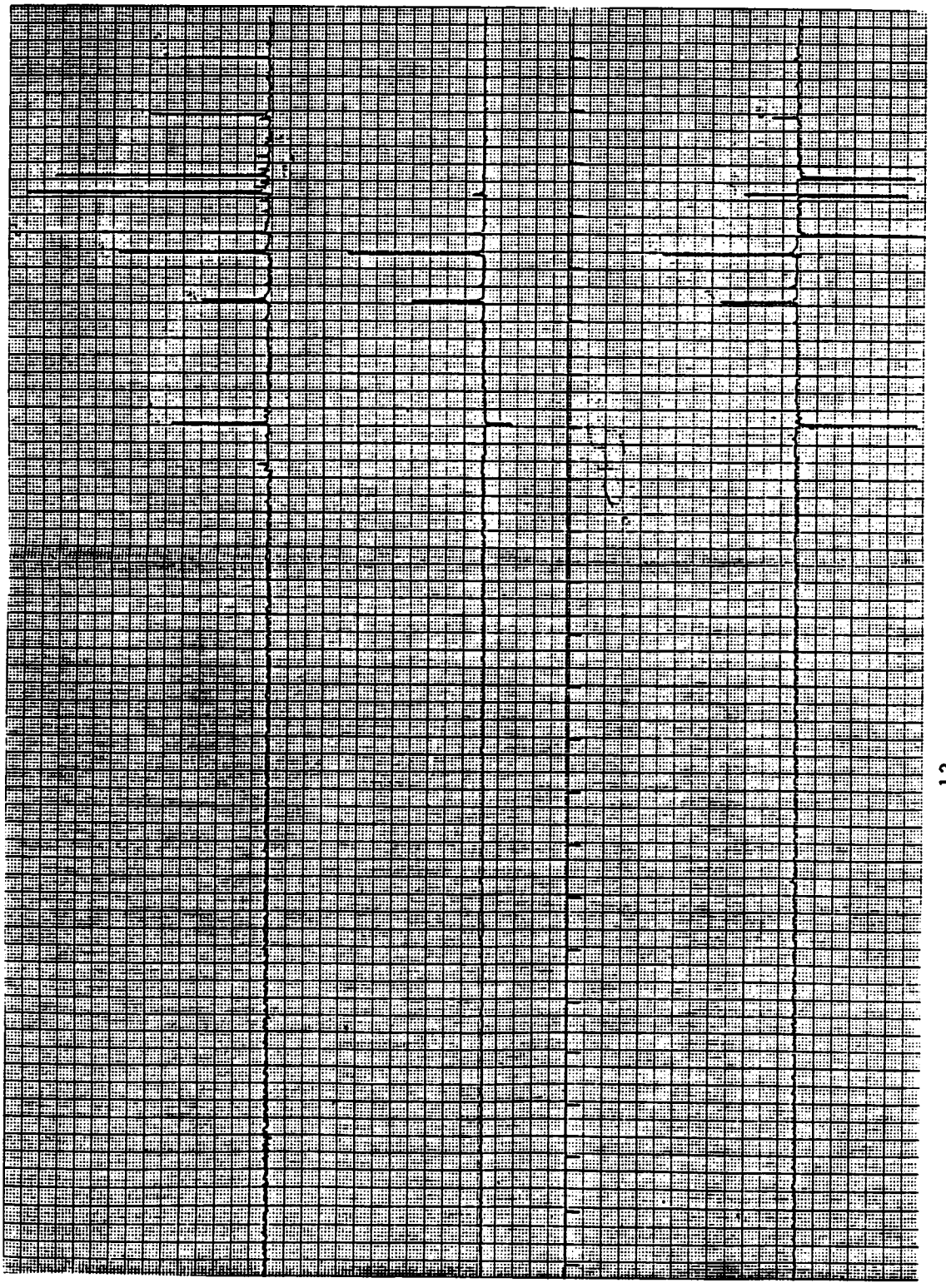
IR spectrum of ketone 121



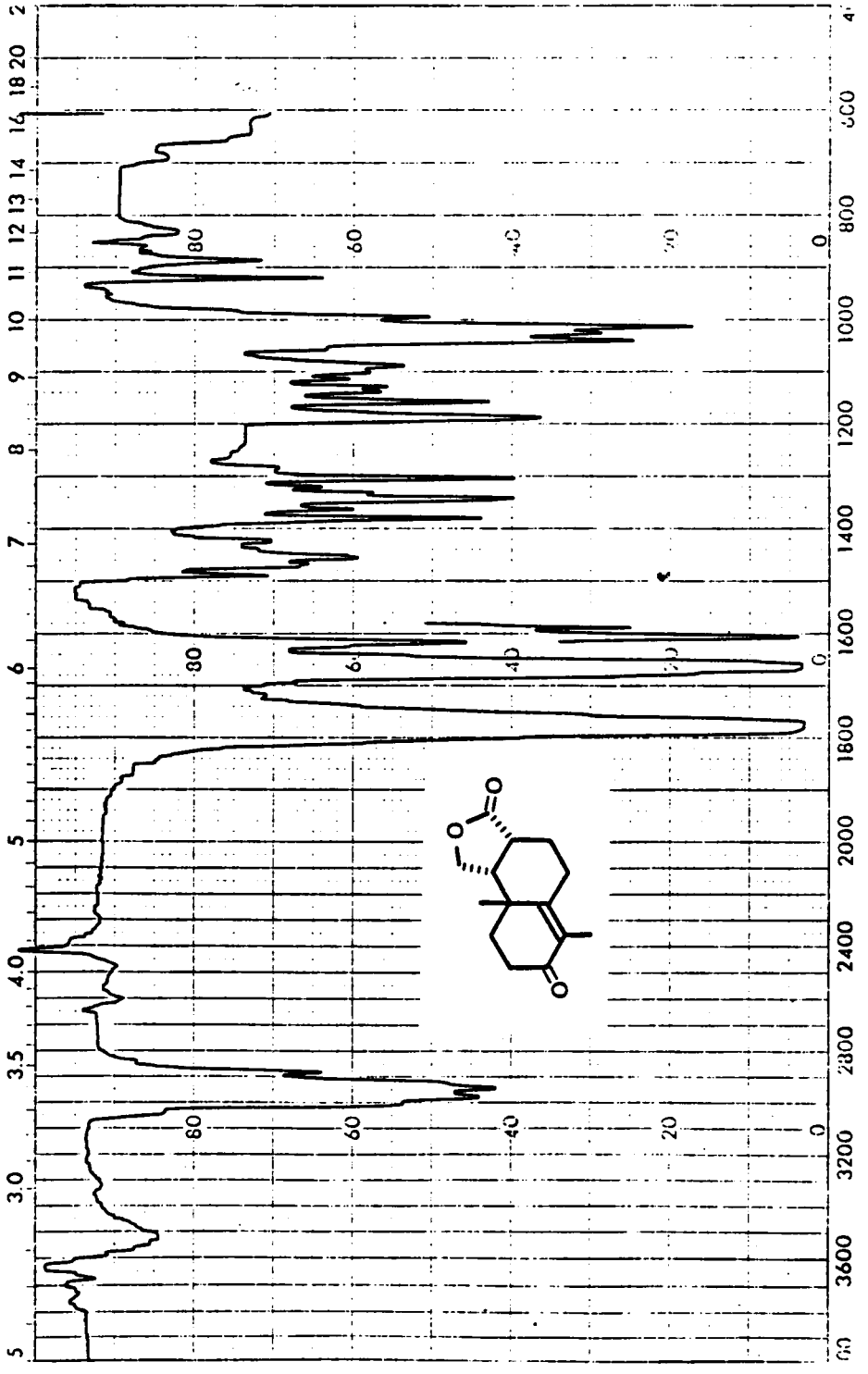
100 MHz ^{1}H NMR spectrum of enone 123



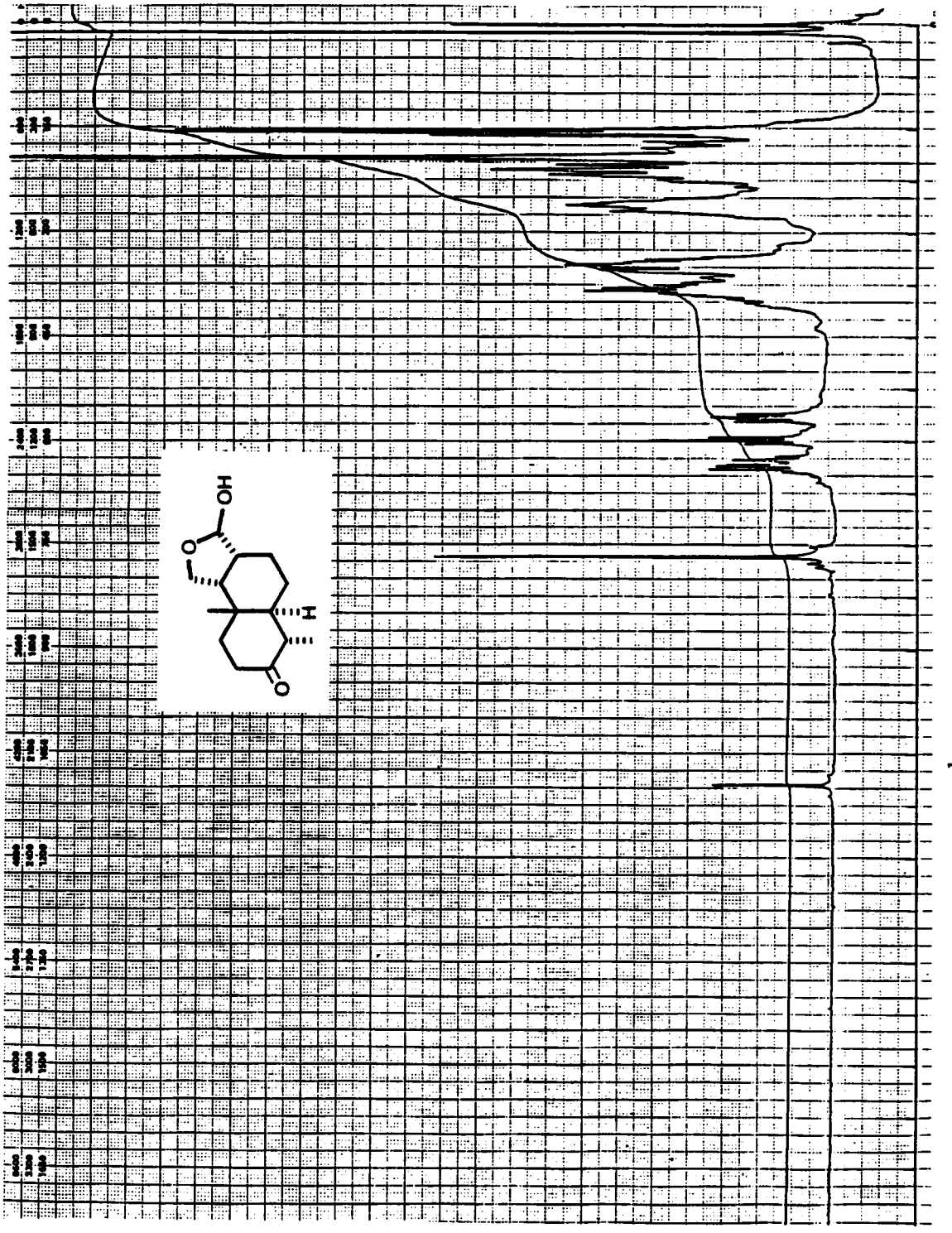
80 MHz ^{13}C NMR decoupled spectrum of enone 123



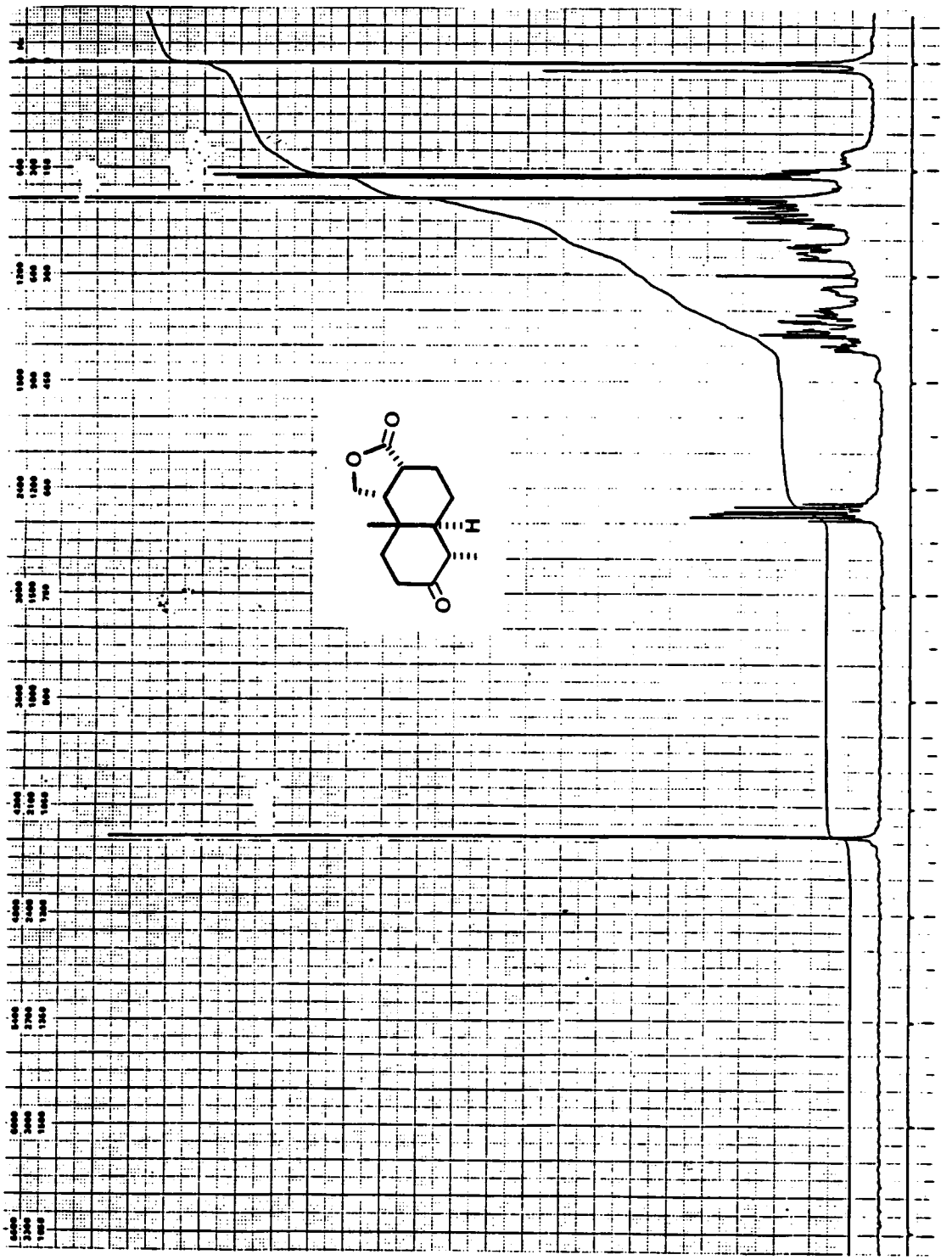
80 MHz ^{13}C INEPT spectra of enone 123



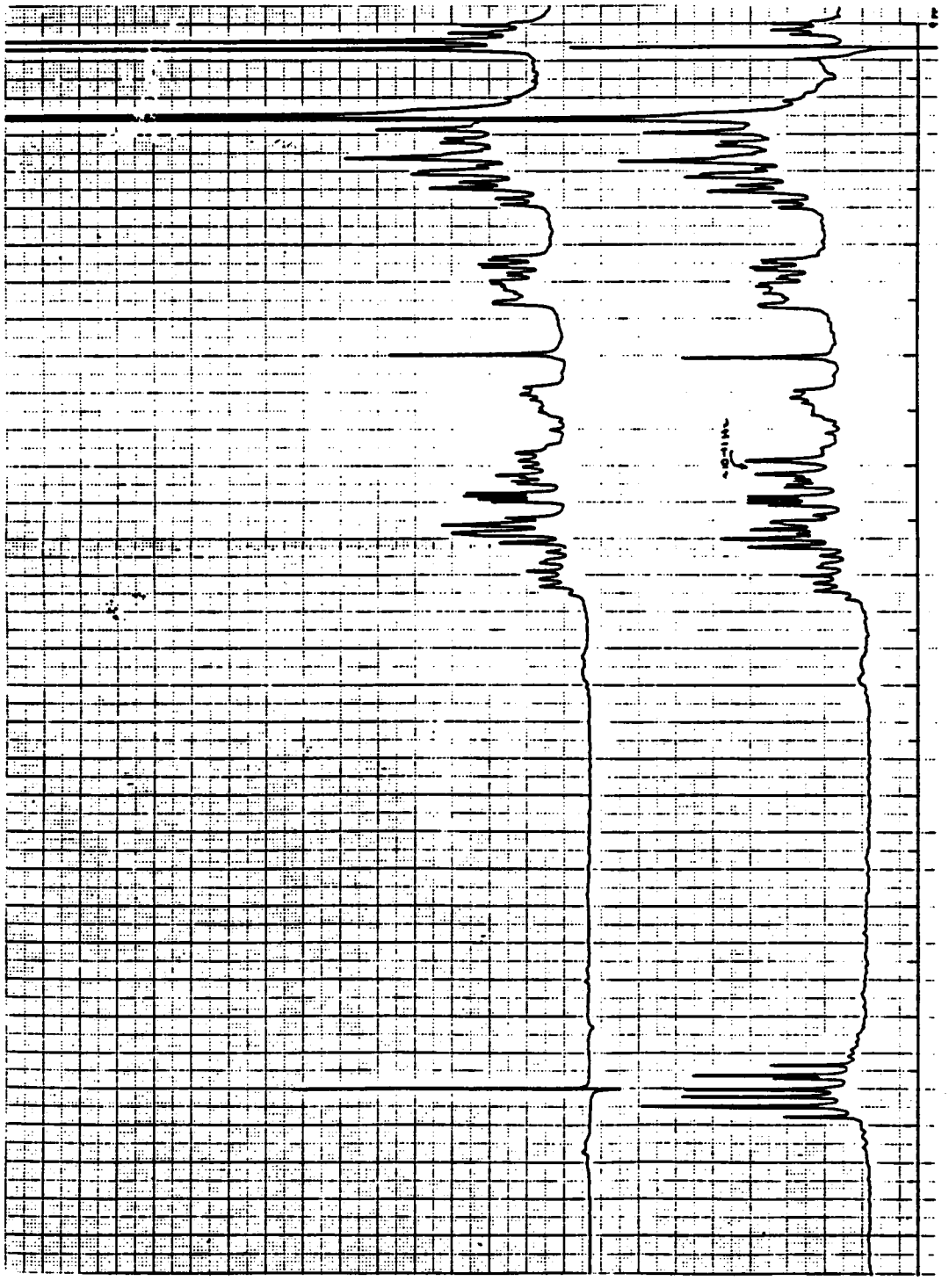
IR spectrum of enone 123



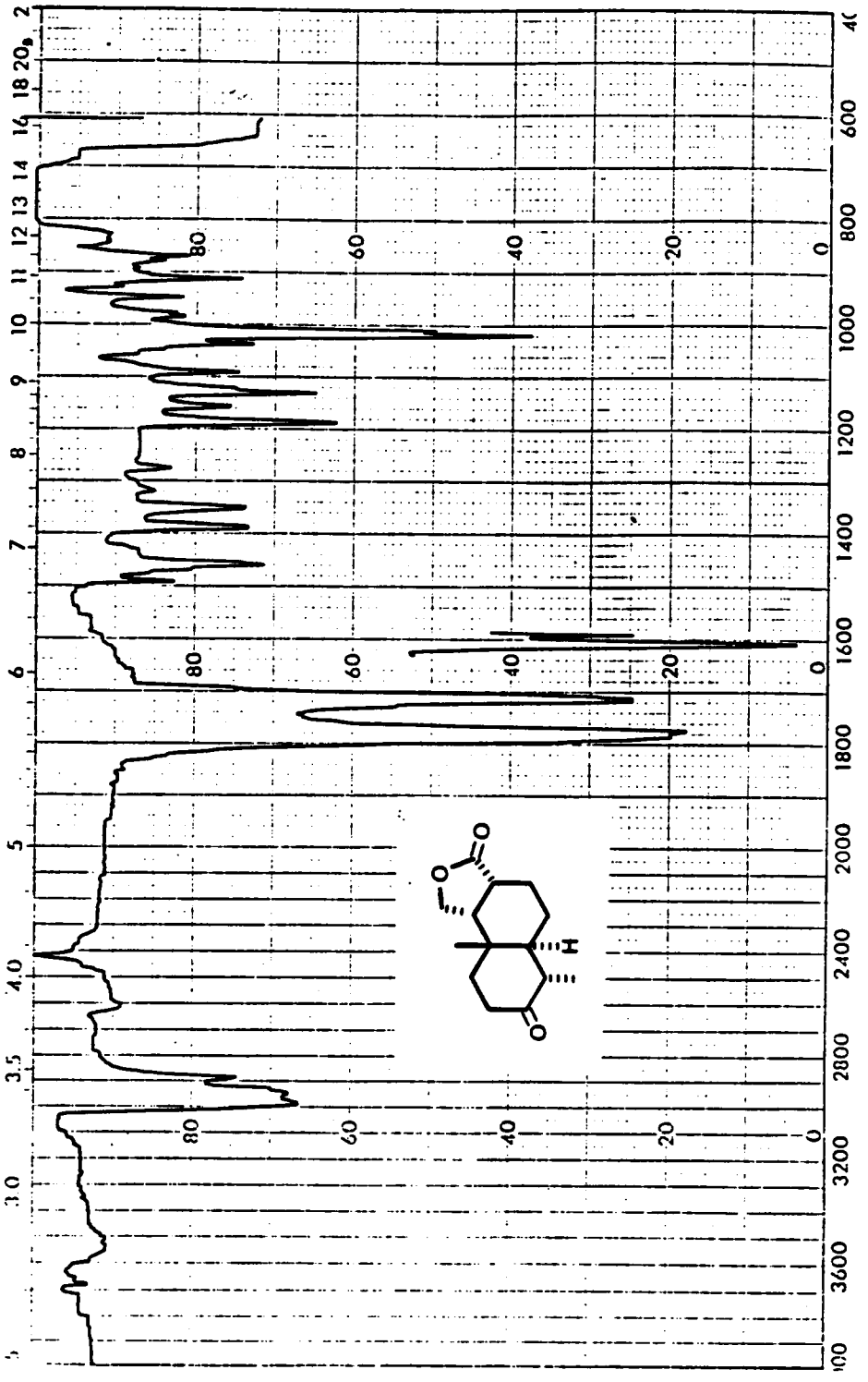
270 MHz ^{1}H NMR spectrum of lactol 124



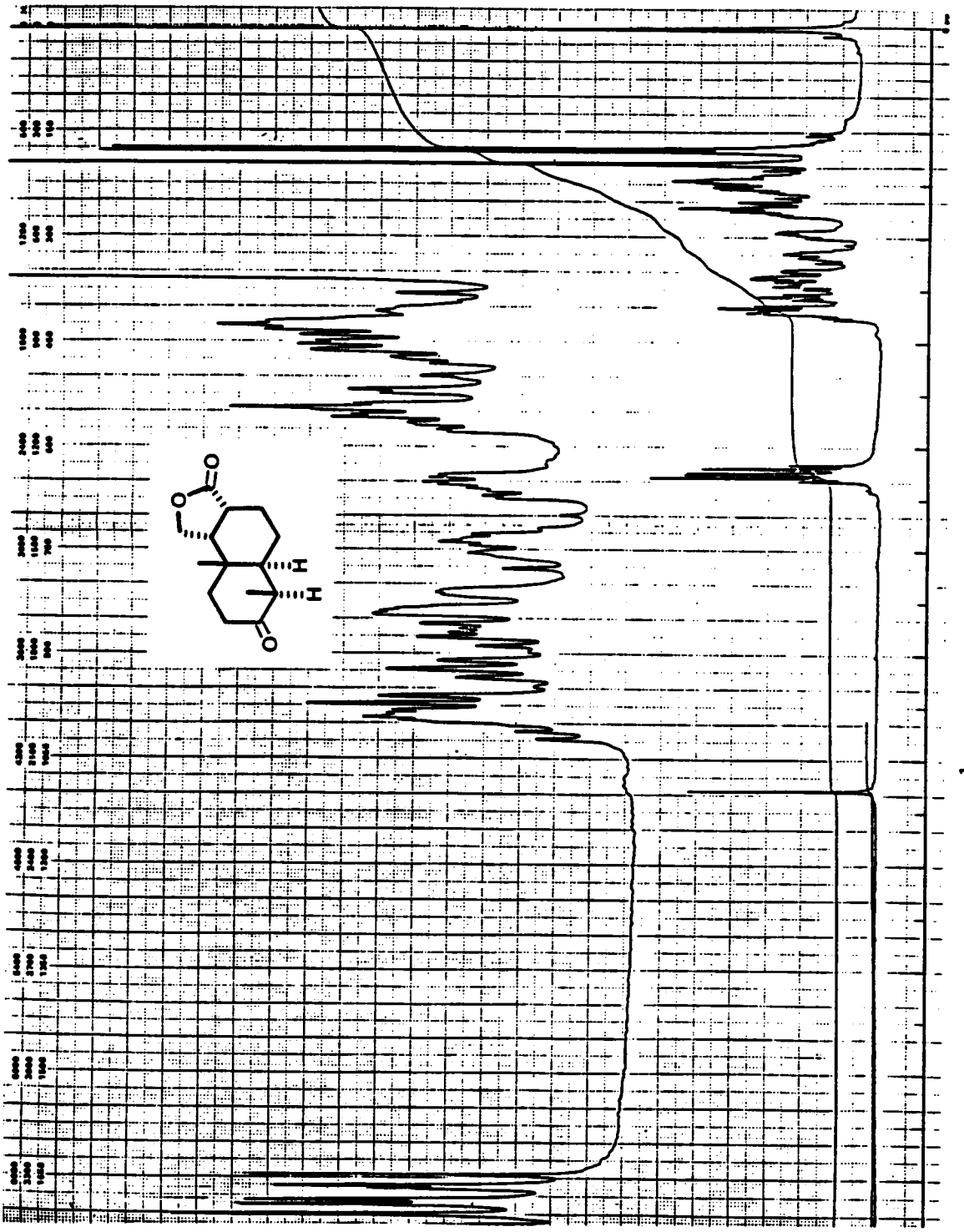
270 MHz ^{1}H NMR spectrum of ketone 125



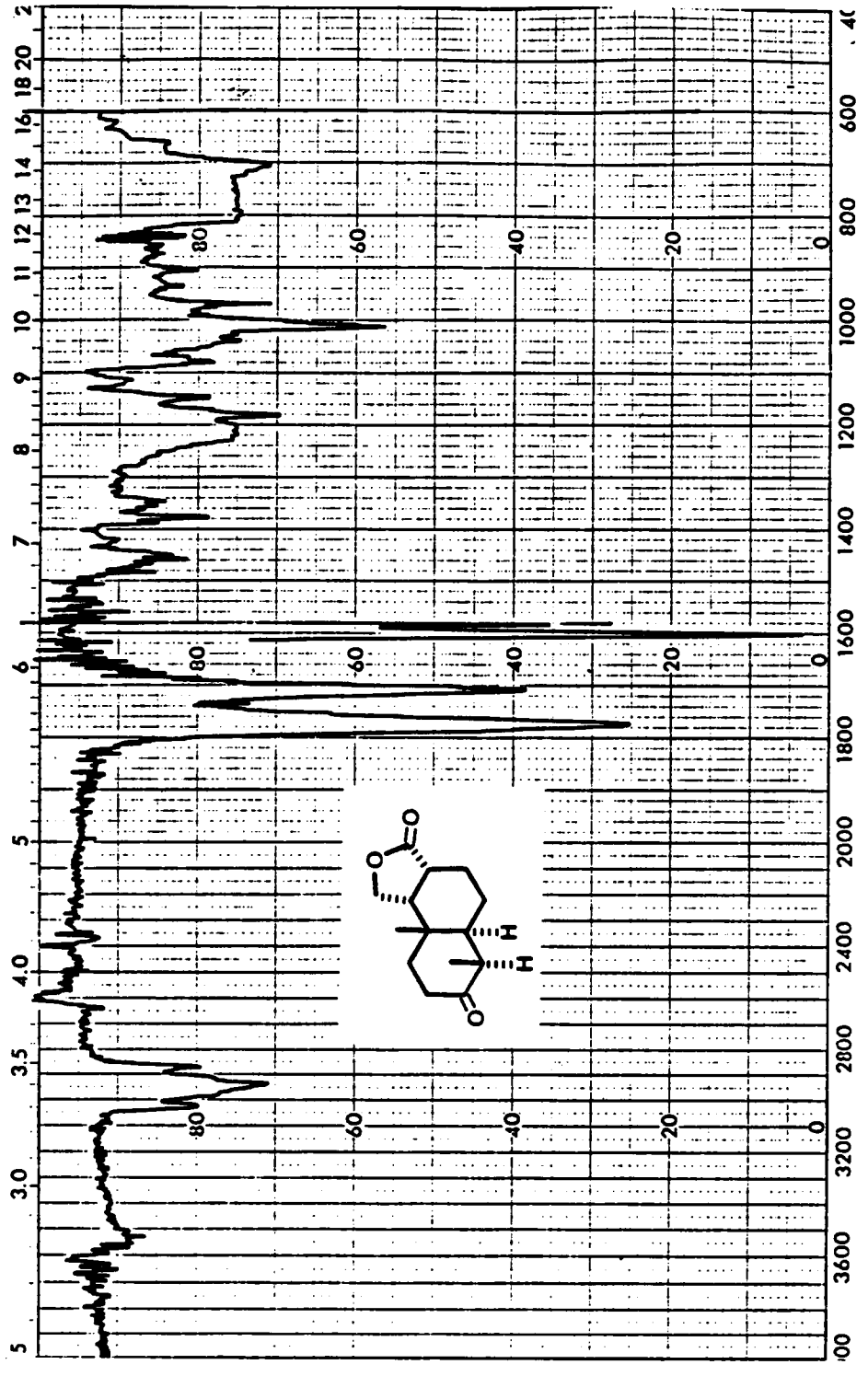
270 MHz ^{1}H NMR spectrum of 125; irradiation of the C-4 methyl group



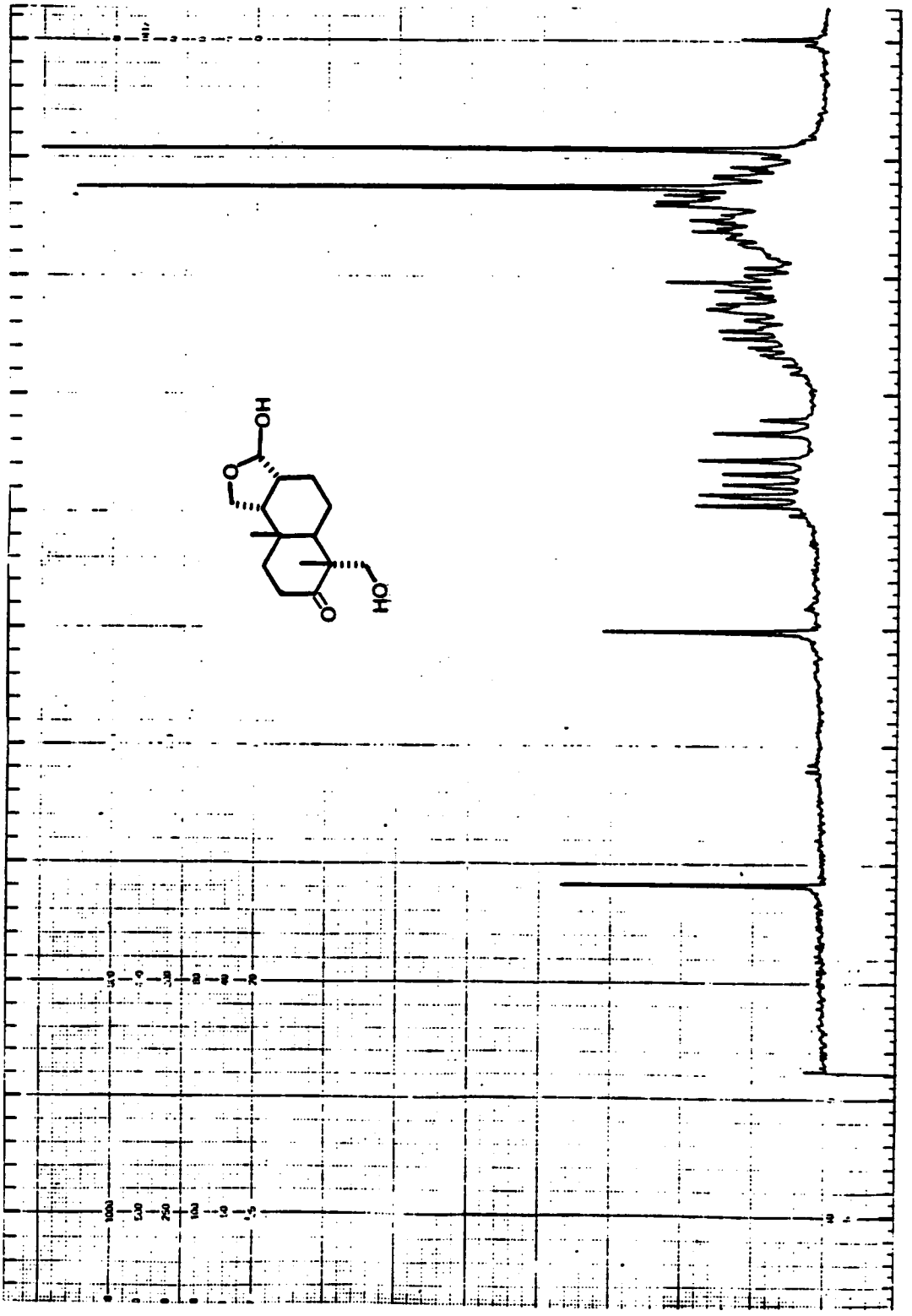
IR spectrum of ketone 125



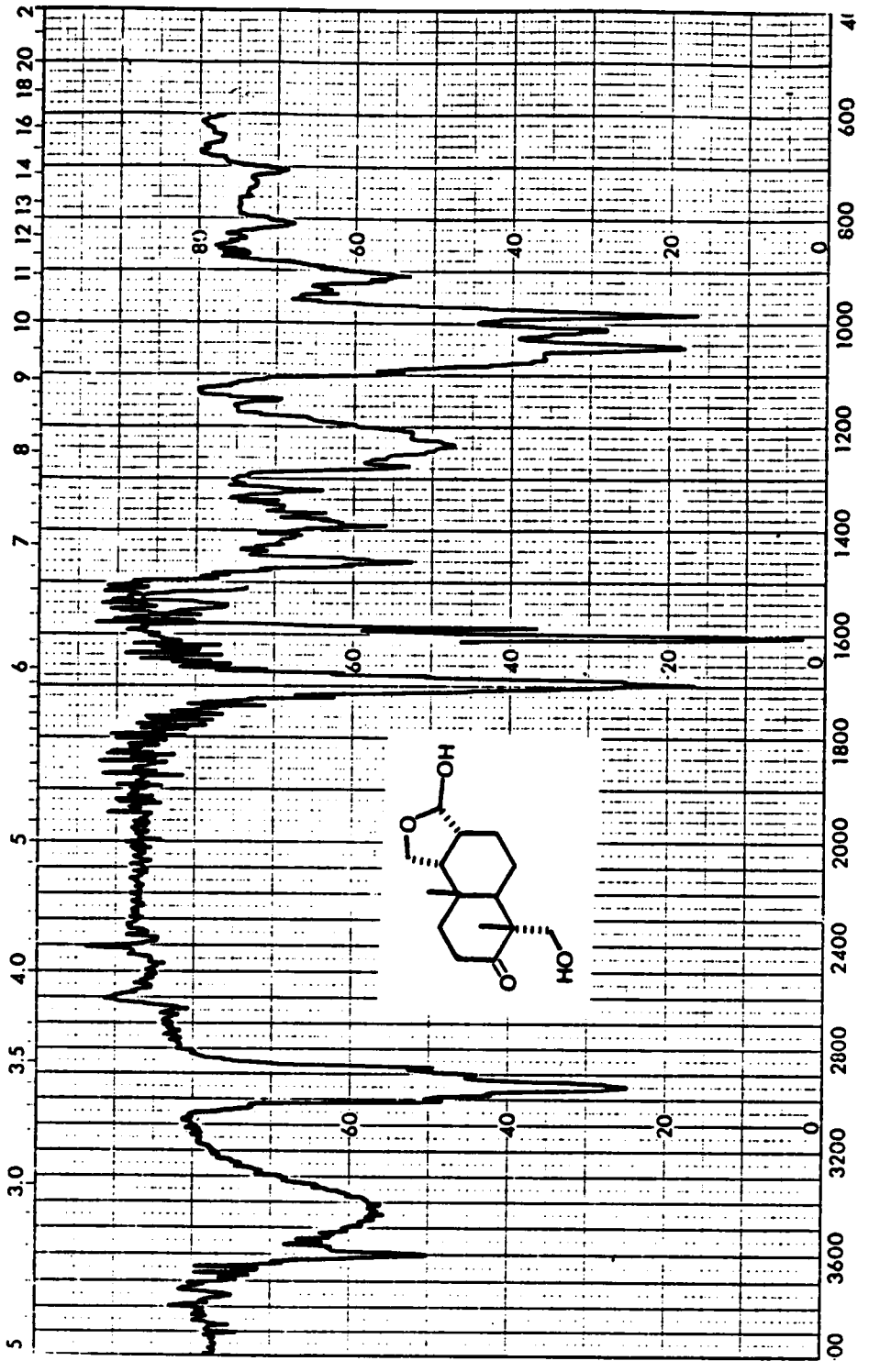
270 MHz ^{1}H NMR spectrum of ketone 126



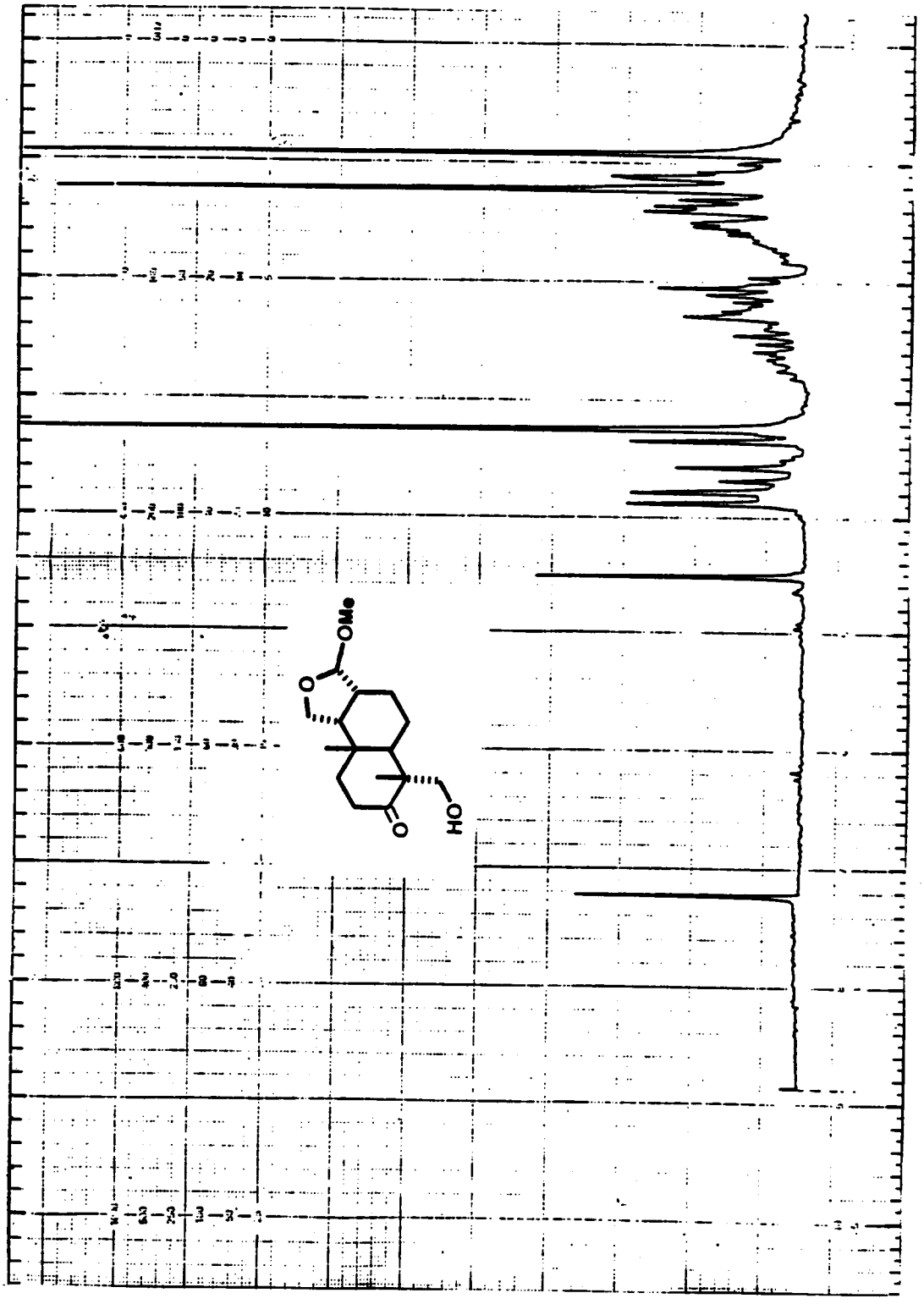
IR spectrum of ketone 126



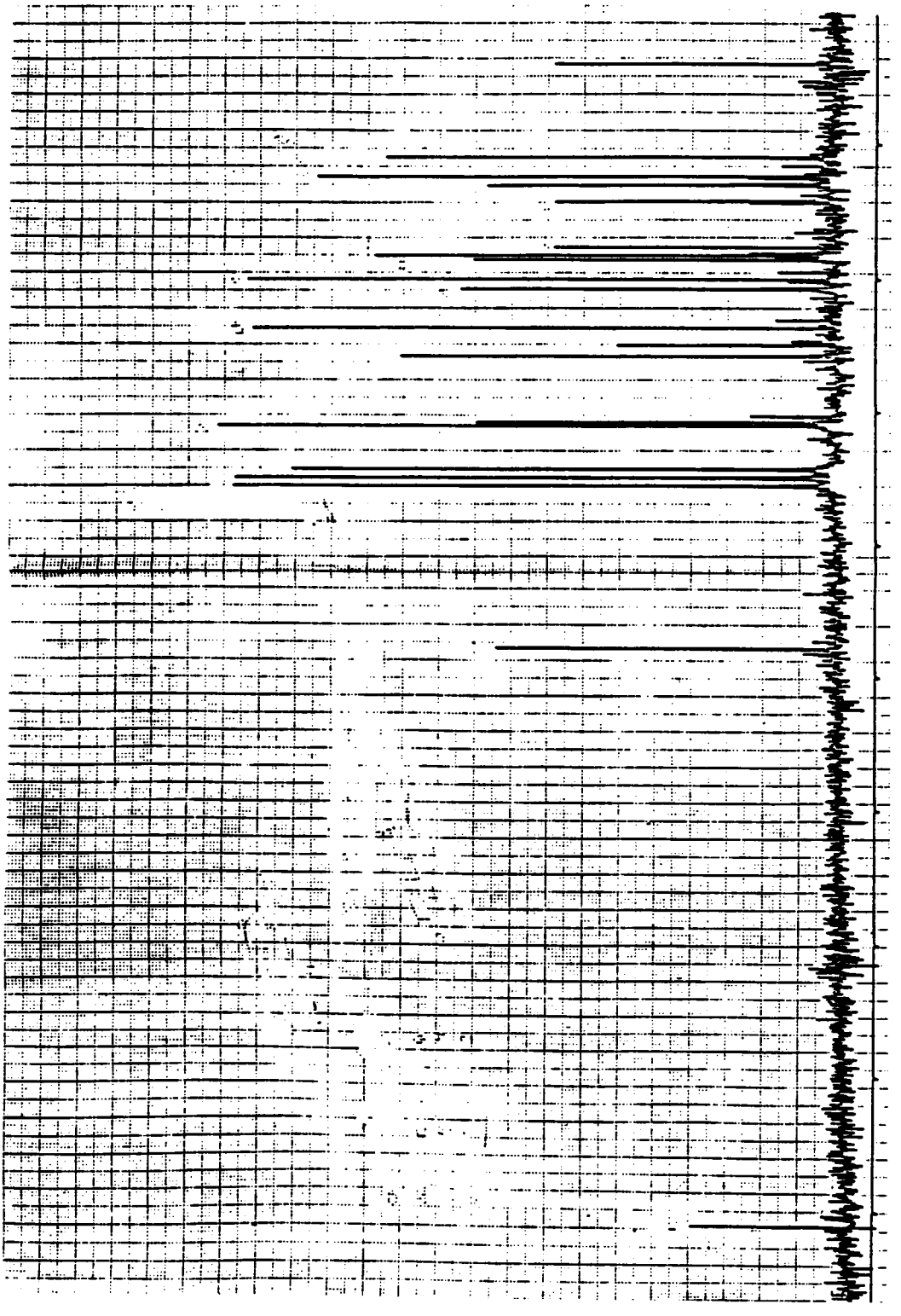
100 MHz ^{1}H NMR spectrum of lactol 127



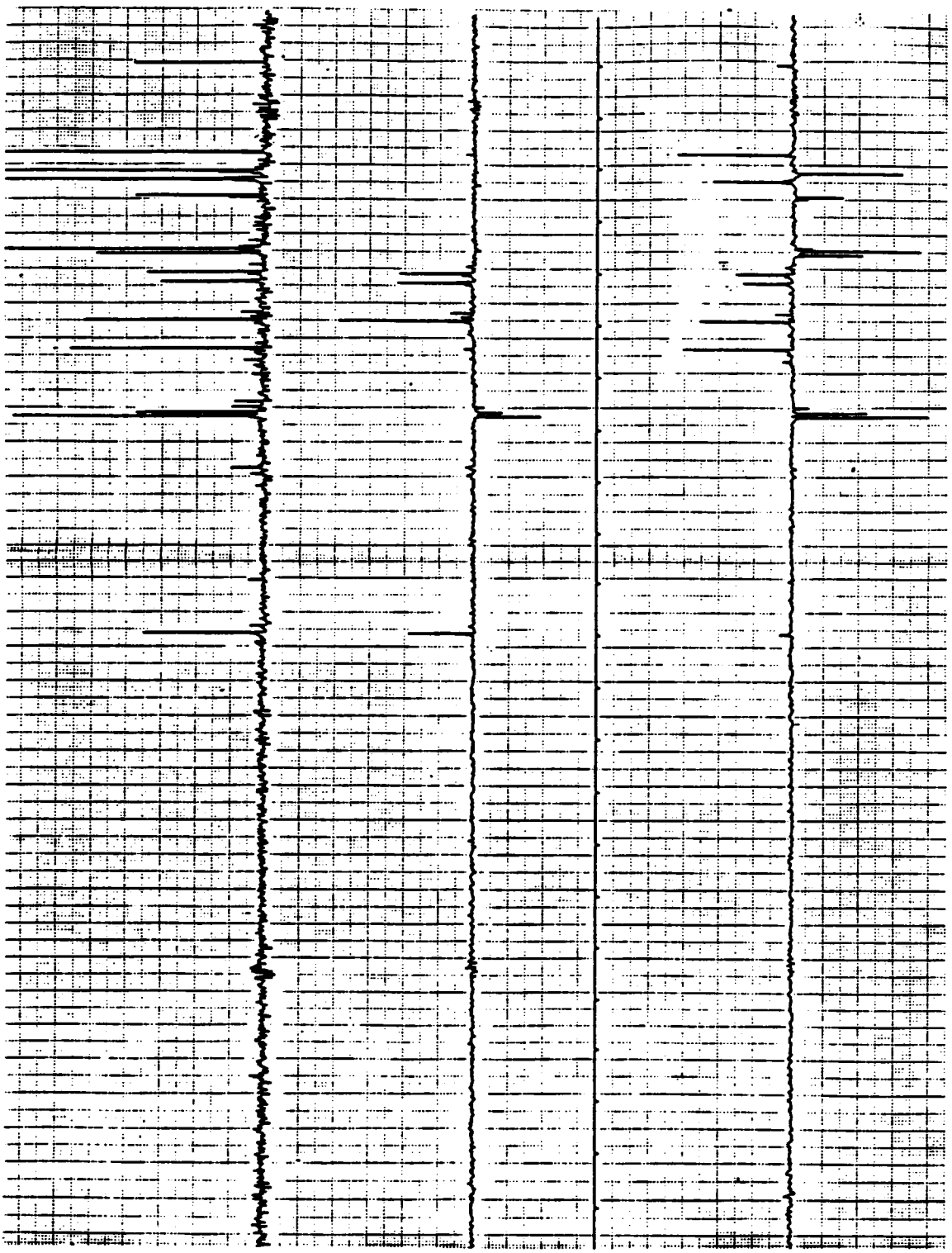
IR spectrum of lactol 127



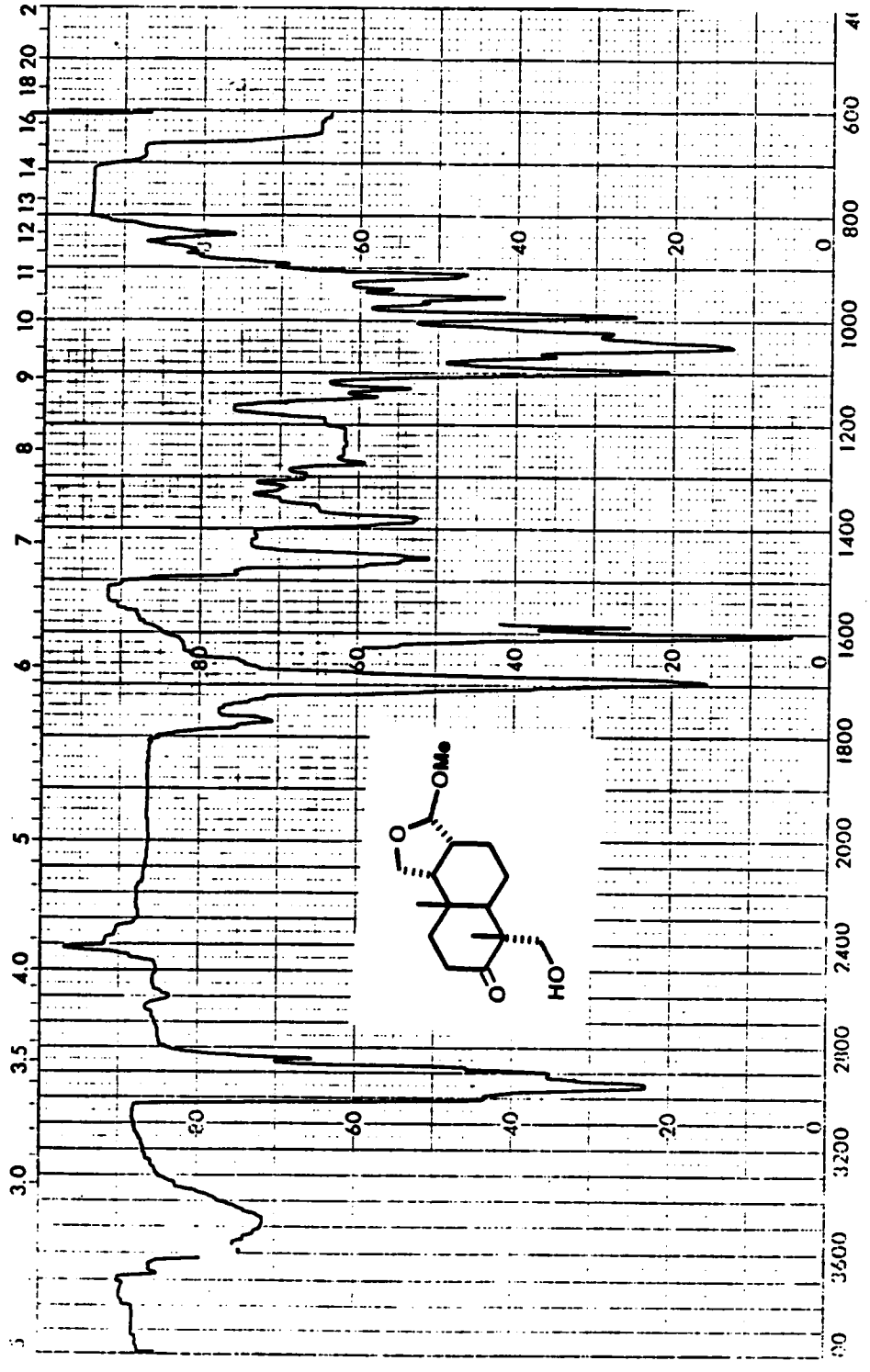
100 MHz ^{1}H NMR spectrum of alcohol 128



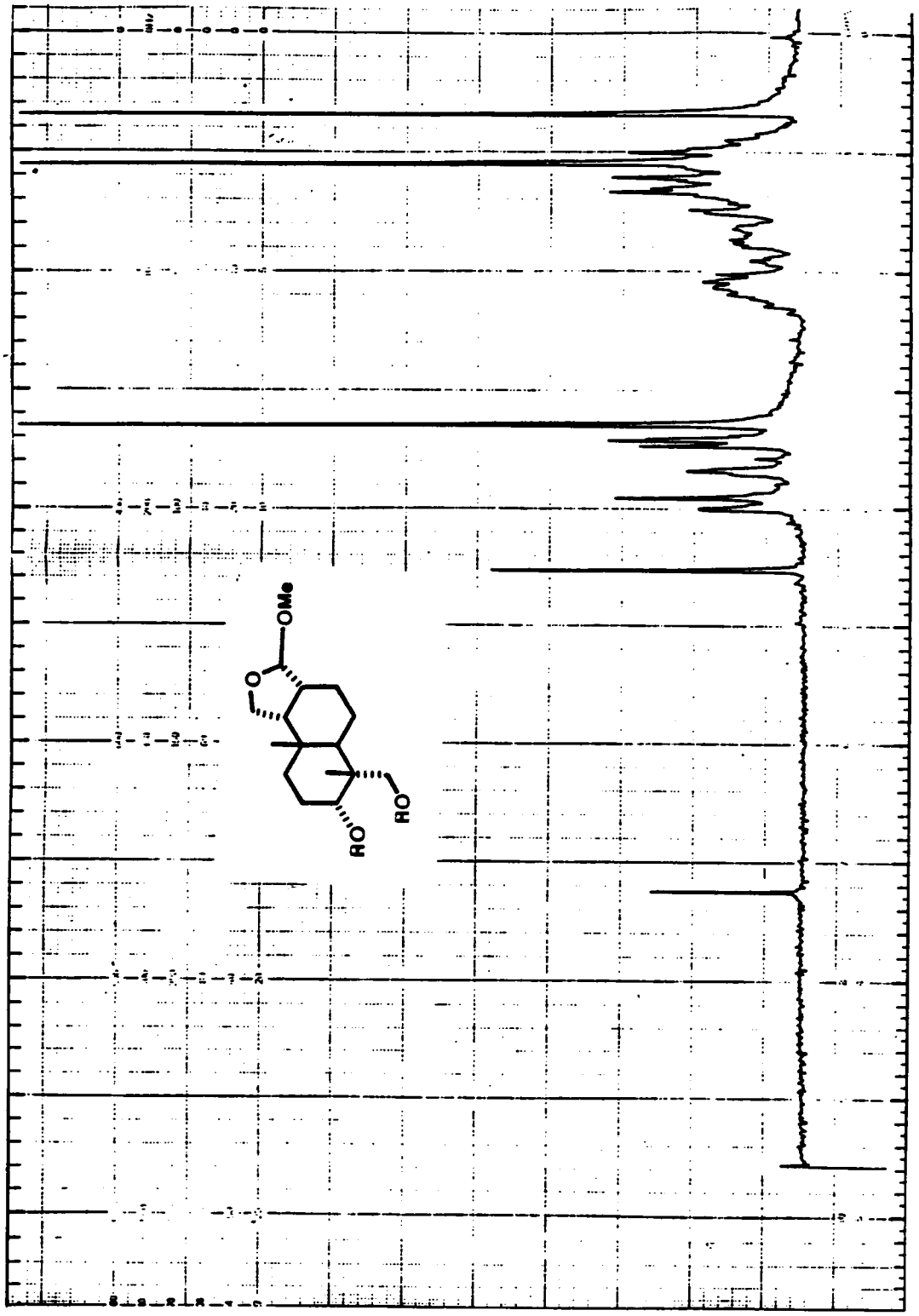
80 MHz ^{13}C NMR decoupled spectrum of alcohol 128



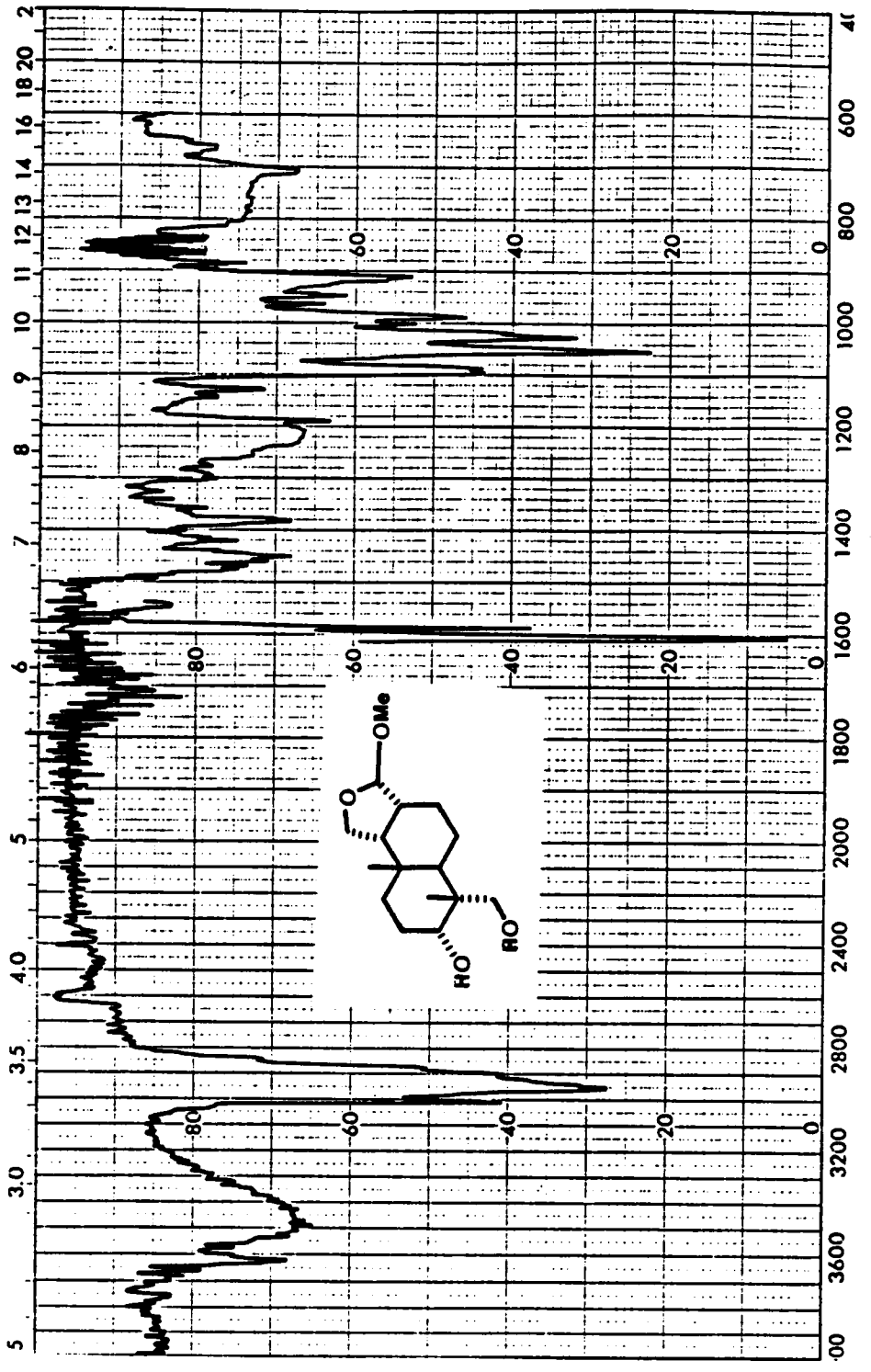
80 MHz ^{13}C INEPT spectra of alcohol 128



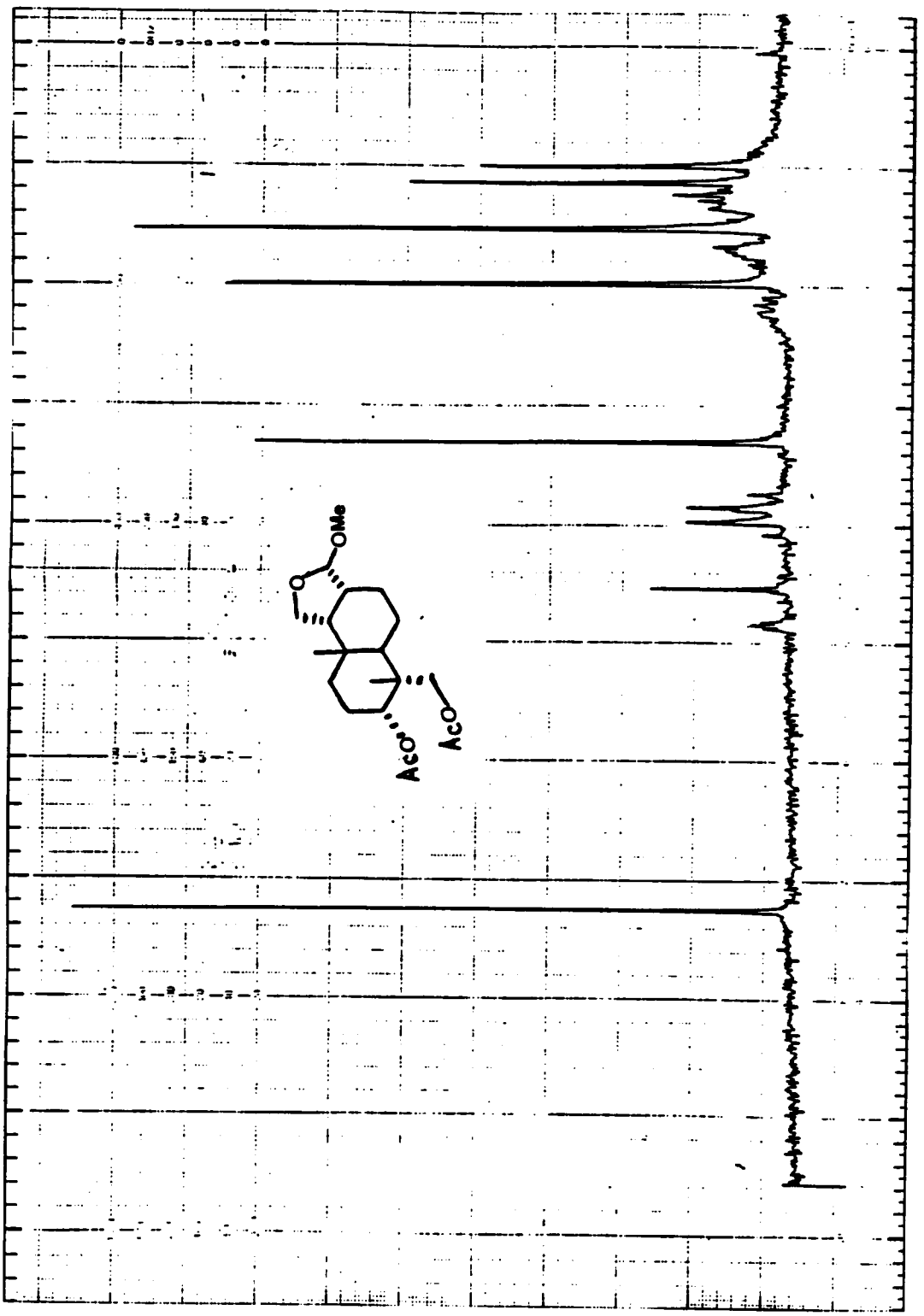
IR spectrum of alcohol 128



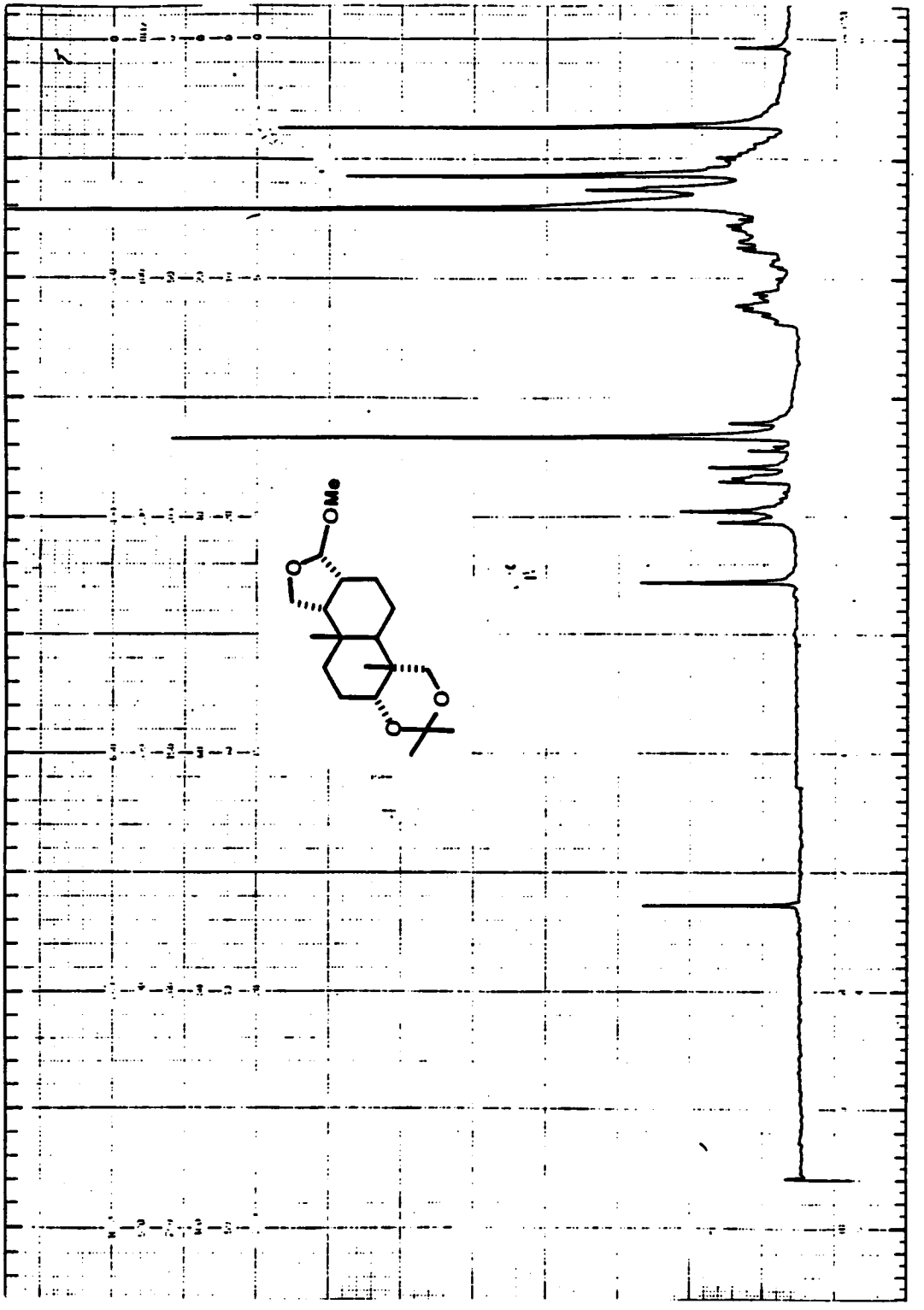
100 MHz ^{1}H NMR spectrum of diol 129



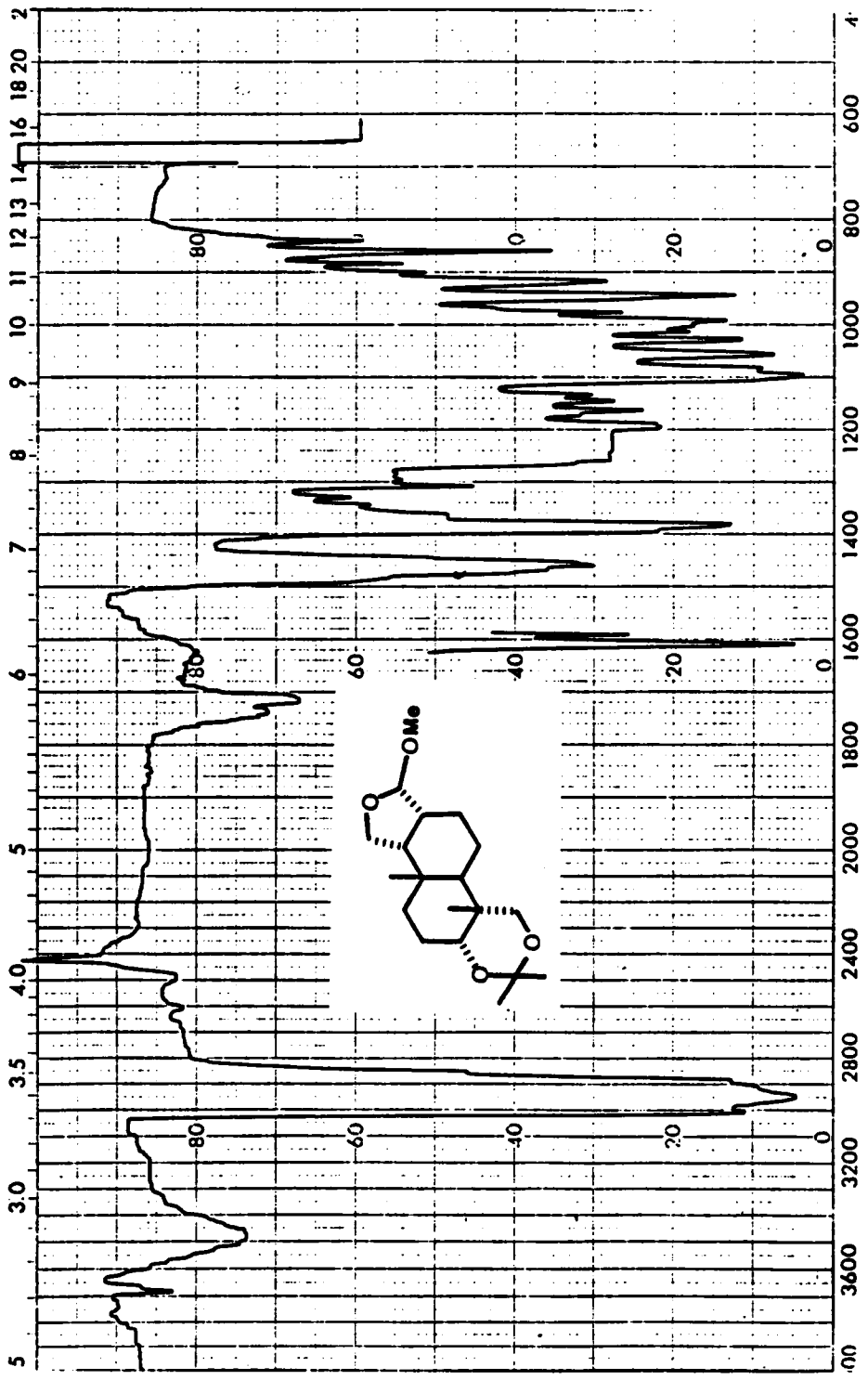
IR spectrum of diol 129



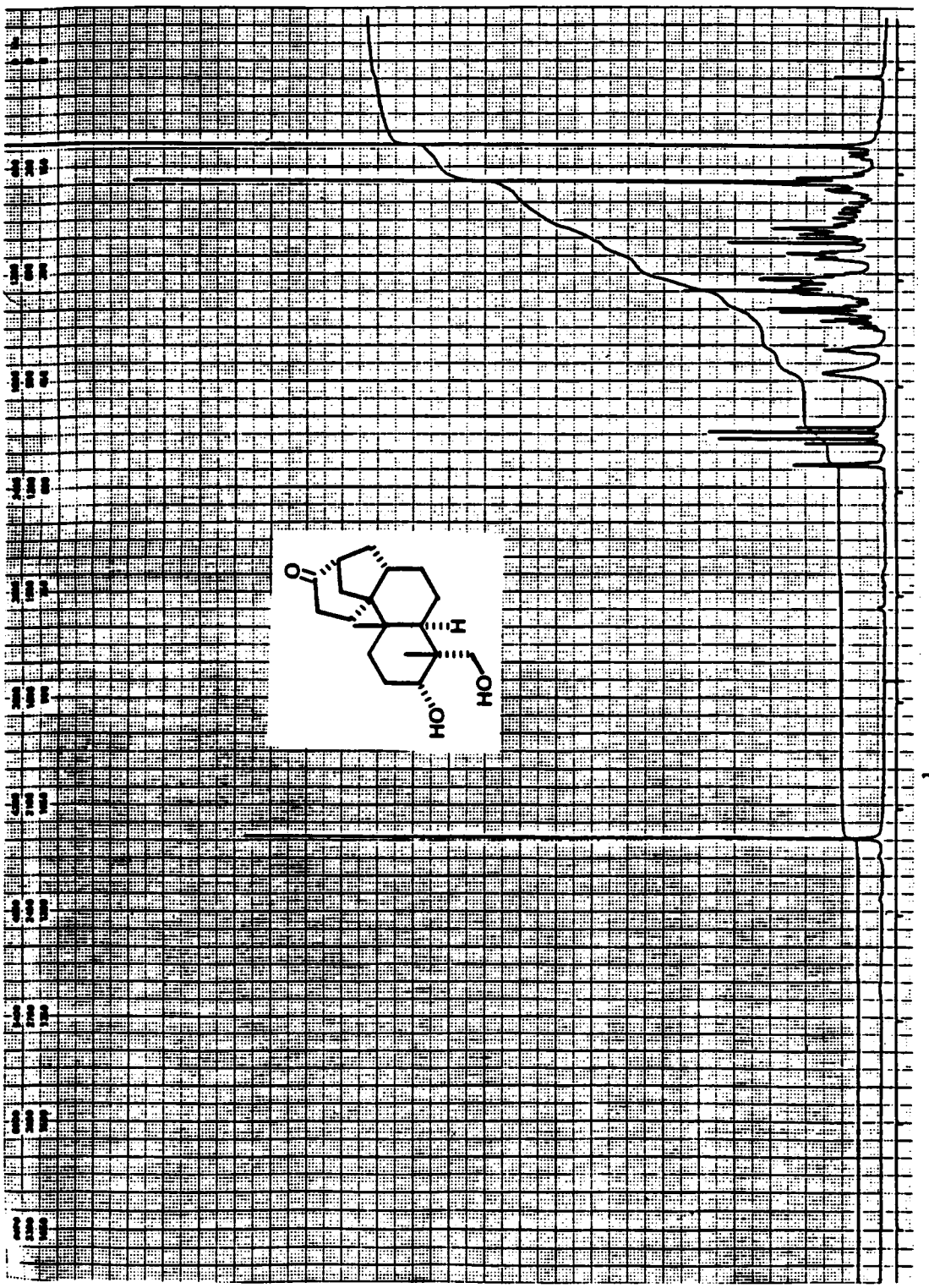
100 MHz ^{1}H NMR spectrum of diacetate 130



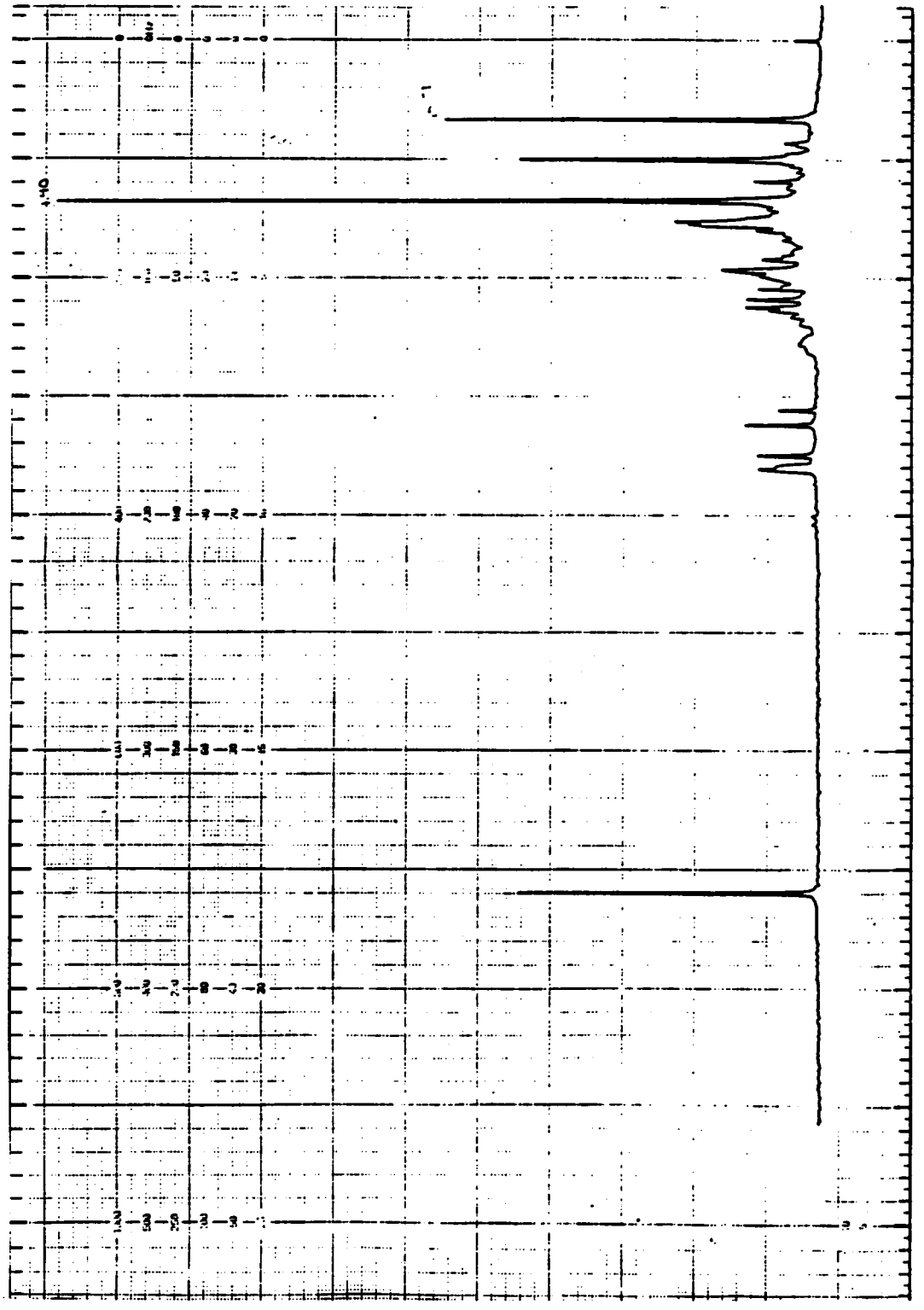
100 MHz ^{1}H NMR spectrum of ketal 131



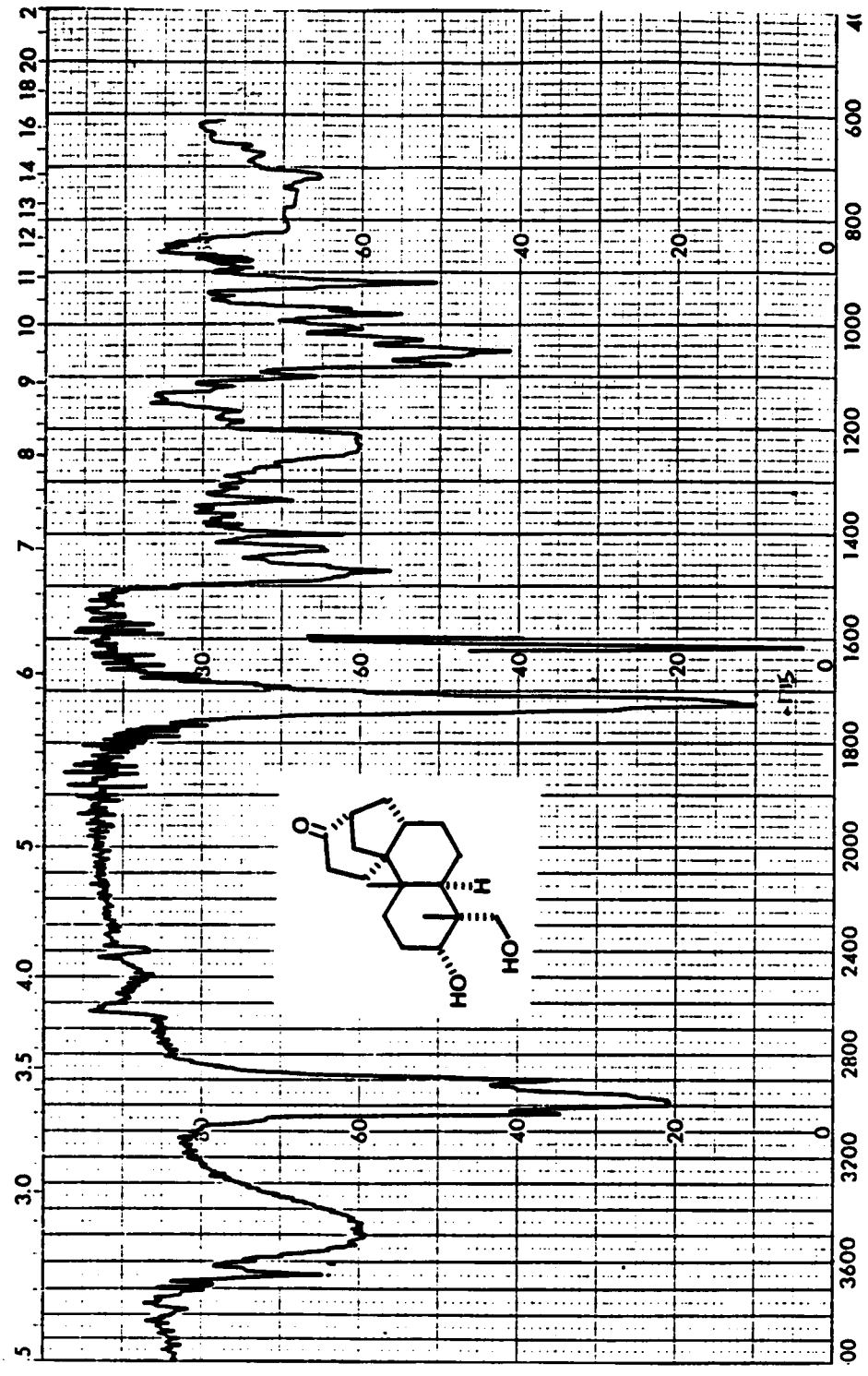
IR spectrum of ketal 131



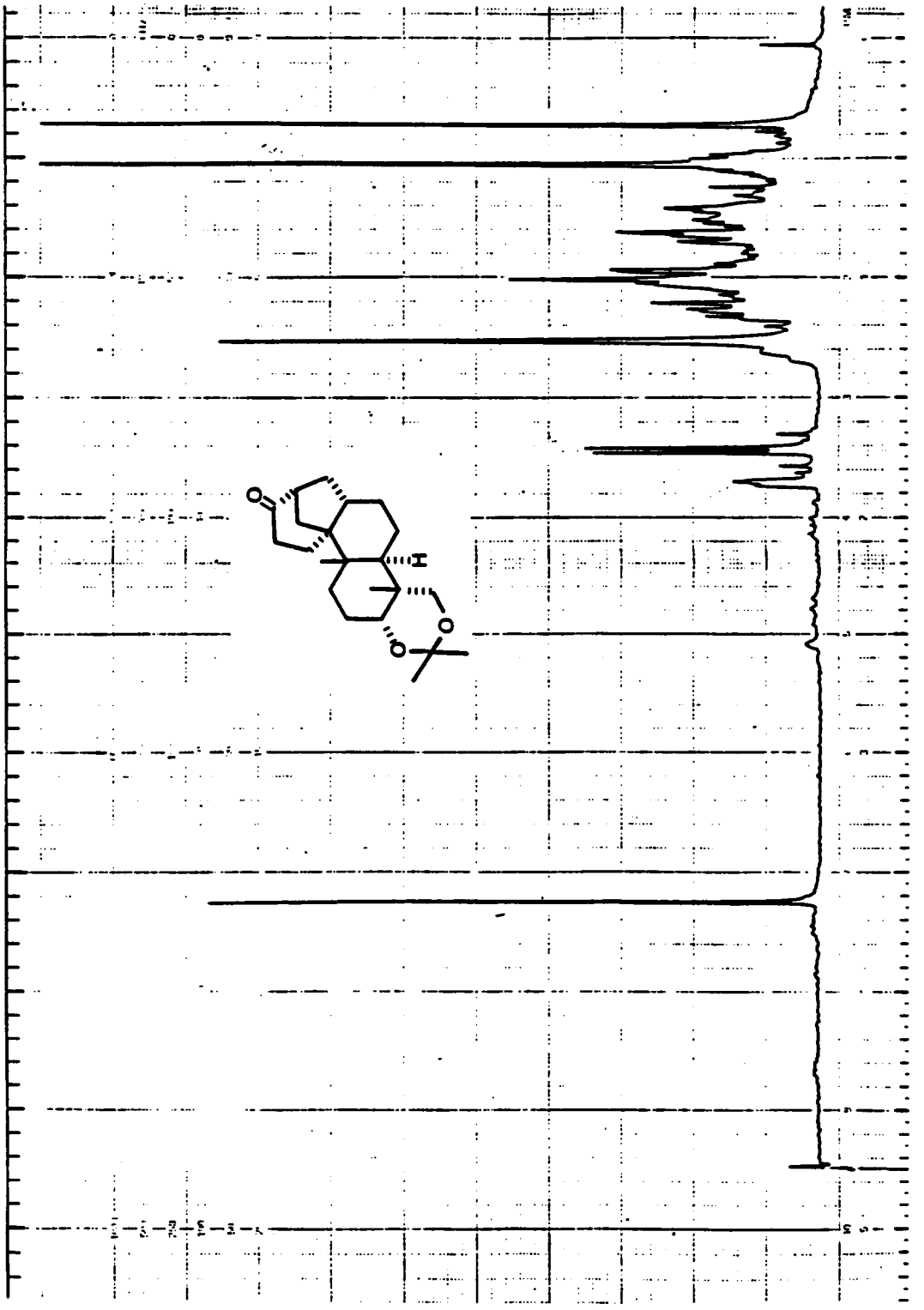
270 MHz ^{1}H NMR spectrum of authentic ketone 3



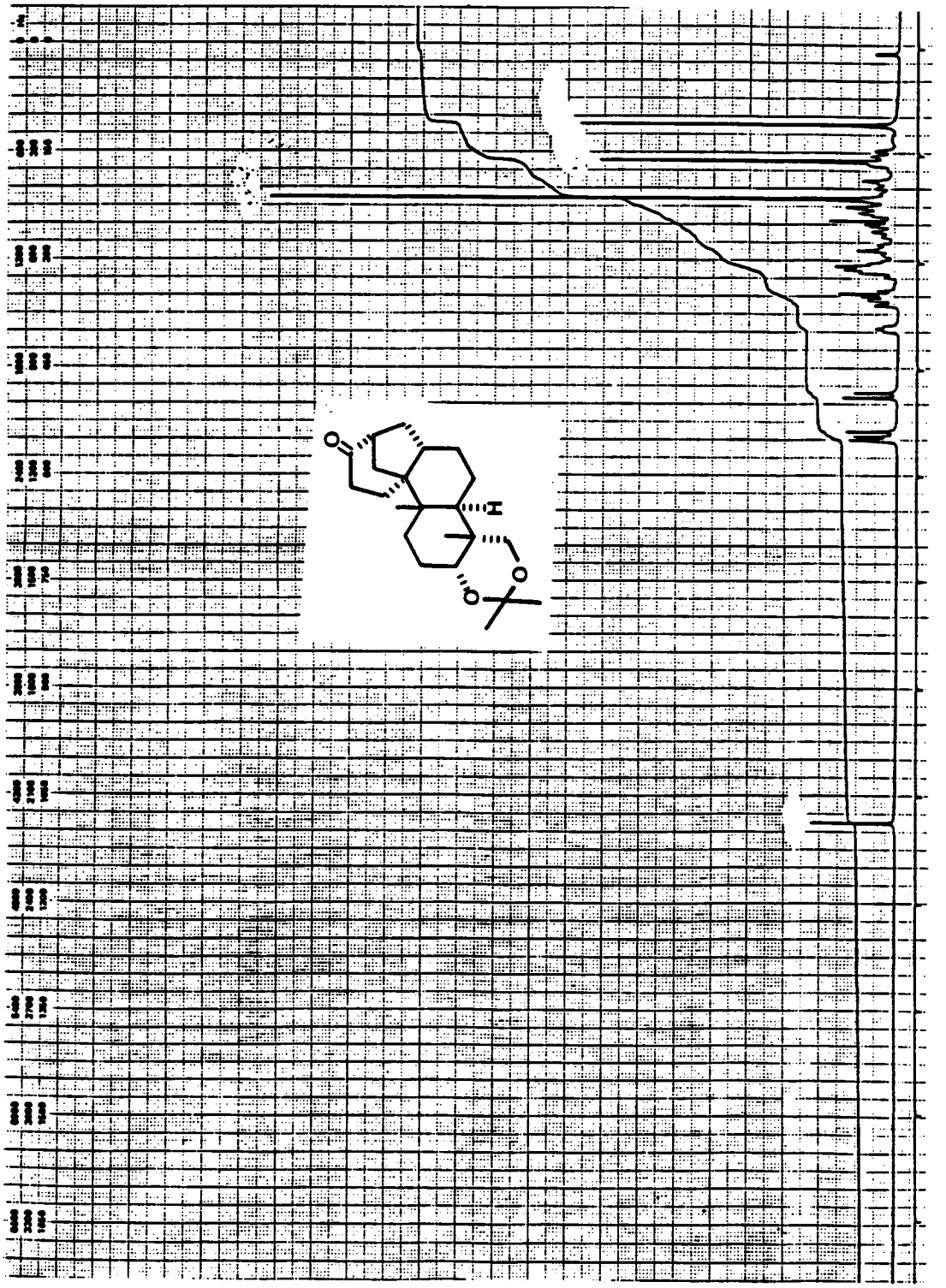
100 MHz ^{1}H NMR spectrum of authentic ketone 3



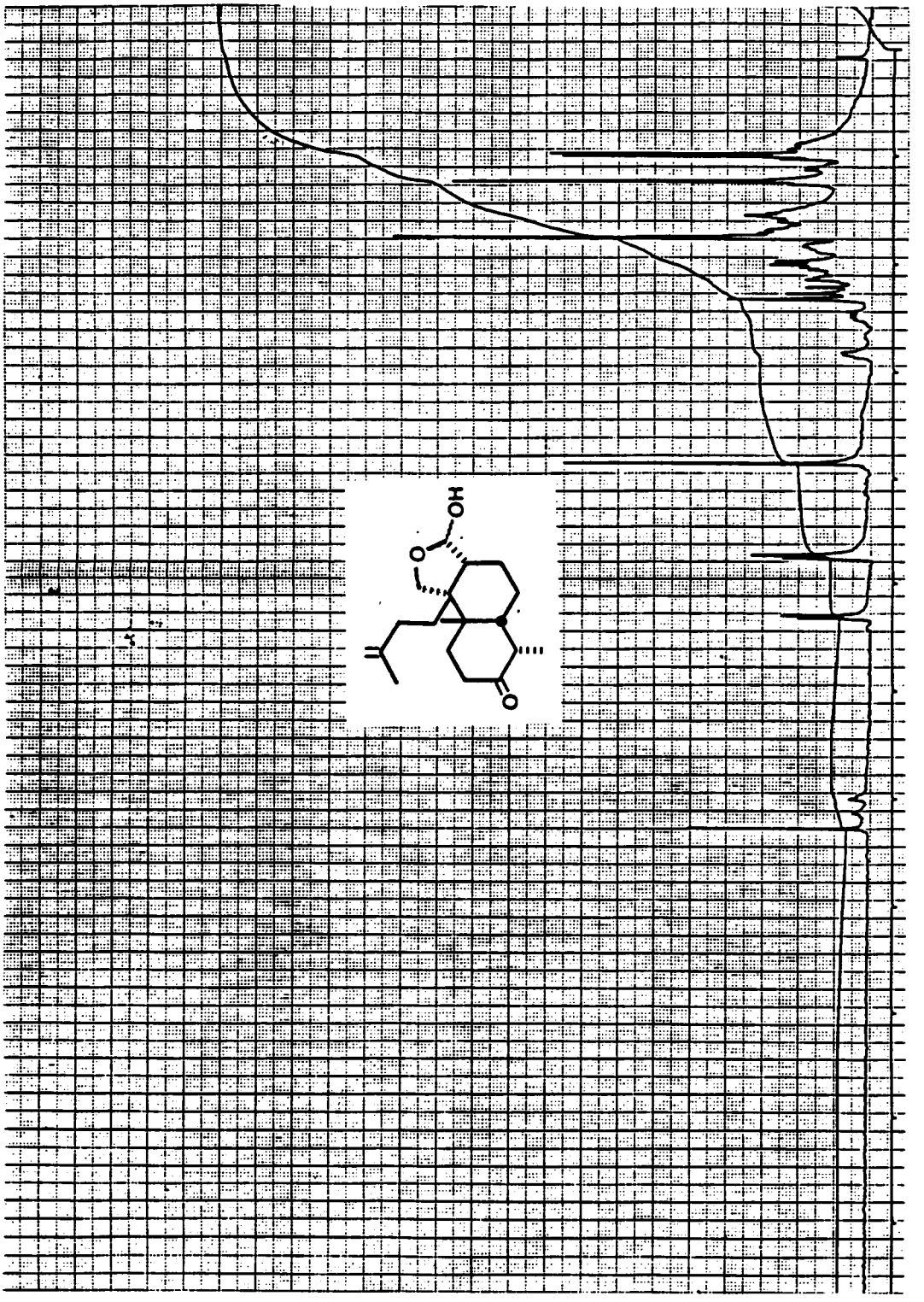
IR spectrum of authentic ketone 3



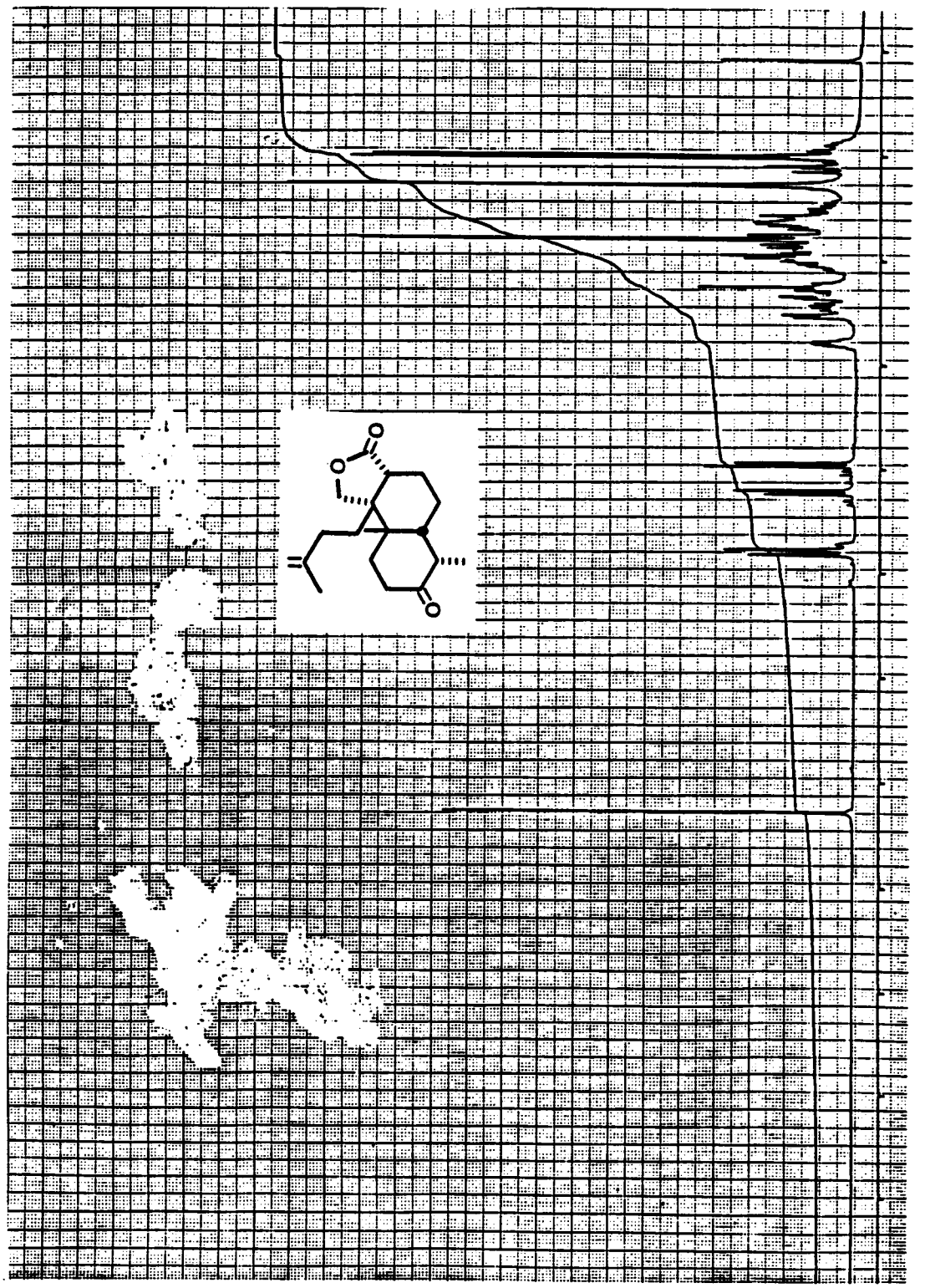
100 MHz ^{1}H NMR spectrum of authentic ketone 4



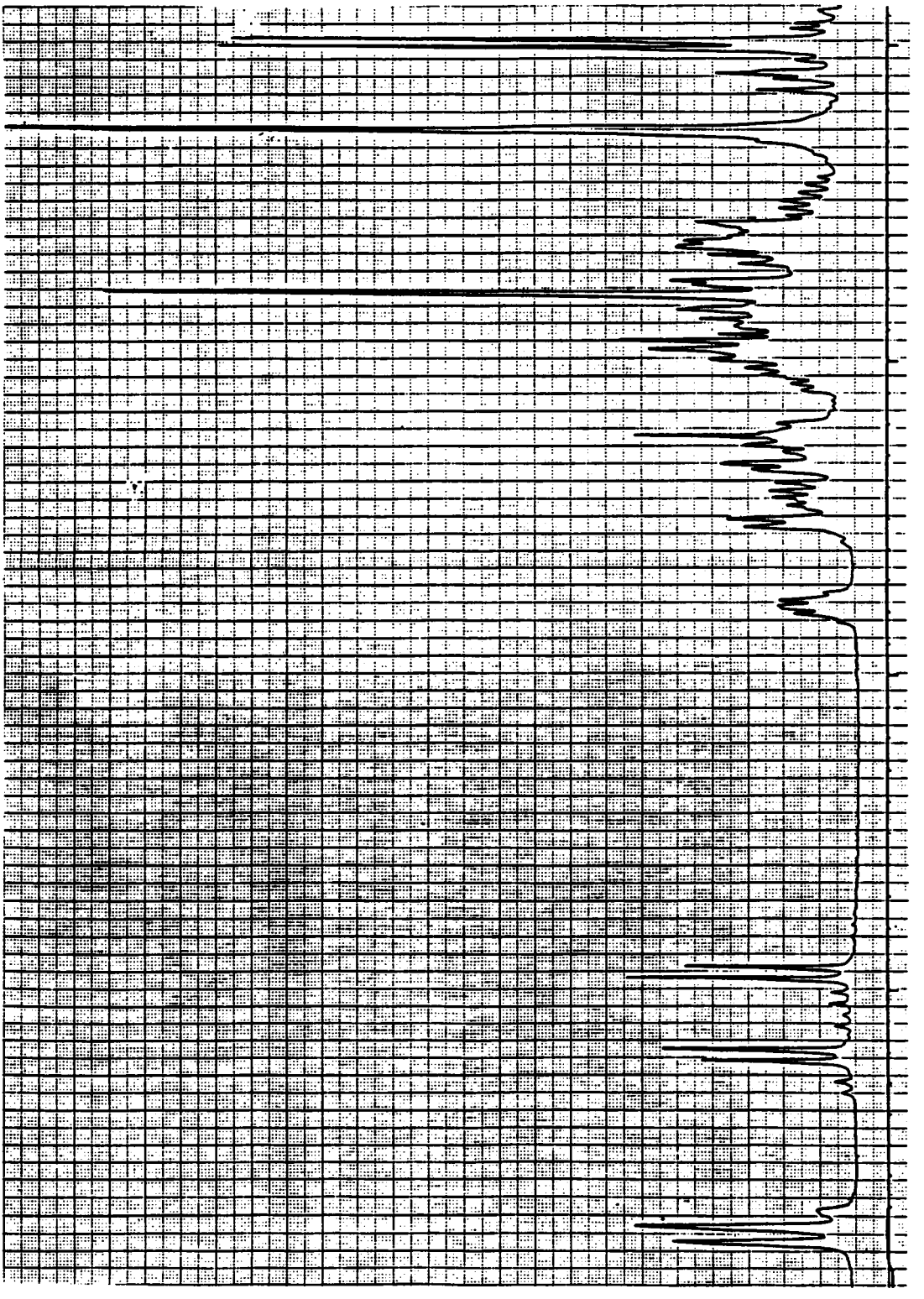
270 MHz ^{1}H NMR spectrum of authentic ketone 4



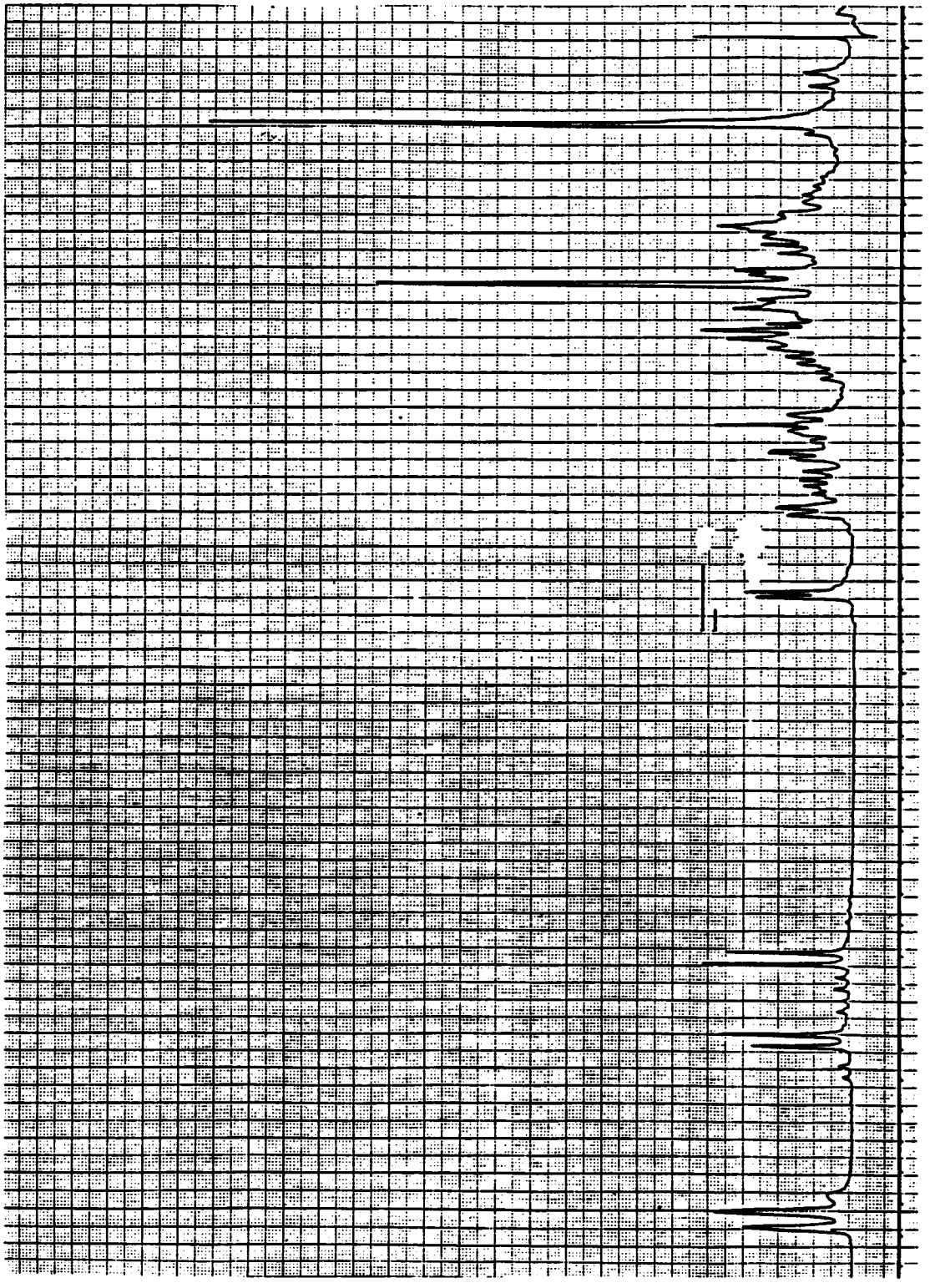
270 MHz ^{1}H NMR spectrum of lactol 132



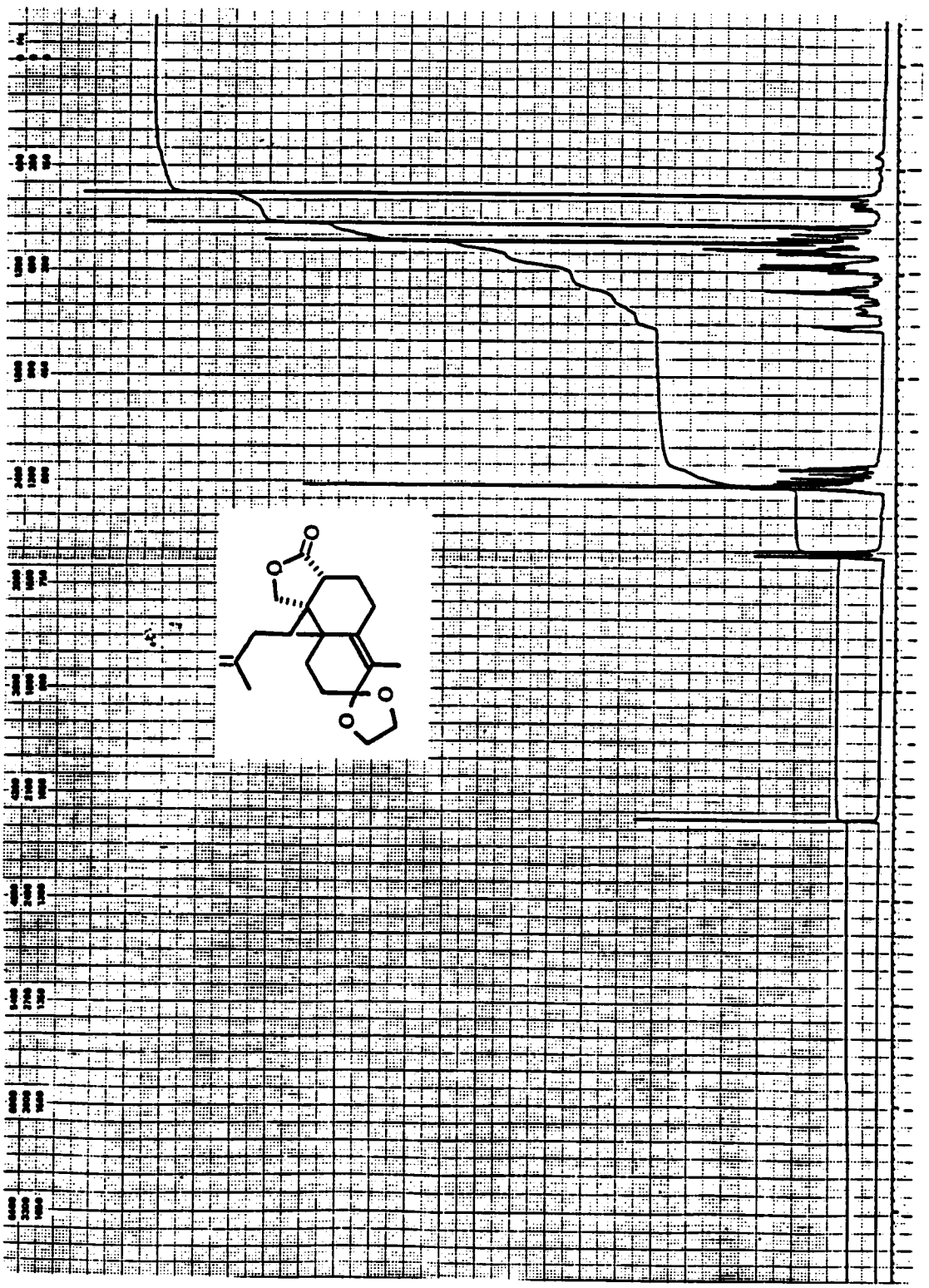
270 MHz ^{1}H NMR spectrum of ketone 133



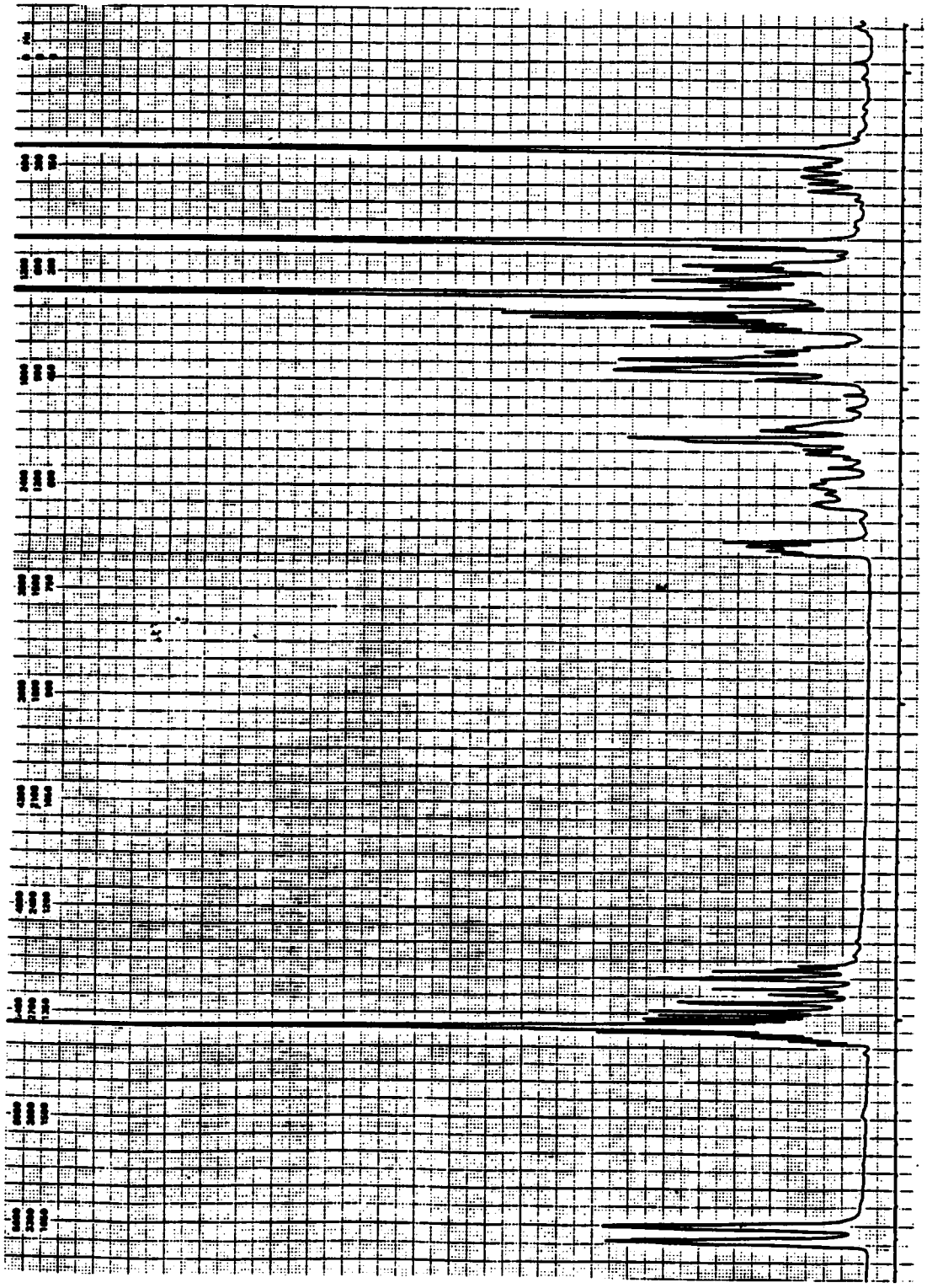
expanded 270 MHz ^{1}H NMR spectrum of ketone 133



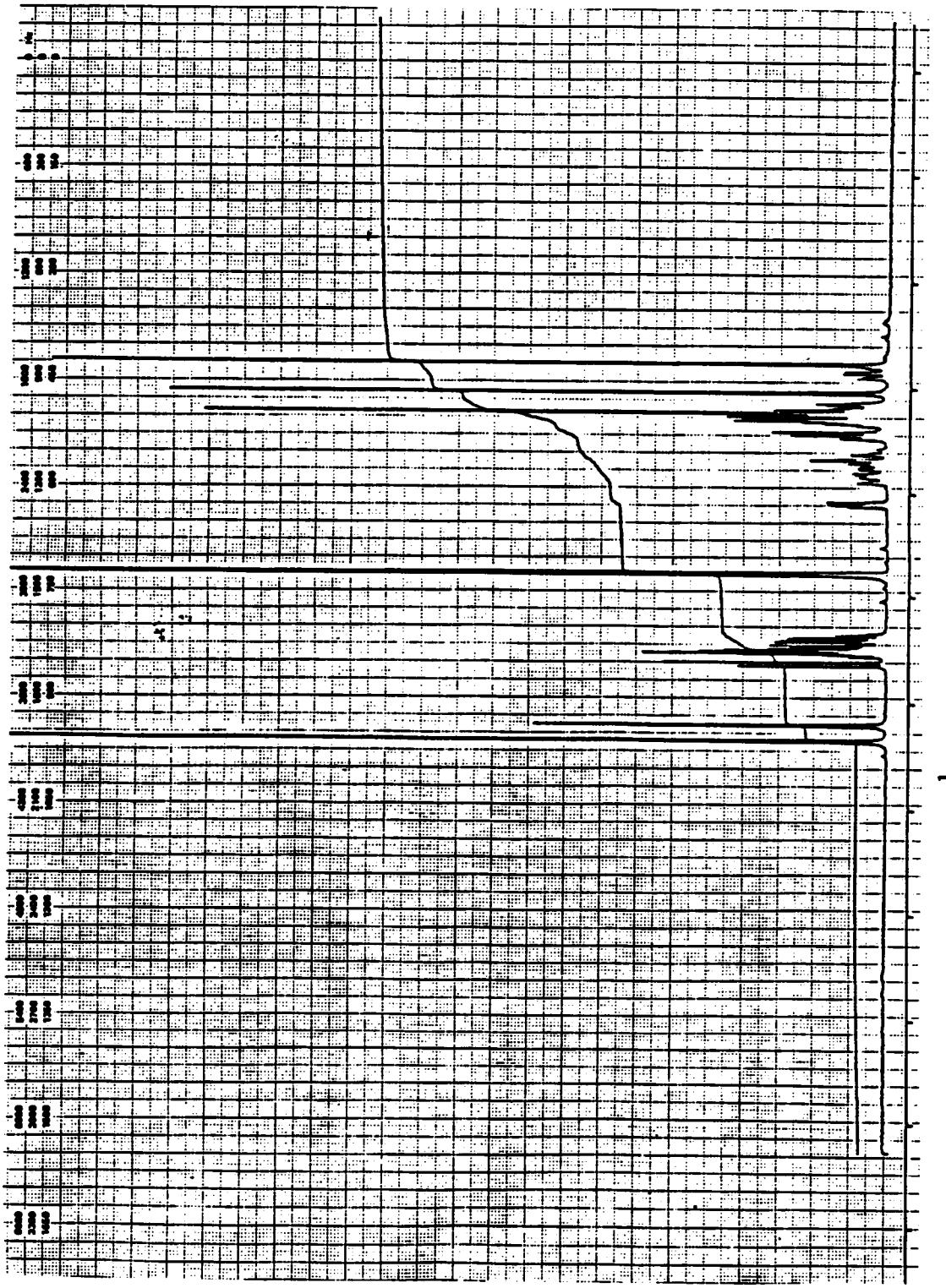
270 MHz ^{1}H NMR spectrum of ketone 133; irradiation of the C-4 methyl group



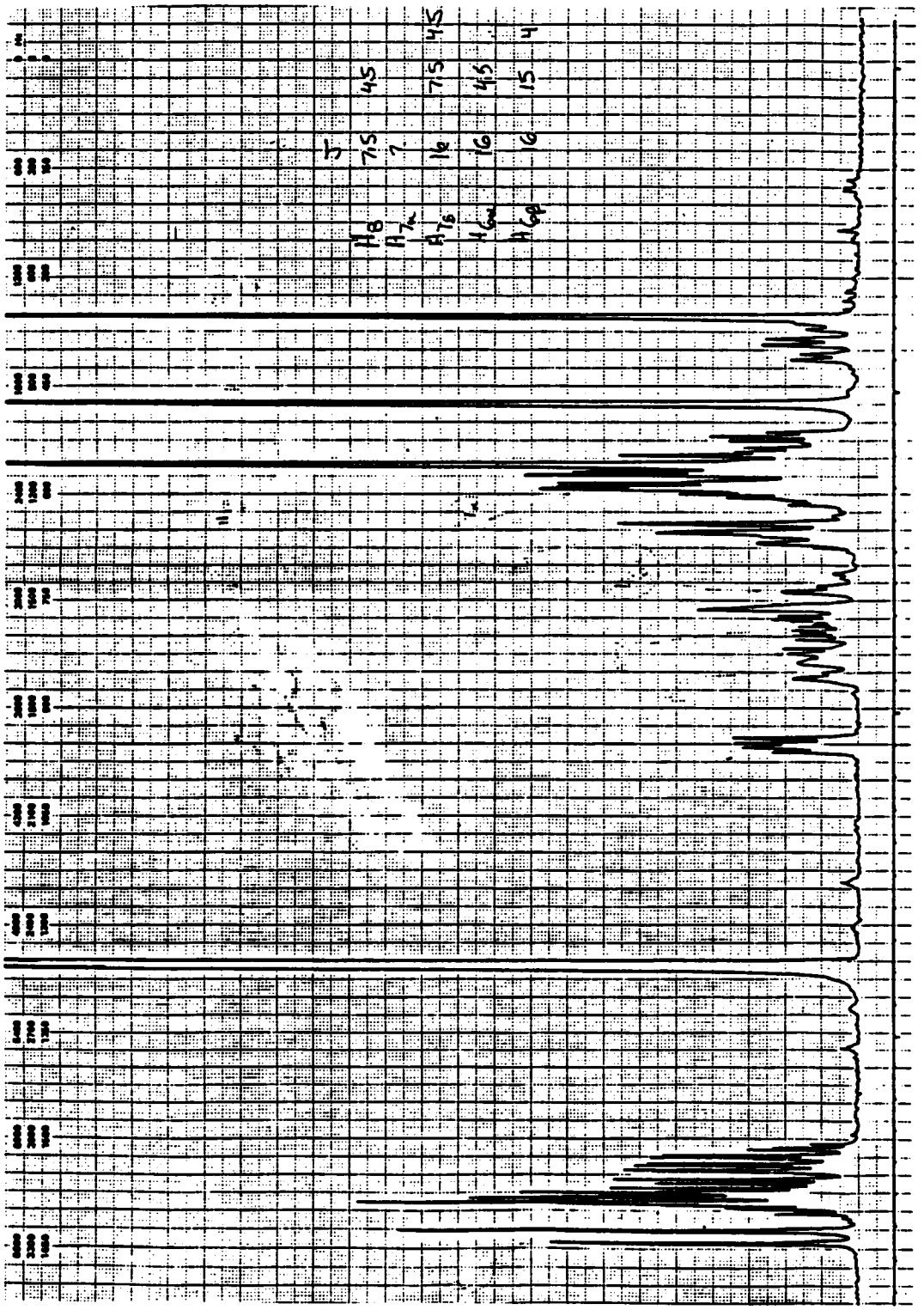
270 MHz ^{1}H NMR spectrum of ketal 134



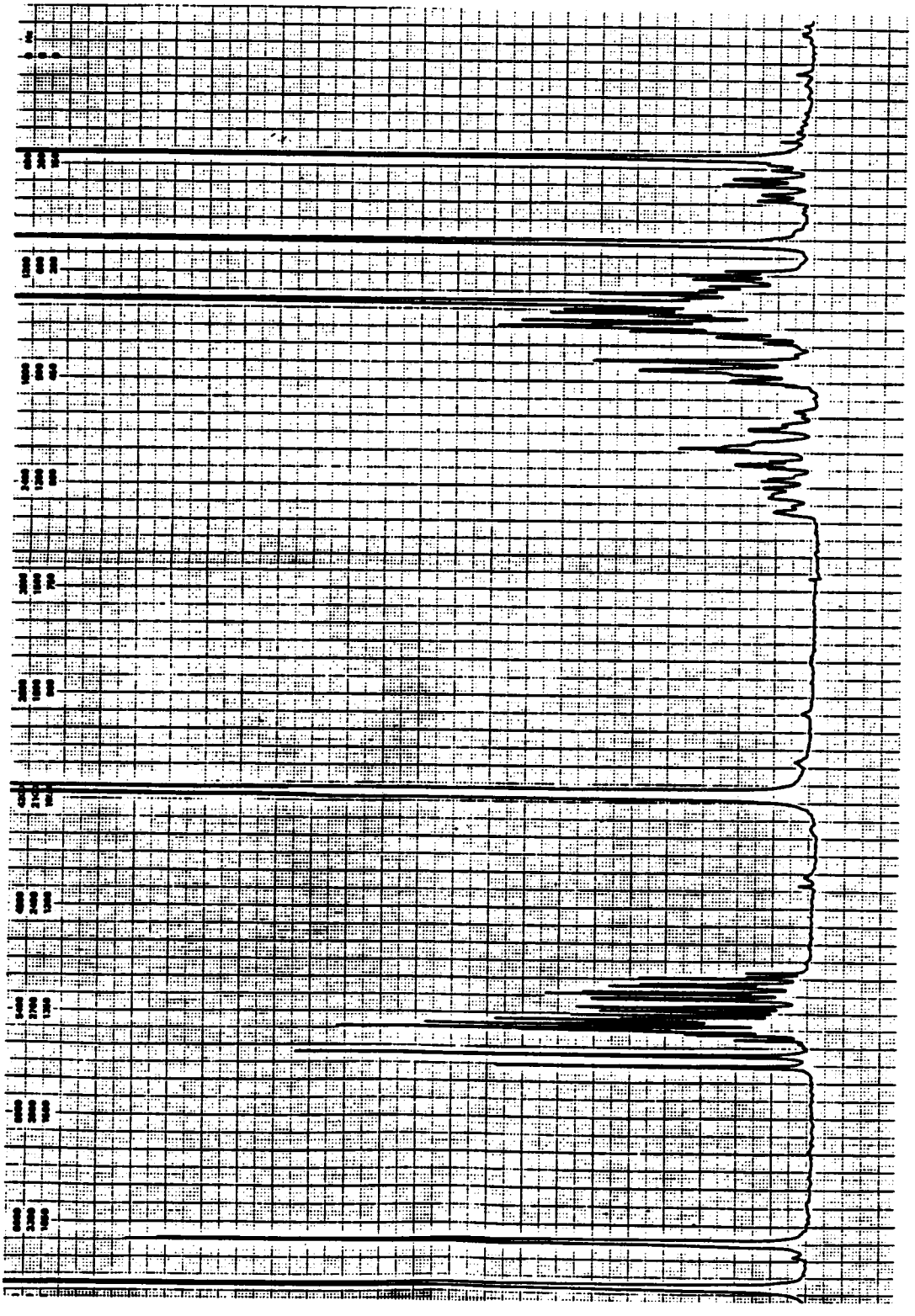
expanded 270 MHz ^{1}H NMR spectrum of ketal 134



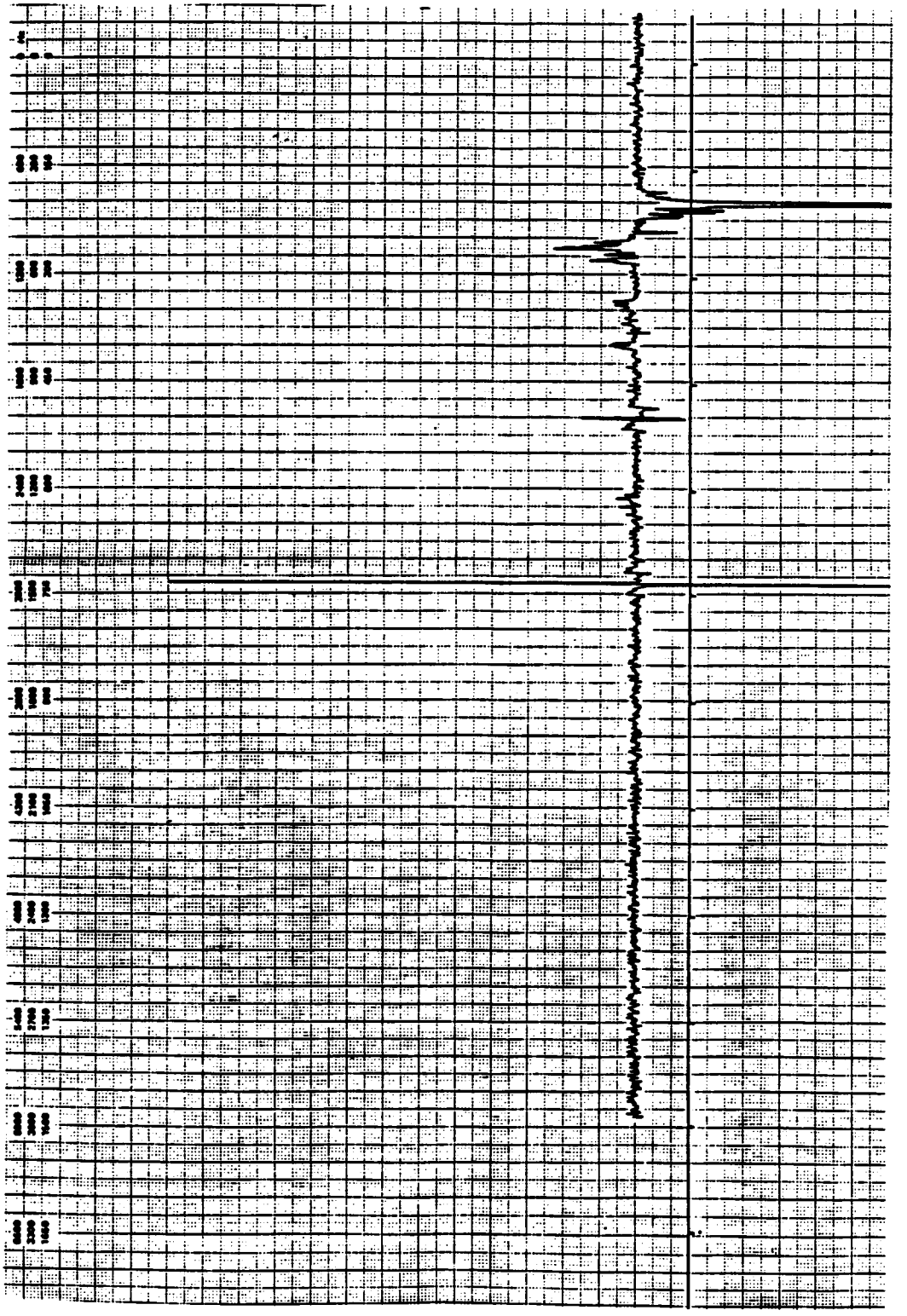
270 MHz ^1H NMR spectrum of ketal 134 in CD_3OD



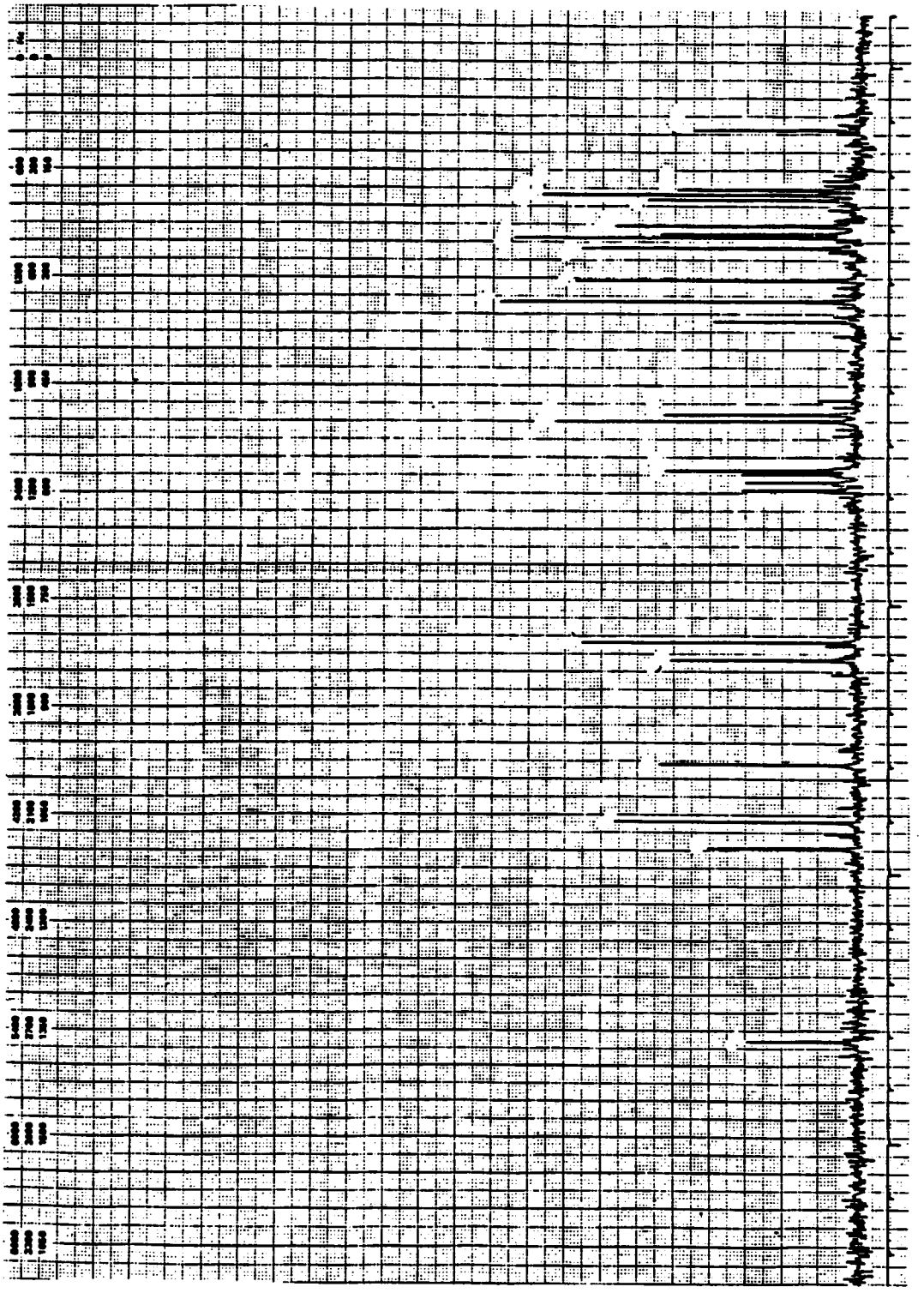
expanded 270 MHz ^{1}H NMR spectrum of ketal 134 in CD_3OD



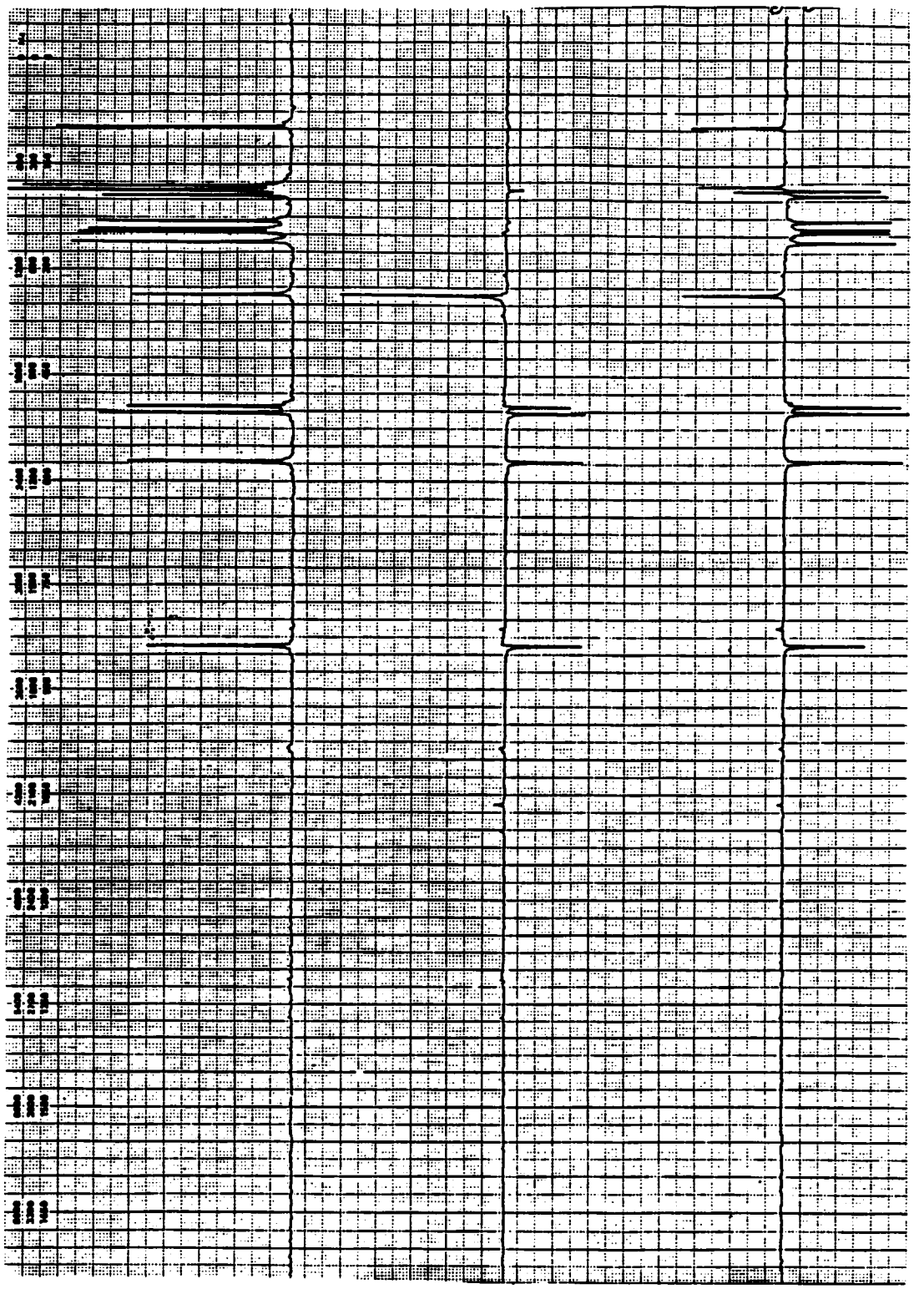
270 MHz ^{1}H NMR spectrum of ketal 134; irradiation of C-8 proton in CD_3OD



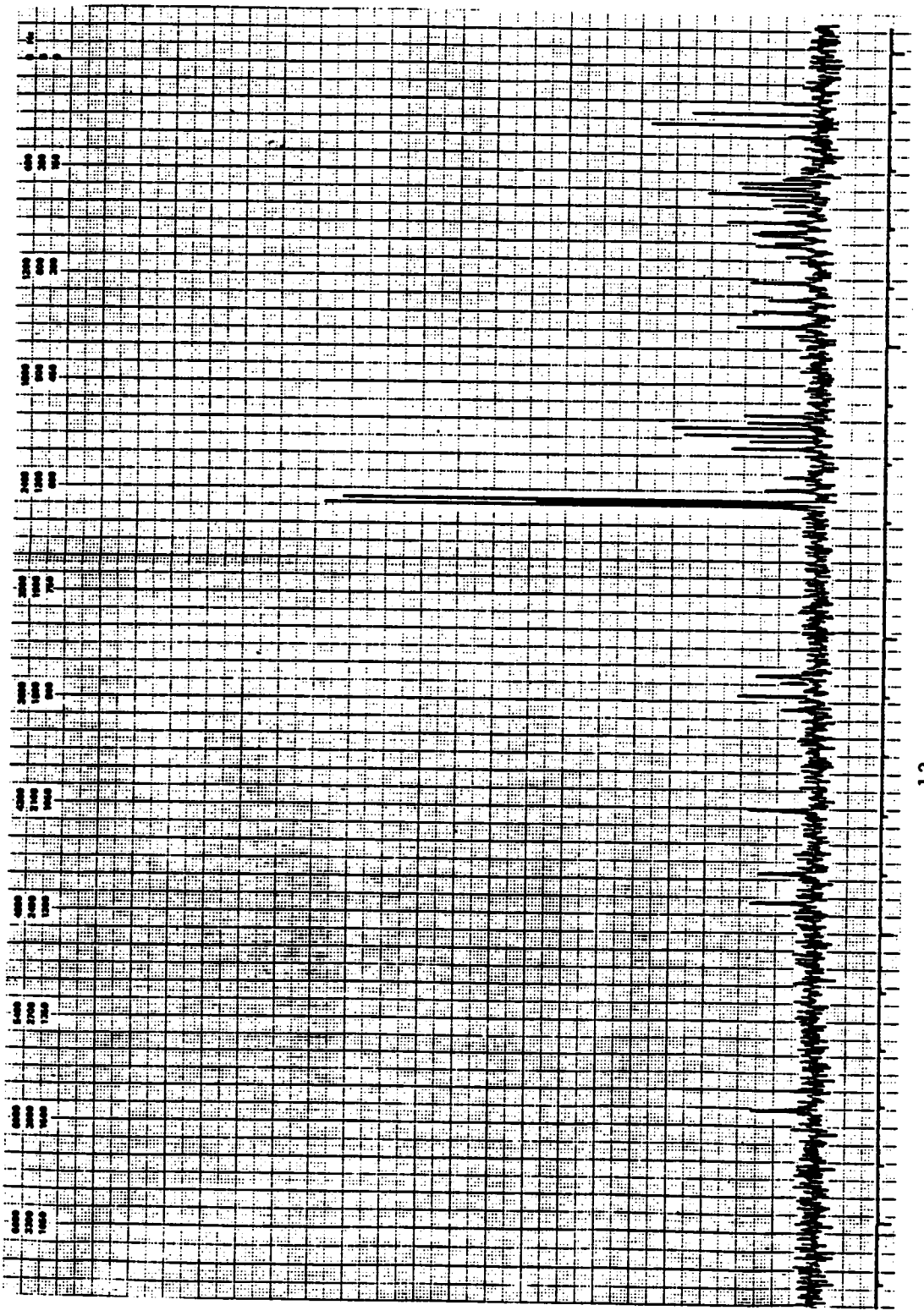
270 MHz ^{1}H NOE difference NMR spectrum of ketal 134; irradiation of C-10 methyl group in CD_3OD



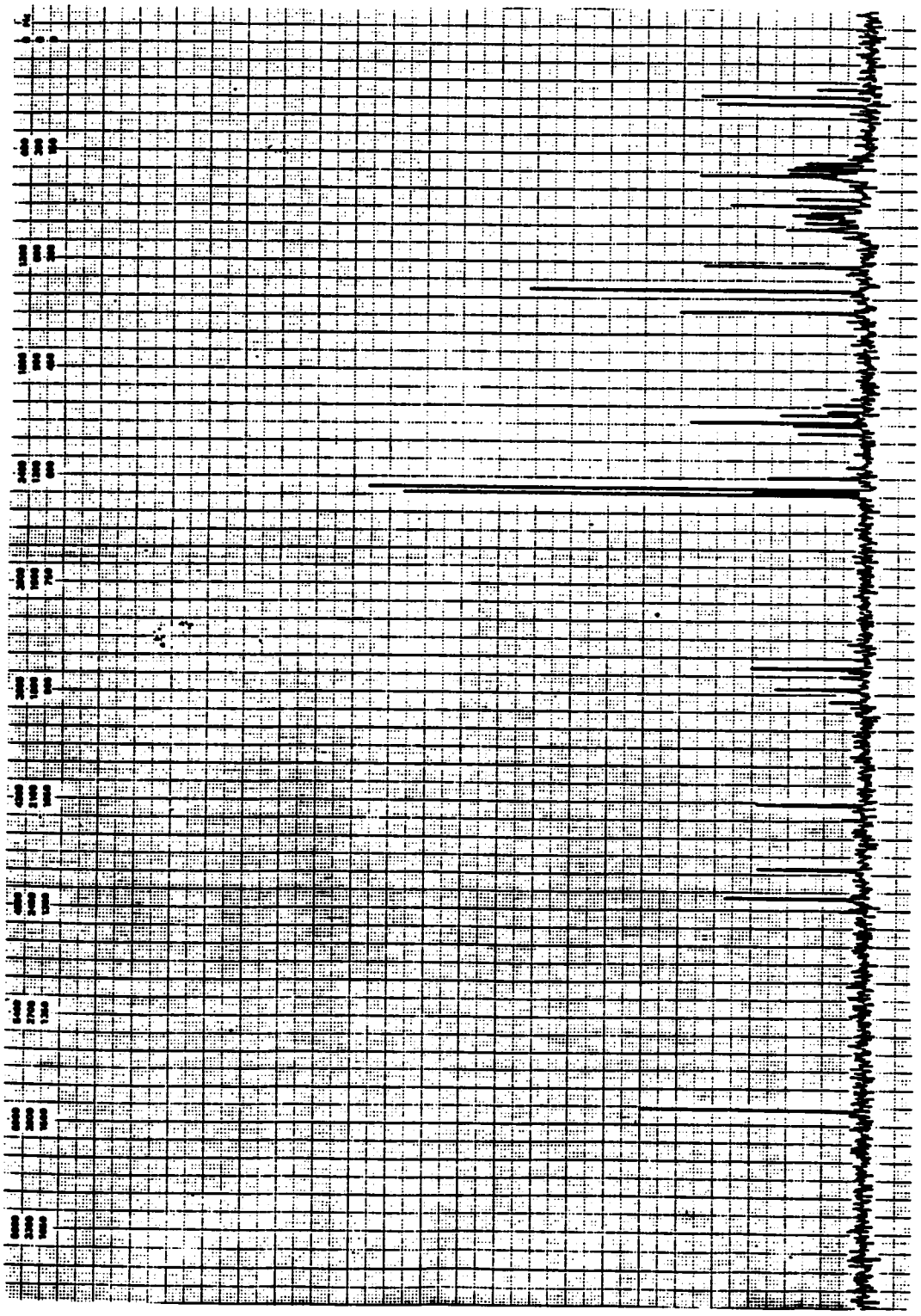
80 MHz ^{13}C decoupled NMR spectrum of ketal 134



80 MHz ^{13}C INEPT spectra of ketal 134

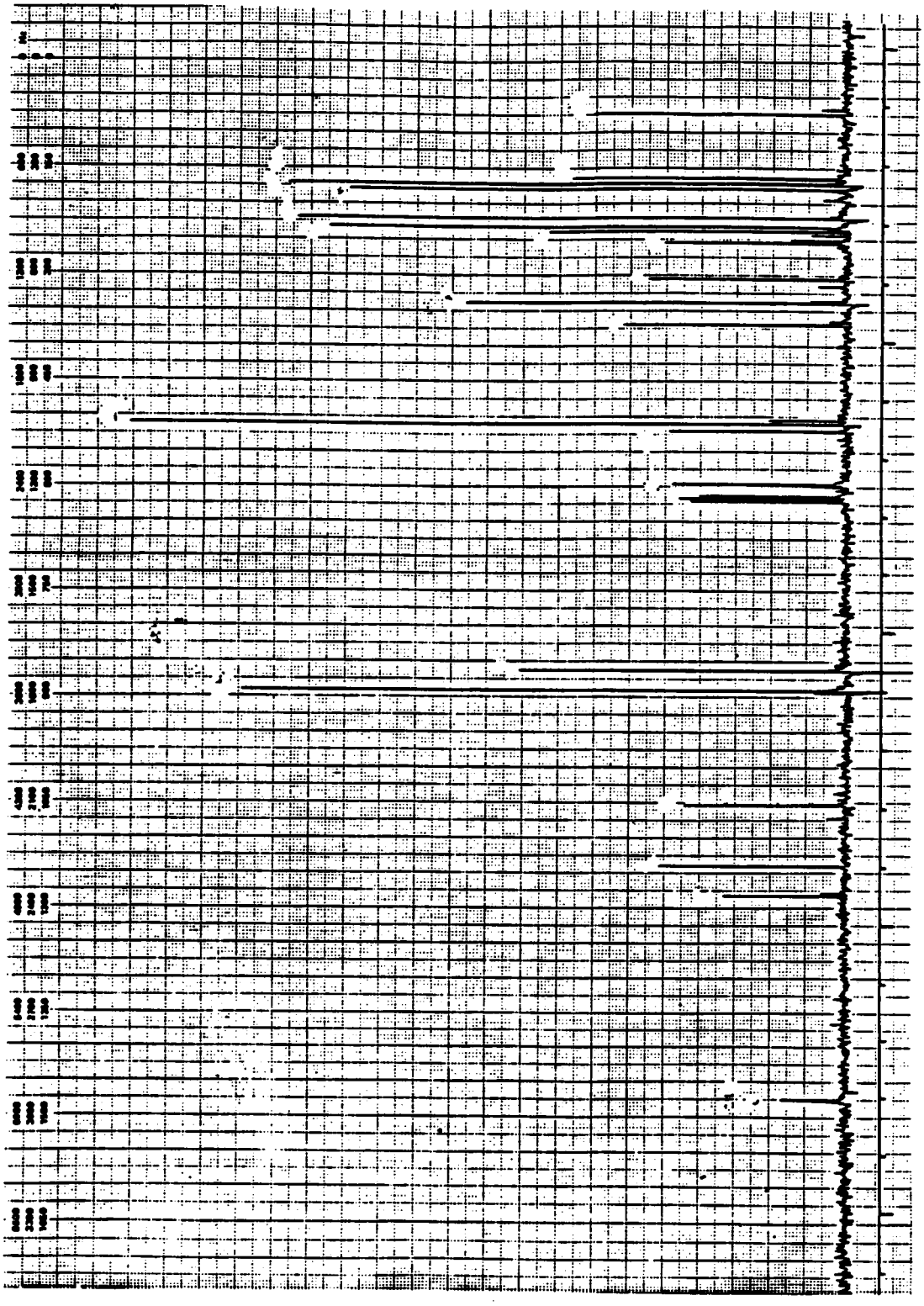


270 MHz ^{13}C coupled NMR spectrum of ketal 134

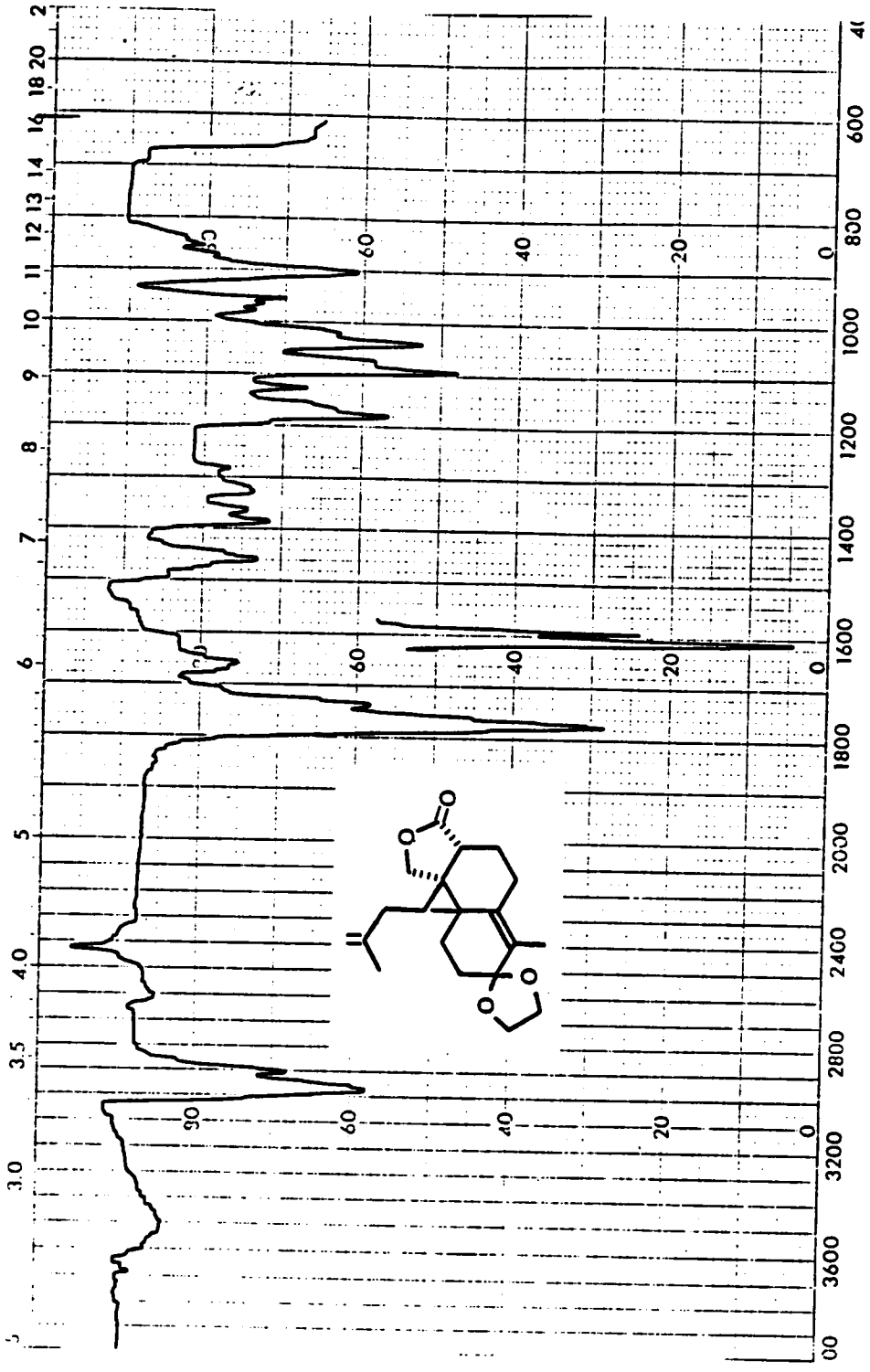


270 MHz ^{13}C NMR coupled spectrum of ketal 134;

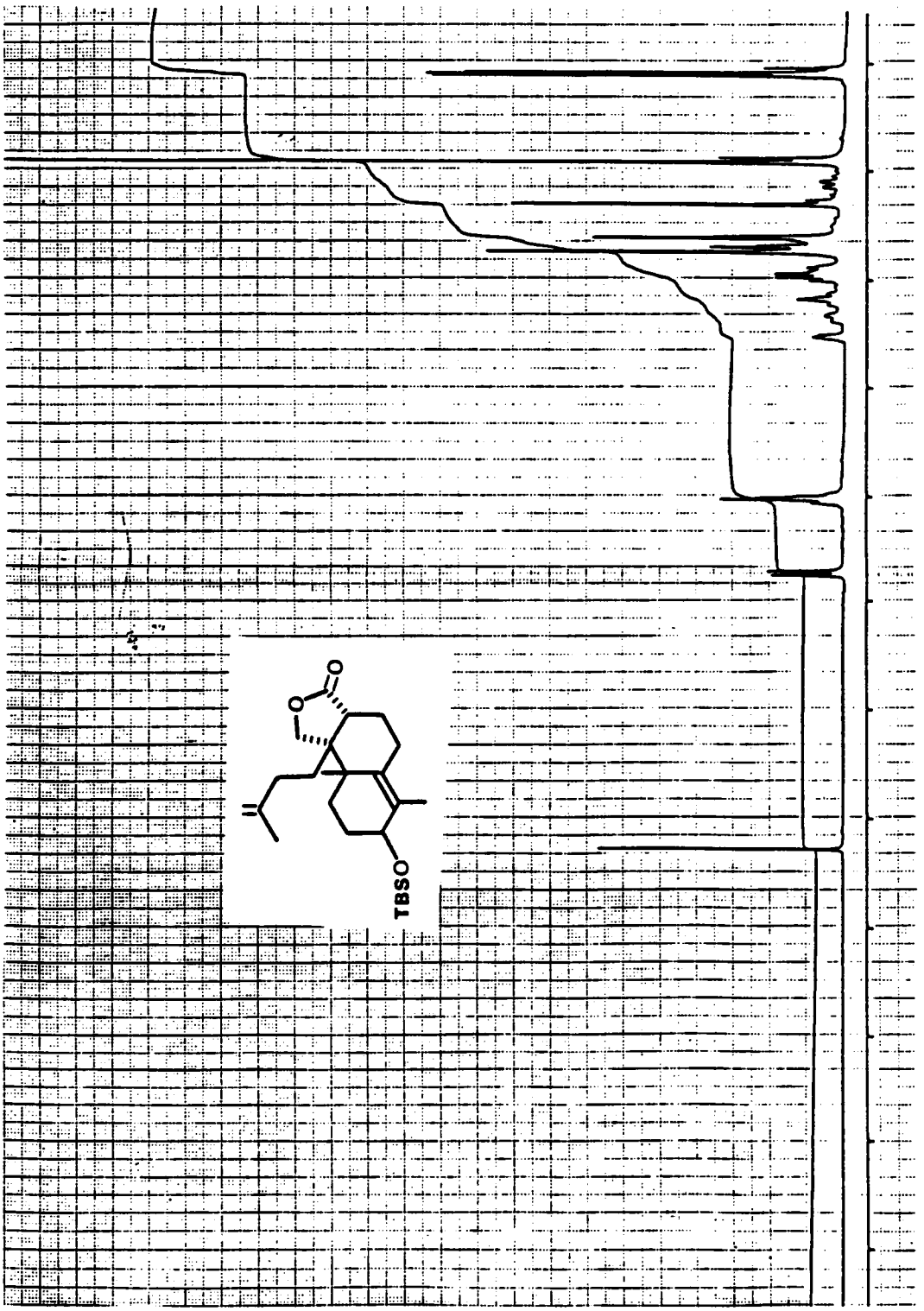
irradiation of the C-8 proton



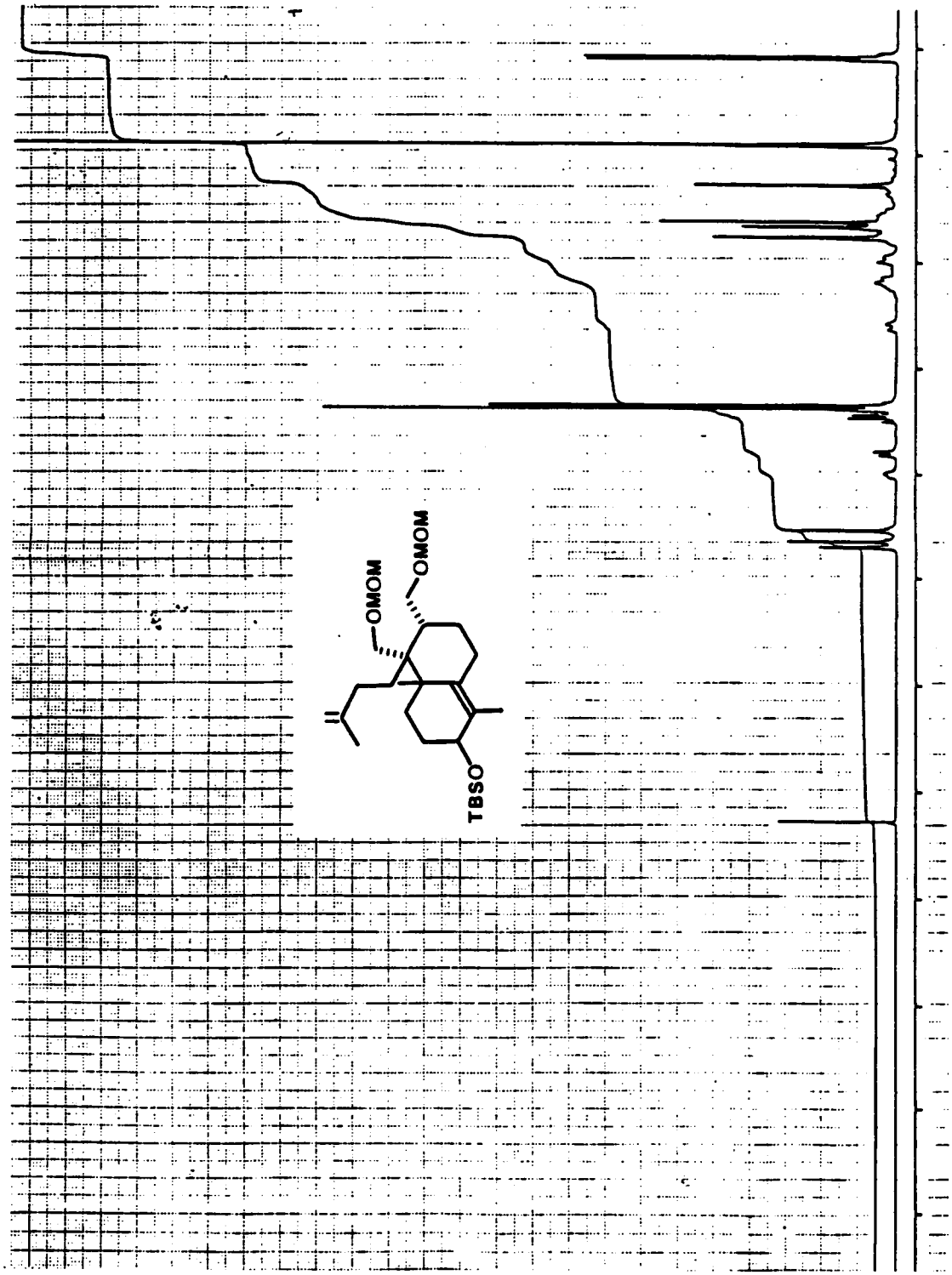
270 MHz ^{13}C decoupled NMR spectrum of ketal 134



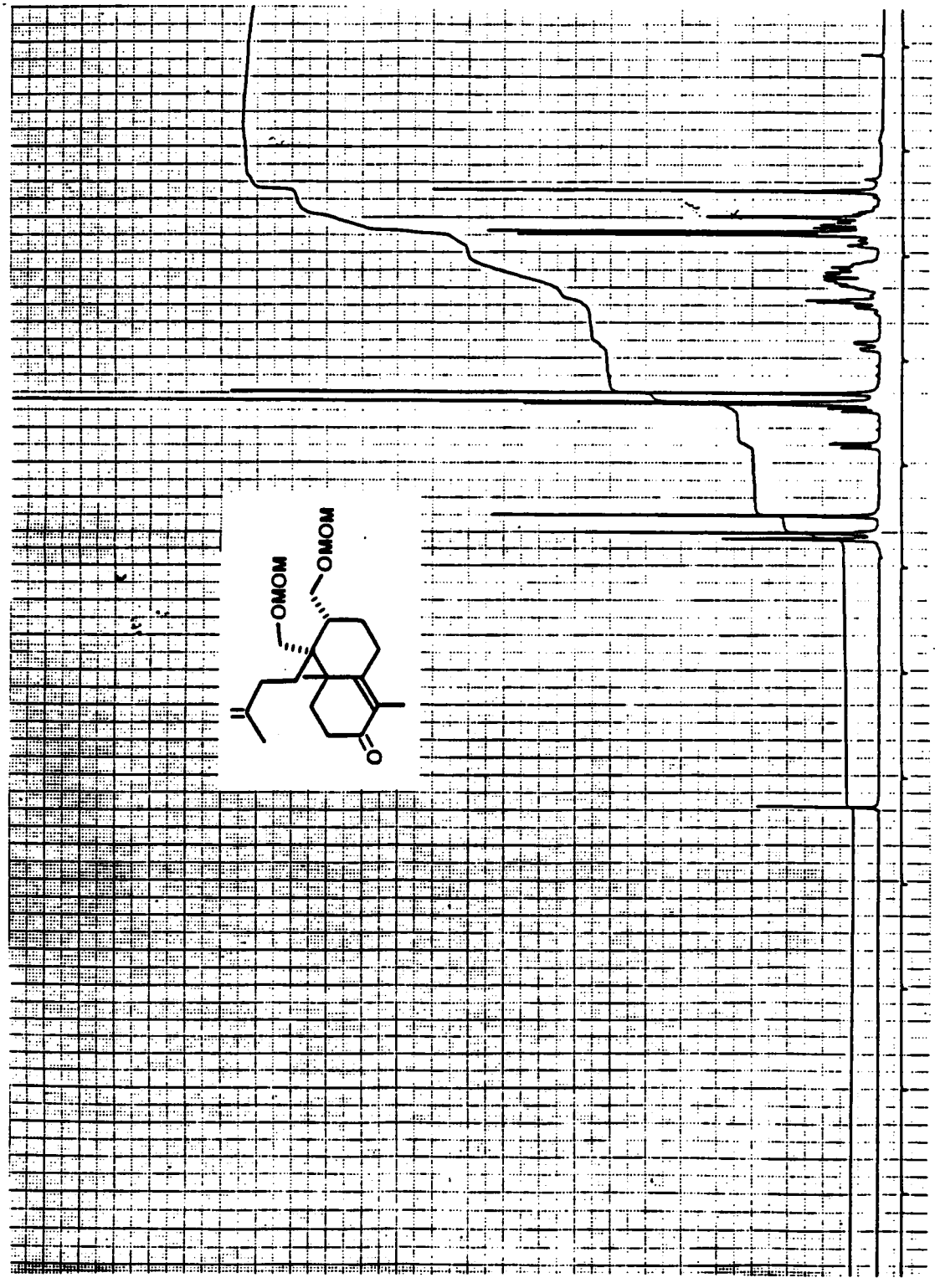
IR spectrum of ketal 134



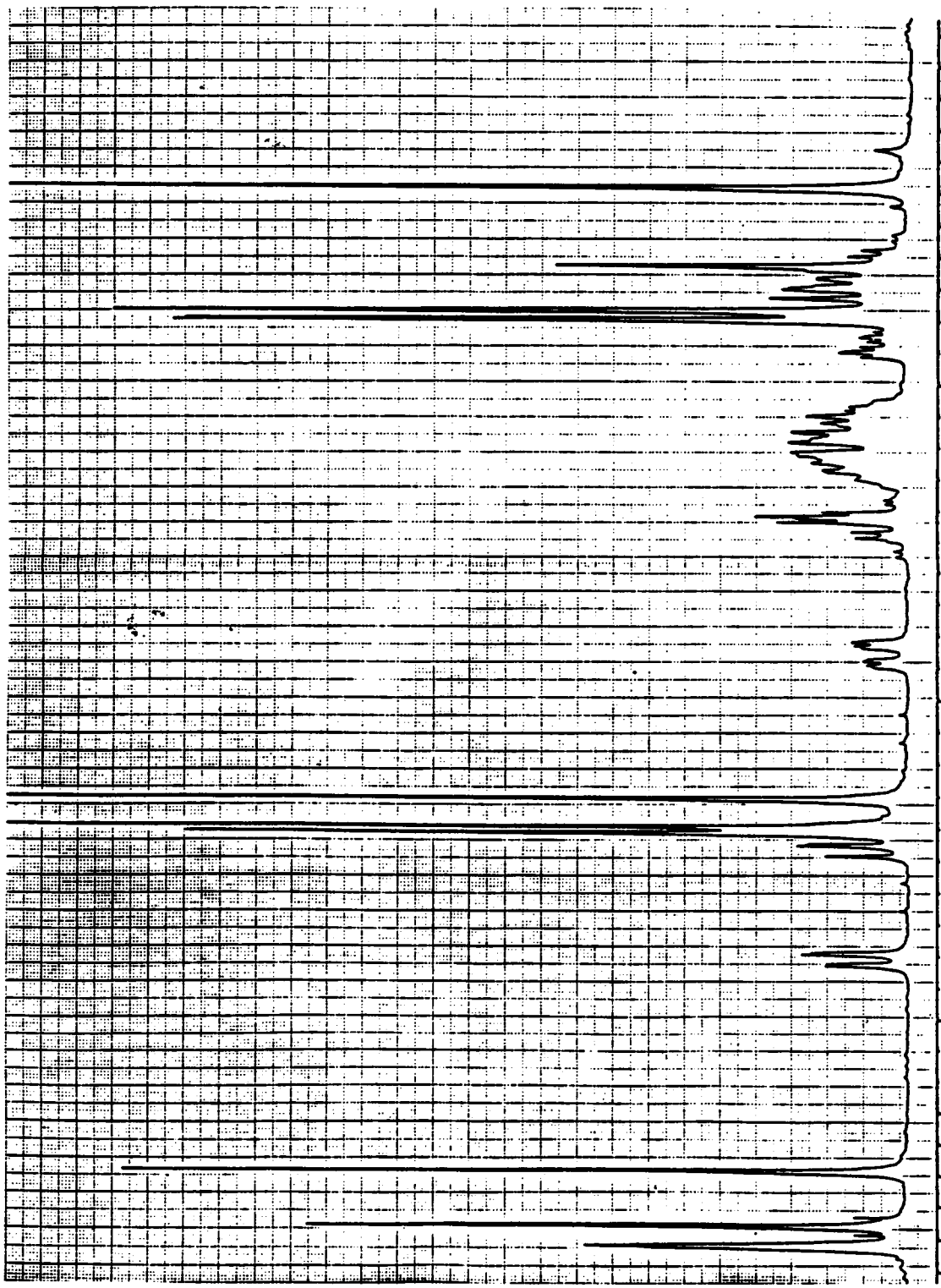
270 MHz ^{1}H NMR spectrum of t-butyldimethylsilyl ether 136



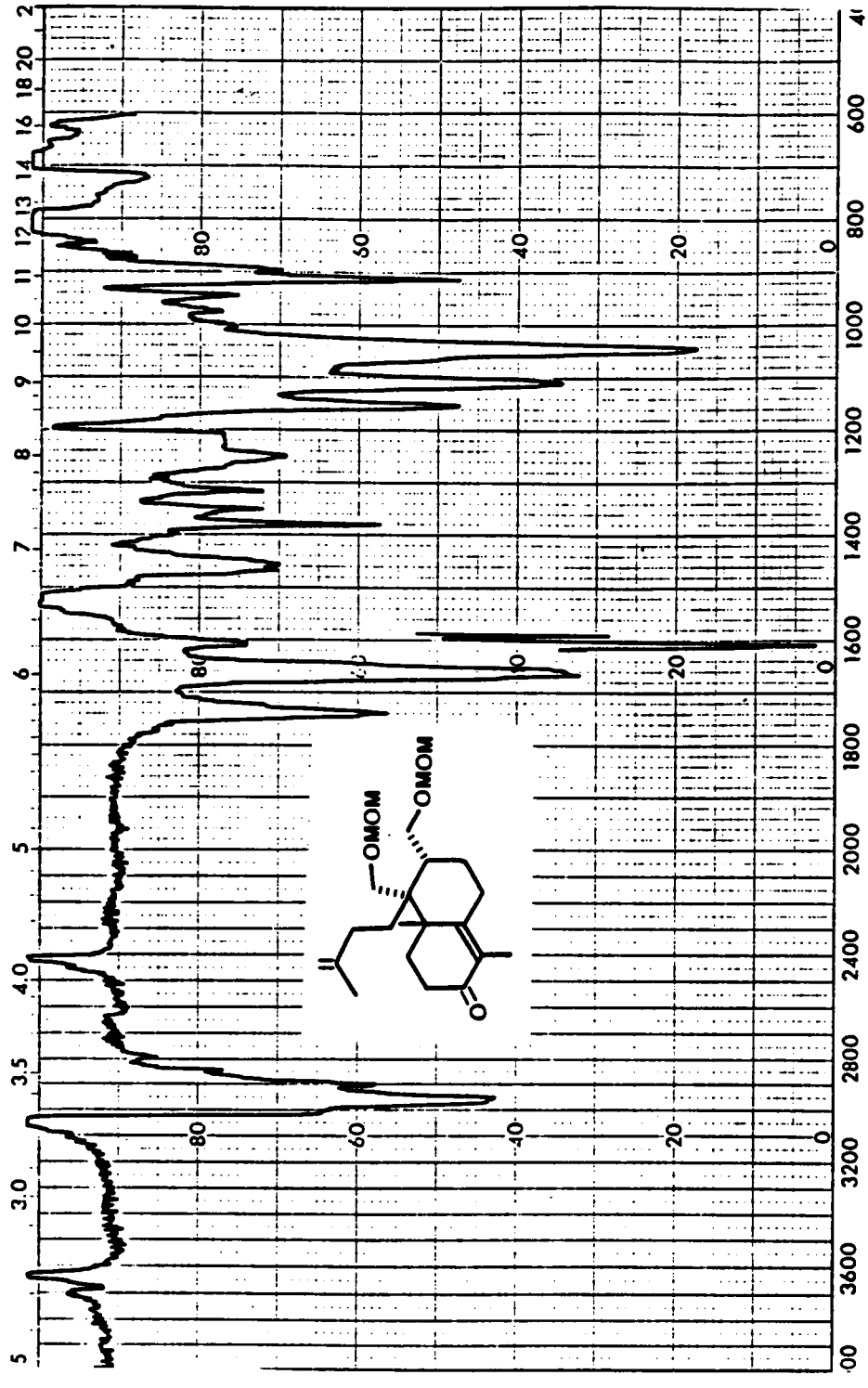
270 MHz ^{1}H NMR spectrum of bis-methoxymethyl ether 137



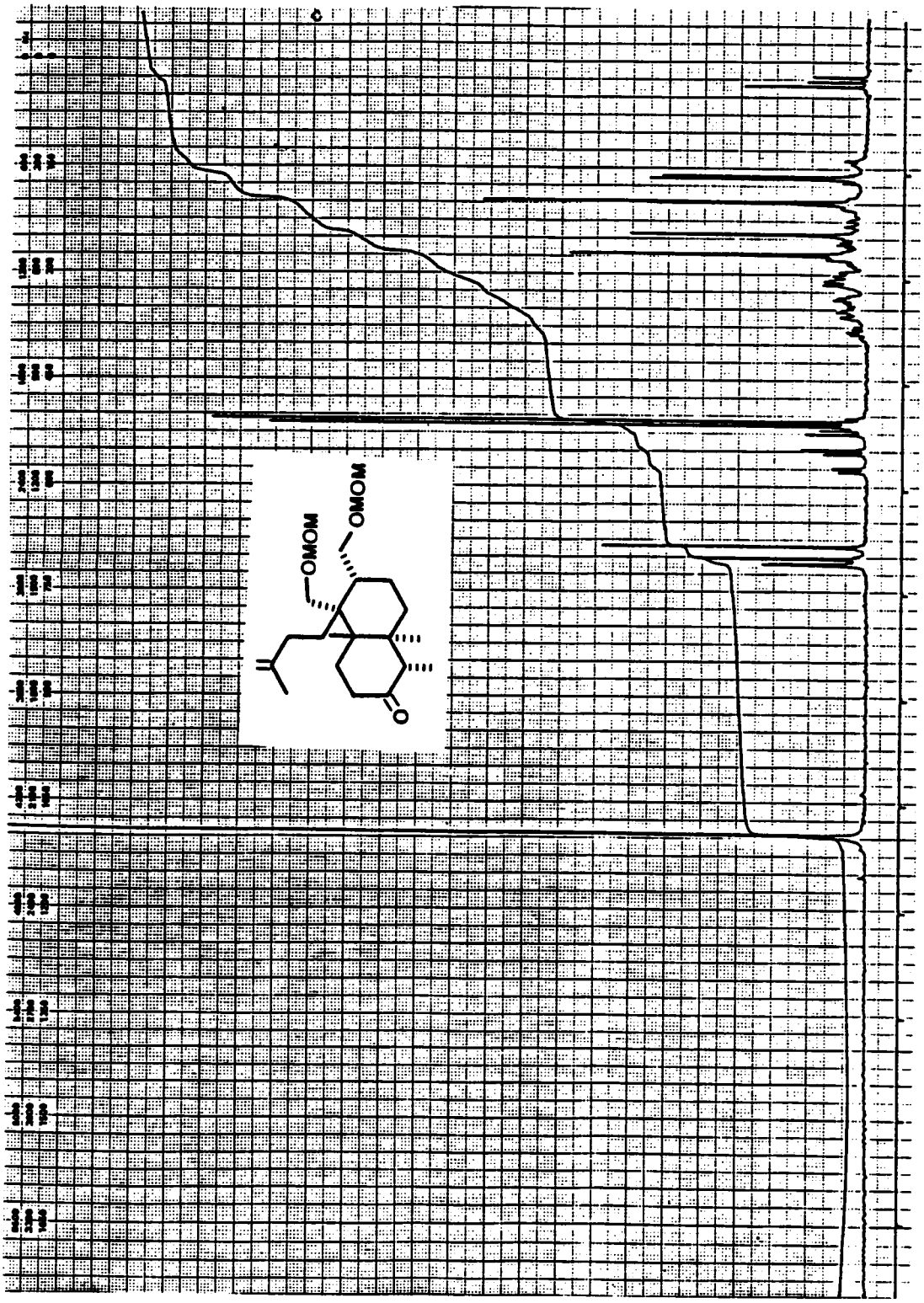
270 MHz ^{1}H NMR spectrum of enone 135



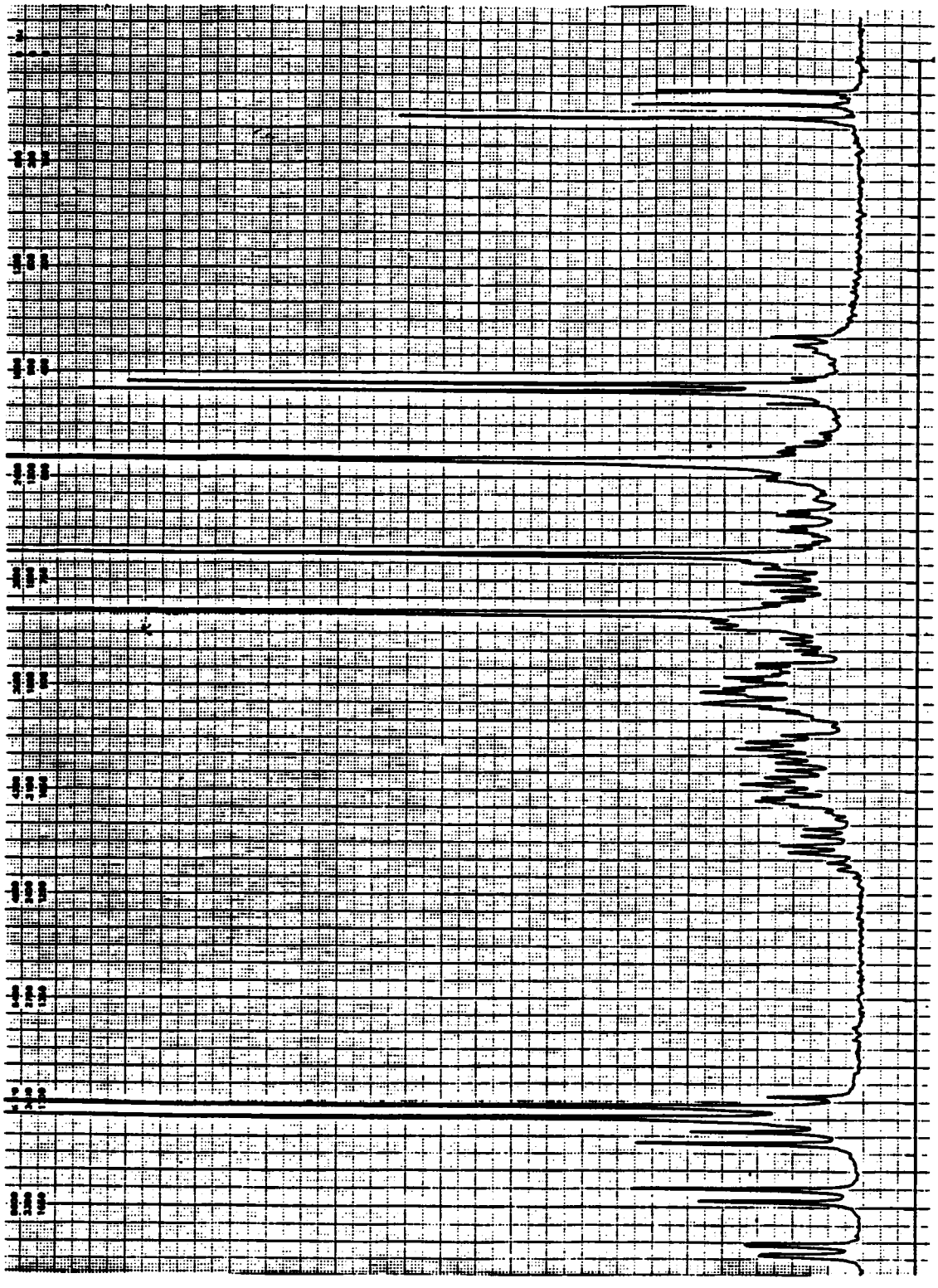
expanded 270 MHz ^{1}H NMR spectrum of enone 135



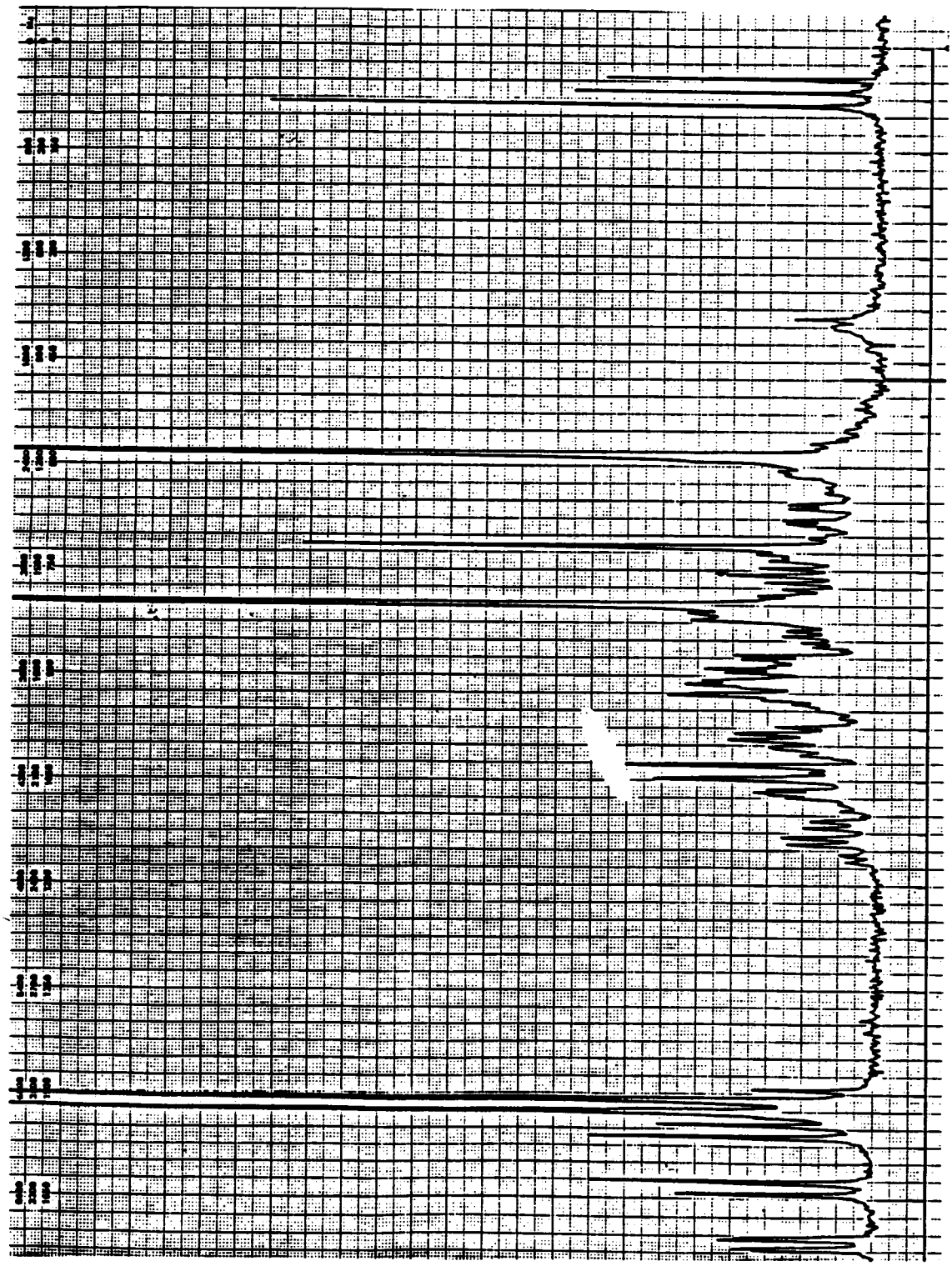
IR spectrum of enone 135



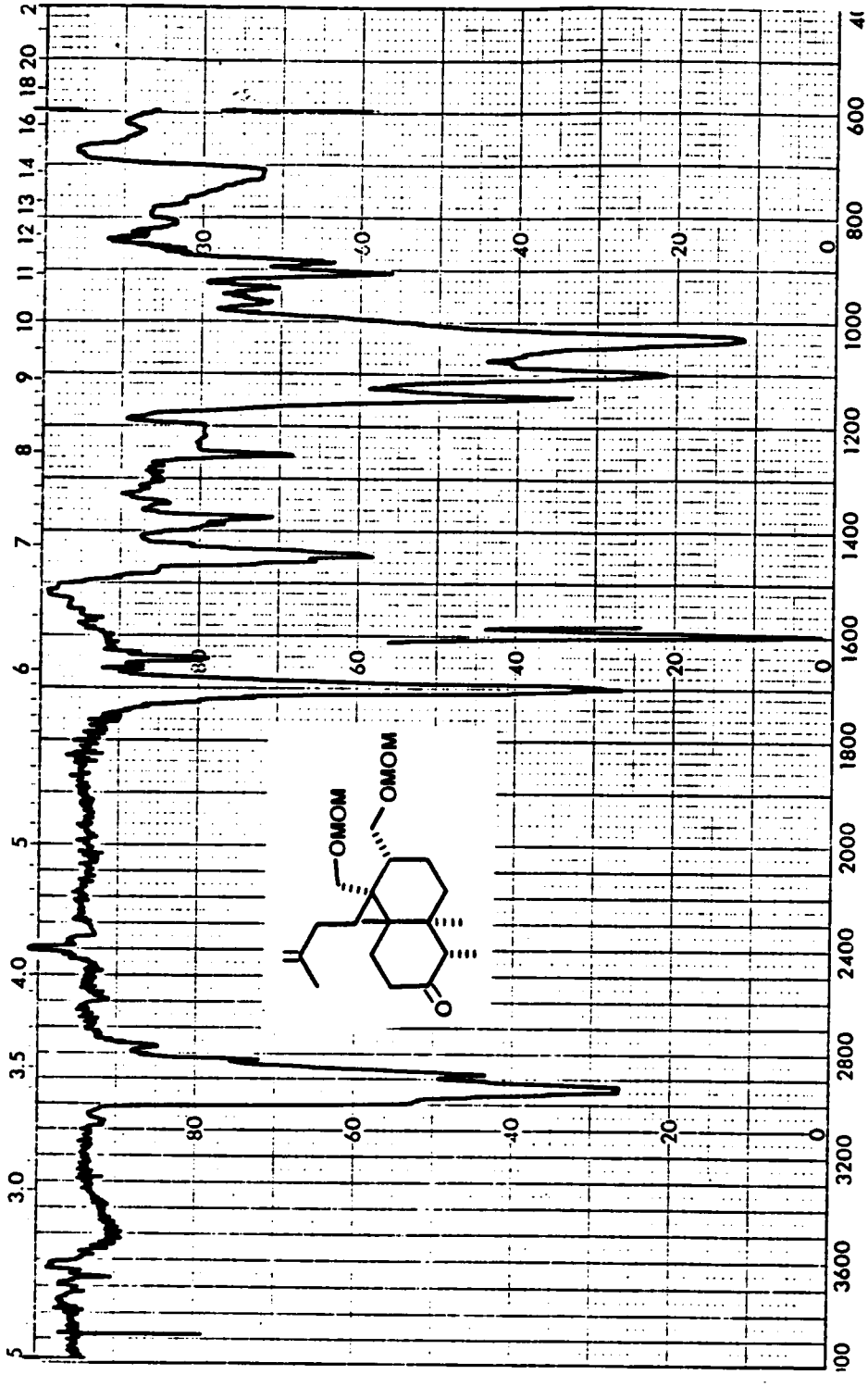
270 MHz ^{1}H NMR spectrum of ketone 138



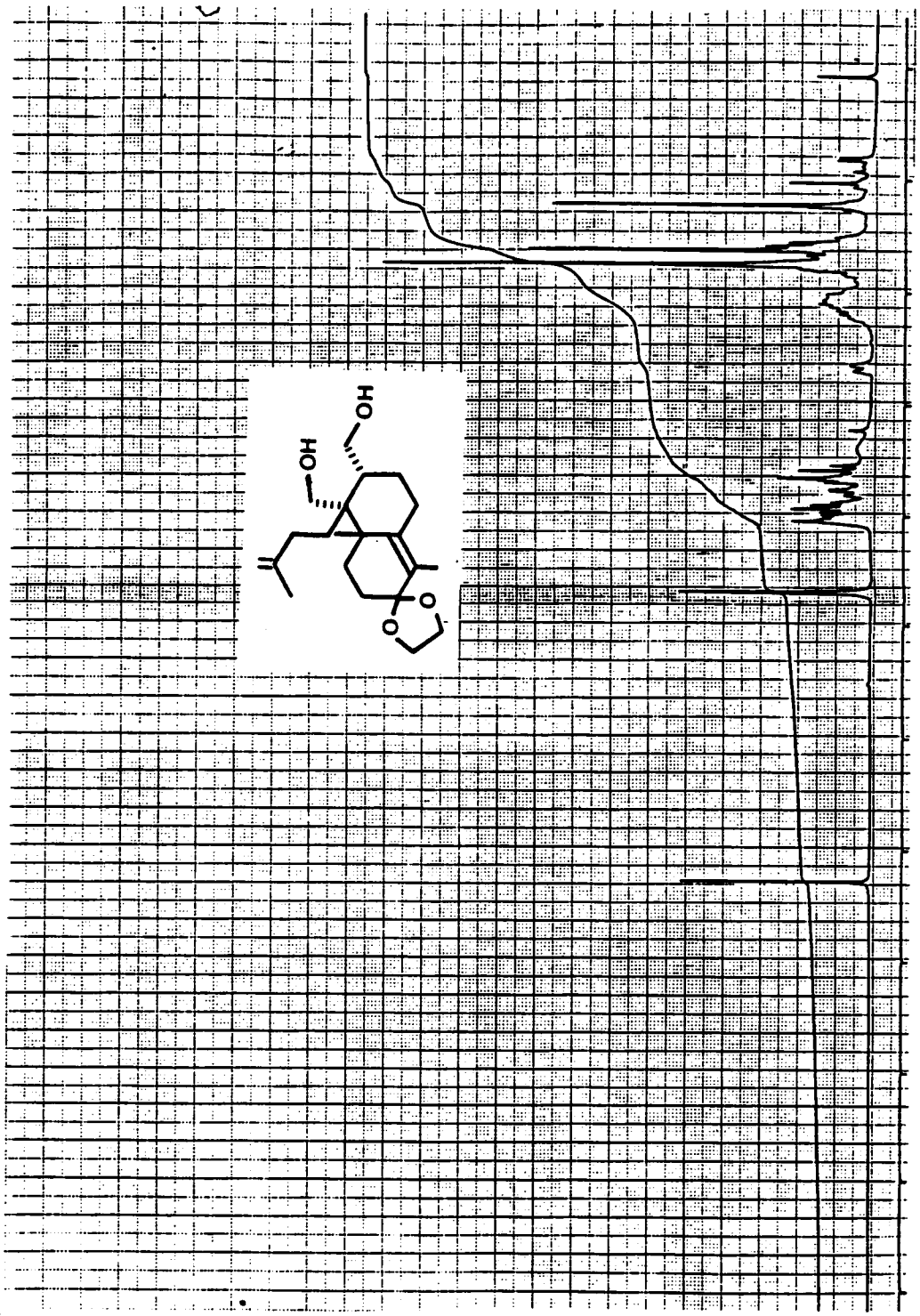
expanded 270 MHz ^{1}H NMR spectrum of ketone 138



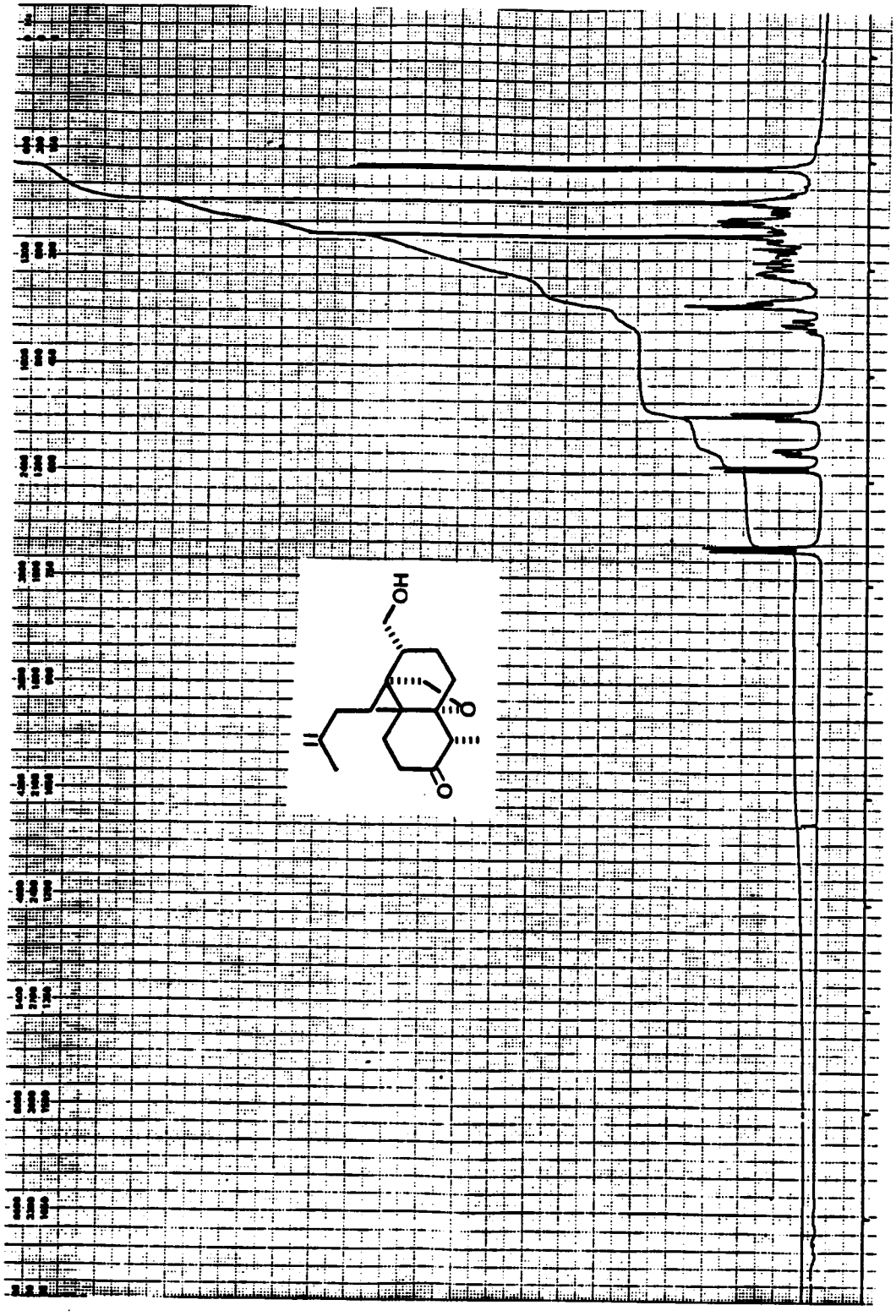
270 MHz ^{1}H NMR spectrum of ketone 138; irradiation of C-4 Methyl group



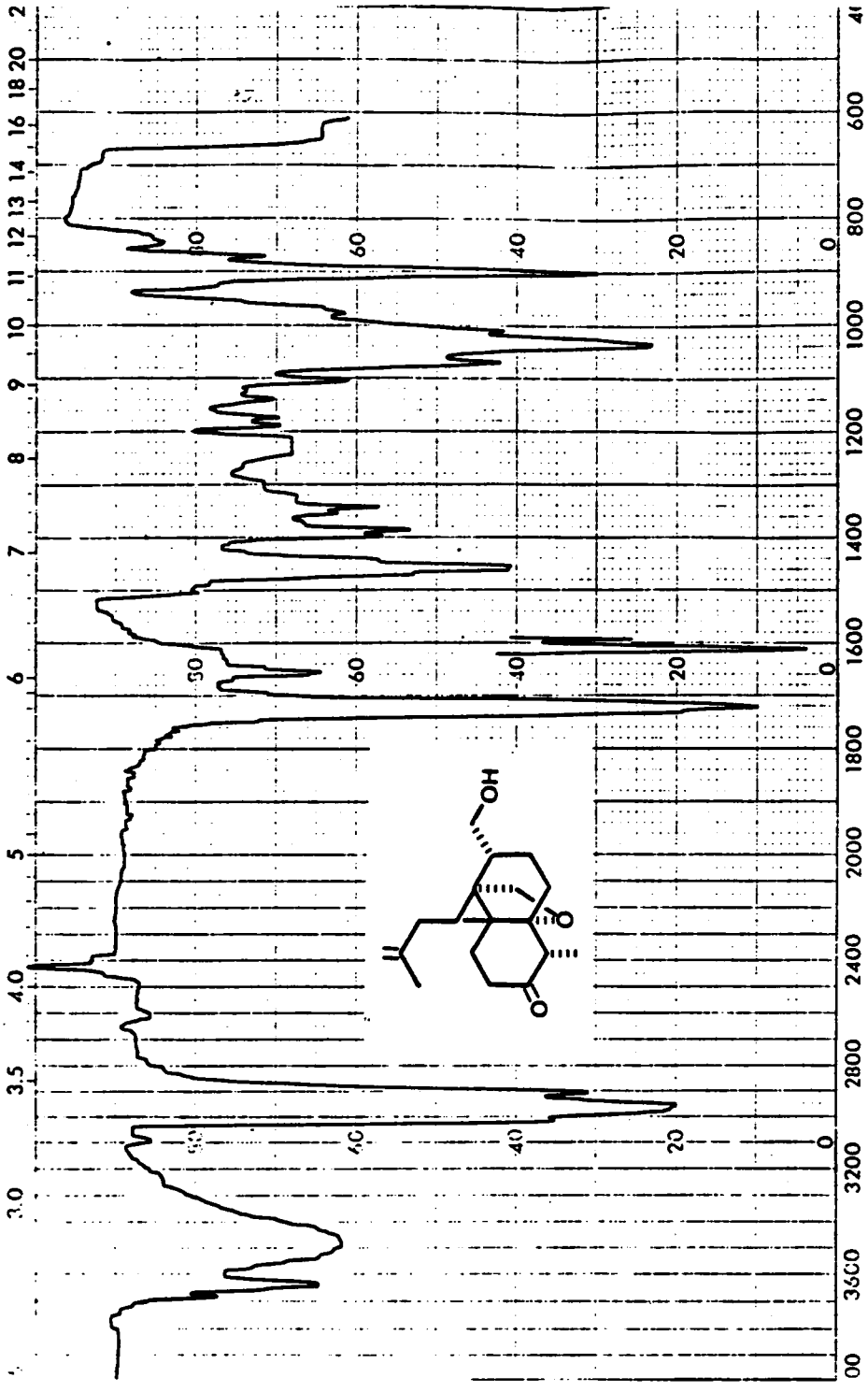
IR spectrum of ketone 138



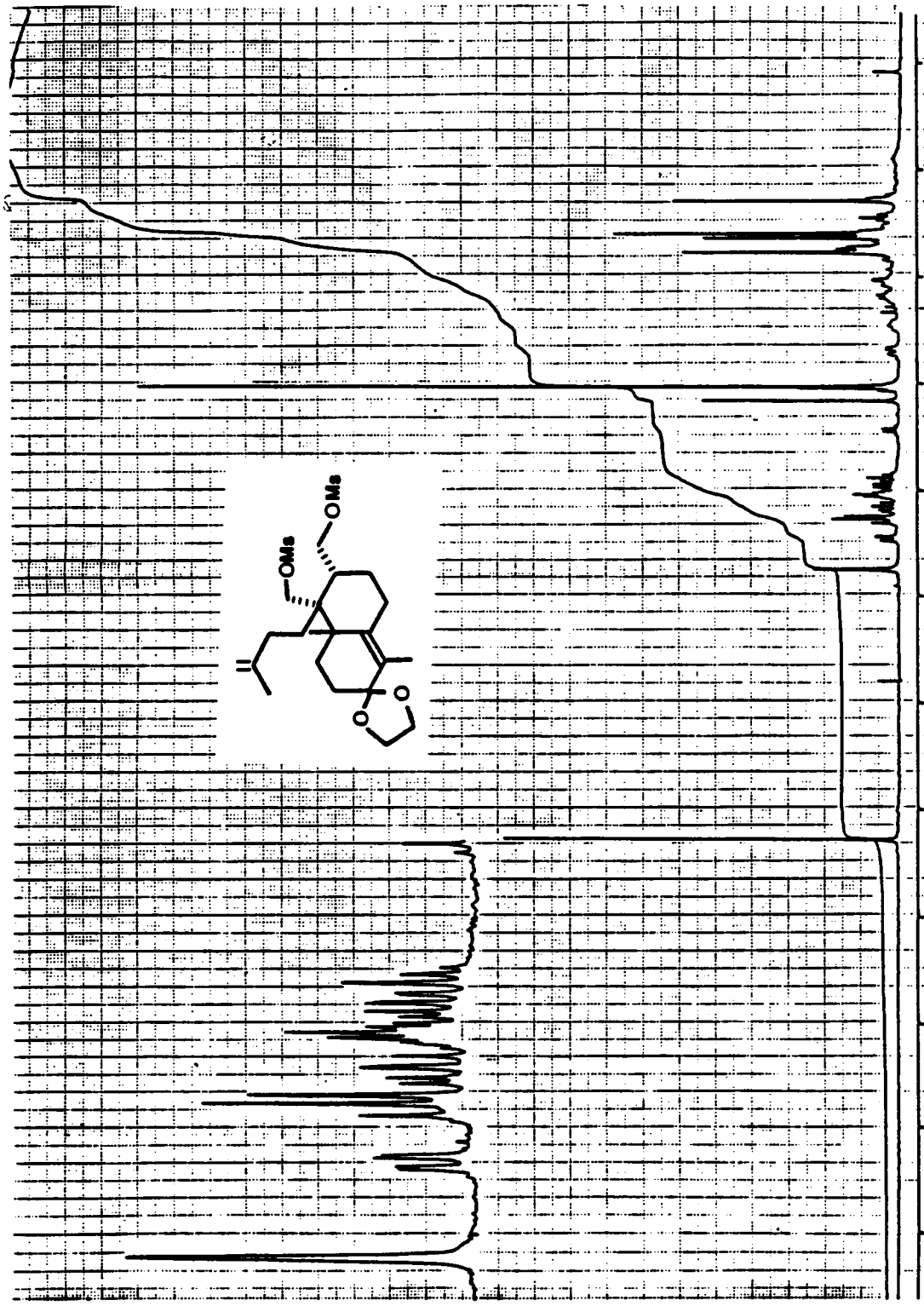
270 MHz ^1H NMR spectrum of diol 145



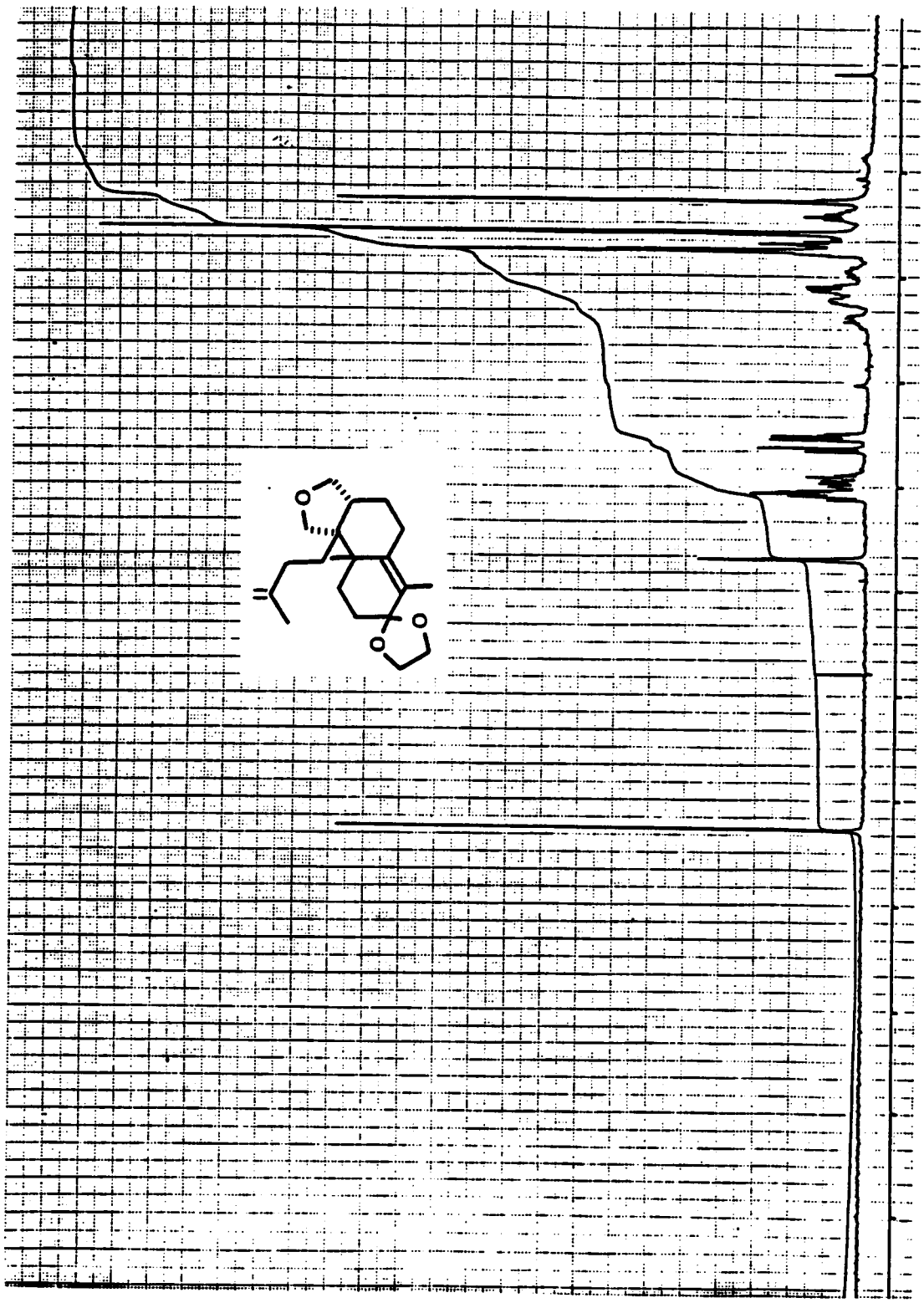
270 MHz ^{1}H NMR spectrum of ketone 146



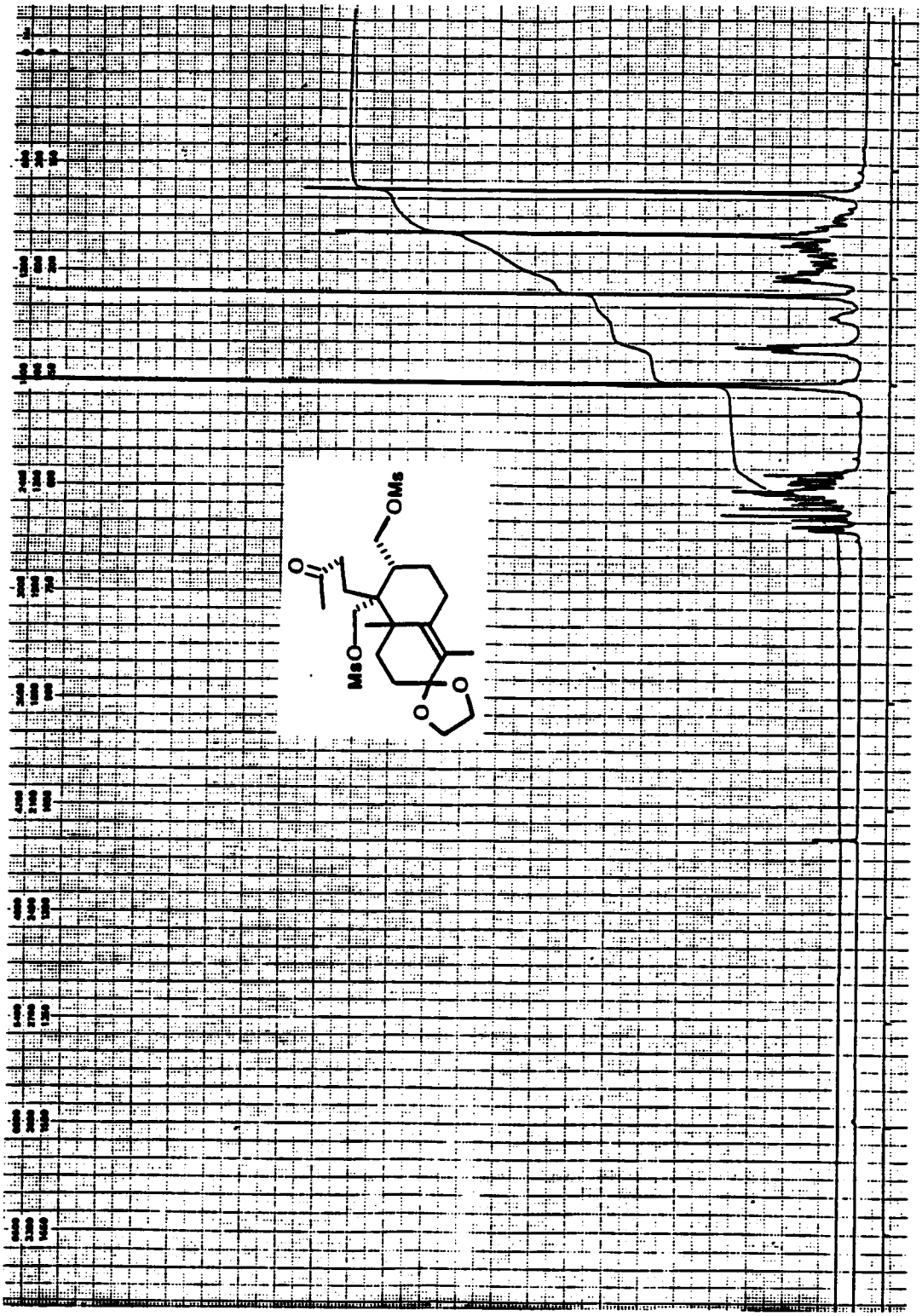
IR spectrum of ketone 146



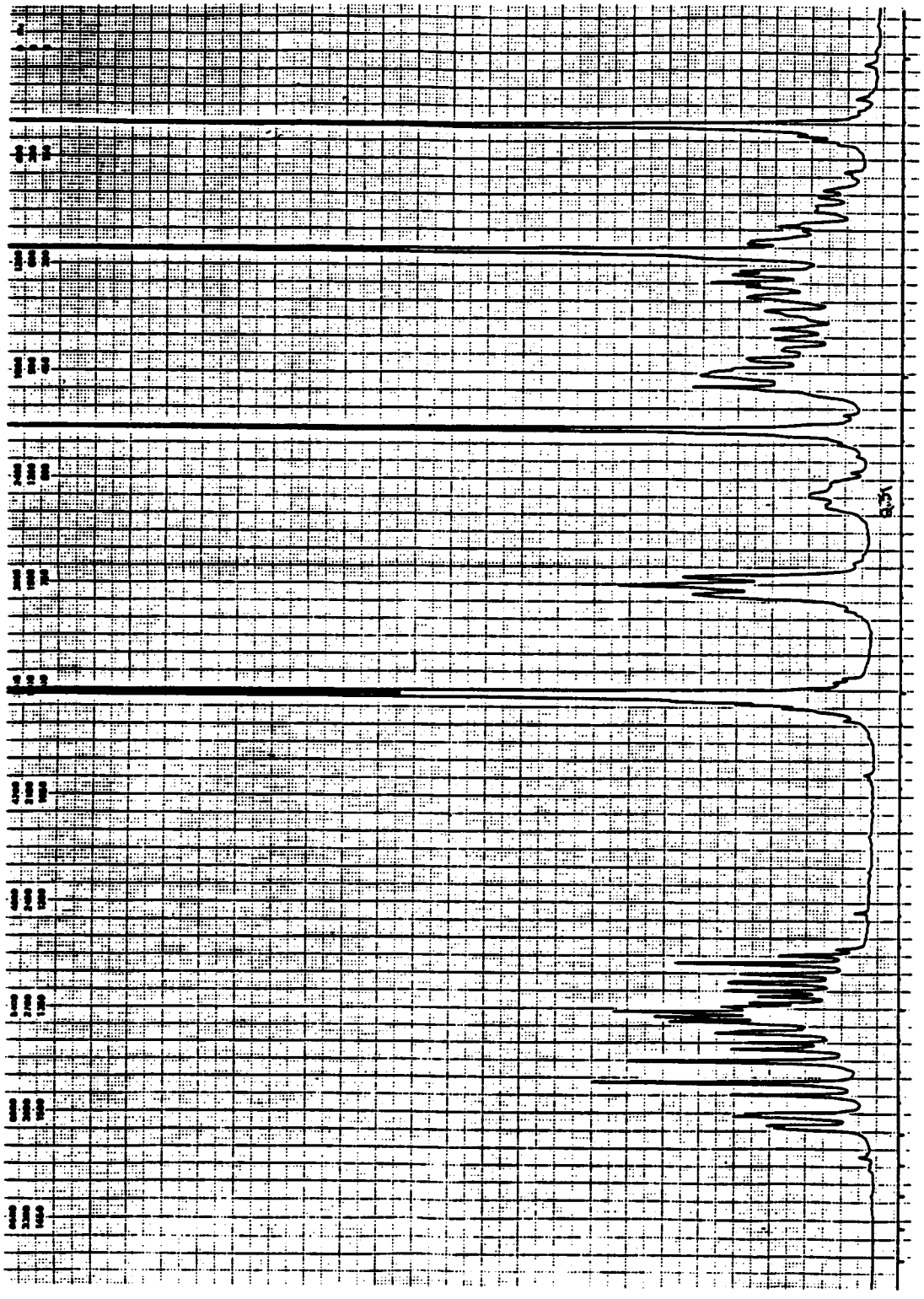
270 MHz ^{1}H NMR spectrum of bis-mesylate 148



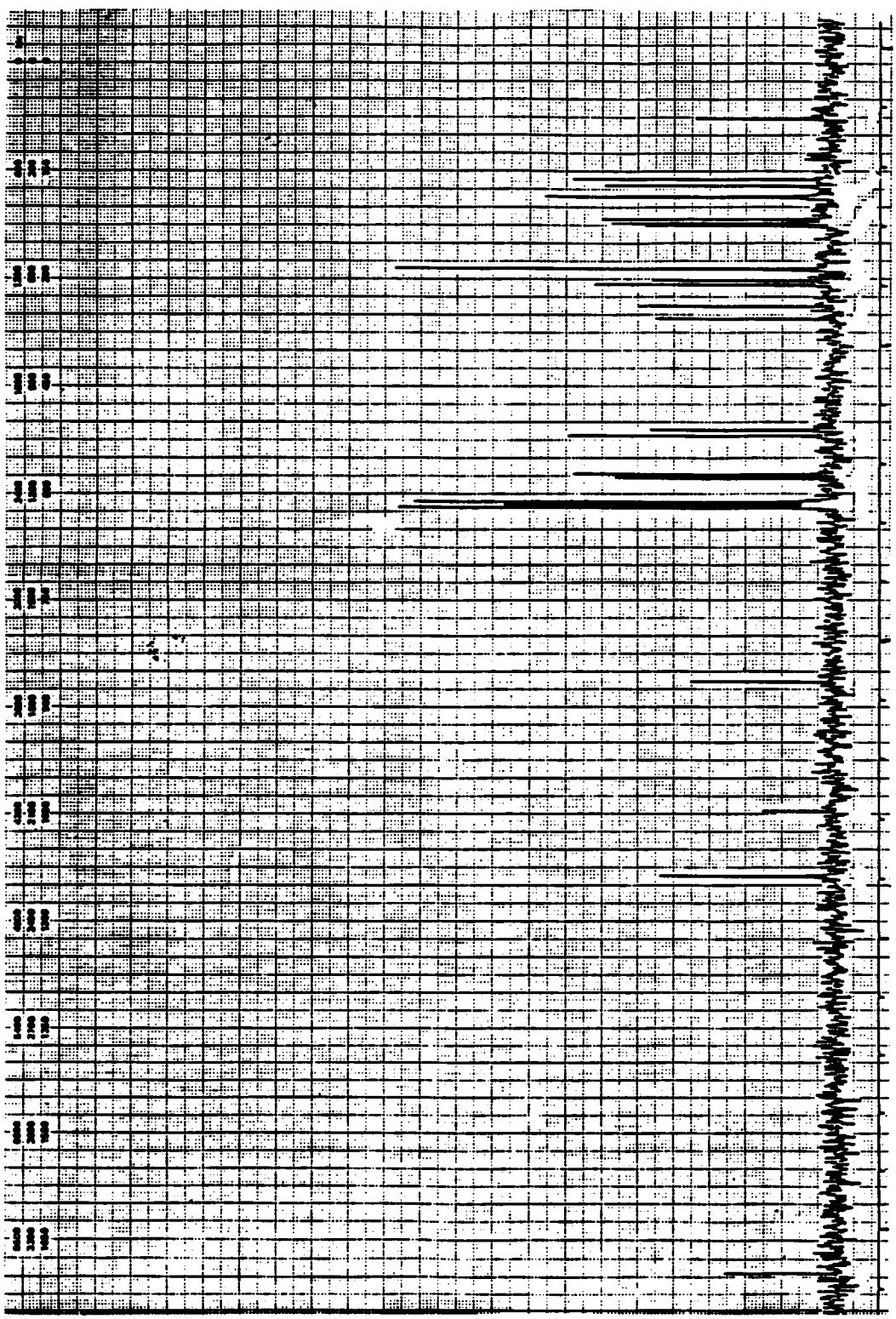
270 MHz ^1H NMR spectrum of furan 147



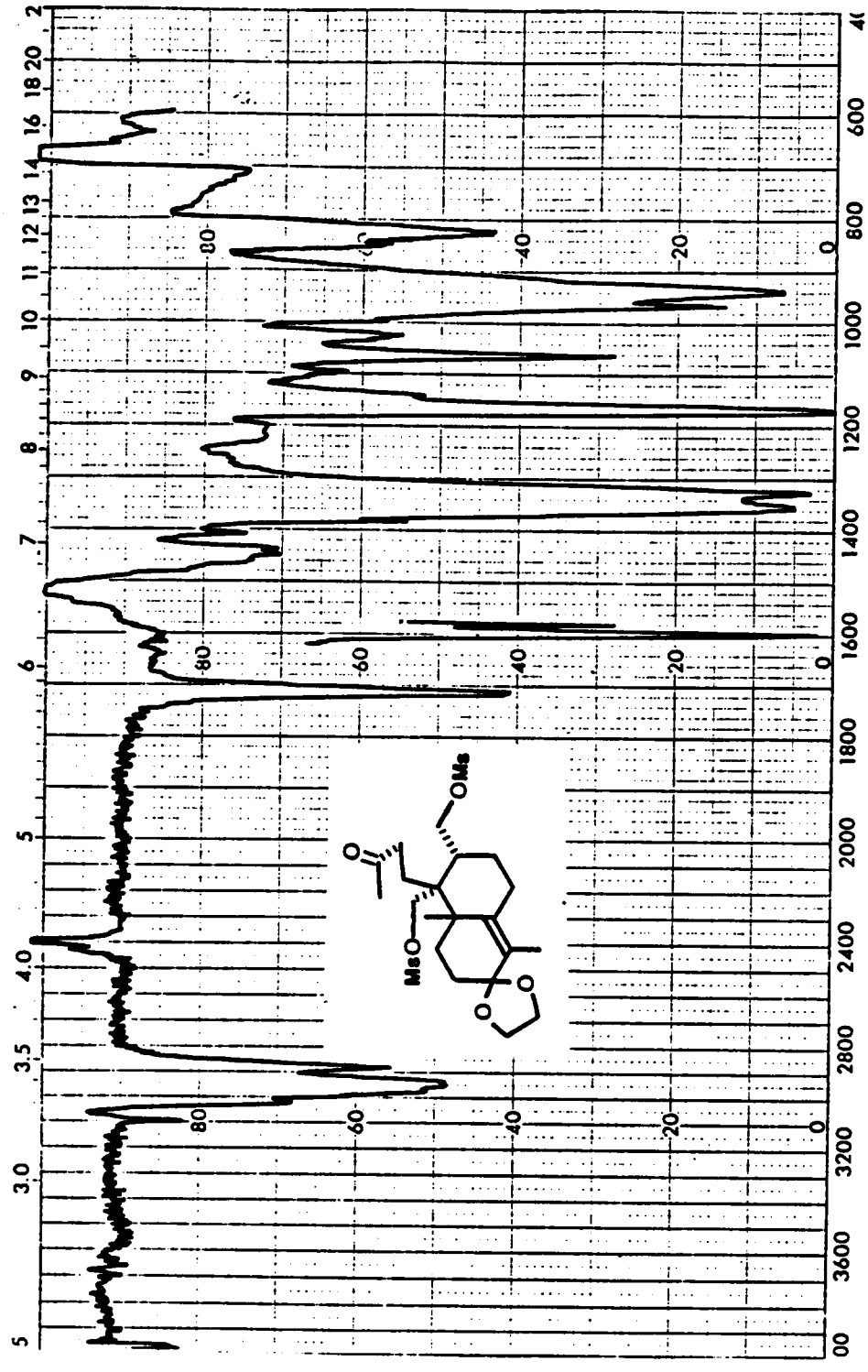
270 MHz ^{1}H NMR spectrum of bis-mesylate 139



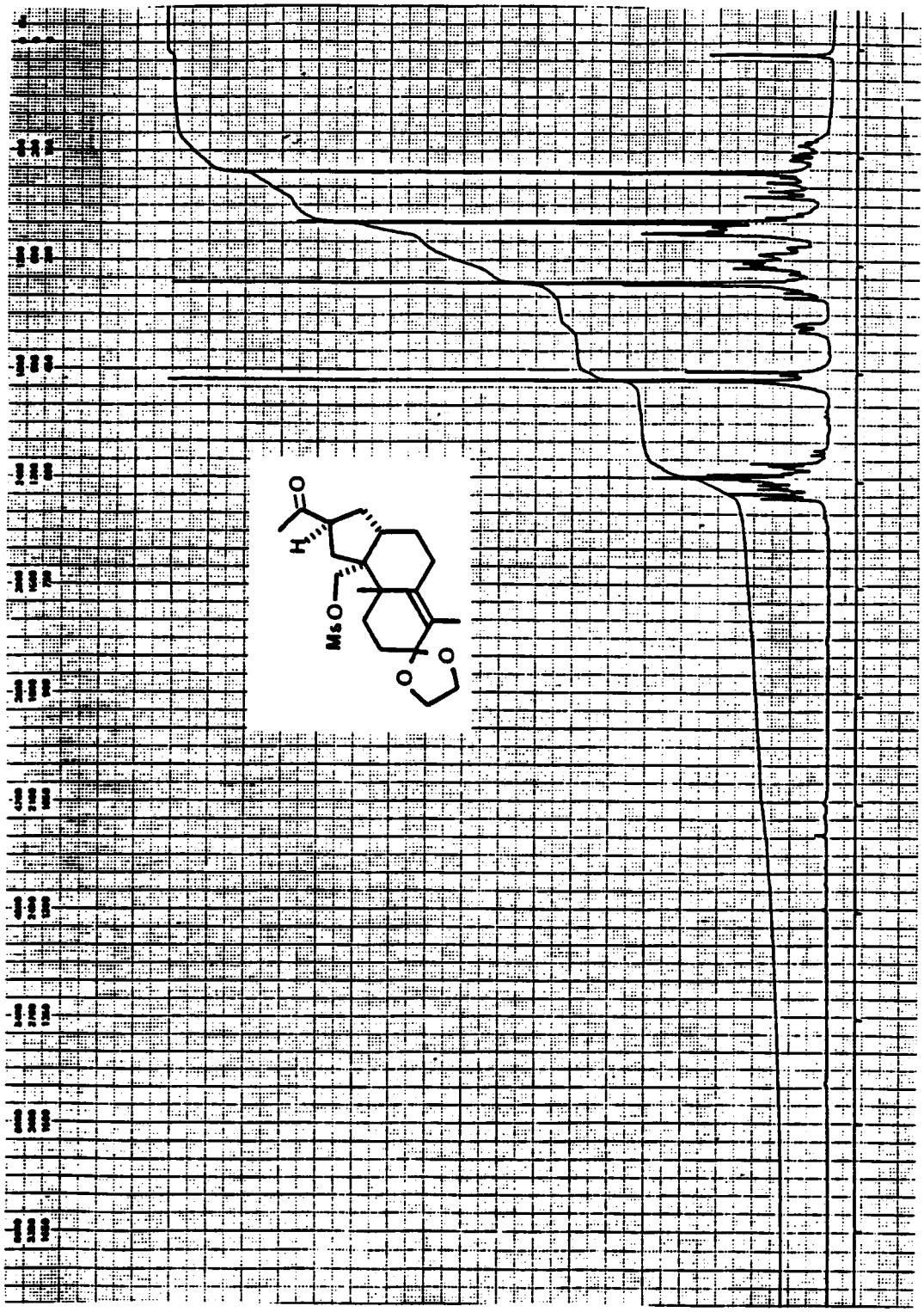
expanded 270 MHz ^{1}H NMR spectrum of bis-mesylate 139



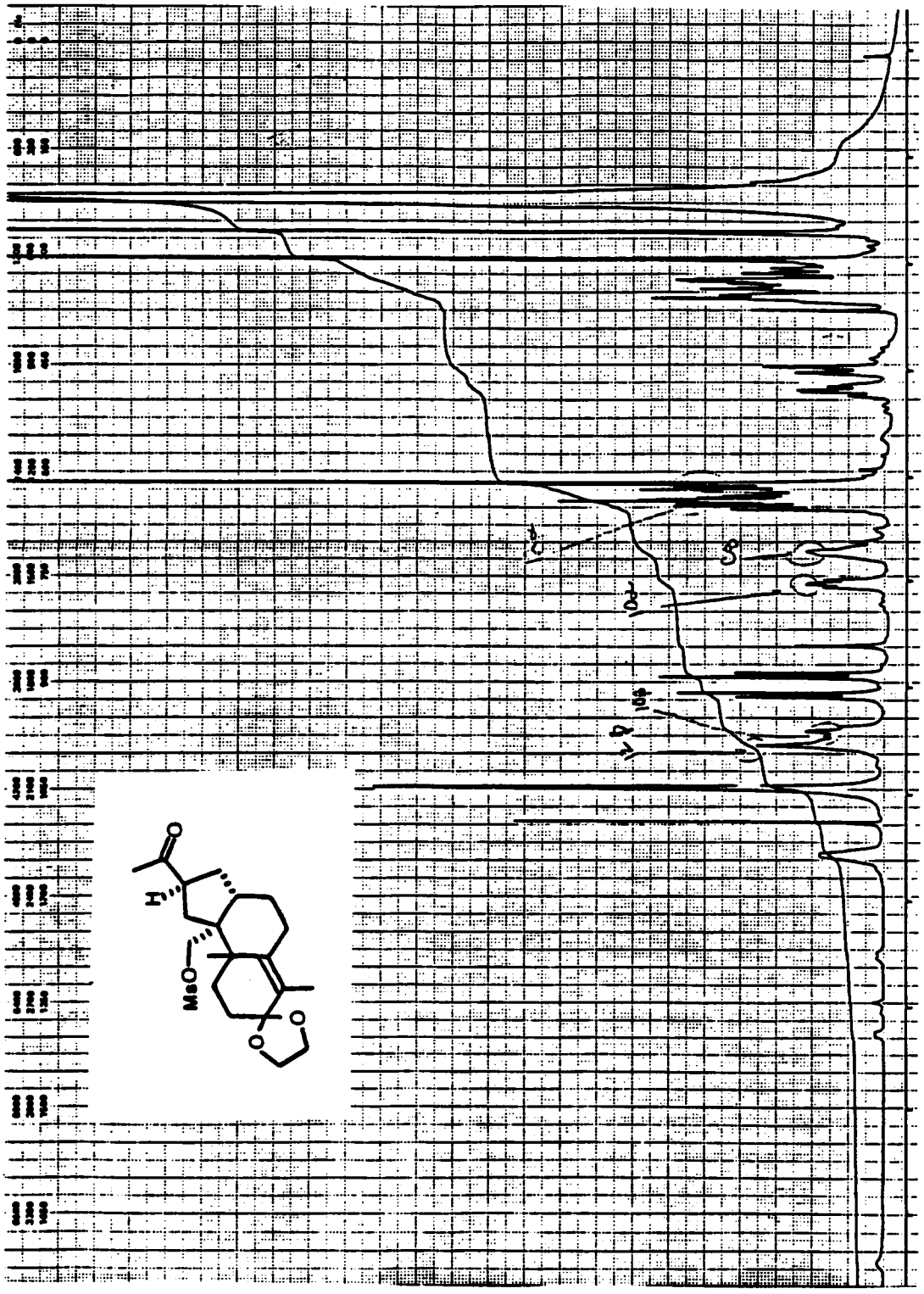
270 MHz ^{13}C decoupled NMR spectrum of bis-mesylate 139



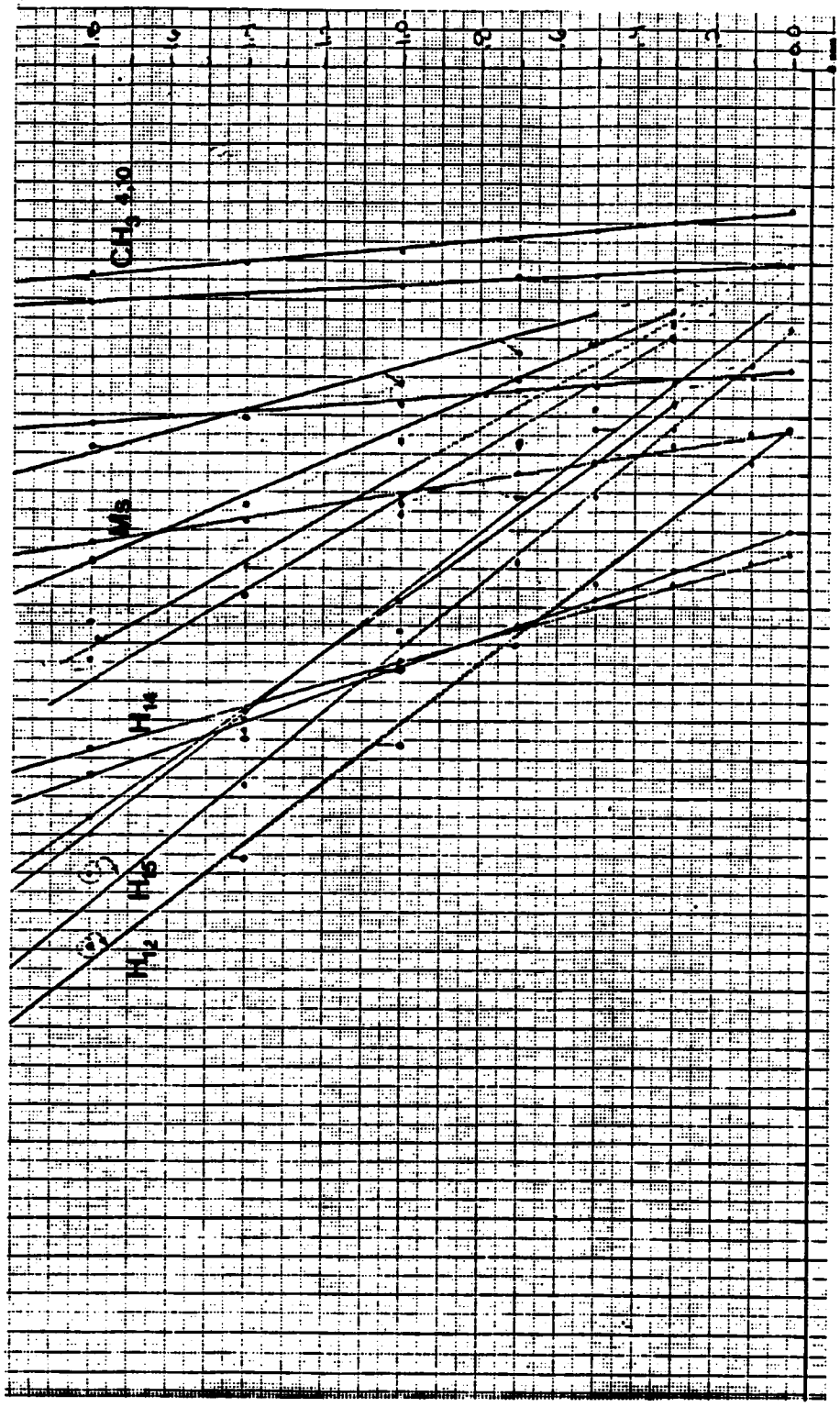
IR spectrum of bis-mesylate 139



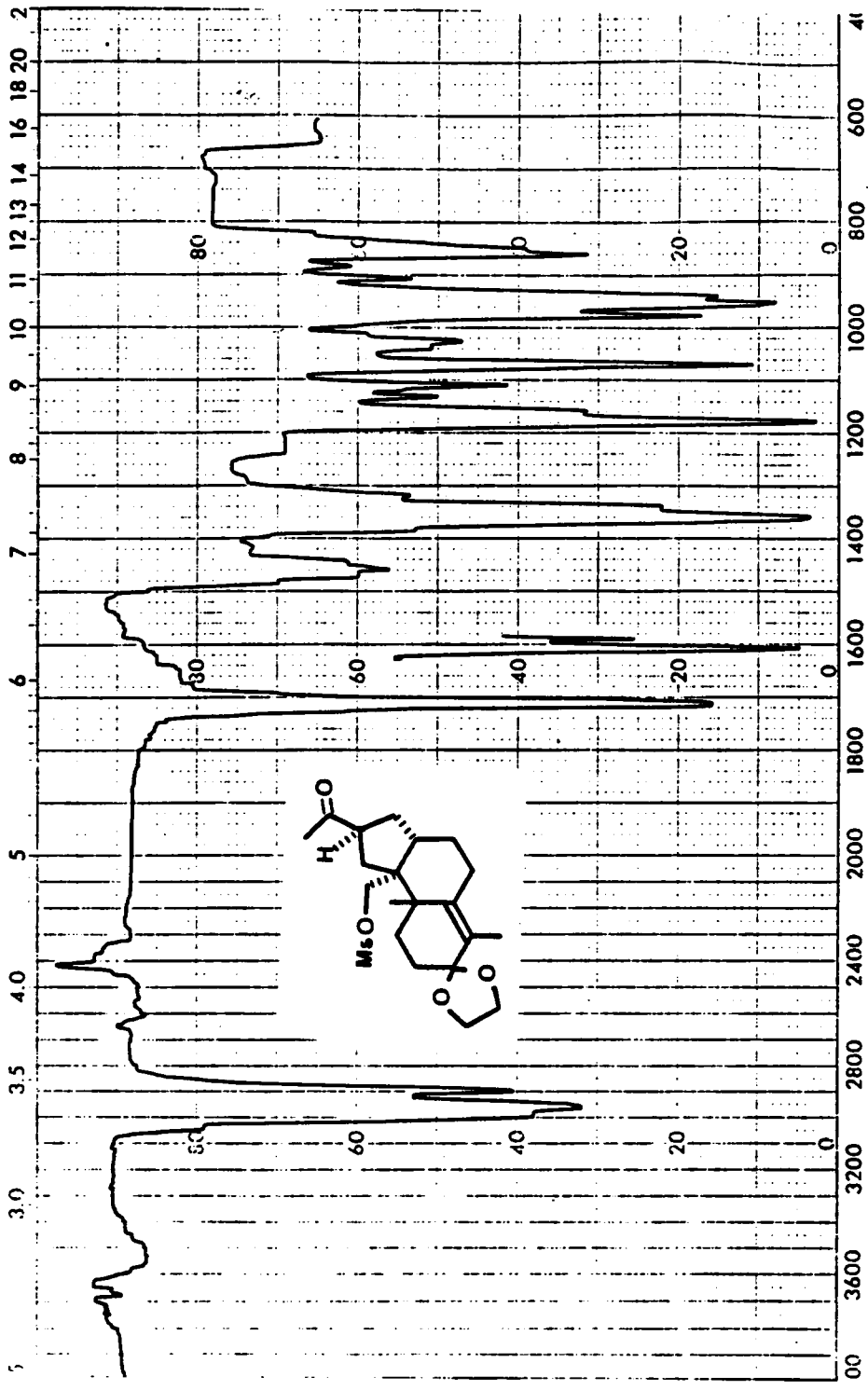
270 MHz ^{1}H NMR spectrum of ketone 142a



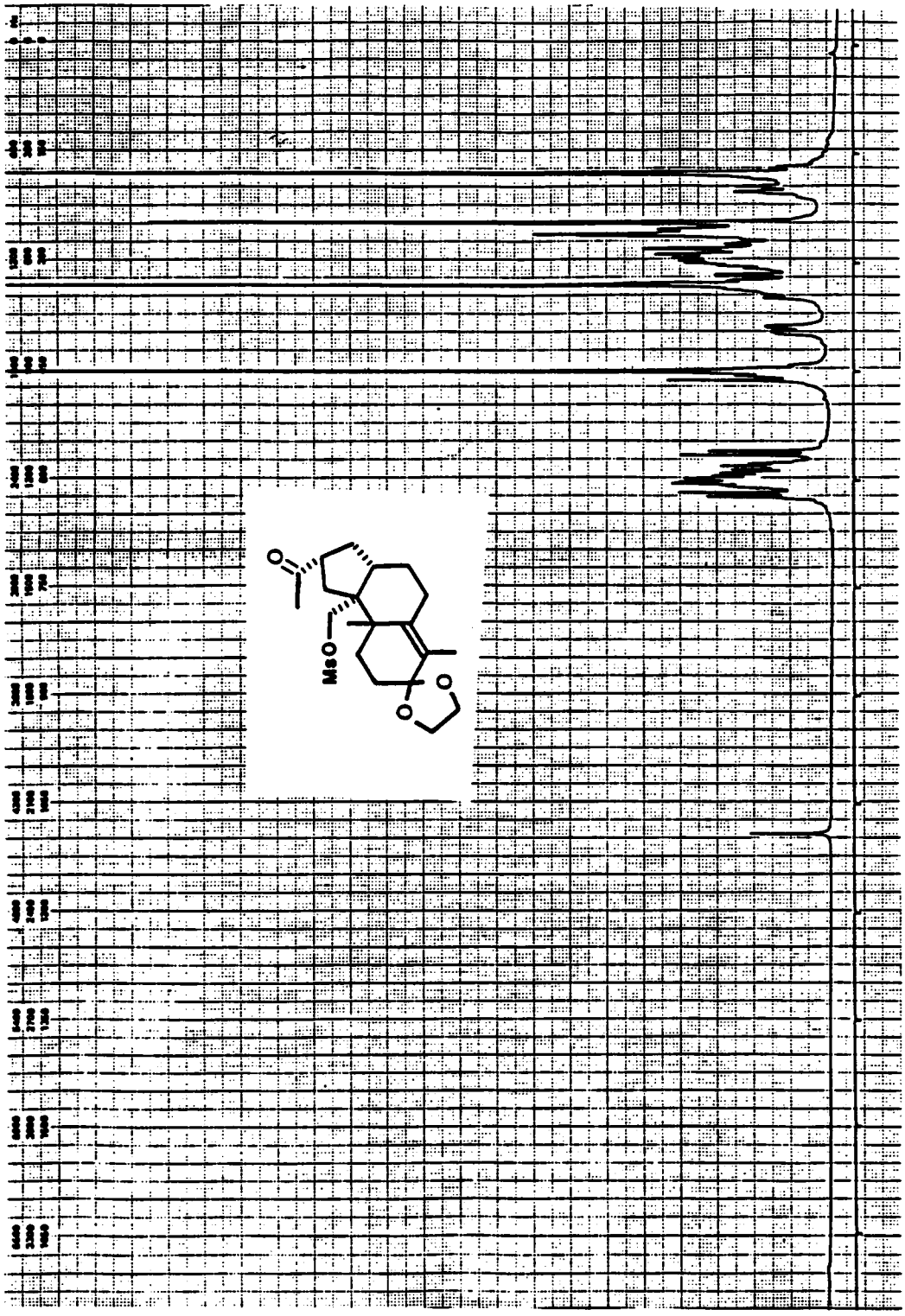
270 MHz ^{1}H NMR spectrum of ketone 142a with Eufod



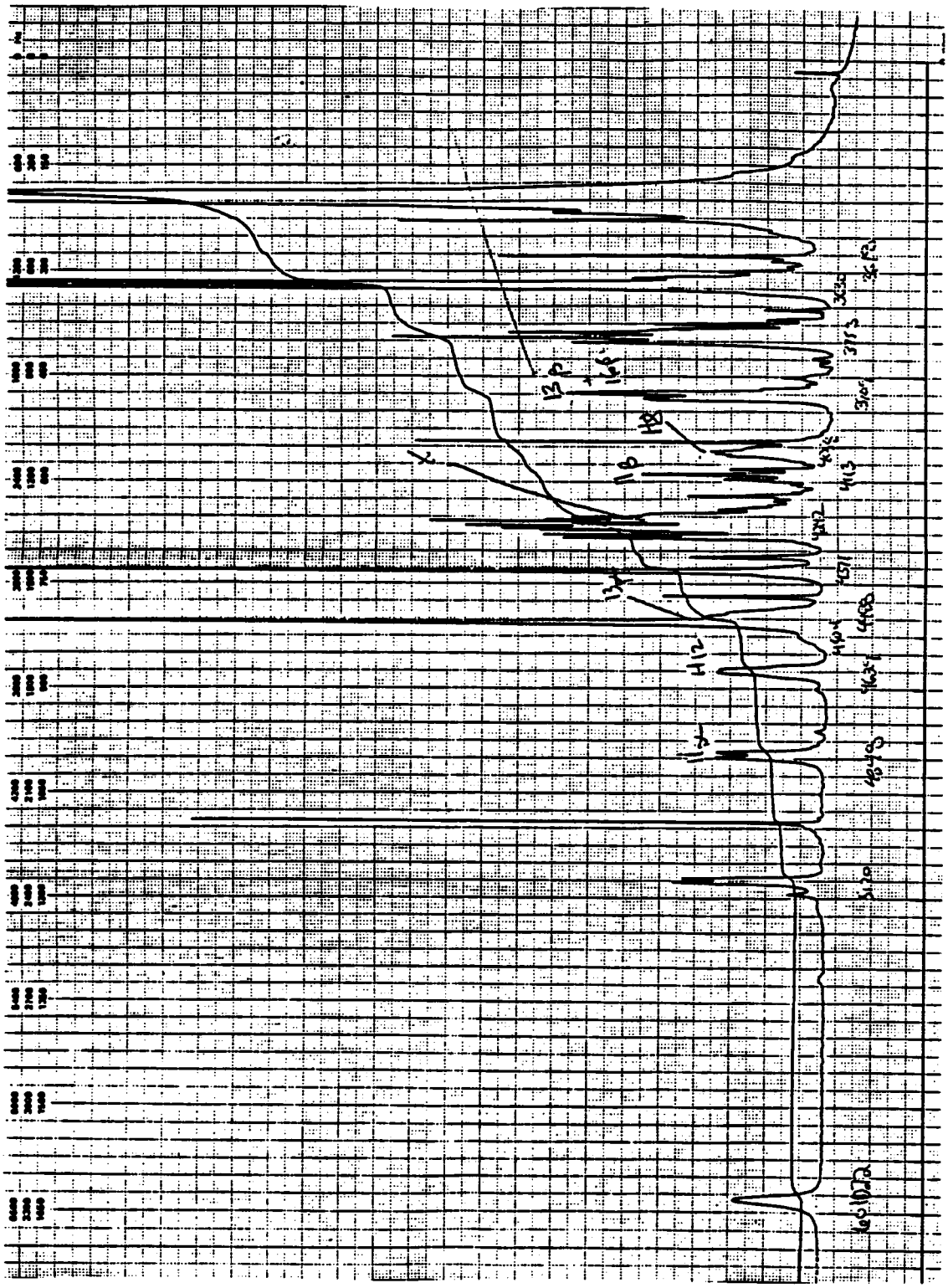
Chemical shift versus addition of Eufod for ketone 142a



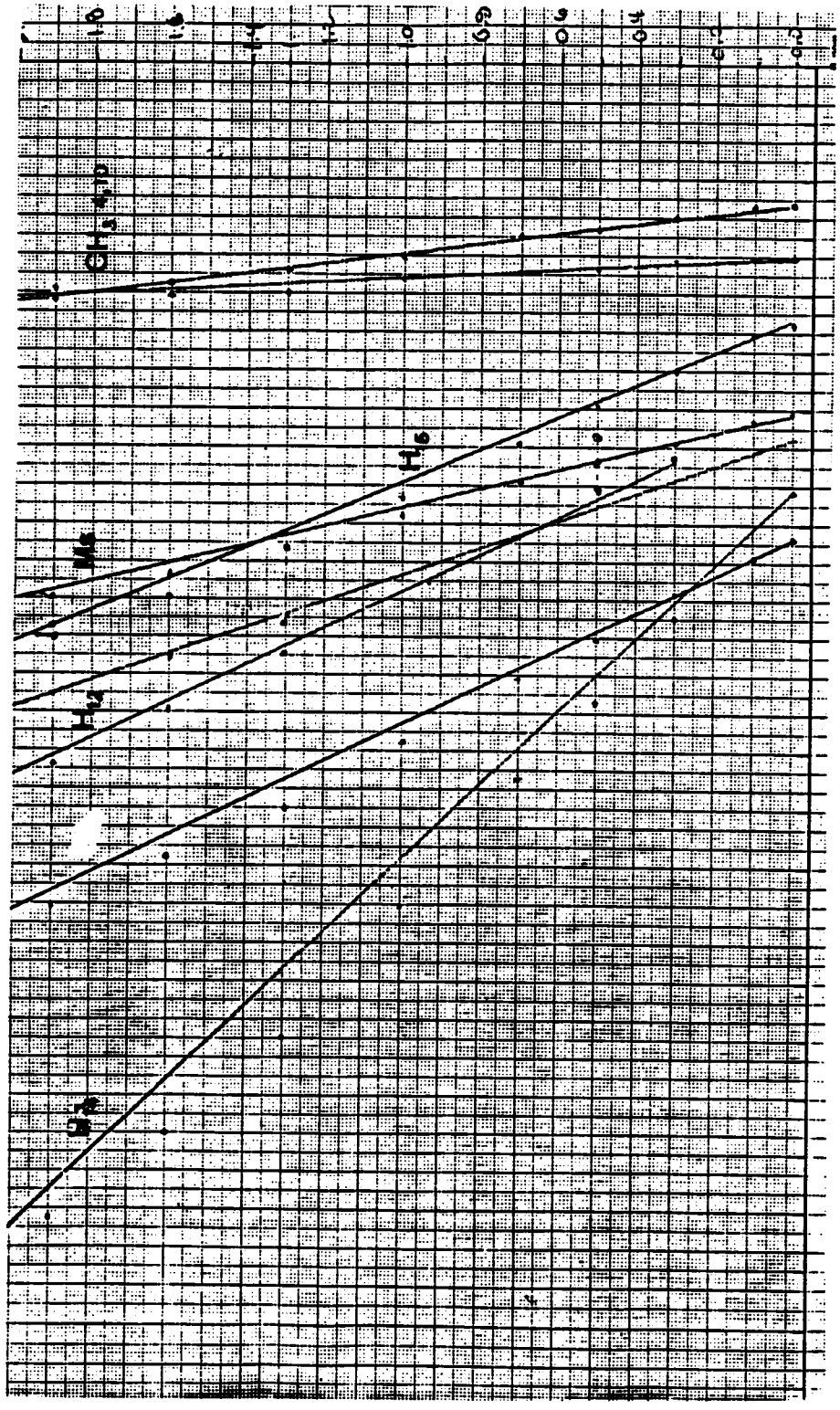
IR spectrum of ketone 142a



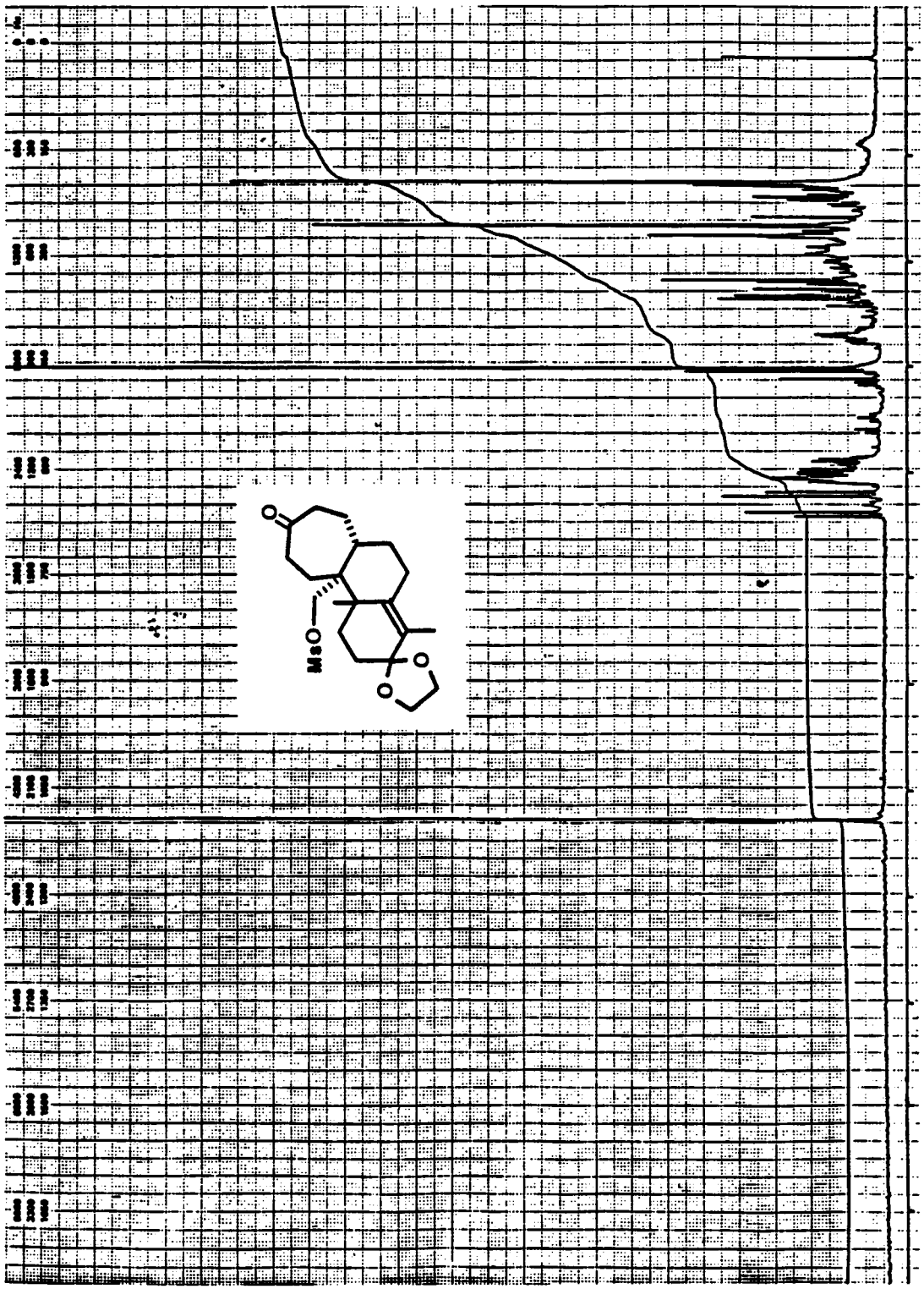
270 MHz ^{1}H NMR spectrum of ketone 142b



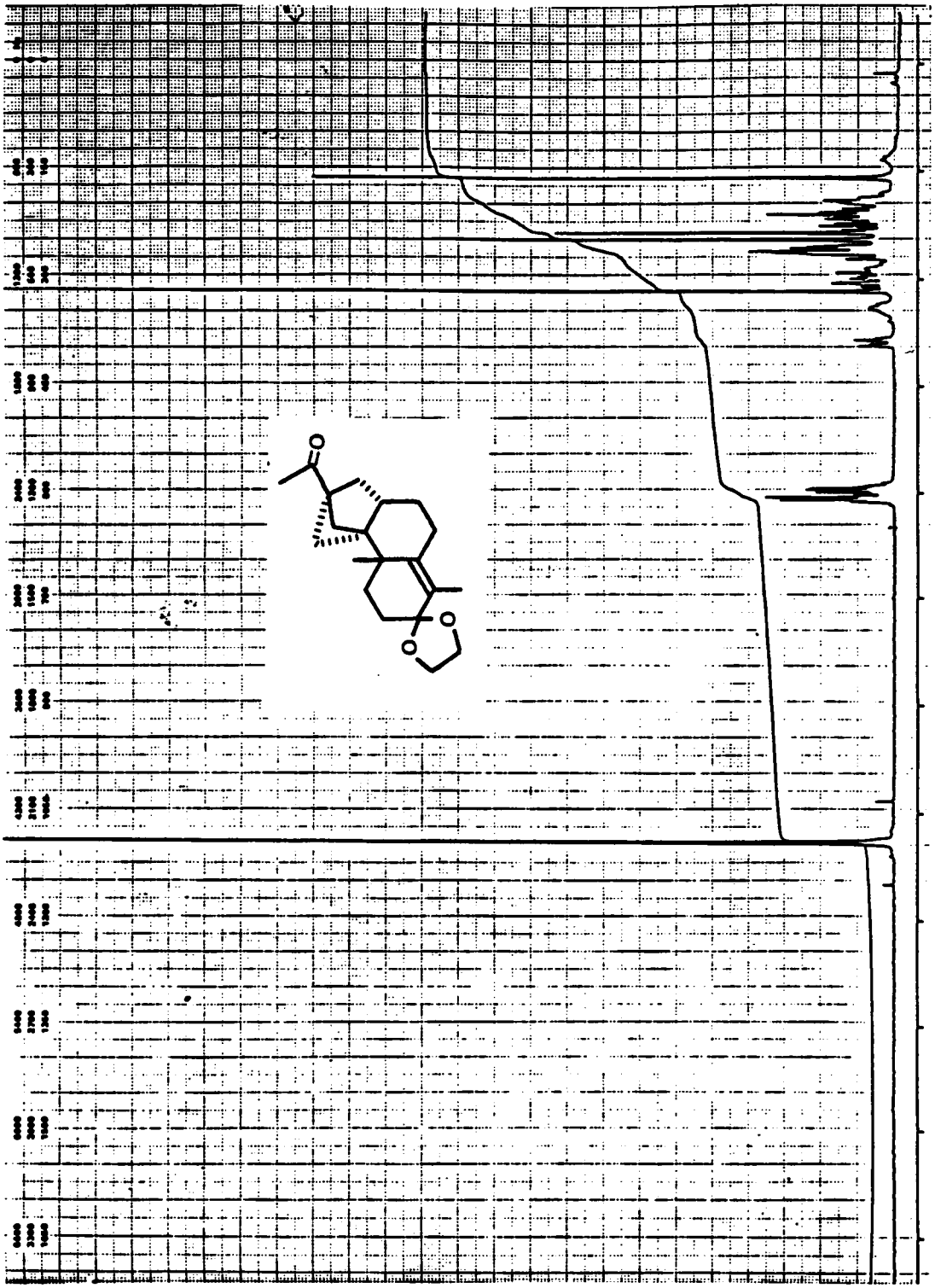
270 MHz ^{1}H NMR spectrum of ketone 142b with Eufod



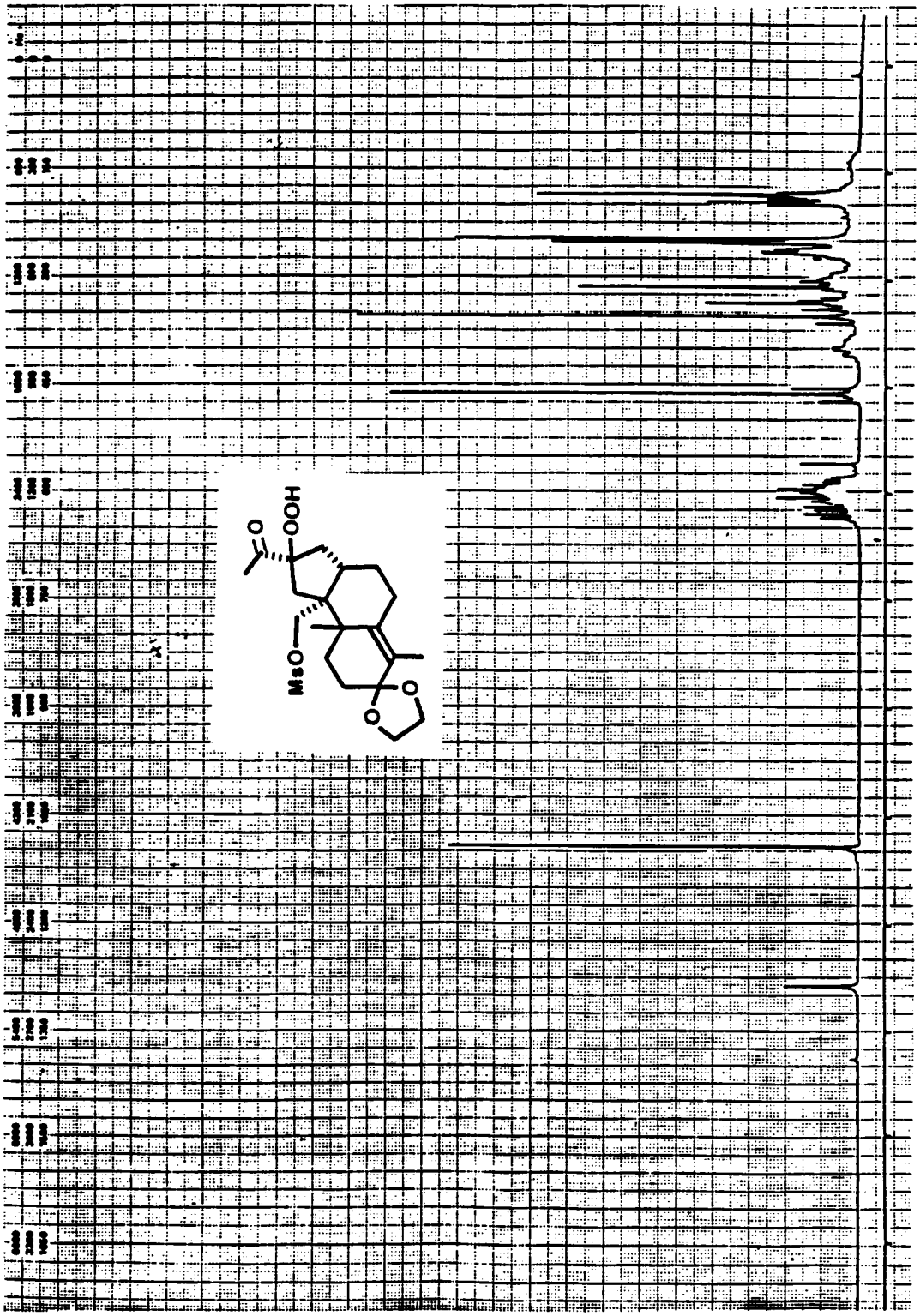
Chemical shift versus addition of Eufod to ketone 142b



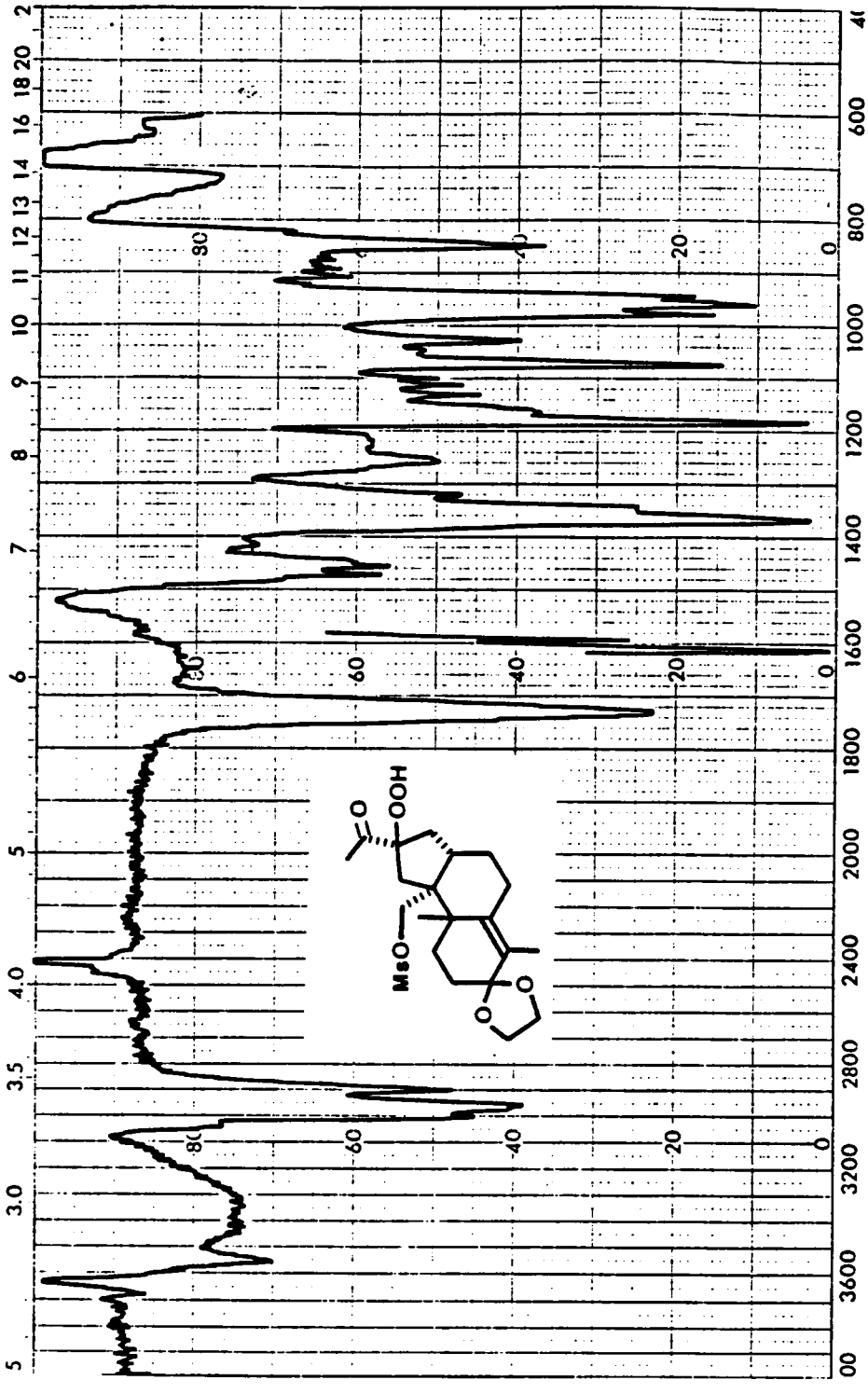
270 MHz ^{1}H NMR spectrum of ketone 144



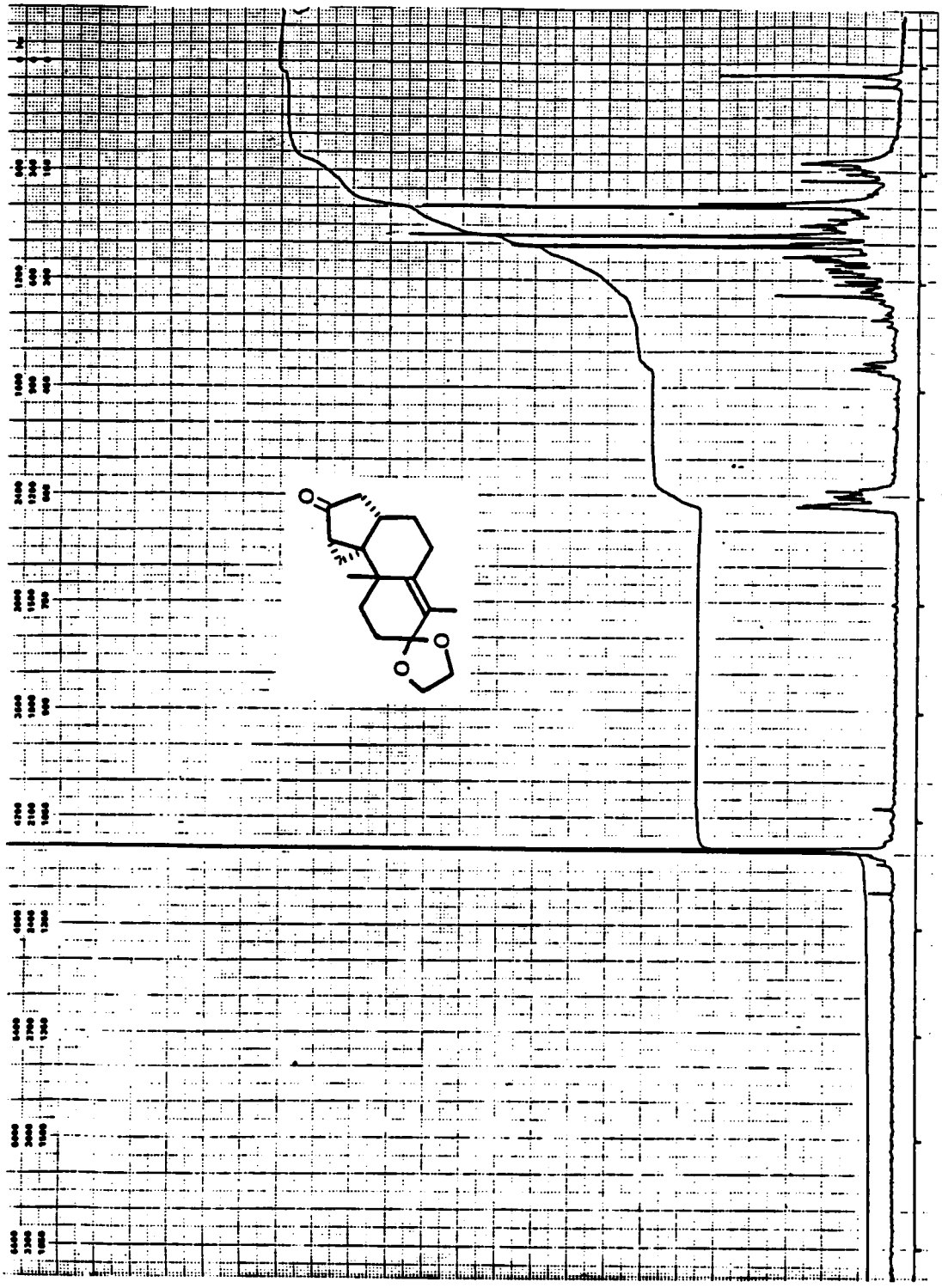
270 MHz ^{1}H NMR spectrum of ketone 149



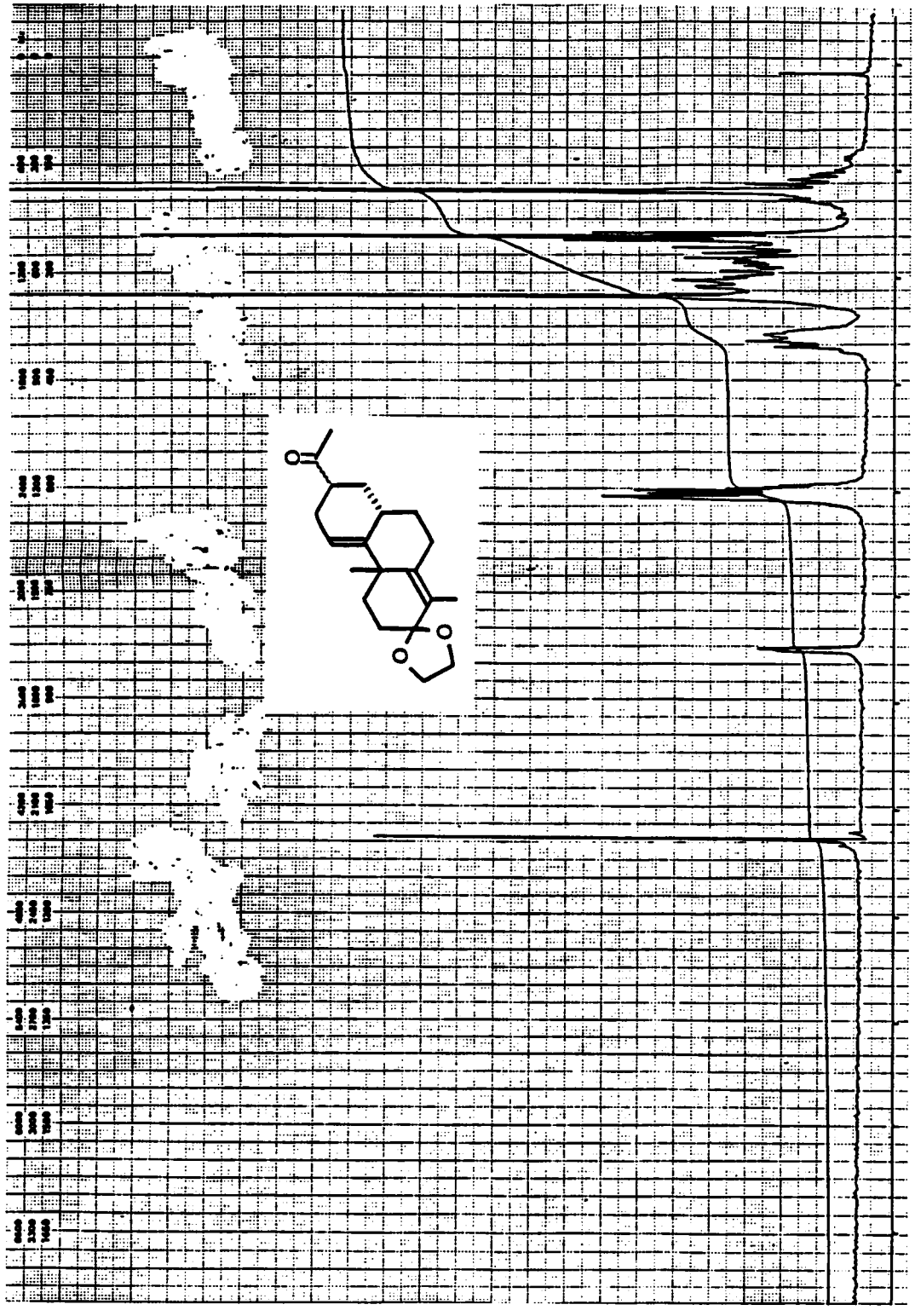
270 MHz ^{1}H NMR spectrum of hydroperoxide 151



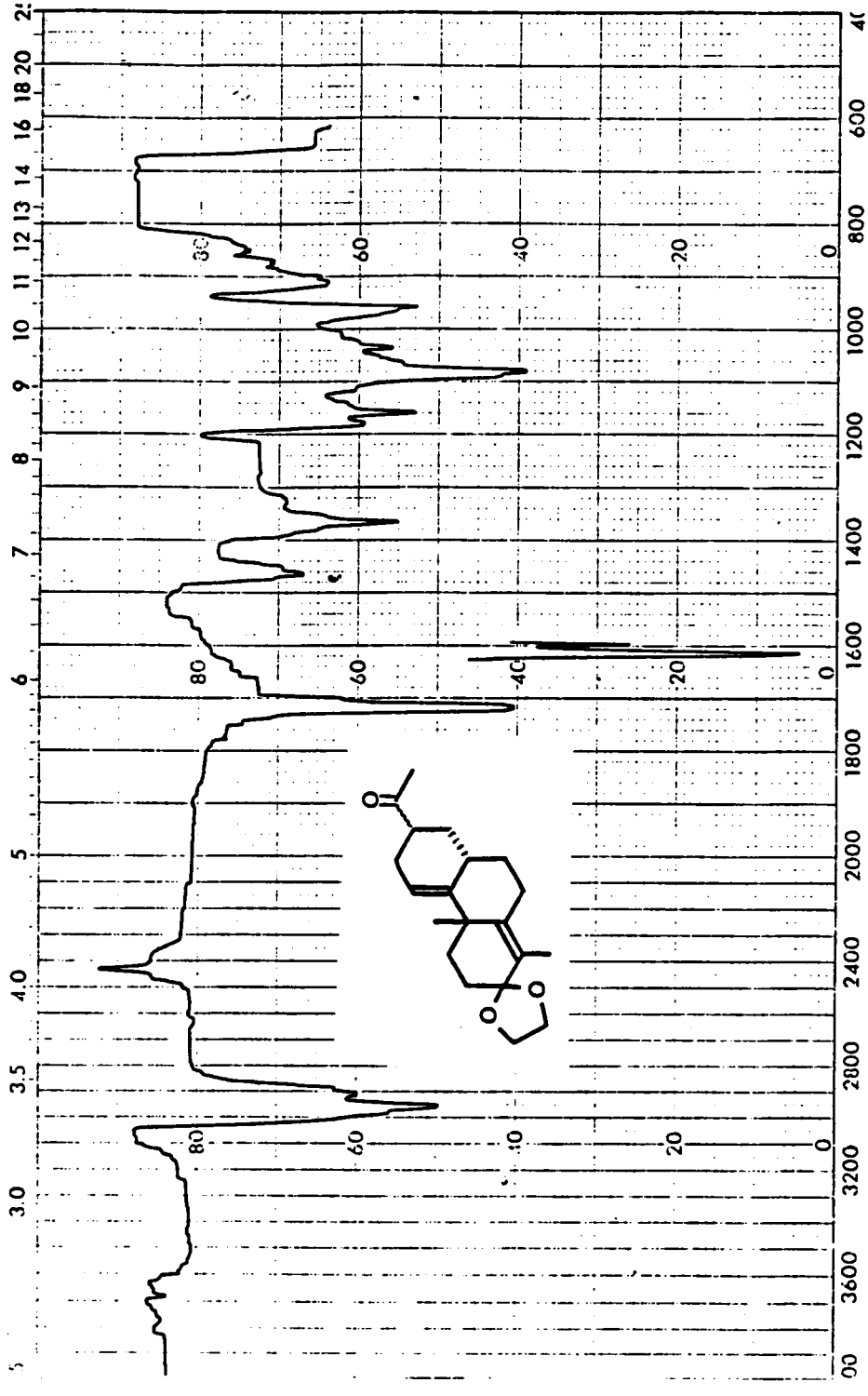
IR spectrum of hydroperoxide 151



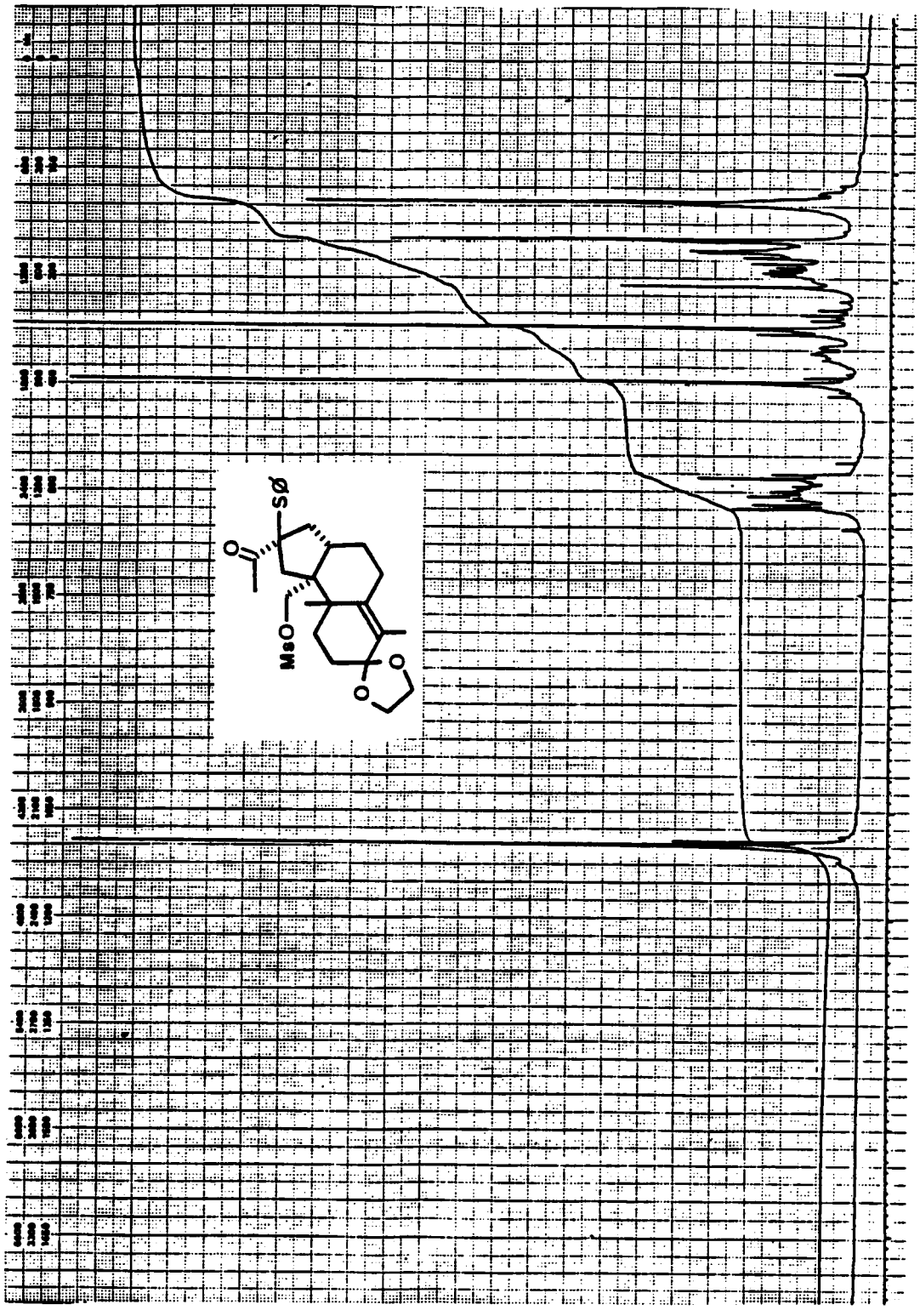
270 MHz ^{1}H NMR spectrum of ketone 150



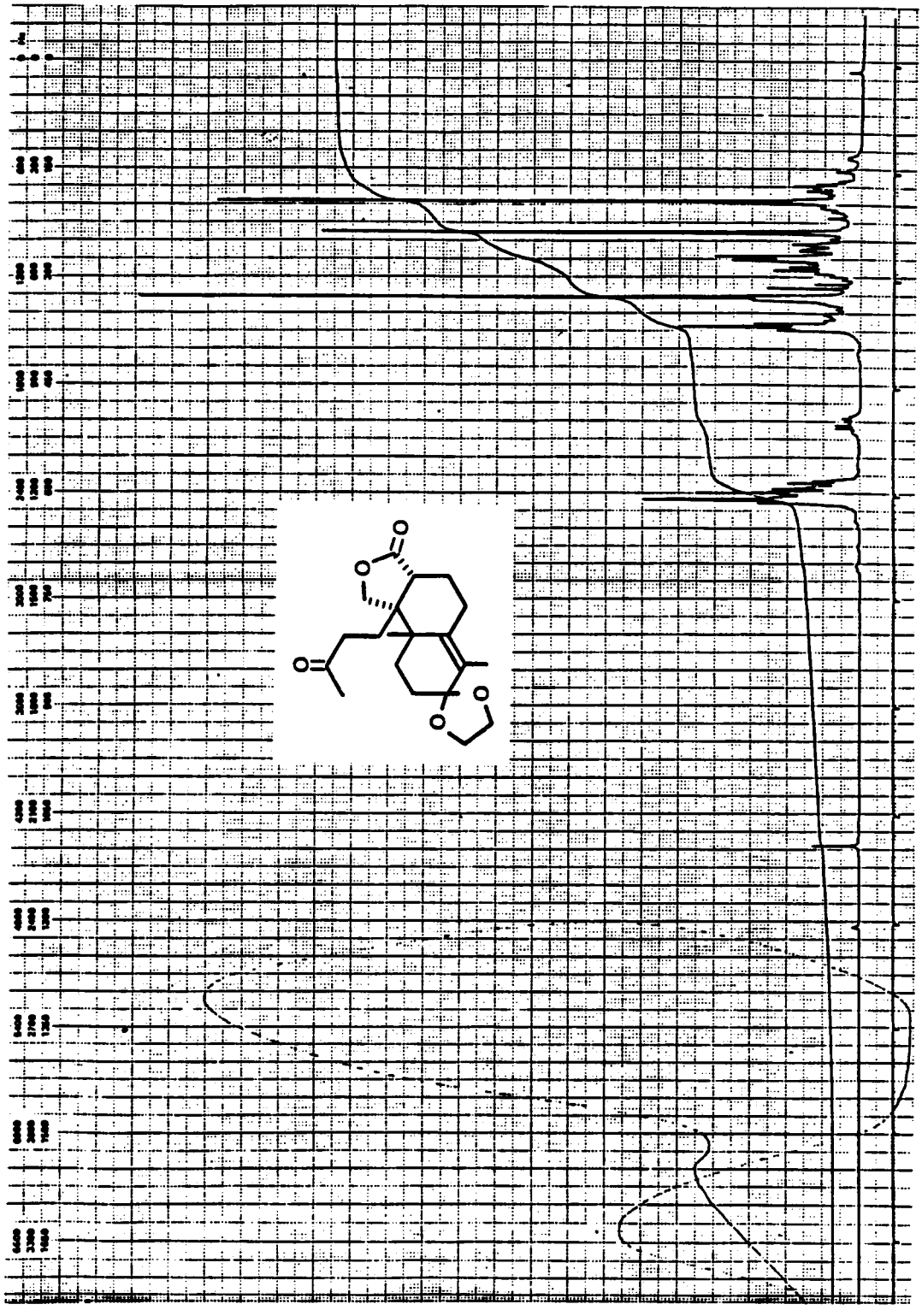
270 MHz ^{1}H NMR spectrum of ketone 154



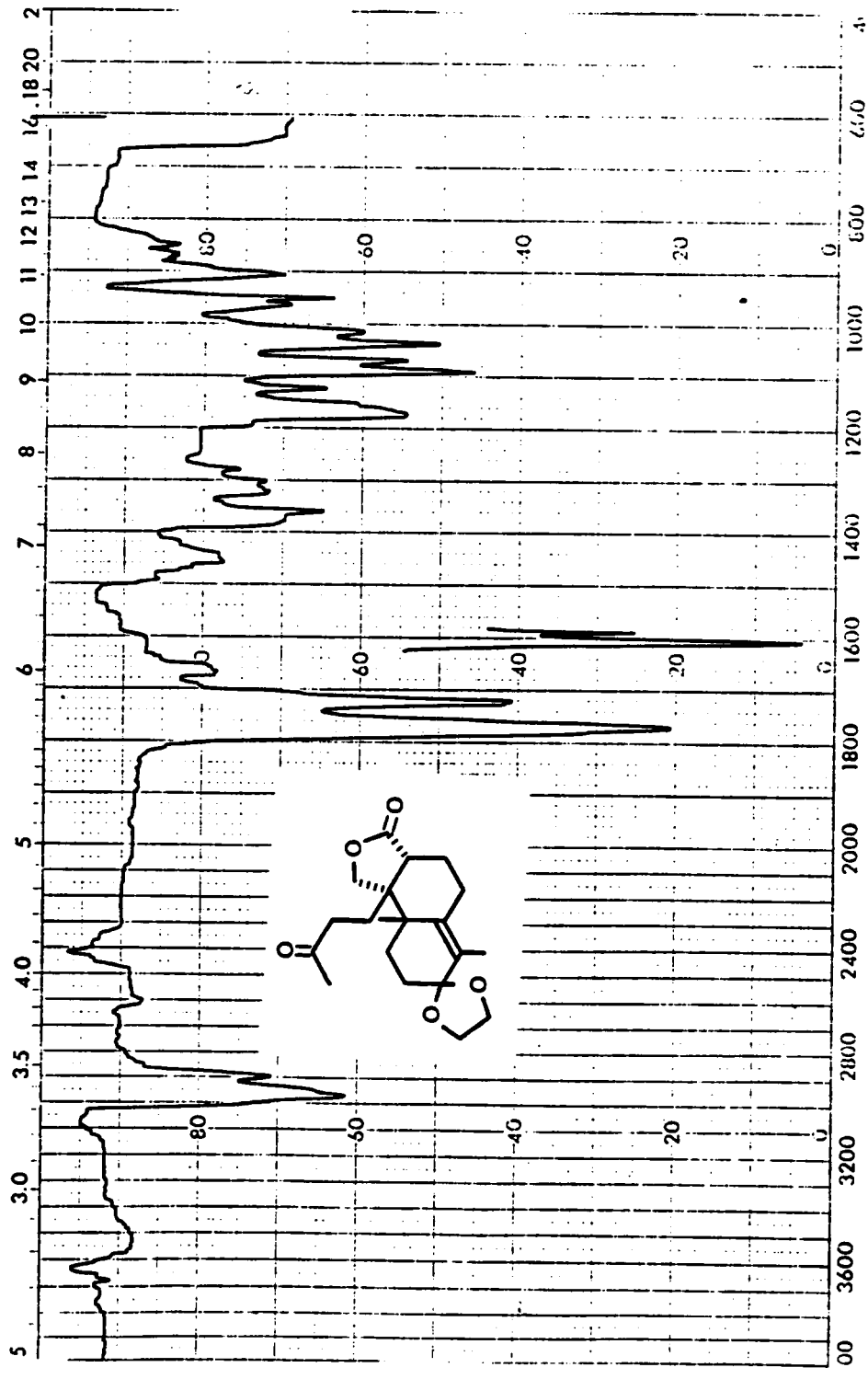
IR spectrum of ketone 154



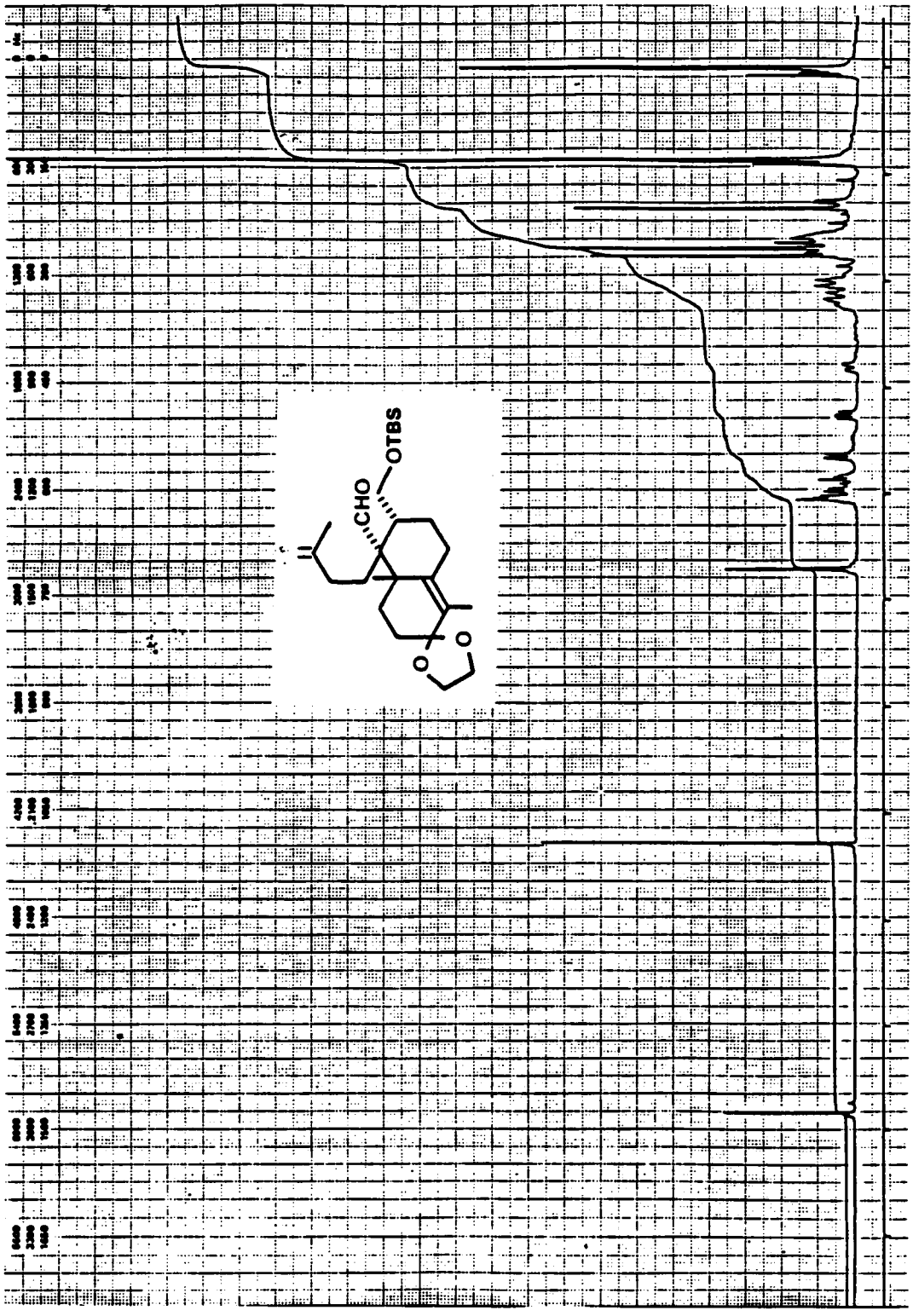
270 MHz ^{1}H NMR spectrum of sulfide 155



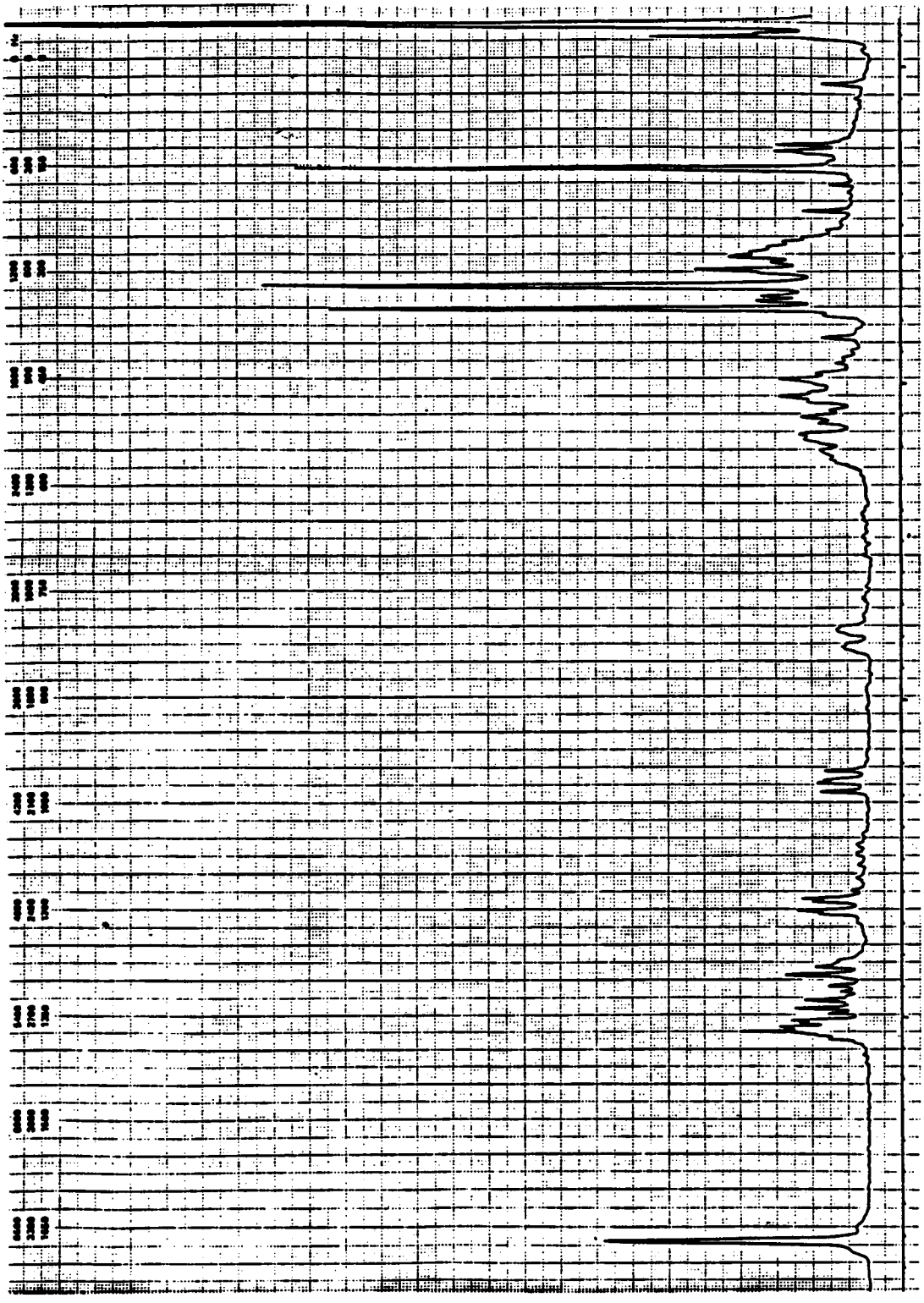
270 MHz ^{1}H NMR spectrum of ketone 158



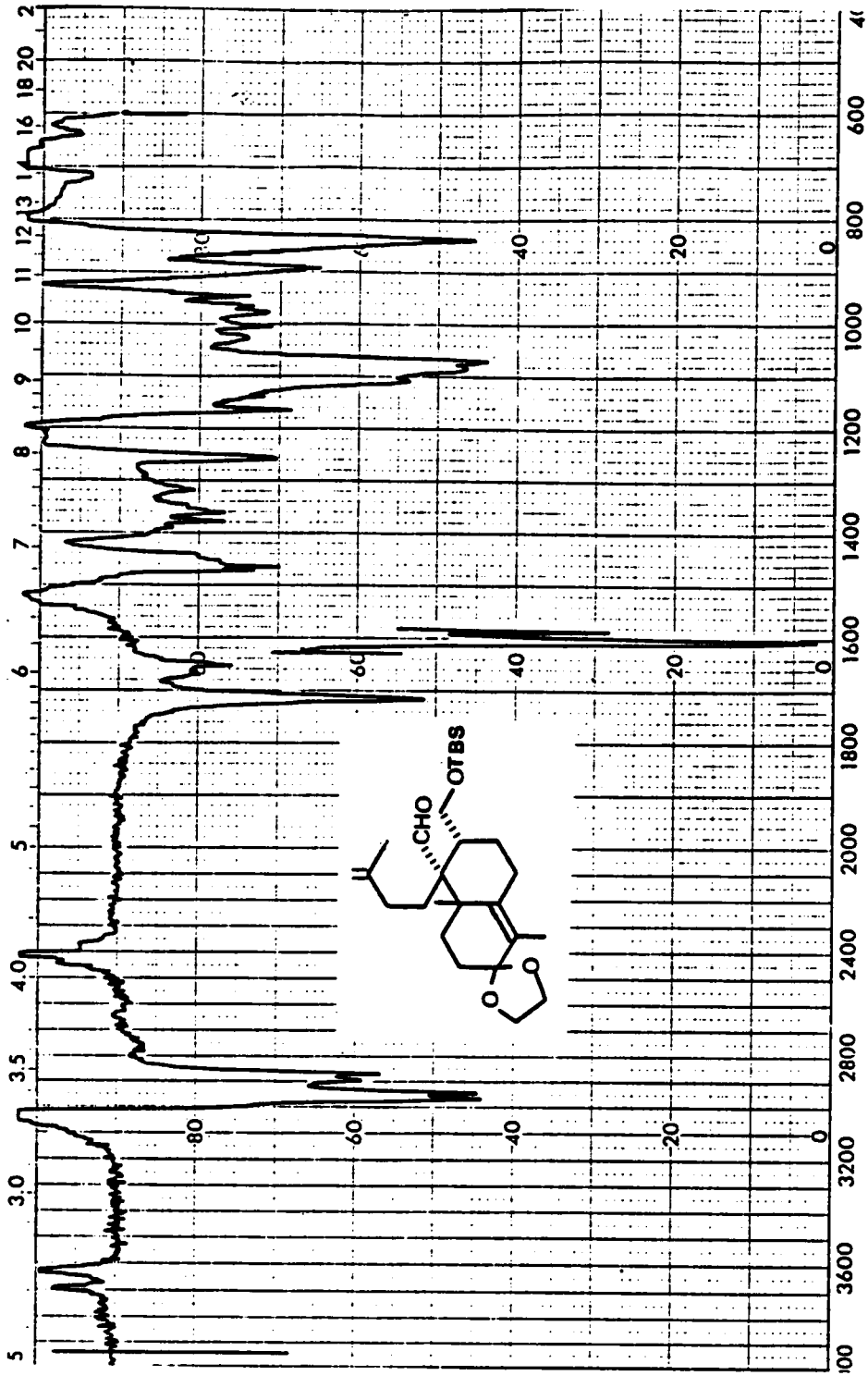
IR spectrum of ketone 158



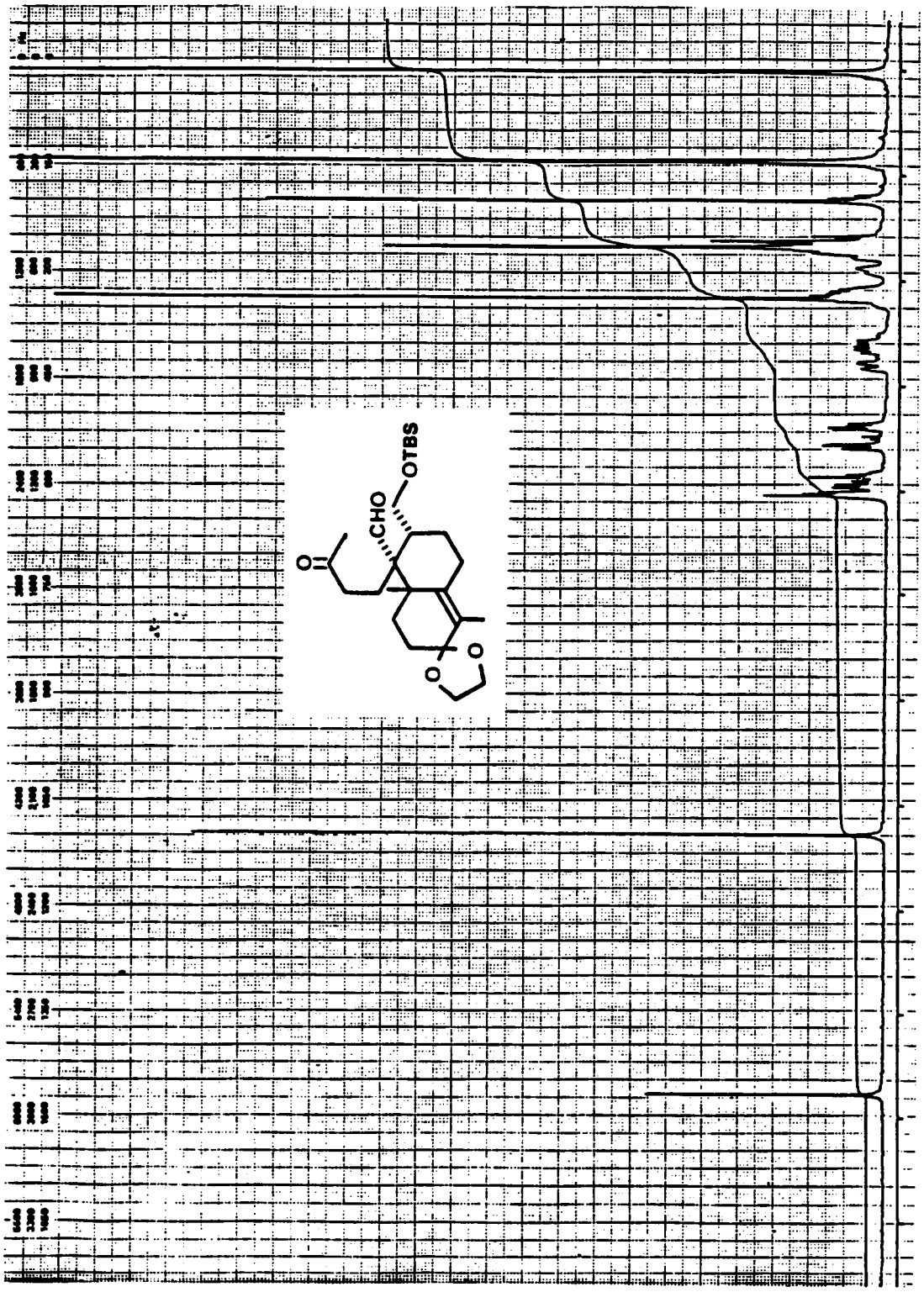
270 MHz ^{1}H NMR spectrum of aldehyde 159



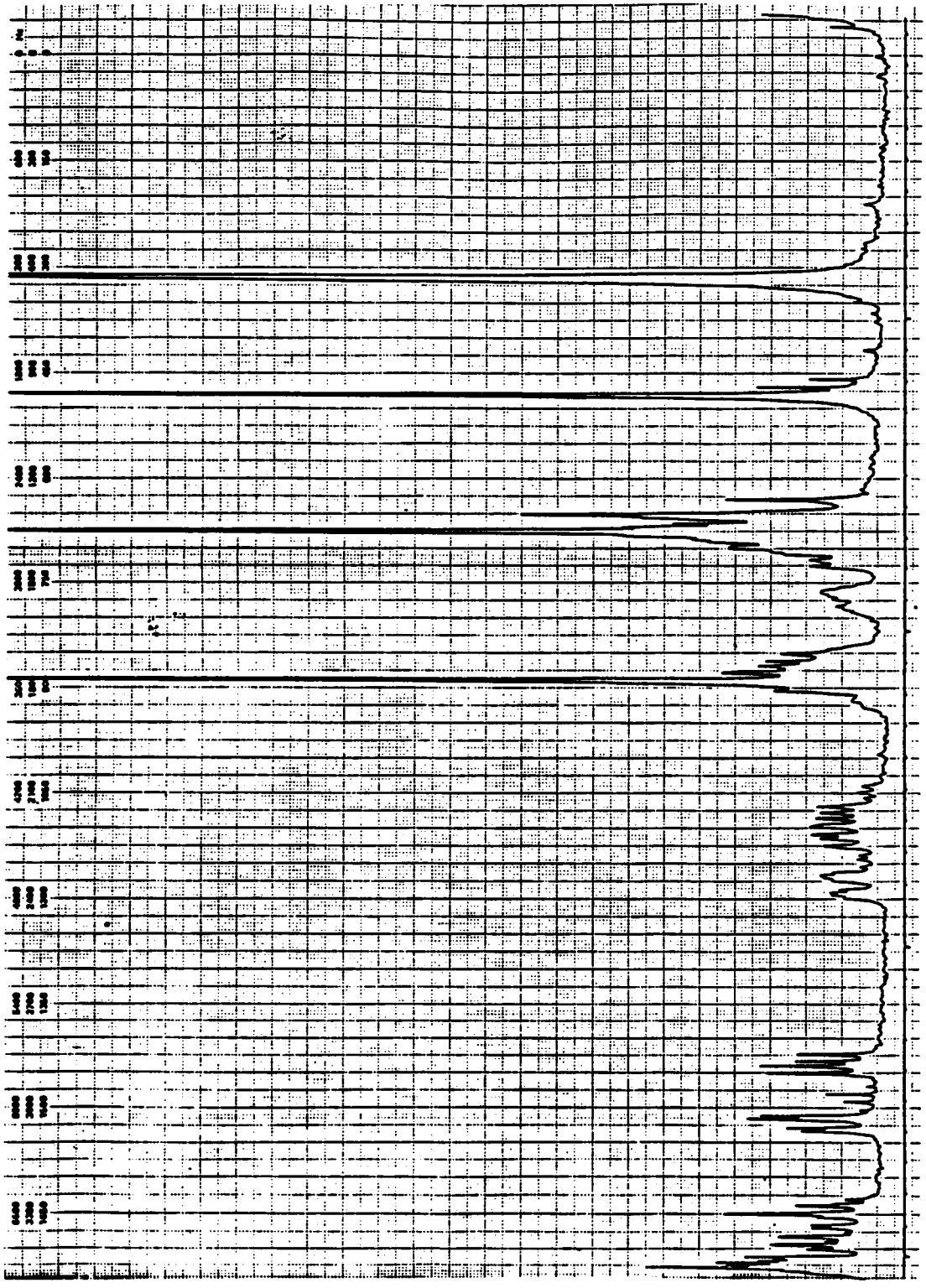
expanded 270 MHz ^{1}H NMR spectrum of aldehyde 159



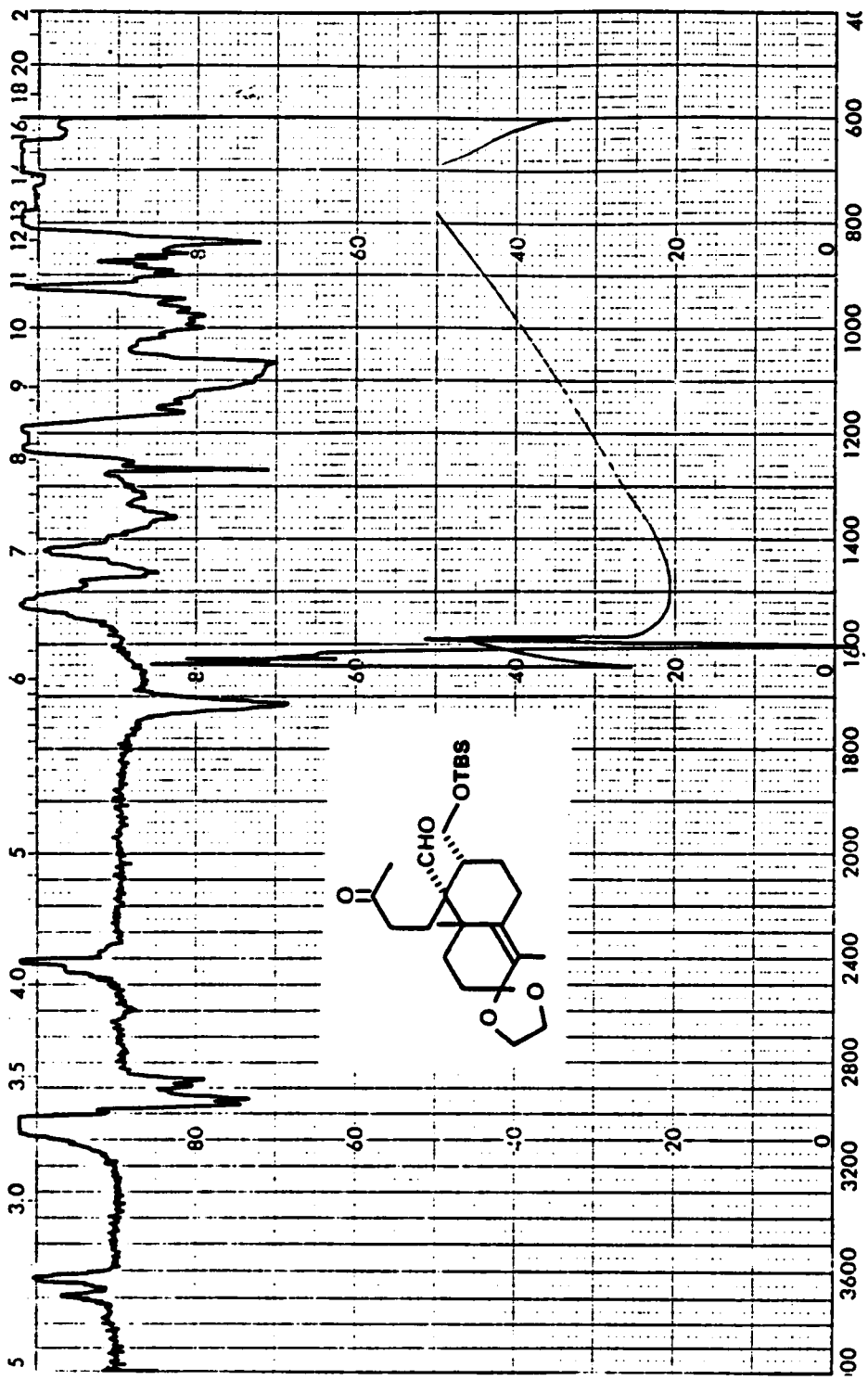
IR spectrum of aldehyde 159



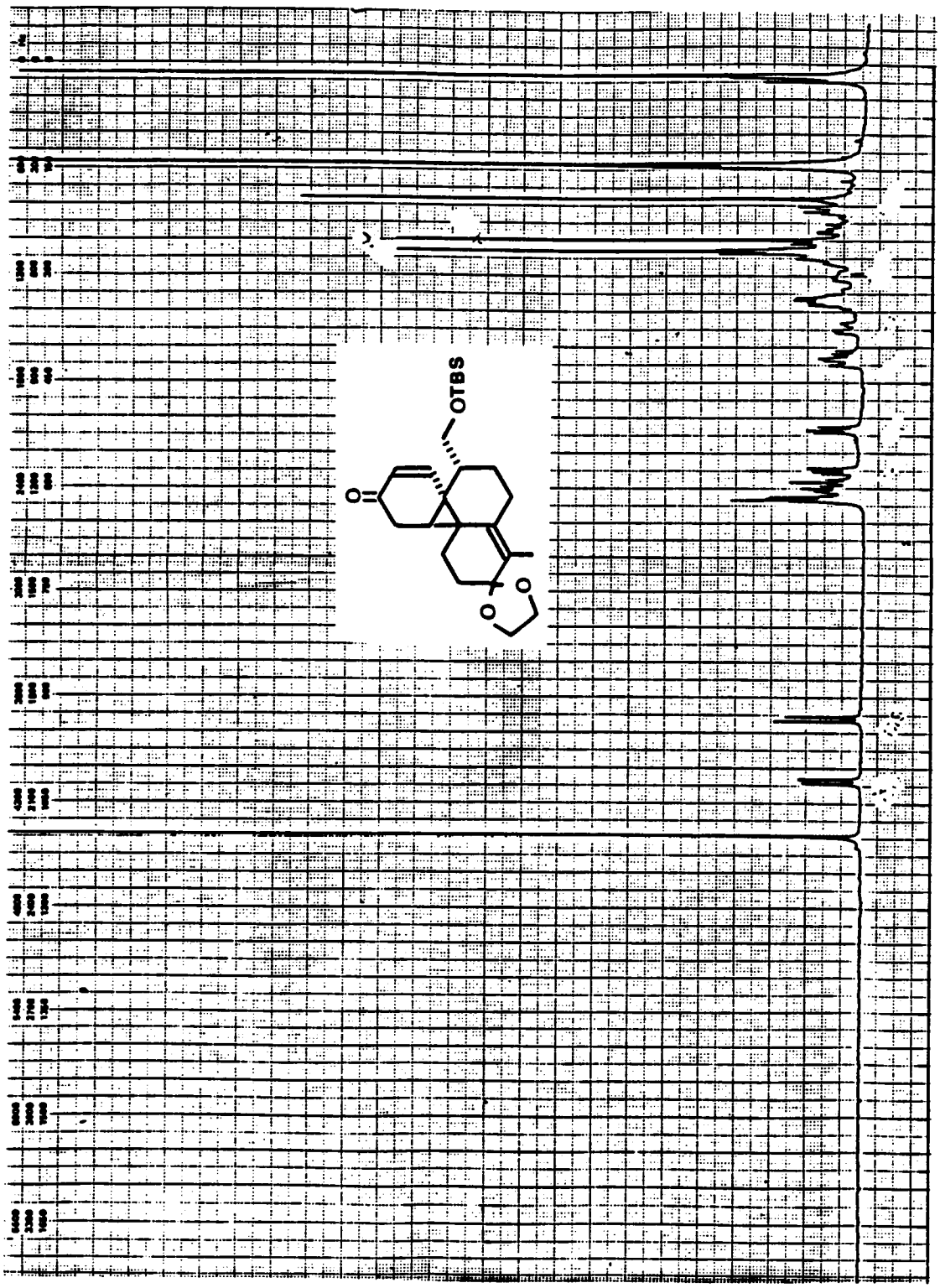
270 MHz ^{1}H NMR spectrum of aldehyde 157



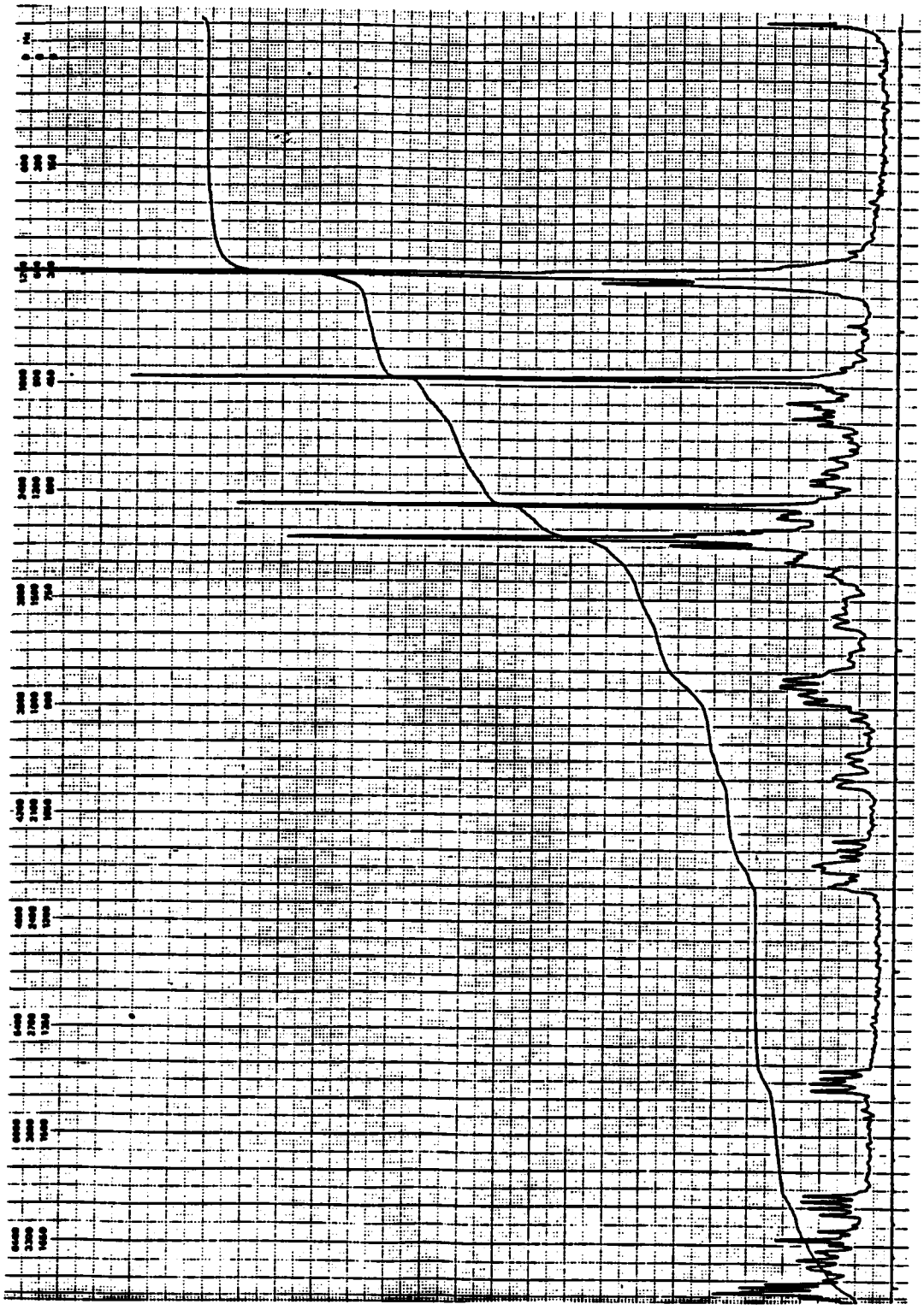
expanded 270 MHz ^{1}H NMR spectrum of aldehyde 157



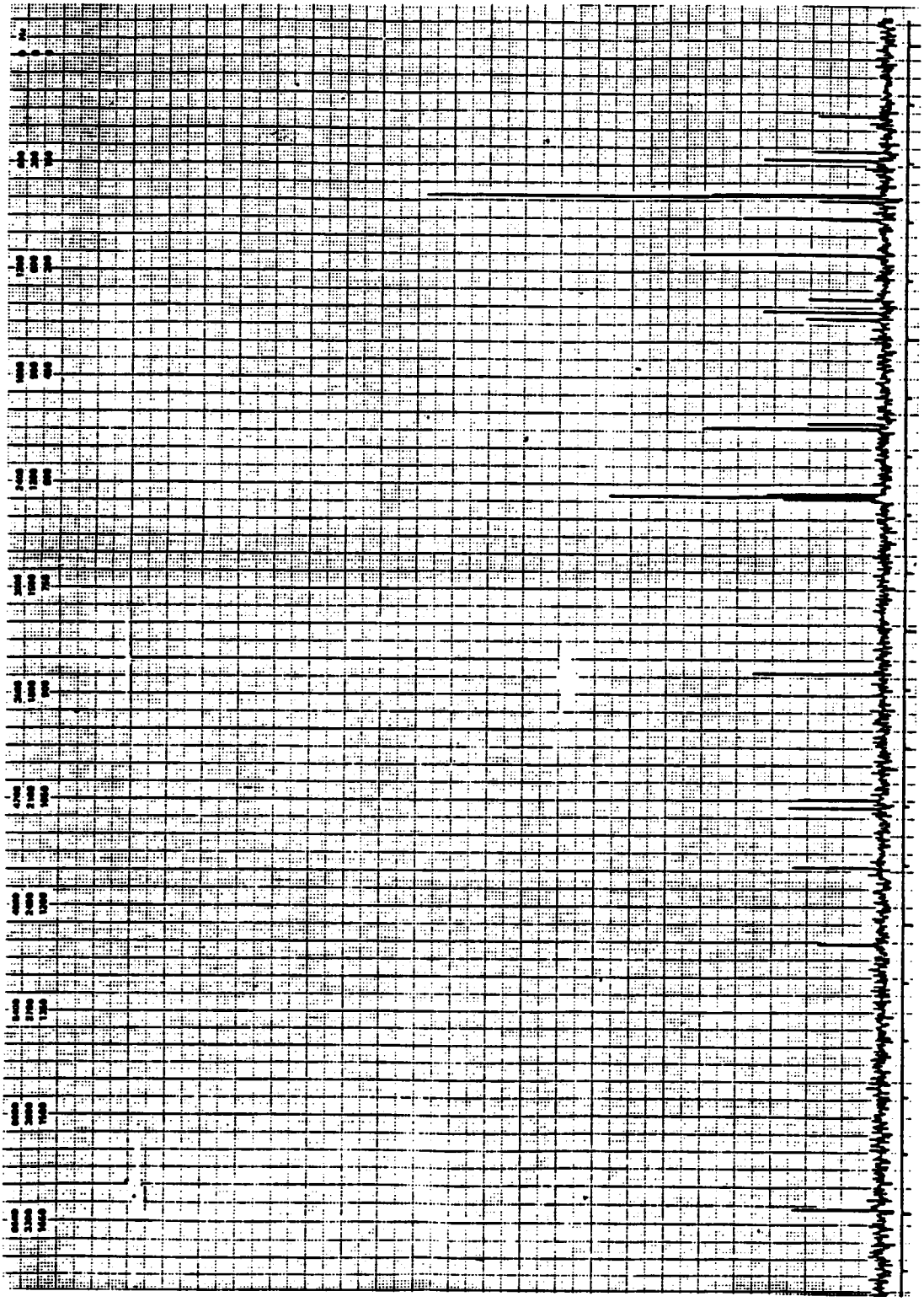
IR spectrum of aldehyde 157



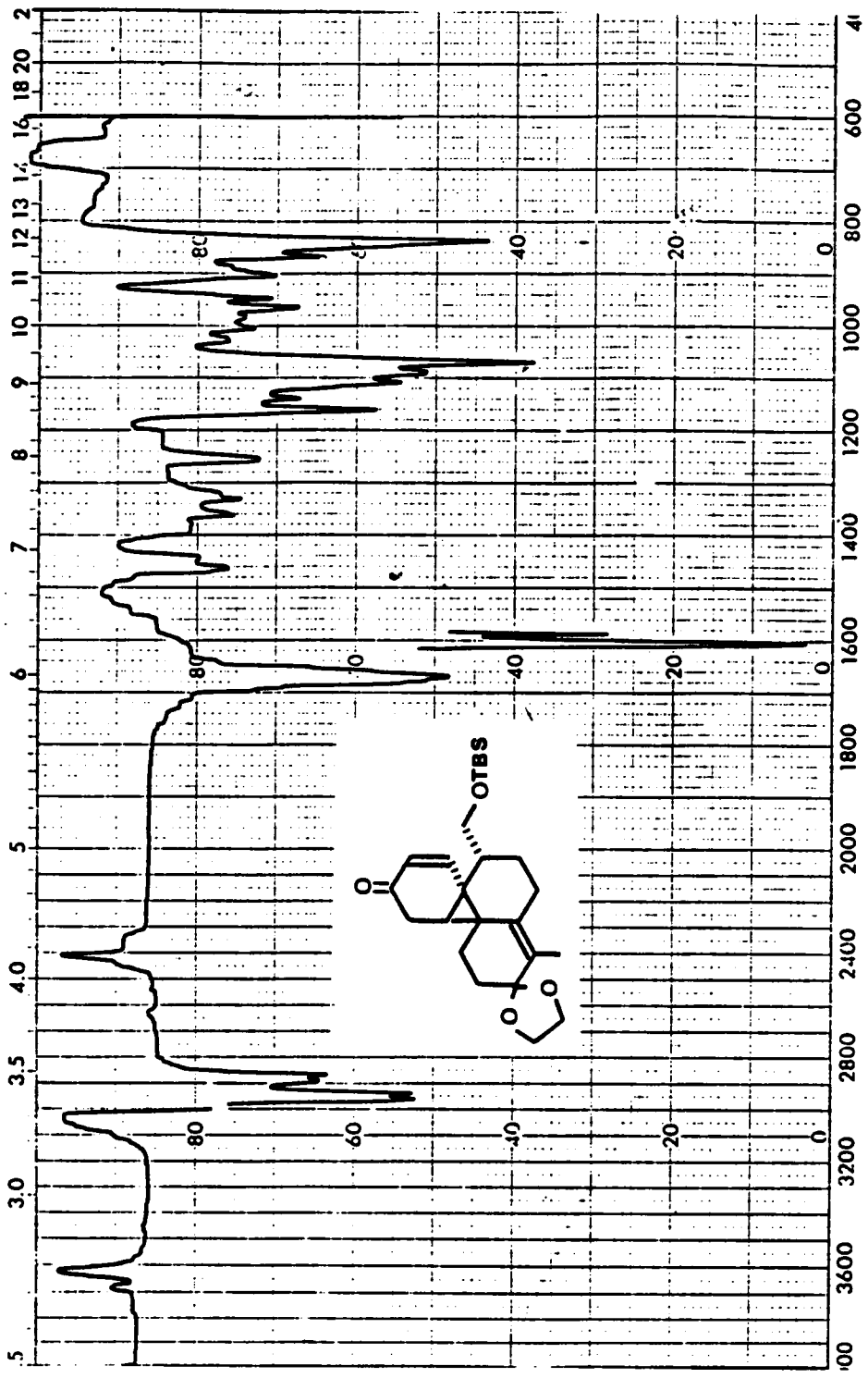
270 MHz ^{1}H NMR spectrum of spiro enone 160



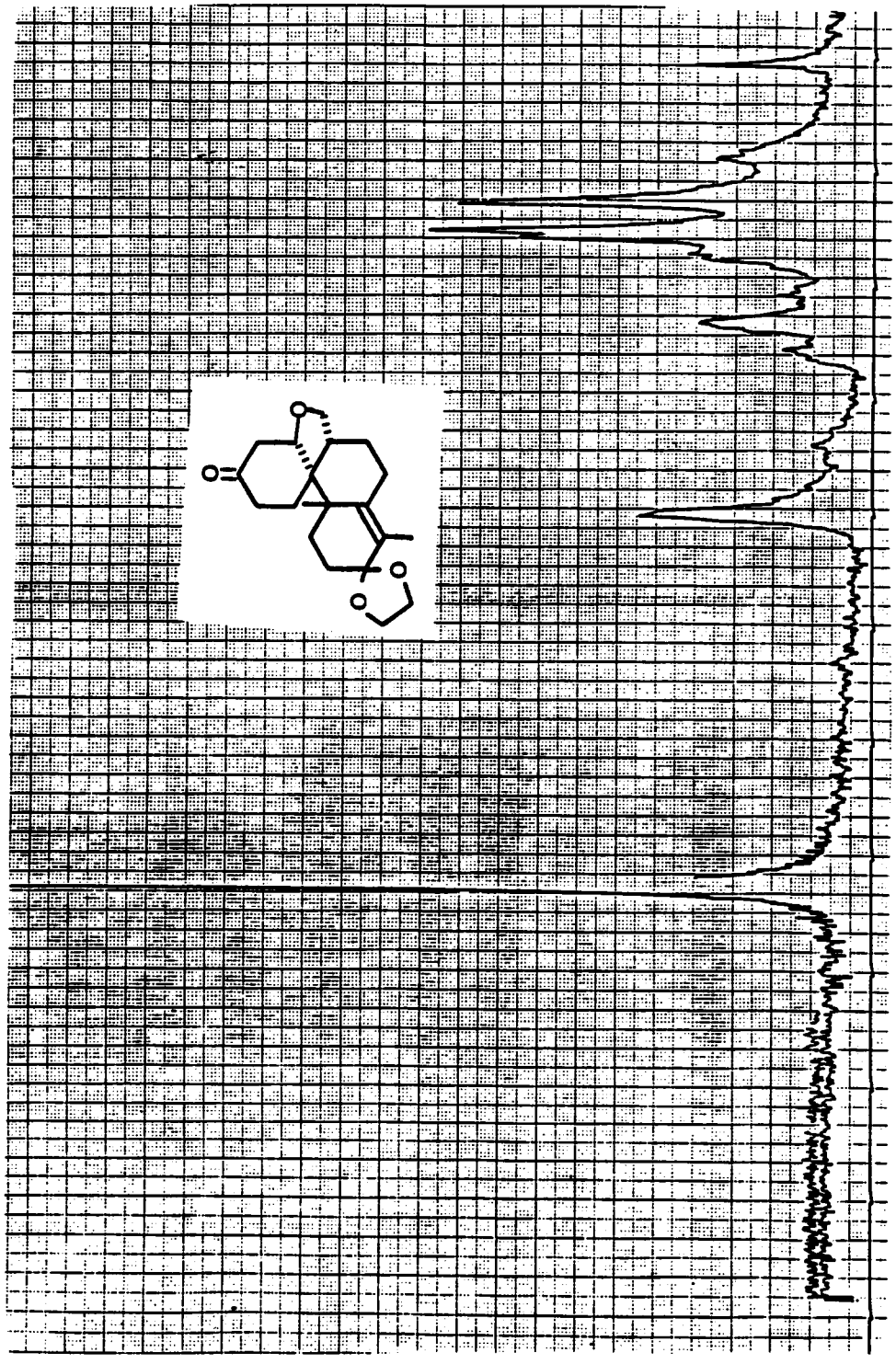
expanded 270 MHz ^{1}H NMR spectrum of spiro enone 160



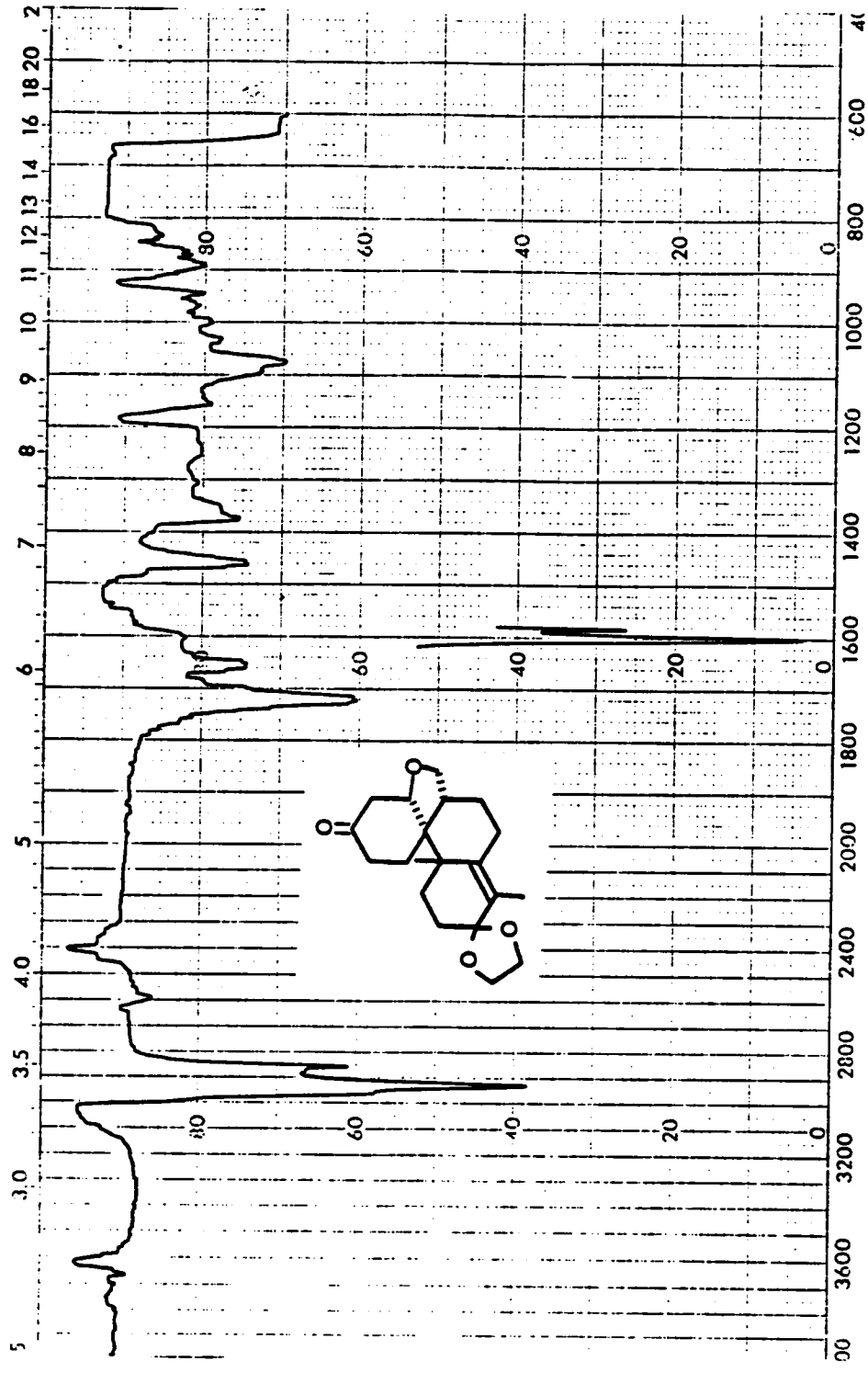
270 MHz ^{13}C NMR decoupled spectrum of spiro enone 160



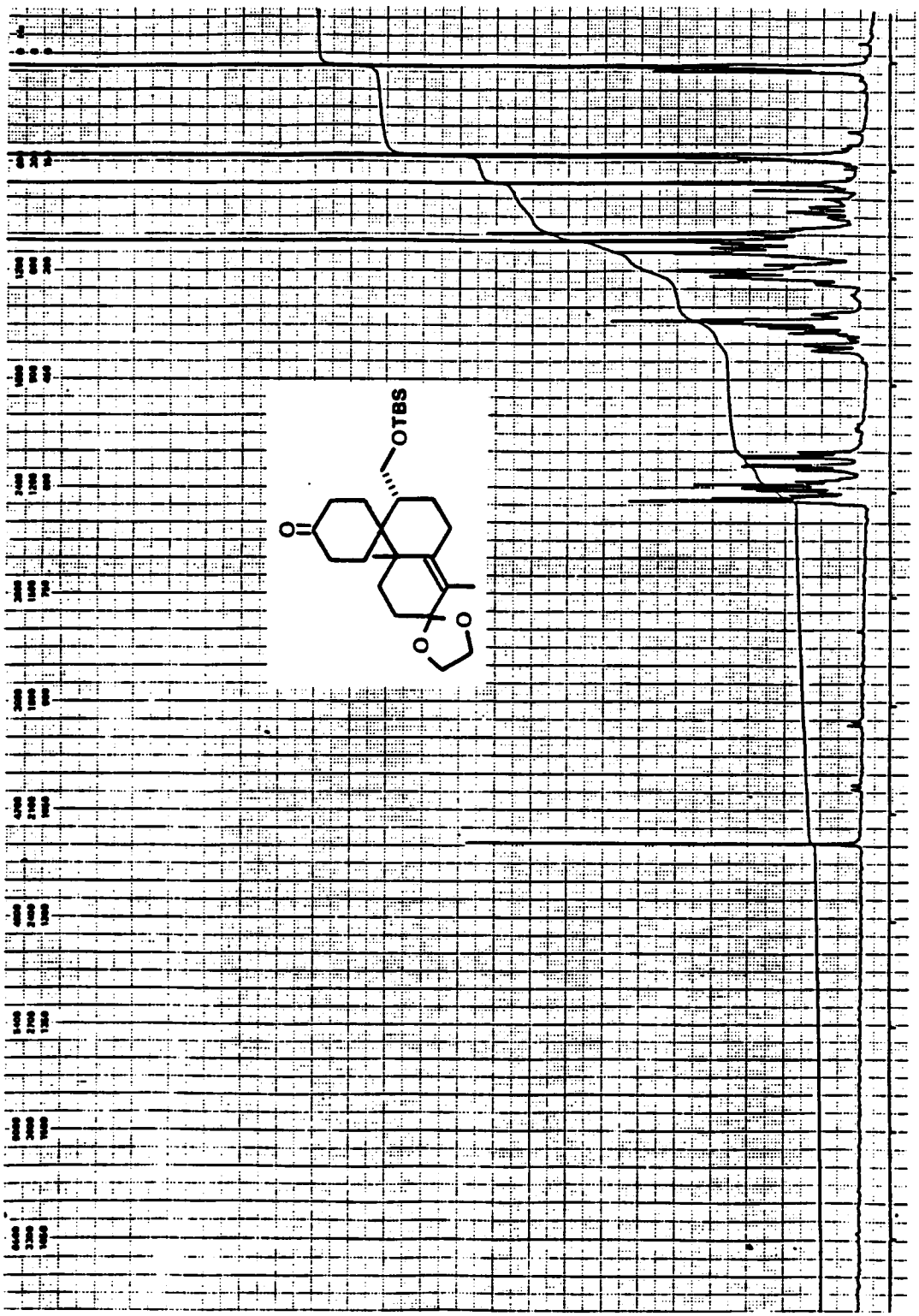
IR spectrum of spiro enone 160



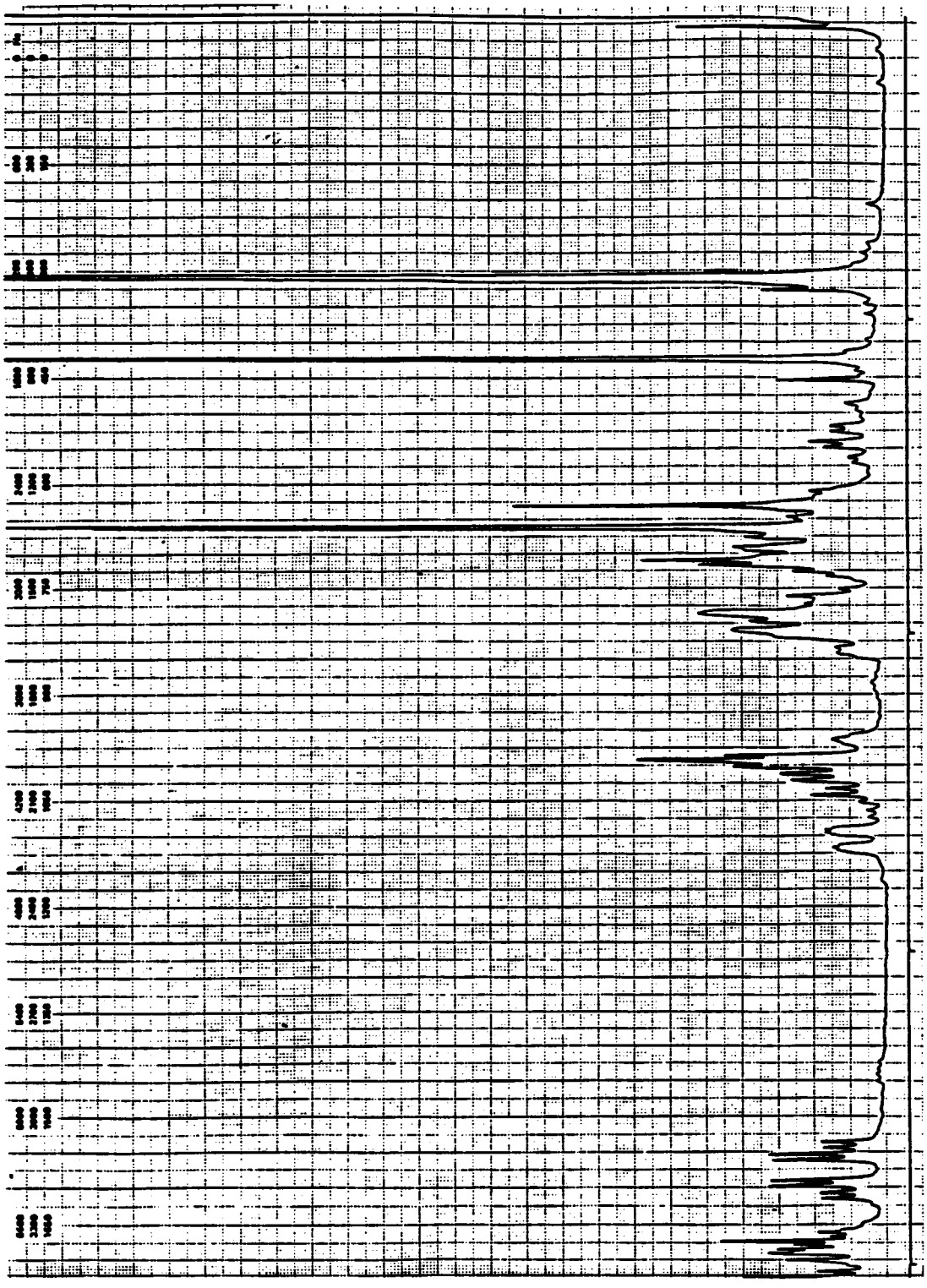
80 MHz ^{1}H NMR spectrum of furan 161



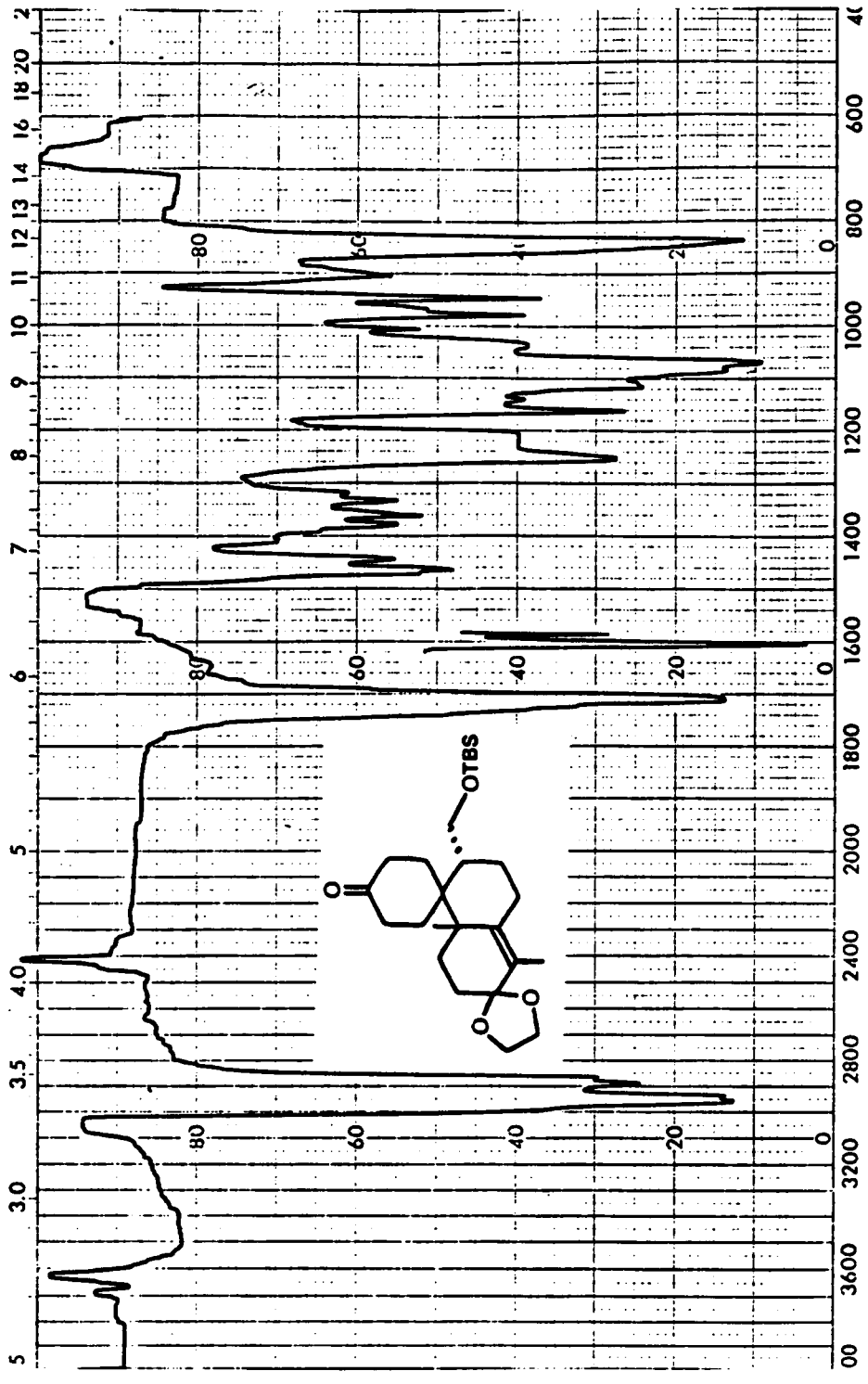
IR spectrum of furan 161



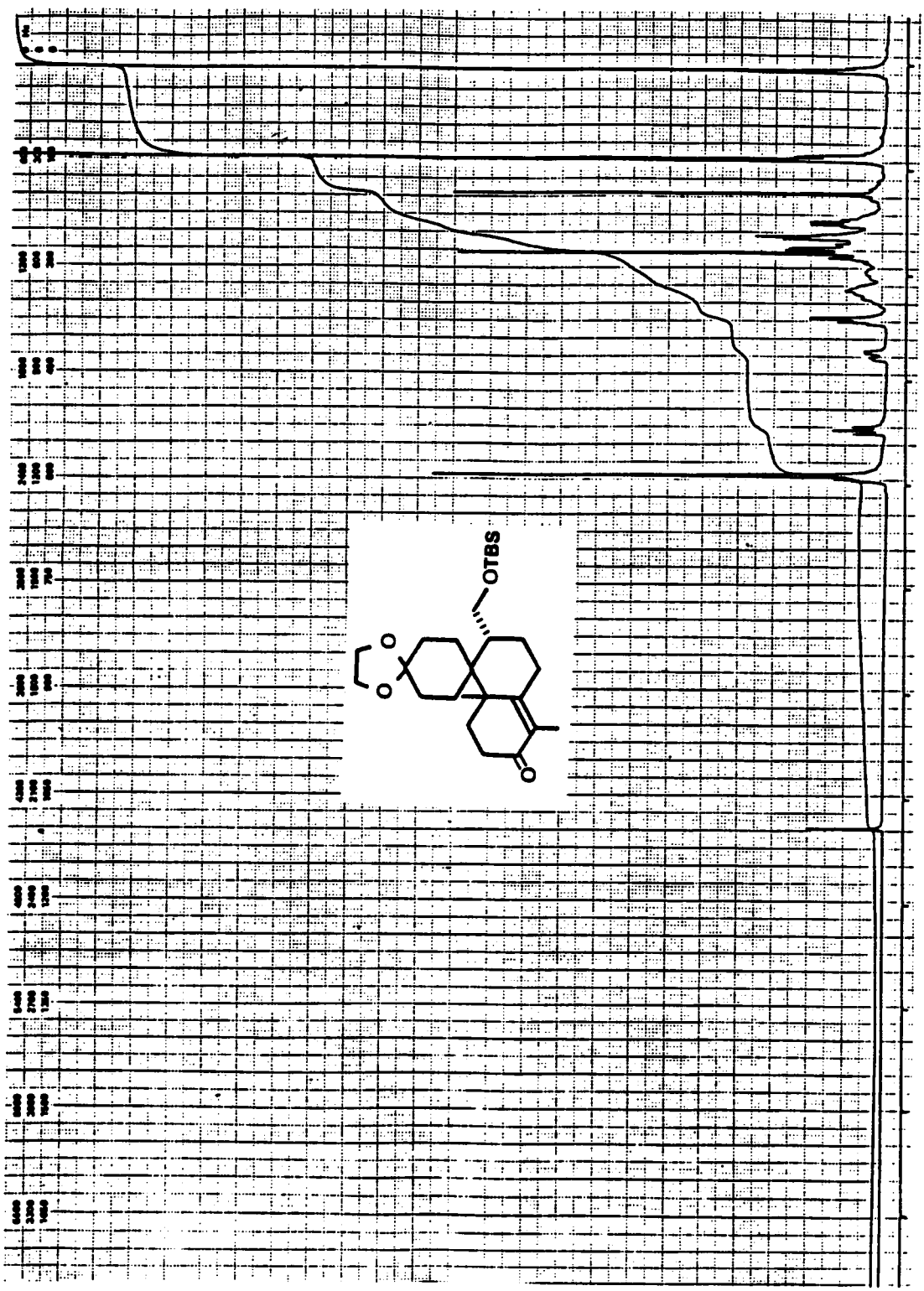
270 MHz ^{1}H NMR spectrum of ketone 162



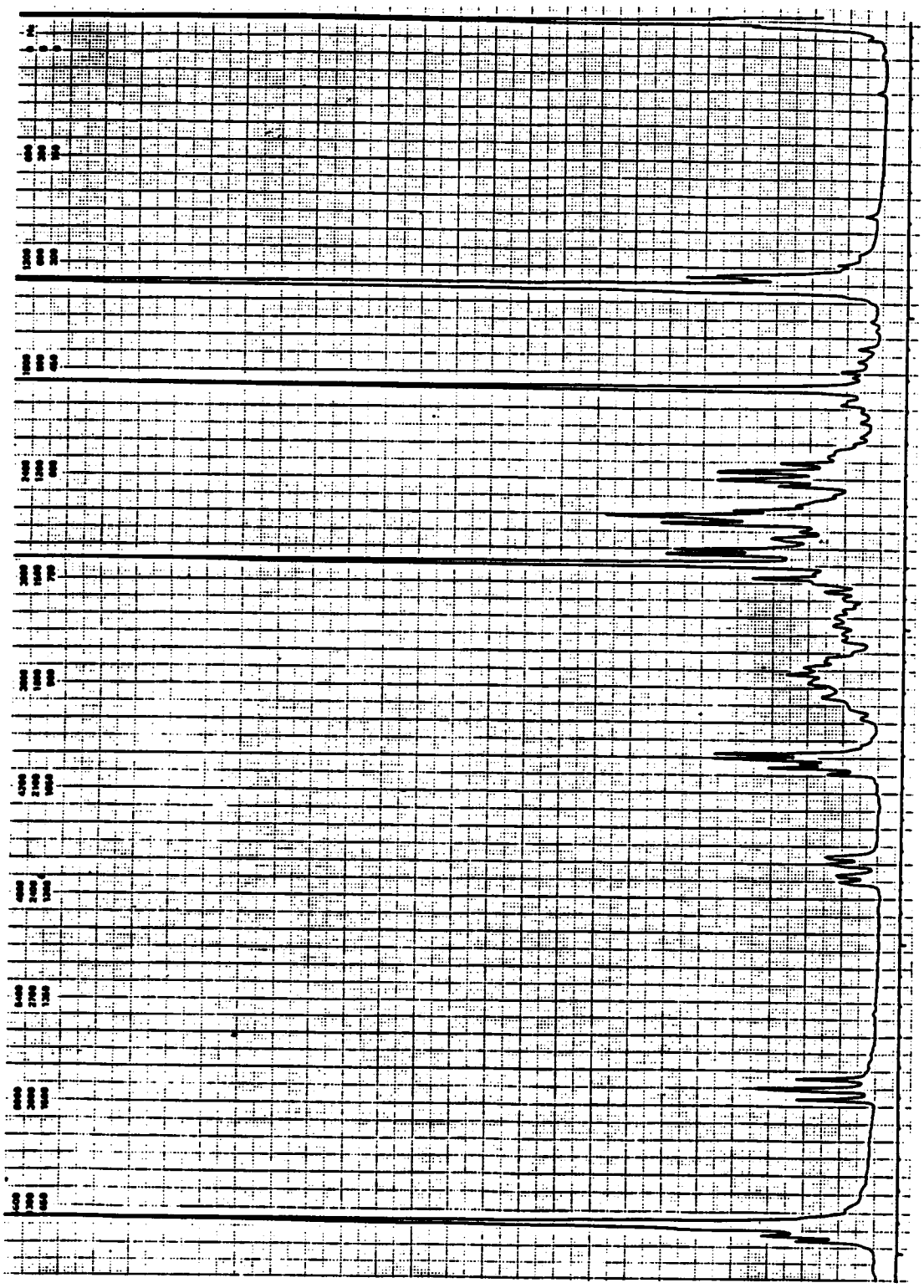
expanded 270 MHz ^{1}H NMR spectrum of ketone 162



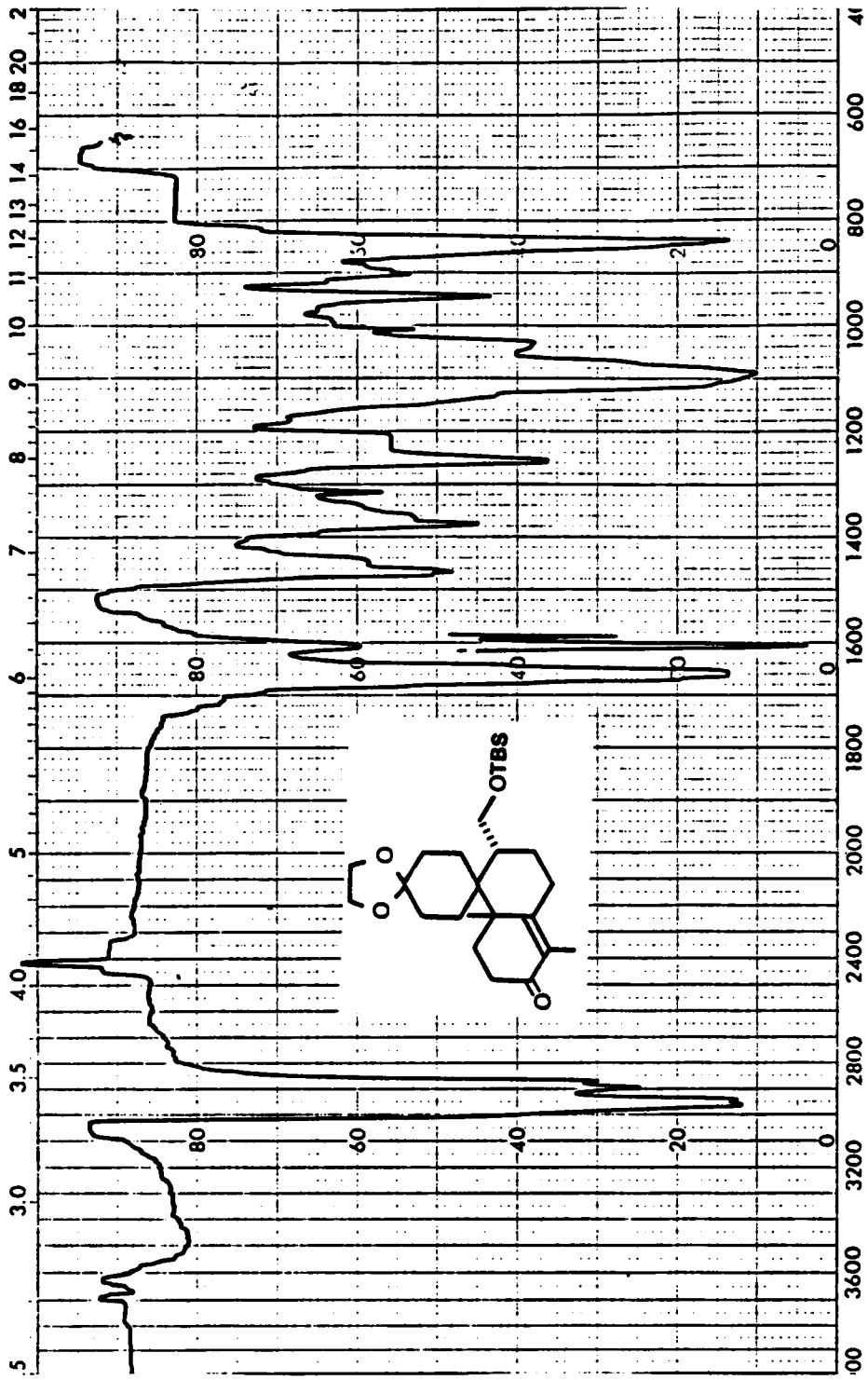
IR spectrum of ketone 162



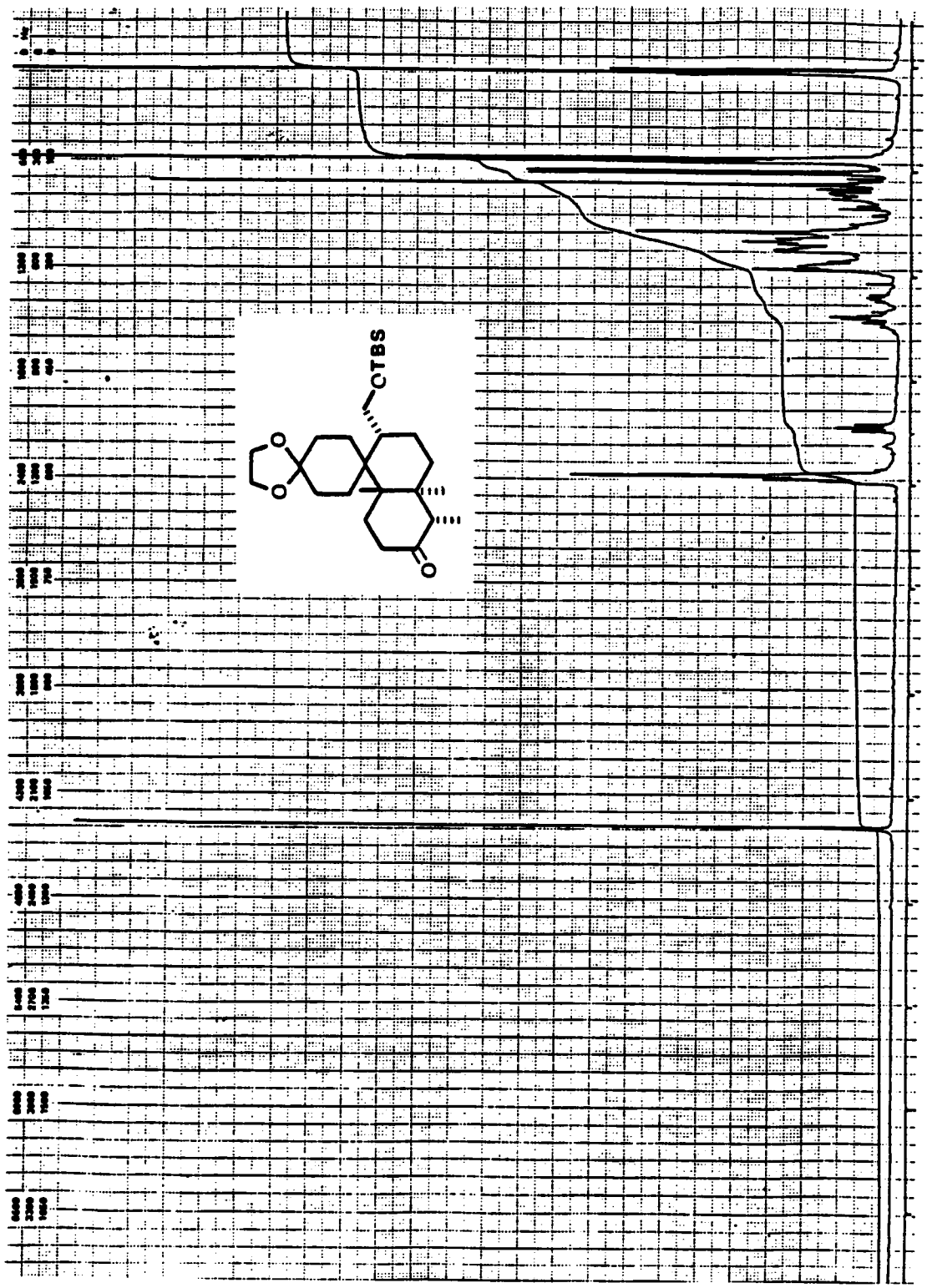
270 MHz ^{1}H NMR spectrum of enone 163



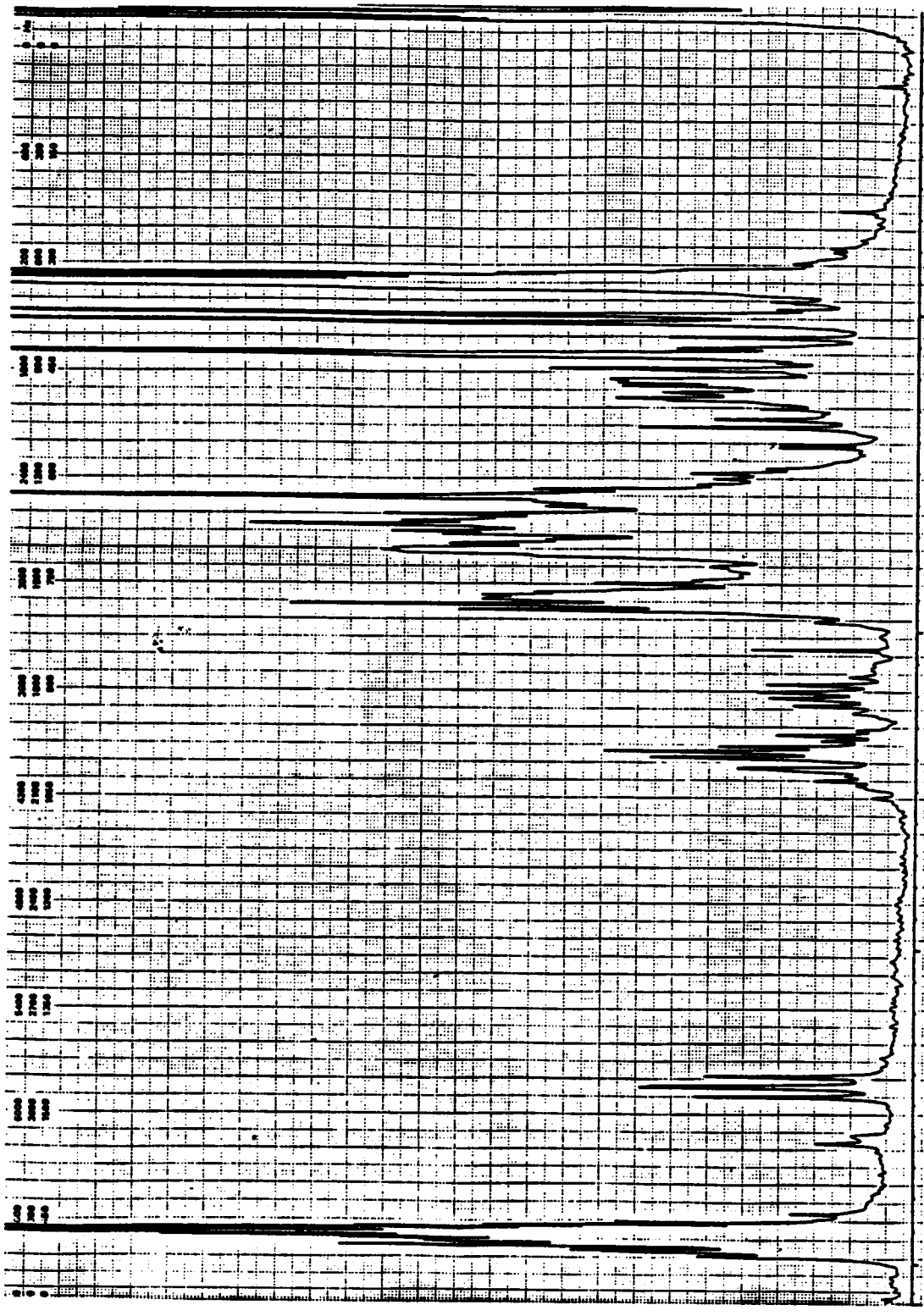
expanded 270 MHz ^{1}H NMR spectrum of enone 163



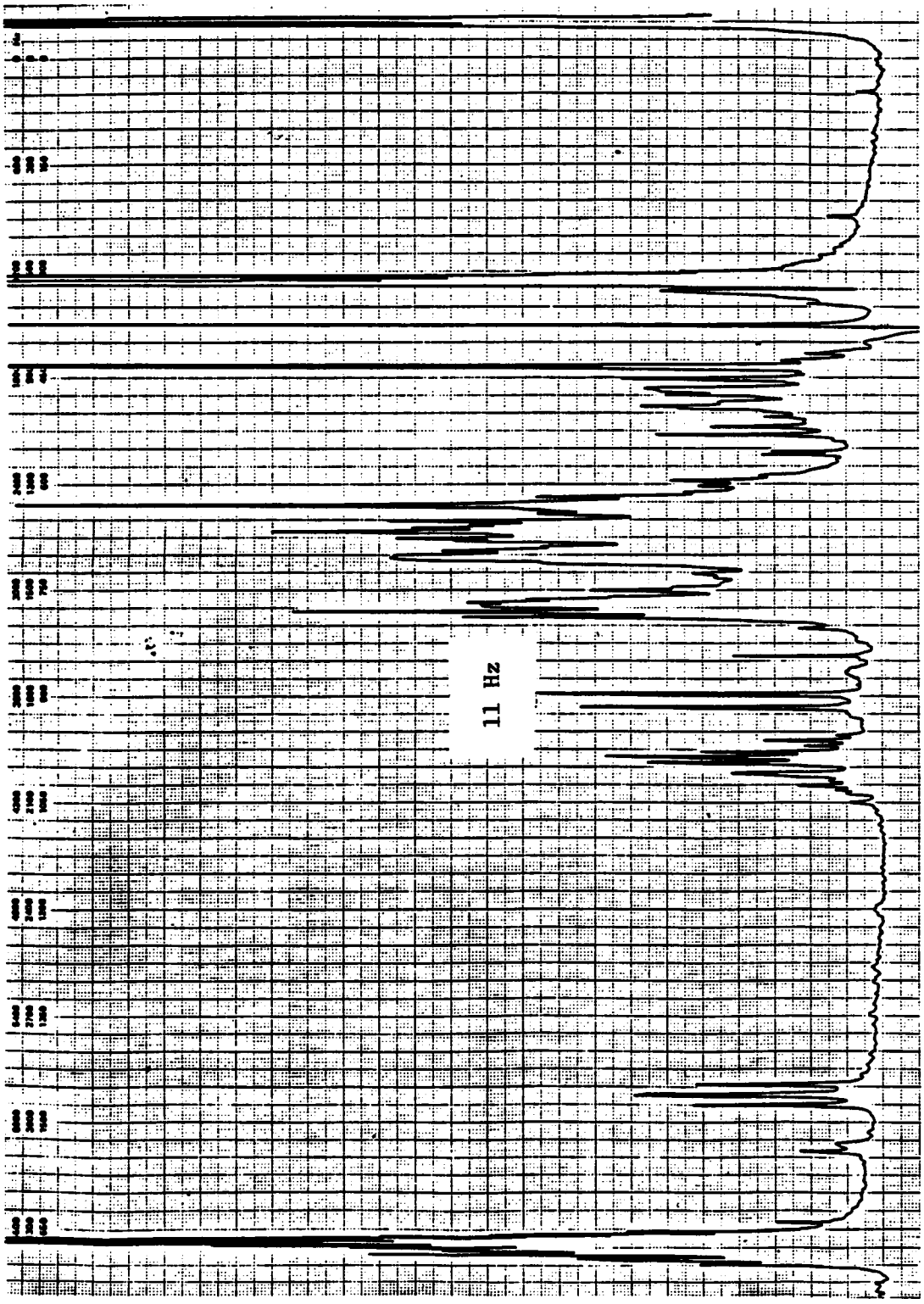
IR spectrum of enone 163



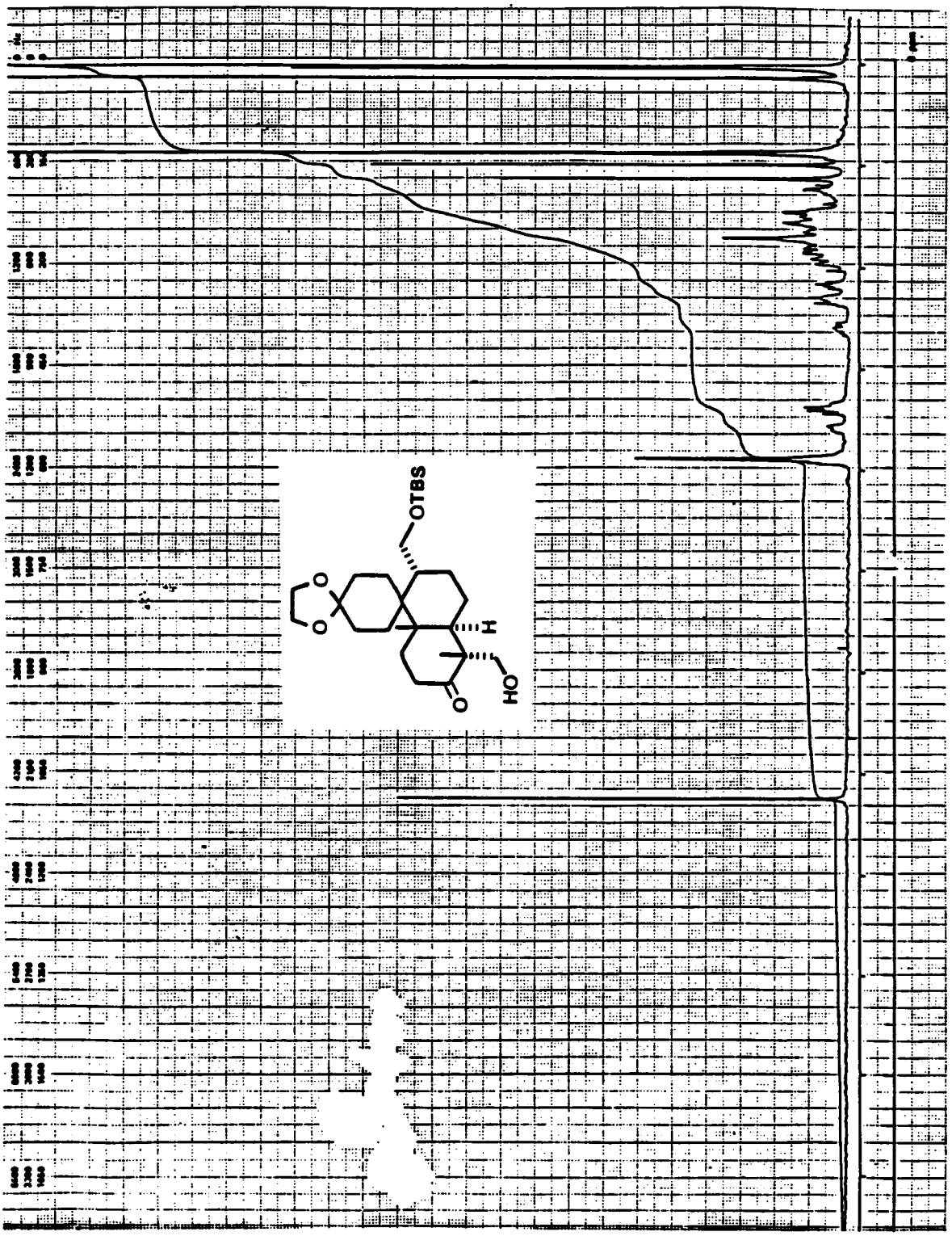
270 MHz ^{1}H NMR spectrum of ketone 164



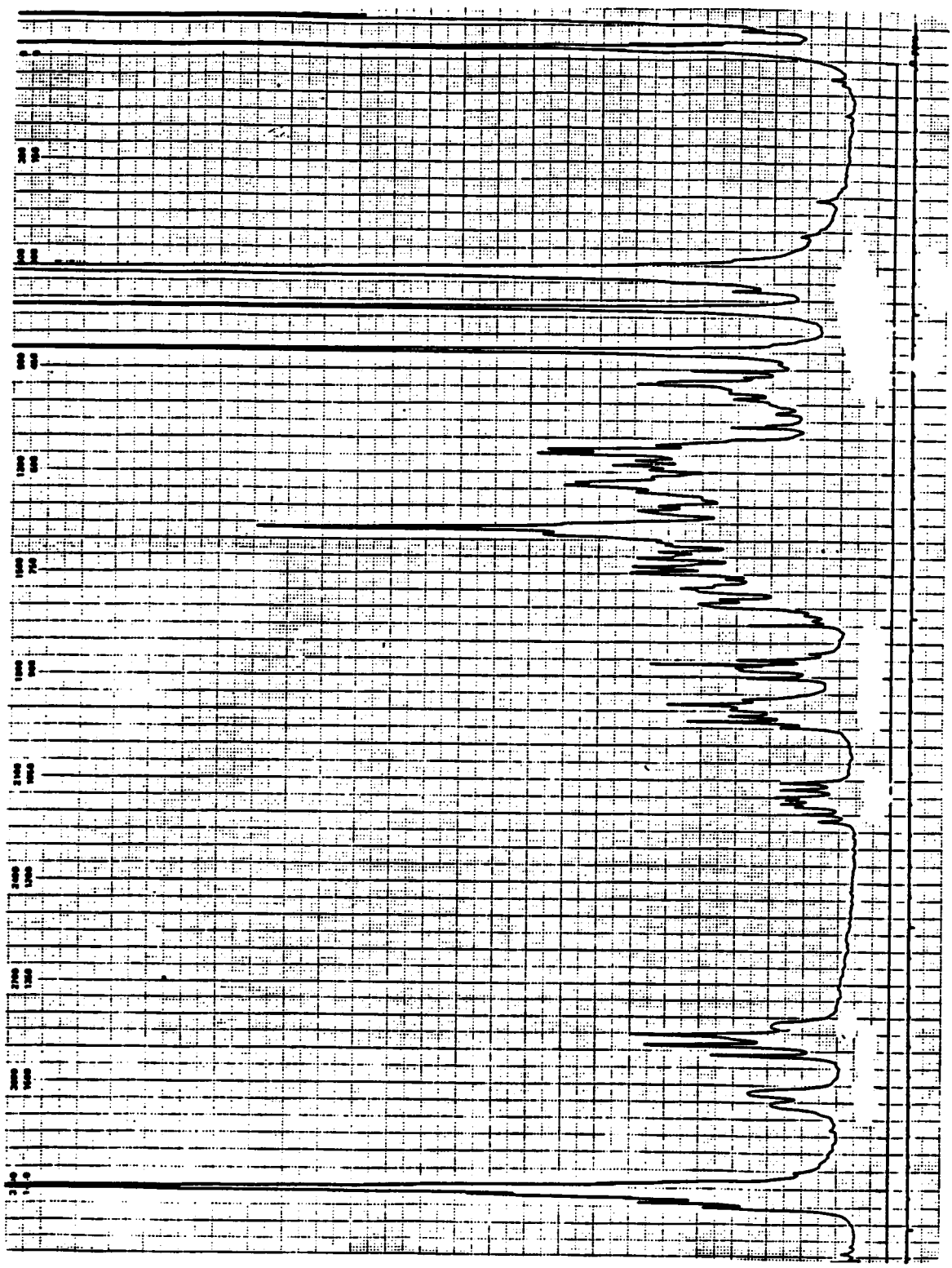
expanded 270 MHz ^{1}H NMR spectrum of ketone 164



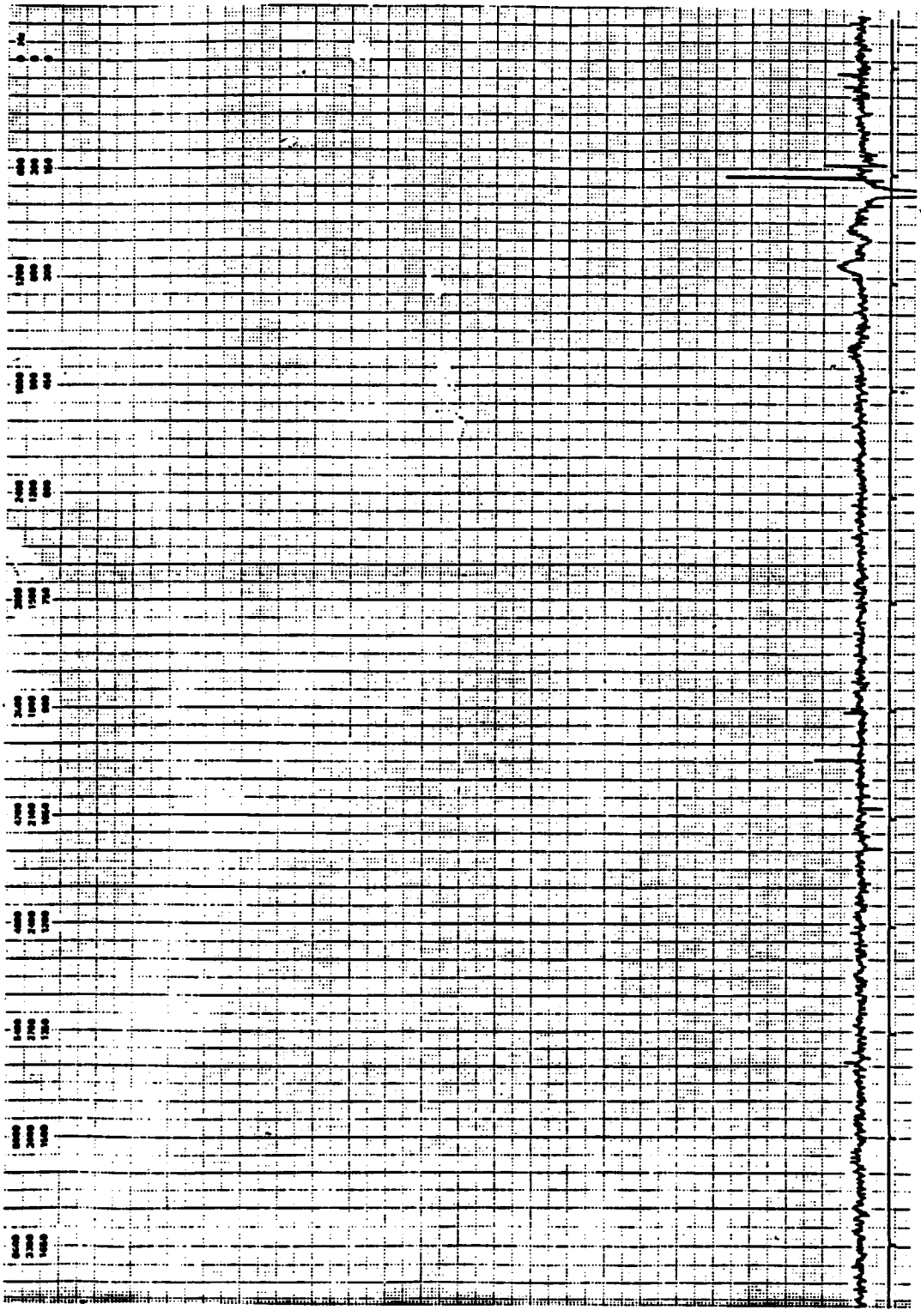
270 MHz ^{1}H NMR spectrum of ketone 164; irradiation of C-4 methyl group



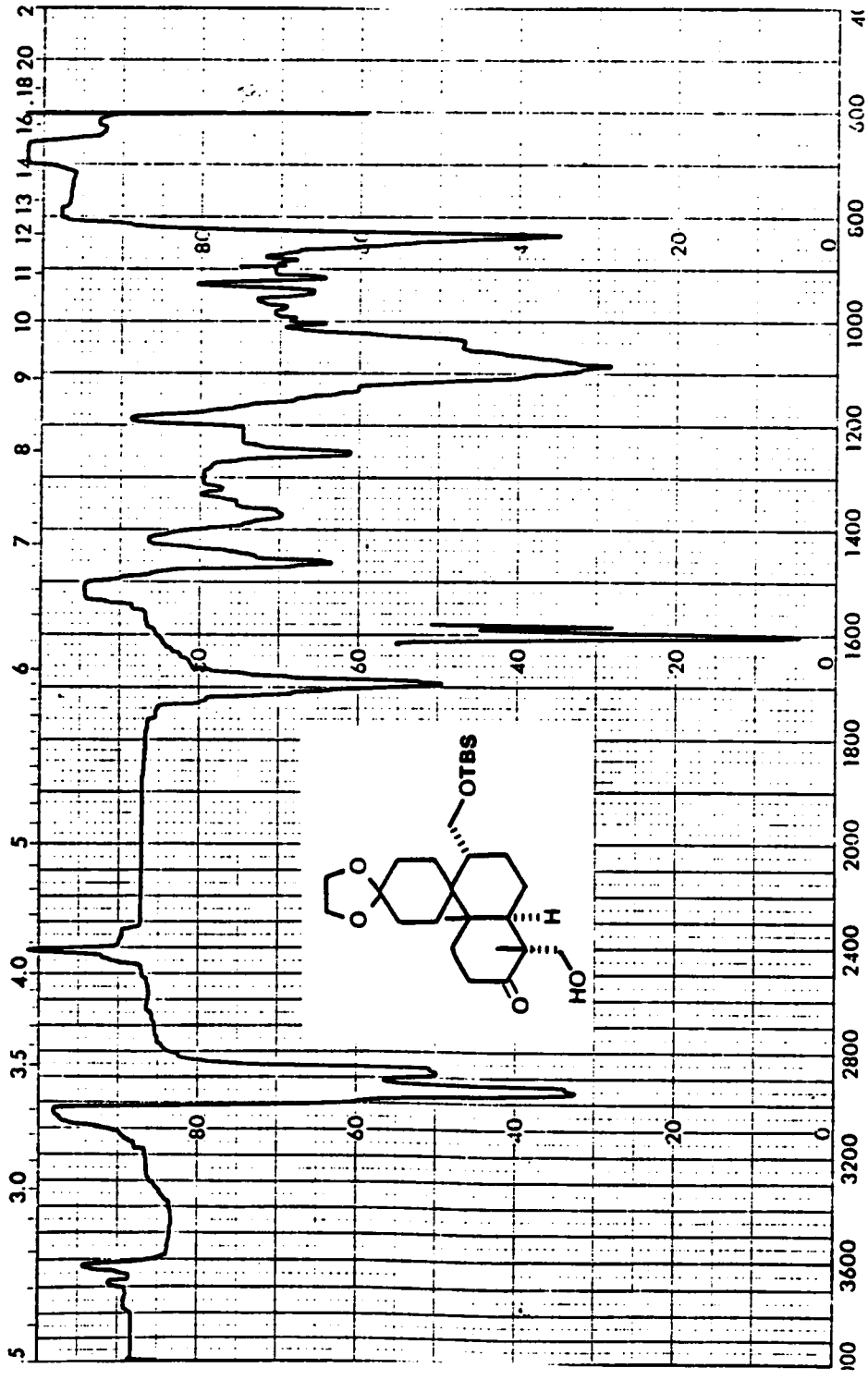
270 MHz ^{1}H NMR spectrum of ketone 165



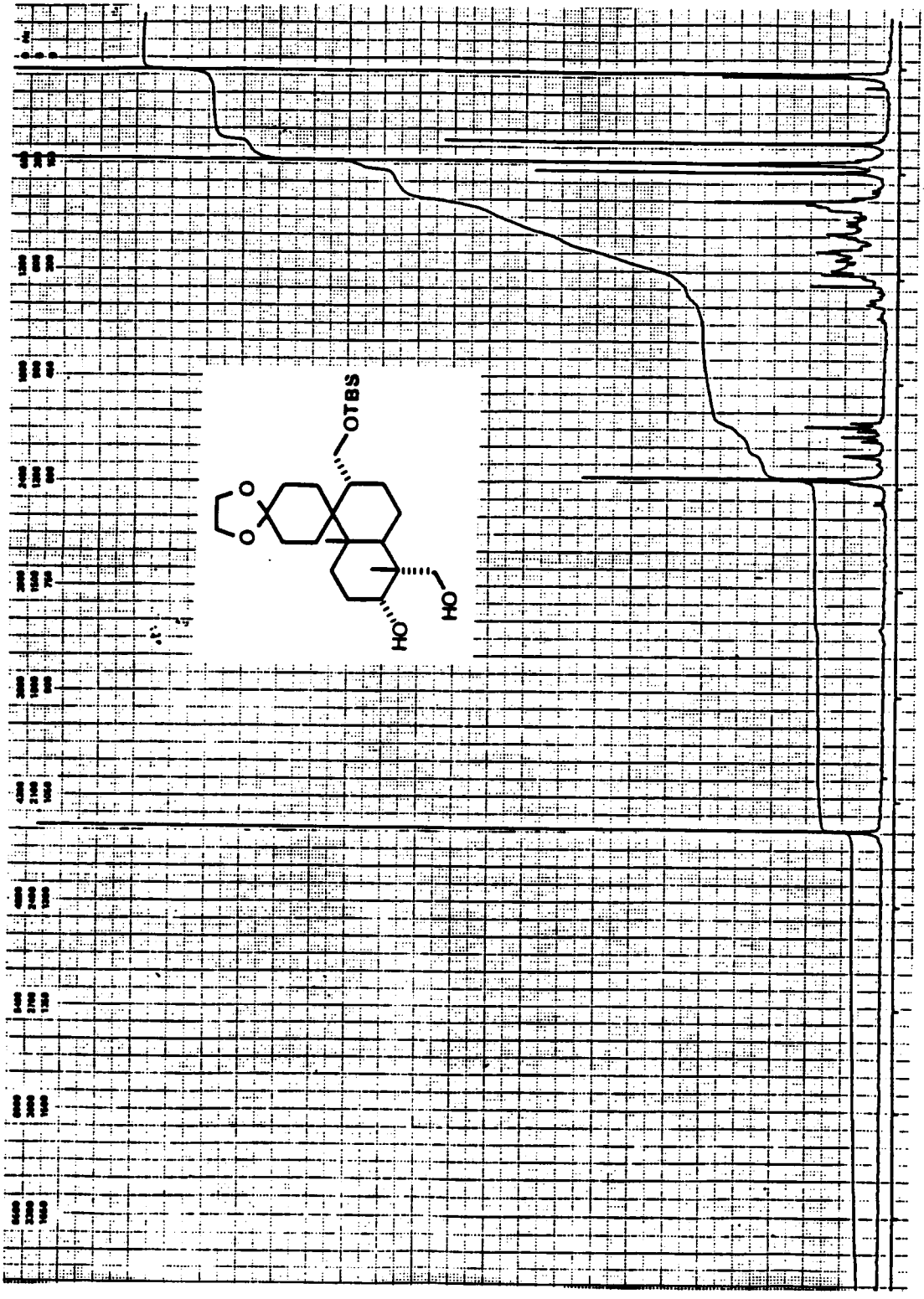
expanded 270 MHz ^{1}H NMR spectrum of ketone 165



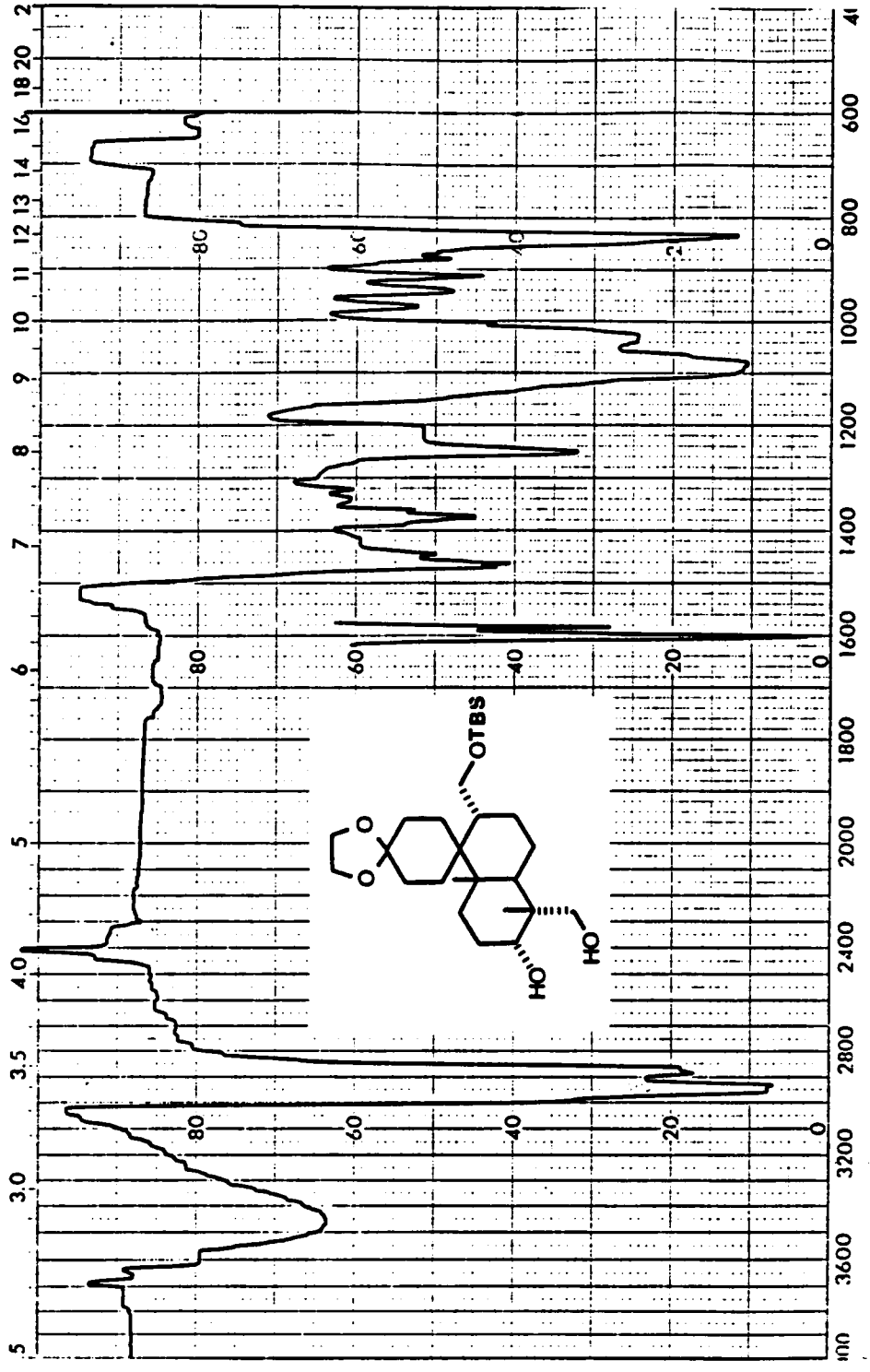
270 MHz ^{1}H NOE difference spectrum of ketone 165; irradiation of C-10 methyl group



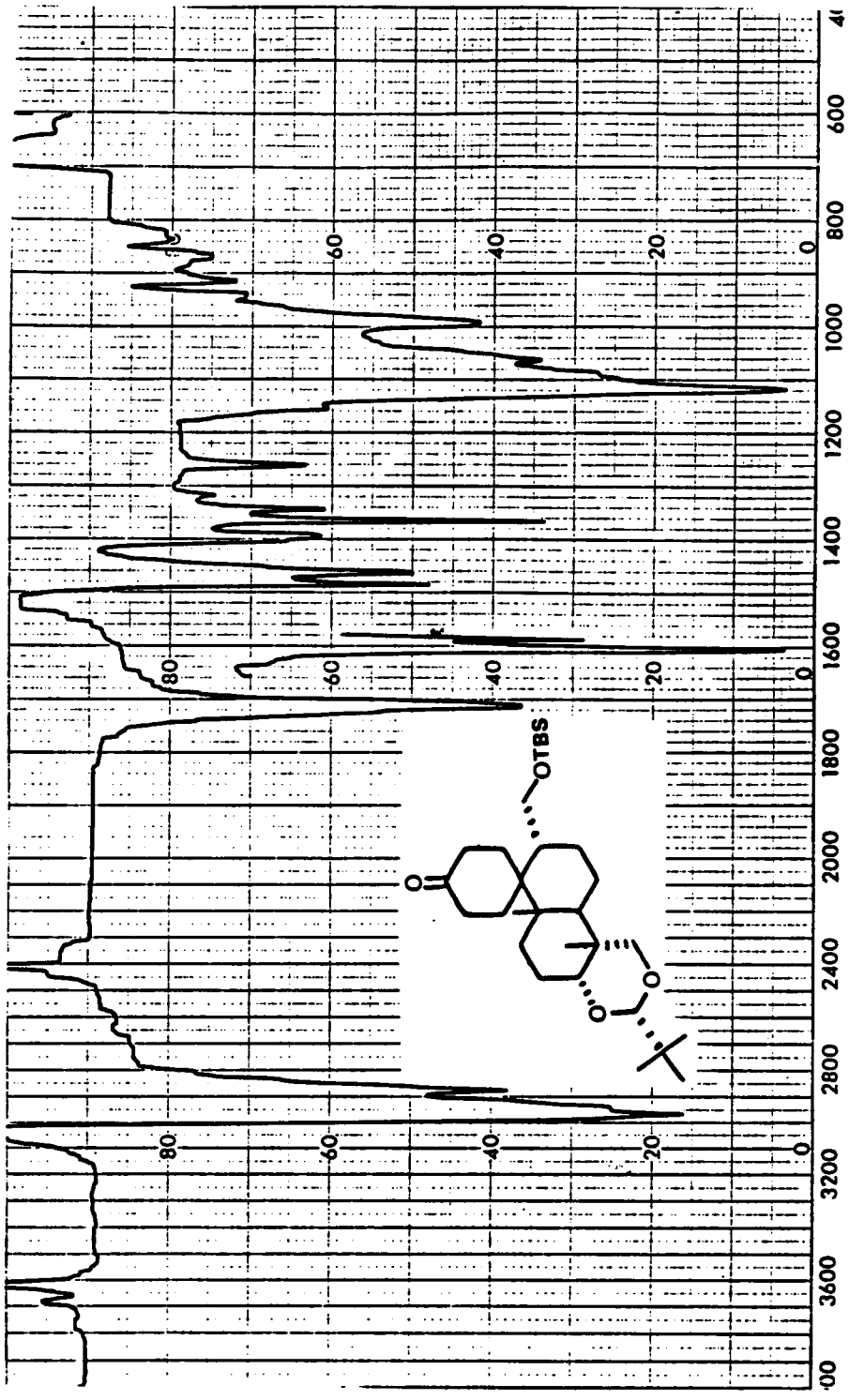
IR spectrum of ketone 165



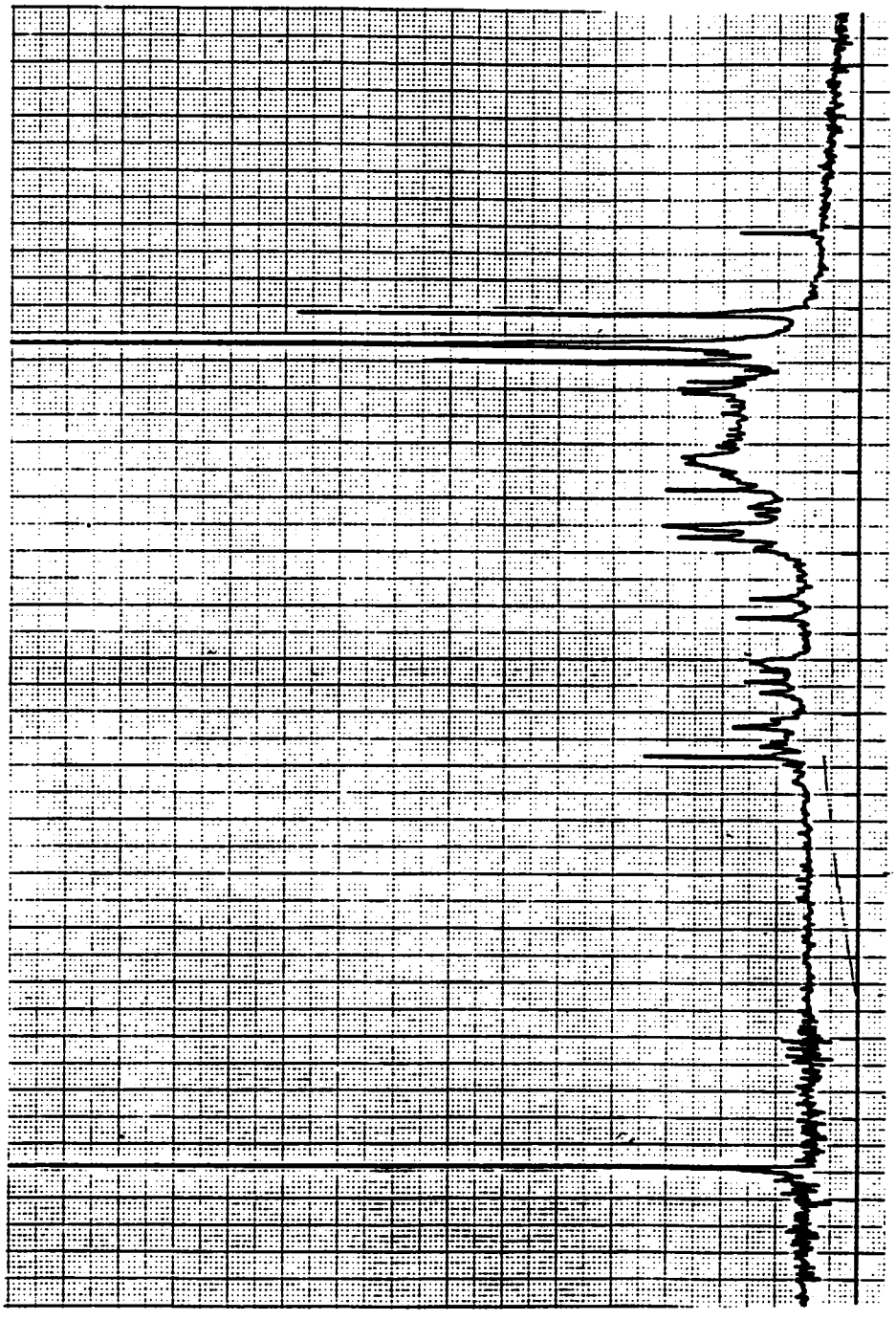
270 MHz ^{1}H NMR spectrum of diol 166



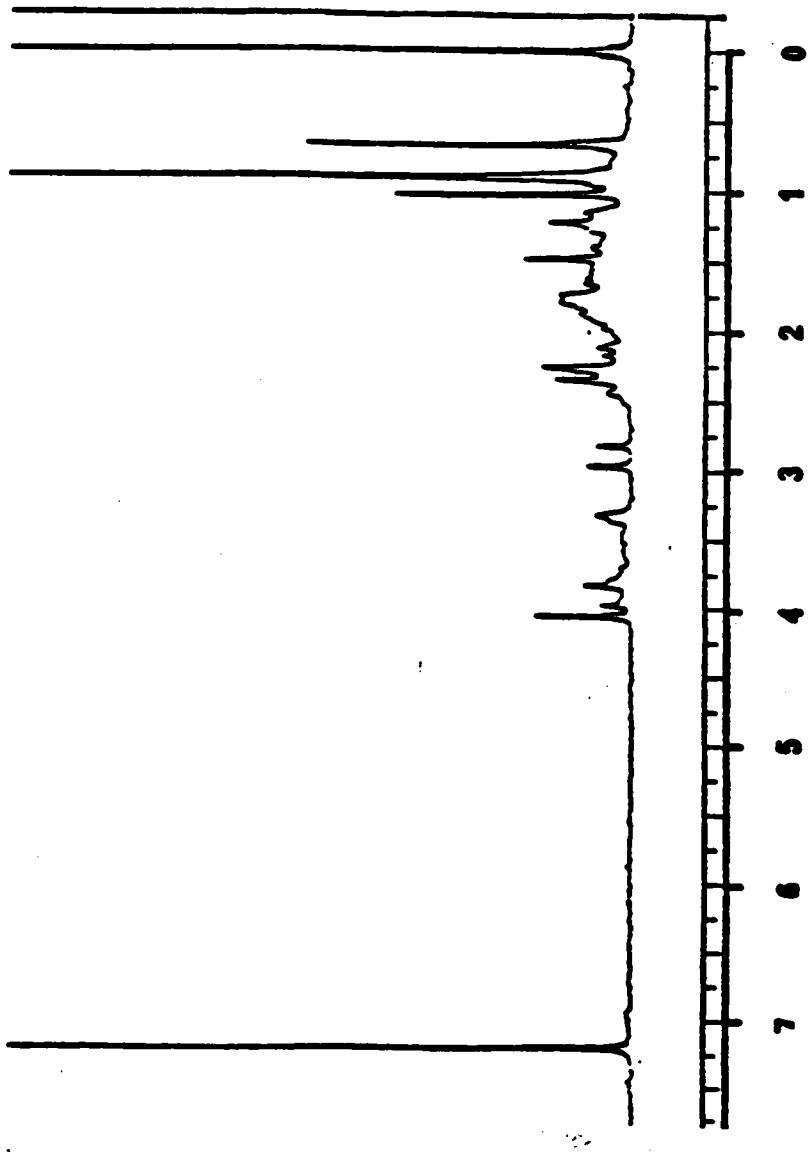
IR spectrum of diol 166



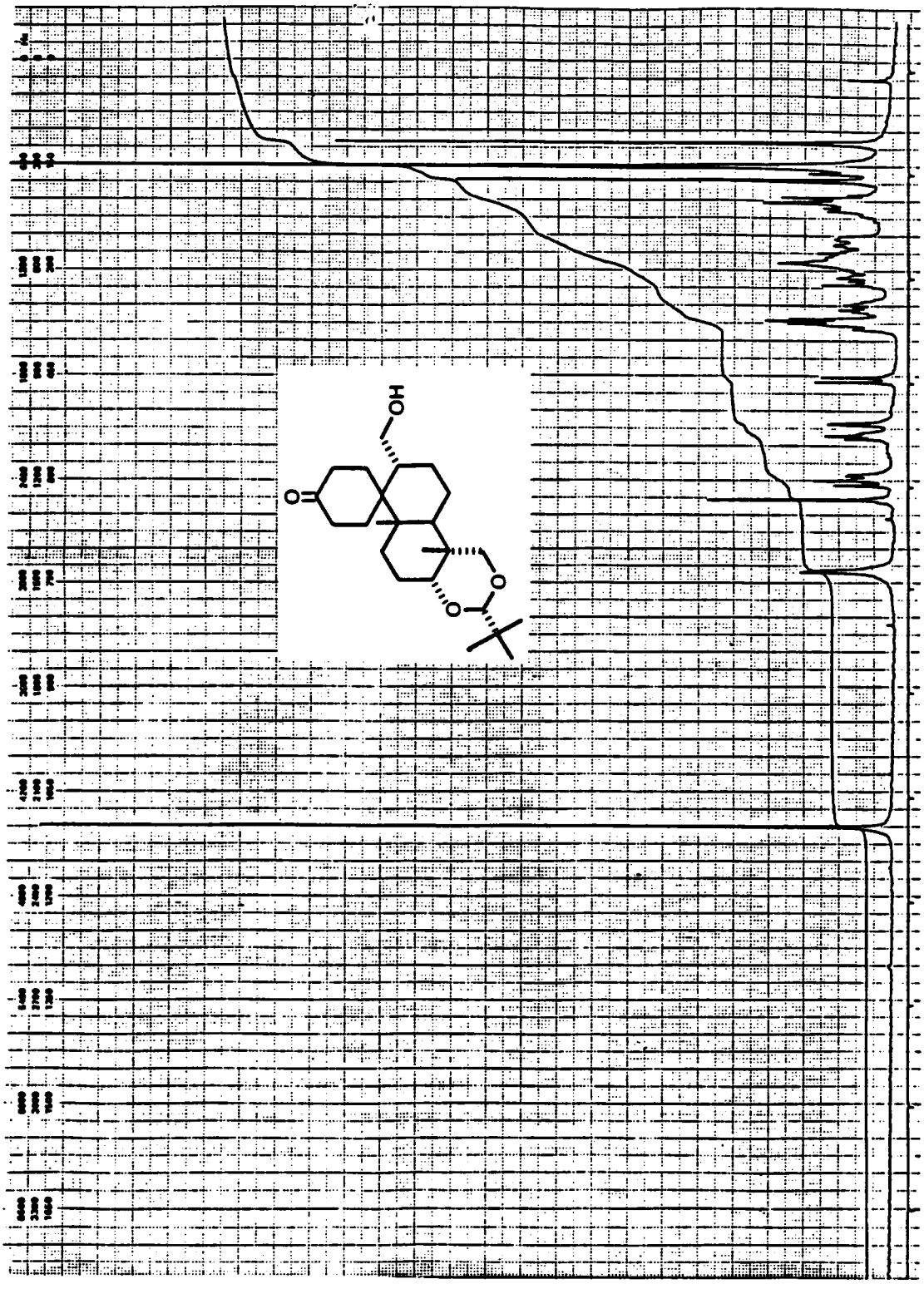
IR spectrum of ketal 167



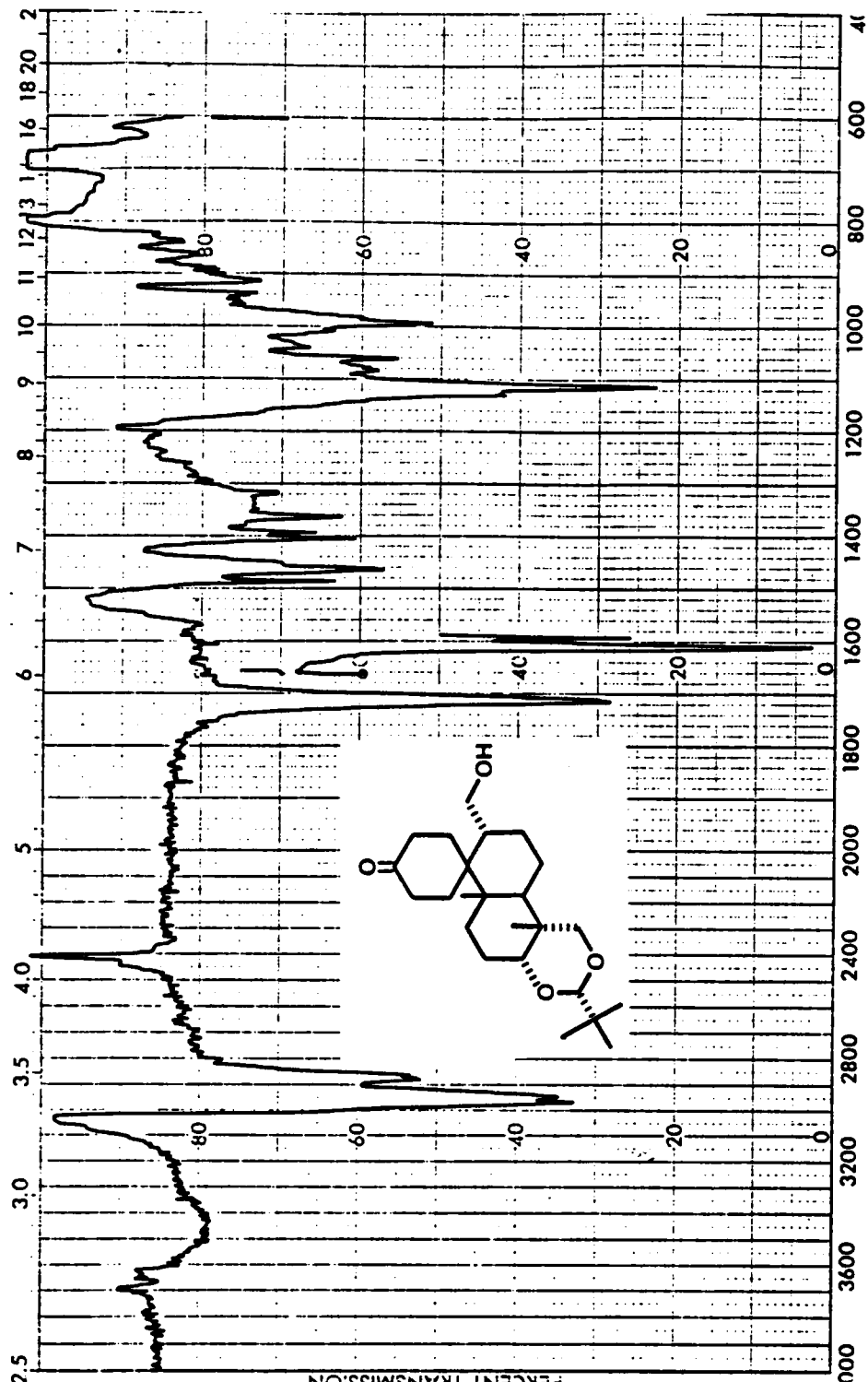
80 MHz ^{1}H NMR spectrum of synthetic alcohol 168



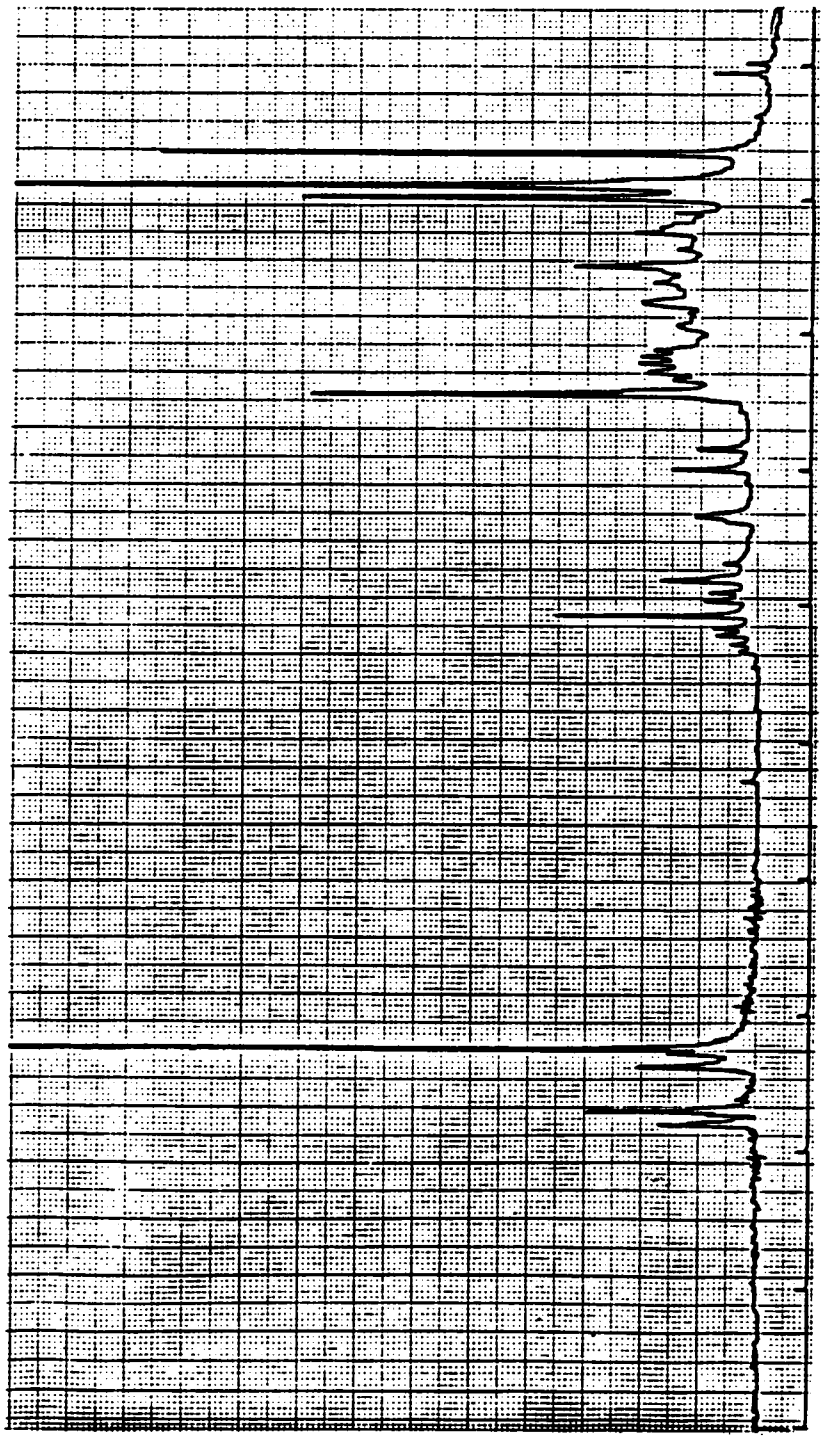
80 MHz ^{1}H NMR spectrum of authentic alcohol 168



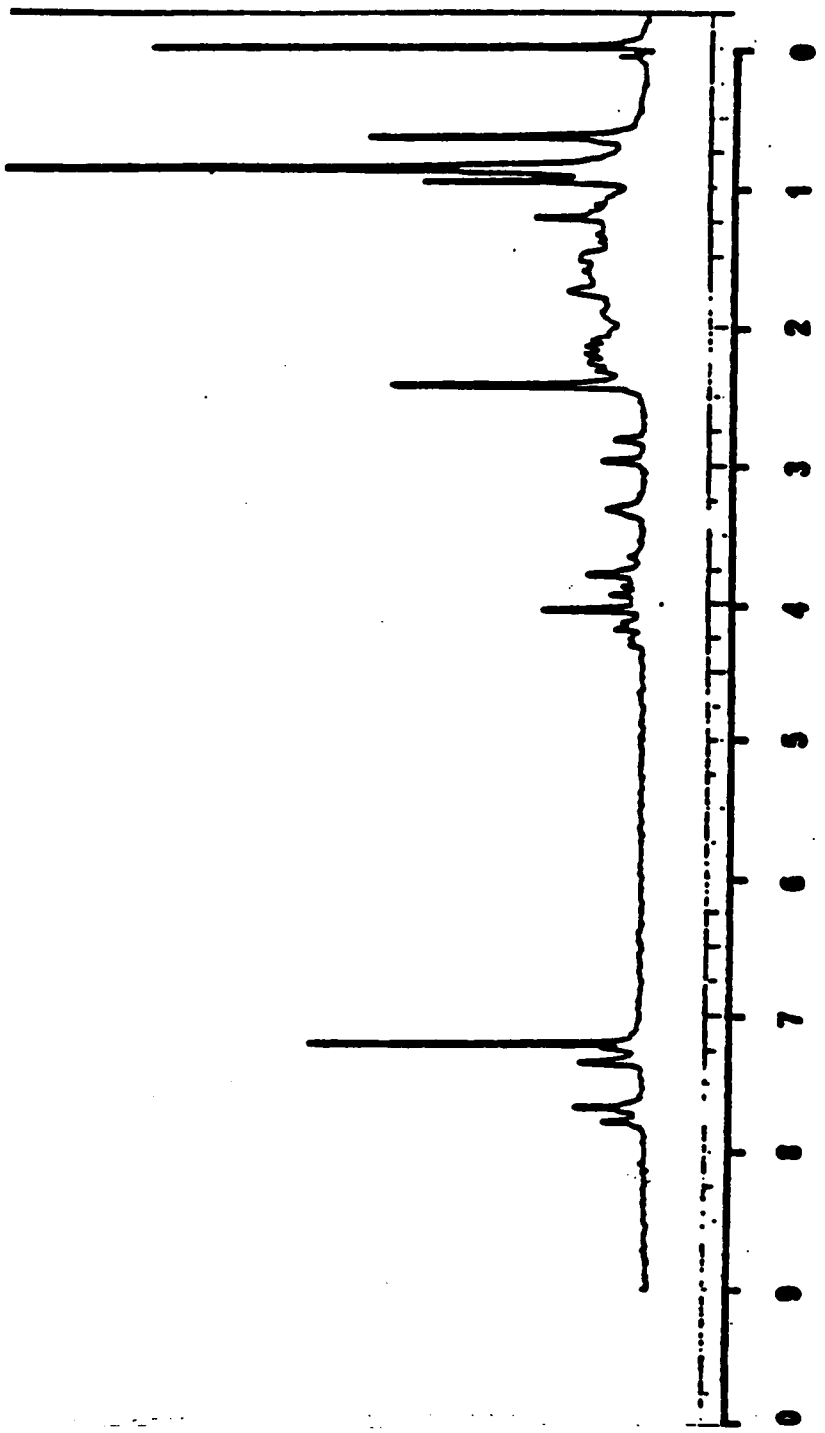
270 MHz ^{1}H NMR spectrum of synthetic alcohol 168



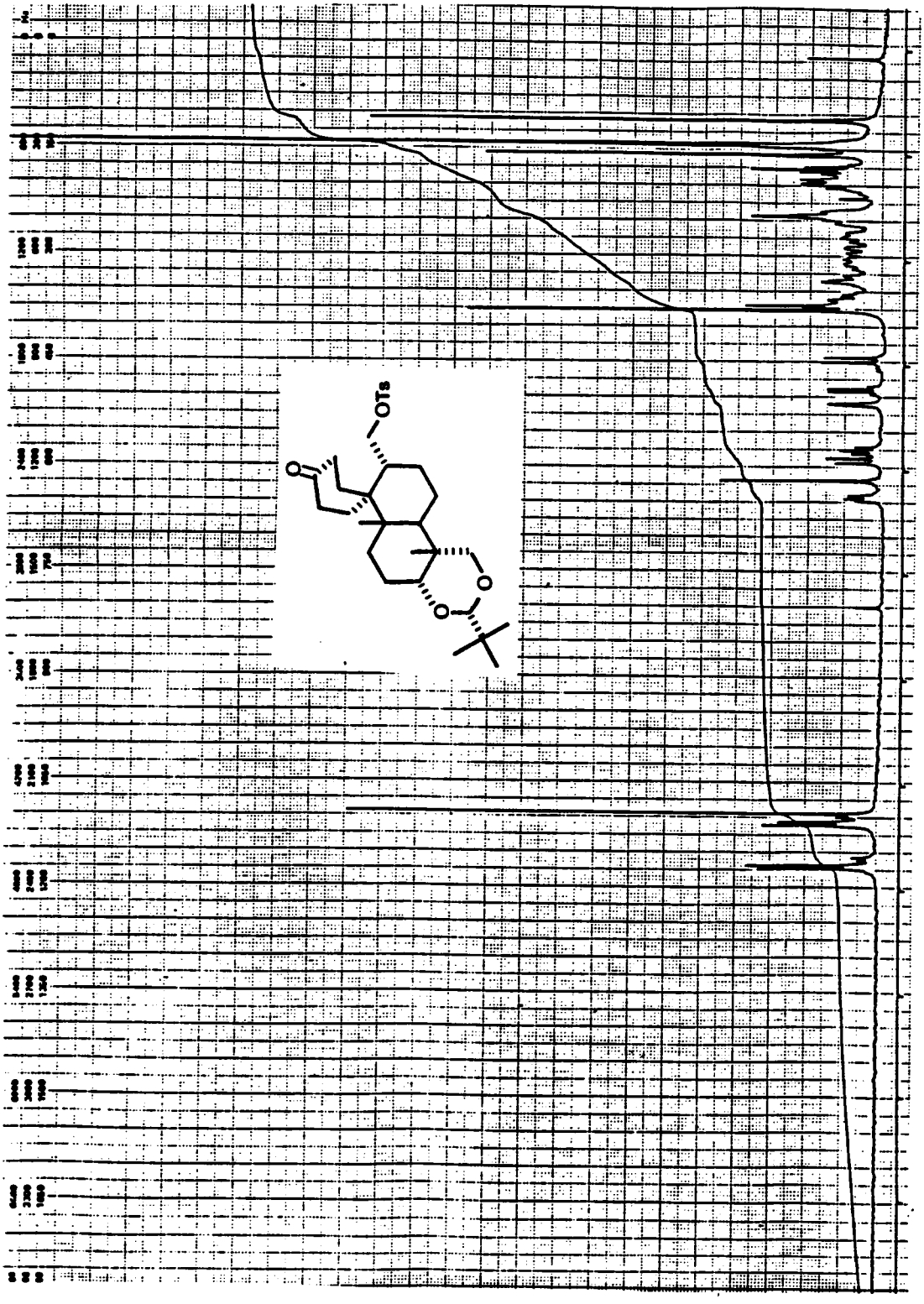
IR spectrum of synthetic alcohol 168



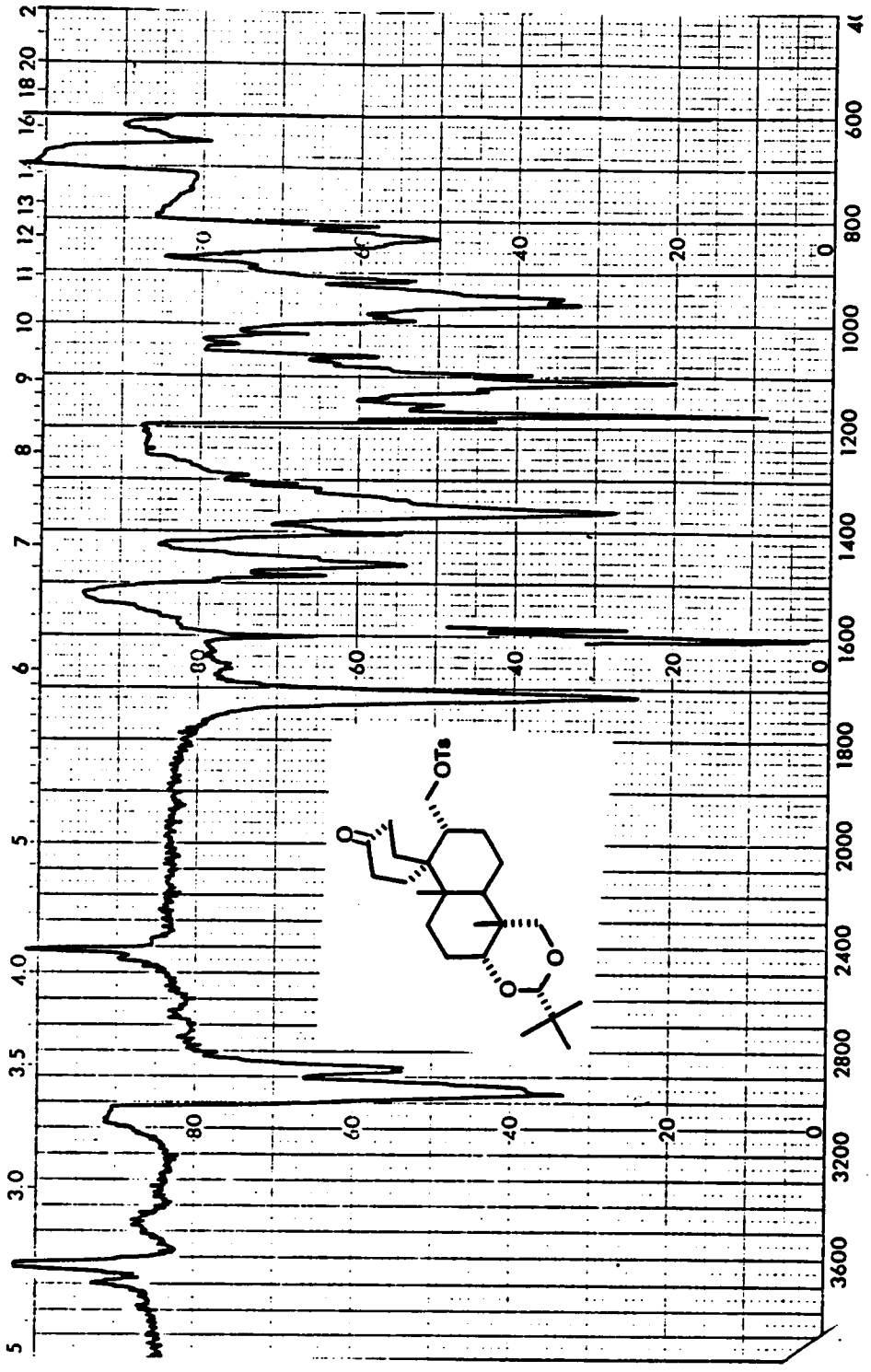
80 MHz ^{1}H NMR spectrum of synthetic tosylate 169



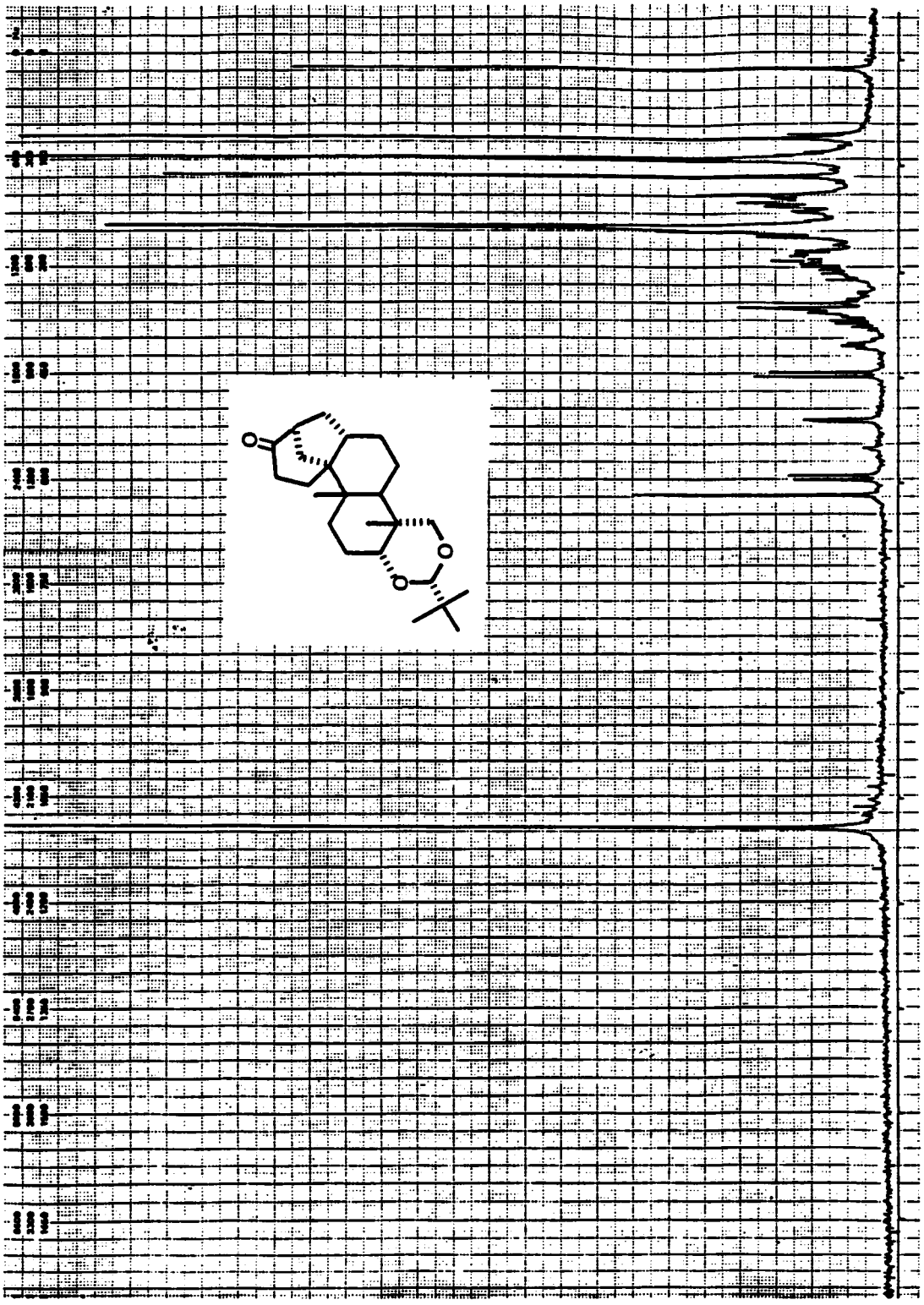
80 MHz ^{1}H NMR spectrum of authentic tosylate 169



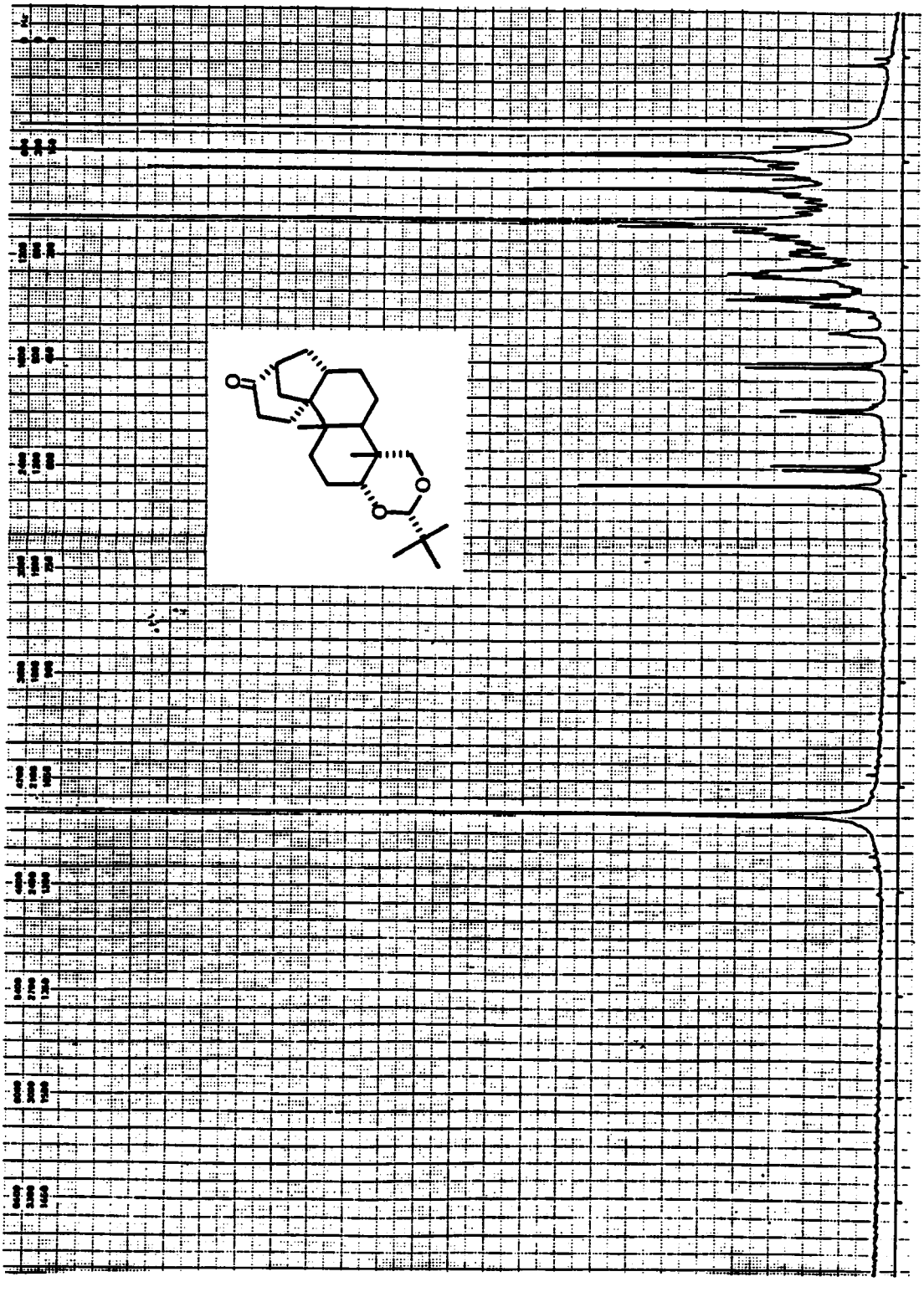
270 MHz ^{1}H NMR spectrum of synthetic tosylate 169



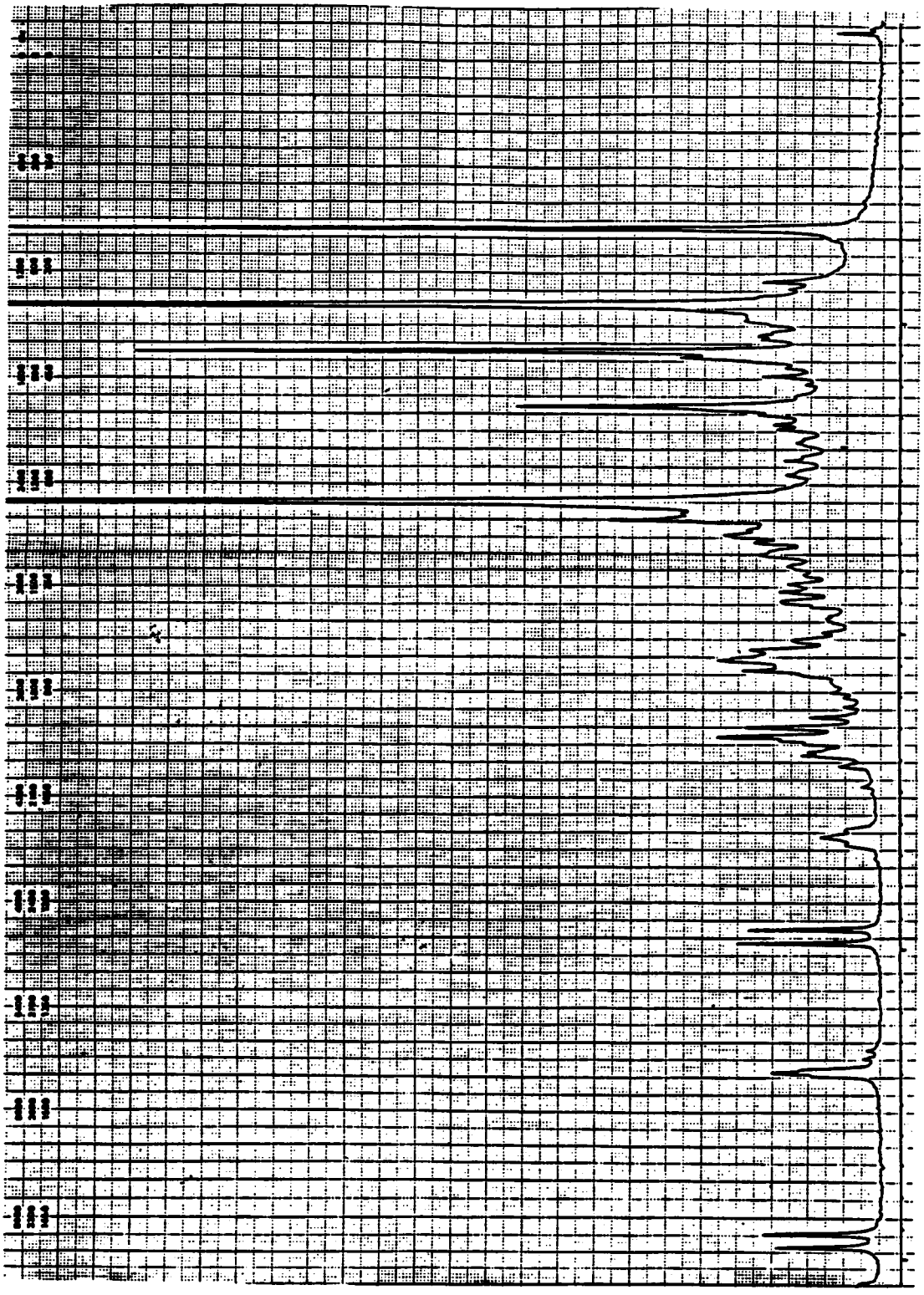
IR spectrum of synthetic tosylate 169



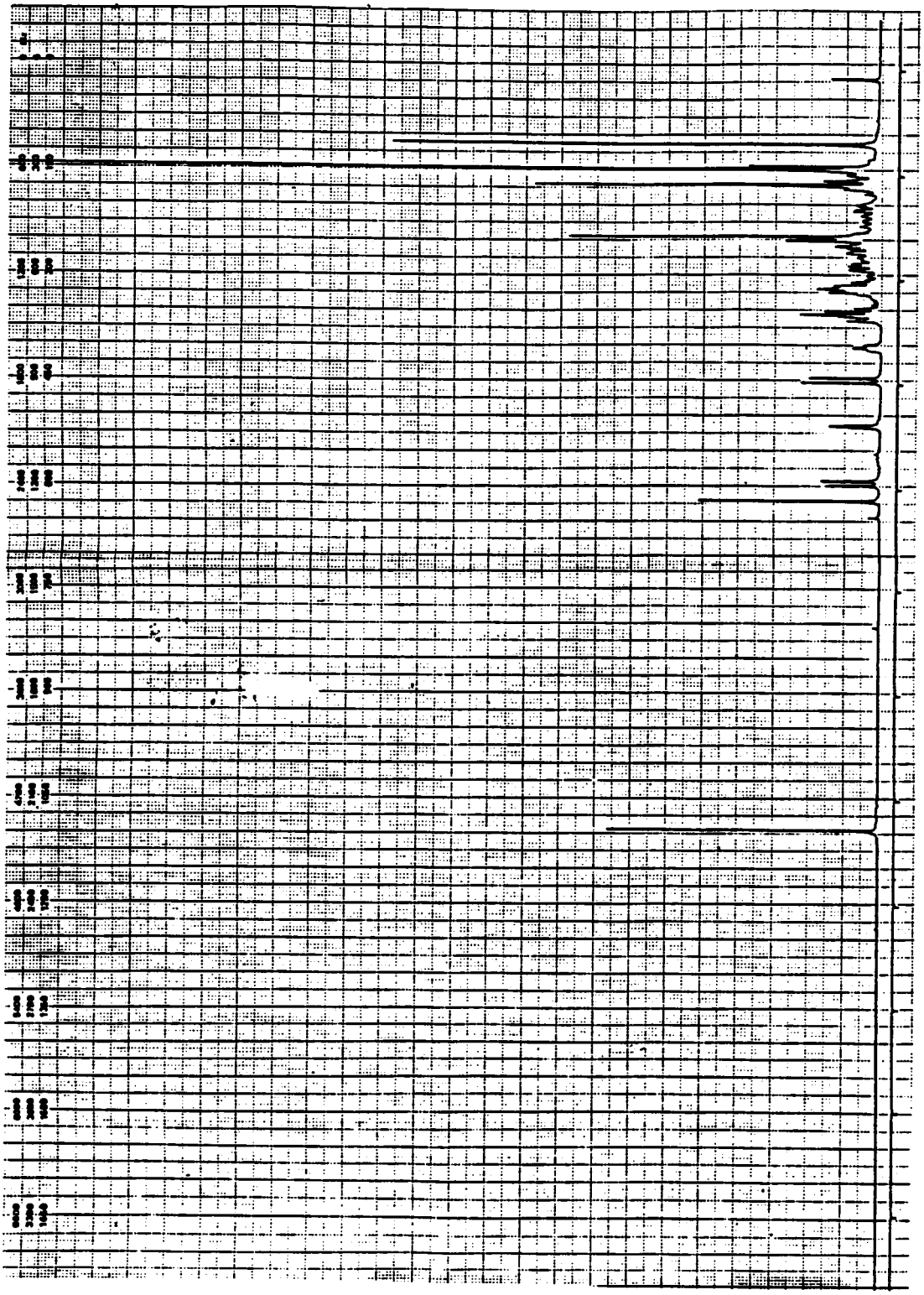
270 MHz ^{1}H NMR spectrum of ketone 170



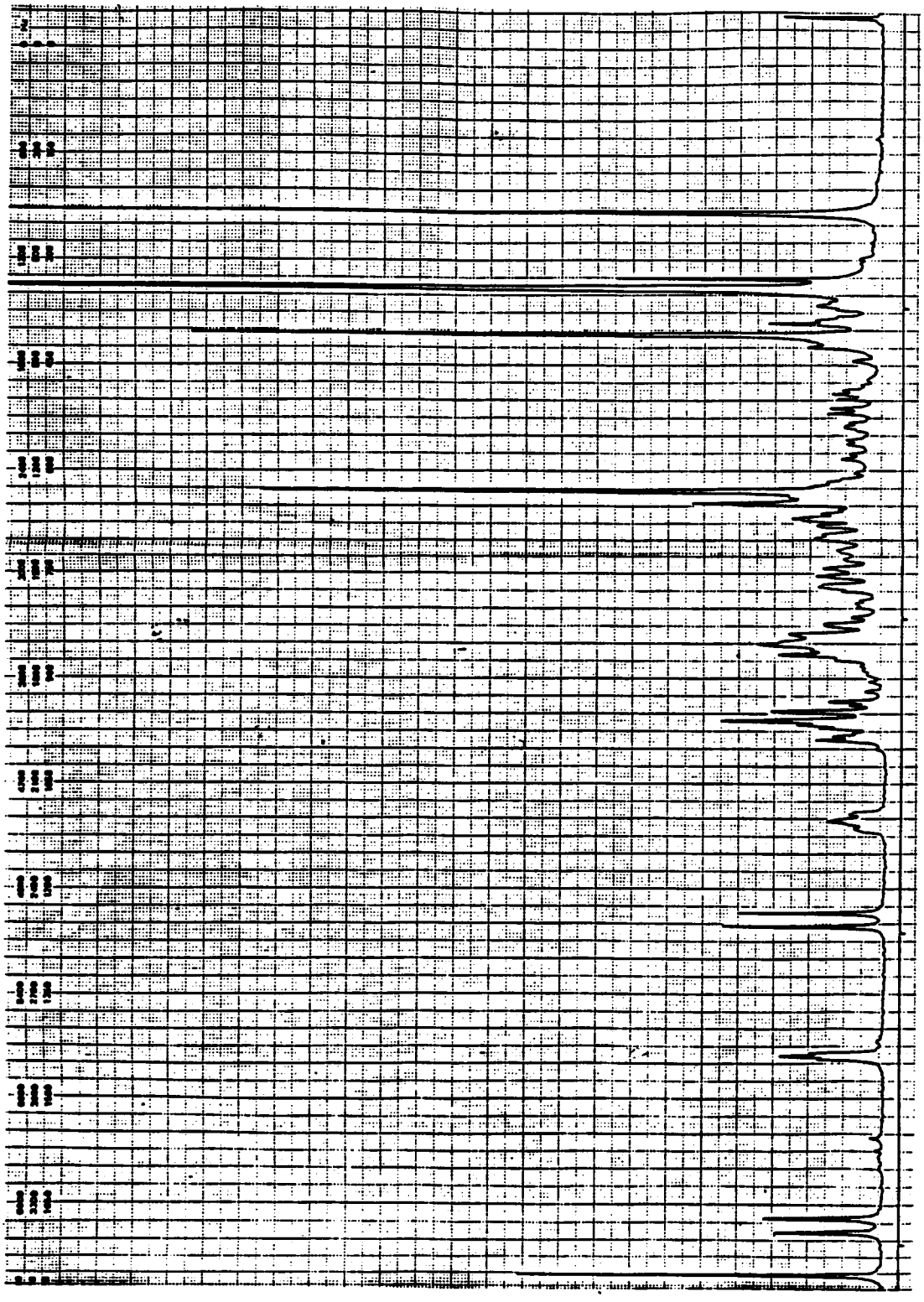
270 MHz ^{1}H NMR spectrum of synthetic ketone 27



expanded 270 MHz ^{1}H NMR spectrum of synthetic ketone 27



270 MHz ^{1}H NMR spectrum of authentic ketone 27



expanded 270 MHz ^{1}H NMR spectrum of authentic ketone 27

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