NMR AND X-RAY DIFFRACTION ANALYSES OF 2,6-DIARYLTETRAHYDROPYRAN-4-ONES AND CERTAIN SPIROLACTONE DERIVATIVES

By

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TABLE OF CONTENTS

Chapter Page

LIST OF TABLES

LIST OF FIGURES

LIST OF PLATES

CHAPTER I

INTRODUCTION

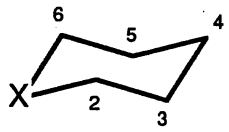
Conformational analysis of six-membered ring systems is considered fundamental in organic chemistry and is treated in virtually all introductory organic textbooks. A number of physical methods have been used to determine conformations of organic compounds. An excellent review of the physical methods applied to conformational problems has been presented by Eliel, Allinger, Angyal and Morrison.[23] Of the methods covered, NMR spectroscopy ranked among the most useful for experimental investigation. The general applications of NMR spectroscopy have been extensively reviewed elsewhere.[12,36,80,81] Of the parameters available, chemical shift data, including lanthanide-induced shifts,[1,2,31] and coupling constant analyses are the most useful for conformational analysis of cyclic compounds.[44]

Stereochemistry and ^{1}H NMR Analysis

The four principal, measurable quantities in an NMR experiment are the chemical shift, the coupling constant, the relaxation time, and line-shape changes. Perhaps the most useful of these variables for conformational analysis are the chemical shift and the coupling constant. In 1958, Lemieux and co-workers[54] were one of the first groups to show that NMR spectra could be employed to investigate the conformation and configuration of six-membered ring compounds.

Relative shift differences between protons within a spectrum have sometimes proven more useful in ^{1}H NMR analyses than absolute proton chemical shifts. For example, Jackman[35] showed the chemical shift difference of 29 Hz between the axial and equatorial

protons in cyclohexane could be adequately explained by the diamagnetic anisotropy of the β carbon-carbon single bonds. Chemical shift differences between axial and equatorial protons, $\Delta\delta_{ae}$, have been reported for pentamethylene heterocycles **1**. Lambert[45,46] found



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that the chemical shift difference between protons on the γ-carbon, $\Delta\delta_{ae}$ (γ), was predominantly due to the anisotropy effect of the C(2)-C(3) and C(5)-C(6) single bonds. In all of the cases presented, the axial proton resonated at a higher field than the corresponding equatorial proton. Diamagnetic anisotropy effects were also used to explain $\Delta\delta_{ae}$ (α) and $\Delta\delta_{ae}$ (β).[46] However, a simple double cone of magnetic anisotropy directed along the C-X axis could not adequately explain the shielding behavior of these bonds. Lambert[46] concluded that the diamagnetic anisotropy model for heterocyclic ring compounds was complex. He proposed that a model like those suggested[46] for N–N=O and C=O groups might be more appropriate.

Vicinal coupling constants ($^3J_{HH}$) have been of value in determining the orientation of protons in six-membered ring compounds. On the basis of valence bond calculations, Karplus[39] presented an approximate relationship between the dihedral angle (ϕ) and $^3J_{HH}$. The expression, which is referred to as the Karplus equation, is generally presented as equation (1). However, dependence of the coupling constant on factors other than the

$$^3J_{HH} = A - B\cos^2\phi + C\cos 2\phi \qquad (1)$$

dihedral angle were clearly stated by Karplus.[40] The $^3J_{HH}$ value is dependent upon the electronegativity of the substituents, the C–C bond length, the H–C–C bond angle, and specific orientations of substituents in addition to the dihedral angle.[3,90] Although the original work of Karplus was based upon the analysis of alkanes and alkenes,[39] the

results have been applied to many areas, including the study of conformational analysis of six-membered rings. Unfortunately, many extrapolations have been made which the original theory does not truly accommodate.

Early in the application of the Karplus equation, Lambert[43,44,47] proposed a method for determining the nature of non-chair and distorted chair conformations in six-membered ring compounds. Lambert's R-value method [eq. (2)] was originally[44] applied to rapidly

$$R = \frac{J_{trans}}{J_{cis}} = \frac{J_{aa} + J_{ee}}{J_{ae} + J_{ea}} \qquad (2)$$

inverting six-membered ring systems. In a later publication, Lambert[43] defined four structural categories for using the R-value method. These areas were: (1) compounds containing a CH_2CH_2 moiety with two rapidly equilibrating, equivalent conformers; (2) compounds containing a CH_2CH_2 moiety in a completely static system which contains measurable, first-order J values; (3) compounds containing a CH_2CHR moiety with two rapidly equilibrating, equivalent conformers; and (4) compounds containing a $CHRCH_2CHR'$ moiety in a completely static molecule with R and R' oriented anti (or trans) to one another. There are some theoretical limitations to the R-value method of analysis, but, according to Lambert,[43] the only practical limitation is the availability of accurate $^3J_{HH}$ values.

The R-values were first used qualitatively to describe possible distortions in the chair form of six-membered rings. Lambert[44] found that for molecules with approximately the same dihedral relationships as in unsubstituted cyclohexane, the R-value was in the range of 1.9 to 2.2. Following the guidelines established by Lambert,[47] values of R below 1.8 would be obtained for rings that were flattened, and values above 2.5 would be obtained for puckered chair compounds. The method remained essentially qualitative until Buys[15] presented a quantitative extension. By using eqs (1) and (2) and assuming trigonal projection symmetry, Buys derived an expression which related R to ϕ:

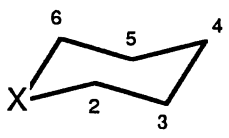
$$\cos^2\phi = \frac{3}{2 + 4R} \qquad (3)$$

Calculation of the dihedral angle from R-values was now possible. An R-value of 1.9 to 2.2, which corresponds to cyclohexane-type structures, gives a dihedral angle of 56-58°. R-values for several pentamethylene heterocycles have been published.[45]

^{13}C NMR Analyses

Observations of carbon-13 nuclei by the use of NMR spectroscopy were first reported in 1957.[33,49] However, the advancement of ^{13}C NMR spectroscopy to the status of being a practical research tool for the organic chemist did not occur until the early 1970's when the recording of ^{13}C NMR spectra in the Fourier transform mode became possible. A complete review of ^{13}C NMR spectroscopy will not be presented here because such reviews may be found in current publications.[14,55,78]

Carbon-13 NMR spectroscopy is now generally recognized as one of the most useful techniques available for making stereochemical assignments and assisting in structural elucidation.[24] The applications are, for the most part, based on empirical correlations of the ^{13}C chemical shifts and, to some extent, on the use of $^{1}J_{CH}$ coupling constants. This discussion will be limited to the analysis of compounds with the general structures **1**, **2**, and **3**. Analyses will be made within each class of compound and



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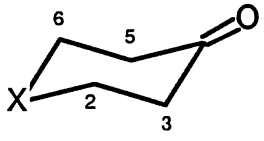

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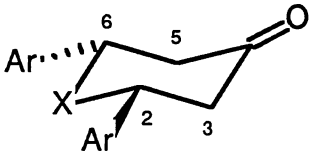

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between the classes. Specific emphasis will be given to changes in chemical shift values upon addition of a carbonyl moiety and the addition of aryl groups to the heterocyclic ring.

In 1976, Lambert and co-workers[48] presented a comprehensive study of the ^{13}C chemical shifts for a large group of heterocycles. Data were given for C, Si, Ge, Sn, N,

P, As, O, S, Se, Te, Br^+ and I^+ pentamethylene heterocycles in various states of substitution (see Table I for a partial list of ^{13}C data). In the pentamethylene heterocycles

TABLE I

^{13}C CHEMICAL SHIFT DATA FOR PENTAMETHYLENE HETEROCYCLES[48]

1

Compound	X	Chemical Shift[a,b] C(2,6)	C(3,5)	C(4)
1a	O	68.0	26.6	23.6
1b	NCH_3	56.7	26.3	24.3
1c	NH	47.5	27.2	25.5
1d	S	29.3	28.2	26.9
1e	CH_2	27.7	27.7	27.7
1f	Se	20.2	29.1	28.4
1g	Te	–2.1	29.9	30.9

[a]In parts per million (ppm), downfield from tetramethylsilane (TMS).
[b]All samples were run neat.

studied, the chemical shifts of the α- and γ-carbons were influenced primarily by the electronegativity of the heteroatom. For the α-carbons [α to the heteroatom or C(2,6)], the linear relationship between the chemical shift and the electronegativity had a slope of approximately 50 ppm/electronegativity unit. Sulfur was the only analog which deviated greatly from this relationship. The authors noted this deviation and commented "Either the electronegativity is not known accurately for sulfur, which appears to be the deviant point, or there is another factor that contributes modestly to the α chemical shift in thiane alone."[48] A plot of the chemical shift for the γ-carbon [γ to the heteroatom or C(4)] versus the electronegativity of the heteroatom had some scatter but was essentially linear with a slope of -5 ppm/electronegativity unit. The heteroatom was also an important determinant in the chemical shift of the β-carbons [β to the heteroatom or C(3,5)], but this chemical shift was also sensitive to the presence of an axial substituent on the heteroatom. A significant (~5 ppm) upfield shift of the β-carbon was observed when an axial substituent was present on the heteroatom such as when X = N-alkyl.[48]

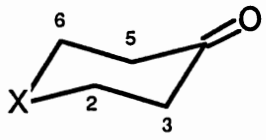
The effect of adding an oxo moiety to cyclohexanes[88] and 1-heteracyclohexanes[30,67] has been investigated. Hirsch and Havinga[30] studied a series of 1-hetera-4-cyclohexanones and reported that the shielding effect on the α-carbon was very small from addition of an oxo group. Comparison of the chemical shifts of the α-carbons in the pentamethylene heterocycles and the corresponding shifts in the 1-hetera-4-cyclohexanones (see Table II) revealed a small upfield shift (< 1 ppm) for all of the α-carbons except in the sulfur analog. The reason for this downfield shift (0.7 ppm) in the sulfur analog is not known. Chemical shift values for the α-carbons in the 1-hetera-4-cyclohexanones show the same overall trend as that found by Lambert[48] in the pentamethylene heterocycles: O > NCH_3 > S > CH_2 > Se. Thus the chemical shift of the α-carbon in 1-hetera-4-cyclohexanones appears to be influenced primarily by the electronegativity of the heteroatom.

The effect on the β-carbon by adding an oxo group [C(4)=O] to a six-membered

heterocyclic ring is significant. A downfield shift of 14-16 ppm is commonly observed. This shift is likely due to the electrostatic electron withdrawal by the carbonyl moiety, similar to that of the heteroatom (see Table II).

TABLE II

^{13}C CHEMICAL SHIFT DATA FOR 1-HETERA-4-CYCLOHEXANONES



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Compound	X	Chemical Shift[a] C(2,6)	C(3,5)	C(4)	Δppm $[C(4)_{2x}-C(4)_{1x}]$[b]	Source
2a	O	67.7	42.8	206.2	182.6	30
2b	NCH_3	55.3	41.0	207.1	182.8	30
2c	S	30.0	44.0	208.0	181.1	30
2d	CH_2	27.2	41.9	210.3	182.6	85
2e	Se	19.3	43.7	209.3	180.9	82

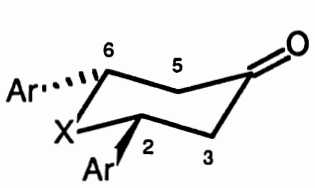
[a]In ppm, downfield from TMS with $DCCl_3$ as the solvent.
[b]Obtained by comparing the C(4) chemical shift in **2** with the C(4) chemical shift in **1**.

In analyzing the effects of heteroatoms on ^{13}C chemical shifts, Eliel and

Pietrusiewicz[24] referred to four types of effects: (1) the γ-gauche effect; (2) the γ-anti effect; (3) the effect of lone pairs of electrons; and (4) other effects. The authors noted that the γ-gauche effect should operate in the heteracyclohexane system. The γ-gauche effect was defined as the ". . . upfield shifting for atoms more electronegative than carbon (O, N) and downfield shifting for the less electronegative atoms (P, Se, Te, As)."[24] In an earlier publication,[48] it had been concluded that the effect was always upfield shifting. These earlier findings were discounted, because the only atom studied which was less electronegative than carbon, was sulfur. As noted earlier,[48] the authors questioned the published electronegativity value for sulfur. Since Lambert's publication, the selenium analog has also been synthesized, and the ^{13}C data[82] for 4-selenanone are now available. As can be seen in Table II, the C(4) chemical shifts for the 1-hetera-4-cyclohexanones are all upfield from the corresponding C(4) chemical shift in cyclohexanone (**2d**). Due to the observed order of chemical shifts for the C(4) carbon in **2a-2e** [CH_2 > Se > S > NCH_3 > O], there must be other influences on the C(4) carbon in addition to the γ-gauche effect. Jones and Hassan[37] have proposed that an electronic field effect between the heteroatom and the carbonyl moiety influences the C(4) chemical shift.

An exhaustive literature search did not reveal a study of a chemical shift change in C(4) upon incorporation of the carbonyl moiety in a heteracyclohexane system. Table II contains the Δppm [$C(4)_{2x}$-$C(4)_{1x}$] values which were obtained by comparing the chemical shift values of **1a**, **1b**, **1d**, **1e** and **1f** with those of **2a-2e**. Values of Δppm [$C(4)_{2x}$-$C(4)_{1x}$] may be divided into two groups: (1) puckered ring compounds and (2) flattened ring compounds. The **2a**, **2b** and **2d** rings are all slightly puckered[45] and the Δppm [$C(4)_{2x}$-$C(4)_{1x}$] values for these compounds are very similar (182.7 $\pm$ 0.1 ppm). The flattened ring compounds,[45] **2c** and **2e**, have Δppm [$C(4)_{2x}$-$C(4)_{1x}$] values which are distinctly lower (181.0 $\pm$ 0.1 ppm). A definitive reason for this difference is not known, but it may be due to the differences in the ring geometries. Such differences may also be part of the reason why the C(4) chemical shifts in **2a-2e** do not follow the γ-gauche effect.

Berlin and co-workers[67] reported a series of 1-hetera-2,6-diaryl-4-cyclohexanones (**3, 4**), but most of the compounds also contained alkyl substituents (methyl or ethyl) at



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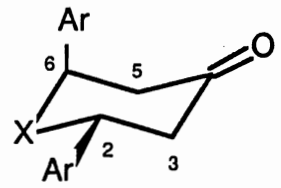

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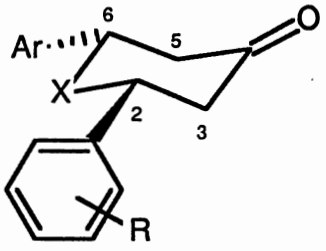
X(1), C(3) or C(5). An extensive review of the 1-hetera-2,6-diaryl-4-cyclohexanone system is not available and will be presented here. The results of a complete literature search through 1986 for the NMR spectral data of 1-hetera-2,6-diaryl-4-cyclohexanones may be found in Table III. Examination of the data reveals an α-substituent effect in the order O > HCH_3 > NH > S > P > CH_2 > Se. This is similar to that reported by Hirsch and Havinga[30] for 1-hetera-4-cyclohexanones, with the exception that Hirsch and Havinga did not report chemical shift data for the phosphorus and selenium analogs. The effects of the phenyl groups on the chemical shifts were found by comparing those of **2a-2e** with those for the diphenyl analog (**3b, 3e, 3f, 3a, 3g**). Table IV shows the chemical shift differences for the α-, β- and γ-carbons. The α-carbon shows the most varied effect. The deshielding influence of the cis diphenyl groups increases as the electronegativity of the heteroatom decreases. The β-carbon is deshielded but to a lesser extent than the α-carbon. All of the γ-carbons exhibit a small shielding effect (0.1 to 1.5 ppm). This shielding may be due to a γ-anti effect or to small field effects.

An additional comment needs to be made concerning the data in Table III. The trans-substituted compounds (**4b, 4f, 4k, 4l, 4m**) exhibit a γ_a-shielding effect on C(2) due to the axial C_6H_5–C bond. In **4b** and **4f**, which certainly undergo ring reversal at room temperature, the ^{13}C shift values are an average for C(2) and C(6). In the phosphorus analogs (**4k, 4l,** and **4m**), which do not undergo ring reversal, C(2) and C(6), as well as C(3) and C(5), are magnetically nonequivalent, and thus resonances are observed for each

TABLE III

NMR DATA FOR 1-HETERA-2,6-DIARYL-4-CYCLOHEXANONES



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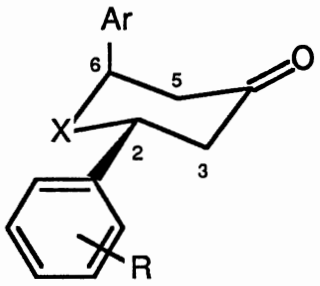

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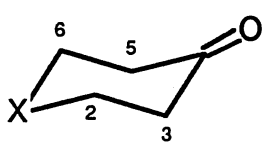
Compound	R	X	Chemical Shift[a,b] H(2,6)	H(3,5)	C(2,6)	C(3,5)	C(4)	H(2,6)	H(3,5)	C(2,6)	C(3,5)	C(4)	Source
a	H	CH_2	3.10	1.6-2.8	43.62	48.23	208.82						67, 76
b	H	O	4.86	2.68-2.77	78.95	49.71	206.08	5.16	2.85-2.95	73.53	46.44	206.47	67
c	H	NH	4.06	2.56	60.89	50.10	206.68						67, 76
d	*o*-Cl	NH			56.4	47.8	207.0						28
e	H	NCH_3	3.30	2.60	69.89	50.54	205.81						67, 76
f	H	S	4.23	2.94	48.15	50.24	206.78	4.22	2.91	43.78	48.41	205.78	8, 67
g	H	Se	4.55	2.95-3.41	41.46	50.33	208.46	4.62	3.30-3.10				57, 91
h	*p*-CH_3	Se	4.53	2.92-3.39	41.20	50.51	208.74						57
i	*p*-OCH_3	Se	4.68	2.59-2.85	38.71	48.35	209.16						57
j	*p*-Cl	Se	4.52	2.88-3.36	40.60	50.01	207.42						56
k	H	PPh	2.60-4.05[c]		44.76	48.54	207.00	3.60-4.05	2.44-3.35	C(2) 38.80 C(6) 36.32	C(3) 42.68 C(5) 46.14	209.70	68, 69
l	H	O PPh	3.50-4.10 [H_a(2,6),H_e(3,5)] 2.70-3.20 [H_a(3,5)]		44.78	44.80	205.80	3.48-4.10	2.80-3.45	C(2) 46.43 C(6) 38.19	C(3) 42.65 C(5) 45.05	207.14	68, 69
m	H	S PPh	3.60-4.30 [H_a(2,6), H_e(3,5)] 2.60-3.15 [H_a(3,5)]		45.57	44.54	205.57	3.68-4.40	2.74-3.40	C(2) 51.68 C(6) 38.00	C(3) 43.02 C(5) 44.95	207.16	68, 69

[a]Shifts are in parts per million downfield from TMS.
[b]All samples were run in $DCCl_3$ except **4k** which was run in C_6D_6.
[c]Signals for H(2), H(3), H(5), and H(6) occur in this range.

carbon.

TABLE IV

THE EFFECT OF *cis*-2,6-DIPHENYL SUBSTITUTION ON HETEROCYCLIC KETONES **2** and **3**



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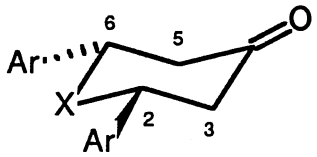

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X	α-effect[a]	β-effect[b]	γ-effect[c]
O	11.3	6.9	–0.1
NCH_3	14.4	9.5	–1.3
CH_2	16.4	6.3	–1.5
S	18.1	6.5	–1.2
Se	22.2	6.6	–0.8

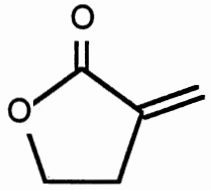
[a]Obtained by comparing the C(2,6) chemical shift in **3** with the corresponding C(2,6) shift in **2**.
[b]Obtained by comparing the C(3,5) chemical shift in **3** with the corresponding C(3,5) shift in **2**.
[c]Obtained by comparing the C(4) chemical shift in **3** with the corresponding C(4) shift in **2**.

As mentioned earlier, $^1J_{CH}$ coupling constants may be used to study the

conformation of heterocyclic compounds.[10] It has been shown that for pyranoses,[9] 2,6-dicyanopiperidines,[11] and piperidine α-amino nitriles[11] a 10 Hz difference frequently exists between the $^1J_{CH(ax)}$ and $^1J_{CH(eq)}$ coupling constants. The $^1J_{CH(eq)}$ value was always greater than $^1J_{CH(ax)}$, for example, as in pyranoses which had $^1J_{CH(ax)}$ = 170 Hz and $^1J_{CH(eq)}$ = 160 Hz. Bock and Thørgerson[11] commented that assessment of the $^1J_{CH}$ coupling constant may be the best method for determining the anomeric configuration of pyranoses.

Synthesis and Biological Activity of Selected α-Methylene-γ-butyrolactones

A wide variety of natural products have been isolated which contain an α-methylene-γ-butyrolactone ring **5**. It has been estimated that α-methylene-γ-butyrolactones represent



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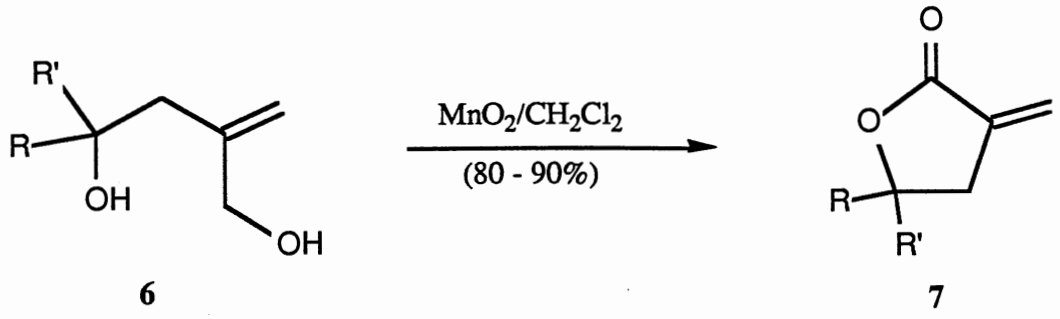
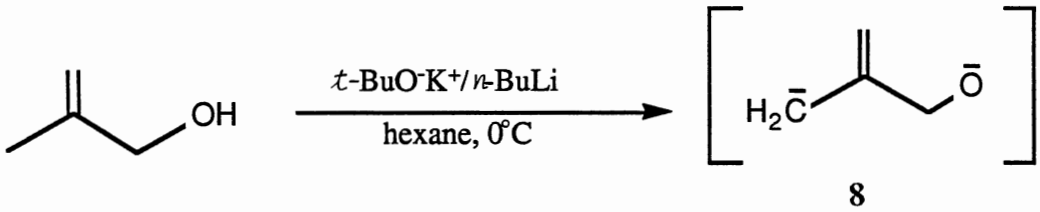
10% of the known natural products.[32] A number of compounds bearing this functionality have been synthesized with the goal of developing effective clinical drugs, since the natural occurring compounds with an α-methylene-γ-butyrolactone moiety have therapeutic indices which prevent their clinical use.[32,63] It is beyond the scope of this discussion to present a review of the literature in this area; however, a few examples will illustrate the variety of approaches currently employed in the synthesis of α-methylene-γ-butyrolactones since the latter were part of our work.

Oxidation of diols **6** by manganese dioxide affords α-methylene-γ-butyrolactones **7**

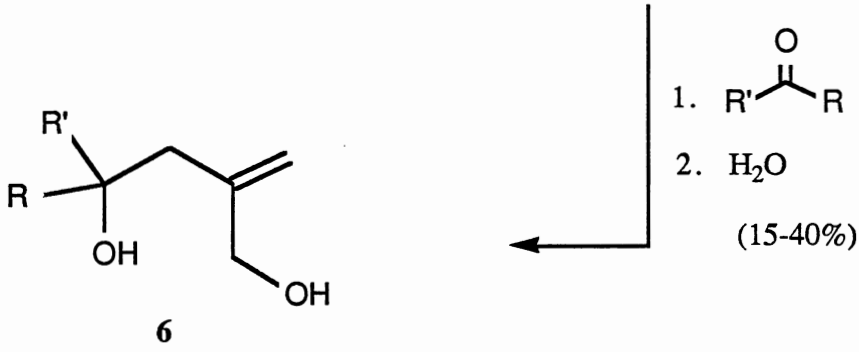


6 **7**

in very good yields.[16] One method of forming the necessary diols **6** is to treat dianion **8** with a carbonyl compound.[16]

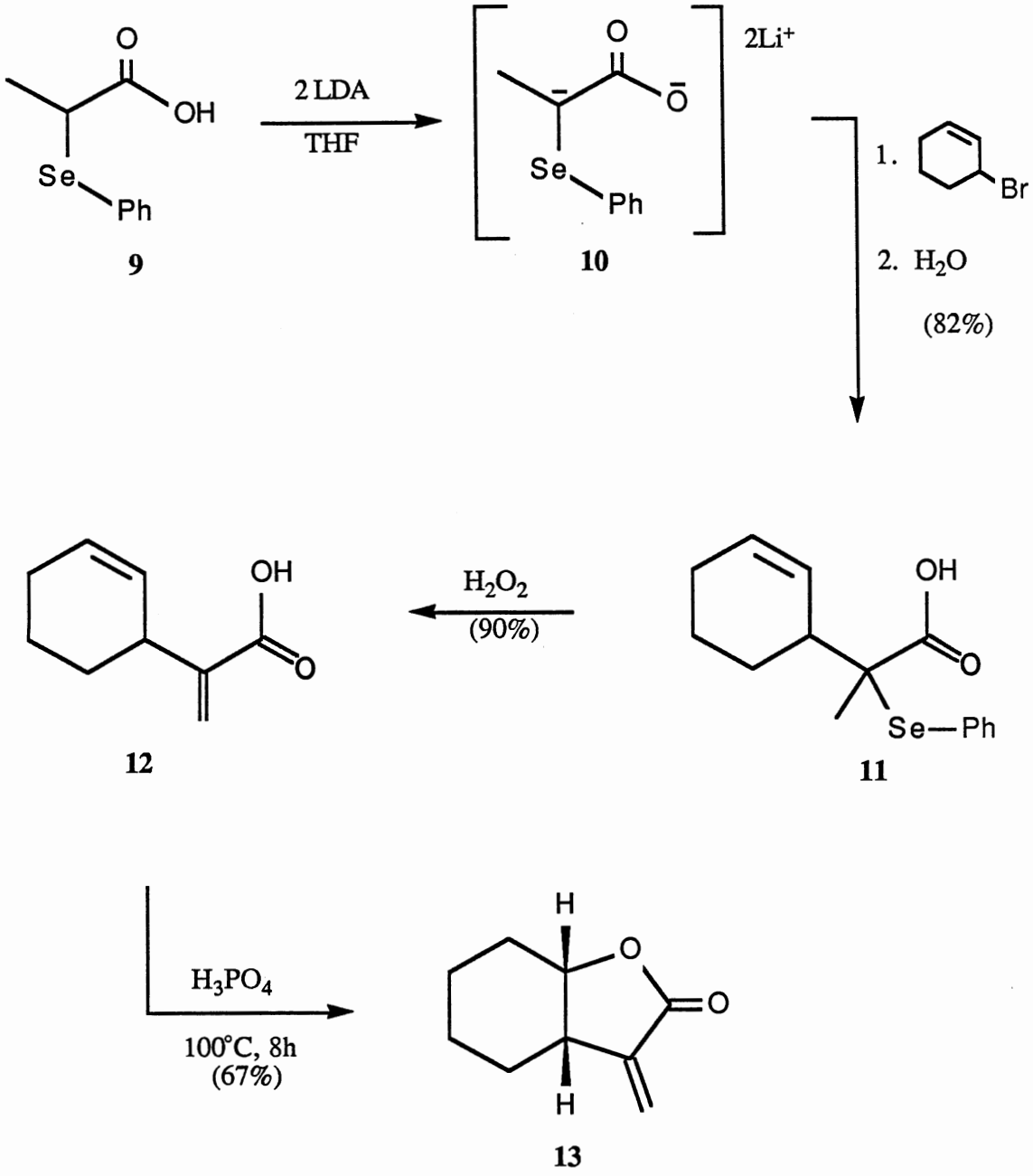


8

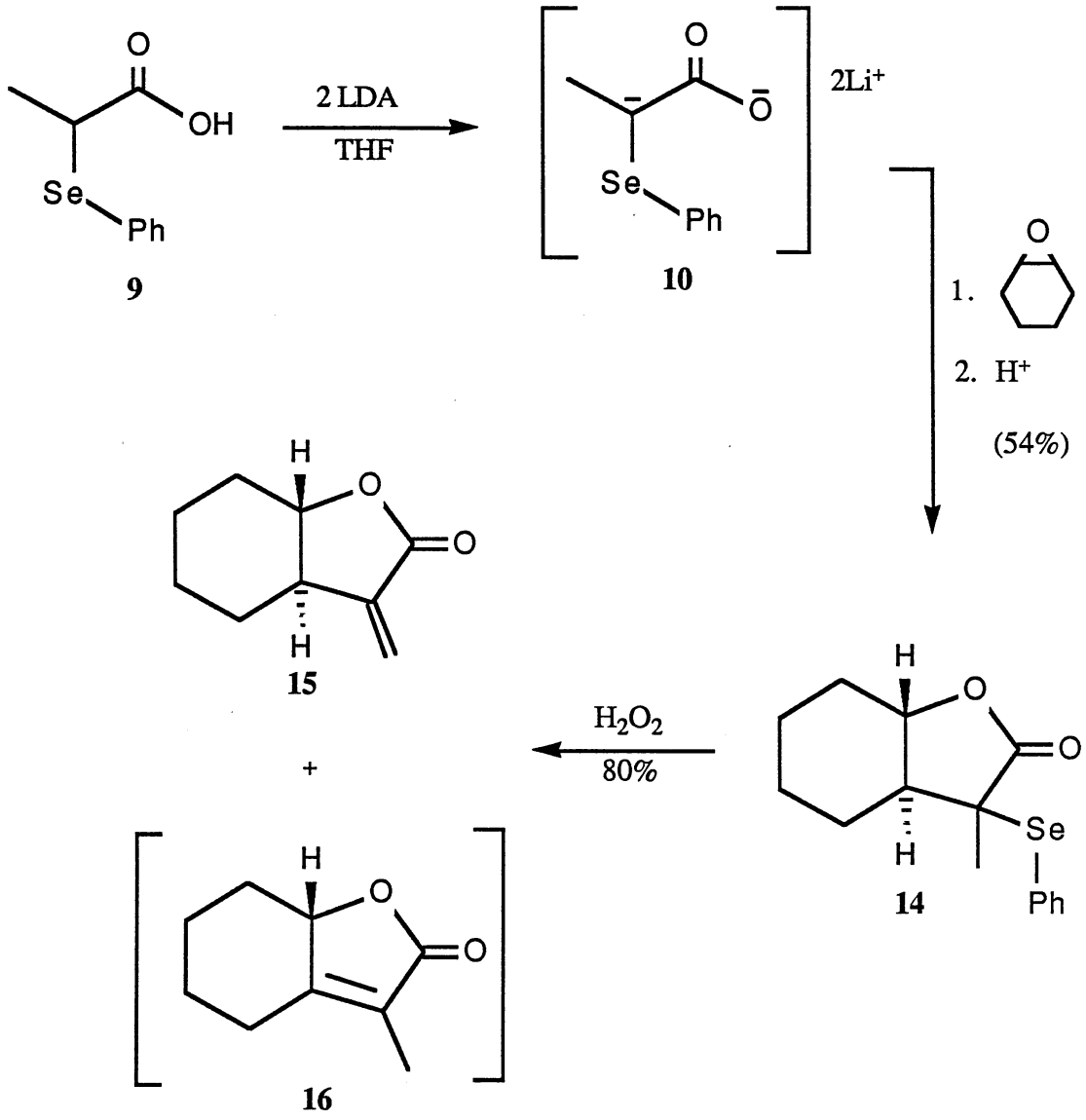


6

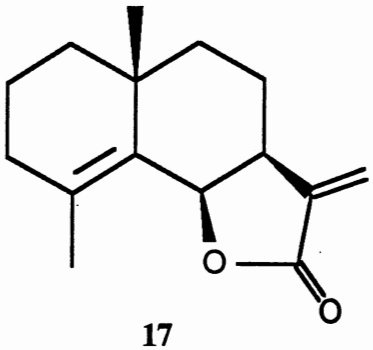
Cyclization of γ,δ-unsaturated acids has been utilized in the synthesis of α-methylene-γ-butyrolactones. Petragnani and Ferraz[62] used this technique (**9** → **10** → **11** → **12** → **13**) to prepare lactone **13**. The dilithio derivative **10** was formed by reacting 2-(phenylseleno)propanoic acid **9** with two equivalents of lithium diisopropylamide



(LDA). Dianion **10** reacted with 3-bromocyclohexene to give the γ,δ-unsaturated acid **11**. Selenoxide elimination converted **11** into the α-methylene-γ,δ-unsaturated acid **12**. Heating **12** with phosphoric acid gave the desired lactone **13** in an overall yield of 49%. The trans isomer **15** was also synthesized (**9** → **10** → **14** → **15**) using the organoselenium reagent **9**. The dianion **10** reacted with cyclohexene oxide (followed by selenoxide elimination)

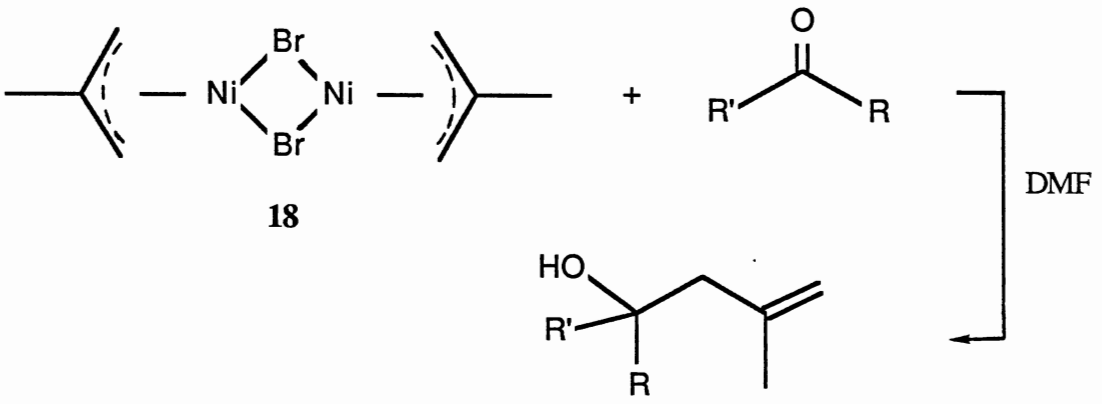


selenoxide elimination) to give the *trans*-lactone **15**. Formation of the endocyclic isomer **16** was minor (< 10%) and pure **15** was obtained by chromatography (silica gel) in a yield of 80%. Very recently, Petragnani and Ferraz[64] used this same procedure to synthesize (±)-frullanolide (**17**).



17

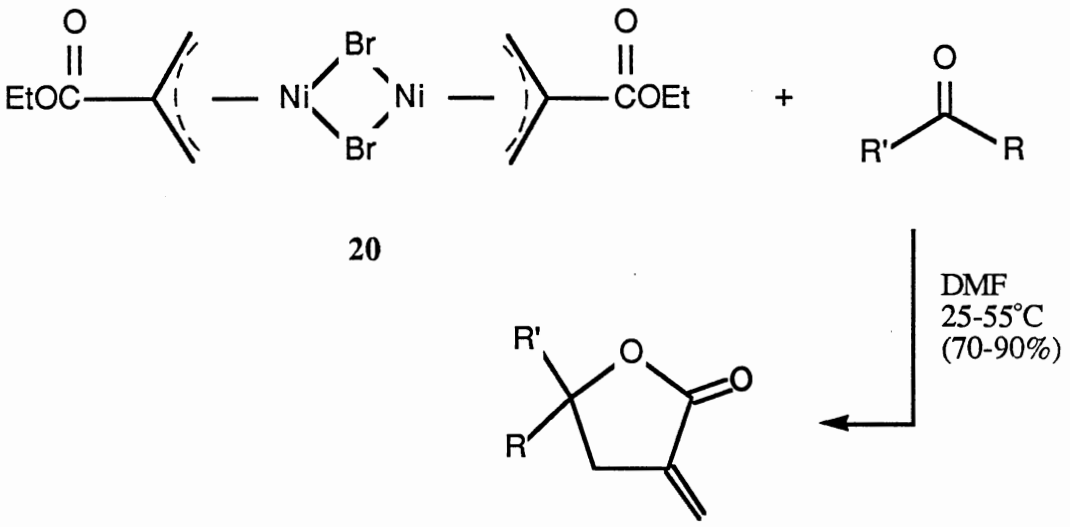
The ability of π-allylnickel halide complexes **18** to react with different



18

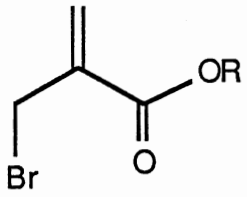
19

functionalities to form C–C bonds has been explored to generate allylic alcohols **19**.[29] On this basis, the reaction of the 2-ethoxycarbonyl-substituted reagent **20** with aldehydes and ketones furnished α-methylene-γ-butyrolactones in high yield.[29]



20

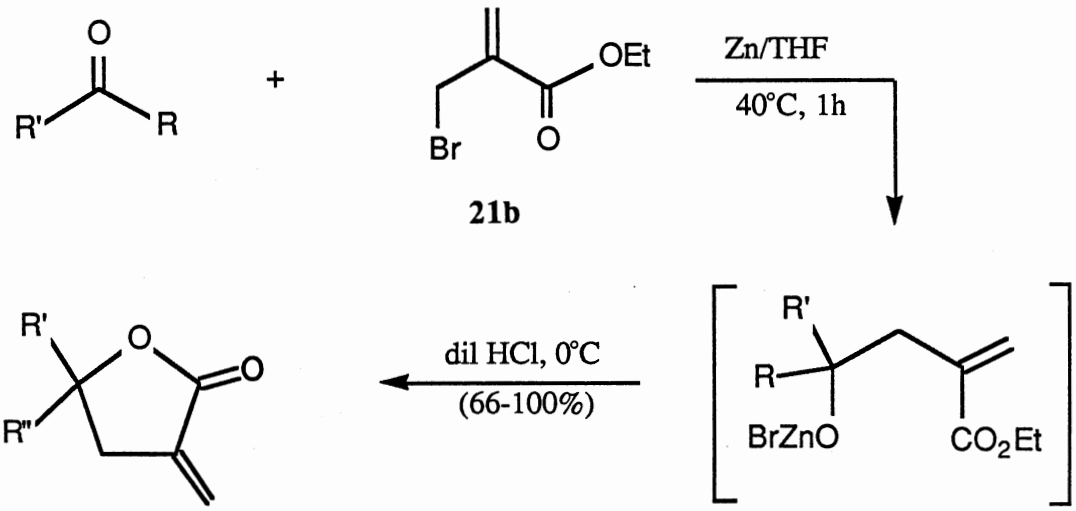
Perhaps the most important building blocks in the synthesis of γ-substituted lactones are the 2-(bromomethyl)acrylic esters **21**. Öhler and co-workers[59] prepared a variety



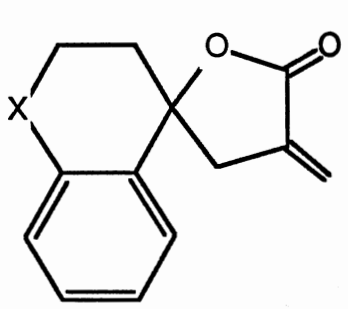
21

a. $R = CH_3$
b. $R = CH_2CH_3$
c. $R = C(CH_3)_3$

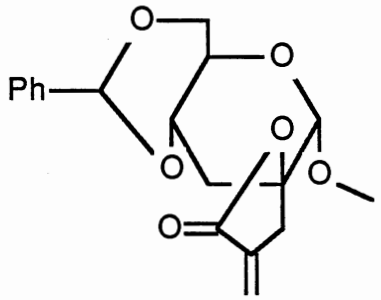
of α-methylene-γ-butyrolactones by using 2-(bromomethyl)acrylic esters in a Reformatsky-type reaction with carbonyl compounds in a simple, one-step approach.



Benezra and co-workers[75] reported the synthesis of more than thirty lactones using this method. Spirolactones were obtained by Ramalingan and Berlin[66] using this general reaction with one minor change. The authors used ice-cold H_2SO_4 (5%) as the lactonizing agent instead of dil HCl. The ester **21b** was allowed to react with several substituted heterocyclic ketones to give lactones containing heteroatoms in the carbon skeleton (e.g. **22**).



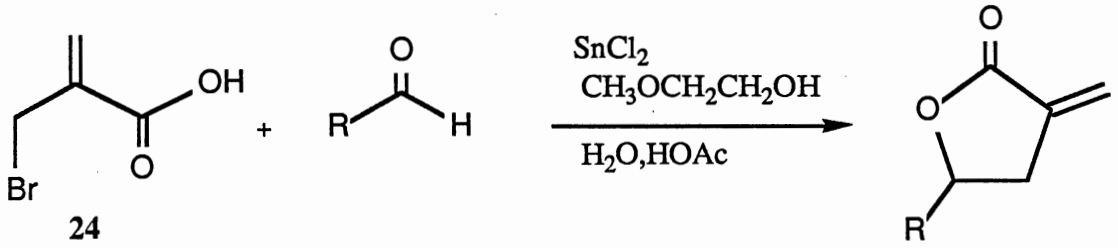
22



23

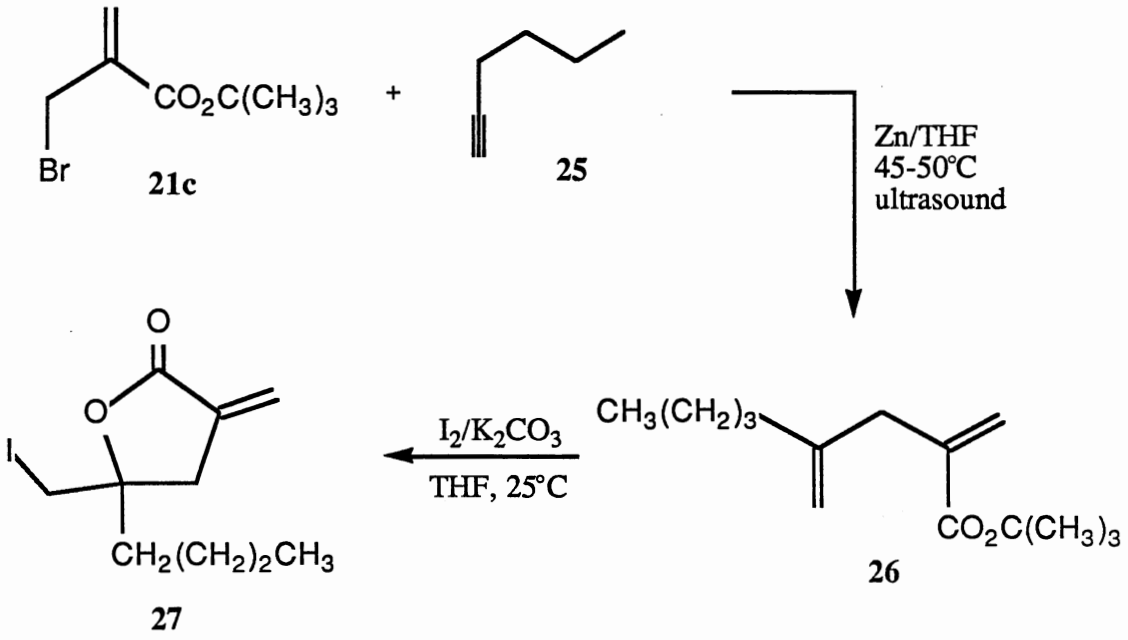
In an attempt to decrease the cytotoxicity of α-methylene-γ-butyrolactones, Csuk and co-workers[22] prepared some spiro lactones of carbohydrate derivatives (e.g. **23**) starting with ethyl 2-(bromomethyl)acrylate. Recently, several related and new α-methylene-γ-butyrolactone derivatives of substituted nucleic acids were obtained.[52,74] Some of these

novel compounds displayed excellent antitumor activity. 2-(Bromomethyl)acrylic acid (**24**) was shown to undergo lactonization with aromatic and aliphatic aldehydes in the



presence of $SnCl_2$ in very good yields.[87]

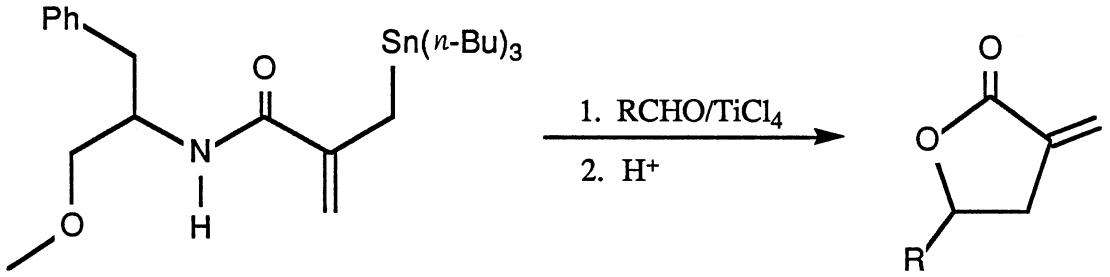
Knochel and Normant[41] noted that alkyl 2-(bromomethyl)acrylates add regiospecifically to terminal alkynes in the presence of zinc to give α-methylene-γ,δ-unsaturated esters. When 1-hexyne (**25**) was allowed to react with ester **21c**, diene **26**



was obtained in a yield of 70%. Conventional iodo-lactonization gave lactone **27** in a yield of 90%.

Several methods are known for the α-methylation of a lactone unit through hydroxymethylation,[84] aminomethylation,[71] decarboxylative methylation,[38] and deacylative methylation.[86] A review[32,63] should be consulted for more details.

Tanaka and co-workers[79] outlined a Lewis acid-mediated asymmetric synthesis of α-methylene-γ-butyrolactones using *N*-mono-substituted 2-[(tributylstannyl)methyl]propenamides derived from optically active amines. Good to excellent yields with 80%



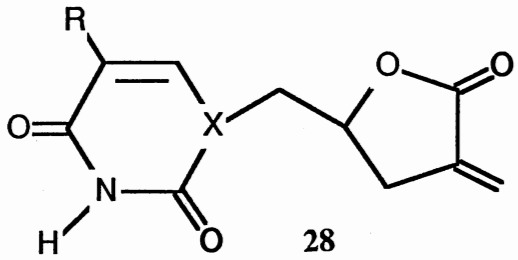
enantiomeric excess were reported.

α-Methylene lactones exhibit cytotoxic, antitumor and bactericidal properties. Several studies have been presented which describe the relationship between structure and activity.[17,42,75] For example, it has been shown that α-methylene-γ-butyrolactones act as cysteine scavengers.[73] Consequently, these lactones may be considered as alkylating agents which are biologically active via a Michael addition with certain biological nucleophiles. Compounds which contain an α-methylene-γ-butyrolactone sub-unit have demonstrated reactivity with mercapto-rich enzymes, including glycogen synthetase[77] and phosphofructokinase.[27]

Several α-methylene-γ-butyrolactone derivatives of nucleic acid bases have been screened for *in vivo* antitumor activity. Table V shows the biological activity of uracil- and thymine-substituted α-methylene-γ-butyrolactones and the corresponding derivatives **28a-28d**.[53] The pyrimidine derivatives were assayed for their *in vivo* antitumor activity against Walker 256 carcinosarcoma, P-388 lymphocytic leukemia, and B-16 melanotic

TABLE V

BIOLOGICAL ACTIVITY OF URACIL AND THYMINE α-METHYLENE-γ-BUTYROLACTONES AND THEIR DERIVATIVES[53]



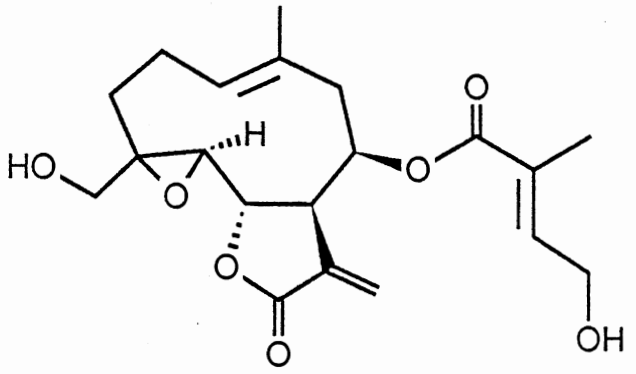
28

a. R = H
b. R = CH_3
c. R = $CH_2OC(O)CH{=}CHC_6H_5$
d. R = $CH_2OC(O)C_6H_2$-3,4,5-$(OCH_3)_3$

Compound	N[a]	Walker 256 ascites Avg days survived[b] (2.5 mg/kg)	T/C[c]	P-388 lymphocytic leukemia Avg days survived (25 mg/kg)	T/C	B-16 melanotic melanoma Avg days survived (25 mg/kg)	T/C
28a	6	10.13/7.75	131	11.50/10.00	115	13.51/12.20	111
28b	6	12.70/10.00	127	12.70/10.00	127	27.00/22.00	123
28c	6	23.80/11.30	211	12.30/9.50	130	27.60/19.60	141
28d	6	23.70/11.30	209	13.50/9.50	142	25.30/19.60	129

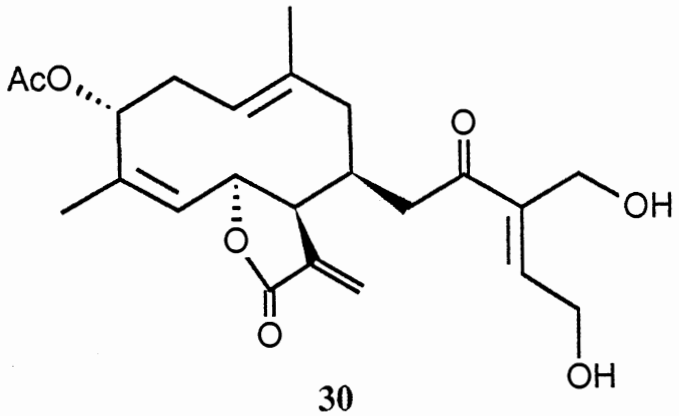
[a]N is the number of animals per group.
[b]Treated/control animals.
[c]A compound is active if it exhibits a T/C of ≥ 125%.

melanoma according to protocols of the National Cancer Institute (NCI). Compounds **28b-28d** displayed significant activity against all three types of tumors. The authors found it significant that derivatives **28b, 28c** and **28d** were active with all three groups since eupahyssopin (**29**)[51] and eupaformosanin (**30**)[50] (two natural occurring germacranolide



29

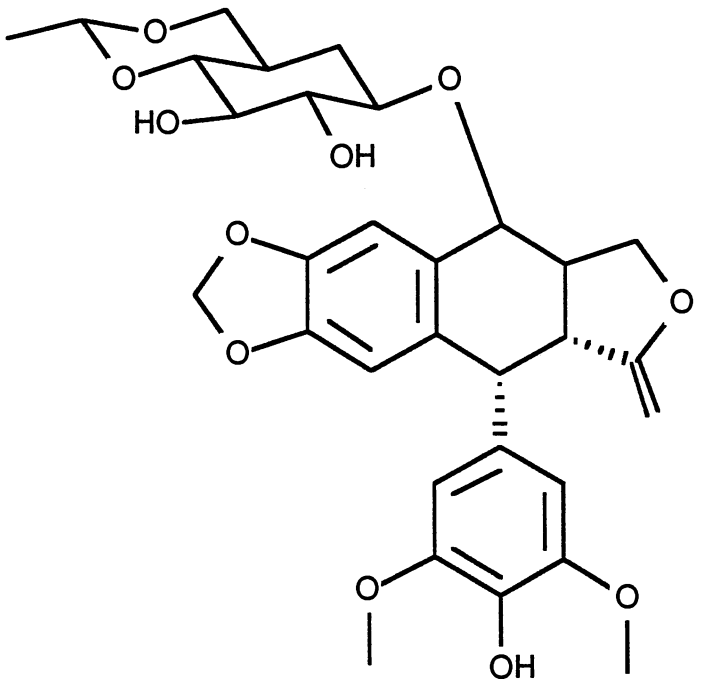
antitumor agents which are highly active in the Walker 256 screen) were *inactive* in the B-16 assay.



30

α-Methylene-γ-butyrolactones covalently linked to purines have recently been synthesized and their biological activity has been reported.[52] ED_{50} values for compounds

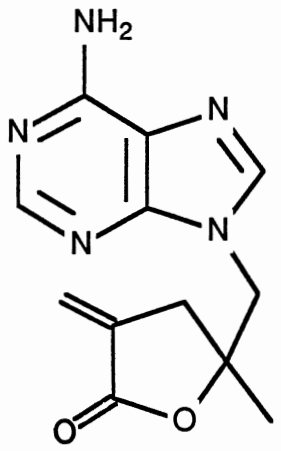
31, **32**, **33**, and etoposide (**34**), which is currently undergoing clinical trials, are presented in Table VI. The α-methylene-γ-butyrolactone-bearing purines were selective in terms of cytotoxicity. In the KB human carcinoma of the pharynx screen and the P-388 lymphocytic leukemia screen, the purine derivatives were essentially inactive. Potent activity was demonstrated, however, against the growth of murine L-1210 lymphoid leukemia. All three purine derivatives exhibited ED_{50} values of ≤ 2 μg/mL (see Table VI).



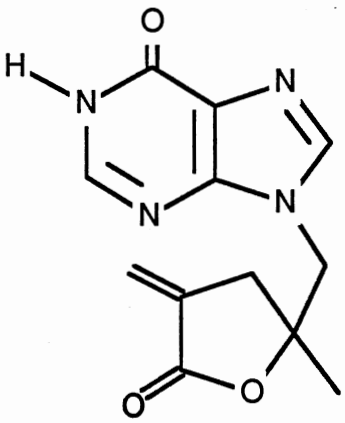
34

TABLE VI

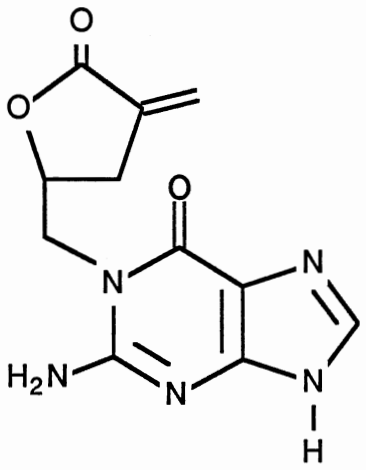
CYTOTOXICITY OF α-METHYLENE-γ-BUTYROLACTONE-BEARING PURINES[52]



31



32



33

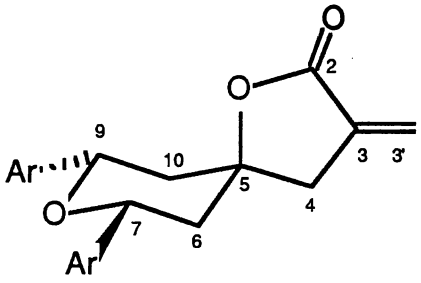
Compound	ED_{50}[a], μg/mL		
	KB	P-388	L-1210
31	5.0	> 20	0.3
32	> 10	> 20	2.0
33	> 10	> 20	1.3
34 (etoposide)		1.71	1.58

[a]For significant activity, an ED_{50} value of ≤ 4 μg/mL is required.

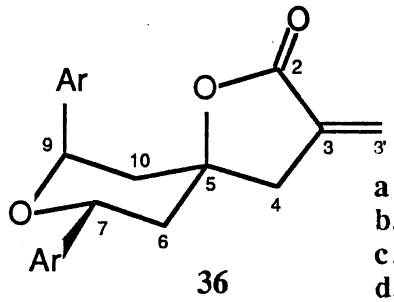
CHAPTER II

RESULTS AND DISCUSSION

The varied and promising pharmacological activities demonstrated by compounds containing an α-methylene-γ-butyrolactone moiety have stimulated considerable interest. We have developed syntheses for several novel spiro-α-methylene-γ-butyrolactones **35a-d** and **36a-b**, which are the first examples in this family of heterocycles. Both ^{1}H and ^{13}C



35



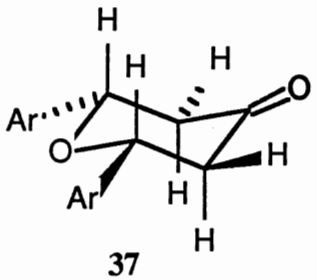
36

a. Ar = C_6H_5
b. Ar = 2-$H_3COC_6H_4$
c. Ar = 2-ClC_6H_4
d. Ar = 2-$H_3CC_6H_4$

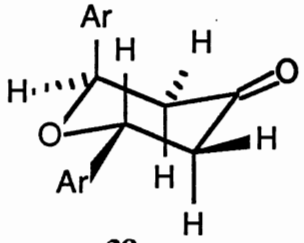
NMR spectral data were used to determine the configuration of atoms in the systems and the conformation of the spirolactones. The tetrahydropyran ring exists in a flattened chair form. The C(5)-O(1) bond was tentatively assigned as axial based on the NMR spectral data and on the preferred stereochemistry of certain known spirolactones.[58,60]

The spirolactones were synthesized via a Reformatsky-type reaction of ethyl 2-(bromomethyl)acrylate with an appropriate ketone.[59] The initial step in this project involved the synthesis of ketones **37a-g** and **38a-c** which, although very rare, could subsequently serve as key synthons for the corresponding spirolactones. In order to determine unequivocally the precise stereochemistry of ketones **37a** and **38a** (note that **3b** and **4b** in Table III of the Introduction have been renumbered **37a** and **38a**, respectively),

it was deemed necessary to perform X-ray diffraction analyses on each ketone and this was done by Dr. E. M. Holt. The results of the X-ray diffraction analyses are also presented.



37



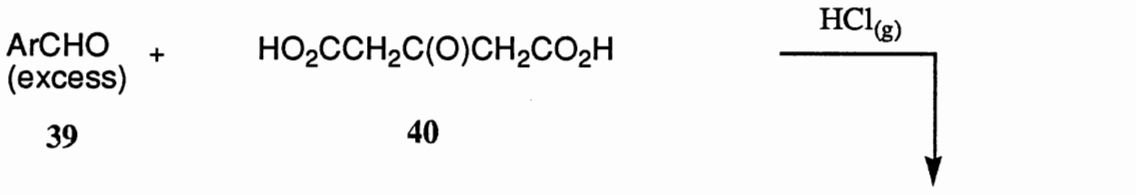
38

a. Ar = C_6H_5
b. Ar = 2-$H_3COC_6H_4$
c. Ar = 2-ClC_6H_4
d. Ar = 2-$H_3CC_6H_4$
e. Ar = 4-$H_3COC_6H_4$
f. Ar = 4-$H_3CC_6H_4$
g. Ar = 2,5-$(H_3C)_2C_6H_3$

The conformation and stereochemistry of the tetrahydropyran-4-ones were studied via ^1H and ^{13}C NMR analyses. The $^3J_{H(2)H(3)}$ coupling constants indicate that the tetrahydropyran-4-ones exist in flattened chair forms.

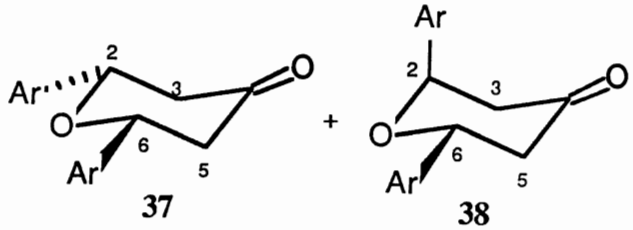
Syntheses and Spectral Analyses of 2,6-Diaryltetrahydropyran-4-ones

The cis and trans isomers of 2,6-diphenyltetrahydropyran-4-one (**37a**, **38a**) were obtained from the condensation of benzaldehyde (**39a**) with 1,3-acetonedicarboxylic acid



39 **40**

a. Ar = C_6H_5
b. Ar = 2-$H_3COC_6H_4$
c. Ar = 2-ClC_6H_4
d. Ar = 2-$H_3CC_6H_4$
e. Ar = 4-$H_3COC_6H_4$
f. Ar = 4-$H_3CC_6H_4$
g. Ar = 2,5-$(H_3C)_2C_6H_3$
h. Ar = 1-$C_{10}H_7$
i. Ar = 3,4-$(H_3CO)_2C_6H_3$
j. Ar = 2-HOC_6H_4
k. Ar = 4-HO(3-H_3CO)C_6H_3



37 **38**

(**40**).[6,7,8,20,21,65] In 1978, Baliah and Mangalam[7] reported that the cis isomer **37a** was the only product formed if the reaction mixture was cooled to -10°C, and the trans isomer **38a** was generated in good yield if the reaction was allowed to proceed at room temperature. Baxter and Whiting[8] also reported that the cis isomer **37a** was favored when the reaction was carried out at -10°C, but by careful fractional recrystallization, the authors were able to isolate a small amount of the trans isomer **38a**. These results differed from the previously published work,[6,20,21,65] which found that if the reaction was allowed to proceed at -10°C, the trans isomer **38a** was the major product isolated.

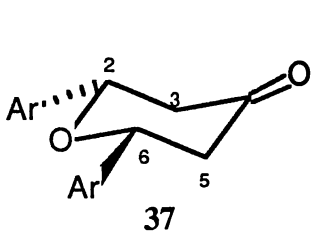
In our hands, when the reaction mixture was cooled to -10°C, the cis isomer **37a** was formed in good yield, but it was always contaminated with a small amount (<10%) of the trans isomer. The pure cis product **37a** was isolated by recrystallization (hot ethanol). When the reaction was carried out at room temperature, the quantity of each isomer generated was large and variable. The inconsistency observed in the formation of the trans isomer **38a** is most likely the result of the instability of 1,3-acetonedicarboxylic acid (**40**). Decomposition of the latter is rapid even in the cold. Only **37a** and **38a** have been reported in the literature in this family of 2,6-diaryltetrahydropyran-4-ones.

The same general synthetic scheme for ketones *cis*-**37a** and *trans*-**38a** was used to produce ketones **37b-g** and **38b-c**. The 2-methoxyphenyl isomers **37b** and **38b** were obtained in a total yield of 63% based on the condensation of three equivalents of 2–anisaldehyde (**39b**) with one equivalent of 1,3-acetonedicarboxylic acid (**40**). The isomeric mixture of ketones generated was separated on the Chromatotron. Following the general procedure for use of the Chromatotron (see Experimental Section), 1.0 g of an isomeric mixture of ketones was dissolved in a minimum amount of chloroform (<5 mL), and this solution was slowly added onto the 4-mm silica gel plate which was previously saturated with hexanes. As the separation proceeded, two bands were observed on the plate. The bands were usually separated by 1 cm of space by the time the first band reached the edge of the plate. Each fraction was collected and the product was crystallized

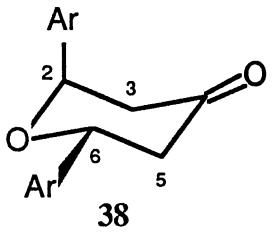
to afford the pure isomers. The melting points of the two isomers were very similar (*cis*-**37b**: 170-171°C; *trans*-**38b**:168-169°C). In order to verify the integrity of the two isomers, NMR analyses were performed, along with a mixture melting point determination (mixture mp 145-155°C).

The cis and trans isomers **37c** and **38c** were very difficult to separate. All chromatographic techniques (TLC, column, and the Chromatotron) which were applied to this separation were unfruitful. However, the isomers were purified by dissolving the isomeric mixture of ketones in acetone and, upon evaporating the solvent, the isomers crystallized in two distinct forms, namely square blocks and oval shaped crystals, which could be separated with tweezers. By ^{1}H and ^{13}C NMR analyses, the square blocks were determined to be the *cis*-isomer **37c**, and the oval blocks were the *trans*-isomer **38c**.

The remaining cis ketones **37d-g** were isolated and purified by recrystallization. In each case, a small quantity of the trans isomer was present (^{1}H NMR analysis) in the crude precipitate. After recrystallization, the trans isomer was no longer observable in the ^{1}H NMR spectra. All attempts to isolate the trans isomers **38d-g** were unsuccessful. Several attempts to synthesize and isolate ketones **37h-k** and **38h-k** were also



37



38

h. Ar = 1-$C_{10}H_7$
i. Ar = 3,4-$(H_3CO)_2C_6H_3$
j. Ar = 2-HOC_6H_4
k. Ar = 4-$HO(3\text{-}H_3CO)C_6H_3$

unsuccessful as evidenced by a very high (>90%) presence of unreacted aldehyde.

In order to test the accuracy of ^{1}H NMR analysis to determine the presence of small amounts of a trans isomer, two experiments were conducted using known amounts of **37b** and **38b**. In the first case a test sample was prepared by dissolving 1 mg of **38b** (~5%) and 19 mg of **37b** in 0.7 mL of $DCCl_3$. The observed peaks at δ 5.52 [H(2,6)], 2.94 [H_e(3,5)], and 2.71 [H_a(3,5)] as well as the two peaks observed for the methoxy protons

[δ 3.82, 3.76 (in a 20:1 ratio for cis:trans from the integration)], clearly indicate the presence of the trans isomer **38b**. In the second experiment, a sample was prepared by dissolving 0.5 mg of **38b** (~2.5%) and 19.5 mg of **37b** in 0.7 mL of $DCCl_3$. The ratio of cis:trans isomers was 35:1 based on the integration of signals at δ 5.22 and 5.52, respectively.

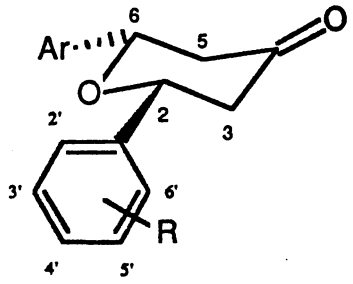
Much information concerning the stereochemistry of ketones **37a-g** and **38a-c** can be gleaned from the ^1H NMR spectral data (see Table VII). Certain common characteristics deserve mention. The signals for H(2) and H(6) in the cis ketones **37a-g** occur either as a doublet of doublets (dd) or as a dd merged into a triplet (t) at $\delta \cong 5$. The corresponding signals for H(2,6) in the trans isomers **38a-c** are significantly downfield in the range of 5.1-5.6. Comparison of the signals for H(2,6) in the cis ketones **37a-c** with the corresponding signals for H(2,6) in trans ketones **38a-c** reveals a downfield shift of 90 Hz (see Table VII) for the latter. Presumably, **38a-c** are mobile systems and thus the signals due to H(2,6) are an average arising from a ring reversal process.[18,26]

The ^{13}C NMR spectral data are recorded in Table VIII. The presence of the axial aryl groups in the trans isomers causes upfield shifts (Δ ppm) of 5.42, 4.51 and 5.14 for C(2,6) in **38a**, **38b** and **38c**, respectively, when compared to the chemical shifts of C(2,6) in the cis isomers **37a**, **37b** and **37c**. There is also a small shielding effect (3.27, 2.61 and 2.16 ppm) for C(3,5) when an axial phenyl group is present at C(2) [or C(6)]. The ortho substituent on the aromatic ring (**37b**, **c**, **d** and **g**) resulted in enhanced shielding of C(2,6). This shielding is presumably caused by a steric effect due to the orientation of the aromatic rings. This is in agreement with the findings of Hasan and co-workers for 2,6-diarylpiperidin-4-ones[28] and supported by diagnosis of space-filling models of **37a**.

In order to determine unequivocally the precise stereochemistry of the tetrahydropyran-4-ones, X-ray analyses were obtained for ketones **37a** and **38a** by Dr. E. M. Holt (see Table IX for crystal data). The *cis*- and *trans*-2,6-diphenyltetrahydropyran-4-ones (**37a**, **38a**) display similar details of connectivity, both isomers

TABLE VII

^{1}H NMR DATA FOR TETRAHYDROPYRAN-4-ONES

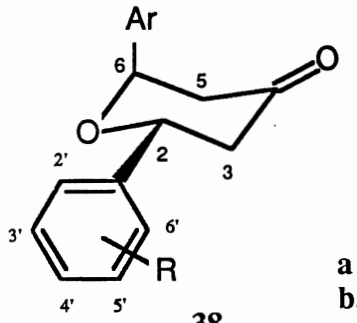


37

a. Ar = C_6H_5
b. Ar = 2-$H_3COC_6H_4$
c. Ar = 2-ClC_6H_4
d. Ar = 2-$H_3CC_6H_4$
e. Ar = 4-$H_3COC_6H_4$
f. Ar = 4-$H_3CC_6H_4$
g. Ar = 2,5-$(H_3C)_2C_6H_3$

Compound	Chemical Shift[a]		
	H (2,6)	H (3,5)	Other
37a	4.86 (dd, 2 H, J= 9.9, 4.2 Hz)	2.68-2.77 (m, 4 H)	7.3-7.5 (m, 10 H, Ar-H)
37b	5.22 (dd, 2 H, J= 11.6, 1.9 Hz)	2.48 [dd, 2 H, H_a(3,5), J=14.5, 11.6 Hz] 2.85 [dd, 2 H, H_e(3,5), J=15.1, 1.9 Hz]	3.82 [s, 6 H, H(OCH_3)] 6.91 [d, 2 H, H(6')] 7.09 [t, 2 H, H(4')] 7.32 [t, 2 H, H(5')] 7.77 [d, 2 H, H(3')]
37c	5.27 (dd, 2 H, J= 11.4, 2.1 Hz)	2.51 [dd, 2 H, H_a(3,5), J=14.9, 11.4 Hz] 2.94 [dd, 2 H, H_e(3,5), J=14.7, 1.5 Hz]	7.34 [d, 2 H, H(6')] 7.40-7.60 [m, 4 H, H(4',5')] 7.84 [d, 2 H, H(3')]
37d	5.03 (t, 2 H, J= 8 Hz)	2.70 (d, 4 H, J=8 Hz)	2.36 [s, 6 H, H(CH_3)] 7.15-7.65 (m, 8 H, Ar-H)
37e	4.77 (dd merged into t, 2 H)	2.67-2.70 (m, 4 H)	3.81 [s, 6 H, H(OCH_3)] 6.90 [d, 4 H, H(3',5')] 7.36 [d, 4 H, H(4',6')
37f	4.78 (dd merged into t, 2 H)	2.66-2.70 (m, 4 H)	2.36 [s, 6 H, H(OCH_3)] 7.18 (d, 4 H, Ar-H) 7.32 (d, 4 H, Ar-H)
37g	4.99 (dd, 2 H, J= 9, 5 Hz)	2.66-2.72 (m, 4 H)	2.33 [s, 6 H, H(CH_3)] 2.38 [s, 6 H, H(CH_3)] 7.08 (bs, 4 H, Ar-H) 7.45 (bs, 2 H, Ar-H)

TABLE VII (continued)



38

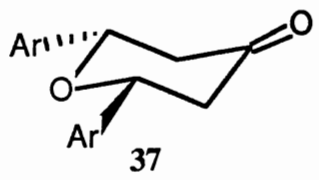
a. Ar = C_6H_5
b. Ar = 2-$H_3COC_6H_4$
c. Ar = 2-ClC_6H_4

Compound	Chemical Shift[a]		
	H (2,6)	H (3,5)	Other
38a	5.16 (dd merged into t, 2 H)	2.85 [dd, 2 H_a(3,5), J=15.0, 5.1 Hz] 2.95 [dd, 2 H, H_e(3,5) J=14.9, 6.5 Hz]	7.3-7.4 (m, 10 H, Ar-H)
38b	5.52 (dd, 2 H, J=7.4, 4.9 Hz)	2.71 [dd, 2 H, H_a(3,5), J=16.1, 7.9 Hz] 2.94 [dd, 2 H, H_e(3,5), J=16.1, 4.9 Hz]	3.76 [s, 6 H, H(OCH_3)] 6.88 [d, 2 H, H(6')] 6.99 [t, 2 H, H(4')] 7.29 [t, 2 H, H(5')] 7.48 [d, 2 H, H(3')]
38c	5.56 (dd, 2 H, J=8.2, 4.7 Hz)	2.77 [dd, 2 H, H_a(3,5), J=16.1, 8.2 Hz] 3.01 [dd, 2 H, H_e(3,5), J=15.8, 4.7 Hz]	7.24-7.37 [m, 6 H, H(4',5',6')] 7.55 [dd, 2 H, H(3')]

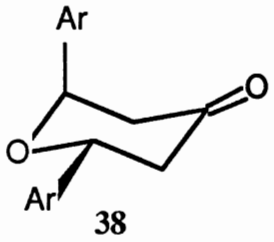
[a]NMR values are in δ units downfield from TMS.

TABLE VIII

^{13}C CHEMICAL SHIFT DATA FOR TETRAHYDROPYRAN-4-ONES



37



38

a. Ar = C_6H_5
b. Ar = 2-$H_3COC_6H_4$
c. Ar = 2-ClC_6H_4
d. Ar = 2-$H_3CC_6H_4$
e. Ar = 4-$H_3COC_6H_4$
f. Ar = 4-$H_3CC_6H_4$
g. Ar = 2,5-$(H_3C)_2C_6H_3$

Compound	Chemical Shift[a]			
	C (3,5)	C (2,6)	C (4)	Other
37a	49.71	78.95	206.08	Ar-C: 140.70, 128.63, 128.08, 125.63
37b	48.41	73.45	207.03	OCH_3, 55.18; Ar-C: 155.15, 129.70, 128.39, 125.80, 120.72, 110.10
37c	47.65	75.67	204.85	Ar-C: 138.38, 131.27, 129.54, 129.06, 127.40, 126.86
37d	48.53	76.37	206.46	CH_3, 19.05; Ar-C: 138.84, 134.22, 130.49, 127.86, 126.54, 125.41
37e	49.64	78.66	206.45	OCH_3, 55.28; Ar-C, 159.37, 132.95, 127.06, 113.95
37f	49.73	78.88	206.45	CH_3, 21.15; Ar-C, 137.87, 137.80, 129.25, 125.66
37g	48.51	76.48	206.73	2-CH_3, 18.62; 5-CH_3, 21.19; Ar-C: 138.46, 135.96, 131.24, 130.45, 128.59, 126.07
38a	46.44	73.53	206.47	Ar-C: 139.79, 128.62, 128.06, 126.69
38b	45.80	68.94	208.54	OCH_3, 55.19; Ar-C: 156.53, 129.24, 128.95, 127.56, 120.62, 110.63
38c	45.49	70.53	206.84	Ar-C: 137.56, 132.92, 129.91, 129.37, 128.78, 127.06

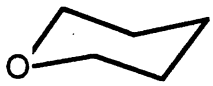
[a]Chemical shift values are in ppm downfield from TMS.

TABLE IX

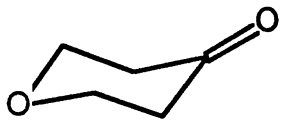
CRYSTAL DATA FOR *cis*-**37a** AND *trans*-**38a**

	37a	**38a**
Formula	$C_{17}H_{16}O_2$	$C_{17}H_{16}O_2$
M.W.	252.3	252.3
a	29.834 (2) Å	10.436 (5) Å
b	8.214 (4)	5.281 (2)
c	11.761 (5)	12.952 (6)
α	90.0°	90.0°
β	107.18 (5)	110.90 (4)
γ	90.0	90.0
V	2753.5 (27) $Å^3$	666.8 (5) $Å^3$
F (000)	1072	268
μMoK_α	0.733 cm^{-1}	0.756 cm^{-1}
λMoK_α	0.71069 Å	0.71069 Å
D_{calc}	1.217 g cm^{-3}	1.256 g cm^{-3}
Z	8	2
Meas refl	6464	2024
Obs refl	1770	798
R	8.75%	5.35%
R_w	15.8%	6.8%
G. O. F.	0.64	0.28
Space group	$P2_1/n$	$P2_1$
Octants meas	±h, +k, +1	±h, +k, +1

containing 1-oxa-4-cyclohexanone rings substituted with phenyl groups at the C(2)- and C(6)-positions (see Figures 1 and 2 for the conformation and numbering of atoms). Average bond distances within the heterocyclic ring [C=O, 1.19(2) Å; C-O, 1.44(2) Å; C-C, 1.50(2) Å] were all normal values (see Tables X and XI for bond angles and distances) compared to the values in cyclohexanone[4,72] for C=O [1.24(1) Å] and C-C [1.54(1) Å] and for the C-O [1.42(2) Å] bond in tetrahydropyran.[13] Similarly, distances within the phenyl rings were all nonremarkable as were the bond angles. Moreover, the cis and trans arrangement of the substituents at C(2) and C(6) appears to make no *large* difference in the bond angles observed within the framework of the heterocyclic ring. The average of such angles observed in the cis molecule **37a** equaled those of the trans isomer **36a** within experimental error. Two rings were clearly in a chair form, with the carbonyl end flattened and the oxo end only very slightly flattened. Both relatives, tetrahydropyran (**41**)[13,70] and tetrahydropyran-4-one (**42a**),[4] exist in flattened chair forms.[4,13,26,70]



41



42a

Analysis of the dihedral angles was somewhat difficult since significant differences exist in these found for each of the two molecules (**37: A and B**) within the asymmetric unit of the solid cis isomer (see Table XII). It was impossible to determine the precise values for the torsional angles between H(2) and H(3) [or H(5) and H(6)] since the position of the protons was not refinable in the X-ray analysis. Using estimated hydrogen positions, values were calculated for all torsional angles between substituents across the C(2)-C(3) bond and across the C(5)-C(6) bond (Figure 3). It must be emphasized that these torsional angles are *estimates* and thus can only be used to describe *qualitatively* the conformation of the heterocyclic ring. The values shown are nevertheless consistent

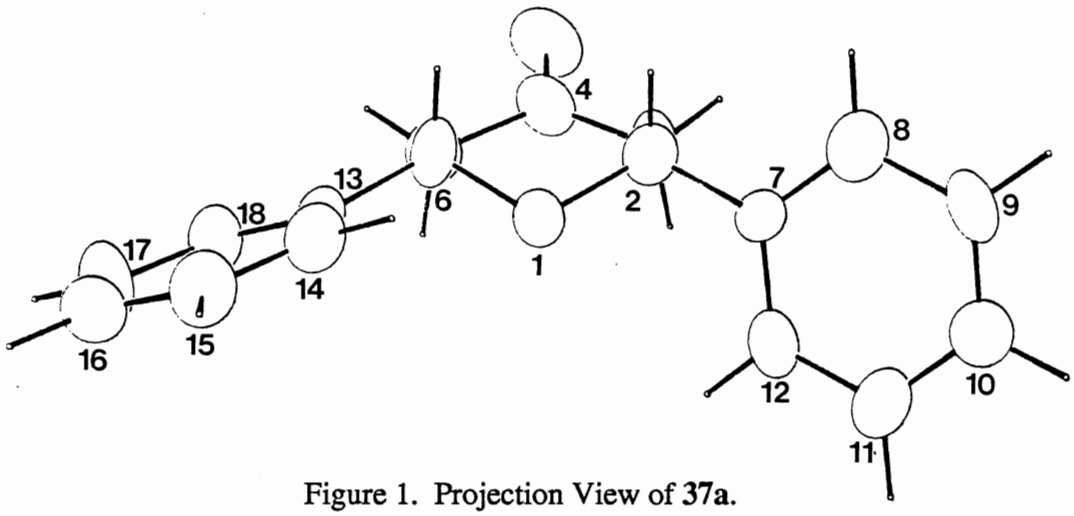


Figure 1. Projection View of **37a**.

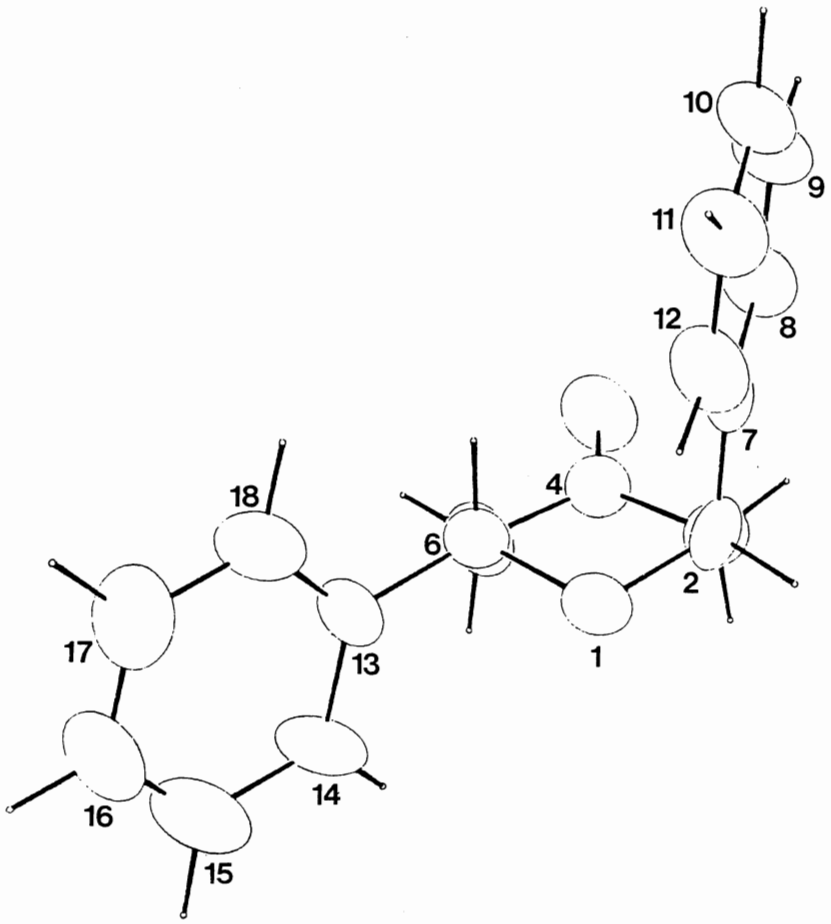


Figure 2. Projection View of **38a**.

TABLE X

BOND DISTANCES (Å) FOR **37a** AND **38a**

	37a		**38a**
	molecule A	molecule B	
O(1)-C(2)	1.43 (2)	1.44 (2)	1.43 (1)
O(1)-C(6)	1.46 (1)	1.44 (2)	1.43 (2)
C(2)-C(3)	1.51 (2)	1.49 (2)	1.53 (1)
C(3)-C(4)	1.53 (2)	1.50 (2)	1.49 (2)
C(4)-O(4)	1.18 (2)	1.20 (2)	1.20 (1)
C(4)-C(5)	1.51 (2)	1.49 (2)	1.48 (1)
C(5)-C(6)	1.49 (2)	1.48 (2)	1.51 (2)
C(2)-C(7)	1.53 (2)	1.50 (2)	1.52 (2)
C(6)-C(13)	1.49 (2)	1.51 (2)	1.52 (1)
C(7)-C(8)	1.38 (2)	1.35 (2)	1.39 (2)
C(8)-C(9)	1.39 (2)	1.40 (3)	1.36 (2)
C(9)-C(10)	1.40 (2)	1.34 (3)	1.37 (1)
C(10)-C(11)	1.35 (2)	1.34 (3)	1.38 (2)
C(11)-C(12)	1.38 (2)	1.38 (3)	1.35 (2)
C(12)-C(7)	1.39 (2)	1.37 (2)	1.39 (1)
C(13)-C(14)	1.38 (2)	1.38 (2)	1.36 (2)
C(14)-C(15)	1.40 (2)	1.40 (2)	1.38 (1)
C(15)-C(16)	1.34 (2)	1.36 (2)	1.36 (2)
C(16)-C(17)	1.36 (2)	1.37 (2)	1.35 (2)
C(17)-C(18)	1.37 (8)	1.41 (2)	1.37 (1)
C(18)-C(13)	1.38 (2)	1.37 (2)	1.38 (2)

TABLE XI

BOND ANGLES (°) FOR KETONES **37a** AND **38a**

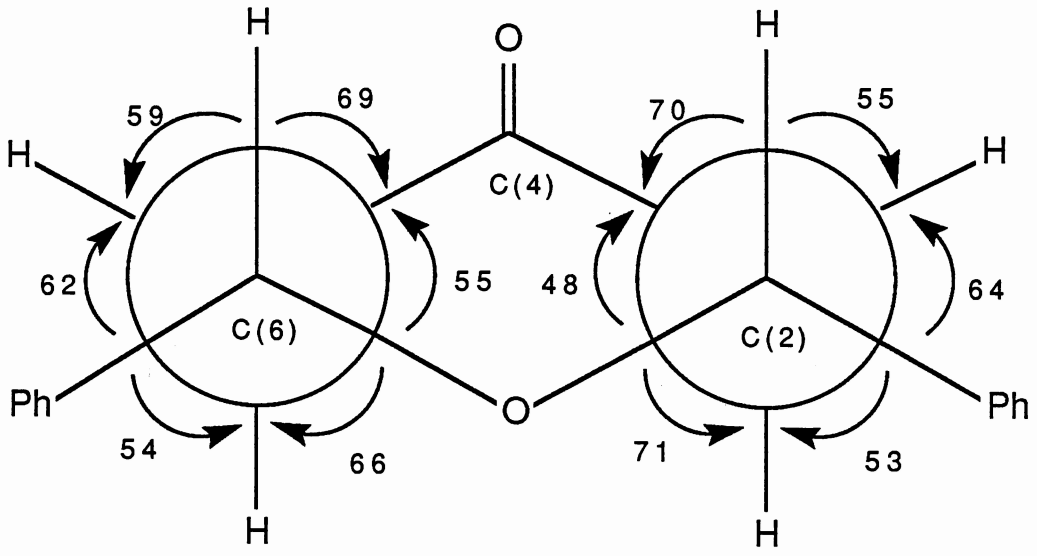
	37a		**38a**
	molecule A	molecule B	
C(2)-O(1)-C(6)	111 (1)	113 (1)	112 (1)
O(1)-C(2)-C(3)	110 (1)	110 (1)	110 (1)
C(3)-C(2)-C(7)	114 (1)	113 (1)	114 (1)
O(1)-C(2)-C(7)	106 (1)	110 (1)	111 (1)
C(2)-C(3)-C(4)	111 (1)	114 (1)	112 (1)
C(3)-C(4)-C(5)	114 (1)	114 (1)	114 (1)
O(4)-C(4)-C(5)	123 (1)	122 (2)	124 (1)
O(4)-C(4)-C(3)	123 (1)	123 (1)	122 (1)
C(4)-C(5)-C(6)	114 (1)	113 (1)	112 (1)
C(5)-C(6)-O(1)	111 (1)	111 (1)	110 (1)
O(1)-C(6)-C(13)	110 (1)	109 (1)	107 (1)
C(5)-C(6)-C(13)	112 (1)	118 (1)	114 (1)
C(2)-C(7)-C(8)	119 (1)	119 (1)	124 (1)
C(2)-C(7)-C(12)	124 (1)	122 (1)	119 (1)
C(8)-C(7)-C(12)	116 (1)	119 (1)	117 (1)
C(7)-C(8)-C(9)	122 (1)	119 (2)	120 (1)
C(8)-C(9)-C(10)	119 (1)	122 (2)	123 (1)
C(9)-C(10)-C(11)	119 (1)	118 (2)	117 (1)
C(10)-C(11)-C(12)	121 (1)	122 (2)	121 (1)
C(11)-C(12)-C(7)	122 (1)	120 (2)	122 (1)
C(6)-C(13)-C(14)	120 (1)	119 (1)	120 (1)
C(6)-C(13)-C(18)	121 (1)	123 (1)	121 (1)
C(14)-C(13)-C(18)	118 (1)	118 (1)	119 (1)
C(13)-C(14)-C(15)	120 (1)	121 (1)	121 (1)
C(14)-C(15)-C(16)	120 (1)	121 (1)	120 (2)
C(15)-C(16)-C(17)	121 (1)	118 (1)	120 (1)
C(16)-C(17)-C(18)	120 (1)	121 (2)	121 (1)
C(17)-C(18)-C(13)	121 (1)	121 (1)	120 (2)

with a flattened chair. The angles found which describe the orientation of the aromatic rings were, however, instructive (see Tables XIII and XIV). The cis isomer **37a** has both phenyl rings in equatorial positions, with the planes of the phenyl rings being almost mutually perpendicular (78.2, 81.2° two forms in the unit cell). One ring is nearly perpendicular (87.3, 88.0°) to the seat of the chair (perpendicular also to the C-C bonds [C(2)-C(3) and C(5)-C(6)] forming the sides of the seat of the chair), and the other subtends an angle of 17.0, 18.3° with the seat of the chair and is thus close to coplanarity with the seat of the chair. The trans isomer **38a** shows an angle of 38.7° between the planes of the two phenyl rings, with the plane of the equatorial ring subtending an angle of 69.4° to the seat of the chair. The axial ring is roughly perpendicular (78.9°) to the seat of the chair, and it is also nearly co-planar with the C(2)-C(3) bond in the side of the chair.

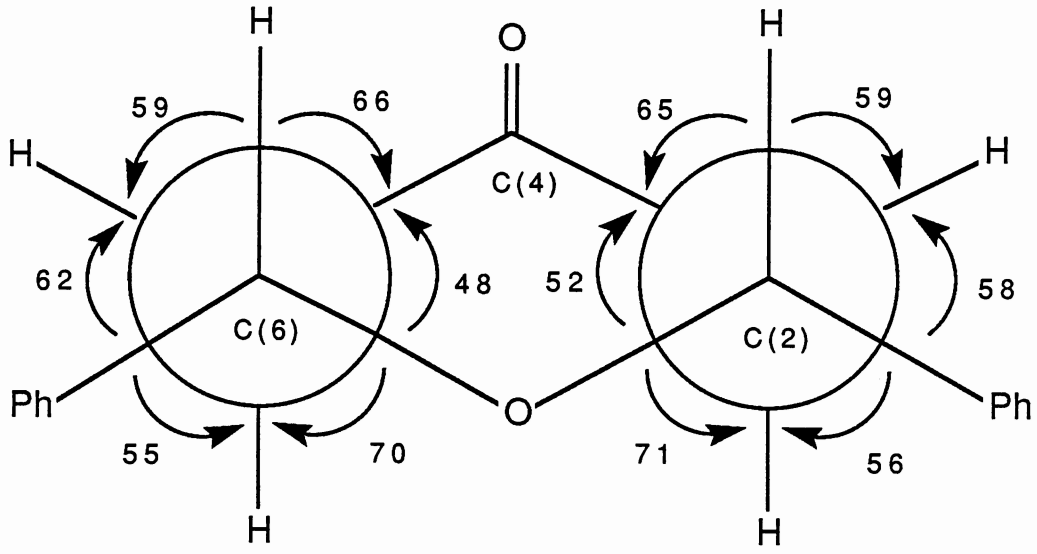
TABLE XII

DIHEDRAL ANGLES (°) FOR KETONES **37a** AND **38a**

	cis **37a**		trans **38a**
	molecule A	molecule B	
O(1)-C(6)-C(5)-C(4)	48 (1)	52 (2)	53 (1)
C(2)-O(1)-C(6)-C(5)	-63 (1)	-62 (1)	62 (1)
C(3)-C(2)-O(1)-C(6)	65 (1)	59 (1)	-61 (1)
C(4)-C(3)-C(2)-O(1)	-55 (1)	-48 (2)	52 (1)
C(5)-C(4)-C(3)-C(2)	43 (2)	41 (2)	-46 (1)
C(6)-C(5)-C(4)-C(3)	-40 (2)	-43 (2)	46 (1)



Molecule A



Molecule B

Figure 3. Dihedral Angles (°) for the Two Molecules in the Asymmetric Unit of cis Ketone **37a** as Calculated from the X-ray Data.

TABLE XIII

ANGLES (°) BETWEEN PLANES FOR **37a**

		Molecule A/Molecule B		
	Phenyl ring C(13)-C(18)	Chair seat C(2), C(3), C(5), C(6)	C(3), C(4), C(5)	C(2), O(1), C(6)
Phenyl ring C(7)-C(12)	78.2 81.2	18.3 88.0	32.5 57.5	51.3 43.8
Chair seat C(2), C(3), C(5), C(6)	87.3 17.0	—	37.7 37.9	57.8 54.5
C(3), C(4), C(5)	58.5 36.2	37.7 37.9	—	20.1 16.5
C(2), O(1), C(6)	42.8 51.5	57.8 54.4	20.1 16.5	—

TABLE XIV

ANGLES (°) BETWEEN PLANES FOR **38a**

	Phenyl ring C(13)-C(18)	Chair seat C(2), C(3), C(5), C(6)	C(3), C(4), C(5)	C(2), O(1), C(6)
Phenyl ring C(7)-C(12)	38.7	78.9	88.3	88.3
Chair seat C(2), C(3), C(5), C(6)	69.4	—	41.9	55.9
C(3), C(4), C(5)	77.8	41.9	—	14.0
C(2), O(1), C(6)	67.2	55.9	14.0	—

As was previously mentioned, the R-value method proposed by Lambert has been used to estimate the dihedral angle in certain types of molecules.[43,44,47] The trans ketones **38a-c** are three such molecules. Each contains a CH_2CHR moiety with two rapidly equilibrating, equivalent conformers. The ^3J, R and calculated ϕ values are listed in Table XV. The calculated dihedral angle for **38a** was 49°. This is smaller than the angle obtained from the X-ray data (52-53°) for solid **38a**. However, both values suggest the compound exists in a flattened chair form. The calculated dihedral angles for **38b** and **38c** (53.4° and 54.7°, respectively) indicate that these compounds also exist in flattened chair forms in solution.

The R-value method cannot be applied to the study of the conformation of cis ketones **37a-g**.[43] The Karplus relationship conceivably might be used to estimate the angle between two vicinal protons. The original Karplus equation,[39,40] as well as the modified equations proposed by Gandour[19] and Altona,[25,26] were used in our work to estimate the torsional angle between vicinal protons [H(2)-C(2)-C(3)-H(3) or H(6)-C(6)-C(5)-H(5)] in cis ketones **38a**, **b**, **c** and **g**. The calculated angles obtained from the ^1H NMR spectra of the aforementioned cis ketones are presented in Table XVI. The dihedral angles obtained from the Karplus and Gandour equations are in reasonably good agreement. The Altona equation, however, yielded values which were consistently smaller when the Huggins electronegativity scale was used. Due to this discrepancy, a modification was made in that the Cavanaugh[18] and Allred-Rockow electronegativity scales were used in the Altona equation. The results (see Table XVI) from using the Cavanaugh electronegativity scale are in much better agreement with the values obtained from the Karplus and Gandour equations.

The torsional angle calculated for **37a** (~49°) corresponds to a flattened chair form of the six-membered tetrahydropyran-4-one ring. This is in agreement with the X-ray data already presented (Table XII). The torsional angle obtained for **37g** (~53°) is also indicative of a flattened chair. The values (70° and 69°, respectively) obtained for **37b** and

TABLE XV

DIHEDRAL ANGLES (°) CALCULATED FROM ^3J VALUES FOR TRANS KETONES **38a-c**

Compound	J_{trans}	J_{cis}	R	ϕ^a
38a	6.5	5.2	1.25	49
38b	7.9	4.9	1.61	53
38c	8.2	4.7	1.74	54

[a]Dihedral angle of O(1)-C(2)-C(3)-C(4) or O(1)-C(6)-C(5)-C(4).

TABLE XVI

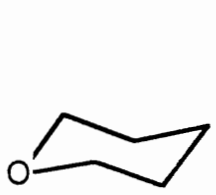
TORSIONAL ANGLES (°) CALCULATED FROM ^3J (Hz) VALUES[a]

		Equation				
				Altona[b]		
Compound	^3J	Karplus	Gandour	Huggins	Cavanaugh	Allred-Rockow
37a	4.2	48	49	43	48	46
37b	1.9	70	74	60	68	63
37c	2.1	69	71	58	66	61
37g	3.6	53	54	47	52	50

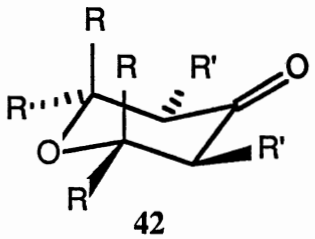
[a]Three separate electronegativity scales were used with the equation proposed by Altona.
[b]The angle between $H_a(2)$-$H_e(3)$ and $H_a(6)$-$H_e(5)$.

37c from the Karplus equation are much higher than even that found in cyclohexanone (56.3°)[12] and therefore are suspect. The ortho methoxy and chloro groups almost certainly alter steric as well as electronic effects on H(2,6) and possibly on H(3,5).[37] The equations used in the calculation of the torsional angles do not adequately compensate for these effects.

An extensive literature search for structural data on relevant model compounds such as tetrahydropyran (**41**), tetrahydropyranone (**42a**), 3,5-dimethyltetrahydropyran-4-one (**42b**) and 2,2,6,6-tetramethyltetrahydropyran-4-one (**42c**) proved unfruitful. However, X-ray data for 6,8-bis(2-chlorophenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (**43**) was

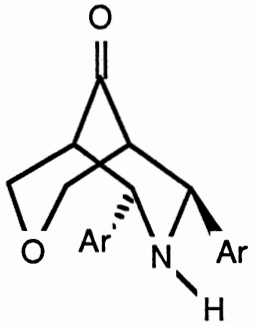


41



42

a. R = R' = H
b. R = H, R' = CH_3
c. R = CH_3, R' = H



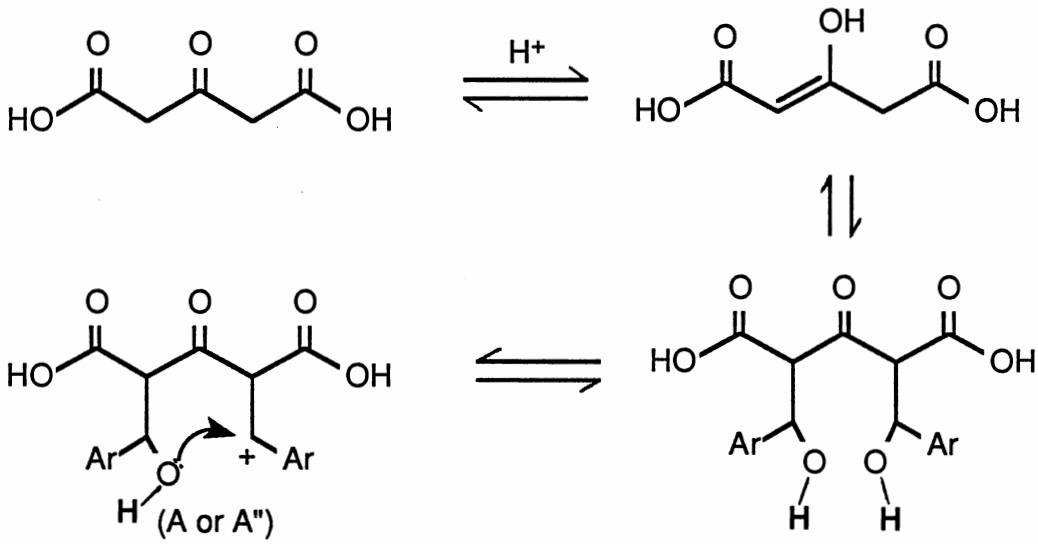
43

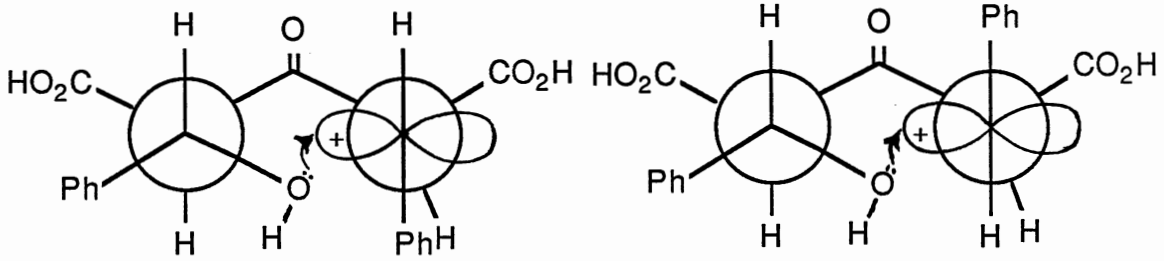
found.[5] The dihedral angle [O(3)-C(2)-C(1)-C(9)] was determined to be 57.2°. This is somewhat larger than the angles obtained for ketones **37a** and **38a**, but this is presumably due to the substitution at C(1,5), which likely forces the carbonyl end of the tetrahydropyran ring up toward a more perfect chair form.

In summary, it has been possible to prepare several members of the family of *cis*-2,6-diaryltetrahydropyran-4-ones and three members of the corresponding trans isomers. Structural analyses on two isomers (**37a** and **38a**) suggests both are flattened chairs but with carbonyl groups still exposed and vulnerable to attack by large nucleophiles.

The formation of only small amounts of trans ketones **38b-g** leads us to speculate on the possible cause for this situation. Under the conditions employed (namely allowing the

reagents to react in the absence of solvent), an acidic medium is present in which the enol of the starting ketone should readily form. A reasonable mechanism which could develop is outlined below. After the initial attack of the enol on the aldehyde, a second enol must form and attack a second equivalent of the aldehyde to form a diol, presumably as shown. Generation of cation **A** or **A'** from the diol gives, in our opinion, the key intermediates



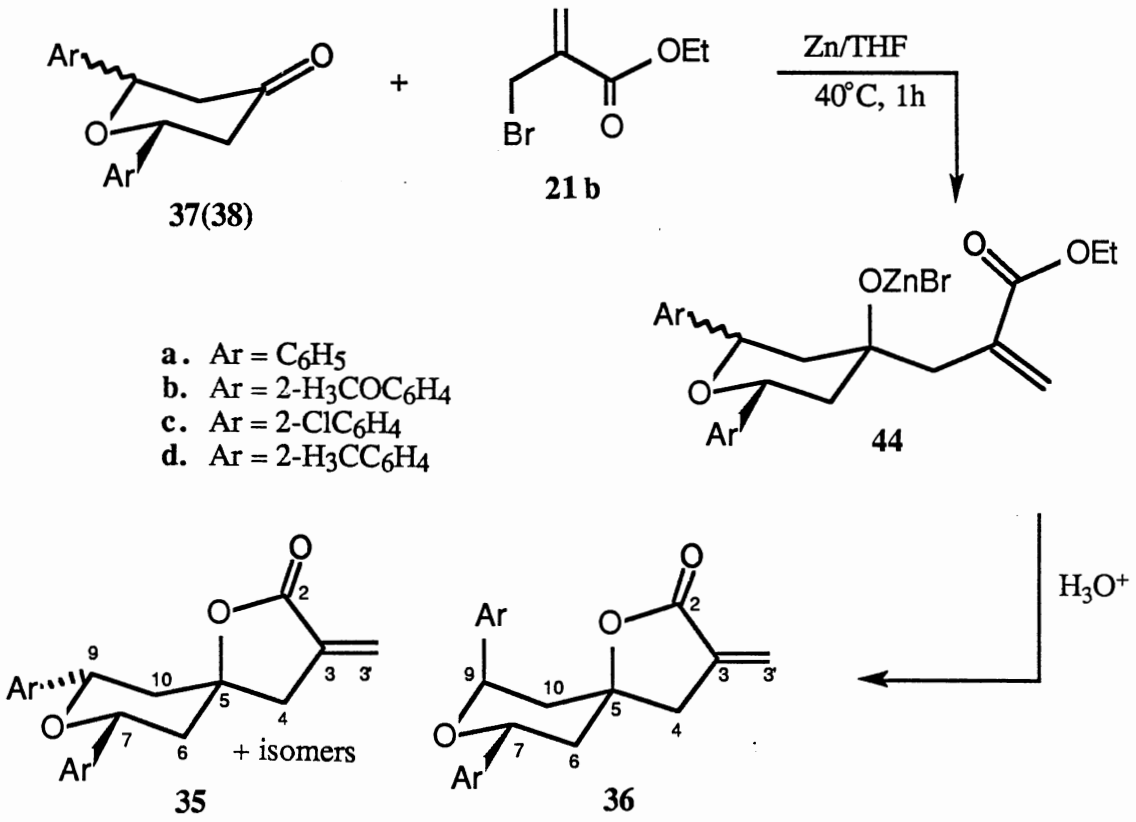


A **A'**

from which the stereochemistry of the final ketone is created. Assuming that the empty orbitals and attached substituents on the sp^2 carbon (cation carbon) are best accommodated in the intermediate (and transition states to be formed) as shown in **A** (or **A'**), attack by the residual HO group on the empty orbital in **A** should give the cis isomer. Attack as shown in **A'** should yield the trans isomer. Different steric effects between the aryl group on the sp^2 carbon in **A** versus in **A'** are obvious. Although axial C-H 3,5-interactions are greater in **A**, the gauche interactions in **A'** are substantial and involve the Ar, C=O, and CO_2H groups. To be sure it is problematical if these suggested intermediates are correct, but one might suspect the gauche interactions to be significant and perhaps are greater than the axial 3,5-interactions. Thus, the formation of the cis isomer from **A** has a tentative defense. An alternative mechanism to consider is that involving formation of an enone via an elimination of a proton from **A** (or **A'**). However, it seems to us that attack of the HO group on the upper or lower face of the double bond (in conjugation with the C=O group) would be a high energy process since the intermediate would also require the C-H or C-Ar bond to be directed towards the center of the developing ring. Although the evidence is not conclusive, we tend to favor the first mechanism as illustrated.

Syntheses and Spectral Analyses of Spiro α-Methylene-γ-butyrolactones

The synthetic scheme involved generation of γ-hydroxy esters (or salt precursors thereof) from the Reformatsky-type reaction of ethyl 2-(bromomethyl)acrylate (**21b**) with the appropriate ketone.[54,66,75] Lactonization of the γ-hydroxy esters **44** provided spiro α-methylene-γ-butyrolactones **35a-d** and **36a-b**. Lactones **35a-d** were isolated as crystalline solids after purification on the Chromatotron while lactones **36a-b** could be isolated as only viscous oils. All efforts to crystallize **36a** and **36b** have proved unfruitful.



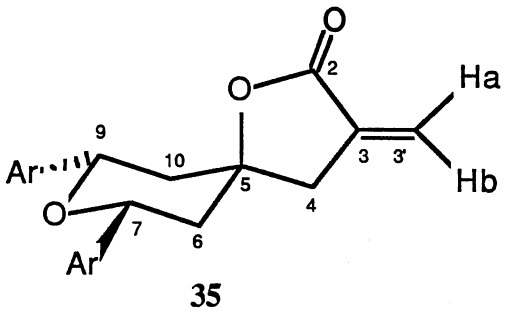
The ^{1}H NMR spectral data are reported in Table XVII. Assignments of the signals at $\delta \cong 5.7$ and 6.3 for $H_b(3')$ and $H_a(3')$, respectively, were based on the empirical correlation (eq 4) developed by Tobey[83] and Pascual, Meier and Simon[61] for estimating

$$\delta = 5.28 + Z_{gem} + Z_{cis} + Z_{trans} \quad (4)$$

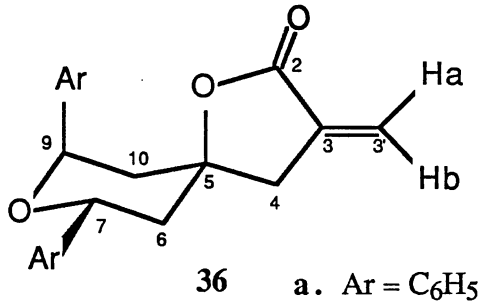
the chemical shift of a proton on a double bond. The calculated values of δ 5.58 for $H_b(3')$ and δ 6.14 for $H_a(3')$ agree closely with the experimentally determined values for each lactone (see Table XVII). The signal at $\delta \cong 5.2$ corresponds to protons H(7,9). The observed coupling constants $^3J_{H(7a),H(6a)} = {}^3J_{H(9a),\ H(10a)} \cong 11.3$ Hz, indicate that the C(7)-H and C(9)-H bonds are axial in **35a-d**. The ^{1}H NMR spectra for **36a-b** were non-first order, and therefore accurate coupling constants could not be determined. The torsional angle between $H_a(7)$ and $H_a(6)$ [$H_a(9)$ and $H_a(10)$] in the cis lactone **35a-d** was calculated from the observed ^{3}J values using the modified Karplus equation proposed by

TABLE XVII

^{1}H NMR DATA FOR SPIROLACTONES



35



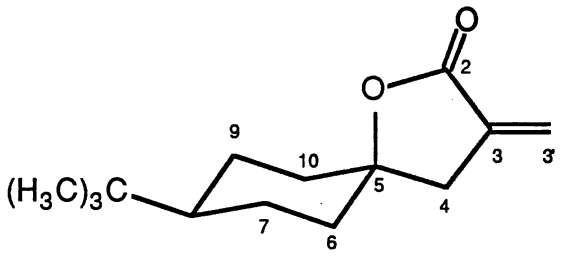
36

a. Ar = C_6H_5
b. Ar = 2-$H_3COC_6H_4$
c. Ar = 2-ClC_6H_4
d. Ar = 2-$H_3CC_6H_4$

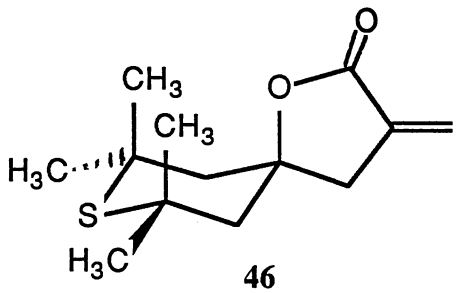
	Chemical Shift[a]				
Compound	H(3')[b]	H(4)	H(6,10)	H(7,9)	Other
35a	5.69 (H_b) 6.32 (H_a)	2.80[c]	1.85 (dd, 2 H, J=13.8, 11.7 Hz) 2.11 (d, 2 H, J=13.8 Hz)	5.03 (dd, 2 H, J=11.4, 1.5 Hz)	7.3-7.5 (m, 10 H, Ar-H)
35b	5.64 (H_b) 6.30 (H_a)	2.70[c]	1.67 (dd, 2 H, J=13.5, 11.4 Hz) 2.22 (d, 2 H, J=13.8 Hz)	5.41 (dd, 2 H, J=11.4, 1.5 Hz)	3.79 (s, 6 H, OCH_3) 6.8-7.6 (m, 8 H, Ar-H)
35c	5.68 (H_b) 6.33 (H_a)	2.78[c]	1.70 (dd, 2 H, J-13.7, 11.5 Hz) 2.32 (d, 2 H, J-14.2 Hz)	5.44 (dd, 2 H, J=11.3, 1.6 Hz)	7.2-7.7 (m, 8 H, Ar-H)
35d	5.68 (H_b) 6.32 (H_a)	2.79[c]	1.85 (dd, 2 H, J=14.0, 11.5 Hz) 2.07 (d, 2 H, J=14.4 Hz)	5.23 (dd, 2 H, J=11.3, 1.7 Hz)	2.35 (s, 6 H, CH_3) 7.1-7.6 (m, 8 H, Ar-H)
36a	5.38 (H_b) 6.03 (H_a)	2.51[c]	1.92 (dd, 1 H,J=14.1, 5.0 Hz) 2.00 (d, 2 H, J=5.9 Hz) 2.28 (dd, 1 H, J=14.1, 6.0 Hz)	4.95 (m, 2 H)	7.1-7.4 (m, 10 H, Ar-H)
36b	5.35 (H_b) 5.99 (H_a)	2.67 (dt, 1 H)[d] 2.85 (dt, 1 H)[e]	2.16 (dd, 1 H, J=13.2, 3.9 Hz)[d] 2.30-2.45 (m, 3 H)	5.22 [dd, 1 H, H(7), J=9.6, 3.9 Hz] 5.38 [dd→t, 1 H, H(9)]	3.81 (s, 3 H, OCH_3) 3.82 (s, 3 H, OCH_3) 6.9-7.6 (m, 8 H, Ar-H)

[a]All data are given in δ values downfield from TMS.
[b]A and M portion of an AMX_2 pattern where $J_{AM} < J_{AX} \cong 2.5$ Hz. The center of the triplet is taken as the peak position.
[c]Three line pattern resulting from X_2 of AMX_2 pattern where $J_{AX} \cong J_{MX} \cong 2.5$ Hz. The center of the triplet is taken as the peak position.
[d]Y portion of an AMXY pattern where $J_{AY} \cong J_{MY} = 2.7$ Hz and $J_{XY} = 16.8$ Hz.
[e]X portion of an AMXY pattern where $J_{AX} \cong J_{MX} = 2.4$ Hz.

Collucci, Jungk and Gandour.[19] A ^3J value of 11.4 Hz (for **35a** and **35b**) reflects a dihedral angle of 174.5° and a ^3J value of 11.3 Hz corresponds to a dihedral angle of 172.5°. These values are consistent with the dihedral angle of a flattened chair form of a six-membered heterocyclic ring.[12] The six-membered rings in *cis*-8-*tert*-butyl-3-methylene-1-oxaspiro[4.5]decan-2-one (**45**)[58] and 2,2,6,6-tetramethyl-9-methyl-ene-7-oxa-1-thiaspiro[4.5]decan-8-one (**46**)[60] were also shown to be flattened.

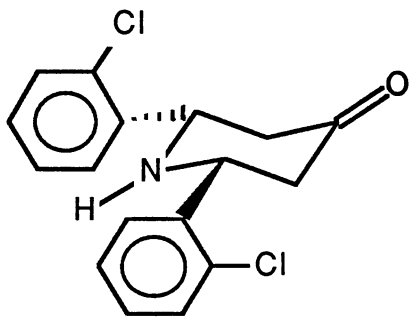


45

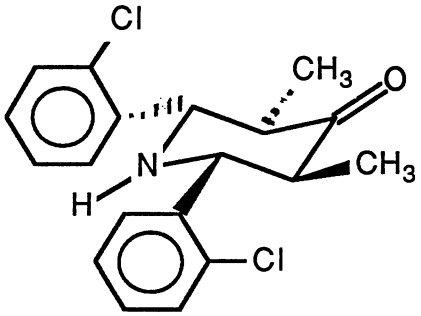


46

The ^{13}C NMR spectral data are reported in Table XVIII. A shielding effect was observed in C(7,9) for **35b-d** relative to the C(7,9) signal in **35a**. A similar shielding was observed in **36b** relative to **36a**. This shielding, which is similar to that observed in the parent ketones **37b-d** and **38b**, is presumably caused by the ortho substituent on the phenyl rings. Such effects have been noted in substituted piperidin-4-ones **47** and **48**.[28]



47

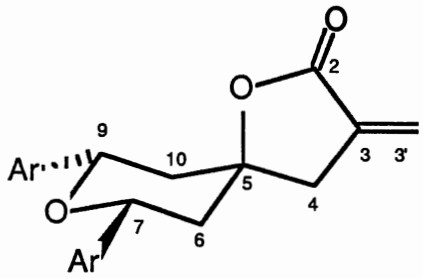


48

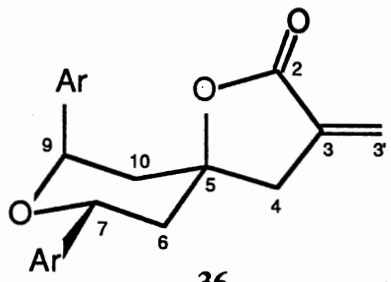
Comparison of the chemical shift for the α-carbon [C(2,6)] in the parent tetrahydropyran-4-ones **37a-d** (see Table VIII) with those of the corresponding carbon atoms [C(7,9)] in spirolactones (See Table XVIII) revealed an upfield shift (~3 ppm) for the latter. This

TABLE XVIII

^{13}C CHEMICAL SHIFT DATA FOR SPIROLACTONES



35



36

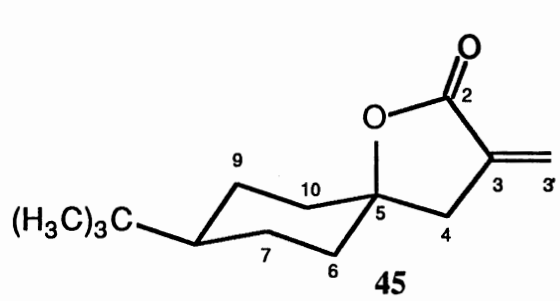
a. Ar = C_6H_5
b. Ar = 2-$H_3COC_6H_4$
c. Ar = 2-ClC_6H_4
d. Ar = 2-$H_3CC_6H_4$

Compound	Chemical Shift[a]									
	C(2)	C(3)	C(3')	C(4)	C(5)	C(6)	C(7)	C(9)	C(10)	Other
35a	169.37	134.22	123.35	40.56	81.07	44.84	75.47	75.47	44.84	Ar-C: 141.71, 128.41, 127.62, 125.72
35b	169.83	134.87	122.71	40.66	81.54	43.58	70.11	70.11	43.58	OCH_3, 55.32; Ar-C: 155.65, 130.77, 128.17, 126.20, 120.67, 110.17
35c	169.20	134.21	123.33	40.42	80.64	42.91	72.87	72.87	42.91	Ar-C: 139.30, 131.47, 129.44, 128.66, 127.12, 126.97
35d	169.46	134.25	123.43	40.59	81.30	43.54	72.87	72.87	43.54	CH_3, 19.12; Ar-C: 139.76, 134.41, 130.29, 127.43, 126.24, 125.41
36a	168.84	134.46	122.55	40.13	80.49	41.44	70.40	71.70	39.64	Ar-C: 140.61, 140.20, 128.47, 128.26, 127.35, 127.25, 125.96, 125.54
36b	169.52	135.20	122.15	40.59	81.57	41.36	67.08	68.35	39.99	OCH_3, 55.21, 55.12; Ar-C: 155.96, 155.74, 129.88, 129.80, 128.31, 128.20, 126.62, 126.40, 120.81, 120.57, 110.34, 110.19

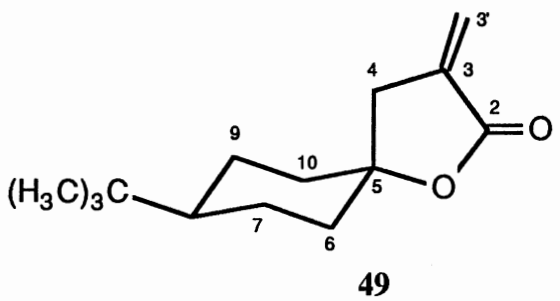
[a]All data are given in ppm downfield from TMS.

TABLE XIX

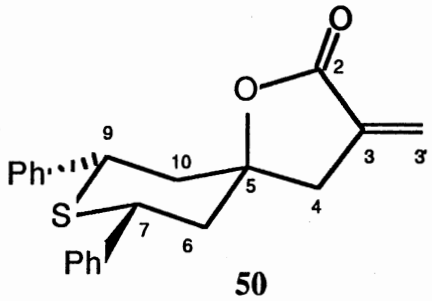
^{13}C CHEMICAL SHIFT DATA FOR LACTONES **45**, **49** AND **50**



45



49



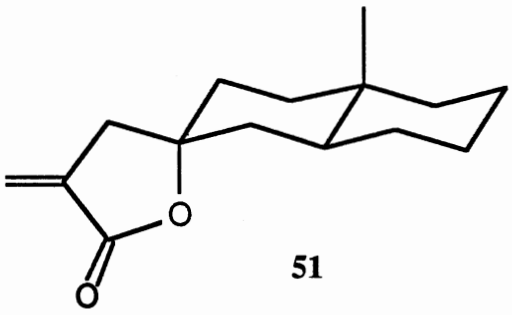
50

Compound	Chemical Shift[a]								
	C(2)	C(3)	C(3')	C(4)	C(5)	C(6,10)	C(7,9)	C(8)	Other
45	169.64	135.48	121.71	40.64	82.34	38.10	22.94	46.98	$\underline{C}(CH_3)_3$, 32.34 $C(\underline{C}H_3)_3$, 27.50
49	166.35	135.48	121.91	37.30	83.97	37.46	24.05	46.63	$\underline{C}(CH_3)_3$, 32.18 $C(\underline{C}H_3)_3$, 27.50
50	168.93	133.93	123.33	41.51	82.54	43.97	45.29		Ar-$\underline{C}$: 140.17, 128.55, 127.58, 127.29

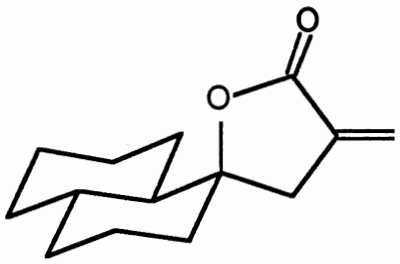
[a]All data are given in ppm downfield from TMS.

upfield shift is reasonably defended to arise from an γ_a-effect of the C(5)-O(1) bond.[24,45,46] A similar but smaller (1-2 ppm) effect was observed in lactones **36a** and **36b**.

The ^{13}C NMR spectral data[60] for model lactones **45**, **49** and **50** may be found in Table XIX. There is a notable upfield shift (3-4 ppm) of C(4) in **49** compared to C(4) in **45**, in **35a-d** and in **36a-b**, which is presumably due to the γ_a-effect of the axial C(5)-C(4) bond. There is also a significant upfield shift (~3 ppm) in C(2) of **49** compared to C(2) in **45**, **35a-d** and **36a-b**. From the observed ^{13}C NMR data, as well as the preferential formation of *cis*-8-*tert*-butyl-3-methylene-1-oxaspiro[4.5]decan-2-one (**45**) rather than the trans isomer **49** along with the preferred crystallization (C-O axial) of 2,2,6,6-tetramethyl-9-methylene-7-oxa-1-thiospiro[4.5]decan-8-one (**46**),[68] we tentatively assign the C(5)-O(1) bond as axial in **35a-d**. In addition, Benezra and coworkers[75] recently reported the syntheses of **51** and **52**. Both C-O axial and C-O equatorial isomers were formed, but in each case the major product was the C-O axial isomer.



51



52

The ^{13}C NMR data for trans lactones **36a** and **36b** indicate the presence of a static system. Chemical shifts for carbons C(7) and C(9) as well as C(6) and C(10) were observed (see Table XVIII). Eight aromatic carbons were recorded for **36a**, and twelve aromatic carbons were observed for **36b**. This is also indicative of a static ring system. The static ring systems in **36a** and **36b** are novel and unexpected since a dynamic system

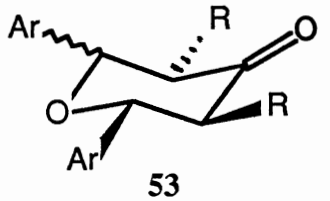
is more reasonable in view of work on the simple cyclohexane analogue[58] and on **46**.[60]

In summary, the synthesis of lactones **35a-d** and **36a-b** have been achieved and a stereochemical diagnosis has been put forth. Samples of these lactones will be sent shortly to Dr. V. Narayanan of the National Cancer Institute for examination in several new screens established for predicting potentially useful anticancer agents.

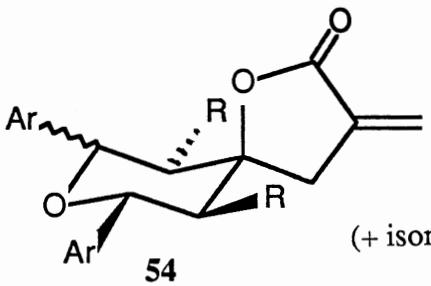
CHAPTER III

SUGGESTIONS FOR FUTURE WORK

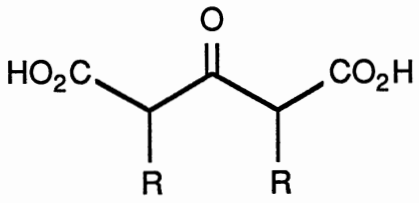
In view of the development of methodology to obtain the required tetrahydropyran-4-ones and the corresponding spiro lactones, it would seem potentially useful to assess the anticancer activity before attempting modifications. Should any member of the lactones exhibit useful activity in one or more of the screens at the National Cancer Institute, it would seem logical to explore such structural changes as altering the geometry around the spiro lactone by introducing alkyl groups at C(3,5). Such a change could well enhance the specificity of action since the addition of a mercapto group from an enzyme or protein to the lactone will undoubtedly pose stereochemical requirements for the Michael-type condensation. Thus, one group of ketones perhaps worthy of synthesis is **53** and these would lead to lactones **54**. Consequently, one approach using 2,4-dialkyl-3-oxo-glutaric acids **55** should give ketones **53** in our method. A base-catalyzed process using appropriate ketones **56** would likewise be worthy of examination. It appears that at least one enolizable proton is necessary to initiate the condensation to form members of **53**. In addition, potential solubilizing groups (such as R_2N groups) might be added to the aryl ring system for improving hydrophilicity.



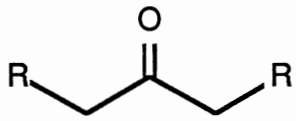
53



54 (+ isomers)

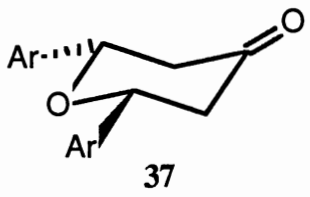


55

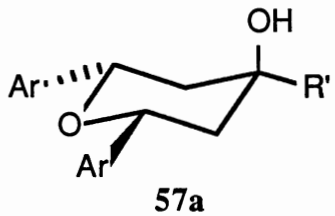


56

The lack of model compounds in this family makes configurational assignments difficult. Simple addition products prepared from the reaction of the ketones with Grignard or lithium reagents would provide useful analogues in terms of diagnosing, perhaps, whether the C-O bond is axial or equatorial as shown in **57a-b** and **58a-b.**

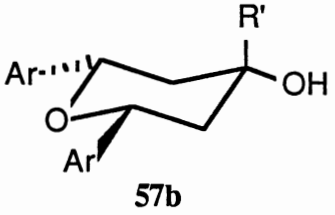


37

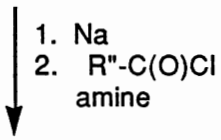


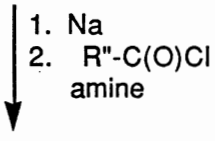
57a

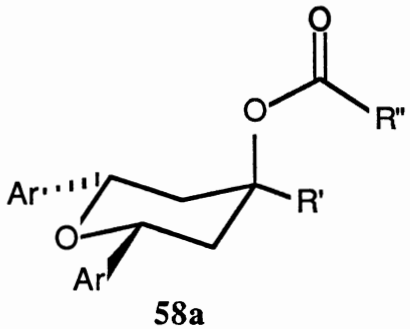
+



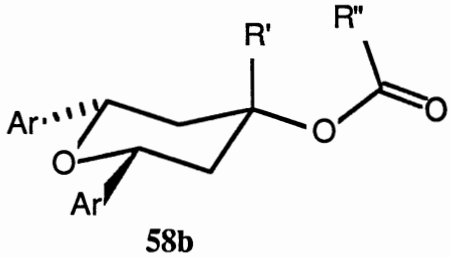
57b







58a



58b

CHAPTER IV

EXPERIMENTAL SECTION

General Information

The ^{1}H and ^{13}C NMR spectral data were obtained on a Varian XL-300 NMR spectrometer operating at 299.944 MHz for ^{1}H NMR and at 75.429 MHz for ^{13}C NMR. All NMR data were recorded in δ or ppm values downfield from TMS with $DCCl_3$ as the solvent. NMR data for all compounds synthesized may be found in Tables VII, VIII, XVII and XVIII. IR spectral data were obtained in KBr pellets (unless otherwise specified) on a Perkin-Elmer 681 IR spectrophotometer. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and were uncorrected. Chromatography was accomplished using a Chromatotron Model 7924T (Harrison Research Inc., 840 Moana Court, Palo Alto, California 94306) as described in the Instruction Manual with silica gel as the adsorbent. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Starting Materials

Reagents (commercially available) were purified before use when deemed necessary. The purity of 1,3-acetonedicarboxylic acid (**40**) was critical to the successful formation of the tetrahydropyran-4-ones. Crystals of highest purity (mp 136.5-137.0°C d, lit[89] 135°C d) were obtained by recrystallization from ethyl acetate, followed by washing with dry ether and drying for 12 h over P_2O_5 under vacuum (RT, 0.01 mm Hg). Tetrahydrofuran (THF) was freshly distilled over sodium before use. Zinc powder

(Fisher Scientific) was activated by vigorously stirring 15 g of the powder in 100 mL of 5% HCl for 5 min. After washing with water (4 x 50 mL), the powder was then washed with 2 portions (50 mL) each of ethanol, acetone and ether. This activated zinc powder was then immediately transferred to a beaker, covered with a Kimwipe, and dried under vacuum (30 min, RT, 0.01 mm Hg) over P_2O_5.

Procedures

General Procedure for Using the Chromatotron

The plates used for the centrifugal chromatography were prepared by shaking 115 g (0-5°C) of silica gel (PF_{254} type 60, EM Science) and 200 mL (0-5°C) of distilled water in a 500-mL Erlenmeyer flask for 60 sec. The slurry was then poured onto the previously washed glass plate (120 mm radius) beginning with the edge and moving inward with a spiral pattern. The plate was allowed to stand (30 min) and then placed on a rotor and turned (RT) for 24 h. The plate was scraped with the equipment provided with the Chromatotron to give a 4 mm thick plate with an inner radius of 40 mm and an outer radius of 113 mm.

For separations, a sample was dissolved in a minimum amount of chloroform and slowly added to the plate (previously saturated with hexanes) through the string wick provided with the Chromatotron. The initial band was approximately 10 mm wide. The nitrogen flow rate was kept constant throughout the separation at 15 mL/min. The separation was then accomplished by using a gradient elution series with hexanes as the nonpolar solvent and a mixture of ethyl acetate and chloroform (1:1) as the polar solvent system. The rate of change of the gradient was adjusted according to the observed degree of separation of the bands. The bands were observed by using a Mineralight lamp (Model UVGL-25) on the short wave setting. After a separation was completed, the plate was washed with chloroform, absolute ethanol, and dry ether.

***cis*-7,9-Diphenyl-3-methylene-1,8-dioxa-spiro[4.5]decan-2-one (35a)**

Into the inner chamber of a double-walled flask equipped with a nitrogen inlet, a nitrogen outlet, two condensers (one for each chamber), a pressure-equalizing addition funnel (with a rubber septum sealing with 14/20 ground-glass joint), and a magnetic stirrer were placed 1.26 g (5.00 mmol) of *cis*-2,6-diphenyltetrahydropyran-4-one (**37a**), 0.360 g (5.50 mmol) of freshly prepared Zn powder and 5.0 mL of dry THF. With a gas-tight syringe, 0.70 mL (0.98 g, 5.0 mmol) of ethyl 2-(bromomethyl)acrylate (**21b**) and 3 mL of dry THF were carefully added into the pressure-equalizing addition funnel. Heating (boiling methanol was in the outer chamber) and stirring were initiated and ester **21b** was added dropwise over a period of 1 h. After addition of ester **21b** was completed, heating and stirring were continued for an additional 3.5 h. The solution appeared light green in color, and approximately 90% of the Zn had reacted. Heating was terminated, but the reaction mixture was stirred for an additional 30 min. The mixture was then transferred, using a disposable pipet, into 30 mL of stirred, ice-cold H_2SO_4 (5%). The acidic mixture was stirred for 15 min and then poured into a separatory funnel (125 mL). The acidic mixture was extracted with chloroform (3 x 25 mL) and the combined extracts were dried ($MgSO_4$) for 7 h. The solvent was removed (rotary evaporator) and the resulting light yellow oil [IR (neat) analysis showed only one C=O stretch at 1770 cm^{-1}] was separated by the general procedure described for the Chromatotron. For this separation, the solvent flow was approximately 7 mL/min. The elution series used can be found in Table XX. The lactone **35a** was collected during solvent fractions 6 and 7 (40-45 min after the separation was initiated). The entire separation was completed in 1 h. The solvent was removed (rotary evaporator), and the resulting light yellow oil was crystallized (hot methanol) to give 0.66 g (41%) of lactone **35a** as white crystals: mp 100.0-101.5°C; IR 1770 cm^{-1} (C=O); NMR data - see Tables XVII and XVIII. Anal. Calcd for $C_{21}H_{20}O_3$:

C, 78.73; H, 6.29. Found: C, 78.31; H, 6.29.

TABLE XX

GRADIENT ELUTION SERIES USED FOR SEPARATION OF **35a**

Solvent Fraction	Volume	Composition (Hexanes:EtOAc:$HCCl_3$)
1	50 mL	10:0:0
2	50 mL	9:0.5:0.5
3	50 mL	8:1.0:1.0
4	50 mL	7:1.5:1.5
5	50 mL	6:2.0:2.0
6	50 mL	6:2.0:2.0
7	50 mL	5:2.5:2.5
8	50 mL	5:2.5:2.5

***cis*-7,9-bis(2-Methoxyphenyl)-3-methylene-1,8-dioxaspiro[4.5]decan-2-one (35b)**

Freshly prepared Zn powder (0.14 g, 2.1 mmol), *cis*-2,6-bis(2-methoxyphenyl) tetrahydropyran-4-one (**37b**) (0.624 g, 2.00 mmol) and 5 mL of dry THF were placed in the nitrogen-flushed, inner chamber of a double-walled flask equipped as for the preparation of **35a**. Ethyl 2-(bromomethyl)acrylate (**21b**; 0.39 g, 2.0 mmol) in 3 mL of dry THF was introduced into the pressure-equalizing addition funnel. Heating was initiated, and ester **21b** was added dropwise to the above solution over a period of 15 min. After the addition was complete, the reaction mixture was stirred for an additional period

of 5 h at about 65°C. Heating was terminated, but the reaction mixture was stirred for an additional 0.5 h and was then transferred via a disposable pipet into 50 mL of stirred, ice-cold H_2SO_4 (5%). The reaction flask was rinsed with 3 mL of dry THF, and this washing was also added to the stirred acid solution. A white precipitate which formed was filtered out, washed with water (5 x 20 mL) and dried over P_2O_5 under vacuum (12 h) to give 0.785 g (100%) of lactone **35b**. Pure **35b** was obtained by using the previously described general procedure with the Chromatotron. After removing the solvent (hexanes, EtOAc, $HCCl_3$), the white solid isolated was recrystallized (hot hexanes) to afford 0.65 g (83%) of lactone **35b**: mp 156.5-157.0°C; IR 1760 cm^{-1} (C=O); NMR data - see Tables XVII and XVIII. Anal. Calcd. for $C_{23}H_{24}O_5$: C, 72.61; H, 6.36. Found: C, 72.57; H, 6.46.

<u>*cis*-7,9-bis(2-Chlorophenyl)-3-methylene-1,8-dioxaspiro[4.5]decan-2-one (35c)</u>

Into the inner chamber of a double-walled flask equipped as for **35a** were placed 0.066 g (1.01 mmol) of freshly prepared Zn powder, 0.321 g (1.0 mmol) of *cis*-2,6-bis(2-chlorophenyl)tetrahydropyran-4-one (**37c**) and 5.0 mL of dry THF. Ester **21b** (0.16 mL, 0.193 g, 1.0 mmol) in 3 mL of dry THF was introduced into the pressure-equalizing addition funnel. Heating was started, and ester **21b** was added dropwise over a period of 40 min. After the addition was complete, the addition funnel was rinsed with dry THF (2 mL) and the reaction mixture was stirred for an additional 4 h at about 65°C. Heating was then terminated, but the reaction mixture was stirred for an additional period of 0.5 h and then transferred into 50 mL of stirred, ice-cold H_2SO_4 (5%). The acidic mixture was stirred for 15 min and extracted with chloroform (3 x 25 mL). The combined extracts were dried ($MgSO_4$) for 8 h, and the solvent was removed (rotary evaporator). The resulting light yellow oil [IR (neat) analysis showed a large C=O stretch at 1770 cm^{-1}

with a small shoulder at 1720 cm^{-1}] was separated following the general procedure described for the Chromatotron. The gradient elution series used for this separation can be found in Table XXI. The lactone **35c** was collected in solvent fractions 3 and 4 (25-30 min after the separation procedure was initiated). The solvent was removed (under N_2) and the resulting white solid was analyzed: 150.2 mg (39%); mp 146.5-148.0°C; IR 1770 cm^{-1} (C=O), 1675 cm^{-1} (C=C); NMR data – see Tables XVII and XVIII. Anal. Calcd. for $C_{21}H_{18}O_3Cl_2$: C, 64.79; H, 4.66. Found: C, 64.72; H, 4.61.

TABLE XXI

GRADIENT ELUTION SERIES USED FOR SEPARATION OF **35c**

Solvent Fraction	Volume[a]	Composition (Hexanes:EtOAc:$HCCl_3$)
1	50 mL	8:1.0:1.0
2	50 mL	7:1.5:1.5
3	50 mL	6:2.0:2.0
4	50 mL	5:2.5:2.5
5[b]	50 mL	0:0.0:1.0

[a]Solvent flow rate was 5-6 mL/min.
[b]Used to clean plate of residual sample.

***cis*-7,9-bis(2-Methylphenyl)-3-methylene-1,8-dioxaspiro[4.5]decan-2-one (35d)**

Into the inner chamber of a double-walled flask equipped as for **35a** were placed 0.066 g (1.01 mmol) of freshly prepared Zn powder, 0.280 g (1.00 mmol) of *cis*-2,6-bis-(2-methylphenyl)tetrahydropyran-4-one (**37d**) and 5.0 mL of dry THF. Ester **21b** (0.16

mL, 0.193 g, 1.01 mmol) in 3 mL of dry THF was introduced into the pressure-equalizing addition funnel. Heating was initiated, and ester **21b** was added dropwise over a period of 0.5 h. After the addition was complete, the reaction mixture was stirred for an additional 6 h at about 65°C. Heating was terminated, and after cooling (0.5 h), the reaction mixture was transferred into 50 mL of stirred, ice-cold H_2SO_4 (5%). The acidic mixture was stirred for 15 min and extracted with ether (3 x 25 mL). The combined extracts were dried ($MgSO_4$, 8 h), and the solvent was removed (rotary evaporator). The resulting oil [IR (neat) analysis showed a large C=O stretch at 1770 cm^{-1} (lactone) and a small shoulder at 1720 cm^{-1} (starting ketone **37d** and ester **21b**)] was separated following the general procedure described for the Chromatotron. The gradient elution series used for this separation can be found in Table XXII. The lactone **35d** was collected in solvent fraction 3. Removal of the solvent with a stream of N_2 left a white crystalline solid: 152 mg (43.7%); mp 151.0-153.0°C; IR 1775 cm^{-1} (C=O); NMR data – see Tables XVII and XVIII. Anal. Calcd. for $C_{23}H_{24}O_3$: C, 79.28; H, 6.94. Found: C, 78.93; H, 7.02.

TABLE XXII

GRADIENT ELUTION SERIES USED FOR SEPARATION OF **35d**

Solvent Fraction	Volume[a]	Composition (Hexanes:THF)
1	50 mL	9:1
2	50 mL	8:2
3	50 mL	6:4
4[b]	50 mL	0:10

[a]Solvent flow rate was 5-6 mL/min.
[b]Used to remove residual sample.

***trans*-7,9-Diphenyl-3-methylene-1,8-dioxa-spiro[4.5]decan-2-one (36a)**

Into the inner chamber of a double-walled flask equipped as for **35a** were placed 0.17 g (2.6 mmol) of freshly prepared Zn powder, 0.63 g (2.5 mmol) of *trans*-2,6-diphenyltetrahydropyran-4-one (**38a**) and 5.0 mL of dry THF. Ester **21b** (0.40 mL, 0.48 g, 2.5 mmol) in 3 mL dry THF was introduced into the pressure-equalizing addition funnel. The heating mantle was started, and ester **21b** was added dropwise over a period of 0.5 h. After the addition was complete, the reaction mixture was stirred for an additional 4 h at about 65°C. Heating was then terminated, but the reaction mixture was stirred for an additional 0.5 h and then transferred with a disposable pipet into 30 mL of stirred, ice-cold H_2SO_4 (5%). The acidic mixture was stirred for 15 min and extracted with chloroform (3 x 25 mL). The combined extracts were dried ($MgSO_4$) for 7 h. The solvent was removed (rotary evaporator) and the resulting oil [IR (neat) analysis showed a large C=O stretch at 1765 cm^{-1} with a small shoulder at 1720 cm^{-1}] was separated following the general procedure described for the Chromatotron. The gradient elution series used for this separation can be found in Table XXIII. The lactone **36a** was collected from solvent fraction 6 (30-35 min after the separation procedure was initiated). The entire separation was completed in 45 min. The solvent was removed (rotary evaporator) and attempts to obtain a solid crystalline material were unsuccessful, thus the compound was analyzed as an oil: IR (neat) 1765 cm^{-1}; NMR data - see Tables XVII and XVIII. Unfortunately, a satisfactory elemental analysis could not be obtained although the spectral data were fully supportive of the structure.

TABLE XXIII

GRADIENT ELUTION SERIES USED FOR SEPARATION OF **36a**

Solvent Fraction	Volume[a]	Composition (Hexanes:EtOAc:$HCCl_3$)
1	50 mL	9:0.5:0.5
2	50 mL	8:1.0:1.0
3	50 mL	7:1.5:1.5
4	50 mL	6:2.0:2.0
5	50 mL	5:2.5:2.5
6	50 mL	5:2.5:2.5

[a]Solvent flow rate was 8-9 mL/min.

***trans*-7,9-bis(2-Methoxyphenyl)-3-methylene-1,8-dioxaspiro[4.5]decan-2-one (36b)**

Freshly prepared Zn powder (0.0144 g, 0.22 mmol), 3 mL of THF, and ketone **38b** (0.0648 g, 0.21 mmol) were placed in the nitrogen-flushed inner chamber of a double-walled flask equipped as for **35a**. The outer chamber was filled with 50 mL of low boiling petroleum ether (bp 38-59°C). Ester **21b** (0.041 g, 0.21 mmol) was placed in the pressure-equalizing addition funnel along with 3 mL of dry THF. Heating and stirring were initiated, and the dropwise addition was begun. After 30 min, the addition of ester **21b** was complete, and the temperature of the boiling petroleum ether was 38°C. After stirring at this temperature for 3 h, heating was terminated and the flask was allowed to cool to room temperature (~ 30 min). The reaction mixture was transferred with a disposable pipet into 50 mL of stirred, ice-cold H_2SO_4 (5%). The reaction flask was

rinsed with 3 mL of THF, and this washing was also added to the stirred acid solution. After extracting with chloroform (3 x 25 mL) and drying the combined organic extracts overnight ($MgSO_4$), the mixture was separated using the general procedure with the Chromatotron (see Table XXIV).

Lactone **36b** was collected during fractions 5 and 6 (28-35 min after separation was started). The solvent was removed and attempts to obtain a crystalline solid failed, so the compound was analyzed as an oil: IR (neat) 1765 cm^{-1} (C=O); NMR data - see Tables XVII and XVIII. A satisfactory elemental analysis could not be obtained although all spectral data were in accord with the structure.

TABLE XXIV

GRADIENT ELUTION SERIES USED FOR SEPARATION OF **36b**

Solvent Fraction	Volume[a]	Composition (Hexanes:EtOAc:$HCCl_3$)
1	50 mL	9:0.5:0.5
2	50 mL	8:1.0:1.0
3	50 mL	7:1.5:1.5
4	50 mL	6:2.0:2.0
5	50 mL	5:2.5:2.5
6	50 mL	5:2.5:2.5

[a]Solvent flow rate was 9-10 mL/min.

cis-2,6-Diphenyltetrahydropyran-4-one (37a)

A mixture of 1.461 g (10.0 mmol) of 1,3-acetonedicarboxylic acid (**40**, mp 135.0-135.5°C) and 4.245 g (40.0 mmol) of benzaldehyde (**39a**, bp 43°C @ 2 mm Hg) was placed in a 2-necked, round-bottom flask (25 mL) equipped with both an $HCl_{(g)}$ inlet and outlet. This reaction mixture was then cooled with an ice/NaCl bath to -15°C. After a thorough mixing of the ingredients (10 min), $HCl_{(g)}$ was bubbled (~2 bubbles/sec) into the slurry. This was accomplished by connecting an $HCl_{(g)}$ lecture bottle to a disposable pipet with Tygon tubing and then placing the pipet into one neck of the flask. The pipet was held in place by wrapping parafilm around the neck of the flask. This wrapping also sealed the neck of the flask. The second neck of the flask was fitted with an adapter and an outlet line of Tygon tubing which allowed the excess $HCl_{(g)}$ to pass through a saturated solution of Na_2CO_3, thus neutralizing the excess $HCl_{(g)}$.

The $HCl_{(g)}$ was allowed to pass through the mixture (~2 bubbles/min) for 0.5 h. During this time, the color of the reaction mixture changed from white, then to pink, and finally to orange. This resulting orange slurry was washed with H_2O (20 mL) and neutralized (Na_2CO_3, satd solution) to pH 9-10. This mixture was extracted with ethyl ether (3 x 25 mL), and the resulting aqueous layer was allowed to stand for 48 h. A white, granular solid precipitated from the solution. After filtering the precipitate and drying it over P_2O_5 under vacuum (24 h, RT, 0.01 mm Hg) 1.69 g (67%, mp 68.0-70.5°C) of an isomeric mixture of ketones was obtained. Recrystallization (hot ethanol) gave a pure sample (1.42 g, 56%) of *cis*-2,6-diphenyltetrahydropyran 4-one (**37a**): mp 69-70°C (lit[8] mp 69-70°C); IR 1720 cm^{-1} (C=O); NMR data - see Tables VII and VIII.

trans-2,6-Diphenyltetrahydropyran-4-one (38a)

A mixture of 1.461 g (10.0 mmol) of 1,3-acetonedicarboxylic acid (**40**) and 4.245 g (40.0 mmol) of benzaldehyde (**39a**) was placed into a 2-necked, 25-mL, round-bottom

flask equipped with an $HCl_{(g)}$ inlet, an $HCl_{(g)}$ outlet, and a magnetic stirrer. After thorough mixing (5 min), $HCl_{(g)}$ was passed (~2 bubbles/sec) through the slurry for 0.5 h. The resulting orange syrup was washed with water (25 mL) and neutralized (Na_2CO_3, satd solution) to pH 9. This basic mixture was transferred to a 125-mL separatory funnel and washed with ether (3 x 20 mL). The aqueous layer was transferred to a 125 mL Erlenmeyer flask which was covered, and allowed to stand (48 h) at room temperature. The white precipitate which formed was filtered out, washed with water (2 x 25 mL) and dried over P_2O_5 under vacuum (24 h, RT, 0.01 mm Hg) to yield 0.863 g (34.2%) of an isomeric mixture of ketones. Recrystallization (hot ethanol) gave a pure sample of ketone **38a**: mp 131-133°C (lit[8] mp 131°C), IR 1715 cm^{-1} (C=O); NMR data - see Tables VII and VIII.

2,6-bis(2-Methoxyphenyl)tetrahydropyran-4-ones (37b & 38b)

Into a 50-mL, 2-necked, round-bottom flask equipped with an $HCl_{(g)}$ inlet and an outlet were placed 2.192 g (15.0 mmol) of 1,3-acetonedicarboxylic acid (**40**) and 10 mL of dry THF. To the resulting clear solution was added 5.5 mL (6.2 g, 45 mmol) of 2-anisaldehyde (**39b**, bp 67-68°C/0.5 mm Hg). A water bath (RT) was placed under the flask to maintain the reaction mixture at room temperature. Then $HCl_{(g)}$ was passed (~2 bubbles/sec) through the solution for 1 h, during which time the color of the reaction mixture changed from colorless, to yellow, and then finally to orange. After removing the THF (rotary evaporator), the resulting oil was neutralized (Na_2CO_3, satd. solution) to pH 9-10. The slurry was then transferred to a separatory funnel (60 mL) and extracted with ethyl ether (3 x 30 mL). The aqueous layer was transferred to a 125-mL Erlenmeyer flask and then allowed to stand (48 h) at room temperature. The resulting white precipitate was filtered, washed with water (50 mL) and dried over P_2O_5 under vacuum (24 h, RT, 0.01

mm Hg) to yield 2.94 g (63%) of an isomeric mixture of ketones. By the general procedure described for the Chromatotron, 1.00 g of the mixture of isomeric ketones was separated. See Table XXV for the gradient elution used. The first band (0.75 g) was found to be *cis*-2,6-bis(2-methoxyphenyl)tetrahydropyran-4-one (**37b**). Recrystallization (hot hexanes) gave a pure sample (0.59 g, 59%) of ketone **37b**: mp 170.0-171.0°C; IR 1710 cm^{-1} (C=O); NMR data - see Tables VII and VIII). Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.69; H, 6.37. The second band eluted was crystallized (hot ethanol) to yield 0.21 g (21%) of *trans*-2,6-bis(2-methoxyphenyl)tetrahydropyran-4-one (**38b**): mp 168.0-169.0°C; IR 1715 cm^{-1} (C=O); NMR data - see Tables VII and VIII. Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.89; H, 6.52.

TABLE XXV

GRADIENT ELUTION SERIES USED FOR SEPARATION OF **37b** AND **38b**

Solvent Fraction	Volume[a]	Composition (Hexanes:EtOAc:$HCCl_3$)
1	25 mL	10:0.0:0.0
2	50 mL	8:1.0:1.0
3	50 mL	8:1.0:1.0
4	50 mL	7:1.5:1.5
5	50 mL	7:1.5:1.5
6	50 mL	6:2.0:2.0
7	50 mL	6:2.0:2.0

[a]Solvent flow rate was 8 mL/min.

2,6-bis(2-Chlorophenyl)tetrahydropyran-4-ones (37c & 38c)

Into a 50-mL, 3-necked, round-bottom flask equipped with a magnetic stirrer, an $HCl_{(g)}$ inlet and an $HCl_{(g)}$ outlet was placed a mixture of 0.548 g (3.75 mmol) of 1,3-acetonedicarboxylic acid (**40**) and 1.406 g (10.0 mmol) of 2-chlorobenzaldehyde (**39c**). $HCl_{(g)}$ was passed (~2 bubbles/sec) through the slurry for 0.5 h. During this time, the color of the solution changed from cream to orange. After stopping the $HCl_{(g)}$, the slurry was neutralized (Na_2CO_3, satd solution) to pH 9-10 and then transferred to a separatory funnel (60 mL) and washed with ethyl ether (3 x 25 mL). The ether extracts were placed in small vials, labelled and saved. The aqueous layer was transferred to an Erlenmeyer flask (125 mL) and allowed to stand for 48 h. The resulting white precipitate was filtered, washed with water (50 mL) and dried under vacuum (24 h, RT, 0.01 mm Hg) over P_2O_5 to yield 0.321 g (27%) of a mixture of isomeric ketones. The mixture was dissolved in acetone (10 mL) and allowed to stand (about 24 h) until crystals formed on the bottom of the beaker. Two types of crystal were evident, namely square blocks and oval-shaped crystals. The square blocks were found to be *cis*-2,6-bis(2-chlorophenyl)-tetrahydropyran-4-one (**37c**): mp 146-147°C; IR 1715 cm^{-1} (C=O); NMR data - see Tables VII and VIII. Anal. Calcd. for $C_{17}H_{14}O_2Cl_2$: C, 63.57; H, 4.39; Cl, 22.08. Found: C, 63.79; H, 4.37; Cl, 22.18. The oval crystals were analyzed and determined to be *trans*-2,6-bis(2-chlorophenyl)tetrahydropyran-4-one (**38c**): mp 101.5-102.5°C; IR 1720 cm^{-1} (C=O); NMR data - see Tables VII and VIII. Anal. Calcd. for $C_{17}H_{14}O_2Cl_2$: C, 63.57; H, 4.39; Cl, 22.08. Found: C, 63.51; H, 4.40; Cl, 22.51.

***cis*-2,6-bis(2-Methylphenyl)tetrahydropyran-4-one (37d)**

Into a 25-mL, 2-necked, round-bottom flask equipped with an $HCl_{(g)}$ inlet and an

$HCl_{(g)}$ outlet, and a magnetic stirrer were placed 5.0 mL (5.2 g, 43 mmol) of 2-tolualdehyde (**39d**) and 2.192 g (15 mmol) of 1,3-acetonedicarboxylic acid (**40**). Stirring was initiated and the mixture was cooled to -10°C with an ice/NaCl bath. Then $HCl_{(g)}$ was allowed to pass (0.75 h, 3 bubbles/sec) through the slurry. The mixture was then neutralized (Na_2CO_3, satd solution) to pH 9-10 and this mixture was transferred to a separatory funnel (60 mL) and then washed with ethyl ether (3 x 20 mL).

The aqueous layer was allowed to stand at room temperature for 48 h. The white precipitate which formed was filtered out, washed with water (50 mL), and dried over P_2O_5 under vacuum (24 h, RT, 0.01 mm Hg) to yield 0.582 g (14%) of an isomeric mixture of ketones: mp 96.5-98.5°C. Then 0.50 g of the mixture was dissolved in 30 mL of hot hexanes. After cooling to room temperature, the solution was placed in the freezer. The fine needles which formed were filtered out cold and dried under vacuum (24 h) over fresh wax chips to yield 0.39 g (78% from recrystallization) of *cis*-2,6-bis(2-methylphenyl)tetrahydropyran-4-one (**37d**): mp 99.0-100.0°C; IR 1715 cm^{-1} (C=O), NMR data - see Tables VII and VIII. Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.62; H, 7.42.

<u>*cis*-2,6-bis(4-Methoxyphenyl)tetrahydropyran-4-one (37e)</u>

Into a 2-necked, 25-mL, round-bottom flask equipped with an $HCl_{(g)}$ inlet, an $HCl_{(g)}$ outlet, and a magnetic stirrer were placed 2.3 g (17 mmol) of *p*-anisaldehyde (**39e**, bp 82°C/1.0 mm Hg) and 0.548 g (3.75 mmol) of 1,3-acetonedicarboxylic acid (**40**, mp 135.0-136.0°C d). The $HCl_{(g)}$ was passed (~2 bubbles/sec) through the slurry for 0.25 h, during which time the color changed from white to red. The slurry was neutralized (Na_2CO_3, satd solution) to pH 9-10. As the solution was neutralized, the color changed from red to light yellow. The mixture was then transferred to a separatory funnel (60 mL) and extracted with ether (3 x 20 mL). The aqueous layer was covered and allowed to

stand at room temperature for 48 h. The light yellow precipitate which formed was filtered out and washed with water (50 mL). After drying over P_2O_5 under vacuum (12 h, RT, 0.01 mm Hg), 0.158 g (13.5%) of ketone **37e** was obtained: mp 126.0-127.0°C (sealed, evacuated tube); IR 1720 cm^{-1} (C=O); NMR data - see Tables VII and VIII. Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.10; H, 6.62.

***cis*-2,6-bis(4-Methylphenyl)tetrahydropyran-4-one (37f)**

Into a 25-mL, 2-necked, round-bottom flask equipped with an $HCl_{(g)}$ inlet, an $HCl_{(g)}$ outlet, and a magnetic stirrer were placed 2.92 g (20.0 mmol) 1,3-acetonedicarboxylic acid (**40**) and 5.0 mL (5.1 g, 43 mmol) *p*-toluadehyde (**39f**). Stirring was initiated and $HCl_{(g)}$ was allowed to pass (~2 bubbles/sec) through the slurry for a period of 0.3 h. To the orange solid mass in the flask was added Na_2CO_3 (satd solution) until pH 9 was reached. After extracting with ether (3 x 25 mL), the aqueous layer was allowed to stand (48 h) at room temperature. The white/cream colored precipitate which formed was filtered, washed with water (2 x 20 mL), and dried (24 h, RT, 0.01 mm Hg) to yield 2.663 g (48%) of a mixture of isomeric ketones. Recrystallization (hot hexanes) afforded 1.018 g (18%) of pure ketone **37f**: mp 92.0-92.5°C; IR 1765 cm^{-1} (C=O); NMR data - see Tables VII and VIII. Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.38; H, 7.34.

***cis*-2,6-bis(2,5-Dimethylphenyl)tetrahydropyran-4-one (37g)**

A mixture of 4.384 g (30.0 mmol) of 1,3-acetonedicarboxylic acid (**40**) and 13.0 mL (12.4 g, 92 mmol) of 2,5-dimethylbenzaldehyde (**39g**) was placed in a 50-mL, 3-necked, round-bottom flask equipped with an $HCl_{(g)}$ inlet, an $HCl_{(g)}$ outlet and a magnetic stirrer.

The $HCl_{(g)}$ was passed (~2 bubbles/sec) through the slurry for 1 h, during which time the color of the slurry changed from cream to red/orange. The slurry was then neutralized (Na_2CO_3, satd solution) to pH 9-10. As the solution reached pH 7, the color changed from red/orange to yellow. After extraction with ethyl ether (3 x 25 mL), the solution was allowed to stand at room temperature for 24 h. The white precipitate (0.723 g, 7.8%) was filtered out, washed with water (50 mL), and dried under vacuum (24 h, RT, 0.01 mm Hg) over P_2O_5. The precipitate was crystallized (hot hexanes) to yield 0.427 g (4.6%) of *cis*-2,6-bis(2,5-dimethylphenyl)tetrahydropyran-4-one (**37g**): mp 107.0-108.0°C; IR 1715 cm^{-1} (C=O); NMR data - see Tables VII and VIII. Anal. Calcd. for $C_{21}H_{24}O_2$: C, 81.79; H, 7.84. Found: C, 81.81; H, 8.08.

2,6-bis(1-Naphthyl)tetrahydropyran-4-one (37h & 38h)

A mixture of 0.548 g (3.75 mmol) of 1,3-acetonedicarboxylic acid (**40**) and 2.35 g (15 mmol) of 1-naphthaldehyde (**39h**) was placed in a 25-mL, 2-necked, round-bottom flask equipped as for **38a**. The $HCl_{(g)}$ was passed (~2 bubbles/sec) through the mixture for a period of 0.5 h. The slurry was then neutralized (Na_2CO_3, satd solution) until pH 9 was reached. After extracting with ethyl ether (3 x 25 mL), the aqueous solution was allowed to stand (RT, 24 h). The off-white precipitate which formed was filtered out, washed with water (3 x 25 mL), and dried under vacuum (24 h, RT, 0.01 mm Hg) over P_2O_5 to yield 0.153 g (11.6%) of a mixture of isomeric ketones. Separation of the isomers was not achieved either by fractional crystallization or chromatography on silica gel or alumina (neutral).

2,6-bis(3,4-Dimethoxyphenyl)tetrahydropyran-4-one (37i & 38i)

A mixture of 1.20 g (8.2 mmol) of 1,3-acetonedicarboxylic acid (**40**) and 3.56 g

(21.4 mmol) of 3,4-dimethoxybenzaldehyde (**39i**) was placed in a 25-mL, 2-necked, round-bottom flask equipped as for **38a**. The $HCl_{(g)}$ was passed through the mixture for 0.25 h after which time the material in the flask was black in color. Following the usual work-up (see **38a**), a light brown precipitate (0.268 g, 8.8%) was obtained. NMR and TLC analyses revealed a complex mixture of compounds. The IR and ^1H NMR analyses did not reveal the presence of a carbonyl group for the expected ketones.

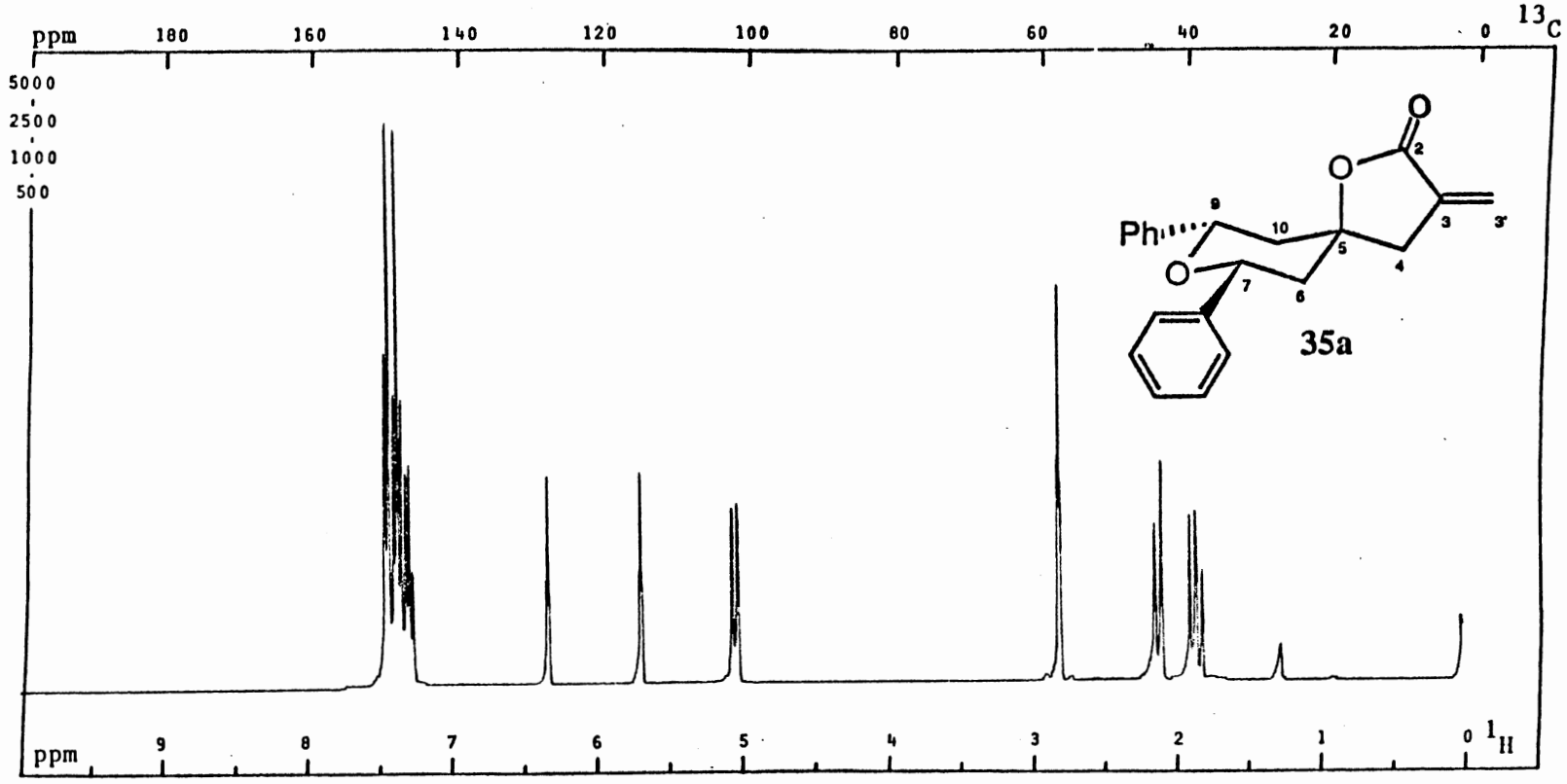
2,6-bis(2-Hydroxyphenyl)tetrahydropyran-4-one (37j & 38j)

A mixture of 0.73 g (5.0 mmol) of 1,3-acetonedicarboxylic acid (**40**) and 1.83 g (5.0 mmol) of 2-hydroxybenzaldehyde (**39j**) was placed in a 25-mL, 2-necked, round-bottom flask equipped as for **38a**. The $HCl_{(g)}$ was passed through the mixture for 0.5 h. Following the usual work-up (see **38a**), no precipitate formed from the aqueous solution. It was presumed that the expected ketones did not form.

2,6-bis(3-Methoxy-4-hydroxyphenyl)tetrahydropyran-4-one (37k & 38k)

A mixture of 0.731 g (5.0 mmol) of 1,3-acetonedicarboxylic acid (**40**) and 2.28 g (15 mmol) of vanillin (**39k**) was placed in a 25-mL, 2-necked, round-bottom flask equipped as for **38a**. The $HCl_{(g)}$ was passed through the mixture for a period of 0.3 h. Following the usual work-up procedure (see **38a**), no precipitate formed from the aqueous solution. It was assumed the ketones required did not form.

Plate I



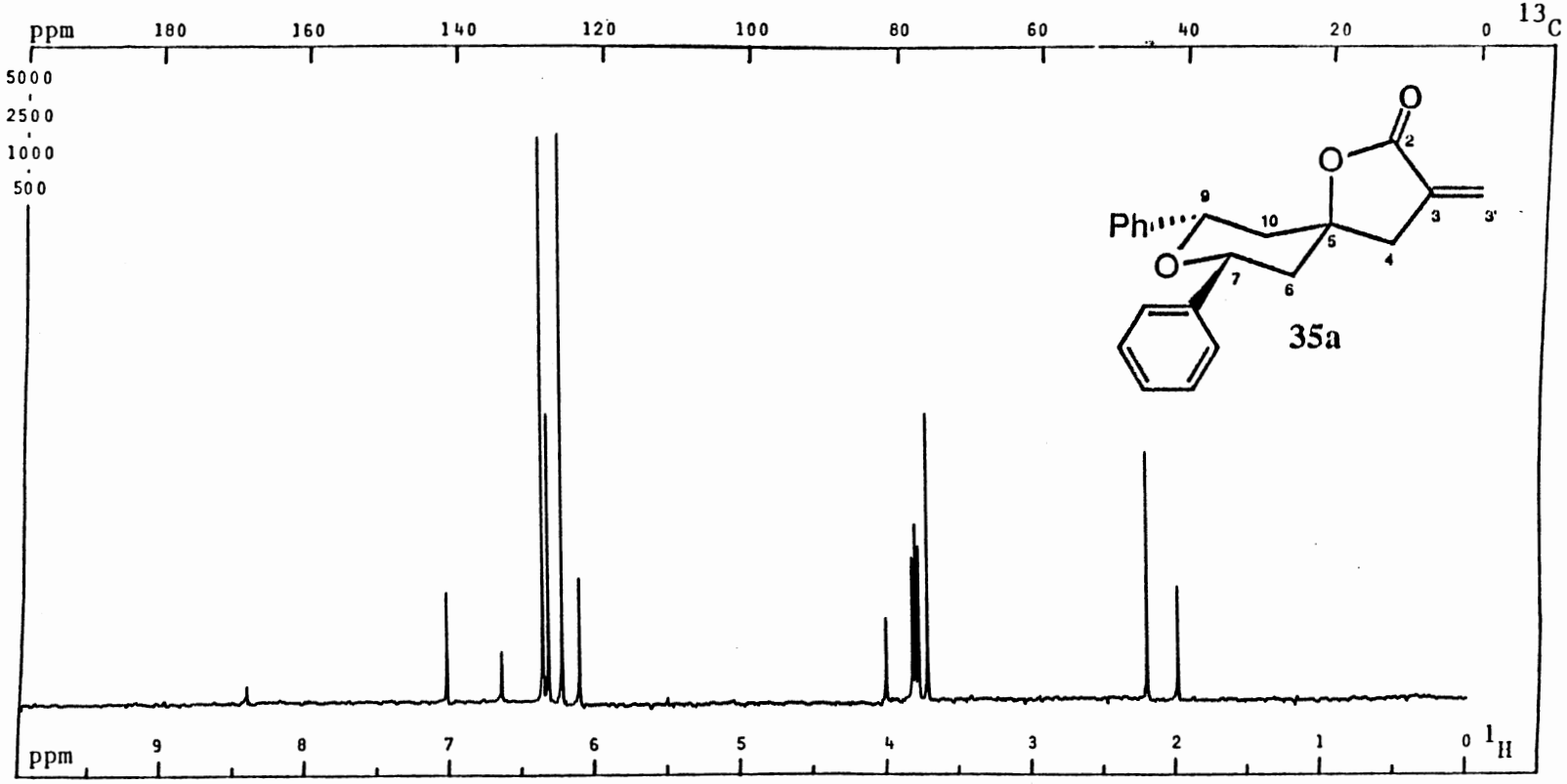
^{1}H NMR Spectrum of **35a**

PFT X CW _ ; Solvent: DCCl ; SF: 299.94 MHz; WC: 2999.4 Hz; T: RT °C; NT: 16.

Size: 16 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: -- Hz; Lock: ^{2}H ; D1,D5: 0.500 s.

DC: Y, N ; Gated Off:A or D ; DO: Hz; RF(Power): 8 W/dB; NBW: 200 Hz; LB: 0.500 Hz.

Plate II



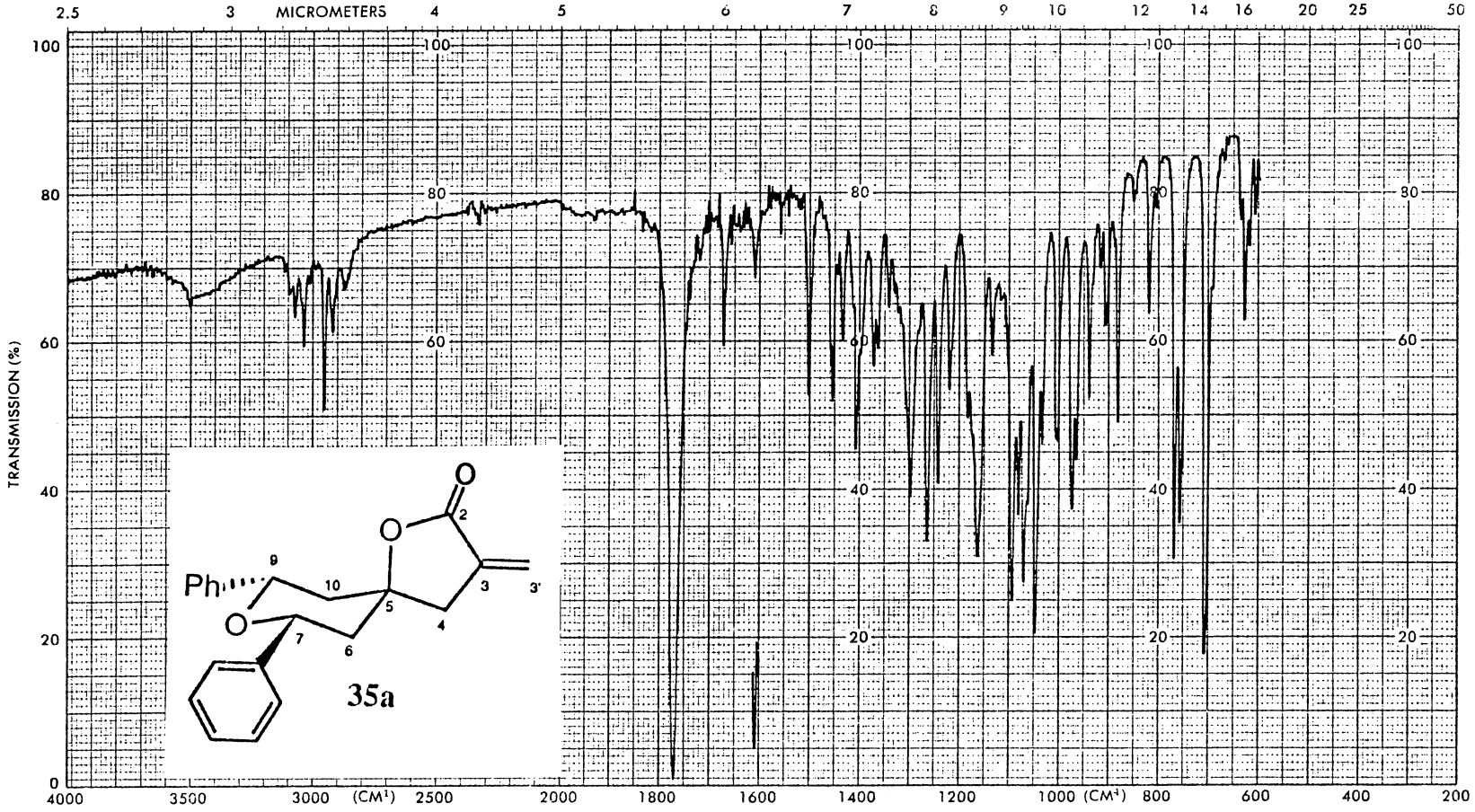
^{13}C NMR Spectrum of **35a**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC:15085.9 Hz; T: RT °C; NT: 120.

Size: 20 K; PW/RF: 12.5 µs/dB; TO: 1000 Hz; FB: -- Hz; Lock: ^{2}H ;D1,D5: 4.000 s.

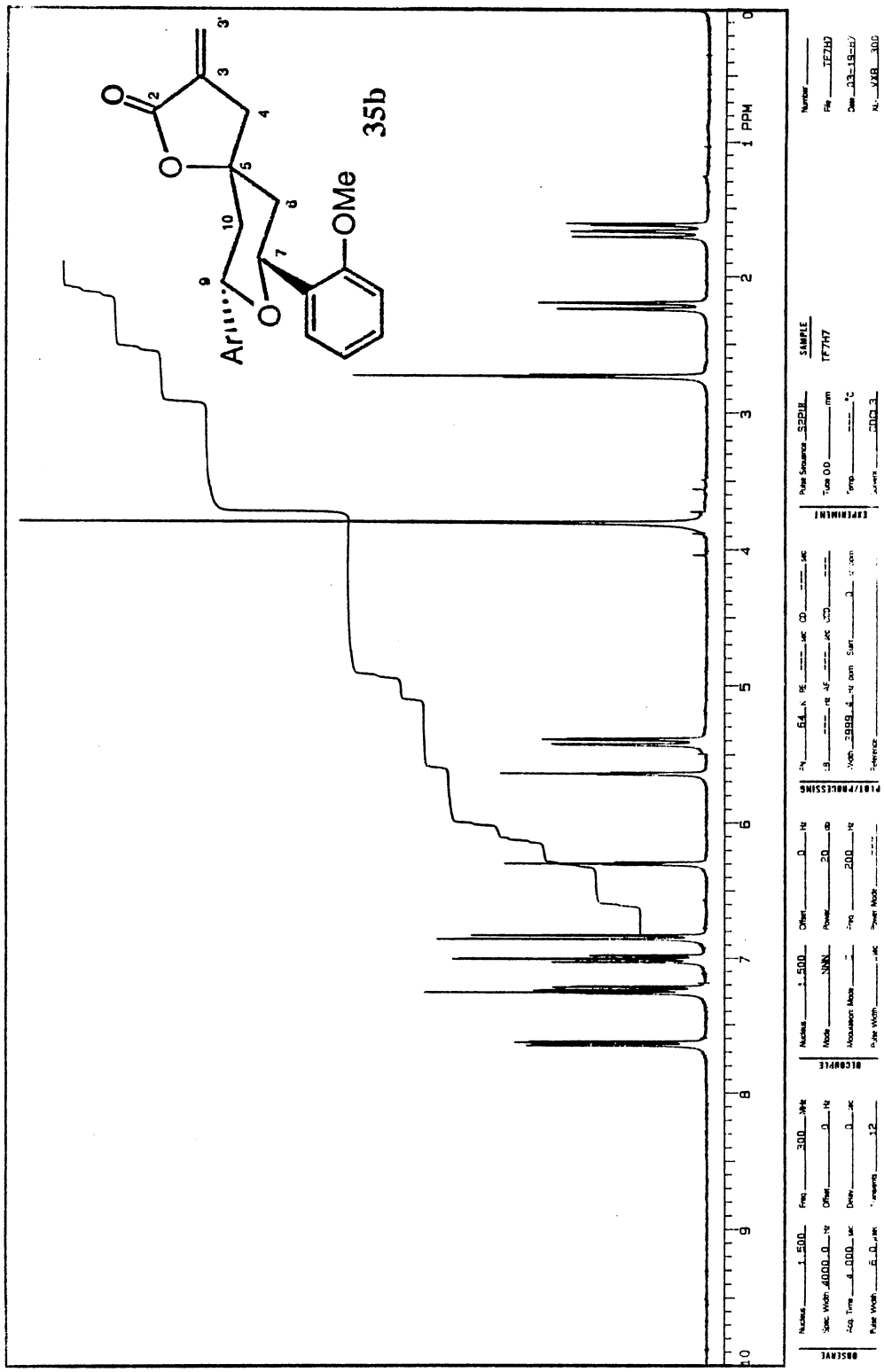
DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 1.500 Hz.

Plate III



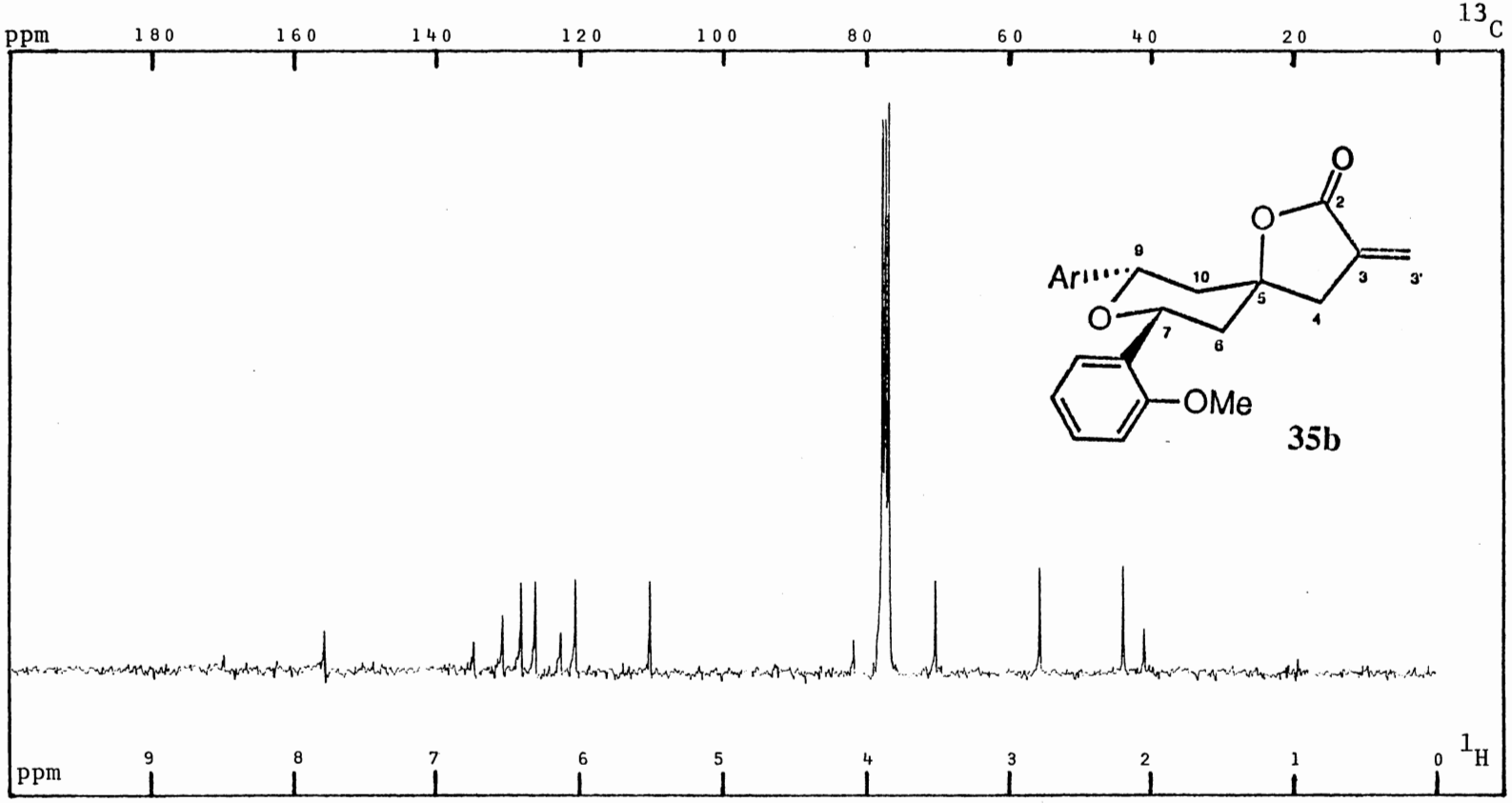
IR Spectrum of **35a**

Plate IV



^{1}H NMR Spectrum of **35b**

Plate V



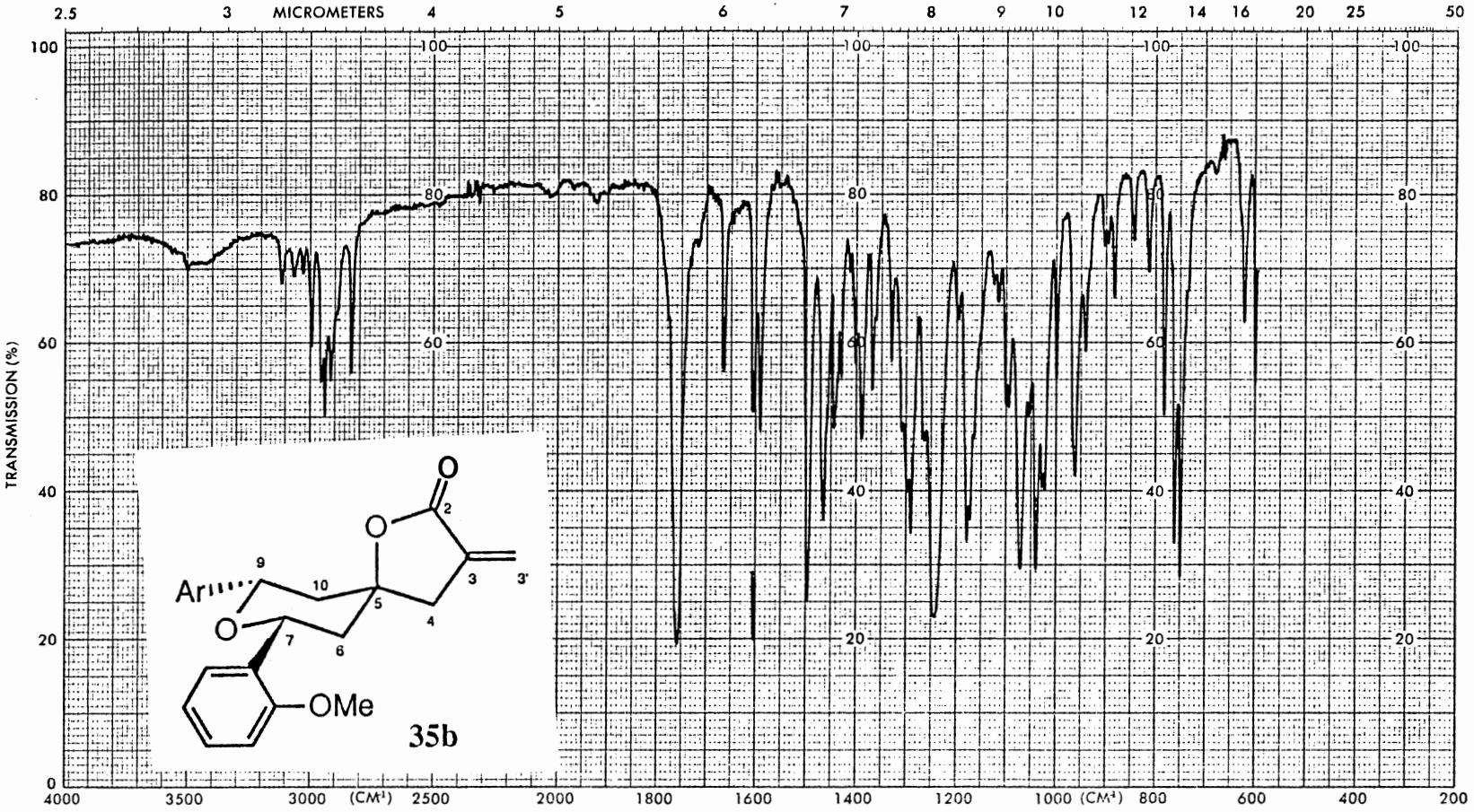
^{13}C NMR Spectrum of **35b**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC:15085.9 Hz; T: RT °C; NT: 800.

Size: 2 K; PW/RF: 12.0 μs/dB; TO: 1000 Hz; FB: -- Hz; Lock: ^2H ;D1,D5: 4.000 s.

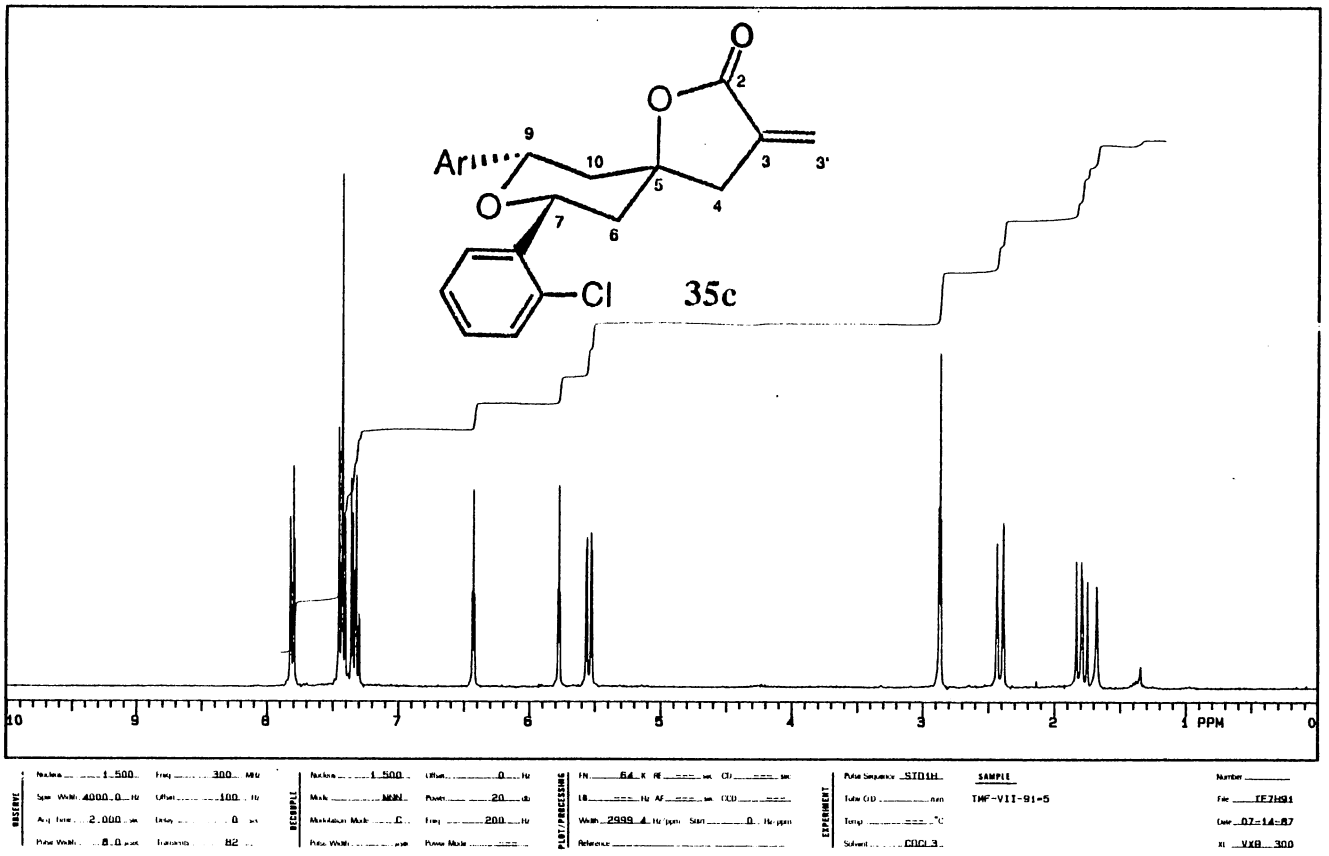
DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 0 Hz; LB: 1.000 Hz. Hz.

Plate VI



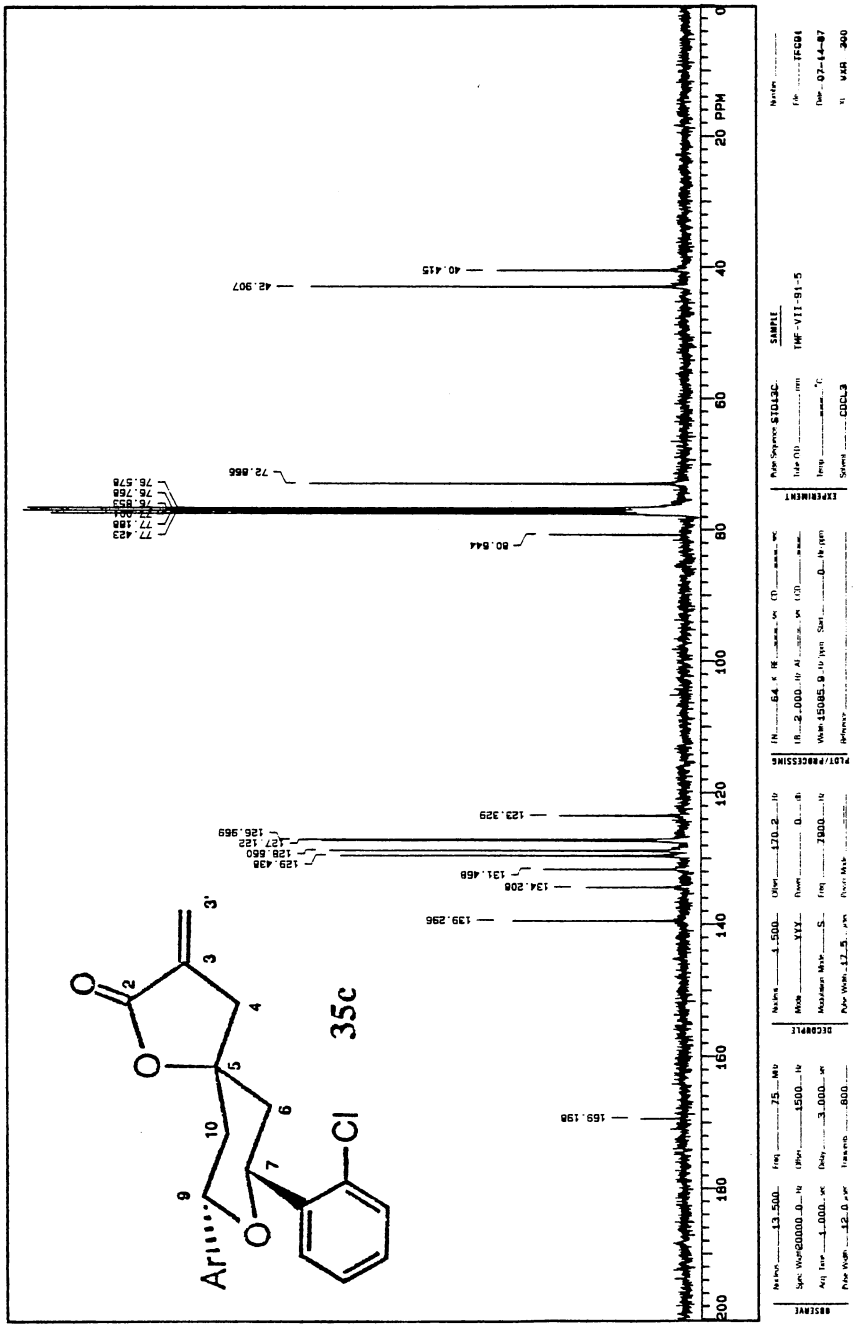
IR Spectrum of **35b**

Plate VII



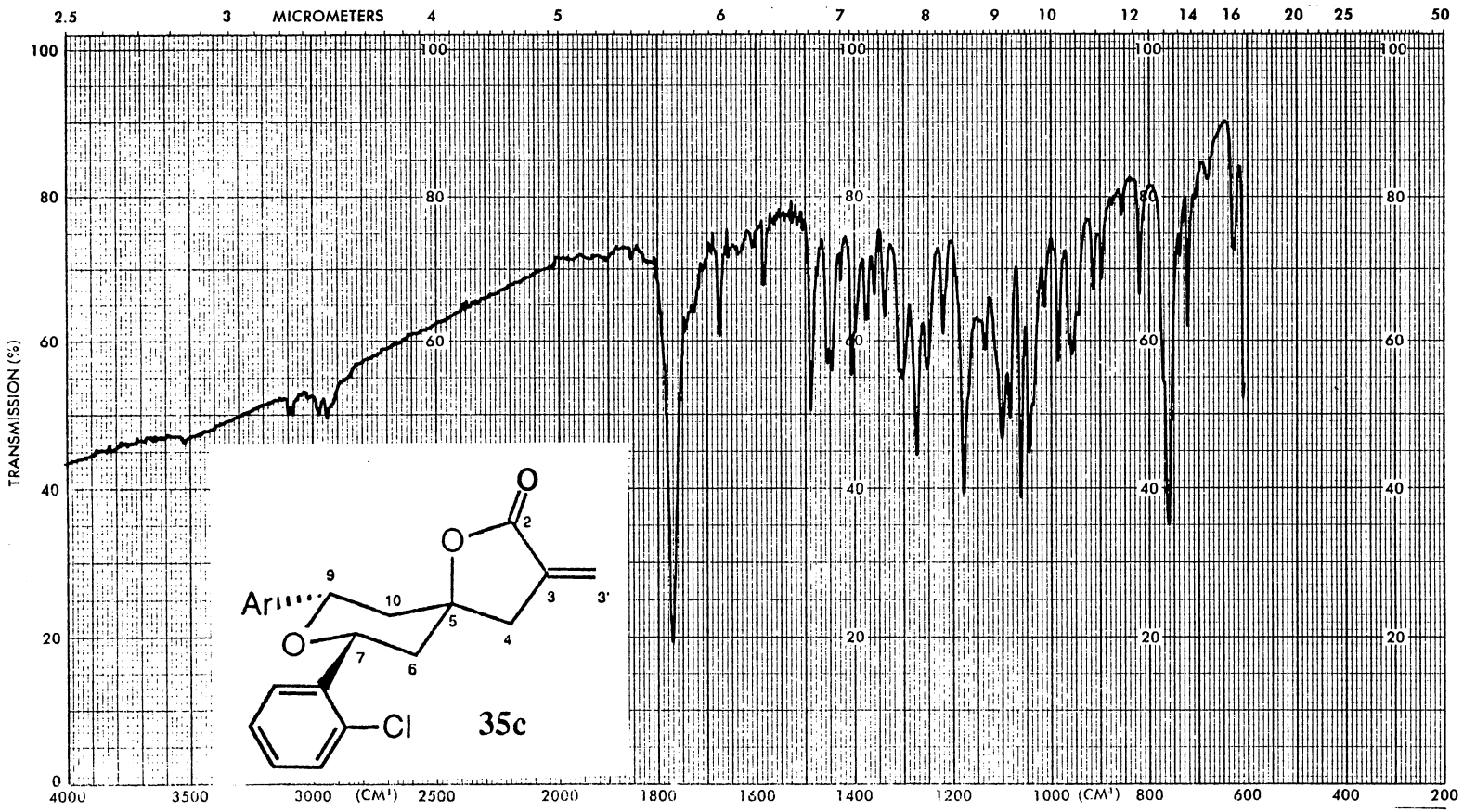
^{1}H NMR Spectrum of **35c**

Plate VIII



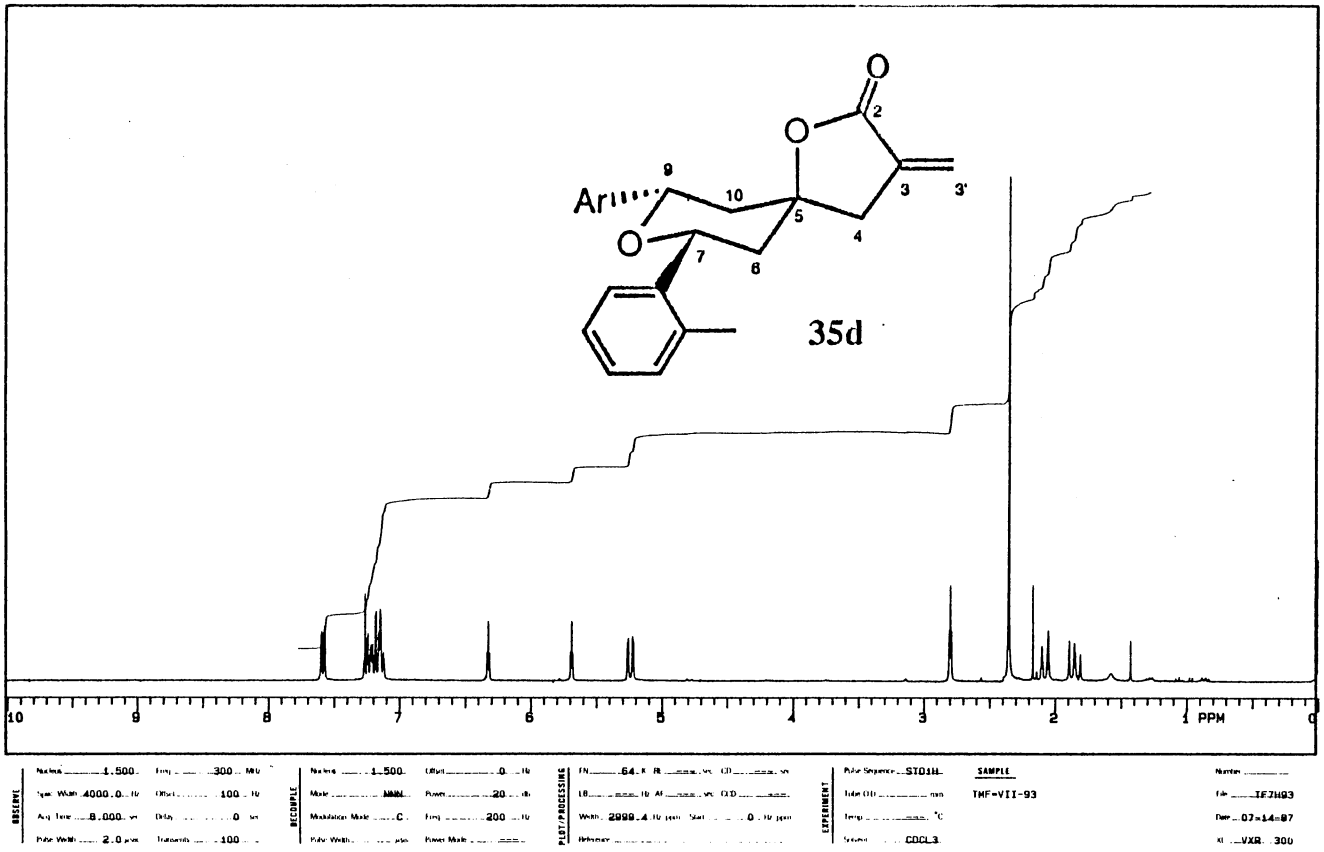
^{13}C NMR Spectrum of 35c

Plate IX



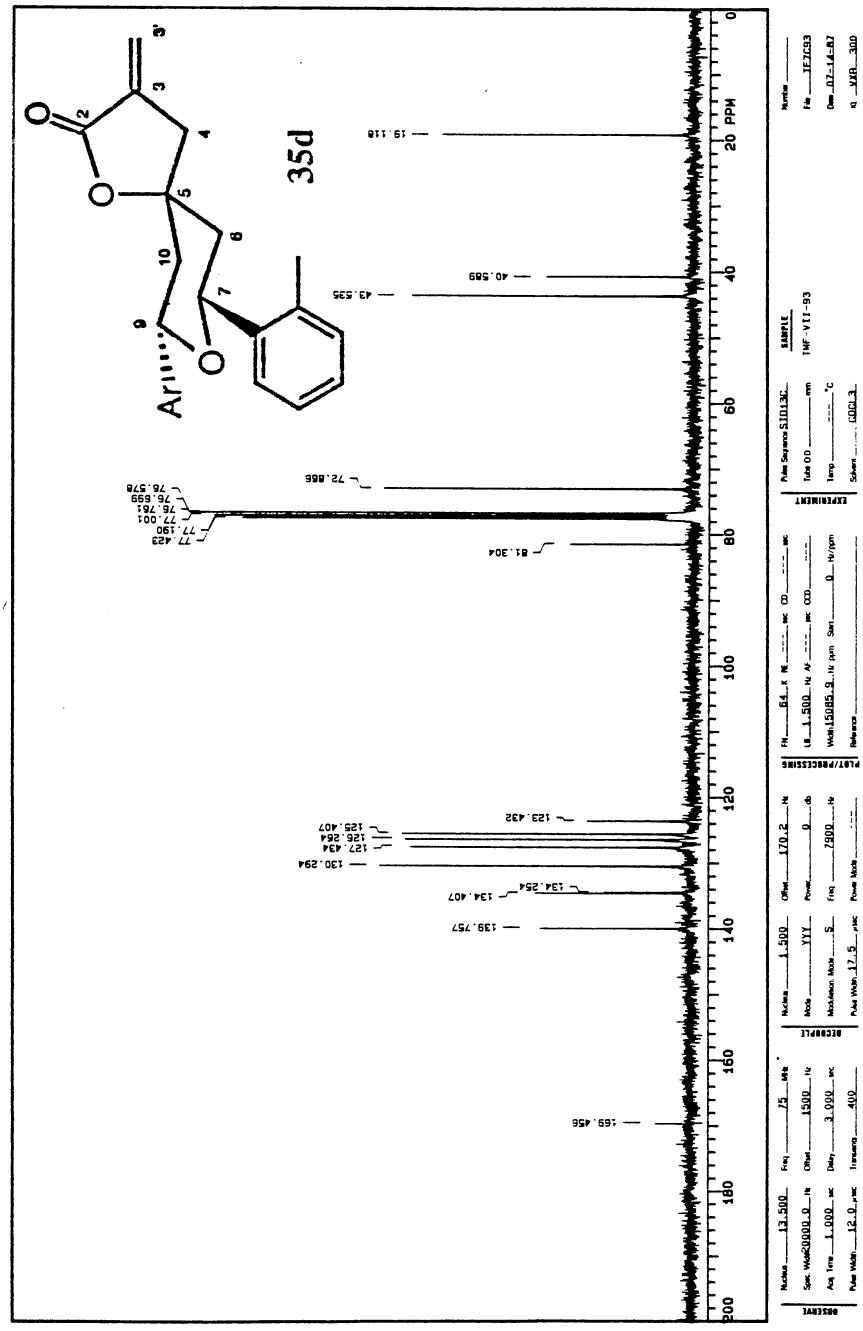
IR Spectrum of **35c**

Plate X



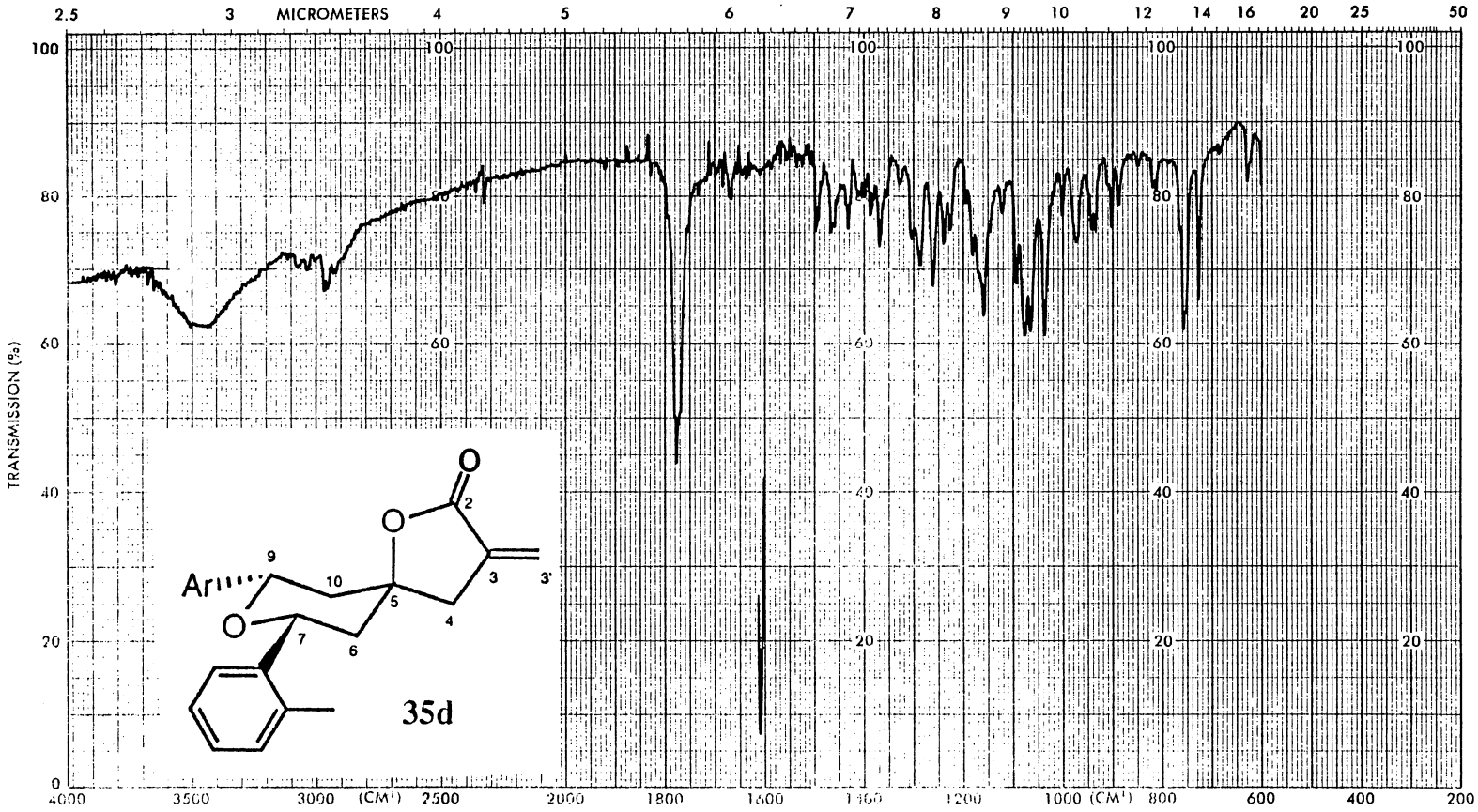
^{1}H NMR Spectrum of **35d**

Plate XI



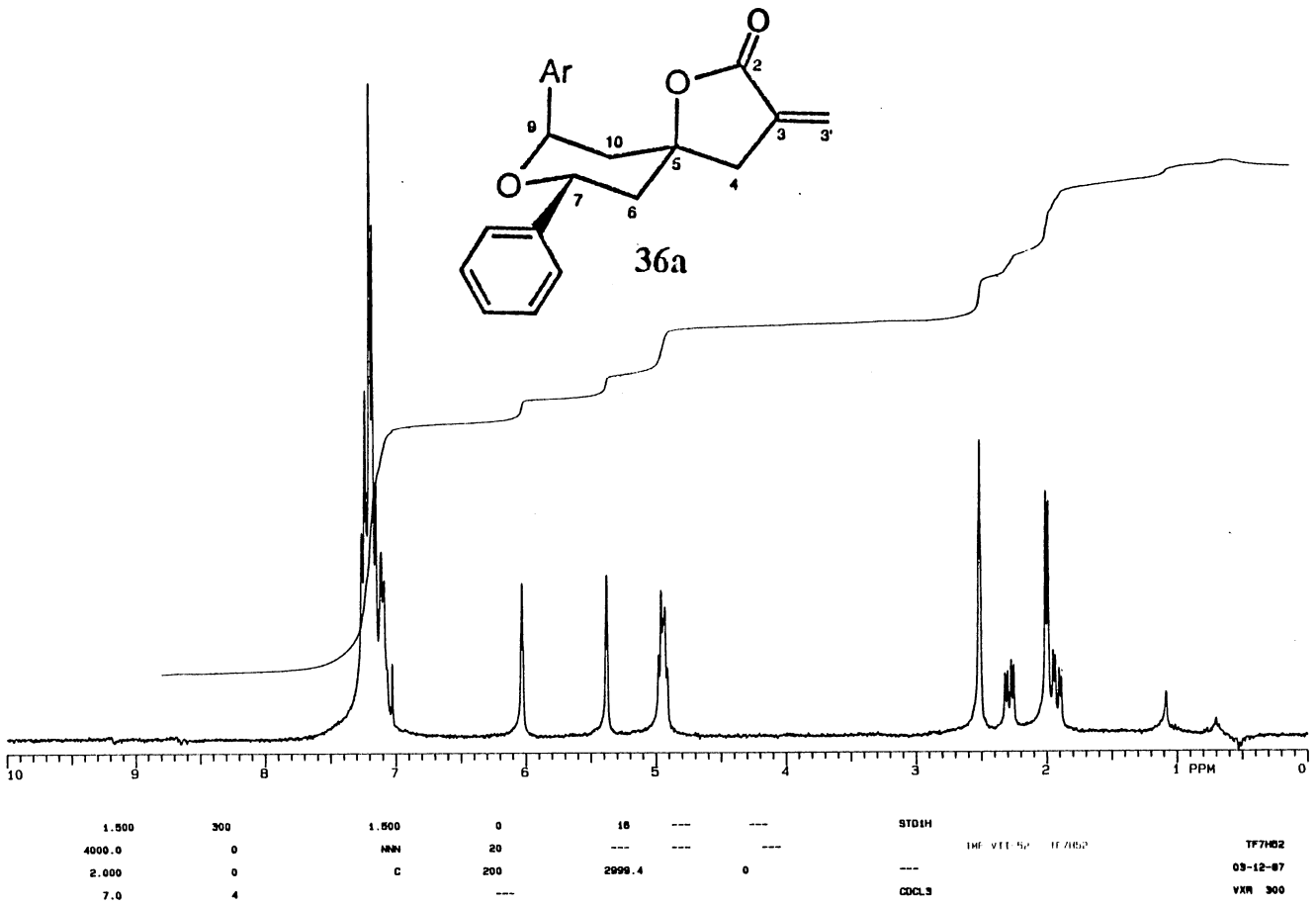
^{13}C NMR Spectrum of **35d**

Plate XII



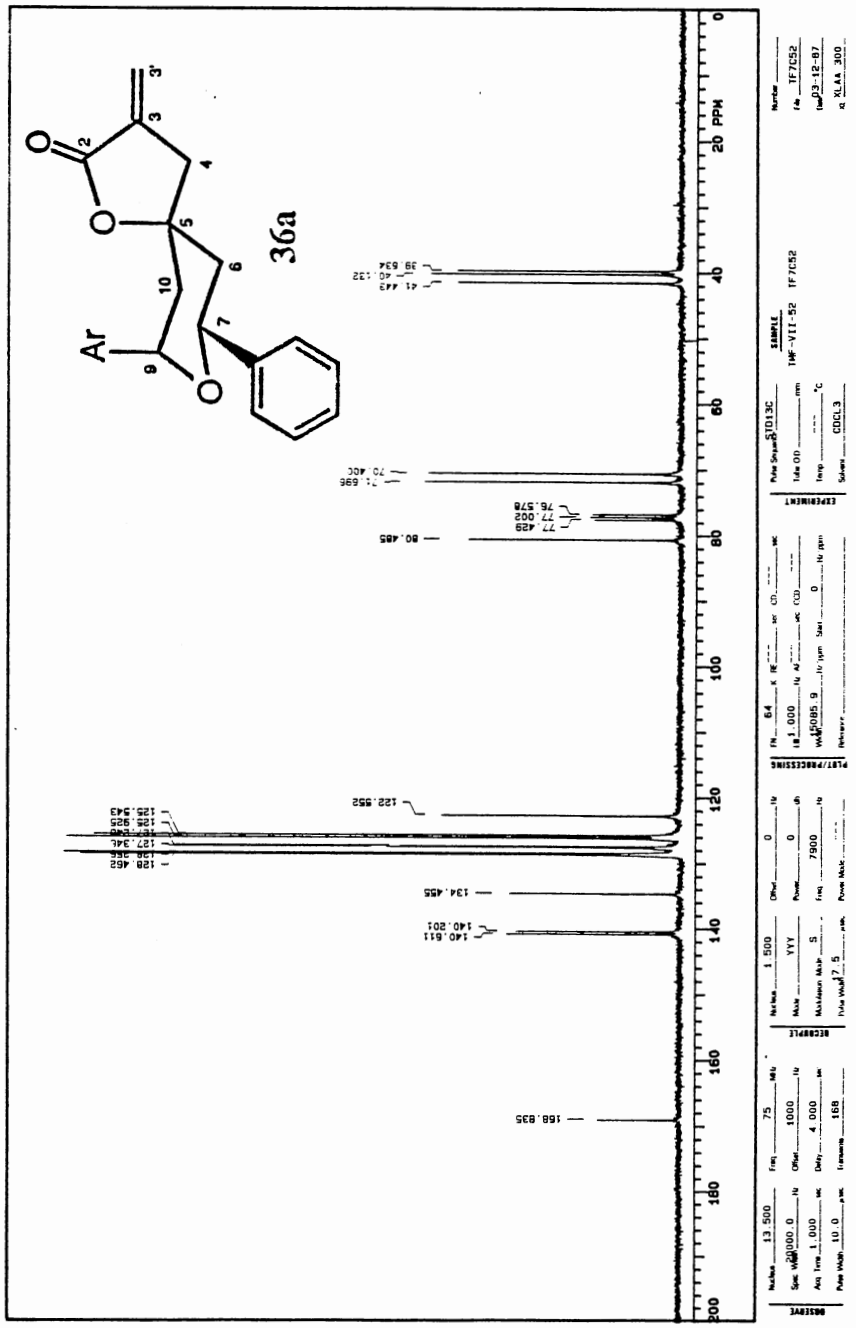
IR Spectrum of **35d**

Plate XIII



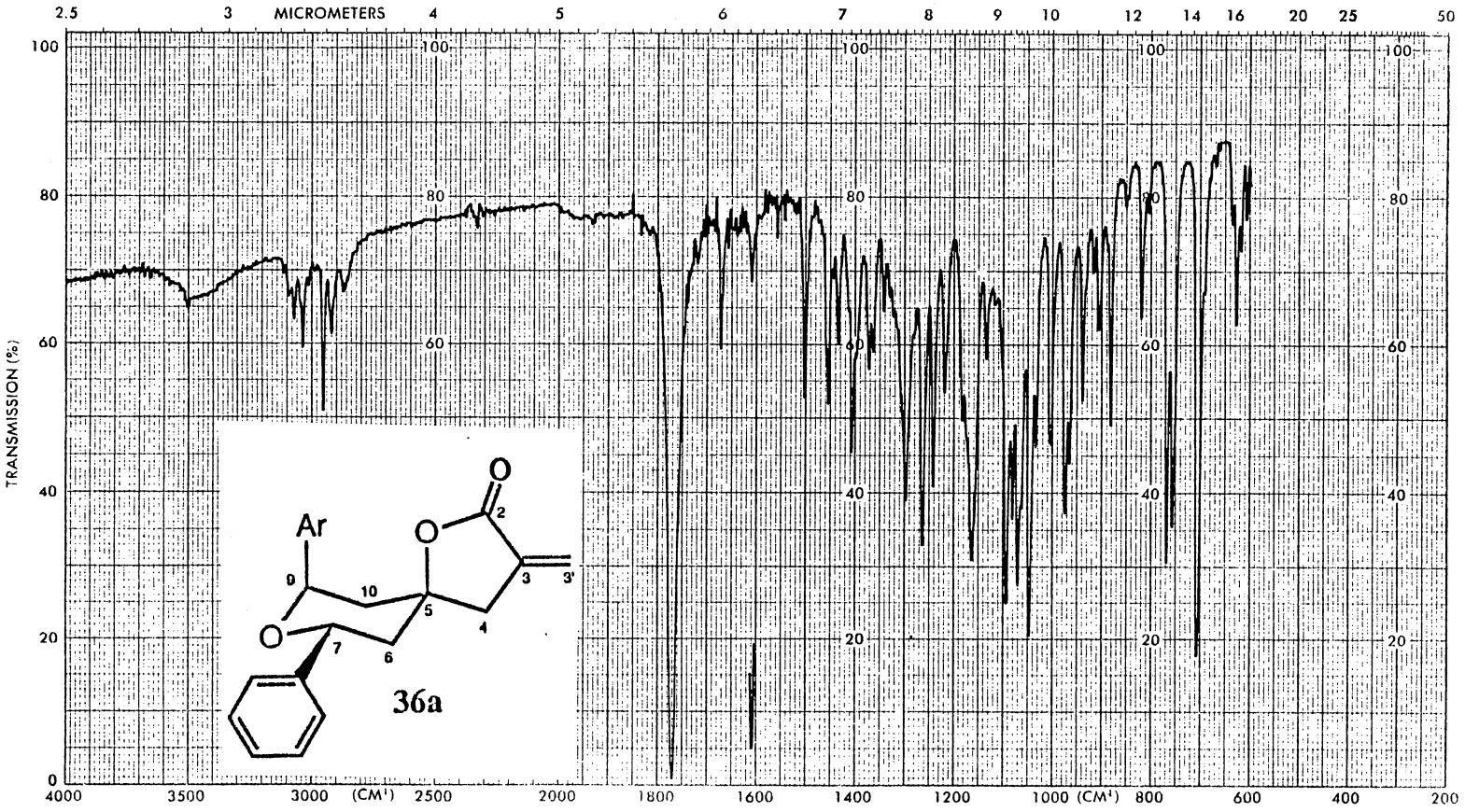
^{1}H NMR Spectrum of **36a**

Plate XIV



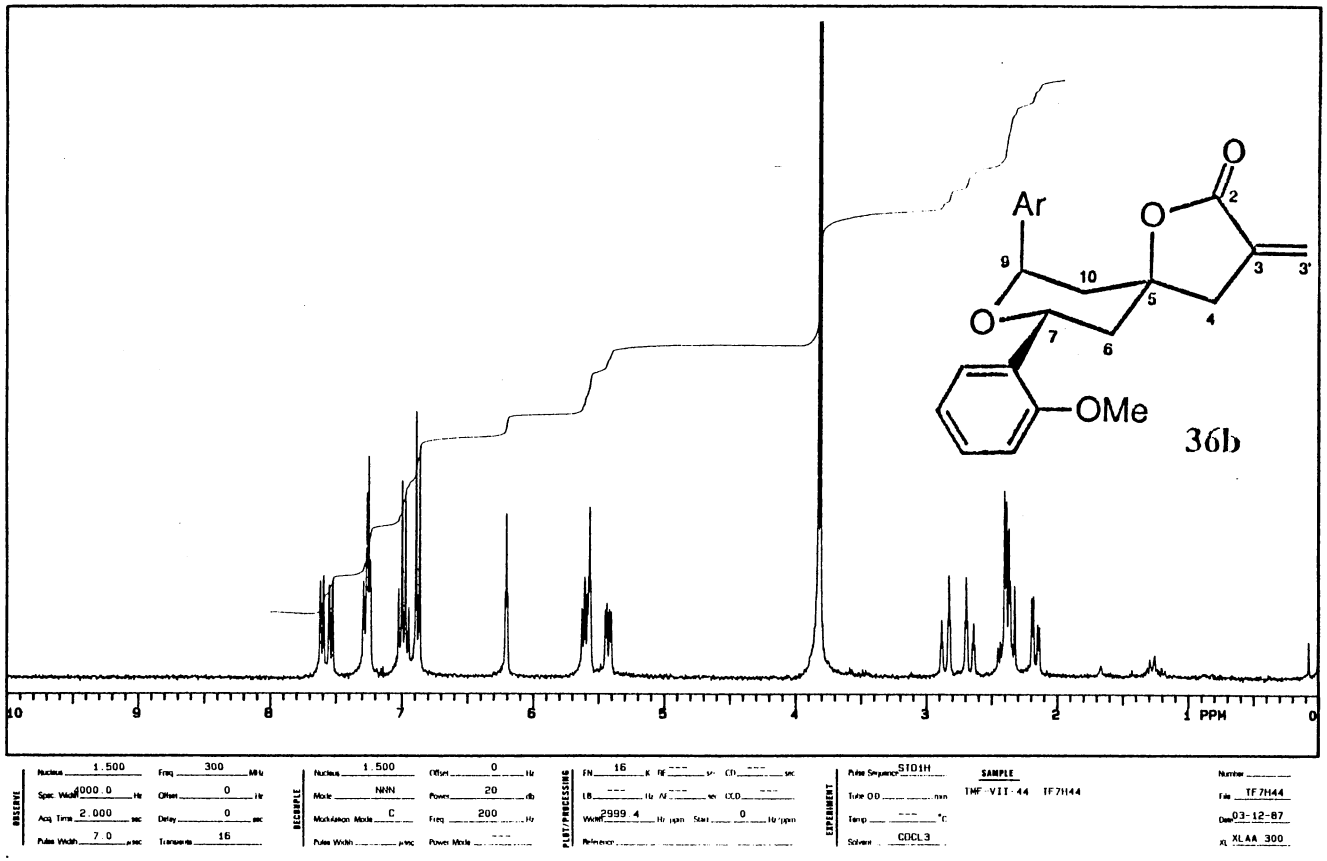
^{13}C NMR Spectrum of 36a

Plate XV



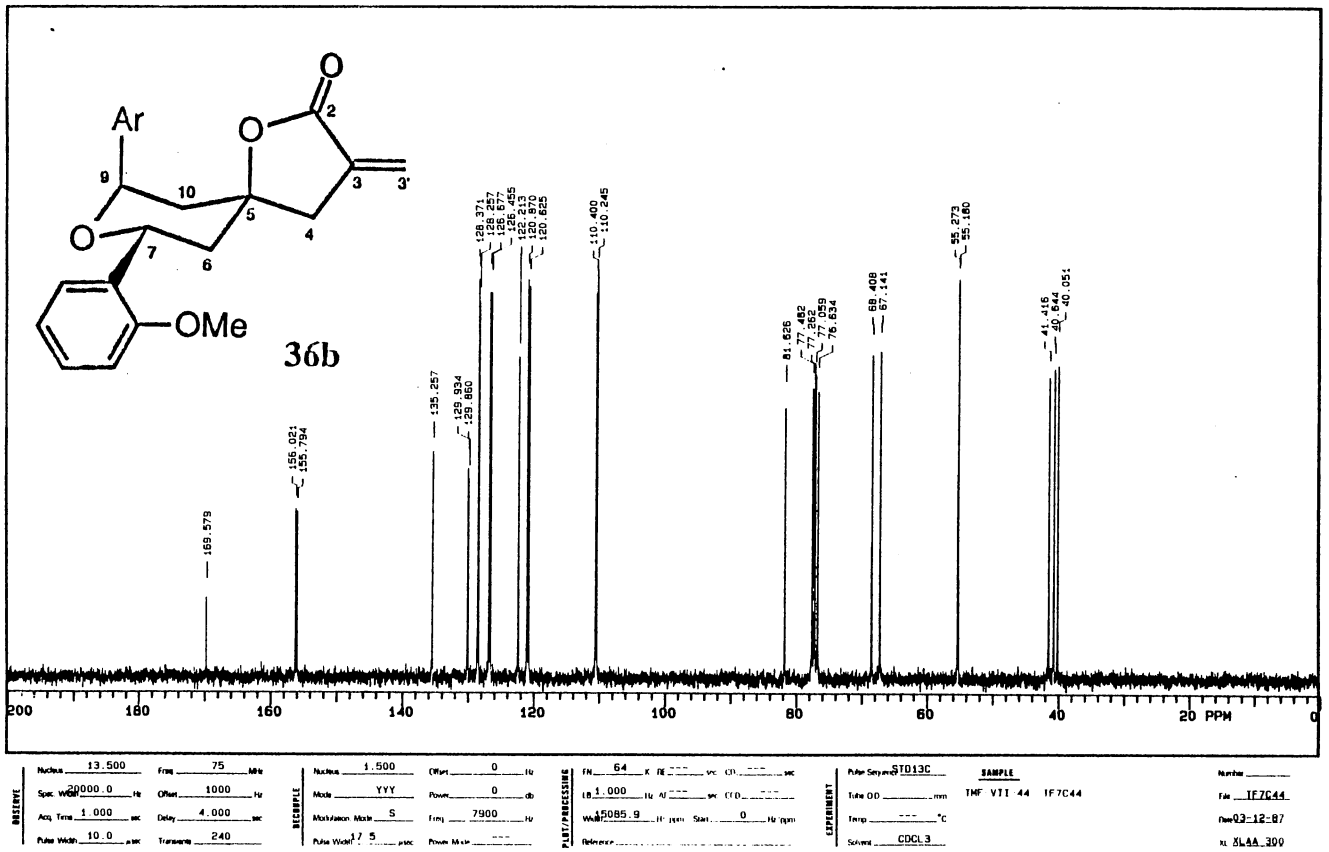
IR Spectrum of **36a** (film)

Plate XVI



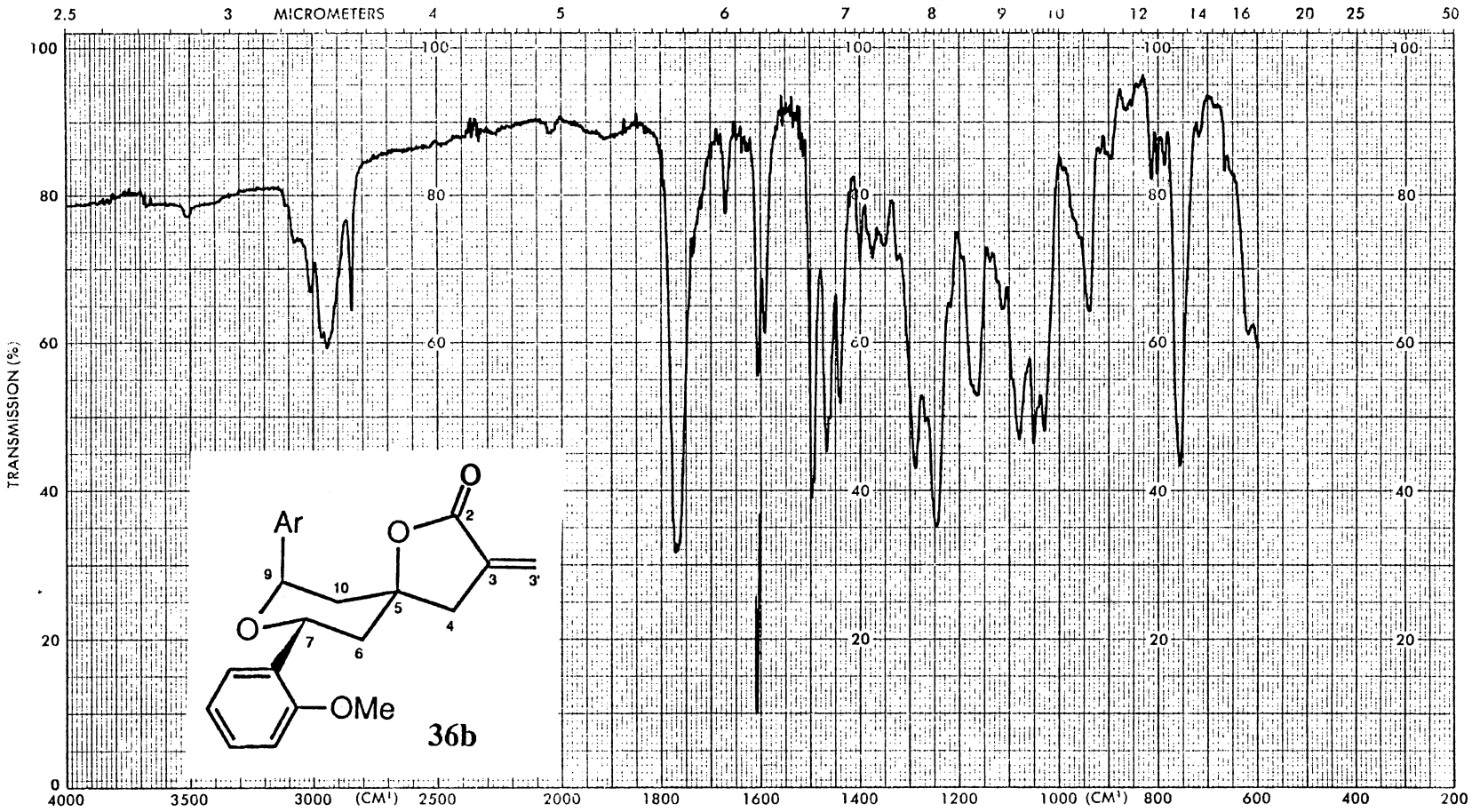
^{1}H NMR Spectrum of **36b**

Plate XVII



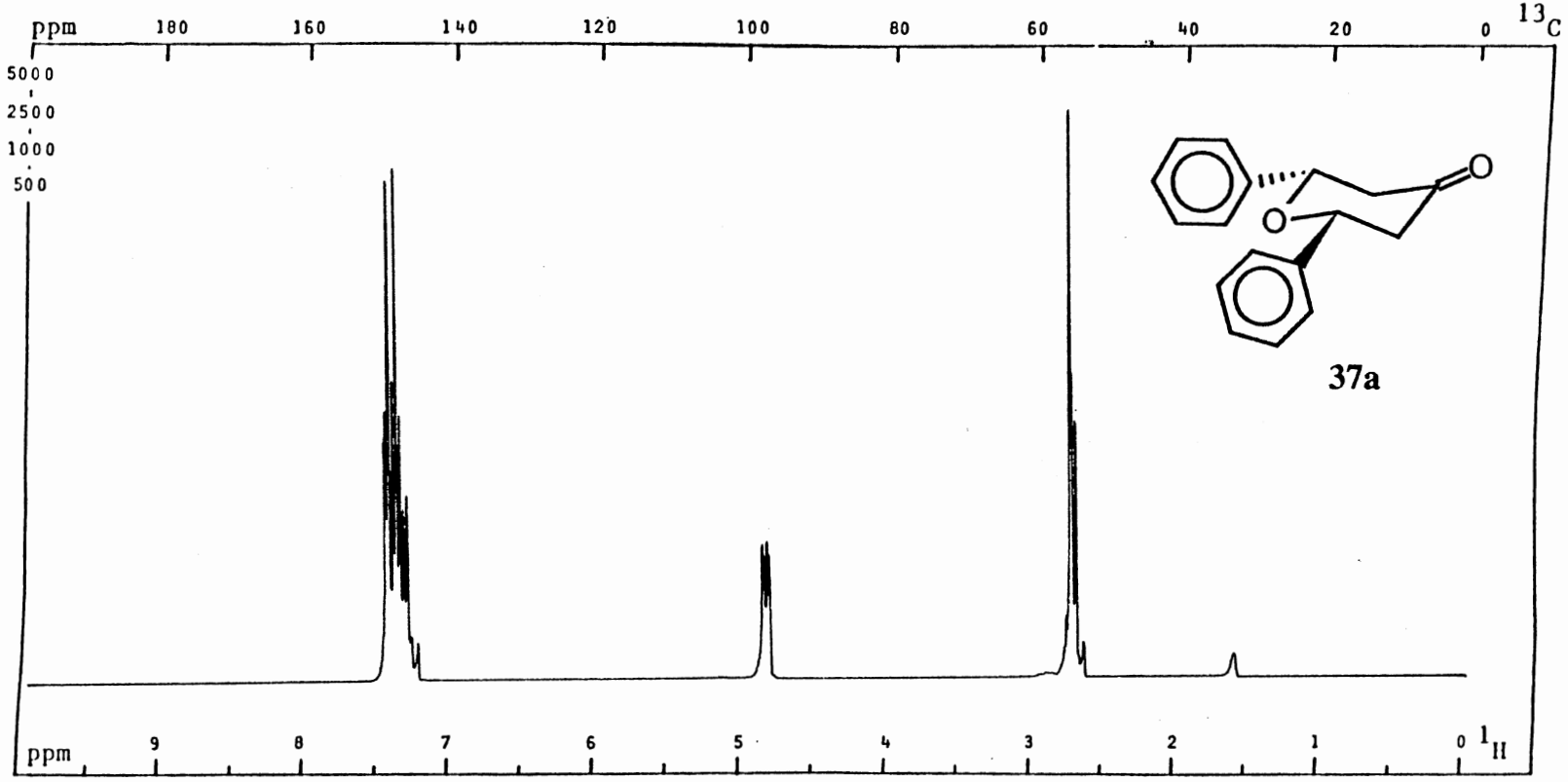
^{13}C NMR Spectrum of **36b**

Plate XVIII



IR Spectrum of **36b** (film)

Plate XIX



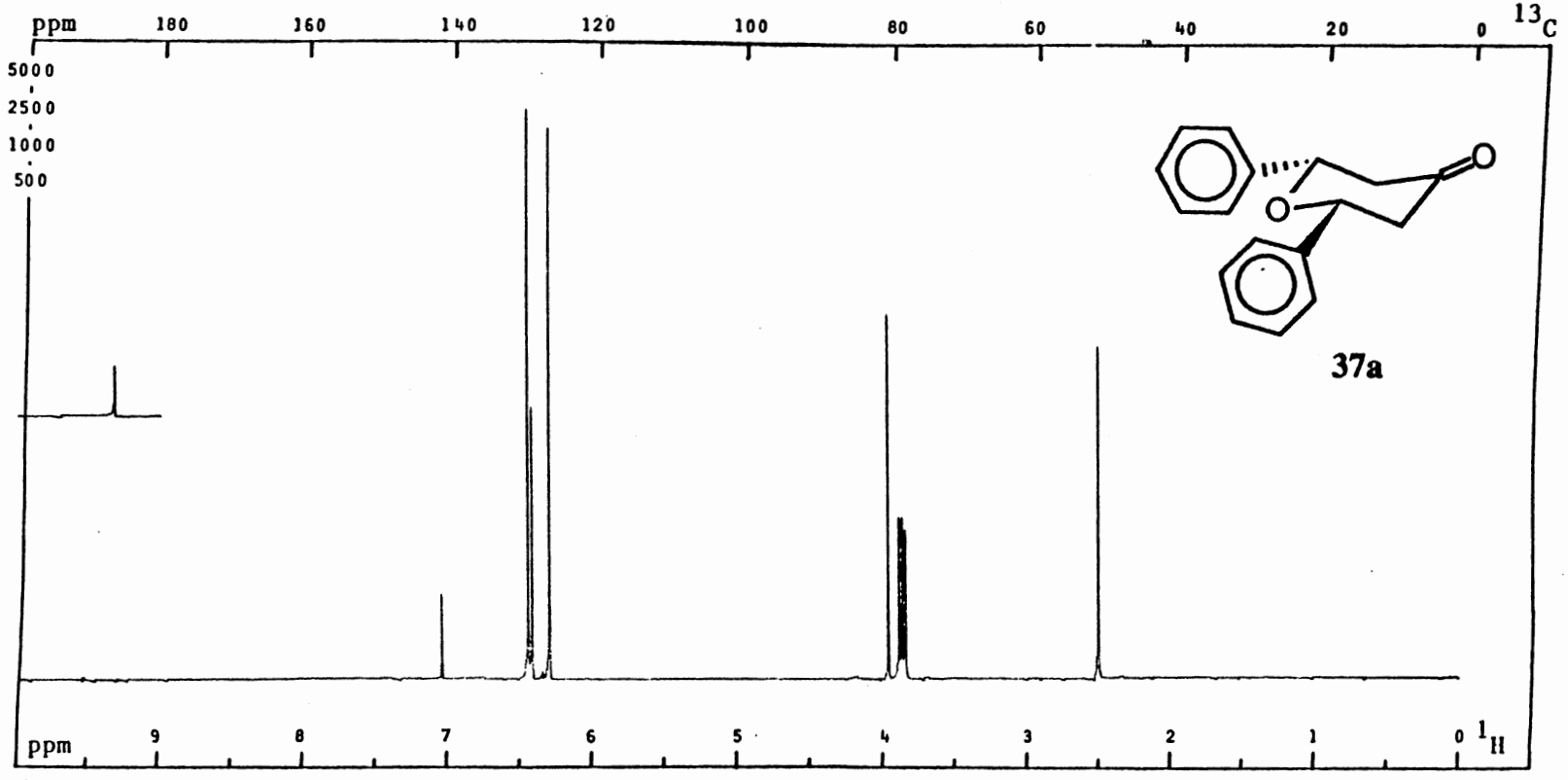
^{1}H NMR Spectrum of **37a**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8 .

Size: 8 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: -- Hz; Lock: ^{2}H ; D1,D5: 0.500 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: 200 Hz; LB: 0.500 Hz.

Plate XX



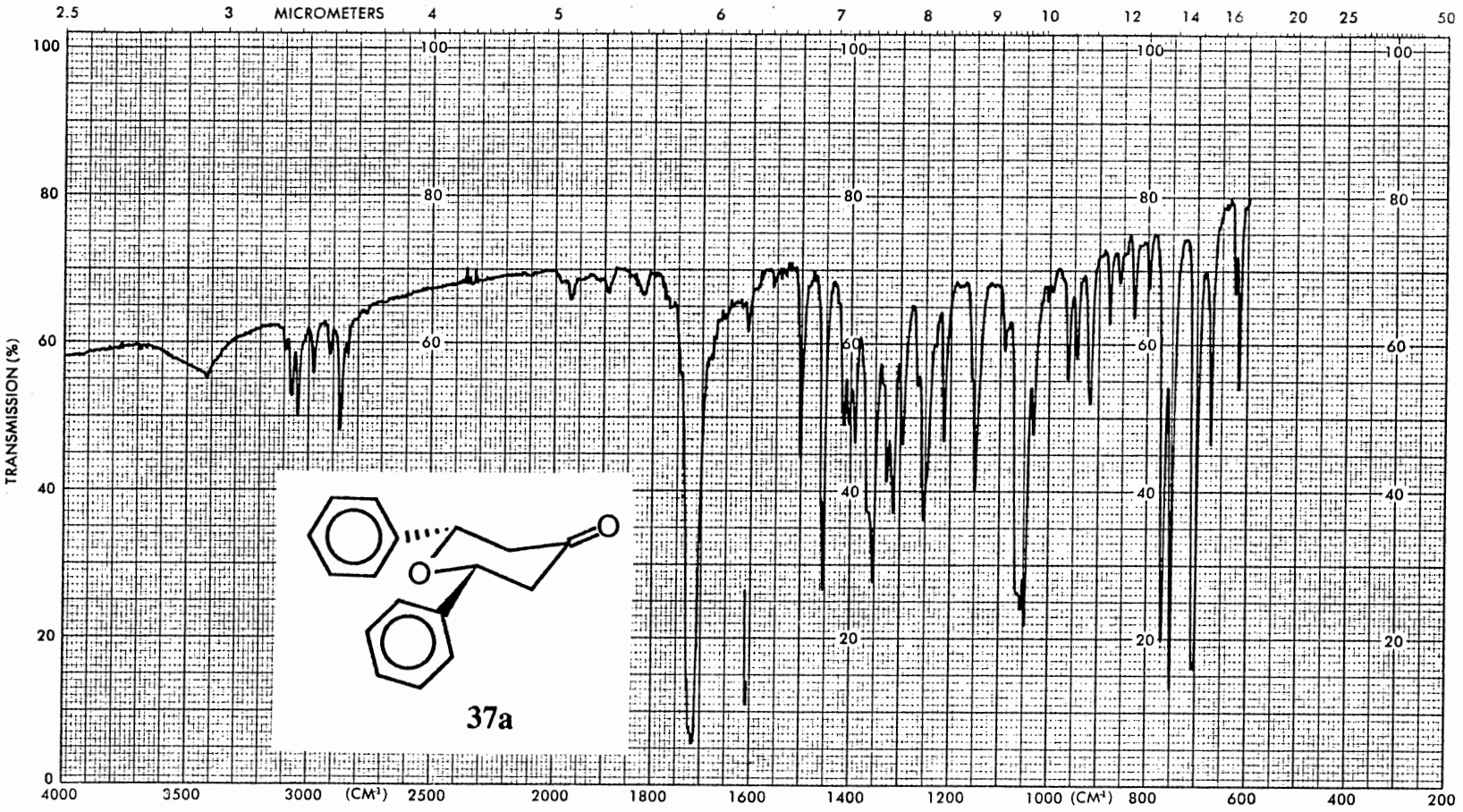
^{13}C NMR Spectrum of **37a**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 600 .

Size: 16 K; PW/RF: 14.0 µs/dB; TO: 1000 Hz; FB: -- Hz; Lock: ^2H ; D1,D5: 3.000 s.

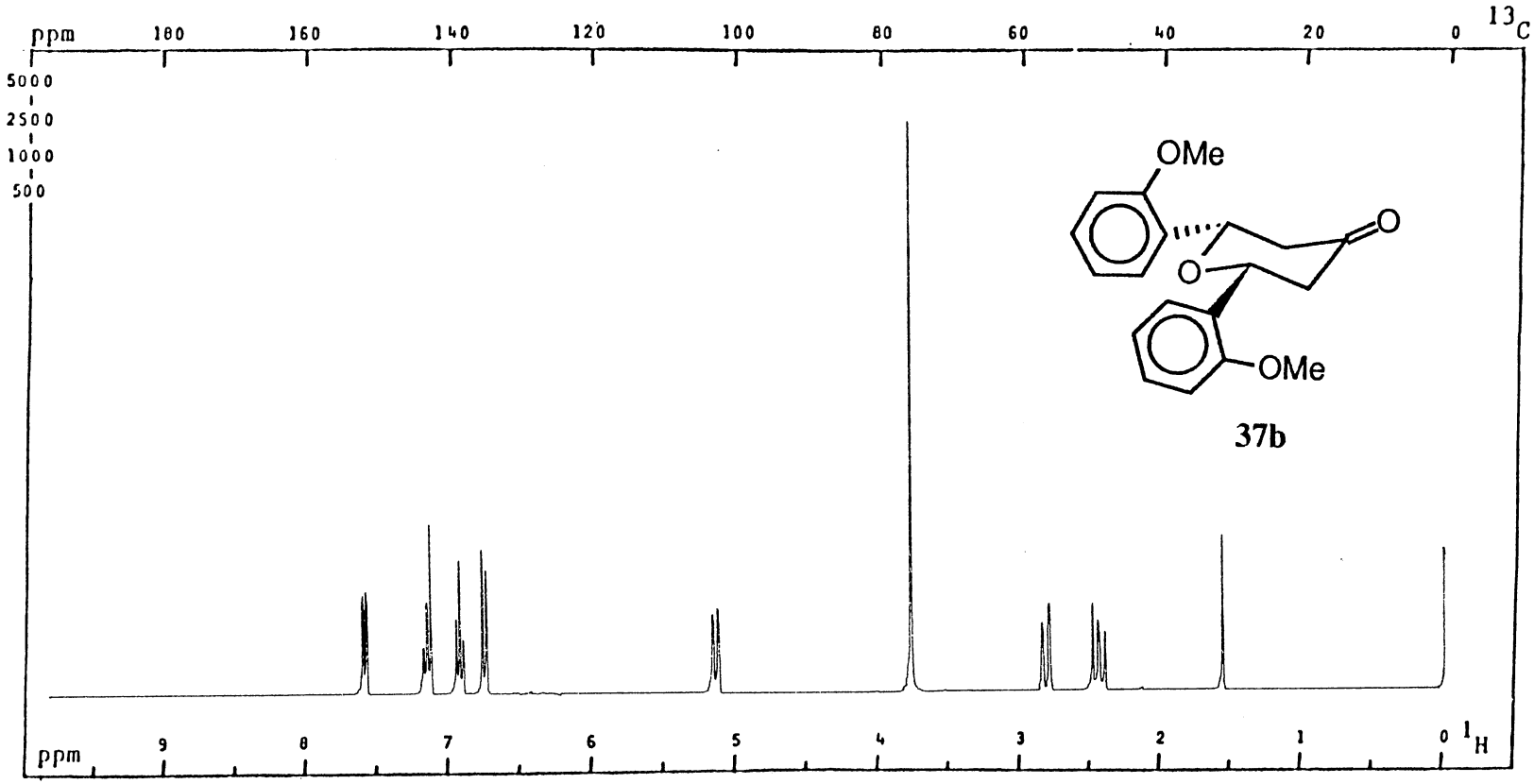
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 1.500 Hz.

Plate XXI



IR Spectrum of **37a**

Plate XXII



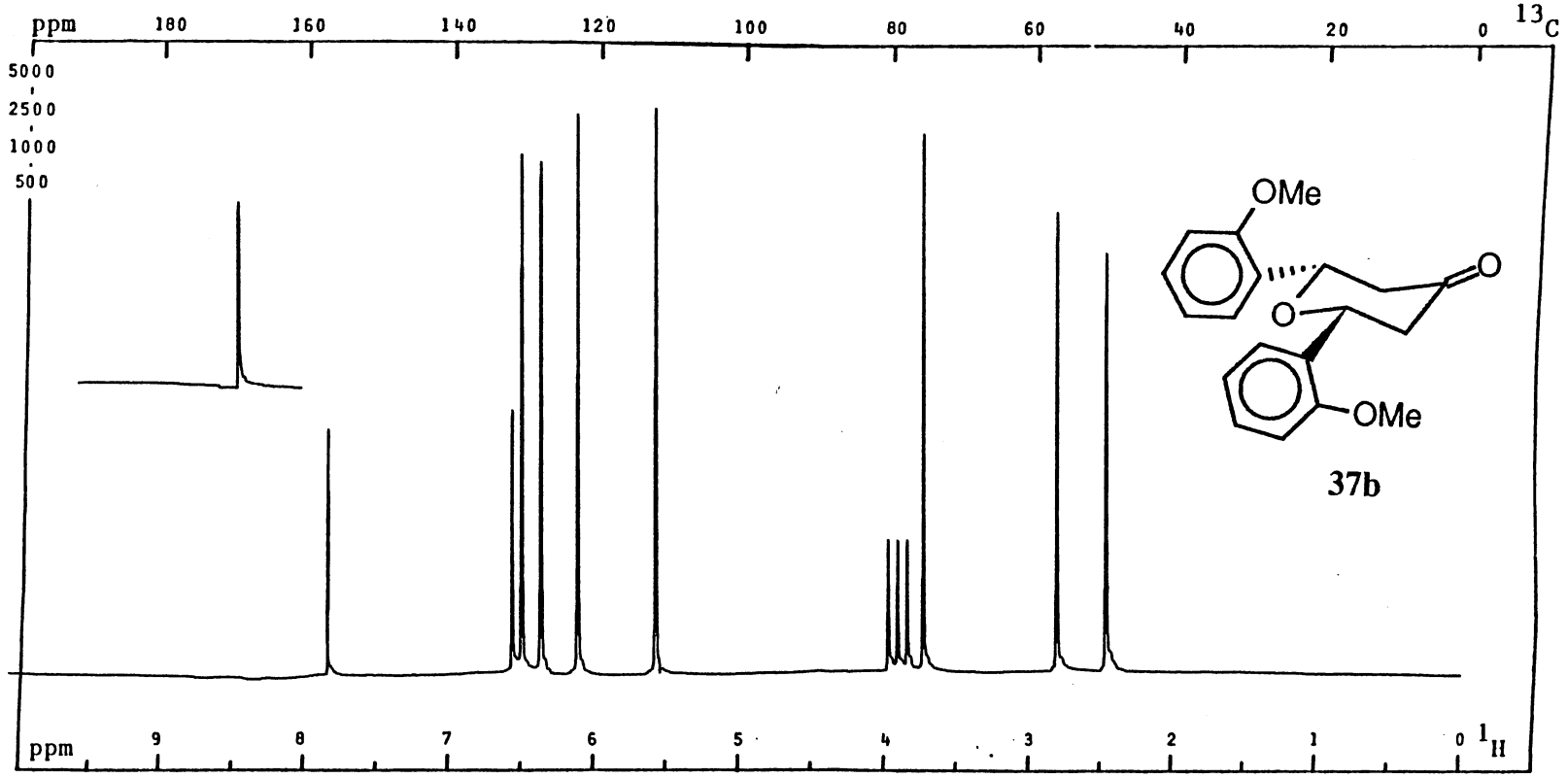
^{1}H NMR Spectrum of **37b**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.994 MHz; WC: 2999.4 Hz; T: RT °C; NT: 40.

Size: 16 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: -- Hz; Lock: ^{2}H ; D1,D5: 0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 0 Hz; LB: 0 Hz.

Plate XXIII



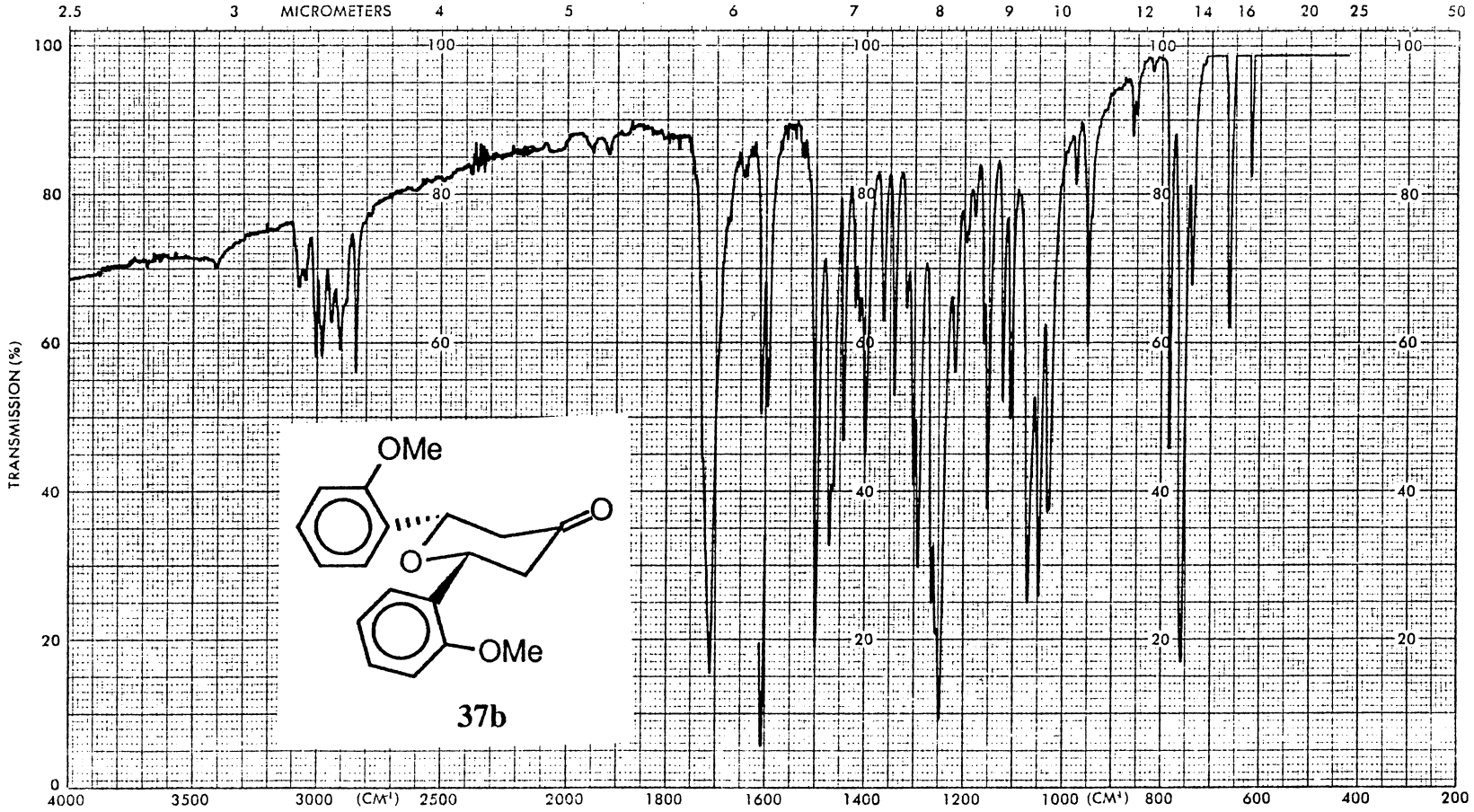
^{13}C NMR Spectrum of **37b**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 25.20 MHz; WC: 5000 Hz; T: RT °C; NT: 38000 .

Size: 16 K; PW/RF: 15 µs/dB; TO: 35101 Hz; FB: -- Hz; Lock: ^{2}H ; D1,D5: 4.000 s.

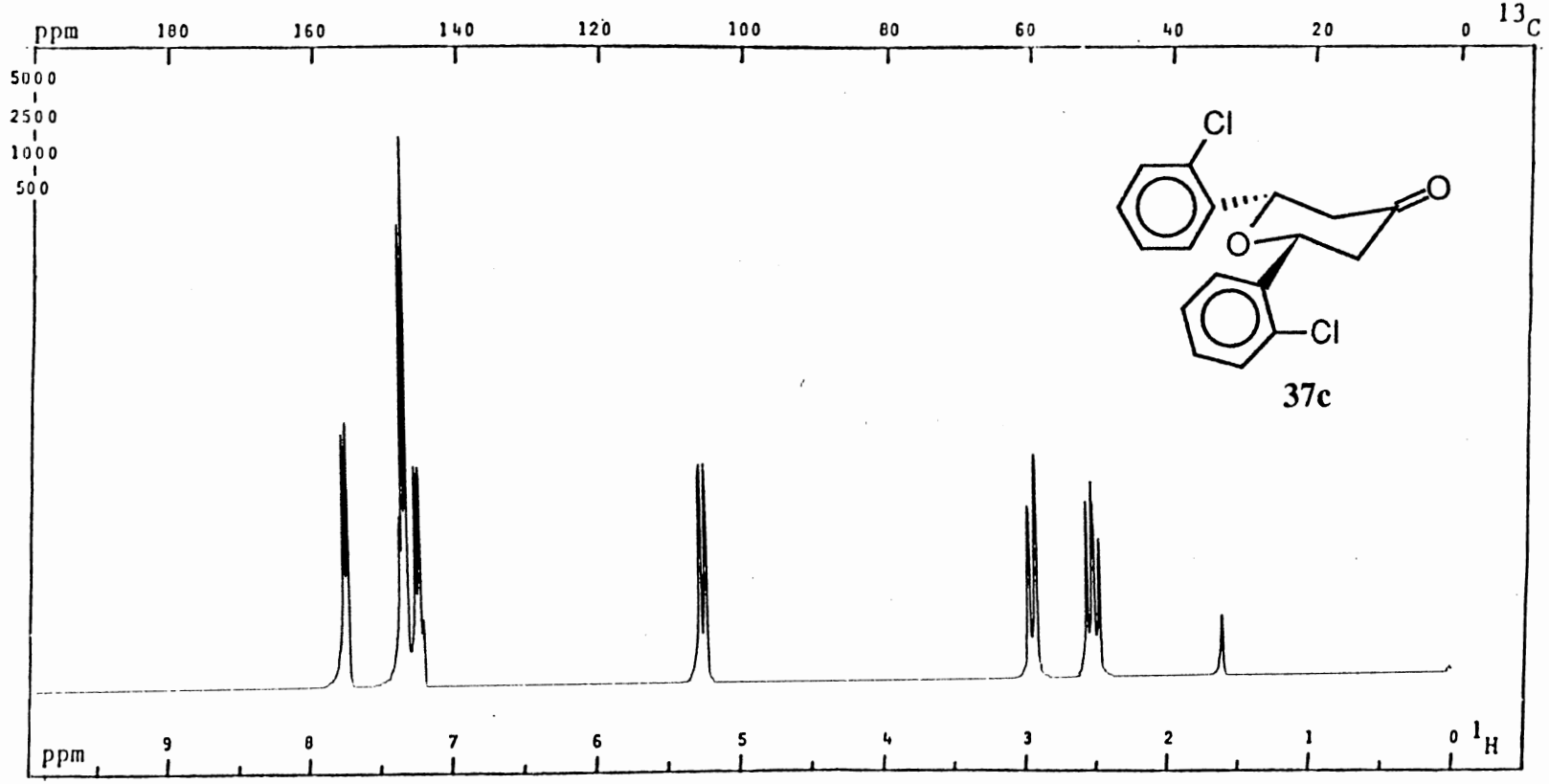
DC: Y, N ; Gated Off:A or D ; DO: 45316 Hz; RF(Power): 119 W/dB; NBW: Hz; LB: 1.500 Hz.

Plate XXIV



IR Spectrum of **37b**

Plate XXV



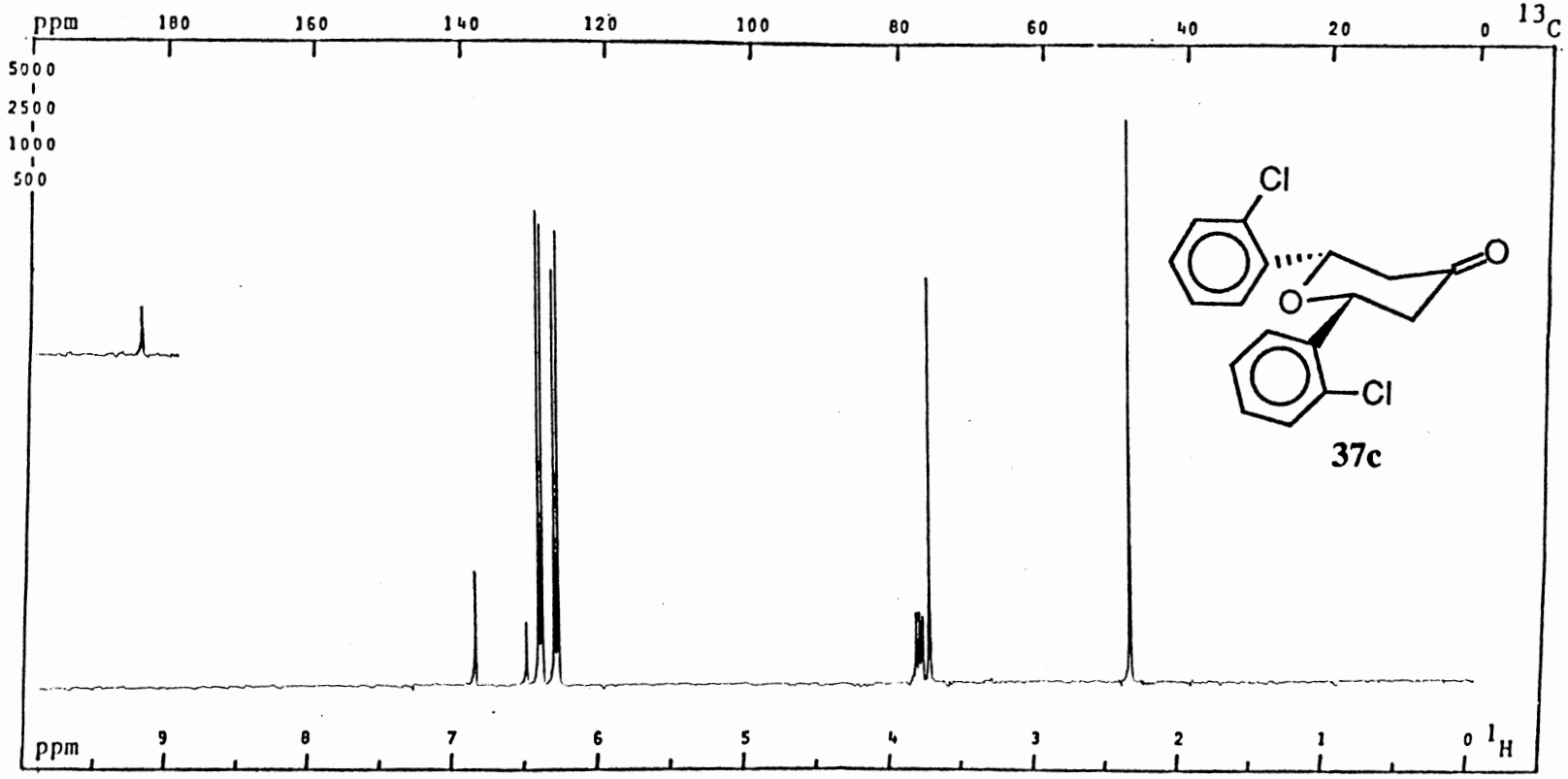
^{1}H NMR Spectrum of **37c**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 4 .

Size: 12 K; PW/RF: 5.0 μs/dB; TO: 0 Hz; FB: -- Hz; Lock: ^{2}H ; D1,D5: 0 s. s.

DC: Y, N ; Gated Off:A or D ; DO: 424.7 Hz; RF(Power): 10 W/dB; NBW: 0 Hz; LB: 1.000 Hz.

Plate XXVI



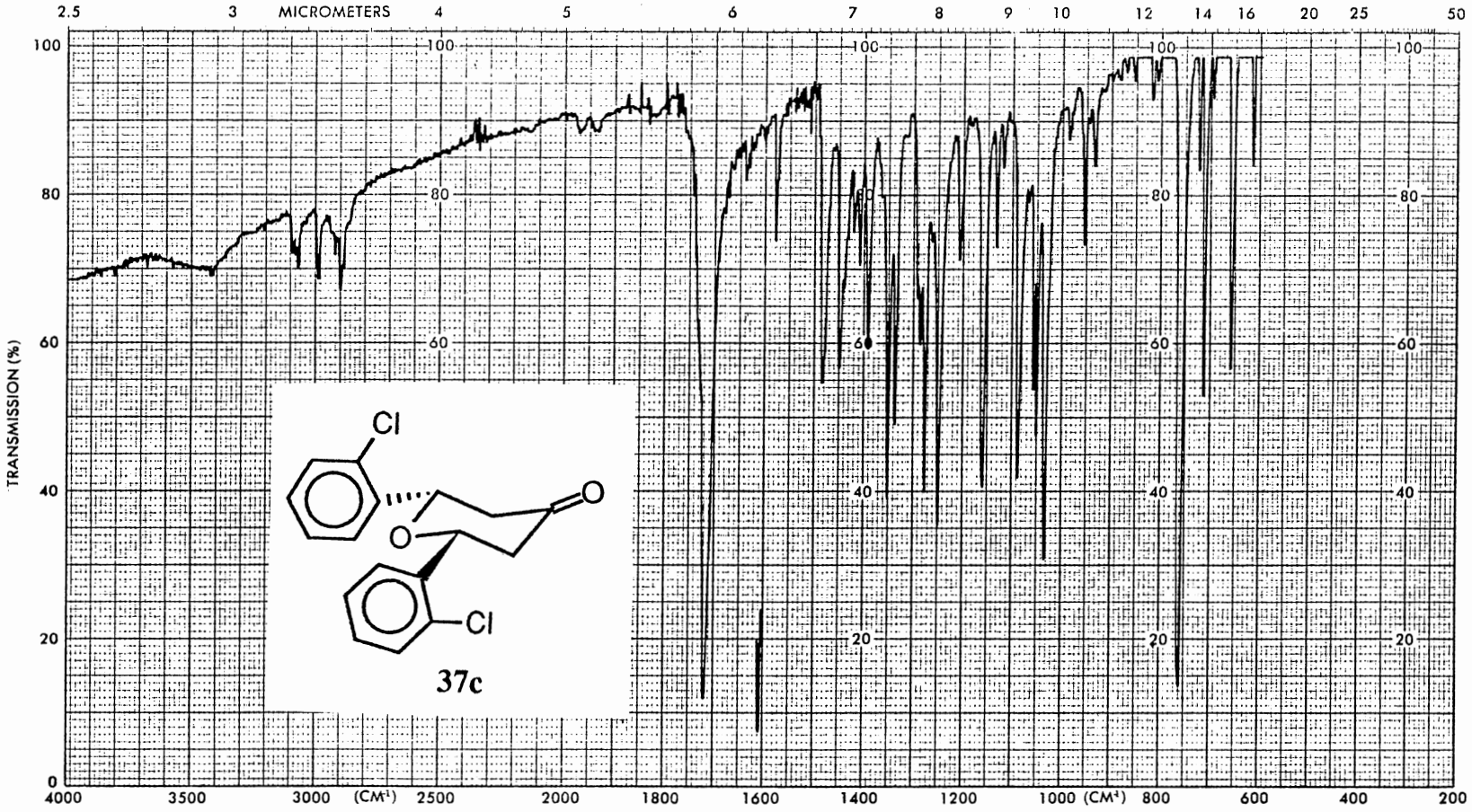
^{13}C NMR Spectrum of **37c**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC:15085.9 Hz; T: RT °C; NT: 600 .

Size: 16 K; PW/RF: 14.0 µs/dB; TO: 1500 Hz; FB: -- Hz; Lock: ^{2}H ; D1,D5: 1.000 s.

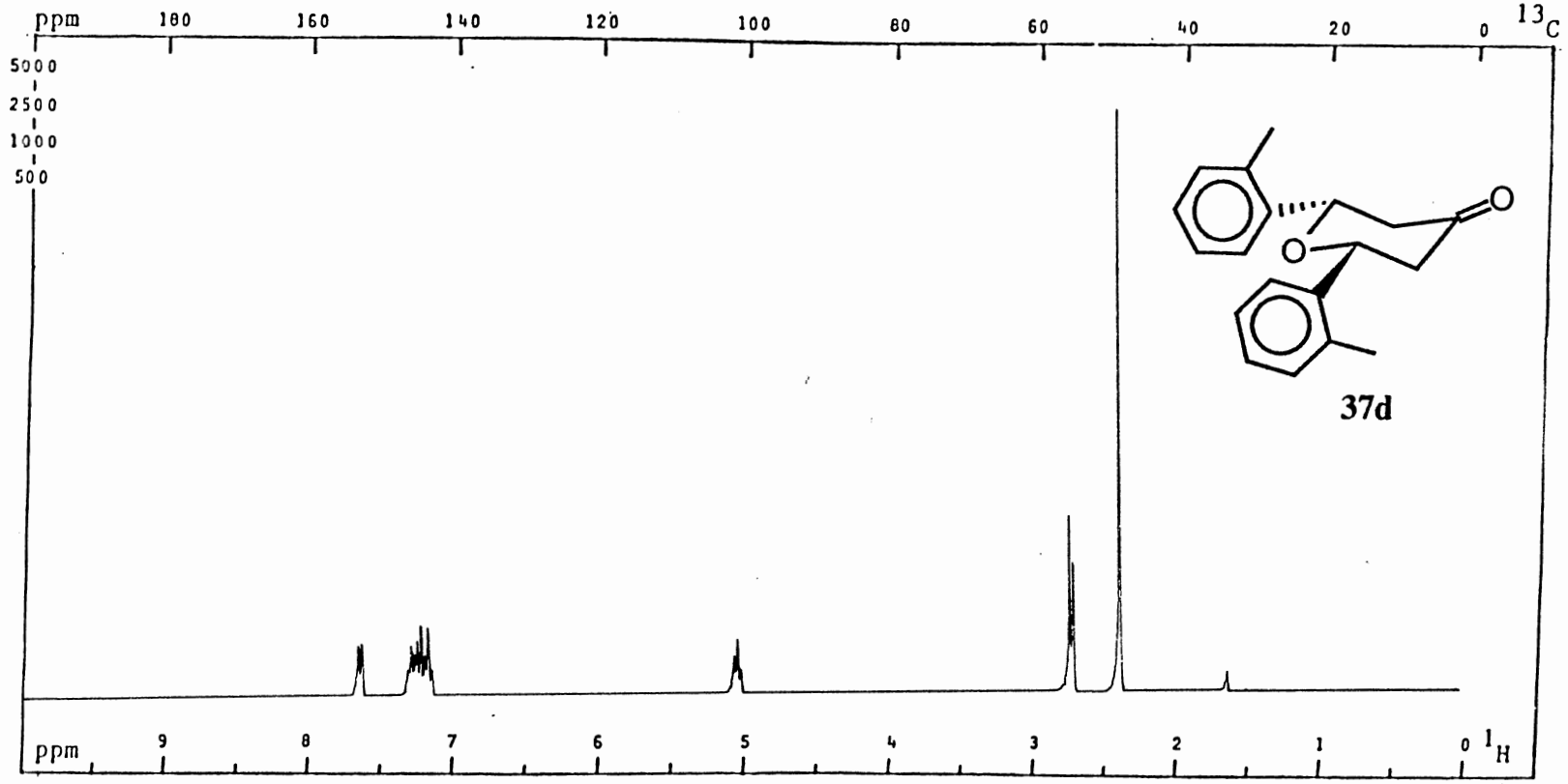
DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 3.000 Hz.

Plate XXVII



IR Spectrum of **37c**

Plate XXVIII



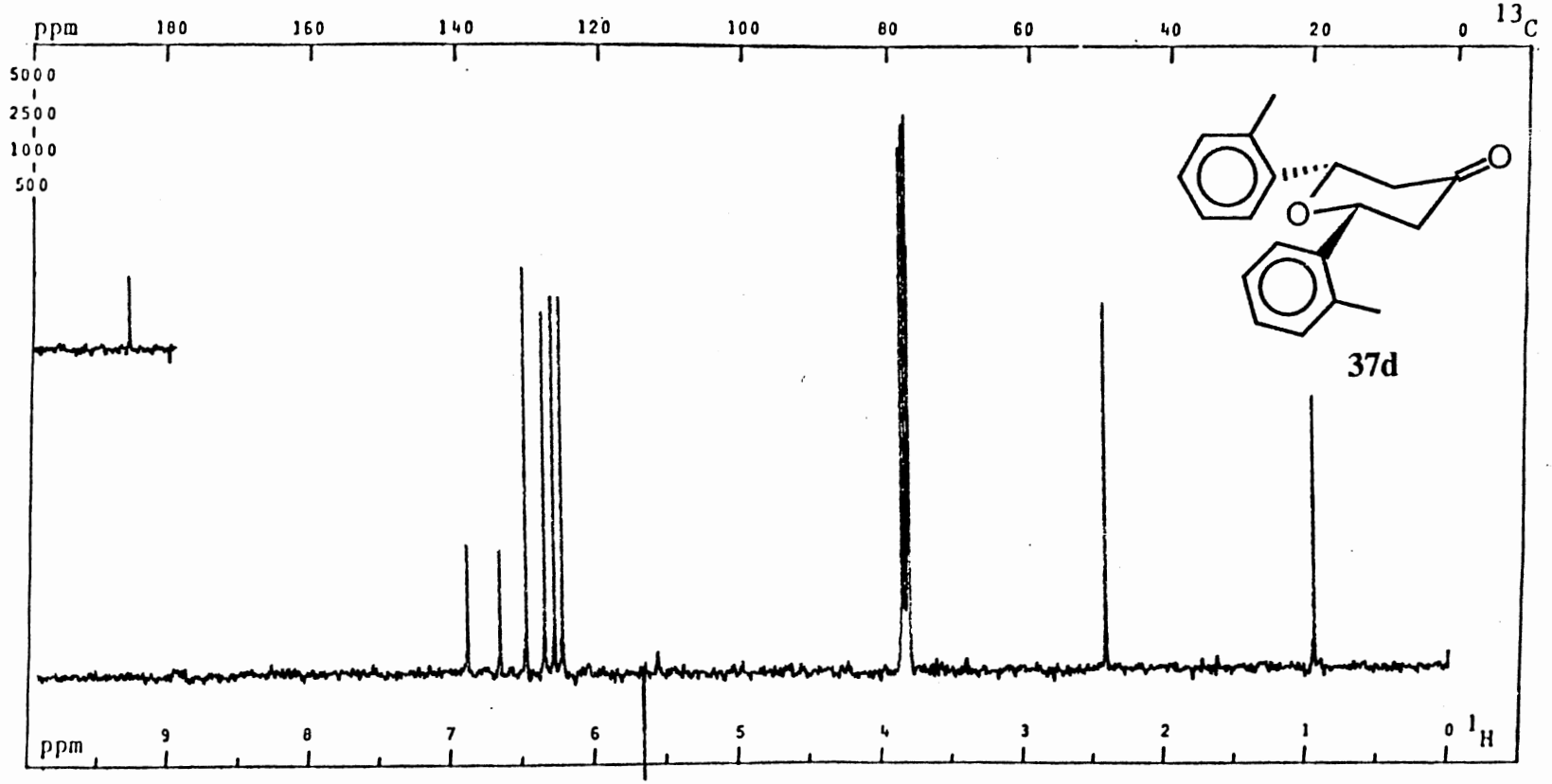
^{1}H NMR Spectrum of **37d**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 4 .

Size: 32 K; PW/RF: 5.0 μs/dB; TO: 0 Hz; FB: -- Hz; Lock: ^{2}H ; D1,D5: 0 s. s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 0 Hz; LB: 0 Hz. Hz.

Plate XXIX



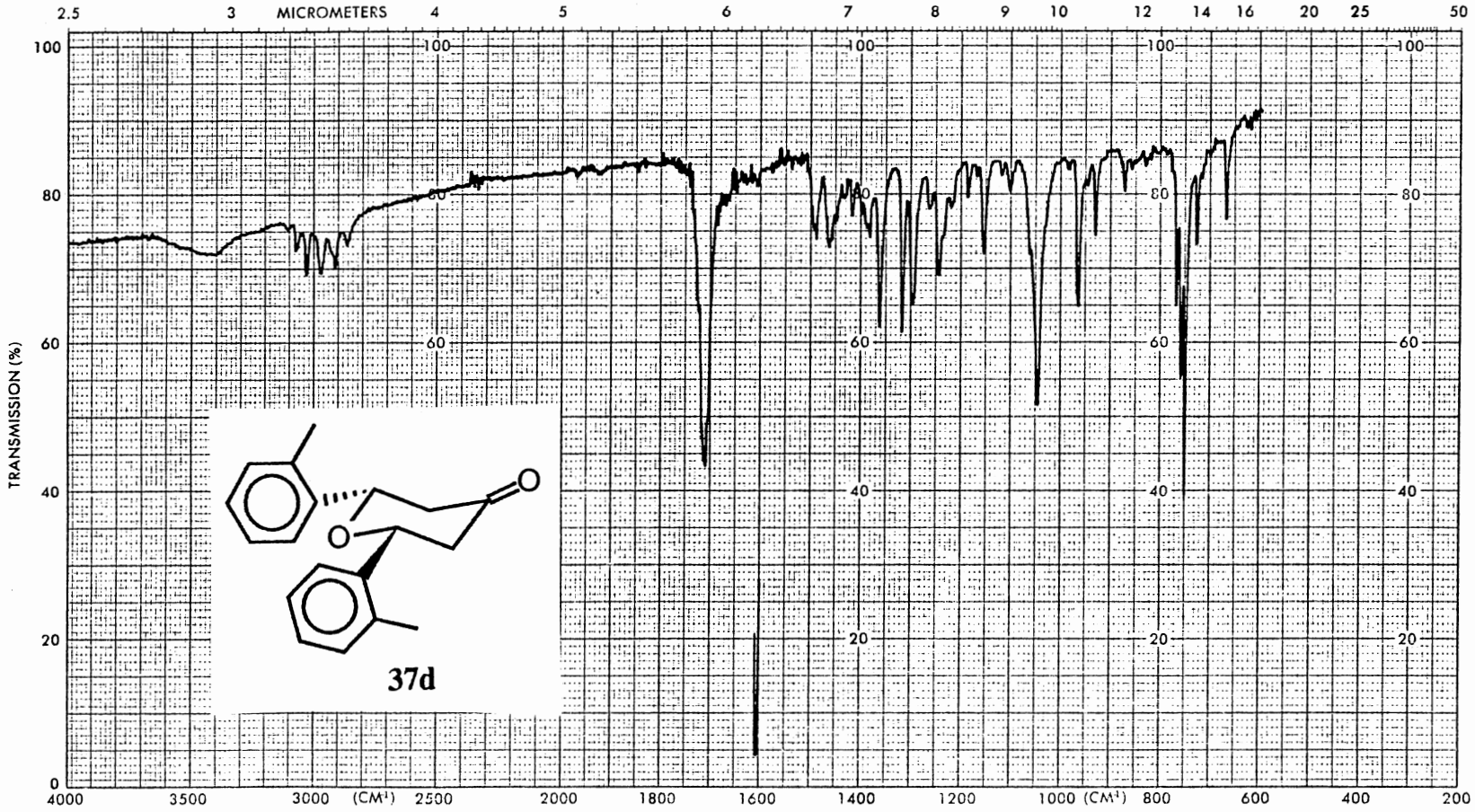
^{13}C NMR Spectrum of **37d**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 240

Size: 20 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: -- Hz; Lock: ^{2}H ; D1,D5: 5.000 s.

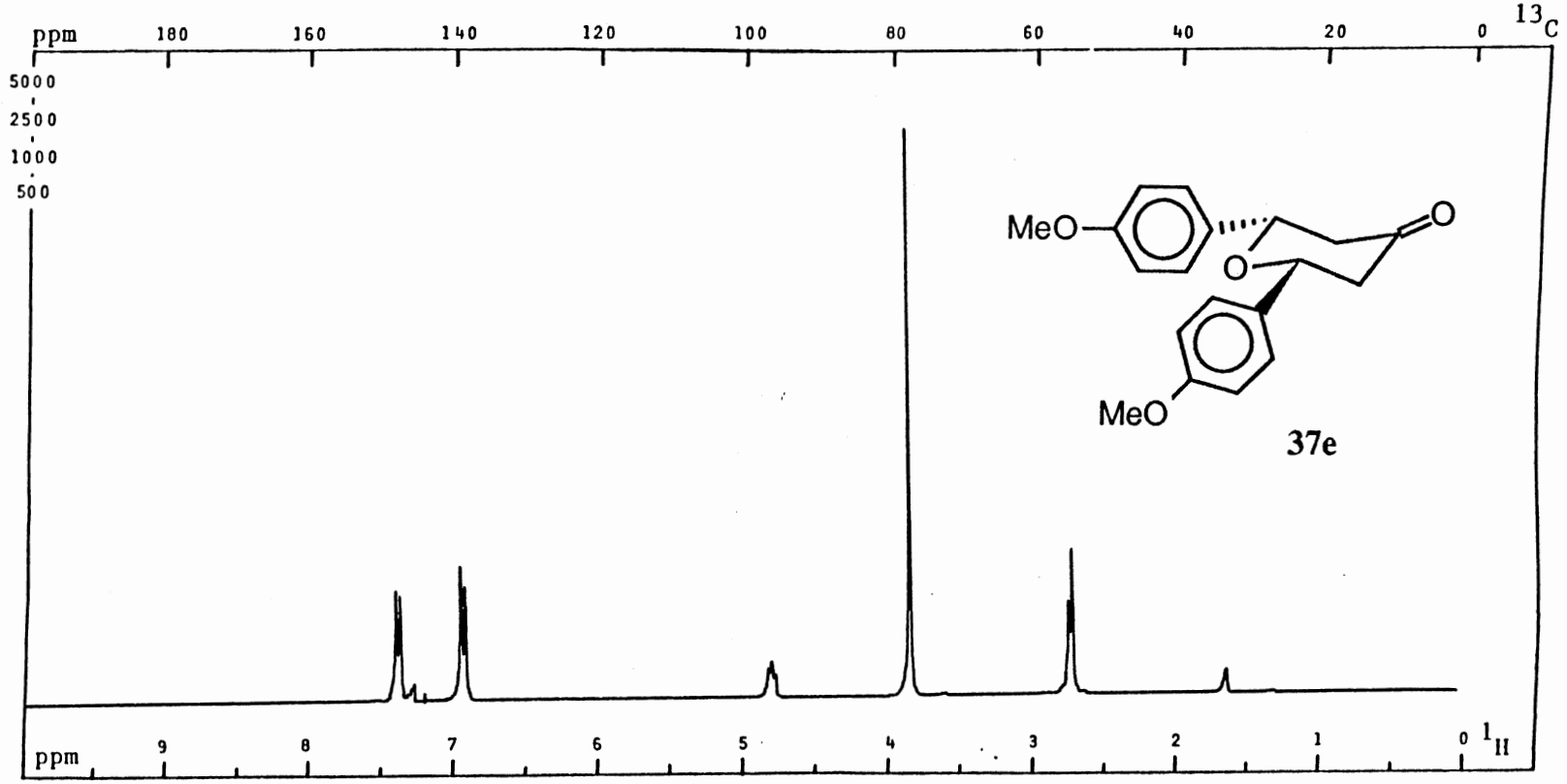
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 1.000 Hz.

Plate XXX



IR Spectrum of **37d**

Plate XXXI



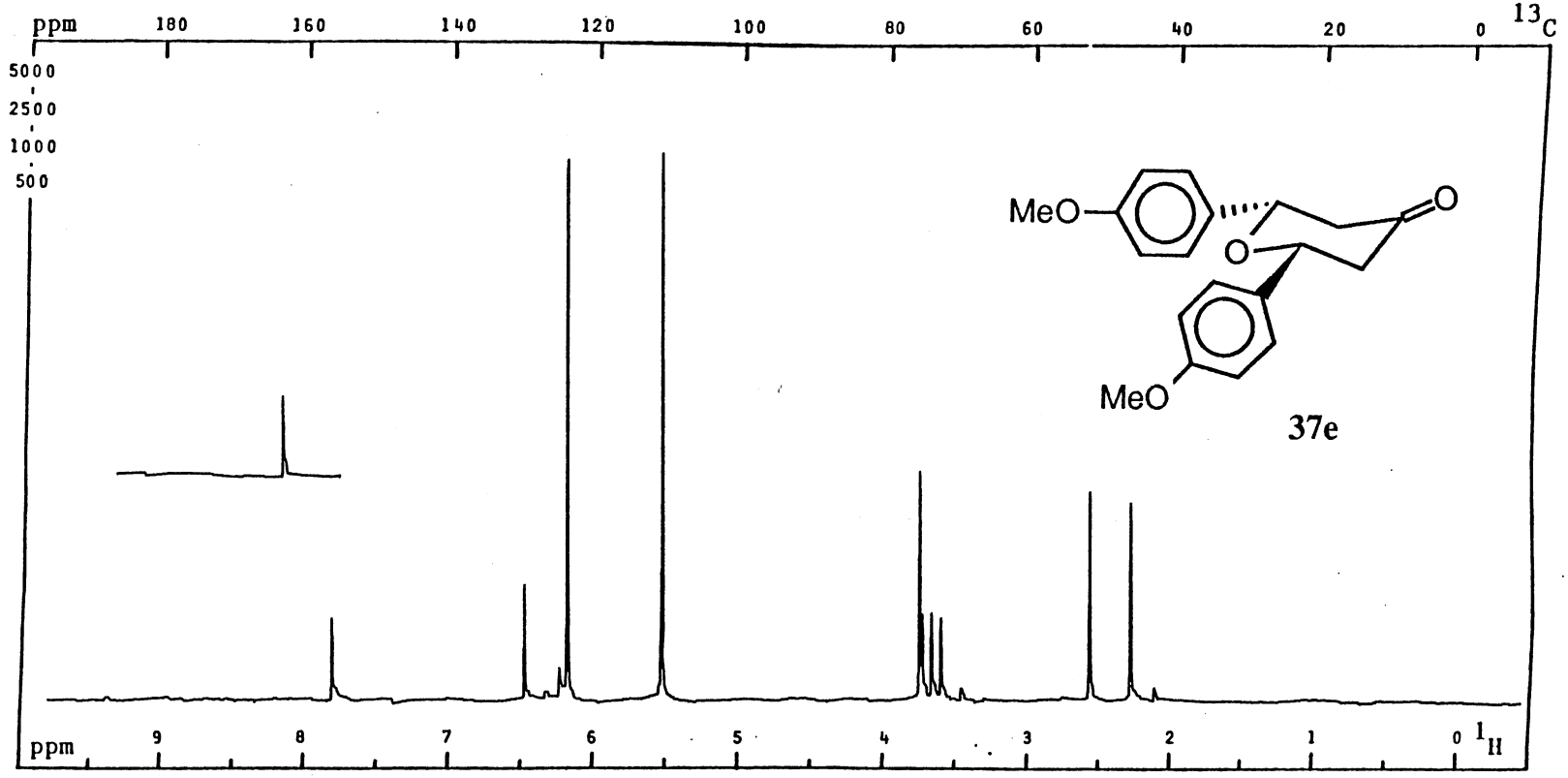
^{1}H NMR Spectrum of **37e**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2601.0 Hz; T: RT °C; NT: 8 .

Size: 8 K; PW/RF: 6.0 µs/dB; TO: 0 Hz; FB: -- Hz; Lock: ^{2}H ; D1,D5: 0 s. s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 15 W/dB; NBW: 200 Hz; LB: 0 Hz.

Plate XXXII



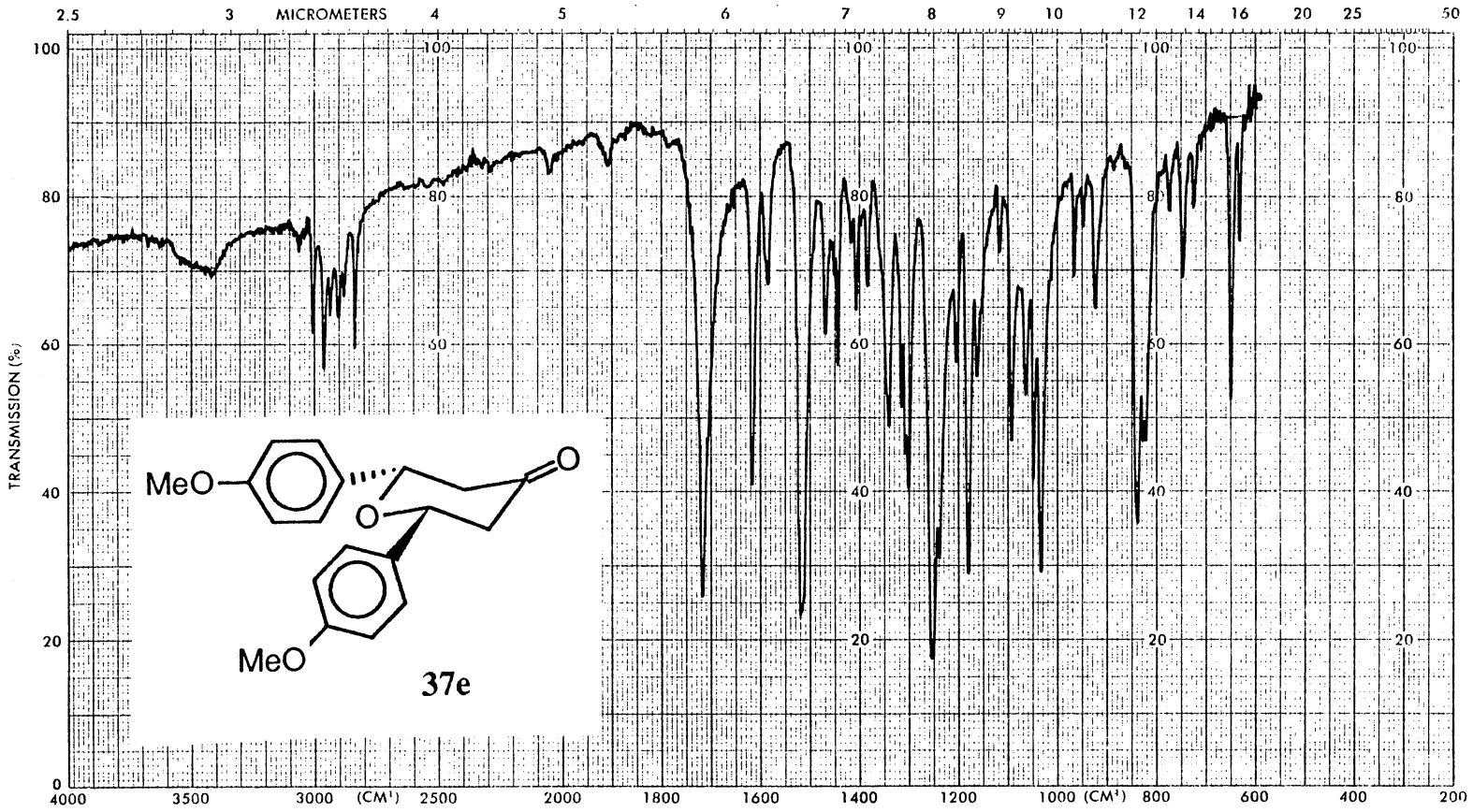
^{13}C NMR Spectrum of **37e**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 25.2000 MHz; WC: 252.00 Hz; T: RT °C; NT: 16384 .

Size: 5 K; PW/RF: 15 μs/dB; TO: 0 Hz; FB: -- Hz; Lock: ^2H ; D1,D5: 4 s. s.

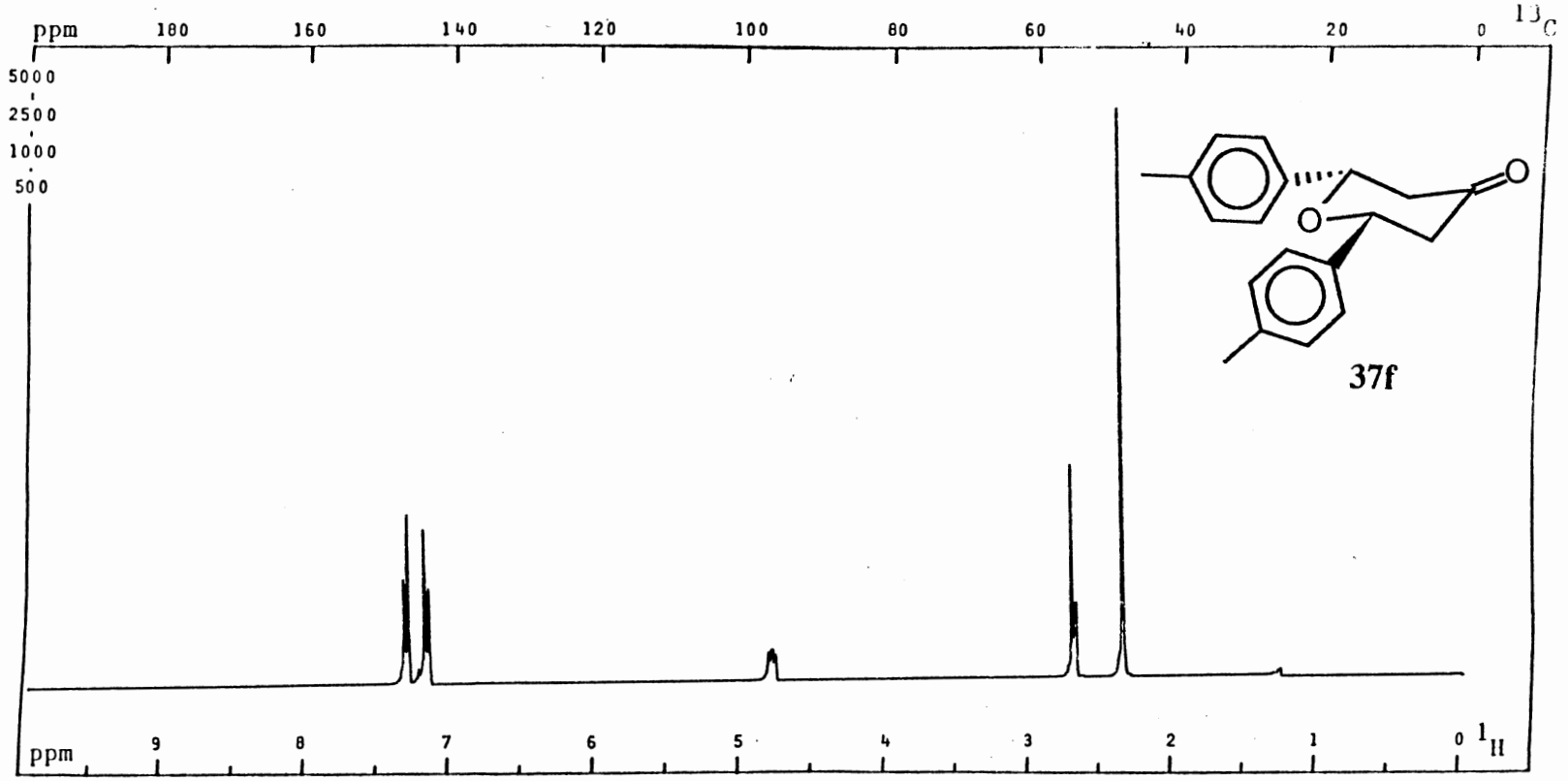
DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 50 W/dB; NBW: 0 Hz; LB: 0 Hz.

Plate XXXIII



IR Spectrum of **37e**

Plate XXXIV



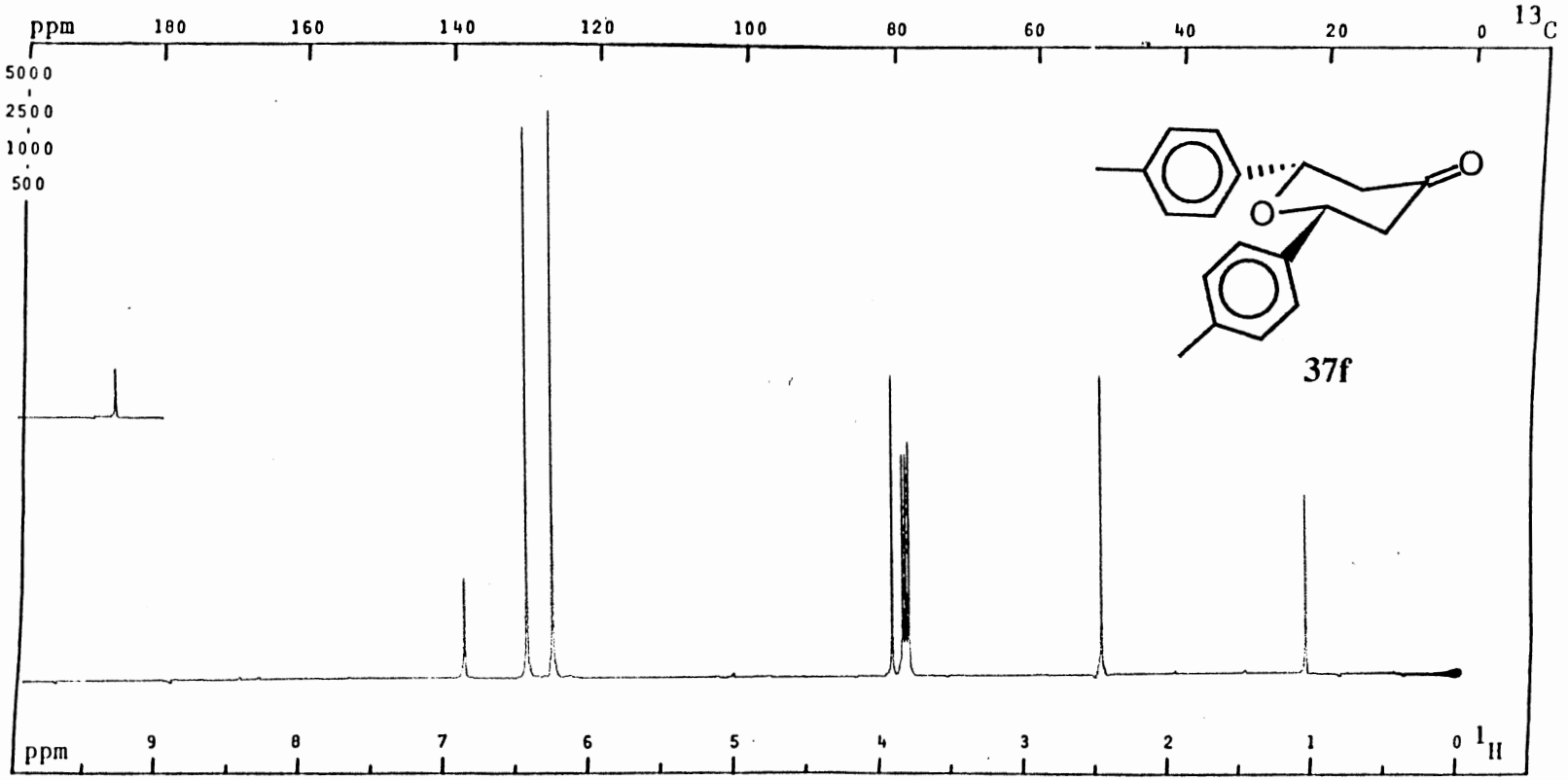
^{1}H NMR Spectrum of **37f** .

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 4 .

Size: 8 K; PW/RF: 6.0 µs/dB; TO: 0 Hz; FB: -- Hz; Lock: ^{2}H ; D1,D5: 0.500 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 13 W/dB; NBW: 200 Hz; LB: 0 Hz. Hz.

Plate XXXV



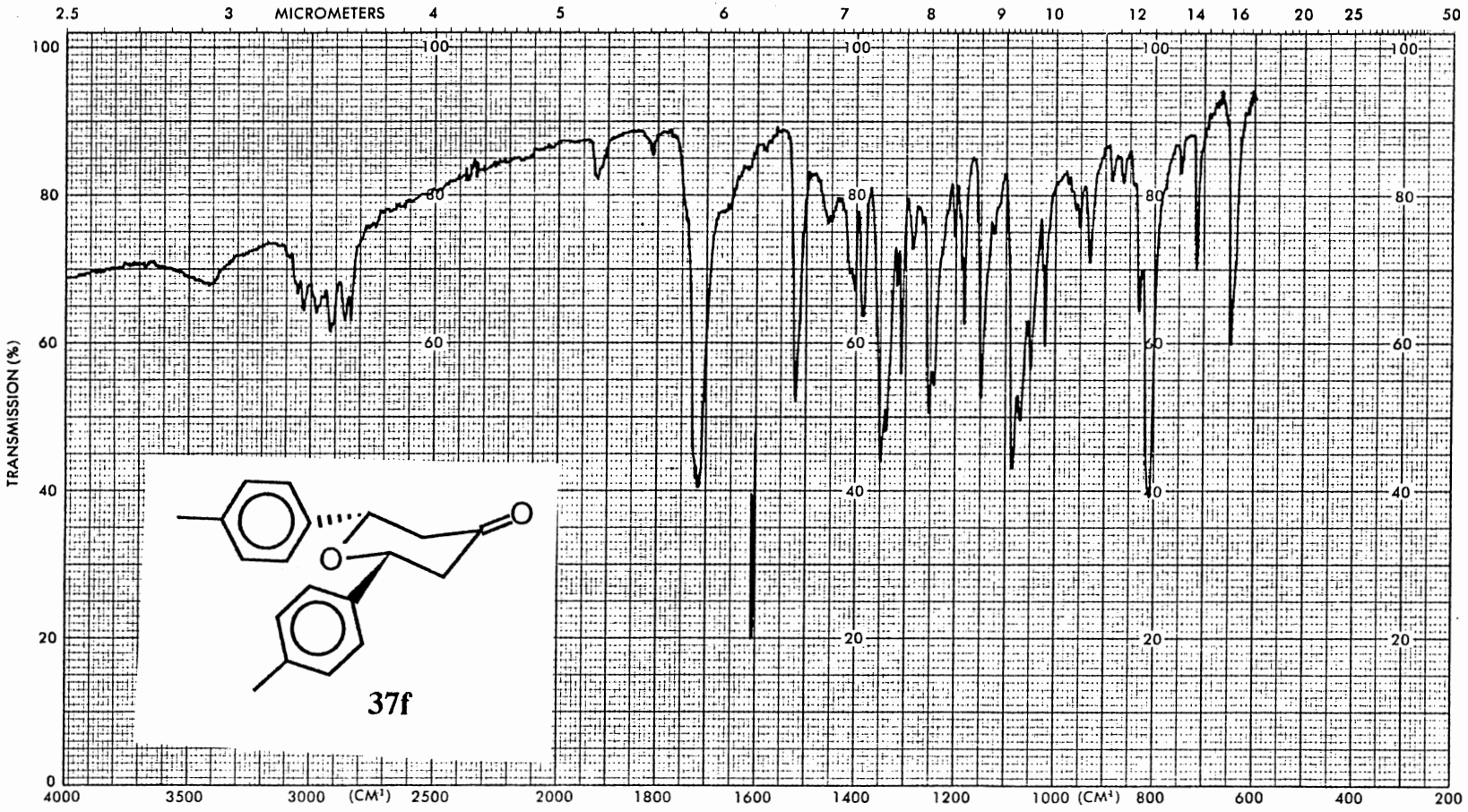
^{13}C NMR Spectrum of **37f**

PFT _X_ CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WG: 15085.9 Hz; T: RT °C; NT: 1120 .

Size: 2 K; PW/RF: 14.0 µs/dB; TO: 0 Hz; FB: -- Hz; Lock: ^2H ; D1,D5: 4.000 s.

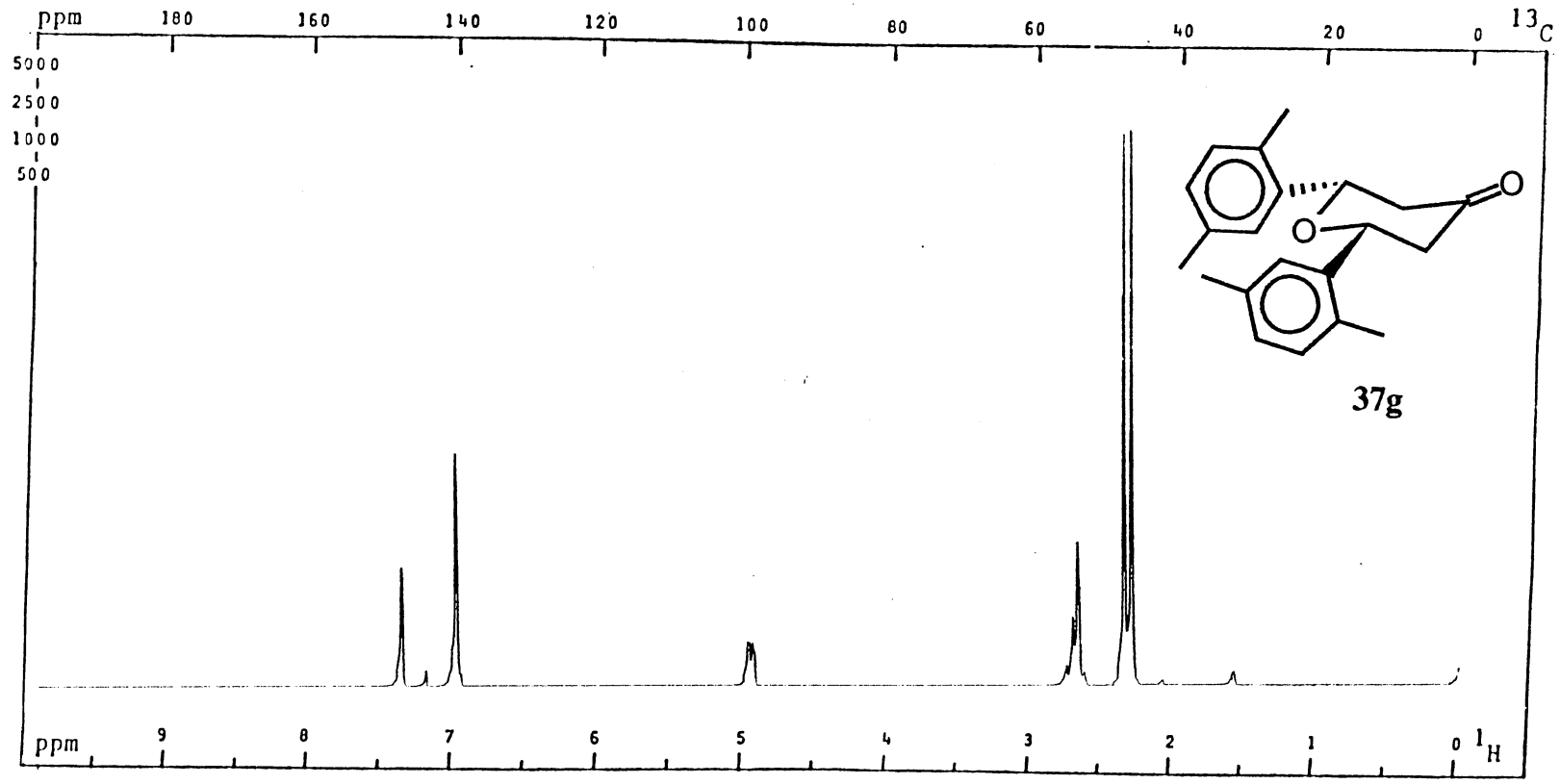
DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 4.000 Hz.

Plate XXXVI



IR Spectrum of **37f**

Plate XXXVII



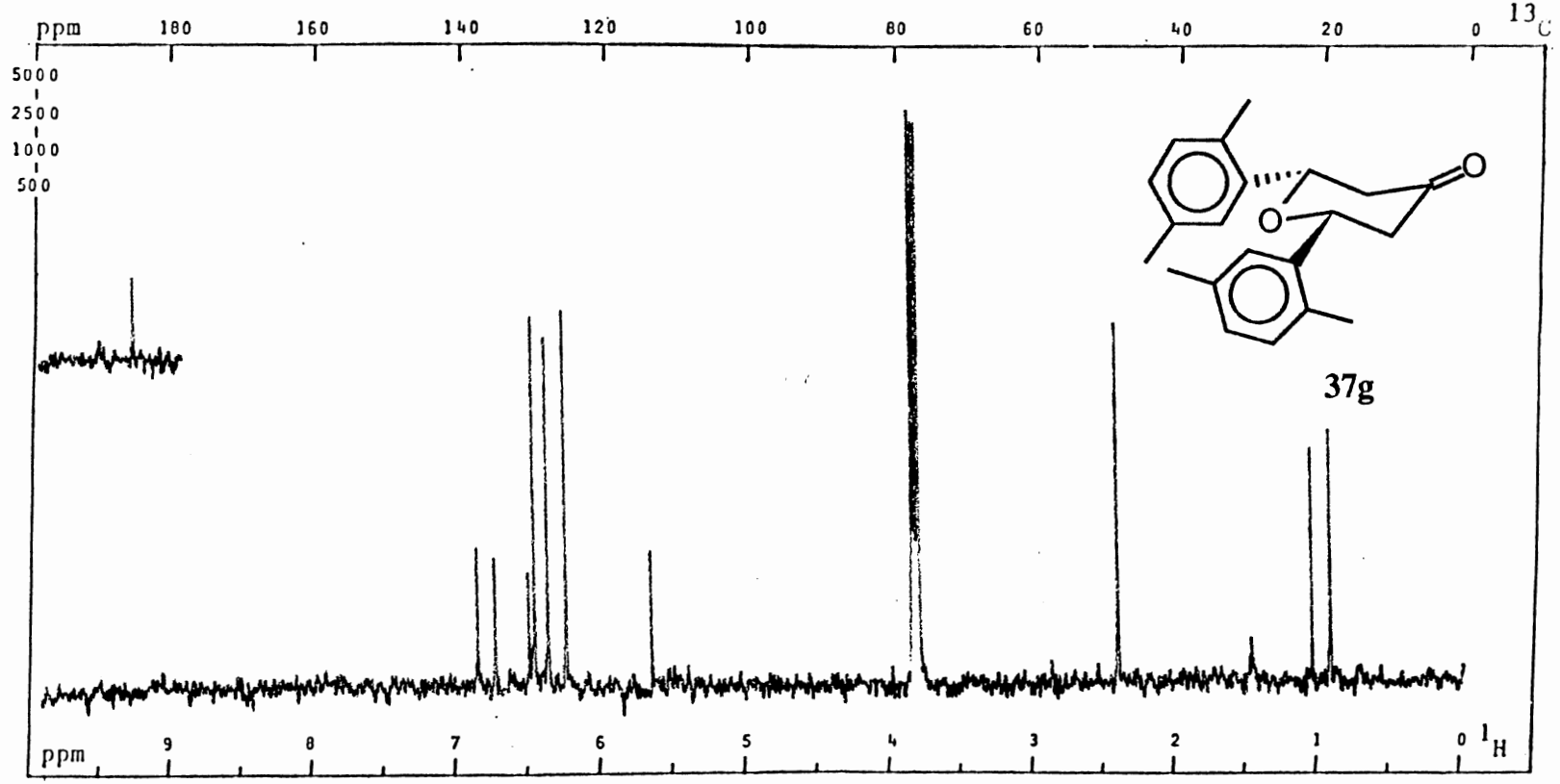
^{1}H NMR Spectrum of **37g**.

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 12 .

Size: 12 K; PW/RF: 5.0 μs/dB; TO: 0 Hz; FB: -- Hz; Lock: ^{2}H ; D1,D5: 0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: 0 Hz; LB: 0 Hz. Hz.

Plate XXXVIII



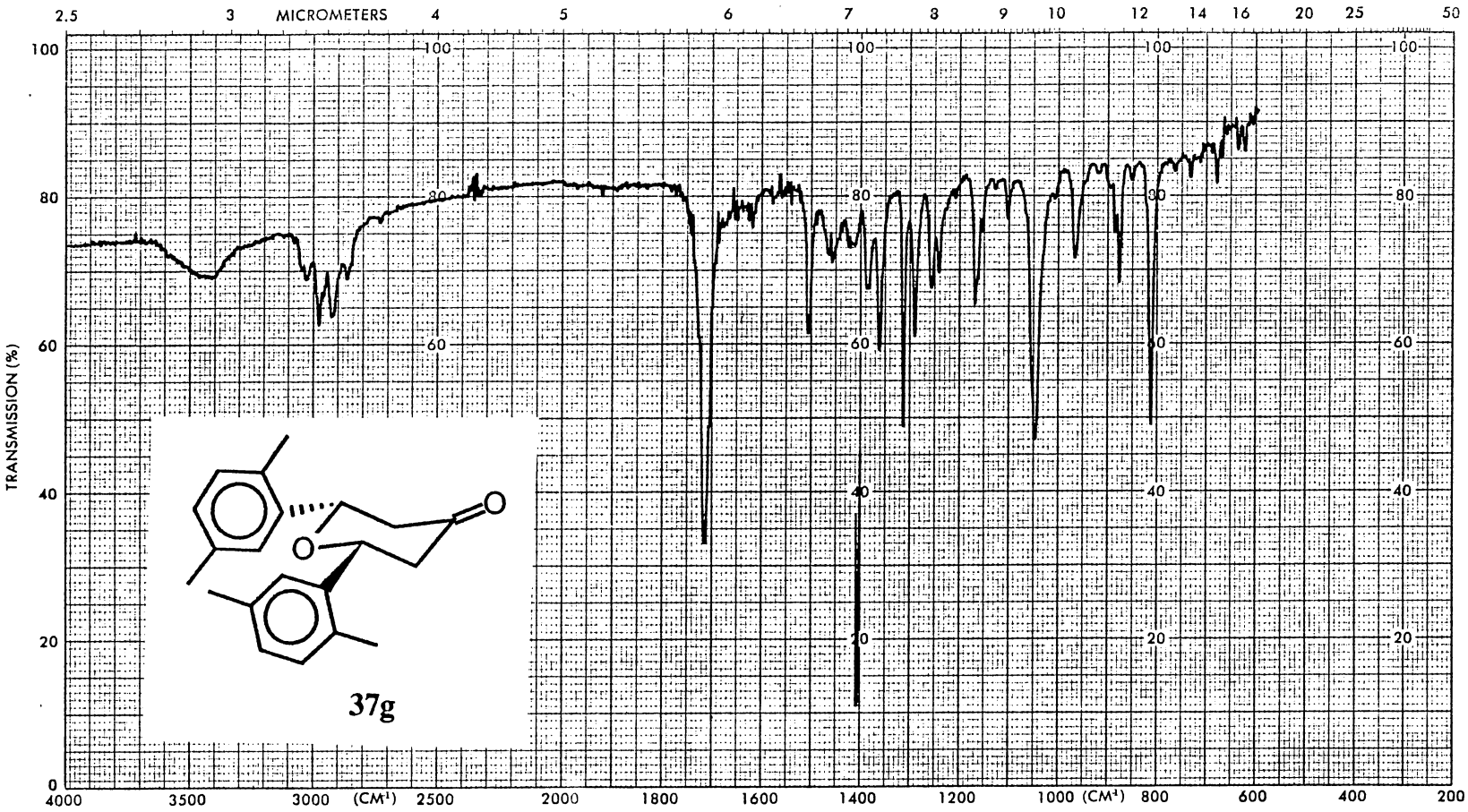
^{13}C NMR Spectrum of **37g**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9Hz; T: RT °C; NT: 240

Size: 20 K; PW/RF: 12.0 μs/dB; TO: 1000 Hz; FB: -- Hz; Lock: ^{2}H ; D1,D5: 5.000 s.

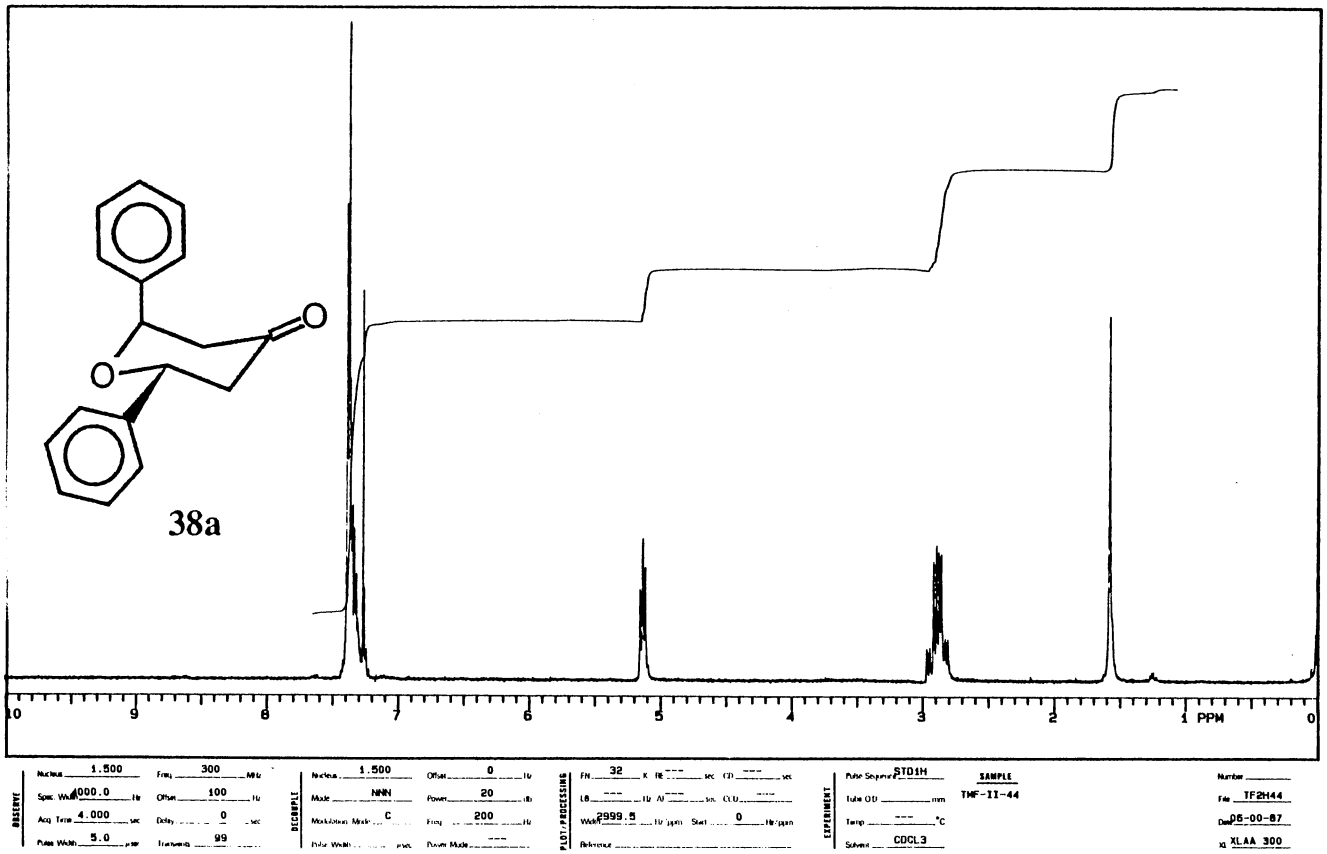
DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 1.000 Hz.

Plate XXXIX



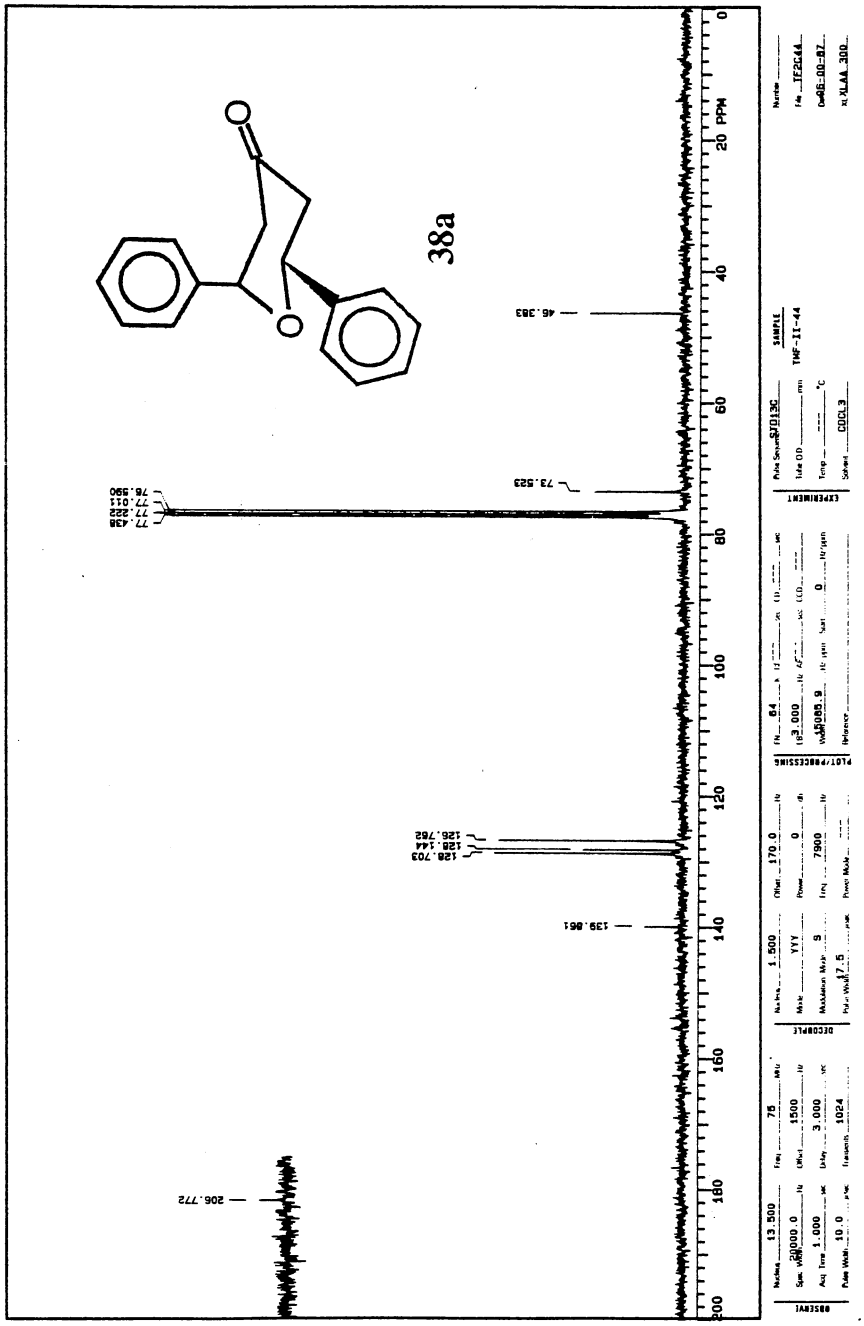
IR Spectrum of **37g**

Plate XL



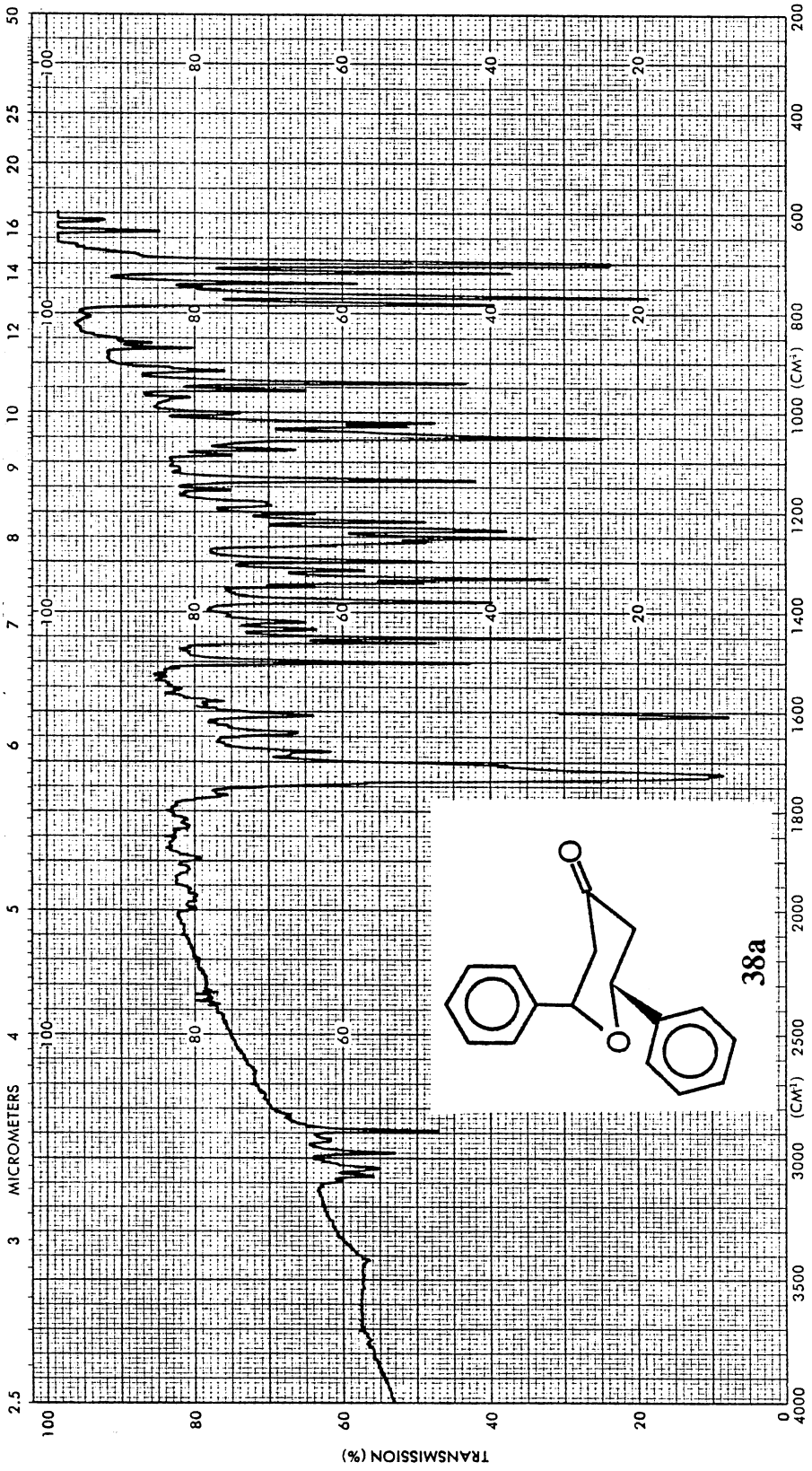
^{1}H NMR Spectrum of **38a**

Plate XLI



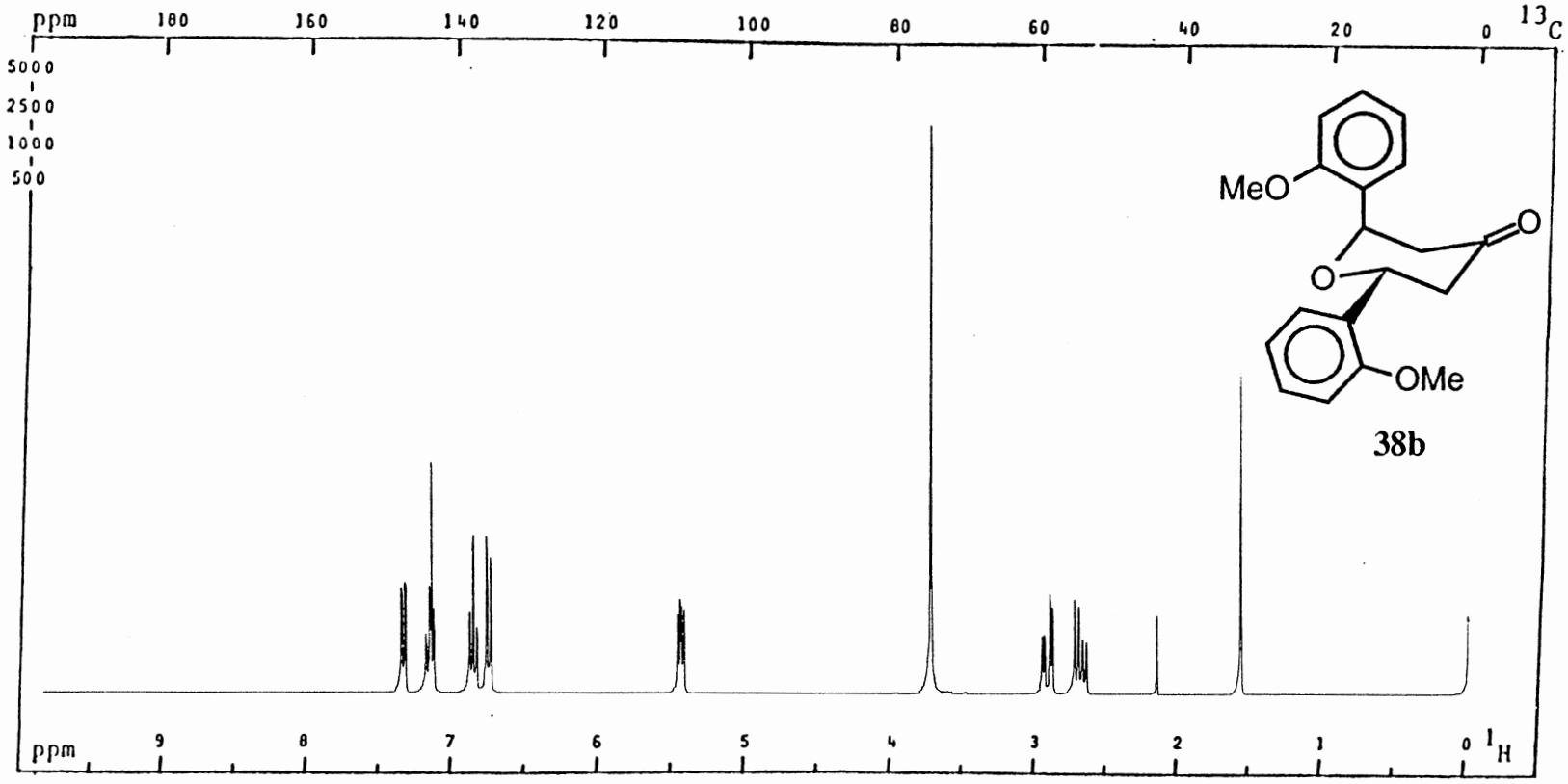
^{13}C NMR Spectrum of 38a

Plate XLII



IR Spectrum of **38a**

Plate XLIII



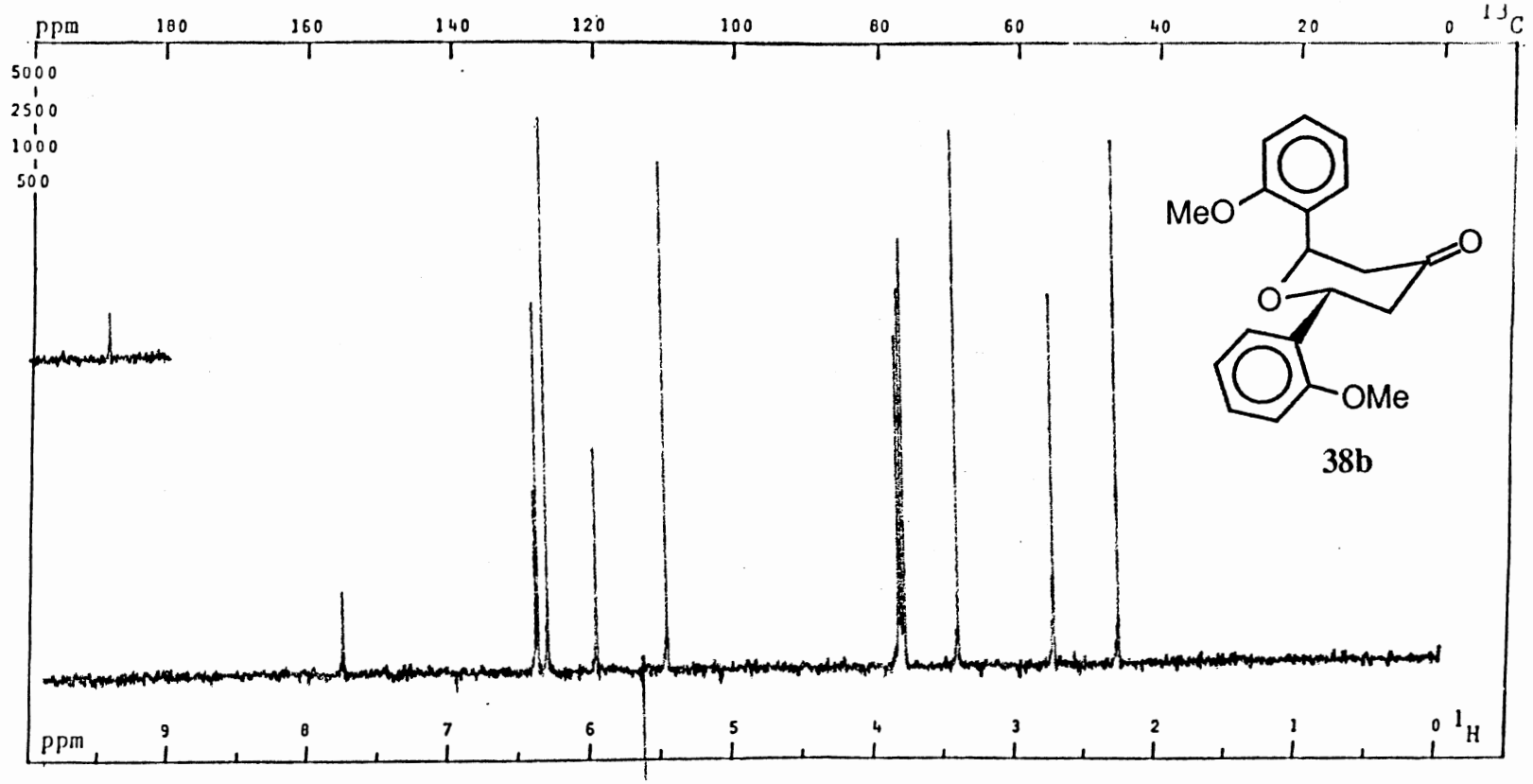
^{1}H NMR Spectrum of **38b**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.94 MHz; WC: 2999.4 Hz; T: RT °C; NT: 40

Size: 16 K; PW/RF: 5.0 μs/dB; TO: 1000 Hz; FB: -- Hz; Lock: ^{2}H ; D1,D5: 0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 0 Hz; LB: 0 Hz.

Plate XLIV



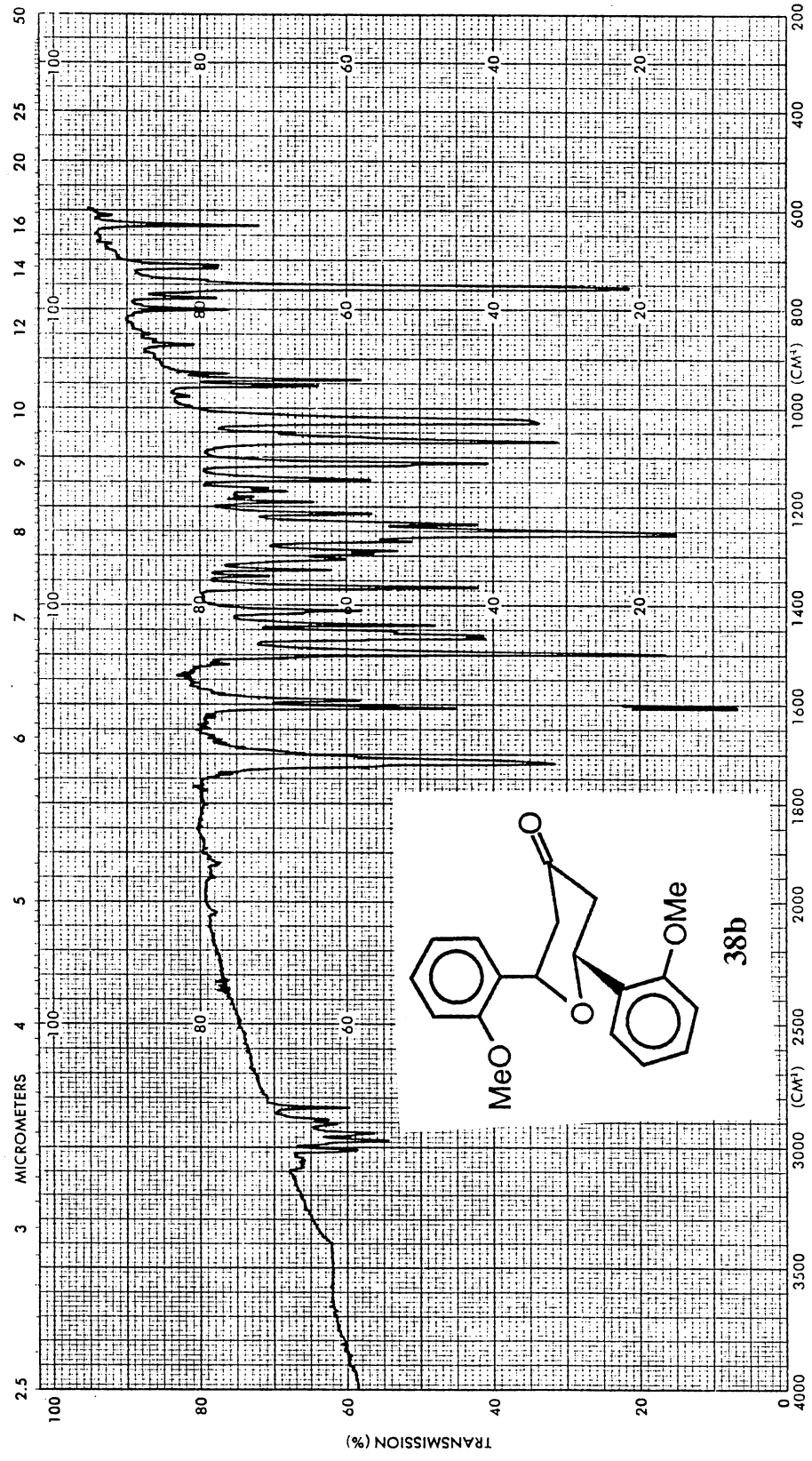
^{13}C NMR Spectrum of **38b**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 440

Size: 16 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: -- Hz; Lock: ^2H ; D1,D5: 4.000 s.

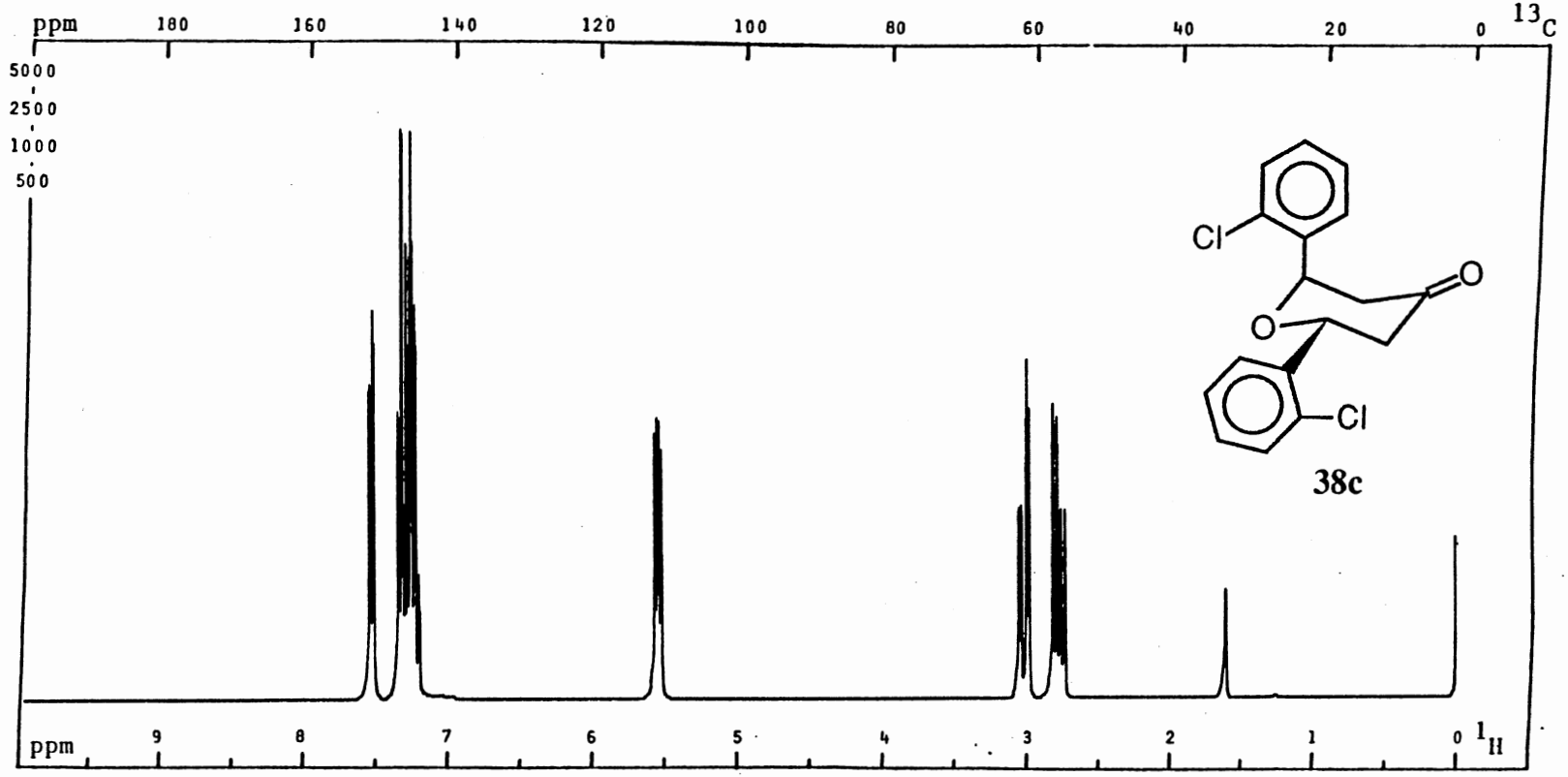
DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 0 Hz.

Plate XLV



IR Spectrum of **38b**

Plate XLVI



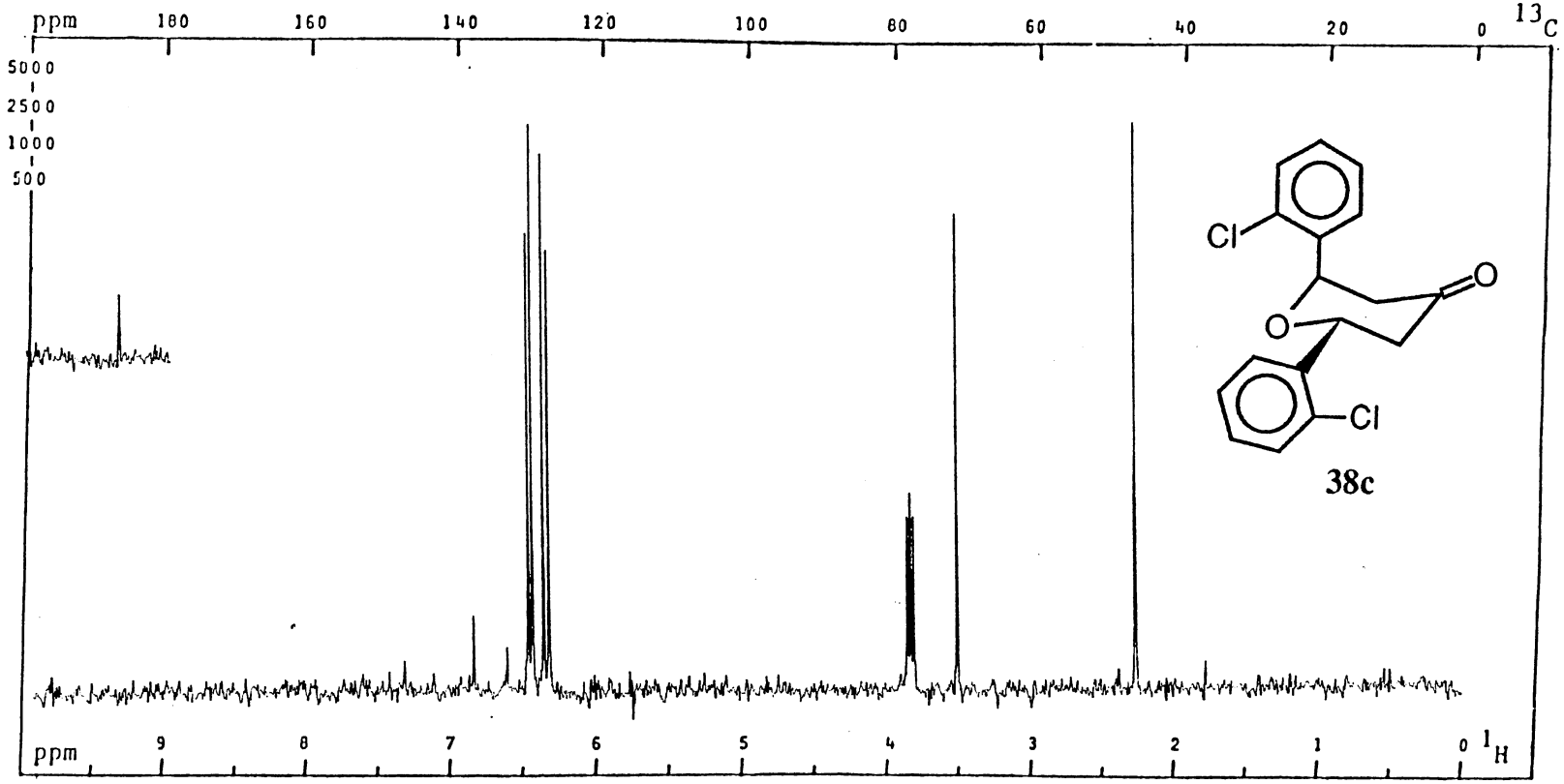
^{1}H NMR Spectrum of **38c**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 24 .

Size: 20 K; PW/RF: 5.0 μs/dB; TO: 0 Hz; FB: -- Hz; Lock: ^{2}H ;D1,D5: 0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 12 W/dB; NBW: 200 Hz; LB: 0 Hz.

Plate XLVII



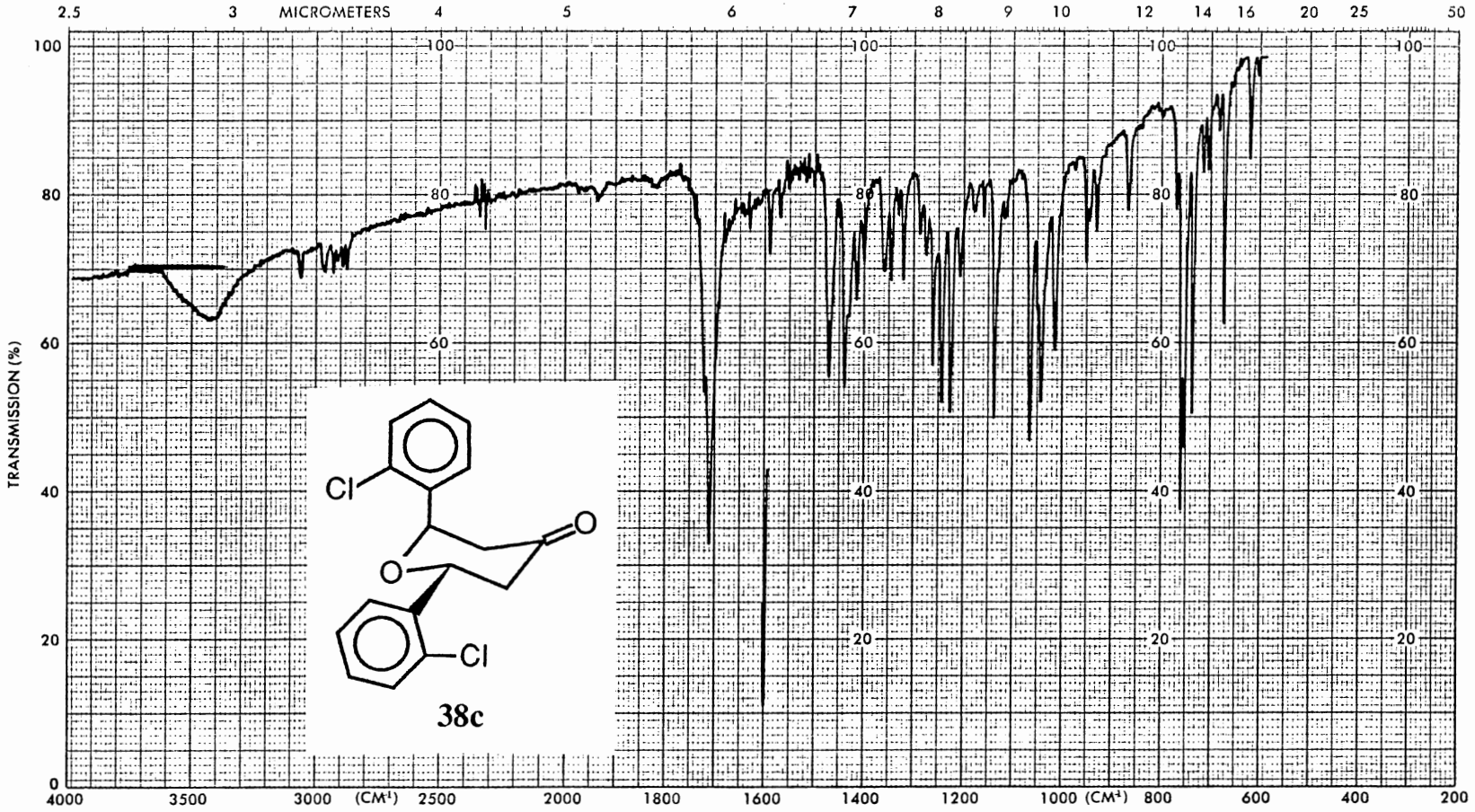
^{13}C NMR Spectrum of **38c**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9Hz; T: RT °C; NT: 240 .

Size: 16 K; PW/RF: 14.0 μs/dB; TO: 1500 Hz; FB: -- Hz; Lock: ^{2}H ;D1,D5: 1.000 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 3.000 Hz.

Plate XLVIII



IR Spectrum of **38c**

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