REGIOCHEMISTRY OF DIALKYL CADMIUM ADDITION TO *cis*- AND *trans*-HEXAHYDROPHTHALIC ANHYDRIDES

By

VASUDHA BALASUBRAMANIAN

Master of Science

Pune University

Pune, India

1982

Submitted to the Faculty of the
Graduate College of the
Oklahoma State University
in partial fulfillment of
the requirements for
the Degree of
MASTER OF SCIENCE
December, 1987

REGIOCHEMISTRY OF DIALKYL CADMIUM ADDITION TO *cis*- AND *trans*-HEXAHYDROPHTHALIC ANHYDRIDES

Thesis Approved:

E. J. Eisenbraun
Thesis Adviser

J. Paul Denton

I. Dwaine Eberly

Norman N. Durham
Dean of the Graduate College

ACKNOWLEDGEMENTS

I wish to express my gratitude to Dr.E.J.Eisenbraun for his guidance,understanding and encouragement throughout this study. Many thanks also go to Dr.J.P.Devlin and Dr.I.D.Eubanks for serving on my graduate committee.

I also wish to thank the members of the faculty and the staff of the Chemistry Department for their assistance during the course of this work. I would also like to thank Mr.Stan Sigle for his help in obtaining NMR spectra.

My deepest gratitude to my parents,for their constant and unstinting love,understanding and support.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF SPECTRA

LIST OF SCHEMES

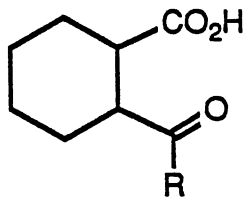
SYMBOLS AND ABBREVIATIONS

anal.	analysis	q	quartet
bp	boiling point	s	singlet
°C	degree Celsius	TMS	tetramethyl-
δ	scale (NMR), dimensionless		silane
d	doublet	t	triplet
DMF	dimethyl formamide		
g	gram		
GC	gas chromatography		
Hz	Hertz		
h	hour		
ir	infrared		
lit.	literature		
M	molar		
m	multiplet		
mg	milligram		
mL	milliliter		
mp	melting point		
min	minute		
mol	mole		
NMR	nuclear magnetic resonance		

CHAPTER I

INTRODUCTION AND HISTORICAL

The main thrust of this thesis is on the synthesis of gamma-oxocyclohexanecarboxylic acids of the following general formula:



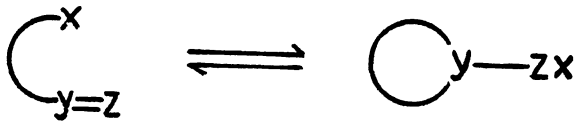
R = CH_3
R = t-Bu

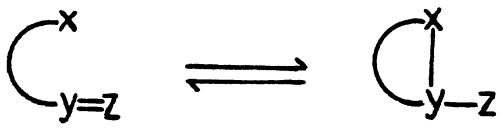
The purpose in these syntheses,as will be presented in more detail,is to obtain a series of structurally related gamma-oxocyclohexanecarboxylic acids for use in the study of intramolecular interaction of functional groups which is generally known as tautomerism.

The word tautomerism was proposed by Laar[1] in 1886 to describe the mobile equilibrium between two compounds having weakly bonded hydrogen atoms. But it was only towards the end of the century that a related reversible isomeric change,namely ring-chain tautomerism in which one of the tautomeric forms is cyclic,was recognized. Since then,studies in this area have become a field of great interest to chemists.

A compound must fulfill certain requirements in order to exhibit ring-chain tautomerism:[2]

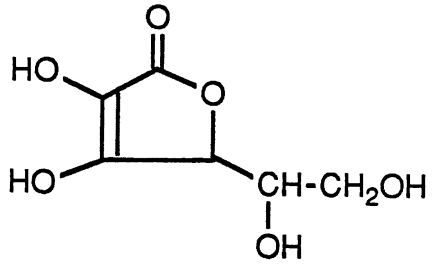
1) It must possess at least two functional groups: one containing a multiple bond involving a heteroatom and the other capable of effecting an additive reaction at the multiple bond.



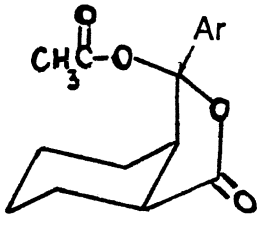


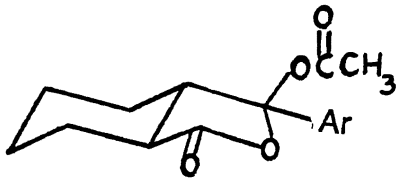
2) Stability And Proximity Effects:

a) The stability of the ring tautomers is strongly dependent on the number of atoms in the ring e.g.four-membered ring lactones are not favored because of the obvious ring strain. Five- or six- membered rings are formed preferentially and usually a five- membered ring is formed in preference to a six- membered ring,as shown below for ascorbic acid.



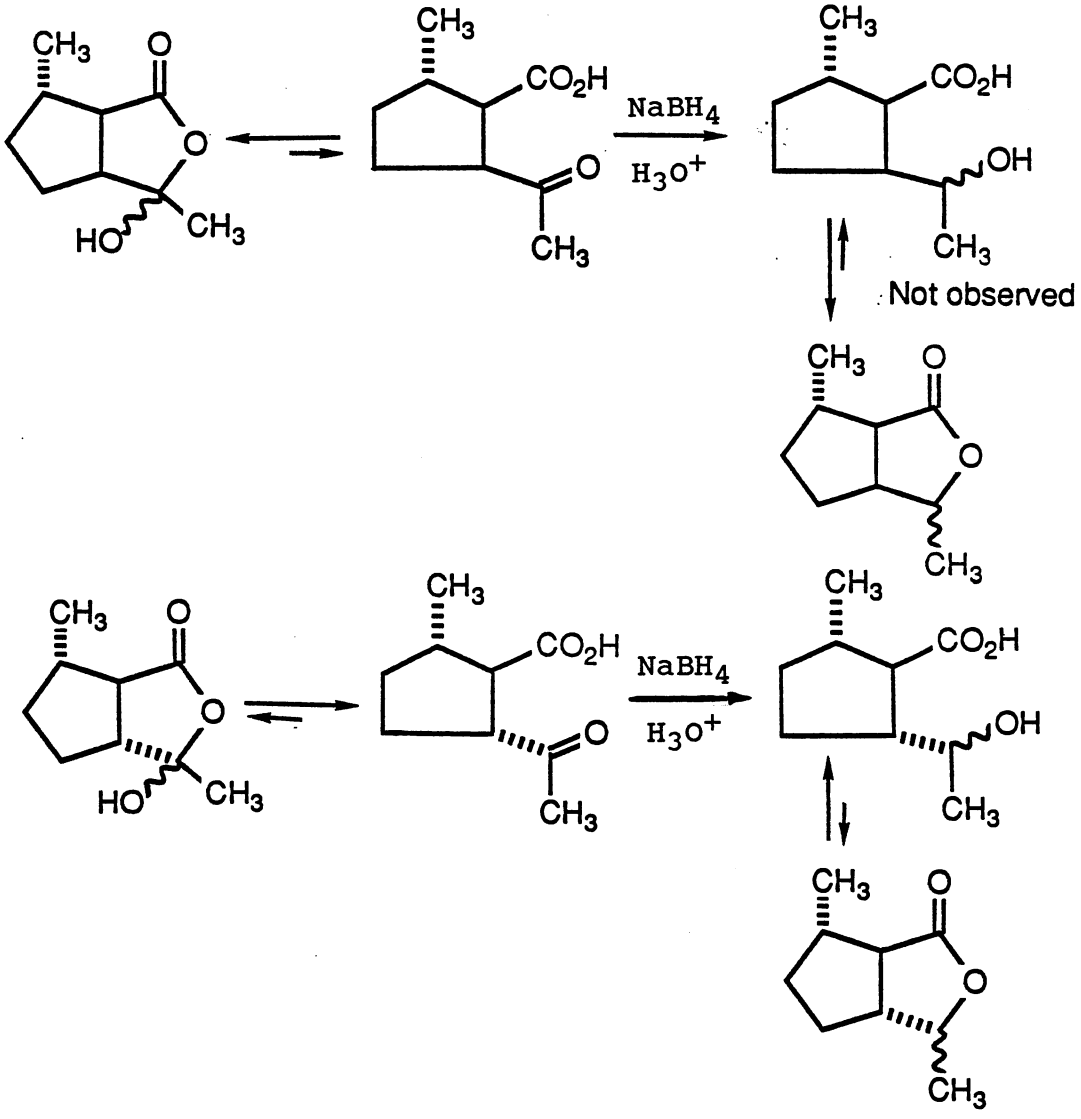
b) The tendency of the chain tautomer to cyclize will depend on the spatial proximity of groups X and YZ.e.g.both <u>cis</u>- and <u>trans</u>-p-bromobenzoylcyclohexane carboxylic acids form cyclic pseudo acetates-the axial-equatorial and diequatorial conformers.[3a]





However,in the case of the nepetonic acids shown below,the cis isomer readily forms the cyclic hydroxy lactone,whereas the trans isomer does not. When these keto acids are reduced,the cis isomer appears only as a pair of lactones,with no evidence for the presence of the <u>cis</u>-hydroxy acids.[3b]

In contrast,the <u>trans</u>-hydroxy acid fails to cyclize on heating or treatment with acid.

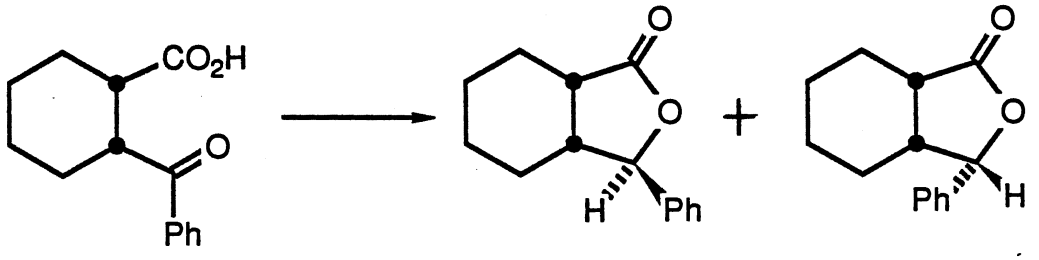


c)The size and flexibility of the ring also have important effects on the proximity of the groups and hence the ease of ring formation.

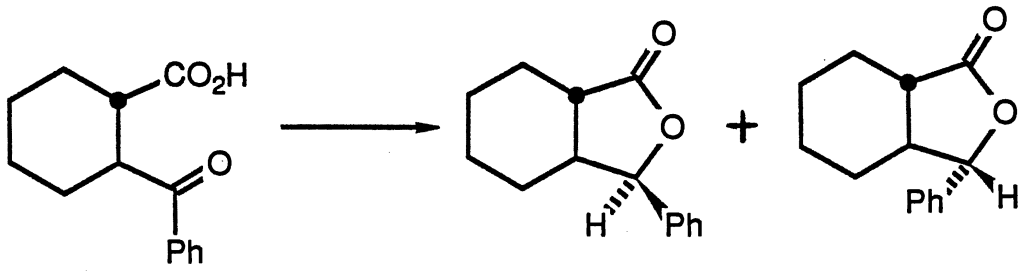
Ring-chain isomerism in amides,keto-, imino-, and cyano-carboxylic acids have been studied. Of particular interest are the ring-chain isomeric interconversions proceeding by intramolecular reversible addition reactions to the carbonyl group - as observed in the gamma- and delta-oxo acids,and as shown above for cis-nepetonic acid.

Thus in summary,the feasibility of ring-chain tautomerism,coupled with the intramolecular hydrogen bonding,influences the reactivity of the gamma-oxoacids.

Earlier studies[4] showed that reduction of cis- and trans-2-benzoylcyclohexanecarboxylic acids **(1a)** and **(1b)** gave a varied product ratio of gamma-hydroxy acids on reduction with hydrogen,in the prescence of platinum oxide, as compared to reduction with lithium triethylborohydride. The products were isolated and analyzed as the lactones **2a,2b,2c and 2d**.

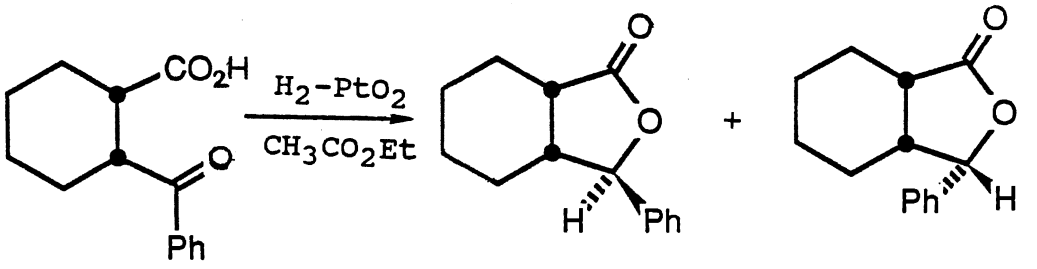


1a 2a 2b

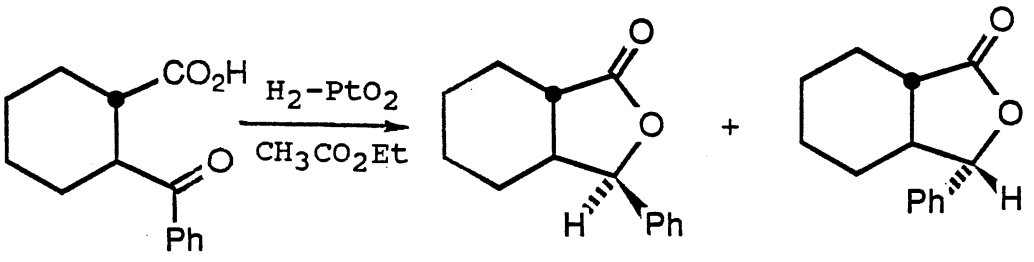


1b 2c 2d

It was observed that hydrogenation of the <u>cis</u> acid **1a**,using platinum oxide in ethyl acetate, gave the stereoisomeric <u>cis</u>-lactones **2a** and **2b** in a ratio of 26:74; whereas the trans isomer gave the stereoisomeric <u>trans</u>-lactones **2c** and **2d** in a ratio of 35:65.[5]

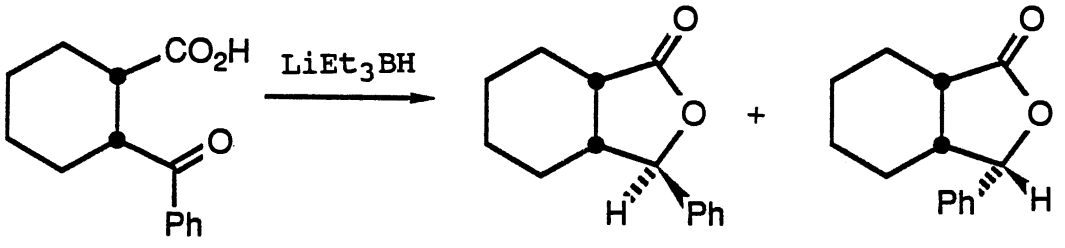


1a **2a** **2b**

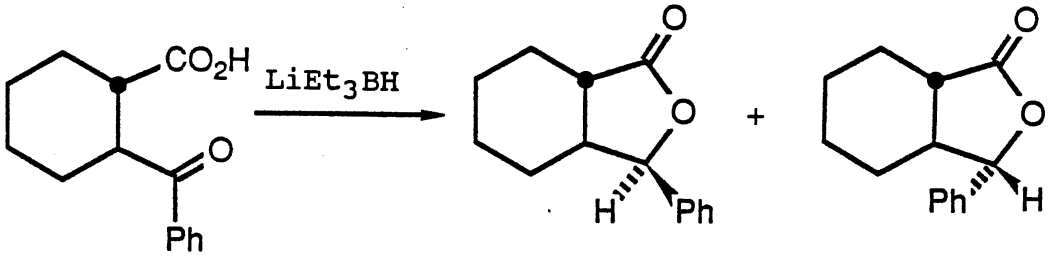


1b **2c** **2d**

However, reduction with lithium triethylborohydride resulted in a reversal of the ratios. The ratio of lactones **2a** and **2b** now became 94:6; and that of **2c** and **2d**, 55:45.[5]



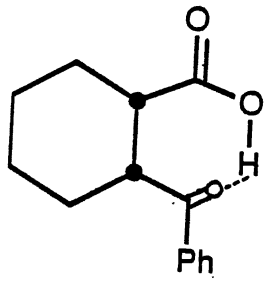
1a **2a** **2b**



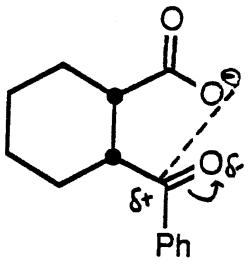
1b **2c** **2d**

The following conformational changes were proposed to account for the reversal of the gamma-lactone ratios:[6]

It was assumed that intramolecular association during the reaction caused the reversal in the ratios. In the case of catalytic hydrogenation using platinum oxide in ethyl acetate the carboxyl group remains protonated. Intramolecular hydrogen bonding between the hydrogen of the carboxyl group and the oxygen of the ketone carbonyl,as shown below,is thought to cause the orientation of the ketone carbonyl group with intramolecular hydrogen bonding controlling the stereochemistry of the catalytic hydrogenation.



However,when lithium triethylborohydride is used as a reducing agent,the intermediate shown below is formed from rapid deprotonation of the carboxyl group. This step is much faster than that of reduction of the ketone carbonyl.



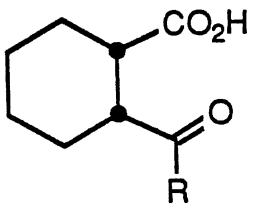
Subsequent intramolecular association between the carboxylate anion and the ketone carbonyl carbon results in blocking the approach of the hydride on one side, whereas there is a clear access on the other.

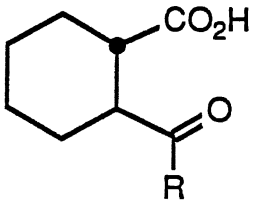
It was assumed that the carboxylate anion is oriented as shown above by attraction to the carbon moiety and repulsed from the oxygen of the carbonyl group and thus the ketone carbonyl is rotated away from the position assumed during hydrogen bonding. This offers a reasonable explanation for change in the ratio of lactone products with change in type of reducing agent.

But this mechanism failed to determine whether the phenyl group exercises any influence during the reaction. The influence could arise from the steric bulk of the phenyl group or from an electronic effect produced by the electron cloud of the phenyl ring.

One way to resolve this question would be to replace the phenyl group by alkyl groups having different steric requirements and to observe the results of the reductions of the gamma-oxoacids to the lactones using catalytic hydrogenation and lithium triethylborohydride.

Hence we sought the synthesis of the cis and trans isomers of the following gamma-oxoacids:





3a, R = CH_3

4a, R = t-Bu

3b, R = CH_3

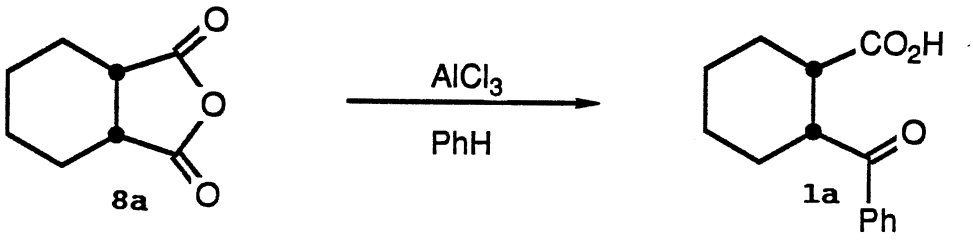
4b, R = t-Bu

Literature Examples Of gamma-Oxoacid Synthesis:

gamma-Oxoacids may be synthesized in a variety of ways. The following synthesis routes are known to provide such acids. However, with one exception,these general reactions do not lead to the target gamma-oxoacids.

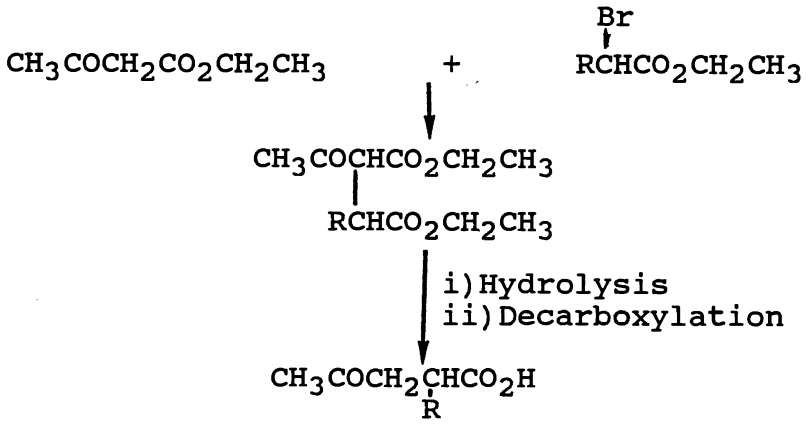
1) Friedel-Crafts Reaction:

This reaction was used successfully in the synthesis of the acid **1a** as shown below. However,it cannot be used if an aliphatic group is substituted for the phenyl group thus it is not suitable for this study.[5]



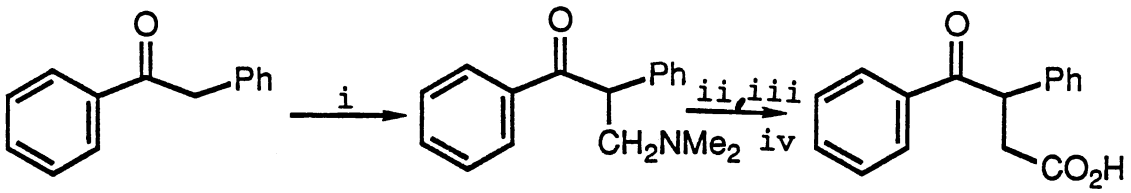
2) Acetoacetic Ester Condensation:

This reaction[7,8] sequence is useful for synthesis of monoalkyl gamma-oxoacids:



3) Mannich Reaction:

The carboxyl function may be introduced via a Mannich reaction with subsequent quarternization of the amine followed by cyanide displacement and hydrolysis.[9]



i) $(CH_3)_2\overset{+}{N}H\overset{-}{Cl}$, CH_2O, HCl

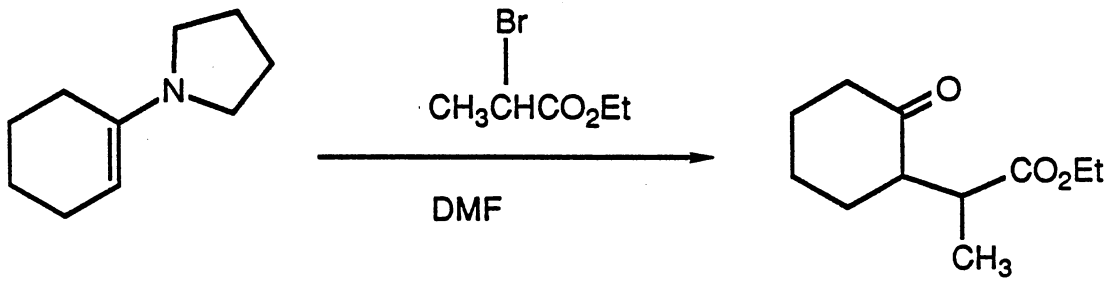
ii) CH_3I

iii) KCN, CH_3OH

iv) 6M HCl

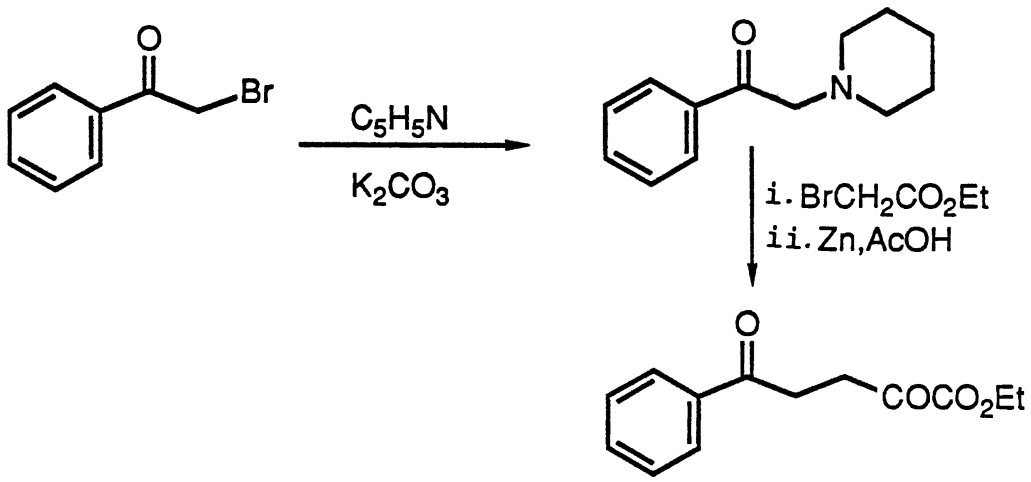
4) Enamine Reaction:

Enamines react with alpha-bromoesters and the resulting substituted enamine may be selectively hydrolyzed with retention of the ester function[10] and subsequent hydrolysis to the gamma-oxoacid.



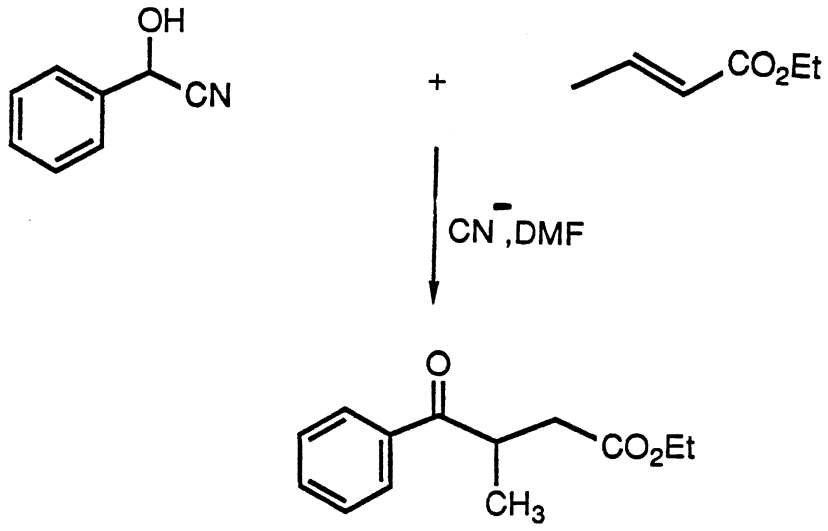
5) Ylide Reaction:

The reaction of an alpha-keto pyridinium ylide with an alpha-bromoester and subsequent reduction of the pyridinium salt by zinc in acetic acid provides a gamma-oxoester.[11]



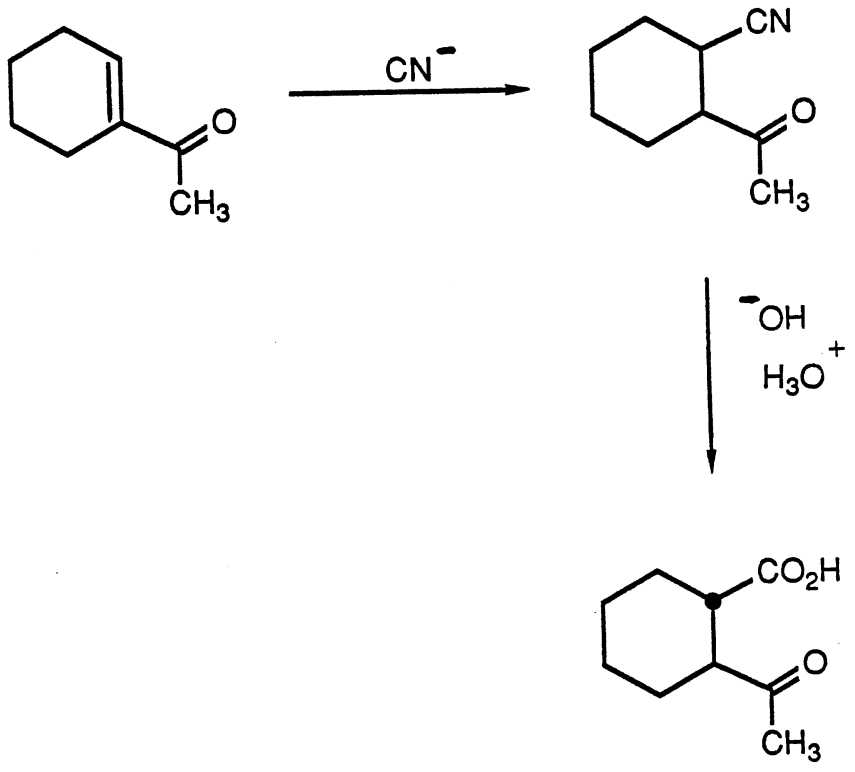
6) Michael Reaction:

Acyl anion equivalents undergo conjugate addition to unsaturated esters. In the example outlined below, the carbonyl function is masked and activated as a cyanohydrin.[12,13]



7) Addition Of Cyanide Ion:

Addition of cyanide ion to conjugated unsaturated ketones has been used to prepare gamma-oxoacids as shown below.[14] While this synthesis gives the correct carbon skeleton,the cis isomer being thermodynamically less stable than the trans isomer will not be present or is present as a minor component. Further,the necessary 2-trimethylacetylcyclohexene needed to prepare 2-trimethyl-acetylcyclohexanecarboxylic acid would be difficult to prepare and purify.



CHAPTER II

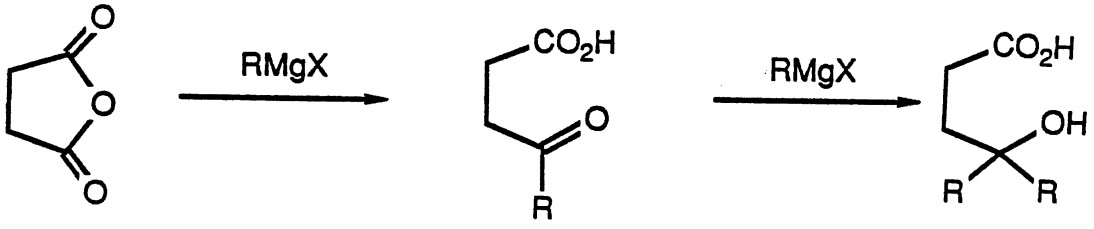
RESULTS AND DISCUSSION

The synthesis routes to the gamma-oxoacids,with the exception of conjugate addition of the cyanide ion to the alpha,beta-unsaturated ketones described in chapter I,are not suitable for the synthesis of the target gamma-oxoacids.

In this chapter,work leading to the successful synthesis of the gamma-oxoacids **3a,3b,4a** and **4b,** using dialkyl cadmium reagents as shown in Schemes II and III, will be presented. The actual chronology of the work involved the use of the Grignard and alkyllithium reagents before the dialkyl cadmium work was carried out. However,since these reactions failed to give the desired products,their use is described last.

Organozinc,organocadmium,organolithium and Grignard reagents have been found to be generally useful in reactions with cyclic anhydrides to form the gamma-oxoacids.[15,18]

The use of the Grignard and organolithium reagents in this case has been restricted because of the tendency of these reagents to undergo further addition to the ketone carbonyl group of the gamma-oxoacids to form hydroxy acids,as shown below.[16]



The methods developed to overcome this problem provide a useful illustration of some of the ways in which organometallic chemistry has developed.

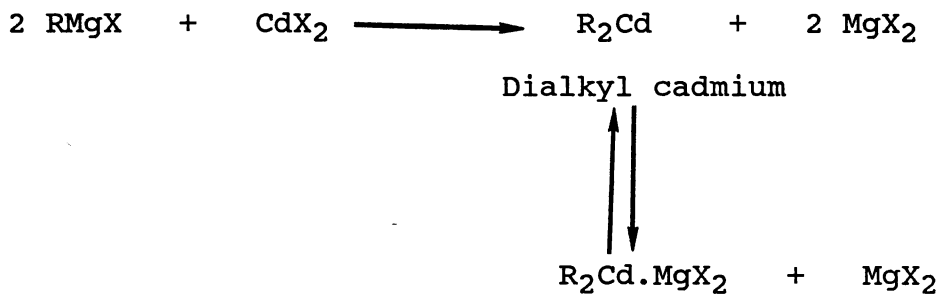
One of these methods is to add one mole of cadmium chloride to two moles of the Grignard reagent,thereby generating the organocadmium compound.[17]

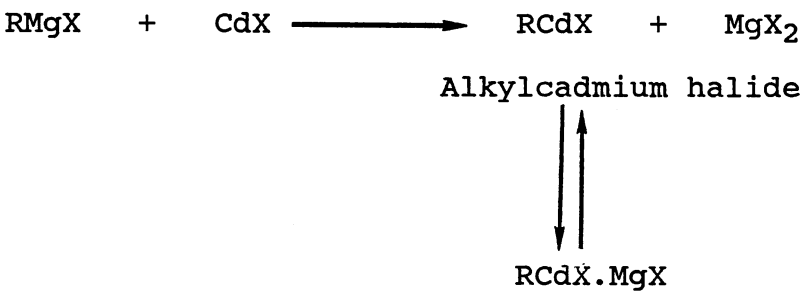
$$2RMgCl + CdCl_2 \longrightarrow R_2Cd + 2MgCl_2 .$$

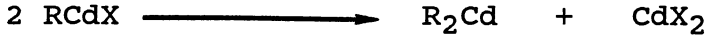
The scope of the cadmium method is greater,since the organocadmium reagents fail to react further with most functional groups. The superiority of the cadmium reagent arises from its easy preparation and its lower reactivity towards the carbonyl group.[18]

The cadmium reagent exists as R_2Cd or as RCdX, depending on the method of preparation. The most common procedure is to prepare the cadmium reagent by addition of a cadmium salt (usually the chloride or bromide) to a solution of a Grignard or a lithium reagent in diethyl ether or another solvent.[18,20] The resulting insitu reagent,used directly,contains one or two molar equivalents of magnesium halide depending on the relative amounts of organometallic reagent and cadmium salt.

The following equations describe the equilibria involved when a Grignard reagent is added to a cadmium halide:[19]







These reactions of the Grignard reagents with cadmium chloride,bromide or iodide(the former being most commonly used) in 1:1 and 2:1 ratios in ether have been studied in an attempt to define composition of the so called organocadmium reagent in solution. The studies involved elemental analyses and infrared examination of both soluble and insoluble reaction products. When the reagent is prepared using a Grignard : CdX_2 ratio of 2:1,it seems to consist of only R_2Cd + MgX_2 . In a 1:1 ratio,the reaction seems to afford MgX_2 and an equilibrium mixture of R_2Cd and CdX_2.[19]

Scope And Limitations Of The Organocadmium Reagents:

a) The Alkyl or Aryl Halide:[21]

Several investigators[22,23,24b] have reported that the use of alkyl iodide in preparing the Grignard reagent results in much lower yields of the cadmium derivative. The bromide was reported to give the best yields. In the case of the n-butyl halides the same order prevails.

b) The Organic Radical:

Aromatic cadmium reagents form cadmium derivatives readily;[22,23,24b,25] but the only alkyl radicals which may be utilized satisfactorily are the primary ones.[24a] Gilman and Nelson[24b] and later Cason[24a] reported that secondary and tertiary cadmium reagents are too unstable even at $0^{\circ}C$, to allow their effective use in synthesis. Our studies show that the secondary (isopropyl) and the tertiary (tert-butyl) cadmium reagents have reasonable stability in refluxing ether.

c) The Cadmium Halide:

Gilman and Nelson[24b] have shown that cadmium chloride is as effective as cadmium bromide for preparing cadmium reagents. Since the bromide is more expensive and much more hygroscopic, the chloride is generally used. Gilman and coworkers[24b] have also reported that yields are approximately the same from a dialkyl cadmium compound and an alkyl cadmium halide. The former is used because it requires only half as much cadmium chloride.

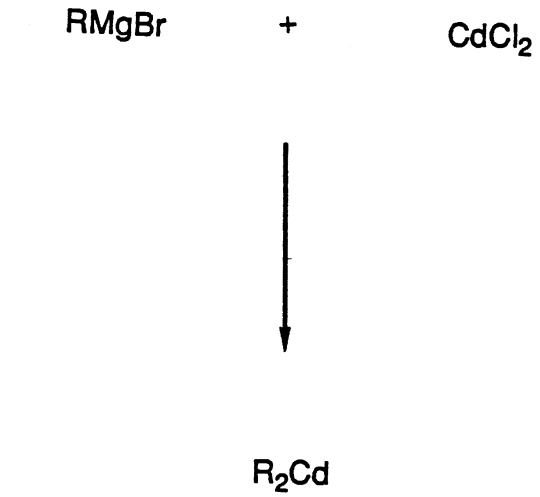
d) The Acid Chloride or Anhydride:

Organocadmium reagents will react with acid anhydrides.[22,23,26,27] Contrary to our observations, earlier investigators have reported low yields of the gamma-oxoacids with the use of anhydrides. We consider that these low yields resulted from diminished reactivity at low temperature.

The routes used to synthesize the gamma-oxoacids 3a,4a and 3b,4b are outlined in schemes II and III. The reaction using the dialkyl cadmium reagents (methyl and tert-butyl) with cis-hexahydrophthalic anhydride (8a) selectively gave the cis-gamma-oxoacids 3a and 4a respectively, in yields of about 73% and 50%. The lactones 5a and 6a were isolated as the neutral fractions. (Scheme II).

A similar reaction with the trans-hexahydrophthalic anhydride (8b) selectively gave the trans-gamma-oxoacids 3b and 4b. The lactones 5b and 6b were isolated as the neutral fractions. (Scheme III).

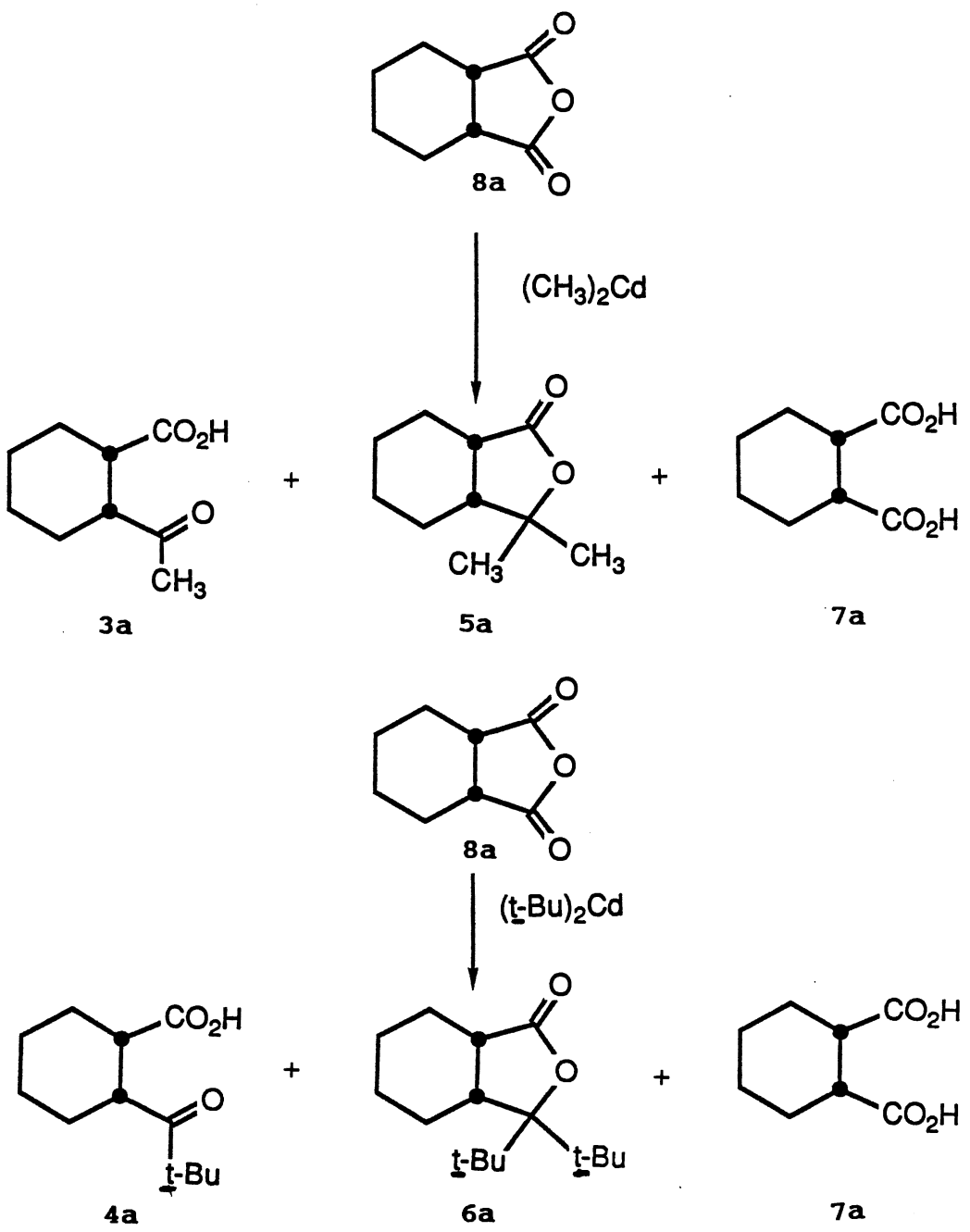
SCHEME I



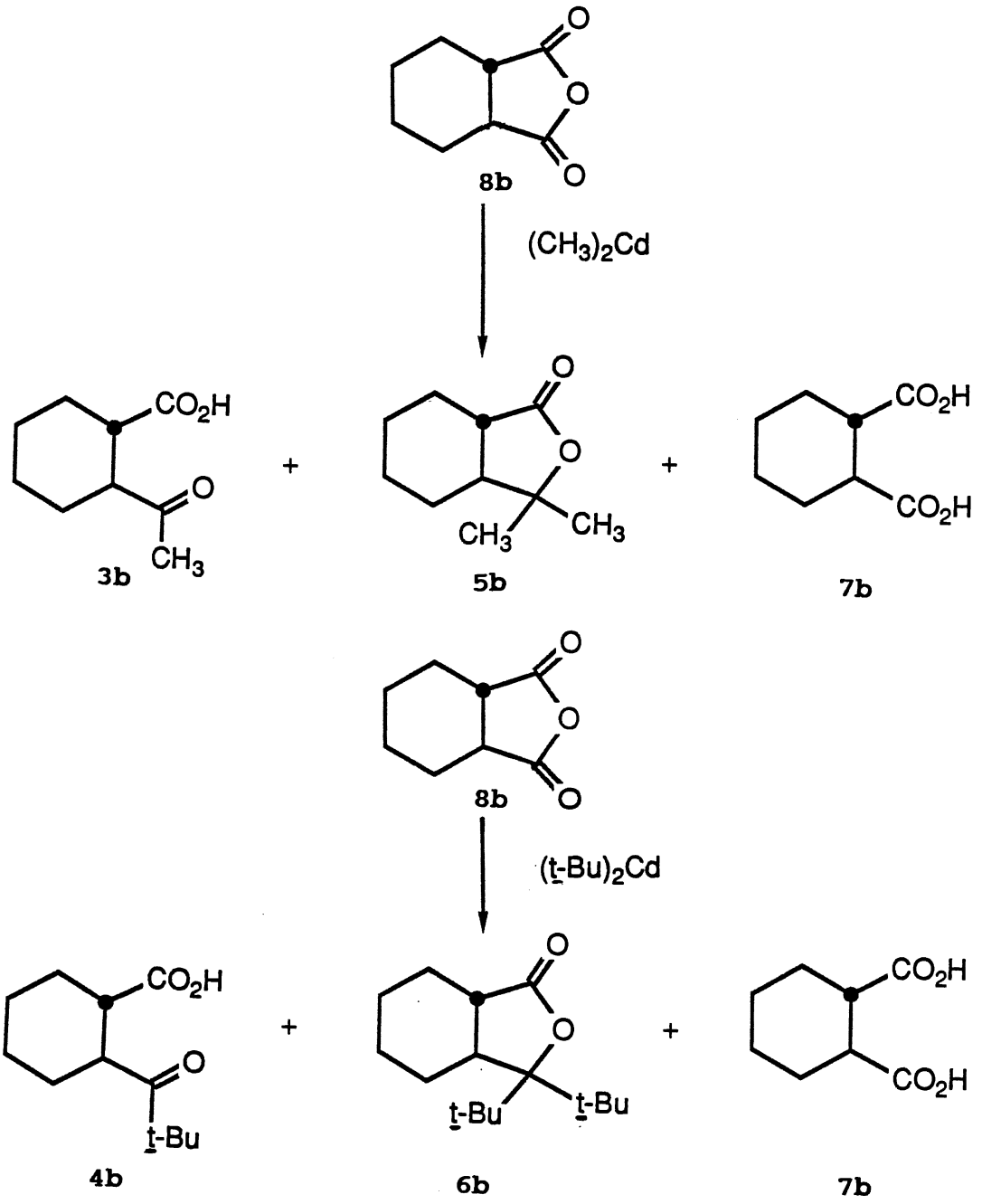
R = CH_3

R = t-Bu

SCHEME II


8a
(CH3)2Cd
CO2H
O
CH3
3a
+
O
O
O
CH3
CH3
5a
+
CO2H
CO2H
7a
8a
(t-Bu)2Cd
CO2H
O
t-Bu
4a
+
O
O
O
t-Bu
t-Bu
6a
+
CO2H
CO2H
7a

SCHEME III


8b
(CH3)2Cd
CO2H
O
CH3
3b
+
O
O
CH3
CH3
5b
+
CO2H
CO2H
7b
8b
(t-Bu)2Cd
CO2H
O
t-Bu
4b
+
O
O
t-Bu
t-Bu
6b
+
CO2H
CO2H
7b

All of the reactions were monitored by gas chromatography. Conversion of the reaction mixture to the methyl ester,by treatment with diazomethane, and subsequent analysis by gas chromatography on 5% Carbowax coated on acid-washed Gas Pack indicated the formation of the cis-gamma-oxoacids as the sole product.

The infrared spectra of the gamma-oxoacids gave no evidence for the presence of a lactol form in equilibrium with the oxo acid.

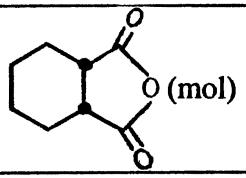
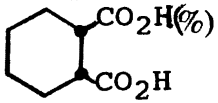
The ratio of the Grignard reagent to the anhydride starting material seems to be very important in determining the products formed,especially in the tert-butyl series. The temperature also seems to be an important factor. (Table 1).

The reaction with the dimethyl cadmium reagent following the procedure given by de Benneville[23] uses a Grignard reagent to anhydride ratio of 2:1. This procedure results in the sole formation of the cis-2-acetylcyclohexanecarboxylic acid **(3a)** with none of the trans isomer detected.

With the use of the di-tert-butyl cadmium reagent, it became necessary to modify the procedure specified for this reagent by de Benneville[23] and Cason,[18] by increasing the reaction temperature from that of Dry Ice originally specified to that of refluxing ether as was done with the dimethyl cadmium reagent. A reaction carried out at -78° C, using a Grignard reagent to anhydride ratio of 3:1, resulted in a 90% recovery of cis-1,2-cyclohexane-dicarboxylic acid (7a). The same reaction carried out at a reflux temperature, using a Grignard reagent to anhydride ratio of 2:1, gave a 40 : 50 : 10 mixture of the trans and cis isomers and cis-1,2-cyclohexanedicarboxylic acid (7a). Using a Grignard reagent to the anhydride ratio of 3:1 under refluxing conditions yielded the cis isomer 4a in a yield of about 50%, along with about 10% of the recovered cis-1,2-cyclohexanedicarboxylic acid (7a). The trans isomer 4b was not observed.

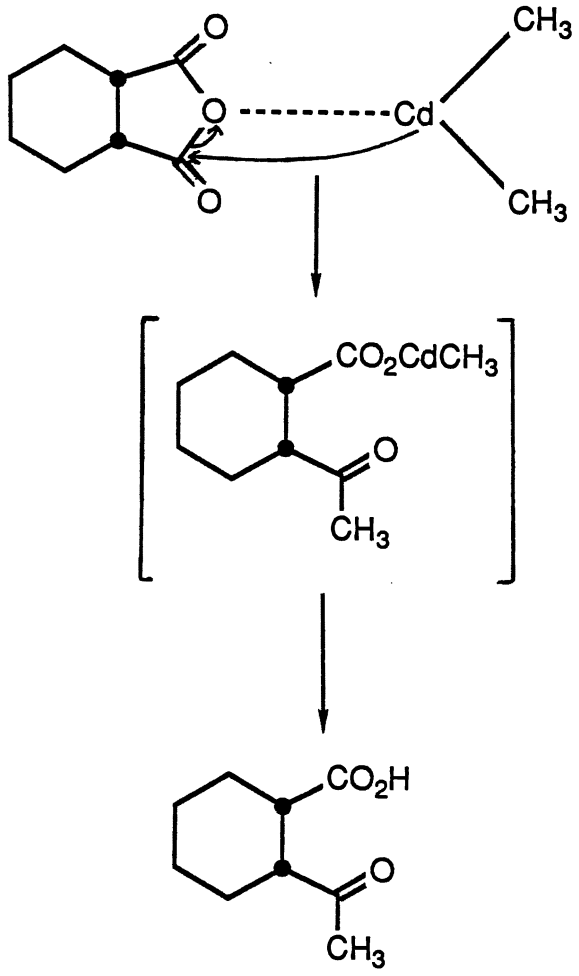
TABLE I

SYNTHESIS OF cis-2-TRIMETHYLACETYLCYCLOHEXANECARBOXYLIC ACID (4a)

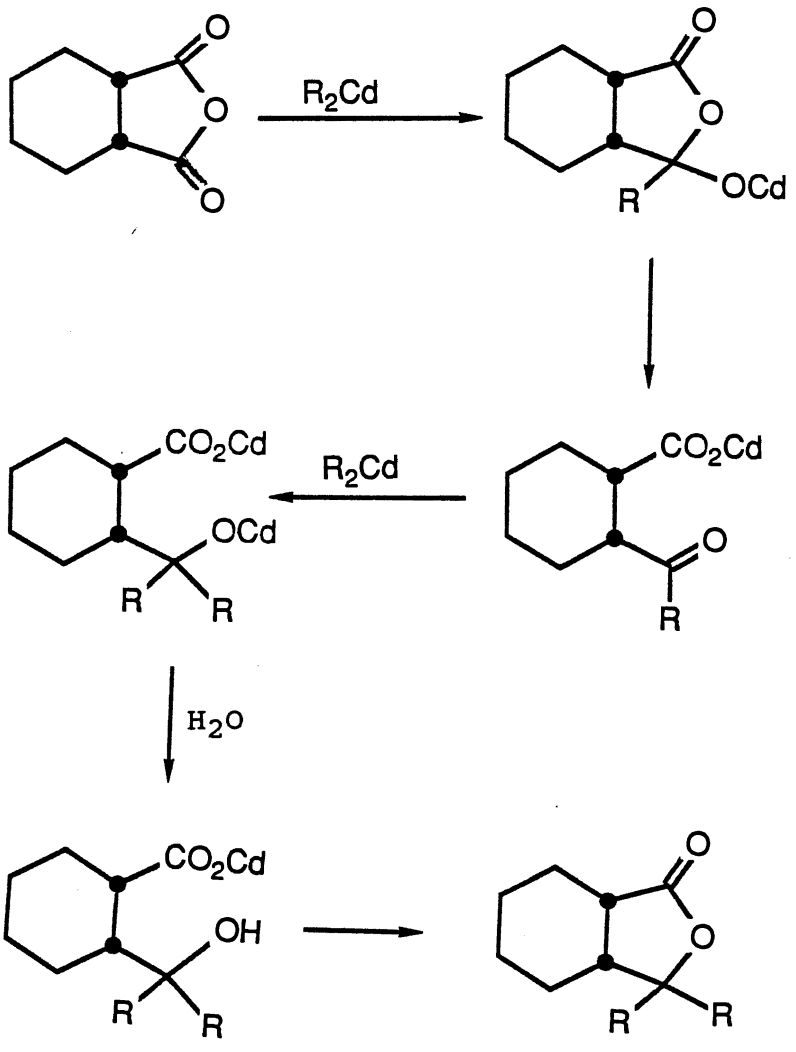
REACTION NUMBER	CADMIUM CHLORIDE (mol)	 (mol)	t-BuMgCl (mol)	REACTION CONDITIONS	PRODUCT (% YIELD)	RECOVERED  (%)
1	0.074	0.081	0.152	Refluxing ether	4a:50 4b:40	10
2	0.093	0.063	0.18	-78°C	—	90
3	0.103	0.07	0.20	Refluxing ether	4a:50	10
4	0.103	0.07	0.20	Refluxing ether	4a:50	10
5	0.103	0.07	0.20	Refluxing ether	4a:50	10

The following mechanism has been proposed to explain the formation of gamma-oxoacids:[28]

An initial coordination of cadmium with the central oxygen atom is followed by cleavage of one of the carbon-oxygen single bonds.

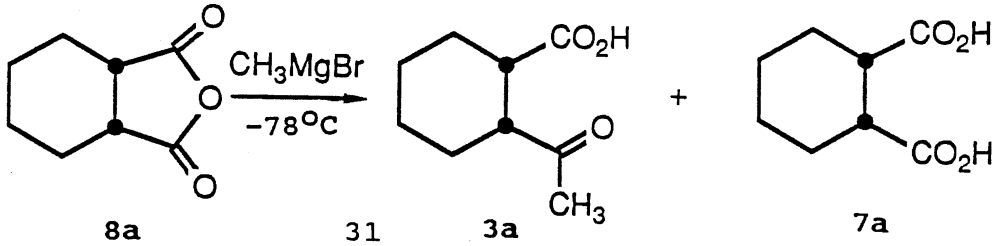


An increase in the proportion of the Grignard reagent to anhydride, causes an increase in the formation of the neutral fraction.[29] This can be rationalized as follows:



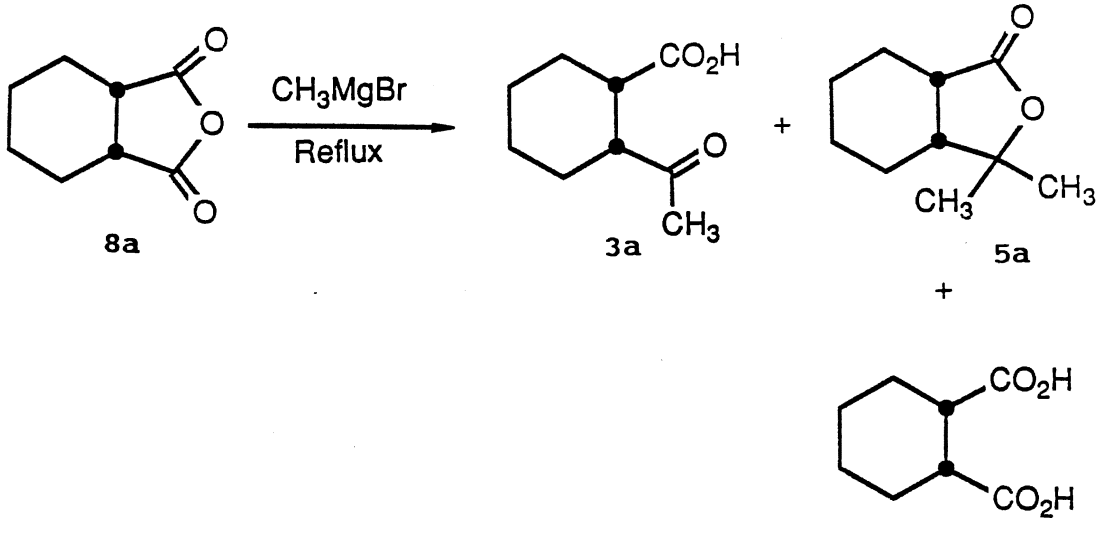
Attempted Use Of Methyl Grignard And Methyl Lithium In The Synthesis Of **3a** And **3b:**

Newman's method[30], involving the reaction of <u>cis</u>-hexahydrophthalic anhydride **(8a)** with methylmagnesium bromide at Dry Ice temperature resulted in a 98% recovery of the <u>cis</u>-1,2-cyclohexanedicarboxylic acid **(7a)** and 2% of <u>cis</u>-2-acetylcyclohexanecarboxylic acid **(3a)**.



8a **3a** **7a**

The same reaction[31] carried out in ether at reflux temperature resulted in the formation of 90% of <u>cis</u>-1,2-cyclohexanedicarboxylic acid **(7a)**, 2% of <u>cis</u>-2-acetylcyclohexanecarboxylic acid **(3a)** and 8% of the lactone **5a.**

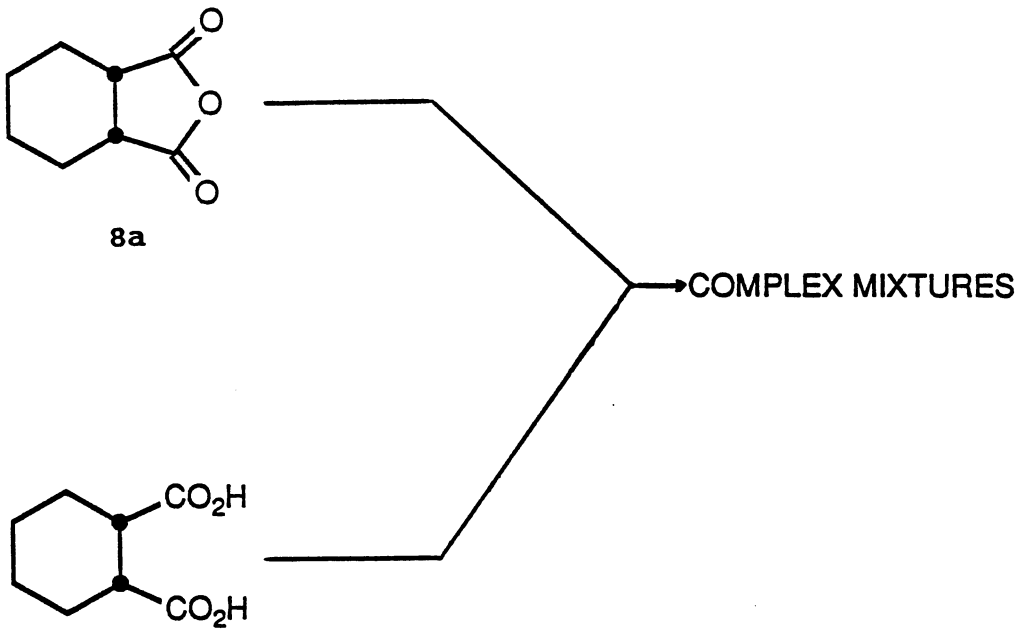


8a **3a** **5a**

+

7a

The reaction with alkyl lithium reagents also proved to be unsuccessful. Reactions of both cis-1,2-hexahydrophthalic anhydride (8a) and cis-1,2-cyclohexanedicarboxylic acid (7a) with methyl lithium gave complex mixtures as shown by gas chromatography of the methyl esters. No attempt was made to separate and identify these products.



8a

7a

CHAPTER III

EXPERIMENTAL

General:

Proton NMR spectra were determined at 300 MHz on a Varian XL-300A. Proton chemical shifts are reported in (ppm) downfield from an internal TMS standard for solutions in $CDCl_3$, unless otherwise noted. ^{13}C NMR were obtained at 75.43 MHz on a Varian XL-300. Chemical shifts are reported in ppm using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer 197 Infrared spectrophotometer. Gas chromatographic analyses were obtained using 5% carbowax on acid-washed Gas Pack. Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected.

MATERIALS: All compounds obtained from commercial sources were used without further purification unless otherwise noted.

cis-2-Acetylcyclohexanecarboxylic Acid (3a)

a) Grignard Reaction:

i) Reaction of Methylmagnesium Bromide with cis-Hexahydrophthalic Anhydride (8a) at Reflux in Ether:

cis-Hexahydrophthalic anhydride (8a), 7.7 g (0.05 mol) was dissolved in 200 mL anhydrous ether in a 500 mL flask fitted with a mechanical stirrer and a reflux condenser. To this was slowly added 16.7 mL of 3M methyl magnesium bromide,with stirring,over a period of 35 min. After addition of the Grignard reagent was complete, the reaction mixture was stirred and heated at reflux for 3 h. Decomposition of the reaction mixture with ice and ammonium chloride solution,followed by work up of the reaction mixture,gave 90% of cis-1,2-cyclohexanedicarboxylic acid (7a) and 2% of cis-2-acetylcyclohexanecarboxylic acid (3a). The lactone 5a was isolated as the neutral fraction in a 8% yield.

ii) Reaction of Methylmagnesium Bromide with cis-Hexahydrophthalic Anhydride (8a) at Dry Ice temperature:

A solution of 4.2 g (0.027 mol) of cis-hexahydrophthalic anhydride (8a) in 100 mL dry ether was cooled by a mixture of dry ice and acetone. To this cold solution was slowly added 4.6 mL of 3M methylmagnesium bromide with stirring. Addition of the Grignard reagent was carried out during 1 h. The reaction mixture was then stirred for a period of 3 h. Decomposition of the reaction mixture with ammonium chloride followed by work up gave 98% of cis-1,2-cyclohexanedicarboxylic acid (7a) and 2% of cis-2-acetylcyclohexanecarboxylic acid (3a).

b) Methyl Lithium reaction:

i) Reaction of Methyl Lithium with cis-1,2-cyclohexanedicarboxylic Acid (7a):

cis-1,2-cyclohexanedicarboxylic acid (7a),10.014 g

(0.058 mol) was dried in a dessicator over concentrated sulfuric acid for a period of 24 h. It was then dissolved in about 100 mL dry ether. To this was added 147 mL (0.25 mol) of methyl lithium in hexane over a period of 1.5 h with constant stirring. After addition was complete,the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was decomposed by pouring onto ice. Work up and GC analyses of the reaction mixture revealed a complex mixture of products. No attempt was made to isolate and analyze these products.

ii) Reaction of Methyl Lithium with cis-Hexahydrophthalic Anhydride **(8a)**:

A 3.1 g (0.02 mol) sample of cis-hexahydrophthalic anhydride **(8a)** was dissolved in about 100 mL dry ether with stirring. To this solution was added 133 mL (0.1 mol) of methyl lithium in hexane,with stirring over a period of 1.5 h. Work up and analysis of the reaction mixture by GC indicated a complex mixture of products. No attempt was made to isolate and analyze the products.

Synthesis of cis-2-Acetylcyclohexanecarboxylic Acid (3a) Using the Dimethyl Cadmium Reagent:

c) Synthesis of the Dimethyl Cadmium Reagent:

To an ice cold solution of methylmagnesium bromide 62.5 mL (0.1875 mol) was added slowly 20.174 g (0.11 mol) of finely pulverized anhydrous cadmium chloride (oven dried for 12 h,at 150°C),with constant stirring. The ice bath was then removed and the solution stirred for half an hour. No attempt was made to isolate and analyze the reagent.

The procedure for the synthesis of the di-tert-butyl cadmium reagent was the same ,except that tert-butyl-magnesium chloride was used in lieu of methylmagnesium bromide.

d) Reaction with Dimethyl Cadmium:
Dimethyl Cadmium Reaction with cis-Hexahydrophthalic Anhydride (8a):

The reaction mixture containing the dialkylcadmium reagent was surrounded by an ice bath. cis-Hexahydro-

phthalic anhydride (8a),15.4 g (0.1 mol) was added dropwise with stirring,as a solution in dry ether. The addition was accomplished over a period of 15 to 30 min. After addition was complete, the ice bath was removed, and the contents of the flask were heated on a water bath for a period of 1 to 1.5 h under a gentle ether reflux with constant stirring. At the conclusion of the reflux period the reaction mixture was cooled. The flask was surrounded with ice and the reaction mixture was acidified with 10% sulfuric acid,until the pH of the solution was about 2. When hydrolysis was complete,the ether layer was separated and combined with the ether washing of the aqueous layer.

Isolation of gamma-Oxoacid, 3a:

The ether solution obtained from the hydrolysis was carefully washed with 10% potassium carbonate solution. The potassium carbonate solution was then filtered and the filtrate was acidified with sulfuric acid to a pH of 2. The solution became turbid but the gamma-oxoacid did not precipitate. Back extraction of the aqueous layer with ether,drying over magnesium sulfate and stripping the ether yielded 12.2 g (73%) of cis-2-acetylcyclohexanecarboxylic

acid (3a) as a pale yellow oil. On standing this oil slowly crystallized out as a white solid. Recrystallization from a mixture of ether and Skelly B gave pure cis-2-acetylcyclohexanecarboxylic acid (3a): mp 75-77°C; ^{1}H NMR ($CDCl_3$) δ 11.40 (CO_2H),2.83 (m,1),2.81 (m,1),2.18 (s,3),2.08 (m,2),1.81 (m,2),1.44 (m,4); ^{13}C NMR ($CDCl_3$) ppm 210.15 (CO),180.31(CO_2H),50.02,42.34,27.89,26.06,25.97,23.82,23.66. Anal. Calcd for $C_9H_{14}O_3$: C,63.51;H,8.29. Found: C,63.61; H,7.92.

Drying over magnesium sulfate and stripping the ether layer yielded 0.3 g (2%) of lactone 5a as the neutral fraction : mp 61-64°C; ^{1}H NMR ($CDCl_3$)δ3.00 (m,1),2.25 (m,2),1.75 (m,2),1.59 (m,2),1.36 (s,6),1.1 (m,3); ^{13}C NMR ($CDCl_3$) ppm 177.78 (CO),84.13,43.54,40.01,26.18, 25.22,23.67,22.99,22.93,22.66.

trans-2-Acetylcyclohexanecarboxylic Acid (3b)

a) Reaction with Dimethyl Cadmium:

Synthesis of trans-2-Acetylcyclohexanecarboxylic Acid (3b) Using the Dimethyl Cadmium Reagent:

trans-Hexahydrophthalic anhydride (8b), 15.4 g (0.1

mol) was added slowly with stirring to the dimethyl cadmium reagent. The dimethyl cadmium reagent was prepared according to the earlier procedure. Following the procedure described for the synthesis of cis-2-acetylcyclohexane-carboxylic acid **(3a)**,the final work up of the reaction mixture yielded 12.6 g (74%) of trans-2-acetylcyclohexane-carboxylic acid **(3b)** as a pale yellow oil which crystallized on standing into a white crystalline solid, mp 132-133° C; (lit.mp 133-134° C). Recrystallization from ether gave the pure trans isomer. ^{1}H NMR ($CDCl_3$) δ 11.01 (CO_2H), 2.70 (m,1),2.67 (m,1),2.20 (s,3),2.05 (m,2),1.83 (m,2),1.31 (m,4);^{1}3C NMR ($CDCl_3$) ppm 211.07 (CO),181.61 (CO_2H), 51.85, 44.06,28.89,28.60, 28.37,25.60,25.43.

The lactone **5b** was isolated as the neutral fraction in a 10% yield. ^{1}H NMR ($CDCl_3$) δ 2.18 (m,2),1.89 (m,4), 1.43 (m,4),1.27 (s,6); ^{13}C NMR ($CDCl_3$) ppm 176.73 (CO),85.64,52.42,43.91,27.25,26.11,25.63,25.48,25.36,20.70.

a) Epimerization Reaction:

Epimerization of cis-2-Acetylcyclohexanecarboxylic-Acid **(3a)**:

cis-2-Acetylcyclohexanecarboxylic acid (3a), 5 g (0.029 mol) was dissolved in 250 mL of 10% sodium hydroxide solution and the mixture heated at reflux for 3 h under a nitrogen atmosphere. A small aliquot was withdrawn,and converted to the methyl ester with diazomethane. GC analysis of the methyl ester indicated a complete epimerization of the cis isomer to the trans isomer.

The reaction mixture was cooled and acidified with concentrated hydrochloric acid to pH 2. The solution became turbid but the gamma-oxoacid did not precipitate out. Back extraction with ether followed by drying and stripping gave 4.5 g (90%) of the trans-2-acetylcyclohexanecarboxylic acid (3b) as a pale yellow oil which slowly crystallized into a white solid. Recrystallisation from ether gave the pure compound. ^{1}H NMR and ^{13}C NMR data matched with the product obtained from the cadmium reaction.

cis-2-Trimethylacetylcyclohexanecarboxylic Acid (4a)

Synthesis of cis-2-trimethylacetylcyclohexanecarboxylic Acid (4a) Using the Di-tert-butyl Cadmium Reagent:

a) Synthesis of the Di-tert-butyl Cadmium Reagent:

To an ice cold solution of 100 mL (0.2 mol) of tert-butylmagnesium chloride, was added 18.33 g (0.103 mol) of finely pulverized anhydrous cadmium chloride (oven dried at 150°C for about 12 h),with constant stirring. After addition was complete,the ice bath was removed and the solution stirred for half an hour.

b) Reaction with Di-tert-butyl Cadmium:

Di-tert-butyl Cadmium Reaction with cis-Hexahydro-phthalic Anhydride **(8a)**:

The reaction mixture containing the di-tert-butyl cadmium reagent was surrounded by an ice bath. cis-hexahydrophthalic anhydride **(8a)**, 10.78 g (0.07 mol),was added dropwise,with stirring,as a solution in dry ether. The remainder of the procedure was the same as that for the dimethyl cadmium reaction. Work up of the reaction mixture gave 7.5 g (50%) of cis-2-trimethylacetylcyclohexane-carboxylic acid **(4a)**,as a pale yellow oil which slowly crystallized into a white crystalline solid.

Recrystallization from a mixture of ether and hexane gave the pure cis isomer, mp 110-113 °C; ^{1}H NMR ($CDCl_3$) δ 11.0 (CO_2H) ,3.46 (m,1),2.49 (m,1),2.25 (m,2),2.01 (m,2),1.42 (m,4),1.20 (s,9); ^{13}C NMR ($CDCl_3$) ppm 217.32 (CO),180.83 (CO_2H),44.65,43.87,43.12,27.35,27.10, 25.28,24.32,21.91.

A mixture of the lactone **6a** and an unidentified product was isolated as the neutral fraction in a 40% yield.

trans-2-Trimethylacetylcyclohexanecarboxylic Acid (4b)

a) Reaction with Di-tert-butyl Cadmium:

Synthesis of trans-2-Trimethylacetylcyclohexane-carboxylic Acid **(4b)** Using the Di-tert-butyl Cadmium Reagent:

The synthesis of the di-tert-butyl cadmium reagent was carried out according to the earlier procedure. The reaction mixture containing the di-tert-butyl cadmium reagent was surrounded by an ice bath. To this cold solution was added trans-hexahydrophthalic anhydride **(8b)**,10.78 g (0.07 mol) slowly and with stirring. Completion of the reaction following the earlier

procedure,followed by work up of the reaction mixture gave 5.7 g (38%) of the trans-2-trimethylacetylcyclohexanecarboxylic acid **(4b)**. Recrystallization from a mixture of ether and hexane gave the pure compound, mp 142-145 C; ^{1}H NMR ($CDCl_3$) δ 10.2 (CO_2H),3.11 (m,1), 2.79 (m,1),2.11 (m,2),1.80 (m,2),1.34 (m,4),1.26 (s,9); ^{13}C NMR ppm 218.60 (CO),181.64 (CO_2H),46.80,44.91,44.32, 29.91,28.90,27.23,25.43,25.28.

The lactone **6b** was isolated as the neutral fraction in a 29% yield. ^{1}H NMR ($CDCl_3$) δ 3.71 (m,1),3.67 (m,1), 1.95 (m,4),1.72 (m,4),1.16 (s,9),1.14 (s,9); ^{13}C NMR ppm 175.66 (CO),90.56,46.20,43.65,32.89,29.31,25.20,24.46, 24.34,24.24.

b) Epimerization Reaction:

Epimerization Reaction of cis-2-Trimethylacetyl cyclohexanecarboxylic Acid **(4a)**:

An 8 g (0.038 mol),sample of cis-2-trimethylacetyl-cyclohexanecarboxylic acid **(4a)** was dissolved in 50 mL of 10% sodium hydroxide solution and heated at reflux temperature for 3 h under a nitrogen atmosphere. A small

aliquot was withdrawn,converted to the methyl ester with diazomethane. GC analysis of the methyl ester indicated a partial epimerization of the cis isomer to the trans isomer. An additional 250 mL 10% of sodium hydroxide was added and reflux continued. The mixture was analyzed at regular intervals by GC.

Epimerization was complete after 28 h. Work up of the reaction mixture gave 7.3 g (91%) of trans-2-trimethylacetylcyclohexanecarboxylic acid as a pale yellow oil,which slowly crystallized into a white solid. Recrystallization from a mixture of ether and hexane gave the pure compound. ^{1}H NMR and ^{13}C NMR data matched with the data obtained from the product of the cadmium reaction.

BIBLIOGRAPHY

1. Laar,C.Ber.1886,19,730.

2. Jones,P.R.Chem.Revs.1963,63,461-487.

3a. Kohler,E.P.;Jansen,J.E.J.Am.Chem.Soc.1938,60,2142.

3b. Bates,R.B.;Eisenbraun,E.J.;McElvain,S.M.J.Am.Chem.Soc. 1958,80,3420.

4. Pourahmady,N.Ph.D Thesis,Oklahoma State University, 1981,pp 6.

5. Pourahmady,N.Ph.D Thesis,Oklahoma State University, 1981,pp 13.

6. Pourahmady,N.;Eisenbraun,E.J.J.Org.Chem.1983,26,3067.

7. Cason.J.Org.Syn.1945,25,19.

8. Swann,S.;Oehler,R.;Buswell,R.J.Org.Syn.;Collective Vol.II,pp 276.

9. McEvoy,F.J.;Allen,G.R.Jr.J.Org.Chem.1973,38,4044.

10. Stork,G.;Brizzolara,A.;Landesman,H.;Szumuzkovicz,J.; Terrell,R.J.Am.Chem.Soc.1963,85,207.

11. Henrick,C.A.;Ritchie,E.;Taylor,W.C.Austral.J.Chem. 1967,20,2441.

12. Stetter,H.;Schreckenberg,M.Angew.Chem.Internat.Edn. 1973,12,81.

13. Stetter,H.ibid.1976,15,639.

14. Lapworth,A.;Clarke,R.W.L.J.Chem.Soc.1906,89,1869.

15. Gilman.Org.Chem.Vol.I,2nd Edn.,pp 489-580,John Wiley & Sons,New York,1943.

16. Gilman,Fothergill,Parker.Rec.trav.chim.1929,48,751.

17. Sanders,J.R.J.Organomet.Chem.1970,25,277.

18. Cason,J.Chem Revs.1946,40,15.

19. Jones,P.R.;Desio,P.J.Chem.Revs.1978,78,Number 5, 491-516.

20. Shirley,D.A.Org.React.1954,8,28.

21. Cason,J.Chem.Revs.1946,40,18.

22. Cason,J.J.Am.Chem.Soc.1946,68,2078.

23. de Benneville,P.L.J.Org.Chem.1941,6,462.

24a. Cason,J.;Fessenden,R.J.Org.Chem.1960,25,477.

24b. Gilman,H.;Nelson,J.F.Rec.trav.chim.1936,55,518.

25. Cole,W.;Julian,P.L.J.Am.Chem.Soc.1945,67,1369.

26. Cason,J.J.Am.Chem.Soc.1942,64,1106.

27. Cason,J.;Prout,F.S.J.Am.Chem.Soc.1944,66,46.

28. Shirley,D.A.Org.React.1954,8,30.

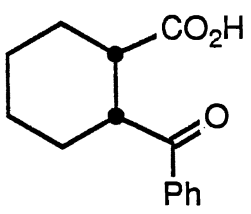
29. Jones,P.R.;Congdon,S.L.J.Am.Chem.Soc.1959,81,4291-4.

30. Newman,M.S.;Booth,W.T.Jr.J.Am.Chem.Soc.1945,67,154.

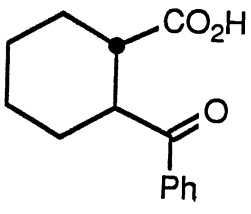
31. Ellingboe,E.;Fuson,R.C.J.Am.Chem.Soc.1934,56,1777.

APPENDIX A

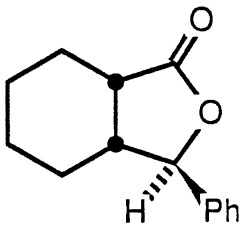
GLOSSARY OF STRUCTURES



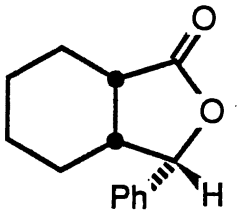
1a



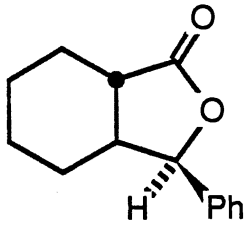
1b



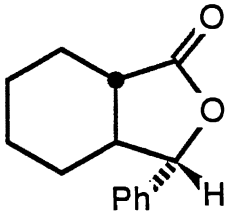
2a



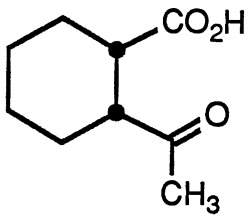
2b



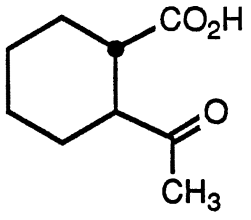
2c



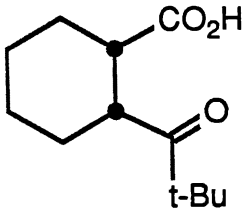
2d



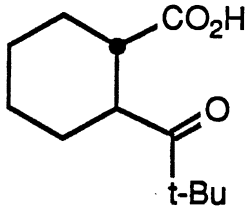
3a



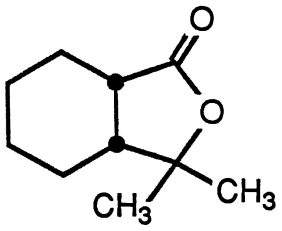
3b



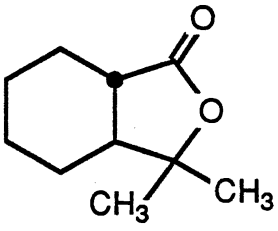
4a



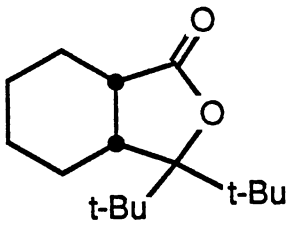
4b



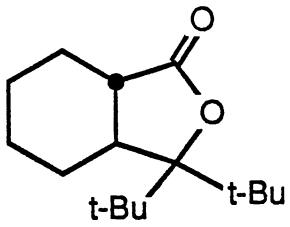
5a



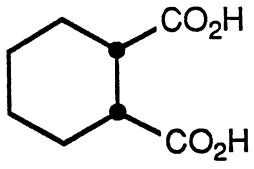
5b



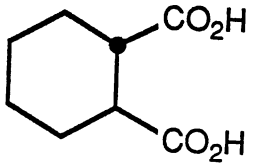
6a



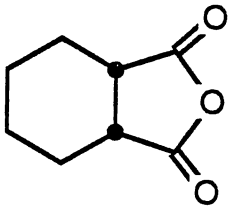
6b



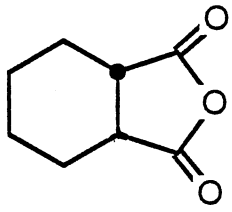
7a



7b



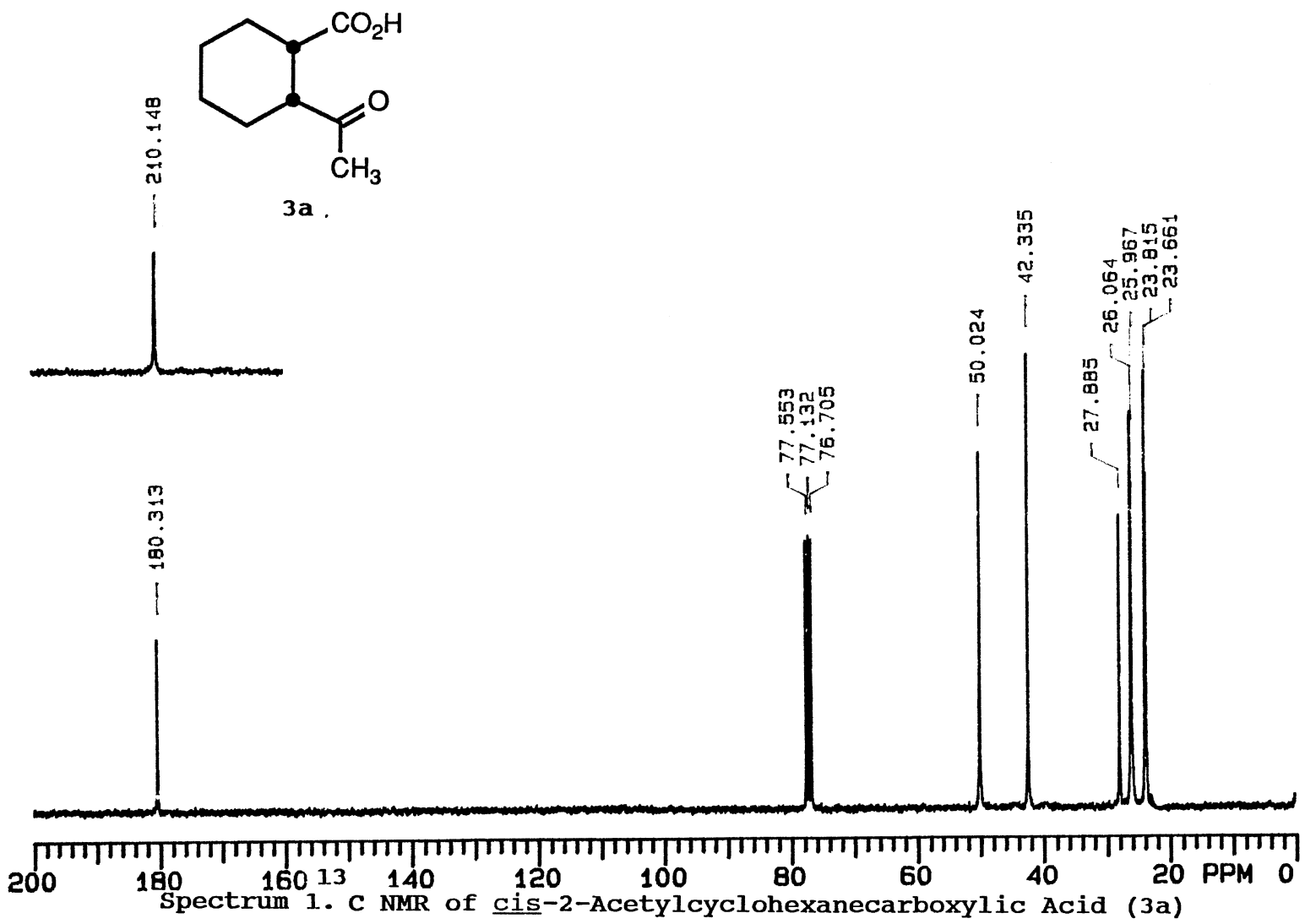
8a



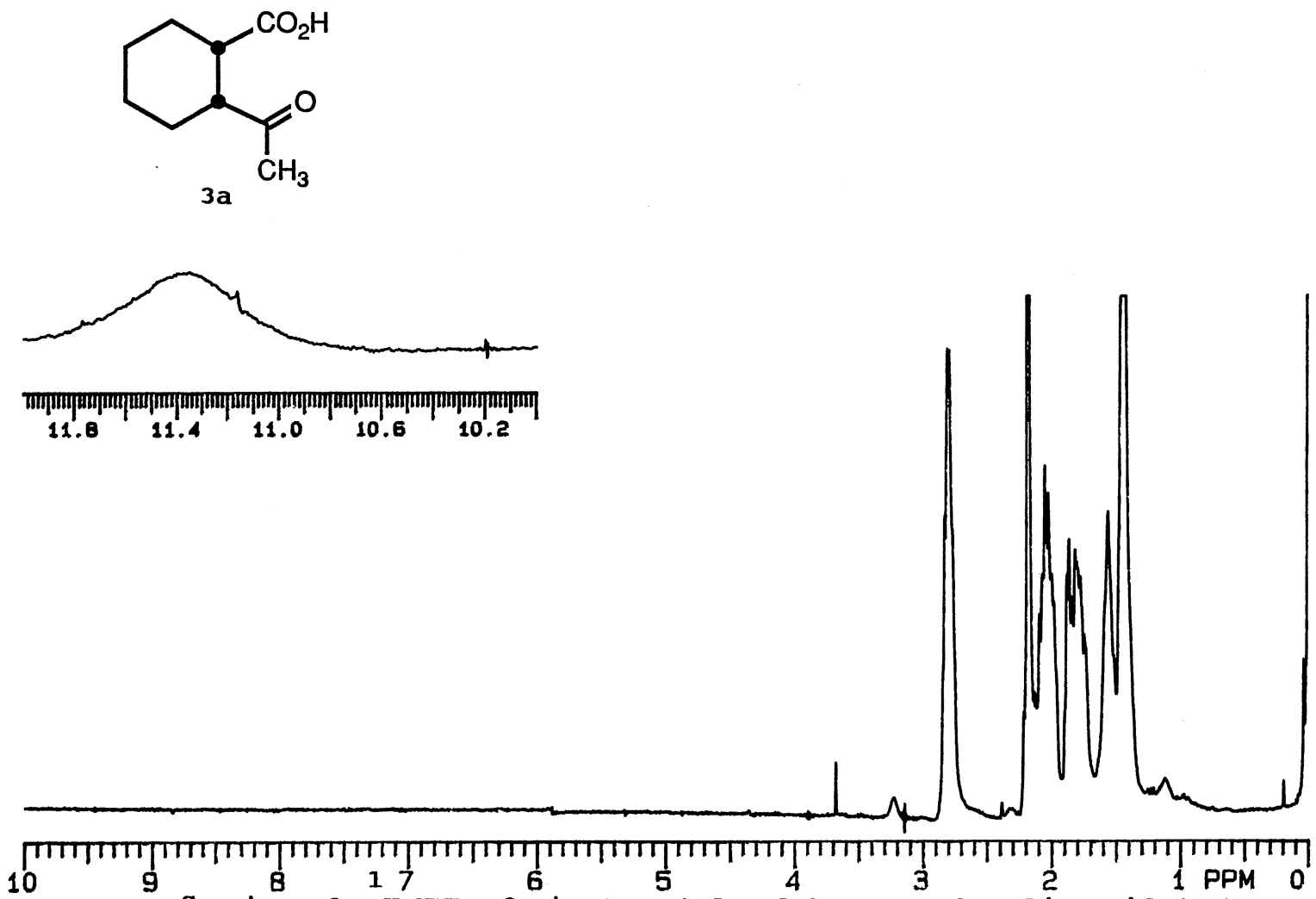
8b

APPENDIX B

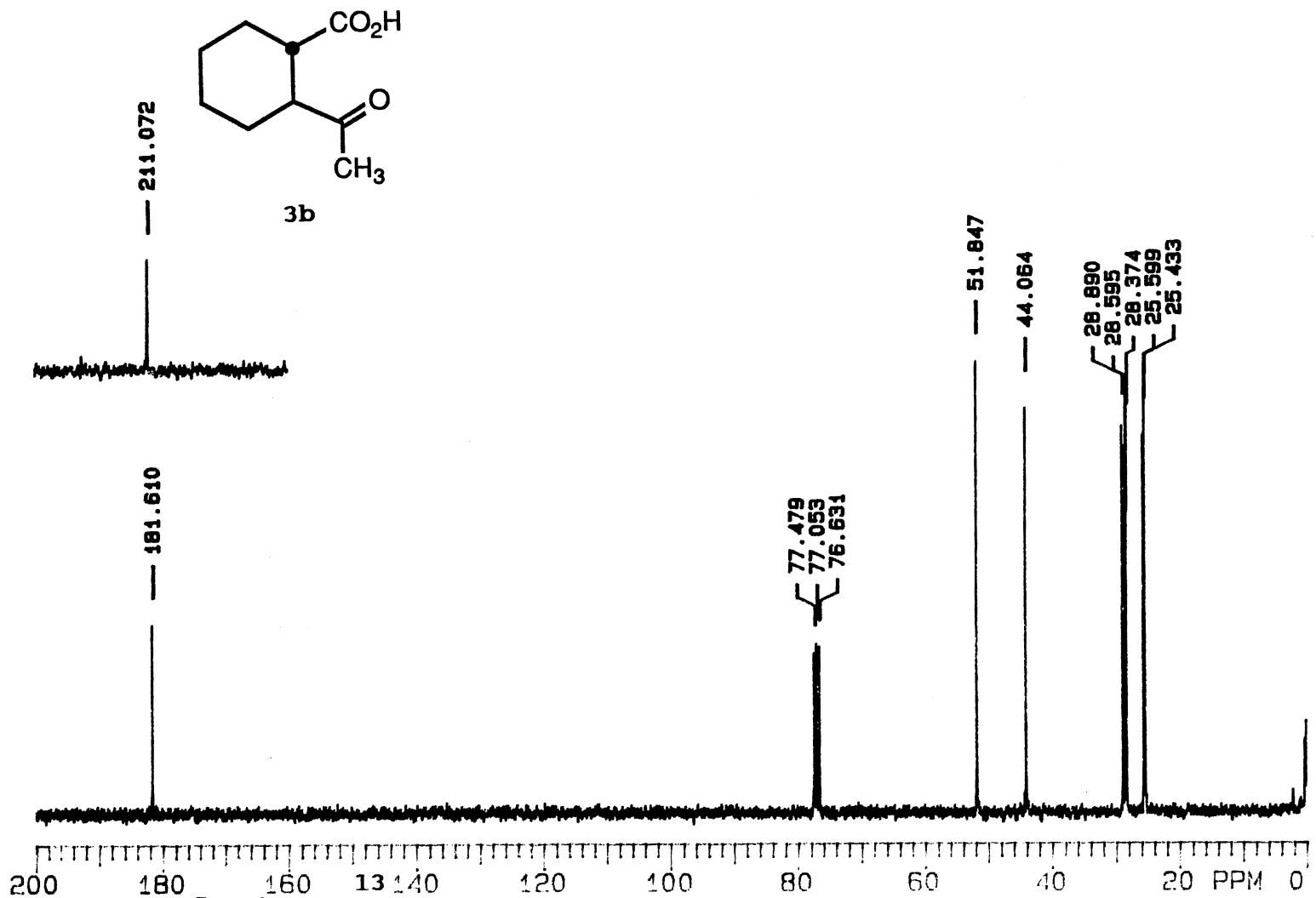
SELECTED SPECTRA



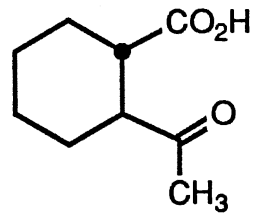
Spectrum 1. ^{13}C NMR of <u>cis</u>-2-Acetylcyclohexanecarboxylic Acid (3a)



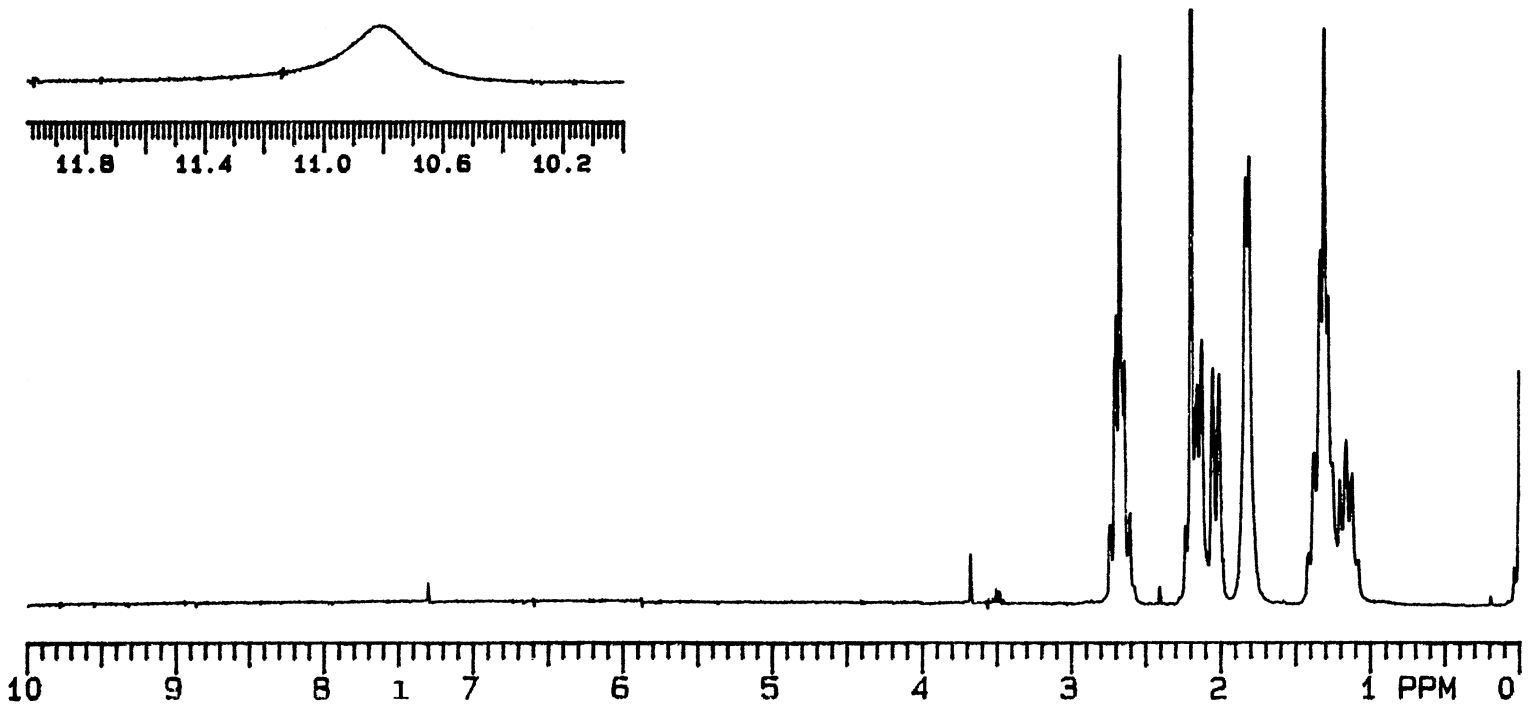
Spectrum 2. H NMR of <u>cis</u>-2-Acetylcyclohexanecarboxylic Acid (3a)



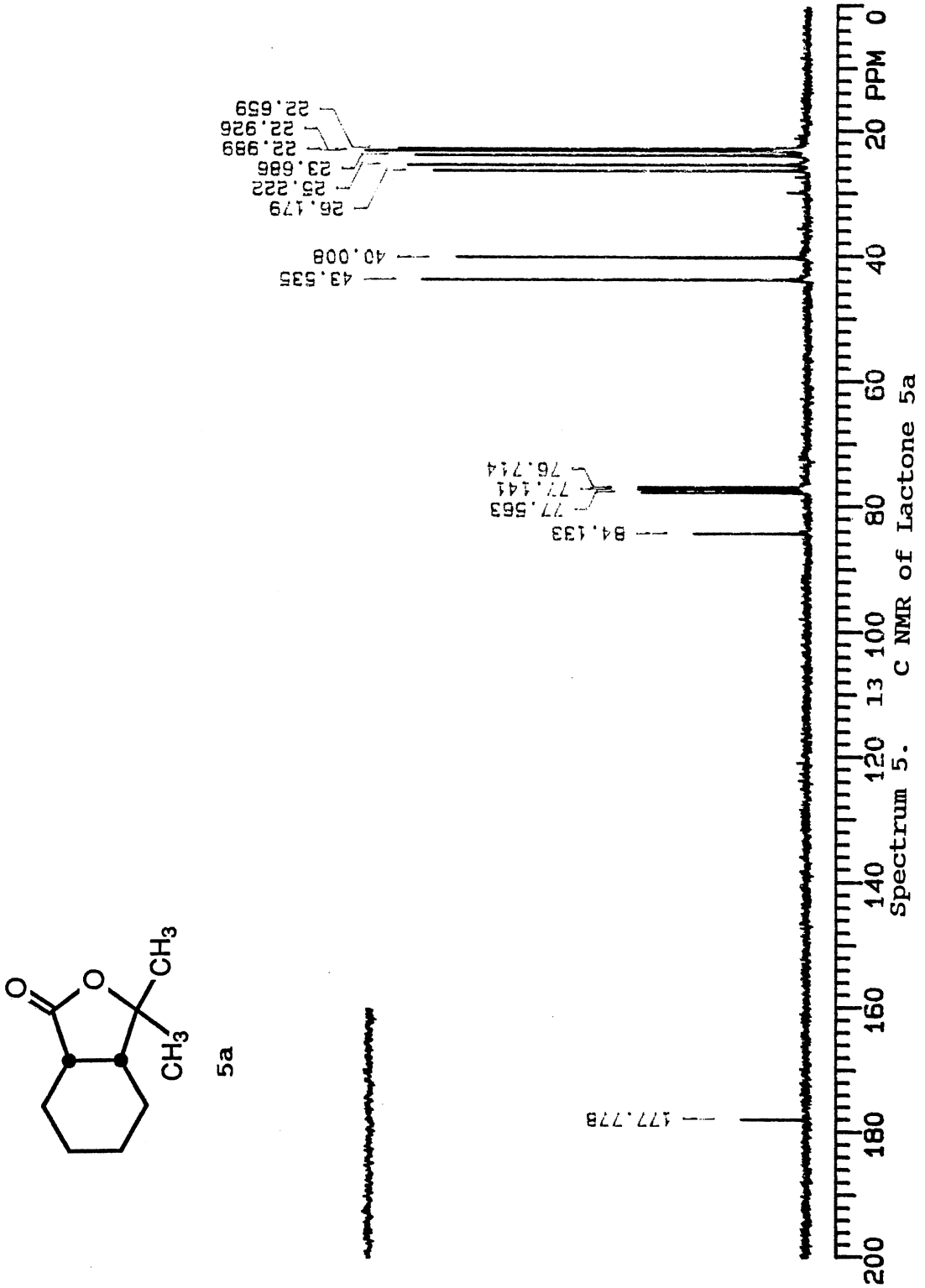
Spectrum 3. C NMR of <u>trans</u>-2-Acetylcyclohexanecarboxylic Acid (3b)



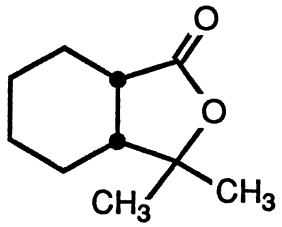
3b



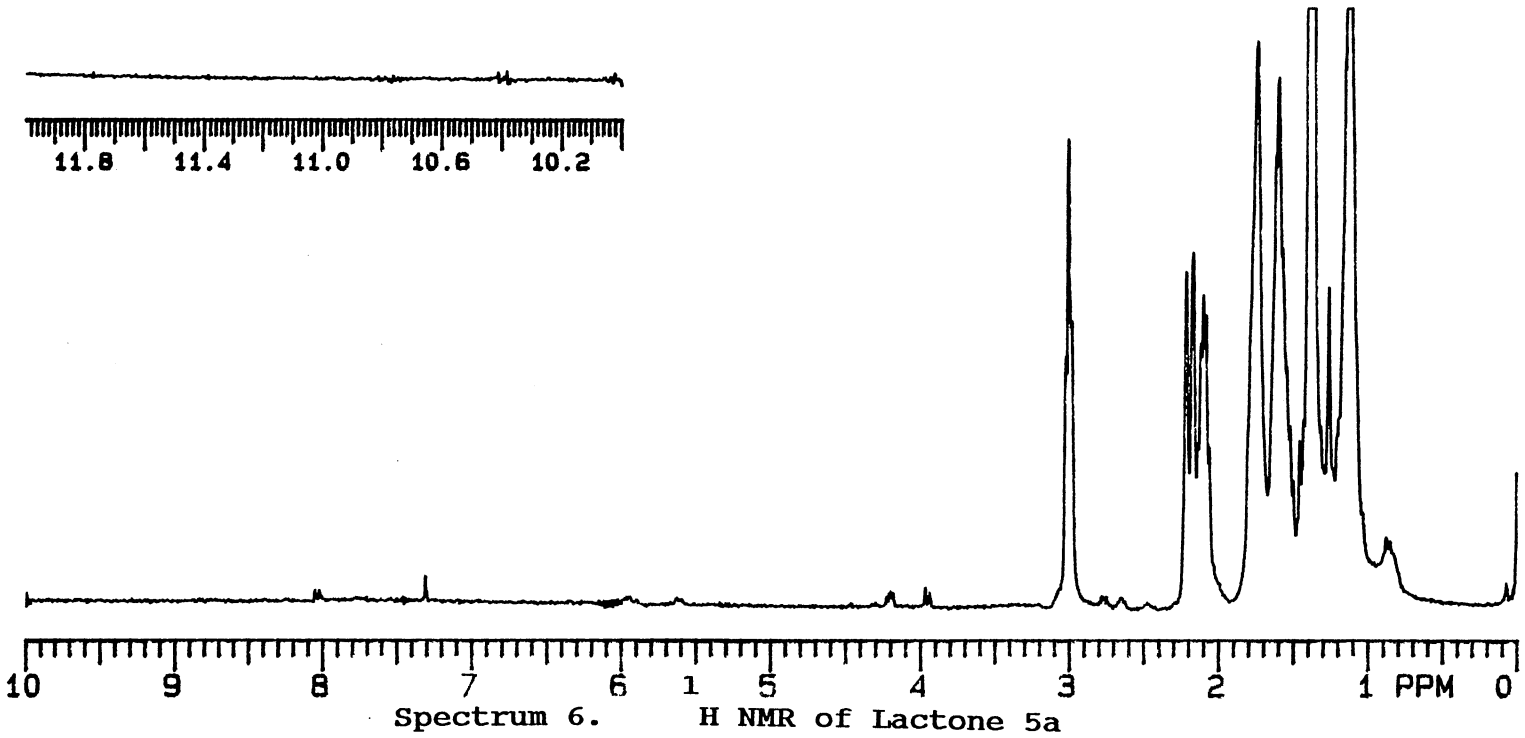
Spectrum 4: H NMR of <u>trans</u>-2-Acetylcyclohexanecarboxylic Acid (3b)



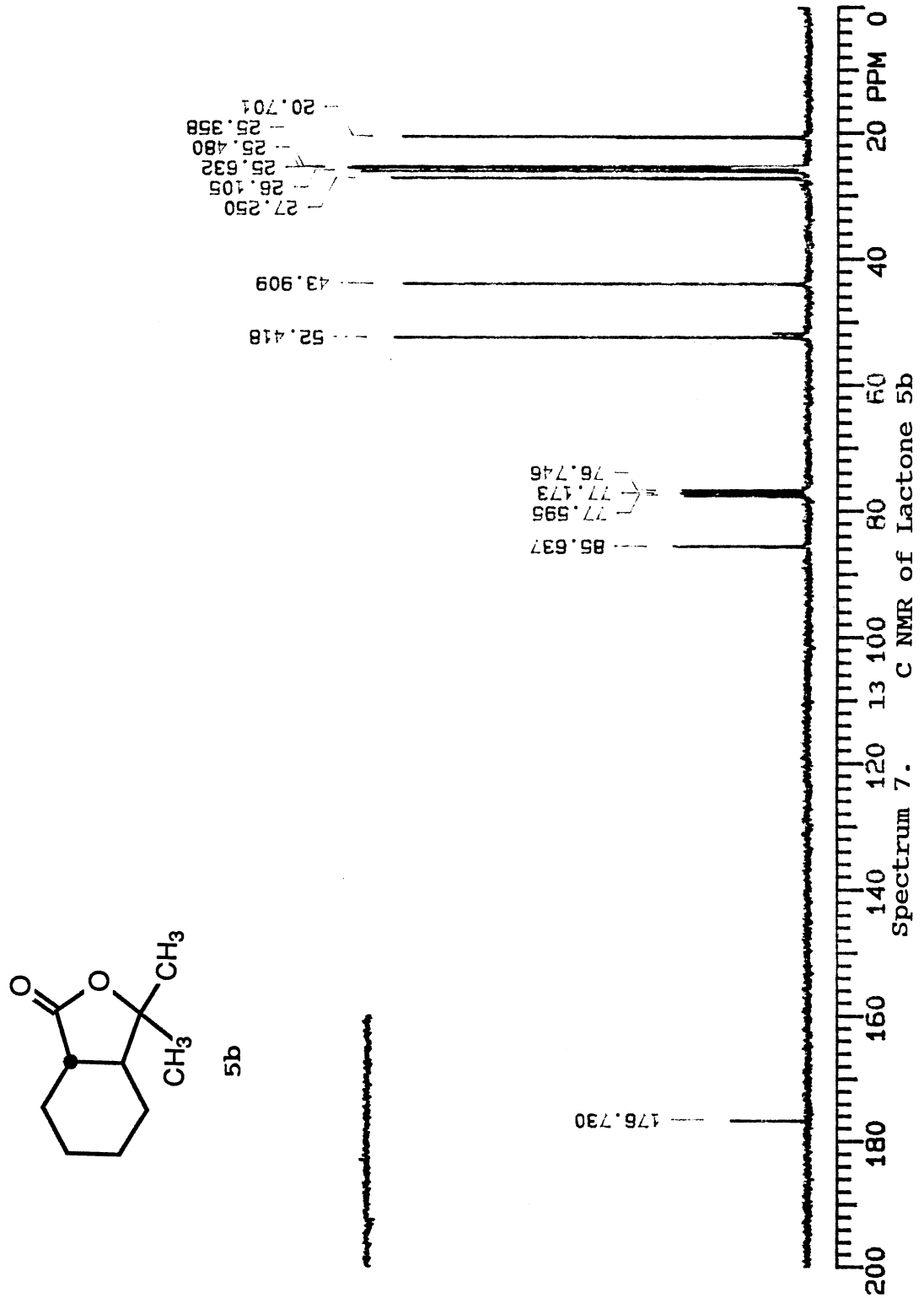
Spectrum 5. C NMR of Lactone 5a



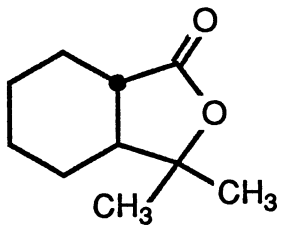
5a



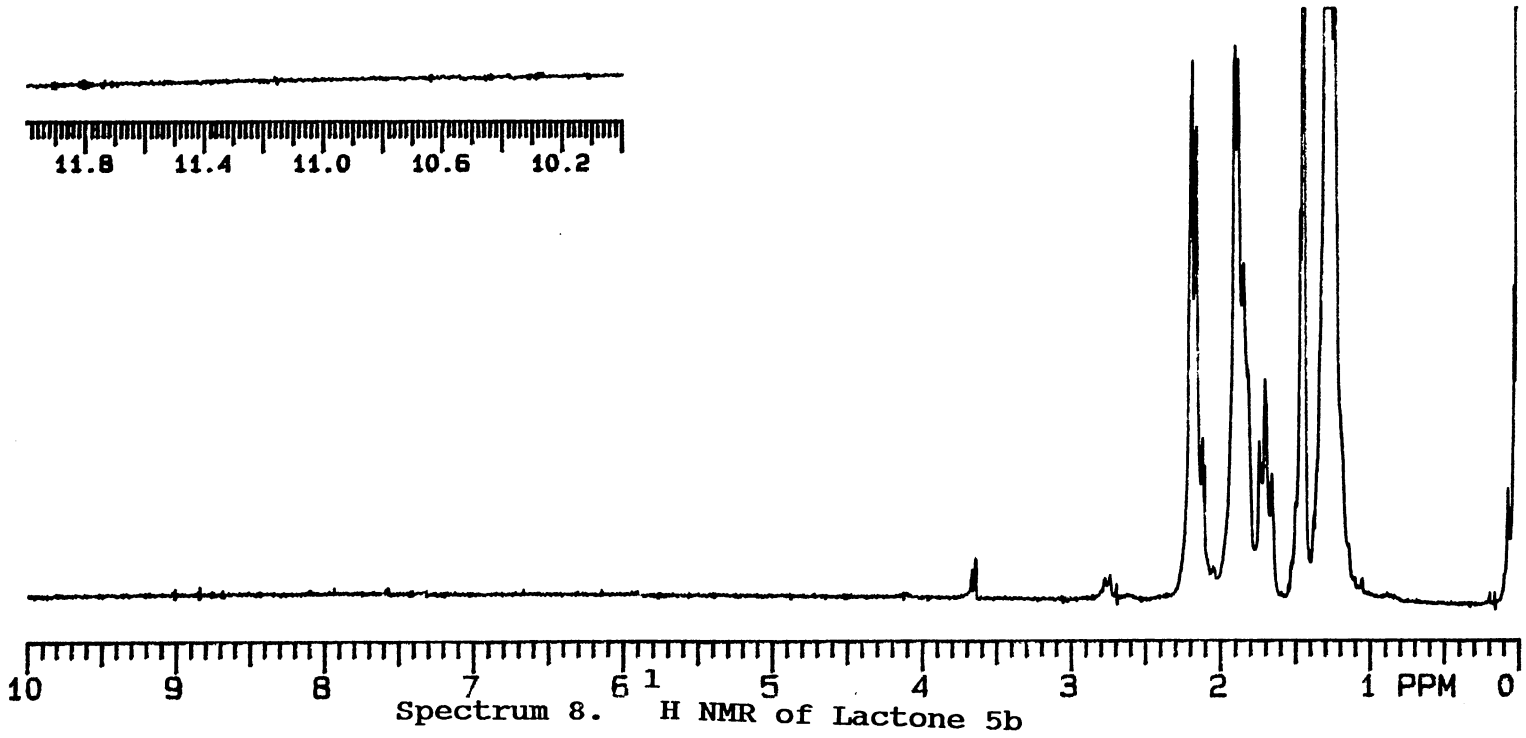
Spectrum 6. H NMR of Lactone 5a


20.701
25.358
25.480
25.632
26.105
27.250
43.909
52.418
76.746
77.173
77.595
85.637
176.730
200
180
160
140
120
100
80
60
40
20
0
PPM
13 C NMR of Lactone 5b
O
O
CH3
CH3
5b

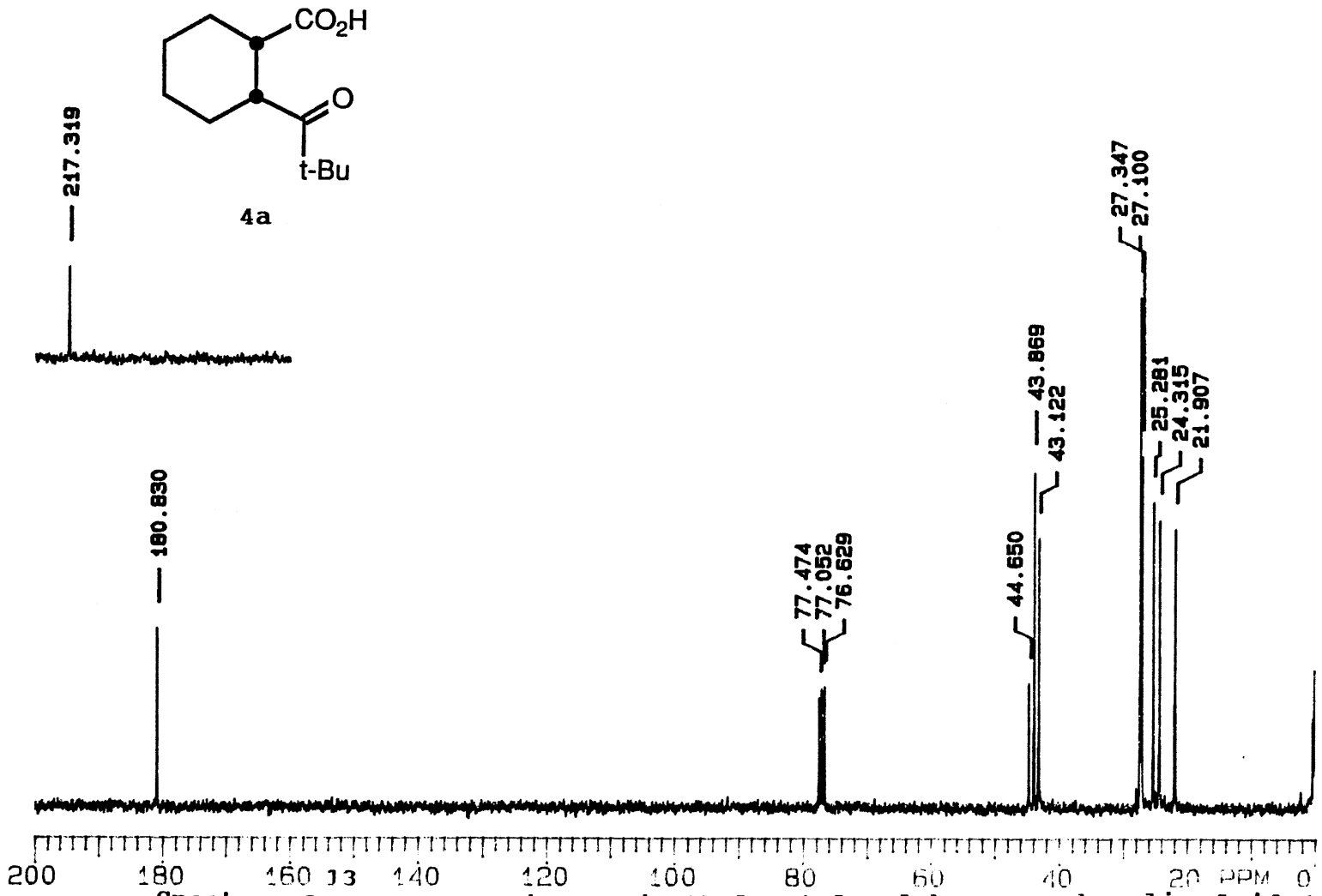
Spectrum 7.



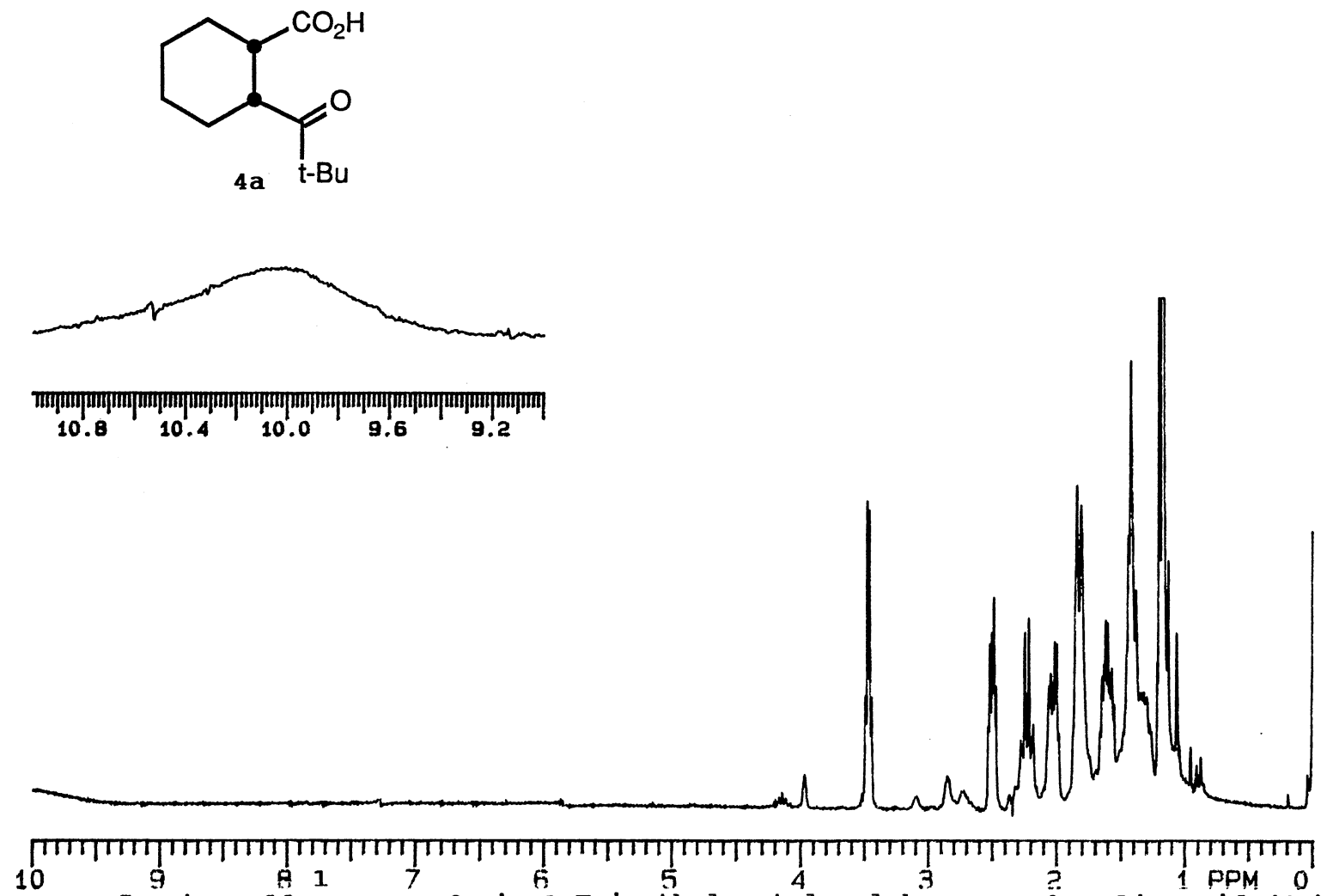
5b



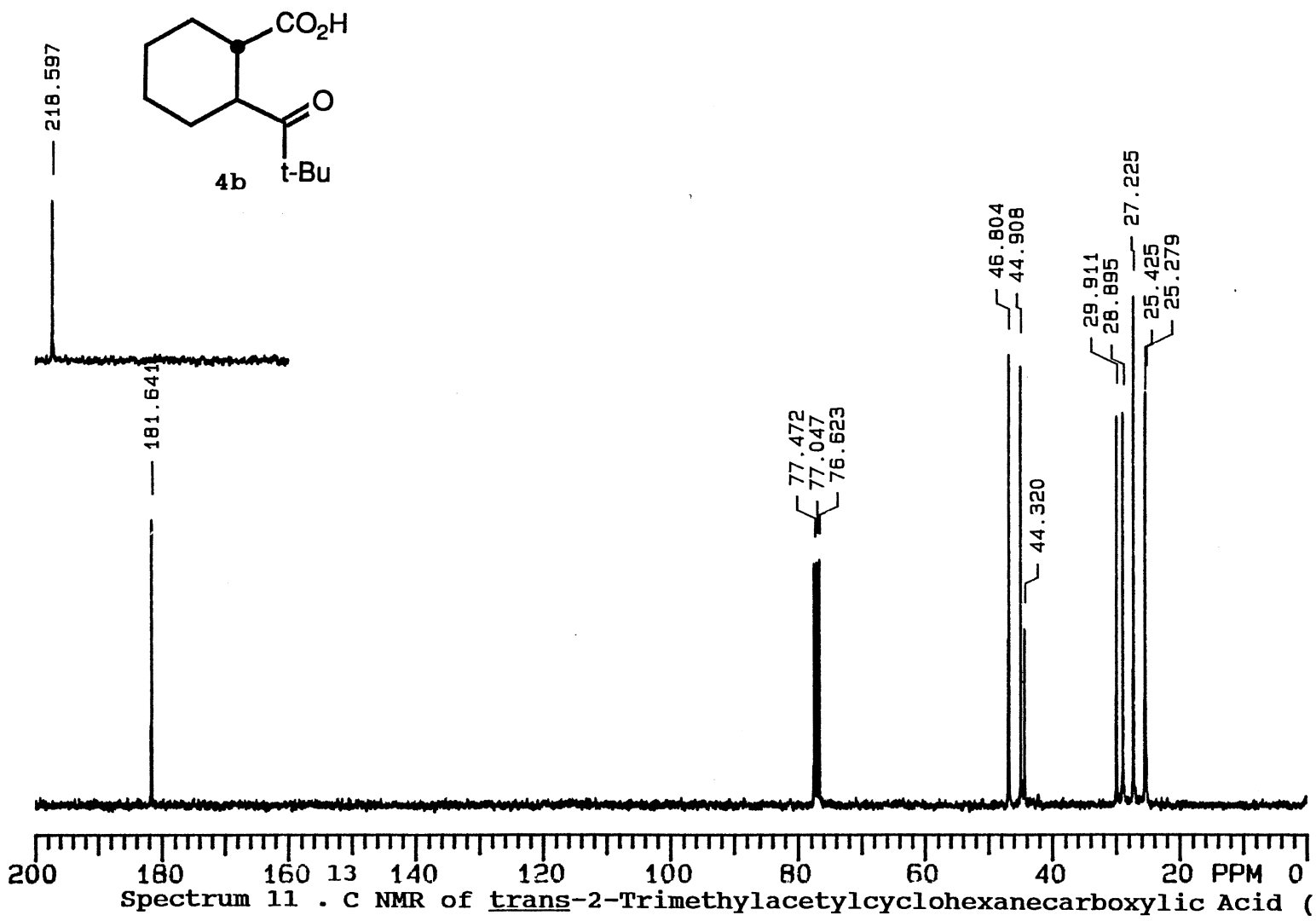
Spectrum 8. ^{1}H NMR of Lactone 5b



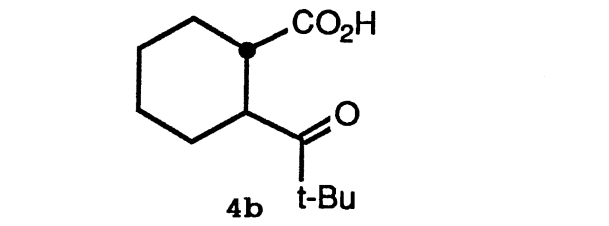
Spectrum 9. C NMR of cis-2-Trimethylacetylcyclohexanecarboxylic Acid (4a)



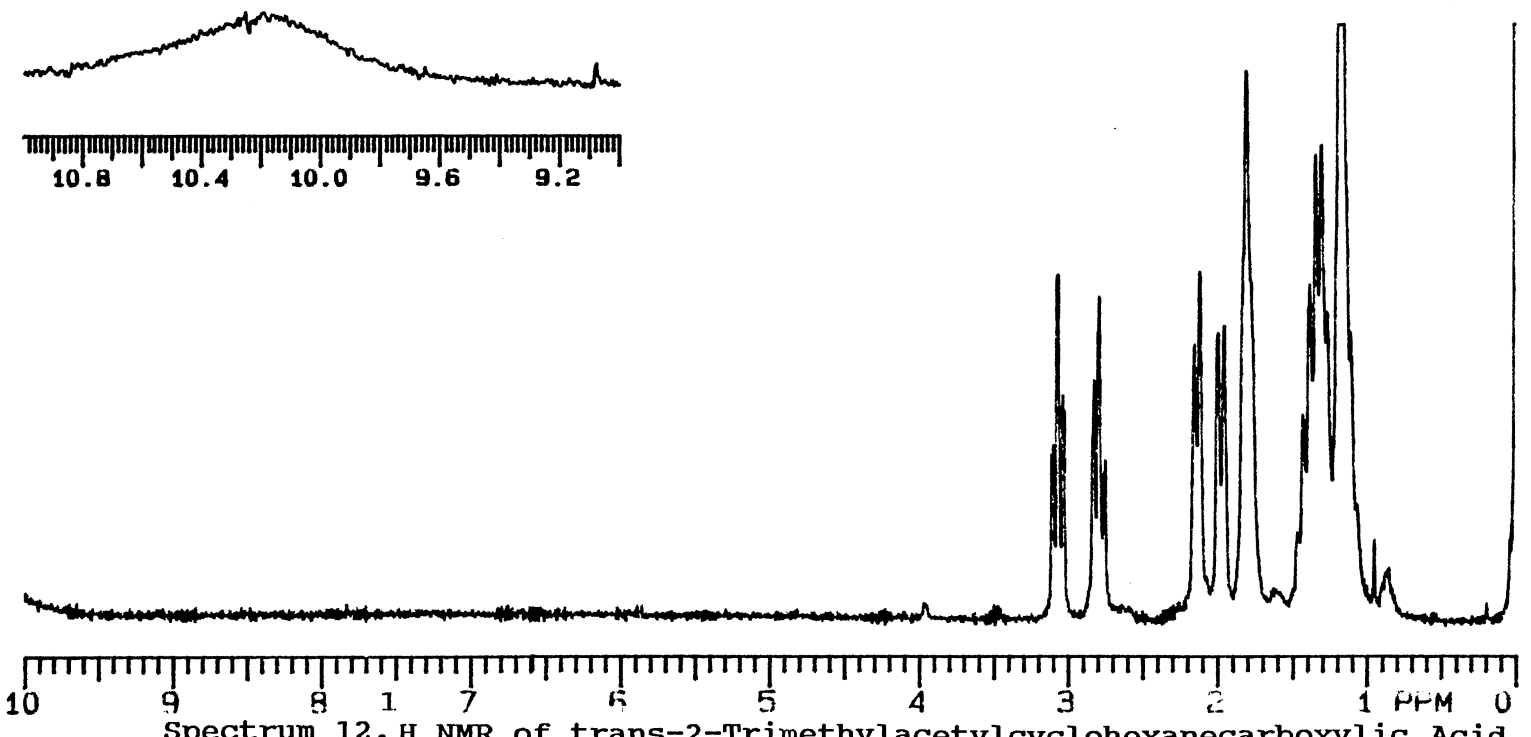
Spectrum 10. H NMR of <u>cis</u>-2-Trimethylacetylcyclohexanecarboxylic Acid (4a)



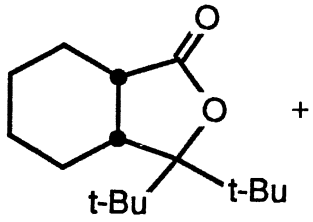
Spectrum 11 . C NMR of <u>trans</u>-2-Trimethylacetylcyclohexanecarboxylic Acid (4b)



4b

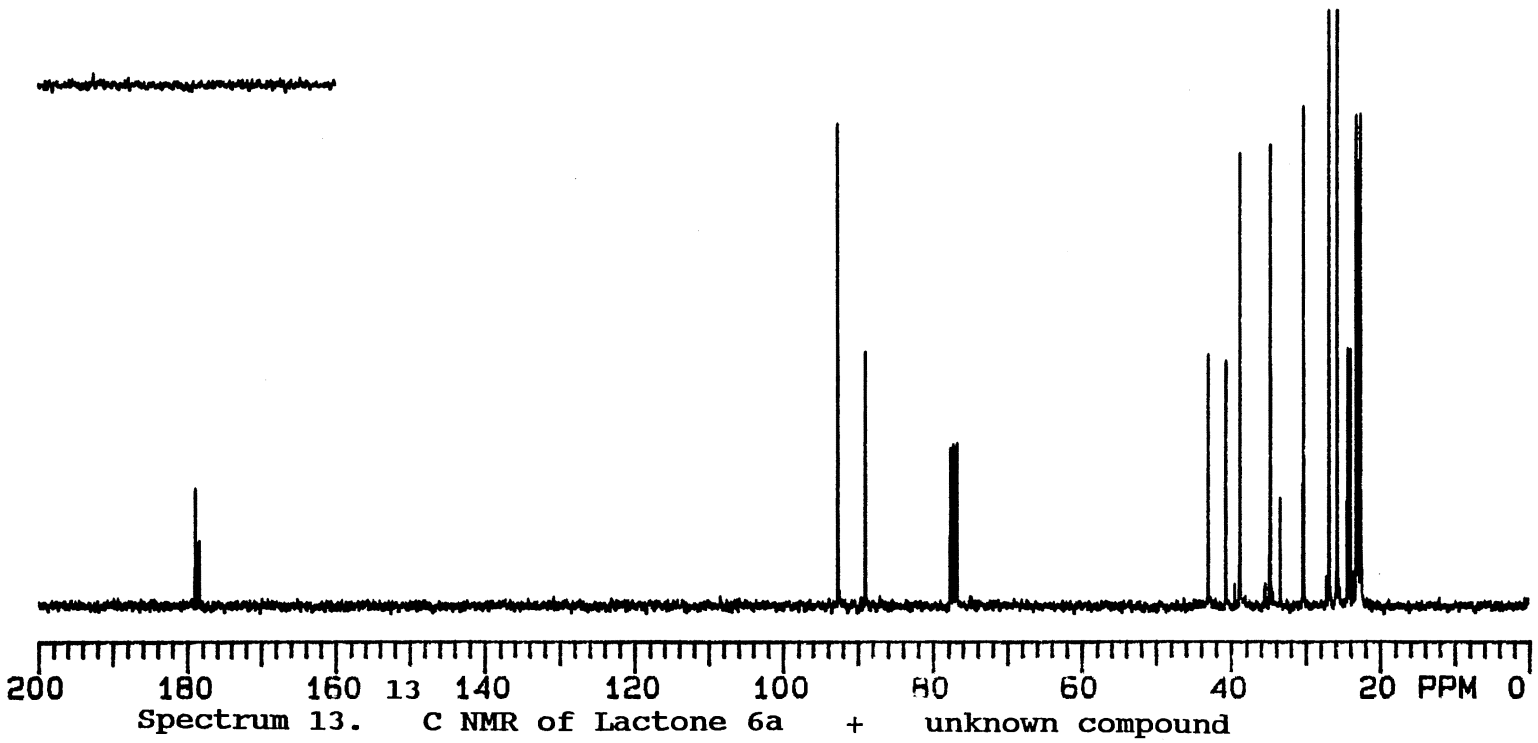


Spectrum 12. H NMR of <u>trans</u>-2-Trimethylacetylcyclohexanecarboxylic Acid (4b)

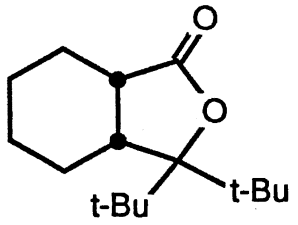


+ unknown compound

6a

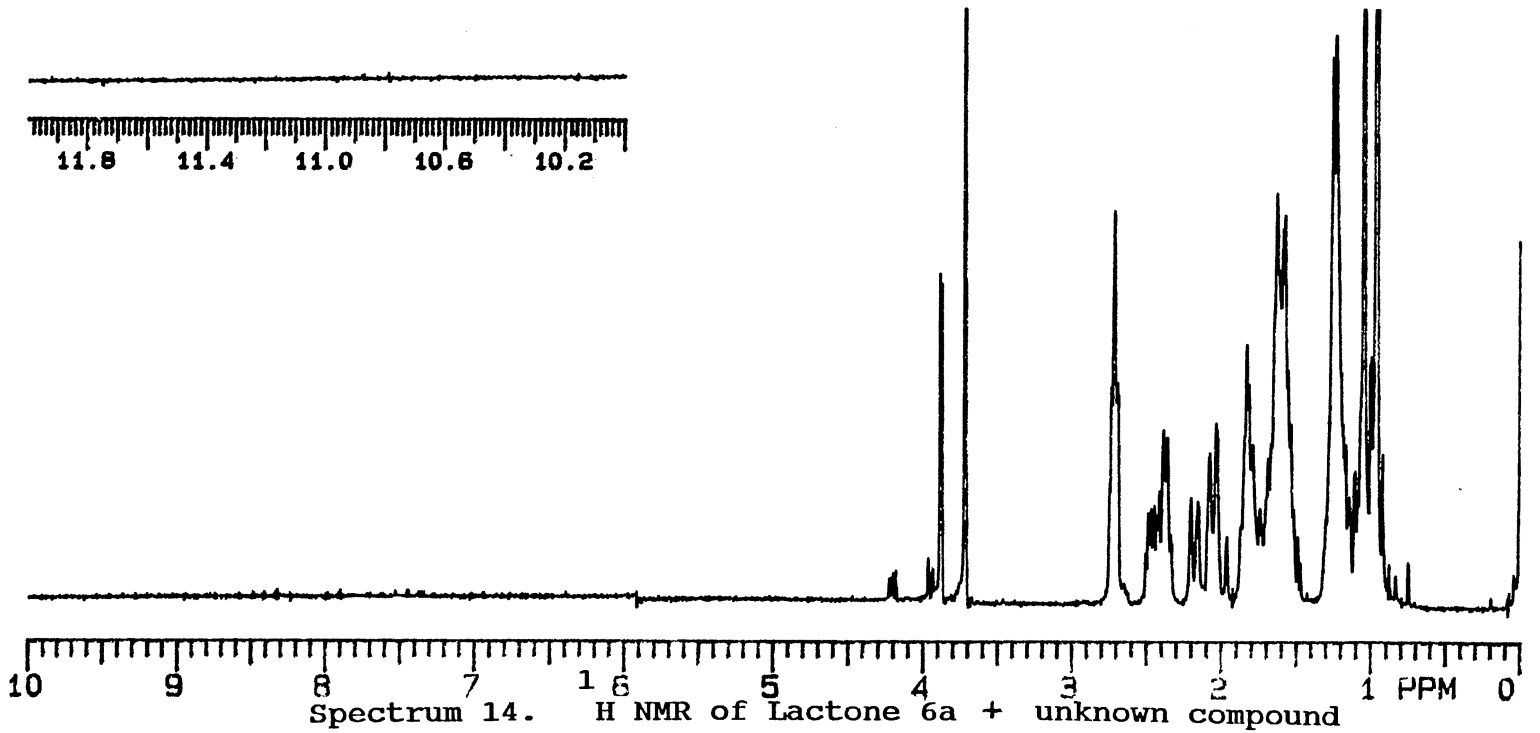


Spectrum 13. C NMR of Lactone 6a + unknown compound

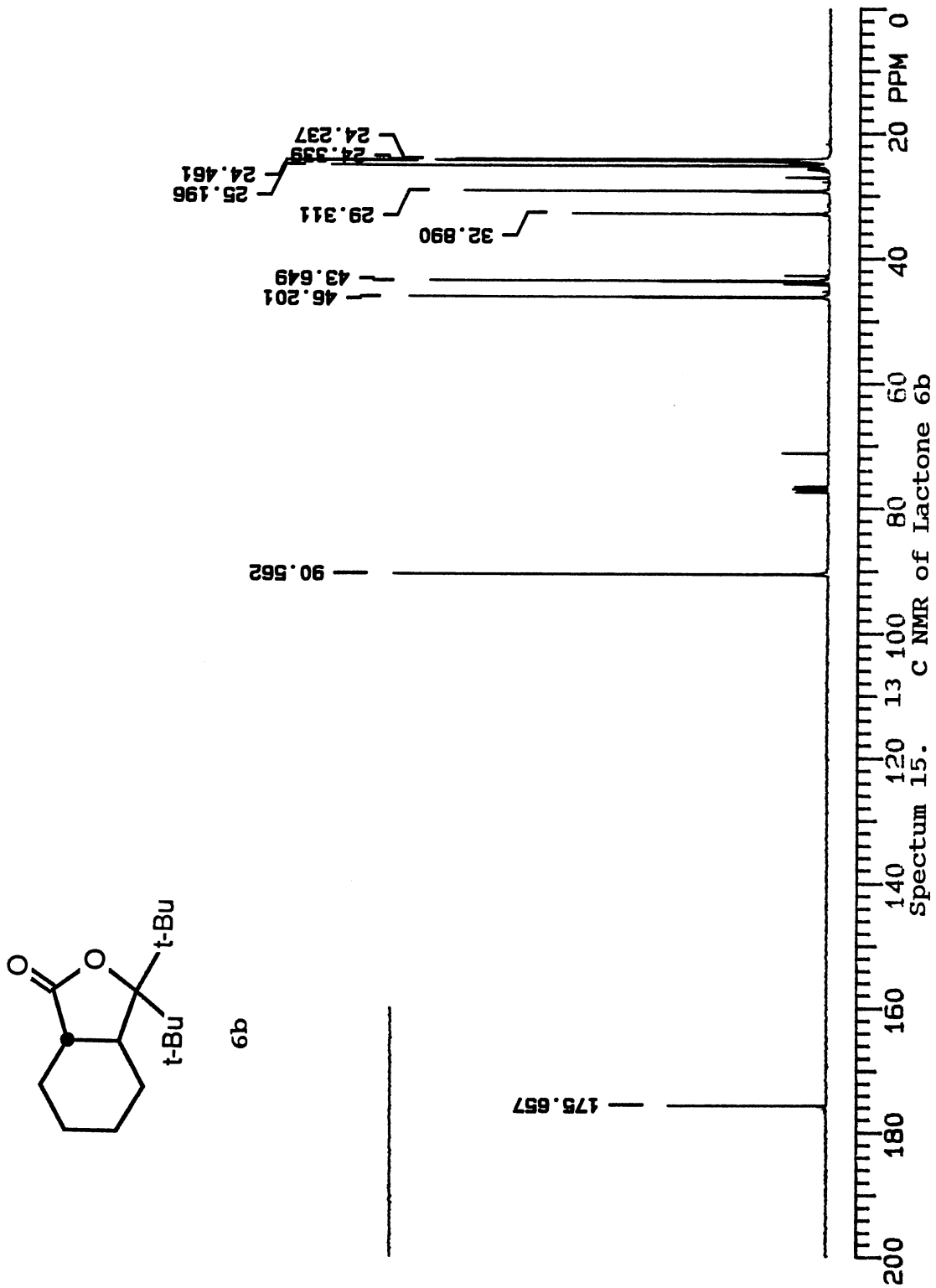


6a

+ unknown compound

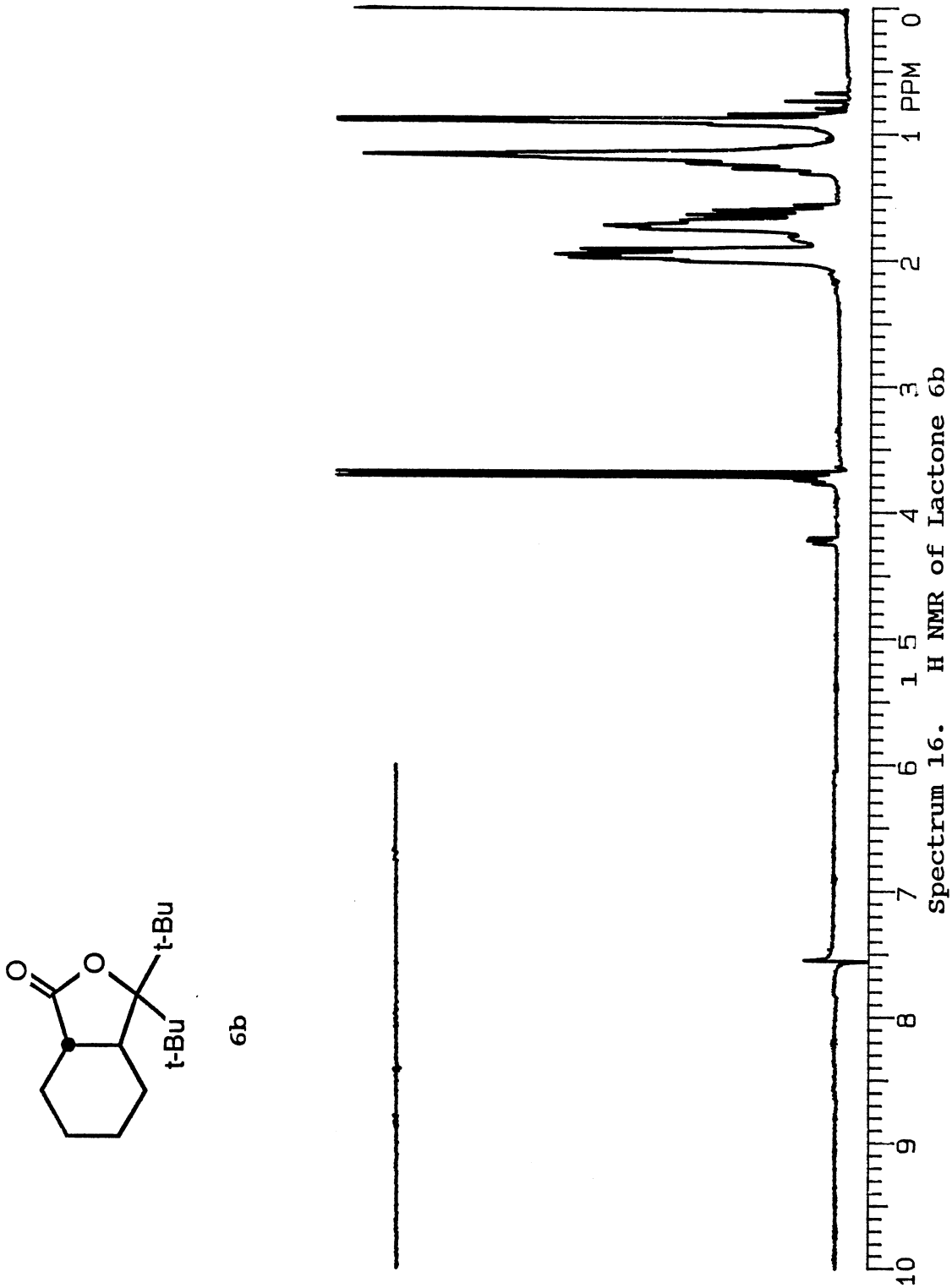


Spectrum 14. H NMR of Lactone 6a + unknown compound



Spectum 15. C NMR of Lactone 6b

6b



Spectrum 16. H NMR of Lactone 6b

VITA

Vasudha Balasubramanian

Candidate for the Degree of

Master of Science

Thesis: REGIOCHEMISTRY OF DIALKYL CADMIUM ADDITION TO

<u>cis</u>- AND <u>trans</u>-HEXAHYDROPHTHALIC ANHYDRIDES

Major Field: Chemistry

Biographical:

Personal Data: Born in Tanjore, India, August 3, 1959, the daughter S.K.Balasubramanian and Vijayalakshmi Balasubramanian.

Education: Graduated from St.Felix High School, Pune, India, in 1975; received the Bachelor of Science degree from Fergusson College, Pune, in 1980, with a major in Chemistry; received the Master of Science degree from Pune University, Pune, in 1982; completed the requirements for the Master of Science degree from Oklahoma State University, in December 1987.

Professional Experience: Graduate Teaching Assistant, Department of Chemistry, Oklahoma State University, 1984 to 1985; 1985 to 1986; 1986 to 1987; Graduate Research Assistant, Department of Chemistry,Oklahoma State University,summer 1985, 1986, 1987.