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Preparation and properties of poly beta-(L-Malic acid) and its benzyl ester :: functional polyesters of potential biomedical importance/

Ronald T. Wojcik
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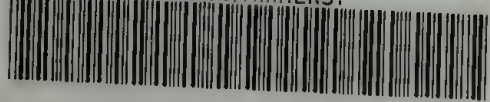
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PREPARATION AND PROPERTIES OF POLY BETA-(L-MALIC ACID)
AND ITS BENZYL ESTER: FUNCTIONAL POLYESTERS
OF POTENTIAL BIOMEDICAL IMPORTANCE

A Dissertation Presented

By

RONALD T. WOJCIK

Submitted to the Graduate School of the
University of Massachusetts in partial fulfillment
of the requirements for the degree of

DOCTOR OF PHILOSOPHY

September 1984

Polymer Science and Engineering

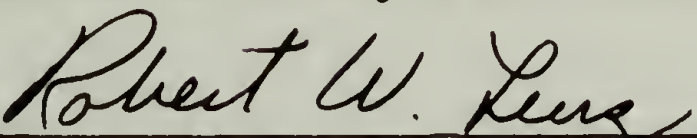
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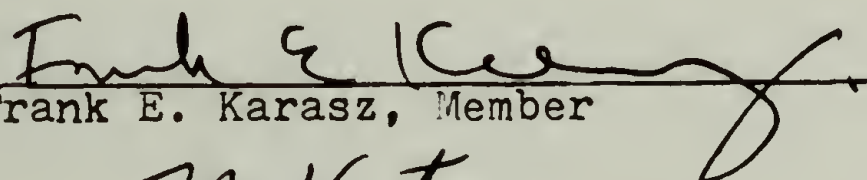
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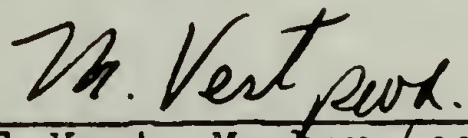
RONALD T. WOJCIK

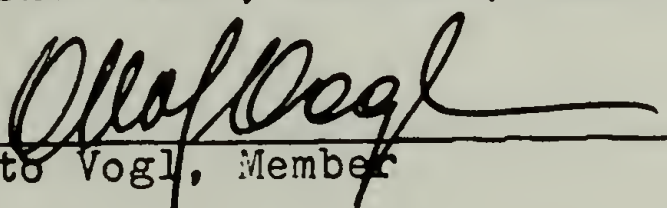
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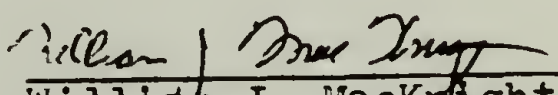

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For my wife and daughters

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ABSTRACT

Polymerization of Poly(L-Malic Acid)

and its Benzyl Esters

(February, 1983)

Ronald T. Wojcik

B.S., Ithaca College

M.S., Polytechnic Institute of New York

Directed by: Professor Robert W. Lenz

The purpose of this research is to prepare and characterize poly(Beta-L-Malic acid) and its benzyl ester derivative from the intermediate optically active malolactone. The polymer prepared from the racemic malolactone will be investigated and its physical properties compared to the optically active poly(malic acid).

The starting compounds for the lactone synthesis will be the racemic and optically active malic acid (L-form). They are readily available in both optical forms and the L-malic acid is a naturally occurring product.

Polymerization of the benzyl ester of the optically active lactone will be carried out using selected anionic and cationic initiators. The reaction mechanism will be studied, with particular emphasis on the stereochemistry of the polymerization reaction and the physical properties of the isolated polymers. Future work will include the determination of the effect of stereoregularity on

biological activity, biocompatibility and biodegradability of the polymers.

The synthetic goals of the thesis are to obtain polymers having greater than 90% isotactic configuration (corresponding to greater than 90% optical purity of the lactone) and having a molecular weight in the range 10,000-20,000. The polymerization conditions, specifically the temperature, solvent and monomer/initiator concentrations ratio, will be varied to determine the effects on the polymerization kinetics and ultimately the molecular weights.

Modifications of the polymerization conditions affected overall yield of isolated polymer. However, they seem to cause no effect on the molecular weight of the polymer. Varying the initiator, polymerization temperature, and solvent gave polymers with different molecular weight distributions (MWD) and yields but had no effect on the number average molecular weight (\overline{M}_n). Differential scanning calorimetry and optical rotary dispersion spectroscopy demonstrated that the polymer possesses excellent stereoregularity.

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C H A P T E R I

INTRODUCTION

This dissertation describes the synthesis and characterization of racemic and optically active poly(malic acid) and its benzyl ester derivative from the intermediate malolactone. This work is part of an extensive effort in this laboratory in the general area of biopolymer drugs and polymer drug carriers.

Section I discusses the concept of polymeric pharmaceuticals.

Section II describes various methods of preparing polymers containing active pharmaceuticals and properties of these materials.

Section III discusses the assumptions justifying the preparation and biological study of poly(malic acid).

Section IV discusses the biodegradability of polyesters.

Section V discusses the influences on biological activity due to the stereochemical configuration of the repeat unit.

Section VI describes the preparation of poly(malic acid).

I. Polymeric Drugs and Long Term Release of Biological Agents - General Review

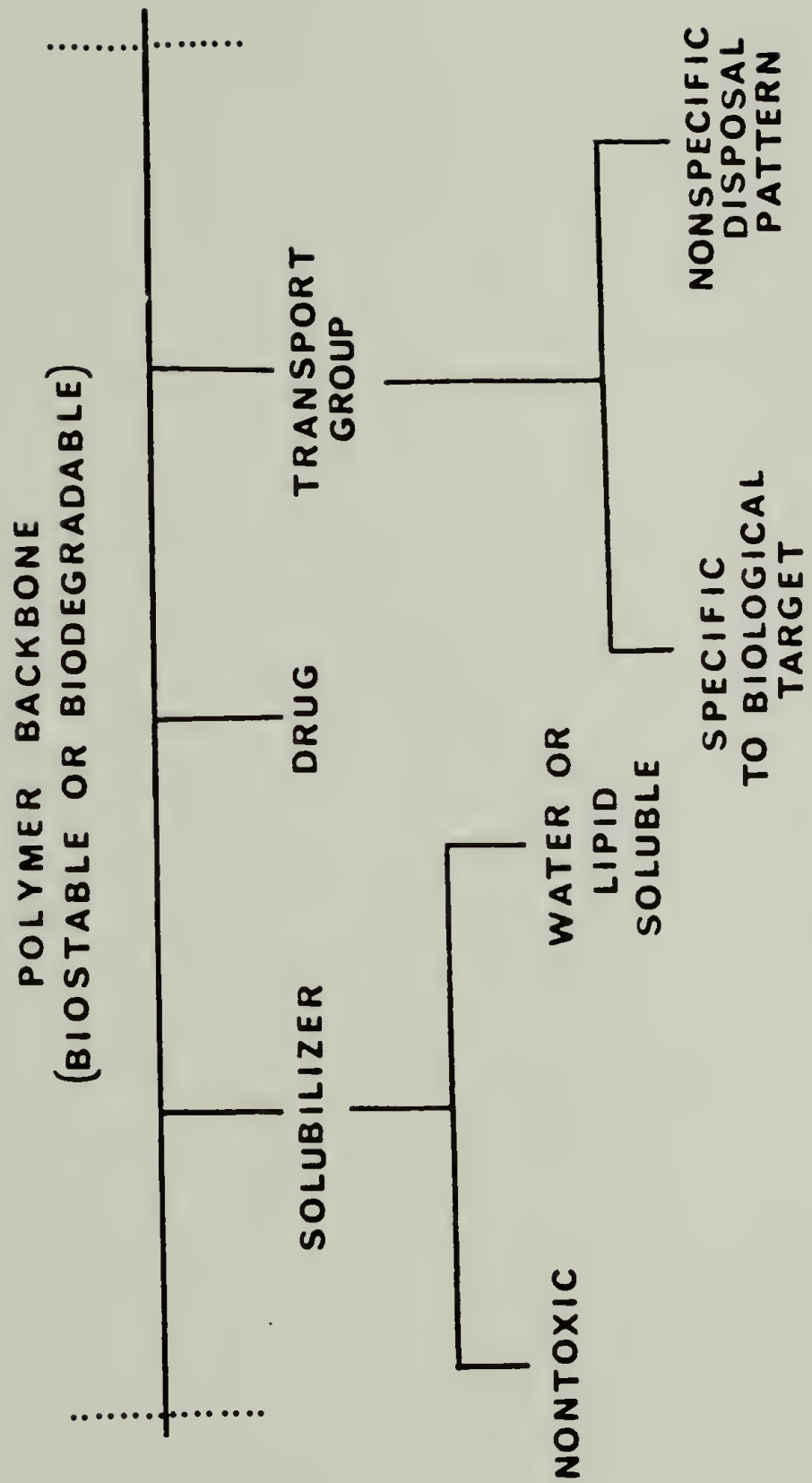
Pharmacologically active polymers and polymers containing pharmacologically active units, both synthesized

in the polymer backbone and attached to the main polymer chain, have been receiving a great deal of attention in recent years, which is evident by the number of recent publications and symposia related to this topic.¹⁻¹⁰ Ringsdorf¹¹ has defined his conception of an "ideal" polymeric drug. His model consists of a multicomponent polymer built up from different functional units providing the desired biological properties to the entire molecule. A schematic diagram illustrating this model is given in Fig. 1.

The significant features of this diagram show the polymer backbone itself may be made biostable or biodegradable. The build-up of units along the backbone can be accomplished by known chemical techniques. The "solubilizer" unit makes the molecule water or lipid soluble and reduces the toxicity. The "drug" must be attached to the backbone or may be synthesized into the polymeric backbone without influencing its biological activity. Finally, the "transporting" moiety can be a specific group directing the polymer to the desired target.

Researchers have taken the various parts of the Ringsdorf model and incorporated his theories into their research efforts. By complexing a specific drug with a polymer, drugs otherwise unable to diffuse across a cell membrane will carry it into the cell along with the polymer molecule.¹² The use

Figure 1. Ringsdorf's model of an "ideal" polymeric drug.



of liposomes and of DNA-complexes as carriers for drugs¹³
has been demonstrated in the literature.

An additional benefit of using polymers as drug carriers can be derived from the possibility of modifying the polymer structure to prepare a number of different polymeric drugs with a variety of activities and cell¹⁴ distribution patterns. This goal may be accomplished by known techniques, such as copolymerization, crosslinking, molecular weight distribution and tacticity, etc., and is in sharp contrast to low molecular weight drugs which often¹⁵ lose activity completely with minor changes in structure. Changes in polymer structure and size can affect the ability to localize the drug and achieve the necessary required concentrations of drugs in the diseased areas.

II. Research Efforts in Polymer Drug Systems

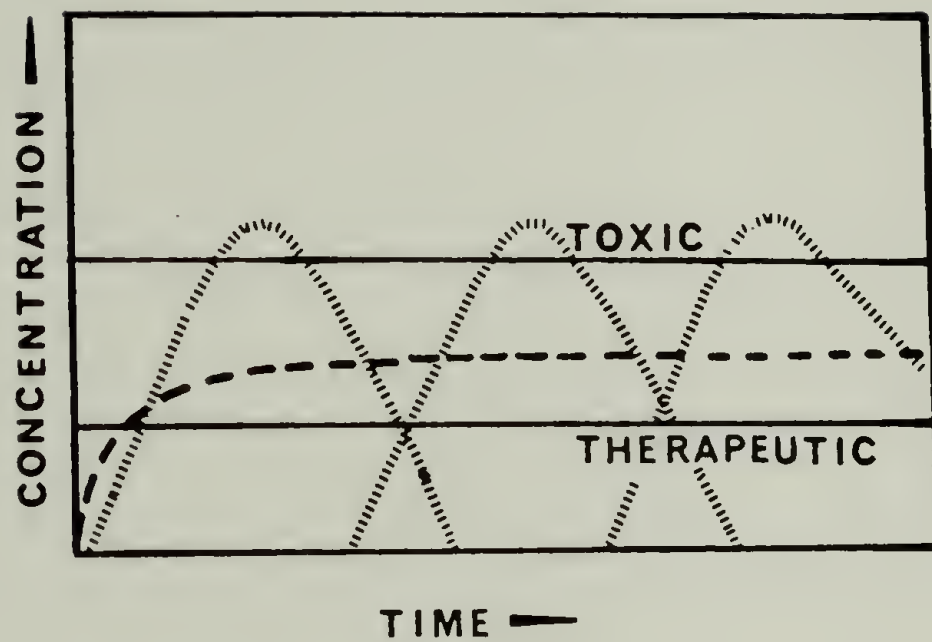
The majority of work in the area of polymeric drugs has centered about the development of polymers which provide sustained release of drugs, herbicides, and insecticides, at the desired rate and with minimal effects on the environment. The present method of drug administration, oral or injection, requires that drugs be administered at periodic intervals, in order to maintain the minimum concentration of active agent in the body, minimum effective level. Periodic administration of the drug causes problems, specifically involving drug concentration levels in the body.

Alternating high and low levels of the drugs, rather than a constant concentration, are usually found in the host. These fluctuations in drug concentration lead to undesirable side effects. The excess drug can come into contact with non-diseased parts of the body, causing common side effects. If the drug concentration in the body is low, there is not enough drug to provide the desired therapeutic response in the host.

Fig. 2 illustrates, in schematic terms, the previously described finding, that drug concentration varies with time, depending on the administration method.

Attempts to solve the problems of drug concentration variation have been unsuccessful. When a low molecular weight drug is implanted at the diseased site, it will migrate throughout the body, and we will observe drug loss by deterioration or excretion. Fig. 3 shows the possible drug pathways in the body. Clearly, a drug system which releases the active agent at a constant and controlled rate over the desired time interval would eliminate the problem of drug wastage, with few side effects, and be a definite improvement over the presently used methods of drug administration. The Ringsdorf model theorized that a drug can be targeted, localized, and released following a defined rate, and would be the one step closer to the "ideal" drug delivery system. A number of differing methods for controlling the release rate of drugs have emerged in recent

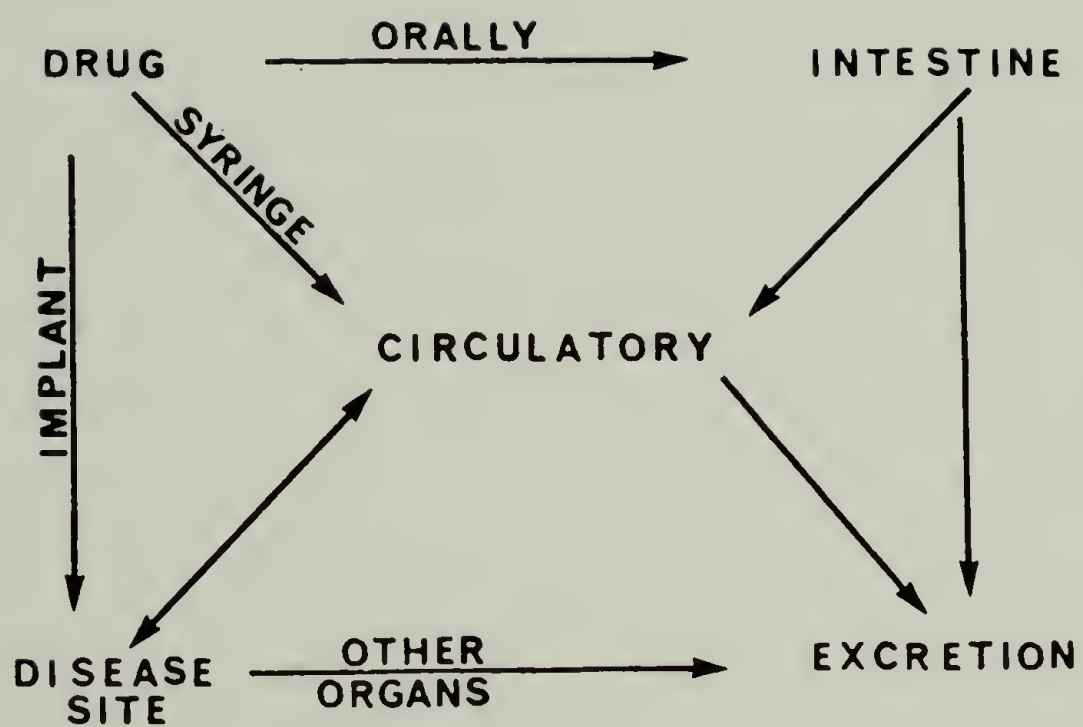
Figure 2. Schematic diagram showing drug concentration versus time for an ideal drug delivery device and a conventional drug delivery device.



ideal - - - - -

conventional

Figure 3. Drug pathways in the body.



years. All of them have the similarity of incorporating polymers as a vital part of the mechanism for controlling the drug release. The following sections explain these ongoing research efforts.

A. Membrane Encapsulated Reservoir Device. Using this method, the active drug or core material is encapsulated by a permeable polymeric membrane, which controls the release rate of the drug. The drug core material may be dispersed as a homogeneous suspension or solution within the polymeric membrane in order to maintain a constant rate of drug release. The following Fig. 4 illustrates a membrane encapsulated reservoir device.

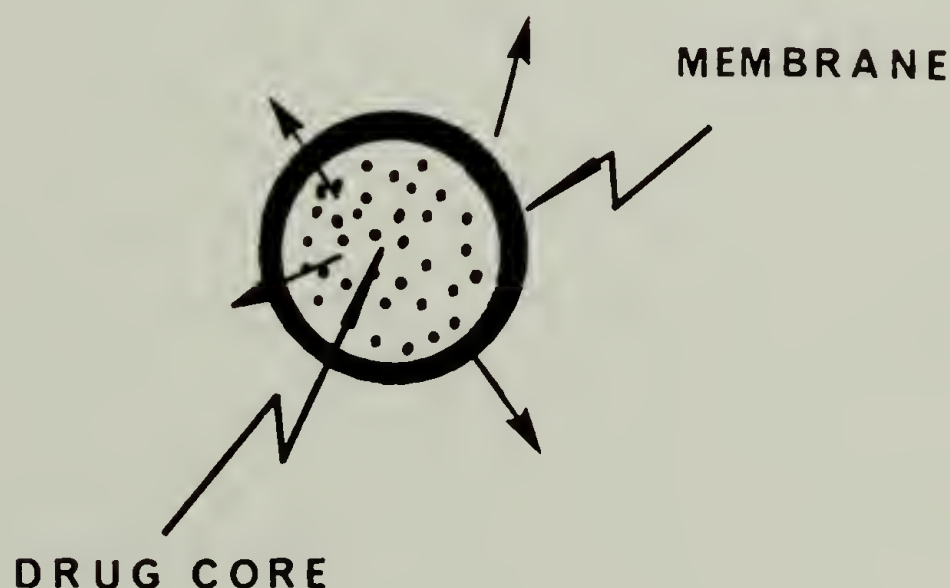


Figure 4. Membrane Encapsulated Reservoir Device.

The release rate will follow first order kinetics and decay, more or less exponentially with time, as the agent activity in the reservoir decreases. If a membrane is designed so that the drug concentration is saturated in the membrane, zero order kinetics may be achieved and concentration of drug versus time will be constant. These devices may be made in many sizes, from microcapsules to macrocapsules (microns to millimeters).

B. Matrix Devices (Diffusional). Matrix devices are systems in which the active agent is not encapsulated per se, as previously described, but rather dispersed throughout a polymeric carrier. The agent will migrate out from the device and into the environment, and the rate will depend on the rate of diffusion of the agent through the matrix as shown in the following Fig. 5.

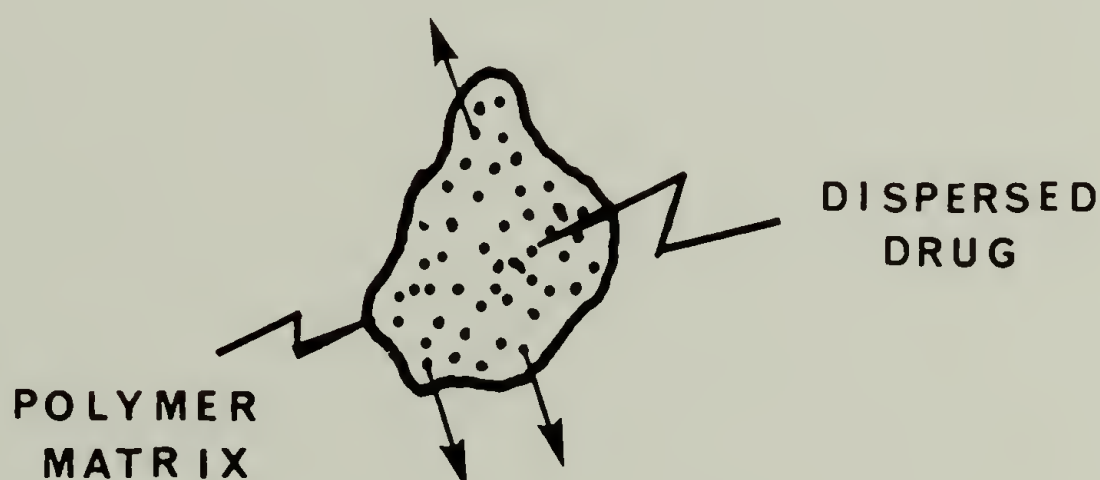


Figure 5. Matrix Device.

For this example, the diffusion rate is not zero order, so that the concentration of drug will vary with time.

In a matrix device, the active drug can diffuse through the polymer on its own, at a reasonable rate, or, it may require some external agent, i.e. water, to penetrate and swell the device to facilitate the diffusion. This environmental agent may function to physically unbind the drug from the polymer matrix, or, as a simple plasticizer, to aid in diffusion so as to increase the rate.

C. Erodible Devices. Erodible device carriers may be used as devices for the controlled release of biologically active materials. One of the devices consists of functional polymers, either linear or crosslinked, with the active agent linked by a covalent bond to the polymer backbone as pendant groups. As the linkages connecting the active agents to the polymer are cleared, for example by hydrolysis, the drugs are released, leaving behind the polymer backbone.

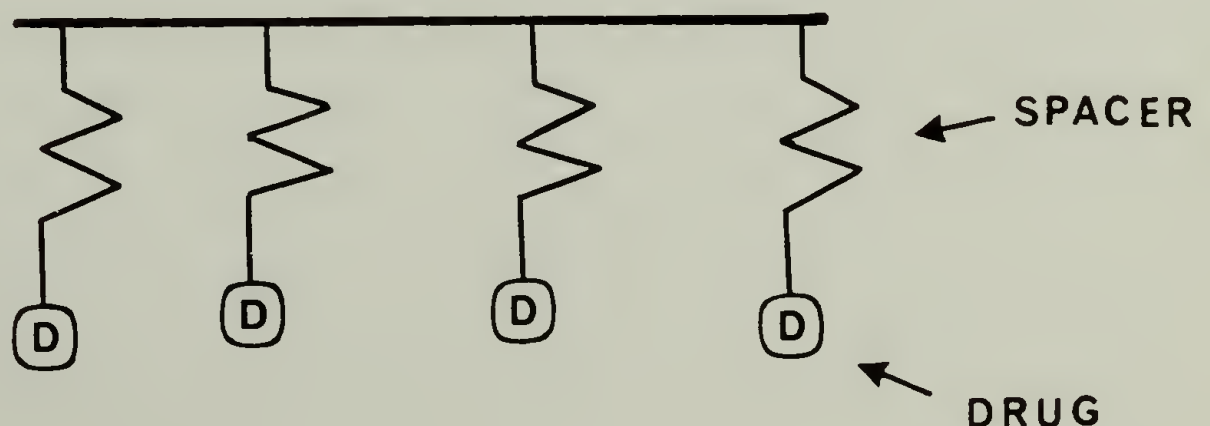


Figure 6a. Erodible Polymer Carriers

A second example of an erodible device is one which incorporates the active agent into the backbone of a polymer chain. As the linkages holding the chain together are broken, the active agent is freed and enters the environment.



Figure 6b. Erodible Polymer Carriers.

Another similar system consists of the active agent dispersed throughout an erodible polymer matrix. As the polymer erodes, the drug is released into the surroundings.

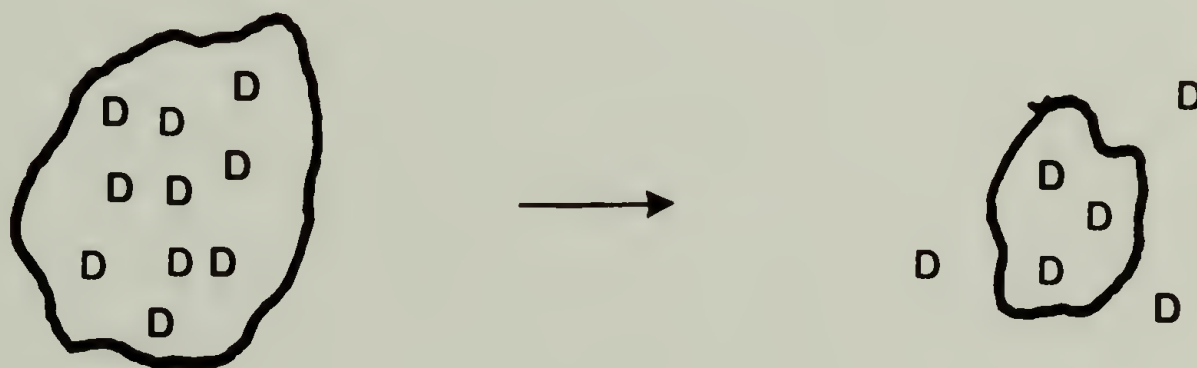


Figure 6c. Erodible Polymer Device.

The latter two examples of controlled release devices, the drug incorporated into the main chain and the erodible

matrix, degrade in the body as the active agent is released. This behavior has the obvious advantage of leaving no residual polymer carrier in the body, thereby, eliminating the problems associated with retrieving the polymer carrier. The erosion products must be non-toxic and pose no health or environmental hazard of their own.

All of the above mentioned systems have been investigated to some extent and many examples of these systems are cited in the literature.¹⁶ As an introduction to this thesis, I have described the different devices which may be used to deliver drugs by methods other than the conventional oral or injection. I will now describe additional various classes to which the general class of polymer drug may be divided.

The first class of polymer drug which may be considered is that in which the pharmacological effect is due entirely to the macromolecular nature of the drug. Neither the monomer nor a low molecular weight analog exhibits biological effects. Disintegration of the polymer via biological degradation leads to complete loss of activity. In a number of cases, the polymers are cationic or anionic polyelectrolytes and they possess a wide range of biological activity. Two of the most widely studied polyanions are the copolymers of divinyl ether and maleic anhydride (pyran copolymer-¹⁷ DIVEMA) in which there has been partial hydrolysis of the

anhydride moiety to yield the anion¹⁸ and the complex of poly (inosinic acid) and poly(cytidylic acid) (poly I-poly C complex).¹⁹ It appears that for polyanions to show biological activity they must have a high density of pendant carboxylate groups on the polymer backbone. Three important related activities which polyanions possess are the abilities to induce interferon production, stunt tumor growth, and inhibit viral infection.

As was previously mentioned, a second type of polymer drug is that in which the biologically active group is incorporated into the polymeric main chain. This structure requires the drug to possess bifunctionality to undergo either homopolymerization or copolymerization. The biological activity of a polymer requires either one of two action modes: either the polymer itself, being biologically active, requires no degradation for biological activity or the polymer must degrade to show activity. There are numerous examples of these types of polymeric drugs in the literature.²⁰ Some specific examples include the work of Tirrell²¹ and Diets²² on the preparation of 4-, 5-vinyl-salicylate acid derivatives and bithionol polycarbonate.

A third group of polymer drugs are these in which biologically active groups are attached to the polymer main chain. The drug may be attached directly as a pendant

group or with spacers of specified lengths. Here again, there are two modes for biological activity: the polymer possesses all of the activity and no degradation is necessary, or, the polymer must release the pendant group to show activity.

The final class of polymer drugs is that in which the polymer and drug are complexed with each other either ionically or non-ionically.²³

After this introduction concerning research efforts to prepare drugs and drug delivery devices, I hope to have convinced the reader that there are existing needs which justify research and development of new techniques in drug delivery. One of the most compelling arguments, not specifically discussed, involves the development of new anti-cancer drugs. Since these drugs are extremely toxic to normal cells, their activity on the disease can only be accomplished by more rapid metabolism by the cancer cells to minimize dangerous side effects.²⁴ The drug must be effective within a narrow limit of time and concentration. Conventional methods for drug delivery cannot fulfill the requirements for using new anti-cancer drugs.

III. Preparation and Properties of Polymeric Pharmaceuticals

After this brief introduction, I will describe the objective of this research. As previously described, there

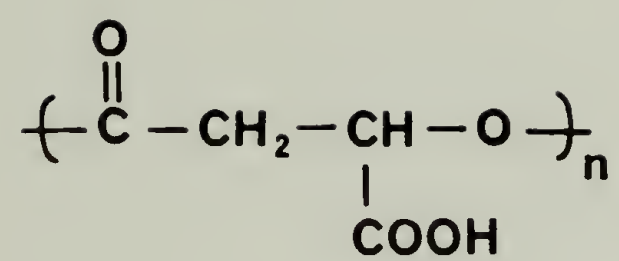
are many synthetic polymers used as biopolymer drugs and polymer drug carriers. However, the use of these polymers may cause serious problems due to the potential difficulties in the metabolism and elimination from the body of the degradation products by normal metabolic pathways. In most cases it is unknown if degradation products are non-toxic to the body. Moreover, at times the nature of the degradation products is unknown. Therefore, the purpose of this research is to prepare a polymer which can be used either as a biopolymer drug or drug carrier system, and, after its biological function is complete, the polymer will degrade to a non-toxic low molecular weight residue capable of elimination. This concept has not been synthetically attempted except in the development of degradable coatings for sustained drug release.

The polymer chosen for preparation and study is poly(malic acid) and specifically poly(L-malic acid). The polymer structure is shown in Fig. 7.

This polymer is a polyester with a pendant carboxylic acid group, which impart solubility on conversion to the carboxylate ion. The reasons for the choice of this polymer for preparation and study as a polymer drug are as follows:

1) polyesters show good biocompatibility and examples are poly(glycolic acid),²⁵ poly(lactic acid),²⁶ and copolymers of poly(lactic acid-co-glycolic acid)²⁷

Figure 7. Poly(L-malic acid).



2) poly(glycolic acid),²⁸ poly(lactic acid),²⁹ and their copolymers,³⁰ as well as poly(beta-hydroxy butyrate)³¹ are reported to be biodegradable in the body;

3) pendant carboxylic acids on polymers can be used to impart water solubility or attach drugs containing alcohol or amine groups;³²

4) polyanions from carboxyl-containing polymers can be pharmacologically active themselves;³³

5) the presence of an asymmetric carbon atom in the repeat unit provides an opportunity to study the effects of chirality on biological activity.

IV. Polyester Biodegradability

Beck and co-workers³⁴ studied the biodegradability of poly(glycolic acid), poly(lactic acid) and their copolymers. They found that these polymers would hydrolyze at the surface. The reaction followed zero order kinetics for the polymer. Other synthetic polymers show little or no biological degradation.³⁵

V. Asymmetric Carbon Atom

There are few studies where stereochemical configuration of the repeat unit in the polymer has an influence on biological activity. Katchalski and coworkers³⁶ found inconclusive results when they correlated anti-bacterial activity to changes in configuration of amino acid copolymers.

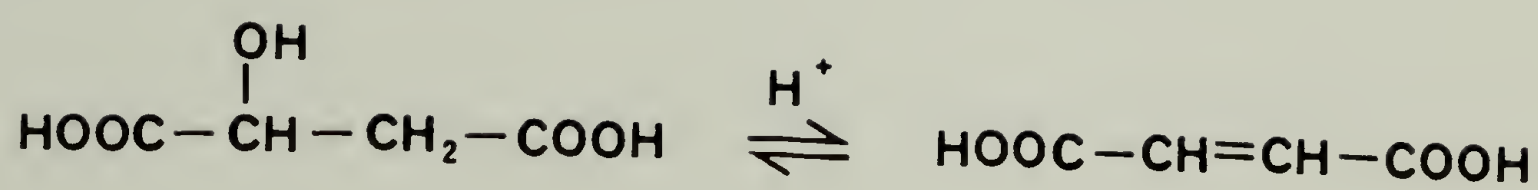
VI. Poly(Malic Acid) Preparation

Synthesizing poly(malic acid) and poly(L-malic acid) directly from malic acid would be very difficult, if not an impossible assignment. It is possible to envision a polymer prepared by self-esterfication of the acid. However, the acid will rapidly undergo dehydration to yield maleic or fumaric acid shown in Fig. 8.³⁷

The normal synthetic routes, when applied to converting malic acid to form polymer, would, in fact, generally lead to the conversion of the hydroxy acid to maleic or fumaric acid and not the polyester.

The polyester can be prepared by ionic polymerization of the corresponding lactone monomer. A survey of the literature shows that poly(beta-malolactone benzyl ester) and poly(malic acid) have been reported by Vert and Lenz.³⁸ They quoted yields ranging from 10-55% of polymer having a molecular weight of 3000-8000. They used as a starting material bromosuccinic acid, formed the beta lactone of the corresponding benzyl ester, polymerized the lactone and then hydrogenated the polymer with no backbone degradation to cleave the benzyl ester to the carboxylic acid.³⁹ They prepared the benzyl ester to eliminate potential problems associated with the ionic polymerization methods.⁴⁰ The carboxylic group could react with the initiator or undergo chain transfer and/or termination.⁴¹

Figure 8. Dehydration reaction of malic acid to yield maleic or fumaric acid.



After careful review of the literature, I decided that I could not use this synthetic route to prepare the optically active malolactone because it was believed that L-bromosuccinic acid will undergo racemization⁴² during the lactonization step. Justification for this theory will be given later in Chapter II, specifically the section on the preparation of lactone from salts of Beta-haloacids.⁴³ Gutovsky and coworkers prepared the malolactone starting from the iodosuccinic acid. His synthesis gave very low yields, and the monomer was of questionable purity.

Surveying the literature, one will not find many methods to prepare beta-substituted-beta-lactones from the corresponding hydroxy acid. Fortunately, a method to prepare the lactone was found which was suitable for this thesis.⁴⁴ Masamune prepared the following beta-substituted-beta-lactones from the corresponding thiol esters of the acid shown in Fig. 9. What was considered essential to the present project, was that the lactone be formed without breaking the beta carbon-oxygen bond so that the optical activity is left unaffected in the lactonization reaction. Hence, the asymmetry is not affected.

The reaction scheme, Fig. 10, outlines the method I used to prepare the beta-lactone from malic acid.

This scheme will be described in complete detail in the following chapter.

Figure 9. Masamune's reaction for the preparation of beta-substituted-beta-lactones from the corresponding thiol esters of the acid.

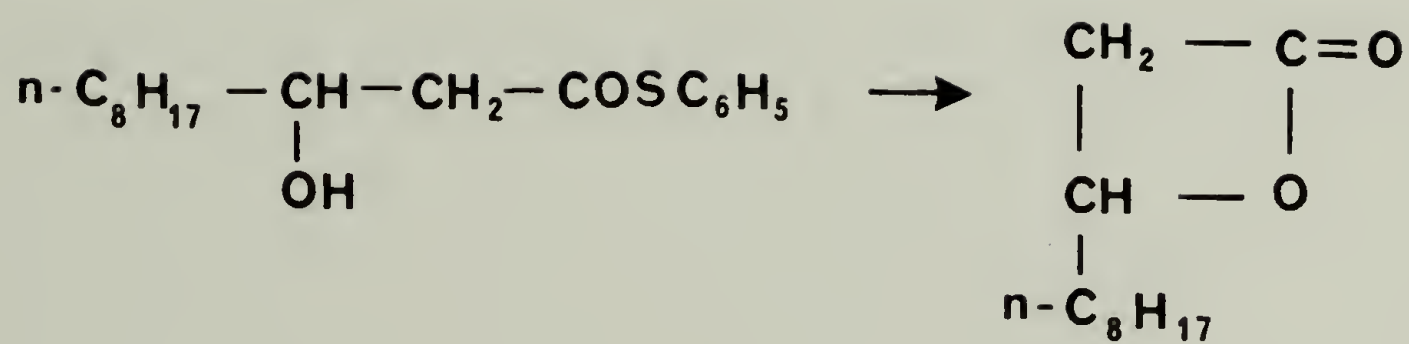
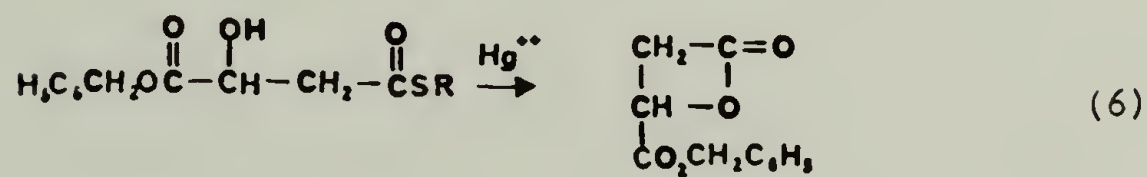
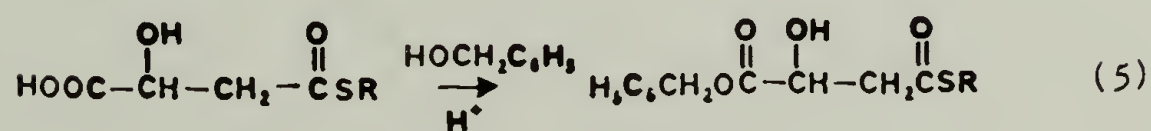
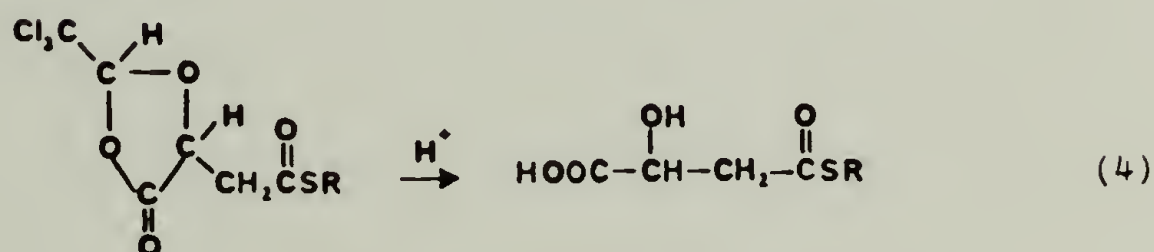
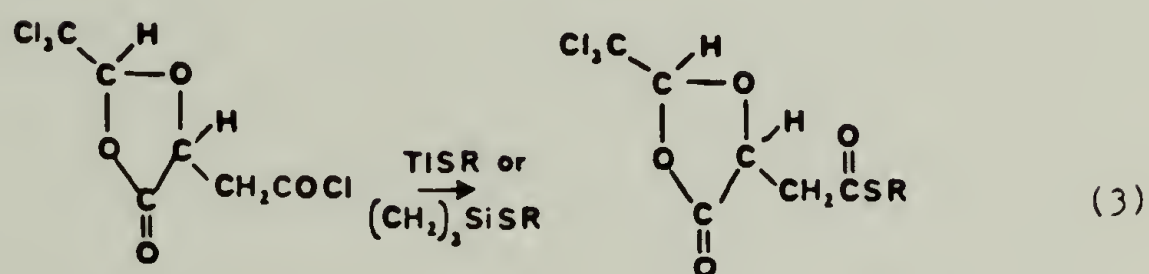
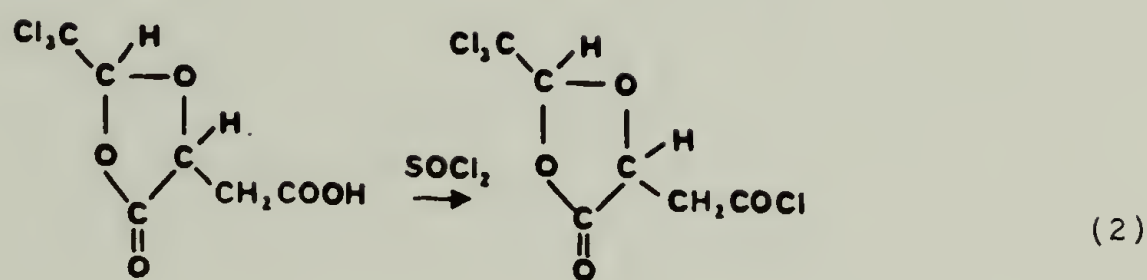
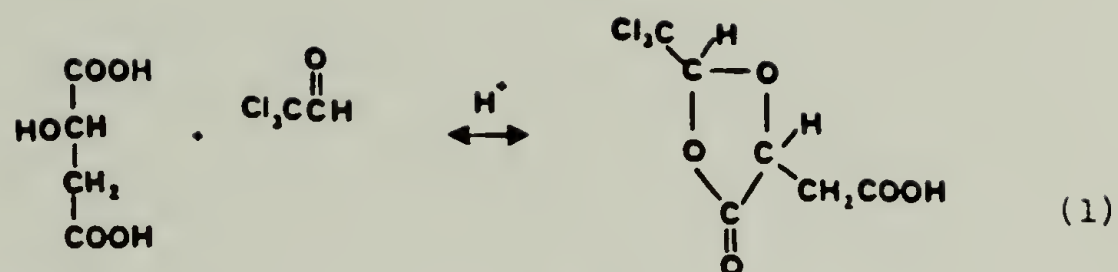


Figure 10. Method for the preparation of malolactone benzyl ester. Reaction (1) involves blocking the hydroxy and alpha carboxylic acid group. Reaction (2) describes the formation of the reactive acid chloride. The thiol ester is formed in reaction (3). Reaction (4) shows the unblocking reaction step. The benzyl ester protecting group is prepared in reaction (5). The desired malolactone is prepared in reaction (6).



The polymerization of the lactone will be investigated using different cationic and anionic initiators.

The polymer is expected to be isotactic and, therefore, crystalline. The polymerization conditions and the characterization of the physical properties of the polymer will be described in a subsequent chapter.

C H A P T E R II

PREPARATION OF THE MALOLACTONE ESTER MONOMER

I. Introduction

It was apparent from the start of this work that a fundamental requirement for ultimate success centered about preparing monomers and polymers having very high optical purity. Only with the isolation of these materials would it be possible to make a conclusive investigation of the effect of stereoregularity on the biological activity, biodegradability, and biocompatibility of the polymers, as well as an investigation of the stereochemistry of the polymerization reaction and the physical properties of the polymers. Thus, an optical purity of a minimum 90% was established as the goal for the monomer synthesis and this purity will provide a polymer with approximately 90% isotactic dyad configuration.

The resolution of a mixture of optical isomers remains a "black art" in which trial and error is the main approach utilized and the final outcome is uncertain at the start of the work. A pair of enantiomers may be separated by the following methods:

Conversion to diastereomers and
fractional crystallization

Differential absorption

Biochemical process

Mechanical separations by selective
crystallization

Differential reactivity

Conversion to diastereomers involves the formation of a salt by reacting the racemic mixture with an optically active substance (acid-base) followed by separation using fractional crystallization. This method is commonly used as a method for obtaining optically pure compounds.

Differential absorption employs a column packed with a chiral material and the enantiomers are separated by selective absorption.

The biochemical process occurs by the destruction of one enantiomer by a living organism.

Mechanical separation is a process for separating enantiomers using selective crystallization. Pasteur separated (+) and (-) tartaric acid using this method.

Differential reactivity is a method for separating enantiomers utilizing the difference in chemical reactivities of the enantiomer pair. The reaction is terminated before completion resulting in an enrichment in the mixture of one of the enantiomers.

All of the above described methods used for separating enantiomers were compared and rejected because of predictable, inherent problems in the methods which would make it impossible to accomplish the primary goal of achieving 90% optically pure monomer. There are other methods which have been used for preparing materials with high optical purity, however, these are not separation methods, but synthetic methods:

1. Asymmetric Synthesis.
2. Stereospecific Synthesis - starting from chiral precursors

It is almost impossible to prepare optically active compounds from inactive starting materials, ⁴⁵ true asymmetric synthesis is impossible. Also, the results shown in the literature, when this method is employed, usually demonstrate that the final product will have low optical purity, around 20-30%.

The final method which has been used to prepare optically pure materials involves stereospecific synthesis from chiral precursors. The fundamental requirement for using this method is the availability of starting compounds having high optical purity. Also, the synthetic reaction scheme must not affect the chiral centers. There can be no making nor breaking of chemical bonds at the chiral center. ⁴⁶ Overberger and Kaye utilized this method in the preparation of optically active caprolactones.

After comparing all the methods, the method of choice for this work is the final method described, which is stereospecific synthesis from chiral precursors. Malic acid can be purchased having optical purity around 99%.

II. Preparation of Beta-Substituted Beta-Lactones

A review of the literature demonstrates that four possible reaction routes exist for preparing beta-substituted beta-lactones.

A. From Salts of Beta-haloacids. Starting from the bromo or iodosuccinic acid, the lactone can be prepared by the following S_N2 -type ring closure reaction (Fig. 11).

Vert and Lenz³⁸ prepared the racemic malolactone benzyl ester using this procedure, starting from the bromosuccinic acid. The optically active starting compound, L-bromosuccinic acid, can be synthesized with high optical purity from L-aspartic acid.⁴⁷ Agostini used this procedure to prepare optically active beta-butyrolactone. He found that during the lactonization, 18% racemization occurred because the chiral center is the site of a side reaction. Agostini gave three possible ways by which racemization could have occurred: (1) by S_N2 attack of bromide ions formed in the reaction on the beta-carbon (Fig. 12a); (2) by an S_N1 reaction mechanism during the replacement of the bromine atom (Fig. 12b); and (3) by racemization of the lactone after it has been formed.

The first alternative, racemization of the bromosuccinic acid prior to attack by the carboxylate anion, is most likely.⁴⁸ Holmberg prepared the optically active bromosuccinic acid and observed complete racemization during the lactonization step.

B. Ketene and Carbonyl Compounds. To prepare the lactone a ketene may be reacted with glyoxylic acid or its ester (Fig. 13).

Figure 11. The preparation of a beta lactone from the corresponding bromo or iodosuccinic acid.

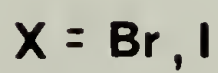
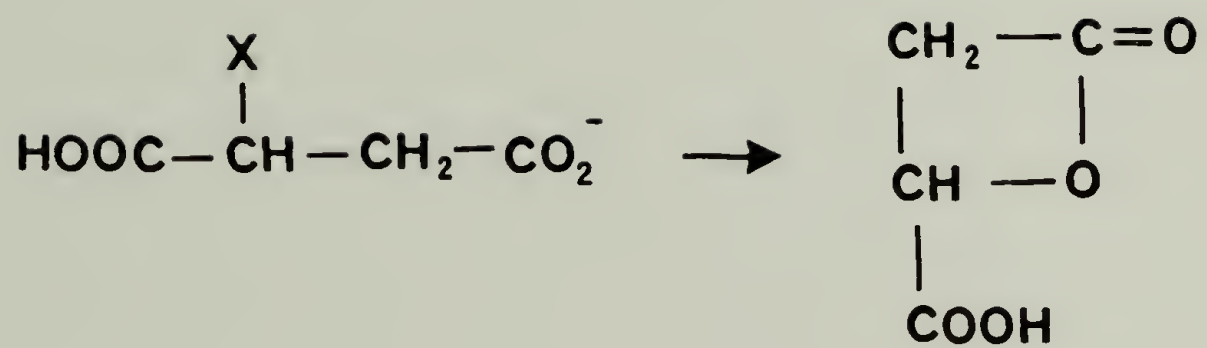
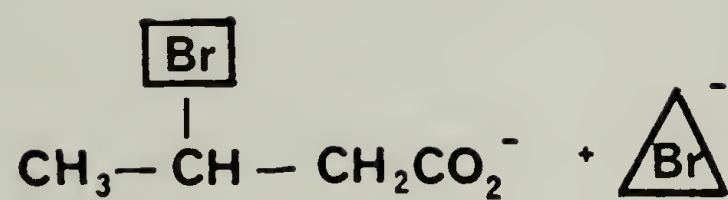


Figure 12a. Racemization by S_N2 attack of bromide ions formed in the reaction on the beta-carbon.



↓ RACEMIZATION

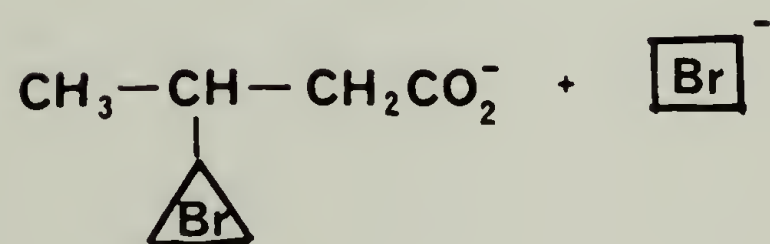
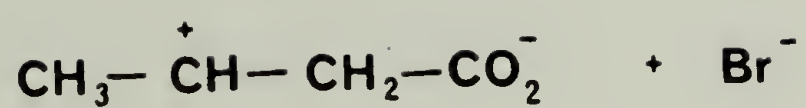


Figure 12b. Racemization by an S_N1 reaction mechanism during the replacement of the bromine atom.



$\text{S}_{\text{N}}1$ ↓ RACEMIZATION

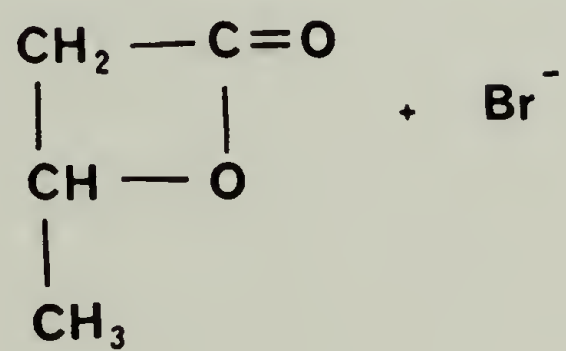
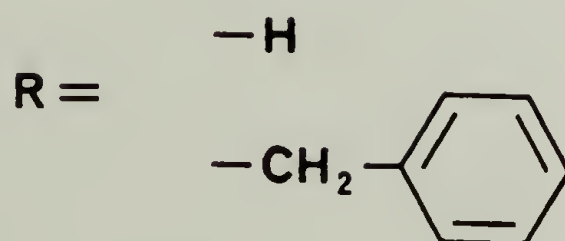
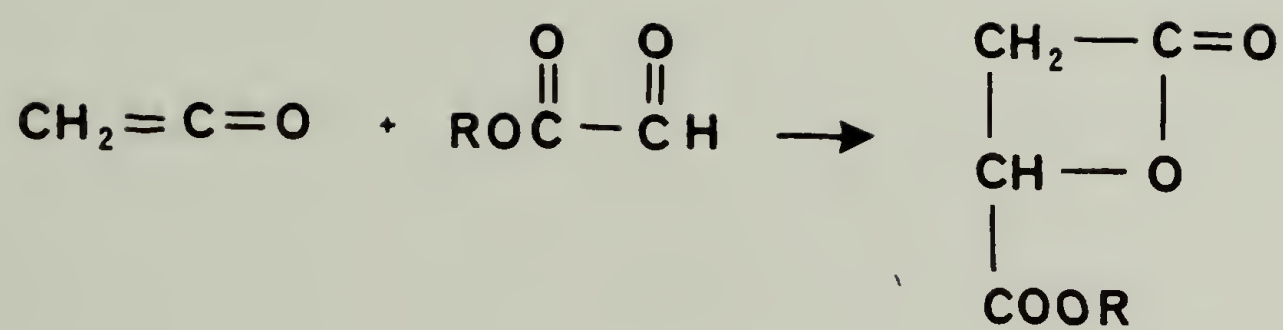


Figure 13. Preparation of a beta-lactone by reaction of a ketene with a glyoxylic acid or its ester.

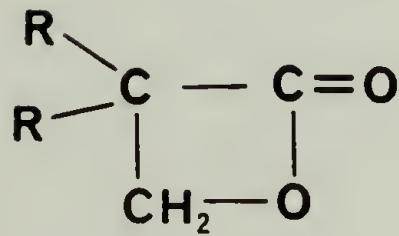
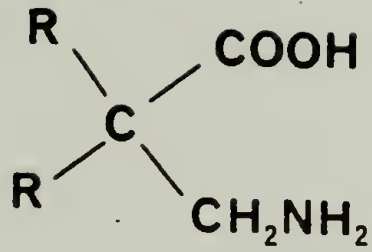


Dimerization of the ketene is a complicating side reaction product. The synthesis of the lactone from the ketene and the aldehyde start from symmetric intermediates. The product may require a separation of optical isomers and this separation method is unknown. Wynberg and Staring⁴⁹ recently synthesized optically pure beta(tri-chloromethyl)-beta-propiolactone by this method using a quinidine catalyst. To date, no one has prepared optically active malolactone by this method.

C. Diazotization of Beta-aminocarboxylic acids. Testa⁵⁰ has prepared optically active lactones using this method. He has found this method to be extremely useful if the alpha-carbon is substituted. I attempted this reaction starting from aspartic acid following the reaction conditions defined by Testa (Fig. 13a). I was unable to isolate any lactone or observe lactone formation when following the reaction using infrared or proton-NMR spectroscopy. I discontinued working with this method because it is as yet an unproven method for the preparation of beta-substituted beta-lactones.

D. Beta-hydroxycarboxylic acids. Several methods have been developed for preparing beta-lactones from beta-hydroxy acids. Whether these methods are applicable for preparing beta-substituted beta-lactones is as yet unproven. Examples in the literature showing that a hydroxy acid is converted

Figure 13a. Preparation of a beta-lactone by diazotization of beta-aminocarboxylic acid.



$\text{R} = \text{alkyl, aryl}$

to a corresponding beta-lactone are explained as follows. Torvonen et. al.,⁵¹ upon recrystallization of 5-hydroxy camphoric acid from acetic anhydride, found the formation of the corresponding beta-lactone (Fig. 13b). He also found that this compound could be lactonized at room temperature using acetyl chloride.⁵² Diassi and DyLion⁵³ reacted ethyl chloroformate with yohimbic acid at room temperature and isolated acceptable yields of the lactone product (Fig. 13c). Philp et. al.⁵⁴ reacted p-toluene-sulfonyl chloride with 2,3 dihydroxycyclopentane-1-carboxylic acid and isolated excellent yields of the beta-lactone (Fig. 13d). Finally, Testa et. al.⁵⁵ reacted 2-ethyl-3-hydroxymethyl butyric acid in a cold benzene-pyridine solution with thionyl chloride. They isolated a low yield of the lactone (Fig. 13e).

I investigated and evaluated all of the previously described methods to determine their applicability for the preparation of beta-malolactone, using the racemic malic acid as the starting material and reacting with the appropriate reagents. For the reaction of malic acid with acetic anhydride or acetyl chloride, the reaction conditions were investigated and modified, but no lactone was isolated. The reaction was investigated by infrared and proton-NMR spectroscopy. There was no indication of lactone formation using a wide range of experimental conditions. Similar results were found with ethyl

Figure 13b. Recrystallization of 5-hydroxycamphoric acid from acetic anhydride to yield the corresponding beta-lactone.

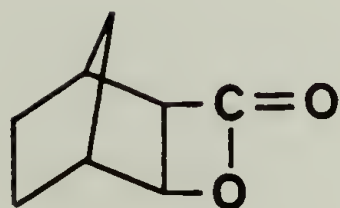
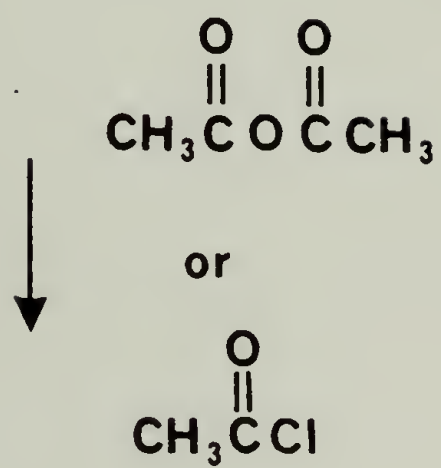
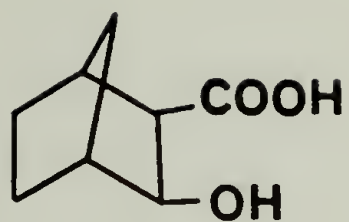


Figure 13c. Lactone formation from the reaction of ethyl chloroformate with yohimbic acid.

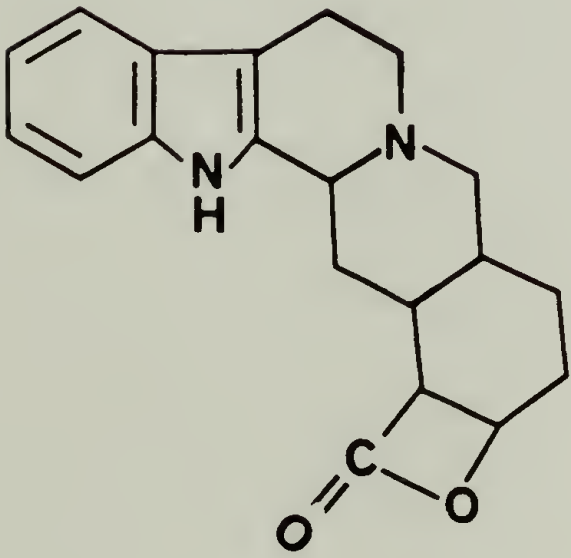
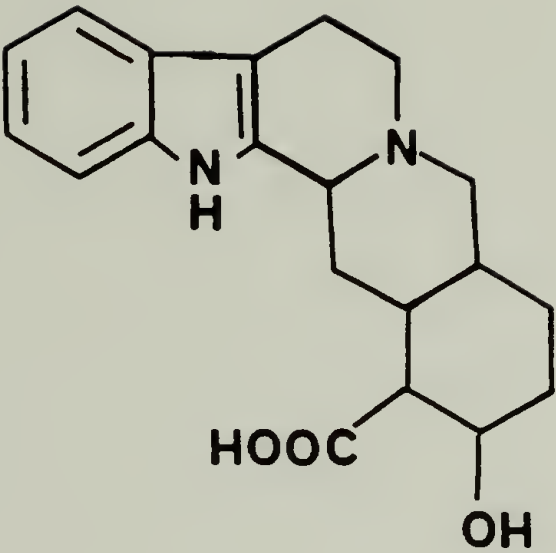


Figure 13d. Beta-lactone formation from the reaction of p-toluenesulfonyl chloride with 2,3-dihydroxycyclopentane-1-carboxylic acid.

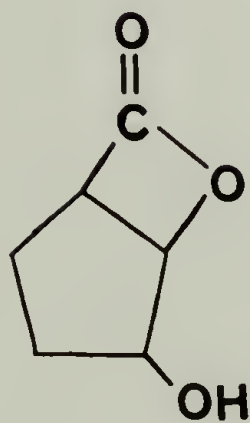
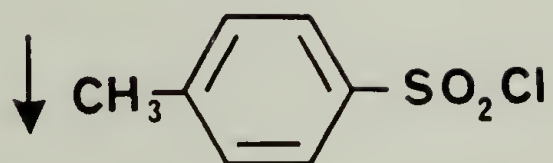
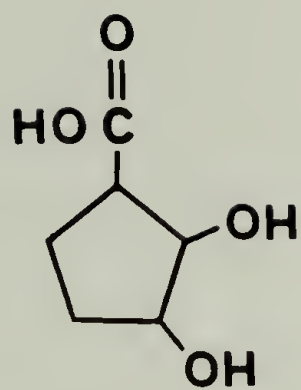
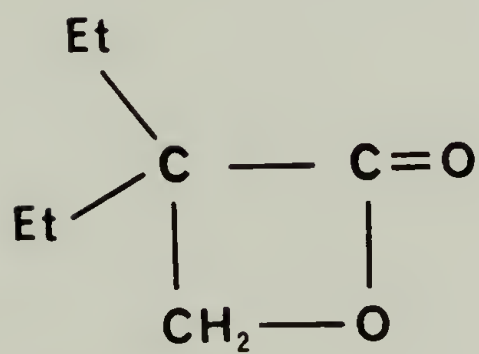
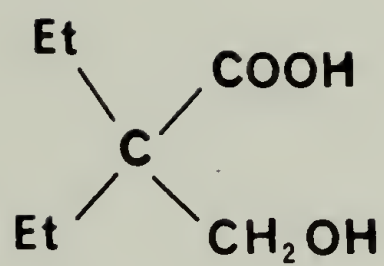


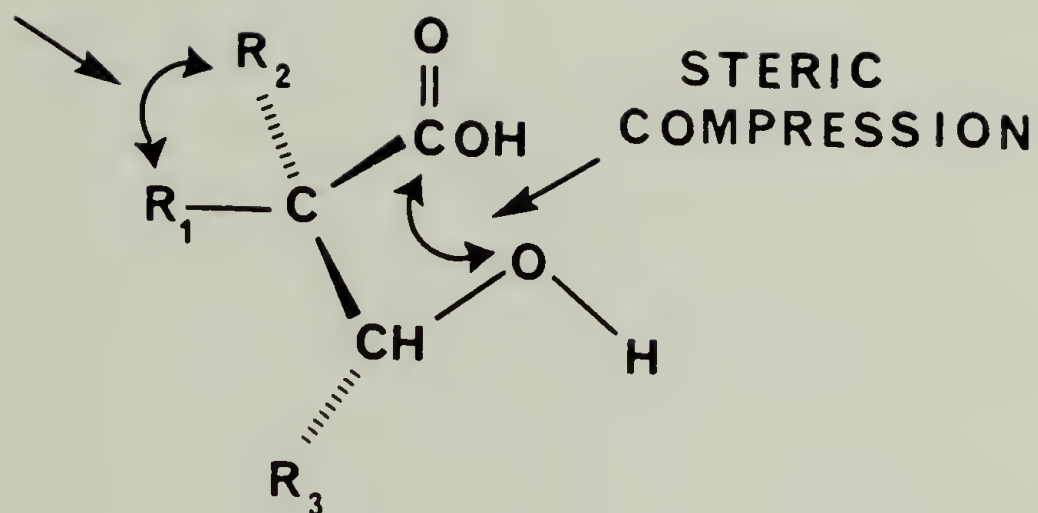
Figure 13e. Reaction of 2-ethyl-3-hydroxymethyl butyric acid with thionyl chloride.



chloroformate, p-toluenesulfonyl chloride and thionyl chloride. One can explain these results after careful examination of the structures of the starting compounds from which the beta-lactone was successfully prepared. In all instances, the carboxylic acid and beta-hydroxy group are held in a fixed position due to the rigid ring structure of the compounds, for example, 5-hydroxy camphoric acid, Yohimbic acid, and 2,3-dihydroxycyclopentane-1-carboxylic acid. For the example, 2-ethyl-3-hydroxymethyl butyric acid, the molecule contains gem disubstituted large bulky groups. The yield of lactone obtained using this reaction was very low. A similar result was obtained with the previously described diazotization reaction. One can conclude that for lactone formation to occur, the alpha-position of the molecule must be substituted with bulky alkyl or aryl groups. Also, lactonization occurs if the two reacting groups, the carboxylic acid and beta-hydroxy are held in a fixed cis position by attachment to a rigid molecule. Steric factors must play an important role in the lactone formation. The lack of steric compression at the alpha-carbon caused by the repulsion of the gem alkyl groups makes it impossible to have the carboxylic acid and hydroxyl group in a position of close proximity so that the lactone is formed (Fig. 14). On examination of the structure of the molecule capable of formation of the lactone, the reacting groups are in the cis position on

Figure 14. Diagram showing the necessity of steric compression at the alpha-carbon bringing the reactive groups into a position of close proximity to form the lactone.

STERIC
REPULSION



$R_1 = R_2 = \text{alkyl, aryl}$

a rigid molecule. The kinetics for lactone formation should be favorable due to the proximity of the two reacting groups. For malic acid, the reacting groups are able to rotate around the alpha-beta carbon bond lowering the frequency of group collision.

Recently, Masamune⁴⁴ has discovered a method for the preparation of beta-substituted beta-lactones (Fig. 9). His starting material is a beta-hydroxy thiol ester catalyzed by a mercuric salt. This method is attractive because this reaction does not involve bond breakage or formation at the asymmetric carbon, eliminating the possibility of racemization during lactone formation. Masamune quotes very good yields of lactone using this reaction. He predicts general applicability for the preparation of beta-substituted beta-lactones using this reaction.

III. Reaction Mechanism for Preparation of Malolactone

Masamune was optimistic about the potential of the reaction. However, since he gave only one example for the preparation of beta-alkyl butyrolactone and no additional work appears in the literature, I decided as a first approach, to investigate this reaction using a model system and evaluate its potential prior to initiating the work with the more complex malic acid. The model compound chosen

was beta-hydroxybutyric acid. The reaction scheme used to prepare the lactone is outlined in Fig. 15. Starting from the beta-hydroxybutyric acid, this compound was first reacted with diethyl chlorophosphate to form the intermediate anhydride. This compound is reacted with thallium 2-methyl-2-propane thiolate to yield the corresponding thiol ester. The lactonization was performed following Masamune's procedure and 63% butyrolactone was isolated after distillation. The elemental analysis and infrared analysis confirmed the lactone structure. The infrared spectra was identical to beta-butyrolactone prepared by Agostini⁴⁷ using an alternative method.

Once convinced that the reaction invented by Masamune had the best possibility for success for preparing the optically active lactone from L-malic acid, I now was faced with the necessary task of developing a reaction scheme which would ultimately provide the optically pure lactone. I do not intend to keep the reader in suspense by going through each step to the final reaction and, like a detective in a murder mystery, provide clue after clue until revealing the final solution. The reaction scheme is outlined in Fig. 16 and with the ultimate solution revealed, I now intend to describe in detail each step of the reaction explaining the success and failures which ultimately led to the final reaction which is the formation of the beta lactone. In order to utilize the

Figure 15. Reaction scheme for the preparation of beta-butyrolactone.

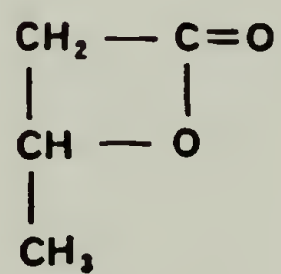
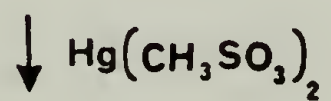
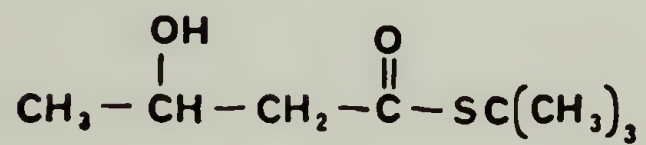
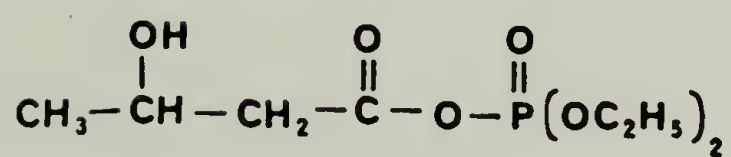
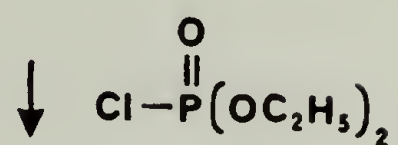
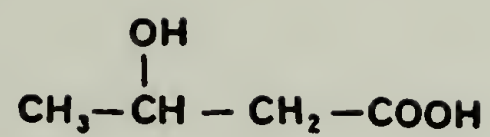
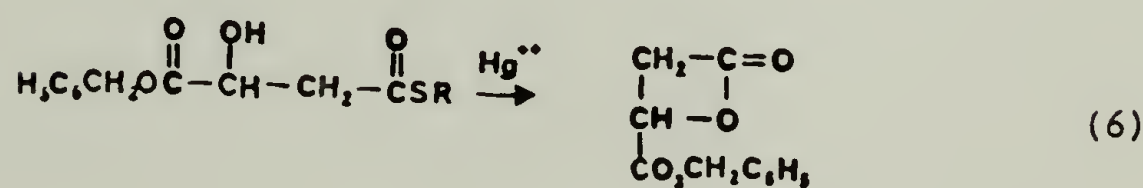
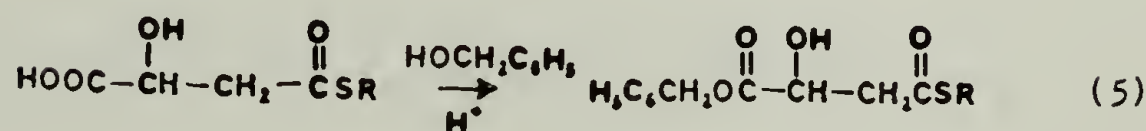
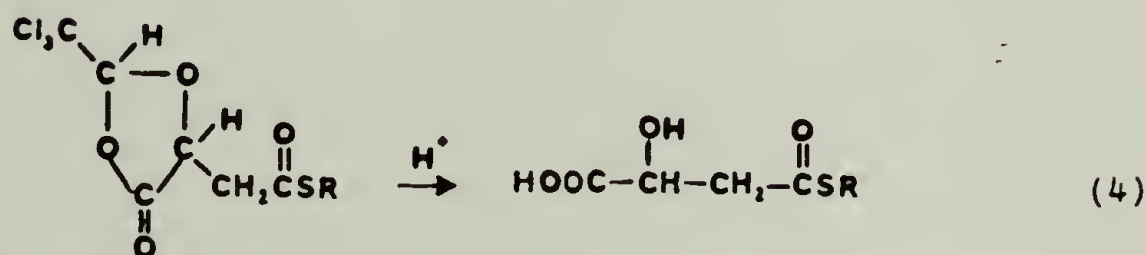
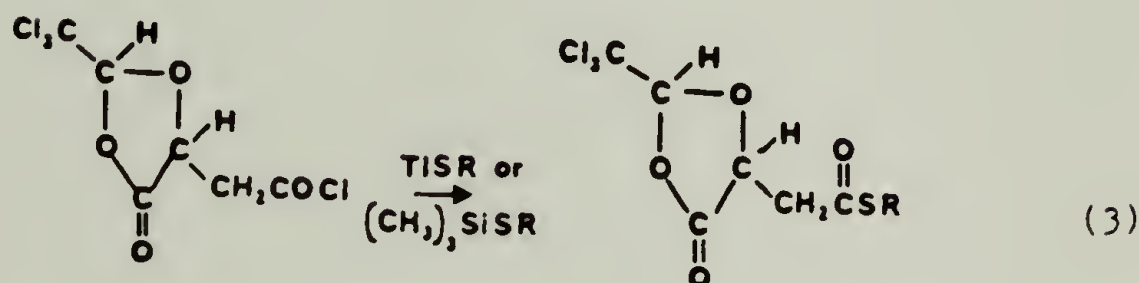
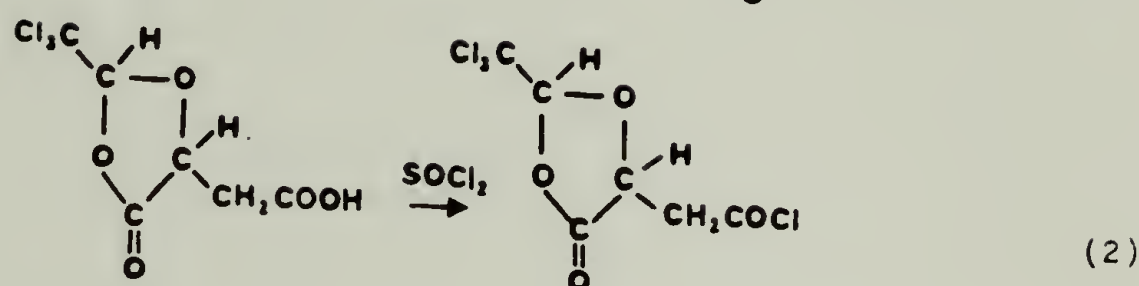
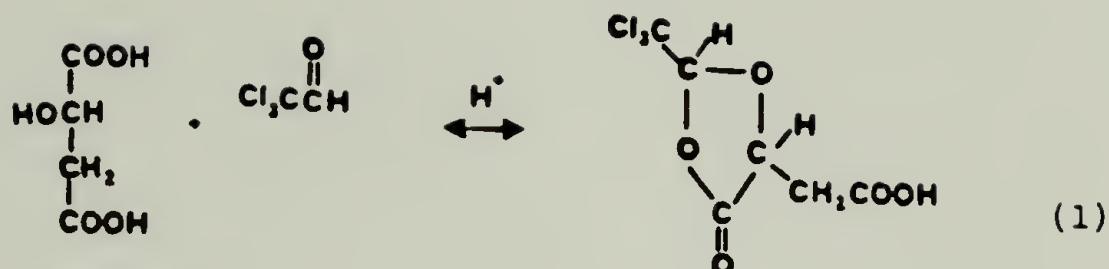


Figure 16. Reaction scheme for the preparation of malolactone benzyl ester.



Masamune reaction, the final step in the monomer synthesis must be the reaction of the mono thiol ester of malic acid and mercuric salt (Fig. 17).

In their preparation of the racemic malolactone, Vert and Lenz³⁸ made the corresponding benzyl ester of the lactone. Lenz hypothesized that it would be difficult to polymerize the lactone unless the pendant carboxylic acid was blocked so as to eliminate potential side reactions during the polymerization. The carboxylic acid could react with the ionic initiator or may undergo chain transfer and/or termination.⁴⁰ They blocked the pendant carboxylic group with benzyl alcohol in order to later utilize the well known unblocking reaction which involves hydrogenation of the benzyl ester yielding toluene and carboxylic acid.⁵⁶ They performed this hydrogenation on the polymer shown in Fig. 18 and, because of the mild conditions used for hydrogenation, found no cleavage of the polymer chain and no decrease in molecular weight.

I decided to prepare the optically active polymer from the lactone of malic acid, also by blocking off the pendant carboxylic group with the benzyl ester. Therefore, the final reaction step in the proposed monomer synthesis should be the reaction of the mono benzyl and thiol mixed esters of malic acid with the mercuric salt catalysts as described in Masamune's procedure (Fig. 19).

To obtain this compound from malic acid, the formation of the thiol ester and benzyl ester linkages must be

Figure 17. Reaction of the mono thiol ester of malic acid and a mercuric salt to form the corresponding beta-lactone.

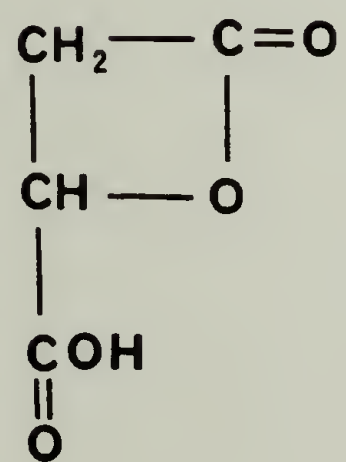
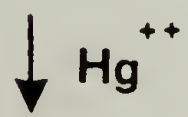
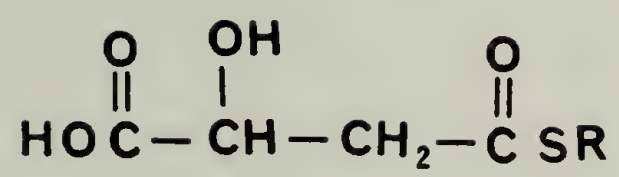


Figure 18. Hydrogenation of poly(malolactone benzyl ester) to yield poly(malic acid).

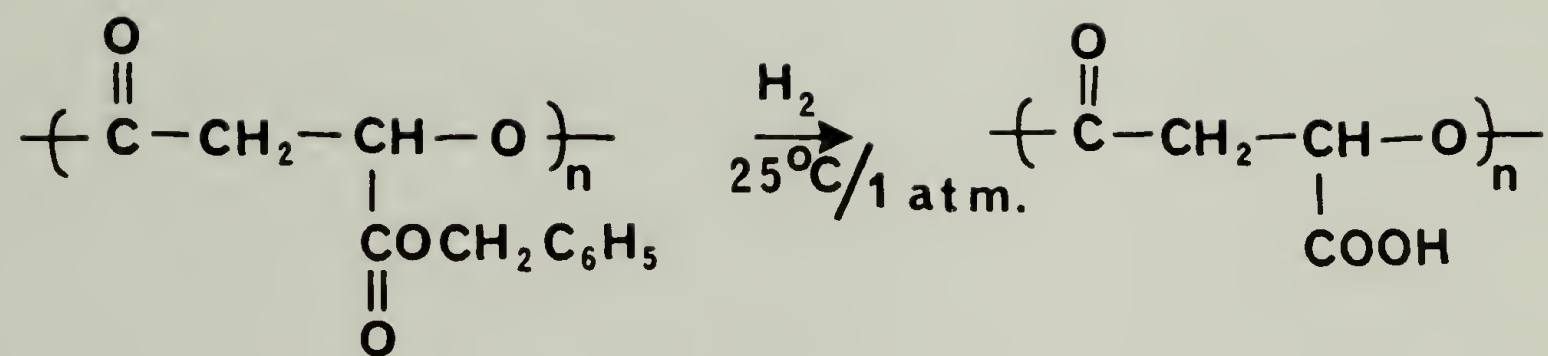
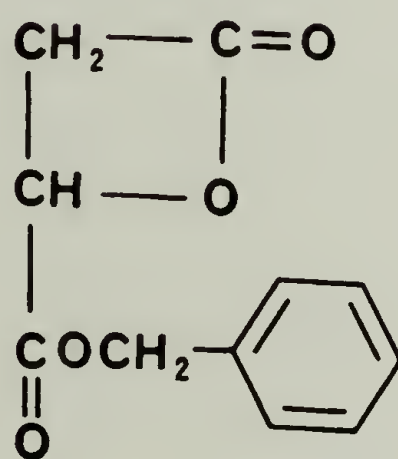
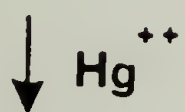
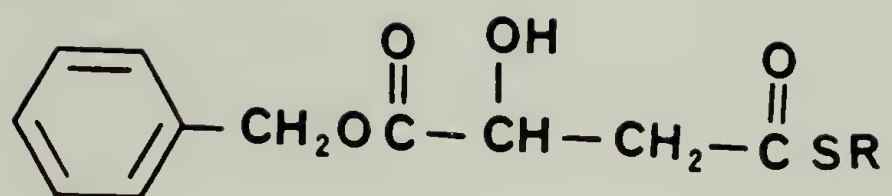


Figure 19. Reaction of a mono benzyl and thiol mixed esters of malic acid with a mercuric salt catalyst to yield the corresponding beta-lactone.



specific to the beta-carboxylic and alpha-carboxylic groups, respectively. Regardless of the reaction order, the reactivity of the two carboxylic groups on malic acid is not expected to be so different as to yield a clean reaction product. However, I attempted to prepare the anhydride from malic acid with the intention of reacting it with benzyl alcohol and separating the two different monobenzyl ester components, and then reacting the compound with the free beta-carboxylic group with the mercaptan to prepare the thiol ester. Following the literature procedure, I prepared the malic acid anhydride using the silver salt of the carboxylate.⁵⁷ Low yields, 10%, were obtained, and the product was of low purity. The predictable difficulties involved in the purification and separation made it necessary to take a new approach to the synthesis of the lactone, which is to block off one of the carboxylic groups as the first step in the synthesis.

IV. Preparation of Malic Acid Chloralide

During the past 20 years, there has been a great deal of interest in the use of protective (blocking) groups, especially for the synthesis of large complex organic molecules. The greatest activity has been in the field of peptide chemistry where the total synthesis of insulin and bovine ribonuclease have been achieved. The literature

describing this area has demonstrated that a commonly used reaction for protecting carboxylic acid groups having an alpha-amino group on the same molecule would involve the reaction of the amino acid with phosgene to form a Leuch anhydride⁵⁸ as shown in Fig. 20a. Iwakura, et.al.⁵⁹ found that the Leuch anhydride will react with benzyl alcohol using acidic conditions and yield the corresponding amino ester (Fig. 20b). Utilizing this blocking reaction, one has the opportunity to block the functional groups, perform the necessary reactions, and unblock to the corresponding amino benzyl ester. For carboxylic acids, having alpha-hydroxy groups on the molecule, there is a similar blocking reaction which occurs by an intramolecular acetal reaction (Fig. 21). The intramolecular acetal reaction forms the five-membered 1,3-dioxolan-4-one. What is important to this work is that the dioxolanone reacts with a nucleophile through the ester linkage and does not react at the ether linkage so that racemization does not occur during the unblocking reaction. A number of papers in the literature have described this reaction. Soulier and Farines⁶⁰ have prepared a number of different dioxolanones by the condensation of alpha-hydroxy acids of various carbonyl compounds. Lemieux⁶¹ has prepared a number of dioxolanones by the reaction of alpha-hydroxy acid and acetone. Eggerer and Grünewälder⁶² prepared the racemic and

Figure 20a. Reaction of an amino acid with phosgene to form a Leuch anhydride.

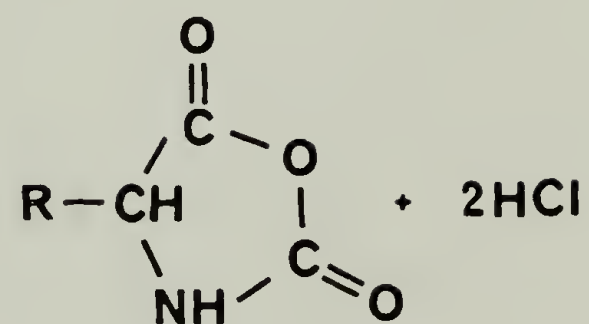
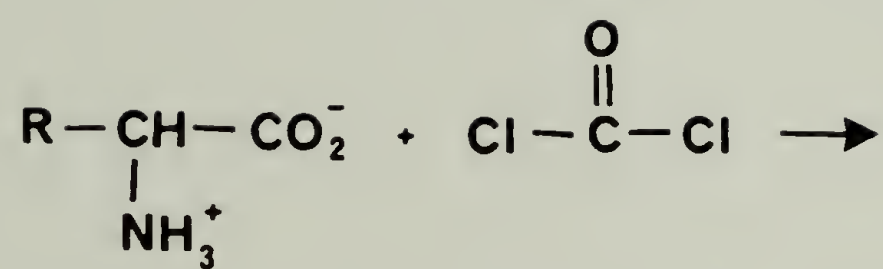


Figure 20b. Reaction of a Leuch anhydride with benzyl alcohol yielding the amino ester.

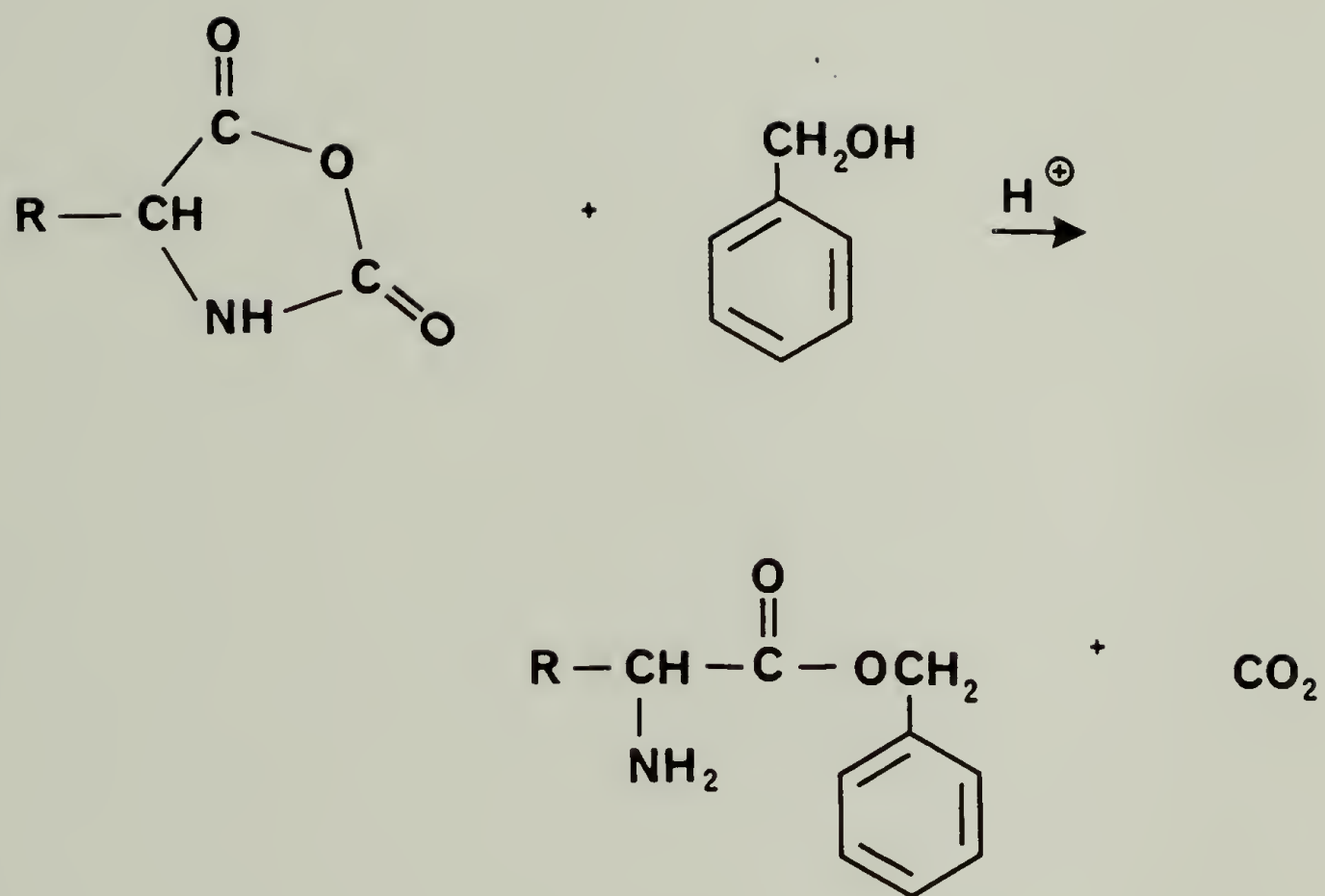
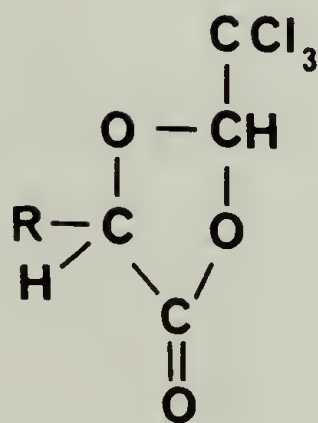


Figure 21. Intramolecular acetal reaction.

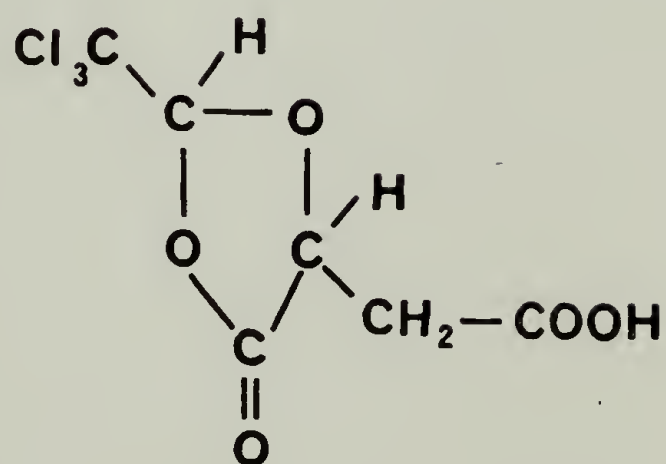
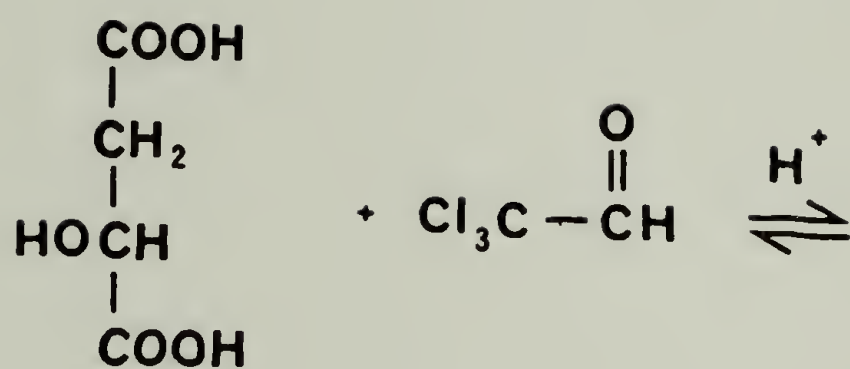


optically active malic acid chloralide using trichloroacetaldehyde. They gave no explanation for the use of chloral, but since a ready supply of this material exists at this institution, I decided to use their reaction method. The blocking reaction using chloral and malic acid can be illustrated by Fig. 22. The dioxolanone prepared from the racemic malic acid, after recrystallization, was a white crystalline solid showing a sharp melting point, 174-176°C (literature, 175°C). This compound displayed the characteristic identifying peaks in the infrared, carbon-13, and proton-NMR spectra which supports the proposed structure. The compound was analyzed having 98.7% purity as determined by analytical High Pressure Liquid Chromatography.

The compound prepared from L-malic acid, after recrystallization, was a white crystalline solid with a sharp melting point, 142-144°C (literature, 141°C) and showed the identical infrared, carbon-13, and proton NMR spectra as the malic acid chloralide prepared from the racemic malic acid. Its purity was found to be 99% as determined by analytical HPLC.

Having succeeded with the blocking reaction, the next step in the preparation of the lactone involves the preparation of the thiol ester. There are numerous methods described in the literature for the preparation of thiol esters from carboxylic acids and acid chlorides.

Figure 22. Reaction of chloral and malic acid yielding the corresponding malic acid chloralide.



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Liu and Kai published an excellent review article outlining the different methods. I investigated a few of these methods, the first being the preparation of the thiol ester by reacting malic acid chloralide with diethyl chlorophosphate⁶⁴ as shown in Fig. 23, followed by the reaction with the thallium salt of 2-methyl propyl thiolate⁶⁵ (Fig. 24). After recrystallization, the S-(malic acid chloralide) ter-butylate was isolated having an overall yield of 65%. The compound is a white powdery material showing the characteristic absorptions for thiol ester by infrared analysis. A number of reaction conditions were investigated with the goal to improve the overall yield of product, however, no significant increases in yield were observed from these changes.

A second method investigated involves reacting the dioxolanone of malic acid chloride with 2-methylpropyl thiol in tetrahydrofuran and pyridine solution⁶⁶ (Fig. 25). After workup, the isolated product was a black, viscous oil having no characteristic peaks for the thiol ester. Attempted crystallization of this oil failed to produce the isolated thiol ester. The black oil was a complex mixture of undefinable components. Varying the reaction parameters did nothing to indicate the capability of forming the thiol ester.

The third method which was investigated, and the one which proved very successful, involves the reaction of

Figure 23. Reaction of malic acid chloralide with diethyl chlorophosphate.

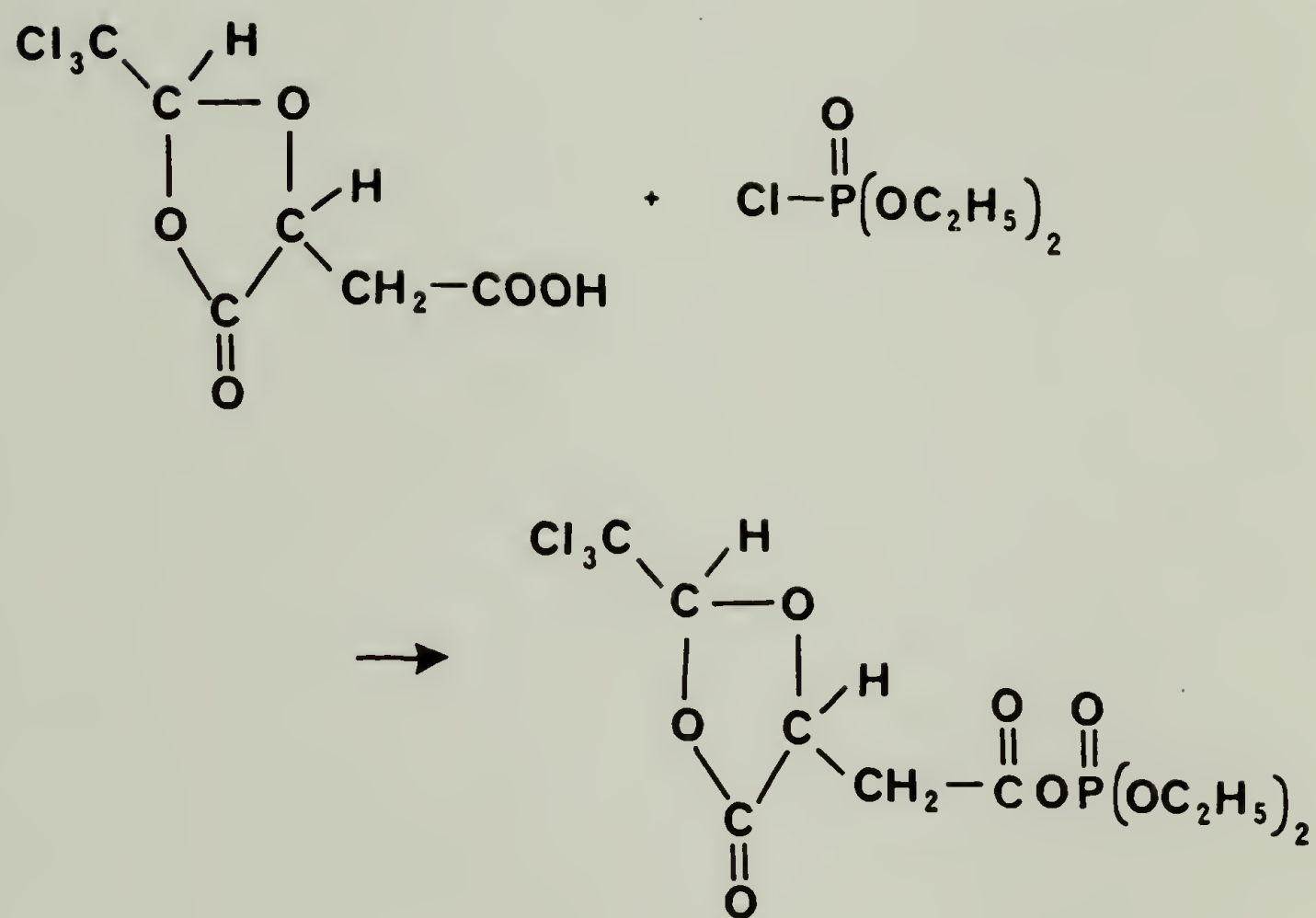


Figure 24. Synthesis of the thiol ester.

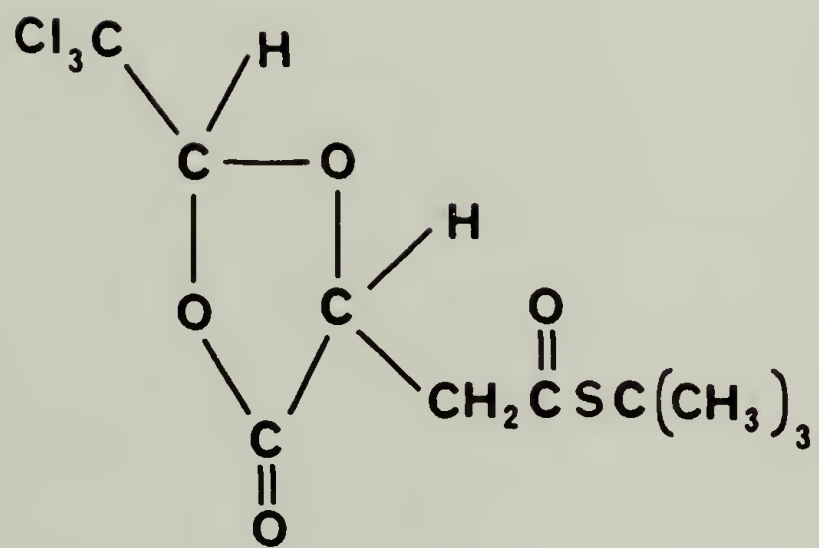
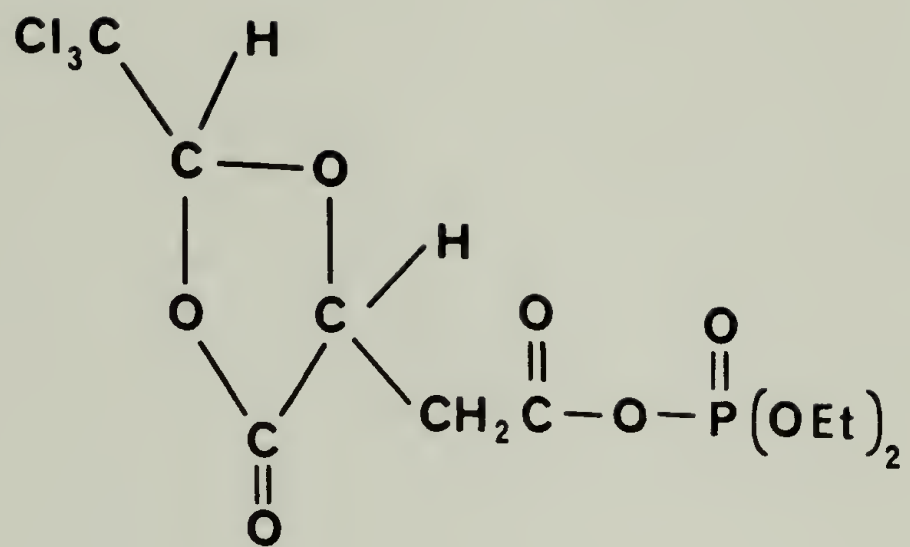
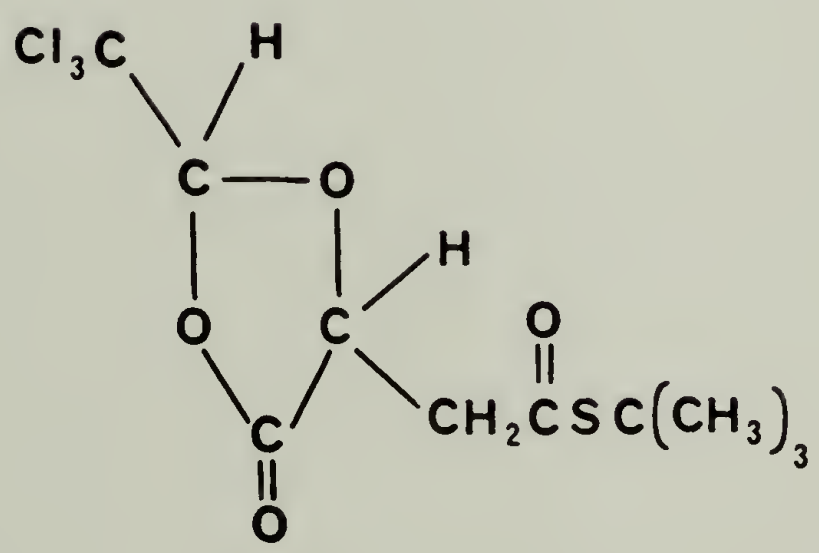
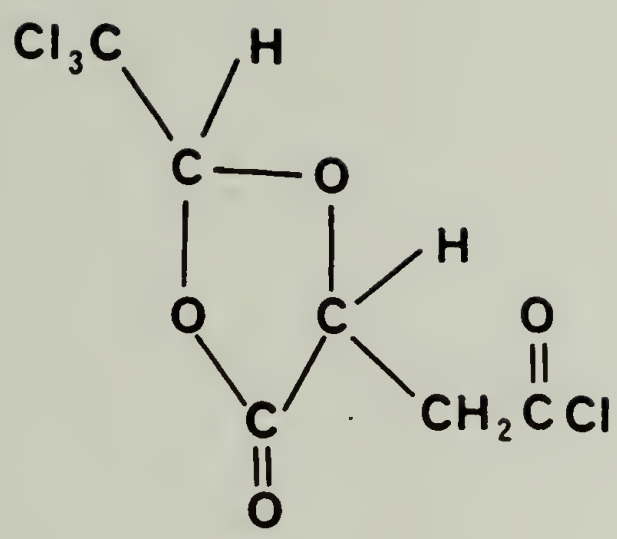


Figure 25. Reaction of malic acid chloralide chloride with 2-methylpropyl thiol.



the malic acid chloralide chloride with a preformed thallium thiolate salt.⁶⁷ The malic acid chloralide chloride was obtained in excellent yields by refluxing the malic acid chloralide with thionyl chloride (Fig. 26) followed by recrystallization. Infrared, carbon-13, and proton-NMR spectra had the peaks characteristic for this compound. After recrystallization, the racemic compound showed a melting point 79-81°C (literature 78-80°C). The optically active compound was also prepared in excellent yields and this compound had a melting point 71-72°C (literature 70-72°C). The infrared, proton NMR, carbon-13 spectra were identical to those of the racemic compound. Reacting the malic acid chloralide chloride with the thallium salt of 2-methylpropyl thiol, yielded 80% of the corresponding thiol ester (Fig. 27). After recrystallization, the racemic compound had a melting point 101-103°C. The optically active compound had a melting point 96-98°C. The elemental analysis infrared, proton NMR, and carbon-13 confirmed the formation of the S-(malic acid chloralide) ter-butylate. The racemic compound was of 94.7% purity and the optically active compound was of 92.1% purity as determined by High Pressure Liquid Chromatography.

The thallium thiolate salt must be freshly prepared⁶⁸ prior to the reaction with the malic acid chloralide chloride. It is prepared by reacting thallium ethoxide

Figure 26. Reaction of malic acid chloralide with thionyl chloride.

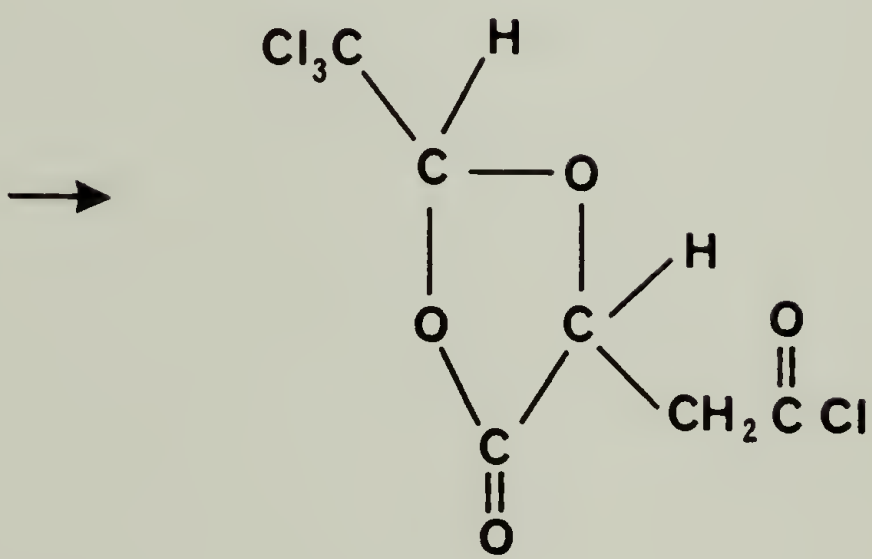
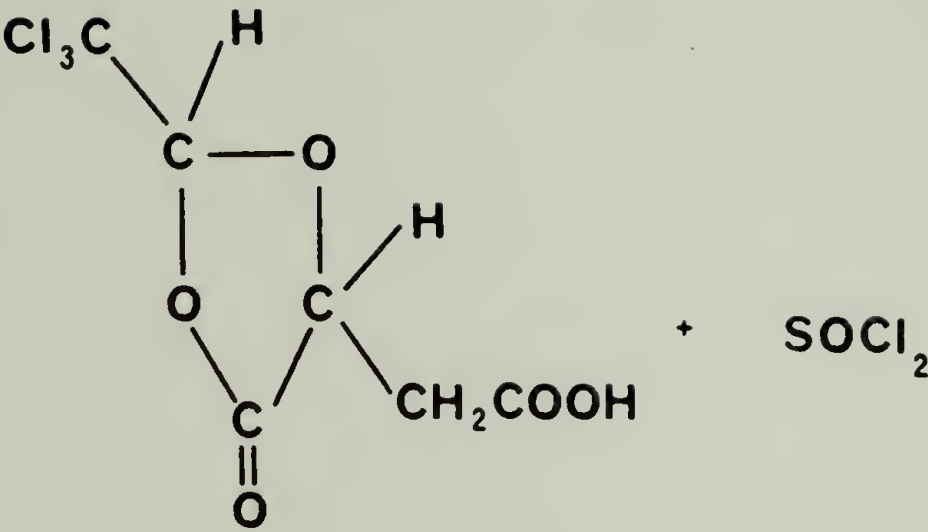
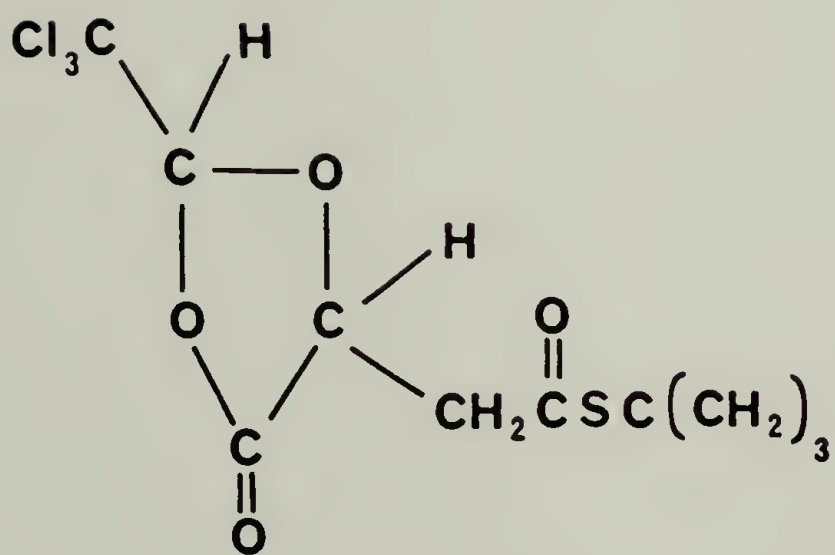
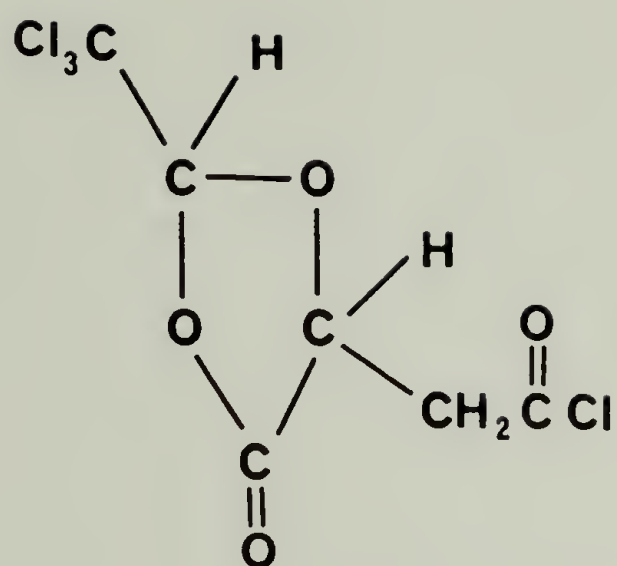


Figure 27. Reaction of malic acid chloralide chloride with the thallium salt of 2-methylpropyl thiol.



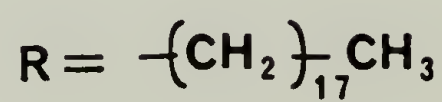
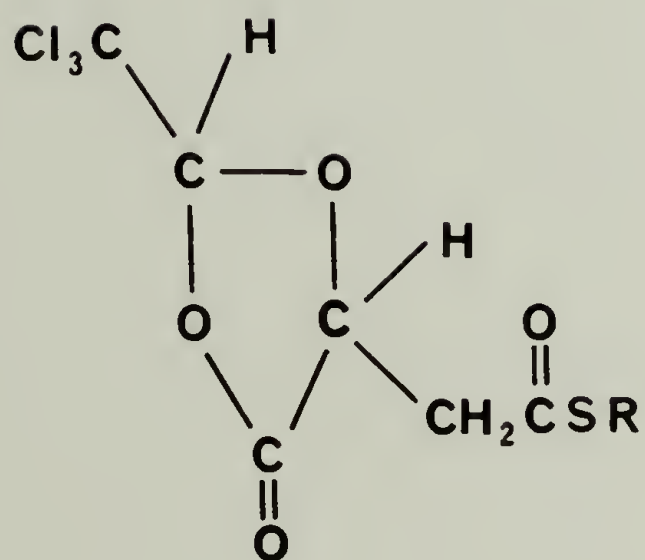
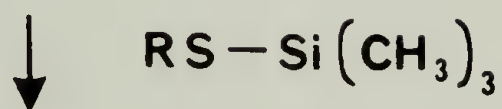
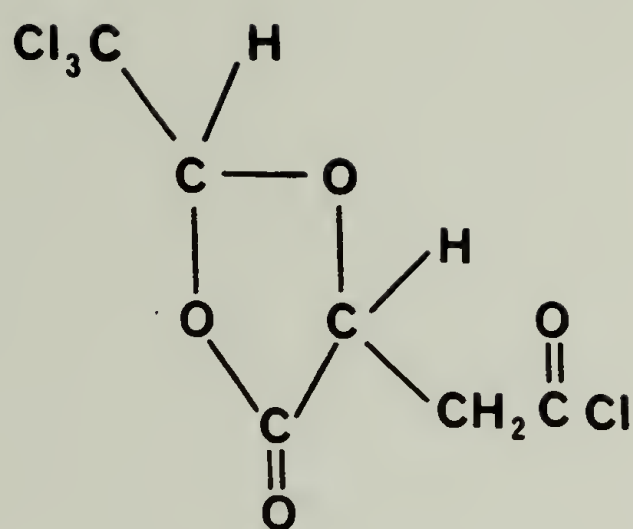
with an equal molar amount of the appropriate mercaptan. Upon addition of the reactants, a bright yellow salt precipitates from solution. This salt is easily oxidized so that care must be exerted during isolation, and subsequent filtration, specifically by performing the reaction under inert atmosphere. Elemental analysis and infrared analysis confirmed the formation of the salt.

The final method chosen for investigation involves the reaction of the chloralide chloride with alkyl trimethyl silyl sulfide⁶⁹ (Fig. 28). After recrystallization of the S-(malic acid chloralide) alkylate a 60% yield of the resultant optically active thiol ester was isolated. The racemic compound was not prepared by this method, but it is assumed that the results would be similar to those for the optically active compound. Analytical HPLC demonstrated the purity of the product to be 92.7%. Spectral analysis of this compound was identical to the products obtained from the previously described reactions.

Using each of the previously described methods, different thiol esters were prepared with different S-alkyl groups. The following Table 1 lists the thiol esters and their properties.

The next step in the lactone synthesis is a most critical one to the ultimate success of preparing the lactone. The S-(malic acid chloralide) alkylate is reacted with a nucleophile such as water to yield the corresponding

Figure 28. Reaction of malic acid chloralide chloride with alkyl trimethyl silyl sulfide.



alpha-hydroxy compound with either a carboxylic acid or an ester group.

This unblocking reaction must take place without disturbing the bonding configuration around the chiral carbon atom so that racemization of the carbon center cannot occur. A number of papers have been found in the chemical literature giving strong evidence which can be used to predict that the unblocking reaction goes through a mechanism which can be described by reaction of the nucleophile with the carbonyl of the five-membered dioxolanone ring rather than the competitive acetal hydrolysis reaction. Salomaa⁷⁰ studied acid hydrolysis of various 1,3-dioxolan-4-one and 1,3 dioxolane compounds. His results provide strong evidence that the dioxolane group hydrolysis by the acetal hydrolysis mechanism, and the observed kinetic data is easily understood using the A-1⁷¹ or S_N1cA mechanism as shown below; if stereochemical factors are taken into account (Fig. 29).

1,3-Dioxolan-4-one have both the ester and acetal group available for hydrolysis and either of various reaction paths may occur. Salomaa demonstrated that the dioxolanone, under acid conditions, hydrolysis by the A_{AC}2 mechanism (Fig. 30) and not the A_{Al}1 mechanism (Fig. 31).

Investigation of the A_{AC}2 mechanism demonstrates that the chiral center is not involved in the reaction, therefore, racemization should not occur during the hydrolysis

Figure 29. A-1 or SN1cA hydrolysis mechanism.

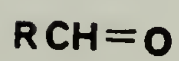
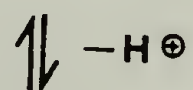
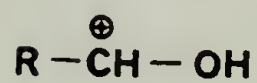
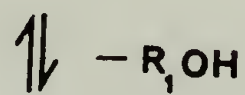
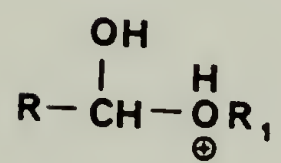
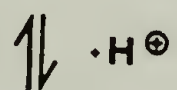
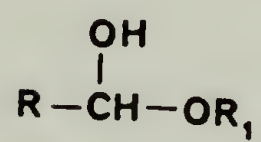
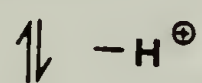
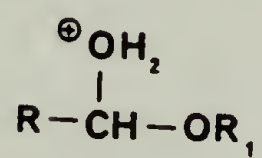
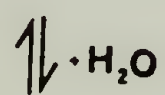
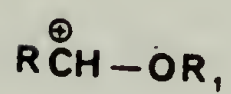
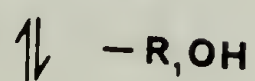
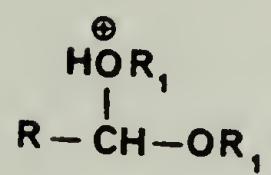
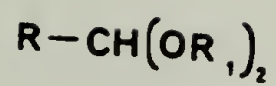


Figure 30. A_{AC}^2 hydrolysis mechanism.

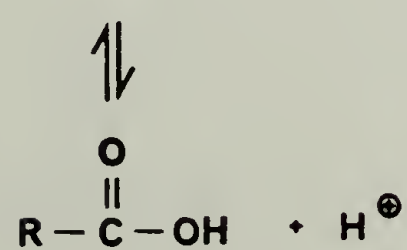
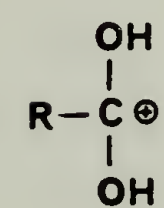
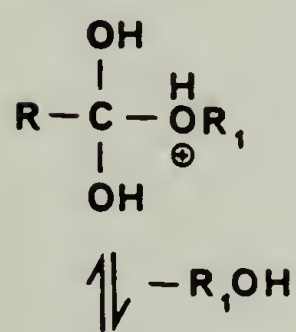
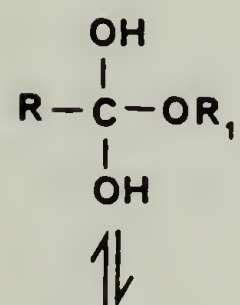
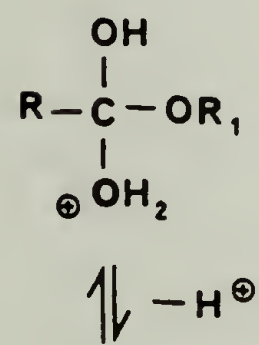
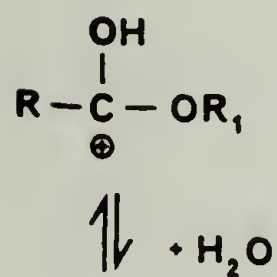
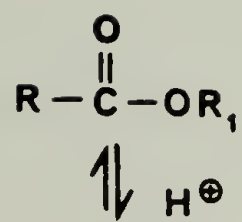
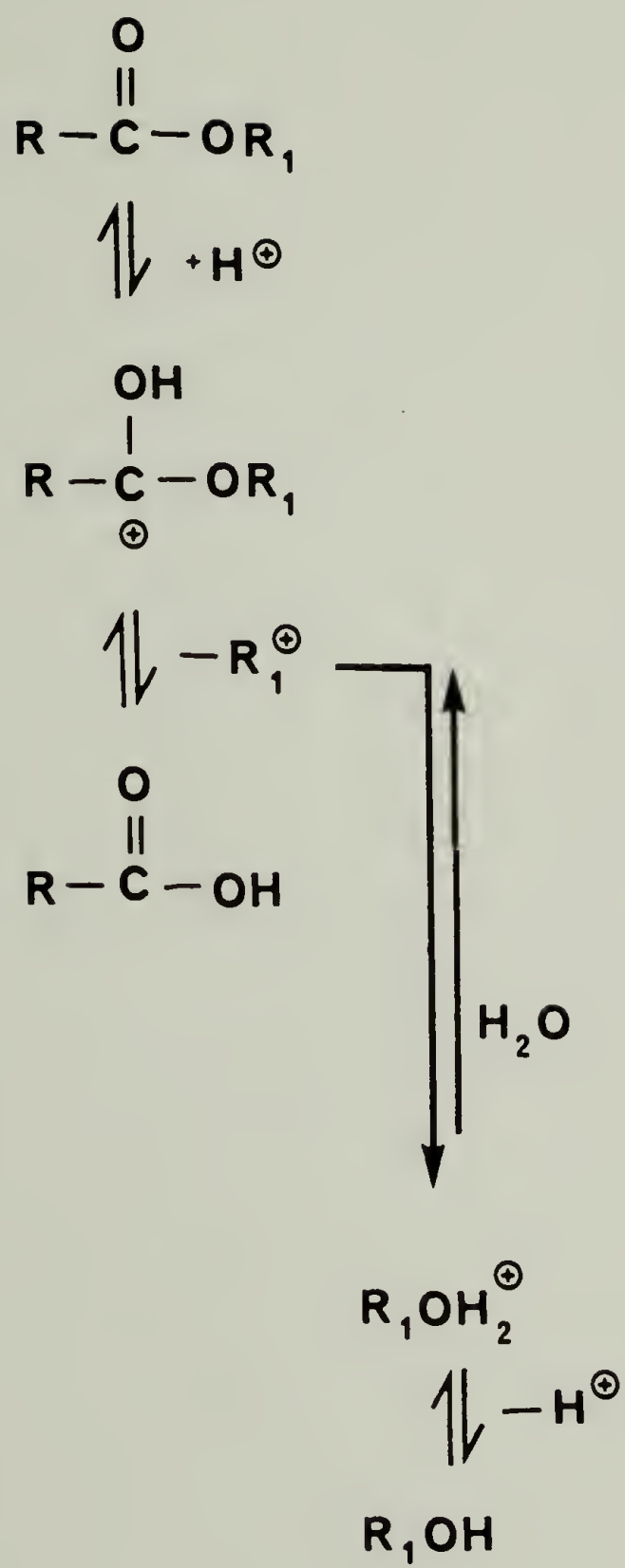


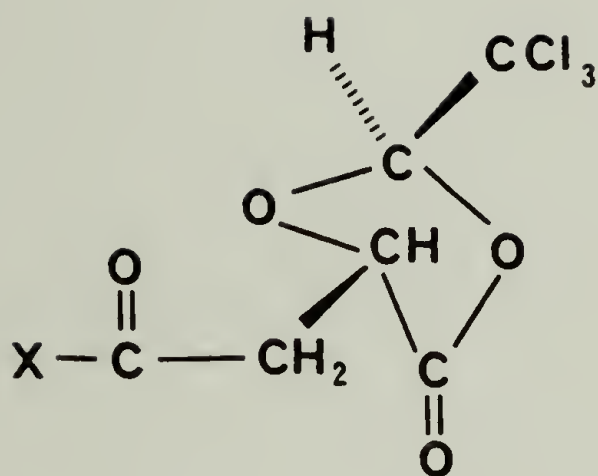
Figure 31. A_{Al} hydrolysis mechanism.



step by this mechanism. Salomaa theorized that the confirmation of a substituted dioxolanone ring is most like that of cyclopentanone or methylenecyclopentane namely "a half chair" form with the doubly bonded carbon located on the average in the plane of the ring. The transition state of the A-1 hydrolysis, in which the bond between the 1,2-carbon-oxygen ring atoms, has a partial double bond character, and must assume either a planar form or preferentially an "envelope" form (Fig.32).

It may be inferred from the above model and from experimental observations that there is considerable angle strain in the transition states in comparison to the corresponding forms derived from dioxolanes in which the carbon atom 4 possesses sp^3 -hybridized bonds. These steric factors explain the observation that a normal A-1 hydrolysis mechanism is severely retarded in dioxolanones as compared to dioxolanes. A change of hybridization to sp^3 at the carbon atom 4 of the transition state accelerates the hydrolysis of the dioxolanone. This is most easily achieved by nucleophilic attack of water at this carbon atom 4. In addition to involving the proton uptake equilibrium, the hydrolysis process presumably also involves a water-carbonyl equilibrium followed by a rate determining unimolecular decomposition of the intermediate formed. Alternately, the rate determining step could be that between the carbonyl carbon atom of the protonated

Figure 32. Transition state of the A-1 hydrolysis.



$X = \text{OH}, \text{Cl}, \text{SR}$

substrate and the water molecule, as indicated by the kinetic data.

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Eggerer and Gr^unew^ualder hydrolyzes the optically active S-(malic acid chloralide)-N-capryloyl-cysteamine using strongly acidic conditions to form the corresponding optically active hydroxy acid. Their work demonstrated that, during the hydrolysis, no racemization occurred at the chiral carbon atom.

The literature has shown that it is possible to react a strong base, such as ammonia, with a dioxolanone group. Audrieth and Sveda⁷² ran this reaction and isolated as the major product the corresponding hydroxy amide compound (Fig. 33).

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Lemieux⁷³ demonstrated that it is possible to react a dioxolanone directly with methanol, under acidic conditions, and form the hydroxy ester (Fig. 34).

From the work of these authors, a number of approaches are shown to be feasible as methods to unblock the dioxolanone group and attain useful intermediates for the synthesis. It is unknown, however, if these reactions can be performed successfully in the presence of the thiol ester group and this information must be empirically determined. I attempted to prepare the S-(beta-hydroxy succinyl benzyl ester) octadecylate directly from the S-(malic acid chloralide) octadecylate following the procedure outlined by Lemieux. All attempts to prepare this compound were unsuccessful. The major product isolated

Figure 33. Reaction of a dioxolanone group with ammonia.

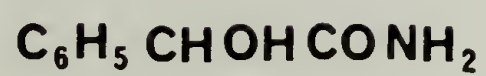
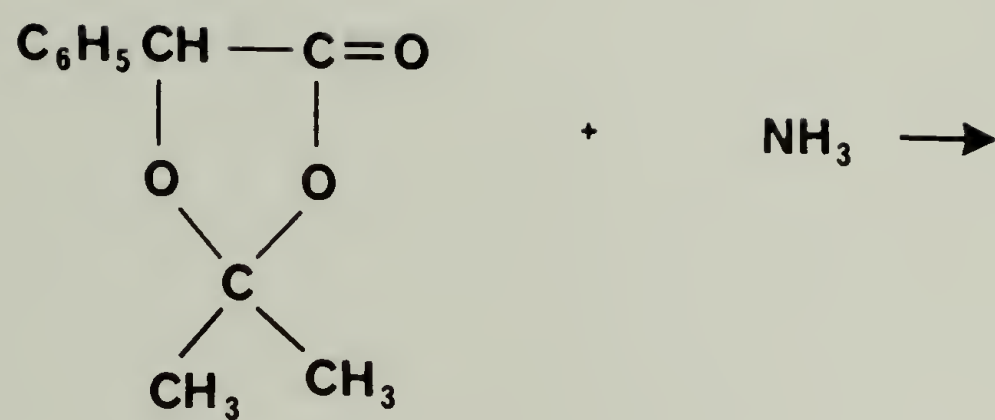
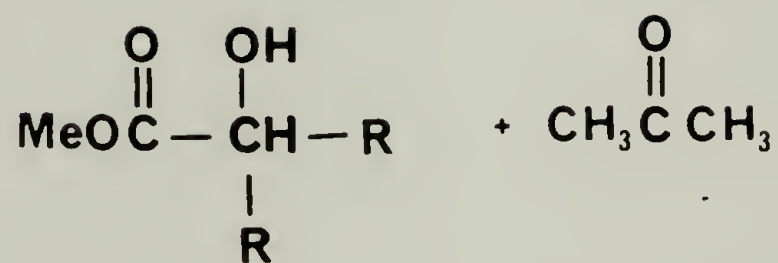
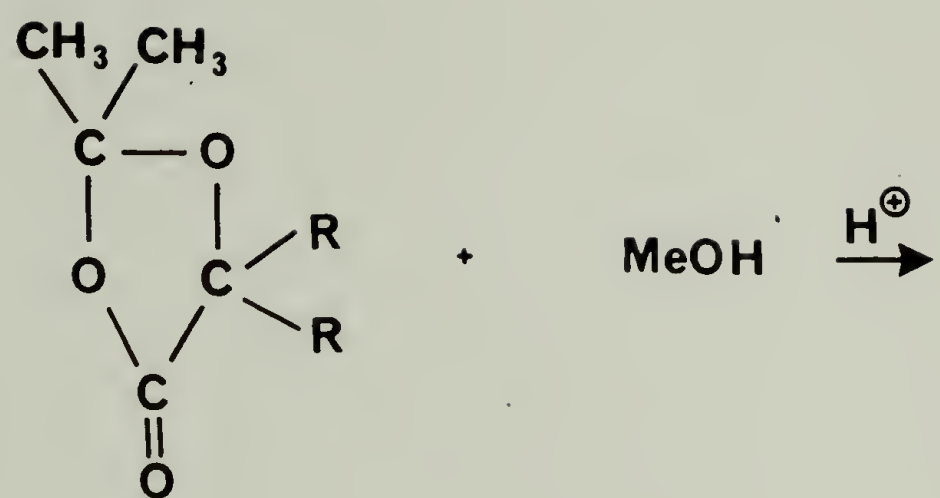


Figure 34. Reaction of a dioxolanone directly with methanol.



was the dibenzyl ester of malic acid and low molecular weight polymer (Fig. 35).

The product mixture was complex to analyze. However, strong spectral evidence, as well as chromatographic separation of the products demonstrated that the dibenzyl ester and polymer were the major components formed in the reaction. It is well known in the literature from research done on the synthesis of biological compounds that the equilibrium for an ester interchange reaction of the thiolester lies strongly in favor of ester formation,⁷⁴ that is to the right in the reaction shown in Fig. 36. The conditions used for reacting the dioxolanone with benzyl alcohol were also favorable for the reaction of the benzyl alcohol with the thiol ester, so that the more thermodynamically stable ester was isolated rather than the thiol ester.

Because of the unfavorable thermodynamics properties encountered in preparing the S-(beta-hydroxysuccinyl benzyl ester) octadecylate, I chose to perform the acid hydrolysis of the dioxolanone prior to forming the ester (Fig. 37). I chose this reaction course for the following reasons:

- (1) the literature reveals that under strong acid conditions ($\text{pH} < 2$), the hydrolysis of the thiol ester is much slower than a corresponding ester (75);
- (2) the dioxolanone group has been demonstrated to hydrolyze quite easily under strong acid conditions without affecting the chiral group in the ring structure.

Figure 35. Reaction of S-(malic acid chloralide) octadecylate directly with benzyl alcohol.

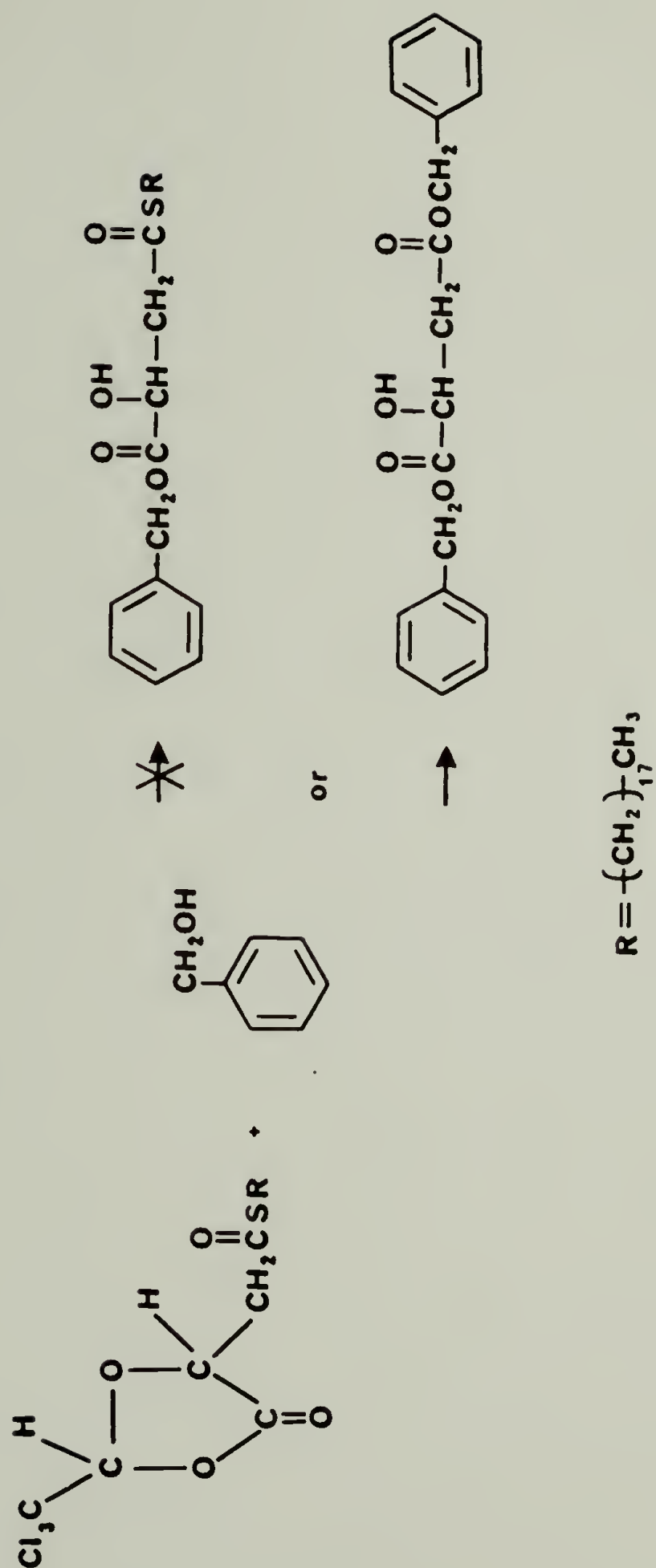


Figure 36. Ester interchange reaction of the thiol ester.

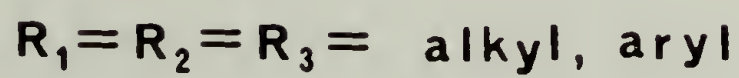
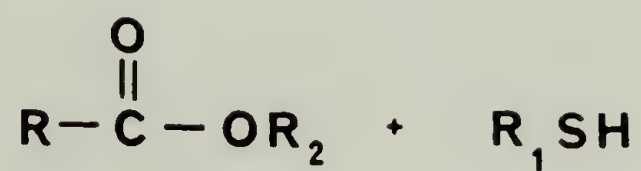
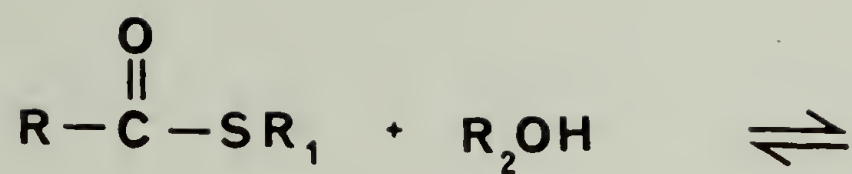
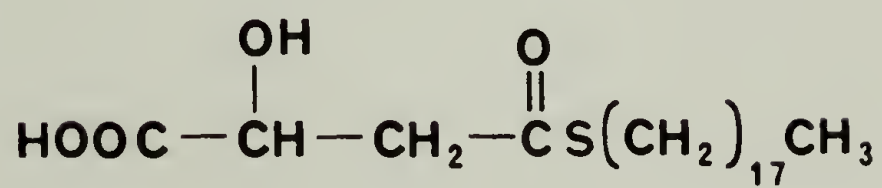
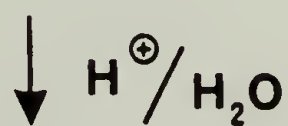
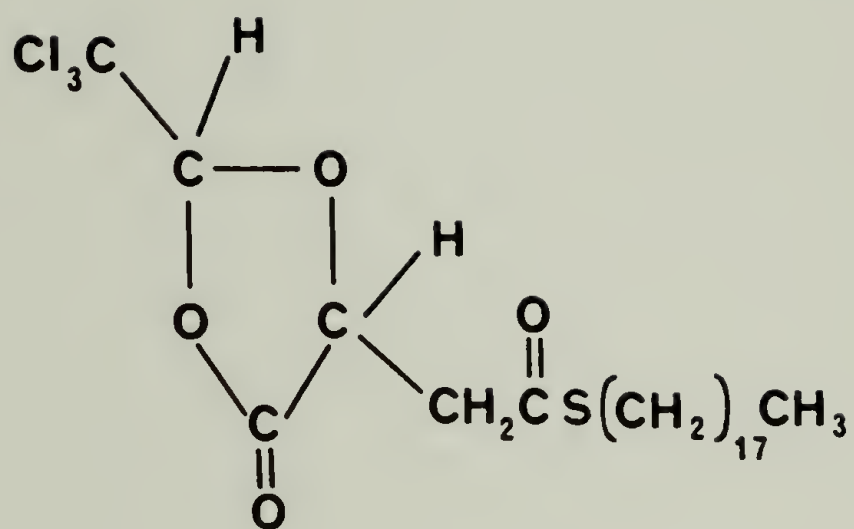


Figure 37. Acid hydrolysis of the dioxolanone.



- (3) after isolation of the S-(beta-hydroxy succinyl) octadecylate, success in making the benzyl ester seemed more reasonable based on the literature reference.

As described, the S-(malic acid chloralide) octadecylate was acid hydrolyzed, leading to a very interesting observation. The chemical nature of the R-group of the thiol ester played a critical role in the isolation of the final product. After hydrolysis and subsequent extraction with organic solvents and water washing, if the R-group was a t-butyl or phenyl, no product yield was isolated after solvent removal. The mass balance demonstrated that during the reaction sequence, the starting material was lost. After repeated experiments gave identical results, I changed the chemical nature of the compound by attaching a long aliphatic tail using linear C₁₂ and C₁₈ groups to the thiol ester. This simple modification made it possible to isolate the hydrolyzed product. The following Table 2 shows the results obtained for the different experiments. Infrared, carbon-13 and proton NMR spectroscopy, as well as base saponification and elemental analysis all confirmed the proposed structures for the S-(beta-hydroxysuccinyl) alkylates.

A number of different reactions were investigated to prepare the S-(beta-hydroxysuccinyl benzyl ester) octadecylate. The S-(beta-hydroxysuccinyl) octadecylate was reacted with compounds which react with the carboxylic acid forming a

TABLE 2

PREPARATION OF S-(BETA-HYDROXYSUCCINYL) ALKYLATES

R- Group	Polymer Yield %		Melting Point °C	
	racemic	optically active	racemic	optically active
ter- butyl	0	0	-	-
phenyl	0	0	-	-
dodecyl	52	49	109	101
octadecyl	60	53	100	94

better leaving group. These compounds can be considered to be promoters for esterification. The reagents were chosen because the literature revealed that these compounds could activate the esterification reaction in the presence of a hydroxy group on the reacting molecule.

Trifluoroacetic anhydride was reacted with S-(beta hydroxy succinyl) octadecylate to form the mixed anhydride intermediate, as shown in Fig. 38.

By following the reaction conditions outlined by Parish and Stock⁷⁶, I was unable to isolate the desired product. The isolated product was a complex mixture of undefined components. Thin layer chromatography and column chromatography were used to separate the components, but none of the components showed the characteristic absorptions for the S-(beta hydroxysuccinyl benzyl ester) octadecylate.

Dicyclohexylcarbodiimide was reacted with S-(beta hydroxy succinyl) octadecane according to the reaction conditions used by Smith, et. al.⁷⁷ The reaction mechanism is proposed to be as shown in Fig. 39.

The above mechanism has been studied by Doleschall and Lempert.⁷⁸ I performed the reaction and was able to isolate a 25% yield of the racemic S-(beta hydroxysuccinyl benzyl ester) octadecylate. This compound was separated by column chromatography and the infra-red, carbon-13, proton NMR spectra and elemental analysis supported the

Figure 38. Reaction of trifluoroacetic anhydride with S-(beta-hydroxysuccinyl) octadecylate.

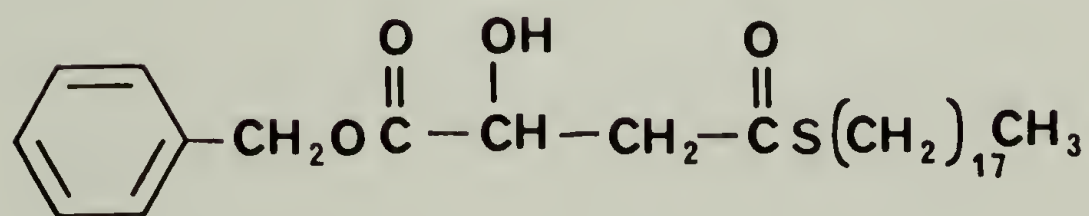
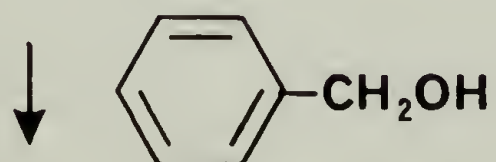
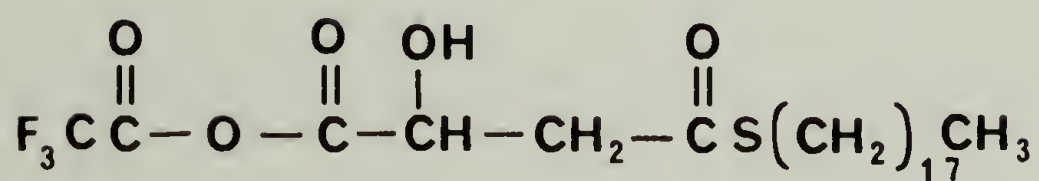
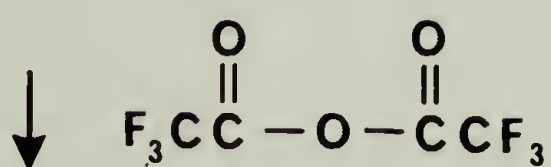
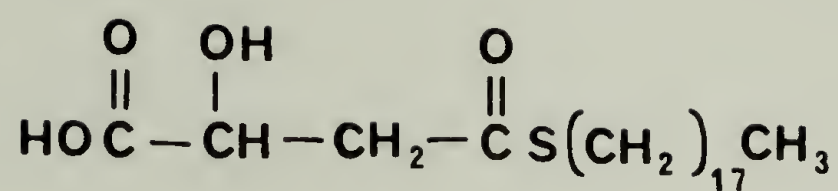
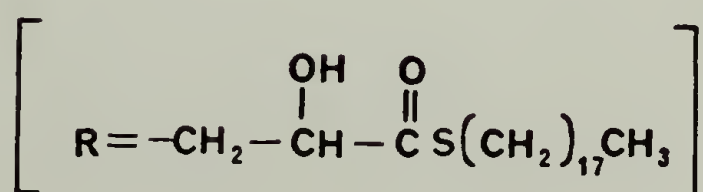
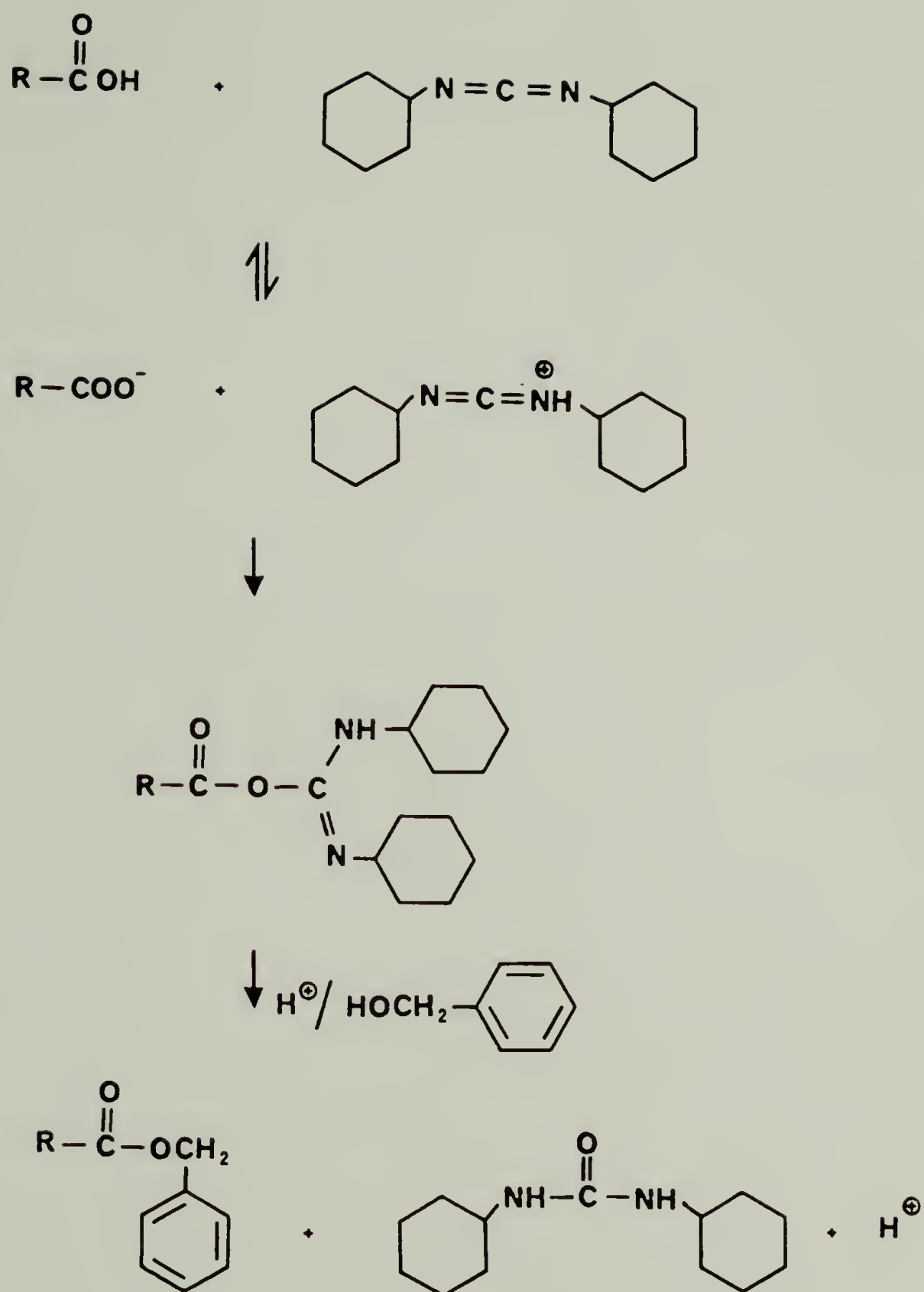


Figure 39. Reaction of dicyclohexylcarbodiimide with
S-(beta-hydroxysuccinyl) octadecylate.



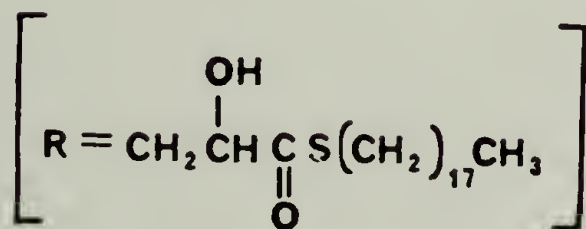
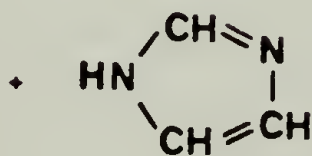
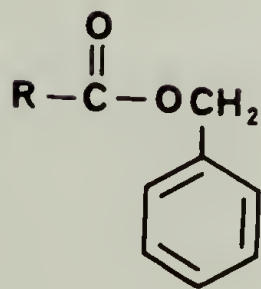
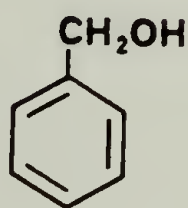
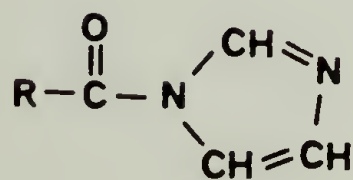
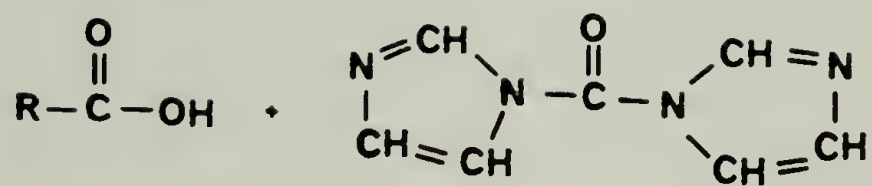
proposed structure. The optically active material had a melting point of 49-51°C and the racemic material had a melting point of 64-67°C. The yield of the optically active material was 13%. I decided to investigate other methods of promoting esterification prior to optimizing the yield of this reaction.

N,N-carbonyldiimidazole was reacted with the S-(beta hydroxysuccinyl) octadecylate as shown in Fig. 40, according to the reaction condition specified by Staab and Mannschreck.⁷⁹ Using this reaction, the racemic S-(beta hydroxysuccinyl benzyl ester) octadecylate could be prepared in 36% yield after purification using column chromatography. The optically active material was prepared having an overall yield of 39%. The various spectral data, as well as elemental analysis, confirmed the compound structure.

Both of the methods used to prepare the ester by reaction with dicyclohexylcarbodiimide or N,N-carbonyldiimidazole demonstrated their potential for being useful to prepare the benzyl ester of the desired material. The only drawback, using these reactions, is the overall yields which are somewhat low.

Prior to optimizing one of the above reactions, I chose to look at the simple esterification of the S-(beta hydroxysuccinyl) octadecylate by reacting it with benzyl alcohol and p-toluenesulfonic acid. Because the literature

Figure 40. Reaction of N,N-carbonyldiimidazole with
S-(beta-hydroxysuccinyl) octadecylate.



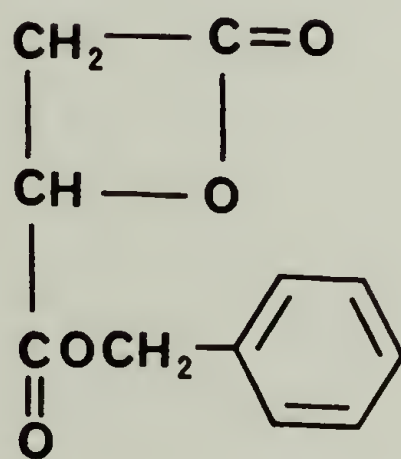
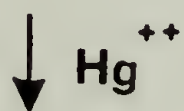
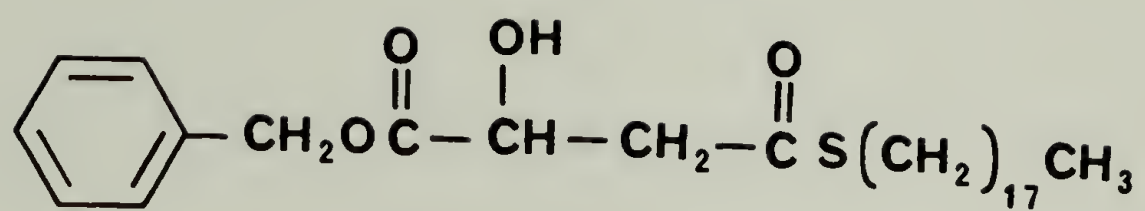
demonstrated that thiol esters are stable to acid conditions at $\text{pH} < 2$,⁸⁰ I attempted the esterification reaction at various temperatures. At reaction temperatures greater than 50°C , I isolated the dibenzyl ester of malic acid and other undefined products. At temperatures below 40°C , I isolated the desired product S-(beta-hydroxy succinyl benzyl ester) octadecylate. The racemic compound was obtained in an overall yield of 65% and the optically active compound in a yield of 72%. The compound was isolated as a white powdery substance after recrystallization. The compound gave identical spectra to the compounds prepared by the other previously discussed preparation methods. Because of its simplicity, simple direct esterification was the reaction of choice and optimization of the other described methods using esterification promoters was not attempted.

The final step in the synthesis of the lactone monomer takes place through the formation of the malolactone benzyl ester from the S-(beta-hydroxy succinyl benzyl ester) octadecylate using the reaction discovered by Masamune. This reaction consists of intramolecular esterification to form a beta lactone from a thiol ester and beta hydroxy group using a mercuric catalyst as shown in Fig. 41.

V. Lactonization by Masamune Reaction

Masamune discovered the reaction for the preparation of the beta lactone by accident. He was trying to prepare

Figure 41. Formation of malolactone benzyl ester from S-(beta-hydroxysuccinyl benzyl ester) octadecylate.



tylonolide, the aglycone of a 16-membered macrolide antibiotic, tylosin.⁸¹ He found during the attempted formation of the C-16 lactone by an intramolecular esterification using the thiol ester, that the hydroxy on the beta position led to the preparation of the beta lactone, as shown in Fig. 42.

To prepare the C-16 lactone, the beta hydroxyl group had to be blocked. Masamune performed a number of experiments for the purpose of defining the exact mechanism of this reaction. He studied the following reaction of the thiol ester with different alcohols using mercuric methanesulfonate as the catalyst as illustrated in Fig. 43. Some of the results are listed in the following Table 3. Masamune's experimental results demonstrated the following points:

- 1) The $S \rightarrow O$ ester conversion proceeds smoothly even if R_1 and R_2 are bulky.
- 2) There is no ketene formed as an intermediate during the reaction, which is illustrated by the experiment with the deuterium on the alpha carbon;
- 3) The reaction in some cases is very fast; and
- 4) The yields of the ester formed are excellent.

Masamune ran the reaction in the absence of alcohol and found spectral evidence to support the proposed formation of a mixed anhydride as shown in the Fig. 44. With the addition of alcohol to the reaction, the ester is

Figure 42. Preparation of the beta-lactone on the tytonolide molecule.

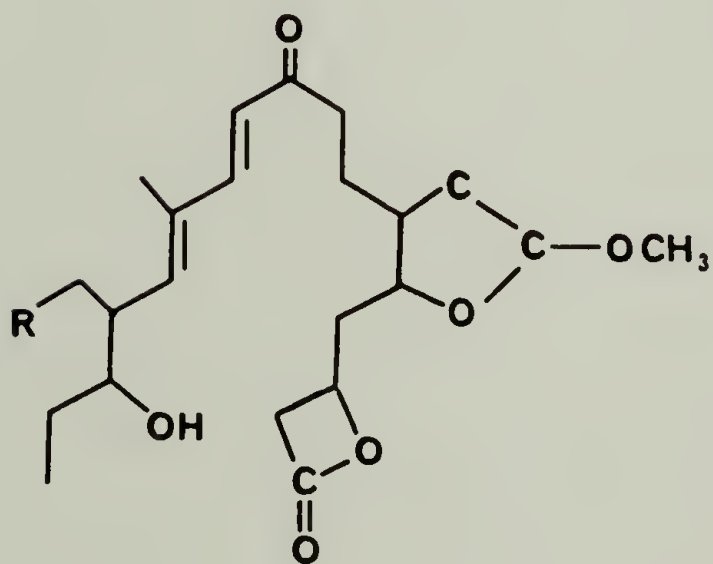
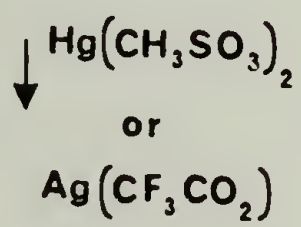
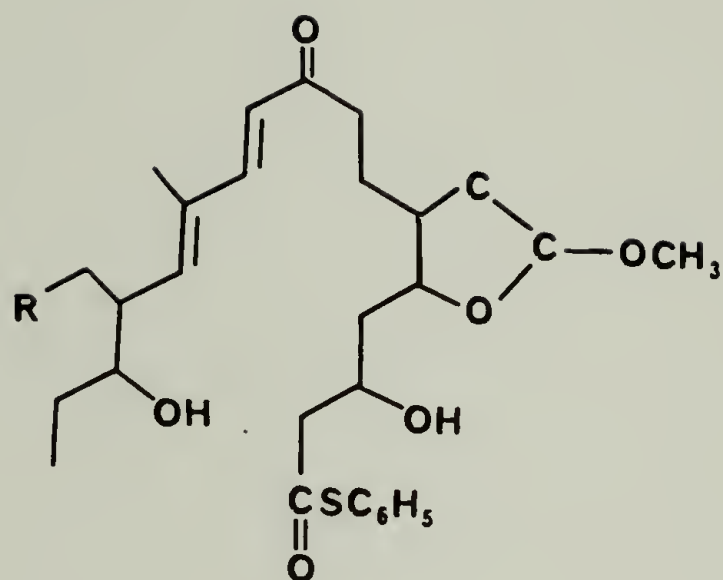


Figure 43. Reaction of a thiol ester with various alcohols using a mercury (II) salt as the catalyst.

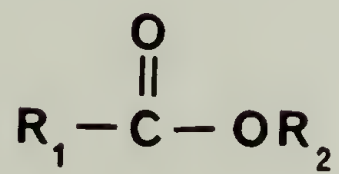
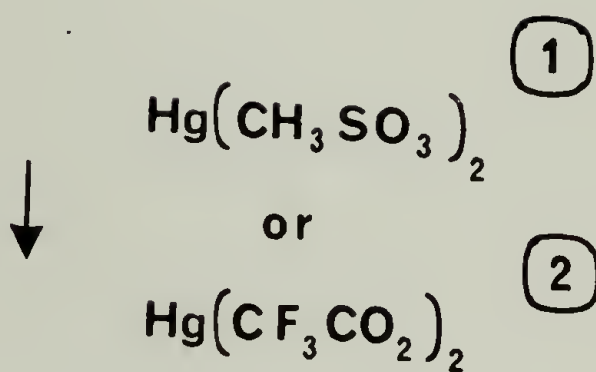
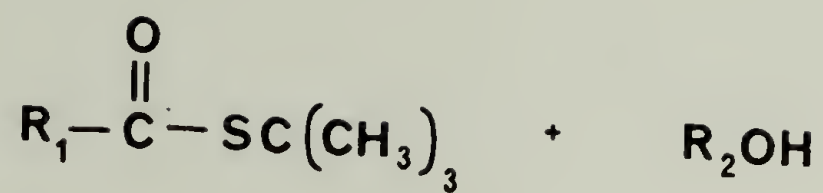


TABLE 3

PREPARATION OF ESTERS FROM THIOL ESTERS

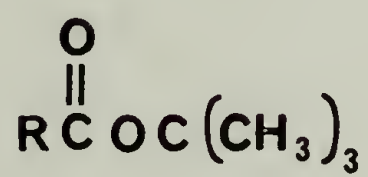
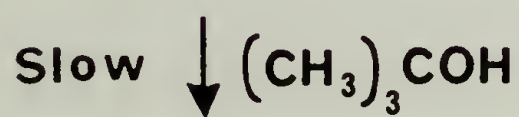
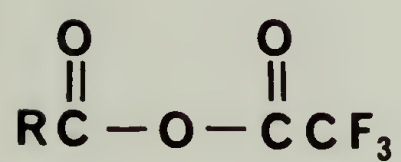
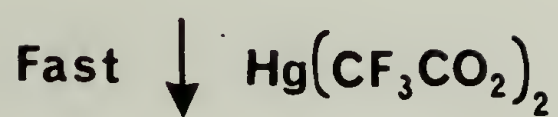
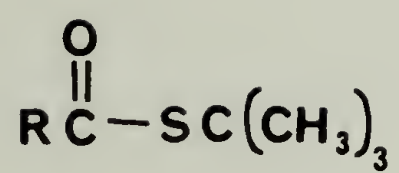
R_1 Group	R_2OH Group	Catalytic Reagent	Yield %
phenyl	ter-butyl	1,2	100
phenyl	isopropyl	1	75
phenyl	$((CH_3)_2CH)_2CH-$	1	95
phenyl	$c-C_6H_{11}CH_2-$	1	88
ter-butyl	ter-butyl	1	90
$CH_3-CH-CH_2-$	ter-butyl	1	85
$CH_3(CH_2)-C(C_2H_5)D-$	ter-butyl	1	100

Reaction Temperature: 25 °C

Reaction Time: 5 minutes

Solvent: acetonitrile

Figure 44. Formation of the mixed anhydride intermediate followed by the slow reaction with alcohols.



R = alkyl

formed but the reaction is 10 times slower than the direct $S \rightarrow O$ ester conversion. Masamune concluded that the major course of the reaction is the direct conversion $S \rightarrow O$ ester involving an intermediate complex similar to that shown as follows by Fig. 45. In this intermediate, the soft-soft interaction between the sulfur and $Hg(II)$ and the hard-hard combination of the hydroxy and acyl groups follow the concept of hard-soft acids and bases.

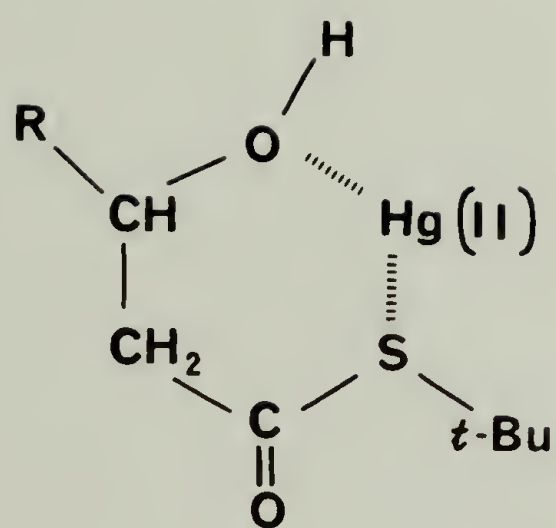
VI. Theory of Hard-Soft Acids and Bases

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In 1963, Pearson published a notable paper on the concept of hard and soft acids and bases. Pearson's concept rationalized and predicted chemical reactivities, selectivities and stabilities of compounds without the complications of the entanglements of electronic, steric and a variety of other effects. In essence, his idea succeeded in conveying the practical idea that any type of chemical bond one chooses (strong sigma or pi type bond, ligand metal interaction, charge transfer complex or a solvation bond) may be described as an acid bound to a base. Accepting this premise as true, one must also be prepared to adopt the view that there are two general classes of acids and two general classes of bases.

Chemical entities including atoms, molecules, ions, and free radicals are categorized as "hard" or "soft" Lewis acids or bases.

Figure 45. Intermediate complex in the formation of thiol esters.



R = Methyl

The characteristics are as follows:

Hard acids - acceptor atoms are small, have high positive charge and do not contain unshared pairs in their valence shells. They have low polarizability and high electronegativity.

Hard bases - donor atoms are of high electronegativity and low polarizability and are difficult to oxidize. They hold their valence electrons tightly.

Soft acids - acceptor atoms are large, have low positive charge and contain unshared pairs of electrons in their valence shell. They have high polarizability and low electronegativity.

Soft bases - donor atoms are of low electronegativity and high polarizability and are easy to oxidize. They hold their valence electrons loosely.

From classical theory, a strong acid and strong base form a stable complex, whereas a weaker acid forms a less stable complex. The strength of the acid and base are improved by increased charge and decreased radius of cation or anion. The complex stability may be characterized by two parameters:

intrinsic strength (S)

softness parameter (σ)

Therefore the reaction is characterized by the equilibrium constant K as defined in the following Fig. 46.



$$\log K = S_A S_B + \sigma_A \sigma_B$$

Figure 46. Acid-Base Complex Stabilities

The "rule of thumb" is that acids show greater affinity for bases of the same class. Hard acids (acceptors) form strong complexes with hard bases (donors), but bind reluctantly or weakly to soft bases. This rule has nothing to do with acid or base strength but merely says that the complex A:B will have greater stability if both A and B are hard or if both are soft. This rule is not a theory but a generalization based on experimental evidence.

The following Tables 4 and 5 give a few examples of hard-soft acids and bases. It is difficult to draw an exact conclusion on the hardness or softness of a compound so that some materials are classified as borderline between hard and soft.

Thioacids or thiol esters have been observed to precipitate certain soft heavy metal cations as the sulfides. This precipitation of the heavy metal sulfide occurs nearly instantaneously for copper, silver, thallium, mercury and lead. Addition of a hard base nucleophile forms new acylation products at increased rates.⁸³

TABLE 4

CLASSIFICATION OF LEWIS ACIDS

Hard	Soft
H^+ , Li^+ , Na^+ , K^+ , Be^{2+} , Mg^{2+} , Ca^{2+} , Sr^{2+} , Mn^{2+} , Al^{3+} , Sc^{3+} , Ga^{3+} , In^{3+} , N^{3+} , Cl^{3+} , Cr^{3+} , Co^{3+} , Fe^{3+} , As^{3+} , CH_3Sn^{3+} , Si^{4+} , Ti^{4+} , Th^{4+} , U^{4+} , Ce^{3+} , $(CH_3)_2Sn^{2+}$, MoO^{3+} , BF_3 , $B(OR)_3$, $Al(CH_3)_3$, $AlCl_3$, RSO_2^+ , $ROSO_2^+$, SO_3 , Cl^{7+} , Cr^{4+} , CO_2	Cu^+ , Ag^+ , Tl^+ , Hg^+ , Pd^{2+} , Cd^{2+} , Pt^{2+} , Hg^{2+} , CH_3Hg^+ , Tl^{3+} , BH_3 , RS^+ , I^+ , Br^+ , HO^+ , RO^+ , I_2 , Br_2 , trinitrobenzene, quinones, O, Cl, Br, I, N, metal atoms, bulk metals, carbenes
Borderline: Fe^{2+} , Co^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+} , Pb^{2+} , Sn^{2+} , Sb^{3+} , SO_2 , R_3C^+ , $C_6H_5^+$	

TABLE 5

CLASSIFICATION OF LEWIS BASES

Hard	Soft
H_2O , OH^- , F^- , CH_3CO_2^- , SO_4^{2-} , CO_3^{2-} , ClO_4^- , NO_3^- , ROH , RO^- , R_2O , NH_3 , RNH_2 , N_2H_6	R_2S , RSH , RS^- , I^- , SCN^- , $\text{S}_2\text{O}_3^{2-}$, R_3P , R_3As , $(\text{RO})_3\text{P}$, CN^- , RCN , CO , C_2H_4 , C_6H_6 , H^- , R^-

Borderline: $\text{C}_6\text{H}_5\text{NH}_2$, $\text{C}_5\text{H}_5\text{N}$, N_3^- , N_2 , Cl^- , Br^- , NO_2^- ,
 SO_3^{2-}

It has been observed for the reaction of a thiol ester with silver cation followed by reaction with water, that two silver ions are needed per thiol ester group.⁸⁴ This result can be explained by the fact that, in a silver-sulfur bond, metal to ligand electronic feed-back involves the $d_{\pi} - d_{\pi}$ bonding and has the effect of leaving the positivity of the sulfur atom only slightly enhanced. The sulfur is then able to use its remaining pair of 3p electrons to coordinate with yet another heavy metal ion until high positive charge on the sulfur precludes further coordination and produces a good leaving group. The order of leaving group activities may be written as shown in Fig.47.

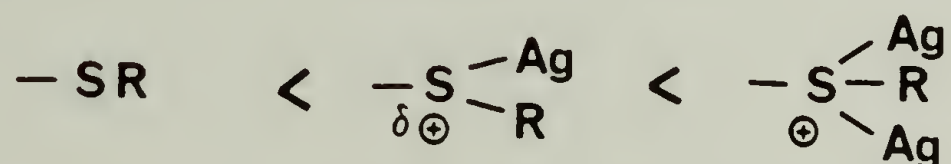


Figure 47. Leaving Group Activities

It may be that this kind of multi-coordination is general for soft polarizable bases interacting with soft acids (analogous to the multiplicity of oxidation numbers characteristic of soft bases), so that many reactions, in which assistance derives from soft leaving group/soft acid interaction, will be of high kinetic order in reference to the assisting acid.

VII. Preparation of Malolactone Benzyl Ester

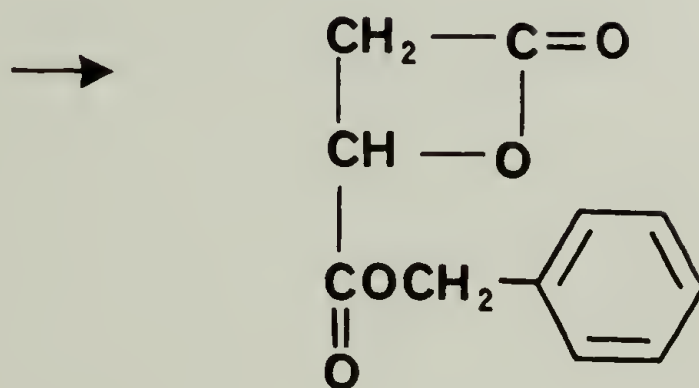
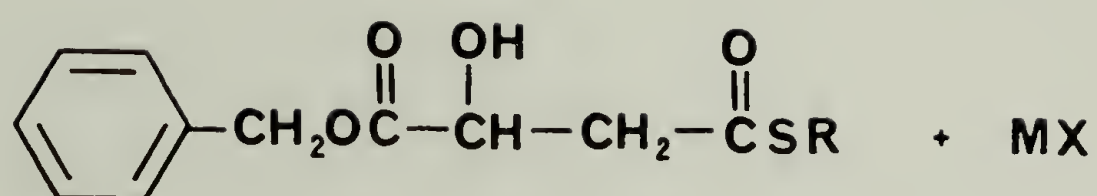
The experimental finding that hard acids complex strongest with hard bases and soft acids complex strongest

with soft bases leads to the conclusion that to utilize the Masamune reaction to prepare the beta lactone from S-(beta hydroxy succinyl benzyl ester) octadecylate one must match chemical reactivities of the thiophilic cation agent to the thiol ester. The general reaction scheme is shown in Fig. 48, and the two variables which can be manipulated are (1) the type of R group present, the alkyl or aryl group bonded to the sulfur atom, and (2) the type of MX, the thiophilic cation compound. The results of the various experimental conditions are summarized in the following Table 6.

Mercuric methanesulfate and mercuric toluenesulfonate were the only thiophilic cations which yielded the lactone. Silver, copper (I) and copper (II), and thallium (III) were also tried but in no case was the lactone peak (1850 cm^{-1}) observed following the reaction by infrared spectroscopy.

The lactone once formed was quite unstable and decomposed if not purified rapidly using preparative high pressure liquid chromatography. The lactone could be purified on a silica gel column using methylene chloride as the liquid phase. Once purified, the lactone was stable. The racemic malolactone benzyl ester was an oil and this compound had a boiling point of $115^{\circ}\text{C}/0.001\text{ mm}$. The optically active lactone was a solid material which melted at 37°C and subsequent purification by distillation showed

Figure 48. The general reaction scheme for the preparation of beta-lactones from thiol esters using mercury (II) salts.



R = alkyl, aryl

M = thiophilic cation

TABLE 6

PREPARATION OF MALOLACTONE BENZYL ESTER

R-Group	MX	Solvent	Reaction Temperature °C	Reaction Time minutes	Yield %	Purity %
$-(CH_2)_{17}CH_3$	$Ag(CF_3CO_2)$	CH_3CN	30	60	0	-
$-(CH_2)_{17}CH_3$	$Ag(CF_3SO_3)$	CH_3CN	30	60	0	-
$-(CH_2)_{17}CH_3$	$AgBF_4$	CH_3CN	30	60	0	-
$-(CH_2)_{17}CH_3$	$Cu(CF_3SO_3)$	CH_3CN	30	60	0	-
$-(CH_2)_{17}CH_3$	$Cu(CF_3CO_2)$	CH_3CN	30	60	0	-
$-(CH_2)_{17}CH_3$	$Cu(CF_3CO_2)_2$	CH_3CN	30	60	0	-
$-(CH_2)_{17}CH_3$	$Hg(CF_3CO_2)_2$	ϕCN	50	60	0	-
$-(CH_2)_{17}CH_3$	$Hg(CH_3\phi SO_3)_2$	ϕCN	55	60	$90^a, 75^b$	-
$-(CH_2)_{17}CH_3$	$Hg(CH_3SO_3)_2$	$CH_3(CH_2)_2CN$	92	20	$50^c, 40^d$	$99^e, 99^f$
-phenyl	$Hg(CH_3\phi SO_3)_2$	ϕCN	55	60	70^g	-
$-(CH_2)_{17}CH_3$	$Tl(CF_3CO_2)_3$	ϕCN	30	60	0	-

- (a) yield of racemic lactone determined by infrared spectroscopy
 (b) yield of optically active lactone determined by infrared spectroscopy
 (c) yield of racemic lactone determined after purification by H.P.L.C.
 (d) yield of optically active lactone determined after purification by H.P.L.C.
 (e) purity of racemic lactone determined by analytical H.P.L.C.
 (f) purity of optically active lactone determined by analytical H.P.L.C.
 (g) yield determined by infrared spectroscopy

a boiling point 105°C/0.001 mm. The infrared, proton NMR, and carbon-13 spectra showed the characteristic peaks for the lactone. The spectral data was the same as reported by Vert and Lenz³⁸ for the preparation of the racemic monomer.

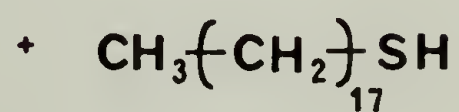
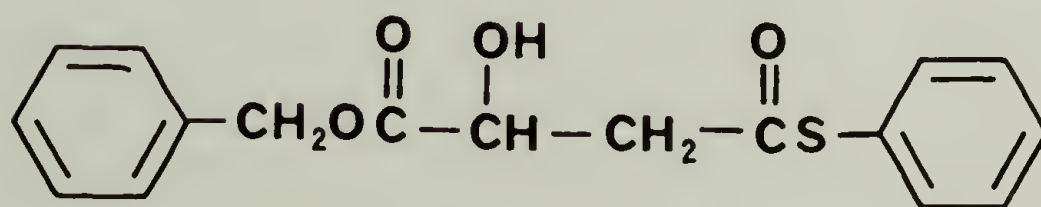
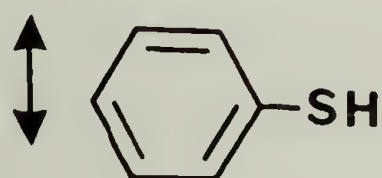
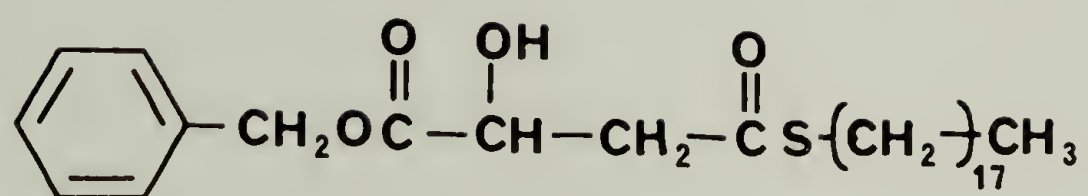
The previous table described the preparation of the lactone from S-(beta hydroxy succinyl benzyl ester) phenylate. This compound was prepared by thiol ester interchange reaction from the S-(beta hydroxy succinyl benzyl ester) octadecylate. As previously described, the S-(beta hydroxy succinyl) phenylate cannot be prepared by the lactone synthesis described because of the problem of isolating the compound in the hydrolysis of the 1,3-dioxolan 4-one.

There is an excellent paper on thiol ester interchange written by Sasin et. al.⁸⁵ Using his procedure for the reaction shown in Fig. 49, I isolated 37% yield of the S-(beta hydroxy succinyl benzyl ester) phenylate after purification by column chromatography.

The compound had an infrared spectrum which gave the characteristic absorptions of the benzyl ester and thiol ester. The proton NMR had the characteristic peaks for the compound.

This compound was lactonized using mercuric toluene-sulfonate to determine the effect of the group attached to the sulfur on the lactonization yield. Contrary to the

Figure 49. Sasin et. al.⁸⁵ method for thiol ester interchange reaction.



results given by Masamune, I found no significant difference in the ability of the compound to form the lactone.

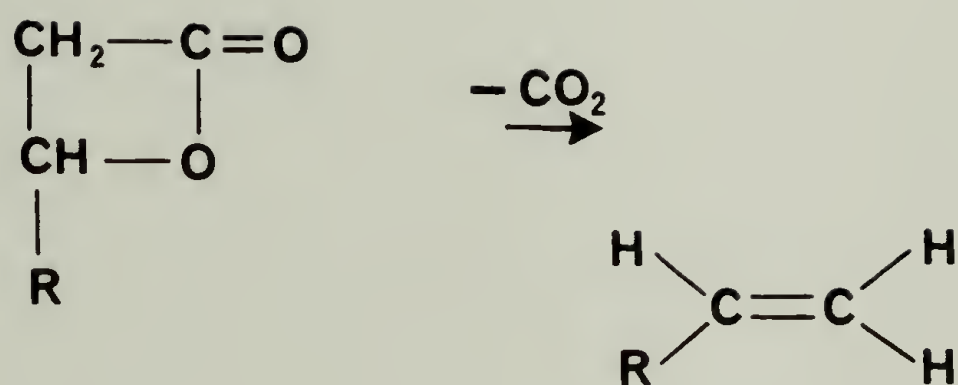
A very interesting feature of the lactonization reaction using mercury (II) as the thiophilic cation is the observation that the lactonization is more successful at higher reaction temperatures (90°C) than at room temperature, as per Masamune's experimental conditions. Brewster, et. al.⁸⁶ found that beta substituted beta lactones decompose losing carbon dioxide to the corresponding double bonded compound at temperatures $>50^{\circ}\text{C}$ (Fig. 50).

There are also other papers⁸⁷ in the literature which predict the decomposition of beta substituted beta lactones at high temperatures. The reaction involving intramolecular cyclization of a beta hydroxy and thiol ester groups using thiophilic cation (Masamune)⁴⁴ appears to work very well at high temperatures but not at low temperatures (25°C, 50°C, 75°C) where no lactone is formed.

VIII. Chiroptical Properties of Malolactone Benzyl Ester and the Intermediates in the Lactone Synthesis

As was previously discussed, the synthetic scheme outlined for preparing the optically active malolactone benzyl ester monomer was followed because at no time during the reaction sequences were bonds made or broken at the chiral carbon, hence, no racemization should occur. The optical rotatory dispersion (ORD) results for the intermediates are listed in Table 7 and the accompanying

Figure 50. Decomposition of beta-substituted-beta-lactones to the corresponding alkene.



R = alkyl

figures 51-56. Optical rotatory dispersion is a method to observe changes in optical rotation with wavelength. ORD is a useful technique for determining the optical activity of a compound.

(α) is called the specific rotation and is dependent on wavelength and temperature as indicated by use of subscript and superscript, respectively.

$$(\alpha)_{\lambda}^T = \alpha / lc$$

α is the observed angle of rotation, l is the path length of the cell in decimeters, and c is the concentration in grams per milliliter.

Optical rotatory power is a property of molecules. To eliminate the effect of molecular weight on rotatory power one can define a new term molecular rotation, (M).

$$(\overline{M}) = (\overline{\Phi}) = \alpha \cdot \text{molecular weight} / 100$$

The results listed in Table 7 show that all the intermediates are optically active. The lactone has a

Figure 51. Optical rotatory dispersion curve of L-malic acid chloralide.

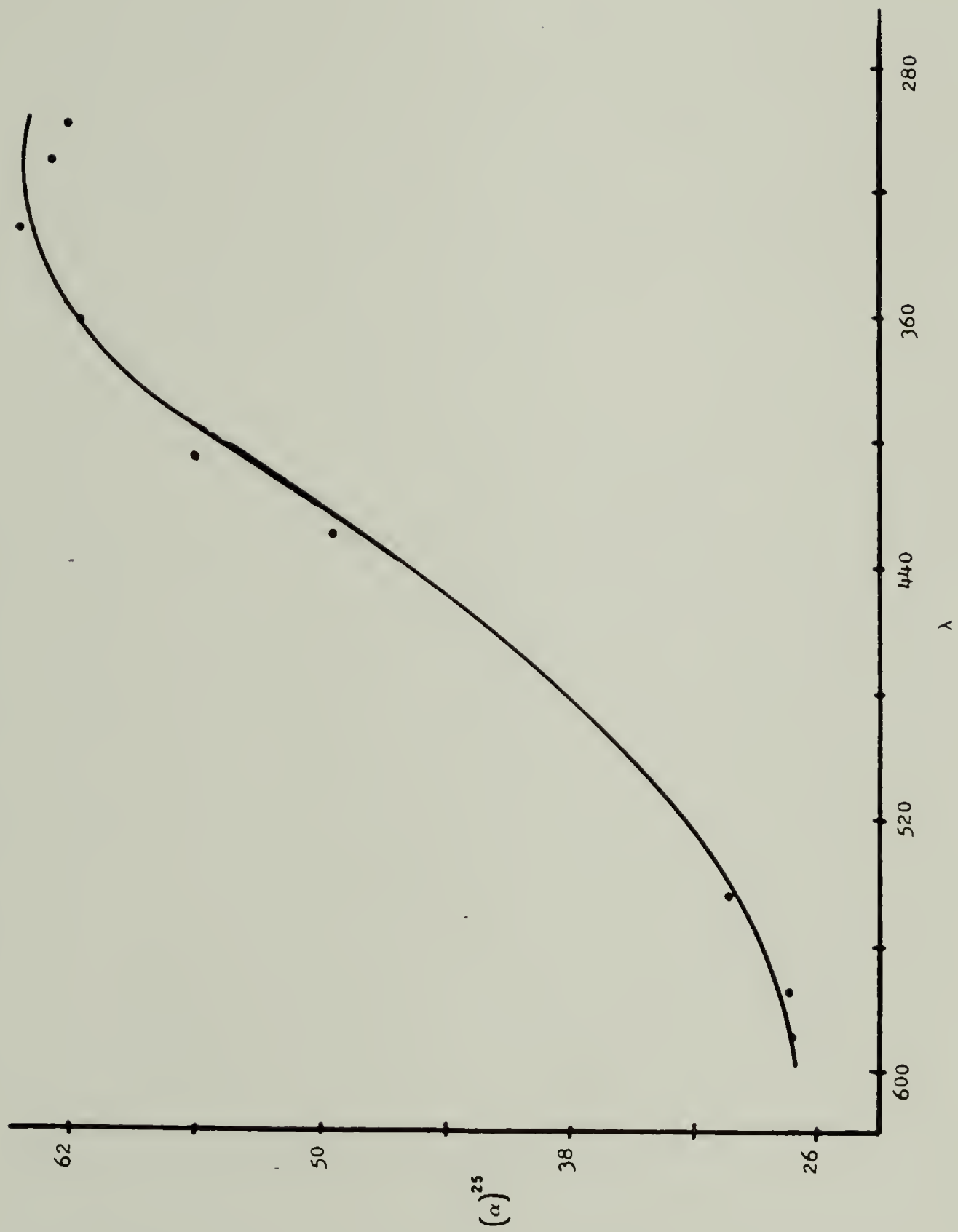


Figure 52. Optical rotatory dispersion curve of L-malic acid chloralide chloride.

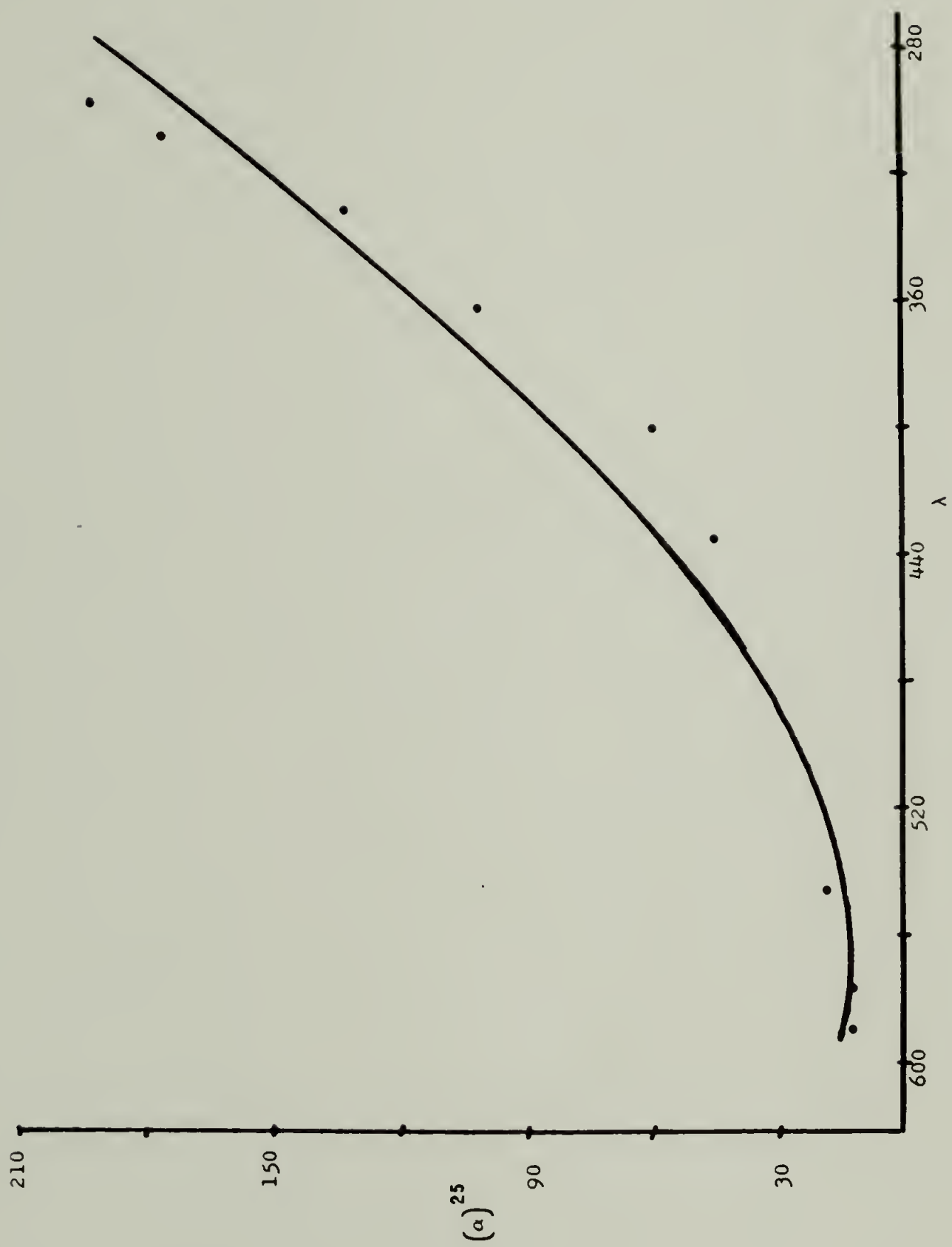


Figure 53. Optical rotatory dispersion curve of S-(L-malic acid chloralide) octadecylate.

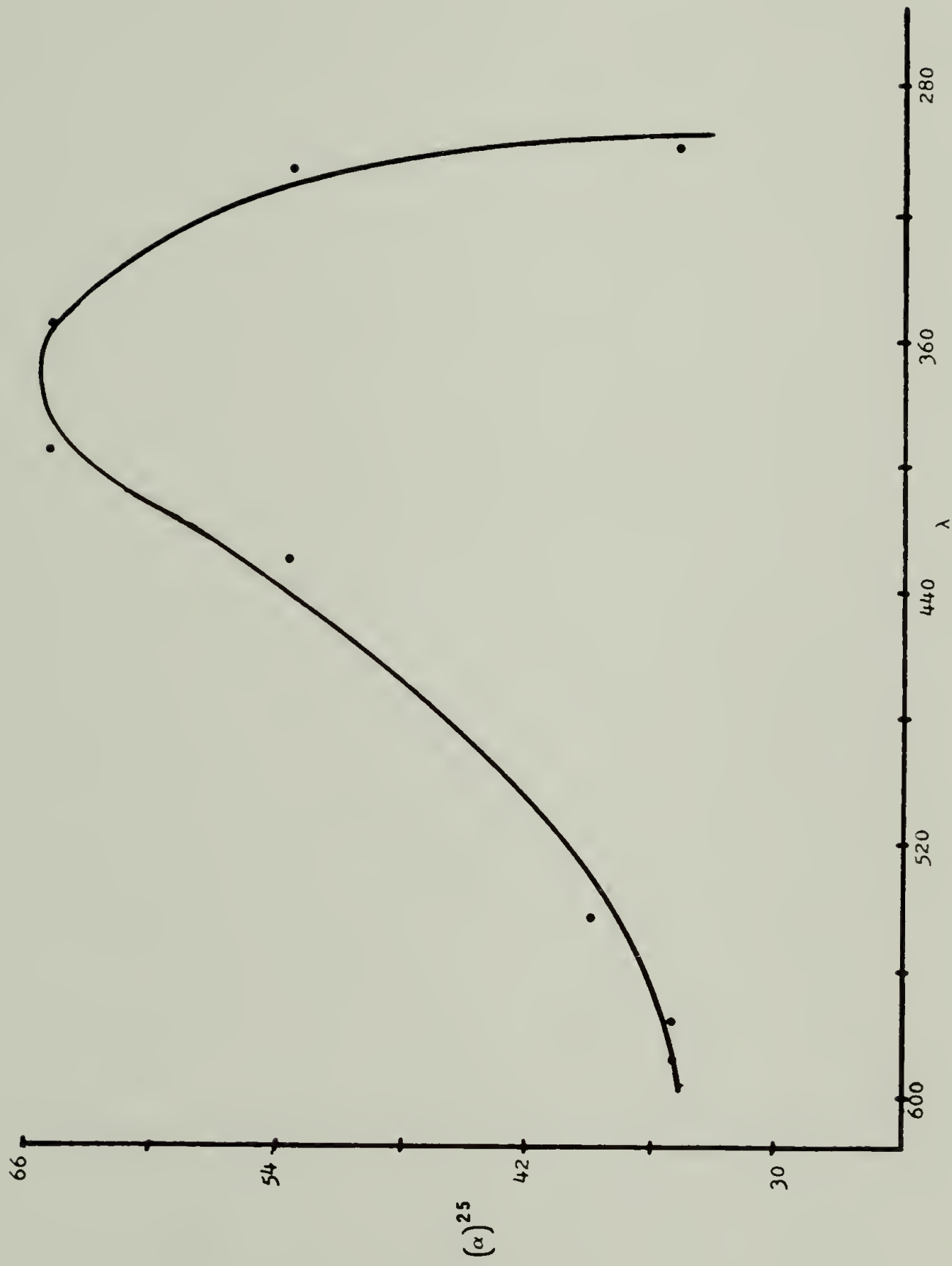


Figure 54. Optical rotatory dispersion curve of S-(beta-L-hydroxysuccinyl) octadecylate.

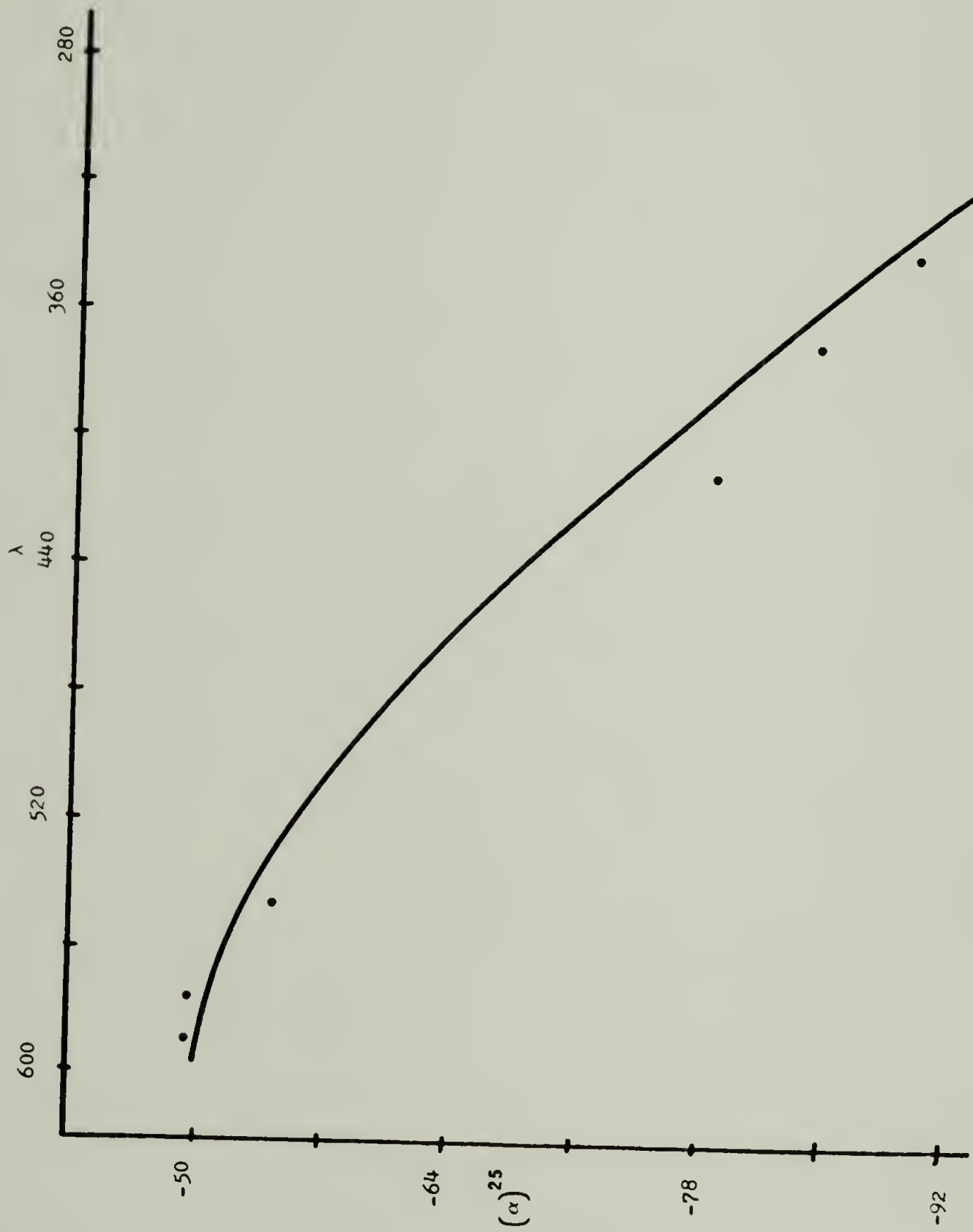


Figure 55. Optical rotatory dispersion curve of S-(beta-L-hydroxysuccinyl benzyl ester) octadecylate.

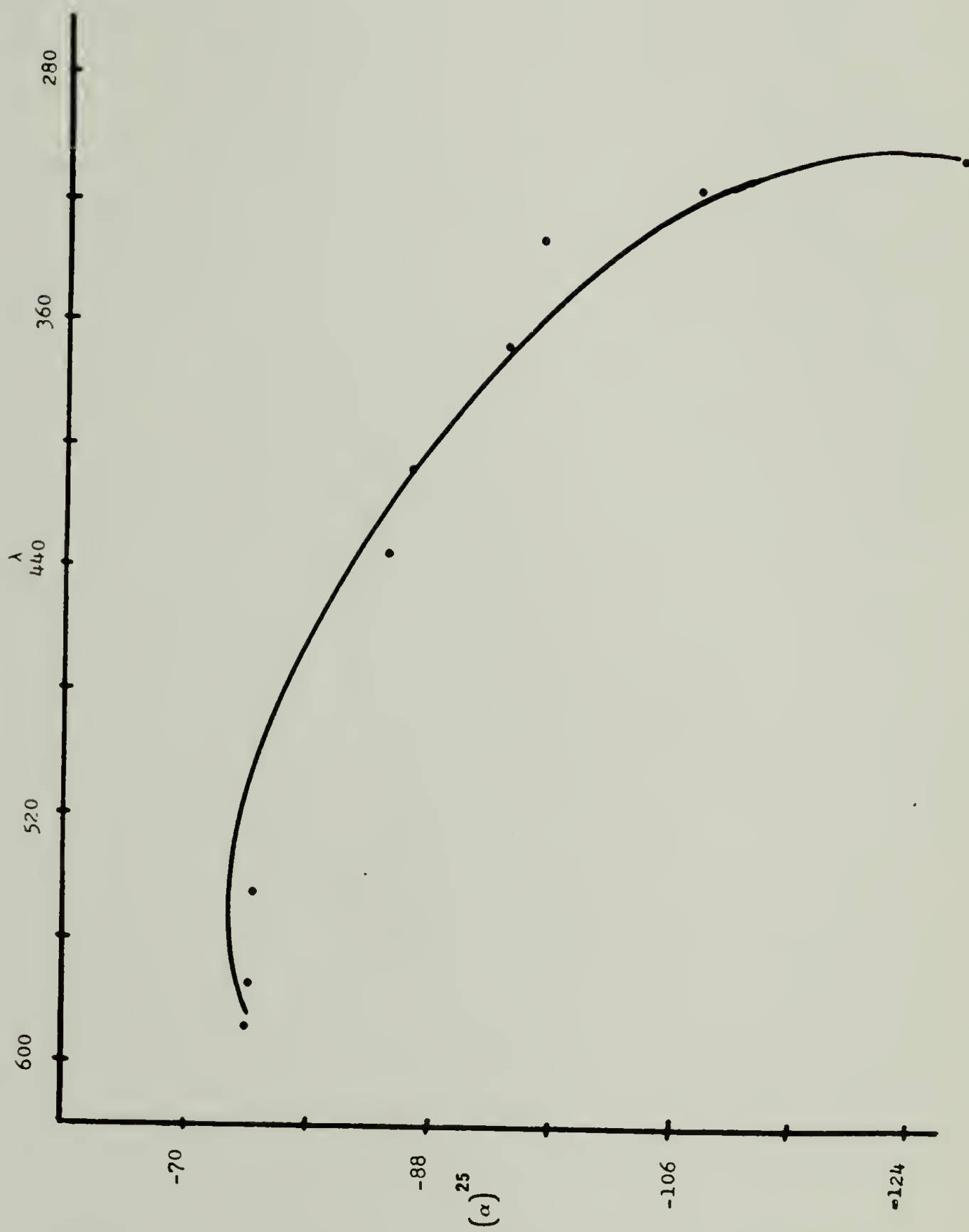


Figure 56. Optical rotatory dispersion curve of L-malolactone benzyl ester.

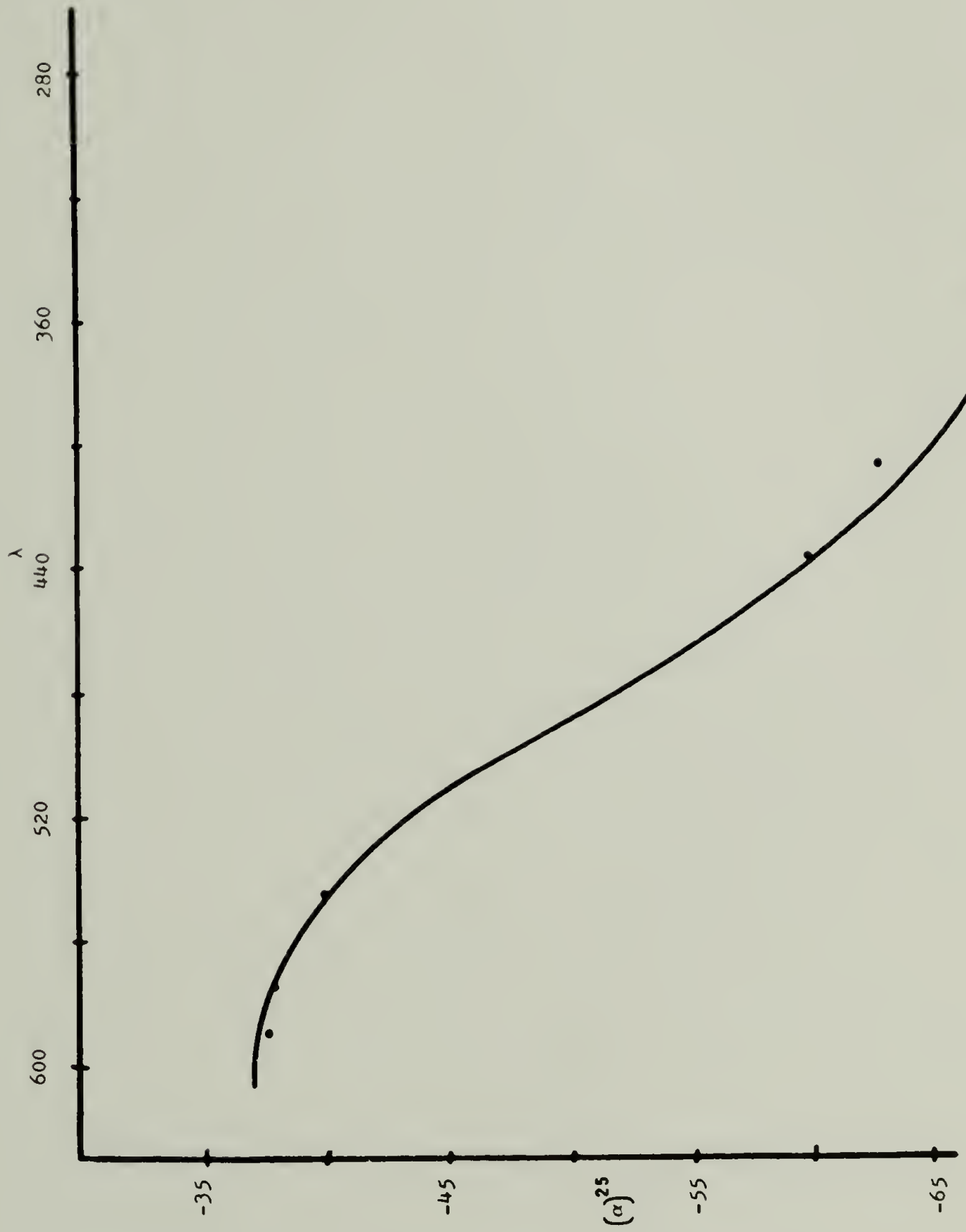


TABLE 7

OPTICAL ROTATORY DISPERSION OF MALOLACTONE BENZYL
ESTER AND THE INTERMEDIATES IN THE LACTONE SYNTHESIS

λ	L-malic acid chloralide	L-malic acid chloralide chloride	S-(L-malic acid chloralide)- octadecylate	S-(beta-L- hydroxy- succinyl)- octadecylate	S-(beta-L- hydroxy- succinyl benzyl ester)- octadecylate	L-malo- lactone benzyl ester
(nm)	(c=3.5, dioxane)	(c=2.0, dioxane)	(c=3.5, dioxane)	(c=2.0, dioxane)	(c=2.0, dioxane)	(c=2.0, dioxane)
	----- (α) ²⁵ -----					
589	+27	+12	+35	-49	-75	-37
576.96	+27.2	+12.0	+35.0	-49.0	-75.8	-37.1
546.08	+31.5	+19.4	+39.8	-54.0	-75.8	-39.5
435.83	+49.3	+48.5	+54.7	-76.0	-82.9	-59.2
407.79	+56.1	+63.0	+59.7	-79.8	-85.3	-63.1
366.34	+61.8	+101.94	+64.7	-84.3	-94.8	-67.3
334.15	+64.8	+135.0	+64.9	-90.1	-104.3	-69.6
313.2	+63.1	+179.8	+54.5	-93.6	-108	-70.1
302.2	+62.1	+194.5	+35	-95.5	-127.9	-69.3

specific rotation $(\alpha)_D^{25} : -37^\circ$. Unfortunately, this compound has not been previously prepared in a pure form so there is no literature reported on its optical purity to compare with in order to determine the absolute optical purity of the lactone which was prepared by this method.

IX. Optical Purity of L-Malolactone Benzyl Ester

There are two approaches to the problem of determining optical purity of a mixture of enantiomers. The first approach involves partial or total separation of the enantiomers. The list of available methods include conversion to diastereomers, biochemical processes and mechanical separation. These methods were described earlier in the discussion of the various methods to prepare optically active compounds.

In the second approach, the enantiomers are not separated physically. Polarimetry (ORD, and Circular Dichroism), nuclear magnetic resonance chemical shifts and integrated intensities, gas chromatography and correlative methods (preparing a compound with known optical activity) are used to provide a measure of optical purity and do not require physical separation of the enantiomers.

If we have resolved a racemic mixture by one of the methods described, we can determine optical purity from the calculated specific rotation knowing the specific rotation of the pure material $(\alpha)_{\max}$. We define optical purity as follows.

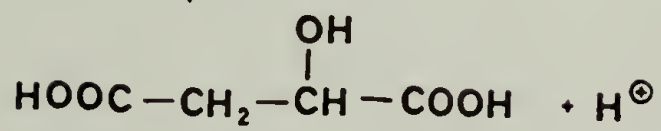
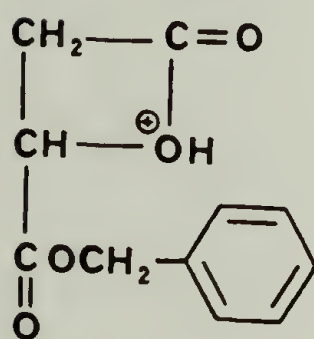
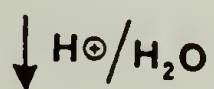
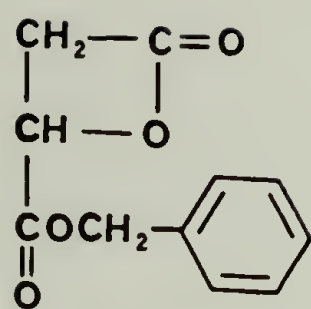
$$\% \text{ optical purity} = \frac{(\alpha) \text{ measured}}{(\alpha) \text{ maximum}} \times 100$$

Assuming that a linear relationship between (α) and concentration exists, optical purity is equal to the percent excess of one enantiomer over the other

$$\text{optical purity} = \frac{(R) - (S)}{(R) + (S)} \times 100 = \%R - \%S$$

Of the available methods for determining $(\alpha)_{\text{max}}$, I chose to hydrolyze the malolactone benzyl ester to the starting compound, malic acid and determine (α) for the acid. The maximum specific rotation of L-malic acid is -28.5° (pyridine). The lactone was hydrolyzed under acid conditions and the water soluble malic acid was isolated. Under strong acid conditions ($\text{pH} \leq 4$), the hydrolysis reaction, shown in Fig. 57 has been determined to occur with retention of configuration at the chiral center.⁸⁸

Figure 57. Hydrolysis of malolactone benzyl ester.



I isolated 37% of the malic acid which had a specific rotation $(\alpha)_D^{25} = -26^\circ$ giving an overall optical purity of the monomer as 90.9%.

$$\% \text{ optical purity} = \frac{-26.0}{-28.5} = 90.9\%$$

Having achieved one of the major goals of this thesis, which was to isolate lactone having greater than 90% optical purity, I now attempted the polymerization of the optically active and racemic lactone monomers.

X. Summary

Since the formation of the optically active malolactone benzyl ester was the most important reaction in the monomer synthesis, I would like to discuss this reaction in greater detail, especially with regard to monomer preparation, purification and analysis of monomer purity.

Although different thiophilic cations were studied to determine their use for preparing the lactone, the salts of mercury were found to be the best catalyst for preparing the lactone. Mercuric methanesulfonate would give low yields of lactone (25%) after purification using High Pressure Liquid Chromatography. Mercuric toluenesulfonate

gave higher yield (70%), however the yields would vary with the different mercury (II) salts made by different batch reactions. Copper and silver salts were found to be ineffective in preparing the lactone.

Benzonitrile or butyronitrile were used as the solvent for the lactone preparation. Methylene chloride, toluene and tetrahydrofuran were used as the solvent but none were found useful for lactone formation. Acetonitrile was used as solvent and a low yield of lactone was found (<10%) as determined by infrared analysis. The reason acetonitrile was considered to be a poor solvent for lactone formation was because the reaction temperature was only 80°C and not the best temperature, 90°C, because of the refluxing temperature of acetonitrile.

Sodium phosphate was used as a buffer added to the reaction and 90°C was the best reaction temperature found. At reaction temperature lower than 90°C, no lactone was formed as determined by infrared analysis.

The lactone would decompose unless purified by high pressure liquid chromatography (Waters 500A-Preparative) using a silica gel column and methylene chloride as the liquid phase. There were three peaks in the chromatogram, two impurities and the lactone. There was excellent separation between the components and the lactone peak was easily isolated. After solvent removal, the lactone was distilled from calcium hydride at 115°C/0.001 mm for the

racemic material and 105°C/0.001 mm for the optically active lactone.

The lactone could be analyzed by infrared (1850 cm^{-1}), proton-NMR and Carbon-13 NMR spectroscopy, because of the specific lactone ring structure.

C H A P T E R I I I

POLYMERIZATION OF MALOLACTONE ESTER MONOMER

I. INTRODUCTION

A survey of the literature reveals that there has not been a great deal of research done on the preparation of poly(beta-substituted-beta-lactones). From the work reported, as well as from the greater quantity of work reported on the polymerization of a similar structured monomer, beta-propiolactone, one can draw conclusions concerning the polymerization mechanisms and polymer structure and properties which might be expected.

It is predicted that L-malolactone benzyl ester may be polymerized to the corresponding polyester having acceptable molecular weights using anionic and cationic initiators.

A number of initiators have been used to polymerize lactones. However, to study them all would be beyond the scope of this thesis. Different initiators were chosen for the polymerization of malolactone benzyl ester and they may be divided into the following classes:

Macrozwitter Ion Initiators

- Betaine
- Triethyl amine
- Tertiary Phosphines

Base Initiators

- Tetraethyl Ammonium Benzoate
- Sodium Acetate

Cationic Catalysts

- Ferric Chloride
- Aluminum Chloride
- Triphenylmethyl Hexafluoroantimonate
- Triphenylmethyl Tetrafluoroborate

Organometallic Catalysts

- Triethylaluminum
- Diethyl Zinc

Base Initiators/Crown Ether Complexes

- Sodium Acetate/dibenzo-18-crown-6-ether
- Sodium Hydroxide/dibenzo-18-crown-6-ether
- Potassium Acetate/15-crown-5-ether
- Potassium Hydroxide/15-crown-5-ether

II. Macrozwitter Ion Initiators

Initiators such as betaine have been postulated to form macrozwitter ions when used as catalysts for the polymerization of beta-lactones as shown in Fig. 58.

NMR and infrared data have confirmed the structure of the macrozwitter ion.⁸⁹ For the studies with triethylamine⁹⁰ and betaine,⁹¹ electrophoresis shows the presence of a quaternary ammonium cation and a carboxylate anion group present in the same polymer.

Objections to the zwitterion polymerization mechanism based on the premise that a high Coulombic energy is associated with charge separation, have been shown invalid. The propagating chains do not need to be linear with increasing distance between the ionic end groups. They may be cyclic or paired with another chain during polymerization (Fig. 59).

In theory, chain transfer to monomer should not occur, but compounds with abstractable hydrogen atoms (acidic)

Figure 58. Macrozwitter ion polymerization mechanism for beta lactones.

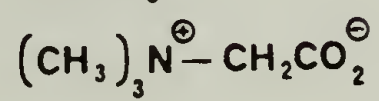
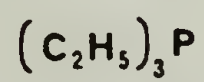
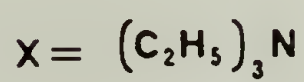
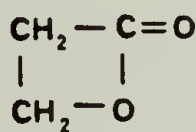
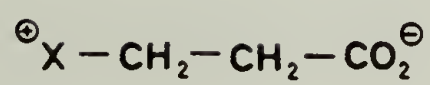
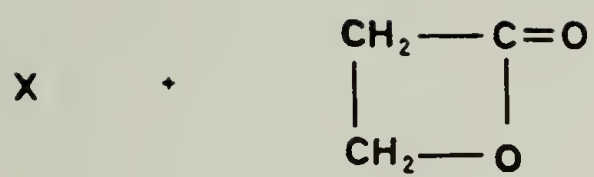
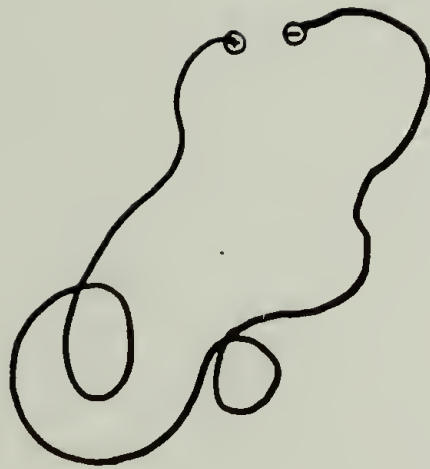


Figure 59. Schematic diagram illustrating how opposite charged end groups come in contact during zwitter ion polymerization.



OR



have been demonstrated to be excellent chain transfer agents, for example, beta-propiolactone.

The polymerization mechanism is considered to be "living", but termination may occur at high temperatures.

I was hesitant to investigate this class of initiators for the polymerization of malolactone benzyl ester because Etienne⁹² observed that beta-substituted-beta-lactones do not polymerize by anionic initiators. He theorized that steric effects due to the substituents on the beta carbon hinder polymerization. Vert and Lenz³⁸ found that racemic malolactone benzyl ester will polymerize with triethylamine and betaine. They assumed that the electron withdrawing nature of the beta ester linkage activates nucleophilic attack at the beta carbon and overcomes the steric effects. Iida, et. al.⁹³ found the same effect when he synthesized poly(beta-chloromethyl-beta-propiolactone) with triethylaluminum/water as the initiator. They found that the electron withdrawing nature of the trichloromethyl group enhanced the rate of polymerization and suppressed the steric hindrance.

In summary, I chose to investigate various examples of this class of initiators because:

(1) the macrozwitter ion formation mechanism has been shown to give polymers of moderate molecular weight (approximately 10,000) which are acceptable for biopolymer drugs and polymeric drug carriers

(2) if the polymerization is "living", the molecular weight distribution MWD should be narrow ($M_w/M_n \ll 2$) and the MWD is a critical parameter for polymer drugs because of the known phenomena that large molecules cause erythrocyte aggregation;⁹⁴ and

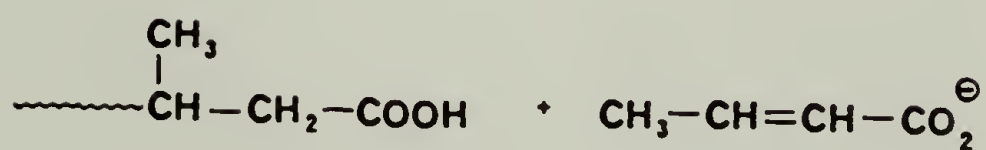
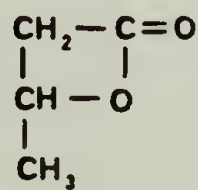
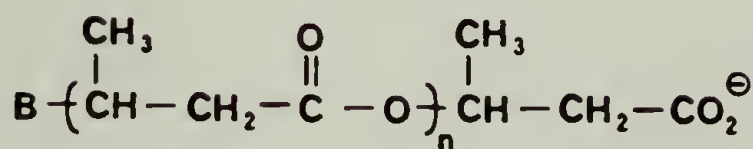
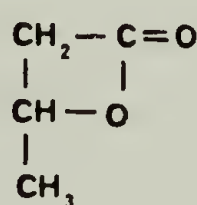
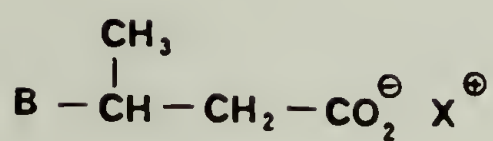
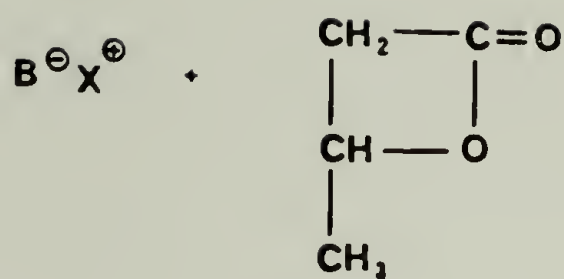
(3) the polymerization mechanism is unique for lactones.

III. Basic Initiators

There are a number of reports in the chemical literature which have examined the polymerization of beta-propiolactone and beta-butyrolactone using anionic initiators. Shiota et. al.⁹⁵ was able to obtain poly(beta-hydroxypropionate) having a degree of polymerization of 250 ($M_n = 18,000$) using sodium acetate and a catalytic amount of water. Yamashita, et. al.⁹⁶ investigated the preparation of the same polymer, and found that base catalysts were rather inefficient for producing high molecular weight polymer. With potassium acetate, the resulting polymers had end groups which were disubstituted double bonds. Yamashita hypothesized that the unsaturated end groups were formed by the chain transfer to monomer. He suggested a polymerization mechanism to account for these results (Fig. 60a).

In the proposed mechanism, initiation and propagation are described by attack at the beta carbon atom, in the lactone ring, thereby breaking the ring carbon to ring

Figure 60a. Polymerization mechanism involving base initiators.



$B^{\ominus}X^{\oplus} = \text{BASE CATALYST}$

oxygen bond. Chain transfer to monomer would occur by proton abstraction at the alpha carbon atom followed by an elimination reaction to form the salt of crotonic acid.

The purpose of investigating this class of initiators, therefore, is to compare the results of the synthesis of poly(L-malolactone benzyl ester) with those expected for the Yamashita mechanism and to determine if the polymerization mechanism is "living" for the synthesis of poly(L-malolactone benzyl ester).

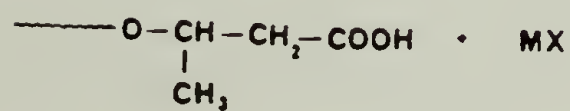
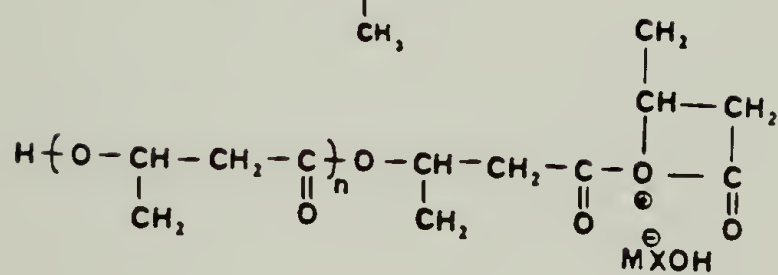
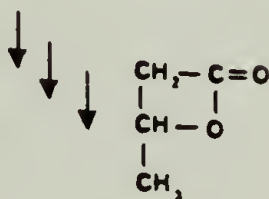
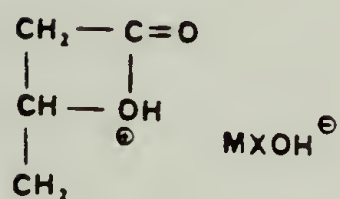
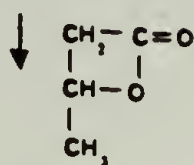
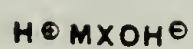
IV. Cationic Initiators

Cherdron et. al.⁹⁷ found that cationic initiators, specifically acetyl perchlorate, formed poly(beta hydroxypropiolactone) with higher molecular weight than the corresponding polymers prepared with the anionic catalysts.

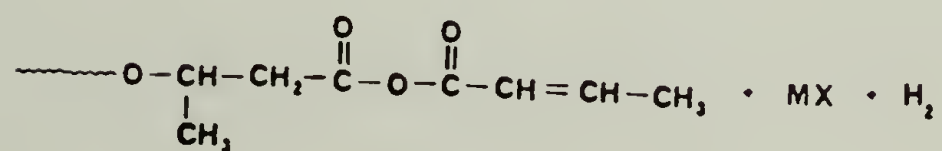
Based on his work, he suggested a polymerization mechanism using stannic chloride as the catalyst (Fig. 60b).

As with all electrophilic species, the initiation step is described by attack on the lactone ring oxygen. Propagation takes place with nucleophilic attack by the monomer on the lactone carbonyl to form the oxonium ion intermediate which propagates through acetyl carbon-oxygen cleavage. Termination occurs by two different mechanisms involving the gegenion; either (1) attack at the lactone ring carbonyl or (2) hydrogen abstraction from the end group.

Figure 60b. Polymerization mechanism involving cationic initiators.



or



Representative cationic initiators were studied to determine the following:

(1) compare with the results obtained with anionic initiators, specifically the effect on the chiral center; and

(2) compare with the results of the polymerization of L-malolactone benzyl ester based on the Yamashita proposed mechanism.

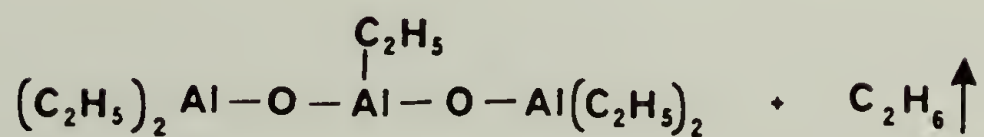
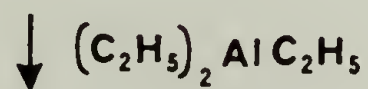
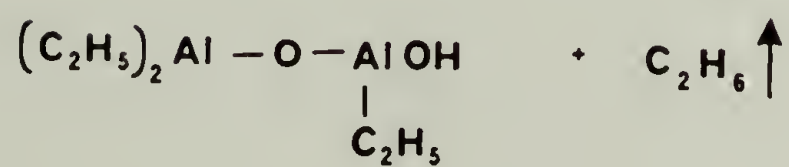
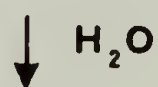
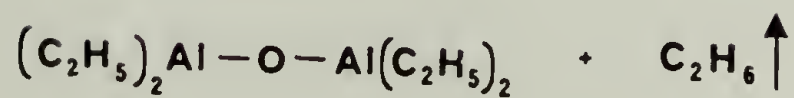
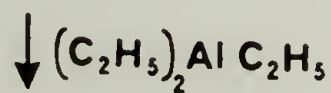
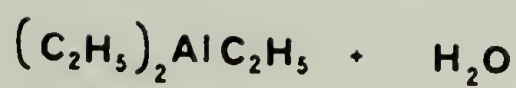
Malolactone benzyl ester was polymerized using trityl carbenium ion salts (triphenylmethyl hexafluoroantimony and triphenylmethyl tetrafluoroborate) as initiators. Khomgakov et. al.⁹⁸ studied the effects of these salts as initiators for beta-propiolactone and proposed a mechanism for the polymerization reaction.

V. Organometallic Catalysts

Cherdron et. al.⁹⁹ polymerized beta-propiolactone to the highest known molecular weight using aluminum alkyls (triethylaluminum/water) as the initiator system. Yamashita, et. al.¹⁰⁰ studied the formation of the catalyst itself, that is, the product formed as a result of the reaction between water and triethylaluminum. They assumed from the products isolated that the following reactions are operative (Fig. 61).

As the reaction proceeds, the number of Al-O linkages increase but solubility of the catalyst decreases as does

Figure 61. Products from the reaction of water and triethylaluminum.



the ability to polymerize the lactones. If triethylaluminum was reacted with the beta-butyrolactone without water, the following compounds were isolated, and these most likely, are the initiating species if no water is present (Fig. 62).

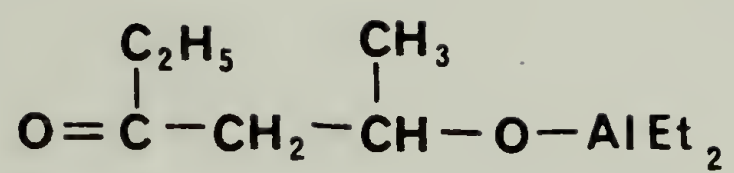
Agostini, et. al.¹⁰¹ proposed a mechanism for the polymerization of beta-butyrolactone using triethylaluminum/water as the catalyst. According to his proposed mechanism (Fig. 63), the configuration of the polymer should be retained the same as the optically active monomer.

Vert and Lenz³⁸ polymerized racemic malolactone benzyl ester with triethylaluminum/water and obtained highly crystalline polymer as described by DSC analysis. The triethylaluminum/water catalyst has been demonstrated to be capable of preparing stereoregular polymers from acetaldehyde¹⁰², epoxides¹⁰³, and lactones.¹⁰⁴

Iida, et. al.¹⁰⁵ polymerized beta-chloromethyl-beta-propiolactone with this catalyst system and found that the electron withdrawing nature of the trichloromethyl group enhances the polymerization and suppresses the steric effect in comparison to the behavior of an electron releasing group such as an alkyl group.

One of the objectives of this research is to prepare very high molecular weight polymer for polymer characterization and biological testing. Triethylaluminum/water and the diethyl zinc will be investigated as catalysts for

Figure 62. Initiating species in the polymerization using triethylaluminum without water.



or

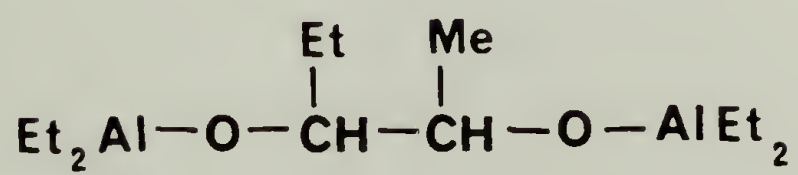
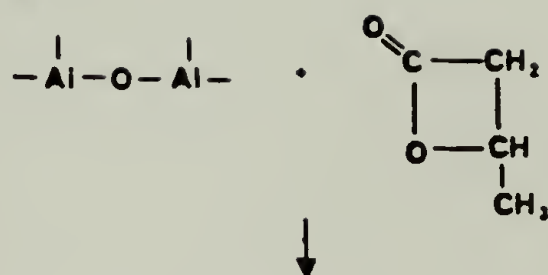
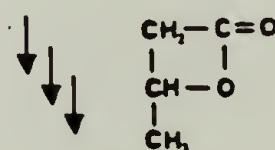
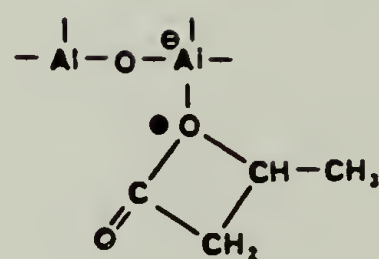


Figure 63. Agostini, et. al.¹⁰¹ proposed mechanism for the polymerization of beta-butyrolactone using triethylaluminum/water as the catalyst.

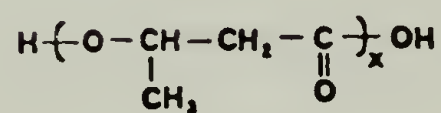
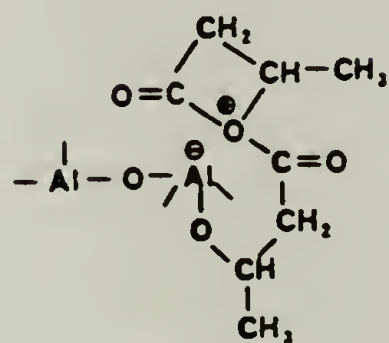
Initiation:



propagation:



termination:



the polymerization of malolactone benzyl ester. Vergara and Figini¹⁰⁶ obtained poly(D-beta-hydroxybutyrate) having molecular weight 174,000, using diethyl zinc as the initiator.

VI. Base Catalysts/Crown Ether Complexes

Anionic initiators have been shown to be capable of polymerizing specific lactones without termination or transfer. Beta-substituted-beta-lactones undergo transfer by hydrogen abstraction from the alpha carbons. Penczek et. al.¹⁰⁷ investigated the polymerization of beta-propiolactone using anionic catalysts with crown ethers, a chelating agent for the cation counter-ion. The rates of polymerization of lactones with anionic catalysts are low at moderate temperatures¹⁰⁸ and increasing the temperature leads to side reactions. Penczek found that the rate of propagation of beta-propiolactone with sodium acetate and dibenzyl-18-crown-6-ether increased by not less than a factor of 10^2 in comparison with the rate of reaction without the crown ether. The substantial increase in rate allows us to lower the polymerization temperature and slow down the previously mentioned transfer step.

VII. Results for the Polymerization of Optically Active and Racemic Malolactone Benzyl Ester

My intention is not to keep the reader in suspense concerning the results obtained from polymerization

attempts on the optically active and racemic malolactone benzyl ester monomers. An overall semi-complete listing of the pertinent results can be found in the following Tables 8 and 9.

The experimental conditions and results including monomer concentration, solvent type, ratio of initiator to monomer, polymerization temperature, reaction time, percent conversion, percent yield, molecular weight by GPC, ratio of weight average-to number average molecular weight as an indication of MWD and specific rotation are listed for the experimental reactions.

Some of the experimental results can be predicted, but data, such as the molecular weights, require an explanation. It is my purpose to reason out and explain the data in relation to the discussion of the initiators and the polymerization of other beta-substituted-beta-lactone monomers.

VIII. Thermal Studies of the Polymers

Thermal analysis was performed using a Perkin-Elmer Model 2B Differential Scanning Calorimeter under a nitrogen atmosphere and using sealed aluminum DSC caps.

Upon examination of the DSC thermogram for the poly(L-malolactone benzyl ester), one is immediately aware of the similarity of the melting endotherms of the various polymers obtained from the optically active monomers

TABLE 8

EXPERIMENTAL CONDITIONS AND RESULTS FOR THE POLYMERIZATION
OF OPTICALLY ACTIVE MALOLACTONE BENZYL ESTER

Monomer moles /liter	Initiator	Polymerization Temperature °C	days	Conversion ^a %	Yield %	M_{GPC}^b	M_w/M_n	Melting ^c Point °C	Glass ^d Transition Temperature °C	$(\alpha)_D^{25}$
bulk	NEt ₃ ^e	30	28	80	30	2050	2.09	130-150	26	+10.6
bulk	NEt ₃ ^e	70	3	90	50	2200	1.41	140-160	25.5	+13
bulk	NEt ₃ ^e	70	5	100	80	2900	1.41	130-150	26	+12
CH ₂ Cl ₂ ^f	NEt ₃ ^e	30	28	40	20	2600	2.1	140-160	25	+10.6
toluene ^f	NEt ₃ ^e	30	28	40	10	2100	1.98	130-150	25	-
bulk	φCO ₂ NEt ₄ ^e	0	60	100	40	1800	2.69	120-150	26	-
bulk	φCO ₂ NEt ₄ ^e	30	28	75	40	3200	1.95	135-160	27	+9.8
bulk	φCO ₂ NEt ₄ ^e	70	3	90	50	2200	1.41	140-160	26	+13.0
bulk	φCO ₂ NEt ₄ ^e	70	3	100	75	7300	1.44	140-165	27	+13.8
CH ₂ Cl ₂ ^f	φCO ₂ NEt ₄ ^e	30	28	45	20	2500	2.0	130-160	25	+11.0
toluene ^f	φCO ₂ NEt ₄ ^e	30	28	40	25	3500	2.1	135-160	26	+11.9
bulk	FeCl ₃ ^g	30	28	50	10	2500	2.2	130-160	25	-
bulk	FeCl ₃ ^g	70	7	50	25	1800	1.99	140-160	25	-6.5
bulk	FeCl ₃ ^g	70	7	80	40	3200	2.05	135-150	25	-7.5
bulk	betaine ^e	30	28	60	22	2300	2.1	135-150	26	+11.2

TABLE 8 (continued)

Monomer $\frac{\text{moles}}{\text{liter}}$	Initiator	Polymerization Temperature	Time	Conversion ^a	Yield ^b	M_{GPC}	M_w/M_n	Melting ^c Point °C	Glass ^d Transition Temperature °C	(α) _D ²⁵
CH ₂ CL ₂ ^f	FeCl ₃ ^g	30	28	20	5	1800	2.35	125-150	25	-7.8
toluene ^f	FeCl ₃ ^g	30	28	20	0	-	-	-	-	-
bulk	$\phi_3\text{CSbPF}_6$ ^g	30	1	100	20	470	2.1	-	-	-
CH ₂ CL ₂ ^f	$\phi_3\text{CSbPF}_6$ ^g	30	1	100	0	-	-	-	-	-
toluene ^f	$\phi_3\text{CSbPF}_6$ ^g	30	1	100	10	640	2.0	-	-	-
bulk	$\phi_3\text{CBF}_4$ ^g	30	28	50	10	450	2.05	-	-	-
toluene ^f	$\phi_3\text{CBF}_4$ ^g	30	28	10	0	-	-	-	-	-
bulk	Et ₂ Zn ^g	50	24	100	55	850	1.25	110-135	25	-
toluene ^f	AlEt ₃ ^g	70	10	90	50	2812	2.09	135-165	26	-12.0
bulk	NaO ₂ CCH ₃ ^{e,h}	0	60	75	35	2100	2.83	125-157	26	-
bulk	NaO ₂ CCH ₃ ^{e,h}	30	2	75	45	3350	1.35	140-160	26	+13.2
bulk	NaOH ^{e,h}	30	6	85	20	1350	1.28	140-160	25	+9.5
bulk	KO ₂ CCH ₃ ^{e,i}	30	3	80	38	2200	1.41	130-150	25	+11.6
bulk	KOH ^{e,i}	30	4	60	28	1060	1.21	135-145	26	+10.2

(a) Determined by infrared spectroscopy

(b) Polystyrene standards

(c) Temperatures where DSC-curve starts slope change and returns to baseline

(d) Given as midpoint

(e) Initiator to monomer concentration in moles is 10⁻³

(f) Monomer concentration is 2.5 M

(g) Initiator to monomer concentration in moles is 10⁻²

(h) Dibenzo-18-crown-6-ether is used in 1 to 1 molar ratio with initiator

(i) 15-crown-5-ether is used in 1 to 1 molar ratio with initiator

TABLE 9

EXPERIMENTAL CONDITIONS AND RESULTS FOR THE POLYMERIZATION
OF RACEMIC MALOLACTONE BENZYL ESTER

Monomer moles liter	Initiator	Polymerization Temperature °C	days	Conversion ^a %	Yield %	M _{GPC} ^b	M _w /M _n	Melting ^c Point °C	Glass ^d Transition Temperature °C	(α) _D ²⁵
bulk	NEt ₃ ^e	70	5	100	65	3100	1.5	-	25	-
bulk	φCO ₂ NEt ₄ ^e	70	5	100	80	2900	1.42	-	25	-
bulk	FeCl ₃ ^g	70	14	35	15	2600	1.95	-	25	-
bulk	AlCl ₃ ^g	70	20	25	10	1000	2.1	-	-	-
bulk	betaine ^e	70	5	70	40	2300	1.41	-	25	-
bulk	φ ₃ CSbF ₆ ^g	30	1	100	10	410	2.05	-	-	-
bulk	φ ₃ CBF ₄ ^g	30	30	45	5	-	-	-	-	-
toluene ^f	AlEt ₃ ^g	70	5	75	35	2980	2.1	-	25	-
bulk	Et ₂ Zn ^g	50	18	100	50	640	1.28	-	-	-
bulk	NaO ₂ CCH ₃ ^{e,h}	30	1	100	80	2860	1.30	-	25	-
bulk	KO ₂ CCH ₃ ^{e,i}	30	2	90	60	2940	1.25	-	25	-

(a) Determined by infrared spectroscopy
(b) Polystyrene standards
(c) Temperatures where DSC-curve starts slope change and returns to baseline
(d) Given as midpoint
(e) Initiator to monomer concentration in moles is 10⁻³
(f) Monomer concentration is 2.5 M
(g) Initiator to monomer concentration in moles is 10⁻²
(h) Dibenzo-18-crown-6-ether is used in 1 to 1 molar ratio with initiator
(i) 15-crown-5-ether is used in 1 to 1 molar ratio with initiator

regardless of the catalyst system, temperature, or monomer concentration used to prepare the polymers. Multiple melting endotherms were observed in the analysis by DSC for these highly crystalline optically active polymers. All of the polymers had a multitude of sharp endothermic peaks in the temperature range of approximately 140-160°C. There was an endothermic absorption about 60-70°C, and area analysis of these peaks gave a value of 5% of the total area. All the DSC analyses were performed on polymers precipitated out of the reaction mixture and unannealed. Some chosen representative DSC spectra are shown in Fig. 64-68.

The phenomena of multiple melting endotherms has been reported in a number of literature references.¹⁰⁹⁻¹¹³ Allegrezza¹¹⁴ wrote an excellent review about this phenomena. If polymorphism is not considered as the cause of the multiple endotherms, then the cause may be explained by two separate theories:

(1) Multiple endotherms are a manifestation of two different morphologies, and

(2) Multiple endotherms are a melting and recrystallization phenomena.

Bell and Dumbleton¹¹⁵ proposed that this phenomena is a general occurrence due to the formation of two different crystalline morphologies. The higher temperature peak represents a kinetically favored extended chain crystal. The lower temperature peak is the more stable thermo-

Figure 64. DSC spectra for the polymerization of malolactone benzyl ester using triethylamine in bulk at 70°C.

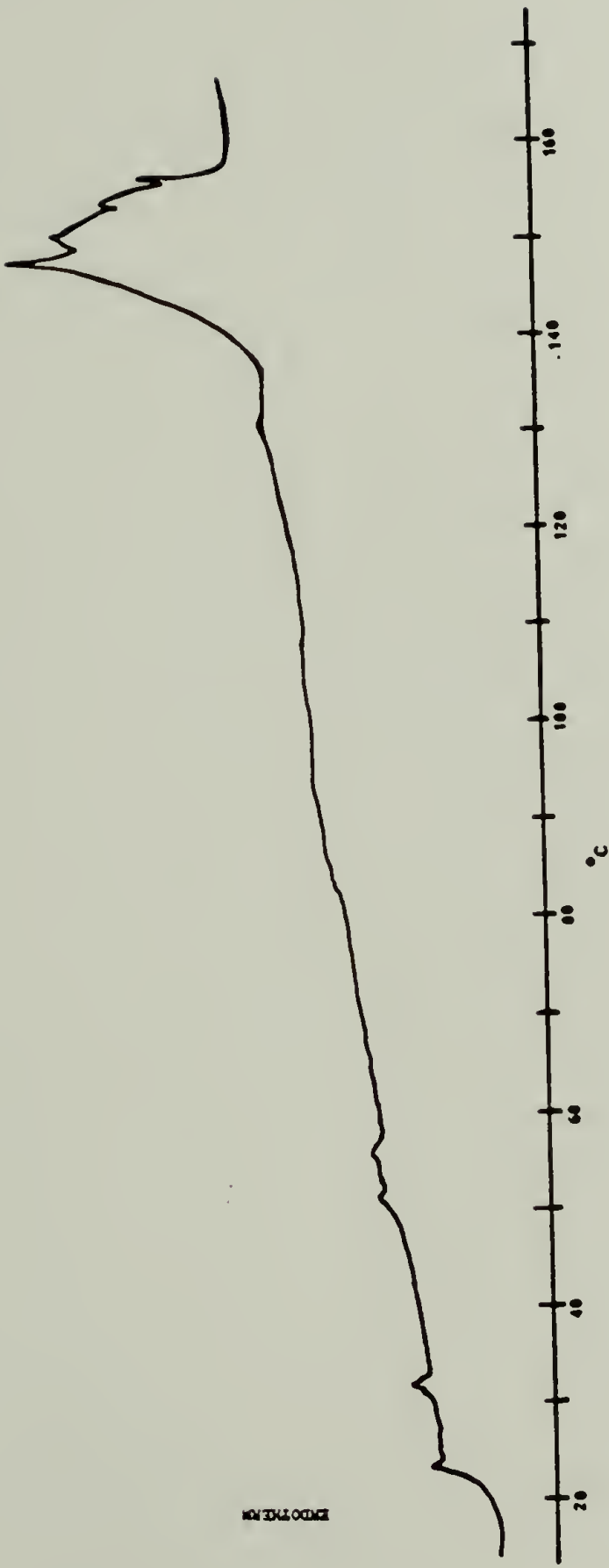


Figure 65. DSC spectra for polymerization of malolactone benzyl ester using tetraethylammonium benzoate in bulk at 70°C.

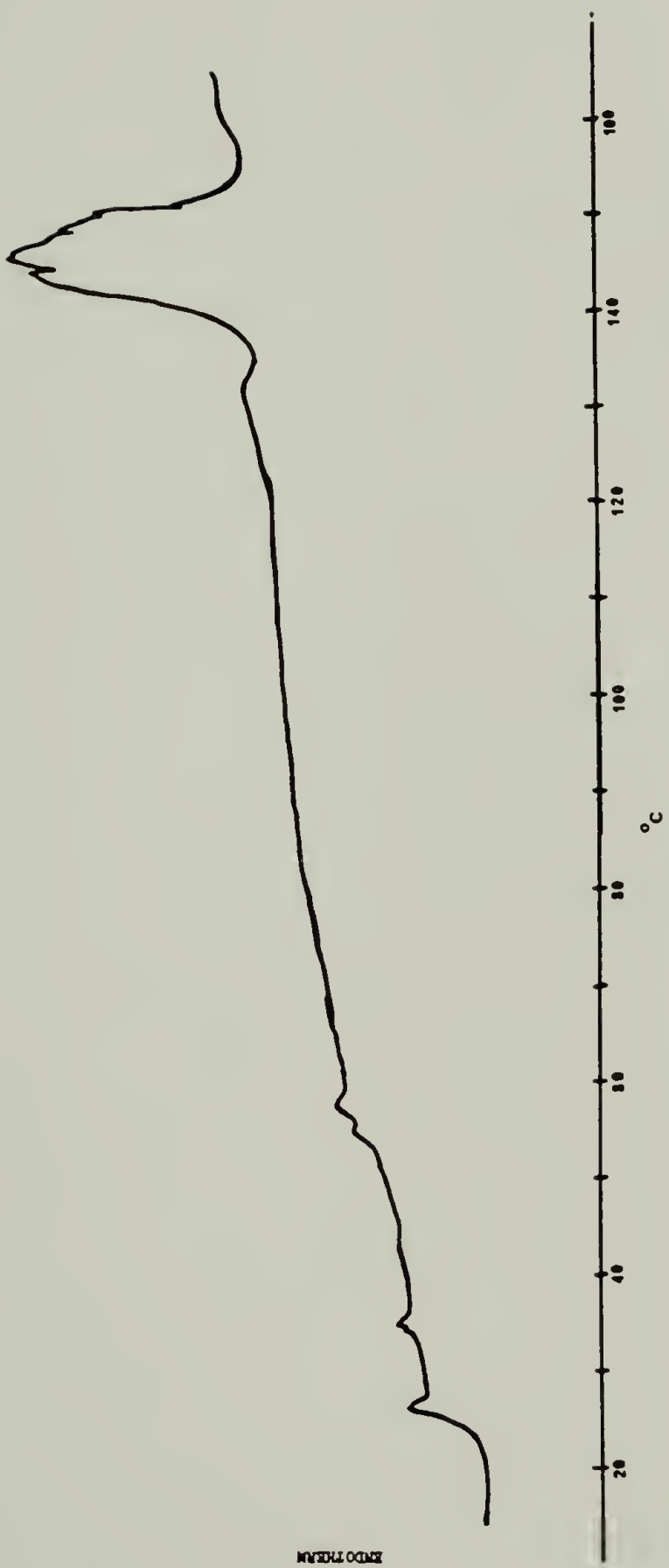


Figure 66. DSC spectra for the polymerization of malolactone benzyl ester using ferric chloride in bulk at 70°C.

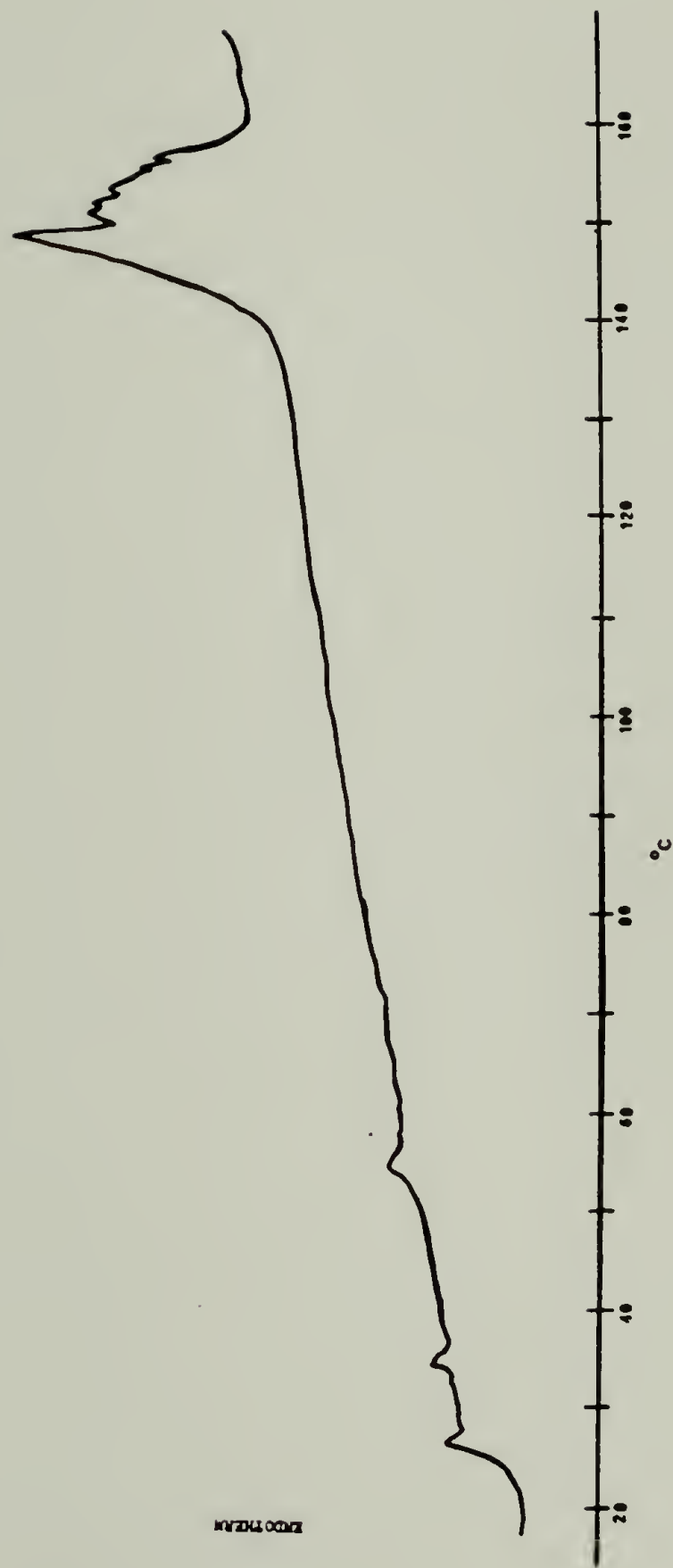


Figure 67. DSC spectra for the polymerization of malolactone benzyl ester using triethylaluminum/water in toluene at 70°C.

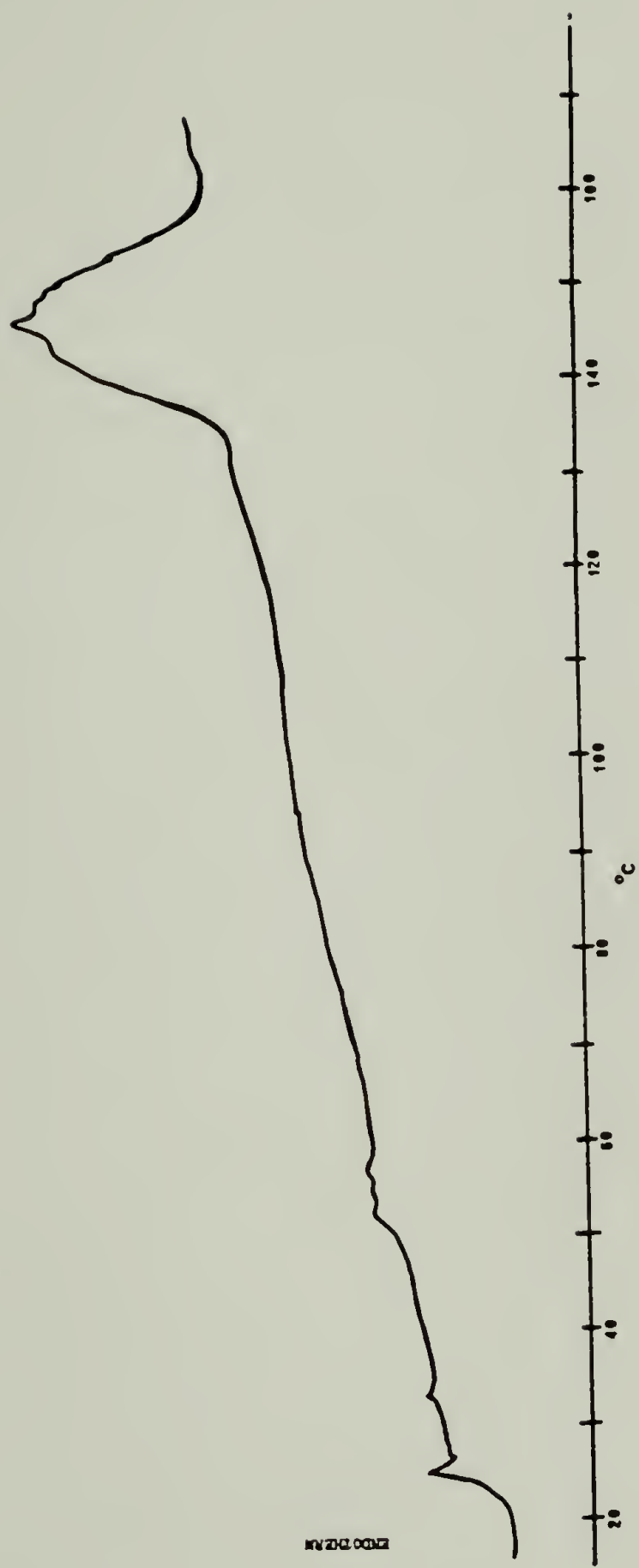
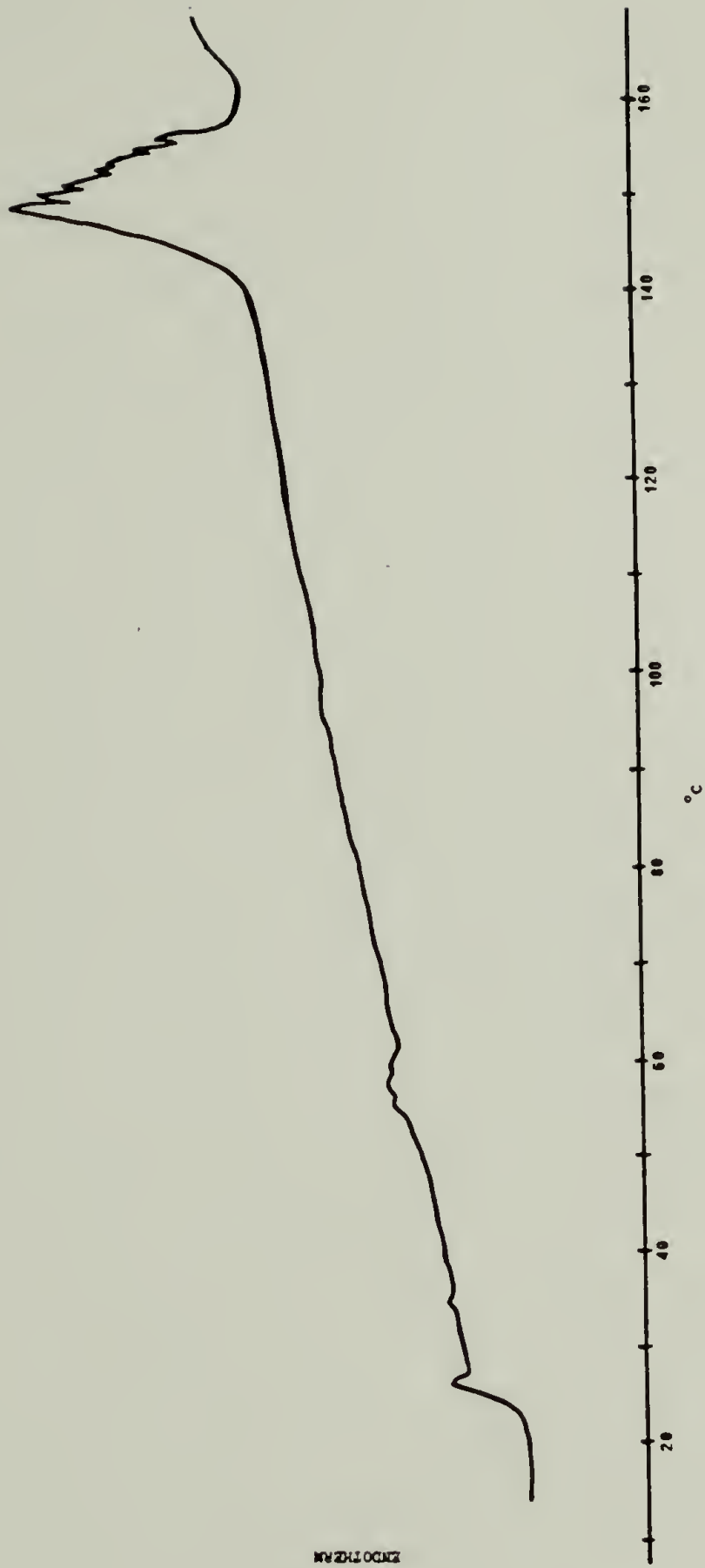


Figure 68. DSC spectra for the polymerization of malolactone benzyl ester using sodium acetate/dibenzo-18-crown-6-ether in bulk at 30°C.



dynamically favored extended chain crystal. Their proof rested on their observations of the effect on the endotherm of increased heating rates.

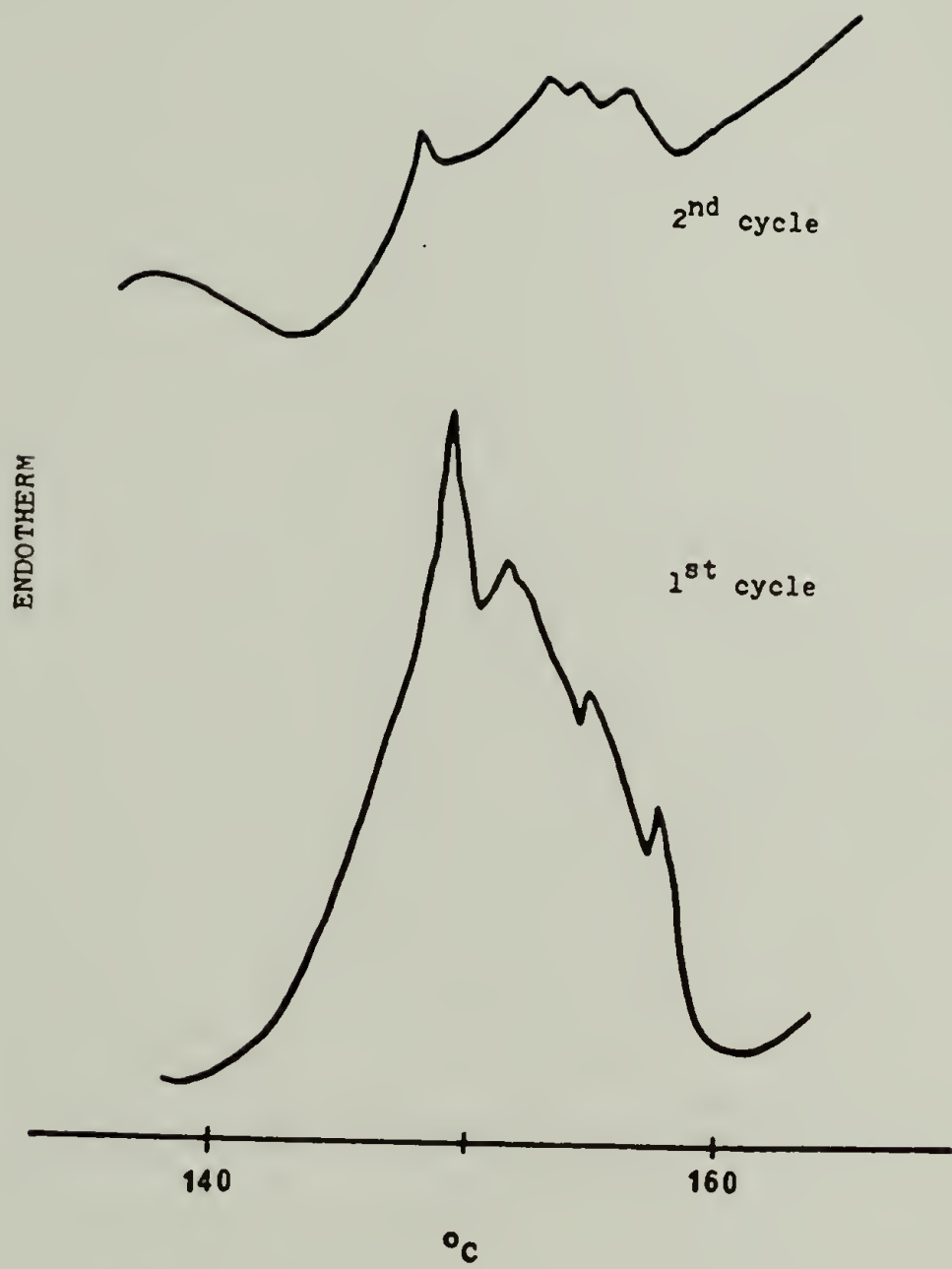
The polymer prepared with triethylamine initiated at 70°C reaction temperature in the absence of solvent was analyzed by DSC at different heating rates. There seems to be little change in the DSC thermograms. The lower temperature peak (thermodynamically controlled) did not increase at the expense of the other peaks (kinetically controlled).

On cooling the sample and reheating (cycling) at the same temperature (Fig. 69), one observes a small exothermic (crystallization) peak during cooling after the first cycle. On reheating the sample, the melting endotherm was found to be smaller in the second cycle in comparison to the first. In the third cycle, the peak was not observed. Area analysis showed that after the second cycle the endothermic peak area was 20% of the peak after the first cycle.

It was assumed that the cooling rate was too fast for recrystallization to occur, and annealing below the melting point was needed. A number of attempts at annealing the sample below the melting point apparently produced no improvement in polymer morphology and, hence, no changes in the DSC thermograms.

It has been demonstrated by Overberger,¹¹⁶ in the case of poly-(R)-(+)-7-hydroxy-4-methylheptanoic acid, that the

Figure 69. DSC spectra, cycling, for the optically active polymer prepared with triethylamine in bulk at 70°C.



polymer with higher optical purity and greater stereoregularity could crystallize whereas the incorporation of 10% of the enantiomeric monomer was sufficient to inhibit crystallization. This effect may be true in the present case, too. In the DSC study of the optically active poly(L-malolactone benzyl ester), crystallization was not obtained upon cooling, which may be due to the 5% enantiomeric monomer present.

The optically active polymer has a glass transition temperature (T_g) at 25.77°C (midpoint).

Analysis of the racemic polymer of similar molecular weights showed only a glass transition temperature (T_g) at 24.6°C (midpoint) but no crystallization endotherms.

Vert and Lenz observed that racemic poly (malolactone benzyl ester) has a glass transition temperature at $60-80^{\circ}\text{C}$. I offer no explanation why there is so large a difference in their observed glass transition temperature to the T_g I observed. Their results are listed in Table 10.

They hypothesized that the large difference in crystallinity between the optically active and racemic polymers is readily explained by differences in polymer stereoregularity, and in only one case was a crystalline polymer obtained from the racemic monomer, that for the polymerization catalyzed by triethylaluminum/water. No solvent residue remains in the samples. All the samples were dried under identical conditions in vacuum at 50°C . According to GPC data, no

TABLE 10

EXPERIMENTAL CONDITIONS AND RESULTS FROM THE RESEARCH OF
VERT AND LENZ³⁸ FOR THE POLYMERIZATION OF MALOLACTONE BENZYL ESTER

Monomer $\frac{\text{moles}}{\text{liter}}$	Initiator	Polymerization Temperature	Time	Conversion ^a %	Yield %	M_{GPC}^b	M_w/M_n	Melting ^c Point °C	Glass ^d Transition Temperature °C	$(\alpha)_D^{25}$
bulk	NEt ₃ ^e	25	21	65	40	7000	-	-	79	-
bulk	φCO ₂ NEt ₄ ^e	50	7	40	20	2000	-	-	-	-
bulk	betaine ^e	25	21	80	55	7000	-	-	80	-
bulk	betaine ^e	60	3	100	30	2500	-	-	-	-
toluene ^f	FeCl ₃ ^g	50	7	-	30	-	-	-	76	-
toluene ^f	AlEt ₃ ^g	50	7	-	10	-	-	165-185	-	-

- (a) Determined by infrared spectroscopy
- (b) Based on polystyrene standards
- (c) No melting point observed by DSC except for AlEt₃
- (d) DSC observed peak
- (e) Initiator to monomer concentration in moles is 10⁻³
- (f) Monomer concentration is 2.5 M
- (g) Initiator to monomer concentration in moles is 10⁻²

large differences in molecular weight could account for a melting point depression between the optically active and racemic polymers.

IX. Gel Permeation Chromatography

Gel permeation chromatography was performed using a Waters 200 Gel Permeation Chromatograph with tetrahydrofuran as the solvent and polystyrene standards for determining number average and weight average molecular weights.

The results listed in the tables summarizing the polymerization data demonstrate that, for all the described experiments, the polymer isolated had a relatively low molecular weight.

The optically active polymers had molecular weights in the range of $M_n=450-7300$ (DP=2-35). The molecular weight distribution ranged from $M_w/M_n = 1.21-2.69$. The racemic polymers had molecular weights and molecular weight distributions also in this range.

In order to explain these findings, each catalyst subclass will be discussed separately.

X. Macrozwitter Ion Initiators

Table 11 lists all the pertinent data that will be discussed. At 70°C polymerization temperature, using triethylamine as the initiator in bulk, the polymer had a

TABLE 11
EXPERIMENTAL CONDITIONS AND RESULTS FOR THE POLYMERIZATION
OF MALOLACTONE BENZYL ESTER USING MACROZWITTER ION INITIATORS

Monomer moles liter	Initiator	Polymerization Temperature °C	Time days	Conversion %	Yield %	M_{GPC}^b	M_w/M_n	Melting Point °C	Glass ^d Transition Temperature °C	$(\alpha)_D^{25}$
bulk ^g	NEt ₃ ^e	70	5	100	65	3100	1.5	-	25	-
bulk ^g	betaine ^e	70	5	70	40	2300	1.41	-	25	-
bulk ^h	NEt ₃ ^e	30	28	80	30	2050	2.09	130-150	26	+10.6
bulk ^h	NEt ₃ ^e	70	3	90	50	2200	1.41	140-160	25.5	+13
bulk ^h	NEt ₃ ^e	70	5	100	80	2900	1.41	130-150	26	+12
CH ₂ Cl ₂ ^{f,h}	NEt ₃ ^e	30	28	40	20	2600	2.1	140-160	25	+10.6
toluene ^{f,h}	NEt ₃ ^e	30	28	40	10	2100	1.98	130-150	25	-
bulk ^h	betaine ^e	30	28	60	22	2300	2.1	135-150	26	+11.2

{a} Determined by infrared spectroscopy
{c} Temperatures where DSC-curve starts slope change and returns to baseline
{d} Given as midpoint
{e} Initiator to monomer concentration in moles is 10⁻³
{f} Monomer concentration is 2.5 M
{g} Racemic malolactone benzyl ester
{h} Optically active malolactone benzyl ester
(b) Polystyrene standards

M_n of 2900 and M_w/M_n of 1.41. The narrow MWD suggested this class of initiators gives a "living" polymerization mechanism. This result corroborates the proposed literature data that this class of initiator gives a "living" propagation mechanism. The low number average molecular weight and high conversion data show that chain transfer to monomer is a complicating side reaction. By definition, a "living" polymerization does not involve transfer to monomer, therefore although the MWD curve is narrow the polymerization mechanism is not "living". The GPC curve for the polymer formed is shown in Fig. 70.

At 30°C reaction temperature, the triethylamine initiator in bulk yielded a polymer with a M_n of 2300 and M_w/M_n of 2.1. The MWD data (Fig. 71) indicates the polymerization mechanism is not "living". The reaction rate is much slower, and the overall conversion is only 60%. No improvement is observed using solvents, either methylene chloride or toluene, and the observed rate of polymerization was slow. And, the MWD data demonstrate the polymerization is not a "living" system.

Using betaine as the initiator at 30°C polymerization temperature in bulk, the GPC-MWD curve gave the same symmetrical shape and size distribution.

To explain why the polymerization mechanism is not "living" at the lower polymerization temperatures, one can hypothesize that at the slower rates of polymerization,

Figure 70. GPC curve for the polymer made using triethylamine in bulk at 70°C.

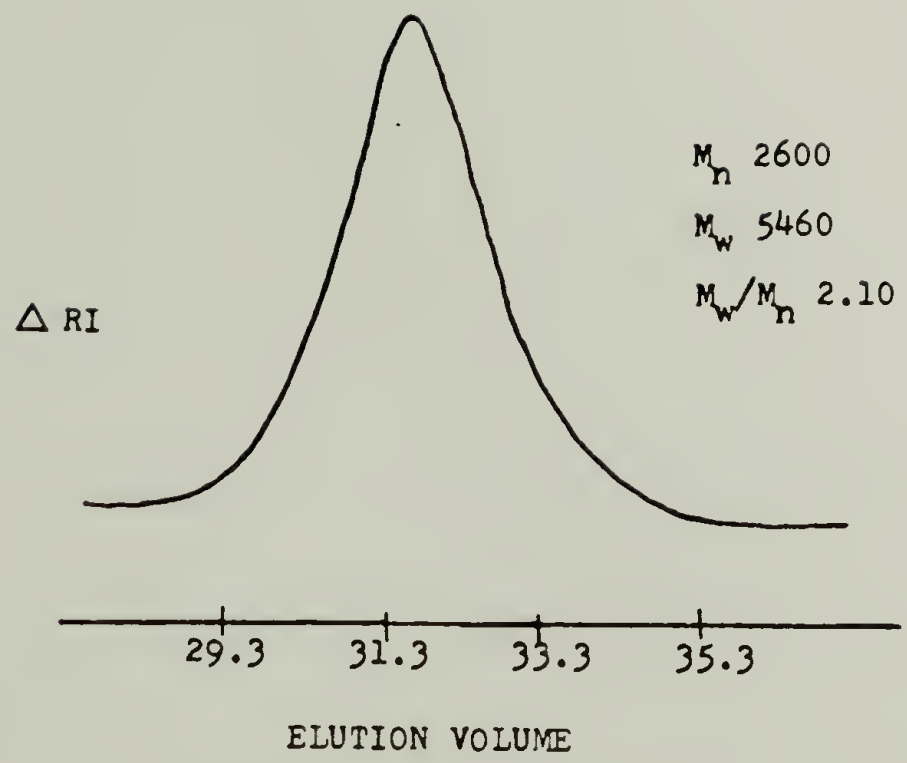
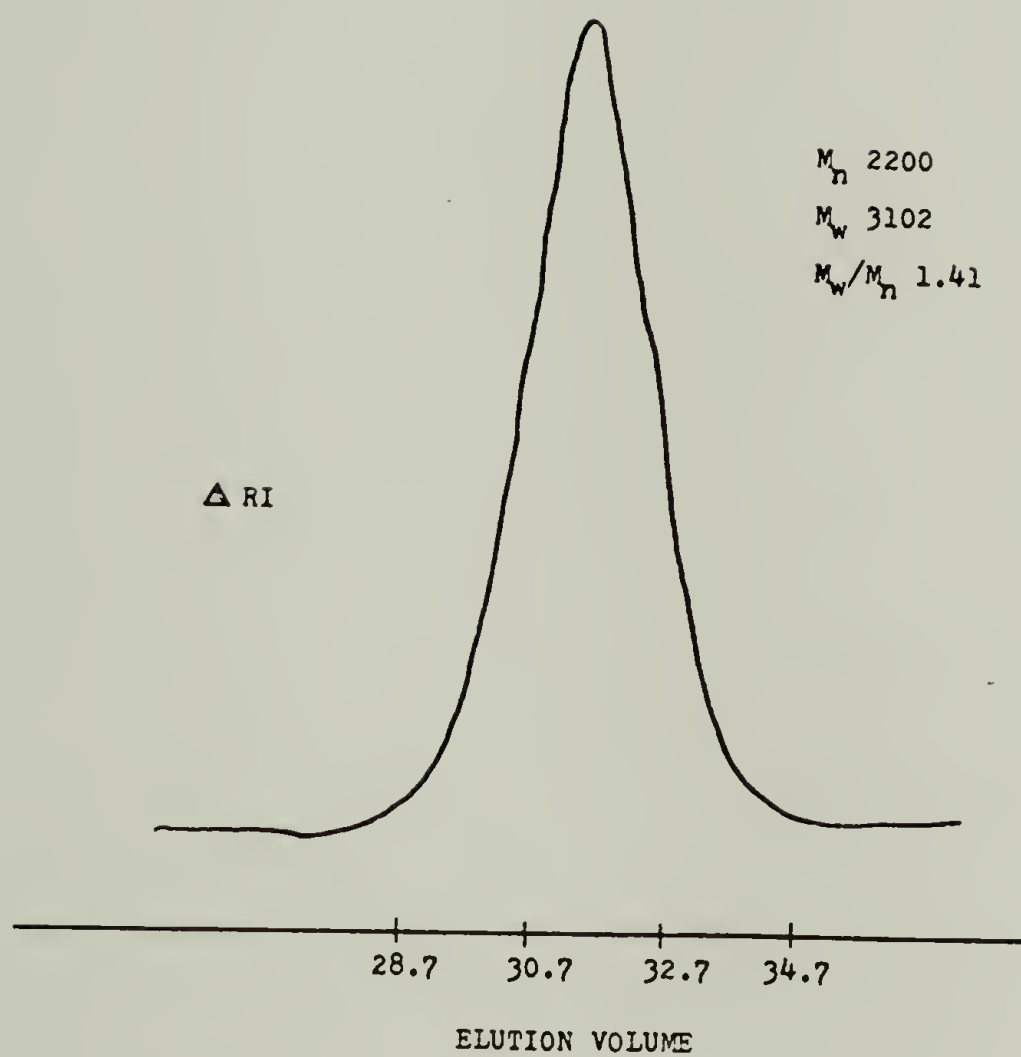


Figure 71. GPC curve for the polymer prepared using triethylamine in bulk at 30°C.



the rates for the side reactions (transfer) are more competitive, hence, a broader MWD curve is obtained.

XI. Anionic Initiators

Using tetraethylammonium benzoate as the initiator in bulk at 70°C reaction temperature, the MWD is narrow ($M_w/M_n = 1.44$); lowering the reaction temperature, the molecular weight distribution broadened (Table 12). The GPC plots were uniformly symmetrical, as shown in Fig. 72 for the polymer prepared at 70°C. The results indicate that at lower reaction temperatures or using solvent, the rate of polymerization was slower so that competing side reactions (transfer) hindered the occurrence of a "living" mechanism.

XII. Cationic Initiators

Cationic initiators, such as ferric chloride, gave polymers having low molecular weights and the molecular weight distributions were not narrow ($M_w/M_n > 2$) as shown in Table 13.

There appeared to be a prominent chain transfer reaction in the polymerization but because of low conversions, it is unknown if the chain transfer to monomer is the side reaction.

The trityl salts are not good initiators for the polymerization of beta-substituted-beta-lactones, because

Figure 72. GPC curve for the polymer prepared using tetraethylammonium benzoate in bulk at 70°C.

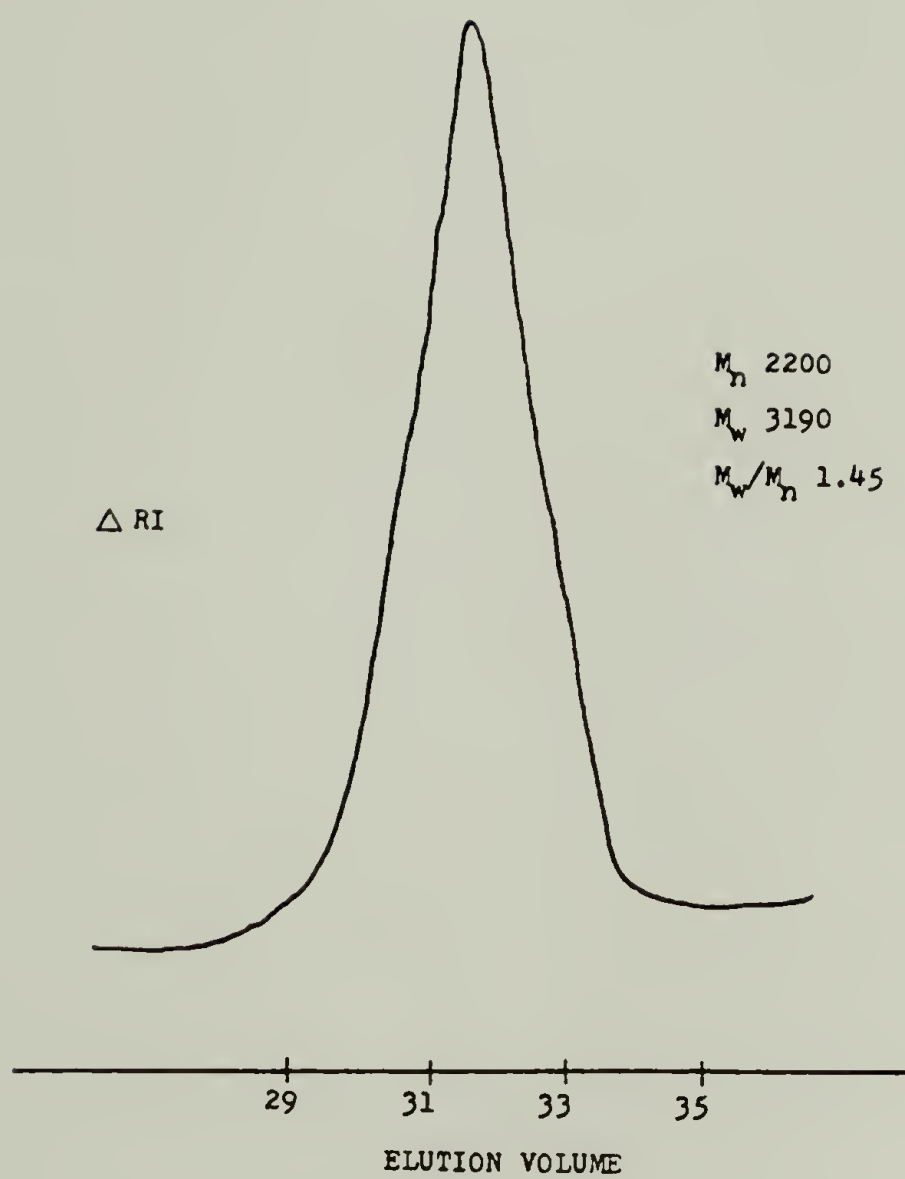


TABLE 13

EXPERIMENTAL CONDITIONS AND RESULTS FOR THE POLYMERIZATION
OF MALOLACTONE BENZYL ESTER USING CATIONIC INITIATORS

Monomer moles liter	Initiator	Polymerization Temperature °C	days	Conversion ^a %	Yield %	M _{GPC} ^b	M _w /M _n ^h	Melting ^c Point °C	Glass ^d Transition Temperature °C	(α) _D ²⁵
bulk ^g	FeCl ₃ ^e	70	14	35	15	2600	1.95	-	25	-
bulk ^g	AlCl ₃ ^e	70	20	25	10	1000	2.1	-	-	-
bulk ^g	φ ₃ CSbF ₆ ^e	30	1	100	10	410	2.05	-	-	-
bulk ^g	φ ₃ CBF ₄ ^e	30	30	45	5	-	-	-	-	-
bulk ^h	FeCl ₃ ^e	30	28	50	10	2500	2.2	130-160	25	-
bulk ^h	FeCl ₃ ^e	70	7	50	25	1800	1.99	140-160	25	-6.5
bulk ^h	FeCl ₃ ^e	70	7	80	40	3200	2.05	135-150	25	-7.5
CH ₂ Cl ₂ ^{f,h}	FeCl ₃ ^e	30	28	20	5	1800	2.35	125-150	25	-7.8
toluene ^{f,h}	FeCl ₃ ^e	30	28	20	0	-	-	-	-	-
bulk ^h	φ ₃ CSbF ₆ ^e	30	1	100	20	470	2.1	-	-	-
CH ₂ Cl ₂ ^{f,h}	φ ₃ CSbF ₆ ^e	30	1	100	0	-	-	-	-	-
toluene ^{f,h}	φ ₃ CSbF ₆ ^e	30	1	100	10	640	2.0	-	-	-
bulk ^h	φ ₃ CBF ₄ ^e	30	28	50	10	450	2.05	-	-	-
toluene ^{f,h}	φ ₃ CBF ₄ ^e	30	28	10	0	-	-	-	-	-

(a) Determined by infrared spectroscopy

(b) Polystyrene standards

(c) Temperatures where DSC-curve starts slope change and returns to baseline

(d) Given as midpoint

(e) Initiator to monomer concentration in moles is 10⁻²

(f) Monomer concentration is 2.5 M

(g) Racemic malolactone benzyl ester

(h) Optically active malolactone benzyl ester

of predominant chain transfer. Khomgkov, et. al.¹¹⁷ showed that carbenium ion will abstract a proton from beta-substituted-beta-lactones and this reformed by reaction with the growing end group as shown by Fig. 73.

XIII. Organometallic Catalysts

Using triethylaluminum/water as the catalyst, the polymer had a molecular weight of 2812 and M_w/M_n of 2.09. Vert and Lenz³⁸ obtained a highly crystalline methanol insoluble fraction when the racemic malolactone benzyl ester was polymerized with triethylaluminum, but I did not obtain similar results. The following Fig. 74 shows the GPC plots for the optically active polymer.

Diethylzinc was found to be a poor catalyst for the polymerization. The data is summarized in Table 14.

XIV. Anionic Catalysts / Crown Ethers

There was no significant improvement in molecular weight using anionic initiators complexed with crown ethers. The rates of polymerization were much faster at lower temperatures. With the addition of a crown ether, the reaction time was significantly increased achieving high reaction conversions in shorter times. The data is summarized in Table 15.

Figure 73. Khomgkov, et. al.¹¹⁷ proposed mechanism for the abstraction of a proton from a beta-substituted-beta-lactone using a carbenium ion.

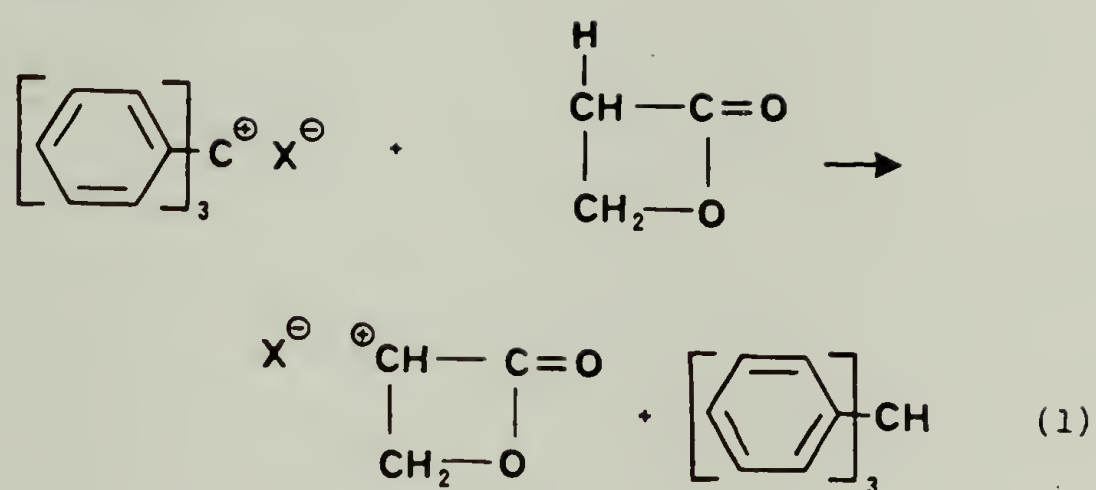
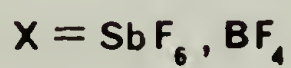
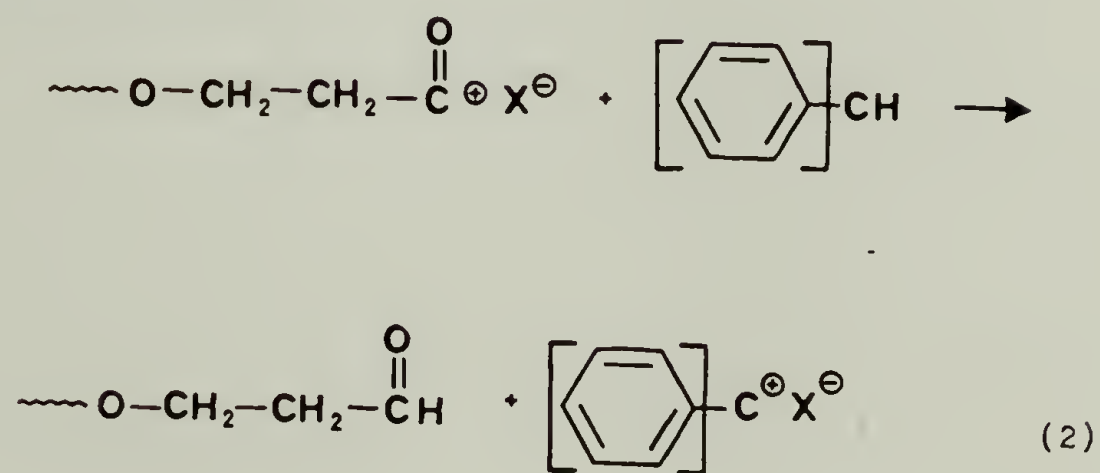
INITIATION:CHAIN TRANSFER:

Figure 74. GPC curve for the polymer prepared using triethylaluminum/water at 70°C in toluene.

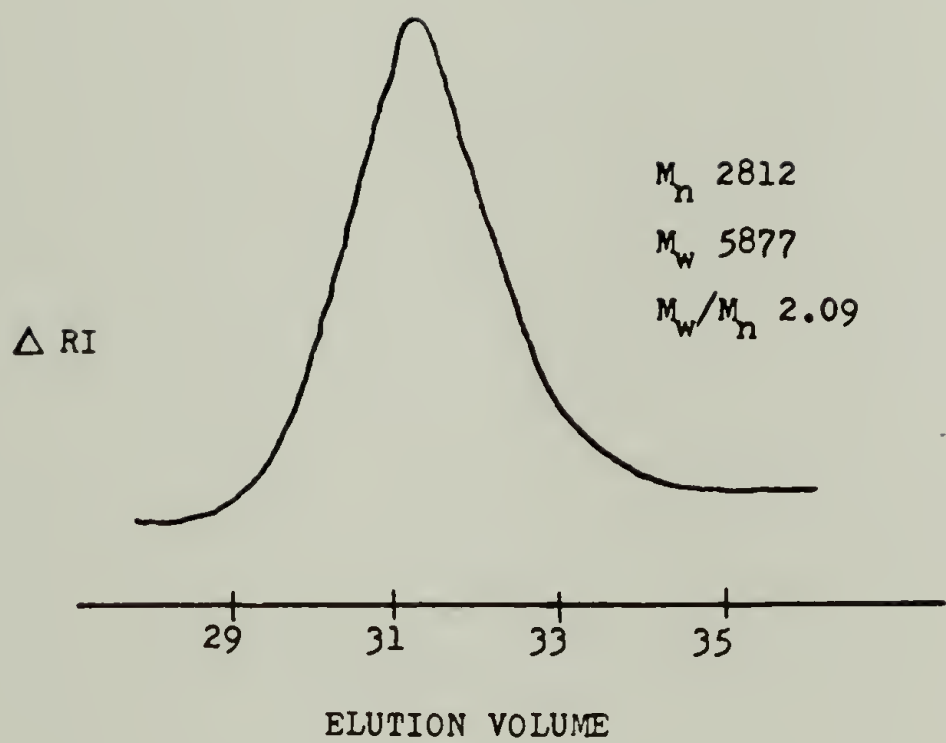


TABLE 14
EXPERIMENTAL CONDITIONS AND RESULTS FOR THE POLYMERIZATION
OF MALOLACTONE BENZYL ESTER USING ORGANOMETALLIC INITIATORS

Monomer moles liter	Initiator	Polymerization Temperature Time		Conversion %	Yield %	M _{GPC}	M _w /M _n	Melting Point °C	Glass Transition Temperature °C	(α) _D ²⁵
		°C	days							
toluene ^{f,g}	AlEt ₃ ^e	70	5	75	35	2980	2.1	-	25	-
bulk ^g	Et ₂ Zn ^e	50	18	100	50	640	1.28	-	-	-
toluene ^{f,h}	AlEt ₃ ^e	70	10	90	50	2812	2.09	135-165	26	-12.0
bulk ^h	Et ₂ Zn ^e	50	24	100	55	850	1.25	110-135	25	-
(a) Determined by infrared spectroscopy										
(c) Temperatures where DSC-curve starts slope change and returns to baseline										
(d) Given as midpoint										
(e) Initiator to monomer concentration in moles is 10 ⁻²										
(f) Monomer concentration is 2.5 M										
(g) Racemic malolactone benzyl ester										
(h) Optically active malolactone benzyl ester										

TABLE 15
EXPERIMENTAL CONDITIONS AND RESULTS FOR THE POLYMERIZATION
OF MALOLACTONE BENZYL ESTER USING ANIONIC CATALYSTS/CROWN ETHERS

Monomer moles liter	Initiator	Polymerization Temperature °C	Time days	Conversion %	Yield %	M _{GPC}	M _w /M _n	Melting Point °C	Glass Transition Temperature °C	(α) _D ²⁵
bulk ^f	NaO ₂ CCH ₃ ^{e,h}	30	1	100	80	2860	1.30	-	25	-
bulk ^f	KO ₂ CCH ₃ ^{e,i}	30	2	90	60	2940	1.25	-	25	-
bulk ^g	NaO ₂ CCH ₃ ^{e,h}	0	60	75	35	2100	2.83	125-157	26	-
bulk ^g	NaO ₂ CCH ₃ ^{e,h}	30	2	75	45	3350	1.35	140-160	26	+13.2
bulk ^g	NaOH ^{e,h}	30	6	85	20	1350	1.28	140-160	25	+9.5
bulk ^g	KO ₂ CCH ₃ ^{e,i}	30	3	80	38	2200	1.41	130-150	25	+11.6
bulk ^g	KOH ^{e,i}	30	4	60	28	1060	1.21	135-145	26	+10.2

(a) Determined by infrared spectroscopy

(c) Temperatures where DSC-curve starts slope change and returns to baseline

(d) Given as midpoint

(e) Initiator to monomer concentration in moles is 10⁻³

(f) Racemic malolactone benzyl ester

(g) Optically active malolactone benzyl ester

(h) Dibenzo-18-crown-6-ether is used in 1 to 1 molar ratio with initiator

(i) 15-crown-5-ether is used in 1 to 1 molar ratio with initiator

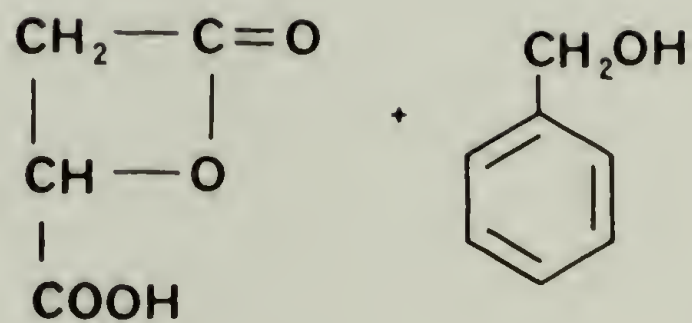
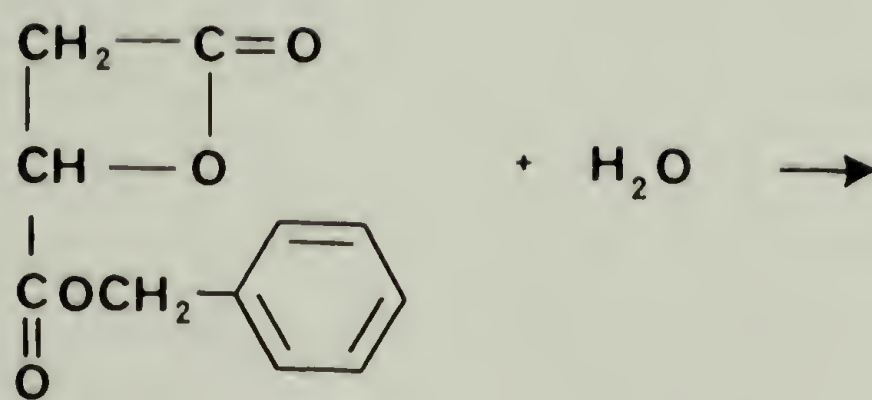
XV. Summary

I was unable to obtain high molecular weight polymer with any of the initiator systems. Chain transfer is considered to be a competing side reaction; however the occurrence of a transfer reaction cannot be considered as the only explanation for the low molecular weight of the isolated polymers.

Vert¹¹⁸ has hypothesized that impurity in the monomer is an additional problem. Although the monomer was purified by high pressure liquid chromatography and distillation, a reactive impurity was most likely still present. The impurity is assumed to be malolactone carboxylic acid formed by hydrolysis of the malolactone benzyl ester during the purification (Fig. 75).

The presence of this compound can explain the low molecular weight polymer obtained; however, further work is needed to understand this problem.

Figure 75. Vert's¹¹⁸ hypothesized mechanism for the formation of the impurity in malolactone benzyl ester.



C H A P T E R I V

POLYMER STRUCTURE - PROPERTY RELATIONSHIPS

I. Review - Optical Activity Versus Polymer Crystallinity

Optical activity in polymers depends on the type of symmetry existing in the repeat unit. The repeat unit in the polymer backbone must not consist of an equal amount of two enantiomers. The repeating units must be asymmetric. The number of repeating units having an asymmetric structure of a given type must differ from the number of repeat units of the opposite type; otherwise, the optical rotation caused by one unit (D) will be balanced by an equal and opposite rotation from the other unit (L). For this reason, polymers prepared from racemic monomer mixtures will show no optical rotation, unless the polymerization is controlled by a stereoelective catalyst. This type of catalyst preferentially selects one of the isomers over the other. The isomer not selected will remain unpolymerized as the low molecular weight monomer which allows for an easy separation from the polymer formed. There are a number of examples of stereoelection polymerization reactions in the literature,^{119a} and polymers prepared with these catalysts exhibit optical activity.^{119b}

One can isolate a polymer prepared from a mixture of chiral stereoisomers in which the products consist of a mixture of pure D- and L- pure polymers (pure isolactic polymers), or a polymer mixture consisting of equal amounts

of D- and L- blocks, a stereoblock of polymers containing blocks of two different isotactic polymers. The catalyst preferentially incorporates one of the chiral monomers into a growing polymer chain, and, hence, this type of catalyst is defined as a stereoselective catalyst.

An example of a stereoelective polymerization reaction is the polymerization of D,L-propylene oxide using diethyl zinc/(+) borneol as catalyst (Fig. 76a).^{119a}

An example of a stereoselective polymerization is the polymerization of D,L-propylene oxide with zinc alkyl-methanol¹²⁰ as initiator (Fig. 76b).

An excellent review article on stereoselective and stereoelective polymerization has been written by T. Tsuruta.¹²¹

The previous discussion has dealt with the methods by which polymers are prepared having configurations of the asymmetric repeating units regularly repeating themselves. The literature has repeatedly illustrated that only those polymers with a very high degree of regularity of chemical and geometrical structure may crystallize. Stereoregular (stereospecific) polymers consist of highly ordered sequences of monomer units. A polymer containing substituent groups bonded to the backbone may be stereoregular if the configurations of the substituted carbon atoms in the sequence of repeating units have an isotactic or syndiotactic or other ordered structure, hence, polymer crystallinity.

In the present study, the polymer has a chiral center

Figure 76a. Stereoelective polymerization.

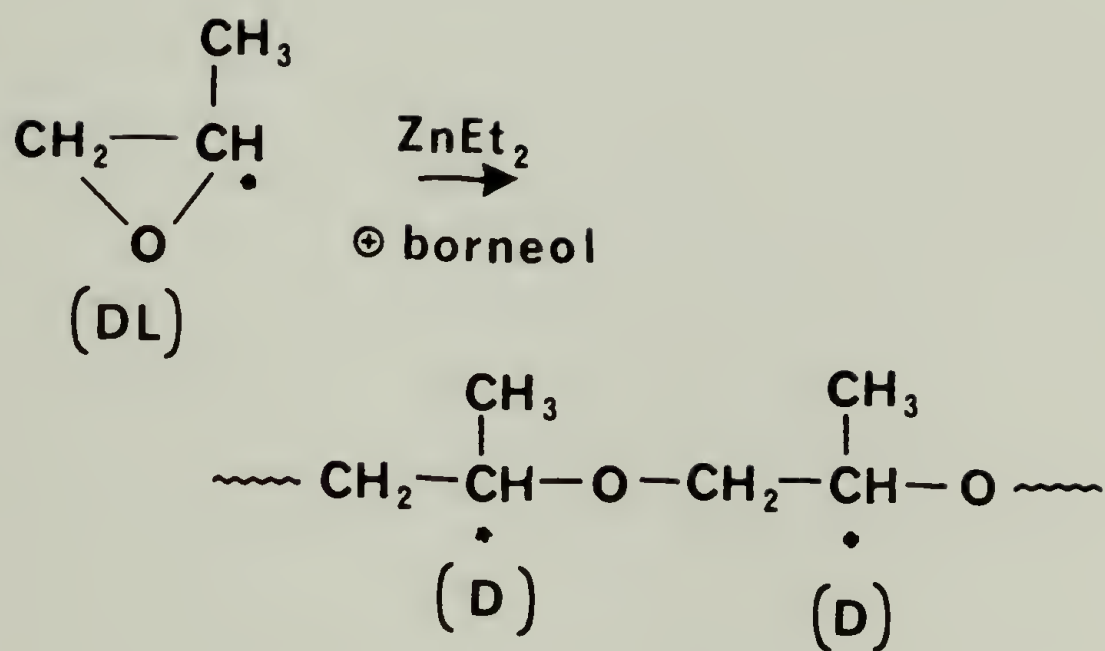
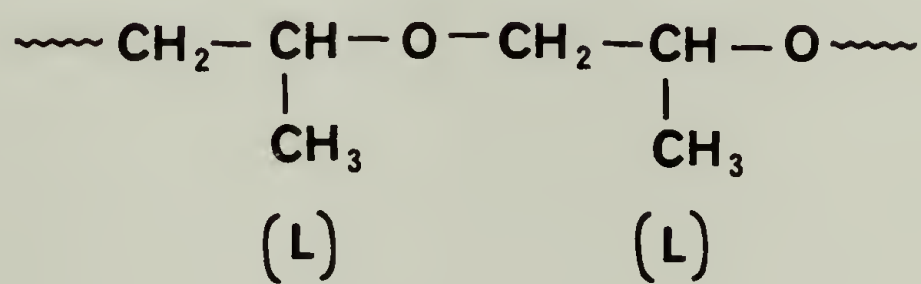
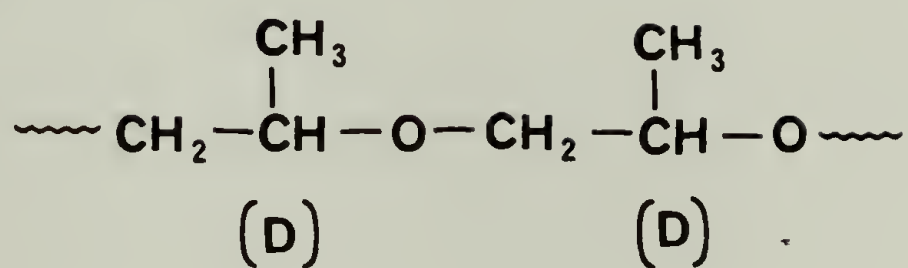
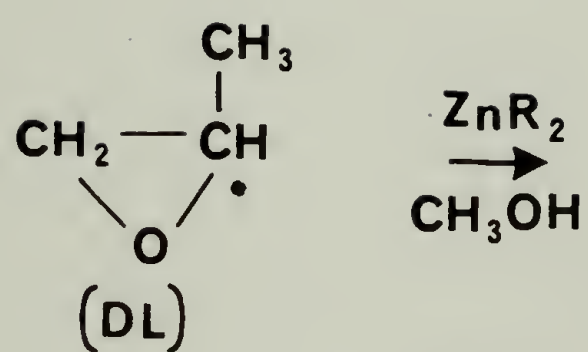


Figure 76b. Stereoselective polymerization.



at the beta carbon (Fig. 77).

The repeating unit has an intrinsic asymmetry and optically active poly(malolactone benzyl ester) can be obtained by three different methods:

- (1) by polymerization of optically active monomers;
- (2) by stereoelective polymerization; and
- (3) by resolution of racemic mixtures of polymers.

As already stated, the method based on polymerizing optically active monomers is the principal method used in this thesis. Stereoselective polymerization of the racemic monomer was carried out to a very limited extent.

Stereoelective polymerization was avoided because of the lack of specific knowledge concerning stereoelective catalysts available for the polymerization of malolactone benzyl ester. The resolution of racemic mixtures of polymers did not seem suitable because it is necessary to have a product which contained a physical mixture of pure D- and L-polymers. This method has been successful for separating racemic poly-4-methyl-1-hexane¹²² and poly(DL-propylene oxide).¹²³ Hatada, Harris, and Vogl¹²⁴ have demonstrated success in separating racemic poly(alpha-methylbenzyl methacrylate) using optically active poly(chloral) as the resolving substrate as shown in Fig. 78.

The specific rotation (α) of compounds varies as a function of the wavelength of the incident light. If the specific rotation is plotted against wavelength, the optical rotatory dispersion curve (ORD) is obtained. For a

Figure 77. Poly(L-malolactone benzyl ester).

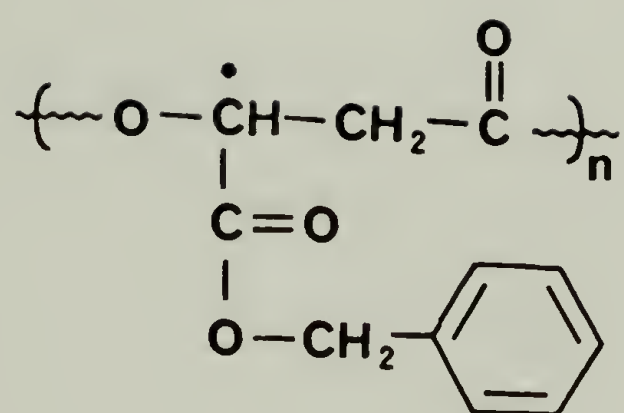
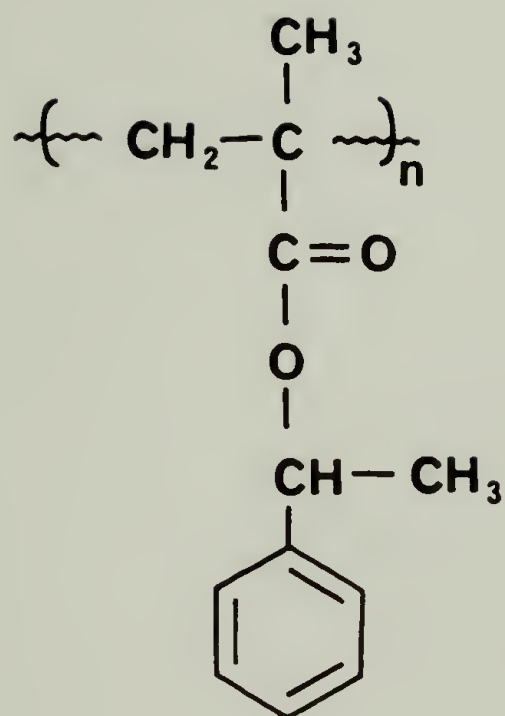
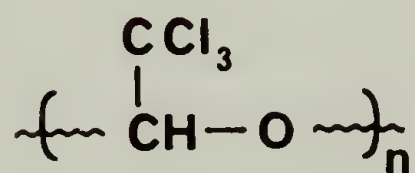


Figure 78. Hatada, Harris and Vogl¹²⁴ demonstrated success in separating racemic poly(alpha-methylbenzyl methacrylate) using optically active poly-(chloral).



POLY(ALPHA-METHYLBENZYL METHACRYLATE)



POLY(CHLORAL)

compound containing no chromophore in the region of wavelength examined, the optical activity will decrease in magnitude with increasing wavelength, and a plain positive or plain negative ORD-curve is obtained, depending upon whether it rises or falls with decreasing wavelength. If the compound has one or more chromophores which give rise to an absorption in the wavelength examined, the ORD-curve will be "anomalous" and show one or more extrema (peaks, troughs, or shoulders) at the wavelength where the chromophore absorbs.

For the region in which no chromophore absorption bands are observed, Drude¹²⁵ proposed the following equation:

$$(\alpha) = A_0 / \lambda^2 - \lambda_0^2$$

The term $A_0 / \lambda^2 - \lambda_0^2$ defines the contribution to the total specific rotation at any wavelength, where A_0 is a constant, λ_0 is the wavelength of the closest absorption maximum, and λ is the wavelength of the incident light. The above expression is referred to as the one-term Drude equation and applies for compounds having one chromophore. By rearranging the equation one obtains:

$$(\alpha) \lambda^2 = A_0 + \lambda_0^2 (\alpha)$$

Plotting $(\alpha) \lambda^2$ against (α) should give a straight line if the one-term Drude equation is obeyed. If a curvature is observed in such a plot, this result indicates that an anomalous behavior, such as a Cotton-effect, can be expected.

For compounds containing two different chromophores, two absorption maxima are obtained, and a two-term Drude equation applies as follows:

$$(\alpha) = A_1 / \lambda^2 - \lambda_0^2 + A_2 / \lambda^2 - \lambda_1^2$$

The first term corresponds to the rotatory contribution of the chromophore at λ_0 and the second term refers to the second chromophore at λ_1 .

In the case of a polymer, the total rotation can be formed by two contributions, one part is due to the asymmetric repeating unit, and the other can come from the conformation of the macromolecule if a regular or ordered conformation is formed; e.g., a helix. The conformational part of the rotation can be significant in the case of stereoregular

polymers and can be used to determine the extent of a secondary structure such as a helix.

Moffitt and Yang¹²⁶ derived an expression for polypeptides and proteins having a helical conformation as follows:

$$(\overset{1}{m})_{\lambda} = (\alpha) \cdot \frac{3}{n^2 + 2} \cdot \frac{M_o}{100} = \frac{a_o \lambda_o^2}{\lambda^2 - \lambda_o^2} + \frac{b_o \lambda_o^4}{(\lambda^2 - \lambda_o^2)^2}$$

where n is the refractive index of the solvent; a_o , b_o and λ_o are constants; M_o is the molecular weight of the repeating unit and $(\overset{1}{m})_{\lambda}$ is the molar rotation.

By multiplying both sides with $\lambda^2 - \lambda_o^2 / \lambda_o^2$ one obtains:

$$(\overset{1}{m})_{\lambda} \cdot \frac{\lambda^2 - \lambda_o^2}{\lambda_o^2} = a_o + b_o \cdot \frac{\lambda_o^2}{\lambda^2 - \lambda_o^2}$$

One then plots $(\overset{1}{m})_{\lambda} \lambda^2 - \lambda_o^2 / \lambda_o^2$ against $\lambda_o^2 / \lambda^2 - \lambda_o^2$ and obtains a straight line if the Moffitt equation is obeyed. Validity of the Moffitt equation indicates the occurrence of a helical conformation.

When an optically active medium is traversed by a plane polarized light in the spectral range in which an optically active chromophore absorbs, not only does the

plane of polarization rotate at an angle, but the resulting light is also elliptically polarized; that is, the medium exhibits circular dichroism (CD).

The molar ellipticity (θ) is defined by the following expression:

$$(\theta) = 2.303 \frac{4500}{\pi} (\epsilon_L - \epsilon_R)$$

Where ϵ_R and ϵ_L are the molar extinction coefficients for left-and right-circularly polarized light, the above equation can be rewritten to give the following.

$$(\theta) = 3300 (\epsilon_L - \epsilon_R) = 3300 \cdot \Delta \epsilon$$

CD measurements have been used in polymer chemistry especially for monitoring the helix-coil transition of poly-peptides.^{127, 128}

The combination of the phenomena of unequal absorption (CD) and unequal velocity of transmission (ORD) of left and right circularly polarized light in the region in which optically active absorption bands are observed is a phenomenon called the Cotton effect.

The CD-curve will have its maximum at the absorption maximum. The ORD-curve has a cross-over at the band center but extends with measurable intensity far out in both directions from the center. The CD-spectrum, on the other hand, can be observed only in the immediate neighborhood of the absorption band. For the Cotton band to be positive, both the rotation on the long wavelength side, and the CD-curve are positive at all points. For a negative Cotton band, these curves would be inverted.

II. Chiroptical Properties

In the present study, optically active poly(malolactone benzyl ester) was obtained by the ring opening polymerization of the corresponding lactone, using various initiators. The lactone of (-) rotation gave polymers of either (+) or (-) rotation depending on the initiator. The ORD results are given in the following Table 16 for the monomer and polymers prepared with triethylamine at 70°C in bulk, tetraethylammonium benzoate at 70°C in bulk, and ferric chloride at 70°C in bulk.

The ORD results obeyed the one-term Drude equation for solutions of the polymer in dioxane (Fig. 79-82), so there is at present a good indication that no secondary structures exist for the polymer in solution.

TABLE 16
OPTICAL ROTATORY DISPERSION OF POLY(BETA-L-MALOLACTONE
BENZYL ESTER) AND ITS MONOMER

λ (nm)	L-malo- lactone benzyl (c=2.0, dioxane)	Poly(beta-L-malolactone benzyl ester)		
		NEt ₃ ^a (c=2.0, dioxane)	ϕ CO ₂ NEt ₄ ^b (c=2.5, dioxane)	FeCl ₃ ^c (c=2.0, dioxane)
		----- (α) ²⁵ -----		
589	-37	+13	+11.0	-7.5
576.9	-37.1	+13.65	+11.5	-7.6
546.1	-39.5	+15.4	+13.0	-9.1
435.8	-59.2	+26.6	+22.9	-17.2
407.78	-63.1	+31.4	+28.6	-20.9
404.7	-	+31.8	+27.1	-21.2
366.3	-67.3	+42	+36	-31.3
(a) Polymerization ran at 70°C in bulk				
(b) Polymerization ran at 70°C in bulk				
(c) Polymerization ran at 70°C in bulk				

Figure 79. One-term Drude equation for L-malolactone benzyl ester.

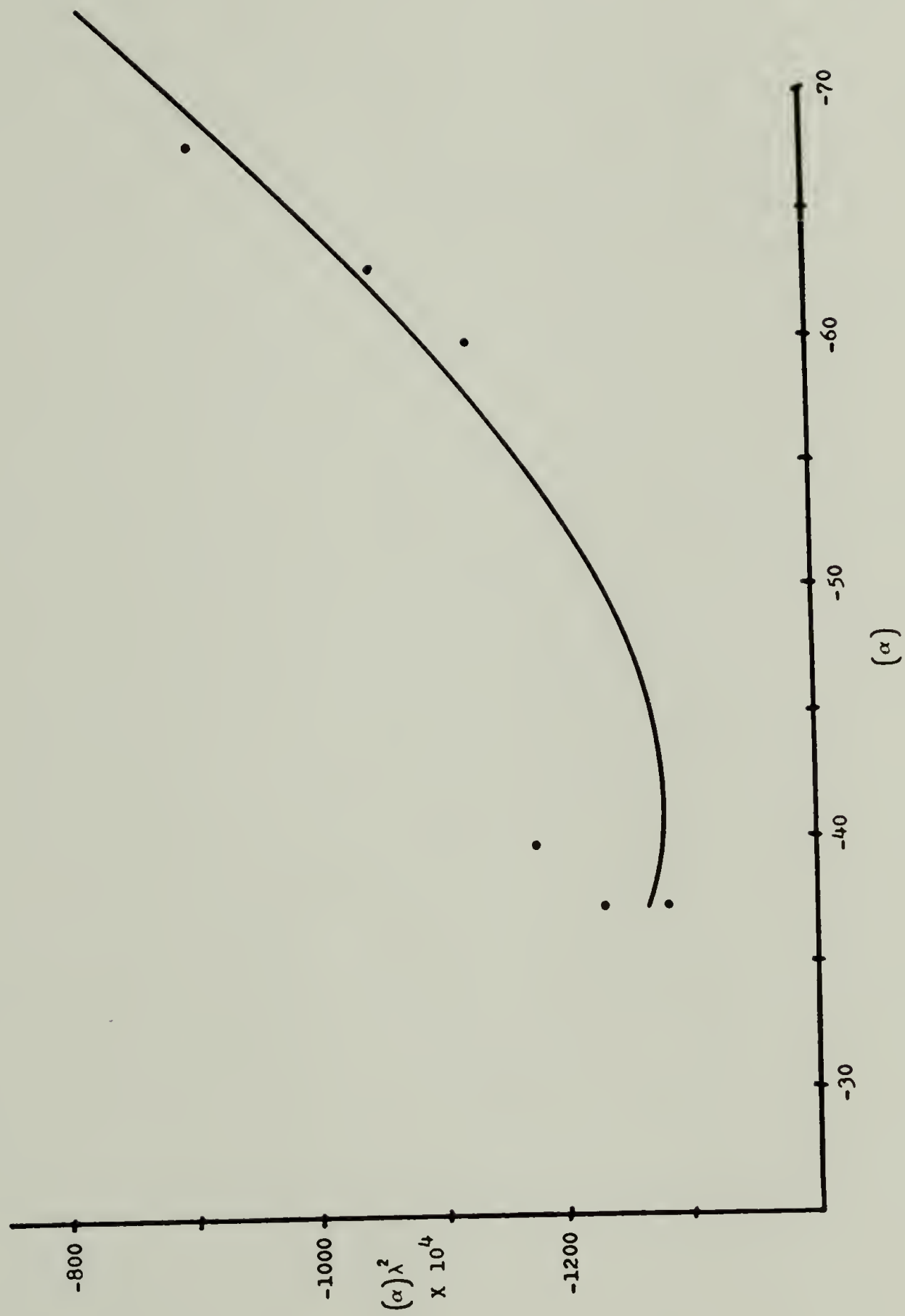


Figure 80. One-term Drude equation for the polymer made using triethylamine in bulk at 70°C.

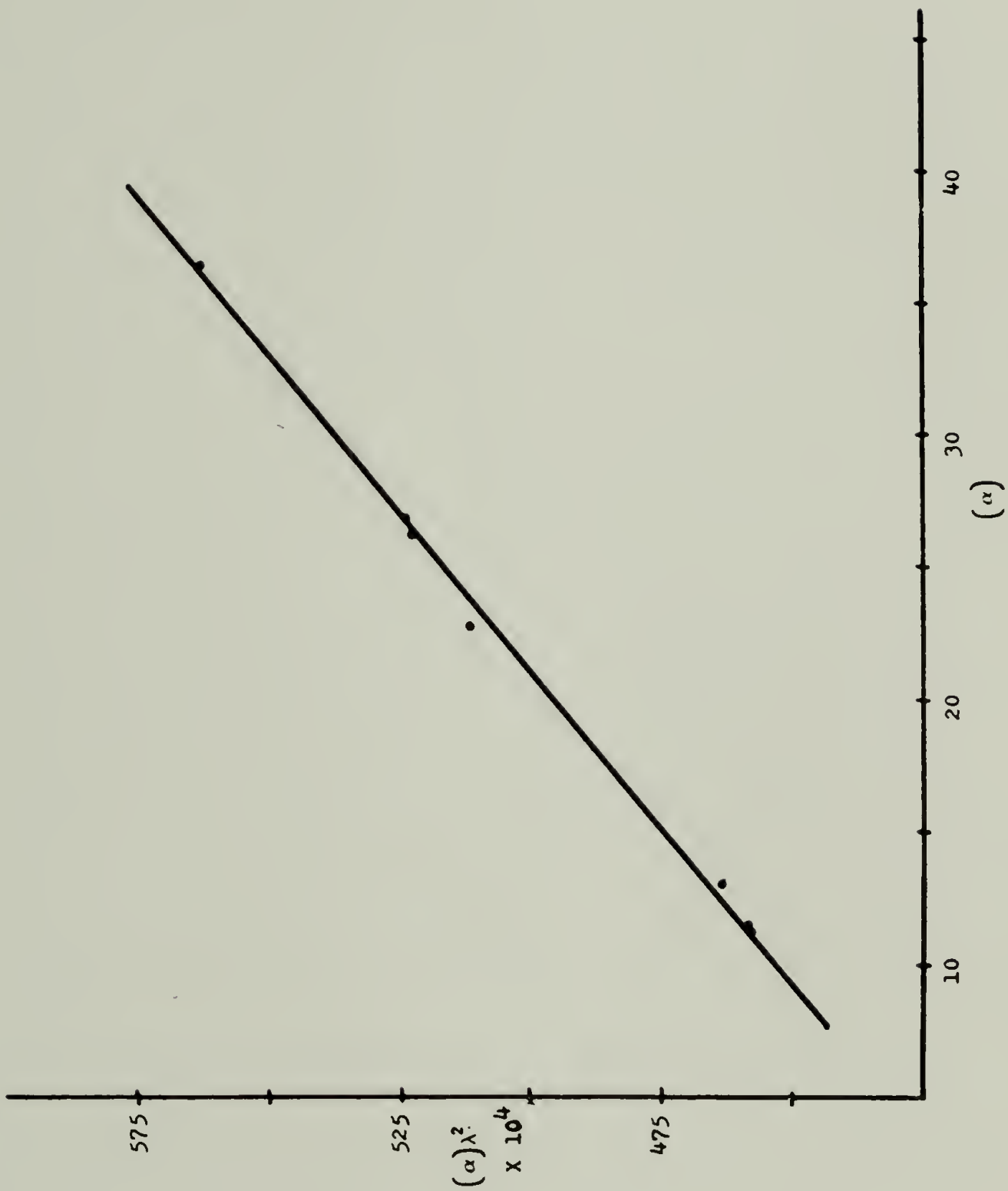


Figure 81. One-term Drude equation for the polymer made using tetraethylammonium benzoate in bulk at 70°C.

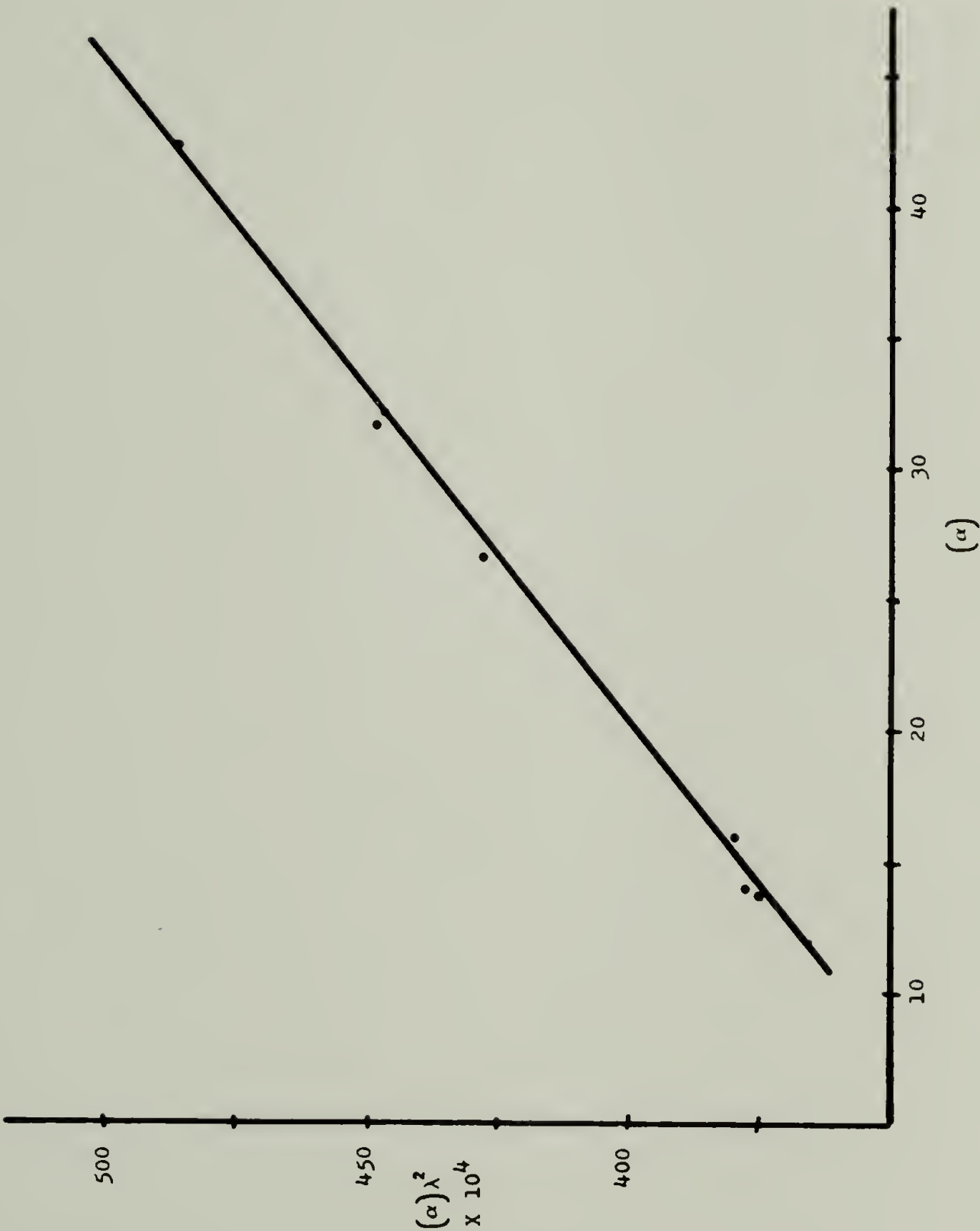
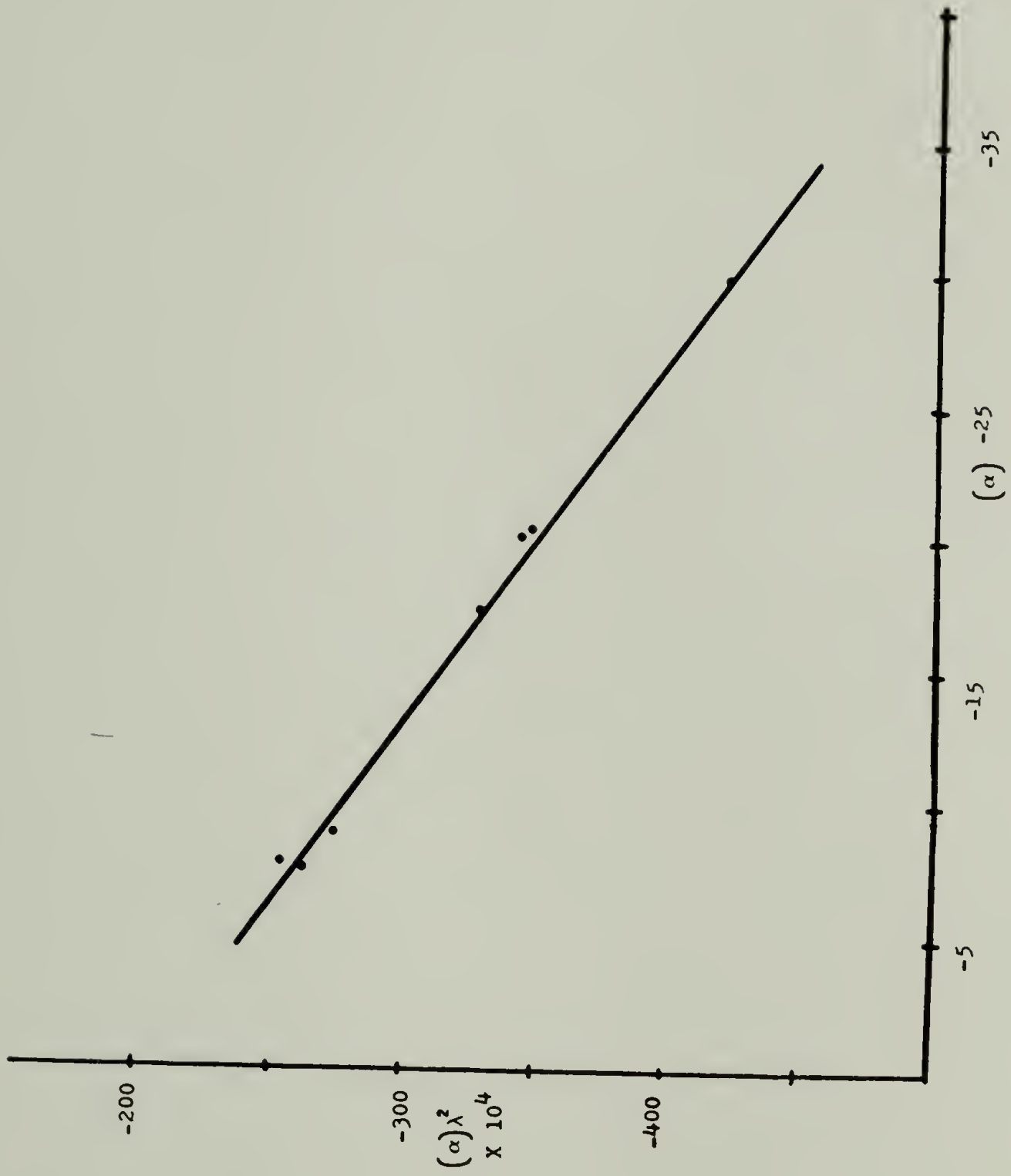


Figure 82. One-term Drude equation for the polymer made using ferric chloride in bulk at 70°C.



III. Infrared Analysis of the Polymers

Infrared spectra of the different optically active polymers obtained from the L-malolactone benzyl ester monomer showed no difference when compared. The spectra from the racemic polymer also showed no difference. The major absorption was at 1760cm^{-1} and corresponded to the ester carbonyl stretching mode. Peaks at $2900\text{-}3100\text{cm}^{-1}$ corresponded to methyl, methylene, and acyl hydrogen stretching. In the range of $1230\text{-}1130\text{cm}^{-1}$, two strong bands corresponded to -C-O-C- stretch.

IV. NMR Studies of the Polymer

There is practically no difference in the NMR-spectra of the racemic and optically active polymers. All of the spectra show four absorptions; at 7.30 ppm (5H) for the phenyl ring, at 5.5 ppm (H) for the hydrogen attached to the beta carbon, 5.1 ppm (2H) for the methylene group of the benzyl ester, and at 2.9 ppm (2H) for the hydrogens attached to the alpha carbon.

V. Carbon-13 Analysis

There were no differences observed for the carbon-13 spectra of the optically active and racemic polymers. All

the spectra had seven absorptions for the seven different carbons of the repeating unit.

VI. Summary and Conclusions

The optically active and racemic forms of poly(malolactone benzyl ester) were prepared from the corresponding optically active and racemic monomers. The presence of crystallinity and melting point in the optically active polymers, but not in the racemic polymer as formed with homogeneous initiators determined by DSC, demonstrated the formation of the stereoregular isotactic optically active polymer for the former but an atactic polymer for the latter. The chiroptical properties of the optically active poly(L-malolactone benzyl ester) were recorded in solution. There appears to be preliminary evidence to suggest that no secondary structure is formed in dioxane.

One of the objectives of this work was to obtain poly(L-malic acid) having a molecular weight of approximately 10,000. To this end, I have as yet been unsuccessful; however, the information gained about monomer preparation, polymerization mechanism and polymer structural analysis, are noteworthy accomplishments, justifying the research effort.

C H A P T E R V

EXPERIMENTAL SECTION

I. Materials

The following chemicals were purchased from the indicated suppliers.

acetic acid	B
acetone	F
acetic anhydride	A
acetonitrile	E
acetyl chloride	A
aluminum chloride	F
ammonium chloride	A
L-aspartic acid	A
Barium oxide	F
benzene	F
benzonitrile	A
benzyl alcohol	A
betaine	A
butyronitrile	A
calcium chloride	F
calcium hydride	F
chloral	P
chloroform	F
copper powder	F
15-crown-5-ether	A
cupric carbonate	F
cuprous oxide	F
dibenzo-18-crown-6-ether	A
dicyclohexyl-carbodiimide	A
diethyl phosphorochloridate	A
diethylzinc	A
dimethylformamide	A
p-dioxane (gold label)	A
dodecane thiol	A
ethylchloroformate	A
ethyl acetate	F
ferric chloride	F
n-hexane	F
1,1,1,3,3,3-hexamethyl-disilazane	A

3-hydroxybutyric acid	A
hydrochloric acid	B
DL-malic acid	A
L-malic acid	A
methanesulfonic acid	A
mercury acetate	F
methanol	F
methylene chloride	F
2-methylpropyl-2-thiol	A
molecular sieve (3A)	MCB
N,N-carbonyldiimidazole	A
octadecyl mercaptan	A
oxalic acid	A
petroleum ether	B
pentyl alcohol	A
pentadecyl mercaptan	A
potassium bicarbonate	M
potassium acetate	F
potassium hydroxide	F
pyridine	E
silver nitrate	A
silver tetrafluoroborate	A
silver trifluoroacetate	A
sodium acetate	F
sodium bicarbonate	M
sodium hydroxide	F
sodium methoxide	F
sodium nitrite	A
sodium phosphate, dibasic	F
sodium sulfate	F
tetraethyl ammonium benzoate	A
tetrahydrofuran	F
thallous ethoxide	A
thiolphenol	A
thionyl chloride	A
toluene	F
p-toluenesulfonic acid	A
p-toluenesulfonyl chloride	A
tributylamine	A
triethyl aluminum	EC
trifluoromethane sulfonic acid	A
1(trimethylsilyl) imidazole	A

triethylamine	A
trifluoroacetic anhydride	A
trifluoroacetic acid	A
triphenylmethyl carbenium hexafluoroantimonate	A
triphenylmethyl carbenium tetrafluoroborate	A
triphenyl phosphite	A
thalllic trifluoroacetate	A

Sources: A = Aldrich Chemical Co.; B = J.T. Baker Chemical Co.; E = Eastman Organic Chemicals; F = Fisher Scientific Co.; M = Mallinkratt Chemical Works; MCB = Matheson, Coleman and Bell; EC = Ethyl Corporation Co.; P = Chemicals provided by research group of Professor Otto Vogl, University of Massachusetts.

II. Purification of Solvents and Reagents

Distillations were carried out using a 30 cm Vigreux column equipped with a variable reflux ratio distillation head. Reduced pressure distillations were carried out with magnetic stirring and a Cartesian-type diver manostat.

Acetonitrile was distilled (bp 81.5°C) from phosphorous pentoxide and stored over molecular sieves under argon. Butyronitrile (bp 115°C) and benzonitrile (bp 80°C/10 mm)

were purified in a like manner.

Benzene was distilled (bp 80°C) from potassium/sodium alloy (50/50) and stored over molecular sieve under argon.

Benzyl alcohol (bp $100^{\circ}\text{C}/25\text{ mm}$) was distilled prior to use, as was acetyl chloride (bp 52°C), ethylchloroformate (bp 93°C) and acetic anhydride (bp 142°C).

Chloral was provided having 92-97% purity by Professor O. Vogl's research group and used immediately after purification.

Chloroform (bp 61°C) was washed three times with equal volumes of water, dried over CaCl_2 , then distilled and stored over molecular sieve.

Dimethylformamide (bp 153°C) was distilled from calcium hydride and stored over molecular sieves.

1,1,1,3,3,3 Hexamethyldisilazane (bp 125°C) was distilled prior to use.

3-Hydroxybutyric acid was distilled under reduced pressure (bp $128^{\circ}\text{C}/0.5\text{ mm}$) using a Kugelrohr apparatus.

Methylene chloride (bp 40°C) was stirred over calcium hydride for 24 hours, then distilled and stored under an argon atmosphere.

Methanesulfonic acid (bp $167^{\circ}\text{C}/10\text{ mm}$) was distilled prior to preparation of the mercury salt.

Pyridine (bp 115°C) was distilled from metallic sodium and stored over barium oxide.

Tetrahydrofuran (bp 67°C) was stirred over calcium hydride for 24 hours, then distilled under an argon atmosphere and stored under argon.

Thionyl chloride (bp 79°C) was distilled from triphenyl phosphite at 77°C . The distillation was run very slowly to avoid formation of the yellow color.

Tributylamine (bp 112°C) and triethylamine (bp 87°C) were distilled from calcium hydride and stored under argon.

Toluene (bp 112°C) was stirred over calcium hydride for 24 hours, then distilled under argon, and stored under argon.

All other solvents and reagents were used as received.

III. Purification of Polymerization Catalysts

Betaine was dried in a vacuum oven at 100°C for 48 hours and then stored in a vacuum desicator.

Aluminum chloride was sublimed at $200^{\circ}\text{C}/10\text{ mm}$.

Ferric chloride was sublimed at $200^{\circ}\text{C}/10\text{ mm}$.

Sodium acetate, sodium hydroxide, potassium acetate, and potassium hydroxide were dried in a vacuum oven at 110°C for 7 days at 3 mm pressure.

Tetraethylammonium benzoate was recrystallized from

benzene, filtered under an argon atmosphere and stored in a desicator.

Triethylamine (bp 67°C) was refluxed over potassium hydroxide and then distilled from calcium hydride. The amine was stored under an argon atmosphere.

Triethyl aluminum and diethylzinc were used as received.

Triphenylmethyl carbenium hexafluoroantimonate and triphenylmethyl carbenium tetrafluoroborate were each dissolved in toluene and phosphorous pentaoxide was added to the solution. The solution was stirred for two hours, filtered and hexane was added to precipitate the trityl salt. The salt was filtered under an argon atmosphere and stored under an argon blanket.

The crown ethers were either used as received or they were first reacted with the basic catalysts in dry methanol to form the complex. The complex was dried in a vacuum oven for 7 days.

All other catalysts and reagents were used as received.

IV. Diazotization of L-Aspartic Acid

The following procedure was described by Testa, et. al.⁵⁰ and by D'Hondt.¹²⁹ In a 100 ml, 3-neck round bottom flask, fitted with a thermometer and dropping funnel, was

dissolved 4.8 g (0.0695 moles) of sodium nitrite in 12.5 ml water with stirring by a magnetic bar. The solution was cooled in an ice bath to 0-5 °C, after which a solution of 3.46 g of L-aspartic acid in 62.5 ml of 25% acetic acid was added slowly, drop by drop. The addition was complete in about 1.5 hours. Stirring was continued for another hour at 0-5 °C, and the solution extracted with ether, washed with water and dried over sodium sulfate. The ether, as well as the remaining acetic acid, was distilled off under reduced pressure. The isolated product weighed 0.5 grams and did not give an absorption band for the lactone (1850 cm^{-1}) using infrared spectroscopy.

The reaction conditions were varied using different rates of addition of the aspartic acid (4, 6, and 10 hours), different reaction temperatures and reaction times, but none of these variations gave the lactone product.

V. Recrystallization of Malic

Acid from Acetic Anhydride

The following reaction was described by Toivonen, et al.,⁵¹ as follows: in a 100 ml round bottom flask, 6.7 g (0.05 moles) malic acid was recrystallized from 25 ml hot acetic anhydride. Upon recrystallization, the formation of the beta lactone was not observed using

infrared spectroscopy. The recrystallization was repeated using 25 ml acetic acid with no change in the final result.

VI. Reaction of Malic Acid
with Acetyl Chloride

The following procedure was described by Toivonen⁵² and was slightly modified: 6.7 g (0.05 moles) malic acid was added to 20 ml acetyl chloride in a 100 ml round bottom flask. The reaction was stirred for 24 hours at 30 °C, the acetyl chloride was removed under reduced pressure, and the product was analyzed by infrared spectroscopy. No absorption band was observed to indicate the presence of the lactone. The reaction was repeated with the addition of 50 ml dry pyridine as solvent. This modification was unsuccessful in forming the lactone as determined by infrared spectroscopy.

VII. Reaction of Malic Acid
with Ethyl Chloroformate

The following procedure has been described by Diassi and Dylion.⁵³ To a 100 ml round bottom flask, 1 g (0.0075 moles) malic acid was added to 45 ml dry pyridine. The solution was placed in an ice bath. At a solution temperature of 5 °C, 2.87 ml (0.03 moles) of ethyl

chloroformate was added dropwise. The solution turned dark red, and foaming was observed during the addition. The flask was removed, and the solution was allowed to warm to room temperature. After standing overnight, the solution was poured into 100 ml water. A yield of 0.025 g of an oily product was isolated and analyzed by infrared spectroscopy. No lactone band was observed at 1850 cm^{-1} by infrared spectroscopy. Further modifications in reaction time and temperature failed to produce the desired product.

VIII. Reaction of Malic Acid
with p-Toluenesulfonyl Chloride

This reaction has been described by Philp, et. al.⁵⁴ as follows: to a 100 ml round bottom flask was added 1 g (0.0075 moles) malic acid, 25 ml dry pyridine and 7.15 g (0.038 moles) p-toluenesulfonyl chloride. The solution was placed in a freezer at 5°C and left overnight. The flask was warmed to 25°C and 1 M HCl was added in sufficient amounts so as to slightly acidify the reaction mixture, followed by the addition of 50 ml water. The solution was extracted with ether (4 times). The ether extract was washed with 1 M HCl solution and dried. After removal of the solvent, the isolated oily product

weighed 0.1 g. Infrared analysis showed the oil was not the lactone. Modifications in the reaction procedure produced no change in the final result. The desired lactone product could not be made by this method.

IX. Reaction of Malic Acid
with Thionyl Chloride

The procedure for this reaction has been described by Testa, et. al.⁵⁵ as follows: 1 g (0.0075 moles) of malic acid, 1 ml dry pyridine, 25 ml dry benzene, and 8.2 ml (0.113 moles) of distilled thionyl chloride were added to a 100 ml round bottom flask. The solution was placed in a freezer at -5 to 0 °C and left overnight. Upon removal, the flask was warmed to 25 °C, the benzene and thionyl chloride were removed under reduced pressure using a Rotovap. The oily product was diluted with 100 ml ether and washed with water. The wash water was extracted with ether and the ether extracts were combined and dried with sodium sulfate. After removal of the ether, under reduced pressure, the oily product obtained was analyzed by infrared spectroscopy showing no formation of the lactone. The procedure was modified with respect to reaction time and temperature, however, none of the changes resulted in the formation of the lactone.

X. Preparation of 2-Methylpropyl-2-
Thiol Ester of Beta- Hydroxy
Butyric Acid

To a 250 ml three neck round bottom flask fitted with a gas inlet, outlet, and magnetic stirrer was added 2 g (0.019 moles) 3-hydroxybutyric acid and 2.8 ml (0.02 moles) of triethylamine in 100 ml tetrahydrofuran (anhydrous). To this solution was added a solution of 2.89 ml (0.02 moles) diethyl phosphorochloridate in 50 ml of anhydrous tetrahydrofuran dropwise at room temperature under an argon atmosphere. The mixture was stirred for three hours. The precipitated triethylamine hydrochloride was removed by filtration and washed with 25 ml of tetrahydrofuran. To the combined filtrate and washing solution was added 5.91 g (0.02 moles) thallous 2-methylpropyl-2-thiolate and the mixture was stirred overnight at room temperature. The tetrahydrofuran was evaporated under reduced pressure and then ethyl acetate was added to the residue. The work-up consisted of washing with water and drying with sodium sulfate. The product contained 3.35 g of the thiol ester which was slightly pale yellow and an oil. Infrared showed a strong absorption at 1680 cm^{-1} ($\text{O}=\text{C}-\text{S}$ stretching) and no carboxylic acid absorption at 1710 cm^{-1} . See infrared spectra No. 1. The thiol ester

could not be crystallized from any of the available organic solvents, and distillation at reduced pressures gave a complex mixture of impure isolated products.

Attempted column chromatography of the thiol ester, using benzene as the mobile phase and silica gel as the support phase, failed to improve the purity of this impure product mixture. At this stage, I decided to use this impure mixture to attempt the preparation of the lactone.

XI. Preparation of Beta- Butyrolactone

Into a 250 ml three neck, round bottom flask equipped with an argon inlet and magnetic stirrer, was added 1.76 g (0.01 mole) of the 2-methylpropyl-2-thiol ester of 3-hydroxybutyric acid and reacted with 7.8 g (0.02 moles) mercury (II) methanesulfonate and 11.35 g (0.16 moles) sodium phosphate dibasic and 100 ml dry acetonitrile at 25 °C. The reaction was stirred at 25 °C for one hour. The solvent was removed to one-half volume under reduced pressure using a Rotovap, and the solution was filtered. The filtered solid was washed with ether. The ether and filtrate were combined and washed with bicarbonate solution and water until neutral and dried over sodium sulfate. The

solvent was removed under reduced pressure leaving 0.793 g of an oily heel. Distillation of this oil from calcium hydride at 5 mm pressure and 40 °C gave 0.583 g of beta-butyrolactone. The infrared analysis showed a strong lactone carbonyl absorption at 1850 cm^{-1} (O=C stretching). See infrared spectra No. 2.

ANAL. calcd. for $\text{C}_4\text{H}_6\text{O}_2$: C, 55.35%; H, 6.98%; O, 37.2%. Found: C, 55.35%; H, 7.16%; O, 37.49%.

XII. Preparation of Malic Acid Chloralide

The following procedure was described by Eggerer and Grunewalder.⁶² To a 250 ml 3-neck round bottom flask fitted with a nitrogen inlet, thermometer, and stirrer was added 13 g (0.1 mole) D,L-malic acid and 16 g (0.12 moles) chloral. The flask was cooled to 0 °C, then 25 ml (0.26 moles) of concentrated sulfuric acid was added and the solution stirred for two hours. The solution was allowed to warm to room temperature and left stirring overnight. The contents of the flask consisted of sulfuric acid and a crystalline pulp to which was added 200 g of ice and extracted four times with 50 ml of ethyl acetate. The organic phase was washed with water and dried over sodium sulfate. The solvent

was removed under reduced pressure, and the crystalline solid was recrystallized from dry toluene. 21.2 g of a white crystalline product was isolated. The compound had a melting point 173-175 °C.

ANAL. calcd. for $C_6H_5O_5Cl_3$: C, 27.52%; H, 1.90%; O, 30.53%; Cl, 40.05%. Found: C, 27.72%; H, 1.86%; O, 29.40%; Cl, 41.00%.

L- malic acid chloralide was prepared in the same manner. To a 100 ml 3-neck, round bottom flask fitted with a nitrogen inlet, thermometer, and stirrer was added 2.68 g L- malic acid, 4.4 g chloral and 5 ml concentrated sulfuric acid. The same reaction and work-up procedure was followed. A crystalline, white solid was isolated, and the yield of the isolated compound was 3.45 g (68%). The product had a melting point 142-145 °C and a specific rotation $(\alpha)_D$ of 27° ($c=3.5$, dioxane). The literature values are as follows: melting point 141 °C, and $(\alpha)_D^{28} = 39.1$ ($c=2.2$, alcohol), $(\alpha)_D = 31$ (acetone) and $(\alpha)_D = 36$ (glacial acetic acid).

ANAL. found for $C_6H_5O_5Cl_3$: C, 27.10%; H, 2.01%; O, 29.80%; Cl, 41.09%.

The infrared, proton NMR and Carbon-13 spectra for the optically active and the racemic malic acid chloralide show the characteristic absorptions for these compounds. The infrared spectra of the racemic compound

(KBr) showed absorptions at 1825 cm^{-1} (dioxolanone carbonyl, $\text{O}=\text{C}$ stretching) and 1710 cm^{-1} (carboxylic acid, $\text{O}=\text{C}$ stretching). See infrared spectra No. 3. The ^1H NMR spectrum ($\text{d}_1\text{-CHCl}_3$) showed peaks at δ 3.08 ($\text{CH}_2\text{C}(\text{O})\text{OH}$, 2H), 4.89 ($\text{C}(\text{O})\text{CH-O}$, 1H), 5.88 (O-CH-O , 1H), and 10.89 ($\text{C}(\text{O})\text{OH}$, 1H). See proton NMR spectra No.1. ^{13}C NMR spectrum ($\text{d}_1\text{-CHCl}_3$) showed peaks at δ 196.33 ($\text{C}(\text{O})\text{OH}$), 170.82 (dioxolanone carbonyl carbon), 105.65 (Cl_3C), 72.40 ($\text{C}(\text{O})\text{-CH-O}$), 31.83 ($\text{C}(\text{O})\text{-CH}_2$) and 99.09 ($\text{Cl}_3\text{C-CH-O}$). See ^{13}C NMR spectra No.1.

The infrared (KBr), proton ($\text{d}_1\text{-CHCl}_3$), and carbon-13 NMR ($\text{d}_1\text{-CHCl}_3$) spectrums for the optically active compound were identical to the spectra for the racemic compound. See infrared spectra No. 4, proton NMR spectra No.2, and carbon-13 NMR spectra No. 2.

XIII. Preparation of Malic

Acid Chloralide Chloride

The procedure for the preparation of this compound was given by Eggerer and Grunewalder,⁶² as follows: to a 250 ml 3-neck, round bottom flask, fitted with a refluxing condenser, thermometer and stirrer was added 13.2 g (0.05 mole) of malic acid chloralide and 21.5 ml distilled thionyl chloride. The solution was refluxed

under exclusion of moisture for 72 hours, then the solvent was removed under reduced pressure. Crystallization of the residue from absolute petroleum ether (Skelly C) gave 13.18 g (94%) of a slightly pale yellow crystalline compound of melting point 74-76 °C. The compound was recrystallized from petroleum ether giving 12.6 g of a white crystalline compound of melting point 79-80 °C.

ANAL. calcd. for $C_6H_4O_4Cl_4$: C, 25.64%; H, 1.43%; O, 22.86%; Cl, 50.07%. Found: C, 25.90%; H, 1.38%; O, 23.00%; Cl, 49.72%.

L- malic acid chloralide chloride was prepared in a similar manner giving 13.18 g (94%) of a white crystalline compound with a melting point 80-82 °C. Recrystallization of the compound gave a melting point 83-84 °C and specific rotation $(\alpha)_D = 12$ ($c=2.0$, dioxane). The literature reports melting points for this material 70-72 °C.

ANAL. found for $C_6H_4O_4Cl_4$: C, 25.10%; H, 1.46%; O, 22.60%; Cl, 50.86%.

The infrared, proton NMR and carbon-13 MNR spectra for these compounds show the characteristic absorptions for the optically active and racemic malic acid chloralide chloride. The infrared spectra of the optically active compound (KBr) shows a strong absorption at 1825 cm^{-1}

(dioxolanone carbonyl, $\text{O}=\text{C}$ stretching) and at 1770 cm^{-1} (acid chloride carbonyl, $\text{O}=\text{C}$ stretching). See infrared spectra No. 5. The ^1H NMR spectrum ($\text{d}_1\text{-CHCl}_3$) showed peaks at δ 3.52 ($\text{CH}-\text{C}(\text{O})\text{OH}$, 2H), 4.87 ($\text{O}=\text{C}-\text{CH}-\text{O}$, 1H) and 5.92 ($\text{O}-\text{CH}-\text{O}$, 1H). See proton NMR spectra No. 3. ^{13}C NMR spectrum ($\text{d}_1\text{-CHCl}_3$) showed peaks at δ 171.38 (dioxolanone carbonyl carbon), 170.1 ($\text{O}=\text{C}-\text{Cl}$), 105.2 (Cl_3C), 70.53 ($\text{O}=\text{C}-\text{CH}-\text{O}$), 52.3 ($\text{O}=\text{C}-\text{CH}_2$) and 99.15 ($\text{Cl}_3\text{C}-\text{CH}-\text{O}$). See ^{13}C NMR spectra No. 3.

The infrared (KBr), proton NMR ($\text{d}_1\text{-CHCl}_3$) and carbon-13 NMR spectra ($\text{d}_1\text{-CHCl}_3$) for the racemic compound were identical to the spectra for the optically active compound. See infrared spectra No. 6, proton NMR spectra No. 4, and carbon-13 NMR spectra No. 4.

XIV. Preparation of S-(Malic Acid Chloralide) Alkylate

A. Reaction of malic acid chloralide with diethyl chlorophosphate and thallous thiolate salt. This method has been previously described by Masamune, as follows: the general method for preparing the thiol ester of malic acid chloralide involves the use of a 50 ml 3-neck round bottom flask with a gas inlet, thermometer and stirrer into which is placed 527 mg (2.0 m moles) of racemic malic acid chloralide and 222 mg (2.2 m moles) of

triethylamine in 10 ml of anhydrous tetrahydrofuran. To this solution was added 3.63 mg (2.1 m moles) of diethyl phosphorochloridate in 5 ml of dry tetrahydrofuran under an argon atmosphere. The mixture was stirred at room temperature for three hours, and the precipitated triethylamine hydrochloride was removed by filtration and washed with 10 ml of tetrahydrofuran. To the combined filtrate and washings was added 650 mg (2.2 m moles) of thallous (I) 2-methyl-2-propane thiolate, and the mixture was stirred at room temperature overnight. The tetrahydrofuran was evaporated under reduced pressure and ethyl acetate was added to the residue. The organic phase was washed with water and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was crystallized from petroleum ether.

After recrystallization, a white crystalline product 0.44 g (65%) was isolated, which had a melting point 105-107 °C. Infrared spectra analysis (KBr) showed an absorption at 1830 cm^{-1} (dioxolanone carbonyl) and an absorption at 1680 cm^{-1} (thiol ester carbonyl, $\text{O}=\text{C}-\text{S}$ stretching). See infrared spectra No. 7.

The racemic S-(malic acid chloralide) phenylate was prepared by this method using 690 mg (2.2 m moles) of thallous (I) benzene thiolate. A white crystalline

compound weighing 0.285 g (40%) was isolated having a melting point of 110-111 °C and showing a strong absorption at 1690 cm^{-1} (O=C-S stretching) and at 1825 cm^{-1} (dioxolanone carbonyl) as shown by infrared spectroscopy. See infrared spectra No. 8.

B. Reaction of malic acid chloralide chloride with a mercaptan compound. In a 10 ml round bottom flask equipped with a stopper was added 0.55 g (5.0 m moles) thiolphenol dissolved with 1.27 g malic acid chloralide chloride in 5 ml absolute peroxide-free tetrahydrofuran and 1.0 ml (12.5 m moles) of dry pyridine. This solution was stored at room temperature and left overnight in a sealed flask. The solution was poured into 40 ml of ethyl acetate and washed with an aqueous hydrochloric acid solution, bicarbonate solution and water and dried over sodium sulfate. The solvent was removed under a vacuum using a Rotovap. Attempted crystallization of the black oil product failed to yield the desired thiol ester.

This method was also used to attempt the preparation of S-(malic acid chloralide)-2-methyl-2-propanate. The same reaction scheme was applied, substituting 0.45 g (5.0 m moles) 2-methyl-2-propane thiol. Again, the reaction was unsuccessful for preparing the desired thiol ester.

C. Reaction of malic acid chloralide chloride with thallous thiolate salt. This procedure was described by Masamune, et. al.,⁴⁴ as follows: in a 100 ml round bottom flask equipped with stirrer was added 8.58 g (0.03 moles) of malic acid chloralide chloride in 50 ml of dry tetrahydrofuran. To this solution was added, at 25°C, 9.69 g (0.033 moles) of thallous (I) 2-methyl-2-propane thiolate. After the addition of the thiol salt, the reaction was stirred for two hours at 25 °C. The solution was filtered to remove the thallium chloride formed and the salt was washed with additional tetrahydrofuran. The filtrate and extracts were combined and the solvent removed under reduced pressure using a Rotovap. The thiol ester of malic acid chloralide was recrystallized using petroleum ether. The yield was 87%, and the compound had a melting point of 101-103 °C. The infrared spectrum was identical to that of the compound prepared in method A. The optically active compound of S-(malic acid chloralide)-2-methyl-2-propylate was also prepared by this method following the procedure already described. The yield of the product was 85% and the melting point was 97-98 °C. The infrared spectrum was identical to that of the racemic material. See infrared spectra No. 9.

Additional thiol ester compounds were prepared using this method. S-(malic acid chloralide) phenylate was prepared by using 10.4 g (0.033 moles) thallium benzene thiolate. This compound was obtained in 85% yield with a melting point of 110-111 °C. The infrared spectra showed an absorption at 1690 cm^{-1} (O=C-S stretching). The infrared spectra was identical to that of the compound prepared by method A.

The dodecyl- and pentadecyl- compounds were also prepared, and the yields and melting points are given in a previous chapter. See infrared spectra No. 10 and No. 11, respectively.

The optically active and racemic S-(malic acid chloralide) octadecylate was prepared by this method. The isolated products were white crystalline materials. The racemic compound had a yield of 87% and a melting point 88-89 °C.

ANAL. calcd. for $\text{C}_{24}\text{H}_{41}\text{Cl}_3\text{O}_4\text{S}$; C, 54.34%; H, 7.74%; Cl, 19.81%; O, 12.1%; S, 6.8%. Found: C, 54.6%; H, 7.41%; Cl, 19.94%; O, 11.25%; S, 6.8%.

The optically active S-(malic acid chloralide) octadecylate was found in a yield of 89% and melting point 81-82 °C and specific rotation $(\alpha)_D = 35^\circ$ (c=3.5, dioxane).

ANAL. found for $\text{C}_{24}\text{H}_{41}\text{Cl}_3\text{O}_4\text{S}$; C, 53.9%; H, 7.71%; Cl, 20.09%; O, 12.36%; S, 5.94%.

The infrared, carbon-13, and proton NMR spectra for these compounds show the characteristic absorptions. The infrared spectrum of the racemic compound shows an absorption at 1825 cm^{-1} (dioxolanone carbonyl) and at 1680 cm^{-1} (thiol ester carbonyl, $\text{O}=\text{C}-\text{S}$ stretching). See infrared spectra No. 12. The ^1H NMR spectra (d_8 -toluene) showed absorptions at δ 0.5-1.5 (aliphatic protons, 35H), 2.54 ($\text{S}-\text{CH}_2$, 2H), 2.56 ($\text{O}=\text{C}-\text{CH}_2$, 2H), 4.12 ($\text{O}=\text{C}-\text{CH}-\text{O}$, 1H), 5.42 ($\text{Cl}_3\text{C}-\text{CH}-\text{O}$, 1H). See proton NMR spectra No. 5. The ^{13}C NMR spectrum (d_1 - CHCl_3) showed peaks at δ 194.85 (thiol ester carbonyl), 172.61 (dioxolanone carbonyl), 105.25 (Cl_3-C), 72.6 ($\text{O}=\text{C}-\text{CH}-\text{O}$), 50.5 ($\text{O}=\text{C}-\text{CH}_2$), 98.0 ($\text{Cl}_3\text{C}-\text{CH}-\text{O}$), 33.0 ($\text{S}-\text{CH}_2$), 32.3 ($\text{S}-\text{CH}_2-(\text{CH}_2-)_{17}$), 29.8 (CH_2-CH_3). See ^{13}C NMR spectra No. 5.

The infrared (KBr), proton NMR (d_8 -toluene), and ^{13}C NMR spectra (d_1 - CHCl_3) for the optically active compound were identical to the spectrums for the racemic compound. See infrared spectra No. 13, proton NMR spectra No. 6, and ^{13}C NMR spectra No. 6.

D. Reaction of malic acid chloralide chloride with trimethyl silyl octadecyl thiolether. This method has been previously described by Talley,⁶⁹ as follows: 3.95 g (11.0 m moles) octadecyl trimethyl silyl sulfide

was added to a stirred solution of 2.82 g (10 m moles) L- malic acid chloralide chloride in dry chloroform under a argon blanket at room temperature. The solution was warmed to 50 °C and held for six hours. Afterwards, the solvent and chlorotrimethyl-silane were removed by distillation under reduced pressure and the residue product was crystallized from petroleum ether. The thiol ester had identical physical properties to the compound described and prepared by method C.

XV. Reaction of S-(Malic Acid Chloralide)
Octadecylate with Benzyl
Alcohol

In a 50 ml 3-neck, round bottom flask equipped with a stirrer, thermometer and gas inlet, 1.0 g (1.9 m moles) of S-(malic acid chloralide) octadecylate was added to 10 ml (96.6 m moles) of benzyl alcohol. Hydrogen chloride gas was bubbled into the solution until the pH was strongly acid ($\text{pH} < 3$). After the gas addition was completed, the flask was sealed off and the contents were stirred for two hours. Ether was added to the solution and the solution was washed with water until neutral, and dried over sodium sulfate. The residue, after removal of the ether, was analyzed

by infrared spectroscopy which revealed that the thiol ester absorption band was not present in the spectra, as was the absorption band for the dioxolanone. I hypothesized that the reaction products consisted of the dibenzyl ester of malic acid and a low molecular weight polymer. An absorption at 1750 cm^{-1} was indicative of an ester linkage which was clearly present.

None of the variations in the reaction procedure conditions produced the desired result which was the formation of the S-(beta-hydroxy succinyl benzyl ester) octadecylate compound.

XVI. Hydrolysis of the 1,3
Dioxolan-4-one Blocking
Group

To a 500 ml 3-neck round bottom flask equipped with stirrer and thermometer, was added 4.0 g (7.52 m moles) of S-(malic acid chloralide) octadecylate, 40 ml of distilled pyridine and 40 ml of distilled dimethylformamide. Slowly by dropwise addition was 20 ml of concentrated hydrogen chloride solution added to the flask. The temperature of the solution increased with the addition of the hydrochloric acid. The rate of acid addition was correlated to the temperature rise, so that the temperature of the solution did not exceed

65 °C. After the addition of the HCl, the reaction was allowed to stir for six hours, addition of 20 ml HCl was repeated and the solution was stirred for six additional hours. The operation was repeated with 20 ml HCl, twice more. At 24 hours after the start of the hydrochloric acid addition, the reaction was terminated. The mixture was poured over 300 g of ice, saturated with ammonium chloride. Ether was added and the organic phase was extracted from the water phase. This operation was repeated a total of four times. The ether phase was washed with potassium bicarbonate solution. This operation was repeated twice, until the solution was basic. The water was reacidified with concentrated hydrochloric acid and extracted with ethyl acetate. The ethyl acetate was washed with water and dried over sodium sulfate. The solvent was recrystallized from petroleum ether.

A white powdery material was isolated with a yield of 60% (2 g) and a melting point 99-100 °C.

ANAL. calcd. for $C_{22}H_{42}O_4S$; C, 65.67%; H, 10.5%; O, 15.9%; S, 7.93%. Found: C, 66.7%; H, 9.8%; O, 15.5%; S, 8.0%.

The optically active S-(beta-hydroxy succinyl) octadecylate was also prepared using this reaction method.

The compound had a yield of 53%, a melting point of 93-94 °C and a specific rotation $(\alpha)_D$ 45° (c=2, dioxane).

ANAL. found for $C_{22}H_{42}O_4S$: C, 65.3%; H, 10.7%; O, 16.0%; S, 8.0%.

The infrared, proton NMR and carbon-13 NMR spectra all had the expected characteristic peaks to support the proposed structure of the compounds. The infrared spectra (KBr) of the racemic compound showed a broad absorption at 1680 cm^{-1} (carboxylic acid and thiol ester carbonyls). See infrared spectra No. 14. The ^1H NMR spectra ($d_1\text{-CHCl}_3$) showed peaks at δ 0.5-1.5 (aliphatic protons, 35H), 2.80 (S-CH_2 , 2H), 2.80 (O=C-CH_2 , 2H and C-OH , 1H), 4.52 (O=C-CH-OH , 1H). See ^1H NMR spectra No. 7. The ^{13}C NMR spectra ($d_1\text{-CHCl}_3$) showed peaks at δ 197.0 (O=C-S), 179.5 (HO-C=O), 67.9 (HO-CH), 53.10 (O=C-CH_2), 33.0, 30.8, and 30.0 (aliphatic carbons). See ^{13}C NMR spectra No. 7.

The infrared spectra (KBr) of the optically active compound showed the same absorptions as the racemic compound. See infrared spectra No. 15. The proton NMR spectra ($d_1\text{-CHCl}_3$) and the ^{13}C NMR spectra ($d_1\text{-CHCl}_3$) for the optically active compound were identical to the racemic compound ^1H NMR and ^{13}C NMR spectra. See proton NMR spectra No. 8 and ^{13}C NMR spectra No. 8.

As was previously discussed, the S-(malic acid chloralide) octadecylate was hydrolyzed using acid conditions leading to a very interesting observation. The chemical nature of the group attached to the sulfur atom played a critical role in the isolation of the final product. After hydrolysis and subsequent extraction with organic solvents and washing with water, if the R-group attached to the sulfur atom was a ter-butyl or phenyl, no product was isolated after the removal of the solvent. A mass balance demonstrated that during the reaction sequences, the starting compound was lost. After repeated experiments gave identical results, I changed the chemical nature of the R-group compound by attaching a long aliphatic tail by using C₁₂, C₁₅, or C₁₈ groups to form the thiol ester. This simple modification made it possible to isolate the hydrolyzed product.

XVII. Preparation of S-(Beta-
Hydroxysuccinyl Benzyl
Ester) Octadecylate

A. Reaction of trifluoroacetic anhydride with S-(beta-
hydroxysuccinyl) octadecylate. Parish and Stock⁷⁶
have proposed two methods for preparing esters using

the mixed anhydride intermediate. In the first method to a 100 ml round bottom flask equipped with stirrer, was added 3.63 g (9.0 m moles) of S-(beta-hydroxysuccinyl) octadecylate and 5 ml (36 m moles) trifluoroacetic anhydride. The acid dissolved with slight heating. 5 ml (48 m moles) of benzyl alcohol was added and the reaction was stirred at room temperature for one hour. After completion of the reaction, the solution was washed with a sodium bicarbonate solution and water until neutral and dried over sodium sulfate. The solvent was removed under reduced pressure. The residue was a complex mixture of products. Thin layer chromatography was used to separate the components, however, none gave the desired infrared absorptions for the benzyl ester.

The second reaction procedure consisted of adding 3.63 g (9 m moles) S-(beta-hydroxysuccinyl) octadecylate and 0.94 ml (9 m moles) benzyl alcohol with 5 ml (36 m moles) trifluoroacetic anhydride. The resulting solution was stirred at room temperature for one hour. Benzene was added to the solution and the work-up was the same as described in the first procedure. The desired product was not isolated from the reaction mixture.

B. Reaction of dicyclohexylcarbodiimide with S-(beta-hydroxysuccinyl) octadecylate. The reaction procedure was described by Smith, et. al.⁷⁷ as follows: to a 100 ml round bottom flask equipped with a magnetic stirrer was added a solution prepared from 2.0 g (4.9 m moles) S-(beta-hydroxysuccinyl) octadecylate, 2.39 ml (10 m moles) tri-n-butylamine, 25 ml benzyl alcohol, and 10.32 g (100 m moles) dicyclohexylcarbodiimide. The flask was flushed with argon, and the reaction mixture was stirred at 25 °C for 72 hours. After completion of the reaction, oxalic acid was added to decompose the unreacted dicyclohexylcarbodiimide. The solvent was removed by using high vacuum distillation. The residue was separated by using column chromatography with benzene as the mobile phase and silica gel as the solid phase. S-(beta-hydroxysuccinyl benzyl ester) octadecylate was isolated. The product was obtained as a white crystalline material after crystallization from methanol having a yield of 17% (0.42 g). The compound had a melting point of 65-66 °C.

The infrared, proton NMR and ¹³C NMR spectra all had the expected characteristic peaks to support the proposed structure for the compound. The infrared spectra (KBr) showed an absorption at 1740 cm⁻¹ (benzyl ester carbonyl) and at 1680 cm⁻¹ (thiol ester carbonyl).

See infrared spectra No. 16. The ^1H NMR spectra ($\text{d}_1\text{-CHCl}_3$) showed peaks at δ 0.5-1.5 (aliphatic protons, 35H), 2.80 (S-CH_2 , 2H, O=C-CH_2 , 2H and C-OH , 1H), 4.50 (O=C-CH-OH , 1H), 5.15 ($\text{O-CH}_2\text{-C}_6\text{H}_5$, 2H) and 7.25 (aromatic protons). See proton NMR spectra No. 9. The ^{13}C NMR spectra ($\text{d}_1\text{-CHCl}_3$) showed absorptions at δ 194.6 (thiol ester carbonyl), 173.27 (benzyl ester carbonyl), 67.76 (HO-CH), 53.46 (O=C-CH_2), 32.01, 29.77, and 29.43 (aliphatic carbons), 128.64 and 128.31 (aromatic carbons). See ^{13}C spectra No. 9.

The optically active compound was prepared and isolated using the same procedure. The compound had an overall yield of 13% and melting point 53-54 $^\circ\text{C}$. The specific rotation $(\alpha)_D = -70^\circ$ ($c=3$, dioxane) was obtained for this compound.

The infrared spectra (KBr), proton NMR, and ^{13}C NMR spectra ($\text{d}_1\text{-CHCl}_3$) for the optically active compound showed the same absorptions as for the racemic compound. See infrared spectra No. 17, proton NMR spectra No. 10, and ^{13}C NMR spectra No. 10. The infrared spectrum was taken as a KBr pellet. The proton NMR spectrum was obtained for the optically active and racemic compound using deuterated chloroform. The carbon-13 spectra was taken using deuterated chloroform as the solvent.

C. Reaction of N,N-carbonyldiimidazole with S-(beta-hydroxysuccinyl) octadecylate. The reaction was prepared according to the method outlined by Staab and Mannschreck,⁷⁹ as follows: to a 100 ml 3-neck round bottom flask fitted with a stirrer was added 2.0 g (5.0 m moles) S-(beta-hydroxysuccinyl) octadecylate, 0.81 g (5.0 m moles) N,N-carbonyldiimidazole and 10 ml dry tetrahydrofuran. The solution was stirred for two hours at 25 °C. Meanwhile, 0.52 ml (5.0 m moles) benzyl alcohol, 5 ml dry tetrahydrofuran and 0.005 g (0.2 m moles) sodium were refluxed for two hours. Afterwards, the salt of the benzyl alcohol was added slowly to the first solution at 25 °C. The final solution was stirred for 48 hours. The solvent was removed and the residue was chromatographed using benzene as the mobile phase and silica gel as the solid phase.

Racemic S-(beta-hydroxysuccinyl benzyl ester) octadecylate was isolated in a yield of 36%. After recrystallization from methanol, the compound had a yield of 29% and a melting point of 63-65 °C. The infrared spectrum was identical to that of the compound prepared by method B.

The optically active S-(beta-hydroxysuccinyl benzyl ester) octadecylate was also prepared having a final

yield after recrystallization from methanol, of 36% and a melting point of 54-55 °C. The infrared spectra of the optically active compound was identical to the product prepared by method B.

D. Direct preparation of S-(beta-hydroxysuccinyl benzyl ester) octadecylate. To a 500 ml round bottom flask equipped with a magnetic stirrer, was added 15 g (37.3 m moles) S-(beta-hydroxysuccinyl) octadecylate, 45 ml (435.0 m moles) benzyl alcohol, 300 ml dry benzene and 0.75 g (4.0 m moles) p-toluenesulfonic acid. The reaction was stirred under the exclusion of moisture for 24 hours at 30 °C. The solution was washed with sodium bicarbonate solution, water and dried over sodium sulfate. The solvent was removed under high vacuum. The residue was crystallized from methanol.

The racemic S-(beta-hydroxysuccinyl benzyl ester) octadecylate product was obtained in a yield of 65% with a melting point of 66-67 °C.

ANAL. calcd. for $C_{29}H_{49}O_4S$: C, 70.59%; H, 9.94%; O, 12.98%; S, 6.49%. Found: C, 70.90%; H, 9.40%; O, 12.90%; S, 6.80%.

The optically active product was obtained in a yield of 72% with a melting point 52-54 °C and a specific

rotation (α)_D = -75° (c=2, dioxane).

ANAL. found for C₂₉H₄₉O₄S: C, 69.5%; H, 10.2% O, 13.0%; S, 7.30%.

The infrared (KBr), proton NMR (d₁-CHCl₃), and ¹³C NMR (d₁-CHCl₃) spectra show identical absorptions for the racemic and optically active compounds as the spectra for the compounds prepared by method B.

XVIII. Preparation of
Malolactone
Benzyl Ester

The procedure described by Masamune⁴⁴ was followed with slight modifications, as follows: to a 250 ml 3-neck round bottom flask equipped with a thermometer, stirrer, and argon inlet was added 1.0 g (2.0 m moles) S-(beta-hydroxysuccinyl benzyl ester) octadecylate, 1.6 g (4.0 m moles) mercury (II) methanesulfonate, 9.0 g (127.0 m moles) sodium phosphate dibasic (ultradry), and 50 ml butyronitrile. The reaction was stirred at 90 °C for 20 minutes. The solvent was removed and replaced with ether. The solution was filtered and the solid product was slurried with ether several times and filtered. The ether solutions were combined and washed with sodium bicarbonate solution, water and dried over sodium sulfate. The solvent was removed under reduced

pressure using a Rotovap. The residue was purified using preparative high pressure liquid chromatography. The HPLC chromatogram showed the lactone peak separate from impurities eluting at 8.6 minutes when the flow rate using methylene chloride solvent was 100 ml per minute. Silica gel was used as the solid phase. The lactone was isolated after the removal of the solvent under reduced pressure. The residue was distilled using high vacuum at 115°C/0.001 mm pressure. The racemic compound was isolated in 50% yield and was a clear oil. The purity of the lactone was 99% as determined by analytical high pressure liquid chromatography.

ANAL. calcd. for $C_{11}H_{10}O_4$: C, 64.05%; H, 4.85%; O, 31.90%. Found: C, 64.22%; H, 5.01%; O, 30.77%.

The optically active compound was prepared by the same method and purified by preparative HPLC, using the same conditions as used for the racemic compound. The HPLC chromatogram showed the lactone peak separate from impurities eluting at 8 minutes when the flow rate was 100 ml per minute. The optically active compound was distilled at 105°C/0.001 mm pressure. The yield of the isolated lactone was 40% and the melting point was 35-37°C and the specific rotation was $(\alpha)_D = -37^\circ$ ($c = 2$, dioxane).

ANAL. found for $C_{11}H_{10}O_4$: C, 64.19%; H, 4.99%; O, 30.82%.

The infrared, proton NMR and carbon-13 NMR spectra had the expected characteristic peaks to support the proposed structure for the compounds. The infrared (neat) for the racemic compound showed an absorption at 1850 cm^{-1} (lactone carbonyl) and at 1750 cm^{-1} (benzyl ester carbonyl). See infrared spectra No. 18. The ^1H NMR spectra ($\text{d}_1\text{-CHCl}_3$) showed peaks at δ 3.45 (C(=O)-CH_2 , 2H), 4.70 (C(=O)-CH-O , 1H), 5.2 (C(=O)-O-CH_2 , 2H), 7.25 (aromatic protons). See ^1H NMR spectra No. 11. The ^{13}C NMR spectra ($\text{d}_1\text{-CHCl}_3$) showed absorptions at δ 171.84 (benzyl ester carbonyl), 169.42 (lactone carbonyl), 71.76 (C(=O)-CH-O), 52.14 ($\text{C(=O)-CH}_2\text{-CH}$), 69.12 ($\text{O-CH}_2\text{-C}_6\text{H}_5$), 132.64 and 132.46 (aromatic carbons). See carbon-13 NMR spectra No. 11.

The infrared spectra (neat) for the optically active compound showed the same absorptions as the racemic compound. See infrared spectra No. 19. The ^1H NMR spectra ($\text{d}_1\text{-CHCl}_3$) and the ^{13}C NMR spectra ($\text{d}_1\text{-CHCl}_3$) for the optically active compound were identical to the spectra for the racemic compound. See proton NMR spectra No. 12 and carbon-13 NMR spectra No. 12.

The lactone may also be prepared using mercuric p-toluenesulfonate as the catalyst and benzonitrile as the solvent. The same molar ratios as used for the

mercuric methanesulfonate and butyronitrile must be employed. The reaction is run at 55 °C and the reaction time is one hour. For this reaction, best results are obtained if the lactone is in solution with one-third of the used solvent and is added dropwise slowly into a solution of the catalyst, buffer, and solvent. The work-up is the same as previously described.

Infrared analysis showed a yield of 75% as determined by peak analysis using infrared spectroscopy.

The infrared and proton NMR spectral analysis was identical to the analysis reported by Vert and Lenz.³⁸

XIX. Thiol Ester Interchange Reaction

To 4.93 g (0.01 moles) of S-(beta-hydroxysuccinyl benzyl ester) octadecylate in a 200 ml round bottom flask, fitted with a reflux condenser, was added a mixture of 1.21 g (0.011 mole) benzenethiol, 0.05 g (0.001 mole) sodium methoxide and 20 ml dry pyridine. After the mixture was heated on a steam bath, the pyridine was removed by distillation under reduced pressure. The product was dissolved in 100 ml of ether and washed with water. The solution was dried over sodium sulfate, and the solvent was removed on a Rotovap. The residue was purified by column chromatography using benzene

as the liquid phase and silica gel as the stationary phase. The S-(beta-hydroxysuccinyl benzyl ester) phenylate was isolated as a white crystalline product. The yield was 37% and the melting point was 72 °C.

ANAL. calcd. for $C_{17}H_{16}O_4S$: C, 64.55%; H, 5.06%; O, 20.25%; S, 10.14%. Found: C, 63.98%; H, 5.32%; O, 20.10%; S, 10.60%.

The infrared spectra (KBr) was not helpful in supporting the proposed structure showing absorptions at 1750 cm^{-1} (benzyl ester carbonyl) and at 1690 cm^{-1} . The ^{13}C NMR spectra (d_1 - $CHCl_3$) was helpful in structural determination showing absorptions at 196.8 (thiol ester carbonyl) and 173.5 (benzyl ester carbonyl) but not the absorption peaks for the long aliphatic chain. See ^{13}C NMR spectra No. 13. The infrared spectra is also included see infrared spectra No. 20.

XX. Acid Hydrolysis of L-
Malolactone Benzyl
Ester

To a 250 ml round bottom flask was added 1 g of L-malolactone benzyl ester, 50 ml pyridine and 10 ml concentrated HCl. The solution was heated at 70 °C for 12 hours. The solution was diluted with 50 ml

water and extracted with ether. The water phase was removed, with the pyridine, using reduced pressure. The residue was analyzed by infrared spectroscopy and was shown to be malic acid. See infrared spectra No.21. The yield of the residue was 37%, and the specific rotation of the residue was $(\alpha)_D = -26^\circ$ ($c=5$, pyridine).

XXI. Preparation of Mercury (II)
Sulfonate Salts¹³⁰

To a 250 ml round bottom flask fitted with a stirrer was added 15.9 g (0.05 mole) mercury acetate and 100 ml glacial acetic acid. The reaction temperature was raised to 80 °C, and 9.6 g (0.1 mole) methanesulfonic acid was added. The reaction mixture was stirred for one hour at 80 °C. The reaction mixture was filtered and the crystalline solid was washed with ether. The white crystalline compound was the mercuric methanesulfonate salt. The yield of the salt was 93% and the melting point was 275 °C. See infrared spectra No. 22.

ANAL. calcd. for $C_2H_6O_6S_2Hg$; C, 6.14%; H, 1.54%; O, 24.57%; S, 16.42%. Found: C, 5.63%; H, 1.41%; O, 30.97%; S, 15.05%.

Mercury (II) p-toluenesulfonate may also be prepared by the preceeding method. The yield of the salt is 92%, and the melting point is 290 °C. See infrared spectra No.23.

ANAL. calcd. for $C_{14}H_{14}O_6S_2Hg$: C, 30.96%; H, 2.58%; O, 17.70%; S, 11.81%. Found: C, 29.02%; H, 2.42%; O, 22.85%; S, 11.08%.

XXII. Preparation of

Cuprous Trifluoroacetate¹³¹

Cuprous oxide was extracted with trifluoroacetic acid containing trifluoroacetic anhydride in a stream of hydrogen gas. 1.0 g of cuprous oxide to 10 ml of trifluoroacetic acid containing 1 ml of trifluoroacetic anhydride was used for the extraction. The hydrogen gas was bubbled into the solution for 30 minutes. A white cuprous trifluoroacetate crystallized out of the solution and was filtered under argon gas and washed with ether under an argon atmosphere. The salt was filtered under argon. The purity of the salt could not be determined due to its reactivity with air and moisture (soft acid). The salt was impure but was investigated as a lactonization catalyst.

XXIII. Preparation of

Thallous Thiolate

To a 100 ml round bottom flask equipped with a stirrer, argon inlet and thermometer was added 78.8 g (22.38 ml, 0.316 mole) thallous ethoxide and 540 ml of dry benzene under an argon atmosphere. To this solution

was added a solution of 100 g (0.35 moles) octadecyl mercaptan in 100 ml benzene. The reaction was performed at 25 °C. After the addition of the mercaptan solution, the reaction was stirred for one hour at 25 °C. The yellow precipitate was filtered off, under an argon atmosphere. The precipitate was washed with pentane and dried in a vacuum oven at room temperature. A bright yellow powdery material was isolated in a yield of 98.5%. See infrared spectra No. 24.

ANAL. calcd. for $C_{18}H_{37}STl$: C, 44.13%; H, 6.56%; S, 7.56%. Found: C, 43.9%; H, 6.62%; S, 7.50%.

Thallium benzene thiolate was prepared by this method having a yield of 97%. See infrared spectra No. 25.

ANAL. calcd. for C_6H_5STl : C, 22.97%; H, 1.60%; S, 10.23%. Found: C, 22.72%; H, 1.64%; S, 10.29%.

Thallium 2-methyl-2-propane thiolate was prepared by this method with a yield of 97%. See infrared spectra No. 26.

ANAL. calcd. for C_4H_9STl : C, 16.36%; H, 3.07%; S, 10.96%. Found: C, 16.11%; H, 2.99%; S, 11.10%.

Thallium dodecylthiolate and thallium pentadecylthiolate were prepared by this method. For both compounds, the yields were greater than 90%.

XXIV. Preparation of

Trimethylsilyl Thioethers 132

To a 100 ml round bottom flask is added 1.61 g (11.5 m moles) of 1-(trimethylsilyl) imidazole which was cooled to 5 °C in an ice bath. 3.3 g (11.5 m moles) of octadecyl mercaptan was added to the solution while it was stirring with a magnetic stirrer. The temperature was allowed to warm to 25 °C after the mercaptan addition. The solution stirred for 24 hours. At the end of this time, pentane was added and the solid was filtered off and washed with additional pentane. The pentane fractions were combined and the solvent was removed by Rotovap using reduced pressure. The residue was purified by high pressure liquid chromatography (preparative) using benzene as the mobile phase and silica gel as the support phase. The yield of the compound was 58% and the melting point was 42 °C. See infrared spectra No. 27 and proton NMR spectra No. 13.

XXV. Preparation of
Cuprous Triflate¹³³

To a 100 ml round bottom flask was charged 2.5 m moles of copper (II) triflate and copper powder (2.5 m moles) in 25 ml of acetone and 1.25 ml of acetonitrile. The solution was heated at reflux for one hour under the exclusion of moisture and air. A light blue solution

formed, the solvent was removed and the salt isolated under an argon atmosphere. The purity of the salt was not determined, however the salt was evaluated as a lactonization catalyst.

XXVI. Preparation of
Cupric Triflate 134

To a 500 ml round bottom flask was added 5.0 g (0.04 moles) of cupric carbonate, 200 ml acetonitrile and 12 g (0.08 moles) of trifluoromethanesulfonic acid. The acid was added very slowly due to the evolution of carbon dioxide. The solution was stirred for 30 minutes and filtered under argon. The resulting blue filtrate was concentrated to dryness. The blue salt was rinsed with petroleum ether several times. The salt was redissolved in acetonitrile and ether was added until the solution turned cloudy. The solution was cooled at -20°C in a freezer. A light blue precipitate was filtered off and dried in a vacuum oven at 130°C . 8 g of the product were isolated.

XXVII. Preparation of
Malic Acid Anhydride 135

To a 250 ml round bottom flask was added 13 g (0.1 moles) of malic acid and 100 ml of distilled water

and 1.8 g (0.1 moles) ammonia was bubbled into the solution. To this solution was added 17.0 g (0.1 mole) of silver nitrate and the reaction was stirred for one hour. Ether was added to precipitate the silver malate which was filtered off. The salt was dried in a vacuum oven which was sealed to light. 4.0 g of the silver malate was suspended in ether (30 ml) and 2.0 g of thionyl chloride was added to the flask. The flask was sealed off and shaken for one hour. Sulphur dioxide was removed from the solution after it was filtered by bubbling in carbon dioxide for 24 hours. The ether was removed by using a Rotovap and reduced pressure. The residue was a complex mixture of byproducts. Infrared spectroscopy showed the anhydride may be present in small amounts by observing the $1800\text{-}1700\text{ cm}^{-1}$ absorption region. The anhydride could not be isolated by conventional purification techniques. Modifications in the preparation method failed to yield the anhydride.

XXVIII. Polymerization of
Malolactone Benzyl Ester

A. Macrozwitterion Catalysts. The catalyst used for the different polymerization reactions were betaine and triethylamine. The reactions were carried out in

bulk, or in either methylene chloride or toluene. The polymerization temperature was either 30 °C or 70 °C. The ratio of initiator to monomer in moles was 10^{-3} . If the reaction was carried out in solvent, the monomer concentration was 2.5 M. The physical properties of the polymer were similar in all cases. The molecular weight ranged from 2000-3000 (M_{GPC}). The molecular weight distribution became narrower at the higher reaction temperature possibly indicating the occurrence of a living propagation mechanism. The specific rotation of the polymer had a sign opposite to that of the monomer.

B. Basic Catalysts. The catalyst used for the various polymerizations was tetraethylammonium benzoate. The reaction was carried out in bulk or either in methylene chloride or toluene. If a solvent was used for the reaction, the monomer concentration was 2.5 M. The polymerization temperature was either 0 °C, 30 °C, or 70 °C. The ratio of initiator to monomer in moles was 10^{-3} . The polymers had a molecular weight close to 3000 (M_{GPC}). The molecular weight distributions became narrower at the higher polymerization temperature. The specific rotation of the polymers had a sign opposite to the sign of the monomer.

C. Cationic Catalysts. The catalysts used for this type of polymerization were either ferric chloride, aluminum chloride, triphenylmethyl carbenium hexafluoroantimonate, and triphenylmethyl carbenium tetrafluoroborate. The polymerization reactions were run in bulk, methylene chloride or toluene. The polymerization temperatures were either 30 °C or 70 °C. The ratio of initiator to monomer in moles was 10^{-2} . If the polymerization was carried out in solvent, the monomer concentration was 2.5 M. Ferric chloride appeared to be the best of the catalysts tested. The trityl salts repeatedly gave polymers of low molecular weight. For ferric chloride, the molecular weight distribution M_w/M_n was 2.0 regardless of the reaction temperature. The specific rotation of the polymers were the same sign as the monomer.

D. Organometallic Catalysts. The catalysts used for the polymerizations were either triethylaluminum or diethylzinc. The reactions were carried out in bulk for the diethyl zinc catalyst and in toluene for the triethylaluminum, however for both, the monomer concentration was neat or 2.5 M, respectively. The polymerization temperatures were 50 °C with the diethyl zinc and 70 °C with the triethylaluminum. The ratio of initiator to

monomer in moles was 10^{-2} . The physical properties of the polymers, using triethylaluminum, were similar to the results obtained for the cationic catalysts. Diethylzinc appears to be a very poor catalyst as indicated by the low molecular weight of the isolated polymer. The specific rotation of the polymers was the same sign as that of the starting monomer.

E. Base Catalysts/Crown Ethers. The initiators used were sodium acetate, sodium hydroxide, potassium acetate, and potassium hydroxide. The dibenzo-18-crown-6-ether was used to complex with the sodium cation. 15-crown-5-ether was used to complex with the potassium cation. The reaction was carried out in bulk. The polymerization temperature either was 30 °C or 0 °C. The ratio of initiator to crown ether was 1 to 2 in moles. The polymers had the same molecular weights as those obtained for the base catalysts particularly for tetraethylammonium benzoate. There was a significant increase in rates of polymerization at the lower polymerization temperatures compared to those for the other anionic catalysts.

The results of the polymerization of the racemic and optically active malolactone benzyl ester are listed in entirety in Tables 8 and 9.

XXIX. Infrared Analysis of
the Polyesters Made
from Malolactone Benzyl Ester

The infrared spectra of the different optically active polymers obtained from the L-malolactone benzyl ester monomer showed no differences when compared. The spectra for the racemic polymers also showed no differences in the peak position or intensity. The racemic polymers had an infrared spectra similar to the optically active polymer infrared spectra. The major absorption was at 1760 cm^{-1} and corresponded to the ester carbonyl stretching mode. Peaks at $2900\text{-}3100\text{ cm}^{-1}$ corresponded to methyl, methylene, and acyl hydrogens stretching. In the range of $1230\text{-}1130\text{ cm}^{-1}$, two strong bands correspond to C(=O)-O-CH stretching. See infrared spectra No. 28 for an infrared spectra of the optically active polyester. See infrared spectra No. 29 for an infrared spectra of the racemic polymer. The polymers were prepared using tetraethylammonium benzoate in bulk at $70\text{ }^{\circ}\text{C}$.

XXX. Proton NMR of the
Polyesters Made from
Malolactone Benzyl Ester

There is practically no difference in the NMR

(proton) spectra for the racemic and optically active polymers. All of the spectra show four absorptions: at δ 7.30 (aromatic protons, 5H), 5.50 (C(O)-CH-O, 1H), 5.10 (C(O)-CH₂-C₆H₅, 2H), 2.90 (C(O)-CH₂-CH, 2H). See proton NMR spectra No. 14 for a spectra of a representative optically active polyester. See proton NMR No. 15 for a spectra for a representative racemic polyester.

XXXI. Carbon-13 NMR Analysis
for the Polyesters

There were no differences observed for the ¹³C NMR spectra of the optically active or racemic polyesters. All the spectra showed seven absorptions at δ 169.01 and 168.83 (benzyl ester and polymer backbone ester), 68.40 (C(O)-CH-O), 67.40 (C(O)-CH₂-C₆H₅), 33.32 (C(O)-CH₂-CH), 129.94 and 128.54 (aromatic carbons). See ¹³C NMR spectra No. 14 and No. 15 for representative spectra for the optically active and racemic polyester, respectively.

XXXII. Measurements

Infrared spectra were recorded on Perkin-Elmer Model 727 or Model 283 spectrophotometers. Solid samples were measured as KBr pellets and liquid samples were measured between NaCl plates. The infrared spectra for the polymers were measured as films cast from

dichloromethane solution. The peak assignments were made to the nearest 5 cm^{-1} .

The ^1H NMR spectra were recorded on a 90 MHz EM 390 Varian spectrometer. Solutions were 15 to 25% in deuterated chloroform or deuterated toluene.

The optical rotation dispersion curves (ORD) were measured on a Perkin-Elmer 141 MC polarimeter using dioxane as the solvent.

The thermal analysis for the polymers were taken on a Perkin-Elmer DSC-2 differential scanning calorimeter at a scanning rate of $20^\circ\text{C}/\text{minute}$. The instrument was calibrated against indium standard.

The melting points of the low molecular weight compounds were measured on a MEL-TEMP capillary point apparatus and are uncorrected.

The malolactone benzyl ester was purified using a Waters 500A High Pressure Liquid Chromatography Apparatus. Methylene chloride was used as a solvent and silica gel was the chromatographic phase.

The purity of the malolactone benzyl ester was determined using a Waters 440 High Pressure Liquid Chromatography Apparatus with a refractive index detector. Methylene chloride or methylene chloride tetrahydrofuran (50-50) was used as the solvent and silica gel as the chromatographic phase.

Microanalyses were done by the Microanalytical Laboratory Office of Research Services, University of Massachusetts, Amherst, Massachusetts.

XXXIII. Future Work

The objectives of this research were two-fold. The first was to develop a synthetic scheme for the preparation of optically active malolactone benzyl ester. This synthetic objective has been successfully completed.

The second objective was to prepare polymers having molecular weight in the range 10,000-20,000 (M_{GPC}). This objective has not been completed. The highest molecular weight that has been isolated is 3500 (M_{GPC}). Monomer impurity is considered the main difficulty to achieving high molecular weight. Future work should include study and evaluation of purification methods for beta-substituted-beta-lactones, for example, the use of isocyanates as purification compounds.

Part of the second objective was to evaluate different initiator systems and determine their effect on the properties of the resultant polymers. A number of different catalysts were studied as well as different solvents and reaction temperatures and their ultimate effect on the polymer properties.

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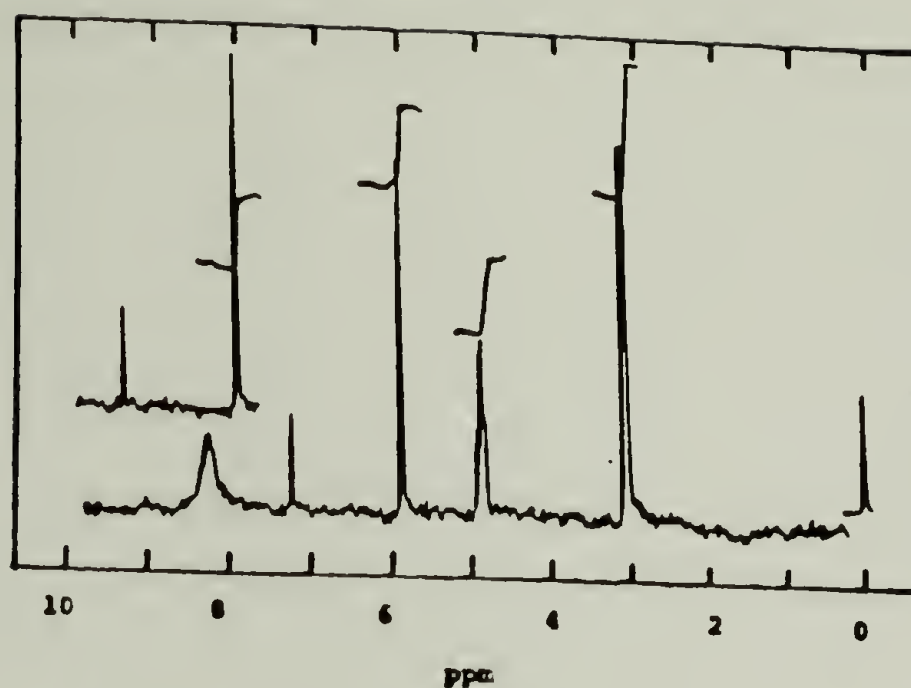
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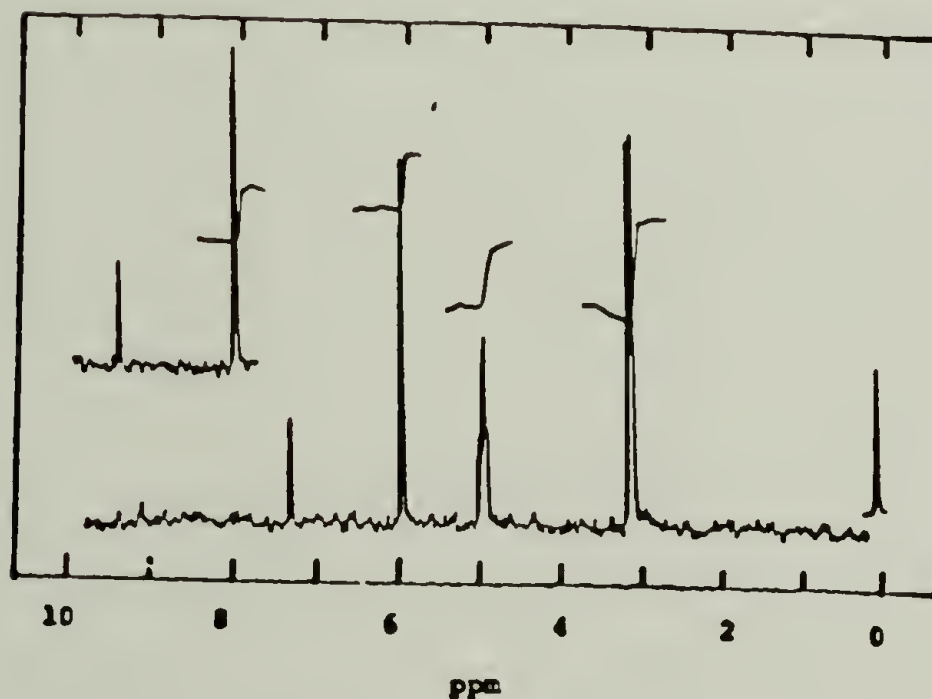
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A P P E N D I X A

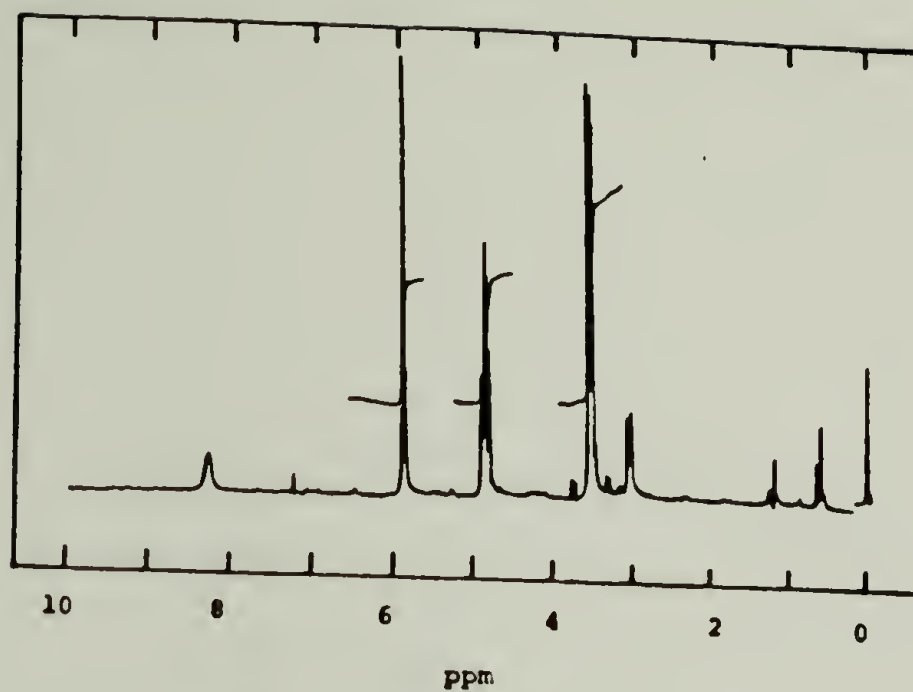
PROTON MAGNETIC RESONANCE SPECTRA



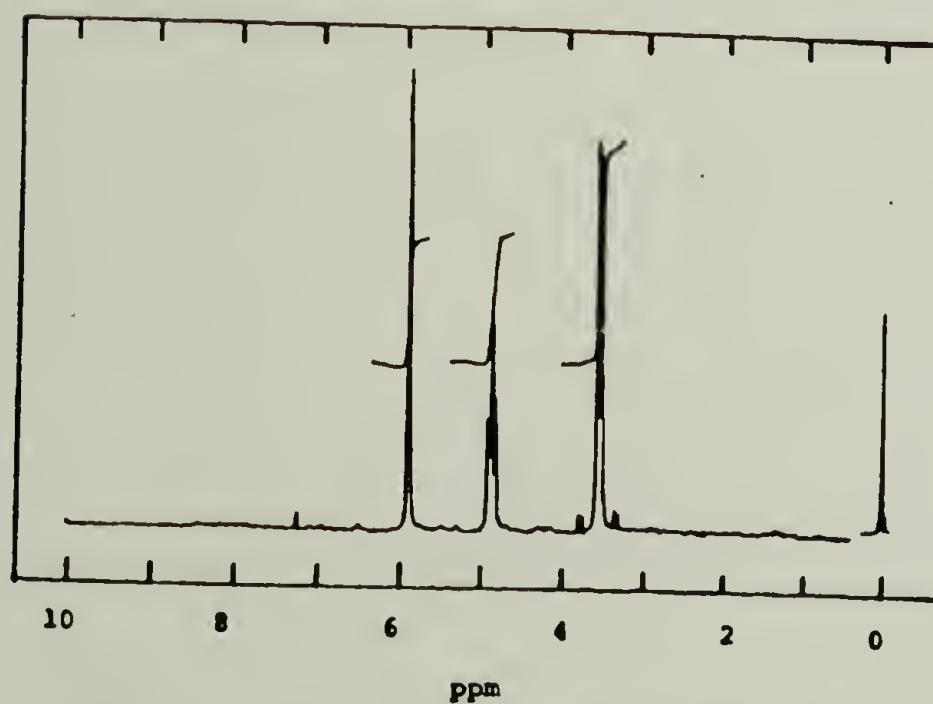
Proton NMR Spectra No. 1. Racemic
malic acid chloralide.
The spectra was shifted 3 ppm
to show the carboxylic acid proton.



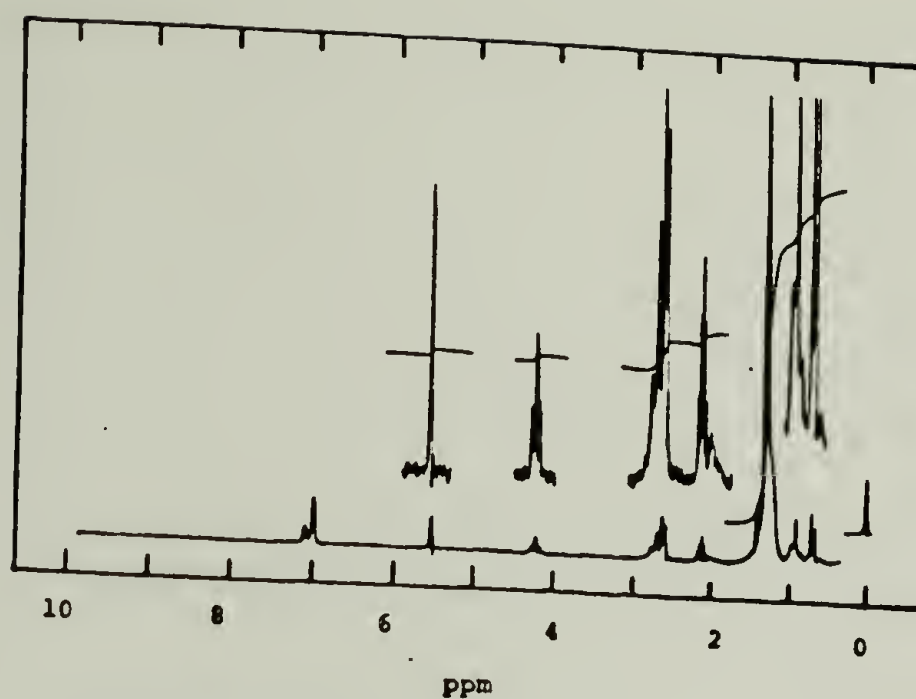
Proton NMR Spectra No. 2. Optically
active malic acid chloralide.
The spectra was shifted 3 ppm
to show the carboxylic acid proton.



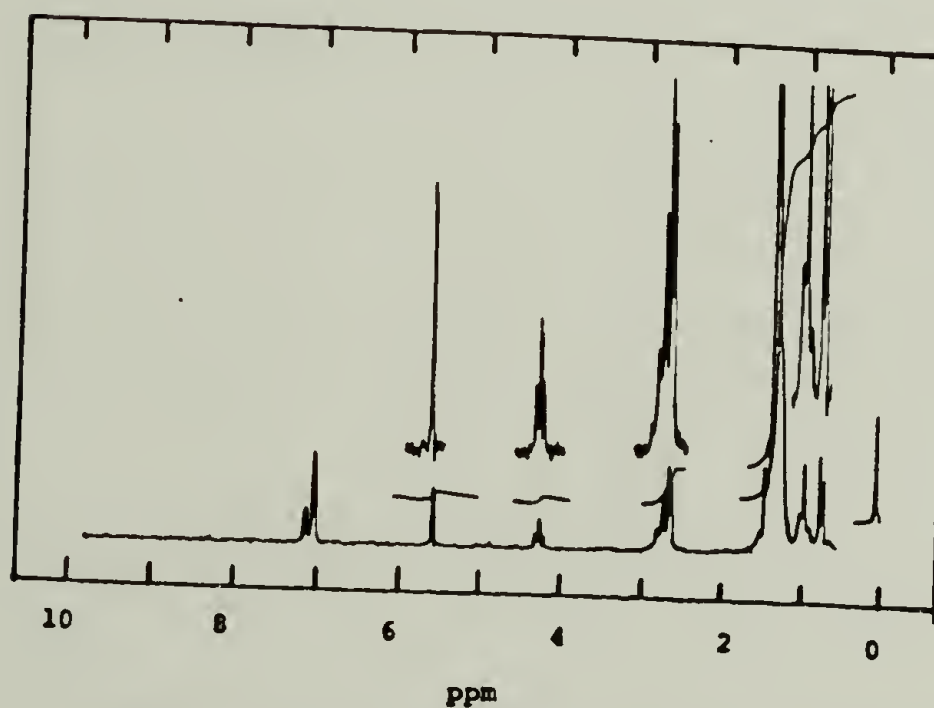
Proton NMR Spectra No. 3. Racemic
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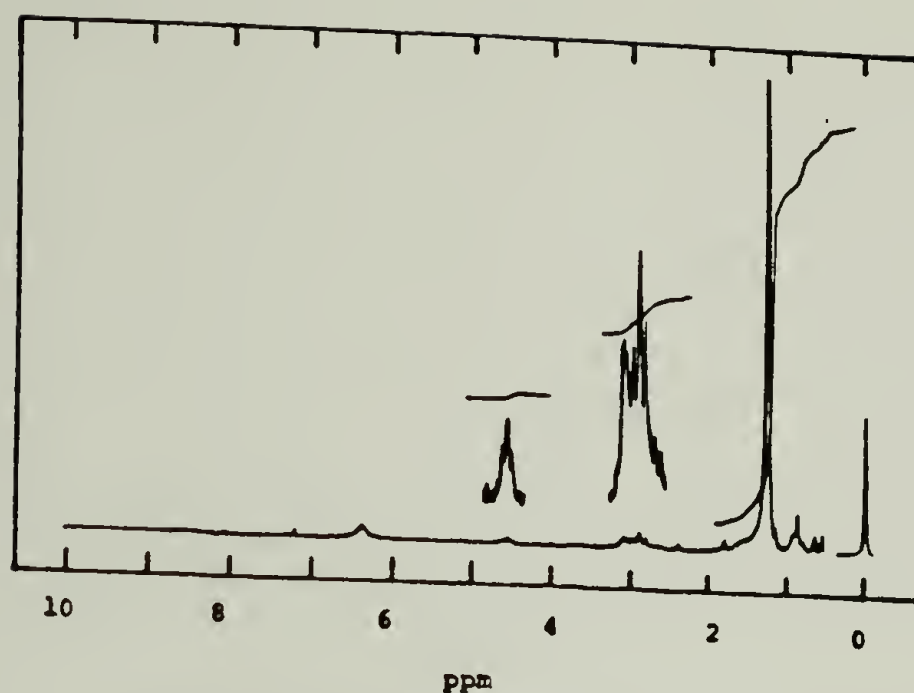
Proton NMR Spectra No. 4. Optically
active malic acid chloralide
chloride.



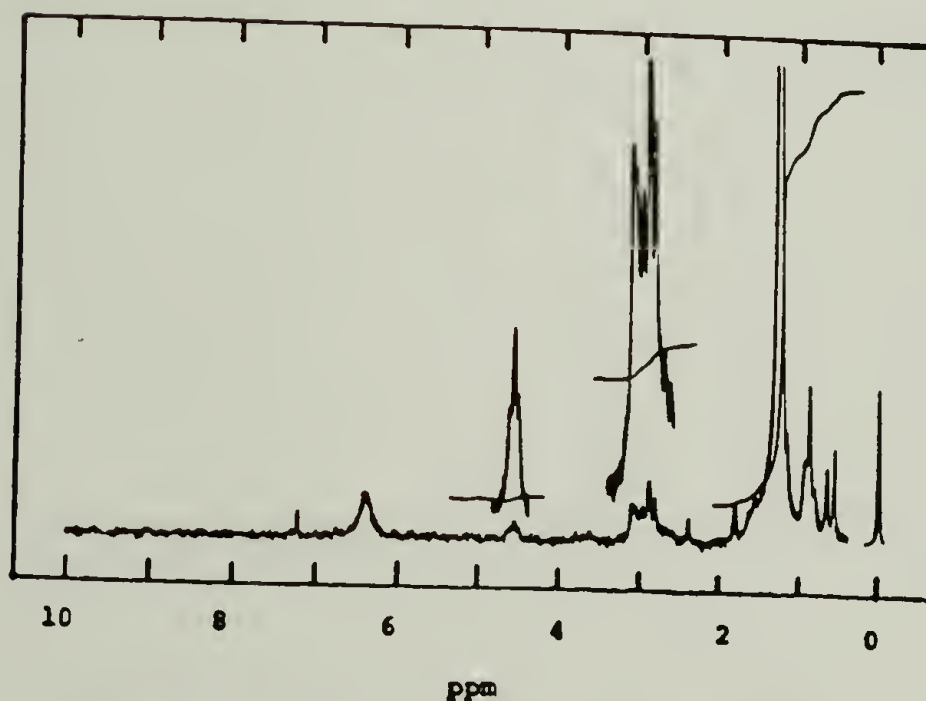
Proton NMR Spectra No. 5. Racemic
S-(malic acid chloralide)
octadecylate.



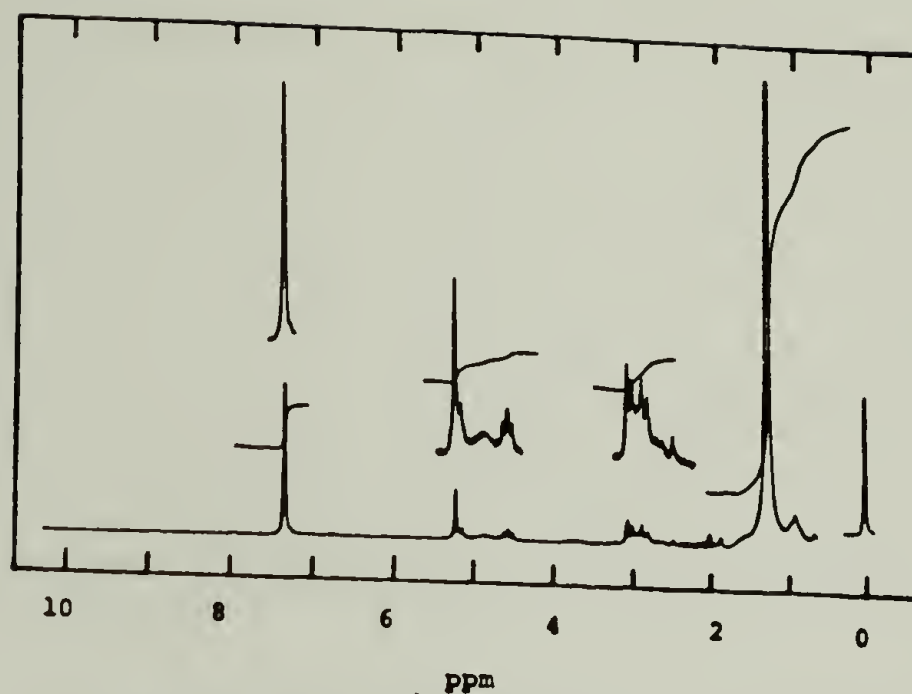
Proton NMR Spectra No. 6. Optically
active S-(malic acid chloralide)
octadecylate.



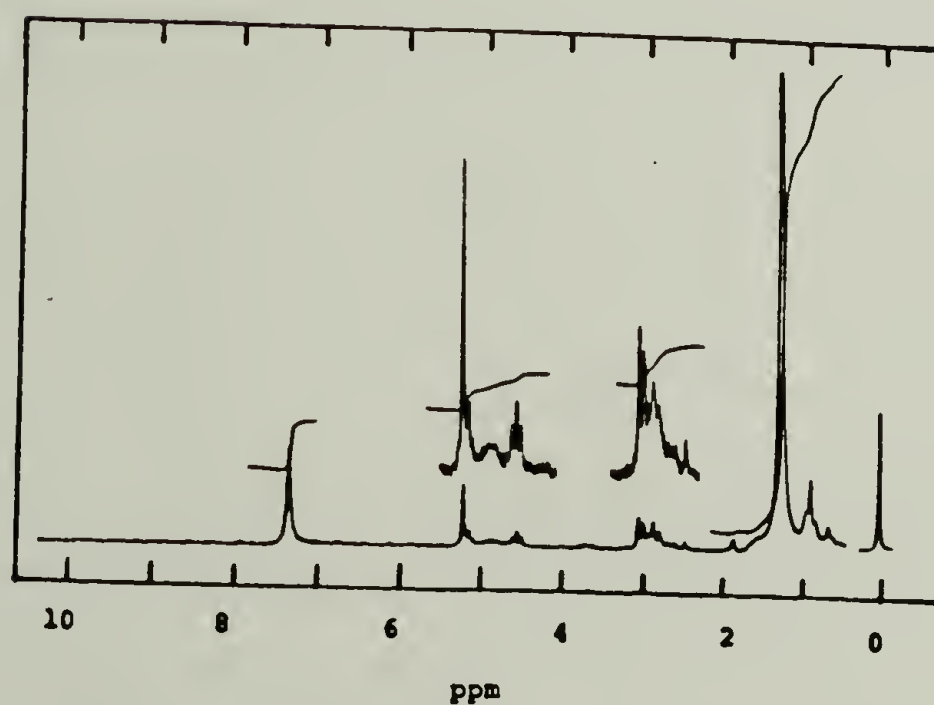
Proton NMR Spectra No. 7. Racemic
S-(beta-hydroxysuccinyl)
octadecylate.



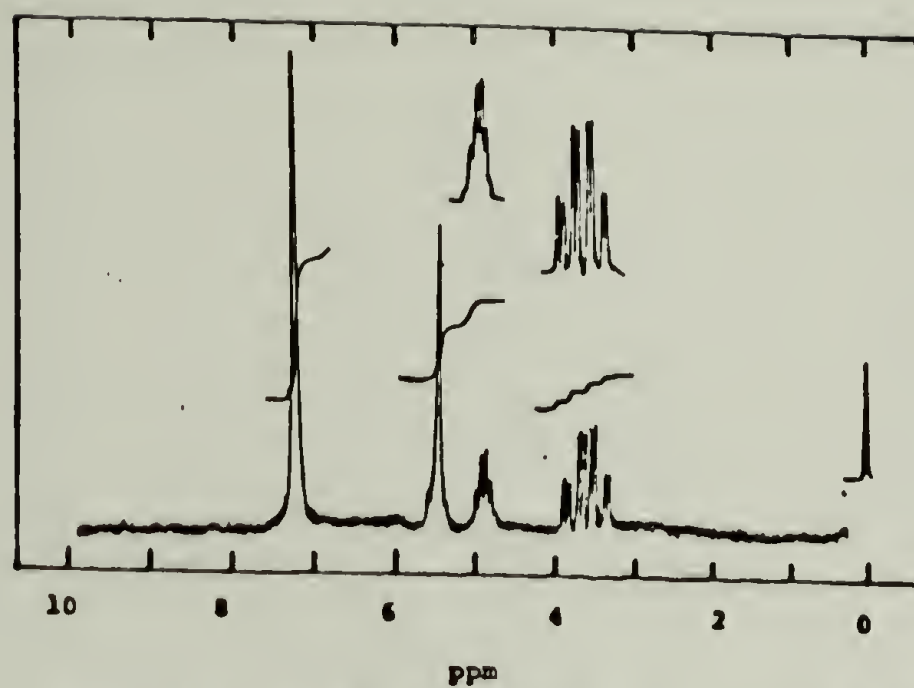
Proton NMR Spectra No. 8. Optically
active S-(beta-hydroxysuccinyl)
octadecylate.



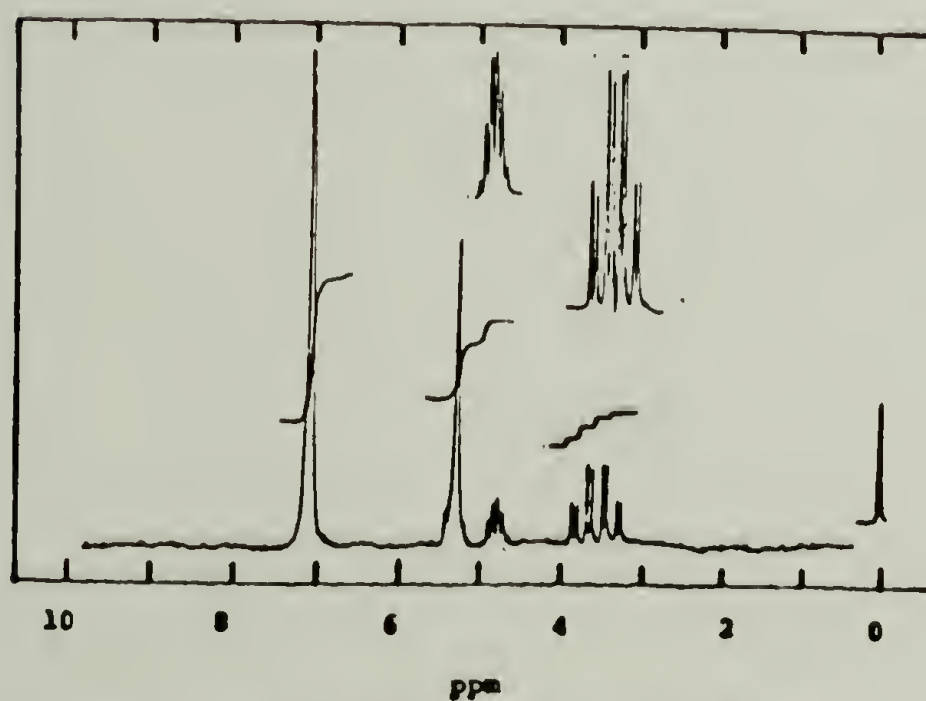
Proton NMR Spectra No. 9. Racemic
S-(beta-hydroxysuccinyl benzyl
ester) octadecylate.



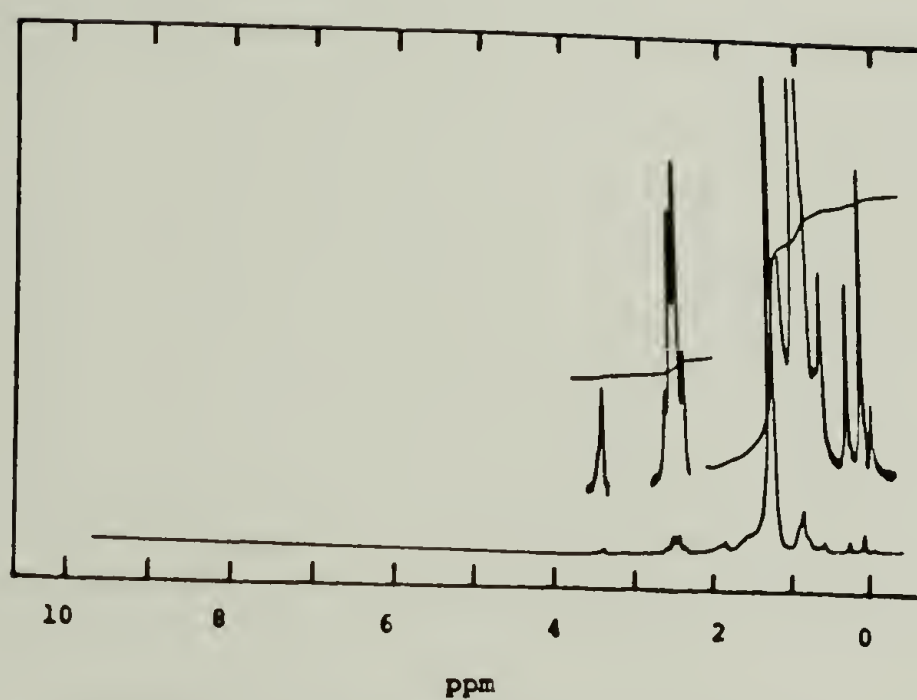
Proton NMR Spectra No. 10. Optically
active S-(beta-hydroxysuccinyl
benzyl ester) octadecylate.



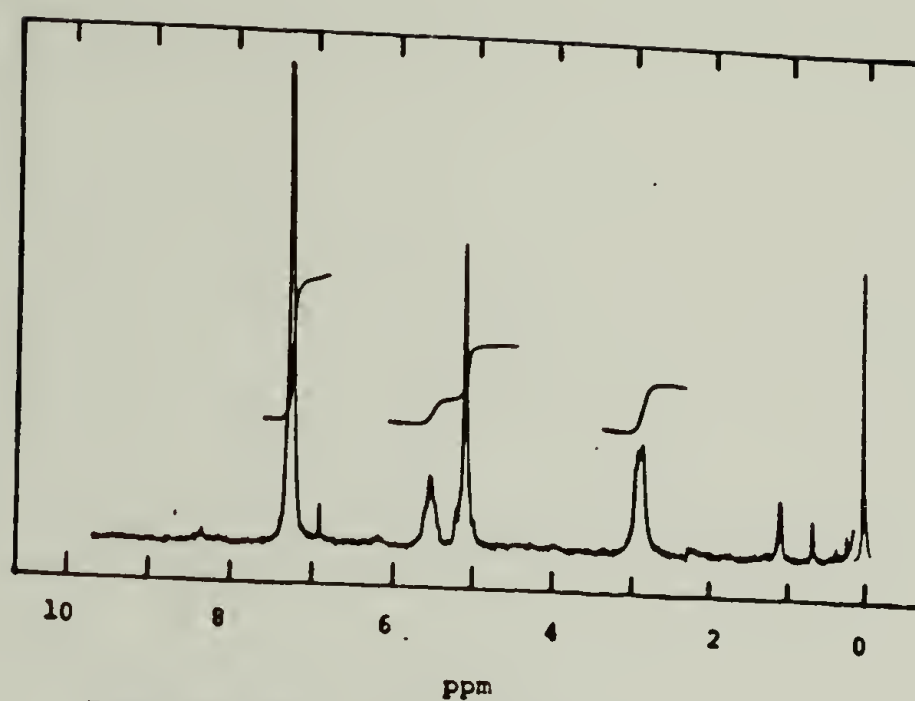
Proton NMR Spectra No. 11. Racemic
malolactone benzyl ester.



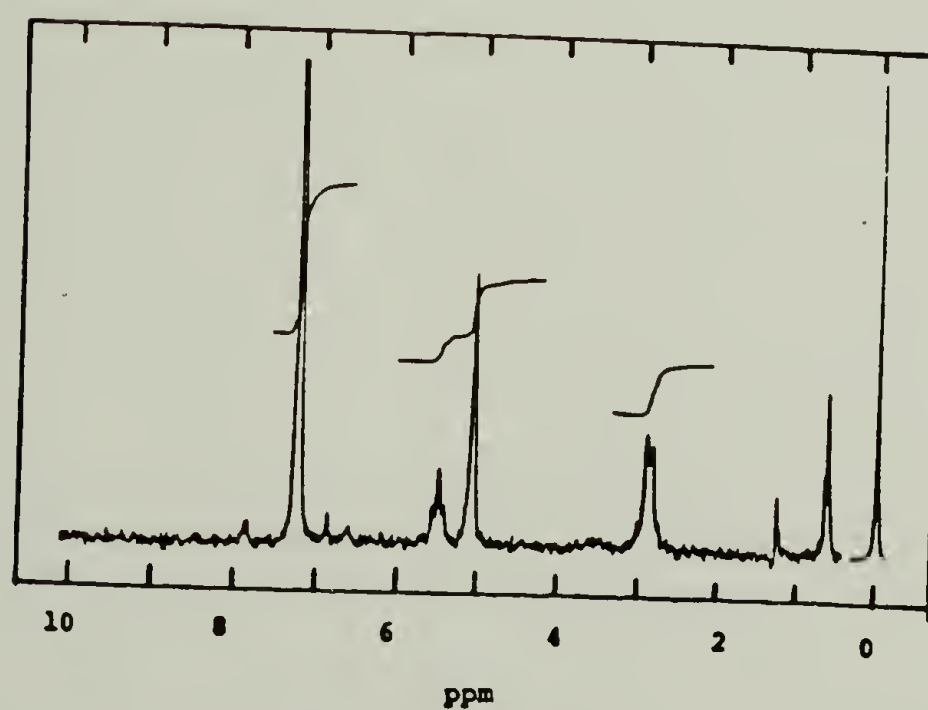
Proton NMR Spectra No. 12. Optically
active malolactone benzyl ester.



Proton NMR Spectra No. 13.
Octadecyl trimethylsilyl
sulfide.



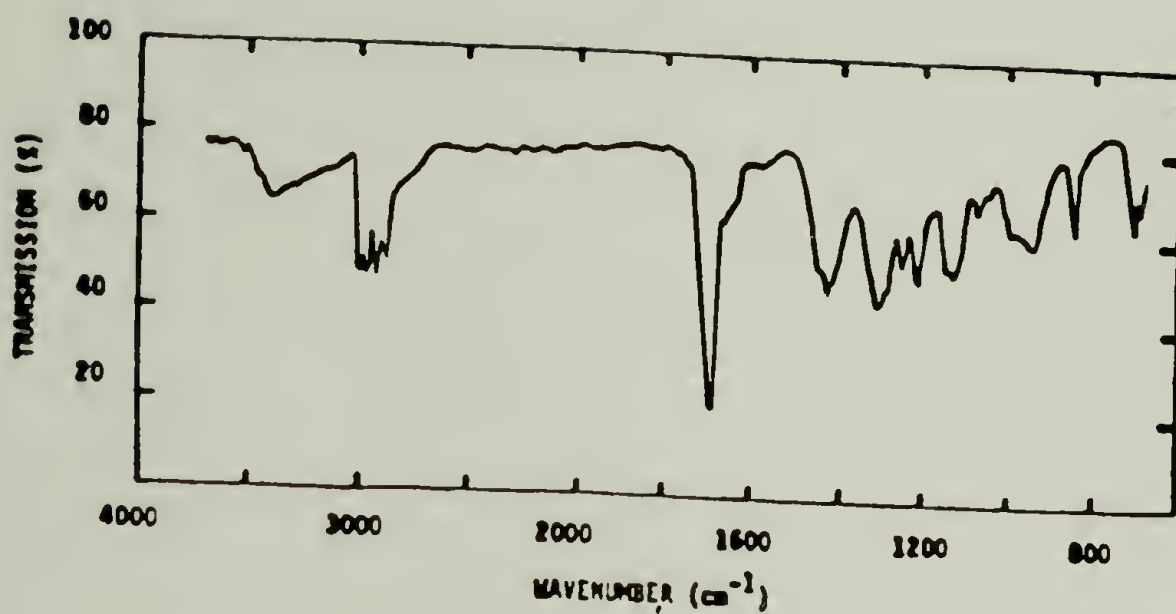
Proton NMR Spectra No. 14. Racemic
poly(malolactone benzyl ester).



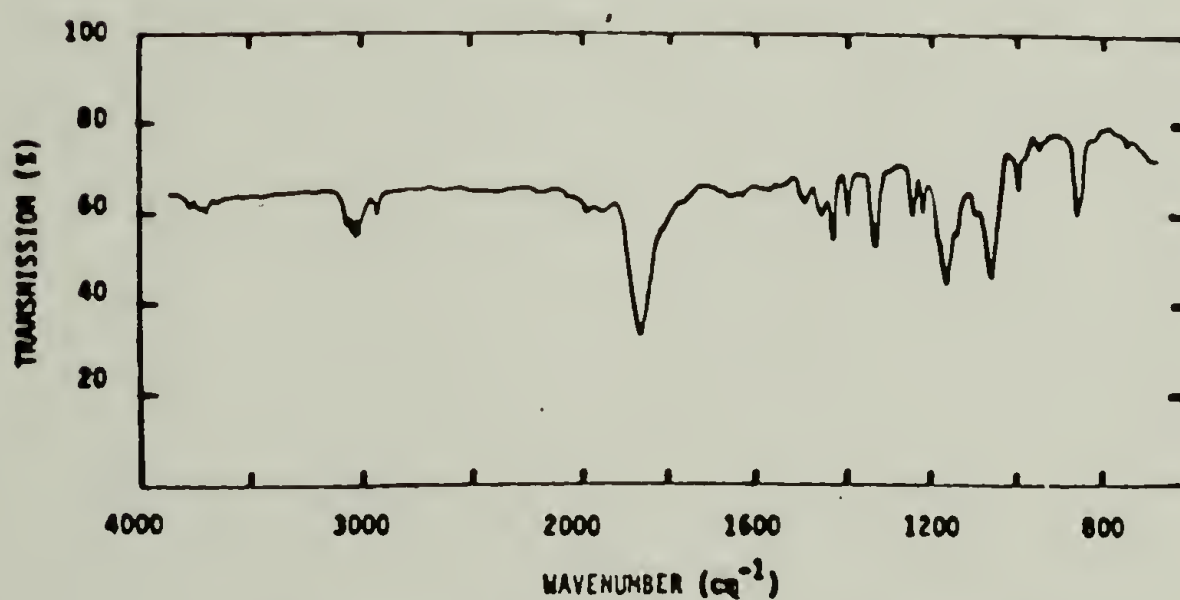
Proton NMR Spectra No. 15. Optically
active poly(malolactone benzyl
ester).

A P P E N D I X B

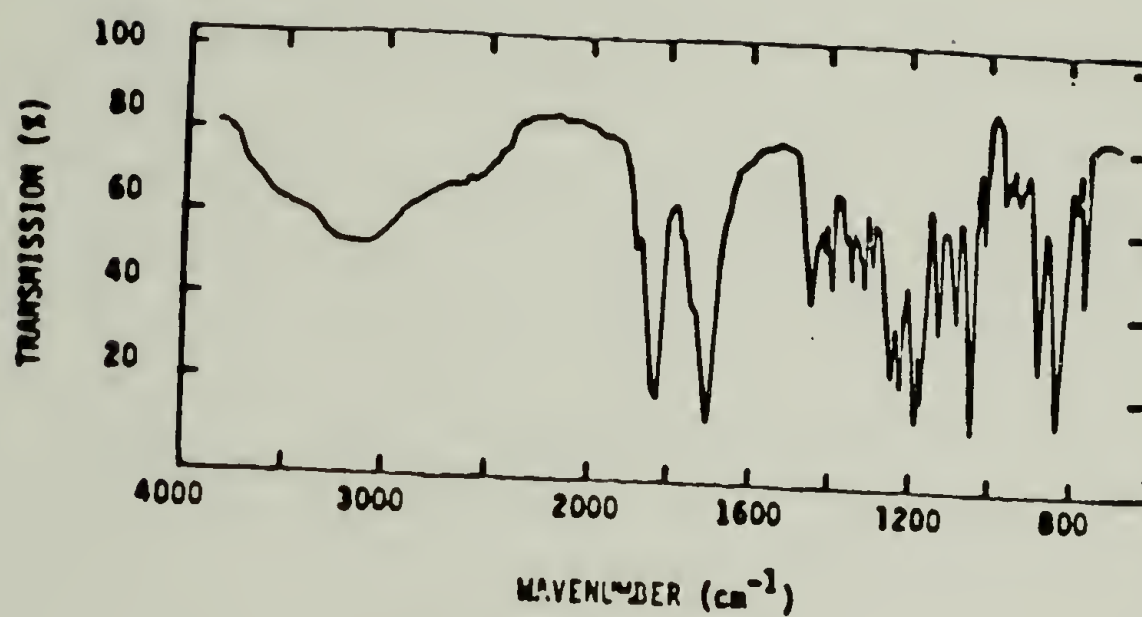
INFRARED SPECTRA



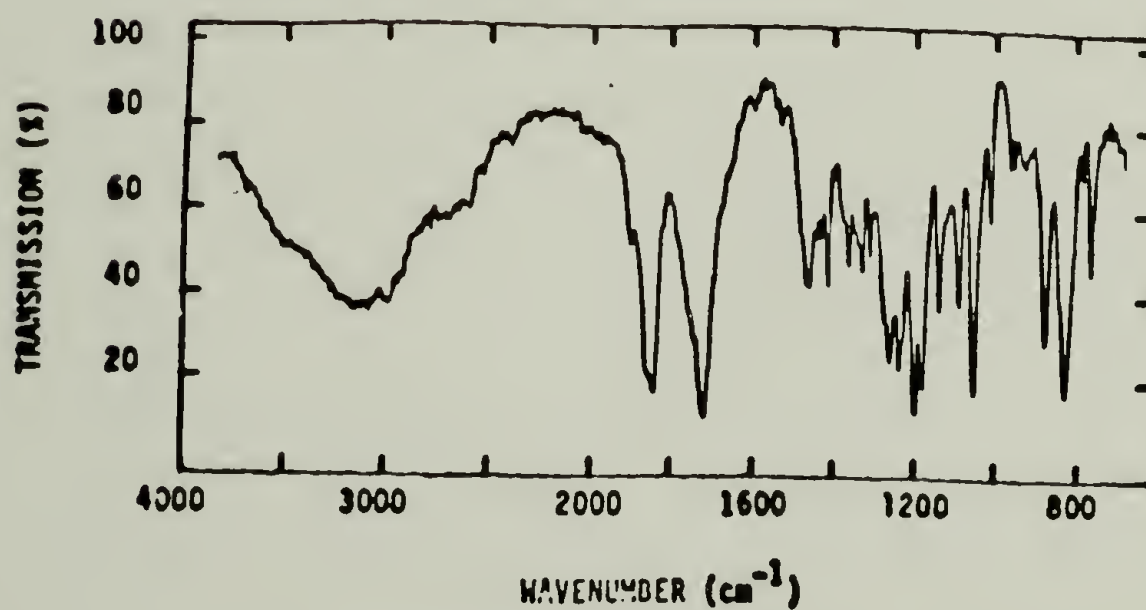
Infrared Spectra No. 1. 2-Methylpropyl-
2-Thiol Ester of Beta-Hydroxy
Butyric Acid.



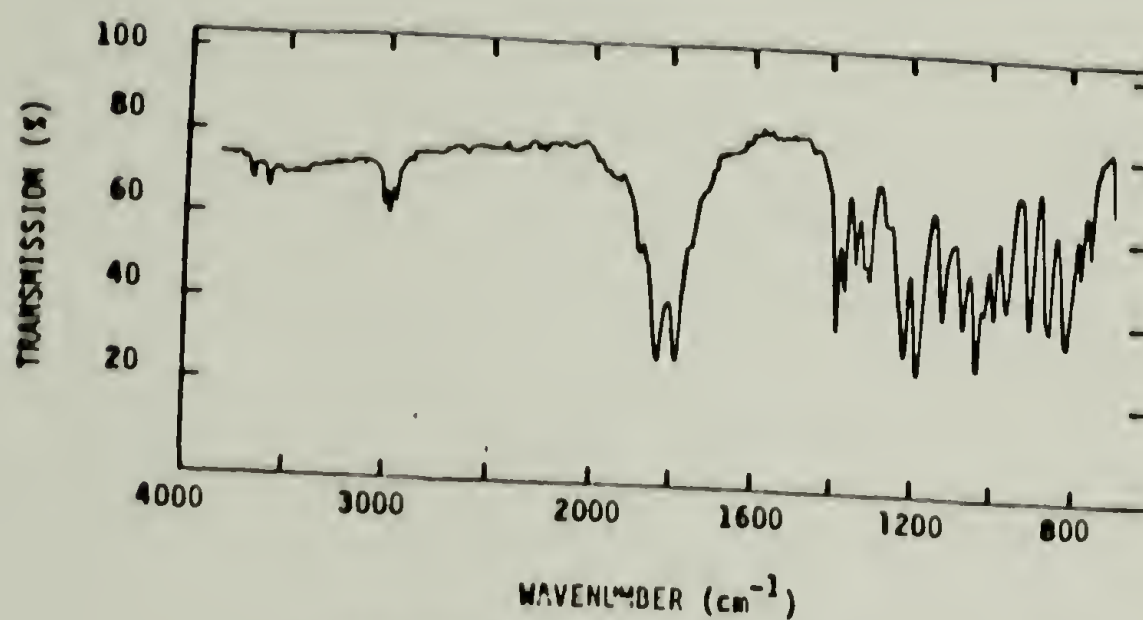
Infrared Spectra No. 2. Beta-
Butyrolactone.



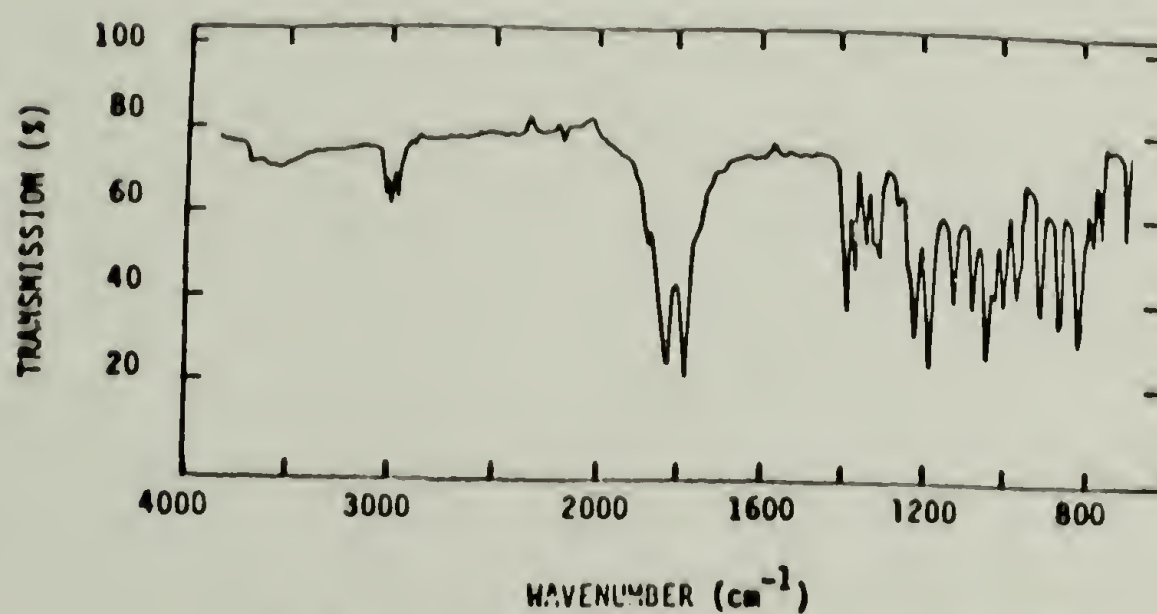
Infrared Spectra No. 3. Racemic
malic acid chloralide.



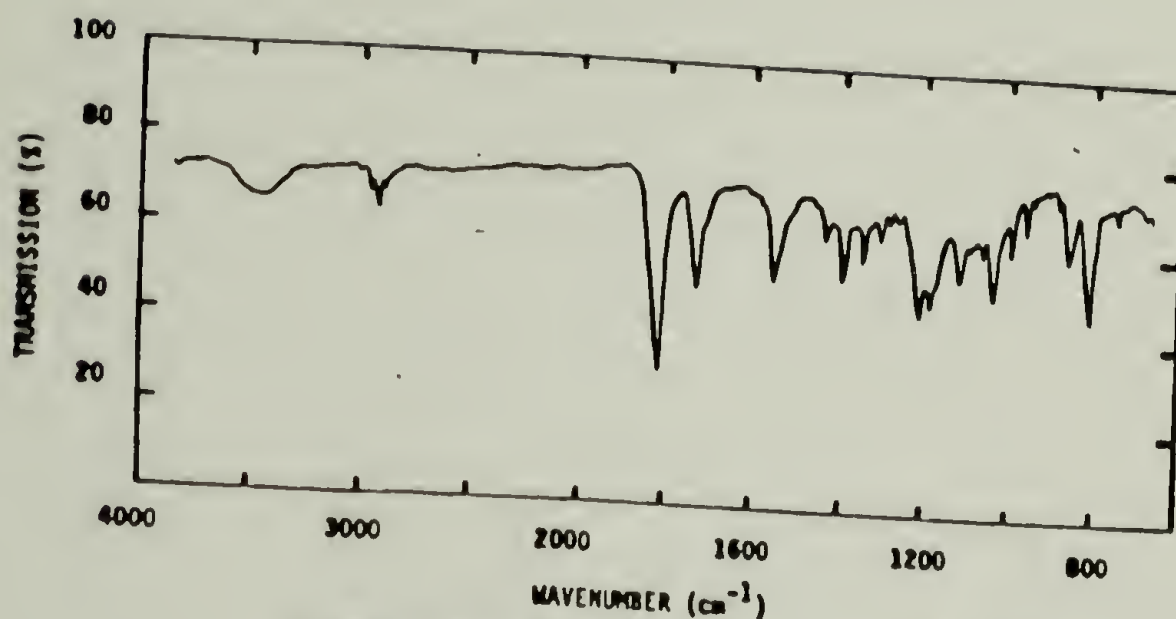
Infrared Spectra No. 4. Optically
active malic acid chloralide.



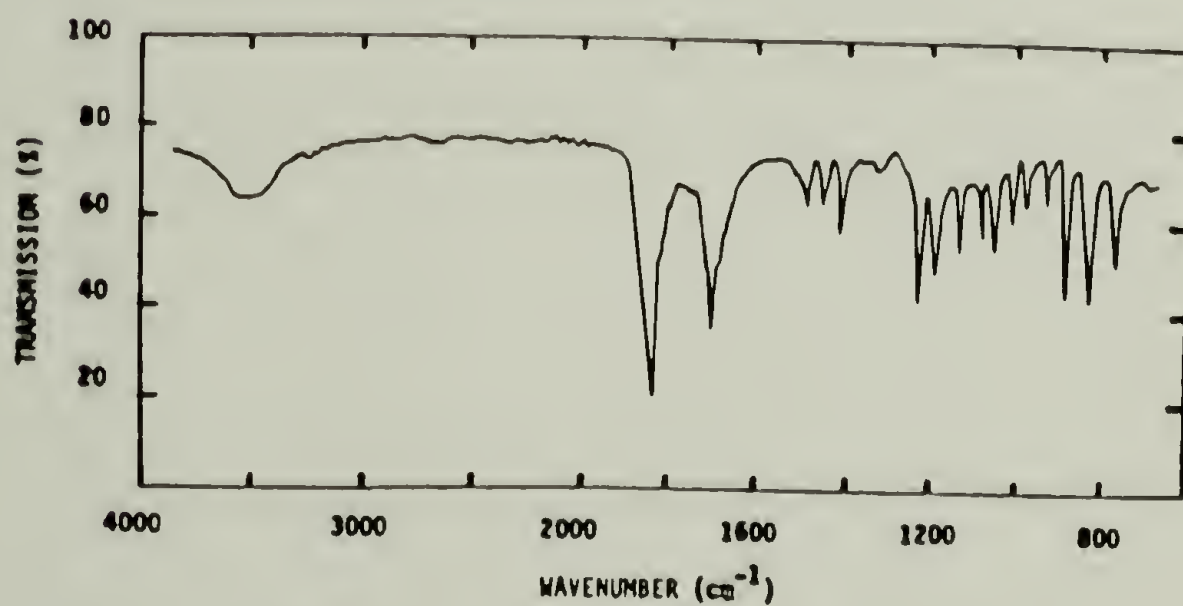
Infrared Spectra No. 5. Racemic
malic acid chloralide chloride.



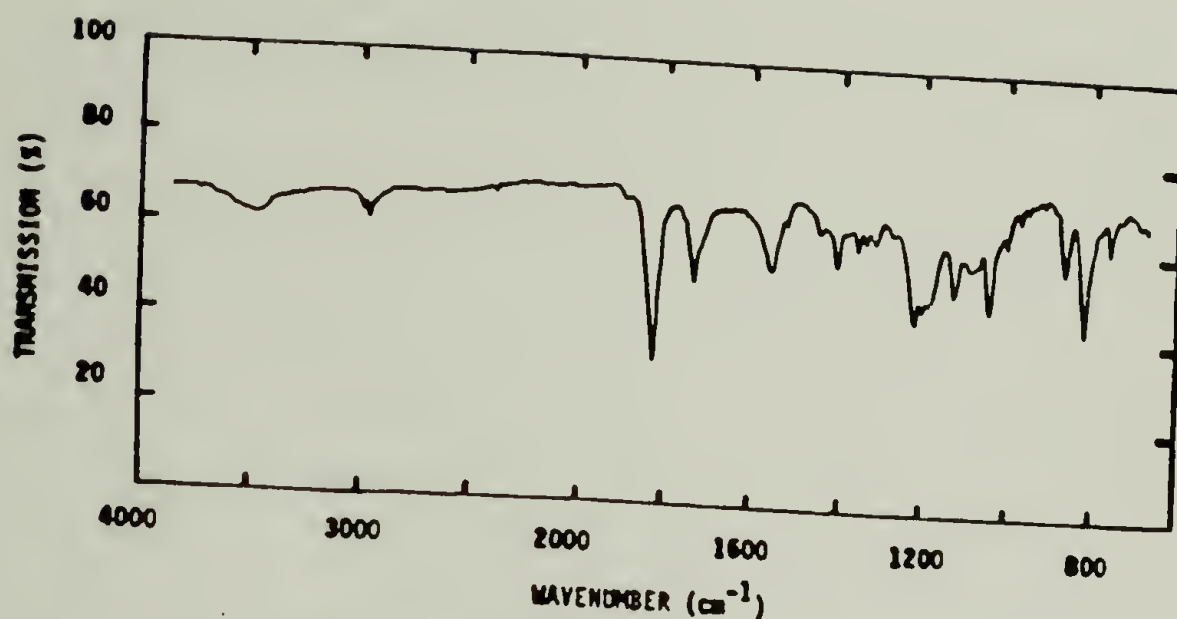
Infrared Spectra No. 6. Optically
active malic acid chloralide chloride.



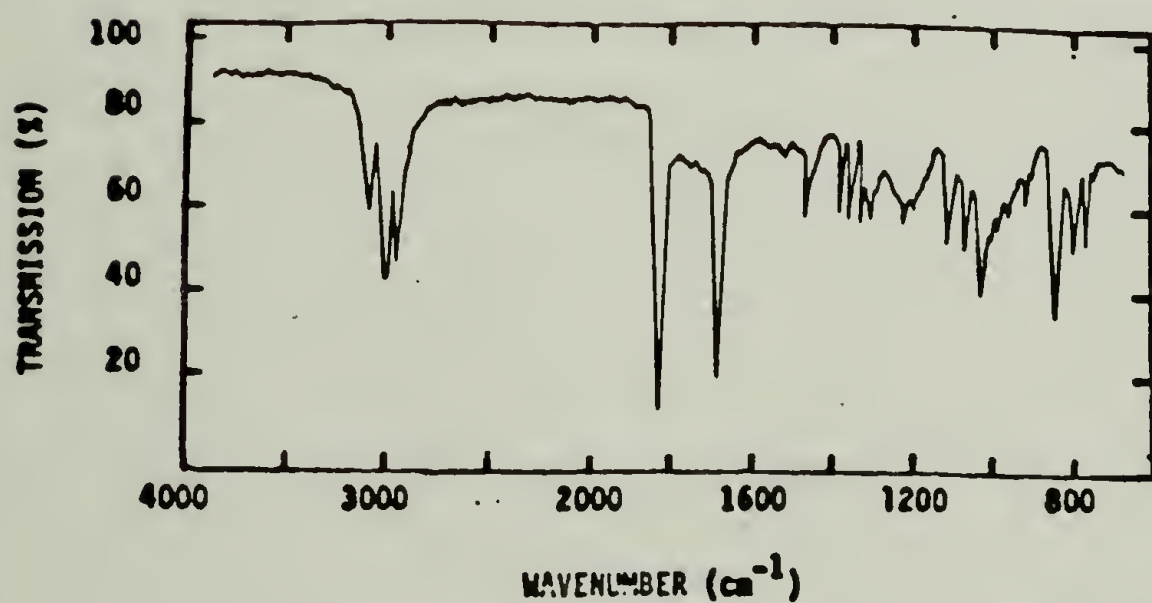
Infrared Spectra No. 7. Racemic
S-(malic acid chloralide)-
2-methyl-2-propanate.



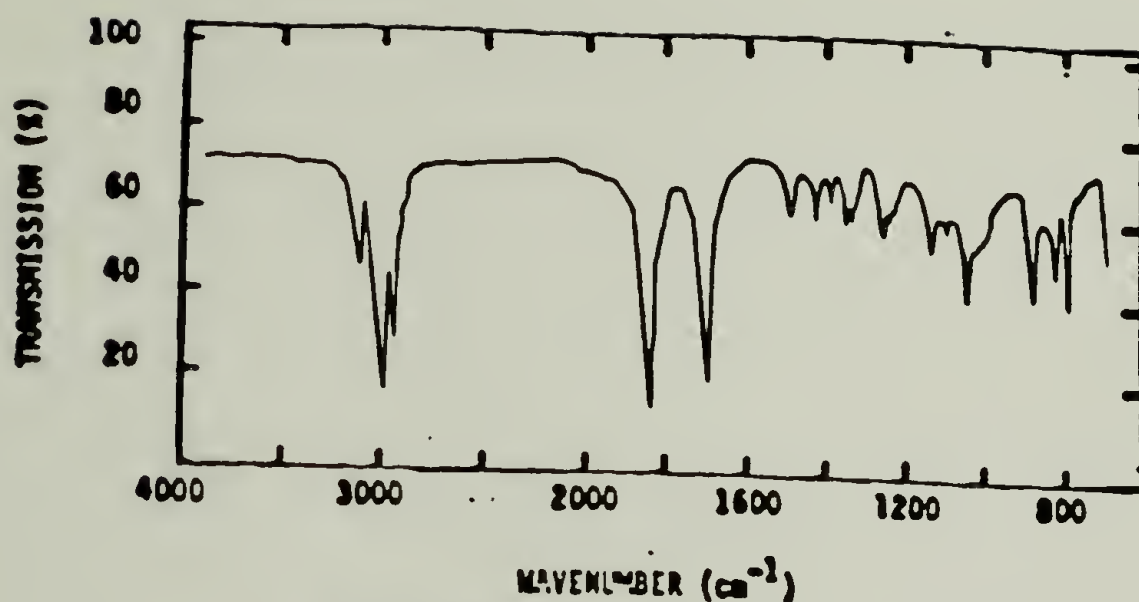
Infrared Spectra No. 8. Racemic
S-(malic acid chloralide) phenylate.



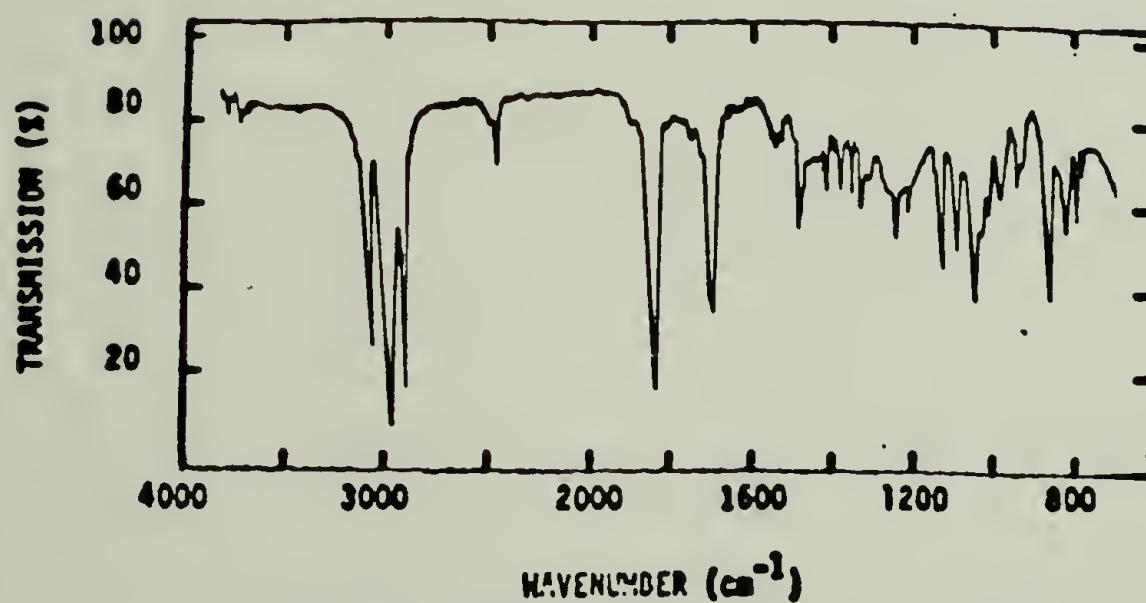
Infrared Spectra No. 9. Optically active S-(malic acid chloralide)-2-methyl-2-propanate.



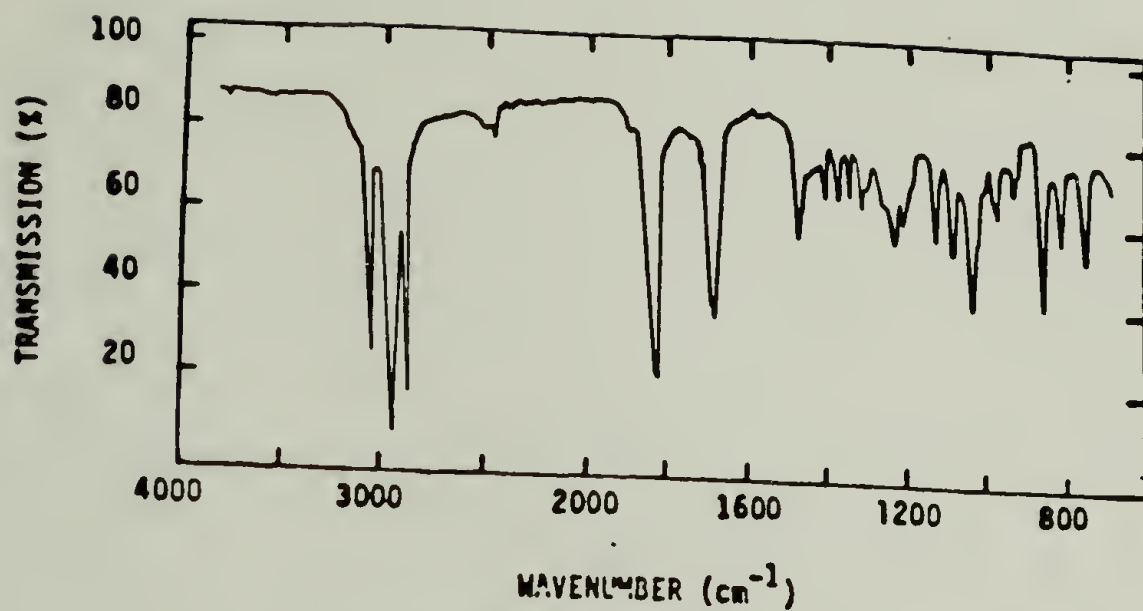
Infrared Spectra No. 10. Racemic S-(malic acid chloralide) dodecanate.



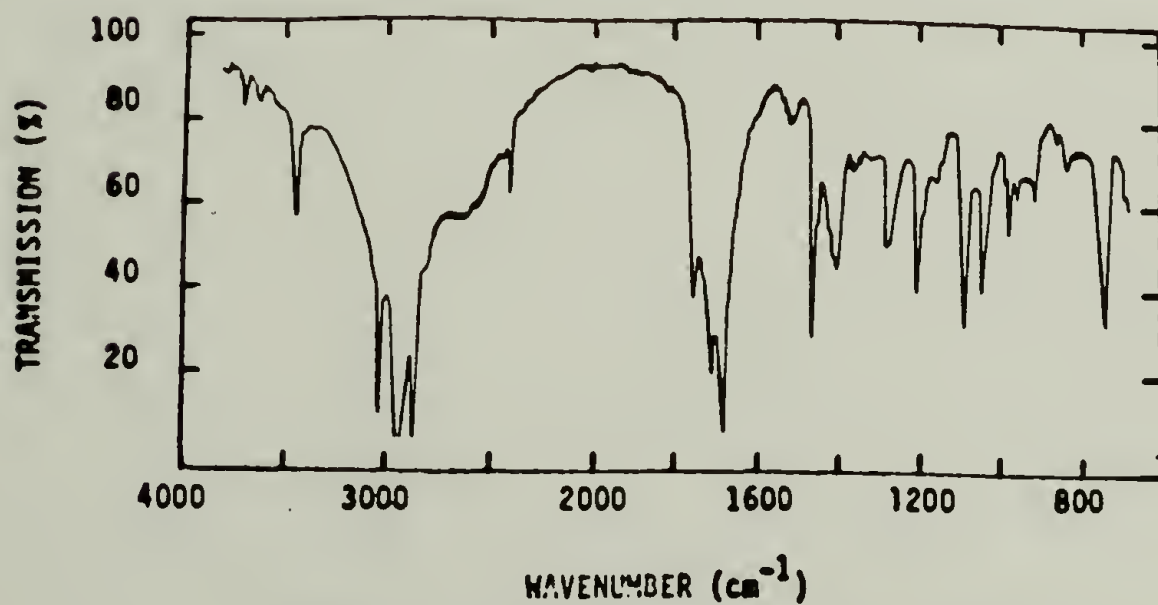
Infrared Spectra No. 11. Racemic
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pentadecanate.



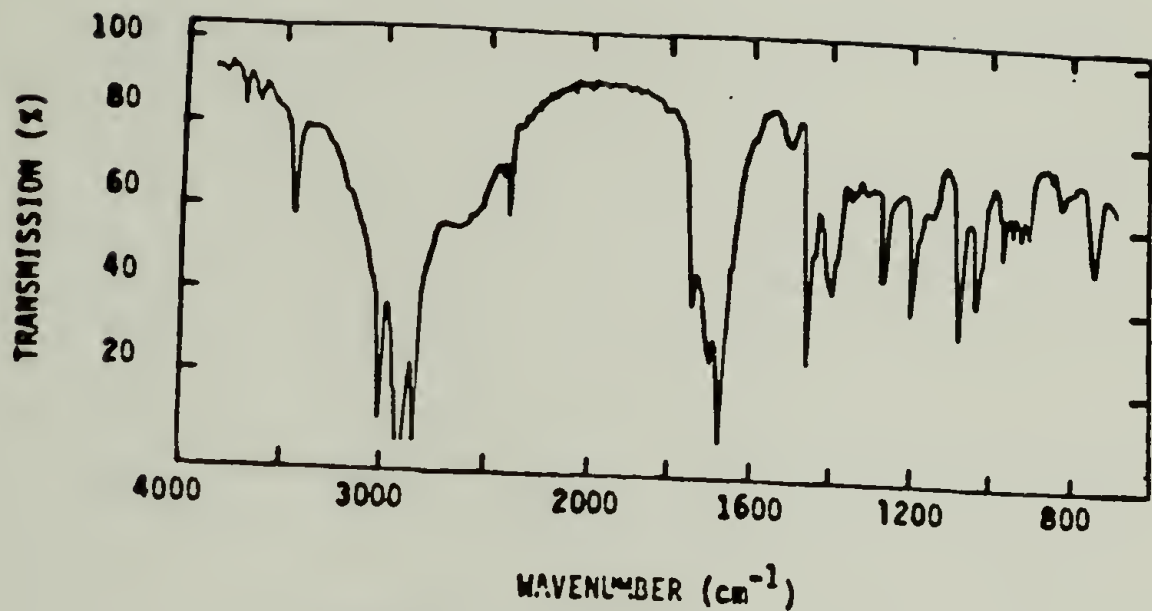
Infrared Spectra No. 12. Racemic
S-(malic acid chloralide)
octadecylate.



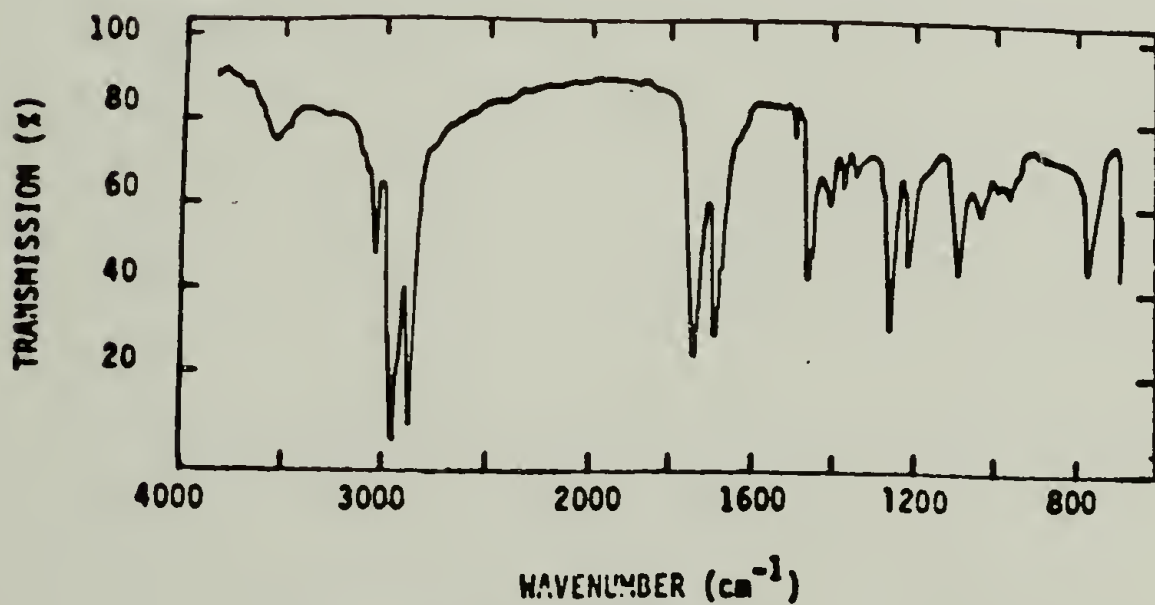
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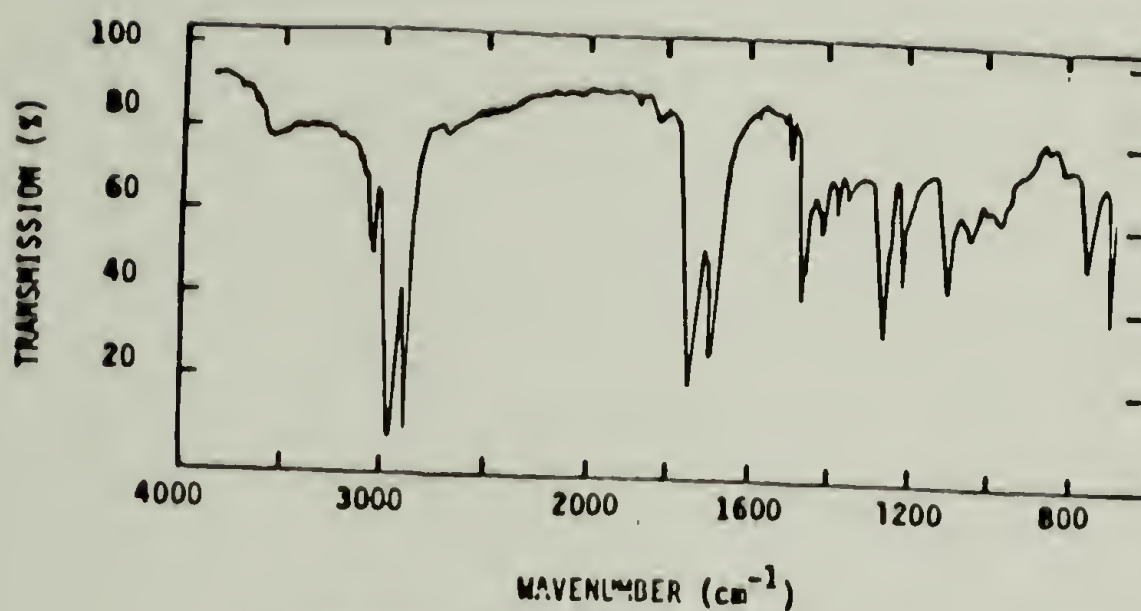
Infrared Spectra No. 14. Racemic S-(beta-hydroxy succinyl) octadecylate.



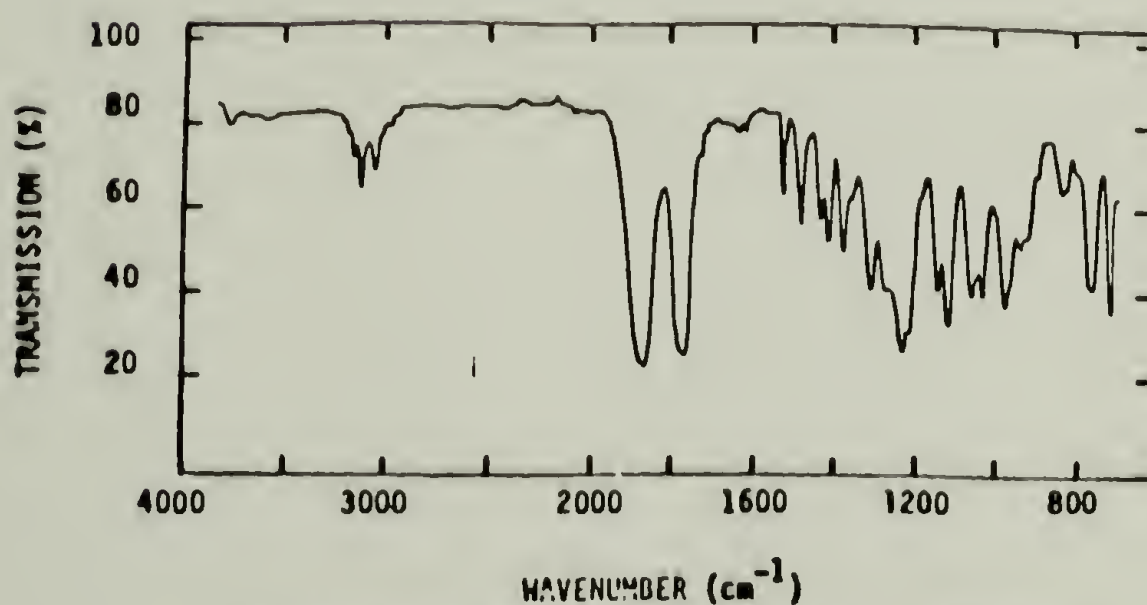
Infrared Spectra No. 15. Optically active S-(β -hydroxy succinyl) octadecylate.



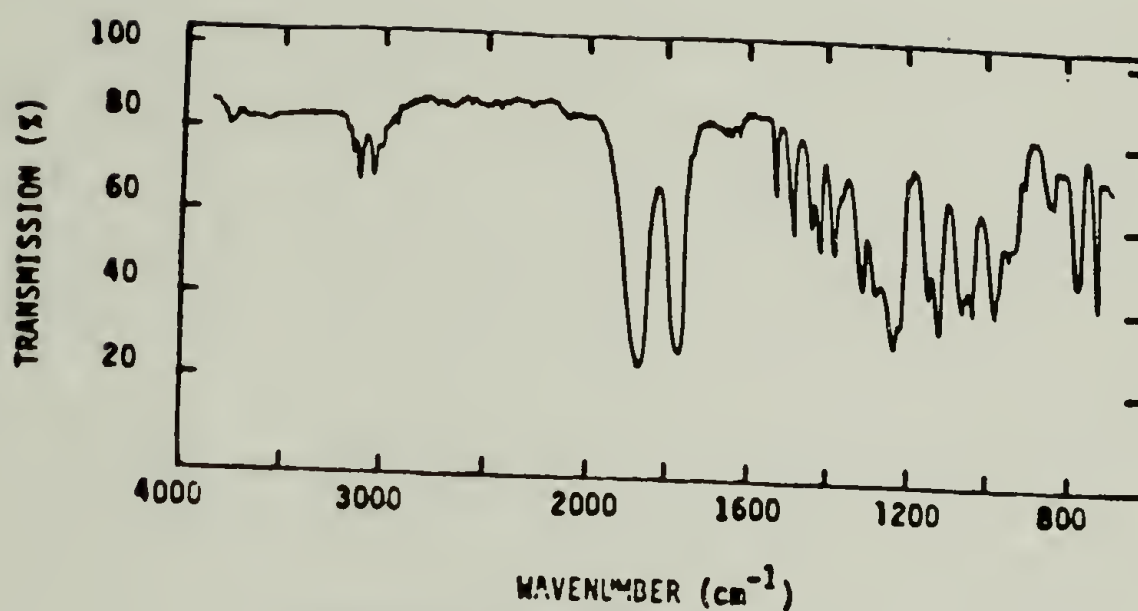
Infrared Spectra No. 16. Racemic S-(β -hydroxysuccinyl benzyl ester) octadecylate.



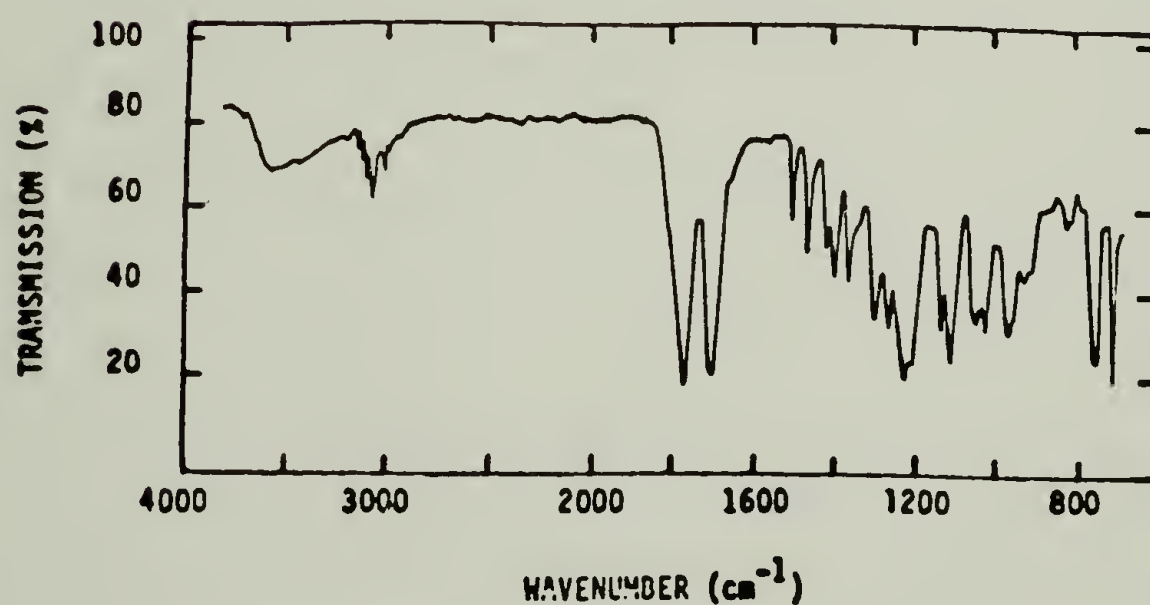
Infrared Spectra No. 17. Optically active S-(beta-hydroxysuccinyl benzyl ester) octadecylate.



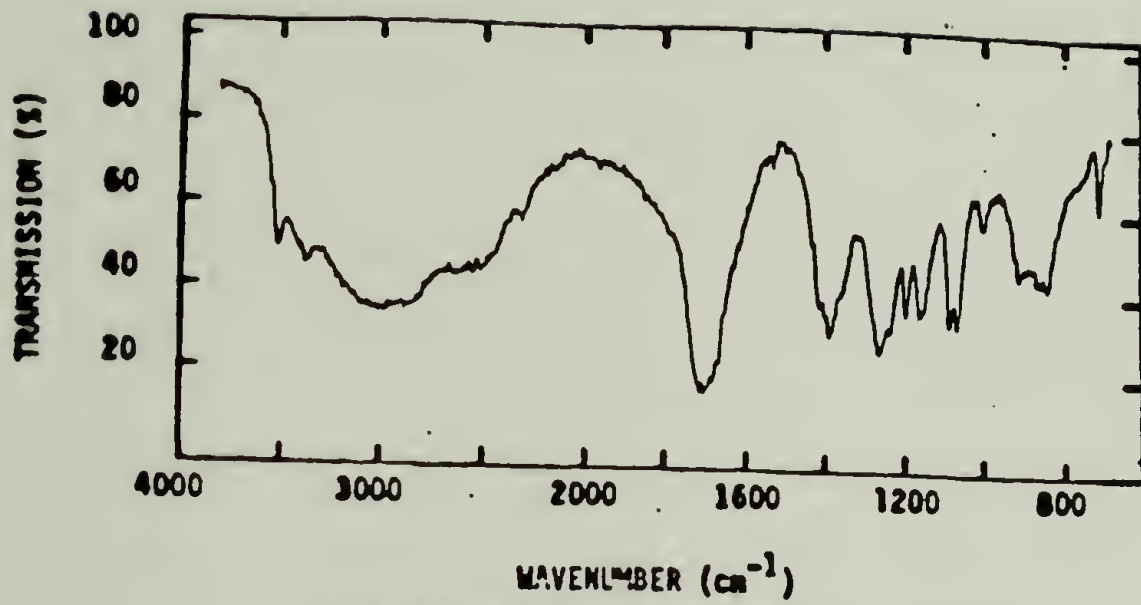
Infrared Spectra No. 18. Racemic malolactone benzyl ester.



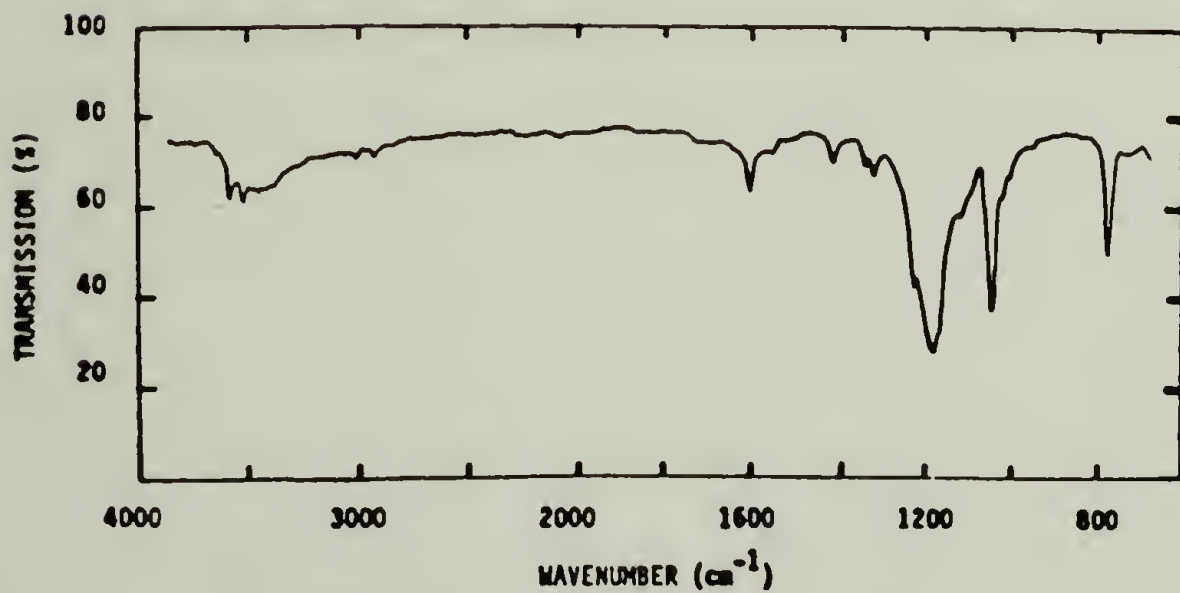
Infrared Spectra No. 19. Optically active malolactone benzyl ester.



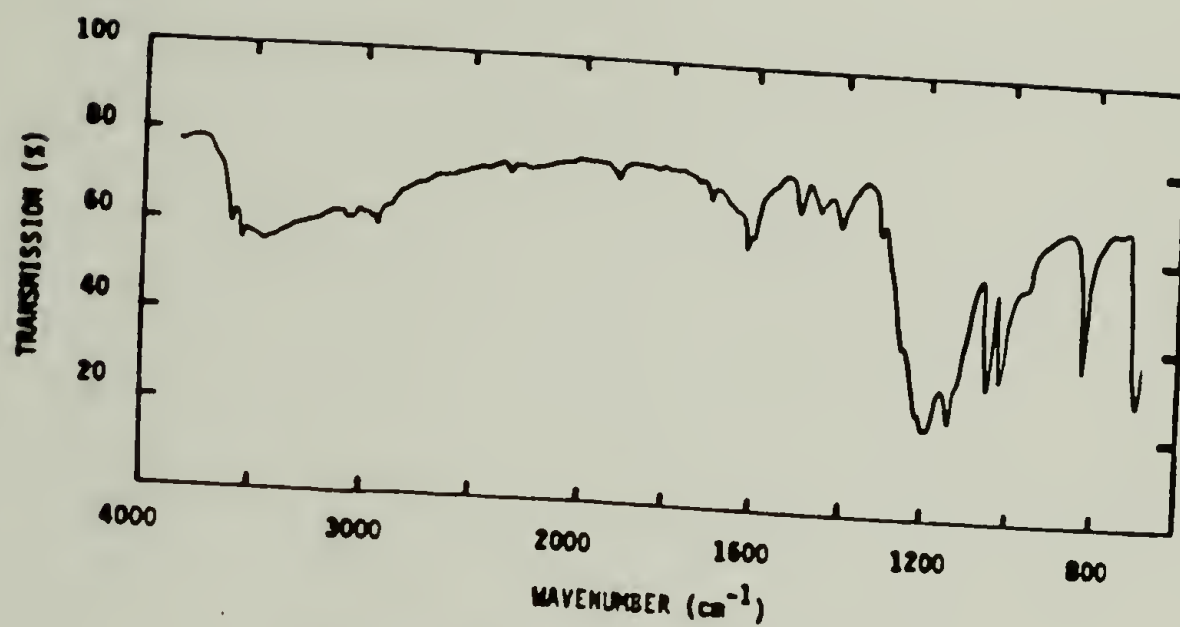
Infrared Spectra No. 20. Racemic S-(beta-hydroxysuccinyl benzyl ester) phenylate.



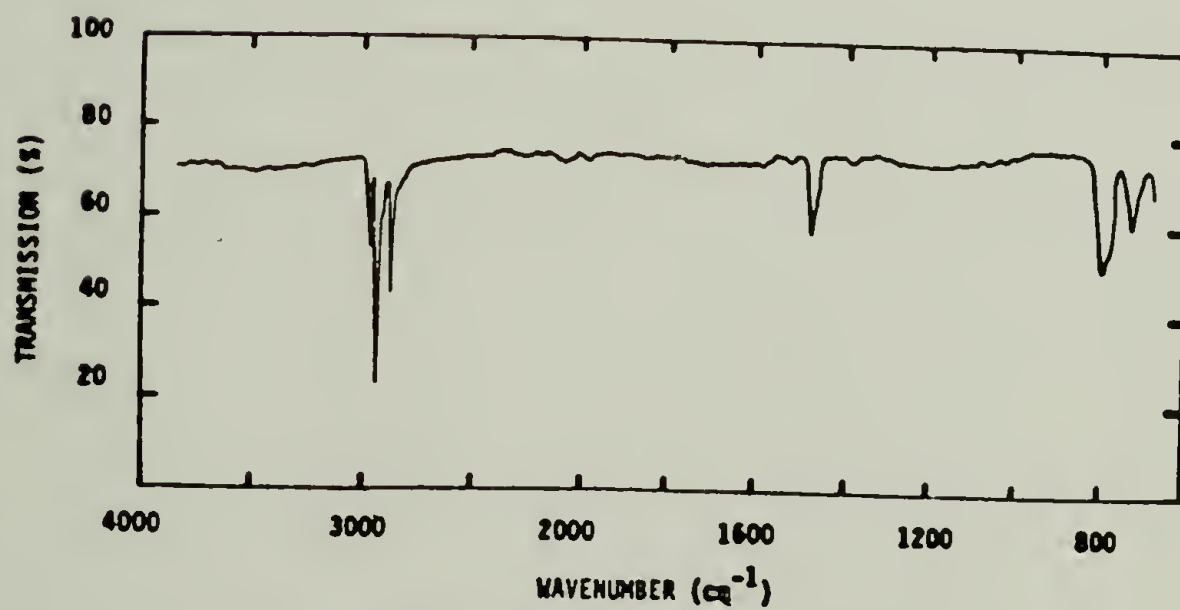
Infrared Spectra No. 21. Recovered
malic acid after acid hydrolysis.



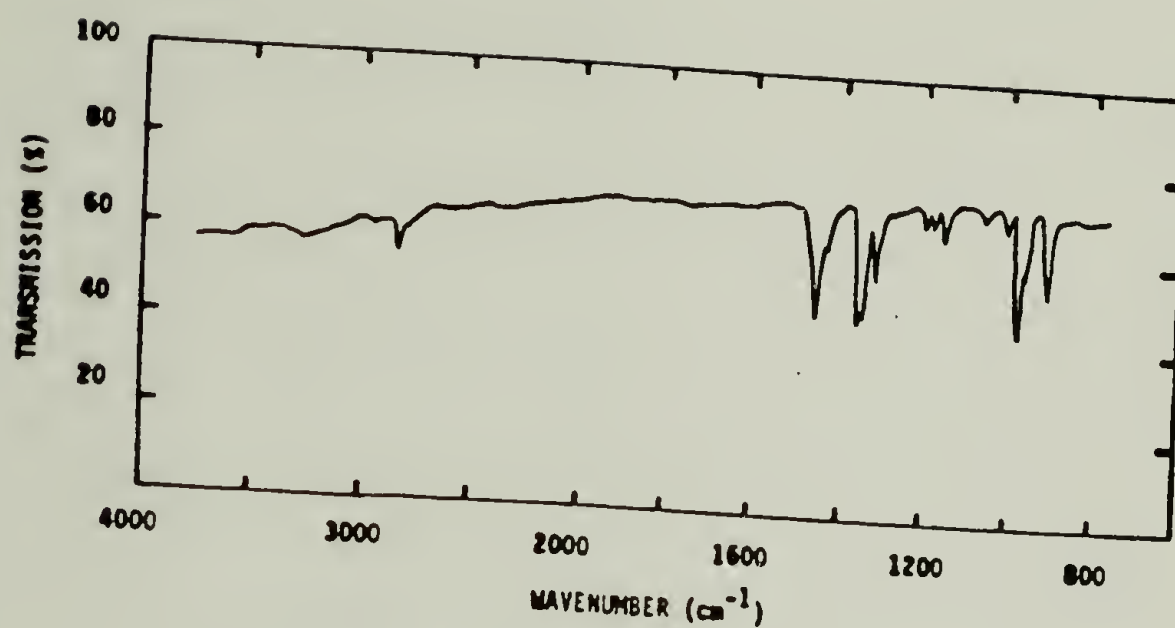
Infrared Spectra No. 22.
Mercuric methanesulfonate.



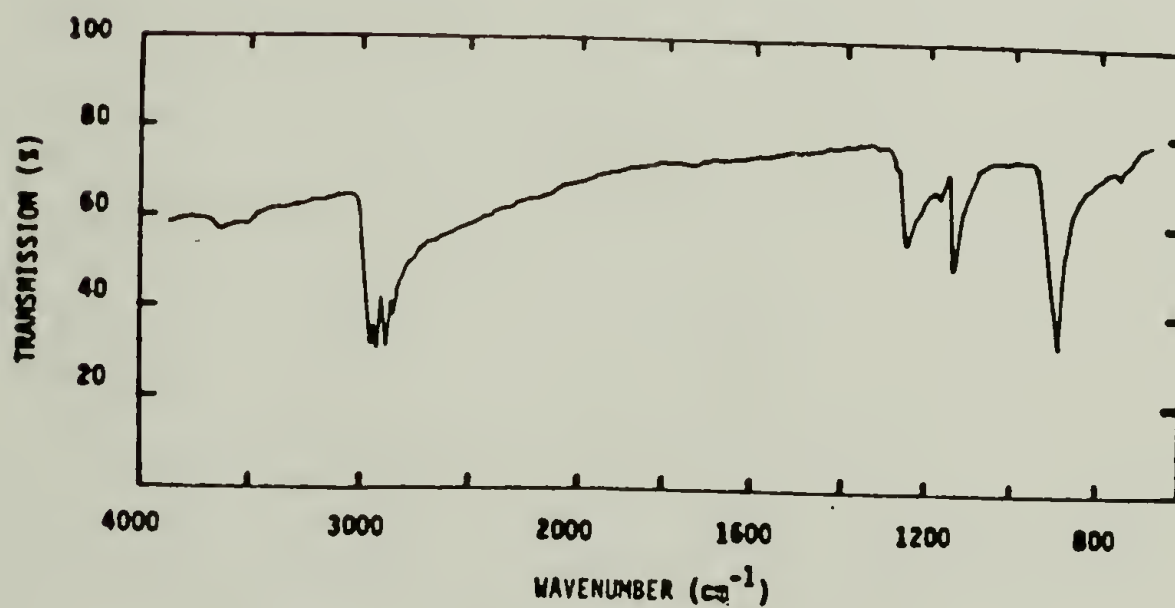
Infrared Spectra No. 23.
Mercuric p-toluenesulfonate.



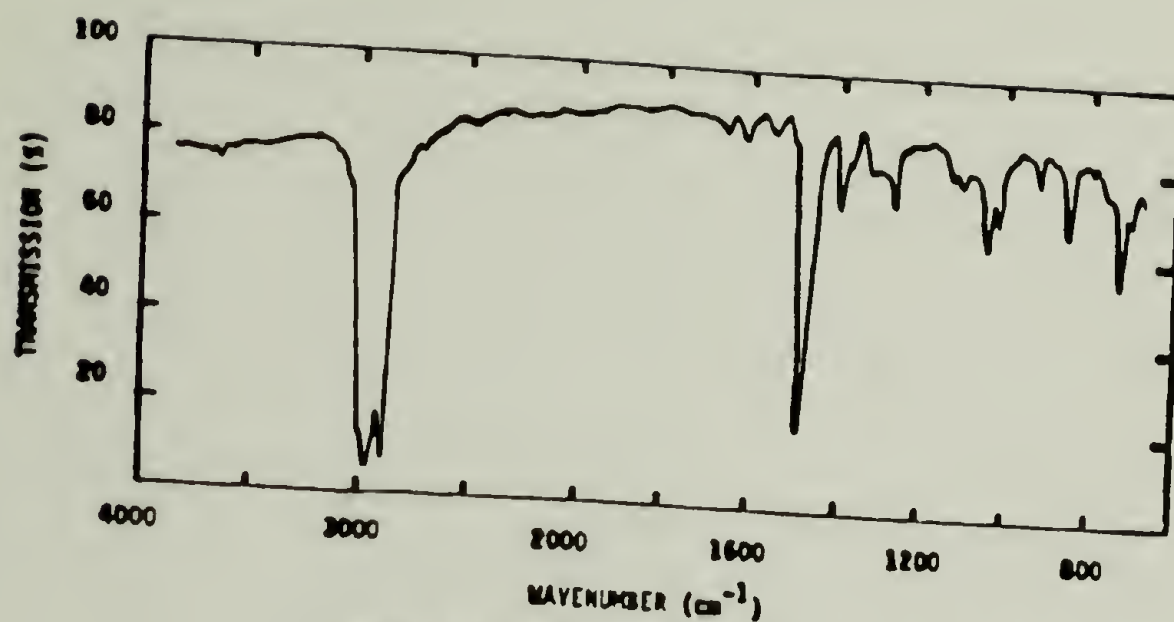
Infrared Spectra No. 24.
Thallium octadecylthiolate.



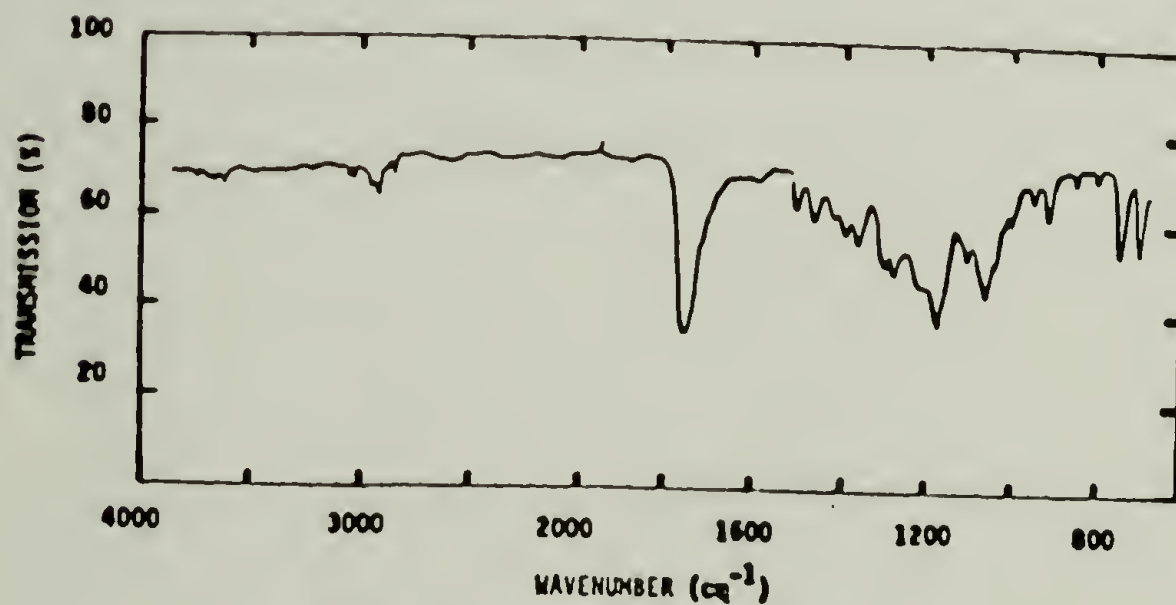
Infrared Spectra No. 25.
Thallium benzene thiolate.



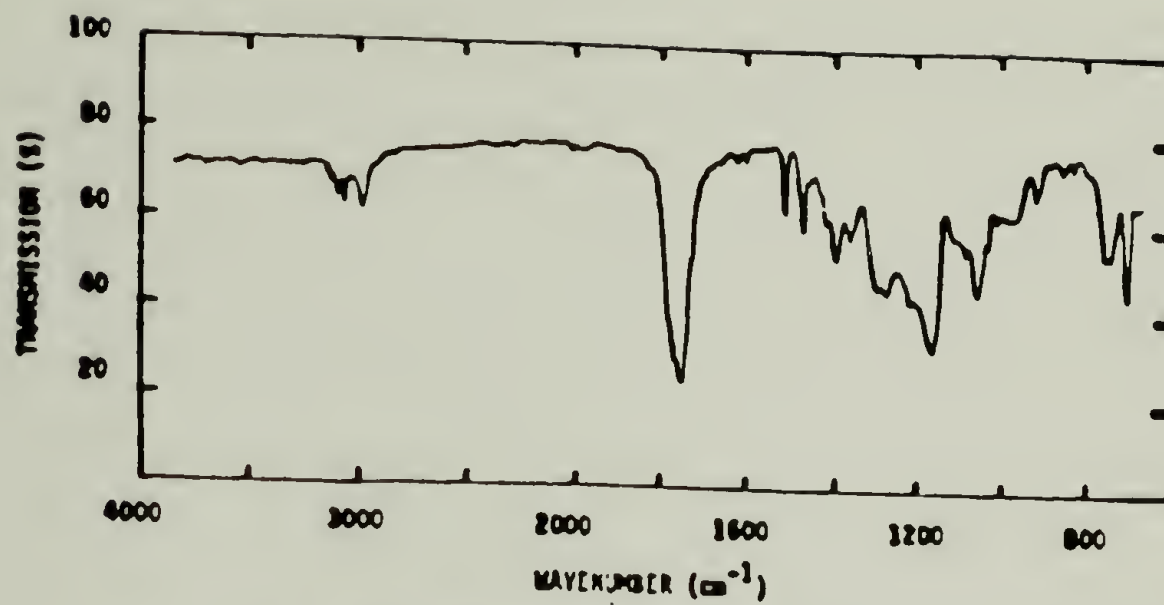
Infrared Spectra No. 26.
Thallium 2-methyl-2-propane
thiolate.



Infrared Spectra No. 27. Octadecyl trimethylsilyl sulfide.



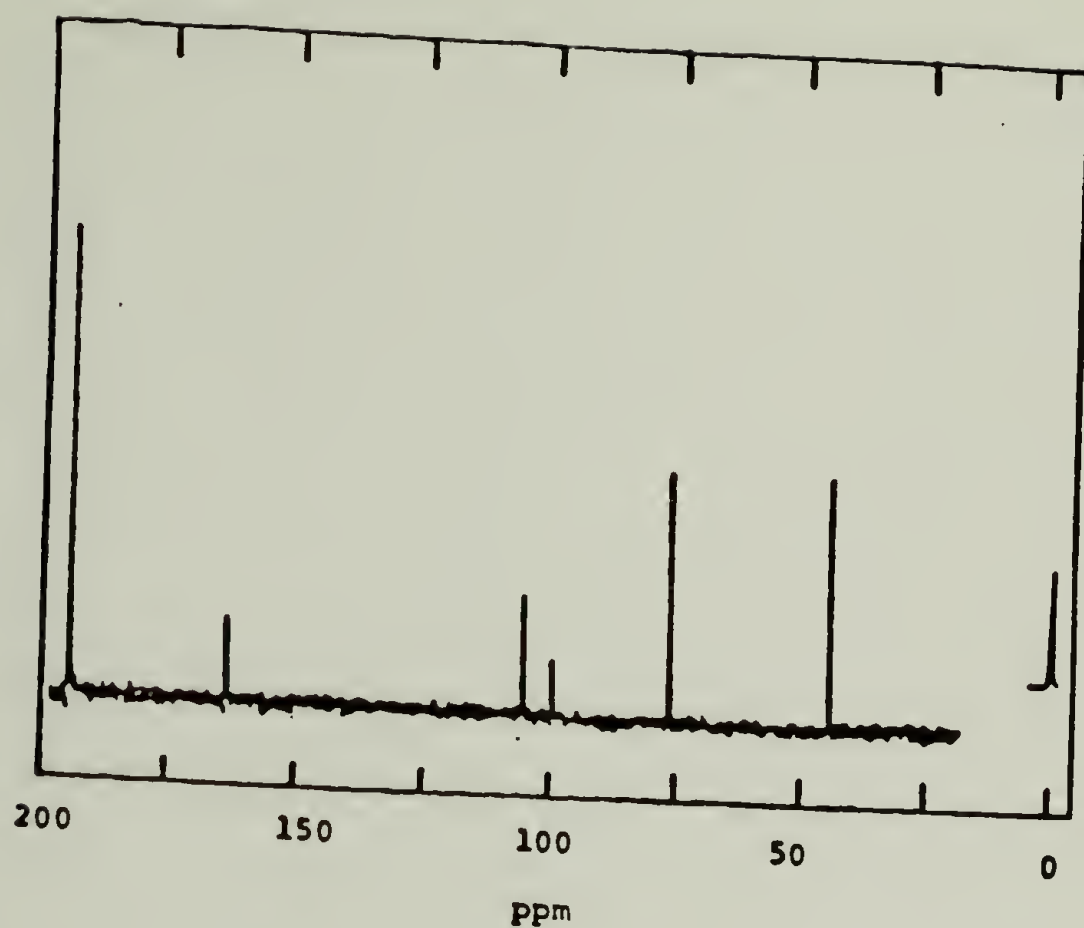
Infrared Spectra No. 28. Racemic poly(malolactone benzyl ester).



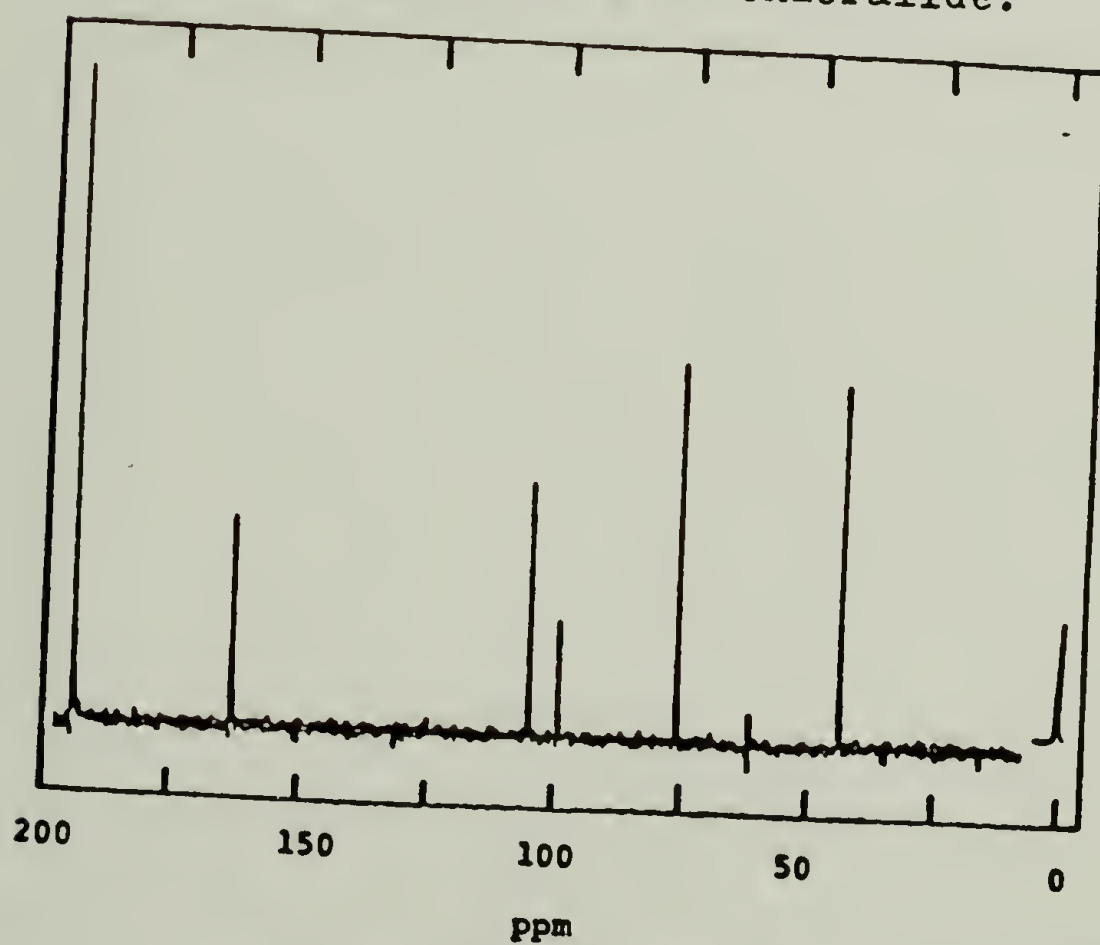
Infrared Spectra No. 29. Optically active poly(malolactone benzyl ester).

A P P E N D I X C

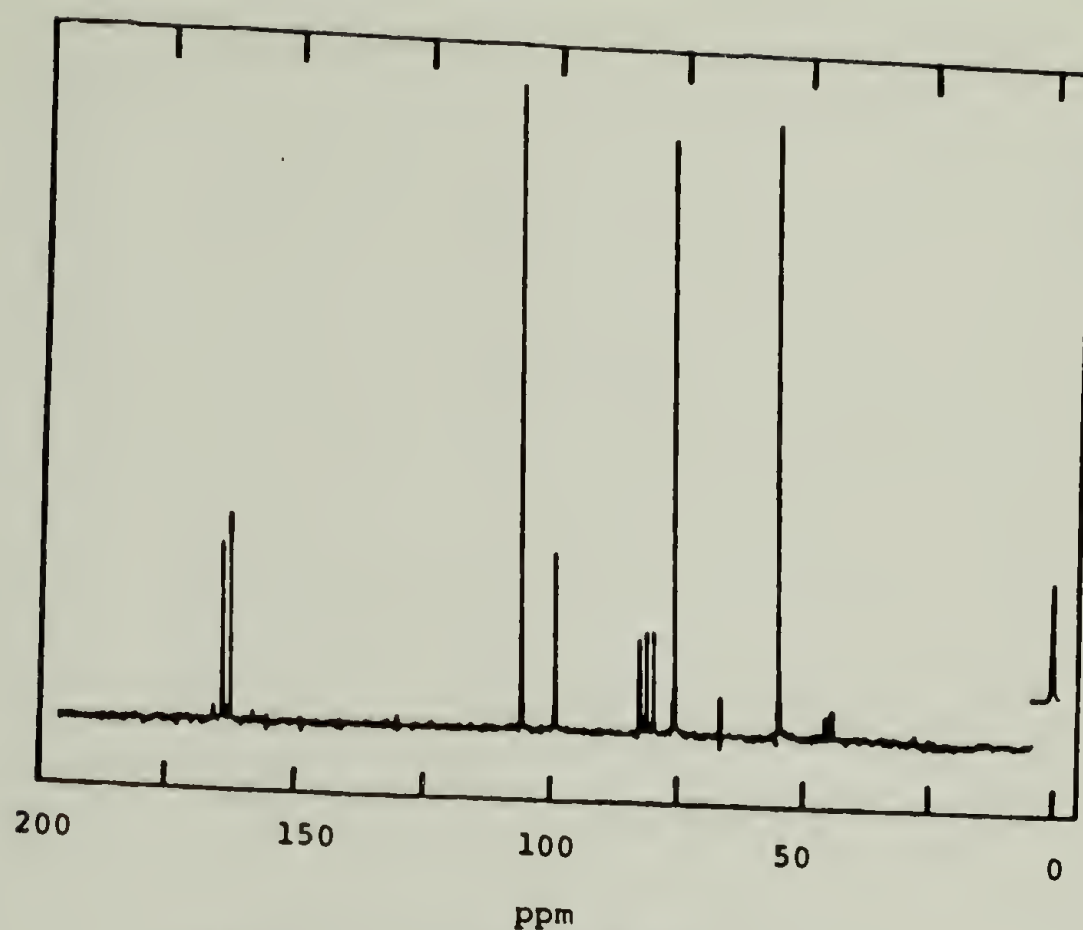
CARBON-13 MAGNETIC RESONANCE SPECTRA



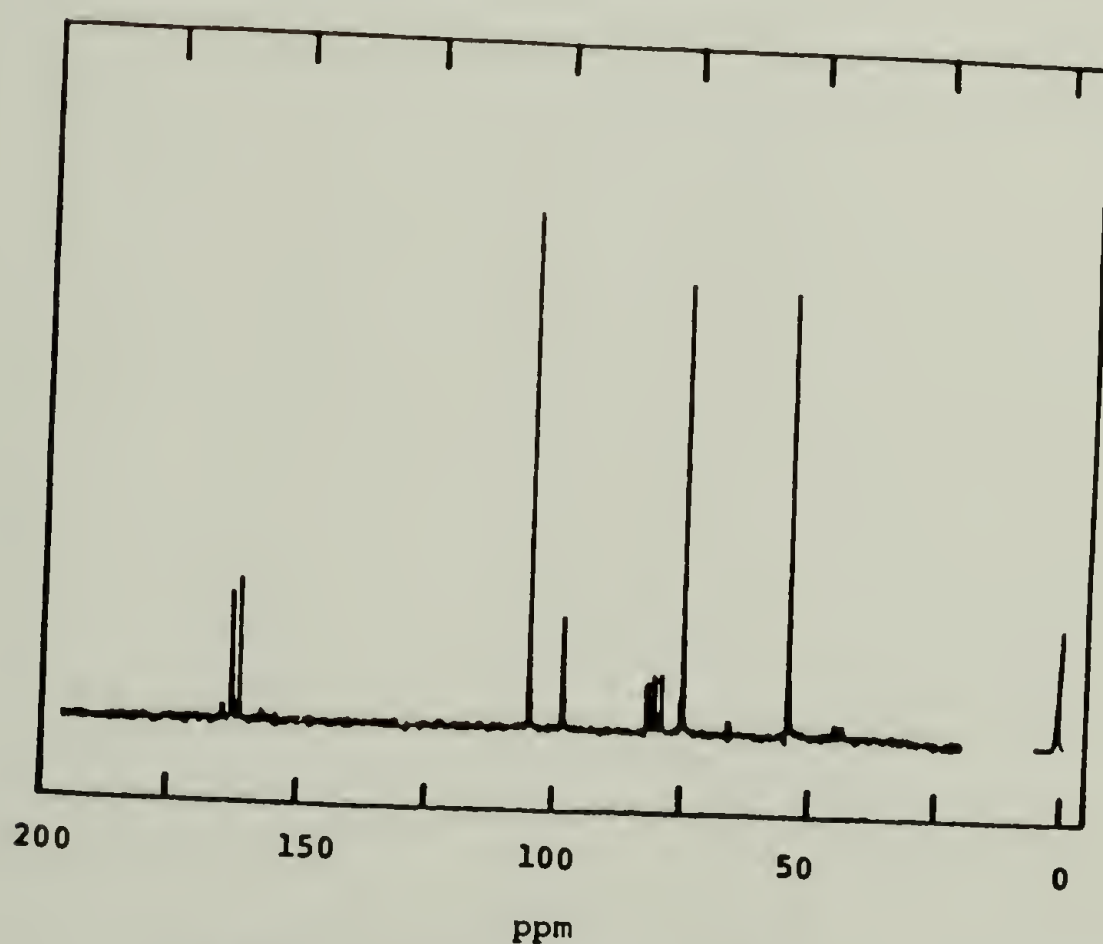
Carbon-13 NMR Spectra No. 1.
Racemic malic acid chloralide.



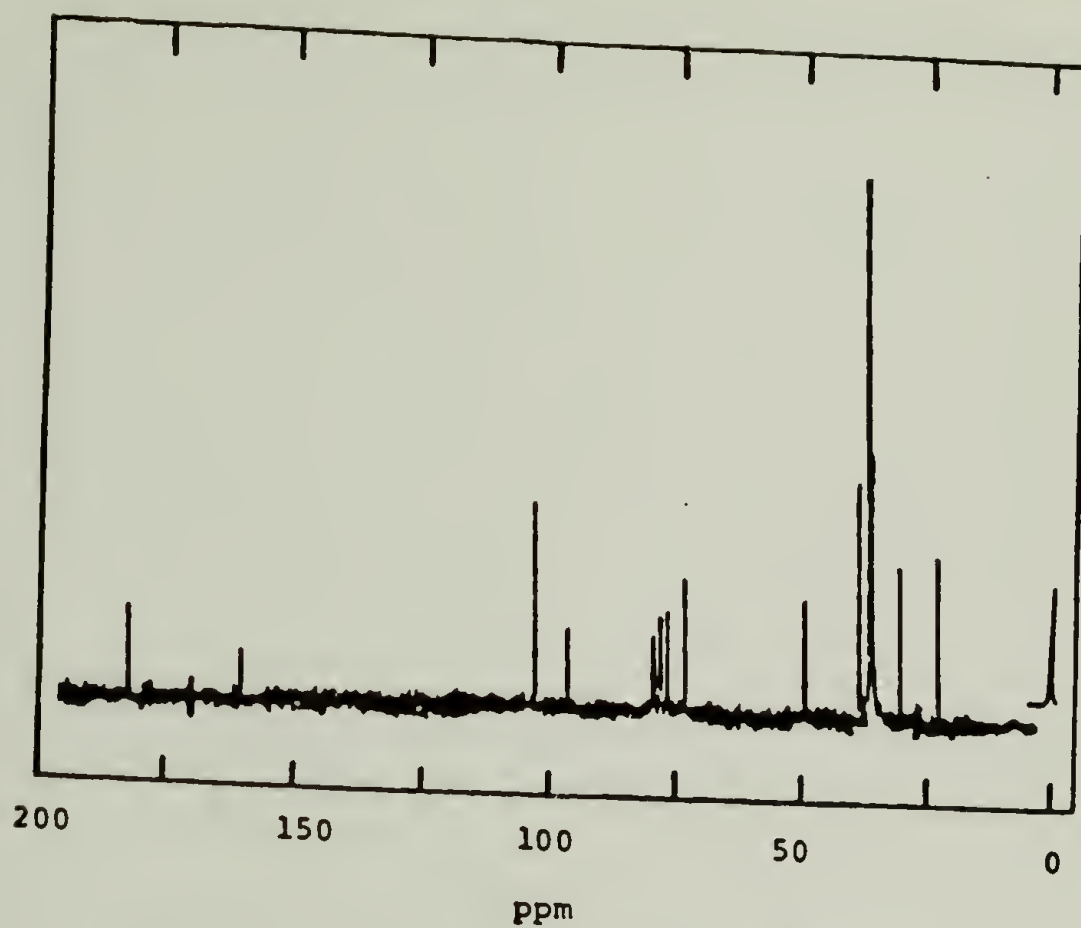
Carbon-13 NMR Spectra No. 2. Optically
active malic acid chloralide.



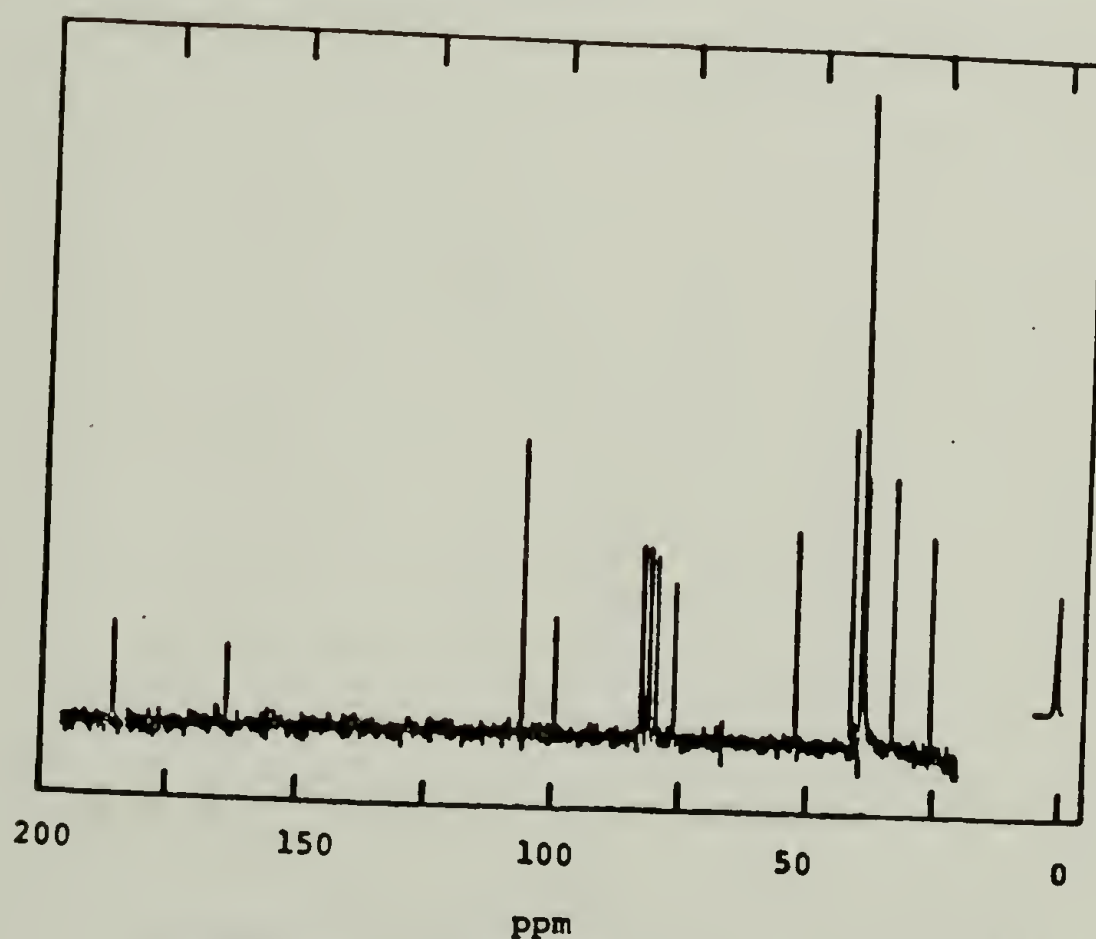
Carbon-13 NMR Spectra No. 3. Racemic
malic acid chloralide chloride.



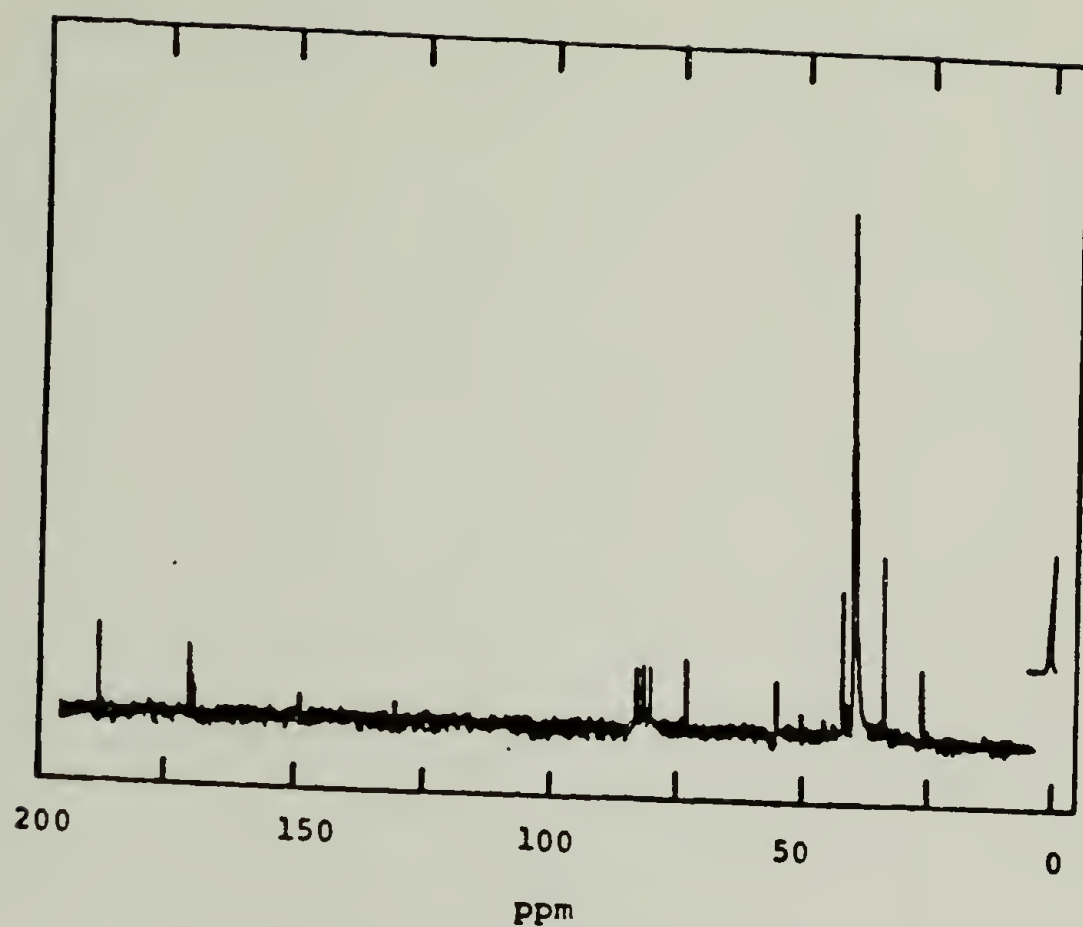
Carbon-13 NMR Spectra No. 4. Optically
active malic acid chloralide
chloride.



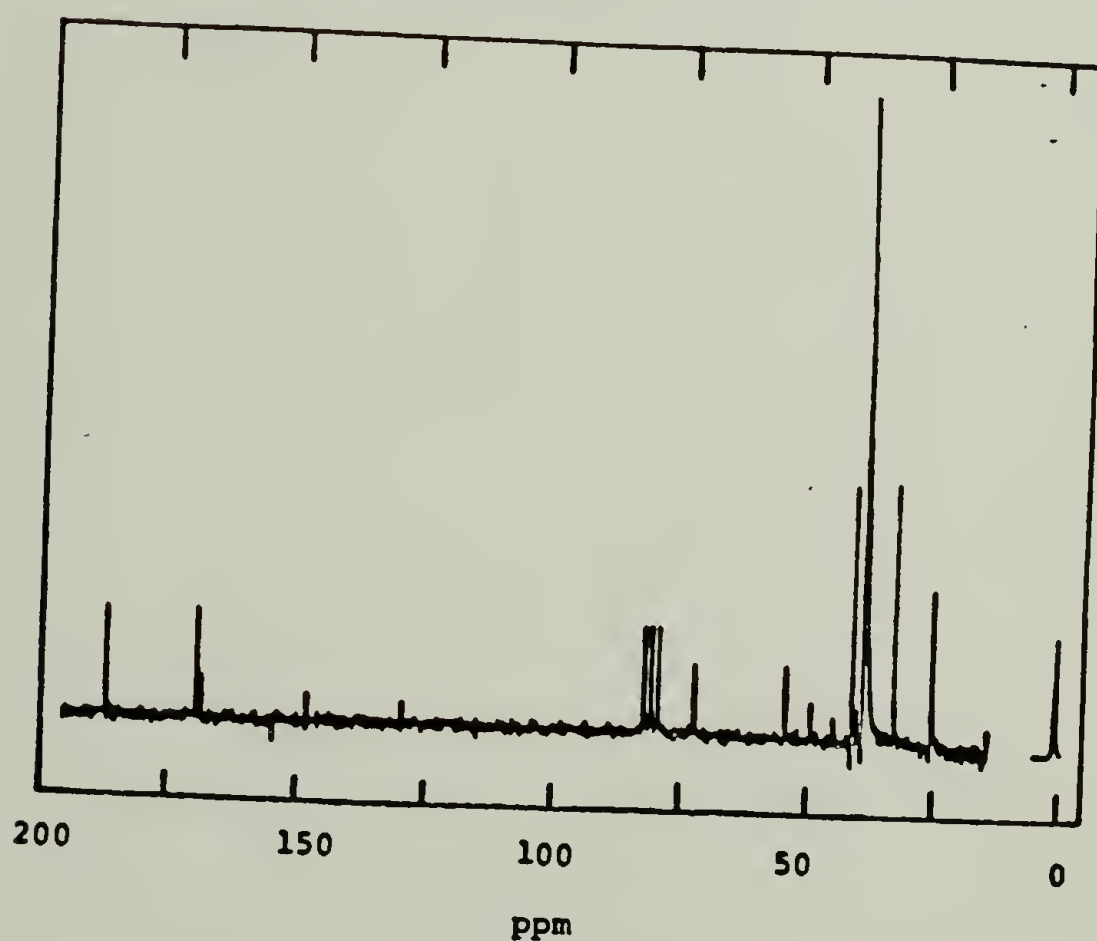
Carbon-13 Spectra No. 5. Racemic
S-(malic acid chloralide)
octadecylate.



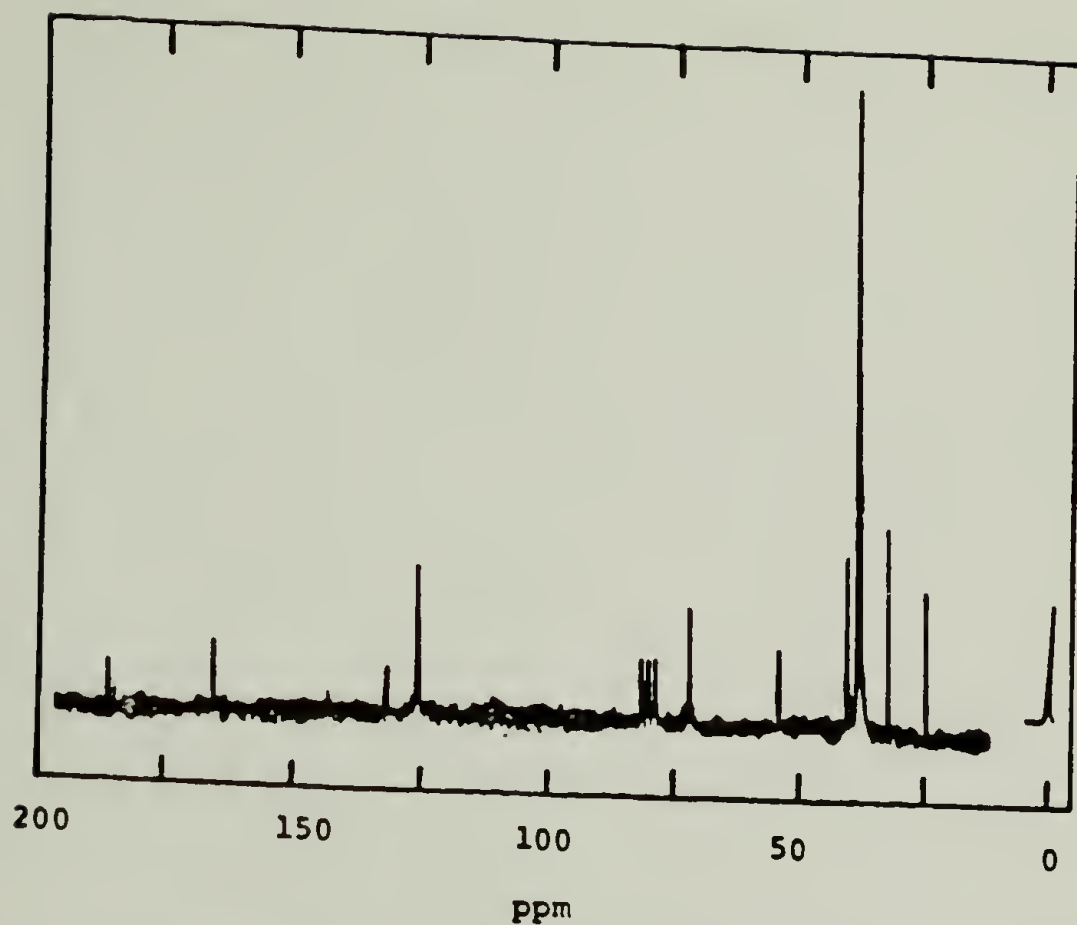
Carbon-13 Spectra No. 6. Optically
active S-(malic acid chloralide)
octadecylate.



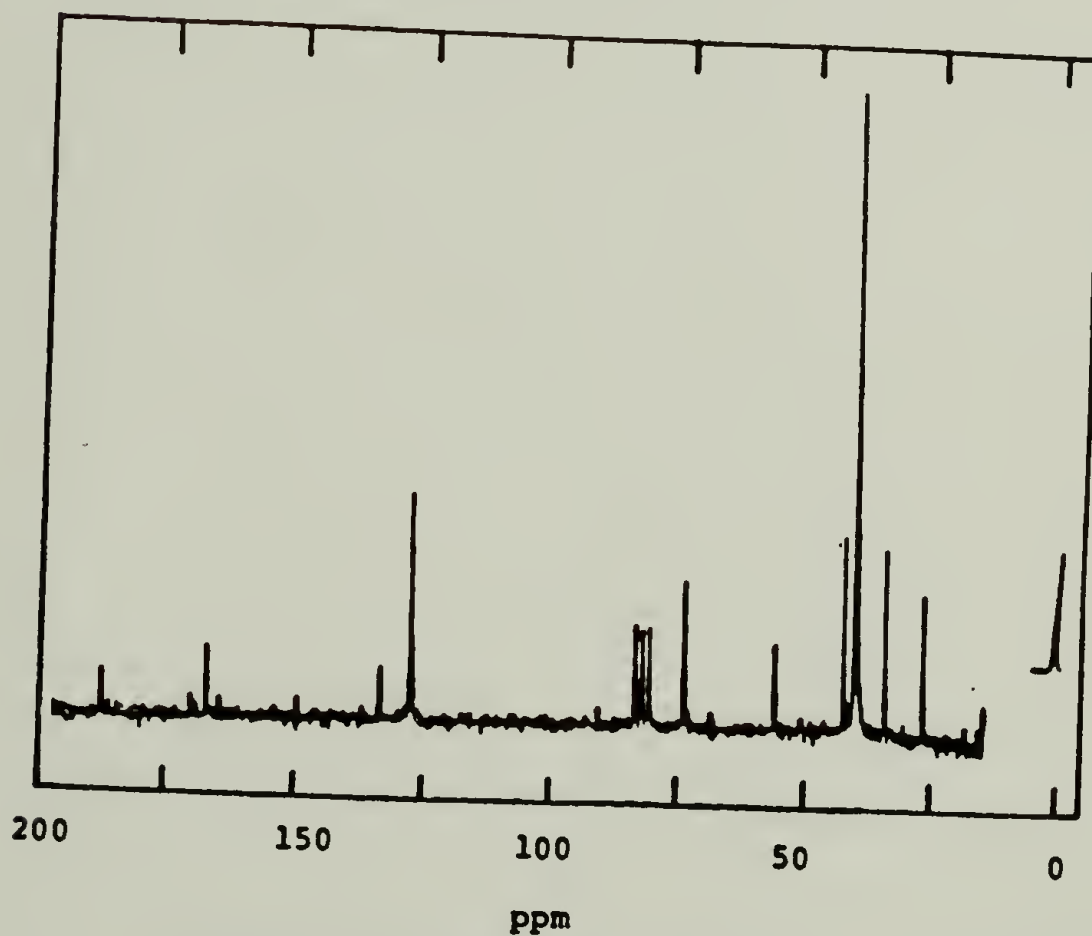
Carbon-13 NMR Spectra No. 7. Racemic
S-(beta-hydroxysuccinyl)
octadecylate.



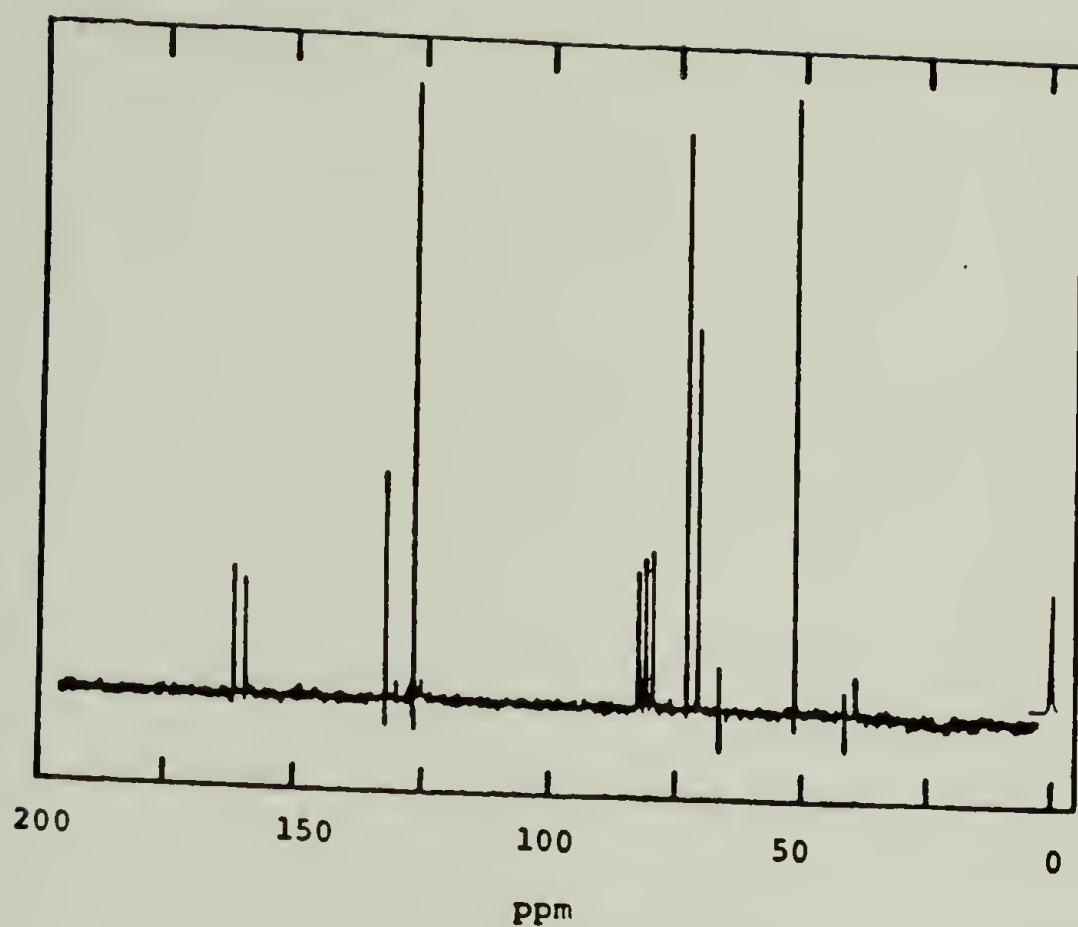
Carbon-13 NMR Spectra No. 8. Optically
active S-(beta-hydroxysuccinyl)
octadecylate.



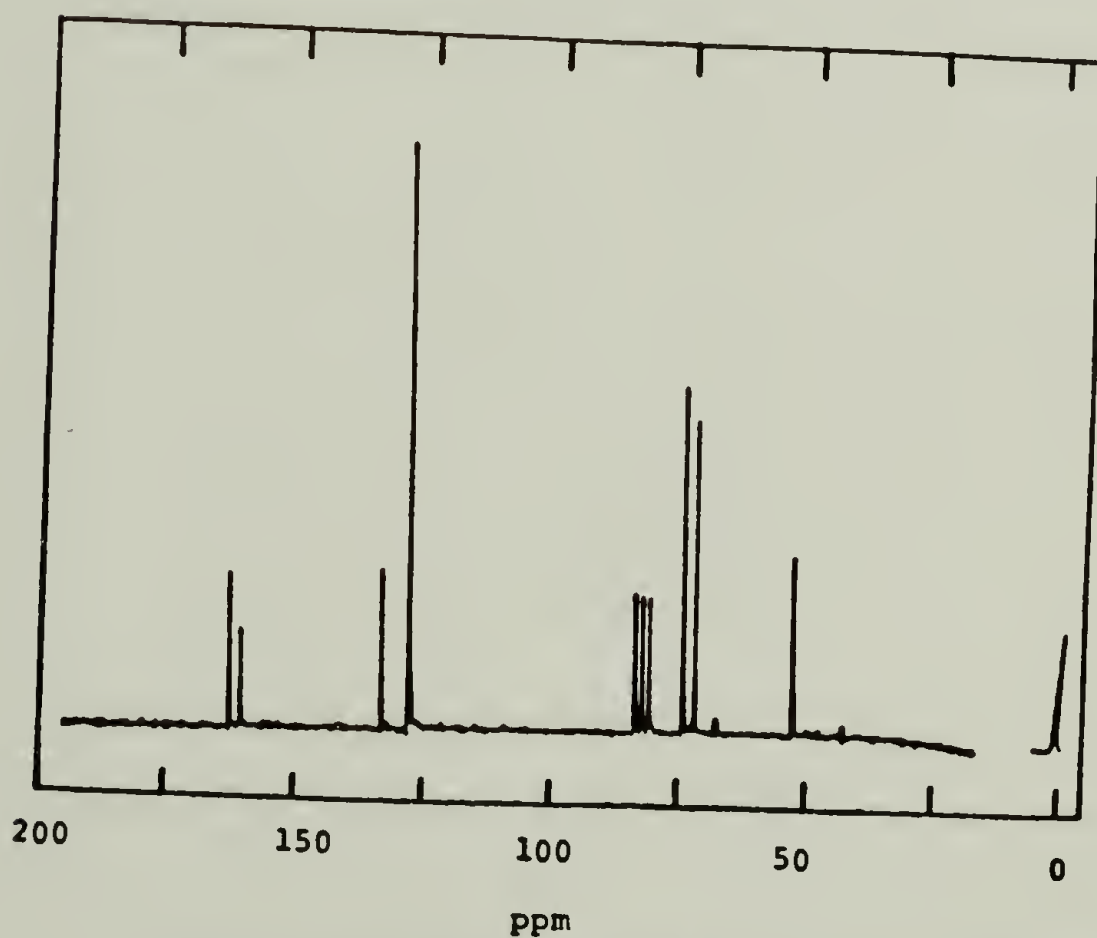
Carbon-13 NMR Spectra No. 9. Racemic S-(beta-hydroxysuccinyl benzyl ester) octadecylate.



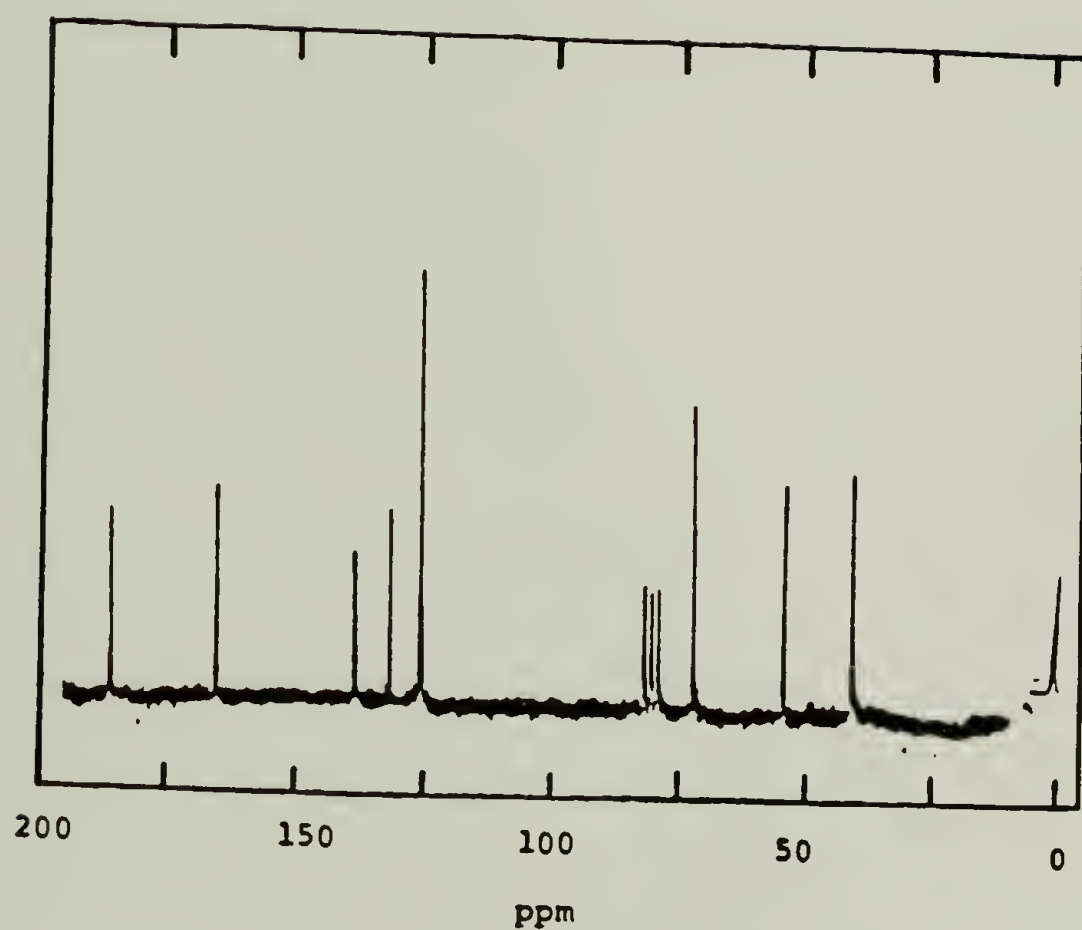
Carbon-13 NMR Spectra No. 10. Optically active S-(beta-hydroxysuccinyl benzyl ester) octadecylate.



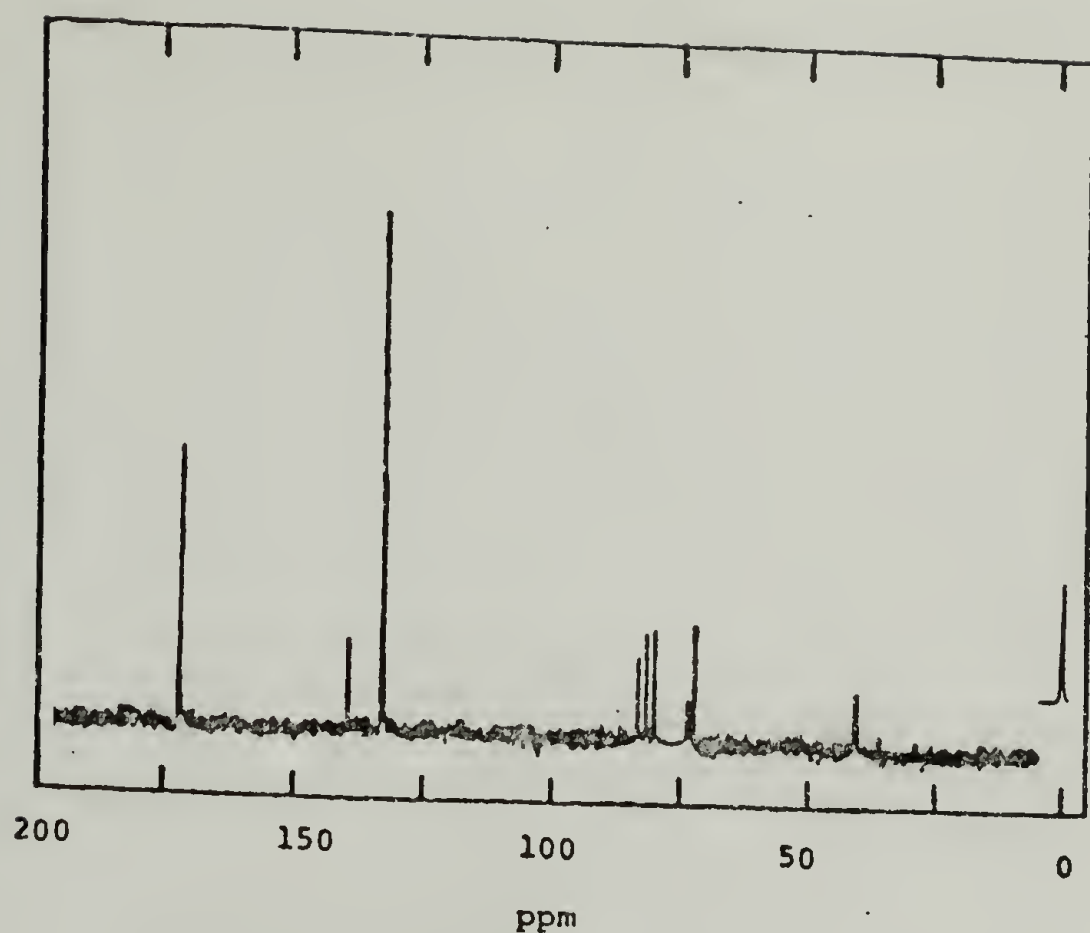
Carbon-13 NMR Spectra No. 11. Racemic malolactone benzyl ester.



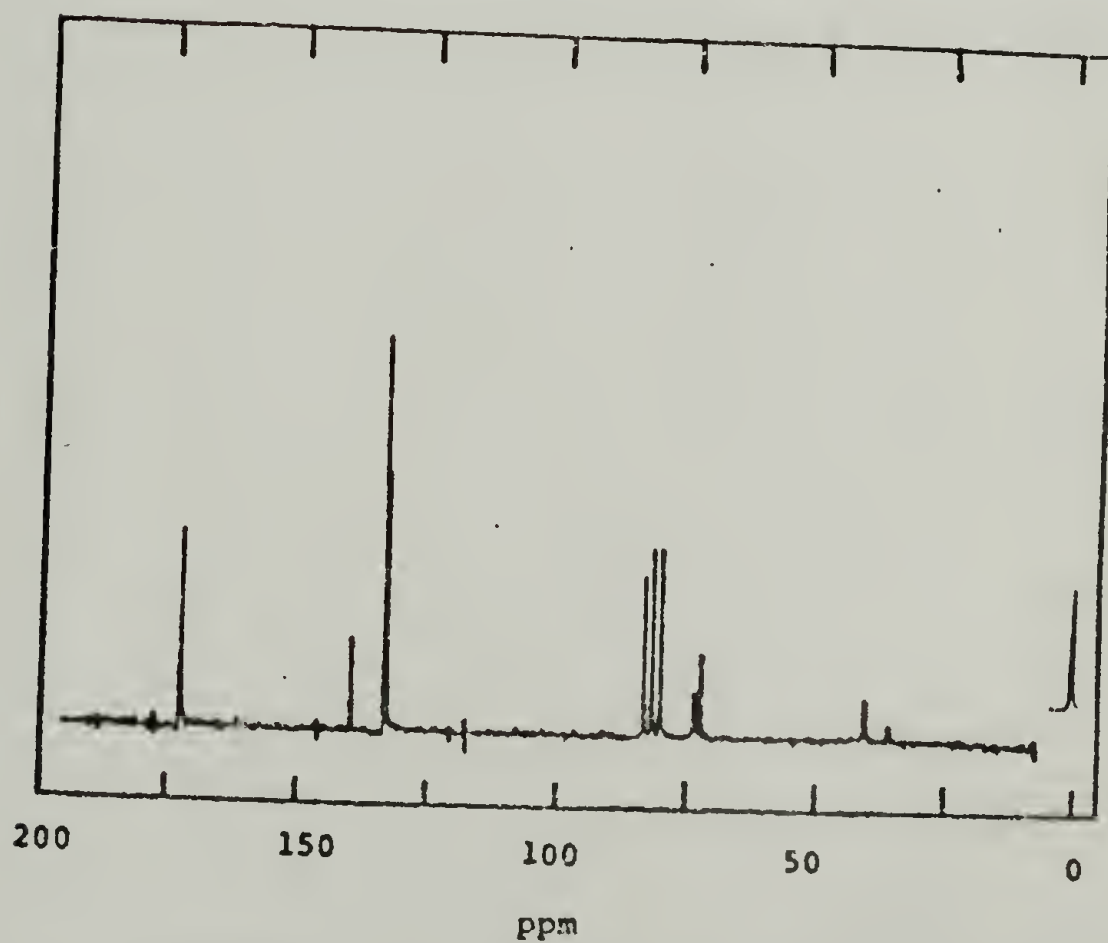
Carbon-13 NMR Spectra No. 12. Optically active malolactone benzyl ester.



Carbon-13 NMR Spectra No. 13.
Racemic S-(beta-hydroxysuccinyl
benzyl ester) phenylate.



Carbon-13 NMR Spectra No. 14. Racemic poly(malolactone benzyl ester).



Carbon-13 NMR Spectra No. 15. Optically active poly(malolactone benzyl ester).

