

**DETERMINATION OF THE RELATIVE
STEREOCHEMISTRY OF ADDUCTS RESULTING
FROM THE ADDITION LITHIUM DIENOLATES TO MICHAEL
ACCEPTORS**

by
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APPROVED:



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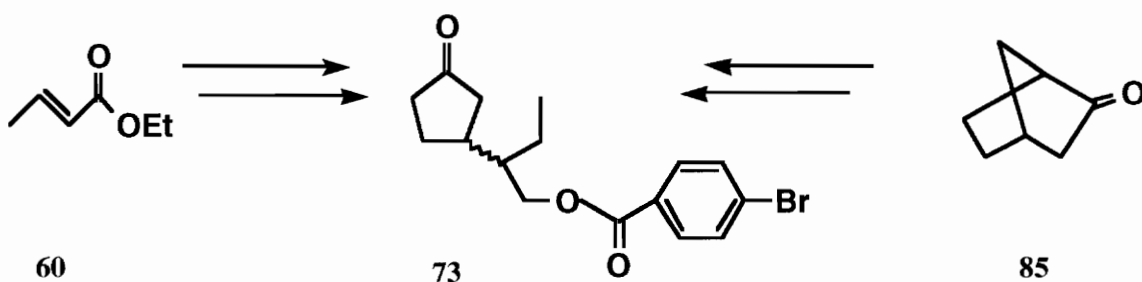
Sherita D. McLamore

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(ABSTRACT)

The addition of the lithium dienolate of ethyl crotonate to 2-cyclopentenone was studied to determine the stereochemical outcome of this Michael addition. Proof of the stereochemistry was provided *via* the unambiguous synthesis and comparison of ketone **73** from norcamphor **85**.



Acknowledgments

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To my wonderful parents with love.

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LIST OF ABBREVIATIONS

Ar	Aromatic
Bn	Benzyl
DMPU	Dimethyl-2-oxo-hexahydropyrimidine
E	Entgegen (across)
Et	Ethyl
GC	Gas Chromatography
HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
<i>i</i>-Pr	<i>iso</i> -Propyl
LAH	Lithium Aluminum Hydride
LDA	Lithium Diisopropylamide
<i>m</i>-CPBA	<i>meta</i> -Chloroperbenzoic Acid
Me	Methyl
NMR	Nuclear Magnetic Resonance
<i>p</i>	<i>para</i>
Ph	Phenyl
R	Alkyl Group
R	Rectus (right)
S	Sinister (left)
<i>t</i>-Bu	<i>tert</i> -Butyl
TBSCl	<i>tert</i> -Butyldimethylchlorosilane
THF	Tetrahydrofuran
TOCSY	Total Correlation Spectroscopy

- X** Halogen
- Z** Zusammen (together)

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LIST OF NAME REACTIONS

Baeyer Villager Reaction

Horner-Emmons Wittig Reaction

Jones Oxidation

Michael Reaction

Swern Oxidation

I. INTRODUCTION

One of the primary goals in contemporary synthetic organic chemistry has been the development of methodology for selective carbon-carbon bond formation. Today, however, the focus of research is not just on the formation of carbon-carbon bonds but on the stereoselective formation of carbon-carbon bonds. Various reactions have been developed to yield stereoselective carbon-carbon bond formation, for example: Diels-Alder, aldol, Reformatsky, and the Michael reactions.

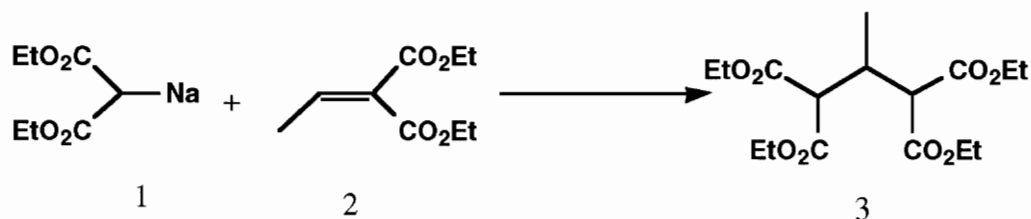
The Michael reaction in particular has proven to be an excellent synthetic tool for carbon-carbon bond formation. This reaction comprises the conjugate addition of active methylene compounds to α,β -unsaturated systems and has been the focus of several reviews.¹⁻⁹ Michael addition reactions have been viewed as vinylogous aldol additions, however, unlike the aldol reaction, Michael additions are not used extensively by nature in biosynthesis and thus are not widely used for natural product synthesis.⁷

The work herein focuses primarily on the stereochemical outcome of the addition of dienolate species to Michael acceptors, processes which are far less common than the aforementioned reactions.

II. HISTORICAL

II-1 General overview of Michael addition reactions

The nucleophilic addition of dienolate species to enones represents an important extension of the Michael reaction but has been the focus of only a few studies.¹⁰⁻¹¹ In its simplest form, the term Michael addition is used to specify the stereoselective addition of a nucleophile to a conjugated system in a 1,4 manner. This type of conjugate addition was initially reported by Claisen and Komnenos in 1883 who described the addition of diethyl sodiomalonate to diethyl ethylidenemalonate (Scheme 1).¹²



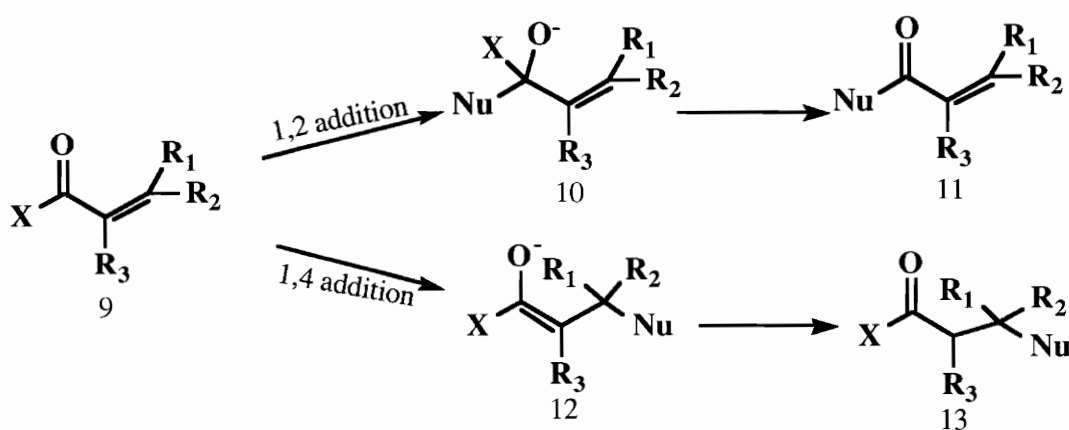
Scheme 1

Research in the area of conjugate additions began in 1887 with Michael's first paper which focused on the addition of the enolates of malonates and β -keto esters yields ethyl cinnamates (Scheme 2).¹³

Figure 2: Groups commonly attached to conjugate acceptors

Regiochemistry of Addition

The nature of the conjugate acceptor has proven to be an extremely important factor in conjugate addition reactions. Michael acceptors are considered ambident electrophiles and competing 1,2- and 1,4-addition of the nucleophilic species must be considered (Scheme 3).



Scheme 3

However one can, with a certain degree of confidence, predict the regiochemical outcome of the reaction. As one might expect, when X is a bulky group or an electron donating group, 1,4-addition is favored and when R₁ and/or R₂ are bulky groups 1,2- addition would be expected.

The nucleophilic enolate in the Michael reaction is appropriately called the donor. The first published Michael reaction utilized the sodium salt of malonates (scheme 1). With almost a century of development, many variations in this reaction necessitate that Michael donors be categorized into three groups:¹⁴

1. Carbanions stabilized by π -conjugation with one heteroatom (i.e. ketones, esters, amides, imines and nitro- / nitrile-stabilized carbanions)
2. Carbanions stabilized by π -conjugation with more than one heteroatom
3. Carbanions stabilized by one or more α -heteroatoms

Stereochemistry of Addition

Studies on the nucleophilic enolate species involved in the Michael reaction have been diverse. Heathcock and co-workers found that there exist a strong correlation between the geometry of the enolate species and the relative stereochemistry of the Michael adduct based of a chelated eight membered transition state as shown in figure 3.⁷ They concluded that the generation and use of *E* enolates leads to syn products while the generation and use of *Z* enolates leads to anti products when the R group is larger than ethyl.¹⁷ This concept is further illustrated by the data in table 1.⁷

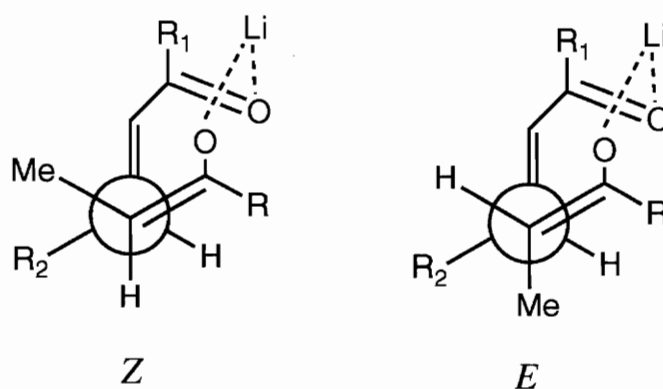
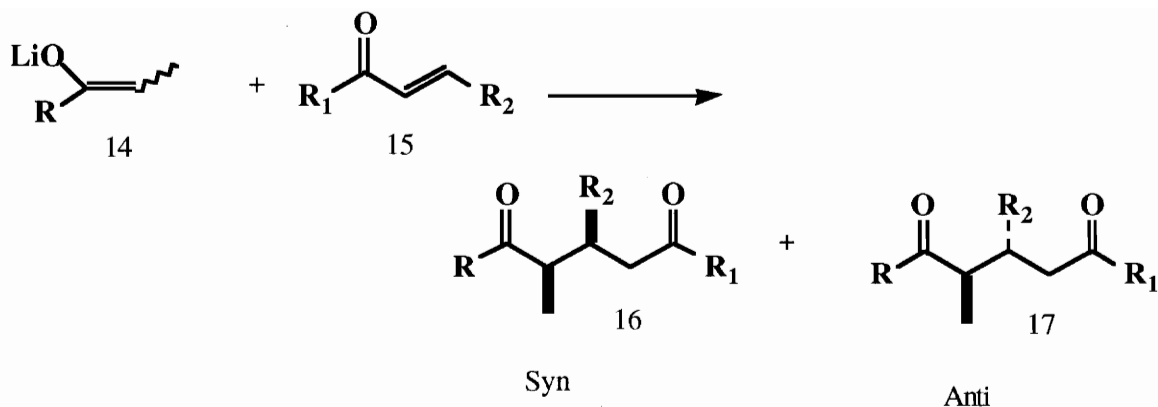


Figure 3: Transition state of the Michael reaction



Scheme 4

Table 1 (scheme 4): Generation and use of *E* enolates lead *syn* products while the generation and use of *Z* enolates lead to *anti* products.

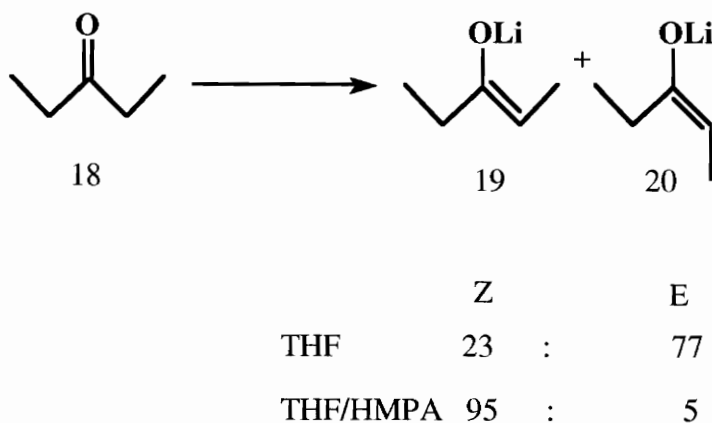
	<i>Enolate</i>		<i>Enone</i>			
	<u>R</u>	<u>E:Z</u>	<u>R₁</u>	<u>R₂</u>	<u>Solvent</u>	<u>Syn:Anti</u>
1	t-Bu	<1:99	t-Bu	Ph	THF	<1:99
2	Ph	2:98	t-Bu	Ph	THF	2:98
3	Ph	2:98	t-Bu	Ph	THF / HMPA	4:96
4	Ph	2:98	Me	Me	THF	<3:97
5	Ph	2:98	i-Pr	Me	THF	<3:97
6	Ph	2:98	-(CH ₂) ₃ -		THF	-----
7	i-Pr	4:96	t-Bu	Ph	THF	5:95
8	Et	15:85	t-Bu	Ph	THF	12:88
9	Ph	87:13	t-Bu	Ph	THF	83:17
10	i-Pr	90:10	t-Bu	Ph	THF	90:10
11	Et	81:19	t-Bu	Ph	THF	39:61
12	Et	81:19	t-Bu	Ph	THF / HMPA	68:32

The nomenclature for enolates follows the Cahn-Ingold-Prelog system developed for olefins; however, the anionic species "OM" is always highest priority.⁷

Enolate Chemistry

Selective methods of enolate anion generation have been found. For example, it has been concluded that bulky alkyl amides under tightly coordinating conditions (i.e. lithium counter ion and ethereal solvents) normally lead to higher percentages of *E* enolates while ketones with large groups that are α to the carbonyl yield exclusively or almost exclusively *Z* enolates.⁷ Finally, it was also concluded that *Z* enolates are favored when weaker bases are used under dissociating conditions.

Ireland's group found that the inclusion of hexamethylphosphoramide (HMPA) has a profound effect on enolate geometry.¹⁵ Apparently, the inclusion of HMPA leads predominately to the *Z* enolate while the exclusion of HMPA leads predominately to the *E* enolate (scheme 5)



Scheme 5

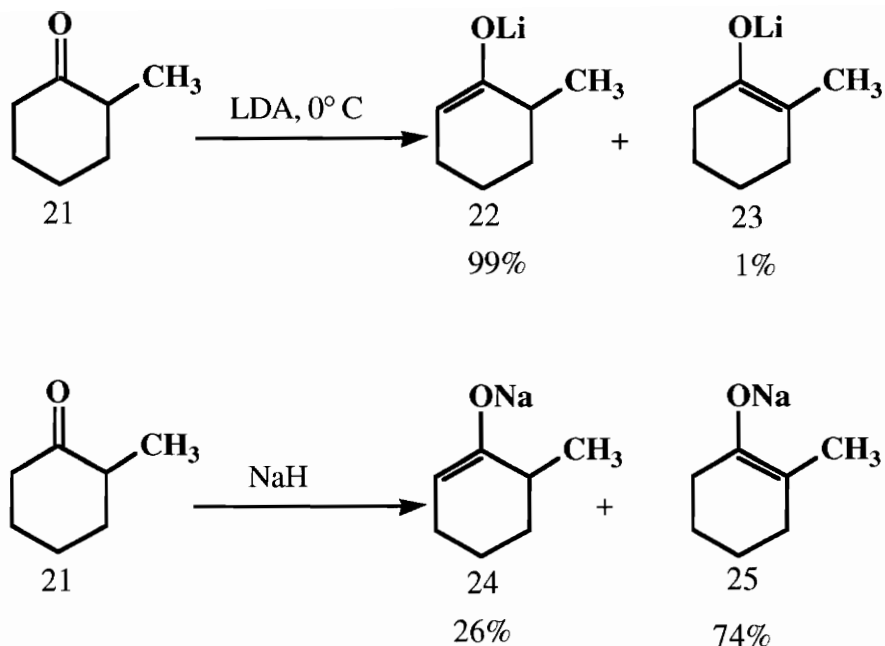
It is not clear exactly how HMPA reverses the selectivity of reactions; however, Ireland and co-workers have attributed this selectivity to the equilibration of the enolate to the more thermodynamically stable *Z* isomer because of a breakdown of enolate/solvent

aggregates. They indicated the importance of using a more hindered base and implied that it was beneficial to quench the enolate species during the reaction.¹⁶

Although HMPA has proven to be extremely useful in the area of selective enolate generation, it is a proven carcinogen in animals and poses serious risk to humans.¹⁷ It was suggested in a study by Mukhopadhyay and Seebach that the cyclic urea N,N'-dimethyl-2-oxo-hexahydropyrimidine (DMPU) is a suitable substitute for HMPA.¹⁷

In a more recent study by Ireland and co-workers, DMPU was used as a method of selectively generating enolates of ethyl propionate. The results of this study indicated that increasing amounts of DMPU led to as much as 93% *Z* isomer isolation.¹⁸

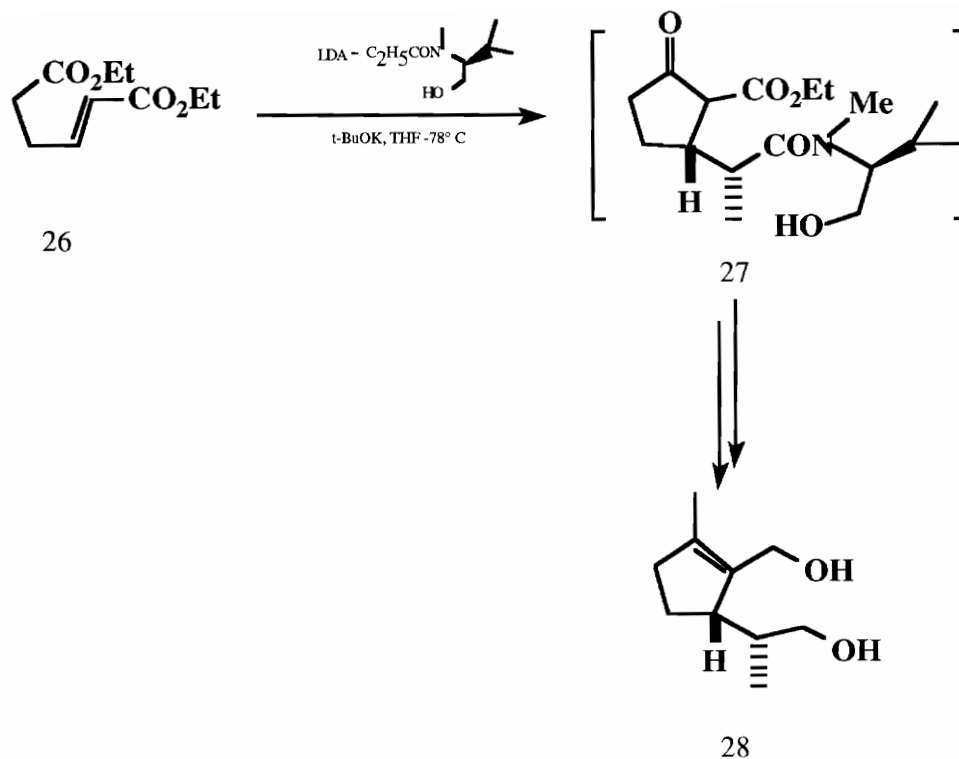
Finally, when considering enolate chemistry, one must consider the generation of the thermodynamic or kinetic enolate anions. The formation of these two isomers under varying conditions was studied in detail by House and co-workers.¹⁹ As exemplified with *i*-propyl methyl ketone, the kinetic enolate results from the abstraction of the less hindered methyl proton. When the more hindered methine proton is abstracted, a more thermodynamically stable enolate results. The ratio of these enolates depends on the reaction conditions. Strong bulky bases in aprotic solvents yield kinetic enolates while weaker bases in protic solvents yield thermodynamic enolates for example (scheme 6)



Scheme 6

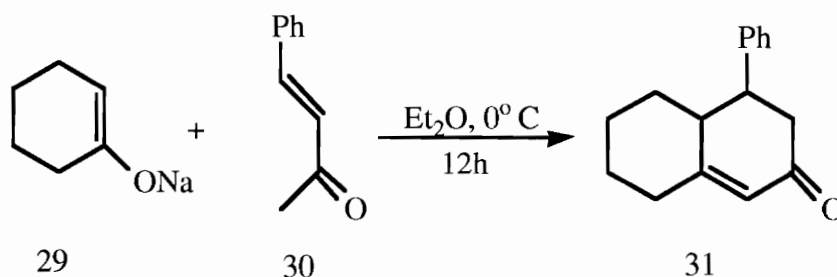
Applications of the Michael Reaction

A general scheme for the one-pot Michael reaction between enolate anions and enones is shown in scheme 5. A more specific example of the diastereoselectivity of the Michael reaction was provided by Yamaguchi and co-workers in their stereoselective synthesis of (+)-dehydroiridodio and (-)-isodehydroiridodio. Their synthesis involved the Michael addition of chiral amide enolates to α,β -unsaturated esters followed by a Dieckman condensation (scheme 7).²⁰



Scheme 7

The most recognized and widely used application of the Michael reaction is probably the Robinson annulation. This reaction is a two step process that combines Michael reaction with an internal aldol reaction. The first reaction of this type was reported by Robinson and Rapson in 1935 and involved the addition of 4-phenyl-3-buten-2-one to the enolate of cyclohexanone to produce octalone in one step (Scheme 8).²¹



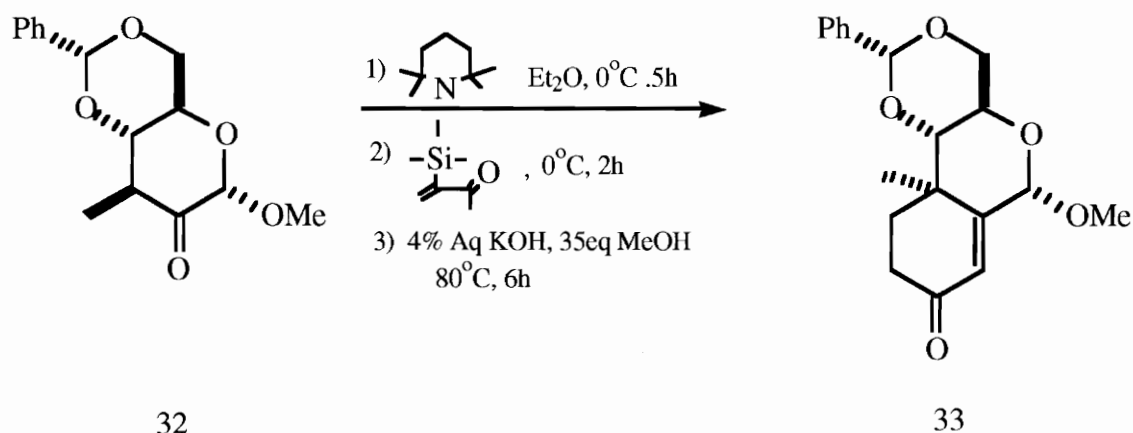
Scheme 8

Although not as common, researchers have found that aldehydic enolates also undergo Robinson annulations. For example, Cook and co-workers successfully synthesized 4,4-dimethyl cyclohexenone in approximately 35% yield from the addition of 2-methylpropanal to 3-buten-2-one.²²

The Robinson annulation is indeed an excellent synthetic tool but not without limitations. Some of the limitations of this reaction include:⁸

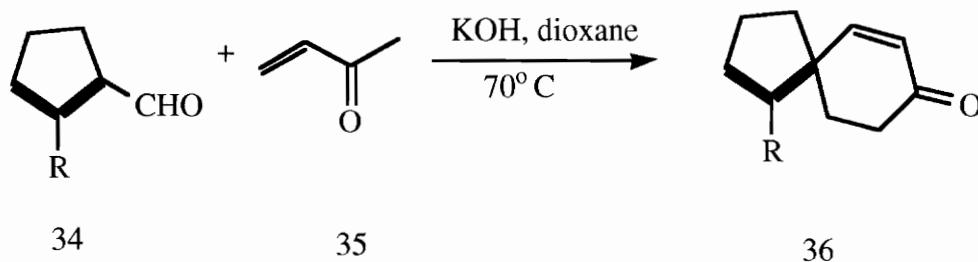
- (1) Selectivity of enolate formation
- (2) Michael addition /competing polymerization
- (3) Equilibration of the intermediate enolate
- (4) Ring closure
- (5) Dehydration

Polymerization is one of the major problems in the Robinson annulation. Stork and co-workers found a solution to this problem. In 1973, they introduced the use of α -silylalkenones in place of the standard alkenones (Scheme 9).²³ These silyl substituents have been found to stabilize the charge of the enolate. This stabilization enhances thermodynamic control and provide steric hindrance thereby minimizing 1,2- addition and slowing further addition of the enolate. Additionally, these groups are easily removed and react successfully under protic or aprotic conditions.



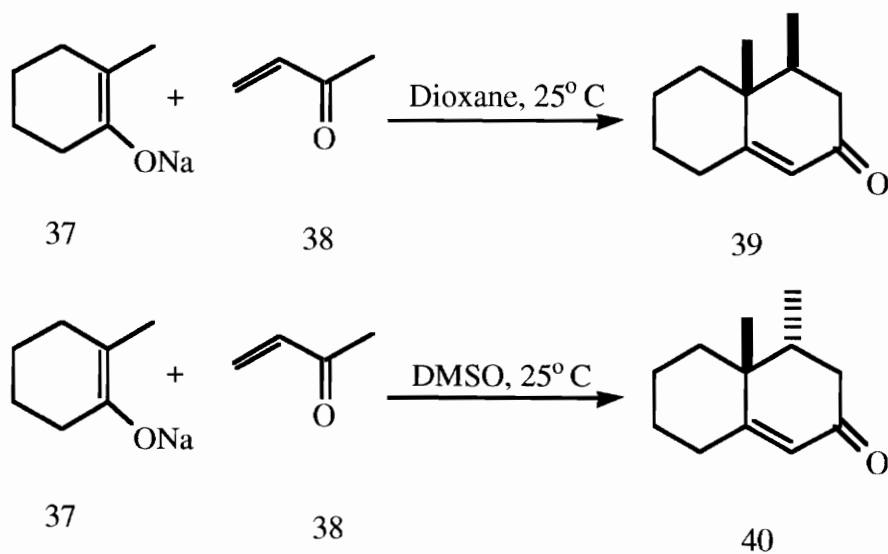
Scheme 9

Another application of the Robinson annulation was determined by Pesaro and co-workers in their synthesis of (-)-acorenone and (+)-acorenone B *via* a Robinson spiroannulation (Scheme 10).²⁴



Scheme 10

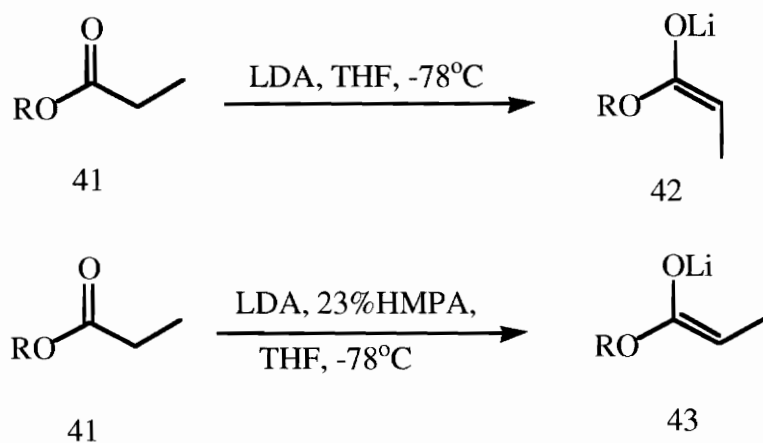
The problems associated with enolate formation in the Robinson annulation was addressed by Scanio and co-workers. These researchers were able to selectively produce in good yield either the *cis* or *trans* isomer by altering the solvent (Scheme 11).²⁵



Scheme 11

II-2. Michael additions of ester enolate anions and enones

Michael reactions involving ester enolate anions parallel the reactions involving ketones and aldehydes. Enolate geometry is crucial in these reactions as well. Ireland and co-workers have developed conditions which allows one to selectively generate either the *E* or *Z* enolate from an ester (scheme 12).²⁶ These results were established through the Claisen rearrangements of allyl esters. They concluded that deprotonation in THF with 23% HMPA yields the *Z* enolate while deprotonation in pure THF yields the *E* enolate. Both enolates were obtained in > 80% selectivity.



Scheme 12

Work by Ireland was later confirmed by x-ray analysis of the lithium enolate of *t*-butyl propionate obtained by Seebach.⁷ A cyclic transition state (figure 3) was proposed by Ireland to explain the stereochemical outcome of the LDA/THF reaction. Again, the exact role of HMPA remains debatable, however, to date, there is no other reliable method to generate *Z* ester enolates in absence of HMPA.

The correlation between ester enolate geometry parallels that of the aforementioned ketones and aldehyde and is further illustrated in Tables 2 and 3.⁷

Table 2 (Scheme 4): Generation and use of *E* ester enolates lead to *syn* products while generation and use of *Z* ester enolates lead to *anti* products.

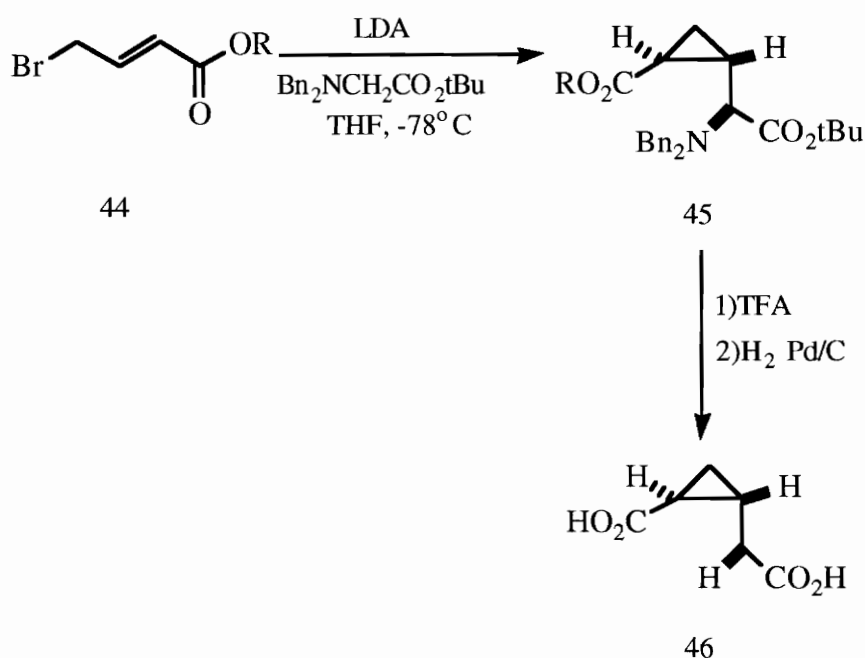
	<u>Ester Enolate</u>		<u>Enoate</u>			
	<u>R</u>	<u>R₁</u>	<u>E/Z</u>	<u>R₂</u>	<u>Solvent</u>	<u>Anti/Syn</u>
1	Et	Me	Z	Me	THF-Hexanes-HMPA	>95:5
2	Et	Me	<i>E</i>	Me	THF-Hexanes-HMPA	90:10
3	Et	Me	<i>E</i>	Me	THF-Hexanes	76:24
4	Et	Me	Z	n-C ₄ H ₉	THF-Hexanes-HMPA	>95:5
5	Et	Me	Z	n-C ₇ H ₁₅	THF-Hexanes-HMPA	>95:5
6	Et	Me	Z	Ph	THF-Hexanes-HMPA	94:6
7	Et	Me	Z	CO ₂ Et	THF-Hexanes-HMPA	74:26
8	Et	Et	Z	Me	THF-Hexanes-HMPA	>95:5
9	Et	Et	Z	n-C ₇ H ₁₅	THF-Hexanes-HMPA	>95:5
10	Et	Et	Z	Ph	THF-Hexanes-HMPA	>95:5
11	Et	Et	Z	CO ₂ Et	THF-Hexanes-HMPA	86:14
12	Et	n-C ₈ H ₁₇	Z	Me	THF-Hexanes-HMPA	>95:5
13	<i>t</i> -Bu	Me	<i>E</i>	Me	THF-Hexanes	<5:95
14	<i>t</i> -Bu	Me	<i>E</i>	n-C ₄ H ₉	THF-Hexanes	<5:95
15	<i>t</i> -Bu	Me	<i>E</i>	n-C ₇ H ₁₅	THF-Hexanes	<5:95

Table 3 (Scheme 4): Generation and use of *E* ester enolates lead to *syn* products while generation and use of *Z* ester enolates lead to *anti* products.

	<u>Enolate</u>		<u>Enone</u>			
	<u>R</u>	<u>E:Z</u>	<u>R₁</u>	<u>R₂</u>	<u>Solvent</u>	<u>Syn:Anti</u>
1	<i>t</i> -Bu	Z	<i>t</i> -Bu	Me	THF/HMPA	13:87
2	<i>t</i> -Bu	<i>E</i>	<i>t</i> -Bu	Me	THF	95:5
3	<i>t</i> -Bu	12:88	<i>t</i> -Bu	Et	THF/HMPA	5:95
4	<i>t</i> -Bu	11:89	<i>t</i> -Bu	Ph	THF/HMPA	7:93
5	<i>t</i> -Bu	95:5	<i>t</i> -Bu	Ph	THF/HMPA	94:6
6	<i>t</i> -Bu	Z	tris	Me	THF/HMPA	35:65
7	<i>t</i> -Bu	<i>E</i>	tris	Me	THF/HMPA	30:70
8	<i>t</i> -Bu	<i>E</i>	mes	Me	THF	>95:5
9	<i>t</i> -Bu	<i>E</i>	tris	Me	THF	95:5

With few exceptions, it has been concluded that *E* ester enolates generate exclusively *syn* product while *Z* ester enolates generate exclusively *anti* products.⁷

A more specific example of the usefulness of the diastereoselectivity of the Michael addition of ester enolates to enones was published by Yamaguchi and co-workers in their synthesis of (\pm)-CCG-II (Scheme 13).²⁷

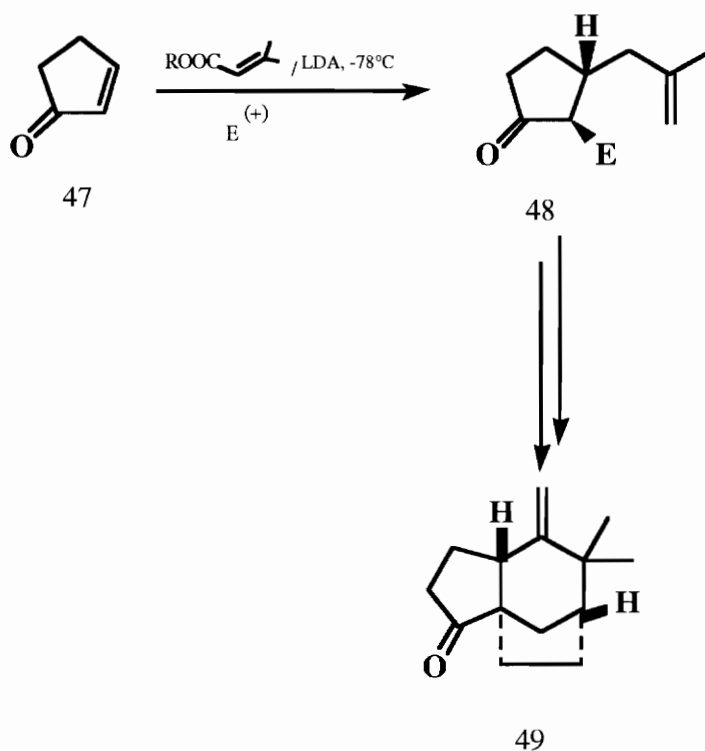


Scheme 13

Another example of the ester enolate addition was furnished by Stefanovsky and Viteva.²⁸ In an effort to prove the dependence of the kinetic diastereoselectivity of the Michael reaction on the reaction medium, Stefanovsky added ester enolates to *Z*-methyl cinnamate. They concluded that the geometry of the donor had a potent effect on the stereochemical outcome of the Michael adduct. Their conclusion was based on the eight membered transition state shown in figure 3.

II-3. Michael additions of ester dienolate anions to enones

As previously mentioned, Michael additions of dienolate anions to enones are far less common than the aforementioned reactions and have not been thoroughly studied. Research in this area was pioneered by Oppolzer and co-workers in their enantioselective synthesis of (-)-khusimone.¹⁰ Their synthesis utilized the Michael addition of the lithium dienolate of a chiral senecioate to 2-cyclopentenone (scheme 14). The stereochemistry of this Michael addition reaction was determined by X-ray crystallography and explained by the eight membered, chelated transition state shown in figure 4.



Scheme 14

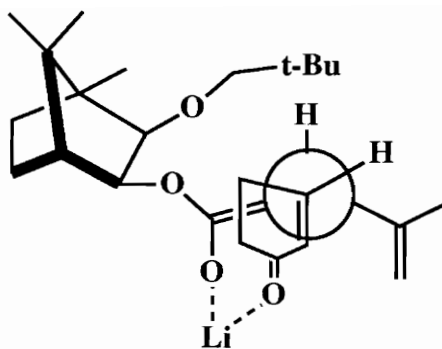
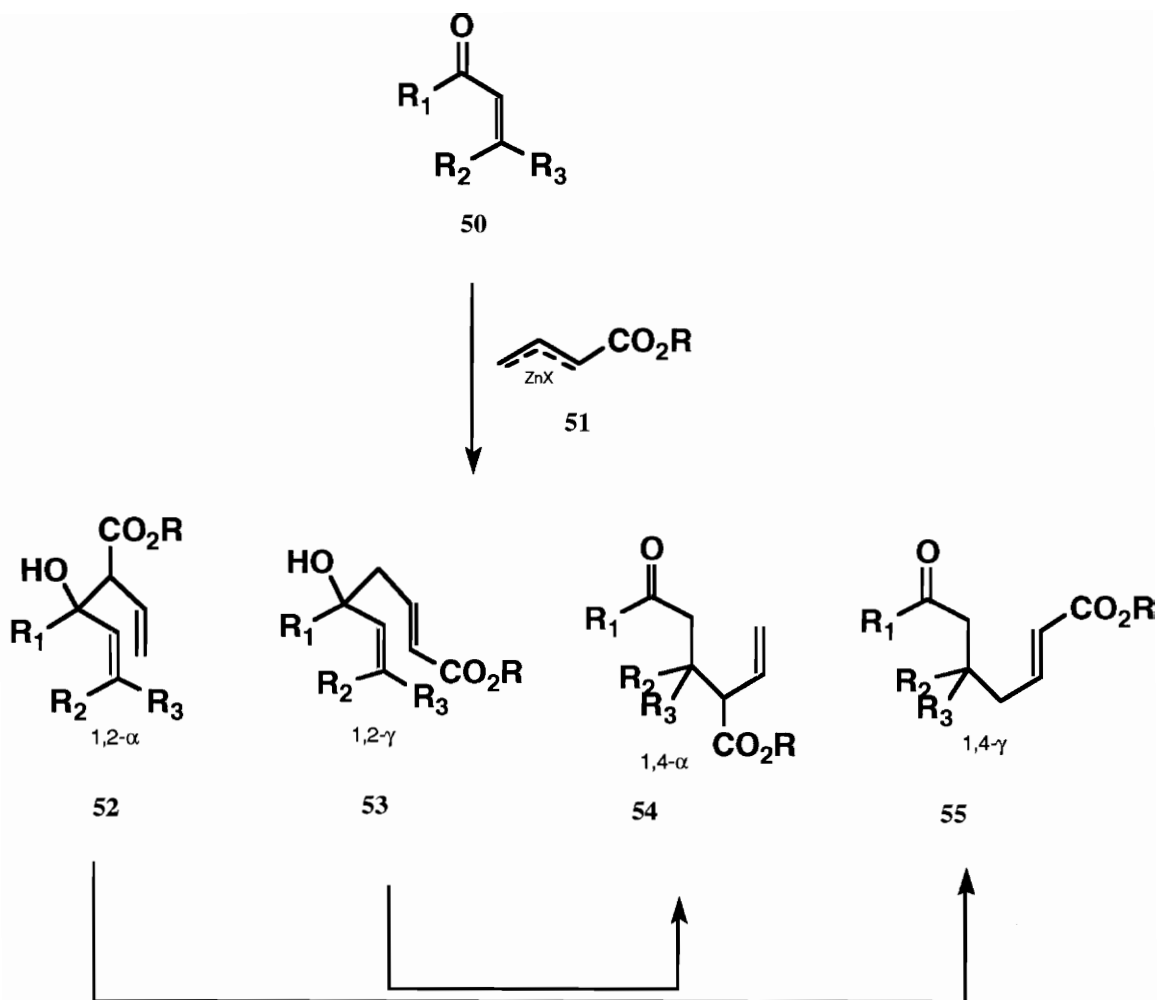


Figure 4: Proposed transition state for the Michael dienolate addition

Another study which related to dienolate additions was published by Hudlicky and co-workers in 1985.¹¹ Their research focused on the additions of vinylogous Reformatsky reagents to ambident electrophiles. In their study, nucleophilic organozinc derivatives of ethyl 4-bromocrotonate were added to a variety of α,β -unsaturated carbonyl compounds. The results of this research provided detailed information on the regiochemical outcome of these reactions which included experimental conditions that governed the regiochemical outcome (scheme 15). These researchers found that by varying the reaction conditions each of the four regioisomers became attainable. Additionally, data was obtained which enabled the researchers to gain insight on the mechanistic details of these reactions.



Scheme 15

$R = \text{ethyl}$; $R_1, R_2, R_3 = \text{CH}_3, \text{H}, \text{alkyl}$; $X = \text{Br}$

III. RESULTS and DISCUSSION

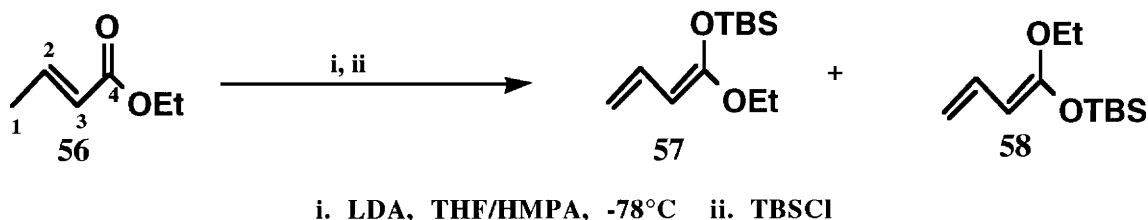
III-1 Introduction

As described in the historical (section II), the highly stereoselective Michael reaction has had a profound influence in modern synthetic organic chemistry. It should be clear why the stereoselective addition of an enolate to an α,β -unsaturated system is a useful tool for the organic chemist. As previously mentioned, Heathcock has shown that the geometry of simple ester enolates determines the stereochemistry of the Michael adducts. The stereoselective addition of a dienolate to an α,β -unsaturated system would provide a useful extension of this method. The aforementioned consideration combined with the lack of research in the area of dienolates incited our investigation. Thus, our research focused on the determination of the stereochemical outcome of the addition of lithium dienolate of ethyl crotonate **56** to the Michael acceptor, 2-cyclopentenone.

III-2 Determination of the enolate geometry for the lithium dienolate derived from ethyl crotonate

The lithium dienolate of ethyl crotonate was generated by the addition of ethyl crotonate to a solution of LDA in THF and HMPA at -78°C . The resultant dienolate anion was quenched with *t*-butyldimethylsilyl chloride at -78°C and the products were analyzed by ^1H NMR. Integration of the O-methylene protons indicated that the product was a 9:1 mixture of two isomers, **57** and **58** (scheme 16). At this point we deemed it crucial to determine the geometry of the major isomer. Our assignment of the enolate geometry from reactions run in the presence of HMPA was therefore based on previous nOe difference experiments studies of silyl enol ether **57** (scheme 16) by Barbieri-Arhancet.²⁹ This study found a 12% enhancement on the proton attached to carbon 3 upon irradiation of the O-methylene group of the major isomer. From this, it was concluded that the

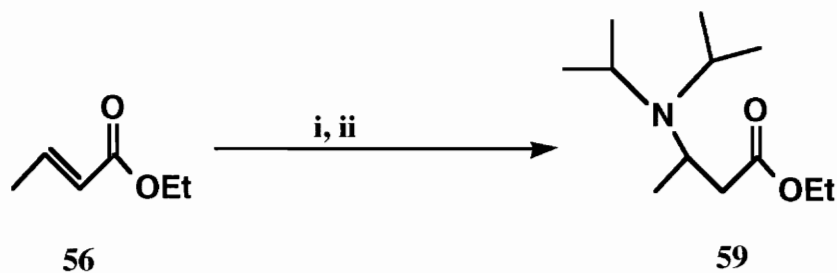
geometry of the major isomer was *Z*. This results were in concurrence with those obtained by Hertler and co-workers.³⁰



Scheme 16

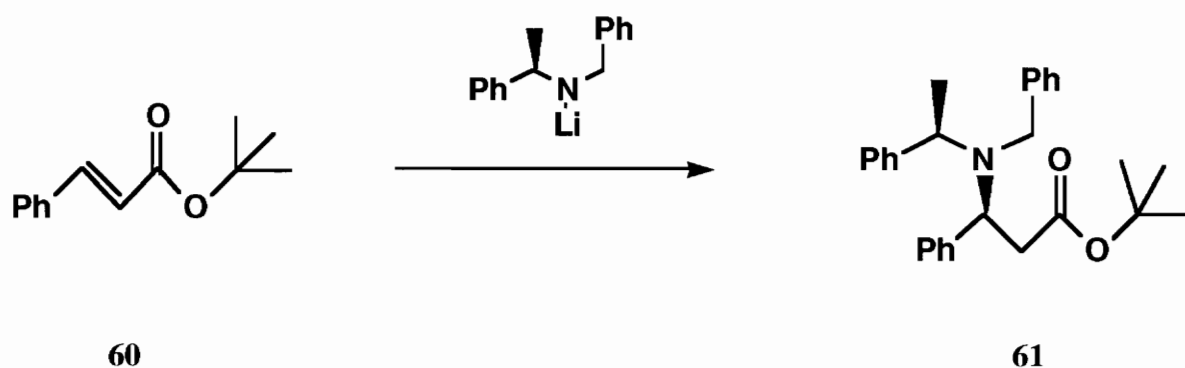
In an effort to maximize the formation of either one of the isomers, other reaction conditions were examined. Literature precedent suggests that the inclusion of a greater volume of HMPA (v/v 23%) enhances the selectivity of the enolate geometry.³¹ We found no substantial change in the *Z* to *E* enolate ratio upon the inclusion of additional HMPA. The aforementioned reaction (scheme 16) was also repeated substituting DMPU for HMPA (as mentioned in section II-1, DMPU was found to be a HMPA substitute) We found that this HMPA substitute gave very similar results (*i.e.* *Z/E* = 7/1) under the same reaction conditions.

In an attempt to generate the *E* isomer as the major product, the deprotonation was repeated without HMPA (scheme 17). In contrast to the HMPA containing reaction (scheme 16), this reaction produced adduct **59** *via* the 1,4 addition of lithium diisopropylamine to ethyl crotonate. Although we were surprised by this result, we found that it was not unprecedented. Davis and co-workers published similar results in their asymmetric synthesis of phenylisoserine derivatives for the Taxol C-13 side chain (scheme 18).³²



i. LDA, THF, -78°C , ii. TBSCl

Scheme 17



Scheme 18

Other attempts to generate the *E* isomer exclusively, which included the use of a variety of bases (i.e. triethylamine, sodium bis(trimethylsilyl)amide, etc.), were all unsuccessful. In most cases, only unreacted started material was isolated.

The results of these dienolate studies are summarized in table 4.

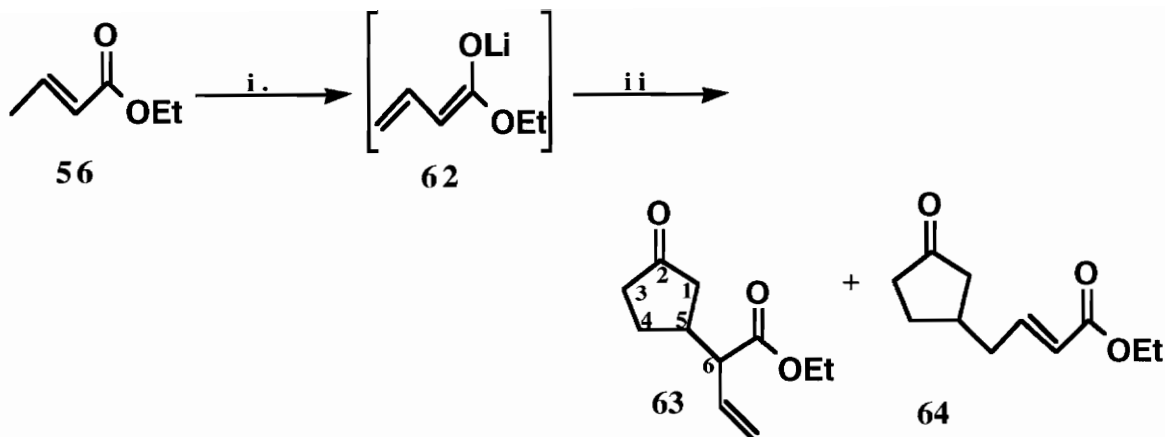
Table 4: Summary of dienolate studies

Reaction Conditions	Z : E Ratio
THF, 1 eqv. HMPA, -78° C	9:1
THF, 23% HMPA (v/v), -78° C	9:1
THF, 1 eqv. DMPU, -78° C	7:1
THF, -78° C	no E or Z products isolated

The determination of the ratio and geometry of our dienolate species was a small but crucial task in our research. As previously mentioned, we concluded that the two dienolates were isolated in a 9:1 ratio with the *Z* isomer being the major product. Our next task was to carry out the addition of this nucleophilic dienolate species **62** to our selected enone which is described in the next section.

III-3 Additions of dienolate anions to 2-cyclopentenone

With the stereochemistry of the dienolate species established, our attention focused on the addition of such species to 2-cyclopentenone. 2-Cyclopentenone was added to a performed solution of the lithium dienolate of ethyl crotonate in THF at -78° C. This reaction was quenched at -78° C with NH₄Cl and extracted with diethyl ether. The combined organic extracts were concentrated under reduced pressure giving an 8:1 mixture of two ketones, the α -1,4 adduct **63** and the γ -1,4 isomer **64** respectively (scheme 19) in quantitative yield.



Scheme 19

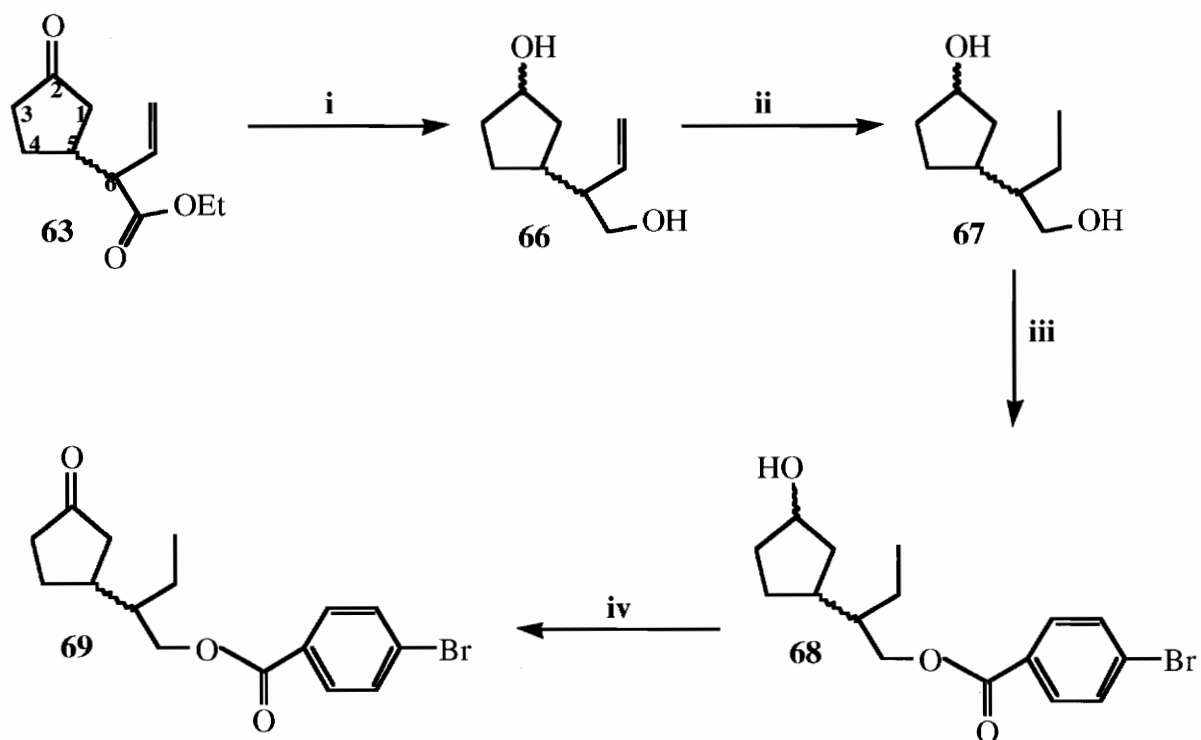
III-4 Determination of the relative stereochemistry of Michael adducts

Having successfully prepared Michael adduct **63**, our next task was to determine the relative stereochemical relationship between the protons attached to carbons 5 and 6 of ketone **63** (scheme 19). Unfortunately, one major problem associated with studying the stereoselectivity of Michael addition reactions is the determination of the configuration of the product(s). To date structural assignment relies on X-ray crystallography, chemical interconversion or conversion to known compounds.

Our first attempt to ascertain the stereochemical relationship between the protons of interest involved the synthesis of a crystalline derivative of the Michael suitable for X-ray analysis. Literature precedent has shown that *p*-bromobenzoate derivatives are often crystalline and suitable for X-ray analysis. With this in mind, we decided to make bromobenzoate **69** as described in the next section (scheme 20).

The synthesis of benzoate **69** began with the LiAlH₄ reduction of the crude Michael adduct **63** in THF to give diol **66**. The Michael adduct was used in its crude form in an effort to prevent epimerization of the proton attached to carbon 6 which is very acidic being both allylic and α to an ester. The olefin was smoothly hydrogenated in ethyl acetate in the presence of a palladium catalyst yielding the fully saturated diol **66**. Treatment of the diol with 1.1 equivalents of sodium hydride followed by the addition of 1 equivalent of *p*-bromobenzoylchloride gave the protected alcohol **68**. The reduction of adduct **63** resulted in an unwanted, asymmetric center at carbon 2. In order to remove this stereocenter, the secondary alcohol was oxidized to the corresponding ketone with the Jones reagent to give the desired bromobenzoate **69** (scheme 20).

Unfortunately after careful purification bromobenzoate **69** remained an oil and no suitable crystals were obtained. Extensive characterization of this compound indicated that we had actually isolated a mixture of the two diastereomers of bromobenzoate **69** (ratio: 9:1 by GC; *ca.* 4:1 by HPLC and *ca.* 4:1 by ¹H NMR).



**i. LAH, THF, ii. H₂/Pd, EtOAc, iii. NaH, *p*-Bromobenzoyl chloride, CH₂Cl₂
iv. Jones reagent (CrO₃/ H₂SO₄)**

Scheme 20

Surprised by this result, we examined its relevance. If the addition of dienolates to Michael acceptors is stereoselective, then in our study, we would have expected the 9:1 mixture of dienolates **57** and **58** to translate into a 9:1 mixture of diastereoisomers. At this stage, one would be tempted to conclude that the addition of the dienolate of ethyl crotonate to 2-cyclopentenone is not stereoselective.

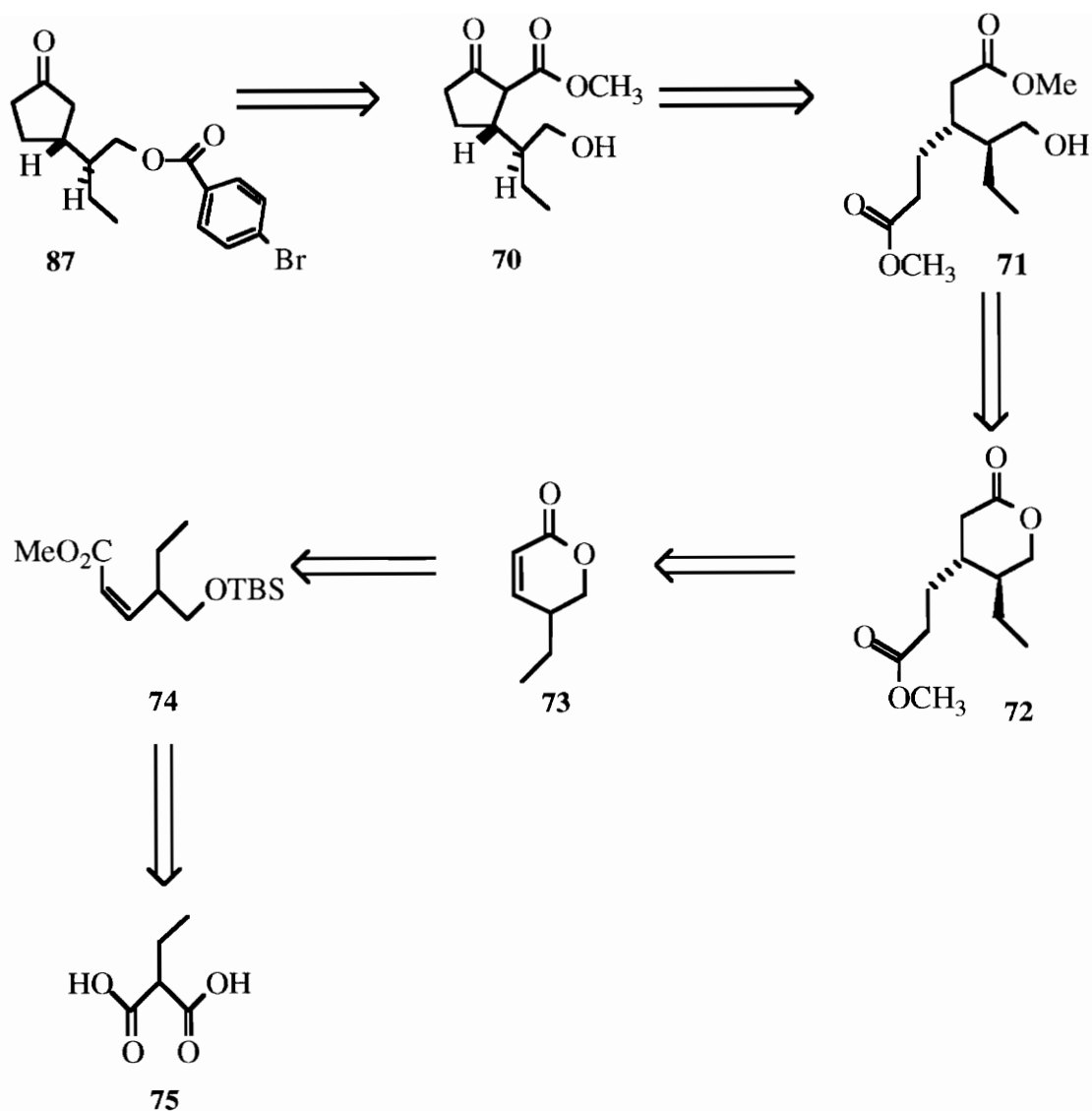
Even though a diastereomeric mixture of benzoates was obtained, we needed to determine the relative stereochemistry of both the major and minor isomers. Thus, an independent synthesis of bromobenzoate **69** was required. It was crucial that the route we chose provided either an *anti* or a *syn* relationship between protons 5 and 6 both

stereospecifically and reliably. Our efforts in this area are described in sections III-4a and III-4b.

The question of the stereospecificity of the addition of the dienolate to the enone will be addressed again later.

III-4a First approach

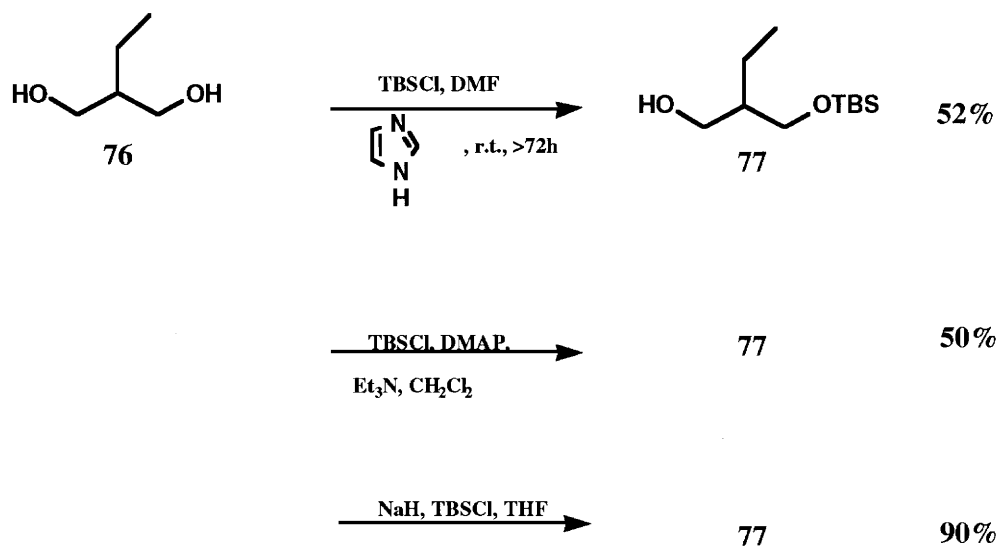
We envisioned that the cyclopentane ring could be derived from the β -ketoester via ester hydrolysis and subsequent decarboxylation. The β -ketoester would be formed from the dieckman condensation of the diester available from the lactone through transesterification. The required *trans* relationship of the protons would be secured by the 1,4-addition of a suitable methylpropioate equivalent to the lactone. This lactone would form a key intermediate in the synthesis, which itself could be prepared from the diacid by the described protocol (schemes 22-25).



Scheme 21

Thus, the proposed synthesis of benzoate **69** began with the reduction of ethyl malonic acid **75** to the corresponding diol **76** (scheme 22). Initially, this reduction was achieved with borane/THF complex in low yield. This procedure involved the addition of the borane/THF complex. in THF to a solution of the diacid. After stirring at room temperature for *ca.* 4 hours, the reaction was cooled to 0° C and quenched with water. The product was isolated by flash chromatography in *ca.* 30 % yield. Ultimately, this

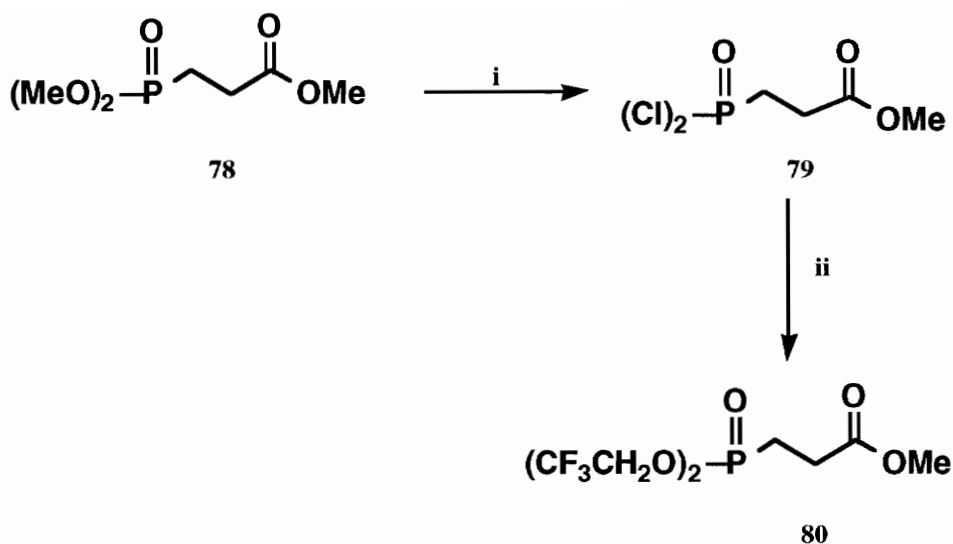
reduction was achieved in >90% yield with LiAlH₄. A solution of diacid **75** in THF was added to a heterogeneous mixture of LiAlH₄ and THF. The work-up involved the addition of ethyl acetate and dilute aqueous sulfuric acid as described in Vogel.³³ The LiAlH₄ reduction proceeded smoothly and was amenable to large scale preparation. The next step in the synthesis involved the monoprotection of diol **76** as a silyl ether. This reaction was carried out under various conditions as outlined in scheme 22.



Scheme 22

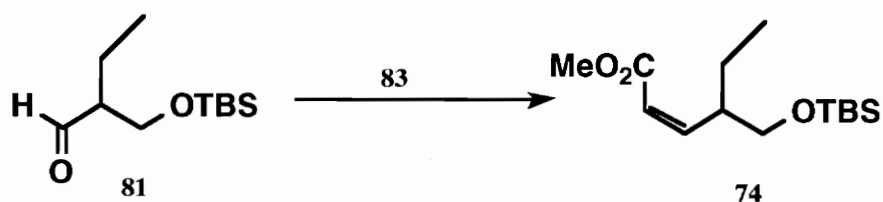
Oxidation of the monoprotected alcohol **76** under Swern conditions gave aldehyde **81**. The crude aldehyde **81** was then reacted with a Horner-Emmons Wittig reagent **83** to give (±)-methyl *Z*-4-*t*-butyldimethylsilyloxymethylhex-2-enoate **74** (scheme 24) in 57% yield over the two steps as described by Fukumoto and co-workers.³⁴

The Horner-Emmons Wittig reagent was synthesized according to Still's method wherein neat PCl₅ was added to trimethylphosphonoacetate to give the dichlorophosphonoester **79**.³⁵ Ester **79** was combined with trifluoroethanol and Hunig's base to give the trifluoroethylphosphonoester **80** (scheme 23).



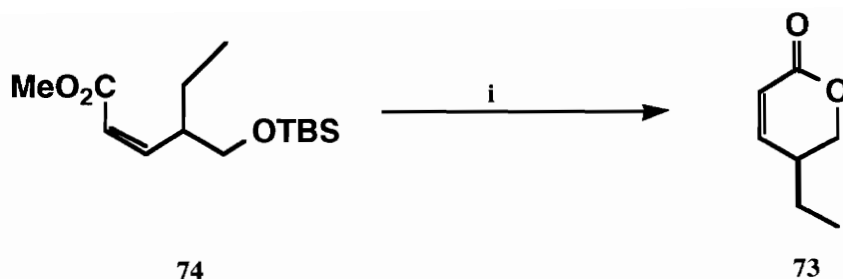
i. PCl_5 , ii. diisopropyl ethyl amine, $\text{CF}_3\text{CH}_2\text{OH}$

Scheme 23



Scheme 24

The final step in the synthesis of lactone **73** required the removal of the silyl protecting group and subsequent ring closure. The deprotection was achieved by the addition of a solution of tetrabutyl-ammonium fluoride to ester **74** at -40°C . This mixture was allowed to slowly warm to -10°C as described by Fukumoto and co-workers.³⁴ The product was in *ca.* 25% yield (scheme 25). In retrospect, we speculated that these harsh conditions may have led to the degradation of the starting materials. We further concluded that running the reaction at a lower temperature may have improved the overall yield.



i. TBAF, THF, r.t., 6h

Scheme 25

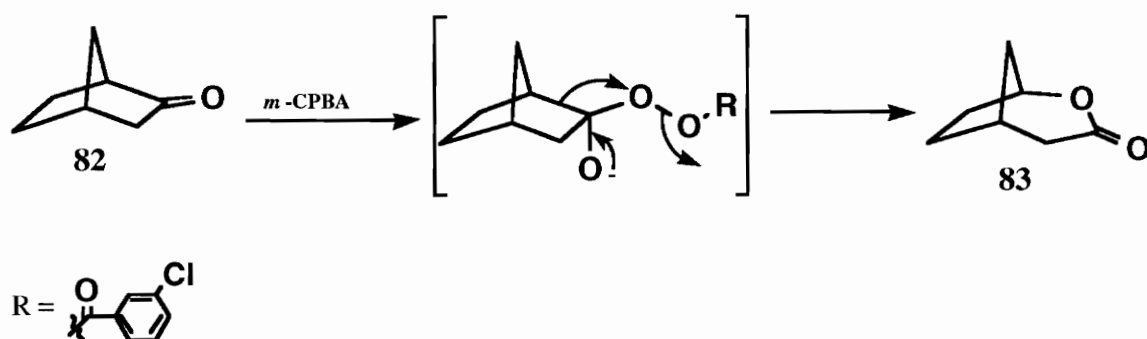
The next step in the synthesis involved the addition of allyl cuprate to lactone **75**. We attempted this alkylation by adding neat allyl bromide to magnesium turnings in diethyl ether. The solution was transferred to a different flask and cooled to -30°C . To this flask was added neat CuI followed by lactone **73** in THF. The reaction was allowed to stir for 2.5 hour and was quenched with saturated aqueous ammonium chloride. This alkylation was attempted several times with a number of minor alterations but to no avail. It was concluded that because starting material was isolated in most cases, the problem was in the formation of the Grignard reagent.

At this point the synthesis of bromobenzoate **69** was under halfway complete. This, combined with the large number of steps that remained and the low overall yield of the intermediate lactone, prompted us to find a more efficient benzoate synthesis.

A second stereoselective approach to the bromobenzoate **69** was conceived and is discussed in detail in the next section.

III-3 Second Approach

The second attempt in the synthesis of bromobenzoate **69** began with the Baeyer-Villiger oxidation of norcamphor **82** with *m*-CPBA to 2-oxabicyclo[3.2.1]octan-3-one **83** exclusively as reported by Meinwald and co-workers (scheme 26).³⁶



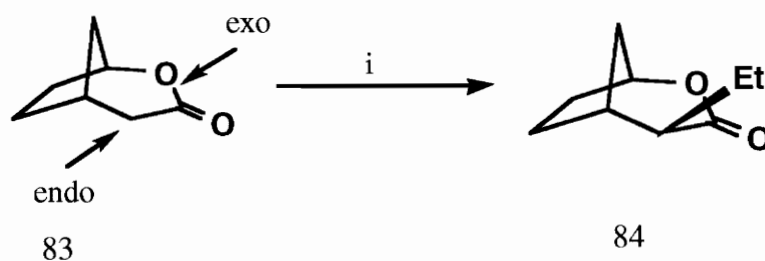
Scheme 26

It was envisioned that alkylation of this bicyclic system would give a product of known stereochemistry since the relationship between the incoming alkyl group and the bridgehead proton could be assessed. We were aware that alkylation could occur from either the less hindered *exo* face or the more hindered *endo* face (scheme 27). Because of this steric bias, it was expected that alkylation would be achieved selectively from the *exo* face as in similar [2.2.1.] oxidations.³⁷

Initial attempts to achieve this alkylation involved enolate formation at -78°C followed by addition of excess iodoethane. The ensuing mixture was allowed to gradually warm to room temperature in an effort to force the reaction to completion. Although the reaction did not appear complete by thin layer chromatography, the reaction was stopped by the addition of saturated aqueous ammonium chloride. The aqueous layer was extracted with ethyl acetate and the product was further purified by flash

chromatography. ^{13}C NMR indicated that *ca.* a 1:1 mixture of the *exo* and *endo* alkylated product was isolated in *ca.* 55% yield. All attempts to separate these isomers, including preparative HPLC, were unsuccessful.

In a paper by Tankano and co-workers,³⁷ alkylation of lactone **82** was described. In this paper the alkylation was carried out under kinetic conditions with iodomethane and 1-bromopropane (-40°C). Following Tankano's procedure, one product was isolated as evidenced by ^1H and ^{13}C NMR (scheme 27).



i. LDA, EtI, THF, -78°C

Scheme 27

Having isolated one isomer from the alkylation we now had to be certain of the stereochemistry of this product. The Cache computer molecular modeling program indicated that in the most stable conformation of the *endo* isomer there was approximately an 49° angle between the protons attached to carbons 1 and 2 and 82° for the most stable conformation of the *exo* product (figure 5). According to the Karplus equation,³⁸ an angle of 49° should have a large coupling constant whereas an angle of 82° should have a coupling constant near 0 hertz (figure 5). After TOCSY NMR experiments, we were able to conclude that the product isolated from the kinetic alkylation showed no coupling between the two protons of interest which suggested a dihedral angle of *ca.* 90° . We therefore concluded that we had isolated the *exo* alkylated product (as will be discussed later in this section, selective synthesis of the *endo* isomer

gave the expected large a coupling between the two protons of interest). These results were consistent with our expected results and results previously reported in the literature.³⁷

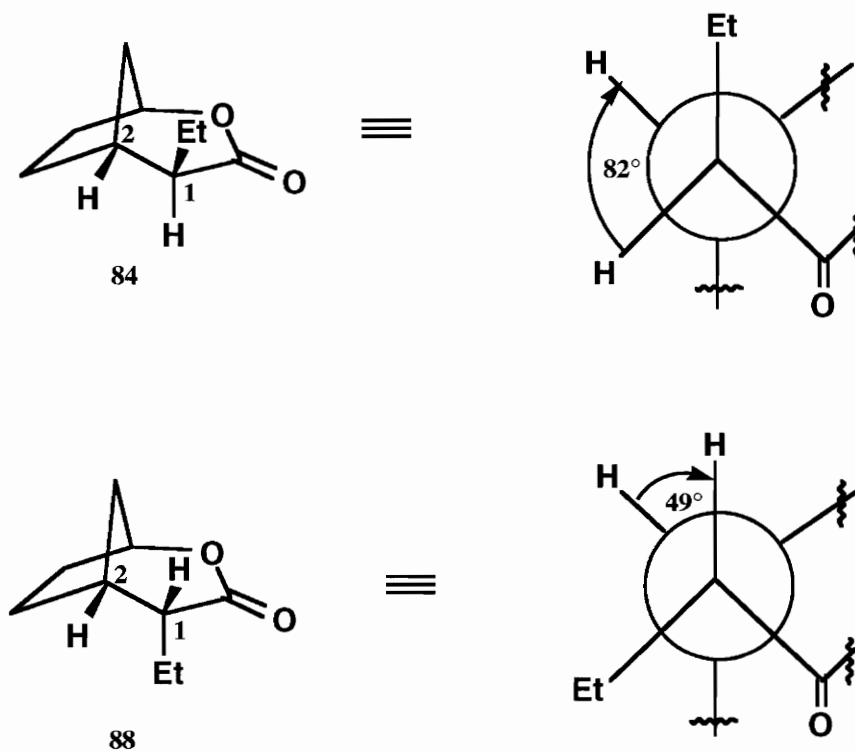
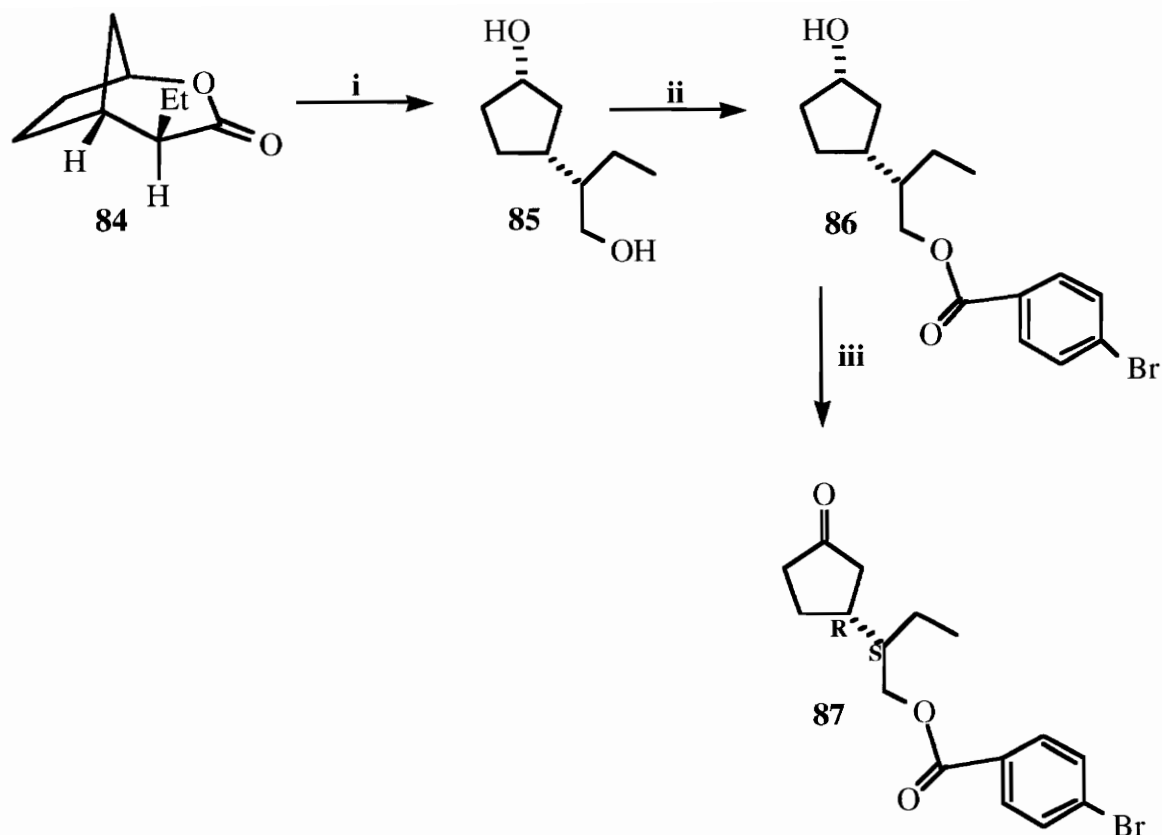


Figure 5: Newman Projection of *Exo* and *Endo* Alkylated Lactone

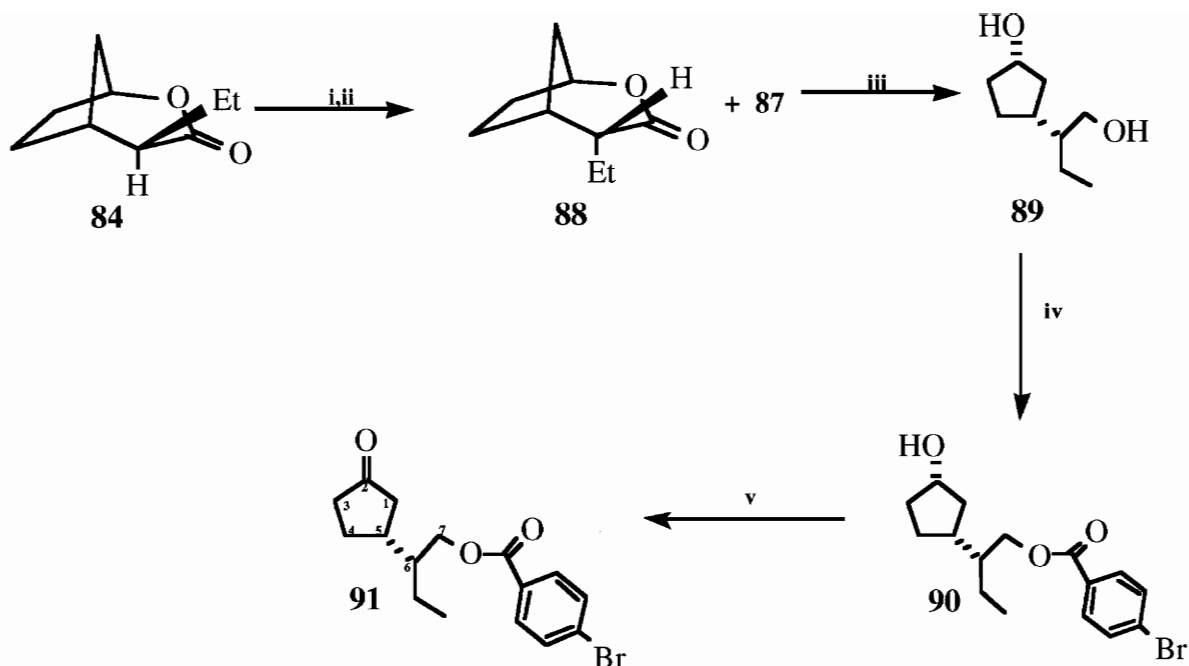
With the stereochemistry of lactone **83** confirmed we were now able to proceed with the synthesis. Exhaustive reduction of lactone **84** was achieved with LiAlH_4 gave diol **85** in quantitative yield and the primary alcohol of diol **87** was then protected as the corresponding bromobenzoate. The final step of this synthesis was the Jones oxidation of the secondary alcohol to the corresponding ketone to give bromobenzoate **69** (scheme 28).



i. LDA, EtI, THF, -78°C --> -30°C, ii. LAH, THF, iii. NaH, *p*-Bromobenzoyl chloride, C H₂Cl₂, iv. Jones reagent (CrO₃, H₂SO₄)

Scheme 28

Having obtained and identified one diastereoisomer of benzoate **69**, our next task was to synthesize the other stereoisomer in order to make an effective comparison. The synthesis of the other diastereoisomer began with generation of the lithium enolate anion of the *exo* isomer **84** followed by a kinetic quench with saturated aqueous sodium sulfate at -78° C as described by Tankano and co-workers.³⁷ Isolated from this reaction was a 9:1 mixture of the *endo* and *exo* isomers respectively (scheme 29).



i. LDA, THF, -78°C , ii. saturated aq. Na_2SO_4 iii. LAH, THF, iv. NaH, *p*-Bromobenzoyl chloride, CH_2Cl_2 , v. Jones reagent (CrO_3 , H_2SO_4)

Scheme 29

As previously mentioned, isomers **84** and **88** were inseparable thus we were forced to take the 9:1 mixture to the bromobenzoate **91** as previously described (scheme 34).

With both stereoisomers of benzoate **69** in hand, we could now make an effective comparison. Because compounds **87** and **91** were diastereomers, we expected the spectroscopic data to be similar yet distinguishable. This was indeed the case. The ^1H NMR spectra for the protons attached to carbon 7 (figure 5) had a unique splitting pattern for the two diastereomers. The ^1H NMR for bromobenzoate **87** isolated from the *exo* alkylated lactone appeared as a close pair of double doublets while the corresponding ^1H NMR for bromobenzoate **91** isolated from the *endo* product appeared simply as a doublet. A careful comparison of the ^1H NMR and ^{13}C NMR spectra of bromobenzoates **69**, **87** and **91** (figures 6 and 7) indicated that the major product isolated

from the Michael addition reaction (scheme 19) had the relative stereochemistry found in bromobenzoate **87** which was isolated from the *exo* product.

From Oppolzer's study,¹⁰ we were able to propose a transition state for the Michael addition of the dienolate of ethyl crotonate to 2-cyclopentenone (figure 8). We were further able to infer that the results obtained in this study were in concurrence with those previously obtained by Heathcock⁷ and Oppolzer¹⁰.

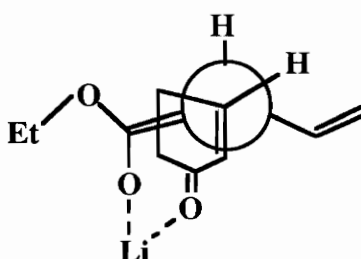


Figure 8: Proposed transition state for the dienolate addition of ethyl crotonate to 2-cyclopentenone

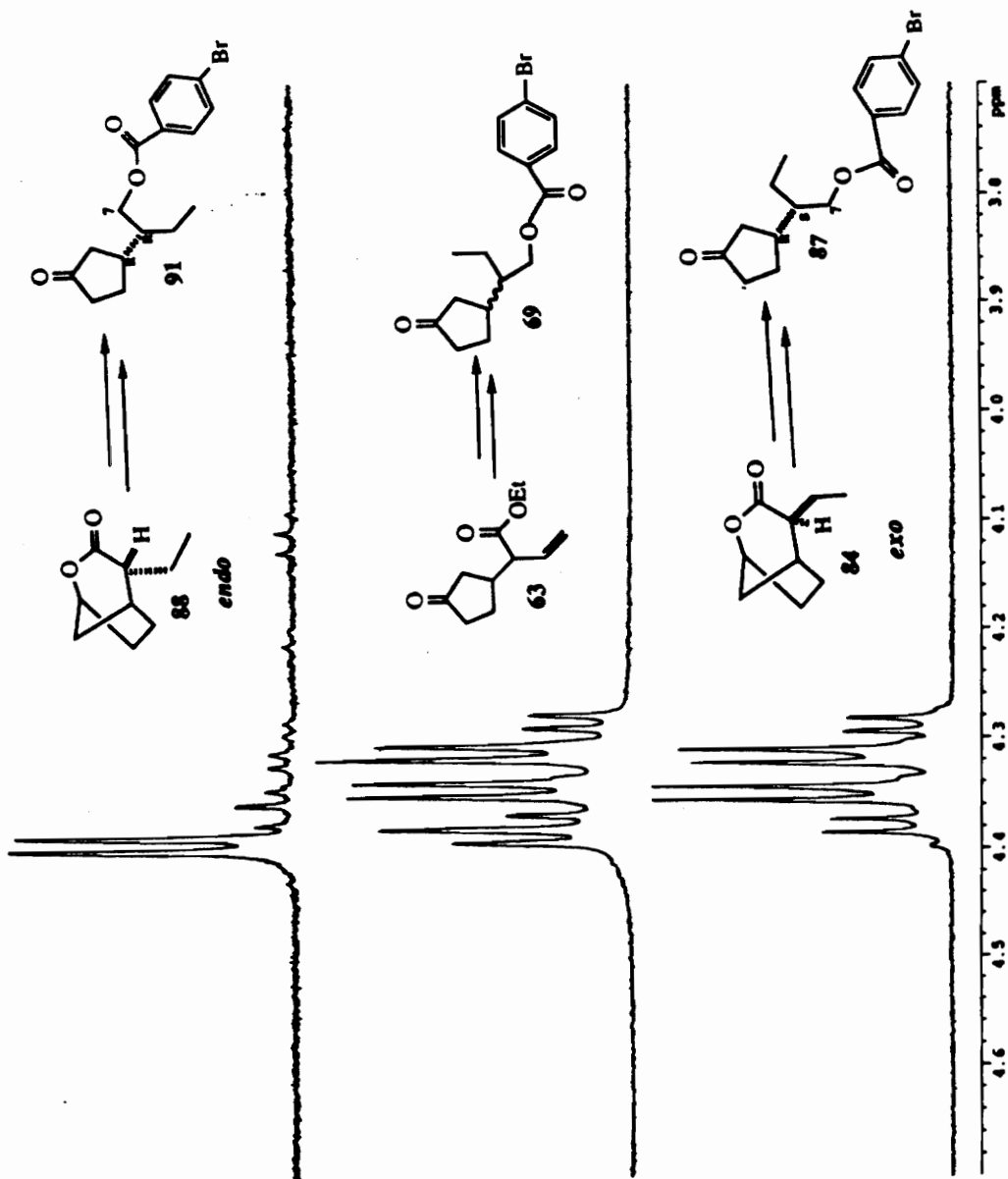


Figure 6: ^1H NMR Spectra of Compounds 69, 87 and 91

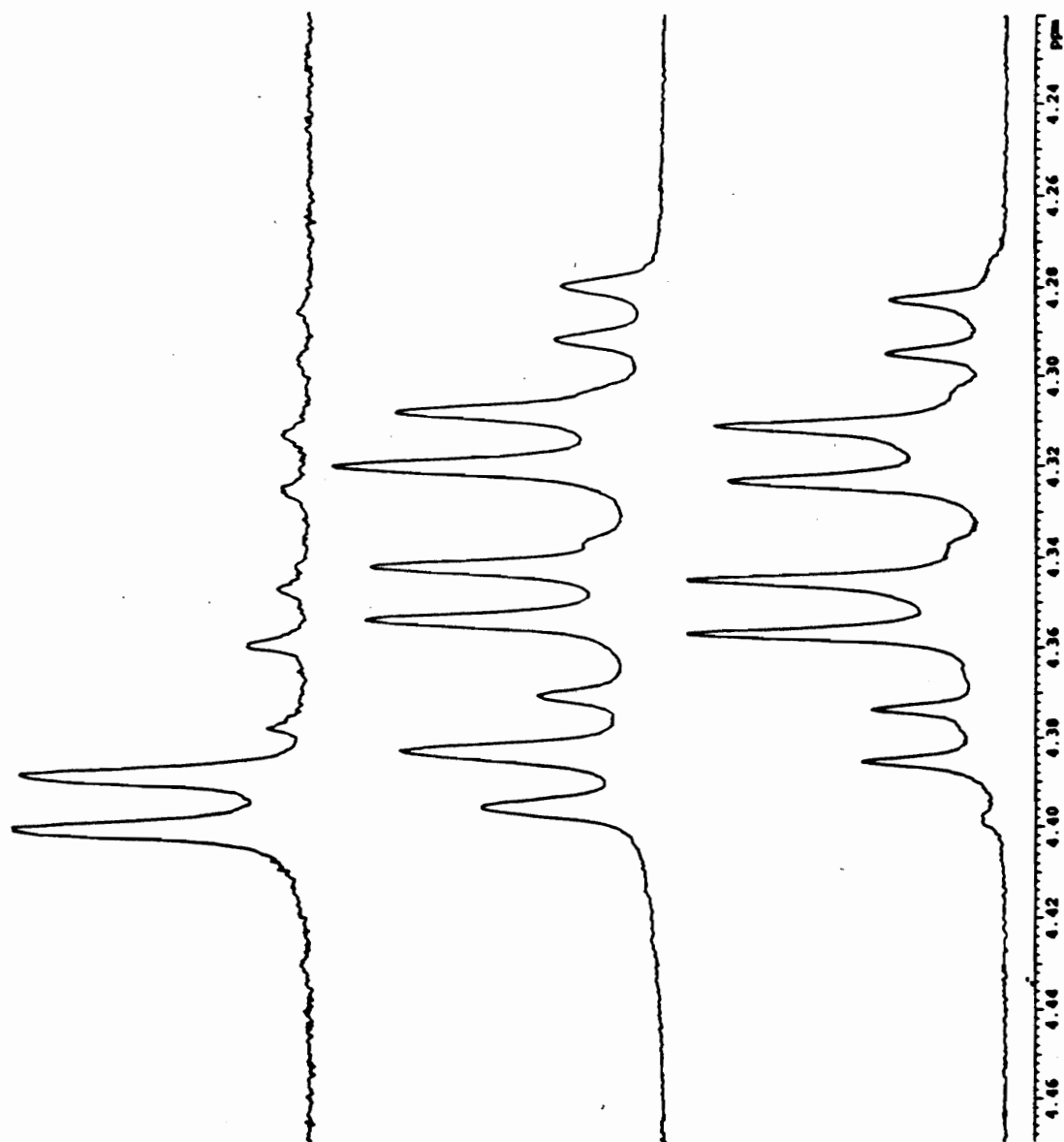


Figure 7: Expanded ¹H NMR Spectra of Compounds 69, 87 and 91

IV. CONCLUSION and FUTURE WORK

From this research it is clear that the addition of the 9:1 mixture of the *Z*:*E* enolates of ethyl crotonate to 2-cyclopentenone results in the formation of a 4:1 mixture of two diastereoisomers as indicated in section III-4. We found that this 4:1 mixture of diastereoisomers could be converted to bromobenzoate **69** in *ca.* the same ratio. Furthermore it was concluded, after a careful comparison, that the major isomer isolated from the addition of the dienolate of ethyl crotonate to 2-cyclopentenone (scheme 22) has a relative configuration of (R,S) at the two newly formed stereocenters as indicated below (figure 8).

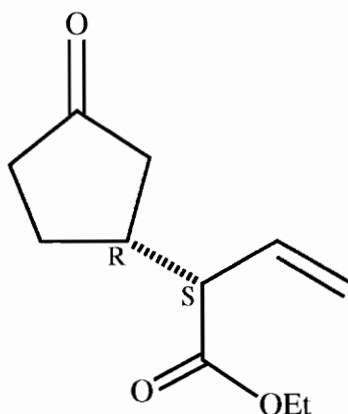


Figure 8: Major product from the dienolate addition to 2-cyclopentenone

At this point it is not clear why a 9:1 mixture of enolates yields an approximate 4:1 diastereomeric mixture of adduct **63**; however, several inferences may be drawn from these results. One can deduce that the Michael addition of the dienolate of ethyl crotonate is not stereoselective or that epimerization of the center occurred sometime after the initial adduct was formed. The data in the chemical literature suggests that hydrogenation of diol **70** using palladium as the catalyst could possibly result in the

epimerization of the proton attached to carbon 6 *via* olefin migration prior to reduction.⁴⁰⁻⁴² It is also possible to infer that this addition was stereospecific, however, the dienolates have different reactivities. Obviously this study leaves a number of unanswered questions; however, the objective of the research was accomplished in that an effective comparison of the Michael adduct derivative (bromobenzoate **69**) and derivatives of known stereochemistry (bromobenzoates **87** and **91**) was made and the products were identified.

Future work in this area will include isolation of both TBS-protected dienolates (possibly by preparative HPLC) regeneration of the dienolate anion and subsequent addition of these nucleophilic dienolate species to a variety of α,β -unsaturated systems. The issue of epimerization during hydrogenation will be addressed by careful monitoring of the course of the reaction and by the use of different catalyst. This will provide answers to some of the ambiguities and make a broader generalization of the stereospecificity of the addition of dienolates to Michael acceptors.

V. EXPERIMENTAL

General. Unless otherwise noted, commercial reagents were used without further purification. Ethyl crotonate **56** was purchased from Aldrich and washed with 5% NaHCO₃ followed by saturated aqueous CaCl₂ and distilled from CaCl₂ as described by Perrin and Armarega.³⁹ Diisopropyl ethyl amine was purchased from Aldrich and distilled from CaH. Esters **79** and **80** were prepared according to Fukomoto's procedure.³⁴ Aldehyde **81**, ester **82** and lactone **73** were prepared according to Still's procedure.³⁵ Bicyclic lactone **83** was prepared according to Mienwald's procedure.³⁶

All moisture sensitive reactions were carried out under an argon atmosphere. Glassware used in these reactions was flame-dried under vacuum with an internal argon sweep prior to use. Solvents used in these reactions were distilled prior to use. THF was distilled from sodium and benzophenone and dichloromethane was distilled from calcium hydride.

Unless otherwise noted, ¹H NMR and ¹³C NMR were recorded on either a Bruker WP-270 or Varian UN-400 instrument. Multiplicities are expressed as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet) and br (broad). Coupling constants are indicated in parentheses and expressed in hertz.

Thin-layer chromatography was performed on silica gel 60F-254 plates and flash chromatography on Kieselgel 60 (230-400 mesh) from EM reagents.

Mass spectra were recorded on either a Varian MAT-112 instrument (low resolution) or a double focusing VG 7070 E-HF instrument (exact mass) and all infrared spectra were obtained on a Perkin-Elmer 283B instrument.

3[-2-(ethyl-3-butenate)]-1-cyclopentanone (63). To a freshly prepared solution of lithium diisopropylamide (2.14 g, 20 mmol) in THF (40 mL) was added hexamethylphosphoramide (4.0 mL, 20 mmol) under argon at 0°C. The reaction was cooled to -78°C and neat ethyl crotonate (2.5 mL, 20 mmol) was added. After stirring at -78°C for two hours, cyclopenten-1-one (.84 mL, 10 mmol) in THF (26 mL) was added over 20 minutes. After 30 minutes stirring, the mixture was allowed to warm to room temperature and treated with saturated aqueous ammonium chloride. The solution was diluted and extracted with four portions of ethyl ether. The combined organic layers were washed with six portions of water followed by brine then dried (MgSO₄). Evaporation of the solvents gave a yellow oil. This yellow oil was used crude in the following reaction.

3[-2-(but-3-en-1-ol)]cyclopentan-1-ol (66) To a stirred solution of LiAlH₄ (152 mg, 4.0 mmol) in THF (15 mL) was added crude **63** (320 mg, 1.6 mmol) in THF (5 mL) at room temperature. The resulting mixture was allowed to stir for 2 hours under argon. Ethyl acetate was added slowly followed by cold 2M H₂SO₄. The solution was diluted and extracted with four portions of ethyl acetate. Evaporation of the solvent gave a pale yellow oil. Chromatography of the oil on silica gel (95:5, CH₂Cl₂:MeOH) gave diol **66** as a colorless oil (140 mg, 56%).

R_f: 0.375 (CH₂Cl₂/MeOH 10:1)

IR: (neat) cm⁻¹ 3300, 3100, 2960, 2220, 1680, 910

¹H NMR: (CDCl₃) δ 1.3-2.3 (m, 7H), 3.4 (ddd, J = 13.48, 8.57, 2.84, 1H)

¹³C NMR: (CDCl₃) δ 27.5 (CH₂), 35.0 (CH₂), 37.5 (CH), 38.5 (CH), 39.3 (CH₂), 40.5 (CH₂), 52.5 (CH), 64.5 (CH₂), 72.5 (CH), 119 (CH₂), 123 (CH₂) 139 (CH)

MS: (CI, 70eV) m/z (rel. intensity) 157 (m+) (10), 139 (18), 121 (100), 108 (30), 93 (52), 79 (48), 67 (50), 55 (18)

HRMS calcd for C₉H₁₆O₂: 157.1228550 **Found:** 157.1228550 error: 1.5 ppm

3[-2-(butan-1-ol)]cyclopentan-1-ol. (67) To a stirred solution of diol **66** (114 mg, 0.73 mmol) in ethyl acetate (15 mL) was added 10% palladium on activated carbon. The reaction was allowed to stir under hydrogen atmosphere for 2 hours. The product was filtered through celite followed by filtration through a short plug of silica to yield diol **67** as a pale yellow oil. (107 mg, 93%)

R_f: 0.400 (CH₂Cl₂/MeOH 10:1)

IR: (neat) cm⁻¹ 3370, 2960, 2925, 2870, 2450, 1460, 1010, 905, 725

¹H NMR: (CDCl₃) δ 0.9 (ddd, J=14.87, 7.39, 1.70, 3H), 1.2-2.2 (m, 12H), 3.65 (m, 2H) 4.3 (m, 1H)

¹³C NMR: (CDCl₃) δ 11.25(CH₃), 11.5 (CH₃), 21.25 (CH₂), 22.0 (CH₂), 28.1 (CH₂), 28.4 (CH₂), 34.9 (CH₂), 35.2 (CH₂), 37.7 (CH), 38.35 (CH), 38.37 (CH₂), 40.5 (CH₂), 46.25 (CH), 46.31 (CH)

MS: (CI, 70eV) m/z (rel. intensity) 159 (m+) (9), 141 (33), 123 (100), 109 (25), 93 (12), 81 (87), 67 (60), 55 (18)

HRMS calcd for C₉H₁₈O₂: 159.1385050 **Found:** 159.138275 error: -1.4 ppm

3-[-2-*p*-bromobenzoyl-3-butenolate]cyclopentan-1-ol (68) To a clean, dry flask was added diol **67** (83 mg, 0.52 mmol), CH₂Cl₂ (3 mL) and neat triethylamine (0.09 mL, 0.62 mmol). The resulting solution was allowed to stir at room temperature for approximately 15 minutes the solution of *p*- bromobenzoyl chloride (126.5 mg, 0.57 mmol) in CH₂Cl₂

(2.0 mL) was added. The resulting solution was allowed to stir under argon at room temperature for 48 hours. After the addition of water, the aqueous layer separated and extracted with CH₂Cl₂. The combined organic extracts were dried (MgSO₄). Evaporation of the solvent gave a pale yellow oil. Chromatography of the oil on silica gel (2:1, hexane:ethyl acetate) gave alcohol **68** as a colorless oil (81 mg, 46%).

R_f: 0.344 (Hex/EtOAc 3:1)

IR: (neat) cm⁻¹ 3400, 2960, 2865, 1645, 1590, 1270, 1200, 1010, 750

¹H NMR: (CDCl₃) δ 0.95 (t, J = 7.269, 3H), 0.96 (t, J = 7.16, 3H), 1.2-2.1 (m, 10H), 2.15-2.3 (m, 1H), 4.2-4.42 (m, 3H), 7.55 (d, J = 6.89, 2H), 7.87 (d, J = 6.34, 2H)

¹³C NMR: (CDCl₃) δ 11.06 (CH₃), 22.4 (CH₂), 22.9 (CH₂), 28.0 (CH₂), 35.0 (CH₂), 35.5 (CH₂), 39.7 (CH), 40.0 (CH₂), 41.7 (CH₂), 44 (CH), 44.5 (CH), 65.6 (CH₂), 66.0 (CH₂), 72.5 (CH), 73.0 (CH), 128.0 (C), 129.2 (C), 131.75 (CH), 131.07 (CH), 163 (C)

MS: (CI, 70eV) m/z (rel. intensity) 341 (m+) (9), 323 (12), 203 (25), 185 (45), 123 (100), 81 (55), 67 (30)

Calcd for C₁₆H₂₁O₃Br: C 56.316% H 6.203% **Found**: C 56.1% H 6.25%

3-[-2-*p*-bromobenzoyl-3-butanoate]cyclopentan-1-one (69) To a stirred solution of alcohol **68** (612 mg, 1.8 mmol) in acetone (10 mL) was added 8N Jones reagent (10 drops). The resulting solution was allowed to stir for *ca.* 20 minutes. After the addition of water, the reaction mixture was transferred to a separatory funnel and extracted with 3 portions of ethyl acetate. The combined organic extracts were dried (MgSO₄). Evaporation of the solvent gave a deep green oil. Chromatography of the oil on silica gel (2:1, hexane:ethyl acetate) gave keton **69** as a colorless oil (506 mg, 83%).

R_f: 0.34 (Hex/EtOAc 3.5:1)

IR: (neat) cm^{-1} 2945, 2910, 1620, 1580, 1470, 1450, 1380, 1260, 1110, 1090, 1000, 745, 720

^1H NMR: (CDCl_3) δ 1.00 (overlapping pair of t, $J = 7.48$, 3H), 1.4-1.74 (m, 4H), 1.9-2.02 (m, ^1H), 2.10-2.51 (m, 5H), 4.3 (dd, $J = 11.44, 4.73$, ^1H), 7.86 (d, $J = 8.39$, 2H)

^{13}C NMR: (CDCl_3) δ 10.94 (CH_3), 21.58 (CH_2), 22.56 (CH_2), 27.81 (CH_2), 27.92 (CH_2), 38.69 (CH_2), 38.75 (CH), 43.67 (CH_2), 43.4 (CH_2), 44.26 (CH), 44.31 (CH), 64.85 (CH_2), 65.67 (CH_2), 128.15 (C), 128.9 (C), 130.99 (CH), 131.78 (CH), 165.78 (C), 218.57 (C)

MS: (CI, 70eV) m/z (rel. intensity) 339 (m^+) (14), 321 (2), 183 (90), 130 (100), 109 (40), 96(47), 83 (60), 69 (15)

Calcd for $\text{C}_{16}\text{H}_{19}\text{O}_3\text{Br}$: C 56.651% H 5.645% **Found:** C 56.76% H 5.67%

2-oxabicyclo-4-ethyl[3.2.1]octan-3-one (84) To a freshly prepared solution of lithium diisopropyl amine (7.9 mmol) in THF (30 mL) was added lactone **82** (1g, 7.9 mmol) in THF (40 mL) at -78°C . This mixture was allowed to stir at that temperature for 30 minutes. Neat iodoethane (0.63 mL, 7.9 mmol) was added and the reaction was allowed to stir at -30°C for 6 hours. After the addition of saturated aqueous, NaSO_4 the reaction was allowed to warm to room temperature. The organic layer was removed and the aqueous layer was extracted with 2 portions of ethyl acetate. The combined organic layers were dried (MgSO_4). Evaporation of the solvent gave a yellowish oil. Chromatography of the oil on silica gel (2:1, hexane:ethyl acetate) gave lactone as a colorless oil (486 mg, 40%).

R_f: 0.29 (Hex/EtOAc 2:1)

IR: (neat) cm^{-1} 2960, 2865, 2240, 1720, 1460, 1370, 1240, 1200, 1170, 1160, 1000, 960, 720

¹H NMR: (CDCl₃) δ 0.95 (t, J = 7.44, 3H), 1.4-1.65 (m, 3H), 1.75-2.1 (m, 5H), 2.25 (ddt, J = 22, 12, 3, ¹H), 3.4 (br t, J = 5.604, 4.95, ¹H), 4.75 (br m ¹H)

¹³C NMR: (CD₃OD) δ 17.25 (CH₃), 30.899 (CH₂), 34.39 (CH₂), 36.98 (CH₂), 37.11 (CH₂), 339.89 (CH), 56.68 (CH), 44.5 (CH), 65.6 (CH₂), 89.37 (CH)

MS: (CI, 70eV) m/z (rel. intensity) 155 (m+) (70), 126 (55), 109 (100), 95 (12), 81 (20), 67 (63)

HRMS calcd for C₉H₁₄O₂: 155.1072049 **Found:** 155.1069 error -2.0

3[-2-(butan-1-ol)]cyclopentan-1-ol. (85) To a stirred solution of lithium aluminum hydride (8.1 mL, 8.1 mmol, 1M soln. in THF) in THF (30 mL) was added bicyclic lactone **84** (500 mg, 3.2 mmol) at room temperature. The reaction was allowed to stir under argon for 20 hours. After the addition of H₂O (0.32 mL), 10% NaOH (0.32 mL) and H₂O (0.96 mL), the reaction was filtered. The filtrate was washed with *ca.* 150 mL of ethyl acetate. The combined organic layers were dried (MgSO₄). Evaporation of the solvent gave crude alcohol **85** as a white solid. Recrystallization from toluene gave alcohol **85** as a white, slightly crystalline solid (479 mg, 97%).

Rf: 0.375 (CH₂Cl₂/MeOH 10:1)

IR: (neat) cm⁻¹ 3340, 2960, 2245

¹H NMR: (CDCl₃) δ 0.9 (t J = 7.201, 3H), 1.2-1.8 (m, 8H), 1.9 (br m, ¹H), 2.1 (m, ¹H), 3.65 (m, 2H), 4.1 (br m, ¹H)

¹³C NMR: (CDCl₃) δ 11.28 (CH₃), 22.31(CH₂), 28.21 (CH₂), 35.38 (CH₂), 39.33 (CH), 39.44 (CH₂), 46.84 (CH), 63.54 (CH₂), 73.60 (CH)

MS: (CI, 70eV) m/z (rel. intensity) 159(m+) (15), 141 (30), 123 (50), 110 (20), 93 (20), 81 (94), 67 (100), 55 (45)

Calcd for C₉H₁₈O₂: C 68.313% H 11.465% **Found:** C 68.06% H 11.33%

3-[-2-*p*-bromobenzoyl-3-butenoate]cyclopentan-1-ol (86) To a clean dry flask was added diol **85** (366 mg, 2.3 mmol), CH₂Cl₂ (20 mL) and neat triethylamine (0.39 mL, 2.8 mmol). The resulting solution was allowed to stir at room temperature for approximately 15 minutes the solution of *p*- bromobenzoyl chloride (565 mg, 2.6 mmol) in CH₂Cl₂ (5.0 mL) was added. The resulting solution was allowed to stir under argon at room temperature for *ca.* 48 hours. After the addition of water, the aqueous layer separated and extracted with CH₂Cl₂. The combined organic extracts were dried (MgSO₄). Evaporation of the solvent gave a pale yellow oil. Chromatography of the oil on silica gel (2:1, hexane:ethyl acetate) gave alcohol **86** as a colorless oil (472 mg, 60%).

R_f: 0.30 (Hex/EtOAc 2:1)

IR: (neat) cm⁻¹ 3400, 2960, 2865, 1645, 1590, 1270, 1200, 1010, 750

¹H NMR: (CDCl₃) δ 0.95 (t J = 7.3, 3H), 1.72-1.96 (m, 3H), 2.16-2.25 (p, J = 7.2, 1H), 4.25-4.38 (m, 3H), 7.58 (d, J = 8.24, 2H), 7.87 (d, J = 8.39, 2H)

¹³C NMR: (CDCl₃) δ 11.06 (CH₃), 22.38 (CH₂), 28.23 (CH₂), 35.32 (CH₂), 39.81 (CH), 40.51 (CH₂), 41.7 (CH₂), 44.45 (CH), 66.19 (CH₂), 66.0 (CH₂), 127.95 (C), 129.31 (C), 131.71 (CH), 131.03 (CH), 164.0 (C)

MS: (CI, 70eV) *m/z* (rel. intensity) 341 (m+) (3.0), 323 (3), 306 (1), 288 (1.3), 183 (30), 123 (100), 93 (25), 81 (42), 67 (35)

HRMS calcd for C₁₆H₂₁O₃Br: 341.0752309 **Found**: 341.0747 error -1.6

3-[-2-*p*-bromobenzoyl-3-butanoate]cyclopentan-1-one (87) To a stirred solution of alcohol **85** (467 mg, 1.37 mmol) in acetone (15 mL) was added the Jones reagent (8N). The resulting solution was allowed to stir for *ca.* 20 minutes. After the addition of water, the reaction mixture was transferred to a separatory funnel and extracted with 3 portions of ethyl acetate. The combined organic extracts were dried (MgSO₄). Evaporation of

the solvent gave a deep green oil. Chromatography of the oil on silica gel (2:1, hexane:ethyl acetate) gave ketone **87** as a colorless oil (421 mg, 91%).

R_f: 0.34 (Hex/EtOAc 3.5:1)

IR: (neat) cm^{-1} 2945, 2910, 1620, 1580, 1470, 1450, 1380, 1260, 1110, 1090, 1000, 745, 720

¹H NMR: (CDCl_3) δ 1.00 (t, $J = 7.5$, 3H), 1.43-1.75 (m, 4H), 1.91-2.01 (dd, $J = 10.07$, 1H), 2.10-2.51 (m, 5H), 4.30 (dd, $J = 11.55$, 4.88, 1H), 4.37 (dd, $J = 11.51$, 4.73, 1H) 7.59 (d, $J = 8.39$, 2H)

¹³C NMR: (CDCl_3) δ 10.94 (CH_3), 21.58 (CH_2), 27.81 (CH_2), 38.70 (CH_2), 38.75 (CH), 43.67 (CH_2), 43.27 (CH_2), 44.27 (CH), 64.67 (CH_2), 128.16 (C), 128.98 (C), 130.99 (C), 131.79 (CH), 165.79 (C), 218.57 (C)

MS: (CI, 70eV) m/z (rel. intensity) 341 (m^+) (4.5), 185 (45), 139 (100), 109 (20), 96 (25), 83 (35)

Calcd for $\text{C}_{16}\text{H}_{19}\text{O}_3\text{Br}$: C 56.651% H 5.645% **Found**: C 56.77% H 5.72%

2-oxabicyclo-4-ethyl[3.2.1]octan-3-one (88) To a freshly prepared solution of LDA (84.5 mg, 0.79 mmol) in THF (20 mL) was added lactone **84** (100 mg, 0.79 mmol) in THF (15 mL) at -78°C . This mixture was allowed to stir at that temperature for 20 minutes. After the slow addition of saturated aqueous Na_2SO_4 , the reaction was allowed to warm to room temperature. The aqueous layer was extracted with three portions of ethyl acetate. The combined organic layers were dried (MgSO_4). Evaporation of the solvent gave a colorless oil. Chromatography of the oil on silica gel (2:1, hexane:ethyl acetate) gave a 9:1 mixture of lactones **88:84** (91 mg, 91%).

R_f: 0.29 (Hex/EtOAc 2:1)

IR: (neat) cm^{-1} 2960, 2880, 1720, 1730, 1375, 1135, 1005

¹H NMR: (CDCl₃) δ 0.9 (t, J = 7.25, 3H), .99 (t, J = 7.2, 0.5H), 1.42(m, 1H), 1.6-2.1 (m, 5H), 2.25 (ddt, J = 22, 12, 3, 0.16H), 2.38 (m, 1H), 2.48 (br m, 1H), 4.75 (br m 1H)

¹³C NMR: (CDCl₃) δ 11.63 (CH₃), 21.857 (CH₂), 22.34 (CH₂), 32.12 (CH₂), 342.36 (CH₂), 37.38 (CH₂), 49.45 (CH), 80.69 (CH), 80.90 (CH), 184.5 (C)

MS: (CI, 70eV) m/z (rel. intensity) 155 (m+) (70), 126 (55), 109 (100), 95 (12), 81 (20), 67 (63)

HRMS calcd for C₉H₁₄O₂: 155.1072049 **Found:** 155.1069 error -2.0

3[2-(butan-1-ol)]cyclopentan-1-ol. (89) To a stirred solution of lithium aluminum hydride (138 mg, 1.29 mmol) in THF (5 mL) was added lactone **88** (65 mg, 0.51 mmol) at room temperature. The reaction was allowed to stir under argon for 20 hours. After the addition of H₂O (0.138 mL), 10% NaOH (0.138 mL) and H₂O (0.414 mL), the reaction was filtered. The filtrate was washed with *ca.* 50 mL of ethyl acetate. The combined organic were dried (MgSO₄). Evaporation of the solvent gave alcohol **89** as a colorless oil. Chromatography of **89** on silica gel (2:1 hexane:ethyl acetate) gave alcohol **89** as a colorless oil (59 mg, 90%).

R_f: 0.40 (CH₂Cl₂/MeOH 10:1)

IR: (neat) cm⁻¹ 3340, 2960, 2920, 2870, 1465, 1040

¹H NMR: (CDCl₃) δ 0.9 (t, J = 7.17, 3H), 1.3-1.78 (m, 8H), 1.94 (br m, 1H), 2.14 (m, 1H), 3.66 (m, 2H), 4.3 (br m 1H)

¹³C NMR: (CDCl₃) δ 11.31 (CH₃), 22.24 (CH₂), 27.30 (CH₂), 29.66 (CH₂), 35.66 (CH₂), 39.05(CH), 46.78(CH), 463.37 (CH₂), 73.50 (CH)

MS: (CI, 70eV) m/z (rel. intensity) 159 (m+) (10), 141 (25), 123 (80), 109 (70), 93 (30), 81 (82), 67 (100)

HRMS calcd for C₉H₁₄O₂: 159.1385050 **Found:** 159.1379 error -3.8

3-[-2-*p*-bromobenzoyl-3-butenoate]cyclopentan-1-ol (90) To a clean dry flask was added alcohol **89** (15 mg, 0.1 mmol), CH₂Cl₂ (3 mL) and neat triethylamine (0.02 mL, 0.12 mmol). The resulting solution was allowed to stir at room temperature for approximately 15 minutes the solution of *p*-bromobenzoyl chloride (24 mg, 0.11 mmol) in CH₂Cl₂ (2.0 mL) was added. The resulting solution was allowed to stir under argon at room temperature for *ca.* 48 hours. After the addition of water, the aqueous layer was separated and extracted with CH₂Cl₂. The combined organic extracts were dried (MgSO₄). Evaporation of the solvent gave a pale yellow oil. Chromatography of **90** on silica gel (2:1, hexane:ethyl acetate) gave alcohol **90** as a colorless oil (17 mg, 52%).

R_f: 0.30 (Hex/EtOAc 2:1)

IR: (neat) cm⁻¹ 3400, 2960, 2865, 1645, 1590, 1270, 1200, 1010, 750

¹H NMR: (CDCl₃) δ 0.95 (m, 3H), 1.35-1.96 (m, 10H), 2.25 (m, 1H), 4.25-4.38 (m, 3H), 7.58 (d, J = 8.29, 2H), 7.87 (d, J = 8.21 2H)

¹³C NMR: (CDCl₃) δ 11.41 (CH₃), 22.33 (CH₂), 28.25 (CH₂), 34.99 (CH₂), 39.7. (CH), 40.21 (CH₂), 41.67 (CH₂), 44.78 (CH), 65.96 (CH₂), 66.0 (CH₂), 128.00 (C), 129.51 (C), 132.01 (CH), 132.73 (CH).

MS: (CI, 70eV) *m/z* (rel. intensity) 341 (m+) (3.5), 323 (5), 306 (2), 288 (1), 183 (41), 123 (100), 93 (20), 81 (45), 67 (40)

HRMS calcd for C₁₆H₂₁O₃Br: 341.0752309 **Found**: 341.074112 error: -3.3 ppm

3-[-2-*p*-bromobenzoyl-3-butanoate]cyclopentan-1-one (91) To a stirred solution of alcohol **90** (25 mg, 0.073 mmole) in acetone(5 mL) was added 8N Jones reagent (4 drops). The resulting solution was allowed to stir for *ca.* 20 minutes. After the addition of water, the reaction mixture was transferred to a separatory funnel and extracted with 3

portions of ethyl acetate. The combined organic extracts were dried (MgSO₄). Evaporation of the solvent gave a deep green oil. Chromatography of the oil on silica gel (2:1, hexane:ethyl acetate) gave ketone **91** as a colorless oil (23 mg, 92%).

R_f: 0.34 (Hex/EtOAc 3.5:1)

IR: (neat) cm⁻¹ 2945, 2910, 1620, 1580, 1470, 1450, 1380, 1260, 1110, 1090, 1000, 745, 720

¹H NMR: (CDCl₃) δ 0.99 (overlapping pair of t, J = 7.47, 3H), 1.3-2.58 (m, 10H), 4.40 (d, J = 4.58, 2H), 7.59 (d, J = 8.39, 2H), 7.88 (d, J = 8.39, 2H)

¹³C NMR: (CDCl₃) δ 11.01 (CH₃), 22.57 (CH₂), 327.93 (CH₂), 29.67 (CH₂), 38.87 (CH₂), 38.88 (CH), 43.55 (CH₂), 44.32 (CH), 64.80 (CH₂), 128.16 (C), 129.02 (C), 131.00 (CH), 131.80 (CH)

MS: (CI, 70eV) m/z (rel. intensity) 159(m+) (15), 141 (30), 123 (50), 110 (20), 93 (20), 81 (94), 67 (100), 55 (45)

Calcd for C₉H₁₈O₂: C 68.313% H 11.465% **Found**: C 68.12% H 11.31%

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VII. SELECTED SPECTRA

1. 3[-2-(but-3-en-1-ol)]cyclopentan-1-ol (**66**).

^1H NMR (270 Hz)	57
^{13}C NMR (270 Hz)	58
2. 3[-2-(butan-1-ol)]cyclopentan-1-ol. (**67**).

^1H NMR (270 Hz)	59
^{13}C NMR (270 Hz)	60
3. 3[-2-*p*- bromobenzoyl-3-butenoate)]cyclopentan-1-ol (**68**).

^1H NMR (270 Hz)	61
^{13}C NMR (270 Hz)	62
4. 3[-2-*p*- bromobenzoyl-3-butanoate)]cyclopentan-1-one (**69**).

^1H NMR (400 Hz)	63
^{13}C NMR (400 Hz)	64
5. 2-oxabicyclo-4-ethyl[3.2.1]octan-3-one (**84**).

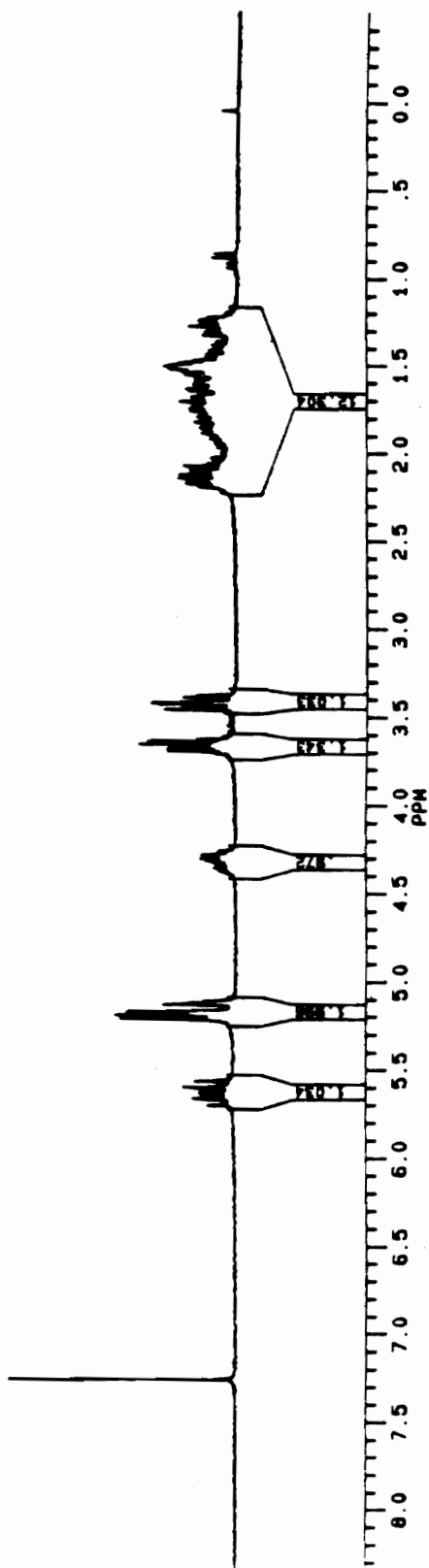
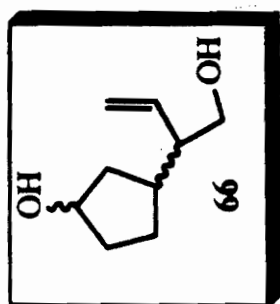
^1H NMR (270 Hz)	65
^{13}C NMR (270 Hz)	66
TOCSY NMR (400 Hz)	67
HETCOR NMR (270 Hz)	68
6. 3[-2-(butan-1-ol)]cyclopentan-1-ol. (**85**).

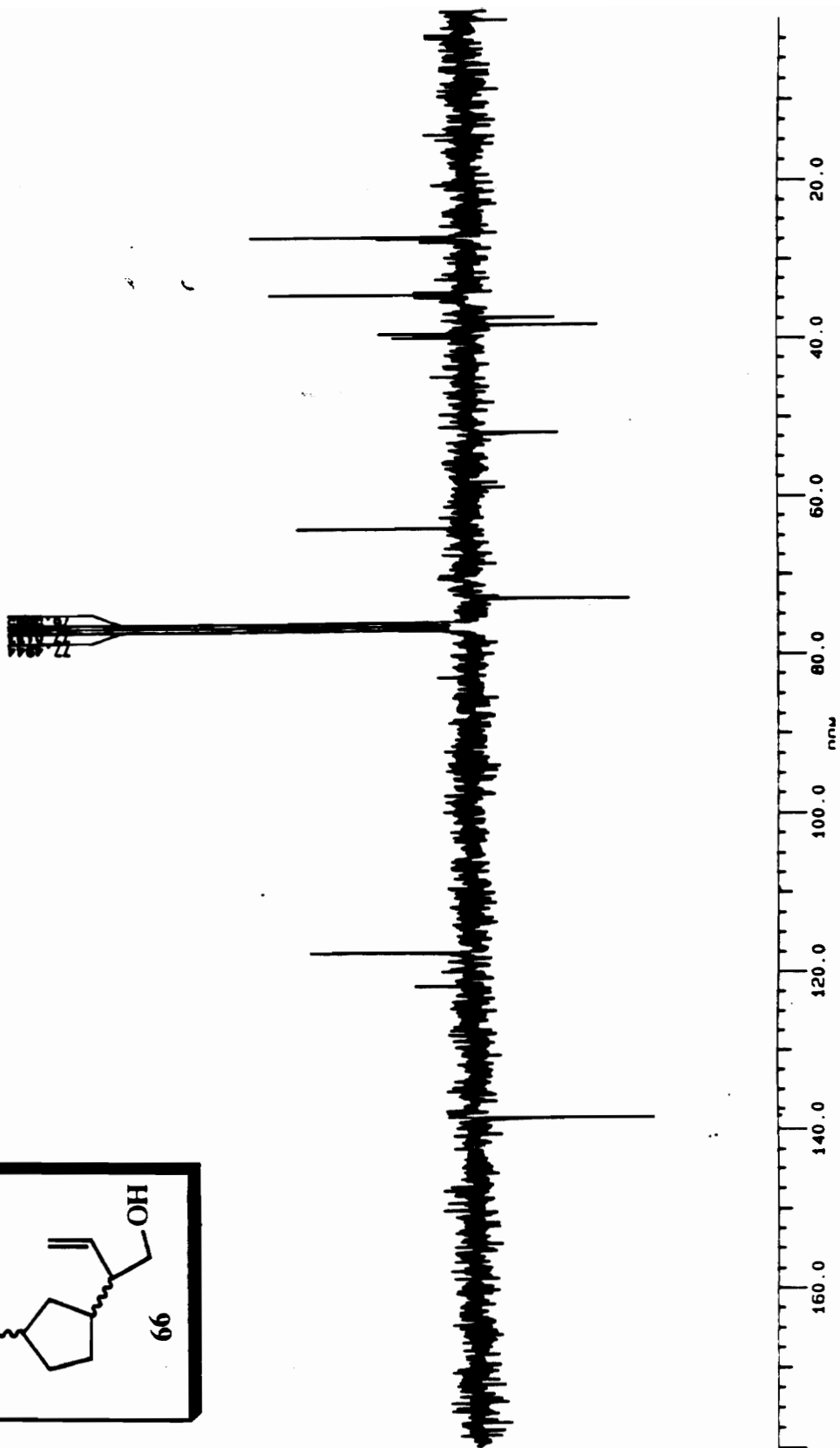
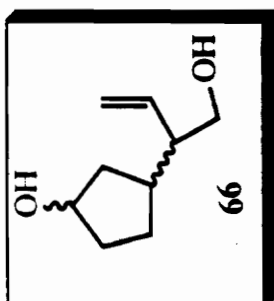
^1H NMR (270 Hz)	69
^{13}C NMR (400 Hz)	70
7. 3[-2-*p*- bromobenzoyl-3-butenoate)]cyclopentan-1-ol (**86**)

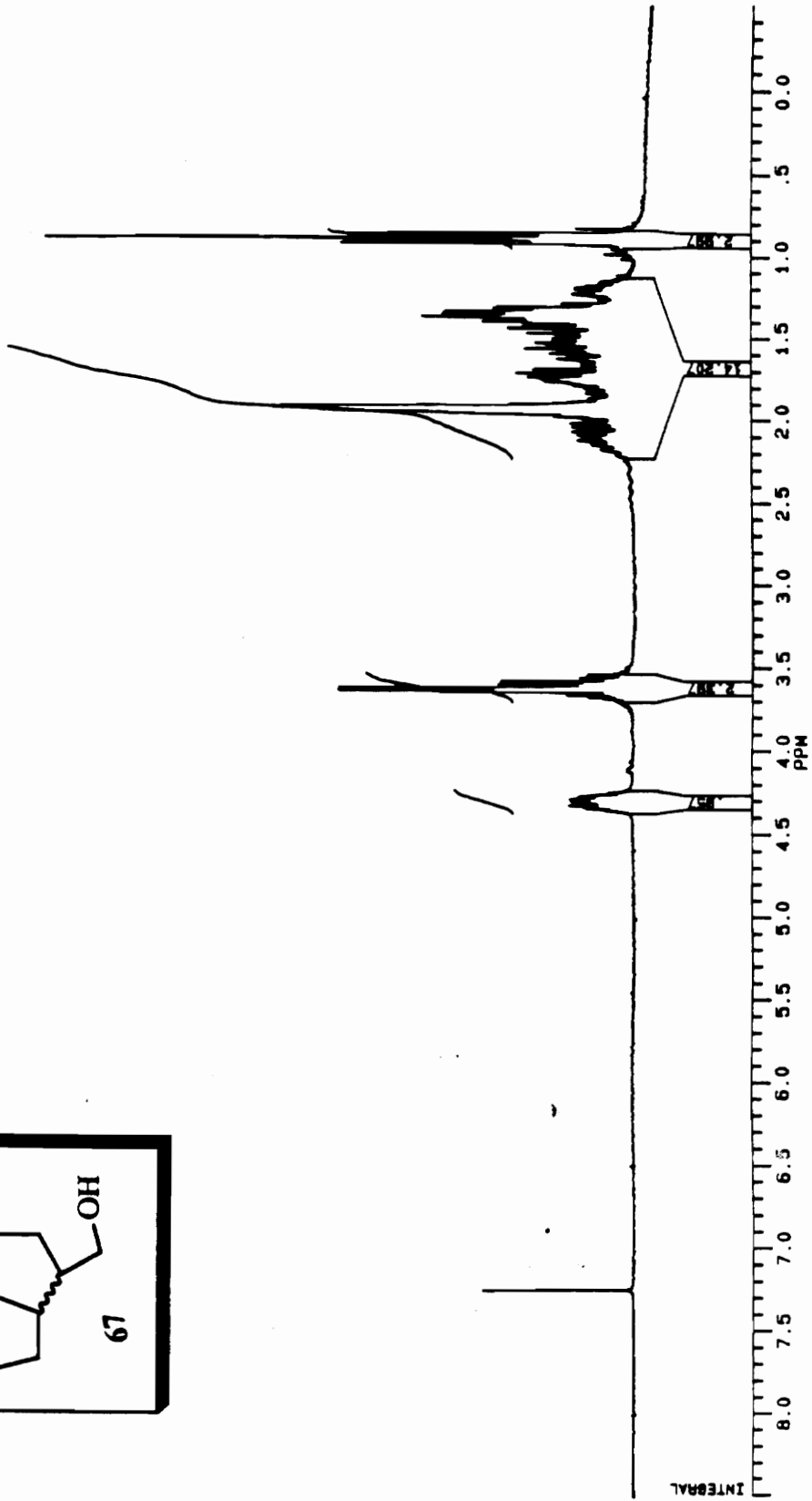
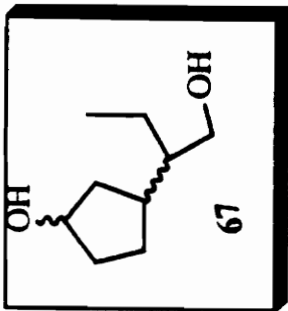
^1H NMR (400 Hz)	71
^{13}C NMR (400 Hz)	72
8. 3[-2-*p*- bromobenzoyl-3-butanoate)]cyclopentan-1-one (**87**).

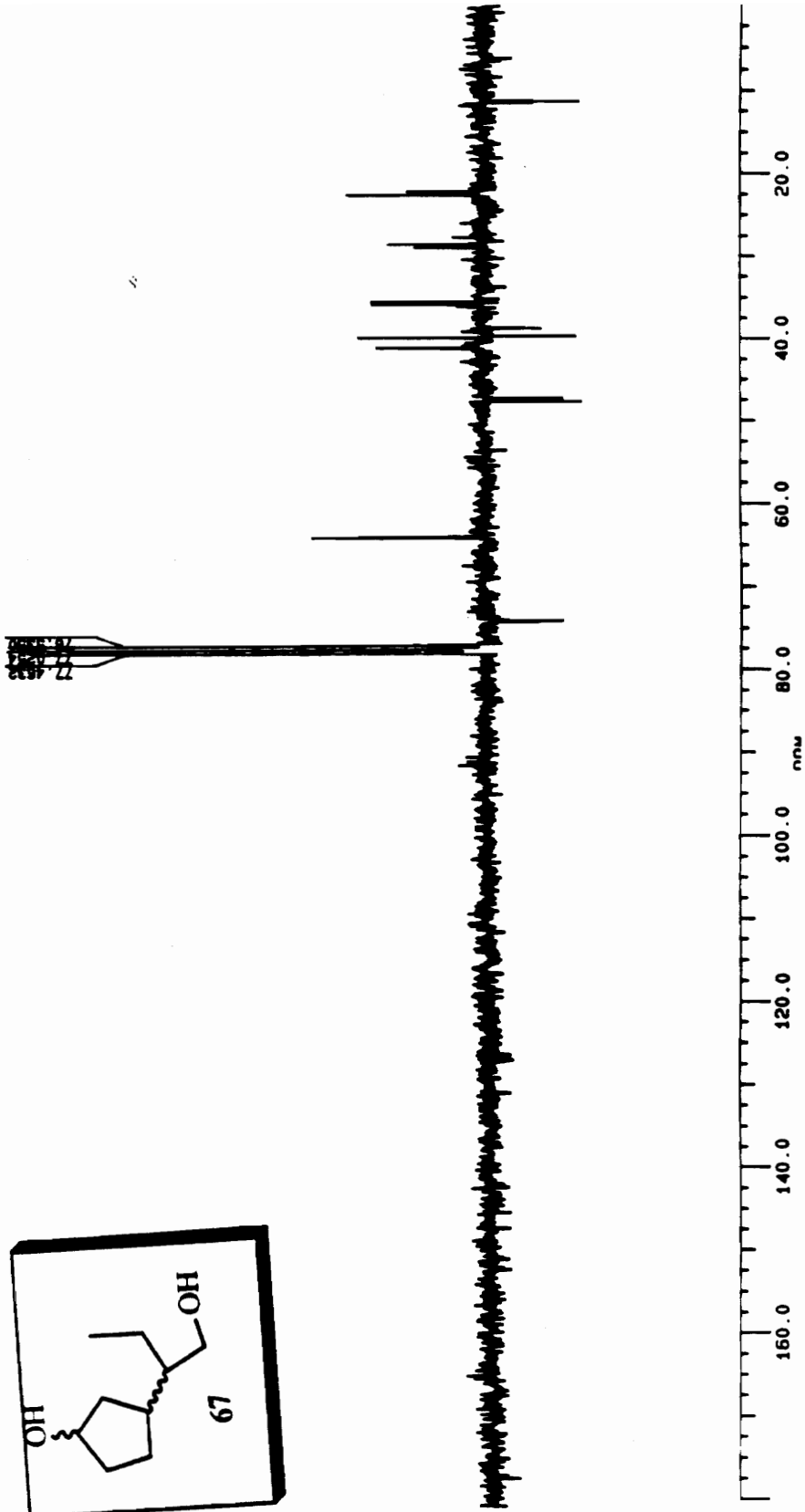
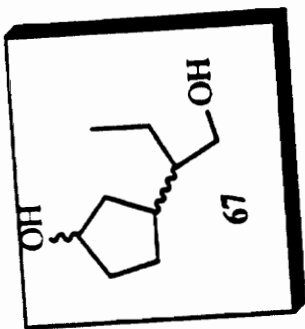
^1H NMR (400 Hz)	73
^{13}C NMR (400 Hz)	74
9. 2-oxabicyclo-4-ethyl[3.2.1]octan-3-one (**88**).

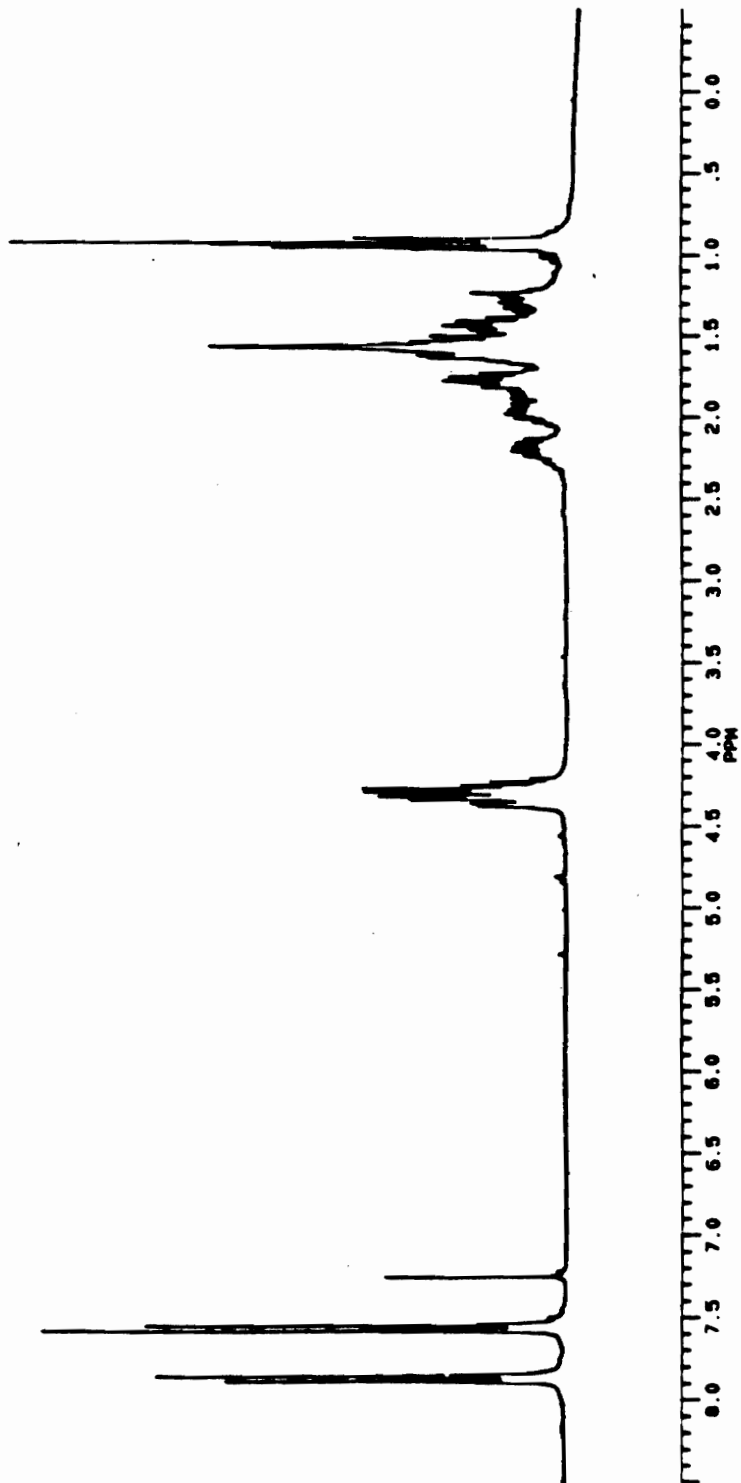
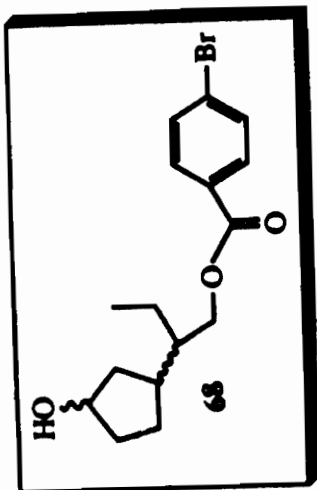
¹ H NMR (400 Hz)	75
¹³ C NMR (400 Hz)	76
TOCSY NMR (400 Hz)	77
10. 3[-2-(butan-1-ol)]cyclopentan-1-ol. (89) .	
¹ H NMR (400 Hz)	78
¹³ C NMR (400 Hz)	79
11. 3-[-2- <i>p</i> - bromobenzoyl-3-butanoate)]cyclopentan-1-one (91) .	
¹ H NMR (400 Hz)	80
¹³ C NMR (400 Hz)	81

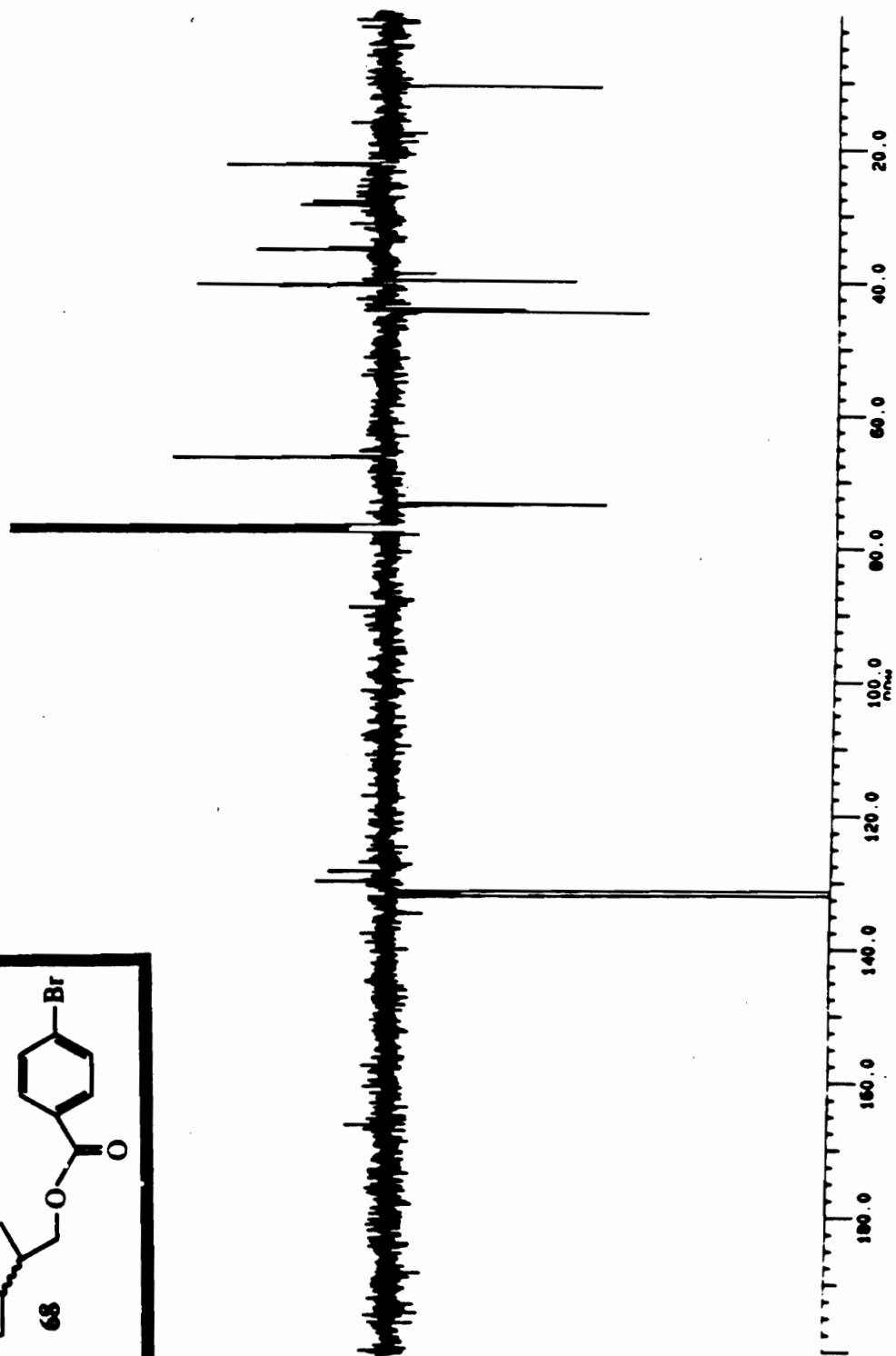
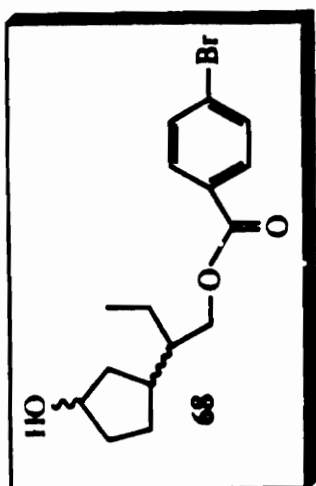


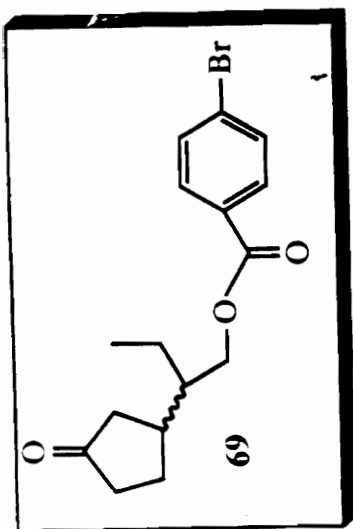






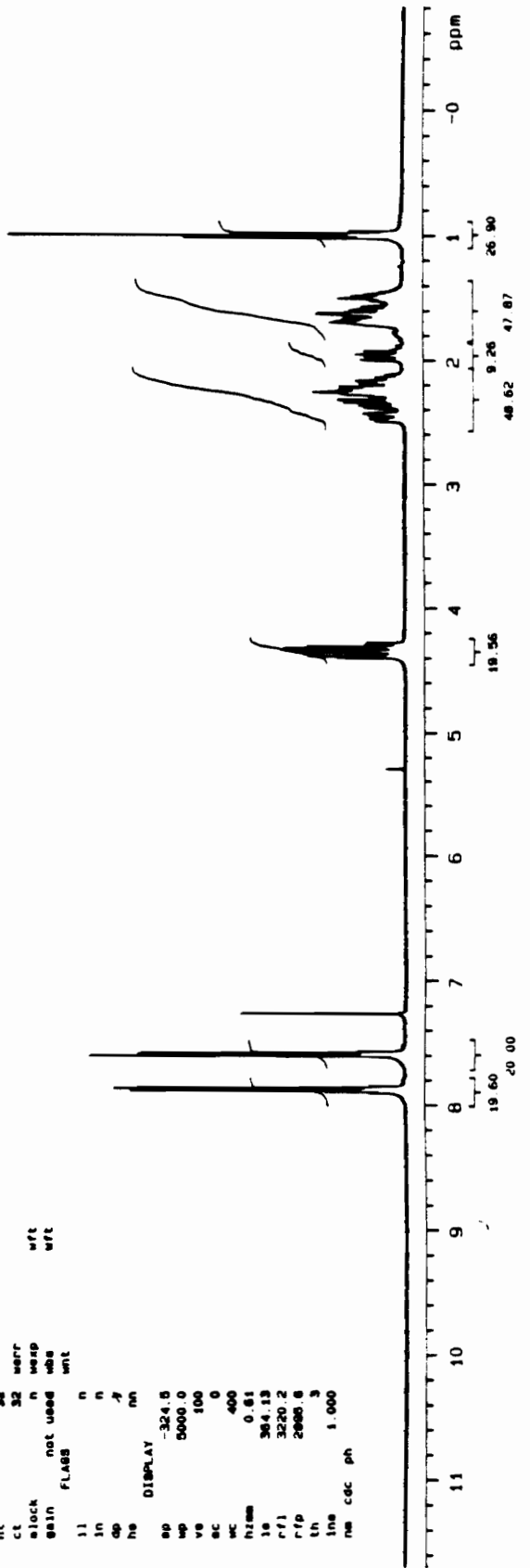


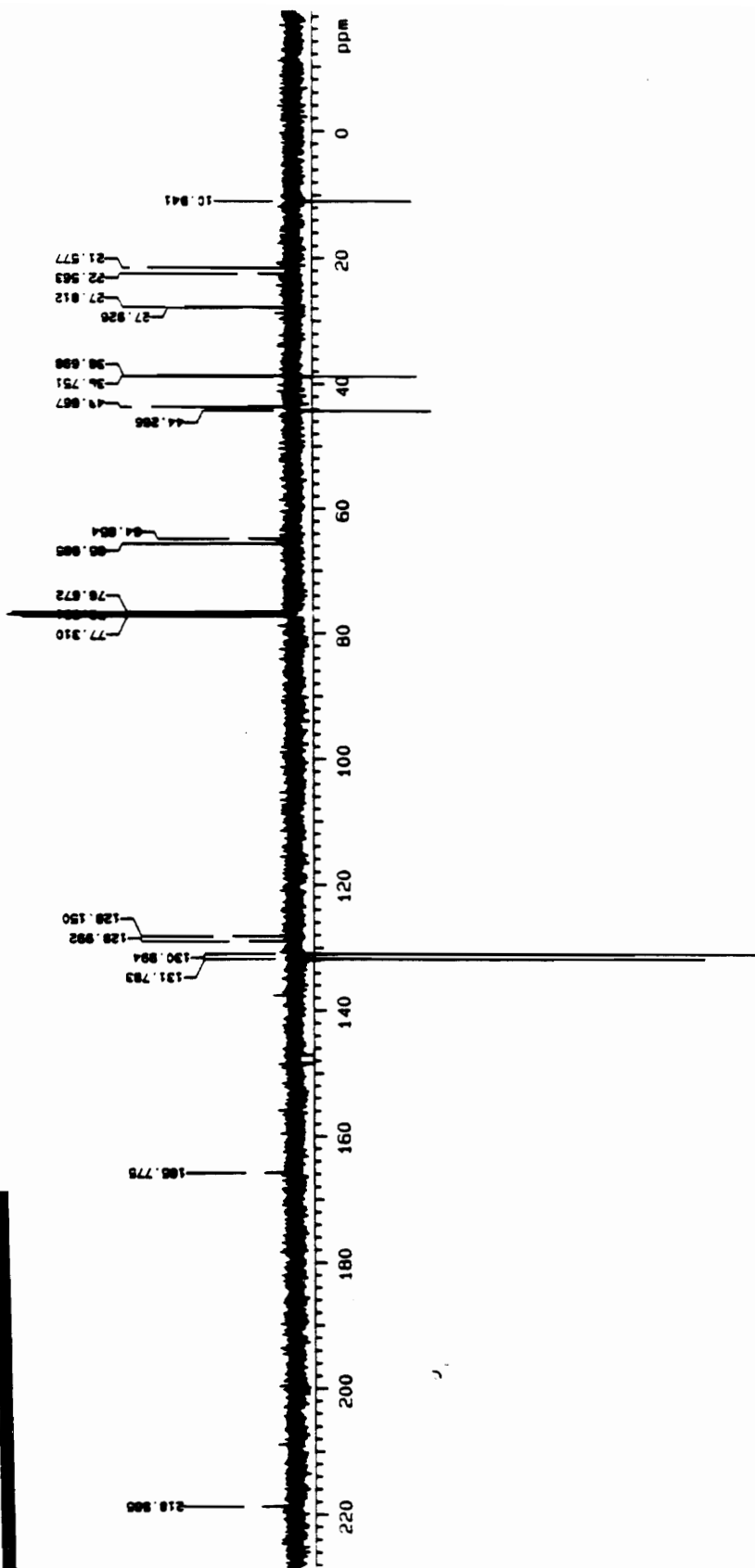
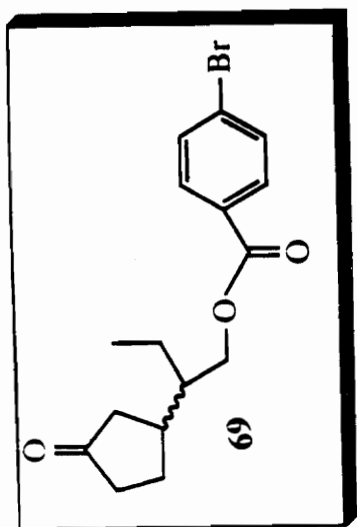


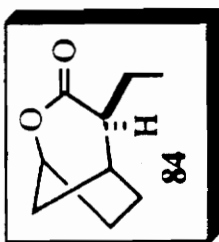


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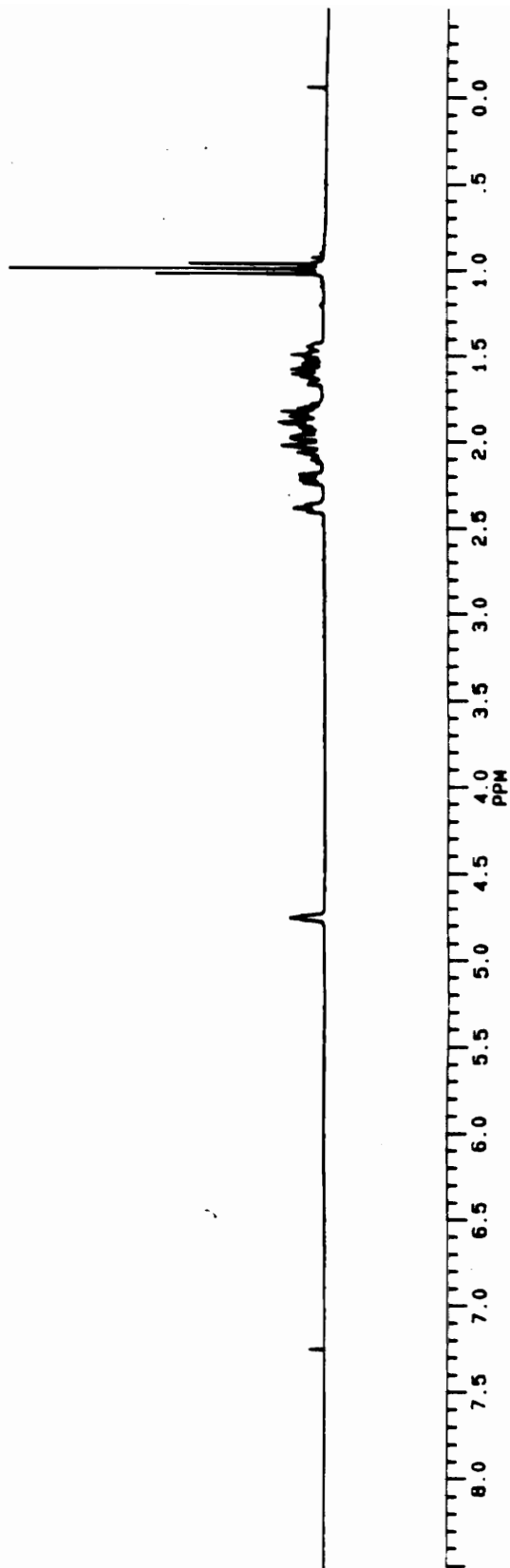
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          nt      32
          ct      32  werr
          alock  n  wexp      wft
          gain  not used  wba      wft
          FLAGs
          11      n
          in      n
          op      /
          he      mh
          DISPLAY -324.8
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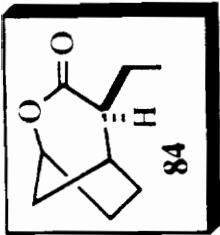






84



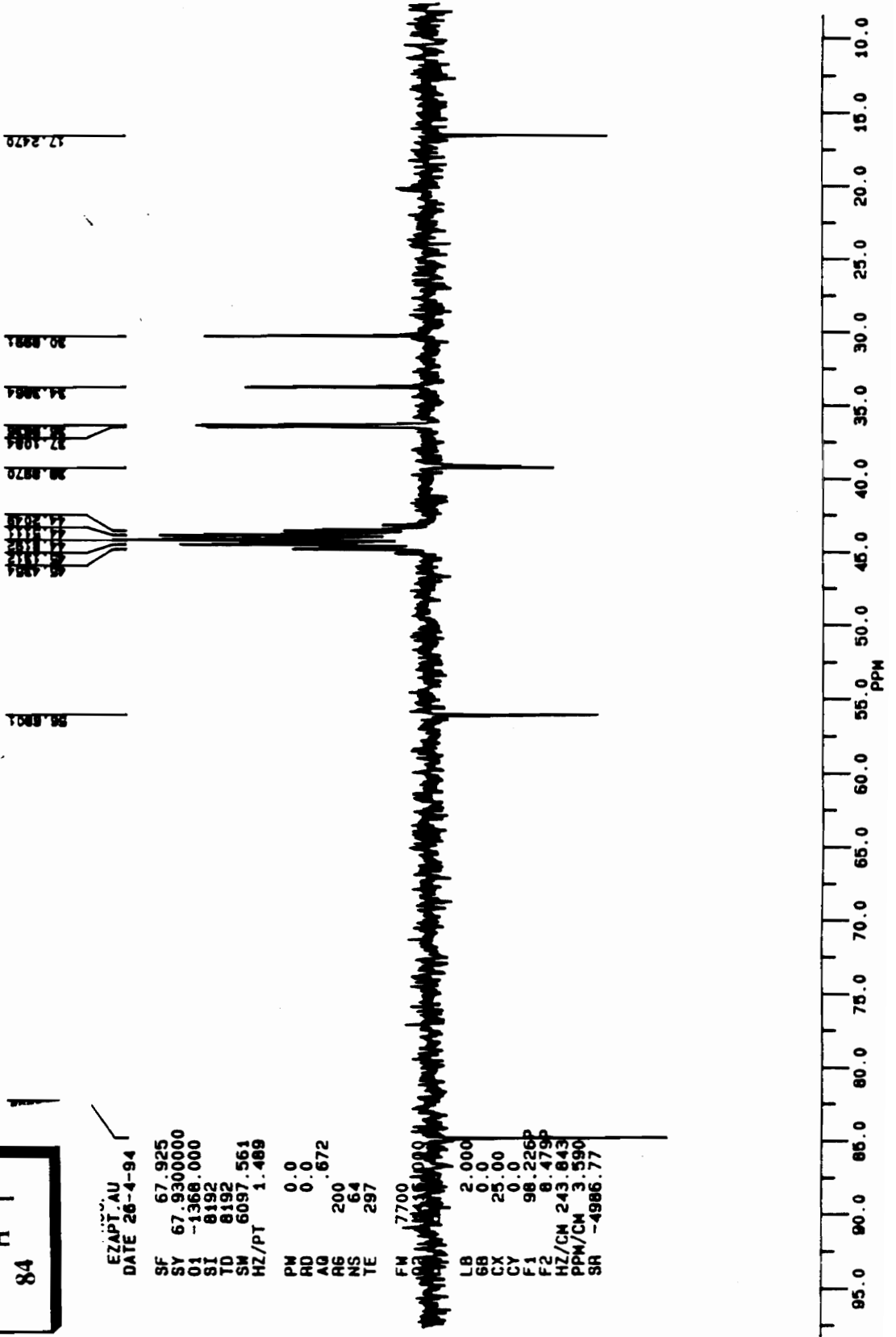


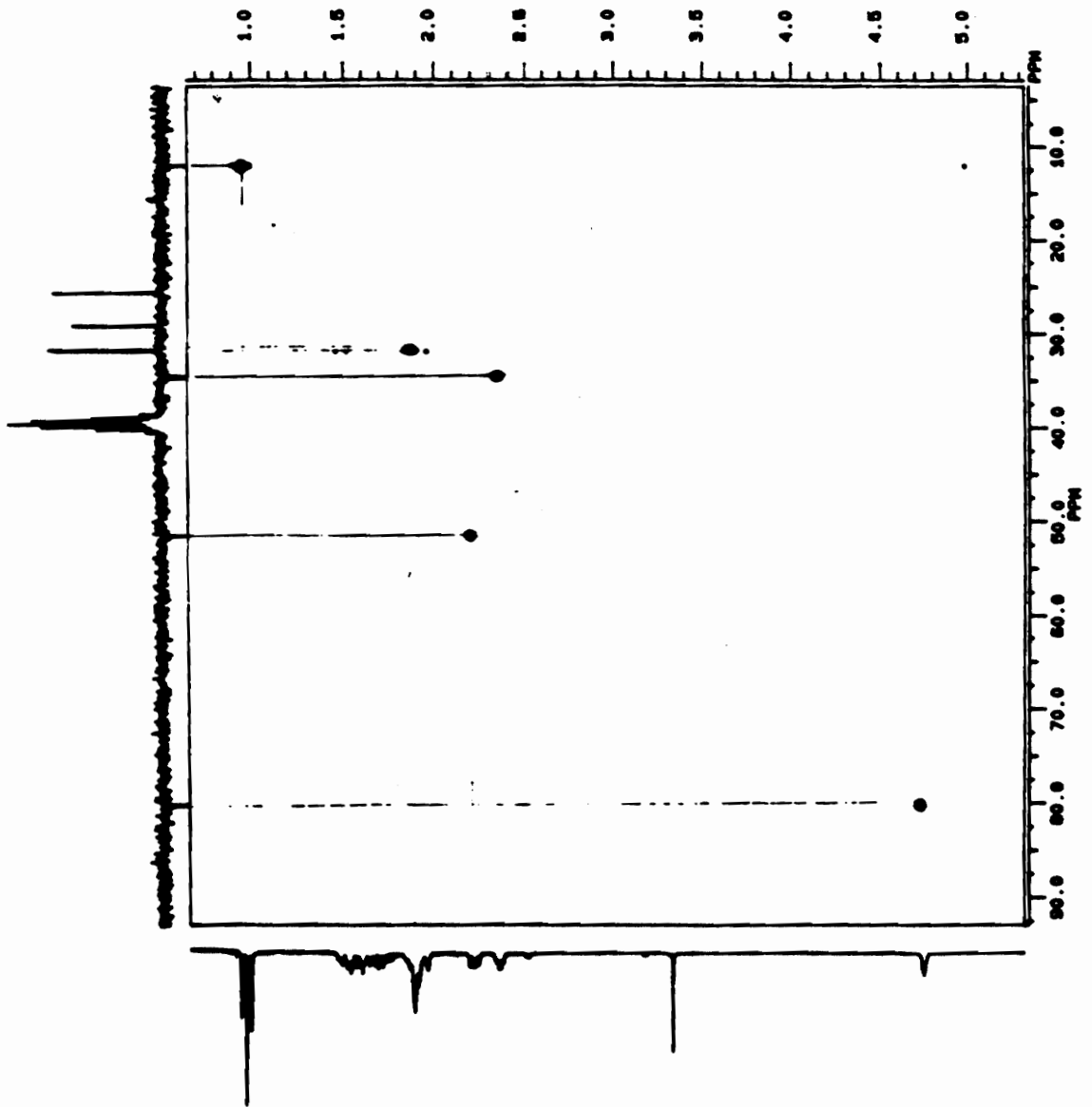
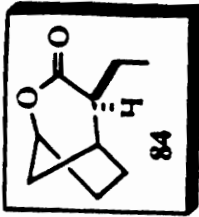
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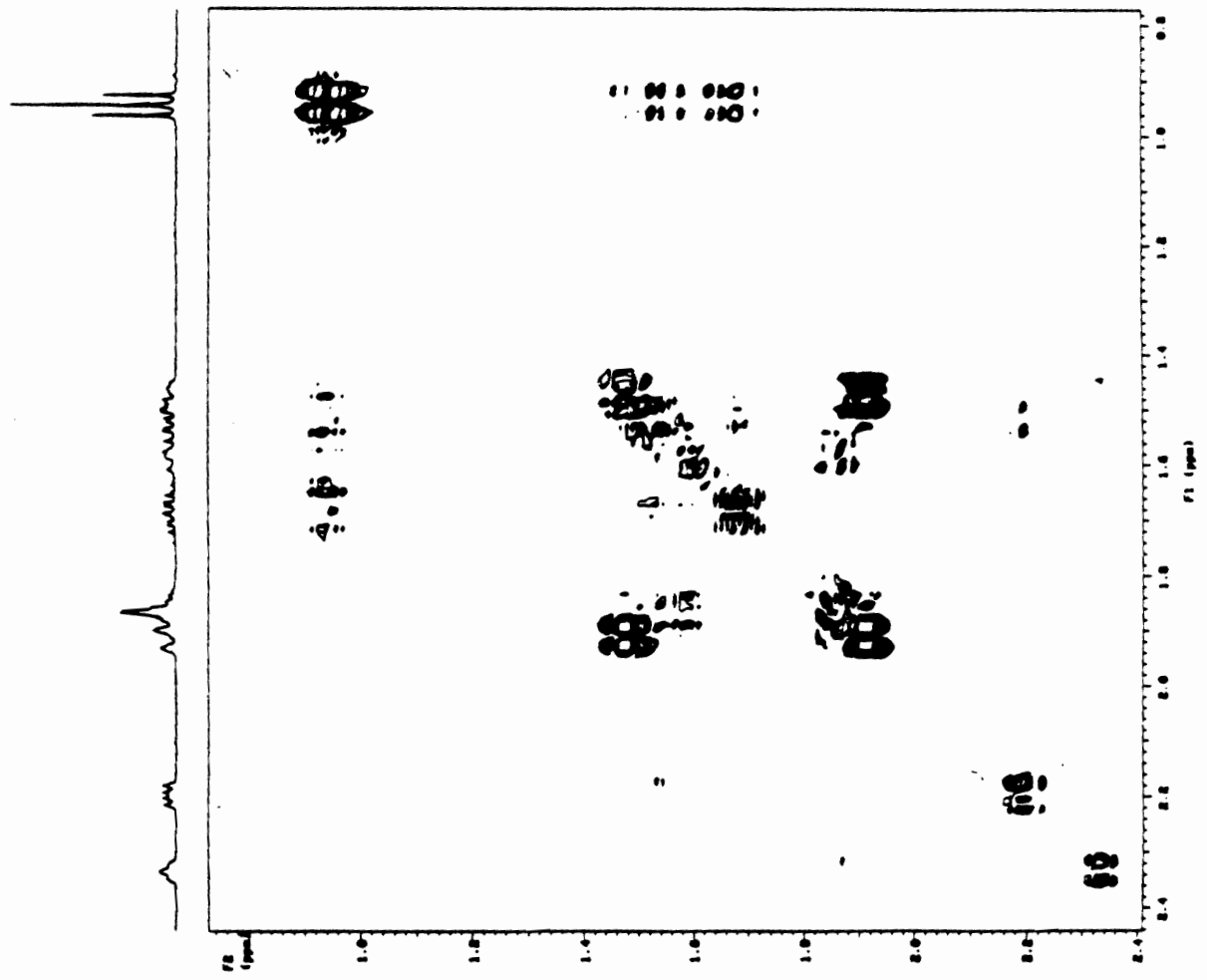
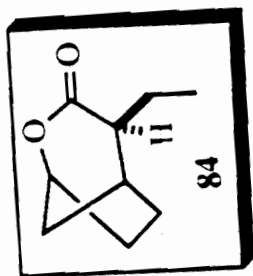
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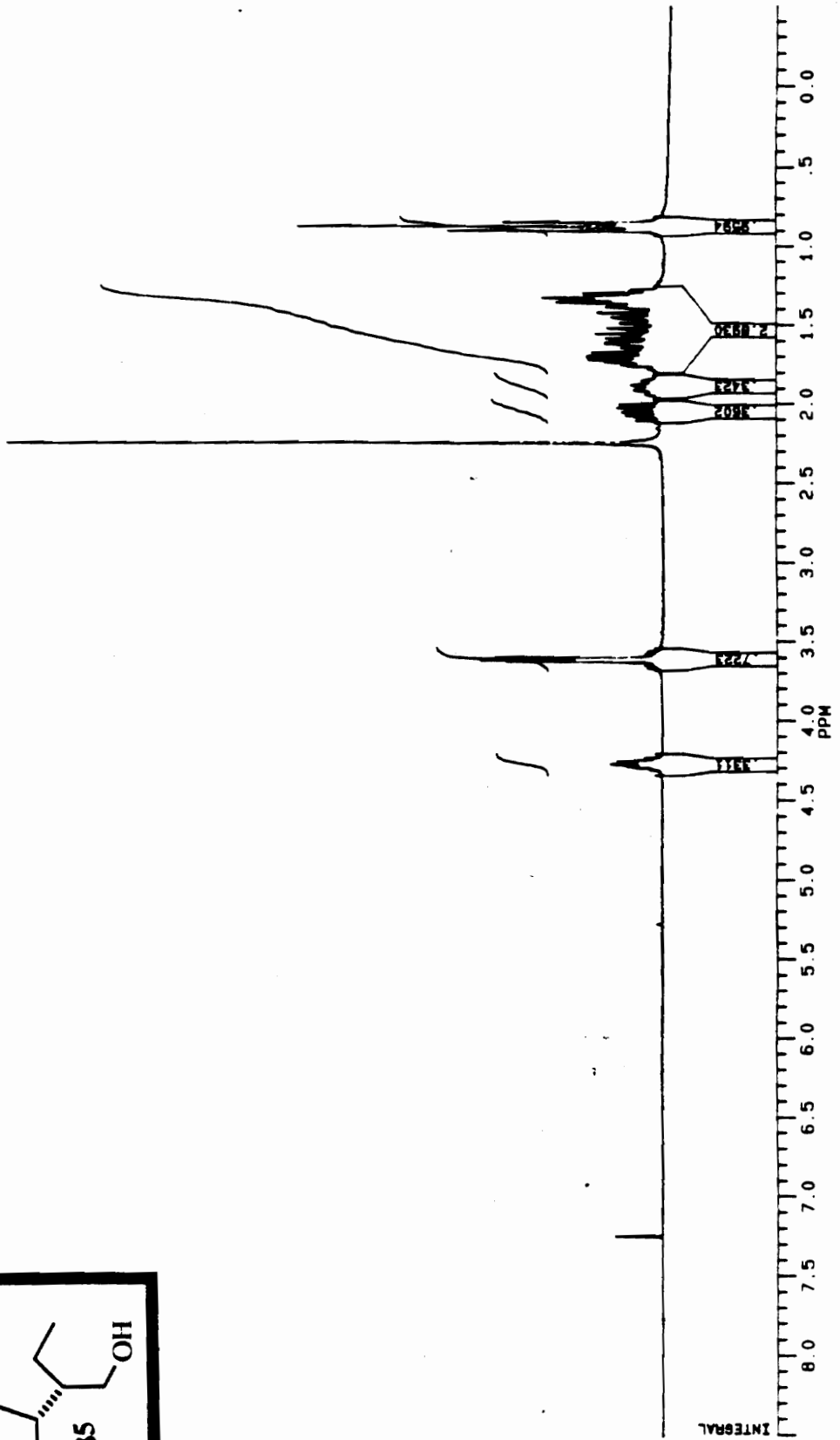
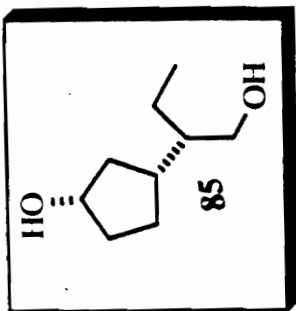
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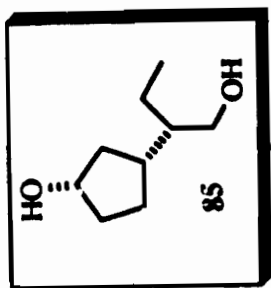
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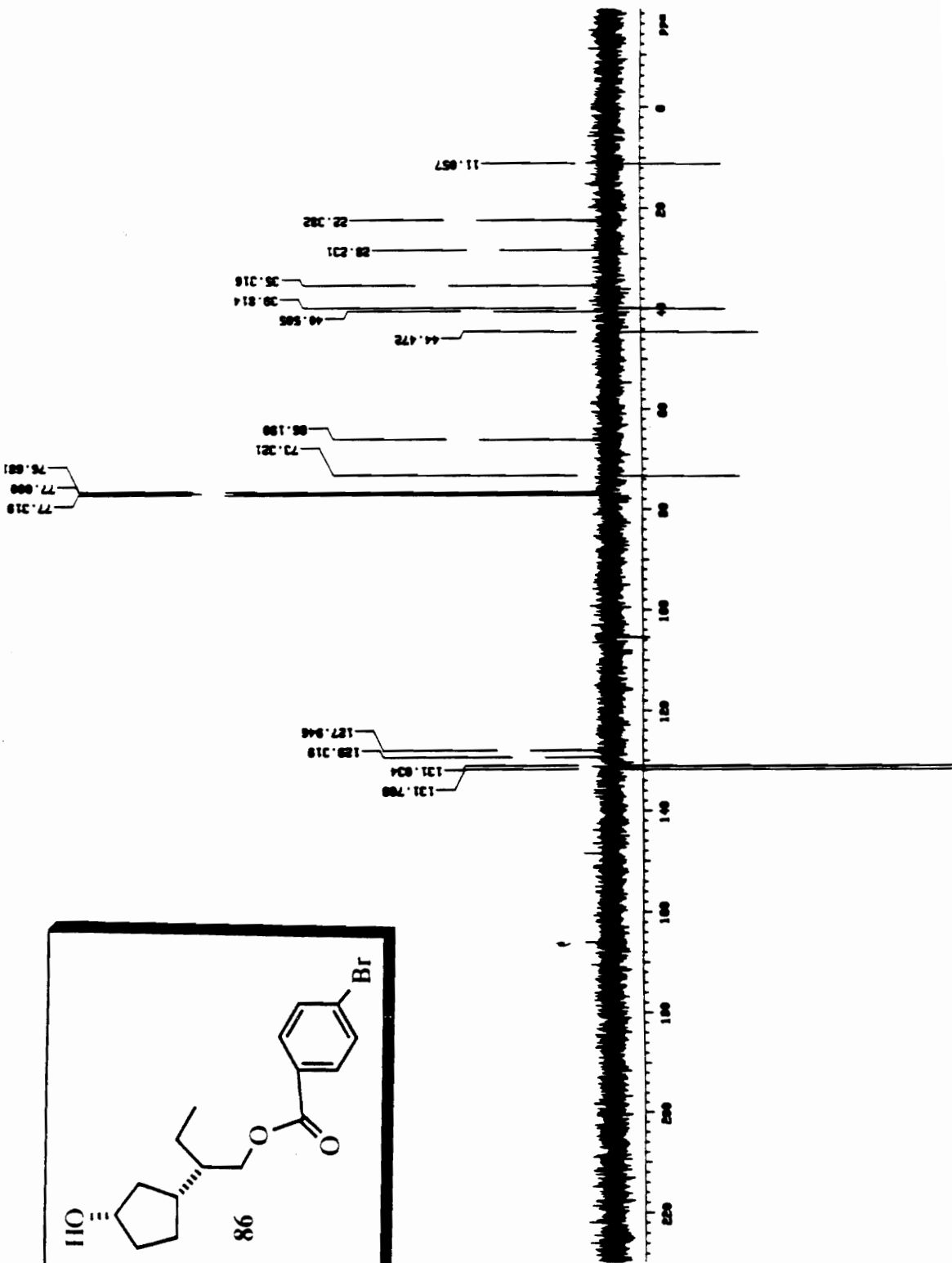
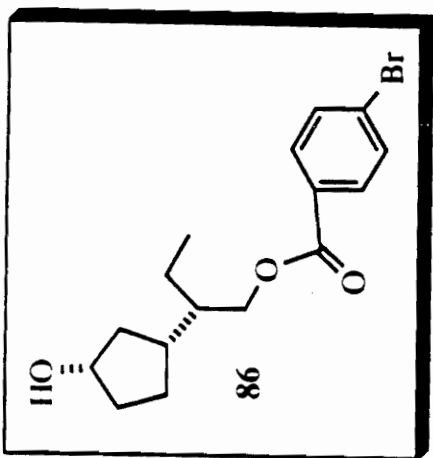


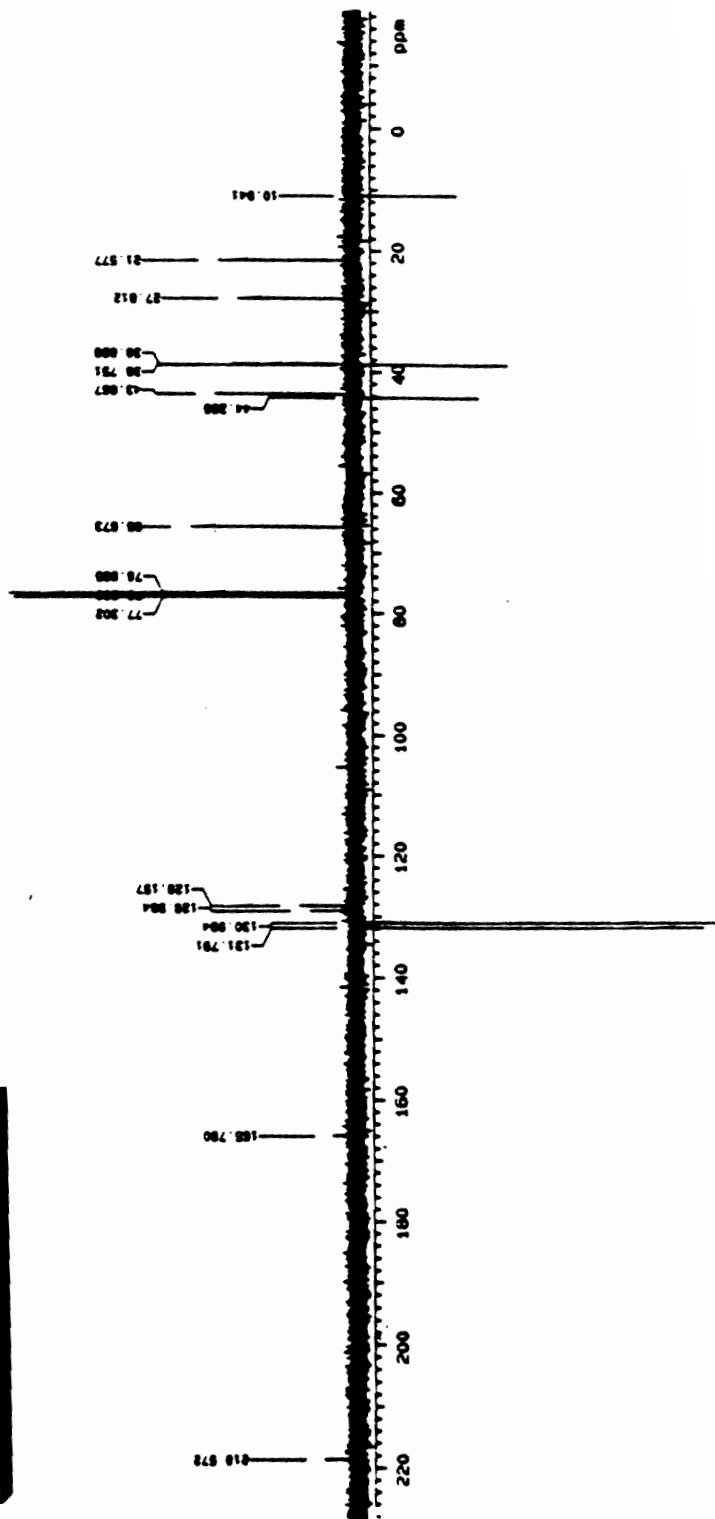
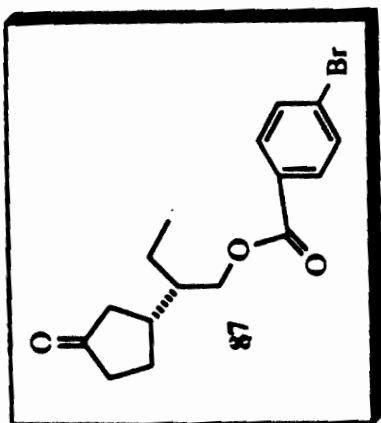


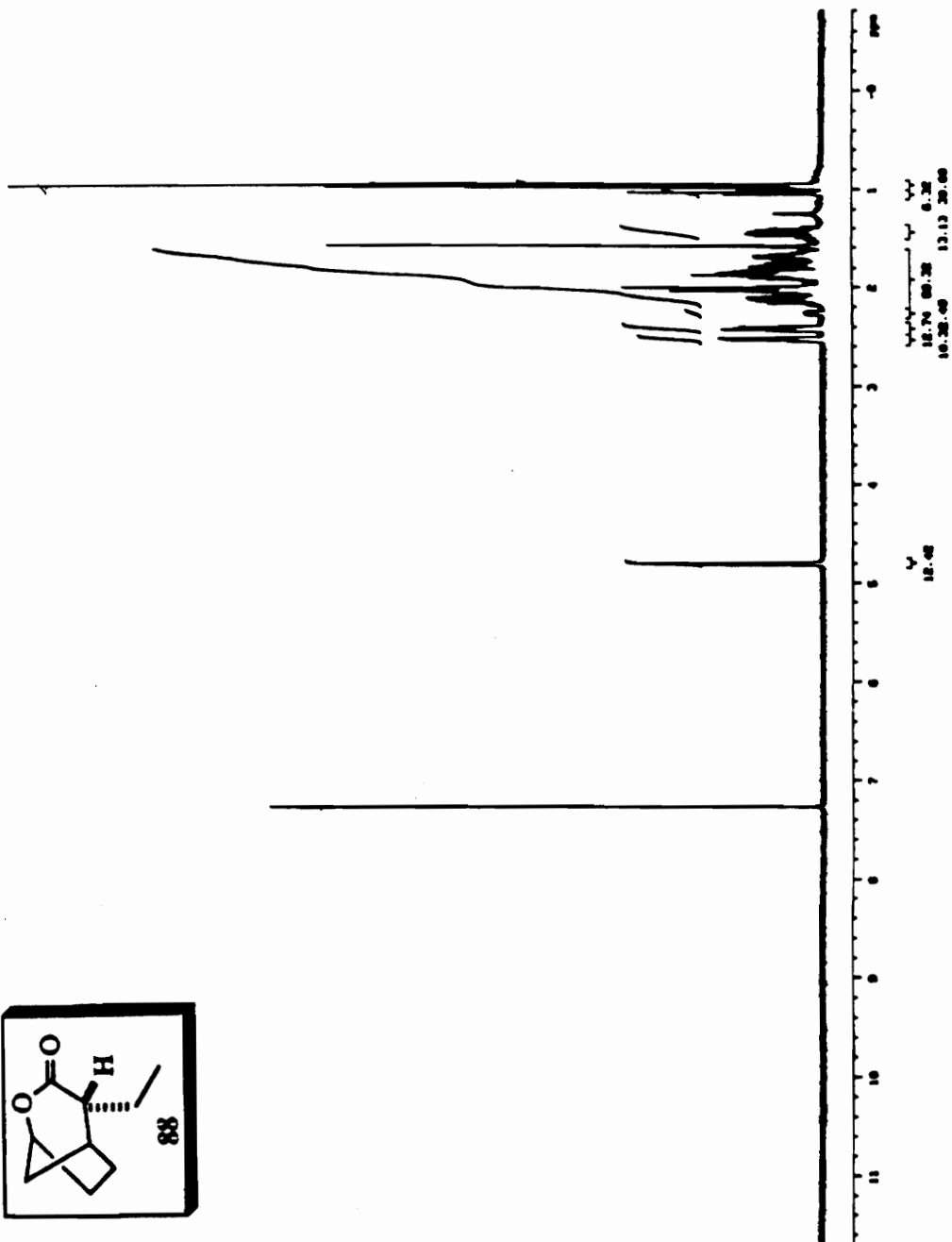
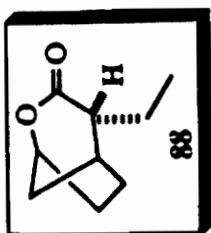


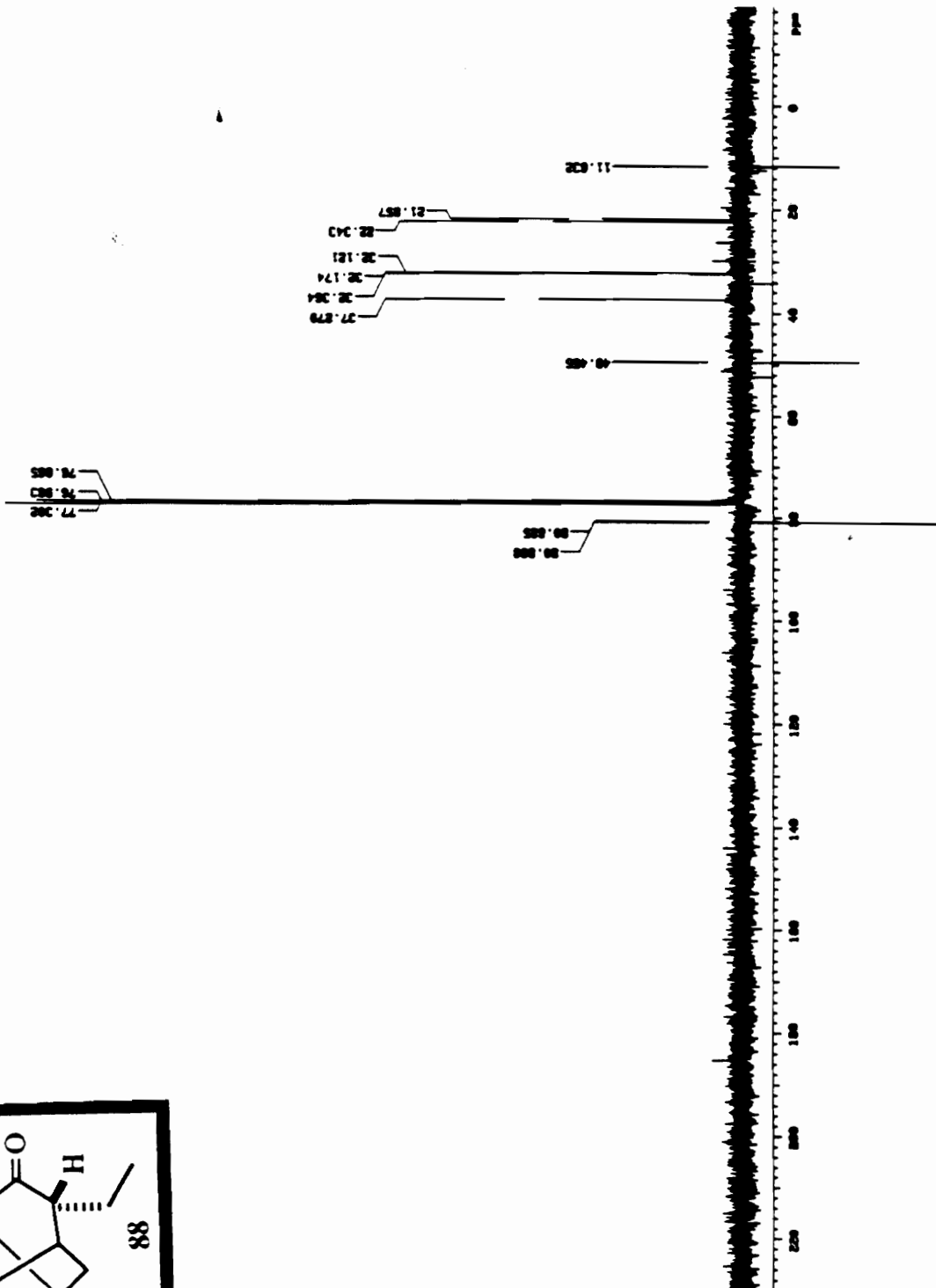
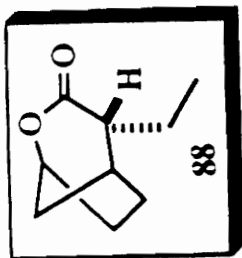
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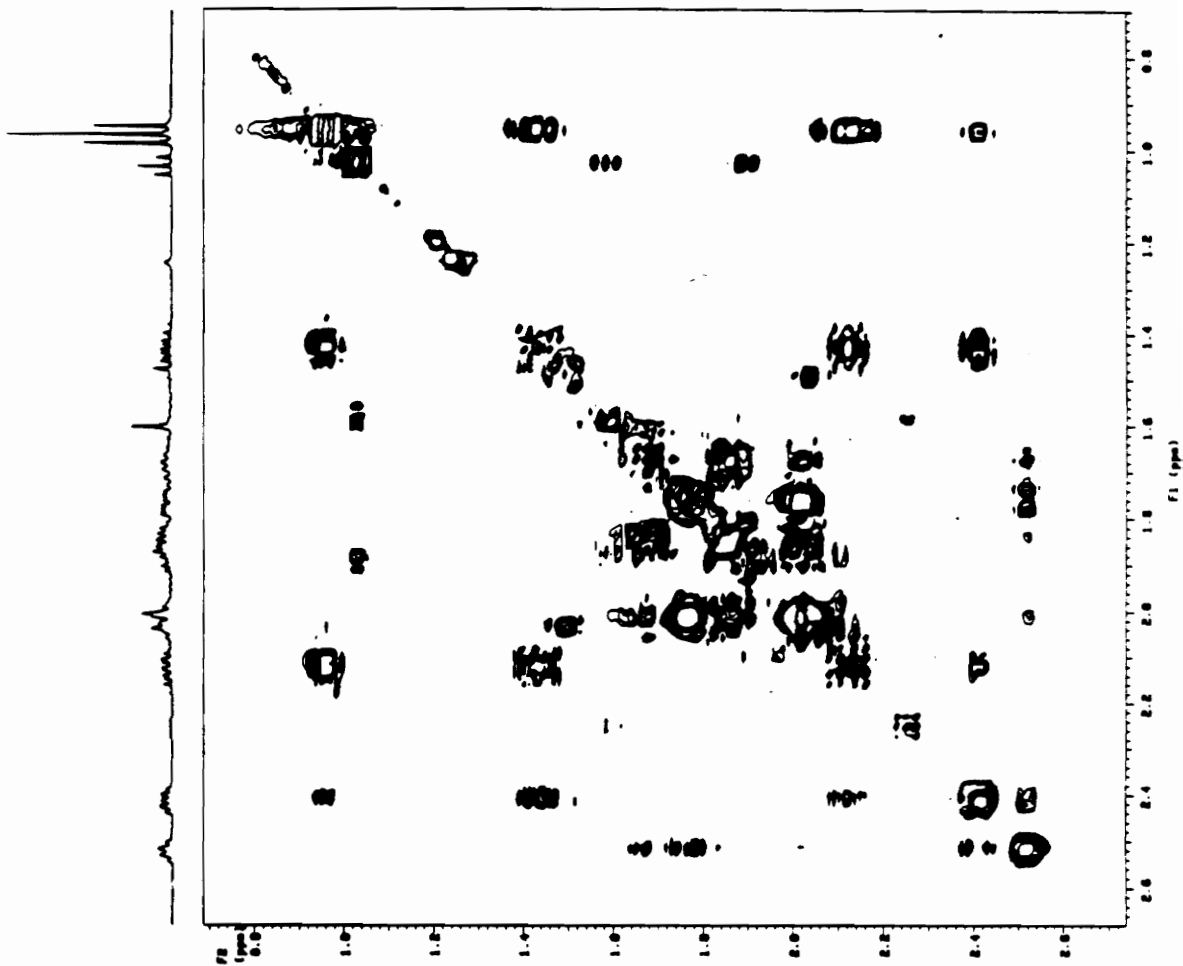
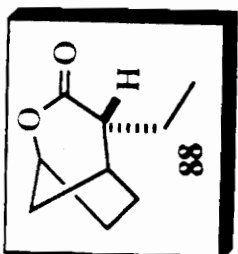
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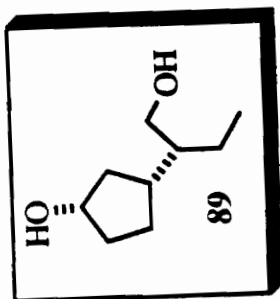


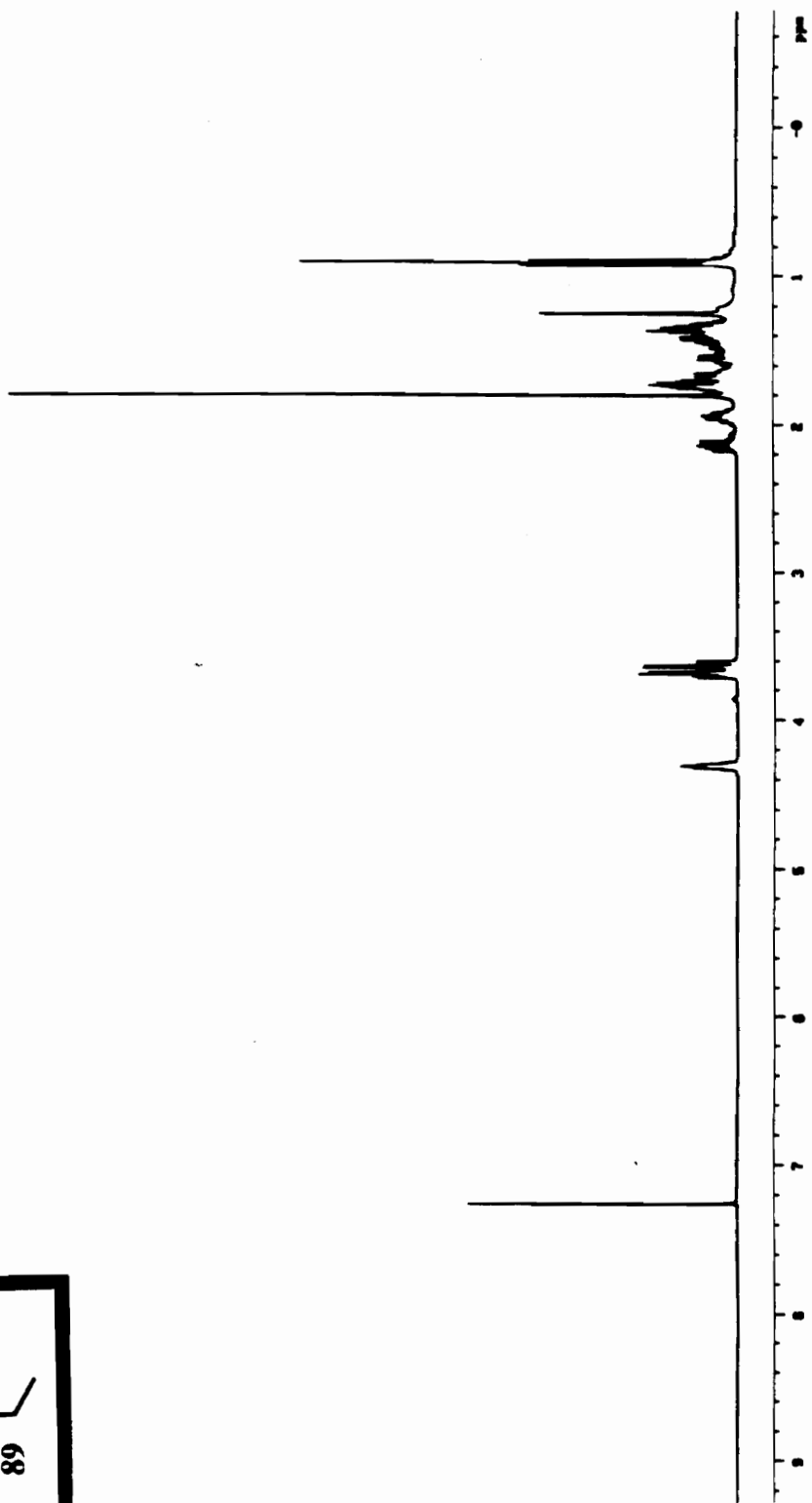
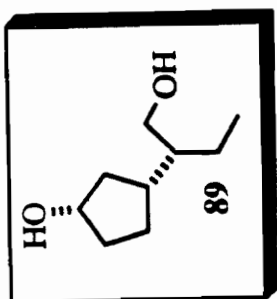


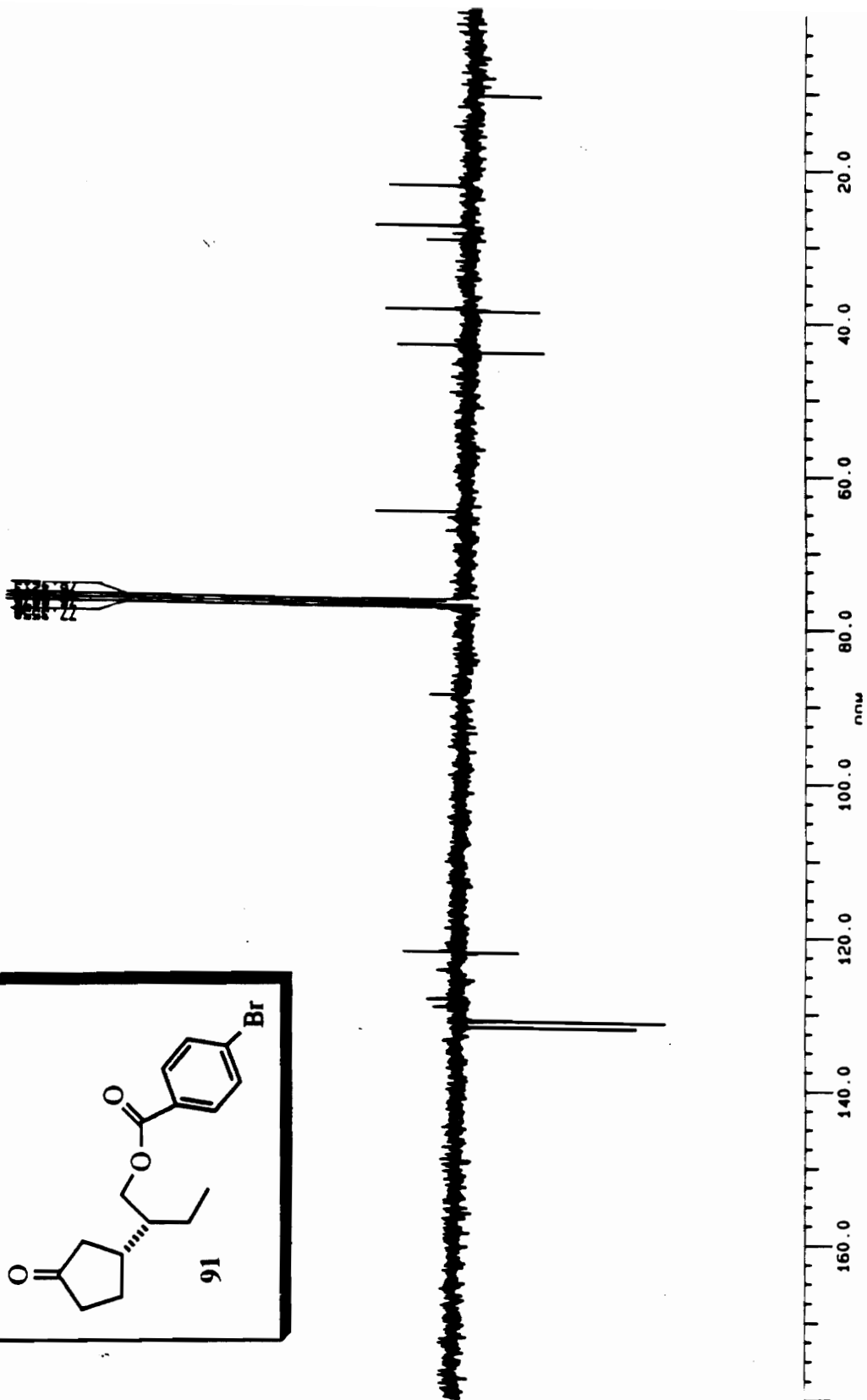
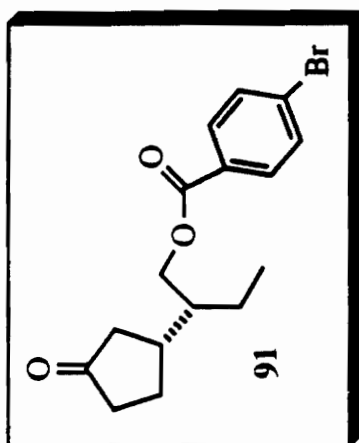


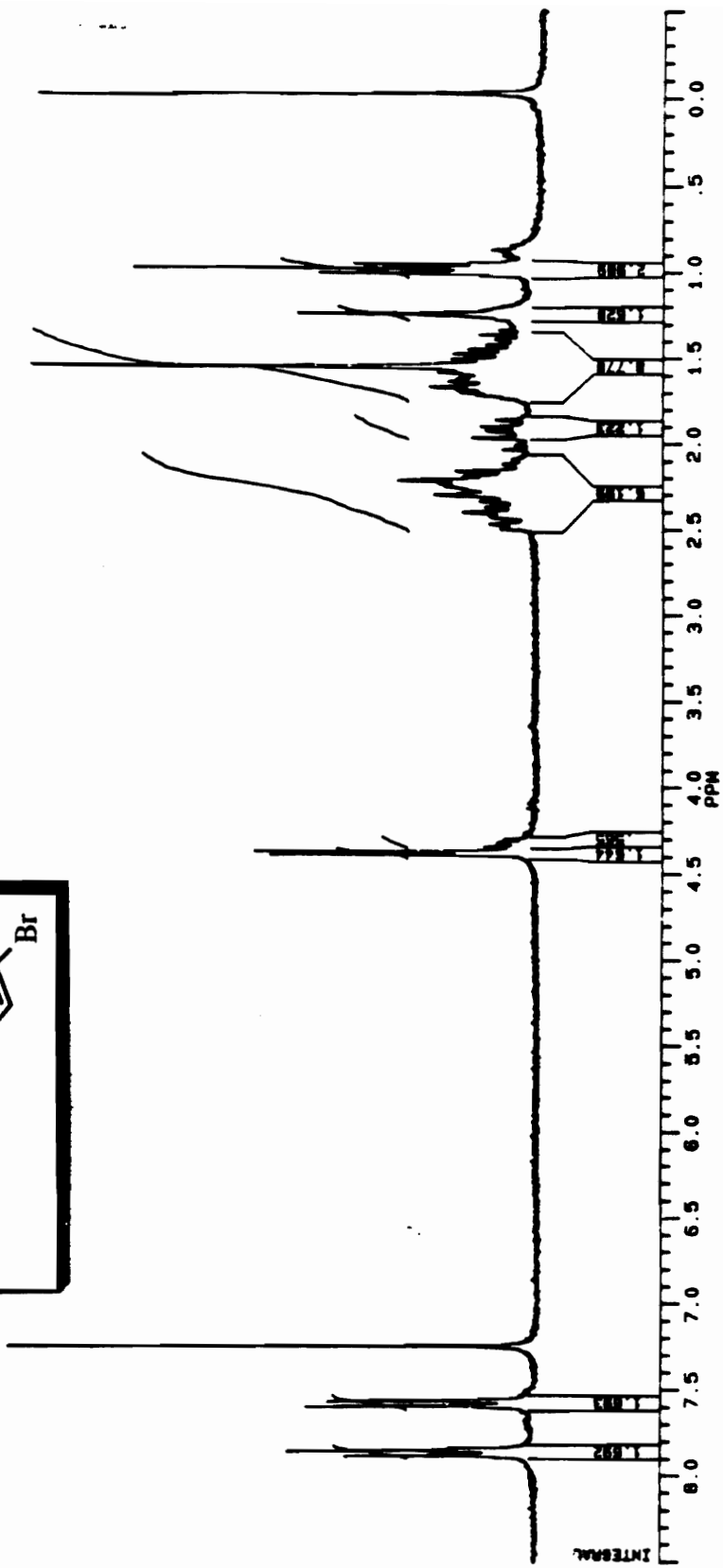
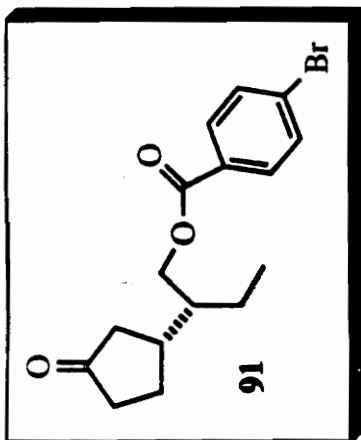








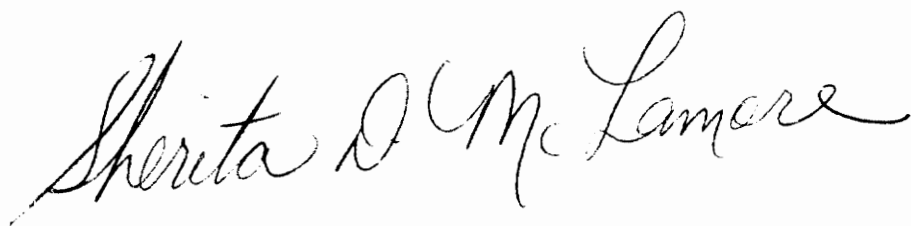




VIII. VITA

Sherita Dolores McLamore, the daughter of Harkless and Frances McLamore, was born on May 14, 1970. She was raised in the inner city of Washington, D.C. with her two sisters, Barbara McLamore-Purdie and Joetta McLamore, where she attended and graduated from Ballou Sr. High School. Upon graduation, Sherita entered Clark-Atlanta University where she received a B.S. in Chemistry in 1992. Because of her interest in chemistry, the author chose to pursue graduate studies at VPI & SU where she obtained a M.S. in organic chemistry under the direction of Professor Tomas Hudlicky.

Currently, the author continues to study organic chemistry. She is pursuing her Ph.D. at the University of Florida at Gainesville in the research group of Professor Tomas Hudlicky.

A handwritten signature in cursive script that reads "Sherita D. McLamore". The signature is written in black ink and is centered on the page.