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PART I. ELECTROPHILE STRUCTURE AS A FACTOR IN ALKYLATIONS OF CAMPHOR DERIVATIZED GLYCINATES. PART II. PUMMERER REACTIONS OF S-OXIDES OF 1,3-OXATHIOLAN-5-ONES AND 1,3-THIAZOLIDIN-4-ONES.

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PART I

ELECTROPHILE STRUCTURE AS A FACTOR IN ALKYLATIONS OF CAMPHOR DERIVATIZED GLYCINATES

PART II

PUMMERER REACTIONS OF S-OXIDES OF 1,3-OXATHIOLAN-5-ONES AND 1,3-THIAZOLIDIN-4-ONES

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A Dissertation

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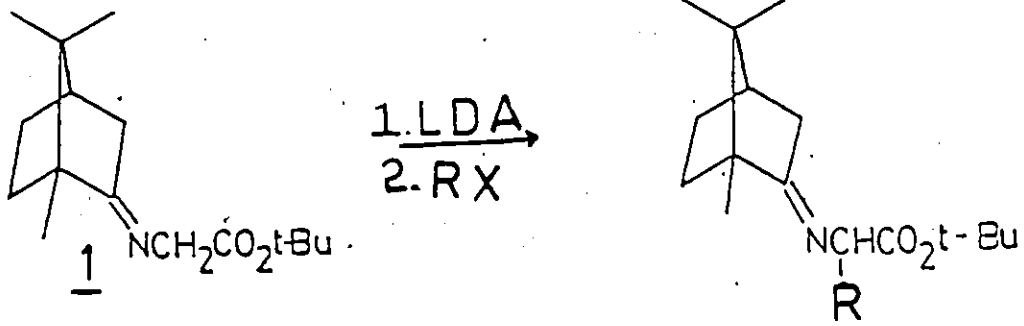
Abstract

Part I Electrophile Structure as a Factor in Alkylations of Camphor Derivatized Glycinates

Alkylation reactions of the camphor imine of t-butyl glycinate 1 were found to proceed with varing amounts of diastereofacial selectivity depending on the electronic nature of the alkylating agent. Saturated alkyl halides gave diastereomeric execesses up to 67%. Allylic and benzylic alkylating agents reacted to provide diastereomeric excesses up to 98%. A transition state model which involves a favorable electronic interaction between the pi system of the alkylating agent and the lithium enolaate has been proposed to explain the enhanced diastereoselectivities observed for these types of alkylating agents.



(1-Bromoethyl)benzene, 3-bromocyclohexene, and 5,5-dimethyl-3-bromocyclohexene were found to react to give only two of the four possible diastereomers. It was determined that the stereochemically pure center of the products from these reactions was C-3 (by amino acid numbering).

Palladium mediated allylation reactions of the sodium enolate of 1 were also possible.

Part II Pummerer Reactions of S-Oxides of 1,3-Oxathiolan-5-ones and 1,3-Thiazolidin-4-ones

Attempts to capture the sulfur stabilized carbonium ion intermediate of the Pummerer reaction of 1,3-oxathiolan-5-ones and 1,3-thiazolidin-4-ones with olefins and benzene are described. The reactions were unsuccessful with the oxathiolanones studied. Substitutions at the 5-position of 3-methyl-1,3-thiazolidin-4-one have been achieved using trifluoroacetic anhydride as the catalyst. 5-Phenyl substitutions of all thiazolidinones were easily performed utilizing an excess amount of concentrated sulfuric acid as the catalyst. Aldol and alkylation reactions of the 3-methyl-thiazolidinone were also successful.

This manuscript is dedicated to Pamela

May her sacrifices reap large benefits

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Table of Contents

Abstract iii
Dedication v
Acknowledgements vi
List of Tables viii
List of Figures ix
List of Abbreviations xiii

Chapter I
Electrophile Structure as a Factor in Alkylations of Camphor Derivatized Glycinates

Introduction 1

Results and Discussion 21

A. Primary Alkylation Reactions 23
B. Secondary Alkylation Reactions 33

Chapter II
Pummerer Reactions of S-Oxides of 1,3-Oxathiolan-ones and 1,3-Thiazolidin-4-ones

Introduction 58

Results and Discussion 67

A. Oxathiolanones 67
B. Thiazolidinones 73
C. Alkylation and Aldol Reactions 81

Summary and Conclusions 86

Chapter III
Experimental

General Information 95

Experimental Procedures 97

Appendix A
^{1}H NMR Spectra of Camphor Imines of Glycinates 106

References 123

Vita Auctoris 129

List of Tables

Table		Page
1.	Products and Yields of Alkylation Reactions With Primary Alkylating Agents	24
2.	Products and Yields of Alkylation Reactions With Secondary Alkylating Agents	34
3.	Products and Yields of Alkylation Reactions With Two Equivalents of Secondary Alkylating Agents	41
4.	^{1}H NMR Spectra of Camphor Imines of t-Butyl Glycinates	48
5.	^{13}C NMR Spectra of Camphor Imines of t-Butyl Glycinates	51
6.	Infrared Spectra of Camphor Imines of t-Butyl Glycinates	57
7.	Microanalyses of Camphor Imines of t-Butyl Glycinates	58
8.	^{1}H NMR Spectra of Oxathiolanones and Thiazolidinones	88
9.	^{13}C NMR Spectra of Oxathiolanones	90
10.	^{13}C NMR Spectra of Thiazolidinones	91
11.	Infrared Spectra of Oxathiolanones and Thiazolidinones	93
12.	Elemental Analyses of Oxathiolanones and Thiazolidinones	94

List of Figures

Figure		Page
1.	Energy diagram for an asymmetric reaction	2
2.	Use of CDA's in asymmetric synthesis	3
2a.	Zimmerman-Traxler transition state model	4
3.	1-(R)-Camphor	5
4.	Camphor as a CDA in a Diels-Alder reaction	6
5.	Camphor as a CDA in substitution with copper reagents	6
6.	Camphor as a CDA in alkylation reactions	7
7.	Camphor derived oxazoline in alkylation reactions	8
8.	Camphor directed bromination	9
9.	Amino acid synthesis directed by camphor	9
10.	Electrophilic glycinate reaction with nucleophiles	10
11.	Electrophilic glycinate reaction with organoboranes	11
12.	Chiral amino acids from electrophilic glycinates	12
13.	Amino acid synthesis from bis-lactim ethers	13
14.	Chiral amino acid synthesis from chiral imidazolidinones	13
15.	Phase transfer catalysed synthesis of amino acids	14
16.	Reaction of imine anions with 4-bromo-2-butenoates	15
17.	Chiral pyrrolidine mediated synthesis of amino acids	16
18.	Alkylation of chiral imines of glycinates	17
19.	Proposed conformation of hydroxypinanone enolate	17
20.	Transamination of camphor imines	18
21.	McIntosh model for alkylation of chiral glycinates	20
22.	Alkylation reaction of 1	21
23.	Dependance of HMPA on yield and de's	22

24.	General transition states in alkylation reactions	25
25.	Regiospecific enolate formation of cyclopentanones	28
26.	Lithium-π arene coordination	29
27.	Distortion of 7-Lithionorbornadiene	30
28.	Lithium-π arene coordination in alkylations of 1	30
29.	Catalytic Hydrogenation of 3g	33
30.	Diaxial interactions of cyclohexyl iodide	36
31.	Transamination of 3k,	37
32.	Catalytic hydrogenation of 3m	39
33.	Transition states of Re face approach of (1-bromoethyl) benzene	40
34.	Crystal structure of 3m	42
35.	Allyl palladium mediated alkylations	45
36.	Metal hydride reduction of oxathiolanones	59
37.	Pyrolysis of 1,3-oxathiolanones	60
38.	Proposed mechanism for RaNi desulfuration of oxathiolanones	60
39.	Synthesis of enethiols from oxathiolanones	61
40.	Reaction of electrophilic oxathiolanone	62
41.	Mechanism of the Pummerer Reaction	63
42.	Reaction of electrophilic oxathiolanones with olefins	65
43.	Reaction of Pummerer reaction intermediate with sulfides and thiols	65
44.	DMSO oxidation of alcohols to carbonyls	66
45.	Preparation of iminosulfuranes	66
46.	Oxidation of oxathiolanones	68
47.	Postulated pathway for formation of 9	69
48.	Postulated mechanism for formation of 10	70
49.	Pummerer reaction of 8a	71

50.	Intramolecular nature of acetoxy migration	71
51.	Reaction of 8a with TFAA in nucleophilic solvents	72
52.	Generation of the Pummerer intermediate by Lewis acids	73
53.	Reaction of 8a using catalytic amounts of Lewis or proton acids	74
54.	Formation and oxidation of 1,3 thiazolidinones	75
55.	The Pummerer reaction of thiazolidinones	76
56.	Intermolecular capture of the Pummerer intermediates by olefins	76
57.	The "ene" nature of intermolecular capture	77
58.	Tamura's examples of intermolecular capture	78
59.	Intermolecular capture of Pummerer reaction intermediate by 2-alkenes	79
60.	Tamura's cyclization reaction using the Pummerer	79
61.	The tight ion pair in formation of 16	80
62.	Oae's ^{18}O labelled sulfoxide studies	81
63.	Pummerer intermediate generation by Lewis acids	82
64.	Alkylation of thiazolidinones	83
65.	Aldol reaction of thiazolidinones	85

List of Abbreviations

Ac	acetyl
9-BBN	9-borabicyclo-[3.3.1]-nonane
Bz	benzyl
CDA	chiral directing agent
DIBAL	diisobutylaluminum hydride
DMSO	dimethyl sulfoxide
HMPA	hexamethylphosphoramide
HSAB	Hard and Soft Acids and Bases
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
MS	Mass Spectra
$Pd(dppe)_2$	palladium bis(diphenylphosphinoethane)
Ph	phenyl
PPA	polyphosphoric Acid
RaNi	raney nickel
TEA	triethyl amine
TFA	trifluoroacetic acid,
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
Ts	tosyl
TS	transition state
de	diastereomeric excess
ee	enantiomeric excess

CHAPTER 1

ELECTROPHILE STRUCTURE AS A FACTOR IN ALKYLATIONS OF CAMPHOR DERIVATIZED GLYCINATES

Introduction

The formation of carbon-carbon bonds in a stereospecific fashion (asymmetric synthesis) has become a prime directive for the synthetic chemist during the last fifteen years and great strides toward this end have been achieved for a large variety of reaction types. The recent publication of a series of monographs[1] devoted to the current state of this art attests to the interest and importance of this subject.

The underlying principle responsible for successful asymmetric synthesis is that different stereoisomers of the product arise from diastereomeric transition states of unequal energy (Figure 1). The magnitude of this energy difference ($\Delta\Delta G$) is reflected in the ratio of enantiomers (or diastereomers) of the product that are formed. This energy difference can be calculated on the basis of the Gibbs Free Energy equation.

$$\Delta\Delta G = -RT \ln K,$$ where K is the ratio of stereoisomers formed

From this equation it can be calculated that the energy difference between diastereomeric transition states which give rise to a 3:1 ratio of stereoisomers is only 0.65 kcal mol^{-1}. As the ratio of stereoisomers increases, the value of $\Delta\Delta G$ rises exponentially so that the energy difference between transition states forming a 95:5 ratio of stereoisomers is in the range of 1.75 kcal mol^{-1}. The slight nature of these values is brought into perspective when one considers that the activation energy for conversion of one chair form of cyclohexane to the other chair form is about 10 kcal/mol[2].

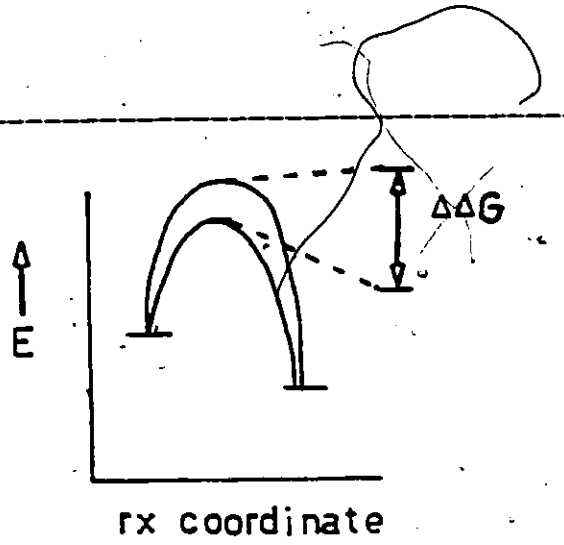


Figure 1. Energy diagram for an asymmetric reaction.

By convention, the ratio of enantiomers (or diastereomers) formed in a given reaction is expressed as "% enantiomeric (or diastereomeric) excess" (%ee, %de). The value is calculated using the following formula:

$$\%\ ee = \frac{\text{amount enantiomer A} - \text{amount enantiomer B}}{\text{amount enantiomer A} + \text{amount enantiomer B}} \times 100$$

By today's standard a reaction must provide at least 90% ee (or de) to be considered synthetically useful.

A chiral influence must be involved in the mechanism for a reaction to proceed through a diastereomeric transition state. When a chiral influence is not present in a reaction between two prochiral molecules, the possible transition states are enantiomeric and therefore equal in energy. As a result, asymmetric synthesis is not possible. The chiral influence can be incorporated as part of one reactant, the solvent, or in a catalyst. Many successful strategies involve the derivatization of one of the reactants with a naturally occuring chiral molecule. When the reaction is completed, the chiral directing agent (CDA) is removed to provide enantiomerically enriched or

pure product. This process is depicted in Figure 2.

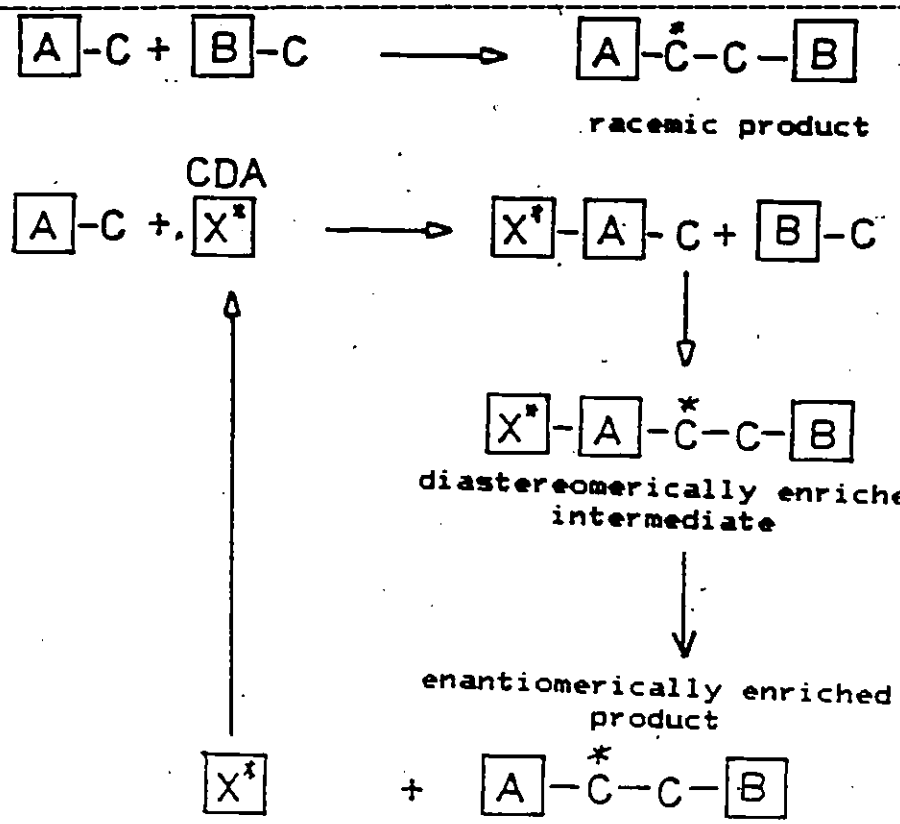


Figure 2. Use of CDA's in asymmetric synthesis.

The exact nature of the chiral influence on the diastereomeric transition states varies with different reactions. Of the reactions involving enolates, the Aldol types are best understood in this regard. The Zimmerman-Traxler transition state model[3] accounts for most of the stereochemical results obtained for lithium, boron, magnesium, and zinc enolates. The model states that the *Z*- and *E*-enolates react with carbonyl compounds through one of four different six-membered chair-like transition states. The stereochemistry of the product can be predicted *a priori* by examining the possible steric interactions that would be present in the transition state. The model predicts that *Z*-enolates will give predominantly *syn* aldols while

the *anti* aldols arise from the *E*-enolates (Figure 2a). The initially proposed model has been modified to include skewed chair transition state conformations[4]. These account for the generally larger stereoselectivities observed for *Z*-enolates.

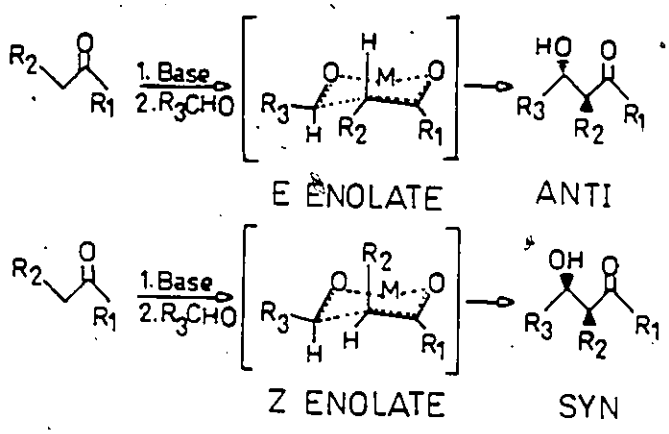


Figure 2a. Zimmerman-Traxler transition state model

A global transition state model, such as that proposed by Zimmerman and Traxler, to explain the stereochemical outcome of alkylation reactions does not exist. In accordance with the Hammond postulate[5], the transition state structure of alkylation reactions should more closely resemble the reactants than the products. This argument has been used to explain the preference for "equatorial alkylations" of cyclohexanone enolates[4]. In most other cases π-facial selectivity in approach of the electrophile can be explained using steric considerations only.

One naturally occuring chiral molecule that has been frequently utilized as a CDA is camphor (Figure 3). The molecule is readily available in both enantiomeric forms and its rigid bicyclic structure is well suited for use in asymmetric synthesis. In many cases the products derived from reactions

that employ camphor as a CDA are crystalline and occasionally diastereomerically pure compounds can be obtained by recrystallization.

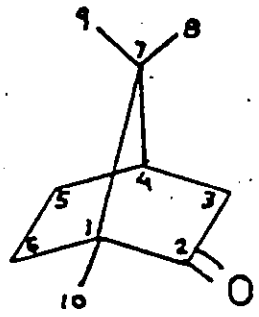


Figure 3. 1-(R)-Camphor.

We sought to synthesize optically active amino acids by alkylating glycinate esters which were derivatized with camphor. Previous work from our research group showed that camphor was a useful CDA in this regard.

Oppolzer's group has been very active in using camphor as a chiral directing agent. They reported that high stereoselectivities were obtained in Lewis acid mediated intra-[7] and intermolecular[8] Diels-Alder reactions of camphor derived sultams. The high de's (>90%) were attributed to internal chelation of the Lewis acid so as to restrict rotation of the C(O)N and C(O)C_α bonds. In this reacting conformation the approach of the diene to the Si face was hindered by the C-8 methyl group of camphor (Figure 4). Reductive cleavage gave back the chiral directing agent which could be recycled.

High de's (>93%) were obtained in the addition of alkyl[9] and alkenyl[10] copper reagents to a structurally modified camphor enoate (Figure 5). The neopentyl ether substitution of camphor

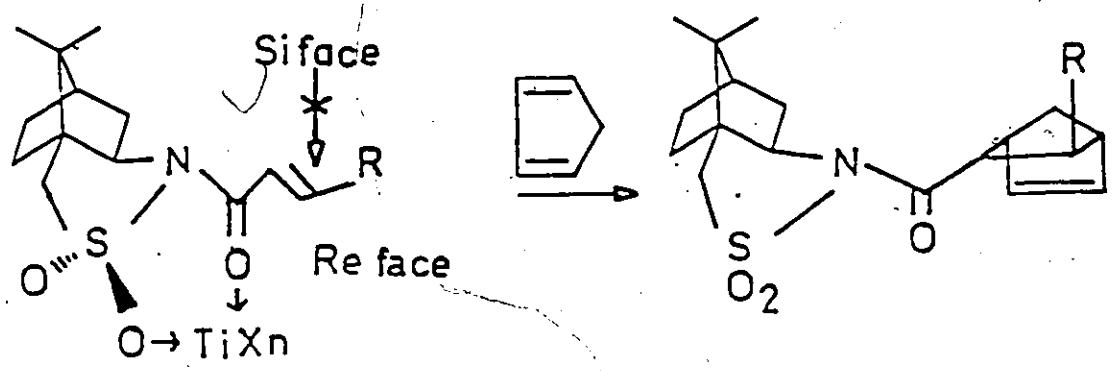


Figure 4. Camphor as a CDA in a Diels-Alder reaction.

inhibits approach of the reagent from a direction that is parallel to the plane of the camphor six-membered ring. Saponification of the product returned the CDA and gave the chiral β-substituted carboxylic acid.

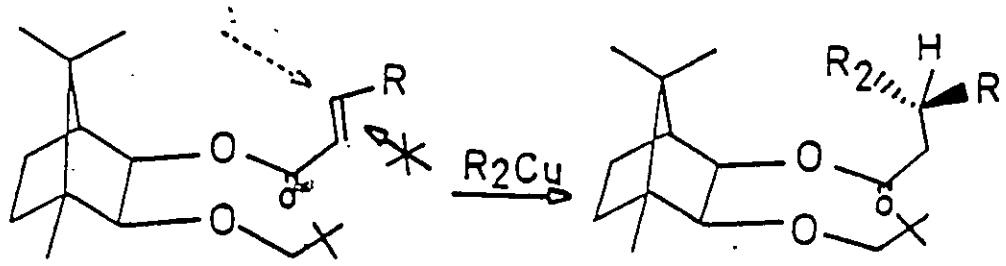


Figure 5. Camphor as a CDA in substitution with copper reagents.

Camphor has also been utilized as a chiral directing agent in alkylation reactions. Oppolzer *et al.*[11] used a camphor sulfonamide to direct approach of alkylating agents to the Si face of an ester enolate (Figure 6). The authors make no comments about the conformation of the enolate that reacts preferentially. However, because good de's (78%-89%) are

obtained, a lithium coordination to the sulfonamide function such that this group hinders Re face approach to the enolate may be proposed. LAH reduction of the diastereomeric mixture of products provided good yields of alcohols and regenerated the CDA.

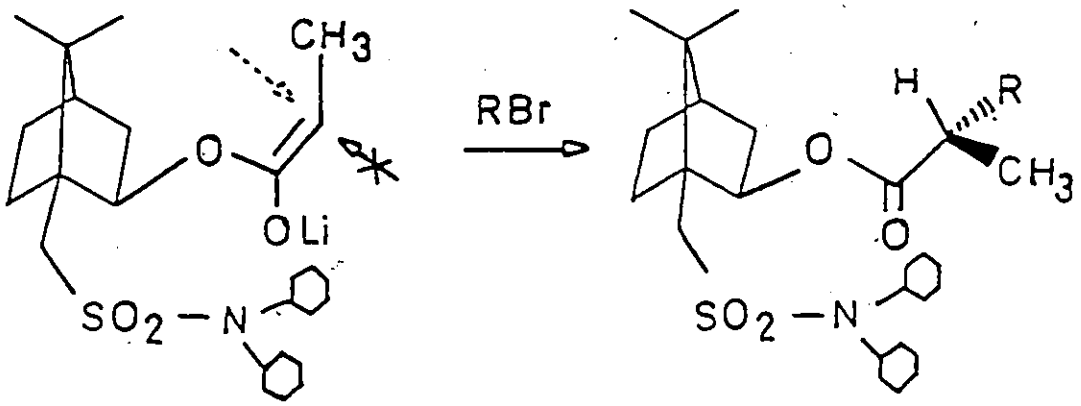


Figure 6. Camphor as a CDA in alkylation reactions.

Kelly and Arvantis[12] reported that stereoselective alkylation reactions of a camphor based oxazoline (Figure 7). In this case, the C-8 methyl group of camphor hinders approach of the electrophile from a direction perpendicular to the plane of the camphor six-membered ring. Based on the absolute (R)-configuration of the α-hydroxy acids obtained after hydrolysis, the authors concluded that because the configuration of the enolate was stable, the lithium atom of the enolate must be coordinated to the nitrogen of the oxazoline. The alternate coordination of lithium to the oxygen of the oxazoline would make the top face of the enolate the Re face and bottom side attack of the electrophile would give the (S)-enantiomer of the hydroxy acid. One of the drawbacks of this approach toward hydroxy acids is that the chiral oxazoline required a multistep synthesis from

camphor. Hydrolysis of the alkylated product gave only low yields of hydroxy acids and the chiral moiety required several synthetic steps to be regenerated.

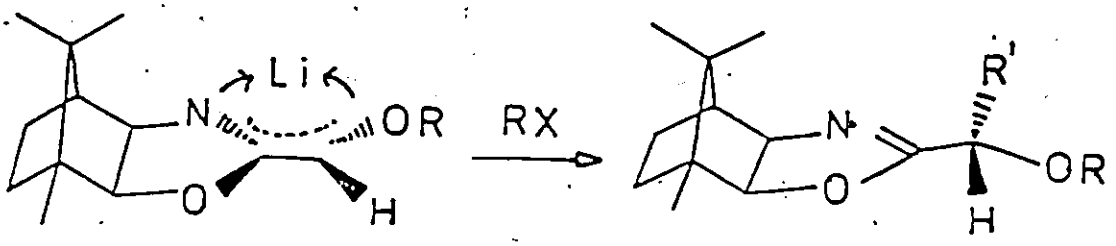


Figure 7. Camphor derived oxazoline in alkylation reactions.

Oppolzer and Dudfield[13] made use of camphor-10-sulfonamide derived esters in the stereoselective formation of halohydrins and, subsequently terminal epoxides (Figure 8). De's of between 54% and 77% were obtained. Recrystallization gave diastereomerically pure products. In these cases the chiral moiety blocks approach of the reagent from a direction that is parallel to the plane of the camphor six-membered ring.

As an extension to this work Oppolzer *et al.*[14] very recently reported that an Sn2 type substitution by azide ion of the optically pure camphor derivatized halides proceeded smoothly. Transesterification removed the CDA and subsequent hydrogenation afforded good yields of amino acids with very high optical purity (>93% ee) (Figure 9).

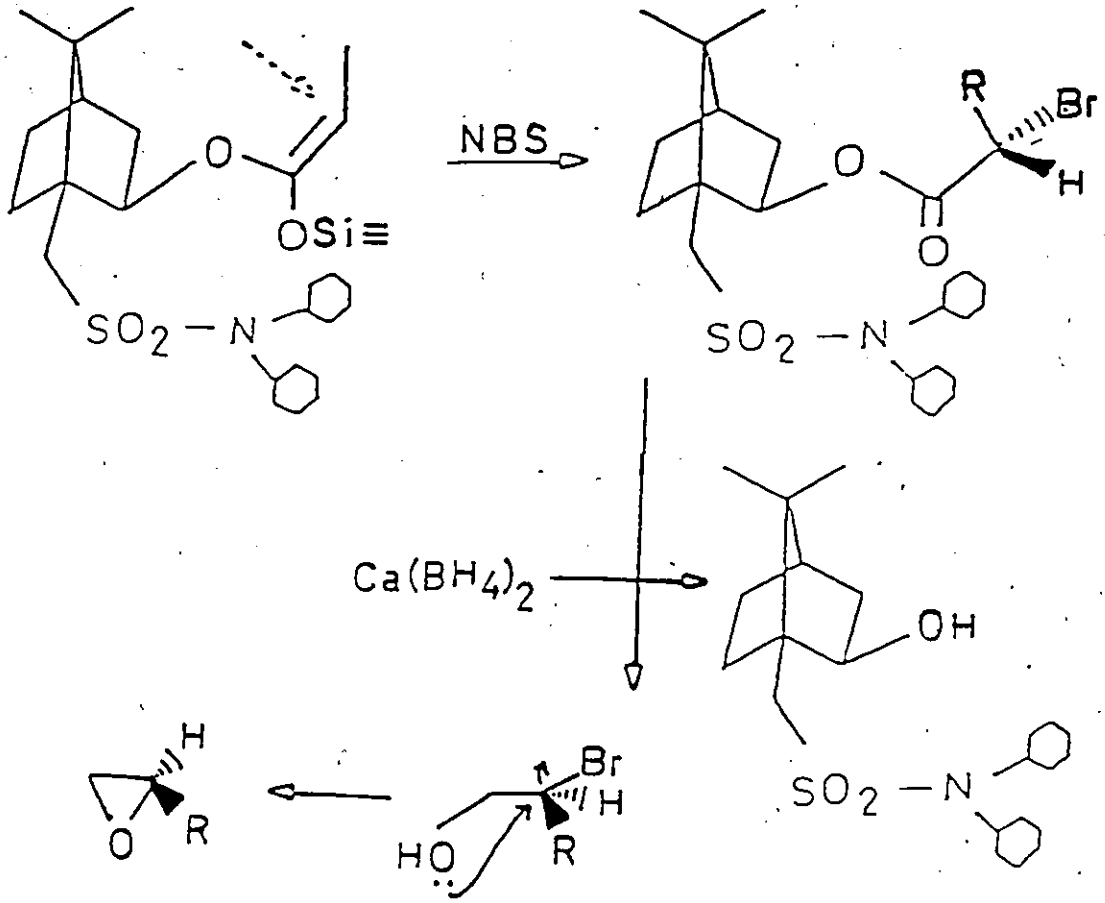


Figure 8. Camphor directed bromination.

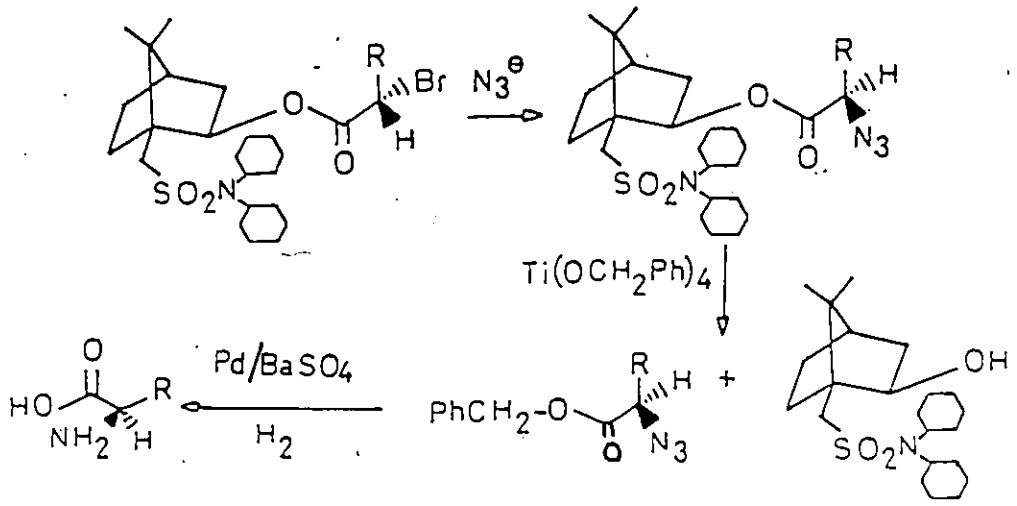


Figure 9. Amino acid synthesis directed by camphor.

α-Amino acids[15] are simple chiral molecules of significant biological interest. To the organic chemist they are important members of the chiral pool[15a] and the literature is replete with different strategies used for their synthesis in both racemic and optically active forms. Most methods make use of glycine or other amino acids as templates from which to construct higher homologues. In these cases the acidic amine hydrogens have usually been protected as either an imine or a tertiary amine. Esters are typically used as acid protecting groups.

O'Donnell's group has illustrated the utility of electrophilic glycinates in the synthesis of amino acids. It reported that the 2-acetoxybenzophenone imine of ethyl glycinate was subject to nucleophilic attack by alcohols, thiols, and organocuprates[14,17]. Hydrolysis of the imine function provided the glycine ester in good yields (Figure 10).

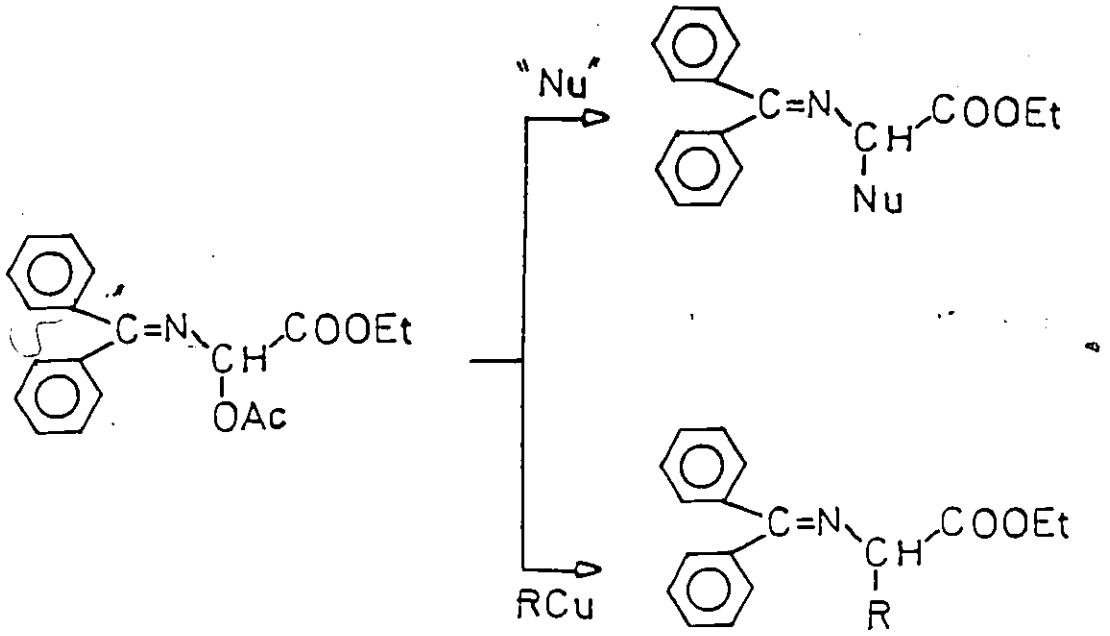


Figure 10. Electrophilic glycinate reaction with nucleophiles.

The same research group also showed[18] that the imine was subject to carbon-carbon bond forming reactions with organoboranes. Good to excellent yields were obtained upon treatment of the imine in the presence of a hindered potassium phenoxide with reagents prepared from 9-BBN (Figure 11).

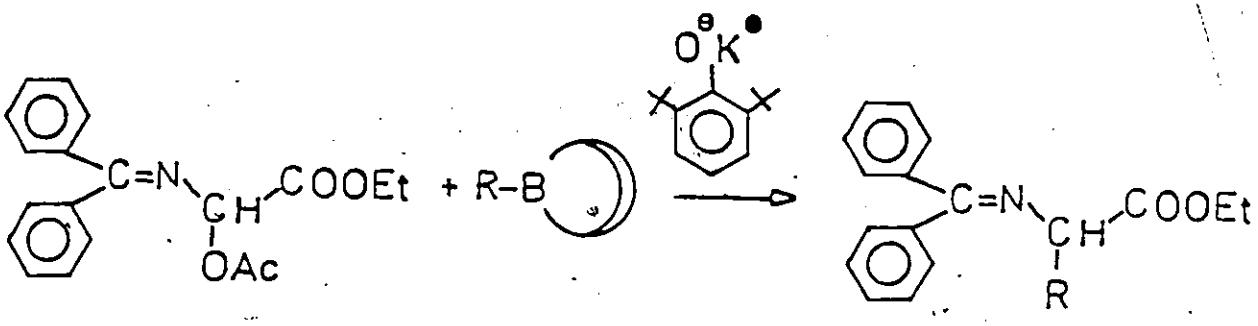


Figure 11. Electrophilic glycinate reaction with organoboranes.

A recent report from Williams *et al.*[19] showed that asymmetric amino acid synthesis can be achieved using electrophilic glycinates. They were able to prepare the optically pure bromine compound shown in Figure 12. Nucleophilic displacement of bromide ion with organocuprates, Grignard reagents, and silyl enol ethers proceeded with almost complete diastereofacial selection. Catalytic hydrogenation afforded the amino acid in fair yields. However, there remain problems with this approach to chiral amino acids. The generation of optically pure bromolactone involved a resolution of enantiomers in the first step of a multistep synthesis. Further, hydrogenation to afford the amino acid destroyed the chiral directing agent such that it could not be recycled. Clearly this method would be inappropriate as a general route to optically pure amino acids.

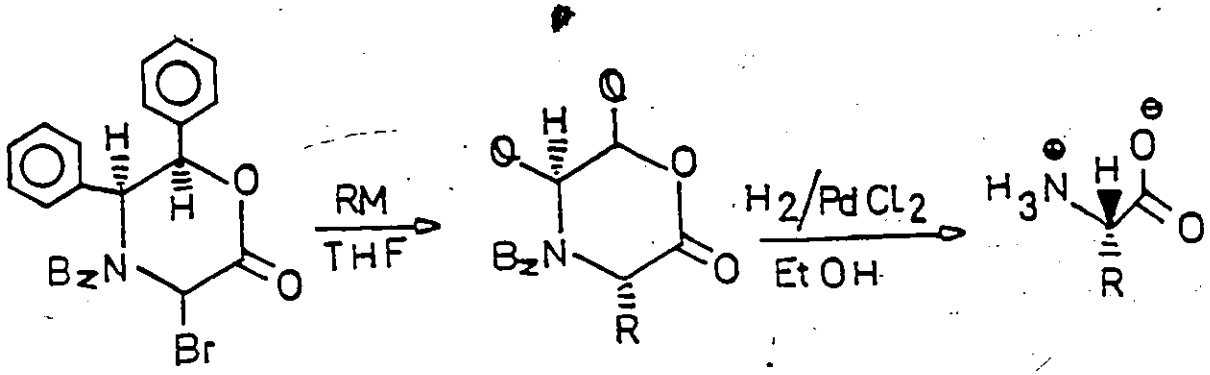


Figure 12. Chiral amino acids from electrophilic glycinates.

Anionic approaches to amino acid synthesis are more common than the electrophilic glycinate strategy shown above. Schollkopf *et al.*[20-22] prepared optically active amino acids using alkylation and aldol reactions of the lithium enolate of chiral bis-lactim ethers (Figure 13). These were easily formed in three steps from readily available, stereochemically pure valine or O,O-dimethyl-α-methyldopa and glycine esters. Approach of the electrophile to the enolate occurred trans to the large substitutent. Enantiomeric excesses of greater than 80% were obtained in all cases. The method was also shown to be applicable for the asymmetric synthesis of α-disubstituted amino acids. Though the chiral bis-lactim ether required a multistep synthesis, the regeneration of the chiral template in the final step without loss of optical purity makes this method attractive.

Seebach's group has employed an alternate strategy in the synthesis of chiral amino and hydroxy acids[23]. Using methods that they had previously developed[24] they were able to synthesize optically active imidizolidinone A (Figure 14) from

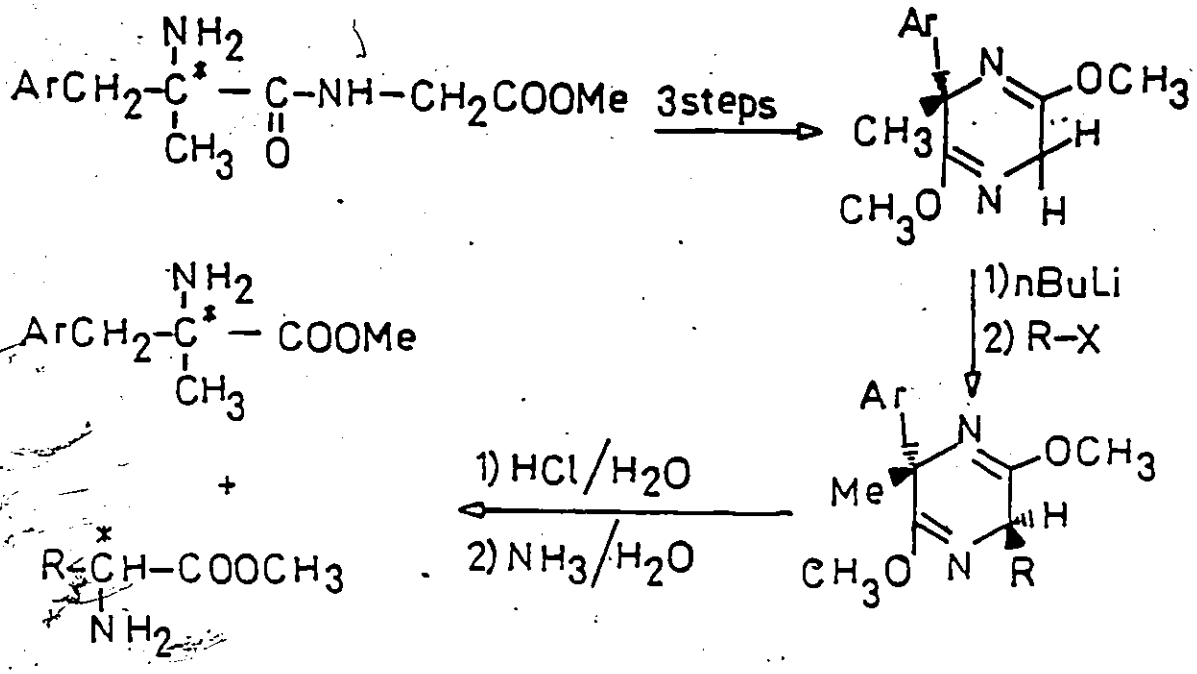


Figure 13. Amino acid synthesis from bis-lactim ethers.

(S)-O-benzylserine and pivaldehyde. Deprotonation with LDA at reduced temperature gave the enantiomerically pure enolate B which was readily alkylated with methyl and benzyl iodides to yield diastereomerically pure C. Hydrolysis afforded the enantiomerically pure amino acid. When racemic A was used trans alkylation occurred almost exclusively.

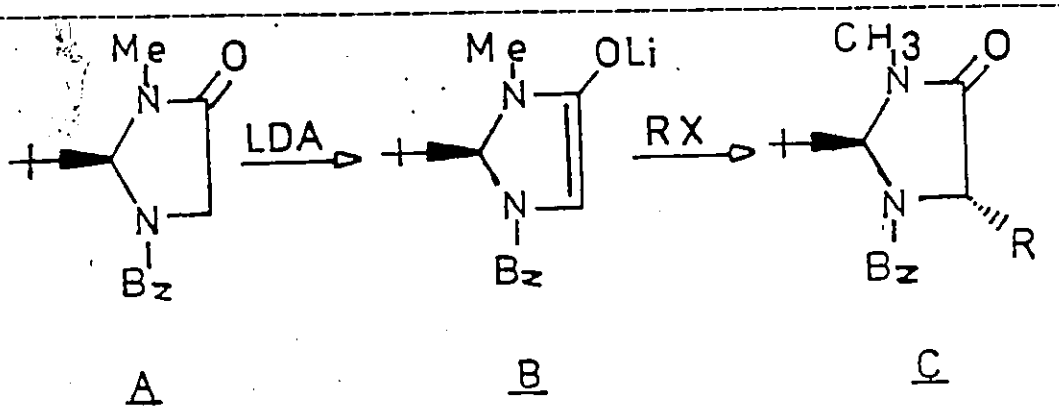


Figure 14. Chiral amino acid synthesis from chiral imidizolidinones.

Other anionic routes to amino acids involve additions of electrophiles to enolates of glycinate imines. Alkylations of benzylidene derivatives of glycinates ($C_6H_5CH=NCH_2COOR$) were successful with reactive alkylating agents[23,24]. Michael reactions with this reagent gave 1,4-addition products exclusively. 1,2-Additions of carboxyl stabilized imine anions to enones and carbonyls have not been observed[24]. Aldol reactions are possible with the anion of N,N-dialkyl glycinates[27].

O'Donnell *et al.* reported that Schiff bases of glycinate esters can be alkylated under phase transfer conditions using either potassium hydroxide[28] or potassium carbonate[29] (Figure 15). In general, yields in excess of 70% were obtained with most alkylating agents. The attractive features of this method were the simplicity, low costs, and high yields that could be obtained. Further, the method can be used for large scale preparations of amino acids.

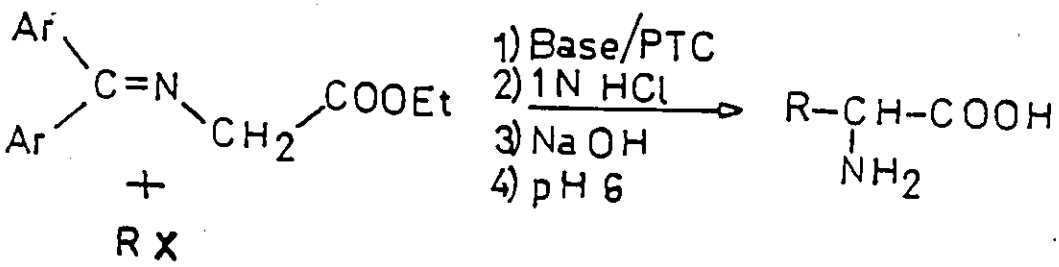


Figure 15. Phase transfer catalysed synthesis of amino acids.

Joucla *et al.*[30] recently reported that enolates of imines derived from benzophenone and α-amino esters undergo nucleophilic

substitution reactions with 4-bromo-2-butenoate in the presence of HMPA and THF (Figure 16). When HMPA was omitted from the reaction, mixtures of cyclopropane derivatives were formed in an addition-elimination reaction. The role that HMPA plays in this and other systems is not understood but its strongly coordinating nature may disaggregate the tetrameric (or higher) lithium enolate, thus altering the reaction.

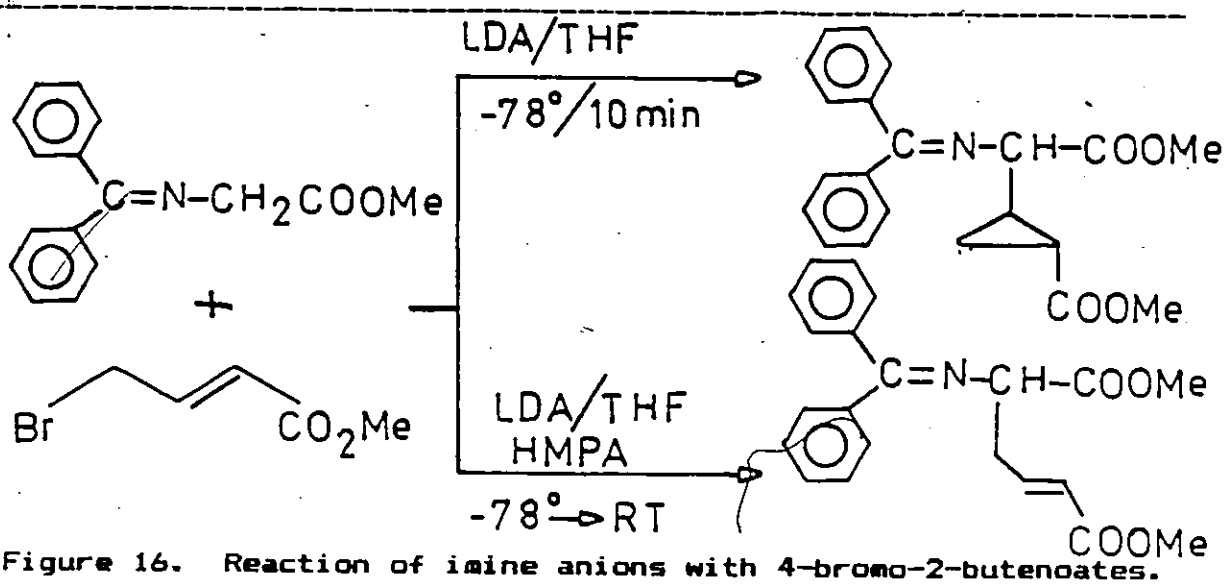


Figure 16. Reaction of imine anions with 4-bromo-2-butenoates.

Asymmetric synthesis of amino acids by alkylations of glycinate imines has been achieved by derivatizing the imine with a chiral directing agent. The CDA has been attached to the oxygen atom as part of an ester. Alternately, the chiral influence has been attached to the nitrogen atom of the imine.

Katsuki *et.al*[31] have used a chiral amide function to achieve high ee's in the alkylative synthesis of amino acids (Figure 17). Methyl iodide and benzyl bromide reactions took place smoothly. Secondary iodides required conversion to the corresponding triflates for satisfactory chemical yields. The (2S, 5S)-amide

gave (S)-amino acids after hydrolysis. This required that approach of the electrophile occured to the Si face of the *Z*-enolate.

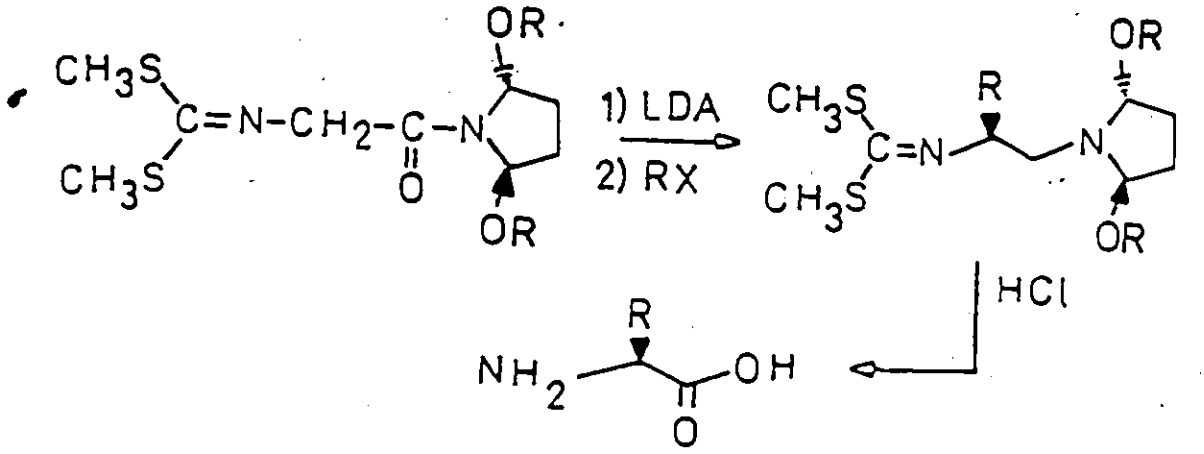


Figure 17. Chiral pyrrolidine mediated synthesis of amino acids.

An alternate approach to optically active amino acids make use of imines derived from chiral ketones and glycinates. Yamada *et al.* found that alkylations of glycinate imines of (1S,2S,5S) 2-hydroxypinan-3-one[32,33] proceed with much higher stereoselectivities than with glycinate imines of (-)menthone[34] (Figure 18). The low stereoselectivities found in the alkylation of the menthone imine may be due to non-stereoselective addition to the enolate, or epimerization of the reaction center due to deprotonation of the monoalkylated product.

The results of the alkylation of the 2-hydroxypinanone imine were curious. If the proposed lithium chelated dianion is correct, the configurations of the amino esters obtained indicate that approach of the alkylating agent to the enolate must have occured from the most hindered face of the enolate (Figure 19). Further, there appeared to be little relationship between the

steric requirement of the alkylating agent and the de obtained.

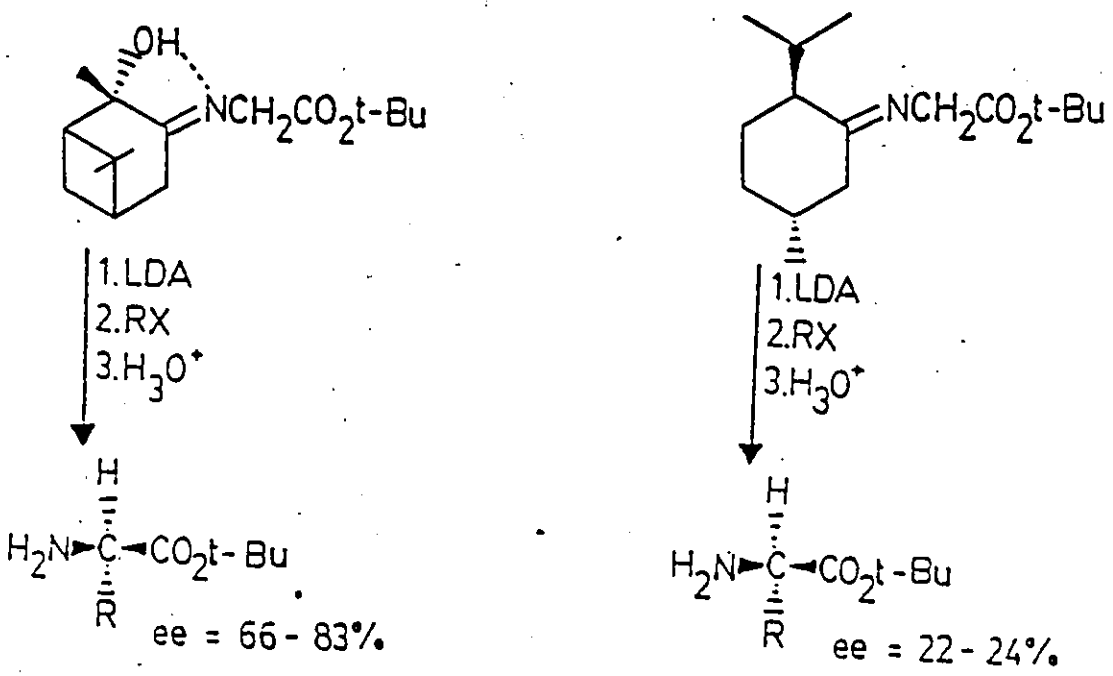


Figure 18. Alkylation of chiral imines of glycinates.

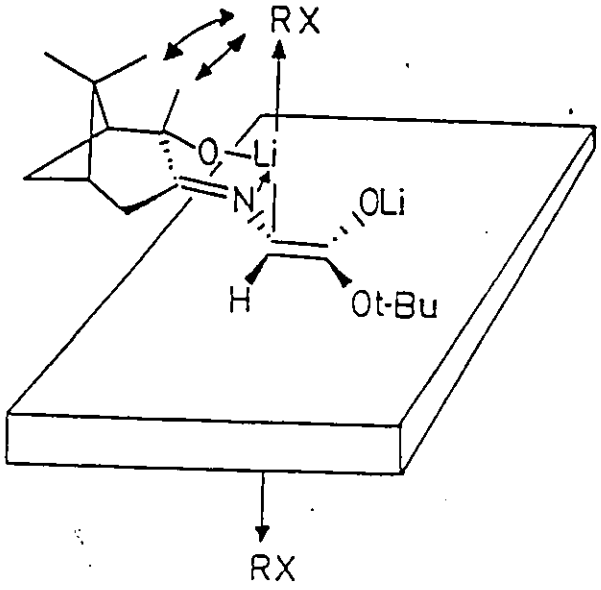


Figure 19. Proposed conformation of hydroxypinanone enolate.

Methyl iodide gave a higher optical yield (83% ee) than did the larger benzyl bromide (66% ee). The authors pointed out that, even in the presence of excess alkylating agent no dialkylated products were observed. This however does not constitute absolute proof that only the kinetic products were obtained because a deprotonation-reprotonation process may have occured without dialkylated products being formed.

McIntosh and Mishra[33,34] studied the alkylation reactions of the camphor imine of t-butyl glycinate. They found that alkyl halides gave up to 60% de. Allylic alkylating agents afforded de's in the range of 75% while benzyl bromide gave solely one diastereomer. Transamination of the benzylated imine provided the (R)-phenylalaninate indicating that the alkylating agent reacted from the less hindered Re face only (Figure 20).

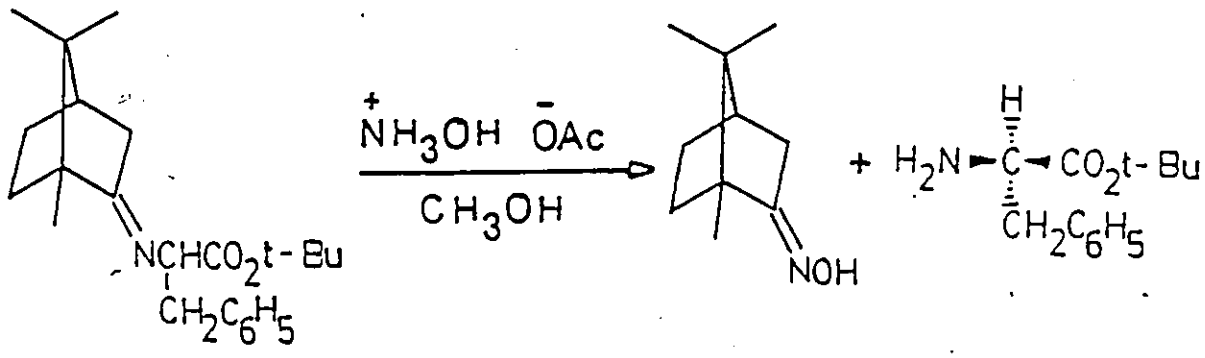


Figure 20. Transamination of camphor imines.

They also showed that only the kinetic products were obtained in the alkylation reactions of the t-butyl glycinate. Attempted deprotonation of monobenzylated material and subsequent quenching with D_2O showed no deuterium incorporation. This

indicated that a second deprotonation could not be achieved. Consistant with this result was the fact that no dialkylated materials were found during any alkylation reactions.

The benzylation reaction of the methyl glycinate analogue gave a 3:1 ratio of diastereomers. A second deprotonation with LDA followed by quenching with D_2O gave 50% deuterium incorporation and a 1:1.5 ratio of diastereomers. Based on this result they concluded that the lower de observed in this case could be the result of epimerization of the chiral center due to deprotonation and reprotonation during the reaction even though no doubly alkylated materials were observed.

Based on the stereochemical results of the alkylation reaction of the t-butyl glycinate McIntosh and Mishra postulated that the enhanced de's observed with allylic and benzylic alkylating agents were a result of the reaction proceeding through a transition state in which the unsaturated portion of the alkylating agent was eclipsed with the enolate ring so that a favorable electronic interaction between the enolate and the alkylating agent could occur (Figure 21). In this conformation molecular models suggest that a significant steric bias for approach of the alkylating agent to the Re face of the enolate exists.

As an extension of the study initiated by McIntosh and Mishra, the present work examined the alkylation reactions of the camphor imine of t-butylglycinate with alkylating agents of various structural and electronic characteristics. We sought to understand and refine the proposed model as well as to determine the scope and limitations of this alkylation process as a route

for synthesizing optically active amino acids.

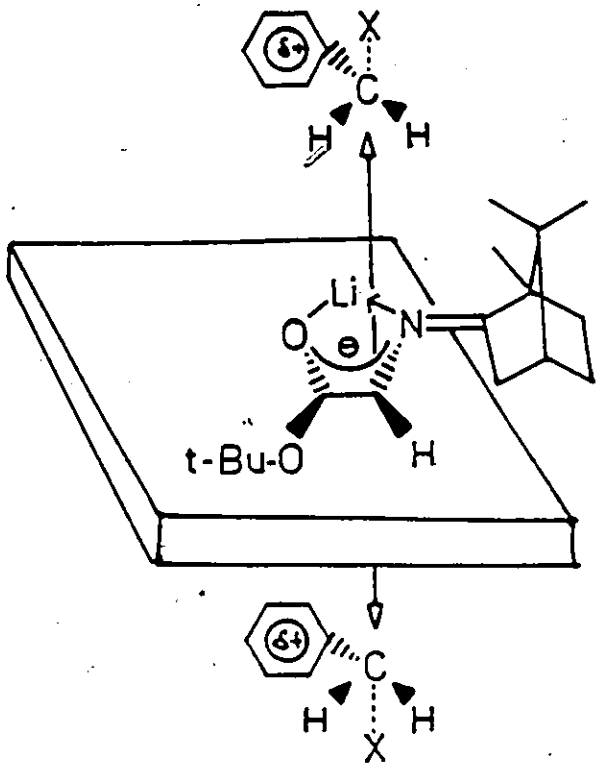


Figure 21. McIntosh model for alkylation of chiral glycinates.

Results and Discussion

The 1-(R)-camphor imine of t-butyl glycinate (1) was prepared as described previously by McIntosh and Mishra[33,34]. The authors pointed out that due to the steric requirements of the C-10 angular methyl group of camphor, the imine double bond was expected to possess the E-configuration. This conclusion was based on examination of molecular models and the absence of any signals arising from a second diastereomer in either the 300 MHz ^{1}H NMR or 75 MHz ^{13}C NMR.

The lithium enolate of 1 was easily generated at -78°C using lithium diisopropylamide in THF. The exact conformation of the enolate was expected to be the one in which the lithium atom is coordinated to the imine nitrogen as is illustrated in Figure 22.

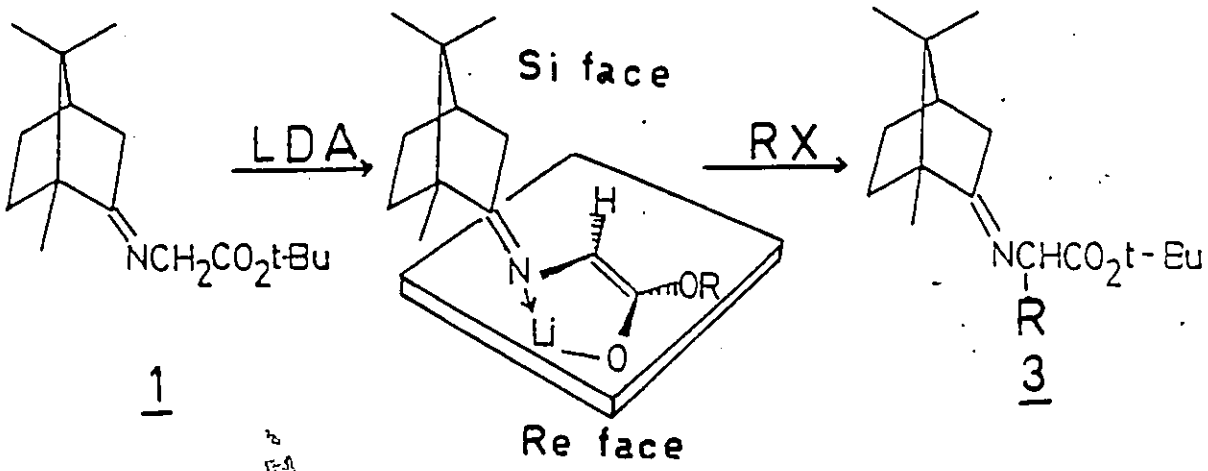
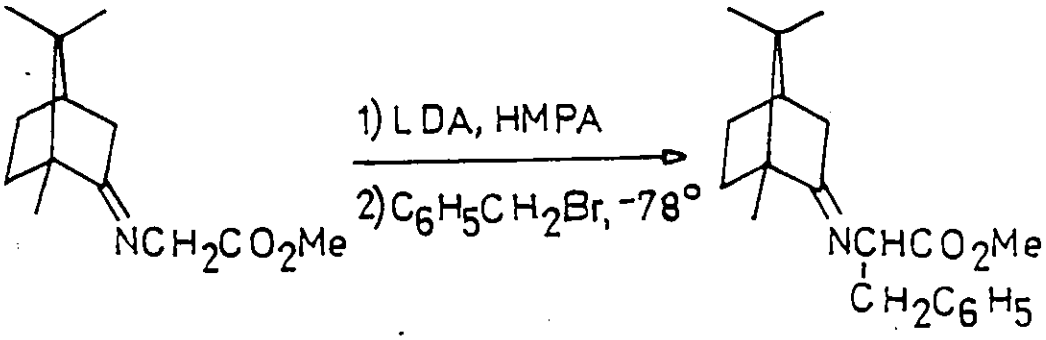


Figure 22. Alkylation reaction of 1.

Internal coordination of metal ions in metal enolate systems is well documented and in some cases, provides the structural organization required for asymmetric synthesis in acyclic systems[4]. The effect of this coordination of lithium is to provide a planar five-membered enolate system. Because the

approach of an electrophile to the enolate must occur from a direction that is perpendicular to the plane of the enolate[37], it was felt that the C-8 methyl group of camphor should impede approach of an electrophile to the Si face of the enolate relative to the Re face.

The alkylation reactions of 1 were carried out at reduced temperature (-78°C or -20°C) in THF containing 1 equivalent of HMPA. Lithium enolates are well known to form tetrameric and higher aggregates[38]. The presence of HMPA facilitates the alkylation process. McIntosh and Mishra[35,34] showed that the benzyl bromide alkylation of the methyl ester analogue of 1 in the absence of HMPA resulted in reduced chemical yields. When 2 equivalents of the additive were used the observed de's decreased appreciably (Figure 23). The mode of action of HMPA is still controversial but dissociation of the polymeric lithium aggregate may account for the increased yields in the presence of HMPA[39].



Equivalents of HMPA	Yield	Diastereomeric Ratio
0	40%	1:3
1	73%	1:3
2	70%	1:2

Figure 23. Dependance of HMPA on yield and de's[35,34].

The alkylating agents chosen for this study were either primary or secondary in nature. Saturated and unsaturated examples from both classes were examined. The stereochemical outcome of the alkylation reactions was analysed quantitatively by 300 MHz ^{1}H NMR data (Appendix A). The methine proton adjacent to the ester carbonyl function of substituted imines (C-2 by amino acid numbering) had a characteristic chemical shift for each diastereomer formed in a given reaction. Integration of these different signals provided a measure of the ratio of diastereomers present. Line heights were used to determine %de in cases where the signals for diastereomers were too close together for accurate integration. In cases where diastereomers could be clearly distinguished, de calculations based on line heights agreed with calculations based on integration to within 4%. In some cases the t-butyl singlet and the singlets for the methyl groups of camphor for each diastereomer were discernable. McIntosh and Mishra[30,34] reported that the methine proton of the (R,R) isomer always appeared at lower field than the same signal for the (R,S) isomer. The 75 MHz ^{13}C NMR also showed separate signals for some carbons of each diastereomer. The exact carbons which exhibited this behavior varied with the alkylating agent used.

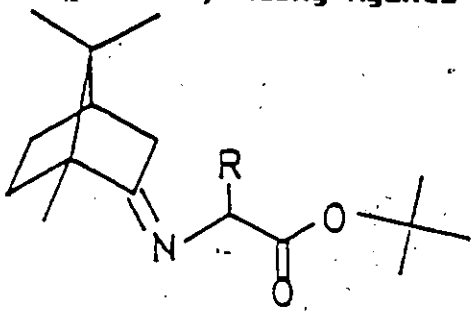
A. Primary Alkylating Agents

The stereochemical outcome and chemical yield of the reaction of 1 with primary alkyl halides are summarized in Table 1.

Entry 1 shows that ethyl iodide reacted to give a 2:1 mixture of diastereomers (33% de). This value was consistant

Table 1

Products and Yields of Alkylation Reactions With Primary Alkylating Agents



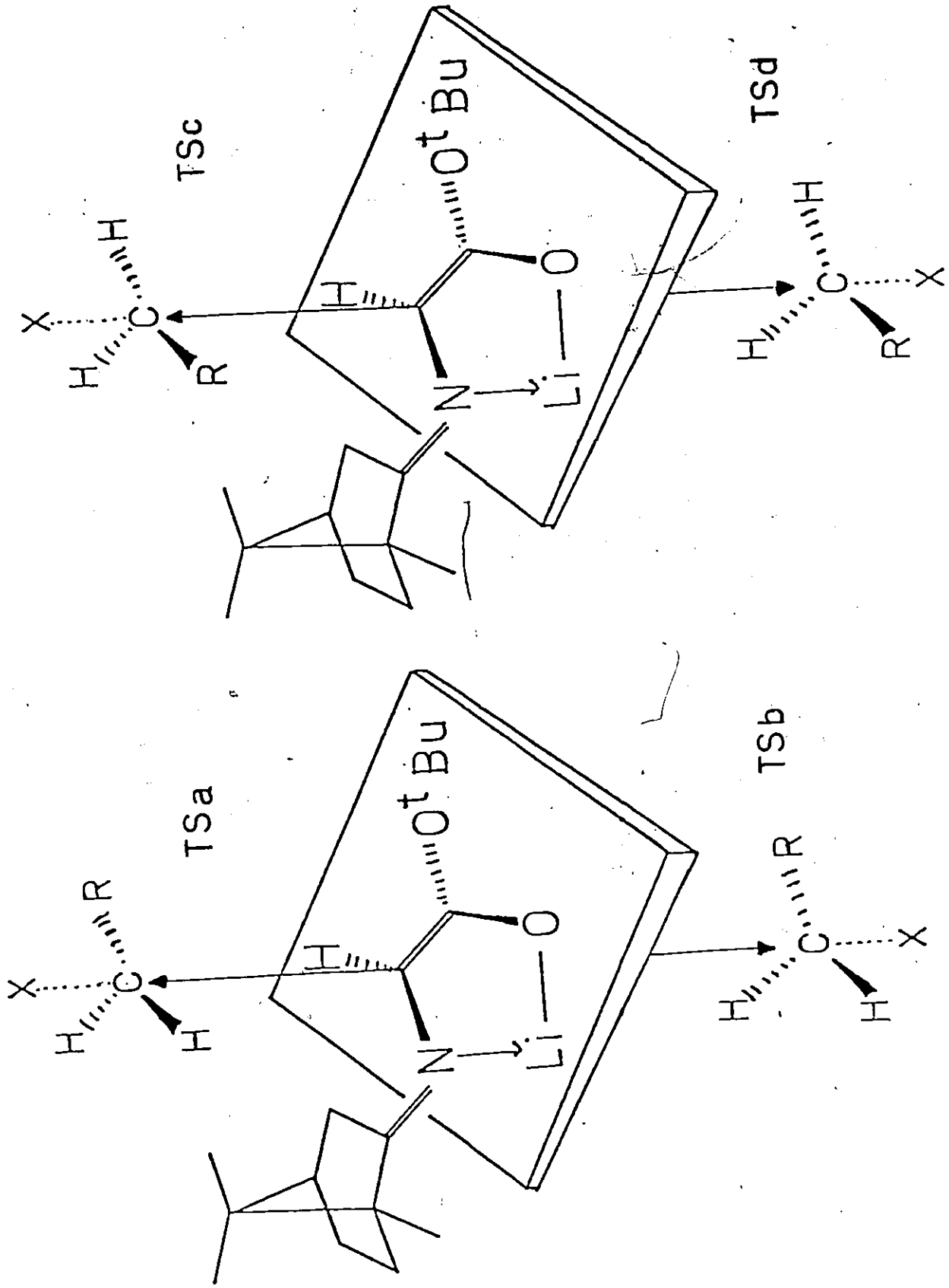
Entry	Cpd	R	X	Yield[a]	Temp	%de
1	3a	Ethyl	I	38 [81]	-78	33
2	3b	o-Methylbenzyl	Br	74	-78	98
3	3c	1-Napthylmethyl	Cl	31 [93]	-78	93
4	3d	4-Nitrobenzyl	Br	69	-78	51
5	3e	Methallyl	Br	60	-78	72
6	3f	$(CH_3)_2C=CHCH_2$	Br	80	-78	33
7	3g	Propargyl	Br	78	-78	67

[a] the values in brackets are based on unrecovered imine

with the postulate put forth by Mishra[34] which stated that saturated alkylating agents gave higher de's with increasing steric bulk. She found that MeI gave 0% diastereomeric excess of methylated product while n-butyl and isobutyl iodides gave de's of 60%.

Examination of space filling models shows that the alkylation reaction with primary reagents can proceed through four general transition states (Figure 24) depending on the orientation and direction of approach of the electrophile to the enolate. The sterically most favored transition states are TS_a

Figure 24. General transition states in alkylation reactions.



and TS_B because the bulk of the molecule is oriented away from the camphor moiety.

Comparing the result of the present study with those of McIntosh and Mishra[33,34] it can be concluded that de's much above 60% are unattainable for this class of alkylating agent using the conditions that were employed (-78°C). Increasing the chain length to longer than 3 carbons has no effect on de's because the added steric bulk is removed from the reaction center to a position where the C-8 methyl group of camphor has little effect (compare nBu and isoBu).

The reaction of o-methylbenzyl bromide with the imine at -78°C gave high de's. This result is consistant with the observation by McIntosh and Mishra[33,34] that benzyl bromide reacted stereospecifically to give only one diastereomer (100% de). They explained that the enhanced de was a result of the reaction proceeding through a transition state in which the aromatic group was "eclipsed" with the enolate ring system (Figure 24: TS_C or TS_D). The authors claimed that an extra stabilization was gained through a favorable electronic interaction between the partial positive charge in the aromatic system (generated at the transition state) and the π electrons of the enolate. Molecular models showed that in this conformation there would be a much larger steric bias for approach of the alkylating agent to the Re face (Figure 24: TS_D) of the enolate and that the 2-(R)-diastereomer should be be formed. Transamination gave the expected 2-(R)-phenylalaninate.

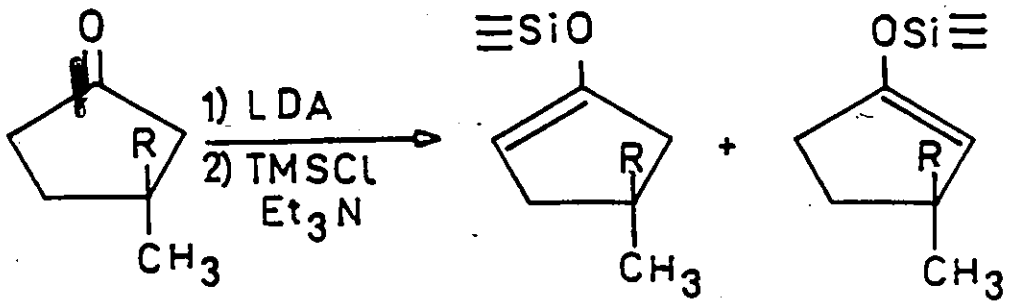
Their results with allylic alkylating agents support this hypothesis. Allyl bromide and methallyl chloride gave de's of

76%. Both these reagents should favor a transition state in which the π system is oriented above or below the enolate ring system. The smaller de's, relative to that which was obtained for benzyl bromide, were due to the smaller steric requirements of the allylic reagent thus allowing more Si face approach (TS_c).

The result of the reaction with methallyl bromide obtained in this study (Entry 5 in Table 1) was in agreement with the above observation. A de of 72% was obtained. That the reaction of methallyl chloride required a temperature of -40°C[38,34] while the methallyl bromide reacted readily at -78°C illustrates the importance of the leaving group to the reactivity of the alkylating agent. Although the difference in temperature did not affect the stereoselectivity of the reaction, it will be demonstrated later that this variable can have a significant effect on the diastereomeric excess that is obtained in some cases.

While the results of the present study do not refute the hypothesis that there is an electronic interaction between the π system of the alkylating agent and the enolate, another somewhat different explanation seems plausible.

In 1977 Posner and Lentz[40,41] reported the results of their study of regioselective lithium enolate formation of cyclopentanones. They found that cyclopentanones bearing a methyl group and a phenyl group in the 3-position underwent deprotonation at room temperature with LDA and the resulting enolate could be trapped as the silyl enol ether. They observed that enolate formation occured preferentially toward the phenyl group (Figure 25).



R =			
	Ph	1.0	3.3
	pMePh	1.0	4.3
	pMeOPh	1.0	7.6
	pO_2NPh	1.0	0.9
	$PhCH_2$	1.0	6.1
	nBu	1.0	0.3

Figure 25. Regiospecific Enolate Formation of Cyclopentanones .

Since the phenyl group is situated at the β-carbon, resonance stabilization of the enolate could not account for the observed regioselectivities. Inductive forces were also ruled out since the greater electron withdrawing pNO_2Ph substituent gave lower regioselectivity than the electron donating p-methoxy analogue. Further, the second highest regioselectivity observed was for the benzyl substituted cyclopentanone whose inductive effects would be exceedingly small. The authors postulated that the cause of this phenomenon was a lithium-arene π coordination brought about through an electronic interaction of the electron donating aromatic system and the electropositive lithium atom (Figure 26). Similar results were obtained in the corresponding cyclohexanone series[41].

Similar metal-π coordinations have been used to explain the increased optical yield obtained in 1,4-addition reactions of chiral cuprates with enones[42] and Yoshida *et.al*[43] suggested that

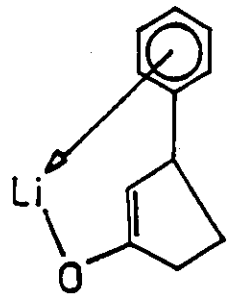
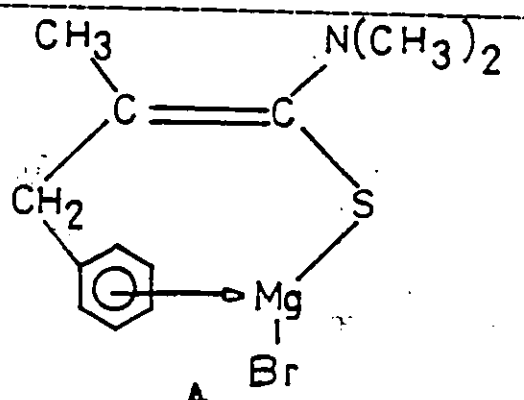


Figure 26. Lithium-π Arene Coordination

a magnesium-phenyl$_{ipso}$ coordination is responsible for the low nucleophilicity of A in aldol reactions with aldehydes.



A

Further evidence for the coordination of lithium with π bonds was provided by calculations performed by Nagese and Houk[44]. They showed that the structure of 7-lithionorbornadiene is slightly distorted relative to norbornadiene such that the lithium atom was moved closer to the neighbouring π bond (Figure 27). The authors calculated that about 30 kcal/mol of stabilization was afforded by internal coordination with the alkene. However it must be noted that no strongly coordinating solvent was included in these calculations.

Based on these observations an alternate model to explain the alkylation reactions of 1 with allylic and benzylic reagents

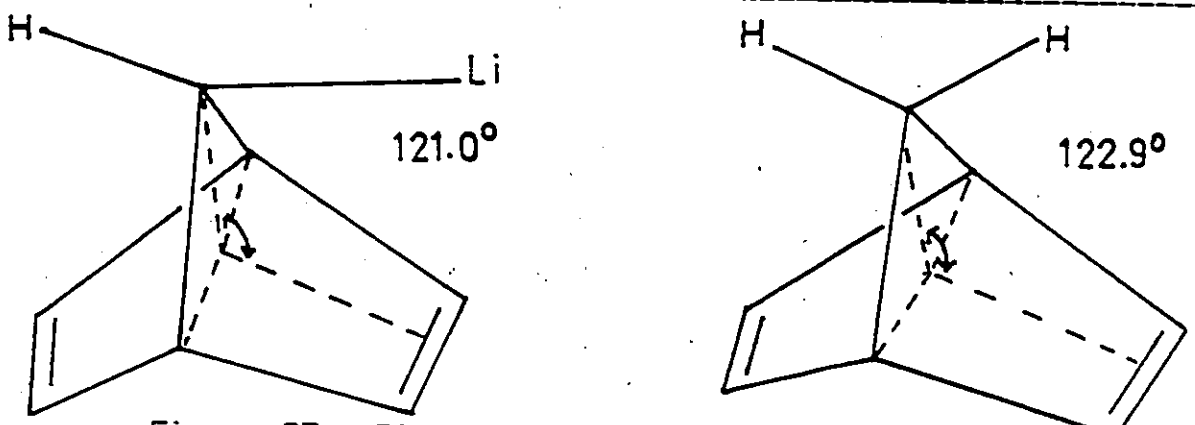


Figure 27. Distortion of 7-Lithionorbornadiene

can be postulated. The high diastereoselectivities (relative to alkyl halides) observed may be a result of approach of the alkylating agent with the TT system eclipsing the enolate ring such that a lithium-TT bond coordination can occur (Figure 28).

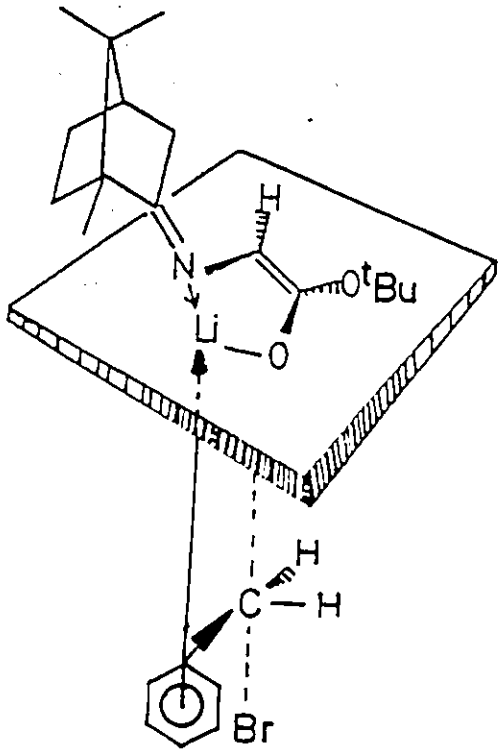


Figure 28. Lithium-TT arene coordination in alkylations of 1.

New experimental evidence supporting a model where coordination of some type is important includes the lower diastereoselectivity observed for p-nitrobenzyl bromide. The coordinating ability of this aryl group is less than the aryl groups of benzyl bromide, o-methylbenzyl bromide, and (1-chloromethyl)napthalene by virtue of its lower electron donating characteristic[45]. The lower de cannot be a result of reaction at the Si face with the aryl group oriented above of the enolate ring (Figure 24: TS_C) since the magnitude of the steric interaction with camphor of this reagent appears to be the same as for benzyl bromide. The minor diastereomer must arise from Si face approach with the aryl group situated away from the enolate system (Figure 24: TS_A).

The lower de's observed for allylic alkylating agents were attributed to the smaller steric requirements of these reagents. Molecular models show that Si face approach is much less hindered than in the cases of benzylic reagents.

Experiments to distinguish between this model and that proposed by McIntosh and Mishra are difficult to design. The strongly coordinating solvents (THF, HMPA) in the reaction could be expected to coordinate to lithium much more strongly than would the π systems which are relatively weak donors. The HSAB principle[44] supports this. On the other hand, π-π interactions are well known[47]. Nevertheless, the previously cited results obtained by Posner[40,41] do show that the results of Li-π interactions can be observed. Such weak interactions are sufficient to cause de's of the order of those observed because the magnitude of the energy difference between the

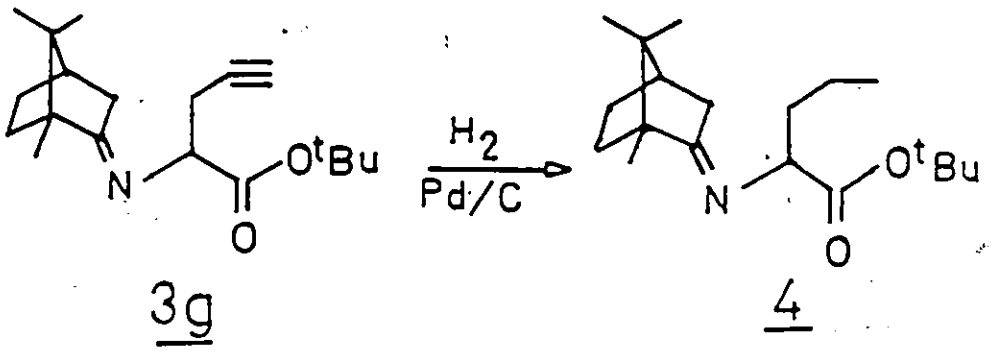
diastereomeric transition states is quite small (<2 kcal mol^{-1}). Subsequent results are discussed in terms of the Li-π coordination model but are equally well explained using the enolate-π model.

One rather disconcerting result was observed in alkylations with crotyl bromide[34] and 1-bromo-3-methyl-2-butene. De's of 60% and 33% respectively were found with these alkylating agents. The common structural feature of these reagents was the presence of a methyl group trans to the reaction site. The presence of this group must destabilize the alignment of the lithium-π coordination in some fashion such that the molecule reacts with the R group oriented away from camphor (Figure 24: TS_a, TS_b). How this destabilization arises is not understood. However based on the de obtained for alkylation reactions with cyclohexenyl systems that will be presented later, the cause of this destabilization is almost certainly due to the trans-substituent.

A possible complicating factor in the allylic cases which should be considered is the intervention of a Sn2' alkylation mechanism. In all allylic examples studied the Sn2' mechanism would give the same product as the Sn2 pathway. Mishra[48] noted one instance of an Sn2' reaction. 3-Chloro-1-butene reacted with the methyl ester of imine 1 to afford rearranged product. With the current level of our understanding about the details of the alkylation reaction, it cannot be stated definitively whether the occurrence of this pathway should increase or decrease the de's obtained. Deuterium labelling studies would appear to be necessary for an investigation of this type. However, the high de's obtained in the benzylic cases where Sn2' reactions are

impossible suggest that the intervention of this pathway, if it has any effect, can only reduce the observed de's.

The lower de (67%) observed for the reaction of propargyl bromide was not unexpected. The reaction is believed to proceed through a transition state in which the Li-π bond coordination occurs. However because the molecule is linear the steric bias for approach from the Re or Si faces is small. A single recrystallization of the product gave diastereomerically pure 3g. Catalytic hydrogenation of this material provided diastereomerically pure propyl substituted imine 4 (Figure 29).



3g 4

Figure 29. Catalytic hydrogenation of 3g

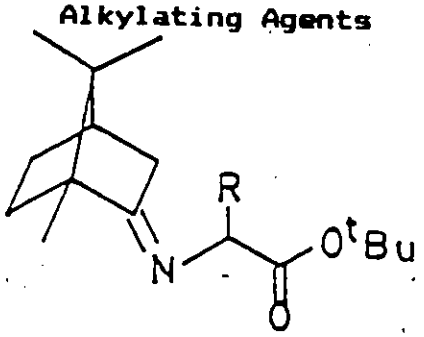
B. Secondary Alkylating Agents

The results of reactions of 1 with secondary alkylating agents are shown in Table 2.

The reaction of 1 with isopropyl iodide at -78°C gave a low yield (20%) of 3h as a mixture of two diastereomers formed in a ratio of 5:1 (67% de). This value is consistent with the results observed with the primary alkyl halides discussed previously. It is assumed that the molecule reacts preferentially from the Re

Table 2

Products and Yields of Alkylation Reactions With Secondary Alkylating Agents



Entry	Cpd	R	X	Yield[a]	Temp	%de (ratios)[b]
1	3h	isoPr	I	20 (80)	-78	67
2		isoPr	I	86	-20	65
3	3i	2-Butyl	I	40	-20	(3.4/2.6/1.0/1.0)
4	3j	C_6H_{11}	I	0 (99)	-20	--
5	3k	$C_6H_5CHCH_3$	Br	50 (99)	-78	80
6		$C_6H_5CHCH_3$	Br	60	-20	(2.4/1.5/1.0)
7	3l	$C_6H_5CHCH_2CH_3$	Br	31 (64)	-20	(4.4/3.0/1.4/1.0)
8	3m	3-cyclohexenyl	Br	54 (70)	-78	63
9	3n	5,5-diMe-3-cyclo-hexenyl	Br	11 (99)	-78	70
10	3o	CH_2=CHCHCH$_3$	Cl	0 (99)	-20	--
11	3p	HC≡C-CH-CH$_3$	Br	40 (82)	-78	(3.9/2.7/1.3/1.0)

[a] values in brackets are based on unrecovered imine
[b] in cases where more than two diastereomers are formed ratios are reported

face with the orientation of the terminal methyl groups away from the enolate ring system (TS_a). The low chemical yield obtained could be improved to 86% by repeating the reaction at -20°C. The increase in temperature did not significantly affect the de obtained (65%).

2-Iodobutane did not react at -78°C. At a temperature of -20°C a 40% yield of a 3i was obtained. Because the reaction led to a product in which two new chiral centers were present, there existed the possibility of four diastereomers being formed. The isolated product was indeed a mixture of four diastereomers isolated in a ratio of 3.4/2.6/1.0/1.0. Note that two diastereomers constituted 75% of the mixture. These are believed to be a result of Re face approach of the alkylating agent to the enolate. Examination of molecular models did not allow a prediction to be made about the absolute configuration at the second chiral center of the predominant isomer.

Cyclohexyl iodide (Entry 4) did not react at -78°C or -20°C. This result was not surprising because the general reactivity of this ring system in alkylations is known to be small[47]. The axial protons at positions 2 and 6 may interact with the enolate such that approach of the carbon bearing the leaving group may be hindered (Figure 30).

All alkylation reactions of secondary allylic and benzylic reagents led to products in which two new chiral centers are formed. Because of this, it is possible that the products isolated could be mixtures of up to four diastereomers.

Alkylation reactions of secondary benzylic reagents gave some surprising results. (1-Bromoethyl)benzene was found to react

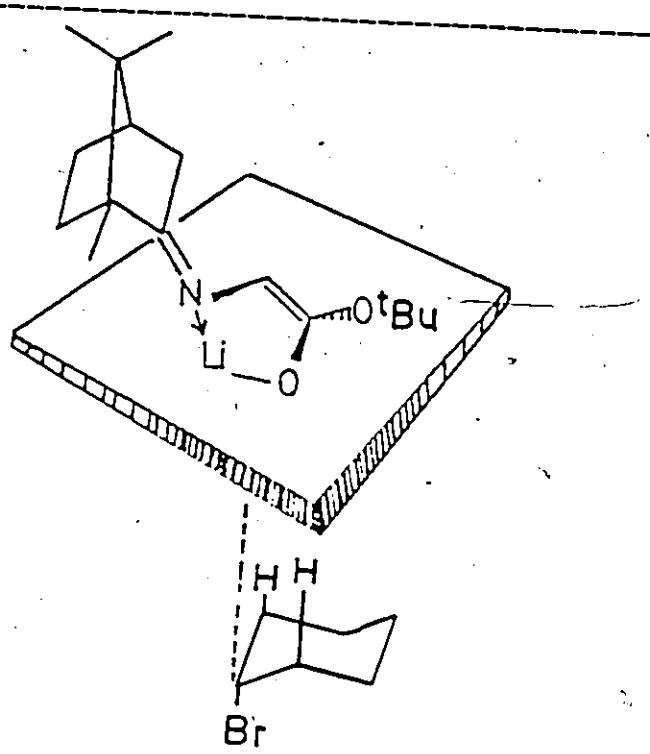


Figure 30. Diaxial Interactions of Cyclohexyl Iodide

with the enolate of 1 at -78°C to give a 50% yield of 3k. High field ^{1}H NMR of this material showed what appeared to be three doublets for the methine proton at C-2 (by amino acid numbering) but decoupling studies showed that one of these signals arises from an unrelated system (impurity). The presence of only two doublets for the methine proton (ratio 9:1) indicated that only two of the four possible diastereomers were formed in this reaction. This result requires that one of the two newly formed chiral centers must be stereochemically pure. The data do not allow a decision as to which one of the chiral centers is stereochemically homogeneous.

Transamination of 3k with hydroxylamine acetate gave the phenethyl substituted amino ester (5) as a 9:1 mixture of diastereomers (Figure 31). This result was consistant with the

presence of two diastereomers of 3k.

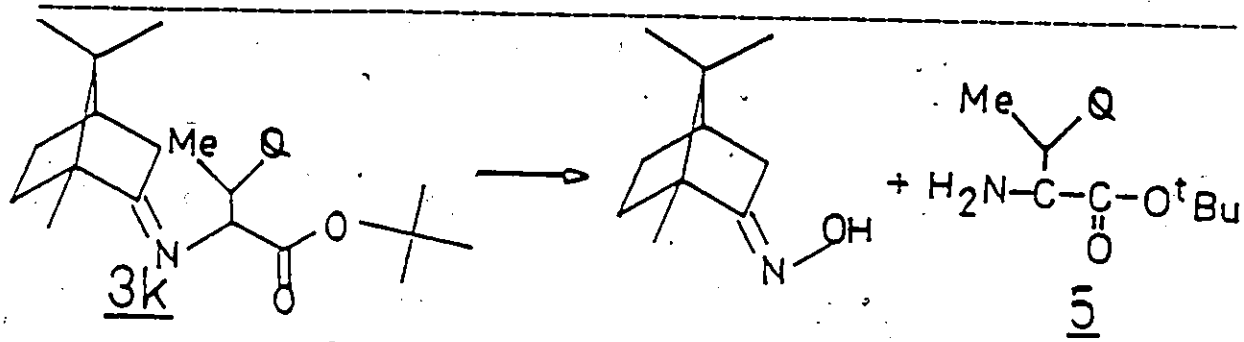


Figure 31. Transamination of 3k

The alkylation reaction with (1-bromopropyl)benzene required a temperature of -20°C. Four diastereomers of 3l in a ratio of 4.4/3.0/1.4/1.0 were isolated in a 31% chemical yield. Note that two of these isomers again account for 75% of the product mixture.

It was intriguing that (1-bromoethyl)benzene gave only two diastereomers while the present case gave all four possible diastereomers. In an attempt to explain this anomaly the reaction of (1-bromoethyl)benzene was repeated at -20°C. Under these reaction conditions a mixture of at least three diastereomers was found. This result indicates that the difference in energies between the transitions states ($\Delta\Delta G$) giving rise to the four diastereomers of 3l are smaller than those giving rise to the diastereomers of 3k. As has been noted, changing the reaction temperature from -78°C to -20°C in some cases does not significantly affect the observed de's, whereas in other cases, significant changes do occur. These results serve to indicate how delicately balanced are the various factors that determine the stereochemical selectivity. In general, it appears that the benzylic electrophiles are much more sensitive to temperature effects than are alkyl ones, even though the same

center of the imine is being affected in each case.

The reactions of secondary allylic halides gave the same type of results. Reaction of 1 with 3-cyclohexenyl bromide provided 54% of only two diastereomers of 3m in a ratio of 5:1 (63% de). The same results were observed with the reaction of 3-bromo-5,5-dimethyl-cyclohexene. This reaction proceeded at -78°C to provide an 11% yield of 3n as two diastereomers (70% de).

The fact that these two reagents react to give reasonable de's (>60%) provides evidence for the conclusion that to obtain significant de's allylic reagents must not possess a trans-substitutent. Attempts to prepare 1-methyl-3-bromocyclohexene from the corresponding alcohol so that this hypothesis could be tested with allylic ring systems were unsuccessful. The product isolated from these attempts was 1-methyl-1,3-cyclohexadiene generated from elimination of HBr.

As in the reaction of (1-bromoethyl)benzene, the presence of only two diastereomers of 3m and 3n indicates that one of the newly formed chiral centers is stereochemically pure. The question as to which one of the chiral centers of 3m was homogeneous was easily answered. Destruction of the chiral carbocyclic center by catalytic hydrogenation (Figure 32) gave a molecule for which only two diastereomers can exist. High field ^{1}H NMR data from the product of this reaction showed the presence of two diastereomers. Since racemization was not expected to occur it was concluded that the stereochemically pure center of 3m was the allylic one. Based on this result the stereochemically pure center of 3k and 3n can tentatively be assigned to the benzylic and allylic carbons respectively.

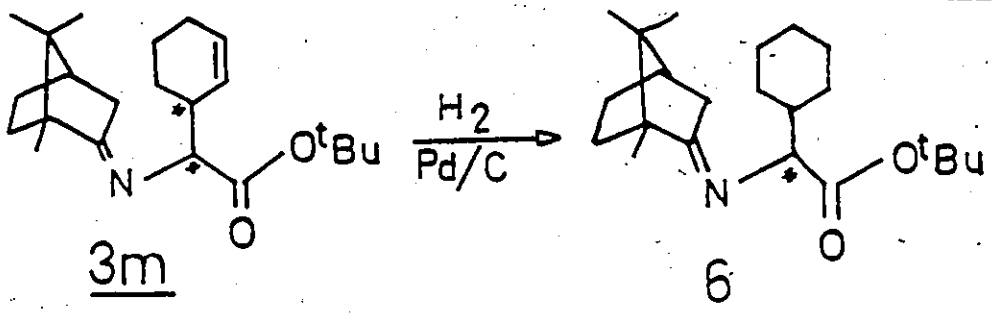


Figure 32. Catalytic hydrogenation of 3m

Note also that the product of this hydrogenation reaction (6) is the same as would be expected if the cyclohexyliodide reaction had been successful. This methodology does provide an alkylative approach into this class of substituted imine.

The conclusion that the stereochemically pure carbon of 3k, 3m, and 3n is C-3 suggests that one enantiomer of the alkylating agent must react preferentially. Examination of space filling molecular models of the expected transition state leading to 3k does provide a clear explanation as to why this should occur. It is assumed that a Li-π arene coordination occurs and that Re face approach of the alkylating agent is prefered to Si face attack as was shown for the primary alkylating agents. In this diastereofacial approach the methyl group of (1-bromoethyl)benzene will be near either the t-butyl function or the endo proton at C-3 of camphor depending on the enantiomer of the alkylating agent that reacts (Figure 33).

To test this hypothesis the reactions of (1-bromoethyl)benzene, 3-bromocyclohexene, and 3-bromo-5,5-dimethyl-cyclohexene were repeated using two equivalents of alkylating agent (i.e. one equivalent of each enantiomer). The results are summarized in Table 3.

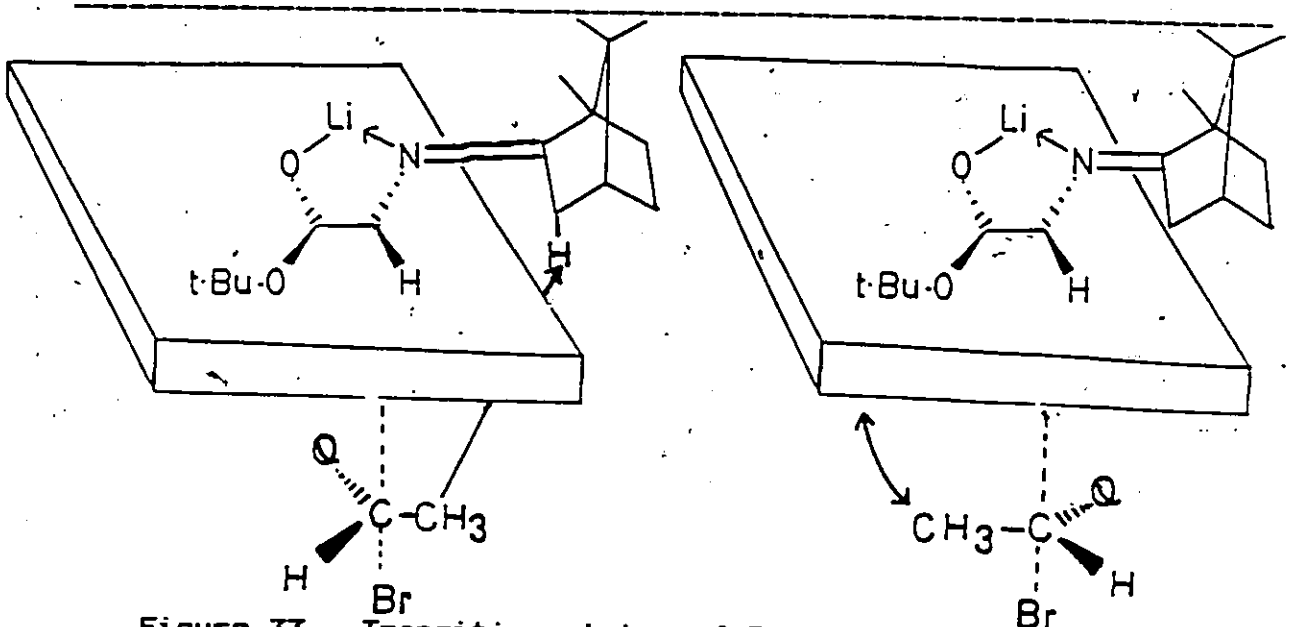


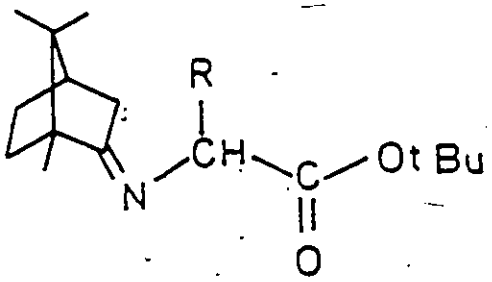
Figure 33. Transition states of Re face approach of (1-bromoethyl)benzene

Entry 1 shows that the chemical yield of the product from the reaction with (1-bromoethyl)benzene improved from 50% to 60%. The de remained unchanged. The interesting result of this reaction was that the recovered alkylating agent had strong optical activity ($[\alpha]_D$ -63° (c 2.1 EtOH)) and possessed the same direction of rotation as the known S-enantiomer[88]. This requires that the R enantiomer of the alkylating agent reacts preferentially over the S enantiomer. Because the reaction was expected to occur with inversion of configuration, it was concluded that the major diastereomer formed in this reaction had the (2R, 3S) configuration (by amino acid numbering). Attempts to prepare a crystal suitable for X-ray analysis were unsuccessful.

Using two equivalents of 3-cyclohexenyl bromide (Entry 2) improved the yield marginally from 54% to 66%. However the de was

Table 3

Products and Yields of Alkylation Reactions With Two Equivalents of Secondary Alkylating Agents[a]



Entry	Cpd	R	X	Yield	Temp	%de
1	3k	$C_6H_5CHCH_3$	Br	60	-78	80
				[50]		[80]
2	3m	3-cyclohexenyl	Br	66	-78	89
				[54]		[63]
3	3n	diMe-3-cyclohexenyl	Br	66	-78	76
				[11]		[70]

[a] value in brackets are for the reaction with 1 equivalent.

improved dramatically from 63% to 89%. A single recrystallization provided diastereomerically pure 3m. Single crystal X-ray analysis[31] showed that the absolute configuration of the imine was (2R, 3S) (Figure 34). The crystal structure also proved that the imine bond geometry was in fact *E* thus confirming the expectations of McIntosh and Mishra[33,34].

The reaction of 1 with two equivalents of 3-bromo-5,5-dimethyl-cyclohexene gave a de of 76% - not significantly different from the de obtained (75%) when one equivalent of alkylating agent was used. The chemical yield however was improved from 11% to 66%.

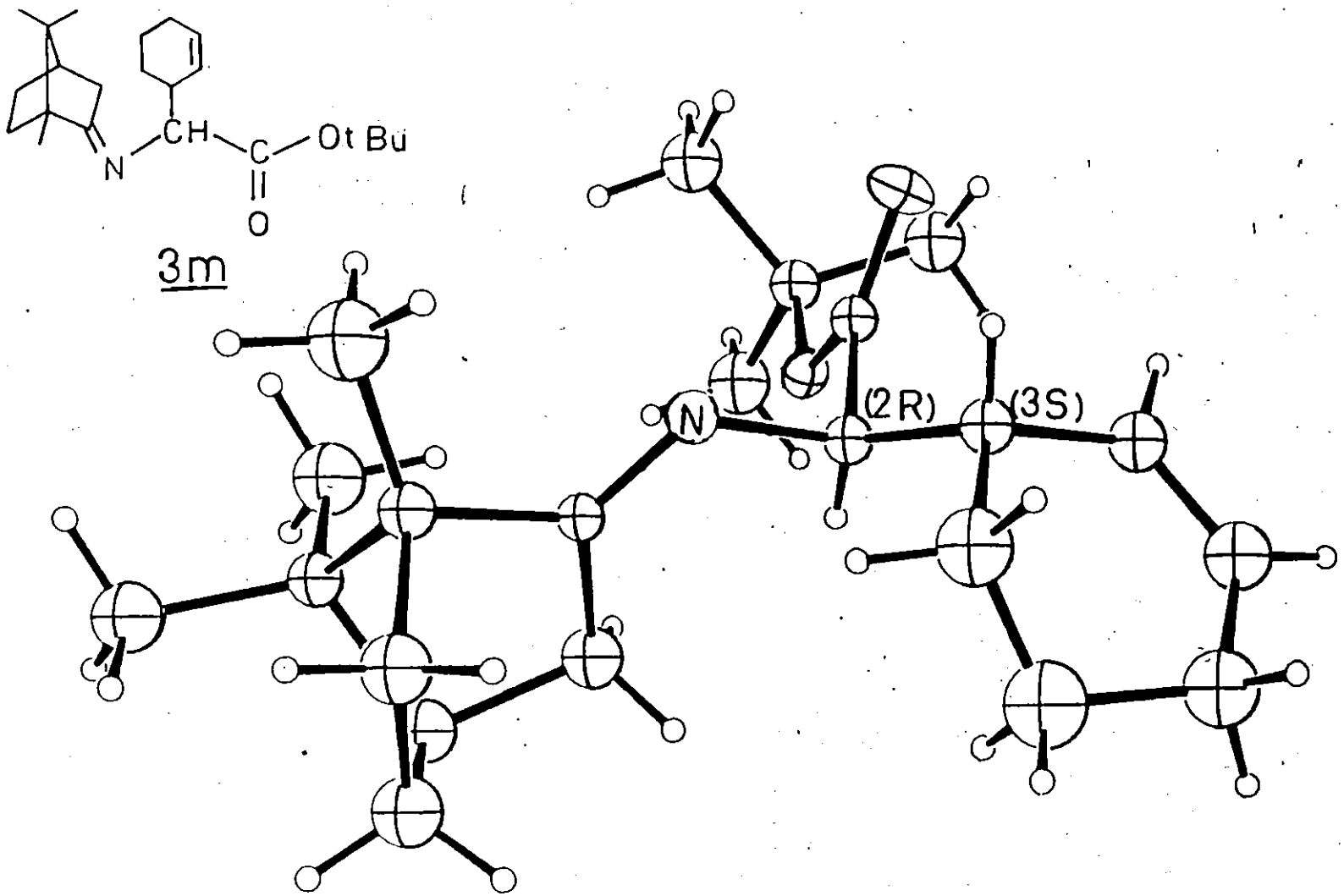


Figure 34. Crystal structure of 3m.

These dramatic results are very strong evidence for the hypothesis that one enantiomer of the alkylating agent reacts preferentially over the other enantiomer. Masamune[82] has coined the term "double chiral induction" to describe this kind of situation. In double asymmetric synthesis the interaction of two homochiral reactants can lead to very much higher diastereoselectivities than is possible in (single) asymmetric synthesis. For this to occur however, the homochiral reagents must be "matched". Matched reagents are those in which the respective diastereofaces possess little or no opposing interactions in the transition state. "Mismatched" pairs of chiral reagents give lower diastereoselectivities than are seen in single asymmetric synthesis in analogous systems.

Masamune reported in a recent publication[82] that this hypothesis applies to a number of reaction types in which very high de's were obtained. He also applied this strategy in the asymmetric synthesis of sugars and macrolides.

In the case of (1-bromoethyl)benzene, the imine enolate and the (R)-enantiomer of the alkylating agent constitute a matched pair system. The mismatched pair would be the corresponding (S)-enantiomer and the imine enolate. As discussed previously, the interaction between the endo proton on C3 of camphor and the methyl group of (1-bromoethyl)benzene appears to be responsible for the fact that the (S)-enantiomer is part of the mismatched pair. The cause for mismatched pairs in the reaction of the cyclohexenyl alkylating agents was not apparent through examination of space filling models.

It was interesting to note that the reaction of styrene oxide was unsuccessful. This result was not unexpected. Mishra found that aldol reactions of the lithium enolate of 1 were also unsuccessful. This result was attributed to the fact that the imine is a soft base while the carbonyl carbon of the ketone or aldehyde is a hard acid. The Hard and Soft Acids and Bases (HSAB) concept, developed by R.G. Pearson[44], states that soft bases prefer to react with soft acids, and hard bases with hard acids. Soft bases (or acids) are characterized by high polarizability, large size, and empty low energy orbitals. Hard bases (or acids) have the opposite properties.

Stork[24] has used this hypothesis to explain why 1,4-addition of imine enolates to conjugated ketones is prefered over 1,2-addition.

The final entry of Table 2 shows that 2-bromo-3-butyne gave a mixture of all four possible diastereomers. This result was not surprising in view of the result obtained with propargyl bromide. The linearity of the molecule avoids any large interactions with the chiral directing agent. Note however that again two diastereomers make up 75% of the product mixture. Because no allene was formed, the Sn2' alkylation mechanism was not involved in this reaction.

One preliminary experiment on an alternate approach to the chiral alkylations of imine 1 has been carried out. Reaction of the sodium enolate of 1 with allyl acetate at 25°C in the presence of $Pd(dppe)_2$ gave a 50% yield of 6a (33% de) (Figure 35). The rationale for this experiment lay in the assumption that the π-allyl palladium electrophile should be sterically more demanding

than simple allyl halide. Since the bulky complexed palladium atom is known to be displaced in a trans manner[33], its interaction with C-8 of the camphor moiety during attack from the Si face was expected to hinder this mode of reaction, leading to enhanced diastereoselectivity. The results obtained do not support this conclusion. It may be that the sodium - π or sodium enolate - π coordination is not as strong as the corresponding lithium case. The higher reaction temperature could also play an important role in the diastereoselectivity of the reaction as was seen in the alkylations of lithiated enolates. Further work must be carried out before any definitive conclusions can be made.

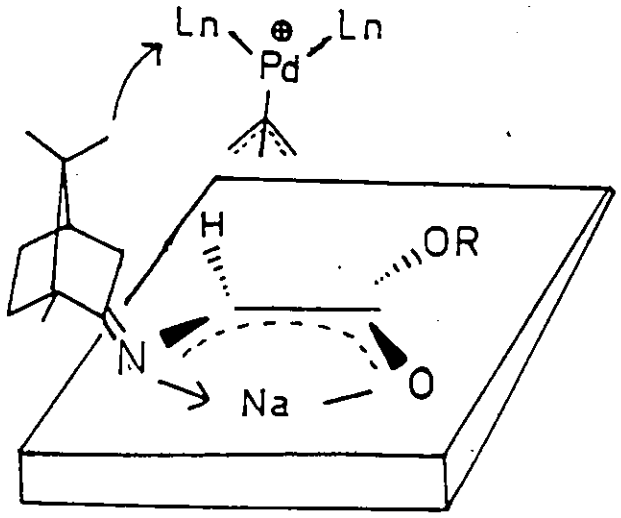
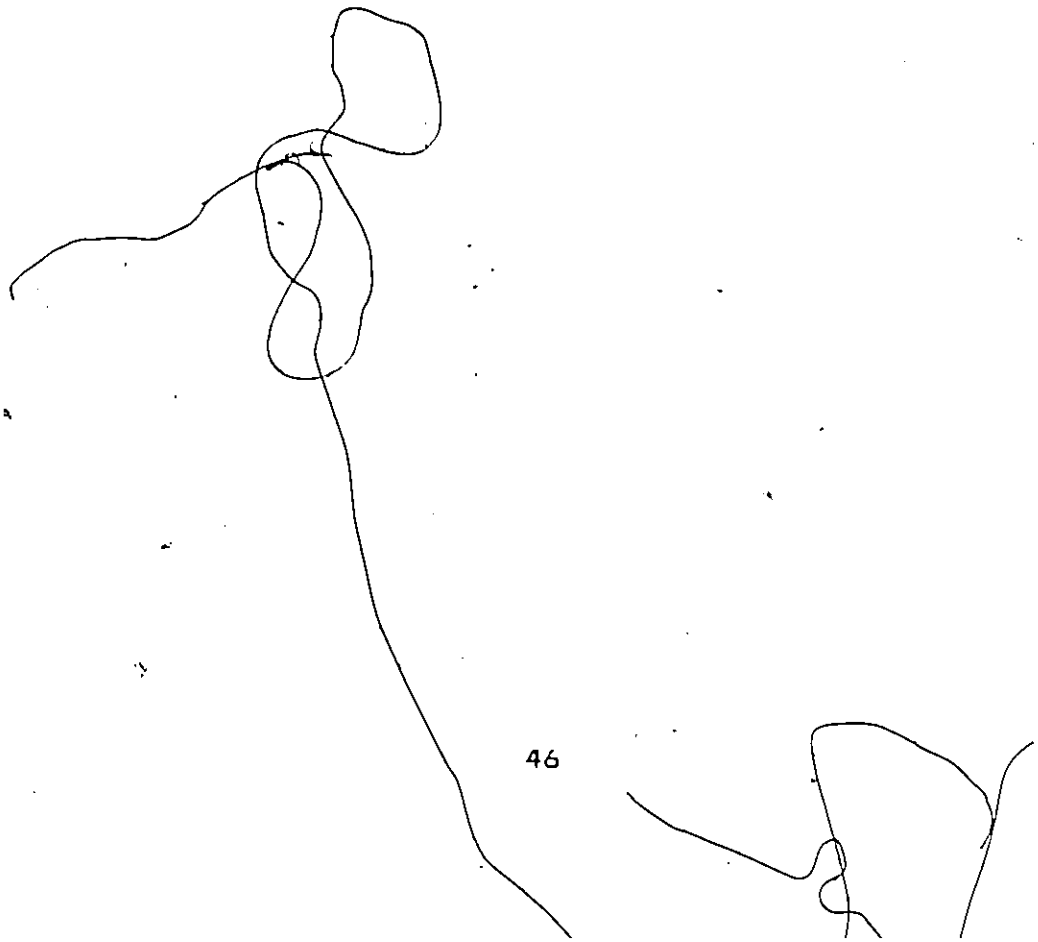


Figure 35. Allyl palladium mediated alkylations.

The work presented here has shown that good to excellent de's can be obtained in the alkylation reactions of 1 with allylic and benzylic halides. The enhanced de's for these types of reactions can be explained using a model in which the π

system of the alkylating agent is coordinated to the lithium atom of the enolate. In some cases, one enantiomer of secondary alkylating agents reacts preferentially over the other enantiomer. These are excellent examples of double asymmetric synthesis.

Future considerations regarding the chemistry of 1 include an examination of the role that Sn2' reactions play in the de's obtained from allylic alkylating agents, the use of Lewis acids to catalyse aldol reactions and epoxide alkylations, and palladium mediated reactions of allylic compounds. Investigations into the stereochemical nature of the deprotonation process of the glycinate are also of interest. Chirally pure monodeuterated glycine would be valuable in this regard. The information obtained from these studies would add to our knowledge about the utility of the t-butyl glycinate imine of camphor for generating optically active amino acids that has been conveyed here.



Compound	R group
3a	ethyl
3b	o-methylbenzyl
3c	1-napthylmethyl
3d	4-nitrobenzyl
3e	methallyl
3f	$(CH_3)_2C=CHCH_2$
3g	propargyl
3h	isopropyl
3i	2-butyl
3k	$C_6H_5CHCH_3$
3l	$C_6H_5CHCH_2CH_3$
3m	3-cyclohexenyl
3n	5,5-diMe-3-cyclohexenyl
3p	$HC\equiv C-CH-CH_3$

Table 4

^{1}H NMR Spectra of Camphor Imines of t-Butyl Glycinates

ENTRY	CMPD	CHEMICAL SHIFT (in ppm downfield from TMS)
1	3a:	3.73 [3.68] (dd, 1H, J = 8.4, 5.1 Hz), 2.48 - 2.31 (m, 1H), 2.03 - 1.65 (m, 4H), 1.44 [1.45] (s, 9H), 1.2 - 1.40 (m, 4H), 1.01 (s, 3H), 0.94 (s, 3H), 0.87 [0.867] (t, 3H), 0.82 [0.78] (s, 3H)
2	3b:	7.19 - 6.98 (m, 4H), 4.00 (dd, 1H, J = 10.3, 3.6 Hz), 3.25 (dd, 1H, J = 13.5, 3.6 Hz), 3.06 (dd, 1H, J = 13.6, 10.35 Hz), 2.38 (s, 3H), 2.25 - 2.15 (m, 2H), 1.73 - 1.41 (m, 3H), 1.45 (s, 9H), 1.10 - 0.90 (m, 2H), 0.96 (s, 3H), 0.84 (s, 3H), 0.72 (s, 3H)
3	3c:	8.20 - 7.23 (m, 7H), 4.17 (dd, 1H, J = 10.2, 3.3 Hz), 3.83 (dd, 1H, J = 13.5, 3.3 Hz), 3.55 - 3.35 (m, 1H), 2.05 - 1.80 (m, 4H), 1.47 (s, 9H), 1.45 - 1.20 (m, 3H), 0.91 (s, 3H), 0.76 (s, 3H), 0.64 (s, 3H)
4	3d:	8.08 (d, 2H), 7.40 (d, 2H), 4.05 (dd, 1H, J = 9.7, 4.1 Hz), 3.42 - 3.08 (m, 2H), 2.40 - 2.20 (m, 1H), 1.98 - 1.45 (m, 3H), 1.43 (s, 9H), 1.42 - 1.03 (m, 3H), 0.98 (s, 3H), 0.80 (s, 3H), 0.70 (s, 3H)
5	3e:	4.75 -4.65 (m, 2H), 3.96 (dd, 1H, J = 8.4, 5.4 Hz), 2.63 - 2.34 (m, 3H), 1.97 - 1.55 (m, 6H), 1.42 [1.43] (s, 9H), 1.36 - 1.09 (m, 3H), 0.97 (s,

3h), 0.91 (s, 3H). 0.79 [0.70] (s, 3H)

6 3f: 5.09 - 4.98 (m, 1H), 3.80 (dd, 1H, J = 9.0, 5.7 Hz), 2.65 - 2.05 (m, 4H), 2.00 - 1.75 (m, 3H), 1.70 (m, 3H), 1.68 (s, 3H), 1.48 (s,9H), 1.48 - 1.20 (m, 2H), 1.00 (s, 3H), 0.92 (s, 3H), 0.75 (s, 3H)

7 3g: 4.05 (dd, 1H, J = 9, 5.4 Hz), 2.68 (ABMX system, 1H, J_{AB} = 16.8 Hz, J_{AM} = 8.8 Hz, J_{AX} = 2.6 Hz, J_{BX} = 2.6 Hz), 2.49 - 2.41 (m, 1H), 2.09 - 1.80 (m, 4H), 1.75 - 1.65 (m, 1H), 1.42 (s, 9H), 1.28 - 1.19 (m, 3H), 1.00 (s, 3H), 0.95 (s, 3H), 0.82 (s, 3H)

8 3h: 3.46 [3.42] (d, 1H, J = 8 Hz), 2.48 - 2.20 (m, 2H), 2.22 - 1.60 (m, 4H), 1.44 [1.46] (s, 9H), 1.43 - 1.2 (m, 2H), 1.00 (s, 3H), 0.79 [0.76] (s, 3H), 0.95 [0.93] (d, 3H, J = 6 Hz), 0.87 [0.88] (d, 3H, J = 6 Hz)

9 3i: 3.52 (d, 1H, J = 8.4 Hz), [3.60 (d, J = 7.3 Hz)], [3.58 (d, J = 7.3 Hz)], 2.22 (m, 1H), 2.14 - 1.72 (m, 5H), 1.39 (s, 9H), 1.40 - 1.00 (m, 4H), 0.97 (s, 3H), 0.93 - 0.8 (m, 9H), 0.78 - 0.71 (m, 3H)

10 3k: 7.28 - 7.18 (m, 5H), 3.96 [3.93] (d, 1H, J = 8 Hz), 3.49 (dq, 1H, J = 7, 8 Hz), 2.43 - 2.20 (m, 2H), 1.93 - 1.45 (m, 5H), 1.28 (s, 9H), 1.29 (d, 3H, J = 7 Hz), 1.04 (s, 3H), 0.93 (s, 3H), 0.77 (s, 3H)

11 3l: 7.40 - 7.15 (m, 5H), 4.01 [3.98, 3.97, 3.96] (d, 1H, J = 9 Hz), 3.30 - 3.14 (m, 1H), 2.55 - 2.25 (m, 1H), 2.2 - 1.37 (m, 8 Hz), 1.23 [1.26] (s,

9H), 1.06 [1.07] (s, 3H), 0.95 [0.96] (s, 3H), 0.86 - 0.72 (m, 6H)

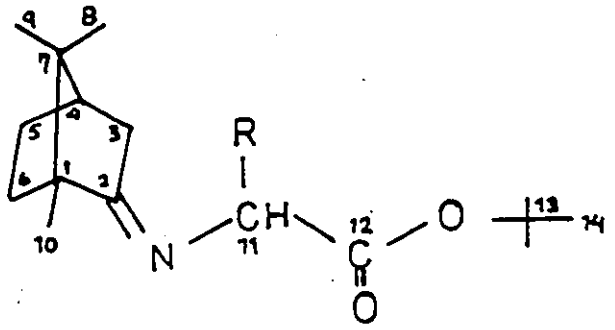
12 3m: 5.8 - 5.45 (m, 2H), 3.63 [3.61, 3.60] (d, 1H, J = 9 Hz), 2.90 - 2.76 (m, 1H), 2.55 - 2.29 (m, 1H), 2.05 - 1.10 (m, 12H), 1.42 [1.44] (s, 9H), 0.97 [0.99] (s, 3H), 0.91 [0.92] (s, 3H), 0.77 [0.74] (s 3H)

13 3n: 5.70 - 5.48 (m, 2H), 3.59 [3.52] (d, 1H, J = 9Hz), 2.91 - 2.75 (m, 1H), 2.50 - 2.48 (m, 1H), 1.98 - 1.50 (m, 7H), 1.48 (s, 9H), 1.48 - 1.00 (m, 3H), 0.98 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H), 0.76 (s, 3H)

14 3p: 3.78 [3.75, 3.73, 3.71] (d, 1H, J = 8.4 Hz), 3.18 - 3.05 (m, 1H), 2.52 - 2.35 (m, 4H), 2.05 - 1.45 (m, 4H), 1.41 [1.40, 1.42, 1.43] (s, 9H), 1.09 [1.21] (d, 3H, J = 7 Hz), 0.95 [0.96] (s, 3H), 0.91 (s, 3H), 0.76 [0.77] (s, 3H)

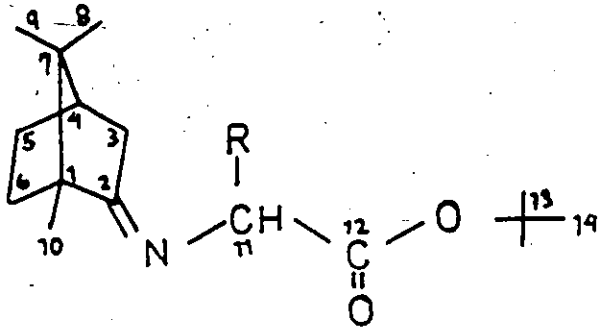
Table 5

^{13}C NMR Spectra of Camphor Imines of t-Butyl Glycinates



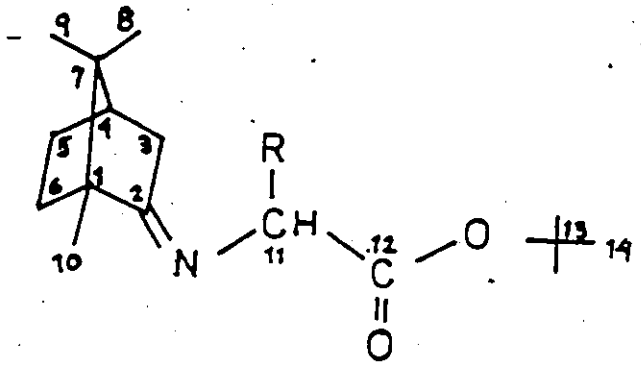
Entry	Cmpd	C-1	C-2	C-3	C-4	C-5	C-6
1	3a	53.9	183.8	35.8 [36.1]	44.0	27.5 [27.4]	31.9
2	3b	53.7	184.6	35.7 [35.6]	43.5	26.9	32.3
3	3c	53.6	184.4	35.6	43.3	26.9	31.4
4	3d	54.1	185.8	36.0	93.5	27.3	31.9 [31.8]
5	3e	53.9	184.2	35.9	43.8	27.4	32.1
6	3f	53.9 [54.0]	183.9	36.2 [35.9]	44.0 [43.9]	27.6	32.3
7	3g	54.1	186.1	36.0 [35.9]	43.9	27.4	32.3 [31.9]
8	3h	54.1	184.3	36.3 [35.9]	44.0	27.7 [27.66]	32.4 [32.1]
9	3i	53.9	184.2	36.2 [36.1] [35.7]	43.8 [43.9]	27.5 [32.2]	32.3 [47.1] [32.0]
10	3k	54.2	185.1	36.2	43.9	27.5	32.23 [32.2]
11	3l	54.1	185.2	36.3 [35.9]	43.8 [43.9]	27.71 [27.6] [27.5] [27.4]	32.0

Entry	Cmpd	C-1	C-2	C-3	C-4	C-5	C-6
12	3m	54.1	184.7	36.4	43.9 [43.9]	27.5	32.3
13	3n	54.0	184.5	36.3	43.9	27.5 [27.4]	32.3 [32.1]
14	3p	54.2		36.2 [36.0]	43.9 [44.0]	27.5 [27.4]	32.3 [32.1]



Entry	Cmpd	C-7	C-8	C-9	C-10	C-11	C-12
1	3a	47.2	19.5	18.9 [18.8]	11.4 [11.3]	66.7 [66.4]	169.3
2	3b	46.8	19.1 [19.4]	18.6 [18.9]	11.2 [11.5]	65.7	171.3
3	3c	46.6	19.2	18.7	11.3	65.6	171.3
4	3d	47.1	19.4	18.8 [18.6]	11.4	65.9 [65.8]	170.2
5	3e	47.1	19.5	18.9	11.4	63.9	171.2
6	3f	47.1	19.6 [19.3]	18.9	11.5	65.5 [65.6]	171.6
7	3g	47.2	19.5	18.9	11.3	69.4 [69.2]	169.9
8	3h	47.3	19.6	19.1	11.6	72.3 [71.9]	171.3
9	3i	47.2 [47.1]	19.5 [19.4]	19.0 [18.8]	11.6 [11.5]	69.4 [72.3] [71.0] [70.0]	171.3
10	3k	47.3	19.5	19.1 [19.0]	11.7	71.5	170.6
11	3l	47.3	19.4 [19.6]	19.0 [18.9]	11.7 [11.6]	71.3 [71.1]	170.3

Entry	Cmpd	C-7	C-8	C-9	C-10	C-11	C-12
12	3m	47.3	19.4	18.9	11.5	70.3	170.9
13	3n	47.1	19.4	18.9	11.5	70.3	170.8
14	3p	47.3	19.4	18.9	11.3	69.9 [69.8]	169.6



Entry	Cmpd	C-13	C-14	R
1	3a	80.4	28.1	32.4, 10.4[10.4]
2	3b	80.7	27.9	137.1 [136.7], 130.4 [130.9], 129.7 [130.1], 126.5 [125.9], 125.6 [125.1], 43.2, 19.8 [19.6]
3	3c	80.8	28.0	134.9, 133.7, 123.1, 128.6, 128.1, 126.9, 125.7, 125.3, 125.1, 124.1, 35.2
4	3d	81.4	27.9	147.0, 130.6, 130.5, 123.1, 38.6
5	3e	80.7	27.9	142.4, 112.3, 40.7, 23.0
6	3f	80.5	28.1	133.6, 120.9 [120.6], 19.0, 18.0, 32.0 [31.8]
7	3g	81.2	28.0 [28.1]	81.4, 63.8 [64.2], 22.5 [22.7]
8	3h	80.4	28.1 [28.2]	18.5, 31.3 [31.1]
9	3i	80.3	28.0 [28.1]	24.9 [26.4], 15.6 [15.7, 14.9 14.8] 37.4 [37.6, 37.7], 10.9 [11.0, 11.3]
10	3k	80.6	27.9	128.2, 128.1, 126.4 [126.3], 144.4, 42.9, 17.3

Entry	Cmpd	C-13	C-14	R
12	3m	80.5	28.1 [28.0]	128.9, 128.2, 37.9, 25.3, 24.9, 20.9
13	3n	80.6	28.0	127.3, 126.9, 39.3 [38.5], 37.0, 29.2, 25.3, 25.2
14	3p	80.9	27.9	16.5 [17.6], 28.8 [29.3], 69.3 [69.1]

Table 6

Infrared Spectra of Camphor Imines of t-Butyl Glycinates[1]

ENTRY	CMPD	ABSORPTION (cm^{-1})			
1	3a:	1155.7	1684.3	1737.3	2937.7
2	3b:	1152.3	1683.1	1736.4	2958.3
3	3c:	1151.9	1683.0	1735.4	2957.3
4	3d:	1153.2	1343.9	1732.3	1518.8
5	3e:	1143.8	1680.9	1735.3	2970.4
6	3f:	1150.8	1685.0	1737.6	2959.6
7	3g:	1156.4	1683.5	1726.2	2962.8
8	3h:	1137.1	1683.9	1738.1	2958.8
9	3i:	1158.2	1684.6	1735.3	2960.8
10	3k:	1151.5	1681.8	1733.7	2983.1
11	3l:	1148.6	1681.2	1735.2 [1721.0]	2959.8
12	3m:	1147.0	1678.0	1731.6	2938.7
13	3n:	1147.6	1682.4	1739.1	2952.6
14	3p:	1154.2	1682.4	1737.5	2962.3

[1] The four strongest peaks are reported.

Table 7

Microanalyses of Camphor Imines of t-Butyl Glycinates[a]

ENTRY	CMPD	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
1	3b	78.00	9.54	3.79	77.75	9.41	3.62
2	3c	79.95	8.69	3.45	79.18	8.61	3.26
3	3f	75.62	10.57	4.19	75.45	10.74	4.27
4	3g	75.20	9.63	4.61	75.32	9.82	4.53
5	3h	74.21	10.81	4.55	74.53	10.98	4.97
6	3i	74.71	10.97	4.35	75.46	11.04	4.42
7	3k	77.83	9.32	3.81	77.70	9.36	3.94
8	3l	78.28	9.72	3.65	78.19	9.55	3.37
9	3m	76.03	10.73	4.03	76.21	10.83	4.09
10	3n	77.37	10.28	3.75	77.18	10.13	3.55
11	3p	75.66	9.84	4.41	75.65	9.88	4.33

[a] Mass spectra were taken in the FI mode and all compounds showed their molecular ion peak.

CHAPTER 2

PUMMERER REACTIONS OF S-OXIDES OF 1,3-OXATHIOLAN-5-ONES AND 1,3-THIAZOLIDIN-4-ONES

INTRODUCTION

1,3-Oxathiolan-5-ones (7) are five membered ring heterocycles that have served as precursors to a number of useful molecular types. McIntosh and Siddiqui[54] reported that these are readily reduced with diisobutylaluminum hydride to the corresponding 2-mercaptoaldehydes, which were previously difficult to obtain[55]. α-Mercaptoaldehydes can be used to generate dihydrothiophenes[54-57] (Figure 36) which are useful as intermediates in a number of syntheses[54-60]. McIntosh and Mishra[41] were also successful in reducing this heterocycle with LAH to the 2-mercaptoalcohol which has been utilized by others[42-45] in the synthesis of epoxides (Figure 36).

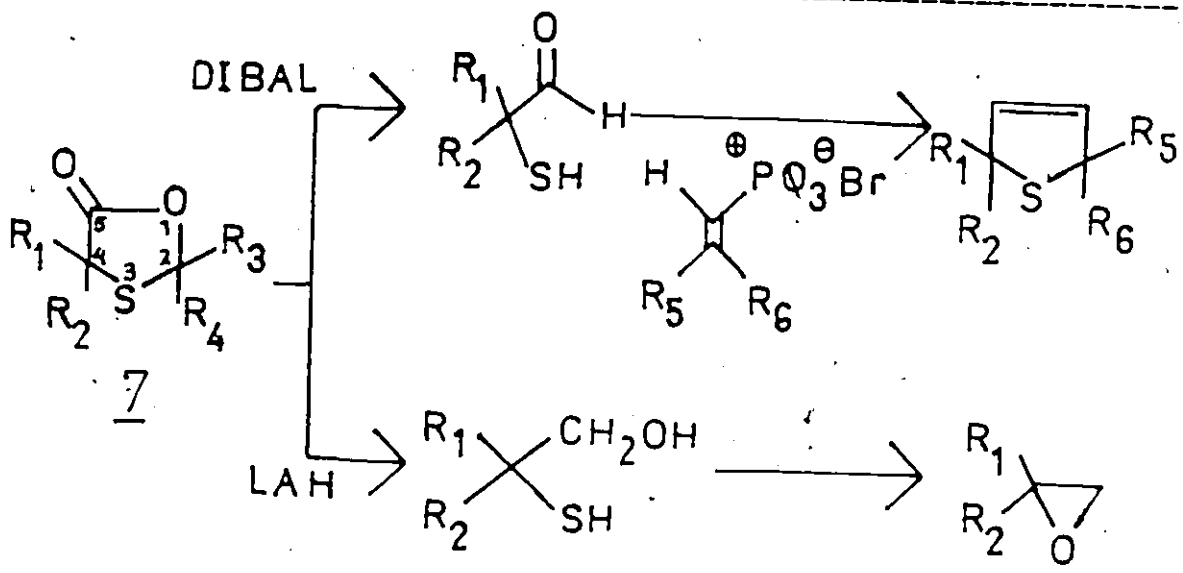


Figure 36. Metal hydride reduction of oxathiolanones

Cameron and Pinnick[44] reported that flash vacuum pyrolysis of 1,3-oxathiolanones gives the corresponding thiiranes in nearly quantitative yields. The reaction is stereospecific and goes with inversion of configuration (Figure 37). Thiiranes have been

used to generate olefins[47] and β-aminomercaptans[48].

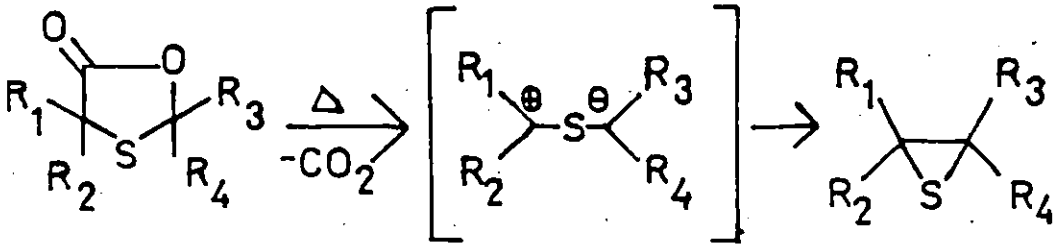


Figure 37. Pyrolysis of 1,3-oxathiolanones

Raney nickel desulfurizations of this heterocycle have also been achieved by Romo de Vivar and Romo[49]. The original carbonyl compound and products derived from reaction between the solvent and diphenyl ketene were obtained. The authors postulate that the reaction goes by way of a 1,4-biradical which rearranges to a 1,2-biradical (Figure 38).

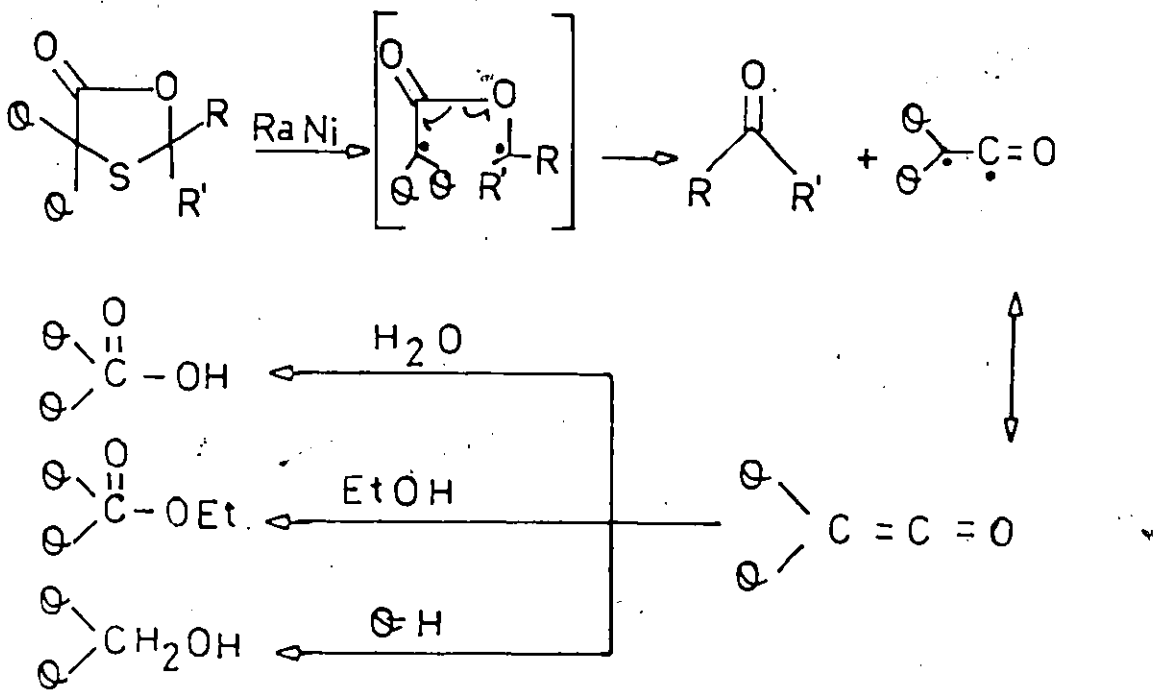


Figure 38. Proposed mechanism for RaNi desulfuration of oxathiolanones

The possibility of providing a general route to 2-mercaptoaldehydes of varying structure prompted McIntosh and co-workers to examine methods for substituting the C-4 position of 7. They found that the lithium enolate of the 3,3-dimethyl-oxathiolanone reacts with aldehydes and ketones to give diastereomeric mixtures (where applicable) of aldol products[7m].

Helquist[71] made use of this methodology for the synthesis of enethiols (Figure 39).

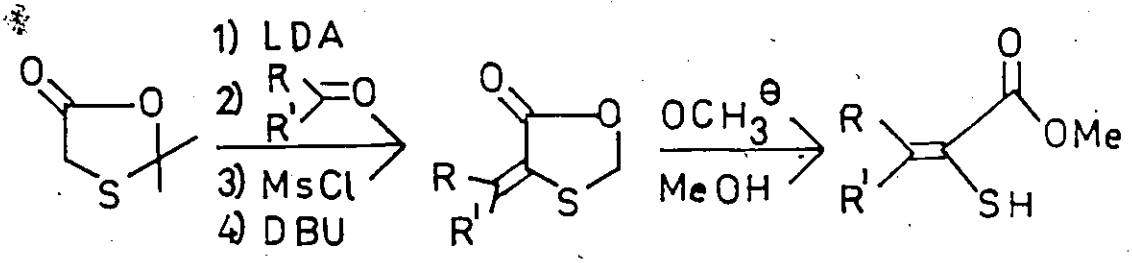


Figure 39. Synthesis of enethiols from oxathiolanones

McIntosh *et.al*[7m] also examined the alkylation chemistry of oxathiolanones. They reported that, unlike the aldol reactions, alkylations cannot be used as a general method for substituting the 4-position of 1,3-oxathiolanones. Successful alkylation reactions were restricted to 4-methyl substituted heterocycles and very reactive alkylating agents (e.g. allyl and benzyl).

The limited scope of enolate chemistry of oxathiolanones suggests that creating the "umpolung" situation would add to the breadth of its utility in synthesis (Figure 40). That is, using the heterocycle as an electrophile in reactions with nucleophiles might be a superior method for attaining substitution. To achieve this, a Pummerer type reaction would be an appropriate

method.

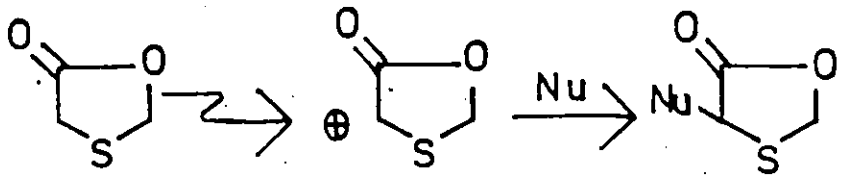


Figure 40. Reaction of electrophilic oxathiolanone

Sulfoxides bearing an acidic α-hydrogen will readily undergo an unusual reaction with electrophilic agents such that the sulfoxide function is reduced and the α-carbon is oxidized. This reaction, commonly known as the Pummerer Reaction, was first observed by Pummerer in 1909[72]. He noted that α-phenylsulfinyl acetic acid, when treated with dry HCl, gave α-chloro-α-phenylthioacetic acid.

The mechanism of the reaction has been the subject of debate for many years. The actual pathway to the products appears to depend on the particular nature of both the sulfoxide and the acylating agent. In general, the mechanism can be thought of as four consecutive steps, any one of which have been found to be rate determining in individual cases (Figure 41)[73]. The majority of mechanistic studies make use of acetic anhydride or trifluoroacetic anhydride as the electrophilic reagent.

The first step of the reaction is acylation of the sulfinyl oxygen to form an acyloxysulfonium salt. Swern[74] isolated such a species by reacting dimethyl sulfoxide with trifluoroacetic anhydride at -60°C. Upon warming to room temperature the Pummerer product was obtained. The effect of this first step in

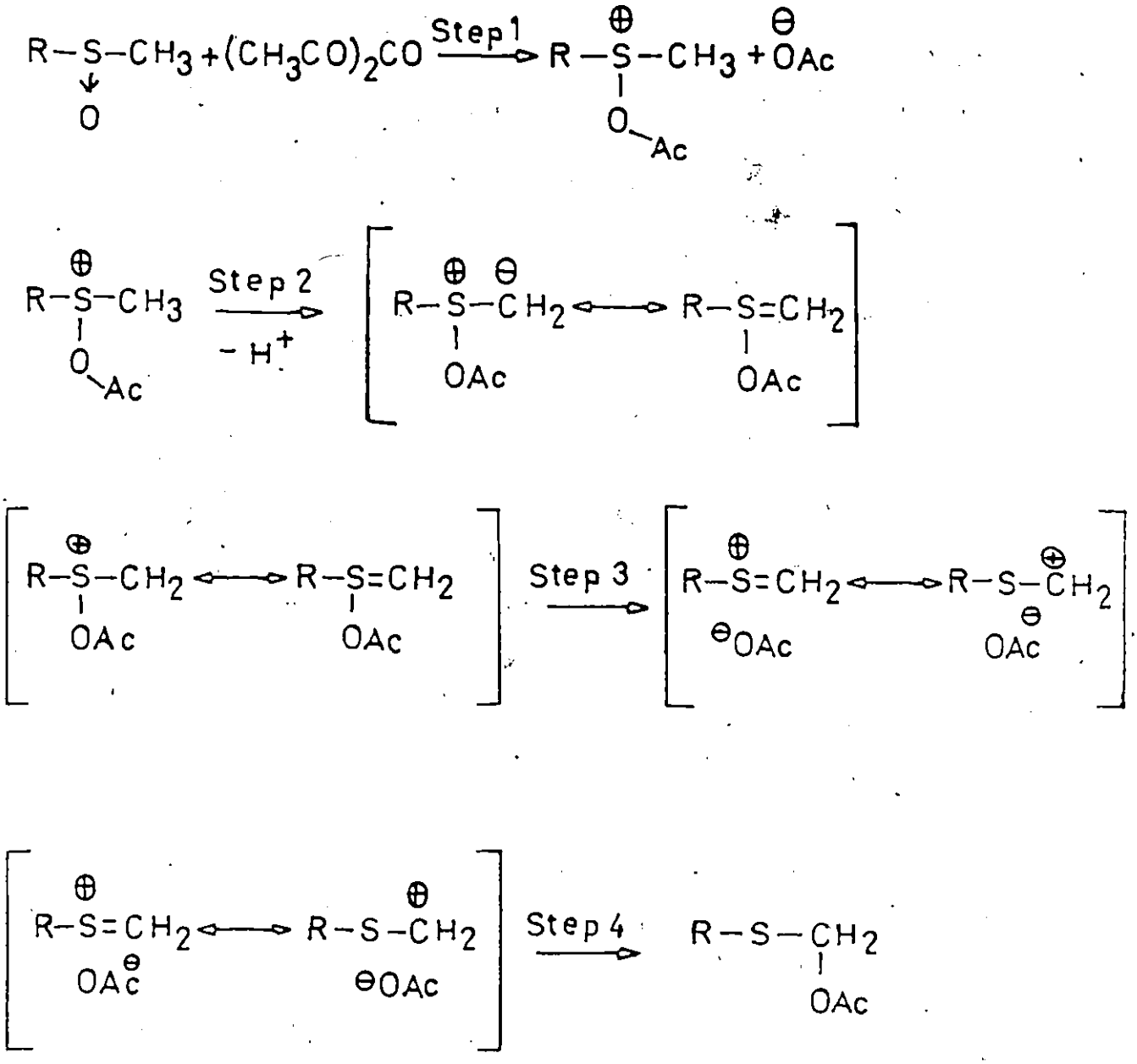


Figure 41. Mechanism of the Pummerer Reaction

the reaction sequence is to confer increased acid character on the α-hydrogen such that removal by the acetate ion in the second step is facilitated. The second step leads to an acyloxysulfonium ylid. The importance of proton removal in step

two is seen in the regiochemistry of the product. Because the acyloxy group migrates to the carbon from which the proton was removed a great amount of regioselection is acquired. In general, the acyloxy group will migrate to the carbon bearing the most acidic hydrogen; however steric factors must be considered[73,75].

The third step in the reaction sequence is S-O bond cleavage. This results in the formation of a sulfur stabilized carbonium ion which may or may not be involved as an intimate ion pair. The life time of the ion pair depends largely on the nature of the substitutents, solvent, and acylating agent[73].

The recombination of the acetate ion and the sulfur stabilized carbonium ion is the fourth step in the reaction. It is very fast simply because it is the joining of two oppositely charged species. The most contentious point of the mechanism is whether the reaction occurs in an intramolecular or an intermolecular fashion. Evidence suggests that the acetoxy migration may occur either way depending on the nature of the participants[73].

Given that the mechanism is as outlined above, it was expected that olefins or aryl functionalities would be able to capture the sulfur stabilized carbonium ion intermediate (Figure 42). There are a number of precedents which show that this intermolecular reaction might be possible.

Tanikagi and coworkers[74] have shown that the trifluoroacyloxy sulfonium salts of a number of sulfoxides could be generated at -80°C. These were found to react with sulfides and thiols to give the sulfur substituted products (Figure 43).

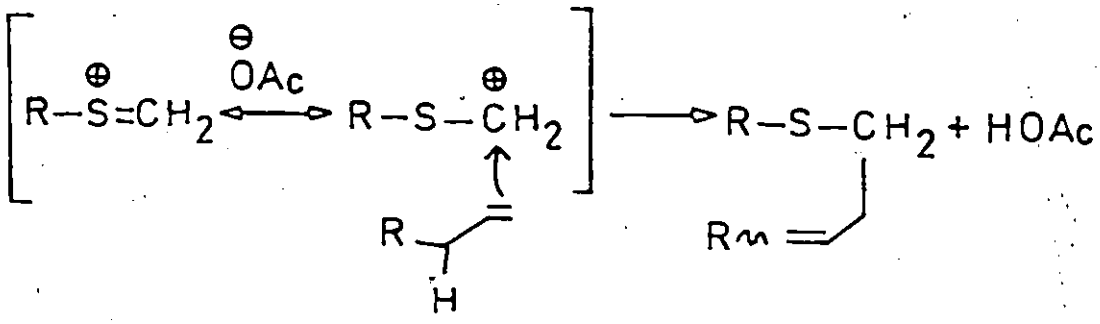


Figure 42. Reaction of electrophilic oxathiolanones with olefins.

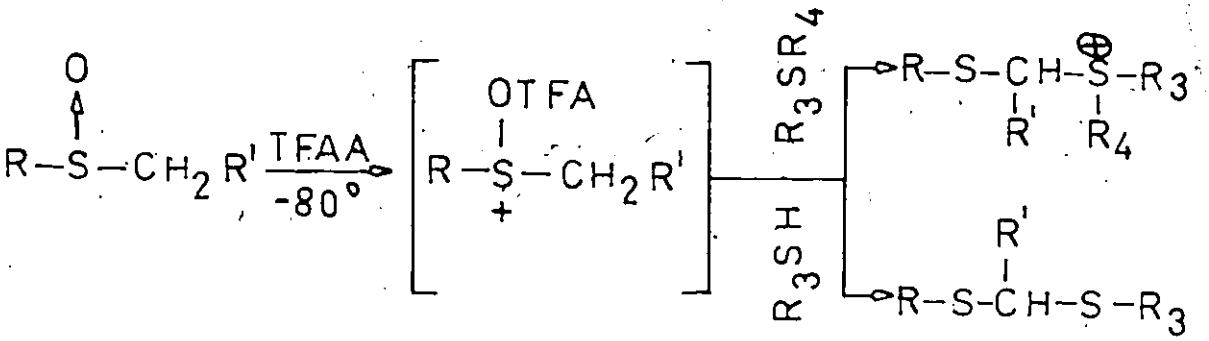


Figure 43. Reaction of Pummerer intermediate with sulfides and thiols.

Swern[77] reported that the TFAA generated Pummerer intermediate of dimethylsulfoxide oxidizes alcohols to the carbonyl compounds. Small amounts of ethers (up to 30%) were also obtained (Figure 44). The exact products depend on the reaction temperature.

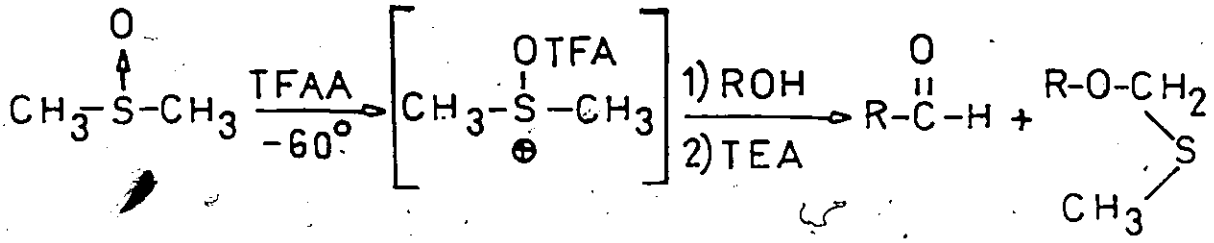


Figure 44. DMSO oxidation of alcohols to carbonyls.

Swern[78] was also able to show that aryl amines, aryl amides and aryl sulfonamides react with the sulfur stabilized carbonium ion at temperatures below -30°C to give iminosulfuranes (Figure 45). While this is not an example of a carbon bond forming reaction, it indicates that it is possible to capture the Pummerer intermediate.

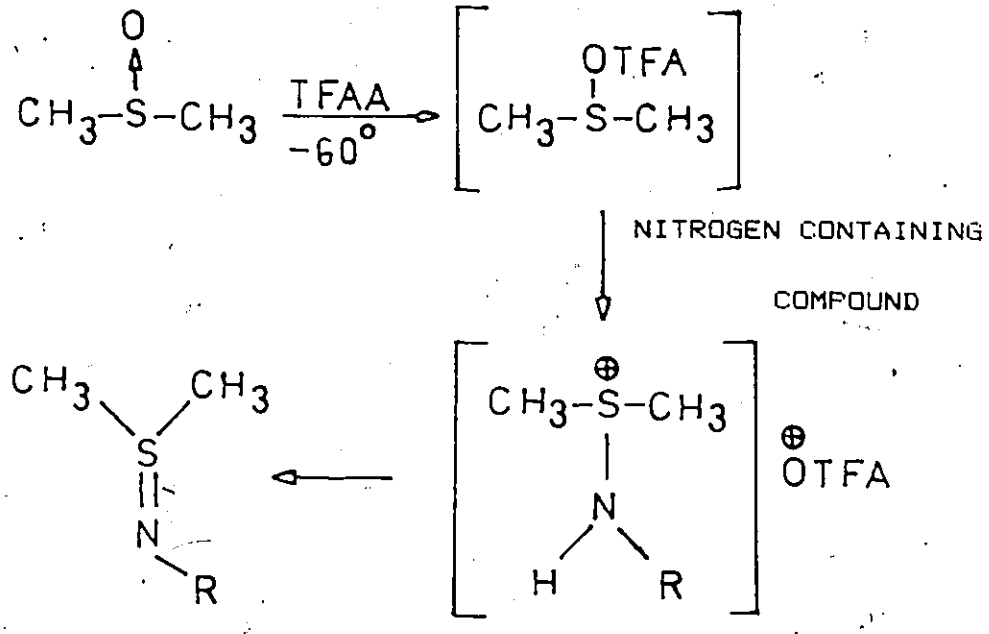
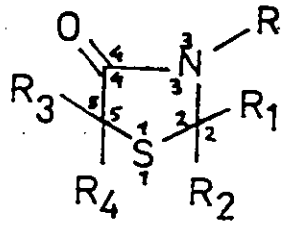


Figure 45. Preparation of iminosulfuranes.

This approach to substituting the 4-position of oxathiolanones should also be successful in the reactions of other sulfur containing heterocycles. 1,3-thiazolidin-4-ones are the lactam analogues of oxathiolan-5-ones. This class of



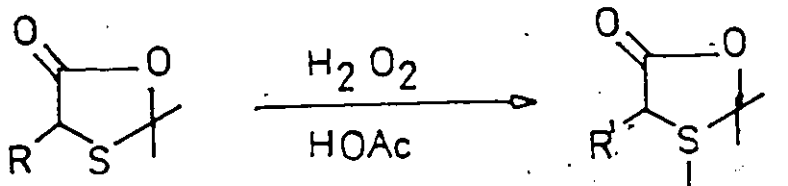
heterocycle possesses a wide variety of biological activity and has been the subject of many studies in this regard[79]. Their synthetic utility however has not been convincingly demonstrated. Most chemical studies of this heterocycle have centered around substituting various positions of the ring using aldol type chemistry[80,81]. The resulting arylidene and alkylidene derivatives are subject to the expected reactions of α,β-unsaturated carbonyl compounds[78] (i.e. 1,4-addition of Grignard reagents, and halogenations). Alkaline hydrolysis of the heterocycle to the corresponding mercaptoacid has been reported. Metal hydride reductions and desulfurizations of this class of molecule have not been attempted.

RESULTS AND DISCUSSION

A. OXATHIOLANONES

To initiate the study of the Pummerer and Pummerer type reactions three 1,3-oxathiolan-5-ones (7) were prepared as described previously[84,78].

Oxidation of 7a in cold glacial acetic acid and excess hydrogen peroxide gave the corresponding sulfoxide 8a smoothly and in high yield (Figure 46). Overoxidation to the sulfone was not detected. The nucleophilic character of the sulfoxide is reduced due to the electron withdrawing characteristic of the carbonyl function and more strenuous oxidation procedures are required to effect the overoxidation[82].



7 — a R = H; b R = Me; c R = Et — 8

Figure 46. Oxidation of oxathiolanones.

Oxidation of 7b utilizing the same procedure gave a low yield of an unstable oil identified as the alcohol 9 (Figure 47). Proton NMR of this material showed an exchangable proton at 4.78 ppm. The IR spectra also showed the characteristic strong OH absorption. Compound 9 is believed to be formed by aqueous hydrolysis of the Pummerer reaction product that is generated *in situ* after oxidation occurs.

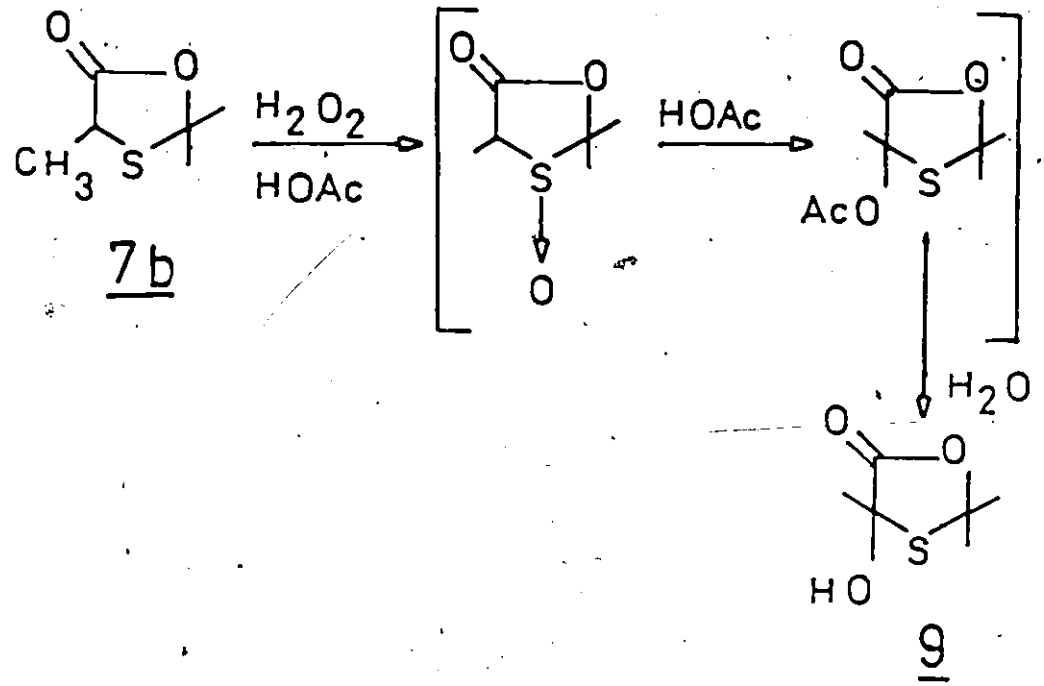


Figure 47. Postulated pathway for formation of 9.

Oxidation of 7c utilizing the same procedure provided an inseparable, three component mixture of products. These were identified as the starting sulfide, the expected sulfoxide 8c, and an elimination product 10. Evidence for 10 comes from ^{1}H NMR data in which a quartet at 6.8 ppm is observed. It is thought that the acetic anhydride initiates the Pummerer reaction and the sulfur stabilized carbonium ion is quenched by elimination of a proton in the alkyl side chain as is illustrated in Figure 48. This idea is supported by the results of Monteiro and Germal[23]. They observed that treatment of α-alkyl-β-oxo carbonyl compounds with acetic anhydride and a trace of pTsOH gave the corresponding alkylidene products. Although they offer no explanation for this reaction other than it involves a Pummerer rearrangement the same mechanism as Figure 48 can be invoked.

Oxidation of 7c with MCPBA or t-butylhydroperoxide did not improve these results.

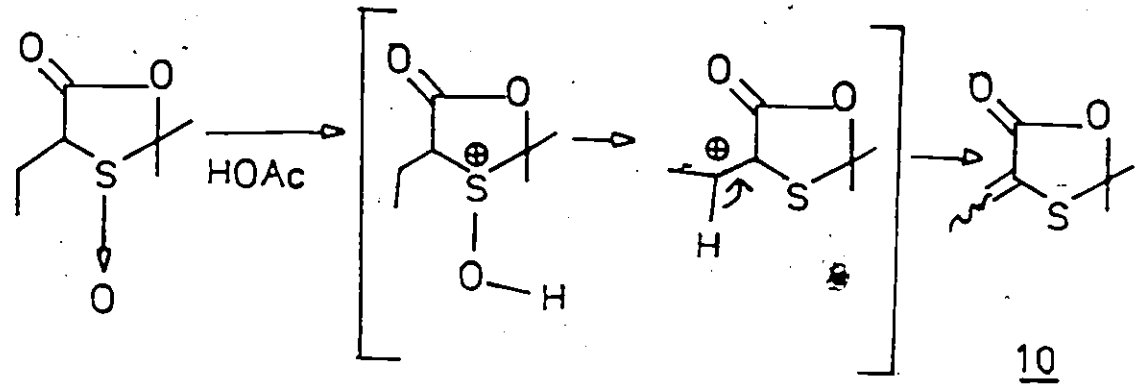


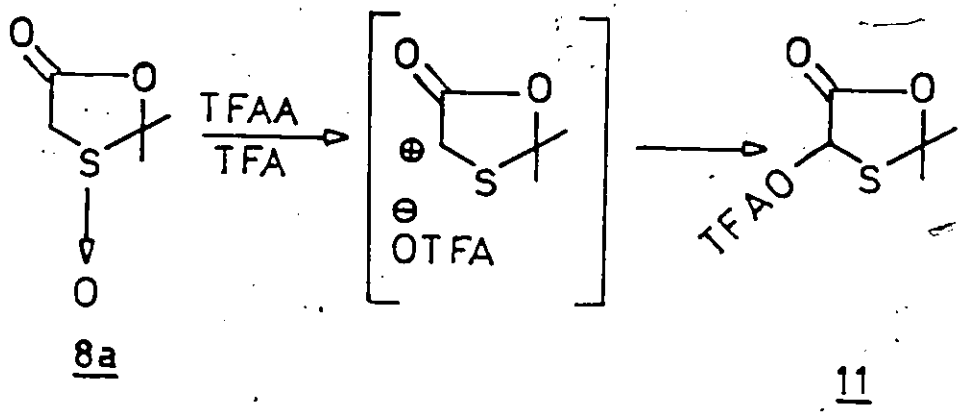
Figure 48. Postulated mechanism for formation of 10.

While the sulfoxides of oxathiolan-5-ones which bear an alkyl group in the 4-position are very labile compounds whose use in synthesis would be unattractive, the nature of sulfoxide 8a lends itself to examination of Pummerer and Pummerer type chemistry as a route to substituting the 4-position of 1,3-oxathiolan-5-ones.

Compound 8a reacted cleanly with trifluoroacetic anhydride in trifluoroacetic acid to yield the 4-trifluoroacetoxy product 11 (Figure 49). Although this material is very heat sensitive and decomposes upon attempted distillation, this result indicates that the molecule is subject to the Pummerer reaction under the TFAA/TFA conditions employed. This demands that the sulfur stabilized carbonium ion required for intermolecular capture by olefins is generated during the reaction.

Kay and co-workers[84] reported that the Pummerer reaction of 2,2-dialkyl-1,3-oxathiolan-5-ones (12) with acetic anhydride

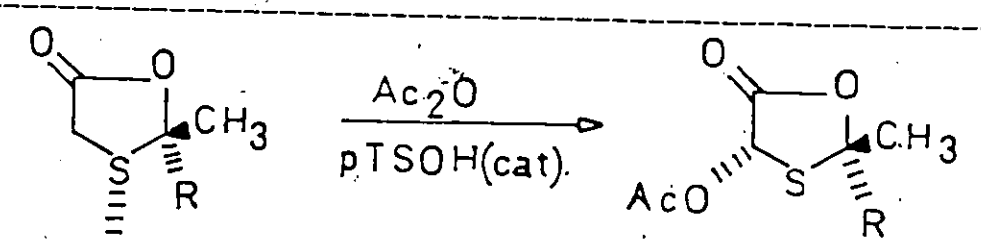
proceeds in an intramolecular fashion. They found that the acetoxy group was introduced on to the side of the ring (13)



8a 11

Figure 49. Pummerer reaction of 8a.

formerly occupied by the S-oxide bond (Figure 50). If an intermolecular reaction had occured the acetoxy group should have attached itself stereoselectively to the side of the heterocycle that is *cis* to the smallest alkyl group at C-2.



a R = iPr
b R = tBu
c R = Et

12 13

Figure 50. Intramolecular nature of acetoxy migration.

It was felt that the use of the less nucleophilic trifluoroacetic anhydride would allow a nucleophilic solvent to compete for the carbonium ion.

Repeating the TFAA reaction shown in Figure 49 utilizing

benzene or 1-hexene as the solvent gave the 4-trifluoroacetoxy molecule 11 as the only product (Figure 51). Clearly the intermolecular reaction cannot compete with the intramolecular migration.

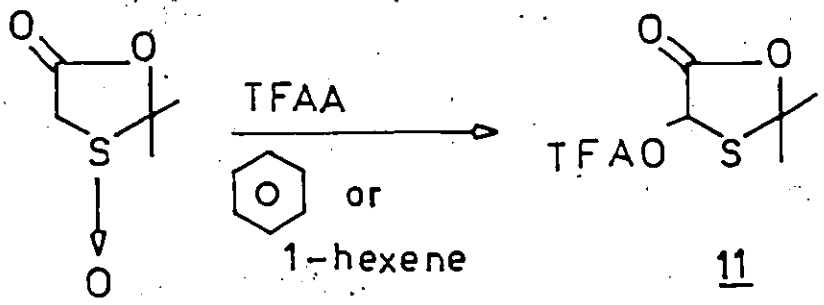


Figure 51. Reaction of 8a with TFAA in nucleophilic solvents.

Based upon these results it was hoped that the Pummerer intermediate might be generated by some other electrophilic species that could not react further in an intramolecular fashion.

Lewis acids are defined[85] as any species which has a vacant orbital, while a Lewis base is a species that possesses an unshared pair of electrons. The sulfoxide function meets the requirement for a Lewis base and would be expected to react with a Lewis acid. If this were to occur a positive charge would develop on the sulfur of the lactone thus generating the sulfur stablized carbonium ion required for the intermolecular Pummerer reaction (Figure 52).

The literature is replete with examples in which Lewis acids are used to catalyze reactions. The most dramatic cases come from the field of Diels-Alder[86] and ene[87] reaction chemistry. In these cases complexation of the Lewis acid to the carbonyl

function of dienophiles or enophiles creates an electron deficiency in the unsaturated part of the molecule such that the diene or the ene moiety reacts with a much lower activation energy.

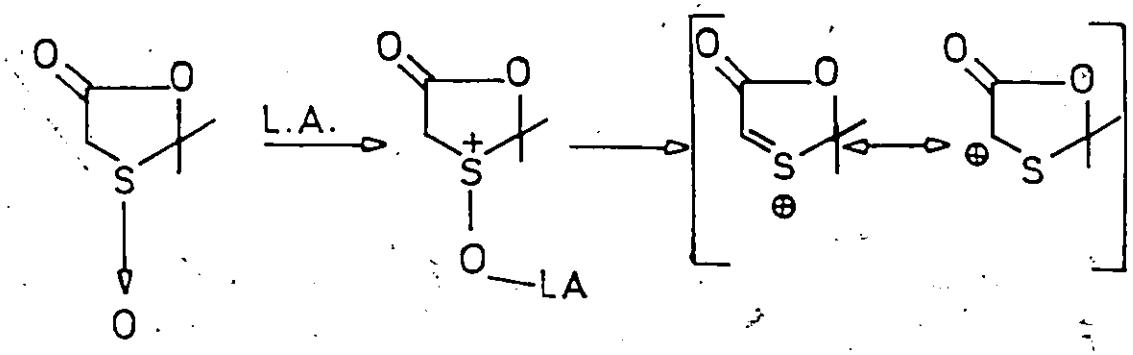
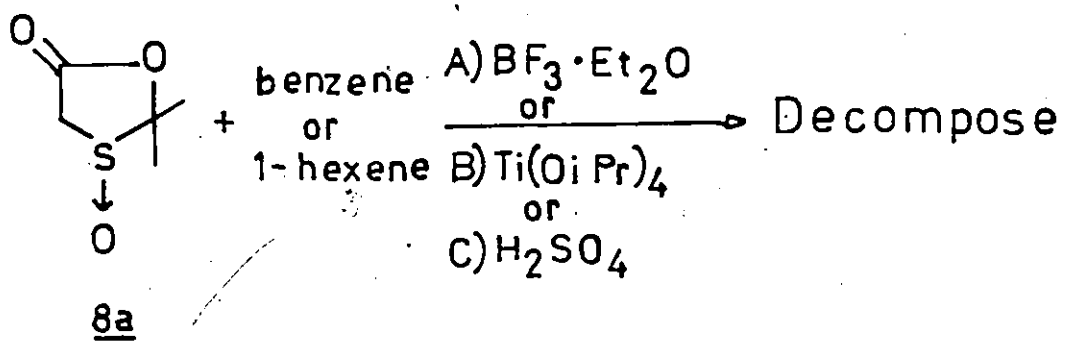


Figure 52. Generation of the Pummerer intermediate by Lewis acids.

Attempts at using catalytic amounts of BF_3-etherate in hexene, benzene, or anisole to effect an intermolecular reaction with oxathiolanones led to intractable mixtures of products. There was no evidence in the crude reaction mixtures for intermolecular capture of the Pummerer intermediate. Using $Ti(OiPr)_4$ as the electrophile in benzene resulted in inseparable ring opened products (C=O 1720 cm^{-1}). Clearly, this heterocycle was sensitive to the Lewis acid conditions that were employed.

The generation of the required sulfur stabilized carbonium ion using sulfuric acid should also be possible. The proton has a vacant orbital and should accept electrons from the oxygen of the sulfoxide function in the same way as the Lewis acids. In all cases using a catalytic amount of acid resulted in decomposition of the starting material with no identifiable products being isolated (Figure 53).



8a

Figure 53. Reaction of 8a using catalytic amounts of Lewis or protonic acids.

These results demonstrate that this heterocycle is a very labile material - much like 8b and 8c. The molecule is subject to rapid decomposition upon treatment with both mineral and Lewis acids even in catalytic amounts. Attempts to capture the TFAA generated intermediate in an intermolecular fashion were unsuccessful.

B. THIAZOLIDINONES

Because the corresponding lactams of oxathiolanones were expected to be more stable and the DIBAL reductions of these molecules were expected to be routine, attention was turned to these heterocycles. Five examples of 1,3-thiazolidin-4-ones (14a-e) were examined.

Compounds 14c[■■] and 14d[■▼] were prepared as previously described. All other thiazolidinones were synthesized by condensing the corresponding ketimine and 2-mercaptoacetic acid with the azeotropic removal of water. Peroxide oxidation of all sufides to the sulfoxides (15) was straightforward with no evidence of any sulfone being formed (Figure 54). Sulfoxides 15d and 15e were insoluble in most organic solvents and were not

suitable for further investigation. The lactam nitrogen must be substituted in order for the molecule to possess appropriate solubility characteristics.

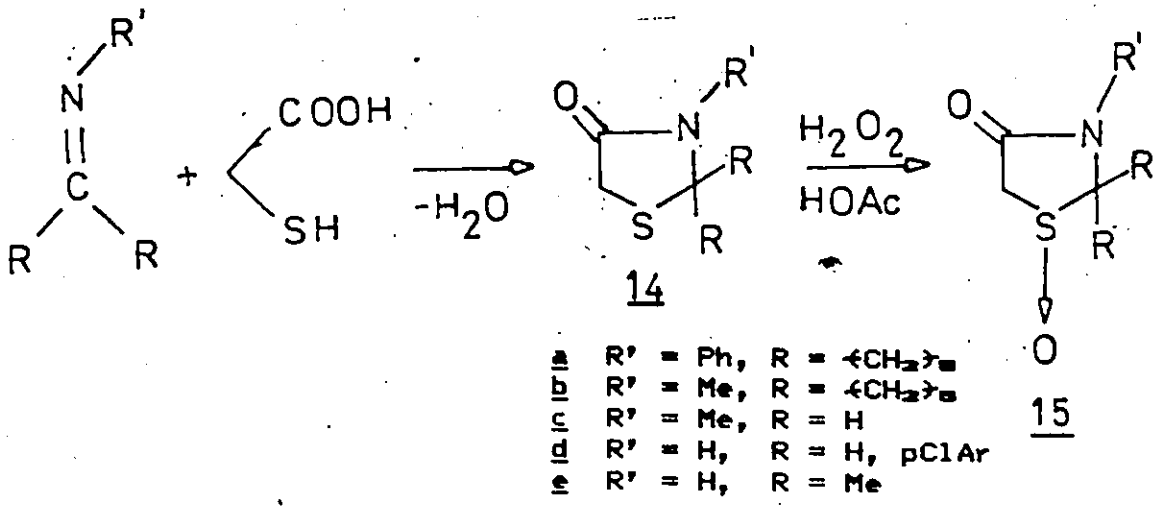


Figure 54. Formation and oxidation of 1,3-thiazolidinones.

Reaction of 15a with acetic anhydride and a catalytic amount of pTsOH in methylene chloride[84] gave a good yield of 5-acetoxythiazolidinone 16a. Compounds 15b and 15c reacted with TFAA and TFA to provide the corresponding 5-trifluoroacetoxy products 16b and 16c. 16b was isolated as the alcohol due to hydrolysis during the aqueous work-up procedure. These results indicate that the Pummerer reaction is possible on these heterocycles and that the sulfur stabilized carbonium ion that is required for intermolecular capture is actually formed (Figure 55).

Attempts to capture this carbonium ion by the reaction of TFAA with sulfoxide 15b in benzene led to a mixture of the 5-trifluoroacetoxy product as well as a small amount of the phenyl substituted heterocycle (17). Although this result demands that

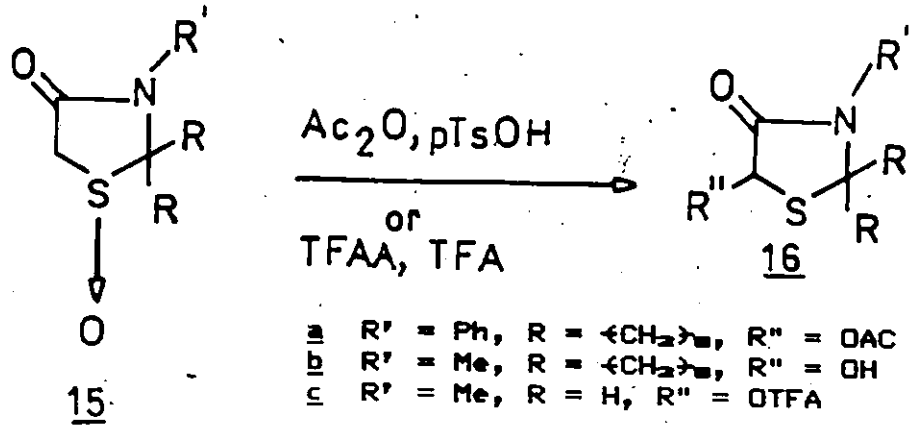


Figure 55. The Pummerer reaction of thiazolidinones.

benzene capture the carbonium ion, the minor amounts obtained indicate that it cannot compete successfully with the intramolecular trifluoroacetoxy migration.

Compound 15c is unlike all others examined in this work in that it possesses no substituent at C-2. The reaction of sulfoxide 15c with TFAA/TFA in 1-hexene or 1-octene gave the "ene" products 18 as a mixture of E and Z isomers in which the E isomer predominated. No trace of the intramolecular reaction was detected (Figure 56).

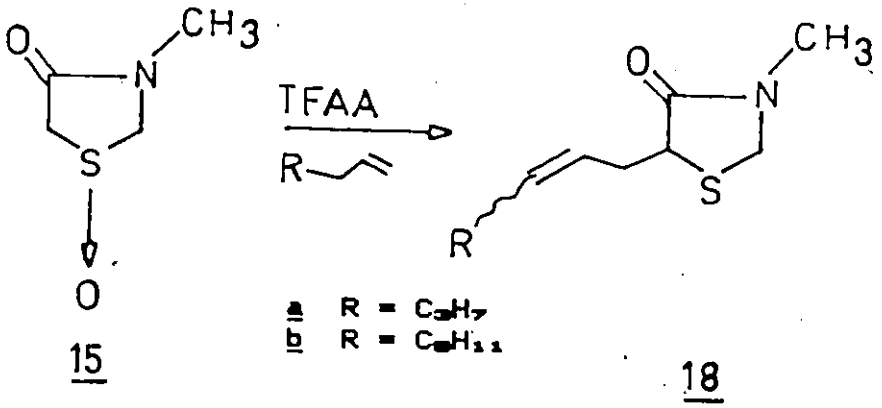


Figure 56. Intermolecular capture of the Pummerer intermediates by olefins.

The ene reaction is defined[71a] as "the indirect substituting addition of a compound with a double bond (enophile) to an olefin with an allylic hydrogen (ene). It involves allylic shift of one double bond, transfer of the allylic hydrogen to the enophile, and bonding between the two unsaturated termini". The Pummerer reaction, in which the carbonium ion is captured by an olefin, is not an ene reaction though it may be viewed as one. The ene is the olefin which contains the allylic hydrogen. The enophile is considered to be the canonical form of the carbonium ion as is illustrated in Figure 57. The reaction involves an allylic shift of one double bond and bonding between the two unsaturated termini.

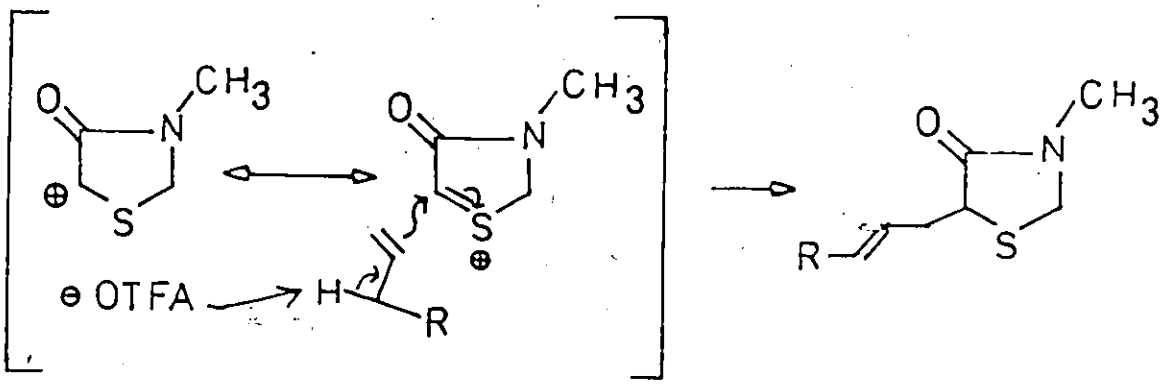


Figure 57. The "Ene" nature of intermolecular capture.

The successful capture of the sulfur stabilized carbonium ion of 15c wherein C-2 is unsubstituted by olefins suggests that the substitution pattern at C-2 of the thiazolidinones may be an important factor in determining the pathway (inter- or intramolecular) that the reaction takes.

Tamura[71a,b] and Ishibashi[71c] reported numerous examples of the Pummerer intermediate being captured by terminal olefins. In

all cases the sulfoxide was flanked by a methylene and a methyl group (Figure 58). There are also several reports[72] of aromatic systems reacting with the sulfur stabilized carbonium ion. However, none of these involve molecules that have substitution patterns more complicated than methylene at the carbons adjacent to the sulfoxide.

From this work it appears that the dialkyl substitution of sulfoxides 15a,b imparts some steric influence on the trifluoroacyloxy sulfonium ion such that the intramolecular migration is favoured over the intermolecular capture by benzene.

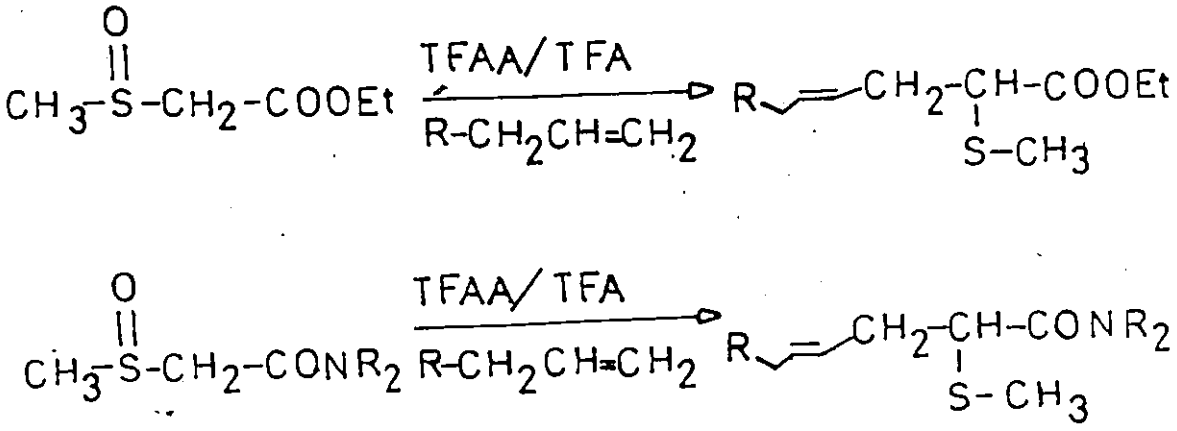


Figure 58. Tamura's examples of intermolecular capture.

Repeating the TFAA/TFA reaction of 15c with 2-alkenes (2-hexene) resulted in inseparable mixtures. These were identified only as substitution products that have either eliminated to give the "ene" adducts or have been captured by the trifluoroacetoxy ion (Figure 59).

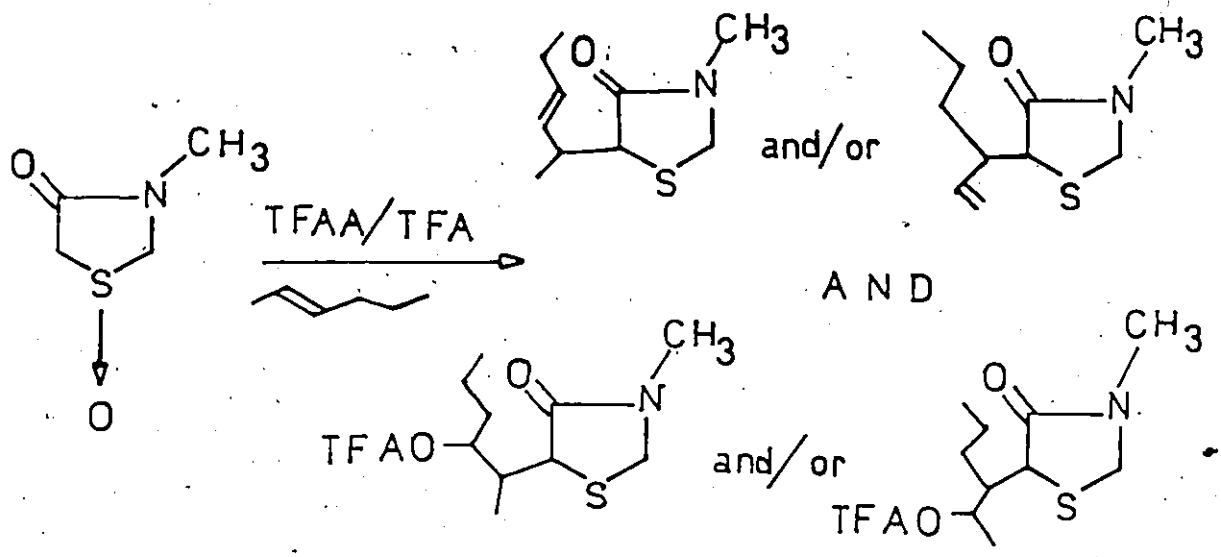


Figure 59. Intermolecular capture of Pummerer intermediate by 2-alkenes

Tamura[93] reported a similar example in which the reaction intermediate had undergone elimination as well as capture by OTFA (Figure 60). It is interesting to note that no 6-membered lactam was formed. In addition, the carbon adjacent to the sulfoxide is a methyl group, providing another example of the importance of the substitution at the α-carbon.

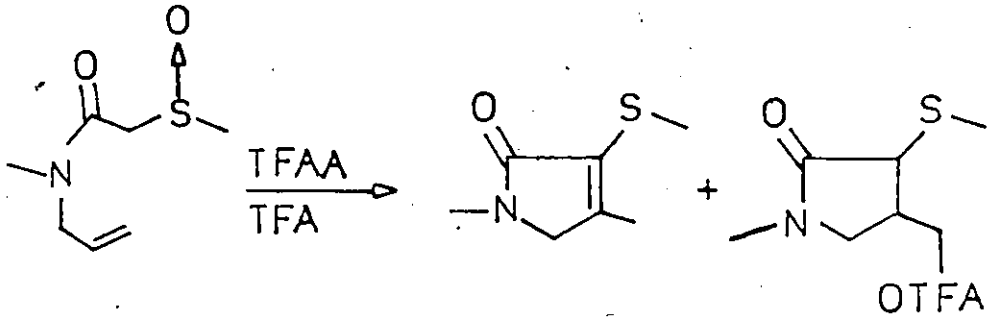


Figure 60. Tamura's cyclization reaction using the Pummerer.

Attempts to generate the carbonium ion from sulfoxides 15a and 15b with a catalytic amount of H_2SO_4 in benzene led to a mixture of starting sulfoxide as the major component, along with

two other inseparable products. These were identified by ^1H NMR and MS data of the crude reaction material as the 5-phenyl (17) and the 5-hydroxy (19) thiazolidinones. The formation of 17 indicates that it is possible to generate and capture, in an intermolecular fashion, the sulfur stabilized carbonium ion with sulfuric acid and benzene. However, the presence of 19 suggests that an intimate ion pair between the carbonium ion and the hydroxide ion exists in the reaction pathway (Figure 61).

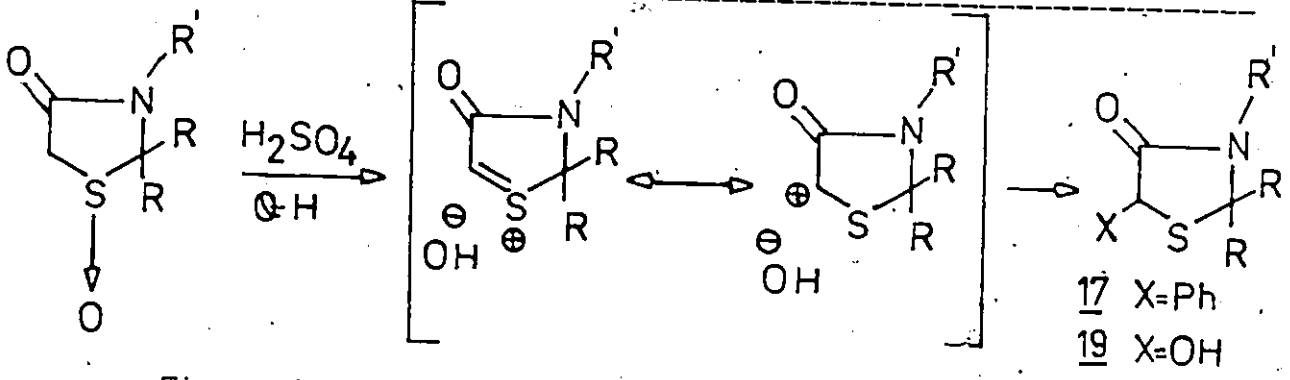


Figure 61. The tight ion pair in the formation of 16.

The proposed tight ion pair is not a new concept in the Pummerer reaction. Numata and Oae[74] showed, using ^{18}O labelled sulfoxide, that the Pummerer reaction of cyanomethyl p-tolyl sulfoxide with acetic anhydride involved an intimate ion pair species. Isolation and analysis of the distribution of ^{18}O in the product revealed that 63% of the label was located at the carbonyl carbon, while the remaining 37% is at the ethereal oxygen. This uneven distribution suggests that the ester precursor is not a dissociated ion pair. They further concluded that two modes of recombination are occurring. The "cyclic mode" involves a five member transition state and since the majority of the label is found in the carbonyl oxygen, this is the major

pathway. The "sliding mode" transition state accounts for the ^{18}O found at the ethereal carbon (Figure 62).

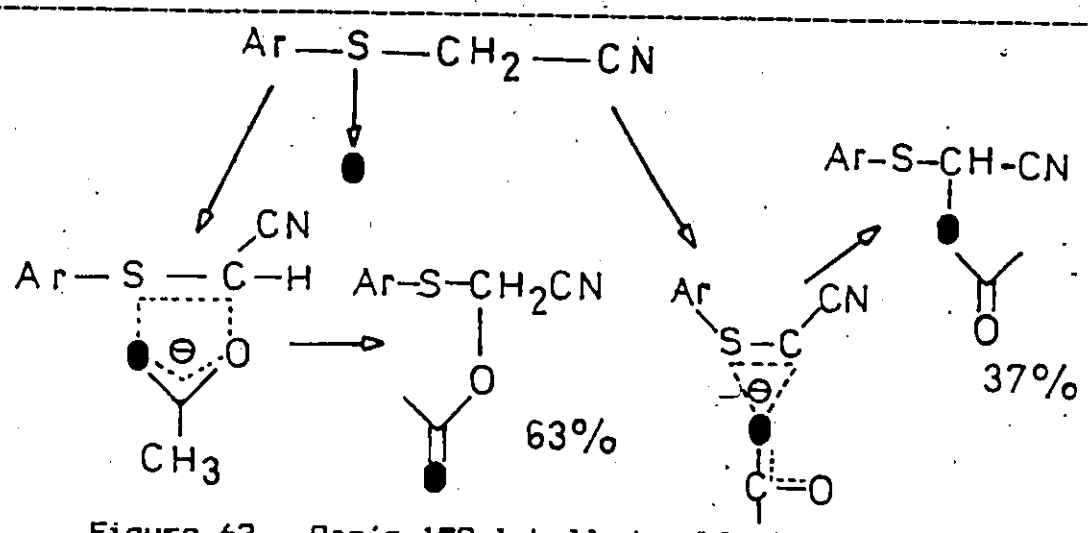


Figure 62. Oae's ^{18}O labelled sulfoxide studies.

Repeating the reaction of the sulfoxides using a large excess of H_2SO_4 in benzene gave excellent yields of the 5-phenylated products (17)[73]. No alcohols (19) were detected in the crude reaction mixtures. This can be rationalized by assuming that the excess sulfuric acid protonates the hydroxide ion that is formed during the reaction resulting in the destruction of the proposed ion pair. Benzene can now compete effectively with the hydroxide ion for the sulfur stabilized carbonium ion. This is the first reported example of an arylation reaction of a Pummerer intermediate induced by a mineral acid. The literature contains a number of examples in which an aryl functionality has captured the sulfur stabilized carbonium ion that was generated by an excess amount of organic acid (p-TsOH, TFA)[74,77]. Included with these are some elegant syntheses of indoles and carbazoles.

Attempts to substitute the 5-position of these lactam heterocycles with simple olefins by using excess sulfuric acid led to an uncontrollable cationic vinyl polymerization process[78]. This method is inappropriate for achieving substitution.

The use of other protonic (PPA, $MeSO_3H$, TFA) or Lewis ($SnCl_4$, BF_3-Et_2O, $AlCl_3$) acids to facilitate substitution of benzene on the thiazolidinone ring led to intractable mixtures of decomposition products. Silica gel and acidic alumina were also inappropriate sources of electrophile in the reaction of 15 with benzene. In these cases only starting sulfoxide was recovered.

It is interesting to note that Stamos[79] was successful in substituting aryl groups onto β-oxo sulfoxides utilizing various Lewis acids ($TiCl_4$, BF_3-etherate, $SnCl_4$) although low reaction temperatures and careful addition of the Lewis acid were required for clean reactions. The examples that he provides make use of a methyl methylene sulfoxide that is analogous to compound 15c (Figure 63).

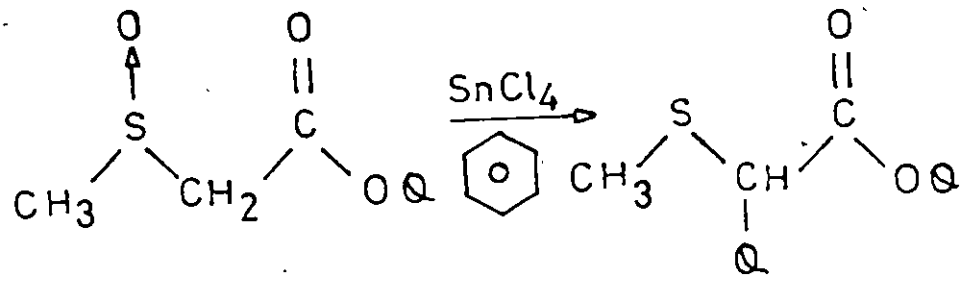


Figure 63. Pummerer intermediate generation by Lewis acids.

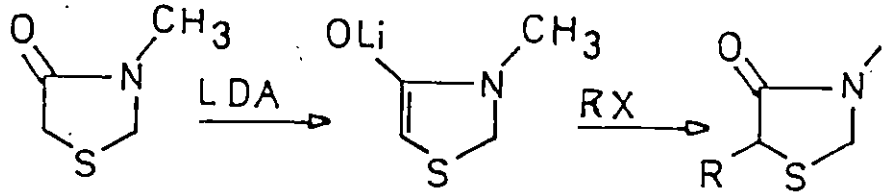
C. ALKYLATION AND ALDOL REACTIONS

Due to the limited scope of the Pummerer reaction as a route to substituting the 5-position of 1,3-thiazolidin-4-ones with

olefinic nucleophiles, the alkylation and aldol reactions of this heterocycle were briefly investigated.

McIntosh and co-workers[7a] reported that alkylations of C-4 monosubstituted 1,3-oxathiolan-5-ones was successful only with very reactive halides (eg. allyl bromide). When C-4 is not substituted, complex mixtures of products were obtained. They concluded that the alkylation of 1,3-oxathiolan-5-ones is not a general route to substituting the 4-position of these heterocycles. To our knowledge, alkylation reactions of 1,3-thiazolidin-4-ones have not appeared in the chemical literature.

Thiazolidinone 14e was readily deprotonated by LDA at -78°C and the resulting enolate was very reactive toward simple alkylating agents. Reaction with n-butyl iodide and one equivalent of HMPA afforded the 5-butyl heterocycle (20a) in good yield. The analogous reaction with methyl iodide provided a 6:1 mixture of mono- and dimethylated products (20b) (Figure 64).



14c

a R = nBu
b R = Me, (Me)

20

Figure 64. Alkylation of thiazolidinones.

These results suggest that the gem-dimethyl substitution at C-2 of the oxathiolanones studied previously may play an important role in determining whether the alkylation reaction occurs cleanly. In any event, the ease of 3-methylthiazolidin-4-one

preparation and the simple nature of its alkylation reactions may provide an alkylative alternative to the oxathiolanones for generating -substituted mercaptoaldehydes.

McIntosh and coworkers also reported[78] that aldol reactions of the oxathiolanone series were successful and gave mixtures of diastereomers where applicable. There are also several examples in the literature which show that aldol reactions of 2-substituted-thiazolidin-4-ones can result in the 5-arylidene[80,81] derivatives.

It was not surprising then to find that benzaldehyde reacted readily with 14e to give a 3:2 mixture of diastereomers 21a and 21b (figure 65). The stereochemical assignment of these structures is based upon IR data. The strong OH absorption did not change when the sample was diluted. This indicated that H-bonding must have occurred between the OH function and the carbonyl. This requires that the conformation of the carbon bearing the OH has this function close to the carbonyl of the heterocycle. The configuration of this center was determined from ^{1}H NMR coupling constants. Assuming a comformation in which hydrogen-bonding between the alcohol and the amide carbonyl oxygen atom predominates, the dihedral angle of the C-5 proton and the carbinol carbon proton in 21a is approximately 90° which leads to a low value of the coupling constant (2.5 Hz.). The angle for 21b is approximately 180° which leads to a 7 Hz. coupling constant.

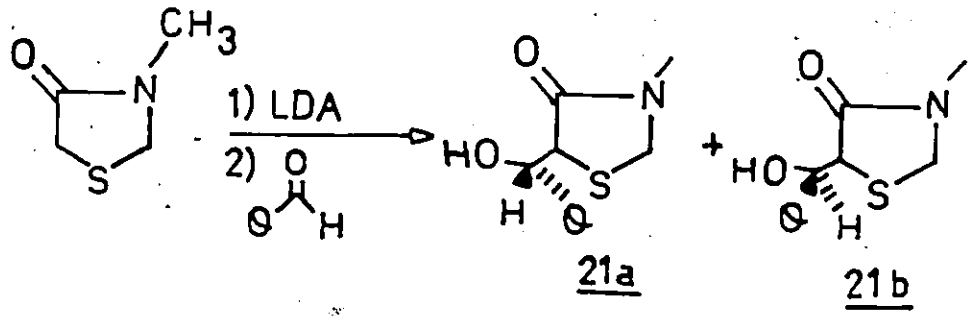


Figure 65. Aldol reaction of thiazolidinones.

Summary and Conclusions

Attempts were made to utilize the Pummerer reaction as a method for substituting the 4-position of 1,3-oxathiolan-5-ones and the 5-position of thiazolidin-4-ones.

The reaction of 2,2-dimethyl-1,3-oxathiolan-5-one-S-oxide with trifluoroacetic anhydride in trifluoroacetic acid afforded the corresponding 4-trifluoroacetoxy-oxathiolanone as the Pummerer reaction product. Attempts to capture the intermediate sulfur stabilized carbonium ion with benzene or 1-hexene were unsuccessful. The intramolecular nature of trifluoroacetoxy migration does not allow the nucleophilic solvent to compete for this intermediate. The use of catalytic amounts of both Lewis and mineral acids resulted in decomposition of the reaction system.

Intermolecular reaction of 1-alkenes with the Pummerer intermediate generated by the action of TFAA on 3-methyl-thiazolidinone provided the "ene" products as a mixture of E and Z isomers. When 2,2-dialkylated-thiazolidinones are used under the same reaction conditions only very small amounts of "ene" products were obtained.

These results, combined with literature reports, indicate that the sulfoxide must be flanked by either methyl or methylene groups for the intermolecular reaction to be successful.

When 2-alkenes are utilized as the nucleophilic solvent, mixtures of elimination and substitution products were obtained.

Excess concentrated sulfuric acid may be employed for the intermolecular reaction of benzene with all thiazolidinones. This method was unsuccessful when alkenes are used as nucleophiles since the conditions cause polymerization of the

olefins.

Lewis acids, in catalytic amounts, were inappropriate for generating the intermediate required for intermolecular reaction with alkenes or benzene.

The aldol reaction of benzaldehyde with 3-methyl-thiazolidin-4-one gave a mixture of diastereomers. Alkylation reactions of this heterocycle were found to be successful suggesting that this is the method of choice for obtaining 5-substituted thiazolidinones and, ultimately 2-mercaptoaldehydes.

TABLE 8

^{1}H NMR Spectra of Oxathiolanones and Thiazolidinones

ENTRY	CMPD	CHEMICAL SHIFT (in ppm downfield from TMS)
1	8a:	3.82 (ABq, 2H, J = 12 Hz), 1.75 (s, 3H), 1.60 (s, 3H)
2	9:	4.78 (bs, 1H, exchanges with D_2O), 1.90 (s, 3H), 1.88 (s, 3H), 1.76 (s, 3H)
3	11:	6.58 (s, 1H), 2.15 (s, 3H), 2.10 (s, 3H)
4	14a:	7.4 -6.9 (m, 5H), 3.9 (s, 2H), 2.3 -0.45 (m, 10H)
5	14b:	3.50 (s, 2H), 2.87 (s,3H), 2.35 -2.07 (m, 10H)
6	15a:	7.7 - 7.0 (m, 5H), 3.65 (ABq, 2H, J = 15 Hz), 2.7 - 0.7 (m, 10H)
7	15b:	3.53 (ABq, 2H, J = 9 Hz), 2.90 (s, 3H), 2.51 - 0.80 (m, 10H)
8	15c:	4.39 (ABq, 2H, J = 11 Hz), 3.53 (ABq, 2H, J = 3 Hz), 3.0 (s, 3H)
9	16a:	7.75 - 6.90 (m, 5H), 6.28 (s, 1H), 2.65 - 0.85 (m, 13H)
10	16b:	5.78 (bs, 1H), 5.57 (s, 1H), 2.86 (s, 3H), 2.43 - 0.67 (m, 10H)
11	16c:	6.38 (d, 1H, J = 2 Hz), 4.56 (ABq, 2H, J = 8 Hz)(high field side further split, d, J = 2 Hz), 3.05 (S, 3H)
12	17a:	7.82 - 7.05 (m, 10H), 5.08 (s, 1H), 2.35 - 0.47 (m, 10H)
13	17b:	7.77 - 7.20 (m, 5H), 5.00 (s, 1H), 2.95 (s, 3H), 2.36 - 0.85 (m, 10 H)
14	17c:	7.23 (m, 5H), 4.80 (s, 1H), 4.30 (s, 2H), 2.90 (s, 3H)
15	18a:	5.78 - 5.03 (m,2H), 4.22 (s, 2H), 3.92 - 3.55 (m, 1H), 2.92 (s, 3H), 2.85 - 0.55 (m, 13H)
16	18b:	5.65 - 5.05 (m, 2H), 4.25 (s, 2H), 3.95 - 3.60 (m, 1H), 2.92 (s, 3H), 2.90 - 0.80 (m, 12H)

17 **20b**: 4.38 (s, 2H), 3.85 (q, 1H, J = 7 Hz), 2.97 (s, 3H), 1.55 (d, 3H, J = 7 Hz), (1.55 (s, 6H) for dimethyl derivative)

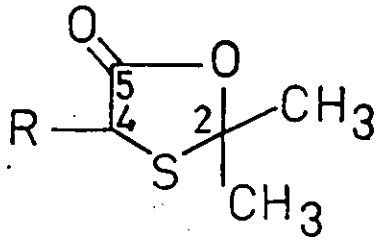
18 **20a**: 4.3 (dd, 2H, J < 1 Hz), 4.0 - 3.5 (m, 1H), 2.95 (s, 3H), 2.5 - 0.70 (m, 9H)

19 **21a**: 7.65 - 7.20 (m, 5H), 5.39 (ABq, 1H, J = 2.2 Hz), 3.60 (d, 1H, J = 2.5 Hz, exchangeable), 4.18 (d, 1H, J = 2.5 Hz), 4.16 (ABq, 2H, J = 7.0 Hz)(high field side split into doublet, J = 2.2 Hz), 2.95 (s, 3H)

20 **21b**: 7.50 - 7.10 (m, 5H), 5.2 (s, 1H, exchangeable), 4.90 (d, 1H, J = 8.5 Hz), 4.25 (d, 1H, J = 7 Hz), 4.15 - 3.95 (m, 2H), 2.75 (s, 3H)

TABLE 9

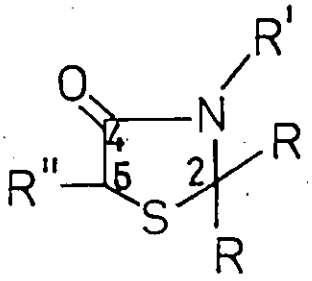
^{13}C NMR of Oxathiolanones



ENTRY	CMPD	C-2	C-4	C-5	Me	R
1	8a	98.5	52.7	169.5	23.1 20.0	
2	9	100.2	86.6	174.3	32.7 30.9 27.6	
3	11	91.1	80.5	166.9	33.3 30.0	156.4q 118.4q

TABLE 10

^{13}C NMR of Thiazolidinones



ENTRY	CMPD	C-2	C-4	C-5	R	R'	R"
1	14a	74.1	171.7	39.2	31.5 24.2 23.4	136.5 130.4 129.3 128.6	
2	14b	73.0	170.1	36.9	26.9 24.1 22.8	30.9	
3	15a	83.5	168.6	51.8	32.7 28.9 24.0 23.6 22.3	135.8 129.9 129.5 128.9	
4	15b	82.1	167.0	51.3	29.7 28.9 27.7 22.8 21.7	29.7	
5	15c	70.2	167.5	54.1		31.1	
6	16a	74.1	168.9	40.6	39.4 24.1 23.9 23.4 21.0	135.9 130.3 129.5 129.1	168.1 30.3
7	17a	72.3	172.3	51.0	40.2 39.8 24.2 23.9 23.6	138.2 130.6 128.7 102.7	136.8 129.3 127.9

8	17b	71.3	170.8	49.9	38.0 37.3 27.7 24.2 22.9		138.1 128.3 128.1 127.5
9	17c	47.7	171.4	50.6			138.3 128.6 128.6 127.9
10	18a	36.9	172.4	47.5		32.2	134.3 133.4 125.0 124.4 32.3 31.3 29.1 28.8 22.3 18.9
11	18b	37.0	174.2	47.6		34.8	134.1 133.3 125.5 124.7 34.5 31.8 31.6 22.6 22.4 18.6
12	20a	47.2	172.9	47.5		33.6	31.2 29.1 22.1 13.8
13	20b	40.7	178.2	46.8		31.3	19.3 (19.1)
14	21a	48.4	171.4	55.4		31.6	140.6 128.7 128.5 127.2 76.5

TABLE 11

Infrared Spectra of Oxathiolanones and Thiazolidinones[1]

ENTRY	CMPD	ABSORPTION
1	8a:	1799, 1780, 1236, 1070 cm^{-1}
2	9:	3500 - 3300, 1750, 1450, 1375 cm^{-1}
3	11:	1800 - 1780, 1240, 1170, 1140 cm^{-1}
4	14a:	2940, 1665, 1490, 1380 cm^{-1}
5	14b:	3020, 2950, 1660, 1400 cm^{-1}
6	15a:	2950, 1680, 1363, 1100 cm^{-1}
7	15b:	3015, 2980, 1680, 1050 cm^{-1}
8	15c:	3010, 1695, 1225, 1055 cm^{-1}
9	16a:	2950, 1780, 1680, 1220 cm^{-1}
10	16b:	2950, 1670, 1395, 1200 cm^{-1}
11	17a:	2950, 1670, 1375, 1200 cm^{-1}
12	17b:	2960, 1660, 1400, 1200 cm^{-1}
13	17c:	3015, 1670, 1390, 1230 cm^{-1}
14	18a:	2970, 2940, 1665, 1400 cm^{-1}
15	18b:	2975, 1670, 1420, 1395 cm^{-1}
16	20b:	3010, 1670, 1500, 1400 cm^{-1}
17	20a:	2980, 2950, 1670, 1400 cm^{-1}
18	21a:	3650 - 3200 (no change upon dilution), 3010, 1670, 1400 cm^{-1}
19	21b:	3704 - 3224 (no change upon dilution), 3008, 1663, 1400 cm^{-1}

1. The four stongest peaks are reported.

TABLE 12

Elemental Analyses of Oxathiolanones and Thiazolidinones

Entry	Compound	Calculated		Found	
		C	H	C	H
1	8a	40.53	5.44	40.06	5.31
2	14a	67.97	6.92	68.08	6.96
3	15a	63.84	6.50	63.65	6.44
4	15b	53.70	7.51	53.79	7.53
5	15c	36.07	5.29	36.32	5.23
6	16a	62.92	6.27	63.16	6.31
7	17a	74.26	6.54	74.52	6.54
8	17b	68.92	7.32	68.83	7.54
9	17c	62.15	5.74	62.09	5.89
10	18a	63.39	9.30	62.78	9.27
11	18b	60.26	8.59	59.92	8.58
12	20a	55.45	8.72	55.44	8.89
13	21a	59.16	5.86	59.18	5.87

CHAPTER 3

EXPERIMENTAL

General Information

All infrared spectra were run on a Perkin-Elmer model 180 instrument, or in the FT mode on a Nicolet 5 DX spectrometer. The ^1H NMR spectra were run at 60 MHz on a Varian EM360 spectrometer or on a Nicolet QE 300 spectrometer at 300 MHz in deuterated chloroform with tetramethylsilane as an internal standard. The data are presented in the format: chemical shift (multiplicity, number of hydrogens, coupling constant). The abbreviations used are: s - singlet, d - doublet, t - triplet, q - quartet, dd - doublet of doublets, m - multiplet, bs - broad singlet. The values in square brackets are for the minor diastereomer. Cnmr spectra were recorded at 22.64 MHz on a Bruker CXP 100 spectrometer or on a Nicolet 300 spectrometer at 75 MHz. Gas chromatographic analyses were performed on a Varian Model 3700 instrument using a 1.5 ft. X 1/8 in. column packed with 5% OV101 on Chromosorb W. Mass spectra were run on a Varian MAT CH 5 instrument in the field ionization (FI), field desorption (FD), or electron impact (EI) mode. Optical rotations were measured on a Perkin-Elmer model 241 polarimeter in 95% ethanol. The concentrations in grams per 100 mL of solvent are included in brackets following the measured optical rotation. Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Microanalyses were done at Galbraith Laboratories, Knoxville, Tenn., Canadian Microanalytical Services, Vancouver B.C.; Guelph Chemical Laboratories, Guelph, Ontario; and Uniroyal Research Laboratories, Guelph, Ontario. Column chromatography utilized silical gel 60 (70-230 mesh) available from Merck.

Reagent grade chemicals were used without further purification unless otherwise specified. Tetrahydrofuran was dried with potassium and benzophenone and distilled under nitrogen. Diisopropylamine was stored over potassium hydroxide. Hexamethylphosphoramide was distilled and stored over type 4A molecular sieves with a mesh size of 10-16 (Fisher). The drying agent was $MgSO_4$ and solvents were removed at reduced pressure.

Experimental Procedures

Preparation of t-Butyl Glycinate Imine of Camphor (1)

The glycinate imine 1 used as starting material in alkylation reactions was prepared according to the procedure outlined by McIntosh and Mishra[33,34].

Preparation of Alkylating Agents

All alkylating agents, except as follows, were obtained from the Aldrich Chemical Co. and were used without further purification.

Methylallyl Bromide (2e). A solution of 20.0 g methallyl alcohol in 40 mL anhydrous ether was charged into a dry 250 mL 3 necked round bottom flask and cooled in an ice bath. Under a nitrogen atmosphere a solution of 37.5 g phosphorous tribromide in 80 mL anhydrous ether was added dropwise over 5.5 h. When the addition was complete water was carefully added and the layers separated. The aqueous was extracted with ether (1 X 25 mL). The organics were combined and washed with aqueous bicarbonate until the washings were basic. Drying, concentrating, and distillation afforded 11.8 g (36%) of methallyl bromide 2e; bp 99°C (760 mm) (lit. 70°C (760 mm)[100]), ^{1}H NMR: 4.8-5.2 (m, 2H), 3.9 (s, 2H), 1.85 (d, 3H, J < 1 Hz).

(1-Bromopropyl)benzene 21. Bromination of the corresponding alcohol using the trimethylsilyl chloride / lithium bromide procedure of Olah *et.al.*[101] afforded, after distillation, a 3 component mixture of which 80% (by ^{1}H NMR) consisted of the required bromide; bp 70°-80°C (14 mm), [lit 46°-50°C (0.2 mm)[102]. ^{1}H NMR: 7.3 (m, >5H), 4.8 (t, 1H, J = 7 Hz), 2.55 - 1.75 (m,

2H), 1.0 (t, 3H, J = 7 Hz).

3-Cyclohexenyl Bromide 2m. A solution of 8.2 g cyclohexene, 17.8 g N-bromosuccinimide, 0.1 g AIBN, and 100 mL carbon tetrachloride was refluxed for 2 h. Filtering, and sequential washing of the filtrate with bicarbonate and water, drying, and concentrating gave the crude product. Distillation yielded 8.0 g (50%) 2m: bp 69°-79°C (16 mm), [lit. 57.5°-58°C (14 mm)][102]. ^{1}H NMR; 5.95 - 5.70 (m, 2H), 5.0 - 4.65 (m, 1H), 2.4 - 1.3 (m, 6H).

5,5-Dimethyl-3-Bromocyclohexene 2n. A four step synthesis was used to effect the conversion of 3,3-dimethyl-1,4-cyclohexandione (A) to 2o. The dione was converted to 5,5-dimethyl-3-isopropoxy-2-cyclohexen-1-one (B) by the method of Cronyn and Goodrich[104]; 83%, bp 93°C (0.8 mm). 5,5-dimethyl-3-cyclohexenone (C) was obtained from B as outlined by Gannon and House[105]; 91%, bp 89°C (28 mm). DIBAL reduction[106] of C afforded the corresponding unsaturated alcohol D; 71%, not purified. D was converted to the bromide 2n using the PBr_3 method outlined for the synthesis of 2e; 71%, bp 92°-94°C (26 mm). ^{1}H NMR: 5.9 - 5.5 (m, 2H), 4.95 - 4.45 (m, 1H), 2.3 - 1.55 (m, 4H), 1.0 (s, 3H), 0.85 (s, 3H).

2-Bromo-3-butyne 2p. 2q was obtained from 3-butyn-2-ol using the method of Lockhart and Bergman[107]; 28%, bp 95°C (760 mm) [lit. 83°-90°C (760 mm)][107].

General Alkylation Procedure

A 50 mL 3 necked round bottom flask was flamed out under nitrogen and cooled in an ice bath. 10 mL dry THF, 2.8 mL n-butyllithium (2.7 M in hexanes, 7.5 mmol), and 1.2 mL diisopropyl amine (8.5 mmol) were charged into the flask. The mixture was

stirred at 0°C for 0.5 h before cooling to -78°C or -20°C. 2.0 g (7.5 mmol) of imine 1 in 10 mL THF was added. The resulting orange solution was stirred for 0.5 h before addition of 10 mL THF containing alkylating agent (1.0 or 2.0 equivalents) and 1.4 mL HMPA (8.0 mmol). The reaction was kept at low temperature for 0.5 - 1.0 h before quenching with 10 mL water. The layers were separated and the aqueous extracted with ether. The combined organics were dried and concentrated to provide the crude product. Purification was achieved by column chromatography (80:20 petroleum ether/diethyl ether). The following solid products were recrystallized from hexanes:

3g: mp 58°-60°C, $[\alpha]_D^{25}$ +122.4 (c 0.254)

3m: mp 80°C, $[\alpha]_D^{25}$ +70.0 (c 1.78)

Transamination to Provide 5

Transamination of 3k was achieved using the procedure outlined by McIntosh and Mishra[33,34].

5: 62%, $[\alpha]_D^{25}$ -30.75 (c 1.06), ^{1}H NMR 7.45 - 7.23 (m, 5H), 3.53 [3.45] (d, 1H J = 6 Hz [7.5 Hz]), 3.13 (dq, 1H, J ≐ 7 Hz, 7Hz); ^{13}C NMR 174.03, 143.48, 128.43, 128.04 [128.15], 126.74, 81.07, 60.85, 43.79, 27.97 [28.17], 15.55; IR 2975.2 cm^{-1}, 1727.6 cm^{-1}, 1250.4 cm^{-1}, 1155.3 cm^{-1}; Anal. calc. C - 71.45, H - 8.65, N - 5.95; found C - 70.31, H - 8.65, N - 6.08.

Hydrogenation Reactions of 3g and 3m

To a hydrogen saturated mixture of 10% Pd on charcoal and 15 mL 95% ethanol was added via syringe 500 mg substituted imine in 10 mL 95% ethanol. The mixture was stirred under hydrogen until the gas was no longer consumed (2 - 3 h). The

mixture was filtered through celite and concentrated. Chromatography on a short column (ether) gave 4 and 6 from 3g and 3m respectively.

4: 71%, ^{1}H NMR 3.78 [3.74] (dd, 1H, J = 11.4, 5.1 Hz), 2.48 - 2.40 (m, 1H), 2.03 - 1.58 (m, 6H), 1.47 (s, 9H), 1.43 - 1.21 (m, 4H), 1.03 (s, 3H), 1.00 (s, 3H), 0.96 (t, 3H, J = 7 Hz), 0.80 (s, 3H); ^{13}C NMR 184.2, 171.8, 80.5, 65.0 [64.6], 53.9, 47.2, 43.9, 36.1, 35.0 [35.8], 32.3 [31.9], 28.0, 27.5 [27.4], 19.5 [19.4], 19.3, 18.9, 13.8, 11.4 [11.3]; IR 2957.9 cm^{-1}, 1735.6 cm^{-1}, 1683.8 cm^{-1}, 1156.1 cm^{-1}.

6: 95%, ^{1}H NMR 3.52 [3.48] (d, 1H, 9 Hz), 2.5 - 2.2 (m, 1H), 2.1 - 1.6 (m, 11H), 1.42 [1.43] (s, 9H), 1.52 - 0.70 (m, 6H), 0.97 (s, 3H), 0.90 [0.91] (s, 3H), 0.75 [0.73] (s, 3H); ^{13}C NMR 184.2, 171.4, 80.5, 71.6, 54.1, 47.3, 43.9, 40.6, 36.4 [35.9], 32.4 [32.1] 30.1 [30.2], 28.9 [26.7], 28.2 [28.3], 27.7, 26.1 [26.0], 19.6, 19.1, 11.6; IR 2928.6 cm^{-1}, 1736.8 cm^{-1}, 1682.3 cm^{-1} 1140.8 cm^{-1}; Anal. calc. C - 76.03, H - 10.83, N - 4.03; found C - 76.21, H - 10.83, N - 4.09.

Allylation by Allyl Acetate and $Pd(dppe)_2$[53b].

80 mg Sodium hydride (60% in mineral oil) was washed with dry THF (3 X 10 mL) before addition of a solution of 500 mg glycinate imine 1 in 10 mL THF. The mixture was stirred for 0.5 h before addition of 45 mg $Pd(dppe)_2$ catalyst and 200 mg allyl acetate. After stirring at 25°C for 25 h, 5 mL water was added and the layers separated. The aqueous was extracted with ether and the combined organics dried and concentrated. Column chromatography (80:20 petroleum ether / diethyl ether) gave 215

mg (38%) 6a. ^{1}H NMR 5.80 - 5.65 (m, 1H), 5.15 - 4.98 (m, 2H), 3.87 (dd, 1H, J = 8.4, 5.3 Hz), 2.76 - 2.25 (m, 3H), 1.95 - 1.59 (m, 4H), 1.40 [1.41] (s, 9H), 1.46 - 1.13 (m, 2H), 0.97 (s, 3H, 0.91 (s, 3H), 0.79 [0.73] (s, 3H). ^{13}C NMR 185.1, 170.9, 134.8 [135.1], 116.9, 80.9, 64.8, 54.0, 47.3, 43.8, 37.1, 36.3, 32.3 [31.9], 28.0, 27.3, 19.5, 18.9 [18.8], 11.3 [11.2]. IR 2971.4, 1735.8, 1680.4, 1150.2.

Pummerer Materials

1,3-Oxathiolan-5-ones (7)[54,78] and thiazolidinones 14c[38] and 14d[87] were prepared by literature procedures.

3-Phenyl-2,2-pentamethylenethiazolidin-4-one (14a). A solution of the ketimine derived from aniline and cyclohexanone (24 g, 0.14 mol) and 15 g (0.16 mol) 2-mercaptoacetic acid was refluxed under a Dean-Stark water separator overnight (3 mL of water was collected). The solvent was removed and the solid residue recrystallized to give 14a; 70%; mp 168°C (EtOH).

5-Methyl-2,2-pentamethylenethiazolidin-4-one (14b). A solution of methylamine in ethanol was prepared as follows. To a mixture of 27 mL of ethanol and 35 mL of 50% aqueous KOH, which was cooled in an ice bath, was added 21.9 g of methylamine hydrochloride. The solution was stirred for 1 h, filtered, and the layers separated. To the organic layer was added 2-mercaptoacetic acid (20.6 g, 0.22 mol) dropwise with stirring at 0°C. Stirring was continued for 1 h, the solvent was removed, the resulting solid dissolved in toluene, and 20 g of cyclohexanone was added. Refluxing under a Dean - Stark water separator followed by evaporation gave an oil which was distilled

to give 14b; 64%; bp 120°C (0.1 mm).

General Oxidation Procedure

In a typical experiment, 0.02 mol of sulfide was dissolved in 10 mL of glacial acetic acid and cooled to 0-5°C. To this was added 1.15 equiv. of 30% hydrogen peroxide dropwise with stirring. The mixture was allowed to come to ambient temperature overnight and diluted with 15 mL of water. Solid sodium bisulfite was added until a negative peroxide test was achieved. The organics were extracted into chloroform and washed with saturated aqueous bicarbonate until the washings were basic. The extracts were dried and the solvent removed to give the crude product, which was purified as noted below.

8a: (Continuous extraction into chloroform was required for acceptable yields.) Chromatographic purification (EtOAc) gave 8a; 87%; mp 77°C

9: Unstable oil (25% crude, not purified)

15a: 86%, mp 166°C (benzene)

15b: 57%, mp 123°C (carbon tetrachloride)

15c: This very water soluble compound was decomposed by continuous extraction into chloroform. Therefore the work-up was modified as follows. After destruction of the excess peroxide, the solvents were removed at room temperature and 0.4 mm. . The residue was taken up in chloroform, stirred with solid K_2CO_3, filtered, and evaporated. The product was crystallized by precipitation from acetone with petroleum ether to give 15c; 55%; mp 109°C (benzene).

Pummerer Rearrangements

In a typical experiment, a solution of 0.2 mol of the heterocycle in 10 - 15 mL of TFA containing 2 equiv. of benzene was cooled to 0°C and 1.1 equiv. of TFAA was added dropwise. The mixture was stirred at 0°C for 3 - 4 h, diluted with water (10 - 15 mL), and extracted with chloroform. The extracts were washed with aqueous bicarbonate solution, dried, and evaporated. In the case of 16a, the reaction mixture consisted of CH_2Cl_2/benzene and a catalytic amount of TsOH, and the electrophile was acetic anhydride.

11: 45%; bp 52°C (0.75 mm),

16a: 55%; mp 132°C (benzene or EtOH),

16b: 70%; mp 163°C (benzene),

16c: 100% crude (not purified); oil.

Reaction with Alkenes

To a cold solution of 15c in 20 mL TFA and 1.5 equiv. of the alkene (1-octene or 1-hexene) was added 1.1 equiv. TFAA dropwise with stirring. After 1 h, the solution was diluted with 20 mL of water and extracted with chloroform. The extracts were washed with aqueous bicarbonate and water, dried, and evaporated to give 18a or 18b. E/Z ratios were determined by the relative peak intensities of the sp^2 carbons in the ^{13}C NMR spectra. When 2-alkenes (cyclohexene, 2-hexene) were used, ^1H NMR spectra and gas chromatography indicated the presence of complex mixtures.

18a: 62%; bp 193°C (13 mm) E/Z = 3:1,

18b: 49%; bp 115°C (0.6 mm) E/Z = 2:1.

Phenylation Reactions

To a vigorously stirred mixture of 5 mL of concentrated H_2SO_4 and 4 mL of benzene was added 0.5 g of the sulfoxide 15c. Stirring was continued until the exotherm ceased (ca. 40 min). The yellow solution was poured over 10 g ice and extracted into methylene chloride. The organics were dried and the solvent evaporated to yield the crude product, which was purified by crystallization or chromatography.

17a: 93%; mp 119-121°C (benzene),

17b: 95%; mp 163°C (benzene),

17c: 76%; oil (chromatography 1:1 EtOAc/benzene)

Attempted Reactions Using Catalytic Amounts of Electrophiles

To stirred solutions of 0.5g of the sulfoxides in alkenes or benzene was added 5-10 drops of H_2SO_4 or Lewis acid. Reaction times ranged from 20 minutes to 48 hours. Work up in the usual manner gave the reaction products.

Alkylation Reactions

All alkylation reactions were run as previously reported [7e]. Compound 20a was obtained as a mixture of mono- and dimethylated products in a ratio of 6:1 as indicated by gas chromatographic analysis.

20a: bp 104°C (11 mm)

20b: 44%; bp 95°C (0.5 mm)

Aldol Condensation

The aldol condensation was run as previously reported[7e]. Compound 21 was obtained as a mixture of two diastereomers (21a

and 21b) in an isolated ratio of 3:2. The total yield was 54%.

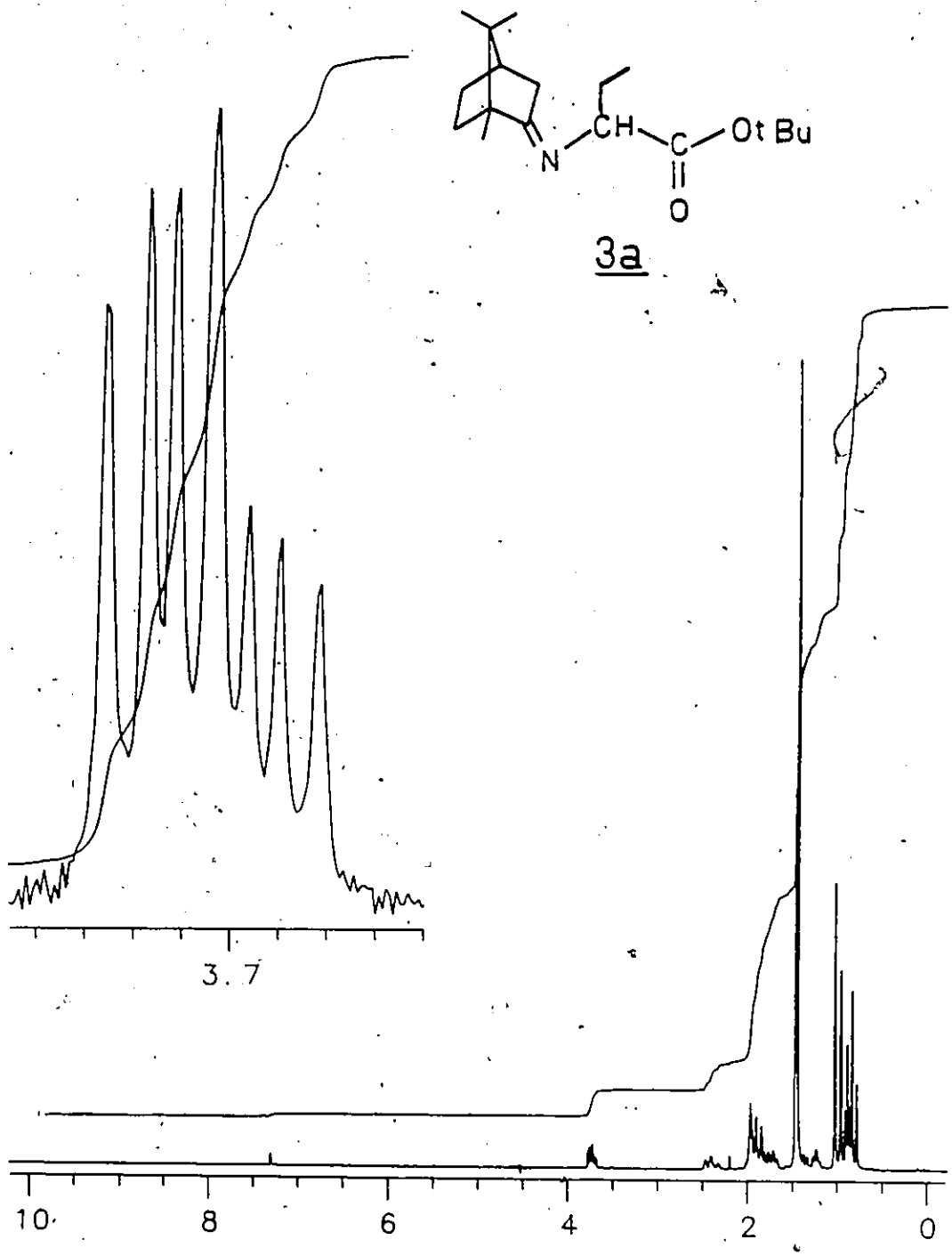
21a: 33%; mp145°C (1:1 EtOAc/benzene),

21b: Oil (dec. on attempted distillation).

APPENDIX A

^{1}H NMR SPECTRA OF CAMPHOR IMINES OF GLYCINATES

^{1}H NMR spectra were recorded at 300 MHz in a $CDCl_3$ solution. The inset spectra are the signals due to the methine proton of C-2 (by amino acid numbering). Each diastereomer showed a unique chemical shift for this proton. Ratios of diastereomers were determined by either integration or line height measurement of these signals.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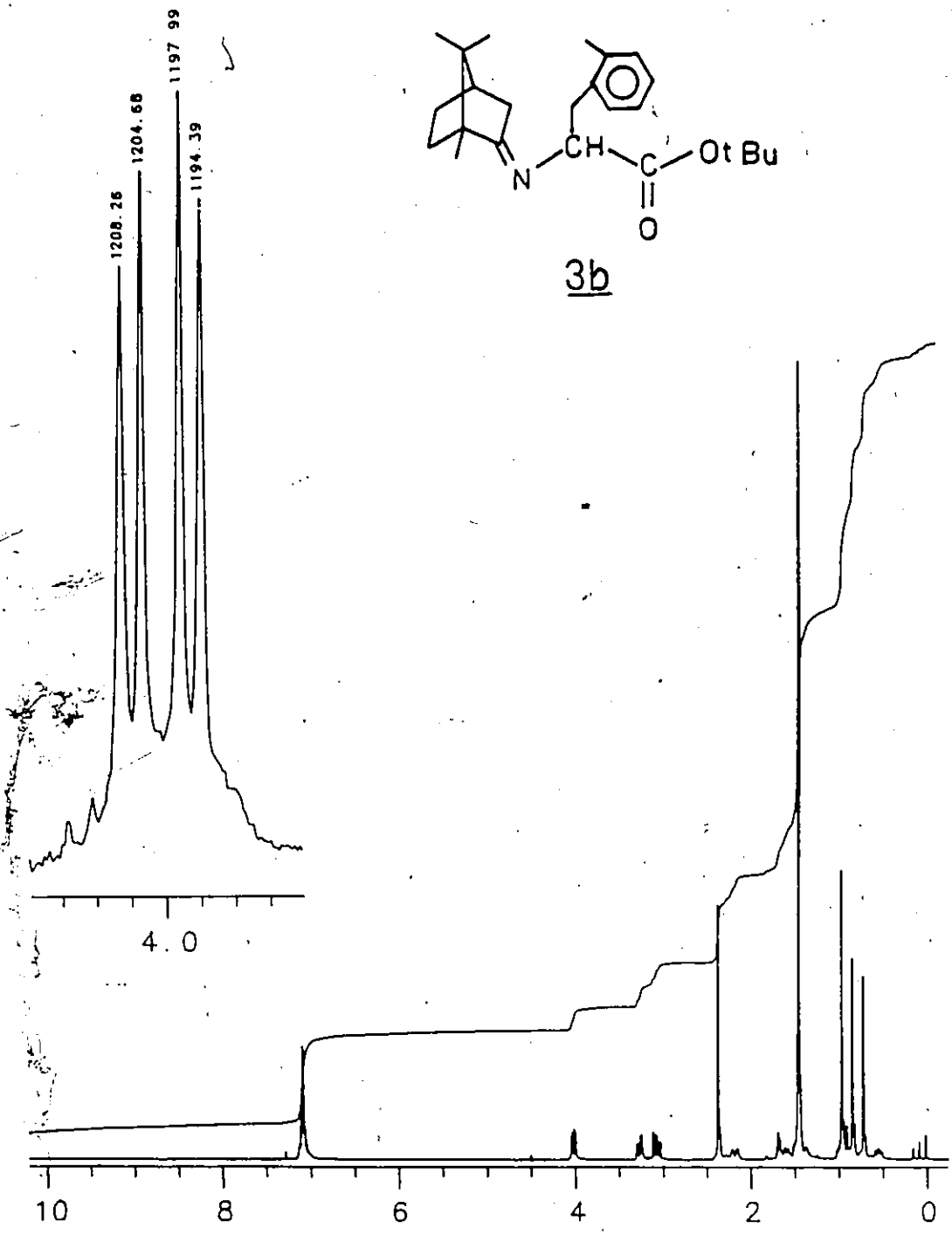

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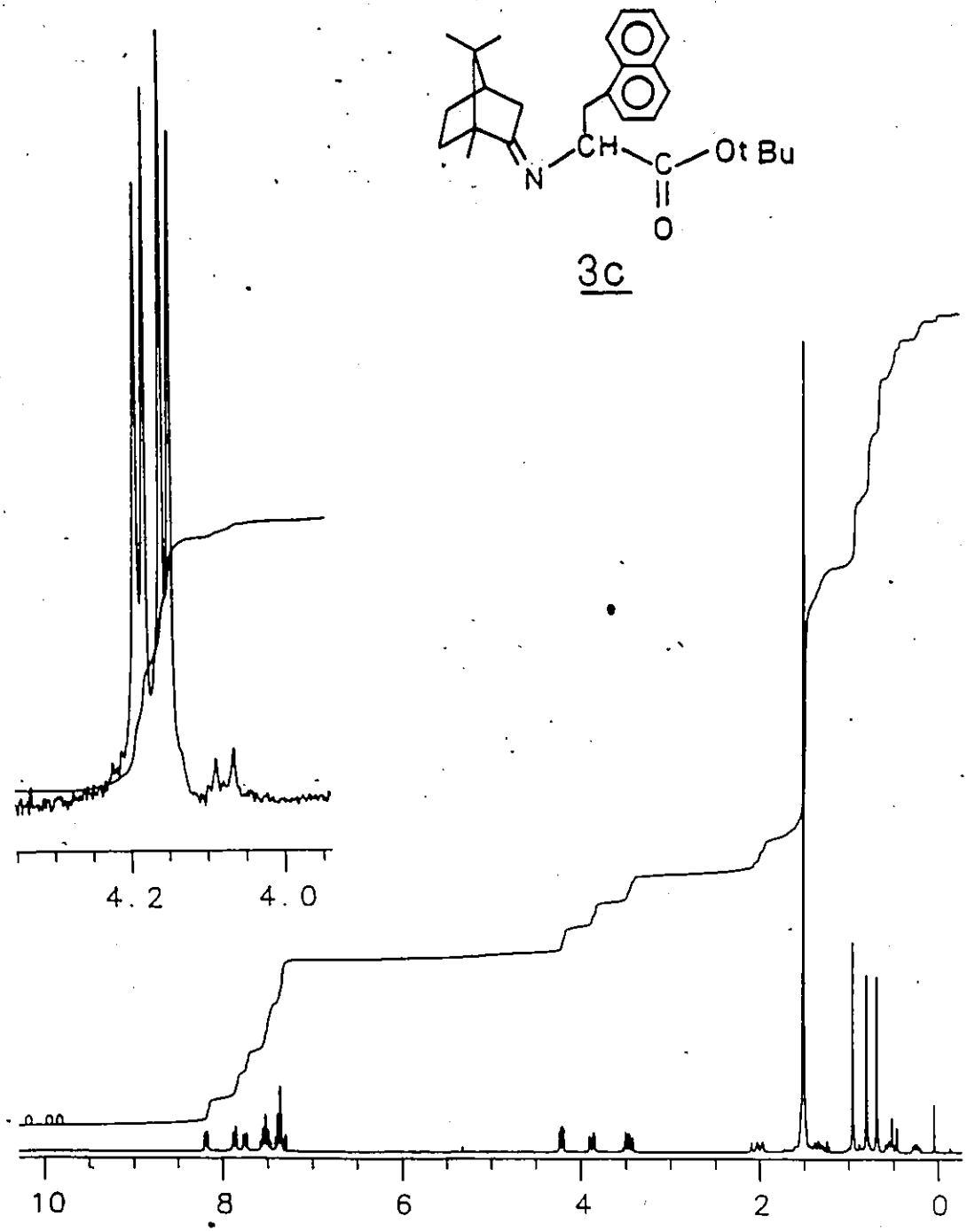

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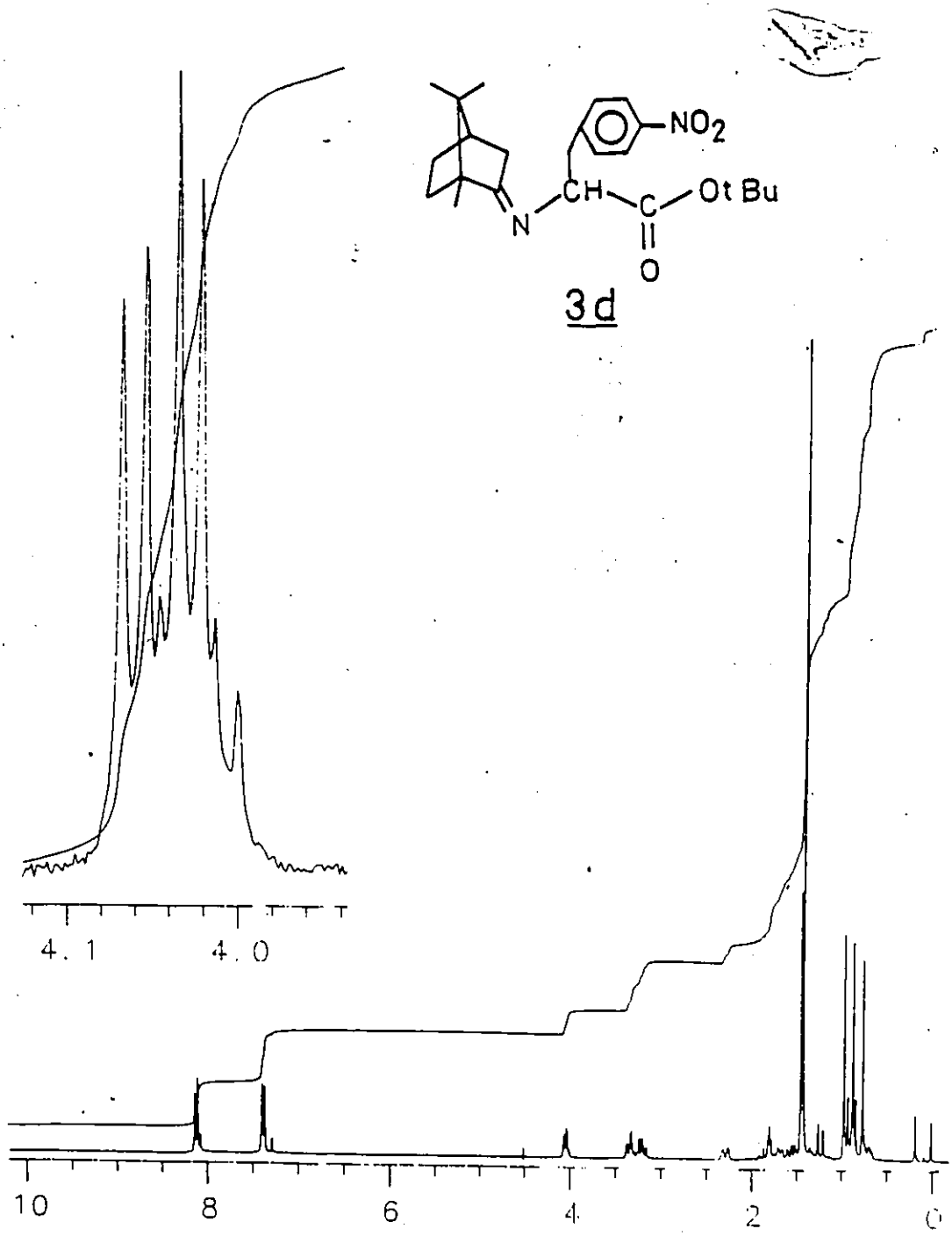

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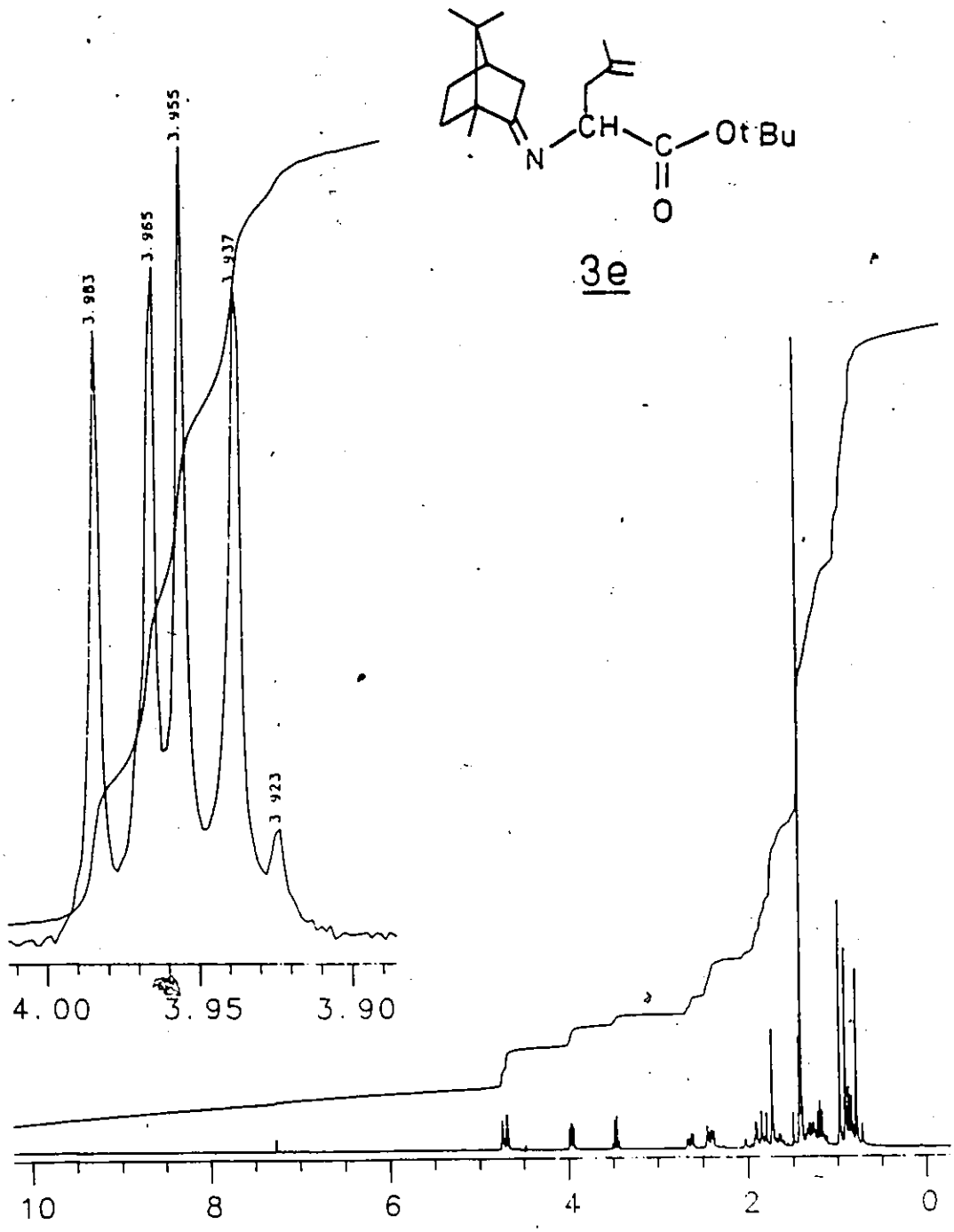
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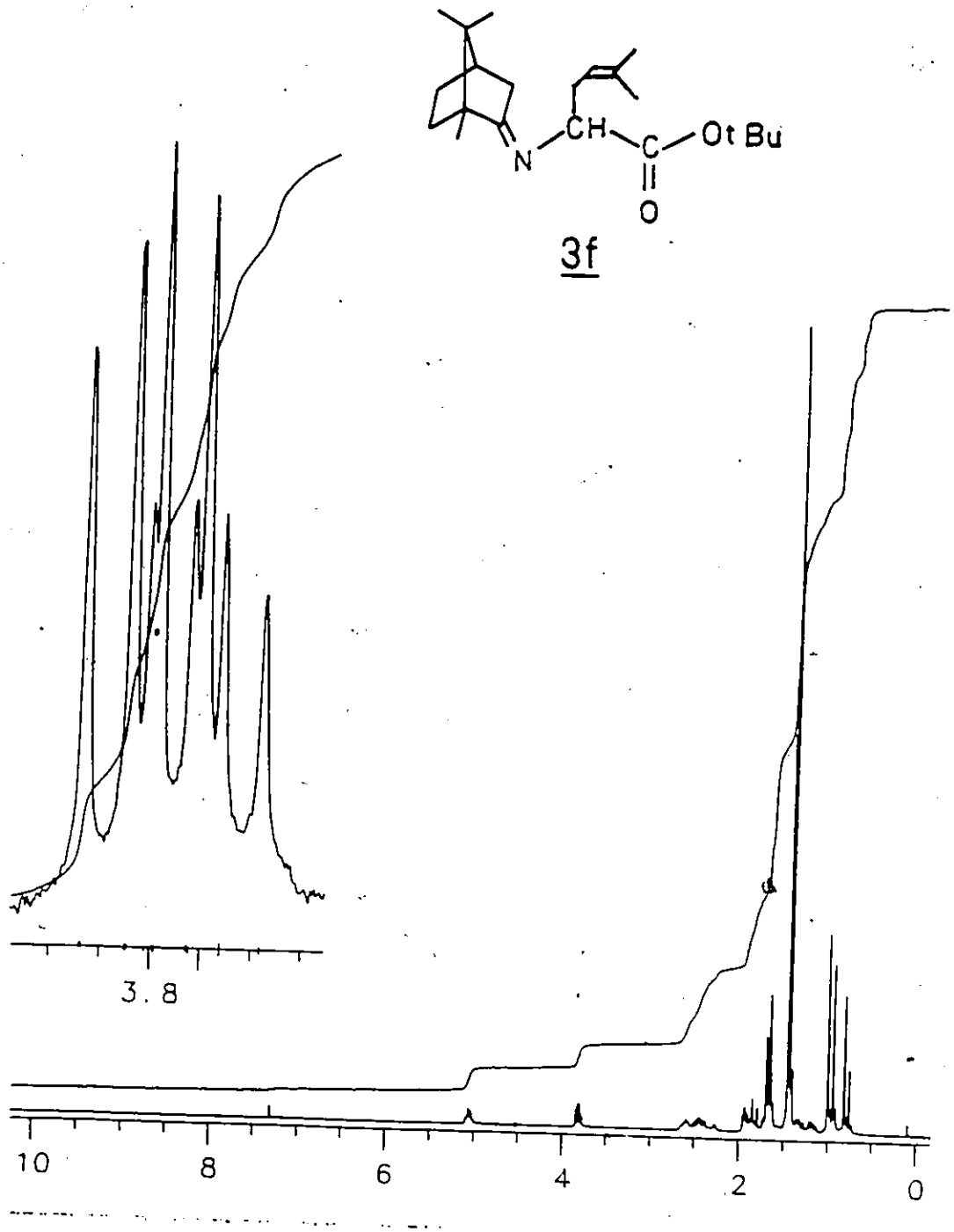
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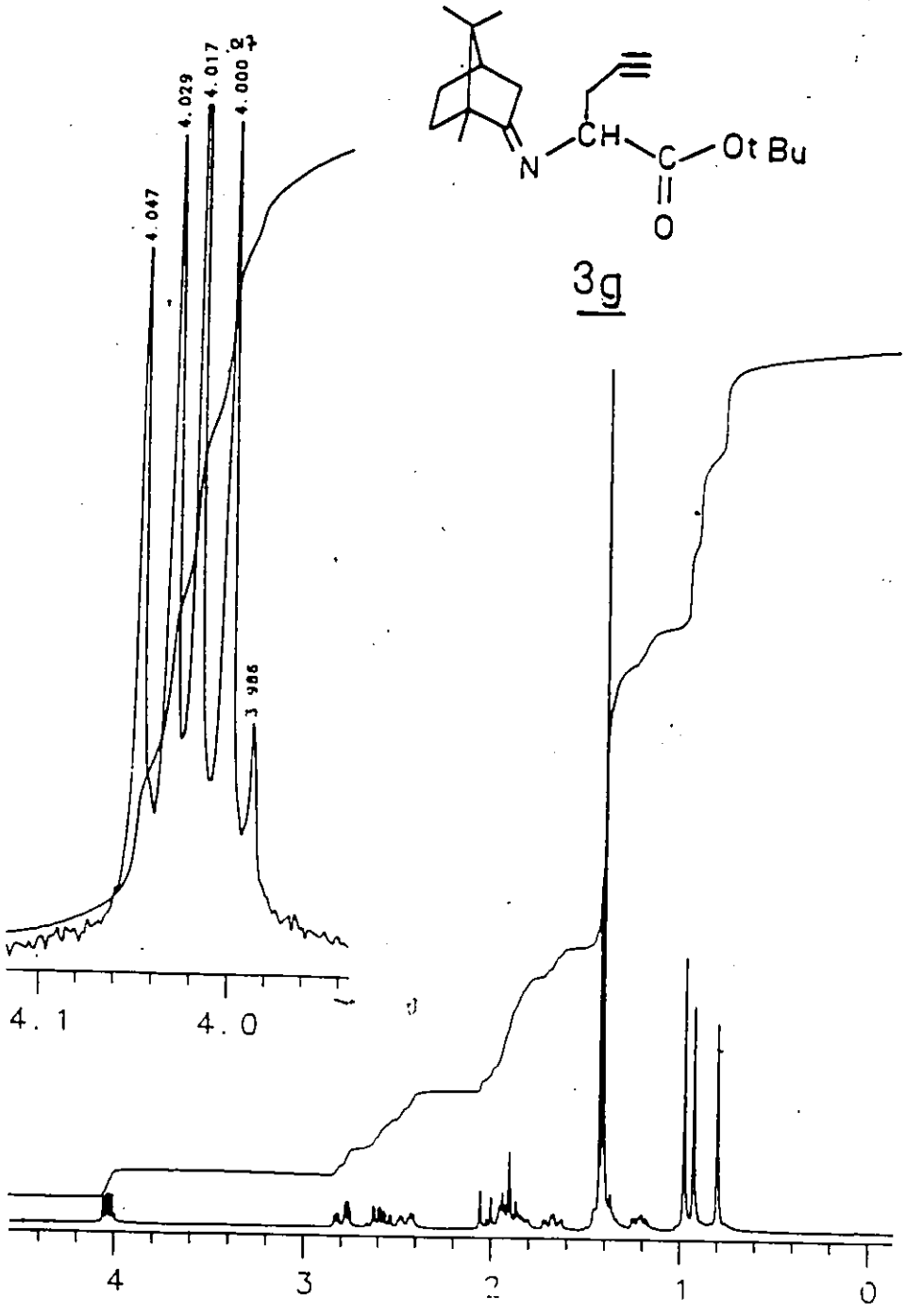
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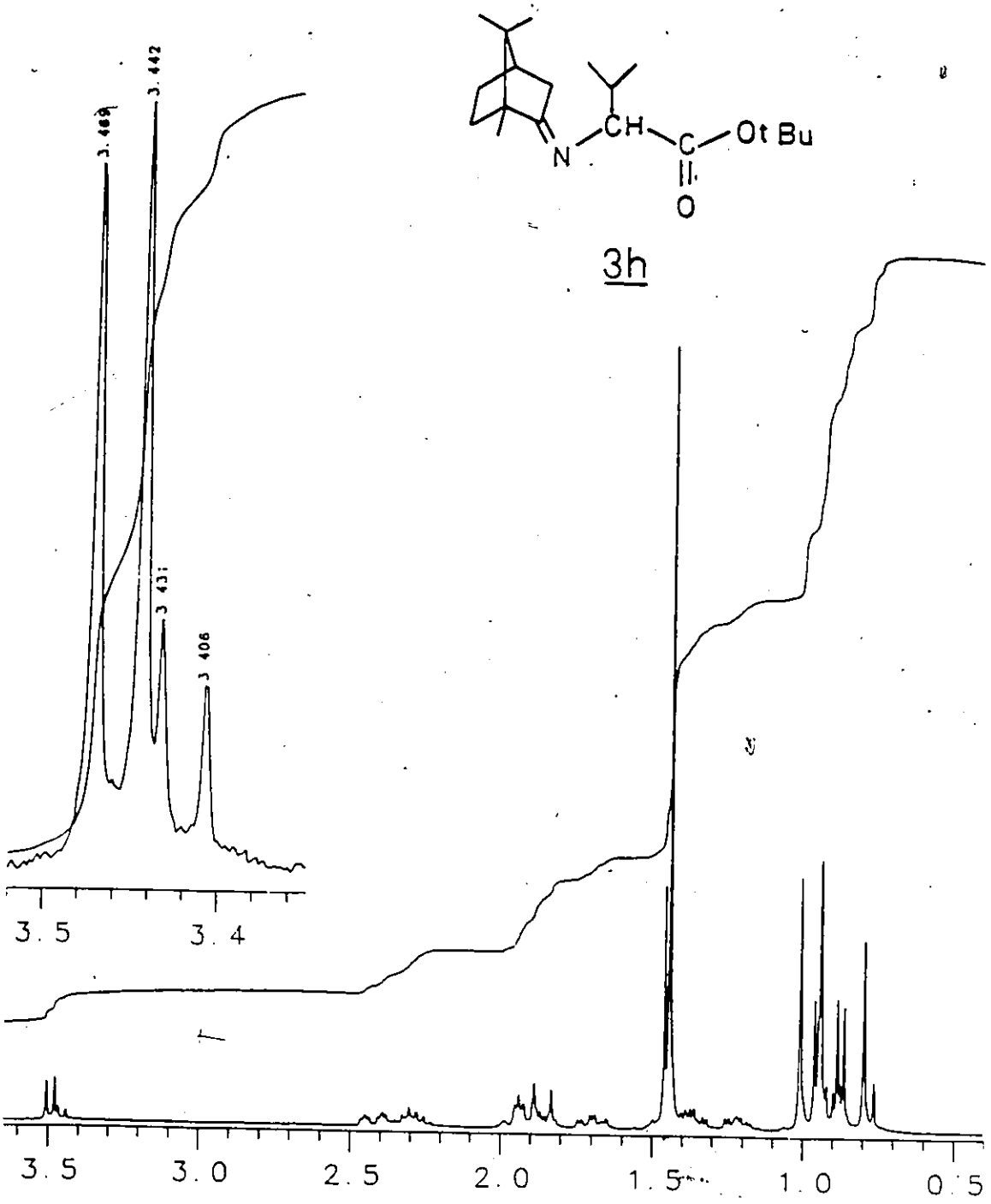
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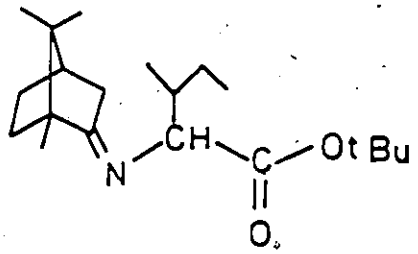
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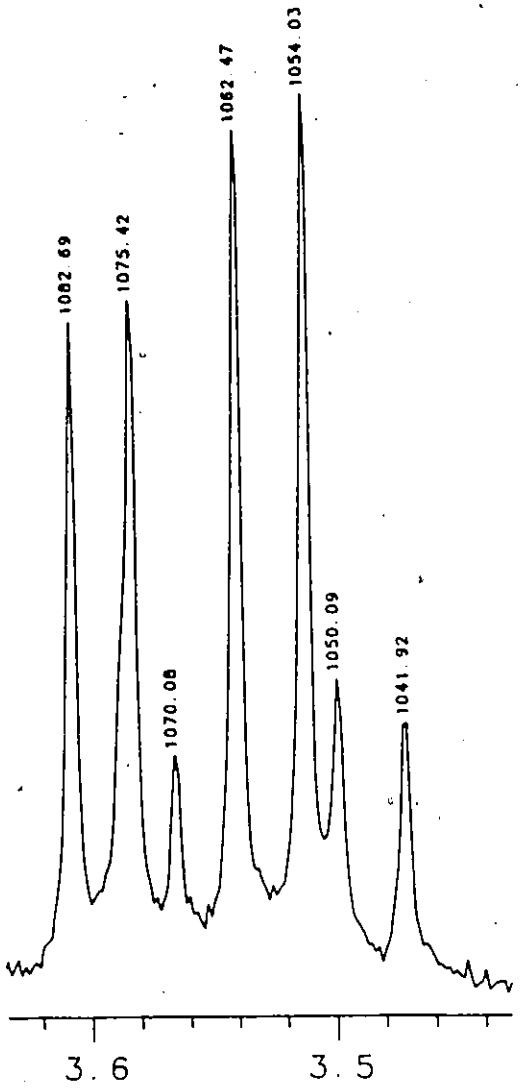
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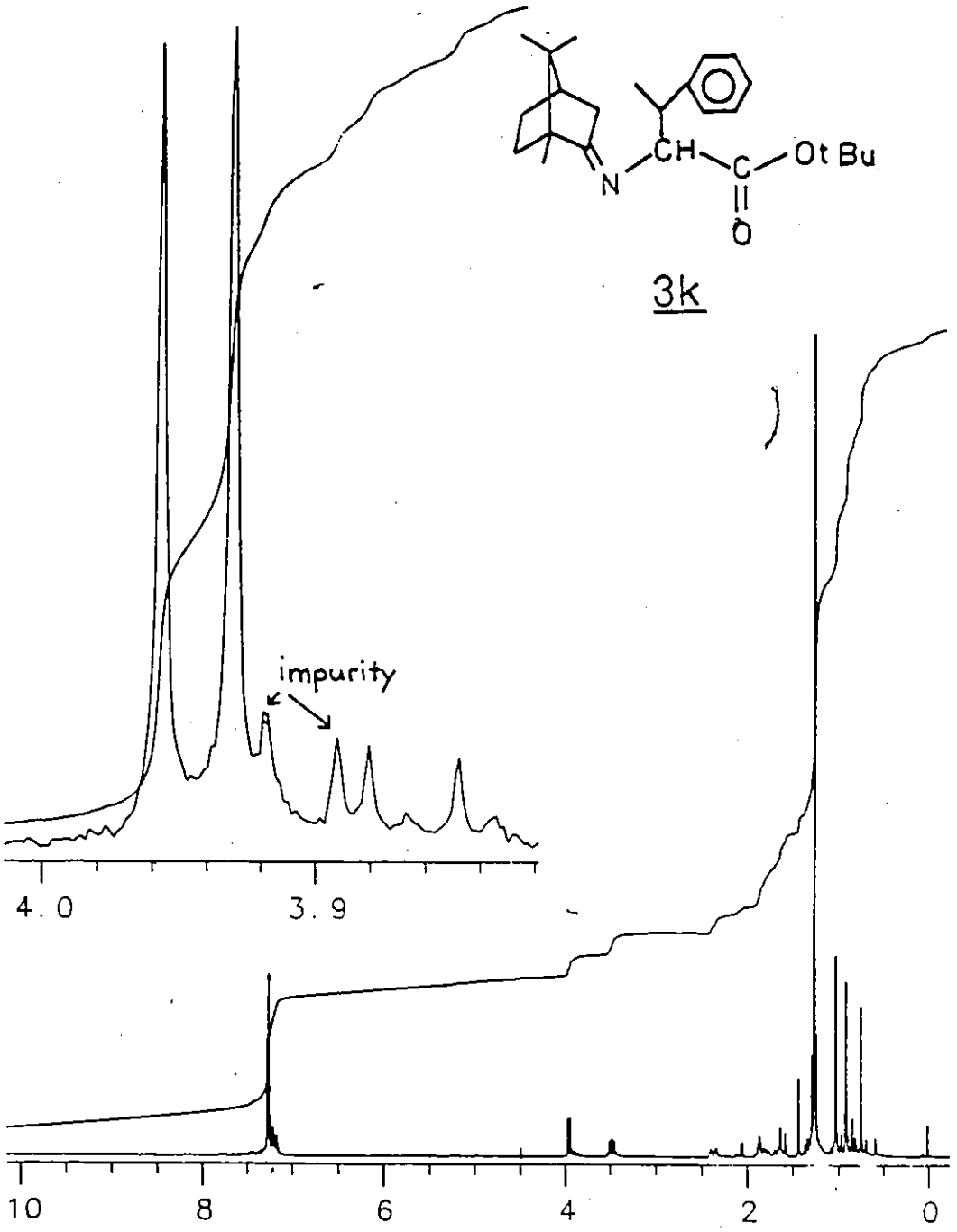
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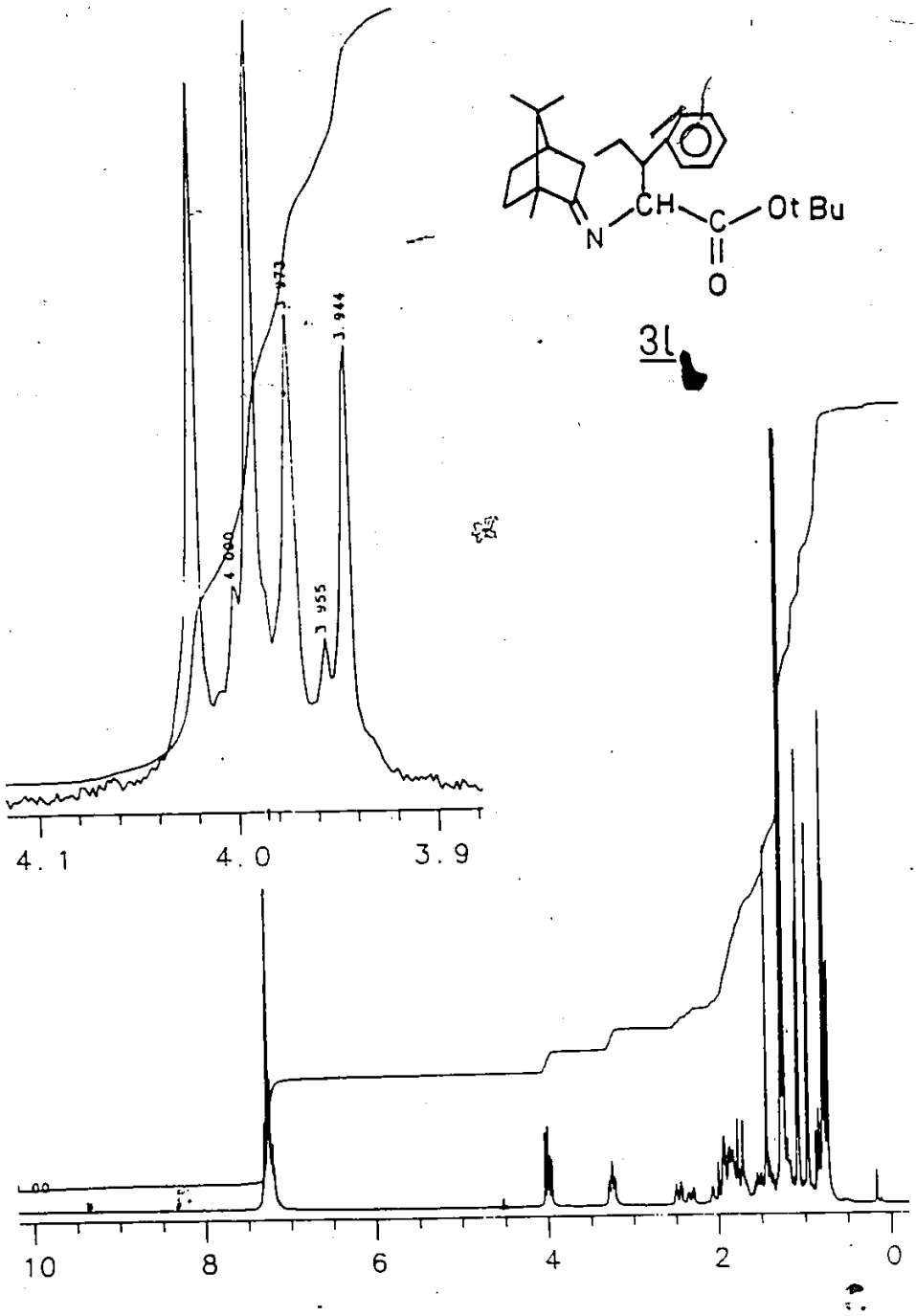

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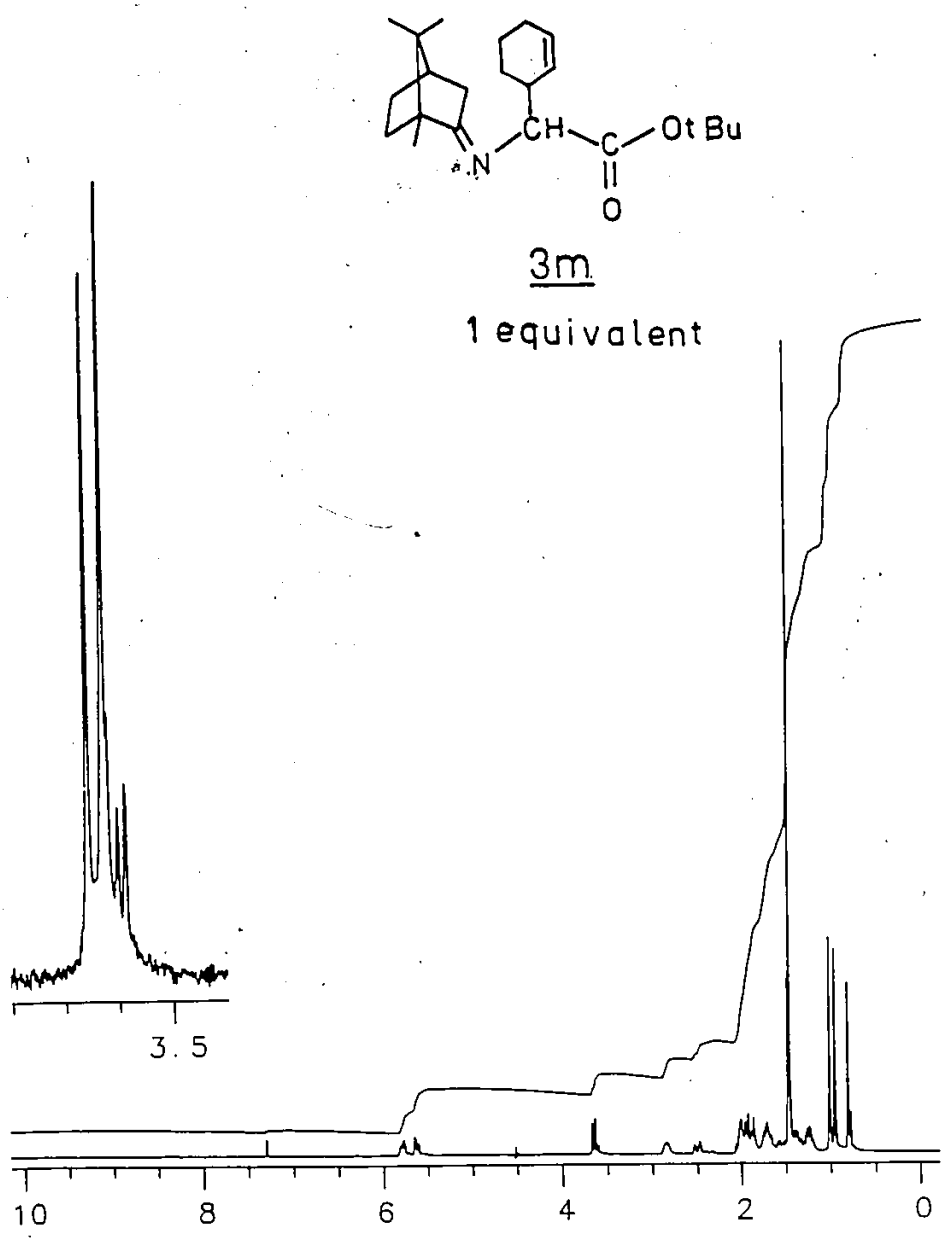
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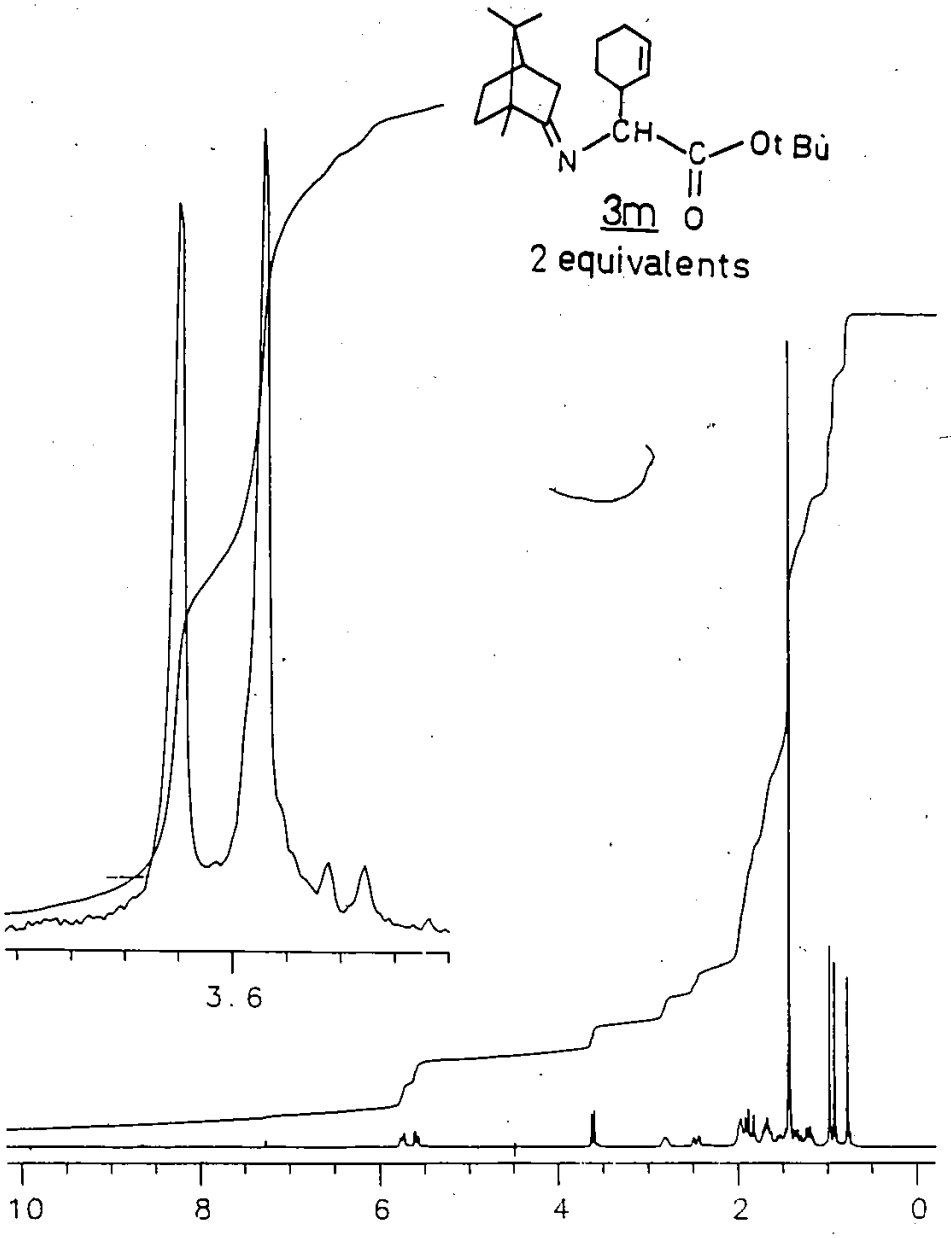
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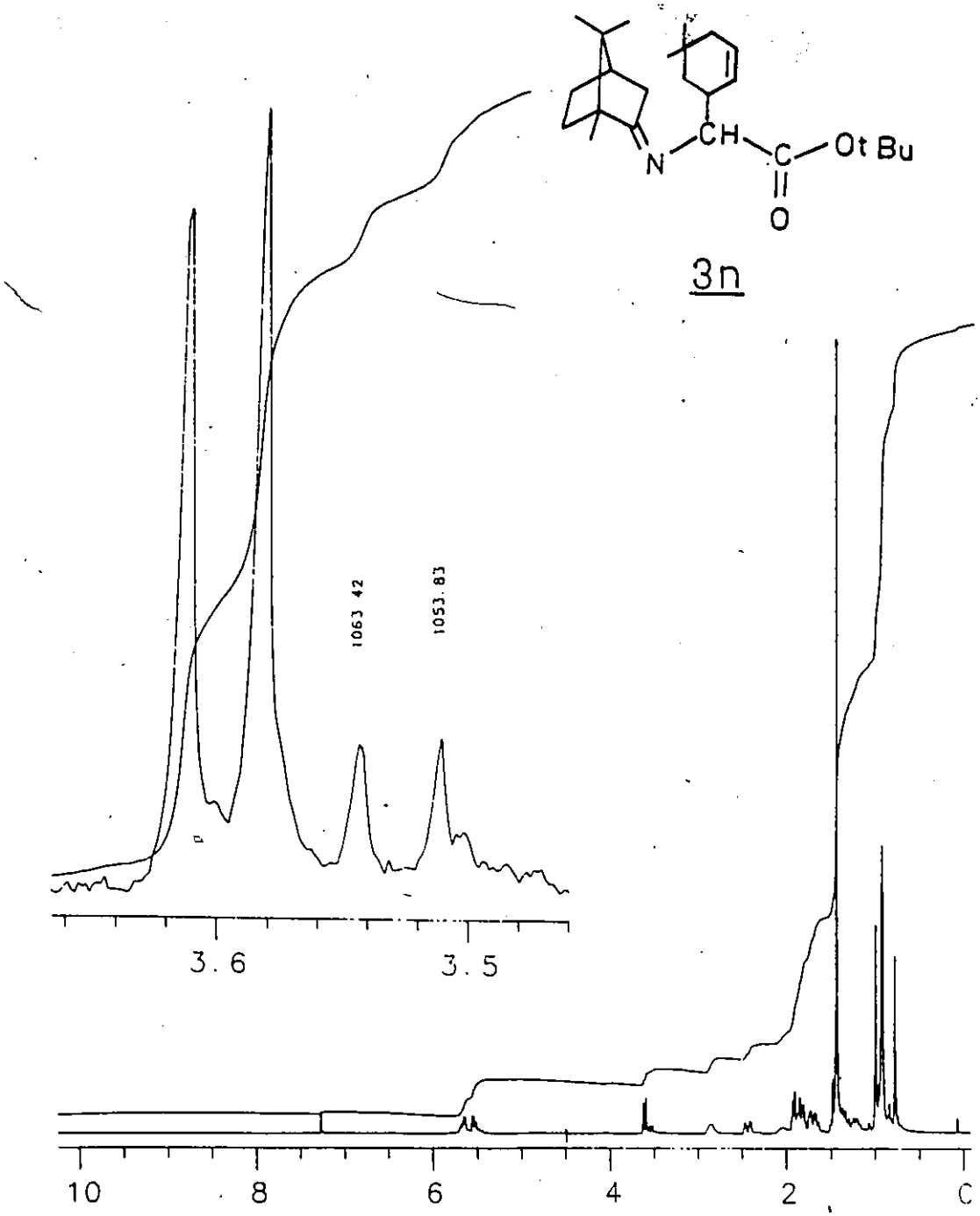
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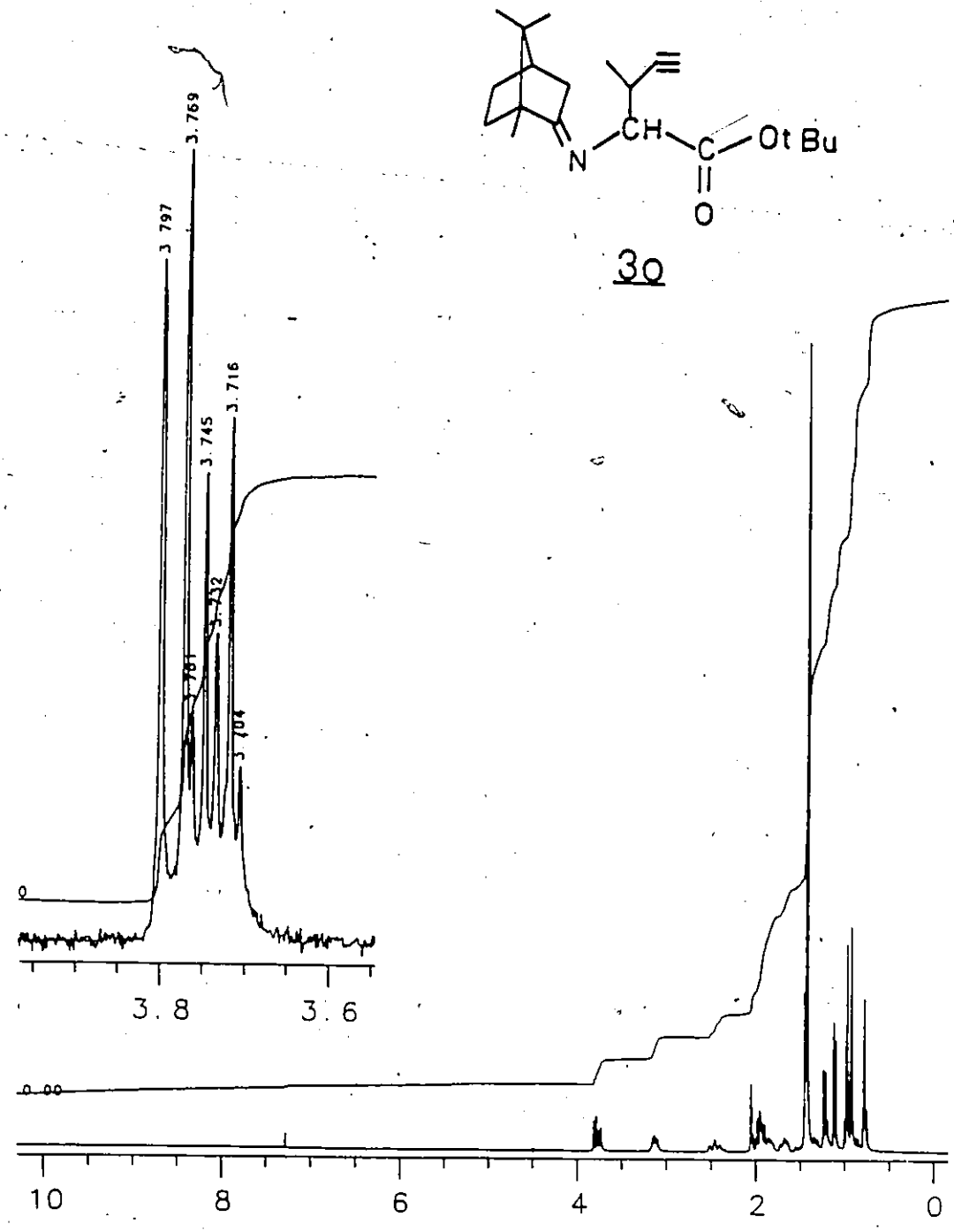
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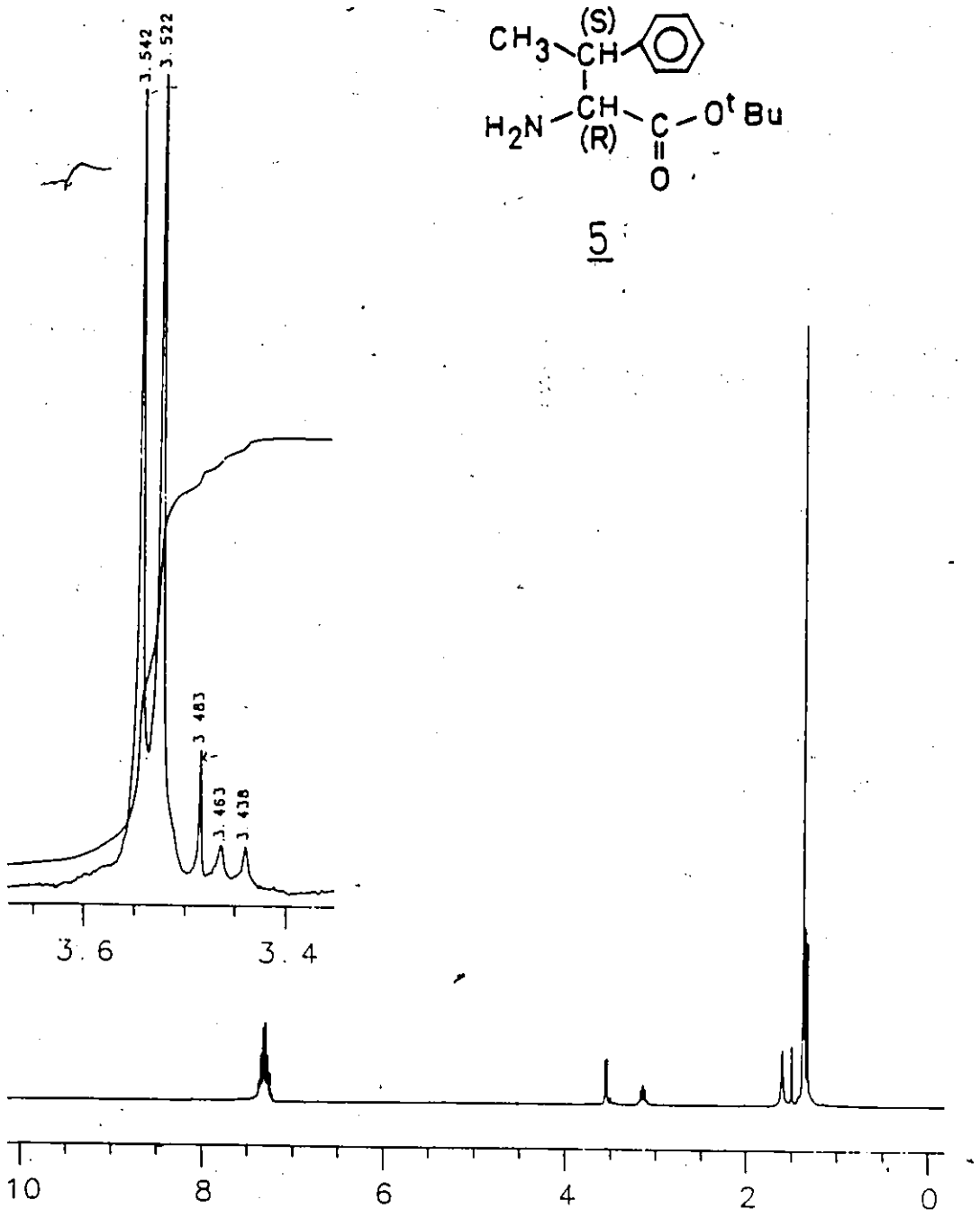

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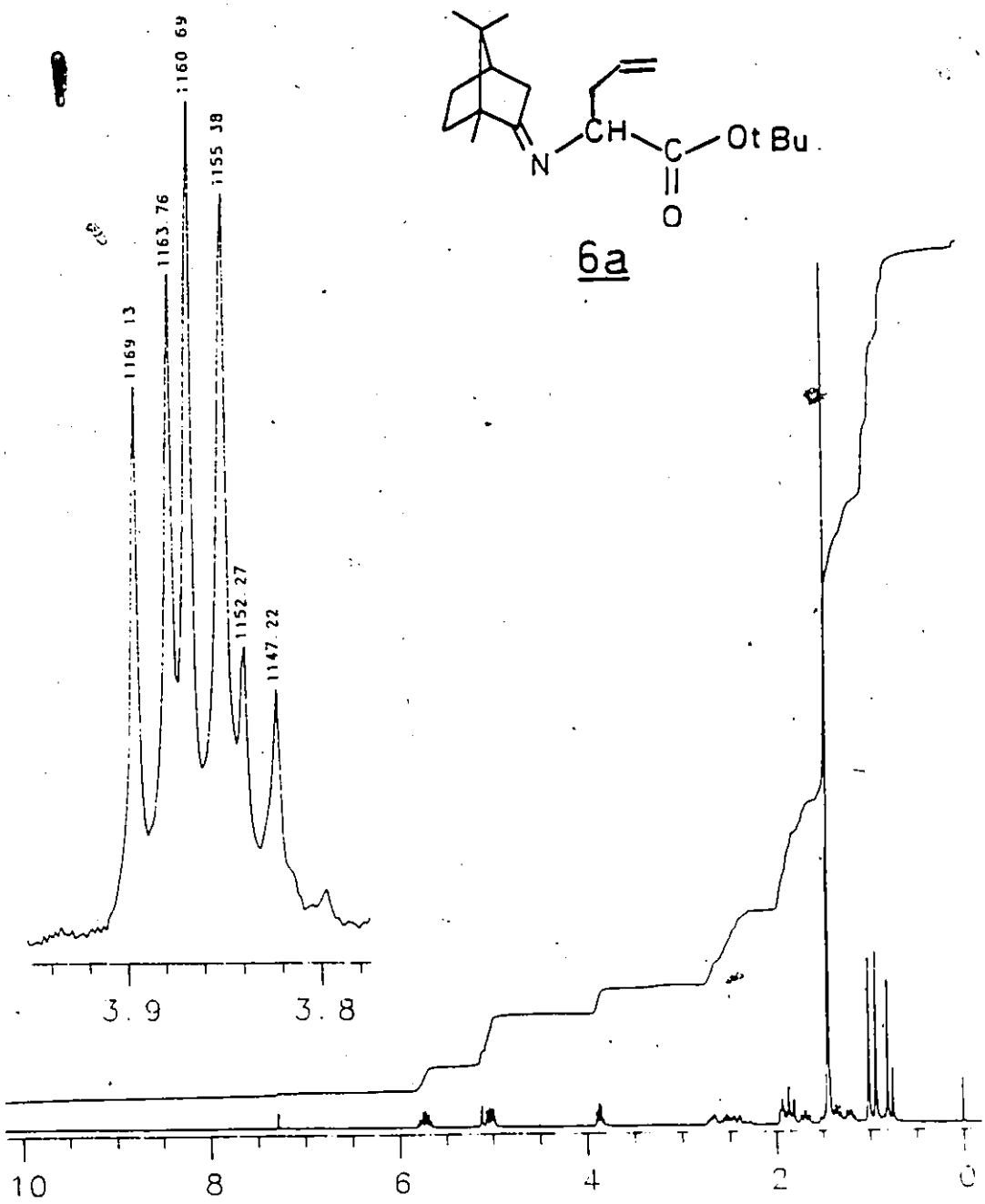
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N
CH
C
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Ot Bu

6a

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granted" everyday activities of Canadians through the eyes of the Chinese foreign students. These everyday activities include: civility, sexuality, partying, Canadian independence, and Canadian feminist attitudes.

According to responses, Canadians are seen to have good civility, they are typified as "well mannered", "polite", and "friendly". They are said to "open doors for others", "having friendly talks with strangers", "help others carry things", "wish others well", "polite in conversation", etc. Perhaps, these to an average Canadian are "taken-for-granted" everyday activities. To fall short of such behaviours in certain specific stiuations, could be considered to be "rude" and "impolite" in this social world. For example, it is "taken-for-granted" that a sales person be polite, and offer assistance when one walks into a shop here. But to the Chinese foreign students such behaviours spell something special and out of the ordinary. According to some respondents, it is uncommon to enquire and care for the general well being of fellow members in Hong Kong. If one was to do, one could be stigmatized as "crazy".

The data showed that subjects typify Canadians as "sexually open", Canadian couples are seen to practice sex after a few outings. For Canadians, at least those encountered by some respondents, it is "taken-for-granted" to have sex after a few outings or after parties. Such practices may be common practices for some university

students, at least those witnessed in residence. A respondent comments:

> I have dated Canadian girls before, and they are very friendly. You can touch them and hold them. It seems so easy. I dated this girl for a few times, we were at her apartment once, I could have done it [have sex] but I didn't...

The data also expressed that Canadian "openness" involves kissing in the public. Some respondents see such acts as embarrassing. They expressed that such behaviour should not be done in public. To some Canadians such behaviours may be "taken-for-granted. To embrace and kiss in public is part of the Canadian culture in welcoming friends and relatives, or sending them away. To avoid such actions in certain situations could be considered to be "rude" or "impolite". Further, Canadians are typified as "daring" when it comes dating. They are perceived to be "straight forward". Some respondents reported that they had witnessed situations where mere acquaintances were asked out for a date. Such behaviours appear to be "taken-for-granted" by those Canadians respondents had encountered.

In terms of "partying", the data reflected that Canadians are typified as "drinking a lot", and behaving in "crazy" manners. Within the residence social world of the University, such behaviours appear to be "taken-for-granted". It is part of the University students' subculture. It is also "taken-for-granted" to have an establishment, such as the University pub, to cater liquor to the students. Another "taken-for-granted" behaviour that the data seemed to indicate is Canadians

bringing liquor when invited for dinner. Such behaviour is considered to be polite and in some incidents expected. From such behaviour, some respondents typify Canadians as "loving to drink". A respondent comments:

> I invited a Canadian girlfriend for dinner once, and she brought wine. I wondered why, because I don't drink. I thought she loves to drink...

The data revealed that in Canadian society, it is "taken-for-granted" that females could visit pubs and drink. Not in Hong Kong. A respondent comments:

> At the pub, I was surprised at the large amount of beer they drink...And there are many females too, and they were drinking...In Hong Kong, most drinking places, girls do not go...Those who drink are usually bar girls.

Responses seemed to indicate that it is "taken-for-granted" that Canadians support themselves in higher education. The data also expressed that it is common to hear Canadian students saying that they have to work in the summer to earn money so that they could come back to school next semester. The indication from the data is that such independence is seemed to be "taken-for-granted" in Canadian social life. Further, the data also showed that in some instances, it is "taken-for-granted" that youngsters do odd jobs to earn some extra allowances. These "taken-for-granted" activities in the Canadian social world are reported to be admired by some respondents. Admiration is how they feel, but they have no knowledge why it is practiced. Their own cultural upbringing has inhibited their comprehension. A respondent comments:

> I find that Canadians are very independent. For example, you kids here deliver newspaper to make an extra allowances...In Hong Kong, parents do not allow their children to go on the streets without someone looking after them...Even when they are older, Canadian students work part-time to support their education. I know people in the Economics department who work full-time in the summer so that they could pay tuition in the fall. I asked them why the parents don't pay for the tuition? Don't they like you going to school? They said their parents could pay but they preferred to pay their own. I don't understand them. In Hong Kong, as long as the family has the resources to support the children, the parents would never allow the children to work to support their education...Over here, sometimes the family may be rich, the children are still expected to work to support themselves.

Another "taken-for-granted" activity in Canadian social world that is reflected in the data is the expectation to leave the family after the children have reached a certain age or are married. To some respondents, such phenomenon is not expected. A respondent comments:

> I know a friend, he told me that he moved out of his parents' home when he was 18. He said that it was time to leave the family and be independent. He didn't have enough money to rent an apartment, so he rented a room with another Canadian family near the University. I see no reason to leave. He could stay with his parents and go to school from there..In Hong Kong, we stay with the parents until we get married. Some families are rich enough, and they have their children's families live with them.

The data also reflected that Canadian females are typified as "mouthy". It is "taken-for-granted" in this social world that females have equal rights and freedom as males. In Hong Kong, females "know their place", and are not expected to voice opinions in public. A female respondent comments:

> I find that Canadian females are not the type that listen and not ask questions. They always have opinions, and they are very daring, they speak out in the public. Chinese girls wouldn't do that. Like in

> Hong Kong, we are taught that girls shouldn't be "mouthy". We are taught by our parents to listen and don't question. For myself, I dare not voice my opinions in public.

The above typifications by respondents reflect some of the "taken-for-granted" everyday activities of Canadians within the social world of Windsor. The data reported that these phenomena are new to respondents and are not seen as "taken-for-granted" behaviours. By typifying certain social aspect of Canadian everyday life, the "taken-for-granted" is thrown into question by the Chinese foreign students, which in turn highlights the difference in perspectives. Hence, through this process of "bracketing" these typifications, the research indirectly reveals the need of coping strategies and that there exist a difference in perceptions in certain social behaviours between subjects and the Canadians they had encountered. One could also conclude that the difference in perspectives reflects the types of strategy employed. This will be discussed further in the next section.

TYPES OF COPING STRATEGY

This section examines the coping strategies employed by respondents during specific reported experiences at the University of Windsor. Coping strategies are categorized into types. In this context, categorizations are derived from respondents' typifications of Canadian civility, sexuality, and "partying", unfamiliarity, and language problems. The aim of this categorization is to examine possible general types of coping strategies that are

espoused by the subjects when dealing with Canadians in their reported experience, and the perceptions, feelings and attitudes associated with each type. — The theory and methodology employed here limit the research from typologizing personalities. After analysing the data, this study typologizes coping strategies in three general types: "reject", "select", and "accept". These typologies are built on reported strategies and are employed as interpretive devices, they do not represent the general attitudinal orientation of respondents. It is possible that strategies fall between these ideal types. Further, it is important to note that these reported strategies are obtained from one time interview, respondents may change coping strategies over time.

The data seemed to suggest that the "reject" type of coping strategy appears to be derived from negative typifications of Canadian civility, sexuality, and "partying". Because of such negative typifications, interactions are claimed to be centered around own co-nationals while avoiding host nationals. Further, responses showed that condemning Canadians and perceiving their own behaviours as "better" seems to be part of this type of strategy.

According to the data, the "reject" type of coping strategy typifies Canadian civility as "well mannered", and "polite" but this type perceives that Canadians "do not really mean it". In sociological terms, perhaps Canadians

are perceived to be doing "front" work. As more information is gathered, Canadian civility is typified as "overplayed", "putting up a show", "superficial", and "not sincere". Termination of social interaction when faced with unfamiliar situations, topics of discussion, and situations where they have problem expressing themselves is a frequent behaviour in this type of strategy. Excuses such as, "I am sorry, I have a class" and "I am meeting a friend", are used. The data seemed to indicate that this type of coping strategy enhances interaction with co-nationals. The data also showed that co-national may not be perceived as "well mannered" as Canadians but once friendship is established, they proved to be more "sincere". In the "reject" type of strategy, Canadians are perceived as "rude" and "do not show respect" to their parents and superiors, and some respondents reported that these are unacceptable behaviours.

In terms of sexuality, the data indicated that the "reject" type of coping strategy typifies Canadians as "sexually open", "sexually easy", and "don't treat sex seriously". Typifications are derived from such criteria as: "having sex after a few dates", "guys brought girls to their rooms after parties", "bringing different girls home", etc. The data expressed that subjects using this type of strategy expressed discomfort when they witnessed such behaviours. "Reject" strategies such as avoiding such scene by walking away, pretending that the interactants are not present, and disassociating from women

who are perceived to have sex with different males are said to be used.

In terms of "partying", the data revealed that the "reject" type of strategy typifies Canadians as "crazy", "wild", "drinking too much", and "really out of hand". Strategies such as "when they have a party I will hide in my room, even though they have invited me" and "I seldom [join his parties], whenever his friends come over, I go to my friend's place or go to the library" are common practices deployed to deal with such unwelcome invitations. "Reject" type of strategy is employed when Canadians are perceived to behave "unacceptably" during such social gatherings. Examples of some of these "unacceptable" behaviours include "throwing bottles", "making too much noise at 4 in the morning", "dancing on tables", etc. It is necessary to inform the reader that such behaviours are perceived to be "unacceptable" in the eyes of the some respondents. In addition, some respondents thought that the Canadians they had encountered perceive such behaviours as "having a good time".

The data revealed that the "reject" type of strategy could be employed by respondents who claimed to be unfamiliar with Canadian society. The data expressed that these respondents employ strategies that enable interaction with Chinese while avoiding Canadians and the usage of intermediaries when encountering Canadians. Further, the data showed that the "reject" strategies are used by

respondents who perceived themselves having language problems when dealing with faculty. These respondents would avoid professors, rely on other students for academic assistance and guess on their own if no help is available. The other set of "reject" strategy reported to be used to deal with Canadian students employed by respondents who claim to be poor in English involves making excuses to leave when they perceive that they could not be involved in a conversation with Canadians and that it would result in an embarrassing situation.

The second type of coping strategy could be classified as "select". The data showed that the "select" type of strategy could have both positive and negative typifications of Canadian civility, sexuality, and "partying". Canadians are typified positively if the new norms and behaviours are perceived to be acceptable, and could be integrated into the foundation of the home culture. Conversely, Canadians are typified negatively the new norms and behaviours are perceived to be unacceptable, and could not be integrated into the foundation of the home culture. Respondents using "select" type of coping strategy adopt more flexible coping strategies. They take a situational approach. These sojourners tend to seek the best from the new culture. The criterion for acceptiblity varies within individuals.

In terms of Canadian civility, the data expressed that Canadians are perceived as "well mannered", "polite", and "friendly" under the "select" type of strategy. Behaviours

such as, "saying "thank you"", "help to open door and carry things", etc. are perceived as positive. The strategy here is to learn from Canadians about public courtesy. Strategies such as, becoming more conscious about their manners in public, reminding themselves to say "thank you", to say "you're welcome", "put on a smile", etc. are used. In conversation, the "select" type of strategy enables users to select topics that they are familiar with so that they could participate. However, the data also revealed that the "select" type of strategy does not encompass avoidance when users are involved in conversations where they perceive themselves having no knowledge. Instead, this type of strategy allows the user to pretend to know the topic by asking simple questions. Similarly, as with the "reject" type of strategy, the "select" strategy typified Canadians as "rude" and "do not respect their parents" when dealing with parents and superiors.

According to the data, the "select" strategy typifies Canadians as "sexually open" but their openness, such as kissing in public, is accepted, and such public behaviour is perceived to be part of Canadian culture. Canadians are perceived as "forward" ("would approach the girl directly and ask her out") when comes to "asking a girl out". The "select" strategy accepts such dating behaviour, and sees Chinese dating behaviour as slow and conventional. Perhaps the preference reflected experiences: "It is hard to ask

Chinese girls out, they take a day or two to give you an answer".

In terms of "partying", the "select" type of strategy has the same typifications as the "reject" strategy. According to the data, Canadians are typified as "wild" and "crazy" in "partying". Such behaviours are deemed as unacceptable. The data showed that some respondents had experienced Canadian "parties". They expressed that such gatherings enhance opportunities for "misconduct" because they had witnessed Canadians drinking excessively and taking drugs. They typify such gatherings negatively when they make comparison with parties organized by the Chinese Students Association. Responses seemed to suggest that as with the "reject" strategy, the "select" strategy also used avoidance in these situations.

In terms of the "select" strategy in the context of language problems, some users claim to keep a list of professors who are deemed as "approachable" and consult professors only as a last resort.

The last type of coping strategy can be classified as "accept". The data indicated that this type of strategy has positive typifications on Canadian civility, sexuality, and "partying". Interacting extensively with Canadians whenever a chance occurs is the prevailing motto. This type of strategy also calls for identifying with the host culture while condemning their own.

In terms of Canadian civility, the data suggested that users of this type typified Canadian as "well mannered",

"friendly", and "polite". This type of strategy allows users to identify with Canadian civility while condemning their own members as "loud". Respondents using "accept" strategy express embarrassment when members speak Cantonese in front of Canadians. With the "accept" strategy, interaction with Canadians is enhanced while co-nationals are avoided. Further, Canadian mannerisms in public is perceived to be "better", while co-nationals are perceived as "rude". By using the "accept" strategy, respondents make every attempt to learn to cope with Canadian behaviour and speech. Some of these strategies involve observing how actors behave in television, learning accent and speech from them, making an effort to talk to Canadians, etc. Further, users of the "accept" type of strategy does not consider Canadian as "rude" to their parents.

With regards to Canadian sexuality, the data expressed that this strategy typifies Canadians as "not that sexually open", and their "openness" is seen as enhancing friendship. Users of this strategy do not avoid such "openness" as "kissing in public" but condone it. Such a strategy calls for reciprocation of actions. For example, as Canadians of different sexes would touch and hold each other with no sexual implications, the strategy would be to practice such behaviours when interacting with Canadians. Users expressed that they had participated in such behaviour when dating Canadian women. Further, users of the "accept" strategy perceive nothing wrong with "scoring"

(to meet a girl and have sex later) in a party. Users of this strategy perceive that such behaviours are common in Canadian "parties".

With the "accept" type of strategy, "partying" is not perceived as "wild" or "crazy" but as opportunity to enhance interaction with Canadians. The "accept" strategy, such as "you have to behave like [Canadians] if you want to interact with them", is used in social gatherings. Further, the "accept" strategy also sees Canadian drinking behaviour as "acceptable", and Canadian parties are perceived as more "fun" while Chinese parties are " less fun". For the "accept" type of coping strategy, condemning other Chinese behaviours and accepting host nationals' seems to be the prevailing method.

In terms of the "accept" strategy used by respondents who claim to be unfamiliar with Canadian society, the data showed that the "accept" strategy enables users to observe and learn from Canadians. For example, "I watch...my landlord...Observing which utensil he used, I followed". In respect to the context of language, the "accept" strategy would allow users to seek professors even they perceive to having language problems. The data seemed to suggest that this strategy enables users to build confidence in themselves by encouraging them think over the questions either in Chinese or English before approaching professors. Further, the "accept" strategy involves the use of television programs as a learning tool. Responses seemed to indicate that such strategy enables users to be

involved in conversation with Canadians.

In summary, the data seemed to suggest that the "reject" strategy is employed to avoid Canadians. This type of strategy is used when respondents feel "uncomfortable" with their new environment and conversing with Canadians. Such a strategy limits interaction with Canadians, and Canadian civility, "partying", and sexuality are perceived as "unacceptable". On the other extreme, the data seemed to suggest that the "accept" type of strategy creates opportunity for respondents to encounter Canadians. This type of strategy facilitates interaction with Canadians, and Canadian civility, "partying", and sexuality are perceived as "acceptable". Between the two extremes is the "select" strategy. Respondents using this type of strategy take an integrative approach. This strategy does not reject all Canadians' behaviours neither does it accept all of them. Rejection or acceptance depends on how the respondent perceives the situation. The data indicated that if the respondent perceives to gain from the experience, he/she would accept if not he/she would reject. In the interest of adjustment, the data seemed to show that the "reject" strategy does not enhance interaction with host nationals. Coversely, responses suggested that the "accept" strategy calls for total acceptance of the foreign culture, and rejection of their own. One has to bear in mind that respondents are temporary members of Canadian society. Their stay in Canada is determined by the length

of time required to complete their education. Users of the "accept" strategy may face the problem of readjustment when they return home. The data further suggested that the "select" strategy seems to allow users to interact with Canadians and at the same time maintain their ethnic identity. Ideally, in light of the reported data and within the framework of this research, the "select" strategies would be the ideal type of coping strategy to deal with unfamiliarity and language problems for some respondents at the University of Windsor.

As stated earlier, these typologies are only general patterns drawn from an aggregate of forty respondents. They are ideal types generated to evaluate the reported strategies of respondents. They represent tendencies rather than discrete reactions of individuals and they are not cross culturally tested. Further, these strategies are derived from the specific reported encounters. They could not be generalized to other social events. They are only part of a recipe of knowledge. In short, these typologies are specifically drived from the findings of this research. In addition, these typologies reflect only what the respondents report they perceive, feel and did when encountering Canadians during these specific experiences, the research is not set up to test the validity of reports through actual behavioural data.

CHAPTER IX

CONCLUSION

On the basis of the analysis of the data, the research reveals that a measure of familiarity could be established by relying on past and present experiences, stock of knowledge, typifications, and images from the media. Familiarity broadens the respondents' scope and perceptions toward unfamiliar culture and creates a familiar social world for them, in which social interaction could be facilitated. The research also reveals that familiarity takes two forms, direct and indirect. The former generates tested recipes for social interaction, while the latter does not. Coping strategies are uncovered as respondents battled with the uncertain and unfamiliar. The data indicated that familiarity enhances social interaction, while little familiarity proves to be an obstacle for social interaction. Hence, this research shows how familiarity plays an important role in social interaction.

In respect to language, the study shows that poor language facility inhibits respondents to make sense of the surrounding social world; inhibits respondents in objectifying their subjective feelings and thoughts; and makes it difficult for respondents to interpret western linguistic symbols and gestures. Poor language facility makes the respondents feel alienated and not a part of the group. The study shows that proficiency in written

language alone is inadequate for face-to-face interaction. Further, poor language facility affects reality construction. The data indicated that two sets of coping strategy are employed by respondents who perceive language problems. One used to deal with faculty and the other with Canadian students. Within each set exists three types of strategy, namely "reject", "select" and "accept" types. This research shows that how having a common language enhances social interaction, while a lack of it proves to be hindering social interaction. Those respondents who perceive to be proficient in English reported that they have no problem interacting with host nationals.

On the matter of typification, the study shows that typifications provide individuals with the guidelines to deal with the routines of everyday life. Through typifications, strangers orient their behaviours and actions in order to establish social interactions with host nationals. The data showed both negative and positive typification schemes of respondents before arrival and how they have changed after arrival. The research also shows the criteria through which respondents used to establish their typifications. In revealing these criteria, the research analyses respondents' perceptions of behaviours offered by Canadians, thereby, revealing the subjective procedures of typifications. Further, the criteria identified in the research spells out the subjects' process of constructing social realities. Finally, the study shows that typifications may have some influence on social

interaction. The data suggested that when respondents perceive that host nationals typify them negatively, they would limit their social interaction with host nationals. These typifications are drawn from the social world at the University and its surrounding communities, such as, they are applicable only within the confine of that social world.

The research identifies three types of coping strategy adopted by the subjects, these are "reject", "select" and "accept" types. From the responses, the "reject" type of strategy is seemed to be used when respondents decide to avoid Canadians, the "select" type is employed to attain the best out of a situation, and the "accept" type is used to "behave like Canadians". These are generated from the specific reported experiences and are part of a recipe knowledge. They do not represent a general approach to deal with Canadians. Discrepancies exist but are beyond the detection of this study. In addition, from the accumulated data some of the "taken-for-granted" assumptions of Canadians in Windsor are analysed through the eyes of the sojourners. This shows the differences in perspectives and in stock of knowledge.

This research took an "inside" approach in examining adjustment of the Chinese foreign students at the University of Windsor. Basically, the research deals with the perceptions, attitudes and feelings associated with familiarity, language and typifications of Chinese foreign

students. The thrust of this research, based on interviews with some forty Chinese foreign students, was to examine these internal factors, which have been construed by the respondents themselves as essential in facilitating their adjustments at the University of Windsor. With the assistance of grounded theory, the present research conveys how the mechanics of social elements, such as familiarity, language, and typifications, affect the process of adjustment. The research may not show quantitatively how these elements affect Chinese foreign students' adjustments at the University of Windsor. However, by revealing the process of how respondents attain familiarity and how they use familiarity when interacting with Canadians, how respondents perceive their language fluency affects social interaction, how typification affects social interaction, and the type of strategy employed in relation to these elements, the research has highlighted the importance of these elements in the adjustment processes of these Chinese foreign students at the University of Windsor. There is also a great deal more that can be said about Chinese foreign students' familiarity, typifications, language problems, coping strategies and their impacts on the adjustment processes. For instance, It is possible that there exist a set of differences in male's and female's coping strategy and reality construction that has not been examined; discrepancies have been detected through the study that need to be examined; and the need to examine criteria that

lead respondents who perceive to fluent in English to begin interaction with host nationals. These and other questions suggest the possibility of further research in this area.

Finally, this research suggests a useful approach to the study of adjustments of foreign students in Canada. The macro aspect of adjustment such as those generated by adaptation models ignore the experiences, perceptions and feelings of foreign students. Micro-level research on adjustment could fill this gap. Perhaps the interaction of micro and macro researches in this field could assure a positive sojourn for these temporary members of Canadian society.

APPENDIX A

STATEMENT OF PURPOSE

I am a graduate student conducting sociological research in partial fulfillment of my Master degree.

The purpose of this research is to find out the adjustment of Chinese foreign students at the University of Windsor.

If you consent to take part in this project, you will be interviewed. The information you give will be kept in strict confidence and will be used for this research only. A tape recorder will be used during this process. Your interview will be part of this research to learn more about the adjustment phenomenon of Chinese foreign students.

I will be glad to explain and answer any questions pertaining to this research.

Thank you.

Lee, Keng Mun
Department of Sociology
University of Windsor.

APPENDIX B

STATEMENT OF CONSENT

I am taking part in this research on my own free will. The purpose of this research has been explained to me. I am aware that all the information I provide during the interview will be kept in strict confidence and will be used for this research only.

Name:

Signature:

Date:

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VITA AUCTORIS

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I was born in Singapore on the 24th of June, 1960 to Mr Lee Tack Kong and Madam Mark Phwee Wan. I began my primary education in 1967 at Canberra Primary School, and graduated in 1972 with Primary School Leaving Certificate (P.S.L.E). I began secondary education the following year at Balestier Hill Technical School and graduated in December, 1976 with a Singapore-Cambridge General Certificate of Education Ordinary Level (G.C.E. "O" level). I enrolled at City School of Commerce for my college education the following year graduating in December, 1978, with a Singapore-Cambridge General Certificate of Education Advanced Level (G.C.E. "A" level). In 1979, I was called up for National Services. Between January 1979 and June 1981, I was a Non-Commissioned Officer with the Singapore Artillery.

In September, 1981 I came to Canada to further my education at the University of Toronto. I graduated in June, 1984 from the University of Toronto with a Bachelor of Arts degree majoring in Sociology and Economics. In September, 1984, I enrolled at the University of Windsor for Graduate work in Sociology. I was a Teaching Assistant for Introductory Sociology from September 1984 to April 1986. I completed course work requirements for the Master of Arts degree in Sociology at the University of Windsor in 1985.