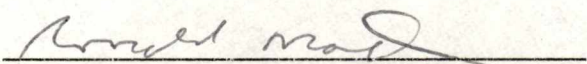
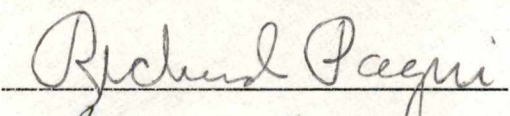
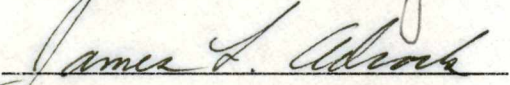
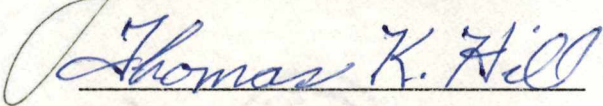


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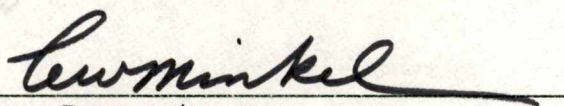
I am submitting herewith a dissertation written by Randall David Hinton entitled "The Stereochemistry of the S_N2 Reaction Between 3-Buten-2-yl-2,4-d 2,6-Dichlorobenzoate and Piperidine." I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.


Ronald M. Magid, Major Professor

We have read this dissertation
and recommend its acceptance:

Accepted for the Council:


Vice Provost
and Dean of the Graduate School

THE STEREOCHEMISTRY OF THE S_N2' REACTION BETWEEN
3-BUTEN-2-YL-Z-4-d 2,6-DICHLOROBENZOATE
AND PIPERIDINE

A Dissertation
Presented for the
Doctor of Philosophy
Degree
The University of Tennessee, Knoxville

Randall David Hinton

August 1990

DEDICATION

This dissertation is dedicated to my father, Frank Douglas Hinton. His life of hard work and faith will always be an inspiration to me.

ACKNOWLEDGEMENTS

In the course of my work at the University of Tennessee I have met and been aided by many people. I would like to thank my co-workers under Dr. Ronald Magid: Dr. Charles Bass, Cyril Thompson, M.S.; and especially Mitchell Rhea. I am very grateful to each of these persons for the time they have spent assisting me and for the helpful suggestions they have made. I would also like to thank my research director, Dr. Ronald Magid, for all of the hours he spent slaving over a hot NMR spectrometer, for always being handy with a reference, and for putting up with me for so long. The other members of my research committee, Dr. Richard Pagni, Dr. James Adcock, and Dr. Tom Hill, receive my gratitude as well. I would also like to thank the Petroleum Research Fund of the American Chemical Society for financial support of part of this research.

ABSTRACT

The S_N2' mechanism has experienced a great deal of controversy since it was first proposed in the late 1930's. While the stereochemical consequences of other substitution reactions are well-known and understood those of the S_N2' have never been fully explored. This is due, in part, to the continuing controversy over its mechanism and, in part, to the observance of differing results from reactions presumed to occur by the same mechanism.

Most stereochemical studies have involved either intramolecular reactions or intermolecular reactions on cyclic substrates. However, these systems introduce biases which may outweigh the stereoelectronic preference of the S_N2' mechanism. This dissertation outlines an intermolecular S_N2' reaction on a deuterium labelled, optically active, allylic, acyclic substrate. Reduction of the double bond of the products of this reaction provides a single compound whose optical activity, after correction for the optical activity of the substrate, for its %D labelling, and for the ratio of E and Z products, is equal to the % syn attack in the S_N2' reaction. This was checked by preparing the same compound from an alcohol of known optical activity.

An impossible result was obtained. The optical activity of the final reduced compound was greater than its maximum as indicated by the alternate synthesis. A repetition of this synthesis provided identical results.

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CHAPTER I

INTRODUCTION

The S_N2' mechanism has experienced a great deal of controversy since it was first proposed in the late 1930's.¹ When initial attempts to discover examples failed, the S_N2' mechanism was labelled unrealizable.² It was only natural that the first definitive example of an S_N2' mechanism was discovered within a year of this proclamation.

Early studies attempted to further develop conditions conducive to the S_N2' mechanism. As data in this area expanded, studies on the stereochemistry of the S_N2' were carried out as well. Although the stereochemical consequences of the S_N1 and S_N2 reactions are well-known and understood, those of the S_N2' have never been fully explored. This is due, in part, to the continuing controversy over its mechanism and, in part, to the observance of differing results from reactions presumed to occur by the same mechanism.

Most stereochemical studies have involved either intramolecular reactions or intermolecular reactions on cyclic substrates, probably due to the relative ease with which the products may be analyzed. However, Magid's group at the University of Tennessee, Knoxville, has long thought that intermolecular reactions on acyclic substrates are the only way to obtain unbiased experimental data which could be used

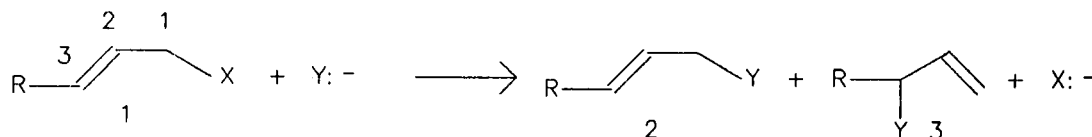
to determine the stereoelectronic preference of the S_N2' mechanism.³ The current work is an attempt to add to data obtained by other members of Magid's group over the previous seventeen years.

CHAPTER II

HISTORICAL PERSPECTIVE

A. General Considerations

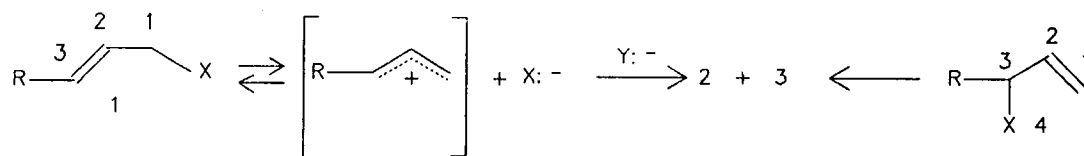
The idea of nucleophilic substitutions was first proposed in the early 1900's.⁴ Limiting first and second order kinetics were proposed and accepted by the majority of chemists over the next few decades.⁵ Mechanisms involving migration of a double bond were first seen during the 1920's.⁶ It was found that substitutions on compounds with double bonds sometimes led to the formation of two different products (Eq.



Equation 1

1). One was the normal product seen in other substitutions (2) and the other was the product which would form if the nucleophile attacked at C-3 and the double bond migrated to between C-1 and C-2 (3). The earliest mechanism proposed for the formation of these products involved formation of an ion-pair which can then recombine to give either the initial compound or its rearranged isomer.⁷ This mechanism is often

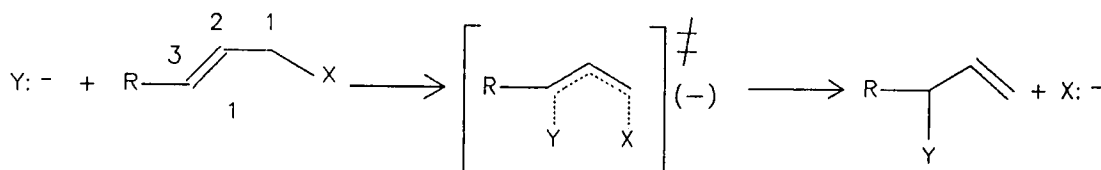
referred to as S_Ni' and it is a special case of the S_N1' mechanism shown here in Eq. 2. It is characterized by the



Equation 2

formation of an identical ratio of 2 and 3 from both 1 and its 3-X-1-ene isomer. Examples of S_Ni' and S_N1' mechanisms were easily found and these mechanisms were quickly accepted.^{7,8}

During the late thirties three chemists separately conceived of the idea of a second order concerted substitution reaction on an allylic substrate occurring with migration of the double bond (S_N2').¹ In this mechanism (Eq. 3) attack by



Equation 3

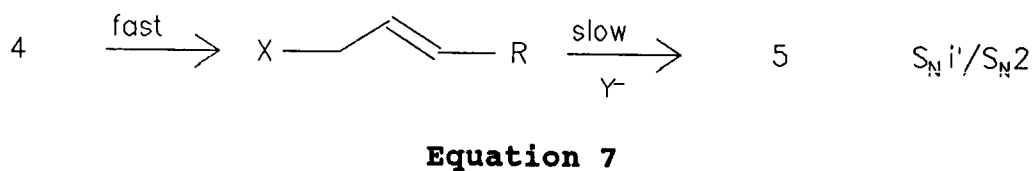
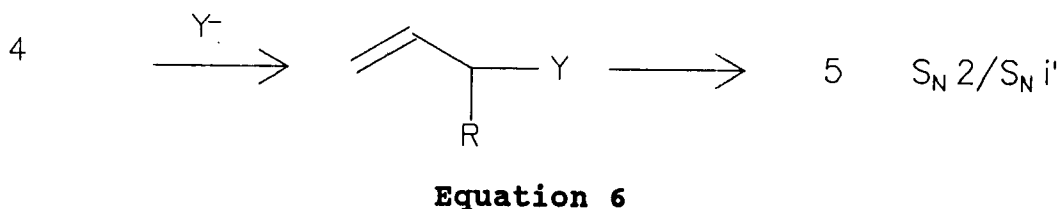
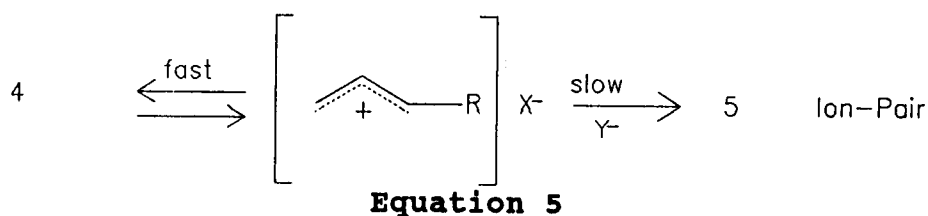
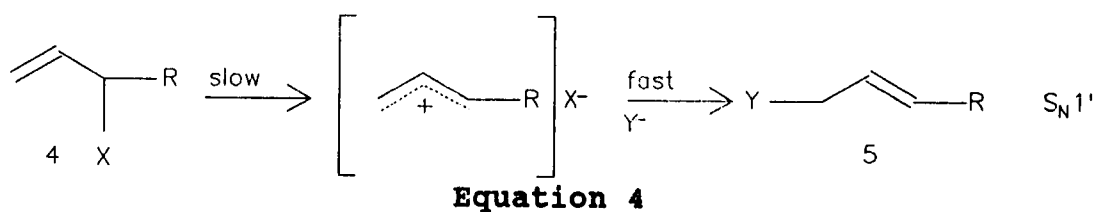
the nucleophile, migration of the double bond, and departure of the nucleofuge all occur in the same step.

Establishing an undeniable example of an S_N2' mechanism proved to be very difficult. Although many reactions were proposed as possible examples of S_N2' mechanisms⁹ most were rejected because they failed to meet one or another of the

three criteria which have been proposed for such a mechanism.¹⁰ Either an S_N2' product was not isolated, or the reaction was not first order in both substrate and nucleophile, or rearrangement of either the substrate or the S_N2 product was not ruled out.

The small amount of S_N2' product in a given reaction, if indeed any was formed, may be explained by the following theoretical considerations. An S_N2' mechanism involves attack by the electrons of a nucleophile on an electron-rich carbon of a double bond. Because of this the S_N2' mechanism is inherently slower than an S_N2 mechanism. The rate of the S_N2 can be reduced by increasing the steric hindrance at the substituted carbon but this will increase the rate of the S_N1 .¹¹

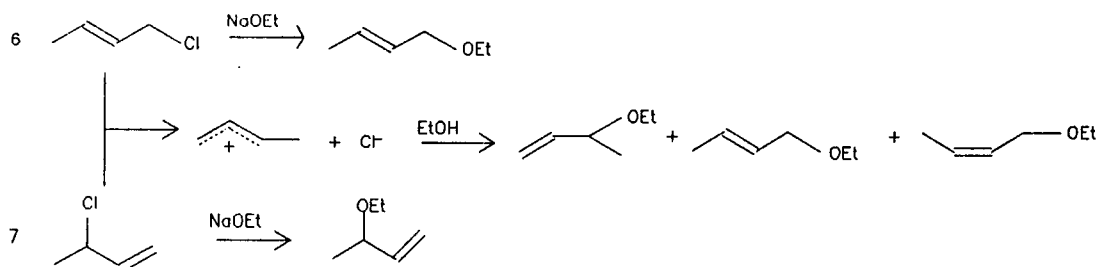
Once an S_N2' product is found the other two criteria must be met to rule out the other mechanisms, shown on the next page, which give rise to " S_N2' " products. The S_N1' mechanism can be discarded if second order kinetics are found but the other three mechanisms are all second order. To disprove the S_N2/S_N1' mechanism one must show that the S_N2 product does not rearrange under the conditions of the reaction. The S_N1'/S_N2 mechanism can be disproved by showing that the substrate does



not rearrange. If the relative rates are reversed, then the reaction will no longer show second order kinetics. It is harder to disprove the ion-pair mechanism. At first glance a lack of substrate rearrangement or double bond isomerization

(which could be detected by replacing one of the H's on C-1 with a D) should suffice, but several researchers have suggested that it is possible that internal return here could be too rapid for such changes to occur.^{5,12}

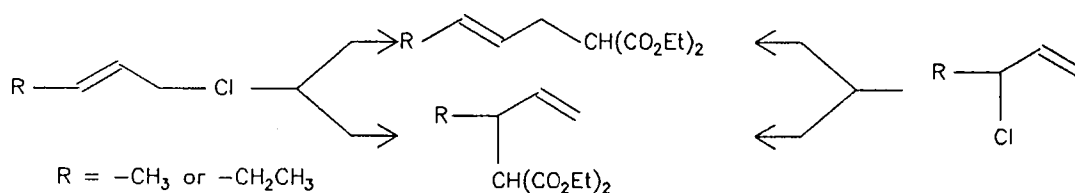
Hughes was the first to perform a study with the specific purpose of finding an example of the S_N2' mechanism.¹³ The reactions he examined were those of sodium ethoxide in ethanol and of pure ethanol with 1-chloro-2-butene (6) and 3-chloro-1-butene (7). The reactions with both nucleophiles are second



Equation 8

order. Only the S_N2 products were formed in the reactions of both of the halides with sodium ethoxide. In the solvolysis reactions both the rearranged and non-rearranged products were seen. However, as they were formed in identical ratios with each halide, both reactions were believed to involve the same allylic cation as shown above. No evidence for the S_N2' mechanism was seen. Roberts *et al.* came to the same conclusion in their study of these reactions a year later.¹⁴

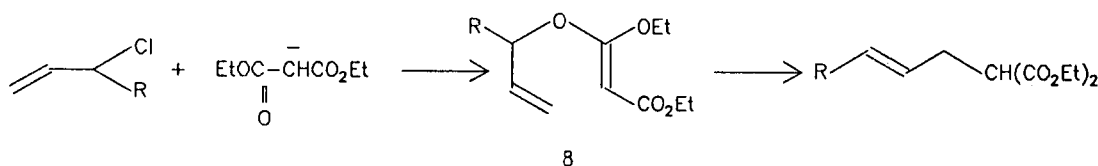
The first example which met the criteria listed earlier was reported by Kepner *et al.* in 1949.^{10a} In this study 1-chloro-2-butene and -pentene and 3-chloro-1-butene and -pentene were treated with sodium diethyl malonate. While the



Equation 9

primary chlorides both yielded less than 1% of the S_N2' products the two secondary chlorides yielded 10% and 23% of the S_N2' products respectively. Neither the chlorides nor the S_N2 products rearranged under the conditions of the reaction.

Dewar proposed an alternative mechanism for the formation of S_N2' products in this reaction.¹⁵ It involves the formation

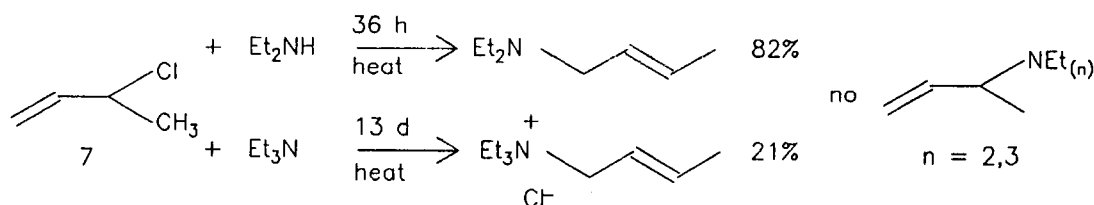


Equation 10

of an O-alkylated compound (8) which undergoes an internal Claisen type rearrangement. Winstein,¹⁶ however, stated that the proposed intermediate would have reacted with the solvent ROH instead of rearranging if it had formed. Stereochemical evidence against this route has also been found. It will be discussed in the next section. DeWolfe and Young¹⁷ reported that other reactions of primary allylic halides with sodium derivatives of acetoacetic and malonic esters gave no O-alkyl products. They also stated that if the intermediate exists, then it should be seen since the reaction was carried out at room temperature and its rate of rearrangement is likely to be low below 150 °C.

Further examples of S_N2' mechanisms were found over the next several years although controversy over the details of the mechanism continued. One of the first classes of nucleophiles to give high yields of S_N2' products was the dialkylamines.¹⁸ For example, diethylamine reacts with 3-chloro-1-butene (7) to give an 82% yield of the S_N2' product after

refluxing in benzene for 36 hours. No S_N2 product was found.



Equation 11

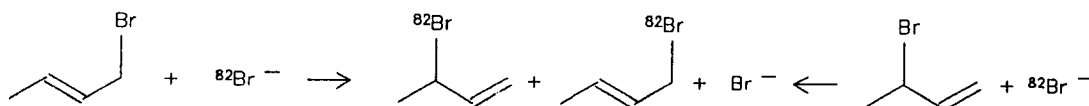
Young *et al.* also studied triethylamine. In this case only 21% of the S_N2' product was obtained after refluxing for 13 days. Both reactions were found to be second order. The authors suggested that hydrogen bonding in the transition state of the reaction between 7 and diethylamine aided that reaction and resulted in its greater yield as compared with triethylamine.

The involvement of the S_N2' mechanism in the reaction with triethylamine is doubtful for several reasons. The harsher conditions of this reaction, as compared to those used with diethylamine, resulted in a significant amount of rearrangement of the 3-chloro-1-butene. It was also found that the S_N2 product completely decomposed after heating for two weeks at 75 °C. The residue was found to contain 4-11% of the S_N2' product. No such behavior was seen with diethylamine.¹⁸

Young *et al.*¹⁹ also studied the reactions of 3-chloro-1-butene (7) with di- and trimethylamine in order to gain more

information about the possible intervention of a hydrogen bonded intermediate in the reaction with several amines. Here the differences in rate and yield were not as great. Dimethylamine was allowed to react with the chloride for seven days at 50 °C. The trimethylamine reaction was carried out under similar conditions. An 82% yield of the S_N2' product was obtained with dimethylamine in benzene solvent, whereas 95% was found when cyclohexane was used as the solvent. The other reaction gave a mixture which consisted of 68-72% of the S_N2' product and 28-32% of the S_N2 product. Both reactions were found to be second order. No first order rearrangements occurred with any of the compounds involved. Because the difference in yields was relatively small they concluded that hydrogen bonding was not required to observe the S_N2' mechanism although it could assist it.

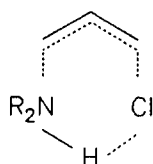
England and Hughes²⁰ argued that S_N2' products were not seen in many reactions because their rate of formation was much lower than that of the S_N2 products. They therefore examined the reaction of both 1-bromo-2-butene and 3-bromo-1-butene with $Li^{82}Br$. Here an S_N2 reaction would not use up any



Equation 12

of the substrate. It would remain available for an S_N2' reaction. The radioactive bromide allowed them to detect the formation of the S_N2 product. With the primary halide they found that the S_N2 reaction is 28,000 times faster than the S_N2' . It proved to be only 60 times faster with the secondary halide. They stated that theirs was the only "indubitable" example of an S_N2' mechanism. deWolfe and Young,²¹ however, believed that this study was incomplete because it did not rule out a possible S_N1 or S_Ni' mechanism catalyzed by the lithium ion.

Because of the uncharacteristically high yields of S_N2' products in reactions between secondary amines and allylic halides, especially when compared with tertiary amines, a



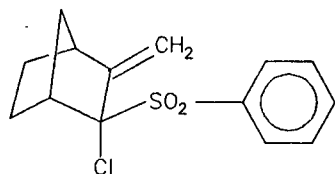
mechanism involving hydrogen bonding between the hydrogen on the nitrogen and the chlorine of the substrate was proposed.¹⁸ Ingold^{5b} and de la Mare²² concurred with this proposal and argued that if this intermediate occurs in the reaction then the mechanism should be referred to as S_Ni' . Bordwell¹¹ thought hydrogen bonding "to be indeed necessary." This also harks back to a mechanism proposed earlier by Burton and Ingold⁷ for observed allylic rearrangements.

The extent to which hydrogen bonding is involved in the transition state was examined by Dittmer and Marcantonio.²³ They performed a kinetic isotope study in which 3-chloro-1-butene was treated with diethylamine or *N*-methylbenzylamine and with their *N*-deuteriated analogues. No isotope effect was seen and they therefore concluded that hydrogen bonding did not play a role in the transition state of this reaction. Bordwell¹¹ disagreed with their conclusions saying that a small isotope effect is expected anyway. He also proposed steric hindrance as a possible cause of better yields with secondary amines. It is hard for this researcher to understand how someone who disagrees with the idea of concerted reactions involving four or more bonds would favor a similar mechanism involving six!

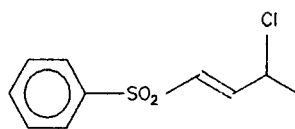
Another type of kinetic isotope effect study was aimed at determining whether or not the mechanism was concerted. A $^{12}\text{C}/^{14}\text{C}$ isotope effect at carbons 1, 2, and 3 of 3-chloro-1-butene in its reaction with dimethylamine was noted by Fry.²⁴ He also noted a $^{35}\text{Cl}/^{37}\text{Cl}$ isotope effect in that reaction. These data are consistent with a concerted mechanism whose transition state involves changes at each of the allylic carbons as well as the leaving group. No isotope effect studies have been carried out on the attacking atom of any of the nucleophiles involved in $\text{S}_{\text{N}}2'$ reactions.

Despite this evidence several people have decided that the $\text{S}_{\text{N}}2'$ reaction is not concerted. Bordwell²⁵ reviewed the

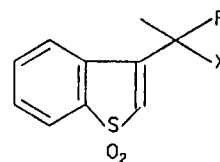
reactions of several secondary and tertiary α -halo allylic compounds, 9 through 12, each of which possessed a sulfonyl



Compound 9



Compound 10

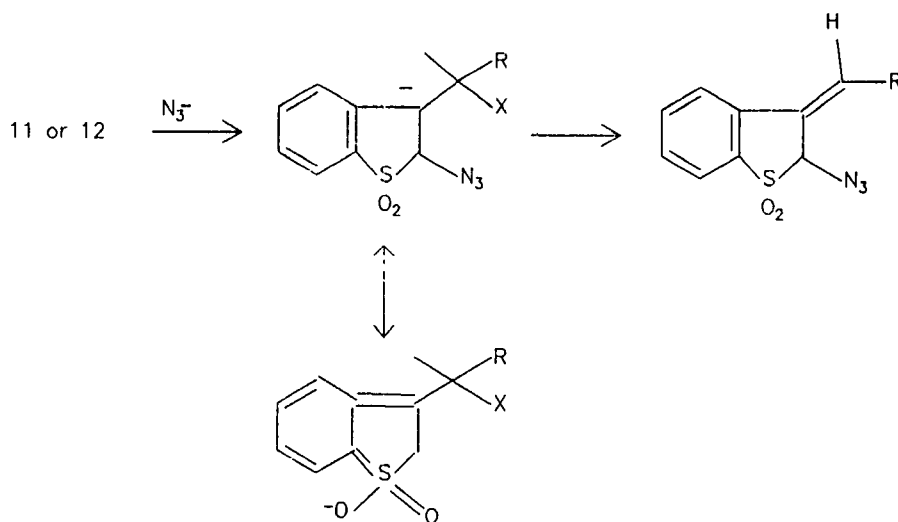


11 R = H, X = Br, Cl

12 R = CH₃, X = Cl

group. He reasoned that these electron withdrawing substituents would make the double bond more susceptible to nucleophilic attack and thus favor the S_N2' mechanism if it were concerted. They would also serve to suppress ionic mechanisms like those shown in Equations 4 and 5 (p. 6). In the case of 9 and 10, the S_N2' product was in fact only seen with a few of the less basic nucleophiles. This supports Bordwell's contention that the actual mechanism is ionic.

The other two compounds did form S_N2' products with several nucleophiles, but relative nucleophile reactivity differed from that seen with 3-chloro-1-butene. Bordwell could not explain the formation of S_N2' -like products here by the cationic S_N1' or ion-pair mechanisms as these should be almost completely suppressed by the sulfonyl group. The presence of the benzene ring led him to propose an anionic mechanism for these reactions (Eq. 13). The sulfonyl group here would stabilize the anionic intermediate. None of these mechanisms, however, explains the isotope effects noted for



Equation 13

amines with acyclic allylic chlorides.^{23,24} It could also be argued that you can't rule out the occurrence of a mechanism in the reaction between two compounds simply by noting its lack in a reaction between two other compounds.

Sneen¹² agreed with Bordwell that the reaction is not concerted, and has proposed an ion-pair mechanism similar to that shown in Equation 5 (p. 6) which would allow a unification of both first order and second order, substitution and elimination reactions.^{12a} He describes the initially formed ion-pair as "an extended bond with considerable ionic character." Thus the double bond cannot rotate and internal return leads only to the original starting material. McLennan says that Sneen's calling a polarized RX molecule an "ion-pair" is merely semantics and can't be used as a solution to chemical problems.²⁶ Bach did not argue against the concertedness of the $\text{S}_{\text{N}}2'$ mechanism. He merely stated that frontier molecular

orbital theory would not lead one to expect it to be concerted.²⁷

de la Mare and Vernon responded to Bordwell's²⁵ attack on their earlier work and presented several arguments against the intimate ion-pair mechanism.²⁸ In addition to the isotope studies mentioned earlier, they said that if the ion-pair is not intimate (i.e. the bond between C-1 and X is completely broken as in Eq. 2, p. 4) then the mechanism requires the build-up of a detectable amount of the rearranged substrate. If the ion-pair is intimate then it is not a question of concertedness but rather one of the synchronism of the bond-making and bond-breaking processes.

This question has been dealt with comprehensively by Dewar.²⁹ Examination of Evans-Polanyi plots³⁰ for several reactions showed that synchronous two-bond processes, like E-2 and S_N2', always require more energy than a combination of two non-synchronous one-bond processes. MNDO calculations also provided evidence for his assertion and show that bond-making slightly precedes bond-breaking.³¹ This mechanism would still allow for the existence of the isotope effects which have been observed.

Bordwell replied to these arguments in 1987.³² He said that Dewar's calculations, while true for gas-phase reactions, would not be applicable to solution chemistry. He examined the reactions of several potassium fluorenides with allylic chlorides. He indicated that these compounds must overcome

a barrier of over 50 kcal to form an anion intermediate in an S_N2' type mechanism. However, it should be noted that Dewar's mechanism does not require the formation of a discrete anion. It merely posits a non-synchronism of bond-making and -breaking.

In addition to studies aimed at elucidating the precise characteristics of the S_N2' mechanism there have been many studies whose purpose was to determine its applicability to various nucleophiles and substrates. Among the nucleophiles which have been shown to react in such a fashion are both ethoxide and thiophenoxide ions (used by de la Mare³³), thiourea and various substituted thioureas (Young and co-workers³⁴), as well as several halides³⁵ and amines^{18,19}.

Likewise, the substrates employed have varied. While chloride has served as the leaving group in a majority of cases, various other moieties have also been used. Among these are bromide,²⁰ and several esters including 2,6-dichlorobenzoate,³⁶ mesitoate,³⁷ and acetate.³⁸

Studies have been done on 3-chloro-1-propene units which have been substituted in various ways. A single substituent is usually placed on C-3 to hinder any S_N2 reaction. de la Mare *et al.* examined a wide variety of compounds including ones with two 3-methyl groups,³³ a 3-*t*-butyl group,³³ and one or two additional 3-chloro atoms.³³ Cyclic substrates have also been examined.^{35,39}

Solvent effects have received little, if any, comment in most studies of S_N2' reactions. Young *et al.*¹⁹ mentioned an increase in the percentage of S_N2' product formed as they changed solvents from acetone to benzene to cyclohexane. No explanation for this effect was given. de la Mare and Vernon⁴⁰ examined the reactions of two halides with sodium thiophenoxide in ethanol/water mixtures. They found that the S_N2' rate increased with the percentage of water but not as much as the S_N2 rate. They also argued that solvent effects should be small, as that is the case with other bimolecular processes involving ions and neutral molecules. Bordwell and Schexnayder¹¹ noted an increase in rates in this order: methanol < benzene < acetone < DMF. They also noted that S_N2 reactions get slower as the solvent is changed from methanol to benzene. Their explanations for this reversal in the S_N2' reaction deal with the specific compounds being used, not the reaction itself.

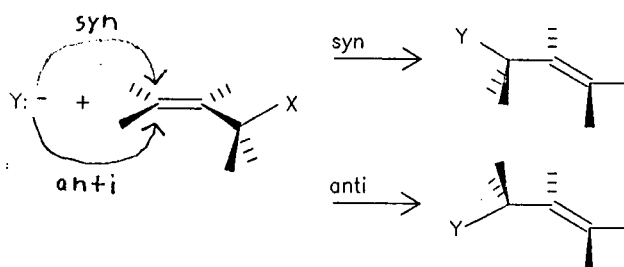
In addition to the more "traditional" types of S_N2' reactions, several involving organometallic reagents have been noted to give S_N2' products. Phenylmagnesium bromide reacts with both 1-chloro-2-butene (6) and 3-chloro-1-butene (7) to give the same 3:1 mixture of 1-phenyl-2-butene and 3-phenyl-1-butene.⁴¹ An ion-pair mechanism was invoked to explain the observed product distribution. S_N2' products have also been formed by this mechanism, as well as concerted and radical

mechanisms, involving alkyllithium reagents,⁴² $\text{CuR} \cdot \text{BF}_3$'s,⁴³ and dialkyllithium cuprates.⁴⁴

Several intramolecular $\text{S}_{\text{N}}2'$ reactions have also been reported.⁴⁵ (These are more appropriately referred to as $\text{S}_{\text{N}}\text{i}'$ or $\text{S}_{\text{N}}\text{c}.$) Many of these occur in biogenetic pathways.⁴⁶

B. Stereochemistry

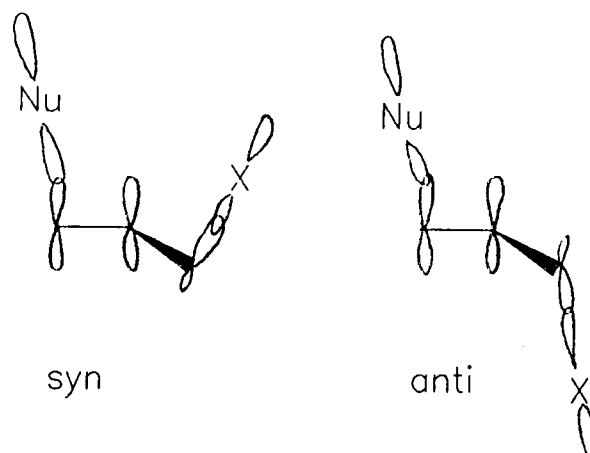
There are two limiting stereochemistries by which the $\text{S}_{\text{N}}2'$ mechanism may occur: syn attack and anti attack. In syn



Equation 14

attack the incoming nucleophile and the leaving group are on the same side of the molecule; in anti attack they are on opposite sides.

If we examine the course of these attacks we can see that syn attack leads to a quasi-cyclic (Hückel arene) transition state. On this basis it should be more favored than the noncyclic transition state which forms in anti attack. However, steric and electrostatic repulsion between the nucleophile and the nucleofuge may be able to overcome this inherent stereoelectronic preference. Much research has been carried out in an attempt to determine whether this preference



actually exists and how other factors influence it.

Early on Winstein discussed the stereochemical preference of the S_N2' mechanism.¹⁶ He argued that synfacial approach would be favored because the movement of electrons would assist formation of the new π -bond by coming in on the back side of the carbon bearing the leaving group. In this way the reaction is related to the S_N2 mechanism.

Fukui predicted the outcome of many classes of reactions on the basis of frontier molecular orbital (FMO) theory.⁴⁷ His treatment of the problem indicated that the S_N2' mechanism should involve preferential syn attack. He argued, however, that this stereoelectronic preference was not great and could be overcome by other influences including sterics.

Drenth⁴⁸ also used FMO theory. He examined the LUMO (lowest unoccupied molecular orbital) of the allylic system and indicated that it should favor syn attack. Jefford *et al.* stated that orbital symmetry arguments also favor syn attack.⁴⁹ Their treatment, however, involved overlap of the orbitals of

the nucleophile with those of the leaving group. This results in a quasi-cyclic transition state with aromatic character. For this reason Jefford prefers to label these reactions S_Ni' .

Mathieu and Rassat divided reactions into two groups: those involving an even number of electron pairs in the transition state and those involving an odd number. Those involving an odd number of electron pairs (including S_N2') should occur without inversion, i. e. syn. The stereochemistry of an extended, or vinylogous, S_N2' (these are also referred to as S_N2'') should change with each additional double bond.⁵⁰

More recently, theoretical studies have examined the effect of altering the substrate, the nucleophile, the nucleofuge, or the solvent. Toromanoff studied several cyclic substrates in light of his torsional angle alteration ideas. He concluded that cyclobutenyl systems should give equal amounts of syn and anti products, cyclopentenyl systems should prefer anti attack and cyclohexenyl systems should prefer syn attack.⁵¹ However, only syn products have been seen in cyclobutenyl systems, and syn attack is actually favored for cyclopentenyl systems.⁵²

The effects of the nucleophile and of the leaving group have also been studied. Epiotis *et al.* compared neutral and charged species.⁵³ On the basis of one-electron factors supported by *ab initio* and semiempirical calculations they decided that neutral nucleophiles should preferentially attack

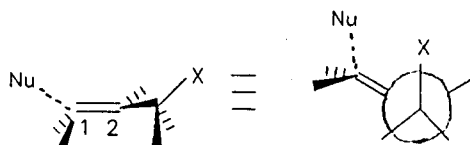
syn while those with charges should prefer to attack anti. Liotta examined monointeractive and ambiphilic nucleophiles and decided that they should react preferentially syn and non-preferentially respectively.⁵⁴ Secondary amines can form hydrogen bonds and are, therefore, classed as ambiphilic.

In the reaction of chloride ion with 3-chloropropene, Bach used *ab initio* calculations to predict preferential anti attack. Ammonia, however, should favor syn attack.²⁷ He also stated that hydrogen bonding or participation of the gegen-cation in the transition state (i.e. Young's disagreement with England's experiment^{20,21}) is a more likely cause of this preference.

Stohrer indicated that ease of removal of the leaving group should determine the favored mode of attack. Those most difficult to remove should favor syn attack while the easier ones should allow more anti attack.⁵⁵ He based his argument on the change in the p-orbital of C-2 in the syn and anti reaction paths. During both displacements this orbital should have characteristics of both sp^2 and sp^3 hybridization. Thus one lobe, the one farther from the nucleophile as it enters and closer to the nucleofuge as it leaves, should be larger than the other. Its size depends upon the amount of negative charge built up in the molecule. In syn attack the large lobe remains on one side of the molecule. In anti attack it must undergo an energetically unfavorable inversion.

While Stohrer felt that syn attack would be favored in either case, Anh said that a concerted S_N2' mechanism requires anti attack while an S_N1 -like mechanism (good leaving group, more ionic in nature) requires syn attack.⁵⁶ Murphy and O'Mahony⁵⁷ extended Anh's analysis to vinylogous systems and stated that the additional double bond would reverse the preferred direction of attack.

Houk, however, believes that these analyses were based on incorrect molecular orbitals.⁵² Use of the proper orbitals indicates that maximum overlap of the σ -HOMO (highest occupied molecular orbital) and π^* -LUMO upon nucleophilic attack occurs with anti-bending of the ethylene moiety of the substrate. This is shown in the drawing below. As the nucleophile



attacks at C-1, C-2 takes on a pyramidal character. C-3 prefers to be in a staggered conformation with the pyramidalized C-2 and the nucleofuge prefers to leave anti-periplanar to the developing negative charge at C-2. He therefore reasoned that syn attack should be favored for concerted reactions as well as those in which bond-forming precedes bond-breaking. Syn attack should also be aided by good nucleophiles, poor nucleofuges, electron-withdrawing groups at C-2, and non-polar solvents. No preference should be seen

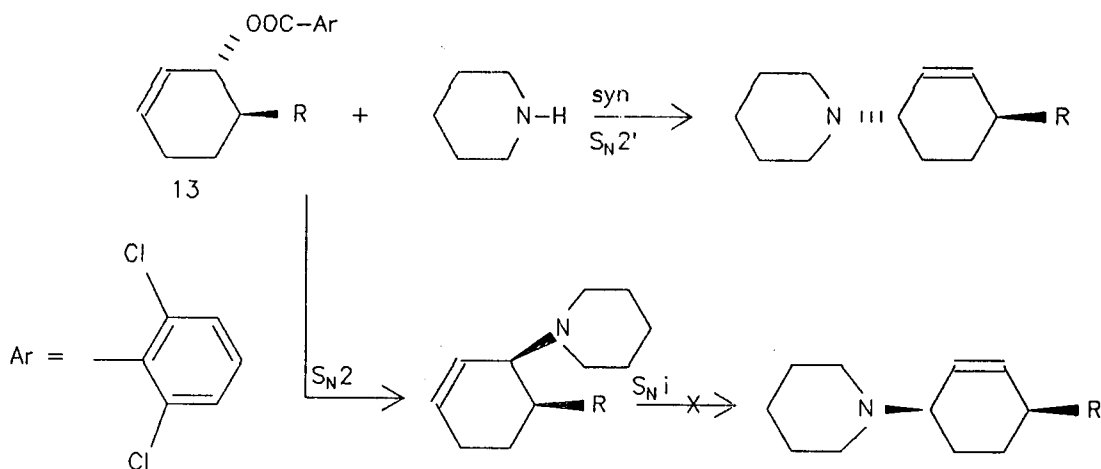
in an ion-pair mechanism unless specific interactions intervene.⁵²

Unlike the previous two predictions on this subject, Houk⁵² believes that S_N2'' (vinylogous) reactions would also prefer syn attack. He has also argued that the charge on the nucleophile and nucleofuge would not affect this syn preference.

Eschenmoser and co-workers reported the failure of the τ -bond model to make a correct prediction of the steric course of several types of reactions including the S_N2' .⁵⁸ The τ -bond model states that the best transition state should be the one in which an anti-periplanar arrangement of the reacting bonds exists. This would thus predict anti attack.

Experimental research in this area began in the 1950's. Stork and White³⁶ determined the syn/anti ratios of several reactions of piperidine and sodium di-*n*-butyl malonate with *trans*-6-alkyl-2-cyclohexen-1-yl 2,6-dichlorobenzoates 13. The alkyl group (methyl, isopropyl or *t*-butyl) serves to block S_N2 attack, to differentiate between S_N2 and S_N2' products, and to differentiate between syn and anti attack.

The reaction between these esters and piperidine was carried out at 130 °C for 24 hours. Under these conditions it was found that the unreacted ester had not rearranged. The reaction was also found to be second order. Intervention of the S_N2/S_Ni' mechanism proposed by Dewar¹⁵ was ruled out by the fact that the stereochemistry of the observed product is



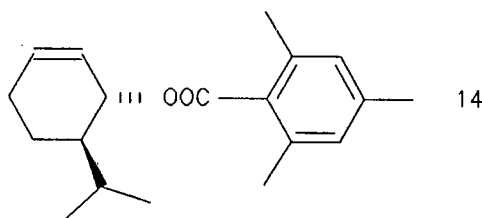
contrary to what is predicted by that route. In each case the amine which formed (in 60-73% yield) was the one corresponding to the syn- S_N2' mechanism.

The product observed in the reaction between the ester and di-*n*-butyl malonate ion depended on the alkyl group of the ester. When R = methyl, only normal S_N2 displacement was seen. With the other two alkyl groups the syn S_N2' product was once again formed exclusively. Young's three criteria^{10b} were met here as well.

The reaction between 13 and piperidine was reexamined in 1977 by Stork and Kreft.³⁷ They felt that this was necessary because of the continued interest in S_N2' reactions and the availability of better analytical methods. In this study R was isopropyl. Under the same conditions used earlier they found that a 10:4 mixture of syn and anti products had been formed. An incomplete reaction between these reagents gave

a more consistent 10:1 ratio of these products. Since the longer reaction increased the amount of anti product formed, they examined the unreacted ester from that reaction to see if it had rearranged. They found 20% of the remaining ester had rearranged. They concluded that the anti product was being formed by an S_N2 reaction on the rearranged ester.

They then examined the mesitoyl ester 14 and found that neither it nor its S_N2 products with piperidine rearranged after heating for 24 h at 130 °C. The S_N2' reaction provided



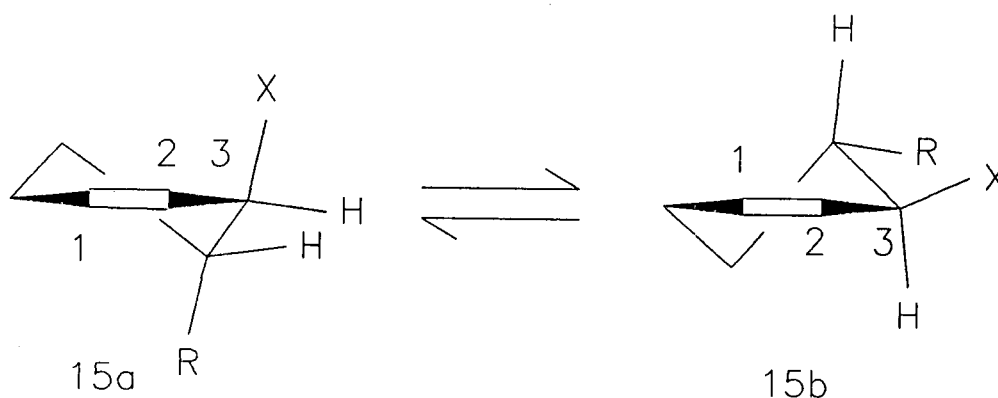
a 98% yield of the syn product and 2% of the anti isomer. The S_N2' product from the cis isomer of 14 was entirely the syn isomer. A moderate (20%) amount of the S_N2 product was formed as well. This rules out a common intermediate in the reactions of cis and trans 14. It also indicates that product stability has little to do with determining the product stereochemistry.

Stork and Kreft³⁷ also examined the reactions of 13 and 14 with sodium propylthiolate. The syn product was predominant once again with 13 but the syn/anti ratio depended on the solvent used. In butanol the ratio was 9:1 and in hexamethyl-

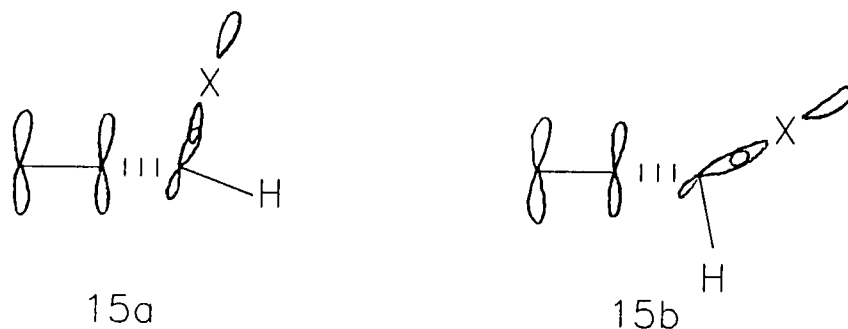
phosphoramidate (HMPA) it was 3:2. With compound 14 in butanol the ratio was actually 1:2.

The reaction of 13 with piperidine was also examined by Dobbie and Overton.⁵⁹ Their results agreed with those obtained by Stork and Kreft above. They concluded that the S_N2' mechanism occurs with 100% syn attack. Any anti product was thought to have formed by rearrangement of the ester followed by S_N2 attack.

As the 1956 study by Stork and White^{36b} has served as the favored proof of syn stereospecificity in S_N2' reactions it should be examined carefully. As stated earlier Toromanoff believed the cyclohexenyl system should favor syn attack.⁴⁵ He based his argument on an analysis of torsional angle

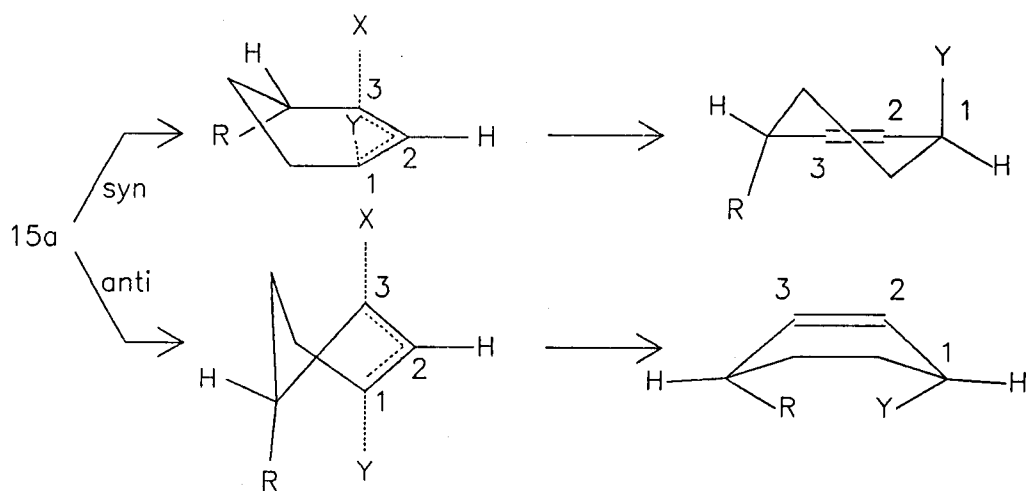


strain. Magid has also pointed out that the cyclohexenyl system possesses an inherent bias towards syn attack.^{3c} The esters used by Stork and White (see Eq. 15, p. 25) exist as a pair of equilibrating half-chair conformers, 15a and 15b, which are present in comparable amounts.^{3c} As stated by the Curtin-Hammett principle, the amount of product arising from either of the rapidly equilibrating conformers does not depend upon their relative populations.⁶⁰ Rather it should depend upon which conformer better facilitates the movement of the π -bond. As the S_N2' mechanism requires migration of the π -bond from between C-1 and C-2 to between C-2 and C-3, overlap between the p-orbital at C-2 and the sp^3 orbital between C-3 and X (the forming p-orbital) should favor this mechanism.



Partially redrawn conformers 15a and 15b show these orbitals. It is clear that greater overlap occurs in conformer 15a.

Syn and anti attack on conformer 15a lead to the transition states and products shown below in equation 17. Syn attack proceeds through a half-chair-like transition state to a product that is in a half-chair conformation. Anti attack leads to boat-like structures. While the boat product of anti



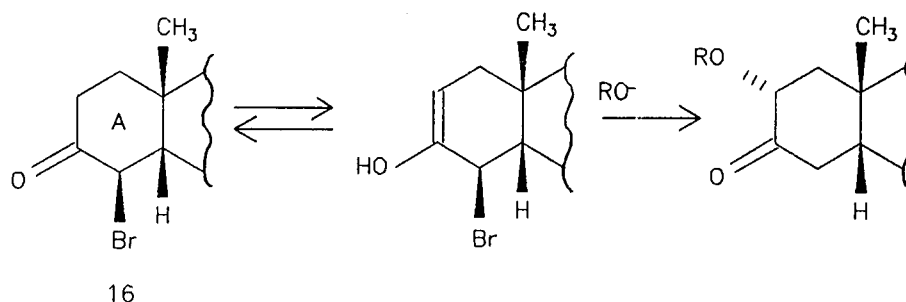
Equation 17

attack will rotate into a more stable half-chair conformation it is the relative stability of the transition states which determines the path the reaction will take. Clearly this conformation favors syn attack.

Stork and White, however, felt that conformation 15b was favored in the equilibrium mixture.^{36b} In conformation 15a the R group is axial. If this is the major conformation involved in the reaction then increasing the size of R from a methyl group to a *t*-butyl group should slow down the reaction. What they actually found was that the rate increased slightly with both nucleophiles. They felt that the lesser degree of orbital overlap in conformation 15b was compensated for by its being the more stable conformation. (However, calculations by Magid have shown that the stabilities of the two conformations are roughly equal^{3c}.) They also noted that the halocodides, which are fixed in a conformation like 15b,

easily undergo S_N2' reactions. This information, however, needs to be compared to reactions of compounds fixed in a 15a-like conformation before any conclusions can be drawn on which direction of attack is stereoelectronically preferred.

Since 1970 many experimental studies have been carried out on the stereochemistry of the S_N2' reaction. These can be divided up into groups based on whether the reaction is inter- or intramolecular and whether the substrate is cyclic or not. One early example of an intermolecular S_N2' reaction on a cyclic substrate is seen in a 1970 study by Satoh and Takahashi.⁶¹ They stated that the reaction of potassium acetate with 4 β -bromo-5 β -cholestane-3-one 16 proceeded through an anti S_N2' mechanism. The A ring of the active enol form of this

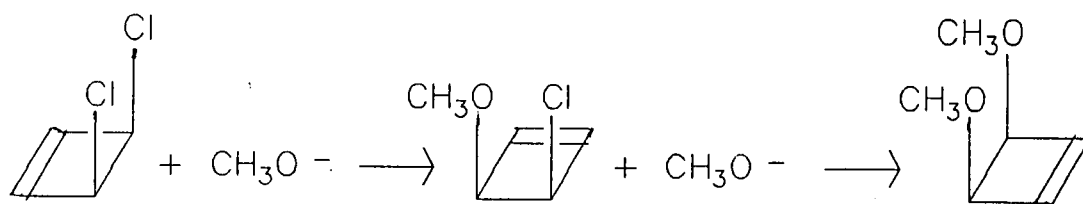


Equation 18

compound is shown. The initial product is the 2 α -acetoxy isomer. Depending on the exact nucleophile and the solvent used, this compound was not isolable but would rapidly rearrange to the 2 β form. The assignment of the mechanism for this reaction lacks much proof. The kinetics of the reaction were not determined and allylic rearrangement of the

bromide was not ruled out. The apparent occurrence of anti attack in this reaction may also be explained by a simple S_N2 attack on the rearranged bromide or by the massive steric bulk of the molecule.

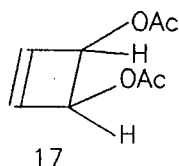
A cyclobutenyl system was studied by Kirmse *et al.*³⁹ Two moles of sodium methoxide were found to react with *cis*-3,4-dichlorocyclobutene. The final product was exclusively the



Equation 19

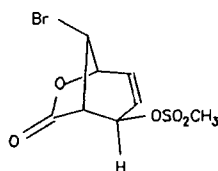
one which would form from successive syn S_N2' displacements. The existence of the syn S_N2' mechanism was established by following the reaction of the 3,4-dideuterio isomer. No vinylic peaks were seen in the NMR spectrum of the product from this isomer and no rearrangement of the starting material occurs. This result disagrees with Toromanoff's theories⁵¹ and is the opposite of what one would expect to see if steric effects were the controlling factor.

A similar occurrence was noted by Houk and co-workers in the 1,5-dipolar addition reaction between *cis*-3,4-diacetoxy



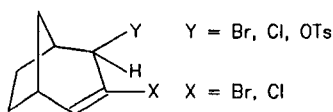
cyclobutene (17) and benzonitrile oxide.⁶² Syn attack was preferred even though the transition state involves electrostatic repulsion between the substrate oxygens and the incoming group. STO-3G molecular orbital calculations on *cis*-3,4-difluorocyclobutene indicate that the sp^2 carbons are slightly pyramidalized, moving the double-bond hydrogens away from the fluorines. This anti bending, which is favored over syn bending by one kcal/mole, should hinder attack anti to the fluorines. A similar effect may also operate with 17 and with Kirmse's compound. Thus the observed preference for syn attack in Kirmse's experiment may be due more to the characteristics of the substrate than to the nature of the reaction. Houk also points out that the syn preference increases as the cycloaddend in 1,3-dipolar additions becomes more nucleophilic but that steric factors can outweigh this preference.

Several bicyclic systems have also been studied. Ikota and Ganem acetolyzed the allylic mesylate 18 with LiOAc in HMPA. The only product was that resulting from syn S_N2' displacement.⁶³ The starting compound was found not to rearrange under the conditions of the reaction and second



Compound 18

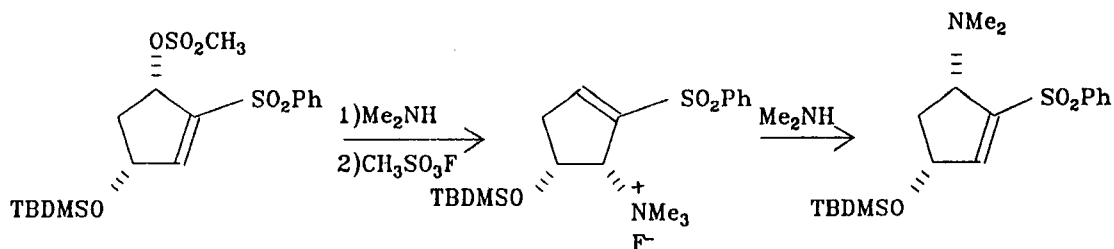
second order kinetics were observed. They argued that a synchronous S_N2' reaction best explained these results and stated that this reaction meets Bordwell's criteria for a genuine concerted, bimolecular, four-bond process. Maskill and Wilson also reported exclusive syn S_N2' attack in the



Compound 19

hydrolysis of 19.⁶⁴ Both of these reactions take place on the exo face of the molecules. The syn preference observed may, therefore, be due to the fact that there is less steric crowding on the exo face of these molecules than on the endo face.

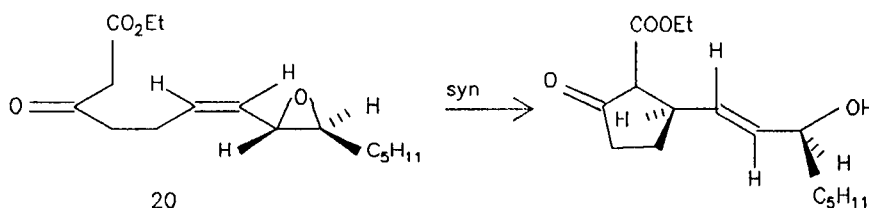
A total synthesis performed by Donaldson and Fuchs⁶⁵ involved two consecutive S_N2' reactions on a cyclopentenyl substrate (Eq. 20). In the first reaction dimethylamine displaces a mesylate group. After methylation the resulting trimethylammonium group is displaced by a second mole of dimethylamine. In both reactions only the syn product was seen. This is evidence that interactions between the nucleophile and the nucleofuge do not always outweigh the stereo-electronic preference of a reaction. This should be taken with a grain of salt, however, as conformational requirements may have forced syn attack once again.



Equation 20

Fuchs and co-workers recently accomplished a similar synthesis with a cyclohexenyl system. Once again syn product was formed exclusively.⁶⁶ The inherent bias of these systems may well have been the cause of this preference.

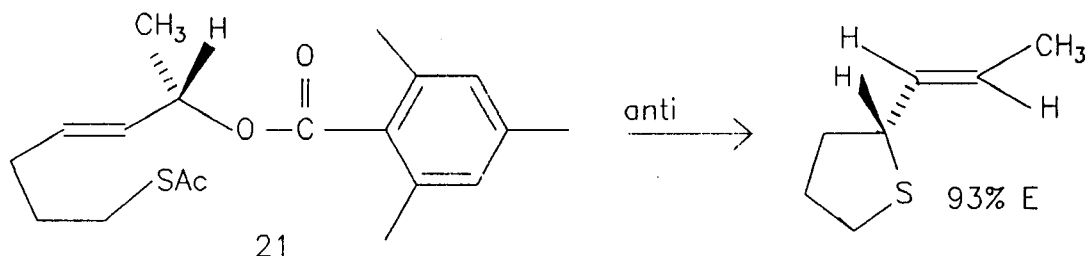
Many groups have studied intramolecular displacements. In 1972 and 1978 Martel and co-workers^{45a,67} treated compound 20



Equation 21

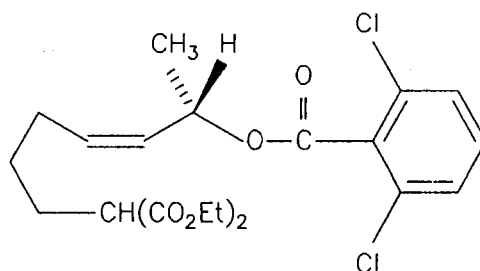
with pyrrolidine, sodium amide and then water. Only the syn product was formed.

Stork and Kreft followed up on this study in 1978 by cyclizing optically pure 7-acetylmercapto-3-hepten-2-yl mesitoate (21) under basic conditions.⁶⁸ This yielded a mixture of *E*- and *Z*-2-propenyltetrahydrothiophene. Virtually 100% anti attack was indicated by the optical purity and absolute configuration of the product.



Equation 22

Due to the observance of opposite modes of attack in these two studies Stork and Schoofs examined the cyclization of compound 22 below.⁶⁹ It was hoped that use of a nucleophile like Martel's and a nucleofuge like Stork's would provide



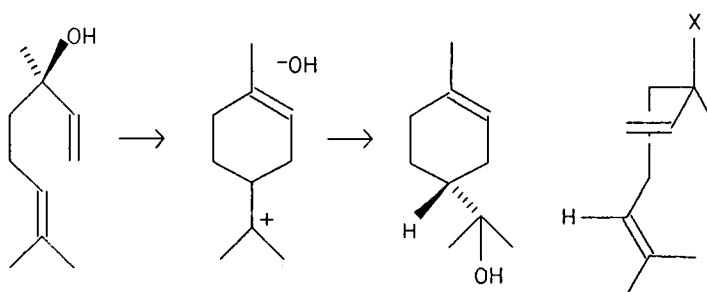
results which would allow them to determine the cause of the different preferences in these two reactions. This compound also led to anti cyclization. The syn preference of compound 20 was, therefore, attributed to the nucleofuge. Stork proposed chelation of the epoxy oxygen by the nucleophile's counterion as the specific cause.

These reactions allowed stereospecific synthesis of tetrahydrothiophene and cyclopentane systems. In a separate study Stork and Poirier attempted to synthesize optically

active tetrahydrofurans and pyrrolidines.⁷⁰ The tetrahydrofurans can be synthesized if the acetylmercapto group of compound 21 is replaced by an alkoxy group, the pyrrolidines if a methylamino group is substituted. Unfortunately the basic conditions of the reaction as well as the poor nucleophiles involved resulted in almost complete racemization of the products. A slight anti preference was noted here. It was also found that this preference could be reversed and, in the case of the alkoxy anion, greatly improved by the addition of palladium (as $(\text{Ph}_3\text{P})_4\text{Pd}$).

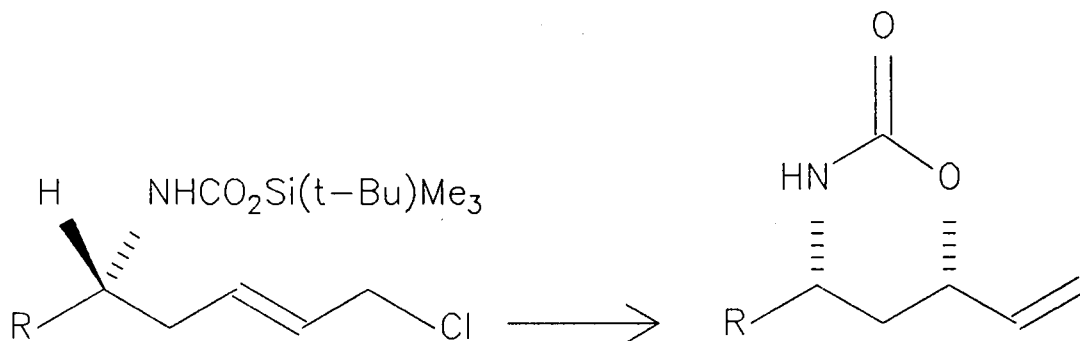
Bäckvall *et al.*³⁸ found a carbanion nucleophile which ejects an ester leaving group in a syn fashion rather than anti as was observed by Stork and Schoofs. The syn preference was about 95% for both compounds.

Cori *et al.* examined the reactions of several terpenoid compounds and found one, linalool, which underwent an anti



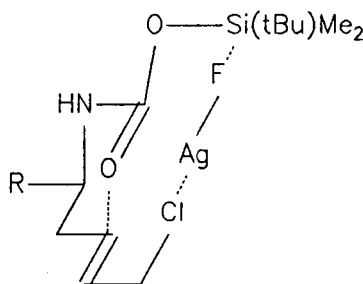
Equation 23

S_N2' reaction to form α -terpineol.⁷¹ Sakaitani and Ohfuné examined the intramolecular reaction shown below. The



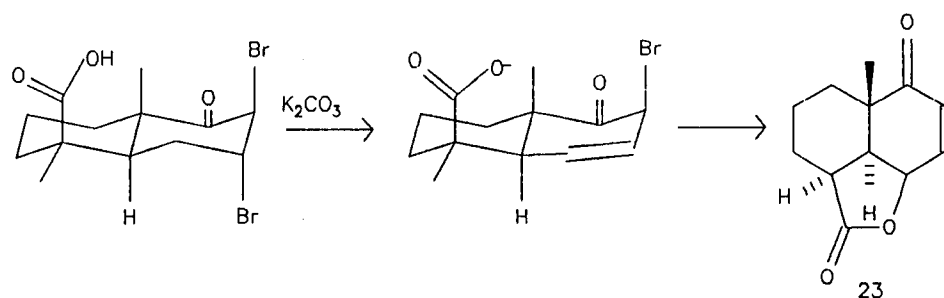
Equation 24

reaction is catalyzed by AgF or tetra-(*n*-butyl)-ammonium fluoride. Only the *E* isomer shown reacts in this fashion.

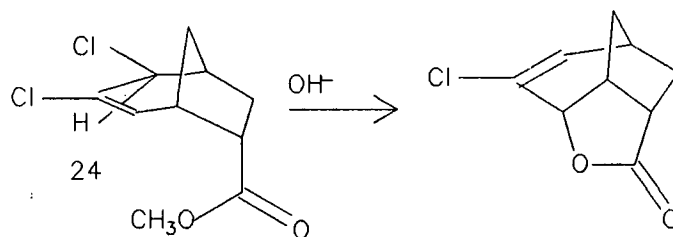


This has led to the proposal of the transition state shown above which would not be available to the *Z* isomer. The product is what would be expected from syn attack. No attempt was made to determine either the kinetics of the reaction or the existence of any rearrangements.⁷²

Welch *et al.* used a syn S_N2' reaction in the synthesis of compound 23.^{45b} Of course this reaction could not have occurred in an anti fashion. Schomburg and Landry found an

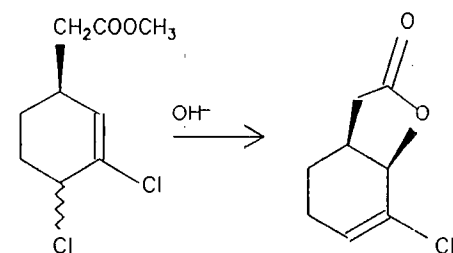
**Equation 25**

example of anti displacement when compound 24 was subjected

**Equation 26**

to basic hydrolysis.⁷³ Here the syn reaction is impossible.

Chiche *et al.* studied the relative rates of cyclization of *cis*- and *trans*-25.⁷⁴ These compounds undergo syn and anti



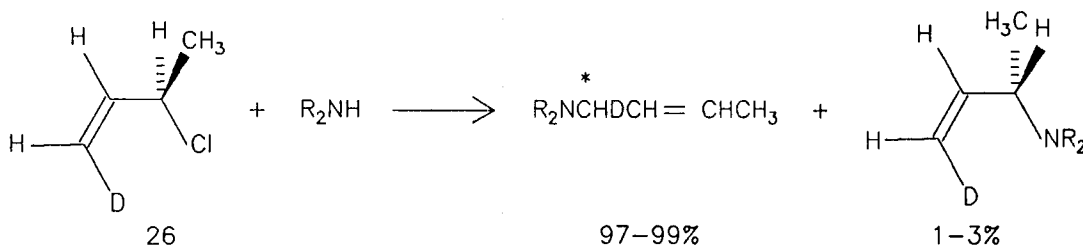
25c and 25t

Equation 27

cyclization respectively with relative rates of 1 and 0.004 in aqueous acetone with or without pyridine. In order for

Welch's and Schomburg's work to have much significance the rates with which their compounds react should be compared with those of the isomers which would force the opposite mode of attack.

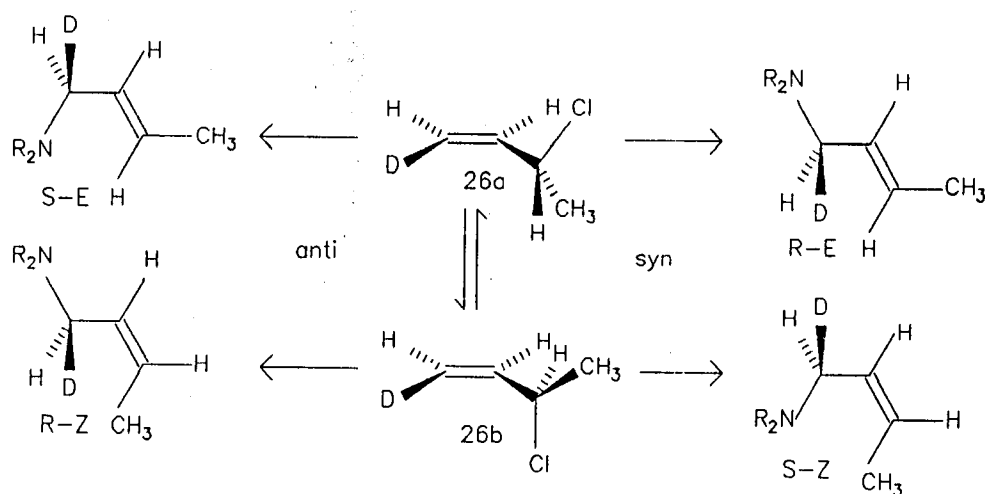
As illustrated above, S_N2' reactions involving cyclic substrates or intramolecular attack possess inherent biases which cloud the issue of syn/anti preference. These reactions have shown synthetic utility however. Very few reactions involving intermolecular attack on an acyclic substrate have been studied. Magid and Fruchey carried out a "very clever"^{27b} study of the reaction of (*R*)-(-)-3-chloro-1-butene-(*Z*)-1-*d* (26) with several secondary amines.^{3b} These reactions were



Equation 28

found to give between 97 and 99% syn S_N2' product with the remainder being the S_N2 product. They did not examine the kinetics of the reaction or the stability of either the product or the reactant as this had been done earlier on the racemic, non-*d* chloride by Young *et al.*¹⁸

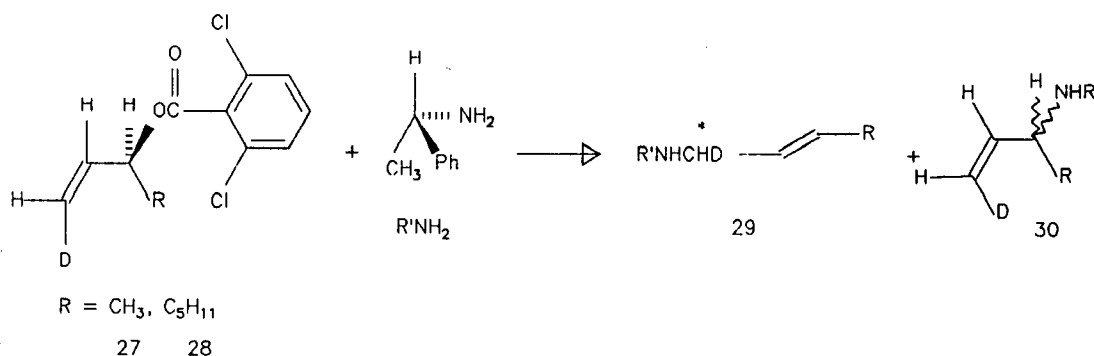
As shown in equation 29 below there are two reactive conformations for 26. Syn attack results in the formation of



Equation 29

(*R*)-*N*-(*E*)-2-buten-1-yl-1-*d* dialkylamine and/or the *S*-*Z* isomer. Likewise, anti attack will form the *S*-*E* and/or *R*-*Z* isomers. The S_N2' product with diethylamine was found to be a 95:5 mixture of *E* and *Z* isomers. As the syn/anti ratio should be identical for both conformations, the *E*/*Z* ratio signifies a maximum optical purity for the reduced compounds of 90% (if the reaction is 100% stereospecific). The optical purity of the reduced mixture was found to correspond to 96% syn displacement (several other corrections were also included). Dimethylamine and piperidine showed 95% and 99% syn displacement.

A similar study was carried out by Oritani and Overton.⁷⁵ They treated two optically pure, deuteriated esters, 27 and 28, with optically pure 1-phenylethylamine. The two major products were the S_N2' product 29 and the S_N2 product 30 formed in a 4:1 ratio. The S_N2 product did not undergo further



Equation 30

reaction with 1-phenylethylamine nor did the esters rearrange (unlike those used by Stork^{36b}) during the reaction or following 48 h of reflux in xylene (or xylene with three equivalents of 2,2,2-trifluoroethanol). The results, as determined by the NMR spectrum of the product mixture taken in the presence of $\text{Eu}(\text{dpm})_3$, showed only 60% syn attack instead of the 97% seen by Magid and Fruchey. Oritani and Overton said that hydrogen bonding of the amino hydrogen with the chloride leaving group would be more effective in creating a syn transition state than it would with the ester leaving group.

Another possible explanation of these results was put forth by Whiting.⁷⁶ He said that polarity differences between the primary amines used by Oritani and Overton and the secondary amines used by Magid and Fruchey could have effected the change. The syn/anti ratio may also have been affected by the concertedness of the two reactions. That is, the better leaving group used by Oritani and Overton may result in the involvement of an ion-pair mechanism which would reduce the stereospecificity of the reaction.²⁵

Georgoulis and Ville studied the ethanolysis of (*R*)-(-)-3-chloro-1-butene-(*Z*)-1-*d* and (*E*)-(*R*)-(-)-3-chloro-1-butene-1,2-*d*₂.⁷⁷ Although the S_N2 reaction is predominant, a 38% yield of the S_N2' products was obtained. They indicated that 94 or 95% of the S_N2' product was formed by syn displacement on the two halides. The reaction is of course pseudo-first order. The possibility of substrate or product rearrangements was not studied.

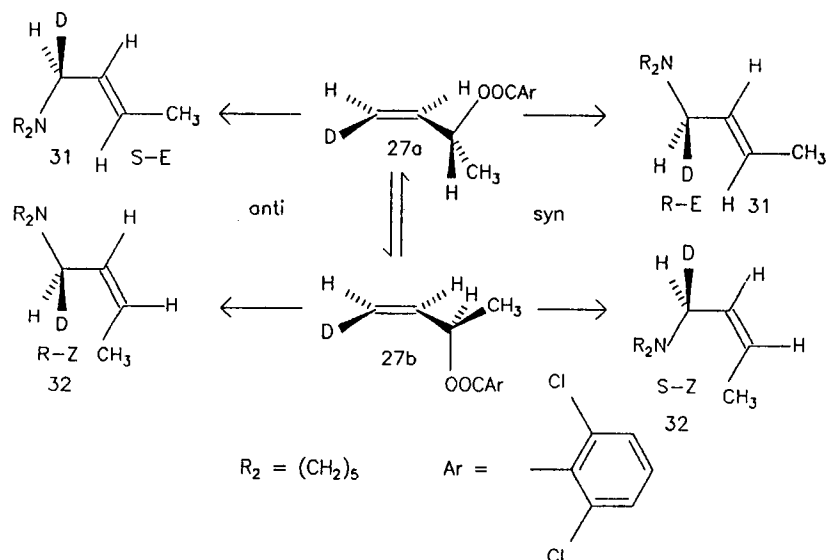
C. Statement of the Problem

An overwhelming majority of the studies carried out on modes of preferential attack in S_N2' reactions involve cyclic and/or intramolecular systems. The inherent conformational biases which they possess makes the usefulness of the information gained thereby doubtful. Few studies of acyclic, intermolecular S_N2' reactions have been carried out. The results obtained have often been contradictory. Acyclic compounds based on a 3-nucleofuge-1-butene pattern have been studied by Magid's^{3b} and Overton's⁷⁵ groups. Although both groups found syn attack to be favored, the degree to which it was favored differed. As both the nucleophile and the nucleofuge differed in these two studies it is impossible to ascribe the observed difference to a single cause, or multiple causes, with a great deal of certainty.

This work shall examine the reactions between one of the esters used by Oritani and Overton (27) and one of the

nucleophiles used by Magid and Fruchey. By reducing the number of variables, the possibility of determining the cause of the syn/anti preference should be increased. Since the reactions between piperidine and cyclohexenyl ester 13³⁶ (Eq. 15, p. 25) or 3-chloro-1-butene^{3b} and those between 27 or 28 and α -phenylethylamine⁷⁵ are all second order, the reaction under study was assumed to be second order as well. Young and Wilk^{19b} showed that the S_N2 product does not rearrange and Overton⁷⁵ detected less than 3% rearrangement of the ester. Studies on similar esters, however, noted greater amounts of rearrangement.^{12c,37} Because of this, tests have been run to determine if 27 would rearrange under the conditions used.

In order to interpret the results of this reaction it is necessary to know what products can be formed and how they are



Equation 31

formed. There are two reactive conformations available to the ester. These are shown above for the R enantiomer. Syn attack would lead to the R-E and S-Z isomers while anti attack would lead to the S-E and R-Z isomers. Once the E/Z ratio is determined the double bond will be reduced and the optical purity and absolute configuration determined. With the additional information of the amount of deuterium labeling and the percent enantiomeric excess (% ee) of the ester, the syn/anti ratio of this reaction can be determined.

As a check, an attempt will be made to synthesize the final tertiary amine by an alternate route through a compound of known absolute configuration and enantiomeric purity.

CHAPTER III

EXPERIMENTAL SECTION

A. General Considerations

The success of several of the experiments carried out in this study required anhydrous, inert media. For these reactions the glassware was dried by heating it for several hours in an oven at or above 120 °C. When removed from the oven it was assembled while still hot and, while cooling, it was flushed with a pre-dried, inert gas (either Ar or N₂) to prevent condensation of atmospheric moisture.

Air-sensitive reagents, especially butyllithium and Alpine-Borane®, were handled with extreme care. Transfers were accomplished by means of syringes or double-ended needles which had also been dried as described above and/or flushed with an inert gas.

Solvents for these reactions were also pre-dried. Methods varied according to the solvent and included distillation from Na/benzophenone (THF, ether), distillation from NaOH (ether), washing with H₂SO₄ (pentane), and the use of hygroscopic solids (e.g. MgSO₄).

Three NMR instruments were employed for this research: a Varian T-60 (60 MHz) for routine identifications, a JEOL FX-90Q (90 MHz) instrument for more precise identifications and

the isomerization check, and a Nicolet NT-200 (200 MHz) instrument for ultimate peak assignments and determination of coupling constants. For the T-60 the solvent used was CCl_4 . The other instruments required a deuteriated solvent; CDCl_3 was used. The internal standard in all cases was TMS.

Two instruments were used to obtain optical rotation measurements. Early measurements were taken on a Rudolph Instruments MP7A41 polarimeter. Few of these readings are included in this report. Most optical measurements reported herein were obtained on a Perkin-Elmer 241 spectrophotometer.

Analytical GC determinations were carried out with a Hewlett-Packard 5750 chromatograph equipped with a Leeds and Northrup Speedomax XL601 recorder or a Houston Instrument OmniScribe (tm) recorder. The instrument was operated with a He carrier gas flow rate of 45 mL/min. Columns were constructed from 10' of 1/8" outside diameter stainless steel. The support used was Chromasorb W (80-100 mesh). Specifications were sometimes varied and are noted where appropriate.

The following analytical columns were used:

- A 15% Carbowax 20M/2.5% KOH
- B 30% Carbowax 20M/5% KOH
- C 10% Carbowax 20M
- D 10% SE-30

Preparative GC separations were carried out on a Varian Aerograph 920 chromatograph equipped with a Speedomax H recorder. Changes from conditions for analytical determina-

tions include increasing the carrier gas flow rate to 60 mL/min, using 1/4" outside diameter aluminum tubing and using 45-60 mesh Chromasorb W as the solid support.

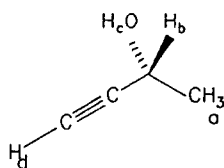
The following columns were used:

E	15% Carbowax 20M
F	20% Carbowax 20M/5% KOH, 12'
G	30% Carbowax 20M/5% KOH
H	10% SE-30, 6'
I	30% SE-30/5% KOH
J	15% Carbowax 20M/5% KOH

Conditions for several reactions involving deuteriated and/or optically active compounds were worked out on their non-deuteriated and/or racemic counterparts. Distillations were performed at atmospheric pressure unless stated otherwise.

B. The Synthesis of (R)-(+)-N-1-Piperidylbutane-1-d

1. Synthesis of (R)-(+)-3-butyn-2-ol (33)⁷⁸



Compound 33

A 2-liter, three-necked, round-bottomed flask was fitted for distillation. An addition funnel was also attached. The receiving flask had a gas inlet. The glassware was assembled

hot and all openings were plugged with rubber septa. The setup was then flushed with dry Ar to remove all traces of water and oxygen.

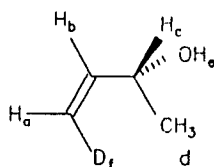
The contents of one bottle (800 mL, 0.4 mol) of 0.5 M (*R*)-Alpine-Borane® (*B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane) in THF (Aldrich) was placed in the distillation flask by means of a double-ended needle. The solvent was then removed by vacuum distillation. (This reaction was also carried out without removing the THF at this point. Similar yields were obtained but more time (ca. 7 days) was required.) A syringe was then used to place 23.82 g (0.350 mol) of 3-butyn-2-one into the addition funnel. It was then dripped into the Alpine-Borane® over the next 20 min and allowed to react overnight (18 h). The THF, which had been distilled earlier, was removed from the receiving flask at this time. This was done by syringe to prevent water and oxygen from entering the reaction vessel.

The solution was then cooled to 0 °C and 26.54 g (0.250 mol) of benzaldehyde was placed in the addition funnel by syringe. Approximately 10 min were allowed for this to drip into the Alpine-Borane® solution. The benzaldehyde reacts with any remaining Alpine-Borane®, liberating the (1*R*)-(+)- α -pinene. The solution was stirred for 30 min and then vacuum-distilled to remove the (1*R*)-(+)- α -pinene. After diluting the solution with 160 mL of dry (CaCl₂) ether, ethanolamine (34.20 g, 0.560 mol) was added to the borane complex slowly through

the addition funnel to release the alcohol. A large amount of precipitate formed as this was done.

The solution was then filtered twice through a celite-covered coarse-frit funnel. The solids were rinsed with ether and acetone until all of the dark color had been removed from them. The organic solutions were combined and dried over K_2CO_3 .

The combined solution was then distilled. Large glassware was used until most of the ether had been removed and then the solution was transferred to a 14/20 size still fitted with a short (10-cm) Vigreux column. The remainder of the ether and the acetone was then removed. The pressure was then reduced to 140 torr and the product was distilled at 55 °C. Analytical GC with column A showed that the product was 89% pure at this stage. The yield was 15.81 g (0.226 mol, 64.5%). The alcohol was then purified by preparative GC using column E. The pure alcohol had $[\alpha]_D^{36} +36.3^\circ$ (c 2.391, dioxane) (lit.⁷⁹ $[\alpha](\text{max}) +52^\circ$, (c 2.3, dioxane). The optical purity is therefore 69.8%. $^1\text{H-NMR}$ ($CDCl_3$) δ 1.475 (d, 3, $J_{ab} = 6.63$ Hz, H_a), 2.467 (d, 1, $J_{bd} = 2.11$ Hz, H_d), 2.7 (br s, 1, H_c), 4.536 (dq, 1, $J_{bd} = 2.10$ Hz, $J_{ba} = 6.62$ Hz, H_b).

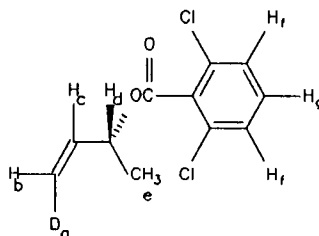
2. Synthesis of (R)-(-)-3-buten-2-ol-(Z)-4-d (34)^{3b,80}**Compound 34**

A 500-mL, three-necked, round-bottomed flask was fitted with a magnetic stirring bar and an addition funnel. All openings were plugged with rubber septa and the setup was flushed with Ar or N₂ for 30 min. THF (100 mL, freshly distilled from Na/benzophenone) and (R)-(+)-3-butyne-2-ol (7.50 g, 107 mmol) were placed in the flask by syringe. This solution was cooled in an ice bath, and lithium aluminum hydride (LAH) (75 mL of 1.0 M in THF, 75 mmol) was syringed into the addition funnel. The LAH solution was dripped into the alcohol solution over 50 min. (Reverse addition was utilized in order to prevent over-reduction.) The alcohol solution bubbled and became cloudy. It was stirred overnight and allowed to come to room temperature.

The flask was cooled to 0 °C again while D₂O (12.87 g, 643 mmol) and 50 mL of THF were placed in the addition funnel by syringe. The D₂O was then added, with much gas evolution, to the flask over 90 min. Precipitates formed during this addition. These were filtered out with a celite covered coarse-frit funnel and the resulting solution was dried overnight with powdered molecular sieves.

The solution was then distilled to remove the ether and most of the THF. A 60.7% yield (4.75 g, 65 mmol) of **34** was obtained. A portion of this was purified by preparative GC with column F and used to determine enantiomeric excess (% ee): α_D^{30} -1.660° (neat, $l = 0.1$), α_{365}^{30} -5.979° (neat, $l = 0.1$), $[\alpha]_D^{30}$ -19.97° (lit⁸¹ $[\alpha](\text{max}) = -33.2^\circ$, neat). This is equivalent to a 60.1% ee. $^1\text{H-NMR}$ (CDCl_3) δ 1.28 (d, 3, $J_{cd} = 6.42$ Hz, H_d), 1.81 (br s, 1, H_e), 4.30 (ddq, 1, $J_{cb} = 5.75$ Hz, $J_{ca} = 1.21$ Hz, $J_{cd} = 6.42$ Hz, H_c), 5.05 (dd, 1, $J_{ab} = 10.41$ Hz, $J_{ac} = 1.21$ Hz, H_a), 5.91 (ddt, 1, $J_{ba} = 10.41$ Hz, $J_{bc} = 5.75$ Hz, $J_{bf}(\text{D}) = 2.61$ Hz, H_b). Less than 3% of the E isomer and the non-deuteriated alcohol was present.

3. Synthesis of (*R*)-(+)-3-buten-(*Z*)-4-*d*-2-yl 2,6-dichlorobenzoate (**27**)



Compound 27

According to the method of Kopecky and Levine⁸² a three-necked, 500-mL, round-bottomed flask with a gas inlet was fitted with an addition funnel, condenser, magnetic stirring bar and an inert gas (N_2 or Ar) line. A 50% NaH/mineral oil suspension (9.6 g, 200 mmol) was placed in the flask and washed a few times with THF (freshly distilled from Na/benzo-

phenone) while flushing with the inert gas. The setup was then flushed with inert gas for an extra 15 min.

(R)-(-)-3-buten-2-ol-(Z)-4-d (2.88 g, 40 mmol) was dissolved in 10 mL of THF and placed in the addition funnel. This solution was added to the NaH at a rate which allowed a gentle reflux to occur. 2,6-Dichlorobenzoyl chloride (9.22 g, 44 mmol) was then placed in the addition funnel along with 40 mL of THF. After cooling the flask to -10 °C the acid chloride solution was added to it over 30 min. The cooling bath was then removed and the solution was stirred for 3 days.

After filtering out the solids the solution was dried with powdered molecular sieves. The solution was concentrated in vacuo and the ester was vacuum distilled (bp 120 °C (2 torr)). A 75.5% yield (7.40 g, 30 mmol) of 27 was obtained: α_D^{25} 0.134° (neat, $l = 0.01$); α_{365}^{25} 0.414° (neat, $l = 0.01$); $^1\text{H-NMR}$ (CDCl_3) δ 1.47 (d, 3, $J_{ed} = 6.50$ Hz, H_e), 5.21 (dd, 1, $J_{bc} = 10.54$ Hz, $J_{bd} = 1.19$ Hz, H_b), 5.68 (ddq, 1, $J_{dc} = 5.83$ Hz, $J_{db} = 1.19$ Hz, $J_{de} = 6.50$ Hz, H_d), 5.94 (ddt, 1, $J_{cb} = 10.53$ Hz, $J_{cd} = 5.83$ Hz, $J_{ca}(D) = 2.63$ Hz, H_c), 7.24 (m, 2, H_g), 7.28 (m, 1, H_f). Using the 60.1% ee found for the alcohol used and assuming 100% retention of configuration in this synthesis, gives $[\alpha]_D^{25} +18.6^\circ$ and $[\alpha]_{365}^{25} +57.4^\circ$ (maxima).

4. Reaction of (27) with piperidine

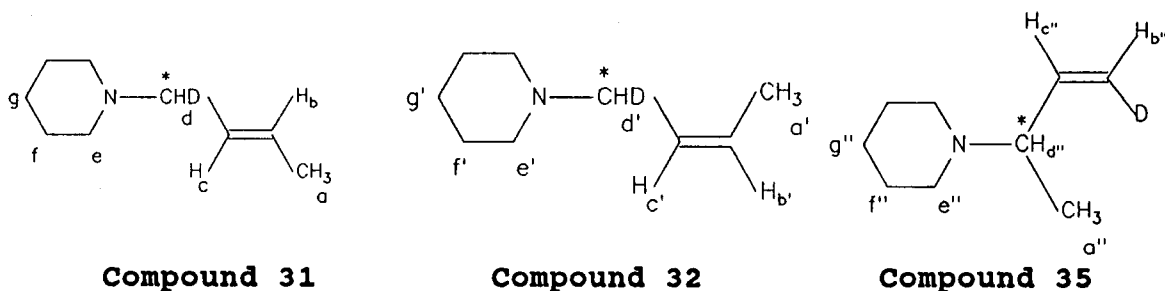
Piperidine (15.00 g, 176.2 mmol) and 27 (8.00 g, 32.5 mmol) were combined in a 50-mL round-bottomed flask fitted with a condenser and magnetic stirring bar and refluxed for

7 days. The solution started out slightly yellow and gradually turned brown even when refluxed at low heat under Ar.

The solution was cooled and some precipitates formed. These dissolved upon addition of 50 mL of 5 N NaOH. The resulting aqueous layer was washed twice with 25-mL portions of ether. The combined organic layers were dried with MgSO_4 and powdered molecular sieves.

The solution was then concentrated in vacuo and distilled under aspirator vacuum. A few times the solution "gummed up" after a small portion of the amine had been distilled. When this occurred the solid was dissolved in 5 N NaOH and this aqueous solution was extracted with ether. The ether layer was then dried and distilled as above.

After the ether was removed the piperidine (bp 30 °C) and the product (bp 72-8 °C) were distilled at reduced pressure (60 mm). The product was purified by preparative GC (column G) to provide 0.524 g (3.74 mmol, 11.5% yield) of *E*- and *Z*-1-piperidyl-2-butene-1-*d* (31 and 32) and 0.130 g (0.93 mmol,



2.86% yield) of (*S*)-(-)-3-piperidylbut-1-ene-(*Z*)-1-*d* (35): *E/Z* mixture: α_D^{24} 0.008° (neat, $l = 0.01$) and α_{365}^{24} 0.028° (neat, l

= 0.01); 35 α_{D}^{24} 0.049° (neat, ℓ = 0.01) and α_{365}^{24} 0.302° (neat, ℓ = 0.01); $^1\text{H-NMR}$ (CDCl_3) 31 and 32: δ 1.4 (m, 2, H_g and $\text{H}_{g'}$), 1.6 (m, 4, H_f and $\text{H}_{f'}$), 1.685 (dd, 3, J_{ab} = 4.84 Hz, J_{ac} = 1.01 Hz, H_a and $\text{H}_{a'}$), 2.36 (br t, 4, H_e and $\text{H}_{e'}$), ca. 2.8 (br m, 1, H_d), ca. 2.9 (br m, 1, $\text{H}_{d'}$), 5.6 (m, 2, H_b , $\text{H}_{b'}$, H_c , and $\text{H}_{c'}$); 35: δ 1.150 (d, 3, $J_{a''d''}$ = 6.63 Hz, $\text{H}_{a''}$), ca. 1.43 (m, 2, $\text{H}_{g''}$), ca. 1.58 (m, 4, $\text{H}_{f''}$), 2.44 (m, 4, $\text{H}_{e''}$), 2.913 (dq, 1, $J_{d''c''}$ = 7.70 Hz, $J_{d''a''}$ = 6.63 Hz, $\text{H}_{d''}$), 5.046 (dd, 2, $J_{b''c''}$ = 10.31 Hz, $J_{b''d}$ = 0.80 Hz, $\text{H}_{b''}$), 5.808 (ddt, 1, $J_{c''b''}$ = 10.27 Hz, $J_{c''d''}$ = 7.70 Hz, $J_{c''d}$ = 2.57 Hz, $\text{H}_{c''}$). $^{13}\text{C-NMR}$ (CDCl_3) 31 and 32: δ 13.068, $\text{C}_{a'}$; 17.765, C_a ; 24.439, C_g and $\text{C}_{g'}$; 25.976, C_f and $\text{C}_{f'}$; 54.374, C_e and $\text{C}_{e'}$; ca. 55 (m, 1, $\text{C}_{d'}$); 61.330 (t, 1, J_{db} = 18.6 Hz, C_d); 126.684 and 127.216, $\text{C}_{b'}$ and $\text{C}_{c'}$; 127.960 and 128.517, C_b and C_c ; 35: δ 17.040, $\text{C}_{a''}$; 24.679, $\text{C}_{g''}$; 26.291, $\text{C}_{f''}$; 50.750, $\text{C}_{e''}$; 63.354, $\text{C}_{d''}$; 114.740, (t, 1, J = 23.6 Hz, $\text{C}_{b''}$); 140.775, $\text{C}_{c''}$.

Analysis of the $^{13}\text{C-NMR}$ spectrum of the mixture of 31 and 32 indicated that the E/Z ratio was 87.3/12.7 and the ratio of the $\text{S}_{\text{N}}2'/\text{S}_{\text{N}}2$ products was 73.7/26.3. The complete product mixture was determined to be: E-64.3%, Z-9.4%, and $\text{S}_{\text{N}}2$ -26.3%.

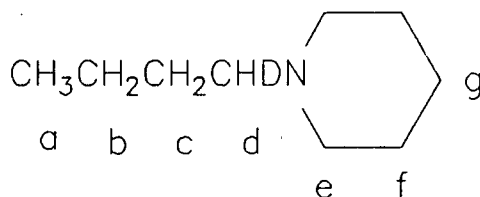
5. Reduction of the double bond of the E/Z mixture^{3b,83}

Half of a solution of 12.17 g (217 mmol) of KOH in 45 mL of water was placed in a 200-mL round-bottomed flask. The solution was stirred as *p*-toluenesulfonhydrazide (20.20 g, 108 mmol; PTSH) was slowly added to it. Each portion of PTSH was allowed to dissolve before another was added. The allylic amine to be reduced (1.014 g, 7.23 mmol) was added to this

clear yellow solution. The rest of the KOH in water was added over the next 10 min and the solution was refluxed for 4 days.

The solution was then cooled and extracted three times with 50-mL portions of ether. The combined organic layers were dried with K_2CO_3 and powdered molecular sieves.

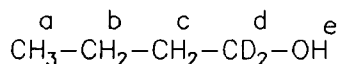
The solution was then concentrated by distilling through a long Vigreux column. The residue (1 mL) was purified by preparative GC (column G) to provide 0.408 g (40% yield) (*R*)-(+)-and (*S*)-(-)-*N*-1-piperidylbutane-1-*d* (36): α_D^{24} 0.022° (neat, $\ell = 0.01$), α_{365}^{24} 0.060° (neat, $\ell = 0.01$), α_D^{24} 0.036° (c



Mixture 36

0.168, ether, $\ell = 0.1$), and α_{365}^{24} 0.117° (c 0.168, ether, $\ell = 0.1$), ^1H -NMR ($CDCl_3$) δ 0.909 (t, 3, $J_{ab} = 7.14$ Hz, H_a), 1.27-1.64 (m, 10, H_b , H_c , H_f , and H_g), 2.247 (tt, 1, $J_{dc} = 7.68$ Hz, $J_{db} = 1.67$ Hz, H_d), 2.364 (m, 4, H_e).

C. Alternate Synthesis of (R)-(+)-N-1-Piperidyl-1-butane-1-d

1. Synthesis of 1-butanol-1,1-d₂ (37)⁸⁴**Compound 37**

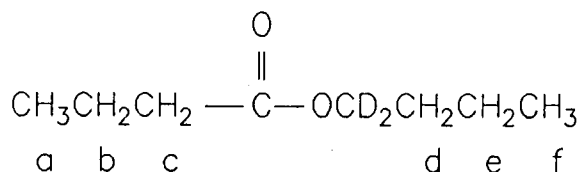
Lithium aluminum deuteride (LAD) (15.00 g, 0.357 mol) was placed in a 500-mL, three-necked, round-bottomed flask which had been oven-dried and flushed with Ar. The flask had been fitted with a condenser, an addition funnel, and a magnetic stirring bar. The LAD was then suspended in 200 mL of dry (Na/benzophenone) ether. Butyryl chloride (64.71 g, 0.607 mol) was dissolved in 150 mL of ether and added to the LAD over 10 h through the addition funnel. After all of the butyryl chloride had been added the solution was stirred for 30 min.

Water was carefully added until the white solution turned gray and the solids clumped together. The solution was then filtered and dried with K₂CO₃. The solids were dissolved in H₂SO₄ and the resulting two-phase solution was distilled. The fraction which came over below 98 °C was kept and dried with K₂CO₃.

The two organic solutions were combined and distilled. Both an azeotrope (bp 92 °C) and a pure fraction of butanol-1,1-d₂ (bp = 116-118 °C) were collected. The azeotrope was

through a short silica gel column. A distinct butanal odor was detected.

The yellow solution was distilled to remove ether until only 35 mL remained. The residue was green, so more ether was added and the resulting precipitates filtered out as above. The solution was then distilled again yielding 3.73 g (51.1 mmol, 68.2% yield) of butanal-1-d: $^1\text{H-NMR}$ (CDCl_3) δ 0.961 (t, 3, $J_{ab} = 7.41$ Hz, H_a), 1.663 (tq, 2, $J_{bc} = J_{ba} = 7.36$ Hz, H_b), 2.407 (t, 2, $J_{cb} = 7.22$ Hz, H_c). No butanol- d_2 or butanal was seen. A fraction which boiled at ca. 160 °C was also collected. NMR indicated that this was deuteriated butyl butyrate: $^1\text{H-NMR}$ (CDCl_3) δ 0.935 (t, 3, $J = 7.18$ Hz, H_f), 0.948 (t, 3, $J = 7.37$ Hz, H_a), ca. 1.4 (m, 2, H_e), ca. 1.6 (m, 4, H_b and d), 2.277 (t, 2, $J_{cb} = 7.37$ Hz, H_c).



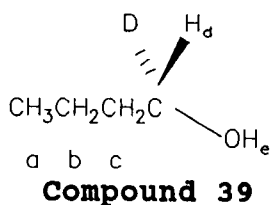
b. Dichromate oxidation

1-Butanol-1,1- d_2 (22.84 g, 0.300 mol) and 85 mL of water were placed in a flask fitted with an addition funnel and magnetic stirring bar and set up for distillation. Potassium dichromate (29.42 g, 0.100 mol) was dissolved in 65 mL of water. Sulfuric acid (22 mL, concd) was then added to this solution which was allowed to cool and placed in the addition funnel.

The alcohol solution was heated until it just began boiling and then the heat was removed. The dichromate solution was added at a rate that just kept the solution boiling. As it was added the solution turned black and a two-phase distillate came over at ~ 84 °C. After all of the dichromate was added heat was reapplied until the distillate reached a temperature of 94 °C.

The acidic distillate was neutralized with Na_2CO_3 , and NaCl was added to ensure separation of phases. The organic layer was removed and dried with Na_2SO_4 . The solution was then distilled through a Vigreux column collecting all that came over below 82 °C. The distillate contained some unreacted alcohol but was mainly the desired butanal-1-*d*: 8.92 g, 124 mmol, 41.2% yield. An additional 6.90 g of the solution was distilled under aspirator pressure. This contained some butanal-1-*d* but was mostly unreacted alcohol and the deuteria-*t*-butyl butyrate seen above.

3. Synthesis of (*S*)-(+)-1-butanol-1-*d* (39)^{78,86}



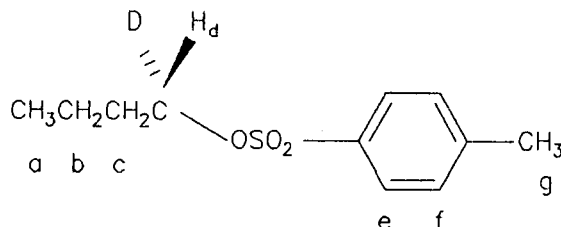
The following glassware was oven-dried overnight, assembled while hot, and then flushed with Ar for 1 hour: 500-mL and 250-mL round-bottomed flasks with side arm, still head,

condenser, vacuum adapter, pressure equalizing addition funnel, ground glass stopper, and magnetic stirring bar. (*R*)-Alpine-Borane® in THF (0.5 M, 492 mL, 246 mmol) was added by cannula and the solvent was removed by vacuum distillation. Argon was readmitted to the apparatus, butanal-1-*d* (10.84 g, 148 mmol) was added, and the solution was stirred overnight.

The solution was then cooled and freshly distilled benzaldehyde (15.47 g, 146 mmol) was added to it. After stirring for 30 min the (1*R*)-(+)- α -pinene was distilled off. The solution was diluted with ether (100 mL) and ethanolamine (20.07 g, 329 mmol) was added. The solution was then stirred for 30 min to allow time for the borane complex with ethanolamine to form. This solid was filtered out and rinsed with ether. The solution was dried overnight with K_2CO_3 . The solution was then distilled to give 4.61 g (61.4 mmol, 41.5% yield) of (*S*)-(+)-1-butanol-1-*d*. (This contained a minimal amount of (1*R*)-(+)- α -pinene.) A sample was purified by preparative GC using Column H: α_D^{25} 0.035° (neat, $l = 1$), $[\alpha]_D^{25}$ +0.435° (neat), %ee = 92.4 $\pm$ 3.6% (lit.⁸⁷ $[\alpha]_D^{27.5}$ +0.471 $\pm$.005°), ^1H -NMR ($CDCl_3$): δ 0.926 (t, 3, $J_{ab} = 7.17$ Hz, H_a), ca. 1.36 (m, 2, H_b), ca. 1.5 (m, 2, H_c), 3.588 (dt, 1, $J_{dc} = 5.72$ Hz, $J_{db} = 1.30$ Hz, H_d), 3.75 (br s, 1, H_e). The ^1H -NMR data are consistent with the presence of a single D on C-1. The ^1H -NMR spectrum of the *O*-acetyl mandelate of 39 indicated 91.3% ee.

4. Synthesis of optically active butyl tosylates

a. (S)-(+)-1-Butyl-1-d *p*-toluenesulfonate (**40**)



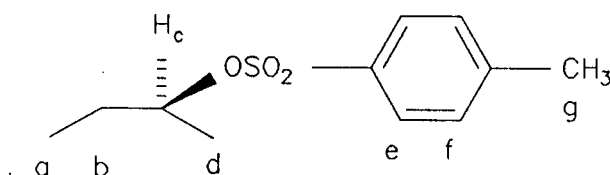
Compound 40

A 200-mL round-bottomed flask was charged with 10.15 g (211.4 mmol) of a 50% NaH/mineral oil suspension. The oil was removed by washing with two 50-mL portions of dry (distilled from Na/benzophenone) THF. Another 50-mL of THF was then added as the solvent. A pressure equalizing addition funnel was connected and the whole apparatus was flushed with Ar for 10 minutes. (S)-(+)-1-butanol-1-d (3.61 g, 48.1 mmol) was dissolved in 25 mL of THF and slowly added to the NaH solution through the addition funnel. The solution was then cooled at 0 °C and *p*-toluenesulfonyl chloride (10.08 g, 52.9 mmol) in 25 mL of THF was slowly added through the addition funnel. The solution was then allowed to come to room temperature.

After stirring for 2 days the solids were filtered off and most of the THF was vacuum distilled off. The residue was purified by eluting it through a column of silica gel with 2% ether/ligroine. After drying the resulting solution with K₂CO₃ the solvent was evaporated. This yielded 7.64 g (33.3 mmol, 69.3% yield) of (S)-(+)-1-butyl-1-d *p*-toluenesulfonate as a

light yellow liquid. At this point the solution contained some mineral oil. It gradually separated out and was removed by pipette. The following optical data were found: α_D^{25} 0.120° (neat, $\ell = 1$), $[\alpha]_D^{25} +0.115^\circ$ (neat), ($d = 1.1319$), $^1\text{H-NMR}$ (CDCl_3) δ 0.850 (t, 3, $J_{ab} = 7.23$ Hz, H_a), ca. 1.3 (m, 2, H_b), ca. 1.6 (m, 2, H_c), 2.439 (s, 3, H_g), 4.005 (tt, 1, $J_{dc} = 6.45$ Hz, $J_{db} = 1.10$ Hz, H_d), 7.344 (2, H_f), 7.789 (2, H_e). The aromatic hydrogens form an AA'XX' pattern.

b. (S)-(+)-2-Butyl *p*-toluenesulfonate (41)

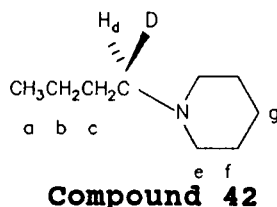


Compound 41

The procedure above was duplicated with (S)-(+)-2-butanol. The following amounts were used: 7.20 g, 150 mmol, 50% NaH/oil; 2.50 g, 33.7 mmol alcohol; 7.07 g, 37.1 mmol *p*-toluenesulfonyl chloride. The reaction was run overnight. After removing the mineral oil by pipette it yielded 3.94 g (17.3 mmol, 51.2% yield) of a light yellow oil: α_D^{22} 1.294° , α_{546}^{22} 1.521° , α_{436}^{22} 2.487° (all neat, $\ell = 1$); $^1\text{H-NMR}$ (CDCl_3) δ 0.804 (t, 3, $J_{ab} = 7.42$ Hz, H_a), 1.235 (d, 3, $J_{dc} = 6.29$ Hz, H_d), ca. 1.57 (m, 2, H_b), 2.429 (s, 3, H_g), 4.544 (tq, 1, $J_{cd} = J_{cb} = 6.21$ Hz, H_c), 7.333 (d, 2, $J_{ef} = 7.98$ Hz, H_f), 7.787 (d, 2, $J_{fe} = 8.36$ Hz, H_e). The aromatic hydrogens give rise to an AA'XX' pattern which was not analyzed.

5. Synthesis of optically active butyl piperidines

a. (R)-(+)-N-1-Piperidylbutane-1-d (42)

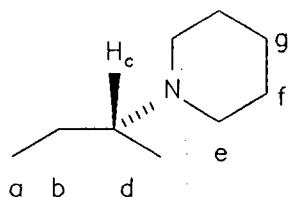


(S)-(+)-1-butyl-1-d p-toluenesulfonate (2.00 g, 8.72 mmol) and piperidine (1.49 g, 17.4 mmol) were combined in a round-bottomed flask and stirred. Voluminous white precipitates formed in the solution after 10 minutes. The yellow color of the sulfonate ester gradually disappeared. After stirring at room temperature for one hour the solution was heated to 95 °C for another hour.

Ether and 10 N NaOH (25 mL of each) were then added and the resulting solution was transferred to a separatory funnel. Upon mixing a suspended solid solution formed. The mixture was filtered to give a white solid (piperidinium p-toluenesulfonate) and two clear liquid layers. The aqueous layer was washed with 20 mL of ether. The combined organic layers were then dried with K_2CO_3 . NMR integration showed that the product was impure so it was taken up in 10 mL of dil HCl. After washing with ether the aqueous phase was neutralized with NaOH. It was then extracted with 10 mL of ether. The organic phase was dried with K_2CO_3 and then concentrated in vacuo. (R)-(+)-N-1-piperidylbutane-1-d: α_D^{24} 0.275° (neat, $l = 0.1$), α_{365}^{24}

0.089° (neat, $\ell = 0.01$), $[\alpha]_D^{24} +4.51^\circ$ (neat), $[\alpha]_{365}^{24} +14.6^\circ$ (neat). The $^1\text{H-NMR}$ data can be found on page 55.

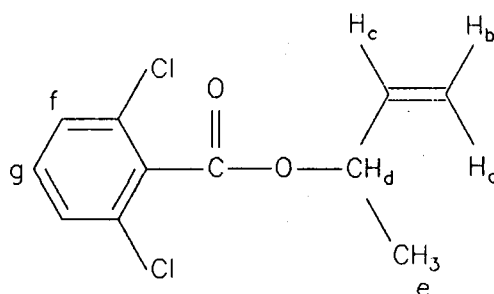
b. (*R*)-(-)-*N*-2-piperidylbutane (43)



Compound 43

The procedure above was duplicated using the following amounts of chemicals: 2.00 g (8.76 mmol) of (*S*)-(+)-2-butyl tosylate; 11.19 g (131.4 mmol) of piperidine. The reaction was run overnight then heated at 95 °C for two hours. It produced 0.17 g (1.21 mmol, 13.8% yield) of a clear liquid: $\alpha_D^{24} -0.434^\circ$, $\alpha_{365}^{24} -1.154^\circ$ (both neat, $\ell = 0.01$); $^1\text{H-NMR}$ (CDCl_3) δ 0.880 (t, 3, $J_{ab} = 7.36$ Hz, H_a), 0.961 (d, 3, $J_{dc} = 6.54$ Hz, H_d), 1.25-1.42 (m, 2, H_b), 1.54 (m, 6, H_f and H_g), 2.38 (m, 1, H_c), 2.44 (m, 4, H_e).

D. Model Compounds

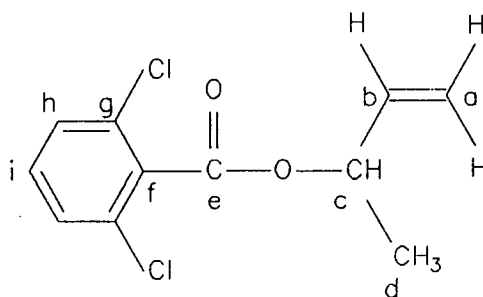
1. Synthesis of 3-buten-2-yl 2,6-dichlorobenzoate (44)**Compound 44**

3-Buten-2-ol (0.72 g, 10 mmol) was dissolved in 5 mL of pyridine and placed in a round-bottomed flask fitted with a reflux condenser. The setup was then flushed with dry nitrogen gas and 2.30 g (11 mmol) of 2,6-dichlorobenzoyl chloride was added. This solution was heated at 100 °C for two hours and then cooled and poured into 75 mL of 5% HCl.

The solution was then extracted with ether. The ether was washed with successive portions of 5% HCl, water, and 10% NaHCO₃, and dried with K₂CO₃.

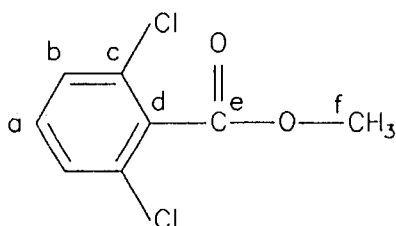
The ether was removed in vacuo and petroleum ether was added causing a precipitate to form. After filtering this out the solution was eluted through a column of alumina with 200 mL of petroleum ether. The solvent was then distilled off and the residue was purified by preparative GC. The yield was estimated at 39%. ¹H and ¹³C-NMR spectra were taken for comparison to the optically active, deuteriated compound: ¹H-

NMR (CDCl_3) δ 1.482 (d, 3, $J_{de} = 6.50$ Hz, H_e), 5.232 (ddd, 1, $J_{bc} = 10.48$ Hz, $J_{ba} = J_{bd} = 1.18$ Hz, H_b), 5.396 (ddd, 1, $J_{ac} = 17.24$ Hz, $J_{ab} = J_{ad} = 1.24$ Hz, H_a), 5.681 (dddq, 1, $J_{dc} = 5.87$ Hz, $J_{db} = J_{da} = 1.22$ Hz, $J_{de} = 6.50$ Hz, H_d), 5.963 (ddd, 1, $J_{cb} = 10.48$ Hz, $J_{ca} = 17.23$ Hz, $J_{cd} = 5.87$ Hz, H_c), 7.266 (m, 2, $J_{gf} = 8.18$ Hz, H_g), 7.311 (m, 1, $J_{fg} = 8.19$ Hz, H_f), H_f and H_g form a typical AB_2 pattern.⁸⁸ ^{13}C -NMR (CDCl_3) δ 19.72 C_d 73.31 C_c ,



116.81 C_a , 127.80 C_h (based on its size and a calculated value of 126.5 for this C), 130.68 C_b , 131.78 C_f or C_g , 133.9 C_g or C_f , 136.67 C_i ; 163.90, C_e .

2. Synthesis of methyl 2,6-dichlorobenzoate (45)



Compound 45

This synthesis followed the procedure of the synthesis of 27 outlined above. The amounts used were as follows: methanol, 0.16 g, 5 mmol; sodium hydride, 1.2 g, 25 mmol; 2,6-dichlorobenzoyl chloride, 1.15 g, 5.5 mmol; THF, 50 mL. The

reaction was allowed to run for one day before workup. A small yield (0.32 g, 31%) of the crystalline product was obtained: $^1\text{H-NMR}$ (CDCl_3) δ 3.98 (s, 3, H_f), ca. 7.31 (m, 3, H_a and H_b). $^{13}\text{C-NMR}$ (CDCl_3) 53.0, C_f ; 127.8, C_b ; 130.9, C_a ; 131.9 and 133.5, C_d and C_c ; 165.2, C_e .

3. Attempted isomerization of 44

a. In ether

A small portion of the racemic allylic ester was allowed to stand at room temperature in ether for several days. The solution was examined by GC for rearrangement after 3, 4, and 6 days. No change was detected.

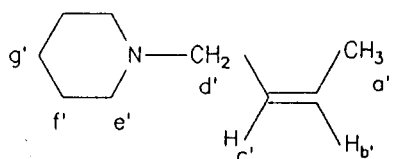
b. In 1,2-diethoxyethane

A small portion of the racemic ester was refluxed in 1,2-diethoxyethane for 6 days. A small amount of precipitates formed and were filtered out. The solvent was then distilled off. The residue was then examined by NMR to determine if any rearrangement had occurred. Only 44 itself was seen.

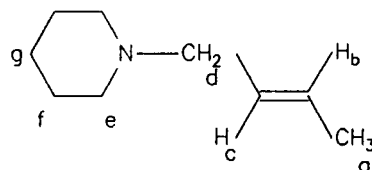
4. Reaction of 1-chloro-2-butene with piperidine^{3b}

To freshly distilled piperidine (5.96 g, 70 mmol) in 25 mL of ether was added a mixture of 1-chloro-2-butene isomers (5.31 g, 59 mmol). Precipitates formed slowly as the reaction mixture was refluxed for one day. The mixture was then added to 100 mL of 5 N NaOH. The aqueous layer was extracted twice with 75-mL portions of ether. The combined organic layers were dried with K_2CO_3 and then KOH.

The ether was then removed in vacuo and the residue was purified by preparative GC (column I). A total of 1.97 g (14 mmol, 24% yield) of *cis*- and *trans*-*N*-1-piperidyl-2-butene (46



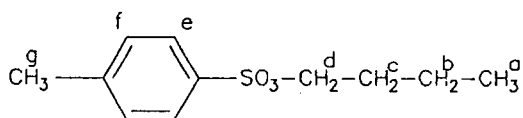
Compound 46



Compound 47

and 47) was obtained: $^1\text{H-NMR}$ (CDCl_3) 46 and 47: δ ca. 1.45 (m, 2, H_g and $\text{H}_{g'}$), ca. 1.55 (m, 4, H_f and $\text{H}_{f'}$), ca. 1.65 (d, 3, $J_{ab} = 5.38$ Hz, H_a and $\text{H}_{a'}$), 2.3 (m, 4, H_e and $\text{H}_{e'}$), 2.86, (m, 2, H_d), 2.88 (m, 2, $\text{H}_{d'}$), 5.5 (m, 2, H_b , $\text{H}_{b'}$, H_c , and $\text{H}_{c'}$); $^{13}\text{C-NMR}$ (CDCl_3) 46 and 47: δ 13.068, $\text{C}_{a'}$; 17.524, C_a ; 24.244, C_g and $\text{C}_{g'}$; 25.779, C_f and $\text{C}_{f'}$; 54.215, C_e and $\text{C}_{e'}$; 55.304, $\text{C}_{d'}$ 61.476, C_d ; 126.392 and 127.098, C_b , and $\text{C}_{c'}$; 127.836 and 128.261, C_b and C_c .

5. Synthesis of 1-butyl tosylate (48)



Compound 48

This synthesis was carried out by the method of Kabalka *et al.*⁸⁹ 1-Butanol (5.0 g, 67.5 mmol) was dissolved in 20 mL of chloroform and cooled to -3°C . Pyridine (10.67 g, 135 mmol) was added to this and then tosyl chloride (14.15 g, 74.2

mmol) over the next hour. The solution was stirred for 5 h while keeping the temperature below 0 °C.

Water (15 mL) and ether (60 mL) were then added to the solution. The resulting organic layer was washed with successive 15-mL portions of 2 N HCl, 10% NaHCO₃, and water and then dried with MgSO₄. TLC indicated that no tosylchloride was present.

The solution was then concentrated in vacuo and analyzed by GC (column B). Ether, CHCl₃, butanol, and pyridine were seen but none of the tosylate. It was also not seen with columns C and D. NMR spectroscopy showed that the product was present, however, so it either decomposes in the GC or has a long retention time (>1 h).

The mixture was then passed through a 20-cm column of silica with 2% ether/ligroine solvent. After concentrating the solution in vacuo and drying with K₂CO₃ 12.03 g (52.7 mmol, 78.1% yield) of butyl tosylate was obtained: ¹H-NMR (CDCl₃) δ 0.861 (t, 3, J_{ab} = 7.29 Hz, H_a), ca. 1.3 (m, 2, H_b), ca. 1.6 (m, 2, H_c), 2.446 (s, 3, H_g), 4.029 (t, 2, J_{dc} = 6.42 Hz, H_d), 7.342 (d, 2, J_{ef} = 8.19 Hz, H_f), 7.779 (d, 2, J_{fe} = 8.13 Hz, H_e). The aromatic hydrogens form an AA'XX' pattern.

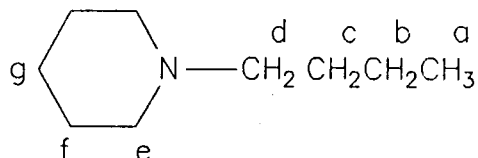
6. Reaction of 1-butyl tosylate and piperidine^{3b}

1-Butyl tosylate (3.00 g, 13.1 mmol) and freshly distilled piperidine (10 g, 0.117 mol) were combined and stirred. The mixture took on a dark orange color and heated up im-

mediately. Crystals began forming in a few minutes and the solution was a mass of crystals after only 30 min.

After standing for 3 days, 20 mL of 5 N NaOH was added. This dissolved the crystals. The aqueous layer was washed twice with 50-mL portions of ether. The combined organic layers were dried with powdered molecular sieves.

The ether was then distilled and the residue was purified by preparative GC (column J) to give 0.239 g (1.70 mmol, 12.9% yield) of *N*-1-butylpiperidine (49): $^1\text{H-NMR}$ (CDCl_3) δ 0.911 (t, 3, $J_{ab} = 7.16$ Hz, H_a), ca. 1.25 (m, 4, H_b and H_g), ca. 1.45 (m, 2, H_c), ca. 1.60 (m, 4, H_f), 2.322 (t, 2, H_d), 2.373 (m, 4, H_e).



Compound 49

E. Attempted $\text{S}_{\text{N}}2'$ Reactions with 44

1. Reaction of 44 with dimethylamine

Dimethylamine (4.60 g, 102 mmol) and 44 (1.00 g, 4.08 mmol) were placed in a pressure bottle and stirred for 36 days at room temperature. The solution was then cooled and opened to the atmosphere allowing excess dimethylamine to escape. A solution of NaOH (50 mL, 5 M) was added to the bottle and the resulting mixture was washed with two 75-mL portions of

ether. The combined organic layers were dried with K_2CO_3 and then KOH.

The ether was then removed in vacuo and the residue was analyzed by NMR for the presence of S_N2' product. Only unchanged ester was found.

2. Reaction of 44 with diethylamine in ether

The racemic ester (1.53 g, 6.24 mmol) was refluxed with diethylamine (11.50 g, 157 mmol) in ether for 2 days. The solution was then washed with 30 mL of 5 N NaOH. The aqueous layer was washed three times with 25-mL portions of ether and the combined organic layers were dried with $MgSO_4$ and then KOH. The ether was removed in vacuo and the residue was examined by NMR. No S_N2 or S_N2' product was seen. Unchanged ester was recovered.

3. Reaction of 44 with piperidine in ether

Freshly distilled piperidine (0.42 g, 4.90 mmol) was dissolved in 10 g of ether and refluxed with 0.60 g (2.45 mmol) of the racemic ester for 10 days. Following this period the reaction mixture was worked up as in the two reactions above. NMR analysis showed that no reaction had occurred.

CHAPTER IV

RESULTS AND DISCUSSION

The ultimate goals of this work were to synthesize an optically active, deuterium labelled ester 27 (p. 51), allow it to react with several secondary amines in an S_N2' fashion, and analyze the products of these reactions to glean information about the S_N2' mechanism and stereochemistry.

(R)-(+)-3-Buten-2-yl-Z-4-d 2,6-dichlorobenzoate 27 was chosen as a possible substrate for S_N2' displacement because of its use by Oritani and Overton⁷⁵ and a desire to expand upon Magid and Fruchey's work on optically active 3-chloro-1-butene-Z-1-d.^{3b} Oritani and Overton had heated a mixture of 27 and (S)-1-phenylethylamine at 130-140 °C for 3 days. The syn/anti ratio they obtained was 62/38. In comparison to this Magid and Fruchey reported nearly 100% syn attack with a chlorine nucleofuge and three secondary amines.

It was decided, therefore, to attempt the reaction of 27 with the secondary amines used by Magid in order to determine if the change in the syn stereoselectivity between the two studies was due to the change of nucleophile or the change of nucleofuge.

Before attempting to carry out the S_N2' reaction on 27 it was necessary to synthesize the racemic, non-d analogue 44 (p.

65). In this way the conditions for the synthesis could be worked out with a less expensive alternative. It would then be possible to determine with which secondary amines the ester would undergo an S_N2' reaction and what the best conditions for such a reaction were.

Oritani and Overton's synthesis of the ester from the aroyl chloride and the alcohol with butyllithium was rejected due to the low yield reported for this type of synthesis.^{12c} Stork and White^{36b} had synthesized the 2,6-dichlorobenzoates of several alcohols including 3-buten-2-ol. Their method was to heat a mixture of 2,6-dichlorobenzoyl chloride and one of the alcohols in pyridine (to remove HCl as it forms) to 100 °C for 2.5 hours. They obtained yields of 69-80%. With 3-buten-2-ol they got a yield of 75%. My attempts to duplicate this yield failed. The best obtained was 39%.

Kopecky and Levine⁸² also tried to synthesize a cyclopentenyl 2,6-dichlorobenzoate by Stork's method. As this failed they changed to a method in which the alcoholic hydrogen was removed by treating it with NaH. 2,6-Dichlorobenzoyl chloride was then added to the cooled (-11 °C) mixture in THF. They were able to get a 71% yield of the ester by this route. After some initial difficulties I was able to synthesize 44 with an average yield of 80%.

There was some difficulty in interpreting the ¹³C-NMR spectrum of 44. As an aid the methyl ester was also synthesized. This allowed relatively certain assignments of the

butenyl peaks. Some uncertainty still exists with the aromatic carbons.

Allylic rearrangement of 44 was not expected. Oritani and Overton had refluxed the ester for 48 h in xylene with three equivalents of 2,2,2-trifluoroethanol. Less than 3% of the rearranged ester was seen. They got the same results when they examined the unreacted ester from the reaction with 1-phenylethylamine.⁷⁵ Kopecky and Levine's ester did not undergo an S_N2' reaction and they did not say if it had rearranged. Stork's cyclohexenyl ester, however, was found to undergo approximately 20% rearrangement under the conditions of the S_N2' reaction.³⁷ He employed a higher temperature and less time for his reaction as compared with the current work. It was, therefore, felt best to examine 44 under the conditions which were to be used for the S_N2' experiments.

Two tests were carried out for the present work. In the first test the ester was allowed to stand in ether for several days at room temperature. It was periodically analyzed by GC. No rearrangement was detected. In the second test the ester was refluxed with 1,2-diethoxyethane for 6 days. Although these conditions were much harsher than those used in the S_N2' reaction no rearrangement was seen.

Compound 44 was then treated with several different secondary amines under varying conditions in the hope that S_N2' reactions would occur. The amines examined were dimethylamine, diethylamine, and piperidine. Reaction with

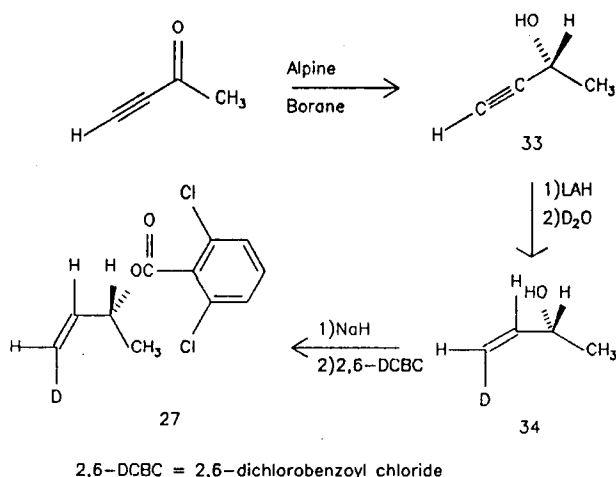
dimethylamine (in a 25:1 excess with 44) was carried out in a pressure bottle without a solvent. The mixture was stirred for 36 days at room temperature. No reaction was seen.

Both diethylamine and piperidine (each in 2:1 excesses) were then allowed to react with the ester while refluxing in ether. These reactions continued for 2 and 10 days respectively. These conditions duplicated those used by Magid and Fruchey for the reactions between these amines and 3-chloro-1-butene^{3b}. No reaction was seen here either. Instead unchanged ester was recovered. This lack of reactivity of the ester was unexpected as the ester group should be at least as good a leaving group as the chloride.

An attempt was then made to achieve reaction by refluxing the reactants in the absence of a solvent. Dimethylamine had already been used without a solvent at room temperature. It was felt best to avoid the danger involved in heating a sealed-tube reaction. The boiling points of diethylamine (56.3 °C) and ether (34.5 °C) are not that far apart so the absence of the solvent should not significantly affect this reaction rate. Piperidine, however, boils at 106 °C and this increase in temperature was felt to be enough to justify an attempt to carry out the reaction without a solvent.

A 14:1 excess of piperidine was, therefore, refluxed with 44 for one week. Analysis of the reaction mixture showed that both the S_N2 and S_N2' reactions had occurred. The majority of the product (approx. 75%) arose from the S_N2' reaction.

Having determined the conditions under which the ester would undergo an S_N2' reaction it was necessary to synthesize its optically active, deuterium labelled analogue (*R*)-(+)-3-buten-2-yl-(*Z*)-4-*d* 2,6-dichlorobenzoate (**27**). The route followed for this synthesis is outlined below:



Equation 32

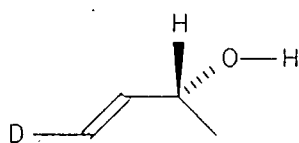
The procedures for the first two reactions in this synthesis were developed by Bass^{3d} and Grant and Djerassi⁸⁰ respectively. Bass examined several possible syntheses of (*R*)-(-)-3-buten-2-ol-(*Z*)-4-*d* (**34**). His best results were obtained by reducing 3-buten-2-one with (*R*)-(+)-Alpine-Borane®. Using this he was able to get a 62% yield of the 73.2% optically pure butynol **33**. Reduction of this compound with LAH followed by workup with D₂O provided **34**.

The Alpine-Borane® reduction was repeated in this work under two separate sets of conditions. In one case the Alpine-Borane® and ketone were allowed to react for 5-7 days

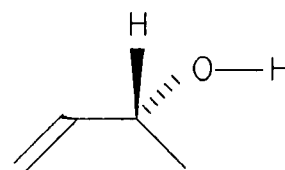
in the THF solvent in which the Alpine-Borane[®] is sold. In the other case the THF was removed prior to addition of the ketone and the reaction was halted after one day.^{78b} Yields were somewhat higher without the solvent present (ca. 75% vs. 54%). Enantiomeric excesses of 73% were typical for both cases.

The optically active butynol (33) was then reduced by the same method used by Magid and Fruchey.^{3b} Reduction with LAH, followed by quenching with D₂O, yielded an allylic alcohol with a deuterium in the Z position.

The optical purity of 34 was then determined. This had to be done at this point because the specific rotation of 27 had not been reported in the literature. It should be noted also that 34 is not the only compound present here. Small amounts of both the *E*-deuteriated (50) and the non-deuteriated



Compound 50



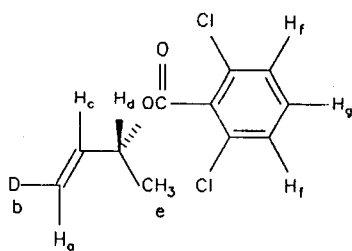
Compound 51

(51) compounds are also present (<2% each). In determining the optical purity, however, the specific rotations of these compounds was assumed to be equal to that of 34. The observed rotation of this sample was $\alpha_D^{30} -1.660^\circ$ (neat, $l = 0.1$). The density of this alcohol is 0.8313 g/mL. This gives a $[\alpha]_D^{30} -19.97^\circ$. Using the literature value of $[\alpha]_D^{30} -33.2^\circ$ ⁸¹ allows

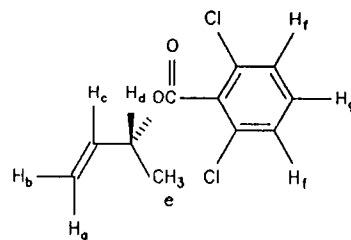
calculation of a 60.1% optical purity. This was surprising considering that 33 was typically 73% optically pure. However, the % ee of the sample of 33 used to make this sample of 34 was not determined (to reduce the amount of compound lost by GC purification) and could have been lower than normal.

Kopecky's method was then applied to this sample of 34 to synthesize 27 in a 75.5% yield. This reaction is assumed to go with 100% retention of configuration. The optical data for this sample of 27 were: α_D^{25} 0.134° and α_{365}^{25} 0.414° (neat, $l = 0.01$). Using the 60.1% ee calculated above leads to the assignment of its specific rotation: $[\alpha]_D^{25} +18.6^\circ$, $[\alpha]_{365}^{25} +57.4^\circ$; (max).

As stated above the deuterium labelling step is not perfect. This does not introduce much error in the optical readings of either 27 or 34. However, following the S_N2' reaction, the stereogenic carbons of 31 and 32 (p. 53) will



Compound 52

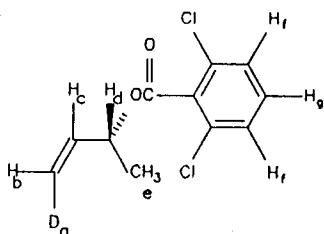


Compound 53

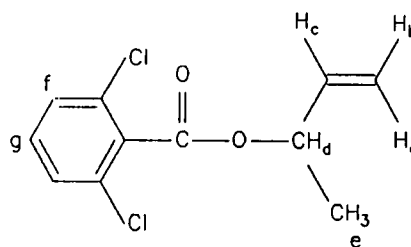
owe their asymmetry to the deuterium atom they bear. The presence of 52 and 53 will, therefore, reduce the maximum

optical activity of the mixture of products from the S_N2' reaction.

The amount of each of these present was determined by examining the 200 MHz-NMR spectra of 27 and 44. In compound



Compound 27



Compound 44

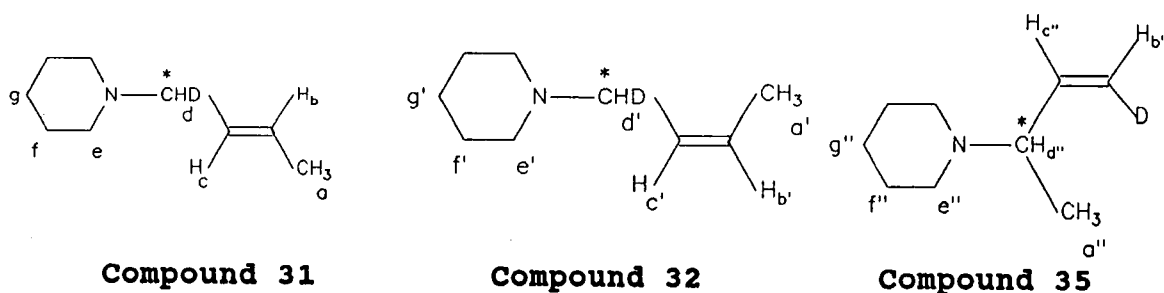
44 H_a shows up as a pair of triplets (due to degenerate coupling constants) at 5.35 ppm and 5.44 ppm. In compound 52, H_a appears as a pair of doublets at 5.34 ppm and 5.42 ppm. Integration from 1089.69 Hz to 1085.52 Hz (relative area 30.38) and from 1085.52 Hz to 1082.83 Hz (relative area 9.21) in the ^1H -NMR spectra of 27 gave the ratio of 53 to 52 present in the sample of 27 used. This procedure was repeated and the average of the two sets of results were used to calculate a ratio of 77.8% to 22.2%.

The total amount of 52 and 53 present in this sample of 27 was obtained by first integrating from 1092.24 Hz to 1082.56 Hz (relative area 34.04), from 1072.75 Hz to 1065.75 Hz (relative area 48.65), and from 1057.15 Hz to 1028.11 Hz (relative area 3563.93). The peaks in the first two integrals are caused by 52 and 53. Multiplying the total of these two integrals by the ratio obtained above gives the relative area

caused by each of these compounds: 52 = 18.4 and 53 = 64.3. The third integral includes peaks of compounds 27 and 53. The peaks of 53 should have the same area as that calculated above and can be subtracted out. This gives a relative area for compound 27 of 3499.63. Using these numbers the sample was calculated to be 97.7% 27, 0.5% 52, and 1.8% 53. This will introduce a correction factor of 0.972 (0.977 - 0.005) for the specific rotation of 42 (p. 63).

These numbers may not be completely accurate as baseline separation between the peaks of compounds 52 and 53 did not occur. Also the percentage of 53 present seems too high considering that the D₂O used was 99.8% pure (Aldrich) and was kept sealed in a desiccator to prevent absorption of atmospheric H₂O.

The optically active, deuterium-labelled ester 27 was then subjected to aminolysis by piperidine. Three compounds are formed in this reaction: 31, 32, and 35. The relative



amounts of each of these compounds in the reaction mixture was determined by analyzing the ¹³C-NMR spectrum of the mixture.

However, it was first necessary to assign the peaks for each of the carbons in these compounds.

Peak assignments for the sp^2 carbons in 31, 32, and 35 were made by analyzing the ^{13}C -NMR spectra of their racemic, non-*d* analogues: 47 and 46 (p. 68). Compounds 47 and 46 were synthesized by treating a sample of mostly *trans*-1-chloro-2-butene with piperidine. This S_N2 reaction should not affect the stereochemistry of the double bond and so the product was assumed to be mostly *trans* as well. Therefore the larger peaks in the NMR spectrum were assigned to 47 while the smaller ones were assigned to 46. This reaction did not produce any of the racemic, non-deuteriated isomer of 35 so any new peaks which showed up in the NMR spectrum of the mixture of products from the S_N2' reaction were assigned to 35.

Integration from 129 ppm to 127.6 ppm for 31, and from 127.6 ppm to 126.45 ppm for 32 gave relative areas of 1000 and 145.5 respectively. This indicates that the E/Z ratio is 87.3/12.7. Integration from 55.10 ppm to 53.76 ppm for the S_N2' products and from 51.26 ppm to 50.27 ppm for the S_N2 product gave relative areas of 1000 and 356.94. Thus the S_N2'/S_N2 ratio is 73.7/26.3. Combining these two ratios allows calculation of the relative amounts of formation for each of these three compounds: 31 - 64.3%, 32 - 9.4%, and 35 - 26.3%.

The ^1H -NMR spectrum was also analyzed to check the E/Z ratio. Integration from 1180.27 Hz to 1147.20 Hz and from

1140.48 Hz to 1080.79 Hz give relative areas of 172.87 for $H_{e''}$ and 983.85 for H_b and H_c . The 74/26 E/Z ratio calculated here is in close agreement with that calculated above.

Because three compounds are still present it is impossible to determine either the % ee or the % syn attack at this point in the reaction scheme. As shown in equation 31 (p. 43), two modes of attack on the two conformations of 27 will lead to four separate S_N2' products. The goal of determining the percentage of syn and anti attack can, theoretically, be attained by two routes. One of these would require separation of the E enantiomers and the Z enantiomers from each other and from the S_N2 product. The optical purity of each set of enantiomers (which should be identical) would then show how much of each optical isomer was present.

The other route would be to determine the amount of E and Z isomers present by some analytical method. Separation from the S_N2 product followed by reduction of the double bond would give a single compound (36, p. 55) whose optical purity, adjusted for the E/Z ratio so determined, signifies the ratio of syn attack to anti attack. For example, if 100% syn attack occurs and only conformer 27a (p. 43) reacts, then the observed specific rotation of saturated amine 36 requires no correction. However, since the other conformer reacts as well, a correction must be made for the Z product which forms from it. An E/Z ratio of 90/10 would reduce the observed rotation to 80% of the maximum since the E/Z ratio is equiv-

alent to the R/S ratio (assuming 100% syn attack). Thus knowing the E/Z ratio allows us to calculate what specific rotation we can expect.

An attempt was made to purify the crude reaction mixture by preparative GC. This technique proved successful in removing 35 (as indicated by the non-integrability of its peaks in the NMR spectrum of the purified mixture) but 32 showed up as a shoulder on the side of the peak caused by 31 and thus could not be separated. The E/Z ratio of this mixture was again determined by ^{13}C -NMR spectroscopy prior to the reduction of the double bond. Two integrations over the pertinent areas were averaged to give relative areas of 997.32 for the trans compound and 169.41 for the cis. The E/Z ratio calculated from these numbers is 85.4/14.6.

Although it could not be directly related to the amount of each compound present, the optical activity of the GC purified mixture of 31 and 32 was determined. The data obtained are in the experimental section. This information was also obtained for the sample of 35 which was collected by preparative GC. From the observed optical rotation it was possible to calculate $[\alpha]_D^{24} +9.59^\circ$ and $[\alpha]_{365}^{24} +59.12^\circ$ (maxima) for 35. These numbers are calculated assuming 100% inversion of configuration from the 60.1% optically pure 27.

Reduction of the double bond of the mixture of 31 and 32 was accomplished by use of diimide which was provided by PTSH. Only a 40% yield of the pure compound (NMR) was obtained after

preparative GC. It should be noted that the conditions for this reduction were worked out on some of the 46/47 mixture mentioned above. The model compound for NMR analysis was synthesized by the reaction between piperidine and butyl tosylate. This route insured that none of the unreduced compound was present.

The syn/anti ratio of the S_N2' reaction could then be determined. The following rotations were observed for mixture 36: α_D^{24} 0.022° (neat, $l = 0.01$), α_{365}^{24} 0.060° (neat, $l = 0.01$), α_D^{24} 0.036° (c 0.168, ether, $l = 0.1$), and α_{365}^{24} 0.117° (c 0.168, ether, $l = 0.1$). The calculation of the specific rotations from each of these observed rotations must include several corrections.

The butenol (34, p. 50) from which this amine was synthesized was only 60.1% optically active. The amine itself can therefore be no more active than this. The observed rotation must also be adjusted to take into account the presence of non-deuteriated and *E*-deuteriated butenols in 34. This factor was calculated earlier and found to be 0.972. The final correction, as explained above, is for the *E/Z* ratio of the unreduced mixture of amines. This was found to be 0.708. This leads to the following equation:

$$[\alpha]_D^{24} = 0.022^\circ \div (0.601 \times 0.8245 \times 0.01 \times 0.972 \times 0.708) = +6.45^\circ \text{ (neat)}$$

where 0.8245 is the density of the amine and 0.01 is the length of the sample tube. Similar calculations for each of

the other three observed rotations gives the following numbers: $[\alpha]_{365}^{24} +17.59^\circ$ (neat), $[\alpha]_D^{24} +5.18^\circ$ (c 0.168, ether), $[\alpha]_{365}^{24} +16.84^\circ$ (c 0.168, ether).

The specific rotation of *S*-(+)-*N*-1-piperidylbutane-1-*d* (42) in ether was reported by Magid and Fruchey for each of these wavelengths: $[\alpha]_D^{24} +4.02 \pm 0.06^\circ$ and $[\alpha]_{365}^{24} +13.46 \pm 0.06^\circ$ (both c 0.1657, ether).^{3b} Fruchey also found α_D 0.033° and α_{365} 0.106° for the optically pure compound (neat, l = 0.01).⁹⁰ After taking the %D labelling for Fruchey's compound into account the specific rotation of a neat sample of optically pure 42 can be calculated: $[\alpha]_D +4.17^\circ$ (neat) and $[\alpha]_{365} +13.39^\circ$ (neat). These numbers and the % ee calculated for each are tabulated below:

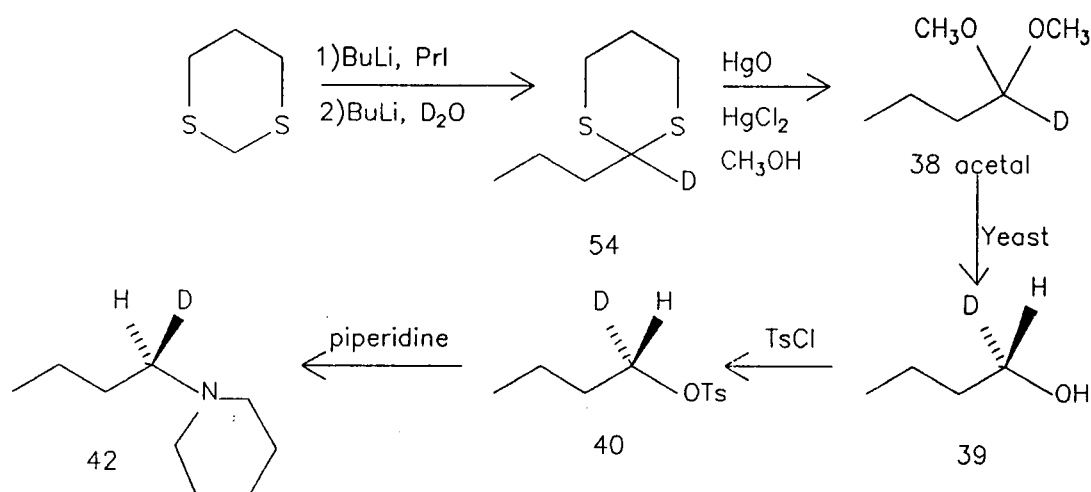
λ	SOLVENT	MIXTURE <u>36</u>	<u>42</u>	% EE of <u>36</u>
D	neat	6.45°	4.17°	155
365	neat	17.59°	13.39°	131
D	ether	5.18°	4.02°	129
365	ether	16.84°	13.46°	125

Average % ee = 135

Two facts in the above data stand out. First, an impossible result has occurred; the % ee cannot be greater than 100. Second, the numbers at different wavelengths, especially for the neat solution, are not consistent. The % ee should be the same at each wavelength rather than differing by as much as 24%. These errors can arise from either of two

possible sources: Magid and Fruchey's synthesis of 42 from 39 or the current synthesis of mixture 36 from 33.

Magid and Fruchey's synthesis of 42 followed the procedure outlined below. NMR integration of 38-acetal and 39 was used to determine the amount of deuterium labelling which had



Equation 33

occurred. The yeast reduction is regarded as stereospecific. Tosylation of 39 does not affect its stereogenic center and the subsequent reaction with piperidine should occur with 100% inversion of configuration. Thus 42 prepared by this route should be optically pure save only for the amount of D labelling.

The results obtained by Magid and Fruchey, however, are suspect for several reasons. One important question deals with the reliability of the specific rotation calculated for the optically pure compound 42. This number was obtained on an older Rudolph polarimeter. While there are several places

where error could be introduced with the use of this instrument, I believe that the inability to control and adequately monitor the temperature at which readings are taken is the most likely source.

It was found with the Perkin-Elmer instrument that the observed rotation of neat 34 changed from -1.771° to -1.660° as the temperature was raised from 20 to 30 °C. Unless this was taken into account the optical purity calculated for 34 would vary from 64.2 to 60.1%. It would have a similar effect on the percent syn attack calculated for the S_N2' reaction. The temperatures listed above are easily attainable in the lab in the course of a year. The temperature inside the sample compartment of the new spectrophotometer can rise to as high as 36 °C after only a few hours of use.

The specific rotation obtained for compound 39 by Magid and Fruchey was only 86% of the literature value.^{3b,91} They surmised that the presence of a highly levorotatory impurity was the cause of this reduction. Their calculations of the specific rotations of 42 assume that the yeast-catalyzed reduction of butanal-1-*d* to 39 actually occurred stereospecifically.

Another area of possible error lies in NMR technology. Magid and Fruchey determined the %D with a 60 MHz instrument. Lack of baseline separation with this instrument precludes much trust in the number attained thereby. Also there is the possibility that some of the levorotatory compound which was

present in 39 was carried along with it in the reaction scheme and was present with 42. Neither of these changes would have much of an effect on the specific rotation of 42. A 3% overcount in the calculation of %D would result in adding 0.14° to the specific rotation of neat 42 at the D line. An undercount here would be almost as likely. Adjusting for the presence of the levorotatory compound would increase the same specific rotation by 0.11°. Taken together, these two would reduce the calculated % ee for neat 42 at the D line to 146.

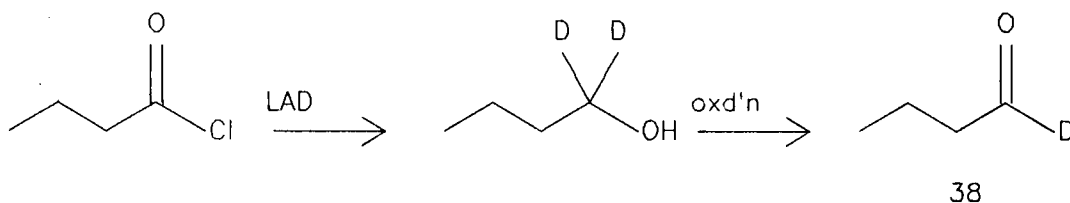
Because of this it was hoped to be able to repeat part of Fruchey's work and synthesize 42 by an alternate route. The only changes in Eq. 33 originally planned were to leave out methanol in the cleavage of 54 (thus producing 38 directly) and to reduce 38 to 39 with (R)-(+)-Alpine-Borane® instead of yeast. These two steps in Magid and Fruchey's synthesis required several weeks to complete and the workup was very tedious. Also, as mentioned above, the 39 that is produced by yeast reduction probably contains a highly levorotatory impurity.

On the other hand the Alpine-Borane® reduction can be carried out overnight on aldehyde 38 itself rather than its dimethylacetal, and its workup is much less tedious. This reduction had already been carried out by Midland *et al.* They did not report a yield but did mention obtaining effectively 100% optical induction.⁸⁶ It was hoped that use of (R)-(+)-

Alpine-Borane® would greatly reduce the reaction time without reducing the % ee attained.

Problems were encountered as attempts were made to cleave 54 in the absence of methanol. Low yields were obtained with several compounds including HgO/HgCl₂, AgNO₃, and HgO/HBF₄. These may have resulted from butanal's high volatility, its solubility in water, and its possible oxidation by some of the cleaving agents. These problems did not exist in the earlier synthesis as the aldehyde was trapped as its acetal and the reduction was carried out in water. Unfortunately the Alpine-Borane® reduction requires anhydrous conditions.

An alternate route for the synthesis of 38 was then proposed as outlined below. The reduction of butyryl chloride



Equation 34

was successful. A 60% yield of 100% labelled (to the limits of detection by 200 MHz NMR) 1-butanol-1,1-d₂ was obtained.

As expected the oxidation was not as successful as the reduction. Several methods were attempted including CrO₃ in pyridine, pyridinium chlorochromate (PCC), and K₂Cr₂O₇/H₂SO₄. Fair yields were obtained with the latter method but it over-oxidizes some of the alcohol and forms significant amounts of

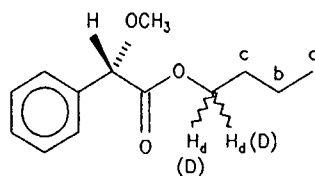
butyl butyrate. However, it was possible to hydrolyze this ester and thus recycle the alcohol. The yield obtained from this oxidation, after adjusting for alcohol recovered in this way, was ca. 50%. The oxidation proceeds almost identically with either 1-butanol or 1-butanol-1,1- d_2 .

The method of oxidation which was used most often, and the one that got the best yields, was the one involving PCC. The main problem with this reagent was the concomitant formation of a tar along with the desired aldehyde. Some aldehyde was trapped in this tar and lost. A successful attempt to reduce the amount of tar formed in this reaction was accomplished by adsorbing the PCC on the surface of some silica gel.

The 100% labelled butanal-1- d obtained from PCC oxidation was then reduced with Alpine-Borane®. A low yield (41.5% at best) was obtained here as well. A small amount of (1R)-(+)- α -pinene codistilled with the product alcohol 39, and had to be removed through GC purification in order to obtain an accurate optical rotation. It was extremely important to separate all of the (1R)-(+)- α -pinene from the 39. Its relatively large rotation ($[\alpha]_D^{21} +50.7^{\circ 91}$) means that even a very small amount contaminating the 39 would have a large effect on its observed rotation. Prior to this purification the sample of 39 was calculated to be over 300% optically pure. No (1R)-(+)- α -pinene was seen in an NMR spectrum of the pure sample. A rotation of 0.035° (neat, $l = 0.1$) at 25° at

the D line was observed for 39 after purification. A specific rotation of $+0.435^\circ$ was calculated from this. The optical purity of the 39 formed by this procedure is therefore 92.4%.

This was lower than expected. A check on the optical purity of this alcohol was, therefore, made by synthesizing its (S)-(+)- α -methoxyphenylacetate (O-methyl mandelate) (55).



Compound 55

The mandelates of 1-butanol and racemic 1-butanol-1-*d* were also prepared so that the peaks could be assigned correctly and to make sure that no kinetic resolution occurred in the synthesis. The important ^1H -NMR data for 55 are as follows: δ 4.080 (tt, 1, $J_{\text{S-dc}} = 6.60$ Hz, $J_{\text{S-dd(D)}} = 1.35$ Hz, $\text{H}_{\text{S-d}}$), 4.113 (tt, 1, $J_{\text{R-dc}} = 6.92$ Hz, $J_{\text{R-dd(D)}} = 1.97$ Hz, $\text{H}_{\text{R-d}}$). The pro-S hydrogen gives rise to three sets of triplets centered at 4.05, 4.08, and 4.12 ppm. The pro-R hydrogen's triplets appear at 4.08, 4.11, and 4.15 ppm. Although baseline separation does not occur here, integration of the outer two sets of triplets should allow a rough determination of the enantiomeric excess of 39. The O-methyl mandelate of *dl*-1-butanol-1-*d* was examined in this manner first. The NMR results confirmed its lack of optical activity. Being thus assured of the effectiveness of this method the O-methyl

mandelate of 39 was synthesized as well. The NMR data for this compound indicated an optical purity of only 62.6%!

An eyeball estimate of the relative sizes of these peaks provides sufficient evidence that this calculation is wrong. The signal at 4.15 ppm was not large enough to distinguish its three separate peaks nor was it large enough for the NT-200 NMR to recognize its existence and assign it a shift value. The result above was probably due to poor phasing of the NMR or to the presence of some unknown impurity. The examination of the initially synthesized (*R*)-(-)-55 was hampered by the presence of bis(2-ethylhexyl) phthalate which had been leached from a short piece of Tygon tubing. This compound has an NMR signal which appears in the 4.15-4.30 ppm area and interferes with the integration of the pertinent peaks of the mandelate. The sample of (*S*)-(+)-55 was not contaminated with this compound.

Because the results with the mandelate were unsatisfactory the (*R*)-(-)-*O*-acetyl mandelate of 39 was also prepared. Parker had synthesized this compound and achieved close to baseline separation with a 300 MHz instrument.⁹² The two hydrogens produce a signal similar to what was seen with 55. Although baseline separation was not expected at 200 MHz it was hoped that an integration similar to the one carried out on 55 would be somewhat more successful. This did in fact turn out to be the case. An enantiomeric excess of 91.3% was calculated with this ester. This number agrees, perhaps

fortuitously, with that obtained by polarimetry and which was, therefore, used in the calculation of the specific rotation of 42 below.

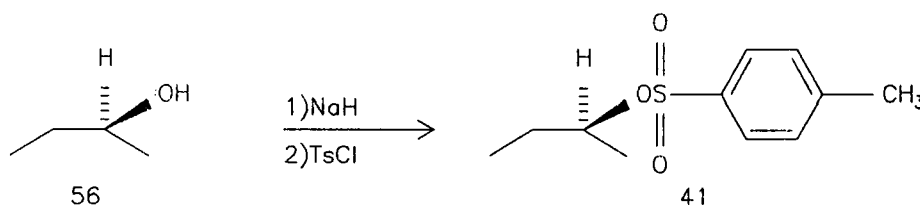
The alcohol was then tosylated to provide it with a better leaving group. Magid and Fruchey's method of synthesis was abandoned due to its low yield and the small amount of alcohol available. Kabalka *et al.* reported virtually a 100% yield in a synthesis involving only a double excess of pyridine.⁸⁸ The two times that this was attempted, however, led to almost complete loss of optical activity by the time the *N*-1-piperidylbutane-1-*d* was formed.

It was unclear whether the loss of optical activity was occurring during the synthesis of the tosylate or during its reaction with piperidine. Magid and Fruchey had synthesized both compounds without apparent loss of optical activity. They reported a small negative rotation for the tosylate. Using the method of Kabalka *et al.*, a rotation for the tosylate could not be obtained. This could be due either to a loss of optical activity in this step or to the presence of opaque impurities. The reading on the polarimeter was non-zero but it fluctuated too much to give credence to any particular number.

It was then suggested that an optically active alkyl tosylate whose specific rotation is known, be prepared.⁹³ If no racemization occurs in this step then the tosylate could be treated with piperidine to see if the S_N2 reaction can be

carried out stereospecifically. Reaction conditions could also be modified to reduce or prevent racemization.

Kenyon *et al.* prepared optically active 2-butyl tosylate.⁹⁴ This secondary tosylate would not form by the method of Kabalka *et al.* so recourse was taken to Kopecky and Levine's method of synthesizing carboxylic acid esters.⁸² This method was also mentioned by Kenyon *et al.*⁹⁴ They made 2-butyl tosylate by both of these methods and by oxidation of the sulfinic acid. Their best yield was actually obtained by the last method but inexperience in this type of reaction and time



Equation 35

constraints precluded its use. The NaH method, shown above, worked fairly well (51% yield) and the specific rotation of the product 41 at 22 °C was in close agreement with the literature value⁹⁴ ($[\alpha]_D^{22} +11.29^\circ$ vs. $+11.10^\circ$ and $[\alpha]_{546}^{22} +13.27^\circ$ vs. $+12.98^\circ$ (all neat)). The % ee at each wavelength is approximately 102%. The rotations had increased slightly after allowing the tosylate to sit for one week. It was noticed that the tosylate had separated out into two layers. The upper layer, which was pipetted away, was oil from the NaH suspension which had not been removed as thought by the THF

washes. The rotation was checked again three weeks later. It did not change over this time period. Whether or not any oil remained in the tosylate it is apparent that the tosylate is not racemizing.

Optically active 41 was then treated with piperidine in a fifteen-fold excess. This reaction occurred with the expected 100% inversion of configuration. No loss of optical activity was seen (95.5% ee for the amine⁹⁴ vs. 95.4% ee for the alcohol and 102% ee for the tosylate). (R)-(-)-N-2-Piperidylbutane was also synthesized by Kenyon *et al.*⁸⁷ from (R)-(-)-2-butylamine and 1,5-dibromopentane. This synthesis was used to confirm the rotation of 36 which had been synthesized from 56. The assignment of an S_N2 mechanism to the reaction between 40 and piperidine is also supported by this result. If a secondary tosylate reacts in an S_N2 fashion then its primary analogue should as well.

These results led to the conclusion that the synthesis of the butyl tosylate by the method of Kabalka *et al.* caused the loss of optical activity. It was, therefore, decided to use the NaH method for synthesizing the tosylate of 39.

The synthesis of (S)-(+)-1-butyl-1-d tosylate (40) by this method was successful (69% yield). However, the specific rotation found did not agree with what Magid and Fruchey had reported earlier.^{3b} Not only were the numbers much higher (α_D^{25} 0.120° vs. -0.007°; neat, $l = 1$) but they had the opposite sign. A possible explanation for this may have been

discovered when an attempt was made to observe the rotations at 20 °C. As the temperature decreased, transmission of light through the sample also dropped and the reading began to fluctuate. No accurate readings could be obtained at this temperature. Even at 25 °C no reading could be obtained at 365 nm (at 30 °C the % transmission increased from 0 to 5 [normally it is over 70] but the reading still fluctuated). The number reported by Magid and Fruchey at this wavelength (-0.070° ; neat, $\ell = 1$) is, therefore, highly suspect.

The 200 MHz NMR spectrum of 40 was also analyzed in order to ensure that the sample of 40 was not contaminated with a minor amount of (1R)-(+)- α -pinene ($[\alpha]_D^{21} +50.7^\circ$ (neat)). Only enough of the alcohol to obtain an accurate optical rotation was purified by preparative GC prior to tosylation. The remaining alcohol still contained (1R)-(+)- α -pinene. It would only take 0.25 mole percent of this compound to result in the change in the rotation which was observed at the D line. However, it was not detected by 200 MHz NMR spectroscopy. Although its largest signals have shifts similar to the signals of the tosylate, that of the alkenyl hydrogen would appear in an uncluttered part of the spectrum. Although this is a relatively small peak in the spectrum of (1R)-(+)- α -pinene it should show up in the spectrum of 40 if 'any' of the compound is present. The NMR spectrometer did reveal the presence of mineral oil in 40. The integrals for H_a and H_b (see structure on p. 61) were both larger than they should

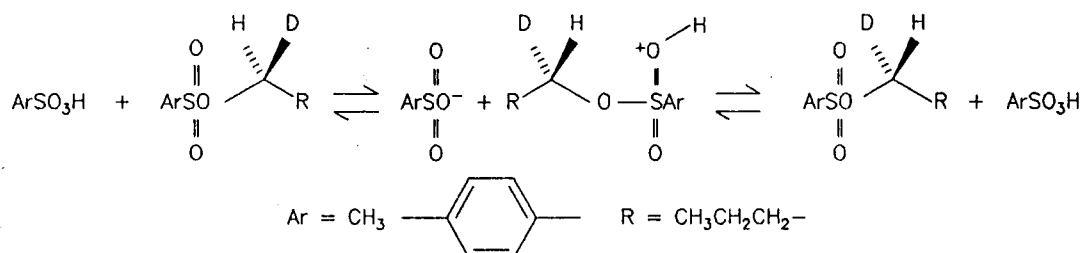
have been in comparison to the other peaks (3.6 and 2.9 vs. 2.0 for H_e).

After four days the tosylate was treated with piperidine in a 2:1 excess.⁸⁷ This was preferred to earlier syntheses as the excess piperidine is easily removed as its solid *p*-toluenesulfonic acid salt. A 50% yield of the desired optically active product (42) was obtained: α_D^{24} 0.030° (neat, $l = 0.01$), α_{365}^{24} 0.096° (neat, $l = 0.01$). This sample of 42 was examined by ¹H-NMR which showed that it contained an impurity in the amount of 6%. After correcting for the concentration of 42 the following numbers were calculated: $[\alpha]_D^{24} +4.18^\circ$ (neat) and $[\alpha]_{365}^{24} +13.4^\circ$ (neat).

These numbers are identical to those obtained by Magid and Fruchey for pure 42.^{3b} The similarity, however, might not reflect reality. The correction which was done on rotation of this sample of 42 to account for the presence of the impurity may have been done incorrectly or may not be theoretically justified (linearity was assumed). However, the numbers reported by Magid and Fruchey for neat 42 and for a 20 vol.% solution of 42 in ether were very close to one another, indicating that concentration does not play a big factor in the specific rotation of 42.

Using these numbers, the % syn of the S_N2' reaction was the same as calculated earlier (p. 85). However, the rotation of the remaining 40 was checked one month after its synthesis. A rotation of ~0.03° was seen at all wavelengths. The

assumption that if the secondary butyl tosylate does not racemize over time then the primary butyl tosylate will not either, is thus proven to be incorrect. A possible explanation for this result is shown in the reaction below. Steric



Equation 36

hindrance must prevent this from occurring, or at least reduce the rate to a minimal amount, with the secondary butyl tosylate. While racemization does occur here, it is not known how much had occurred by the time 41 was treated with piperidine. The agreement between the rotations of 42 calculated here and by Magid and Fruchey may be due either to a low amount of racemization or to a fortuitously similar amount.

If the results from the alternate synthesis of 42 are correct, then it will not be possible to say much about the stereochemistry of the $\text{S}_{\text{N}}2'$ mechanism. Obtention of an impossible result does not lend itself to in-depth analysis. It may be that the reaction between 27 and piperidine occurs with 100% syn stereospecificity. I do not think that it is possible to interpret the data in a way that would allow for this reaction to show any significant degree of anti stereo-

chemistry. In the absence of almost any stereochemical conclusions it is also impossible to draw any conclusions about the importance of the hydrogen bonding mechanism (p. 12) in S_N2' reactions between secondary amines and allyl chlorides.

There are at least four other places in the S_N2' route to 36 where an error may have occurred. The literature value for the specific rotation of allylic alcohol 34 may have been incorrect. Compound 34 may have been contaminated by an optically active compound such as (1R)-(+)- α -pinene. The same thing may also have occurred with mixture 36. Finally, systemic errors in determining specific rotations are possible. Each of these possibilities shall be examined in reverse order.

The observed rotation of mixture 36 at 24 °C in a 1 mm cell was 0.022° at the D line and 0.060° at 365 nm. Literature for the polarimeter states that it is accurate to within $\pm 0.002^\circ$ for readings below 1°. This would introduce a 9.1% error in the rotation at the D line and a 3.3% error at 365 nm. Adjusting the two rotations by the maximum amounts in opposite directions would give a % syn for the S_N2' reaction of 141% at the D line or 135% at 365 nm. If adjustments like this were carried out on the other observed rotations below 1°, then the inconsistency between these two numbers would be completely accounted for.

With the observed rotation of mixture 36 as small as it was it would not take very much of an optically active impurity to affect it. It is possible that the reduced or unreduced S_N2 product was present in mixture 36. A slight possibility also exists that some (1R)-(+)- α -pinene was still present. If the S_N2' reaction is assumed to have gone 100% syn then the observed rotation of mixture 36 at the D line (1 mm cell) would have been 0.0140° . The observed rotations of reduced S_N2 product and (1R)-(+)- α -pinene would be 0.203° and 0.434° respectively. It would take 4.2 mol% or 1.9 mol% of these two compounds respectively to account for the difference between the theoretical maximum observed rotation and what was actually observed.

The presence of any (1R)-(+)- α -pinene here is very unlikely. Several distillations and GC purifications were carried out between its liberation and the determination of the optical activity of mixture 36. It did not show up in any of the NMR spectra of intermediary compounds nor was it seen in the NMR spectrum of mixture 36. It is also clear that the saturated amine from the reduction of 35 is not present. The mixture of products from the reaction between 27 and piperidine was purified by GC in order to remove the 35 which had formed. An NMR spectrum of the GC purified solution did not show any of this compound present. Nor did any of the reduced 35 show up in the NMR spectrum of mixture 36. Other optically active impurities cannot be ruled out. However, analysis of

the NMR spectrum of mixture 36 shows that either they are present in extremely small amounts or their NMR signals appear beneath those of mixture 36.

Since the optical activity of 34 was used as a partial determinant of the maximum rotation of mixture 36 it is necessary to ensure that this number is correct. As stated earlier the optical induction of the Alpine-Borane® reduction of 3-butyn-2-one to 33 was typically around 70%. The LAH reduction of 33 to 34 should not change this. If the literature value for the specific rotation of 33 or 34 is incorrect then the % ee will change unless both are incorrect by the same factor (highly improbable though not impossible). In two cases the optical activities of both 33 and the 34 which was synthesized from it were determined. In the first case these numbers were 69.8% vs. 67.5%; in the second 71.4% vs. 72.0%. This close agreement indicates that the literature values are correct.

The sample of compound 34 which was used in this research was found to have an optical activity of only 60.1%. Analysis of the NMR spectrum of this sample showed that it was pure. The reduction from the normal % ee here is more likely to have been caused by a poor batch of Alpine-Borane® than to have been caused by the presence of an optically active impurity or by a misreading of the polarimeter.

In conclusion it must be admitted that the results can not be an accurate reflection of reality. Where the mirror

cracked, however, has not been ascertained. There are several things which can be done to gain the information necessary to answer that question.

Diastereomeric esters of the unsaturated alcohols 33 and 34 (pps. 47 and 50) should be prepared in order to verify their reported maximum specific rotations. Among the various acids which can be used for this are *O*-methylmandelic acid, *O*-acetylmandelic acid, and Mosher's acid. Care should be taken to insure that kinetic resolution does not occur in the esterification reaction. This could be checked by esterifying the racemic analogues of these alcohols. Baseline separation of the diastereotopic signals should be easier to achieve with these secondary alcohols. The signals of the *O*-methyl mandelate of 2-butanol separated nicely.⁹⁵ If difficulty is encountered a shift reagent such as $\text{Eu}(\text{fod})_3$ could be used with the ester; or a chiral shift reagent such as $\text{Eu}(\text{hfc})_3$ may be utilized directly on the alcohol.

It would also be a good idea to hydrolyze 27 back to 34. This would allow one to see if its optical activity has changed. It may also be possible to check the optical activity of 27 with a chiral shift reagent as mentioned above.

An alternate synthesis of 42 also needs to be tried. If the racemization is occurring as outlined above then a synthesis which precludes the presence of any acid would halt it. One choice might be to attempt oxidation of the sulfinic ester as carried out by Kenyon *et al.*⁸⁷

And, finally, more care needs to be taken in determining rotations with the polarimeter. An extended period of time should be allowed for the instrument to warm up, the temperature of the sample should be closely monitored, and optical readings should be taken on the largest sample possible in order to reduce instrumental error as much as possible.

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