To the Graduate Council:

I am submitting herewith a dissertation written by Olan Stanley Fruchey entitled "The Stereochemistry of the S_N2' Reaction." I 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 Chancellor
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Thesis
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THE STEREOCHEMISTRY OF THE S_N2' REACTION

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

Olan Stanley Fruchey

December 1977

1346902

DEDICATION

The author wishes to dedicate this dissertation to his wife, Sally, for her continued encouragement, patience, understanding, and financial support during the course of this investigation.

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Appreciation is warmly extended to Dr. John W. Larsen and Dr. Fred M. Schell for their many helpful suggestions during the past four years.

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A very sincere appreciation is expressed to the author's parents for their unending love and sacrifices.

ABSTRACT

Allylic compounds are known to undergo nucleophilic substitution yielding variable amounts of the product in which allylic rearrangement has occurred (the S_N2' reaction). Previous theoretical and experimental investigations of the stereochemistry of the S_N2' reaction are inconclusive and often contradictory. The reactions of α-methylallyl chloride with secondary amines are now shown to be stereospecifically syn. Optically active 3-chloro-Z-1-butene-1-d reacts with secondary amines to produce optically active allylic amines which are reduced by diimide to optically active 1-amino-butane-1-d derivatives. Optically pure samples of these derivatives were obtained by yeast reduction of butanal-1-d followed by conversion into the tosylate and then displacement with the secondary amines. Comparison of the specific rotations of the reduced S_N2' products with those of the optically pure material indicates that the reaction is stereospecifically syn: nucleophile attacks the allylic system on the face bearing the leaving group.

A new chlorination reagent (triphenylphosphine-hexachloroacetone) was investigated as to its synthetic utility in the chlorination of allylic alcohols, and found to be highly regio- and stereoselective.

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CHAPTER I

INTRODUCTION

A. Proem

Reactions of allylic compounds are of interest to both synthetic and theoretical chemists. Substitution reactions of allylic compounds occur much more readily than their saturated analogs owing to the activation of the functional group by the double bond. It is for this reason that allylic intermediates are widely utilized by synthetic chemists.

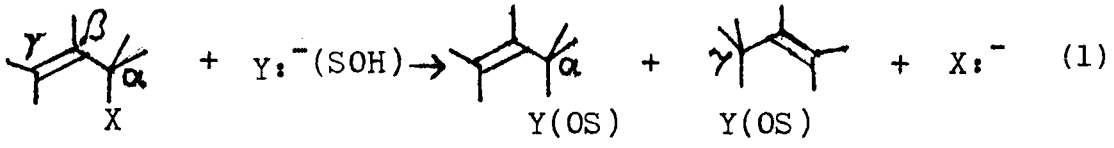
Many natural products such as alkaloids, steroids, and terpenes contain allylic systems. Consequently, substitution reactions of allylic compounds are employed in the laboratory synthesis of natural products such as the essential oils, vitamin A, and prostaglandins.

The theoretical interest in allylic compounds stems from their high reactivity and proclivity for rearrangement. The migration of an electronegative substituent from the α to the γ-position of an allylic system is well documented, and is frequently observed in allylic substitution reactions.

It is for these reasons that several reviews on the chemistry of allylic compounds have appeared in the literature (1).

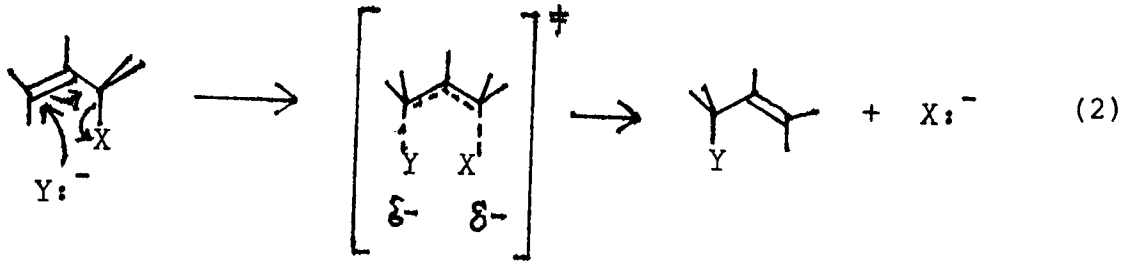
B. Historical Background

It was well established in the 1920's that during nucleophilic substitution (or solvolysis) reactions, allylic halides could yield both a normal substitution product (the new bond formed at the α-carbon) and an abnormal product (the new bond formed at the γ-carbon) (1). Bergmann (2),



(1)

Hughes (3), and Winstein (4) all conceived independently of the possibility of a concerted mechanism in which attack of nucleophile at the γ-position of the carbon-carbon double bond of an allylic halide could result in a shifting of the π-electrons with simultaneous ejection of the halide ion yielding the abnormal allylic substitution product. This process is represented by the symbol S_N2' (substitution, nucleophilic, bimolecular, allylic rearrangement).



(2)

Young (1b) has proposed that at least three conditions must be fulfilled before a reaction can be classified as an example of an S_N2' mechanism:

1. The rate of the reaction must be proportional to the concentration of both the substituting reagent and the compound being substituted (usually this implies second-order kinetics).

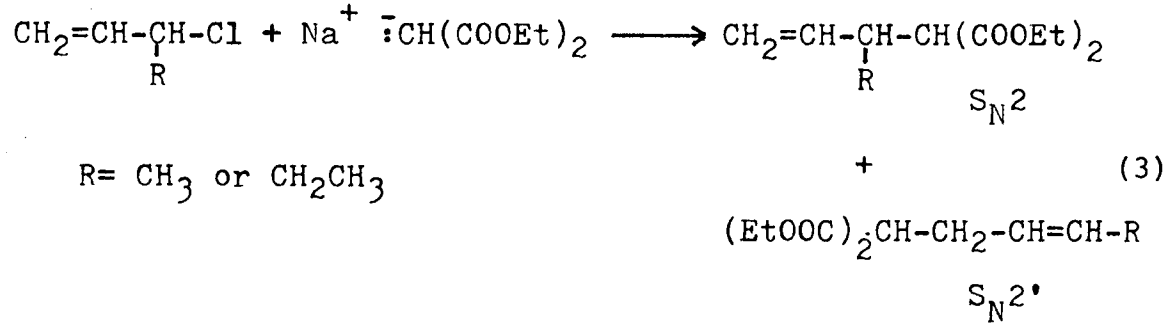
2. The reaction must give isolable amounts of abnormal substitution products.

3. It must be demonstrated that neither the starting material nor the normal substitution product undergoes rearrangement under the conditions of the reaction.

The search for an example of an S_N2' reaction was undertaken in several laboratories during the next few years without any success. As a result of these unsuccessful attempts, Catchpole, Hughes, and Ingold (5) in 1948 concluded on experimental and theoretical grounds that it was highly unlikely that an S_N2' reaction could compete with an S_N2 process. They suggested that the shielding of the γ-carbon atom of the allylic system by the π electrons makes it impossible for the S_N2' mechanism to be realized.

However, in 1949 Kepner, Winstein, and Young (6) reported what they believed to be the first authentic example of an S_N2' reaction. They found that α-methylallyl and α-ethylallyl chlorides react with diethyl sodiomalonate in ethanol

(Equation 3) to yield 10 and 23%, respectively, of the



(3)

rearranged products expected from an S_N2' reaction. Kinetic studies of the reaction with α-ethylallyl chloride showed that it was second order, and it was shown that neither the reactant nor the S_N2 product isomerized under the reaction conditions.

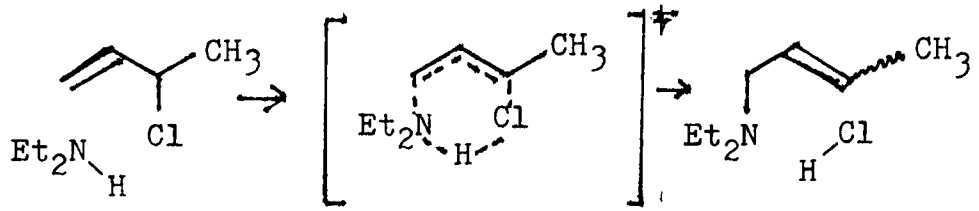
Dewar (7) suggested that the formation of the abnormal product could be explained as S_N2 O-alkylation of the malonate ion, followed by a Claisen rearrangement of the resulting vinyl ether. It seems unlikely that Dewar's postulated ether would undergo a Claisen rearrangement under the mild reaction conditions employed, even if it were formed. Also Stork and White (8) have shown that O-alkylation followed by isomerization definitely does not occur in S_N2' reactions of 6-alkyl-2-cyclohexen-1-yl 2,6-dichlorobenzoates with malonate ion. Winstein (9) has also pointed out that Dewar's vinyl ether intermediate is a ketene acetal which

would be expected to react with the alcohol solvent to give an ortho ester rather than the observed abnormal product.

Once the existence of the S_N2' reaction had been demonstrated, several additional examples were soon discovered. Of particular interest to our work was the report by Young, Webb, and Goering (10) that α-methylallyl chloride reacts with diethyl- or triethylamine (Equation 4)

$$CH_2=CH-\underset{CH_3}{CH}-Cl \xrightarrow[\text{or } Et_3N]{Et_2NH} \begin{matrix} Et_2N-CH_2-CH=CH-CH_3 \\ \text{or} \\ Et_3\overset{+}{N}-CH_2-CH=CH-CH_3 \end{matrix} \qquad (4)$$

to yield exclusively the abnormal product. For diethylamine, reactant stability, kinetic behavior, and product stability data were obtained to show that the reaction fulfilled the three requirements for an S_N2' reaction. The substantially greater reaction rate for the secondary amine, as compared to the tertiary amine, was attributed to a cyclic transition state in which nucleophilic push by nitrogen is accompanied by electrophilic pull by hydrogen. Because of this



(5)

possibility of hydrogen bonding, Ingold (11) has chosen to classify this transformation not as an example of an S_N2' reaction but as an S_Ni' process. As pointed out by Young (1b), hydrogen bonding is a rather weak interaction as compared to the covalent bonding usually involved in the intermediate complexes of an S_Ni' reaction, and it would seem to be largely a matter of personal preference whether to consider this cyclic process a modification of an S_N2' reaction or a borderline case of an S_Ni' process.

The number of allylic substitution reactions which involve an S_N2' mechanism is probably quite large. However, only in a few cases have the kinetics, product compositions, and product stabilities been sufficiently well established to show that this mechanism is responsible for the formation of the observed rearranged products.

The S_N2' reaction is a potential competitor to the S_N2 process whenever an allylic compound undergoes bimolecular substitution. The competitive advantage of the S_N2' reaction is increased by structural and environmental factors which suppress the S_N2 process or which increase the rate of the S_N2' reaction.

The most obvious means of suppressing S_N2 substitution is to introduce bulky substituents at the α-carbon atom, which will sterically retard normal substitution without similarly diminishing abnormal attack. In other words,

α-substituents tend to retard the rate of the S_N2 process relative to the S_N2'. With very few exceptions, S_N2' substitution by anionic reagents is not detectable unless there is at least one α-substituent. Furthermore, two α-substituents or a single bulky α-substituent (like t-butyl) are required before the S_N2' process will predominate. Thus, the reaction of α-methylallyl chloride with ethoxide ion in ethanol yields less than 5% of the rearranged product (12), while α-t-butylallyl chloride yields exclusively the S_N2' product (13). Similarly, sodium thiophenoxide in ethanol reacts with α-methylallyl chloride to produce only a small amount of rearranged product, while α,α-dimethylallyl chloride yields exclusively the rearranged material (12). Likewise α,α-dimethylallyl chloride undergoes S_N2' reaction with thiourea in acetone (14).

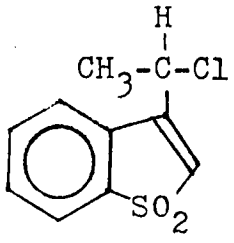
Primary allylic halides appear to undergo only S_N2 substitution. The only cases of S_N2' substitution of primary compounds are the bromide-exchange experiments of England and Hughes (15) and the reaction of ^{14}C-labeled allyl chloride with secondary and tertiary amines (16).

Isotope effects have been measured in order to determine whether reactions of allylic chlorides with secondary amines are concerted and whether such reactions require a cyclic transition state. Fry (17) has determined the heavy atom isotope effects for the reaction of α-methylallyl chloride

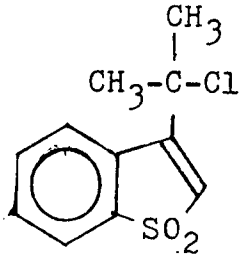
with diethylamine. He found positive $^{12}C/^{14}C$ isotope effects at the α, β, and γ carbons, and also a positive $^{35}Cl/^{37}Cl$ isotope effect for this reaction. He concluded that the reaction is concerted, and that nucleophilic attack by nitrogen at the γ-carbon occurs simultaneously with the rupture of the C_α-Cl bond. However, Dittmer and Marcantonio (18) found no deuterium kinetic isotope effect for the reaction of the same allylic chloride with deuterated amines (Et_2ND and $Ph(CH_3)ND$). They concluded that hydrogen bonding is not an important feature of the transition state.

Bordwell (1a), however, has recently questioned the concept of a concerted S_N2' process. Bordwell's arguments against a synchronous process are based upon his studies of four allylic halosulfone systems (1, 2, 3, and 4). The electron withdrawing sulfone substituent should inhibit a carbonium ion type reaction, while simultaneously activating the γ-position of the double bond to nucleophilic attack. Therefore, Bordwell could study S_N2' reactions in which there was electron withdrawal at the α-position (3), the γ-position (4), or β- plus γ-positions (1 and 2).

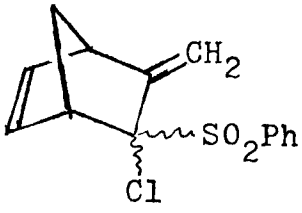
The reactions of Systems 1 and 2 with piperidine in benzene by an S_N2'-like process are complicated by a subsequent rearrangement (Equation 6) involving ring opening and ring closing (19). However, Bordwell and Mecca (20) discovered that when Compound 2 was treated with N_3^-, CN^-,



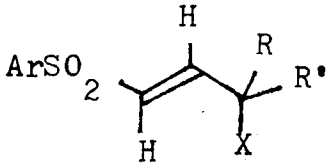
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2

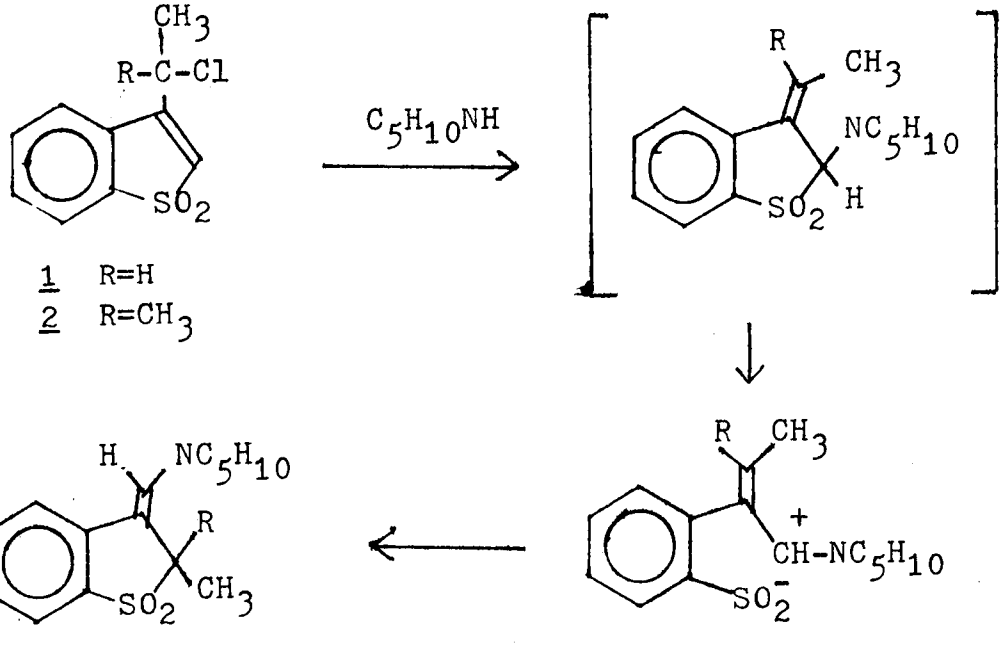


3



R,R'=H or Alkyl

4



1 R=H
2 R=CH_3

(6)

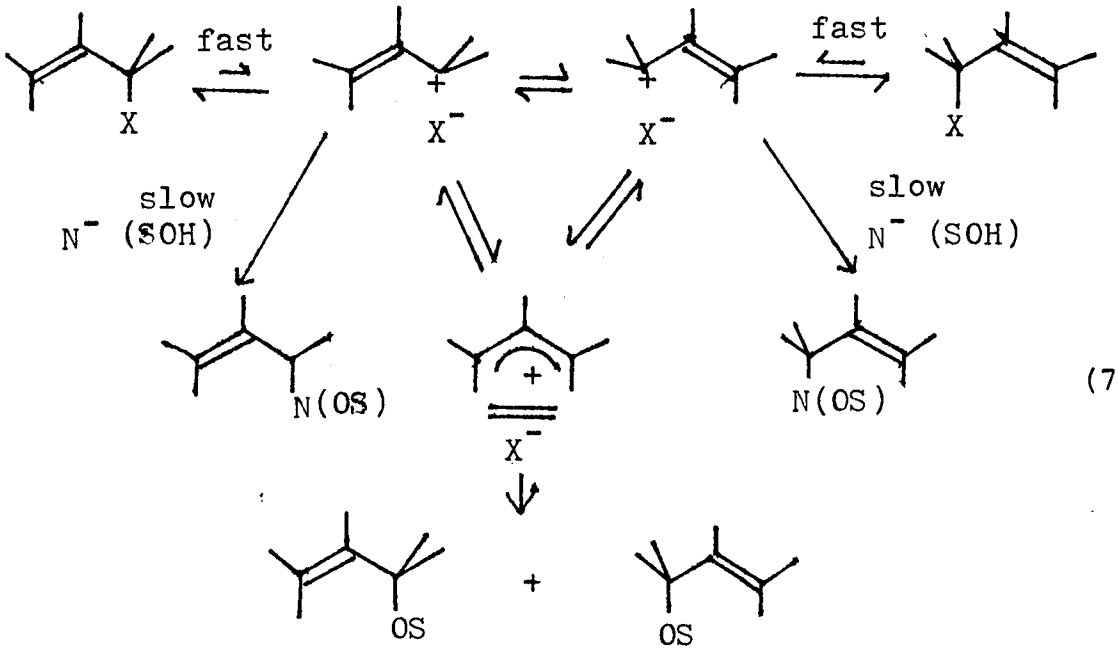
PhS^-, or $PhSO_2^-$ the initially formed S_N2' products were resistant to the ring opening/rearrangement process; they were consequently able to isolate these initial materials.

For Compound 3, both S_N1 and S_N2 reactions should be extremely slow, whereas S_N2' attack at the carbon-carbon double bond should be facilitated by the inductive effect of the sulfone substituent. However, Bordwell and Mecca (21) found Compound 3 to be totally resistant to any attack by nucleophiles. Finally, Compound 4 was shown to give either S_N2 product or double bond isomerization, but no S_N2' product (in spite of the reasonable expectation that it should be highly susceptible to an S_N2' process) (21,22).

On the basis of these results, Bordwell has concluded that the concerted S_N2' mechanism may well be a myth, and that the S_N2' reaction is better explained by the Sneen (23) ion-pair mechanism. Cromwell (24) and co-workers have come to a similar conclusion from studies in which a carbonyl group was used to activate the allylic system.

Sneen et al. (25) have studied the solvolysis of several allylic systems in the presence of added nucleophiles, and have interpreted the results in terms of an ion-pair mechanism (Equation 7). Sneen has postulated rapid formation of a physically discrete ion-pair in which the leaving group is closely associated with the carbon to which it was originally bound. The ion-pair can then suffer nucleophilic

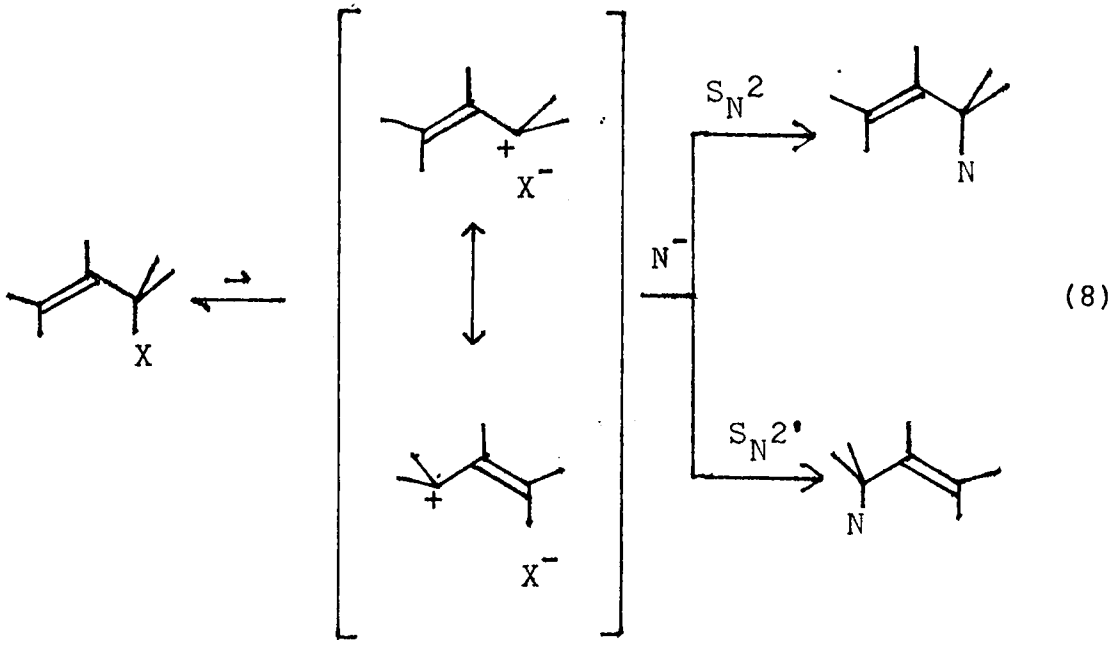
attack at the originally bonded carbon, can interconvert with another discrete allylic ion-pair, or can be transformed into a solvent separated ion-pair. The product spreads that are found in these reactions can be explained as resulting from competition between nucleophilic attack and interconversion with the other intimate ion-pair.



(7)

In Sneen's opinion the concerted S_N2' mechanism is intellectually unreasonable since it requires an unprovoked attack by the nucleophile at the γ-position of an allylic system, a process for which there exists no driving force. However, Sneen believes that the S_N2' ion-pair mechanism (Equation 8) provides a driving force for attack at the

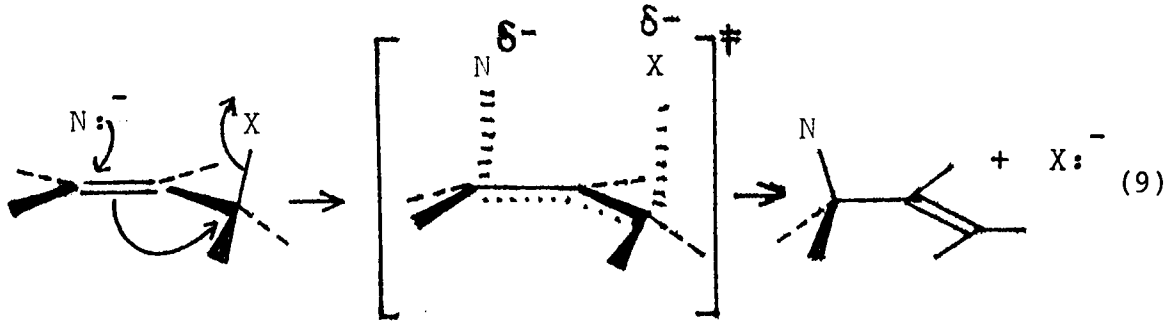
γ-carbon of the ion-pair because the allylic cation develops electron deficiency at this position. Sneen further reasons that a balance between charge density and steric factors determines the proportion of S_N2 and S_N2' products.



(8)

C. Stereochemistry

Winstein (as quoted by Young (1b,c)) was the first to suggest a stereoelectronic preference for the S_N2' reaction. He postulated attack of the nucleophile on the face of the allylic system <u>syn</u> to the leaving group because this displaces the π-electrons in such a manner as to allow them to attack the C_α-X bond from the rear.



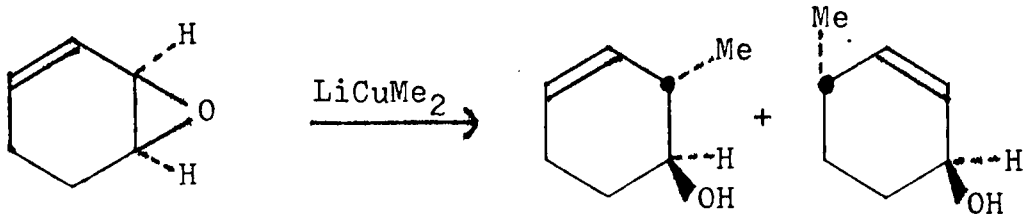
(9)

Subsequent theoretical calculations have also predicted a syn preference. Fukui and Fujimoto (26), using several methods (perturbation molecular orbital theory, frontier orbital theory, HOMO/LUMO interaction theory), have predicted syn attack for the S_N2' mechanism. A similar conclusion has been yielded from calculations performed by Miller (27), Mathieu (28), Liotta (29), and Drenth (30).

Epiotis and co-workers (31), however, have predicted that the mode of attack will be dependent upon the nucleophile. Charged nucleophiles should proceed anti, while neutral nucleophiles should proceed syn. Anh (32) has employed orbital symmetry (Woodward-Hoffmann) calculations which predict that a totally synchronous S_N2' reaction should occur in the anti mode, while the syn mode should be favored for a reaction in which bond breaking is in advance of bond making (but is still a concerted process).

There exists only a very limited number of experimental data concerning the question of the stereochemistry of the S_N2' mechanism.

Staroscik and Rickborn (33) treated 1,3-cyclohexadiene monoepoxide with lithium dimethylcuprate and obtained both a direct ring-opening product and a conjugate addition product (Equation 10). Both products of the reaction had exclusively

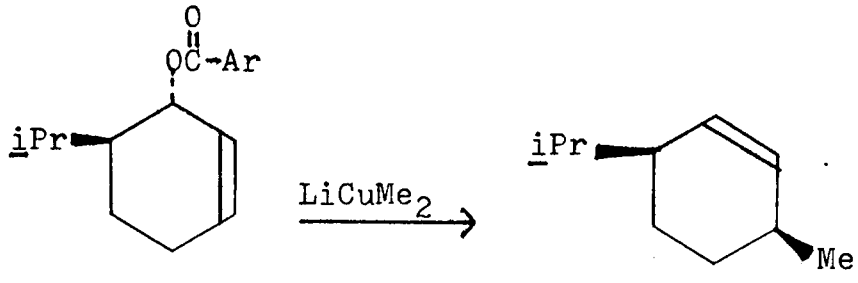


(10)

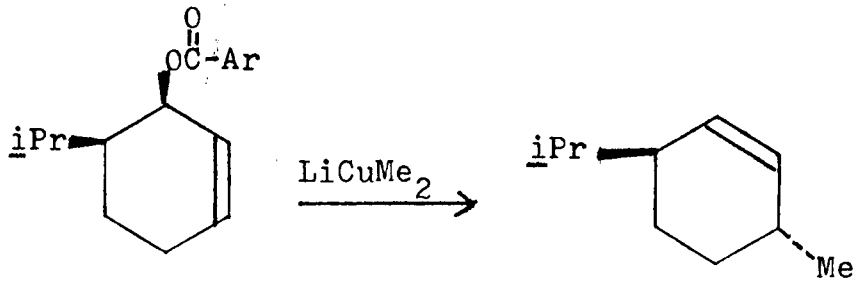
trans stereochemistry. Wieland and Johnson (34a) observed the same results when they ran this reaction. Analogous trans stereochemical results were obtained by Marino and Farina (35) in their studies of reactions of several organocopper reagents with 1,3-cycloalkadiene monoepoxides.

Similarly, Kreft (36) has reported the stereospecific conversion of cis- and trans-6-isopropyl-2-cyclohexenyl mesitoates into p-menth-2-enes when treated with lithium dimethylcuprate (Equations 11 and 12). Again, the conjugate substitution products obtained had exclusive trans stereochemistry. If Kreft's (36), Rickborn's (33), and Marino's (35) rearranged products are viewed as arising from an S_N2' process, then the observed stereochemistry is contrary to that predicted by theory. However, there is evidence that

organocopper reactions involve transfer of an alkyl radical (34).

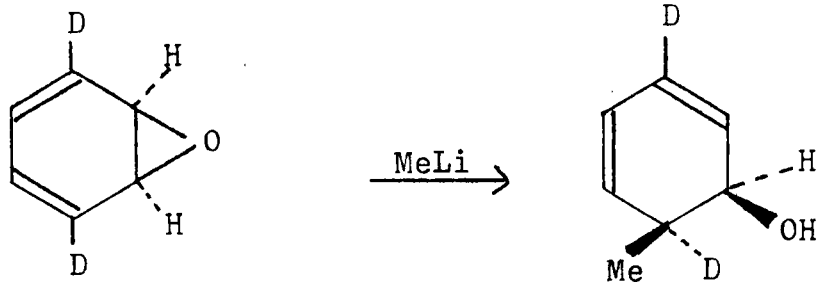


(11)



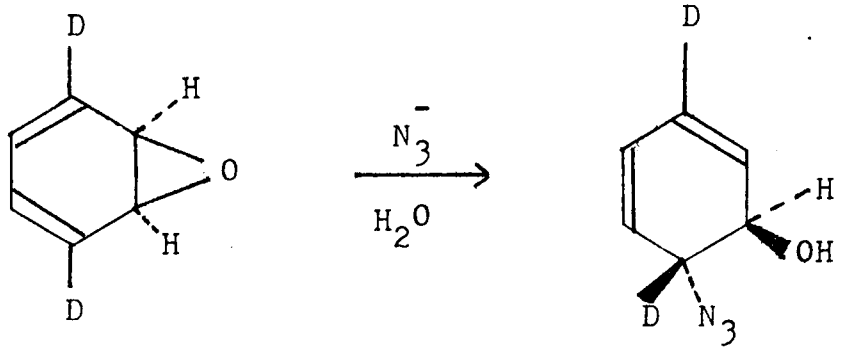
(12)

Foster and Berchtold (37) observed exclusively <u>syn</u> stereochemistry in the 1,6-addition product from the reaction of methyllithium with benzene oxide (Equation 13). This



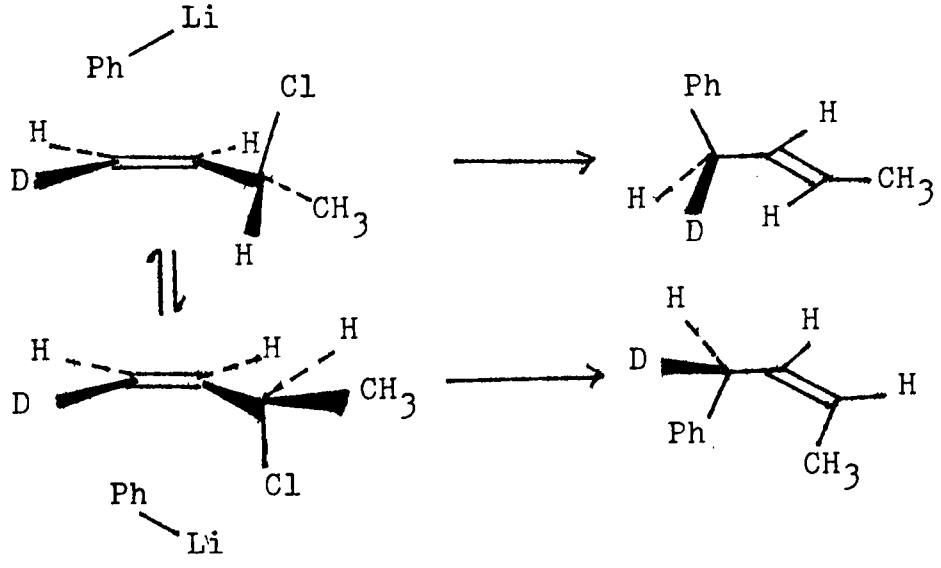
(13)

result is also contrary to theoretical predictions for a doubly allylic system. However, the theoretically predicted trans product was obtained when azide was the nucleophile (Equation 14). Magid and Nieh (39) observed syn attack (at



(14)

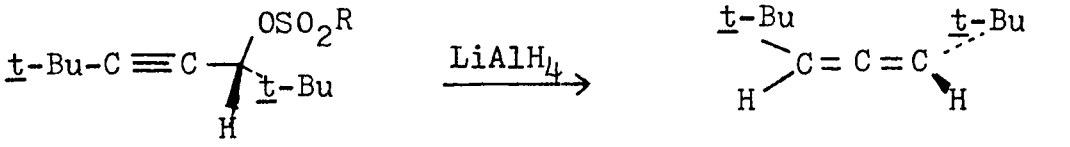
least 95%) in the reaction of optically active and deuterium labeled α-methylallyl chloride with phenyllithium (Equation 15). The reaction yielded 99% rearranged product which



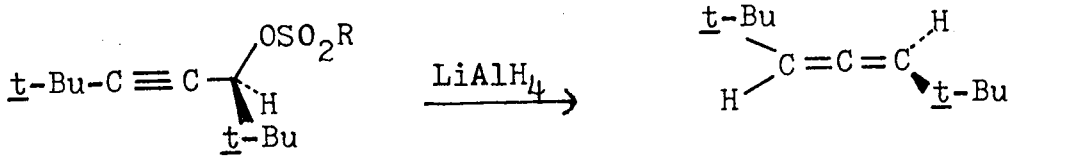
(15)

consisted of an 86/14 mixture of trans and cis alkenes. These results are in good agreement with theory.

Borden and Corey (40) have isolated optically active allenes from the reactions of lithium aluminum hydride with both optically active d-camphor-10-sulfonate esters and tosylates of 1,3-di-t-butylpropargyl alcohol (Equations 16 and 17). The observed rotations of the allene products are



(16)

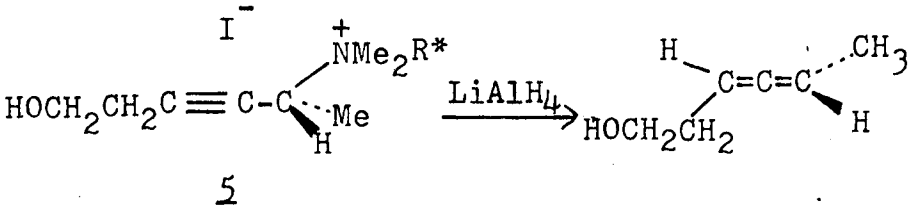


(17)

consistent with hydride attack largely anti to the leaving group.

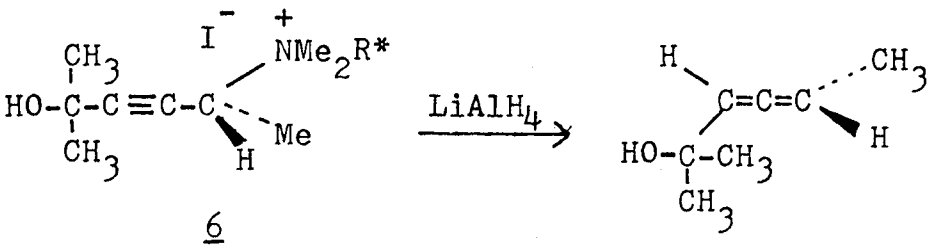
Claesson et al. (41), in contrast to Borden and Corey, obtained optically active allenes which resulted from a syn attack of hydride on propargylic quaternary ammonium salts 5 and 6. Hartshorn and co-workers (42) also observed syn attack in their reactions of propargyl alcohols with lithium aluminum deuteride to produce optically active allenes. Similarly, Jefford and co-workers (43) obtained rearranged

products which resulted from <u>syn</u> attack of hydride on bicyclo[3.2.1]octenyl halides (Equations 20, 21, 22, and 23).



(18)

5

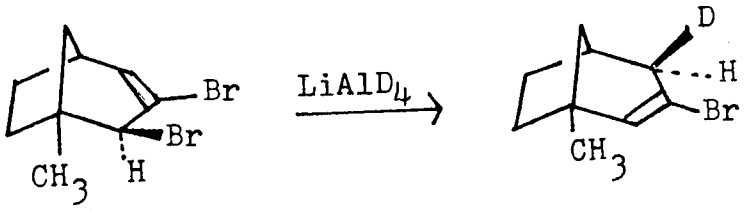


(19)

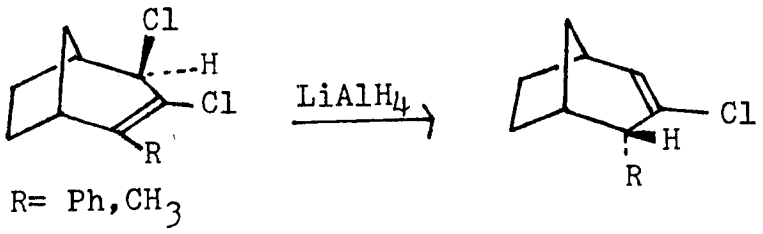
6



(20)



(21)



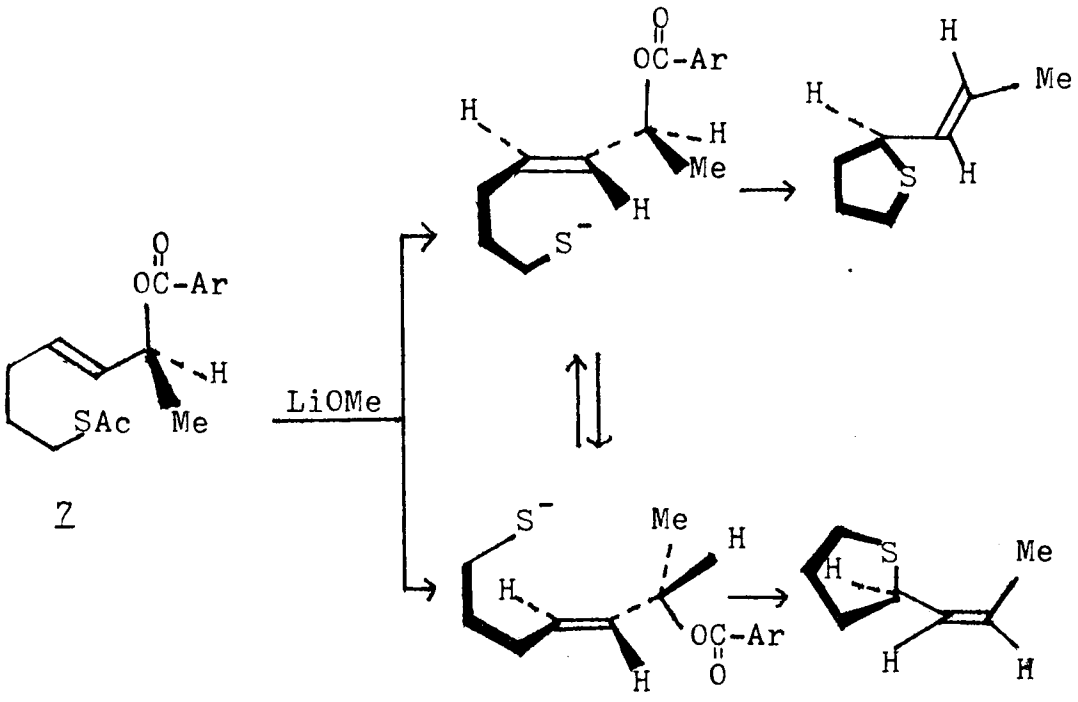
R= Ph, CH_3 (22)



(23)

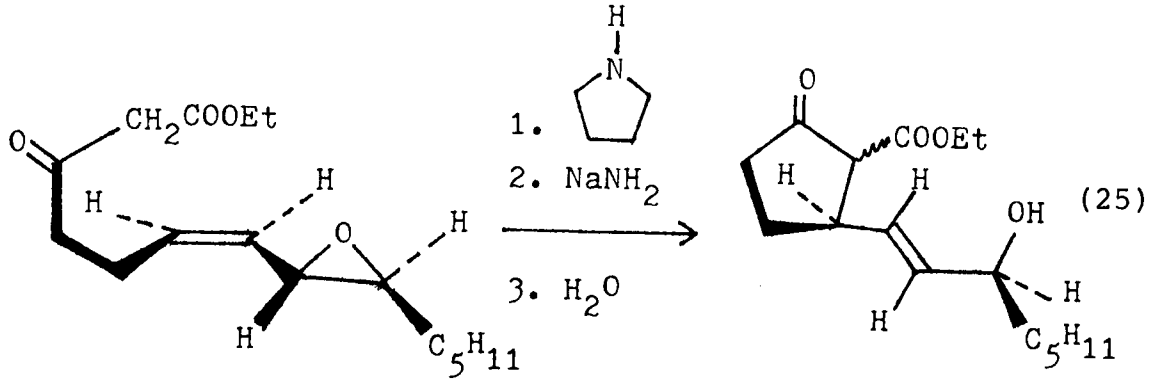
When Stork and Kreft (44) treated (S)-(+)-7 with lithium methoxide in tetrahydrofuran, an intramolecular S_N2' reaction occurred forming 2-propenyltetrahydrothiophene in a 52% yield with an E:Z ratio of 93:7. The optical rotation indicated that the reaction had proceeded largely in the anti mode. However, Martel and co-workers (45) obtained a product resulting from syn attack when they utilized an intromolecular S_N2' process to control stereochemistry in their synthesis of PGA_2 (Equation 25).

Probably, the most definitive study of the stereochemistry of the S_N2' reaction is the work by Stork and White (8,46). They treated Compounds 8, 9, and 10 with piperidine at 130°, both neat and in xylene solvent. The reactions were regio- and stereospecific yielding only the S_N2' products with exclusive syn attack (Equation 26). When

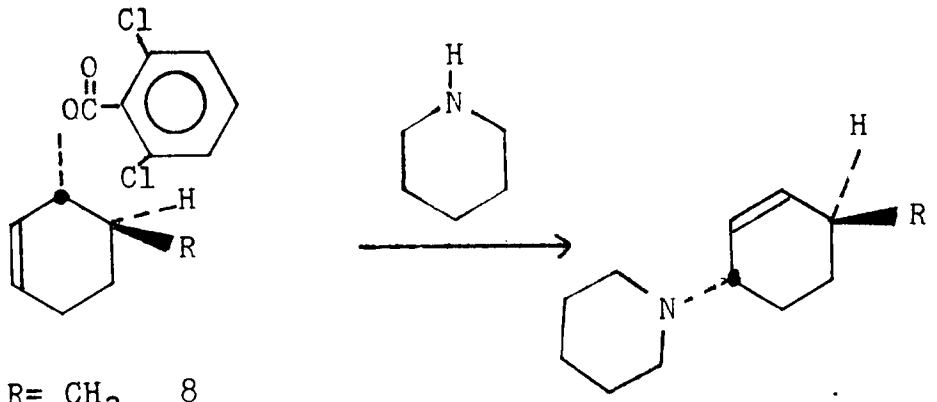

OC-Ar
H
SAc
Me
LiOMe
OC-Ar
H
Me
H
S⁻
H
Me
H
S
H
H
Me
S⁻
Me
H
H
OC-Ar
O
H
S
Me
H
H

Z

(24)


CH2COOEt
O
H
H
O
H
H
C5H11
H
N
1.
2. NaNH2
3. H2O
O
COOEt
H
H
OH
H
H
C5H11

(25)



(26)

R= CH_3 8

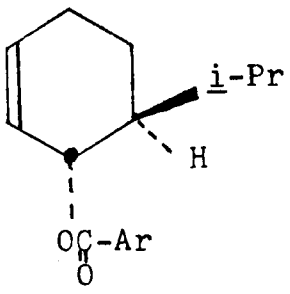
i-Pr 9

t-Bu 10

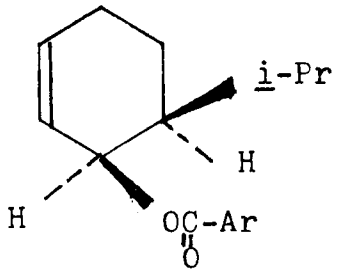
Compound 8 was placed in refluxing 1-butanol with di-n-butyl sodiomalonate, only the S_N2 product with inversion of stereochemistry was obtained. However, the bulkier i-propyl and t-butyl groups in Compounds 9 and 10 sterically inhibited the S_N2 reaction and yielded exclusively the syn attack S_N2' products.

Second order kinetics were established for the reactions of both nucleophiles with Compounds 8, 9, and 10. Stork and White also demonstrated that Compounds 8, 9, and 10 were resistant to allylic isomerization under the reaction conditions. Unfortunately, when Stork and Kreft (47) recently reexamined Compound 9, they found rearrangement of the starting material occurring under the reaction conditions. They observed, however, that the mesitoate related to Compound 9 was stable.

When mesitoate 11 was placed in piperidine at 130°, the isolated amine fraction consisted mostly (92%) of the syn attack S_N2' product with a small amount (ca. 2%) of the anti attack product. The cis mesitoate 12 when treated with piperidine yielded 20% of the S_N2 product (inverted) and 80% of the syn displacement S_N2' product with no trace of the anti displacement isomer.



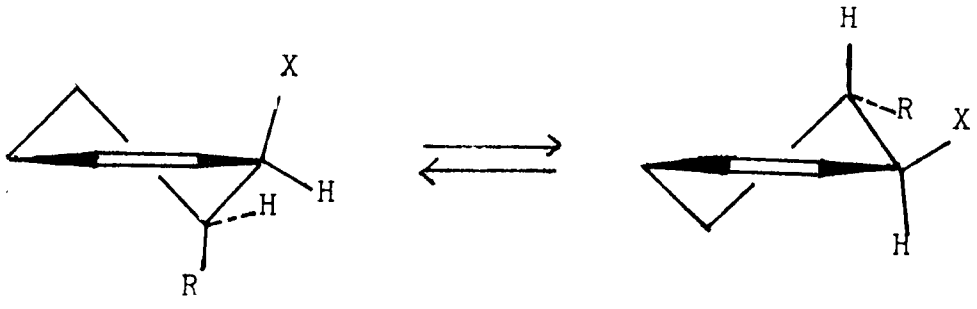
11



12

When Compound 11 was treated with sodium propylthiolate in refluxing 1-butanol it yielded mostly the S_N2 displacement product. The S_N2' product (31.5%) was formed in an 8:1 syn to anti displacement ratio. When hexamethylphosphoramide was used as the solvent in place of 1-butanol the syn to anti ratio was decreased to 2:1. In direct contrast to these results, the anti displacement product predominated in the reaction of Compound 12 with sodium propylthiolate in 1-butanol (35:65::syn:anti).

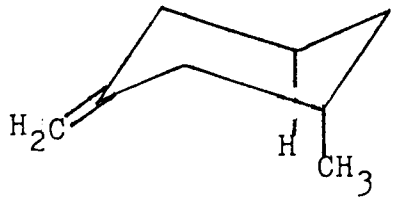
The substrates employed by Stork may lack direct application to S_N2' reactions because of certain steric and conformational biases built into a cyclohexenyl system. These substrates can exist in two half-chair conformations (13 and 14). Unlike a substituted cyclohexane, Conformation



13 ⟷ 14

14 will not be largely favored over Conformation 13 at equilibrium. A pseudo-axial group at C_3 will be disfavored less in a cyclohexene ring than the same group when axial on a cyclohexane, since a pseudo-axial group experiences only one pseudo-axial/axial interaction as opposed to two axial/axial repulsions in the saturated system. Also a pseudo-equatorial group is eclipsed with the adjacent vinylic hydrogen. In cases involving an electronegative substituent, the equilibrium is actually toward the conformation in which the group is pseudo-axial (48). Furthermore, Jensen and Bushweller (49) have observed a decrease in a C_4 substituent's preference for the equatorial position relative to that in a cyclohexane.

To determine an approximate K_{eq} for 13 ⇌ 14, let us use as a model X = acetate and R = methyl. In Conformation 13 there is one 1,3-diaxial methyl/hydrogen interaction which can be estimated as raising the energy by 0.8 kcal/mole (the value Lambert and Clikeman (48c) observed for the one 1,3-diaxial methyl/hydrogen interaction in 3-methyl-exo-methylene-cyclohexane, 15). Also, the pseudo-axial acetate in



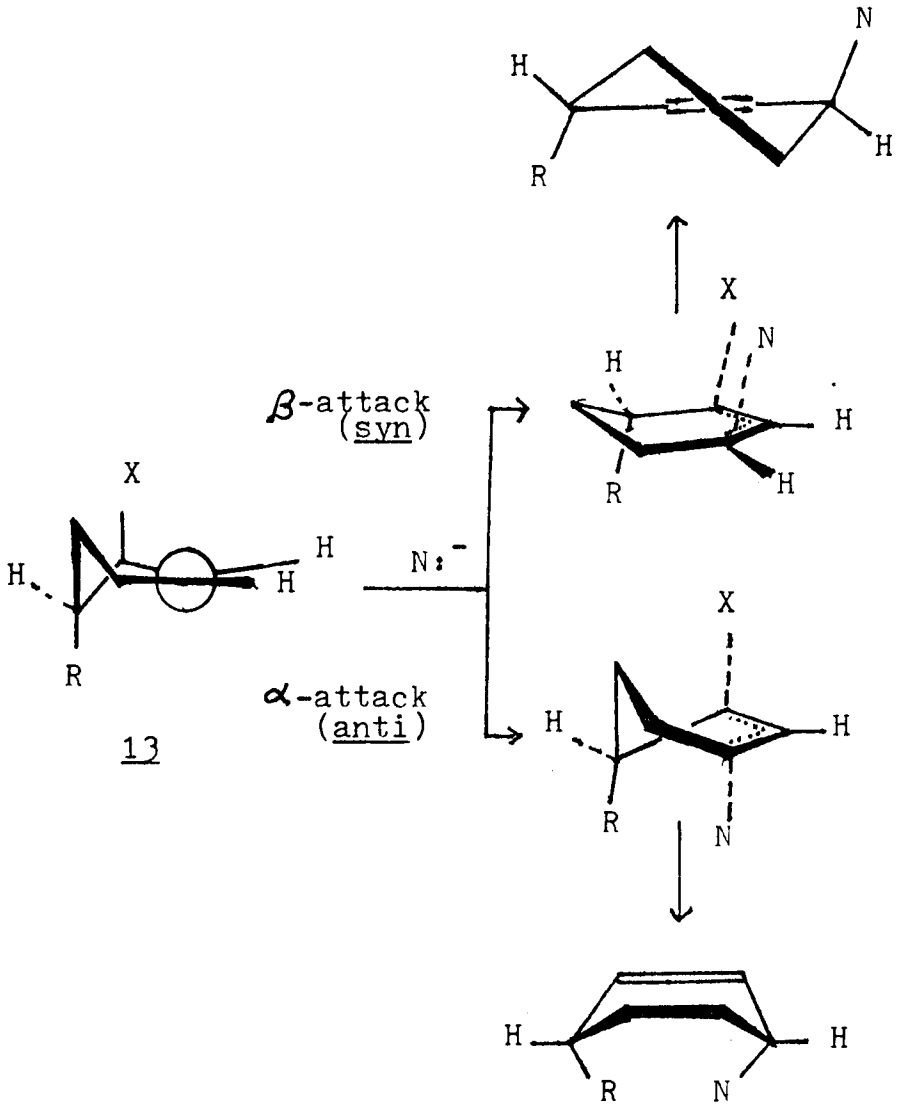
15

Conformation 13 is favored by 0.45 kcal/mole (the value Senda and Imaizumi (48d) found for 2-cyclohexenyl acetate). Therefore, Conformation 13 is disfavored by (0.8-0.45) = 0.35 kcal/mole. Conformation 14 is disfavored by one gauche methyl/acetate repulsion. This interaction can be estimated as 0.35 kcal/mole (one-half the value for the two 1,3-diaxial acetate/hydrogen repulsions of cyclohexyl acetate (48d)). This value is a good estimate as can be seen in the analogy that the gauche methyl/methyl interaction of trans-1,2-dimethylcyclohexane is equal to the 1,3-diaxial methyl/hydrogen repulsion of methylcyclohexane; both are also equal to the value for gauche n-butane (50). Therefore,

Conformations 13 and 14 are both disfavored by 0.35 kcal/mole and one would predict K_{eq} = 1 or a 50/50 mixture of 13 and 14. Thus Stork and White's contention (8) that the equilibrium greatly favors 14 is unwarranted.

The S_N2' reactions of Compounds 8-12 most probably proceed via a conformation like 13 where the pseudo-axial C-X bond is nearly parallel to the p-orbital of the π-bond. Therefore, as the C-X bond ruptures, the developing p-orbital is better able to overlap with the π-system to form the new π-bond of the product.

Valls and Toromanoff (51) have postulated that attack should occur perpendicular to the plane of the double bond of a cyclohexenyl system. Conformation 13 will prefer to undergo perpendicular β-attack rather than α-attack, since the transition state for α-attack resembles a boat conformation (Equation 27). α-Attack is further disfavored because the alkyl group R is actually bent toward the double bond, sterically inhibiting approach from underneath. Goering and Josephson (52) noted similar conformational biases in their studies of acid-catalyzed rearrangements of cis and trans-5-methyl-2-cyclohexenol, but did not develop the argument to the extent needed to cast doubt on the validity of the Stork experiments.



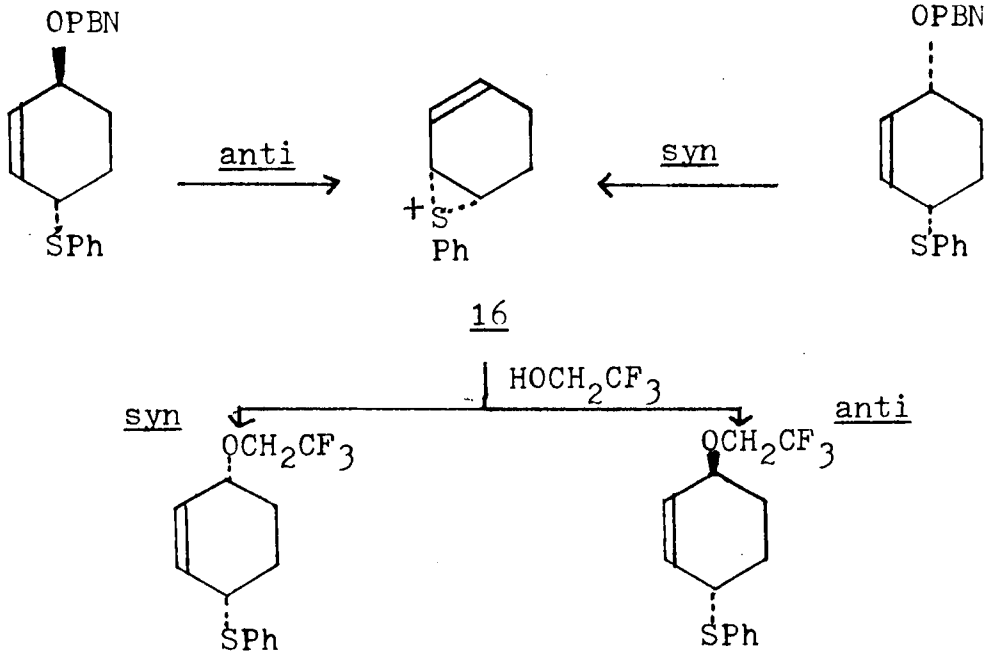
(27)

It should be noted that, if the reaction were proceeding through Conformation 14, α-attack would pass through a half-chair-like conformation transition state while β-attack would occur via a boat-like arrangement, thereby resulting in preferential α-attack (anti). Since the observed results were syn attack, this indicates that Conformation 14 is not the reacting species. Also, Stork and White (8) noted that

as the alkyl substituent on the substrate became bulkier, the rate of the reaction increased; they used this in support of their contention that 14 is the reacting conformation. However, the population of Conformation 13 may actually increase as the R-group becomes bulkier because of the gauche R/X interaction in Conformation 14. Therefore, the Winstein-Holness-Eliel equation (53) would predict an increase in reaction rate as the R-group becomes bulkier. Furthermore, the t-butyl group would be expected to decrease the difference in free energy between the ground state and the transition state as the t-butyl group moves away from the interior of the molecule when the transition state is approached, resulting in an increase in the rate of the reaction.

Consequently, the syn stereochemical preference of Stork's cyclohexenyl systems may have nothing to do with any inherent stereoelectronic preference in the S_N2' reaction and may not be applicable to systems lacking these built-in biases. It should be pointed out that even though Stork was able to obtain predominantly anti attack with the sulfide nucleophile on the cyclohexenyl substrate, this does not indicate that the built-in biases are unimportant. Sulfide is a very unusual nucleophile as can be seen by the fact that Stork's acyclic intramolecular S_N2' reaction involving a sulfide yielded the anti attack product while Martel's (45) intramolecular reaction with a carbanion proceeded syn. In

another case involving sulfur as the nucleophile, Uebel and co-workers (54) have reported that when cis and trans-4-(phenylthio)cyclohex-2-enyl p-nitrobenzoates were solvolyzed in 2,2,2-trifluoroethanol, sulfur participation occurred forming Ion 16 at about equal rates, indicating no stereoelectronic preference for this intramolecular S_N2' process. In addition, solvent attack on Ion 16 yielded equal amounts of syn and anti products which indicates no stereoelectronic preference for this intermolecular S_N2' process, either.

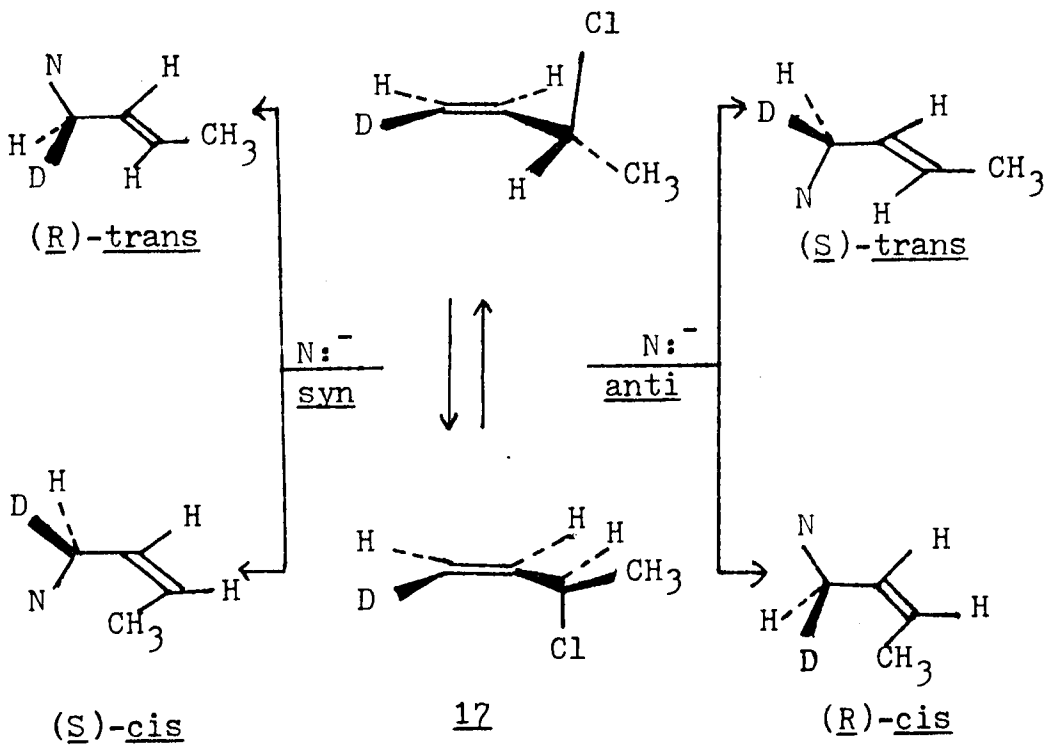


(28)

D. Statement of the Problem

The existing experimental evidence on the stereochemistry of the S_N2' reaction has led to ambiguous results with no definitive conclusions. In order to settle the stereochemical question, an acyclic allylic halide which is free of conformational bias was chosen for the following S_N2' investigation. The substrate utilized was optically active 3-chloro-Z-1-butene-1-d (17), which is merely an isotopic derivative of α-methylallyl chloride (the substrate used by Young and co-workers (6,10)).

The possible S_N2' products for the (R)-(-)-17 isomer are shown in Equation 29. In the products, the (R) and (S)



(29)

designations are assigned by assuming that group N has the highest priority in the Cahn-Ingold-Prelog notation (55).

Compound 17, unlike Stork's substrates, can exist in two rotamers in which the C-X bond is parallel to the π-bond. Both rotamers can react, yielding products which differ in double bond stereochemistry and configuration of the new chiral center. In other words, if the reaction proceeded 100% syn or 100% anti then both cis and trans alkenes would be obtained and when separated, and the double bond reduced, they would have the same absolute rotation differing only in sign. Also, if any mixture of syn and anti attack were to occur, one could obtain the relative percentages, since syn attack yields the (R)-trans product while anti attack yields the (S)-trans product. Therefore, by running S_N2' reactions on Compound 17, separating the cis and trans alkenes, reducing the double bond, and measuring optical activity, one can determine the stereochemistry of the S_N2' reaction.

CHAPTER II

EXPERIMENTAL SECTION

A. General Considerations

In all experiments involving air-sensitive compounds, the glassware was assembled, flame-dried, and maintained under positive nitrogen pressure. A mercury bubbler which was vented to the hood was employed as a release valve for the nitrogen and also served as a trap to prevent air from entering the apparatus. All syringes and hypodermic needles employed in the transfer of air-sensitive substances were dried in the oven at 120° for one hour, assembled hot, allowed to cool, then flushed three times with nitrogen.

All NMR spectra were obtained with a Varian T-60 spectrometer using tetramethylsilane (TMS) as the internal standard. The chemical shifts were recorded in δ units, ppm downfield from TMS.

A Rudolph MP7A41 photoelectric polarimeter was used to determine all optical rotations.

A Hewlett-Packard model 5750 gas chromatograph equipped with a Leeds and Northrup Speedomax XL601 recorder was used for all analytical gas-liquid partition chromatography (glpc) work. Helium was the carrier gas with a flow rate of 45 mL/min. All peak areas were obtained with a series 200 Disc

Integrator (equal molar responses were assumed). The columns were constructed from 1/8 in. od stainless steel tubing and the solid support was Chromosorb W (80-100 mesh).

The analytical columns were:

Column A—10 ft, 10% Carbowax 20M;

Column B—10 ft, 10% SE-30 (Silylated);

Column C—10 ft, 5% UCON 50-HB 280X;

Column D—10 ft, 5% β,β'-Oxydipropionitrile.

Preparative glpc work was performed on a Varian Aerograph, model 920, gas chromatograph equipped with a Leeds and Northrup Speedomax H recorder. A Helium flow rate of 60 mL/min was used. The columns were constructed from 1/4 in. od stainless steel tubing with Chromosorb W (80-100 mesh) solid support.

The preparative columns were:

Column E—6 ft, 10% Carbowax 20M;

Column F—6 ft, 10% SE-30;

Column G—10 ft, 5% UCON-LB 550X;

Column H—6 ft, 20% Carbowax 20M/KOH.

Every reaction with a deuterated compound was originally run with undeuterated material to develop reaction and separation conditions.

B. Preparations

1. Preparation of 2-Propyl-1,3-dithiane-2-d (18) (56)

A solution of 1,3-dithiane (25 g, 0.21 mol) in anhydrous tetrahydrofuran (THF) (200 mL) was stirred at -25° under nitrogen while 2M n-butyllithium solution (0.25 mol) was added. After 1.5 hr the solution was warmed to 0° and treated with 1-iodopropane (27.5 mL, 47.9 g, 0.27 mol). After 12 hr at 3° the solution was cooled to -25° and treated with more 2M n-butyllitium solution (0.31 mol). After standing 1.5 hr at -25° the solution was warmed to 0° and treated with deuterium oxide (>99.7% d; 16 mL) and warmed to room temperature. After 2 hr 2 N hydrochloric acid was added to the organic phase and THF was removed on the rotary evaporator. The residue was extracted with two 150-mL portions of ether; the organic phase was washed with 150 mL of sodium bicarbonate solution and 150 mL of saturated salt solution and then dried over potassium carbonate. The ether was removed on the rotary evaporator yielding an oil (34 g, 99% yield). ^{1}H-NMR (CCl_4) δ 0.9 (broadened t, methyl), 1.5 (m, $-C\underline{H}_2-C\underline{H}_2-CH_3$), 1.9 (m, $-S-CH_2-C\underline{H}_2-$), 2.8 (m, $-S-C\underline{H}_2-$), and the triplet at 3.9 (in the undeuterated material) due to the proton at C-2 was absent. The dithiane derivative was used directly without further purification.

2. Preparation of 1,1-Dimethoxybutane-1-d (19) (56)

Treatment of Dithiane 18 (34 g, 0.21 mol) with a solution of mercuric chloride (134 g, 0.495 mol) in methanol (400 mL) and water (5 mL) followed by addition of mercuric oxide (50 g, 0.23 mol) gave a voluminous precipitate. The mixture was refluxed under nitrogen for 12 hr and then cooled to room temperature. The precipitate was removed by filtration and rinsed with water (500 mL), then slurried with ether (1 L) and filtered. The aqueous phase was saturated with sodium chloride and the organic phase separated. The precipitate was then slurried with pentane (1 L) and filtered. The aqueous phase was extracted with the pentane and the organic phases were combined and washed with a 30% ammonium acetate solution (250 mL) and a saturated sodium chloride solution (250 mL), and dried over potassium carbonate. The ether and pentane were removed by distillation. Then the product was flashed distilled and collected at Dry Ice temperature which yielded a colorless liquid (14 g, 56% yield). ^{1}H-NMR (CCl_4) δ 0.9 (broadened t, 3, $-CH_2-C\underline{H}_3$), 1.5 (m, 4, $CH_3-C\underline{H}_2-C\underline{H}_2-$), 3.1 (s, 6, $OC\underline{H}_3$), and the triplet at 4.3 (in the undeuterated material) due to the proton on C-1 was absent.

3. Preparation of (S)-(+)-1-Butanol-1-d (20) (57)

Acetal 19 (34 g, 0.28 mol) was shaken for 5 min with water (1 L) and hydrochloric acid (5 drops). This solution

was added to a rapidly fermenting mixture of (+)-glucose (1 Kg), water (3 L), and Fleischmann's bakers' yeast (900 g) at room temperature. One week later the mixture was centrifuged to remove the yeast. The liquid was distilled, collecting everything that boiled below 100°. The distillate was saturated with potassium carbonate and the resulting aqueous layer was separated and extracted with ether (500 mL). The combined organic phases were dried (first potassium carbonate, then 3 Å molecular sieves), then fractionated through a long Vigreux column until the residue was a 50/50 mixture of ethanol/Compound 20. This mixture was purified on a preparative gas chromatography column (Column E) yielding (S)-(+)-1-butanol-1-d (11.2 g, 54% yield), $[\alpha]^{25}_{D}$ +0.34 ± 0.01° (neat) [neat, ℓ=0.1, α +0.027°]. Gas chromatographic analysis (Column C) of this purified sample of Compound 20 showed water (0.5%), ethanol (0.5%) and an optically active impurity (0.3%) present. Deuterium analysis by NMR showed 0.96 deuterium atoms per molecule. ^{1}H-NMR (CCl_4) δ 0.9 (broadened t, 3, methyl), 1.3 (m, 4, CH_3-CH_2-CH_2-), 3.5 (m, 1, -CHD-OH), and 4.1 (s, 1, -OH).

4. Preparation of (S)-(-)-1-Butyl-1-d Tosylate (21) (58)

To Alcohol 20 (7 g, 0.095 mol) and p-toluenesulfonyl chloride (28 g, 0.15 mol) at 0° was added pyridine (130 mL) at a constant rate with rapid stirring over a period of one

hour. The reaction was allowed to proceed for two days (3°) and then quenched by pouring the reaction mixture into ice-water (100 mL). The unreacted tosyl chloride was hydrolyzed by stirring the resulting suspension for one hour. Then sulfuric acid (44 mL) in ice (150 g) was added to neutralize the pyridine. The mixture was extracted with ether (250 mL) and then pentane (250 mL). The organic phases were washed with ice-cold dilute sulfuric acid, ice-water, ice-cold dilute sodium hydroxide, and again with ice-water. The combined organic phases were dried (magnesium sulfate) and the solvent removed by flash distillation yielding a yellow oil residue (9 g, 42% yield), $\alpha^{25}\underline{D}$ -0.07 ± 0.01° (neat, ℓ=1) [neat, ℓ=0.1, α -0.007°] and α^{25}_{365} -0.70 ± 0.01° (neat, ℓ=1) [neat, ℓ=0.1, α -0.07°]. ^{1}H-NMR (CCL_4) δ 0.9 (broadened t, 3, $-CH_2-C\underline{H}_3$), 1.5 (m, 4, $-C\underline{H}_2-C\underline{H}_2-CH_3$), 2.4 (s, 3, $ArC\underline{H}_3$), 4.0 (broadened t, 1, -C<u>H</u>D-), and 7.6 (AB pattern, 4, aromatic protons). The alkyl tosylate was used without further purification.

5. <u>Preparation of (R)-(+)-1 Butyl-1-d Azide</u> (<u>22</u>) (59)

Sodium azide (8.6 g, 0.13 mol) and Tosylate <u>21</u> (11 g, 0.049 mol) in hexamethylphosphoramide (100 mL) were heated (110°, 24 hr), and then ice-water (250 mL) was added to the cooled reaction mixture. The upper layer was collected, $\alpha^{26}\underline{D}$ +2.22 ± 0.01° (neat, ℓ=1) [neat, ℓ=0.1, α +0.222°]. The

aqueous layer was extracted with two 125-mL portions of ether. The combined organic phases were washed with a saturated sodium chloride solution (100 mL) then dried (magnesium sulfate). ^{1}H-NMR (CCl_4) δ 0.9 (broadened t, methyl), 1.4 (m, -C<u>H</u>$_2$-C<u>H</u>$_2$-CH$_3$), and 3.2 (broadened t, -C<u>H</u>D-). The alkyl azide was used as the ether solution.

6. <u>Preparation of (R)-(-)-1-Aminobutane-1-d (23)</u> (59)

The above ether solution of Azide <u>22</u> was reduced by adding it to lithium aluminum hydride (2.2 g, 0.058 mol) in anhydrous ether (50 mL) with stirring (20°, 14 hr). The reaction mixture was hydrolyzed (10 mL of water, 5 mL of 5 <u>N</u> sodium hydroxide solution, and then 10 mL of water), filtered, and dried (magnesium sulfate). The hydrochloride was prepared by passing in dry hydrogen chloride gas and was separated by filtering it away from the ether. The free amine was obtained by treating an aqueous solution of the hydrochloride with sodium hydroxide pellets. The amine layer was separated. The aqueous layer was extracted with ether (10 mL) and the combined organic phases were dried (first potassium carbonate, then 3 Å molecular sieves), distilled, and the residue purified by preparative glpc (Column <u>E</u>) yielding 0.8 mL of product, $[\alpha]^{26}_{\underline{D}}$ -0.22 ± 0.01° (neat) [neat, ℓ=0.1, α -0.016°] and $[\alpha]^{26}_{365}$ -0.57 ± 0.01° (neat) [neat, ℓ=0.1, α -0.042°]. ^{1}H-NMR (CCl_4) δ 0.9 (broadened t, methyl), 1.4 (m, -C<u>H</u>$_2$-C<u>H</u>$_2$-), and 2.6 (broadened t, -C<u>H</u>D-).

7. Preparation of (R)-(+)-N,N-Dimethyl-1-aminobutane-1-d (24)

a. Method A (60). In an ice-cooled flask, amine 23 (0.4 mL, 0.3 g, 0.004 mol) was treated with an 88% aqueous solution of formic acid (0.72 g, 0.014 mol) followed by a 36% aqueous solution of formaldehyde (1.02 g, 0.012 mol). The flask was fitted with a reflux condenser and heated (80°, 24 hr). After cooling, dilute hydrochloric acid (0.01 mol) was added and the mixture was extracted with ether (4 mL). The aqueous phase was made basic with a sodium hydroxide solution (0.04 mol) and extracted with ether (5 mL) and then pentane (5 mL). The combined organic phases were washed with water (5 mL) and then dried (first potassium carbonate, then 3 Å molecular sieves). Most of the ether and pentane were removed by distillation. The product was purified by preparative glpc (Column F) yielding 0.12 mL (26% yield) of product, $[\alpha]^{24}_{D}$ +3.17 ± 0.09° (ether) [0.107 g/mL, ℓ=0.1, α +0.034°] and $[\alpha]^{24}_{365}$ + 10.37 ± 0.09° (ether) [0.107 g/mL, ℓ=0.1, α +0.111°]. ^{1}H-NMR (CCl_4) δ 0.9 (broadened t, $-CH_2-CH_3$), 1.4 (m, $-CH_2-CH_2-$), 2.0 (m, $-CHD-$), and 2.1 (s, $-N(CH_3)_2$).

b. Method B. In a pressure bottle, Tosylate 21 (3 g, 0.013 mol) was treated with dimethylamine (50 mL) at room temperature for one week. After most of the dimethylamine was evaporated, water (10 mL) and a 10 N sodium hydroxide solution (10 mL) were added. The mixture was extracted with

ether (50 mL) and the ether was washed with a saturated sodium chloride solution (25 mL), then dried (first magnesium sulfate, then potassium hydroxide pellets, and then 3 Å molecular sieves). Most of the solvent was removed by distillation and the product was purified by preparative glpc (Column F) yielding ca. 0.5 mL of product, $[\alpha]^{24}_{D}$ +3.12 ± 0.06° (ether) [0.1695 g/mL, ℓ=0.1, α +0.053°] and $[\alpha]^{24}_{365}$ +10.32 ± 0.06° (ether) [0.1695 g/mL, ℓ=0.1, α +0.175°].

8. Preparation of (R)-(+)-N,N-Diethyl-1-aminobutane-1-d (25)

Tosylate 21 (2.5 g, 0.011 mol) was treated with diethylamine (100 mL) at room temperature for one week. Ether (125 mL) and then a 10 N sodium hydroxide solution (10 mL) in water (100 mL) were added to the diethylamine solution and the organic phase removed. The aqueous phase was extracted with ether (100 mL) and the combined organic phases dried (first magnesium sulfate, then potassium hydroxide pellets, and then 3 Å molecular sieves). Most of the ether and diethylamine were removed by distillation and the product was purified by preparative glpc (Column E) yielding ca. 0.5 mL of product, $[\alpha]^{24}_{D}$ +5.43 ± 0.03° (ether) [0.348 g/mL, ℓ=0.1, α +0.189°] and $[\alpha]^{24}_{365}$ +18.38 ± 0.03° (ether) [0.348 g/mL, ℓ=0.1, α +0.640°]. ^{1}H-NMR (CCl_4) δ 0.9 (overlapping triplets, methyls), 1.3 (m, $-C\underline{H}_2-C\underline{H}_2-$), 2.2 (m, $-C\underline{H}D-$), and 2.3 (q, $N(C\underline{H}_2CH_3)_2$).

9. Preparation of (R)-(+)-1-Piperidinobutane-1-d (26)

Tosylate 21 (3 g, 0.013 mol) was treated with piperidine (50 mL) at room temperature for two weeks. Ether (50 mL) and then a 10 N sodium hydroxide solution (10 mL) in water (10 mL) were added to the piperidine solution and the organic phase separated. The aqueous phase was extracted with ether (50 mL) and the combined organic phases dried (first magnesium sulfate, then potassium hydroxide pellets, and then 3 Å molecular sieves). The ether and most of the piperidine were removed by distillation through a long Vigreux column and the residue was purified by preparative glpc (Column H) yielding ca. 0.7 mL of product, $[\alpha]^{24}_{D}$ +3.86 ± 0.06° (ether) [0.1657 g/mL, ℓ=0.1, α +0.064°] and $[\alpha]^{24}_{365}$ +12.92 ± 0.06° (ether) [0.1657 g/mL, ℓ=0.1, α +0.214°]. ^{1}H-NMR (CCl_4) δ 0.9 (broadened t, 3, methyl), 1.4 (broadened singlet with fine splitting, 10, $-C\underline{H}_2-C\underline{H}_2-CH_3$ and $N-CH_2-C\underline{H}_2-C\underline{H}_2-C\underline{H}_2-$), and 2.2 (broadened d, 5, $-C\underline{H}D-$ and $-C\underline{H}_2-N-C\underline{H}_2-$).

10. Preparation of Optically Active 1-Buten-3-ol-Z-1-d (27)

According to the method of Grant and Djerassi (61), 1-butyn-3-ol (8 mL, 0.1 mol) in dry THF (50 mL) was treated with a 1 M lithium aluminum hydride-THF solution (62) (110 mL) overnight, then quenched with deuterium oxide (>99.7% d; 13 mL) in dry THF (25 mL), and dried (potassium carbonate). This procedure was repeated five times until there was a

total of 0.5 mol of 1-buten-3-ol-Z-1-d in the THF. Then the alcohol/THF solution was refluxed with phthalic anhydride (81.5 g, 0.55 mol) and pyridine (50 mL, 0.5 mol) for one week (63). The THF was removed on the rotary evaporator leaving an oil which was then mixed with water (100 mL). To this mixture was added an ice-cold 10 N hydrochloric acid solution (50 mL) followed by ether (250 mL). The ether was separated and washed with a saturated sodium chloride solution (50 mL) and dried (magnesium sulfate). The ether was removed on the rotary evaporator yielding an oil with some phthalic anhydride crystals present. The oil was dissolved in benzene (100 mL) and the crystals filtered out. The benzene was removed on the rotary evaporator yielding an oil (45 g) which was dissolved in acetone (200 mL); brucine dihydrate (100 g) was added and dissolved with heating. A salt precipitated out which was recrystallized five times to a constant melting point 162-164° (lit. (63) mp 120-122°). Another 0.5 mol of 1-buten-3-ol-Z-1-d was resolved following the same procedure and the two products were combined yielding 58.4 g of salt. Hydrolysis of the salt was accomplished by shaking with 10 N hydrochloric acid (60 mL) in ice-cold water (150 mL), then extraction with three 150-mL portions of ether and drying over magnesium sulfate. The ether was stripped off on the rotary evaporator leaving an oil (21.4 g), which was hydrolyzed with a 10 N sodium hydroxide solution (24 mL) and

allowed to stand overnight. The aqueous phase was saturated with potassium carbonate and the organic phase separated and dried (potassium carbonate). The product was distilled from calcium oxide (95-97°) yielding a clear liquid (4.1 g) which was purified by preparative glpc (Column E), $\alpha^{30}\underline{D}$ +21.04 ± 0.01° (neat ℓ=1) [neat, ℓ=0.1, α +2.104°] (lit. (64) α_{max} +27.6°). The mother liquor from the recrystallizations was concentrated and worked up in a similar manner yielding product (3.6 g), $\alpha^{24}\underline{D}$ -9.2 ± 0.1° (neat, ℓ=1) [neat, ℓ=0.01, α -0.092°]. ^{1}H-NMR (CCl_4) δ 1.2 (d, 3, J=6 Hz, methyl), 2.6 (s, 1, -O<u>H</u>), 4.2 (quint., 1, J=6 Hz, -C<u>H</u>OH-), 4.9 (d, 1, J=10 Hz, <u>H</u>CD=), and 5.8 (m, 1, =C<u>H</u>-CH-). The vinyl hydrogens were shown to be <u>cis</u> by comparison to a spectrum of authentic Compound <u>27</u> (39).

11. <u>Preparation of (R)-(-)-3-Chloro-Z-1-butene-1-d</u> (<u>17</u>) (65)

Into a flask equipped with a magnetic stirrer were placed hexachloroacetone (20 mL, 34.8 g, 0.13 mol) and (<u>S</u>)-(+)-<u>27</u> (1.3 mL, 1.09 g, 0.015 mol) $\alpha^{30}\underline{D}$ +21.04 ± 0.01° (neat, ℓ=1). The solution was cooled to 0° and triphenylphosphine (4 g, 0.015 mol) was added in small portions over a 20-min period. The mixture was warmed to room temperature and a thick slurry formed. Flash distillation (5 torr, 30 min, ambient temperature) into a Dry Ice-cooled receiver gave a clear volatile material which was purified by preparative

glpc (Column F) yielding ca. 1.0 mL of product, α^{24}_{D} -46.13 ± 0.01° (neat, ℓ=1) [neat, ℓ=0.1, α -4.613°] (lit. (66) α_{max} -61.1°). ^{1}H-NMR (CCl_4) δ 1.6 (d, 3, J=6 Hz, methyl), 4.5 (quint., 1, J=6 Hz, -CHCl-), 5.0 (d, 1, J=10 Hz, HCD=), and 5.9 (m, 1, =CH-CH-). The vinyl hydrogens were shown to be cis by comparison to a spectrum of authentic Compound 17 (39).

The procedure used to prepare Compound 17 was followed for the preparation of many other chloro compounds (see Results and Discussion) with respect to the utility of the hexachloroacetone/triphenylphosphine chlorination technique.

C. Reactions

1. Reaction of (R)-(-)-17 with Diethylamine (10)

To freshly distilled diethylamine (25 mL, 17.7 g, 0.25 mol) was added (R)-(-)-17 (1 mL, 0.01 mol), α^{24}_{D} -46.13 ± 0.01° (neat, ℓ=1) and the mixture was heated at reflux (20 hr). After cooling to room temperature, water (10 mL) was added, followed by a 10 N sodium hydroxide solution (18 mL). The aqueous mixture was extracted with three 25-mL portions of ether, and the combined organic phases dried (first magnesium sulfate, then potassium hydroxide pellets, and then 3 Å molecular sieves). The ether and most of the diethylamine were distilled off using a long Vigreux column. The residue was purified by preparative glpc (Column H) yielding ca.

0.7 mL of N,N-diethyl-1-aminobut-2-ene-1-d (28) which by analytical glpc (Column B) was shown to be a 95:5 mixture of E-28 and Z-28, α^{24}_{D} +1.5 ± 0.1° (neat, ℓ=1) [neat, ℓ=0.01, α +0.015°] and α^{24}_{365} + 6.1 ± 0.1° (neat, ℓ=1) [neat, ℓ=0.01, α +0.061°]. ^{1}H-NMR (CCl_4) δ 1.0 (t, 6, J=7 Hz, $-CH_2-CH_3$), 1.7 (broadened d, 3, J=5 Hz, $=CH-CH_3$), 2.4 (q, 4, J=7 Hz, $-CH_2-CH_3$), 2.9 (broadened s, 1, -HCD-), and 5.4 (m, 2, vinyl protons). The crude reaction mixture before purification was shown by analytical glpc (Column B) to be a 99:1 mixture of S_N2' and S_N2 products.

2. Diimide Reduction of 28 (67)

The 0.7 mL (0.6 g, 0.005 mol) of Amine 28 obtained from the above reaction was placed in a flask with water (75 mL), potassium hydroxide (11.2 g, 0.2 mol), and p-toluenesulfonyl hydrazide (18.6 g, 0.1 mol) and heated at reflux (4 hr). The cooled solution was extracted with ether (40 mL) and the ether phase dried (first potassium carbonate, then 3 Å molecular sieves). Most of the ether was removed by distillation and the residue was purified by preparative glpc (Column H) yielding ca. 0.1 mL of N,N-diethyl-1-aminobutane-1-d (25), $[\alpha]^{25}_{D}$ + 3.5 ± 0.2° (ether) [0.054 g/mL, ℓ=0.1, α +0.019°] and $[\alpha]^{25}_{365}$ + 12.2 ± 0.2° (ether) [0.054 g/mL, ℓ=0.1, α +0.066°]. ^{1}H-NMR spectrum matched that of Compound 25 prepared from Compound 21. The crude reaction mixture

before purification showed 24.8% of unreduced starting material (by glpc) present.

3. Reaction of (S)-(+)-17 with Dimethylamine (68)

A pressure bottle was charged with dimethylamine (50 mL, 34 g, 0.76 mol), ether (25 mL), and (S)-(+)-17 (1.5 mL, 1.4 g, 0.015 mol), α^{24}_{D} +20.2 ± 0.1° (neat, ℓ=1). The contents were allowed to stand at room temperature for one week, after which most of the dimethylamine was allowed to evaporate. A 10 N sodium hydroxide solution (5 mL) in water (5 ml) was added and the aqueous mixture extracted with ether (30 mL). The ether was separated and dried (first potassium carbonate, then 3 Å molecular sieves). Most of the ether was distilled off and the residue was purified by preparative glpc (Column H) yielding ca. 0.5 mL of N,N-dimethyl-1-aminobut-2-ene-1-d (29) which by analytical glpc (Column B) was shown to be exclusively the E isomer, α^{24}_{D} -0.3 ± 0.1° (neat, ℓ=1) [neat, ℓ=0.01, α -0.003°] and α^{24}_{365} -1.4 ± 0.1° (neat, ℓ=1) [neat, ℓ=0.01, α -0.014°]. ^{1}H-NMR (CCl_4) δ 1.6 (broadened d, 3, J=5 Hz, CH_3-CH=), 2.0 (s, 6, -N(CH_3)$_2$), 2.7 (m, 1, -CHD-), and 5.4 (m, 2, vinyl protons). The crude reaction mixture before purification was shown by analytical glpc (Column B) to be a 99:1 mixture of S_N2' and S_N2 products.

4. Diimide Reduction of 29 (67)

The 0.5 mL (0.4 g, 0.004 mol) of Amine 29 obtained from the above reaction was placed in a flask with water (50 mL), potassium hydroxide (11.2 g, 0.2 mol), and p-toluenesulfonyl hydrazide (18.6 g, 0.1 mol) and heated at reflux (4 hr). The cooled solution was extracted with ether (40 mL) and the ether phase dried (first potassium carbonate, then 3 Å molecular sieves). Most of the ether was removed by distillation and the residue was purified by preparative glpc (Column H) yielding ca. 0.1 mL of N,N-dimethyl-1-aminobutane-1-d (24), $[\alpha]^{26}_{D}$ -1.0 ± 0.2° (ether) [0.0549 g/mL, ℓ=0.1, α -0.006°] and $[\alpha]^{26}_{365}$ -3.5 ± 0.2° (ether) [0.0549 g/mL, ℓ=0.1, α -0.021°]. The ^{1}H-NMR spectrum matched that of Compound 24 prepared from Compound 21. The crude reaction mixture before purification showed 30% of unreduced starting material (by glpc) present.

5. Reaction of (S)-(+)-17 with Piperidine (8)

To freshly distilled piperidine (10 mL, 8.6 g, 0.1 mol) was added (S)-(+)-17 (1.2 mL, 1.1 g, 0.012 mol), α^{24}_{D} +20.0 ± 0.1° (neat, ℓ=1) and the mixture was heated at reflux (20 hr). After cooling to room temperature, water (10 mL) was added, followed by a 10 N sodium hydroxide solution (10 mL). The aqueous mixture was extracted with two 25-mL portions of ether, and the combined organic phases dried

(first magnesium sulfate, then potassium hydroxide pellets, and then 3 Å molecular sieves). The ether and most of the piperidine were distilled off and the residue was purified by preparative glpc (Column H) yielding ca. 0.8 mL of 1-piperidinobut-2-ene-1-d (30), which by analytical glpc (Column B) was shown to be exclusively the E isomer, α^{24}_{D} -0.7 ± 0.1° (neat, ℓ=1) [neat, ℓ=0.01, α -0.007°] and α^{24}_{365} -2.2 ± 0.1° (neat, ℓ=1) [neat, ℓ=0.01, α -0.022°]. ^{1}H-NMR (CCl_4) δ 1.4 (broad s, -N-CH_2-CH_2-CH_2-CH_2-), 1.6 (broadened d, methyl), 2.3 (broad s, -CH_2-N-CH_2-), 2.8 (broad s with fine splitting, -CHD-), and 5.4 (m, vinyl protons). The crude reaction mixture before purification was shown by analytical glpc (Column B) to be a 97:3 mixture of S_N2' and S_N2 products.

6. Diimide Reduction of 30 (67)

The 0.8 mL (0.7 g, 0.005 mol) of Amine 30 obtained from the above reaction was placed in a flask with water (50 mL), potassium hydroxide (11.2 g, 0.2 mol), and p-toluenesulfonyl hydrazide (18.6 g, 0.1 mol) and heated at reflux (4 hr). The cooled solution was extracted with ether (50 mL) and the ether phase dried (first magnesium sulfate, then 3 Å molecular sieves). Most of the ether was removed by distillation and the residue was purified by preparative glpc (Column H) yielding ca. 0.15 mL of 1-piperidinobutane-1-d (26),

$[\alpha]^{24}_{\underline{D}}$ -1.3 ± 0.1° (ether) [0.1038 g/mL, ℓ=0.1, α -0.013°] and $[\alpha]^{24}_{365}$ -4.3 ± 0.1° (ether) [0.1038 g/mL, ℓ=0.1, α -0.045°]. ^{1}H-NMR spectrum matched that of Compound 26 prepared from Compound 21. The crude reaction mixture before purification showed 25% of unreduced starting material (by glpc) present.

CHAPTER III

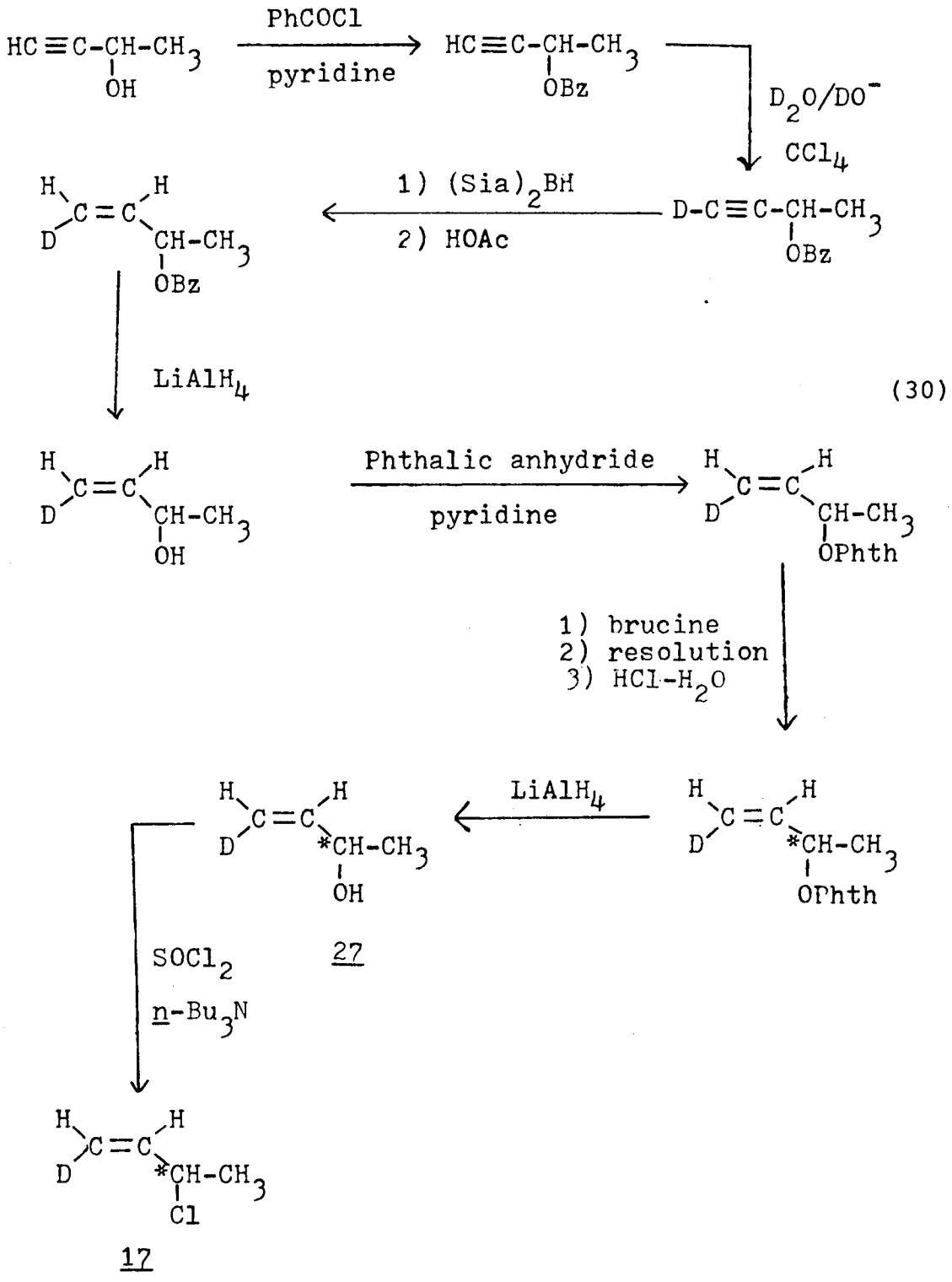
RESULTS AND DISCUSSION

The present investigation into the stereochemistry of the S_N2' reaction began with the synthesis of optically active 3-chloro-Z-1-butene-1-d (17) (page 29).

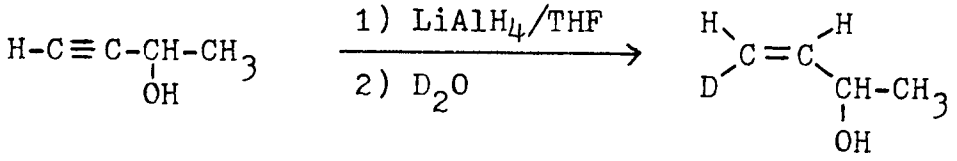
Compound 17 (page 29) had been synthesized (Equation 30) by Magid and Nieh (39) in connection with their stereochemical study of the coupling reaction of phenyllithium with allylic chlorides. In light of the recent work by Grant and Djerassi (61), the original synthesis of Compound 17 (page 29) has been modified.

Grant and Djerassi (61) found that hydride reduction (via lithium aluminum hydride) of 1-alkyn-3-ols proceeds regiospecifically when THF is employed as the solvent. That is, when a 1-alkyn-3-ol is treated with lithium aluminum hydride in THF and then quenched with deuterium oxide, the resulting allylic alcohol is produced with 100% trans addition of hydrogen and deuterium.

It therefore appeared possible to produce 1-butene-3-ol-Z-1-d (27) (page 40) in one step from 1-butyn-3-ol by a lithium aluminum hydride reduction in THF, followed by quenching with deuterium oxide (Equation 31). However, when the reduction was performed by the Grant and Djerassi method (addition of the alcohol to hydride solution), a small amount


PhCOCl
pyridine
D2O/DO⁻
CCl4
1) (Sia)2BH
2) HOAc
LiAlH4
Phthalic anhydride
pyridine
1) brucine
2) resolution
3) HCl-H2O
LiAlH4
SOCl2
n-Bu3N
27
17

(30)



(31)

27

of over-reduced alcohol (deuterated 2-butanol) was formed along with the desired product. It was found, however, that the over-reduction could be eliminated by doing an inverse addition (addition of a lithium aluminum hydride-THF solution to the alcohol in THF).

Because isolation of Alcohol 27 (page 40) was very tedious, the phthalate half-ester was prepared directly from the THF solution of the alcohol. The phthalate ester was then resolved with brucine, and optically active 27 (page 40) was isolated following hydrolysis. The vinyl hydrogens of Alcohol 27 (page 40) were shown to be cis by their characteristic NMR spectrum.

The last step in the preparation of Compound 17 (page 29) involves chlorination of Alcohol 27 (page 40). In the original synthesis, Magid and Nieh accomplished this via thionyl chloride (by the method of Young and co-workers (69)). However, this method of chlorination suffers from two disadvantages. When Magid and Nieh treated (S)-(+)-27 (page 40) (75.7% optically pure) with thionyl chloride, they obtained a 69:31 mixture of Chloride 17 (page 29) and

1-chloro-2-butene-1-d which, upon purification, yielded (R)-(-)-17 (page 29) (50.4% optically pure). Therefore, the thionyl chloride reaction proceeded with a significant amount of racemization and a large amount of rearrangement.

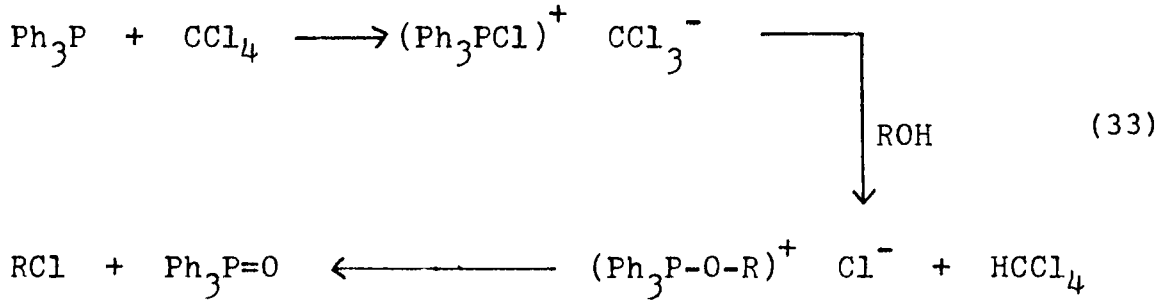
In an effort to alleviate these problems, a new chlorination method was investigated. Snyder (70) had reported the conversion of 1-buten-3-ol into 3-chloro-1-butene by the triphenylphosphine-carbon tetrachloride reagent. This chlorination technique produced an 89:11 mixture of unrearranged and rearranged chloride products (Equation 32).

$$CH_2=CH-\underset{OH}{CH}-CH_3 \longrightarrow CH_2=CH-\underset{Cl}{CH}-CH_3 + \underset{Cl}{CH_2}-CH=CH-CH_3 \quad (32)$$

In non-allylic systems, the triphenylphosphine-carbon tetrachloride system has been shown to yield products with high inversion of configuration (71). Unfortunately, this chlorination system is impractical for the conversion of Alcohol 27 (page 40) into Chloride 17 (page 29) because the boiling point of Chloride 17 (page 29) is close to those of carbon tetrachloride (the solvent for the reaction) and chloroform (one of the reaction products). This makes isolation of 17 (page 29) a difficult task.

In an effort to circumvent this isolation problem, a higher-boiling halogen compound was sought as a substitute

for carbon tetrachloride. The necessary properties of such a halogen compound can be deduced from a close investigation of the presumed overall mechanism of the triphenylphosphine-carbon tetrachloride system (Equation 33) (71f).



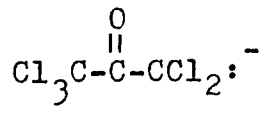
(33)

The halogen compound must be a good source of positive halogen and also possess a good leaving group like Anion 31.

$$Cl_3C:^-$$

31

Hexachloroacetone (HCA) meets all of these requirements. It is high boiling (bp 202°) and has been shown to be a source of positive halogen (72). Also, Anion 32 should be a better leaving group than Anion 31.



32

The reaction of 1-butene-3-ol in HCA with triphenylphosphine is rapid (20 min at 10°) and exothermic, yielding a 94:6 mixture of 3-chloro-1-butene and 1-chloro-2-butene. Also, high stereoselectively was found for the triphenylphosphine-HCA system in the conversion of (R)-(-)-1-buten-3-ol, α^{25}_{D} -7.7° (neat, ℓ=1), 27.9% optically pure, into (S)-(+)-3-chloro-1-butene, α^{25}_{D} +15.1° (neat, ℓ=1), 24.8% optically pure. This means the reaction proceeded with 90% inversion and only 10% racemization.

Encouraged by these results, we treated other allylic alcohols with the triphenylphosphine-HCA reagent (Table I). From the results in Table I it is quite obvious that the triphenylphosphine-HCA system is only useful for primary and secondary allylic alcohols. Tertiary allylic alcohols yield mostly rearranged and elimination products.

This new chlorination technique appears to have great utility for the synthesis of primary and secondary allylic chlorides from their respective allylic alcohols. Furthermore, the geometrical integrity of the double bond is quantitatively preserved, as evidenced by the reactions of (E)- and (Z)-2-buten-1-ol (as well as (E)- and (Z)-2-methyl-

TABLE I

REACTION OF ALLYLIC ALCOHOLS WITH TRIPHENYLPHOSPHINE/ HEXACHLOROACETONE

Alcohol	Percent Yield α-Product[f]	γ-Product[g]	Diene[h]
(E)-$CH_3CH=CHCH_2OH$	99.3[i]	0.7	--
(Z)-$CH_3CH=CHCH_2OH$[a,d]	98[e]	0.5	--
(E)-$CH_3CH=C(CH_3)CH_2OH$[a]	98.5[i]	--	--
(Z)-$CH_3CH=C(CH_3)CH_2OH$[a]	100[i]	--	--
$(CH_3)_2C=CHCH_2OH$[b]	91.3	--	--
$CH_2=CHCH(OH)CH_3$	94	6	--
$CH_2=CHCH(OH)CH_2CH_3$	80.3	6.5	12.1
$CH_2=CHCH(OH)CH(CH_3)_2$	27	15	61
$(CH_3)_2C=CHCH(OH)CH_3$[b]	82[c]	18[c]	--
$CH_2=C(CH_3)CH(OH)CH_3$[b]	92.4	3.3	--
$CH_3CH=CHCH(OH)CH_2CH_3$[b]	67[c]	33[c]	--
$CH_3CH=CHCH(OH)CH(CH_3)_2$[b]	62[c]	38[c]	--
$CH_2=CHC(CH_3)_2-OH$	21.2	43.2	17.7
$CH_2=CHC(CH_3)(OH)CH_2CH_3$	7.1	14.6	46.8

[a] Work performed in collaboration with W. L. Johnson.

[b] Work performed in collaboration with T. G. Allen.

[c] No yield obtained (ratio by NMR).

[d] A 94:6 mixture (glpc) of (Z)- and (E)-2-buten-1-ol.

[e] A 94:6 mixture (glpc) of (Z)- and (E)-1-chloro-2-butene.

[f] Unrearranged product.

[g] Rearranged product.

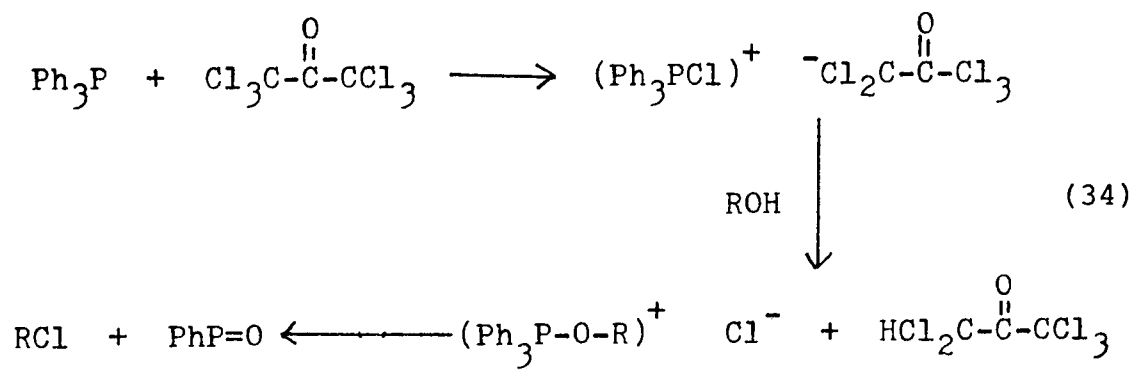
[h] Product due to elimination of hydrogen chloride.

[i] Same geometrical isomer as starting alcohol; no change in double bond geometry.

2-buten-1-ol) with the triphenylphosphine-HCA system (this is also typical of the triphenylphosphine-carbon tetrachloride system (73)).

This new chlorination reaction is very rapid, as indicated by the fact that the chlorination of neopentyl alcohol by triphenylphosphine-HCA takes 45 min (74) (with an 82% yield) as compared to 48 hr (71c) for triphenylphosphine-carbon tetrachloride. Similarly, chlorination of 1-buten-3-ol by triphenylphosphine-HCA takes 20 min while the old method with carbon tetrachloride requires 48 hr (70).

Though no mechanistic study has been applied to the triphenylphosphine-HCA system, it is assumed that the reaction mechanism (Equation 34) is analogous to that of the

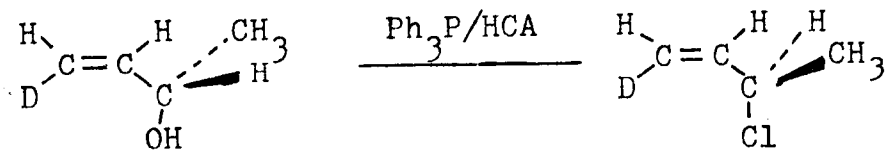


(34)

carbon tetrachloride reaction. This mechanism, however, does not explain why carbon tetrachloride is formed in every reaction involving a primary alcohol. Also, it was noted that the amount of carbon tetrachloride could be decreased

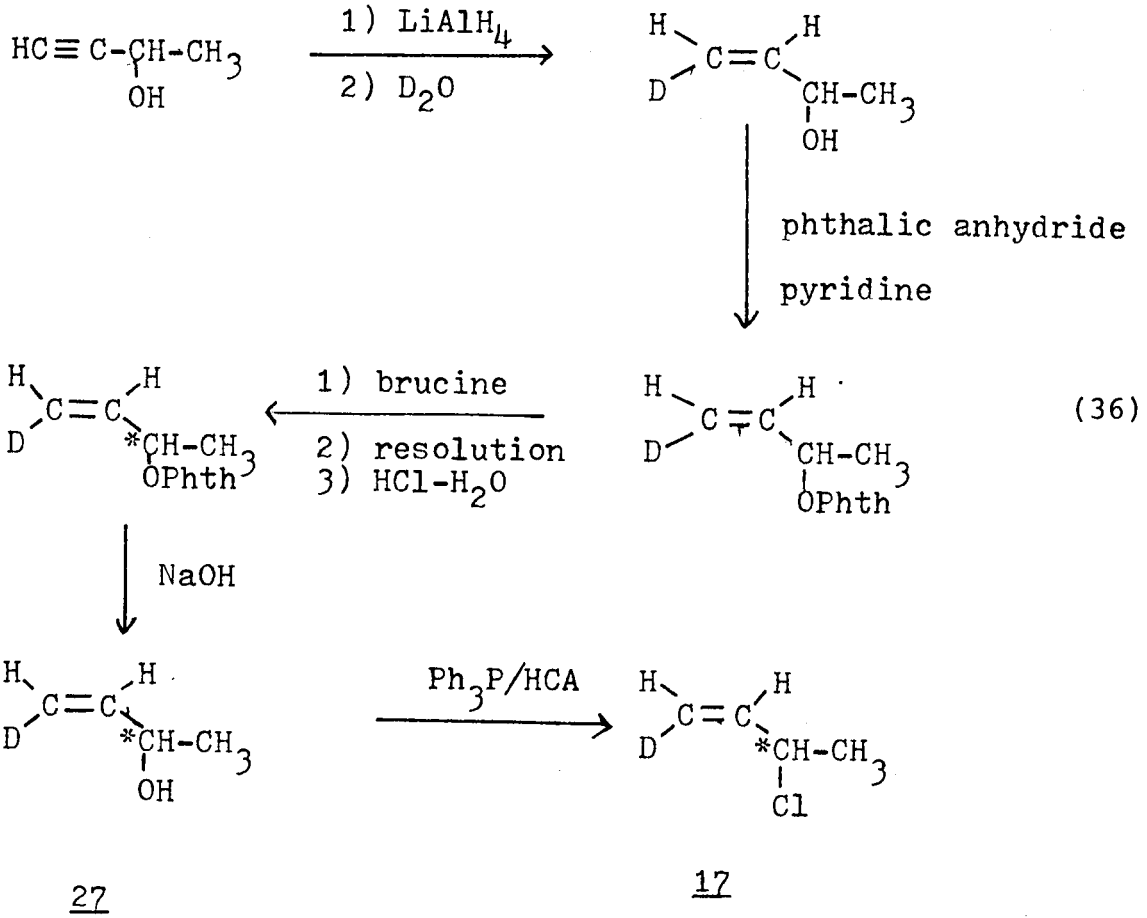
if the alcohol was added to HCA already containing triphenylphosphine as opposed to adding triphenylphosphine to a solution of the alcohol and HCA (74).

Since the triphenylphosphine-HCA system exhibited very high yields along with high regioselectivity and stereoselectivity, as well as quantitative maintenance of double bond integrity, it was chosen as the method of preference for the conversion of optically active 27 (page 40) into optically active 17 (page 29). Reaction of (S)-(+)-27 (page 40), $\alpha^{30}_{\underline{D}}$ + 21.04 ± 0.01° (neat, ℓ=1), 76.2 ± 0.3% optically pure, with triphenylphosphine-HCA proceeded with nearly complete inversion of configuration to (R)-(-)-17 (page 29), $\alpha^{24}_{\underline{D}}$ -46.13 ± 0.01° (neat, ℓ=1), 75.5 ± 0.1% optically pure (Equation 35). The vinyl protons of 17 (page 29) were shown to be cis by their characteristic NMR spectrum.



27 17 (35)

With the above-mentioned modifications, a shorter and more efficient synthesis of Compound 17 (page 29) is available (Equation 36).



(36)

27 17

Now that Substrate 17 (page 29) was available, attention was turned to the problem of analysis of the S_N2' reaction products. Since this investigation was to deal only with secondary amine nucleophiles, the anticipated products from Equation 29 (page 29) would be unsaturated amines. The maximum rotations and absolute configurations of these products were unknown and impractical to obtain. Therefore, analysis depended upon conversion into compounds of known or easily attainable absolute configurations and maximum rotations. By reducing the double bond in the allylic amine

products, one would obtain 1-aminobutane-1-d derivatives (Equation 37) which could be independently synthesized with known stereochemistry.

$$CH_3\text{-}CH{=}CH\text{-}CHD\text{-}NR_2 \longrightarrow CH_3CH_2CH_2CHD\text{-}NR_2 \qquad (37)$$

The reduction of the double bond cannot be accomplished by catalytic hydrogenation since hydrogen-deuterium exchange and loss of optical activity are known to occur on the catalyst surface (75). Therefore, the reduction was performed by the diimide method (76). The reaction was initially attempted by generating diimide in situ from azodicarboxylate (Equation 38) (72).

$$KO_2C\text{-}N{=}N\text{-}CO_2K + 2\ H^+ \longrightarrow CO_2 + HN{=}NH \qquad (38)$$

Unfortunately, this method of generation of diimide was unsatisfactory for the reduction of the unsaturated amines. Diimide was easily generated, but under the acidic conditions of the reaction, disproportionation (Equation 39) dominated and unreacted starting material was obtained along with a few percent of reduction product.

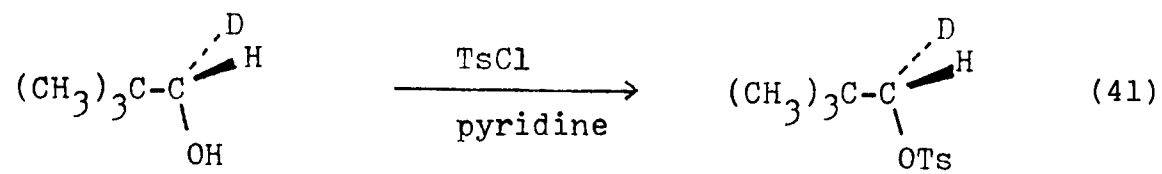
$$2\ HN{=}NH \longrightarrow N_2 + H_2N\text{-}NH_2 \qquad (39)$$

Diimide can also be generated by the thermal cleavage of arenesulfonyl hydrazides in the presence of base (Equation 40) (76). By slightly modifying Dewey and van Tamelen's (67) method of diimide production from p-toluenesulfonyl hydrazide, reductions of the unsaturated amines were accomplished (70-75% reduction).

$$ArSO_2\text{-}NH\text{-}NH_2 \xrightarrow{^-OH} ArSO_2^- + H_2O + HN{=}NH \qquad (40)$$

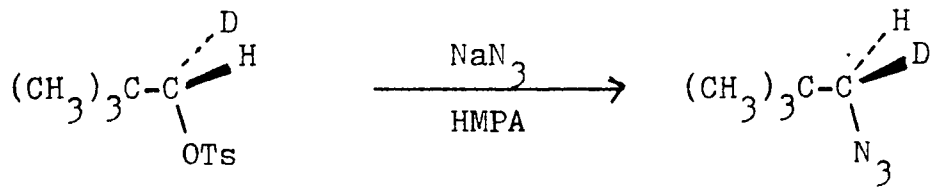
The S_N2' reactions to be studied were Chloride 17 (page 29) with diethylamine, dimethylamine and piperidine. Thus, the absolute configurations and maximum rotations for N,N-diethyl-1-aminobutane-1-d (25) (page 39), N,N-dimethyl-1-aminobutane-1-d (24) (page 38), and 1-piperidinobutane-1-d (26) (page 40) needed to be determined.

Mosher and co-workers (59,78) have developed methods for the synthesis and determination of absolute configuration of 1-deuterio compounds from studies of neopentyl compounds. Starting with (S)-neopentyl-1-d alcohol, the tosylate can be made with 100% retention of configuration (Equation 41).



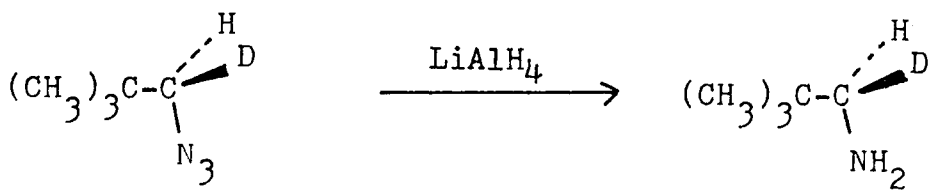
(41)

When (S)-neopentyl-1-d tosylate is treated with sodium azide in hexamethylphosphoramide (HMPA), (R)-neopentyl-1-d azide is formed with, presumably, 100% inversion of configuration (Equation 42).



(42)

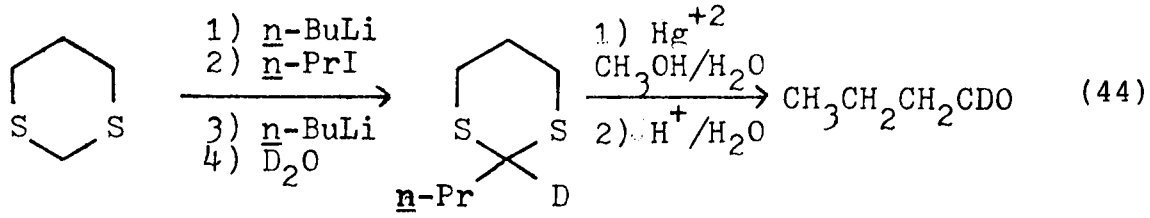
Lithium aluminum hydride reduction of (R)-neopentyl-1-d azide produces (R)-1-aminoneopentane-1-d with 100% retention of configuration (Equation 43).



(43)

Using these stereospecific reactions as a basis for the synthesis and determination of absolute configuration of Amines 24 (page 38), 25 (page 39), and 26 (page 40), the synthesis of (S)-(+)-1-butanol-1-d (20) (page 34) was undertaken. Mosher and co-workers (57) have previously reported the asymmetric reduction of butanal-1-d to (S)-(+)-20 (page 34) by actively fermenting yeast. The butanal-1-d was readily

attainable from 1,3-dithiane by consecutive alkylation and deuteration followed by hydrolysis with mercuric chloride-mercuric oxide (Equation 44) (56). In fact, the aldehyde



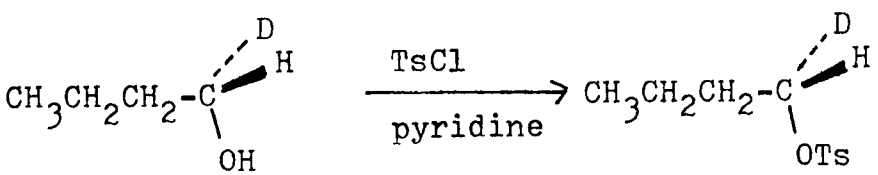
(44)

itself was not obtained but rather the dimethyl acetal which was converted into the aldehyde by shaking with water containing some hydrochloric acid. This aqueous solution of the aldehyde was poured into a rapidly fermenting yeast solution and the desired (S)-(+)-20 (page 34) was obtained. The product had a 96% deuterium content (by NMR) and $[\alpha]^{25}_{D}$ +0.34 ± 0.01° (neat). Correction to 100% deuterium content yields $[\alpha]^{25}_{D}$ +0.35 ± 0.01° (neat).

Yeast reduction is known to be a stereospecific process, but this observed value is only 77% of that cited for optically pure material (57). However, the compound is optically pure, within the detection limits of the Gerlach (79) camphanate ester method. The decrease in the observed rotation is due to the presence of a high-rotating levorotatory impurity (ca. 0.3%) which was separated (but not identified) by glpc. A small amount of alcohol was partly

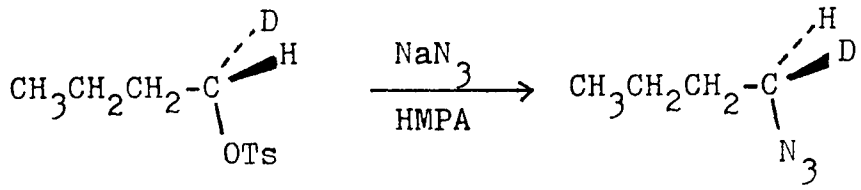
purified by preparative glpc (although some of the optically active impurity still remained) and the optical rotation increased from +0.35° to +0.39°. Since removal of this impurity at this stage would have resulted in huge losses of the alcohol, the (S)-(+)-20 (page 34) was not further purified and was used directly; the impurity was absent by the time that the desired amines were obtained.

The conversion of (S)-(+)-20 (page 34) into the tosylate was accomplished by treating the alcohol with pyridine and p-toluenesulfonyl chloride (Equation 45). Because this should proceed with retention of configuration (analogous to Mosher's neopentyl case) (59,78), the resulting tosylate should also have the S configuration.



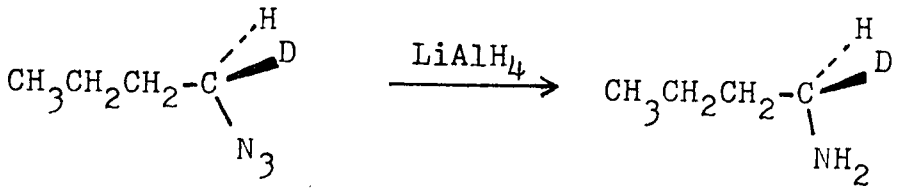
20 21 (45)

Upon treatment of the tosylate with sodium azide in hexamethylphosphoramide (Equation 46), the inverted azide was obtained, $\alpha^{26}\underline{D}$ +2.22 ± 0.01° (neat, ℓ=1) (corrected to 100% deuterium content $\alpha^{26}\underline{D}$ +2.31 ± 0.01°) (unpurified sample). By analogy to Mosher's (59,78) neopentyl case, the azide should have the R configuration.



21 22 (46)

Lithium aluminum hydride reduction of the azide (Equation 47) yields (R)-1-aminobutane-1-d (23) (page 37)

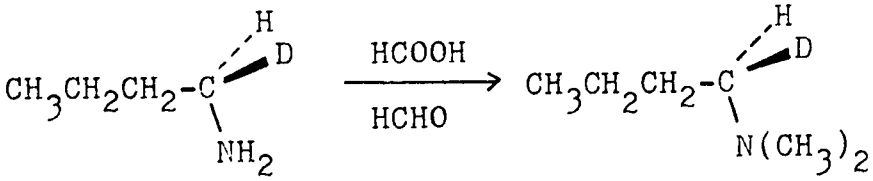


22 23 (47)

with retention of configuration, $[\alpha]^{26}_{\underline{D}}$ -0.23 ± 0.01° (neat) (corrected to 100% deuterium content). It should be noted that the sign of rotation differs from that obtained by Streitwieser and Schaeffer (80), (S)-23 (page 37) $[\alpha]_{\underline{D}}$ -0.009°, but this early work was performed before the advent of glpc capabilities and the material may well have contained impurities.

The primary Amine (R)-(-)-23 (page 37) was converted into N,N-dimethyl-1-aminobutane-1-d (24)(page 38), $[\alpha]^{24}_{\underline{D}}$ +3.30 ± 0.09° (ether) (corrected to 100% deuterium) and $[\alpha]^{24}_{365}$ +10.80 ± 0.09° (ether) (corrected to 100% deuterium),

by Eschweiler-Clarke methylation (Equation 48). Since the

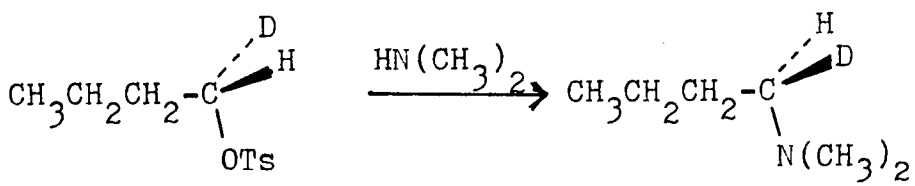


(48)

23 24

methylation does not affect the chiral center, the product will have the R configuration. The specific rotation of tertiary Amine 24 (page 38) is unusually large and unprecedented among saturated chiral deuterium compounds (59,78,81).

Tertiary Amine (R)-(+)-24 (page 38) was also synthesized by direct displacement of Tosylate 21 (page 35) with dimethylamine (Equation 49). This reaction occurs with

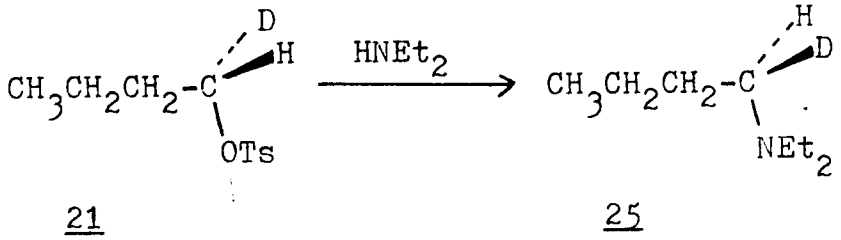


(49)

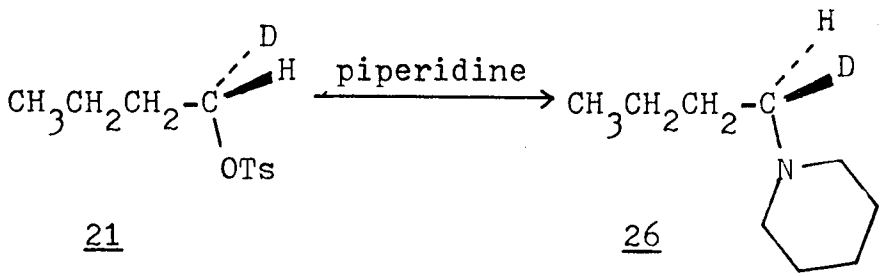
21 24

complete inversion of configuration since (R)-(+)-24 (page 38) obtained in this manner showed the same specific rotations, $[\alpha]^{24}_{D}$ +3.25 ± 0.06° (ether) (corrected to 100% deuterium content) and $[\alpha]^{24}_{365}$ +10.75 ± 0.06° (ether) (corrected to 100% deuterium), as those obtained by the Eschweiler-Clarke method.

Amines (R)-(+)-25 (page 39) and (R)-(+)-26 (page 40) were prepared by direct displacement on Tosylate 21 (Equations 50 and 51). The specific rotations corrected to 100%



21 25 (50)



21 26 (51)

deuterium content are in Table II. Thus, the optical parameters necessary to analyze the S_N2' reactions of interest have been determined.

The first S_N2' reaction examined was Young's (10) α-methylallyl chloride-diethylamine system. Treatment of (R)-(-)-17 (page 29), $\alpha^{24}\underline{D}$ -46.13 ± 0.01° (neat, ℓ=1) (75.5 ± 0.1% optically pure), with diethylamine (Equation 52) produced a 99:1 mixture of S_N2' and S_N2 products. Purification of the S_N2' product by glpc yielded a 95:5 mixture (by glpc) of (E)-28 and (Z)-28 (page 44), $\alpha^{24}\underline{D}$ +1.5 ± 0.1° (neat, ℓ=1) and

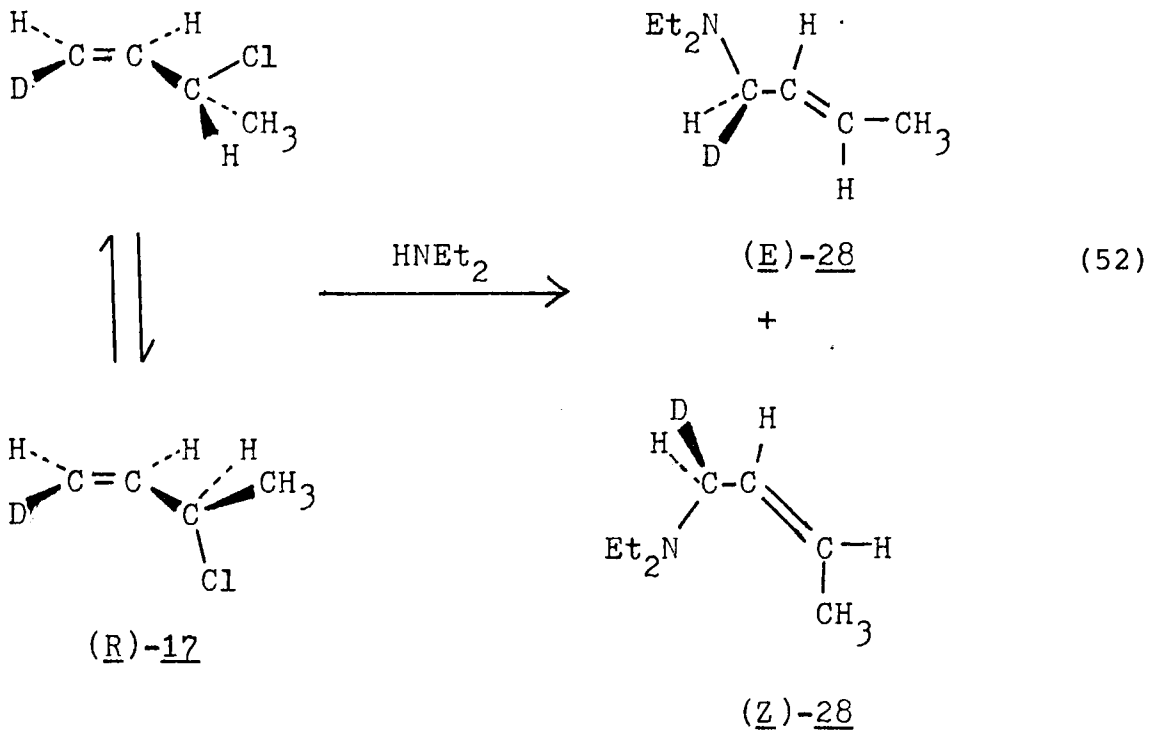
TABLE II

SPECIFIC ROTATIONS OF REFERENCE COMPOUNDS

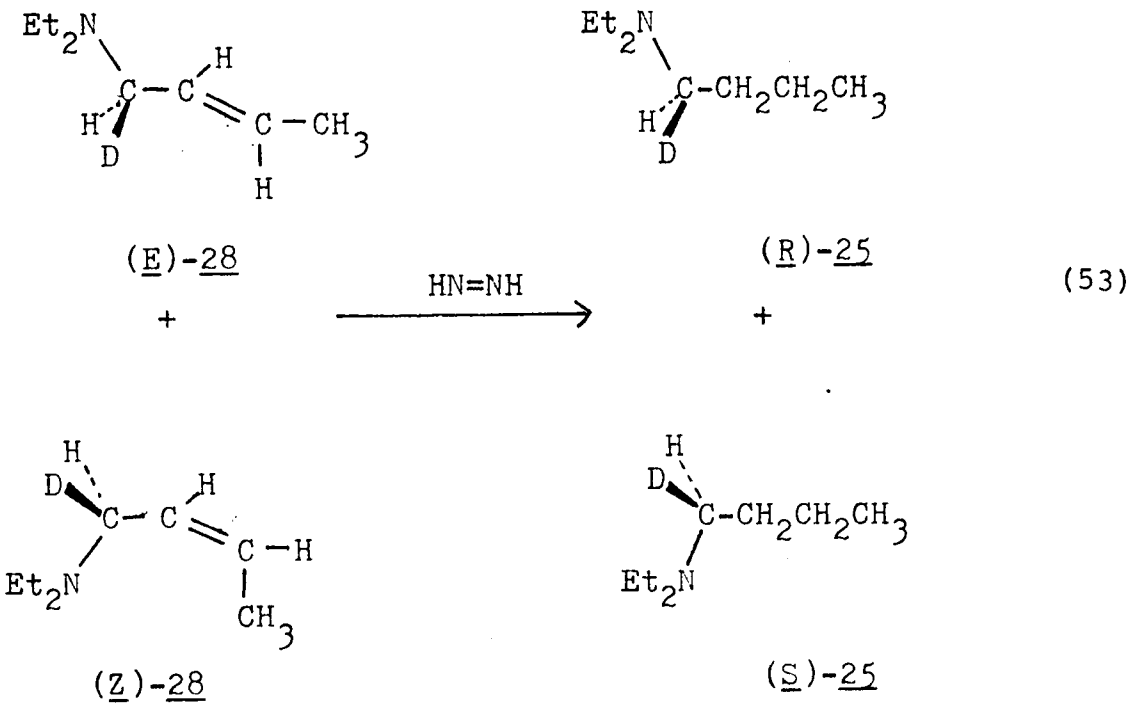
Amine	Specific Rotation[a] 589 nm	365 nm
(R)-(+)-24 (p 38)	+3.25 ± 0.06°	+10.75 ± 0.06°
(R)-(+)-25 (p 39)	+5.66 ± 0.03°	+19.14 ± 0.03°
(R)-(+)-26 (p 40)	+4.02 ± 0.06°	+13.46 ± 0.06°

[a]Rotations were taken in ether solution and are corrected to 100% deuterium content.

α^{24}_{365} +6.1 ± 0.1° (neat, ℓ=1). Reduction by diimide (Equation 53) produced N,N-diethyl-1-aminobutane-1-d (25) (page 39), $[\alpha]^{25}\underline{D}$ +3.5 ± 0.2° (ether) and $[\alpha]^{25}_{365}$ + 12.2 ± 0.2° (ether).



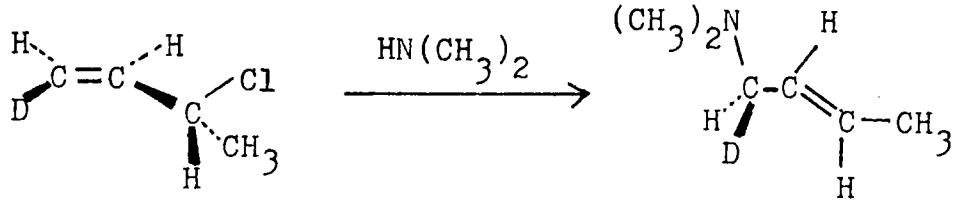
(52)



(53)

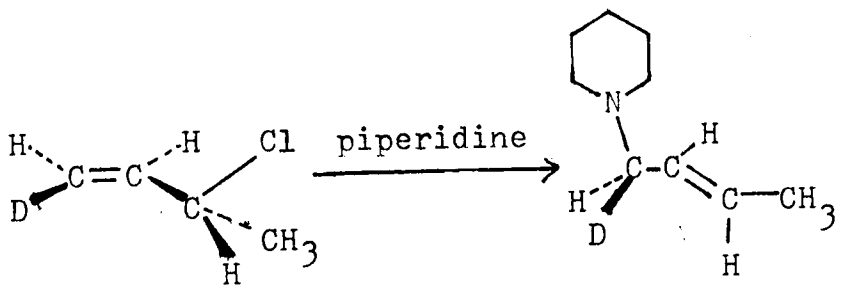
Before the measured specific rotations of 25 (page 39) can be compared to those of the optically pure material, adjustments must be made for the fact that Chloride 17 (page 29) was only 75.5% optically pure. In addition, Alkene 28 (page 44) is a 95:5 mixture of E and Z isomers. Assuming that the Z isomer is produced by the same mechanism as the E isomer, the two stereoisomers should have opposite chiralities; thus, the reduction product 25 (page 39) is at best 90% optically pure. Correction by these two factors gives adjusted specific rotations of +5.2 ± 0.3° and +18.0 ± 0.5° at 589 nm and 365 nm, respectively. Comparison of these numbers with those in Table II (page 67) indicates the S_N2' reaction has occurred with 96 ± 2% or 97 ± 1%, respectively, syn stereochemistry.

Similar reactions were run on (S)-(+)-17 (page 29) using dimethylamine and piperidine (Equations 54 and 55); for comparison with Equation 52, the R enantiomer is shown.



(54)

29



(55)

30

Both reactions produced only the E isomers, along with 1% and 3%, respectively, of the S_N2 product. The glpc column was shown to be capable of separating the E and Z isomers (had both been formed) by analysis of the Z isomers prepared from (Z)-1-chloro-2-butene. Table III contains the adjusted specific rotations for the diimide reduction products from these two reactions.

Comparison of these specific rotations with those of the optically pure material in Table II (page 67) allows one to calculate that the S_N2' reactions have occurred with

TABLE III

ADJUSTED SPECIFIC ROTATIONS OF REDUCED S_N2' PRODUCTS

Compound	Specific Rotations[a] 589 nm	365 nm
(S)-(-)-24 (p 38)	-3.0 ± 0.6°	-10.6 ± 0.6°
(S)-(-)-26 (p 40)	-4.0 ± 0.3°	-13.1 ± 0.3°

[a]Rotations in ether solution.

95 ± 9% (589 nm) and 99 ± 3% (365 nm) syn stereochemistry for the dimethylamine reaction, and with 99 ± 4% (589 nm) and 99 ± 1% syn stereochemistry for the piperidine reaction. It is reasonable to conclude that the S_N2' reactions of secondary amines are stereospecific when one takes into account the uncertainty in the reported maximum rotation of 17 (page 29).

This stereochemical study does not settle the question of whether the S_N2' reaction is concerted or stepwise (ion-pair mechanism). However, these results do prove that secondary amines attack the allylic system exclusively on the face bearing the leaving group. This syn preference is in agreement with theoretical predictions as well as Young's (10) hypothesized six-membered cyclic transition state (Equation 5, page 5) involving hydrogen bonding. It seems unlikely that the syn preference is totally due to the hydrogen bonding since Dittmer and Marcantonio (18) concluded that such bonding is an unimportant feature of the transition state. Therefore, the observed syn stereochemistry is most probably due to an inherent stereoelectronic preference in the S_N2' reaction.

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