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The City University of New York, Ph.D., 1972
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2-PHENYL-2-BUTYL MAGNESIUM CHLORIDE: STRUCTURE, STABILITY, STEREOCHEMISTRY

by

STEVEN LOWENKRON

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

1972

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

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ABSTRACT

This thesis describes the synthesis, in high yield (66%), of 2-phenyl-2-butyl magnesium chloride using conventional techniques. It was found that upon standing the Grignard reagent undergoes a heretofor unobserved self dimerization reaction. The reagent quantitatively dimerizes to yield 3,4-dimethyl-3,4-diphenylhexane within 2.5 hours at ambient temperatures, and within 40 hours at 0°, regardless of the amount of solid magnesium present in the reaction mixture.

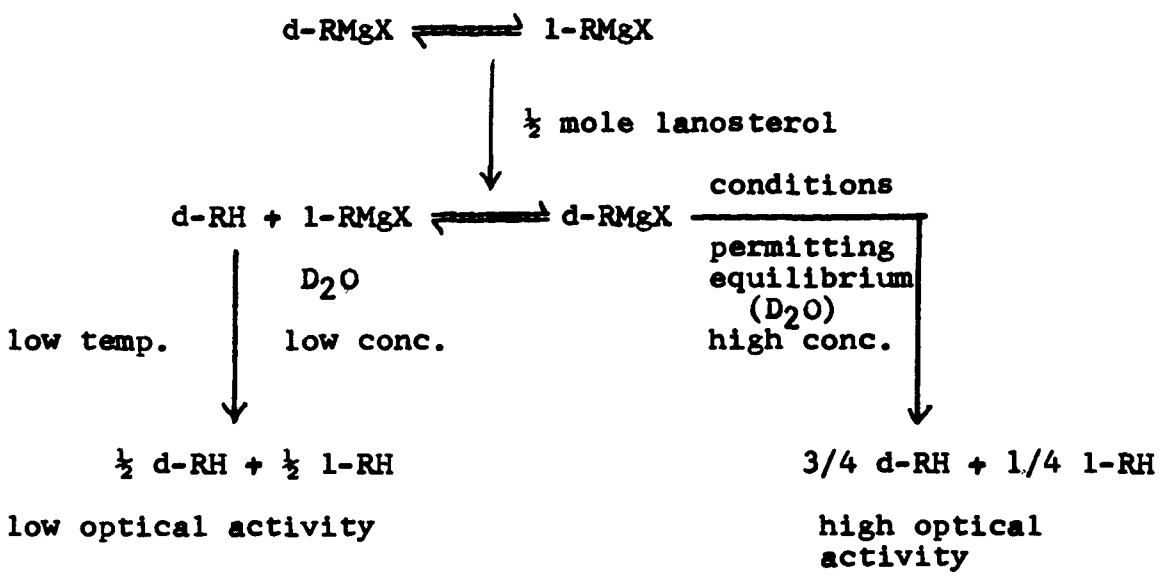
Several optically active compounds that have an acidic proton near the asymmetric center were reacted with racemic 2-phenyl-2-butyl magnesium chloride in an attempt to produce optically active 2-phenylbutane. Of the compounds tested, only lanosterol reacted with the Grignard reagent to produce optically active 2-phenylbutane. The optical purities of the 2-phenylbutanes produced were usually between 5 and 11%.

Under varied experimental conditions, one half an equivalent of lanosterol was reacted with one equivalent of Grignard reagent followed by quenching the unreacted Grignard reagent with deuterium oxide. The variation in the optical purities of the 2-phenylbutanes produced from these reactions was used as the basis for the study of the chemistry of the 2-phenyl-2-butyl Grignard reagent.

The results of this study show that the 2-phenyl-2-butyl Grignard reagent, at a concentration of ~0.3 molar in THF, exists as an equilibrium mixture of d and l forms. The rate of inversion between the two enantiomeric forms was too fast to measure experimentally even at temperatures as low as -68°. The addition of excess triethylamine to the THF solution of the Grignard reagent would be expected to slow the rate of inversion. Yet in the presence of this mixed solvent system the rates of inversion were still too fast to measure. (An optically active half life of the Grignard reagent of 1.3 seconds could have been measured.)

Upon dilution of the Grignard reagent to ~0.03 molar, the rate of inversion between the d and l forms was sufficiently slow to allow its measurement. The rate of inversion at -68° of a 0.027 molar solution of the Grignard reagent in THF was 12%/second. This value corresponds to a optically active half life of ~4 seconds. The rate of inversion of the Grignard reagent in a 0.025 molar solution of THF containing a 24 molar excess of triethylamine at -68° was 3.8%/second. (An optically active half life of ~13 seconds) These results are summarized in the figure on the next page.

The reaction of 2-phenyl-2-butyl magnesium chloride with one half of an equivalent of lanosterol followed by quenching the remaining Grignard reagent with oxygen



in dilute solution (~0.03 molar) and low temperatures (-68°) produced optically active 2-phenylbutane and optically active 2-phenyl-2-butanol. This is the first report of the successful trapping of an optically active acyclic Grignard reagent.

The 2-phenylbutane and 2-phenyl-2-butanol produced from the above reaction have the opposite absolute configurations. This result was interpreted to indicate that the protonation and oxidation reactions of the Grignard reagent proceded via similar stereochemical mechanisms.

The production of optically active 2-phenyl-2-butanol also gives evidence to support the hypothesis that oxidation of Grignard reagents proceed via a polar rather than a radical mechanism inasmuch as a radical reaction

would lead to a racemic alcohol.

The addition of N, N, N', N', tetramethylethylenediamine (TMED) to the 2-phenyl-2-butyl Grignard solution in THF almost completely destroys the stereospecificity of the reaction between the Grignard reagent and lanosterol. The addition of TMED to Grignard solutions is known to cause a shift in the Schlenk equilibrium toward the RMgX species. Thus, it was concluded that R_2Mg was the species responsible for the production of optically active 2-phenylbutane.

To Carole, Wendy, and Robin

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HISTORICAL BACKGROUND

In 1900, Victor Grignard reported[1] that alkyl halides react with magnesium in ether solution to form highly versatile reagents. These reagents have proven to be so complex, that their chemistry has not yet been elucidated.

At present, there is little evidence available concerning the configurational stability of the carbon-magnesium bond in saturated compounds. NMR evidence has shown that primary alkyl Grignard reagents are not configurationally stable.[2,3] The data shows that primary Grignard reagents undergo rapid inversion at the carbon-magnesium bond. The rates of inversion are reversibly temperature dependent; and decrease with decreasing temperature. At room temperature, these reagents invert approximately 10 times/second in diethyl ether and 3 times/second in tetrahydrofuran.[2] The rate of Grignard inversion is dependent upon the concentration of the Grignard solution as well as the basicity of the solvent. The inversion rate is decreased in dilute solution and in the more basic medium.

The rate of inversion of the 3,3-dimethylcyclobutyl and the 3-methyl-2-butyl Grignard reagents could not be accurately determined using NMR spectroscopy.[2] However, a upper limit of the inversion rate was established for these reagents. The data show that these reagents invert slowly, if at all, on the NMR Time Scale. (By configura-

tionally stable on the NMR Time Scale is meant that inversion must occur more slowly than 2 times/second.[4])

NMR studies of the norbornyl Grignard reagent have shown that it exists in ether solution as a 59:41 mixture of endo and exo isomers.[5] The reaction of the norbornyl Grignard reagent with 50 mole % of benzophenone caused the disappearance of the exo isomer. The resulting mixture was allowed to stand for one day, and the NMR spectrum was rerun. The ratio of endo to exo isomer was once again 59:41. Thus, it was concluded that the norbornyl Grignard reagent equilibrates somewhere between one hour (the time it takes to run an NMR spectrum) and one day.

There have been many attempts to prepare an optically active Grignard reagent from an optically active halide in which the halogen is directly attached to the asymmetric center. Acyclic halides such as (-)-2-iodobutane,[6] (+)-2-bromooctane,[7,8] and optically active 1-phenylethyl bromide[6] have been shown to give rise to optically inactive products. A Grignard reagent prepared from a cyclic halide, (-)-3,3-dimethylcyclohexyl chloride, is also reported to yield racemic acid on carbonation.[9] The only exception has been the 2,2-diphenyl-1-methylcyclopropyl Grignard reagent.[10] This reagent does not racemize in tetrahydrofuran over a period of 3 hours at a temperature of 65°.

Since secondary Grignard reagents invert more slowly

than primary Grignard reagents, it is expected that tertiary Grignard reagents invert even more slowly. Recently, Parris and Ashby[11] have reported NMR studies of t-butyl magnesium chloride in ether and tetrahydrofuran. As a result of these studies, they were able to estimate the inversion rate in tetrahydrofuran. At 42° the inversion rate of t-butyl magnesium chloride was approximately 0.25 times/second. The lack of any additional data on tertiary systems is probably due to the complexity of their NMR spectra in addition to the difficulty usually encountered in preparing pure tertiary Grignard reagents.

In light of the above, a chemical method was sought in which one could study the configurational stability of a tertiary Grignard reagent. The preparation of an optically active tertiary Grignard reagent would enable one to study the configurational stability of the reagent by measuring the reagent's rate of racemization. In addition, the stereochemistry of the Grignard reagent could be studied.

THEORETICAL CONSIDERATIONS

This work was designed to determine whether tetrahedral acyclic Grignard reagents invert rapidly as shown by existing NMR data, or if they invert slowly as was demonstrated for the cyclopropyl and norbornyl Grignard reagents.

The reaction that was chosen for this study is shown in equation 1 where R*H (inducing agent) is an optically

1. $\underline{R}MgX + R^*H \longrightarrow \underline{R}^*H + R^*MgX$

active compound with an active hydrogen near the asymmetric center. $\underline{R}MgX$ is the Grignard reagent formed from the reaction of a tertiary halide with magnesium. The tertiary halide, although optically inactive, must contain a center of chirality at the carbon to which the halogen is attached.

A Grignard reagent that has its asymmetric center bonded to the magnesium can be represented by

2. $DMgX \rightleftharpoons LMgX$

where D and L represent the two enantiomeric alkyl groups, if existing NMR data are correct. However, if the Grignard reagent is optically stable, it can be represented by

3. $\frac{1}{2}DMgX + \frac{1}{2}LMgX$

By employing the reaction shown in equation 1, and varying the relative amounts of active hydrogen compound (inducing agent) and Grignard reagent, one should be able to differentiate chemically between the two possible representations. The type of optical activation shown in equation 1 is termed a kinetic resolution[12] because it is in a sense a separation of enantiomers based on differential rates of reaction.

For the purpose of clarity, the induction reaction is assumed to produce a hydrocarbon of 100% optical purity. The following experiments should allow one to differentiate between equations 2 and 3:

(a) Reaction of 1 mole of Grignard reagent with 1 mole of inducing agent.

(b) Reaction of 1 mole of Grignard reagent with ½ mole of inducing agent followed by ½ mole of water.

(c) Reaction of 1 mole of Grignard reagent with ½ mole of inducing agent followed by ½ mole of carbon dioxide or any other suitable electrophile.

If the rapid equilibrium form is correct, then (a) would give

4. $\frac{1}{2}DMgX \rightleftharpoons \frac{1}{2}LMgX \xrightarrow{R^*H}$ DH (could also be LH)

where the hydrocarbon is 100% optically pure; (b) would give

5. $\frac{1}{2}DMgX \rightleftharpoons \frac{1}{2}LMgX \xrightarrow{\frac{1}{2}R^*H} \frac{1}{2}DH + \frac{1}{2}DMgX \rightleftharpoons \frac{1}{2}LMgX$

$$\xrightarrow{\frac{1}{2}H_2O} \frac{1}{2}DH + \frac{1}{4}DH + \frac{1}{4}LH$$

where the hydrocarbon is 50% optically pure; (c) would give

6. $\frac{1}{2}DMgX \rightleftharpoons \frac{1}{2}LMgX \xrightarrow{\frac{1}{2}R^*H} \frac{1}{2}DH + \frac{1}{4}DMgX \rightleftharpoons \frac{1}{4}LMgX$

$$\xrightarrow{\frac{1}{2}CO_2} \frac{1}{2}DH + \frac{1}{4}LCOOH + \frac{1}{4}\ DCOOH$$

where the hydrocarbon is 100% optically pure and the carboxylic acid is racemic.

If the no equilibrium form is correct, then (a) would give

7. $\frac{1}{2}DMgX + LMgX \xrightarrow{R^*H} \frac{1}{2}DH + \frac{1}{2}LH$

where the hydrocarbon is racemic; (b) would give

8. $\frac{1}{2}DMgX + \frac{1}{2}LMgX \xrightarrow{\frac{1}{2}R^*H} \frac{1}{2}DH + \frac{1}{2}LMgX \xrightarrow{\frac{1}{2}H_2O} \frac{1}{2}DH + \frac{1}{2}LH$

where the hydrocarbon is racemic; (c) would give

$$9.\quad \tfrac{1}{2}DMgX + \tfrac{1}{2}LMgX \xrightarrow{\tfrac{1}{2}R^*H} \tfrac{1}{2}DH + \tfrac{1}{2}LMgX \xrightarrow{\tfrac{1}{2}CO_2} \tfrac{1}{2}DH + \tfrac{1}{2}LCOOH$$

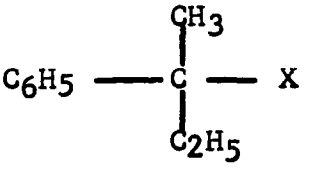
where the hydrocarbon and the carboxylic acid are 100% optically active. If neither extreme is correct, then intermediate results would be obtained.

Regardless of which form is correct, a large body of information concerning the stability of the carbon magnesium bond can be obtained by varying the temperature, basicity of the solvent, concentration and the elapsed time between the completion of the R*H addition and the addition of the second reagent (i.e. D_2O, CO_2).

THE PREPARATION AND STABILITY OF 2-PHENYL-2-BUTYL MAGNESIUM CHLORIDE

The theoretical discussion requires the utilization of a tertiary halide which has an asymmetric center at the carbon to which the halogen is attached. The relative configurations of the halide and its derivatives must be known. The specific rotations of the corresponding hydrocarbon and its derivatives should be reasonably large in order to enable one to obtain results which are reproducible for small values of asymmetric induction.

The system that was chosen for this thesis was



X = H, Cl, OH, etc.

(2-Phenyl-2-Butyl)-X

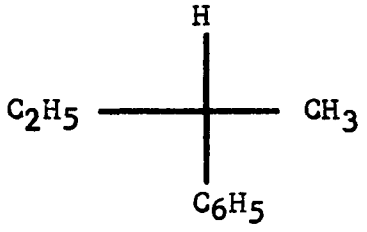
The relative configurations as well as the specific rotations of the derivatives of the 2-phenyl-2-butyl system are shown in Figure 1.

The synthesis of 2-chloro-2-phenylbutane was accomplished using the reaction scheme shown in Figure 2.

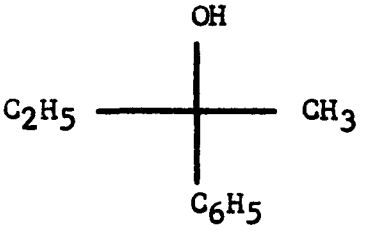
In reports of the synthesis of 2-phenyl-2-butanol

Figure 1

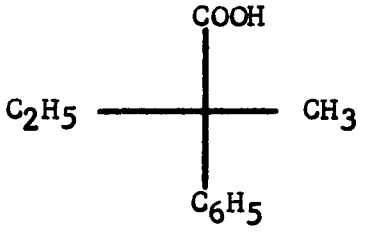
The Relative Configurations and Specific Rotations of the 2-Phenyl-2-Butyl System



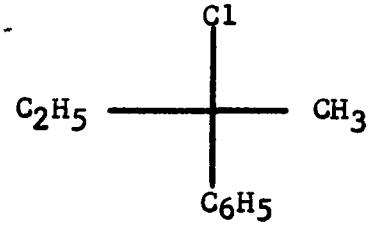
$[\alpha]_D^{20}$ -27.3° [13]



$[\alpha]_D^{27}$ -17.7° [13]



$[\alpha]_D^{23}$ +30.2° (c = 4.5 C_6H_6) [13]



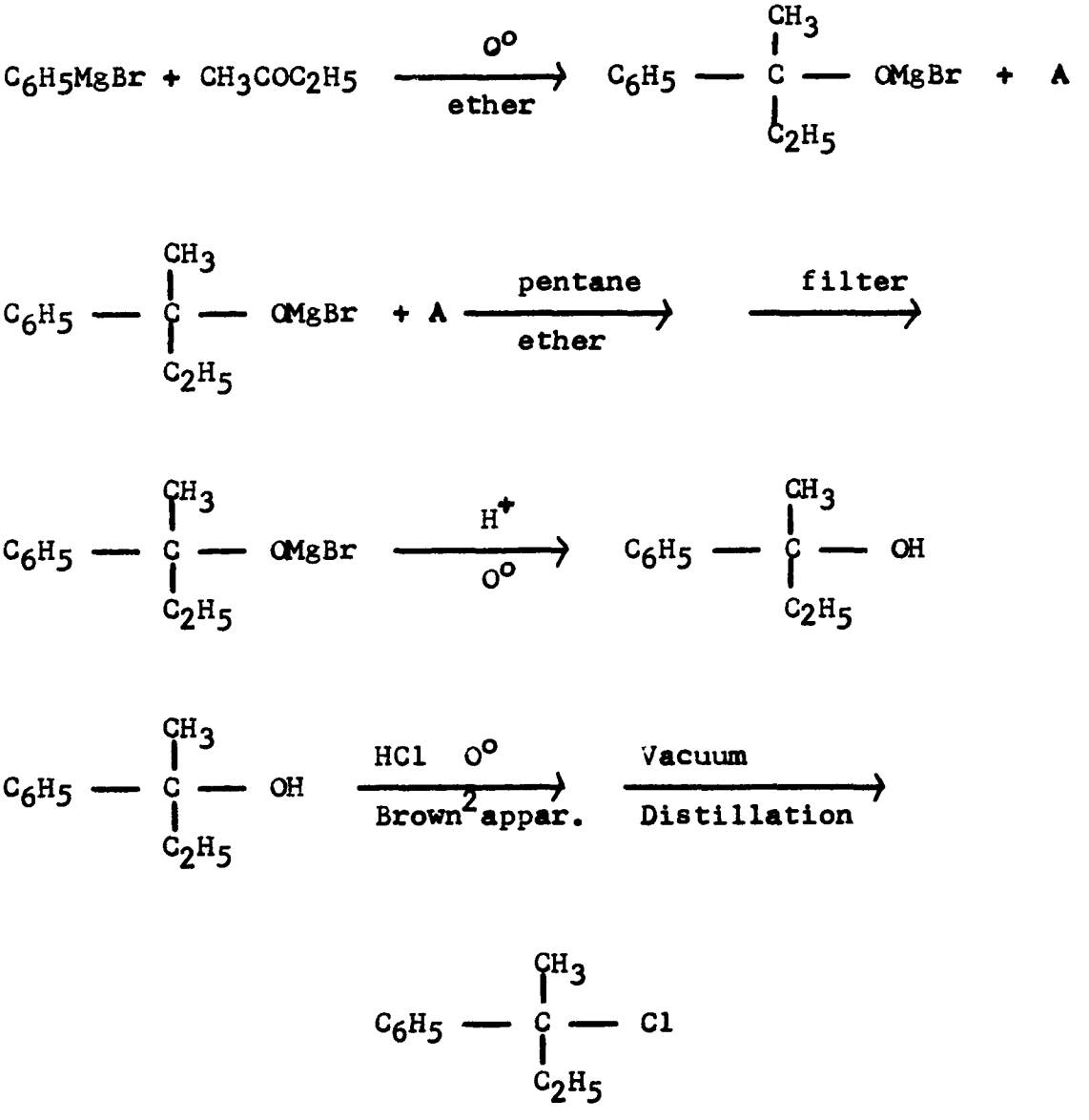
$[\alpha]_D^{23}$ -13.90°*

* This value represents the highest value obtained for the halide. The alcohol from which the halide was synthesized was 80.4% optically pure.[14]

using phenyl magnesium bromide and methyl ethyl ketone, the alcohol could not be obtained pure by standard isolation procedures.[15,16] (The alcohol contained traces of biphenyl after being vacuum distilled.) Zeiss[16] converted the alcohol to the hydrogen phthalate. The hydrogen phthalate was purified by crystallization and

Figure 2

The Synthesis of 2-Chloro-2-Phenylbutane

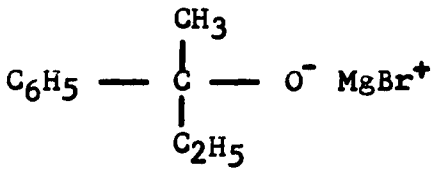


A = C_6H_5Br, $CH_3COC_2H_5$, C_6H_6, C_6H_5-C_6H_5, etc.

the pure alcohol was then regenerated by treating the hydrogen phthalate with lithium aluminum hydride. The yield of impure alcohol was 82%; however, the yield of pure alcohol on regeneration was only 40%. The 2-phenyl-2-butanol was obtained pure by Cram[17] using methyl magnesium iodide and propiophenone. The yield, however, was not reported. When 2-phenyl-2-butanol was synthesized from ethyl magnesium bromide and acetophenone, in this laboratory, the yield of alcohol was only 36%.

Preparation of 2-phenyl-2-butanol by the method of Zeiss[16] yielded the alcohol with biphenyl as well as a small amount of olefinic impurities (α-ethyl styrene and <u>cis</u> and <u>trans</u>-2-phenyl-2-butene). Attempted vacuum distillation (0.5 mm Hg) of the alcohol on a 3 ft. spinning band column yielded only olefinic products.

It was observed, however, that the addition of methyl ethyl ketone to phenyl magnesium bromide in ether gave a white precipitate. This precipitate is assumed to be the magnesium bromide alkoxide salt of 2-phenyl-2-butanol.



In a separate experiment the alkoxide salt was washed

on a Buchner funnel with copious quantities of ether and pentane prior to hydrolysis. In this way, the alkoxide salt was separated from all of the organic impurities, such as benzene, biphenyl, unreacted bromobenzene and methyl ethyl ketone. Hydrolysis of the alkoxide salt with dilute hydrochloric acid yielded 75% (average of all experiments) of 2-phenyl-2-butanol which was free from impurities without further purification. A small amount of the product (5-10%) was lost due to hydrolysis of the alkoxide salt by moisture in the air. However, this small loss was tolerated because of the relative ease with which the alcohol was obtained.

The synthesis of 2-chloro-2-phenylbutane has been previously reported;[14,15,18] in each case the halide could not be purified by distillation due to its purported instability. In the present work, the 2-phenyl-2-butanol was treated with hydrogen chloride using a Brown[2] (square) apparatus,[19] and the halide was vacuum distilled (0.1 - 0.5 mm Hg). As the distillation proceeded, the pressure could not be maintained below 0.5 mm Hg. At the completion of the completion of the distillation the pressure was 3-4 mm Hg. The product obtained was a mixture of α-ethyl styrene and cis and trans-2-phenyl-2-butene. However, it was observed that the halide dissolved the lubricant which sealed the distilling flask to the distillation apparatus.

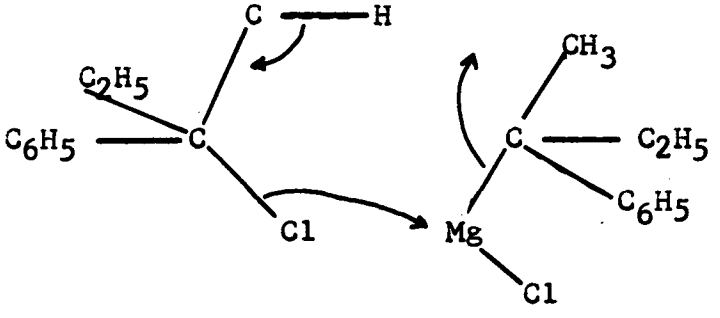
Consequently, a one piece distillation apparatus which did not have a joint between the distilling flask and the distillation apparatus was constructed. (see pg. 106) Distillation of the halide now proceeded smoothly with the pressure being easily maintained below 0.5 mm Hg. The distilled halide was always at least 95% pure. The impurities were ∝-ethyl styrene and cis and trans-2-phenyl-2-butene. The purity of the halide usually depended on the amount of halide that was being distilled, as well as the distillation pressure. Evidently, continuous heating of a large quantity (> 200 grams) of halide at slightly elevated pressures causes the partial decomposition of the compound.

The conversion of 2-chloro-2-phenylbutane to 2-phenyl-2-butyl magnesium chloride in high yield proved to be an extremely difficult problem. Reports of the preparations of various tertiary alkyl magnesium chlorides have shown that optimum yields were obtained with approximately 3 - 4 molar (in halide) solutions with approximately a 10% excess of magnesium.[20] Allyl magnesium chloride is also prepared under similar conditions.[21] Benzyl magnesium chloride is usually prepared at concentrations of halide of 2 - 3 molar.[22,23]

The yields of 2-phenyl-2-butyl magnesium chloride from the reactions of 2-chloro-2-phenylbutane with magnesium in THF were consistently low (10-15%) at 0°

using the recommended procedures. The reaction of 2-chloro-2-phenylbutane in THF with magnesium at 66° (boiling THF) yielded 0% 2-phenyl-2-butyl magnesium chloride. Great difficulty was encountered when attempts were made to form the Grignard reagent in ether. The yields were always close to 0% in this solvent.

In THF Grignard formation is facile. However, the yields of Grignard reagent are poor because of side reactions that occur once the reagent is formed. The side products formed are a mixture of approximately 50% 2-phenylbutane and approximately 50% of a mixture consisting of α-ethyl styrene and cis and trans-2-phenyl-2-butene (olefinic mixture). The mechanism for the formation of these side products has not yet been elucidated, however, the formation of these side products is thought to involve a bimolecular six membered transition state.[24]



The 2-phenyl-2-butyl magnesium chloride reacts with 2-chloro-2-phenylbutane, thus reducing the overall

production of Grignard reagent.

In reactions of 2-phenyl-2-butyl magnesium chloride with active hydrogen compounds (inducing agents - see next section) the product that is formed is optically active 2-phenylbutane. However, the optically active product is diluted 85 - 90% with a mixture that is half racemic 2-phenylbutane and half olefinic mixture. The olefinic compounds are not easily separated from the 2-phenylbutane. If the asymmetric induction reaction produced 100% optically active 2-phenylbutane, the observed rotation of the product mixture would be $24.2^{\circ} \times 0.10 = 2.42^{\circ}$. However, the asymmetric induction reactions produced 2-phenylbutane that was only about 10% optically pure. In addition, in most reactions only one half an equivalent of inducing agent was employed. Thus, the maximum rotation of the product is decreased by an additional factor of two. The maximum observable rotation of the product mixture would be $2.42 \times 0.5 \times 0.1 = 0.12^{\circ}$. Thus it would be nearly impossible to observe small changes in the percent asymmetric induction by varying experimental parameters employing the impure Grignard reagent.

A method for purifying the Grignard reagent was sought in order to increase the accuracy of the asymmetric induction experiments. Grignard reagents can be crystallized by slow removal of the solvent.[25,26] The composition of the crystal is usually RMgX·2(solvent).

Therefore, in principle, the 2-phenyl-2-butyl Grignard reagent and its impurities could be introduced into a vacuum line and all of the volatile impurities could be separated from the Grignard reagent by trap to trap distillation. The only remaining impurity would be magnesium chloride. (The disproportionation reaction between 2-phenyl-2-butyl magnesium chloride and 2-chloro-2-phenylbutane yields one equivalent of magnesium chloride for every one half an equivalent of 2-phenylbutane and one half an equivalent of olefin produced.) The Grignard reagent and magnesium chloride could be redissolved in THF and the purified reagent could be used for induction reactions. This procedure was carried out on several occasions. In all experiments the yield of Grignard reagent upon redissolution was 0%. The destruction of the Grignard reagent was inexplicable at that time. (The vacuum line method, however, was practical for the purification of 3-methyl-3-octyl magnesium bromide. The method is described in the appendix.) The vacuum line technique was abandoned in favor of a precipitation method.

Grignard reagents are generally insoluble in non-coordinating media.[27] Therefore, it was decided to precipitate the 2-phenyl-2-butyl magnesium chloride (as well as magnesium chloride) by the addition of a large excess of a non-coordinating solvent (i.e. pentane) to

the Grignard solution. The Grignard reagent was separated from the pentane by filtration. In this way the Grignard reagent could be washed several times with additional portions of solvent. The Grignard reagent and magnesium chloride were then redissolved in THF. When this procedure was carried out at ambient temperatures, the yield of Grignard reagent upon redissolution was 0%. When the temperature of the reaction mixture was lowered to -68°, the yield of Grignard reagent was never more than 4 - 5%. It was decided to abandon the precipitation method of purifying the Grignard reagent because of the large amount of starting materials and work required in order to produce a single piece of data.

At this time it was decided to try to improve the yield of 2-phenyl-2-butyl magnesium chloride by varying the experimental conditions used in the preparation of the Grignard reagent. The possibility that the 2-chloro-2-phenylbutane was undergoing an elimination reaction in the solvent (THF) prior to addition to the magnesium was ruled out when a 50% solution of THF and 2-chloro-2-phenylbutane was shown by NMR spectroscopy to be stable for 18 hours at 37°.

The 2-phenyl-2-butyl Grignard reagent, as already discussed, was suspected of undergoing a disproportionation reaction. (equation 10) When the radical R of RCl contains a beta hydrogen atom that is reactive there is

10. $C_{10}H_{13}MgCl + C_{10}H_{13}Cl \longrightarrow C_{10}H_{14} + C_{10}H_{12} + MgCl_2$

a tendency for the halide to undergo the disproportionation reaction.[24] To provide evidence that the 2-phenylbutane and olefinic mixture found in all of the 2-phenyl-2-butyl magnesium chloride preparations came from the disproportionation reaction, the following experiments were conducted. In the first experiment a 9:1 solution of 2-chloro-2-phenylbutane and methylmagnesium chloride in THF was prepared. NMR spectra were run on the sample at various time intervals. Within 105 minutes at 37° all of the methylmagnesium chloride had disappeared with the corresponding formation of methane. In the second experiment a 1:1 solution of 2-chloro-2-phenylbutane and methylmagnesium chloride in THF was prepared. The methylmagnesium chloride disappeared within 65 minutes. Thus equation 10 appears to be a significant side reaction in the preparation of 2-phenyl-2-butyl magnesium chloride.

The results of varying the relative amounts of magnesium and halide, as well as varying the temperature, addition rate of halide and delay time* are shown in Table 1.

---

* The elapsed time between the completion of the addition of halide and the quenching of the Grignard reagent with deuterium oxide.

Table 1

The Variation of Experimental Conditions to Improve the Yield of 2-Phenyl-2-Butyl Magnesium Chloride

#	Hal M[a]	Mg/Hal[b]	T°	HAR[c]	DT(min)[d]	%Dimer[e]	%GR[f]
1	4.0	1.1	amb	0.99	100	24	0
3	4.0	11.0	0	0.67	90	43	20
4	4.0	1.1	0	5.9	95	62	0
5	0.4	1.1	0	0.77	110	51	31
6	0.4	1.1	0	0.72	45	32	44
7	0.4	11.0	0	0.57	35	12	66
10	0.4	1.1	-20	0.54	30	27	53

a The molar concentration of 2-chloro-2-phenylbutane based on the total volume of solvent present. b The molar ratio of magnesium to 2-chloro-2-phenylbutane. c The rate of addition of 2-chloro-2-phenylbutane to the magnesium in mmol/min. d The elapsed time between the completion of the halide addition and the quenching of the Grignard reagent with deuterium oxide. e The amount of 3,4-dimethyl-3,4-diphenylhexane that was isolated. f The calculated yield of 2-phenyl-2-butyl magnesium chloride based on the amount of 2-phenylbutane-2-D isolated.

The reaction conditions in reaction #4 are similar to the conditions under which the 2-phenyl-2-butyl magnesium chloride was usually prepared. The Grignard reagent was stirred for 95 minutes after the completion of the halide addition. At this time an excess of deuterium oxide was added to the reaction mixture. The NMR spectrum of the product mixture showed it to be completely devoid of 2-phenylbutane-2-D, the product of the reaction between 2-phenyl-2-butyl magnesium chloride and deuterium oxide. In addition 62% of the product mixture consisted of a mixture of dl and meso-3,4-diphenyl-3,4-dimethylhexane (dimer). These results were inexplicable at that time. The significance of reporting the delay time will become clear in the ensuing discussion.

The Grignard reagent was then prepared at room temperature and the solution quenched with deuterium oxide 100 minutes after the completion of the halide addition (reaction #1). The yield of Grignard reagent was 0%, and the yield of dimer dropped to 24%. Evidently there are at least two competing side reactions that are destroying the Grignard reagent. At ambient temperatures, the predominant reaction is disproportionation, and at 0°, the predominant reaction is coupling.

The rate of Grignard formation has been shown to depend on the amount of available magnesium surface present.[28] If, however, the number of moles of magnesium

present were the same for several experiments, the amount of magnesium surface present should be relatively constant. (This argument is true only if the magnesium used was from the same lot and had been dried and stored under similar conditions.) In addition, the rate of Grignard formation depends on the concentration of halide.[23,29] Therefore, the rate of 2-phenyl-2-butyl Grignard formation can be written as

$$11. \quad \text{rate}_{gf} = k_1 \left[C_{10}H_{13}Cl\right] S_{mg}$$

where S_{mg} is equal to the available surface area of the magnesium that can enter into a reaction with 2-chloro-2-phenylbutane. The rate of disproportionation can be written as

$$12. \quad \text{rate}_{dis} = k_2 \left[C_{10}H_{13}Cl\right]\left[C_{10}H_{13}MgCl\right]$$

The rate of disproportionation is assumed to be first order in each reactant.

The combination of equations 11 and 12 gives equation 13.

$$13. \quad \frac{\text{rate}_{gf}}{\text{rate}_{dis}} = \frac{k_1}{k_2} \times \frac{S_{mg}}{\left[C_{10}H_{13}MgCl\right]}$$

Equation 13 predicts that excess magnesium and dilution of the Grignard reagent will favor Grignard formation over disproportionation.

The preparation of 2-phenyl-2-butyl magnesium chloride in the presence of a 10 mole excess of magnesium led to a 20% yield of Grignard reagent, with a 42% yield of dimer at a delay time of 90 minutes (reaction #3, Table 1). Thus the amount of magnesium present in the reaction mixture does play an important role in determining product distribution in the preparation of 2-phenyl-2-butyl magnesium chloride.

In another experiment, the concentration of the halide was reduced from 4.0 to 0.4 molar (reaction #5, Table 1). The yield of Grignard reagent was 31% and the yield of dimer was 51% at a delay time of 110 minutes.

Equation 13 also predicts that if in addition to excess magnesium being added to the reaction flask, the halide concentration is reduced, the yield of Grignard reagent would even be higher. With both dilution of the halide to 0.4 molar and the addition of a 10 mole excess of magnesium, the yield of Grignard reagent jumped to 66% with a 12% yield of dimer at a delay time of 35 minutes (reaction #7, Table 1).

The formation of dimer is not fully understood at this time. Equations 11 - 13 do not account for its formation. However, examination of the data for

reactions #5, 6 and 8 (Table 1) reveals that the amount of dimer present is related to the delay time. The longer the delay time, the greater the amount of dimer that is formed. In addition, the yield of Grignard reagent decreases with increasing delay time.

In order to study these phenomena more closely, the 2-phenyl-2-butyl Grignard reagent was prepared under conditions similar to those of reaction #7 (Table 1). On completion of the halide addition, one half of the Grignard solution was removed by syringe and placed in a flask not containing magnesium. Each of the solutions was warmed to room temperature and left to stand. Aliquots were removed periodically from each flask and quenched with deuterium oxide. The aliquots were analyzed for hydrocarbon* by gas chromatography. Within 2.5 hours the concentration of hydrocarbon was reduced from ~0.05 molar to 0.005 molar in both experiments. The tenfold reduction in the concentration of hydrocarbon indicates that, at the time of quenching, the Grignard reagent had been consumed (dimerized). When a similar experiment was conducted at 0°, the Grignard reagent dimerized completely after 40 hours. In another experiment, the Grignard reagent was kept at 0° for

*Hydrocarbon will be used to denote a mixture of 2-phenylbutane and 2-phenylbutane-2-D. In cases where there is no 2-phenylbutane-2-D present, hydrocarbon is defined as 2-phenylbutane.

4 hours and then warmed to 25°. All of the Grignard reagent dimerized 2.5 hours after being warmed to 25°.

The small amount of hydrocarbon that was present in each experiment was formed in a disproportionation reaction. The hydrocarbon did not contain any 2-phenylbutane-2-D, the hydrolysis product of 2-phenyl-2-butyl magnesium chloride and deuterium oxide. The concentration of olefin (α-ethyl styrene and cis and trans-2-phenyl-2-butene) was approximately 0.005 molar regardless of the concentration of hydrocarbon.

The small but constant concentration of olefin leads one to the conclusion that all of the 2-chloro-2-phenylbutane was consumed prior to dimerization. The halide decomposes under the conditions for gas chromatographic analysis of the hydrocarbon. If the halide was present, the "concentration" of olefin would have been higher than 0.005 molar. In addition, if unreacted halide was present and reacted with Grignard reagent to form dimer, the "concentration" of olefin would change with time. The data leads one to conclude that 2-phenyl-2-butyl magnesium chloride is unstable.

The small but constant concentration of olefin, in addition to the small concentration of hydrocarbon at the completion of the dimerization reaction, leads one to conclude that the formation of dimer is a quantitative reaction once the halide has been consumed.

The dimer is formed from the Grignard reagent and does not involve magnesium in the rate determining step. (The rate of dimerization was independent of the amount of magnesium present in the reaction flask.)

The formation of dimer can be represented by equation 14.

14. $2C_{10}H_{13}MgCl \longrightarrow C_{20}H_{26} + ?$

No attempt was made to isolate the inorganic species (possibly $MgCl_2$ and $Mg^{\cdot}$) formed in the dimerization reaction.

Many Grignard preparations yield small amounts of coupling product. With the exception of phenyl magnesium bromide, the coupling product is thought to be formed from a Wurtz reaction between the Grignard reagent and the halide (equation 15).

15. $RMgX + RCl \longrightarrow R\text{-}R + MgCl_2$

(This argument excludes those reactions in which radical inducers, i.e. $CoCl_2$, are added to the reaction mixture.)

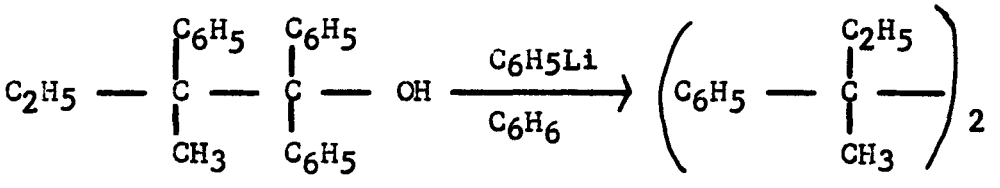
Although the mechanism of the dimerization reaction was not further investigated, there is a large body of evidence available which indicates the mechanism by which the reaction proceeds.

There is some evidence to show that phenyl magnesium bromide will couple.[30] However, the reaction is not nearly quantitative. Also phenyl magnesium bromide is stable and it is sold commercially.

The thermal and photolytic decompositions of azocumene,[31] azobis-2-phenylbutane,[32,33] and azobis-2-phenyl-3-methylbutane,[32,33] at temperatures up to 100° yield predominantly (> 95%) dimeric products. In addition, in the last case the ratio of dl to meso dimer was usually about 1 regardless of the conditions employed. In a few cases (Table 1), the dimer mixture was analyzed. The ratio of meso to dl 3,4-diphenyl-3,4-dimethylhexane varied between 1.6 and 2.1:1.

In the base catalyzed cleavage of optically active 2-methyl-1,1,2-triphenyl-1-butanol by phenyl lithium in benzene, 3,4-diphenyl-3,4-dimethylhexane was produced.[33] The mechanism of this reaction was concluded to be radical in nature because no 2-phenylbutane was formed. The 2-phenylbutane is one of the products of carbanionic cleavage. The reaction is shown in equation 16.

16.



The 3,4-diphenyl-3,4-dimethylhexane produced was always

racemic. In addition, the cleavage of 2-methyl-1,1,2-triphenyl-1-butanol and similar compounds under carbanionic conditions (in the presence of a proton donor solvent) never produced coupling product.[34]

Eliel[35] studied the hydrogen abstraction-dimerization of optically active 2-phenylbutane by means of methyl radicals obtained from the pyrolysis of acetyl peroxide. Although the dimer (3,4-diphenyl-3,4-dimethylhexane), a mixture of dl and meso forms, was optically inactive, the recovered 2-phenylbutane was only slightly racemized (~2%). (The ratio of dl to meso dimer was not determined.) This result suggested that the reaction

17. $R\cdot + R'\text{-}H \longrightarrow R'\cdot + R\text{-}H$

where both R and R' are 2-phenyl-2-butyl, had occurred to a minor extent. The possibility that hydrogen transfer was faster than racemization was eliminated by the addition of a 10 mole excess of cumene-α,β,-D_2 to the reaction mixture which yielded only 1 - 2% of 2-phenylbutane-2-D. It was also shown that the dimerization proceeded without any disproportionation since no olefinic products were found. In light of the above evidence it is concluded that the dimerization of 2-phenyl-2-butyl magnesium chloride proceeds via radical coupling.

The dimerization of 2-phenyl-2-butyl magnesium chloride was carried out in this laboratory at ambient temperatures. The work of Eliel,[35] on the other hand, was conducted at temperatures of 125 - 130°. Thus, the Grignard coupling reaction would not be expected to racemize any optically active 2-phenylbutane that is present in the reaction mixture to a significant extent. The importance of this argument will become clear when the stereochemistry of the 2-phenyl-2-butyl Grignard reagent is discussed. (see next section)

The data from reaction #10 (Table 1) indicate that the yield of 2-phenyl-2-butyl magnesium chloride could be further increased if reaction #7 were run at -20°. However, from a practical standpoint, it is easier to conduct reactions employing a circulating coolant at 0° than at -20°. In addition, the 66% yield of Grignard reagent is somewhat deceiving. The 12% dimer does not in reality represent an impurity in the isolation of optically active 2-phenylbutane. The 2-phenylbutane is easily separated from the dimer by distillation. Thus the stereochemical studies are not affected by the presence of dimer. Therefore, it was decided to use the conditions of reaction #7 (Table 1) for the preparation of the 2-phenyl-2-butyl magnesium chloride to be used in the induction reactions. The purity of the Grignard reagent, excluding dimer, was

between 80 and 85% in most of the 2-phenyl-2-butyl magnesium chloride preparations for use in the induction reactions.

The concurrent running of several induction reactions was desired. Thus the 2-phenyl-2-butyl Grignard reagent had to be prepared on a reasonably large scale. Aliquots would have to be taken from the original preparation and placed in separate reaction flasks. In addition, the concentration of the Grignard reagent had to be known approximately. This meant that additional aliquots were to be removed from the original preparation and analyzed.

The normal method for accomplishing these transfers is to use syringe techniques. However, it was shown in this laboratory, that transfer of dilute Grignard solutions led to inconsistent results. Therefore, it was necessary to design an apparatus that would allow the transfer of the Grignard reagent without allowing moisture or oxygen contamination. The apparatus so constructed, employing modified syringe techniques, (see experimental section pg 124) had the following features:

a- The Grignard reagent could be prepared on a large scale (approximately 100 mmoles) at any desired temperature.

b- Measured quantities of the Grignard reagent could be removed from the apparatus without moisture or

oxygen contamination.

c- The apparatus has a filtering device which allows the isolation of the Grignard reagent free from magnesium.

d- Many aliquots of the Grignard reagent can be removed from the apparatus without contamination of the remaining Grignard reagent.

The apparatus also reduced the amount of work required for running the induction experiments. In the running of individual reactions, aliquots of the Grignard solution have to be removed for analysis. In multiple runs, a single analysis is sufficient for all of the experiments. (In practice, however, the first and last aliquots were analyzed for Grignard reagent. In all cases both of these "controls" showed identical Grignard concentrations.)

ASYMMETRIC INDUCTION REACTIONS

The reaction that was chosen for the exploratory work of finding an inducing agent (R*H) was

18.

$$\tfrac{1}{2}R^*H + 1\ C_{10}H_{13}MgCl \longrightarrow \tfrac{1}{2}C_{10}H_{14} + \tfrac{1}{2}C_{10}H_{13}MgCl$$

$$\downarrow \text{1 hour}$$

$$\tfrac{1}{2}C_{10}H_{14} + \tfrac{1}{2}C_{10}H_{13}D \xleftarrow{D_2O}$$

Reaction 18 was chosen because it was assumed that even if tertiary Grignard reagents invert slowly, they should at least partially racemize within one hour and lead to optically active 2-phenylbutane.

Deuterium oxide (D_2O) was employed instead of water in order to simplify the calculations required in analyzing the products. (see experimental section) The specific rotations of 2-phenylbutane and 2-phenylbutane-2-D are almost identical ($\alpha_D^{25}\ C_{10}H_{14} = 24.2°$,[36] $\alpha_D\ C_{10}H_{13}D = 24.0°$,[36]). Therefore the possible presence of optically active 2-phenylbutane-2-D instead of 2-phenylbutane would not lead to any significant error in calculating the results.

Theoretically, the problem requires the selection of an inducing agent. This compound must be optically active and have an active hydrogen near the asymmetric center. Furthermore, with the exception of the active hydrogen, the compound must be inert to Grignard reagents.

Easy separation of the inducing agent from 2-phenylbutane is desirable but not essential.

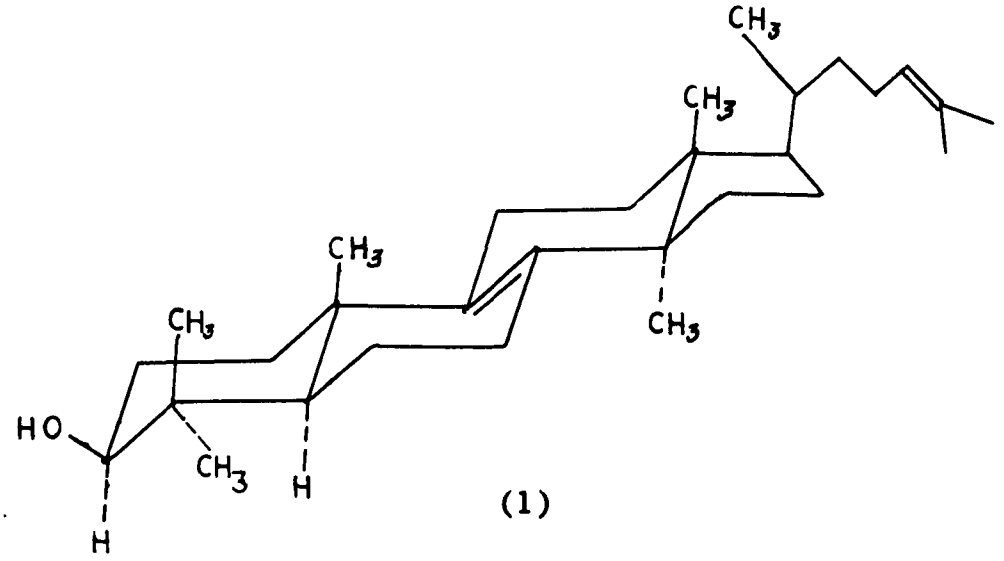
The basis of kinetic resolution is that there be a differential in the rates of the reactions between the dl pair and the resolving agent. Some resolving agents will work better than others. Therefore, some compounds will not be effective as inducing agents.

The selection of an inducing agent proved to be a difficult problem. The compounds that were initially selected were; lanosterol (1), d-(+)-∝-phenethyl amine (2), d-(+)-camphor-10-sulfonic acid (3), d-(+)-camphor (4), and d-(+)-ketopinic acid (5). Of these compounds the only one that reacted with 2-phenyl-2-butyl magnesium chloride to yield optically active 2-phenylbutane was lanosterol (1). The "observed inductions" (see pg) for the 2-phenylbutane products were between 5 and 10%. Compound 4 did not react with 2-phenyl-2-butyl magnesium chloride at -68° within one hour.

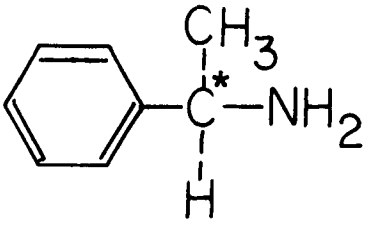
An attempt was made to find an inducing agent that would yield higher observed inductions. Several new compounds were synthesized, namely: (N-l-(-)-∝-phenethyl) benzene sulfonamide (6), (N-t-butyl)-d-(+)-ketopinamide (7), (N-d-(+)-∝-phenethyl)-d-(+)-camphor-10-sulfonamide (8), (N-l-(-)-∝-phenethyl)-d-(+)-camphor-10-sulfonamide (9), and (N-d-(+)-∝-phenethyl)-d-(+)-ketopinamide (10). (The carbonyl group in

Figure 3

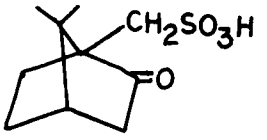
Asymmetric Active Hydrogen Compounds that were reacted with 2-Phenyl-2-Butyl Magnesium Chloride



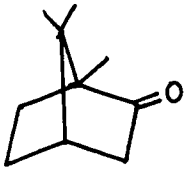
(1)



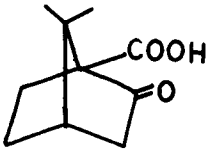
(2) - (d)-(+)



(3) - (d)-(+)

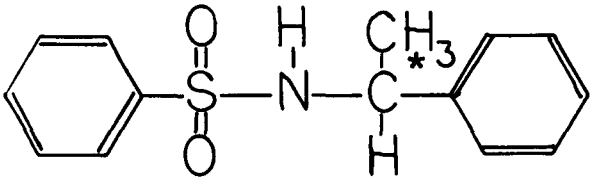


(4) - (d)-(+)

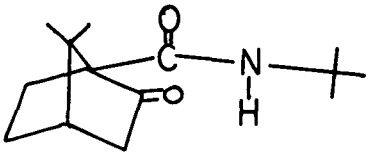


(5) - (d)-(+)

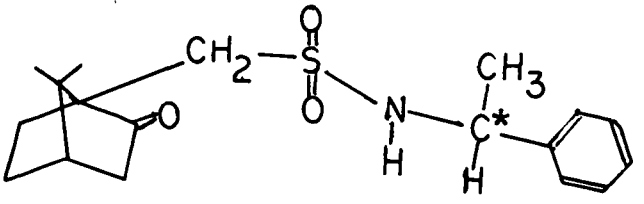
Figure 3 (continued)



(6) - (d)-(+)

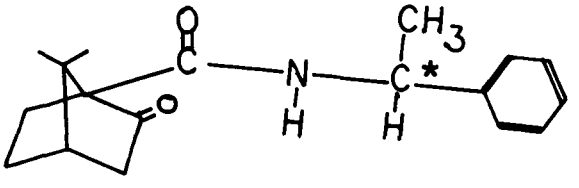


(7) - (d)-(+)



(8) - (d)-(+) — (d)-(+)

(9) - (d)-(+) — (1)-(-)



(10) - (d)-(+) — (d)-(+)

camphor derivatives reacts very slowly, and only through enolization, with Grignard reagents. After five hours at 20° in ether, the reaction between camphor and methyl magnesium iodide consumes only 14% of the Grignard reagent.[37] Similarly, the reactions of the carbonyl and sulfonyl groups of carboxylic acids, amides and sulfonamides react slowly if at all with Grignard reagents.) These compounds were selected because with the exception of (6) and (7) there are two large optically active moieties bonded to the nitrogen. It was hoped that the presence of two large groups would place the active hydrogen in a highly asymmetric environment. However, the reaction of these compounds with 2-phenyl-2-butyl magnesium chloride always produced racemic 2-phenylbutane.

Although the optical purities of the 2-phenylbutanes which were formed in reactions with lanosterol were small, it was found that varying the reaction conditions have led to some very interesting results.

It is convenient at this time to define some parameters that will be used in the ensuing discussion.

Induction (I) - the optical purity of that fraction of product that came from reaction with the inducing agent (lanosterol).

Optical Purity of Residue (OPR) - the optical purity of that fraction of product that did not come from the reaction with the inducing agent.

Observed Induction (OI) - the optical purity of the product multiplied by the mole ratio of Grignard reagent to lanosterol, or by equation 19.

19. $(OI) = (G/L)(OP)$

where OI = observed induction
G = mmoles of 2-phenyl-2-butyl magnesium chloride
L = mmoles of lanosterol
OP = optical purity of the product 2-phenylbutane

The optical purity of the product (OP) can be related to the above by:

20. $(OP) = (L/G)(I) - (OPR)\ (G-L)/G$

The (OI) can be related by:

21. $(OI) = (G/L)(OP) = (I) - (OPR)\ (G-L)/(L)$

when (OPR) = 0

22. $(OI) = (I)$

Equation 20 although rigorously correct, does not allow for direct comparison of OPR's unless the ratios for L/G in all experiments are identical. The above equations (19 - 22) were developed using a constant value of L/G because the theoretical considerations

were developed in a similar manner. However, experimentally a constant value for L/G could not be attained. Thus, a new parameter has to be defined which will allow for direct comparison of the optical purities of the residues regardless of the value for L/G.

Corrected Optical Purity of the Residue (COPR) - the optical purity of that fraction of the product that came from the optically active Grignard reagent that was generated as a result of the induction reaction.

23. $(COPR) = (OPR)\ (G-L)/(L)$

when $G = 2L$, OPR = COPR.
Therefore OI can be related by:

24. $(OI) = (I) - (COPR)$

The OPR seems to be a parameter of limited usefulness because the value for L/G changes from experiment to experiment. However, the value for OPR is important in the sense that it tells whether there is an experimentally detectable optical activity in the entire residue. This information is valuable if one is to plan experiments where the residue is quenched with an electrophile other than hydrogen.

In order to determine the value for induction (I)

in the product 2-phenylbutane, it was necessary to isolate that fraction of the product that came only from reaction with lanosterol. This could be accomplished in two ways: a - The reaction of one equivalent of lanosterol with one equivalent of 2-phenyl-2-butyl magnesium chloride or b - The reaction of one half an equivalent of lanosterol with one equivalent of 2-phenyl-2-butyl magnesium chloride followed by one half an equivalent of an electrophile other than hydrogen, i.e. CO_2. Experimentally, the simpler method is to use a. In order for method a to give satisfactory results, however, the Grignard reagent must be inverting faster than the rate of lanosterol addition. Method b will give satisfactory results regardless of whether the Grignard reagent is inverting rapidly or not at all. However, the unique dimerization reaction that 2-phenyl-2-butyl magnesium chloride undergoes would be an ideal reaction to use in obtaining the value for I. The dimerization reaction is quantitative, easy to run, and free from the pitfalls that are always present whenever another reagent is used. The 2-phenylbutane formed in the reaction comes only from the reaction with lanosterol;

25. $$C_{10}H_{13}MgCl + \tfrac{1}{2}Lan\text{-}OH \longrightarrow \tfrac{1}{2}C_{10}H_{14}^{*} + \tfrac{1}{2}C_{10}H_{13}MgCl + \tfrac{1}{2}Lan\text{-}OMgCl$$

$$\tfrac{1}{2}C_{10}H_{13}MgCl \longrightarrow \tfrac{1}{4}C_{20}H_{16}$$

where * = optically active

It has been shown[38,39] that the rate of reaction of Grignard reagents depends on the basicity of the solvent. The more basic the solvent the slower the reaction. The rate of addition of ethyl magnesium bromide to benzonitrile (a reaction similar in observed behavior to the reaction of methyl magnesium bromide with benzophenone) decreases as the basicity of the solvent increases.[38] The observed variation in reaction rate is also in agreement with the mechanism for Grignard additions to ketones proposed by Ashby,[39] in which he argues that the rate determining step is the breaking of a solvent magnesium bond. Pocker and Exner,[40] in their work on deuterium isotope effects in the decomposition of Grignard reagents by oxygen acids (water, methanol, etc.) report that the k_H/k_D for THF was greater than ether. Although the arguments concerning the rate determining step in the Grignard additions were inconclusive, the evidence does seem to support the hypothesis that the basicity of the solvent plays an important role. Therefore, one would expect the rate of the protonation reactions of 2-phenyl-2-butyl magnesium chloride to exhibit similar behavior. As the rate of the protonation reaction decreases, the

reaction between 2-phenyl-2-butyl magnesium chloride and lanosterol should become more selective and the value for I should increase. The reaction shown in equation 25 was run under varied conditions. The results are summarized in Table 2. The values for I were the highest for the reaction with triethylamine (TEA) added (10.4%, 0.12M Grignard reagent), followed by only THF as solvent (8.8%, 0.27M) and the lowest for the reaction with N,N,N',N',-tetramethylethylene-diamine (TMED) added (0.1%, 0.077M). The low value obtained for TMED is suprising. The almost total destruction of the stereospecificity of the reaction in which TMED was added is inexplicable at this time and will be discussed later.

The values for I remained relatively constant with dilution. The values are 9.7% (0.024M Grignard reagent) with TEA added and 8.4% (0.033M) with THF. The rate of the protonation reaction will decrease with dilution, but it does not necessarily follow that the transition state leading to optically active 2-phenylbutane will be altered. Ashby[11] has reported that the Schlenk equilibrium does not shift with dilution, as was expected. Therefore it is reasonable to expect that the value for I does not vary greatly with dilution.

The use of OI in place of I has been employed in the reporting of the results. OI is independent of

Table 2

Reactions of One Half of an Equivalent of Lanosterol with 2-Phenyl-2-Butyl Magnesium Chloride Followed by Dimerization of the Remaining Grignard Reagent[a]

#	T° GR[b]	T° L[c]	A/GR[d]	L/GR[e]	M GR[f]	%OP[g]	%OI[h]
17	-68	<-40	31 TEA	0.41	0.12	10.4	10.4
45	-68	<-40	28 TEA	0.39	0.024	9.7	9.7
11	-68	<-40	---	0.38	0.27	8.8	8.8
44	-68	<-40	---	0.31	0.033	8.4	8.4
21	-68	<-40	49 TMED	0.64	0.077	0.1	0.1

a After the lanosterol was reacted with the Grignard reagent, the Grignard reagent in excess was allowed to dimerize by standing at room temperature for 18 hours. b The temperature of the 2-phenyl-2-butyl magnesium chloride solution prior to reaction with lanosterol. c The maximum temperature of the lanosterol THF solutions prior to reaction with the Grignard reagent. d The molar ratio of amine to Grignard reagent. e The molar ratio of lanosterol to Grignard reagent prior to reaction. f The concentration of the Grignard reagent prior to reaction with lanosterol. g The optical purity of the product 2-phenylbutane corrected for olefin, alcohol, and preformed 2-phenylbutane (the 2-phenylbutane that was formed prior to reaction of the Grignard reagent with lanosterol). h The observed induction of the 2-phenylbutane product. For dimerization reactions I = OI, because OPR = 0.

any theoretical implications concerning the structure of Grignard reagents. As such, it gives an accurate account of the effect that varying of the experimental parameters has on the structure of Grignard reagents.

If the OI's could be made to vary then clues to the structure of the Grignard reagent could be uncovered. The reaction conditions were varied in order to observe the effect that the various parameters had on the OI. The reaction that was used primarily was the reaction of one half of a mole of lanosterol with one mole of 2-phenyl-2-butyl magnesium chloride followed by the quenching of the unreacted Grignard reagent with deuterium oxide. (Only an approximate value for the Grignard concentration was known prior to the reaction of 2-phenyl-2-butyl magnesium chloride with lanosterol. The amount of Grignard reagent present was not determined until after the reactions were run. The reaction scheme is not changed if either 30, 40 or 50 mole % lanosterol is used per mole of 2-phenyl-2-butyl magnesium chloride. The fraction of lanosterol per mole of Grignard reagent is reported in the tables.)

The ensuing discussion will demonstrate why low temperatures were used to determine the values for I in the different solvent systems.

Reactions were run to determine the effect of temperature on OI. The results are shown in Table 3.

Table 3

Reactions of One Half of an Equivalent of Lanosterol with 2-Phenyl-2-Butyl Magnesium Chloride Followed by Quenching of the Remaining Grignard Reagent with Deuterium Oxide: The Effect of Temperature on the Observed Induction of 2-Phenylbutane.

#	A/GR[a]	M GR[b]	L/GR[c]	LAT(s)[d]	DT(s)[e]	T° GR[f]	T° L[g]	%OI[h]
14	19 TEA	0.15	0.27	5.0	0	-68	<-40	12.1
24	34 TEA	0.11	0.48	6.5	60	-68	0	10.3
33	40 TEA	0.09	0.65	12.0	4800	-68	amb.	4.5
1	---	0.27	0.25	12.0	0	-68	<-40	5.9
5	---	0.30	0.33	9.0	40	-68	<-40	7.3
22	---	0.28	0.35	9.4	60	-68	0	5.5
29	---	0.25	0.39	5.0	120	-68	amb.	4.3
31	---	0.23	0.52	8.0	4800	-68	amb.	3.6
35	---	0.021	0.58	6.0	900	amb.	amb.	0.3
36	---	0.26	0.38	16.7	0	amb.	amb.	1.1

a The molar ratio of amine to Grignard reagent. b The concentration of the Grignard reagent prior to reaction with lanosterol. c The molar ratio of lanosterol to Grignard reagent prior to reaction. d The lanosterol addition time in seconds. e The elapsed time between the completion of the lanosterol addition and the quenching of the Grignard reagent with deuterium oxide. f The temperature of the Grignard solution prior to reaction with lanosterol. g The temperature of the lanosterol THF solution prior to reaction with Grignard reagent. h The observed induction for the 2-phenybutane product.

In experiments with TEA present the OI increased from 4.5 to 12.1% with a decrease in temperature. The highest OI is at a Grignard temperature of -68° and a maximum lanosterol solution temperature of -40°. The results follow the same trend (0.3 to 7.3%) when only THF was present. Thus it appears that the best conditions for obtaining high OI's are at the lower temperatures.

The lanosterol solutions were added to the Grignard solutions from jacketed addition funnels. Many experiments were run concurrently, consequently, the addition rate of the lanosterol solutions will vary from run to run. Table 4 shows the effect of lanosterol addition rate on OI. It can be observed from the table that there is no direct correlation between addition rate and OI. Therefore, in discussing results the rate of lanosterol addition can be neglected when OI is involved. However, OPR and COPR will depend on the lanosterol addition rate as will be discussed later.

Most of the reactions reported were run at low temperatures. Although some of the exploratory work was not carried out under these conditions, the trends observed at the higher temperature conditions, can also be expected to occur at the lower temperatures.

In order to trap the optically active enantiomer which is produced when lanosterol reacts with 2-phenyl-2-butyl magnesium chloride, conditions have to be attained

Table 4

Reactions of One Half of an Equivalent of Lanosterol with 2-Phenyl-2-Butyl Magnesium Chloride, Followed by Quenching of the Remaining Grignard Reagent with Deuterium Oxide: The Effect of Lanosterol Addition Rate on the Observed Induction of 2-Phenylbutane.

#	T° GR[a]	T° L[b]	A/GR[c]	M GR[d]	L/GR[e]	LAR[f]	%OI[g]
2	-68	<-40	---	0.27	0.25	7.4	5.5
1	-68	<-40	---	0.27	0.25	9.9	5.9
4	-68	<-40	---	0.30	0.33	13.3	5.9
5	-68	<-40	---	0.30	0.33	12.9	7.0
3	-68	<-40	---	0.31	0.31	11.3	7.3
6	-68	<-40	---	0.31	0.34	6.7	7.5
7	-68	<-40	---	0.25	0.51	8.5	7.9
29	-68	amb	---	0.25	0.39	23.4	4.3
30	-68	amb	---	0.23	0.53	6.3	3.6
13	-68	<-40	20 TEA	0.15	0.27	20.2	12.9
14	-68	<-40	19 TEA	0.15	0.27	24.5	12.1

a The temperature of the Grignard solution prior to reaction with lanosterol. b The temperature of the lanosterol THF solution prior to reaction with the Grignard reagent. c The molar ratio of amine to Grignard reagent. d The concentration of the Grignard reagent prior to reaction with lanosterol. e The molar ratio of lanosterol to Grignard reagent prior to reaction. f The lanosterol addition rate in mmoles/minute. g The observed induction of the 2-phenylbutane product.

in which the inversion rate of the Grignard reagent is slow compared to the lanosterol addition time. To one mole of 2-phenyl-2-butyl magnesium chloride was added one half mole of lanosterol and the remaining Grignard reagent was quenched with an excess of deuterium oxide at various time intervals after the completion of the lanosterol addition. The results are summarized in Table 5. If Grignard inversion is slow as compared to the lanosterol addition time, then COPR will have a value other than zero. The reactions in Table 5 compare OI and COPR versus delay time for Grignard concentrations of 0.15 - 0.31 M. If COPR had a value of zero then from Table 2 one would expect to obtain values for OI of 8.6 and 10.0% for THF and THF-TEA respectively. The results show an average value of 6.5% for THF and 12.4% for THF-TEA regardless of delay time employed. The values for COPR were calculated (Table 5) using values for I obtained from Table 2 of 8.6% and 10.0% for THF and THF-TEA respectively. In order for the values of AOPR to be meaningful, one of two possibilities must be observed. 1. The value of COPR will remain constant as the delay time increases. (Ideally the value for COPR should equal zero. If, however, COPR has a value other than zero it would indicate that the value chosen for I is in doubt.) 2. The values for COPR decrease as the delay time increases.

Table 5

Reactions of One Half of an Equivalent of Lanosterol with 0.15 - 0.31 Molar Solutions of 2-Phenyl-2-Butyl Magnesium Chloride, Followed by Quenching of the Remaining Grignard Reagent with Deuterium Oxide: The Effect of Delay Time on the Observed Induction of 2-Phenylbutane.

#	A/GR[a]	T° GR[b]	T° L[c]	M GR[d]	L/GR[e]	LAT[f]	DT[g]	%OI[h]	COPR[i]
1	---	-68	<-40	0.27	0.25	12.0	0	5.9	2.7
2	---	-68	<-40	0.27	0.25	16.0	5	5.5	3.1
3	---	-68	<-40	0.31	0.31	10.0	10	7.3	1.3
4	---	-68	<-40	0.30	0.33	9.0	20	5.9	2.7
5	---	-68	<-40	0.30	0.33	9.0	40	7.0	1.6
6	---	-68	<-40	0.31	0.34	18.5	3600	7.5	1.1
14	19 TEA	-68	<-40	0.15	0.27	5.0	0	12.1	2.1
13	20 TEA	-68	<-40	0.15	0.27	6.0	5	12.9	2.9
29	---	-68	amb	0.23	0.39	5.0	3600	4.3	---
30	---	-68	amb	0.23	0.53	23.0	7200	3.6	---

a The molar ratio of amine to Grignard reagent. b The temperature of the Grignard solution prior to reaction with lanosterol. c The temperature of the lanosterol THF solution prior to reaction with the Grignard reagent. d The concentration of the Grignard reagent prior to reaction with lanosterol. e The molar ratio of lanosterol to Grignard reagent prior to reaction. f The lanosterol addition time in seconds. g The elapsed time in seconds between the completion of the lanosterol addition and the quenching of the unreacted Grignard reagent with deuterium oxide. h The observed induction of the 2-phenylbutane produced. i The values were calculated using values for I of 8.6% for THF and 10.0% for TEA.

If case 1 is found, the conclusion is that the residue is racemizing prior to its reaction with the quenching agent. If, on the other hand, case 2 is found, the conclusion is that the residue is not racemizing completely prior to its reaction with the quenching agent. The data in Table 5 agree with case 1. The values for COPR are 2.1 $\pm$ 0.8 and 2.5 $\pm$ 0.4 for THF and THF-TEA respectively. Thus the above data leads to the conclusion that the Grignard reagent is racemizing completely prior to the reaction with the quenching agent.

The lack of close agreement between the experiments of Tables 2 and 4 (and thus a non-zero value for COPR) can be explained by the following difficulties encountered in running the respective reactions. The temperatures of the Grignard solutions were relatively easy to reproduce. The reaction vessel was immersed in an isopropyl-dry ice mixture and the Grignard solution was stirred. There was no heat loss due to circulation of the coolant. As stated in the experimental section, the temperature of -40° for the lanosterol solutions is a maximum value. There is great difficulty encountered in cooling a jacketed flask below 0°. The temperature of a solution in a jacketed flask that is cooled by a circulating coolant will depend on several factors. The room temperature and humidity will vary from month to month. The circulation speed of the coolant will vary from

experiment to experiment. The coolant that was used was an equilibrium mixture of dry-ice isopropyl alcohol. The liquid is saturated with carbon dioxide and it is difficult to circulate the coolant at a high rate using a centrifugal circulation pump. The presence of frost on the pump, connecting tubing, and the flask cause a rise in the lanosterol solution temperature. The dry-ice breakes up into small chips which partially clog the pump, thus slowing down the circulation of the coolant. Anhydrous conditions are required for the reactions, thus it is nearly impossible to measure the temperature of the lanosterol solutions prior to its addition to the Grignard reagent. The temperature of the lanosterol solutions as measured on several occasions was never above -40° and usually was between -45 and -50°. However, a variation of lanosterol solution temperatures of 10° is not unlikely and therefore a variation in OI from experiment to experiment is reasonable.

NOTE The arguments advanced on page 46 maintain that in order for the values obtained for COPR to be meaningful, one of two possibilities must be observed. One of these possibilities was indeed observed; namely, the value for COPR remained constant as the delay time was increased. Thus it was concluded that the residue of the Grignard reagent was racemizing completely prior to

its being quenched with deuterium oxide. It was also argued, that if the value of COPR was constant and other than zero, the value chosen for I was in doubt. The average value obtained for COPR for the reaction of the Grignard reagent in THF was 2.1 ± 0.8. (For THF-TEA the value was 2.5 ± 0.4,) The average value for OI in Table 5 for the Grignard reagent in THF was 6.5 ± 0.8. The value chosen for I was obtained from Table 2 (8.6%). The lack of close agreement for the values of the OI's from the different experiments was explained by the difficulties encountered in the running of the various experiments. Therefore, one cannot assume that the values obtained from Table 2 are any more "correct" than the values obtained from Table 5. Thus it was decided to average the values obtained from all experiments run in the same solvent system. (In Table 5 OI = I because the Grignard reagent is inverting rapidly.) The average values obtained are 7.1% ± 0.9% for THF and 11.3 ± 1.2% for THF-TEA. These average values are chosen to be the <u>real</u> I for the respective solvent systems. When these values are used for the data in Table 5, the average value for COPR is 0.8 ± 0.5% and 1.2 ± 0.6% for THF and THF-TEA respectively. Thus it can be seen that when the average value of I obtained from all experiments is used for the calculation of the COPR's from Table 5, the values obtained for COPR are close to

zero within experimental error.

Table 6 shows the effect of solvent basicity on OI when one half of a mole of lanosterol reacts with one mole of 2-phenyl-2-butyl magnesium chloride, followed by quenching of the remaining Grignard reagent with deuterium oxide on the completion of the lanosterol addition. The values for OI in Table 6 also show that the Grignard reagent is inverting rapidly (COPR = 0 within experimental error) as already demonstrated in Table 5.

TEA is many orders of magnitude more basic than THF. However, the difference in I between the two solvent systems is approximately a factor of two. TMED coordinates with magnesium as a bidentate ligand, and therefore should be effectively more basic than TEA. As the basicity of the solvent increases, the rate of the reaction between lanosterol and 2-phenyl-2-butyl magnesium chloride would be expected to decrease. The slower reaction should be more stereoselective and the value for I should increase in the order

$$THF < TEA < TMED.$$

To rationalize the data presented in Table 6, the species present in the solution have to be considered. These apparent inconsistences will be discussed after all of the data have been presented.

The data in Table 5 show that the 2-phenyl-2-butyl

Table 6

Reaction of One Half of an Equivalent of Lanosterol with 0.15 - 0.27 Molar Solutions of 2-Phenyl-2-Butyl Magnesium Chloride, Followed by Quenching of the Remaining Grignard Reagent with Deuterium Oxide; The Effect of Solvent Basicity on the Observed Induction of 2-Phenylbutane.

#	T° GR[a]	T° L[b]	L/GR[c]	LAT[d]	DT[e]	M GR[f]	A/GR[g]	%OI[h]	COPR[i]
1	-68	<-40	0.25	12.0	0	0.27	---	5.9	1.2
14	-68	<-40	0.27	5.0	0	0.15	19 TEA	12.1	0.8
19	-68	<-40	0.34	4.0	0	0.15	25 TMED	0.1	0.0

a The temperature of the Grignard solution prior to reaction with lanosterol. b The temperature of the lanosterol THF solutions prior to reaction with the Grignard reagent. c The molar ratio of lanosterol to Grignard reagent prior to reaction. d The lanosterol addition time in seconds. e The elapsed time in seconds between the completion of the lanosterol addition and the quenching of the unreacted Grignard reagent with deuterium oxide. f The concentration of the Grignard reagent prior to reaction with lanosterol. g The molar ratio of amine to Grignard reagent. h The observed induction of the 2-phenylbutane produced. i The values for COPR were calculated using values of 7.1% 11.3% and 0.1% for I with THF, THF-TEA, and THF-TMED respectively.

Grignard reagent is inverting rapidly at low temperatures. (The COPR's are equal to zero within experimental error.) The optically active half life* of the Grignard reagent at -68° is less than 3 seconds in THF (0.25 M) and less than 1.3 seconds in THF-TEA (0.27 M). (These optically active half lives were not measured. The values quoted here are the upper limits that could have been measured. It was assumed that if the optically active half life of the Grignard reagent was greater than one quarter of the lanosterol addition time, it would have been measureable with the experimental techniques employed.)

Attempts were made to find conditions in which the rate of Grignard inversion could be slowed sufficiently (COPR $\neq$ 0) in order to trap the optically active Grignard reagent formed when one half of a mole of lanosterol reacts with one mole of 2-phenyl-2-butyl magnesium chloride.

The data in Table 2 show that I is concentration independent. However, it has been shown[11] that the rate of inversion of primary and secondary Grignard reagents is concentration dependent. The inversion

*The optically active half life of the Grignard reagent is defined as the time it takes the optical activity of of the Grignard reagent to be reduced to one half its original value.

rates have been shown to follow second order kinetics. Therefore, the rate of inversion of 2-phenyl-2-butyl magnesium chloride should be decreased when the reagent is diluted. Consequently, the rate of racemization would decrease because

26. rate of racemization = 2 X rate of inversion.

Also, the rate of inversion of Grignard reagents has been shown to be slower in media of higher basicity.[2a,2b] Thus it would appear that if one employed low temperatures, the shortest delay times experimentally feasible, high dilution and high basicity of solvent (excluding TMED), it should be possible to slow the inversion process sufficiently in order to trap the enantiomeric Grignard reagent which remains initially when one half of a mole of lanosterol is reacted with one mole of 2-phenyl-2-butyl magnesium chloride.

The results are shown in Table 7. The dilution of 2-phenyl-2-butyl magnesium chloride with THF from 0.31 M to 0.031 M reduced the OI approximately 50%. The reaction with TEA present would be expected to give a larger reduction in OI. The decrease in OI in 2-phenyl-2-butyl magnesium chloride (0.031 M) with TEA present was about 90%. This is the first time anyone has reported evidence of successfully trapping an optically

Table 7

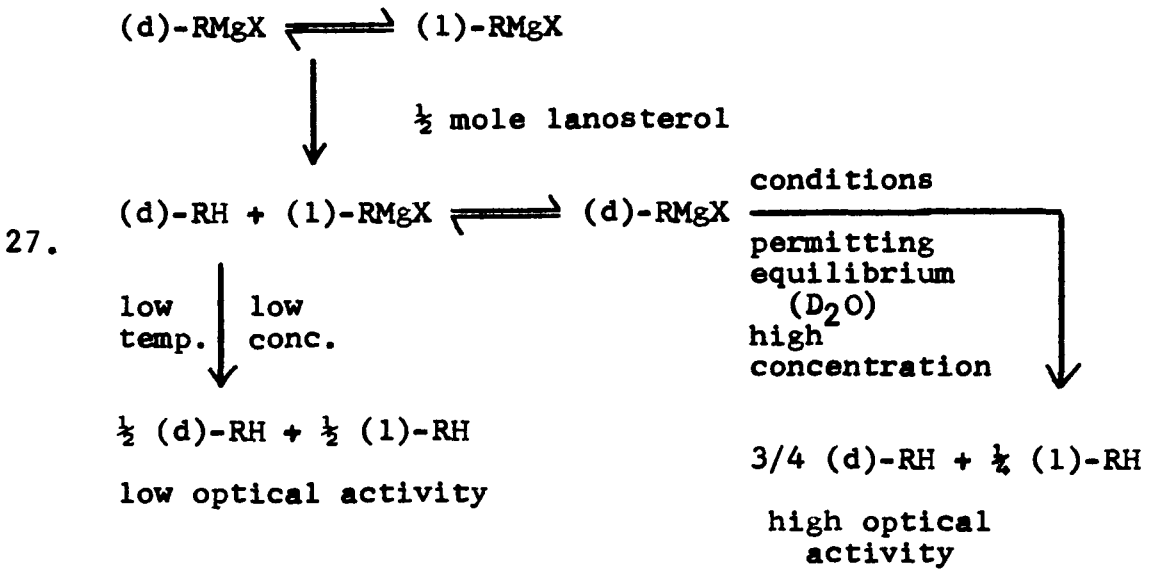
Reaction of One Half of an Equivalent of Lanosterol with 0.027 - 0.31 Molar Solutions of 2-Phenyl-2-Butyl Magnesium Chloride, Followed by Quenching of the Remaining Remaining Grignard Reagent with Deuterium Oxide; The Effect of the Concentration of the Grignard Reagent on the Observed Induction of 2-Phenylbutane.

#	T° GR[a]	T° L[b]	L/GR[c]	A/GR[d]	LAT[e]	DT[f]	M GR[g]	%OI[h]	%OPR[i]	%COPR[i]
1	-68	<-40	0.25	---	12.0	0	0.31	5.9	0.4	1.1
8	-68	<-40	0.36	---	7.8	0	0.031	3.3	2.1	3.8
14	-68	<-40	0.27	19 TEA	5.0	0	0.15	12.1	0.3	0.8
15	-68	<-40	0.34	24 TEA	5.8	0	0.027	1.3	5.2	10.0

a The temperature of the Grignard solution prior to reaction with lanosterol. b The temperature of the lanosterol THF solutions prior to reaction with the Grignard reagent. c The molar ratio of lanosterol to Grignard reagent prior to reaction. d The molar ratio of amine to Grignard reagent. e The lanosterol addition time in seconds. f The elapsed time in seconds between the completion of the lanosterol addition and the quenching of the unreacted Grignard reagent with deuterium oxide. g The concentration of the Grignard reagent prior to reaction with lanosterol. h The observed induction of the 2-phenylbutane produced. i The values for OPR and COPR were calculated using values of 7.1 and 11.3% for I with THF and THF-TEA respectively.

active Grignard reagent. Equation 27 summarizes the results obtained from Table 7.

27.



At this time it is convenient to define a new term: Stereochemical Stability of the Grignard Reagent (SSG).

28. SSG ≡ COPR/I

Thus, the SSG for 0.031 M 2-phenyl-2-butyl magnesium chloride in THF is 3.8/7.1 = 0.53, and the SSG for 0.027 M 2-phenyl-2-butyl magnesium chloride in THF-TEA is 10.0/11.3 = 0.89.

The SSG however, is not a very useful term by itself. The SSG refers to the optical purity of the Grignard reagent at a specific time along the reaction pathway. As such it does not tell how fast the Grignard reagent

is racemizing but how much it has racemized at a given time.

If one assumes that the rate of Grignard racemization is independent of lanosterol addition rate, and that the "average time" of the lanosterol addition is the time when the residue has the highest optical purity, then, the rate of racemization of 2-phenyl-2-butyl magnesium chloride can be calculated using equation 29.

$$29. \quad \% \text{ Racemization/second} = \frac{(1 - SSG)}{\bar{t}} \times 100$$

where $\bar{t} = \frac{t_2 - t_1}{2}$

t_2 = The time of completion of the lanosterol addition.

t_1 = The time at the start of the lanosterol addition.

Employing equation 29 the values for the rates of racemization of 2-phenyl-2-butyl magnesium chloride are 12%/second for THF (0.031 M) and 3.8%/second for THF-TEA (0.027 M). Similarly, if one employs equation 26, the rate of inversion of 2-phenyl-2-butyl magnesium chloride at -68° is $\sim$ 6%/second and $\sim$1.9%/second in THF and THF-TEA respectively. Thus the optically active half lives of the Grignard reagent at these conditions is $\sim$4 seconds in THF and $\sim$13 seconds in THF-TEA. These results agree qualitatively with published

reports of the lifetimes of primary Grignard reagents. (see Historical Background) These studies have shown that the rate of inversion decreases with solvent basicity.

The high values obtained for COPR in dilute solutions (Table 7) lead to the conclusion that one should be able to react the optically active residues with an electrophile other than hydrogen. Thus, two optically active products would be obtained from a single experiment. The isolation of an optically active compound formed in the reaction between the Grignard reagent and an inactive electrophile would prove the hypothesis already presented concerning the optical stability of the 2-phenyl-2-butyl Grignard reagent. In addition, the isolation of two optically active products from an experiment will provide one with information concerning the stereochemistry of the respective reactions.

The first electrophile that was reacted with the 2-phenyl-2-butyl Grignard reagent was carbon dioxide. In general, carbon dioxide reacts with Grignard reagents to produce the corresponding carboxylic acids in high yield. In addition, the yields of acid usually increase with decreasing reaction temperature.[41] (This condition is ideally suited for the system being studied.) One main advantage of using carbon dioxide is that the products (2-phenylbutane and 2-phenyl-2methyl butanoic

acid) are easily separated quantatively from each other. The results of all reactions in which one half an equivalent of lanosterol and one half an equivalent of carbon dioxide were reacted with one equivalent of 2-phenyl-2-butyl magnesium chloride are summarized in Table 8.

As can be seen from the table, with the exception of reaction #48, the values for I of the 2-phenylbutane are much lower than expected. The values for I should be 7.1% for THF and 11.3% for THF-TEA. Reaction #48 was run by reacting the Grignard reagent with one half an equivalent of lanosterol followed by quenching of the unreacted Grignard reagent with carbon dioxide gas. The reaction of the Grignard reagent with carbon dioxide gas is a slow reaction in comparison with the optically active half life of the Grignard reagent. Thus the carboxylic acid produced must necessarily be racemic.

In all of the other reactions shown in Table 8, the carbon dioxide was dissolved in THF ($T = < -40^{o}$) and added to the Grignard reagent in solution. In reactions #42 and 43 the reaction mixture was quenched with deuterium oxide 5 minutes after a twofold excess of carbon dioxide was added to the Grignard solution. The <u>hydrocarbon</u> product contained 2-phenylbutane-2-D. The above experiments indicate that the reaction between

Table 8

The Reactions of 2-Phenyl-2-Butyl Magnesium Chloride with Lanosterol and Carbon Dioxide[a]

#	A/GR[b]	L/GR[c]	M GR[d]	LAT[e]	DT[f]	CAT[g]	DT2[h]	%I-HYD[i]	%I-AC[j]
12	---	0.26	0.26	20.0	k	20.0	1	3.3	0.11
18	31 TEA	0.28	0.12	14.8	k	14.8	30 D_2O[m]	1.9	0.83
42	---	0.37	0.027	10.5	0	5.4	300 D_2O[m]	3.2	0.61
43	24 TEA	0.34	0.027	9.0	0	6.3	300 D_2O[m]	3.1	0.44
46	---	0.30	0.034	7.8	0	9.5	1	3.6	0.03
47	22 TEA	0.33	0.029	11.7	0	5.4	1	1.1	0.09
48	---	0.31	0.034	17.9	29.5	3600	1	5.4	0.33

a The temperature of the Grignard solutions prior to reaction with lanosterol was -68°. The temperature of the lanosterol and the carbon dioxide-THF solutions was <-40°. b The molar ratio of amine to Grignard reagent. c The molar ratio of lanosterol to Grignard reagent prior to reaction. d The concentration of the Grignard reagent prior to reaction with lanosterol. e The lanosterol addition time in seconds. f The elapsed time between the completion of the lanosterol addition and the beginning of the carbon dioxide addition. g The carbon dioxide addition time in seconds. h The elapsed time between the completion of the carbon dioxide addition and the addition of a quenching agent. i The induction of the 2-phenylbutane produced. j The optical purity of the 2-phenyl-2-methyl butanoic acid corrected for that fraction of the acid that cannot be optically active. k Both the carbon dioxide and the lanosterol were dissolved in the same solution and added to the Grignard reagent simultaneously. l The unreacted Grignard reagent was allowed to dimerize by standing overnight at room temperature. m The hydrocarbon produced contained both 2-phenylbutane and 2-phenylbutane-2-D.

2-phenyl-2-butyl magnesium chloride (0.027 M) and carbon dioxide at -68° is relatively slow as compared to the optically active half life of the Grignard reagent.

In a separate experiment the relative reactivities of lanosterol and carbon dioxide with 2-phenyl-2-butyl magnesium chloride were determined. The relative reactivities were determined by adding one equivalent of 2-phenyl-2-butyl magnesium chloride to two equivalents of lanosterol and two equivalents of carbon dioxide dissolved in THF (inverse addition). The ratio of the 2-phenylbutane to 2-phenyl-2-methyl butanoic acid produced was 2.7 : 1. Thus it was established that lanosterol reacts faster than carbon dioxide with 2-phenyl-2-butyl magnesium chloride. In addition both the hydrocarbon and the acid produced were racemic.

At this time it was decided to dissolve the lanosterol and carbon dioxide in THF in the same flask and add both reagents simultaneously to the 2-phenyl-2-butyl Grignard reagent. Thus the delay time between the addition of the lanosterol and the carbon dioxide is reduced to a minimum. (reactions #12 and 18) The results of these experiments were similar to those of reactions #42, 43, 46 and 47. In all of the carbonation experiments the acid produced was alqays racemic.

On one occasion it was noticed that the stopcock supporting the carbon dioxide-THF solution was leaking

slightly. In all of the experiments the carbon dioxide was dissolved in the THF by bubbling the gas through the solvent in a closed system. Thus there was probably a small pressure buildup in the flask which caused the stopcock to leak.

In light of these results it is likely that in all the experiments in which carbon dioxide was dissolved in the THF the stopcocks leaked. Thus a small amount of carbon dioxide was mixed with the Grignard reagent prior to the reaction of the Grignard reagent with lanosterol. The carbon dioxide would then complex with the Grignard reagent (or react to some small extent) and the transition state between the lanosterol and the Grignard reagent would then necessarily be altered. Thus, the low values obtained for induction (I) in the 2-phenylbutane produced is reasonable.

Although the problems encountered in the carbonation reactions were largely experimental, the results indicate that the reaction between the 2-phenyl-2-butyl magnesium chloride and carbon dioxide is too slow to yield an optically active acid. Therefore the use of carbon dioxide was abandoned.

It is well known that Grignard reagents react with oxygen to produce alcohols. However, the method is not very frequently used because the transformation is not often desired and can usually be accomplished

by other means.

The oxidation of a Grignard reagent can be carried out by two different methods depending on the product desired. When the Grignard reagent is added to oxygen, the product is the corresponding hydroperoxide. If, on the other hand, oxygen is added to the Grignard reagent, the product is the corresponding alcohol.

Grignard reagents react with oxygen to form the alcohol via the two step sequence[42]

30.
$$RMgX + O_2 \longrightarrow ROOMgX$$
$$ROOMgX + RMgX \longrightarrow 2\ ROMgX$$

The mechanism of this reaction has not been elucidated. There is evidence, however, to support the hypothesis that the reaction proceeds via polar transition states.[42] It was hoped that both steps in the reaction sequence proceeded via similar stereochemical mechanisms, i.e. retention or inversion. However, if one of the steps produced racemic product, the only observable effect would be a low value obtained for the optical purity of the 2-phenyl-2-butanol.

Goebel and Marvel[43] have shown that the rate of the reaction of Grignard reagents with oxygen increases with decreasing temperature. In addition Walling[42] has shown that t-butyl magnesium chloride in ether

reacts with oxygen to form the hydroperoxide faster than acetone, n-butyraldehyde and diphenyl amine. If the rate of the reaction of 2-phenyl-2-butyl magnesium chloride and oxygen at -68° is fast compared to the rate of racemization of the Grignard reagent, the 2-phenyl-2-butanol should be optically active.

Since all attempts to dissolve oxygen in THF in appreciable quantities failed in this laboratory, the addition of oxygen to the Grignard solution would have to be carried out by the use of syringe techniques. The temperature of the oxygen in the syringe would be approximately 25°. Therefore the oxidation of the 2-phenyl-2-butyl Grignard reagent could not be carried out under optimum conditions.

It appears that oxygen is less than an ideal quenching agent. However, a search for an electrophile that would react with 2-phenyl-2-butyl magnesium chloride both quantitatively and at a high rate to yield a product of known stereochemistry proved disappointing. Thus it was decided to react the 2-phenyl-2-butyl Grignard reagent in dilute solution with one half an equivalent of lanosterol and one half an equivalent of oxygen. The results are summarized in Table 9.

As can be seen from the table the experiments were successful in trapping the optically active Grignard reagent in both dilute THF and THF-TEA solutions. The

Table 9

The Reactions of One Half an Equivalent of Lanosterol with 0.027 - 0.030 Molar Solutions of 2-Phenyl-2-Butyl Magnesium Chloride Followed by Quenching of the Remaining Grignard Reagent with Oxygen.[a]

#	L/GR[b]	A/GR[c]	M GR[d]	LAT[e]	DT[f]	OAT[g]	%I-HYD[h]	AC-HYD[i]	%I-ALC[j]	AC-ALC[k]
41	0.38	---	0.027	12.9	0	9.7	6.7	R-(-)	1.5	R-(+)
50	0.32	22 TEA	0.030	11.0	0	13.2	9.4	R-(-)	3.0	R-(+)

a The temperature of the Grignard solutions prior to reaction of the Grignard reagent with lanosterol was -68°. The temperature of the lanosterol-THF solutions was at least -40°. b The molar ratio of lanosterol to Grignard reagent prior to reaction. c The molar ratio of amine to Grignard reagent. d The concentration of the Grignard reagent prior to reaction with lanosterol. e The lanosterol addition time in seconds. f The elapsed time in seconds between the completion of the lanosterol addition and the quenching of the Grignard reagent with oxygen. g The oxygen addition time in seconds. h The induction of the 2-phenylbutane produced. i The absolute configuration of the optically active fraction of the 2-phenylbutane product. j The induction of the 2-phenyl-2-butanol product. k The absolute configuration of the fraction of the 2-phenyl-2-butanol that is optically active.

percent induction for the alcohol in THF was 1.5% and in THF-TEA 3.0%.

In the reactions of 2-phenyl-2-butyl magnesium chloride with lanosterol and carbon dioxide the values of I for the acid obtained were as high as 0.8%. However, in discussing the data, the optical purities of the acids were assumed to be too low to be meaningful. In reporting the values for I of 2-phenyl-2-butanol, an induction of 1.5% was assumed to be evidence of the successful trapping of the optically active Grignard reagent. To understand why the oxygen experiments were assumed to be successful and the carbonation reactions were not, one must consider the errors involved in computing the values for I in both types of experiments.

The maximum rotation in concentrated solution of any of the acids produced was 0.044°. Although the polarimeter used could report rotations to 0.001°, the readings in the last decimal place were never reproducable. Thus the minimum error in the rotations of the carboxylic acids was 0.04 ± 0.01 or 25%. In addition, the direction of the rotation of the acids fluctuated between + and -. Therefore, it was concluded that all the 2-phenyl-2-methyl butanoic acids produced were racemic. However, the observed rotations of the 2-phenyl-2-butanols produced were +0.175 and +0.261° (neat). An error of 0.01 in these readings would not change the observed

rotations significantly (~5%). The alcohols produced in the oxidation of the Grignard reagent are indeed optically active. Thus, this is the first report where anyone has been able to produce an optically active acyclic Grignard reagent and react it with an optically inactive electrophile to produce an optically active product.

The calculated values for the rate of racemization of the 2-phenyl-2-butyl Grignard reagent from the data in Table 9 are ~7%/second and ~6%/second for THF and THF-TEA respectively. The values obtained from the data in Table 7 were 12%/second and 3.8%/second for THF and THF-TEA. To explain the discrepancy in the results one must consider the relative rates of the reactions of the species involved.

Pocker and Exner[40] have shown that deuterium isotope effects from the reactions of oxygen acids (i.e. water, methanol, and phenol) with Grignard reagents do not vary significantly and are generally between 1.0 and 1.5. However, the isotope effects from carbon acids vary between 1.4 and 10.8. This evidence suggests that most oxygen acids react with Grignard reagents at similar rates (lanosterol and deuterium oxide). Furthermore, they hypothesized that the reaction pathway for all oxygen acids involves replacement of a metal coordinated solvent molecule by the oxygen

acid. Although there have been no reports on the relative reactivity of water and oxygen with Grignard reagents, it seems reasonable to expect that the rate of protonation is faster than oxidation.

The calculations of the rates of racemization of 2-phenyl-2-butyl magnesium chloride from the data in Tables 7 and 9 were based on the hypothesis that the reagents reacted with the Grignard reagent instantaneously. If the rate of the reaction of the 2-phenyl-2-butyl Grignard reagent with oxygen is slow compared with the rate of the protonation reaction, the rate of racemization of the Grignard reagent calculated using equation 29 would lead to incorrect results. Therefore, in calculating the rate of racemization of the 2-phenyl-2-butyl Grignard reagent, the values obtained from the data in Table 7 where both reagents are oxygen acids would describe the behavior of the Grignard reagent more accurately than the data in Table 9 where both reagents are not oxygen acids.

Although the rate of racemization of 2-phenyl-2-butyl magnesium chloride cannot be accurately calculated from the data of the oxidation reactions, the data does supply evidence concerning the stereochemistry of the reagents involved. The products obtained from the reaction of one half an equivalent of lanosterol and one half an equivalent of oxygen with the Grignard

reagent (2-phenylbutane and 2-phenyl-2-butanol) have the opposite absolute configuration (see page 9 and Table 9). These products can arise from two different stereochemical mechanisms, i.e. retention-retention or inversion-inversion.

As previously discussed, the product obtained from the reaction of organometallic compounds with oxygen acids (page 67) is thought to proceed via a four center transition state. If this hypothesis is correct, then the protonation reaction of organometallic compounds with oxygen acids proceeds via a retention mechanism. Consequently, the oxidation reaction would also proceed via a retention mechanism.

The production of optically active alcohol also gives supportive evidence concerning the polar nature of the oxidation reaction. The thermal decomposition of optically active azo-bis-2-phenylbutane leads to racemic product[32] (dimer). This reaction is known to proceed via a radical mechanism. Thus, if the oxidation reaction proceeded via a radical mechanism, the product obtained would be racemic.

In the theoretical discussion (page 4) it was stated that if the 2-phenyl-2-butyl Grignard reagent is inverting rapidly (as is indeed the case for the experiments in concentrated ~ 0.3 M solution) then when one equivalent of lanosterol reacts with one

equivalent of Grignard reagent the optical purity of the 2-phenylbutane produced should be twice as large as the optical purity of the 2-phenylbutane from the reaction of one half an equivalent of lanosterol and one equivalent of Grignard reagent. The OI, however, should remain constant. Table 10 summarizes the results of several experiments in which one equivalent of 2-phenyl-2-butyl magnesium chloride was reacted with an excess of lanosterol. From the table it can be seen that the OI's are much lower than expected. In addition, when an excess of lanosterol was added to the Grignard solution, at a lanosterol solution temperature of -40°, not all of the Grignard reagent reacted with the lanosterol within 2 minutes.

Table 11 summarizes all the experiments where lanosterol reacted with the 2-phenyl-2-butyl Grignard reagent in the presence of TMED. The values obtained for OI in all of the experiments were low (less than 2%).

There are two results that the theoretical statement cannot justify: 1- the low values obtained for OI when reacting lanosterol with 2-phenyl-2-butyl magnesium chloride in the presence of TMED and 2- the low values for OI obtained when reacting one equivalent of 2-phenyl-2-butyl magnesium chloride with an excess of lanosterol.

Table 10

The Reactions of Excess Lanosterol (5 - 200%) with 2-Phenyl-2-Butyl Magnesium Chloride

#	T° GR[a]	T° L[b]	A/GR[c]	DT[d]	M GR[e]	L/GR[f]	L*/GR[g]	OP-HYD[h]	%OI[i]
10	-68	<-40	---	120	0.26	1.28	0.70	1.14	1.6
16	-68	<-40	26 TEA	120	0.14	1.05	0.73	0.74	1.1
23	-68	0	---	120	0.28	1.11	1.00	1.92	1.9
25	-68	0	34 TEA	120	0.11	1.47	1.00	2.53	2.5
9	-68	<-40	---	60	0.020	1.64	0.64	1.02	1.6

a The temperature of the Grignard solution prior to reaction with lanosterol. b The temperature of the lanosterol-THF solutions prior to reaction with the Grignard reagent. c The molar ratio of amine to Grignard reagent. d The elapsed time in seconds between the completion of the lanosterol addition and the quenching of the reaction mixture with deuterium oxide. e The concentration of the Grignard reagent prior to reaction with lanosterol. f The molar ratio of lanosterol to Grignard reagent prior to reaction. g The fraction of the Grignard reagent that reacted with the excess lanosterol. h The optical purity of the hydrocarbon corrected for preformed 2-phenylbutane and olefin and alcohol. i The observed induction of the 2-phenylbutane product.

Table 11

Reactions of Lanosterol with 2-Phenyl-2-Butyl Magnesium Chloride; Reactions in the Presence of N,N,N',N', Tetramethylethylenediamine (TMED).

#	T° GR[a]	T° L[b]	A/GR[c]	M GR[d]	L/GR[e]	DT[f]	%OI[g]
21	-68	<-40	49 TMED	0.077	0.67	h	0.1
19	-68	<-40	25 TMED	0.15	0.34	0	0.6
20	-68	<-40	27 TMED	0.14	1.00	120	0.6
27	-68	0	39 TMED	0.094	0.51	60	1.9
28	-68	0	39 TMED	0.094	1.00	120	0.9
34	-68	amb	39 TMED	0.096	0.64	3600	1.2

a The temperature of the Grignard solution prior to reaction with lanosterol. b The temperature of the lanosterol-THF solutions prior to reaction with the Grignard reagent. c The molar ratio of TMED to Grignard reagent. d The concentration of the Grignard reagent prior to reaction with lanosterol. e The molar ratio of lanosterol to Grignard reagent prior to reaction. f The elapsed time between the completion of the lanosterol addition (in seconds) and the quenching of the remaining Grignard reagent with deuterium oxide. g The observed induction of the 2-phenylbutane product.

As already discussed (page 51) one would expect that as the basicity of the solvent increased the reaction between lanosterol and the Grignard reagent should become more selective. The almost total lack of stereospecificity of the reactions in the presence of TMED would indicate that something other than the relative basicity of the solvents is responsible for the observed trends in I.

The results of the reactions of excess lanosterol with the 2-phenyl-2-butyl Grignard reagent would seem to indicate that the Grignard reagent is inverting slowly. This is clearly not the case since the optically active Grignard reagent could not be trapped in 0.3 molar solutions wheras in dilute solutions (0.03 M), the optically active Grignard reagent was trapped. Thus it seems from the results in Tables 10 and 11 that the theoretical approach to the problem may have been somewhat naive. In order to explain the results of the reactions between excess lanosterol and 2-phenyl-2-butyl magnesium chloride and also the results where TMED was present one must consider the species that are present in a Grignard solution.

It is well known that Grignard reagents in ethereal solution can be represented by the Schlenk equilibrium.[44]

31. $R_2Mg + MgX_2 \rightleftharpoons 2RMgX \rightleftharpoons$ Dimer $\rightleftharpoons$ Trimer

In THF[45] and TEA[46] solutions Grignard reagents have been shown to be monomeric. Thus, in these solvents the Grignard reagent can be represented by

32. $R_2Mg + MgX_2 \rightleftharpoons 2RMgX$

Grignard solutions in THF have been shown to contain substantial quantities of both RMgX and R_2Mg.[47] The measured value of the equilibrium constant for several Grignard reagents, regardless of the nature of the R group, in THF was ~ 4.

The study of primary and secondary Grignard reagents in TEA have shown that equilibrium 32 lies far to the right.[48] However, for t-butyl Grignard reagents the equilibrium is not as far to the right as are the primary and secondary Grignard reagents.

There is a large body of evidence [48-52] available to support the hypothesis that in Grignard solutions containing TMED, the predominant species present is RMgX·TMED. TMED functions as a bidentate ligand, and therefore acts as a stronger base than TEA which cannot function as a bidentate ligand.

Evidence for this complex has been demonstrated in several laboratories.[48-52] Dimethyl magnesium has been shown to be polymeric in ether.[49] However, addition of TMED to an ethereal solution of dimethyl magnesium

forms the complex $(CH_3)_2Mg \cdot TMED$. This complex is monomeric and volatile.[50]

Abraham and Rolfe[51] have shown that the addition of TMED to a THF-ether solution of ethyl zinc iodide results in the precipitation of a solid which analyzes for $C_2H_5ZnI \cdot TMED$.

House and his co-workers[52] have shown that the rate of exchange between dicyclopentadienyl magnesium and dimethyl magnesium in ether is severly retarded by the addition of TMED. TMED was demonstrated to be distinctly more effective in retarding the rate of exchange than TEA which cannot function as a bidentate ligand. Thus, TMED functions as a stronger base than TEA.

If the relative basicity of the solvents employed in the reactions of 2-phenyl-2-butyl magnesium chloride and lanosterol were the only parameter responsible for a variance in the stereoselectivity of the reactions then as already discussed (pages 51 - 53) the I's should vary in the order THF < TEA < TMED. The experimentally determined order for these solvents (at a Grignard solution temperature of -68° and a maximum lanosterol solution temperature of -40°) is

$$\text{TMED (0.6\%)} < \text{THF (7.1\%)} < \text{TEA (11.3\%)}$$

In addition, although TEA is many times more basic than

THF, the difference in I between the two solvents is approximately a factor of two. Thus, one must consider the species present in a Grignard solution to explain the data.

If one considers equilibrium 32 in the respective solvent systems, the equilibrium shifts to the right producing more RMgX as one changes the solvent from THF to THF-TEA to THF-TMED. Thus, the amount of RMgX present in the reaction mixture in these solvent systems can be represented by THF-TMED $>$ THF-TEA $>$ THF. (Conversely, the amount of R_2Mg present is THF $>$ THF-TEA $>$ THF-TMED.) However, the position of the Schlenk equilibrium is not the only factor responsible for the variation in the value of I. As the basicity of the solvent increases the reaction between lanosterol and the Grignard reagent becomes more stereoselective. Only in the presence of TMED, where there is virtually no R_2Mg present, can the opposing contributory effects of the two parameters be evaluated. Thus, in light of the above arguments, the data lead one to conclude that the species present in the 2-phenyl-2-butyl Grignard solution responsible for producing optically active 2-phenylbutane is di(2-phenyl-2-butyl) magnesium.

This conclusion is further supported by the work of Ashby and Parris[11] in which they have demonstrated that the Schlenk equibibrium (equation 32) shifts toward

the right (RMgX) as the temperature is increased. If the hypothesis concerning the species responsible for induction is correct, then as the reaction temperature of the 2-phenyl-2-butyl Grignard reagent and lanosterol is raised, the Schlenk equilibrium will shift toward RMgX and the value for OI will decrease. The data in Table 3 support this argument.

The low values obtained for OI when an excess of lanosterol was reacted with 2-phenyl-2-butyl magnesium chloride (Table 10) indicates that the theoretical argument was an oversimplification of the behavior of the Grignard reagent.

When the Grignard reagent was at -68° and the lanosterol-THF solution was at 0° (#23 and 25), the OI's obtained were 1.9% and 2.5% for THF (0.28 M) and THF-TEA (0.11 M) respectively. In addition, when the Grignard reagent was at -68° and the lanosterol-THF was at <-40° (#10 and 16), the OI's were even smaller than those at the higher temperatures (1.6% and 1.1% for THF 0.26 M and THF-TEA 0.14 M).

To explain these apparent anomalies one must consider the difference, if any, between the reaction of excess lanosterol with the Grignard reagent and the reaction of one half of an equivalent of lanosterol followed by the quenching of the remaining Grignard reagent with deuterium oxide.

The rate of racemization of 2-phenyl-2-butyl magnesium chloride (Grignard solution temperature of -68°, lanosterol solution temperature -40°) was calculated from the data in Table 7 using equation 29. The values obtained were 12%/second for THF (0.031 M) and 3.8%/second for THF-TEA (0.027 M). As already discussed in the Historical Background, the rate of inversion of Grignard reagents is a bimolecular process involving 2 moles of Grignard reagent. Thus, the rate of inversion of 2-phenyl-2-butyl magnesium chloride can be represented by equation 33.

33. Rate of Inversion = $k \left[GR\right]^2$

The combination of equations 33 and 26 (page 54) gives 34.

34. Rate of Racemization = $(k/2) \times \left[GR\right]^2$

Thus the values for k calculated from the above data are 104 l mole $^{-1}$ sec^{-1} for THF-TEA and 250 l mole^{-1} sec^{-1} for THF. Table 12 shows the calculated rates of racemization of the 2-phenyl-2-butyl Grignard reagent at several concentrations.

As can be seen from the table, the rate of racemization of the 2-phenyl-2-butyl Grignard reagent is sufficiently slow to trap the optically active Grignard

Table 12

Calculated Rates of Racemization for 2-Phenyl-2-Butyl Magnesium Chloride at -68° in THF and THF-TEA.

M GR	Rate of Racemization (%/sec) THF	THF-TEA
0.30	1130	470
0.27	910	380
0.24	720	300
0.21	550	230
0.18	410	170
0.15	280	120
0.12	180	70
0.09	100	42
0.06	45	19
0.03	11	5
0.02	5	2
0.01	1	0.5

reagent when the Grignard concentrations are below 0.06 M for THF and 0.09 M for THF-TEA.

In all experiments (Tables 3 - 6) where deuterium oxide was employed to quench the unreacted Grignard reagent, the concentration of the Grignard reagent after the completion of the lanosterol addition was never below 0.06 M for THF and 0.09 M for THF-TEA. Thus, in all of these experiments, the rate of racemization of the

remaining Grignard reagent was never sufficiently slow so as to enable one to trap an optically active residue. However, for the reaction of excess lanosterol with the 2-phenyl-2-butyl Grignard reagent (Table 10 #10 and 16), the rate of racemization of the Grignard reagent becomes slow when ~75% and 45% of the reagent has been consumed in THF and THF-TEA respectively. Thus, as the addition of the lanosterol continues, the optically active residue is being trapped. Consequently, the values obtained for OI were small as compared to the reactions where deuterium oxide was employed.

The above argument also explains why the values for OI at the lower temperatures (Grignard reagent -68°, lanosterol <-40°) were less than the values obtained at the higher temperatures (Grignard reagent -68°, lanosterol 0°). As the temperature is lowered, the rate of racemization of the Grignard reagent will decrease. Thus the enantiomer that is being trapped at the lower temperatures will have a higher optical purity than the enantiomer trapped at the higher temperatures.

From the available data, one can only speculate upon the reason why excess lanosterol does not completely with 2-phenyl-2-butyl magnesium chloride at -68°. The evidence in the mixed solvent systems indicates that R_2Mg is the species that reacts with lanosterol to form optically active 2-phenylbutane. It is possible that

RMgX reacts slowly, if at all, with active hydrogen compounds. Thus if R_2Mg reacts with lanosterol, when all of the R_2Mg is consumed, the rate of reaction between lanosterol and Grignard reagent will decrease. More R_2Mg will be produced as the equilibrium shifts, however at -68°, reequilibration would be slower than at the higher temperatures, especially in very dilute solution.

Recently, Skell and Girard[53] have reported that ethylmagnesium bromide produced from the reaction of atomic magnesium and ethyl bromide reacts with acetone in the absence of any ethereal solvent to give 90% enolization product. Although a direct correlation cannot be drawn between the two systems, the evidence indicates that the hypothesis has merit.

Employing variable temperature NMR techniques, Ashby and Parris[11] were able to distinguish between the R_2Mg and the RMgX species for t-butyl magnesium chloride in THF and ether. Although the NMR spectrum of 2-phenyl-2-butyl magnesium chloride is more complex than t-butyl magnesium chloride, it was decided to study the temperature dependence of this reagent in THF, THF-TEA and THF-TMED. It was hoped that this study would support the hypothesis concerning the Schlenk equilibrium already fowarded in this thesis. The study, however, proved to be disappointing. The large THF absorbtions obliterated the aliphatic absorbtions of the Grignard reagent. (The

concentration of the Grignard reagent was ~0.3 M. Thus, the solution in the NMR tube contained primarily THF.) The aromatic absorbtions did show some temperature dependence, however, the spectra were too complex for analysis.

SUMMARY

The asymmetric induction experiments were designed to find conditions under which the rate of racemization of the 2-phenyl-2-butyl Grignard reagent could be measured. The degree of asymmetric induction (I) for the reaction of the Grignard reagent with lanosterol was determined under various solvent conditions. The results are summarized in Summary Table 1.

Summary Table 1

The Determination of the Degree of Asymmetric Induction (I) in the Reaction of Lanosterol with 2-Phenyl-2-Butyl Magnesium Chloride at -68° by Reaction of the Grignard Reagent with Approximately One Half an Equivalent of Lanosterol and Allowing the Remaining Grignard Reagent to Dimerize.[a]

#	A/GR[b]	M GR[c]	%I
17	31 TEA	0.12	10.4
45	28 TEA	0.024	9.7
11	---	0.27	8.8
44	---	0.033	8.4
21	49 TMED	0.077	0.1

a See Table 2, page 41 for further details. b The molar ratio of amine to Grignard reagent prior to reaction. c The concentration of the Grignard reagent prior to reaction with lanosterol.

In order to determine the effects that various experimental parameters had on the values of I, several reactions were run in which the 2-phenyl-2-butyl magnesium

chloride was reacted with approximately one half an equivalent of lanosterol followed by quenching the remaining Grignard reagent with deuterium oxide under varied experimental conditions. It was found that I was independent of lanosterol addition rate (Table 4, page 45) and delay time in concentrated ($\sim$0.3 M) solution (Table 5, page 47). The values of I increased when the reaction temperatures were decreased (Table 3, page 43) and when the solvent basicity was increased from THF to THF-TEA (Table 6, page 52 and Table 2, page 41).

In reactions with TMED present, the small values obtained for I were interpreted as being caused by an unfavorable shift in the Schlenk equilibrium (Table 11, pges 72 - 77).

The reactions in which 2-phenyl-2-butyl magnesium chloride was reacted with approximately one half an equivalent of lanosterol followed by quenching the remaining Grignard reagent with deuterium oxide under optimum conditions (low temperature and high dilution of Grignard reagent) were successful in trapping the optically active Grignard reagent. These results are summarized in Summary Table 2.

The reactions of 2-phenyl-2-butyl magnesium chloride with approximately one half an equivalent of lanosterol followed by the quenching of the remaining Grignard reagent with oxygen under optimum conditions

Summary Table 2

The Reaction of Approximately One Half of an Equivalent of Lanosterol with 0.31 - 0.027 M Solutions of 2-Phenyl-2-Butyl Magnesium Chloride Followed by Quenching the Remaining Grignard Reagent with Deuterium Oxide; the Effect of Grignard Concentration on the Observed Induction (OI) of 2-Phenylbutane[a]

#	LAT[b]	M GR[c]	%OI[d]	%COPR[e]	R[f]
1	12.0	0.31	5.9	1.1	>16
8	7.8	0.031	3.3	3.8	12
14	5.0	0.15[g]	12.1	0.8	>40
15	5.8	0.027[g]	1.3	10.0	3.8

a The reactions were run at a Grignard solution temperature of -68° and a maximum lanosterol solution temperature of -40°. (See Table 7 page 55 for further details.) b The lanosterol addition time in seconds. c The concentration of the Grignard reagent prior to reaction with lanosterol. d The observed induction of the product 2-phenylbutane. e The corrected optical purity of the residue. f The % racemization/second of the optically active Grignard reagent. g Approximately a 20 molar excess of TEA was added to the Grignard reagent prior to reaction with lanosterol and deuterium oxide.

(low temperature and high dilution of Grignard reagent) were successful in the production of both optically active 2-phenylbutane and optically active 2-phenyl-2-butanol. These results are summarized in Summary Table 3. Thus the first successful trapping of an optically active acyclic Grignard reagent was accomplished. In addition, the rate of racemization of a Grignard reagent was measured by chemical means. Evidence was

Summary Table 3

The Reaction of Approximately One Half an Equivalent of Lanosterol with 0.027 - 0.030 M Solutions of 2-Phenyl-2-Butyl Magnesium Chloride Followed by Quenching of the Remaining Grignard Reagent with Oxygen.[a]

#	M GR[b]	% I HYD[c] (R-)[d]	% I ALC[e] (R+)[d]
41	0.027	6.7	1.5
50	0.030[f]	9.4	3.0

a The reactions were run at a Grignard solution temperature of -68° and a maximum lanosterol solution temperature of -40°. (See page 65 Table 9 for further details.) b The concentration of the Grignard reagent prior to reaction with lanosterol. c The induction (I) of the 2-phenylbutane produced. d absolute configuration e The induction (I) of the 2-phenyl-2-butanol produced. f A 22 molar excess of TEA was added to the Grignard reagent prior to reaction with lanosterol and oxygen.

presented to show that bis(2-phenyl-2-butyl) magnesium was the species that reacts with lanosterol to produce optically active 2-phenylbutane. Evidence was also presented which supports the hypothesis that Grignard oxidations proceed via a polar mechanism.

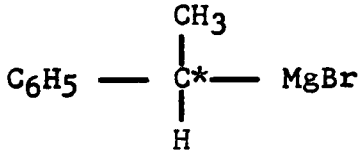
FUTURE WORK

The 2-phenyl-2-butyl — lanosterol reaction system appears to be ideally suited for further study in the chemistry of organometallic compounds. The reactions of lanosterol with bis(2-phenyl-2-butyl) magnesium would complement the work of this thesis. The reactions of bis(2-phenyl-2-butyl) magnesium in the presence of TMED is expected to yield 2-phenylbutane with higher optical purities than observed in this work. Perhaps under a suitable set of reaction conditions the reaction scheme developed here can be used as a synthetic method for preparing compounds of high optical purity, thus omitting the many laborious recrystallizations that are usually required in such cases.

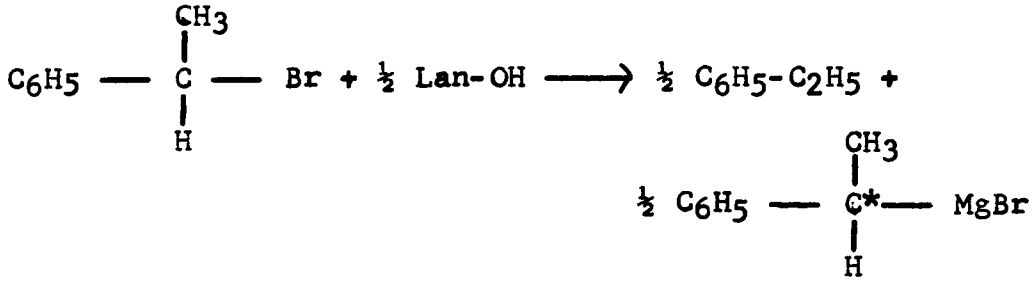
The work can also be extended to include the 2-phenyl-2-butyl Grignard system with para substituents in the phenyl ring. The preparation of the para - methyl, methoxy, fluoro, and dimethylamino derivatives, for example, would change considerably the nature of the carbon magnesium bond. The nature of the carbon magnesium bond will also be altered if the halogen bonded to magnesium is changed from chlorine to bromine to iodine. The reactions of these Grignard reagents with lanosterol should lead to varied amounts of induction. In this way one can learn more about the mechanism of Grignard reactions.

A logical extention of this work presented in this thesis would be to prepare the corresponding alkali metal derivatives and react them with lanosterol. In this way the optical stability, as well as the chemistry of these compounds, can be studied.

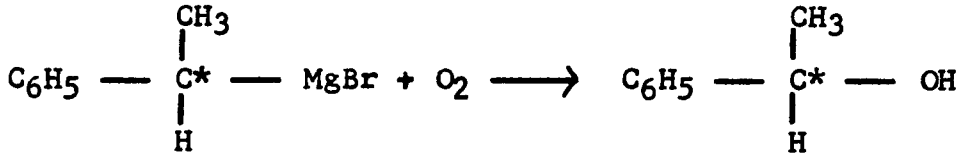
If the results of the above proposed research prove favorable, perhaps the work can be extended to include secondary Grignard reagents. The Grignard reagent formed in the reaction of α-phenethyl bromide with magnesium is capable of asymmetry around the carbon magnesium bond.



The reaction of this Grignard reagent with one half an equivalent of lanosterol, for example, would yield ethyl benzene, a compound incapable of existing in enantiomeric forms, and the remaining Grignard reagent which would be optically active.



The optically active Grignard reagent can then be quenched with oxygen, for example, to produce optically active ∝-phenethyl alcohol.



EXPERIMENTAL SECTION

Instruments

Infrared spectra were taken on a Perkin Elmer model 237 infrared spectrophotometer. The NMR spectra were run on a Varian A-60 except for the NMR spectra of 2-phenyl-2-butyl magnesium chloride at various temperatures and concentrations which were determined using a Varian HA-100. Quantitative analyses of the products of the induction reactions were carried out on a Carle "Basic" Gas Chromatograph. For preparative purposes, the Varian 1520 Autoprep was used. Polarimetric measurements were carried out on an O. C. Rudolph & Sons Automatic Polarimeter, model # 26201. Elemental analyses were done by Schwartzkopf Microanalytical Laboratory.

Analytical Methods

Gas Chromatography

Gas chromatographic analyses were carried out using either a 5 ft X 1/8 in column with 5% potassium hydroxide and 5% carbowax 20 M on chromosorb WHP or a 5 ft 1/8 in column packed with 8% carbowax 1540 on anakrom ABS. The column temperatures were usually 135°. The internal standard used was p-xylene (Eastman - yellow label). The peaks obtained were symmetrical and their areas were found by taking height X width at half height.

In a typical analysis 0.4414 g of p-xylene was added to a 20 ml solution of hydrolyzed 2-phenyl-2-butyl magnesium chloride in THF. The resulting solution was dried over potassium carbonate. The ratio of the areas of 2-phenylbutane to p-xylene was found to be 2.09. The weight in grams of the 2-phenylbutane in the THF solution was found by employing equation 35.

35.
$$\text{grams of 2-phenylbutane} = 1.19 \times \text{grams of p-xylene} \times \frac{\text{area of 2-phenylbutane}}{\text{area of p-xylene}}$$
$$= 1.19 \times 0.4414 \times 2.09$$
$$= 1.01 \text{ grams of 2-phenylbutane}$$

where 1.19 is the "response ratio"[54] (C) and is equal to;

36.
$$C = \frac{\text{grams of 2-phenylbutane}}{\text{grams of p-xylene}} \Big/ \frac{\text{area of 2-phenylbutane}}{\text{area of p-xylene}}$$

The purity of the 2-phenylbutane isolated from the induction reactions was found by analyzing the components present (α-ethyl styrene, cis and trans-2-phenyl-2-butene, 2-phenylbutane and 2-phenyl-2-butanol). The response ratio (C') for 2-phenyl-2-butanol and 2-phenylbutane was found to be 1.06.

37.
$$C' = \frac{\text{grams of 2-phenylbutane}}{\text{grams of 2-phenyl-2-butanol}} \Big/ \frac{\text{area of 2-phenylbutane}}{\text{area 2-phenyl-2-butanol}}$$

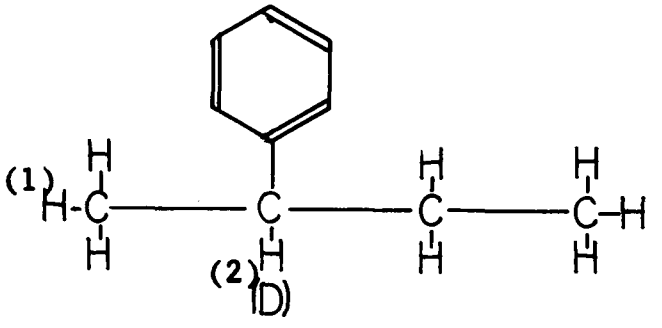
The physical properties of the olefinic impurities are more closely related to 2-phenylbutane than to 2-phenyl-2-butanol. The response ratio for the 2-phenyl-2-butanol and 2-phenylbutane is only 1.06. Therefore, it can be assumed that the response ratio for the olefinic impurities (C^{u}) is equal to 1.00. The relative retention time of the components of the mixture were; p-xylene, 1; 2-phenylbutane, 1.8; trans-2-phenyl-2-butene, 2.2; α-ethyl styrene, 2.7; cis-2-phenyl-2-butene, 3.9; 2-phenyl-2-butanol, 10.9.

NMR Analysis of 2-Phenylbutane and 2-Phenylbutane-2-D Mixtures

The ratio of 2-phenylbutane to 2-phenylbutane-2-D was determined by analysis of their NMR spectra. This method utilizes the difference in the coupling constants of H and H (J = 7 cps) and H and D (J = 1 cps) for the methyl protons (Figure 4, #1) and the methyne proton or deuterium (Figure 4, #2) in 2-phenylbutane and 2-phenylbutane-2-D. In addition the method takes advantage of the different nuclear spins of hydrogen ($\frac{1}{2}$) and deuterium (1). The chemical shift of the methyl protons (#1) remain essentially constant at 8.8 tau whether the carbon (benzyllic) is substituted with hydrogen or deuterium. An example of the application of this analytical method is illustrated in Figure 5 which shows an expanded spectrum of the methyl proton region obtained from the

Figure 4

The Protons used in the Analysis of Mixtures of 2-Phenylbutane and 2-Phenylbutane-2-D



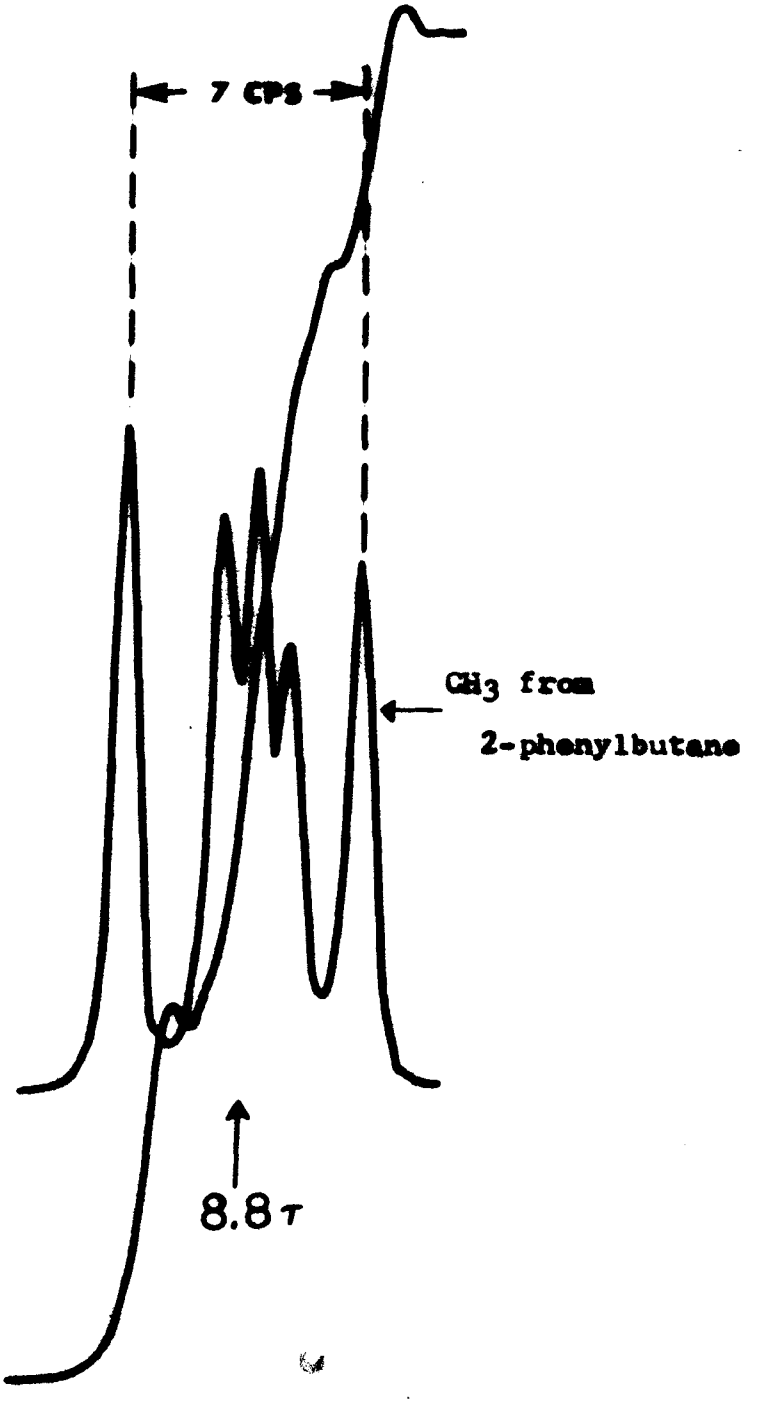
mixture produced in Experiment # 22. The integration of the spectrum showed that the relative areas of the outer peaks (2-phenylbutane, J = 7 cps) to the inner peaks (2-phenylbutane-2-D, J = 1 cps) were in a ratio of 86 : 109 = 0.79. The presence of 2-phenyl-2-butanol, ∝-ethyl styrene, and cis and trans-2-phenyl-2-butene do not in any way effect the analysis.

Induction Reactions; Product Analysis and Calculations

a) Reactions Involving Lanosterol and Deuterium Oxide

Several induction reactions were run concurrently. In order to reduce the number of steps involved in the work ups, an aliquot of the 2-phenyl-2-butyl Grignard reagent was hydrolyzed with deuterium oxide and analyzed

Figure 5



60 Mc SPECTRUM OF METHYLPROTONS OF 2-PHENYLBUTANE AND 2-PHENYLBUTANE-2-D, 100 CPS SWEEP WIDTH.

for hydrocarbon (see page 23 for definition of hydrocarbon). The hydrocarbon is produced from several sources. It comes from spurious water present in each reaction flask, from a side reaction in Grignard formation, and mainly from the reaction of the Grignard reagent with deuterium oxide, or in induction reactions from lanosterol and deuterium oxide.

The concentration of hydrocarbon is assumed to be constant for all reactions in the same experiment. For purposes of clarity the following terms are defined.

P_h - The amount of hydrocarbon in mmoles that is produced by hydrolysis of the Grignard reagent in the control.

P_{gh} - The amount of hydrocarbon in mmoles that is produced by the hydrolysis of the Grignard reagent in the induction reaction.

P_{gd} - The amount of hydrocarbon in mmoles that is produced in the induction reactions when a fraction of the Grignard reagent was allowed to dimerize.

In experiments where the unreacted Grignard reagent is allowed to dimerize, the difference in the amount of hydrocarbon in the control and the induction reaction is equal to the number of mmoles of Grignard reagent that dimerized (assuming that the volumes of the control and the induction reaction are the same).

When one half of a mole of lanosterol is caused to react with one mole of Grignard reagent followed by

quenching of the unreacted Grignard reagent with deuterium oxide, or when one mole of lanosterol is reacted with one mole of Grignard reagent then

$$P_h = P_{gh}$$

(provided there are equal amounts of Grignard solution in the control and in the induction reaction).

$P_h \neq P_{gh}$ when one half of a mole of lanosterol reacts with one mole of Grignard reagent followed by quenching of the unreacted Grignard reagent with CO_2 or O_2. In cases where electrophiles other than hydrogen are used $P_h - P_{gh}$ = mmoles of product from other electrophile.

Sample Calculation (from reaction #6)

In order to determine the amount of hydrocarbon (P_h) in the control, a 20 ml aliquot of 2-phenyl-2-butyl magnesium chloride solution was hydrolyzed with 0.2 ml of deuterium oxide. The internal standard (0.4410 grams of p-xylene) was added to the hydrolyzed solution and the mixture was dried over potassium carbonate. The amount of P_h was determined by gas chromatography and found to be 6.65 mmoles (0.897 grams).

The amount of Grignard solution for the induction reaction using 2.07 mmoles of lanosterol followed by quenching the remaining Grignard reagent with deuterium oxide was also 20 ml. Therefore, the maximum amount of hydrocarbon (P_{gh}) that could be isolated from this

reaction was 6.65 mmoles (0.897 grams) because $P_{gh} = P_h$. The amount of product actually isolated was 0.7900 grams. The product was analyzed by gas chromatography yielding: 87.3% hydrocarbon, 5.0% 2-phenyl-2-butanol, and 7.7% olefinic compounds (∝-ethyl styrene, and cis and trans-2-phenyl-2-butene). The yield of hydrocarbon (P_{gh}) was found by employing equation 38.

38.
$$\% \text{ yield} = \frac{100 \times (\text{amount of product isolated}) \times (\text{fraction of hydrocarbon in product})}{P_{gh}}$$

$$= \frac{100 \times (0.7900) \times (0.873)}{0.897}$$

$$= 77\%$$

The observed rotation of the product was - 0.498° (1 dec neat) at 25°.

The NMR spectrum of the product showed the ratio of 2-phenylbutane to 2-phenylbutane-2-D to be 0.64 : 1.

The number of mmoles of 2-phenyl-2-butyl magnesium chloride (D) that reacted with deuterium oxide was found by using equation 39.

39.
$$\frac{\text{mmoles of 2-phenylbutane}}{\text{mmoles of 2-phenylbutane-2-D}} = \frac{P_{gh} - \text{mmoles of 2-phenylbutane-2-D}}{\text{mmoles of 2-phenylbutane-2-D}}$$

$$0.64 = \frac{6.65 - D}{D}$$

D = 4.05 mmoles

The amount of lanosterol used was 2.07 mmoles. Therefore, since the lanosterol reacted prior to the deuterium oxide, the number of mmoles of Grignard reagent present was 4.05 + 2.07 = 6.12 mmoles. The remaining 2-phenylbutane (0.53 mmoles) was formed either from a side reaction in Grignard formation or from some residual water that remained in the flask during the drying procedure. The relative amounts of lanosterol and deuterium oxide were: 2.07/6.12 X 100 = 34% lanosterol, and 4.05/6.12 X 100 = 66% deuterium oxide.

The percent OI was calculated using equation 40.

$$\% \text{ OI} = \frac{\alpha \text{ obs}}{\alpha \text{ max. for 2-phenylbutane}} \times \frac{P_{gh}}{\text{mmoles of inducing agent*}}$$

40.

$$\times \frac{100}{\text{fraction of product that is } \underline{\text{hydrocarbon}}}$$

$$= \frac{-0.498 \times 6.65 \times 100}{-24.2 \times 2.07 \times 0.873}$$

$$= 7.6\%$$

b) Reaction with Lanosterol and Grignard Dimerization Sample Calculation (from reaction # 11)

The amount of hydrocarbon (P_h) in 20 ml of the

* This value represents the number of mmoles of hydrocarbon that can be optically active.

control was determined as in part a, and found to be 6.39 mmoles (0.863 grams).

To a 20 ml solution of 2-phenyl-2-butyl magnesium chloride was added 2.06 mmoles of lanosterol. The excess Grignard reagent was allowed to dimerize. The product was hydrolyzed, dried and diluted to 250 ml. A 10 ml aliquot was removed and analyzed for hydrocarbon by gas chromatography using 0.0870 grams of p-xylene as the internal standard. The analysis showed 0.414 grams (3.09 mmoles) of hydrocarbon (P_{gd}). The amount of product isolated was 0.3789 grams. The product was analyzed by gas chromatography yielding: 77.2% hydrocarbon, 8.8% 2-phenyl-2-butanol, and 14% olefinic compounds. The yield of hydrocarbon was determined by using equation 38, and found to be 72%.

The observed rotation of the product was -1.098° (1 dec neat) at 22°.

The number of mmoles of Grignard reagent that was present prior to reaction was found by using equation 41.

41. mmoles of Grignard reagent = $P_h - P_{gd}$ + mmoles of inducing agent

= 6.39 - 3.09 + 2.06

= 5.36

The relative amount of lanosterol used was 2.06/5.36 X 100 = 38%. The relative amount of Grignard

reagent that dimerized was 5.36 - 2.06/5.36 X 100 = 62%. The percent OI was calculated using equation 40 with the following modification: P_{gd} is substituted for P_{gh}. The percent OI was found to be 8.8%.

c) Reactions with Lanosterol, Another Electrophile (CO_2, O_2) and Grignard Dimerization.

Sample Calculation (from reaction # 12)

The amount of hydrocarbon (P_h) in 20 ml of the control was determined as in part a, and found to be 0.877 grams (6.50 mmoles).

To a 30 ml solution of 2-phenyl-2-butyl magnesium chloride was added 1.98 mmoles of lanosterol and 4.0 mmoles of carbon dioxide. The excess Grignard reagent was allowed to dimerize.

Prior to the vacuum line distillation of the product the neutral fraction was diluted to 250 ml and a 10 ml aliquot removed. The aliquot was analyzed for hydrocarbon (P_{gd}) by gas chromatography using 0.0563 grams of p-xylene as internal standard. (In experiments where oxygen is used the yield of alcohol is also obtained by gas chromatographic analysis of the aliquot.) The analysis showed 0.535 grams (4.00 mmoles) of P_{gd}. The amount of product isolated was 0.5660 grams. The product was analyzed by gas chromatography and yielded 87.2% hydrocarbon, 1.8% 2-phenyl-2-butanol, and 11.0%

olefinic compounds. The yield of hydrocarbon was found by using equation 38 where P_{gd} is substituted for P_{gh} and found to be 91%. The observed rotation of the product was - 0.337° (1 dec neat) at 20°.

The number of mmoles of Grignard reagent that was present prior to the induction reaction was determined by using equation 41, and found to be 7.73. (The value for P_h had to be multiplied by 3/2 because the volume of Grignard reagent used in the induction reaction was 30 ml.)

The relative amount of lanosterol used was 1.98/7.73 X 100 = 26%. The percent OI was calculated using equation 40 with the following modification: P_{gd} is substituted for P_{gh}. The percent OI was found to be 3.3%. The yield of 2-phenyl-2-methyl butanoic acid was 0.2727 grams (1.52 mmoles). The observed rotation of the acid was - 0.007° (1 dec c = 67 benzene). Therefore, the amount of Grignard reagent that dimerized was 7.73 - 1.98 - 1.52 = 4.23 mmoles. Therefore, the relative amount of carbon dioxide that reacted was 1.52/7.73 X 100 = 20%. (The isolation of the carboxylic acid is assumed to be quantitative. If all of the acid was not isolated, only the relative amounts of the reagents would be affected and not the stereochemical results. For example, if only 80% of the acid was isolated, the relative amount of carbon dioxide that

reacted would be 24%.) The optical purity of the acid was determined using equation 42.

42. Optical Purity = $I = \frac{\alpha_{obs}}{\alpha_{max}} \times 100$

$= \frac{-0.007}{21.57} \times 100$

$= 0.03\%$

The percent yield of acid based on the amount of carbon dioxide used was 1.52/4.00 X 100 = 38%.

d) Reaction with Lanosterol and Another Electrophile (CO_2, O_2).

The calculations involved are similar to those in the previous section with the exception of the calculation of the number of mmoles of Grignard reagent present prior to the reaction with the inducing agent and other electrophile. The number of mmoles of Grignard reagent present is calculated using equation 41 where P_{gh} is substituted for P_{gd}. ($P_h - P_{gh}$ is equal to the number of mmoles of product from the other electrophile.)

e) Reactions with Excess Lanosterol

In most of the reactions where excess lanosterol was employed, not all of the Grignard reagent was consumed. The reactions were always quenched with deuterium oxide

after the addition of excess lanosterol. In the reactions where 2-phenylbutane-2-D was formed, the calculations were made as described in section a.

In reactions where all of the Grignard reagent was consumed by reaction with lanosterol (The reactions where the lanosterol solution temperature was 0^{o}.) the number of mmoles of Grignard reagent present was assumed to be the same as a comparison run. All other calculations involved were identical to those in section a.

Preparation of 2-Phenyl-2-Butanol [16]

To 110 grams (4.57 moles) of magnesium turnings (Baker) in a three neck, three liter round bottom flask equipped with a Tru-bore stirrer and a reflux condenser, was added 706 grams (4.5 moles) of bromobenzene (Baker) in 1090 ml of anhydrous ether (Baker). The solution was allowed to stand overnight, and 324 grams (4.5 moles) of methyl ethyl ketone (Fisher) dissolved in 324 ml of ether was added dropwise to the cooled ($T = 0^{o}$) Grignard solution. The adduct formed in this reaction is insoluble in ether, thus the reaction mixture became extremely thick. The mixture was then poured onto a Buchner funnel and washed with copious quantities of anhydrous ether and pentane. To the remaining solids (2-phenyl-2-butoxy magnesium bromide and unreacted magnesium) was added 5000 ml of a mixture of 10% hydrochloric acid and ice.

The resulting mixture was extracted with ether and the ether phase was washed with water until the washings were neutral. The ether phase was dried over sodium carbonate, and the solvent was removed under vacuum to yield 501 grams (74%) of 2-phenyl-2-butanol; NMR (CCl_4) tau 9.27 (t, J = 7 cps, 3H); 8.56 (s, 3H); 7.13 (s, 1H); 7.29 (m, 2H); 2.82 (m, 5H). The alcohol had a yellow green color (the pure alcohol is colorless). The purity of the alcohol was checked by gas chromatography through a 15 ft 3/8 in, 20% SE 30 on diataport S, 80 - 100 mesh column at a temperature of 190°. In a separate experiment the following retention times were determined: 2-phenyl-2-butanol, 10 minutes; bromobenzene, 4.3 minutes; methyl ethyl ketone, 0.9 minutes; trans-2-phenyl-2-butene, 3.6 minutes; α-ethyl styrene, 5.7 minutes; cis-2-phenyl-2-butene, 7.9 minutes. The alcohol showed a single peak at a retention time of 10 minutes. The alcohol was used without further purification in the synthesis of 2-chloro-2-phenylbutane.

Preparation of 2-Chloro-2-Phenylbutane

At 0°, 100 grams (0.67 moles) of 2-phenyl-2-butanol was chlorinated in a Brown[2] (square) apparatus.[19] When the addition of hydrogen chloride had stopped, the halide was removed from the apparatus and washed with an equal volume of ice and water. The halide was dried over

magnesium sulfate and type 4A molecular sieves (Linde) at 0°. The halide was filtered, and distilled in a one-piece distillation apparatus (Figure 6) to yield 91 grams (81%) of 2-chloro-2-phenylbutane; bp 44 -46° (0.3 mm Hg), lit.[14] decomposes on distillation; $\underline{n}^{25}D$ = 1.5190; NMR (CCl_4) tau 2.67 (m, 5H); 7.90 (q, J = 7 cps, 2H); 8.15 (s, 3H); 9.15 (t, J = 7 cps, 3H).

Method of Analysis for Halogen

To 0.0549 grams (0.326 mmoles) of 2-chloro-2-phenylbutane was added 3.511 ml of 0.1073 N sodium hydroxide and 5 ml of 95% ethyl alcohol. The solution was refluxed for 15 minutes. Two drops of phenophthalein indicator was added to the cooled solution, and standard hydrochloric acid (0.100 N) was added until the solution became colorless. The solution was then back titrated with sodium hydroxide. Total sodium hydroxide 3.564 ml. Total hydrochloric acid 0.538 ml.

Calculation:

3.564 ml NaOH X 0.1073 meq/ml = 0.381 meq

0.538 ml HCl X 0.100 meq/ml = 0.054 meq

meq = 0.327 meq: # meq of halide = 0.326

Therefore, the halide is 100% pure.

A graph of refractive index vs % purity of 2-chloro-2-phenylbutane is shown in Figure 7. (The impurities present are α-ethyl styrene and cis and trans-2-phenyl-2-butene. These impurities are a result of dehydro-

Figure 6

One-Piece Distillation Apparatus used in the Preparation of 2-Chloro-2-Phenylbutane

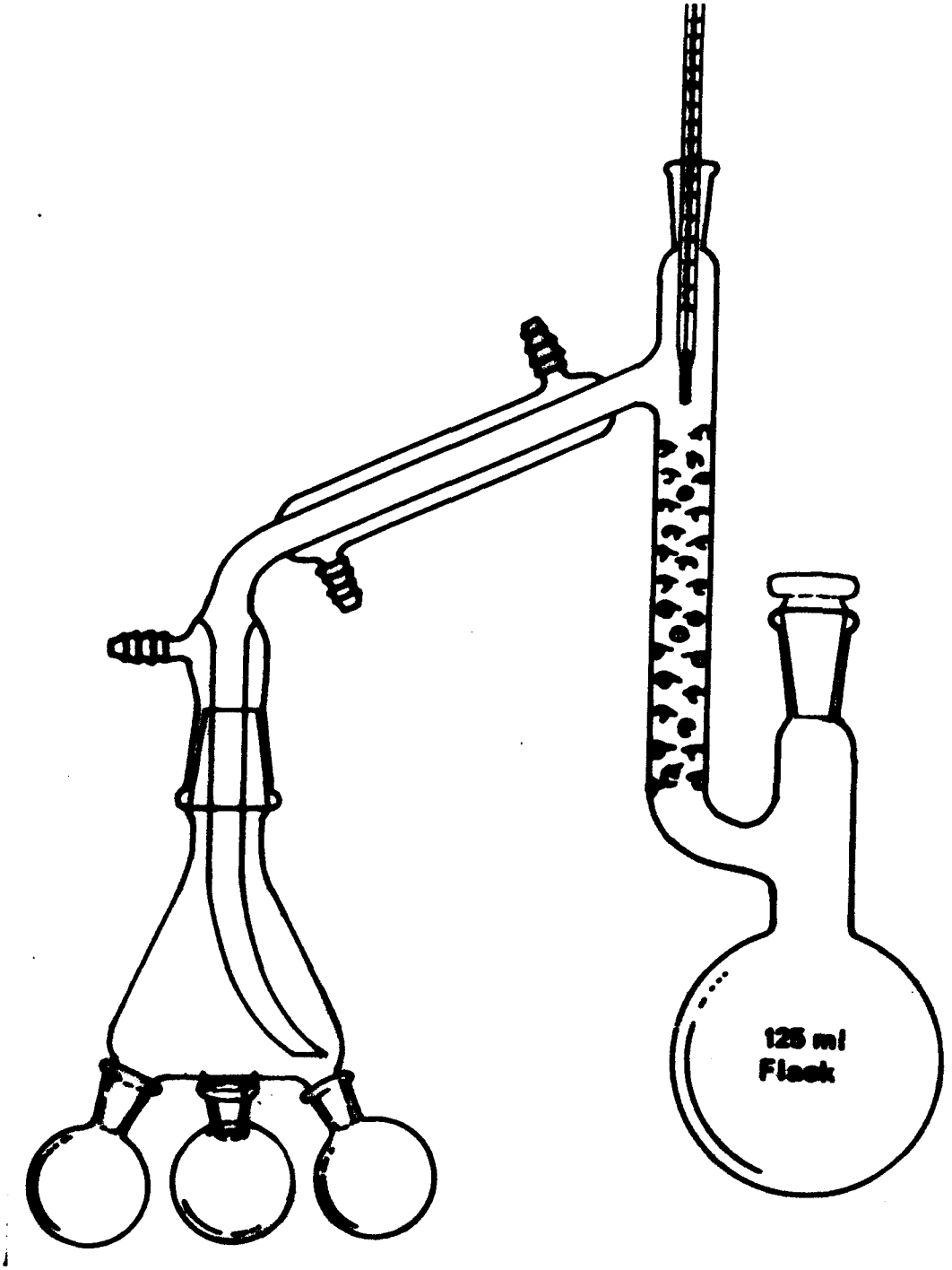
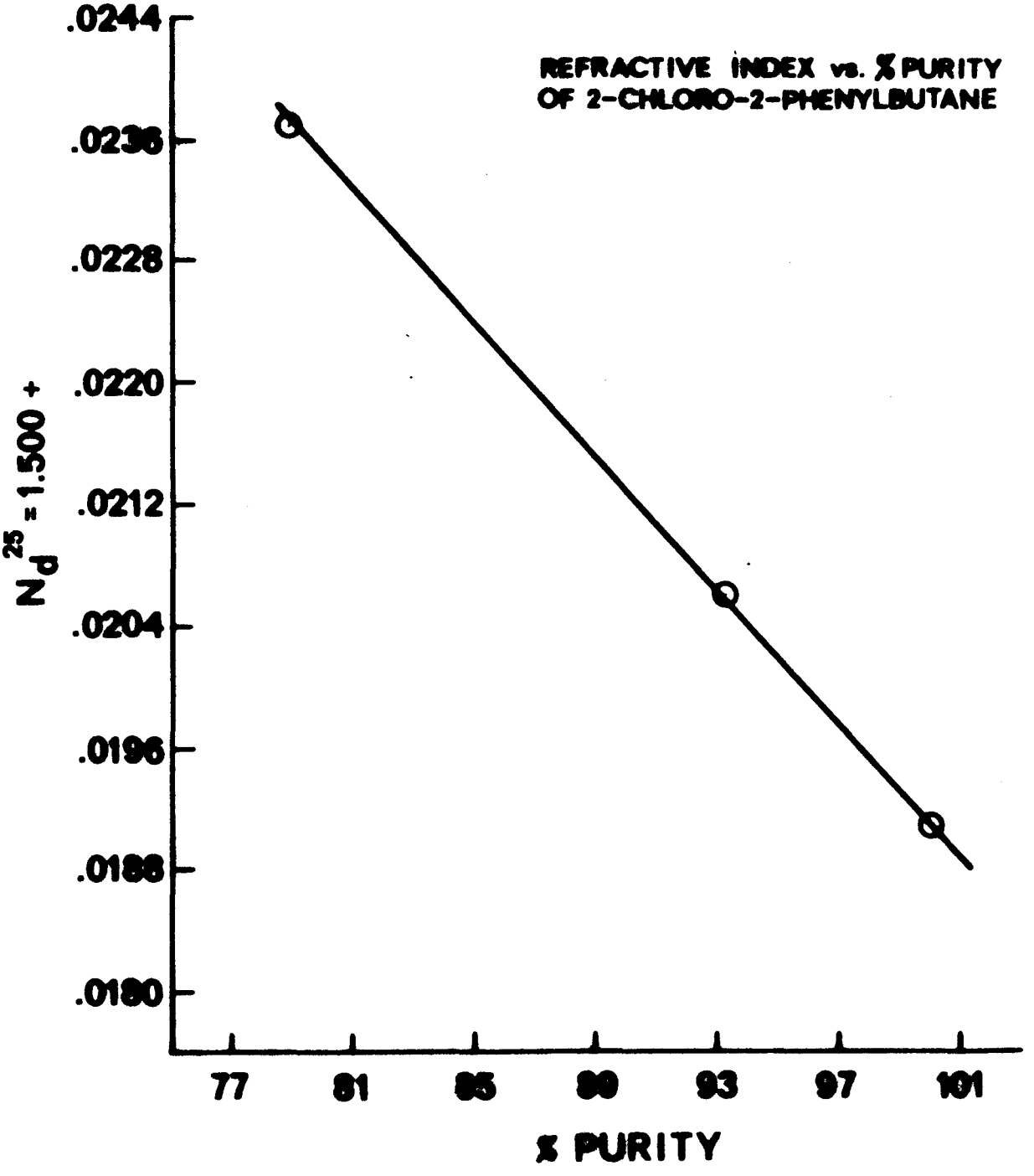


Figure 7


REFRACTIVE INDEX vs. % PURITY
OF 2-CHLORO-2-PHENYLBUTANE
.0244
.0236
.0228
.0220
.0212
.0204
.0196
.0188
.0180
$N_d^{25} = 1.500 +$
77
81
85
89
93
97
101
% PURITY

halogenation of the 2-chloro-2-phenylbutane during distillation.)

Dehydration of 2-Phenyl-2-Butanol

To 2-phenyl-2-butanol a twofold excess of 10% sulphuric acid (v/v) was added, and the mixture was refluxed (T = 130°) for 12 hours. The mixture was allowed to cool, and the layers were separated. The mixture of olefins was distilled (bp 80 -90°; 45 mm Hg), dried over magnesium sulfate, and stored in brown bottles. The olefins were not washed acid free prior to distillation. A trace of acid was desirable to complete any dehydration that had not taken place prior to distillation. The olefins that were formed, cis and trans-2-phenyl-2-butene and α-ethyl styrene, were analyzed by NMR spectroscopy and found to be in a ratio of 9 : 1.

Separation and Characterization of the Olefins Formed in the Dehydration of 2-Phenyl-2-Butanol

The three olefins formed in the dehydration of 2-phenyl-2-butanol were separated by preparative gas chromatography. A 20 ft 3/8 in carbowax 20 M on 30% (60 - 80 mesh) chromosorb P column was employed at a temperature of 175°. The relative retention times were: #1, 12.8 minutes; #2, 16.3 minutes; and

#3, 22.8 minutes. Fraction #1 (trans-2-phenyl-2-butene), $n^{25}D$ = 1.5190, lit.[55] $n^{25}D$ = 1.5192; ir (neat) cm^{-1} 1690 (m); 825 (m); NMR (external TMS, neat) cps 428 (m, 5H); 326 (q, J = 7 cps, split into q, J = 1 cps, 1H); Fraction #2 (α-ethyl styrene), $n^{25}D$ = 1.5259, lit.[56] $n^{25}D$ = 1.5264; ir (neat) cm^{-1} 1690 (s); 900 (m); NMR (external TMS) cps 400 (m, 5H); 265 (q, J = 1 cps, 1H); 280 (s, 1H); 110 (q, J = 7 cps, 2H); 26 (t, J = 7 cps, 3H); Fraction #3 (cis-2-phenyl-2-butene), $n^{25}D$ = 1.5390, lit.[55] $n^{25}D$ = 1.5393; ir (neat) cm^{-1} 1685 (m); 827 (m); NMR (external TMS) cps 400 (m, 5H); 315 (q, J = 7 cps, split into q, J = 1 cps, 1H); 82 (s, split into d, J = 1 cps, 3H); 67 (d, J = 7 cps, split into doublet of doublets, J = 1 cps, 3H).

Preparation and Characterization of 2-Phenylbutane

The olefinic mixture (21 grams, 160 mmoles) prepared in the dehydration of 2-phenyl-2-butanol was hydrogenated using the internal hydrogenation procedure of Brown[57] with 5% Pd on charcoal (Eastman) as the catalyst. The product was distilled to yield 16 grams (66%) of 2-phenylbutane; bp 170 -171° (760 mm Hg), lit.[58] 173° (760 mm Hg); $n^{25}D$ = 1.4871, lit.[58] $n^{20}D$ = 1.4892; NMR (CCl_4) tau 2.85 (m, 5H); 8.50 (m, 2H); 8.78 (d, J = 7 cps, 3H); 9.20 (t, J = 7 cps, 3H). The purity of the product was checked by gas chromatography

and shown to be > 99% pure.

Method for Transferring Molecular Sieves

In addition to their ability to absorb moisture, molecular sieves also absorb oxygen. Therefore, one must take special precautions in transferring molecular sieves from one vessel to another. Figure 8 show the method for transferring molecular sieves without oxygen or moisture contamination.

Preparation of Materials used in Grignard Reactions

Nitrogen

Prepurified nitrogen (Matheson) was passed through a tower containing lithium and calcium hydrides.

Magnesium

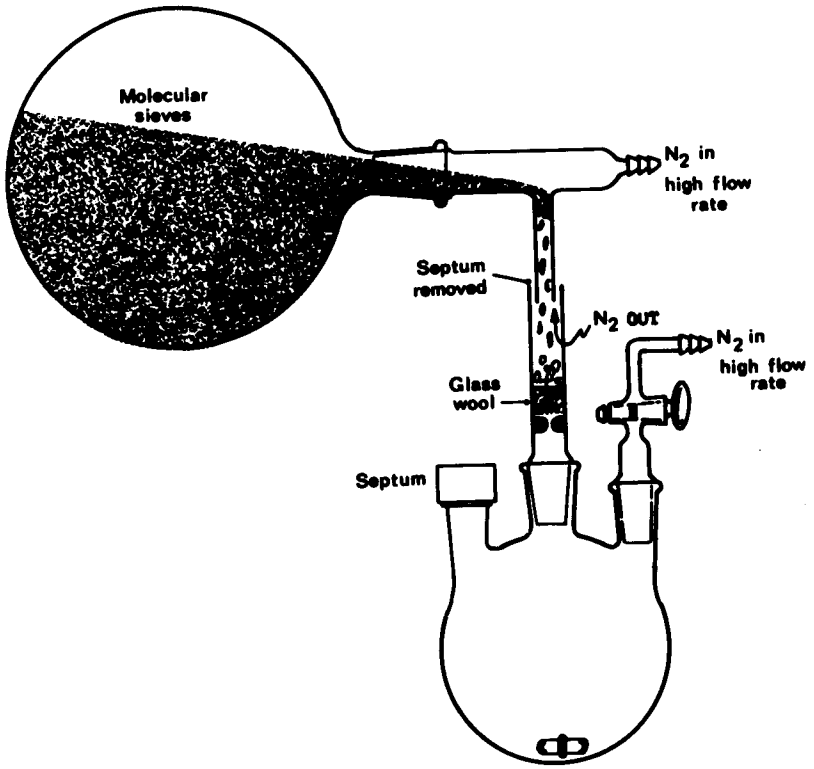
Magnesium turnings (Baker, lot #35005, assay 99.9+% Mg, 0.001% Cu, 0.001% In, 0.003% Fe, 0.005% mn, 0.0001% Si.) was washed several times with anhydrous ether (Baker). Most of the ether was drained and the residual ether removed under vacuum. The magnesium was heated for 24 hours (100° and 0.1 mm Hg) and stored under nitrogen until used.

Tetrahydrofuran

Tetrahydrofuran (Baker Analyzed Reagent) was distilled as needed under nitrogen (Matheson - prepurified) from lithium aluminum hydride (Metal Hydrides).

Figure 8

Method used for Transferring Molecular Sieves



Triethyl Amine

Triethyl amine (Hall) was distilled as needed under nitrogen from calcium Hydride (Fisher).

N,N,N',N', - Tetramethylethylenediamine

N,N,N',N', - tetramethylethylenediamine (Aldrich) was distilled as needed under nitrogen from calcium hydride (Fisher).

Molecular Sieves

Type 4A molecular sieves (Linde) were heated for two days (T = 100°, 0.1 mm Hg). The system was flushed with nitrogen and reevacuated several times during the procedure in order to replace all of the entrapped oxygen. The molecular sieves were stored under nitrogen until used.

2-Chloro-2-Phenylbutane

The 2-chloro-2-phenylbutane was removed from the freezer and allowed to come to room temperature. Nitrogen was then passed through the halide to remove dissolved oxygen and hydrogen chloride. (A small amount of hydrogen chloride is formed due to the decomposition of the halide.)

Syringes and Needles

All syringes and needles were dried at 130° for 24 hours and stored in a desiccator over phosphorus pentoxide.

Septa

All septa were stored in a desiccator over potassium hydroxide.

Lanosterol

Lanosterol (Aldrich) was recrystallized 3 times from acetone methanol. The residual solvent was removed under vacuum. The lanosterol was dried in a vacuum desiccator (0.1 mm Hg) over phosphorus pentoxide. The lanosterol was stored in a desiccator until used; mp 140 - 141°, lit.[59] mp 140 -141°.

d-(+)-α-Phenethylamine

d-(+)-α-Phenethylamine (Aldrich) was distilled as needed under nitrogen from potassium hydroxide.

d-(+)-Camphor-10-Sulfonic Acid

d-(+)-Camphor-10-sulfonic acid (Aldrich) was recrystallized from tetrahydrofuran-cyclohexane. The white crystals were washed with ether. The acid was dried in a vacuum desiccator (0.1 mm Hg) over phosphorus pentoxide and stored in a desiccator until used; mp 200 - 202, lit.[60] mp 202 - 203.

d-(+)-Ketopinic Acid

d-(+)-Ketopinic acid was prepared by the method of Bartlett and Knox,[61] from d-(+)-camphor-10-sulfonyl chloride.[62]. The ketopinic acid was sublimed under vacuum (0.1 mm Hg) and stored in a desiccator until used; mp 232 -233°, lit.[62] mp 233 -234°.

d-(+)-Camphor

d-(+)-Camphor (Eastman white label) was stored in a desiccator over phosphorus pentoxide until used; mp 177 - 178, lit.[63] mp 179°.

(N-l-(-)-α-Phenethyl) Benzene Sulfonamide

(N-l-(-)-α-Phenethyl) benzene sulfonamide was prepared by the method of Shriner, Fuson and Curtin[64] from l-(-)-α-phenethylamine and benzenesulfonyl chloride. The sulfonamide was recrystallized from 95% alcohol, and dried in a vacuum desiccator over phosphorus pentoxide (0.1 mm Hg); mp 100 - 101°, NMR ($CDCl_3$) tau 2.10 - 2.90 (m, 10H); 4.40 (d, J = 7 cps, 1H); 5.50 (p, J = 7 cps, 1H); 8.60 (d, J = 7 cps, 3H).

Anal calcd for $C_{14}H_{15}NO_2S$: C, 64.34%; H, 5.78%. Obsd: C, 64.46%; H, 5.68%.

(N-d-(+)-α-Phenethyl)-d-(+)-Ketopinamide

To 0.8 grams (4.0 mmoles) of d-(+)-ketopinic acid chloride (prepared by reacting d-(+)-ketopinic acid with thionyl chloride) in 17 ml of benzene was added 0.53 ml (4.2 mmoles) of d-(+)-α-phenethylamine. The resulting solution was heated on a steam bath for 2 minutes. The reaction mixture was washed with 5 ml of water, 15 ml of 10% HCl, 10 ml of 10% NaOH and 10 ml of water. The resulting solution was dried over magnesium sulfate and the benzene removed under vacuum. The resulting greenish-yellow oil was distilled (0.1 mm Hg) and the product recrystallized from hexane to yield 0.53 grams (48%)

of (N-d-(+)-α-phenethyl)-d-(+)-ketopinamide; mp 70 -71.5°; NMR ($CDCl_3$) tau 2.70 (m, 5H); 4.83 (m, 1H); 7.18 -8.70 (m, 8H); 8.52 (d, J = 7 cps, 3H); 8.75 (s, 3H); 8.99 (s, 3H).

Anal calcd for $C_{14}H_{15}NO_2$: C, 75.75%; H, 8.12%. Obsd: C, 75.75%; H, 7.85%.

(N-l-(-)-α-Phenethyl)-d-(+)-Camphor-10-Sulfonamide

(N-l-(-)-α-Phenethyl)-d-(+)-camphor-10-sulfonamide was prepared by the method of Shriner, Fuson and Curtin[64] from l-(-)-α-phenethylamine and d-(+)-camphor-10-sulfonyl chloride (prepared by reacting d-(+)-camphor-10-sulfonic acid with phosphorus pentachloride). The sulfonamide was recrystallized from dilute ethanol and dried in a vacuum desiccator (0.1 mm Hg) over phosphorus pentoxide; mp 95.5 - 96.5°; NMR ($CDCl_3$) tau 2.68 (m, 5H); 3.82 (d, J = 7 cps, 1H); 5.31 (m, 1H); 7.32 (d, J = 7 cps, 2H); 8.00 (m, 7H); 8.42 (d, J = 7 cps, 3H) 9.19 (s, 3H); 9.50 (s, 3H); $[\alpha]_D^{29}$ = -17.1° (C = 5.83 in ethanol).

Anal calcd for $C_{18}H_{25}NO_3S$: C, 64.40%; H, 7.51%. Obsd: C, 64.28%; H, 7.45%.

(N-d-(+)-α-Phenethyl)-d-(+)-Camphor-10-Sulfonamide

(N-d-(+)-α-Phenethyl)-d-(+)-camphor-10-sulfonamide was prepared by the method of Shriner, Fuson and Curtin[64] from d-(+)-α-phenethylamine and d-(+)-camphor-10-sulfonyl chloride (prepared by reacting d-(+)-camphor-10-sulfonic acid with phosphorus pentachloride). The

sulfonamide was recrystallized from absolute ethanol; mp 117 - 118°; NMR ($CDCl_3$) tau 2.80 (m, 5H); 4.21 (d, J = 7 cps, 1H); 5.34 (m, 1H); 6.98 (q, J = 16 cps, 2H); 7.30 - 9.50 (m, 7H); 8.48 (d, J = 7 cps, 3H); 9.05 (s, 3H); 9.18 (s, 3H).

Anal calcd for $C_{18}H_{25}NO_3S$: C, 64.40%; H, 7.51%. Obsd: C, 64.30%; H, 7.42%.

d-(+)-(N-t-Butyl)-Ketopinamide

To 0.8 grams (4.0mmoles) of d-(+) ketopinic acid chloride (prepared by reacting d-(+)-ketopinic acid with thionyl chloride) dissolved in 17 ml of benzene was added 0.44 ml (4.2 mmoles) of t-butyl amine. The resulting solution was heated on a steam bath for 2 minutes. The reaction mixture was washed with 5 ml of water, 15 ml of 10% HCl, 10 ml of 10% NaOH, and 10 ml of water. The resulting solution was dissolved in ether and dried over sodium sulfate. The ether was removed under vacuum and the amide was distilled (0.1 mm Hg) to yield a colorless liquid. The amide was stored in a desiccator until used; NMR ($CDCl_3$) tau 8.65 (s, 9H); 8.75 (3, 3H); 9.05 (s, 3H); 7.20 8.70 (m, 8H).

Anal calcd for $C_{14}H_{23}NO_2$: C, 70.84%; H, 9.76%. Obsd: C, 70.57%; H, 9.59%.

Carbon Dioxide

Carbon dioxide (Matheson - bone dry grade) was

passed through a tower containing silica-gel.

Oxygen

Oxygen (Matheson - ultra high purity) was used without further purification.

Variation in Reaction Conditions to Optimize the Yield of 2-Phenyl-2-Butyl Magnesium Chloride

The 2-chloro-2-phenylbutane was added to the magnesium (Baker lot # 34001) in the conventional manner. The reaction conditions were varied and the results are shown in Tables 13 and 14.

The yield of Grignard reagent was determined by quenching the solution with deuterium oxide and analyzing (as described earlier) the hydrocarbon produced. The amount of olefin present was determined by gas chromatography of the 2-phenylbutane fraction. The mixture of meso and dl 3,4-diphenyl-3,4-dimethylhexane (dimer) was isolated by distillation (T = 180°, 0.5 mm Hg) of the residue from the 2-phenylbutane fraction; NMR ($CDCl_3$) tau 2.7 -2.9 (m, 10H); 7.50 - 8.18 (m, 2H); 8.20 - 8.68 (m, 2H); 8.72 (s, 6H); 9.42 (t, J = 7 cps, 6H). The dimer mixture was dissolved in absolute ethanol, and the meso isomer was crystallized at -17°; mp 91 - 92°, lit.[65] mp 93°. The NMR spectrum of the meso isomer was identical to the NMR spectrum of the mixture. In a few cases, the dimer mixture was analyzed by gas chromatography

Table 13

Variation in Reaction Conditions to Optimize the Yield of 2-Phenyl-2-Butyl Magnesium Chloride; Product Data

#	M GR[a]	Mg/Cl[b]	%D[c]	DT[d]	%HYD[e]	%DIMER	%GR[f]
1	4.0	1.1	0	100	---	24	---
2[g]	4.0	1.1	0	90	---	49	---
3	4.0	11.0	64	90	85	43	20
4	4.0	1.1	0	95	---	62	---
5	0.4	1.1	77	110	92	51	31
6	0.4	1.1	82	45	94	32	44
7	0.4	11.0	88	35	94	12	66
8	0.4	1.1	83	30	94	29	49
9	0.4	1.1	---	50	0	5.1	0
10	0.4	1.1	90	30	94	27	53

a The concentration of the Grignard reagent based on the total volume of solvent present. b The molar ratio of magnesium to 2-chloro-2-phenylbutane. c The percentage of 2-phenylbutane-2-D in total hydrocarbon. d The elapsed time in minutes between the completion of the halide addition and the quenching of the reaction mixture with deuterium oxide. e The percent hydrocarbon in the product. The remaining fraction is olefinic compounds. f The yield of Grignard reagent based on the amount of 2-phenylbutane-2-D isolated. g No reaction after one hour, the solution was warmed to 0° and the reaction started.

Table 14

Variation in Reaction Conditions to Optimize the Yield of 2-Phenyl-2-Butyl Magnesium Chloride; Reaction Conditions

#	mmoles Magnesium	mmoles $C_{10}H_{13}Cl$	Solvent	ml Solvent in Magnesium	ml Solvent in $C_{10}H_{13}Cl$	T°	HAR[a]
1	67.5	59.3	THF	5	10	amb	0.99
2	67.5	59.3	THF	5	10	-68	0.71
3	683	59.3	THF	5	10	0	0.67
4	66.8	59.3	THF	5	10	0	5.9
5	67.2	59.3	THF	50	100	0	0.77
6	66.8	59.3	THF	50	100	0	0.72
7	663	59.3	THF	50	100	0	0.57
8	66.8	59.3	THF	50	100	0	0.39
9	68.0	59.3	Et_2O	50	100	0	0.90
10	66.8	59.3	THF	50	100	-20	0.54

a The additon rate in mmoles/minute of the 2-chloro-2-phenylbutane solution to the magnesium.

on a 2 ft X ¼ in 20% SE - 30 on Chromosorb W-H.P. (80/100 mesh) column at 160°. The relative retention times were; dl isomer, 4.6 minutes; meso isomer, 6.2 minutes. The ratio of meso to dl isomer varied between 1.6 - 2.1 : 1. The molecular weight of the meso isomer was determined (Rast) and found to be 235 (calcd for dimer 266).

NMR Studies of Side Reactions in the Formation of 2-Phenyl-2-Butyl Magnesium Chloride

a) A 50% solution (v/v) of THF and 2-chloro-2-phenylbutane was mixed. NMR spectra (T = 37°) were run on the sample at various intervals. The spectra showed no decomposition of the halide within 18 hours.

b) A 9 : 1 solution of 2-chloro-2-phenylbutane and methylmagnesium chloride (Fisher) was mixed. Within 105 minutes, the spectrum of the mixture (T = 37°) showed the disappearance of all the methyl magnesium chloride (tau = 11.2 ppm) and the formation of methane 9.7 ppm). When a 1 : 1 solution was made, all the methyl magnesium chloride disappeared within 65 minutes.

Stability of 2-Phenyl-2-Butyl Magnesium Chloride

T = 0°

To 0.86 moles of magnesium turnings (Baker lot # 34001) in 50 ml of THF (Baker) at 0°, was added 0.029

moles (5 grams) of 2-chloro-2-phenylbutane in 25 ml of THF over a period of 130 minutes (t = 0 minutes at completion of the halide addition). At t = 15 minutes, 20 ml of the Grignard solution were removed by syringe and placed in a flask not containing magnesium. Both of the solutions were kept at 0° throughout the experiment. At various time intervals, 1 ml aliquots were removed from both solutions and quenched with water. The aliquots were dried over potassium carbonate and analyzed by gas chromatography for 2-phenylbutane. The results are show in Table 15.

Table 15

The Rate of Dimerization of 2-Phenyl-2-Butyl Magnesium Chloride in THF at 0°

time (hours)	conc X 10^3 g $C_{10}H_{14}$/ml magnesium present	conc X 10^3 g $C_{10}H_{14}$/ml no magnesium present
0.3	52	52
18.3	39	32
13.3	38	30
31.4	24	20
40.5	6	8
49.8	7	8
66.5	8	8
90.8	8	8

T = 25°

The above experiment was repeated with the following alteration. At t = 5 minutes, the cooling baths were removed and the Grignard solutions were allowed to warm up to 25°. The results are shown in Table 16.

Table 16

The Rate of Dimerization of 2-Phenyl-2-Butyl Magnesium Chloride in THF at 25°

time (hours)	conc X 10^3 g $C_{10}H_{14}$/ml magnesium present	conc X 10^3 g $C_{10}H_{14}$/ml no magnesium present
0.3	46	46
1.2	43	--
2.6	6	--
2.8	--	17
3.5	6	--
4.7	8	10
20	7	8

T = 0° for 4,16 hours, T = 25° for 8,33 hours

The above experiment was repeated with the following alteration. At 4.16 hours, the cooling baths were removed and the Grignard reagents were allowed to warm up to 25°. The results are shown in Table 17.

On one occasion, after the Grignard reagent had dimerized the residual hydrocarbon was analyzed for 2-phenylbutane-2-D. The analysis showed the presence

Table 17

The Rate of Dimerization of 2-Phenyl-2-Butyl Magnesium Chloride in THF at 0 and 25°

time (hours)	conc X10^3 g $C_{10}H_{14}$/ml magnesium present	conc X 10^3 g $C_{10}H_{14}$/ml no magnesium present	T°
0.4	46	--	0
0.8	48	47	0
1.5	50	44	0
2.5	51	41	0
3.9	46	32	0
4.8	44	36	25
5.5	40	36	25
6.8	5	9	25
7.5	3	4	25
8.0	3	4	25

of only 2-phenylbutane.

Preparation of 2-Phenyl-2-Butyl Magnesium Chloride

The apparatus used in the preparation of 2-phenyl-2-butyl magnesium chloride is shown in Figure 9. The apparatus was flamed in a stream of nitrogen by placing stopcocks A and B in position A. The direction of the nitrogen flow was from N_2B to N_2A and N_2D to N_2C (Figure 10, Nitrogen Flow Diagrams, position 1) The apparatus was opened at N_2A with a high flow of nitrogen, and 1.03 moles (25 grams) of magnesium was added to the

Figure 9

The Apparatus used for the Preparation of 2-Phenyl-2-Butyl Magnesium Chloride

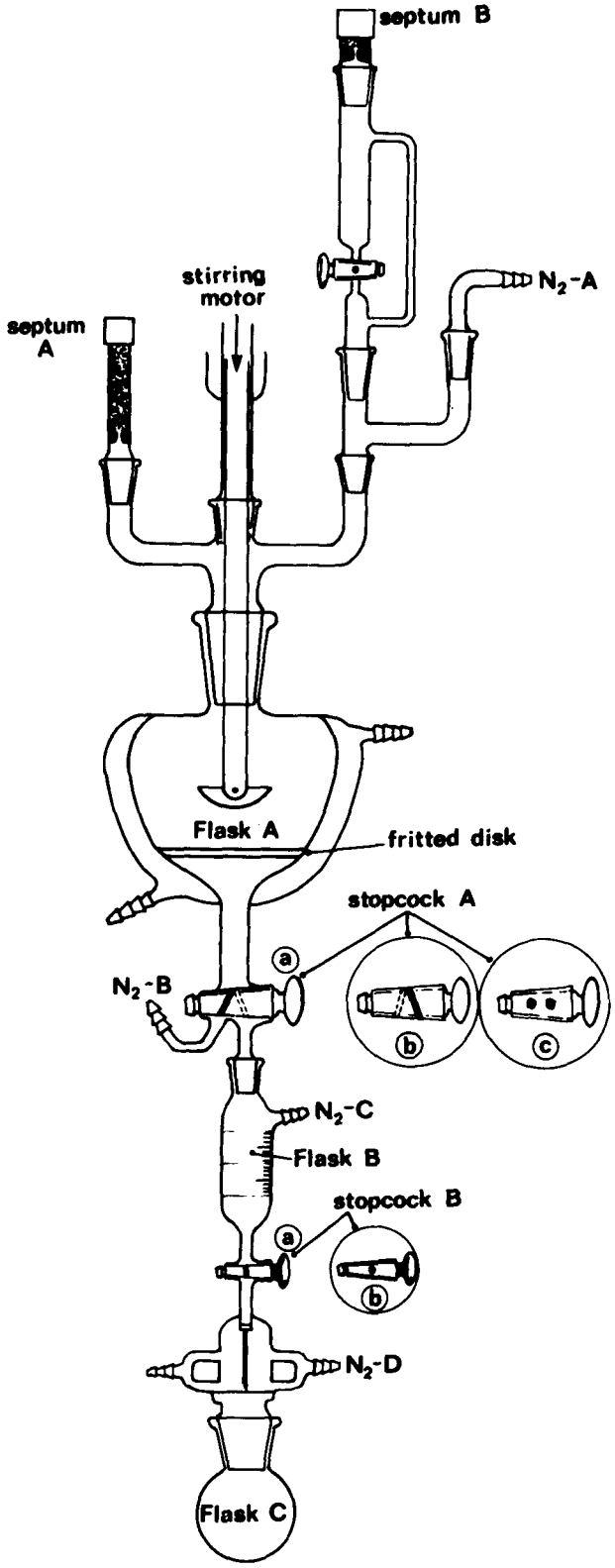
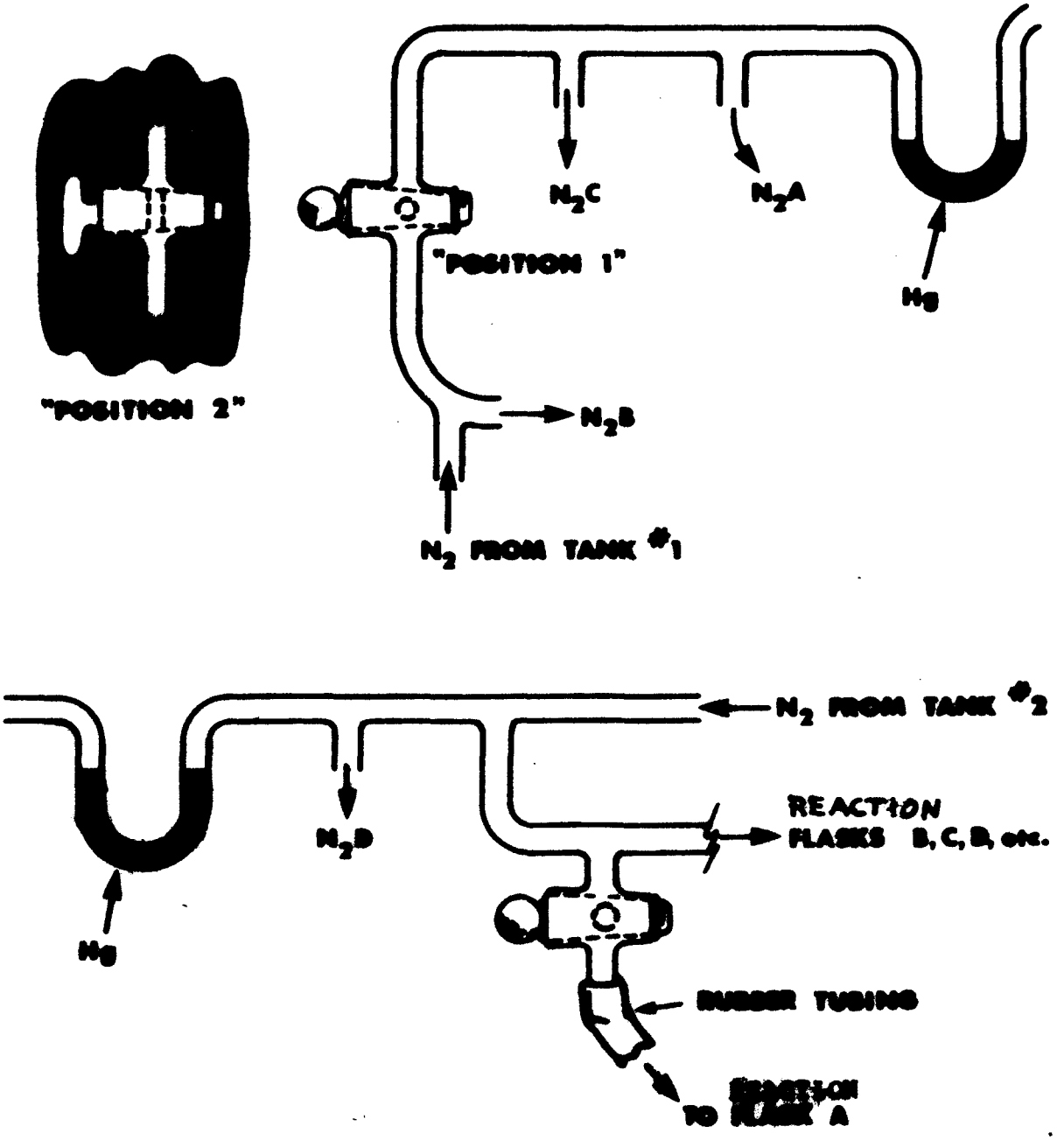


Figure 10

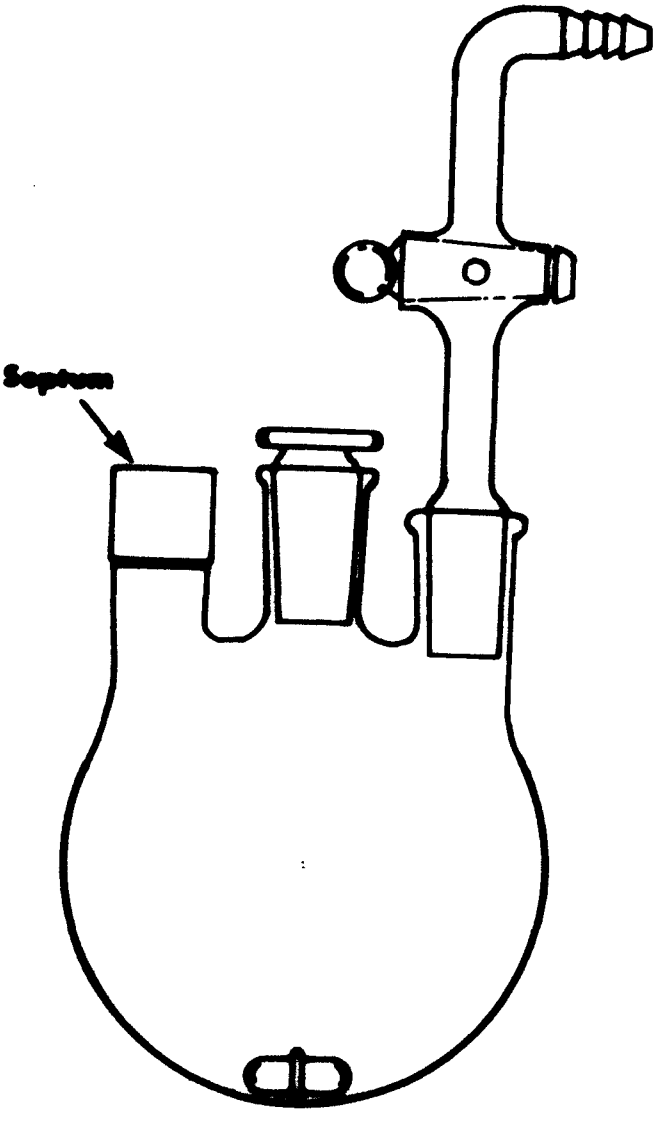
NITROGEN FLOW DIAGRAMS



reaction flask. The apparatus was reflamed and allowed to stand overnight in a stream of nitrogen. The molecular sieves were added to the tubes upon which septums A and B are attached to the apparatus by turning the nitrogen flow on high and, at the same time, removing the septums at A and B. The nitrogen flow from N_2B to N_2A was adjusted so that all the liquid put into flask A would be held above the filter. Through septum A was added 3 mmoles (0.5 grams) of 2-chloro-2-phenylbutane and 10 ml of THF. Through septum B was added 116 mmoles (19.5 grams) of 2-chloro-2-phenylbutane and 70 ml of THF. The contents of flask A were stirred for 5 minutes in order to start the reaction. The nitrogen flow was increased from N_2B to N_2A and flask A was cooled to 0^o by circulating ice water through the jacket on the flask. Once the reaction had started, 200 ml of THF was added through septum A. Stopcock A was turned to position C (Figure 10, Nitrogen Flow Diagrams, position #2). The halide solution was added dropwise over a period of approximately 3 hours and stirred for an additional hour. Stopcock A was turned to position B and a 20 ml aliquot was drawn into flask B with stopcock B in position B. The nitrogen flow from N_2D was turned on very high while flask C was removed. The sample was removed from the apparatus by puncturing the septum on reaction flask A (Figure 11) with the syringe needle

Figure 11

The Reaction Flasks used in the Asymmetric Induction Reactions



REACTION FLASK "A"

Figure 11 (continued)

The Reaction Flasks used in the Asymmetric Induction Reactions

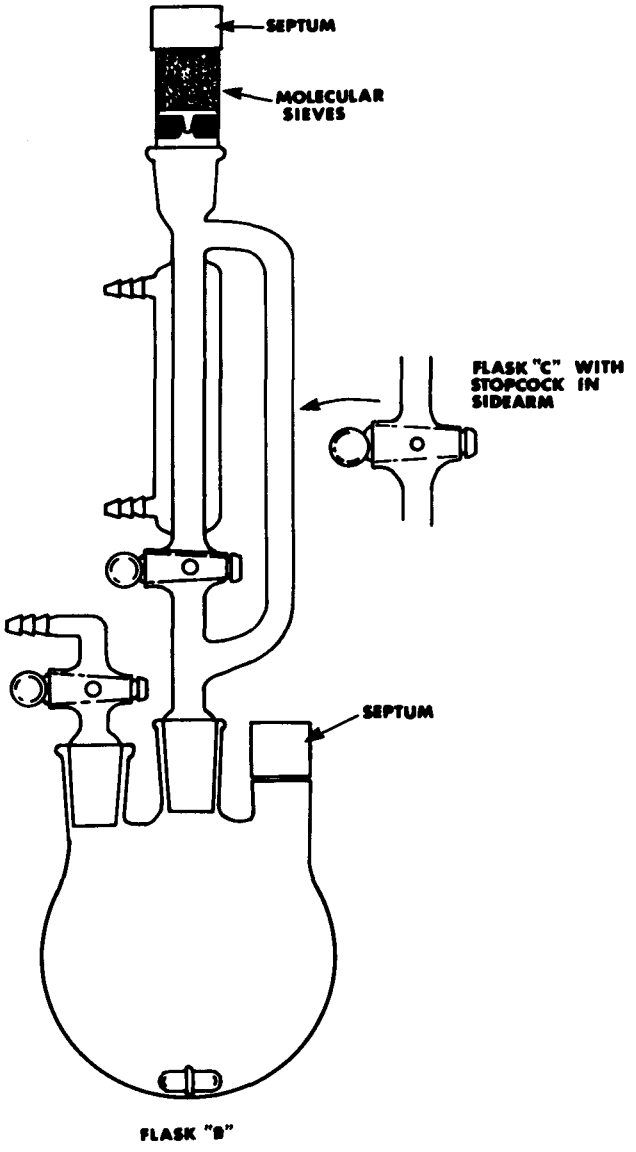
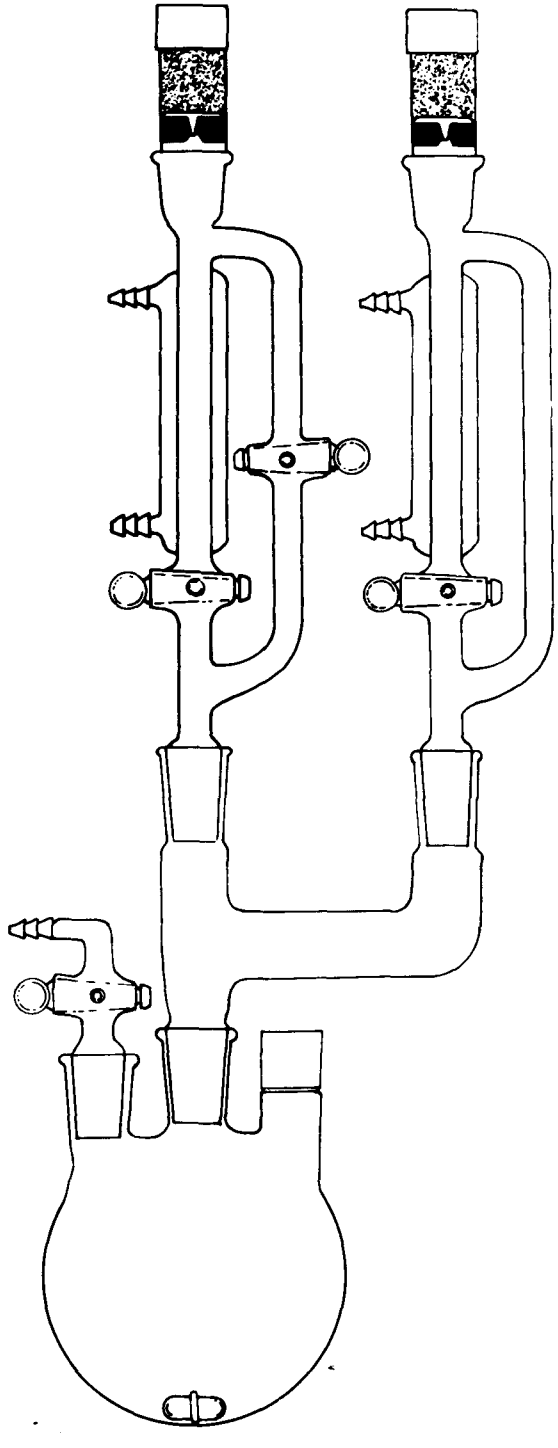


Figure 11 (continued)

The Reaction Flasks used in the Asymmetric Induction Reactions



FLASK "D"

on the bottom of flask B. After the aliquot was removed, flask C was replaced while the nitrogen flow through N_2D was decreased. The aliquot was hydrolyzed with 0.2 ml of deuterium oxide and analyzed as previously described. After the Grignard reagent was analyzed, additional aliquots were removed, in a similar manner, into reaction flasks B, C and D (Figure 11). The last aliquot taken was in a flask of reaction flask A (Figure 11) and used as a final control. The aliquots were cooled to -68° preparatory to their use in asymmetric induction reactions.

Asymmetric Induction Reactions; Experimental Conditions

a) The Reaction of One Half an Equivalent of Lanosterol with 2-Phenyl-2-Butyl Magnesium Chloride, Followed by Quenching of the Remaining Grignard Reagent with Deuterium Oxide.

(General Procedure)

The requisite amount of Grignard reagent (usually 20 ml, 4 - 6 mmoles of 2-phenyl-2-butyl magnesium chloride) was introduced into reaction flask B (Figure 11). The Grignard solution was cooled to the desired temperature (usually -68°) by immersing the flask containing the Grignard reagent in a bath which was at the appropriate temperature. (For a temperature of -68° the bath contained

an equilibrium mixture of dry-ice and isopropyl alcohol). Depending on the experiment that was to be run, the Grignard solution was either not altered, or the solution was diluted with THF, TEA, TMED, or any desired combination of these solvents. The diluents were always added to the Grignard solution through the molecular sieves atop the addition funnel. The requisite amount of lanosterol (usually 0.85 grams, 2 mmoles) was dissolved in 20 - 30 ml of THF and added by syringe into the addition funnel. The lanosterol solution was brought to the desired temperature by circulating a cooling bath through the jacket on the addition funnel. In experiments where dry-ice isopropyl alcohol was circulated through the jacket on the addition funnel, the temperature of the lanosterol THF solution, as measured on several occasions, was at a maximum of -40°. The temperature of the lanosterol solution was usually between -45 and -50°. The cooling bath was circulated through the jacket of the addition funnel for one half hour. The lanosterol was then added all at once to the stirred Grignard solution. The lanosterol addition time was usually between 5 and 20 seconds. After the completion of the lanosterol addition (t = 0 seconds), and after waiting the desired time, 0.2 ml (10 mmoles) of deuterium oxide was added by syringe directly into the Grignard solution. (A 0 second delay is one where the deuterium oxide was added simultaneously

with the completion of the lanosterol addition.) The reaction mixture was then warmed to room temperature by removing the cooling baths.

b) The Reaction of Excess Lanosterol (5 - 200%) with 2-Phenyl-2-Butyl Magnesium Chloride.

(General Procedure)

The procedure was the same as that described in section (a) up to the point where the addition of the lanosterol was completed. After the addition of the excess lanosterol, the reaction mixture was stirred for 2 minutes. At this time 0.2 ml (10 mmoles) of deuterium oxide was added by syringe to the reaction mixture in order to quench any unreacted Grignard reagent. The reaction mixture was warmed to room temperature by removing the cooling bath.

c) The Reaction of One Half of an Equivalent of Lanosterol with 2-Phenyl-2-Butyl Magnesium Chloride, Followed by Quenching of the Remaining Grignard Reagent with Carbon Dioxide.

(General Procedure)

The requisite amount of Grignard reagent (usually 20 ml, 4 - 6 mmoles of 2-phenyl-2-butyl magnesium chloride) was introduced into reaction flask D (Figure 11). The Grignard reagent was cooled, diluted with THF and TEA if desired, and the lanosterol solution prepared as described in section (a). To the addition funnel with

the stopcock in the side arm was addeded 15 ml of THF. (The purpose of the stopcock was to prevent carbon dioxide from getting into the Grignard solution prior to the reaction of the Grignard reagent with lanosterol.) The stopcock in the side arm was closed and the THF was cooled to at least -40° by circulating dry-ice isopropyl alcohol through the outer jacket. To the cooled THF was added 100 ml (4.5 mmoles) of carbon dioxide. The carbon dioxide appeared to dissolve readily in the THF. (On one occasion it was observed that the stopcock supporting the solution of carbon dioxide and THF did appear to be leaking slightly.) The lanosterol solution was then added to the stirred Grignard solution all at once. The THF-carbon dioxide solution was added to the resulting mixture upon completion of the lanosterol addition (0 second delay). The THF-carbon dioxide addition time was usually between 5 and 15 seconds. To the product mixture was added 0.2 ml (10 mmoles) of deuterium oxide from 30 to 300 seconds after the completion of the THF-carbon dioxide addition. The reaction mixture was then warmed to room temperature by removing the cooling baths.

d) <u>The Reaction of 2-Phenyl-2-Butyl Magnesium Chloride with Lanosterol and Carbon Dioxide, Followed by Dimerization of the Remaining Grignard Reagent</u>.

(General Procedure)

The procedure was the same as that described in section (c) up until the point of the completion of the THF-carbon dioxide addition. After the completion of the THF-carbon dioxide addition, the cooling baths were removed and the reaction mixture was allowed to warm to room temperature. The mixture was allowed to stand for 18 hours in order to dimerize any unreacted Grignard reagent. After 18 hours, 0.2 ml (10 mmoles) of deuterium oxide was added to the reaction mixture.

e)<u>The Reaction of One Half of an Equivalent of Lanosterol and One Half of an Equivalent of Carbon Dioxide with 2-Phenyl-2-Butyl Magnesium Chloride (Simultaneous Addition)</u>.

The procedure was the same as that described in section (a) up to the point where the lanosterol was added to the Grignard solution. The only exception was that reaction flask C (Figure 11) was used instead of reaction flask B. At this point the stopcock in the sidearm of the addition funnel was closed and 100 ml (4.5 mmoles) of carbon dioxide was dissolved in the THF-lanosterol solution. The mixture of THF, lanosterol and carbon dioxide was added to the stirred Grignard solution all at once. The reaction mixture was then either quenched with 0.2 ml (10 mmoles) of deuterium oxide 30 seconds after the completion of the addition of the THF, carbon dioxide and lanosterol, or left to stand at room temperature for 18 hours before it was quenched

with deuterium oxide.

f) The Reaction of One Half of an Equivalent of Lanosterol with 2-Phenyl-2-Butyl Magnesium Chloride, Followed by Quenching of the Remaining Grignard Reagent with Carbon Dioxide (Gas).

The Grignard reagent was added to a modification of reaction flask B (Figure 11). One additional joint was added to the flask (by using a Claisson adapter) to allow for the intake of carbon dioxide gas. The procedure was the same as that described in section (a) up to the point of completion of the lanosterol addition. After a delay time of 30 seconds, carbon dioxide gas was passed over the stirred Grignard solution for 1 hour. The carbon dioxide flow was stopped and the reaction mixture was quenched with 0.2 ml (10 mmoles) of deuterium oxide.

g) The Reaction of One Half of an Equivalent of Lanosterol with 2-Phenyl-2-Butyl Magnesium Chloride, Followed by Quenching of the Remaining Grignard Reagent with Oxygen (Gas).

The procedure was the same as that described in section (a) up to the point of completion of the lanosterol addition. At this point 100 ml (4.5 mmoles) of oxygen was added by syringe directly to the reaction mixture (0 second delay). The reaction mixture was stirred for 5 minutes and then it was quenched with 0.2 ml (10 mmoles) of deuterium oxide.

h) The Reaction of 2-Phenyl-2-Butyl Magnesium Chloride with Lanosterol and Oxygen, Followed by Dimerization of the Remaining Grignard Reagent.

The procedure was the same as that described in section (g) up to the point of completion of the oxygen addition. At this point the reaction mixture was stirred for 30 minutes. The cooling baths were removed, and the reaction mixture was left to stand for 18 hours at room temperature. After 18 hours, 0.2 ml (10 mmoles) of deuterium oxide was added to the reaction mixture.

i) The Reaction of 2-Phenyl-2-Butyl Magnesium Chloride with Deuterium Oxide (Control).

(General Procedure)

The requisite amount of Grignard reagent (usually 20 ml) was introduced into reaction flask A (Figure 11). To the stirred Grignard solution was added 0.2 ml (10 mmoles) of deuterium oxide.

Isolation of Products of Reactions with 2-Phenyl-2-Butyl Magnesium Chloride

a) Reactions Involving Lanosterol, Lanosterol and Deuterium Oxide, or Lanosterol and Grignard Dimerization

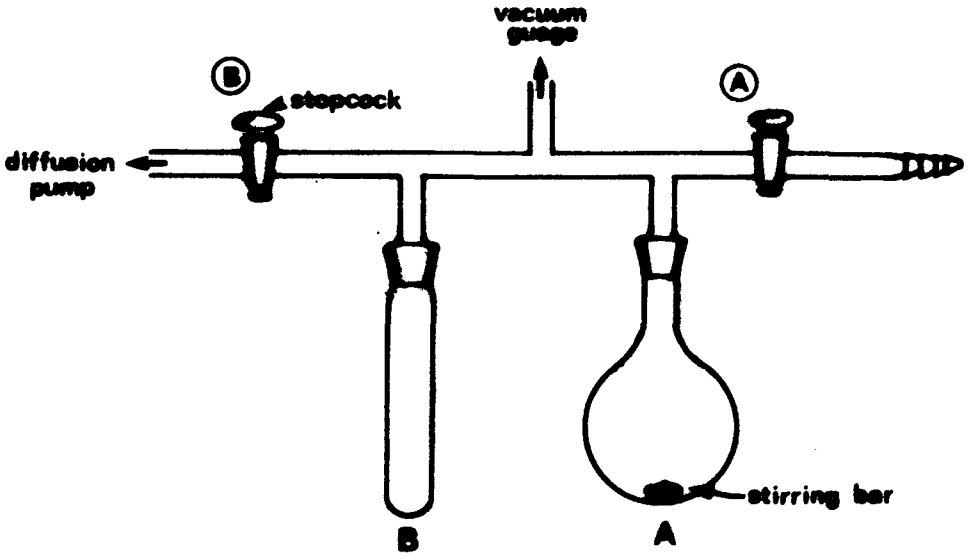
(General Procedure)

After the Grignard reagent was reacted with lanosterol, lanosterol and deuterium oxide, or lanosterol and Grignard dimerization, the product mixture in each experiment

was acidified with 10% HCl. Sodium chloride was then added to saturate the aqueous layer. (In reactions in which there was more than 50 ml of solvent present, the mixture was concentrated to a volume of approximately 50 ml on a steam bath through a 25 cm Vigreaux column prior to the addition of the acid.) The product mixture was extracted with four 125 ml portions of pentane (Matheson - practical) thus separating 2-phenylbutane, lanosterol, 2-phenyl-2-butanol, ∝-ethyl styrene, cis and trans-2-phenyl-2-butene and dl and meso-3,4-diphenyl-3,4-dimethylhexane (dimer) from the aqueous layer. The pentane fraction was dried over potassium carbonate, filtered and concentrated on a steam bath through a 25 cm Vigreaux column to a volume of approximately 10 ml. (In reactions where excess Grignard reagent was dimerized, the pentane fraction was initially adjusted to a volume of 250 ml. A 10 ml aliquot was removed and analyzed for hydrocarbon (P_{gd}) by gas chromatography. The pentane fraction was then concentrated to a volume of 10 ml through a 25 cm Vigreaux column on a steam bath.) The pentane solution was transferred to a vacuum line (Figure 12). Pentane, 2-phenylbutane, 2-phenyl-2-butanol, ∝-ethyl styrene and cis and trans-2-phenyl-2-butene (product mixture) were separated from lanosterol and dimer by trap to trap distillation (described in section (b). The pentane was removed from

Figure 12

Vacuum Line used for the Isolation of Optically Active 2-Phenylbutane



Vacuum Line

the product mixture on a steam bath through a 25 cm Vigreaux column. The product mixture was distilled (T = 90 - 100°, 45 mm Hg). The amount of product mixture varied from experiment to experiment; the usual yield was 0.5 - 1.0 grams (65 - 80% of hydrocarbon). Each product mixture was analyzed by gas chromatography. The product mixture usually contained a minimum of 80% 2-phenylbutane. Rotations (1 dec.) were taken on a neat sample of each of the product mixtures without

further purification of the product mixture; α_{obs} = 0.1 - 1.1°; lit.[13] α_{max} = -24.2°.

b) Vacuum Line Distillation

(General Procedure)

The mixture containing 2-phenylbutane, 2-phenyl-2-butanol, α-ethyl styrene, cis and trans-2-phenyl-2-butene, lanosterol, dimer and pentane was introduced into tube A (Figure 12). The mixture was frozen by placing a Dewar flask filled with liquid nitrogen (T = -195°) around tube A. Stopcock A was closed, stopcock B was opened, and the apparatus was evacuated employing a two stage mercury diffusion pump. After the system was evacuated, stopcock B was closed and the liquid nitrogen bath removed from flask A. The mixture in in tube A was allowed to warm up to room temperature. The mixture was then refrozen, and the system re-evacuated. The freeze-thaw process was continued until the system was degassed. (Four cycles were usually needed.) Tube B was then cooled with liquid nitrogen while tube A was heated to ~90° with a water bath. The mixture of 2-phenylbutane, α-ethyl styrene, cis and trans-2-phenyl-2-butene, 2-phenyl-2-butanol and pentane were distilled into tube B. On completion of the distillation, the entire apparatus was allowed to come to room temperature. Stopcock A was opened and tube B removed. (The actual pressure attained in the distillation could not be

accurately determined. The minimum pressure that the vacuum gage, Hasting vacuum gage, model # G.V. -3, could register was 10^{-3} mm Hg. The two stage mercury diffusion pump can attain a vacuum of 10^{-5} mm Hg.)

c) Reactions Involving Lanosterol and Carbon Dioxide (General Procedure)

The procedure followed was the same as that described in section (a) until the point where the organic phase was dried. Instead of drying the organic phase, it was washed with three 20 ml portions of 10% potassium hydroxide. The potassium hydroxide phase was extracted with three 50 ml portions of pentane. The organic layers were combined and dried over potassium carbonate. The product mixture was isolated as described in section (a). The potassium hydroxide solution was acidified with 10% HCl. The 2-methyl-2-phenyl-butanoic acid was extracted with three 100 ml portions of pentane. The organic layer was dried over magnesium sulfate, filtered and the pentane evaporated through a 25 cm Vigreaux column on a steam bath. The resulting pale yellow solid was sublimed twice (T = 50°, 0.1 mm Hg) yielding 0.1 - 0.3 grams of 2-methyl-2-phenyl-butanoic acid. The acid in all experiments had a mp of 56 -57°; lit.[13] 56 - 57° (racemic acid). Each acid isolated was then dissolved in benzene. (The concentration usually used was 40 - 90 grams of acid per 100 ml of benzene.) The observed rotation of the acid from each

reaction was essentially 0.0°; lit.[13] $[\alpha]_D^{23}$ = 30.2° (C = 4.5 benzene).

d) Reactions Involving Lanosterol and Oxygen, or Lanosterol Oxygen and Grignard Dimerization

The procedure is the same as that described in section (a) until the point of completion of the vacuum line distillation. After the vacuum line distillation, the product mixture was chromatographed on alumina. (150 grams of neutral alumina, 80 - 200 mesh) The column was eluded with hexane. The 2-phenylbutane, α-ethyl styrene and cis and trans-2-phenyl-2-butene was eluded with the first 100 ml of solvent. The solvent was then changed to ether and the alcohol was eluded with 200 ml of solvent. The mixture of 2-phenylbutane, α-ethyl styrene and cis and trans-2-phenyl-2-butene was distilled and analyzed as described in section (a). The 2-phenyl-2-butanol was vacuum distilled (T = 90 - 100°, 0.1 mm Hg) to usually yield 0.2 - 0.3 grams of alcohol. The alcohol was analyzed by gas chromatography and showed a single peak at t = 72 minutes. Rotations were taken on a neat sample (1 dec.) of each alcohol; $\alpha_{obs} = +(0.17 - 0.25°)$; lit.[13] $\alpha_{max} = +17.18°$.

e) Control

The procedure was the same as that described in section (a) until the point where the product mixture was distilled on the vacuum line. At this point the

product mixture was distilled (T = 90°, 45 mm Hg). The yield was usually 0.7 - 1.0 grams (~90%) of hydrocarbon. The NMR spectrum of the hydrocarbon usually showed a 2-phenylbutane/2-phenylbutane-2-D ratio of 0.1.

The Reaction of Excess Lanosterol and Carbon Dioxide with 2-Phenyl-2-Butyl Magnesium Chloride. (Inverse Addition)

To the addition funnel atop of reaction flask C (Figure 11) was added 20 ml (2.84 mmoles) of 2-phenyl-2-butyl magnesium chloride. To the reaction flask was added 2.3137 grams (5.4 mmoles) of lanosterol in 70 ml of THF. The lanosterol solution was cooled to -68° and 121 ml (5.4 mmoles) of carbon dioxide was dissolved in the lanosterol THF solution. The Grignard reagent was cooled by circulating dry-ice isopropyl alcohol through the jacket on the addition funnel for one half hour. The temperature of the Grignard solution was <-40°. At this time, the Grignard reagent was added to the stirred lanosterol-THF-carbon dioxide solution over a period of 45 seconds. The hydrocarbon product mixture and the 2-methyl-2-phenyl-butanoic acid were isolated as already described (page 140). The yield of 2-phenylbutane, corrected for impurities, was 0.2787 grams (2.08 mmoles). The yield of 2-methyl-2-phenyl-butanoic acid was 0.1356 grams (0.76 mmoles). The rotation of the hydrocarbon

product mixture was α_{obs} = + 0.069°, 1 dec. neat (0.4% optically active). The rotation of the 2-methyl-2-phenyl-butanoic acid was α_{obs} = - 0.081°, 1 dec. C = 38 in benzene (0.6% optically active). The ratio of 2-phenylbutane to 2-methyl-2-phenyl-butanoic acid was 2.08/0.76 = 2.73.

Reactions of 2-Phenyl-2-Butyl Magnesium Chloride with One Half of an Equivalent of Various Asymmetric Active Hydrogen Compounds, Followed by Quenching of the Remaining Grignard Reagent with Deuterium Oxide.
(General Procedure)

The Grignard reagent was prepared as described on page 123. All Grignard solutions were cooled to -68° (dry-ice isopropyl alcohol). The active hydrogen compounds were dissolved in THF and added at ambient temperatures to the stirred Grignard solutions. After a delay time of 60 - 115 minutes the remaining Grignard reagent was quenched with deuterium oxide. The 2-phenylbutane products were isolated using a procedure similar to that of the reaction of 2-phenyl-2-butyl magnesium chloride with lanosterol and deuterium oxide (page 136). The hydrocarbon produced was found to be racemic in all cases. The results are summarized in Table 18.

Table 18

Reactions of 2-Phenyl-2-Butyl Magnesium Chloride with One Half of an Equivalent of Various Asymmetric Active Hydrogen Compounds, Followed by Quenching of the Remaining Grignard Reagent with Deuterium Oxide

Act H[a]	T° GR[b]	T° H[c]	H/GR[d]	M H[e]	HAR[f]	M GR[g]	H/D[h]	DT[i]	%HYD[j]	%OI[k]
A-CH_2SO_3H	-68	amb	0.54	0.048	4.3	0.019	1.90	80	87	0.0
A-COOH	-68	amb	0.31	0.003	0.16	0.019	0.92	90	95	0.0
A-CH_2SO_2-B	-68	amb	0.49	0.046	5.2	0.019	1.63	70	49	0.0
$C_6H_5SO_2$-B	-68	amb	0.51	0.047	3.8	0.019	1.70	90	80	0.0
C-H	-68	amb	0.40	0.049	7.3	0.019	1.22	60	72	0.0
A-CH_2SO_2-C	-68	amb	0.69	0.060	4.1	0.032	3.04	115	90	0.0
A-(C=O)-C	-68	amb	0.69	0.060	5.6	0.032	3.00	95	71	0.0
A-(C=O)NH--(t-Bu)	-68	amb	0.69	0.060	2.6	0.032	3.00	80	91	0.0

a Asymmetric active hydrogen comounds. b The temperature of the Grignard reagent prior to reaction. c The temperature of the active hydrogen compounds prior to reaction with the Grignard reagent. d The molar ratio of the active hydrogen compound to Grignard reagent prior to reaction. e The molar concentration of the active hydrogen compound in THF. f The addition rate in mmoles/minute of the active hydrogen compound to the Grignard reagent. g The molar concentration of the Grignard reagent prior to reaction. h The molar ratio of 2-phenylbutane to 2-phenylbutane-2-D in the product. i The delay time in minutes. j The percent yield of hydrocarbon. k The observed induction of the 2-phenylbutane produced. A = d-(+)-camphoryl, B = l-(-)-α-phenethyl, C = d-(+)-α--phenethyl.

Table 19

Reactions of One Half of an Equivalent of Lanosterol with 2-Phenyl-2-Butyl Magnesium Chloride Followed by Quenching of the Remaining Grignard Reagent with Deuterium Oxide

	Reagents and Conditions									
#	ml GR[a]	mmoles I[b]	M L[c]	T° GR[d]	T° L[e]	ml A[f]	DT[g]	LAR[h]	LAT[i]	ml THF[j]
1	30	1.98	0.13	-68	<-40	---	0	9.9	12.0	---
2	30	1.96	0.13	-68	<-40	---	5	7.4	16.0	---
3	20	1.89	0.13	-68	<-40	---	10	11.3	10.0	---
4	20	1.99	0.13	-68	<-40	---	20	13.3	9.0	---
5	20	1.93	0.13	-68	<-40	---	40	12.9	9.0	---
6	20	2.07	0.14	-68	<-40	---	3600	6.7	18.5	---
7	20	2.56	0.17	-68	<-40	---	3600	8.5	18.0	---
8	20	2.00	0.067	-68	<-40	---	0	15.4	7.8	180
13	30	2.02	0.13	-68	<-40	20 TEA	5	20.2	6.0	---
14	30	2.04	0.14	-68	<-40	20 TEA	0	24.5	5.0	---
15	20	2.04	0.068	-68	<-40	20 TEA	0	21.1	5.8	180
19	20	1.99	0.066	-68	<-40	20 TMED	0	29.9	4.0	---
22	20	1.99	0.066	-68	0	---	60	12.7	9.4	---

(Continued)

Table 19 (Continued)

#	ml GR[a]	mmoles L[b]	M L[c]	To GR[d]	To L[e]	ml A[f]	DT[g]	LAR[h]	LAT[i]	ml THF[j]
24	20	1.99	0.066	-68	0	20 TEA	60	18.4	6.5	---
27	20	1.95	0.065	-68	0	20 TMED	60	30.8	3.8	---
29	20	1.95	0.13	-68	amb	---	3600	23.4	5.0	---
30	20	2.40	0.12	-68	amb	---	7200	6.3	23.0	---
31	20	2.58	0.17	-68	amb	---	3600	19.3	8.0	180
32	20	1.97	0.13	-68	amb	---	4800	23.6	5.0	180
33	20	2.38	0.12	-68	amb	20 TEA	4800	11.9	12.0	---
34	20	2.45	0.12	-68	amb	20 TMED	3600	18.4	8.0	---
35	20	2.45	0.12	amb	amb	---	900	24.5	6.0	---
36	20	2.02	0.067	amb	amb	---	0	7.3	16.7	---

a The volume of Grignard stock solution that was used. b The number of mole of lanosterol that was reacted with the Grignard reagent. c The molar concentration of the lanosterol THF solution that was added to the Grignard reagent. d The temperature of the Grignard solution prior to reaction. e The temperature of the lanosterol THF solution prior to reaction. f The volume of amine that was added to the Grignard reagent prior to reaction. g The elapsed time in seconds between the completion of the lanosterol addition and the quenching of the unreacted Grignard reagent with deuterium oxide. h The rate of the lanosterol addition to the Grignard reagent in mmoles/minute. i The lanosterol addition time in seconds. j The volume of THF that was added to the Grignard reagent prior to reaction with lanosterol.

Table 20

Reactions of One Half of an Equivalent of Lanosterol with 2-phenyl-2-Butyl Magnesium Chloride Followed by Quenching of the Remaining Grignard Reagent with Deuterium Oxide

Product Data

#	g Prod[a]	%HYD[b]	Product Composition % HYD[c]	ALC[d]	OLEF[e]	H/D[f]	∝-obs[g]	Pgb[h]	mmoles GR[i]
1	1.1651	84	88.7	2.8	8.5	0.48	-0.274	9.16	7.98
2	1.1186	80	88.2	3.4	8.4	0.48	-0.252	9.16	7.96
3	0.7817	75	86.3	5.5	8.2	0.57	-0.437	6.65	6.13
4	0.8127	80	88.1	4.1	7.8	0.65	-0.369	6.65	6.02
5	0.7655	76	88.7	3.8	7.5	0.65	-0.435	6.65	5.96
6	0.7900	77	87.3	5.0	7.7	0.64	-0.498	6.65	6.12
7	0.6784	74	87.3	3.5	9.2	1.60	-0.657	6.53	5.07
8	0.6553	67	86.1	4.2	9.7	0.74	-0.224	6.20	5.56
13	1.0008	71	88.0	3.4	8.6	0.72	-0.608	9.16	7.35
14	1.0315	75	90.1	2.5	7.4	0.64	-0.592	9.16	7.61
15	0.7074	71	86.3	5.4	8.3	0.61	-0.083	6.39	6.01
19	0.6685	65	84.5	1.9	13.5	0.64	-0.035	6.39	5.89
22	0.7579	78	90.3	2.5	7.2	0.79	-0.370	6.50	5.62

(Continued)

Table 20 (Continued)

#	g Prod[a]	%HYD[b]	Product Composition % HYD[c]	ALC[d]	OLEF[e]	H/D[f]	∝-obs[g]	P_{gh}[h]	mmoles GR[i]
24	0.7441	73	85.6	5.5	8.9	1.91	-0.654	6.50	4.22
27	0.6822	69	88.5	3.3	8.2	2.44	-0.122	6.50	3.84
29	0.7268	80	89.2	2.7	7.9	0.96	-0.301	5.95	4.99
30	0.8369	82	83.5	6.2	10.2	2.03	-0.269	6.38	4.50
31	0.6892	71	81.7	7.0	11.4	1.92	-0.439	6.53	4.84
32	0.6023	65	86.0	5.8	8.3	1.68	-0.393	5.95	4.19
33	0.6743	67	85.1	4.2	10.7	4.05	-0.343	6.38	3.64
34	0.6933	65	80.6	6.6	12.7	3.55	-0.095	6.38	3.85
35	0.8270	78	80.7	6.6	12.8	2.57	-0.025	6.38	4.24
36	0.6996	79	94.4	---	5.6	0.90	-0.080	6.31	5.29

a The grams of product mixture isolated. b The percent yield of hydrocarbon. c The fraction of the product mixture that was hydrocarbon. d The fraction of the product mixture that was 2-phenyl-2-butanol. e The fraction of the product mixture that was olefin. f The ratio of 2-phenylbutane to 2-phenylbutane-2-D in the product mixture. g The observed rotation of a neat sample of the product mixture. h The total number of mmoles of hydrocarbon present in the reaction mixture. i The total number of mmoles of Grignard reagent that was present prior to reaction with lanosterol.

Table 21

Reactions of One Half of an Equivalent of Lanosterol with 2-Phenyl-2-Butyl Magnesium Chloride Followed by Quenching of the Remaining Grignard Reagent with Deuterium Oxide

Results

#	A/GR[a]	DT[b]	T° GR[c]	T° L[d]	OP-OA[e]	OP-HYD[f]	L/GR[g]	M GR[h]	%OI[i]
1	---	0	-68	<-40	1.27	1.46	0.25	0.27	5.9
2	---	5	-68	<-40	1.18	1.36	0.25	0.27	5.5
3	---	10	-68	<-40	2.09	2.26	0.31	0.31	7.3
4	---	20	-68	<-40	1.73	1.91	0.33	0.30	5.9
5	---	40	-68	<-40	2.02	2.25	0.33	0.30	7.0
6	---	3600	-68	<-40	2.35	2.55	0.34	0.31	7.5
7	---	3600	-68	<-40	3.11	4.00	0.51	0.25	7.9
8	---	0	-68	<-40	1.07	1.19	0.36	0.031	3.3
13	20 TEA	5	-68	<-40	2.85	3.55	0.27	0.15	12.9
14	19 TEA	0	-68	<-40	2.70	3.25	0.27	0.15	12.1
15	24 TEA	0	-68	<-40	0.40	0.43	0.34	0.027	1.3
19	25 TMED	0	-68	<-40	0.17	0.18	0.34	0.15	0.6
22	---	60	-68	0	1.69	1.95	0.35	0.28	5.5

(Continued)

Table 21 (Continued)

#	A/GR[a]	DT[b]	T° GR[c]	T° L[d]	OP-OA[e]	OP-HYD[f]	L/GR[g]	M GR[h]	%OI[i]
24	34 TEA	60	-68	0	3.15	4.85	0.48	0.11	10.3
27	39 TMED	60	-68	0	0.56	0.95	0.51	0.094	1.9
29	---	3600	-68	amb	1.40	1.67	0.39	0.25	4.3
30	---	7200	-68	amb	1.33	1.89	0.53	0.23	3.6
31	---	3600	-68	amb	2.22	2.99	0.53	0.022	5.6
32	---	4800	-68	amb	1.89	2.68	0.47	0.022	5.7
33	40 TEA	4800	-68	amb	1.67	2.94	0.65	0.091	4.5
34	39 TMED	3600	-68	amb	0.48	0.80	0.64	0.096	1.2
35	---	900	amb	amb	0.13	0.19	0.58	0.21	0.3
36	---	0	amb	amb .	0.35	0.42	0.38	0.26	1.1

a The molar ratio of amine to Grignard reagent prior to reaction. b The elapsed time in seconds between the completion of the lanosterol addition and the quenching of the remaining Grignard reagent with deuterium oxide. c The temperature of the Grignard solution prior to reaction with lanosterol. d The temperature of the lanosterol-THF solutions prior to reaction with the Grignard reagent. e The optical purity of the product mixture corrected for olefin and alcohol. f The optical purity of the product mixture corrected for preformed 2-phenylbutane in addition to OP-OA. g The molar ratio of lanosterol to Grignard reagent prior to reaction. h The molar concentration of the Grignard reagent prior to reaction. i The observed induction of the 2-phenylbutane produced.

Table 22

The Reaction of One Half of an Equivalent of Lanosterol with 2-Phenyl-2-Butyl Magnesium Chloride, Followed by Dimerization of the Remaining Grignard Reagent

	Reagents and Conditions									
#	ml GR[a]	mmols L[b]	M L[c]	T° GR[d]	T° L[e]	ml A[f]	DT[g]	LAR[h]	LAT[i]	ml THF[j]
11	20	2.06	0.069	-68	<-40	---	18	10.7	11.6	---
17	20	1.92	0.064	-68	<-40	20 TEA	18	9.4	12.3	---
21	20	1.98	0.066	-68	<-40	20 TMED	18	12.2	9.7	---
26	20	1.76	0.070	-68	0	20 TEA	18	13.2	8.0	---
44	20	2.04	0.068	-68	<-40	---	18	7.6	16.2	180
45	20	2.02	0.067	-68	<-40	20 TEA	18	14.8	8.2	180

a The volume of Grignard stock solution that was used in the reaction. b The number of moles of lanosterol that was reacted with the Grignard reagent. c The molar concentration of the lanosterol-THF solution that was added to the Grignard reagent. d The temperature of the Grignard solution prior to reaction. e The temperature of the lanosterol-THF solution prior to reaction. f The volume of amine that was added to the Grignard solution prior to reaction. g The elapsed time between the completion of the lanosterol addition and the quenching of the reaction mixture with deuterium oxide (time in hours). h The rate of the lanosterol addition to the Grignard reagent in mmoles/minute. i The lanosterol addition time in seconds. j The volume of THF that was added to the Grignard reagent prior to reaction with lanosterol.

Table 23

The Reaction of One Half of an Equivalent of Lanosterol with 2-Phenyl-2-Butyl Magnesium Chloride, Followed by Dimerization of the Remaining Grignard Reagent

Product Data

#	g Prod[a]	%HYD[b]	Product Composition % HYD[c]	ALC[d]	OLEF[e]	H/D[f]	∝-obs[g]	P_{gd}[h]	mmoles GR[i]
11	0.3879	72	77.2	8.8	14.0	---	-1.098	3.09	5.36
17	0.4337	72	81.9	6.9	11.4	---	-1.079	3.66	4.65
21	0.5622	67	87.3	7.6	8.8	---	+0.004	5.25	3.08
26	0.4239	68	83.8	4.3	11.9	---	-0.895	4.03	4.24
44	0.3588	85	84.2	6.4	9.4	---	-1.305	2.66	6.62
45	0.4043	61	82.4	9.1	8.4	---	-0.965	4.05	5.20

a The grams of product mixture isolated. b The percent yield of hydrocarbon. c The fraction of the product mixture that was hydrocarbon. d The fraction of the product mixture that was 2-phenyl-2-butanol. e The fraction of the product mixture that was olefin. f The ratio of 2-phenylbutane to 2-phenylbutane-2-D in the product mixture. g The observed rotation of a neat sample of the product mixture. h The total number of mmoles of hydrocarbon present in the reaction mixture after Grignard dimerization. i The total number of mmoles of Grignard reagent present prior to reaction of the Grignard reagent with lanosterol.

Table 24

The Reaction of One Half of an Equivalent of Lanosterol with 2-Phenyl-2-Butyl Magnesium Chloride, Followed by Dimerization of the Remaining Grignard Reagent

Results

#	A/GR[a]	DT[b]	T° GR[c]	T° L[d]	OP-OA[e]	OP-HYD[f]	L/GR[g]	M GR[h]	%OI[i]
11	---	18	-68	<-40	5.88	8.8	0.38	0.27	8.8
17	31 TEA	18	-68	<-40	5.45	10.4	0.41	0.12	10.4
21	49 TMED	18	-68	<-40	0.02	0.05	0.67	0.077	0.05
26	34 TEA	18	-68	0	4.41	10.1	0.42	0.11	10.1
44	---	18	-68	<-40	6.41	8.35	0.31	0.033	8.4
45	28 TEA	18	-68	<-40	4.84	9.71	0.39	0.024	9.7

a The molar ratio of amine to Grignard reagent prior to reaction. b The elapsed time in hours between the completion of the lanosterol addition and the quenching of the reaction mixture with deuterium oxide. c The temperature of the Grignard reagent prior to reaction with lanosterol. d The temperature of the lanosterol-THF solutions prior to reaction with the Grignard reagent. e The optical purity of the product mixture corrected for olefin and alcohol. f The optical purity of the product mixture corrected for preformed 2-phenylbutane and OP-OA. g The molar ratio of lanosterol to Grignard reagent prior to reaction. h The molar concentration of the Grignard reagent prior to reaction. i The observed induction of the 2-phenylbutane produced. For dimerization reactions OI = I.

Table 25

The Reaction of Excess Lanosterol (5 - 200%) with 2-Phenyl-2-Butyl Magnesium Chloride

Reagents and Conditions

#	ml GR[a]	mmoles L[b]	L*[c]	M L[d]	T° GR[e]	T° L[f]	ml A[g]	DT[h]	LAR[i]	LAT[j]	ml THF[k]
9	9	3.00	1.17	0.120	-68	<-40	---	1.0	11.9	15.1	81
10	9	2.96	1.61	0.099	-68	<-40	---	1.0	6.4	17.9	---
16	10	2.94	2.04	0.099	-68	<-40	10 TEA	2.0	23.8	7.5	---
20	10	2.99	2.70	0.100	-68	<-40	10 TMED	2.0	24.9	7.2	---
23	20	6.13	5.62	0.200	-68	0	---	2.0	19.6	18.8	---
25	20	6.24	4.22	0.208	-68	0	20 TEA	2.0	39.4	9.5	---
28	20	6.27	3.84	0.209	-68	0	20 TMED	2.0	40.4	9.3	---

a The volume of Grignard stock solution that was used in the reaction. b The number of mmoles of lanosterol that was added to the Grignard reagent. c The number of mmoles of lanosterol that reacted with the Grignard reagent. d The molar concentration of the lanosterol-THF solution that was added to the Grignard reagent. e The temperature of the Grignard solution prior to reaction with lanosterol. f The temperature of the lanosterol-THF solution prior to reaction with the Grignard reagent. g The volume of amine that was added to the Grignard solution prior to reaction. h The elapsed time in minutes between the completion of the lanosterol addition and the quenching of the reaction mixture with deuterium oxide. i The rate of addition of the lanosterol-THF solution in mmoles/minute. j The lanosterol addition time in seconds. k The volume of THF that was added to the Grignard solution prior to reaction with lanosterol.

Table 26

The Reaction of Excess Lanosterol (5 - 200%) with 2-Phenyl-2-Butyl Magnesium Chloride

Product Data

#	g Prod[a]	%HYD[b]	Product Composition % HYD[c]	ALC[d]	OLEF[e]	H/D[f]	α-obs[g]	P_{gh}[h]	mmoles GR[i]
9	0.2264	46	75.1	13.3	11.6	3.20	-0.123	3.45	1.83[j]
10	0.2828	69	88.1	6.4	5.6	3.04	-0.200	2.80	2.30
16	0.3277	61	79.9	11.1	8.9	3.20	-0.121	3.20	2.80[j]
20	0.2804	51	76.8	14.1	9.1	---	-0.009	3.20	2.80[j]
23	0.7739	80	90.5	2.7	8.1	---	-0.363	6.50	5.62[j]
25	0.6558	63	84.0	5.5	10.5	---	-0.335	6.50	4.22[j]
28	0.6804	67	86.4	5.0	8.8	---	-0.116	6.50	3.84[j]

a The grams of the product mixture isolated. b The percent yield of hydrocarbon. c The fraction of the product mixture that was hydrocarbon. d The fraction of the product mixture that was 2-phenyl-2-butanol. e The fraction of the product mixture that was olefin. f The ratio of 2-phenylbutane to 2-phenylbutane-2-D in the product mixture. g The observed rotation of a neat sample product mixture. h The total number of mmoles of hydrocarbon present in the reaction mixture after reaction. i The total number of mmoles of Grignard reagent present prior to reaction of the Grignard reagent with lanosterol. j The value for the number of mmoles of Grignard reagent was assumed to be equal to the number of mmoles of Grignard reagent in a comparison run.

Table 27

The Reaction of Excess Lanosterol (5 - 200%) with 2-Phenyl-2-Butyl Magnesium Chloride

			Results						
#	A/GR[a]	DT[b]	T° GR[c]	T° L[d]	OP-OA[e]	OP-HYD[f]	L/GR[g]	M GR[h]	%OI[i]
9	---	1.0	-68	<-40	0.67	1.02	0.64	0.020	1.6
10	---	2.0	-68	<-40	0.94	1.14	0.70	0.26	1.6
16	26 TEA	2.0	-68	<-40	0.64	0.74	0.73	0.14	1.1
20	27 TMED	2.0	-68	<-40	0.05	0.06	1.00	0.14	0.06
23	---	2.0	-68	0	1.66	1.92	1.00	0.28	1.9
25	34 TEA	2.0	-68	0	1.64	2.53	1.00	0.11	2.5
28	39 TMED	2.0	-68	0	0.54	0.92	1.00	0.094	0.9

a The molar ratio of amine to Grignard reagent prior to reaction. b The elapsed time in minutes between the completion of the lanosterol addition and the quenching of the reaction mixture with deuterium oxide. c The temperature of the Grignard solution prior to reaction with lanosterol. d The temperature of the lanosterol-THF solutions prior to reaction with the Grignard reagent. e The optical purity of the product mixture corrected for olefin and alcohol. f The optical purity of the reaction mixture corrected for preformed 2-phenylbutane and OP-OA. g The molar ratio of lanosterol to Grignard reagent prior to reaction. h The molar concentration of the Grignard reagent prior to reaction with lanosterol. i The observed induction of the 2-phenylbutane product.

Table 28

The Reactions of 2-Phenyl-2-Butyl Magnesium Chloride with Lanosterol and Oxygen

Reagents and Conditions

		(mmol O)[c]			(T° O)[f]				(OAR)[k]	(OAT)[m]	
#	ml GR[a]	mmol L[b]	M L[d]	T° GR[e]	T° L[f]	ml A[g]	DT 1[h]	DT 2[i]	LAR[j]	LAT[l]	ml THF[n]
		(4.4)			(amb)				(13.6)	(9.7)	
41	20	2.01	0.067	-68	<-40	---	0	0.083	9.4	12.9	180
		(4.4)			(amb)				(20.0)	(13.2)	
50	20	2.07	0.069	-68	<-40	20 TEA	0	18	11.3	11.0	180

a The volume of Grignard stock solution that was used in the reaction. b The number of moles of lanosterol that was added to the Grignard reagent. c The number of moles of oxygen gas that was added to the Grignard reagent. d The molar concentration of the lanosterol-THF solution that was added to the Grignard reagent. e The temperature of the Grignard reagent prior to reaction with lanosterol. f The temperature of the lanosterol-THF solution that was added to the Grignard reagent. The oxygen was added to the Grignard reagent at ambient temperatures. g The volume of amine that was added to the Grignard reagent prior to reaction. h The elapsed time in seconds between the completion of the lanosterol addition and the addition of oxygen to the Grignard reagent. i The elapsed time in hours between the completion of the oxygen addition and the quenching of the reaction mixture with deuterium oxide. j The lanosterol addition rate in mmole/minute. k The oxygen addition rate in mmoles/minute. l The lanosterol addition time in seconds. m The oxygen addition time in seconds. n The volume of THF that was added to the Grignard solution prior to reaction of the Grignard reagent with lanosterol.

Table 29

The Reactions of 2-Phenyl-2-Butyl Magnesium Chloride with Lanosterol and Oxygen

Product Data

#	(g ALC-P)[b] g HYD-P[a]	(%ALC)[d] %HYD[c]	HYD prod. composition % HYD[e]	ALC[f]	OLEF[g]	H/D[h]	(∝-obs ALC)[j] ∝-obs HYD[i]	P_{gh}[k]	mmoles GR[l]
	(0.1675)	(48)					(+0.175)		
41	0.3157	61	83.3	---	16.6	4.16	-0.848	3.22	5.33
	(0.3315)	(91)					(+0.261)		
50	0.4088	67	75.0	---	25.0	---	-1.020	3.45[m]	6.53

a The grams of the product mixture isolated that contained hydrocarbon. b The grams of 2-phenyl-2-butanol isolated. c The percent yield of hydrocarbon. d The percent yield of 2-phenyl-2-butanol. e The fraction of the product mixture containing hydrocarbon that was hydrocarbon. f The fraction of the product mixture containing hydrocarbon that was alcohol. g The fraction of the product mixture containing hydrocarbon that was olefin. h The ratio of 2-phenylbutane to 2-phenylbutane-2-D in the product mixture. i The observed rotation of a 1 dec. neat sample of the product mixture containing hydrocarbon. j The observed rotation of a 1 dec. neat sample of 2-phenyl-2-butanol. k The total number of mmoles of hydrocarbon present in the reaction mixture after reaction. l The total number of mmoles of Grignard reagent that was present prior to reaction. m For dimerization reactions $P_{gh} = P_{gd}$

Table 30

The Reactions of 2-Phenyl-2-Butyl Magnesium Chloride with Lanosterol and Oxygen

Results

#	A/GR[a]	DT 1[b]	DT 2[c]	T° GR[d]	T° L[e]	OP-O[f]	OP-HYD[g]	(ALC/GR)[h] L/GR[h] (0.45)	M GR[i]	%I-HYD[j]	%I-ALC[k]
41	---	0	0.083	-68	<-40	4.20	6.73	0.38	0.027	6.7	1.5
50	22TEA	0	18	-68	<-40	5.62	9.37	(0.37) 0.32	0.030	9.4	3.0

a The molar ratio of amine to Grignard reagent. b The elapsed time in seconds between the completion of the lanosterol addition and the addition of oxygen to the Grignard reagent. c The elapsed time in hours between the completion of the oxygen addition and the quenching of the reaction mixture with deuterium oxide. d The temperature of the Grignard solution prior to reaction with lanosterol. e The temperature of the lanosterol-THF solutions prior to reaction with the Grignard reagent. f The optical purity of the product mixture containing hydrocarbon corrected for olefin. g The optical purity of the product mixture containing hydrocarbon corrected for preformed 2-phenylbutane in addition to OP-O. h The molar ratio of either lanosterol or oxygen to Grignard reagent. i The molar concentration of the Grignard reagent prior to reaction with lanosterol. j The induction of the 2-phenylbutane produced. k The induction of the 2-phenyl-2-butanol corrected for that fraction of the alcohol that cannot be optically active.

Table 31

The Reactions of 2-Phenyl-2-Butyl Magnesium Chloride with Lanosterol and Carbon Dioxide

Reagents and Conditions

#	ml GR[a]	(mmol C)[c] mmol L[b]	(M C)[e] M L[d]	T° GR[f]	T° L[g]	ml A[h]	DT 1[i]	DT 2[j]	(CAR)[l] LAR[k]	(CAT)[n] LAT[m]	ml THF[o]
		(4.0)	(0.13)						(12.0)	(20.0)	
12	30	1.98	0.066	-68	<-40	---	p	18 hr	5.9	20.0	---
		(4.4)	(0.15)						(18.1)	(14.8)	
18	20	1.85	0.062	-68	<-40	20 TEA	p	30 s	7.5	14.8	---
		(8.8)	(0.59)						(99.2)	(5.4)	
42	20	2.01	0.067	-68	<-40	---	0	300 s	11.5	10.5	180
		(8.8)	(0.59)						(85.0)	(6.3)	
43	20	2.01	0.067	-68	<-40	20 TEA	0	300 s	12.2	9.9	180
		(8.8)	(0.59)						(56.3)	(9.5)	
46	20	2.07	0.069	-68	<-40	---	0	18 hr	15.9	7.8	180
		(8.8)	(0.59)						(99.1)	(5.4)	
47	20	2.08	0.069	-68	<-40	20 TEA	0	18 hr	10.7	11.7	180
		(gas)	(---)						(gas)	(3600)	
48	20	2.08	0.069	-68	<-40	---	29.5	18 hr	7.0	17.9	180

a The volume of Grignard stock solution that was used in the reaction. b The number of mmoles of lanosterol that was added to the Grignard reagent. c The number of mmoles of carbon dioxide that was added to the Grignard reagent. d The molar concentration of the lanosterol-THF solution. e The molar concentration of the carbon dioxide-THF solution. f The temperature of the Grignard solution prior to reaction. g The temperature of the lanosterol-THF solution prior to reaction. h The volume of amine that was added to the Grignard reagent prior to reaction. i The elapsed time in seconds between the completion of the lanosterol addition and the addition of carbon dioxide to the Grignard reagent. j The elapsed time between the completion of the carbon dioxide addition and the quenching of the reaction mixture with deuterium oxide. k The lanosterol addition

(Continued)

Table 31 (Continued)

rate in mmoles/minute. l The carbon dioxide addition rate in mmoles/minute. m The lanosterol addition time in seconds. n The carbon dioxide addition time in seconds o The volume of THF that was added to the Grignard solution prior to the reaction of the Grignard reagent with lanosterol. p The lanosterol and carbon dioxide solutions were added simultaneously.

Table 32

The Reactions of 2-Phenyl-2-Butyl Magnesium Chloride with Lanosterol and Carbon Dioxide

Product Data

#	(g AC-P)[b] g HYD-P[a]	(%AC)[d] %HYD[c]	HYD prod. composition % HYD[e]	ALC[f]	OLEF[g]	H/D[h]	(∝-obs AC)[j] ∝-obs HYD[i]	C = AC[k]	P_{gh}(d)[n]	mmol GR[m]
	(0.2727)	(20)					(-0.007)	(67)		
12	0.5660	91	87.2	1.8	11.0	---	-0.337		4.00	7.73
	(0.0700)	(11)					(-0.009)	(20)		
18	0.4875	77	82.1	6.6	11.4	1.35	-0.119		4.50	4.75
	(0.2986)	(31)					(+0.044)	(51)		
42	0.4582	76	87.0	5.0	8.0	1.28	-0.349		3.91	5.40
	(0.3148)	(30)					(-0.031)	(52)		
43	0.4763	60	86.8	4.8	9.4	1.45	-0.252		4.20	5.90
	(0.6416)	(76)					(+0.005)	(93)		
46	0.3386	71	78.3	9.0	12.7	---	-0.508		2.77	6.83
	(0.6152)	(80)					(-0.013)	(92)		
47	0.3775	72	82.6	4.8	12.7	---	-0.138		3.22	6.39
	(0.5179)	(62)					(+0.030)	(39)		
48	0.3358	70	79.2	8.3	12.5	---	-0.759		2.82	6.79

a The grams of the product mixture isolated that contained hydrocarbon. b The grams of 2-phenyl-2-methylbutanoic acid isolated. c The percent yield of hydrocarbon. d The percent yield of 2-phenyl-2-methylbutanoic acid based on the amount of available Grignard reagent. e The fraction of the product mixture containing hydrocarbon that was hydrocarbon. f The fraction of the product mixture containing hydrocarbon that was alcohol. g The fraction of the product mixture containing hydrocarbon that was olefin. h The ratio of 2-phenylbutane to 2-phenylbutane-2-D in the product mixture. i The observed rotation of a neat sample (1 dec.) of the product mixture containing hydrocarbon. j The observed rotation of the acid in benzene solution (1 dec). k The concentration of the acid in bezene in grams/100 ml of solvent. m The total number of mmoles of Grignard reagent present prior to reaction. n The total number of mmoles of hydrocarbon present in the reaction mixture after reaction.

Table 33

The Reactions of 2-Phenyl-2-Butyl Magnesium Chloride with Lanosterol and Carbon Dioxide

Results

#	A/GR[a]	DT 1[b]	DT 2[c]	T° GR[d]	T° L[e]	OP-OA[f]	OP-HYD[g]	(AC/GR)[i] L/GR[h]	M GR[j]	%I-HYD[k]	%I-AC[l]
12	---	m	18 hr	-68	<-40	1.60	3.3	0.26 (0.20)	0.26	3.3	0.11
18	31 TEA	m	30 s	-68	<-40	0.60	0.74	0.39 (0.11)	0.12	1.9	0.83
42	---	0	300 s	-68	<-40	1.65	3.22	0.37 (0.31)	0.027	3.2	0.81
43	24 TEA	0	300 s	-68	<-40	1.20	3.10	0.34 (0.30)	0.027	3.1	0.44
46	---	0	18 hr	-68	<-40	2.68	3.59	0.30 (0.53)	0.034	3.6	0.03
47	22 TEA	0	18 hr	-68	<-40	0.69	1.07	0.33 (0.54)	0.029	1.1	0.09
48	---	29.5[n]	18 hr	-68	<-40	3.96	5.37	0.31 (0.42)	0.034	5.4	0.33

a The molar ratio of amine to Grignard reagent. b The elapsed time in seconds between the completion of the lanosterol addition and the addition of carbon dioxide to the Grignard reagent. c The elapsed time between the completion of the carbon dioxide addition and the quenching of the reaction mixture with deuterium oxide. d The temperature of the Grignard reagent prior to reaction with lanosterol. e The temperature of the lanosterol-THF solutions prior to reaction with the Grignard reagent. f The optical purity of the product mixture containing hydrocarbon corrected for olefin and alcohol. g The optical purity of the product mixture containing hydrocarbon corrected for preformed hydrocarbon in addition to OP-OA. h The molar ratio of lanosterol to Grignard reagent prior to reaction. i The molar ratio of carbon dioxide to Grignard

(Continued)

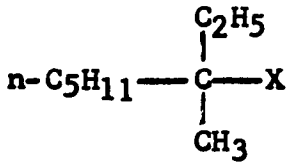
Table 33 (Continued)

reagent. The fraction of the total Grignard reagent that reacted with carbon dioxide. j The molar concentration of Grignard reagent prior to reaction with lanosterol. k The induction of the 2-phenylbutane produced. l The induction of the 2-phenyl-2-methylbutanoic acid produced. m The lanosterol and carbon dioxide were added simultaneously. n Carbon dioxide gas was passed over the Grignard solution from 29.5 seconds to 3600 seconds.

APPENDIX

The appendix is a summary of work initially carried out on another Grignard system. The results of this preliminary investigation are significant because the results of this thesis predict that the Grignard system chosen would not lead to induction. This information can be valuable for contemplated future work in which similar reactions on other Grignard systems will be tried.

The system initially chosen for this thesis was



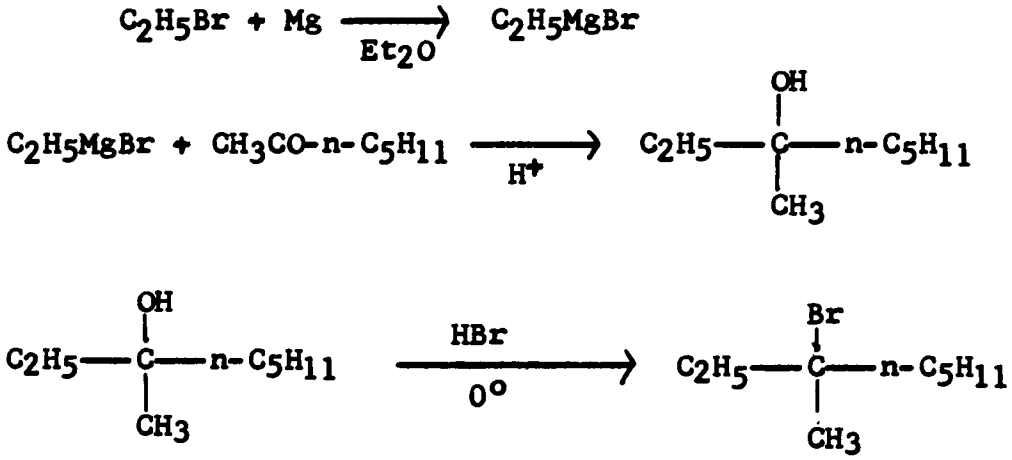
X = H, Br, OH, etc.

(3-Methyl-3-Octyl)-

The 3-bromo-3-methyloctane was synthesized using the reaction scheme shown in Figure 13.

Figure 13

Synthesis of 3-Bromo-3-Methyl octane



Prior to this thesis, the 3-bromo-3-methyloctane and similar compounds had been prepared but could not be purified by distillation because of their purported instability. However, it was discovered in this laboratory, that if the halide was worked up at 0° (see experimental section) the compound could be distilled under vacuum. The yield of 3-bromo-3-methyloctane was generally high (85 - 90%).

Preparation of 3-methyl-3-octyl magnesium bromide in THF usually afforded the Grignard reagent in 17% yield. The Grignard reagent was purified by separating the volatile impurities (unreacted bromide, 3-methyloctane and disproportionation products) from the Grignard reagent employing the vacuum line techniques described in the experimental section.

To one equivalent of 3-methyl-3-octyl magnesium bromide at -68° was added ~0.4 equivalents of lanosterol in THF at room temperature ($\sim 25^{\circ}$). The resulting 3-methyloctane was removed by vacuum distillation and found to be racemic.

There is abundant evidence available to show that the molecular rotation of a compound is a measure of the dissymmetry around the asymmetric center providing that the molecule contains only one asymmetric center.[66] The molecular rotations (M_D) of 3-methyloctane and 2-phenylbutane are 10.9 and 32.4 respectively. If one assumes

that the relative values of the molecular rotations of these two compounds are a measure of the dissymmetry of the transition states between the respective Grignard reagents and lanosterol, then the lack of stereospecificity for the reaction between 3-methyl-3-octyl magnesium bromide and lanosterol can be explained.

The reaction of lanosterol with 2-phenyl-2-butyl magnesium chloride under conditions similar to those of the reaction of 3-methyl-3-octyl magnesium bromide with lanosterol produced 2-phenylbutane that was $\sim$4% optically pure (reactions 29 and 30). Thus one would expect the 3-methyloctane produced to be $\sim$1% optically pure. (An optical purity of 1% corresponds to an observed rotation of 9.38 X 0.01 = 0.1°.) An optical purity of $\sim$1% would severly hinder the measurement of small changes in optical activity as one varied experimental parameters. Assuming that one conducted experiments employing the 3-methyl-3-octyl Grignard reagent and lanosterol at optimum conditions, and the hydrocarbon produced was optically active, the data produced would be expected to have values approximately 1/3 that of the 2-phenyl-2-butyl system. Clearly, these results would not have had any real significance.

EXPERIMENTAL SECTION

Synthesis of 3-Methyl-3-Octanol[67]

To a three neck, three liter round bottom flask equipped with a Tru-bore stirrer, refluxing condenser and a pressure equalizing addition funnel containing 3.35 moles (362 grams) of ethyl bromide (Fisher) dissolved in 300 ml of anhydrous diethyl ether (Baker), was added 3.35 moles (80.3 grams) of Grignard grade magnesium turnings (Baker), and 600 ml of anhydrous ether. At first a few ml of the ether-halide solution was added to the magnesium. The reaction started almost immediately. The initial reaction was allowed to subside and 400 ml of ether was added to the Grignard solution. The rate of addition of halide was adjusted so as to maintain gentle refluxing of the ether (about 1 drop/second - addition time was four hours). After the addition of the halide was completed, the solution was left to stand overnight. The Grignard reagent was cooled in an ice-salt bath and three moles (342 grams) of 2-heptanone (Eastman) in 228 ml of anhydrous ether was added with continued stirring over a period of three hours. After the addition of the ketone was complete, the solution was stirred for an additional thirty minutes. The solution was hydrolyzed with 283 grams of crushed ice mixed with 147 grams of concentrated sulfuric acid. The ether layer was separated from the water layer and washed

with water. The ether extract was dried over sodium carbonate, filtered and distilled to yield 327 grams (78%) of 3-methyl-3-octanol, bp 70 - 72° (5 mm Hg); lit.[67] bp 36 - 37° (3 mm Hg); n_D^{20} = 1.4324, lit.[67] n_D^{20} = 1.4324.

3-Bromo-3-Methyloctane

Anhydrous hydrogen bromide (Matheson) was passed from a capillary tube through 0.76 moles (113 grams) of 3-methyl-3-octanol at 0°. The bromide addition was stopped when a distinct water layer, containing the approximate theoretical amount of water (13.7 ml), had formed. The halide was transferred to a chilled separatory funnel and washed with 5% sodium bicarbonate (0°) and water (0°). The halide was then dried over calcium chloride at 0°, filtered and distilled to yield 143 grams (88%) of 3-bromo-3-methyloctane, bp 53 - 55° (3 mm Hg), lit.[68] decomposes on distillation; n_D^{25} = 1.4561, lit.[68] n_D^{20} = 1.4545. (Note: To date, the successful distillation of this compound has not been reported. Therefore, the physical properties observed here cannot be expected to agree with reported values.) The halide showed negative results for unsaturation with bromine in carbon tetrachloride, and also with 2% potassium permanganate. An infrared spectrum of the halide showed the absence of hydroxide (3200 - 3600 cm^{-1}) as well as the absence of unsaturation

(1620 - 1680 cm^{-1}).

Anal calcd for $C_9H_{19}Br$: C, 50.18%; H, 9.24%. Obsd: C, 52.22%; H, 9.41%.

Preparation of 3-Methyl-3-Octyl Magnesium Bromide

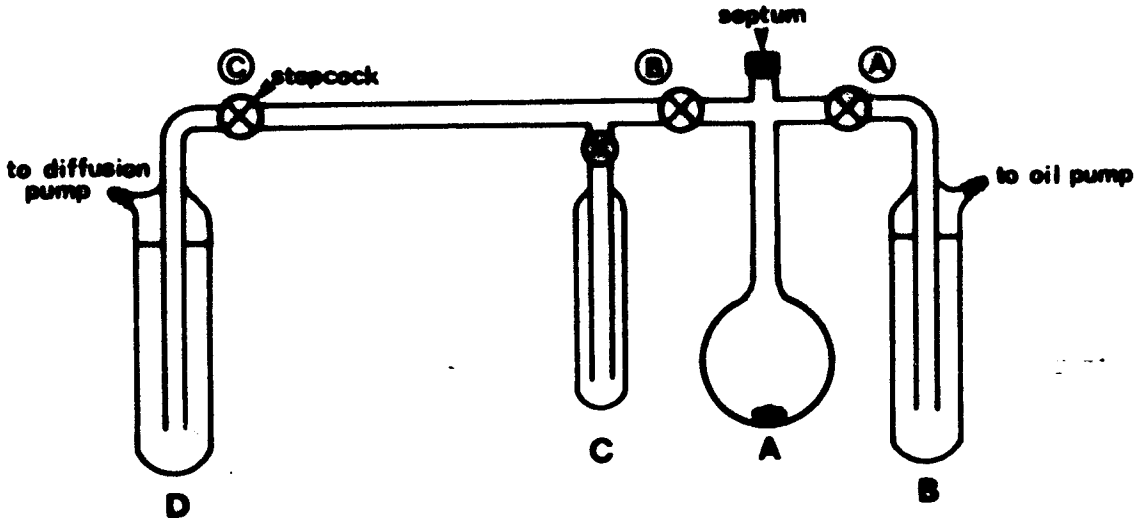
To 1.8 grams (74 mmoles) of magnesium in 4 ml of THF was added 15.2 grams (73.4 mmoles) of 3-bromo-3-methyloctane in 18.4 ml of THF over a period of 90 minutes. After completion of the halide addition the resulting solution was stirred for one hour. The yield of 3-methyl-3-octyl magnesium bromide was found by acid titration of a 1 ml aliquot of the Grignard solution. The average yield for this reagent was 17%.

Reaction of Lanosterol with an Excess of 3-Methyl-3-Octyl Magnesium Bromide

The Grignard solution (described in the previous section) was introduced with a syringe into flask A of the vacuum line (Figure 14). The THF was distilled under vacuum (0.1 mm Hg) into flask B by closing stopcock B and opening stopcock A. Liquid nitrogen was used throughout the experiment as a coolant to trap the volatile materials being distilled from the reaction flask. The 3-methyloctane, olefinic side products and unreacted 3-methyl-3-bromooctane were distilled into flask D by employing a mercury diffusion pump

Figure 14

The Vacuum Line used in the Purification of 3-Methyl-3-Octyl Magnesium Bromide



Vacuum Line

(10^{-3} - 10^{-5} mm Hg), over a period of 20 hours (stopcock A is closed and stopcocks B and C are opened). To the remaining solids in flask A (3-methyl-3-octyl magnesium bromide and magnesium bromide) was added enough THF to bring the total volume to 40 ml. (There was 12.4 meq of 3-methyl-3-octyl magnesium bromide present, therefore, the concentration of the Grignard reagent was 0.31 molar.) The Grignard solution was cooled to -68° (isopropyl alcohol and dry ice) and 2.16 grams (5.07 mmoles) of lanosterol dissolved in 15 ml of THF

was added by syringe in 9 seconds to the stirred Grignard solution. The reaction mixture was frozen with liquid nitrogen and the system degassed by employing the mercury diffusion pump. The THF and 3-methyloctane were distilled into flask C (stopcock B open, stopcocks A and C closed) by trap to trap distillation. Flask C was removed from the vacuum line and the THF was evaporated through a 25 cm Vigreaux column on a steam bath. The product was distilled to yield 0.36 grams (55%) of 3-methyloctane, bp 143 - 144° (760 mm Hg), lit.[69] bp 143 - 144° (760 mm Hg); $\alpha_{obs} = 0.00°$ (1 dec. neat); lit.[69] $[\alpha]_D^{17} = +9.38°$.

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