UNIVERSITY OF ILLINOIS

December 28 1987

THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

Bret W. Frost

ENTITLED Stereoselectivity of Catecholborane Reductions of Cyclohexenone Tosylhydrazones

IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE

DEGREE OF Bachelor of Science in Liberal Arts and Sciences

Robert M. Coates
Instructor in Charge

APPROVED:

HEAD OF DEPARTMENT OF Chemistry

Stereoselectivity of Catecholborane Reductions of Cyclohexenone Tosylhydrazones

By

Bret W. Frost

Thesis

for the

Degree of Bachelor of Science

in

Liberal Arts and Sciences

College of Liberal Arts and Sciences

University of Illinois

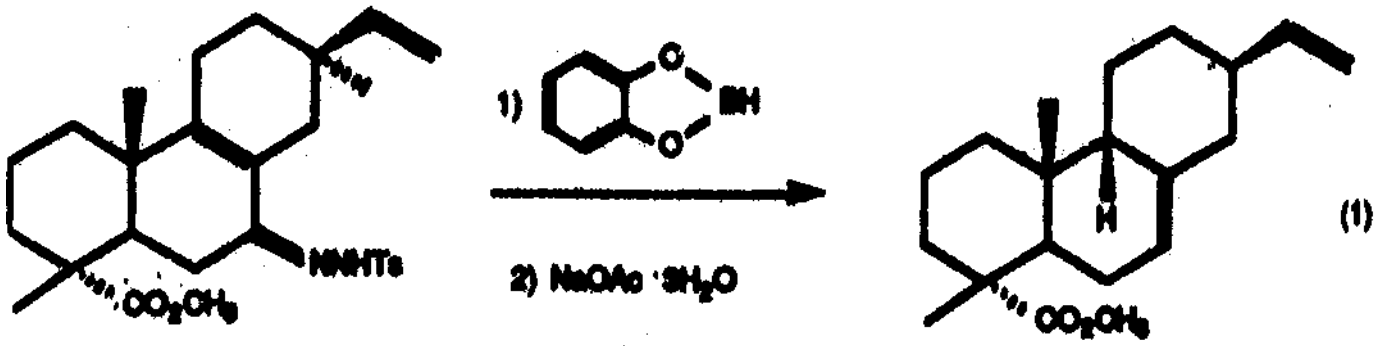
Urbana, Illinois

1987

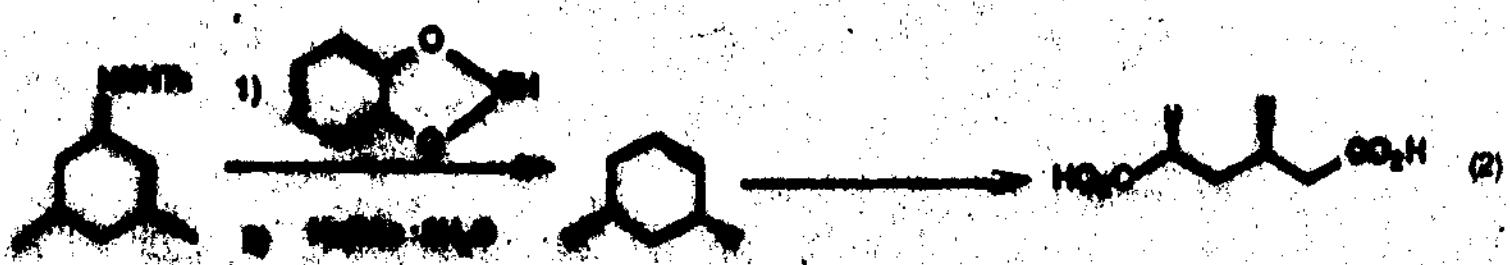
Table of Contents

Introduction

In research involving diterpene synthesis[1], one reaction that proved interesting was the formation of methyl 9β-primara-7,15-dien-18-oate by catecholborane reduction of the 8-en-7-one tosylhydrazone (Equation1). The reduction was found to be highly stereoselective and produced the thermodynamically less stable 9β isomer.



This project, a collaboration with Dr. Min Chu, was initiated to determine whether the same stereoselectivity would be found in monocyclic and bicyclic compounds. If so, it could be very useful in organic synthesis. For example, a compound such as 3,5-dimethyl-2-cyclohexenone tosylhydrazone, would produce trans-3,5-dimethyl-2-cyclohexene. Cleavage of the double bond would produce the diacid, which is a potentially useful compound (Equation 2)



Catecholborane reductions of tosylhydrazones have been reported before. Papers by G.W. Kabalka[2] and D. Taber[3] showed that reductions of tosylhydrazones of α,β-enones with catecholborane give good yields of the rearranged alkenes, but neither paper investigated the stereoselectivity of the process. A literature search revealed that the stereochemistry of the catecholborane reduction of tosylhydrazones had not been studied in depth prior to the present investigation.

Results and Discussion

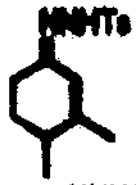
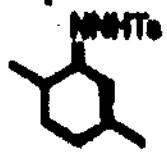
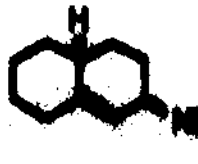
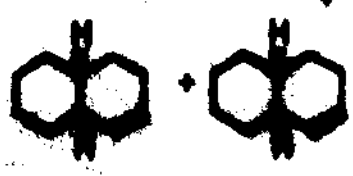
In the first part of this research, the tosylhydrazones of 3,4- , 3,5- , and 3,6-dimethyl-2-cyclohexenones were reduced with catecholborane. These monocyclic compounds were selected because they are the simplest and analysis of their conformations and steric interactions should be more straightforward. Furthermore, the stereochemistry of the resulting dimethylcyclohexenes can be determined simply by hydrogenation. The reductions of the tosylhydrazones of the bicyclic compounds 4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone and (R)-4,4a,5,6,7,8-hexahydro-4a-methyl-2(3H)-naphthalenone were also studied. These compounds are more rigid than the monocyclic substrates and the reduction products can also be compared to known compounds, or further hydrogenated to known saturated compounds.

3,4- and 3,6- Dimethyl-2-cyclohexenones and 4,4a,5,6,7,8-[illegible] were reduced by [illegible] reduction [illegible] were [illegible]

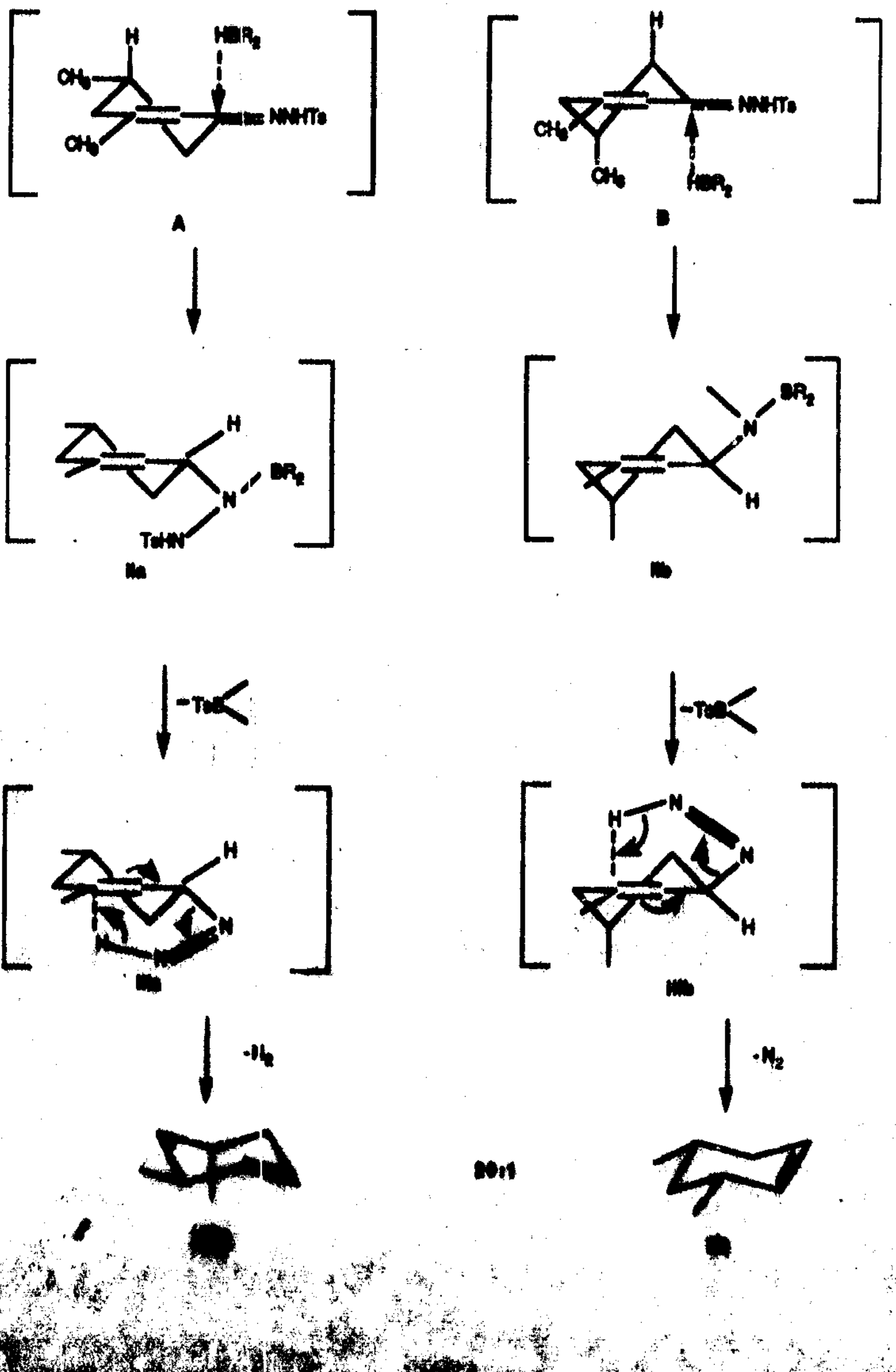
catalyzed hydrolysis and equilibration to the conjugated ketones[4]. The tosylhydrazones were prepared by condensation of the enones with tosylhydrazide in ethanol at 70°C [5]. All of the toslyhydrazones were mixtures of syn and anti isomers with ratios varying from 2:1 (1:2) to 4:1 (1:4).

The catecholborane reductions were conducted in chloroform solution at 0°C to 25°C , followed by refluxing in the presence of sodium acetate according to the procedure of Kabalka, et. al.[6] The trans/cis ratios and yields of the various cyclohexenes are shown in Table I. The stereochemistry of the first four products was established by Dr. Chu via catalytic hydrogenation and capillary GC comparisons with authentic samples. In the last case, the major product was identified as cis by comparison of its ^{1}H NMR data with the literature values.

TABLE 1 Structures, trans / cis Ratios, and Yields of Cyclohexenes Produced by Catecholborane Reduction of Cyclohexenone Tosylhydrazones

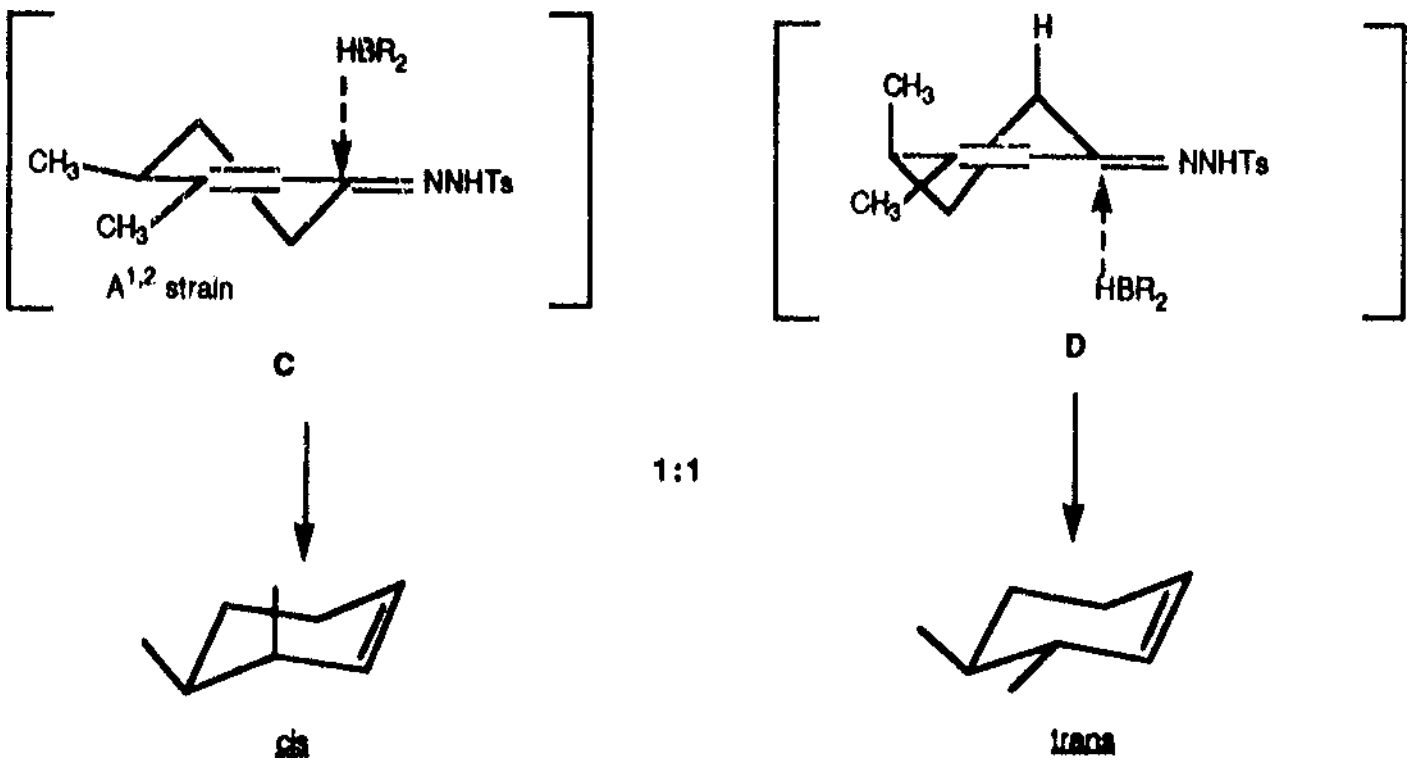
Entry	α, β–Enone	Products	Ratio Trans: Cis	Yield (%)
1			20:1	85
2			1:1	85
3			1:3	83
4			1:4	65
5			1:9	70

SCHEME 1



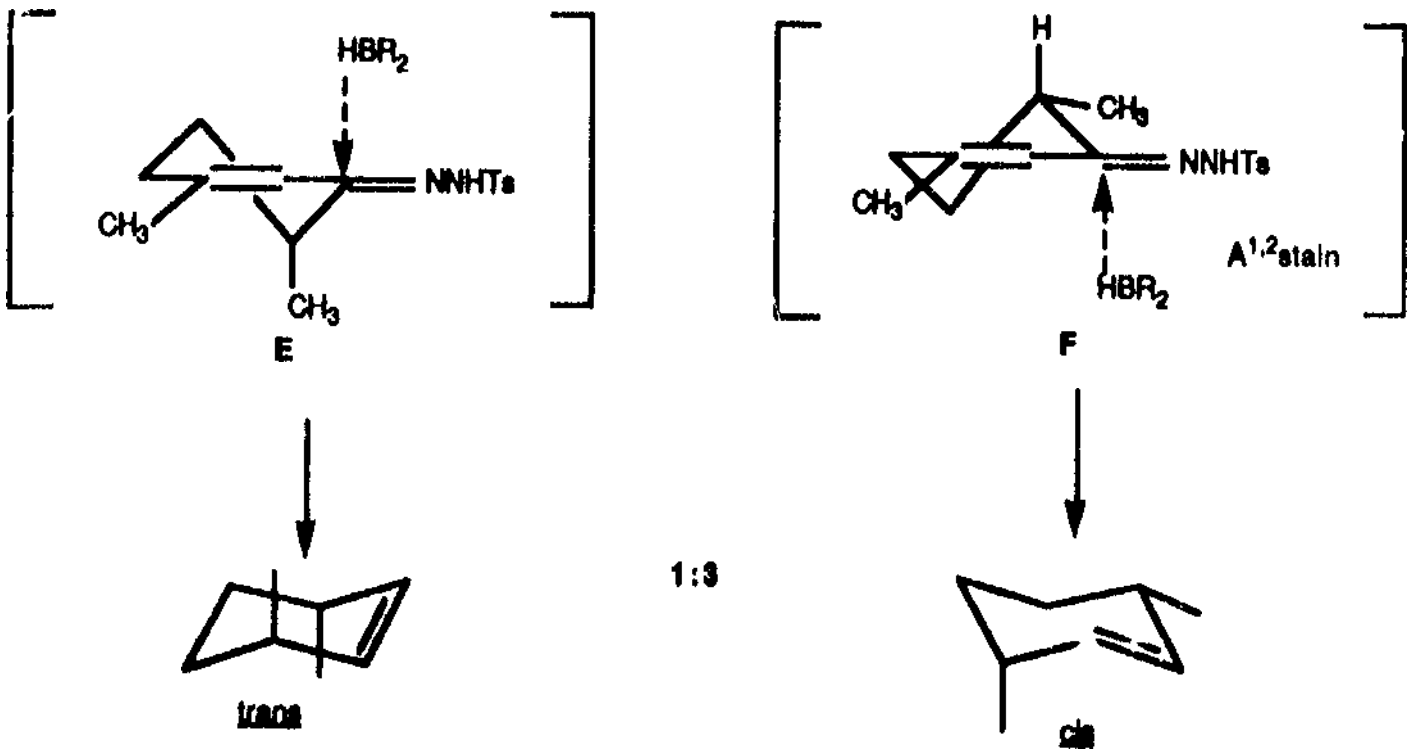
The contrathermodynamic tendency of the reaction is clearly demonstrated by the predominant formation of the less stabie trans-3,5-dimethylcyclohexene (entry 1, 20:1 ratio). The stereoselectivity can be rationalized by assuming that the hydride is transferred preferably via quasiaxial transition states, A and B. Quasiaxial attack is favored for stereoelectronic reasons. In this orientation, the forming C-H bond is aligned to maximize orbital overlap with the adjacent double bond, and thereby to stabilize the transition states. Transition state B is evidently destabilized by an incipient 1,3-diaxial interaction between the axial C5 methyl group and the attacking boron hydride. The axial hydride attack produces adducts iia and iib , which then lose tosylcatecholborane to form the diazene intermediates iiia and iiib. This is followed by intramolecular hydrogen transfer and nitrogen elimination to form the final products. The diagram indicates that the stereochemistry is established in the first step by the hydride attack. In case A, transfer of the hydrogen can only occur on the same face as the C5 methyl group, while in case B it can occur only on the opposite face.

SCHEME 2



The reduction of the tosylhydrazone of the 3,4-dimethyl isomer resulted in a 1:1.isomer ratio. In this case, transition state C is apparently destabilized by $A^{1,2}$ strain between the adjacent methyl groups to about the same extent as transition state D is destabilized by a 1,3 diaxial interaction.

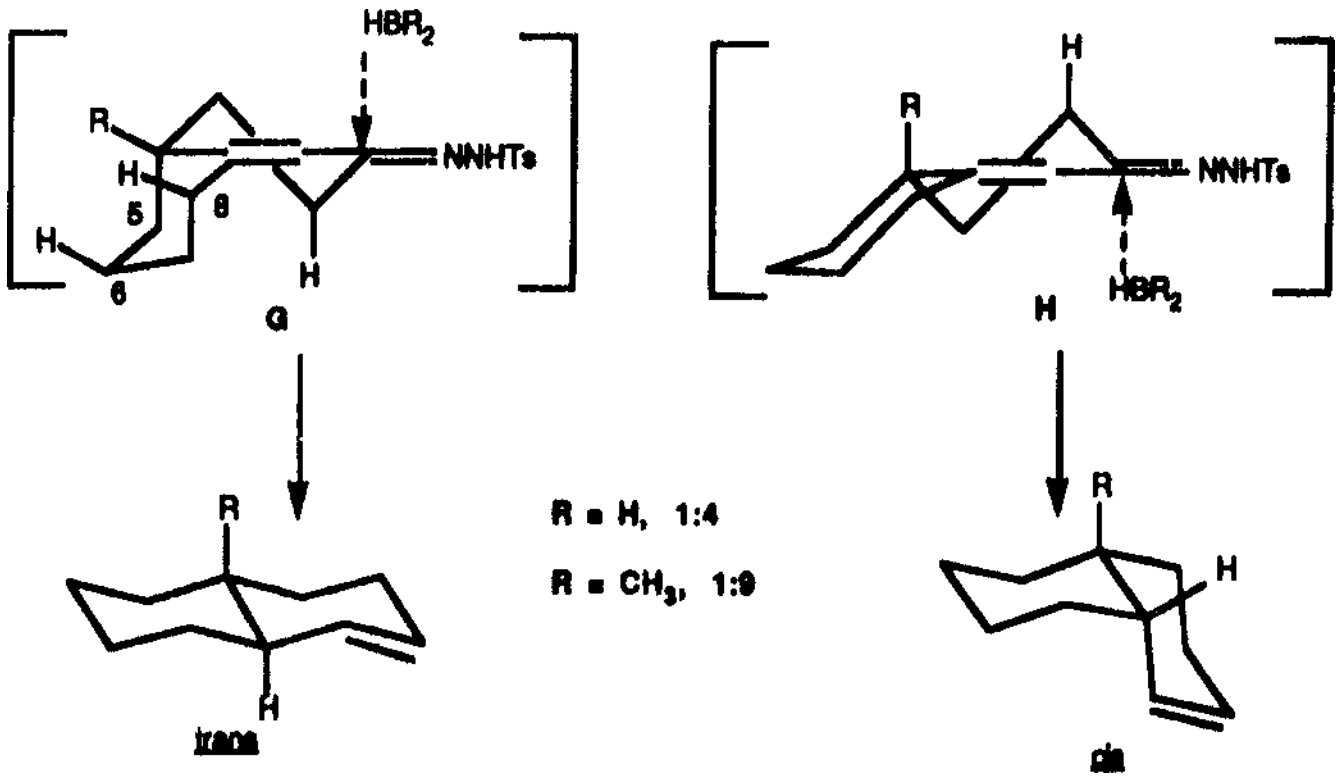
SCHEME 3



Predominant formation of cis-3,6-dimethylcyclohexene from 3,6-dimethyl-2-cyclohexenone tosylhydrazone is attributed to the higher energy of transition state E having an axial methyl group. However, the existence of $A^{1,2}$ strain in the favored transition state F reduces the energy difference between E and F such that 25% of the trans isomer is formed via transition state E.

Reduction of the two octalone tosylhydrazones afforded cis-fused octalins as the major products in both cases (1:4 and1:9 ratios). Transition state G is evidently disfavored by 1,3-interactions between the quasiaxial C5 CH_2 groups and the C3 axial hydrogens. The lower proportion of the trans product when the angular methyl group is present may be attributed to 1,3-diaxial interaction of the methyl group and the axial hydrogens at C6 and C8 in transition state G (R=CH_3).

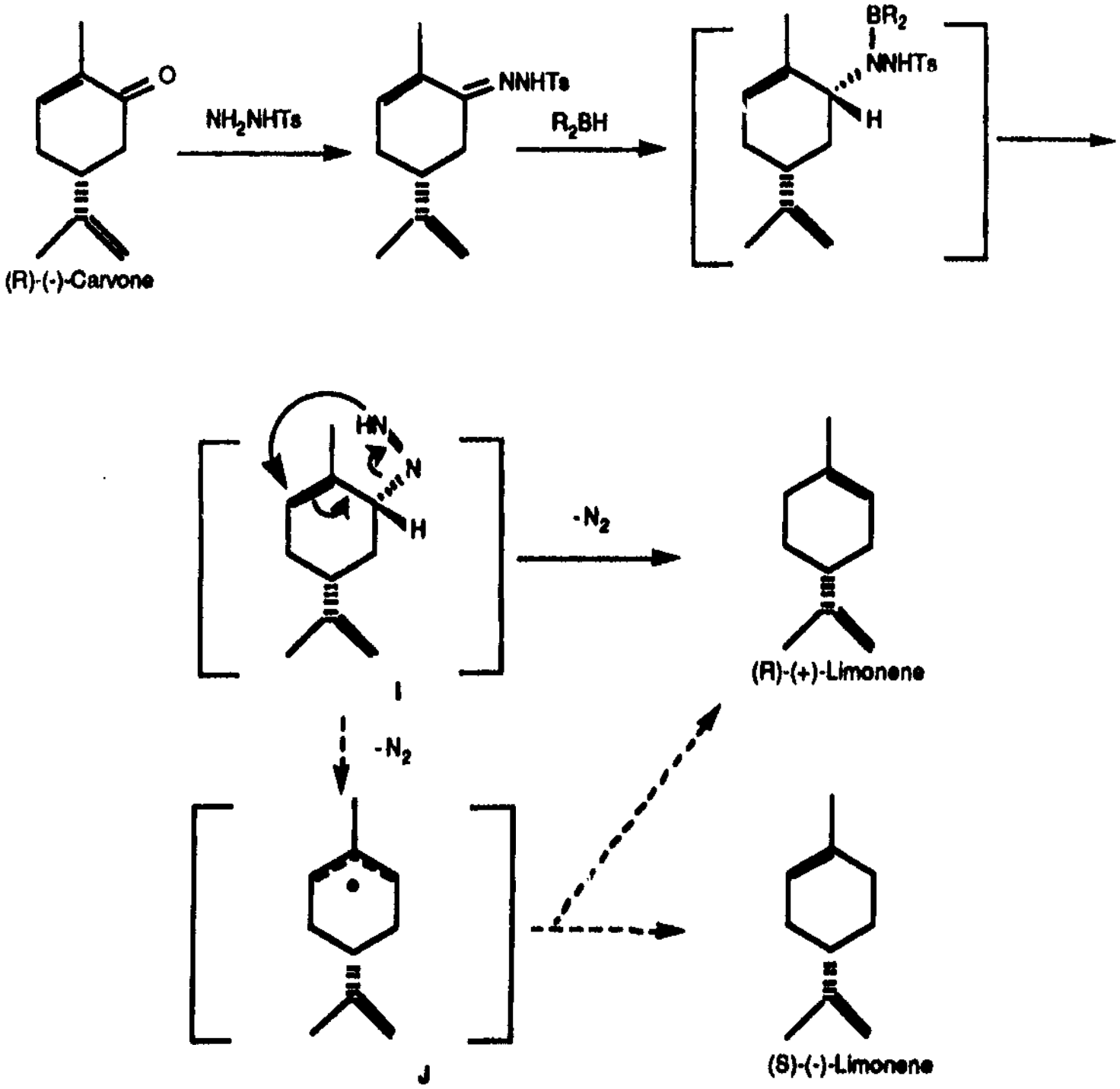
Scheme 4



The reduction of the tosylhydrazone of (R)-(-)-carvone (93% optical purity) was carried out to determine whether rearrangement

of the double bond position is complete. If an allylic radical was formed from the diazene intermediate (I → J), racemic limonene should be formed to some extent.

SCHEME 5



The optical purity of the resulting (R)-(+)-limonene was 87% which indicates at most a decrease of 6% in optical purity. It is therefore clear that the predominant (88%), if not exclusive, pathway followed is the concerted diazene fragmantation leading to the rearranged (R)-(+)-limonene. The maximum amount of racemic

limonene formed via the symmetrical radical intermediate would be 12%.

However, it should be noted that crystallization of the tosylhydrazone could have increased the optical purity somewhat. If the optical purity of the tosylhydrazone had been 100%, the 13% loss of optical activity after catecholborane reduction would indicate that 26% of the limonene was formed from the allylic radical intermediate.

The high retention of optical purity (94%) contrasts with that resulting from lithium aluminum hydride reduction[7]. Felkin and Verrier have reported that the reduction of carvone tosylhydrazone with this aluminum hydride reagent gave limonene retaining only 60% of the original optical activity.

In each of the five entries we saw that the catechol borane reduction was highly selective. This reduction produces the less stable isomer in a good ratio unless there is a hinderance with the system. This reduction can prove to be useful in the synthesis of many organic compounds.

Experimental

Preparation of Dimethylcyclohexenones: The following procedure is similar to the one reported by Wilds and Nelson[4].

3,6-Dimethyl-2-cyclohexenone.: A solution of 0.255 g (3.67 mmol) of lithium in 30 mL of liquid ammonia was stirred and maintained at reflux under nitrogen as 1 g (7.35 mmol) of 2,5-dimethylanisole (Aldrich Chemical Co.) in 3 mL of distilled ether was

added. The solution was allowed to reflux for 2 h using a dry ice condensor. The ammonia was then evaporated, and the remaining lithium was quenched with ethanol. Water was added and the product was extracted with ether. The ethereal solution was dried ($MgSO_4$), and the solvent was evaporated. The resulting liquid was dissolved in 20 mL of ethanol containing 20 drops of concentrated hydrochloric acid. This solution was refluxed for 50 min, diluted with water, and extracted with ether. The ether was washed with 5% sodium bicarbonate, dried ($MgSO_4$), and evaporated. Purification by column chromatography with 4:1 hexane:ether as a eluant afforded 0.621 g (85%) of 3,6-dimethyl-2-cyclohexenone: ^1H NMR (500 MHz, $CDCl_3$), δ 1.32(d, 3H, J = 6 Hz, CH_3), 1.94(s, 3H, =C-CH_3), 1.60-2.30(m, 5H, $2CH_2$, CH), 5.84(s, 1H, C=CH); IR (neat), 2957 (CH), 1670(C=O) cm^{-1}.

3,4-Dimethyl-2-cyclohexenone: yield, 0.405 g (45%); ^1H NMR (500 MHz, $CDCl_3$), δ 1.19(d, 3H, J =11 Hz, CH_3), 1.95(s, 3H, CH_3), 1.70-2.55(m, 5H, $2CH_2$, CH), 5,85(s, 1H, C=CH); IR (neat) 2936 (CH), 1676 (C=O) cm^{-1}.

4,4a,5,6,7,8-Hexahydro-2(3H)-naphthalenone: After column chromatography, the spectral data showed no evidence of β,γ-isomer. yield, 0.648 g (70%); ^1H NMR (500 MHz, $CDCl_3$), δ 1.10-2.50(m, 13H, $6CH_2$, CH), 5.82(s, 1H, C=CH); IR (neat) 2930 (CH), 1674 (C=O) cm^{-1}.

General Procedure for Tosylhydrazone Preparation: The following procedure is a modified version of the one reported by Djerassi[5]. All of the tosylhydrazones were mixtures of syn and anti isomers with ratios ranging from 2:1 (or 1:2) to 4:1 (or 1:4) as determined from their ^1H NMR spectra.

3,5-Dimethyl-2-cyclohexenone Tosylhydrazone (A,B) : A suspension of 2.7 g (14.5 mmol) of p-toluenesulfonylhydrazide (Aldrich Chem. Co.) in a solution of1.5 g (12.1 mmol) of the enone in 10 mL of absolute ethanol was stirred and heated in a water bath at 70°C until all of the tosylhydrazide dissolved. Stirring was continued for 3 h, after which 90% of the solvent was evaporated, and the remaining residue was dissolved in 5 mL of chloroform. Addition of pentane to the cloud point followed by cooling at -20°C for 8 h gave 3.34 g (95%) of white crystalline solid. Recrystallization from chloroform and pentane gave the analytical sample: mp 159-161°C; syn / anti ratio, 1:4 (or 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80(d, 0.65H, J = 6.8 Hz, CH_3), 0.99(d, 2.35H, J = 6.8 Hz, CH_3), 1.62-2.66(m, 5H, $2CH_2$, CH), 1.80(s, 2.35H, =C-CH_3), 1.85(s, 0.65H, =C-CH_3), 2.42(s, 3H, $ArCH_3$), 5.92(s, 0.78H, C=CH), 6.17(s, 0.22H, C=CH), 7.30(d, 2H, J = 8.3 Hz, ArH at C3′) ,7.48(br, 1H, NH), 7.86(d, 2H, J = 8.3 Hz, ArH at C2′).

Anal. Calcd. for $C_{15}H_{20}N_2SO_2$: C, 61.64; H, 6.85; N, 9.59. Found C, 61.55; H, 6.87; N, 9.58.

3,4-Dimethyl-2-cyclohexenone Tosylhydrazone (C,D): yield, 2.82 g (80%); mp 137-138°C; syn / anti ratio, 1:4 (or 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04(d, 2.3H, J = 7.0 Hz, CH_3), 1.08(d, 0.7H, J = 7.0 Hz, CH_3), 1.81(s, 2.3H, =C-CH_3), 1.87(s, 0.7H, =C-CH_3), 1.81-2.31(m, 5H, $2CH_2$, CH), 2.42(s, 3H, $ArCH_3$), 5.89(s, 0.77H, C=CH), 6.30(s, 0.23H, C=CH), 7.24(br, 1H, NH), 7.30(d, 2H, J = 8.3 Hz, ArH at C3′) 7.89(d, 2H, J = 8.3 Hz, ArH at C2′).

Anal. Calcd. for $C_{15}H_{20}N_2SO_2$: C, 61.64; H, 6.85; N, 9.59. Found C, 61.34; H, 6.99; N, 9.53.

3,6-Dimethyl-2-cyclohexenone Tosylhydrazone (E,F): yield, 2.64 g (75%); mp 174-175°C ; syn / anti ratio, 1:3 (or 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05(d, 2.25H, J = 6.8 Hz, CH_3), 1.11(d, 0.75, J = 6.8 Hz, CH_3), 1.86(s, 2.25H, =C-CH_3), 1.94(s,0.75H, =C-CH_3), 1.42-2.38(m, 5H, 2CH_2, CH), 2.42(s, 3H, ArCH_3), 5.84(s, 1H, C=CH), 6.10(br, 1H, NH), 7.30(d, 1.5H, J = 8.5 Hz, ArH at C3′), 7.35(d, 0.5H, J = 8.5 Hz, ArH at C3′), 7.80(d, 0.5H, J = 8.5 Hz, ArH at C2′), 7.86(d, 2H, J = 8.5 Hz, ArH at C2′).

Anal. Calcd. for $C_{15}H_{20}N_2SO_2$: C, 61.64; H, 6.85; N, 9.59. Found C, 61.71; H, 7.05; N, 9.69.

4,4a,5,6,7,8-Hexahydro-2(3H)-naphthalenone Tosylhydrazone (G,H): yield, 3.26 g (85%); mp121-123°C; syn / anti ratio, 1:2 (or 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91-2.53(m, 13H, 6CH_2CH), 2.42(s, 2H, ArCH_3), 5.86(s, 0.66H, C=CH), 6.08(s, 0.33H, C=CH) 7.30(d, 1.3H, J = 8.3Hz, ArH at C3′), 7.39(d, 0.7H, J = 8.3 Hz, ArH at C3′), 7.79(d, 0.7H, J = 8.3 Hz, ArH at C2′) 7.83(br, 1H, NH), 7.86(d, 1.3H, J = 8.3 Hz, ArH at C2′).

Anal. Calcd. for $C_{17}H_{22}N_2SO_2$: C, 64.14; H, 6.94; N, 8.81. Found C, 63.85: H, 7.03; N, 8.80.

(R)-4,4a,5,6,7,8-Hexahydro-4a-methyl-2(3H)-naphthaleone Tosylhydrazone (G,H): yield, 3.61 g (90%); mp162-164°C; syn / anti ratio, 1:3 (or 3:1); ^{1}H NMR (360 Hz, $CDCl_3$) δ 1.08(s, 2.25H, CH_3), 1.13(s, 0.75H, CH_3), 1.16-2.58(m, 12H, 6CH_2), 2.41(s, 3H, ArCH_3), 5.86(s, 0.75H, C=CH), 6.00(s, 0.25H, C=CH), 7.30(d, 2H, J = 8.3 Hz, ArH at C3′), 7.83(br, 1H, NH), 7.86(d, 2H, J = 8.3 Hz, ArH at C2′).

Anal. Calcd. for $C_{18}H_{24}N_2SO_2$: C, 65.06; H, 7.23; N, 8.43. Found C, 64.92; H, 7.24; N, 8.40.

(R)-(-)-Carvone Tosylhydrazone : was prepared from (R)-(-)-carvone, $[\alpha]_D$ - 58° (neat) (Aldrich Chemical Co.). The optical purity of the starting carvone was 93% based upon a literature rotation of $[\alpha]_D$ - 62.3° ($CHCl_3$) for presumably optically pure carvone. The yield of the tosylhydrazone was 3.29 g (81%); mp162-163°C; $[\alpha]_D^{23}$= -35.2° (C2.5, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 1.71(s, 3H, CH_3), 1.79(s, 3H, =C-CH_3, 1.85-2.44(m, 4H, $2CH_2$), 2.43(s, 3H, ArCH_3), 2.64(dd, 1H, J = 4.0, 15.8 Hz, CH), 6.07(br d, 1H, J = 4.0 Hz, C=CH), 7.31(d, 2H, J = 8.3 Hz, ArH at C3'), 7.71(br, 1H, NH), 7.87(d, 2H, J = 8.3 Hz, ArH at C2').

Anal. Calcd, for $C_{17}H_{22}N_2SO_2$: C, 64.12; H, 6.97; N, 8.80, Found C, 64.40; H, 7.01; N, 8,97.

General Procedure for Tosylhydrazone Reduction: The following reduction procedure is similar to that reported by Kabalka[6]. In the case of low boiling olefins, solvent was removed by distillation rather than rotary evaporation.The isomer ratios were determined by capillary GC analysis conducted by Dr. Chu on a 30-m, DB-5 column at 50°C unless otherwise specified. The purity of the products was judged to be greater than or equal to 90-95 % by GC analysis and inspection of the ^1H NMR spectra.

3,4-Dimethylcyclohexene: A three-necked flask containing 1.752 g (6.00 mmol) of 3,4-dimethyl-2-cyclohexenone tosylhydrazone dissolved in 5 mL of chloroform was alternately evacuated and filled with nitrogen three times. The solution was stirred and cooled in an ice bath as 0.80 mL (6.60 mmol) of catecholborane was added.The cooling bath was removed and the solution was stirred and allowed to warm to room temperature. After 1 h, 1.60 g(12.0 mmol) of sodium acetate trihydrate and 5 mL of

chloroform were added and the resulting suspension was stirred and refluxed for 1 h. The cooled solution was washed with water, 5% sodium carbonate, and saturated.sodium chloride.The organic layer was dried ($MgSO_4$) and the ether was removed by distillation at atmospheric pressure. The product was purified by flash chromatography using 7:1 pentane to ether as an eluant and fractions were analyzed by thin layer chromatography. Combination of the appropriate fractions followed by distillation at atmosperic pressure afforded 0.521 g (85%) of a 1:1 mixture of cis and trans isomers: ^{1}H NMR (500 MHz $CDCl_3$) δ 0.88, 0.89, 0.97, 0.98(4d, 6H, J = 7.5 Hz, $2CH_3$), 5.43-5.65(m, 2H, 2CH=CH), .

3,5-Dimethylcyclohexene: yield, 0.527 g (85%); trans/cis ratio, 20:1; ^{1}H NMR (500 MHz, $CDCl_3$), δ trans 0.94, 0.99(2d, 6H, J = 6.6, $2CH_3$), 1.38-2.28(m, 6H, $4CH_2$, 2CH), 5.58(br, 2H, CH=CH).

3,6-Dimethylcyclohexene: yield, 0.509 g (83%); trans/cis ratio, 1:3; ^{1}H NMR (360 MHz, $CDCl_3$), δ trans .089, 0.97(2d, 6H, J =7.0 Hz, $2CH_3$), 5.51(s, 2H, CH=CH); cis 0.87, 0.95(2d, 6H, J = 7.0 Hz, $2CH_3$), 5.46(s, 2H, CH=CH).

3,4,4a,5,6,7,8,8a-Octahydronaphthalene: yield, 0.585 g (65%); trans/cis ratio, 1:4; ^{1}H NMR (500 MHz, $CDCl_3$) δ cis 0.85-1.85(m, 11H, $5CH_2CH$), 1.95-2.07(m, 2H, =C-CH_2), 2.19(br, 1H, =C-CH), 5.49-5.63(m, 2H, CH=CH).

cis-1,2,3,4,4a,5,6,8-Octahydro-4a-methylnaphthalene: yield, 0.676 g (70%), trans/cis ratio, 1:9; ^{1}H NMR (500 MHz, $CDCl_3$), δ 0.94(s, 3H, CH_3), 1.03-1.79(m, 11H, $5CH_2CH$) ,2.03(br, 2H,=C-CH_2), 5.46-5.80(m, 2H, CH=CH). The spectral data agree with the values in the

literature[8]. The isomer ratio of was determined by GC analysis at (100°C).

(R)-(-)-Limonene: yield, 0.603 g (72%); $[\alpha]_D^{25}$ +108.4° (c,0.35, $CHCl_3$), (optical purity= 87% based on lit.[9] $[\alpha]_D$ +123.8°); ^1H NMR (360 MHz, $CDCl_3$), δ 1.65(s, 3H, CH_3), 1.73(s, 3H, =C-CH_3), 1.41-2.16(m, 7H, 3CH CH), 4.71(s, 2H, C=CH_2), 5.40(br, 1H, C=CH).

References

1. Unpublished paper by Dr. Min Chu.

2. Kabalka, G.W.; Newton, R.J.; Chandler, J.H.; *J Chem. Soc., Chem Comm.* 1978, 726.

3. Taber, D.F; Anthony, J.M., *Tetrahedron Lett.* 1960, 21, 2779.

4. Wilds, A.L.; Nelson, N.A., *J. Am. Chem. Soc.* 1953, 75, 5360.

5. Djerassi, C.; Taylor, E.J., *J. Am. Chem. Soc.* 1976, 98, 2275.

6. Kabalka, G.W.; Hutchins, R.; Natale, N.R.; Yang, D.T.C.; Broach, V., *Org. Synth.* 1980, 59, 42.

7. Verrier, M.; Elphimoff-Felkin, I., *Tetrahedron Lett.* 1968, 12,1515.

8. Brown, R.S.; Marcinko,R.W.; Tse, A., *Can. J. Chem.* 1979, 57, 1890.

9. Beinstein, V, 88.