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CARBENE CHEMISTRY. I. STEREOCHEMICAL INTEGRITY AT C SUB ALPHA I--ETC(U)  
FEB 78 J R BALLYEAT

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AN ABSTRACT OF THE THESIS OF

10 JOHN ROBERT BALLYEAT for the degree of <sup>Thesis,</sup> MASTER OF SCIENCE

in Chemistry (Organic) presented on Feb 22, 1978

6 Title: CARBENE CHEMISTRY. I. STEREOCHEMICAL INTEGRITY AT C<sub>α</sub> IN KETONE TOSYLHYDRAZONES. II. HYDROGEN MIGRATION IN 2-CARBENA-6,6-DIMETHYLNORBORNANE.

Abstract approved: P. K. Freeman  
Dr. Peter K. Freeman



The tosylhydrazones of exo-3-deuteriocamphor and 2-deuterio-2,4-dimethyl-3-pentanone were treated with N-bromosuccinimide (NBS) and pyruvic acid to regenerate the parent ketones. The ketones from the pyruvic acid cleavage show a significant loss of deuterium. The ketones from the NBS cleavage show no loss of deuterium, indicating that stereochemical integrity at C<sub>α</sub> is maintained during the NBS cleavage.

C SUB ALPHA

The tosylhydrazones and corresponding lithium salts of exo and endo-3-deuterio-6,6-dimethylnorbornan-2-one are found to maintain their stereochemical integrity at C<sub>α</sub>. Thermal and photolytic decomposition of the lithium salts reveals a 3,2 hydride migration preference of 19:1 in favor of the exo hydrogen. Torsional interactions in the hydride migration transition state of a classical singlet carbene are suggested as an explanation for the observed stereoselectivity.

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Carbene Chemistry. I. Stereochemical Integrity  
at C $\alpha$  in Ketone Tosylhydrazones. II. Hydrogen  
Migration in 2-Carbena-6,6-dimethylnorbornane

by

John Robert Balyeat

A THESIS

submitted to

Oregon State University

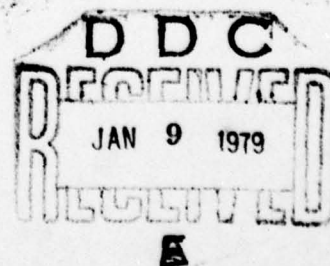
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Master of Science

Completed February 1978

Commencement June 1978



APPROVED:

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Date thesis is presented Feb 22, 1978

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"The heavens are telling of the glory of God; And their expanse is declaring the work of His hands... For He Himself knows our frame; He is mindful that we are but dust. As for man, his days are like grass. As a flower of the field so he flourishes. When the wind has passed over it, it is no more, and its place acknowledges it no longer. But the lovingkindness of the Lord is from everlasting to everlasting on those who fear Him. And His righteousness to children's children, to those who keep His covenant, and remember His precepts to do them." Psalms 19:1, 103:14-18.

The culmination of my studies here at O.S.U. has been long awaited and I would like to thank the many people who have made it possible. Special thanks go to Dr. P. K. Freeman for his guidance and optimism; also to Ron and Bev Heusser and Mr. and Mrs. Lyle Knower for a home away from home. I would like to thank my parents for their encouragement through the years and their concern for my spiritual growth. Most of all I thank my wife, Marcia, for her patience and support, her love and prayers during this time.

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## CARBENE CHEMISTRY

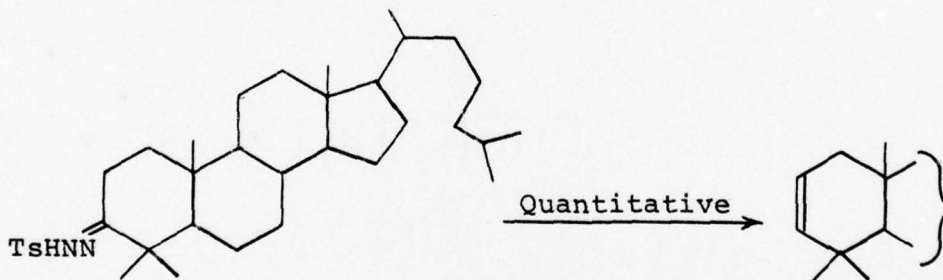
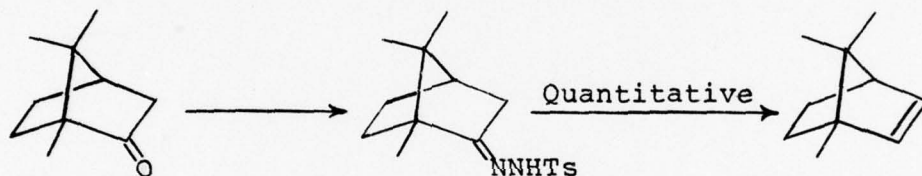
### PART I. STEREOCHEMICAL INTEGRITY AT C<sub>α</sub> IN KETONE TOSYLHYDRAZONES

#### INTRODUCTION

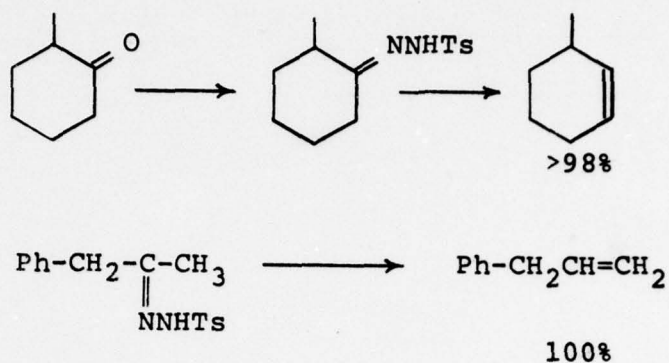
Interest in the chemistry of p-toluenesulfonylhydrazones has grown appreciably in recent years. Tosylhydrazones, as well as their alkali metal salts, have come into their own as important synthetic intermediates. For the purpose of providing the background for the chemistry investigated, a brief summary of current literature as it portrays tosylhydrazone chemistry will be discussed. The examples presented are by no means exhaustive. Considerations for the basis of selection include mechanistic interest, synthetic usefulness, and timeliness. Since the examples cover an extremely wide range of application, a meaningful classification scheme is somewhat difficult in a paper of this size. For our purposes, tosylhydrazone chemistry will be discussed in terms of four functional areas: (1) those reactions which are known to proceed through carbenes or dianions and generally produce products of increased unsaturation; (2) those reactions which involve reduction, including alkylative reduction, at the carbonyl carbon; (3) reactions involving molecules

containing heteroatoms other than oxygen and nitrogen; and (4) reactions involving deuterium incorporation.

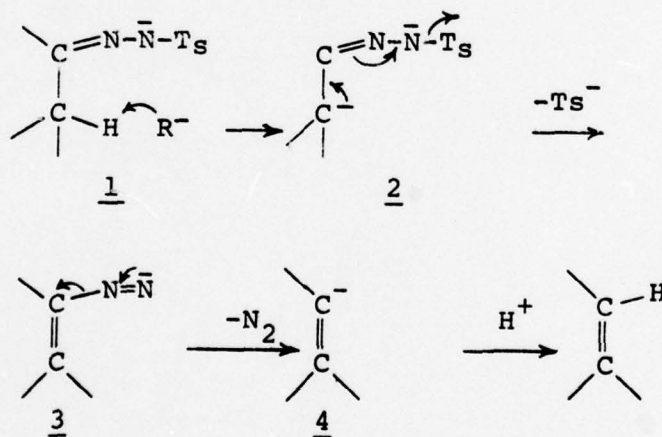
The first example of the first class of reactions (those producing greater unsaturation in the carbon skeleton) is the well known and synthetically useful conversion of a ketone to an alkene via the tosylhydrazone. This sequence was developed primarily by Shapiro (3, 6). Treatment of the tosylhydrazone with two equivalents or more of an alkyl lithium reagent (usually MeLi or n-BuLi) affords the olefin in excellent yields. In situations where it is



possible to form more than one alkene, the less substituted alkene is formed almost exclusively (3, 6). It is quite apparent from the following examples that acidity of the  $\alpha$  protons is not as important as once thought. Shapiro has postulated that "regiospecificity is largely controlled by the configuration of the carbon-nitrogen double bond ...



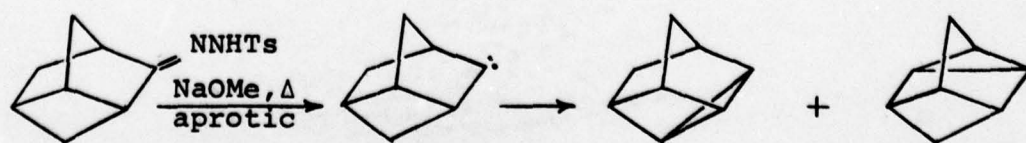
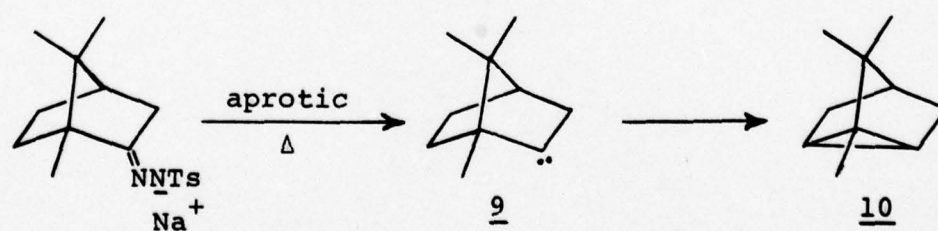
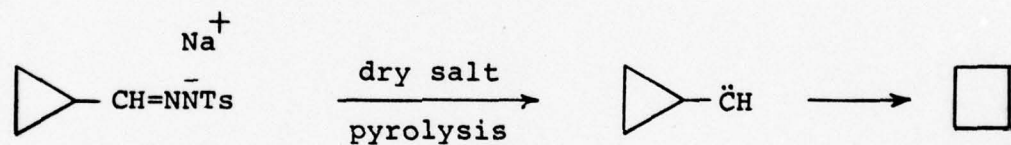
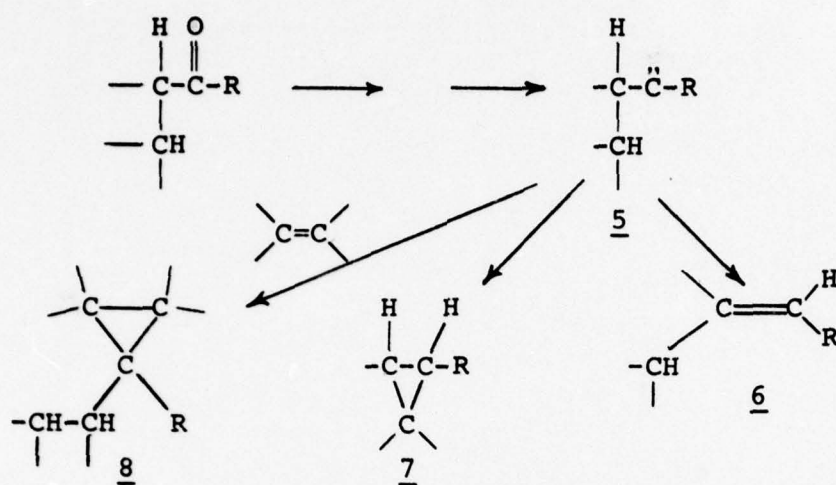
an  $\alpha$ -hydrogen syn to the tosyl group is selectively eliminated" (6). The mechanism proposed for the formation of the alkenes involves a dianion intermediate 2 shown in scheme 1.



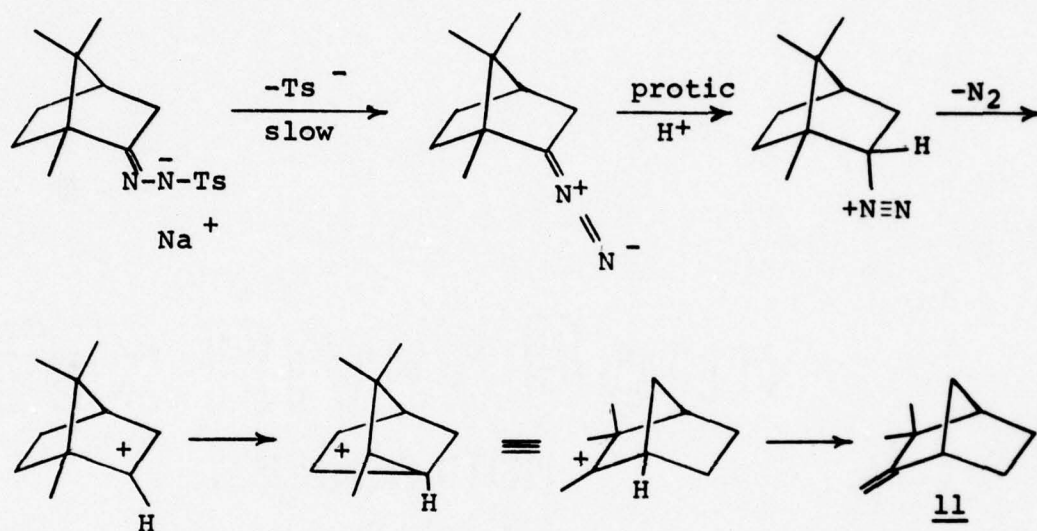
Scheme 1

Loss of  $\text{N}_2$  from 3 produces the mono anion 4 which abstracts a proton from the solvent. It was once believed that the abstraction of a proton from 1 and the loss of  $\text{Ts}^-$  were concerted (thus bypassing the dianion 2). Recently, how-





If the decomposition is conducted in protic solvents the reaction proceeds through a carbonium ion mechanism (1, 2, 4, 5, 8). This mechanism is illustrated for the case of camphor tosylhydrazone (8) in scheme 3.

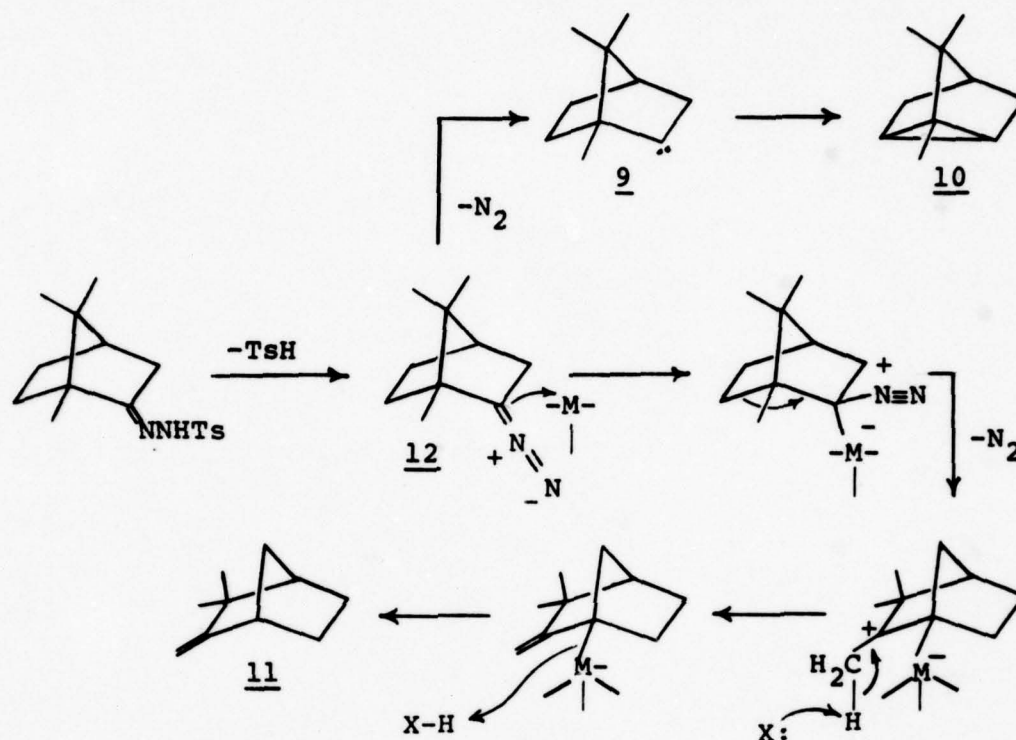


Similarly, decomposition of cyclopropanecarboxaldehyde tosylhydrazone in protic solvents yields bicyclobutane (4, 5):



Along a similar vein, Shapiro (7) has investigated the action of trivalent metal cations upon tosylhydrazones. Treatment of camphor tosylhydrazone with  $\text{LiAlH}_4$  in THF gives a 60:40 mixture of camphene 11 and tricyclene 10. The tricyclene arises from the insertion of the carbene 9 while the

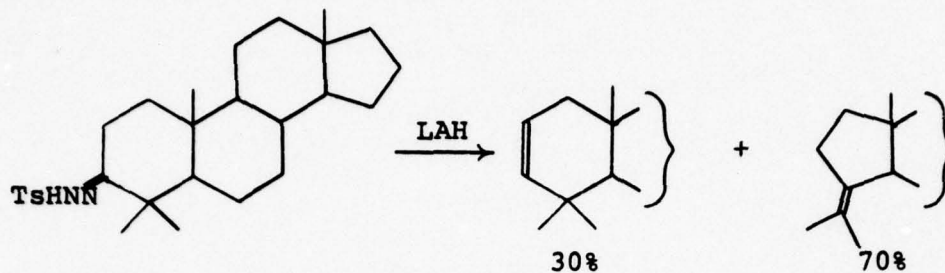
camphene results from reaction of the metal with diazocamphane 12. The proposed mechanism is shown in scheme 4.



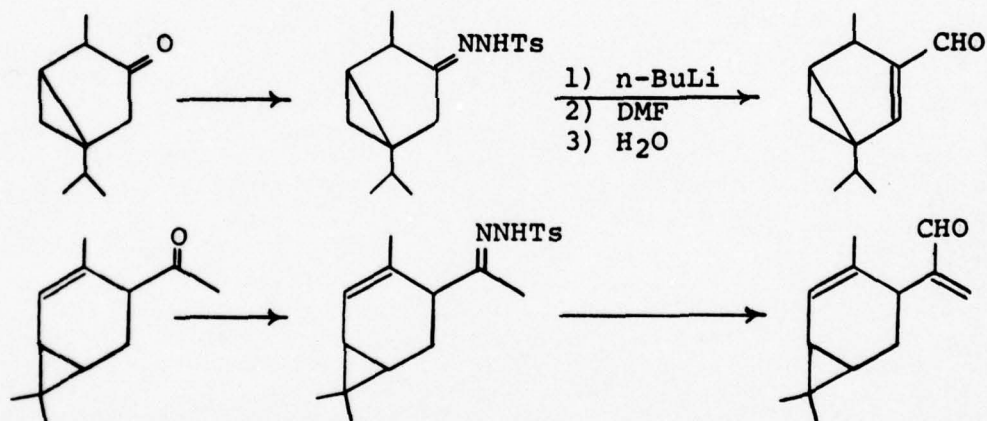
Scheme 4

Additional work using LiBH<sub>4</sub> led to an increased amount of tricyclene due to the decreased ability of boron to interact with diazocamphane 12. The reaction with LAH has been applied to various steroids, generating the rearranged product as the major component (7).

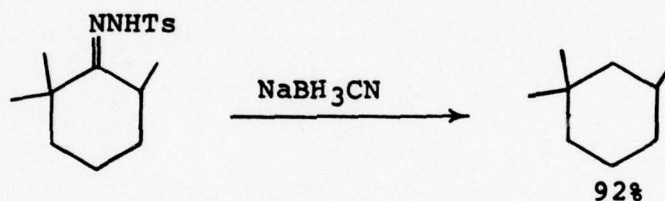
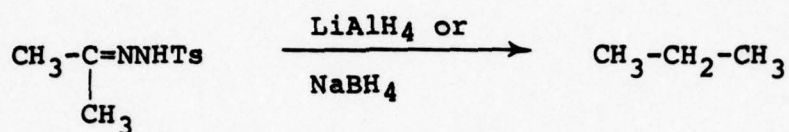
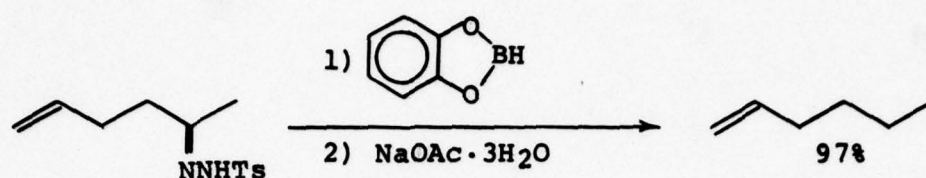
The final reaction of the first classification group offers a convenient and versatile route to  $\alpha,\beta$ -unsaturated aldehydes (11). The tosylhydrazone is treated with four equivalents of n-BuLi which eventually gives the mono anion



4 (scheme 1). A nucleophilic attack on the carbonyl carbon of dimethylformamide, followed by hydrolysis affords the unsaturated aldehyde in acceptable yields (ca. 60%).

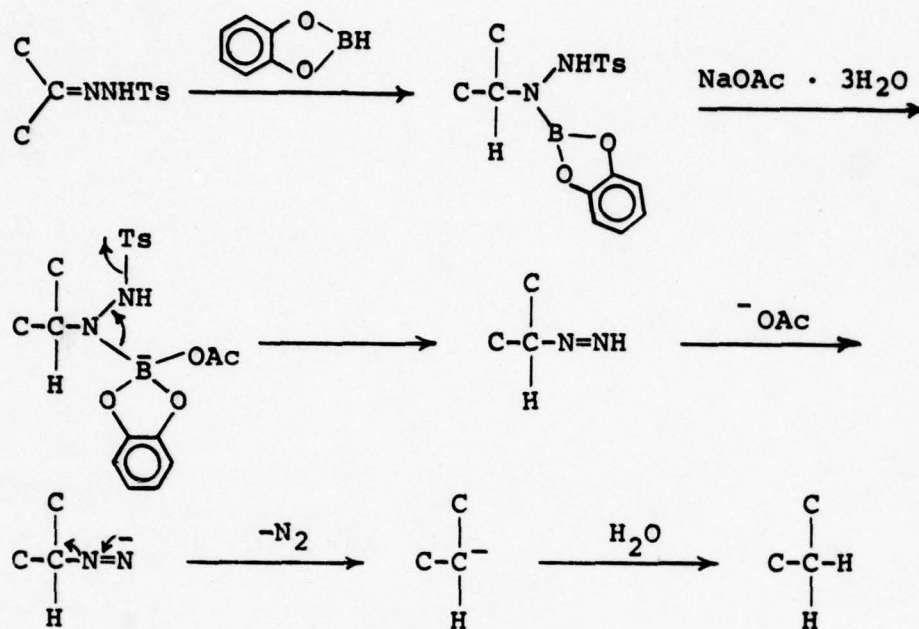


The second class of reactions is that in which there is some sort of reduction at the original carbonyl carbon. In the simplest case the carbonyl center is converted to a methylene. Catecholborane (25), lithium aluminum hydride (27), sodium borohydride (27), and sodium cyanoborohydride (28) have all been used very successfully for this purpose.

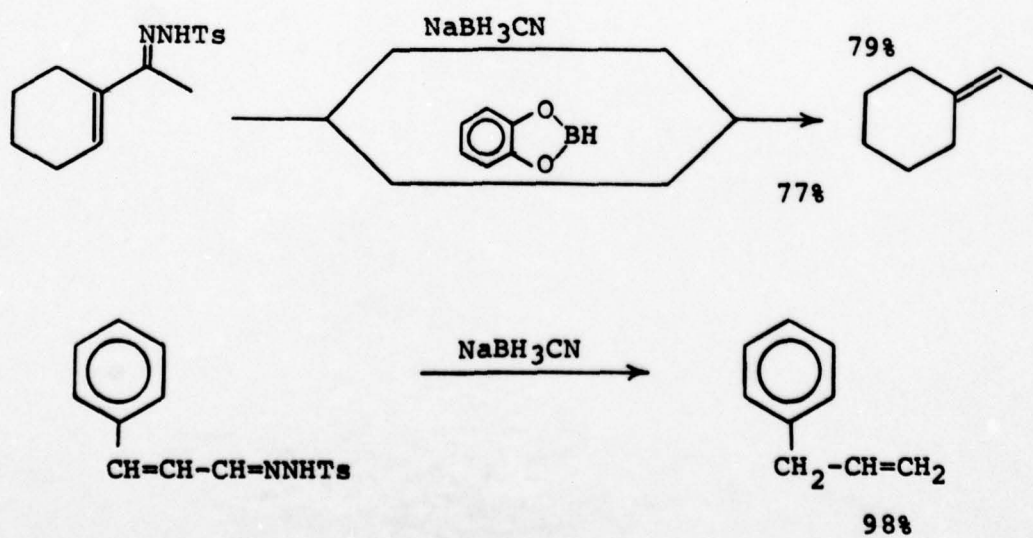


A mechanism for the catecholborane reaction has been proposed by Kabalka (25) in which there is an initial addition of the borane across the carbon-nitrogen double bond. This mechanism is shown in scheme 5.

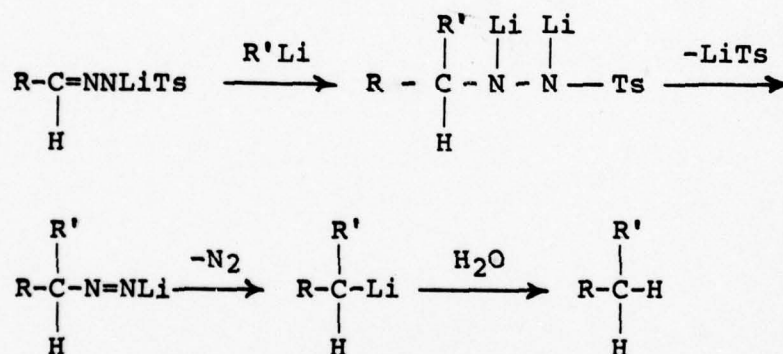
A second example of reduction with hydrogen is one in which there is migration of a double bond.  $\alpha,\beta$ -Unsaturated tosylhydrazones when treated with catecholborane (29) or sodium cyanoborohydride (26, 28) yield rearranged alkenes as products. This reaction might be particularly useful in the generation of exocyclic and non-conjugated double bonds. In view of the high percentage of rearranged alkene (exclusive in some cases) it is likely that the first step of the



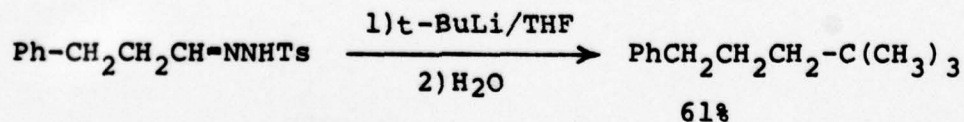
reaction is a 1,4-addition. This hypothesis might be checked by simply using catecholborane- $d_1$  and looking for vinyl protons in the NMR spectra.



The third and fourth examples of the reduction class are alkylative reductions. The reductive alkylation of aldehyde tosylhydrazones has been studied by Vedejs (12). He has found that the addition of alkyllithium reagents does not produce the dianion (as it does with ketone tosylhydrazones) but rather adds across the carbon-nitrogen double bond, due in part to decreased steric interactions and increased positive charge at the carbonyl carbon. Yields to date have been only moderate (30-60%). Vedejs' mechanism is shown in scheme 6, followed by a typical reaction.

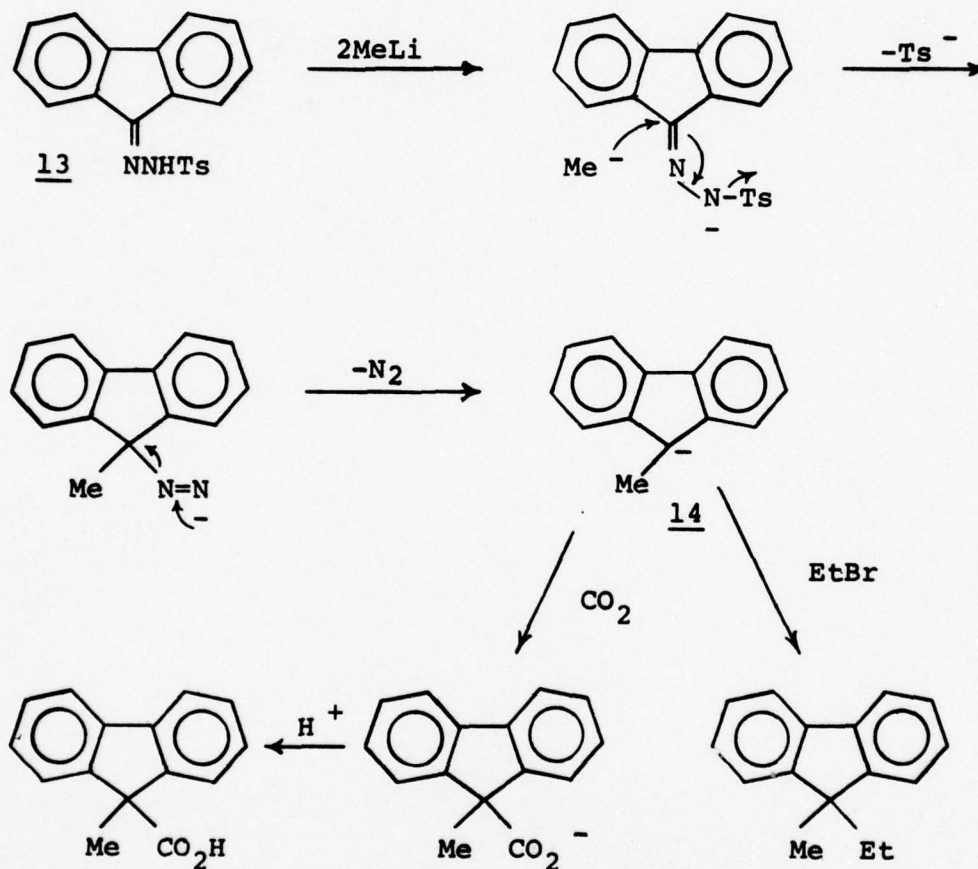


Scheme 6



The reductive alkylation of fluorenone tosylhydrazone 13 is the final example of the second class. Shapiro (9) has employed the tosylhydrazone as a successful precursor to the 9,9-disubstituted fluorenes. Since there are no  $\alpha$

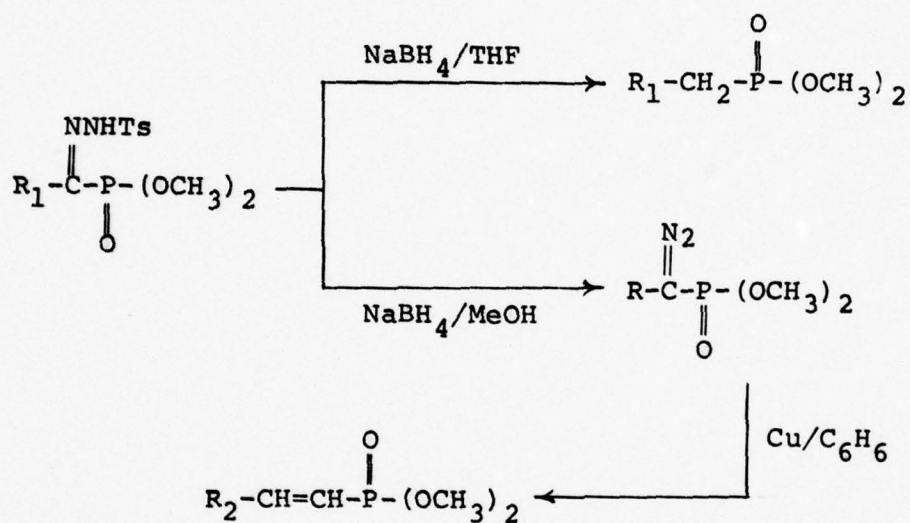
hydrogens to abstract, treatment of the tosylhydrazone with two equivalents of MeLi yields the anion 14 which then reacts as a typical nucleophile. This sequence is depicted in scheme 7.



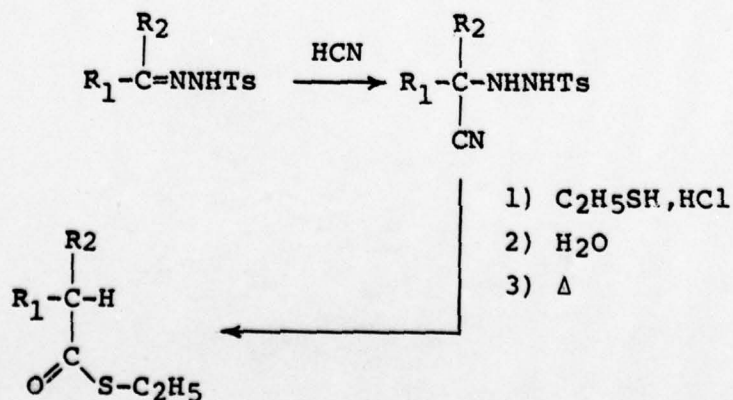
Scheme 7

The third class of tosylhydrazone chemistry deals with molecules containing the heteroatoms phosphorus and sulfur. The discussion of this class will be brief but will illustrate some of the innovative uses of tosylhydrazones.

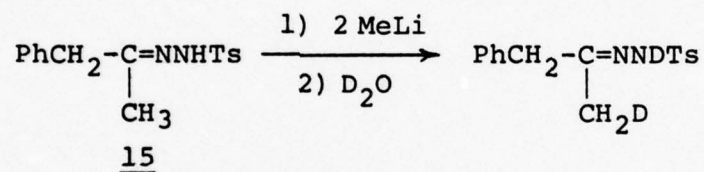
Rosini (22) has successfully reduced ketophosphonates via the tosylhydrazone and has additionally synthesized various 1-diazoalkane phosphonates which are readily converted to alkene phosphonates upon treatment with a suspension of Cu/Benzene.



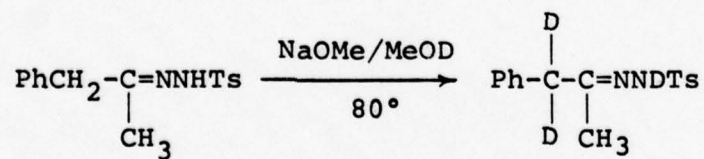
The addition of HCN across the tosylhydrazone C,N double bond is the first step in the preparation of alkyl thiocarboxylates in the method of Caglioti (23):



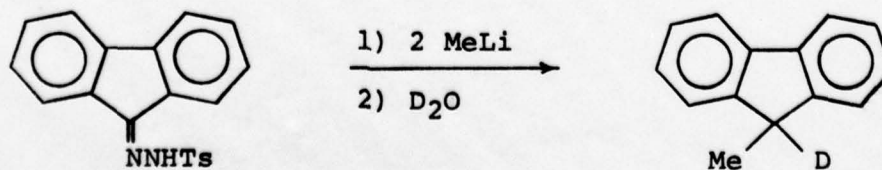
The fourth and final class of reactions are those which utilize the tosylhydrazone as an efficient means of incorporating deuterium. The use of deuterium labeling is extremely important in organic mechanistic studies and examples presented offer some attractive means of incorporation. Mechanisms for these reactions have been covered in the discussion of classes one and two and will not be covered here. The first example comes from Shapiro (6). Dianion 2 (scheme 1) may be trapped with  $D_2O$ :



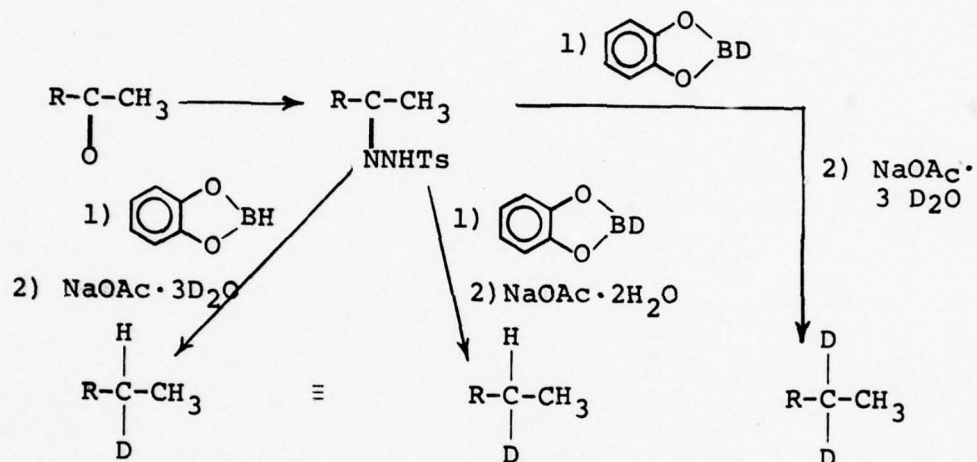
An interesting contrast is seen when 15 is treated with sodium methoxide in MeOD (6) resulting in perdeuteration at the benzylic position.



Shapiro has also trapped anion 14 (scheme 7) with  $D_2O$  in reductive alkylation sequence of fluorenones (9):



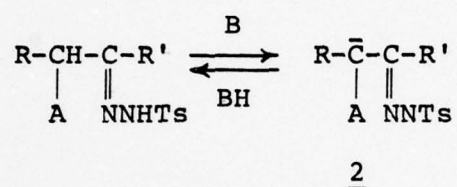
A method of deuterium incorporation successfully used by Kabalka (25), utilizes various combinations of catecholborane- $d_1$  and  $D_2O$  to effect the placement of one or two deuterium atoms. These are shown in scheme 8. Reductions using  $LiAlD_4$  are well known and will not be discussed.



Scheme 8



Assuming that  $C_\alpha$  is able to maintain stereochemical integrity during tosylhydrazone formation, rather drastic conditions (usually NaOMe or MeLi) are then employed in the formation of the alkali metal salt and its subsequent decomposition (a common preparative carbene sequence). As previously seen, stereochemistry at  $C_\alpha$  could be affected.



Quite obviously, Shapiro's elimination procedure (3, 6) (scheme 1) destroys  $C_\alpha$  stereochemical integrity intentionally on one side for sure, and possibly both sides.

Considering the wide range of tosylhydrazone usage, there are a large number of situations in which it is desirable to maintain stereochemical integrity at  $C_\alpha$ . This research group alone has had numerous occasions arise in which a knowledge of the  $C_\alpha$  stereochemistry was critical. (One such instance is described in Part Two of this thesis.) It would be very desirable then to have some method available for the determination of  $C_\alpha$  stereochemistry. The paramount consideration is, of course, that whatever analytical method is chosen, it must be completely passive with respect to  $C_\alpha$ . Of lesser importance are such factors as cost, convenience, simplicity and speed.

Practically speaking, there are two alternatives. The first is a direct comparison of ketone and tosylhydrazone spectra (uv, ir, nmr). Mass spectral data is not likely to be of much help (even when  $C_{\alpha}$  contains deuterium) since molecules containing more than one or two heteroatoms generally produce erratic results (33). Additionally, the tosyl portion of the spectra may dominate or entirely mask any information concerning  $C_{\alpha}$ . The use of shift reagents may be of some help in these cases (nmr).

The second approach involves the conversion of the tosylhydrazone back to the ketone followed by spectroscopic analysis of the two ketones. Spectra may now be compared directly without interference. The obvious disadvantage is that one runs the risk of having the cleavage reaction affect the stereochemistry at  $C_{\alpha}$ . In fact if the stereochemistry does turn out to be different, the change may have occurred during the formation of the tosylhydrazone, its cleavage, or both. Although the literature offers an abundance of cleavage methods, there are no studies which were concerned with the question of  $C_{\alpha}$  stereochemistry. Several methods of tosylhydrazone cleavage are shown in Table 1.

The basic approach used was to look for a cleavage reaction whose conditions were mild enough so as not to cause enolization at  $C_{\alpha}$ . Additionally, a reaction of high yield was desirable. The stereochemical trap chosen was

Table 1. Tosylhydrazone Cleavage Methods.

General Method	Specific Reagents
exchange methods	pyruvic acid (21)
	acetone (18)
	acetone/BF <sub>3</sub> (19)
oxidative methods	ozonolysis (14)
	sodium hypochlorite (16)
	N-bromosuccinimide (17)
	sodium peroxide (20)
non-redox	titanous ion (15)

simple but very conclusive. Through the use of deuterium labeling at C<sub>α</sub> (which is easily accomplished) the initial ketone and final ketone (that which had been to tosylhydrazone and back) could be conveniently compared by low voltage mass spectroscopy (Appendix B). No loss of deuterium would mean that enolization takes place in neither the formation nor cleavage of the tosylhydrazone. Furthermore, stereochemical integrity at C<sub>α</sub> is maintained. However, if there is a loss of deuterium, further experiments would be necessary to determine which step contributed to the loss of deuterium. Since neither of the two reactions are capable of increasing the amount of deuterium, there is no way for one reaction to coincidentally negate the effect of the other.

Eight methods in common use were applied to the cleavage of camphor tosylhydrazone. The results are summarized in Table 2.

Table 2. Camphor Tosylhydrazone Cleavage Results.

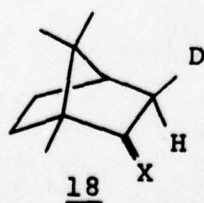
Method	% Conversion <sup>a</sup>	Additional Products <sup>b</sup>
acetone or acetone/H <sup>+</sup>	30-40	yes
cyclopentanone	55	yes
CH <sub>3</sub> I/95% EtOH	0	yes
NaOCl	20	yes
ozone	5	no
NBS/MeOH, Acetone	20-40	yes
NBS/H <sub>2</sub> O, Acetone	50-70 <sup>c</sup>	yes
pyruvic acid	50-70	yes

<sup>a</sup>VPC analysis; p-cymene used as internal standard

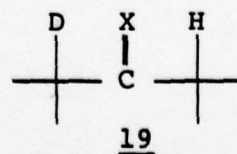
<sup>b</sup>Additional products were not identified

<sup>c</sup>86-100% with diisopropyl ketone tosylhydrazone; 98% with 6,6-dimethyl-norbornan-2-one tosylhydrazone

Exo-3-deuteriocamphor (36) 18 and 2-deuterio-2,4-dimethyl-3-pentanone 19 (diisopropyl ketone) were selected as representative ketone substrates.



a) X=O  
b) X=NNHTs

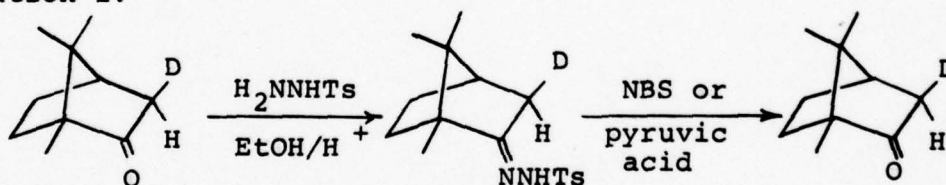


a) X=O  
b) X=NNHTs

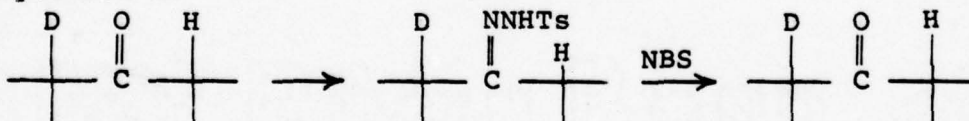
In the case of 18a it has been shown (35,36) that the exo-3-deuterium should be lost in preference to the endo-3-hydrogen (even considering the isotope effect). Thus enolization of either 18 or 19 should result in a loss of deuterium.

Two cleavage methods were also selected for use in the initial phase of experiments. These were chosen strictly on the basis of yield of ketone (Table 2). The first method was the exchange with pyruvic acid after the method of Hershberg (21). The second was a modification of Rosini's NBS reaction (17) using H<sub>2</sub>O in place of MeOH. The substrates and processes of interest are summarized by the following equations:

Equation 1:



Equation 2:



Mass spectral results for equations 1 and 2 are summarized in Tables 3 and 4 respectively.

It was also of interest to know whether or not any deuterium may have been lost from C<sub>α</sub> during the formation of the lithium salts of tosylhydrazones since these salts

Table 3. Mass Spectral Results for the Camphor Sequence (Equation 1).

d Content of Initial Ketone	d Content of Final Ketone	
	pyruvic acid	NBS
% d <sub>0</sub> 7.0 ± 0.4 <sup>a</sup>	63.1 ± 1.0	7.1 ± 0.4
% d <sub>1</sub> 79.3 ± 0.4	32.8 ± 1.0	79.2 ± 0.4
% d <sub>2</sub> 13.7 ± 0.3	4.1 ± 0.5	13.7 ± 0.2

<sup>a</sup>Standard deviation

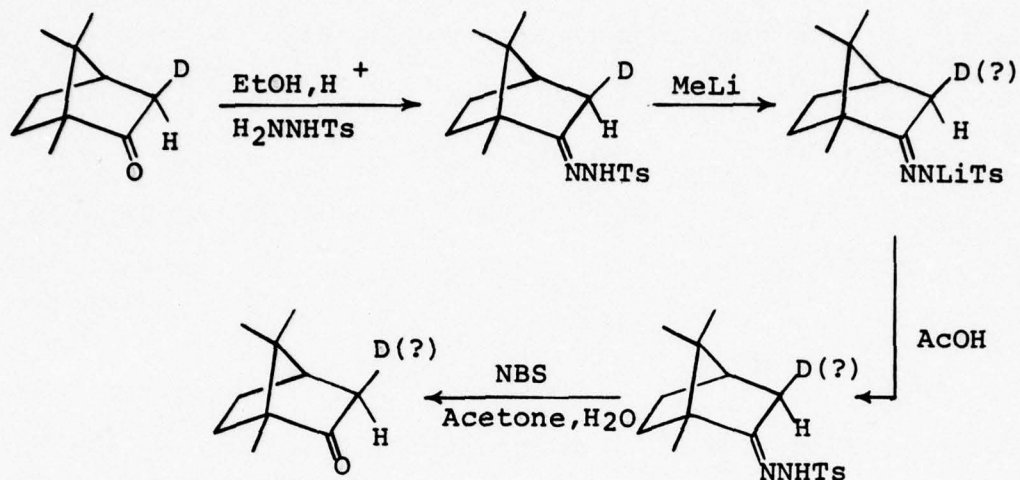
Table 4. Mass Spectral Results for the Diisopropylketone Sequence (Equation 2).

d Content of Initial Ketone	d Content of Final Ketone	
	NBS	
% d <sub>0</sub> 27.4 ± 0.6 <sup>a</sup>	27.7 ± 1.1	
% d <sub>1</sub> 49.1 ± 0.6	49.8 ± 1.1	
% d <sub>2</sub> 23.5 ± 0.5	22.5 ± 0.9	

<sup>a</sup>Standard deviation

are widely used as carbene precursors. The lithium salt of camphor tosylhydrazone was prepared using exactly an equivalent of MeLi. The salt was converted back to the tosylhydrazone with 0.1 N acetic acid. NBS was then used to regenerate the ketone. This sequence is summarized in scheme 10. The mass spectral results are summarized in Table 5.

In looking at the pyruvic acid cleavage (Table 3) of camphor tosylhydrazone, it is readily apparent that C<sub>α</sub> has been altered as indicated by the large increase in % d<sub>0</sub>



Scheme 10

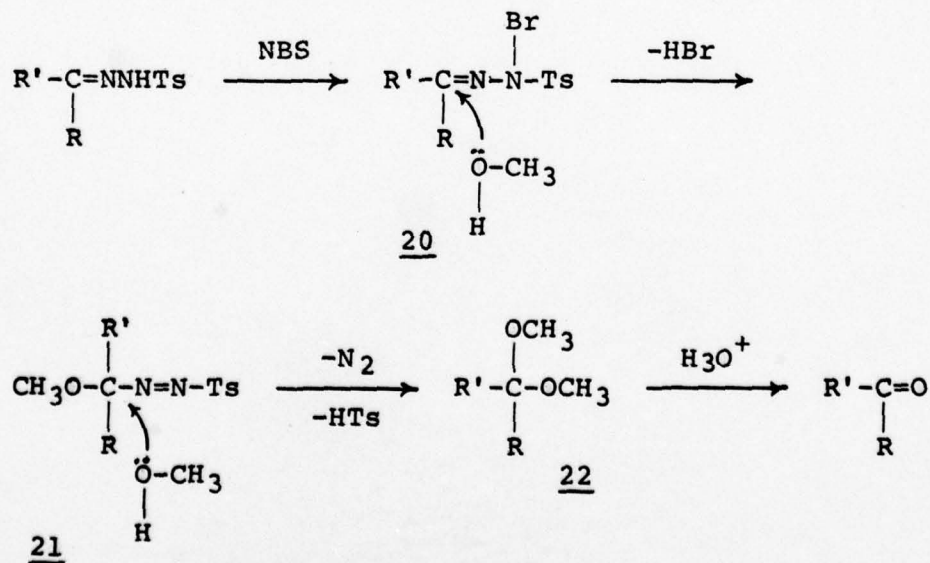
Table 5. Mass Spectral Results for the Lithium Salt Sequence (Scheme 10).

d Content of Initial Ketone		d Content of Final Ketone	
% d <sub>0</sub>	7.0 ± 0.4 <sup>a</sup>		7.4 ± 0.4
% d <sub>1</sub>	79.3 ± 0.4		78.8 ± 0.6
% d <sub>2</sub>	13.7 ± 0.3		13.8 ± 0.8

<sup>a</sup>Standard deviation

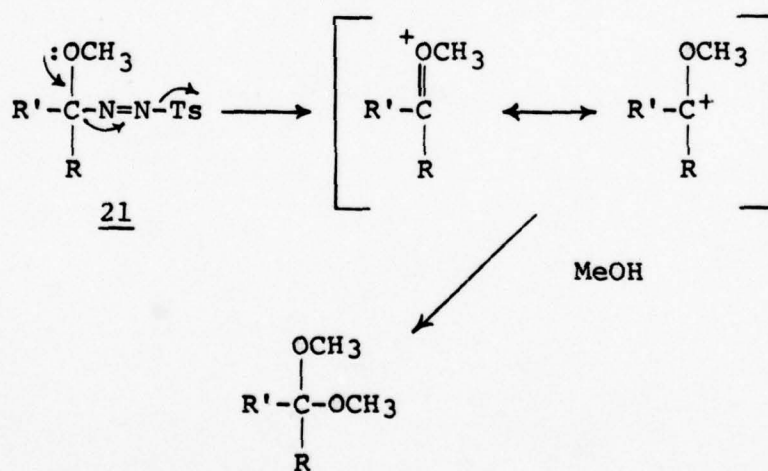
(7.0% → 63.1%). Percent d<sub>1</sub> and d<sub>2</sub> show a corresponding decrease. At this point one could only conclude that enolization had occurred either in the tosylhydrazone formation or subsequent cleavage (or in both). However, when coupled with the results from the NBS cleavage some definite conclusions may be drawn. In the NBS reaction there is no loss of deuterium and therefore no enolization at C<sub>α</sub> in

either the tosylhydrazone formation or cleavage. Furthermore, since the tosylhydrazones were all prepared in the same manner, we know that the pyruvic acid exchange method of cleavage does cause enolization. The formation of the lithium salt of camphor tosylhydrazone also is free of any enolization at  $C_\alpha$  as evidenced by the data in Table 5. The  $d_0$ ,  $d_1$ , and  $d_2$  composition is the same before and after the reaction sequence. What do the results indicate in relation to the original problem? There does exist a suitable method for checking the stereochemistry at  $C_\alpha$  in ketone tosylhydrazone sequences. The method of Rosini (17) using N-bromosuccinimide is simple, fast, and no detectable enolization at  $C_\alpha$  occurs. From a theoretical standpoint, Rosini envisions the mechanism in Scheme 11.



Scheme 11

Presumably the NBS serves as a  $\text{Br}^+$  transfer agent (30, 31) in the formation of the N-bromotosylhydrazone 20. HBr is then easily expelled following a nucleophilic attack by MeOH on the carbonyl carbon leading to the mono-ether 21. The next step is rather curious, however. It may be inferred from the representation presented that Rosini views the second attack by MeOH and expulsion of  $\text{N}_2$  as a concerted ( $\text{S}_{\text{N}}2$ ) process. In view of the reaction conditions (polar, ionic), the tertiary center, the excellent leaving groups, and the presence of a methoxy group to greatly stabilize the incipient carbonium ion, an  $\text{S}_{\text{N}}1$  mechanism seems much more reasonable (Scheme 12).



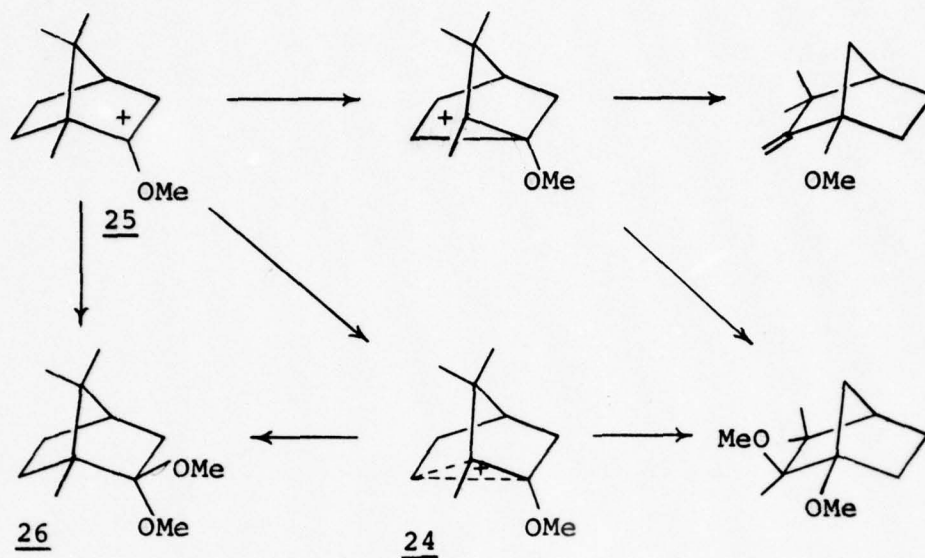
Scheme 12

In the case of camphor, where an  $\text{S}_{\text{N}}2$  displacement is especially unlikely due to steric considerations, a carbonium ion of some sort is almost certain. It could be asked whether a non-classical carbonium ion 24 might be

involved. Based upon the most likely configuration of the methoxy group (exo), the answer is probably not, since the leaving group must necessarily be endo.



Even if the non-classical ion is not formed directly, the classical ion may "leak" over to the non-classical. There is also the possibility that the classical ion may rearrange to a different classical ion. An analogous case was covered earlier. When camphor tosylhydrazone is treated with  $\text{LiAlH}_4$ , a high percentage of camphene is formed, presumably proceeding through a rearranged carbonium ion. In the event of the generation of either non-classical or rearranged carbonium ions, a mixture of products might well be expected. Scheme 13 depicts some of these possibilities. On the other hand, it could be argued that since the classical ion 25 is probably formed initially, rearrangements are not too likely due to the fact that the methoxy group stabilizes 25 and thus leads only to 26. The experimental facts are that Rosini's procedure always leads to a large number of unidentified products (up to ten according to VPC analysis). In fact the ketone rarely accounted for more than 30% of the product mixture. Our modification of Rosini's procedure (using  $\text{H}_2\text{O}$  in place of  $\text{MeOH}$ )



Scheme 13

significantly reduced the number of additional products and consequently gave us much better yields of the desired ketones.

As for further experimentation, the most interesting work focuses around a more precise understanding of the NBS reaction. Numerous unidentified peaks need to be characterized, some of which may reveal details of the mechanism. A kinetic study of this reaction would be an interesting challenge, especially since the reaction goes to completion in something less than 60 seconds. In the light of the success of tosylhydrazone cleavage (NBS), a logical step would be to extend this reaction to other classes of similar compounds: hydrazones, 2,4-dinitrophenylhydrazones, oximes, or semi-carbazones for instance.  $C_{\alpha}$  stereochemistry is

important in these cases as well. Rearranged products  
could well be of interest here also.

## EXPERIMENTAL

Melting points were measured using either a Buchi melting point apparatus or a Mel-Temp device and are uncorrected. NMR spectra were recorded at 100 MHz with a Varian HA-100 or at 60 MHz with a Varian Anaspec EM-360. Infrared spectra were obtained with either a Beckman IR-8 or a Perkin-Elmer Model 621. Vapor-phase chromatographic analyses were carried out using a Varian Aerograph A-90-P, an 18 ft. x 0.25 in. 5% OV-17 on 60/80 chromosorb G column; yields were determined using p-cymene as an internal standard; the VPC detector was interfaced with a Hewlett Packard 3373B digital integrator.

Deuterium analyses were accomplished via a low-voltage, mass spectral technique using a Varian MAT CH-7 spectrometer, interfaced with a PDP-8/m computer. Before analyzing a deuterated sample, the non-deuterated sample was run in order to determine the exact intensities of P, P+1, and P+2 at a voltage that eliminated the P-1 peak (usually 18-20 eV). The molecular ion region was scanned 10-20 times; the mean and standard deviations are reported. (For a more complete description of the technique, see Appendix B.)

Spectral grade  $\text{CDCl}_3$  was supplied by Merck, Sharp, and Dohme;  $\text{CCl}_4$  by Mallinckrodt;  $\text{D}_2\text{O}$  by Stohler Isotope Chemicals. Pyruvic acid was purified by distillation in vacuo using a Kugelrohr distillation apparatus.

2-Deuterio-2,4-dimethyl-3-pentanone.  $\text{CH}_3\text{OD}$  was prepared by the general method of Streitwieser (34). Using carefully dried apparatus, a solution prepared from 15 ml of  $\text{CH}_3\text{OD}$ , 3.0 g (0.026 mol) of ketone, and 0.08 g of Na was stirred for 9 hr at room temperature. The solution was then quenched with  $\text{D}_2\text{O}$ , extracted with ether, washed with  $\text{H}_2\text{O}$ , and dried over  $\text{MgSO}_4$ . NMR ( $\text{CCl}_4$ )  $\delta$  2.7 (heptet, 0.9 H,  $J=7$  Hz), 1.06  $\delta$  (M, 12 H); mass spectrum %  $d_0 = 27.4 \pm 0.6$ , %  $d_1 = 49.1 \pm 0.6$ , %  $d_2 = 23.5 \pm 0.5$ .

2-Deuterio-2,4-dimethyl-3-pentanone tosylhydrazone. Ketone (2.2 g, 0.019 mol), tosylhydrazine (3.56 g, 0.019 mol), 40 ml of ethanol (95%), and 1 drop concn HCl were combined and the resulting solution placed on a steam bath for 4 hr. The solvent was largely removed by evaporation. Refrigeration produced 3.5 g (65%) of a white crystalline solid which was used without further purification, mp 95-99. An analytical sample of undeuterated tosylhydrazone had a mp of 106.9-108.7°C.

Anal calcd for  $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$ : C, 59.54; H, 7.85. Found: C, 59.66; H, 7.87.

3-Deuteriocamphor. An adaptation of the procedure of Tidwell (35d) was used. In a dry 250-ml round-bottom flask, 60 ml of reagent grade dioxane and 30 ml of  $\text{D}_2\text{O}$  were combined. The flask was cooled to 0°, and 0.08 g of Na was added in three portions. The ice bath was removed and the solution was allowed to come to room temperature. Camphor

(2.0 g, 0.013 mol) was dissolved in 5 ml of dioxane and then added to the above solution. After 30 hr of stirring, the solution was extracted with ether, washed with H<sub>2</sub>O, and dried over MgSO<sub>4</sub>. Mass spectrum % d<sub>0</sub> = 7.0 ± 0.4, % d<sub>1</sub> = 79.3 ± 0.4, % d<sub>2</sub> = 13.7 ± 0.3.

The Tosylhydrazone 18b and the Lithium Salt of Tosylhydrazone 18b. Tosylhydrazone 18b was prepared as described above for 2,4-dimethyl-3-pentanone, giving a 75% yield, mp 157-159° (2). The lithium salt of the tosylhydrazone was prepared by treating 18b (0.2916 g, 0.908 mmol) in 10 ml of THF with 1 equiv of methyllithium (2 M solution in THF). The lithium salt was then reconverted to tosylhydrazone by neutralization with 0.1 N acetic acid. This mixture was extracted with ether, washed with H<sub>2</sub>O and dried over MgSO<sub>4</sub>. Evaporation of solvent gave 80% recovery of 18b.

The Tosylhydrazone to Ketone Conversion Using N-Bromosuccinimide (NBS). This procedure is an adaption of the method of Rosini (17). Tosylhydrazone (10<sup>-4</sup> mol) and internal standards, if desired, were dissolved in a mixture of 14 ml of acetone and 4 ml of water. When dissolution was complete, the mixture was cooled to 0° using an ice/water bath. N-Bromosuccinimide (4 x 10<sup>-4</sup> mol) was then added. Stirring, using a teflon coated stir bar, was continued for 2 min. (Evolution of N<sub>2</sub> was apparent after 10-15 seconds, and the resulting solution was yellow). The

reaction was quenched with 1-2 ml of saturated sodium bisulfite. The ice bath was removed and the stirring continued while adding ca. 10 ml of water. The ketone was extracted with ether, and the combined organic extracts were washed with water, 10%  $\text{Na}_2\text{CO}_3$ , and then dried over  $\text{MgSO}_4$ .

The Tosylhydrazone to Ketone Conversion Using Pyruvic Acid. Tosylhydrazone ( $10^{-4}$  mol) was combined with  $10^{-4}$  mol p-cymene (internal standard), 4 ml of glacial acetic acid, 1 ml of  $\text{H}_2\text{O}$ , and 0.5 g of purified pyruvic acid. The solution was heated at reflux for 2 hr. After cooling it was extracted with ether; washed with  $\text{H}_2\text{O}$ , 10%  $\text{Na}_2\text{CO}_3$ ,  $\text{H}_2\text{O}$ , and dried over  $\text{MgSO}_4$ . Yields were typically ca. 75%.

## CARBENE CHEMISTRY

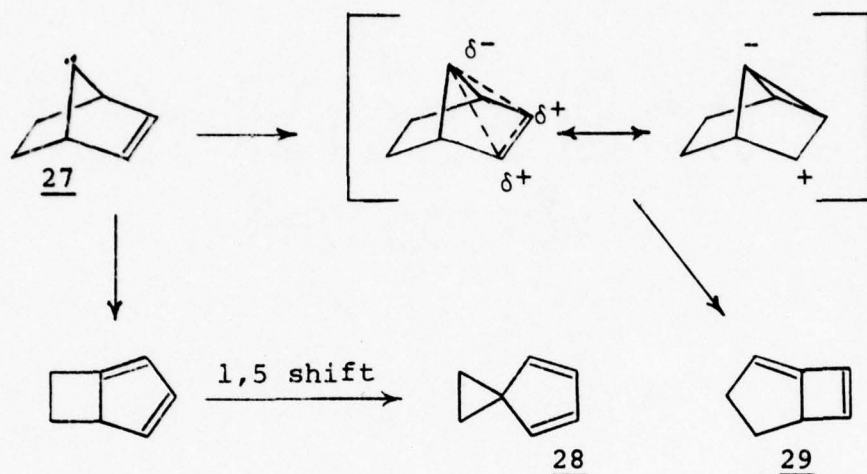
PART II. HYDROGEN MIGRATION IN  
2-CARBENA-6,6-DIMETHYLNORBORNANE

## INTRODUCTION

Part II of this thesis investigates the behavior of 2-carbena-6,6-dimethylnorbornane. Examining the chemistry of this carbene could aid considerably our understanding of non-classical intermediates and the stereochemistry of 1,2 hydrogen migrations. This introduction provides the background material pertinent to these areas and consists of three sections: (1) the possible existence of non-classical carbenes, (2) theoretical aspects of the 1,2 hydrogen migration, and (3) experimental findings as they relate to the stereochemistry of the 1,2 hydrogen migration.

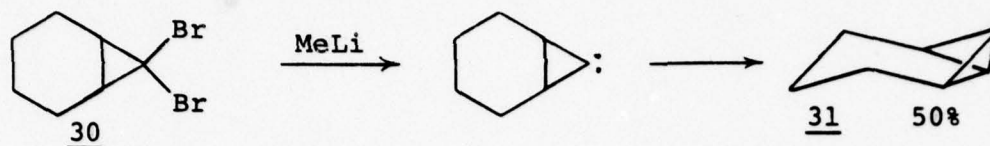
Since the hybridization of the carbonium ion and the singlet carbene are both  $sp^2$ , delocalization utilizing the empty p-orbital of the carbene analogous to delocalization in carbonium ions might be expected. Non-classical delocalization of the carbonium ion is most widely accepted in systems where there is participation by either cyclopropyl or pi bonds (55-59). Evidence is growing that this may also be true in the case of carbenes. Moss and co-workers (62) have reported on the thermal decomposition of 7-norbornenone tosylhydrazone 27 which gives 28 (67%) and 29 (7%) as the

major products. A bishomocyclopropenyl interaction is advanced to account for the formation of 29 as shown in scheme 14.

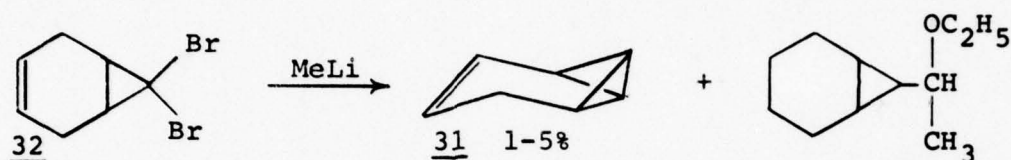


Scheme 14

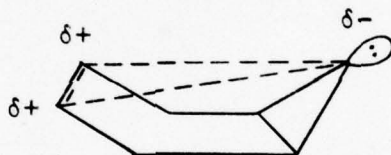
Intuitively, it is expected that a delocalized (non-classical) carbene should be of lower energy and thus more selective in its reactions than the non-delocalized carbene. Two independent studies confirm this. The Klumpp and Vrieling (64) treatment of 7,7-dibromobicyclo[4.1.0]heptane 30 with MeLi gives tricyclo[3.1.1.0<sup>6,7</sup>]heptane 31 as the major product in 50% yield. On the other hand, treatment of 7,7-dibromobicyclo[4.1.0]hept-3-ene 32 with MeLi produces only 1-5% of the tricyclic compound 31. The major product involves an intermolecular insertion into the C,H bond of the ether solvent. The authors suggested that the



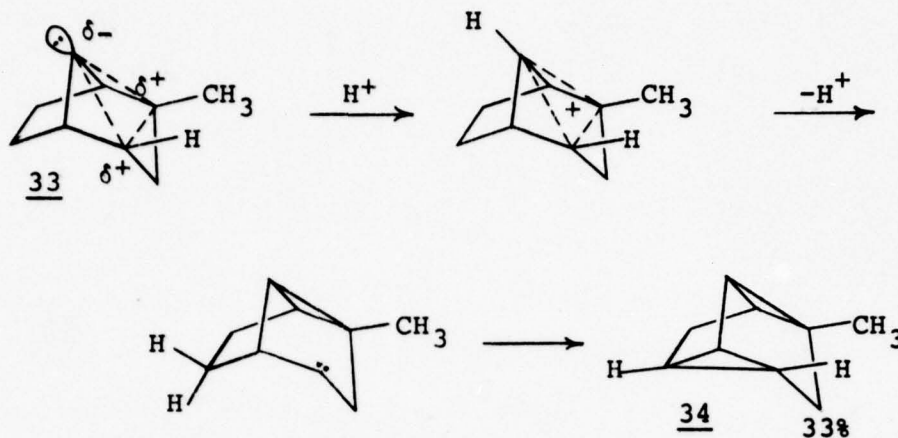
pi-bond is able to stabilize the carbene through the boat



conformation, making it more selective.



Strong evidence for carbene delocalization by a cyclopropyl bond has been provided by Freeman and co-workers (67) who considered the endo-8-carbenatricyclo[3.2.1.0<sup>2,4</sup>]octane intermediate **33**. The authors postulated that an intermolecular process involving the solvent and the delocalized carbene was responsible for the insertion product **34**. No 1,3 insertion of the initial carbene is observed which contrasts sharply with the results of Moss and Whittle (68) in the 7-carbenanorbornane system **35**. The complete lack of an analogous insertion product in the case



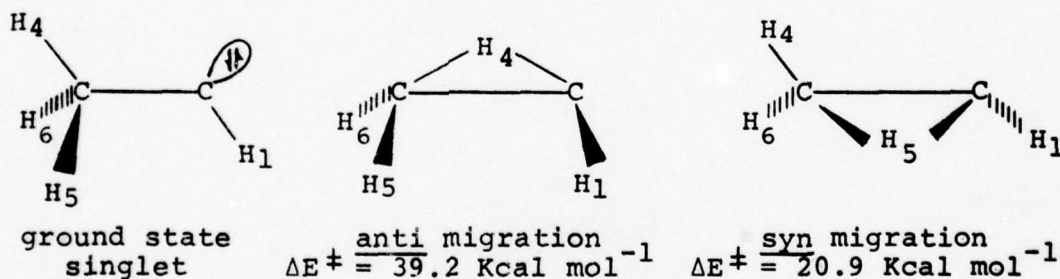
of 33 was supposedly the consequence of a longer-lived carbene through cyclopropyl delocalization.



The 1,2 migration of hydrogen in carbenes to generate alkenes is commonplace (53). The simplest and most studied of all 1,2 migrations is that of methylcarbene (ethylidene) to ethylene. This reaction could take place in a variety of ways depending upon the electronic state of the reactant carbene and the product ethylene. Yates *et al.* investigated several of these possibilities using the principle of least motion (PLM) approach (46, 50). Interestingly, the pathway of least energy is the triplet-triplet conversion. The second lowest is singlet-singlet. In both these pathways, the  $\text{CH}_2$  planes of the ethylene are perpendicular. The

singlet carbene to ground state (planar) ethylene is third lowest in total energy.

A marked contrast to the PLM conclusions is found in a non-empirical, *ab initio* study, also by Yates (51). Surprisingly, he reports that the groundstate of methylcarbene is actually the singlet, albeit by only  $0.3 \text{ kcal mol}^{-1}$ . The reaction pathway of lowest energy is from the lowest lying singlet carbene to the ground state, planar ethylene. Additionally, Yates calculates the transition state energies of the syn and anti modes of migration. Thus the migration of either syn hydrogen ( $H_5$  or  $H_6$ ) results in a transition state  $20 \text{ kcal mol}^{-1}$  lower in energy than that



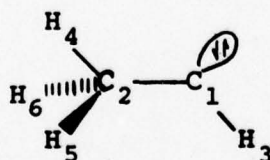
in anti ( $H_4$ ) migration). The syn hydrogens are  $30-35^\circ$  from being coplanar with the empty p-orbital of the carbene shown above.

A follow-on report by Yates (47) elaborates on the syn migration. This study employs a charge distribution analysis and reveals that charge transfer is not a gradual process. Charge transfer from the methyl to the methine

carbon is nearly completed by the time the transition state is reached. The author believed that such an early charge transfer implied a pseudo-hydride migration in the early stages of the reaction. Yates provided the following summary:

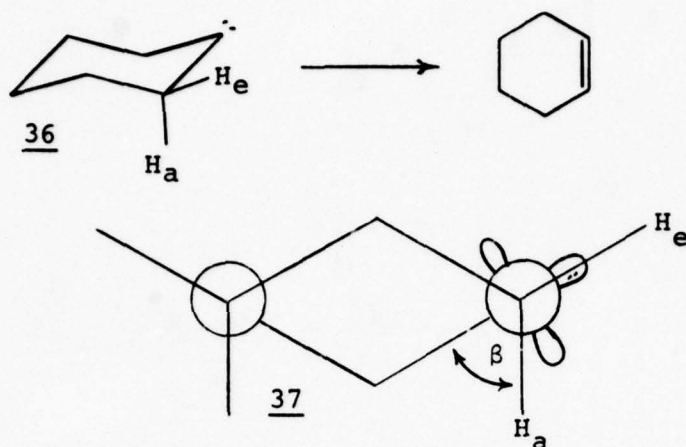
The simplest description of the mechanism of the electronic rearrangement is to envisage an electron pair "following" a migrating hydrogen toward the center of the carbon-carbon bond spreading its density rapidly about that bond until it is fully delocalized and thus becomes the new ethylenic  $\pi$  bond. After the transition state, the hydrogen continues its motion as a pseudo-proton toward the lone pair which, because of its spatial environment, does not contribute to the  $\pi$  bond but is utilized for the formation of the new C-H bond (47).

A semi-empirical study by Bodor and Dewar (49) also predicts a preference for syn migration. Dewar, however, explains the syn preference in terms of hyperconjugative effects between the C-2-H-5 and C-2-H-6 orbitals and the empty p-orbital of the singlet carbene. The dihedral angle



$\angle H_5 C_2 C_1$  is  $173.7^\circ$  in the reactant carbene, rendering  $H_5$  and  $H_6$  slightly non-equivalent. The formal charges  $-0.0356$  ( $H_4$ ),  $-0.0106$  ( $H_5$ ), and  $+0.0055$  ( $H_6$ ) appear to support Dewar's claim for a hyperconjugative type interaction.

1,2 Hydrogen migrations have also been studied in the cyclohexylidene 36 to cyclohexene reaction. The issue of

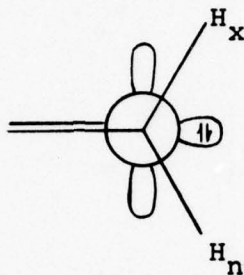


preferential axial vs. equatorial migration is presently far from settled. Using the PLM approach Yates (46) has calculated the minimum energy pathways for both  $H_a$  ( $\beta=60^\circ$ ) and  $H_e$  ( $\beta=180^\circ$ ) migration. The axial migration energy turns out to be substantially lower and the author indicated an "overwhelming preference" for the axial (syn) migration.  $H_a$  is  $30^\circ$  from coplanarity with the empty p-orbital while  $H_e$  is  $90^\circ$ .

Dewar (49) has reached the identical conclusion on the basis of a semi-empirical MINDO/2 study. However, a recent report by Kyba (39) indicated otherwise. Using both MNDO and MINDO/2, he calculated the activation enthalpies for both migrations. Both methods reveal that the activation enthalpies are essentially equal, the equatorial pathway being slightly less than the axial.

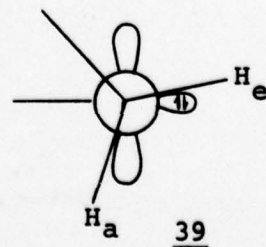
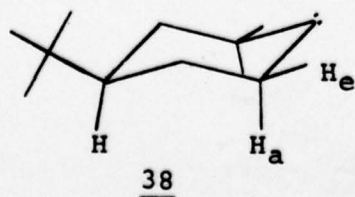
The final system for theoretical consideration is the 2-norbornyl system. The only study on this molecule to date is one by Yates (46) using the least motion technique.

For the cation, exo hydride migration is strongly favored from a consideration of calculated  $E_{\min}$  values as well as total atomic motion, a conclusion independently reached by



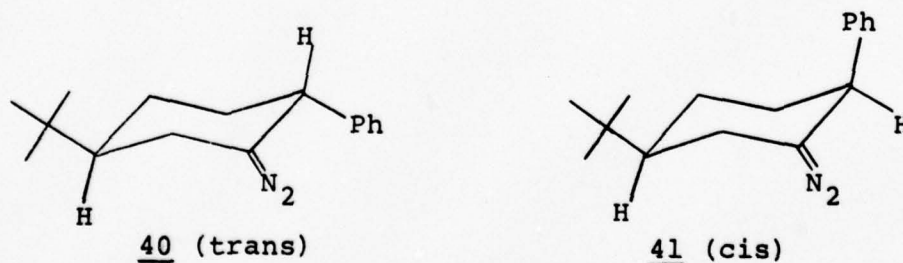
Schleyer (66). The carbene is much less discriminatory which is what one would intuitively expect. From an orbital overlap point of view,  $H_x$  (exo) and  $H_n$  (endo) are symmetrically displaced about the plane containing the two carbon atoms and the filled  $sp^2$  orbital of the carbene. Apparently due to slight torsional interactions, the exo hydrogen is slightly biased toward the empty p-orbital as  $E_{\min}$  calculations favor the exo migration by a very small amount.

Turning now to experimental results, the cyclohexyl and norbornyl systems will be discussed. Kyba and John (38) have investigated the 4-tert-butyl-2,2-dimethylcyclohexylidene system 38 and reported a surprising lack of stereo-

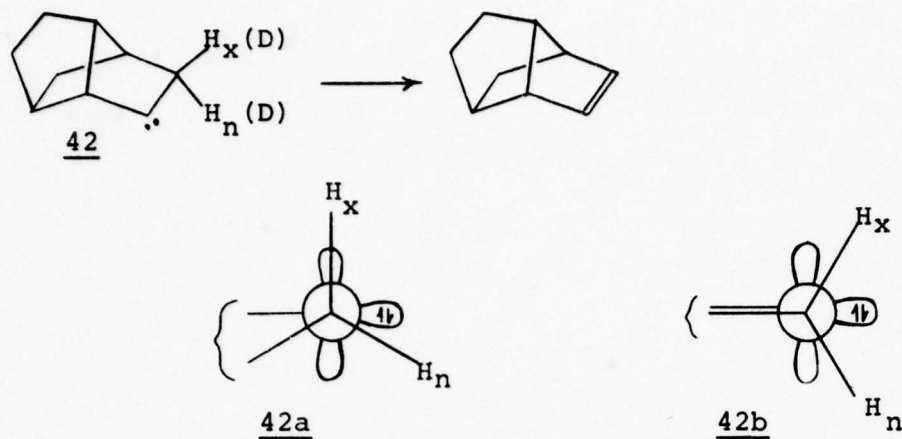


selectivity. Due to the equatorial t-butyl group it was supposed that this system was conformationally rigid. Furthermore, models indicate that  $H_a$  is  $\approx 12^\circ$  from coplanarity with the empty p-orbital, while  $H_e$  is  $\approx 12^\circ$  from coplanarity with the filled carbenic orbital. Thus it appeared to be a good system to test the hypotheses of Yates (46) and Dewar (49) favoring the axial migration (coplanarity with the empty orbital) by a large margin. The migratory ratio is 1.5:1 (axial:equatorial). Thus the predictions of Yates and Dewar are not realized. These findings prompted Kyba's own theoretical study (39), the results of which are in close agreement with his experimental results.

Schechter and Seghers (37) have studied the decomposition of trans **40** and cis **41** 1-diazo-2-phenyl-5-tert-butylcyclohexane. Although a precise interpretation of the

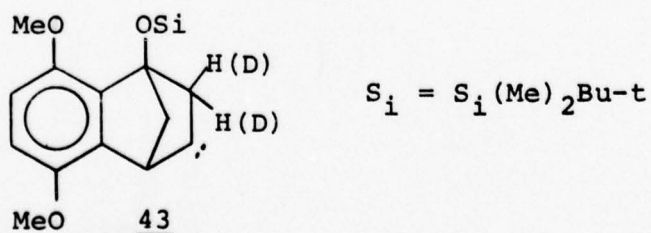


results was unwarranted, the authors felt an axial mode of migration for both hydrogen and phenyl was clearly demonstrated. Two groups have recently investigated 1,2 hydrogen migrations involving the norbornyl skeleton. The brexane system **42** has been studied by Nickon (65). Brexane is biased in that the additional two-carbon bridge twists



the exo and endo protons out of the normal alignment 42b. The actual conformation is 42a where the exo hydrogen is essentially coplanar with the empty p-orbital. The predictions that such coplanarity is highly desirable (41, 47, 48, 49, 50, 51) are nicely borne out; the migratory ratio  $H_x/H_n$  being 138.

Kyba and Hudson have studied the behavior of what they term an "unbiased" norbornyl system 43 (45) as shown below.



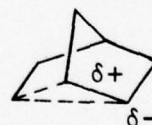
From the appropriately labeled reactants, the migratory ratio  $H_x/H_n$  is found to be 13, which is indicative of a "substantial activation energy difference,  $E_a^n - E_a^x \approx 2.4$  Kcal mol<sup>-1</sup>" (45a).

## DESIGN, RESULTS, DISCUSSION

From the preceding discussion, the existence of numerous discrepancies and inconsistencies is plainly seen. Reconciling these differences, however, is not a simple task and must necessarily begin on a small scale. It seemed to us that insight could be gained, particularly in the norbornyl system, for three reasons. First, theoretical calculations were available. Secondly, the corresponding carbonium ion is well understood. Thirdly, the 2-norbornyl system presented the opportunity to investigate a possible non-classical carbene involving  $\sigma$  delocalization. In the singlet state, delocalization of the empty p-orbital with the C-1-C-6  $\sigma$  bond is analogous to the carbonium ion delocalization (43, 44). Since the stereospecificity of



44 non-classical  
carbonium ion

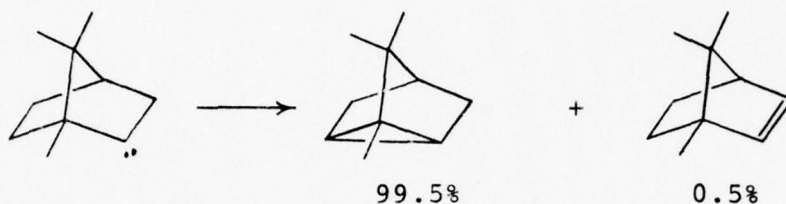


45 non-classical  
carbene

3,2 hydride migrations has been a useful tool in characterizing the 2-norbornyl cation (43, 44), it is reasonable that such information would be of value in characterizing the bivalent carbene as well.

Two problems arise even before investigation of 3,2 hydrogen migration in the 2-carbenanorbornyl system actually

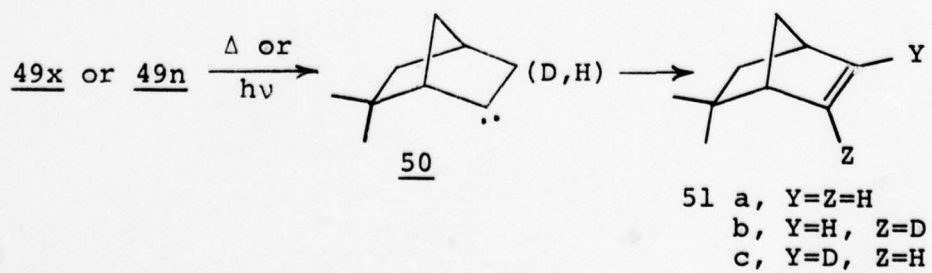
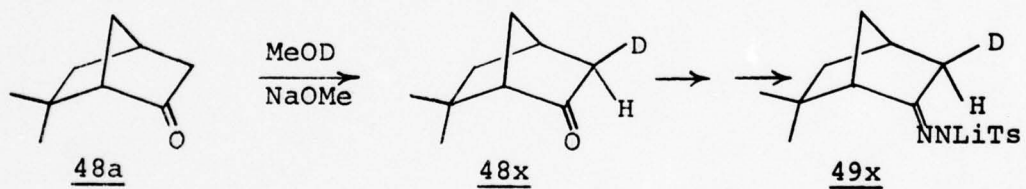
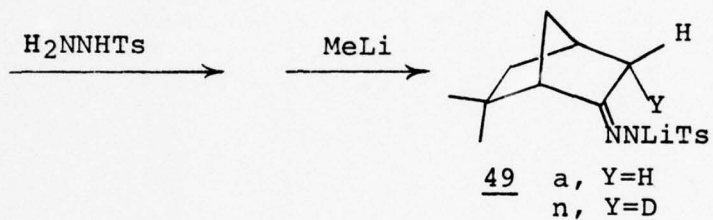
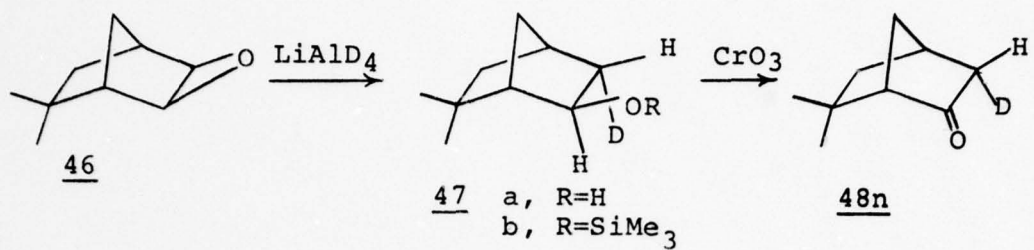
begins. The first is the competitive insertion of the carbene into the C-6 C,H bond. In the case of camphor, this 2,6 insertion is responsible for 99.5% of the total product (40). The second problem is distinguishing between the



migration origin and terminus and involves the tradeoff between a non-biased system (i.e., simple and symmetric) and one in which C-2 and C-3 protons are easily recognizable (i.e., necessarily asymmetric).

The approach of this study was to investigate the behavior of 2-carbena-6,6-dimethylnorbornane. The main reason for this choice of substrate was that it retains much of the simplicity and symmetry of the parent norbornane system. Thus it resembled an unbiased system much more closely than in the system (43) of Kyba (45) discussed in the previous section. Secondly, the synthesis of the appropriately labeled tosylhydrazones was straightforward. The synthetic route summarized in scheme 15 was carried out by Hardy (69) as were the decompositions.

The results of Hardy (69) are presented in Tables 6 and 7. Examination of Table 7 reveals that the stereoselectivity of the 3,2 hydrogen migration is about 95:5 (19:1)



Scheme 15

Table 6. Results of Decomposition of Tosylhydrazone Salts 49x, 49n.<sup>d</sup>

Salt	Type	Mass spectra of <u>51</u>			NMR integration of <u>46</u> <sup>e</sup>		
		d <sub>o</sub>	d <sub>1</sub>	d <sub>2</sub>	C <sub>2</sub>	C <sub>3</sub>	
<u>49x</u>	Pyr <sup>a</sup>	17.9 ± 0.9 <sup>c</sup>	78.3 ± 2.1	3.8 ± 1.5	0.938 ± 0.097	0.222 ± 0.090	
<u>49x</u>	Pyr	9.4 ± 0.3	82.2 ± 1.1	8.4 ± 0.7	0.844 ± 0.028	0.149 ± 0.060	
<u>49n</u>	Pyr	3.4 ± 0.4	96.6 ± 0.4	0.0	0.097 ± 0.011	0.937 ± 0.077	
<u>49x</u>	Phot	43.4 ± 0.5	56.6 ± 0.5	<0.5	0.979 ± 0.071	0.456 ± 0.046	
<u>49n</u>	Phot	5.2 ± 0.2	94.8 ± 0.2	0.0	0.104 ± 0.030	0.947 ± 0.039	

<sup>a</sup> Dry salt pyrolysis. <sup>b</sup> Photolysis in THF. <sup>c</sup> One standard deviation. <sup>d</sup> From the Ph. D. thesis of Thomas A. Hardy. <sup>e</sup> The protons at C<sub>2</sub> and C<sub>3</sub> are indistinguishable in the alkene at 100 MHz. Therefore 51 was converted back to the epoxide 46 for NMR analysis (H<sub>C<sub>2</sub></sub>, δ = 3.10; H<sub>C<sub>3</sub></sub>, δ = 2.96).

Table 7. Corrected Product Compositions from the Decomposition of Tosylhydrazone Salts 49x, 49n.<sup>d</sup>

Salt	Type	51c	51b
49x	Pyr <sup>a</sup>	5.0 ± 1.2% <sup>c</sup>	95.0 ± 2.0%
49x	Pyr	6.2 ± 1.2	93.8 ± 2.0
49n	Pyr	93.5 ± 1.6	6.5 ± 1.2
49x	Phot <sup>b</sup>	3.9 ± 1.4	96.1 ± 2.7
49n	Phot	94.5 ± 1.3	5.5 ± 0.4

<sup>a</sup>Dry salt pyrolysis.

<sup>b</sup>Photolysis in THF.

<sup>c</sup>One standard deviation.

<sup>d</sup>From the Ph. D. thesis of Thomas A. Hardy.

exo:endo for both thermal and photolytic decomposition.

At this point there arose the question of whether or not the composition of the product mixture 51 had been unknowingly influenced by a loss of deuterium (or hydrogen) somewhere along the synthetic route. If it had, the results of Table 7 were meaningless and no conclusions could be drawn about the migration stereoselectivity. As described in Part I, the formation of the tosylhydrazone and its salt provides ample opportunity for epimerization and/or loss of deuterium from C<sub>α</sub>. The tests for these complications are now described. The endo-deuterated alcohol 47a was converted to 47b, the TMS derivative. 47a was converted to the ketone 48n; to the tosylhydrazone; to the lithium salt 49n; then back to the tosylhydrazone; and finally to ketone 48n again (using the NBS reaction). Table 8 lists the mass spectral results. The exo-deuterated

Table 8. Mass Spectral Data for 47b and 48n (before and after conversion to Tosylhydrazone and the Li Salt).

Deuterium Content	Compound		
	<u>47b</u>	<u>48n</u> before	<u>48n</u> after
% d <sub>0</sub>	2.2 ± 0.1	3.2 ± 0.1	3.1 ± 0.1
% d <sub>1</sub>	97.8 ± 0.1	96.8 ± 0.2	96.9 ± 0.2
% d <sub>2</sub>	0.0	0.0	0.0

<sup>a</sup>Standard deviation

ketone 48x was carried through a similar sequence and analyzed by 100 MHz NMR using a  $\text{Eu}(\text{fod})_3$  shift reagent. The integrations of the exo and endo C-3 hydrogens are shown in Table 9. Tables 8 and 9 reveal that there is essentially

Table 9. NMR Integrations<sup>a</sup> for 48x (before<sup>b</sup> and after<sup>c</sup> confersion to tosylhydrazone and the Li Salt).<sup>d</sup>

Ketone	Hydrogen analyzed		
	<u>exo</u> -C-3	C-1	<u>endo</u> -C-3
before	6.7	100	99
after	5.5	100	97

<sup>a</sup>by cut and weight

<sup>b</sup>CAT x 200

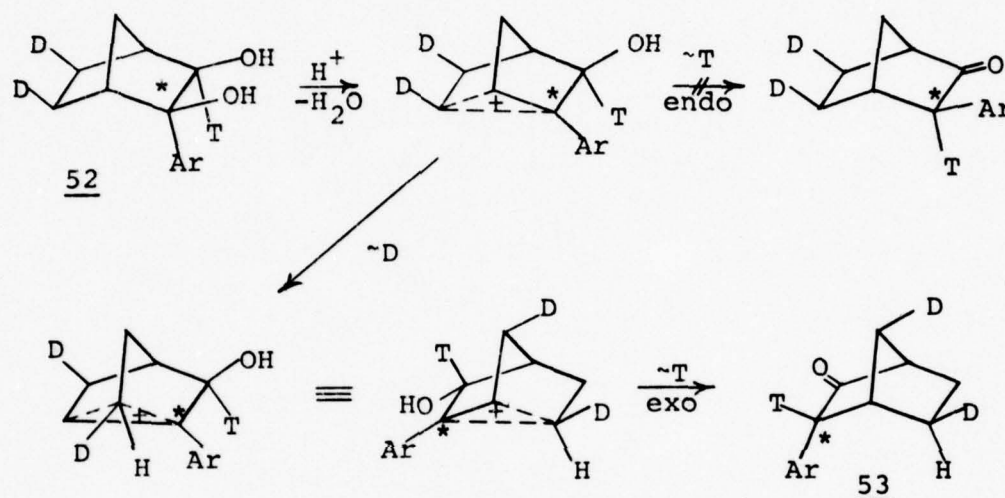
<sup>c</sup>CAT x 96

<sup>d</sup>with the C-1 bridgehead portion at  $\delta$  10.34, the endo proton is at  $\delta$  10.03, the exo proton is at  $\delta$  10.77.

no loss of deuterium in the preparation of the tosylhydrazones and the corresponding lithium salts. Thus no epimerization took place during the synthetic route and the data in Tables 6 and 7 are meaningful.

When compared to the 2-norbornyl cation, the carbene's stereoselectivity (19:1) is very low indeed. Both Berson (43) and Collins (44) have studied the cation in great detail and report a stereoselectivity of greater than 100:1 in favor of exo migration. Collins has investigated the acid catalyzed pinacol rearrangement of 2-arylnorbornan-exo-cis-2,3-diols 52 to endo-3-aryl-2-norbornanones 53 using

extensively labeled compounds. His analysis reveals that >98% of the hydride ( $H^3$ ) migration takes places via an exo pathway and further attributes this high selectivity to the formation of a non-classical carbonium ion (scheme 16).

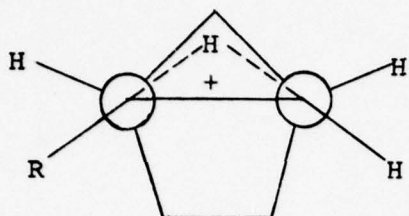
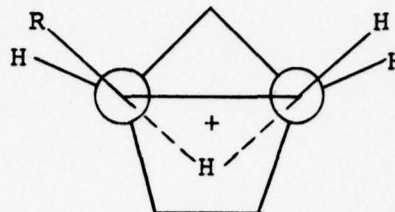


If the 2-norbornyl carbene is non-classical, the exo:endo ratio would be expected to be similar to that of the carbonium ion since delocalization from the C-1-C-6 bond must necessarily block the endo pathway, but permitting the exo migration. Our observation of 5 or 6 percent endo migration argues quite strongly against any  $\sigma$  delocalization. Thus if one assumes a single product determining intermediate, carbene 54 is classical in the usual sense of the word. It has been assumed that the carbenes resulting from either thermal or photolytic decomposition in this study are of the same electronic state, namely the lowest



lying singlet. The basis for this belief is the fact that both methods of decomposition gave the same product ratios (within experimental error) and previously reported results (71) show that triplet carbenes do not undergo hydrogen migration reactions.

Alternative proposals to account for the high selectivity of the cation have been proposed by H. C. Brown (61d) and P. v. R. Schleyer (66). Brown contends that it is not a case of favored exo migration, but one of hindered endo migration. Steric interactions from C-5 and C-6 supposedly do not permit a facile endo shift. Schleyer's approach is quite different. He has examined the geometry for the exo and endo hydride migrations and points out that in the exo migration there is minimal non-bonded interaction in the vicinities of C-1-C-2 and C-3-C-4. However, for the endo migration, non-bonded interaction is significant due to eclipsing of the bridgehead hydrogens with atoms attached to C-2 and C-3. If the usual  $3 \text{ Kcal mol}^{-1}$  is assumed for the barrier to C-C rotation, the endo migration transition state could be up to  $6 \text{ Kcal mol}^{-1}$  less stable than that for

exo migrationendo migration

the exo migration. This alone could easily account for the 100:1 selectivity observed.

The torsional interactions in 2-carbenanorbornane would be expected to be considerably less than for the cation, especially in view of the fact that the kinetic isotope effect is essentially one, suggesting that hydrogen bridging is not well developed in the transition state. Thus it would appear that small differences in the torsional interactions of the exo and endo transition states best account for the 19:1 selectivity observed.

## EXPERIMENTAL

Melting points were obtained using either a Büchi melting point apparatus or a Mel-Temp device and are uncorrected. Boiling points are also uncorrected. NMR spectra were recorded at 100 MHz with a Varian HA-100 or at 60 MHz with a Varian Anaspec EM-360. Infrared spectra were obtained with either a Beckman IR-8 or a Perkin-Elmer Model 621. Vapor-phase chromatographic analyses were carried out using an F and M Model 700 Chromatograph equipped with dual columns and thermal conductivity detectors. The following columns were used: (1) 10 ft. x 0.25 in. aluminum containing 10% Carbowax 20M on Anakrom 70-80 ABS; (2) 8 ft. x 0.25 in. aluminum containing 5% OV-17 on 60-80 Chromosorb G; (3) 9 ft. x 0.25 in. aluminum 10% Carbowax 20M and 1% XF-1150 on Anakrom 70-80 ABS; (4) 18 ft x 0.125 in. stainless steel 10% UCW-98 on 80-100 Diatoport S. Product ratios and percentage yields calculated from chromatographic data are based on relative peak areas measured by a Hewlett-Packard 3373B Integrator. *p*-Cymene was the internal standard. Deuterium analyses were accomplished by a low-voltage, mass spectral technique (fully described in Appendix B) using a Varian MAT CH-7 spectrometer, interfaced with a pdp/8 computer. NMR chemical shift studies were carried out with  $\text{Eu}(\text{fod})_3$  supplied by Norell Chemical Co., Inc.

Preparation of 5,5-Dimethyl-2,3-exo-epoxynorbornene

46. The procedure of Donaldson (70) was used with only minor modifications. Sublimation of the resulting product (20 Torr, pot temperature 70°C) yielded the title compound in 75% yield; NMR (CCl<sub>4</sub>, 100 MHz)  $\delta$  3.10 (doublet of doublets,  $J = 3.5, 0.7$  Hz, 1 H, C-3 proton), 2.96 (doublet of doublets,  $J = 3.5, 0.7$  Hz, 1 H, C-2 proton), 2.34 (unresolved, 1 H bridgehead C-1 proton), 1.90 (broadened singlet, 1 H, bridgehead C-4 proton), 1.34 (broadened doublet,  $J = 4$  Hz, 1 H, exo-C-6 proton), 1.22 (broadened doublet,  $J = 4$  Hz, 1 H, endo-C-6 proton), 1.15 to 0.80 (complex signals including two singlets for the two methyl groups on C-5 at  $\delta$  1.05 and 1.02, 8 H).

Preparation of 6,6-Dimethylnorbornan-2-ol. The procedure of Donaldson (70) was used. Purification by preparative VPC yielded NMR (CCl<sub>4</sub>, 100 MHz):  $\delta$  4.07 (doublet,  $J = 6$  Hz, 1 H, proton  $\alpha$  to hydroxyl), 2.20 (multiplet, 1 H, proton on C-4), 1.68 (singlet, 1 H, C-1 bridgehead proton), 1.63 to 0.73 (complex series of absorptions including methyl singlets at  $\delta$  1.00 and 0.97, 12 H).

Preparation of endo-3-Deuterio-6,6-dimethylnorbornan-2-ol 47a. The reaction was run as described (70) except that 3 equivalents of lithium aluminum deuteride (99.5% d) was heated at reflux with 46 for 3 days. After workup, VPC analysis on column 1 showed the product to consist of a mixture of alcohol and epoxide in a ratio of 70:30.

Analysis of the extent of deuteration was carried out by treating alcohol 47a (0.23 g, 0.0016 mol) with 1 mL of  $\text{Me}_2\text{SO}$  and 0.4 mL of Trisil (Pierce Chemical Co.). The mixture was shaken for 5-10 min and left undisturbed overnight. The organic layer was separated and the  $\text{Me}_2\text{SO}$  layer was extracted once with hexane. The organics were combined and washed once with  $\text{H}_2\text{O}$ , then dried over  $\text{CaCl}_2$ . The trimethylsiloxynorbornane derivative was purified by preparative VPC (column 2). Low voltage mass spectrum showed  $\delta d_1$  as  $97.8 \pm 0.1\%$ . There was no  $d_2$ .

Preparation of 6,6-Dimethylnorbornan-2-one 48a. 6,6-Dimethylnorbornan-2-ol was oxidized by the procedure of Donaldson (70). Distillation of the title ketone (bp  $80-83^\circ\text{C}$ , 18 Torr; lit, bp  $74-75^\circ\text{C}$ , 12 Torr) yielded 51.5% (calculated from epoxide 46); NMR ( $\text{CCl}_4$ , 100 MHz);  $\delta$  2.75 (unresolved, 1 H, bridgehead proton at C-4), 2.02 (slightly broadened singlet, C-1 bridgehead), 1.97-0.80 (complex absorptions including methyl singlets at  $\delta$  1.07 and 0.96, 12 H).

Oxidation of endo-3-Deuterio-exo-6,6-Dimethylnorbornan-2-ol. The crude mixture of 47a and 46 was treated with chromic acid in acetone as described (70). Distillation yielded 48n.

Deuteration of 6,6-Dimethylnorbornan-2-one. The title ketone (1.0 g) was dissolved in 25 mL of methanol- $\text{O-d}$  (99%  $d_1$ ) with a catalytic amount of sodium methoxide and stirred

for 2 hr. at room temperature. After quenching with  $D_2O$  and dilution with water, the solution was extracted with pentane. The pentane was washed with water and brine and dried over sodium sulfate. After removal of most of the pentane by distillation, the ketone was used without further purification for the preparation of tosylhydrazone.

Samples for spectral analysis were separated using VPC column 3. The extent of deuteration at the exo and endo C-3 position was determined by NMR aided by a lanthanide induced shift.  $Eu(fod)_3$  was added until the difference between the exo, endo, and bridgehead positions became large enough to permit accurate determination of the relative areas. The bridgehead hydrogen (C-1) was used as the standard. When the bridgehead hydrogen was  $\delta$  10.34, the exo-3 and endo-3 protons absorbed at  $\delta$  10.77 and 10.03, respectively.

Preparation of 6,6-Dimethyl-2-norbornanone p-Toluene-sulfonylhydrazone. A mixture of 4.5 g (0.033 mol) of 6,6-dimethylnorbornan-2-one and 6.2 g (0.033 mol) of tosylhydrazine in 35 mL of 95% ethanol with 2 drops of concentrated hydrochloric acid was heated at reflux for 3 hr. Several milliliters of water was added, and the solution was cooled to room temperature, then placed in a refrigerator, yielding 5.1 g (0.017 mol), 51%, mp 150-154°C. Recrystallization from ethanol yielded mp 157.5-159°C; IR (0.1 mm,  $CHCl_3$ ): 3200  $cm^{-1}$  (m, N-H stretching), 1662 (m, C=N stretching),

1598 (m, aromatic C=C stretching), and 1170 (s, SO<sub>2</sub>-N stretching); NMR (100 MHz CDCl<sub>3</sub>):  $\delta$  7.89 (singlet, 1 H, N-H),  $\delta$  7.84 and 7.26 (each a doublet, 2 H each, aromatic protons),  $\delta$  2.38 (singlet, 3 H, aromatic methyl),  $\delta$  2.34 (multiplet, 2 H, C-1 and C-4 bridgehead protons),  $\delta$  2.2 to 1.2 (complex signals, 5 H),  $\delta$  0.96 (1 H, buried under methyl),  $\delta$  0.96 and 0.56 (singlets, 3 H each, methyls on C-6).

Preparation of *endo*-3-Deuterio-6,6-dimethylnorbornan-2-one Tosylhydrazone. This preparation was carried out in a manner identical with that described above for the undeuterated tosylhydrazone. Recrystallization from methanol gave mp 156-158°C.

Preparation of *exo*-3-Deuterio-6,6-dimethylnorbornan-2-one Tosylhydrazone. The *exo*-deuterated ketone (about 1 g, 0.08 mol) was placed in 10 mL of methanol-O-d (99% d<sub>1</sub>) with 1.5 g (0.08 mol) of tosylhydrazine (previously recrystallized from methanol-O-d) and a drop of DCl in D<sub>2</sub>O. The solution was heated at reflux for 3 hr.; D<sub>2</sub>O was added, and the solution was allowed to cool to room temperature, then placed in a refrigerator. The crystalline product was recrystallized from methanol-O-d/D<sub>2</sub>O yielding purified tosylhydrazone with mp 156-158°.

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APPENDICES

## APPENDIX A

## Illustrative Ketone Mass Spectral Data



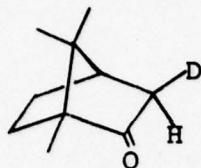
Camphor standard (MW 152)

TIC<sup>a</sup> = 47,000      eV = 20

Scan No.	Peak Intensity (Uncorrected)		
	152	153	154
1	100	10.99	.87
2	100	11.79	.39
3	100	11.32	.52
4	100	11.02	.54
5	100	11.79	.34
6	100	10.72	.47
7	100	10.75	.66
8	100	11.11	.56
9	100	11.36	.58
10	100	10.75	.66

<sup>a</sup>Total Ion Current

## Appendix A (continued)

Product from the pyruvic acid  
cleavage

TIC = 49,000

eV = 20

Scan No.	Peak Intensity (Uncorrected)			
	153	153	154	155
1	100	60.73	13.01	.58
2	100	62.50	14.01	.71
3	100	62.47	11.96	.92
4	100	60.88	13.11	.73
5	100	60.03	12.19	.95
6	100	62.18	11.53	.58
7	100	65.00	12.84	.73
8	100	67.81	13.62	.86
9	100	63.74	12.40	.70
10	100	67.48	13.20	.44
11	100	62.51	13.68	.68

## APPENDIX B

Low Voltage Mass Spectroscopy: A Brief Summary  
of Technique and Sample Calculation  
of % Deuterium

The first step in any determination of deuterium incorporation is to run an unlabeled standard. This serves two functions: (1) one uses it to empirically determine the optimum electron voltage at which the molecular ion peak can be measured accurately while reducing the P-1, P-2, ... peaks to zero intensity. (Peaks at P-1, P-2 ... are due to fragmentation of one or more hydrogen atoms from the molecular ion.) This fragmentation cannot be tolerated because when the deuterated compound is tested, it is not known whether H or D is being lost. Any analysis at that point is meaningless; (2) the standard is also used to determine the naturally occurring abundance of elemental isotopes such as  $C^{13}$ ,  $N^{15}$ ,  $O^{18}$ , or  $Cl^{37}$ . Naturally occurring  $H^2$  is considered negligible (0.015%). It becomes apparent why the abundance of natural isotopes needs to be known when one considers that molecules containing  $C^{13}$ , for example, would show the same molecular ion peak as another molecule containing no  $C^{13}$  but one deuterium atom. Thus, neglect of naturally occurring isotopes leads to erroneous conclusions concerning the actual deuterium content of a molecule.

After ten to twenty scans have been accomplished on the standard, the ionization chamber is evacuated and the deuterated substrate is then admitted. The chamber should be flushed with the deuterated material two or three times to insure that no traces of the standard remain. The molecular ion region of the deuterated compound is then scanned ten to twenty times at the same operating conditions (electron voltage and total ion current) as the standard.

At this point, the tedium begins. If the output of the mass spectrometer is to a stripchart recorder, all the peak heights must be measured and tabulated. In cases where the mass spec is interfaced with a computer, the peak intensities are usually already available in digital format.

The preliminary calculations that are necessary are  $\frac{P+1}{P}$  and  $\frac{P+2}{P}$ . For the standard in Appendix A, scan 1, these are  $\frac{10.99}{100}$  and  $\frac{0.87}{100}$  respectively. These two values are calculated for each scan and then averaged. For the case in point, Ave  $\frac{P+1}{P} = 0.1116$  and Ave  $\frac{P+2}{P} = 0.0056$ .

The deuterated sample may then be analyzed. (Refer to Appendix A, Part Two for a Tabulation of uncorrected peak intensities.)

It is assumed (since we eliminated the P-1 peaks) that the peak at mass 152 is due entirely to the undeuterated molecule. The peak at mass 153, however, comes from two sources: (1) all C<sup>12</sup> + one D; and (2) one C<sup>13</sup> + no D. To get the contribution of the latter to the mass peak 153,

the parent peak (152) is multiplied by  $\frac{P+1}{P}$ . This contribution is then subtracted from the P+1 intensity (mass 153) to obtain the true amount of camphor-d<sub>1</sub>:

$$(100)(.1116) = 11.16 \qquad 60.73 - 11.16 = 49.57$$

The peak at mass 154, comes primarily from three sources (neglecting O<sup>18</sup>): (1) all C<sup>12</sup> + two D; (2) one C<sup>13</sup> + one D; and (3) two C<sup>13</sup> and no D. To uncover the actual amount of camphor-d<sub>2</sub> the following corrections need to be made.

$$(100)(.0056) = .56 \qquad (49.57)(.1116) = 5.53$$

$$.56 + 5.53 = 6.09$$

$$13.01 - 6.09 = 6.92 = \text{camphor-d}_2$$

The peak at mass 155 is the result of a P+1 (mass 154) and P+2 (153) and was thus not considered. The above calculations are applied to each scan's data to obtain the corrected P+1 and P+2. Percent d<sub>0</sub>, d<sub>1</sub>, d<sub>2</sub> are simply found by dividing the particular corrected peak intensity by the sum of the corrected peak intensities:

$$\% d_0 = \frac{100}{100 + 49.57 + 6.92} \times 10^2 = 63.9$$

$$\% d_1 = \frac{49.57}{156.49} \times 10^2 = 31.7$$

$$\% d_2 = \frac{6.92}{156.49} \times 10^2 = 4.42$$

Percent  $d_0$ ,  $d_1$ ,  $d_2$  are found for each scan. The mean and standard deviation may then be calculated. Programs for the HP-55 are found in Appendix C which will apply the above algorithm.

## APPENDIX C

Programs for the Hewlett-Packard 55 Calculator  
to Handle the Computation of %D

Program #1. Calculation of Average  $\frac{P+1}{P}$  and  $\frac{P+2}{P}$

Step 1. Enter program

Step 2. Enter data points (peak intensities)

P+2, ↑, P+1, ↑, P, R/S

Step 3. Calculate average and standard deviation

f,  $\bar{x}$  to get ave  $\frac{P+2}{P}$

↻ to get ave  $\frac{P+1}{P}$

g, s to get  $\sigma$  of  $\frac{P+2}{P}$

↻ to get  $\sigma$  of  $\frac{P+1}{P}$

The program:

<u>Line</u>	<u>Code</u>	<u>Key Entry</u>
1	81	+
2	22	↻
3	31	f
4	34	LST X
5	81	÷
6	11	Σ +
7	-00	GTO
9		∅∅

## Appendix C (continued)

Program #2. Calculation of %d<sub>0</sub>, d<sub>1</sub>, d<sub>2</sub>Step 1. Enter programStep 2. Enter constants

$$\text{STO, } \emptyset \quad \frac{P+1}{P}$$

$$\text{STO, } 1 \quad \frac{P+2}{P}$$

Step 3. Enter data points (peak intensities)

$$P+2, \uparrow, P+1, \uparrow, P, R/S$$

Step 4. Calculate averages and standard deviation

$$f, \bar{x} \quad \text{to get ave \% } d_1$$

$$\begin{array}{c} \curvearrowright \\ \curvearrowleft \end{array} \quad \text{to get ave \% } d_2$$

$$g, s \quad \text{to get } \sigma \text{ for \% } d_1$$

$$\begin{array}{c} \curvearrowright \\ \curvearrowleft \end{array} \quad \text{to get } \sigma \text{ for \% } d_2$$

$$\text{RCL, } 5, \text{ STO, } ., 1,$$

$$\text{RCL, } 4, \text{ STO, } ., 2,$$

$$f, \bar{x} \quad \text{to get ave \% } d_0$$

$$g \quad \text{to get } \sigma \text{ for \% } d_0$$

## Appendix C (continued)

The Program:

Line	Code	Key Entry	Line	Code	Key Entry
1	33	STO	26	61	+
2	09	9	27	81	÷
3	34	RCL	28	34	RCL
4	00	∅	29	08	8
5	71	X	30	31	f
6	51	-	31	34	LST X
7	33	STO	32	81	÷
8	08	8	33	34	RCL
9	34	RCL	34	09	9
10	00	∅	35	31	f
11	71	X	36	34	LST X
12	34	RCL	37	81	÷
13	01	1	38	33	STO
14	34	RCL	39	61	+
15	09	9	40	05	5
16	71	X	41	32	g
17	61	+	42	42	X <sup>2</sup>
18	51	-	43	33	STO
19	41	↑	44	51	+
20	41	↑	45	04	4
21	34	RCL	46	23	↓
22	08	8	47	11	Σ+
23	61	+	48	-00	GTO
24	34	RCL	49		∅∅
25	09	9			

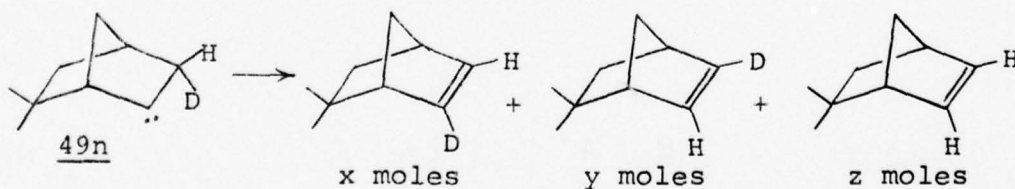
## APPENDIX D

Sample Calculations of  $k_H/k_D$  and  $H_x/H_n$ 

In Appendix B, a low voltage mass spectral technique was described, and some of the inherent problems (naturally occurring isotopes) were pointed out. In this section the percentages of the deuterated compounds will be coupled with  $H^1$ NMR data to produce the actual migratory and kinetic isotope ratios.

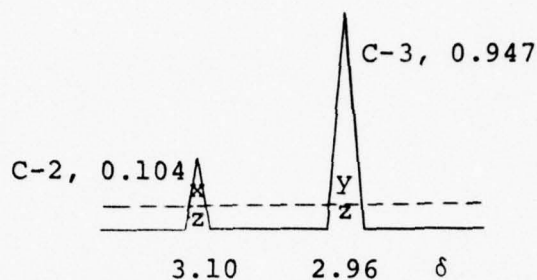
The starting point is the photolysis of 49n (Part II, Table 6). The spectral findings are summarized below along with the reaction equation. The product mixture contains x

Salt	$d_0$	$d_1$	$d_2$	C-2	C-3
<u>49n</u>	$5.2 \pm 0.2\%$	$94.8 \pm 0.2$	0.0	$.104 \pm 0.030$	$.947 \pm 0.039$



moles endo migration product, y moles exo migration product, and z moles of the  $d_0$  alkene resulting from a  $d_0$  contaminant in 49n. From the mass spectral data it is known that  $x+y$  comprise 94.8% of the total and z has 5.2%. The protons at C-2 are from  $x+z$ . C-3 results from  $y+z$ . The total proton equation is, therefore:

$$\begin{aligned}
 x+z &= .104 \\
 + \quad y+z &= .947 \\
 \hline
 x+y+2z &= 1.051
 \end{aligned}$$



It is readily apparent that  $z$  makes an equal contribution to both C-2 and C-3. Intuitively, the correction is simple: subtract the percent of  $z$  from the C-2 and C-3 values to get the actual contributions from  $x$  and  $y$ .

$$x = .104 - .052 = .052$$

$$y = .947 - .052 = .895$$

$$\% \text{ exo migration} = \left( \frac{.895}{.895 + .052} \right) 10^2 = 94.5$$

$$\text{migratory ratio } \frac{\text{exo}}{\text{endo}} = 17.2$$

The above approach no longer holds when the product mixture contains  $d_2$  molecules. In this case a more rigorous solution is required. Line 1 of Table 6, the dry salt pyrolysis of 49x, will serve as an illustration. Molecules containing  $d_2$  contribute to the mass spec percentage but make

Salt	$d_0$	$d_1$	$d_2$	C-2	C-3
<u>49x</u>	17.9±0.9	78.3±2.1	3.8±1.5	0.938±0.097	0.222±0.090

no contribution to the NMR integrations. So the NMR equations are similar to the ones used previously.

$$\begin{array}{r}
 x+z = .222 \\
 \underline{y+z = .938} \\
 x+y+2z = 1.160
 \end{array}$$

The fraction of z present as it relates to x and y ( $d_2\%$  is implicit) is:

$$\frac{z}{x+y+2z} = \frac{17.9}{78.3+2(17.9)} = .157$$

$z = (.157)(x+y+2z)$ , substituting gives

$$\begin{aligned}
 z &= (.157)[(.222-z) + (.938-z) + 2z] \\
 &= (.157)(.222) + (.157)(.938) \\
 &= .182
 \end{aligned}$$

$$\therefore x = .222 - .182 = .040 \text{ (moles } \underline{\text{endo}} \text{ migration)}$$

$$y = .938 - .182 = .756 \text{ (moles } \underline{\text{exo}} \text{ migration)}$$

$$\underline{\text{exo/endo}} = .756/.040 = 18.90$$

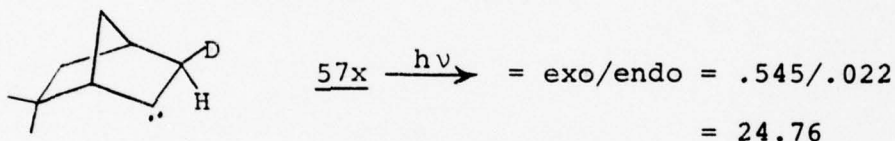
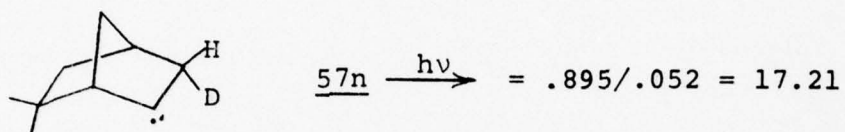
$$\% \underline{\text{exo}} \text{ migration} = (.756)(10^2)/(.756 + .040) = 95.0$$

In a similar fashion, all the other C-2 and C-3 integrations are corrected and the exo/endo percentages calculated.

At this point there arises the temptation to make the numbers say more than they actually do. One must be careful to avoid this and particularly not to lose sight of his precision of measurement. In the case of this study, all results were with experimental error of each other. Thus a consideration of  $k_H/k_D$  was unwarranted even though the migratory ratios for exo H and exo D appeared to vary quite a bit. For the purpose of illustrating the

calculation, the photolytic decompositions 49x and 49n will be considered.

It should be remembered that a calculation  $k_H/k_D$  is possible only if the assumption is made that the isotope effect is equal for both exo and endo migration (38, 7, 65).



Two equations with two unknowns are then solved where  $x$  = kinetic isotope effect and  $y$  = the corrected migratory ratio  $H_x/H_n$ ,

$$y/x = 24.76, \quad yx = 17.21$$

$$y = 24.76x$$

$$(24.76x)(x) = 17.21$$

$$x^2 = .70$$

$$x = .83 = k_H/k_D$$

$$y = (24.76)(.83)$$

$$= 20.60 = H_x/H_n$$