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Synthetic And Mechanistic Features Of Base-catalyzed Homoenolization And Homoketonization

Arthur Jonas Ragauskas

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SYNTHETIC AND MECHANISTIC FEATURES OF BASE-CATALYZED HOMOENOLIZATION AND HOMOKETONIZATION

by

Arthur J. Ragauskas

Department of Chemistry

Submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy

Faculty of Graduate Studies
The University of Western Ontario
London, Ontario
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ABSTRACT

The behavior of a variety of homoenolate anions generated either by hydrolysis of polycyclic ethers (homoketonization) or by base-catalyzed hydrogen abstraction from polycyclic ketones (homoenolization) has been investigated.

A series of polycyclic derivatives of cyclopropanol were prepared and the base-catalyzed ketonization of the corresponding cyclopropoxides was examined to establish the regio- and stereochemistry of the ring cleavage. The examples derived from [2.2.1] and [2.2.2] ketones, by Simmons-Smith cyclopropanation of their silyl enol ethers, were found to undergo ring expansion preferentially while less-strained analogs gave the α-methyl derivatives of the initial ketone. In all cases of ring expansion, the cleavage proceeds with high stereoselectivity favoring inversion of configuration upon protonation (deuteration).

A novel means of generating the 2-trimethylsilyl ethers of substituted homoquadricyclenes was discovered. Base-catalyzed ketonization of these derivatives was found to yield either the tricyclo[3.2.1.$0^{2,7}$] or [3.3.0.$0^{2,8}$] octanone skeletons depending upon the substitution at the 8-position of the starting material.

The Simmons-Smith reaction with t-butyldimethylsilyl enol ether of some polycyclic ketones under concentrated conditions led to cyclopropanation and isomerization to furnish the ring expanded allylic silyl ethers.

The behavior of the 7,7-dimethyltricyclo[3.3.1.$0^{2,7}$]nonan-6-ones under strongly basic conditions was examined to determine the effect of the three-membered ring for comparison with earlier findings for the [3.2.1.$0^{2,4}$] analogs. While the *endo* isomer was found to be stable, the *exo* isomer readily rearranged to 8,8-dimethyltricyclo[4.3.0.$0^{2,4}$] nonan-7-one. Experiments in t-BuOD were carried out to establish the several sites of deuterium incorporation in the initial ketones. These results clearly revealed that the three membered ring influences both the regio- and stereochemistry of β-enolate formation. The observed differences for the *exo* and *endo* isomers of the [3.3.1.$0^{2,4}$]nonanones can be attributed to conformational differences.

Some support for this proposal was provided by the reactivities of *endo*-9,9-dimethyltricyclo[5.3.1.$0^{2,6}$]-undecan-8-one, *endo*-3-t-butyl-3-methylbicyclo[3.2.1]-octan-2-one and *endo*-9-t-butyl-9-methyltricyclo[5.3.1.$0^{2,6}$]-undecan-8-one under strongly basic conditions.

Homoenolization of the 3,3-dimethyl-7-spiro-cyclopropyl and -7-isopropylidene derivatives of norcamphor

provides efficient syntheses of the corresponding 3,3-dimethyl-5-substituted norcamphors. Hydrogenolysis of the 5-spirocyclopropyl derivative furnished the hitherto unknown 3,3,5,5-tetramethylcamphor.

ACKNOWLEDGEMENTS

I would like to express my sincere appreciation and thanks to Dr. J.B. Stothers for his guidance, encouragement and many valuable discussions, academic and otherwise, throughout my graduate program. I wish also to thank the rest of the chemistry faculty who were always available for helpful discussion. Thanks go also to the graduate students and technical staff whose friendship and advice made my stay at Western enjoyable as well as educational.

I am also very grateful to Anne Donovan for her typing of this manuscript.

Finally, and above all, I wish to extend my special thanks to my parents and my wife, Cati, for their support and patience with me during my graduate program.

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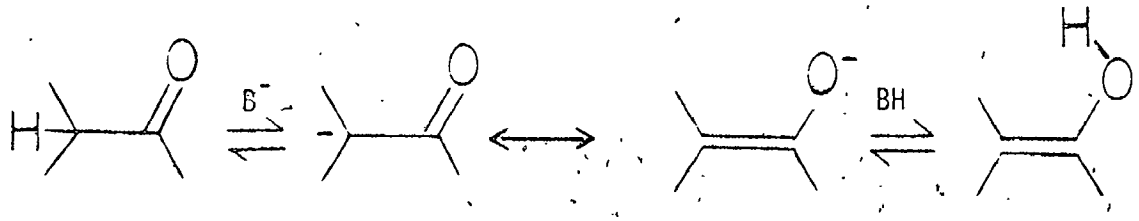
CHAPTER 1

GENERAL INTRODUCTION

The carbonyl group plays a central role in organic chemistry because of its participation in a wide variety of reactions of chemical and biochemical importance (1). Of the several reactions exhibited by carbonyl compounds, many initially involve proton abstraction from the α-position

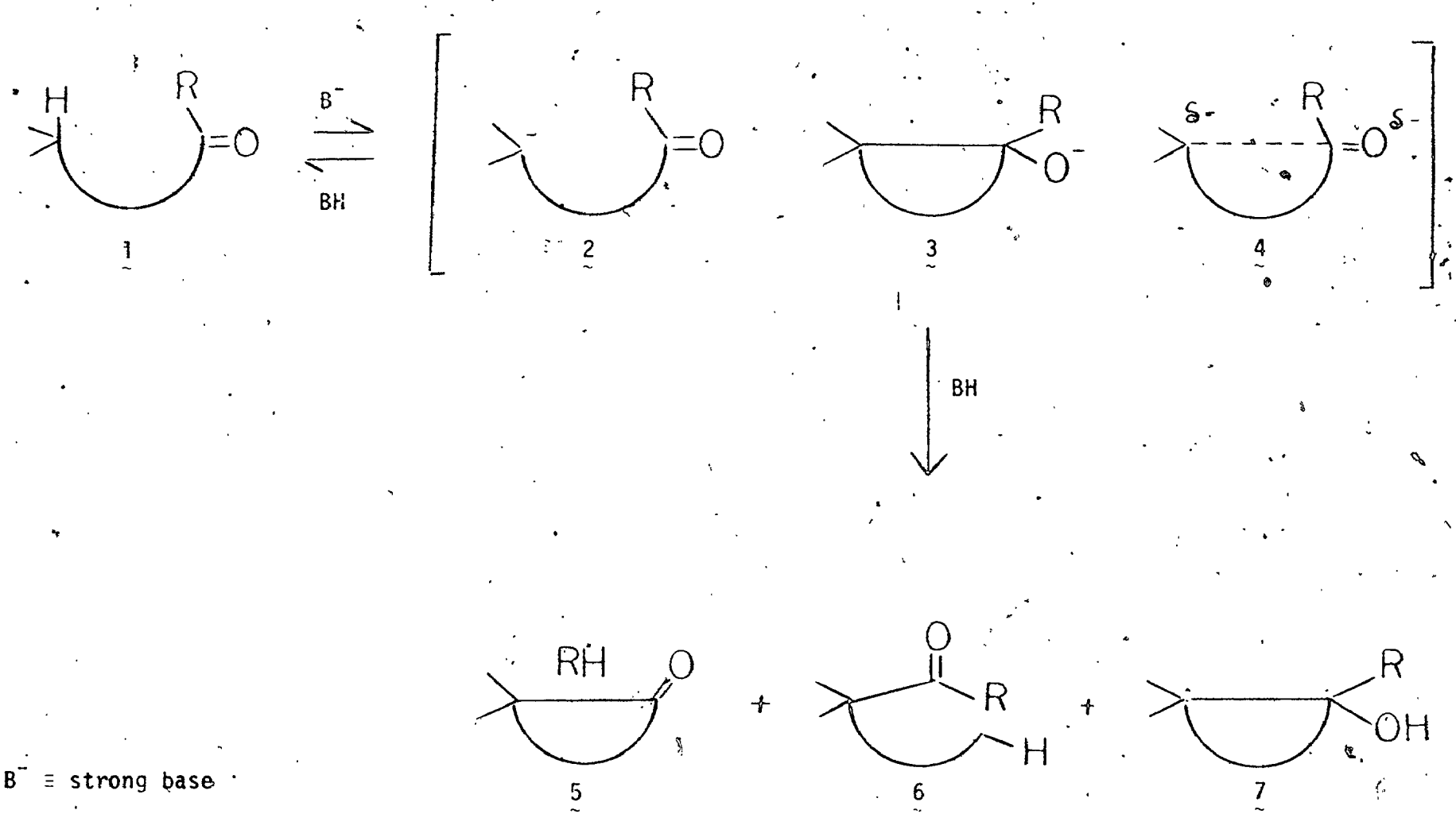


B^- = base

to generate, in basic media, the enolate anion; this process, enolization, is one of the most extensively studied reactions in organic chemistry (2). The enhanced acidity of the α-hydrogen(s) is attributed to both the resonance and inductive effects of the carbonyl group. A comparison of the estimated pK_a values for acetone (~ 20) and for the methyl hydrogens of propane (~ 42) demonstrates that the carbonyl group increases the acidity of the former

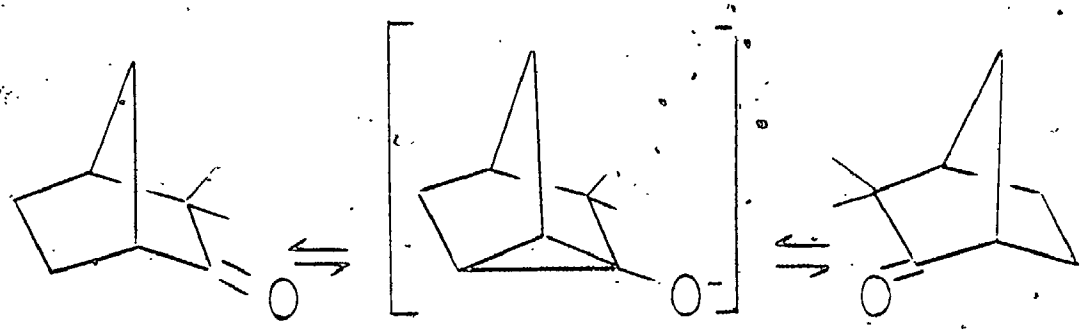
by - 20 pK_a units. The magnitude of this effect suggests that a carbonyl group could activate more remote hydrogens for abstraction to occur upon treatment with a sufficiently strong base (homoenolization). The resulting homoenolates can be described in terms of 2, 3, and 4 as shown in Scheme 1.1. The relative importance of each species may be dependent upon the structure of the initial ketone and it is conceivable that more than one anionic species is generated in a given system. Since it is difficult to define these anions precisely, the use of the cyclic form (3) is employed throughout this thesis as a convenient symbolism for the intermediate homoenolate anion(s). As shown in Scheme 1.1 protonation of the homoenolate anion could in principle furnish starting material (1), two ketones (5,6) and a cycloalkanol (7), although under the conditions employed 5 and 7 are not stable. In addition, protonation of 3 yielding 1 and/or 6 can occur with inversion or retention of configuration. The terminology devised by Stothers (3) provides a convenient method of describing the homoenolization process, with deprotonation β to the carbonyl termed β-enolization, Y-deprotonation termed Y-enolization, et cetera.

A study by Nickon and Lambert (4) on the rates of base-catalyzed $^1H/^2H$ exchange and racemization of (+)3,3-dimethylbicyclo[2.2.1]heptan-2-one (camphenilone) provided the first evidence for homoenolate anions. It was found that the rates of racemization and deuterium

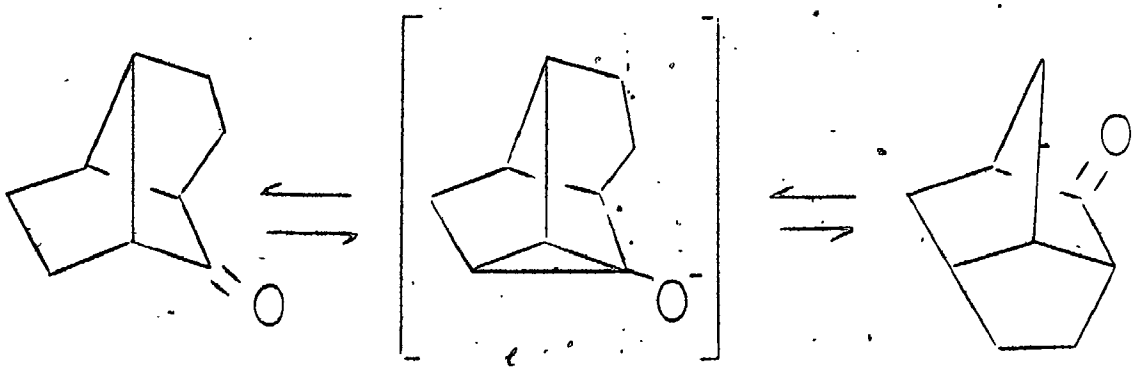


SCHEME 1.1

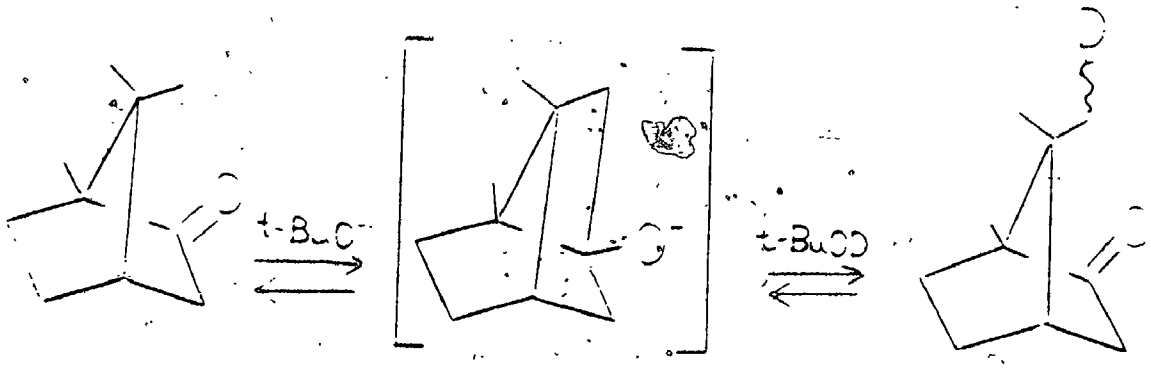
incorporation are approximately the same leading to the conclusion that deprotonation generates a symmetric intermediate, whereby C-1 and C-6 become equivalent and protonation (deuteration) yields the racemic mixture. The



synthetic potential of skeletal rearrangements via homoenolate anions to generate systems otherwise difficult to obtain was also demonstrated in the early investigations of homoenolization by Nickon et al (5). They showed that tricyclo[4.3.0.$0^{3,7}$]nonan-2-one (brexan-2-one) rearranged smoothly in t-BuO^-/t-BuOH at 185°C to tricyclo[4.2.1.$0^{3,7}$]-nonan-2-one (brendan-2-one). Following these discoverres,



several alicyclic and acyclic systems were shown to undergo homoenolization under strongly basic conditions. While most of these cases involve β-enolization, a few examples clearly showed that γ-enolization could also occur. The observation of $^{1}H/^{2}H$ exchange at C-8, the syn-methyl carbon of camphor (6a) and the isomerization of the half-cage ketone 8 to 9 (7) clearly inferred the formation of γ-enolates 10 and 11, respectively.



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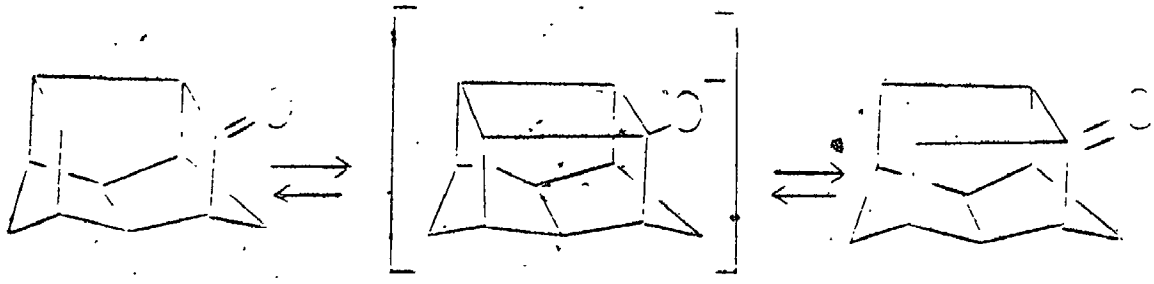


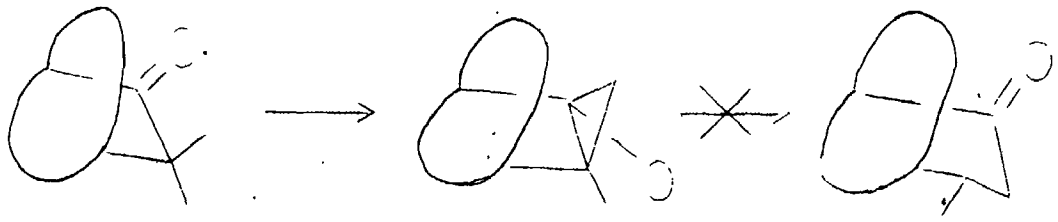
8 11 9

Subsequently it was established that the parent alcohols of 10 and 11, upon treatment with base, gave the same products exclusively (6b, 7).

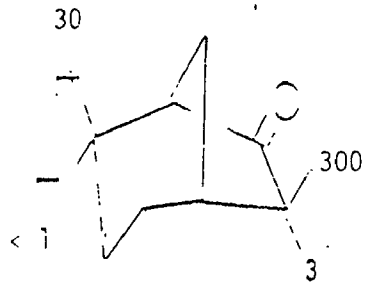
While a variety of bases were examined in the original studies (4) (ethylene glycoxide/ethylene glycol, potassium t-butoxide/dimethylsulfoxide, potassium triphenylmethylate/dioxane) t-BuO^-/t-BuOH remains the medium of choice. Its preparation requires special precautions since trace amounts of water can significantly reduce the base strength of t-BuO^-/t-BuOH (8). The use of t-BuO^-/t-BuOD and ^2H NMR provides a convenient means of establishing the sites of proton abstraction in a given substrate. Since the natural abundance level of ^2H is 0.015%, signals from centres containing 1% ^2H will be approximately two orders of magnitude more intense than the natural abundance signals. If the ^2H NMR spectra are acquired with ^1H decoupling the signal for each non-equivalent deuteron appears as a singlet. Since the spin-lattice relaxation of deuterium nuclei is induced entirely by an intramolecular quadrupole mechanism there is no Overhauser enhancement accompanying proton decoupling. The assignment of the ^2Hmr signals follows directly from the analysis of the ^1Hmr spectrum, because the ^2H and ^1H shieldings are essentially identical on the ppm scale. Integration of the ^2Hmr spectrum provides a relative measure of ^2H content at the individual sites which together with the total deuterium content determined by mass spectrometry permits

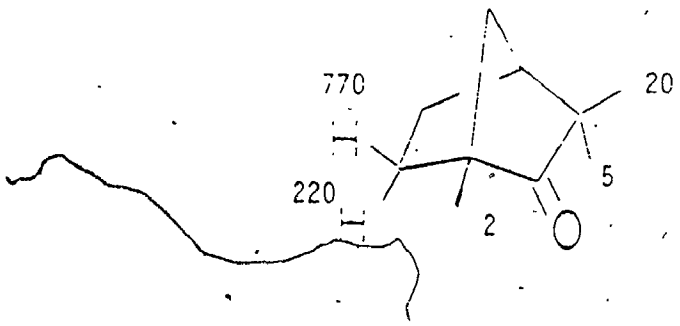
determination of the deuterium incorporation at the various centres undergoing exchange. The correlation between $^{1}H/^{2}H$ exchange and intrinsic reactivities is based upon the assumption that the rate of internal return in t-BuO⁻/ t-BuOD is comparable for the various sites of exchange in alicyclic and acyclic substrates (9).

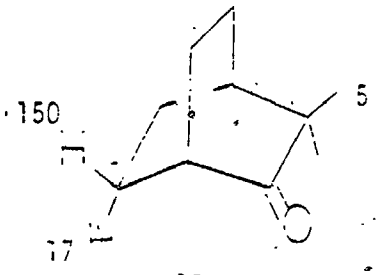
Following Nickon's investigation of camphenilone, a variety of polycyclic and acyclic ketones has been found for which remote proton abstraction occurs under strongly basic conditions. Figure 1.1 serves to illustrate some of the general features of β-enolization in the [2.2.1], [2.2.2] and [3.2.1] ring systems (10-13). From these data it is apparent that *exo*-abstraction of a β-proton is favored over *endo*-abstraction. While protonation of a β-enolate involving a methyl carbon could (conceivably) yield a ring expanded product this has only been observed in one cyclic system examined to date (16). This does occur however,



in acyclic systems, since it was shown by Stothers' group (14) that di-t-butyl ketone (12a) 5,5,7,7-tetramethyl-undecan-6-one (12b) and 2,4-dimethyl-2,4-diphenylpentan-







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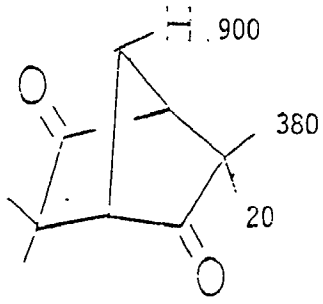
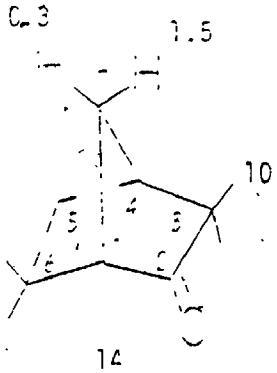


5-oxo-14



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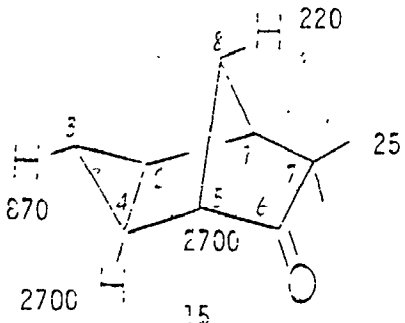
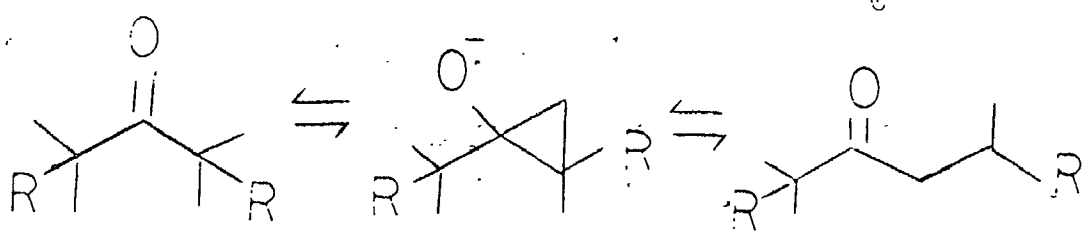


15

FIGURE 1.1: Estimated Rates of $^{1}H/^{2}H$ Exchange *via* ε-enolates at 185°C (k x 10^{ε} sec^{-1}) (13,16)

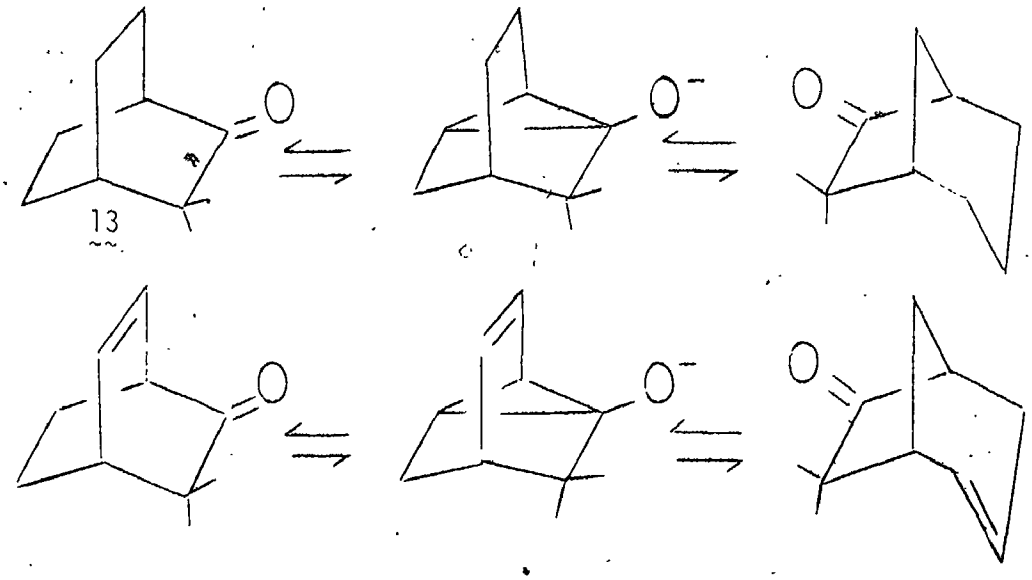
3-one (12c) slowly isomerize under strongly basic conditions.



12

a) R = Me; b) R = *n*-Bu; c) R = C_6H_5

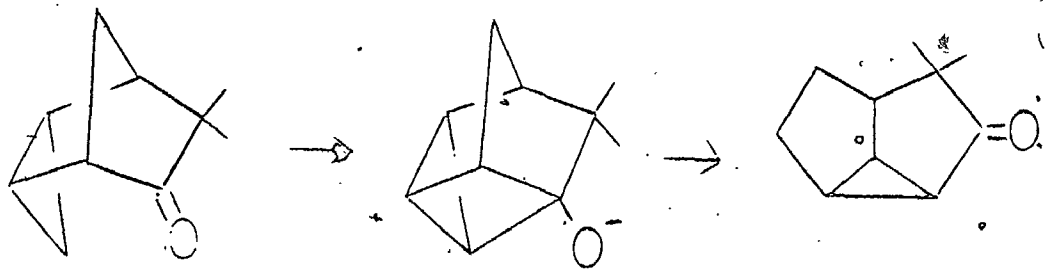
Considerable interest has developed in examining the influence of substituents on the regioselectivity and relative reactivity of homoenolization. Cheng and Stothers (15) found that the introduction of a double bond into the [2.2.2] ring system 13 enhances the reactivity toward



13

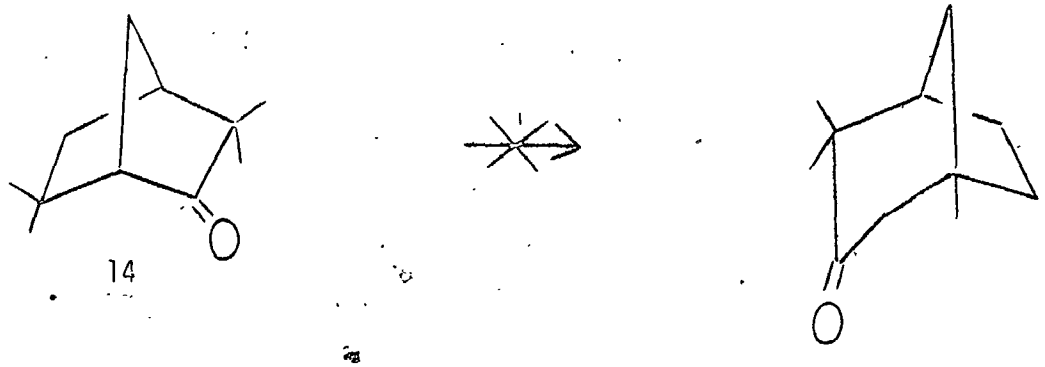
β-enolate formation and subsequent rearrangement to the [3.2.1] skeleton. A comparison of the rates of deuterium exchange for 14 and 5-oxo-14 clearly shows a marked

increase in reactivity for exchange in the latter, which is attributable to an activating effect of the second carbonyl group (16a). The effect of three-membered rings in polycyclic systems has also been examined. Ketone 15 exhibited increased reactivity for exchange at C-5 and C-8 (13) relative to that at C-1 and C-7 in 14. The endo isomer 16a also exhibited increased reactivity for exchange at the α-bridgehead carbon relative to that found for 14. In addition, 16a is smoothly transformed to 4,4-dimethyl tricyclo[3.3.0.$0^{2,8}$]octan-3-one (16b) under homoenolization conditions by Y-enolate formation at C-3,



16a 16b

in contrast to the stability of 14 under the same conditions.

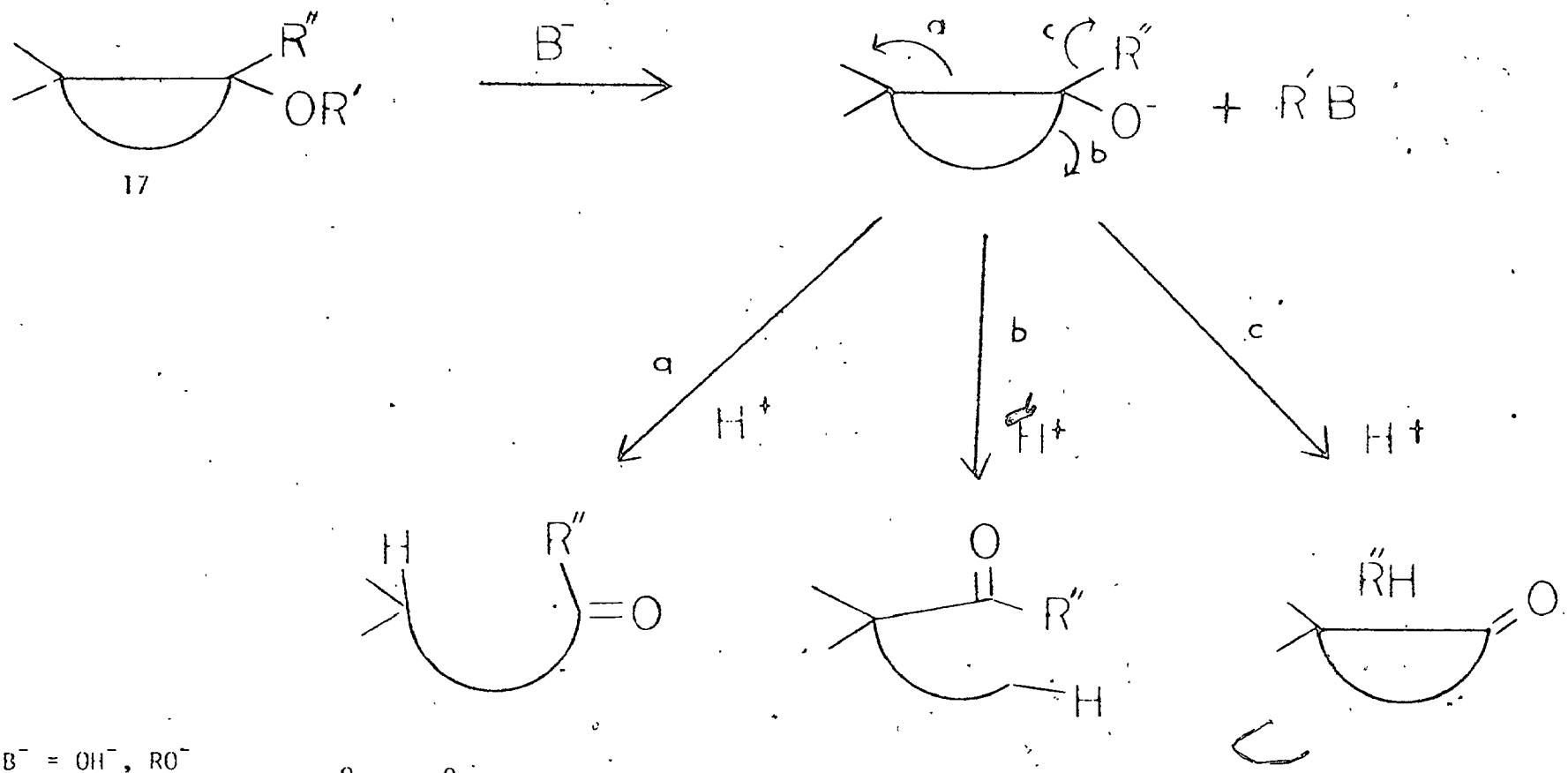


14

These examples show that substituents can influence the regioselectivity and relative reactivity of homoenolization.

A second useful route to homoenolate anions involves mild hydrolysis or alcoholysis of cyclic ethers such as 17 in an alkaline medium (Scheme 1.2). Irreversible homoketonization of the resulting cycloalkoxide can, in principle, occur by three modes, but generally ring cleavage exhibits high regio- and stereoselectivity. Although the stereochemistry is determined by a delicate balance of factors, including solvent effects and the nature of the cycloalkoxide (homoenolate) anion, certain generalizations can be made. In the case of β-enolates, protonations have been observed to occur with high degrees of inversion or retention, while ring cleavage of γ- and δ-enolates in rigid polycyclic systems usually proceeds with retention (16).

The regioselectivity of homoketonization can usually be rationalized in terms of electronic and thermodynamic factors. As examples, 18 and 19 (Figure 1.2) illustrate the general tendency favoring generation of the less highly substituted incipient carbanion. However, the base catalyzed cleavage of 20 clearly shows that the preference for a primary over secondary carbanion can be reversed if the latter is stabilized, in this case, as a benzylic centre. In contrast to the preceding results, the product composition from homoketonization of the birdcage

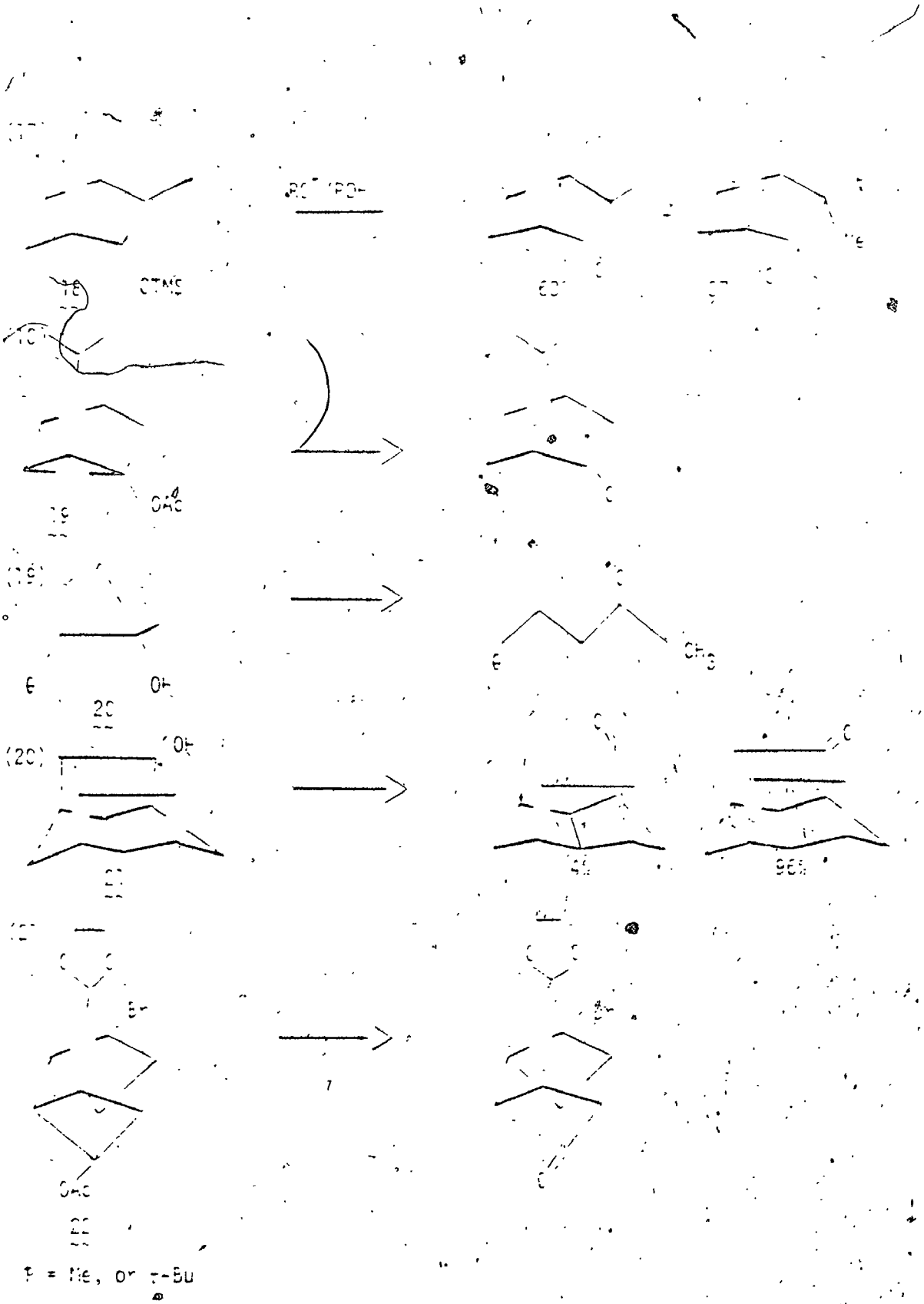


17

B^- = OH^-, RO^-

R' is usually $-SiMe_3$, $-\overset{O}{\overset{\|}{C}}CH_3$, $-\overset{O}{\overset{\|}{C}}H$, H

SCHEME 1.2



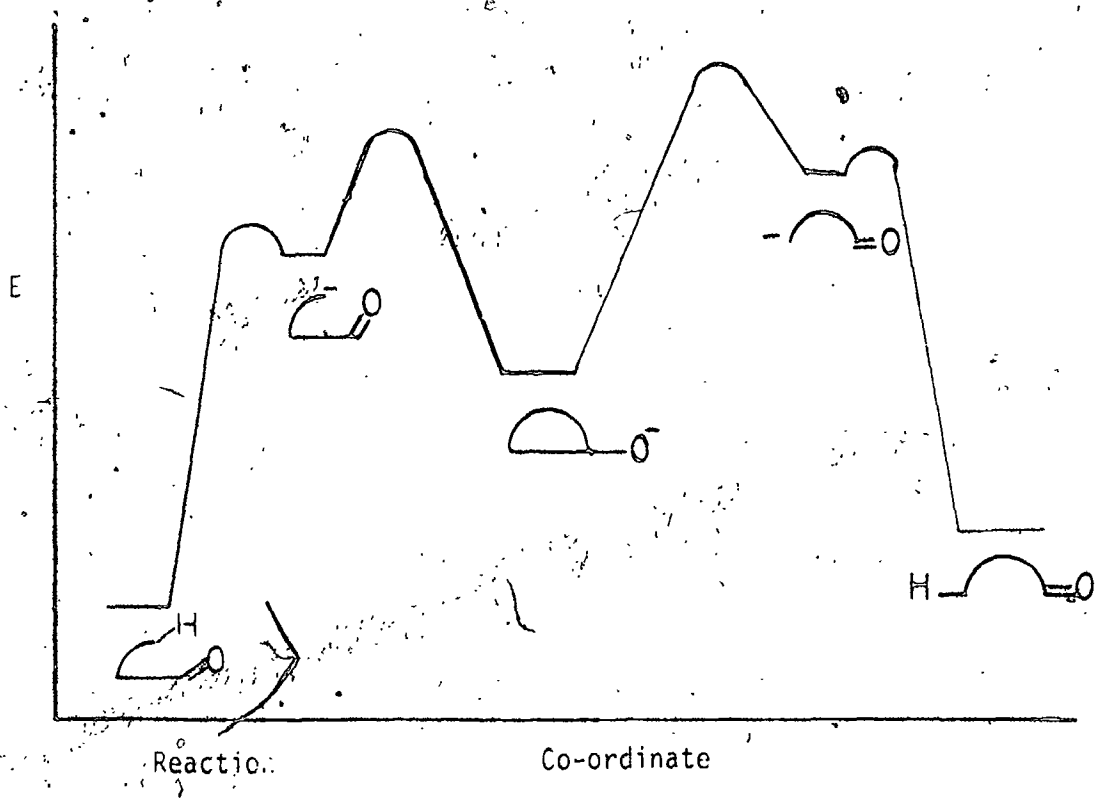
R = Me, or t-Bu

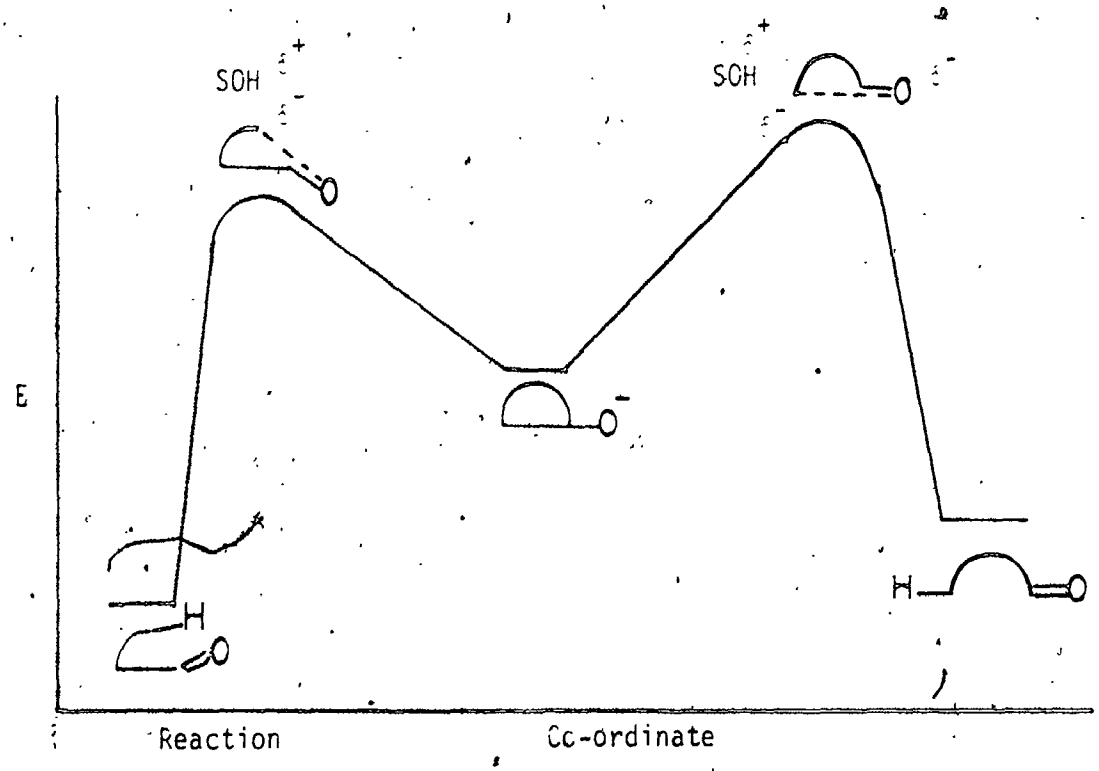
FIGURE 1.2: Regioselectivity of Homoketonization of Homoenolates

alcohol 21 and homocubanol 22 reflects the tendency for ring opening to form the more stable product. It is apparent that the regioselectivity of homoenolate cleavage is governed by the balance between carbanion and product stability; thus the preference between the three modes of ring cleavage in a given system may be difficult to predict.

The mechanism of homoketonization may involve a single transition state or a discrete carbanion as an intermediate, as shown in the energy profile diagrams in Figure 1.3. Since both mechanisms predict that a significant negative charge develops at the carbon centre prior to protonation, the stability of the incipient carbanion is important in determining the regiochemistry of homoketonization. In addition, since protonation occurs well along the reaction co-ordinate the relative stability of the possible products also influences the product composition. The stereochemical course of homoketonization is very much dependent upon the mechanism of ring cleavage, the intricacy of which remains controversial. Thus it is difficult to predict the favored stereochemical pathway in new systems.

In the course of the research presented in this thesis, attention was directed towards increasing our understanding of the factors influencing the regio- and stereochemistry of homoketonization. The results from examinations for several series of polycyclic ring systems are described in Chapters 2 through 8. Some studies





SOH = protic solvent

FIGURE 1.3: Energy Profiles for Homoketonization of Cycloalkoxides

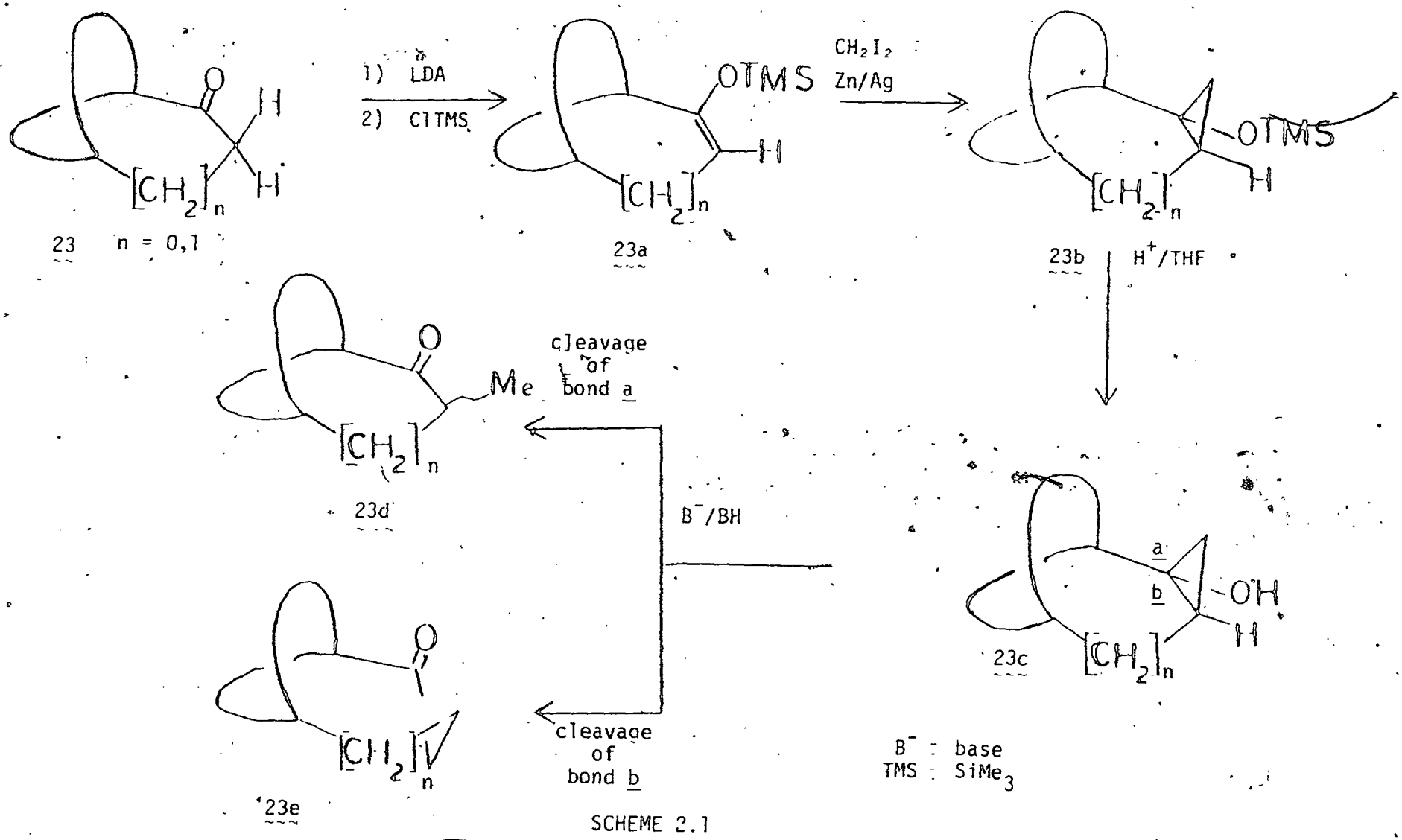
intended to clarify structural features controlling β- and γ-enolization in several related polycyclic systems were carried out; the results of these investigations are presented in Chapters 9 to 12. The experimental details are collected in the final chapter.

CHAPTER 2

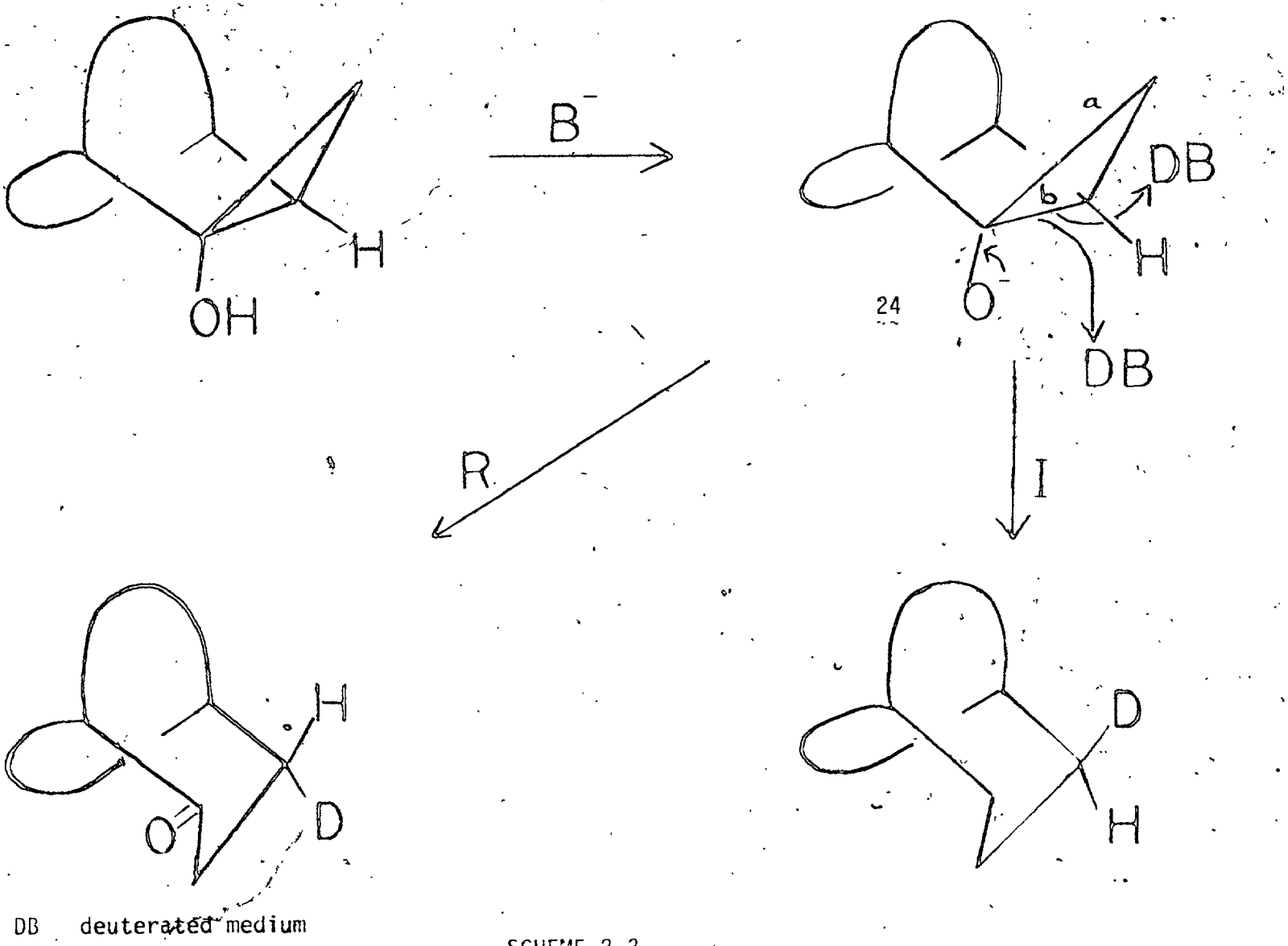
HOMOKETONIZATION OF POLYCYCLIC CYCLOPROPOXIDES

(A) INTRODUCTION

The regiospecific homologation of unsymmetrical ketones has long been the objective of many synthetic procedures. Although the homologation of ketones by diazoalkanes (22), diazoacetic esters (23) and the Tiffeneau-Demjanov reaction (24) often proceeds in good yield, these reactions usually afford both regioisomers. Recently, a new synthetic method for the ring expansion of certain polycyclic ketones was described (25). The procedure, illustrated in Scheme 2.1, circumvents the problem of generating both regioisomers, since the direction of homologation is predetermined by the position of the double bond in 23a. Cyclopropanation of the silyl enol ether with a zinc-silver couple and methylene iodide (26) gave the cyclopropyl silyl ethers 23b. Cleavage of 23b with dilute HCl in THF generated the corresponding cyclopropanol, which upon addition to base readily opened to give ketones 23d and 23e. The product ratio of 23d and 23e appeared to be influenced by two opposing factors. Cleavage of bond a in 23c may be inherently preferred because the primary carbanion is more stable and less hindered for protonation than the secondary carbanion


1) LDA
2) ClTMS
OTMS
CH_2I_2
Zn/Ag
OTMS
H
$[CH_2]_n$
23 n = 0,1
23a
23b
H^+/THF
cleavage of bond a
Me
23d
B^-/BH
a
b
OH
23c
cleavage of bond b
23e
B^- : base
TMS : $SiMe_3$

SCHEME 2.1



DB deuterated medium

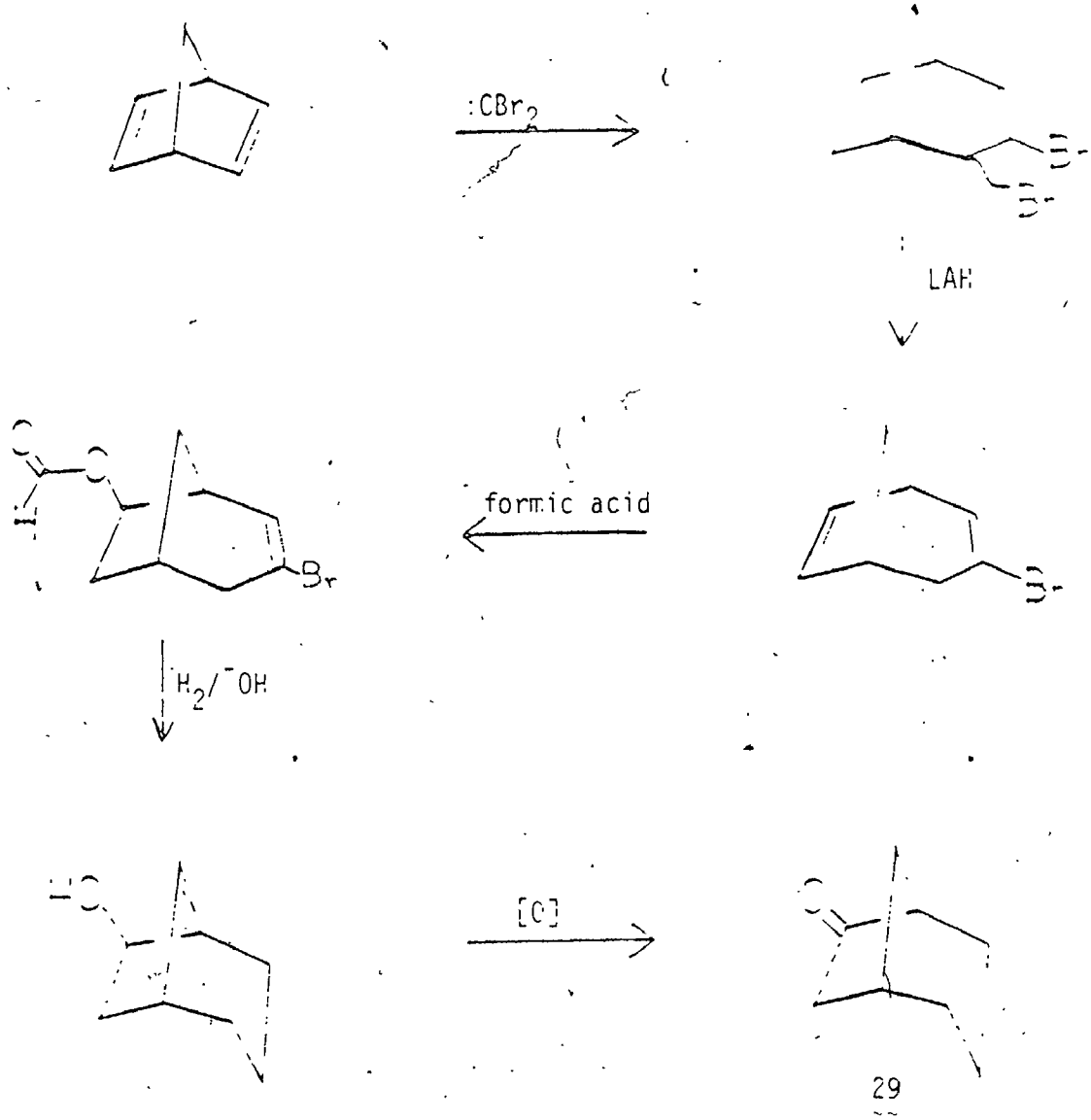
SCHEME 2.2

formed by cleavage of bond b. However, the relief of ring strain resulting from cleavage b may favour this mode, which appears to be the case for [2.2.1] and [2.2.2] ring systems. In addition, preliminary studies on the temperature dependence of the regioselectivity for homoketonization indicated that lower temperatures favour the ring expansion process. Therefore to enhance the synthetic utility of this method the effect of temperature and ring size on the product ratio of 23d and 23e was examined further.

Protonation of the anion generated by cleavage of bond b can proceed with retention or inversion of configuration. These are shown as R and I in Scheme 2.2, which illustrates that the stereochemistry of the process can be determined by homoketonization of 24 in a deuterated medium. In general, homoketonization of cyclopropoxides in polycyclic systems has been found to occur with high degrees of inversion or retention. Thus it was of interest to establish the stereochemistry of protonation (deuteration) upon cleavage of bond b in 24.

(B) RESULTS AND DISCUSSION

The homologation sequence was examined for a series of eight polycyclic ketones, of which four were readily available (camphor (25), norcamphor (26), tricyclo [5.2.1.$0^{2,6}$]undecan-8-one (27), tricyclo[5.3.1.$0^{2,6}$] undecan-8-one (28)). The remaining four compounds 29-32 were prepared as outlined in Scheme 2.3. Treatment of



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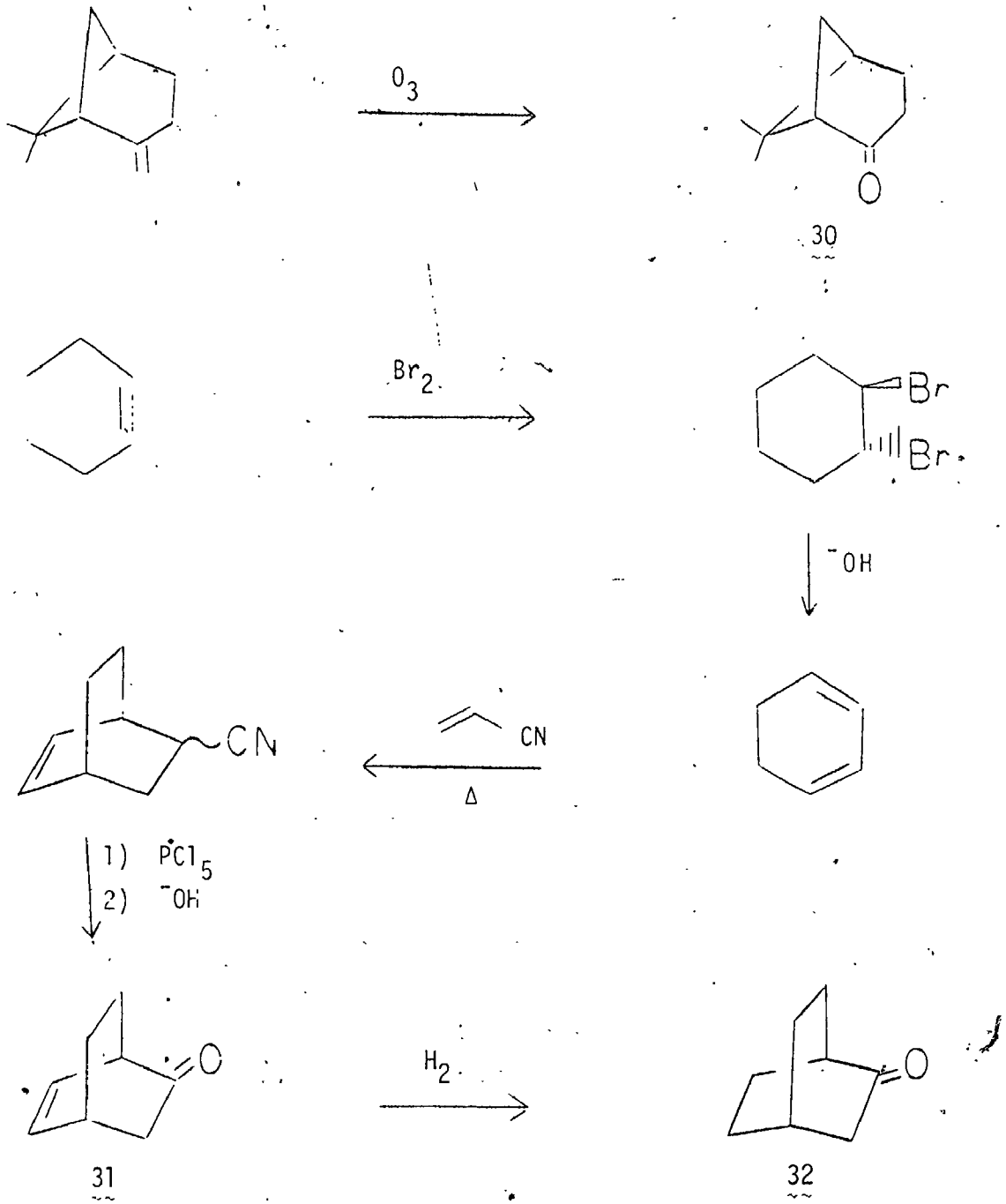
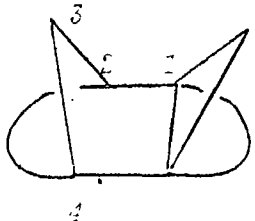
SCHEME 2.3



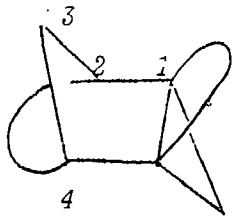
SCHEME 2.3

ketones 25-32 with lithium-diisopropylamide followed by reaction with trimethylsilyl chloride and triethylamine gave the corresponding trimethylsilyl enol ethers (25a-32a) which, with the exception of 28a, have been previously characterized (27-29). Cyclopropanation of the silyl enol ethers, 26a-32a with a zinc-silver couple and methylene iodide gave a single cyclopropyl silyl ether (26b-32b), in each case. In contrast, treatment of 25a with the Simmons-Smith reagent yielded only starting material even after 220 h at reflux. The difference in reactivity for 25a and 26a may be attributed to steric repulsions between the Simmons-Smith reagent and the syn methyl, C-8, in the enol ether of camphor 25a. The ^{13}Cmr data for the cyclopropyl silyl ethers 26b to 32b are listed in Table 2.1.

The orientation of the cyclopropyl methylene in compounds 26b, 27b, and 29b was assigned from the ^{13}Cmr data. Since it has been found (30) that the cyclopropyl



33



34

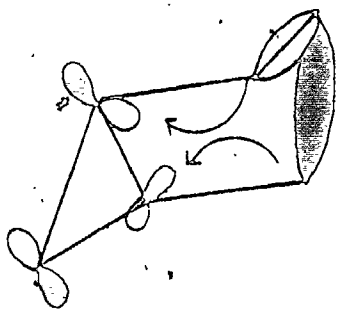
ring exerts specific Y substituent effects if incorporated into a rigid skeleton containing the bicyclo[3.1.0] hexane

TABLE 2.1: ^{13}C shieldings[a] for cyclopropyl silyl ethers 26b-32b

Cpd.	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{11}	C_{12}	TMS
26b	42.5	61.0	9.8	22.2	36.6	29.1	24.7	31.2					1.1
27b	41.1	48.4	(31.3)	28.2	(31.0)	43.7	46.9	62.8	13.8	23.9	24.8		1.2
28b	39.5	(44.8)	(34.7)	28.1	(33.0)	(45.2)	48.8	61.6	15.2	20.2	28.5	33.2	1.4
29b	39.2	62.5	13.7	25.3	34.9	32.2	19.6	29.0	34.3				1.3
30b	47.2	61.0	20.0	16.6	28.6	42.1	41.0	(26.8)	21.4	(26.7)			1.5
31b	38.6	57.5	10.7	18.1	31.6	(129.9)	(132.4)	(21.2)	(25.3)				1.2
32b	32.2	58.1	11.5	23.0	25.3	(22.6)	(26.0)	(23.3)	(25.1)				1.3

[a]All spectra weremeasured for C_6D_6 solution, using the central solvent line as reference (δ_C 1280); similar values in parentheses may be interchanged.

system. In the case of 33, an upfield shift of ca. 11 ppm is observed for C-3, while in 34, a downfield shift of 15-20 ppm was found for C-3. The upfield shift can be viewed as a normal Y-effect, while the downfield shifts have been attributed to charge transfer from the σ framework to the antibonding Walsh orbitals of the three-membered ring (31). An examination of the ^{13}Cmr



shieldings for several bicyclo[3.2.1.$0^{2,4}$]octanes (30) and tricyclo[3.1.1.$0^{2,4}$]heptanes (31) serves to illustrate these effects (Fig. 2.1). Hence the ^{13}Cmr shieldings for C-8 of **26b** (δ_C = 31.2), C-11 of **27b** (δ_C = 24.8) and C-9 of **29b** (δ_C= 34.3) are only consistent with cyclopropanation at the exo face of **26a**, **27a** and **29a**, respectively. An endo cyclopropyl ring in these systems would be expected to deshield the methano bridge substantially, such that its absorption would appear near δ_C 40 (see Fig. 2.1).

An inspection of molecular models for **30a** indicated that cyclopropanation of the double bond should occur from the less hindered face, thereby generating **30b**.

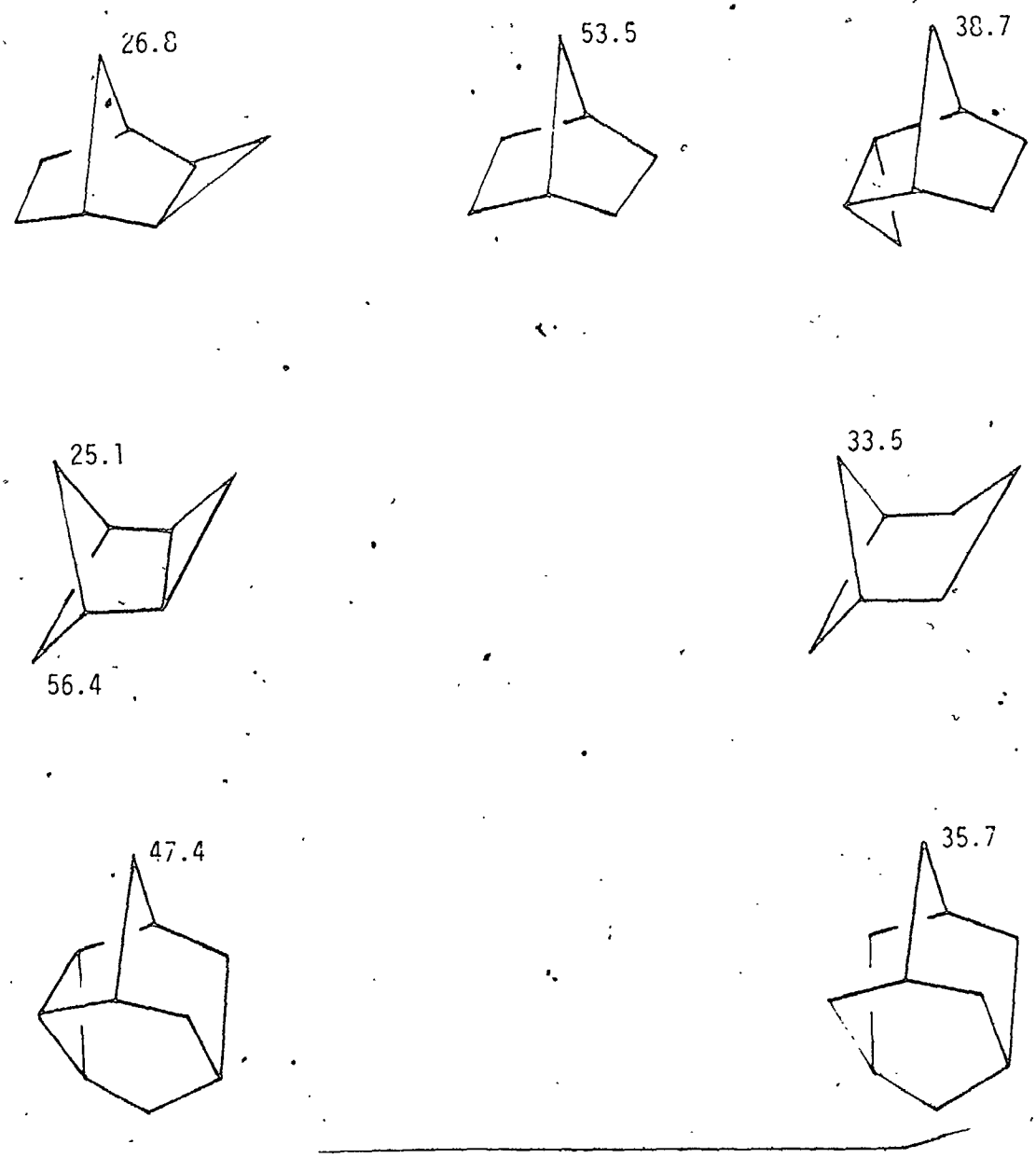
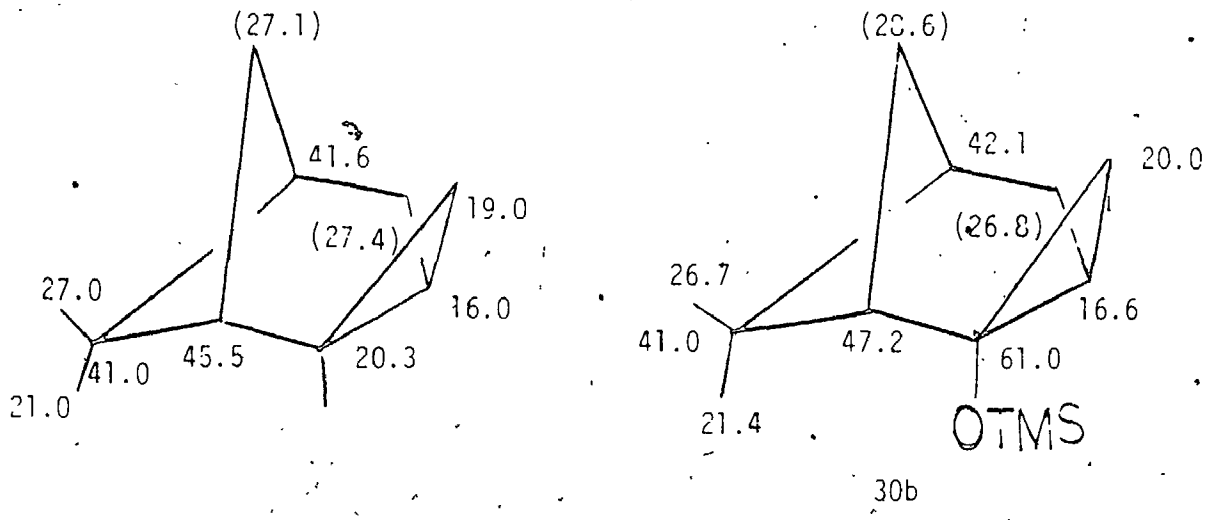


FIGURE 2.1: ^{13}C Shieldinns (δ_C) of Some Bicyclo[3.1.0]-hexane Derivatives (30,31)

The ^{13}Cmr data for exo-2-7,7-trimethyltricyclo[4.1.1.$0^{2,4}$]-octane (32) and 30b indicated that the cyclopropyl methylene



30b

group of 30b is anti to C-7, since the chemical shifts for the two compounds are comparable, taking into account the expected effects of the methyl and trimethylsilyloxy substituents.

Although the stereochemistry of 28b and 31b could not be readily established from the ^{13}Cmr data, the results for 26b, 27b and 29b clearly indicate that methylene transfer from the least hindered direction is favoured. Hence this would suggest that the cyclopropyl methylene group in 28b and 31b is syn to the methano and dimethine bridges, respectively.

Cleavage of the cyclopropyl silyl ethers 26b, 29b, 30b and 31b with dilute HCl in THF gave the corresponding cyclopropanols 26c, 29c, 30c and 31c, respectively.

Compounds 26c, 29c and 31c had been previously characterized (see Table 2.2 for ^{13}Cmr data) while the spectral data (ir, ^{13}Cmr) and precise mass measurement of 30c were in agreement with the assigned structure. It was found that preparative gas-liquid chromatography (glc) of these cyclopropanols gave the *exo* α-methyl ketones 26d, 29d, 30d and 31d (> 80 % glc yield) respectively, with no trace of the *endo*-isomers. At present it seems most reasonable to conclude that the cyclopropanols are not stable to the glc conditions and decompose on the surface of the column packing to yield the α-methyl derivatives, which are stable. Since the α-methyl ketones are not epimerized by glc analysis this would suggest that the stereochemistry of these ketones is predetermined by the stereochemistry of the cyclopropanols. Therefore the transformations 26c → *exo*-26d, 29c → *exo*-29d, 30c → *exo*-30d and 31c → *exo*-31d supports the stereochemical assignments for 26c, 29c, 30c and 31c.

Homoketonization of 26c, 30c and 31c was carried out by rapid addition to a solution of RO^-/ROH at various temperatures (at 0°, 25°C with R = Me, at 83°C with R = *t*-Bu). The ketonic products were isolated by pentane extraction and identified by glc co-injection with authentic samples and/or by their ^{13}Cmr spectra. The results from the base-catalyzed ketonization of the cyclopropanols are listed in Table 2.3.

TABLE 2.2: ^{13}C Shieldings[a] for cyclopropanols 26c, 29c, 30c and 31c

Cpd.	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}
26c	41.9	59.8	9.7	22.5	36.7	28.8	24.6	31.1		
29c	28.5	61.5	13.7	25.6	35.0	(31.9)	19.4	(28.4)	34.2	
31c	38.4	55.9	11.1	18.7	31.8	(132.8)	(129.6)	(21.4)	(25.4)	
30c	46.7	60.2	19.8	17.2	(26.5)	41.7	40.8	(28.6)	21.0	26.3

[a]All spectra were mesured for C_6D_6 solution.

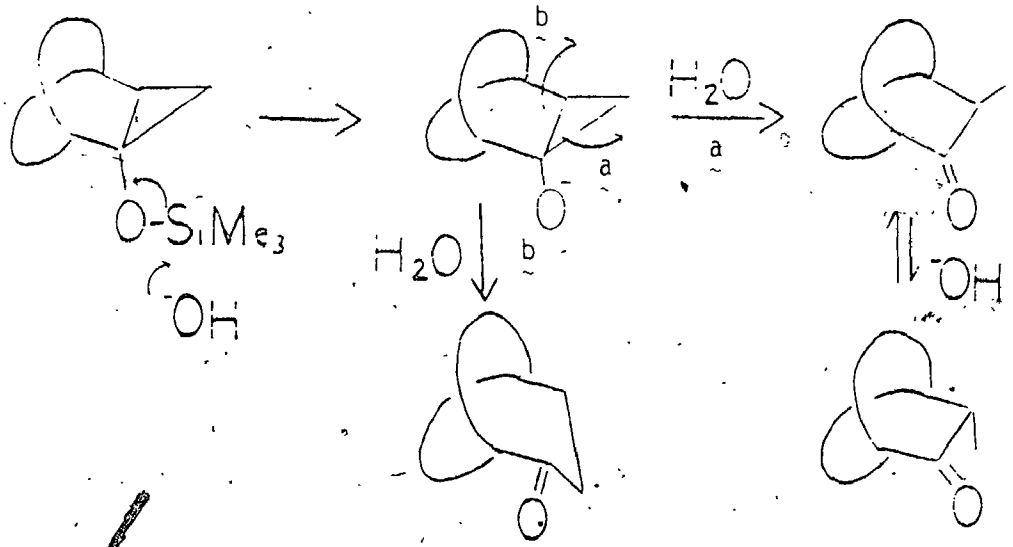
TABLE 2.3: Base-catalyzed[a] homoketonization of 26c, 30c and 31c

Reactant	Temperature (°C)	Product (%)[b] d	e
31c	0	5	95
	25	8	92
	83	13	87
26c	25		>99
	83	7	93
30c	25	100	

[a]1 M RO^-/ROH; R = Me, T = 0°, 25°C, R = t-Bu, T = 83°C.

[b]Averaged for 2-3 runs in each case, measured by glc (FFAP), estimated precision ± 5%.

An alternative and more efficient method of cleaving 23b is by treatment with base which directly effects ether cleavage and homoketonization of the cyclopropyl silyl ether.



Compounds 26b-30b and 32b were opened in this manner and the resulting product distributions are listed in Table 2.4. Under these conditions the initially formed α-methyl ketones can readily epimerize, hence the cleavage of 26b, 29b and 30b gave mixtures of the two α-methyl isomers. In contrast, treatment of 28b with $^-$OH/MeOH gave only the *exo* isomer of 28d; to confirm enolate formation *exo*-28d was treated with MeO^-/MeOD which yielded *exo*-28d-$\underline{d}_1$ only. Therefore *exo*-28d does not epimerize under normal conditions which is analogous to the behaviour of *exo*-3-methylbicyclo[3.2.1]octan-2-one which is also stable under similar conditions (33).

TABLE 2.4: Base-catalyzed[a] cleavage of cyclopropyl silyl ethers

Reactant	Temperature (°C ± 3)	Product (%)[b] d (exo:endo)	e
27b	0		100
	25		>99
	83	6	94
29b	0	40	60
	25	48	52
	83	68 (1:1)	32
26b	25		>99
	83	4 (1:1)	96
28b	25	>94[c]	
30b	25	100 (5:1)[d]	
32b	25	30	70

[a]Ring cleavage of the cyclopropyl silyl ethers at 0° and 25°C was accomplished with 3 M NaOH-MeOH, while at 83°C a 1 M KOH-t-BuOH solution was employed.

[b]Unless otherwise indicated, the product composition was determined by glc analysis; estimated precision ± 5%.

[c]Exo isomer only.

[d]From ^{13}Cmr spectra ± 10%.

In general the relative proportions of the ring-expanded and α-methyl ketones formed by homoketonization of the polycyclic cyclopropoxides were consistent with the previously reported data (25). However, the results for 29b with 3 M methanolic NaOH solution at room temperature (48% 29e, 52% 29d) clearly differed from the previously reported values for homoketonization of 29c, with t-BuO⁻/t-BuOH (30% 29e, 70% 29d) (25), this difference in relative proportions is difficult to explain. The data in Tables 2.3 and 2.4 support the notion that the regioselectivity of homoketonization of these polycyclic cyclopropoxides is influenced by the relative stability of the carbanions and of the ketonic products. It can be suggested that ring expansion is favoured for the more strained ring systems (26b and 31b), since the relief of ring strain resulting from this mode of ring cleavage yields the more stable product, as shown in the energy profile diagram (Fig. 2.2). For the less strained ring systems (28b and 30b) the products from homoketonization of the cyclopropoxides are of presumably comparable energy, and hence the stability of the incipient primary anion favours formation of the α-methyl ketone (Fig. 2.3).

For synthetic purposes this homologation sequence provides a facile method for ring expansion of the [2.2.1] and [2.2.2] ring systems.

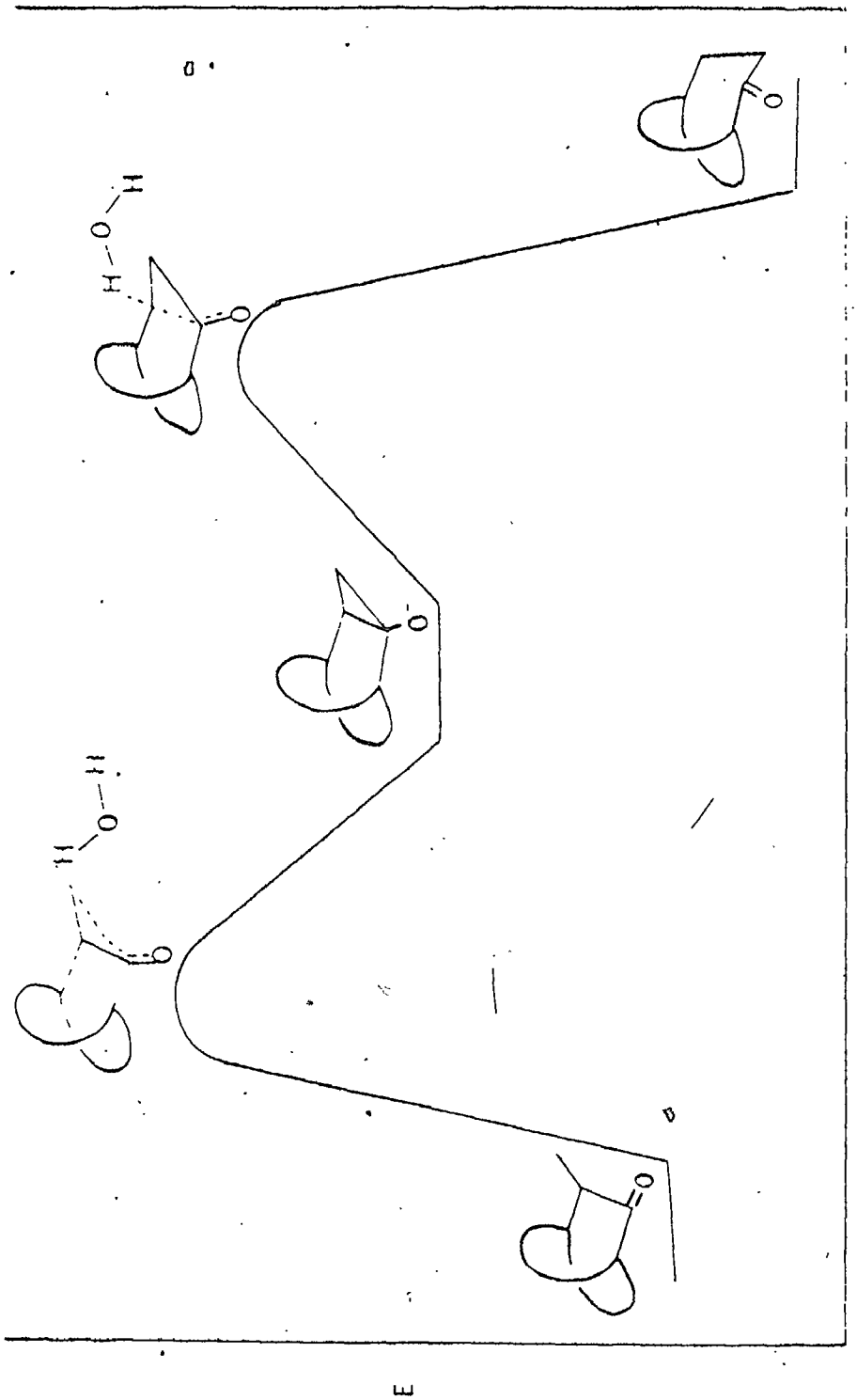


FIGURE 2.2: Energy Profile Diagram for the Homoketonization of 26c, 27c and 31c

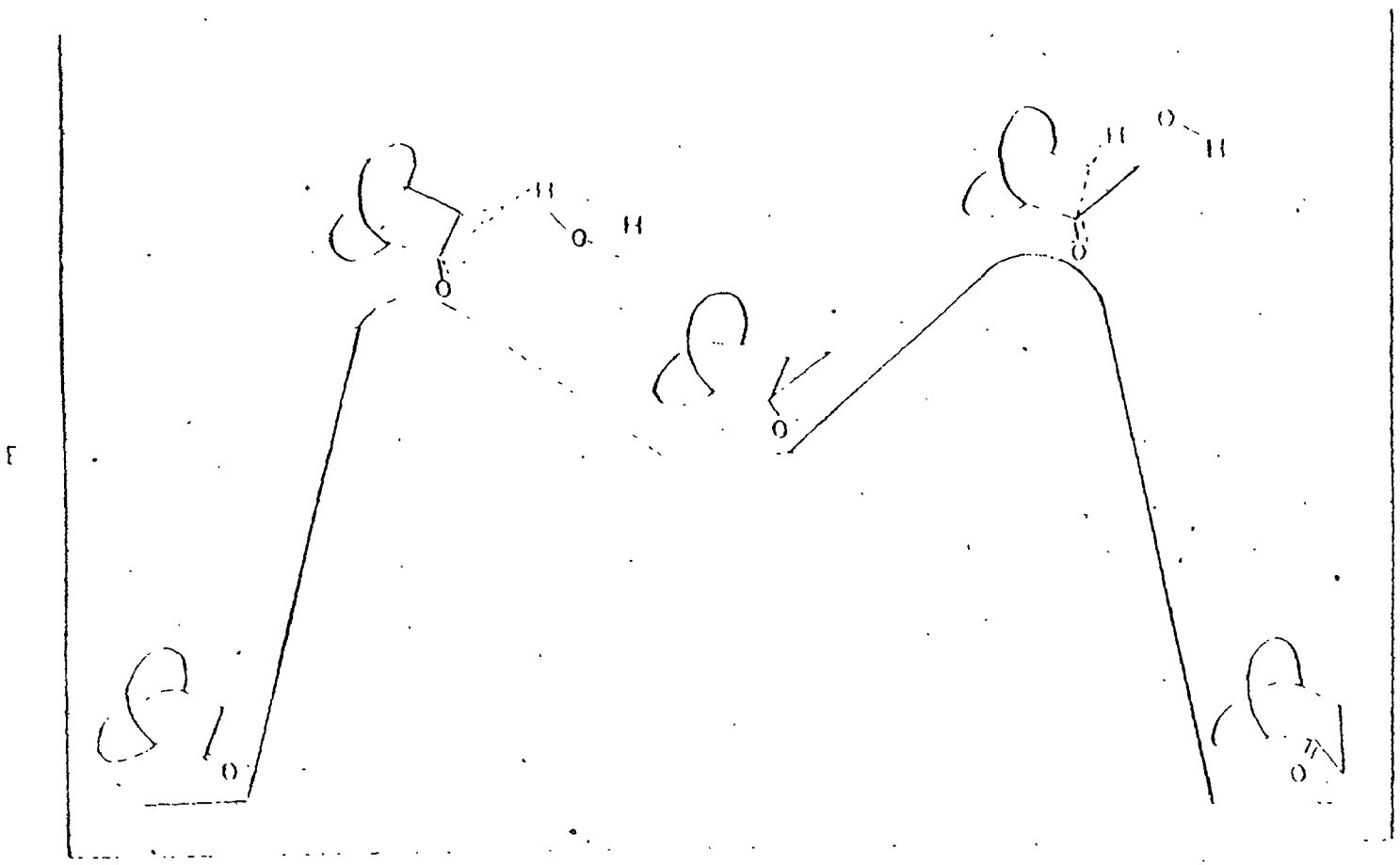
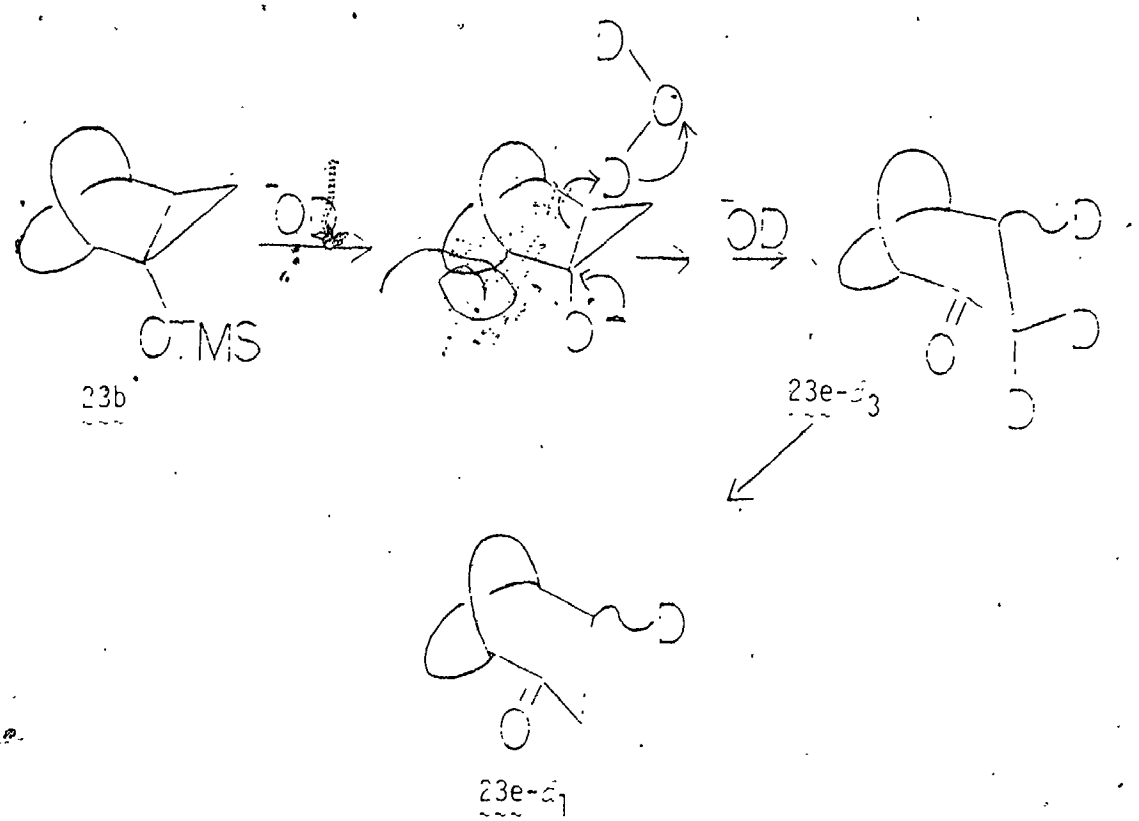


FIGURE 2.3: Energy Profile Diagram for the Homoketonization of 28c and 30c

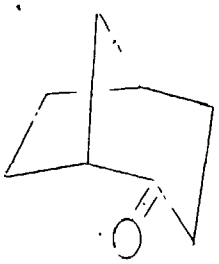
The second interesting aspect of homoketonization of 24 is the stereoselectivity of protonation (deuteration) since bond b cleavage can proceed with retention or inversion of configuration. These are shown as I and R in Scheme 2.2 to illustrate that the stereochemistry of the process can be determined by cleavage in a deuterated medium. The general procedure employed to distinguish between paths I and R consisted of cleaving 23b in $^-$OD/ROD (R = CH_3, t-Bu) followed by treating 23e-d_3 with $^-$OH/MeOH to back exchange the α-deuterium picked up after ketonization; this sequence furnished 23e-d_1. To determine



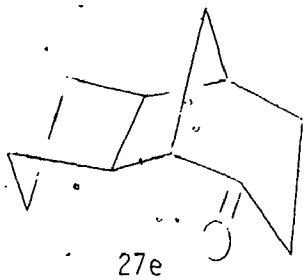
the stereochemistry of the β-deuterium atom the ^{13}Cmr spectrum of a 1:1 mixture of 23e and 23e-d_1 was recorded, since the magnitude of the vicinal $^{13}C-^2H$ coupling

interactions and the ^{2}H-induced isotope shifts depend on the relative orientation of the two nuclei. The dihedral angular dependence of vicinal deuterium induced isotope shifts for the ^{13}C nuclei of polycyclic systems was examined by Jurlina and Stothers (34). For endo-fenchol-2-exo-d_1 (Fig. 2.4) the magnitude of three-bond isotope shifts is a maximum when the dihedral angle defined by the two vicinal nuclei is ~ 0°, since the isotope shifts for the exo-8-methyl carbon (θ ~ 0°) and C-10 (θ ~ 30°) are 0.080 and 0.050 ppm, respectively; while for the remaining vicinally located carbons, $\theta \geq 90°$ the isotope shifts are $\leq$ 0.020 ppm. The magnitude of $^{3}J_{CD}$ is dependent upon the dihedral angle for the two nuclei (ie. a Karplus relationship) and for θ ~ 0° or 180°, $^{3}J_{CD}$ is maximal, thus vicinal C-D couplings are generally resolved.

The cyclopropyl silyl ethers 26b, 27b, 29b and 31b were opened in deuterated media and back-washed with



26e



27e

$^{-}$OH/MeOH. The ring expanded ketones were glc collected and the ^{13}Cmr spectra of 1:1 mixtures of the protio and mono-deuterated compounds were obtained. The ^{2}H effects on

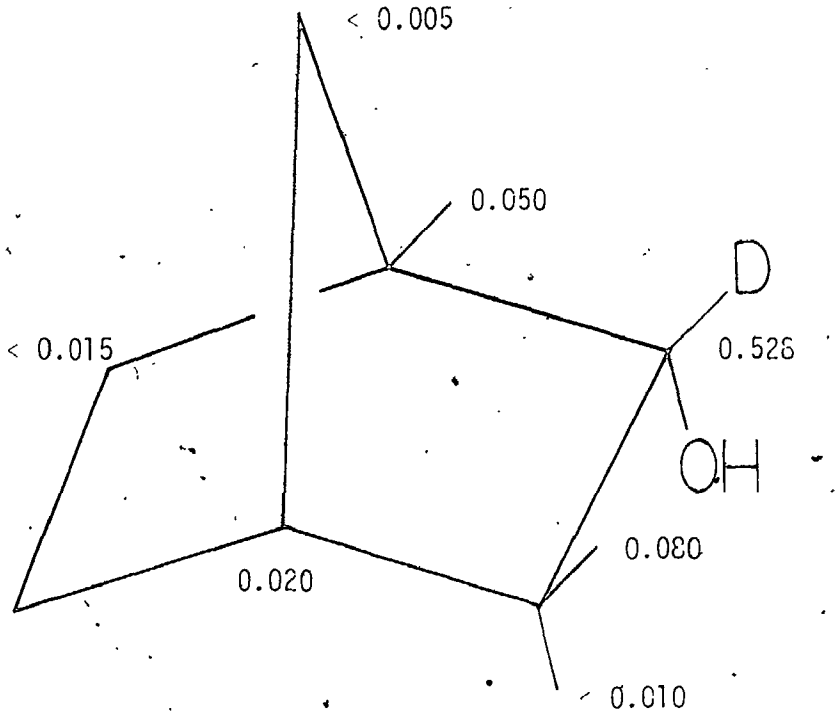
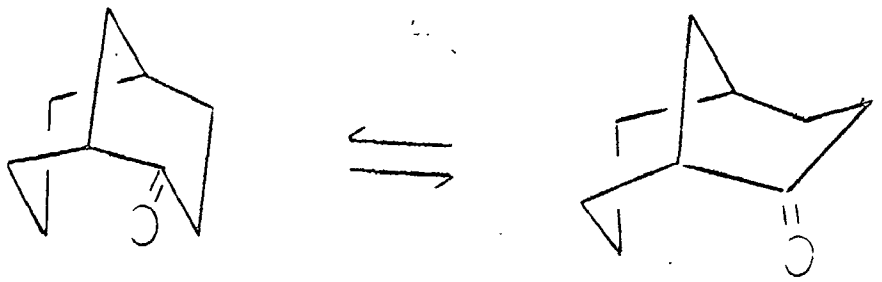
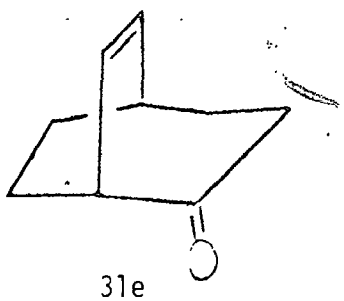


FIGURE 2.4: Deuterium-Induced Shifts (in ppm) for ^{13}C-Nuclei in *endo*-fenchol-2-*exo*-d_1

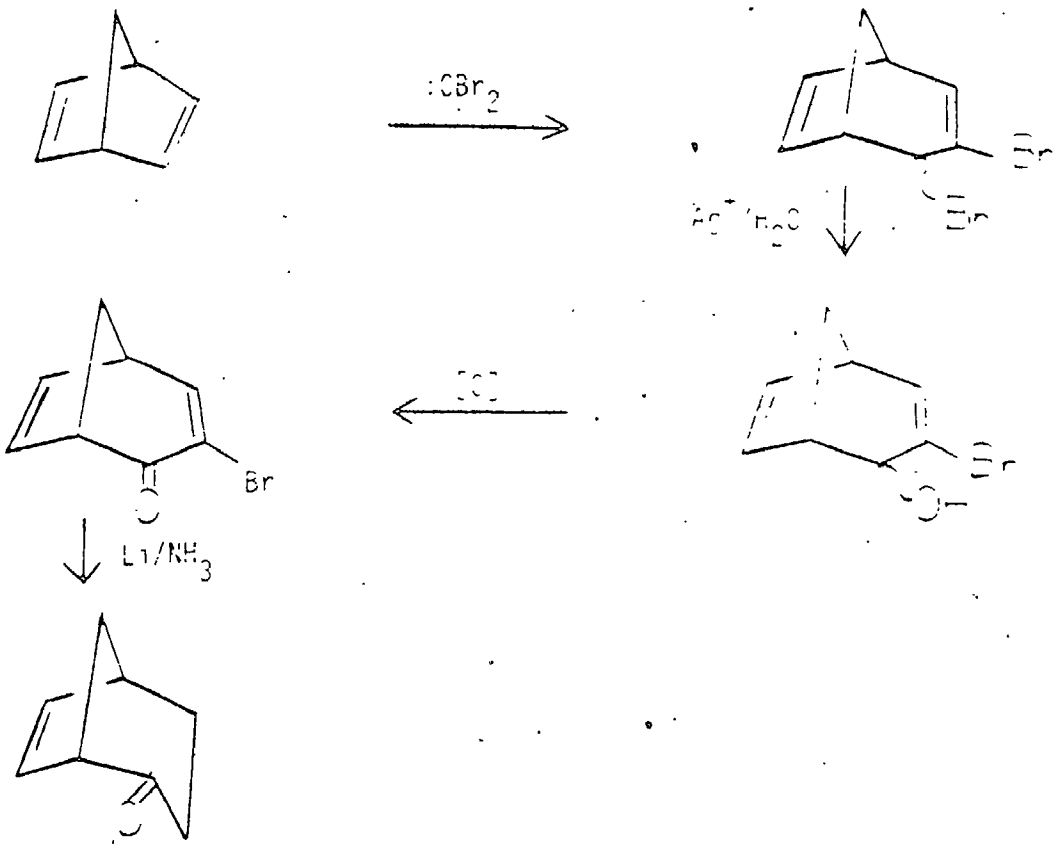
the $^{13}C^{1}H$ results for 26e-d_1, 27e-d_1, 29e-d_1, 31e-d_1 are shown in Figure 2.5 from which it was concluded that the β-^{2}H nucleus is exo in each case. Since the magnitude of $^{3}J_{CD}$ is dependent upon the relative orientation of the two nuclei, a decision regarding the preferred conformation for these flexible ring systems was required. An inspection of molecular models indicated that the six-membered ring of 26e and 27e will favor a chair conformation. For 31e the three carbon bridge is presumably puckered towards the dimethine bridge, while for 29e it had been concluded (35) that both the double-chair and chair-boat conformations are present in solution.



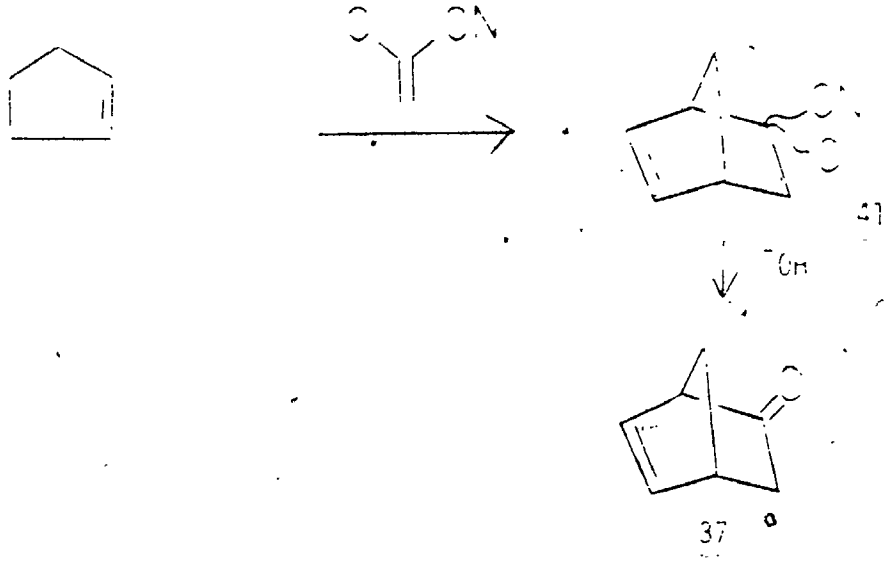
29e 29e



31e



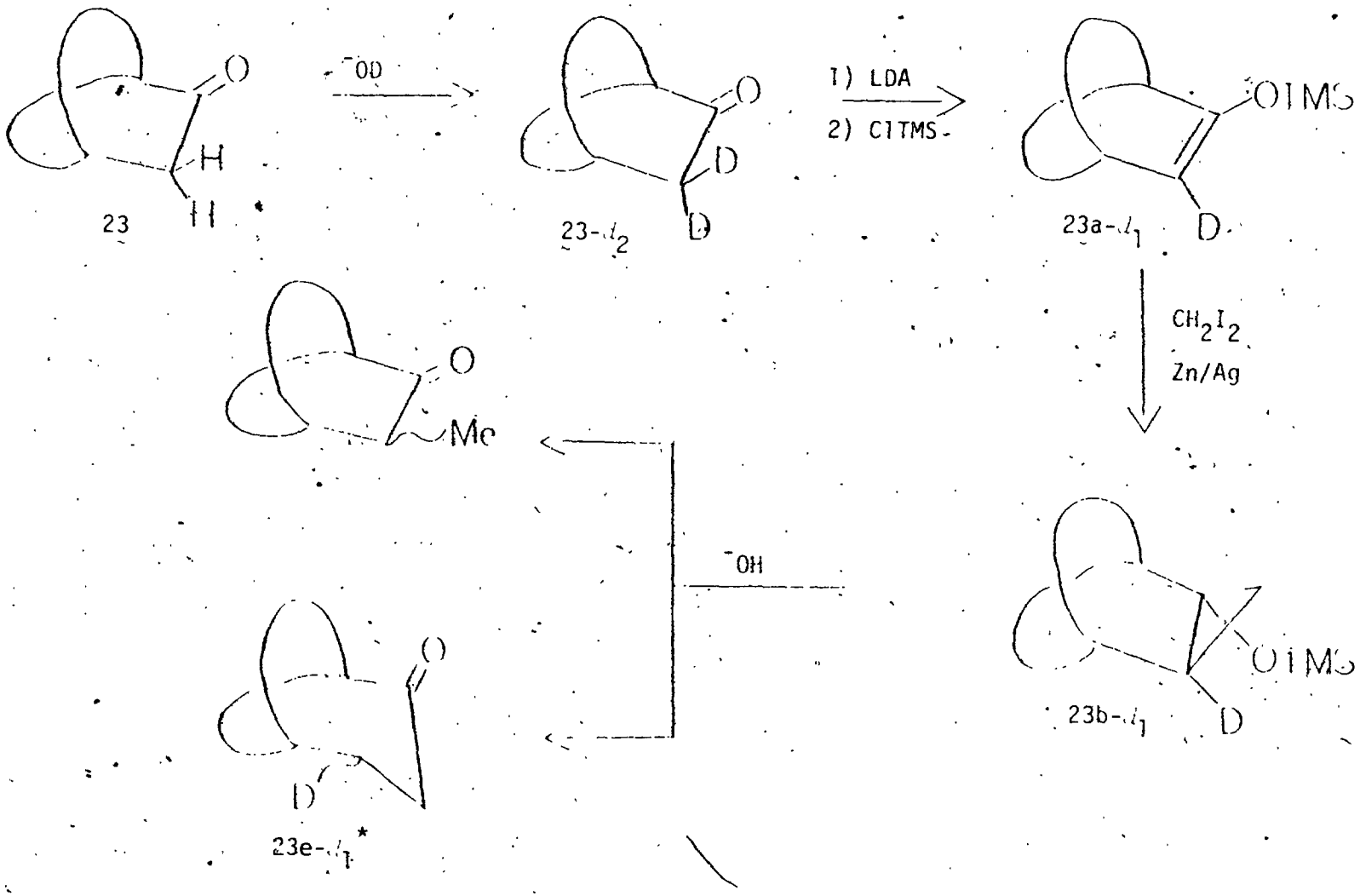
SCHEME 3.1



SCHEME 3.2

The ^{13}Cmr data for 26e-d_1 showed that C-6 is coupled to the deuteron at C-4 (J_{CD} = 1.1 Hz), while the signal for C-8 was only slightly broadened; this is consistent with deuterium antiperiplanar to C-6 and, therefore in the exo-orientation. These data show that the ring cleavage of 26b occurs with inversion. If opening with retention occurred the deuterium nucleus should produce observable coupling with C-8 (δ_C 38.3). An examination of the ^{13}Cmr data for 27e-d_1 and 31e-d_1 showed that the β-deuterium is coupled to C-2 ($^3J_{CD}$ = 1.1 Hz) and to C-9 ($^3J_{CD}$ = 1.3 Hz), respectively, which is consistent with an antiperiplanar arrangement in each case and, thus, the exo-orientation of the β-^{2}H in both ketones. Therefore, base-catalyzed homoketonization of 27b and 31b also occurs with inversion of configuration at the carbanionic site. The vicinal ^{13}C-^{2}H coupling data for 29e-d_1 were more difficult to interpret since unequivocal assignments for C-6 and C-9 (δ_C 32.6, 32.0) had not been established. Nonetheless the signal at δ_C 32.6 exhibited $^3J_{CD}$ = 1.1 Hz and since the β-deuterium in 26e-d_1, 27e-d_1 and 31e-d_1, is exo it was concluded that the same situation obtains for 29e-d_1; it follows that the δ_C 32.6 signal arises from C-6.

To confirm these assignments a second approach was utilized. The initial ketone, 23, was dideuterated in the α-position and converted to 23b-d_1 which was subsequently opened with $^-$OH/MeOH to furnish 23e-d_1[a] (see Scheme 2.4).



SCHEME 2.4

The ^{2}H effects in the ^{13}Cmr spectra of 26e-d_1*, 27e-d_1*, 29e-d_1*, and 31e-d_1* are shown in Figure 2.6. For 26e-d_1* the methano carbon (C-8) exhibited a vicinal coupling of 1.4 Hz while the C-6 signal was only slightly broadened, similarly, in 27e-d_1*, only the methano bridge (C-11) exhibited a vicinal coupling ($^{3}J_{CD}$ = 1.4 Hz). These data indicated that the deuterium atom in 26e-d_1* and 27e-d_1* is antiperiplanar to the methano bridge in each case and, hence, in the *endo* orientation. The ^{13}Cmr spectrum for 31e-d_1* showed that C-6 was coupled to the deuteron at C-4 (J_{CD} = 1.0 Hz) while the signal for C-9 was only slightly broadened. This is consistent with deuterium antiperiplanar to C-6 and therefore in the *endo*-orientation, showing that ring cleavage of 31b occurs with inversion. In the ^{13}Cmr spectrum of 29e-d_1* the signals for C-9 and C-6 were both coupled to the β-deuterium atom by 1.0 and 0.7 Hz, respectively. These data are consistent with deuterium in the *endo* orientation, assuming the ketone adopts the chair-boat conformation. In this conformation the dihedral angle relating the deuterium atom and C-9 is ca. 180°, while it is ca. 10°, between *endo*-4-^{2}H and C-6; hence both carbons are expected to be coupled. In contrast, for the chair, chair conformation only C-9 would exhibit observable coupling; with an *exo*-β-deuterium atom only one vicinal ^{13}C-^{2}H coupling would be observable. These results establish that the cleavage of bond b in 26b, 27b, 29b and 31b proceeds with inversion.

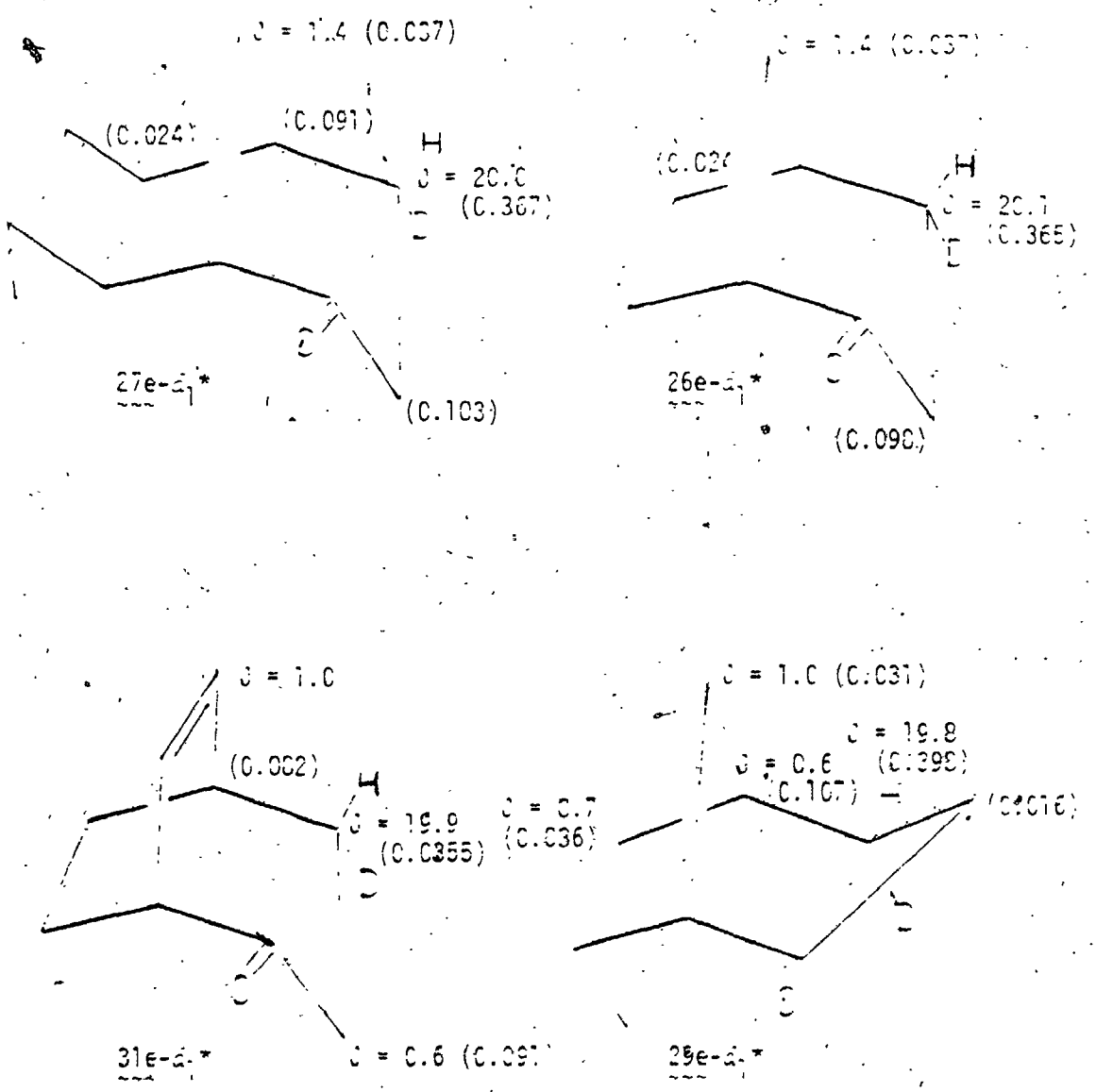


FIGURE 2.6: $^{2}J_{H-^{13}C}$ Coupling Constants (in Hz) and Isotope Shifts (in ppm) for 26e-d_1*, 27e-d_1*, 29e-d_1* and 31e-d_1*

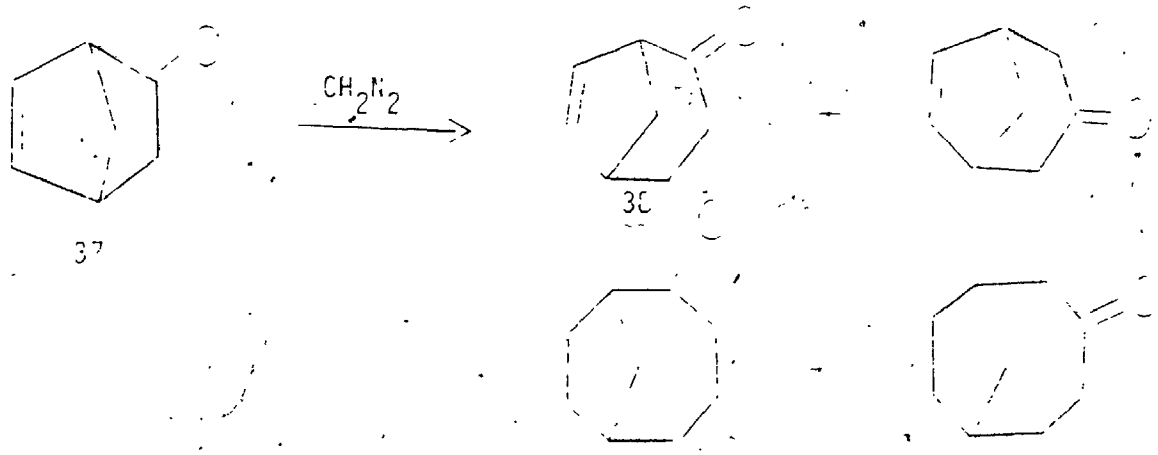
The ^{2}Hmr spectra of the mono-deuterated ketones in the e series (26, 27, 29, 31) were recorded and in each case the data clearly demonstrate that homoketonization is highly stereoselective (> 95%).

CHAPTER 3

THE SYNTHESIS AND HOMOKETONIZATION OF 2-TRIMETHYLSILYLOXYLHOMOQUADRICYCLENE

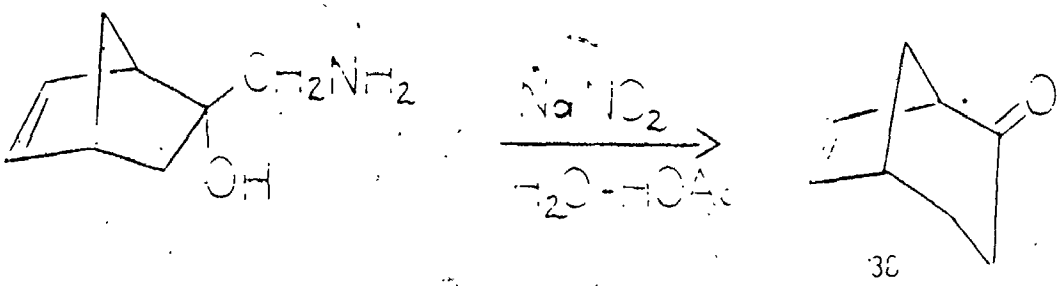
(A) INTRODUCTION

Ring expansion through homoketonization of an appropriate cyclopropyl silyl ether appeared to be a facile method for the homologation of norbornenone (37) to bicyclo[3.2.1]oct-6-en-2-one (38). Literature methods for the synthesis of 38 suffer from overall low yields or require several steps. The most direct approach, consisting of reacting diazomethane with 37 (36) gave a 42%



yield of 38, as determined by glc. The Tiffeneau-Demjanov ring expansion has also been reported (36) to give low yields of 38.

Another route to 38 involves the addition of dibromocarbene to norbornadiene (37). The dibromo

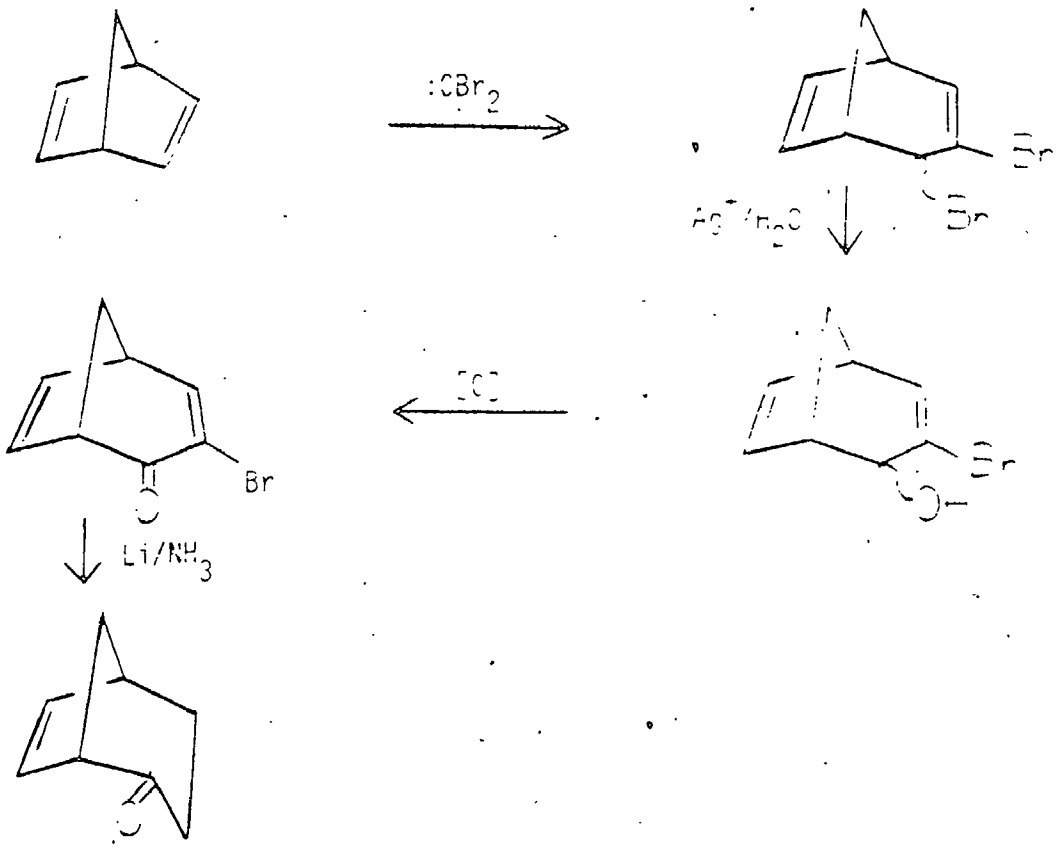


product is then converted to the desired compound, as illustrated in Scheme 3.1.

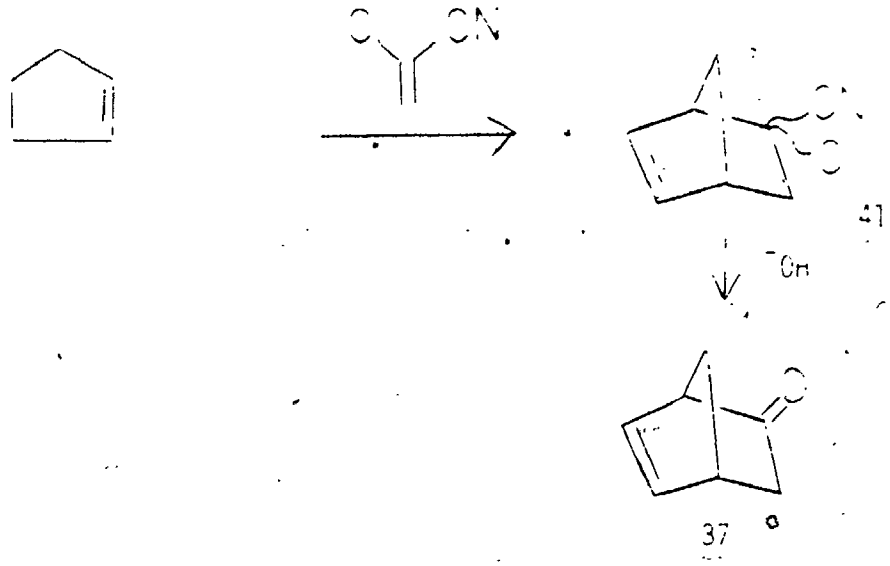
From the results described in Chapter 2 it appeared that homoketonization of 2-trimethylsilyloxyltricyclo-[3.2.1.$0^{2,4}$]oct-6-ene (39) would afford an efficient procedure for the preparation of 38. Since the required silyl enol ether 40 had been synthesized by Jefford (38) in reasonable yield, the only question was the regio-selectivity of cyclopropanation From previous results, methylene addition should occur exclusively at the enolic double bond and the homoketonization was expected to yield mainly 38, by analogy with the results for the norcamphor, bicyclo[2.2.2]octan-2-one and bicyclo[2.2.2]oct-5-en-2-one systems.

(B) RESULTS AND DISCUSSION

The synthesis of 37 was initially achieved by the oxidation of norborn-5-en-2-ol, a commercially available



SCHEME 3.1



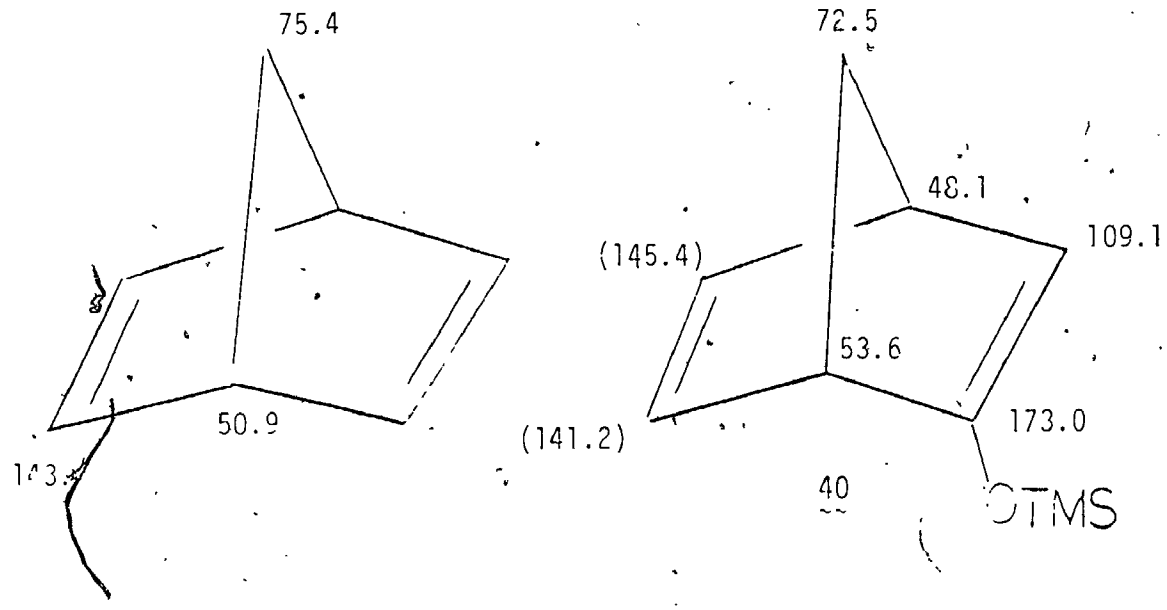
SCHEME 3.2

compound. Oxidation of the alcohol under basic conditions, Sarett reagent (39) or acidic conditions, using a chromic acid solution (40) gave consistently low yields. Consequently this route was abandoned in favour of a modified procedure developed by Freeman et al (41) as illustrated in Scheme 3.2.

The Diels-Alder reaction proceeded smoothly to afford the α-chlorocyano adduct 41 in 97% isolated yield. The IR spectral data for the product agreed with literature values (41) and the ^{13}Cmr spectrum indicated the presence of both epimers. Hydrolysis of 41 gave 37 in 86% yield and the IR and ^{13}Cmr spectral data agreed with literature values (37).

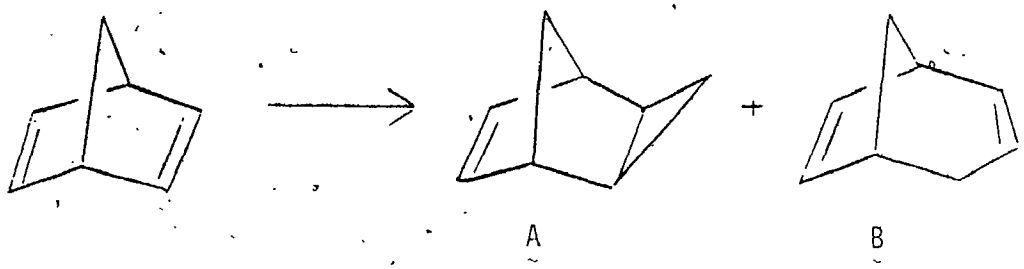
Ketone 37 was then treated with lithium diisopropylamide and the resulting enolate quenched with chlorotrimethylsilane to give 40 in 79% isolated yield. The ^{13}Cmr spectrum exhibited one quaternary signal (δ_C 173.0), five methine peaks (δ_C 145.4, 141.2, 109.1, 53.6, 48.1), one methylene signal (δ_C 72.5) and one methyl peak (δ_C 0.0, $OSiMe_3$). The assignments are straightforward and, based upon appropriate models (42), the chemical shifts agree with expected values. The IR spectrum contained absorptions at 3065 (alkene CH stretch), 2960, 1610 (alkene stretch), 1250 (Si-CH_3 deformation), and 840 cm^{-1} (Si-C stretch) which are consistent with the assigned structure.

Cyclopropanation of 40 afforded a single product 42 which had no olefinic signals in either the ^{1}H or ^{13}Cmr

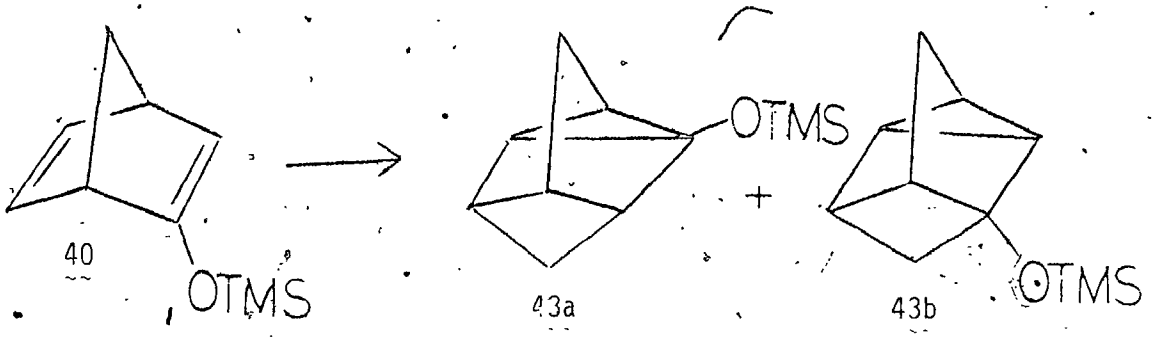


spectra. The ^{13}C spectrum exhibited two methylene signals, five methine peaks, a quaternary signal and the trimethylsilyl peak, indicating that the product resulted from monocyclopropanation of **40**. The determination of the exact mass confirmed the addition of one methylene group and readily dismissed the possibility of a double cyclopropanation product.

It was known that the cyclopropanation of norbornadiene (43) yields in addition to the expected monoadduct, **A** (see next page), and a side product **B**, but the addition product **42** is clearly not similar to **B**. The reaction of halocarbenes with norbornadiene has been shown to occur by both 1,2 and homo-1,4 addition (44). Indeed, the reaction of difluorocarbene with **40** gave a mixture of four adducts (45) as illustrated in Scheme 3.3.

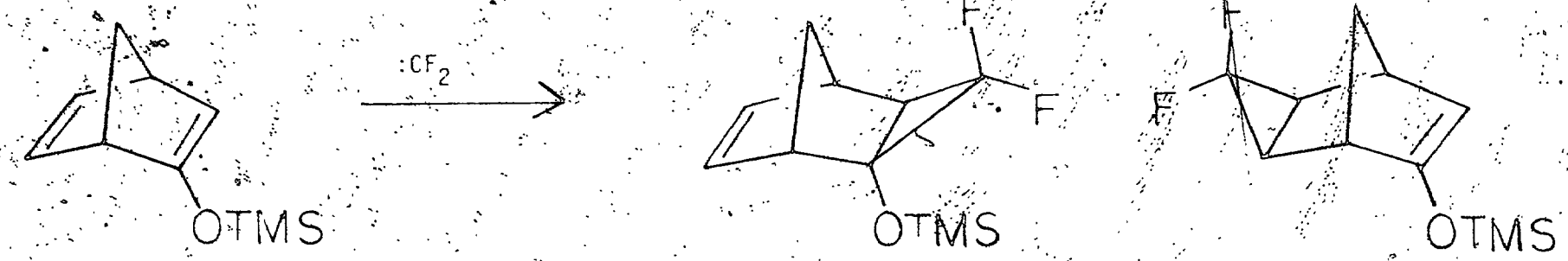


Consequently the Simmons-Smith cyclopropanation of 40 could conceivably lead to the bishomoprismane derivatives 43a and 43b.



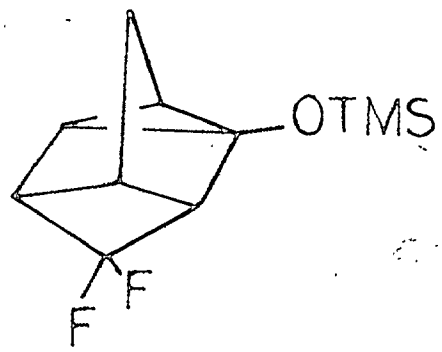
It has also been found that the 1,2 halocarbene-norbornadiene adducts are thermally labile (45) and rearrange to 3,3-difluorotetracyclo $[3.3.0.0^{4,6}0^{2,8}]$octane.

The equivalent reaction also occurs with *exo*-tricyclo$[3.2.1.0^{2,4}]$octene in the presence of a rhodium catalyst (46).

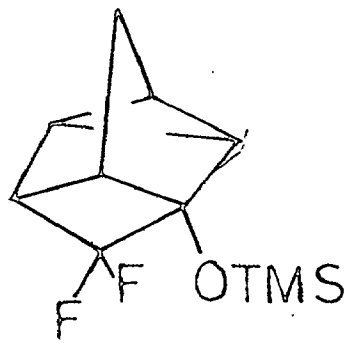


75%

6.0%

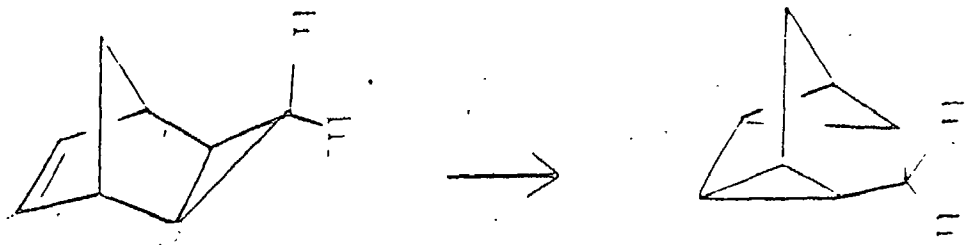


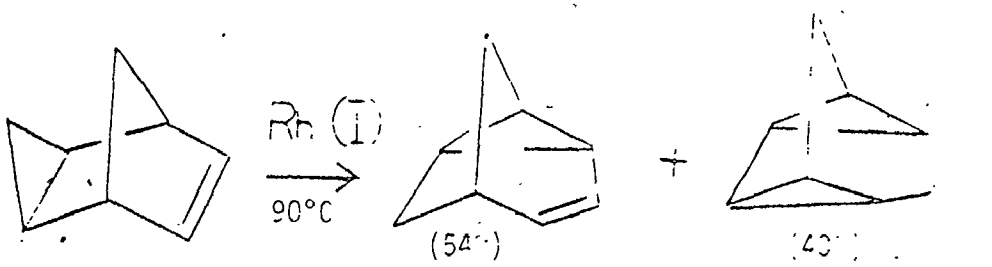
6.0%

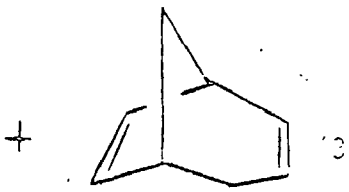


trace amount (not fully characterized)

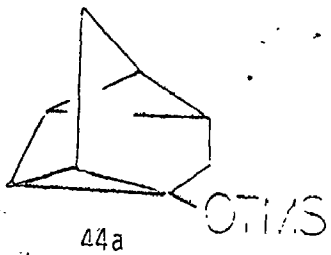
SCHEME 3.3



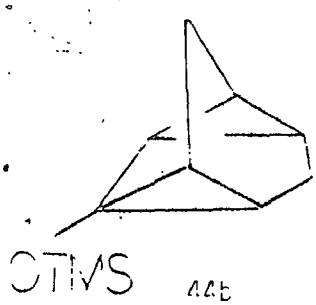




From these results, adduct **42** could be a homoquadricyclene derivative **44a** or less likely **44b**.

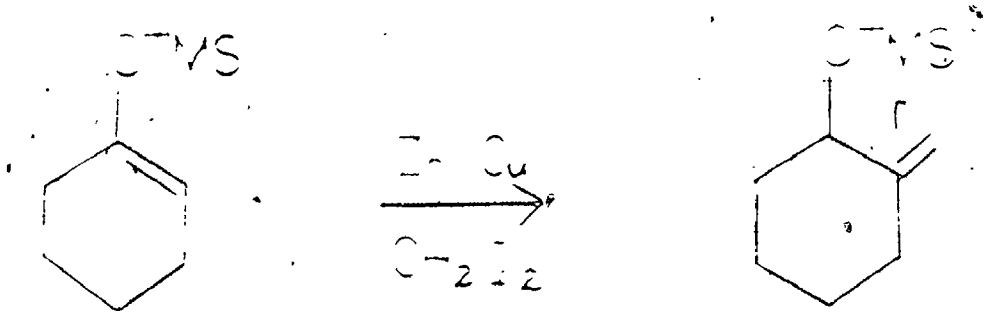


44a

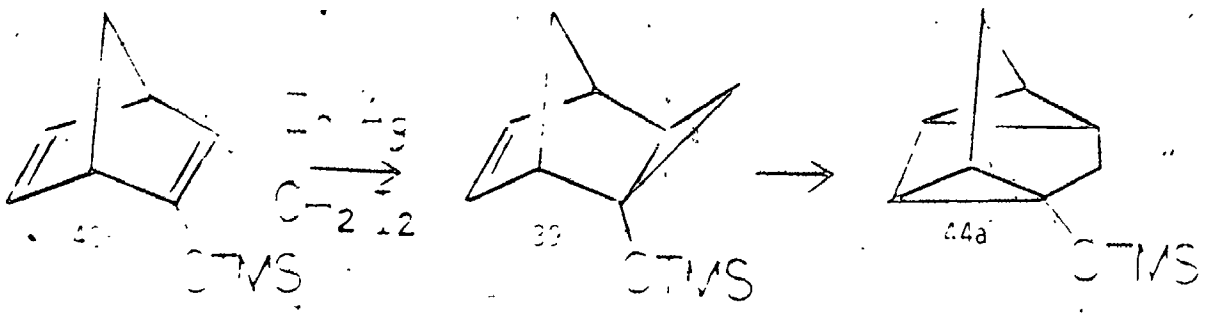


44b

Structure 44a is in accord with the observed data, especially in view of the propensity of the Simmons-Smith reagent to form the 1,2 adduct and to add to the enolic double bond. It has also been observed that under certain conditions the reaction of a silyl enol ether with the Simmons-Smith reagent yields an allylic silyl ether (47).



It is thought that this may occur by initial formation of the cyclopropyl silyl ether followed by Lewis acid catalyzed isomerization to the allylic ether. This suggests the possibility that the initial cyclopropanation of 40 is followed by isomerization in situ to afford 44a:

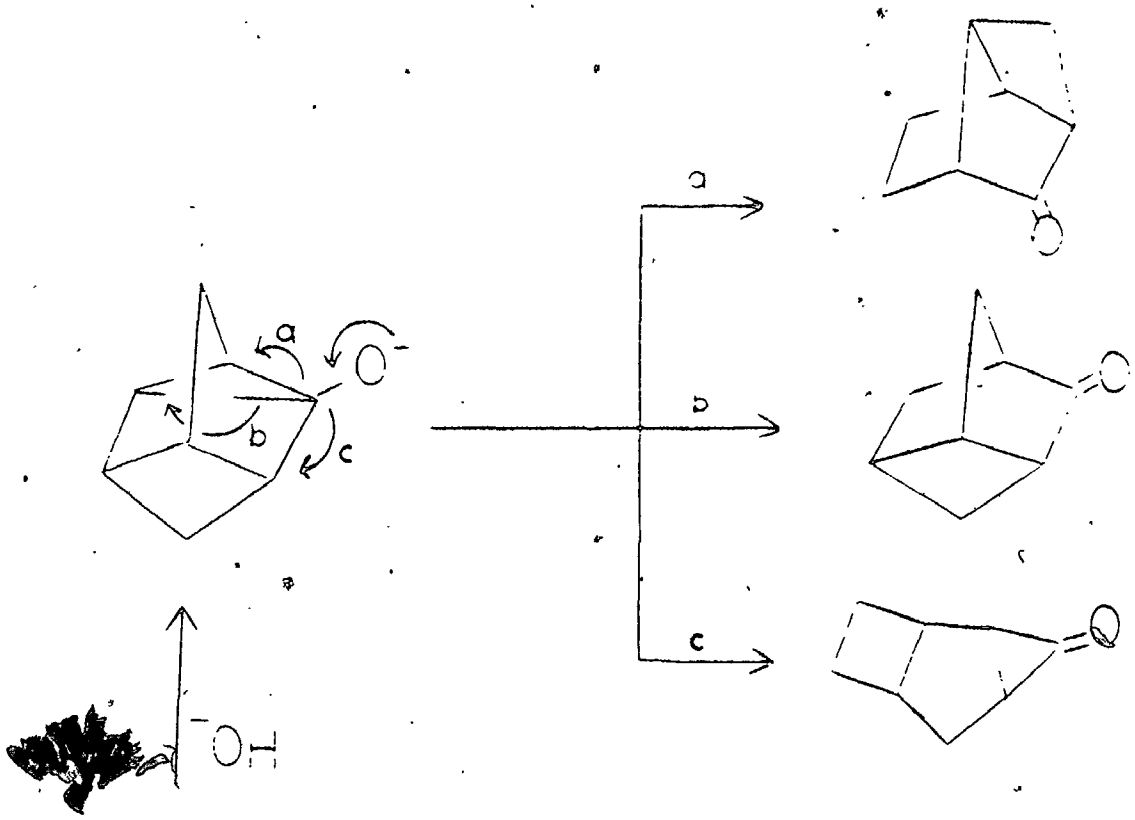


To aid in determining the structure of the addition product 42, the effect of base-catalyzed cleavage was examined in hopes of generating an identifiable ketone by ketonization of the alkoxide arising from ether cleavage. The four suggested structures for the addition product can give rise to eleven different ketones as illustrated in Scheme 3.4.

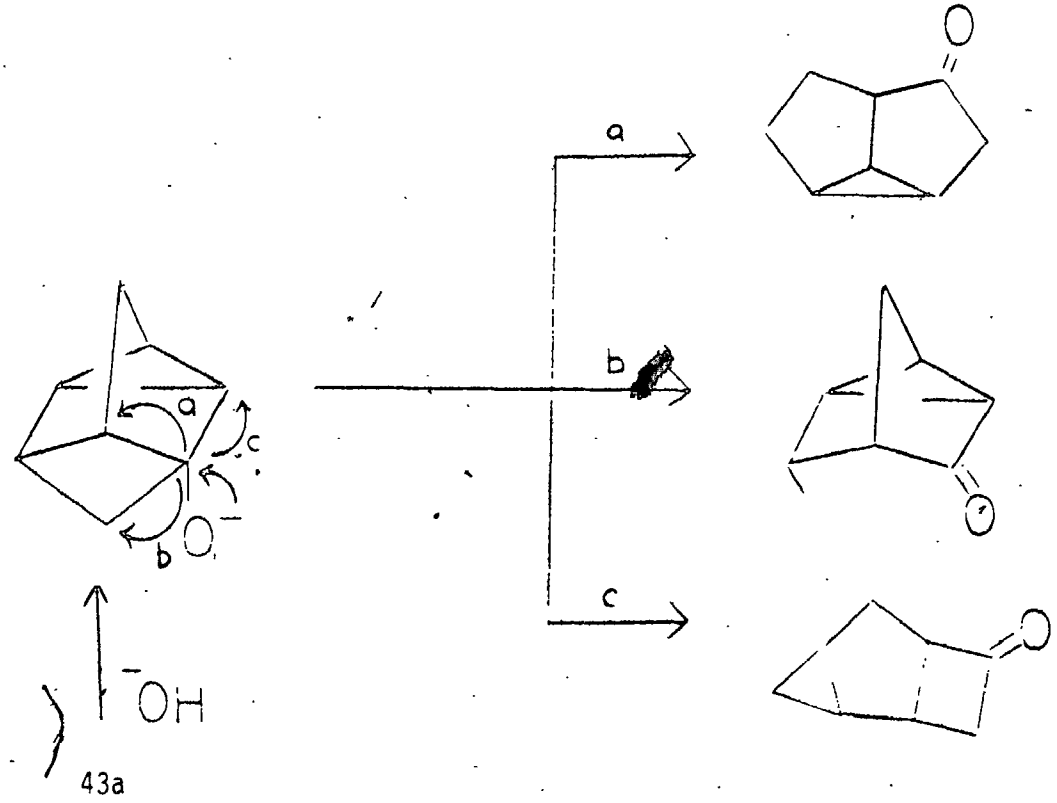
On treatment with base, 42 gave a single ketone in essentially quantitative yield, having carbonyl absorption (ir 1727 cm^{-1}; δ_C 211.7) indicative of a six-membered ring ketone. The ^{13}Cmr spectrum contained five signals in addition to the carbonyl peak: δ_C 9.2 (CH), 14.4 (2 CH), 28.6 (2 CH_2), 33.3 (CH_2) and 47.8 (CH). With the addition of shift reagent ($Eu(fod)_3$) the two more intense signals remained as singlets, showing the ketone to be symmetric. Only ketone 45 fits these data.

The assignment of the ^{13}Cmr chemical shifts for 45 was relatively straightforward. The lowest field methine signal was attributed to C-5, deshielded by the carbonyl. Since the methine absorption at δ_C 14.4 was approximately twice as intense as the signal of δ_C 9.2, this served to distinguish C-1,7 and C-2. Similarly, the methylene signal at δ_C 28.6 was attributed C-6,8 since it was twice as intense as the methylene peak at δ_C 33.3, which was ascribed to C-3.

The ^{1}Hmr spectrum ($CDCl_3$) gave further confirmation. A 1-proton multiplet at δ 1.03 coupled to a

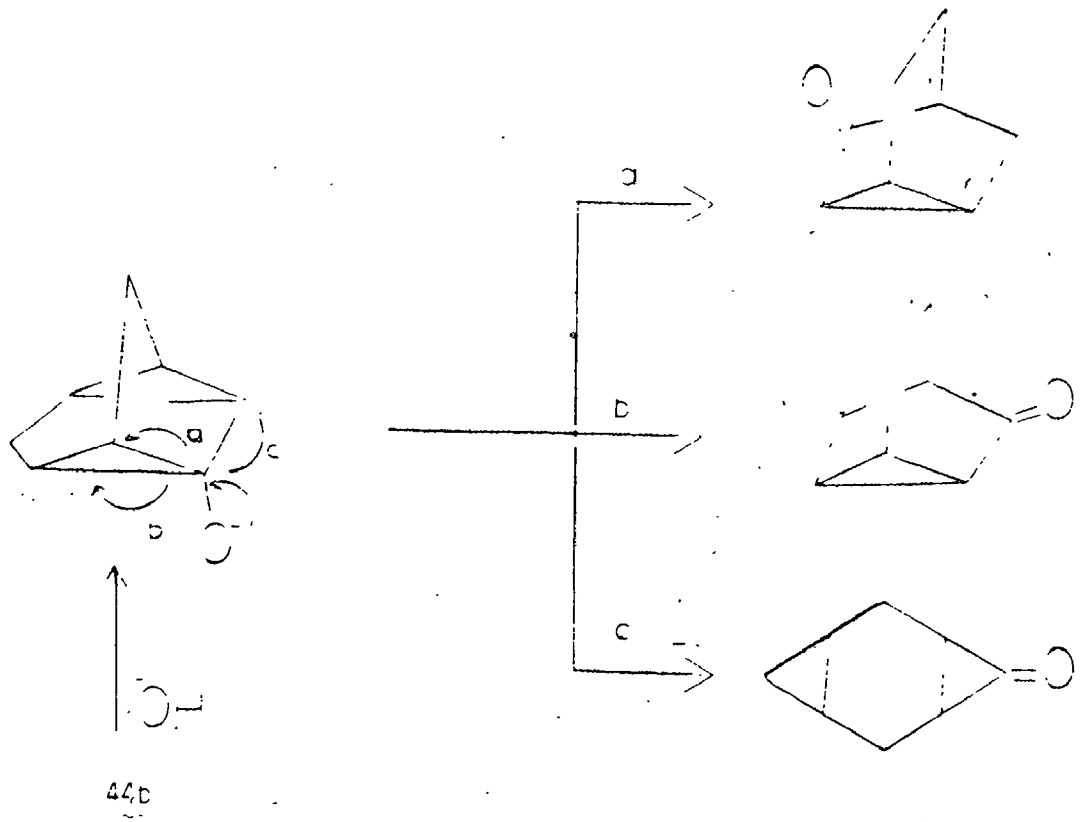


43b

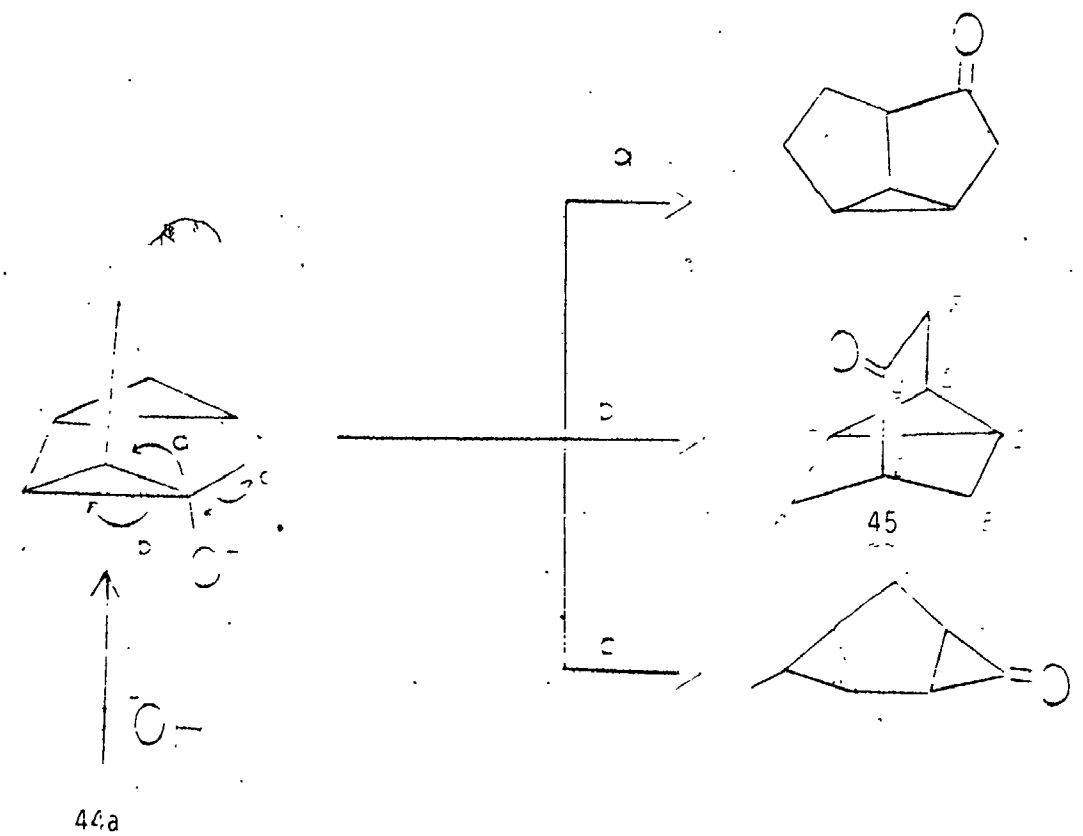


43a

SCHEME 3.4



44b



45

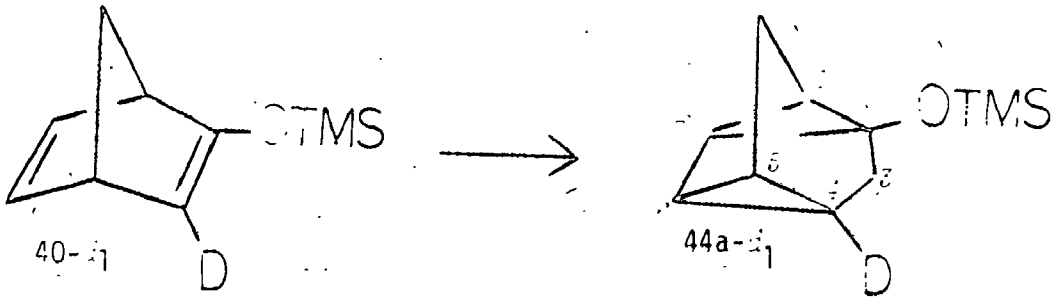
44a

SCHEME 3.4 Continued

sharp 2-proton doublet (J = 2.7 Hz) at 2.52 and a broad 2-proton doublet (J = 7.5 Hz) at 1.46 were readily ascribed to H-2, H-3, and H-1,-7, respectively. A broadened triplet (J = 5.3 Hz) at δ 2.50 due to H-5, and an "AB" pattern for the 6,8-protons were apparent. The A part (δ 2.01) was also coupled to H-5 (J = 5.3 Hz) and H-7 (J = 2 Hz), while the B part (δ 1.85) was a clean doublet (J_{AB} = 12.2 Hz) undoubtedly due to the *endo*-6,8-protons which have dihedral angles of ~ 90° with respect to H-5 and H-1,-7. All spin coupling interactions were confirmed by a series of homonuclear decoupling experiments.

The IR spectrum of 45 and the mp of the 2,4-dinitrophenylhydrazone derivative agreed with the literature values (48). With ketone 45 identified, it followed that the addition product is compound 44a.

To complete the ^{13}Cmr assignments for 44a the cyclopropanation step was repeated, employing 40-d_1 to generate 44a-d_1 (0.80 atoms ^{2}H/molecule). The ^{13}C spectrum of 40-d_1 confirmed the assignment of C-3 to δ_C 109.1, since this signal was significantly attenuated.



An examination of the ^{13}Cmr spectrum of 44a-d_1 showed that the most shielded methine singlet was highly attenuated and accompanied by the expected triplet, J_{CD} = 26 Hz, exhibiting an isotope shift of -0.32 ppm. In addition, three other absorptions were altered, with the signals corresponding to those for 44a strongly attenuated and accompanied by prominent singlets 0.1 ppm toward higher field. These patterns are typically exhibited by carbons geminal to ^{2}H (49) and served to identify C-3, -5, and -6 at δ_C 30.7, 21.5, and 24.4, respectively. The remaining methylene signal, δ_C 25.3, was, therefore, due to C-8 and the signals at δ_C 27.4 and 33.6 arise from C-1 and -7.

As noted previously, the addition product could arise by cyclopropanation of 40 to yield 39 which in turn undergoes a Lewis acid catalyzed isomerization to 44a. The rearrangement was initially attributed to the presence of Ag(I) ion in the reaction mixture. This was discounted by repeating the cyclopropanation reaction with the more usual zinc-copper couple which also afforded 44a, albeit in lower yield. Further discussion concerning the nature of this unusual Simmons-Smith reaction will be deferred until the results of some related systems are examined.

Two aspects of the homoketonization merit comment. Although there are three conceivable modes of ring opening for the β-enolate of 44a shown as a, b, and c in Scheme 3.4, the cyclopropoxide cleavage was apparently regiospecific. It is generally acknowledged that homo-

ketonization is strongly influenced by the thermodynamic stability of the product (16) and on this basis the ring cleavage process labelled c can be readily dismissed. The remaining two pathways labelled a and b both lead to secondary carbanions, the exclusive formation of 45 can be attributed to thermodynamic control of homoketonization or stabilization of the incipient negative charge by the adjacent cyclopropyl ring. The extent to which these two factors influence the homoketonization process will be examined in Chapter 5. The second aspect, stereoselectivity of protonation (deuteration) at the carbanionic site required additional evidence for its clarification. For this purpose the homoketonization was examined in a deuterated medium.

Treatment of 44a with t-BuO$^-$/t-BuOD gave 45-d_x, with 1.12 atoms ^{2}H/molecule, as determined by mass spectrometric analysis. In the ^{1}H spectrum the absorption for *exo*-H-6(8) was significantly attenuated while the clean doublet for *endo*-H-6(8) (δ 1.85) was accompanied by a triplet, J_{HD} = 1.85 Hz, at 1.83. Clearly ring opening proceeded primarily to 45 with inversion of configuration at the carbanionic site. Minor deuteration at C-3 undoubtedly occurred through α-exchange upon generation of the ketone in the deuterated medium. To check for small amounts of deuterium at the *endo*-6(8)-position, the ^{2}Hmr spectrum of the ketone was also examined. This spectrum contained signals at δ 1.85, 2.0, and 2.5 in the ratio

1.0:12.3:3.1, corresponding to 0.21 atoms ^2H at C-3 and 0.91 atoms ^2H at C-6(8) with the latter in the ratio of 12:1 favoring exo-^2H. Further confirmation of the marked preference for *exo*-deuteration at the *β*-methylene position was obtained by examination of the ketone generated by homoketonization of 44a-d_1 in t-BuO$^-$/t-BuOD. The product (2.14 atoms ^2H/molecule) gave a ^2H spectrum having signals at δ 1.45, 2.0, 2.5 with relative intensities 11.6:1.0:12.1:10.0 corresponding to 0.72, 0.062, 0.75, and 0.62 atoms ^2H at C-2, *endo*-6(8), *exo*-6(8), and C-3, respectively. More extensive exchange occurred at C-3 because of a longer reaction time (11.5 vs. 3 h). In any event, homoketonization proceeds with high stereoselectivity (92 ± 1%) favoring inversion of configuration which is in agreement with findings for a wide variety of *β*-enolates (16).

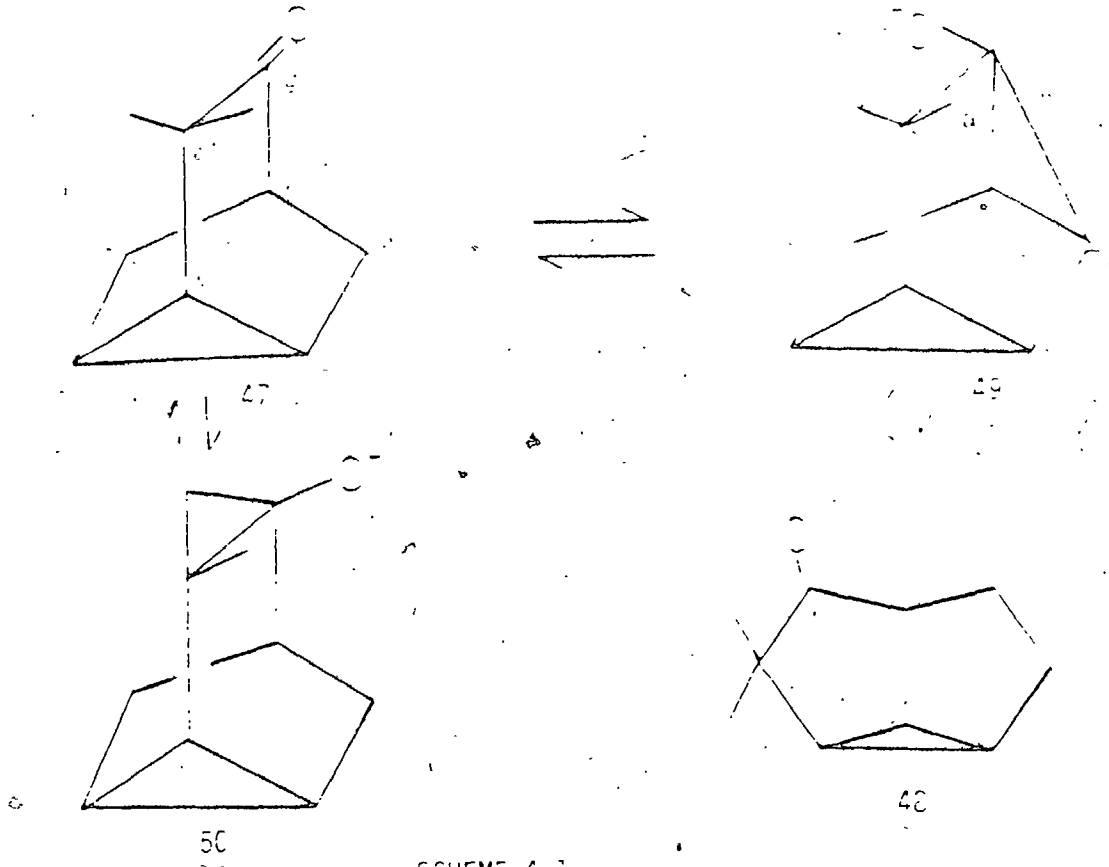
CHAPTER 4

DEUTERIUM EXCHANGE VIA HOMOENOLIZATION IN TRICYCLO[3.2.1.$0^{2,7}$]OCTAN-4-ONE

(A) INTRODUCTION

Having shown that homoketonization of the cyclopropoxide of 44a afforded only 45 with no trace of 46, it was of interest to determine if 3,3-dimethyltricyclo [3.2.1.$0^{2,7}$]octan-4-one (47) would yield 3,3-dimethyl tricyclo[3.3.0.$0^{2,8}$]octan-4-one (48) under homoenolization conditions. In principle, β-proton abstraction of 47 could occur at C-6(8) and at the methyl groups (see Scheme 4.1) resulting in the formation of β-enolates 49 and 50, respectively. Subsequent cleavage of 49 via mode b will generate 48.

To determine the regio- and stereochemistry of proton abstraction in 47 under strongly basic conditions, homoenolization was examined in a deuterated medium. A comparison of the rates of deuterium exchange in 47 with those for 3,3-dimethylbicyclo[2.2.2]octan-2-one (10) would indicate the effect of the cyclopropyl ring of 47 on the homoenolization process.



SCHEME 4.1

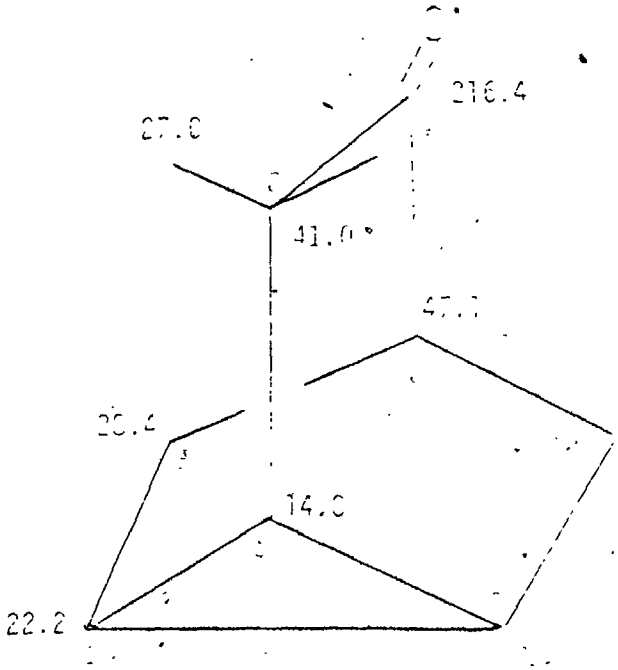


FIGURE 4.1: ^{13}C Shielding Data (δ_C) for 47

(B) RESULTS

Treatment of 45 with $NaNH_2$-Et_2O-MeI (50) furnished the dimethylated ketone 47 whose ^{13}Cmr spectrum contained seven signals: δ_C 216.4 (C=O), 47.1 (CH), 41.0 (-C-), 28.4 (CH_2), 27.0 (Me x 2), 22.2 (CH x 2) and 14.0 (CH). The lowest field methine peak (δ_C 47.1) was attributed to C-5, deshielded by the carbonyl. The relative intensities of the two methine signals at δ_C 22.2 and 14.0 served to distinguish C-1,7 and C-2, respectively. The remaining assignments were straightforward and are summarized in Fig. 4.1.

The ^1Hmr spectrum of 47 was, as expected, similar to that of 45. A one-proton triplet at δ 0.91 (J = 7.6 Hz) coupled to a broadened two proton doublet at δ 1.50 were readily ascribed to H-2 and H-1,7, respectively. A triplet at 2.47 (J = 5.3 Hz) was assigned to H-5, coupled to *exo*-H-6,8 and the strong singlet at δ 1.12 was attributed to the methyl protons. The absorption for the 6,8 protons formed an "AB" pattern, with the A part at δ 1.99 appearing as a broadened four line pattern (J = 12.6, 5.3 Hz) with small coupling to H-1,7. The B part at δ 1.80 was a sharp doublet (J = 12.6 Hz), the absence of significant additional coupling presumably due to the approximately 90° dihedral angle between H-5, H-1(7) and *endo*-H-6(8). All spin-coupling interactions were confirmed by homonuclear decoupling experiments.

TABLE 4.1: Deuterium incorporation in 3,3-dimethylbicyclo[3.2.1.$0^{2,7}$]octan-4-one at 185°C.

Time (h)	^2H content by mass spectrometry[a] 1D	2D	3D	4D	5D	6D	Total Atoms ^2H	^2H assay by ^2Hnmr[b] H1,7	H-5	H-6,8 exo	H-6,8 endo	Me
15	0.37	0.59	0.28	0.05	0.01		1.30	0.04	0.02	0.80	0.43	0.01
30	0.26	0.76	0.66	0.22	0.03	0.01	1.93	0.05	0.06	1.18	0.62	0.02
60	0.07	0.47	1.11	0.97	0.31	0.02	2.96	0.10	0.13	1.64	1.05	0.03

[a]Atoms ^2H ± 3%.

[b]Atoms ^2H ± 5%.

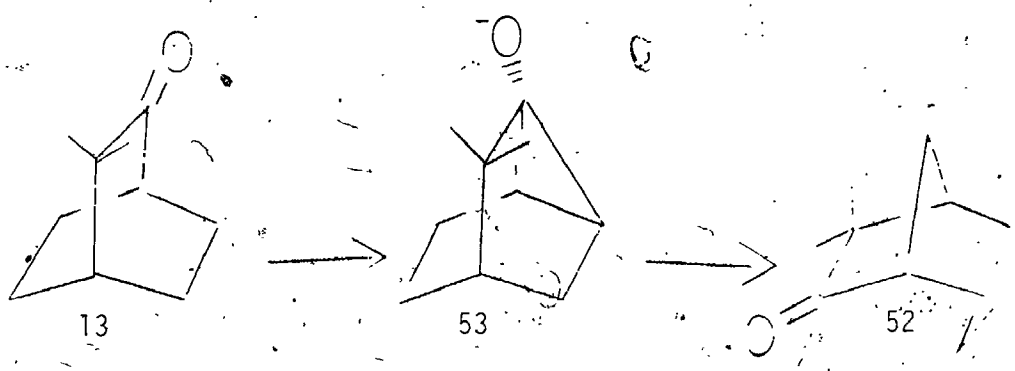
Treatment of 47 with t-BuO$^-$/t-BuOH at 180°C for extended reaction times gave only starting material in high yield (90-100%) from the neutral fraction. No additional material was isolated from the acidic fraction.

Ketone 47 was then treated with t-BuO$^-$/t-BuOD at 185°C for varying periods of time. The neutral product from each run was isolated by preparative glc and examined by ^{2}H and ^{13}Cmr and mass spectrometry. These results are listed in Table 4.1.

Since even trace amounts of water can reduce the base strength of t-BuO$^-$/t-BuOD the rate of deuterium incorporation for 13 was determined with the same stock solution used for the experiments with 47. Treatment of 13 in t-BuO$^-$/t-BuOD at 185°C for 60 h afforded 13-d_x having 2.34 atoms ^{2}H/molecule.

(C) DISCUSSION

From the results in Table 4.1 the approximate pseudo first-order rate constants for ^{2}H exchange in 47 at C-1,7, C-5, *exo*-C-6(8), *endo*-C-6(8) and the methyl positions were found to be 2.8×10^{-7}, 5.2×10^{-7}, 8.4×10^{-6}, 3.8×10^{-6} and 2.8×10^{-8} sec^{-1}, respectively. Deuterium incorporation at C-6(8) was consonant with the formation of β-enolate 49, or its equivalent. In principle, this β-enolate could lead to 48, but none was detected, in contrast to the results of homoenolization of 13, which very slowly rearranges to 52 via the β-enolate.



53. At present, it seems reasonable to conclude that 49 affords only 47 because it is the more stable product.

The first-order rate constants for exchange at the exo- and endo-C-6(8) sites indicate that cleavage of bond a in 49 proceeds preferentially with inversion of configuration (exo-deuteration) over retention by a factor of ca. 2. The stereoselectivity of cleavage is reduced relative to that in 53 for which inversion is favored by a factor of ca. 7. Presumably the enhanced acidity of the cyclopropyl protons over their alicyclic counterparts accounts for minor ^2H incorporation at C-1(7). The incorporation of deuterium at C-5 of 47 is in contrast to the results of 13 and is difficult to explain.

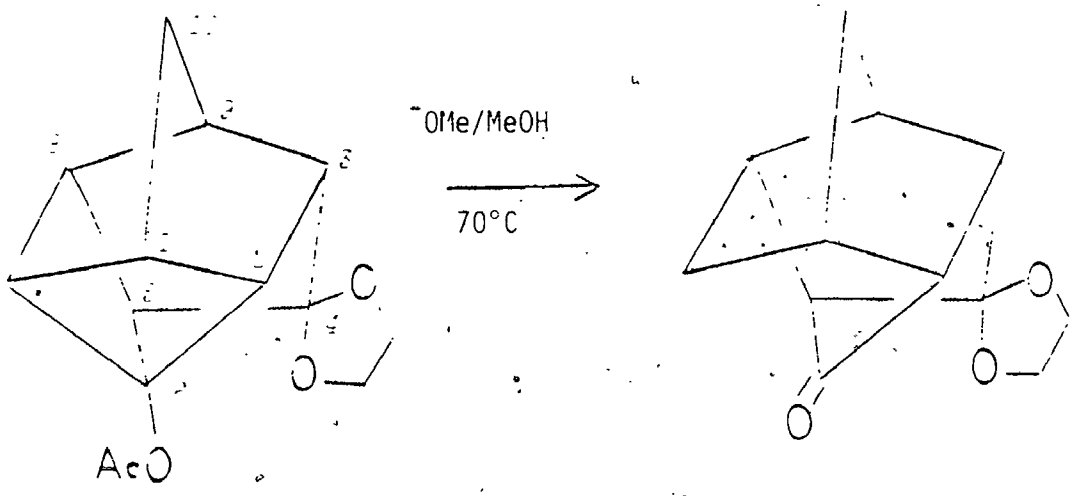
Apart from the enhanced acidity of the cyclopropyl protons, H-1(7) of 47; the rates of deuterium incorporation for 47 and 13 do not differ greatly. Thus to a first approximation the cyclopropane ring does not significantly affect the β-exchange process for 47.

CHAPTER 5

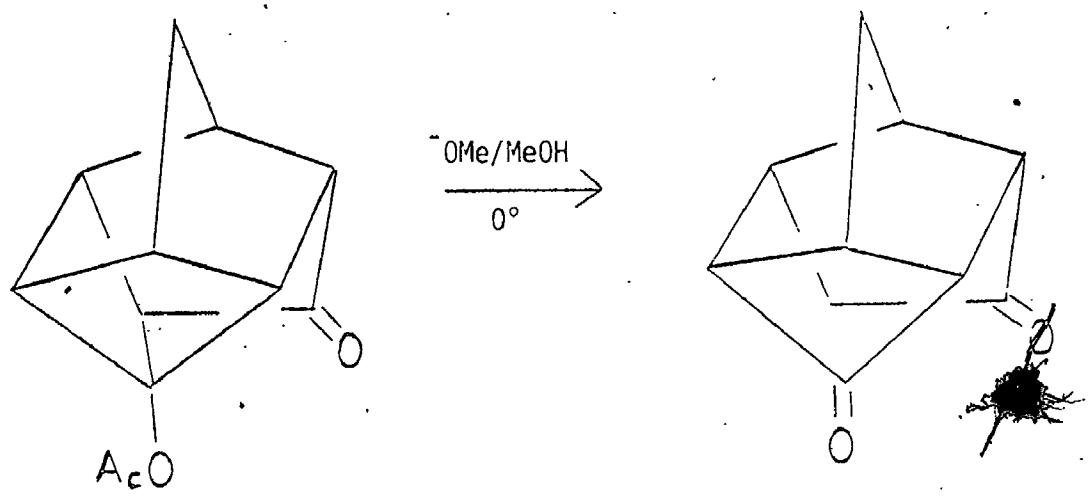
SYNTHESIS OF 6-SPIROCYCLOPROPYL TRICYCLO[3.2.1.$0^{2,7}$]OCTAN-4-ONE

(A) INTRODUCTION

The observation that treatment of the trimethylsilyl enol ether of norbornenone with the Simmons-Smith reagent affords 2-trimethylsilyloxyl-homoquadricyclene, gave reason to investigate the effect of substituents on the reaction course. Secondly, it was of interest to determine the effect of substituents on the homoketonization of the product(s) derived from cyclopropanation since it had been demonstrated that the homoketonization process can be influenced by β-functionalization. Zwanenburg has demonstrated that the regiochemistry of base-induced homoketonization in strained polycyclic alcohols is influenced by substituents which can stabilize the carbanionic intermediates. This directive effect has been demonstrated in the 1,3-bishomocubane cage system (51). Ketal acetate 54 (see Scheme 5.1) with base yielded the thermodynamically controlled homoketonization product 55, while ring cleavage of 56 gave 57. This change in regiochemistry of homoketonization of 54 and 56 was attributed to conjugative stabilization of the carbanionic intermediate formed from cleavage of the C-5,6 bond of 56.



54 55



56 57

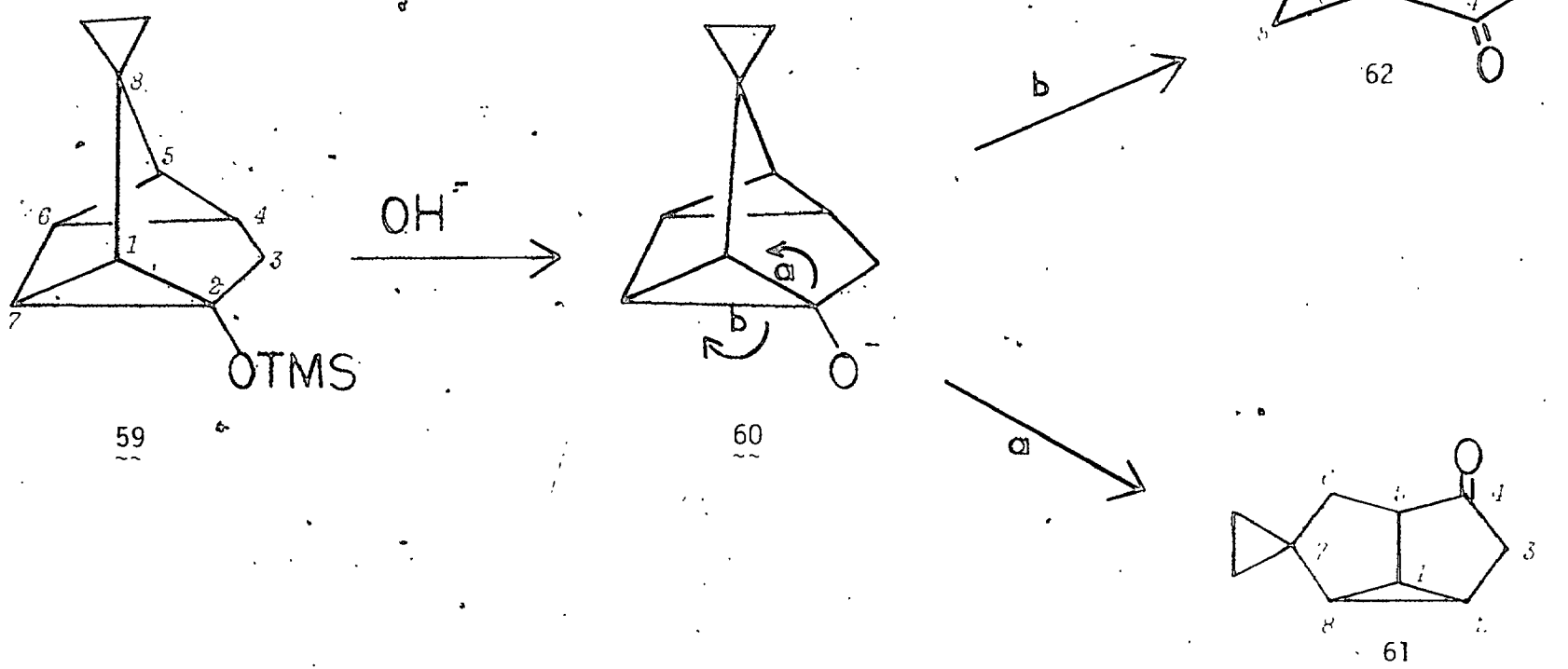
SCHEME 5.1

These results suggested that homoketonization of 44a analogs could be redirected to afford the tricyclo-[3.3.0.$0^{2,8}$]octan-4-one system, through appropriate substitution. This system has synthetic utility since many syntheses of natural products which are polyfused cyclopentanoids (52) are based upon this skeleton.

The degree to which a carbanion can be stabilized by a cyclopropyl ring system has not been established and remains controversial (53). Hence it was of interest to investigate the effect of a spirocyclopropyl group at C-8 in 44a on the homoketonization process, since it may be possible to redirect the homoketonization process dependent upon the degree to which the spirocyclopropyl ring can stabilize the adjacent negative charge. It was anticipated that treatment of the silyl enol ether of 7-spirocyclopropylnorbornenone (58) with the Simmons-Smith reagent would yield the homoquadricyclene derivative 59. Treatment of 59 with base would generate the corresponding cyclopropoxide 60 by ether cleavage and homoketonization could involve either of two bond cleavage modes, labelled as a and b in 60 (Scheme 5.2).

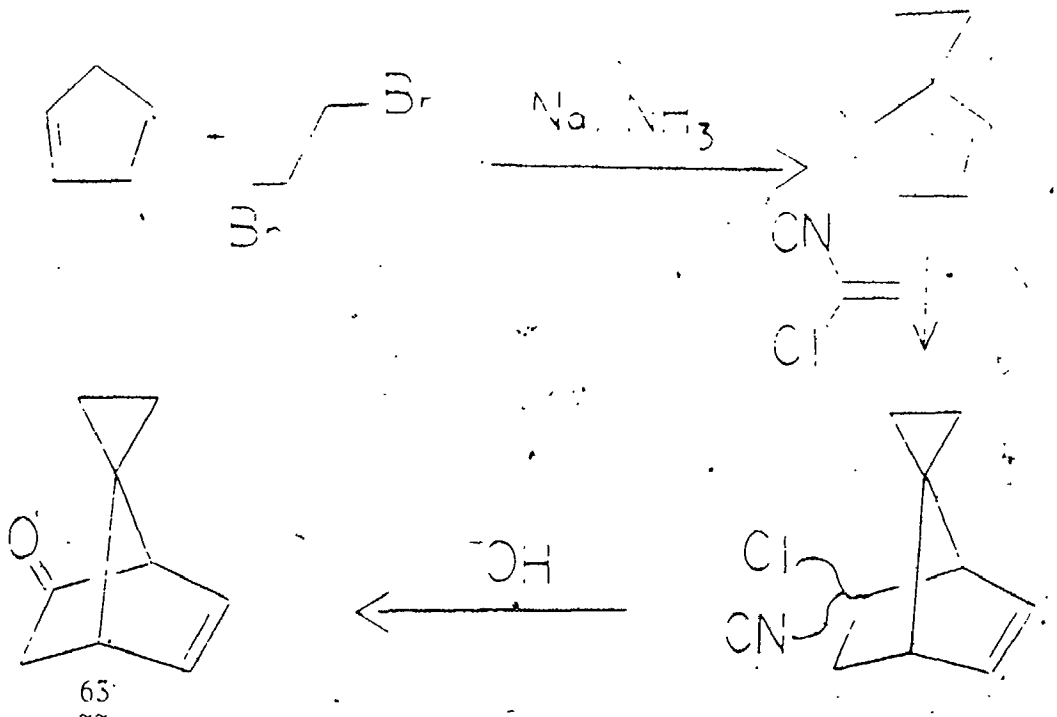
(B) RESULTS AND DISCUSSION

The starting material, 7-spirocyclopropylnorbornenone (63) was synthesized following the procedure developed by Turro (54) and illustrated below.



59 60 62 61

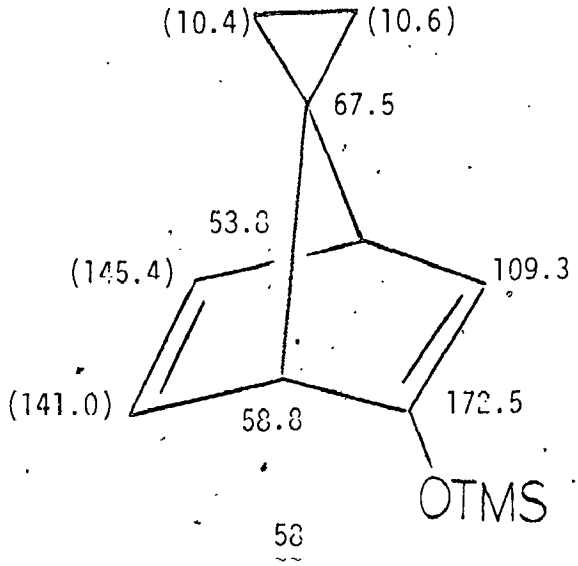
SCHEME 5.2



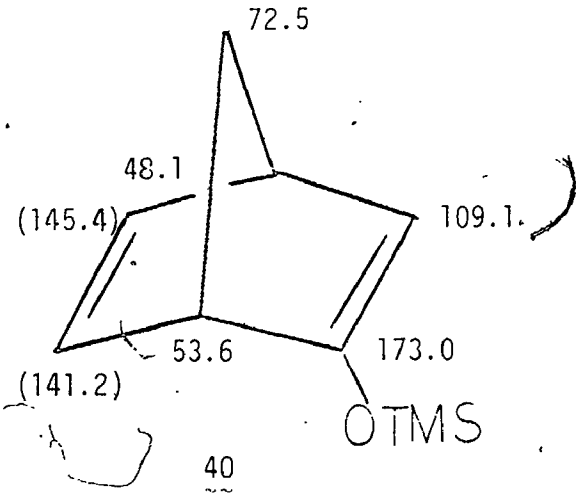
63

The lithium enolate of 63 was generated in the usual manner from LDA and quenched with chlorotrimethylsilane, to afford 58. The ^{1}Hmr spectrum of 58 contained absorptions at (δ (C_6D_6)): 7.44 (1H, d, J = 1.9 Hz), 7.42 (1H, d, J = 1.9 Hz), 5.32 (1H, dd, J = 3.3, 1.1 Hz), 2.64 (1H, m), 2.48 (1H, m), 0.68-0.27 (4H, m) and a strong singlet at 0.10 (Me_3Si). Since the enolic proton absorbs at approximately δ 5.0, the signals at δ 5.32, 7.42 and 7.44 were readily assignable to H-3, -5 and -6, respectively. Two patterns at δ 2.54, and 2.48 were attributed to the bridgehead protons and the four proton multiplet at δ 0.68-0.27 was ascribed to the spirocyclopropyl protons.

The ^{13}Cmr spectrum of 58 exhibited five methine signals (δ_C 145.4, 141.0, 109.3, 58.8, 53.8), two methylene peaks (δ_C 10.6, 10.4), two quaternary signals (δ_C 172.5, 67.5) and the trimethylsilyl absorption at δ_C 0.0. The assignments are straightforward and consistent with those for 40, taking into account the effect of the spirocyclopropyl ring at C-7.



58



40

The IR spectrum, containing absorptions of 3060 (alkene CH stretch), 2960, 1610 (alkene stretch), 1265, 845 cm^{-1} (OSiCH$_3$ stretch), was in agreement with the assigned structure for 58 and the molecular formula, $C_{12}H_{18}OSi$, was confirmed by precise mass measurement.

Cyclopropanation of 58 was accomplished with the same procedure employed for 40 and with similar results. The isolated product had no olefinic signals in the ^{1}H and ^{13}Cmr spectra, and a precise mass measurement confirmed the

addition of one methylene group. These data indicated that cyclopropanation of 58 had generated the corresponding homoquadricyclene derivative 59.

The structure of the product was established by ^{1}Hmr and by the determination of the ^{13}C-^{13}C spin coupling constants from a 1D-INADEQUATE spectrum (55); the results of the latter are summarized in Fig. 5.1. The ^{13}C-^{13}C coupling constants permitted the assignment of the ^{13}C signals for compound 59.

In the ^{1}Hmr spectrum the two lowest field protons at δ 2.27 (doublet, J = 11.7 Hz) and δ 2.12 (J = 11.7, 5.1, 1.5 Hz) form an "AB" pattern and were ascribed to the 3-methylene protons since these are the only protons not part of a cyclopropyl ring. The *endo*-3-proton was coupled to H-4 (J = 5.1 Hz) and H-1 (J = 1.5 Hz, long range "W" coupling), while the *exo*-3-proton appeared as a simple doublet because of its ~ 90° dihedral angle with respect to H-4. The signal for H-1 was identified by the fact that it should contain only one large coupling with H-7 and on this basis the pattern at δ 1.24 (J = 7.3, 1.5, 1.5 Hz) was ascribed to H-1. The two 1.5 Hz couplings were attributed to long range "W" coupling to H-5 and *endo*-H-3. A one proton doublet of doublets at δ 1.98 (J = 7.3, 4.3 Hz) was ascribed to H-7 which is coupled to H-1 and H-6. The latter signal absorbed at δ 1.71 (J = 6.3, 6.3, 4.3 Hz) and was coupled to H-4 (J = 6.3 Hz) and H-5 (J = 6.3 Hz). Multiplets at δ 1.11 (1H), 0.76 (1H), 0.68 (2H) and 0.37

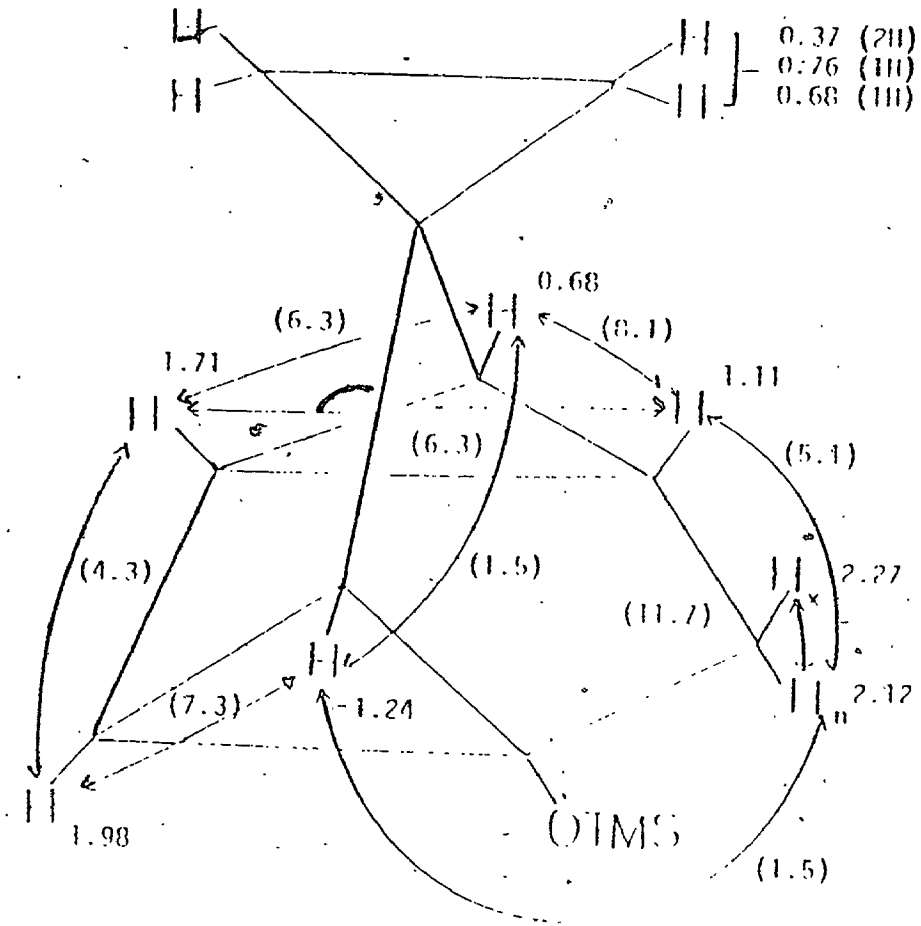


FIGURE 5.2: ^{1}H Shielding[a] and Coupling[b] Data for 59

[a] In ppm from TMS in C_6D_6 solution

[b] The resolvable coupling constants (in Hz) are given in parentheses

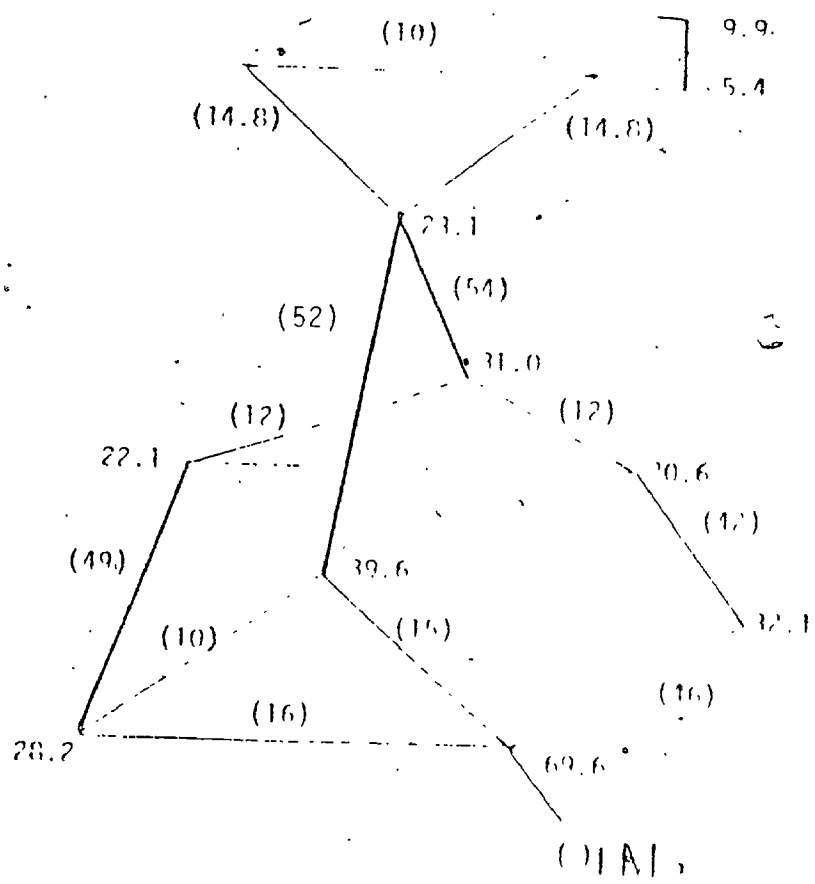


FIGURE 5.3: ^{13}C Shielding Data[a] and Coupling Constants[b] for 59

[a] In ppm from TMS in C_6D_6 solution

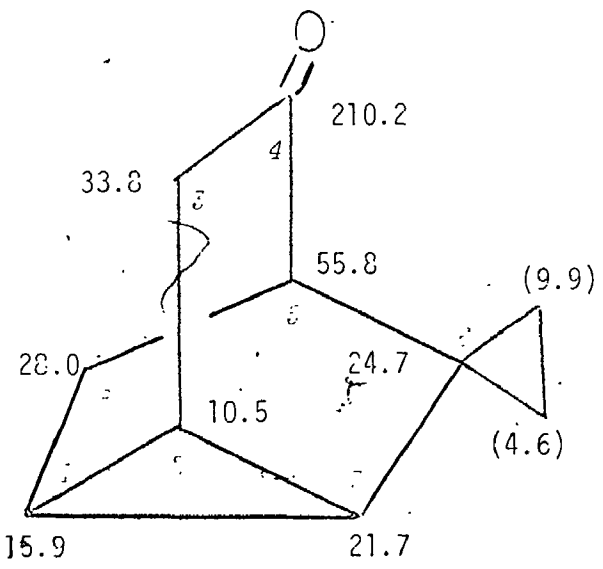
[b] The values in parentheses are the ^{13}C-^{13}C coupling constants (in Hz)

(2H) could not be readily interpreted. Finally, the $Si(Me)_3$ group gave a clean singlet at δ 0.11.

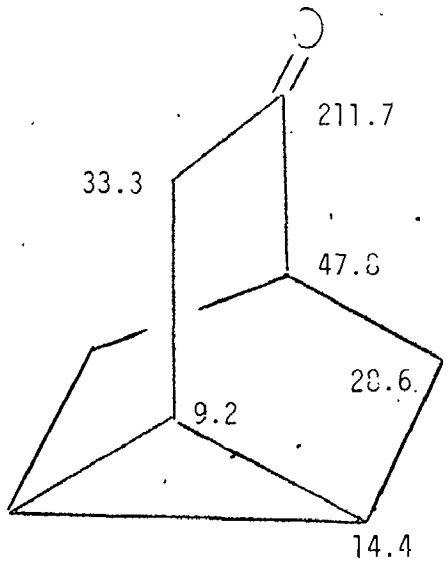
The use of homonuclear decoupling assisted in the assignment of the multiplets. Irradiation of the pattern at δ 0.76 caused no change in the spacings for the multiplet at δ 1.11 or those further downfield, thus it could be assigned to a spirocyclopropyl proton. Double irradiation of the two-proton multiplet at δ 0.68 gave rise to changes in the pattern at δ 0.37, 0.76, 1.11 and 1.71. The changes in the absorptions at δ 0.76 (1H) and δ 0.37 (2H) indicated that these arise from three of the four spirocyclopropyl protons. The second proton of the 0.68 multiplet, therefore, was attributed to H-5 since there was no change in the pattern for *endo*-H-3. Consequently the multiplet at δ 1.11 which had been collapsed to a broad triplet is due to H-4. The elimination of the 1.5 Hz coupling of H-5 to H-1 resulted in the signal for H-1 appearing as a doublet of doublets (J = 7.3, 1.5 Hz). Irradiation at δ 2.12 removed a 5.1 Hz coupling to H-4 reducing the multiplet to a broadened doublet of doublets (J ~ 8.1, 6.3 Hz) due to coupling with H-5 (J ~ 8.1 Hz) and H-6 (J ~ 6.3 Hz). All of the remaining interactions were confirmed by decoupling experiments, which are summarized in Fig. 5.2.

With the structure of 59 established, the homoketonization reaction was examined. On treatment with base, 59 gave a single, neutral product having carbonyl

absorption (ir 1725 cm^{-1}, δc 210.2) indicative of a six-membered ring ketone. The ^{13}Cmr spectrum contained nine signals in addition to the carbonyl peak: δc 55.8 (CH), 33.8 (CH_2), 28.0 (CH_2), 24.7 (C), 21.7 (CH), 15.9 (CH), 10.5 (CH), 9.9 (CH_2) and 4.6 (CH_2). The carbonyl shift indicated that homoketonization of 59 gave 62, the 6-spirocyclopropyl analog of 45, rather than 61 which contains a cyclopentanone moiety. The two highest field methylene signals (δc 9.9, 4.6) and the quaternary signal at δc 24.7 can be attributed to the spirocyclopropyl ring carbons. With allowances for the effects of the spirocyclopropyl ring the remaining ^{13}C chemical shifts were expected to be similar to those of 45.



62



45

Confirmation of these ^{13}C assignments was obtained by measurement of the ^{13}C-^{13}C coupling constants, determined by a 1D-INADEQUATE experiment. The results are summarized in Fig. 5.3. Geminal coupling between C-3 and C-5 was expected since it has been noted (42) that geminal interactions through a carbonyl carbon are relatively large. For example, the $J_{1,3}$ coupling constant for acetone is 16.1 Hz and for 2-butanone it is 15.2 Hz.

The ^{1}Hmr spectrum provided further evidence for structure 62. The two lowest field protons formed an "AB" pattern with the A part at δ 2.65 (broadened dd, J = 20.0, 2.6 Hz) and the B part at δ 2.53 (ddd, J = 20.0, 2.6, 0.8 Hz). This pattern was ascribed to the 3-protons each coupled to H-2 (J = 2.6 Hz). The small 0.8 Hz coupling for the signal δ 2.53 was shown to be due to *exo*-H-8 (δ 2.23) (long range w interaction), hence this signal was ascribed to the 3-proton *syn* to the spirocyclopropyl ring and, therefore, the signal at δ 2.65 corresponds to the *anti*. *Exo*-H-8 at δ 2.23 (J = 12.6, 5.6, 3.4, 0.8 Hz) was coupled to *endo*-H-8 (J = 12.6 Hz), H-5 (J = 5.6 Hz) and H-1 (J = 3.4 Hz). Therefore, the broadened one-proton doublet at δ 1.87 (J = 12.6 Hz) arose from *endo*-H-8, which is not significantly coupled to H-5 and H-1 because of the approximately 90° dihedral angle relationship between these protons. The doublet at δ 1.75 (J = 5.6 Hz) was readily ascribed to H-5 and the multiplet at δ 1.11 (J = 7.5, 7.5, 2.6, 2.6 Hz) to H-2 on the basis of the 2.6 Hz coupling,

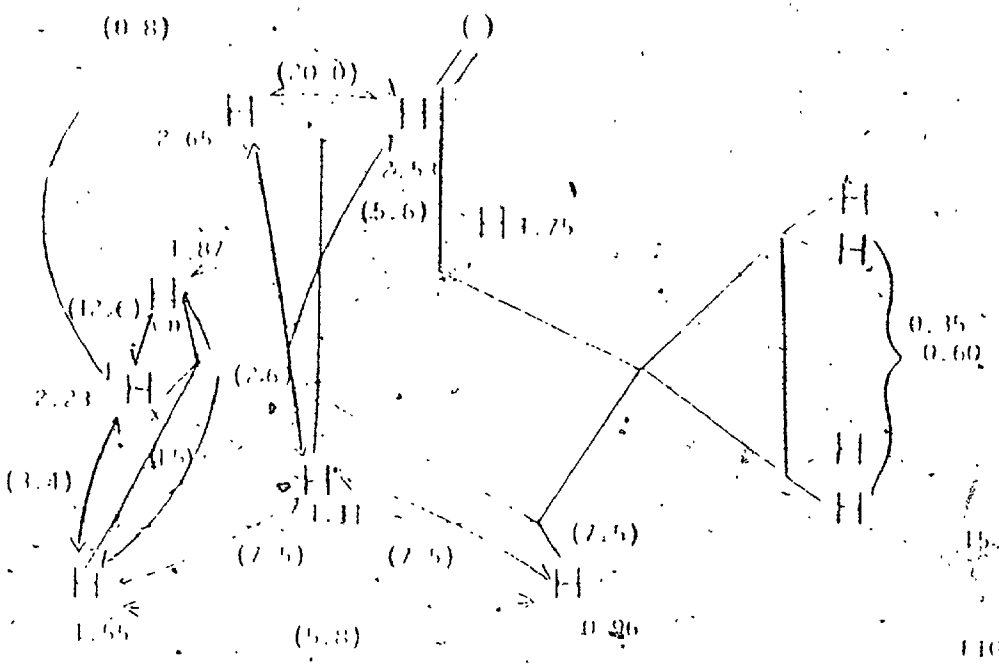


FIGURE 5.4 ^{1}H Shielding (δ) and Coupling Data (in Hz) for 62

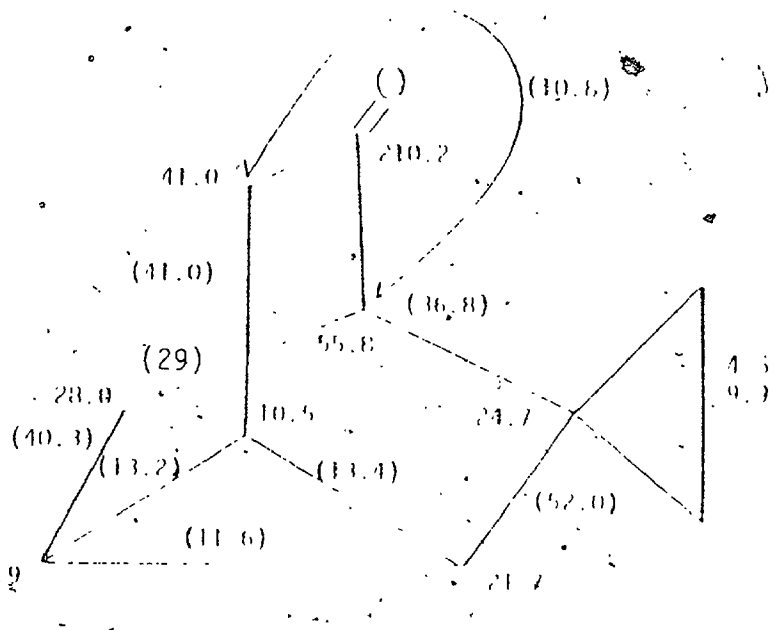
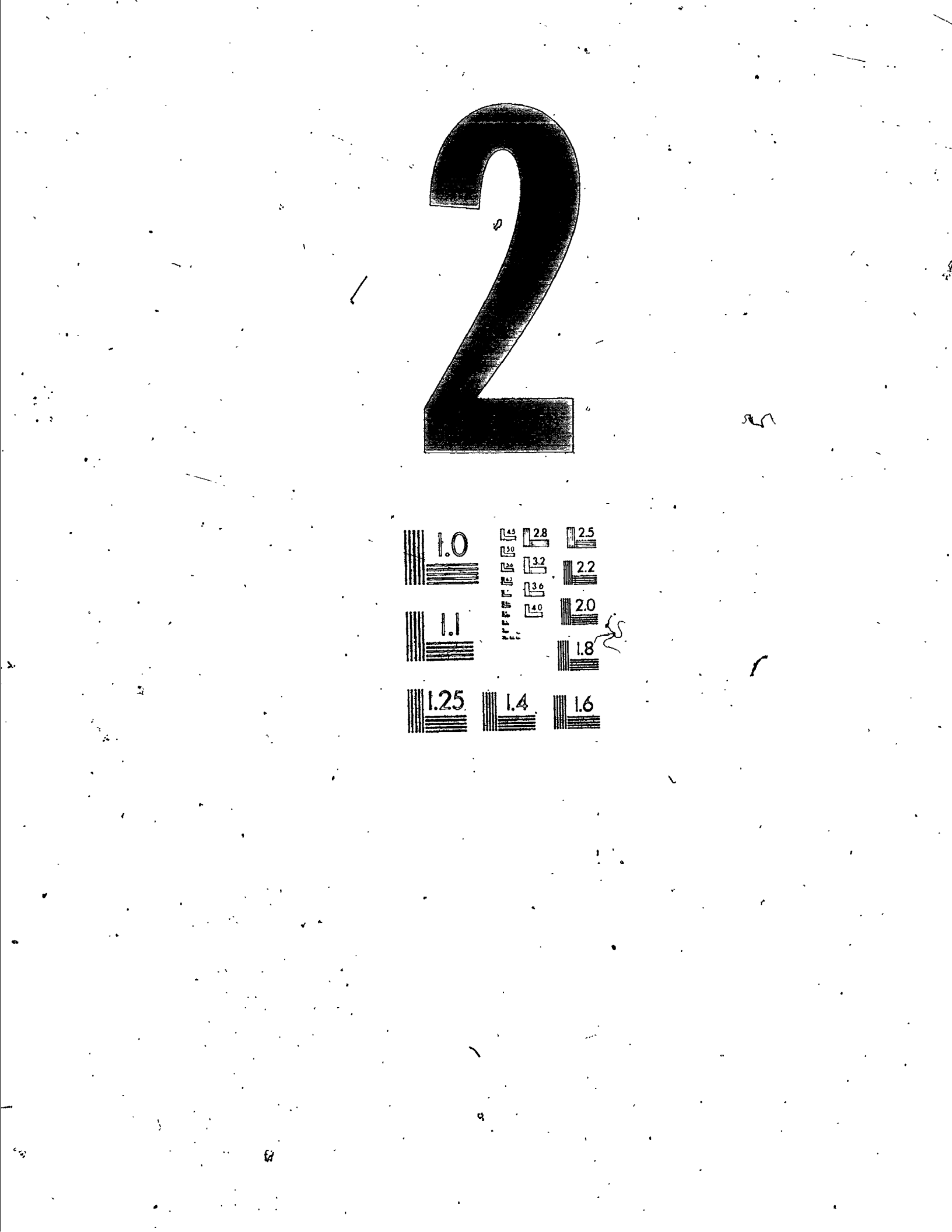


FIGURE 5.5 ^{13}C Shielding Data (ppm) and ^{13}C ^{13}C Coupling Constants (Hz) for 62


2
1.0
1.1
1.25
1.4
1.6
2.8
3.2
3.6
4.0
2.5
2.2
2.0
1.8

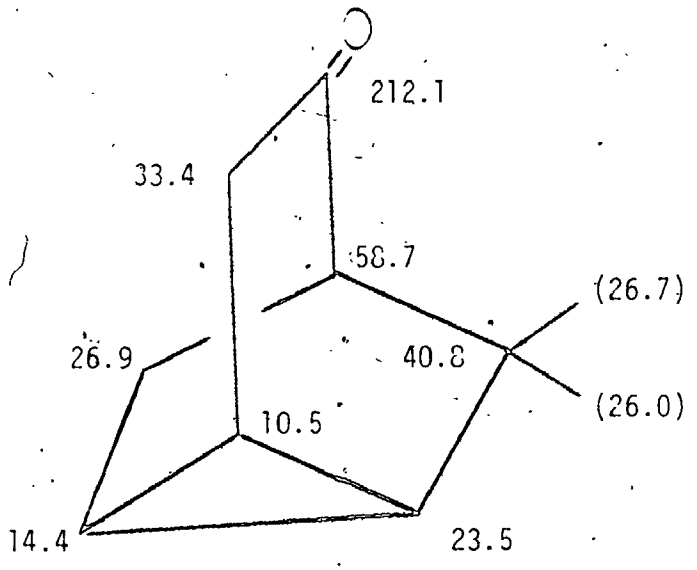
which was common with H-3. The remaining couplings for H-2 were ascribed to H-7 (J = 7.5 Hz) and H-1 (J = 7.5 Hz). A broadened 8-line pattern at δ 0.96 (J = 7.5, 5.8, 0.9 Hz) could be assigned to H-7, which is shielded by the spirocyclopropyl ring and coupled to H-2 (J = 7.5 Hz) and H-1 (J = 5.8 Hz). The remaining small coupling was not identified. A one-proton multiplet at δ 1.55 was attributed to H-1 and the four proton multiplet at δ 0.35-0.60 was ascribed to the spirocyclopropyl protons.

Double irradiation of the exo-8-proton reduced the H-1 pattern to an eight line multiplet (J = 7.5, 5.8, 1.5 Hz) by eliminating a splitting of 3.4 Hz. This pattern was attributed to interactions with H-2 (J = 7.5 Hz), H-7 (J = 5.8 Hz) and endo-H-8 (J = 1.5 Hz), double irradiation of endo-H-8 confirmed the spin coupling interaction to H-1. The remaining couplings were all confirmed by decoupling experiments and the results are summarized in Figure 5.4.

Since 6,6-dimethylbicyclo[2.2.2]octan-2-one had been prepared (56), chemical confirmation of the structure of 62 was attempted by hydrogenation. Treatment of 62 with hydrogen and Pt_2O afforded two new compounds (64,65). Preparative glc (FFAP) furnished a pure ketone 64 and an alcohol 65 contaminated with starting material. The ^{13}Cmr spectrum of 64 exhibited two methylene signals (δ_C 33.4, 26.9), four methine peaks (δ 58.7, 23.5, 14.4, 10.5), a quaternary signal (δ_C 40.8), two methyl peaks (δ_C 26.7, 26.0) and a carbonyl absorption at δ 212.1. The appearance

of two methyl signals and the absence of two spirocyclopropyl methylene peaks showed that hydrogenolysis occurred at the spirocyclopropyl ring. A precise mass measurement of 64 showed the molecular formula to be $C_{10}H_{14}O$ which is consistent with the ^{13}Cmr data.

The ^{13}C assignments for 64 followed from the data for 45 and 62.



64

The ^{1}Hmr spectrum provided further support for structure 64. An "AB" pattern at δ 2.55 (J = 21.0, 2.5 Hz) and δ 2.48 (J = 21.0, 2.5 Hz) was ascribed to the two H-3 protons coupled to H-2. A one-proton eight-line pattern at δ 2.20 (J = 13.3, 5.5, 3.4 Hz) was attributed to exo-H-8 coupled to endo-H-8 (J = 13.3 Hz), H-5 (J = 5.5 Hz) and H-1 (J = 3.4 Hz). Therefore the doublet at δ 2.04 (J = 5.5 Hz) arose from H-5 and the doublet at δ 1.75 (J = 13.3 Hz) was

assigned to *endo*-H-8. A six-line pattern at δ 1.42 (J = 6.5, 6.5, 3.4 Hz) was assigned to H-1 and the two remaining cyclopropyl protons (H-2, -7) gave rise to a complex multiplet at δ 1.00-1.29. The two methyl singlets, were at δ 1.02 and 1.07.

The ^{13}Cmr spectrum of the second fraction from the hydrogenation experiment indicated the presence of **62** and an alcohol, presumably formed by reduction of **64**. Thus, there was no evidence of hydrogenolysis of the remaining three-membered ring.

The stereoselectivity of protonation in the homoketonization of **59** was established with experiments in deuterated media. Treatment of **59** with *t*-BuO$^-$/*t*-BuOD gave **62**-d_x (1.79 atoms ^{2}H/molecule). The ^{13}Cmr spectrum showed that deuterium was incorporated at C-3 and C-8. The original signals for each were significantly attenuated, and that for C-3 was accompanied by a triplet, J_{CD} = 20.5 Hz, exhibiting an isotope shift of -0.33 ppm; for C-8, J_{CD} = 20.9 Hz with an isotope shift of -0.33 ppm. The ^{2}Hmr spectrum of **62**-d_x contained signals for ^{2}H-3, *exo*-^{2}H-8 and *endo*-^{2}H-8 with relative intensities of 10.00: 7.25 : 0.66, corresponding to 1.0 atoms ^{2}H/molecule at C-3 and 0.8 atoms ^{2}H/molecule at C-8 with the latter in the ratio 11:1 favouring *exo*-^{2}H. Therefore homoketonization of **59** proceeds with high stereoselectivity (92% ± 1%) favouring inversion of configuration.

(C) CONCLUSIONS

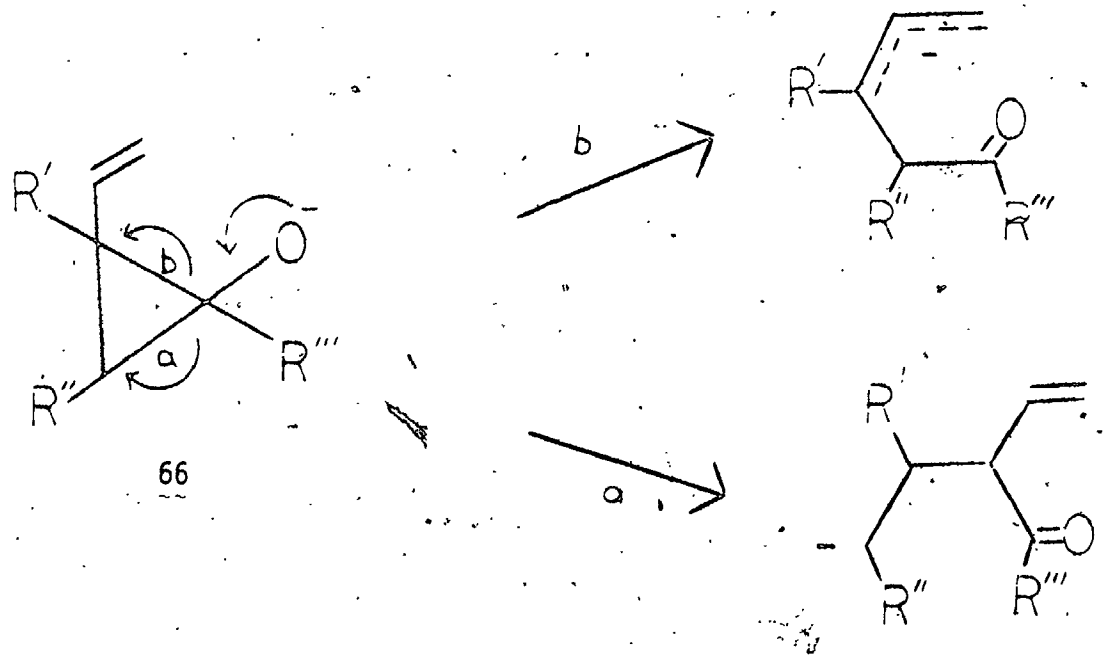
The behaviour of 58 with the Simmons-Smith reagent is analogous to that of 40, cyclopropanation yielded only the rearranged product 59 and no trace of the initial cyclopropanated compound. Homoketonization of 60 is regiospecific with cleavage occurring at the C-2,7 bond, as is the case for 44a. The failure of the 8-spirocyclopropyl group to re-direct homoketonization indicated that the regiospecific ring cleavage of the β-enolates derived from 44a and 59 is due to thermodynamic control of homoketonization. Finally, protonation at the carbanion site proceeds with high stereoselectivity favouring inversion of configuration (92%).

CHAPTER 6

SYNTHESIS AND HOMOKETONIZATION OF SOME SUBSTITUTED 2-TRIMETHYLSILYLOXYLHOMOQUADRICYCLENES

(A) INTRODUCTION

Since the spirocyclopropyl group in 60 did not alter the course of homoketonization, it was of interest to determine whether a more effective carbanion stabilizing functionality could influence this reaction. The ability of a double bond to stabilize an adjacent carbanion is well known; thus the placement of a double bond on the cyclopropoxide ring could bias the ring opening of β-enolate 66. Since cleavage of bond a affords a secondary carbanion, while pathway b leads to an allylic carbanion, the latter process may be favored. Hence, the effect of a



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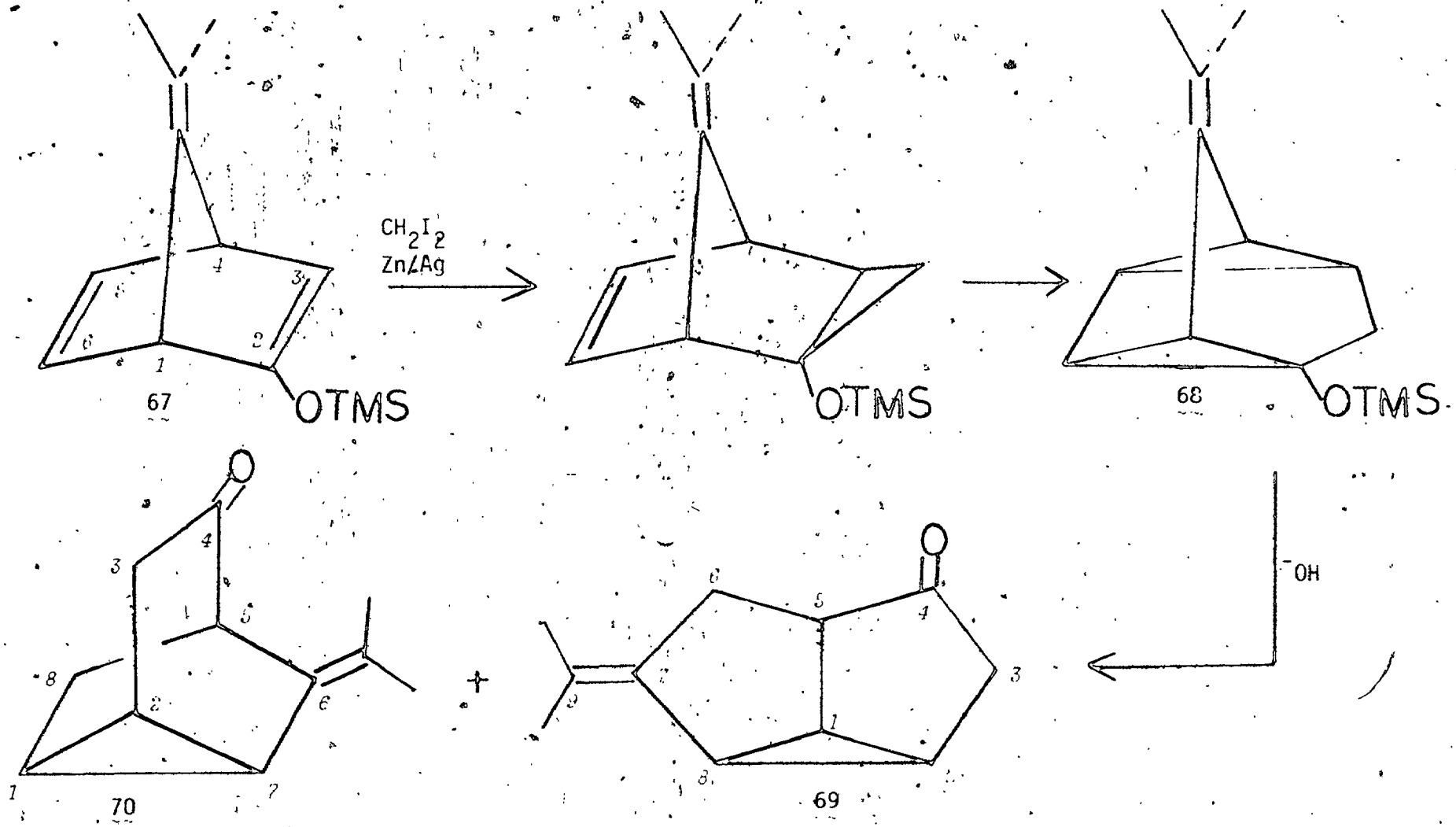


SCHEME 6.1

neighboring double bond on the homoketonization process was examined.

The appropriately substituted homoquadricyclene derivative 68 could be synthesized from the trimethylsilyl enol ether of 7-isopropylidenenorbornenone (67), since it was expected that regiospecific cyclopropanation of the enolic double bond and facile intramolecular cycloaddition of the initial adduct would occur. The 7-substituent of 67 should not interfere with this reaction from the results of cyclopropanation of 58. Treatment of 68 with base could then afford ketone 69 (see Scheme 6.1) provided the double bond re-directs the homoketonization process.

(B) RESULTS AND DISCUSSION

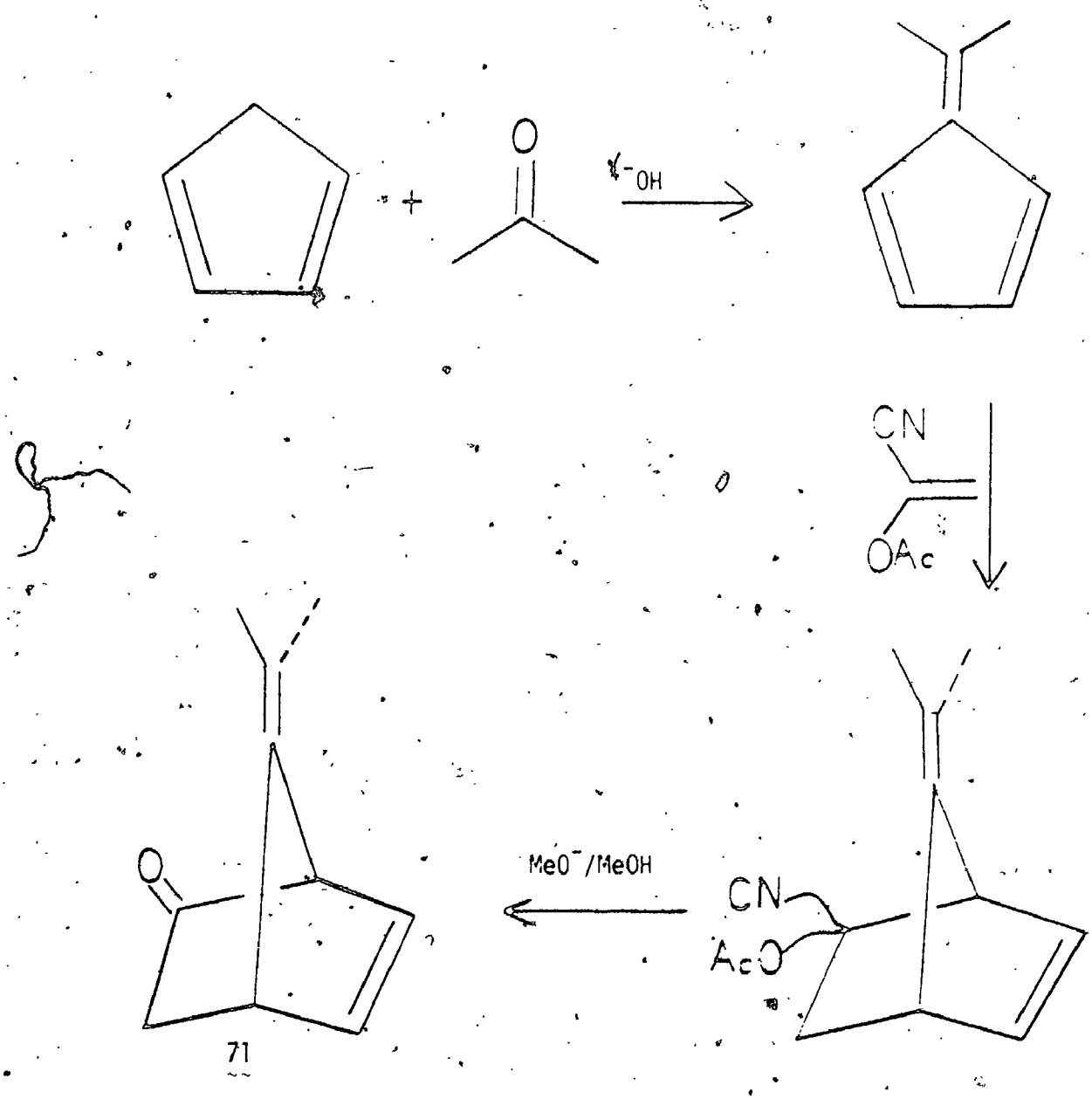
It was anticipated that the desired ketone, 7-isopropylidenenorbornenone (71) could be synthesized by condensing dimethylfulvene with α-chloroacrylonitrile, followed by hydrolysis of the adduct. The Diels-Alder reaction gave the expected adduct in 82% isolated yield and the ^{13}Cmr spectrum indicated the presence of both isomers. Hydrolysis of the mixture under a variety of conditions (KOH and ethylene glycol, KOH and t-butanol, $NaS_2 \cdot 9H_2O$ and ethanol) failed to afford 71 presumably due to facile base-induced ring opening to give the carboxylate of 71. It has been reported (57) that 71 opens to 1-(carboxymethyl)-2-isopropylidenecyclopent-3-ene when treated with unsolvated hydroxide ion in DMSO. The synthesis of 71 was successfully achieved by employing the

procedure developed by DePuy and Story (58), as illustrated in Scheme 6.2.

Ketone 71 was then treated with LDA to generate the corresponding lithium enolate, which was quenched with chlorotrimethylsilane to afford 67 in 81% isolated yield. The IR spectrum of the product contained absorptions at 3050 (CH alkene stretch), 2965, 1610 (alkene stretch), 1250 ($SiMe_3$ stretch) and 844 cm^{-1} ($OSiMe_3$ stretch) which are consistent with the assigned structure.

The ^{1}Hmr spectrum provided further confirmation. A broadened three-line pattern (2H, J = 1.7 Hz) at δ 6.78 was ascribed to part of the AB pattern for H-5, and -6, each coupled to the bridghead protons. A doublet of doublets at δ 5.23 (J = 3.6, 1.3 Hz) was assigned to H-3 coupled to H-1 and -4, which absorbed at δ 3.74 (m) and 3.84 (m), respectively. The two methyl signals of the isopropylidene substituent and the protons of the $OSiMe_3$ group appeared at δ 1.33, 1.30 and 0.0, respectively.

The ^{13}Cmr spectrum contained three quaternary signals (δ_C 93.4, 162.9, 171.8), five methine peaks (δ_C 134.3; 141.3, 109.5, 54.7, 48.9), and three methyl signals (δ_C 18.7, 18.6, 0.1 ($OSiMe_3$)). The assignment of the methine signals was straightforward with the two lower field peaks attributed to C-5 and -6 and the signal at δ_C 109.5 ascribed to C-3, since enolic methine signals usually absorb near δ_C 110.0. The remaining two methine signals were attributed to C-1 and C-4, with C-1 further



71

SCHEME 6.2

downfield because of deshielding by the $OSiMe_3$ substituent. The signal at δ_C 171.8 was assigned to C-2, based upon the ^{13}Cmr chemical shifts of 58 and 60 for which the C-2 signal absorbs at δ_C 172.5 and 173.0, respectively. Consequently the two remaining signals at δ_C 162.9 and 93.4 were ascribed to C-7 and the unsaturated carbon of the isopropylidene substituent.

Cyclopropanation of 67 was initially achieved employing 1.9 equivalents of methylene iodide (see Table 6.1). After the usual work-up, a ^{13}Cmr spectrum of the product indicated that two compounds in a ratio of 1:1 constituted approximately 90% of the product with no starting material present. Two signals at δ_C 70.8 and 70.1 suggested the presence of two silyl ether compounds. From the previous results one of these compounds could be 68 and the two signals at δ_C 133.3 and 121.0 supported this possibility. Therefore, the second compound could arise by cyclopropanation of 68 and the presence of a quaternary signal at δ_C 17.4 reinforced this possibility. All attempts to isolate these two compounds by gas-liquid chromatography led to extensive decomposition of the product, regardless of the nature and condition of the glc column. Therefore to delineate the ^{13}Cmr signals due to the doubly cyclopropanated product 72 the reaction was repeated employing 2.8 equivalents of methylene iodide. The ^{13}C spectrum of this product had the same sets of signals as before, except the ratio was approximately 7:1.

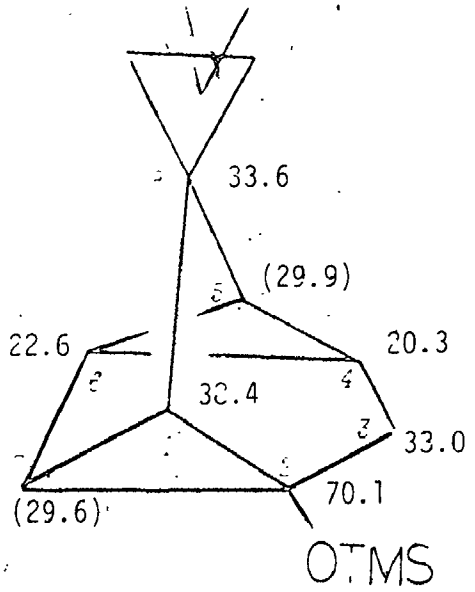
TABLE 6.1: Cyclopropanation experiments with 67

Temp.	Expt	Time (h)	Molar Ratio (CH_2I_2): 67	[67] ($M \times 10^{-3}$)	Product Composition (%)[a] 68	72	71
Reflux (38°C)	1	21	1.2	3.4	75	25	-
	2	18	1.9	3.0	50	50	-
	3	20	2.8	3.2	10	90	-
20°C	4	22	1.2	2.6	60	-	40
	5	24	1.2	3.2	75	-	25
	6	28	1.2	4.2	33	33	33

[a]Estimated by ^{13}Cmr (± 10%).

The ^{13}Cmr data for the major compound consisted of two methylene signals (δ_C 33.0, 25.0), three quaternary peaks (δ_C 70.1, 33.6, 17.4), two methyl signals (δ_C 25.4, 24.2) and five methine signals (δ_C 38.4, 29.9, 29.6, 22.6, 20.3). These data were consistent with structure 72.

The three quaternary signals at δ_C 70.1, 33.6, and 17.4 were ascribed to C-2, C-8 and the dimethylated carbon of the spirocyclopropyl ring, respectively. The low field methylene peak of δ 33.0 was assigned to C-3, and the signal at δ 25.0 was ascribed to the spirocyclopropyl methylene. Based upon the ^{13}Cmr data of **44a** and **59**, the lowest field methine signal at δ 38.4 was assigned to C-1 and the signals at δ_C 29.9 and 29.6 were attributed to C-5 and C-7. The highest field methine absorption at δ_C 20.3 was ascribed to C-4, and the remaining methine at δ_C 22.6 was attributed to C-6.



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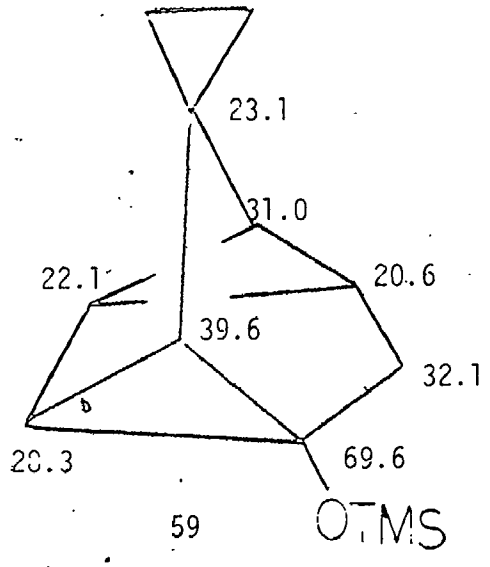
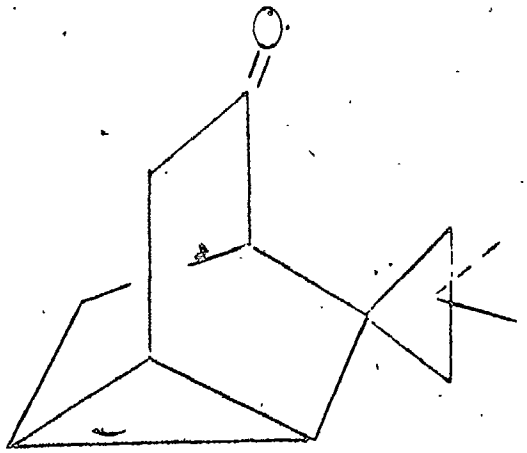


59

With allowance for the effects of the two methyl substituents, the remaining ^{13}C chemical shifts were, as expected, similar to those of 59.

To establish the structure of 72, the cyclopropanation product was treated with base to generate an identifiable ketone, by homoketonization of the cyclopropoxide arising from ether cleavage. Based upon the results of homoketonization of 60, the base catalyzed cleavage of 72 should afford the dimethylspirocyclopropyl analog of 62 (73).



73

On treatment with base, the cyclopropanated product (Expt. 3) afforded two ketones in a 6.4:1 ratio. The major component, purified by glc had carbonyl absorption (ir 1735 cm^{-1}, δ_C 210.8) indicative of a six-membered ring ketone and the molecular formula was found to be $C_{12}H_{16}O$ by precise mass measurement, confirming the addition of two methylene groups.

The ^{13}Cmr spectrum for 73 contained, in addition to the carbonyl peak, two quaternary signals (δ_C 33.0, 17.0), two methyl signals (δ_C 23.5, 22.7), three methylene peaks (δ_C 34.2, 29.3, 22.2) and four methine signals (δ_C 53.8, 20.0, 15.8, 10.4). To aid the ^{13}C assignments for 73, ^{1}H/^{2}H exchange under mild conditions was examined. The ketone was stirred at room temperature in the presence of $^-$OD/MeOD for 8 hr and, in the ^{13}Cmr spectrum of the recovered material (total 1.65 atoms ^{2}H/molecule), the signal at δ_C 34.2 was significantly attenuated. Consequently this signal was ascribed to C-3 and the absorptions at δ_C 29.3 and 22.2 were assigned to C-8 and the spiro cyclopropyl methylene respectively. The lowest field methine peak (δ_C 53.8) was attributed to C-5, deshielded by the carbonyl. From the ^{13}C assignments of 45 and 62 the lowest field cyclopropyl methine signal (δ_C 10.4) was ascribed to C-2 and the highest field (δ_C 20.0) to C-7; the remaining assignments were straightforward.

Additional confirmation of these assignments was obtained from the ^{13}Cmr spectrum of a ~ 1:1 mixture of 73-$\underline{d}_x$ and 73, the data for which are shown in Figure 6.1. As expected, the methine signal of δ 10.4 contained two isotope-shifted signals and the shifts were indicative of a ^{13}C nucleus two bonds removed from one and two deuterium nuclei. The isotope shifts of the two remaining cyclopropyl methine signals are consistent with expectations for

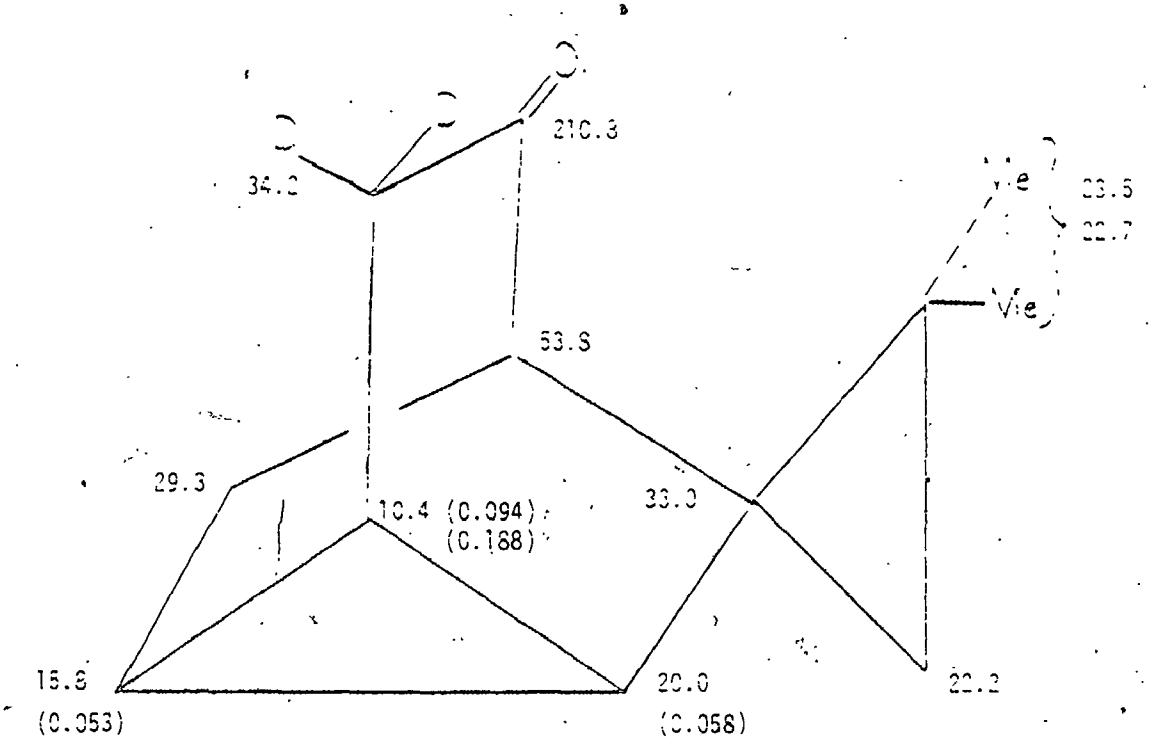


FIGURE 6.1: ^{13}C Shielding Data[a] for 73 and 73-d_2

[a]The values in parentheses are the ^{2}H-induced isotope shifts (in ppm)

structure 73. The remaining two signals (δ_C 29.3, 22.0) which exhibited very small isotope shifts were not readily assigned.

A comparison of the ^{13}C data for 62 and 73 supports the assigned structure for 73.

The ^1Hmr spectrum gave further support. The proton spectra of 73 and 73-d_x showed that the signals at δ 2.57 (J = 20.0, 2.0 Hz) and 2.56 (J = 20.0, 2.0 Hz) were strongly attenuated in the latter spectrum, therefore these absorptions were attributed to the 3-protons coupled to H-2. A one proton eight-line multiplet at δ 2.25 (J = 12.4, 5.8, 3.1 Hz), coupled to doublets at δ 1.87 (J = 12.4 Hz), and δ 2.07 (J = 5.8 Hz) and a 12-line multiplet at δ 1.55 (J = 6.8, 6.8, 3.1; ca. 0.5 Hz), was readily assigned to *exo*-H-8, which is coupled to *endo*-H-8, H-5 and H-1, respectively. The absence of additional significant coupling for *endo*-H-8 was attributed to its approximately 90° dihedral angle relationship with H-1 and H-5. The remaining coupling interactions of H-1 were ascribed to H-2,7 (J = 6.8, 6.8 Hz) and *endo*-H-8. A two-proton multiplet at δ 1.10-1.15 was attributed to the two remaining methine absorptions of the cyclopropyl ring. Two intense singlets at δ 1.17 and 1.03 were readily assigned to the methyl signals and the two highest field doublets at δ 0.42 and 0.28 (J = 4.6 Hz) are due to the protons of the spirocyclopropyl methylene. All of these coupling inter-

actions were confirmed by homonuclear decoupling and the ^{1}Hmr data are summarized in Figure 6.2.

With the structure of 73 established and from the results of homoketonization of 60, the compound which on treatment with base affords 73, must be 72. The formation of 72 results from a stereospecific cyclopropanation of the isopropylidene double bond of 68, but the position of the geminal methyl groups on the spirocyclopropyl group cannot be readily determined from the ^{1}Hmr or ^{13}Cmr spectra. An examination of molecular models indicated that the Simmons-Smith reagent would encounter greater steric hindrance to an approach from side A than B (see Scheme 6.3). If cyclopropanation is hindered by the exo-3-proton then addition would proceed by mode B to afford 72-B. Countering this steric effect is the well-known ability of oxygen functional groups to direct and facilitate the methylene transfer. Consequently the $OSiMe_3$ group could override the steric effects to favour formation of 72-A.

To determine the position of the geminal methyls the product ratio from LAH reduction of 62 was compared to the ratio of the reduction products from 73.

If the methyl groups of 73 are located on the carbon labelled ii (see Scheme 6.4) then the product ratio for LAH reduction of 73 and 62 should be similar. With the methyl groups of 73 on the carbon labelled i the ratio of the two epimers should differ for 73 and 62, because of the

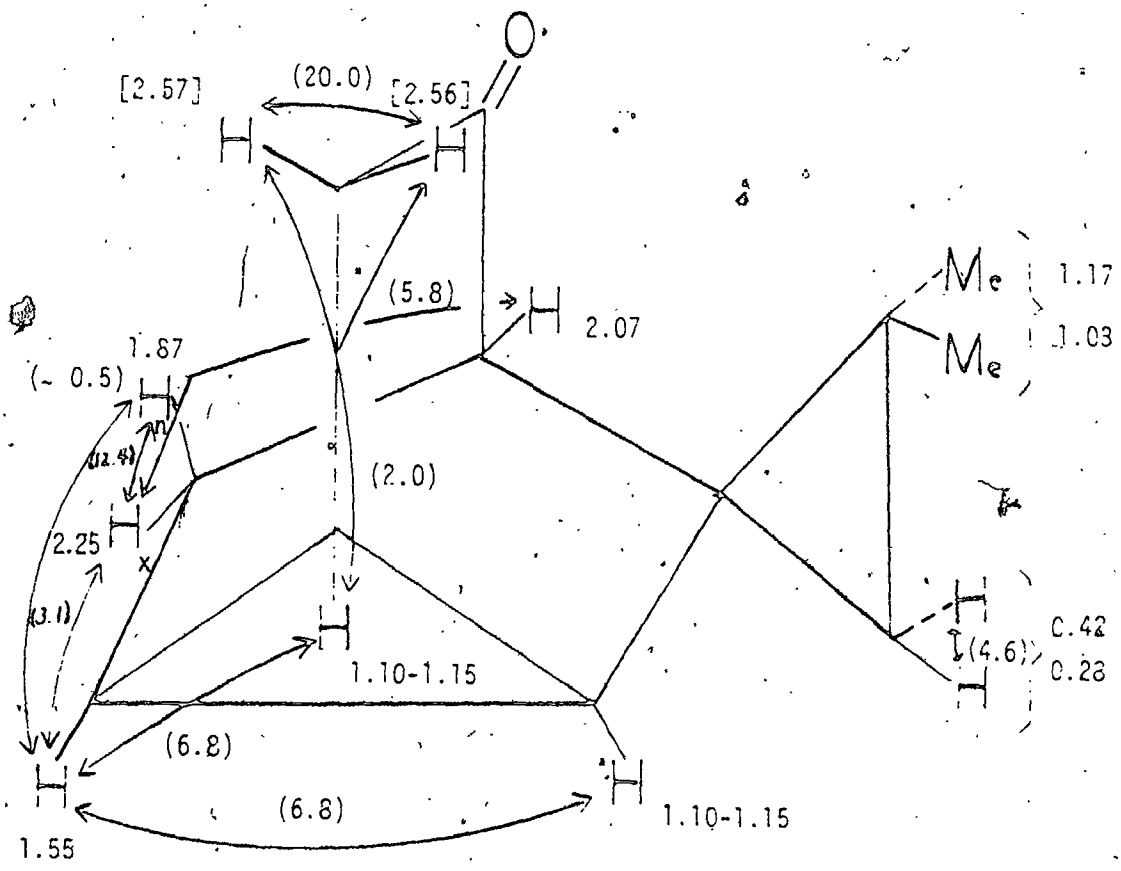
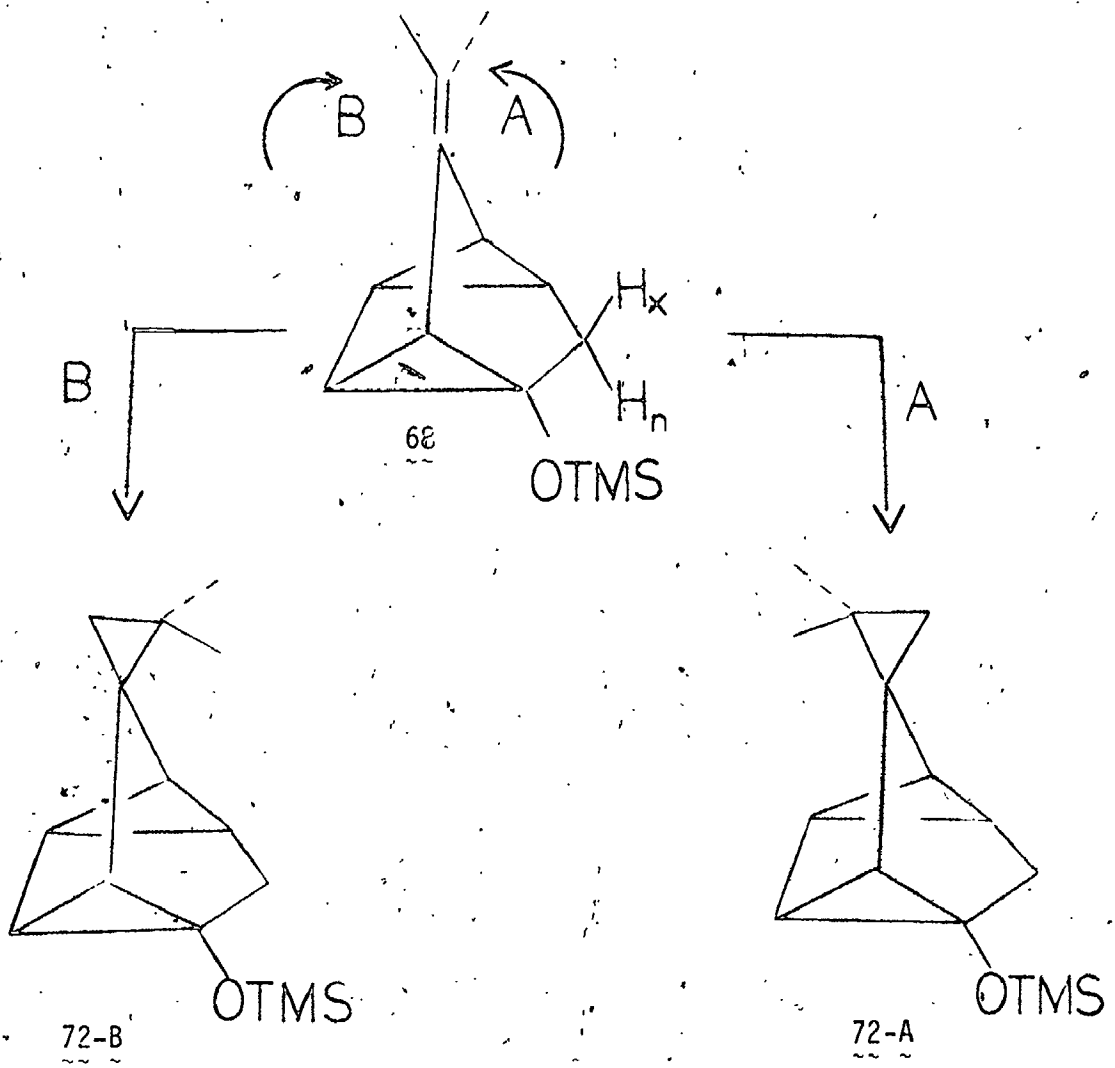


FIGURE 6.2: ^{1}H Shielding (δ) and Coupling Data (in Hz) for 73

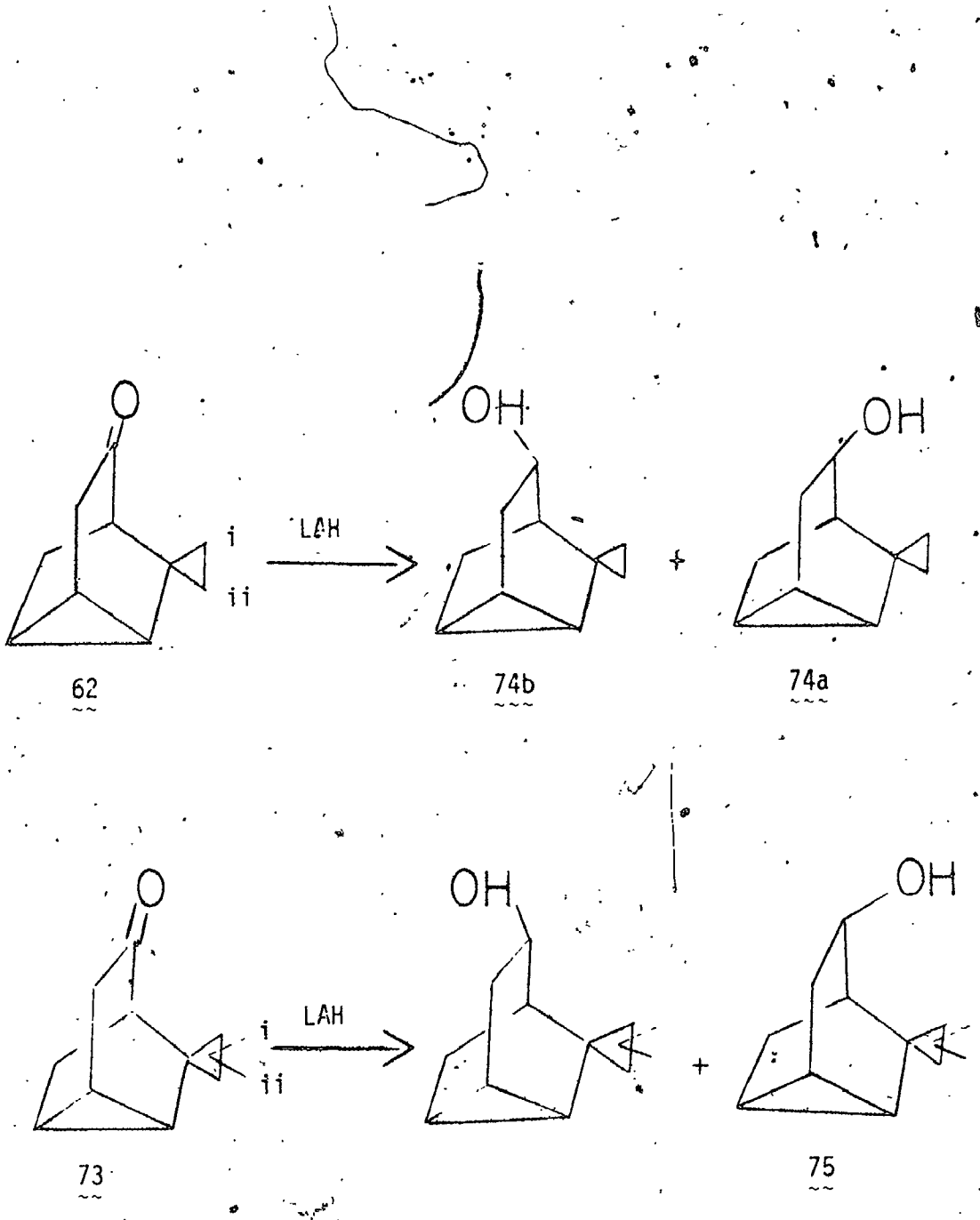


68

72-B

72-A

SCHEME 6.3



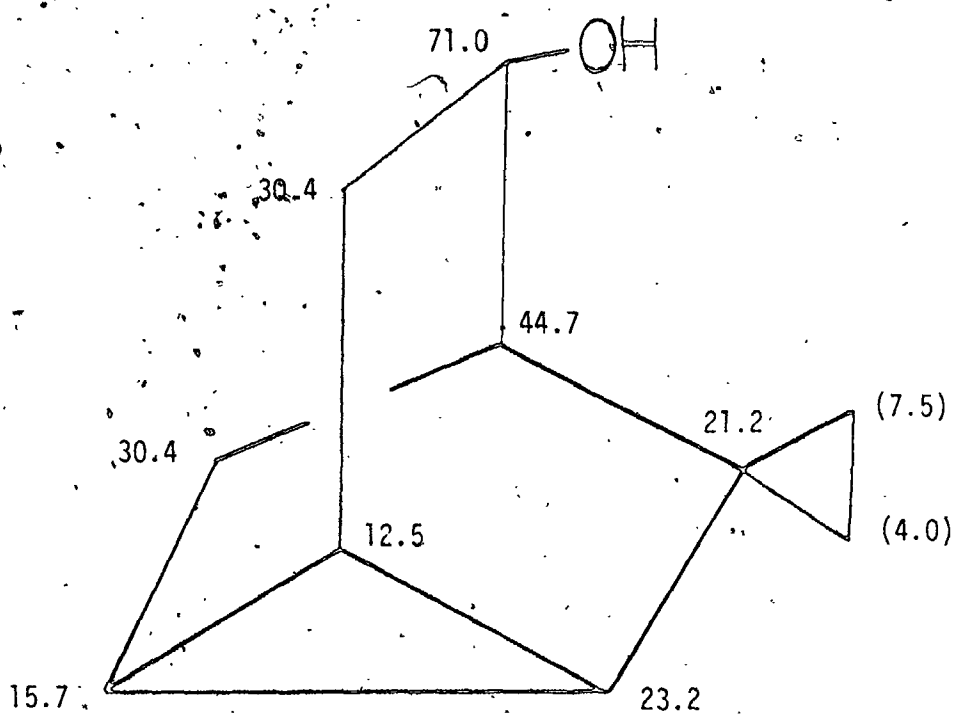
SCHEME 6.4

steric effects of the methyl groups on the LAH reduction of 73.

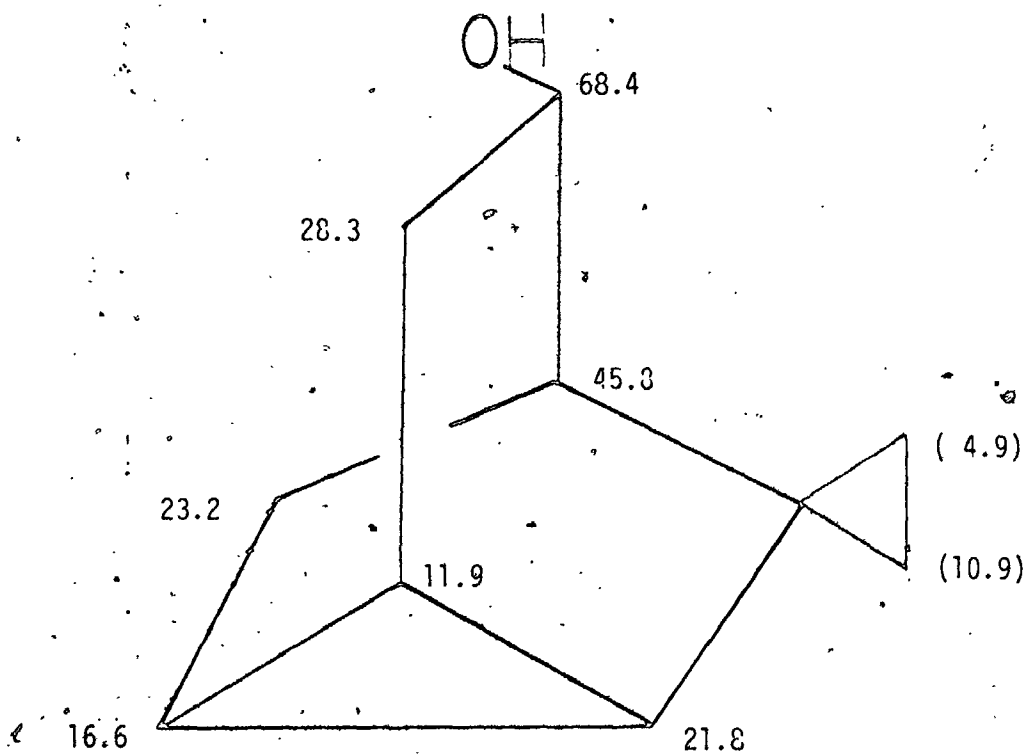
Treatment of 62 with LAH afforded, quantitatively, two alcohols in a 6.5:1 ratio. The ^{13}Cmr assignments for each epimer were relatively straightforward. Of the four methylene signals the two at highest field must be due to the spirocyclopropyl methylene carbons, and C-3, deshielded by the hydroxyl group, should be at lowest field. The two lowest field methine signals were readily ascribed to C-4 (ca. δ_C 70) and C-5. Of the remaining methine absorptions, C-7 was expected to be at lowest field deshielded by the spirocyclopropyl ring and to be internally consistent with the previous results, C-2 should be at higher field than C-1. On this basis the assignments for the major and minor epimers were obtained, as shown in Figure 6.3.

To assign the stereochemistry of the hydroxyl group in the major and minor epimers, the chemical shifts for C-8 were compared. This signal in 74b should be further upfield than in 74a because of the Y shielding effect of the hydroxyl group, consequently the major epimer was 74a. Preferential formation of 74a was expected since the transition state was less subject to steric interactions than that for reduction affording 74b.

The proton spectra provided further suport. In the ^{1}Hmr spectrum of the minor epimer the spirocyclopropyl protons absorbed in the range δ 0.24-0.91. In contrast, for the major epimer, two spirocyclopropyl protons absorbed



Major Epimer (74a)



Minor Epimer (74b)

FIGURE 6.3: ^{13}C Shielding Data (δ_C) for 74a and b

at δ 0.65-0.93 with two at δ 0.08-0.30. This is consistent with the assigned structures, since in the major epimer the protons on carbon i and ii are in distinctly different environments and are expected to have significantly different shieldings. For 74b this difference should be smaller as is reflected in the chemical shifts of these protons.

The LAH reduction of 73 also afforded, quantitatively, two products in a ratio of 18.6:1, and the major product (75) was isolated by gas-liquid chromatography. Its ^{13}C spectrum exhibited two quaternary signals (δ_C 32.8, 18.2), five methine peaks (δ_C 70.6, 43.1, 21.6, 15.6, 12.11), three methylene signals (δ_C 31.3, 30.5, 24.1) and two methyl signals (δ_C 26.0, 23.8). The ^{13}C assignments for the major epimer are based upon the arguments employed for 74a and are given in Fig. 6.4. These data, when compared to the ^{13}Cmr results for 74a and 74b, indicated that the 4-hydroxyl group is syn to the spirocyclopropyl ring.

An examination of the proton spectra of 74a, 74b and 75 provided further support. These data, summarized in Table 6.2 clearly show a striking similarity for 74a and 75, as expected if both compounds have the same stereochemistry at C-4.

A comparison of the product ratio from LAH reduction of 62 (6.5:1) and 73 (18.6:1) indicated that the geminal methyls are located on carbon i.

TABLE 6.2: ^{1}Hmr[a] spectral data for 74a, 74b and 75

Cpd.	74b	74a	75
δ(ppm)	3.93 (H 4, m)	3.69 (H 4, m)	3.72 (H 4, m)
	2.41 (H 3, J 15.1, 9.6, 3.0 Hz)	2.44 (H 3, J=14.8, 9.9, 3.2, 0.6 Hz)	2.43 (H 3, J = 13.8, 9.9, 3.7 Hz)
	2.00 (endo H 8, J 12.0 Hz)	1.95 (exo H-8, J=11.6, 6.5, 3.4, 0.5 Hz)	1.95 (exo H 8, J = 11.6, 5.8, 3.6 Hz)
	1.75 (1H, m)	1.80(H 3, J=14.8, 4.6, 2.2 Hz)	1.67 (H 3, J=13.8, 5.6, 2.0 Hz)
	1.65 (H 3, J=15.1, 4.2, 2.1 Hz)	1.63 (1H, J=8.5 Hz)	1.59 (endo H 8, J=11.6 Hz.)
	1.54 (1H, s)	1.58 (1H, m)	1.54 (H 5, J=5.8, 2.4 Hz)
	1.10 1.42 (3H, m)	1.48 (endo H 8, J=11.6 Hz)	1.38 (2H, m)
	0.24 0.91 (5H, m)	1.28 (2H, m)	1.22, 1.28 (Me x 2)
		0.65 0.93 (3H, m)	0.89 (2H, m)
		0.08 0.30 (2H, m)	0.23 (1H, J=3.7 Hz)
			0.10 (1H, J=3.7 Hz)

[a]All spectra were measured for CDCl$_3$ solution.

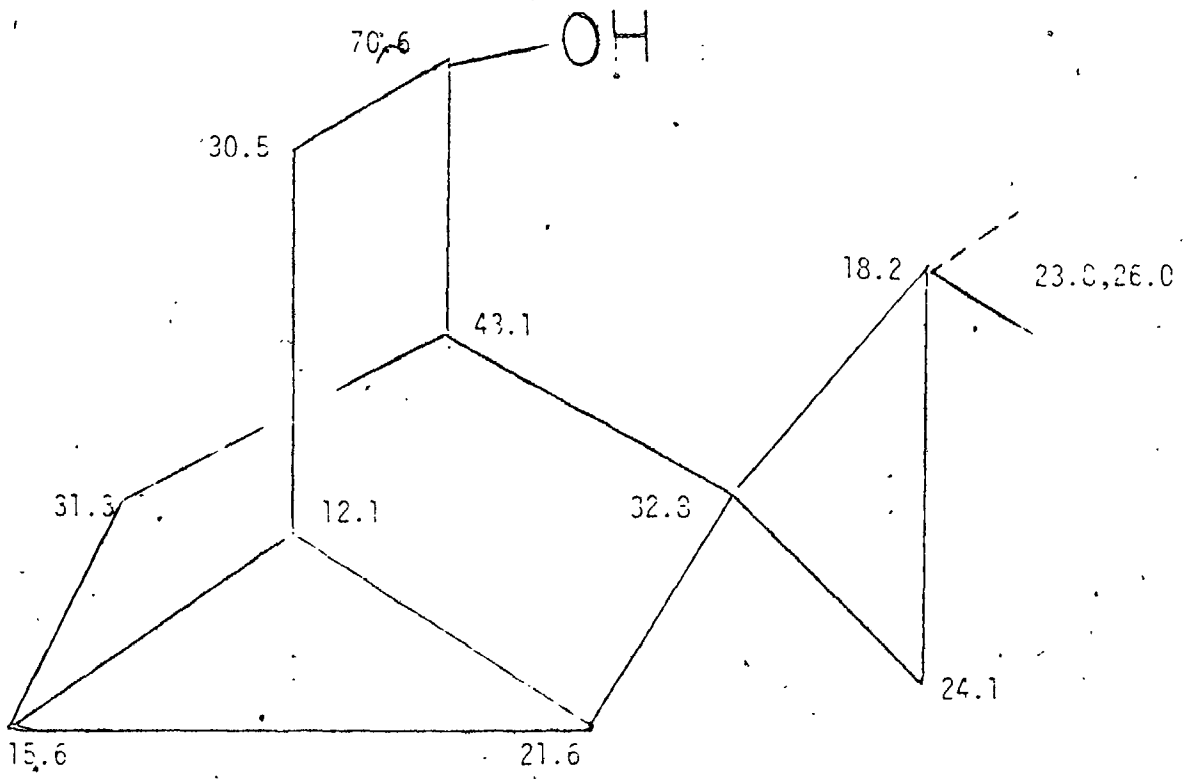


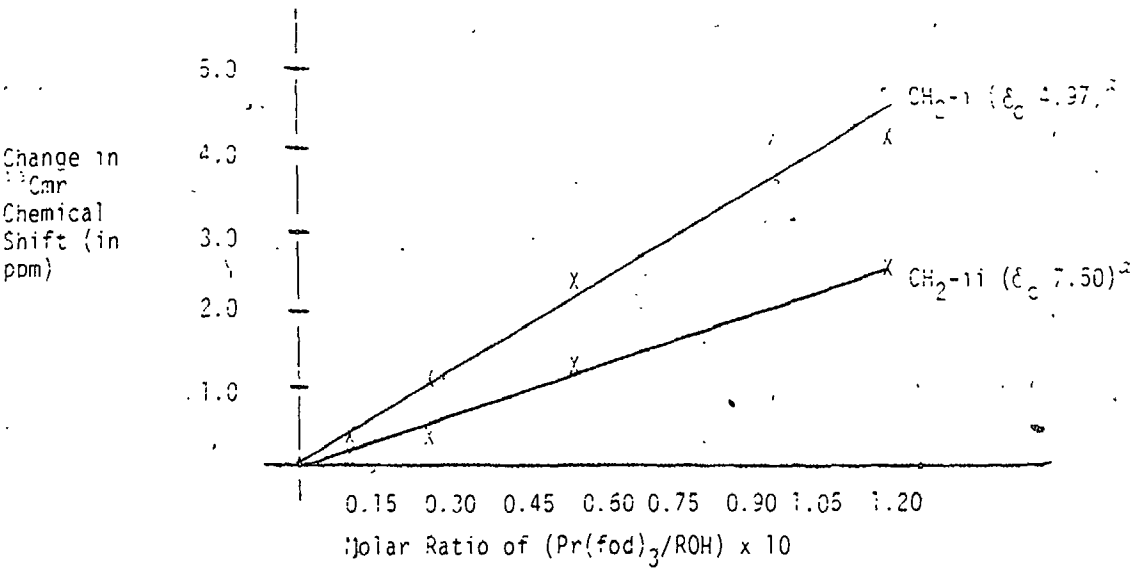
FIGURE 6.4: ^{13}C Shielding Data (δ_C) for 75

A series of shift reagent studies with 74a and 75 completed the ^{13}Cmr spectral analyses. For carbons i and ii, larger changes in chemical shift upon addition of Pr(fod)$_3$ were expected for carbon i since it is closer to the hydroxyl group, to which the shift reagent will complex. This difference in sensitivity to Pr(fod)$_3$ would also confirm the assignments for C-3 and C-8, since C-3 is closer to the hydroxyl group.

From the shift reagent studies of 74a it was apparent (Figure 6.5) that the spirocyclopropyl methylene peak at δ_C 4.97 exhibited a greater sensitivity to added Pr(fod)$_3$ than the signal at δ_C 7.50. Hence these two signals were ascribed to carbons i and ii, respectively. While the difference in ^{13}Cmr chemical shift for C-3 and C-8 (δ_C 30.40, 30.38) was too small for the signals to be distinguished, it was apparent from Figure 6.5 that the two signals exhibited different sensitivities to Pr(fod)$_3$.

Repeating the procedure with 75 confirmed the location of the geminal methyls. The quaternary signal at δ 18.2 exhibited a greater sensitivity to Pr(fod)$_3$ than the signal for the spirocyclopropyl methylene, as shown in Figure 6.6. The change in chemical shift with the addition of Pr(fod)$_3$ also confirmed the assignments for C-3 and C-8. Since as shown in Figure 6.6, the signal at δ 30.5 exhibited a greater sensitivity to Pr(fod)$_3$ than the signal for C-8 (δ_C 31.3).

FIGURE 6.5: Plot of ^{13}Cmr Chemical Shifts vs Mole Ratio of Pr(fod)$_3$ for the Spiro Cyclopropyl Methylene's of 74a



(a) Chemical shift of cyclopropyl methylene with no Pr(fod)$_3$

Plot of ^{13}Cmr Chemical Shifts vs Mole Ratio of Pr(fod)$_3$ for C-3 and C-8 of 74a

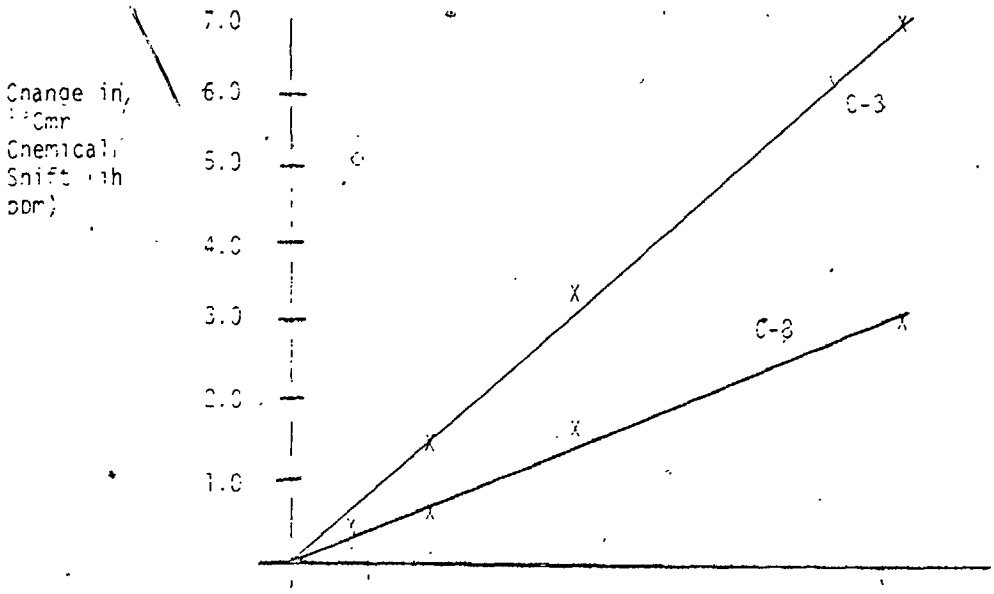
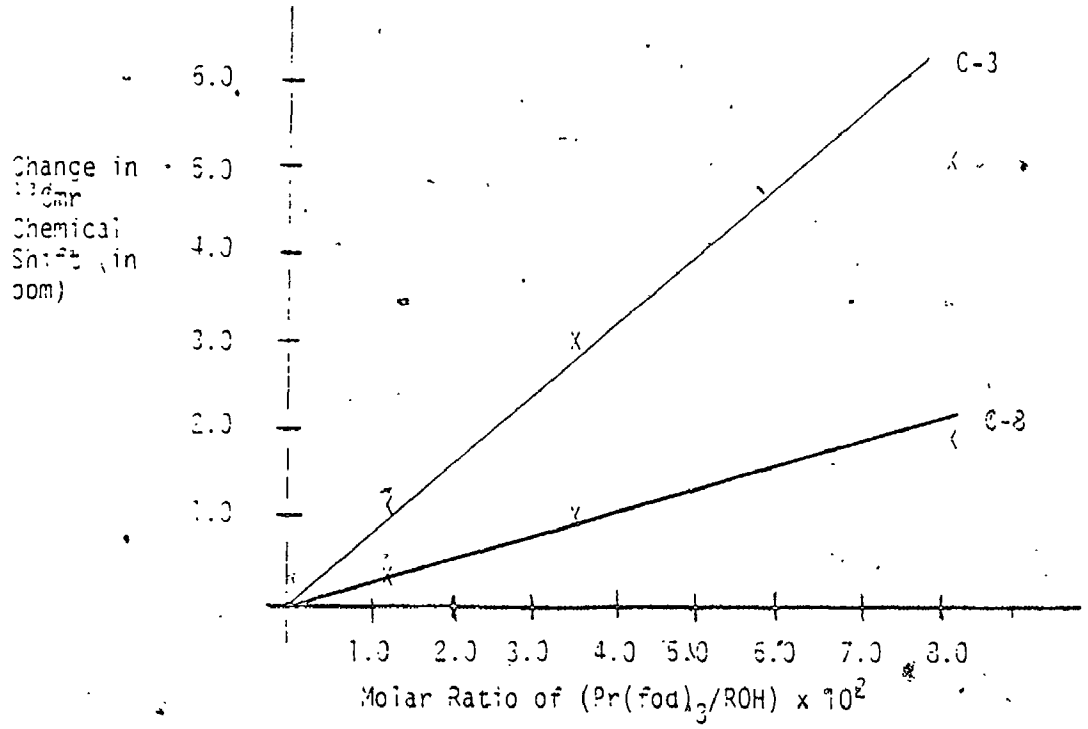


FIGURE 6.6: Plot of ^{13}Cmr Chemical Shifts vs Mole Ratio of $Pr(fod)_3$ for C-3 and C-8 of 75



Plot of ^{13}Cmr Chemical Shifts vs Mole Ratio of $Pr(fod)_3$ for the Spiro Cyclopropyl Methylene and Quaternary Carbons of 75

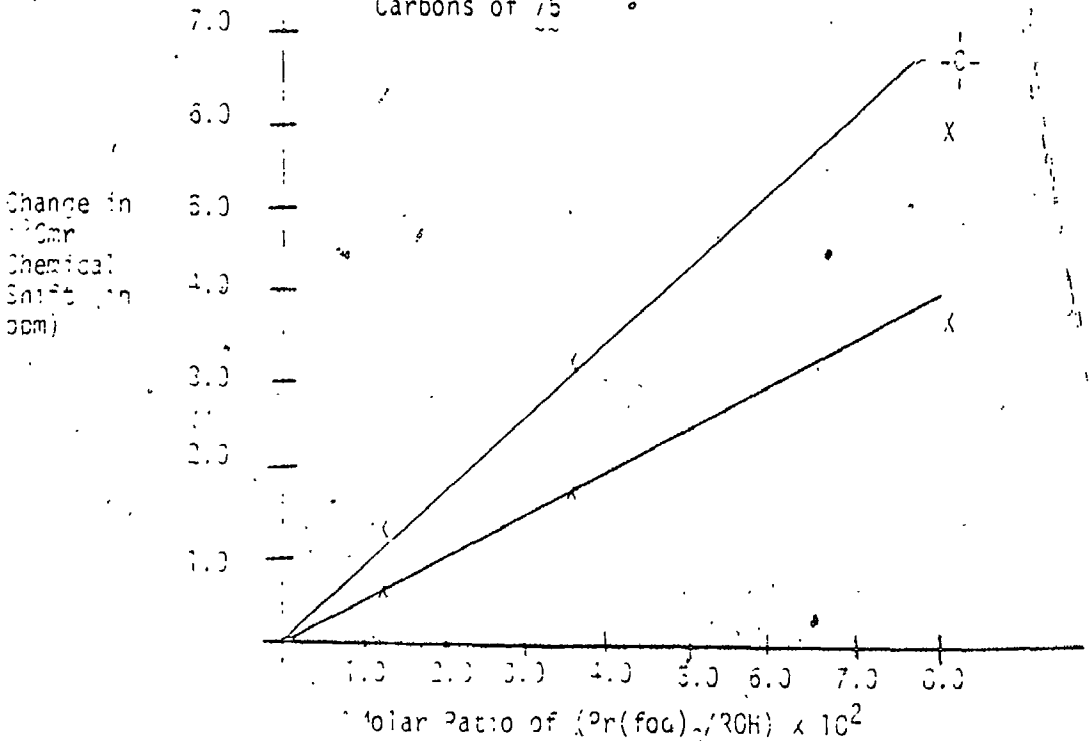


TABLE 6.3: Changes in $^{13}C_{nmr}$ chemical shifts of 74a as a function of Pr(fod)3

Equivalent of $Pr(fod)_3$	Change[a] in $^{13}C_{nmr}$ chemical shifts (ppm)									
	C-1	C-2	C-3 or C-8	C-4	C-5	C-6	C-7	C-8 or C-3	Cyclopropyl Methylene at $\delta_C = 7.50$	Cyclopropyl Methylene at $\delta_C = 4.97$
8.1×10^{-3}	0.12	0.18	0.43	1.13	0.44	0.28	0.17	0.17	0.10	0.24
2.4×10^{-2}	0.51	0.69	1.43	3.62	1.47	0.99	0.64	0.63	0.47	0.89
5.6×10^{-2}	1.28	1.69	3.38	8.41	3.46	2.37	1.54	1.51	1.19	2.15
1.2×10^{-1}	2.62	3.43	6.80	16.85	6.94	4.79	3.13	3.05	2.44	4.36

[a]Determined by subtracting the chemical shift after the addition of $Pr(fod)_3$ from the $CDCl_3$ value.

TABLE 6.4: Changes in $^{13}C_{NMR}$ chemical shifts of 75a as a function of Pr(fod)$_3$

Equivalent of Pr(fod)$_3$	Change[a] in $^{13}C_{NMR}$ chemical shifts (ppm)											
	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	quaternary carbon at δ_C 18.21	cyclopropyl methylene	methyl at δ_C 23.82	methyl at δ_C 26.04
1.1×10^{-2}	0.31	0.48	1.02	2.67	1.03	0.70	0.44	0.36	0.56	0.34	0.30	0.65
3.4×10^{-2}	0.97	1.35	2.82	7.00	2.76	1.91	1.25	1.07	1.58	0.98	0.90	1.81
8.0×10^{-2}	1.84	2.53	5.21	12.89	5.12	3.55	2.35	2.02	2.94	1.84	1.71	3.38

[a]Determined by subtracting the chemical shift after the addition of Pr(fod)$_3$ from the $CDCl_3$ value.

With the position of the two methyl groups established, cyclopropanation of 70 must occur by pathway B. Therefore, steric effects govern the methylene transfer.

From the ^{13}C assignments for 72 it was possible to determine the signals for 68 in the spectrum of the product from cyclopropanation of 67 (Expt. 2). On this basis the ^{13}C spectrum for 68 consisted of twelve signals: C, 70.8, 121.0, 133.3; CH, 21.7, 24.8, 26.8, 30.4, 36.4; CH_2, 32.7; CH_3, 21.8, 22.0 and a trimethylsilyl absorption at δ_C 1.2. These data were consistent with the assigned structure for 68. The signals at δ_C 32.7, 70.8, 121.0 and 133.3 can be readily ascribed to C-3, C-2 and the two olefinic carbons, respectively. The lowest field methine peak at δ_C 36.4 was assigned to C-1, deshielded by the $OSiMe_3$ and isopropylidene substituents. A comparison of the ^{13}C shieldings for 44a and 59 permitted completion of the assignments, as shown in Figure 6.7. With allowance for the effects of the isopropylidene substituent the ^{13}Cmr data fit well with the results for the other homoquadricyclene derivatives.

To optimize the yield of 68, the cyclopropanation reaction was repeated varying the concentrations of reactants, reaction time and temperature. These results are summarized in Table 6.1. From these data the formation of 68 can be optimized by lowering the reaction temperature and employing a 1:1.2 molar ratio of 67:CH_2I_2. The major side product for the room temperature cyclopropanation

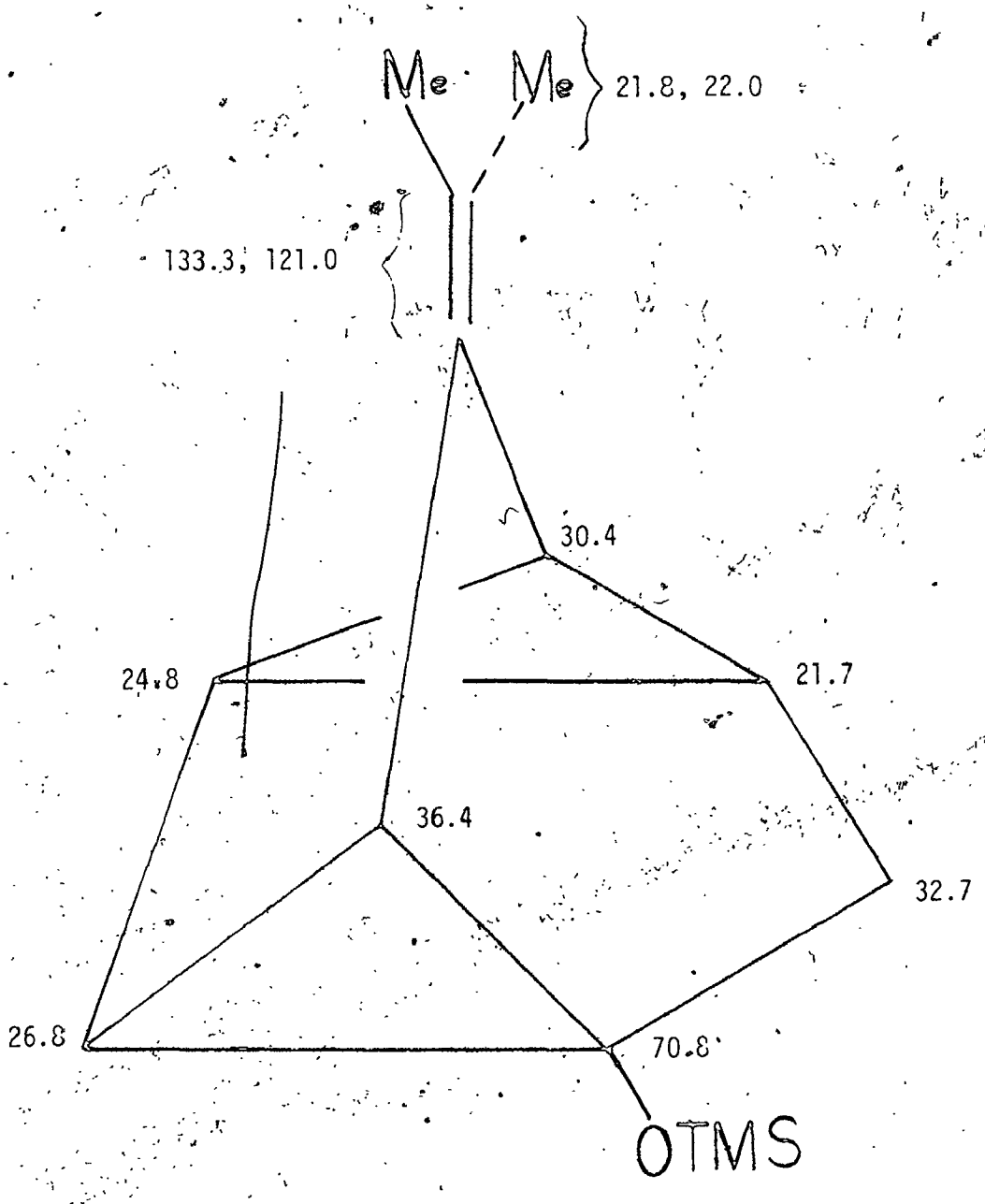
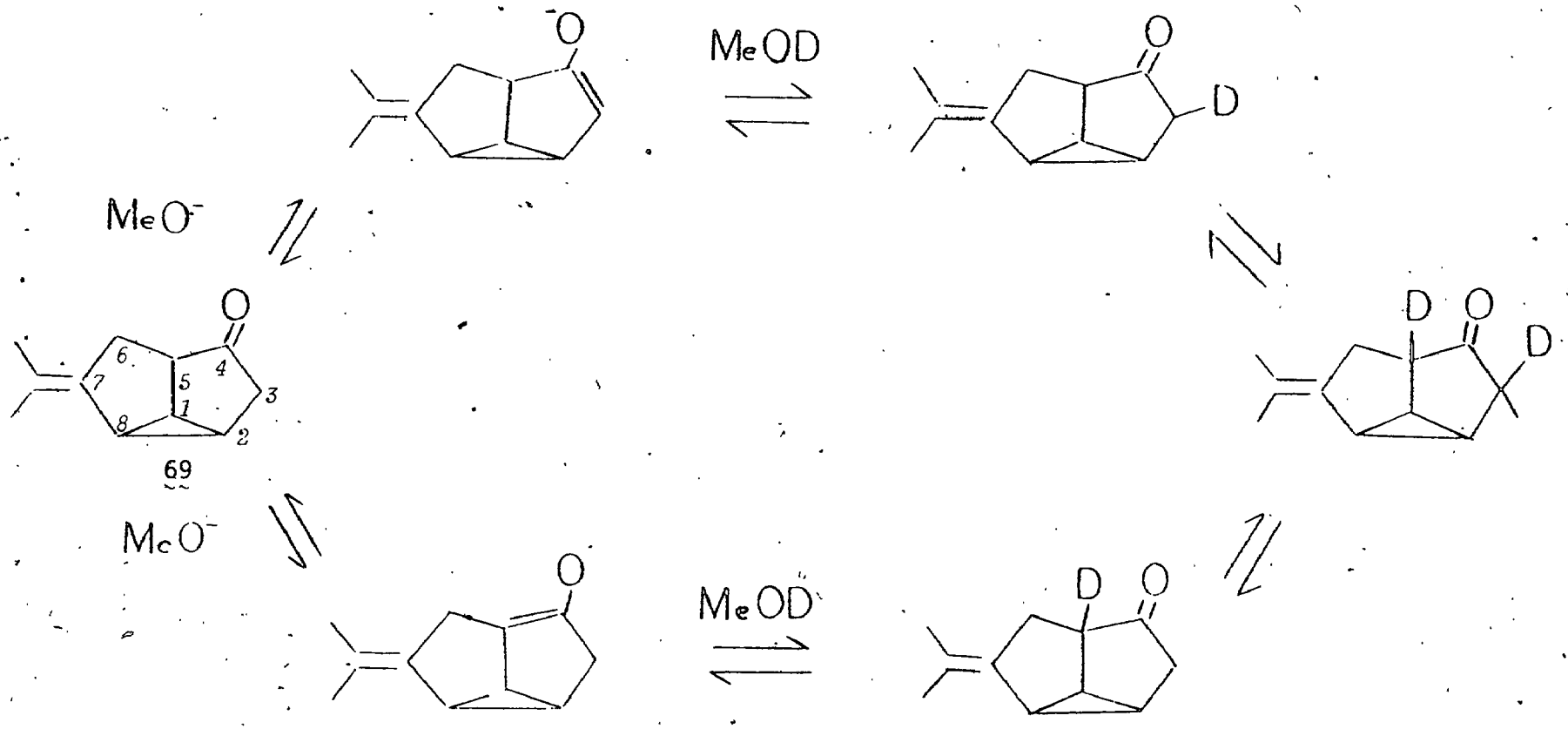


FIGURE 6.7: ^{13}C Shielding Data (δ_C) for 68

reactions was 71, by hydrolysis of 67, possibly catalyzed by trace amounts of acid present in solution.

Treatment of the product mixture from cyclopropanation of 67 (Expt. 1) with base afforded 73 and the homoketonized product from 68. The latter compound (69) isolated by preparative glc, had carbonyl absorption (ir 1748 cm^{-1}, δ_C 222.1) indicative of a five-membered ring ketone. The ^{13}Cmr spectrum contained, in addition to the carbonyl absorption, two quaternary (δ_C 129.8, 126.5), four methine (δ_C 50.3, 30.0, 26.3, 20.6), two methylene (δ_C 43.1, 35.4) and two methyl signals (δ_C 21.6 x 2). These data and the molecular formula, shown by precise mass measurement to be $C_{11}H_{14}O$, are consistent with structure 69.

To aid the ^{13}Cmr spectral analysis, $^1H/^2H$ exchange was examined. It was anticipated that 69 would exhibit exchange at C-3 and C-5, as illustrated in Scheme 6.5. Ketone 69 was stirred at reflux in the presence of MeO^-/MeOD for 1.5 h. In the ^{13}Cmr spectrum of the recovered material (80% yield, 1.59 ^2H/molecule), only the methylene absorption at δ_C 35.4 was strongly attenuated, which served to distinguish the signal for C-3. The absence of deuterium incorporation at C-5 was attributed to a slower rate of exchange at this site, presumably as a result of the increase in ring strain associated with the re-hybridization of C-5 from sp^3 to sp^2. In a second trial, a 1:1 mixture of 69 and 73 was stirred in MeO^-/MeOD



69

SCHEME 6.5

at reflux for 9 h. Gas-liquid chromatography of the recovered material indicated that 69 had decomposed.

With the signal at δ_C 35.4 ascribed to C-3 the remaining absorptions were readily assignable. The lowest field methine signal (δ_C 50.3) was attributed to C-5, deshielded by the carbonyl and not part of a cyclopropyl ring. Of the three remaining methine absorptions, the signal at δ_C 30.0 was assigned to C-8 , deshielded by the isopropylidene substituent. The highest field methine peak was ascribed to C-2, since it has fewer β substituents than C-1. The remaining assignments are straightforward and are shown in Figure 6.8.

Confirmation of these assignments for 69 was achieved by determination of the ^{13}C-^{13}C spin coupling constants with a 1-D INADEQUATE experiment. These data are summarized in Fig. 6.8 and are in accord with the assigned structure. Although geminal interactions (J_{CCC}) are usually small, of the order of 1.5 Hz or less, such interactions across an olefinic or carbonyl carbon can be relatively large. The enhancement of J_{CCC} values for olefinic derivatives has been demonstrated with labelled compounds such as [1-$^{13}CH_3$]-1,3,3,5,5-pentamethylcyclopentene for which $J_{1',5} = 3.17$ Hz (59). Therefore $J_{6,8} = 7.3$ Hz for 69 is in accord with expectations and $J_{3,5} = 14.8$ Hz agrees well with expected J_{CCC} values for carbonyl derivatives, as noted previously.

Additional support for the structural assignment

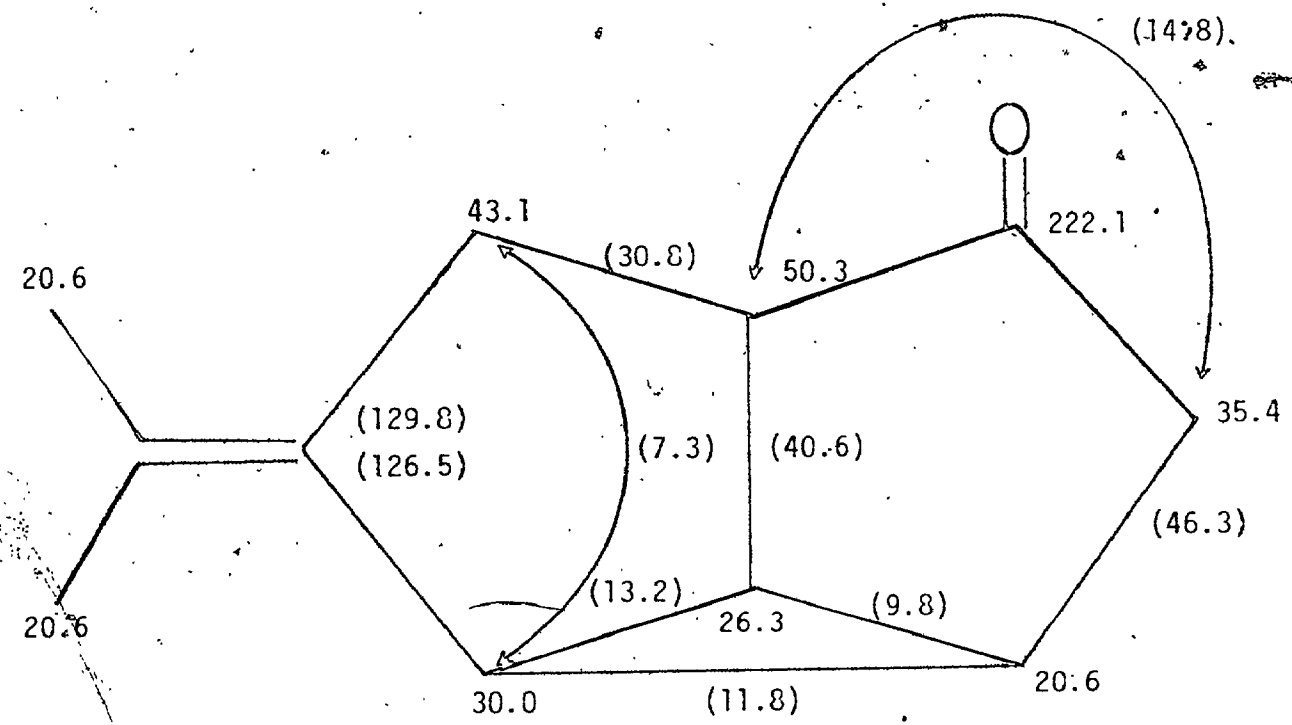


FIGURE 6.8: ^{13}C-Shielding Data (δ_C) and Coupling Constants (in Hz) for 69

for 69 was obtained from its ^{1}Hmr spectrum. The proton spectrum (C_6D_6) consisted of three multiplets at δ2.48 (2H), 2.20 (1H), 1.75 (2H), an eight-line pattern at δ 2.14 (1H, J = 18.7, 6.6, 1.9 Hz), a doublet at δ 1.83 (1H, J = 18.7 Hz), a one-proton absorption at δ 1.23 (ddddd, J = 7.0, 7.0, 6.6, 2, 1 Hz), and methyl doublets at δ 1.59 (J = 2.5 Hz), and 1.44 (J = 1.3 Hz). To increase the dispersion of the proton resonances the ^{1}Hmr spectrum was obtained in the presence of shift reagent.

The proton spectral data for 69, obtained with Eu(fod)$_3$ are summarized in Table 6.5. Homonuclear decoupling showed that the signal at δ 3.45 (spectrum D) coupled to the absorptions at δ 4.86, 3.81 and the two methyl signals. Consequently the multiplet at δ 3.45 is due to *exo*-H-6 coupled to *endo*-H-6 (δ 3.81, J = 15 Hz), H-5 (δ 4.86, m) and to the methyl protons. Double irradiation of the methyl signal at δ 1.91 reduced the splitting for *exo*-H-6 to a broadened four-line pattern (J = 15, 7 Hz). The larger coupling (15 Hz) is the geminal interaction with *endo*-H-6 and J = 7 Hz must be the coupling with H-5. The *endo*-6-proton was not coupled to H-5 or the methyl protons since the relative orientations minimized such interactions. The two signals at δ 4.75 (ddd J = 18.7, 6.6, 1.9 Hz) and 4.26 (bd J = 18.7 Hz) were readily attributed to the 3-protons. Double irradiation of the H-5 absorption reduced the pattern at δ 4.75 to a four-line multiplet by eliminating a splitting of 1.9 Hz, which was

TABLE 6.5: ^{1}Hmr chemical shifts for 69 in the presence of Eu(fod)$_3$

Spectrum	Equivalents of Eu(fod)$_3$	Chemical Shifts[a] (ppm)									
		H-5	*exo*-H-6	*endo*-H-6	*exo*-H-3	*endo*-H-3	H-1	H-8	Me	Me	H-2
A	0.00	2.48	2.48	2.20	2.14	1.83	1.75	1.75	1.59	1.4	1.23
B	0.03	3.27	2.80	2.75	3.00	2.63	2.03	1.96	1.71	1.54	1.50
C	0.06	3.55	2.95	2.95	3.30	2.95	2.12	2.03	1.74	1.57	1.60
D	0.12	4.86	3.45	3.81	4.75	4.26	2.59	2.36	1.91	1.73	2.03

[a]All spectra were measured for C_6D_6 solution.

ascribed to a long range w coupling between H-5 and *exo*-H-3. The remaining 6.6 Hz splitting for *exo*-H-3 was attributed to coupling with H-2, which absorbed at δ 2.03 (br ddd J = 7.0, 7.0, 6.6 Hz). The 7.0 Hz couplings of H-2 were ascribed to interactions with H-1 and H-8. Two additional couplings of H-2 (J = 2, 1 Hz), which were partially resolved in spectrum A, were attributed to coupling with *endo*-H-3 and a long range "w" coupling to H-5. A one-proton broadened doublet at δ 4.26 (J = 18.7 Hz) was ascribed to *endo*-H-3, the small vicinal interaction with H-2 (J = 2 Hz) was attributed to the approximately 90° dihedral angle relationship between these protons. For the remaining two cyclopropyl proton signals (δ 2.59, 2.36) the absorption for H-8 was readily attributed to the doublet of doublets at δ 2.36 (J = 7.0, 7.0 Hz). Consequently, the signal at 2.59 (ddd, J = 7.0, 7.0, 4.6 Hz) was ascribed to H-1 coupled to H-8 (J = 7.0 Hz), H-6 (J = 7.0 Hz) and H-5 (J = 4.6 Hz).

All spin-coupling interactions were confirmed by decoupling experiments and the results are summarized in Figure 6.9. With the complete assignment of the proton spectrum of **69**, the ^{2}Hmr spectrum of **69**-d_y was examined to check for small amounts of deuterium at the 5-position. This spectrum indicated that deuterium incorporation had occurred only at the *exo* and *endo*-3-positions in approximately equal proportions.

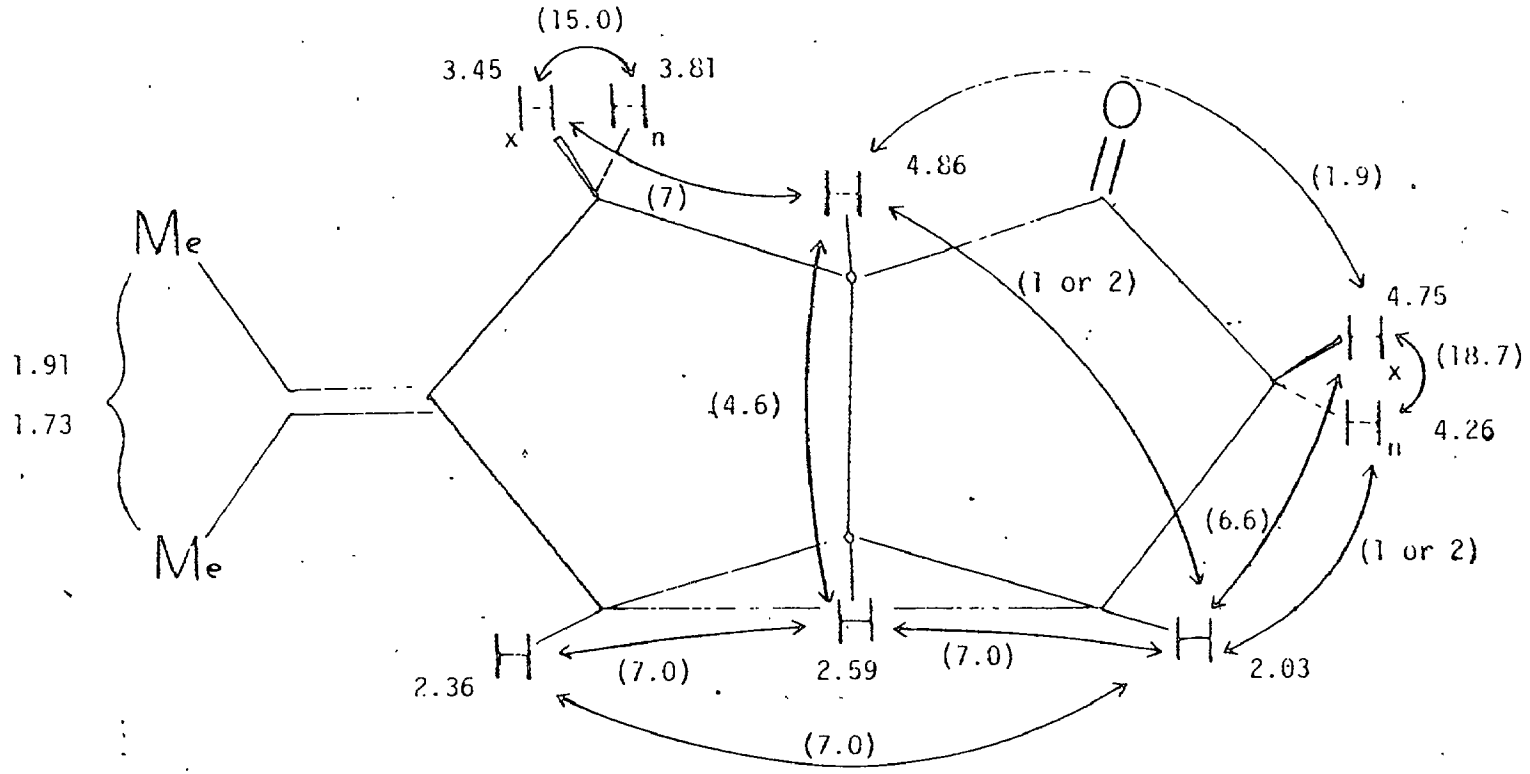


FIGURE 6.9: ^{1}H Shielding[a] (δ) and Coupling Data[b] for 69

[a] In ppm from TMS in C_6D_6 and 0.12 equivalents of Eu(fod)$_3$

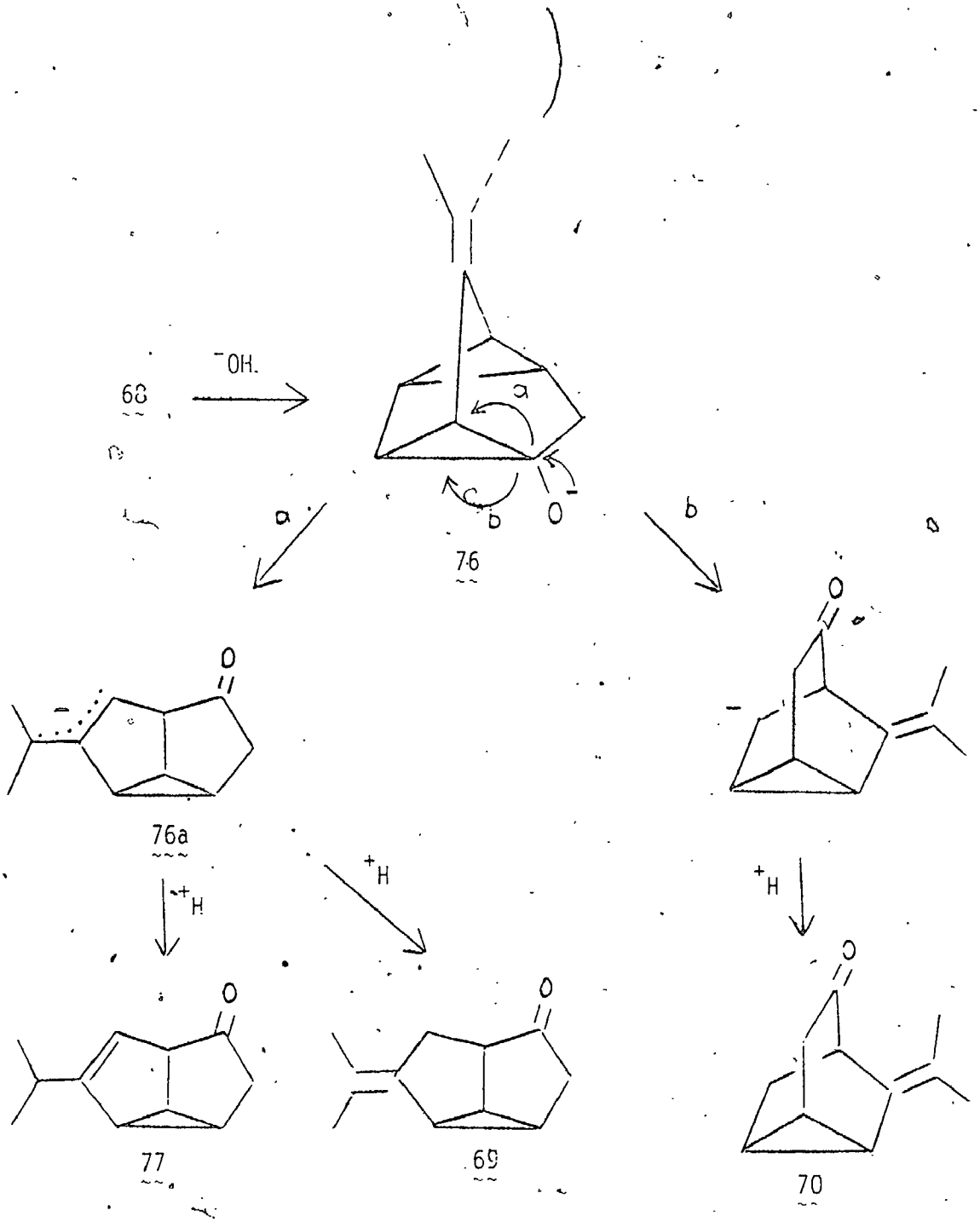
[b] The resolvable coupling constants (in Hz) are given in parentheses

Initially, confirmation of structure 69 was attempted by conversion to tricyclo[3.3.0.$0^{2,8}$]-octan-3-one, a known compound (52). It was anticipated that reduction of the carbonyl group, followed by oxidative cleavage of the double bond would furnish the desired compound. However, Wolff-Kishner reduction of 69 resulted in extensive decomposition, and this approach was abandoned.

To illustrate the feasibility of performing the reaction on a preparative scale, the cyclopropanation reaction was repeated with 710 mg of 67. The resulting product was treated with base and, after work-up, flash chromatography afforded 69 in 67% overall yield.

With the structure of 69 established, homoketonization of cyclopropoxide 76 was re-examined. Although there are two modes for ring-opening of the β-enolate, labelled a and b in Scheme 6.6, the ring cleavage is apparently regiospecific, yielding only 69.

While both modes formally afford secondary carbanions, resonance stabilization of the carbanion can occur in 76a, but the extent to which the negative charge is delocalized cannot be readily determined. In principle, protonation can occur at C-6 and C-9. The absence of 77 suggests that either protonation at C-6 occurs early in the homoketonization process or that 69 is much more stable than 77, i.e. thermodynamic control. With this uncertainty it is difficult to assess the degree of allylic stabilization of the transition state. Nevertheless, the



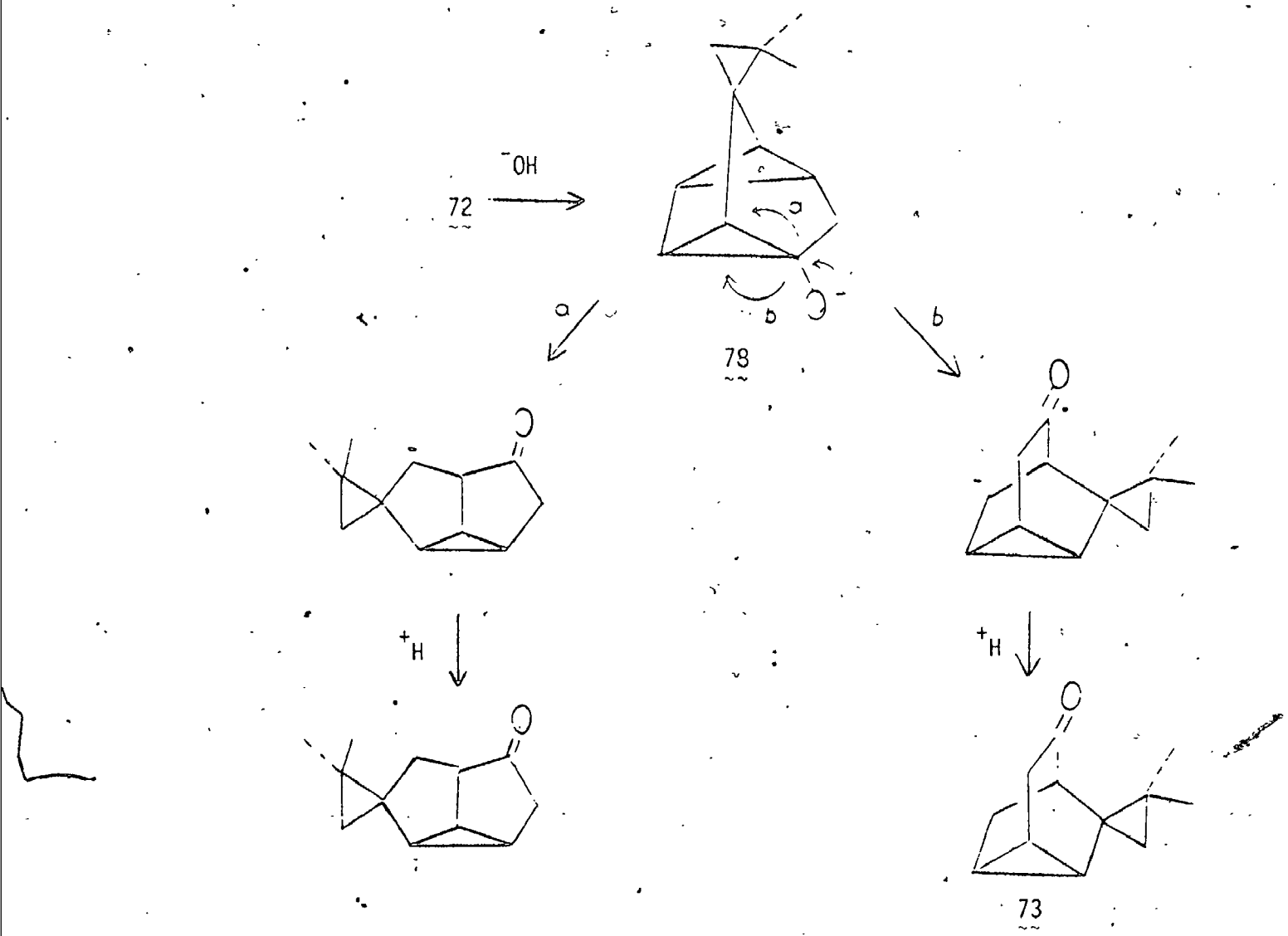
SCHEME 6.6

products from homoenolization of 47 and homoketonization of 44a and 59 indicate that 70 may be more stable than 69 and, thus, the formation of 69 can be attributed to allylic stabilization of the developing negative charge at C-6 of 76a.

In contrast to the behaviour of 68 in a basic medium, homoketonization of the β-enolate of 72 afforded only 73. Thus, while cleavage of the cyclopropoxide can occur by two modes, (a and b in 78, Scheme 6.7), the ring opening proceeds entirely by pathway b. Since cleavages a and b both lead to secondary carbanions, having similar orientations relative to an α-cyclopropyl ring, the exclusive formation of 73 was attributed to thermodynamic control of homoketonization.

The stereochemistry of protonation (deuteration) at the carbanionic site generated from homoketonization required additional evidence for its clarification. For this purpose, the homoketonization was examined in a deuterated medium.

Treatment of 72 with $^{-}$OD/t-BuOD afforded 73-d_x, which from the mass spectral data contained [illegible]2 atoms ^{2}H/molecule. In the ^{1}Hmr spectrum the absorptions at δ 2.25 (*exo*-H-8), 2.57 and 2.56 (3-protons) were significantly attenuated, as were the signals for C-8 and C-3 in the ^{13}Cmr spectrum. Clearly ring opening of 78 proceeded with inversion of configuration at the carbanionic site. To check for small amounts of *endo*-^{2}H-8,



SCHEME 6.7

the ^{2}Hmr spectrum of 73-d_x was recorded. This spectrum contained signals at 2.55, 2.25 and 1.88 with relative intensities of 13.1:3.9:0.4, corresponding to 1.14, 3.4 x 10^{-1} and 3.5 x 10^{-2} atoms ^{2}H at the 3-, *exo*-8 and *endo*-8 positions, respectively. Thus, ring opening of 78 proceeds with high stereoselectivity (93% ± 3%) favouring inversion of configuration, which is in agreement with the previous findings.

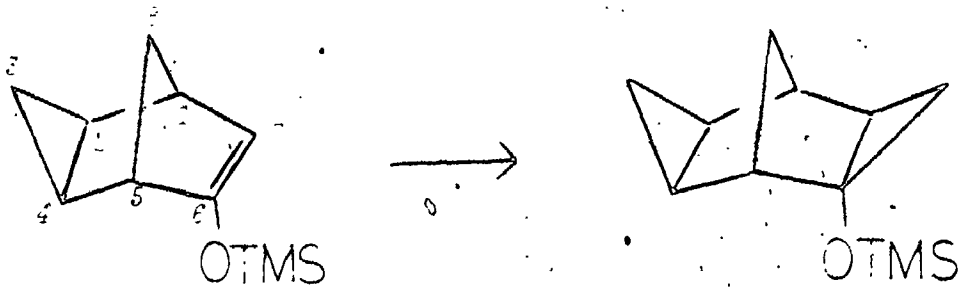
The treatment of 68 with deuterated base afforded 69-d_x, which contained 2.37 atoms ^{2}H/molecule as determined by mass spectrometric analysis. In the ^{13}Cmr spectrum of 69-d_x the absorptions at δ_C 43.1 and 35.4 were significantly attenuated. Ketone 69-d_x was then stirred at room temperature in the presence of $^-$OH/MeOH and, in the ^{13}Cmr spectrum of the recovered material, the signal at δ_C 35.1 was strongly attenuated and accompanied by the expected triplet, J_{CD} = 20.3 Hz. Mass spectrometric analysis of this sample showed it to contain 0.95 atoms ^{2}H/molecule and the ^{2}H spectrum (C_6H_6) exhibited a signal at δ 2.48, showing that deuteration had occurred at the *exo*-6-position. Thus, homoketonization was stereospecific (within experimental limits) with inversion of configuration.

CHAPTER 7

SYNTHESIS AND HOMOKETONIZATION OF 2-TRIMETHYLSILYLOXYLTRICYCLO[3.3.1.0^{6,8}]NONANES

(A) INTRODUCTION

The observation that cyclopropanation of some 2-trimethylsilyloxylbicyclo[2.2.1]heptan-2,5-dienes readily yielded the corresponding 2-trimethylsilyloxylhomoquadricyclene derivatives gave reason to investigate this reaction with other substrates. In particular, the behaviour of 6-trimethylsilyloxyl-exo-tricyclo[3.2.1.0^{2,4}]-oct-6-ene (79a) and its endo isomer (80a) under the Simmons-Smith conditions was of interest since in some respects the cyclopropane ring behaves like a double bond (60). It was anticipated that cyclopropanation of 79a would initially afford 79b, with the newly formed

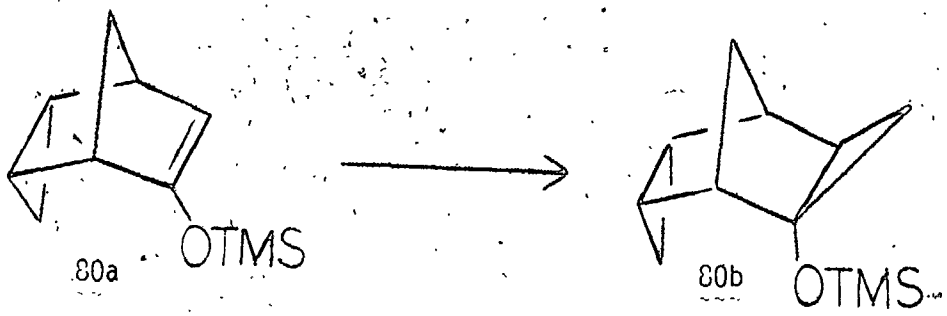


79a 79b

cyclopropyl ring in the exo orientation, from the results of cyclopropanation of 26a. Dependent upon the stability of 79b to the Simmons-Smith conditions this adduct could conceivably undergo a Lewis-acid (M^+) catalyzed

79b 81

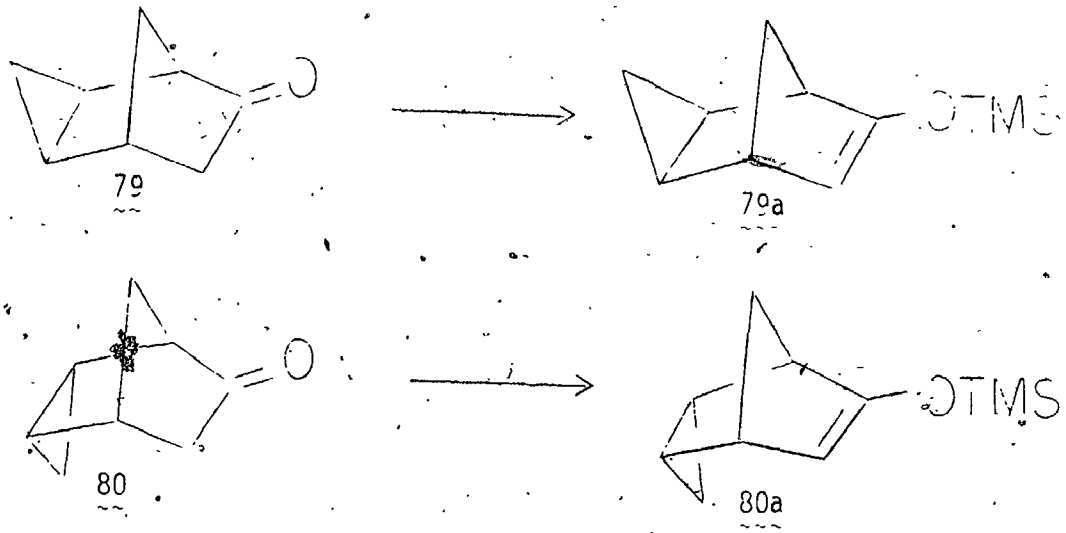
rearrangement to 81, in a manner analogous to that proposed for the conversion of 40 → 44a. In contrast, it was anticipated that the product from cyclopropanation of 80a (80b) would be stable under the conditions of the reaction, since an inspection of molecular models indicated that 80b would not readily rearrange.



80a 80b

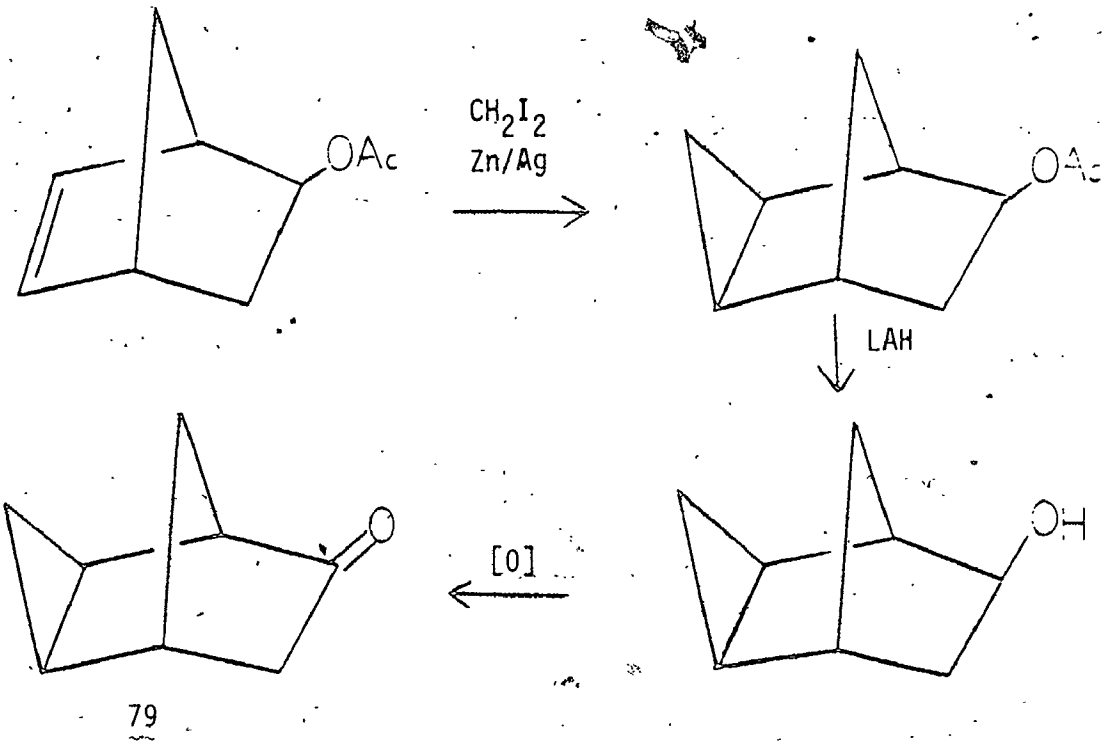
(B) RESULTS AND DISCUSSION.

The silyl enol ethers 79a and 80a were prepared from exo-tricyclo[3.2.1.$0^{2,4}$]octan-6-one (79) and its endo isomer 80, which were synthesized according to literature



methods (30) as outlined in Schemes 7.1 and 7.2, respectively.

As anticipated, treatment of 80a with the Simmons-Smith reagent for 16 h yielded 80b. Its proton spectrum contained five one-proton multiplets at δ 0.36, 0.88, 2.11, 2.18 and 2.33, three two-proton multiplets at δ 0.71, 1.25 and 1.29, and a nine-proton singlet at δ0.18 ($SiMe_3$). The ^{13}Cmr spectrum of 80b consisted of ten signals: C; 58.7; CH, 19.4, 19.7, 22.4, 35.8, 42.7; CH_2, 9.8, 18.5, 45.3 and $SiMe_3$, 1.0. The ^{13}Cmr data were readily assigned as shown in Fig. 7.1, agreeing reasonably



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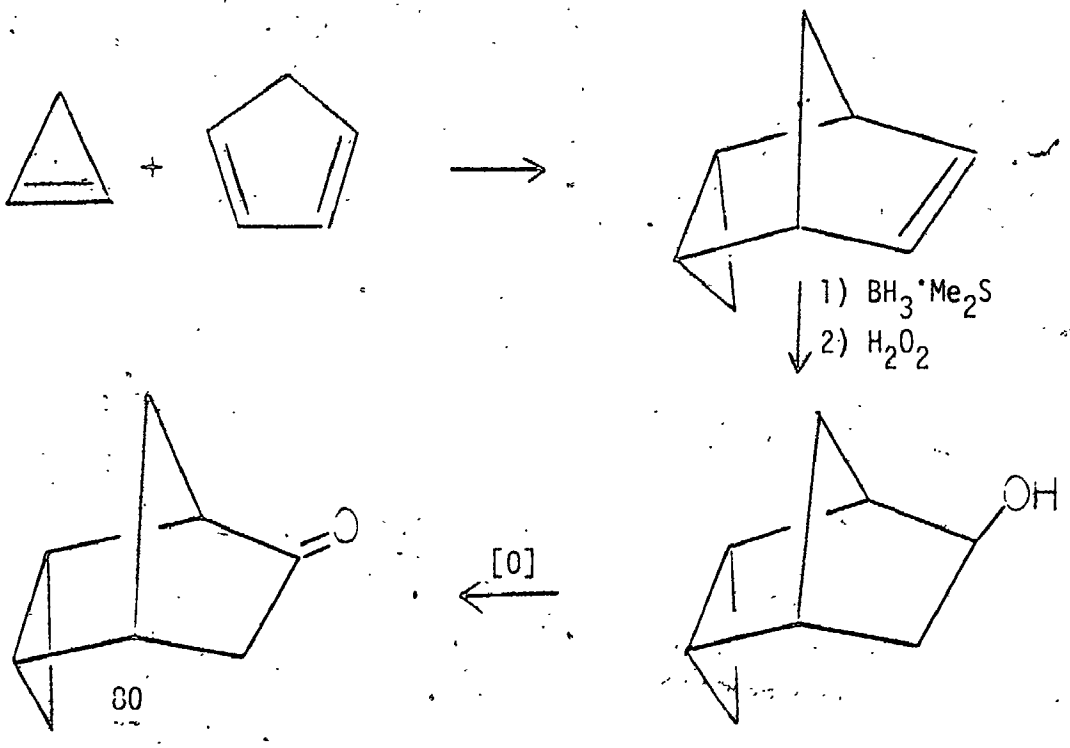
SCHEME 7.1



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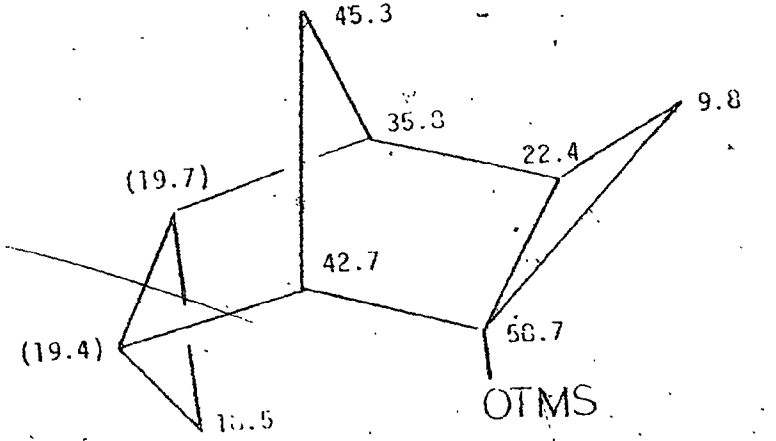
SCHEME 7.2



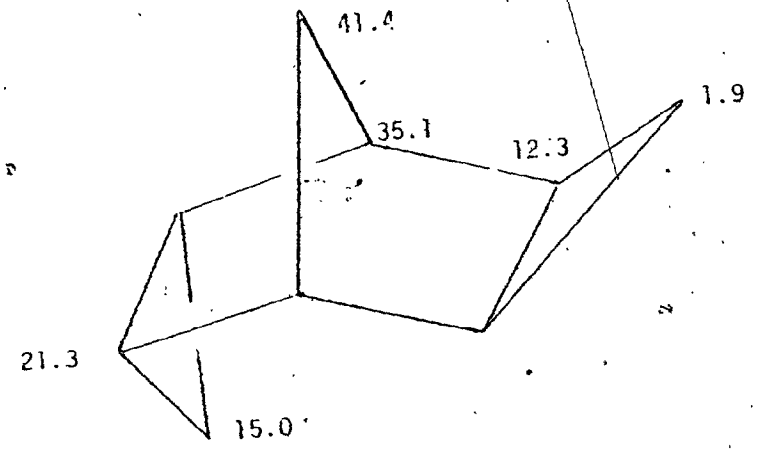
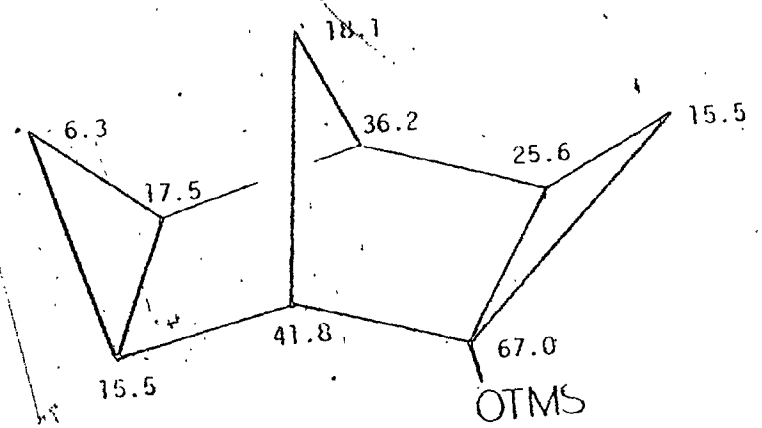


FIGURE 7.1: ^{13}C Shielding Data (δ_C) for 80b and *exo-endo*-tetracyclo[3.3.1.$0^{2,4}$.$0^{6,8}$]nonane (30)



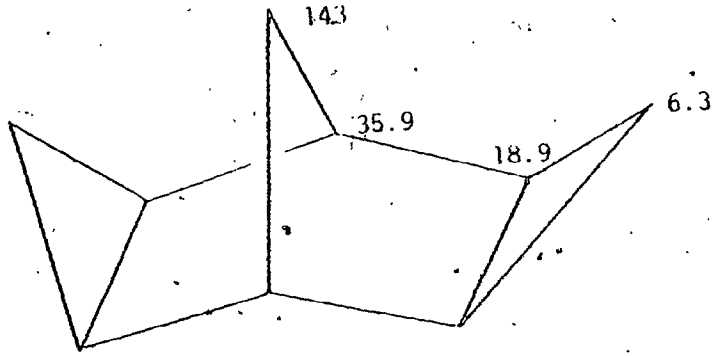
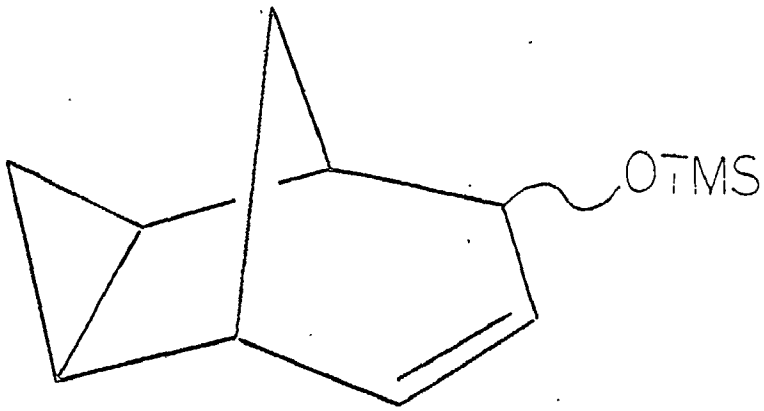


FIGURE 7.2: ^{13}C Shielding Data for (δ_C) 79b and *exo-exo*-tetracyclo[3.3.1.$0^{2,4}$.$0^{6,8}$]nonane (30)

with the reported ^{13}C chemical shifts for exo-endo tetracyclo[3.3.1.$0^{2,4}$.$0^{6,8}$]nonane (30) taking into account the effects of the $OSiMe_3$ group. Hence cyclopropanation occurred at the exo face of 80a. A precise mass measurement of 80b showed the molecular formula to be $C_{12}H_{20}OSi$ which in conjunction with the nmr data is consistent with the tetracyclic structure of 80b.

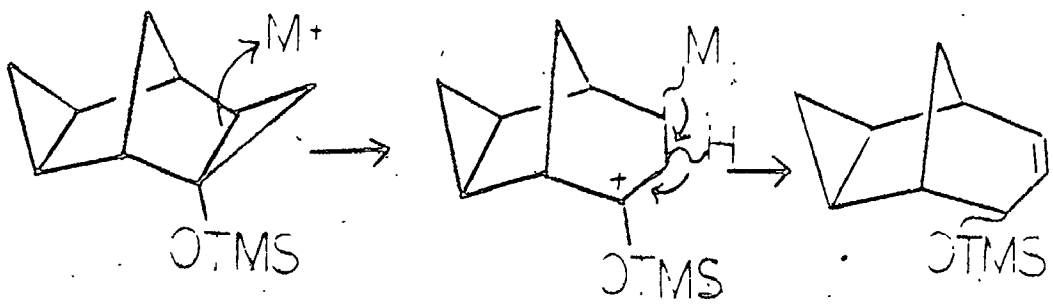
Following the same procedure, 79a was treated with the Simmons-Smith reagent for 15 h and, after work-up, glc analysis of the product mixture showed one major component (ca. 65%). This was collected by preparative glc and its ^{13}Cmr spectrum indicated the presence of two compounds in a ratio of approximately 4:1. The ^{13}Cmr data for the major component consisted of ten signals: C, 67.0; CH, 15.5, 17.5, 25.6, 36.2, 41.8; CH_2, 6.3, 15.5, 18.1 and $SiMe_3$ 1.0, and the minor component also gave rise to ten signals; CH, 15.3, 26.3, 34.6, 42.6, 71.2, 128.3, 137.9; CH_2, 10.3, 23.5 and $SiMe_3$, 0.4. The three high-field methylene signals (δ_C 6.3, 15.5, 18.1) for the major component readily dismissed the possibility that these were due to the rearrangement product 81 but rather, could be readily attributed to C-3 (δ_C 15.5), C-7 (6.3) and C-9 (18.1) of 79b. The remaining absorptions were assignable to 79b as shown in Figure 7.2 and agree well with the reported ^{13}Cmr shielding for *exo-exo*-tetracyclo[3.3.1.$0^{2,4}$.$0^{6,8}$]nonane (30), taking into account the expected substituent effects of the $OSiMe_3$ group.

The ^{13}Cmr shieldings for the minor component were tentatively attributed to 8-trimethylsilyloxyltricyclo-[3.3.1.0]non-6-ene (82), the formation of which could be



82

rationalized as the result of Lewis acid cleavage of the C-2,4 bond in 79b followed by a hydride shift. This process is analogous to that proposed by Murai (47) and is examined further in Chapter 8.



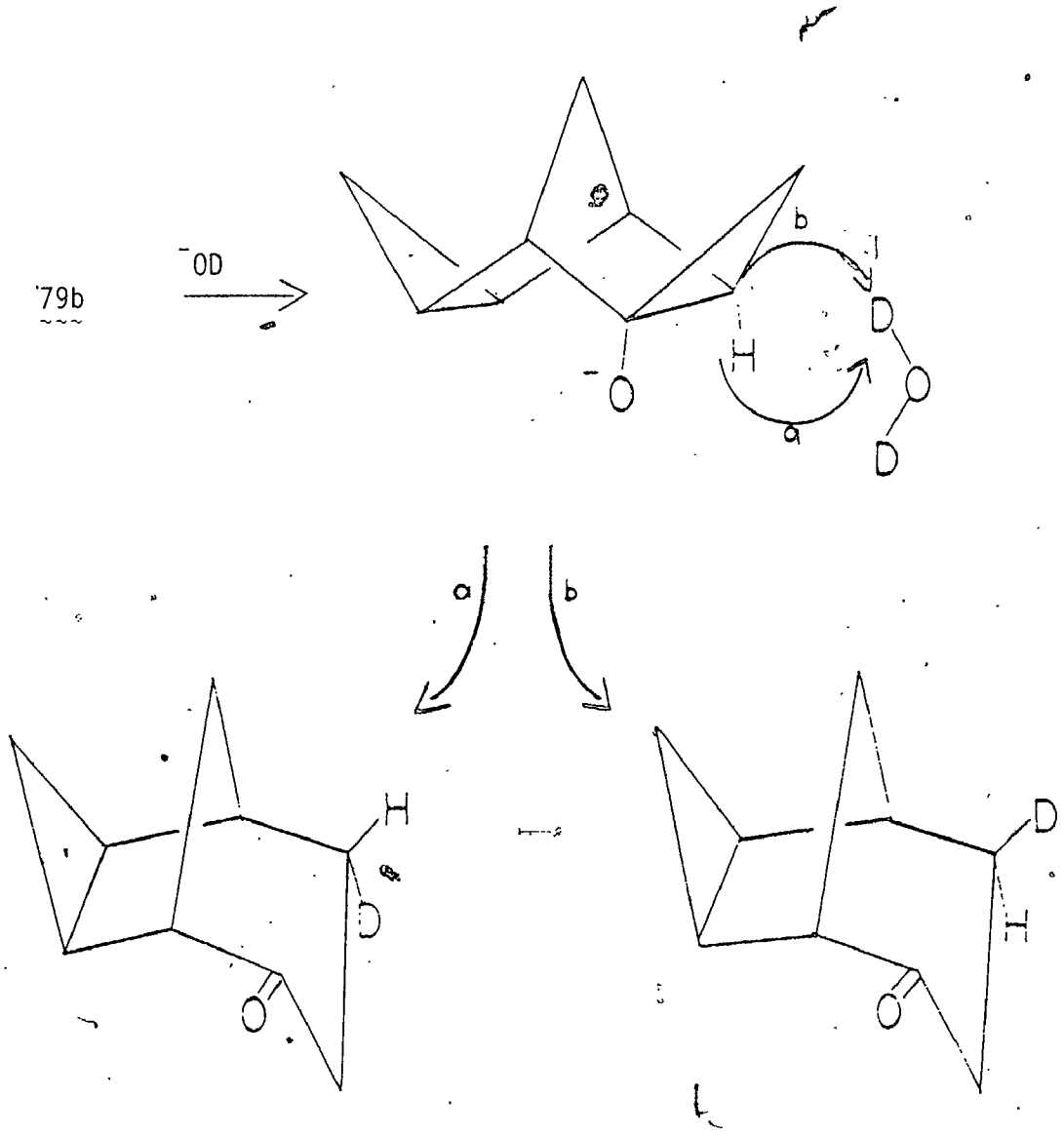
To improve the yield of 79b, silyl enol ether 79a was treated with the Simmons-Smith reagent for 8 h to afford a product mixture containing ca. 80% 79b. A sample of 79b, collected by preparative glc, was shown to be pure by ^{1}H and ^{13}C nmr (i.e. no olefinic signals). The proton spectrum contained the following multiplets: 2.32 δ (1H, dd, J = 3.5, 1.3 Hz), 2.18 (1H, bq), 1.76 (1H, br ddd, J = 7.4, 7.4, 3.5 Hz) and complex absorptions centred at δ 1.06 H (3H), 0.72 (3H) and 0.34 (2H) and the $SiMe_3$ signal at 0.18. A precise mass measurement showed the molecular formula to be $C_{12}H_{20}OSi$ and its infrared spectrum contained absorptions at 3010 (cyclopropyl CH), 2950, 1243 ($SiCH_3$) and 834 cm^{-1} ($SiCH_3$). These data are consistent with the tetracyclic structure 79b.

To examine further the conversion of 79b → 82 the silyl enol ether 79a was treated with the Simmons-Smith reagent for 21 h. Glc analysis of the product showed a complex mixture which was not investigated.

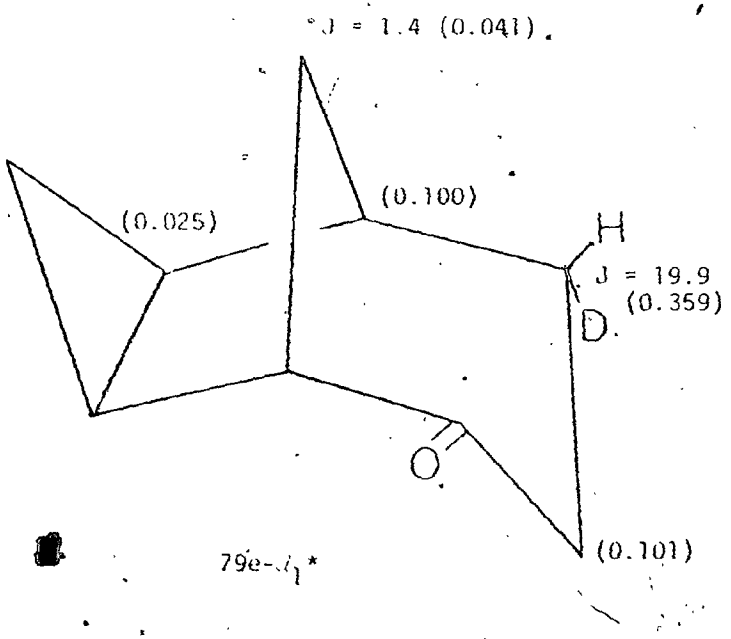
Upon ether cleavage of 79b and 80b with base the resulting cyclopropoxides (79c and 80c, respectively) can ketonize in two ways: to produce the α-methyl derivative of the initial ketone or to undergo ring expansion to the homologous ketone. It was anticipated that the cleavage of these two cyclopropyl silyl ethers would favor ring expansion on the basis of the earlier results. In the event, treatment of both 79b and 80b with ^{-}OH/MeOH at 0°C furnished single ketones having no methyl absorption in

their ^{1}H and ^{13}Cmr spectra. These results are consistent with the observation that ring expansion is the favoured mode of ring cleavage for 26b and 27b. Presumably the fact that *exo*-tricyclo[3.3.1.$0^{2,4}$]nonan-6-one (79e) and its *endo* counterpart (80e) are less strained than the α-methyl derivatives of 79 and 80 governs the course of homoketonization since it has been demonstrated that the process is subject to thermodynamic control.

The opening of the cyclopropoxide anion 79c, generated by base-catalysed cleavage of TMS ether 79b, can proceed in either of two ways, i.e. with retention or inversion of configuration. These are shown as *a* and *b* in Scheme 7.3, respectively. While, in general, ketonizations of cyclopropoxides in polycyclic systems have been found to undergo inversion of configuration, there are some strained systems which exhibit retention. Thus it was of interest to establish the point in the present cases. To distinguish between paths *a* and *b*, 79b was cleaved in $^{-}$OD/*t*-BuOD and the product treated with $^{-}$OH/MeOH to back-exchange the α-deuterium picked up by exchange after the cleavage. The ^{13}Cmr spectrum of a 1:1 mixture of 79e and 79e-d_1 obtained in this manner was recorded to determine the stereochemistry of the deuterium atom at C-8 in the latter material. From this spectrum *exo*-deuterium incorporation was revealed; the observed isotope effects on the ^{13}C shieldings in ppm and the resolved couplings are shown in Figure 7.3. A key feature is the fact that



SCHEME 7.3



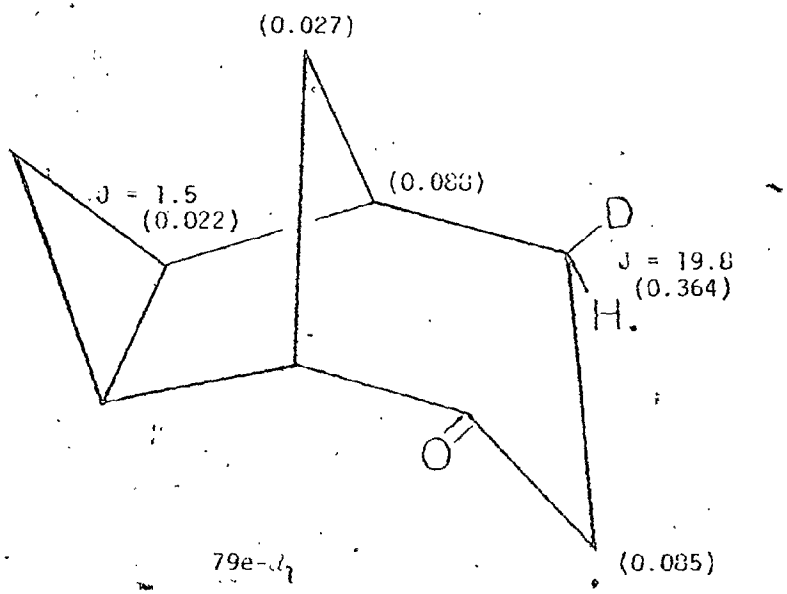


FIGURE 7.3: ^{2}H-^{13}C Coupling Constants (in Hz) and Isotope Shifts (in ppm) for 79e-d_1 and 79e-d_1*

vicinal ^{13}C-^{2}H coupling was readily apparent for the cyclopropyl methine carbon (C-2) with J = 1.5 Hz, while the C-9 signal was only slightly broadened; this is consistent with deuterium antiperiplanar to C-2 and, therefore, in the exo-orientation. To confirm this assignment, a sample of [7,7-$^{2}H_2$]-79 was converted to [8-$^{2}H_1$]-79b which was subsequently opened with $^{-}$OH/MeOH to form 79e-d_1*. The ^{13}Cmr spectrum of a 1:1 mixture of this material and 79e revealed the ^{2}H effects for 79e-d_1* (Figure 7.3). In this case, C-9 exhibited vicinal coupling of 1.4 Hz while the C-2 signal was only broadened by the deuterium, indicating that C-9 and the deuterium atom are antiperiplanar. These results establish that the cleavage of 79c proceeds with inversion. Treatment of 80b with $^{-}$OD/t-BuOD followed by back-exchange with $^{-}$OH/MeOH gave 80e-d_1 for which the ^{2}H effects in its ^{13}Cmr spectrum are shown in Figure 7.4. These constitute good evidence for the presence of *exo*-deuterium at C-8 and, hence, for inversion of configuration upon homoketonization of the cyclopropoxide generated from 80b. For exo-79e-d_1 and *exo*-80e-d_1 it may be noted that the ^{2}H-induced shifts as well as the ^{2}H-^{13}C vicinal coupling with C-2 differ, presumably reflecting conformational differences in the two ring systems. In 80e, the *endo* disposition of C-3 will preclude a chair conformation for the six-membered ring which is probably the favoured arrangement for 79e and in which the dihedral angle relating an *exo*-8-deuterium and

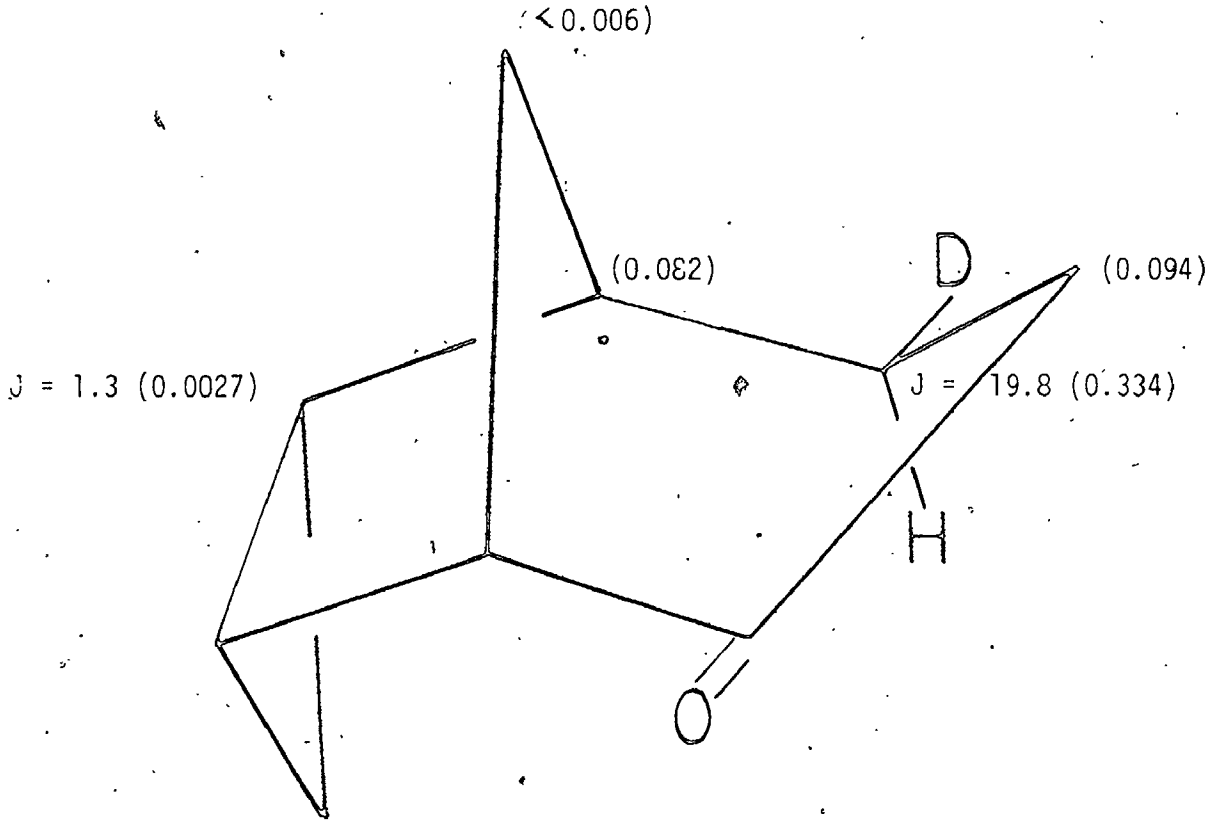


FIGURE 7.4: ^{2}H-^{13}C Coupling Constants (in Hz) and Isotope Shifts (in ppm) for 80e-1

C-2 is - 180°. In contrast, for a boat-like conformation of the six-membered ring, as is likely for *exo*-80e-d_1, this dihedral angle will be reduced to - 120°. Although 79b failed to rearrange to 81 under the Simmons-Smith conditions, the cyclopropanation of the silyl enol ethers 79a and 80a followed by treatment with methanolic NaOH solution provided an efficient means of homologation of the [3.2.1.0] system. The ring-expanded ketones were of interest since the behaviour of the α-dimethylated analogs under strongly basic conditions was to be examined.

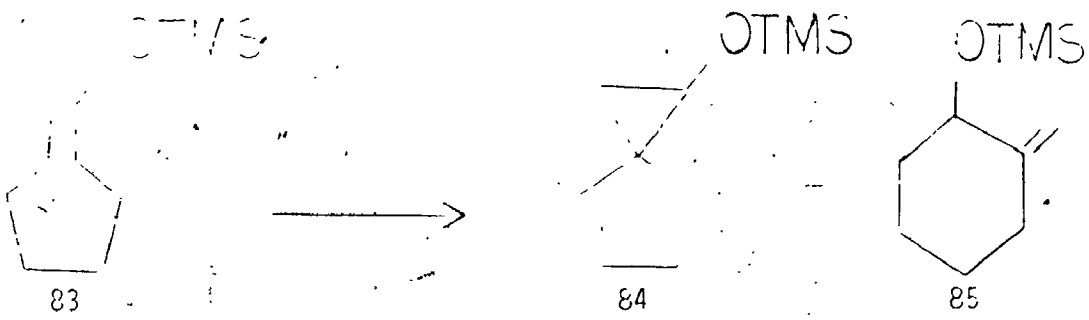
CHAPTER 8

REARRANGEMENT OF POLYCYCLIC CYCLOPROPYL SILYL ETHERS UNDER SIMMONS-SMITH CONDITIONS

(A) INTRODUCTION

As noted in Chapter 7, cyclopropanation of 79a appeared to afford small amounts of 8-trimethylsilyloxyl tricyclo[3.3.1.$0^{2,4}$]non-6-ene (82), a result bearing resemblance to recently reported findings in simpler systems (47). To clarify the nature of this unusual Simmons-Smith product, cyclopropanation of certain other polycyclic silyl enol ethers under conditions favouring skeletal rearrangement was examined.

Recently Murai et al (47) established that the concentration of the Simmons-Smith reagent is an important factor governing product composition. Under their "dilute" conditions ([CH_2I_2] = 0.73 M) cyclopropanation of 83 afforded the expected product 84, while under their



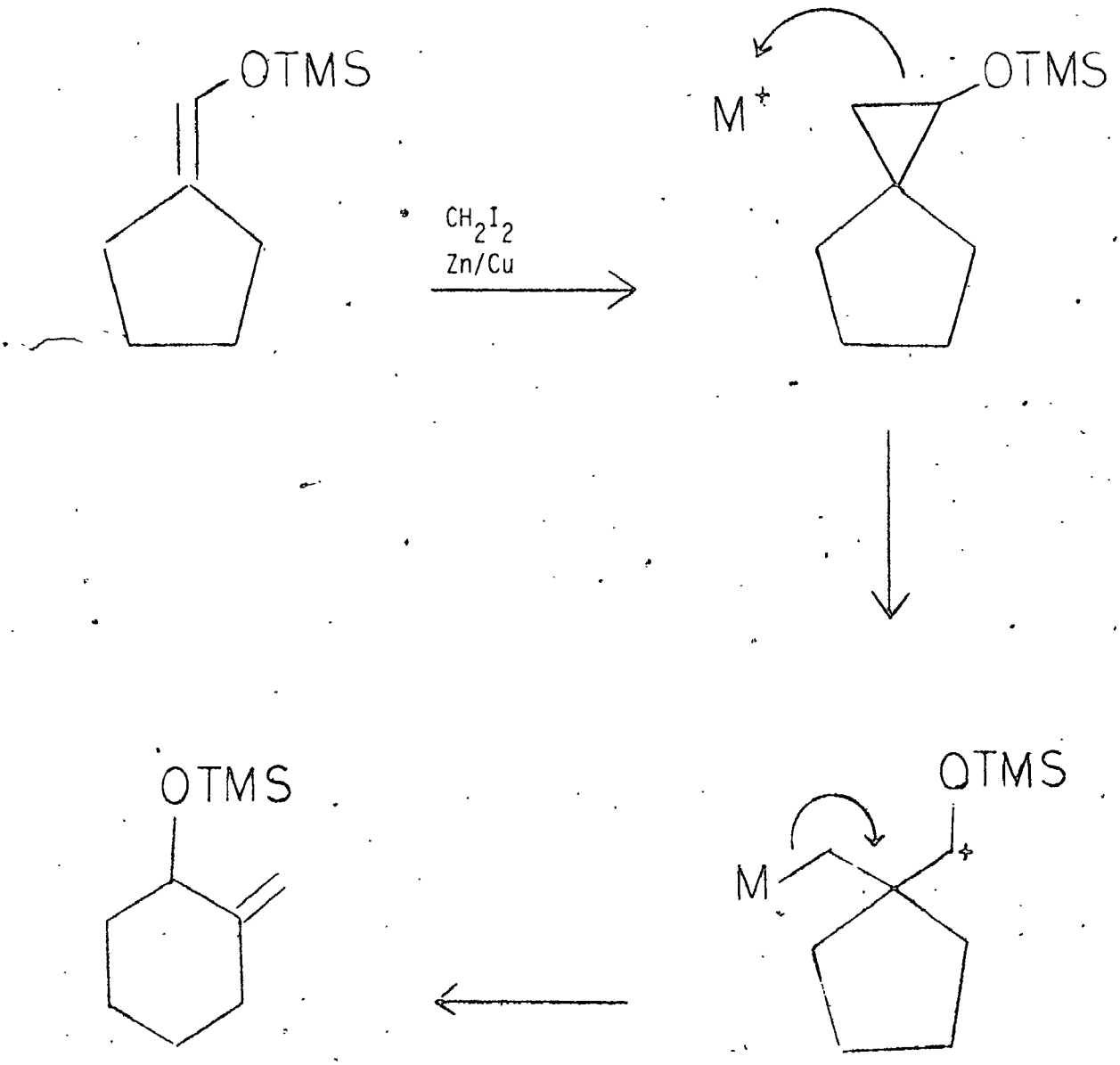
83 84 85

"concentrated" conditions ([CH_2I_2] ≈ 2 M) a mixture of 84 (25%) and 85 (75%) resulted. The authors suggested that the latter product was formed by Lewis acid (i.e. ZnI_2) catalyzed isomerization of 84, as shown in Scheme 8.1.

(B) RESULTS AND DISCUSSION

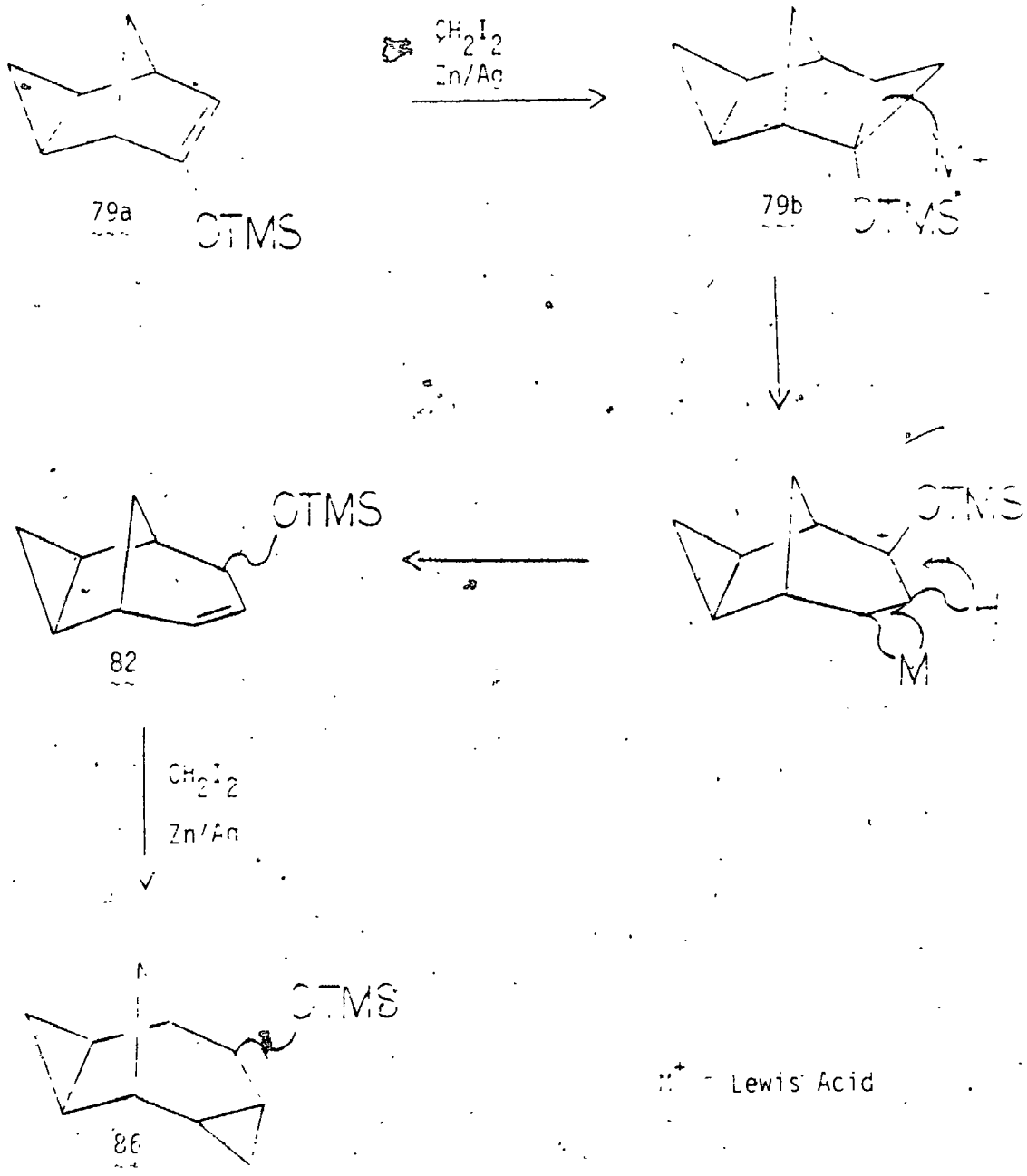
Cyclopropanation of 79a under "concentrated" conditions gave a complex mixture, and preparative glc afforded an analytical sample of the major component 86 (ca. 35% of the total product). Its ^{13}Cmr spectrum consisted of an intense methyl signal (δ_C 0.4), three methylene (δ_C 6.2, 7.5, 17.8) and seven methine signals (δ_C 13.9, 15.2, 20.9, 21.5, 32.8, 42.7, 70.7). The molecular formula, $C_{13}H_{22}OSi$, determined by precise mass measurement, confirmed the addition of two methylene groups to 79a. These data indicated that 86 arose from cyclopropanation of 82. The formation of 86 can be accounted for by attack at the C-2,4 bond of the initially formed adduct 79b (Scheme 8.2) by a Lewis acid, followed by a 1,2 hydride shift to form the allylic silyl ether 82, which could undergo a second cyclopropanation to afford 86. This scheme is analogous to that proposed by Murai with a different mode of ring cleavage.

To gather further evidence for the proposed scheme the cyclopropanation reaction (concentrated conditions) was repeated employing a 1.0:1.1 ratio of 79a:methylene iodide, in an attempt to produce 82. A ^{13}C spectrum of the reaction mixture indicated the major product to be 86.



M^+ ≡ Lewis Acid

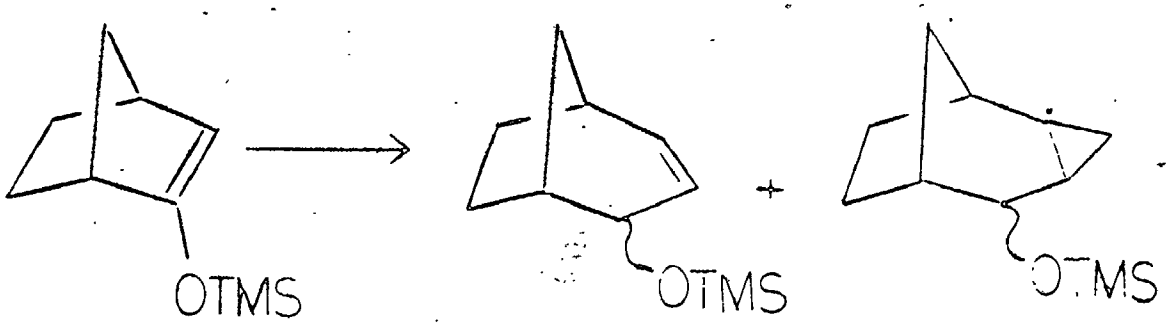
SCHEME 8.1


CH_2I_2
Zn/Ag
79a
OTMS
79b
OTMS
OTMS
M
82
OTMS
CH_2I_2
Zn/Ag
86
OTMS
M^+ - Lewis Acid

SCHEME 8.2

This was attributed to in situ decomposition of 79a resulting in an excess of Simmons-Smith reagent in solution, thereby yielding 86.

If the proposed scheme is correct the effect of the cyclopropyl ring of 79b on the overall reaction would be negligible. Therefore, the silyl enol ether of norcamphor, upon treatment under the same conditions, could afford the ring expanded allylic silyl ether 87 or the cyclopropanation product 88.



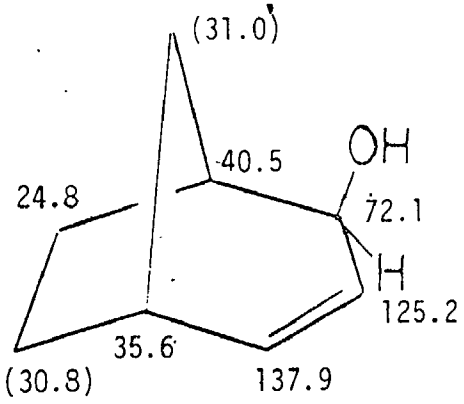
26a 87 88

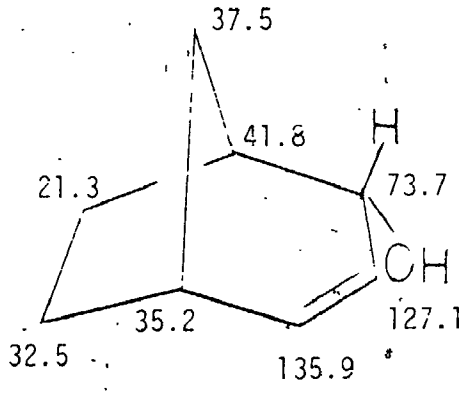
Glc analysis of the product from cyclopropanation of 26a (concentrated conditions) indicated a complex mixture. The spectral data of one of the components isolated by preparative glc (ca. 15% of the total product) was consistent with structure 87. The ^{13}Cmr spectrum contained two sets of signals (rel. int. 2:3) which could be attributed to the two epimers of 87. The assignments for the two epimers followed from the ^{13}C data for the

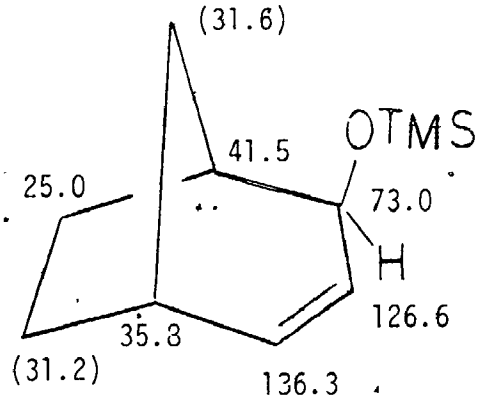
bicyclo[3.2.1]oct-3-en-2-ols (61), as shown in Fig. 8.1.The molecular formula, $C_{11}H_{20}OSi$, by precise mass measurement, was also consistent with structure 87.

To improve the yield of the allylic silyl ether, the cyclopropanation of t-butyldimethylsilyl enol ethers was examined since these derivatives are more resistant to hydrolysis than their trimethylsilyl analogs. To show that t-butyldimethylsilyl enol ethers can be cyclopropanated, 2-t-butyldimethylsilyloxybicyclo[2.2.1]hept-2-ene (89a) was treated with Simmons-Smith reagent under dilute conditions. Gas-liquid chromatography showed the product to be essentially pure with no starting material present. The ^{13}Cmr spectrum consisted of four methylene (δ_C 31.2, 29.0, 24.2, 10.0), three methine (δ_C 42.6, 36.7, 22.4), two quaternary (δ_C 61.2, 18.1) and the methyl signals of the t-Bu(Me)$_2$Si group (δ_C 26.0, -3.5, -3.7). The molecular formula, $C_{14}H_{26}OSi$, found by precise mass measurement, confirmed the addition of one methylene group. These data indicated that cyclopropanation of 89a afforded the expected cyclopropyl derivative 89b. The ^{13}Cmr assignments for 89b were relatively straightforward and are given in Fig. 8.2. The close similarity of the chemical shifts for 89b and 26b is strong evidence for the assigned structure 89b.

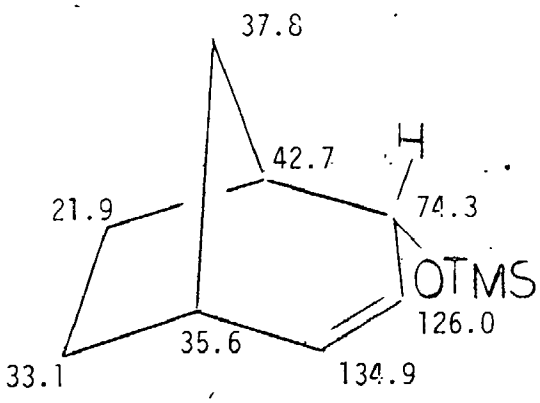
Cyclopropanation of 89a was then repeated under concentrated conditions. In contrast to the results for the trimethylsilyl enol ethers, two compounds (89b, 89c)







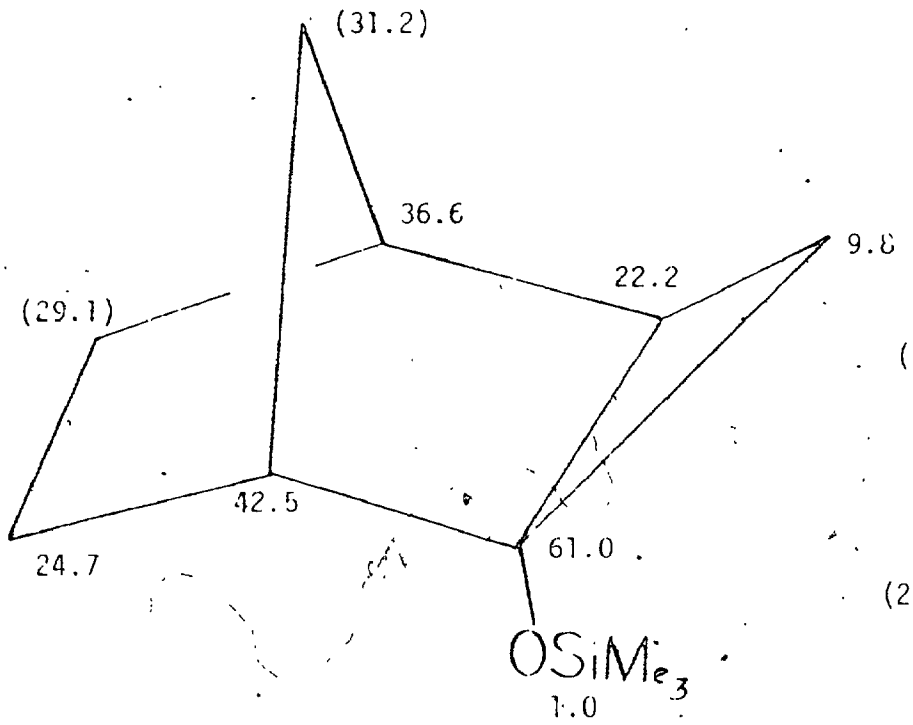
exo-87
Major Epimer



endo-87
Minor Epimer

FIGURE 8.1: ^{13}C Shielding Data (δ_C) for *Exo*- and *Endo*-bicyclo[3.2.1]-oct-2-ene-4-ol (61) and *Exo*- and *Endo*-87[a]

[a]Similar values in parentheses may be interchanged.



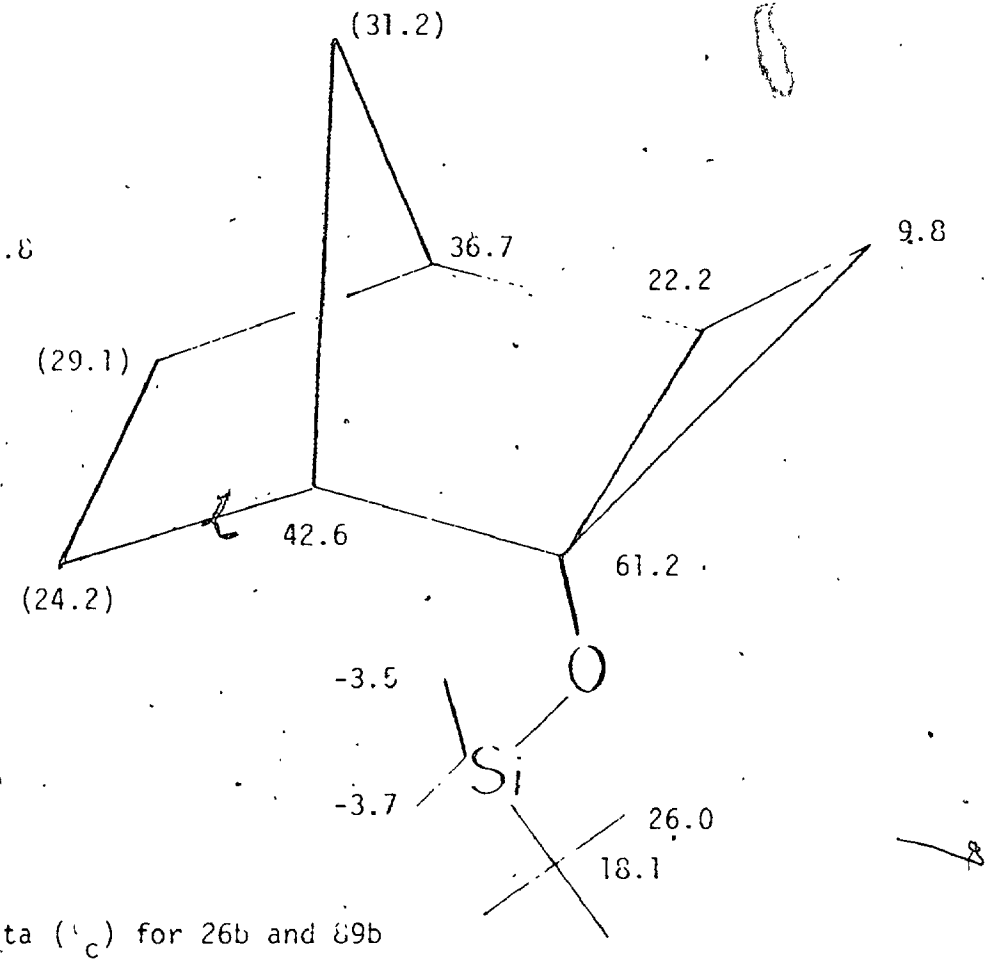


FIGURE 3.2: ^{13}C Shielding Data (δ_C) for 26b and 89b

formed 88% of the total product. The ^{13}Cmr spectrum of the major product (80% glc yield) had twelve signals: -C-, 18.4; CH, 136.2, 126.2, 73.1, 41.6, 35.9; CH_2, 31.6, 31.2, 24.9; and CH_3, 26.2, -4.2, -4.4, which were attributed to **89c**, the *t*-butyldimethylsilyl analog of **87**. The assignments for the ^{13}C signals were made by comparison with those for the bicyclo[3.2.1]oct-3-en-2-ols and both epimers of **87**, these data are listed in Fig 8.3.

The ^{1}Hmr spectrum provided further support. The three lowest field signals at δ 5.98 (broadened ddd, J = 9.6, 6.6, 1.3 Hz), 5.35 (ddd, J = 9.6, 4.0, 1.8 Hz) and 3.71 (broadened dd, J = 4.0, 4.0 Hz) were readily ascribed to H-4, H-3, and *endo*-H-2, respectively. Irradiation of the one-proton multiplet at δ 2.46 removed the 6.6 Hz splitting in the pattern for the H-4 signal, which served to identify H-5. Homonuclear decoupling of the multiplet at δ 2.25 simplified the splittings for H-3 and H-2 by eliminating a 1.8 and 4.0 Hz coupling, respectively. Consequently the signal at δ 2.25 was attributed to H-1. The two strong singlets at δ 0.87 and -0.02 were readily ascribed to the methyl protons of the *t*-butyl group and the silyl methyl protons, respectively. The three remaining two proton multiplets at δ 1.77, 1.52 and 1.16 could not be readily assigned.

The ^{1}Hmr spectrum also contained three additional small absorptions at δ 5.86, 5.19 and 4.50 which were tentatively assigned to H-4, H-3 and H-2 of *endo*-**89c**.

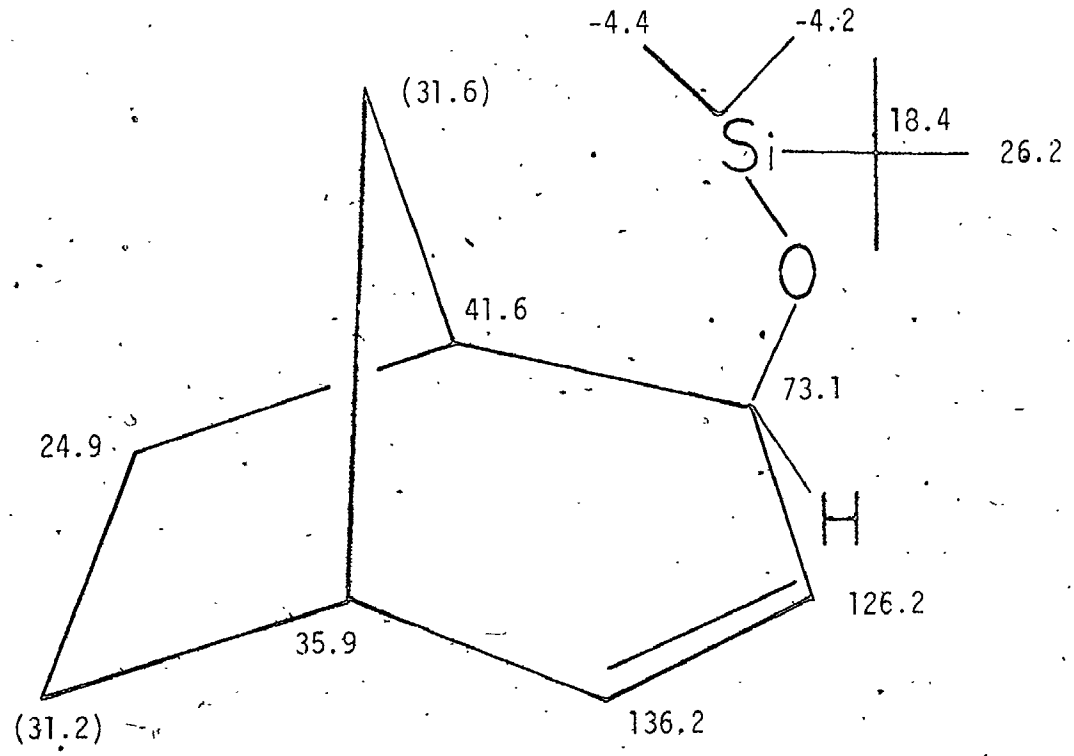
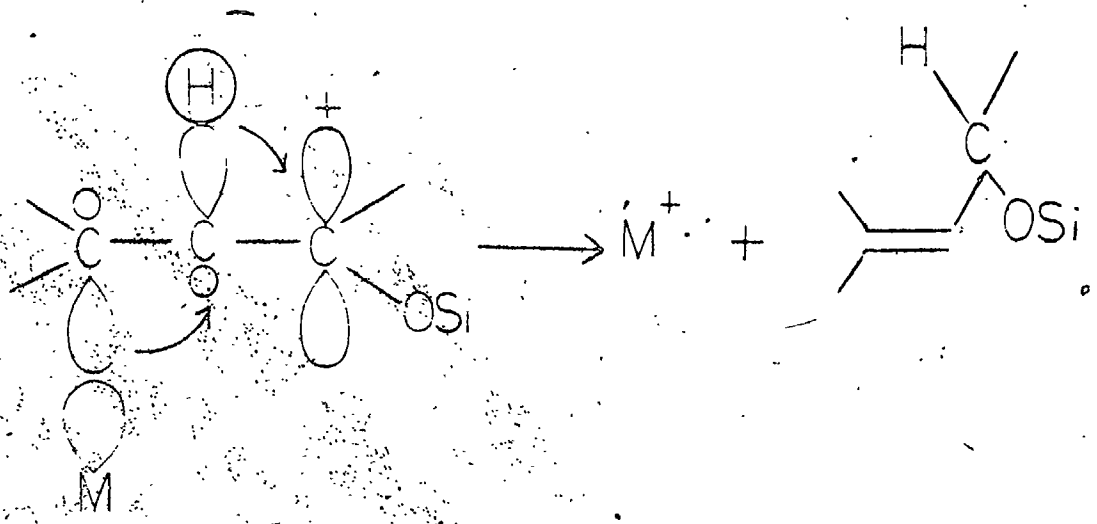


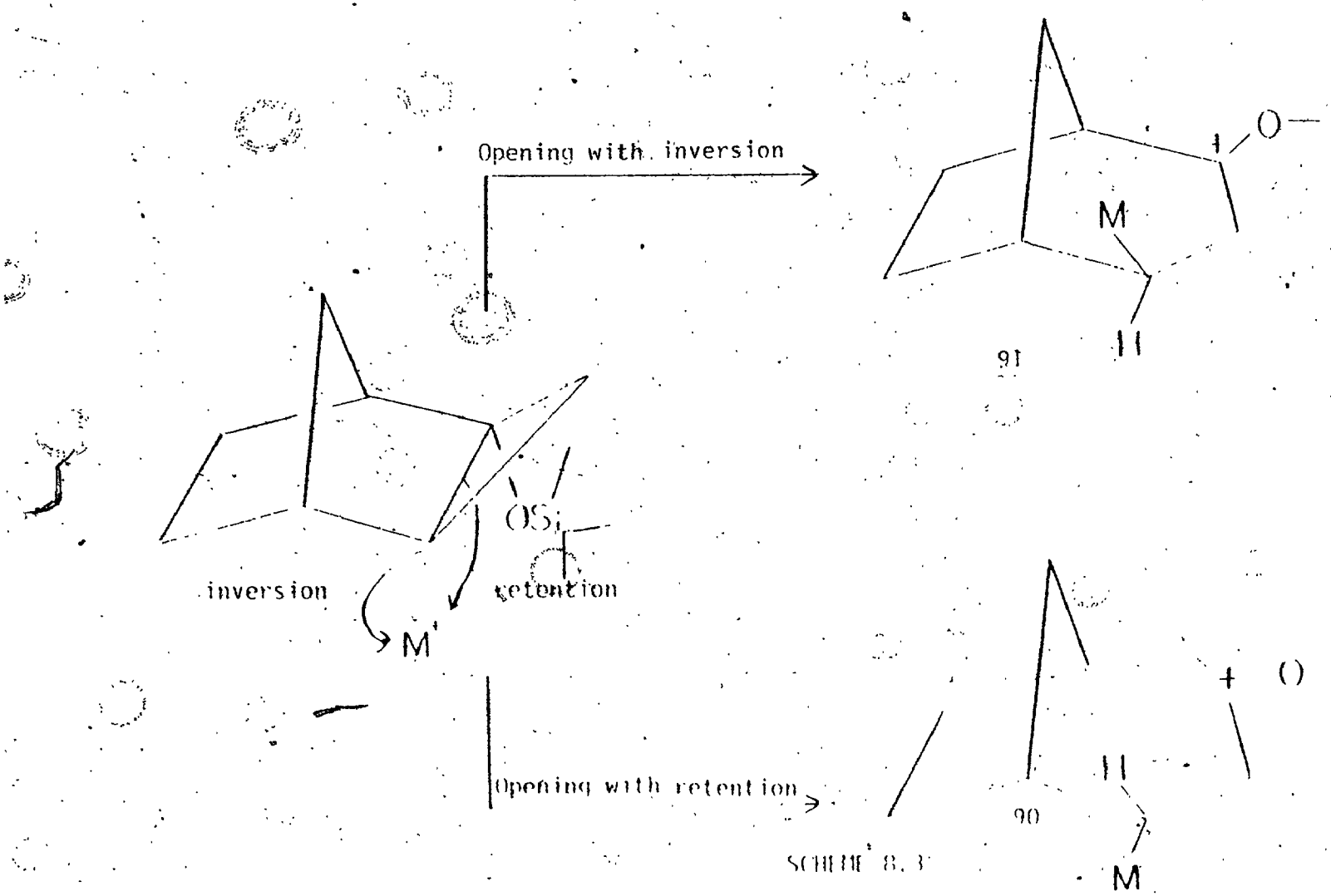
FIGURE 8.3: ^{13}C Shielding Data (δ_C) for 89c

Integration of the H-3 signals indicated a ratio of *endo*-89c to *exo*-89c of ca. 1:11.

The observed ratio of the two epimers of 89c can be rationalized in terms of the proposed reaction sequence. Initial cleavage of the cyclopropyl ring of 89b by a Lewis acid (M^+) can occur either with retention or inversion of configuration at C-4 to afford 90 or 91, as shown in Scheme 8.3. The subsequent 1,2 hydride shift presumably occurs anti to the Lewis acid, since this allows efficient transfer of electron density.



Since the predominant epimer of 89c has the t-Bu(Me)$_2$Si group in the *exo* orientation this indicates that the initial cleavage of 89b occurs with inversion. This mode of ring cleavage may be favoured because the steric repulsions developing during bond breakage with inversion are less than those for cleavage with retention.



91

90

SCHEME 8.3

To support this proposed sequence, cyclopropanation of **89a** (concentrated conditions) was repeated with CD_2I_2 (1.77 atoms ^2H/molecule). If the rearrangement proceeds in the manner described, the product should contain deuterium at C-2 and C-3. Thus treatment of **89a** with CD_2I_2 for 33 h afforded **89b**-d_x (1.88 ^2H/molecule) and **89c**-d_x (1.64 ^2H/molecule) in a 1.0:1.3 ratio. In the ^{13}Cmr spectrum of **89c**-d_x the signals at δ_C 126.2 and 73.1 were strongly attenuated, which is in accord with the proposed mechanism. The ratio of **89b**:**89c** changes from ca. 1:10 to 3:4 with CH_2I_2 and CD_2I_2. This can be attributed to a deuterium kinetic isotope effect indicating that the hydride shift occurs during the rate determining step.

Therefore, it seems reasonable to conclude that cyclopropanation of **89a** (under concentrated conditions), yields **89b** which undergoes a Lewis acid-catalyzed skeletal rearrangement to **89c**, with the release of ring strain as the driving force for this reaction.

Having established that **89a** can be converted to the allylic silyl ether **89c**, it was of interest to examine the scope of this reaction. To this end the t-butyldimethylsilyl enol ethers of tricyclo[5.2.1.$0^{2,6}$]-decan-8-one (**92**), bicyclo[3.2.1]octan-6-one (**93**) and nopinone (**94**) were synthesized. The ^{13}C assignments followed from comparisons with the results for the trimethylsilyl analogs and these data are listed in Table 8.1.

TABLE 8.1: ^{13}C shieldings[a] of some t-butyldimethyl silyl compounds

Cpd.	$SiMe_2$	SiC	$SiCMe_3$	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{11}	Me
89a	4.4, 4.7	18.3	25.8	46.0	161.6	105.3	41.4	24.9	(28.2)	47.2					
92	4.2, 4.5	18.5	26.2	45.4	46.4	(31.2)	(31.2)	(31.6)	50.1	50.7	164.7	107.2	40.9		
93	4.4, 4.7	18.3	25.9	37.8	(26.1)	19.3	(24.5)	(42.8)	157.4	102.1	43.9				
94	3.8, 3.9	18.4	26.1	48.7	159.4	95.9	28.4	41.3	38.9	31.8					26.3 21.6
92c	4.0, 4.2	22.0	26.1	40.8	45.6	(33.0)	26.4	(34.5)	49.7	51.8	72.6	125.0	137.9	27.9	
93b	4.5, 4.7	18.3	26.2	39.3	62.6	13.7	25.5	35.0	32.3	19.6	29.2	34.2			
94b	3.4, 3.5	17.8	25.8	47.1	60.6	39.8	16.5	28.4	42.0	40.8	26.6	21.3	26.7		
94c	4.0, 4.1	18.6	26.3	47.5	71.4	146.7	34.3	39.8	39.8	26.0	19.7	27.1	115.0		

[a] All spectra were measured for C_6D_6 solutions, using the central solvent line as reference (δ_C 128.0).

Treatment of 92 with the Simmons-Smith reagent (concentrated conditions) afforded in high yield the allylic silyl ether 92c. Although the stereochemistry at C-8 was not determined, it was evident from the ^{13}Cmr spectrum (Table 8.1) that the reaction afforded a single epimer (within experimental limits). Under the same conditions 93 afforded only the cyclopropanated product 93b in 75% yield. Cyclopropanation of 94 (concentrated conditions) yielded a two component mixture in 80% yield which appeared to be the normal cyclopropanated product, 94b and an allylic silyl ether 94c. The former gave rise to a ^{13}C spectrum containing highly shielded methylene and methine carbons together with a quaternary signal typical of cyclopropyl carbinyl carbon. These data are entirely consistent with expectations for the simple cyclopropanated product. The second component contained an exo-cyclic methylene group, δ_C 146.7 and 115.0, accompanied by signals for three methine, two methylene, two methyl and a quaternary carbon as well as the absorptions for the t-butyldimethylsilyl grouping. The data clearly defined structure 94c, strictly analogous to the products previously reported by Murai *et al.* (47). Hence, under these conditions the *in situ* skeletal rearrangements of cyclopropyl silyl ethers appears to be of limited synthetic value.

The rearrangement to the allylic silyl ether is consistent with the results for cyclopropanation of

2-trimethylsilyloxylnorbornadiene derivatives, since it was suggested that cyclopropanation of 40 initially affords 39 which undergoes a Lewis acid catalyzed isomerization to 44a. The results for 89a suggest that this may proceed by cleavage of the cyclopropyl ring followed by a cyclo-addition process, which could occur in a concerted or stepwise process. That this reaction occurs under dilute conditions for 40, 58 and 67 may be due to a number of factors, such as (a) the ability of the double bond of 39 to complex with the Lewis acid prior to ring cleavage, (b) the greater ring strain of 39 versus 89a and (c) the absence of *endo*-6,7 protons may reduce the steric interactions between the Lewis acid and the substrate.

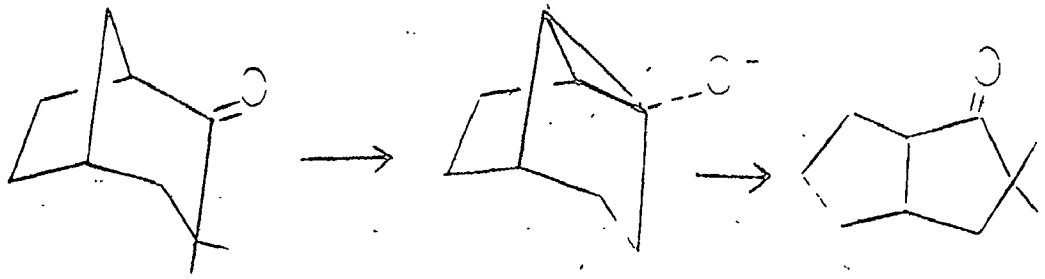
CHAPTER 9

REARRANGEMENT AND DEUTERIUM EXCHANGE IN TRICYCLO[3.3.1.$0^{2,4}$]NONANONES

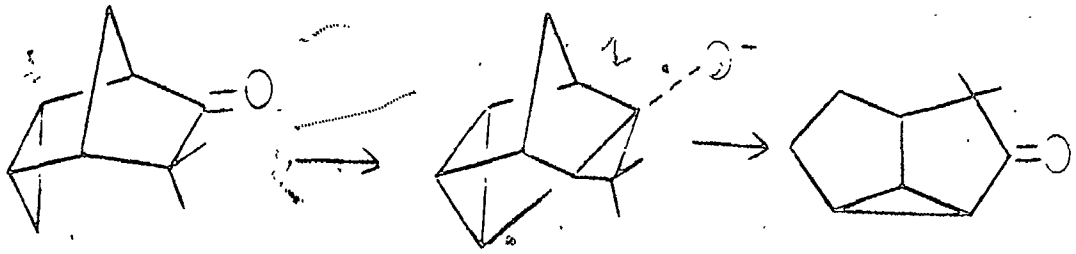
(A) INTRODUCTION

Since Nickon and Lambert's detailed investigation, of the homoenolization of camphenilone (4) several examples in both acyclic and polycyclic systems have been found in which proton abstraction occurs from centres other than the α-carbons under strongly basic conditions (16a). For most of these cases, proton abstraction from β-carbons has been observed but there are a few examples of Y-enolization. Since homoenolate anions have synthetic utility (16) it is of interest to define the factors which govern the regioselectivity and relative reactivity of remote proton abstraction. With a better understanding of both the regio- and stereoselectivity of β- and Y-enolization the scope of their synthetic applications could be enhanced.

Stothers *et al* (3) has shown that under strongly basic conditions 3,3-dimethylbicyclo[3.2.1]octan-2-one (95) rearranges to 3,3-dimethylbicyclo[3.3.0]octan-2-one (96) via the β-enolate 97, while the tricyclic ketone 16a rearranges to 4,4-dimethyltricyclo[3.3.0.$0^{2,8}$]octan-3-one via a Y-enolate (13).

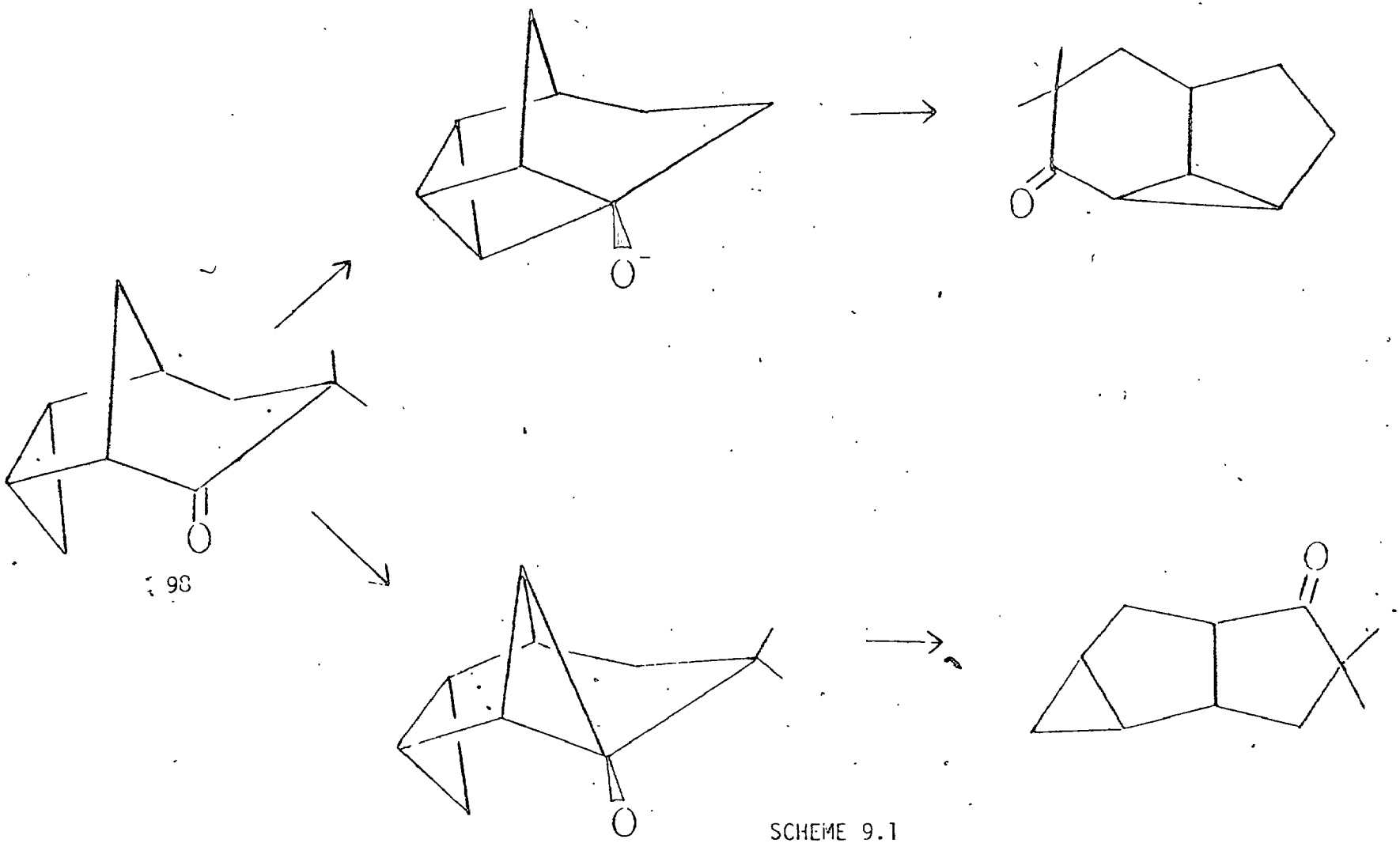


95 97 96



16a 16b

To examine the relative reactivity in a closely related system, the behaviour of the 7,7-dimethyltricyclo-[3.3.1.$0^{2,4}$]nonan-6-ones under homoenolization conditions was examined. By analogy with **95** and **16a** one could envisage proton abstraction to occur from C-3 and C-9 in the *endo* isomer **98** (see Scheme 9.1) constituting an intramolecular competition between Y and β-enolization, respectively. A comparison of the behaviour of the *exo* isomer **99** with that of **15** was of interest because of the unexpected effect of the cyclopropyl ring on the $^{1}H/^{2}H$ exchange experiments for the latter (13).

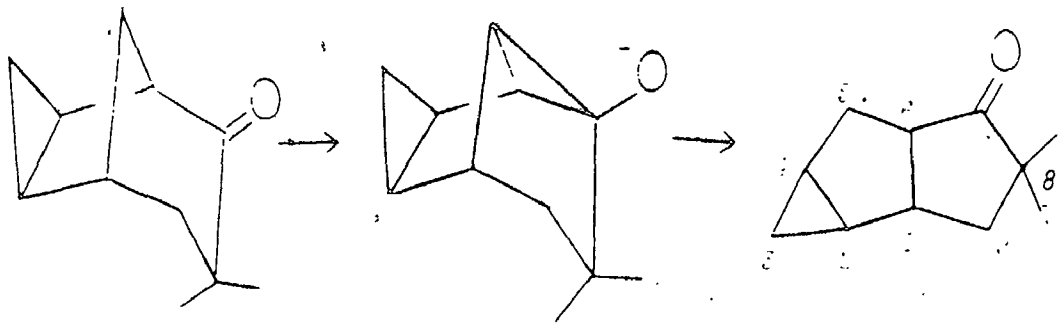


SCHEME 9.1

(8) RESULTS AND DISCUSSION

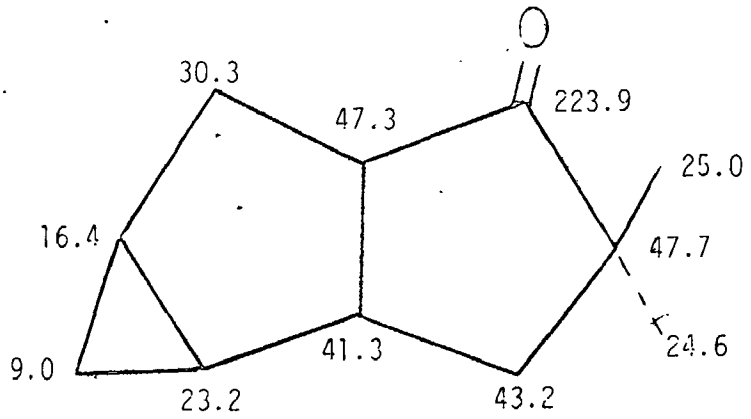
Ketones 98 and 99, prepared by methylation ($NaNH_2$-CH_3I-Et_2O) of 80e and 79e were dissolved in t-BuO^-/t-BuOH (1.26 M) to furnish a solution 0.26 M in ketone. Aliquots were sealed in glass tubes under nitrogen and heated to 180°C for various times. The neutral product (ca. 80% recovery) isolated from homoenolization of 98 was analyzed by glc (FFAP, Carbowax) and ^{13}C NMR. In each case, the starting material was recovered unchanged and there was no indication of the formation of isomeric material in the neutral fraction even after > 200 h at 185°C.

In contrast, under the same conditions and with the same stock solution of t-BuO^-/t-BuOH employed for some of the experiments with 98, the exo-tricyclic ketone 99 was smoothly transformed to a new isomeric ketone 100, which contained a five-membered ring according to its carbonyl absorption data (1730 cm^{-1}; δ_C 223.9). The half-life for the disappearance of 99 and the appearance of 100 was found to be ca. 75 h at 180°C. The ^{13}Cmr spectrum of the product contained ten signals in addition to the carbonyl peak: CH_3, 24.6, 25.0; CH_2, 9.0, 30.3, 43.2; CH, 16.4, 23.2, 41.3, 47.3 and C, 47.7. From these data the ketone could be tentatively assigned structure 100, which could arise by proton abstraction from C-9 of 99 to generate β-enolate 101, subsequently opening with protonation at the original C-5 site. The highest field methylene signal (δ_C 9.0) was



99 101 100

attributed to C-3 while the methine signal at δ_C 47.3 was ascribed to C-6, deshielded by the carbonyl. An examination of a series of methylated [3.3.0] systems (62) shows that the *exo*-methyl isomer absorbs further downfield than the *endo* epimer and on this basis the signals at δ_C 24.6 and 25.0 were assigned to the *endo* and *exo* methyl signals, respectively; the remaining assignments were straightforward.



As further proof of identity, $^{1}H/^{2}H$ exchange under mild conditions was examined. The rearranged ketone was stirred at room temperature in the presence of MeO^{-}/MeOD for 12 h and mass spectrometric analysis of the recovered material indicated that exchange occurred at a single site (0.995 atoms ^{2}H/molecule). As expected, in the ^{13}Cmr spectrum of **100**-d_1 the signal for C-6 (δ_C 47.3) appeared as a 1:1:1 triplet (J_{CD} = 20.8 Hz) with an α-isotope shift of 0.356 ppm. Precise isotope shifts for the signals of the neighbouring carbons were obtained from the spectrum of a 1:1 mixture of **100** and **100**-d_1 and these data are shown in Figure 9.1. The relatively large isotope shifts for the methine carbon at δ_C 41.3 (0.087 ppm) and the methylene carbon at δ_C 30.3 (0.097 ppm) are indicative of carbons geminal to ^{2}H (49). The small isotope shifts exhibited by the cyclopropyl methine at δ 16.4 (0.016 ppm) and the quaternary carbon (0.009 ppm) are consistent with the observed dihedral angular dependence of vicinal ^{2}H-^{13}C isotope shifts (34). Further confirmation of structure **100** was achieved by determination of the ^{13}C-^{13}C coupling constants for the sp^3 carbons of **100** from its INADEQUATE spectrum. These results are collected in Figure 9.2 and confirm the assigned structure (these shieldings (in C_6D_6) differ slightly from those given previously for $CDCl_3$ solution).

The ^{1}Hmr spectrum contained two methyl singlets (δ 1.10, 1.01), one two-proton pattern and eight one-proton

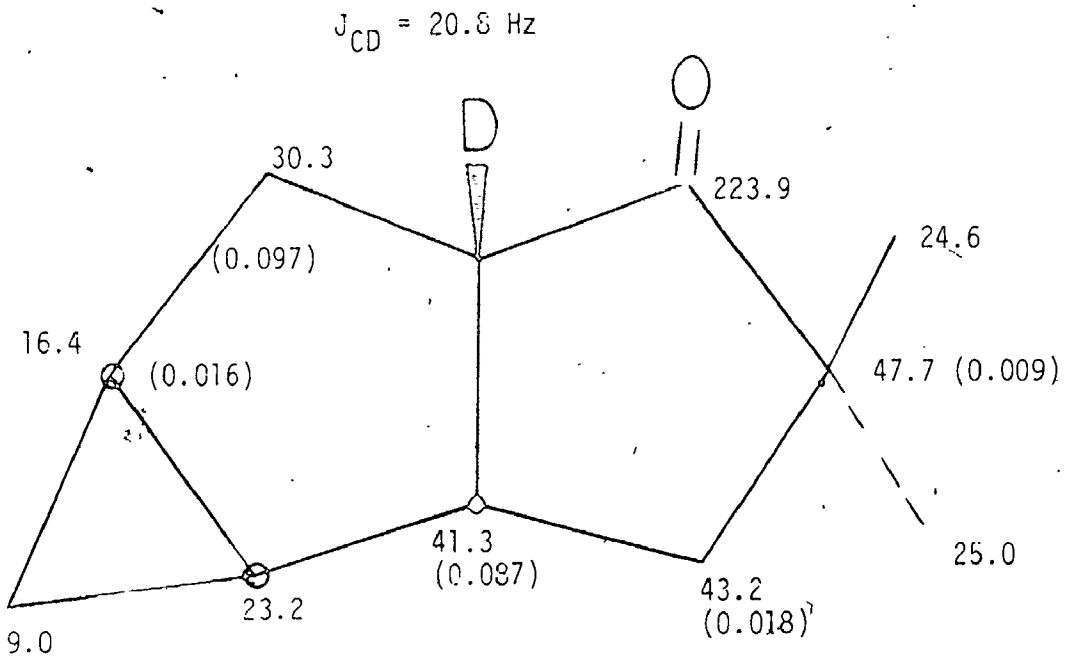


FIGURE 9.1: ^{13}C Shielding Data (σ_C) for 100 and 100-d_1

The values in parentheses are the ^2H-induced shift values in ppm

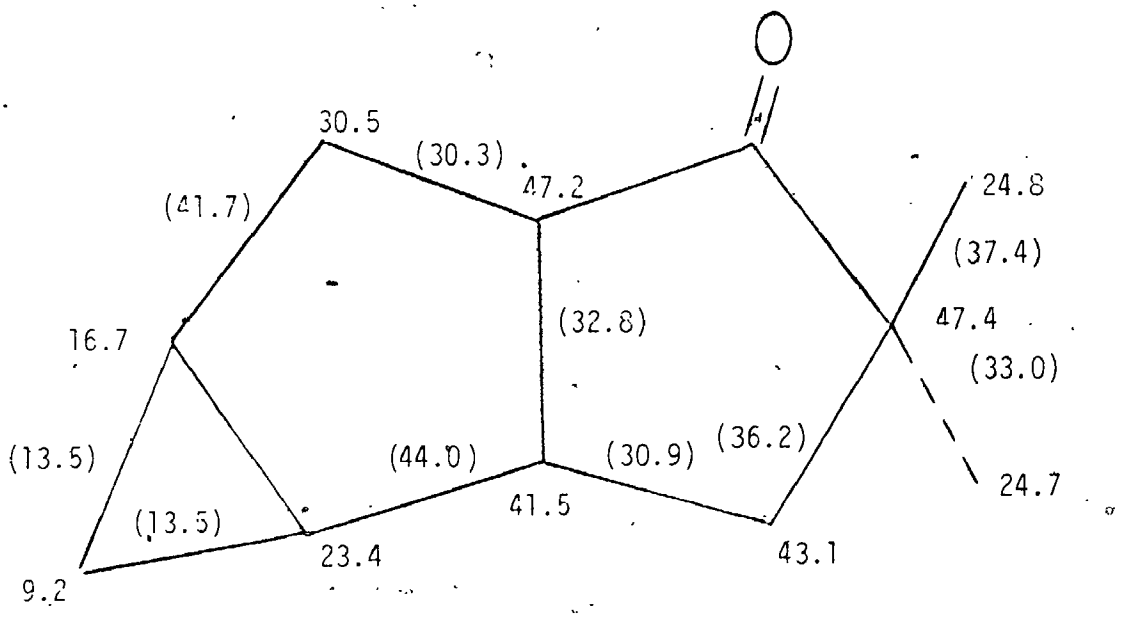
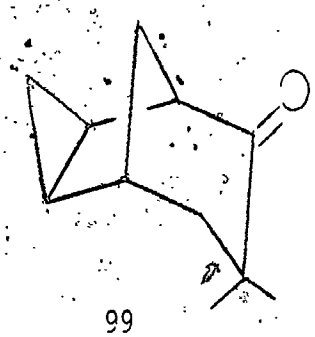


FIGURE 9.2: ^{13}C Shielding Data (σ_C) and Coupling Constants for 100 (in hz)

multiplets. The highest field absorptions at δ 0.02 (ddd, J = 3.9, 3.9, 5.1 Hz) and 0.46 (ddd, 5.1, 7.9, 7.9) were readily attributed to syn-H-3 and anti-H-3, respectively, since $J_{trans} < J_{cis}$ for vicinal coupling in cyclopropyl rings (63). The cyclopropyl methine protons gave rise to a complex multiplet at δ 1.24-1.38, while the absorption at δ 2.40 (ddd, J = 7.4, 9.2, 10.0 Hz) was ascribed to H-6 since this signal is absent in the proton spectrum of 100-d_1. A clear doublet of doublets δ 2.16 (J = 10.0, 13.0 Hz) and an ill-defined eight-line pattern at δ 1.72 were assigned to the 5-protons while a clean multiplet δ 2.00 (ddd, J = 1.6, 7.4, 12.8 Hz) and a broadened doublet of doublets δ 1.49 (J = 11.2, 12.8 Hz) were ascribed to the 9-protons. The lowest field absorption at δ 2.73 (ddd, J = 7.4, 7.4, 11.2 Hz) was attributed to H-1. These assignments were confirmed by spin-decoupling experiments.

The stability of 98 under these strongly basic conditions stands in direct contrast to the behaviour of 95 and 16a which are smoothly transformed to 96 and 16b, respectively, upon treatment with t-BuO⁻/t-BuOH at elevated temperatures (3,13). The original notion that 98 could conceivably provide an intramolecular competition for β- and γ-enolization was clearly incorrect and more subtle factors must play a role in governing isomerization via homoenolization. By analogy with 95, in which proton abstraction from C-8 leads to rearrangement to form 96, it was anticipated that proton abstraction from C-9 in 98

would give the corresponding rearrangement product while proton abstraction from C-3 could provide the [4.3.0.0] homolog of 16b but there is no evidence of formation of isomeric material. On the other hand, 99 is smoothly converted to 100, a rearrangement which is strictly analogous to the 95 → 96 conversion and which must involve proton abstraction from C-9 in 99, as noted above, to form 101 with subsequent opening to 100. The difference in behaviour of 98 and 99 suggests that the relative orientation of the carbonyl group and C-9 must be highly important. While the six-membered ring in 99 can adopt a chair conformation this arrangement is precluded for 98 because of the *endo*-orientation of C-3 and its six-membered ring presumably assumes a boat-like conformation. An inspection of molecular models indicates that the dihedral angle between C-9 and the carbonyl oxygen increases from ca. 120° to ca. 170° with the chair to boat change for the six-membered ring in 99 and 98, respectively. This change



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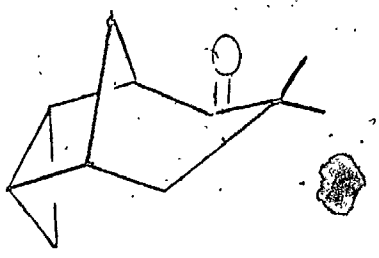


98

tips the Π-system of the carbonyl group away from C-9 thereby rendering potential overlap with a developing carbanionic centre at C-9 less likely. It seems reasonable to suggest that this difference in the relative orientation of the carbonyl group and the methano bridge carbon in 98 and 99 may account for the marked change in reactivity. This proposed relationship between the orientation of the carbonyl group and the site of β-proton abstraction and its effect on reactivity is examined further in Chapter 10.

Although the reluctance of 98 to rearrange via β-enolization at C-9 can be rationalized in terms of the dihedral angle between the methano bridge and the carbonyl group, this explanation does not follow for the failure of 98 to rearrange via Y-enolization at C-3. Since a comparison of the orientation of the carbonyl group with respect to C-3 in 98 and 16a indicates little difference except that the separation between the carbonyl carbon and C-3 is ca. 10% greater in the former. It may be noted that, from Dreiding models, the distance between C-9 and the carbonyl carbon in 99 is comparable to that between C-3 and the carbonyl carbon in 16a, both of which isomerize under the reaction conditions. It may be relevant that there is a similar separation between the carbonyl carbon and the methylene carbon involved in the Y-enolate rearrangement of half-cage ketone 9, to 11 which was the first example of this phenomenon (7). Clearly these results would seem to suggest that for homoenolization to

occur the separation between the carbonyl group and the site of proton abstraction must not exceed some critical value required for effective interaction of the carbonyl group with an incipient carbanionic centre. To gain further insight into the behaviour of 98 and 99 under the reaction conditions the results of $^{1}H/^{2}H$ exchange experiments were also examined.

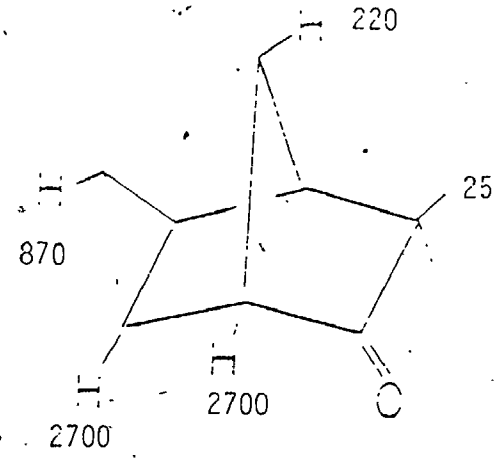
To determine the regio- and stereoselectivity of proton abstraction in 99 under strongly basic conditions, its homoenolization was examined in a deuterated medium. After treatment of 99 in t-BuO$^-$/t-BuOD at 185°C for various times, samples of 99-d_x were collected from the product mixtures by preparative glc. A 40 h sample contained 1.84 atoms ^{2}H/molecule by mass spectrometry and its ^{2}Hmr spectrum revealed six sites of deuterium incorporation for which the relative amounts were measured by integration. These absorptions and the ^{2}H content were found at δ 0.13 (0.38), 0.28 (0.055), 0.87 (0.18), 0.93 (0.22), 1.14 (0.11), and 2.66 (0.89), the assignments for which were obtained by comparison with the ^{1}Hmr spectrum of 99. Its proton spectrum contained two methyl singlets at δ 1.14 and 1.11 which were found to correlate with the ^{13}C methyl signals at δ_C 31.7 and 30.4, respectively; hence the lower field signal (δ_C 31.7) arises from the *exo* methyl group and deuterium exchange of the methyl groups occurred exclusively at the *exo* position, which is consistent with the findings of other studies (16). The two highest field

signals at δ 0.12 (1H, dd, J = 5.4, 7.7, 7.7 Hz) and 0.28 (1H, dd, J = 3.6, 3.6, 5.4 Hz) were readily assigned to the 3-protons. The larger vicinal couplings for the higher field pattern show it to be due to the proton cis to the cyclopropyl methine protons, H-2 (δ 0.79 (m) and H-4 (δ 0.93 (m)) since it is well known that $J_{cis} > J_{trans}$ for vicinal coupling in cyclopropyl rings (63). The bridgehead protons absorbed furthest downfield at δ 2.66 (d, J = 4.4 Hz, H-5) and 1.92 (m, H-1). An AB pattern at δ 0.87 (d, J = 12.5 Hz broadened by small unresolved couplings) and δ 1.00 (m) correlated with the methylene carbon at δ_C 26.0, hence these signals were assigned to the 9-protons. An inspection of molecular models indicated that the dihedral angles between the syn-9-proton and the 1- and 5-bridgehead protons are ~ 90°, thus the slightly broadened doublet at δ 0.87 was assigned to syn-H-9. The remaining AB pattern at δ 1.34 (J = 4.1, 14.0 Hz) and 1.48 (J = 2.0, 2.8, 14.0 Hz) was readily ascribed to the 8-protons. Based upon these data the deuterium exchange occurred at C-3, -4, -5, -9 and the exo-methyl carbon. From the results for a series of samples of 99-d_x recovered after treatment with t-BuO⁻/t-BuOD for 10, 20 and 40 h, the relative proportions of deuterium at the various sites of exchange were determined and these data permitted the extraction of approximate first-order rate constants for the exchange processes which are collected in Fig. 9.3.

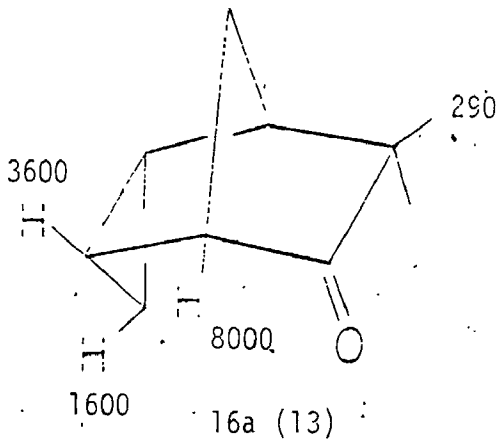
Although 98 was found to be stable under the conditions for rearrangement of 99, this does not preclude the occurrence of $^1H/^2H$ exchange. Consequently samples of 98 were treated with t-BuO$^-$/t-BuOD at 185°C for various times. After 88 h, recovered 98-d_x was found to contain 3.96 atoms ^2H/molecule by mass spectrometry and the ^2Hmr spectrum revealed five sites of incorporation for which the ^2H distribution was determined by integration. The ^2Hmr signals and ^2H content were found to be; δ 0.42 (0.64), 0.60 (0.16), 0.93 (1.66), 1.52 (0.75), 2.77 (0.75). The ^1Hmr spectrum of 98 contained methyl singlets at δ 0.93 and 1.06 which correlate with the ^{13}C methyl signals at δ_C 19.2 and 11.2, respectively, thus it follows that the higher field signal (δ 0.93) arises from the *exo*-methyl group since the less shielded carbon is *exo*. Hence, as expected, 98 undergoes exchange at the *exo*-methyl site preferentially, which is consistent with previous results. The two lowest field multiplets at δ 2.40 and 2.77 were readily attributed to H-1 and H-5, respectively, while the two geminal coupled (J_{AB} = 11.5 Hz) signals at δ 1.77 and 1.86 were ascribed to the 9-protons. The 3-protons absorb at δ 0.42 and 0.60, $^2J_{AB}$ = 6.3 Hz, with the higher field component exhibiting additional couplings of 8.1 Hz to two protons and 1.8 Hz to one other proton; the lower field component contained a coupling of 3.6 Hz to two other protons. The higher field absorption, δ 0.42 was assigned to the *exo*-H-3 ($J_{cis} > J_{trans}$ for vicinal coupling in

cyclopropyl rings) and the small 1.8 Hz coupling was subsequently shown to be due to a long-range coupling to the H-9 absorption at δ 1.86, by spin decoupling, thus identifying the latter as the syn proton. Irradiation of the 3-methylene protons also served to identify the multiplets at δ 1.40 and 1.52 as the signals for H-2 and -4. The remaining broadened doublet at δ 1.10 (J = 14.5 Hz) and a doublet of doublets at δ 1.42 (J = 7.5, 14.5 Hz) were ascribed to the *endo*- and exo-H-8 signals, respectively. From these data, it was concluded that deuterium exchange occurred at C-3, -4, -5 and the exo-methyl sites in 98. The deuterium exchange experiment was then repeated using reaction times of 3, 6, 12 and 19 h; analysis of the recovered 98-d_x (ms, ^{2}Hmr) allowed the extraction of the approximate first-order rate constants for the exchange processes.

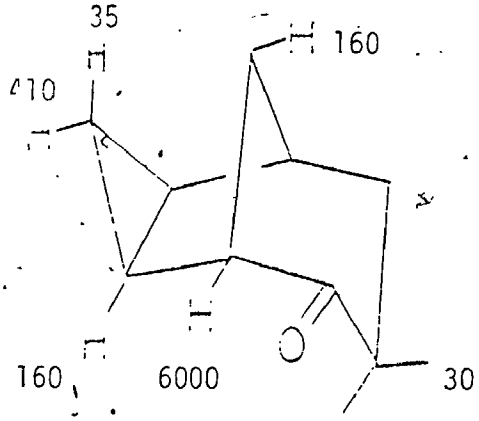
The approximate first-order rate constants for exchange at the various sites in 98 and 99 are given in Figure 9.3, together with the earlier results (13) for their [3.2.1.0] analogs, 15 and 16a. In each case, exchange at the 3-methylene sites is highly stereoselective, indicative of steric hindrance, and the rates for the more reactive proton are comparable, although this centre is only involved in enolate rearrangement in the case of 16a. This seems to indicate that the carbonyl group has little influence on proton abstraction from C-3 and the reactivity of these protons can be attributed to



15 (13)



16a (13)



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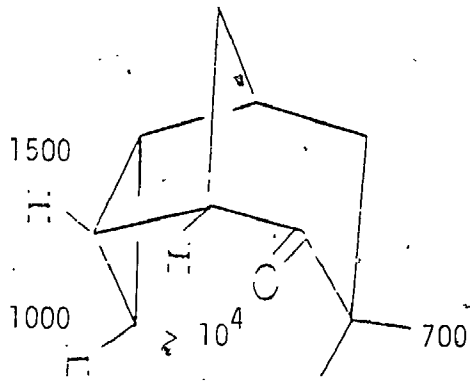

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FIGURE 9.3: Estimated Rates ($k \times 10^8$ sec^{-1}) of $^1H/^2H$ Exchange at 125°C

the fact that cyclopropyl methylene hydrogens are more acidic than their alicyclic counterparts. On the other hand, their less acidic vicinal neighbours, the cyclopropyl methine hydrogens, are distinctly activated by the carbonyl group since exchange occurred only at C-4 in each compound with no evidence of exchange at C-2. It is curious, however, that the rate of exchange at C-4 in 99 is slower than that at C-3 while the reverse was found for 16a, 98 and 15. The detection of exchange at the methano bridge in the related systems, fenchone and 3,3,6,6-tetramethyl-norcamphor, is relatively recent (64). Hence it is interesting that the syn-proton at this position undergoes exchange selectively but only in the *exo* series, 99 and 15, and at comparable rates. In the bicyclic systems, syn exchange is strongly favored but proceeds at only ca. 1/100 of the rate found for 99 and 15 this increased reactivity is difficult to explain. The incorporation of a syn-deuterium at C-9 in 99 would suggest that the cleavage of β-enolate 101 to regenerate 99 proceeds with retention of configuration if this is indeed the mode of exchange. However, the absence of deuterium at the corresponding position in 95 (C-8) indicated that the conversion of 95 → 96 is unidirectional. For 99 it is conceivable that exchange at C-9 involves a different intermediate species than 101. As already noted, methyl exchange occurred preferentially at the *exo*-groups, with the puzzling difference that this process is distinctly faster in the

endo-examples 16a and 98 than their *exo* counterparts, 99 and 15. Clearly, rather subtle factors govern the reactivity of exchange in these compounds and additional data are required before definitive interpretations can be devised.

CHAPTER 10

BEHAVIOUR OF TRICYCLO[5.3.1.$0^{2,6}$]UNDECANONE AND BICYCLO[3.2.1]OCTANONES UNDER STRONGLY BASIC CONDITIONS

(A) INTRODUCTION

The examination of the 7,7-dimethyltricyclo-[3.3.1.$0^{2,4}$]nonan-6-ones under strongly basic conditions had shown that the *endo*-isomer was stable, while the *exo*-isomer readily rearranged to **100**. This difference in reactivity was attributed to the relative orientation of the carbonyl group and the methano bridge for the two isomers, which for these cases is governed by the conformation of the six-membered ring. These results indicate that β-enolate formation does not readily occur if the dihedral angle between the carbonyl oxygen and the β-carbon approaches ca. 170°. The deuterium exchange data for a series of polycyclic ketones, shown in Figure 10.1, tend to support this view since in each case exchange does not readily occur at any β-carbon with a dihedral angle approaching 170° with respect to the carbonyl oxygen. In general, efficient exchange occurs at those β-sites for which the dihedral angle varied from ca. 0° to ca. 130°, although slow exchange at *endo* α-methyl groups indicates that additional factors also govern the reactivity of exchange.

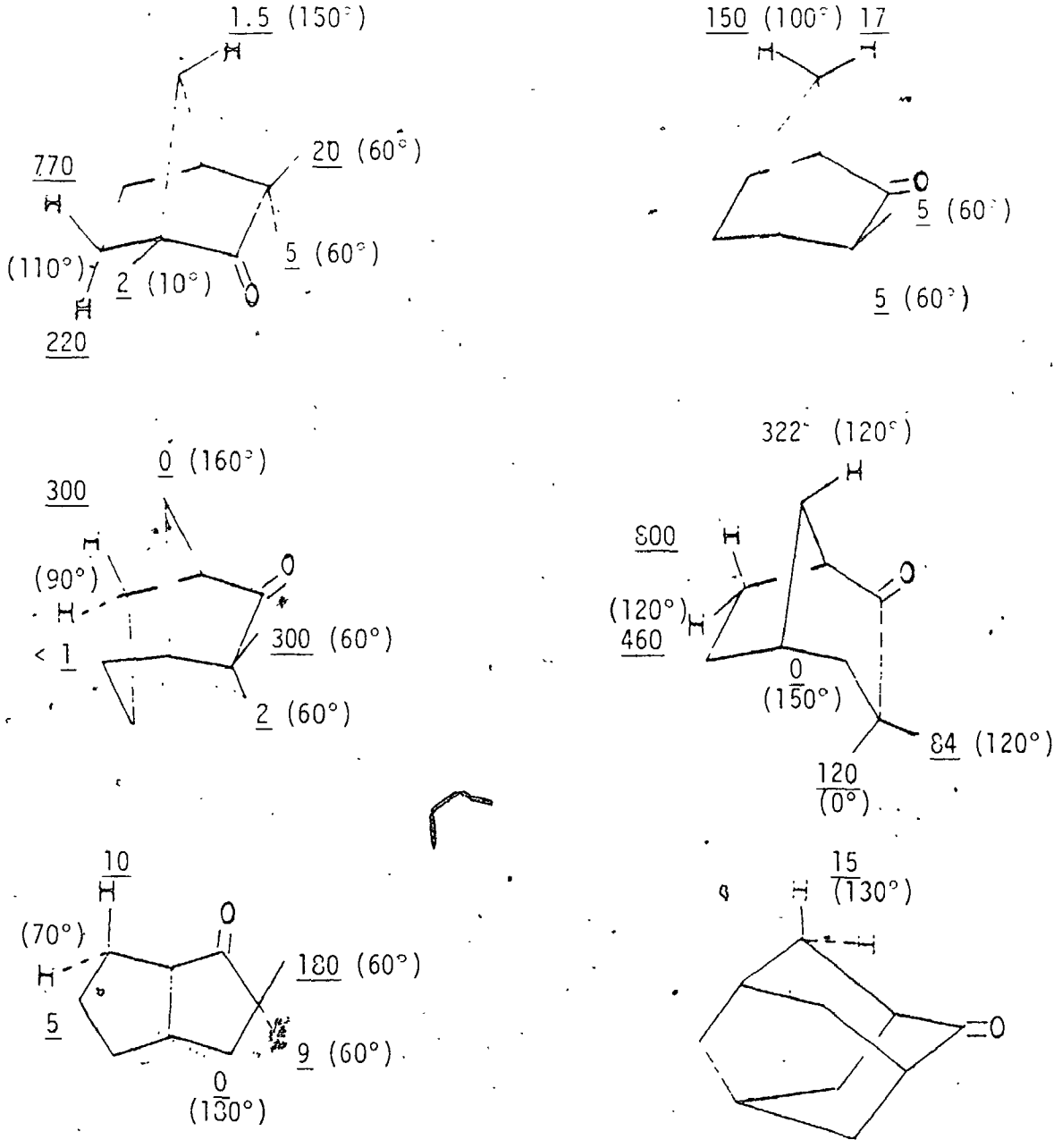
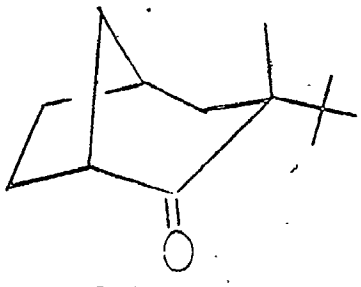


FIGURE 10.1: Deuterium Exchange Rates. ($k \times 10^{8}$ sec^{-1}) by β-enolization[a] at 185°C in t-BuO$^-$/t-BuOD (16)

[a]The pseudo first-order rate constants for exchange are underlined, while the dihedral angles defined by the β-carbon and the carbonyl oxygen are in parentheses

[b]The rate factor was obtained from the rate of rearrangement (see Figure 10.2)

The homoenolate skeletal rearrangements shown in Figure 10.2 are consistent with the exchange data. In each case the six-membered ring presumably adopts a chair-like conformation preferentially; thus the dihedral angle relating the developing carbanionic site and the carbonyl oxygen will be near 120°. To examine the sensitivity of homoenolate rearrangements to the orientation of the carbonyl group and the developing carbanionic site the behaviour of *endo*-3-t-butyl-3-methylbicyclo[3.2.1]octan--2-one (104), *endo*-9-t-butyl-9-methyltricyclo-[5.3.1.$0^{1,5}$]undecan-8-one (105), 9,9-dimethyl-*endo*-tricyclo[5.3.1.$0^{1,5}$]undecan-8-one (106), and *exo*-3-t-butyl-3-methylbicyclo[3.2.1]octan-2-one (107) under typical homoenolization conditions were examined. For ketones 104, 105 and 106 the six-membered ring presumably assumes a boat-like conformation because of the *endo* t-butyl group or the trimethylene bridge.



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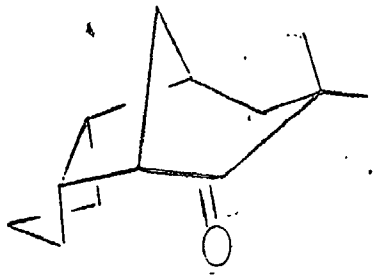
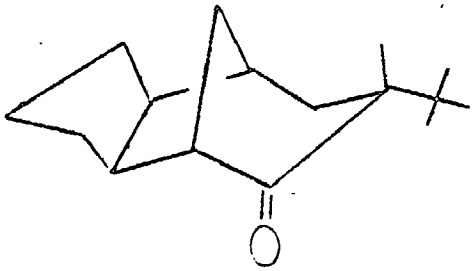


106



105

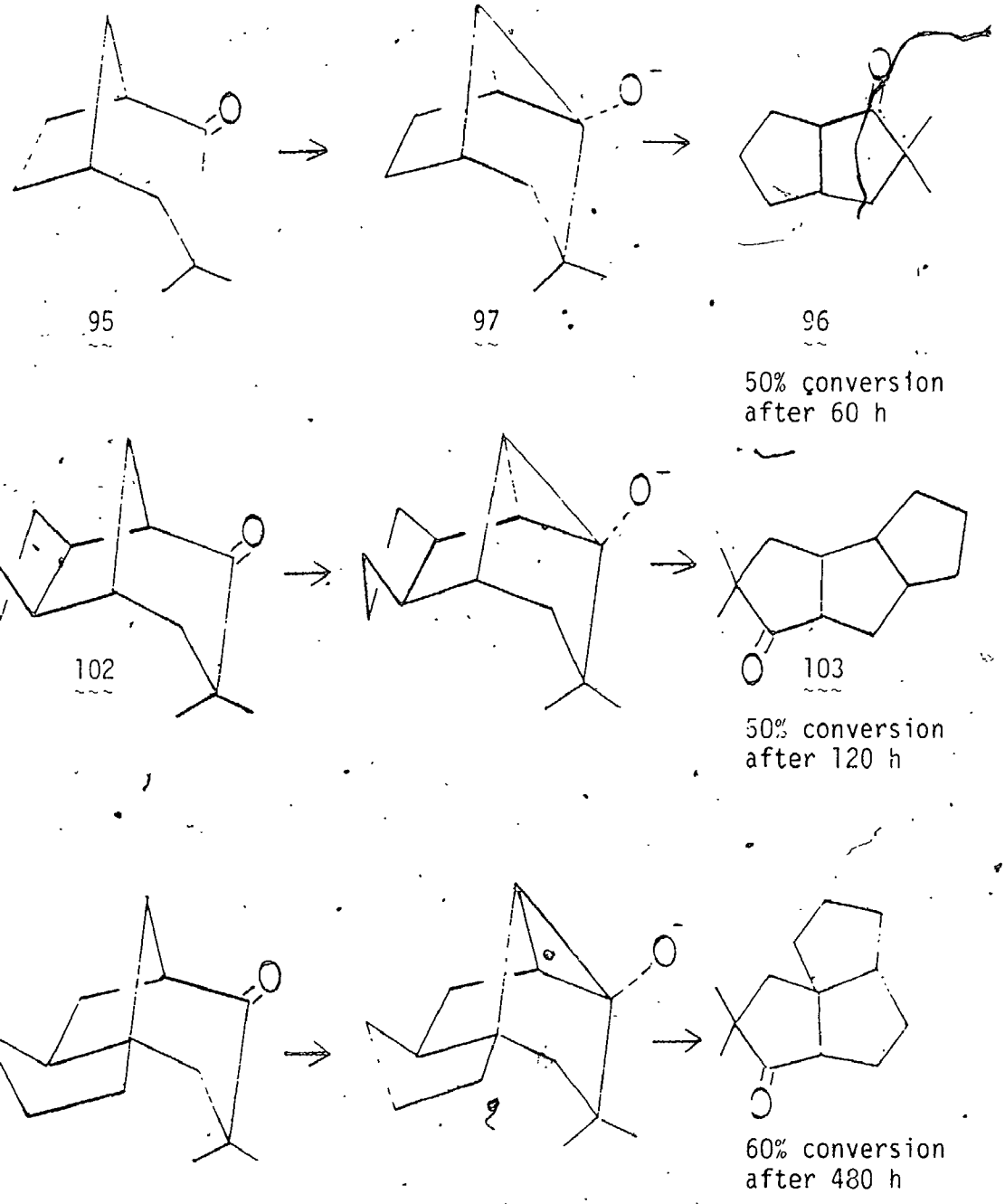
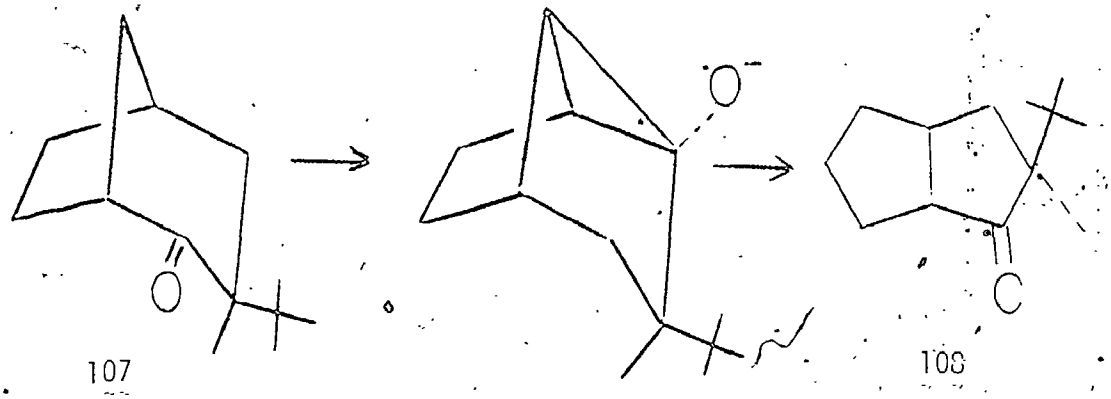


FIGURE 10.2: Homoenolate Skeletal Rearrangement[a]

[a]Experimental conditions: t-BuO$^-$/t-BuOH, 185°C

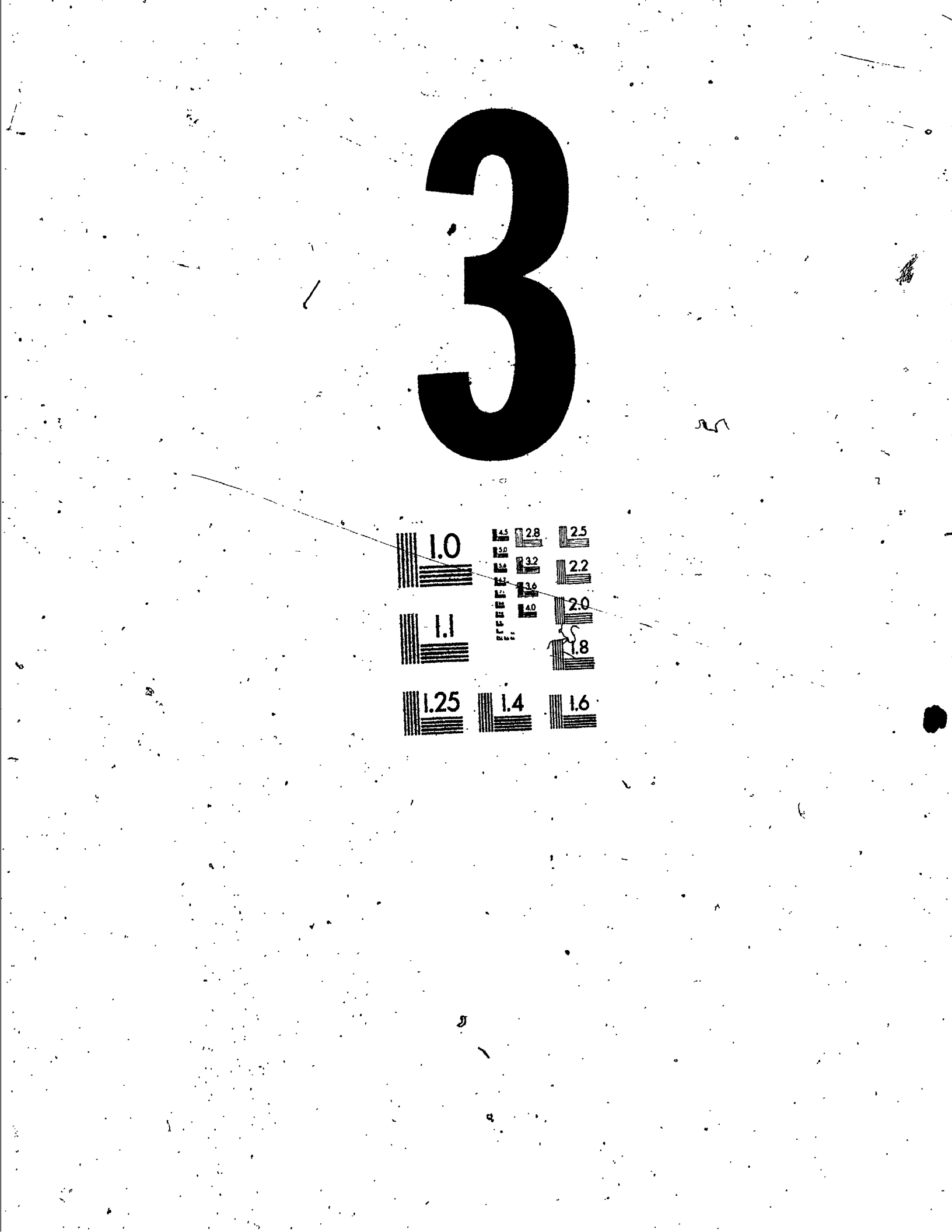
Therefore by analogy with 98; it was anticipated that these three compounds would not rearrange via β-enolate formation at the methano bridge. The reactivity of 107 under strongly basic conditions was of interest since its six-membered ring could assume a chair-like conformation allowing it to undergo a base-catalyzed rearrangement to exo-3-t-butyl-3-methylbicyclo[3.3.$0^{1,5}$]octan-2-one (108).



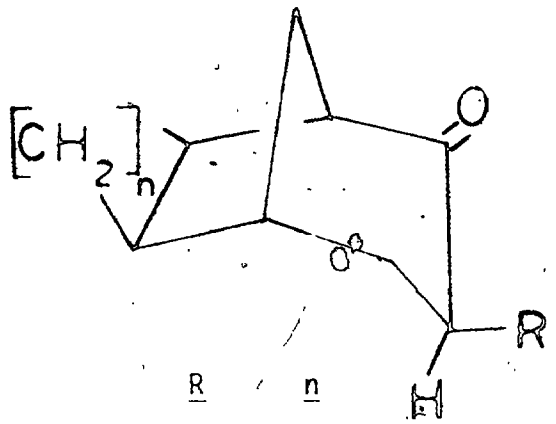
107 108

(B) SYNTHESIS

The synthetic sequence used for the preparation of ketones 104, 105 and 107 is given in Scheme 10.1. Ketones 104a and 105a were readily available and the α-methyl ketone 107a was prepared by methylation of 104, using LDA and methyl iodide. The silyl enol ethers 104b, 105b and 107b were obtained by treatment of the corresponding ketone

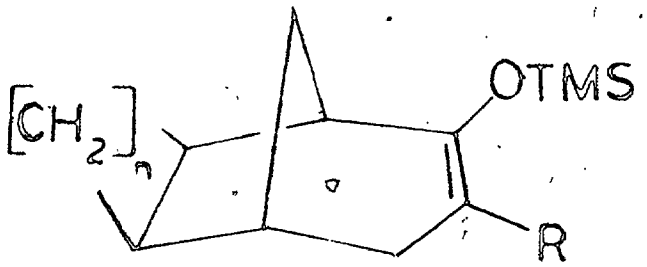

3
1.0
1.1
1.25
1.4
1.6
2.8
3.2
3.6
4.0
2.5
2.2
2.0
1.8

SCHEME 10.1



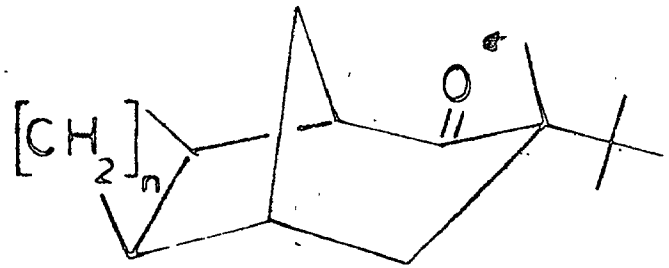
	R	n
28	H	3
104a	H	0
107a	CH_3	0

1) > LDA
2) ClTMS



(28a, 104b, 107b)

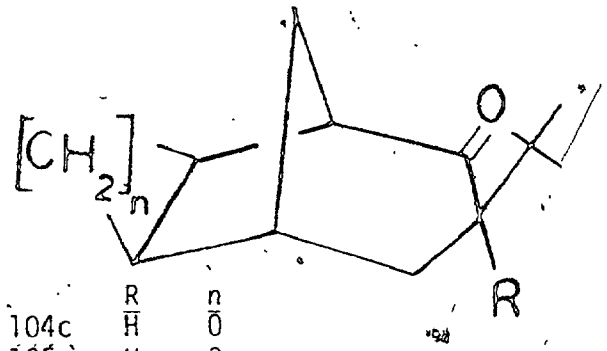
-BuCl
$TiCl_4$



104 n = 0
105 n = 3

for
104c and 105c

LDA
MeI

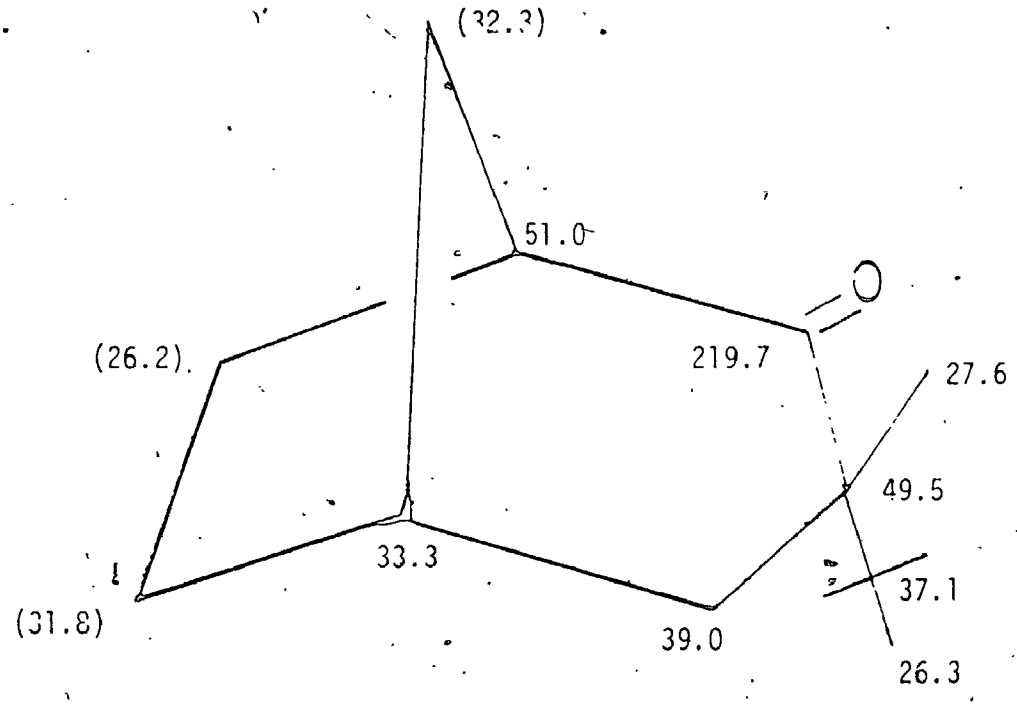


	R	n
104c	H	0
105c	H	3
107	Me	0

with LDA followed by the addition of trimethylsilyl chloride and triethylamine. Maier's procedure (67) for t-butylation of silyl enol ethers provided an efficient means for the conversion of 104b and 105b, to 104c and 105c, respectively. The treatment of 104c and 105c with $MeO^-/MeOD$ afforded only 104c-d_1 and 105c-d_1, which is consistent with the assigned stereochemistry of the α-t-butyl group since the analogous methyl derivatives 107a and 28d when treated with $MeO^-/MeOD$ yield only deuterated starting material.

Following the t-butylation procedure employed with 104b, alkylation of 107b gave a complex mixture containing ca. 70% 107a and 9% 107. Varying the conditions for alkylation did not improve the yield of 107 and an analytical sample was collected by preparative glc for characterization. Its ^{13}Cmr spectrum contained eleven signals: CH_3, 25.8, 26.3 (rel. int. 1:3); CH_2, 28.0, 29.6, 33.6, 40.7; CH, 35.0, 52.6; C, 37.9, 50.5 and C=O, 220.2. The infrared spectrum contained strong carbonyl absorption at 1698 cm^{-1} and its molecular formula was shown to be $C_{13}H_{22}O$, by precise mass measurement. Assuming that t-butylation occurred in the exo direction, these data agreed well with the assigned structure for 107. The reduced efficiency of alkylation for 107b may be attributed to the increased steric repulsions between the substrate and the bulky tertiary cation, $(CH_3)_3C^+$.

Methylation of 104c was initially attempted following the procedure employed for 107a (1.5 equivalents LDA and 3.0 equivalents of CH_3I added at -70°C) which furnished a product mixture containing ca. 36% of 104. A series of methylation procedures was then examined ($NaNH_2$/MeI, KH/MeI) which failed to increase the yield of 104. Hence, LDA alkylation of 104c was repeated using 1.2 equivalents of base and after the addition of 104c the mixture was stirred at room temperature for 30 min. before the addition of CH_3I. This change in procedure led to a 95% yield (by glc) of 104. Its ^{13}Cmr spectrum consisted of eleven signals; CH_3, 26.3, 27.6 (relative intensity 3:1); CH_2, 26.2, 31.8, 32.3, 39.0; CH, 33.3, 51.0; C, 37.1, 49.5, and a carbonyl absorption at δ_C 219.7. A comparison of the ^{13}C shieldings for 104 and 107 clearly indicated that exo-methylation occurred and the assignments for both isomers are shown in Figure 10.3. The IR spectrum of 104 contained strong carbonyl absorption at 1698 cm^{-1} and the molecular formula, determined by precise mass measurement, was found to be $C_{13}H_{22}O$. These data agree well with the assigned structure. Repeated methylation of 105c with LDA and methyl iodide gave a product mixture containing 94% of 105. Its ^{13}Cmr spectrum of 105 had fourteen signals: CH_3, 26.4, 27.9 (rel. int. 3:1); CH_2, 26.5, 27.8, 34.1, 39.6; CH, 39.3, 45.0, 50.9, 57.5; C, 37.2, 50.1 and C=O, 219.2. The ^{13}Cmr data for the α-methyl carbons of 107 (δ_C 25.8), 104 (δ_C 27.6) and 105 (δ_C 27.9) was consistent with



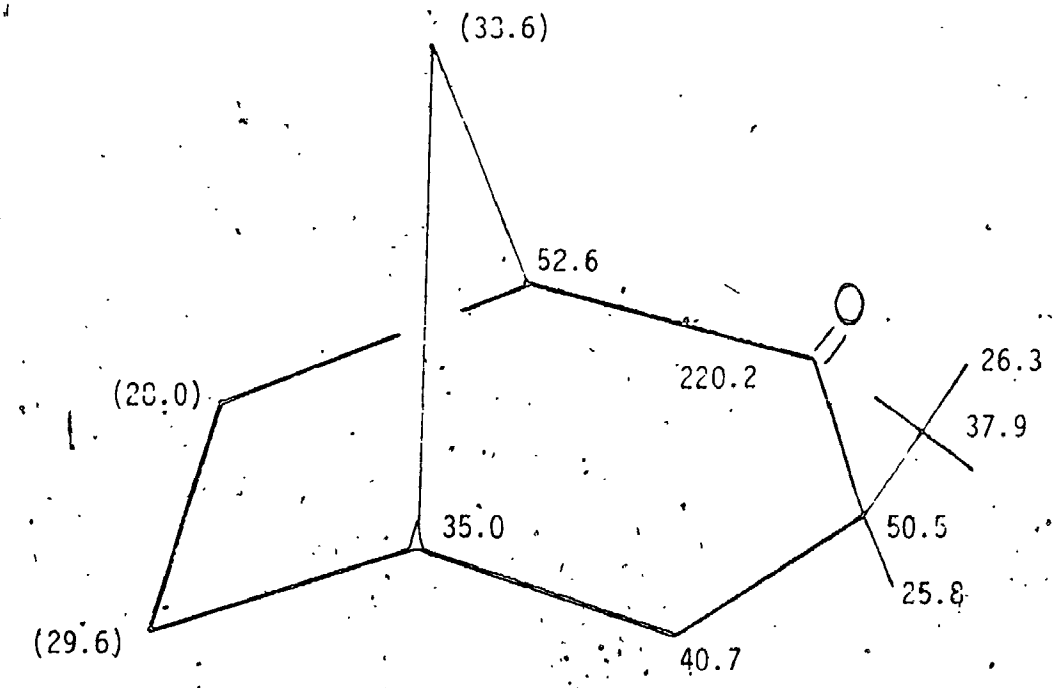
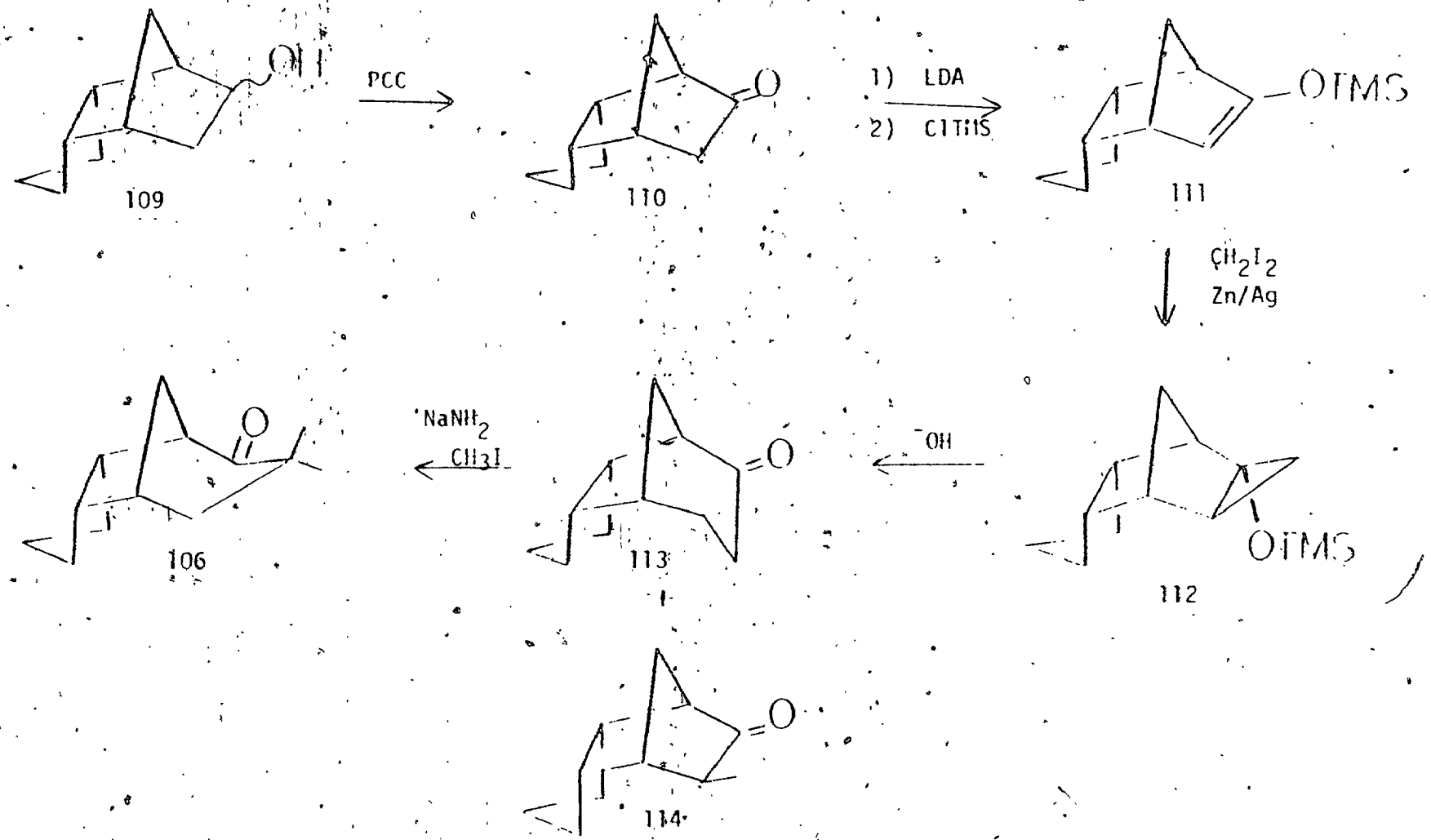


FIGURE 10.3: ^{13}C Shielding Data (δ_C) for 104 and 107

methylation of 105c occurring in the exo direction. The infrared spectrum contained a strong carbonyl absorption at 1698 cm^{-1} and the molecular formula was shown by precise mass measurement to be $C_{16}H_{26}O$. These data were consistent with the assigned structure for 105.

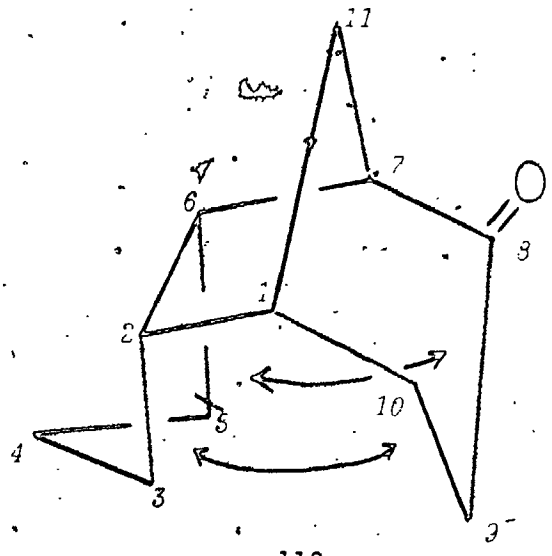
Ketone 106 was prepared from the known tricyclic alcohol 109 (68), as outlined in Scheme 10.2. Oxidation of 109 with PCC afforded 110 in 85% yield which upon treatment with LDA at -70°C followed by reaction with trimethylsilyl chloride and triethylamine gave 111 in 89% yield. It was anticipated that treatment of 111 with the Simmons-Smith reagent would provide smooth conversion to 112. Gas-liquid chromatography of the product mixture from cyclopropanation indicated the presence of two components in a ratio of 2.3:1. These were collected by preparative glc and shown to be 112 (major component) and 114. The formation of the latter product suggests that 112 is unstable to the Simmons-Smith conditions and undergoes ring opening to 114, possibly due to trace amounts of acid present in solution. Hence, the cyclopropanation reaction was repeated monitoring the course of the reaction by ^{1}Hmr and the usual work-up procedure gave 112, which by glc was > 80% pure. Treatment of the product mixture from cyclopropanation with $^-$OH/MeOH at 0°C afforded a 1:2.1 mixture of 114 and 113, respectively. Flash chromatography furnished pure 113 in 56% yield. The spectral data for the series 110-114 agreed with literature values (27).



109 110 111 112 113 114 106

SCHEME 10.2

Since the product ratio from homoketonization of 112 clearly differed from that for 27b, the reaction was examined at room temperature. Thus pure samples of 112 were treated with 3 M methanolic sodium hydroxide solution and glc analysis of the product mixture indicated a 1.7:1 mixture of 113 and 114, respectively. As discussed previously, homoketonization of polycyclic cyclopropoxides is influenced by a variety of factors. At present it seems reasonable to suggest that 112 affords a greater proportion of the methyl ketone 114 than that found for the exo isomer 27b, because the relief of strain upon formation of the ring expanded ketone is less for the endo compound. This can be attributed to strain arising from torsional interactions between the C-2,3 and -9,10 bonds and the C-5,6 and -8,9 bonds in the ring-expanded product 113.



113

Treatment of 113 with $NaNH_2$-Et_2O-MeI furnished 106. Its IR spectrum contained strong carbonyl absorption at 1703 cm^{-1} and a precise mass measurement showed the molecular formula to be $C_{13}H_{22}O$. The ^{13}Cmr spectrum of 106 had thirteen signals: CH_3, 27.9, 34.3; CH_2, 26.6, 27.3, 35.4, 35.6; CH, 35.7, 46.8, 47.7, 53.0; C, 40.6 and C=O, 219.6. The assignments given in Figure 10.4 followed from consideration of the shielding effects expected for the methyl groups on the ^{13}C chemical shifts of 113. The proton spectrum of 106 consisted of four multiplets at δ_C 2.63 (3H), 2.32 (2H), 1.27-1.79 (9-H) and 1.10 (1H), a sharp doublet at δ 2.18 (1H, J = 13.0 Hz) and two intense methyl signals at δ 1.15 and 1.03.

(C) HOMOENOLIZATION OF 104, 105, AND 106

Following the usual procedure, ketone 106 was dissolved in t-BuO$^-$/t-BuOH (1.26 M) to furnish a solution 0.26 M in 106. Aliquots of this solution were transferred to glass tubes under nitrogen, sealed under vacuum, and immersed in an oil bath at 185°C for varying periods of time. The neutral product (quantitative yield) from each tube was isolated by pentane extraction and analyzed by glc (FFAP, Carbowax) and ^{13}C spectroscopy. In each case, the starting material was recovered unchanged with no indication of the formation of isomeric material in the neutral fraction even after > 150 h at 185°C. A second series of tubes heated to 200°C for varying periods also

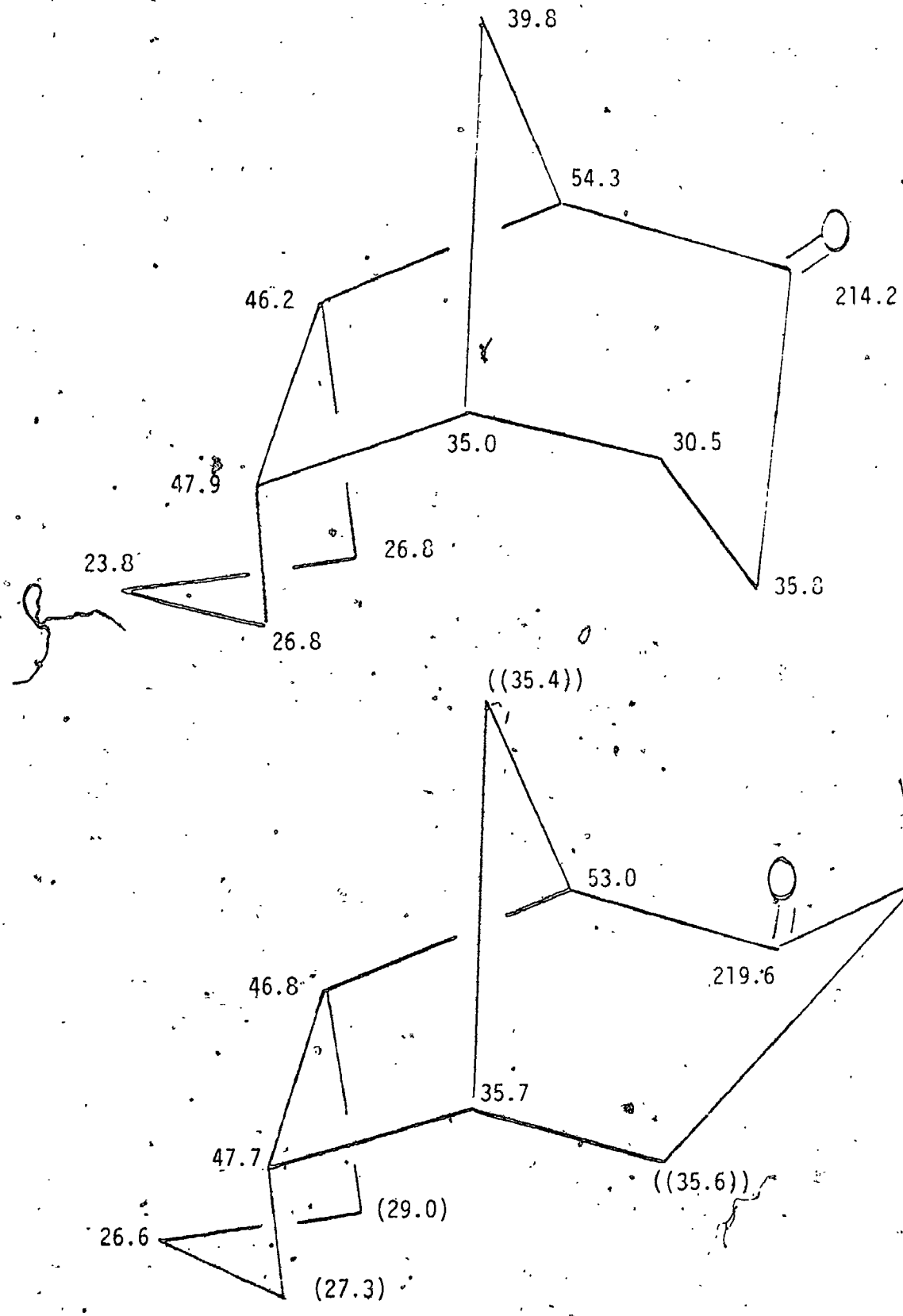


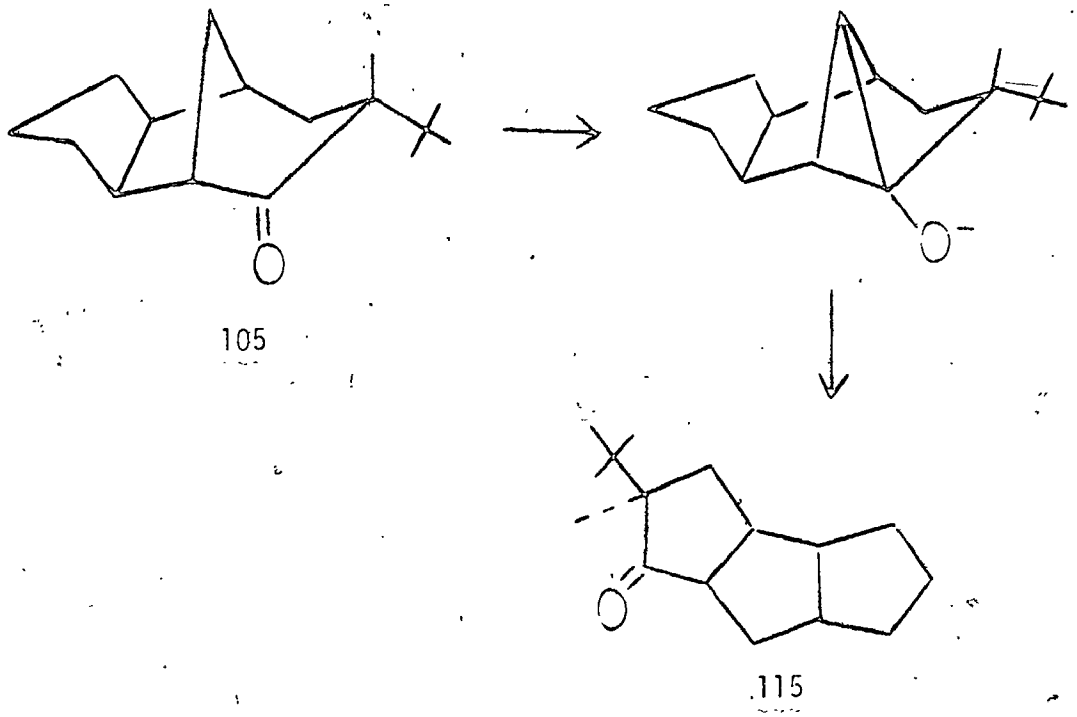
FIGURE 10.4: ^{13}C Shielding Data (δ_C) for 106 and 113 (27)

yielded only starting material (95% yield), even with a reaction time > 220 h.

The rate-depressing effect of water on t-BuO⁻/t-BuOH catalyzed reactions is well recognized (19), hence to insure that the apparent stability of 106 was not the result of inadvertently reduced base strength, a 1:1 mixture of 106 and 102 in t-BuO⁻/t-BuOH (same stock solution used for 106) was heated to 185°C for 645 h. Gas-liquid chromatography (FFAP) of the neutral product (93% recovery) indicated that the product mixture contained 103 (20%), 102 (29%) and 106 (51%). Since the yield of 103 from 102 was consistent with literature values (65) these results confirm the stability of 106 under strongly basic conditions.

Treatment of 105 (> 95% pure) with t-BuO⁻/t-BuOH (at 185°C) for 65 h yielded only starting material (80% recovery), while the 131 h-run (185°C) afforded a trace amount (ca. 1%) of a new component (115). To increase the yield of 115 a second series of tubes was heated at 200°C for varying periods of time. Gas-liquid chromatography of the neutral product (> 75% recovery) from the 240 h run showed that the product mixture consisted of 105 (92%) and 115 (8%). Doubling the reaction time did not significantly increase the relative yield of the latter component, a sample of 115 was collected by preparative glc. A precise mass measurement of 115 showed the molecular formula to be $C_{16}H_{26}O$ and its carbonyl absorption data (1730 cm^{-1},

δ_C 224.1) was indicative of a five-membered ring ketone. The ^{13}Cmr spectrum contained thirteen signals in addition to the carbonyl absorption: CH_3, 19.2, 26.1 (rel. int. 1:3); CH_2, 26.9, 34.1, 34.3, 34.6, 39.2; CH, 44.3, 45.6, 52.9 and C, 34.0, 56.4. These data suggested that 115 could be *endo*-4-t-butyl-4-methyl-cis, anti, cis-tricyclo-[6.3.0.0^{2,6}]undecan-3-one, formed by β-enolization at C-11 of 105 with subsequent cleavage of the original C-7,8 bond.



105

115

To establish that the slow isomerization (105 → 115) was not due to the presence of water in the base solution, a 1:1 mixture of 105 and 102 was treated with t-BuO$^-$/t-BuOH (same stock solution used for 105) at 185°C for 552 h. Glc analysis of the neutral contained 103 (24%), 102 (26%), 115

(3%) and 105 (47%). The approximately 1:1 mixture of 103 and 102 established that the low yield of 115 was not due to reduced base strength.

Solutions of 104 and t-BuO$^-$/t-BuOH were heated at 185° and 200°C for varying periods of time. Gas-liquid chromatography of the neutral product (> 80% recovery) from the 40 h-run (185°C) revealed two poorly resolved peaks, while a ^{13}C spectrum of the product mixture showed two sets of signals with relative intensities of 5.4:1. The ^{13}C spectrum for the major component contained eleven signals: CH_3, 26.3, 27.6 (rel. int. ca. 1:4); CH_2, 26.2, 31.8, 32.3, 39.0; CH, 33.3, 51.1; C, 37.1, 49.5 and C=O, 219.9 while the minor component exhibited ten signals: CH_3, 25.8, 28.0, 29.6, 33.6, 40.7; CH_2, 35.0, 52.6; C, 37.9, 50.5 and C=O, 220.2. The predominant set of peaks was readily ascribed to the starting material and the remaining absorptions were attributed to 107, with its t-butyl methyl signal coincident with the corresponding signal from 104. The product composition for the neutral fraction as a function of time is given in Table 10.1. These data show that, under the conditions employed, 104 rearranges to 107, which does not readily isomerize to 108.

(D) DISCUSSION

The stability of 106 under strongly basic conditions stands in direct contrast to the behaviour of 102 which is transformed to 103 (Figure 10.2) upon

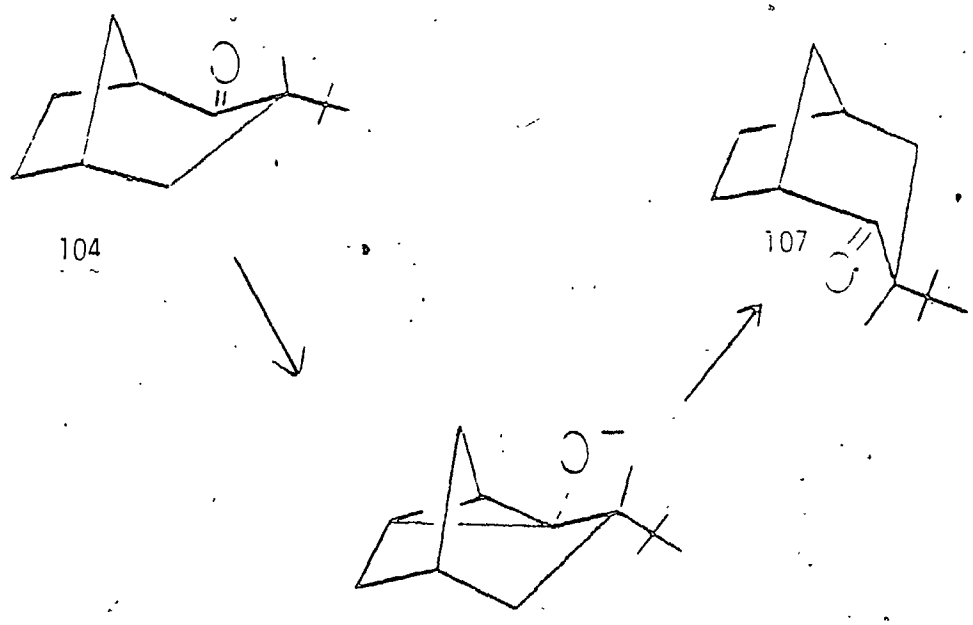
TABLE 10.1: Composition of the neutral product obtained from homoenolization (t-BuO⁻/t-BuOH) for 104

Temperature (°C)	Time (h)	Product (%)[a] 104	107
185	40	85	15
	230	50	50
200	97	40	60

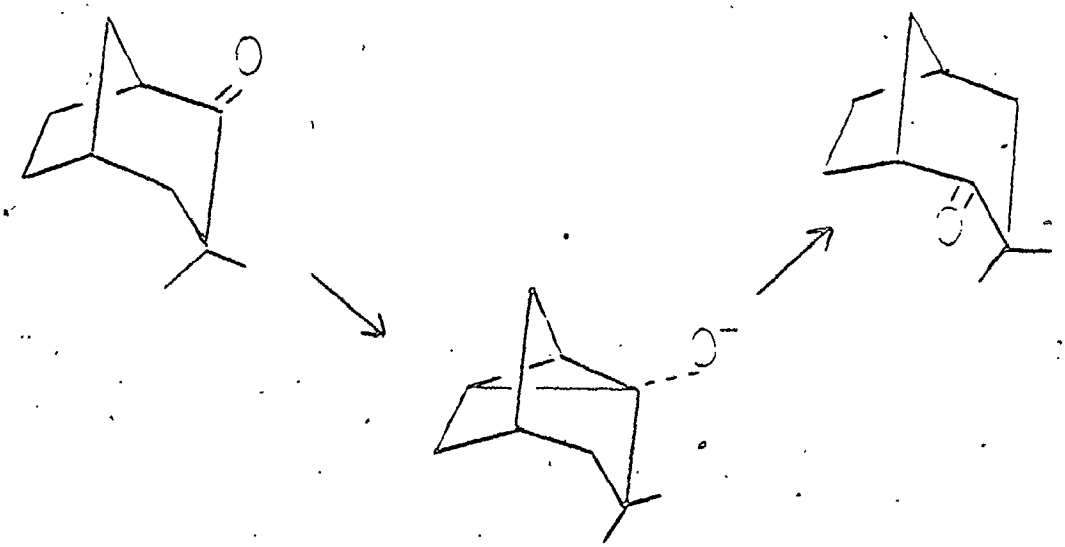
[a]Relative proportions were determined from the ^{13}Cmr spectra ± 10%.

treatment with t-BuO$^-$/t-BuOH at elevated temperatures (65). This difference in behaviour is analogous to that found for the *exo*, and *endo*-isomers of 7,7-dimethyltricyclo-[3.3.1.$0^{2,4}$]nonan-6-one and is consistent with the suggestion that the relative orientation of the carbonyl group and the site of β-proton abstraction is highly important for rearrangement *via* β-enolization. In **102** the six-membered ring can adopt a chair-like conformation, while for **106** this arrangement is precluded because of the *endo* orientation of the trimethylene-bridge and its six-membered ring presumably adopts a boat-like conformation. With this conformational change the dihedral angle between C-11 and the carbonyl oxygen changes from *ca.* 120° to *ca.* 170° in **102** and **106**, respectively. Hence the results for **102** and **106** are consistent with the suggestion that the dihedral angle between the carbonyl oxygen and the site of β-proton abstraction must be $\leq$ *ca.* 130° for β-enolization to occur readily. The observed reluctance of **105** to rearrange *via* β-enolization at C-11 is also in agreement with the proposed orientational effect since its six-membered ring presumably favours a boat-like conformation because of the *endo*-t-butyl group. Therefore the dihedral angle between C-11 and the carbonyl oxygen is *ca.* 170°.

The isomerization of **104** → **107** under strongly basic conditions occurs by β-enolization at C-7 of **104**,



which is analogous to the racemization process reported for 3,3-dimethylbicyclo[3.2.1]octan-2-one (3).



An inspection of molecular models indicates that the dihedral angle between C-7 and the carbonyl oxygen in 104 ca. 90° while the angle defined by C-8 and the carbonyl oxygen is ca. 170°. Clearly the behaviour of 104 under homoenolization conditions is consistent with the proposed orientation effects. The apparent stability of the rearranged product 107 is more difficult to rationalize since its six-membered ring can adopt a chair-like conformation and hence, was expected to rearrange to 108 under the conditions employed.

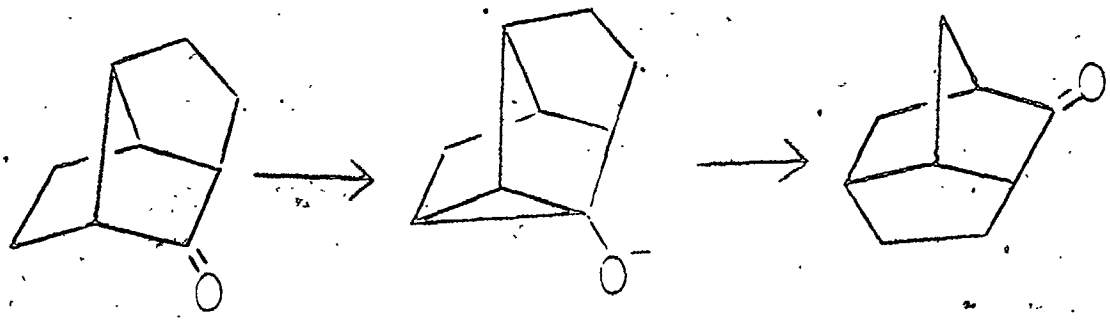
In summary, the behaviour of 104, 105 and 106 under strongly basic conditions supports the suggestion that the rate of rearrangement *via* β-enolization is influenced by the relative orientation of the carbonyl group and the site of proton abstraction. At present it seems most reasonable to conclude that this orientation effect is due to the orbital overlap of the incipient negative charge and the antibonding orbitals of the carbonyl group (which are minimized when the dihedral angle is ≤ 130°), although clearly additional data are required to confirm this interpretation.

CHAPTER II

REARRANGEMENTS VIA HOMOENOLIZATION IN SUBSTITUTED BICYCLO[2.2.1]HEPTANONES

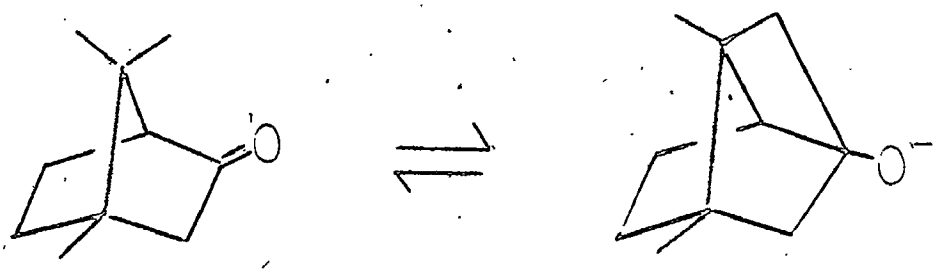
(A) INTRODUCTION

The synthetic potential of skeletal rearrangements via homoenolate anions to generate systems otherwise difficult to obtain by other routes was first demonstrated by Nickon et al. (5), who found that brexan-2-one when treated with t-BuO⁻/t-BuOH at 185°C rearranged to brendan-2-one.



Since this discovery, several examples of homoenolate rearrangements of acyclic and polycyclic systems have been reported (16). To gain further information on both the synthetic scope and mechanistic features of homoenolization the behaviour of 3,3,7,7-tetramethylbicyclo[2.2.1]heptan-

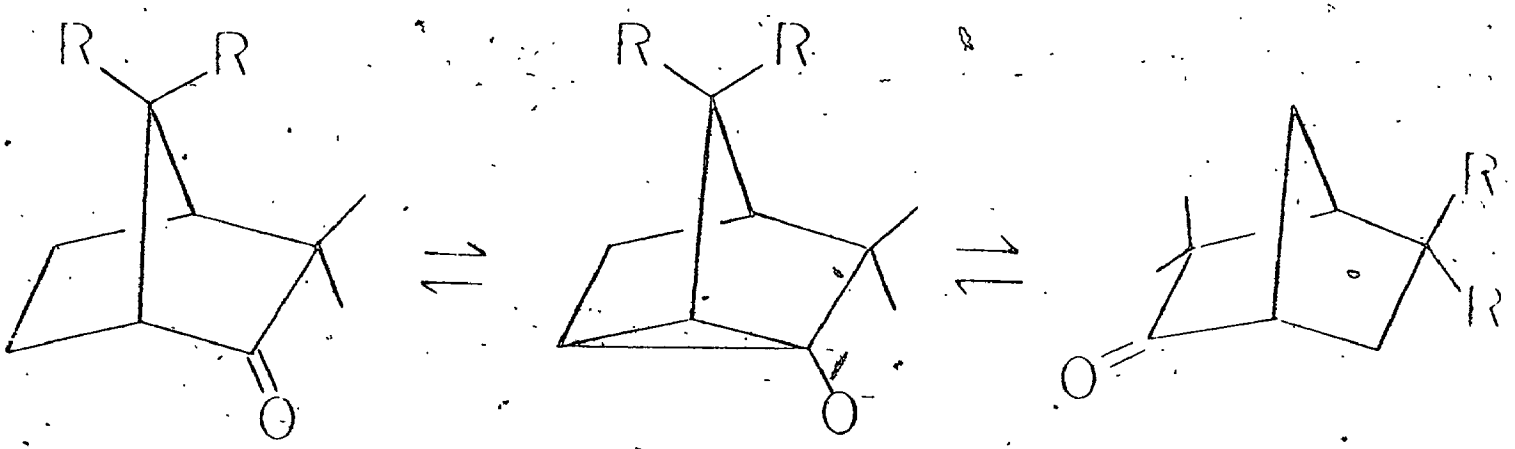
2-one (116a) and 3,3-dimethyl-7-spirocyclopropylbicyclo-[2.2.1]heptan-2-one (116b) under strongly basic conditons was examined. As shown in Scheme 11.1 homoenolization of 116a could, in principle, afford the highly hindered 3,3,5,5-tetramethylbicyclo[2.2.1]heptan-2-one (117a), which is one of the few tetramethylnorbornanones not yet synthesized. Alternatively, homoenolization of 116b (see Scheme 11.1) could yield 3,3-dimethyl-5-spirocyclopropylbicyclo[2.2.1]heptan-2-one (117b), which upon hydrogenolysis will furnish 117a. Furthermore, since camphor undergoes slow $^{1}H/^{2}H$ exchange at the syn-7-methyl on treatment with t-BuO$^-$/t-BuOD (185°C), it is conceivable



that 116a could isomerize via the Y-enolate 118.

(B) SYNTHESIS

Following the method described by Turro and Farrington (54) and outlined in Scheme 11.2, 7-spirocyclopropylbicyclo[2.2.1]heptan-2-one (120) and 7,7-dimethylbicyclo[2.2.1]heptan-2-one (121) were readily prepared from 63. Treatment of 120 and 121 with $NaNH_2$-Et_2O-MeI furnished 116b and 116a, respectively. The ^{13}Cmr spectrum of 116b

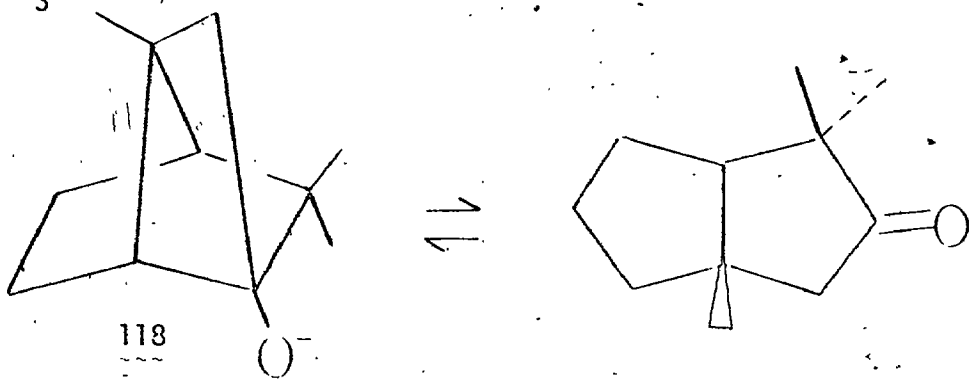


116a (R = $-CH_2-$)
116b (R = CH_3)

119a
119b

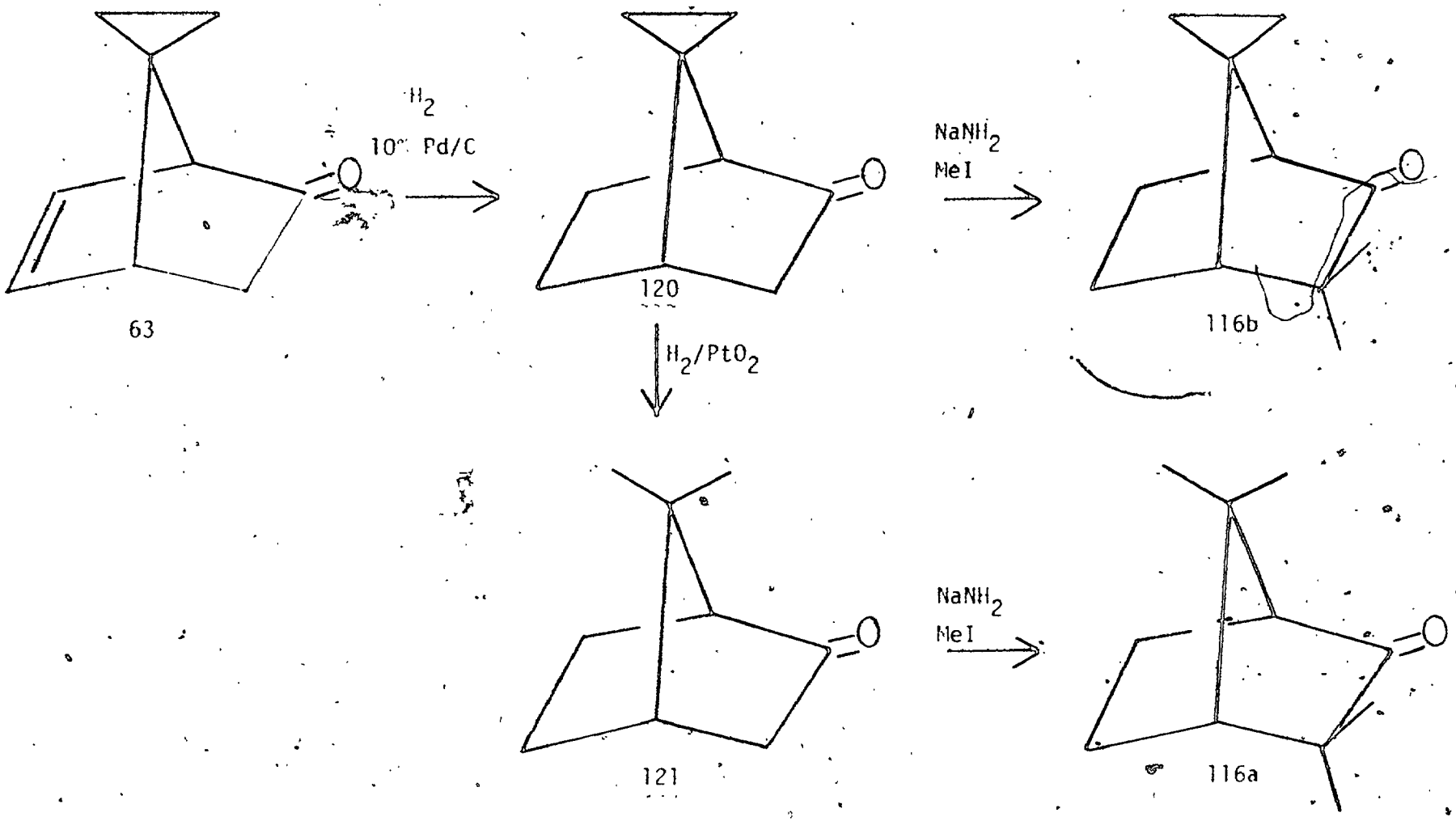
117a
117b

for R = CH_3



118

SCHEME 11.1



SCHEME 11.2

consisted of eleven signals: CH_3, 22.1, 23.3; CH_2, 3.8, 8.9, 23.6, 24.7; CH, 55.1, 55.5; C, 32.3, 49.5 and C=O, 221.8. To aid the assignments for 116b, the ^{13}Cmr assignments of 120 were unequivocally established by determination of the $^{13}C,^{13}C$ spin coupling constants from the 1-D INADEQUATE spectrum and these data are shown in Figure 11.1. The assignments for 116b, shown in Figure 11.2, readily followed by consideration of the effects expected for the methyl substituents on the shieldings of 120. The proton spectrum of 116b contained two methyl signals at δ 1.20 and 1.07 and three complex absorptions at δ 0.27-0.52 (2H), 0.73-0.97 (2H) and 1.49-2.19 (6H). The infrared spectrum exhibited absorptions at 3070 (cyclopropyl CH_2), 2960 and 1742 cm^{-1}, and precise mass measurement showed its molecular formula to be $C_{11}H_{16}O$. These data are consistent with structure 116b.

Ketone 116a exhibited a ^{1}Hmr spectrum having methyl singlets at δ 1.04, 1.09, 1.13 and 1.23, a one-proton multiplet at δ 1.47 and complex absorption at δ 1.68-2.10 (5H). Its ^{13}Cmr spectrum contained eleven signals: CH_3, 22.8, 25.2, 26.4, 27.4; CH_2, 23.3, 23.4; CH, 53.2, 59.4; C, 47.0, 45.0 and C=O, 224.2 which were readily assigned from the ^{13}C shieldings for 121, which had been reported (69); these data are shown in Figure 11.3. The ir spectrum contained absorptions at 2960 and 1750 cm^{-1} and, as shown by precise mass measurement, its molecular formula is $C_{11}H_{18}O$. These data agree well with structure 116a.

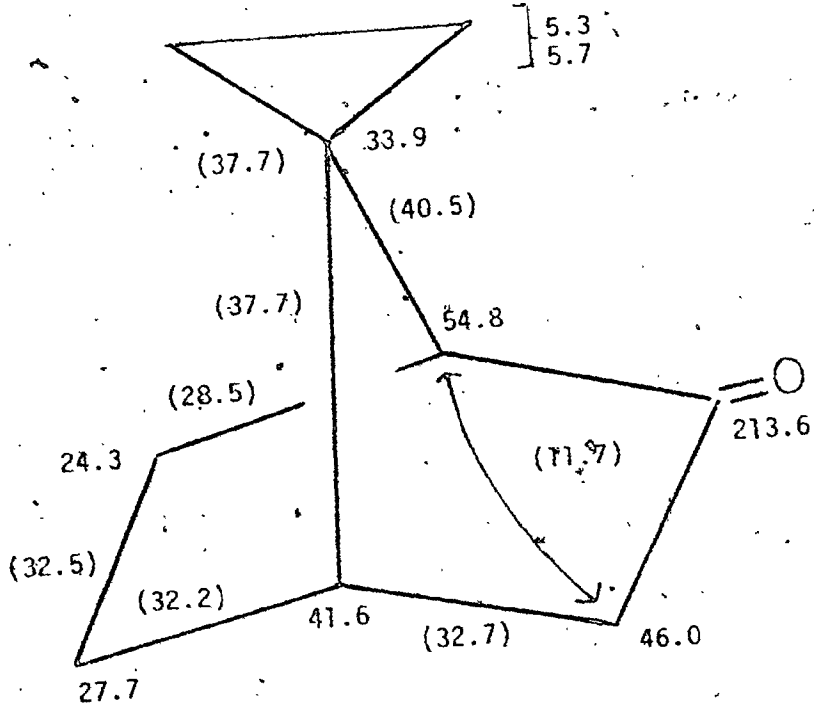


FIGURE 11.1 ^{13}C Shielding Data (δ_C) for Coupling Constants (in Hz) for 120

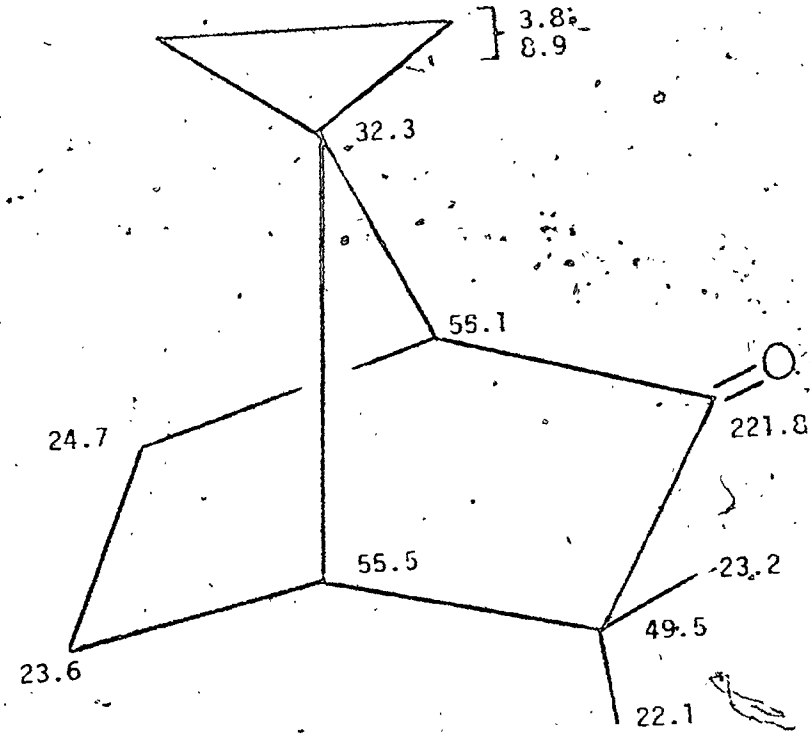
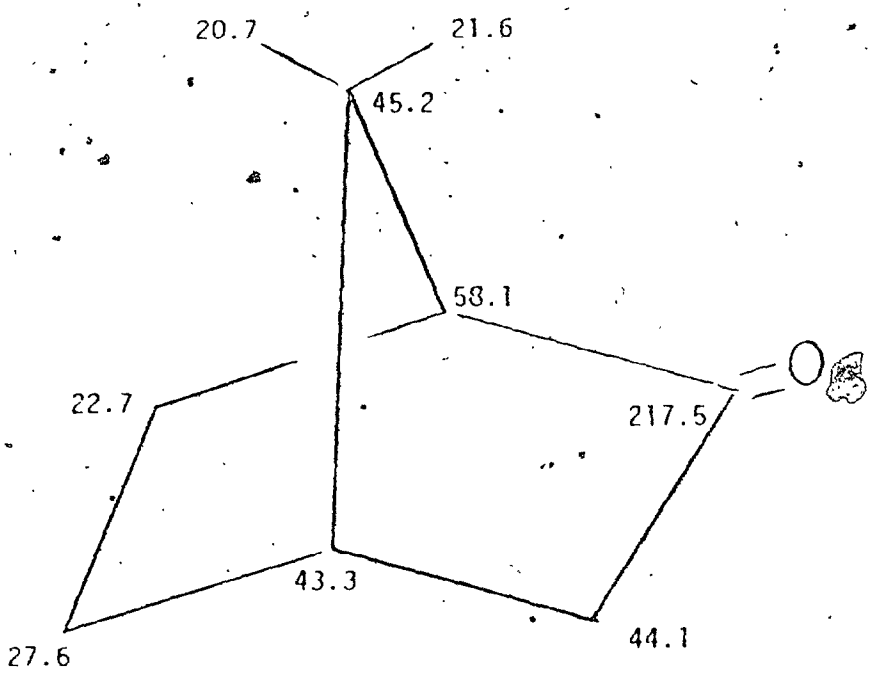
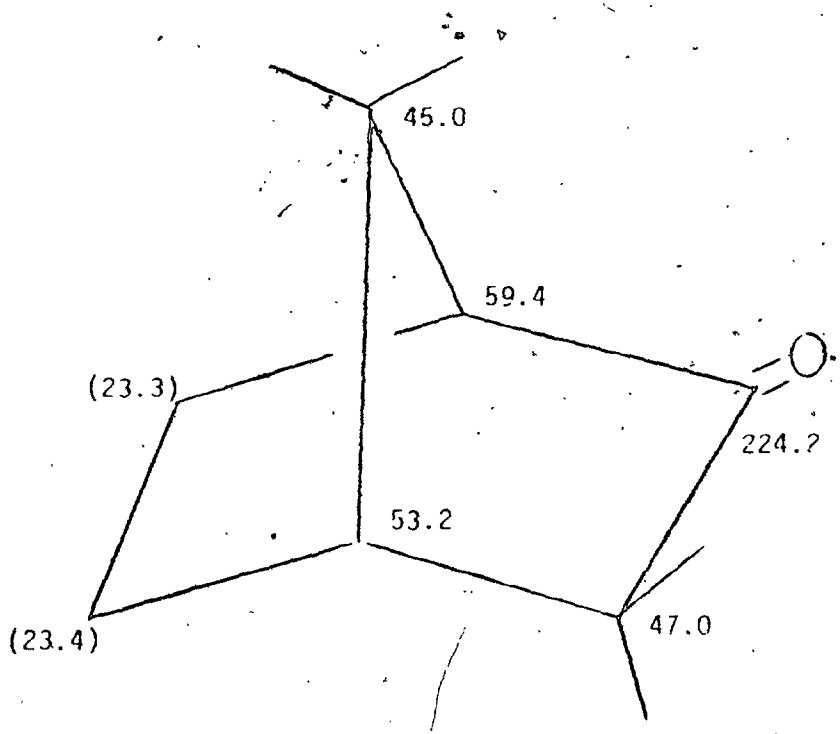


FIGURE 11.2: ^{13}C Shielding Data (δ_C) for 116b



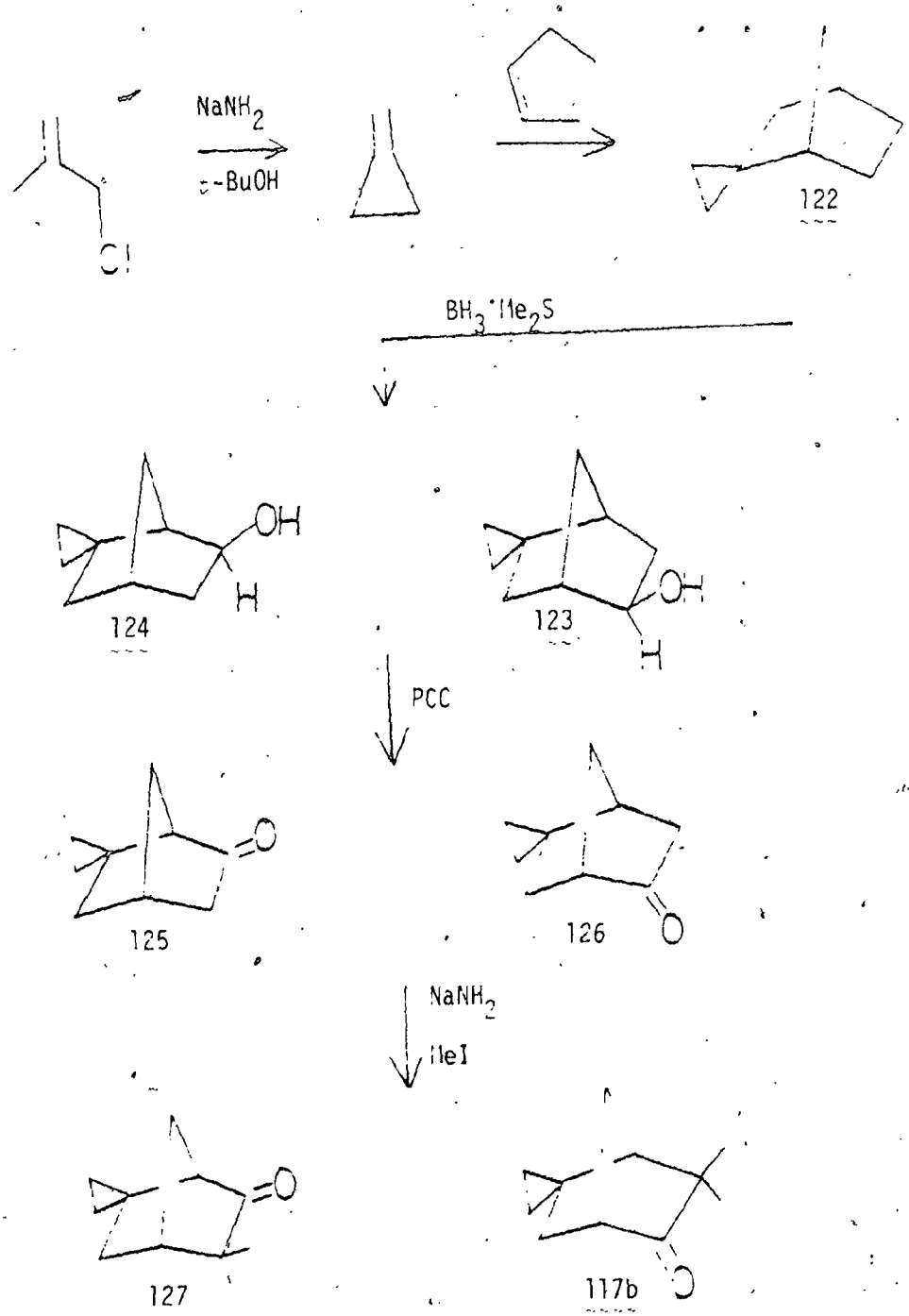


Me = 22.9, 25.2, 26.4, 27.4

FIGURE 11.3: ^{13}C Shielding Data (δ_C) for 116a and 121 (69)

To facilitate the analysis of the product mixture from homoenolization of 116b a sample of 117b was prepared by an alternative route as outlined in Scheme 11.3. Treatment of 2-methyl-3-chloropropene with sodium amide in t-BuOH and THF gave methylenecyclopropane (70), which was reacted with cyclopentadiene to yield the known olefin 122 (71). Hydroboration of 122 with 1.0 M borane-methyl sulfide complex furnished a 1:1 mixture of alcohols 123 and 124, which were not separable by gas-liquid or thin layer chromatography. Oxidation of the alcohols with PCC afforded the corresponding ketones 125 and 126, which were also not separable. Treatment of the mixture with $NaNH_2$-Et_2O-MeI for three cycles furnished the desired dimethylated analogs 117b and 127, which were separable by glc.

Ketone 117b was found to have the molecular formula $C_{11}H_{16}O$, by precise mass measurement, and its infrared spectrum contained absorptions at 3080 (cyclopropyl CH_2), 2990 and 1740 cm^{-1}. The ^{13}Cmr spectrum contained eleven signals: CH_3, 23.0, 23.4; CH_2, 11.0, 13.9, 35.4, 35.8; CH, 51.9, 54.3; C, 22.4, 48.0 and C=O, 222.8 which were readily assigned, as shown in Figure 11.4. The ^1Hmr spectrum gave further support for the tricyclic structure of 117b. Three high-field multiplets at δ 0.26 (1H), 0.47 (1H), and 0.69-0.81 (2H) were readily ascribed to the cyclopropyl protons and the methyl signals appeared as sharp singlets at δ 1.02 and 1.17. A one-


NaNH2
t-BuOH
Cl
122
BH3·Me2S
OH
H
124
OH
H
123
PCC
125
126
NaNH2
MeI
127
117b

SCHEME 11.3

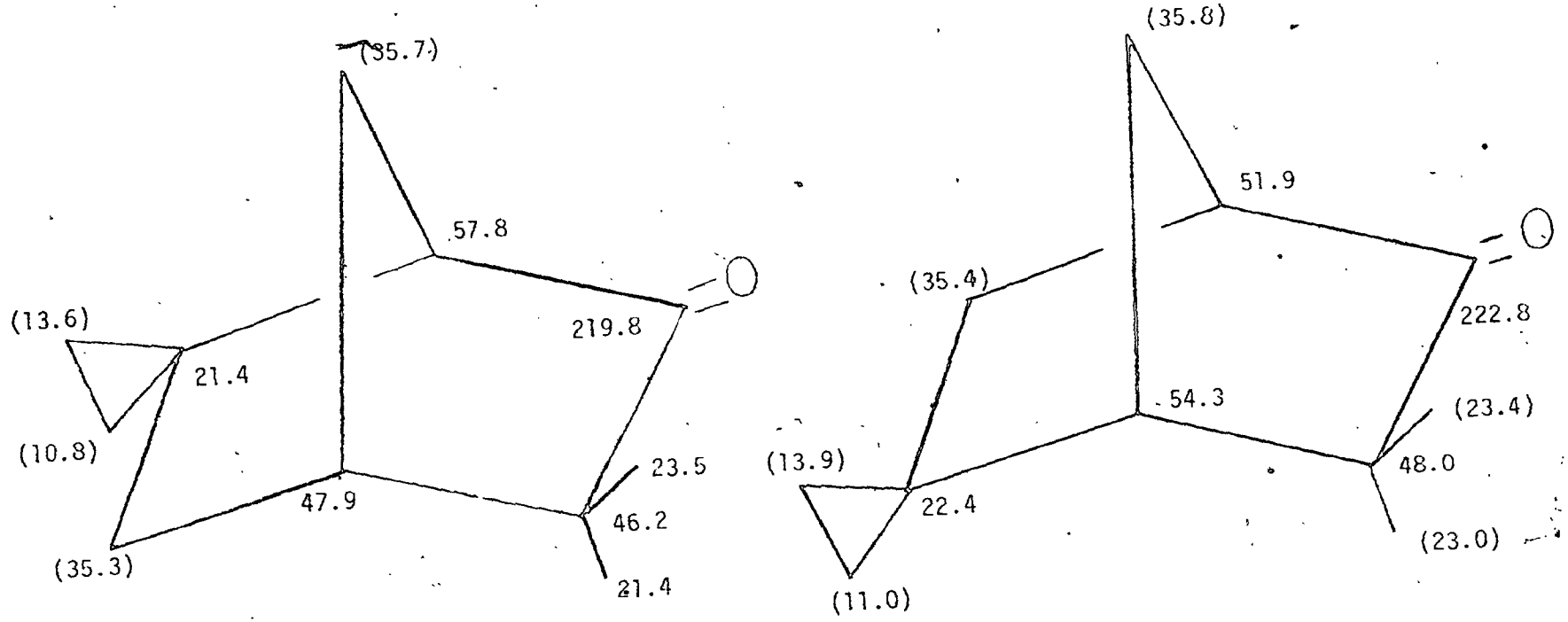


FIGURE 11.4: ^{13}C Shielding Data (δ_C) for 117b and 127

proton doublet of doublets at δ 1.79 (J = 12.4, 5.4 Hz) coupled to a broadened doublet at δ 1.66 (J = 12.4 Hz) and a multiplet at δ 2.67 (J = 5.4 Hz) were assigned to exo-H-6, endo-H-6, and H-1, respectively. A broadened one-proton singlet at δ 1.48 was attributed to H-4 and the absorptions for the syn- and anti-7-protons appeared at δ 2.02 and 1.99 as an AB pattern (J = 11.4 Hz), with additional small couplings to H-1 (J = 1.5 Hz) and H-4 (J = 1.5 Hz). These coupling interactions were confirmed by homonuclear decoupling experiments.

The second ketonic product 127 exhibited an ir spectrum containing absorptions at 3030 (cyclopropyl CH_2), 2921 and 1737 cm^{-1}. The ^{13}Cmr spectrum contained eleven signals: CH_3, 21.4, 23.5; CH_2, 10.8, 13.6, 35.3, 35.7; CH, 47.9, 57.8; C, 21.4, 46.2 and C=O 219.8 which were readily assignable as shown in Figure 11.4. Its ^1H spectrum contained six one-proton multiplets, one four-proton multiplet and two methyl singlets at δ 1.08 and 1.10. The cyclopropyl methylene protons appeared as a complex absorption at δ 0.43-0.73. A one-proton doublet of doublets at δ 1.84 (J = 12.5, 3.6 Hz) coupled to a multiplet at δ 2.33 (J = 3.6 Hz) and a four-line pattern at δ 1.64 (J = 12.5 Hz) were assigned to exo-H-5, H-4 and endo-H-5, respectively. The additional coupling for endo-H-5 (J = 2.5 Hz) arises from a long range w coupling to syn-H-7 at δ 2.05 (br.d, J = 10.5 Hz). The large 10.5 Hz coupling for syn-H-7 was readily attributed to the

geminal interaction with *anti*-H-7 at δ 1.89 (ddd, J = 10.5, 1.4, 1.4 Hz). The remaining two 1.4 Hz splittings for *anti*-H-7 were due to coupling with H-4 and H-1 (δ 1.76, m). These coupling interactions were confirmed by homonuclear decoupling experiments.

(C) HOMOENOLIZATION EXPERIMENTS

Following the usual procedure, 116a was dissolved in t-BuO⁻/t-BuOH (1.26 M) to furnish a solution 0.26 M in 116a. The reaction solution was then transferred to a series of glass tubes under nitrogen, sealed under vacuum and heated to 185°C for varying periods of time. The neutral product (> 80% recovery) from each tube was isolated by pentane extraction and analyzed by gas-liquid chromatography and ^{13}Cmr. While glc analysis indicated that only one component was present in the neutral product, its ^{13}Cmr spectrum clearly showed that the product mixture consisted of 116a and the isomeric 117a (δ_C 223.7). The proportions of ketones 116a and 117a as a function of time are given in Table II.1. From these data it is apparent that the new component (117a) reaches a maximum concentration of 17% after ca. 200 h at 185°C. Two additional tubes containing a 1:1 mixture of 116a and 102 were prepared in a similar manner and heated to 200°C. The product obtained after 344 h contained ca. 45% 103, 5% 102, 8% 117a and 42% 116a. With the efficient isomerization of 102 to 103, the low yield of 117a cannot be attributed to reduced base strength because of the presence of water.

TABLE 11.1: Composition of the neutral product from homoenolization (185°C) of 116a

Temperature (°C)	Time (h)	Product (%)[a] 116a	117a
185	60.5	93	7
	192.0	86	14
	256.0	83	17
200	246.0	80[b]	20
	344.0	83[b]	17

[a]Relative proportions were determined from the ^{13}Cmr spectra ± 10%.

[b]Determined from treating a 1:1 mixture of 102 and 116a.

Therefore these data indicate that the 83:17 mixture of 116a and 117a represents the equilibrium value.

Eleven signals in the ^{13}Cmr spectrum of the neutral product derived from treating 116a with t-BuO$^-$/t-BuOH (185°C) for 256 h, were due to ketone 117a: CH_3, 24.3, 27.7, 29.2, 34.6; CH_2, 35.6, 41.4; CH, 50.9, 58.1; C, 38.2, 49.0 and C=O, 223.7, which were assigned as shown in Figure 11.5.

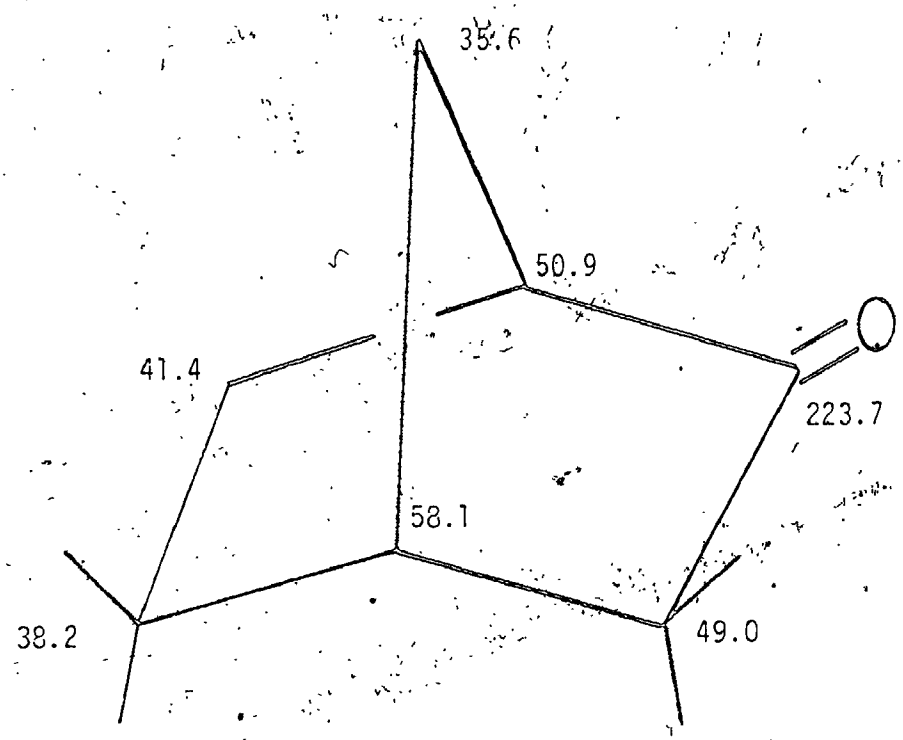
To confirm this structure and to develop a more efficient synthesis of 117a, the behaviour of 116b under strongly basic conditions was examined at 185°C for varying periods of time. The neutral product (quantitative recovery) from each tube was isolated by pentane extraction and examined by ^{13}Cmr. The spectrum of the product from a 90 h run contained two sets of signals in a ratio of 3:7, which were readily attributed to 116b and 117b, respectively. Since neither the neutral product mixture nor the corresponding LAH reduction products could be resolved by gas-liquid or thin layer chromatography, the distribution of 116b and 117b in the neutral fractions was determined by ^{13}Cmr and these results are given in Table 11.2. From these data it is apparent that 117b reaches a maximum concentration of ~ 70% in ca. 60 h.

To confirm the equilibrium distribution of 116b and 117b, ketone 117b was treated with t-BuO$^-$/t-BuOH (1.26 M) at 185°C for varying periods of time. The neutral product (> 92% recovery) from each tube was isolated and

TABLE 11.2: Composition of the neutral product from homoenolization (185°C) of 116b

Time (h)	Product (%)[a] 116b	117b
5	76	24
10	58	42
18	53	47
90	30	70
187	33	67

[a]Relative proportions were determined from the ^{13}Cmr spectra ± 10%.



Me = 24.3, 27.7, 29.2, 34.6

FIGURE 11.5: ^{13}C Shielding Data (δ_C) for 117a

analyzed in the manner described above. The compositions of the neutral fractions are given in Table 11.3, and show that, at equilibrium, 117b is favoured over 116b by a factor of approximately two.

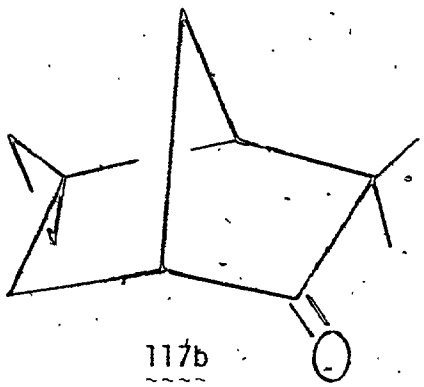
The behaviour of ketone 127 under strongly basic conditions was also examined following the usual procedure. In contrast to 116a, 116b, and 117b, but not unexpectedly, ketone 127 showed no reaction even after > 400 h at 185°C.

Having established that 116b and 117b are interconvertible under strongly basic conditions, attention was turned to the conversion of 117b → 117a. Hydrogenation (54) of the product mixture from homoenolization of 116b (187 h at 185°C) furnished a 37:63 mixture (95% recovery) of ketone 116a and an alcohol, 128 (3360 cm^{-1}). Thus, hydrogenolysis of the spirocyclopropyl rings in 116b and 117b occurred as well as reduction of the carbonyl of 117b, as shown in Scheme 11.4. The ^{13}Cmr spectrum of alcohol 128 contained eleven signals: CH_3, 22.8, 29.2, 34.1, 34.9; CH_2, 34.6, 35.8; CH, 44.0, 59.5, 79.1 and C, 38.2, 49.0 and the proton spectrum displayed four methyl singlets at δ 1.03, 1.05, 1.11 and 1.22 with multiplets centred at δ 0.90 (2H, m), 1.38 (1H, m), 1.60 (3H, m), 2.31 (1H, m) and 3.74 (1H, bt J = 4.5 Hz). The latter signal was readily attributed to the 2-proton and upon addition of D_2O this pattern collapsed to a broadened doublet (J = 4.5 Hz), thereby establishing that the hydroxyl group was in the

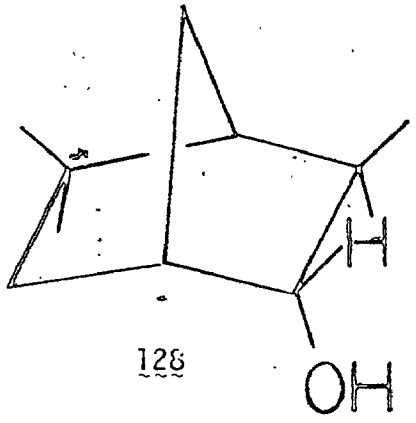
TABLE 11.3:. Composition of the neutral product from homoenolization (185°C) of 117b

Time (h)	Product (%)[a] 117b	116b
10	90	10
20	88	12
30	77	23
43	70	30
108	70	30

[a]Relative proportions were determined from the ^{13}Cmr spectra ± 10%.

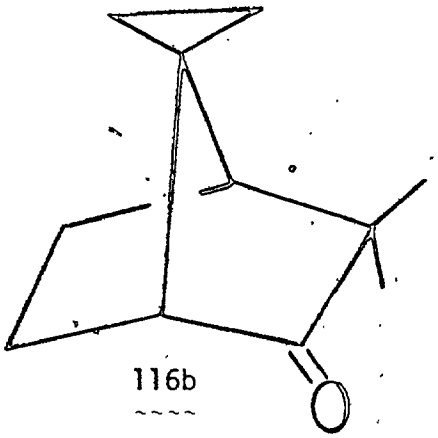


117b

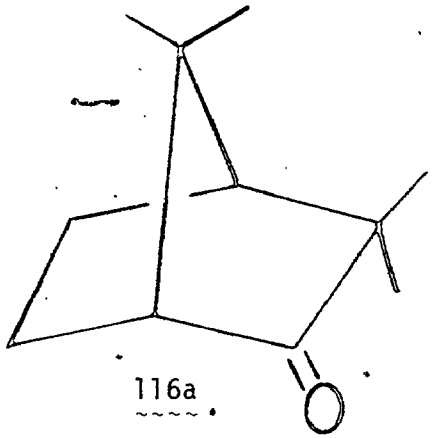


128

H_2/PtO_2



116b



116a

SCHEME 11.4

endo position. A precise mass measurement showed the molecular formula to be $C_{11}H_{20}O$ which in conjunction with the ^{13}C and ^{1}Hmr data is consistent with structure 128.

Treatment of 128 with PCC furnished ketone 117a in 89% yield. Its proton spectrum contained six one-proton multiplets and three methyl singlets at δ 1.14 (3H), 1.17 (3H) and 1.23 (6H). A one-proton eight-line pattern at δ 1.76 (J = 13.2, 5.8, 1.2 Hz) coupled to two one-proton multiplets at δ 2.52 (J = 5.8 Hz) and δ 1.83 (J = 1.2 Hz) and a broadened doublet of doublets at δ 1.39 (J = 13.2, 1.8 Hz) were readily ascribed to exo-H-6, H-1, H-4 and endo-H-6, respectively. The remaining coupling for endo-H-6 (J = 1.8 Hz) was attributed to a long range w interaction with the syn-7-proton at δ 1.94 (m). The remaining multiplet at δ 2.00 was ascribed to the anti-7-proton. These coupling interactions were confirmed by homonuclear decoupling experiments. A precise mass measurement showed the molecular formula to be $C_{11}H_{18}O$ and its ^{13}Cmr spectral data were identical to those obtained for the homoenolate rearrangement product of 116a. On the basis of these data, this ketone is 117a.

To confirm that ketones 116a and 117a are interconvertible under strongly basic conditions, 117a was treated with t-BuO⁻/t-BuOH at 185°C for 85 h. Upon work-up, it was established by ^{13}Cmr that the neutral product (> 90% recovery) consisted of a ~ 1:1 mixture of 116a and 117a.

(D) CONCLUSION

With the structure of 117b confirmed by independent synthesis, the conversion of 116b → 117b must occur by deprotonation at C-6 to yield the β-enolate 119b, which then suffers cleavage of the original C-1,2 bond to generate 117b or returns to starting material. The hydrogenation of 117b and subsequent oxidation completed the synthesis of 117a. Its ^{13}C spectral data clearly showed that ketone 117a is formed by homoenolization of 116a. This conclusion was confirmed by treating 117a with t-BuO⁻/t-BuOH at 185°C to furnish a mixture of 116a and 117a clearly demonstrating that these ketones are interconvertible *via* β-enolate 119a. Presumably, at equilibrium, 116a is favoured because it is less strained. The product from homoenolization of 116a also clearly established that rearrangement *via* Y-enolate 118 is insignificant.

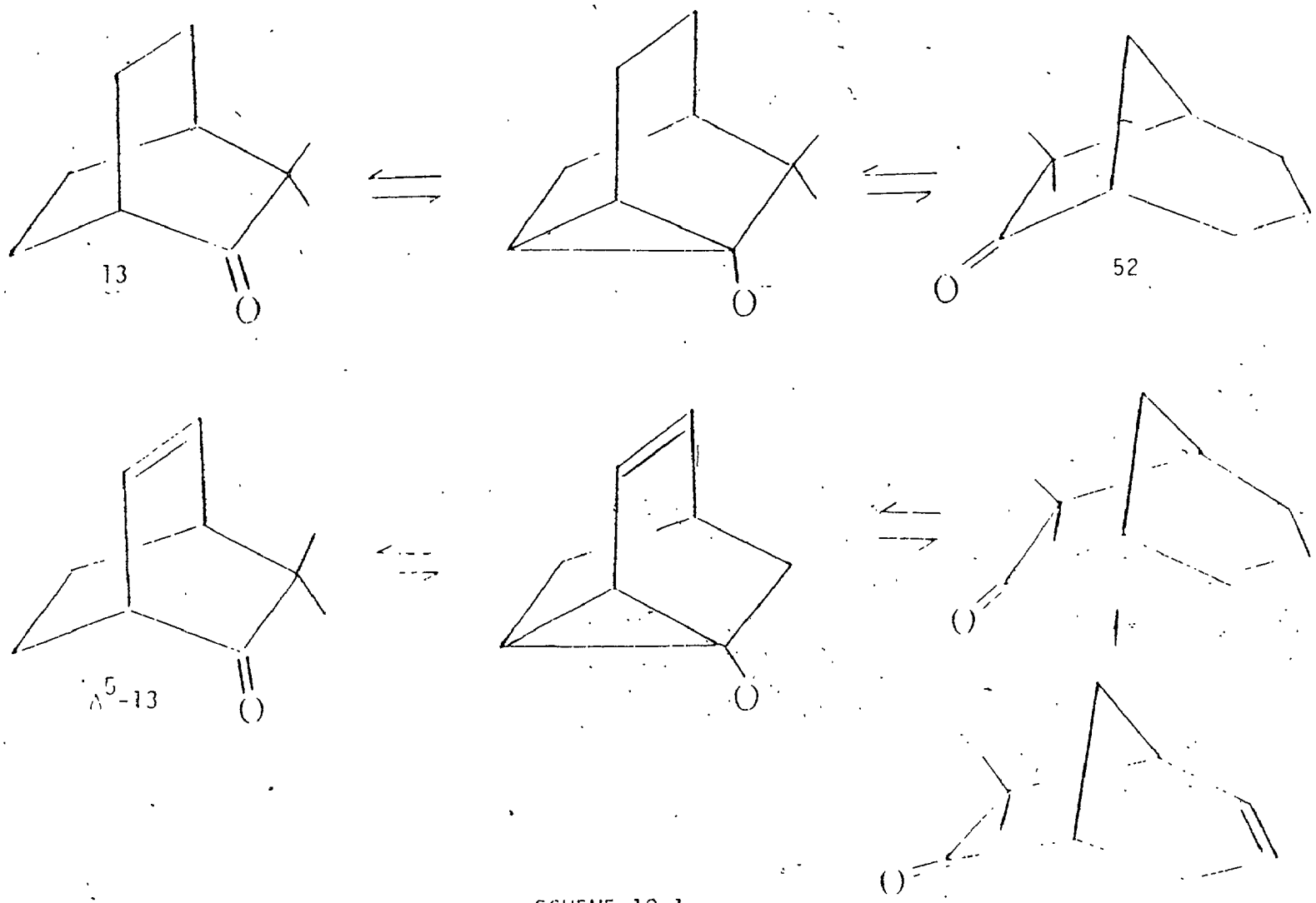
CHAPTER 12

HOMOENOLIZATION OF 3,3-DIMETHYL-7-ISOPROPYLIDENE-BICYCLO[2.2.1]HEPTAN-2-ONE

(A) INTRODUCTION

A study by Stothers et al (72) of 3,3-dimethyl-bicyclo[2.2.2]octan-2-one (13) and 3,3-dimethylbicyclo-[2.2.2]oct-5-en-2-one (Δ^5-13) in strongly basic media had shown that the [2.2.2] and [3.2.1] skeletons are inter-convertible, as shown in Scheme 12.1. From more detailed studies (10,15) it was found that at equilibrium 52 was favoured over 13 by a factor of 4, and the half-life for equilibration was > 500 h at 185°C. In contrast, equilibration of Δ^5-13 and $\Delta^2(\Delta^3)$-52 (185°C) was attained rapidly, with a half life of approximately 7 h, to yield a 8:48:44 mixture of Δ^5-13, Δ^2- and Δ^3-52, respectively. Clearly the introduction of the double bond into the [2.2.2] system enhances its reactivity towards β-enolate formation and subsequent rearrangement to the [3.2.1] skeleton. In addition, the double bond tends to increase the bias of the equilibrium towards the latter system.

Since homoenolate anions have synthetic utility it was of interest to define more precisely the rate accelerating effect of a β,Y double bond on the isomerization process in other polycyclic systems. For



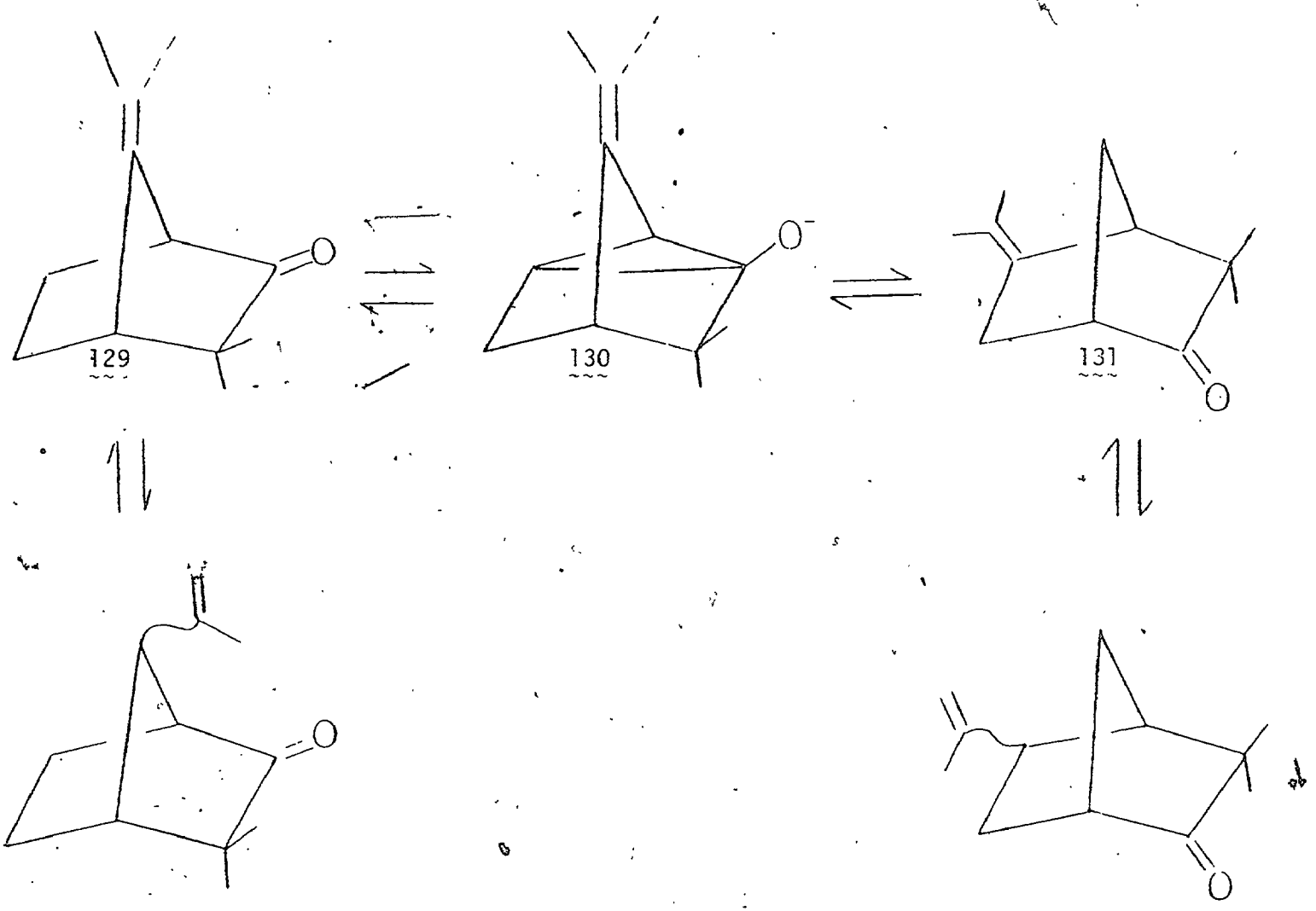
SCHEME 12.1

this purpose the behaviour of 3,3-dimethyl-7-isopropylidenebicyclo[2.2.1]heptan-2-one (129) under strongly basic conditions was examined. By analogy with previous studies of [2.2.1] systems (16), it was anticipated that β-proton abstraction could occur at C-6, resulting in the formation of 130 (Scheme 12.2), subsequent cleavage of which could regenerate 129 or give 131. Both of these ketones could, in principle, undergo isomerization of the double bond, to yield a variety of isomers.

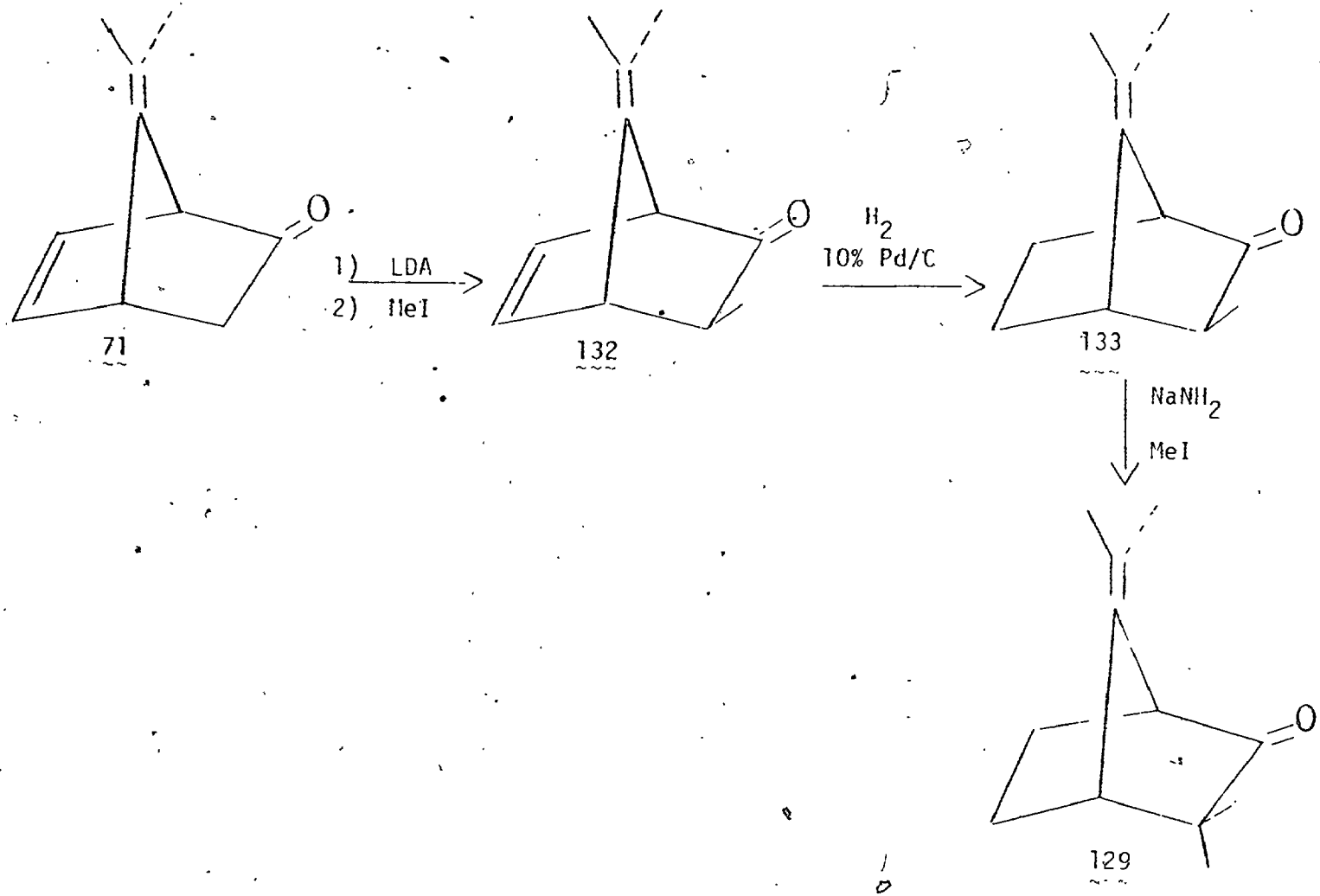
(B) SYNTHESIS

Ketone 129 was prepared from 7-isopropylidenebicyclo[2.2.1]hept-5-en-2-one (71), as shown in Scheme 12.3. Since hydrogenation of 71 has been reported (58) to occur at both sites of unsaturation, it was anticipated that hydrogenation of the less hindered 5,6-double bond in ketone 132 may be favoured. Hence, ketone 71 was methylated under kinetic control and the ^1H spectrum of the product clearly showed that *exo*-methylation had occurred since H-3 (δ 2.14), was coupled only to the 3-methyl protons (J = 7.3 Hz), indicative of its *endo* orientation. Hydrogenation of 132 at atmospheric pressure afforded 133 in quantitative yield which, upon treatment with $NaNH_2$-Et_2O-MeI furnished the desired dimethylated analog 129.

Ketone 129 (1747 cm^{-1}, CCl_4), $C_{12}H_{18}O$ (by precise mass measurement), exhibited a ^1Hmr spectrum having



SCHEME 12.2



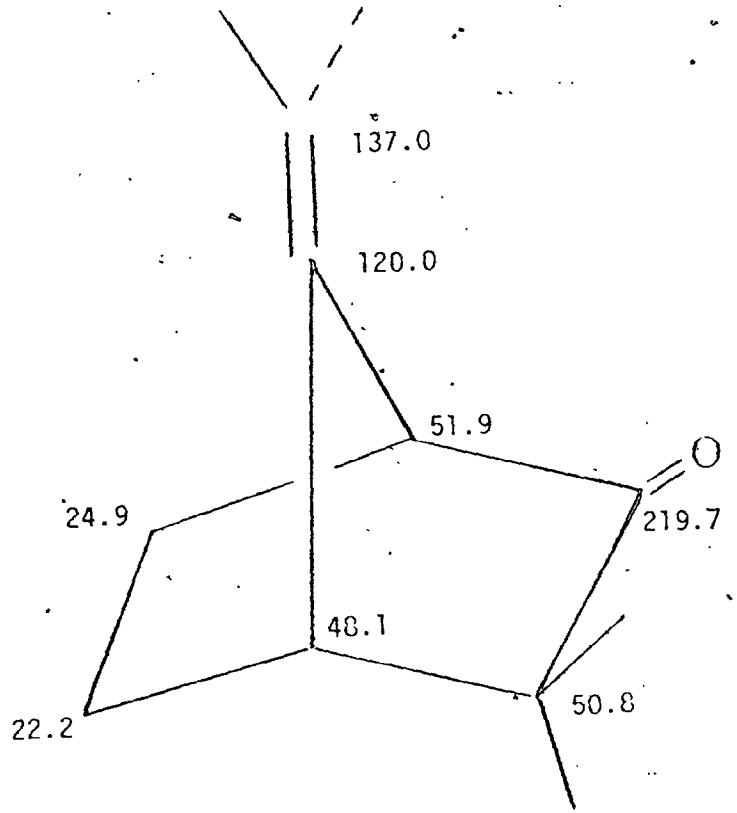
71 132 133 129

SCHEME 12.3

prominent methyl singlets at δ 1.03, 1.07, 1.68 and 1.73 with multiplets at δ 3.06 (1H, dd J = 5.2, 1.5 Hz), 2.64 (1H, dd J = 5.2, 1.5 Hz) and complex absorptions at δ 1.76-1.92 (2H, m) and δ 1.50-1.68 (2H, m). Its ^{13}Cmr spectrum had eleven signals (δ_C, $CDCl_3$): CH_3, 20.0, 20.3, 20.6, 24.4; CH_2, 22.2, 24.9; CH, 48.1, 51.9; C, 50.8, 120.0, 137.0 and C=O, 219.7. These data are entirely consistent with structure 129 as shown in Figure 12.1. A comparison of the carbonyl shielding for ketone 116a (δ_C 224.2, $CDCl_3$) and 129 revealed that the latter was shifted upfield by 4.5 ppm. Similar upfield shifts have been found for a variety of β,γ unsaturated polycyclic ketones (73) and have been attributed to homoconjugation.

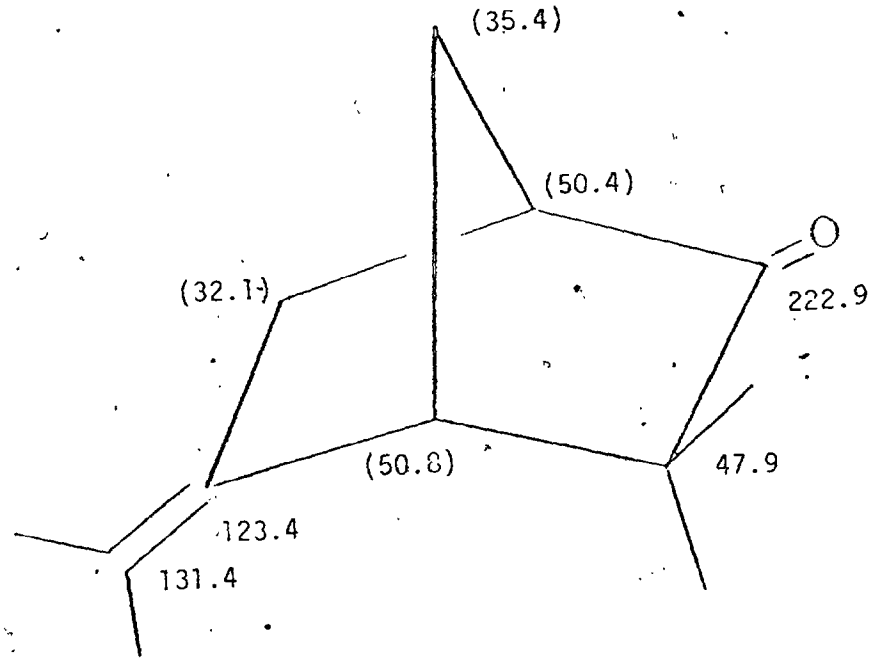
(C) HOMOENOLIZATION EXPERIMENTS

Following the usual procedure, ketone 129 was dissolved in t-BuO$^-$/t-BuOH (1.26 M) to furnish a solution 0.26 M in 129. Aliquots of this solution were transferred to glass tubes under nitrogen, sealed under vacuum, and immersed in an oil bath at 185°C for varying periods of time. Although the contents of each tube were dark brown in colour upon removal from the oil bath, the neutral product, isolated by pentane extraction, represented > 90% recovery. Glc analysis of the neutral product showed that ketone 129 and a new component 131, constituted > 95% of the product. The proportions of 129 and 131 in the neutral fraction as a function of time are given in Table 12.1,



Me = 20.0, 20.3, 20.6, 24.4

FIGURE 12.1: ^{13}C Shielding Data (δ_C) for 129



Me = 20.1, 21.0, 21.8, 22.5

FIGURE 12.2: ^{13}C Shielding Data (δ_C) for 131

TABLE 12.1: Composition of the neutral product from homoenolization (185°C) of 129

Time (h)	Product (%)[a] 129	131
8	45	55
25	20	80
44	7	93
98	5	95

[a]Determined by glc (FFAP) ± 3%.

showing that the amount of 131 reaches a maximum of - 95% after ca. 60 h. A sample of 131 was readily obtained by preparative glc and the remaining minor components were not investigated.

The ir spectrum of 131 contained two strong absorptions at 2964 and 1753 cm^{-1}, and precise mass measurement showed the molecular formula to be $C_{12}H_{18}O$. Its ^{13}Cmr spectrum had eleven signals (δ_C, $CDCl_3$): CH_3, 20.1, 21.0, 21.8, 22.5: CH_2, 32.1, 35.4; CH, 50.4, 50.8; C, 47.9, 123.4, 131.4 and C=O, 222.9. These shieldings were readily assignable to the bicyclic structure 131, as shown in Figure 12.2. A comparison of the carbonyl shielding for 129 (δ_C 219.7, $CDCl_3$) with that for 131, shows that the latter is shifted upfield by 3.2 ppm, which is consistent with reduced interaction with the Y,δ double bond (73). The proton spectrum of 131 provided further support for the assigned structure. The two highest field singlets at δ 0.94 and 1.10 were readily attributed to the 3-methyl groups. The methyl signals of the isopropylidene substituent, deshielded by the double bond, absorbed at δ 1.64 (br.s) and δ 1.73 (dd J = 1.7, 1.7 Hz) and were coupled to *endo*-H-6 and *exo*-H-6 which absorb at δ 2.03 (bd J - 16 Hz) and 2.43 (bd J - 16 Hz), respectively. Double irradiation of the *exo*-H-6 absorption changed the pattern at δ 2.73 (m), hence this multiplet was attributed to H-1. Since irradiation of the broad singlet at δ 2.92 caused no significant change in the absorption patterns for *exo*- and

endo-H-6 or H-1, this signal was assigned to H-4. The two remaining signals at δ 1.60 (bd J ~ 10 Hz) and δ 2.09 (bd J ~ 10 Hz) were attributed to the syn and *anti* 7-protons.

On the basis of these data, structure 131 was assigned to his ketone.

(D) DISCUSSION

The relatively smooth conversion of 129 → 131 shows that isomerization of the double bond in the starting material and product was insignificant. From the results of Table 12.1, the pseudo first-order rate constant for the transformation of 129 → 131 was estimated to be 2×10^{-5} sec^{-1}; a comparison of the rate of conversion of 116a → 117a (4×10^{-7} sec^{-1}) clearly indicates that the double bond of 129 increases the rate of isomerization by a factor of 100. At equilibrium, 131 is favoured presumably because of reduced strain.

These findings are similar to those for ketones 13 and Δ^5-13, demonstrating clearly that a properly orientated β,γ double bond can significantly enhance both the rate of appearance and the yield of rearranged product obtained by homoenolization.

CHAPTER 13

EXPERIMENTAL

(A) GENERAL

Melting points and boiling points are uncorrected. Gas liquid chromatography was carried out on Varian 920 and 3700 instruments, using columns of 10% Carbowax 20 M (16' x ¼"), 6% FFAP (18' x ¼"), 10% SE-30 (6' x ¼"), on Chromosorb W, as indicated. Thin layer chromatography was done on Kiesel gel 60 F_{254} plates and flash chromatography columns were prepared as described in the literature (87). Tetrahydrofuran (THF) and diethyl ether were dried over Na/benzophenone and freshly distilled before use.

Diisopropyl amine, triethyl amine, t-butyl alcohol and pyridine were distilled from CaH_2 onto 4 Å sieves; methyl iodide was dried over 4 Å sieves. Pentane and cyclopentadiene were freshly distilled before use.

Infrared spectra were recorded with a Beckmann 4250 instrument and mass spectra were obtained on a Varian MAT-311A system at 70 ev (direct inlet).

(B) NMR SPECTRA

Routine ^{1}Hmr spectra were recorded with either Varian T-60 or EM-360 instruments while data for pure

samples were collected with a Varian XL-200 or 300 instrument; ^{13}C and ^{2}Hmr were also obtained on the latter two instruments. Chemical shifts for ^{1}Hmr spectra were obtained using $CDCl_3$ or C_6D_6 solutions (ca. 10% w/v) with TMS as internal reference. The ^{13}Cmr spectra were measured in $CDCl_3$ or C_6D_6 solutions and shieldings were measured relative to TMS or the central line of the $CDCl_3$ or C_6D_6 triplets, respectively. A comparison of the fully decoupled ^{13}C spectra with those obtained either with the INEPT (88), APT (89) or DEPT (90) sequences identified the methyl, methylene, methine and quaternary carbon signals. The 1D INADEQUATE spectra (55) were obtained with the C13SAT pulse sequence of the XL software.

(C) EXPERIMENTAL FOR CHAPTER 2

Commercial camphor, norcamphor and tricyclo-[5.2.1.$0^{2,6}$]decan-8-one were employed for these studies without further purification. The preparations of bicyclo[2.2.2]octan-2-one, bicyclo[2.2.2]oct-5-en-2-one, nopinone and tricyclo[5.3.1.$0^{2,6}$]undecan-8-one have been described (10, 72, 74, 65).

Synthesis of bicyclo[3.2.1]octan-6-one (29)

A five-stage synthesis was used to obtain this compound (Scheme 2.3). Following the procedure of LaPrade and associates (75) norbornadiene was reacted with the dibromocarbene to yield mainly exo-3,4-dibromobicyclo-

[3.2.1]octadiene along with smaller amounts of the endo epimer and exo-3,6-dibromotricyclo[3.2.1.$0^{2,7}$]oct-3-ene. The norbornadiene adducts were then treated with LAH to furnish 3-bromo-bicyclo[3.2.1]octadiene (25% overall yield).

3-Bromobicyclo[3.2.1]oct-2-en-6-yl formate

A modification of the procedure of Wiberg and Hess (76) was used. The 3-bromobicyclo[3.2.1]octadiene (43.8 g, 2.38 x 10^{-1} mol) was added to a 88% formic acid solution (290 mL) and the mixture was stirred for 5 days. The mixture was then diluted with H_2O (400 mL) and neutralized with sodium bicarbonate. The product was extracted with Et_2O (2 x 100 mL) and the combined extracts were washed with H_2O and dried over Na_2SO_4. Removal of the solvent gave the desired bromoformate (51 g) in 93% yield.

Bicyclo[3.2.1]octan-6-ol

To a solution of 3-bromobicyclo[3.2.1]-oct-2-en-6-yl formate (20 g, 8.7 x 10^{-2} mol) in THF (75 mL) and 2 M aqueous NaOH solution (93 mL) was added 5% Pd on charcoal (3.70 g) and the mixture hydrogenated in a Parr shaker (50 psi H_2 pressure) for 25 h. After filtering and diluting the mixture with H_2O (100 mL), the product was extracted with pentane and the combined extracts dried over Na_2SO_4. Removal of the solvent gave exo-bicyclo[3.2.1]-octan-6-ol (9.0 g, 7.1 x 10^{-2} mol) in 82% yield, which was

pure by glc (FFAP); ^{13}Cmr shieldings agreed with reported values (61).

Bicyclo[3.2.1]octan-6-one (29)

Oxidation of *exo*-bicyclo[3.2.1]octan-6-ol (6.3 g, 5.0 x 10^{-2} mol) with sodium dichromate/H_2SO_4 in ether according to Brown et al (procedure B, 40), gave 29 (3.3 g, 63% yield) which exhibited the same ir (ν_{max} (film): 1740 cm^{-1}) and ^{13}Cmr spectra as those reported (33).

Preparation of 26-d_2, 28-d_2, 29-d_2 and 31-d_2

A modification of the procedure of Hunter et al. (77) was used to prepare 31-d_2. To a mixture of anhydrous potassium carbonate (0.02 g) and D_2O (2.00 mL) was added 31 (0.50 g, 4.1 x 10^{-3} mol) and the mixture was refluxed under a nitrogen atmosphere for 17 h. The product was then extracted with pentane (3 x 12 mL) and the combined extracts dried over Na_2SO_4. After removal of the solvent, sublimation gave 0.46 g of 31-d_2 (91% recovery) and the ^{13}Cmr spectrum of this product indicated almost complete exchange of the α-methylene hydrogens.

Following the same procedure, 26 (5.00 g, 4.54 x 10^{-2} mol) was treated with D_2O (22.70 mL) and anhydrous potassium carbonate (2.70 g), at reflux for 18 h. After an additional cycle the ^{13}Cmr spectrum of the product (4.27 g, 84%), recovered by pentane extraction, indicated almost complete exchange of the α-methylene hydrogens.

Deuteration of **28** (4.00 g, 2.67 x 10^{-2} mol) was accomplished by treatment with 1.20 g anhydrous potassium carbonate and 12 mL D_2O for four cycles of 10½, 39½, 158 and 83 h at reflux. This gave **28**-d_2 (2.10 g, 52%), and based upon its ^{13}Cmr spectrum, almost complete exchange of the α-methylene hydrogens had occurred.

Ketone **29** (2.00 g, 2.02 x 10^{-2} mol) was initially treated with a mixture of anhydrous potassium carbonate (2.5 g) and D_2O (25 mL) at reflux for 12 h, which yielded 2.00 g of **29**-d_x. The ^{13}Cmr spectrum of **29**-d_x indicated ca. 50% exchange of the α-methylene hydrogens. Hence, a solution of **29**-d_x (2.00 g) in dioxane (4 mL) was added to a 1 M NaOD-D_2O solution (25 mL) and refluxed under nitrogen for 16 h. The product was extracted with pentane (3 x 25 mL) and the combined extracts were washed with H_2O (2 x 20 mL) before drying over Na_2SO_4. Removal of the solvent gave **29**-d_2 (1.50 g, 74%) and its ^{13}Cmr spectrum showed almost complete exchange of α-methylene hydrogens.

General Procedure Employed for the Synthesis of Silyl Enol Ethers

Freshly distilled THF and diisopropylamine were added to a flame dried-flask, equipped with magnetic stir bar, serum caps and under a nitrogen atmosphere, and cooled to -78°C. Upon the addition of *n*-butyllithium in *n*-hexane via syringe, the mixture was stirred for 30-45 min before dropwise addition of a solution of the ketone in THF.

While stirring was continued for an additional 30-45 min. a quenching solution consisting of chlorotrimethylsilane, triethylamine and THF was prepared in a flame-dried, nitrogen-purged centrifuge tube. The precipitate was removed by centrifugation and the clear colorless liquid was added by syringe to the enolate solution. The reaction mixture was then stirred at -78°C for a brief period of time and then allowed to warm to room temperature. After stirring for an additional 0.5-3 h, the mixture was treated in either of two ways: (Procedure A) the addition of a cold (0°C) saturated aqueous Na_2CO_3 solution or (Procedure B) the solution was cooled to 0°C, and with vigorous stirring, a cold (0°C) saturated aqueous Na_2CO_3 was added. The product was isolated by pentane extraction and purified by Kugelrohr distillation.

Compounds **25a**, **29a**, **30a**, **31a** and **32a** were obtained following procedure A, while the remaining silyl enol ethers were recovered using procedure B. The purity of each product was usually > 90%, as determined by glc (FFAP) for all compounds except **27** and **28** which are unstable to glc conditions and hence, their purity was assessed by their ^{13}Cmr spectra.

Physical data for silyl enol ethers **25a**-**32a**:

25a: b.p. 110-115°C/10 Torr (lit. (28) 74.5-75.5°C/1.9 Torr); ir (film): 3092, 2962, 1622, 1330, 1252, 890, 848 cm^{-1}; ^{13}Cmr (C_6D_6) δ_C: 160.9 (C), 103.2 (CH),

54.9 (C), 53.7 (C), 49.9 (CH), 31.8 (CH_2), 27.9 (CH_2), 20.3 (Me), 20.0 (Me), 10.3 (Me), 0.0 ($SiMe_3$).

26a: b.p. 85-90°C/10 Torr; ir (film): 3080, 2958, 1605, 1334, 1225, 848 cm^{-1}; ^{13}Cmr (C_6D_6) δ_C: 161.5 (C), 105.0 (CH), 47.2 (CH_2), 45.9 (CH), 41.4 (CH), 28.2 (CH_2), 24.8 (CH_2), -0.1 ($SiMe_3$).

27a: b.p. 92-94°C/0.4 Torr; ir (film): 3080, 2950, 1610, 1245, 835 cm^{-1}; ^{13}Cmr (C_6D_6) shieldings agreed with literature values (27).

28a: b.p. 85-90°C/0.2 Torr; ir (film): 3059, 2950, 1660, 1246, 1181, 839 cm^{-1}; ^{13}Cmr (C_6D_6) δ_C: 158.0 (C), 97.3 (CH), 54.2 (CH), 50.1 (CH), 46.7 (CH), 40.5 (CH), 35.0 (CH_2), 33.7 (CH_2), 33.1 (CH_2), 30.3 (CH_2), 28.6 (CH_2), 0.6 ($SiMe_3$); ^{1}Hmr (C_6D_6) δ: 4.49 (1H, m), 2.95 (1H, dd J = 12.2, 8.0 Hz), 1.46-2.32 (10H, m), 0.80-1.30 (3H, m), 0.2 ($Si(Me)_3$). *Exact mass* calcd. for $C_{14}H_{24}OSi$: 236.1596; found: 236.1594.

29a: b.p. 110-115°C/15 Torr; ir (film): 3070, 2940, 1622, 882 cm^{-1}; ^{13}Cmr (C_6D_6) δ_C: 157.1 (C), 101.9 (CH), 44.1 (CH_2), 42.6 (CH), 38.0 (CH), 26.9 (CH_2), 24.6 (CH_2), 19.4 (CH_2), 0.2 ($SiMe_3$).

30a: b.p. 95-105°C/10 Torr (lit. (29) 5°C/8 Torr (29)); ir (film): 3040, 2938, 1646, 1255, 870, 835 cm^{-1}; ^{13}Cmr (C_6D_6) δ_C: 159.4 (C), 95.5 (CH), 48.4 (CH), 41.2 (CH), 38.7 (C), 31.5 (CH_2), 28.2 (CH_2) 26.2 (CH_3), 21.2 (CH_3), 0.4 ($SiMe_3$). *Exact mass calcd for* $C_{12}H_{22}OSi$: 210.1440; found: 210.1441.

31a: b.p. 60-64°C/17 Torr; ir (film): 3054, 2955, 1657, 1250, 1190, 842 cm^{-1}; ^{13}Cmr (C_6D_6): 156.3 (C), 136.0 (CH), 132.9 (CH), 105.3 (CH), 42.4 (CH), 36.0 (CH), 25.8 (CH_2), 24.8 (CH_2), 0.0 ($SiMe_3$)

32a: b.p. 64°C/17 Torr; ir (film): 3044, 2926, 1642, 1248, 1200, 914, 858 cm^{-1}; ^{13}Cmr (C_6D_6) δ_C: 159.9 (C), 105.1 (CH), 36.0 (CH), 30.4 (CH), 27.3 (CH_2 x 2), 26.4 (CH_2 x 2), 0.2 ($SiMe_3$).

The silyl enol ethers were then treated with the Simmons-Smith reagent without further purification.

Preparation of the Zinc-Silver Couple

To a hot, stirred solution of glacial acetic acid (100 mL) and silver acetate (100 mg) was added granular Zn (17 g) and the resulting mixture was stirred for 30 sec. The Zn-Ag couple formed was isolated by decantation and washed with anhydrous diethyl ether (5 x 100 mL). The Zn-Ag couple was then placed in a round bottom flask, evacuated overnight and stored in a dark place.

Cyclopropanation of 26a

A modification of the procedure of Conia et al. (26) was used to cyclopropanate 26a. To a flask fitted with a reflux condenser, nitrogen purge and magnetic stirrer was added zinc-silver couple (3.54 g, 5.41×10^{-2} mol) and the apparatus was then flame dried. After cooling, methylene iodide (2.38 g, 2.95×10^{-2} mol) in

anhydrous ether (10 mL) was added and the mixture warmed until refluxing occurred without external heating. Upon cessation of reflux a solution of 26a (2.99 g, 1.64 x 10^{-2} mol) in Et_2O (35 mL) was added and this mixture was refluxed for 25.5 h. After cooling to 0°C a pyridine-ether solution (ca. 1:1) was added till no further precipitation occurred. The resulting precipitate was removed by filtration and washed with Et_2O. After removal of solvent from the filtrate, the residue as taken up in pentane; further filtration was required to remove the last traces of precipitate. The solvent was then removed and the product (2.10 g, 65%) was isolated by Kugelrohr distillation (110-115°C/15 Torr), which glc (FFAP) indicated to contain traces (< 4%) of two impurities. An analytical sample (prep glc) was collected for characterization; ir (film): 3085, 2980, 1340, 1245, 835 cm^{-1}; ^{13}Cmr: see Table 2.1.

Following the same general procedure compounds 27a (rxn time = 25.5 h), 28a (17 h), 29a (18 h), 30a (22.5 h x 2) and 32a (6 h) were cyclopropanated. For 31a (24 h) the molar equivalents of Zn/Ag couple and methylene iodide were reduced to 2.0 and 1.3 equivalents, respectively. The physical properties of 27b-32b follow.

27b: b.p. 56-58°C/0.3 Torr, 80% recovery (> 96% pure); ir (film): 3060, 2940, 1250, 833 cm^{-1}; ^{13}Cmr: see Table 2.1). *Exact mass* calcd for $C_{14}H_{24}OSi$: 236.1596; found: 236.1601.

28b: (product was isolated by removal of pentane and collected by preparative glc). 76% recovery, ca. 50% pure; ir (CCl_4): 3010, 2960, 1195, 830 cm^{-1}; ^{13}Cmr see text. Exact mass calcd for $C_{15}H_{26}OSi$: 250.1753; found: 250.1759.

29b: b.p. 130-135°C/15 Torr, 74% recovery (> 93% pure); ir (film): 3070, 2955, 1254, 879, 840 cm^{-1}; ^{13}Cmr: see Table 2.1.

30b: b.p. 75-80°C/2 Torr, 65% recovery (pure by glc (PFAP)) (cyclopropanation of **30a** required two cycles); ir (film): 3078, 2920, 1239, 1186, 838 cm^{-1}; ^{13}Cmr: see text. Exact mass calcd for $C_{13}H_{24}OSi$: 224.1596; found: 224.1591.

31b: b.p. 75-80°C/5 Torr, 98% recovery (> 93% pure); ir (film): 3050, 3008, 2950, 1255, 1198, 841 cm^{-1}; ^{13}Cmr: see text.

32b: b.p. 75-80°C/15 Torr, 56% recovery (> 93% pure) ir (film): 3078, 2944, 1250, 1195, 840 cm^{-1}; ^{13}Cmr: see Table 2.1.

Preparation of Cyclopropanols

To a solution composed of 10% 0.1 M aqueous HCl and 90% THF was added the cyclopropyl silyl ether and the mixture was stirred at room temperature for 0.5-3 h. The THF was then removed under reduced pressure and the residue was taken up in pentane and dried over Na_2SO_4 (or $MgSO_4$). Removal of the pentane yielded the corresponding

cyclopropanol. Following this procedure compounds **26b**, **29b**, **30b** and **31b** were converted to **26c**, **29c**, **30c** and **31c** respectively, which with the exception of **30c** had been previously reported (25).

30c: m.p. 92-95°C (recrystallized from pentane-methanol); ir (CCl_4): 3610, 3079, 2918, 1185 cm^{-1}; ^{13}Cmr (C_6D_6) δ_C: 59.8 (C), 46.9 (CH), 42.0 (CH), 40.9 (C), 28.7 (CH_2), 26.8 (CH_2), 26.5 (CH_3), 21.2 (CH_3), 20.1 (CH_2), 17.1 (CH). *Exact mass* calcd for $C_{10}H_{16}O$: 152.1196; found: 152.1201.

Homoketonization of **26c**

To a 1.26 M t-BuOK/t-BuOH solution (10 mL) was added **26c** (24 mg, 1.9×10^{-4} mol) and the mixture was stirred for 0.5 h at room temperature. After dilution of the mixture with H_2O (15 mL), the ketonic products were extracted with pentane (3 x 20 mL) and the combined extracts dried over $MgSO_4$. Removal of the solvent gave an oil (20 mg, 83%) which glc (FFAP) indicated was a mixture of **26d** (1%) and **26e** (99%). This procedure was repeated twice more and the average results are reported in Table 2.3. Following the same general procedure **26c** was treated with refluxing t-BuOK/t-BuOH for 5 min and these results are also reported in Table 2.3 (recovery > 79%).

Homoketonization of 30c

To a 1.26 M solution of t-BuOK/t-BuOH (9 mL) was added 30c (60 mg, 3.9×10^{-4} mol) and the mixture was stirred (at room temperature) for 2 h. After dilution of the solution with H_2O, the product was extracted with pentane as described above. Removal of the solvent gave an oil (50 mg, 83%) which by glc (FFAP) and ^{13}Cmr (78) was shown to be a ca. 5:1 mixture of *trans*- and *cis*-3-methylnopinone.

Homoketonization of 31c

A solution of 31c in ether was added to a 1 M CH_3ONa/CH_3OH solution at (A) room temperature, (B, 0°C), and the mixture was stirred (A) overnight (B 30 h). After dilution of the mixture with H_2O the ketonic products were extracted with ether and dried over Na_2SO_4. After removal of the solvent the product composition was determined by glc analysis (FFAP). Homoketonization of 31c was also accomplished using 1 M t-BuOK/t-BuOH at reflux following the procedure described above (recovery > 73%). These results are collected in Table 2.3.

General Procedure Employed for Base-Catalyzed Cleavage of Cyclopropyl Silyl Ethers

To a 3 M methanolic NaOH solution (1.5–6.0 mL) was added the cyclopropyl silyl ether (ca. 20 mg, glc collected) and the mixture was allowed to stir overnight at room temperature before the addition of aqueous 10% NaCl

solution. The ketonic products were extracted with pentane and the combined extracts were washed with an aqueous 10% NaCl solution and with H_2O before drying over Na_2SO_4 (or $MgSO_4$). The solvent was removed by evaporation and the product composition was determined by glc (FFAP) and ^{13}C NMR. The results from homoketonization (recovery > 82%) of 26b-30b and 32b are collected in Table 2.4 (the product compositions listed are the average values from two or three runs).

Base-catalyzed cleavage of 27b and 29b at 0°C was also examined, by treating the cyclopropyl silyl ethers with a pre-cooled (0°C) 3 M methanolic NaOH solution for 22-36 h. The products were recovered and analyzed in the same manner described above (recovery > 80%). Compounds 26b, 27b and 29b were treated with a 1 M KOH/*t*-BuOH solution at reflux for 0.5-2 h and the ketonic products were isolated by pentane extraction (recovery was quantitative) and analyzed by glc. These results are also summarized in Table 2.4.

Preparation of 26b-d_1, 27b-d_1, 29b-d_1 and 31b-d_1

The silyl enol ethers 26a-d_1, 27a-d_1 and 31a-d_1 were prepared following the same general procedure employed for 25a (i.e. 1.6 molar equivalents of LDA), while for 29a-d_1 1.5 molar equivalents of LDA were used. Treatment of 26a-d_1, 27a-d_1, 29a-d_1 and 31a-d_1 with the Simmons-Smith reagent (Zn/Ag couple, CH_2I_2) gave the corresponding

cyclopropyl silyl ethers 26b-d_1, 27b-d_1, 29b-d_1, and 31b-d_1, respectively.

Preparation of 26e-d_1, 27e-d_1, 29e-d_1 and 31e-d_1

A 1 M KOD/t-BuOD solution (1.60 mL) was added to 27b (100 mg, 4.2×10^{-4} mol) and the mixture was stirred under a nitrogen atmosphere for 23 h. After the addition of D_2O (4 mL) the product was extracted with pentane (4 x 6 mL) and the combined extracts were washed with aqueous 10% NaCl solution (2 x 10 mL) and with H_2O (10 mL) before drying over $MgSO_4$. Removal of the solvent gave an oil (67 mg), which by glc analysis (FFAP) was > 76% 27e-d_3; ms: 17.6% d_0, 40.3% d_1, 33.6% d_2, 8.3% d_3 (total 1.33 atoms ^2H/molecule). This material was treated with 3 M methanolic NaOH solution (1.60 mL) and allowed to stand with stirring overnight. After the addition of H_2O (4 mL) the product was extracted with pentane as described for 27e-d_3. Removal of the solvent gave an oil (67 mg) and an analytical sample (prep glc) of 27e-d_1 was collected for characterization; ^2Hnmr ($CHCl_3$): 1.67; ms: 28.5% d_0, 68.7% d_1, 2.8% d_2 (total 0.74 atoms ^2H/molecule).

Following an analogous sequence 26b (0.32 g) was treated with KOD/t-BuOD (1 M, 6 mL) overnight. The deuterated product (0.20 g) was recovered as described above and then treated with methanolic NaOH solution (3 M, 6 mL) overnight. The usual workup procedure gave 26e-d_1;

^{2}Hmr ($CHCl_3$) δ: 1.70; ms: 50.9% d_0, 49.5% d_1 (total 0.50 atoms ^{2}H/molecule).

The cyclopropyl silyl ethers 29b (50 mg)and 31b (55 mg) were treated with a 1 N NaOD/MeOD solution (6 mL and 5 mL, respectively) overnight. The deuterated ketonic products were isolated by pentane extraction and then treated with 3 M methanolic NaOH solution overnight. After the usual workup, preparative glc (FFAP) afforded 29e-d_1; ^{2}Hmr ($CHCl_3$) δ: 2.06; ms: 3.2% d_0, 92.2% d_1, 4.5% d_2 (total 1.01 atoms ^{2}H/molecule) and 31e-d_1; ^{2}Hmr ($CHCl_3$) δ: 1.91; ms: 4.2% d_0, 95.1% d_1, 0.6% d_2 (total 0.96 atoms ^{2}H/molecule).

The ^{13}C data for 26e-d_1, 27e-d_1, 29e-d_1 and 31e-d_1 are collected in Figure 2.5.

Base-Catalyzed Cleavage of 26b-d_1, 27b-d_1, 29b-d_1 and 31b-d_1

A 3 M methanolic NaOH solution (7 mL) was added to 26b-d_1 (45 mg, 2.3 x 10^{-3} mol) and the mixture was stirred overnight at room temperature. After the addition of H_2O (7 mL), the product was extracted with pentane (3 x 15 mL) and the combined extracts were washed with H_2O (2 x 15 mL) before drying over $MgSO_4$. Removal of the solvent by evaporation gave an oil (28 mg, 98% recovery) which by glc was > 99% bicyclo[3.2.1]octan-2-one, a sample of 26e-d_1* was collected by preparative glc; ^{2}Hmr ($CHCl_3$)δ: 1.78; ms: 3.2% d_0, 97.6% d_1 (total 0.98 atoms ^{2}H/molecule).

The cyclopropyl silyl ether 29b-d_1 (0.22 g) was treated overnight with a 3 M methanolic NaOH solution (50 mL) and the usual workup gave 29e-d_1*: ^{2}Hmr ($CHCl_3$) δ: 1.79; ms: 1.2% d_0, 96.7% d_1 (total 0.98 atoms ^{2}H/molecule).

Treatment of 27b-d_1 (48 mg) and 31b-d_1 (120 mg) with 3 M methanolic NaOH solution (9.8 mL and 29 mL, respectively) for 30 min, gave, after the usual workup, 27e-d_1*; ^{2}Hmr ($CHCl_3$) δ: 1.83; ms: 5.4%, 93.2% d_1 (total 0.93 atoms ^{2}H/molecule and 31e-d_1*; ^{2}Hmr ($CHCl_3$) w: 1.76; ms: 8.7% d_0, 91.2% d_1 (total 0.91 atoms ^{2}H/molecule).

For the ^{13}C data for 26e-d_1*, 27e-d_1*, 29e-d_1* and 31e-d_1* see Figure 2.6.

(D) EXPERIMENTAL FOR CHAPTER 3

Norbornenone (37)

After dropwise addition of α-chloroacrylonitrile (8.9 g, 0:1 mol) to freshly distilled cyclopentadiene (8.3 g, 0.125 mol) in benzene (17 mL), the solution was stirred at 45°C for 36 h, under a nitrogen atmosphere. Distillation gave 2-chloro-2-cyanobicyclo[2.2.1]hept-5-ene (15.1 g, 97%), bp 58-61°C/1.5 Torr; ir (film): 3178, 2985, 2235, 1330 cm^{-1}; ^{13}Cmr ($CDCl_3$) major epimer δ_C: 139.3 (CH), 131.7 (CH), 121.2 (-C≡N), 56.4 (C), 55.2 (CH), 48.3 (CH_2), 45.5 (CH_2), 42.7 (CH); minor epimer δ_C: 142.0 (CH), 132.3 (CH), 120.6 (-C≡N), 56.4 (C), 55.9 (CH), 46.8 (CH_2), 46.7 (CH_2), 42.4 (CH). The total product was dissolved in DMSO (88 mL) and a solution of KOH (16.5 g) in water (5.6

mL) was added with stirring. After 30 h, a saturated aqueous solution of NaCl (88 mL) was added, and the product extracted with pentane (4 x 50 mL). The combined extracts were washed with saturated salt solution until the washings were neutral, then once with water. The organic layer was dried ($MgSO_4$) and the solvent evaporated to give 8.7 g of product containing (glc) norbornenone (86%) and starting material (14%). Preparative glc (FFAP) furnished pure 37 as determined by glc and ^{13}Cmr (42).

Preparation of 37-d_2

To a 0.5 N NaOD-D_2O solution (32 mL) was added 37 (2 g), in pentane (1 mL) and the mixture was refluxed for 9.5 h. Pentane extraction as described above gave 37-d_2 (1.1 g); ms: 27.5% d_1, 66.7% d_2 (total 1.60 atoms ^{2}H/molecule).

Preparation of 40

The trimethylsilyl enol ether 40 was obtained from the corresponding ketone (0.76 g, 7.0 x 10^{-3} mol) using LDA (diisopropylamine (1.40 mL, 1.0 x 10^{-2} mol), *n*-BuLi (7.80 x 10^{-3} mol) in *n*-hexane (3.70 mL), THF (8 mL)) and trimethylsilyl chloride (1.30 mL, 1.02 x 10^{-3} mol), triethylamine (0.50 mL, 3.6 x 10^{-3} mol) and THF (3 mL) as described previously. The product was isolated following procedure A and Kugelrohr distillation (90-95°C/5 Torr) gave 40 (1.00 g, 79%); the ^{13}Cmr and ir data are described in the text.

Preparation of 44a

The trimethylsilyl enol ether 40 (0.99 g, 5.5 x 10^{-3} mol) was treated with the Simmons-Smith reagent (Zn-Ag couple (1.20 g, 1.84 x 10^{-2} mol), methylene iodide (0.76 mL, 9.4 x 10^{-3} mol), Et_2O (16 mL)) for 19 h. The usual workup gave 44a (1.06 g, 99%), which glc (FFAP) indicated to contain traces (< 2%) of two impurities; ir (film): 3038, 2960, 1250 cm^{-1}; ^{1}Hmr (C_6D_6) δ: 2.06 (1H, br, dd, J = 12.2, 4.5 Hz), 1.88-1.98 (2H, m), 1.63-1.78 (4H, m), 1.02-1.20 (2H, m), 0.20 (Me_3Si); ^{13}Cmr (see text). *Exact mass* calcd for $C_{11}H_{18}OSi$: 194.1127; found: 194.1127.

Repetition of the sequence, norbornenone → 40 → 44a with 37-d_2 afforded 44a-d_1, ms: 20% d_0, 80% d_1 (total 0.80 atoms ^{2}H/molecule).

Homoketonization of 44a

Treatment of 44a (0.550 g, 2.84 x 10^{-3} mol) with 3 M methanolic NaOH solution (28 mL) for 20 min at room temperature gave after the usual workup 45 (0.333 g, 2.72 x 10^{-3} mol), which glc (FFAP) indicated to be > 95% pure: ir (film): 3040, 2922, 1727 cm^{-1}. *Exact mass* calcd for $C_8H_{10}O$: 122.0732; found: 122.0735.

Ketone 45 gave a 2,4-dinitrophenylhydrazone, mp 191-192°C (lit. (48a) mp 192.5-193°C; (48b) mp 190-190.5°C; (48c) mp 194.5-195°C. *Exact mass* calcd for $C_{14}H_{14}O_4N_4$: 302.1016; found: 302.1017.

Preparation of 45-d_x

A sample of 44a (200 mg) was placed in 2 M t-BuO$^-$/t-BuOD (10 mL) and the solution stirred at room temperature for 3 h. After quenching with water (10 mL), the ketone was extracted with pentane as described above and purified by glc to give 45-d_x, ms: 71.3% d_1 17.3% d_2, 2.1% d_3 (total 1.12 ^{2}H/molecule).

A sample of 44a-d_1 (total 0.80 atoms ^{2}H/molecule), prepared as described above, was homoketonized in a similar fashion with an extended reaction time (11.5 h) to furnish 45-d_x ms: 19.1% d_1, 40.9% d_2, 27.3% d_3, 7.8% d_4 (total 2.14 atoms ^{2}H/molecule).

Cyclopropanation of 40 with a Zn/Cu Couple

To a flask fitted with a reflux condenser, nitrogen purge and magnetic stirrer was added the zinc-copper couple (79) (0.20 g, 3.1 x 10^{-3} mol) and 8 mL of ether. A crystal of iodine was added, and the mixture was stirred until the brown color disappeared. Methylene iodide (0.24 mL, 3.0 x 10^{-3} mol), and a solution of 40 (0.50 g, 2.8 x 10^{-3} mol) in Et_2O (2 mL) was then added and this mixture was refluxed for 15 h with stirring. The same workup employed with the Zn-Ag cyclopropanation reaction gave an oil (0.20 g); glc analysis (FFAP) indicated the product to be ca. 72% pure. An analytical sample (prep. glc) was collected and its ^{13}Cmr spectrum confirmed the formation of 44a.

The reaction with the same ratio of reagents as employed for the zinc-silver cyclopropanation afforded 44a, although in lower yield.

(E) EXPERIMENTAL FOR CHAPTER 4

General Procedure for α,α-dimethylation of Ketones.

To a flame-dried, nitrogen purged flask fitted with reflux condenser and magnetic stirrer was added sodium amide and a solution of ketone in anhydrous Et_2O, and this mixture was refluxed for 2-4 h. Methyl iodide was then added and refluxing was continued for ca. 9-30 h, during which time further additions of methyl iodide were made. The reaction was then cooled to 0°C and water was slowly added. After decanting the organic phase, the aqueous phase was extracted with pentane and the combined organic fractions were washed with H_2O. The washings were reextracted with pentane and the combined extracts dried over $MgSO_4$ before removal of the solvent by evaporation.

Preparation of 47

A mixture of sodium amide (0.39 g, 9.9×10^{-3} mol), Et_2O (14 mL) and 45 (0.22 g, 1.8×10^{-3} mol) was refluxed for 3 h. Methyl iodide (0.68 mL, 1.1×10^{-2} mol) was slowly added and a further addition of CH_3I (0.22 mL, 3.5×10^{-3} mol) was made after 16 h; finally the mixture was refluxed for 3 h. The isolation procedure described above furnished an oil (0.24 g, 89%) which by glc analysis

(FFAP) was found to be > 98% pure; an analytical sample of 47 was collected by preparative glc (FFAP); ir (CCl_2H_2): 3040, 2980, 1712 cm^{-1}. *Exact* mass calcd for $C_{10}H_{14}O$: 150.1045; found 150.1044.

Homoenolization Experiments

The required t-butyl alcohol-O-d_1 was prepared according to the procedure of Young and Guthrie (80). The alcohol was refluxed over CaH_2 under a nitrogen atmosphere to furnish t-butyl alcohol-O-d_1 which was < 0.002 M in water by Karl Fisher titration; t-butyl alcohol was also dried by refluxing with calcium hydride and distilled.

The general procedure followed for the homoenolization studies was essentially as described by Nickon et al. (4, 5). In general, the ketone was added to 1.27 M t-BuOK/t-BuOH(D) ([H_2O] < 0.005 M, prepared by adding freshly cut potassium to a t-BuOH(D) (under a nitrogen atmosphere) to give a solution which was 0.26 M in ketone. Aliquots were transferred under a nitrogen atmosphere to a series of pre-dried thick-walled glass tubes (the ratio of tube volume to base volume was 10:1); the tubes were degassed and sealed under vacuum. After heating at elevated temperatures (185° or 200°C) for varying periods of time the tubes were opened and the contents removed by washing with H_2O (or an aqueous 10% NaCl solution). The ketonic products were isolated by pentane extraction and the combined extracts back-washed

with H_2O (and/or an aqueous 10% NaCl solution). The aqueous washings were reextracted with pentane and the pentane extracts dried over $MgSO_4$. Removal of the solvent by evaporation afforded a neutral organic product (recovery > 70%) and its composition was determined by glc (Carbowax, FFAP, SE-30). In each case, the starting material and/or the rearrangement product(s) were isolated by preparative glc.

(F) EXPERIMENTAL FOR CHAPTER 5

Preparation of 63

Following the procedure reported by Turro and Farrington (54) a mixture of spiro[2,4]hepta-4,6-diene (13.6 g, 1.48×10^{-3} mol), prepared from cyclopentadiene and 1,2-dibromoethane according to the method described by Alder *et al.* (81), and 2-chloroacrylonitrile (15.6 g, 1.78×10^{-3} mol) was stirred at 105°C for 5 h. Distillation afforded 16.0 g of the Diels-Alder adduct, 15.5 g of which was added to a mixture of ethylene glycol (107 mL) and KOH (26.5 g) and stirred at 95°C for 20 h. After the addition of 380 mL of 10% aqueous NaCl solution, the product was extracted with pentane (6 x 100 mL). The combined extracts were washed with brine (2 x 70 mL) and dried over $MgSO_4$. After removal of the solvent, the residue was distilled to give 63 (7.59 g) (bp 89-90°C/16 Torr, lit (54) bp 90-92°C/21 Torr) which was > 85% pure by glc analysis (FFAP). Flash chromatography (Et_2O-petroleum ether, 25:75)

furnished pure 63 (5.9 g, 51% yield); ir (film): 3076, 3000, 1745, 708 cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 0.64 (bs, 4H), 1.98 (d, J = 16.2 Hz, *endo*-H-3), 2.28 (dd, J = 3.1, 16.2 Hz, *exo*-H-3), 2.50 (m, H-1 and -4), 6.20 (m, 1H), 6.62 (dd, J = 2.8,5.6 Hz, 1H); ^{13}Cmr ($CDCl_3$) δ_C: 6.0, 7.0 (2 x CH_2), 38.3 (C-3), 46.0 (C-4), 46.1 (C-7), 60.8 (C-1), 129.4 (C-6), 142.0 (C-5), 212.7 (C-2). *Exact mass* calcd for $C_9H_{10}O$: 134.0732; found: 134.0729.

Trimethylsilyl enol ether of 63 (58)

This compound was prepared following the procedure employed for 37 using diisopropylamine (0.84 mL); THF (8 mL), *n*-butyllithium (2.1 mL, 2.50 M in *n*-hexane and 63 (0.50 g) with a quenching solution of trimethylsilyl chloride (0.76 mL), Et_3N (0.29 mL) and THF (1.5 mL). Kugelrohr distillation of the product isolated by pentane extraction gave crude enol ether (bp 102-106°C/12 Torr, 0.69 g, 90% yield) which glc analysis (Carbowax) indicated to be ~ 95% pure. An analytical sample was collected by preparative glc for characterization: *Exact mass* calcd for $C_{12}H_{18}OSi$: 206.1127; found: 206.1124.

8-Spirocyclopropyl-2-trimethylsiloxyhomoquadricyclene (59)

Cyclopropanation of the silyl enol ether of 63 was carried out as previously described for the parent norbornenone derivative using a zinc-silver couple (1.26 g) and CH_2I_2 (0.85 mL) in Et_2O (2 mL) with the silyl enol

ether (1.2 g) in Et_2O (15.5 mL). The usual work-up furnished an oily liquid (1.14 g) which was ca. 80% pure by glc (SE-30). Pure 59 was obtained by preparative glc; ir (CCl_4): 3078, 2975, 1250, 1154, 840 cm^{-1}. *Exact mass* calcd for $C_{13}H_{20}OSi$: 220.1283; found: 220.1302.

Homoketonization of 59

To 20 mL of 3 M methanolic NaOH was added 59 (485 mg) and the mixture stirred overnight at room temperature. After the addition of H_2O (20 mL), the product was extracted with pentane (3 x 20 mL) and the combined extracts washed with H_2O (3 x 15 mL) before drying over $MgSO_4$. Removal of the solvent gave a yellow oil (330 mg) containing one ketonic component 62 (ca. 90% yield) which was purified by preparative glc (FFAP). Ir (film): 3040, 2930, 1725 cm^{-1}. *Exact mass* calcd for $C_{10}H_{12}O$: 148.0888; found: 148.0882.

Preparation of 62-$\underline{d}_x$

A sample of 59 (90 mg) was placed in a 1.3 M solution of KOD in t-BuOD (1.6 mL) and the mixture stirred at room temperature overnight. Isolation by pentane extraction and purification by glc (FFAP) gave 62-$\underline{d}_x$; ms: 4.6% d_0, 32.6% d_1, 41.7% d_2, 21.5% d_3 (total 1.80 atoms ^2H/molecule).

Hydrogenation of 62

To a solution of 62 (130 mg) in glacial acetic acid (4 mL) was added 27 mg of platinum oxide catalyst and the mixture hydrogenated at 50 psi in a Parr shaker for 21 h. Dilution with H_2O (15 mL) and neutralization with $NaHCO_3$ were followed by removal of the catalyst by filtration. The product was extracted with n-pentane (3 x 10 mL) and the combined extracts dried over $MgSO_4$ before removal of the solvent by evaporation to furnish 130 mg of material. Glc analysis (FFAP) indicated the presence of two components in comparable amounts and samples were collected by preparative glc. ^{13}Cmr spectra of the samples showed one to be a 1:2 mixture of unreacted 62 and a new compound having signals at δ_C: 26.7, 29.4 (2 x CH_3), 28.8, 30.8 (2 x CH_2), 13.1, 14.7, 24.7, 46.8, 71.8 (5 x CH) and 38.3 (C). These data indicate that the new product is probably 6,6-dimethyltricyclo[3.2.1.$0^{2,7}$]octan-4-ol but the compound was not further characterized. The second component obtained by preparative glc was a single ketone identified as 6,6-dimethyltricyclo[3.2.1.$0^{2,7}$]octan-4-one; ir (film): 3030, 2965, 1720 cm^{-1}. Exact mass calcd for $C_{10}H_{14}O$: 150.1044; found: 150.1041.

(G) EXPERIMENTAL FOR CHAPTER 6

Preparation of 7-Isopropylidenenorbornenone (71)

A mixture of cyclopentadiene (66 g) and acetone (58 g) was cooled to 0°C before the dropwise addition of

20% ethanolic KOH solution (20 mL) with stirring (82). Stirring was continued overnight. The organic layer was separated and distilled to furnish 6,6-dimethylfulvene (32.5 g, 31%) bp 42-47°C/11 Torr; lit (83) 44-46°C/10 Torr. A solution of 6,6-dimethylfulvene (3.06 g, 29 x 10^{-3} mol) and 2-acetoxyacrylonitrile (10.00 g, 90 x 10^{-1} mol) in dry pyridine (1.20 mL) was prepared and aliquots were transferred to six, flame-dried, 5 mL thick walled pyrex tubes under a N_2 atmosphere. The tubes were sealed under vacuum and placed in an oil bath at 90°C for 28 h (57). After cooling to room temperature, the contents of the tubes were taken up in CH_2Cl_2. The solvent was removed and the product isolated by flash chromatography using benzene as eluent to furnish an epimeric mixture (7:1) of the 2-acetoxy-2-cyano-7-isopropylidenebicyclo[2.2.1]hept-5-enes (6.0 g, 96% yield) favoring the *endo*-cyano isomer by comparison with the published data (57). This mixture was used directly for the next step.

The mixture of Diels-Alder adducts (2.0 g, 9.2 x 10^{-3} mol) was dissolved in dry methanol (8.8 mL) and added, with stirring, to a 2 M solution of NaOMe in MeOH under a N_2 atmosphere. After stirring for 2.5 h, aqueous 10% NaCl solution (20 mL) was added and the product extracted with methylene chloride (4 x 20 mL). The combined extracts were washed with H_2O before drying over $MgSO_4$. Removal of the solvent gave **71** (1.0 g, 75% yield)

which was > 97% pure by glc (FFAP) analysis; ir (film): 3080, 2920, 1750 cm^{-1}; ^{13}Cmr ($CDCl_3$) δ: 19.4, 19.8 (2 x CH_3), 40.4 (CH_2), 42.0, 57.9, 130.9, 143.1 (4 x CH), 115.2, 146.2 (2 x CH), 218.6 (C=O).

Preparation of 2-Trimethylsilyloxy-7-isopropylidenebicyclo-heptadiene (67).

Following the usual procedure, 71 (0.60 g, 4.0 x 10^{-3} mol) in THF (2 mL) was added dropwise to a THF solution of LDA at -78°C. The LDA was prepared from diisopropylamine (0.92 mL, 6.6 x 10^{-3} mol) in THF (5.5 mL) to which had been added 2.46 M *n*-BuLi in hexane (2.30 mL, 5.66 X 10^{-3} mol). Quenching with chlorotrimethylsilane (0.93 mL, 7.3 x 10^{-3} mol) and triethylamine (0.34 mL, 2.4 x 10^{-3} mol) in THF (2 mL) and extraction with pentane as described earlier gave, after removal of the solvent, 0.71 g of oily 67 (80% yield). Exact mass calcd for $C_{13}H_{20}OSi$: 220.1283; found: 220.1280.

Cyclopropanation of 67

Following the usual procedure the zinc-silver couple (0.53 g, 8.1 x 10^{-3} mol) was placed in a nitrogen-purged flask and the apparatus was flame-dried. After cooling, methylene iodide in anhydrous Et_2O (2 mL) was added and the mixture warmed until refluxing occurred without external heating. Upon cessation of reflux, an ethereal solution of 67 (0.55 g, 2.4 x 10^{-3} mol) was added and the mixture refluxed for several hours. After cooling

to 0°C, a 50:50 mixture of pyridine-ether was added until no further precipitate formed. The precipitate was removed by filtration and the ether evaporated. The residue was taken up in pentane and the traces of precipitate were removed by filtration before evaporation of the solvent. The resulting oily product (0.51 g) was shown to contain a mixture of two adducts by ^{13}Cmr. All attempts to analyze the product by glc (FFAP, SE-30, Carbowax) led to decomposition even if freshly prepared glc columns were used. A series of experiments following this general procedure was carried out as summarized in Table 6.1.

A preparative run was carried out by reacting 710 mg of 67 in Et_2O (9.9 mL) with zinc-silver couple (0.5 g), CH_2I_2, (0.13 mL, 1.6 x 10^{-3} mol) in Et_2O (3 mL) at room temperature for 5.5 h before the addition of more CH_2I_2 (0.13 mL, 1.6 x 10^{-3} mol) and stirring for an additional 20 h. The reaction was quenched and the product isolated in the usual fashion as an oil (700 mg).

The major component in the product from Expt. 1 (Table 6.1) gave rise to a ^{13}C spectrum consistent with structure 68 (see text) while the major component from Expt. 3 exhibited a ^{13}C spectrum readily attributable to 72 as discussed in the text. These structural assignments were confirmed by unequivocal identification of their homoketonization products.

Homoketonization of 68 and 72

The same procedure described above for homoketonization of 59 was employed.

Upon treatment with 3 M methanolic NaOH, the product from Expt. 5 (Table 6.1) afforded a single ketone by glc analysis (FFAP). Although the starting material was a mixture of 71 and 68, it was apparent that 71 did not survive after several hours in base. The structure of the new ketone 69 was established by detailed analysis of its ^{13}C spectrum (see text); ir (CCl_4: 3060, 2910, 1747 cm^{-1}; ^1Hmr (see text). Exact mass calcd for $C_{11}H_{14}O$: 162.1045; found: 162.1039.

Homoketonization of the material from the preparative scale cyclopropanation gave 330 mg of 69, after purification by flash chromatography (7% Et_2O-93% petroleum ether (30-60°C), 64% overall yield from 67.

The product from Expt. 4 (Table 6.1) was stirred at room temperature with 2 mL of a 1 M KOD/t-BuOD overnight. The usual work-up furnished 69-d_x containing 2.48 atoms ^2H/molecule; ms: 1.2% d_0, 4.5% d_1, 46.8% d_2, 50.1% d_3.

A portion of 69-d_x was treated with 3 M methanolic NaOH to furnish 69-d_1 which was found to contain 0.96 atoms ^2H/molecule; ms: 7.0% d_0, 90.6% d_1, 2.6% d_2.

Homoketonization of the mixture of adducts (210 mg) obtained in Expt. 3 (Table 6.1) gave an oily liquid (145 mg, 97% yield) shown to be a 78:12 mixture of

73 and 69 by glc (FFAP), readily separable by preparative glc. ^{1}H and ^{13}Cmr spectra showed that 73 was a single compound; exact mass calcd for $C_{12}H_{16}O$: 176.1201; found: 176.1193; ir (CCl_4): 3050, 2925, 1725 cm^{-1}. A second sample (130 mg) of the same starting material was treated with 1 M KOD/t-BuOD (2 mL) to furnish 85 mg (92% yield) of the mixture of 73-d_x and 69-d_x. After isolation by glc, ketone 73-d_x was found to contain 1.50 atoms ^{2}H/molecule (30.0 d_0, 25.9% d_1, 34.2% d_2, 18.5% d_3). Back-exchange with 3 M methanolic NaOH afforded 73-d_1; 42.0% d_0, 56.8% d_1, 1.1% d_2 (total 0.58 atoms ^{2}H/molecule).

H/D Exchange of 69

A solution of 69 (35 mg) in 1 M MeONa/MeOD (2 mL)was heated under reflux for 90 min. After addition of D_2O (3 mL), the product was isolated by pentane extraction (3 x 8 mL); the combined extracts were washed with 10% aqueous NaCl solution before drying over $MgSO_4$. Evaporation of the solvent gave 30 mg of 69-d_y and an analytical sample was obtained by glc (FFAP); ms: 6.4% d_0, 28.5% d_1, 65.4% d_2, (total 1.59 atoms ^{2}H/molecule). The ^{2}Hmr spectrum (C_6H_6) contained equally intense signals at δ 1.74 and 2.05 (endo- and exo-^{2}H-3, respectively).

Reduction of 62

To a slurry of LAH (38 mg) in anhydrous Et_2O (2 mL) was added a solution of 62 (95 mg) in Et_2O (4 mL)

and the mixture stirred overnight. On cooling to 0°C, excess LAH was destroyed by the cautious addition of H_2O and 10% aqueous NaOH solution (0.2 mL). After stirring, the precipitate was removed by filtration and the solvent removed after drying to furnish 75 mg of product which contained two components by glc analysis (FFAP) in a ratio of 6.5:1; both were isolated by preparative glc.

The major product 74a (mp 67-68°C) was found to be an alcohol; ir (CCl_4): 3630, 3040, 3000, 2940, 1055 cm^{-1}. Exact mass calcd for $C_{10}H_{14}O$: 150.1044; found: 150.1045.

The minor product 74b was also shown to be an alcohol; ir (CCl_4): 3620, 3040, 2925, 1060 cm^{-1}. Exact mass calcd for $C_{10}H_{14}O$: 150.1044; found: 150.1042.

Reduction of 73

Ketone 73 (30 mg) in Et_2O (2.2 mL) was added to a slurry of LAH (20 mg) in Et_2O (1 mL) under a N_2 atmosphere and stirred overnight. The usual work-up afforded an oil (30 mg) which by glc analysis contained two components in a ratio of 18.5:1. A sample of the major component was isolated by preparative glc and identified as 75 on the basis of its ^{13}C spectrum (see text); ir (CCl_4): 3630, 3050, 2940, 1175, 915 cm^{-1}. Exact mass calcd for $C_{12}H_{18}O$: 178.1358; found: 178.1357.

(H) EXPERIMENTAL FOR CHAPTER 7

Endo-tricyclo[3.2.1.$0^{2,4}$]oct-6-ene was prepared according to the prodecure of Closs and Krantz (84).

Preparation of *endo*-bicyclo[3.2.1.$0^{2,4}$]octan-6-ol

After cooling a solution of *endo*-tricyclo[3.2.1.$0^{2,4}$]oct-6-ene (4.76 g, 4.49 x 10^{-2} mol) in hexane (15 mL) to 0°C, a 10 M borane dimethyl sulfide solution (2.69 mL) was added, dropwise. Upon completion of the addition the solution was stirred at room temperature for 3 h and refluxed for an additional 1 h. On cooling to 0°C absolute ethanol (25 mL) was added, followed by 3 M sodium hydroxide solution (9.10 mL). Hydrogen peroxide (30%, 9.10 mL) was then added at such a rate that the temperature of the solution remained < 40°C. The mixture was then refluxed for 1 h, cooled and diluted with brine solution (4 mL). The product was extracted with pentane (4 x 30 mL) and the combined extracts were washed with aqueous 10% NaCl solution (3 x 20 mL) and with H_2O (20 mL). The aqueous fractions were then combined and back-washed with pentane (2 x 30 mL). After drying the organic fractions with $MgSO_4$, Kugelrohr distillation (150-155°C/5.5 Torr) gave 4.18 g of *endo*-tricyclo[3.2.1.$0^{2,4}$]octan-6-ol (75%) and 0.20 g of starting material.

Oxidation of *endo*-tricyclo[3.2.1.$0^{2,4}$]octan-6-ol

To a slurry of pyridinium chlorochromate (PCC) (3.80 g, 1.76 x 10^{-2} mol), filter aid (Celite, 3.8 g), methylene chloride (15 mL) and sodium acetate (0.30 g) was added a solution of *endo*-tricyclo[3.2.1.$0^{2,4}$]octan-6-ol (1.40 g, 1.13 x 10^{-2} mol) in CH_2Cl_2 (15 mL). After stirring for 1.75 h anhydrous ether (23 mL) was added and the resulting precipitate was removed by filtration. The filtrate was washed with aqueous 5% HCl solution (30 mL), aqueous 10% NaOH solution (30 mL) and with H_2O (3 x 30 mL) before drying over $MgSO_4$. Kugelrohr distillation (98-105°C/14 Torr) gave 1.14 g of *endo*-tricyclo[3.2.1.$0^{2,4}$]-octan-6-one (80).

Exo-tricyclo[3.2.1.$0^{2,4}$]octan-6-ol was prepared according to the procedure of Colter and Musso (85).

Preparation of *exo*-tricyclo[3.2.1.$0^{2,4}$]octan-6-one (79)

A solution of *exo*-tricyclo[3.2.1.$0^{2,4}$]octan-6-ol (4.49 g, 3.62 x 10^{-2} mol) in CH_2Cl_2 (48 mL) was added to a slurry of PCC (11.77 g, 5.46 x 10^{-2} mol), sodium acetate (0.88 g), filter aid (11.77 g) and CH_2Cl_2 (48 mL). After stirring for 4.5 h the reaction was worked up in the same manner as above. Removal of the solvent yielded 4.40 g of **79** (quantitative), which was pure by glc analysis (FFAP).

Preparation of 79a

To a stirred solution of LDA (prepared from diisopropylamine (3.31 mL, 2.36 x 10^{-3} mol), THF (23 mL), *n*-BuLi in *n*-hexane (2.5 M, 8.26 mL)) was added 79 (1.80 g, 1.48 x 10^{-3} mol) in THF (4 mL). After stirring for 45 min, the quenching solution (trimethylsilyl chloride (3.37 mL, 2.66 x 10^{-3} mol), triethylamine (1.23 mL) and THF (3 mL)) was added and the mixture was stirred for 2 h at room temperature. The usual workup (procedure B) gave crude 79a which was purified by bulb-to-bulb distillation (90-95°C 4 Torr), 2.57 g, 90% yield; glc analysis (FFAP) indicated > 90% purity. An analytical sample was collected by preparative glc for characterization: ir ($CHCl_3$): 2950, 1598, 1245, 830 cm^{-1}; ^{1}Hmr (C_6D_6) δ: 0.20 (9H, s, $SiMe_3$), 0.5-1.5 (6H, m), 2.53 (2H, bs), 5.05 (1H, bd J - 3 Hz). Exact mass calcd for $C_{11}H_{18}OSi$: 194.1127; found: 194.1125.

Cyclopropanation of 79a

To a mixture of Zn-Ag couple (2.22 g, 3.40 x 10^{-2} mol), methylene iodide (1.50 mL, 1.86 x 10^{-2} mol) and Et_2O (4 mL) was added 79a (2.00 g, 1.03 x 10^{-3} mol) in Et_2O (46 mL). After refluxing for 8 h the reaction was worked up as previously described to yield 79b (1.98 g, 92%) which glc analysis (FFAP) indicated to be ca. 80% pure. An analytical sample (prep. glc) was collected for characterization: ir (film): 3060, 2940, 1242, 832 cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 0.18 ($SiMe_3$), 0.35 (2H, m), 0.72 (3H, m),

1.06 (3H, m), 1.76 (1H, m), 2.18 (1H, m), 2.32 (1H, m). *Exact mass* calcd for $C_{12}H_{20}OSi$: 208.1283; found: 208.1279.

Preparation of 79e

The tetracyclic TMS ether 79b (1.88 g) was added to methanolic NaOH solution and allowed to stir for 24 h at 0°C before the addition of H_2O (70 mL). The product was extracted with pentane as described previously. Removal of the solvent gave 79e (1.09 g, 82%). Preparative glc (FFAP) was used to obtain pure samples for further work. The absence of 79d in the ketonization product was confirmed by glc (FFAP) since samples of the latter were available from earlier studies (30). Ir ($CHCl_3$): 1710 cm^{-1} (C=O); ^{13}Cmr ($CDCl_3$): δ: 33.8 (CH), 17.4 (CH), 5.2 (CH_2), 17.1 (CH), 50.8 (CH), 213.5 (C=O), 35.4 (CH_2), 31.0 (CH_2), 28.3 (CH_2). *Exact mass* calcd for $C_9H_{12}O$: 136.0888; found: 136.0886. ^{13}Cmr ($CDCl_3$): δ: 33.8 (CH), 17.4 (CH), 5.2 (CH_2), 17.1 (CH), 50.8 (CH), 213.5 (C=O), 35.4 (CH_2), 31.0 (CH_2), 28.3 (CH_2).

Preparation of 79e-d_1

To a solution of KOD in t-BuOD (2 M, 2 mL) was added 79b (90mg) and the resulting mixture was stirred overnight, under a nitrogen atmosphere. After the addition of D_2O (3 mL), the product was isolated as described for 79e to furnish 79e-d_3 (60 mg); 0.9% d_0, 2.9% d_1, 19.7% d_2, 76.5% d_3 (total 2.71 atoms ^2H/molecule). Back-exchange

with 3 M methanolic NaOH furnished 79e-d_1 (57 mg): ms: 7.7% d_0, 83.1% d_1, 5.1% d_2 (total 0.93 atoms ^2H/molecule).

Preparation of 79e-d_1*

The sequence 79 → 79e described above was repeated using [7,7-$^2H_2$]-79 as the starting material prepared as follows. To a solution of NaOD-D_2O (0.5 M, 9.5 mL) was added 79 (1.40 g) under a nitrogen atmosphere and the solution was refluxed for 22 h. The reaction mixture was worked-up as described for 26-d_2, to afford 79-d_2 (1.34 g). The ^{13}Cmr spectrum of this product indicated almost complete exchange of the α-methylene hydrogens and this material was employed directly for the generation of 79e-d_1 via 79a-d_1* followed by cyclopropanation and ketonization as described above for 79b and 79e. The resulting product, 79e-d_1* contained 0.71 atoms ^2H/molecule: ms: 9.3% d_0, 70.7% d_1.

Preparation of 80a

Following the usual procedure, ketone 80 (0.72 g, 5.8×10^{-3} mol) was treated with LDA (diisopropylamine (1.30 mL, 9.3×10^{-3} mol), n-BuLi in n-hexane (2.26 M, 3.60 mL) and THF (13 mL)) and trimethylsilyl chloride (1.20 mL, 9.5×10^{-3} mol) triethylamine (0.45 mL, 3.2×10^{-3} mol), and THF (1.0 mL). The reaction mixture was worked-up following procedure B and Kugelrohr distillation gave 80a (0.79 g, 70%), which glc (FFAP) analysis indicated to be >

98% pure; ir ($CHCl_3$): 1610 cm^{-1} (C=C); ^{1}Hmr ($CDCl_3$) δ: 0.30 (9H, s, Me_3Si), 0.50-2.00 (6H, complex absorption), 2.62, 2.72 (1H each, overlapping m), 4.62 (1H, bd, H-7). Exact mass calcd for $C_{11}H_{18}OSi$: 194.1127; found: 194.1123.

Preparation of 80b

Cyclopropanation of 80a was accomplished using Zn/Ag couple (0.87 g, 13 x 10^{-3} mol), methylene iodide (0.59 mL, 7.3 x 10^{-3} mol) in Et_2O (2 mL). After refluxing overnight the reaction mixture was worked-up following the usual procedure to yield 80b (0.70 g) which glc (SE-30) indicated to be > 90% pure. Preparative glc furnished pure samples for characterization and for the following step in the sequence. Exact mass calcd for $C_{12}H_{20}OSi$: 208.1283; found: 208.1277.

Preparation of 80c

Tetracyclic ether 80b was ketonized in 90% yield with methanolic NaOH solution in a manner analogous to that described above for 79b and, as is the case with 79b, a single ketonic product (80c) was obtained; ir ($CHCl_3$): 1715 cm^{-1} (C=O); ^{13}Cmr ($CDCl_3$) δ: 31.3 (CH), 26.4 (CH), 17.1 (CH_2), 24.4 (CH), 48.6 (CH), 214.9 (C=O), 35.0 (CH_2), 22.6 (CH_2), 43.7 (CH_2). Exact mass calcd for $C_9H_{12}O$: 136.0888; found: 136.0888.

Preparation of 80e-d_1

To a 2 M KOD/t-BuOD solution (2 mL) was added 80b (95 mg) and the resulting solution was stirred overnight under a nitrogen atmosphere. After the addition of D_2O (3 mL) the product was recovered by pentane extraction and this afforded 80e-d_3; ms: 2.6% d_0, 7.9% d_1, 35.5% d_2, 54.0% d_3 (total 2.41 atoms ^2H/molecule). Subsequent treatment with methanolic NaOH solution (3.6 M, 2 mL) overnight followed by the usual workup furnished 80e-d_1, the ^{13}Cmr spectrum of which indicated the presence of ca. 0.8 atoms atoms ^2H/molecule at C-8.

(I) EXPERIMENTAL FOR CHAPTERS 8 AND 9

Cyclopropanation of 79a, "Concentrated Conditions"

The Simmons-Smith reagent was prepared from methylene iodide (0.30 mL, 3.7 x 10^{-3} mol), Zn-Ag couple (0.48 g, 7.3 g x 10^{-3} mol) and Et_2O (0.50 mL), in the usual manner. Upon completion of reaction, a solution of 79a (0.45 g, 2.3 x 10^{-3} mol) in Et_2O (0.70 mL) was added and the resulting mixture was refluxed (temp. of the oil bath was ca. 50°C) for 25 h. The workup procedure furnished an oil (0.34 g), which glc analysis (SE-30) indicated was ca. 35% 86 and an analytical sample was collected by preparative glc; ^{13}Cmr (C_6D_6) δ_C: 70.7 (CH), 42.7 (CH), 32.8 (CH), 21.5 (CH), 20.9 (CH), 17.8 (CH_2), 15.2 (CH), 13.9 (CH), 7.5 (CH_2), 6.2 (CH_2), 0.0 ($SiMe_3$). Exact mass calcd for $C_{13}H_{22}OSi$: 222.1440; found: 222.1429

Cyclopropanation of 26a, "Concentrated Conditions"

Cyclopropanation of 26a (0.40 g, 2.2×10^{-3} mol) was accomplished using Zn-Ag couple (0.72 g, 1.1×10^{-2} mol), methylene iodide (0.44 mL, 5.5×10^{-3} mol) and Et_2O (1.7 mL). After stirring at 50°C for 60 h the reaction was worked-up and found to give an oil (0.14 g), which by glc analysis (FFAP) was a complex mixture of components containing ca. 15% 87. Preparative glc furnished a pure sample of 87 for characterization purposes; ir (film): 3040, 2960, 1250,839 cm^{-1}. Exact mass calcd for $C_{11}H_{20}OSi$: 196.1283; found: 196.1289.

Preparation of 89a

To a solution of LDA (diisopropylamine (2.67 mL, 1.9×10^{-2} mol), *n*-BuLi in *n*-hexane (2.50 M, 6.44 mL) and THF (23 mL)) at -78°C was added a solution of norcamphor (1.50 g, 1.36×10^{-2} mol) in THF (3 mL). After stirring for 30 min a quenching solution (THF (3 mL), triethylamine (0.20 mL, 1.4×10^{-3} mol) and t-butyldimethylsilyl chloride (3.30 g, 2.19×10^{-2} mol) was added and this mixture was stirred for 5 h at -78°C and an additional 3 h at room temperature. The usual workup gave, after Kugelrohr distillation (83-87°C/0.4 Torr), 89a (2.52 g, 82%) which glc analysis (FFAP) indicated to be 94% pure. Preparative glc furnished a pure sample of 89a for characterization: ir (film): 2930, 1611, 1328, 830 cm^{-1}. Exact mass calcd for $C_{13}H_{24}OSi$: 224.1596; found: 224.1601.

Preparation of 92, 93 and 94

The t-butyldimethylsilyl enol ethers 92, 93 and 94 were all prepared following the procedure described above for 89a. The physical properties of these silyl enol ethers are summarized below.

i) For the preparation of 92 the addition of triethylamine was omitted.

92: bp 105-110°C/0.2 Torr; ir (film): 2940, 1625, 974 cm^{-1}. Exact mass calcd for $C_{16}H_{28}OSi$: 264.1910; found: 264.1912.

93: bp 60-67°C/0.3 Torr; ir (CCl_4): 2930, 1625, 1227, 875 cm^{-1}. Exact mass calcd for $C_{14}H_{26}OSi$: 238.1754; found: 238.1753.

94: bp 60-64°C/ 1.0 Torr; ir (film): 2930, 1611, 1328, 1130, 830 cm^{-1}. Exact mass calcd for $C_{15}H_{28}OSi$: 252.1910; found: 252.1909.

Preparation of 89b

The silyl enol ether 89a (0.49 g, 2.2×10^{-3} mol) was cyclopropanated as described for 26b using Zn-Ag couple (0.47 g, 7.2×10^{-3} mol), methylene iodide (0.32 mL, 4.0×10^{-3} mol) and Et_2O (6.5 mL). After refluxing for 19 h the usual workup gave 89b (0.36 g, 69%), which glc analysis (FFAP) indicated was > 95% pure. Preparative glc furnished a pure sample of 89b for characterization: ir (CCl_4):

3014, 2960, 1340 cm^{-1}. *Exact* mass calcd for $C_{14}H_{26}OSi$: 238.1753; found: 238.1747.

Cyclopropanation of **89a**, "Concentrated Conditions"

Following the usual procedure, a mixture of methylene iodide (0.44 mL, 5.5×10^{-3} mol), Et_2O (1 mL) and Zn-Ag couple (0.72 g, 1.1×10^{-2} mol) was warmed until refluxing occurred without heating. A solution of **89a** (0.49 g, 2.2×10^{-3} mol) in Et_2O (0.7 mL) was then added and the mixture was refluxed for 33 h (temp. of the oil bath was ca. 50°C). The usual workup furnished an oil (0.50 g), which glc analysis (FFAP) indicated to contain **89b** (8%) and **89c** (80%), the latter component was collected (prep glc) and characterized: ir (CCl_4): 2970, 1070 cm^{-1}. *Exact* mass calcd for $C_{14}H_{26}OSi$: 238.1753; found: 238.1754.

Repeating this reaction with CD_2I_2 (86) gave **89b**-d_x; ms: 1.4% d_0, 10.7% d_1, 87.79% d_2 total 1.87 atoms ^2H/molecule and **89c**-d_x; ms: 3.8% d_0, 29.8% d_1, 65.3% d_2, total 1.64 atoms ^2H/molecule.

Cyclopropanation of **92** and **93**, "Concentrated Conditions"

The silyl enol ethers **92** and **93** were cyclopropanated following the procedure described above for **89a**. Treatment of **92** with the Simmons-Smith reagent (rxn. time = 50 h) gave a mixture containing 80% **92c**,, while cyclopropanation of **93** (rxn. time = 50 h) gave **93b**.

For 92c; *Exact mass* calcd for $C_{17}H_{30}OSi$: 278.2066; found: 278.2069.

For 93b; *Exact mass* calcd for $C_{15}H_{28}OSi$: 252.1909; found: 252.1910.

Dimethylation of 79e

Following the usual procedure a mixture of 79e (0.12 g, 0.90 x 10^{-3} mol), $NaNH_2$ (0.19 g, 4.9 x 10^{-3} mol) and Et_2O (6 mL) was refluxed for 4 h. Methyl iodide (0.33 mL, 5.3 x 10^{-3} mol) was then added and the mixture was refluxed overnight. Following a second addition of CH_3I (0.11 mL, 1.8 x 10^{-3} mol) the mixture was refluxed for an additional 3 h and then worked-up to furnish crude 99. Pure 99 (0.11 g, 76%) was obtained by column chromatography on alumina using pentane-ether, 90:10, as eluent; ir ($CHCl_3$): 1712 cm^{-1} (C=O). *Exact mass* calcd for $C_{11}H_{16}O$: 164.1201; found: 164.1198.

Dimethylation of 80e

After refluxing a mixture of 80e (0.20 g, 1.5 x 10^{-3} mol), $NaNH_2$ (0.33 g, 8.5 x 10^{-3} mol) and Et_2O (15 mL) for 4 h, methyl iodide (0.58 mL, 9.3 x 10^{-3} mol) was added and the mixture was refluxed overnight. Following a second addition of CH_3I (0.19 mL, 3.0 x 10^{-3} mol) the mixture was then refluxed for an additional 3 h and the usual workup gave 98 (0.20 g, 83%); ir ($CHCl_3$): 1703 cm^{-1} (C=O). *Exact mass* calcd for $C_{11}H_{16}O$: 164.1201; found: 164.1201.

(J) EXPERIMENTAL FOR CHAPTER 10

Methylation of 104a

To a stirred solution of LDA (diisopropylamine (1.14 mL, 8.13 x 10^{-3} mol), *n*-BuLi in *n*-hexane (2.50 M, 2.79 mL) at -78°C was added 104a (0.79 g, containing ca. 10% of the isomeric [2.2.2] system) in THF (3 mL) dropwise and the stirring continued for 45 min before methyl iodide (0.90 mL, 1.44 x 10^{-2} mol) was added; the resulting mixture was stirred overnight at room temperature. Aqueous 10% NaCl solution (10 mL) was then added and the product was extracted with pentane (4 x 15 mL). The combined extracts were washed with aqueous 10% NaCl solution(2 x 15 mL) and with H_2O (15 mL) before drying over $MgSO_4$. After removal of the solvent the crude product (0.80 g) was purified by flash chromatography (Et_2O-petroleum ether (30°-60°C), 5:95) to furnish 107a (0.45 g, 57%); ^{13}Cmr data agreed with literature values (33).

Preparation of 104b

2-Trimethylsilyloxybicyclo[3.2.1]oct-2-ene was obtained from the corresponding ketone (0.70 g, containing ca. 10% of the isomeric [2.2.2] system) using LDA (diisopropylamine (1.26 mL, 9.0 x 10^{-3} mol), *n*-BuLi in *n*-hexane (2.50 M, 3.16 mL), THF (6 mL) at -78°C and trimethylsilyl chloride (1.29 mL, 1.0 x 10^{-2} mol), triethylamine (0.50 mL, 3.6 x 10^{-3} mol) and THF (1 mL). The product was recovered following the usual procedure (B)

and Kugelrohr distillation (90-96°C/10 Torr) gave an oil (1.05 g, ca. 90% 104b, 10% 32a by glc).

t-Butylation of 104b

To a flame-dried, nitrogen purged flask equipped with magnetic stirrer and serum cap was added 104b (0.92 g, containing ca. 10% of 32a), t-butyl chloride (0.71 mL, 6.6 x 10^{-} mol) and anhydrous methylene chloride (3 mL). On cooling the solution to -47°C, titanium tetrachloride (0.67 mL, 6.1 x 10^{-3} mol) was rapidly added by syringe. After stirring for 5 h, the mixture was diluted with H_2O (8 ml) and the product was extracted with methylene chloride (4 x 10 mL). The combined extracts were washed with H_2O (2 x 10 mL) and dried over $MgSO_4$. Gas-liquid chromatography (FFAP) indicated that 104c composed ca. 75% of the product mixture, flash chromatography (Et_2O-petroleum ether, 4:96) furnished 104c (0.53 g, 63%); an analytical sample was glc-collected for characterization; ir (CCl_4): 2985, 1714 cm^{-1}; ^{13}Cmr ($CDCl_3$) δ_C: 213.9 (C=O), 52.8 (CH), 52.3 (CH), 38.9 (CH_2), 35.8 (CH_2), 34.8 (CH), 31.7 (C), 28.5 (CH_2), 27.8 (CH_2), 27.7 (Me x 3), mp 35-36°C. Exact mass calcd for $C_{12}H_{20}O$: 180.1514; found: 180.1518.

Preparation of 104c-d_1

Ketone 104c (75 mg) was added to a solution of MeONa-MeOD (1 x 10^{-3} M, 2.6 mL) and the mixture was stirred

overnight under a nitrogen atmosphere. Diluting the mixture with D_2O (4 mL), the product was extracted with pentane and the combined extracts were washed with an aqueous 10% NaCl solution (10 mL) before drying over $MgSO_4$. Removal of the solvent by evaporation afforded 104c-d_1 (70 mg); ms: 3.3% d_0, 96.6% d_1 (total 0.966 atoms ^2H/molecule).

Methylation of 104c

To a solution of LDA (diisopropylamine (0.58 mL, 4.1×10^{-3} mol), *n*-BuLi in *n*-hexane(2.50 M, 1.41 mL), THF (5 mL)) was added 104c (0.53 g, 2.9×10^{-3} mol) in THF (2 mL) dropwise. After stirring at -78°C for 30 min the mixture was warmed to room temperature and stirred for an additional 30 min before methyl iodide (0.56 mL, 9.0×10^{-3} mol) was added and the stirring continued overnight. Aqueous 10% NaCl solution (10 mL) was added and the product was extracted with pentane, as described above. Removal of the solvent by evaporation gave an oil (0.47 g), which by glc (FFAP) analysis contained 4% 104c and 87% 104. Preparative glc furnished pure samples for characterization and for the homoenolization experiments; ir (film); 2975, 1698 cm^{-1}. Exact mass calcd for $C_{13}H_{22}O$: 194.1674; found: 194.1669.

Preparation of 107b

To a solution of LDA (diisopropylamine (0.73 mL, 5.21 x 10^{-3} mol), n-BuLi in n-hexane (2.46 M, 1.86 mL), THF (4.5 mL)) was added 107a (0.45 g, 3.3 x 10^{-3} mol) in THF (1 mL). After stirring the mixture for 45 min the quenching solution (trimethylsilyl chloride (0.75 mL, 5.9 x 10^{-3} mol), triethylamine (0.79 mL, 1.9 x 10^{-3} mol), THF (0.75 mL)) was added and the mixture stirred for 2 h at room temperature. After the usual workup (procedure B), Kugelrohr distillation (105°-110°C/15 Torr) gave 107b (0.50 g), which glc analysis (FFAP) indicated to be ca. 85% pure; an analytical sample was collected by preparative glc; ir (CCl_4): 2980, 1681, 1184, 880 cm^{-1}; ^{13}Cmr ($CDCl_3$) δ_C: 149.7 (C), 106.2 (C), 41.7 (CH), 40.9 (CH_2), 36.6 (CH_2), 34.8 (CH_2), 34.4 (CH), 30.9 (CH_2), 16.0 (Me), 1.1 ($SiMe_3$). *Exact mass* calcd for $C_{12}H_{22}OSi$: 210.1434; found: 210.1435.

t-Butylation of 107b

To a solution of 107b (0.91 g, 4.3 x 10^{-3} mol) and t-butyl chloride (0.66 mL, 6.1 x 10^{-3} mols) in dry methylene chloride (3.2 mL) at -47°C was added titanium tetrachloride (0.66 mL, 6.0 x 10^{-3} mol) with stirring. The reaction mixture was then stirred for 1 h at -47°C and an additional 10 h at room temperature. The mixture was then cooled to 0°C, diluted with H_2O (8 mL) and the product was extracted with methylene chloride as described earlier:

Removal of the solvent furnished an oil (0.70 g), which glc analysis indicated was 77% **107a** and 10% **107**. Preparative glc afforded an analytical sample of **107**: ir ($CHCl_3$): 2950, 1698 cm^{-1}. *Exact mass* calcd for $C_{13}H_{22}O$: 194.1671; found: 194.1671.

t-Butylation of **28a**

8-Trimethylsilyloxytricyclo[5.3.1.$0^{2,6}$]-undecan-8-one(0.73 g, 3.1 x 10^{-3} mol) was t-butylated as described above for **104c**. Flash chromatography (Et_2O-petroleum ether, 4:96) of the product mixture furnished **105c** (0.35 g, 51%), which by ^{13}Cmr contained ca. 5% impurity. An analytical sample of **105c** was further purified by sublimation (mp 69°-70°C); ir ($CHCl_3$): 2945, 1706 cm^{-1}; ^{13}Cmr ($CDCl_3$) δ_C: 213.8 (C=O), 58.7 (CH), 53.2 (CH), 48.1 (CH), 46.4 (CH), 40.4 (CH), 34.5 (CH_2), 34.2 (CH_2), 33.9 (CH_2), 33.2 (CH_2), 31.7 (C), 27.8 (CH_2), 27.7 (Me x 3). *Exact mass* calcd for $C_{15}H_{24}O$: 220.1827; found: 220.1823.

Preparation of **105c**-d_1

A sample of **105c** (40 mg) was placed in 1 x 10^{-3} M MeONa in MeOD (1.3 mL) and the solution stirred at room temperature overnight. After quenching with D_2O (2 mL), the ketone was extracted with pentane as described for **104c**-d_1 and this yielded 31 mg of **105c**-d_1.

Preparation of 105

Ketone **105c** (0.24 g, 1 x 10^{-3} mol) was methylated as described above for **104** (methylation required two cycles) using LDA (diisopropylamine (0.21 mL, 1.5 x 10^{-3} mol), *n*-BuLi in *n*-hexane (2.46 M, 0.53 mL), THF (2 mL)) and methyl iodide (0.20 mL, 3.2 x 10^{-3} mol). The usual workup afforded an oil (0.18 g) which by glc (FFAP) was 94% **105** and 6% **105c** (after the second cycle). Flash chromatography (Et_2O-petroleum ether, 5:95) gave **105** (0.15 g) which was > 95% pure by ^{13}Cmr (preparative glc (SE-30, FFAP, Carbowax) failed to improve the purity of this sample): ir (film): 2960, 1698 cm^{-1}. *Exact mass* calcd for $C_{15}H_{27}O$: 234.1984; found: 234.1981.

Oxidation of 109

To a cooled (0°C), stirred suspension of PCC (6.81 g, 3.16 x 10^{-2} mol), sodium acetate (0.52 g, 6.3 x 10^{-3} mol), filter aid (6.80 g) and methylene chloride (27.60 mL) was added a solution of **109** (3.18 g 2.09 x 10^{-2} mol) in methylene chloride (27.60 mL). After stirring the mixture for 3 h at room temperature, anhydrous ether (60 mL) was added and the insoluble residue was removed by filtration and washed with Et_2O (150 mL). The combined organic fractions were concentrated under reduced pressure and washed with aqueous 10% NaOH solution (3 x 20 mL), aqueous 5% HCl solution (20 mL) and with aqueous 10% NaCl solution (3 x 20 mL) before drying over

$MgSO_4$. Kugelrohr distillation (140-145°C/15 Torr) gave 110 (2.67 g, 85%) pure by glc (FFAP).

Preparation of 111

Treatment of 110 (2.65 g, 1.77×10^{-2} mol) with LDA (diisopropylamine (3.47 mL, 2.48×10^{-2} mol), n-BuLi in n-hexane (2.46 M, 8.62 mL), THF (14 mL) followed by chlorotrimethylsilane (3.59 mL, 2.83×10^{-2} mol) and triethylamine (1.23 mL, 8.8×10^{-3} mol) in THF (4 mL) gave after workup (procedure B) and Kugelrohr distillation (89-94°C/ 0.2 Torr) 111 (3.48 g, 89%): ir (film): 2955, 1614, 1250, 844 cm-1; ^{13}Cmr shieldings agreed with literature values (27).

Cyclopropanation of 111

The silyl enol ether 111 (1.94 g, 9.74×10^{-3} mol) was treated with the Simmons-Smith reagent (Zn-Ag couple (1.83, 2.80×10^{-3} mol), methylene iodide (1.13 mL, 1.40×10^{-2} mol), Et_2O (21 mL)) for 14 h and the usual isolation procedure gave 112 (2.00 g). Glc analysis (FFAP) of the product indicated it to be >90% pure and an analytical sample was collected by preparative glc; ir (film): 2960, 1250, 870 cm^{-1}; ^{13}Cmr shieldings agreed with literature values (27).

Homoketonization of 112

To a cooled (0°C), methanolic NaOH solution (3 M, 19 mL) was added the product mixture from cyclopropanation of 111 (1.00 g) and the resulting mixture was stirred at 0°C for 36 h. Diluting the mixture with aqueous 10% NaCl solution (25 mL), the product was extracted with pentane and dried over $MgSO_4$. Removal of the solvent afforded a yellow oil (0.58 g), which by glc analysis (FFAP) contained a 1.0:2.1 ratio of 114 and 113, respectively. Repeating this procedure afforded an oil (0.70 g) with the same product composition as before. From the two combined fractions, flash chromatography (ethyl acetate-petroleum ether) furnished pure samples of 113 (0.78 g) and 114 (0.38 g).

Dimethylation of 113

Ketone 113 (0.42, 2.6×10^{-3} mol) was dimethylated using $NaNH_2$ (0.55 g, 1.4×10^{-2} mol) in Et_2O (16 mL) and four additions of methyl iodide (0.32 mL, 5.1×10^{-3} mol) after 2, 2, 10 and 4 h. After refluxing for an additional 3 h the usual workup furnished 106 (0.33 g, 67%) and an analytical sample was collected by preparative glc (FFAP) for characterization; ir (CCl_4): 2962, 1703 cm^{-1}. Exact mass calcd for $C_{13}H_{20}O$: 192.1514; found: 192.1519.

(K) EXPERIMENTAL FOR CHAPTER 11

Ketones 120 and 121 were prepared from 63 by the method of Turro (54).

Dimethylation of 121

After a mixture of 121 (0.30 g, 2.2 x 10^{-3} mol), sodium amide (0.47, 1.2 x 10^{-2} mol) and Et_2O (15 mL) was refluxed for 2.5 h, methyl iodide (0.54 mL) was added and two further additions were made after 10 h (0.20 mL) and 2.5 h (0.34 mL). The mixture was then refluxed for 7 h and the usual isolation procedure furnished an oil (0.25 g), which by glc analysis (Carbowax) and ^{13}Cmr spectroscopy was found to be a mixture of 116a (ca. 70%) and 3,7,7-trimethylbicyclo[2.2.1]heptan-2-one (20%). Therefore, the mixture (0.25 g) was treated to a second cycle of $NaNH_2$/MeI which yielded 0.16 g of oily liquid, which glc indicated to contain 90% 116a and 4% 3,7,7-trimethylbicyclo[2.2.1]-heptan-2-one. Preparative glc gave furnished pure samples of 116a; ir (film): 2960, 1750 cm^{-1}. Exact mass calcd for $C_{11}H_{18}O$: 166.1358; found: 166.1356.

Dimethylation of 120

Following the usual procedure, a slurry of Et_2O (24 mL), sodium amide (0.79 g, 2.0 x 10^{-2} mol) and 120 (0.50, 3.7 x 10^{-3} mol) was refluxed for 2 h. Methyl iodide (0.46 mL) was then added and three further additions (0.46 mL) were made after 2, 4 and 11 h. After refluxing for an

additional 3 h the reaction mixture was worked up and flash chromatography (Et_2O-petroleum ether, 5:95) gave 0.31 g of 116b (51%). Exact mass calcd for $C_{11}H_{16}O$: 164.1201; found: 164.1201.

Preparation of 122

A mixture of methylenecyclopropane (3.27 g, 6.06 x 10^{-2} mol) (70), cyclopentadiene (4.90 g, 7.42 x 10^{-2} mol) and hydroquinone (12 mg) was transferred to a series of thick-walled glass tubes (ratio of tube volume to solution was 5:1) and sealed under vacuum. The tubes were placed in an oil bath at 100°C and gradually heated to 190°C over 3.5 h. After 19 h the tubes were cooled, opened and the contents removed with pentane. Distillation (28-30°C/ 18 Torr, lit. (71) 34°C/20 Torr) gave 122 (3.98 g, 55%).

Hydroboration of 122

On cooling a solution of 122 (3.90 g, 3.25 x 10^{-2} mol) in hexane (11 mL) to 0°C, 10 M borane-methyl sulfide solution (1.33 mL, 1.33 x 10^{-2} mol) was added dropwise. Upon completion of the addition the ice bath was removed and the mixture was stirred for 6 h. The excess borane was then slowly decomposed by the addition of ethanol (12.70 mL) followed by 3 M aqueous NaOH solution (4.70 mL). The solution was cooled to 0°C and 30% hydrogen peroxide solution (4.70 mL) was slowly added with stirring, upon completion of this addition the mixture was refluxed for

1.5 h. The mixture was then diluted with H_2O (50 mL), the organic phase was decanted and the aqueous phase was extracted with pentane (3 x 60 mL). After washing the extracts with brine and drying over $MgSO_4$, distillation (49-50°C/0.4 Torr) furnished a 1:1 mixture of 123 and 124 (3.05 g, 68% yield); ir (CCl_4): 3620, 3360, 3080, 2980, 1079 cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 4.08 (1H, br d, J = 6.6 Hz), 3.94 (1H, br d, J = 6.6 Hz), 2.38 (1H, br s), 2.25 (1H, d, J = 5 Hz), 0.80-2.10 (16H, m), 0.20-0.60 (8H, m); ^{13}Cmr ($CDCl_3$ δ_C: 74.7 (CH), 73.5 (CH), 53.0 (CH), 46.6 (CH), 44.4 (CH), 42.0 (CH_2), 40.6 (CH_2), 40.1 (CH_2), 37.7 (CH), 36.4 (CH_2), 35.5 (CH_2), 35.1 (CH_2), 24.8 (CH_2), 21.6 (CH_2), 15.4 (CH_2), 14.2 (CH_2), 9.0 (C), 8.8 (C). Exact mass calcd for $C_9H_{14}O$: 138.1045; found: 138.1047.

Oxidation of 123 and 124

To a slurry of PCC (2.33 g, 1.08 x 10^{-2} mol), sodium acetate (0.18 g, 2.2 x 10^{-4} mol), filter aid (Celite, 2.33 g) and methylene chloride (9.60 mL) was added the 1:1 mixture of 123 and 124 (1.00 g, 7.25 x 10^{-3} mol) in methylene chloride (9.60 mL). After stirring for 3 h the reaction mixture was diluted with anhydrous ether (60 mL), and the supernatant decanted from the black gum. The insoluble residue was washed with Et_2O and the combined organic fractions were washed with 10% NaOH solution and with H_2O before drying over $MgSO_4$. Removal of the solvent gave a 1:1 mixture of 125 and 126 (0.99 g); ir ($CHCl_3$):

3090, 2980, 1765 cm^{-1}; ^{13}Cmr ($CDCl_3$): δ_C: 218.5 (C=O), 215.4 (C=O), 57.6 (CH), 52.1 (CH), 44.2 (CH_2), 44.0 (CH), 43.7 (CH_2), 39.0 (CH_2), 38.4 (CH_2), 38.1 (CH_2), 36.8 (CH), 35.6 (CH_2), 24.4 (C), 21.2 (C), 15.2 (CH_2), 13.8 (CH_2), 10.0 (CH_2), 9.4 (CH_2). Exact mass calcd for $C_9H_{12}O$: 136.0888; found: 136.0885.

Dimethylation of 125 and 126

Following the general procedure, a slurry of sodium amide (1.90 g, 4.87×10^{-2} mol), Et_2O (30 mL) and a 1:1 mixture of 125 and 126 (0.83 g, 6.1×10^{-3} mol) was refluxed for 2 h. Methyl iodide was then added (0.76 mL) and three further additions were made after 2 h (0.76 mL), 4 h (1.52 mL) and 11 h (1.52 mL). After refluxing for an additional 5 h the reaction mixture was worked up to furnish an oil (0.86 g) which by ^{13}Cmr spectroscopy was a mixture of mono- and dimethylated ketones. Two additional cycles furnished a 1:1 mixture (0.77 g) of 127 and 117b, which were separated and collected by preparative glc (FFAP).

For 117b; ir ($CHCl_3$): 3030, 2921, 1737 cm^{-1}. Exact mass calcd for $C_{11}H_{16}O$: 164.1201; found: 164.1967.

For 127; ir (CCl_4): 3080, 2990, 1739 cm^{-1}. Exact mass calcd for $C_{11}H_{16}O$: 164.1201; found: 164.1201.

Hydrogenation of 116b and 117b

An approximately 1:1.6 mixture of 116b and 117b (0.21 g, 1.3 x 10^{-3} mol, the product from homoenolization of 116b for 187 h at 185°C) was added to a pressure vessel containing glacial acetic acid (7 mL) and PtO_2 (0.10 g) and the mixture was treated with hydrogen (50 psi) for 33 h. After the addition of H_2O (10 mL), the mixture was neutralized with Na_2CO_3 and the catalyst was removed by filtration. The neutral solution was saturated with NaCl and extracted with pentane (3 x 20 mL), the combined extracts were then washed with an aqueous saturated Na_2CO_3 solution (10 mL) before drying over $MgSO_4$. Removal of the solvent gave an oil (0.20 g), which glc analysis (FFAP) indicated was a mixture of 116a (37%) and 128 (63%). Flash chromatography (Et_2O-petroleum ether, 10:90) furnished pure samples of 116a (0.78 g, 4.8 x 10^{-4} mol) and 128 (0.10 g, 6.0 x 10^{-4} mol): ir (film): 3360, 2945, 1073 cm^{-1}. Exact mass calcd for $C_{11}H_{20}O$: 168.1514; found: 168.1517.

Oxidation of 128

To a slurry of PCC (0.19 g, 8.8 x 10^{-4} mol), sodium acetate (15 mg), filter aid (Celite, 0.19 g) and methylene chloride (1.60 mL) was added a solution of 128 (0.10 g, 6.0 x 10^{-4} mol) in methylene chloride (1.0 mL). After stirring for 3 h the reaction was worked up as described for the oxidation of 123 and 124. Flash chromatography of the product gave 117a (88 mg, 89%); ir

(film): 2939, 1745 cm^{-1}; ^{13}Cmr ($CDCl_3$) δ_C: 223.7 (C=O), 58.0 (CH), 50.9 (CH), 49.0 (C), 41.4 (CH_2), 38.2 (C), 35.6 (CH_2), 34.6 (CH_3), 29.2 (CH_3), 27.7 (CH_3), 24.3 (CH_3). Exact mass calcd for $C_{11}H_{18}O$: 166.1358; found: 166.1362.

(L) EXPERIMENTAL FOR CHAPTER 12

Monomethylation of 71 (132)

To a stirred solution of LDA (prepared from diisopropylamine (0.53 mL, 3.8×10^{-3} mol), THF (6 mL) and *n*-BuLi in *n*-hexane (2.5 M, 1.30 mL) at -78°C) under a nitrogen atmosphere was added dropwise a solution of 71 (0.40 g, 2.7×10^{-3} mol) in THF (2 mL) and stirring was continued for 35 min. Methyl iodide (0.34 mL, 5.4×10^{-3} mol) was then added and the mixture was stirred overnight at room temperature. Diluting the mixture with aqueous 10% NaCl solution (10 mL) the product was extracted with pentane (4 x 15 mL). The combined extracts were then washed with an aqueous 10% NaCl solution (2 x 15 mL) and with H_2O (15 mL) before drying over $MgSO_4$. Removal of the solvent by evaporation gave 132 (0.43 g, 98%) which was pure by glc analysis: ir (CCl_4): 3080, 2940, 1748 cm^{-1}; ^{13}Cmr ($CDCl_3$) δ_C: 213.4 (C=O), 145.0 (C), 143.0 (CH), 131.3 (CH), 117.6 (C), 57.8 (CH), 48.5 (CH), 44.3 (CH), 19.9 (CH_3), 19.4 (CH_3), 16.0 (CH_3); ^1Hmr ($CDCl_3$) δ: 6.66 (1H, dd, J = 5.8, 2.8 Hz), 6.24 (1H, m), 3.53 (1H, m), 3.34 (1H, m), 2.14 (1H, q, J = 7.3 Hz), 1.68 (CH_3), 1.63 (CH_3), 1.04

(CH_3, d, J = 7.3 Hz). Exact mass calcd for $C_{11}H_{14}O$: 162.1045; found: 162.1039.

Hydrogenation of 132 (133).

To a solution of 132 (0.22 g, 1.4×10^{-3} mol) in 95% ethanol (3.26 mL) was added 10% Pd on activated charcoal and the mixture was hydrogenated (760 Torr) for 6 h. The catalyst was then removed by filtration and the ethanolic solution was diluted with aqueous 10% NaCl solution (6 mL) and extracted with pentane (3 x 8 mL). The combined extracts were washed with aqueous 10% NaCl solution (2 x 10 mL) and with H_2O (10 mL) before drying over $MgSO_4$. The combined aqueous fractions were then backwashed with pentane (20 mL) and the organic washings were combined. Removal of the solvent by evaporation gave 133 (0.22 g, 1.3×10^{-3} mol) in 99% yield, which glc (FFAP) indicated was pure; ir (CCl_4): 2960, 1745 cm^{-1}; ^{13}Cmr ($CDCl_3$) δ_C: 217 (C=O), 136.4 (C), 121.2 (C), 52.0 (CH), 51.3 (CH), 43.7 (CH), 27.1 (CH_2), 24.0 (CH_2), 20.7 (CH_3), 20.3 (CH_3), 15.2 (CH_3); ^{1}Hmr ($CDCl_3$) δ: 3.05 (1H, m), 2.09 (1H, q, J = 7.4 Hz), 1.75-1.90 (3H, m), 1.73 (CH_3), 1.69 (CH_3), 1.48-1.57 (2H, m), 1.02 (CH_3, d, J = 7.4 Hz). Exact mass calcd for $C_{11}H_{16}O$: 164.1201; found: 164.1201.

Methylation of 133 with $NaNH_2$/MeI

Following the usual procedure a mixture of 133 (0.42 g, 2.6×10^{-3} mol), $NaNH_2$ (0.84 g, 2.2×10^{-2} mol)

and Et_2O (8.40 mL) was refluxed for 2.5 h. Methyl iodide (1.00 mL) was then added and four further additions of CH_3I were made after 8 h (0.50 mL), 4 h (0.50 mL), 3 h (0.50 mL), and 2 h (0.31 mL). After refluxing for an additional 17 h the reaction was worked-up to furnish an oil (0.43 g, 94%), which glc analysis (FFAP) indicated was > 98% 129. Preparative glc (FFAP) furnished pure samples for characterization and for the homoenolization experiments; ir (CCl_4): 2970, 1747 cm^{-1}. *Exact* mass calcd for $C_{12}H_{18}O$: 178.1358; found: 178.1361.

REFERENCES

1. G. Berthier, M. Cais, E. Campaigne et al. The Chemistry of the Carbonyl Group, edited by S. Patai, Interscience Publishers, New York (1966).

2. J. Toullec, Advances in Physical Organic Chemistry, 18, 1 (1982).

3. A.L. Johnson, N.O. Petersen, M.B. Rampersad, and J.B. Stothers. Can. J. Chem. 52, 4143 (1974).

4. A. Nickon and J.L. Lambert. J. Am. Chem. Soc. 84, 4604 (1962); 88, 1905 (1966).

5. A. Nickon, H. Kwasnik, T. Swartz, R.O. Williams and J.B. DiGiorgio. J. Am. Chem. Soc. 87, 1615 (1965).

6. (a) A. Nickon, J.L. Lambert, J.E. Oliver, D.F. Covey and J. Morgan. J. Am. Chem. Soc. 98, 2593 (1976); (b) W.D. Dadson and T. Money. Can. J. Chem. 58, 2524 (1980).

7. R. Howe and S. Winstein. J. Am. Chem. Soc. 87, 915 (1965); T. Fukunaga. J. Am. Chem. Soc. 87, 916 (1965).

8. D.J. Cram, B. Rickborn, C.A. Kingsbury and P. Haberfield. J. Am. Chem. Soc. 83, 3678 (1961).

9. D.H. Hunter. Isotopes in Organic Chemistry, edited by E. Buncel and C.C. Lee, 1, p. 151. Elsevier, Amsterdam (1975).

10. A.K. Cheng, J.B. Stothers and C.T. Tan. Can. J. Chem. 55, 447 (1976).

11. A.L. Johnson, J.B. Stothers and G.T. Tan. Can. J. Chem. 53, 212 (1975).

12. N.H. Werstiuk, S. Yeroushalmi and G. Timmins. Can. J. Chem. 61, 1945 (1983).

13. A.K. Cheng, A.K. Ghosh and J.B. Stothers. Can. J. Chem. 62, 1385 (1984).

14. (a) M.B. Rampersad and J.B. Stothers. J. Chem. Soc. Chem. Commun. 709 (1976); (b) R.A. Dyllick-Brenzinger and J.B. Stothers. J. Chem. Soc. Chem. Commun. 108 (1979).

15. A.K. Cheng and J.B. Stothers. Can. J. Chem. 56, 1342 (1978).

16. (a) N.H. Werstiuk. Tetrahedron 39, 205 (1983); (b) D.H. Hunter, J.B. Stothers and E.W. Warnhoff. Rearrangements in ground and excited states. Vol. I (Edited by P. de Mayo), Academic Press, New York, 1, pp. 430-437 (1980).

17. V. Patel and J.B. Stothers. Can. J. Chem. 58, 2728 (1980).

18. D.H. Hunter, A.L. Johnson, J.B. Stothers, A. Nickon, J.L. Lambert and D.F. Covey. J. Am. Chem. Soc. 94, 856 (1972).

19. C.H. DePuy, F.W. Breitbeil and K.R. DeBruin. J. Am. Chem. Soc. 88, 3347 (1966).

20. T. Fukunaga and R.A. Clement. J. Org. Chem. 42, 270 (1977).

21. A.J.H. Klunder and B. Zwanenburg. Tetrahedron Letters 1721 (1971).

22. C.D. Gutsche and D. Redmore. Carbocyclic Ring Expansion Reactions, Chaper 4, Academic Press, New York (1968).

23. W.L. Mock and M.E. Hartman. J. Org. Chem. 42, 459 (1977).

24. P.A.S. Smith and D.R. Baer. Organic Reactions 11, 157 (1960).

25. Y. Hoyano, V. Patel and J.B. Stothers. Can. J. Chem. 58, 2730 (1980).

26. J.M. Denis, C. Girand and J.M. Conia. Synthesis 549 (1972).

27. B.A. Dawson and J.B. Stothers. Org. Magn. Reson. 21, 217 (1983).

28. G.C. Joshi and L.M. Pande. Synthesis 45 (1975).

29. T. Yanami, M. Miyashita and A. Yoshikoshi. J. Org. Chem. 45, 607 (1980).

30. A.K. Cheng and J.B. Stothers. Org. Magn. Reson. 9 355 (1977).

31. M. Christl and R. Herbert. Org. Magn. Reson. 12, 150 (1979).

32. P. Brun, J. Casanova, J. Hatem, J.P. Zahra and B. Waegall. Org. Magn. Reson. 12, 537 (1979).

33. S.H. Grover, D.H. Marr, J.B. Stothers and C.T. Tan. Can. J. Chem. 53, 1351 (1975).

34. J.L. Jurlina and J.B. Stothers. J. Am. Chem. Soc. 104, 4677 (1982) and references therein.

35. E.N. Marvell, G.J. Gleicher, D. Sturmer and K. Salisbury. J. Org. Chem. 33, 3393 (1967).

36. M.A. McKinney and P.P. Patel. J. Org. Chem. 38, 4059 (1973).

37. J.B. Stothers, J.R. Swenson and C.T. Tan. Can. J. Chem. 53, 581 (1975).

38. C.W. Jefford and C.R.Rimbault. J. Am. Chem. Soc. 100, 6515 (1978).

39. J.G. Atkinson, M.H. Fisher, D. Horley, A.T. Morse, R.S. Stuart and E. Synnes. Can. J. Chem. 43, 1614 (1965).

40. H.C. Brown, C.P. Gary and K.T. Lin. J. Org. Chem. 36, 387 (1970).

41. P.K. Freeman, D.M. Balls and D.J. Brown. J. Org. Chem. 33, 2211 (1968).

42. J.B. Stothers. Carbon-13 NMR Spectroscopy, Academic Press, New York (1972).

43. T.J. Katz and S.A. Cerefice. J. Am. Chem. Soc. 93, 1049 (1971).

44. C.W. Jefford, T. Kabengele, J. Kovacs and U. Burger. Tetrahedron Letters 257 (1974).

45. C.W. Jefford and P.T. Huy. Tetrahedron Letters 755 (1980).

46. T.J. Katz, S.A. Cerefice. J. Am. Chem. Soc. 91, 6519 (1969).

47. I. Ryu, S. Murai, S. Otani and N. Sonoda. Tetrahedron Letters 1995 (1977).

48. (a) M. Geisel, C.A.Grob, W.Santi and W. Tschudi. Helv. Chim. Acta 56, 1046 (1973); (b) R.R.Sauers, J.A. Beisler and H. Feilich. J. Org. Chem. 32, 569 (1967); (c) G.T. Lumb and G.W. Whiteman. Tetrahedron 21, 499 (1965).

49. R.J. Abraham and P. Loftus. Proton and Carbon 13 NMR Spectrsocopy, Heydon and Sons, London, pp. 145-48(1978).

50. E.J. Corey, R. Hartmann and P.A. Vatakencherry. J. Am. Chem. Soc. 84, 2611 (1962).

51. W.C.G.M. de Valk, A.J.H. Klunder and B. Zwanenburg. Tetrahedron 971 (1980).

52. M. Demuth and K. Schaffner. Angew. Chem. Int. Ed. Engl. 21, 820 (1982).

53. (a) S. Durmat and H. Köllmar. J. Am. Chem. Soc. 102, 6942 (1980); (b) A. de Meijere. Angew. Chem. Int. Ed. Engl. 18, 809 (1979).

54. N.J. Turro and G.L. Farrington. J. Am. Chem. Soc. 102, 6056 (1980).

55. A. Bax, R. Freeman and S.P. Kempsell. J. Am. Chem. Soc. 102, 4849 (1980).

56. J. M. Conia and G.L. Lange. J. Org. Chem. 43, 555 (1978).

57. A. Oku, Y. Nozaki, H. Hasgawa, J. Nishimura and T. Harada. J. Org. Chem. 48, 4374 (1983).

58. C.H. DePuy and P.R. Story. J. Am. Chem. Soc. 82, 627 (1960).

59. J.L. Marshall. Carbon-Carbon and Carbon-Proton NMR Couplings, Verlag Chemie International, Deerfield Beach, Florida, pp. 81 (1983).

60. J. March. Advanced Organic Chemistry, 2nd Ed., McGraw Hill, New York, pp. 691-694 (1977).

61. C.T. Tan, Ph.D. Thesis. University of Western Ontario, London, Ontario (1978).

62. J.K. Whitesell and R.S. Matthews. J. Org. Chem. 42, 3878 (1974).

63. L.M. Jackmann and S. Sternhell. Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, Pergamon Press Ltd., Oxford, pp. 286 (1969).

64. N.H. Werstiuk, S. Yeroushalmi and G. Timmins. Can. J. Chem. 61, 1945 (1983).

65. B.A. Dawson, A.K. Ghosh, J.L. Jurlina, A.J. Ragauskas and J.B. Stothers. Can. J. Chem. 62, 2521 (1984).

66. J.L. Jurlina, H.A. Patel and J.B. Stothers. Can. J. Chem. 62, 1159 (1984).

67. M.T. Reetz and W.F. Maier. Angew. Chem. Int. Ed., 17, 48 (1978).

68. H.C. Brown, I. Rothberg and D.L. Vander Jagt. J. Org. Chem. 37, 4098 (1972).

69. J.B. Stothers, C.T. Tan and K.C. Teo. Can. J. Chem. 51, 2893 (1973).

70. J.R. Salaun, J. Champion and J.M. Conia. Organic Synthesis 57, 36 (1977).

71. W. Adam, N. Carballeira, E.M. Peters, K. Peters and N.G. Schnering. J. Am. Chem. Soc. 105, 5132 (1983).

72. D.M. Hudyma, J.B. Stothers and C.T. Tan. Org. Magn. Reson. 6, 614 (1974).

73. J.B. Stothers, J.R. Swenson and C.T. Tan. Can. J. Chem. 53, 581 (1975).

74. J. Meinwald and P.G. Gassman. J. Am. Chem. Soc. 82, 5445 (1960).

75. W.R. Moore, W.R. Moser and J.E. LaPrade. J. Org. Chem. 28, 2200 (1963).

76. K.B. Wiberg and B.A. Hess, Jr. J. Org. Chem. 31, 2250 (1966).

77. D.H. Hunter, Y. Lin, A.L. McIntyre, D.J. Shearing and M. Zvagulis. J. Am. Chem. Soc. 95, 8327 (1973).

78. Y. Bessiere, M. Barthelemy, A.F. Thomas, W. Pickenhagen and C. Starkemann. Nouveau Journal de Chimie 2, 365 (1978).

79. R.D. Smith and H.E. Simmons. Organic Synthesis 41, 72 (1961).

80. A.T. Young and R.D. Guthrie. J. Org. Chem. 35, 853 (1970).

81. K. Alder, H.J. Ache and F.H. Flock. Chem. Ber. 93, 1388 (1960).

82. G. Crane, C.E. Boord and A.K.L. Heune. J. Am. Chem. Soc. 67, 1237 (1945).

83. N. Freiesleben. Ger. Patent No. 1, 146, 050 (1963); Chem. Abst. 59, 9914 (1963).

84. G.L. Closs and K.D. Krantz. J. Org. Chem. 30, 2278 (1965).

85. A.K. Colter and R.C. Musso. J. Org. Chem. 30, 2462 (1965).

86. H. Takaya, T. Suzuki, Y. Kumagai, M. Yamakawa and R. Noyori. J. Org. Chem. 46, 2846 (1981).

87. W.C. Still, M. Kahn and A. Mitra. J. Org. Chem. 43, 923 (1978).

88. G.A. Morris and R. Freeman. J. Am. Chem. Soc. 101, 760 (1979).

89. S.L. Patt and J.N. Shoolery. J. Magn. Reson. 46, 535 (1982).

90. D.M. Doddrell, D.T. Pegg and M.R. Bendall. J. Magn. Reson. 48, 323 (1982).

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