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β-ENOLIZATION IN BICYCLIC KETONES

by

David James Muir

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, Canada

April 1994

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ABSTRACT

A variety of bicyclic ketones was prepared and under strongly basic conditions (*t*-BuOK/*t*-BuOH/185°C) their behaviour with respect to β-enolization was examined. Several new compounds were produced upon such treatment; these were identified on the basis of their ^{13}Cmr and ^{1}Hmr spectra.

3,3-Dimethylbicyclo[3.2.2]nonan-2-one slowly rearranged to 3,3-dimethylbicyclo[3.3.1]nonan-2-one, and the latter was stable. Similarly, 3,3-dimethylbicyclo[3.2.2]non-6-en-2-one rearranged to 3,3-dimethyl-bicyclo[3.3.1]non-6-en-2-one, which was not stable. Experiments with 3,3-dimethylbicyclo[3.3.1]-non-6-en-2-one revealed that it was converted into five compounds. The major product, 2,2-dimethyl-4,5,6,7-tetrahydrindan-1-one, arose from a β-enolate rearrangement. However, this enone underwent slow reduction to *cis*- and *trans*-8,8-dimethylbicyclo[4.3.0]nonan-7-one, presumably by single electron transfer from *t*-BuOK. As a result, the use of a β-enolate rearrangement in natural product synthesis was not considered worthwhile. Also, 3,3,7,7-tetramethylbicyclo-[3.3.1]nonan-2,6-dione was found to be reduced to 6-hydroxy-3,3,7,7-tetramethylbicyclo[3.3.1]nonan-2-one.

3,3-Dimethylbenzobicyclo[3.2.1]- and [2.2.2]octen-2-one and 3,3-dimethylbenzobicyclo[3.2.2]nonen-2-one were prepared and then examined under the same conditions as above. It was found that each rearranged to a single ketone; namely, 3,3-

dimethyl-6,7-benzobicyclo[3.3.0]octen-2-one, 7,7-dimethyl-2,3-benzobicyclo[3.2.1]octen-6-one and 3,3-dimethyl-5,6-benzobicyclo[3.3.1]nonen-2-one, respectively. These rearrangement processes, however, are in competition with Haller-Bauer cleavage. The acids resulting from cleavage represented the major products of base treatment. This process precluded synthetic applications of β-enolate rearrangement in these systems.

The highly hindered alkoxide base, potassium 3-ethyl-3-pentoxide was prepared in an effort to retard the cleavage pathway, and while rearrangement was still observed, a predominance of cleavage products was again noted. The effect of several amide bases on the homoenolization of a variety of hindered ketones was also undertaken, in the hope of eliminating reduction caused by *t*-BuOK. Based on the results of this study, only N-lithio-9-azabicyclo[3.3.1]nonane (LABN) appeared to be worthy of further study, although for the systems studied herein, β-enolization was not observed when LABN was used as base.

ACKNOWLEDGEMENTS

First and foremost, I would like to express my sincere gratitude to Prof. J. B. Stothers, for his guidance and support throughout my graduate program, and for the wealth of knowledge, chemical and otherwise, that he has imparted. Dr. Stothers has made this study not only possible, but enjoyable.

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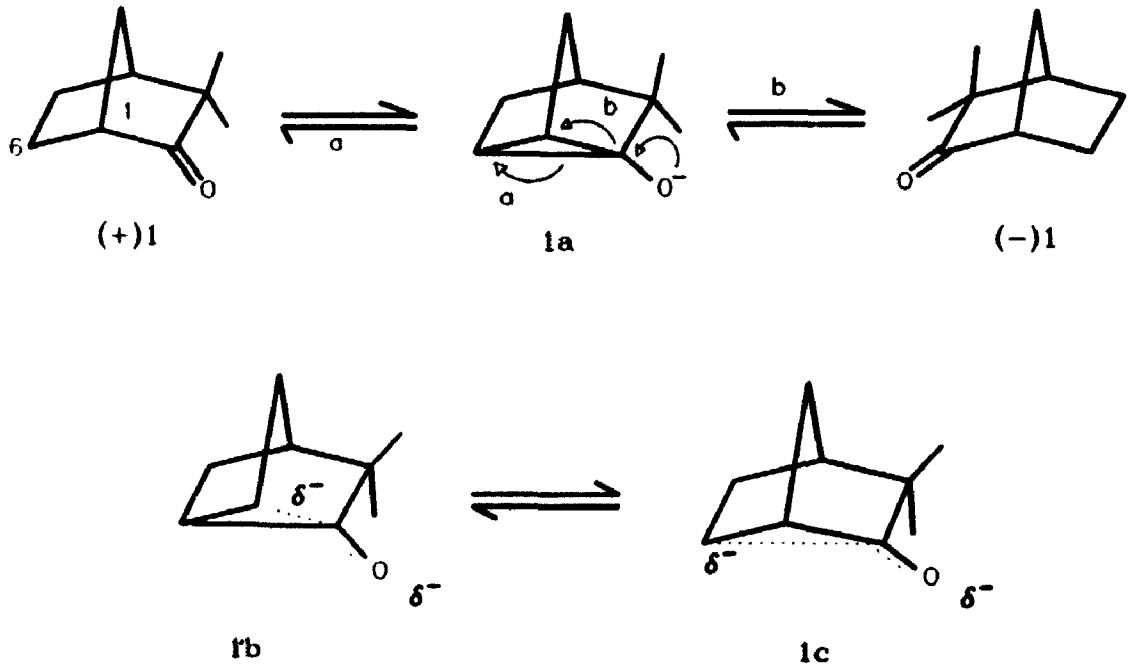
CHAPTER ONE

GENERAL INTRODUCTION

The ability of the carbonyl group to stabilize an adjacent carbanion has been extensively documented. In fact, α-enolate anions have become one of the most useful synthetic building blocks in organic chemistry. A ketone enhances the acidity of its α-protons by approximately 20 pK_a units relative to the corresponding hydrocarbon; the magnitude of this increase gives rise to the notion that protons farther from the carbonyl group might be affected as well.

In 1962, Nickon and Lambert (1) discovered that (+)-camphenilone (+1) was racemized upon treatment with potassium *t*-butoxide (*t*-BuOK) in *t*-butanol-O-d_1 (*t*-BuOD) at elevated temperature. Since racemization was complete upon prolonged treatment, a process must exist whereby C-1 and C-6 become equivalent through a symmetrical intermediate which then partitions equally between the camphenilone enantiomers (Scheme 1-1). Furthermore, up to three atoms of deuterium were incorporated, and the rate of deuterium incorporation equalled the rate of racemization, providing indirect evidence for ^2H incorporation at C-1 and C-6 (2). These results were readily explained by the formation of a 'homoenolate' anion, resulting from abstraction of a β-proton at C-6. While difficult to define precisely, this intermediate anion may be

represented as **1a**, although no conclusive evidence has been presented in support of such a species. There are equivalent intermediates (**1b-1c**) which have greater and lesser degrees of carbanionic nature at C-1 and C-6, thus, **1a** is merely a convenient formalism. References to a β-enolate (or cyclopropoxide) anion will be made throughout this thesis since the observed products can be rationalized through an intermediate analogous to **1a**. However, **1a** is intended as a shorthand notation for the β-enolate; by no means does the use of such a representation imply that other equivalent species are not present.



Scheme 1-1 : Homoenolization of camphenilone

The β-enolate intermediate **1a** may then 'homoketonize', that is, regenerate the ketone with concomitant ring opening of the cyclopropoxide. Ring opening would necessarily induce rupture of either bond *a* to revert to starting material, or bond *b* to lead to a 'rearranged' ketone; in a deuterated solvent, ^2H would become incorporated at C-1 and C-6, respectively. Because this homoenolate was symmetric, there should be preference for neither pathway *a* nor *b*; in fact, a racemic mixture was eventually isolated. However, a related ketone might undergo homoenolization in a similar manner through an unsymmetrical homoenolate, and there may be preference for one route over the other; in either event, the product ketone would be different from the starting material.

Since Nickon and Lambert's initial discovery, studies directed at defining the scope and utility of this so-called homoenolization process have been carried out on a number of cyclic and acyclic ketones (3). In the majority of these systems, α-enolization is blocked by methyl groups and/or impeded by the presence of an α-bridgehead proton, such that only the anti-Bredt enolate could form.

Over the course of these investigations, a number of different base systems has been employed, such as ethylene glycoxide/ethylene glycol, *t*-BuOK/dimethylsulphoxide (DMSO), and potassium triphenylmethide/dioxane. However, the standard base for homoenolization experiments has become *t*-BuOK/*t*-BuOH since it has been the most successful. This base is

conveniently prepared by addition of potassium metal to *t*-butanol, although great care has to be taken to ensure dryness. Generally, conditions are quite harsh, employing ca. 1.0 M base at temperatures of 150 - 240 °C, with 185°C being the typical temperature. Deuterium incorporation experiments are convenient to undertake using *t*-BuOD as solvent, and can provide significant mechanistic data.

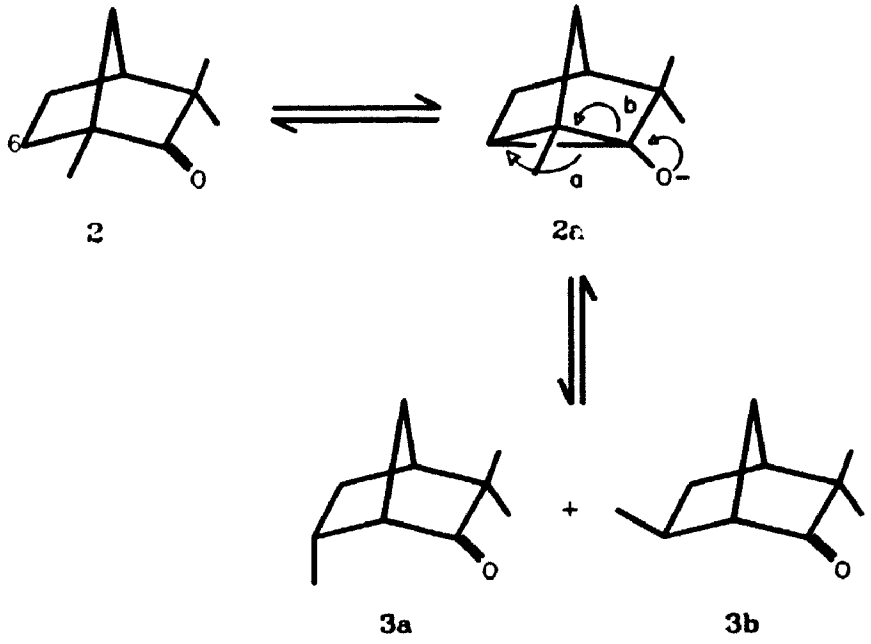
In general, acylic (4) and monocyclic (5) ketones rearrange slowly by homologation through the α-methyl groups. However, polycyclic ketones usually rearrange after proton abstraction from a remote methylene carbon; ^{2}H incorporation experiments have shown that while the α-methyl hydrogens undergo exchange, this β-enolization pathway does not lead to rearrangement. The vast majority of these cases involve rearrangement after abstraction of a β-proton (β-enolization), although there are a few instances involving rearrangement of a γ-enolate in the literature (6).

An aspect of the β-enolization process that has generated some interest is the stereochemical course of the reaction. The mechanism of this process can be viewed as a two-step process; β-enolization to form a cyclopropoxide intermediate (or its equivalent), with subsequent homoketonization to regenerate the ketone. Previous work suggests that β-proton abstraction in bicyclic ketones can only occur from sites that can interact with the carbonyl group (7). From the rate data in the literature it has been found that *exo*-abstraction of a

β-proton from a methylene carbon in bicyclo[2.2.1], [2.2.2] and [3.2.1] systems is preferred by a factor of between two and ten (3). Homoketonization of a β-enolate generally proceeds with a high degree of inversion of configuration, while ketonization of a γ-enolate usually proceeds with retention (7). In general, the partitioning of a β-enolate between two possible ketonic products depends upon the stability of the incipient carbanions. In the absence of a stabilizing group, secondary carbanions are preferred over tertiary; this is in accord with standard carbanion chemistry (8). All other factors being equal, the alleviation of ring strain appears to be a driving force.

About the time of Nickon's initial work, ^{13}C nmr spectroscopy was emerging as a useful technique for structural elucidation, and there was a need for unambiguous signal assignment in simple bicyclic compounds. In the initial studies with camphenilone, the behaviour of fenchone (2) was briefly examined (9), and found to incorporate up to six atoms of deuterium with some evidence for a new ketone. As a consequence, this process appeared to merit attention as a means to incorporate deuterium selectively in related bicyclic ketones. In the hope of achieving selective deuteration for ^{13}Cmr signal assignment, these experiments were later re-investigated (10). Under standard homoenolization conditions (*t*-BuOK/*t*BuOH(D)/185°C), it was found that ^{2}H was incorporated at C-6 and at all three methyl sites, and that

~5% of the product mixture consisted of **3a** and **3b** in a 3:1 ratio (Scheme 1-2). Deuterium incorporation in **2** can be rationalized by the formation of β-enolate **2a**, which arises after abstraction of a β-proton at C-6 in **2**. This intermediate may then homoketonize, with two routes available for subsequent protonation (deuteration). Cleavage of bond *a* leads to starting material deuterated at C-6, while pathway *b* leads to a new ketone, **3**. In this case, the governing factor in the homoketonization of **2a** is the fact that *a* leads to a more stable secondary carbanion, while that from *b* is tertiary. When a 75:25 mixture of **3a** and **3b** was isolated from the homoenolization runs with **2** and retreated with base, a 75:5:20 ratio of **2**:**3a**:**3b** was produced.

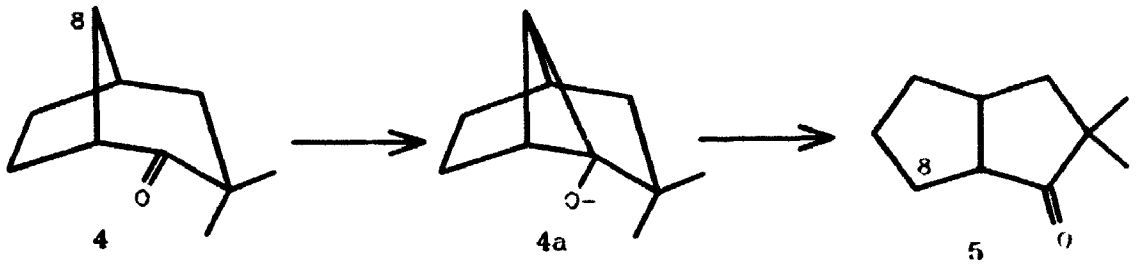


2 2a 3a 3b

Scheme 1-2 : Homoenolization of fenchone

This indicated that the *exo*-proton was preferentially abstracted, since **3b** was less reactive towards base, and thus accumulated while **2** and **3a** equilibrated.

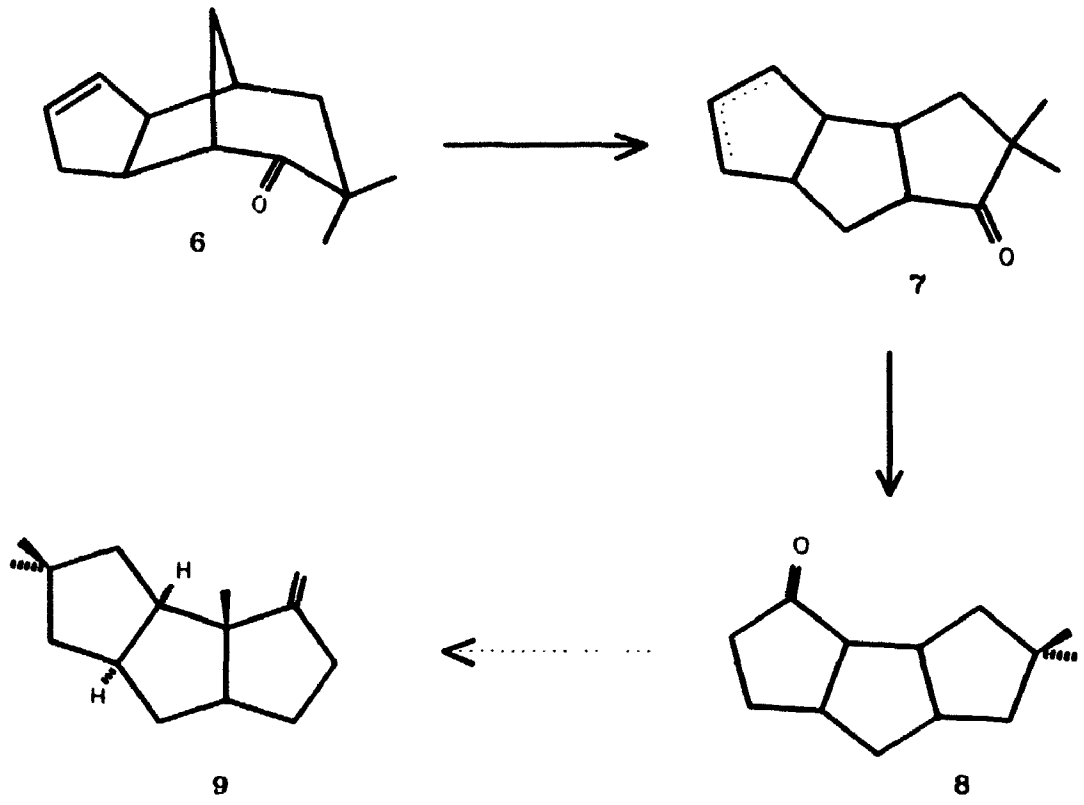
The progression of studies investigating the scope of β-enolization led to one of the most promising rearrangements of a β-enolate, whereby 3,3-dimethylbicyclo[3.2.1]octan-2-one (**4**) rearranged to **5** irreversibly (11). As shown in Scheme 1-3, β-enolate **4a** could be generated by abstraction of a β-proton at C-8 in **4** under homoenolization conditions. This intermediate then homoketonized with concomitant cleavage of the original C-1,C-2 bond, generating **5** stereospecifically in *ca.* 85 % yield.



Scheme 1-3 : ß-enolate rearrangement of **4**

In homoenolization trials with *t*-BuOD as solvent, **4** did not incorporate ^{2}H at the bridging methlyene (C-8), which revealed that the cleavage of **4a** was unidirectional. Also, the lack of ^{2}H at C-8 in **5** showed that the reaction was irreversible. The half-life for this reaction was *ca.* 60 h.

Since the 3,3-dimethylbicyclo[3.3.0]octan-2-one moiety is incorporated in a number of natural products (12), a stereo-controlled β-enolate rearrangement could be envisaged to play a role in the synthesis of certain natural products. Using the modified [3.2.1] system **6** , β-enolization was a key step in the generation of **8**, an intermediate in the synthesis of hirsutene, **9**, as shown in Scheme 1-4 (13).

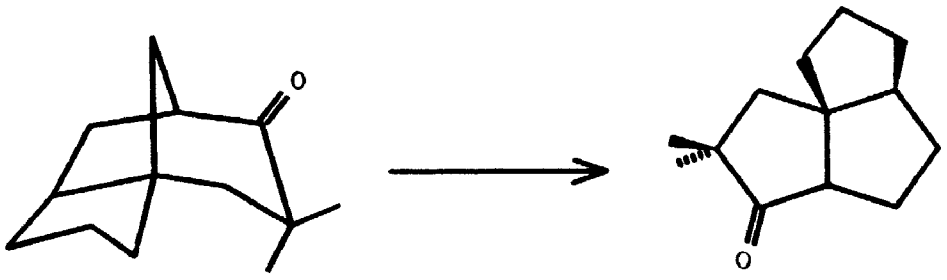


Scheme 1-4 : ß-enolate rearrangement in synthesis

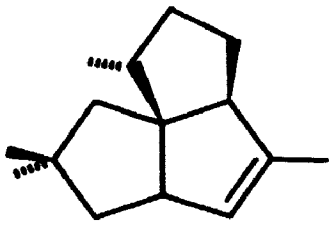
One of the more attractive features of this strategy was that three of the four stereocentres were generated very early in

the sequence, and the β-enolate rearrangement provided the correct configuration at the fourth centre. In theory, resolution of enantiomers early in the sequence could provide an asymmetric synthesis of the ring system of the hirsutanes.

By the same methodology, an entry into the angular triquinane class of compounds has been accomplished via β-enolization (14). The synthesis of **11** (Scheme 1-5) was achieved by subjecting **10** to *t*-BuO⁻/*t*-BuOH/185°C, effecting a β-enolate rearrangement in the same manner as above.



10 11

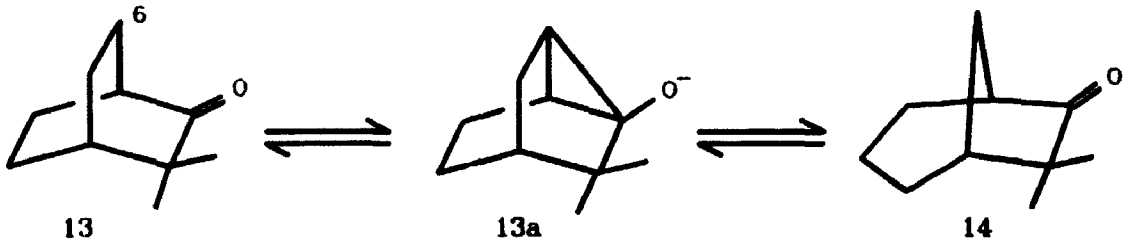


12

Scheme 1-5 : Preparation of the angular triquinane skeleton

Pentalenene, **12**, is the parent of the pentalenolactones, a class of natural products which possess this skeleton. These metabolites have been popular targets of synthesis in past years since the discovery that many have antibiotic activity. While elaboration into **12** is necessary to complete the formal synthesis, the preparation of this unusual ring system demonstrated the potential of a stereocontrolled β-enolate rearrangement in synthesis.

Subsequent to the studies involving the bicyclo[3.2.1] system **4**, the reactivity of 3,3-dimethylbicyclo[2.2.2]octan-2-one, **13**, towards strong base was examined in an effort to assess the synthetic utility of β-enolate rearrangements. It was found (15) that **13** slowly rearranged to the [3.2.1] ketone **14** (Scheme 1-6), after proton abstraction at C-6 in **13** to generate β-enolate **13a**. This rearrangement was found to be reversible, and the equilibrium mixture comprised an 80 : 20 ratio of **14** : **13** with a half-life of ~500 h at 185°C.

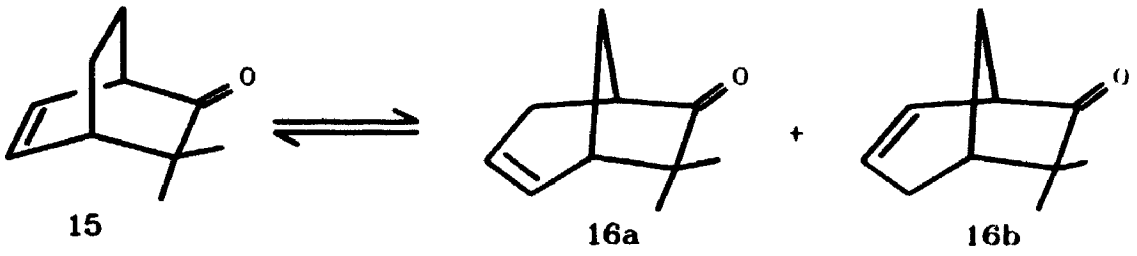


13 13a 14

Scheme 1-6 : Base-catalyzed equilibration of **13** and **14**

If the mechanism for this transformation indeed involves β-enolate **13a**, then subsequent homoketonization should involve the generation of a carbanion, which could be stabilized by the presence of a group such as a double bond. Presumably, the rate of rearrangement for a ketone of this sort would be enhanced by the presence of such an anion-stabilizing group.

Homoenolization studies involving the unsaturated ketone **15** confirmed this hypothesis (16). As expected, it was found that the same skeletal rearrangement occurred in the unsaturated ketone **15** as was observed in **13**, although a mixture of allylic isomers **16a** and **16b** was generated, due to the regioselectivity of protonation of the resultant allylic anion.



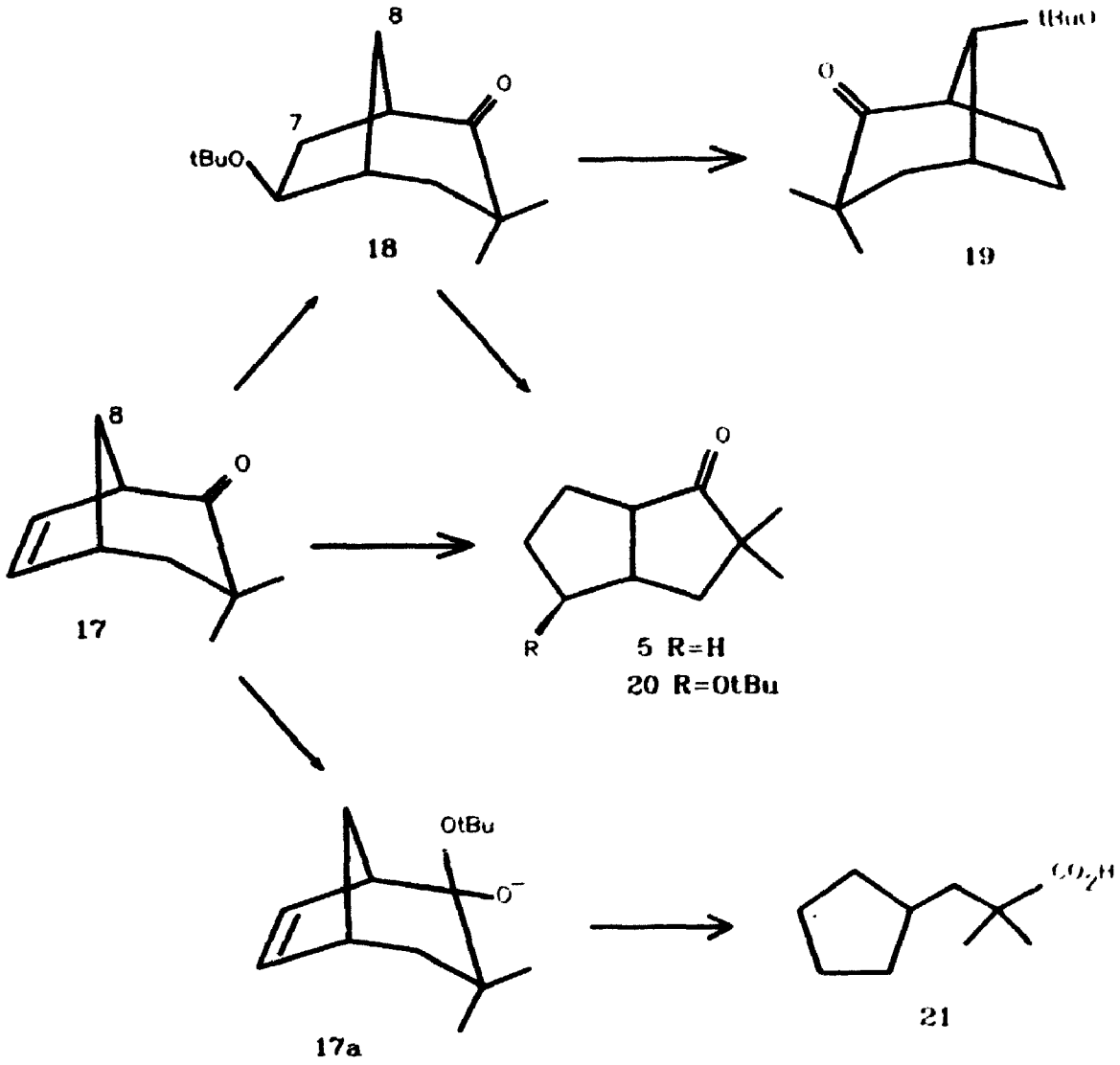
15 16a 16b

Scheme 1-7 : Rearrangement of bicyclo[2.2.2]octenone

The rate of rearrangement for the unsaturated [2.2.2] system was more than 100 times greater than that for the saturated case (Scheme 1-7). The half-life for this transformation was ~8 h, and the equilibrium lay even further on the side of the [3.2.1] species (90 : 10).

The acceleration in the rate of rearrangement arising from the incorporation of a double bond in the [2.2.2] system led to an examination of the effect of a double bond in **4**, to compare the results with the 4→5 rearrangement. As mentioned above, this rearrangement had been used in a natural product synthesis; the incorporation of a double bond could extend synthetic applications, not just because of an acceleration in rate, but due to the presence of a functional group in a rearranged product which may be further manipulated. In sharp contrast to the clean rearrangement of **15**, when **17** was treated (17) under standard conditions, six compounds were produced through three competing pathways and none of the compounds was an unsaturated ketone (Scheme 1-8). In fact, the major product was **5**, arising after proton abstraction from C-8 in **17**, in a similar manner to the formation of **5** from **4**, although an unsaturated [3.3.0] ketone was presumably an intermediate in the former rearrangement. It was believed that reduction of the double bond in this instance occurred after migration into conjugation with the ketone; reduction of α,β-unsaturated ketones in *t*-BuOK is discussed later. By a second route, *t*-butoxide was found to add to the double bond to form **18**. Rearrangement of **18** occurred after proton abstraction from either C-7 or -8 to generate **19** or **20**, respectively. A third pathway was proposed to account for the generation of the two minor isomeric cyclopentenyl acids **21**. Under the strongly basic conditions, these acids were presumed to form after

attack of the base at the carbonyl carbon in **17** to generate **17a**, which subsequently cleaved to generate a cyclopentenyl system in a Haller-Bauer type process. While the *t*-butyl esters would be the initial products of Haller-Bauer cleavage, these have been shown (18) to be unstable under the reaction conditions, and the acids are isolated.



Scheme 1-8 : Base-catalyzed rearrangement of 17

The present study is a continuation of the previous work documented in this Chapter. On the basis of the rearrangement noted for the bicyclo[3.2.1] ketone **4**, the homologous bicyclo[3.3.1] and [3.2.2] systems were chosen for investigation under typical homoenolization conditions; the results of these experiments are discussed in Chapter Two. Since the incorporation of a double bond in the systems listed in the foregoing discussion was seen to enhance β-enolate rearrangement, a logical step was to replace the double bond with an aromatic ring. In Chapter Three, a description of these studies is presented. As mentioned above, *t*-BuOK has become the standard base for homoenolization studies, and methyl groups are the α-blocking group of choice. It was deemed interesting to explore the effect of a change of base and/or α-blocking group and the outcome of these experiments is examined in Chapter Four. Finally, all experimental details and data are collected in Chapter Five.

CHAPTER TWO

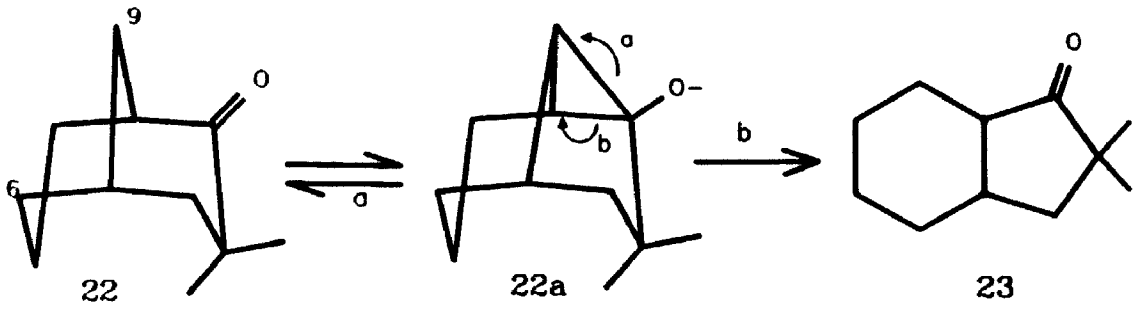
An Examination of β-Enolate Rearrangement in the Bicyclo[3.3.1] and [3.2.2] Ketone Systems

2.1 - INTRODUCTION

In Chapter One, the base-catalyzed rearrangement of 3,3-dimethylbicyclo[3.2.1]octan-2-one (**4**) to 3,3-dimethylbicyclo-[3.3.0]octan-2-one (**5**) was described (Scheme 1-3). This rearrangement has been employed as a key step in the synthesis of certain natural product skeletons and has received some attention because of its potential utility for new synthetic approaches to ring systems difficult to prepare by other methods. As a consequence, it was deemed worthwhile to explore related bicyclic systems in the hope of achieving similar conversions. To this end, 3,3-dimethylbicyclo[3.3.1] nonan-2-one (**22**), was selected for examination.

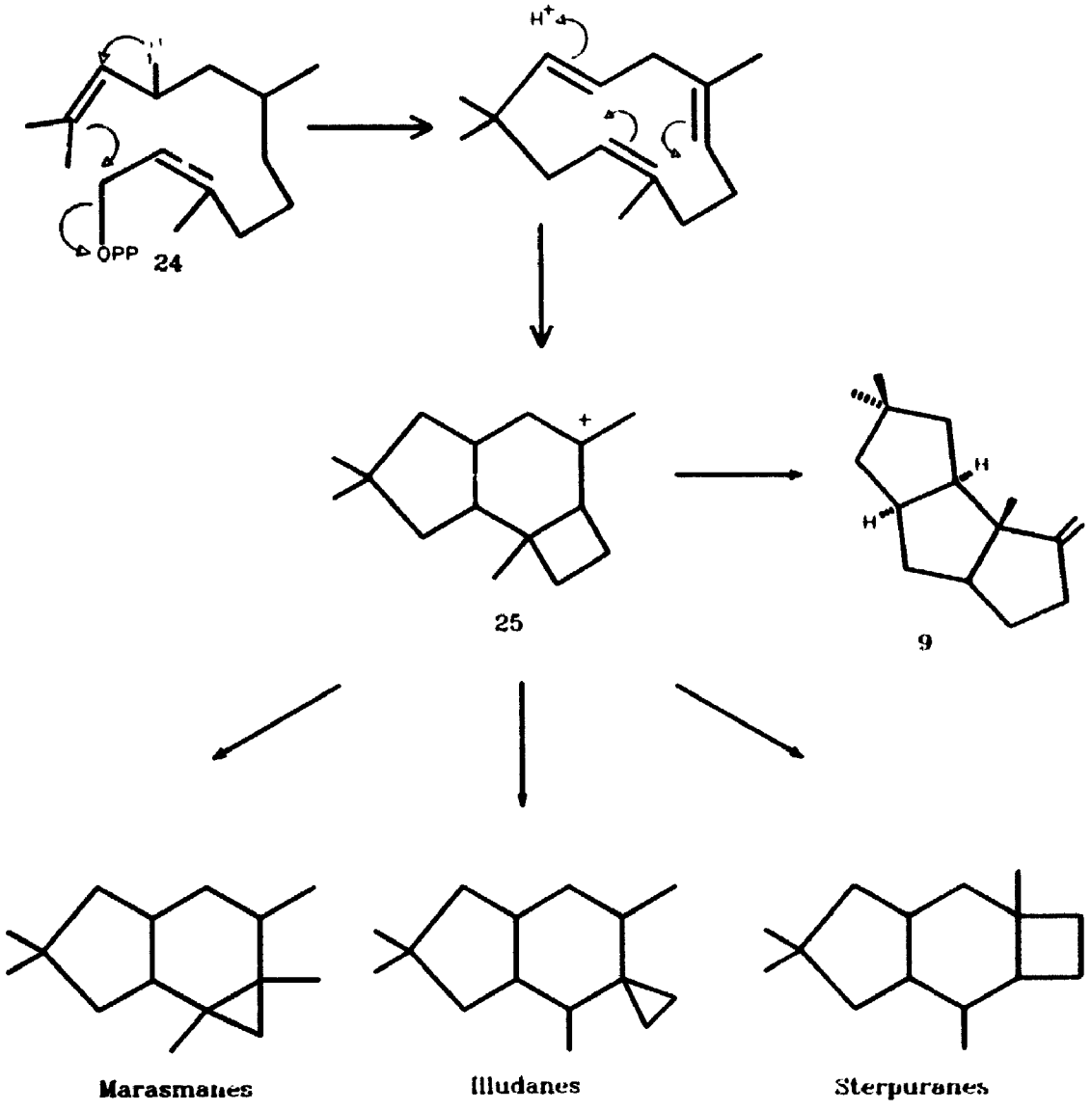
Since the carbonyl group in **4** activated the protons of the bridging 8-methylene group in the [3.2.1] system, it was reasonable to expect that a similiar effect may be found in the [3.3.1] system; under strongly basic conditions, **22a** may be generated after proton abstraction from C-9 in **22** (Scheme 2-1). This intermediate could homoketonize to revert to starting material or to rearrange to the [4.3.0] system **23**. On the basis of the unidirectional ring opening of **4a** to **5**,

opening of **22a** to **23** seemed likely, if **22a** formed from **22**. Furthermore, since the incorporation of a double bond in the [2.2.2] and [3.2.1] systems led to a marked increase in the rate of rearrangement, it was of interest to examine the effect of a double bond in the [3.3.1] skeleton. The presence of a double bond in a rearranged product would enable further functionalization.



Scheme 2-1 : Proposed rearrangement of 22

A striking example of the potential of β-enolization was the synthesis of the ring system of hirsutene, the parent of the hirsutane family of natural products. These sesquiterpenes are fungal metabolites arising from farnesyl pyrophosphate (**24**) via the putative protoilludane cation **25** (Scheme 2-2). From this same intermediate, a number of natural products bearing the 3,3-dimethylbicyclo[4.3.0]nonane skeleton are generated, such as the marasmanes, illudanes, and sterpuranes (19). A number of these compounds have become popular targets of synthesis in recent years owing to their behaviour as antibiotic and/or antitumour agents.



Scheme 2-2 : Sesquiterpenes derived from protoilludane

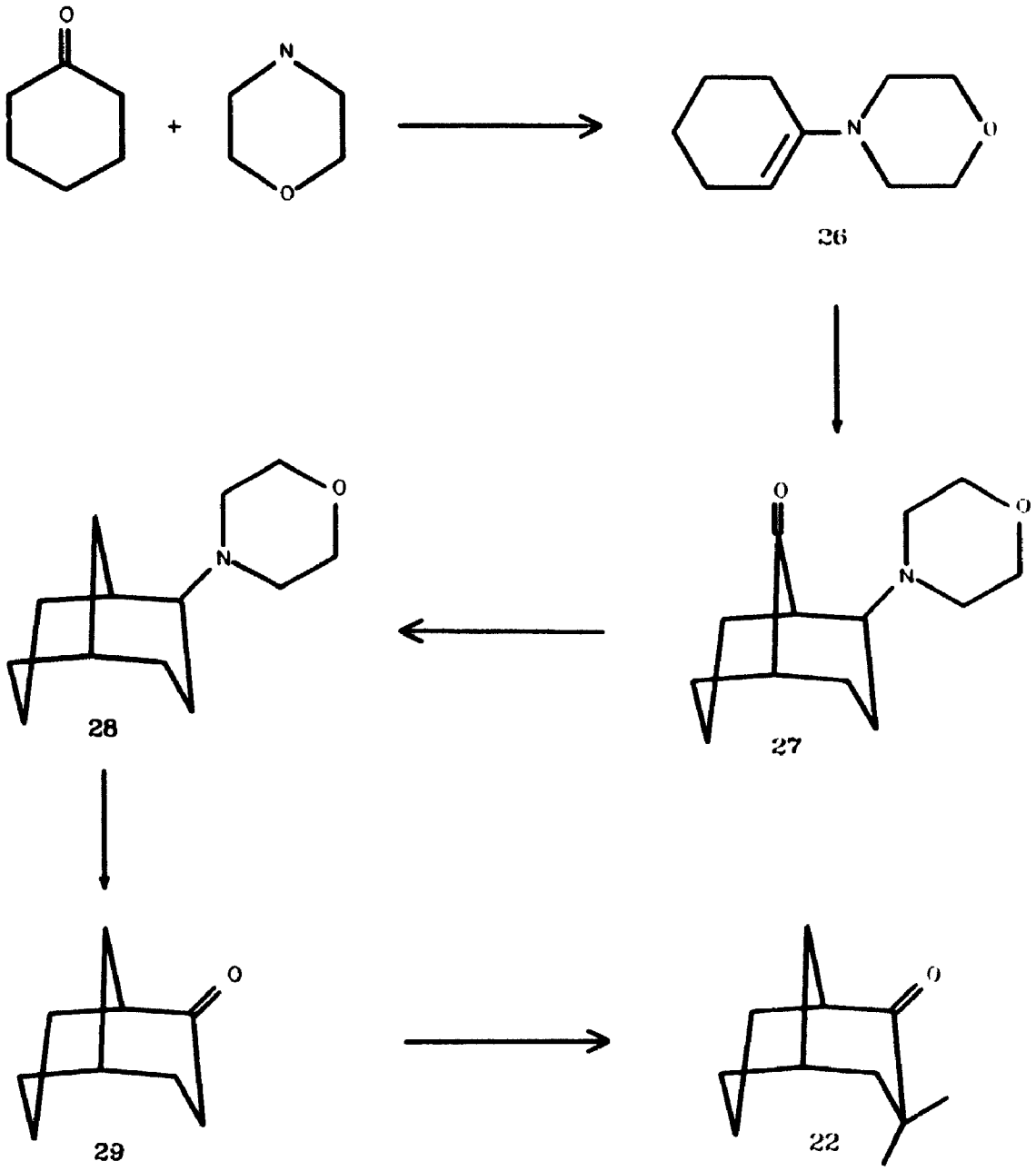
It is conceivable that an entry into the [4.3.0] system via rearrangement of a β-enolate from **22** could ultimately play a role in the synthesis of certain of these natural products.

Natural product synthesis notwithstanding, the goal of this project was to explore the behaviour of the [3.3.1] system with respect to homenolization, relative to the behaviour of the [3.2.1] ketones. Ultimately, the breadth and utility of the homoenolization process may be better defined.

2.2 RESULTS AND DISCUSSION

2.2.1 3,3-Dimethylbicyclo[3.3.1]nonan-2-one (22)

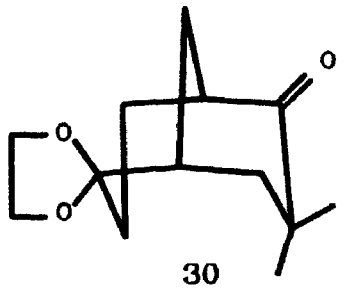
Bicyclo[3.3.1]nonan-2-one (**29**) was prepared by the four-step synthesis described by Inouye *et al.* (20) and shown below in Scheme 2-3. 1-N-Morpholinocyclohexene (**26**) was obtained by the condensation of cyclohexanone with morpholine and added to acrolein to yield 2-N-morpholinobicyclo[3.3.1]-nonan-9-one (**27**). Wolff-Kishner reduction of **27** afforded **28** and the latter was oxidized with mercuric acetate to give **29**. Dimethylation of **29** in our standard fashion ($NaNH_2/CH_3I/Et_2O$) readily furnished the desired ketone **22** (21).



Scheme 2-3 : Synthesis of starting ketone 22

Homoenolization experiments employing potassium *t*-butoxide were conducted in the same manner throughout this study. Samples of a liquid ketone were dissolved in *ca*.1.0 M *t*-BuOK/*t*-BuOH to furnish a solution 0.25 M in ketone. Aliquots (0.5 mL) of this solution were then rapidly transferred to glass tubes under nitrogen which were then degassed and sealed under vacuum. After heating in an oil-bath for the desired length of time, the tubes were cooled, opened, and flushed with brine. Neutral extracts were obtained by pentane extraction of the tube contents, which were then acidified and extracted with ether to provide the acidic fraction. The neutral fractions were initially assayed by glc and ^{13}Cmr. Results given in this study are generally the average of at least triplicate runs; the experiments with *t*-BuOK were found to be highly reproducible. In the case of **22**, tubes were heated at 185°C for times up to 240 h, however, the neutral fraction contained only the starting ketone and no compound was detected in the acidic fraction.

To examine the effect, if any, of oxygen functionality on the homoenolization pathway, ketal **30** was prepared and its behaviour under homoenolization conditions was examined. The ketone was obtained by dimethylation of **33**, an intermediate in a later synthesis (Scheme 2-4). After ketone **30** was treated with *t*-butoxide at 185°C for periods up to 192 h, the



30

starting ketone was recovered unchanged. It should be noted that although the ketal group did not promote β-enolization, it survived the harsh conditions. This could be useful because synthetic applications of β-enolization are hampered by the fact that few functional groups survive the conditions.

The ^{13}Cmr shieldings for **22**, **30**, and all of the [3.3.1] ketones prepared in this Chapter are summarized in Table 2-1. Complete assignment of the ^{1}Hmr signals in **22** was achieved with the aid of ^{1}H{^{1}H} two-dimensional correlation spectroscopy (COSY), using the HOMCOR sequence of the Varian software; these assignments are listed in Chapter Five. After ^{13}C{^{1}H} COSY experiments, complete assignments for the ^{13}Cmr signals were obtained. To show the one-bond interactions, the HETCOR sequence of the Varian software was employed, while the FLOCK sequence (22) was utilized to detect the long-range interactions of the methyl protons. The HETCOR spectrum is reproduced as Figure 2-1, while the FLOCK spectrum is shown in Figure 2-2. From the FLOCK sequence, the long-range interactions of the methyl groups with both the quaternary carbon (δ_C 43.3) and the 4-methylene carbon (δ_C 41.3) were well-resolved; for many of the bicyclic ketones prepared in the present study, a similar interaction between the methyl groups and the nearest methylene proved useful for ^{13}Cmr assignments. The ^{13}Cmr data for **22** in Table 2-1 agree with those given earlier by Hirata *et al.* (21), and confirm their assignments which were reported with some uncertainty.

Table 2-1 : ^{13}C shielding data[1] for [3.3.1] ketones.

Compd	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	Me	Me
22[2]	43.3	223.0	43.3	41.3	26.9	35.4	19.8	33.2	29.9	27.2	31.7
30	41.9	219.0	42.3	36.5	36.5	110.8	30.0	29.6	26.9	27.6	31.5
38	42.4	221.6	42.8	43.9	29.4	126.5	132.1	32.0	29.2	30.2	30.5
39	47.0	215.4	42.7	45.5	25.8	33.6	131.0	126.8	29.0	30.2	32.2
59	42.2	218.3	43.1	41.3	42.2	218.3	43.1	41.3	27.4	28.4	30.1
60	41.9	220.9	42.8	32.7	33.8	79.8	35.5	45.5	28.9	27.5	31.6

[1] In ppm downfield of TMS in $CDCl_3$ solutions.

[2] As reported in ref. 21

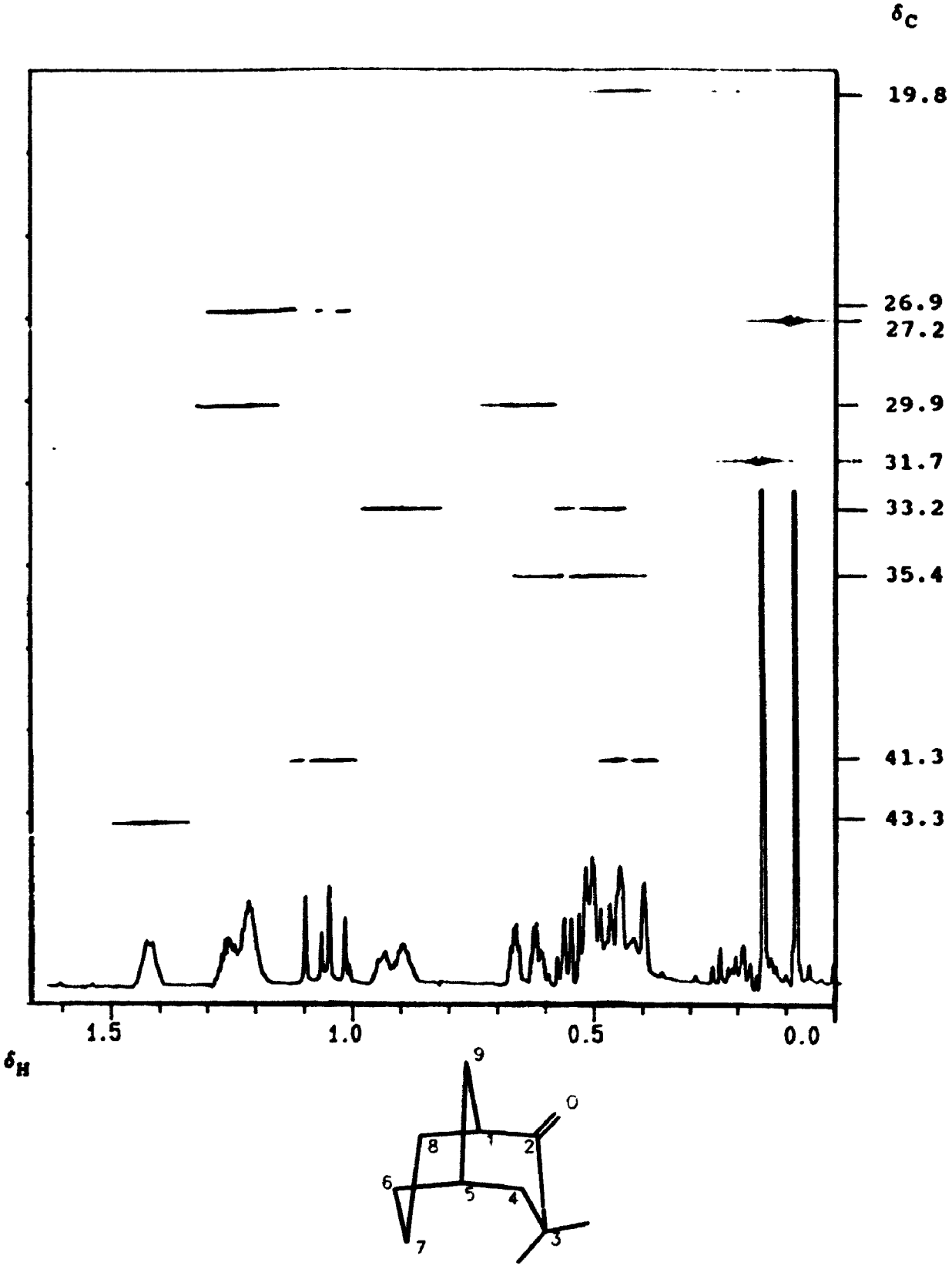


Figure 2-1 : One-bond $^{13}C\{^{1}H\}$ correlation spectrum for 22

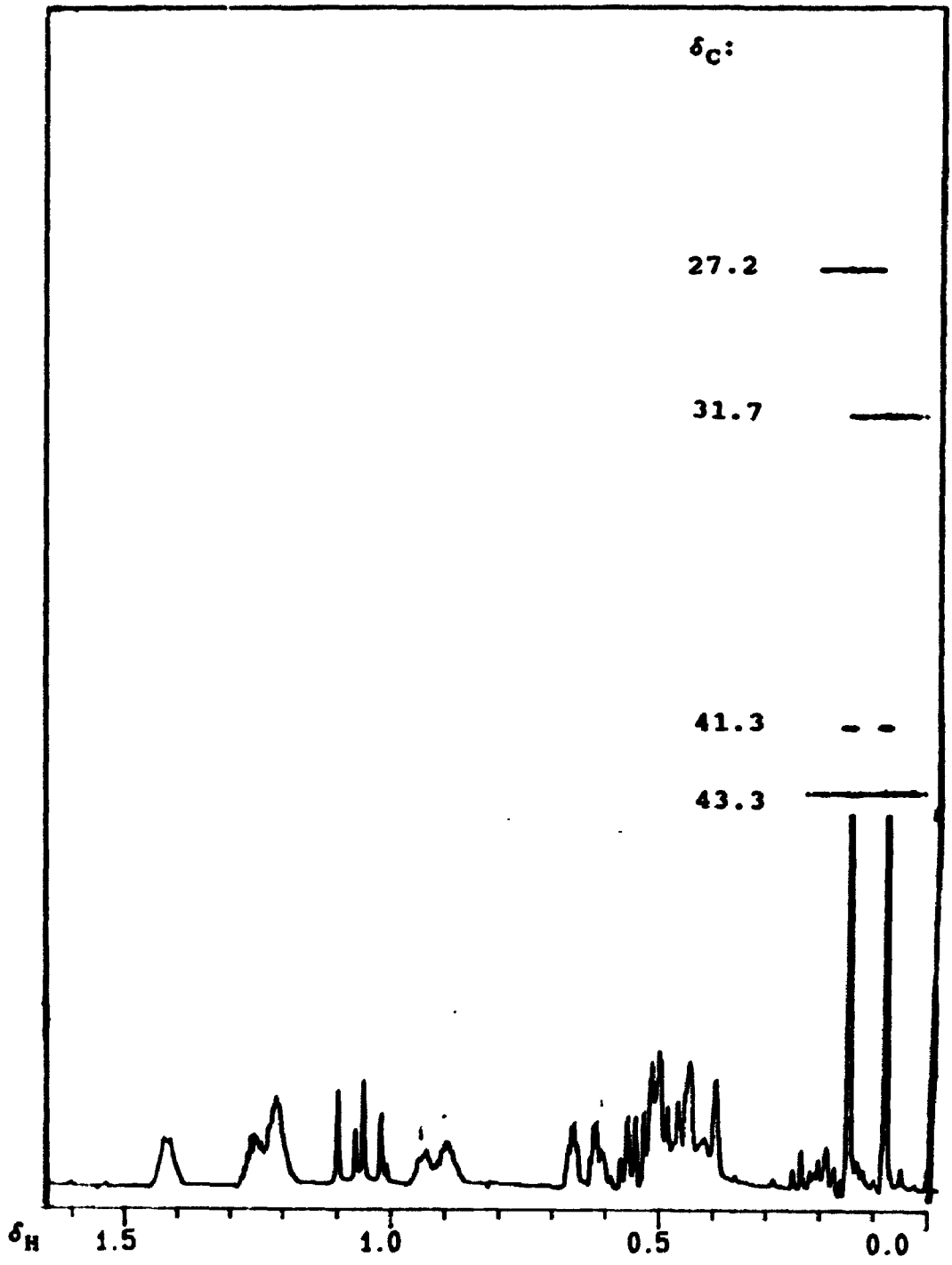
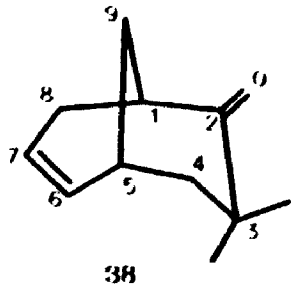


Figure 2-2 : Long-range $^{13}C\{^{1}H\}$ correlation spectrum for 22

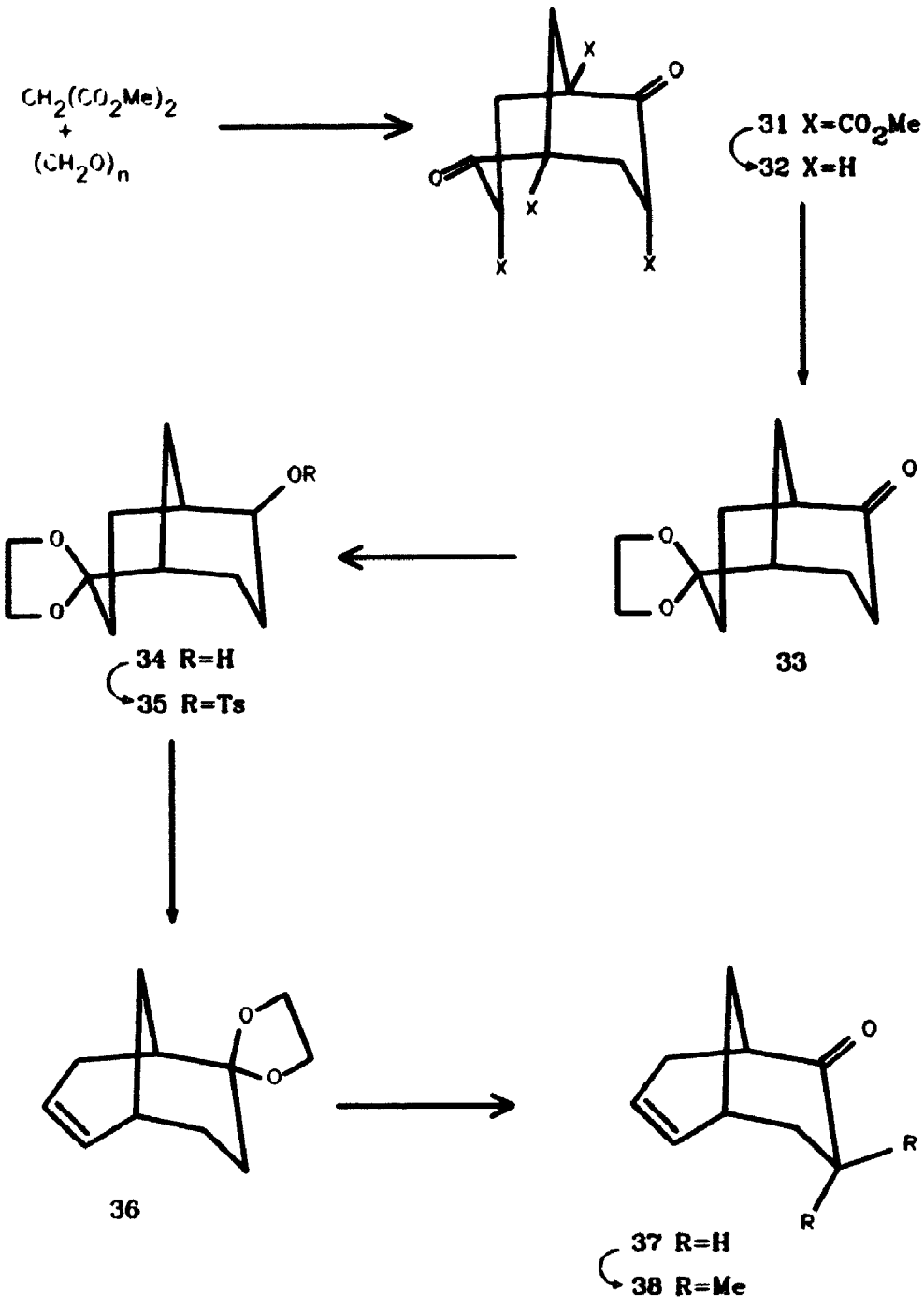
2.2.2 3,3-Dimethylbicyclo[3.3.1]non-6-en-2-one (38)

The parent ketone **37** was prepared by an adaptation of the route of Bishop *et al.* (23), shown in Scheme 2-4. Condensation of dimethyl malonate with paraformaldehyde in the presence of piperidine followed by treatment with NaOMe yielded Meerwein's ester **31** (24) as fluffy crystals. Decarboxylation of **31** with hydrochloric acid in refluxing acetic acid gave diketone **32** (25). The bisketal of **32**, formed from reaction of the diketone with ethylene glycol in benzene, was then equilibrated in acetone/TsOH at room temperature to yield keto-acetal **33** (26). Reduction of the keto-acetal with lithium aluminum hydride (LAH), followed by tosylation gave **35**. The tosylate was eliminated in refluxing pyridine, and the acetal was removed to furnish ketone **37**, which was dimethylated to give ketone **38**.

Specific assignment of the ^{1}Hmr signals for **38** followed from the $^{1}H\{^{1}H\}$ COSY spectrum shown as Figure 2-3. In this spectrum, correlation is shown by the cross peaks: those that lie off the diagonal between the lower left and upper right corners. For example, the four-bond ('W') coupling between *syn*-H-9 and *endo*-H-8 is shown in Figure 2-3. From the $^{13}C\{^{1}H\}$ correlation experiment the assignments for the ^{13}C signals given in Table 2-1 were determined.



38



Scheme 2-4 : Preparation of the starting ketone 38

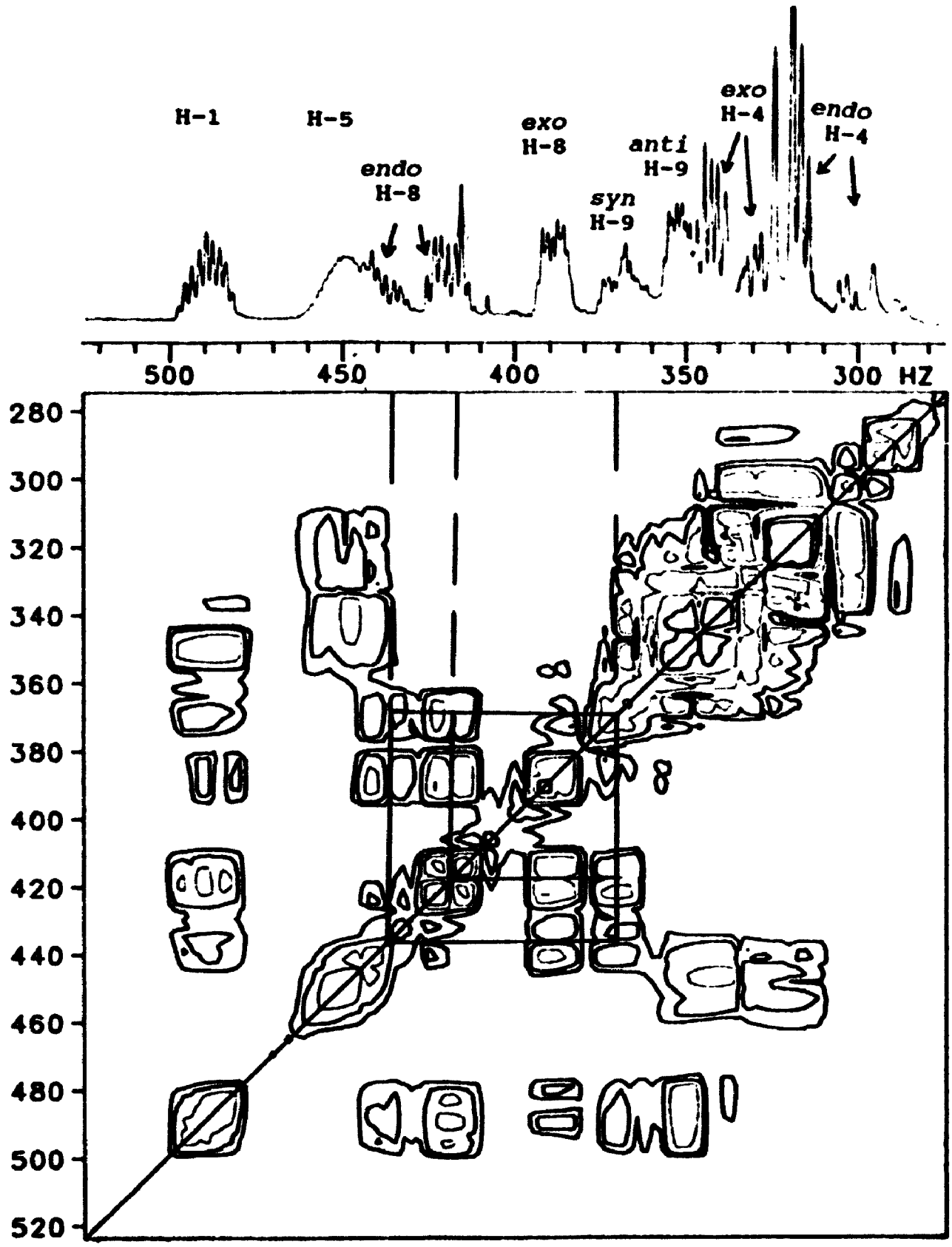
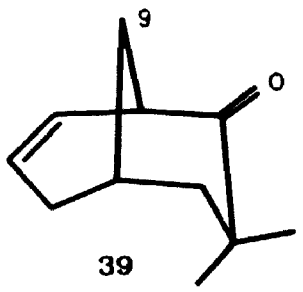


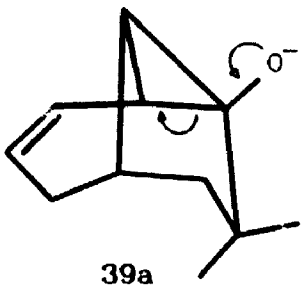
Figure 2-3 : $^{1}H\{^{1}H\}$ Correlation spectrum for 38.

The unsaturated ketone **38** was then treated with *t*-BuOK/*t*-BuOH/185°C. The neutral fractions resulting from the shorter reaction times (<6 h) were shown to contain three ketones, including starting material. The more abundant new ketone could not be separated from **38** by column chromatography, however, its ^{13}Cmr shieldings strongly supported structure **39**, the allylic isomer of **38**. The -6.2 ppm shift of the carbonyl signal in **39** relative to **38** is typical of homoconjugation in a β,γ-enone (27), and the +4.6 and -3.6 ppm shifts for C-1 and -5, respectively, are as expected for this change in the position of the double bond. The specific assignments for the ^{13}Cmr signals were obtained with the aid of a $^{13}C\{^1H\}$ COSY spectrum, and are summarized in Table 2-1 along with those for **38** to aid comparison. Since the allylic protons in **38** are the most acidic, equilibration of **38** and **39** can be expected under the strongly basic conditions.

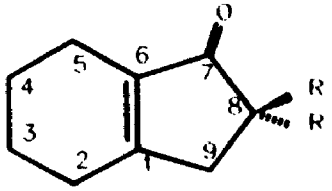


The minor product from these shorter runs was easily isolated by chromatography on alumina. By precise mass measurement, it was shown to be isomeric with the starting ketone, and the infrared and ^{13}Cmr spectra revealed the presence of an α,β-unsaturated ketone. Furthermore, the DEPT spectrum indicated a tetra-substituted double bond and confirmed the absence of methine signals. Finally, the presence of a pair of equivalent methyl signals signified that

a plane of symmetry existed in this molecule. These data led to this compound's assignment as **40b**, originating from proton abstraction at C-9 in **39** to generate β-enolate **39a**.



39a



40a R=H

40b R=Me

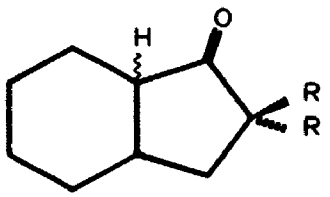
Homoketonization of **39a** with cleavage of the original C-1,C-2 bond leads to an allylic stabilized carbanion which is subsequently protonated to yield an allylic isomer of **40b**. However, no other isomer was detected: **40b** was the only unsaturated [4.3.0] ketone isolated. Presumably, the double bond migrates rapidly into conjugation with the ketone under the reaction conditions, and thus forms **40b**. While abstraction of a proton from C-9 in **38** could lead to a cyclopropoxide similiar to **39a**, rearrangement of **39** seems more likely since an allylic anion intermediate is generated.

The remaining signals in the ^{1}Hmr and ^{13}Cmr spectra could be assigned with the aid of $^{13}C\{^{1}H\}$ and $^{1}H\{^{1}H\}$ correlation spectra and complete ^{13}Cmr shieldings are given in Table 2-2.

Confirmation of this structure was obtained by independent synthesis; dimethylation of tetrahydroindan-1-one **40a**, prepared by the method described by House (28), gave a product with spectral properties identical to those of **40b**.

Subsequent to this work, the preparation of enone **40b** was reported by Mehta (29) in their synthetic efforts towards related natural products, some of which were earlier indicated as potential targets of synthesis for this study (Scheme 2-2). Their synthesis involved cyclopentenone annulation, and was noteworthy because the α,α-dimethylcyclopentenone moiety was generated directly from a carbonyl precursor.

In the product mixtures from runs longer than six hours, the presence of two more compounds was revealed by glc and ^{13}Cmr. Flash chromatography provided a sample enriched (ca. 80%) in these compounds, with **38** and **39** as impurities. The ^{13}Cmr spectrum revealed these compounds to be saturated ketones, with two sets of ten aliphatic signals, including those for two methyl, five methylene, two methine and a quaternary carbon. Identical sets of signals were observed in the ^{13}Cmr spectrum of the product of tetra-n-propyl ammonium per-ruthenate (TPAP) oxidation (30) of the alcohol mixture obtained by reduction of an authentic sample of **40b** with lithium in liquid ammonia (31). Therefore, the saturated ketones found in the product mixtures from homenolization of **38** are the *cis*- and *trans*- isomers of **41b**. Comparison of the ^{13}Cmr shieldings with those for the parent ketones **41a** (32) led to the assignments shown in Table 2-2.



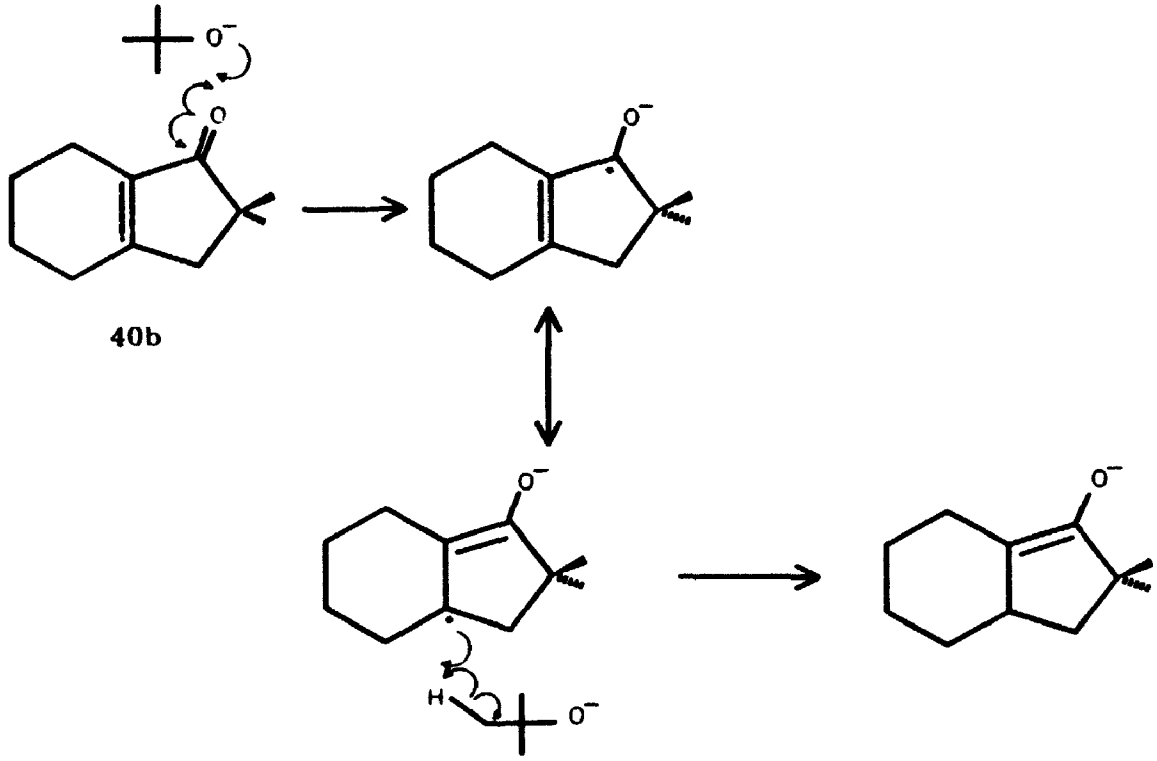
41a R=H
41b R=Me

Table 2-2 : ^{13}C shielding data[1] for [4.3.0] ketones

	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	Me	Me
cis-**41a**	36.0	28.0	23.9	22.7	22.4	49.3	219.5	34.6	25.5		
cis-**41b**	32.5	28.1	23.0	23.8	22.5	48.0	224.4	44.2	40.7	26.5	27.2
trans-**41a**	43.1	32.4	25.7	25.4	24.8	55.3	217.7	36.8	27.5		
trans-**41b**	39.7	32.7	26.1	25.8	25.4	5[illegible].0	222.4	44.9	43.9	24.7	26.3
40b	170.2	28.4	22.3	21.8	20.2	135.9	213.2	43.2	47.2	25.3	
64	168.8	32.0	29.2	25.4	19.1	127.4	213.0	43.1	46.6	25.2	26.7

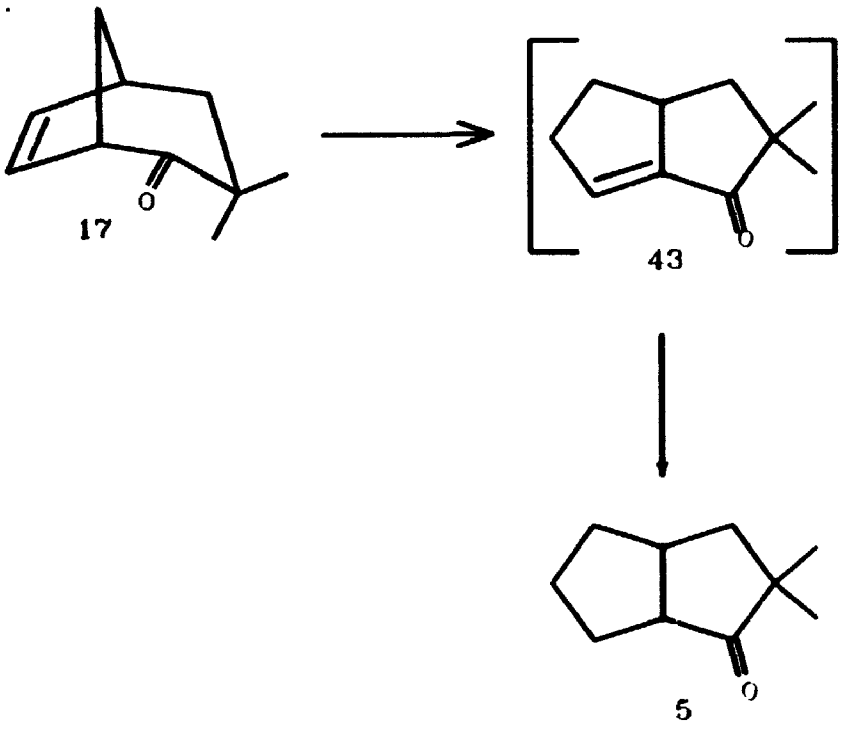
[1] In ppm downfield of TMS in $CDCl_3$ solutions.

Single electron transfer from the *t*-butoxide anion to the carbonyl carbon in **40b**, as illustrated in Scheme 2-5, seems the most likely explanation for the formation of **41b**. The radical anion resulting from said transfer can then abstract a hydrogen atom from solvent to generate the α-enolate of **41b**, which is quenched upon workup.



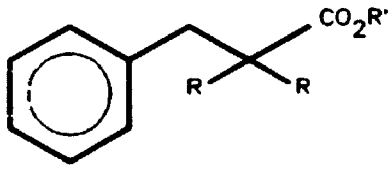
Scheme 2-5 : Proposed mechanism of reduction for enone **40b**

Similar reduction processes have precedent; one such reduction is shown in Scheme 2-6. As mentioned in Chapter One, ketone **17** (17) rearranged to several ketones, and major product was **5**. However, the rate of rearrangement was significantly increased relative to the saturated case, indicating that ketone **43**, or an isomeric enone, was likely involved as an intermediate in the reduction to **5**. In this case (17), single electron transfer from *t*-BuO$^-$ was proposed to account for reduction of the enone. It is interesting to note that **40b** accumulated in the product mixture and was slowly reduced to its saturated end-product, while **43** was reduced too quickly to be observed at all in the product.



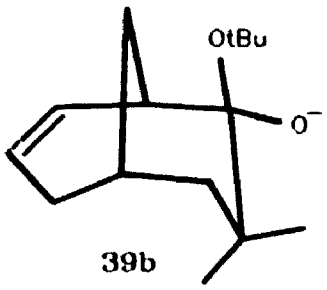
Scheme 2-6 : Precedented reductions in *t*-BuOK

The acidic fraction from the runs with **38** was shown by its ^{13}Cmr spectrum to contain a single compound, $C_{11}H_{14}O_2$ by precise mass measurement. Its infrared, ^{1}Hmr and ^{13}Cmr spectra suggested the presence of an aromatic ring. The aliphatic region of the ^{1}Hmr spectrum had only two singlet signals: δ 1.23 (6H) and 2.92 (2H). The acid was tentatively identified as **46** and this assignment was confirmed by independent synthesis starting with hydrocinnamic acid (**47a**).

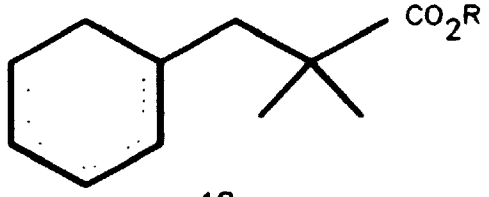


47a R'=R=H
47b R'=Me; R=H
47c R'=R=Me
46 R'=H; R=Me

This acid likely originated from Haller-Bauer cleavage of **39b** which was formed by attack of the base at the carbonyl carbon in **39**. The resulting allylic anion was subsequently protonated to yield **48a**; the cyclohexenyl ring was apparently oxidized under the conditions to generate **46**.



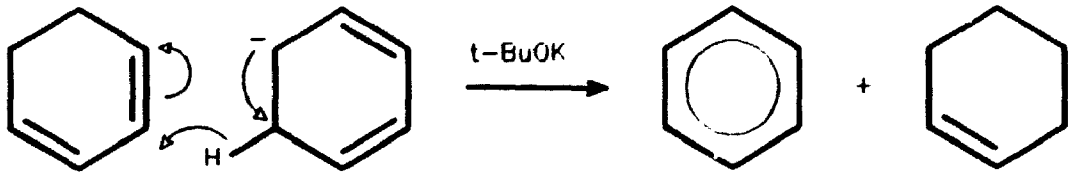
39b

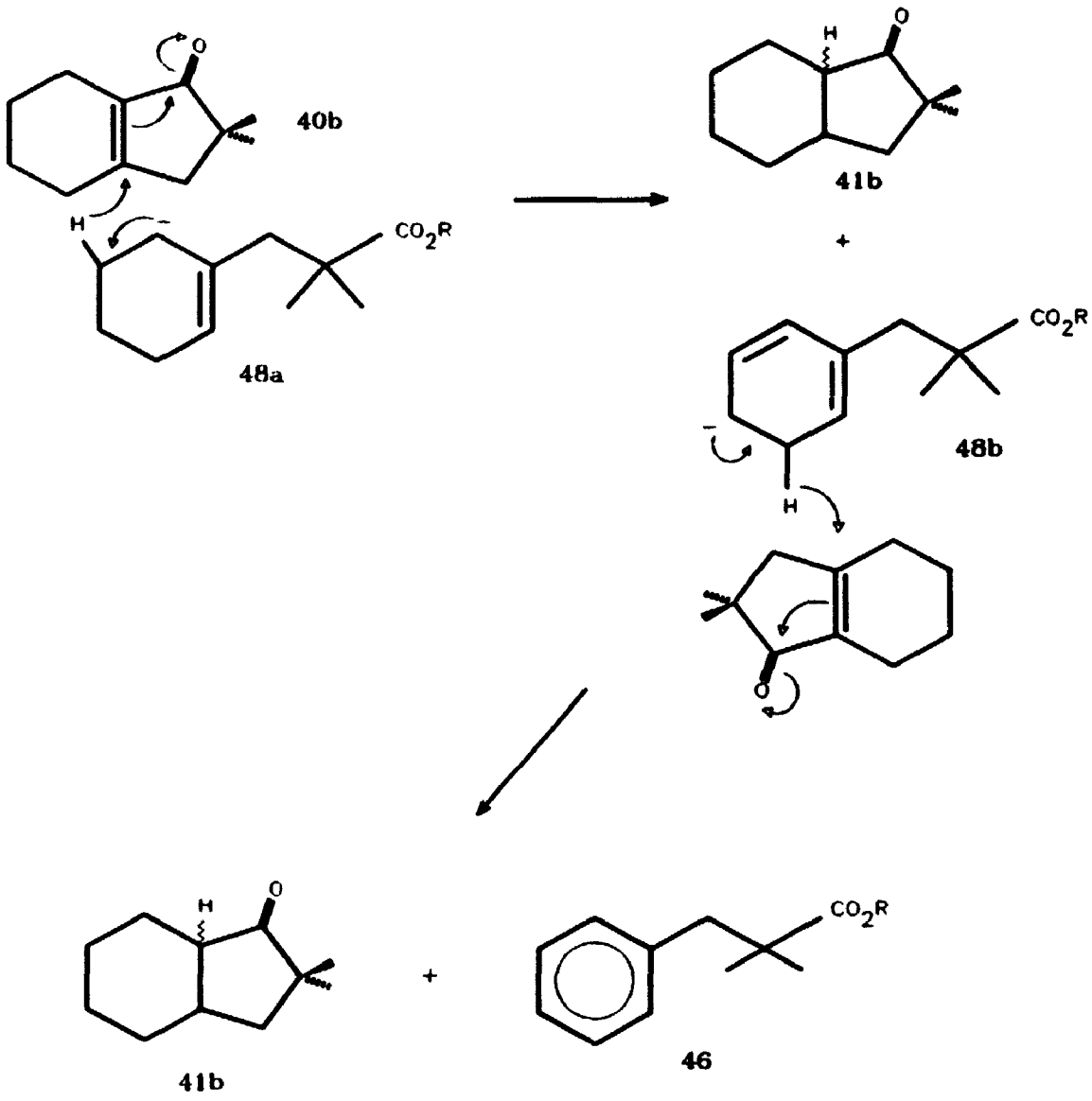


48a

The presence of aromatic acid **46** from these experiments indicated that another mechanism might be operating for the reduction of **40b** (Scheme 2-7). It is conceivable that the transfer of a hydride from **48a** to **40b** could be responsible for the reduction of **40b** and simultaneous oxidation of **48a**. Furthermore, cyclohexadienyl ester **48b**, which results from oxidation of **48a**, could trigger reduction of a second molecule of **40b**, to generate a second molecule of **41b** and aromatic acid **46**, after degeneration of the ester.

There is precedent for hydride transfer of this sort (33) in the reaction of 1,3-cyclohexadiene with *t*-BuOK in DMSO. This reaction involves disproportionation of cyclohexadiene to yield cyclohexene and benzene. The mechanism put forth involved initial proton abstraction from cyclohexadiene and subsequent hydride transfer to a second molecule of cyclohexadiene. Since the homoenolization conditions are sufficiently basic to abstract a proton from a cyclohexenyl species, there is the possibility that **48a** may participate in a similar hydride transfer, in the manner shown in Scheme 2-7, with **40b** as the ultimate hydride acceptor.





Scheme 2-7 : Putative mechanism for formation of 46 and 41b

This pathway, if it occurs, cannot be the sole mechanistic pathway for the reduction of **40b**, since **46** is not present in sufficient concentrations to account for the quantity of **41b** isolated. It would appear more likely that *t*-butoxide causes the reduction of **40b** by the single electron transfer mechanism suggested earlier in this Chapter. The species resulting from oxidation of *t*-BuO$^-$ could in turn oxidize **48a** and **48b**, until the latter are consumed. In any event, it is clear that the oxidation of **48a** must be relatively rapid, as only the aromatic acid was identified.

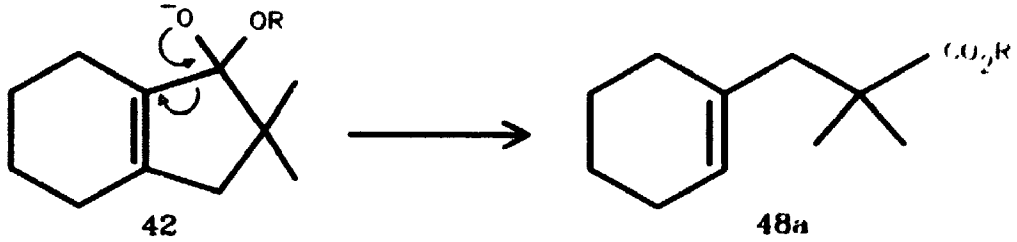
The composition of the products isolated from the experiments with **38** are listed in Table 2-3. From these results, it seemed that the concentration of enone **40b** increased in the early stages of reaction up to a maximum, and then decreased as the enone was slowly consumed by reduction. Furthermore, in all cases, the **38**:**39** ratio remained constant at ~ 60:40. Since the peaks of **38**, **39**, and **41b** overlapped by glc, the data were calculated using a ratio of ^{13}Cmr signal intensities, comparing methylene signals and comparing methyl signals, then averaging the results. On the basis of the data in Table 2-3, and assuming a constant base strength of 1.0 M, the pseudo-first order rate constant for the disappearance of **38** can be calculated to be $k = 3 \times 10^{-5}\ s^{-1}$, or $t_{\frac{1}{2}} \sim 6h$.

Table 2-3 : Composition of the neutral product[1] from homoenolization of **38** (*t*-BuO$^-$/*t*-BuOH/185°C)

Time (h)	**38**	**39**	**40b**	*cis*-**41b**	*trans*-**41b**	**46**
6	37	24	12	-	-	5
12	20	14	26	7	6	6
24	13	9	33	11	10	8
48	6	4	34	15	14	8
72	<2	<1	31	21	20	12

[1] Listed as percentage of the isolated material, calculated using ratios of intensities of ^{13}Cmr signals.

Homenolization experiments using enone **40b** as the initial ketone resulted in product mixtures containing only **40b** and the **41b** isomers in the neutral fraction, and the acidic fraction contained a small amount of acid **46**. The results, given in Table 2-4, clearly show that **40b** was slowly reduced to the saturated ketones **41b**. Neither **38** nor **39** was detected in the product, confirming that the **39** to **40b** rearrangement is unidirectional. The presence of acid **46** from the runs with **40b** indicate that the mechanism for cleavage in this instance presumably involved **42** (Scheme 2-5) as an intermediate. This species could be generated by addition of *t*-BuO$^-$ to the carbonyl in **40b**, and subsequent Haller-Bauer cleavage of **42** would yield **48a** through a vinyl anion. The cyclohexenyl moiety in the initial ester was then oxidized, and the ester subsequently decomposed to acid **46**.



42 48a

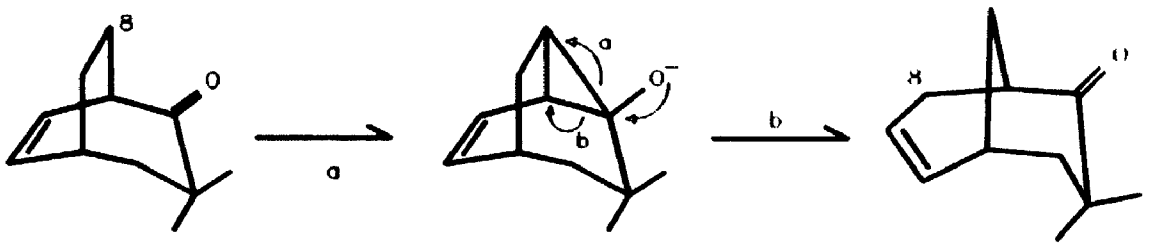
Table 2-4 : Composition of the neutral product from homoenolization of 40b (*t*-BuO$^-$/*t*-BuOH/185°C)[1]

Time (h)	40b	*cis*-41b	*trans*-41b	46
3	71	11	10	-
12	63	17	15	-
24	41	20	18	5
48	31	25	23	10
96	19	28	26	15

[1] Listed as percentage of the isolated material; ratios of neutral products were calculated by glc

2.2.3 3,3-Dimethylbicyclo[3.2.2]non-6-en-2-one (49)

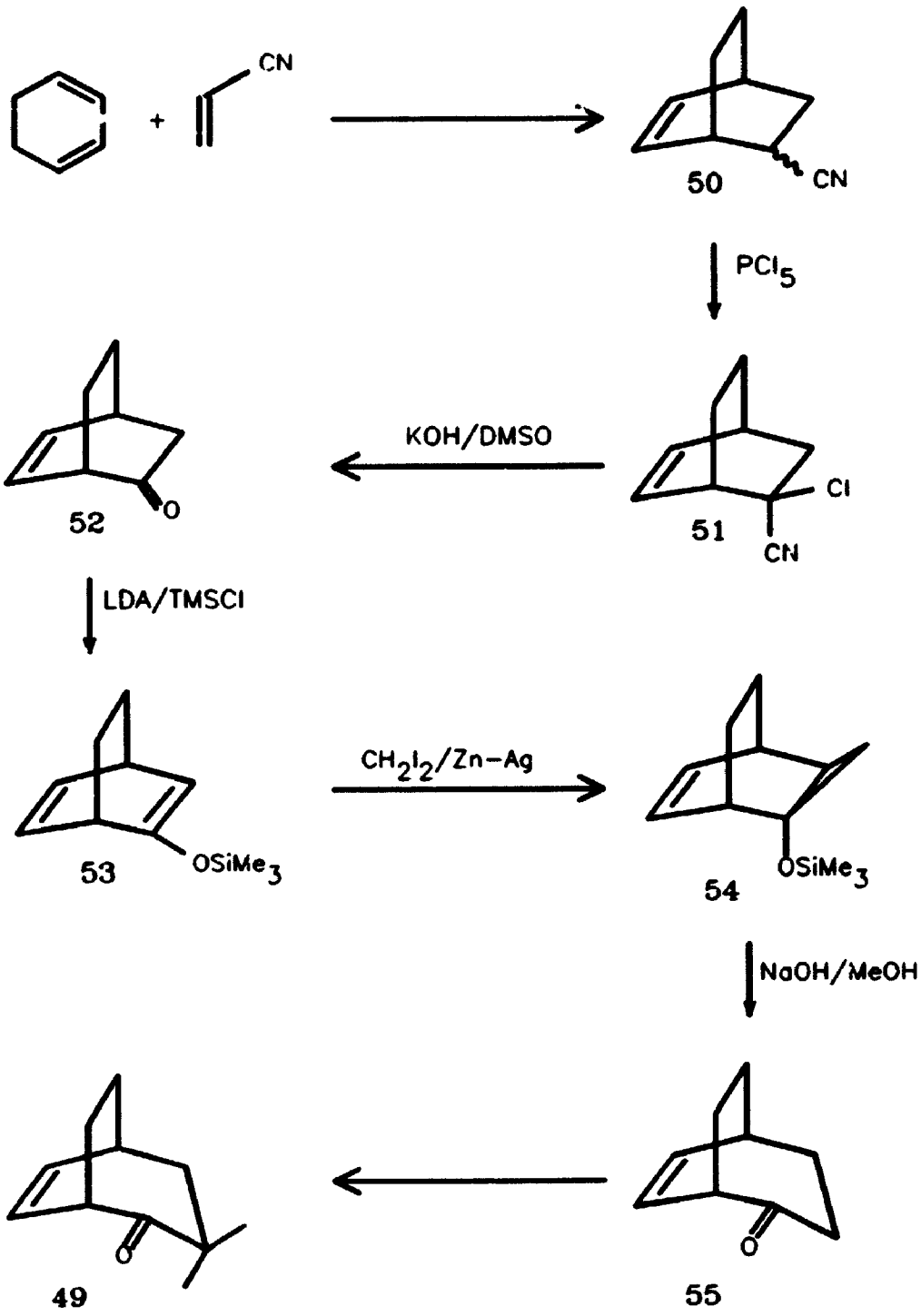
In the initial trials with the unsaturated [3.3.1] ketone **38** it was considered that **49** might arise from **38** through the cyclopropoxide **49a**, as shown in Scheme 2-8.



49 49a 38

Scheme 2-8 : Base-catalyzed rearrangement of 49

Abstraction of a proton from C-8 in **38** could lead to **49a** with homoketonization via pathway *a* leading to **49**. As a result, **49** was synthesized to confirm/deny its presence in the neutral mixtures from the runs with **38**. The synthesis of the parent ketone **55** has been previously described (34), and is shown in Scheme 2-9. Preparation of bicyclo[2.2.2]octenone **52** was straightforward and ring expansion of **52** followed our standard three-step method. This ring enlargement commenced with the preparation of silyl enol ether **53**, which was cyclopropanated under Simmons-Smith conditions to yield **54**. Although the preparation of **54** was uncomplicated, some care had to be exercised to avoid cyclopropanation of the olefin. Treatment of a cyclopropyl silyl ether with 3 N methanolic sodium



Scheme 2-9 : Synthesis of starting ketone 49

hydroxide generates a cyclopropoxide after hydrolysis of the silyl group. The cyclopropoxide can then homoketonize to yield either the ring enlarged product or an α-methyl ketone, depending on which bond is broken. It had been found that although the primary carbanion is more stable, bicyclo[2.2.2]- and [2.2.1] ketones generally exhibit ring expansion, presumably to reduce ring strain. Ring expansion by this means was preferred over other methods, such as the Tiffeneau-Demjanov sequence (35), since only one regioisomer is formed. Ring expansion of the cyclopropoxide in this instance was nearly quantitative and only **55** was identified. Dimethylation by the standard method then smoothly yielded the desired ketone **49**.

While **49** was not detected in the product mixture from the homoenolization of **38**, its behaviour under homoenolization conditions was of interest. Treatment of **49** under the standard conditions resulted in neutral mixtures which displayed the same ^{13}Cmr signals as the mixtures from the runs with **38**. Apparently, **49** rearranged via cyclopropoxide **49a** to **38** and thence to its rearrangement products!

The results from the homoenolization of **49** are summarized in Table 2-5. The rearrangement was unidirectional and considerably slower than that for **38** itself. From the data in Table 2-5, the rate constant for disappearance of **49** was $k = 1 \times 10^{-5}\ s^{-1}$, or $t_{\frac{1}{2}}$ ~24h.

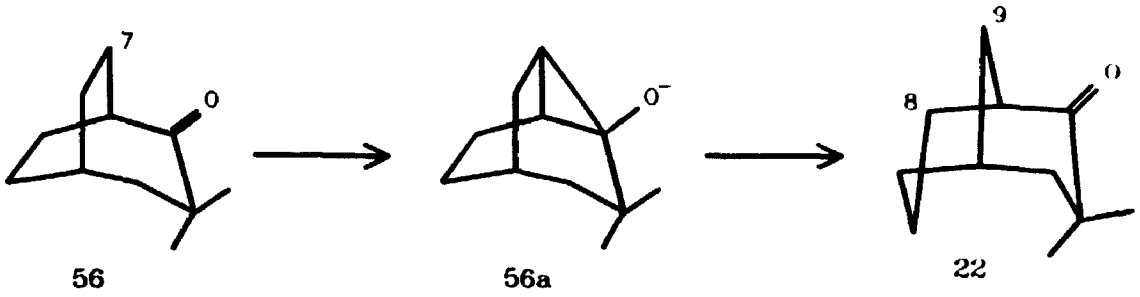
Table 2-5 : Composition of the neutral product from homoenolization of **49** (*t*-BuO$^-$/*t*-BuOH/185°C)[1]

Time (h)	**49**	**38**	**39**	**40b**	*cis*-**41b**	*trans*-**41b**	**46**
12	56	9	6	4	-	-	4
24	47	13	8	9	<2	<2	6
48	27	11	8	22	6	5	6
96	15	8	5	27	13	12	10
144	7	4	3	26	17	16	10

[1] Listed as percent of the isolated material, using ^{13}Cmr signal intensities to calculate neutral product ratios.

2.2.4 3,3-Dimethylbicyclo[3.2.2]nonan-2-one (56)

In light of the rearrangement of **49** under homoenolization conditions, the fate of the saturated analogue **56** was then examined. Hydrogenation of **49** furnished **56** in quantitative yield. Under the typical conditions, **56** rearranged slowly to the bicyclo[3.3.1] system **22**, which was shown earlier to be stable with respect to rearrangement. The results of the runs with **56** are summarized in Table 2-6, from which the pseudo-first order rate of disappearance can be calculated to be $k = 1 \times 10^{-6}\ s^{-1}$, or $t_{\frac{1}{2}}$ ~140 h.



56 56a 22

Scheme 2-10 : Mechanism for rearrangement for **56**

Abstraction of a proton from C-7 in **56** generates **56a**, which may in turn ketonize to **22** (Scheme 2-10). It is interesting to note that in the runs with **22**, there was no evidence of **56** which indicated that the rearrangement of **56** was irreversible, unlike the equilibrium observed for the bicyclo[2.2.2] system **13**. In addition, base treatment of **22** did not yield the desired bicyclo[4.3.0] system **23** (Scheme 2-1), a rearrangement

Table 2-6 : Composition of the neutral product from homoenolization (*t*-BuOK/*t*-BuOH/185°C) of **56**[1]

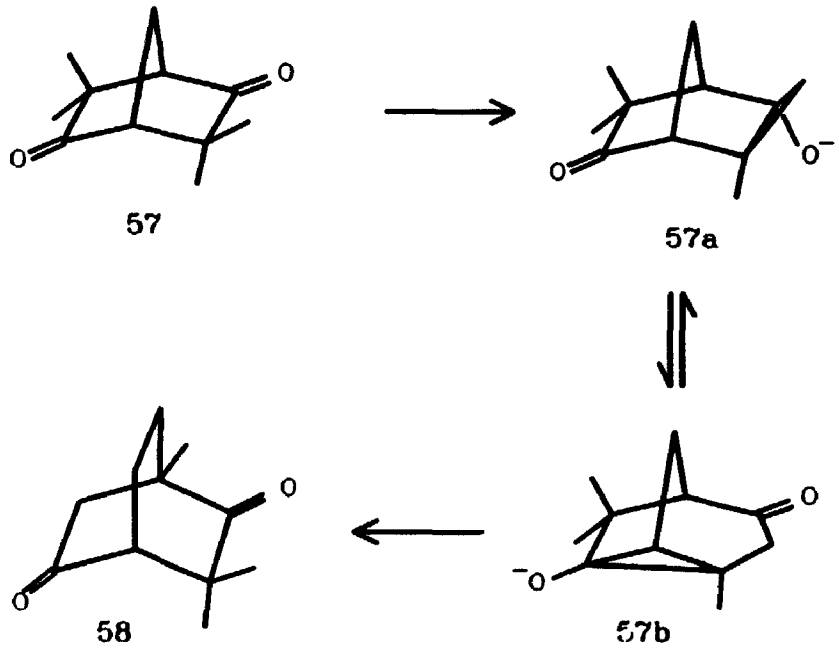
Time (h)	**56**	**22**
96	49	39
192	44	41
240	30	55

[1] Listed as percentage of the isolated product, the ratios were determined by glc

proposed to occur after proton abstraction at C-9. It was of interest to determine the reason for the apparent lack of reactivity of **22**. It may be that **22** underwent β-enolization at either C-8 or C-9, but the incipient cyclopropoxides, **56a** and **22a** (Scheme 2-1), respectively, homoketonized with reversion to **22**. This point was examined by deuterium labelling experiments in work done concurrently with this study (36). Upon treatment with *t*-BuOK/*t*-BuOD, it was found that **22** incorporated ^2H at the bridgehead and exo-methyl sites. Bridgehead exchange of this ketone had been noted in an earlier study (37) under considerably milder conditions (NaOMe/MeOD/100°C) and previous studies have established that *exo*-methyl exchange is faster than *endo*-methyl exchange in related systems (3). However, there was no exchange at remote methylene carbons, showing that neither **56a** nor **22a** appeared to be generated by abstraction of a proton from C-8 or C-9 in **22**, respectively.

2.2.5 Tetramethylbicyclo[3.3.1]nonan-2,6-dione (59)

While there is abundant evidence in the literature concerning the fate of polycyclic monoketones under strongly basic conditions, there is only one example of a rearrangement of a polycyclic diketone (38). The rearrangement of 3,3,6,6-tetramethylbicyclo[2.2.1]heptan-2,5-dione (57) is shown in Scheme 2-11.



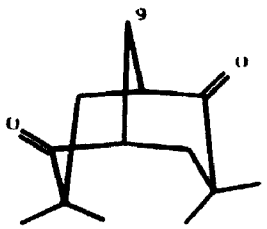
57 57a 57b 58

Scheme 2-11 : Rearrangement of diketone 57

Compound **58** was isolated in 63% conversion after 102 h reaction at 175°C. The proposed mechanism involved initial proton abstraction from the *exo*-methyl group in **57** to generate

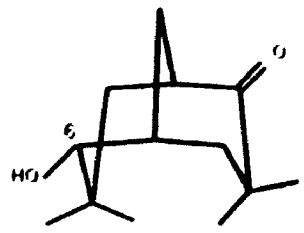
57a which then underwent a 'homoenolate switch' to β-enolate **57b**. Homoketonization of **57b** provided **58** in an essentially irreversible reaction.

Since bicyclo[3.3.1]nonan-2,6-dione (**32**) was readily available as an intermediate in the synthesis of **38** (Scheme 2-4), the behaviour of its tetramethyl derivative, **59**, could prove interesting since the methylene bridge (C-9) is now activated by two carbonyl groups. Subjection of **59** to *t*-BuOK/*t*-BuOH at 185°C produced a complex mixture containing a minimum of eight compounds, none of which was **59**, even after times as short as three hours.



59

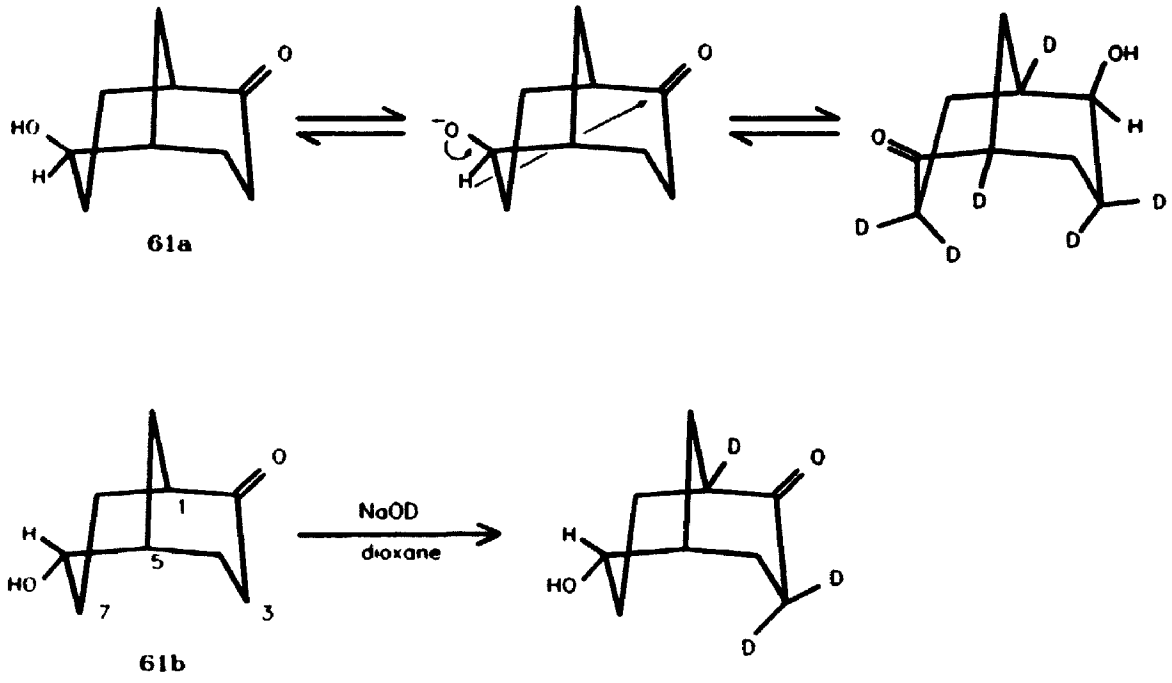
While this mixture was not analyzed in detail, the major component (>50%) was isolated by chromatography on silica and its ^{13}Cmr spectrum contained signals for both an alcohol (δ_C 79.8) and a ketone (δ_C 220.9). The remaining eleven signals in the aliphatic region of the ^{13}Cmr spectrum arose from four methyl, three methylene, two methine and two quaternary carbons. Based upon the spectral data this compound was assigned structure **60**. This assignment was aided by the ^{1}H{^{1}H} and ^{13}C{^{1}H} COSY spectra, which led to the specific assignments of the ^{13}Cmr signals shown in Table 2-1. The stereochemistry at C-6 was assigned on the basis of the ^{1}Hmr spectrum. The proton at C-6 was seen as a sharp doublet (J=4.8 Hz) centred at 3.51 ppm.



60

The relatively large coupling to H-5, and the lack of four-bond ('W') coupling to the *syn*-proton on C-9 indicated that H-6 was in an *exo*- orientation. It is interesting that the *t*-BuO$^-$ reduction proceeded slowly at 120°C.

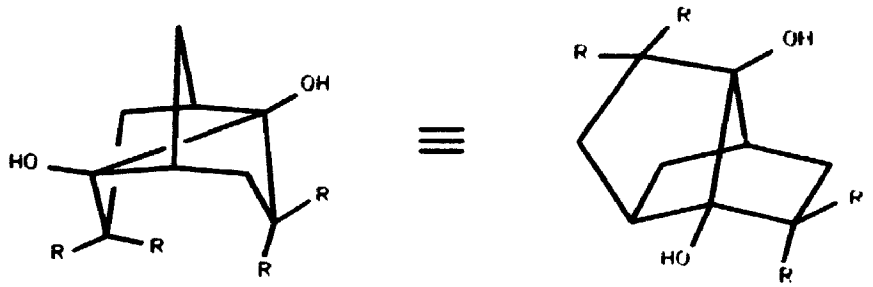
There are two reports in the literature on the [3.3.1] skeleton which reveal an interaction between the C-2 and C-6 positions. First, Parker and Stevenson have shown (39) that *exo*-6-hydroxybicyclo[3.3.1]nonan-2-one (**61a**) incorporated up to six atoms of deuterium when treated with NaOD while the *endo*- isomer **61b** only incorporated three (Scheme 2-12).



Scheme 2-12 : Transanular interaction in the [3.3.1] system

They were able to show that both isomers incorporated ^{2}H at C-1 and C-3, while **61a** picked up an additional three deuterium atoms at C-5 and C-7. Since the carbinyl proton (H-6) was not exchanged, and there was no epimerization at C-6, they concluded that an intramolecular 2,6-hydride shift must be operating for the *exo*-isomer. In a similiar manner, there is the possibility that an interaction between the C-2 and C-6 positions of **59** has some involvement in the reduction to **60**, since there may be some participation of radical anions of the carbonyl groups at high temperature in *t*-BuOK/*t*-BuOH.

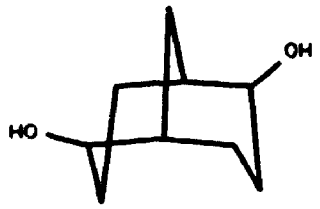
Secondly, Meerwein *et al* (40) were able to link C-2 and C-6 of **32** using sodium amalgam to prepare **62a**, the first example of a tricyclo[4.3.0.$0^{3,7}$] nonane (brexane) ring system.



62a R=H
62b R=Me

If the corresponding tetramethylated derivative **62b** could be prepared from **59**, might it be shown to have some involvement in the reduction of **59**? In the event, **62b** was prepared by

sodium amalgam reduction of **59** in water, and was isolated as a powder in 75% yield. Of note is that Meerwein had prepared a 1:1 mixture of bridged diol **62a** and unbridged diol **63**, while only **62b** was isolated in the sodium amalgam reduction of **59**.

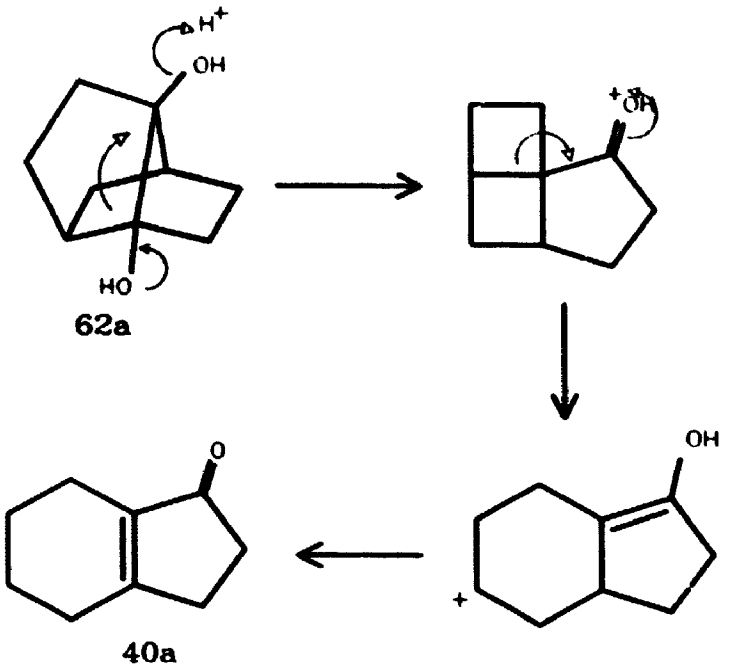


63

However, treatment of **62b** with *t*-BuOK yielded a mess of which nothing, let alone **60**, could be identified. As a consequence, the mystery of the reduction of **59** still stands; it may involve single-electron transfer from *t*-butoxide.

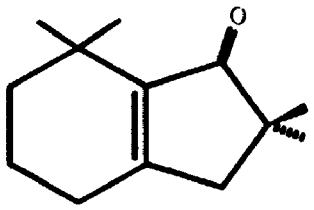
Additionally, Meerwein treated **62a** with sulphuric acid at 160°C and isolated a single product of undetermined structure in 40% yield (41). Upon reinvestigation of this work in 1973, Bishop and Parker (41) assigned its structure as 4,5,6,7-tetrahydroindan-1-one (**40a**). This structure was rationalized on the basis of the mechanism shown as Scheme 2-13, which involved pinacol rearrangement of **62a**.

Attempts to extend this reaction to **62b** were not quite as successful although a very small amount of a compound with a molecular formula of $C_{13}H_{20}O$ by precise mass determination was isolated. The ^{13}Cmr signals of this compound included signals for an enone (δ_C 127.4, 168.8, 213.0), and had some signals in



Scheme 2-13 : Mechanism of formation for 40a from **62a**

common with **40b**, as seen from Table 2-2. These data suggested **64** as a possible structure by analogy with the rearrangement of **62a**. However, too little of the compound was isolated to purify and characterize properly, and the most conclusive evidence was probably its odour; **40a** and **40b** both had a very characteristic sweet odour that was matched by the new enone.



64

2.3 SUMMARY AND CONCLUSIONS

Under strongly basic conditions (*t*-BuOK/*t*-BuOH/185°C), 3,3-dimethylbicyclo[3.2.2]nonan-2-one (**56**) rearranged to 3,3-dimethylbicyclo[3.3.1]nonan-2-one (**22**), with a half-life of 140 h. Ketone **22** was stable under these conditions. 3,3-Dimethylbicyclo[3.2.2]non-6-en-2-one (**49**), underwent an analogous transformation about ten times faster ($t_{\frac{1}{2}}$ ~ 24 h), although its product, 3,3-dimethylbicyclo[3.3.1]non-6-en-2-one (**38**) was not stable. Five products were identified from the homoenolization of **38**, one of which was its Δ^7 isomer, **39**. 2,2-Dimethyl-4,5,6,7-tetrahydroindan-1-one (**40b**) was produced by a β-enolate rearrangement of **39**, and the former suffered slow reduction to the *cis*- and *trans*- saturated [4.3.0] isomers, **41b**. In a relatively minor process, aromatic acid **46** arose from Haller-Bauer cleavage. Reduction was also the predominant reaction when diketone **59** was subjected to strong base treatment, although the mechanism is unclear.

Surprisingly, ^2H incorporation experiments showed that β-enolization of remote methylene groups was not observed at all for **22**, in contrast to the the reactivity of its [3.2.1] homologue, **4**, which underwent β-enolization at the bridging methylene position, and a subsequent irreversible β-enolate rearrangement. The sole difference between these two ring systems is the introduction of an extra methylene unit in the non-reacting ring. The most likely explanation for the lack

of reactivity in the [3.3.1] system is that it adopts an unfavourable conformation for interaction of the methylene bridge (C-9) with the carbonyl π-system. The effect of conformation on β-enolization has been previously examined (42). It was found that the reactivity of a series of bicyclo [3.2.1]octan-2-ones with respect to homoenolization of the methano bridge protons was dependent on the orientation of this group relative to the carbonyl π-system. The results of the present study support the notion that through-space overlap between the carbanion and the ketone is responsible for the occurrence of β-enolization in bicyclic ketones.

The initial premise of this project was that an entry into the 3,3-dimethylbicyclo[4.3.0]nonane system might be achieved through β-enolization of a bicyclo[3.3.1]nonan-2-one. It would now appear that it is possible to prepare the [4.3.0] skeleton from such a rearrangement using an olefinic starting material, since the saturated [3.3.1] system **22** was stable with respect to homoenolization. While *t*-butoxide does not add to the double bond of **38**, as it does for the unsaturated [3.2.1] ketone **17**, reduction under the conditions still does occur. Therefore, the double bond did appear to enable a β-enolate rearrangement in this system, but subsequent migration and reduction of the double bond yielded the saturated [4.3.0] system as the end-product. As a result, the use of a β-enolate rearrangement in the synthesis of certain [4.3.0] systems would not be practical.

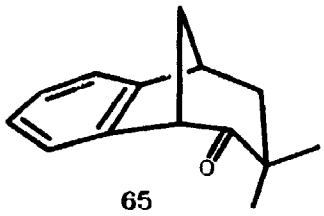
CHAPTER THREE

An Examination of β-Enolization in the Benzobicyclo[3.2.1]-, [2.2.2]- and [3.2.2] Ketone Systems

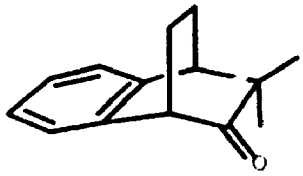
3.1 INTRODUCTION

In the previous two Chapters, the results of experiments involving the base-catalyzed rearrangement of a number of saturated bicyclic ketones were presented. In particular, 3,3-dimethylbicyclo[3.2.1]- and [2.2.2]octan-2-one and 3,3-dimethylbicyclo[3.2.2]nonan-2-one, **4**, **13** and **56**, were shown to undergo β-enolate rearrangements to a single ketone, **5**, **14** and **22**, respectively. In each of these cases, the unsaturated counterpart was found to undergo a similar rearrangement with an enhanced rate constant, the most pronounced acceleration being that for 3,3-dimethylbicyclo[2.2.2]octenone, **15**, which rearranged >100 times faster than its saturated counterpart, **13**. However, for the unsaturated [3.2.1]- and [3.2.2] ketones **17** and **49**, complications arose due to the presence of a double bond, as opposed to the clean rearrangement observed for **15**. The rearrangement products from both of the former systems underwent migration of the double bond into conjugation with the ketone, and subsequent reduction of the α,β-unsaturated ketone. In the case of **17**, *t*-butoxide was also found to add to the double bond.

A logical extension of this research is to examine the effect of replacing the double bond in these systems with an aromatic ring. The activating effect of the π-system is retained, but the complications which arose as a result of the double bond are eliminated. To that end, benzo ketones **65**, **66** and **67** were prepared and their behaviour under homoenolization conditions was examined.



65



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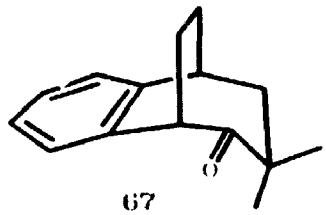
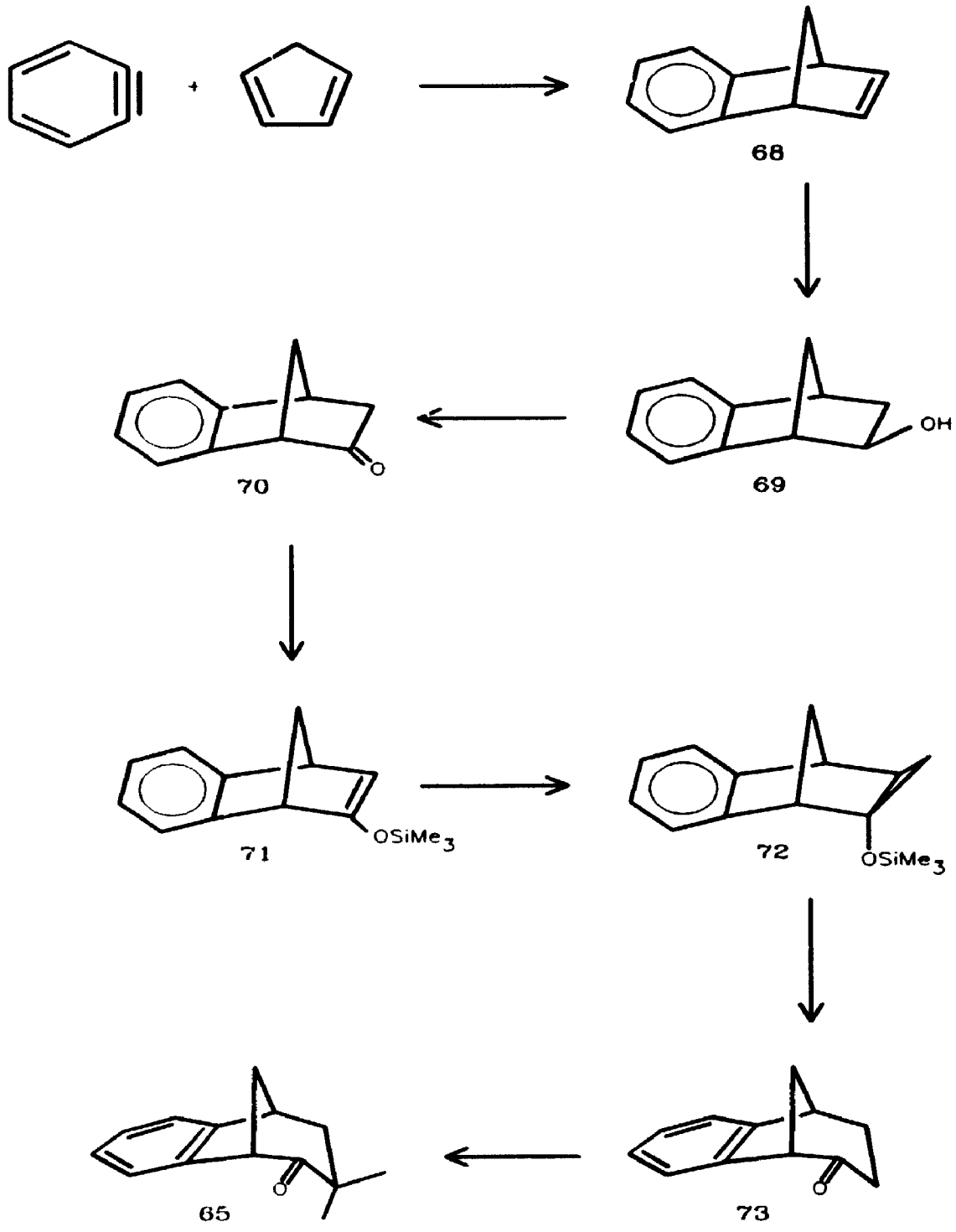


67

3.2 RESULTS AND DISCUSSION

3.2.1 3,3-Dimethylbenzobicyclo[3.2.1]octen-2-one (65)

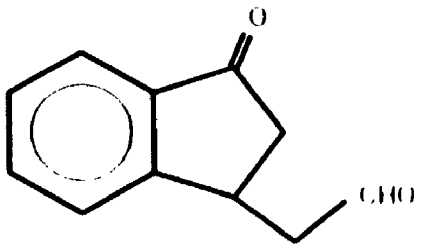
This ketone was prepared by the method outlined in Scheme 3-1. Cycloaddition of benzyne, which was generated from benzenediazonium-2-carboxylate by the method of Crews and Beard (43), with cyclopentadiene provided benzonorbornadiene (**68**) in good yield. The olefin was readily hydroborated and oxidized to give benzonorbornenol **69**. Oxidation of the alcohol using pyridinium chlorochromate (PCC)



Scheme 3-1 : Synthesis of starting ketone **65**

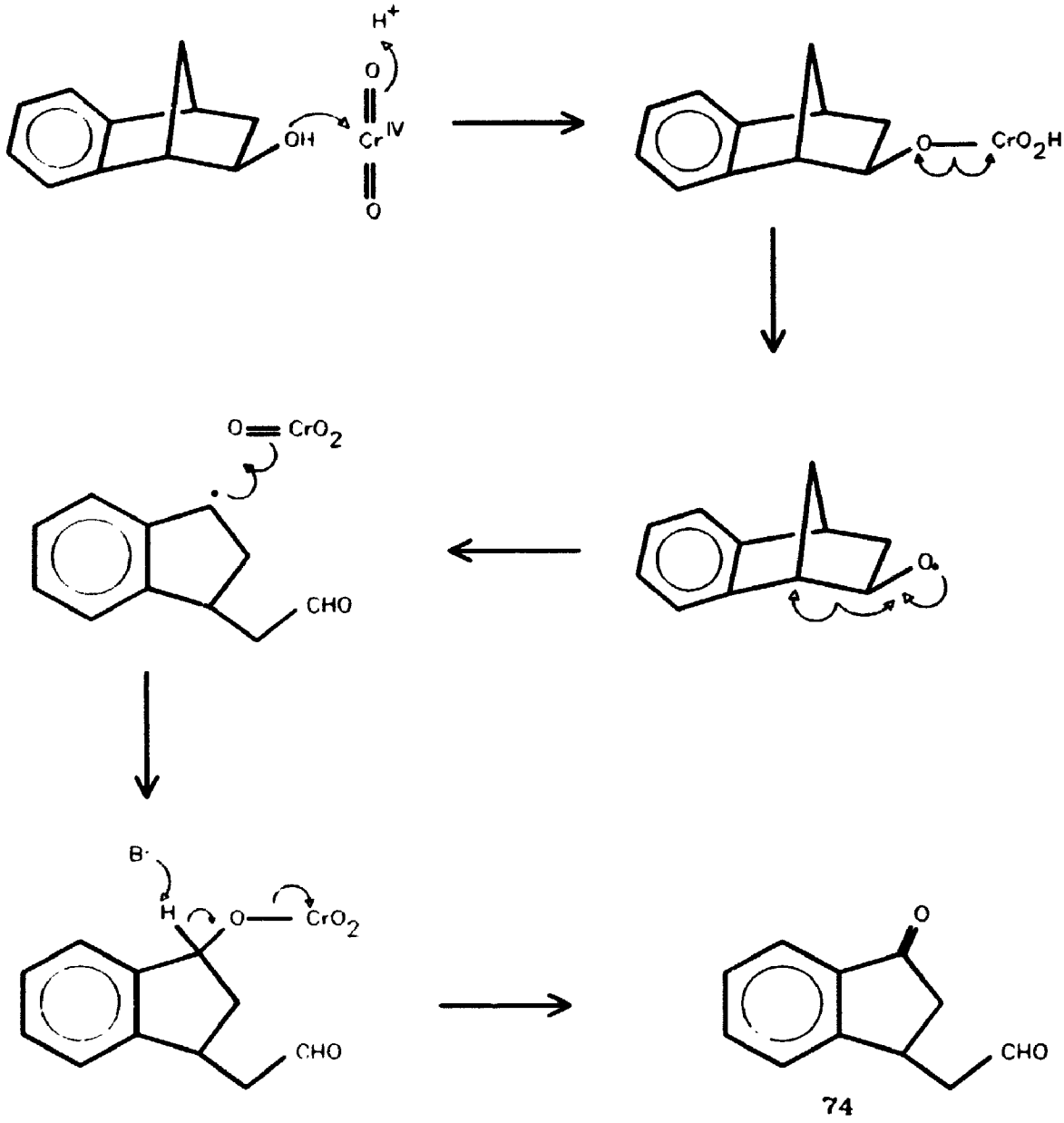
resulted in a 1:1 mixture of ketone **70** and a new compound, which were easily separated by chromatography.

This side-product, $C_{11}H_{10}O_2$ by precise mass determination, had ^{13}Cmr signals for both an aldehyde (δ_C 200.5) and a ketone (δ_C 205.4) in addition to a ortho-disubstituted benzene ring, a methine, and two methylene carbons. In the ^{1}Hmr spectrum, each pair of methylene protons showed large geminal coupling (18.3 and 19.3 Hz) and a small coupling to the methine proton. Furthermore, the aldehydic proton pattern was a triplet, with weak coupling (J=1.0 Hz) to one of the pairs of methylene protons. Thus, C(=O)-CH_2-CH-CH_2-CHO represents a fragment of the molecule which could be assigned structure **74**. A mechanism for the formation of this side-product is shown in Scheme 3-2. Single electron transfer from a chromium(IV) species can form an oxide radical which then induces rupture of the original C-1,C-2 bond to produce a benzyl radical. This radical may then attack a molecule of CrO_3 and form the ketone.



74

As a consequence, oxidation of **69** was then carried out using tetra-n-propyl ammonium per-ruthenante, TPAP (31); this method provided a sample of pure **70** quantitatively. However, large-scale use of TPAP was impractical, so a Swern (44) oxidation was used, since it is more amenable to large scale reactions, and yields are still very high.



Scheme 3-2 : Formation of by-product 74

Ring expansion of benzonorbornenone (70) followed our standard three-step technique described in Chapter Two, which employed homoketonization of a cyclopropoxide as the key step.

This proceeded smoothly and in excellent overall yield, and homoketonization of cyclopropyl silyl ether **72** gave ketone **73** exclusively. Dimethylation of **73** ($NaNH_2/CH_3I/Et_2O$) provided **65**. Complete ^{13}Cmr and ^{1}Hmr assignments were deduced from the results of $^{13}C\{^{1}H\}$ and $^{1}H\{^{1}H\}$ correlation experiments; the assignments are shown in Figure 3-1.

Ketone **65** was then subjected to the typical homoenolization procedure (*t*-BuOK/*t*-BuOH/185°C) for times ranging from 12 to 96 h. It was found by glc and ^{13}Cmr that the neutral mixtures contained **65** and one new ketone whose relative proportion increased with time, as the yield of neutral product decreased. The acidic fraction contained a single acid, and the yield of acid increased with time.

The new ketone was separated from **65** by preparative thin-layer chromatography (tlc) and characterized by its spectral data, which are included in Figure 3-2. A precise mass determination showed this compound to be isomeric with starting material, and its carbonyl absorption (δ_C 226.0, 1738 cm^{-1}) suggested a cyclopentanone ring. The ^{13}Cmr spectrum revealed the presence of a quaternary, two methine, two methylene and two methyl carbons in addition to those in the benzene ring. The methyl singlets in the ^{1}Hmr spectrum (δ 0.68, 1.14) were shown by $^{13}C\{^{1}H\}$ COSY experiments to correlate with the ^{13}Cmr signals at δ_C 25.9 and 25.2, respectively, and with the quaternary and methylene signals at δ_C 46.3 and 43.4.

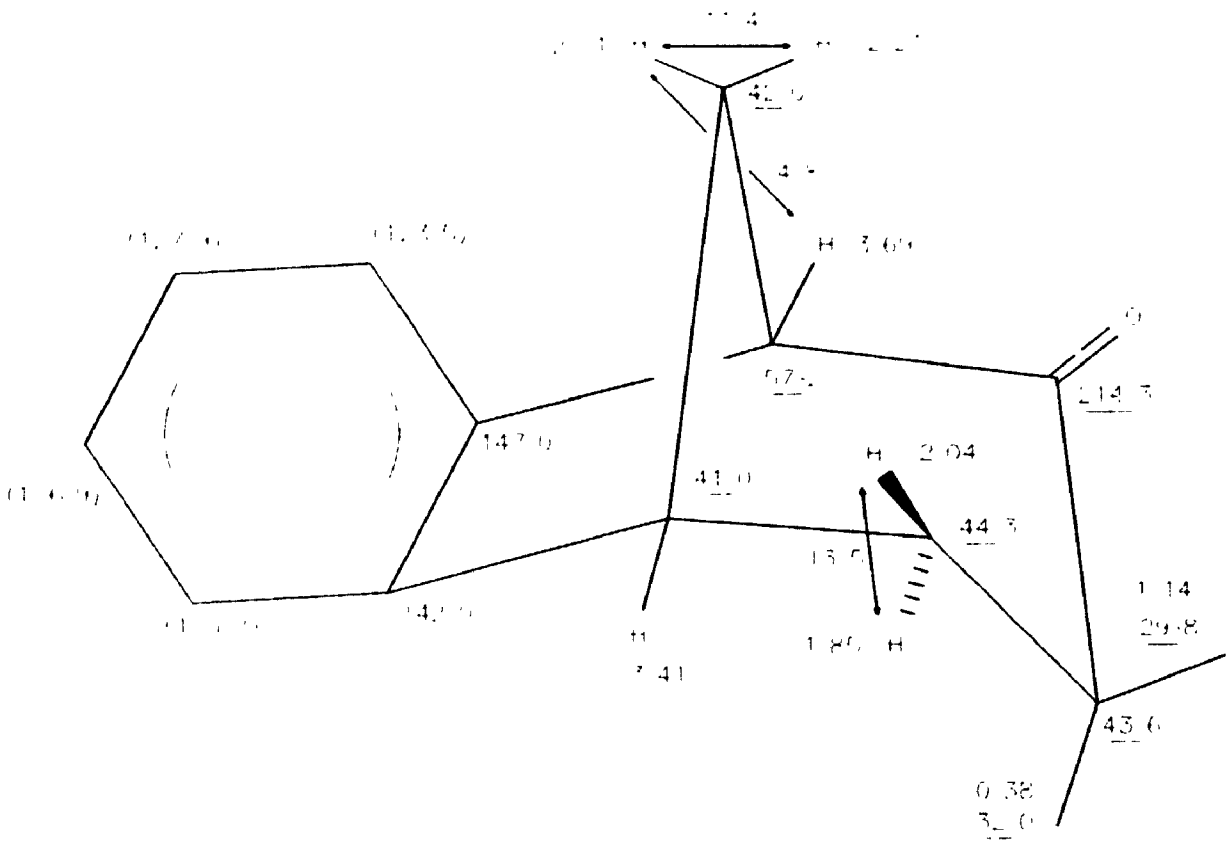


Figure 3-1 : ^{13}Cmr and ^{1}Hmr assignments for 65.

All chemical shifts are reported in ppm downfield of TMS, in $CDCl_3$ solutions. ^{13}Cmr shieldings are denoted by a solid underline, while ^{1}Hmr shieldings are not underlined. Similar values in parentheses may be interchanged. Coupling constants (dashed underline) are given in Hz. For the sake of clarity some coupling constants have been omitted.

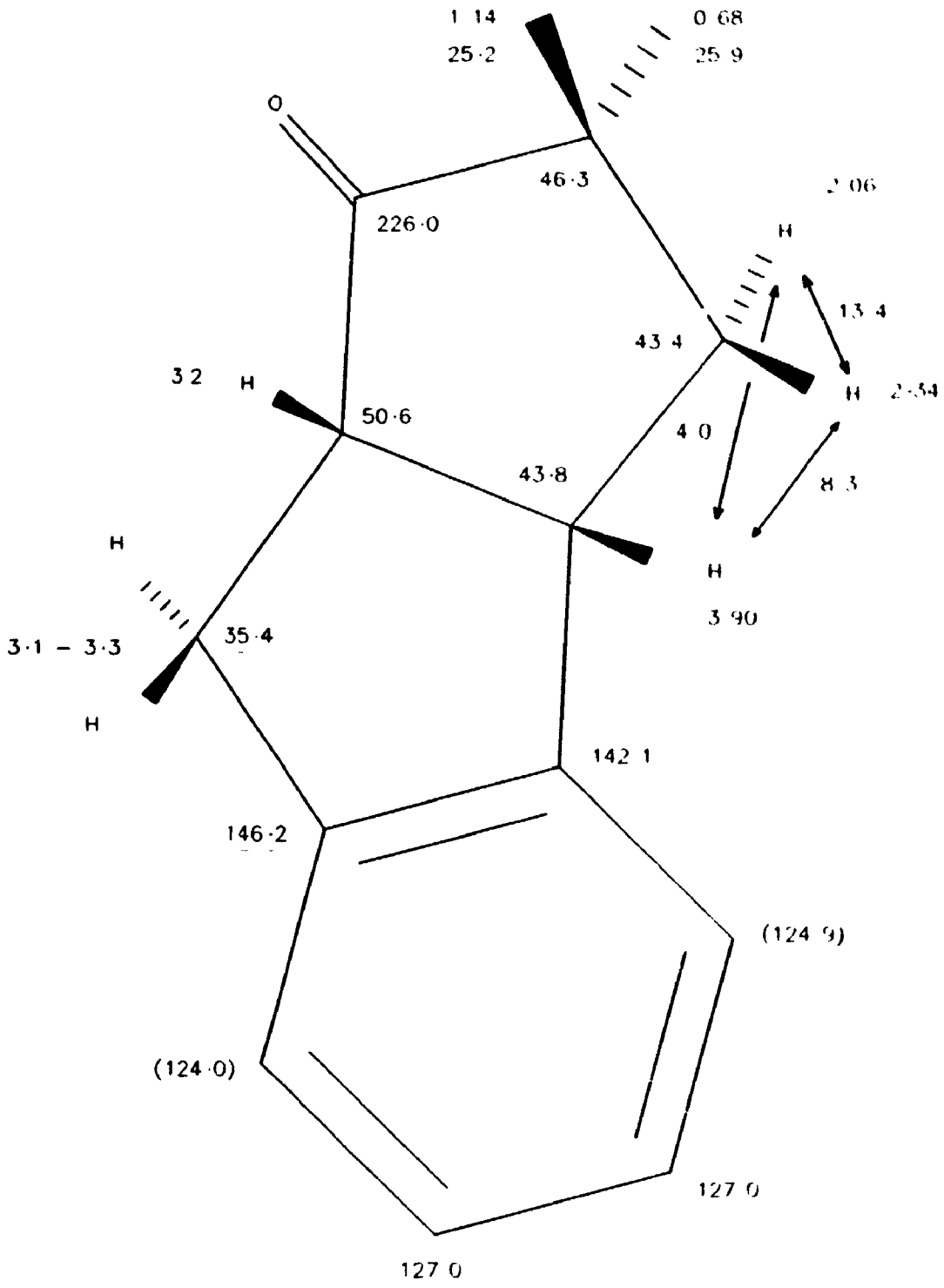
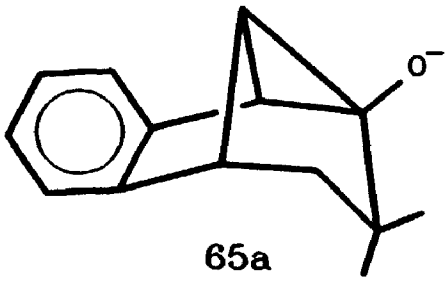


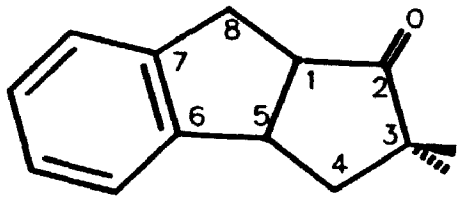
Figure 3-2 : ^{13}Cmr and ^{1}Hmr assignments for 75

These data are presented in accord with Figure 3-1.

The methylene protons bonded to the carbon at δ_C 43.4 appeared as the AB portion of an ABX pattern: δ_A 2.06, δ_B 2.34, J_{AB}=13.4 Hz, J_{AX}=4.0 Hz, J_{BX}=8.3 Hz. The X-proton, bonded to the methine carbon at δ_C 43.8 also couples (J=8.0 Hz) to the other methine proton near δ 3.2, the absorption of which was masked by the remaining pattern at 3.1 - 3.3 ppm. These results indicate the presence of a Me_2-C-CH_2-CH-CH-CH_2- sequence. This compound can be assigned structure **75**, arising by rearrangement of β-enolate **65a** which may be formed by abstraction of a β-proton in **65**; this rearrangement is strictly analogous to the rearrangement of **4** → **5** (Scheme 1-3).

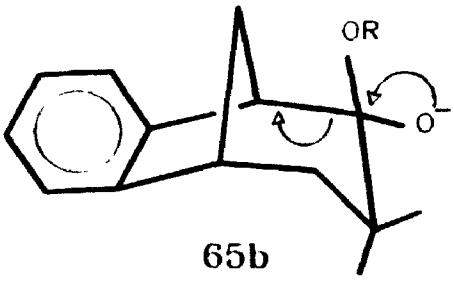


65a

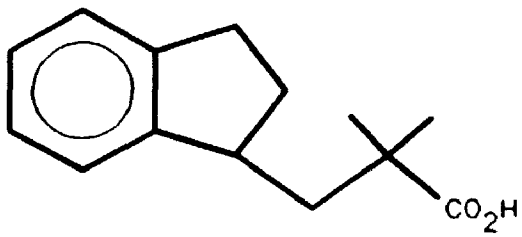


75

The acidic component was purified by recrystallization, mp 105-107°C, and its structure was identified as **76** on the basis of its spectral data. This acid likely arose from



65b



76

Haller-Bauer cleavage of **65b**, which could be formed after attack of base at the carbonyl carbon in **65**.

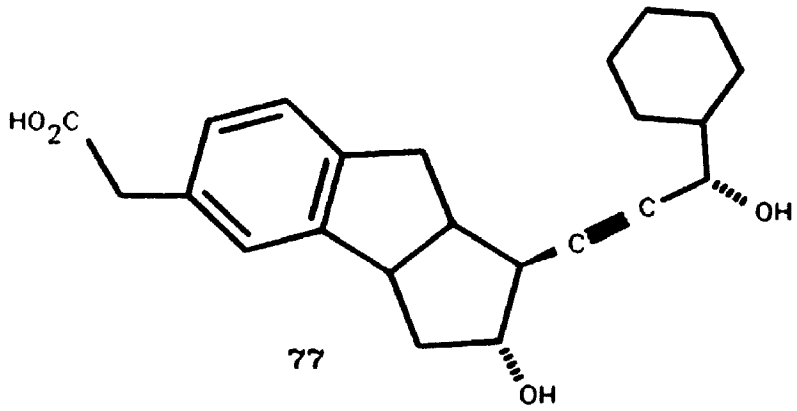
The anion formed by cleavage of the original C-1,C-2 bond is stabilized by the benzene ring, and acid **76** was subsequently isolated. Apparently, benzylic stabilization of the intermediate carbanion is the governing factor in this cleavage, since the only acid isolated resulted from cleavage of **65**: products resulting from cleavage of **75** were not observed. Disappointingly, the yields of this acid are higher than the yields of ketone **75** at all reaction times. The results of these runs are summarized in Table 3-1.

Table 3-1 : Composition of the total product from homoenolization of **65** (*t*-BuOK/*t*-BuOH/185°C)[1]

Time (h)	**65**	**75**	**76**
12	40	15	31
24	27	25	35
48	11	28	46
72	7	37	43
96	3	36	47

[1] Listed as percentage of the isolated material; the relative amounts of **65** and **75** were determined by glc.

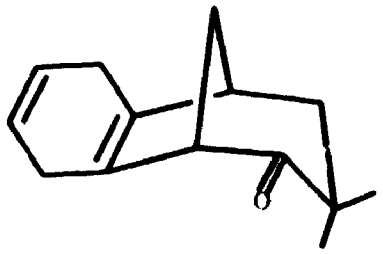
The benzobicyclo[3.3.0]octene skeleton of **75** is the backbone for a class of prostacyclin analogues, represented by the most active of the class, **77** (45). As a result, the synthesis of the ring system of **75** via β-enolization could prove useful if the yield could be improved. However, **77** would be difficult to synthesize via β-enolization, owing to the presence of the hydroxyl in the position of the C-3 methyl groups of the initial rearrangement product from **65**. In spite of this, the preparation of the ring system may be sufficient to stimulate interest in the potential of β-enolate rearrangements. Thus, steps were taken to attempt to improve the yield of this rearrangement.



77

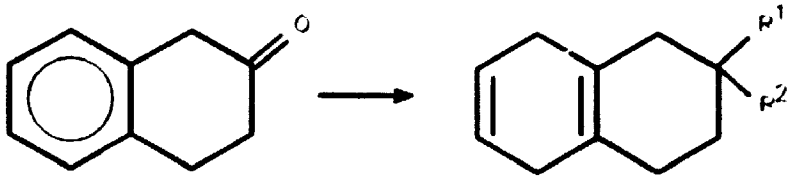
In the hope that a lower reaction temperature would favour homoenolization rather than Haller-Bauer cleavage, runs with **65** were carried out at 160°C. In fact, the reverse was found to be the case and the only product isolated was acid **76**; there was no indication of **75** in the neutral fractions.

The predominance of Haller-Bauer cleavage in the base-catalyzed reaction of the benzo [3.2.1] ketone can be ascribed to the presence of the benzene ring since Haller-Bauer cleavage was not observed at all for the saturated system, **4**, while the unsaturated ketone, **17**, underwent cleavage only to a small extent. Thus, it seemed reasonable that replacement of the benzene ring with a cyclohexadienyl fragment might reduce the quantity of acid resulting from Haller-Bauer cleavage. To this end, it was thought that ketone **78** could be readily prepared by Birch reduction of **65**. While reduction of the ketone was certainly foreseen under the conditions, this was not expected to affect the Birch reduction, and no difficulty in an oxidation to regenerate the ketone was anticipated. However,



78

the presence of alkyl groups on a benzene ring is known to retard Birch reduction (46), so facile reduction of this system was not anticipated. Therefore, a model study was undertaken first, using β-tetralone (**79**), since this ketone has an ortho disubstituted benzene ring, in addition to a carbonyl β- to the arene.



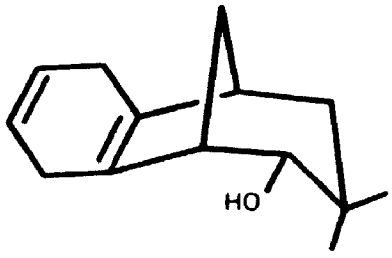
79

80a R^1=OH;R^2=H

80b R^1, R^2= O

Using equal volumes of ethanol and liquid ammonia, in the presence of a large excess of lithium, alcohol **80a** was isolated in good yield after four hours reflux. This alcohol was readily oxidized to **80b** with TPAP, and the product was entirely the cyclohexadienyl ketone, with no evidence for the starting arene **79**, even upon chromatography and standing in air.

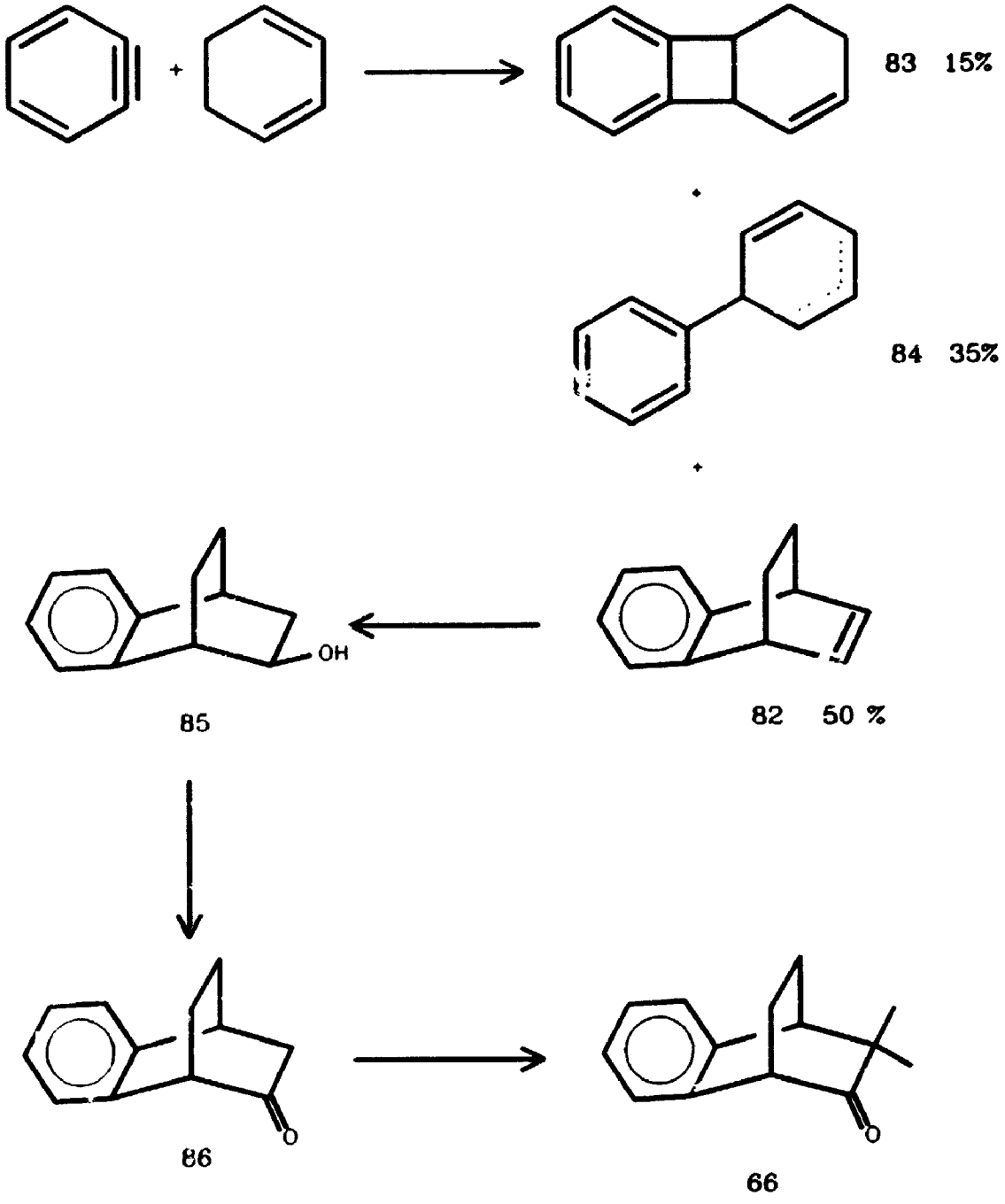
The results with **65**, however, were not analogous to those for the model ketone, **79**. While Birch reduction proceeded smoothly under the conditions of the model study, oxidation of the resultant alcohol **81** with TPAP yielded about 20 % of the starting benzo ketone **65** in addition to the desired ketone **78**. Oxidation by Swern's method was also attempted, but no reaction was observed using either oxalyl chloride or trifluoracetic acid as the electrophile. However, the point became moot upon chromatography, from which the isolated product was almost entirely **65**; air oxidation had resulted in reversion to the aromatic system.



81

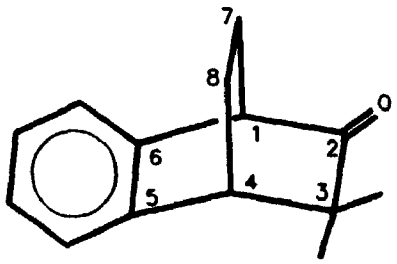
3.2.2 3,3-Dimethylbenzobicyclo[2.2.2]octen-2-one (66)

Compound **66** was prepared by dimethylation of the parent ketone **86**. The synthesis of this ketone was modelled on the method employed for the previous system, **65**, using cyclohexadiene in the initial Diels-Alder reaction, as shown in Scheme 3-3. However, a mixture of products was isolated in the first step, unlike the clean cycloaddition observed in the synthesis of **68**. This result had previously been reported (44) to arise from competing [2+4] (→ **82**), [2+2] (→ **83**) and ene (→ **84**) cycloaddition pathways, although the desired Diels-Alder component **82** was the major product (~50%). Since this mixture co-distilled at 102-106°C/15 Torr, and could not be separated by chromatography, it was used in the subsequent steps in the hope that a separation could be achieved at a later stage. Hydroboration and oxidation yielded alcohol **85** in addition to two other products in a 4:2:1 ratio favouring the desired alcohol. When this mixture was oxidized using Swern's method, a mixture which comprised *ca.* 85% of ketone **86** resulted. Overall, this represented a 50% yield from the olefin mixture; the fate of the undesired olefins in the initial reaction mixture was not investigated further. Ketone **86** was then methylated in the usual way and the desired compound **66** was readily purified by column chromatography. After careful sublimation, an analytical sample of **66** was isolated as a solid, mp 37-38°C (47).



Scheme 3-3 : Synthesis of ketone **66**

The ^{1}Hmr spectrum of this compound was clearly resolved at 300 MHz, and assignment of the ^{1}H signals followed from the results of a ^{1}H-^{1}H decoupling experiment. Irradiating the methine signal at δ 3.55 (H-1) should affect the absorptions for the protons of C-7; the spectra are reproduced as Figure 3-3. The high-field expansion (Figure 3-3b) shows the patterns for the protons on the ethylene bridge (H-7 and H-8). These spectra show that the middle two proton patterns have become simplified relative to those in the unperturbed spectrum. Therefore, the proton patterns at δ 1.71 and 1.99 must be the 7-methylene protons. The higher-field proton of each pair was assumed to lie above the aromatic ring, and are therefore *anti* with respect to the carbonyl. Evidence for this assignment came from molecular modelling and the coupling constants. A steric interaction between *exo*-3-Me and *syn*-H-8 would cause twisting of the ring and a lessening of the dihedral angle between H-4 and *syn*-H-8. Therefore, the C-8 proton with the larger coupling to H-4 is *syn* to the carbonyl (δ 2.20, J=3 Hz), the other C-8 proton is *anti* (δ 1.47, J=2.6 Hz). The same twisting would increase the H-1, *syn*-H-7 dihedral angle and the smaller H-7, H-1 coupling was shown by the lower field proton (*syn*-H-7: δ 1.99, J=2 Hz), thus, the remaining proton is *anti* (δ 1.71, J=3.2 Hz). The assignment of the ^{13}Cmr signals was unambiguous from a ^{13}C{^{1}H} correlation spectrum; all assignments are given in Figure 3-4.



66

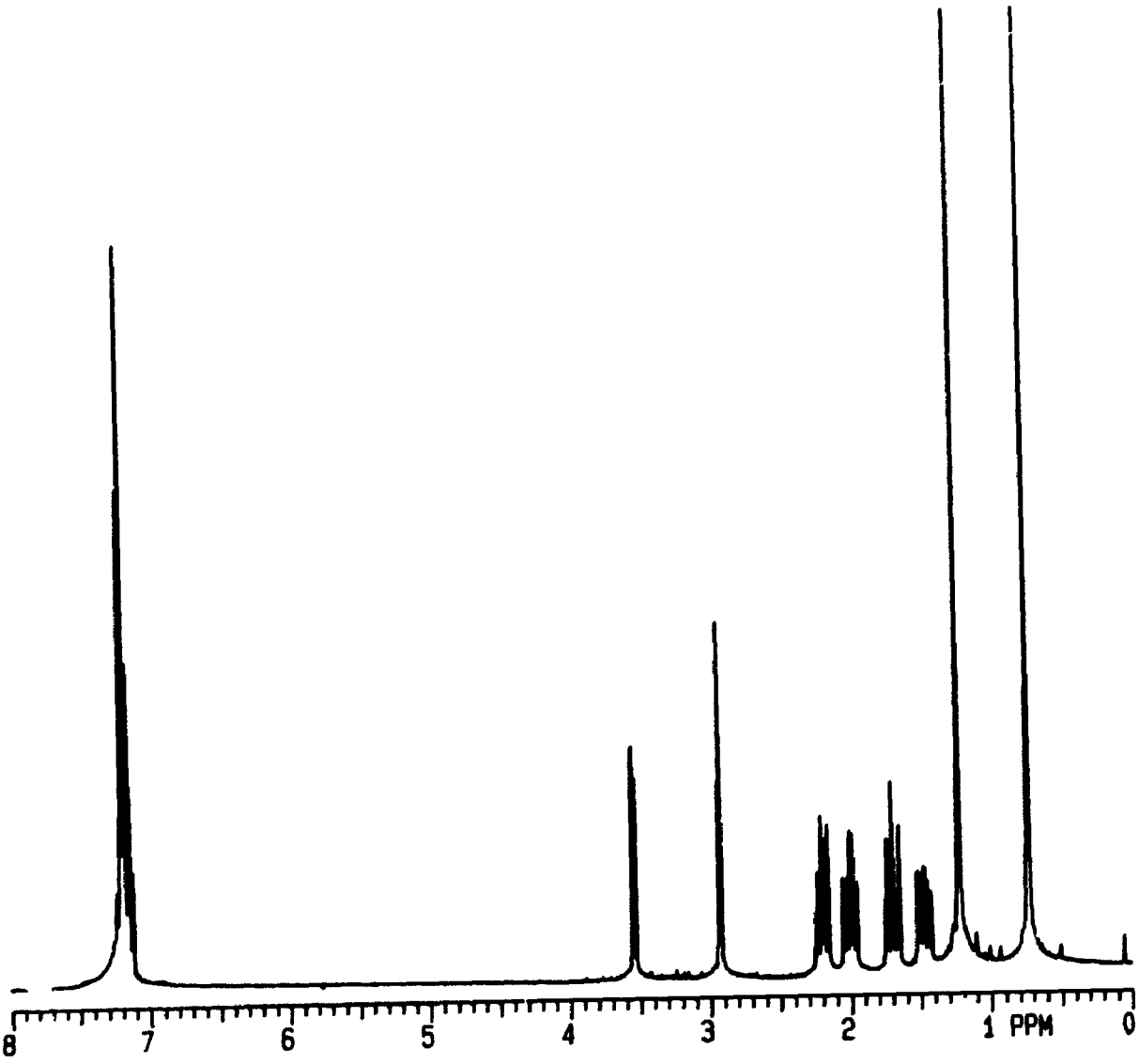


Figure 3-3a : ^{1}Hmr spectrum of **66** before perturbation

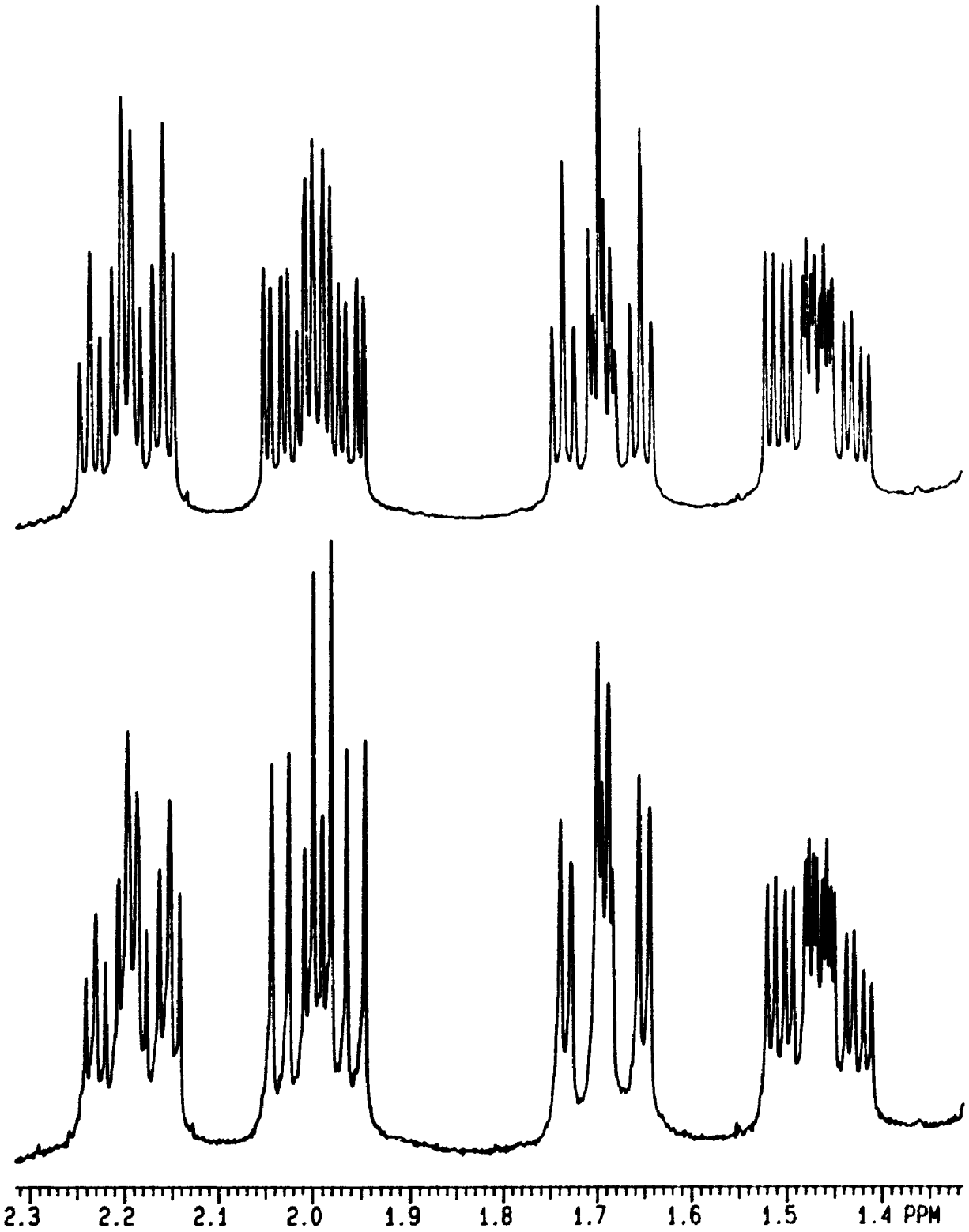


Figure 3-3b : High-field region of the ^{1}Hmr spectrum of **66** with (below) and without (above) irradiation @ 3.55 ppm.

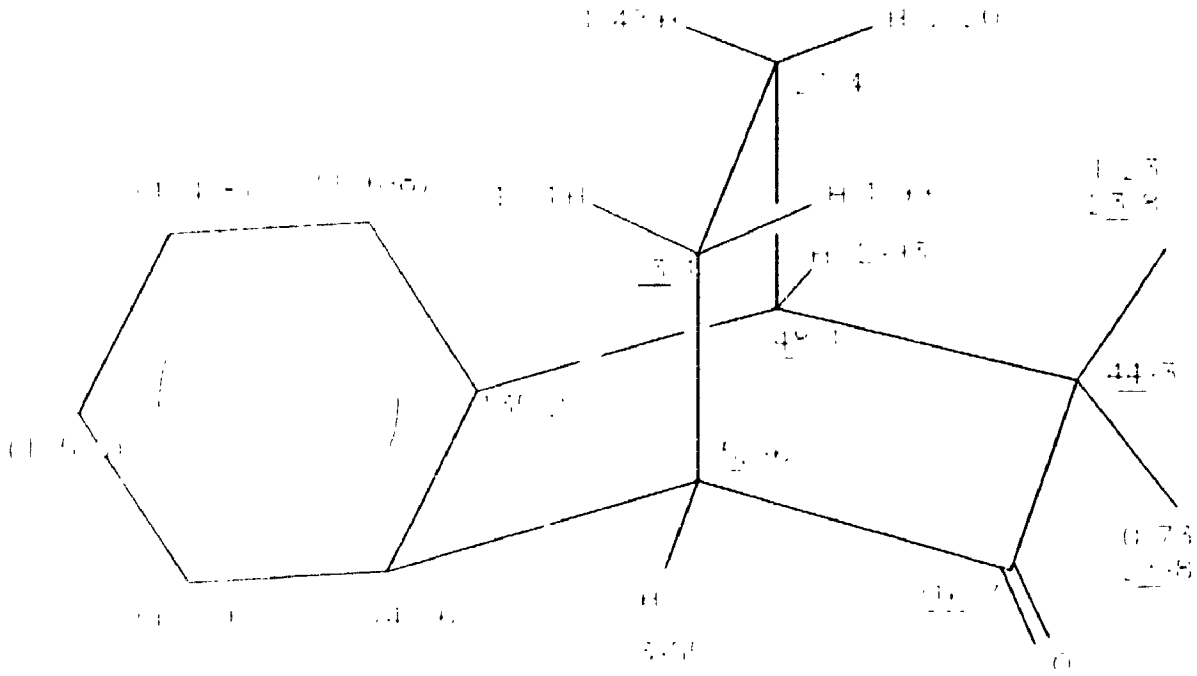
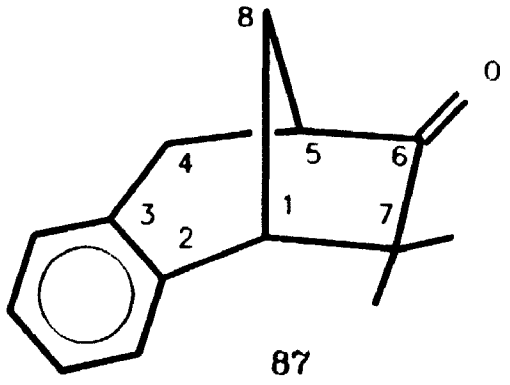


Figure 3-4 : ^{13}C and ^{1}Hmr assignments for **66**

The ^{13}Cmr (underlined) and ^{1}Hmr shieldings are given in ppm downfield of TMS, in $CDCl_3$ solutions. Similar values in parentheses may be interchanged.

A series of homoenolization experiments with this ketone was carried out, from which it was evident that the neutral fractions contained a mixture of **66** and a new ketone whose relative proportions became constant at 47:53 within six hours. As with **65**, the acidic fractions contained a single acid, which represented 43% of the total product after 48 h.

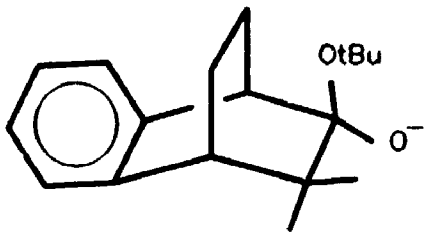
The new ketone was separated from **66** by column chromatography through silica and was shown to be isomeric with **66** by precise mass determination. Its ir and ^{13}Cmr spectrum revealed the presence of a cyclopentanone ring (1738 cm^{-1}, δ_C 226.0), and the molecule was assigned structure **87** by analogy with the rearrangement of **13**. Complete assignments, given in Figure 3-5, were based on the following nmr results. The ^{1}Hmr spectrum contained two methyl singlets, two methylene groups absorbing as AB portions of larger spin systems and two bridgehead methine absorptions as well as the aryl pattern of the benzo substituent. The bridgehead H-1 gave rise to a broadened doublet, δ 2.95, coupled by 4.1 Hz to *syn*-H-8, δ 2.56, that appeared as an eight-line pattern with other couplings to *anti*-H-8 (11.9 Hz), H-5 (5.5 Hz) and *endo*-H-4 (1.3 Hz). The broadening of the H-1 pattern was partly due to coupling with *anti*-H-8 (δ 2.06, dd, J=1.0, 11.9 Hz). A broadened doublet was also observed



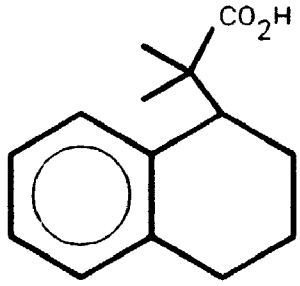
87

for *endo*-H-4 (δ 2.94) which coupled (J=17.2 Hz) to *exo*-H-4 (δ 3.16). *Exo*-H-4 is also coupled (J=5.9 Hz) to the remaining methine, H-5 (δ 2.85, dddd, J=2.0, 2.1, 5.5, 5.9 Hz). The two small couplings to H-5 must be interactions with H-1 and *endo*-H-4, although these couplings were not resolved in the patterns for the latter nuclei.

The acidic fractions each contained a single acid which was found to solidify on standing, and was sublimed to provide an analytical sample, mp 99-101°C. A precise mass determination confirmed $C_{14}H_{18}O_2$ as its molecular formula, and the ir spectrum confirmed that a carboxylic acid was present. By analogy with the formation of acid **76** from **65**, the acid in this instance was assigned structure **88**, and the spectral data supported this assignment. The generation of this acid by



66b



88

Haller-Bauer cleaveage would likely follow the same pathway; that is, addition of *t*-BuO$^-$ to the carbonyl in **66** to give **66b**, followed by cleavage to **88**. Once again, the sole acid identified resulted from the cleavage of **66**, presumably because the intermediate carbanion is benzylic, whereas the corresponding putative intermediate from **87** is not.

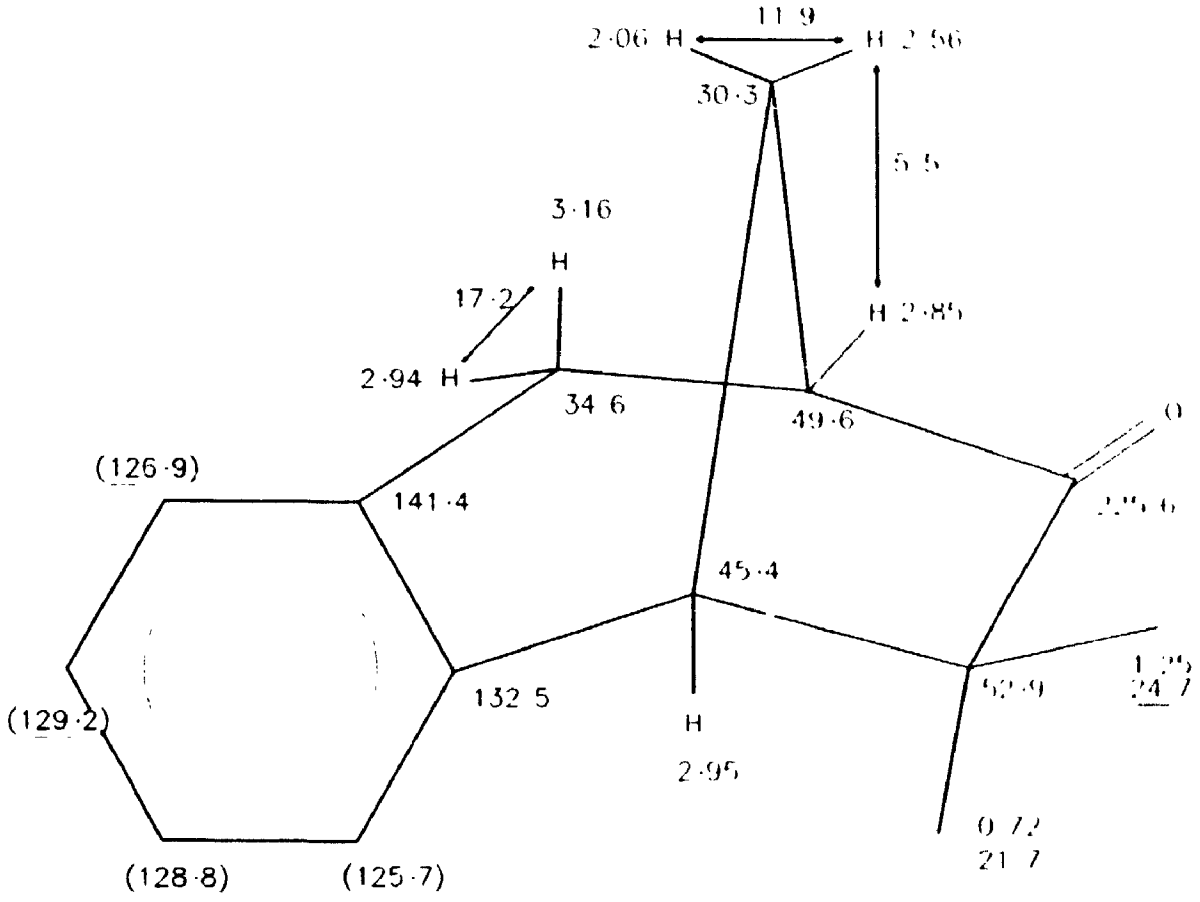
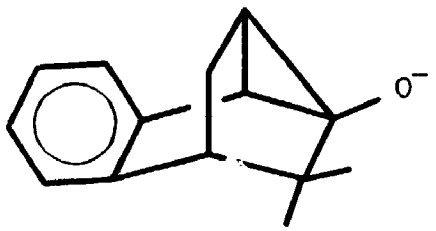


Figure 3-5 : ^{13}Cmr and ^{1}Hmr assignments for 87

The ^{13}Cmr (underlined) and ^{1}Hmr shieldings are given in ppm downfield of TMS. Similar values in parentheses may be interchanged. Coupling constants (dashed underline) are in Hz. Some coupling constants have been omitted for clarity.

The generation of **87** from **66** would proceed by the intermediacy of β-enolate **66a**, after abstraction of a proton from C-8 in **66**, in an identical manner to the rearrangement for the saturated and unsaturated [2.2.2] ketones **13** and **15**. The fact that the ratio of **66** and **87** appeared to become constant between the 3 and 6 h time points indicated that an equilibrium state had been achieved; this result is not surprising in light of the reversible rearrangement observed for both **13** and **15**, although the latter ketones required ~500 h and ~20 h, respectively, to reach equilibrium. It was discouraging that the equilibrium mixture of **66** and **87** was *ca.* 50:50, in contrast to the previous [2.2.2] systems in which the rearranged ketone was the major product, in fact, **16** represented 90% of the neutral mixture from the runs with **15**. However, the presence of the benzene ring clearly increased the reactivity of the [2.2.2] system, since equilibration of **13** and **15** required significantly longer. The composition data from the runs with **66** are given in Table 3-2.



66a

Two further experiments proved that **66** and **87** achieve equilibrium through the common cyclopropoxide intermediate **66a**. First, **87** was isolated and treated with *t*-BuOK and the results, presented in Table 3-3, show that the same ratio (47:53) was obtained from trials with **87** as from those with **66** as the initial ketone, and again, the sole acid isolated was

88. In a second set of experiments, a sample of the neutral product (47:53 mixture of **66** and **87**) was examined under the typical conditions. It was found that the ratio of neutral products remained constant, while the acidic product contained up to 45% **88**, confirming that equilibration must occur to keep a constant ratio, as **66** is consumed by Haller-Bauer cleavage.

Table 3-2 : Composition of the neutral product from homoenolization of **66** (*t*-BuOK/*t*-BuOH/185°C)[1]

Time (h)	**66**	**87**	**88**
3	40	31	16
6	31	35	25
9	31	35	28
12	28	33	30
24	28	31	36
48	25	28	43

Table 3-3 : Composition of the neutral product from homoenolization of **87** (*t*-BuOK/*t*-BuOH/185°C)[1]

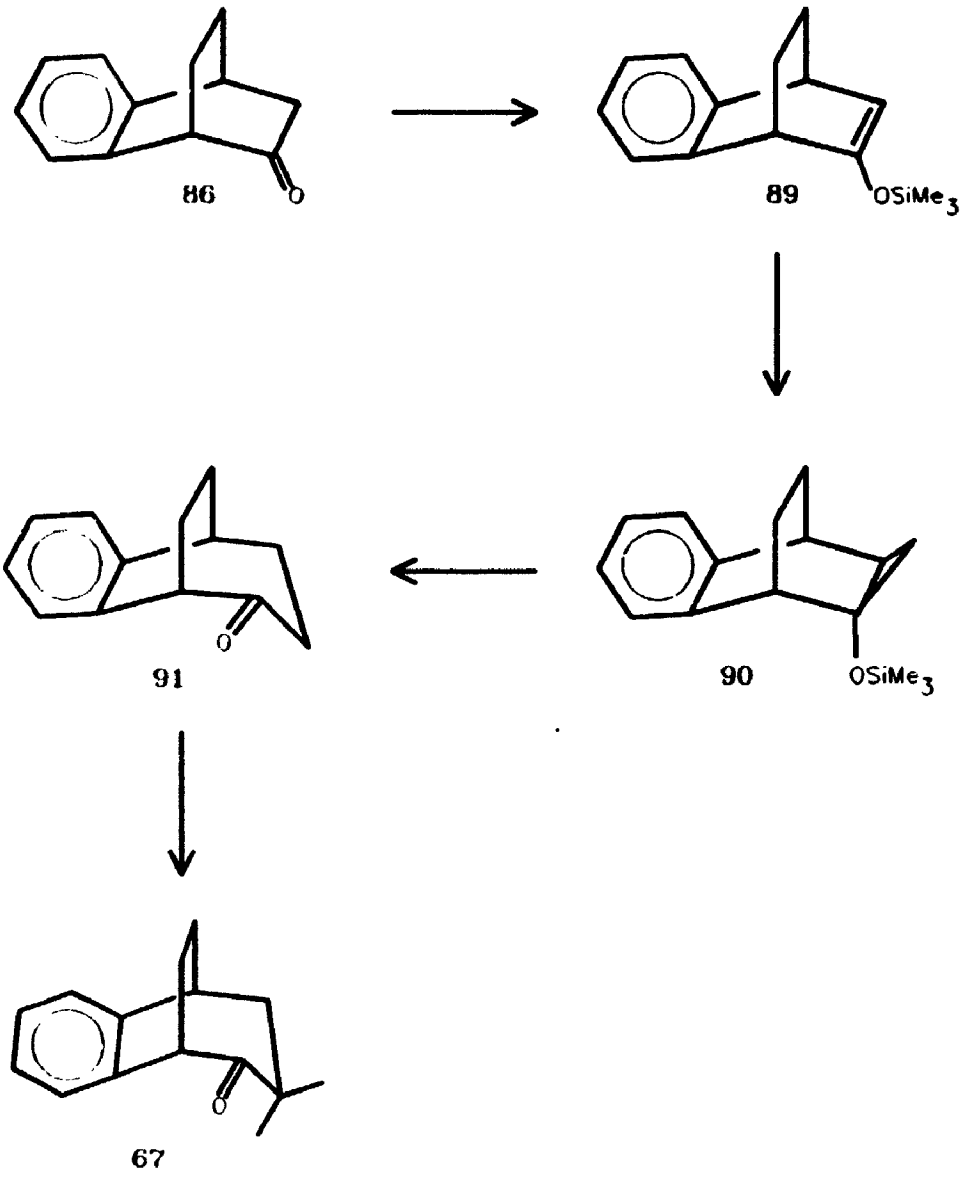
Time (h)	**87**	**66**	**88**
24	23	28	32
48	22	26	43
168	14	16	55

[1] Listed as percentage of the isolated material; the relative amounts of **66** and **87** were determined by glc.

3.2.3 3,3-Dimethylbenzobicyclo[3.2.2]nonen-2-one (67)

With the benzobicyclo[2.2.2] ketone **86** in hand and in light of the rearrangement observed for the [3.2.2] systems **49** and **56**, presented in Chapter Two, it was of interest to examine the behaviour of the benzobicyclo[3.2.2] ketone **67** with respect to base-catalyzed rearrangement. The synthesis of the parent ketone **91** (Scheme 3-4) was straightforward when ring expansion via homoketonization of a cyclopropoxide was employed. Very good yields were obtained in this three-step synthesis which provided **91** as the only identifiable product. Methylation of **91** proceeded smoothly to generate a volatile, solid ketone which sublimed readily, providing an analytical sample of **67** as long white needles, mp 97.5-98.5°C. The ^{1}Hmr spectrum of this compound showed two methyl singlets (δ 0.42 and 1.10) and the two methine protons (δ 3.25 and 3.75) with the remaining three methylene patterns overlapping to give a pattern too complex to decipher. As a consequence, the ^{13}Cmr signals could not be assigned with confidence, although comparisons to previous systems led to the ^{13}Cmr assignments shown in Figure 3-6.

Ketone **67** was then treated with base by weighing the solid ketone directly into a Carius tube, adding the base solution (0.5 mL) to the tube, and then proceeding as for **65** and **66**.



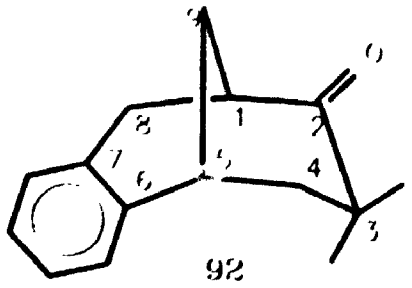
Scheme 3-4 : Preparation of starting ketone **67**.

Figure 3-6 : ^{13}Cmr assignments for **67**

^{13}Cmr assignments, given as ppm downfield of TMS, in $CDCl_3$. Similar values in parentheses may be interchanged.

Similar to **65**, the neutral fractions each contained **67** and a new ketone whose proportion increased with time. The acid fraction again contained only one compound, and the yields increased with time as the yields of the neutral fraction decreased. These results show that the transformation of **67** to the new ketone is approaching completion in 96 h, and that less acid is formed than in the case of ketones **65** and **66**.

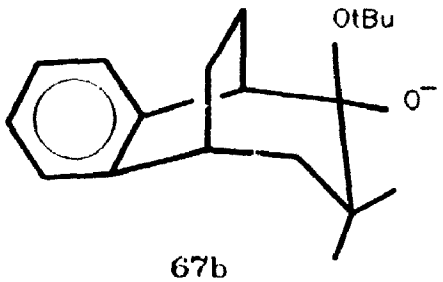
The new ketone was isolated by preparative tlc, and recystallized from ethanol, mp 112-115°C. This ketone was shown to be isomeric with **67** by precise mass measurement, which confirmed $C_{15}H_{18}O$ as the molecular formula. The key features in the ^{1}Hmr spectrum were two methyl singlets (δ 0.49, 1.09) and the absorptions for two pairs of methylene protons as AB portions of ABX spectra. One of these pairs (δ_A 1.95, δ_B 2.05, J_{AB}=13.6 Hz, J_{AX}=2.7 Hz, J_{BX}=4.7 Hz) was correlated with a methine multiplet at δ 3.15 in a $^1H\{^1H\}$ COSY spectrum and with the carbon at δ_C 48.0 in a $^{13}C\{^1H\}$ COSY spectrum. This carbon was shown to correlate with the methyl protons in a long-range $^{13}C\{^1H\}$ COSY spectrum. These results establish the presence of a Me_2-C-CH_2-CH fragment. The second AB pattern (δ_A 2.85, δ_B 3.16, J_{AB}=17.1 Hz, J_{AX}<1 Hz, J_{BX}=7.0 Hz) was correlated with the carbon at δ_C 34.6 and coupled to the second methine proton at δ 2.92. The magnitude of



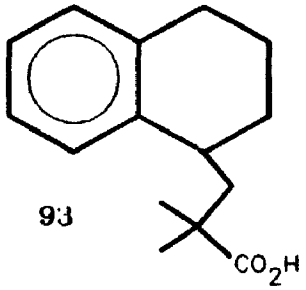
92

the geminal coupling indicated that this methylene is bonded to the aromatic ring. The remaining multiplet in the sp^3 region of the ^{1}Hmr spectrum arose from the methylene group which correlated with the carbon at δ_C 30.2. These data indicated that the compound isolated in the runs with **67** was ketone **92**; full spectral assignments are made in Figure 3-7.

A single acid was isolated from the runs with **67**. This acid was purified by recrystallization, mp 105-107°C, and assigned structure **93** on the basis of its spectral data.



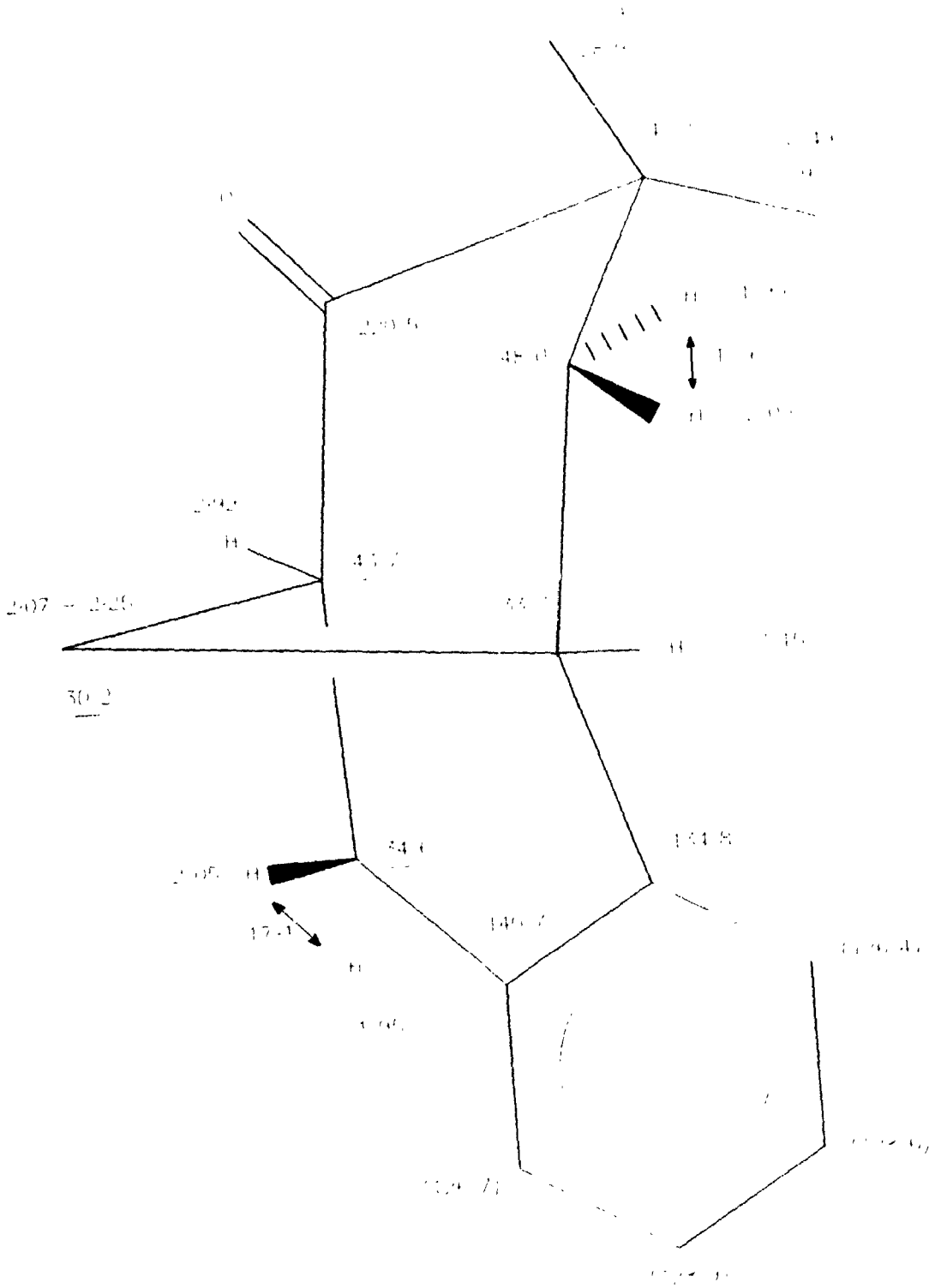
67b



93

This acid presumably arises from the same pathway postulated for the other benzo ketones, **65** and **66**; that is, by cleavage of **67b**, the product of addition of base to the carbonyl. It may be possible that alleviation of ring strain is a driving force for Haller-Bauer cleavage since the yield of **93** in the runs with **67** is somewhat less than that from either **65** or **66**.

The product yields from the runs with **67** are tabulated in Table 3-4.



These data are presented in accord with Figure 3-1.

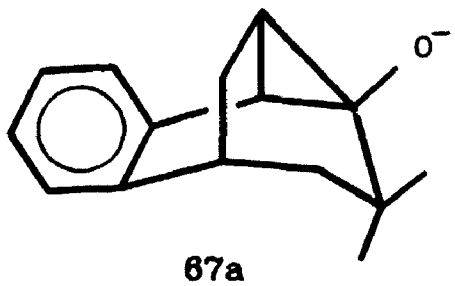
Figure 3-7 : ^{13}Cmr and ^{1}Hmr shielding data for **92**

Table 3-4 : Composition of the neutral product from homoenolization of **67** (*t*-BuOK/*t*-BuOH/185°C)[1]

Time (h)	**67**	**92**	**93**
3	63	8	14
6	53	17	22
12	41	25	25
24	22	43	22
48	6	44	36
96	<2	49	38

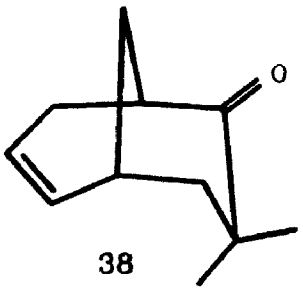
[1] Listed as percent of the isolated material; the relative amounts of **67** and **92** were determined by glc.

Ketone **92** arose by rearrangement of β-enolate **67a** after β-proton abstraction from C-8 in **67**, in the same manner as the rearrangements observed for the saturated and unsaturated bicyclo[3.2.2] systems **56** and **49**. After lengthy treatment (>192 h), ketone **92** was the only compound present in the neutral fractions, which suggested that it was stable



67a

with respect to homoenolization. It is interesting to note that **92** did not undergo a second β-enolate rearrangement after abstraction of a proton at C-9, as was the case in the **49**→**38** rearrangement. In Chapter Two it was suggested that the difference in reactivity between the saturated bicyclo[3.3.1] ketone **22** and unsaturated **38** could be attributed to the ability of bridging methylene (C-9) in **38** to interact with the carbonyl π-system; this effect is dependent upon the conformation of the ring system. It may be that the benzo [3.3.1] ketone **92** adopts a conformation akin to the saturated ketone **22**, and is thus unable to β-enolize; molecular mechanics calculations may be valuable here.



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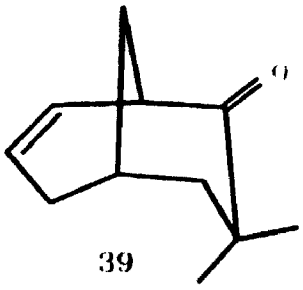


39

However, in Chapter Two it was also stated that rearrangement of the unsaturated [3.3.1] system does not proceed through **38**, but through its allylic isomer, **39**, since the carbanion formed upon homoketonization of the β-enolate from **39** is allylic. It is also possible that **92** is able to β-enolize at C-9, but opening of the incipient β-enolate to the [4.3.0] system, in the manner observed for **39**, is not favoured by benzylic stabilization. Deuterium incorporation trials could reveal whether **92** is capable of β-enolization at C-9.

3.3 SUMMARY

The acceleration in the rate of β-enolate rearrangement noted for several unsaturated bicyclic ketones, relative to their saturated counterparts, led to the premise that incorporation of a benzene ring might also result in a rate enhancement. At the same time, it was hoped that complications noted for unsaturated systems, such as reduction of, or addition to, the double bond might be avoided for the aromatic systems and so provide viable synthetic routes to other polycyclic skeletons. In this Chapter, the syntheses and results of the base-catalyzed rearrangement of ketones **65** - **67** were presented. From these results it can be seen that both hypotheses were correct; that is, the rate of rearrangement was accelerated due to the presence of the aromatic ring and the complications noted for unsaturated systems were not encountered. However, the benzene ring also dramatically accelerated the rate of Haller-Bauer cleavage, and the corresponding carboxylic acids represented, in some cases, >50% of the total product yield. This degree of cleavage clearly doomed any synthetic application of β-enolate rearrangement in these benzo-fused systems, at least, with *t*-BuOK/*t*-BuOH as the base.

CHAPTER FOUR

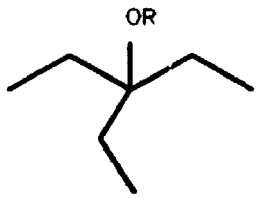
An Examination of the Effect of Base on the β-Enolization Pathway

4.1 INTRODUCTION

In Chapters Two and Three, efforts to extend the use of β-enolization in synthesis were discussed. In both cases, a clean rearrangement could have been used in the preparation of certain polycyclic skeletons. While some degree of success was realized in both projects, these attempts met with side reactions typical of homoenolization studies using *t*-BuOK/*t*-BuOH as the base. Examination of β-enolization in bicyclo-[3.3.1] ketones showed that the rearrangement proceeded only with an unsaturated starting ketone, and that the product was prone to reduction of the α,β-unsaturated ketone formed by migration of the double bond; this type of reduction is precedented with *t*-BuOK as base. The incorporation of a benzene ring into several bicyclic systems was found to increase the rate of rearrangement of these ketones, but also to increase the rate of Haller-Bauer cleavage. While the same skeletal rearrangement was observed with each of these systems as with the corresponding saturated or unsaturated ketone, cleavage represented up to 50 % of the product, rendering synthetic applications inefficient.

However, as mentioned in Chapter One, *t*-BuOK/*t*-BuOH has been used almost exclusively as the base in β-enolization studies. The purpose of this project was to explore the effect of a change of base on β-enolization to compare the results to those obtained with *t*-BuO$^-$ as base. The results of these investigations are discussed in this Chapter.

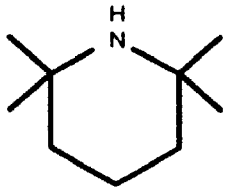
Cleavage of the Haller-Bauer type is a common mode of reaction for hindered ketones in base. In previous Chapters, and previous studies, this cleavage has been postulated to result from attack of the base (*t*-BuO$^-$) at the carbonyl carbon, followed by carbon-carbon bond cleavage. Presumably, a bulkier base may retard Haller-Bauer cleavage. This hypothesis was examined in trials using the highly hindered potassium 3-ethyl-3-pentoxide (**94a**) as base.



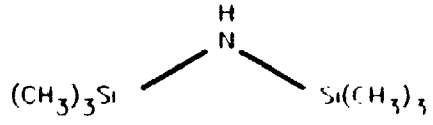
94 R=H
94a R=K

In addition, amide bases have long been recognized as extremely useful synthetic reagents as a result of their strongly basic and proton-specific behaviour. Generally, α-enolization of a ketone occurs readily with amides such as lithium diisopropylamide (LDA) under very mild conditions. It could prove interesting to examine the effect of certain amide bases on the β-enolization of ketones blocked from α-enolization. Hopefully, milder conditions may be employed to effect synthetically useful β-enolate rearrangements without undesirable side reactions. Since amides bearing β-hydrides are known to

reduce carbonyl groups (48), the amines chosen for study must be blocked from β-hydride donation. Secondly, a bulky amine must be employed to suppress nucleophilic addition to the carbonyl. Amines with increased steric hindrance are also known (49) to show increased pK values, and therefore, may be more suitable for β-enolization under milder conditions. Two amines which fit these criteria are 2,2,6,6-tetramethylpiperidine (TMP) and hexamethyl-disilazine (HMDS); these are commercially available since their lithium amides are commonly used in organic synthesis.



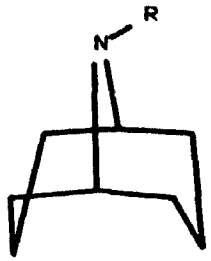
TMP



HMDS

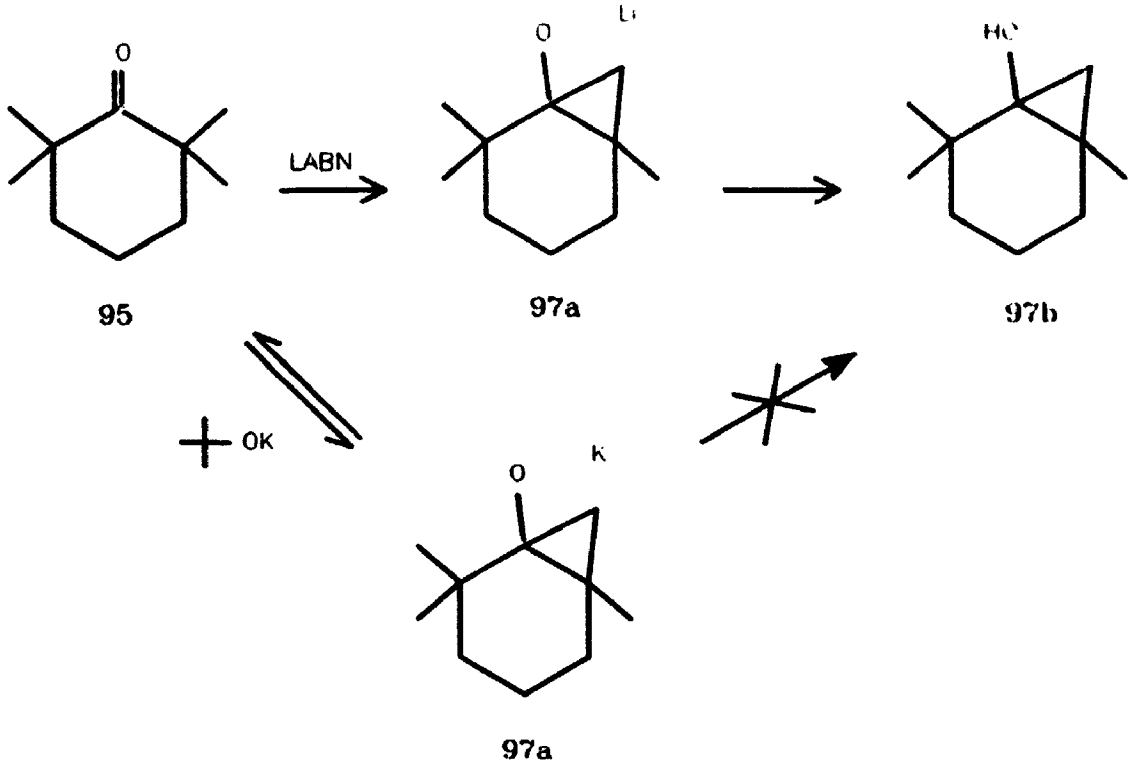
These amines were examined for their potential in β-enolization studies to contrast their behaviour with that of *t*-BuOK. Since previous studies (50) have shown that lithium tetramethylpiperidide (LTMP) is unstable in etheral solvents at temperatures above 0°C, hydrocarbon solvents were employed. These solvents are poor hydride transfer agents, and may also suppress reduction relative to ethers.

Several years ago, Shiner *et al*. reported that the methyl protons of 2,2,6,6-tetramethyl-cyclohexanone (**95**) could be abstracted with N-lithio-9-azabicyclo[3.3.1]nonane (LABN, **96a**), shown in Scheme 4-1 (51). In homoenolization experiments using *t*-BuOK/*t*-BuOD (15), **95** was found to incorporate ^{2}H at the methyl positions, presumably via β-enolate **97a**, although evidence for a ring expanded ketone was not observed; only starting material deuterated at the methyl sites was present. However, with LABN a 97-100 % yield of cyclopropanol **97b** was reported (52). Isolation of the cyclopropanol was in contrast to all previous studies, in which evidence for the intermediate cyclopropoxide was never seen. In fact, cyclopropoxides prepared independently from the corresponding cyclopropyl silyl ether have been found to ring open readily under mildly basic conditions (NaOH/MeOH/20°C), the methodology of which has been used for preparative ring enlargement in this study.



96 R=H
96a R=Li
96b R=K

If **97a** was involved in both the LABN and *t*-BuOK reactions, the sole difference was the cation. It is possible that lithium formed a more stable complex with the β-enolate than potassium and thus survives the reaction, and the cyclopropanol was isolated after acidic workup.

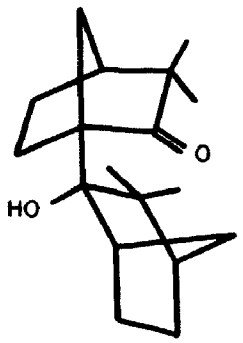


Scheme 4-1 : ß-enolization of **95**

The use of LABN in the β-enolization of hindered ketones seemed to have promise. It would be useful to examine its effect on several hindered ketones to explore its potential. As mentioned above, the cation appeared to play a role in the β-enolization process using amide bases, thus it would be interesting to examine the effect of a change of cation. In all previous homoenolization trials with *t*-BuOK, the (potassium) cyclopropoxide was indicated as the intermediate, and in all of these cases, the β-enolate underwent homoketonization to yield a ketone as the end-product. Based upon the isolation of cyclopropanol **97b** in the reaction

between **95** and LABN, it would appear that a lithium cyclopropoxide is less likely to homoketonize and rearrange into a potentially different ketone. Since the β-enolate rearrangement products were of interest to this study, trials with N-potassium-9-azabicyclo [3.3.1]nonane (KABN, **96b**) were also undertaken.

Bicyclic ketones bearing bridghead α-protons are unacceptable substrates for amide base studies since previous studies have revealed that the bridgehead proton can be abstracted, in defiance of Bredt's rule. For example, camphenilone (**1**), the classic substrate of β-enolization (Scheme 1-1), was found to be deprotonated exclusively at the bridgehead in trials with LABN (52). The product isolated in these reactions was the aldol **98**. Consequently, the ketones examined in the previous two Chapters were not considered worthwhile for study with amide bases, and ketones from previous studies were therefore employed.



98

4.2 RESULTS AND DISCUSSION

4.2.1 Potassium 3-ethyl-3-pentoxide (**94a**)

Although commercially available, the parent alcohol **94** was prepared by Grignard reaction of ethylmagnesium bromide with 3-pentanone; the alcohol was obtained in 95 % yield after distillation from CaH_2. The base was prepared in the standard fashion, by addition of a weighed quantity of potassium to the anhydrous alcohol. Homoenolization experiments using this base were carried out in the same manner as in trials which employed *t*-BuOK/*t*-BuOH, except that the neutral fractions were chromatographed prior to analysis in order to remove the 3-ethyl-3-pentanol, which could not be readily removed by rotary evaporation owing to its low volatility (bp 141°C).

The first system examined with this base was 3,3-dimethylbenzobicyclo[3.2.1]octen-2-one (**65**). The results from these runs are summarized in Table 4-1. By glc and ^{13}Cmr, the presence of ketone **75** was confirmed, revealing that the rearrangement of **65** to **75** (Chapter 3.2.1) occurred in this base. Haller-Bauer cleavage was also noted; acid **76** was the only acid isolated, in keeping with the trials with *t*-BuOK. However, the quantity of acid **76** from the latter trials was significantly less, comprising 47% of the total product after 96 h, while ketone **75** represented 36%, as compared with 67% and 11%, respectively, in the present study.

Table 4-1 : Composition of the product mixture from reaction of **65** and 3-ethyl-3-pentoxide[1].

Time (h)	**65**	**75**	**76**
24	13	11	54
48	9	10	61
96	3	11	67

[1] Listed as percentage of the isolated product; the **65:75** ratio was determined by glc.

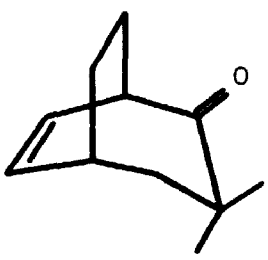
Table 4-2 : Composition of the product mixture from reaction of **49** and 3-ethyl-3-pentoxide[1].

time(h)	**49**	**38,39**	**40b**	**41b**[2]	Acid
24	12	~0	8	61	13
48	<2	~0	12	64	15
96	~0	~0	10	51	27

[1] Listed as percentage of the isolated product; the ratios of neutral products were determined by a ratio of ^{13}Cmr intensities.

[2] The *cis*:*trans* ratio was constant and slightly favoured *trans*-**41b**.

The unsaturated [3.2.2] ketone **49** was then examined, and also found to undergo the same rearrangement as found in trials using *t*-BuOK as base (Chapter 2.2.3). These results are presented as Table 4-2. Rearrangement seemed to proceed more rapidly with potassium 3-ethyl-3-pentoxide than *t*-BuOK, since the starting ketone was completely consumed within 48 h as compared with >144 h in the previous study. Also, the acid fraction constituted more of the product mixture. However, this fraction contained many compounds, including acid **46**, according to the ^{13}Cmr spectrum. Presumably, these acids are olefinic analogues of **46** (**48a** and **48b**), which were proposed (Chapter 2.2.2) as the initial products of cleavage, and are susbsequently oxidized to the aromatic system. However, only **46** was found in experiments with *t*-BuO$^-$.



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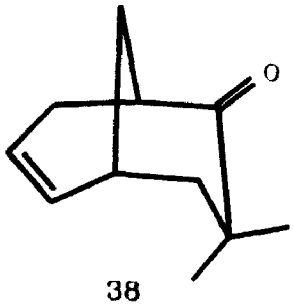

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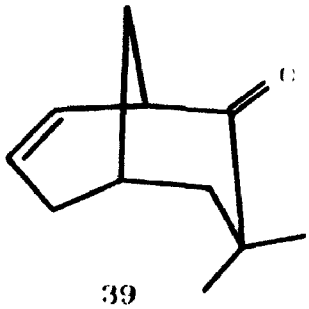

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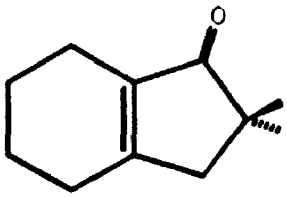
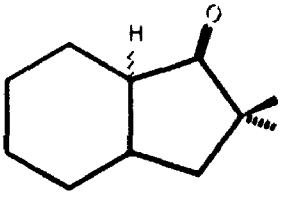
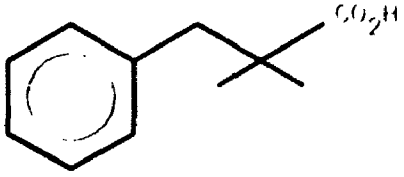


40b

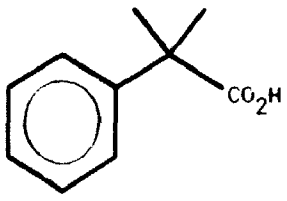


41b



46

Subsequent to these studies, **94a** was examined as a base in the homoenolization of 2,4-dimethyl-2,4-diphenylpentan-3-one (**99**). It has been established (4) that the major mode of reaction for **99** in *t*-BuOK is β-enolization of the methyl protons followed by rearrangement of the resultant β-enolate **99a** to generate **100** as depicted in Scheme 4-2. Ketone **100** may in turn undergo a second β-enolate rearrangement to provide **101**. A second mode of reaction for **100** begins with abstraction of a phenyl proton, followed by attack at the carbonyl carbon to generate **100a**, and subsequent opening of the four-membered ring to form ketone **102**. This pathway, albeit very minor, amounts to an alkyl to aryl migration of an acyl group. Haller-Bauer cleavage, enhanced by benzylic stabilization of the intermediate carbanion, accounted for the the presence of acids **103**, **104** and **105** which arose by cleavage of **99**, **100** and **102**, respectively.



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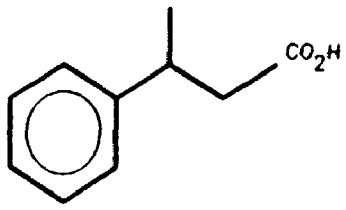

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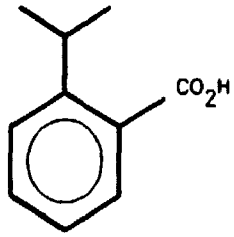

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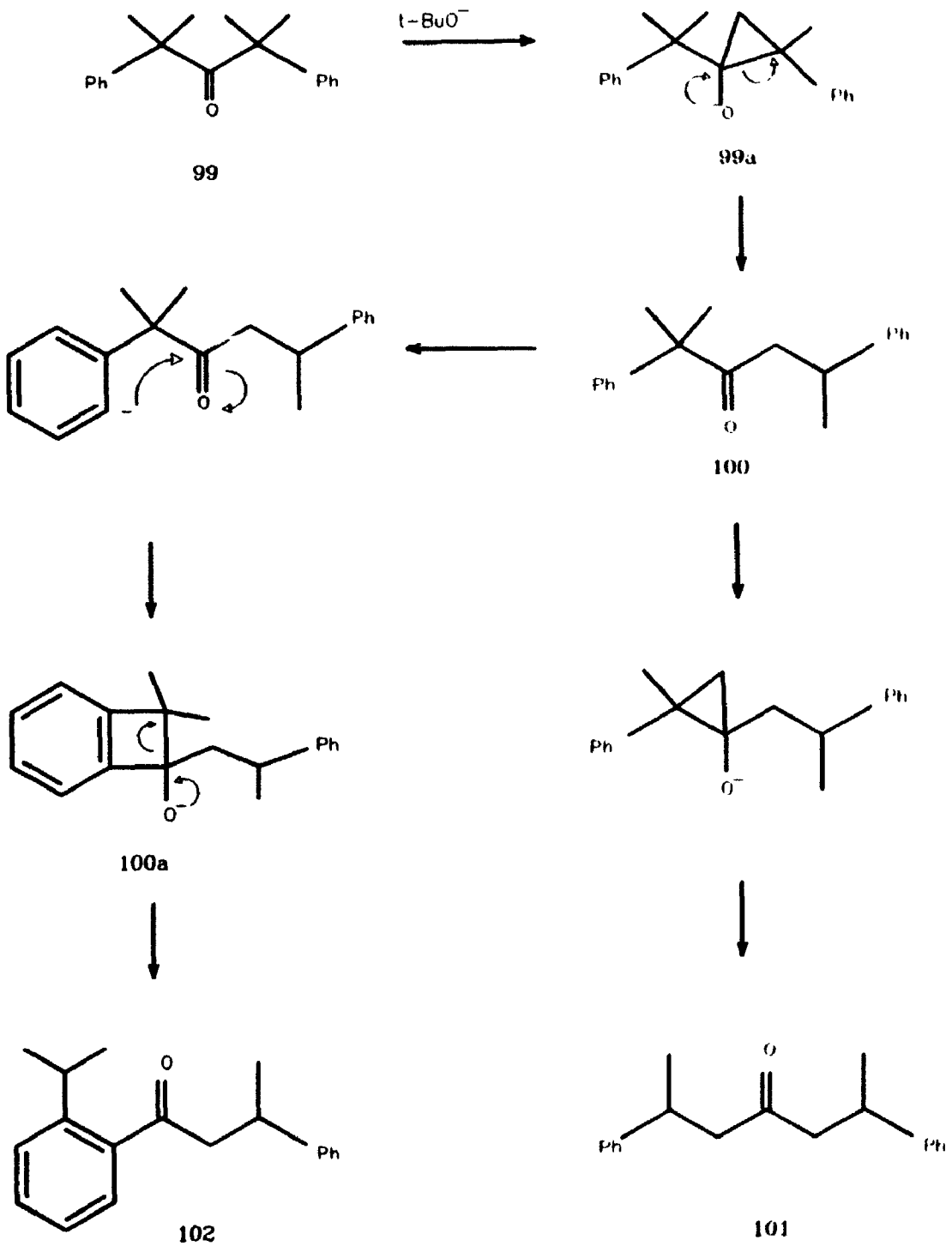


Scheme 4-2 : Rearrangement of 99 via ß-enolization

When ketone **99** was treated with 3-ethyl-3-pentoxide as base, the acidic component comprised the majority of the isolated product. These acids were esterified with diazomethane to estimate their compositions by glc and to compare with previous ^{13}Cmr data. The results for the runs with **99** in 3-ethyl-3-pentoxide are summarized in Table 4-3, accompanied with some results for *t*-BuOK to aid comparison. The neutral products from the shorter reaction times were shown by their ^{13}Cmr spectra to contain **99** - **102**. The yields of neutral products were very low, in fact, after 120 h, the components could not be identified. The acid fraction, however, contained acids **104** and **105**, confirming that rearrangement had indeed occurred with **94a** as base.

From the results with these systems, it was apparent that potassium 3-ethyl-3-pentoxide would not reduce the quantity of Haller-Bauer cleavage, since the quantity of acid is increased in each case relative to trials with *t*-BuOK. The rate of rearrangement also seemed to increase relative to the initial studies with *t*-BuOK/*t*-BuOH.

Table 4-3 : Composition of the total product from homoenolization of **99** with *t*-BuOK and 3-ethyl-3-pentoxide.[1]

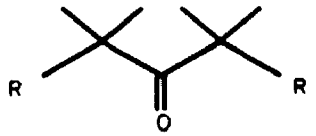
	Time (h)	Neutral[2]	**99**	**100**	**101**	**102**	Acid[2]	**103**	**104**	**105**
t-BuOK[3]	68	63	70	23	6	1	30	58	33	8
	136	42	60	22	16	2	50	39	49	12
	270	25	25	5	60	10	65	40	50	10
with	60	10	54	32	13	-	80	78	8	13
3-ethyl-	120	3	15	<2	83	-	92	77	7	16
3-pentoxide	180	<2	-	-	-	-	95	66	13	21

[1] Ratios of the products were determined using glc.

[2] As percentage of the isolated product.

[3] From ref. (4)

Acyclic ketones **106a** and **106b** were also treated with base **94a**. In *t*-BuOK, these ketones had been found to chain extend through the α-methyl groups, in a manner similar to the rearrangement noted above for **99**, although the processes for **106** were much slower, presumably because the carbanion formed upon homoketonization is not benzylic, unlike that from **99a**.



106a R=CH_3
106b R=$(CH_2)_3CH_3$

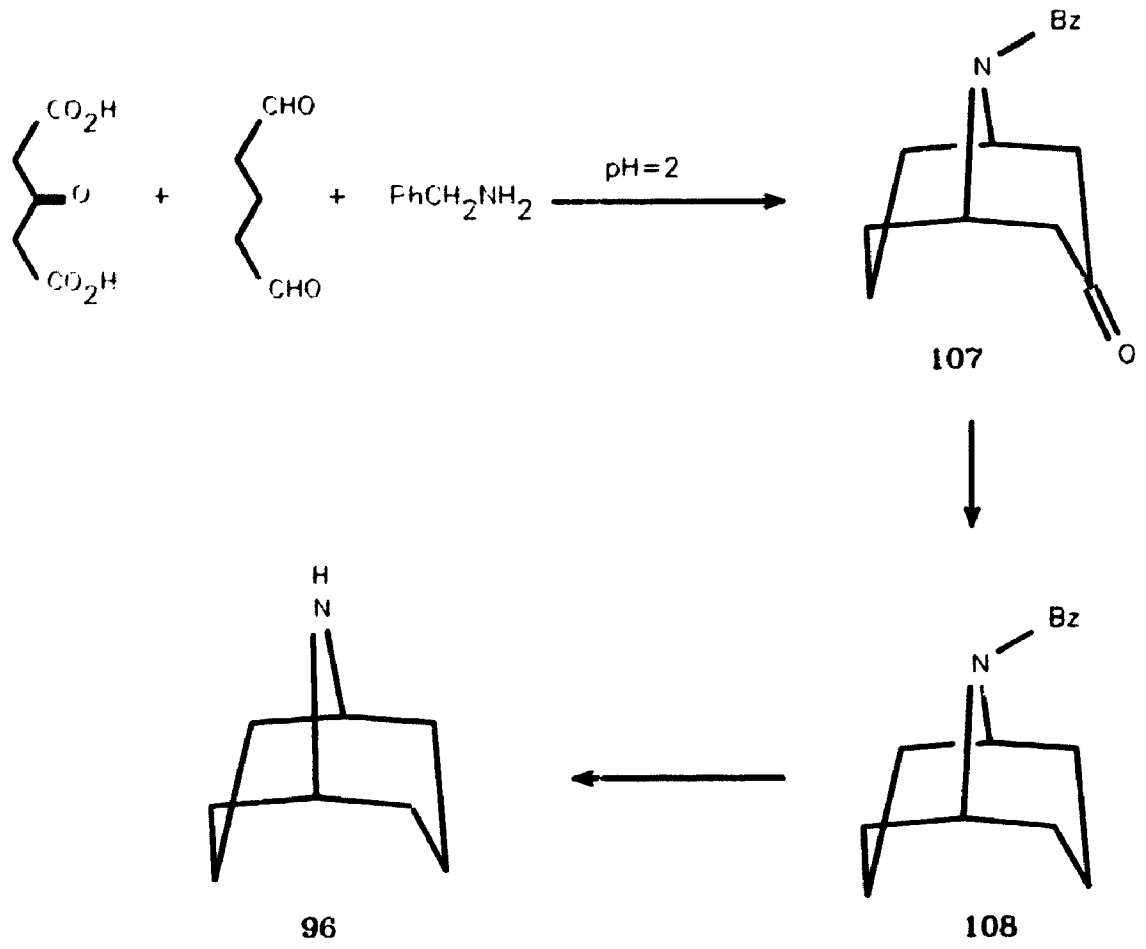
However, the neutral fractions from experiments with **106a** and **106b** in 3-ethyl-3-pentoxide were found to contain only starting material by ^{13}Cmr, and there was no acidic component.

On the basis of the results for these five systems, it can be concluded that while rearrangement via β-enolization still proceeded for some, **94a** did not reduce Haller-Bauer cleavage relative to the runs with *t*-BuOK. It is conceivable that water present in the base solutions used for homoenolization might attack the carbonyl, and result in Haller-Bauer cleavage. Therefore, the presence of water may be blamed for the increased quantity of acid noted in the runs with **49**, **65**, and **99**. However, the water content of the base solutions of **94a** was not higher than that for *t*-butoxide bases by Karl-Fischer titration. Clearly, 3-ethyl-3-pentoxide is not effective as an alternative base for β-enolization.

4.2.2 Amide bases

The synthesis of 9-azabicyclo[3.3.1]nonane (9-ABN, **96**) was effected by the method of Duhayre and Rassat (52), shown in Scheme 4-3. The first step employed a Robinson-Schöpf reaction, in which an aqueous solution of 1,3-acetone dicarboxylic acid, glutaric dialdehyde and benzylamine were stirred overnight, and keto-amine **107** was isolated as a solid. After Wolff-Kishner reduction of the ketone, the benzyl group was removed by hydrogenation at atmospheric pressure to generate 9-ABN. The free amine was a volatile, hygroscopic, low melting solid which decomposed readily, and proved to be quite difficult to use. Its hydrochloride salt, on the other hand, was considerably easier to handle, and a procedure was developed whereby the hydrochloride was stirred with two equivalents of *n*-buLi to generate LABN.

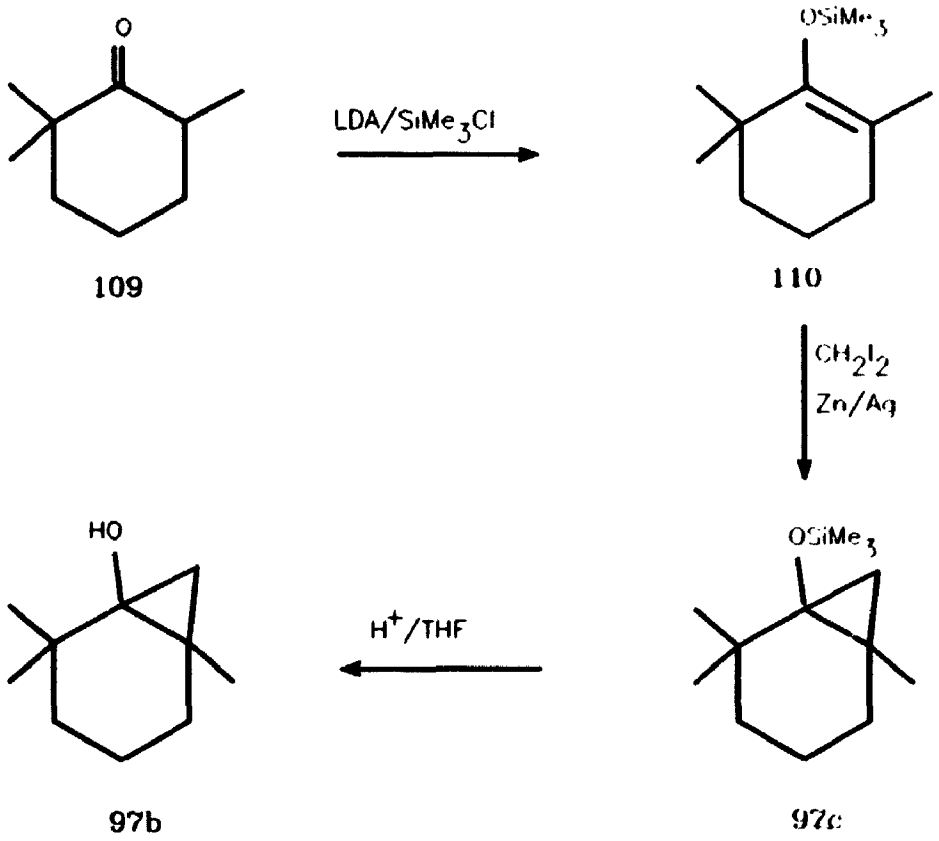
Unless otherwise noted, all homoenolization trials with amide bases were carried out in refluxing heptane (98°C) in the presence of three equivalents of amide. The reactions were worked up with 1N HCl before extraction with ether to provide a neutral fraction. The washings were then made basic by addition of KOH pellets, and extracted with ether to yield a basic fraction; generally this fraction contained only the amine. Generation of an acid by Haller-Bauer cleavage seemed unlikely, and no such acid was isolated in these experiments.



Scheme 4-3 : Synthesis of 9-ABN

In the present study, LABN was initially tested aga nst 2,2,6,6-tetramethylcyclohexanone (**95**) to ensure that the results of the previous study (52) could be duplicated under the reaction conditions chosen herein, because the initial communication did not report experimental details. Although the yields were not as high as those previously reported, cyclopropanol **97b** (Scheme 4-1) was the sole product. Since 2,2,6-trimethylcyclohexanone (**109**) was available from a later

synthesis (Chapter 4.2.4), cyclopropanol **97b** was independently synthesized by the method in Scheme 4-4. After cyclopropanation of silyl enol ether **110**, hydrolysis of the silyl group in **97c** yielded a compound with the same ^{13}Cmr spectrum as the product from LABN treatment of **95**. The structure of cyclopropanol **97b** was thus confirmed.



Scheme 4-4 : Independent synthesis of 97b

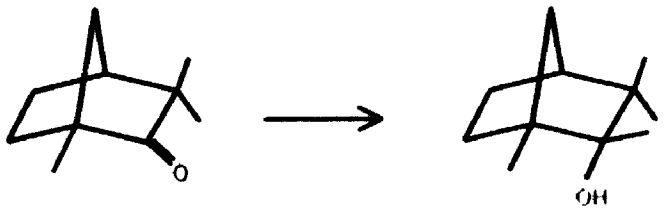
By analogy with the Brown procedure (53) for preparing potassium TMP (KTMP) from LTMP with potassium *t*-butoxide, KABN (**96b**) was prepared and examined as a base for homoenolization. When **95** was treated with KABN, only starting

material was isolated, in sharp contrast to trials with LABN. However, as noted above, reaction of *t*-BuOK with **95** generated potassium **97a** which subsequently reverted to starting material; in retrospect, the results with KABN are not surprising.

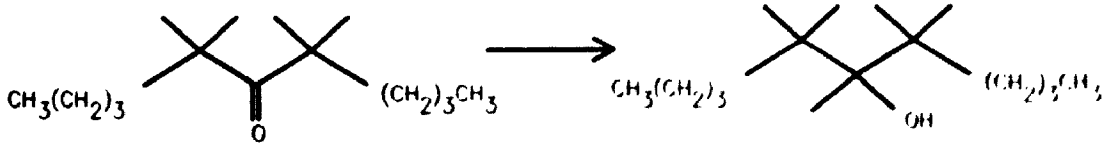
The three systems chosen for initial examination with lithium hexamethyldisilazide (LHMDS), lithium tetramethylpiperidide (LTMP), N-lithio-9-azabicyclo[3.3.1]nonane (LABN) and N-potassium-9-azabicyclo[3.3.1]nonane (KABN) were fenchone (**2**), 2,4-dimethyl-2,4-diphenylpentan-3-one (**99**) and 5,5,7,7-tetramethylundecan-6-one (**106b**). In general, the product recoveries in the experiments with amide bases were quantitative, although reproducibility was poor. While the products were typically the same under identical conditions, product ratios between runs were inconsistent. As a result, the ensuing discussion will focus on the major product(s) of the various reactions rather than a quantitative assessment.

For all three ketones, trials with LHMDS as base gave no reaction and starting material was recovered quantitatively in each case. Lithium hexamethyldisilazide is one of the least basic secondary amides listed in the literature; its pK_a has been calculated to be 25.8 (50). However, LHMDS is several orders of magnitude more basic than *t*-BuOK, so should still be sufficiently basic to abstract a β-proton in these systems. In any event, it is clear from the results with these three ketones that LHMDS is not suitable for β-enolization.

In the experiments with LTMP, addition of a methyl group to the carbonyl carbon was the primary reaction. For both fenchone (**2**) and tetramethylundecanone (**106b**), the presence of **111** and **112** was confirmed by comparsion of the glc and ^{13}Cmr spectrum to those of authentic samples prepared from MeLi and the corresponding ketone. In the case of fenchone, a small amount of reduction was also observed; these products were identified by comparison of their ^{13}Cmr data with the literature values (10) and with those for an authentic sample of *endo*- and *exo*- fenchol prepared by LAH reduction of fenchone.

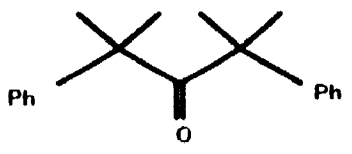


2 111

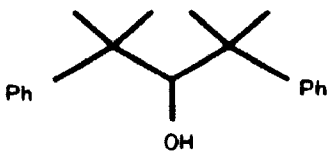


106b 112

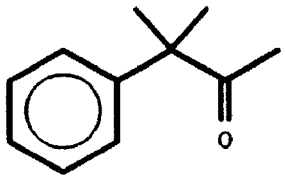
In the runs with 2,4-diphenyl-2,4-dimethylpentan-3-one (**99**) and LTMP, a mixture of several compounds was produced. One of these compounds was readily shown to be the alcohol of reduction, **113**, by comparison to an authentic sample prepared by LAH reduction of **99**. However, the alcohol resulting from addition of a methyl group to the ketone was not observed. Instead, a compound which was identified as **114** was isolated by preparative glc. This compound had two methyl signals in the ^{13}Cmr spectrum at δ_C 25.1 and 27.6, with the former having



99



113

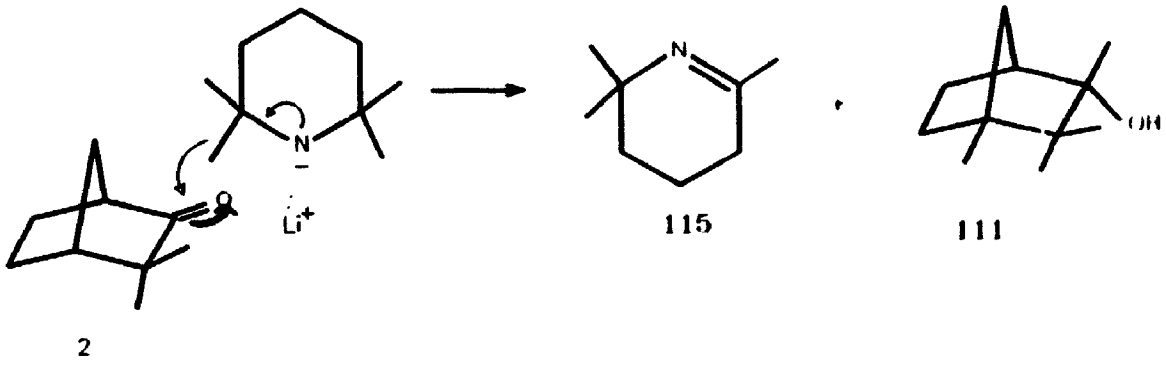


114

twice the intensity of the latter. In addition, a quaternary signal (δ_C 43.4) and a carbonyl peak (δ_C 211.8) were observed, as well as the signals for a phenyl ring. This compound likely arose by addition of a methyl group to **99** followed by bond cleavage to result in the formation of **114** and a cumyl anion. The presence of cumene was therefore inferred, and ^{13}Cmr signals which arise from cumene were identified in the ^{13}Cmr spectrum. Another compound was isolated containing alcohol **113** as an impurity, however, this new compound could not be identified. There was evidence of the presence of a

chain extended ketone of the sort produced by treatment with *t*-BuOK.

In the basic fraction from the reactions with LTMP, imine **115** was identified on the basis of its ^{13}Cmr signals, which were compared to the literature (52), since the transfer of an α-methyl group from LTMP has been previously reported to occur in reactions with **95**. The presence of imine **115** indicated that the mechanism for α-methyl group transfer shown in Scheme 4-5 may be operative; this mechanism is analogous to that for transfer of a β-hydride from LDA proposed by Kowalski (49).



2 115 111

Scheme 4-5 : Mechanism for methyl group transfer from LTMP

Attention was then directed at the effect of LABN on these three ketones. With fenchone as substrate, the glc of the product mixture after 60 h revealed, in addition to the starting material, the presence of a glc peak which accounted for ~10% of the mixture. After collection by preparative glc, this peak was shown to contain a 3:1 mixture of *endo*- and *exo*-fenchol, after comparison of the ^{13}Cmr spectrum to that of an

authentic sample. However, there was no evidence for any other products, in particular the ketone(s) 3 (Scheme 1-2), which arose through a β-enolate rearrangement. To examine the effect of temperature, a solution of LABN was prepared in a dry flask and added to a heptane solution of fenchone in a thick-walled glass tube, which was then sealed under vaccuum. However, at 160°C, reduction was still the sole reaction observed. After 24 h, the product consisted of a 43:40:17 ratio of *endo*-fenchol:fenchone:*exo*-fenchol, with no evidence of a rearranged ketone.

The reduction of benzophenone by LDA was reported by Wittig in 1962 (54), and has since been shown (55) to proceed via a concerted β-hydride transfer from LDA to generate benzhydrol and the imine of LDA. A similar anionic mechanism was proposed by Kowalski in the reduction of a number of α-substituted ketones by LDA (49). This type of process is not possible for LABN, since an analogous β-hydride transfer would require the formation of anti-Bredt imide.

However, previous work has suggested that a single-electron transfer (SET) mechanism operates in the reaction of lithium dialkylamides with a number of compounds (56), including several aliphatic ketones (57), although ketones that react by SET are generally activated by conjugation, such as yneones (58) and aryl ketones (59). If such a radical process was responsible for the reduction observed in the present study with LABN, there is the question of the

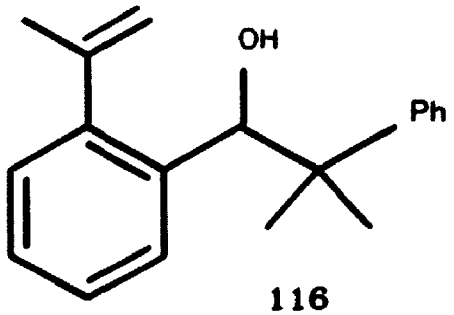
ultimate source of hydrogen atoms. It is possible that the hydrogen was introduced upon aqueous workup. To examine the influence of the workup upon this reduction process, a sealed-tube reaction (72h/160°C) was quenched with D_2O to test for deuterium incorporation. Incorporation of ^2H at the carbinol site in *endo*- or *exo*-fenchol would be clearly shown by characteristic shifts and couplings of neighbouring carbons in the ^{13}Cmr spectrum. However, the ^{13}Cmr spectrum was unaltered. This reduction process is puzzling since a suitable hydride source does not appear to be present. A possible explanation is that somehow the amide, LABN, fragments under the reaction conditions, and is then able to transfer a β-hydride through a mechanism similar to that for LDA (49). However, there was no evidence of a degradation product in the basic fractions.

Similarly, tetramethylundecanone **106b** was not observed to rearrange upon treatment with LABN as base. After 60 h at 100°C, a set of ^{13}Cmr signals, all very weak compared with those of the starting material, appeared in the ^{13}Cmr spectrum. These peaks, <2% of the mixture, could be assigned to the alcohol of reduction by comparison of the ^{13}Cmr spectrum to that of an authentic sample.

The behaviour of these two ketones upon treatment with KABN was also investigated. The results of these reactions were similar to those of the LABN reactions. In fact, reduction was somewhat more efficient with KABN than LABN.

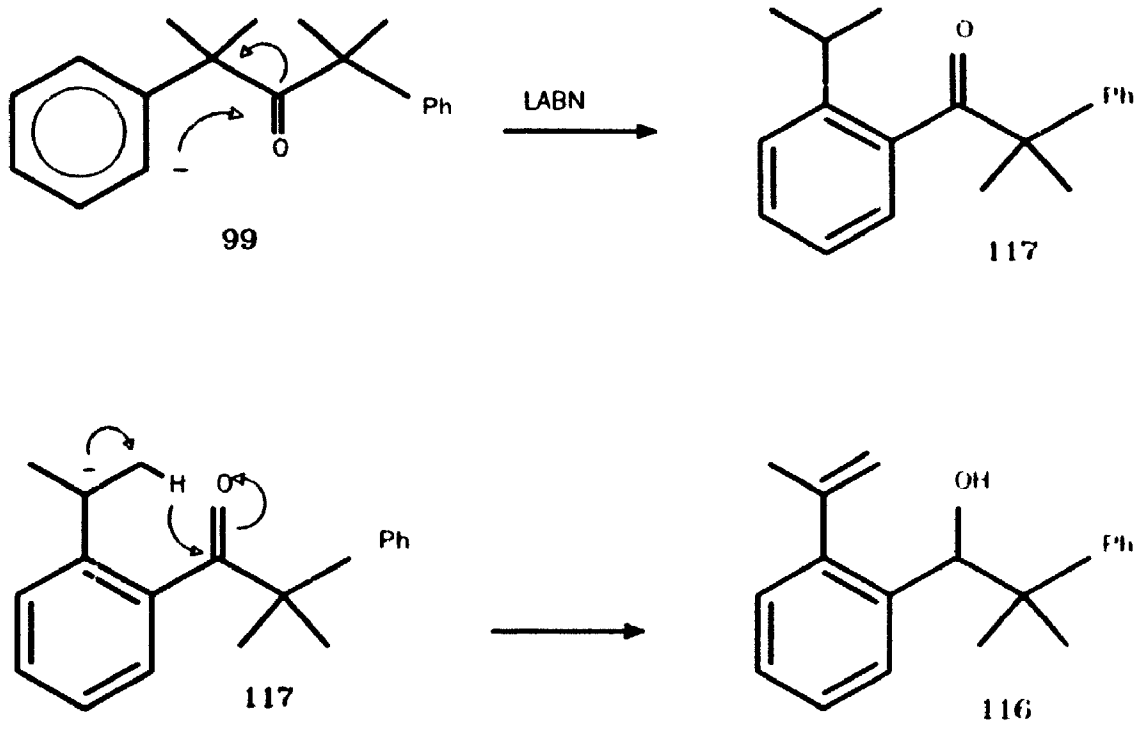
When treated with LABN, the behaviour of 2,4-dimethyl-

2,4-diphenylpentan-3-one (**99**) was observed to be somewhat different from the previous two systems. Within 24 h, the starting material was largely consumed, and replaced with two compounds, one of which was readily shown to be alcohol **113** by comparison to ar. authentic sample as before. The other, separated by preparative glc, had the ^{13}Cmr signals for a secondary alcohol (δ_C 77.2), three methyl groups and a quaternary carbon in addition to twelve resonances from sp^2 carbons. Seven of the latter signals resulted from aryl CH carbons, and two had twice the intensity of the rest, suggesting two pairs of isochronous signals. This would indicate that one of the aromatic rings is disubstituted, while the other is monosubstituted. One of the sp^2 signals (δ_C 116.2) resulted from a CH_2 carbon, indicating a terminal olefin. Since three of the remaining four fully substituted sp^2 carbons were in the benzene rings, the fourth was in the double bond. The ^{1}Hmr spectrum had singlet signals for each of the three methyl groups at δ 0.60, 0.67 and 1.23 which correlated with the ^{13}Cmr signals at δ_C 27.3, 22.5 and 25.3, respectively, in a $^{13}C\{^1H\}$ COSY spectrum. This product was assigned structure **116**, presumably arising by the mechanism shown in Scheme 4-6. Abstraction of a phenyl proton, and subsequent attack of the anion at the carbonyl carbon, could generate **117**



116

in a similar manner to the formation of **102** from **100** with *t*-BuOK (Scheme 4-2). The carbonyl in **117** was subsequently reduced, likely by an intramolecular hydride shift. An identical reduction mechanism has been proposed (60) for a similar system having $NaNH_2$ as base.

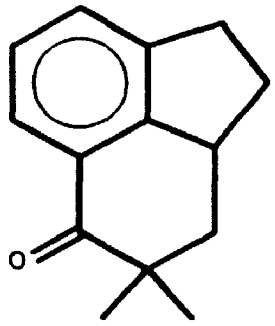


Scheme 4-6 : Mechanism of formation for alcohol **116**

From these results, it seemed clear that the only amide base worthy of further study was LABN. It was disappointing that reactions analogous to that between **95** and LABN were not observed for the other ketones in this study.

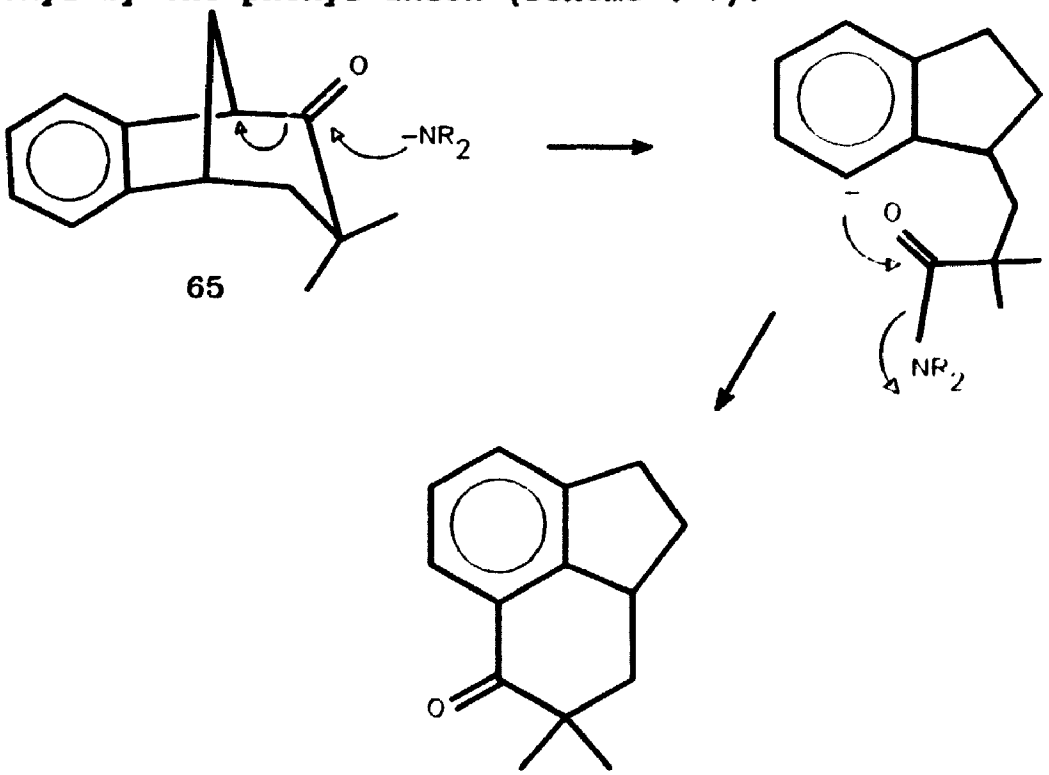
4.2.3 Lithium 9-azabicyclo[3.3.1]nonane

Based upon the results from the preceeding experiments, it was decided to employ LABN as a base with other ketones. Although LABN is known to α-enolize bicyclic ketones bearing α-protons at the bridgehead, as illustrated above in the dimerization of camphenilone, 3,3-dimethylbenzobicyclo-[3.2.1]octen-2-one (**65**) was examined in the hope that β-enolization might occur at a faster rate than α-enolization. After reaction for 24 h, a product mixture that was comprised of starting material and one new ketone was isolated. After separation by preparative glc, this ketone was shown to be isomeric with **65** by precise mass measurement, but was not **75**, the *t*-BuO$^-$ rearrangement product. This new ketone gave ^{13}Cmr signals for three aryl quaternary carbons and three aryl methine carbons. The aryl protons were present as two doublets and a triplet (J=7.5 Hz), clearly indicating the presence of a 1,2,3-trisubstituted aromatic ring. The aliphatic portion of the ^{13}Cmr spectrum contained peaks for two methyl, three methylene, one methine and a quaternary carbon. The methyl protons appeared as singlets (δ 1.23, 1.24) in the ^{1}Hmr spectrum suggesting that the *gem*-dimethyl portion remained intact. After a ^{13}C{^{1}H} correlation experiment, pairs of methylene protons could



118

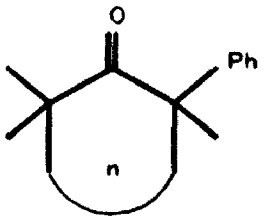
be assigned, however, only geminal couplings for these protons could be deduced. These data suggest, with some degree of uncertainty, that this new compound may have structure **118**. Abstraction of a phenyl proton can be readily envisaged under the conditions, in fact, would be expected since the aryl protons are the most acidic (61). However, it is unlikely that the phenyl anion could stretch across the bicyclic ring system to attack the carbonyl; if the structure of this product is correct, cleavage of the C-1,C-2 bond in **65** must occur prior to attack of the anion. There is the possibility that this putative cleavage is facilitated by attack of the amide at the carbonyl, and subsequent capture of the amide carbonyl by the phenyl anion (Scheme 4-7).



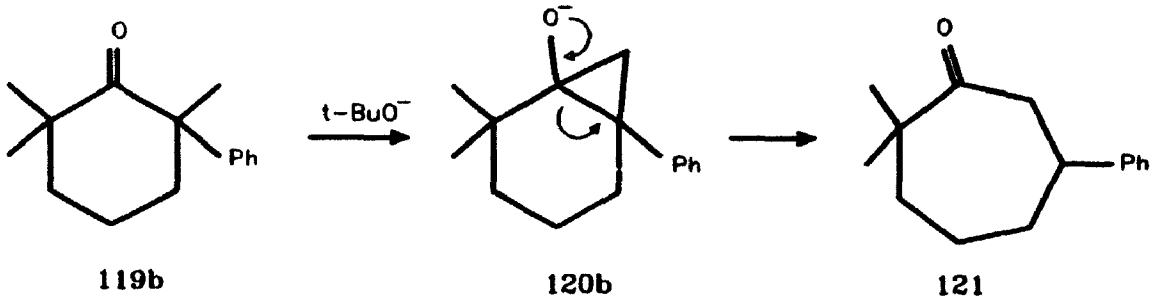
65 118

Scheme 4-7 : Formation of 118

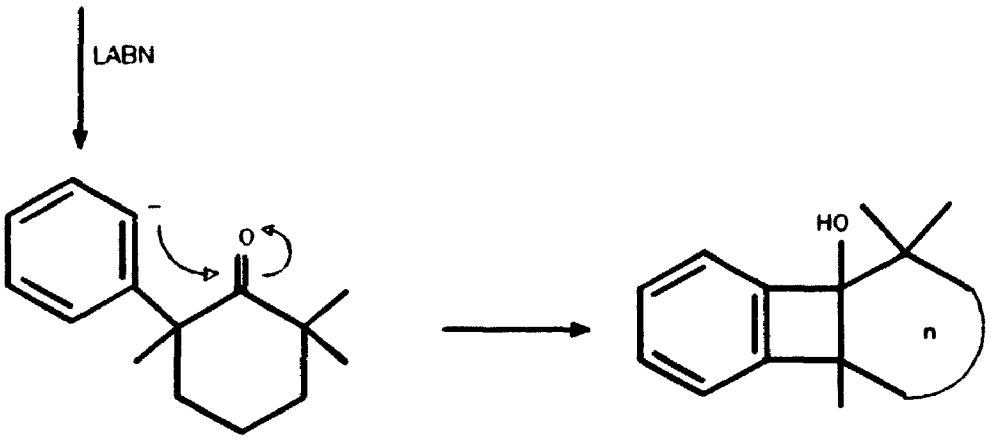
The reactivity of 2,5,5-trimethyl-2-phenylcyclopentanone (**119a**) upon treatment with LABN was then examined. In *t*-BuO$^-$, **119a** had been found (5) to ring enlarge via β-enolization of the 2-methyl group; **119b** underwent the analogous transformation to **121** in the manner depicted in Scheme 4-8. After β-enolization of the α-methyl groups, homoketonization of β-enolate **120b** generated a benzylic anion; this presumably accounted for the rearrangement noted in this system relative to the tetramethyl analogue **95**, which was stable to *t*-BuOK.



119a n=5
119b n=6



119b **120b** **121**

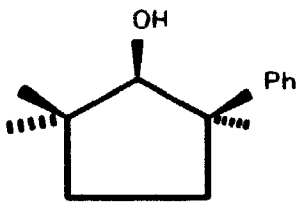


122a n=5
122b n=6

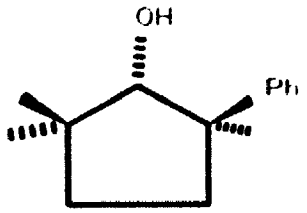
Scheme 4-8 : Rearrangement of 119b with *t*-BuOK and LABN

In a separate study (62), **119b** was treated with LABN and the rearrangement to **121** was observed to a small extent. However, the major pathway involved abstraction of a phenyl proton and subsequent attack at the carbonyl carbon to generate a cyclobutenoxide; benzocyclobutenol **122b** was the major product of this reaction.

In the present study, **119a** was found to generate one major product in addition to two minor ones upon reaction with LABN; all were shown to be alcohols. The new compounds were separated by preparative glc and the major product was shown to be isomeric with starting material on the basis of precise mass measurement. From the ^{13}Cmr spectrum, the presence of a tertiary alcohol (δ_C 92.5), three methyl, two methylene, two quaternary and the signals for a disubstituted benzene ring revealed that the major product was indeed **122a**. The minor products were identified as alcohols **123** by comparison of the spectral data to a sample prepared by LAH reduction of **119a**.



123a



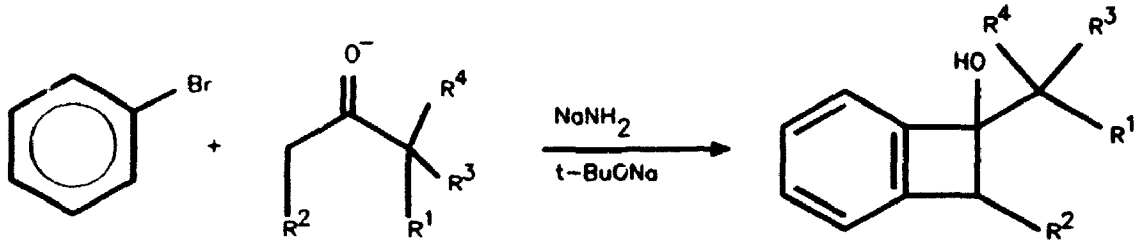
123b

The authentic sample was a 95:5 mixture of the two diastereomers while the proportion of the two minor products in the mixture resulting from reaction of **119a** with LABN was

56:44. Presumably, the diastereomer in excess in each case is the *cis*- isomer **123a**, since the phenyl face of the ring has more hindrance to attack of LAH; this assignment was confirmed by a nuclear Overhauser enhancement (noe) experiment.

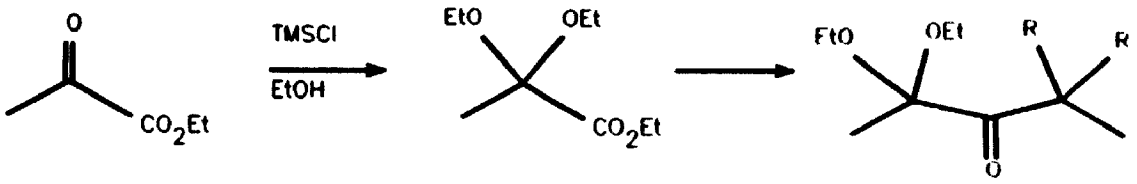
4.2.4 α-Blocking groups

The preparation of benzocyclobutenols (63) and their use in the synthesis of certain medicinally useful compounds (64) have been pioneered by Caubere. The general procedure for their synthesis, shown in Scheme 4-9, involves combining bromobenzene with a ketone in the presence of 'complex base' ($NaNH_2$-ROH) to generate benzyne and the enolate form of the ketone, which then combine to form the benzocyclobutenoxide and yield the benzocyclobutenol upon workup.



Scheme 4-9 : Procedure for synthesis of benzocyclobutenols

The arynic condensation of a ketone enolate was found to proceed more smoothly when a 1,2-diketone monoketal (R^3=R^4=OR) was employed as starting material (65). This result indicated an involvement of the ketal group in the generation of the cyclobutenoxide. This involvement was attributed to complexation of the cation by the ketal, resulting in stabilization of the developing cyclobutenoxide. By analogy, the β-enolate intermediate in the homoenolization process could benefit from a similar stabilizing influence. To examine the effect of a neighbouring ketal on β-enolization, ketal **125b** was prepared by the method in Scheme 4-10.



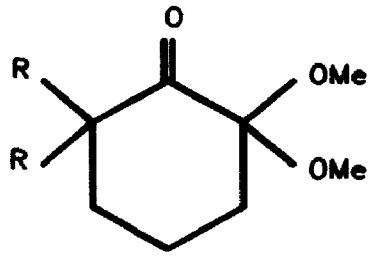
124

125a R=H
125b R=Me

Scheme 4-10 : Preparation of ketal **125b**

The ketone was protected as the diethyl ketal by the method of Chan (66). To add an alkyl group to the carboxyl carbon in **124** without subsequently attacking the incipient ketone, the ketone functionality must be trapped as the enolate which is quenched upon workup to yield the ketone. This was readily accomplished by the addition of triethylamine to a standard Grignard reaction, according to the modification of Kikkawa

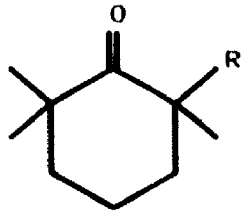
(67). By this method, a 55% yield of **125a** (68) resulted when ethylmagnesium bromide was used as the Grignard reagent. Dimethylation then furnished ketal **125b**, which was used as a substrate in β-enolization studies with *t*-BuOK/*t*-BuOH. The product isolated was predominantly in the acidic fraction, which appeared by ^{13}Cmr spectroscopy to be comprised of three acids. In an effort to separate and identify these compounds, the mixture was then methylated with CH_2N_2. However, the products appeared to decompose upon such treatment, since there were no clearly resolved signals in the ^{13}Cmr spectrum. At this point, studies with **125b** were set aside to study the cyclic ketal **126b**. The preparation of dimethylketal **126a** has been described previously (67). However, methylation in the standard fashion ($CH_3I/NaNH_2/Et_2O$) was unsuccessful, as were attempts to methylate using LDA. Subsequent to this work ,it was realized that **126a** has been found to be efficiently reduced with LDA at -78°C in THF (49). As a consequence, work with this ketone was also set aside.



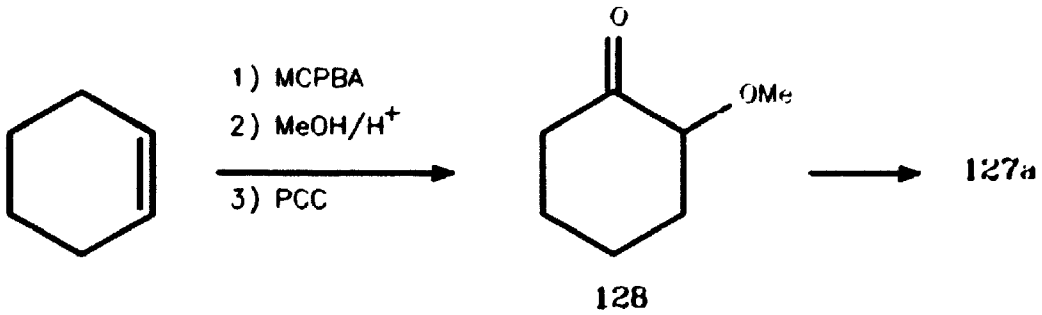
126a R=H

126b R=Me

However, the stabilizing influence that the ketal group was purported to exert in Caubere's studies might be duplicated by interaction with only one oxygen function. As a consequence, the incorporation of an α-methoxy or thiomethyl group may have an effect on β-enolization. To that end, the cyclic ketones **127** were prepared and their behaviour under homoenolization conditions investigated. Ketone **127a** was prepared by trimethylation of **128**, which, although commercially available, was synthesized by the procedure shown in Scheme 4-11. When treated under the standard homoenolization conditions (*t*-BuO$^-$ /*t*-BuOH/185°C), the starting material was entirely consumed within three hours, and replaced by two products in a 2:1 ratio. These compounds were alcohols on the basis of their ^{13}Cmr spectra.



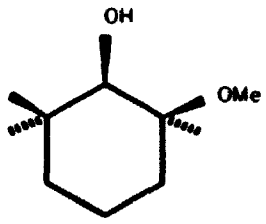
127a R=OMe
127b R=SMe



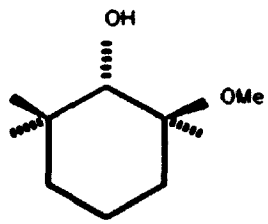
128

Scheme 4-11 : Synthesis of ketone 127a

These alcohols were shown to be **129a** and **129b** by their spectral data, in addition to comparison of the ^{13}Cmr spectra with those of an authentic sample prepared by LAH reduction of **127a**, which yielded the two alcohols in a 60:40 ratio. The major isomer from the homoenolization runs was inferred to be the *cis*-alcohol **129a** on the basis of the following results. Reduction of **127a** with $LiEt_3BH$ yielded only this isomer, while this isomer was the minor product from LAH reduction of **127a**. It has been established (69) that LAH preferentially attacks from the oxygen face in similar systems, since it may complex with the oxygen, while borohydride reagents generally attack from the less sterically encumbered face. In this instance, then, LAH would likely attack from the methoxy side of the ring, while $LiEt_3BH$ would add to the opposite face. The effect of temperature on the *t*-BuOK catalyzed reaction of **127b** was then examined, and it was shown that reduction occurred readily at 160°C; this reduction still proceeded slowly at 125°C.



129a

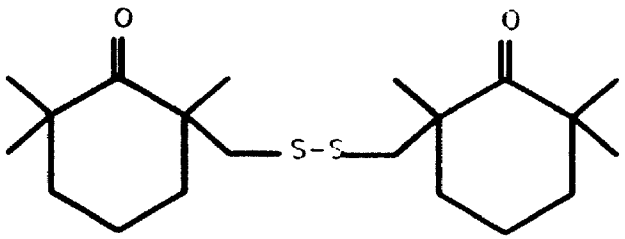


129b

Subsequent to these studies, ketone **127b** was examined with *t*-BuOK. This compound was prepared by trimethylation of

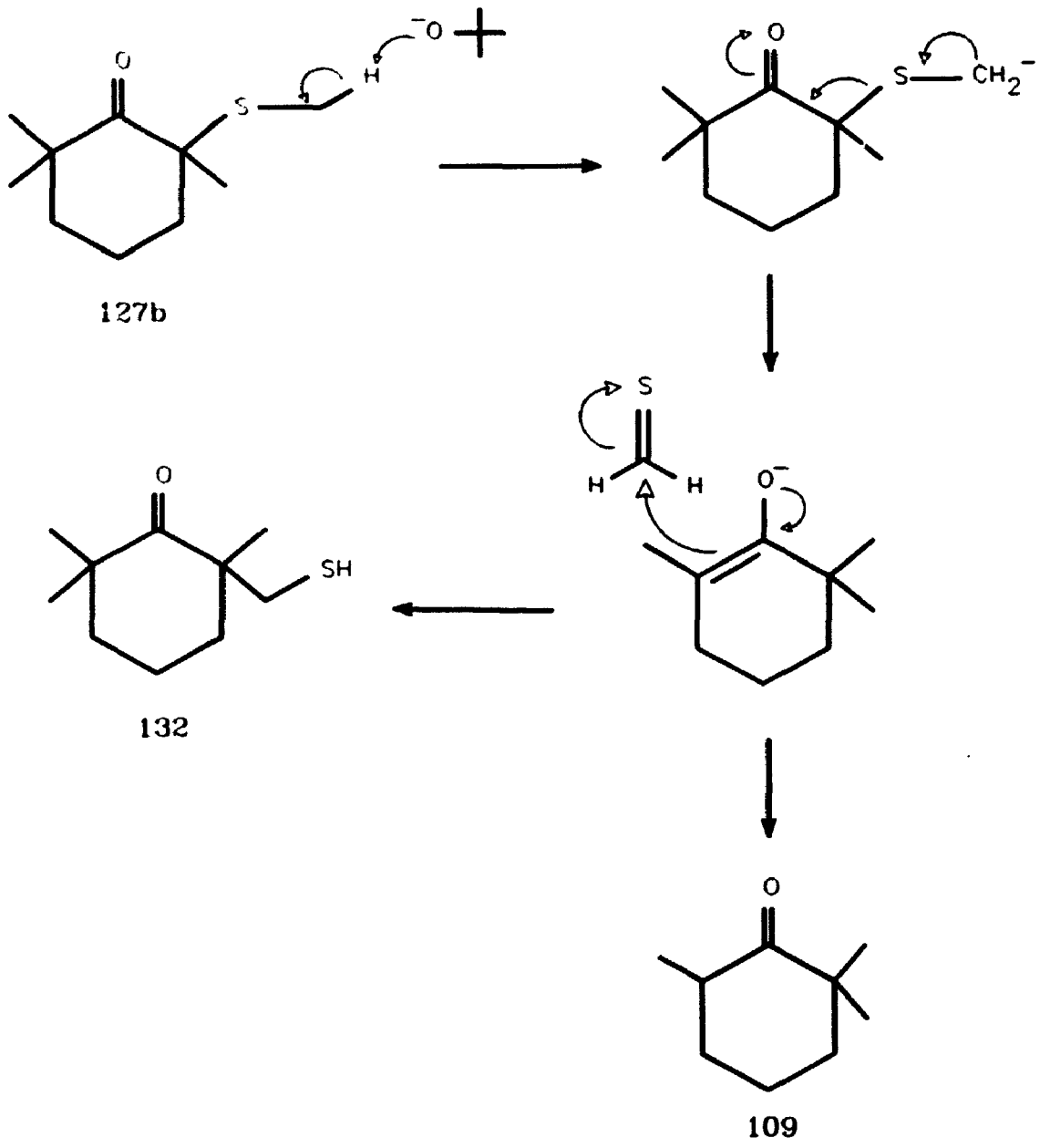
2-methylthiocyclohexanone (67) in the standard fashion ($CH_3I/NaNH_2/Et_2O$). The neutral mixture contained two products in nearly equal proportions at all reaction time points.

One of these compounds was also found in the acidic fraction, and attempts to isolate it by extraction produced a new compound. Its molecular formula was shown to be $C_{20}H_{34}O_2S_2$ by precise mass measurement, suggesting a dimerized compound of some sort. The ^{13}Cmr spectrum was peculiar in that there were eight pairs of nearly isochronous signals; this gave the appearance of a pair of diasteromers. The ^{1}Hmr and ^{13}Cmr spectra indicated that this compound was disulphide **131**.



131

The two components of the neutral fraction were then easily separated by column chromatography over silica. The ^{13}Cmr spectrum of the first compound eluted was identical to that of 2,2,6-trimethylcyclohexanone (**109**), which was prepared independently by dimethylation (2 x LDA/CH_3I) of 2-methyl-cyclohexanone. The second product was shown to be isomeric with starting material by precise mass determination, and exhibited ^{13}Cmr signals for three methyl, four methylene and



Scheme 4-12 : Mechanism of reaction for 127b

two quaternary carbons, in addition to a ketone (δ_C 219.4, 1696 cm^{-1}). This compound was assigned structure **132** (Scheme 4-12) on the basis of these data.

The formation of **109** can be ascribed to abstraction of a proton from the thiomethyl carbon, and subsequent expulsion of **109** as its enolate, depicted in Scheme 4-12. By this mechanism, thioformaldehyde is released, which could be recaptured by the enolate of **109**, to yield **132**. Since the pK_a of a thiol is ~10, **132** may be extracted with dilute base, accounting for the presence of this ketone in the 'acidic' fraction. In air, thiols are known to form disulphides upon basic treatment; this can account for the formation of **131** under similar conditions.

4.3 SUMMARY

A highly hindered alkoxide base, potassium 3-ethyl-3-pentoxide (**94a**), was prepared and used as a base in the homoenolization reactions with several ketones. Although most of these systems underwent the same rearrangement as that found with *t*-BuOK, the quantity of acid arising from Haller-Bauer cleavage increased, in contrast to expectations.

Secondly, three amide bases were examined for their potential in β-enolization. The commercially available amines were hexamethyldisilizane and 2,2,6,6-tetramethylpiperidine, while 9-azabicyclo[3.3.1]nonane was prepared by a three-step route. The former two amides were shown to be wholly unacceptable, since lithium hexamethyldisilazide (LHMDS) caused no reaction in the ketones studied, while lithium tetramethylpiperidide (LTMP) was found to transfer an α-methyl group to the carbonyl. Although N-lithio-9-azabicyclo[3.3.1]-nonane (LABN) had previously been shown to abstract β-protons in tetramethylcyclohexanone (**95**), β-enolization was not observed for any of the ketones studied herein. For both fenchone and tetramethylundecanone, reduction of the carbonyl was the sole reaction that occurred. In the reactions between LABN and ketones containing phenyl rings, abstraction of a phenyl proton was the primary reaction pathway. In these cases, the isolated products could be readily explained by attack of this anion at the carbonyl carbon.

In the course of the preceeding investigations, there was some basis to believe that replacement of the typical α-methyl blocking groups with oxygen functions might enhance β-enolization. To this end, experiments were undertaken to examine the effect of a ketal, methoxy or thiomethoxy group α- to the carbonyl. These trials met with no success; reduction of the ketone and elimination of the α-group were the primary reactions.

CHAPTER FIVE

EXPERIMENTAL

5.1 GENERAL

Boiling points and melting points are uncorrected. Analytical gas-liquid chromatography (glc) was carried out with Varian 940 or 3300 instruments using 1/8" columns of OV-101 (10', 1.5% and 6', 5%, respectively) on Chromosorb W. Preparative glc was performed on a Varian 920 instrument, on 1/4" columns as indicated in the relevant section. Diethyl ether, tetrahydrofuran (THF) and heptane were distilled from sodium/benzophenone before use. Diisopropylamine and t-BuOH were distilled from CaH_2 and stored over 4Å molecular sieves. The concentration of n-butyllithium (n-BuLi) was determined by the double titration method of Gilman (70).

Infrared spectra were recorded using either a Bruker/IBM ftir or a Perkin-Elmer system 2000 ftir. Mass spectral data were obtained with a Finigan MAT 8230 spectrometer using an ionizing voltage of 70 eV for routine spectra and 20 eV for high resolution spectra. Nmr spectra were recorded on Varian XL-200, XL-300, Gemini-200 and Gemini-300 instruments. An APT or a DEPT sequence was employed to determine the multiplicity of the ^{13}Cmr signals. Specific assignments were aided by $^{1}H\{^{1}H\}$ correlation spectra using the HOMCOR sequence of the

Varian software and $^{13}C\{^{1}H\}$ correlation spectra employing the HETCOR sequence of the Varian software for one-bond interactions and the FLOCK sequence (23) for longer range interactions.

5.2 EXPERIMENTAL FOR *CHAPTER 2*

5.2.1 3,3-Dimethylbicyclo[3.3.1]nonan-2-one

2-N-Morpholinocyclohexene (26)

Morpholine (Fisher, 92 mL, 1.04 mol) and cyclohexanone (Fisher, 108 mL, 1.04 mol) were added to a 1L three-necked round-bottomed flask equipped with a Dean and Stark trap and charged with benzene (250 mL) and *p*-toluenesulphonic acid (1 g). The solution refluxed for 3.5 h, and was then distilled to yield **26** (105.3 g, 60%), bp 120-124/8 Torr (lit.(71) 117-120°C/10 Torr).
^{13}Cmr ($CDCl_3$) δ_C: 22.5, 23.0, 24.2, 26.6, 48.2 (2), 66.7 (2), 100.0, 145.1.

2-N-morpholinobicyclo[3.3.1]nonan-9-one (27)

A 500 mL three-necked round-bottomed flask, equipped with condenser amd thermometer, was charged with **26** (21.6 g, 0.13 mol) in benzene (100 mL), and the solution cooled to 0°C. Acrolein (Aldrich, 8.63 mL, 0.13 mol) was then added dropwise

via syringe and the solution stirred at 0°C for 1 h before refluxing for 3 h. The solvent was removed and the residue distilled to yield **27** (24.2 g, 84%), bp 140°C/0.2 Torr (lit.(72) 150-160°C/2.8 Torr).

^{13}Cmr ($CDCl_3$) δ_C: 20.8, 25.1, 27.5, 29.9, 33.7, 45.4, 48.1, 50.8, 67.0, 211.7.

2-N-Morpholinobicyclo[3.3.1]nonane (**28**)

In a 500 mL one-necked round-bottomed flask equipped with a Dean and Stark trap, **27** (47.5 g) was combined with hydrazine hydrate (85%, BDH, 29.2 mL), KOH (41 g) and diethylene glycol (250 mL). The mixture stirred at 120°C until water collection had ceased, and the heat was increased to 200°C at which temperature the mixture stirred for 4 h, before cooling to 0°C and addition of 500 mL ice. The solution was extracted with ether (3x500 mL), then the ethereal extracts were dried and concentrated and the residue was distilled to yield **28** (27.6 g, 62%) bp 86-92°C/0.5 Torr (lit.(74) 120-123°C).

^{13}Cmr ($CDCl_3$) δ_C: 17.7, 21.7, 24.5, 25.1, 28.6, 30.2, 32.1, 32.6, 50.3 (2xCH_2), 64.8 (CH), 67.4 (2xCH_2).

Bicyclo[3.3.1]nonan-2-one (**29**)

Oxidation of **28** (20.8 g) was effected by stirring at 90°C for 2 h, with $Hg(OAc)_2$ (31.8 g) in HOAc (5% w/w H_2O, 200 mL), in a three-necked round-bottomed flask equipped with a condenser and thermometer. The mixture, upon cooling to room

temperature, was added to a rapidly stirred solution of brine (500 mL), the precipitate was removed by filtration and washed with ether (3x100 mL). The layers of the filtrate were separated and the aqueous layer was extracted with ether (4x100 mL). The combined organic extracts were washed with 1N HCl (100 mL) and brine (100 mL) before drying (Na_2SO_4) and removal of solvent. The resultant orange oil, contaminated with HOAc, was passed through a column of silica to yield **29** as an oil (6.3 g, 46%) [lit.(20) 61%, mp 131-134°C].
^{13}Cmr ($CDCl_3$) δ_C: 20.0, 26.0, 27.3, 29.7, 31.8 (CH), 32.4, 39.0, 44.9 (CH), 217.9 (C=O).

GENERAL PROCEDURE FOR THE α,α-DIMETHYLATION OF A KETONE

A flame-dried 3-necked round-bottomed flask equipped with a condenser and magnetic stirrer was charged with $NaNH_2$ (3 equivalents) under a flow of nitrogen. After addition of sufficient dry ether produce a thick slurry, the ketone (1 equivalent) was added in ether and the mixture refluxed for *ca.* 3h. After cooling to room temperature, methyl iodide (3 equivalents) was added and the mixture refluxed for *ca.* 16h before cooling and addition of a second injection of methyl iodide (1 equivalent). The mixture was finally refluxed for a further 3h before cooling to 0°C, and destroying the excess $NaNH_2$ with water. The contents of the flask were transferred

to a separatory funnel containing water and ether and the layers were separated. The aqueous layer was extracted with two more portions of ether. The combined ethereal extracts were washed with brine and dried over anhydrous sodium sulphate before removal of solvent.

After preparation of the parent ketones listed herein, methylation was carried out by this procedure. For each methylated ketone, the yields, isolation procedures and spectral data (where applicable) are listed.

3,3-Dimethylbicyclo[3.3.1]nonan-2-one (22)

Ketone 22 (21) was isolated as an oil in 67% yield upon chromatography on silica.

^{13}Cmr : see Table 2-1.

^{1}Hmr ($CDCl_3$) δ :1.06 (s, 3H, *endo*-3-Me), 1.13 (s, 3H, *exo*-3-Me), 1.15 (m, 1H, *exo*-H-7), 1.41 (d, 1H, J=15.1 Hz, *endo*-H-4), 1.41 (m, 1H, *endo*-H-7), 1.49 (m, 1H, *exo*-H-6), 1.52 (m, 1H, *exo*-H-8), 1.53 (m, 1H, *endo*-H-6), 1.61 (bd, 1H, J=13.5 Hz, *anti*-H-9), 1.90 (m, 1H, *endo*-H-8), 2.03 (dd, 1H, J=15.1, 9.3 Hz), 2.18 (m, 1H, H-5), 2.23 (m, 1H, *syn*-H-9), 2.39 (m, 1H, H-1).

6,6-Ethylenedioxy-3,3-dimethylbicyclo[3.3.1]nonan-2-one(30)

Ketone 33 was dimethylated and 30 was isolated in 81% yield after chromatography on alumina. Recrystallization from EtOH yielded white crystals; mp 54.5-56.0 °C.

Infrared (KBr disc): 1700 cm^{-1}.

Exact mass calculated for $C_{13}H_{20}O_3$: 224.1413; found: 214.1411.

^{13}Cmr (C_6D_6) δ_C: 26.9 (CH_2), 27.6 (CH_3), 29.6 (CH_2), 30.0 (CH_2), 31.5 (CH_3), 36.5 (CH_2, CH), 41.9 (CH), 42.3 (C), 64.1, 64.5 (CH_2O), 110.8 (C), 219.0 (C=O).

^{1}Hmr ($CDCl_3$) δ: 0.96 (s, 3H, *endo*-3-Me), 1.15 (s, 3H, *exo*-3-Me), 1.40-1.47 (m, 2H), 1.61-1.84 (m, 2H), 1.89-1.97 (m, 4H), 2.05 (m, 1H, H-5), 2.30 (m, 1H, H-1), 3.41 (m, 4H,-OCH_2CH_2O-).

GENERAL PROCEDURE FOR HOMOENOLIZATION EXPERIMENTS

The base solution was prepared in the following manner: potassium metal was weighed into a one-necked flask under a flow of nitrogen. Anhydrous *t*-BuOH (water content < 50 ppm by Karl-Fischer titration), stored over molecular sieves in a spearate flask, was added to the potassium by means of a cannula with a pressure of nitrogen; addition proceeded until a sufficient weight of *t*-BuOH had been transferred to yield a 1.0 M solution. The base typically stood at room temperature for several days until potassium dissolution was complete. The reaction mixture was prepared by weighing the ketone into a dry flask and adding the base solution to prepare a solution 0.25 M in ketone. Aliquots (0.5 mL) of this solution were injected into dry thick-walled glass tubes such that the reaction mixture comprised one-tenth of the tube's volume.

This tube was degassed by three freeze-pump-thaw cycles and sealed under vacuum. After warming to room temperature, the tube was heated in an oil-bath (185±1°C, unless mentioned otherwise) for the chosen length of time, then cooled, opened and flushed with brine (20 mL). After extraction with pentane (3x25 mL), the organic layers were washed with NaOH (2x10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated to yield the neutral products. The aqueous washings were acidified and extracted with ether (3x20 mL); the ethereal layers were dried and the solvent was removed to furnish the acidic components.

5.2.2 3,3-Dimethylbicyclo[3.3.1]non-6-en-2-one

Bicyclo[3.3.1]nonan-2,6-dione (32)

The procedure of Lightner *et al* (24) was followed in this preparation. In a three-necked round-bottomed flask equipped with a Dean and Stark trap, the following reagents were combined: dimethyl malonate (425 g, 3.2 mol), paraformaldehyde (77 g, 2.4 mol), piperidine (7 mL) and benzene (750 mL). The mixture stirred at room temperature for 1 h, and was then gradually heated to a gentle reflux for 8 h, then refluxed with water collection for a further 8 h. The solvent was removed by rotary evaporation, and the thick orange residue was poured into a solution of NaOMe prepared from sodium (52 g) and MeOH (650 mL). This solution refluxed for 7 h, and

MeOH was added at intervals to facilitate stirring of the thick solution. The solvent was removed by distillation at reduced pressure, and the residue was poured into ice (1 L), then extracted with ether (2x500 mL). The aqueous layer was neutralized by bubbling CO_2 through the mixture for ~4 h, and the yellow crystals of **31** were collected by filtration (228 g). This product was dissolved in acetic acid (650 mL) and heated to reflux while 6N HCl (400 mL) was added overnight. The mixture continued to reflux for a further 12 h, whereupon it was cooled and the acids were removed by rotary evaporation, before eliminating the final traces on a vaccuum pump to yield **32** as a gummy solid (36.5 g, 30% overall) which was sublimed (80°C/0.5 Torr) to yield white crystalline **32**.

6,6-Ethylenedioxybicyclo[3.3.1]nonan-2-one (**33**)

The diketone **32** (12.5 g) was bisketalized with ethylene glycol (19 mL) in benzene (200 mL) with p-toluenesulphonic acid (300 mg) in the standard method. The solvent was removed by rotary evaporation, and replaced with acetone (200 mL). The mixture was then stirred at room temperature and monitored by glc, until the bisketal was seen to comprise <5% of the mixture. The solvent was removed and the residue patitioned between 5% aqueous $NaHCO_3$ (125 mL) and benzene (100 mL). After removal of solvent, the residue was distilled (103-106°C/0.4 Torr) to yield **33** (14.0 g, 87%) as a clear colourless oil (27).

^{13}Cmr ($CDCl_3$) δ_C: 22.5, 27.2, 29.3, 30.3, 35.5, 37.5, 43.8, 65.4_7, 65.5_6, 110.2, 216.0.

6,6-Ethylenedioxybicyclo[3.3.1]nonan-2-ol (34) and tosylate 35

Alcohol 34 was made by LAH reduction of 33 which was then tosylated to generate 35; both of these compounds were oils. Both of these reactions are standard synthetic reactions, and both are described in reference 24. The ^{13}Cmr shieldings for these compounds were not available and are given below.

For 34 : δ_C: 21.8, 24.2, 29.9, 31.0, 32.8, 33.9, 35.8, 64.1, 64.2, 72.7, 111.0.

For 35 : δ_C: 21.6, 22.2, 24.3, 27.2, 30.7, 31.7, 32.4, 35.3, 64.1, 64.3, 84.1, 111.3, 127.5, 129.7, 134.6, 144.3.

6,6-Ethylenedioxybicyclo[3.3.1]non-2-ene (36)

The tosylate 35 (2.3 g) was taken up in dry pyridine (25 mL) and refluxed overnight, whereupon the mixture was cooled and added to 1N HCl (100 mL) in a separatory funnel. Upon extraction with ether (3x100 mL), and drying of the combined organic layers, removal of solvent yielded a liquid containing 36 (24) (1.0 g, 90%) and a small amount of pyridine.

^{13}Cmr ($CDCl_3$) δ_C: 27.6, 28.0, 28.3, 28.4, 28.9, 36.1, 64.1, 64.3, 111.6, 127.6, 129.9.

Bicyclo[3.3.1]non-6-en-2-one (37)

The acetal was removed by refluxing **36** (1.70 g) in acetone (25 mL) containing p-toluenesulphonic acid (200 mg), while monitoring by glc. After workup with 5% $NaHCO_3$ (100 mL) and extraction with ether (3x100 mL) the organic layers were dried and the solvent removed to yield **37** as an oil (24) (1.066 g, 83 %).

^{13}Cmr ($CDCl_3$) δ_C: 28.3, 29.2, 30.8, 30.9, 36.0, 44.6, 126.5, 130.1, 215.0 (C=O).

3,3-Dimethylbicyclo[3.3.1]non-6-en-2-one (38)

The desired ketone was isolated in 85% yield after flash chromatography (fc) on silica with hexanes as eluent.

Infrared (liquid film): 1700 cm^{-1}.

Exact mass calculated for $C_{11}H_{16}O$: 164.1202; found: 164.1203.

^{13}Cmr ($CDCl_3$) δ_C: 29.2 (CH_2), 29.4 (CH), 30.2 (CH_3), 30.5 (CH_3), 32.0 (CH_2), 42.4 (CH), 42.8 (C), 43.9 (CH_2), 126.5, 132.1 (CH=CH), 221.6 (C=O)

^{1}Hmr ($CDCl_3$) δ: 1.08 (s, 3H, *endo*-3-Me), 1.11 (s, 3H, *exo*-3-Me), 1.77 (dt, 1H, J=13.8, 2.5 Hz, *endo*-H-4), 1.84 (dd, 1H, J=13.8, 5.3 Hz, *exo*-H-4), 1.90 (bd, 1H, J=12.0 Hz, *anti*-H-9), 2.00 (bd, 1H, J=12 Hz, *syn*-H-9), 2.12 (bd, 1H, J=18 Hz, *exo*-H-8), 2.34 (bd, 1H, J=18 Hz, *endo*-H-8), 2.45 (m, 1H, H-5), 2.65 (m, 1H, H-1), 5.64 (m, 1H, H-6), 5.78 (m, 1H, H-7).

4,5,6,7-Tetrahydrindan-1-one (**40a**)

Potassium metal (1.96 g) was dissolved in *t*-butanol (35 mL), in a 100 mL two-necked round-bottomed flask equipped with a condenser and nitrogen inlet. To this solution, diethyl succinate (7.6 mL, 45.7 mmol) was added and refluxed for 5 min before addition of cyclohexanone (4.7 mL, 45.7 mmol), and subsequent reflux for a further 10 min. The mixture was cooled to 0°C and neutralized by addition of ice (150 mL) and 6 N HCl (30 mL). Extraction (3x100 mL ether), drying of the organic extracts ($MgSO_4$) and removal of solvent, followed by distillation of the residue yielded 3-carbethoxy-3-(1-cyclohexenyl)propionic acid (6.45 g, 62%), bp 139-145/0.2 Torr (lit.(73) 150-155°C/0.5 Torr). This product was cyclized by the method of Mathieson (74), using zinc chloride (1.5 g) in acetic anhydride (100 mL) and acetic acid (75 mL). After 4 h reflux, the acid and anhydride were removed by vacuum distillation, and the residue was taken up in acetic acid (50 mL) and HCl (50 mL) and refluxed for 2h. The acids were removed by vacuum distillation and the residue was partitioned between 0.1 N NaOH (100 mL) and ether (100 mL). After separation of the layers, the aqueous layer was extracted with ether (2x100 mL), the combined organic extracts were washed with 1 N HCl (100 mL), brine (100 mL) and dried over $MgSO_4$. Upon removal of solvent, the residue was purified by bulb-to-bulb distillation to yield **40a** as a colourless oil (1.0 g, 28%), bp 100°C/5 Torr (lit. (73) 85°C/2 Torr).

2,2-Dimethyl-4,5,6,7-tetrahydroindan-1-one (**40b**)

A solution of lithium diisopropylamide (LDA) was prepared at -78°C by the addition of n-butyllithium (1.5 mL, 2.5M) to diisopropylamine (0.6 mL) in THF (12 mL). The mixture was stirred for 10 min. before the dropwise addition of 4,5,6,7-tetrahydroindan-1-one **40a** (360 mg) in THF (2 mL), then stirred for 10 min. at -78°C. Methyl iodide (0.5 mL) was then rapidly injected and the solution continued to stir for 15 min, before pouring into 1N HCl solution (25 mL). The product was then extracted with ether (3x25 mL). After a second methylation cycle, the product was purified by column chromatography on silica to give **40b** (390 mg, 89% yield).

Infrared (liquid film): 1649, 1698 cm^{-1}.

Exact mass calculated for $C_{11}H_{16}O$: 164.1202; found: 164.1200.

^{13}Cmr ($CDCl_3$) δ_C: 25.3 (2xCH_3), 20.2, 21.8, 22.3, 28.4 (4xCH_2), 43.2 (C), 47.2 (CH_2), 135.9, 170.2 (C=C), 213.2 (C=O).

^1Hmr ($CDCl_3$) δ: 1.06 (s, 6H), 1.55-1.75 (m, 4H), 2.03-2.13 (m, 2H), 2.22-2.28 (m, 2H), 2.29-2.34 (m, 2H).

cis- and *trans*-8,8-Dimethylbicyclo[4.3.0]nonan-7-one (**41b**)

Following the procedure of House and Rasmusson (29), a solution of enone **40b** (35 mg) in THF (2 mL), containing *t*-butyl alcohol (40 μL), was added to a cold (-78°C) solution of lithium (6 mg) in ammonia (4 mL). After the addition, the cold-bath was removed and the mixture allowed to reflux for 2 h. The reaction was quenched by the addition of water (2 mL),

and the ammonia was allowed to evaporate before water (10 mL) and ether (10 mL) were added. The organic layer was separated and the aqueous phase extracted twice with ether (10 mL). The solvent was evaporated and the residual oil (34 mg) was oxidized directly by the addition of N-methylmorpholino-N-oxide (35 mg) in dichloromethane (10 mL) containing 1 mg of TPAP (30). The reaction mixture stirred for 30 min. before dilution with dichloromethane (20 mL). The solution was washed with 15 mL of each of saturated aqueous Na_2SO_3, brine, saturated aqueous $CuSO_4$, and brine before drying over anhydrous $MgSO_4$. Evaporation of the solvent left an oil (28 mg, 79% overall yield) which by ^{13}Cmr and glc was a 60:40 mixture of the desired *cis*- and *trans*- **41b**.

Infrared (liquid film): 1738 cm^{-1}.

Exact mass calculated for $C_{11}H_{18}O$: 166.1358; found: 166.1366 (*cis*- **41b**), 166.1353 (*trans*-**41b**); these data were obtained by gc/ms using a 30m capillary column (DB-5).

^{13}Cmr : see Table 2-1.

Methyl hydrocinnamate (**47b**)

Diazald (5.0 g) in ether (50 mL) was added dropwise to a mixture of KOH (5.0 g), water (8 mL), ethanol (10 mL) and ether (20 mL). This mixture was warmed in a water bath to distill diazomethane into a flask containing hydrocinnamic acid, **47a** (2.1 g), in ether (50 mL). Methanol (50 mL) was

added to the receiver flask, which was allowed to stand overnight. Drying ($MgSO_4$) and removal of solvent yielded **47b** (2.30 g, 100% yield).

Methyl 2,2-dimethyl-3-phenylpropanoate (**47c**)

Methyl hydrocinnamate was methylated by LDA as described above for **40b**. After two methylation cycles [**47b** (500 mg), diisopropylamine (0.5 mL), n-buLi (1.8 mL), methyl iodide (0.5 mL), THF (12 mL)], **47c** (568 mg, 98%) was isolated as a colourless oil.

2,2-Dimethyl-3-phenylpropionic acid (**46**)

Ester **47c** was heated in 3N NaOH at 80°C for 5 h. The reaction mixture was extracted with ether (2x50 mL) and the aqueous phase acidified to pH 2 before extraction with ether (3x50 mL). The second organic extract was dried over $MgSO_4$ and the solvent was removed to yield **46** (28 mg, 82% yield).
Infrared (liquid film): 2400-3400, 1701 cm^{-1}.
Exact mass calculated for $C_{11}H_{14}O_2$: 178.0994; found: 178.0996.
^{13}Cmr ($CDCl_3$) δ_C: 24.7 ($2xCH_3$), 43.5 (C), 45.9 (CH_2), 126.6, 128.1 (2), 130.3 (2) (aryl CH), 137.6 (aryl C), 184.5 (COOH).
^{1}Hmr ($CDCl_3$) δ: 1.23 (s, 6H), 2.92 (s, 2H), 7.15-7.35 (m, 5H).

5.2.3 3,3-Dimethylbicyclo[3.2.2]non-6-en-2-one

Preparation of 1,3-cyclohexadiene (75)

Dibromocyclohexene- A 1 L three-necked round-bottomed flask equipped with a thermometer and dropping funnel was charged with cyclohexene (145 mL, 1.43 mol) and 300 mL CCl_4, then cooled to -10°C in an ice-salt bath. Bromine (68mL, 1.33 mol) in 100 mL CCl_4 was added at such a rate to keep the reaction temperature below 0°C. The addition took 1.5h and the mixture was stirred at 0°C for a further 1h. The CCl_4 was removed by simple distillation, and the product was distilled through a vigreux column, bp 56-62°C/1 Torr, yield 281.5g (88%). (lit.(76) bp 108-112/25 Torr).

3-methoxycyclohexenone - Sodium (80g, 3.48 mol, 3 eq.) was dissolved in methanol (800 mL) in a 2L one-necked round-bottomed flask equipped with a condenser. Dibromocyclohexanone (281.5g, 1.16 mol) was added all at once and the mixture was refluxed for 16h. The reaction was cooled to 0°C and neutralized with HCl. The NaBr salt was filtered off, and the residue taken up in H_2O (300 mL) and CH_2Cl_2 (300 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (4x250 mL), the organic layers were distilled through a vigreux column at atmospheric pressure to yield 3-methoxycyclohexene (88.1g, 68%), bp 140°C (lit.(76) 130°C).

1,3-cyclohexadiene - 3-methoxycyclohexene (43.3g, 0.387 mol) was placed in the distilling flask of a simple distillation apparatus along with phosphoric acid (6 mL) and triglyme (100 mL). The flask was heated to 200°C, and a colourless liquid distilled at 110°C. The distillate was returned to the distilling flask with a further 6 mL of H_3PO_4. The flask was heated to 160°C, and a biphasic distillate came off at 60°C. NaCl was added to saturate the aqueous layer, the layers were separated, the organic layer was washed with 2 x 20 mL brine, and dried over MgSO4. Filtration yielded 1,3-cyclohexadiene as a colourless liquid (30g, 90%).

5-cyanobicyclo[2.2.2]octene (**50**)

1,3-cyclohexadiene (10.7g, 0.134 mol) and acrylonitrile (7.8g, 0.147 mol) were sealed in a thick walled Carius tube (2/3 full), and heated to 120°C in a sand bath for 16h. The tube was opened and its contents were poured into a flask and pumped under vacuum to remove the excess starting material, to yield **50** (14 g, 76%) as a thick oil (77).

5-chloro-5-cyanobicyclo[2.2.2]octene (**51**)

A 500 mL three-necked round-bottomed flask equipped with an addition funnel, condenser and nitrogen purge was charged with PCl_5 (32.5g, 0.15 mol, 1.5 eq.), pyridine (17.2 mL, 0.21 mol, 2 eq.), and chloroform (150 mL). A solution of **50** (14.0 g, 0.105 mol) in chloroform (100 mL) was then added dropwise,

and the mixture refluxed for 20h. The solution was added to 500 g ice in a separatory funnel, the layers were separated, and the aqueous layers were extracted with 2 x 300 mL ether. The comnbined organic layers were washed with 200 mL saturated aqueous Na_2CO_3, 200 mL brine, and dried over $MgSO_4$. Removal of solvent yielded **51** (78) as a thick oil (14.4 g, 82%).

Bicyclo[2.2.2]octenone (**52**)

A solution of **51** (7.4g, 44.2 mmol) and DMSO (100 mL) were combined in a 250 mL one-necked round-bottomed flask. An aqueous solution of KOH (85%, 25 mL) was added to the reaction mixture, which was then allowed to stir at room temperature for 18h. The solution was added to 500 g ice in a separatory funnel, and extracted with 5 x 300 mL 35-60 petroleum ether. The combined organic layers were washed with H_2O (250 mL), brine (250 mL), and dried over MgSO4 before removal of solvent yielded **52** (78) as a waxy solid (3.15 g, 58%).

Silyl enol ether **53**

A solution of lithium diisopropylamide was prepared in a flame dried flask under dry nitrogen at -78°C by dropwise addition of diisopropylamine (2.84 mL) to n-butyllithium (7.1 mL) in dry THF (20 mL). After stirring for 15 min at -78°C, a solution of ketone **52** (1.54 g) in THF was added and stirring continued for 1 h at -78 °C. A quenching solution of trimethylsilyl chloride (3.2 mL) and triethylamine (0.8 mL) in

THF (2 mL) was prepared in a flame-dried centrifuge tube and purged with nitrogen. The precipitate was removed by centrifugation and the clear solution rapidly added to the reaction mixture which was then allowed to warm to room temperature. The reaction mixture was then poured into sodium carbonate (50 mL) in a separatory funnel and extracted with penatane (3x50 mL). The residue was then purified by bulb-to-bulb distillation (75°C/15 Torr) to yield **53** (1.00 g, 41%).

Cyclopropyl silyl ether **54**

A 25 mL two-necked round-bottomed flask equipped with a condenser and nitrogen purge was charged with zinc-silver (0.84 g) and the entire apparatus was flame-dried under nitrogen. After cooling, methylene iodide (0.55 mL) was added in ether (4 mL). The mixture stirred vigorously until it had ceased to reflux whereupon **53** (1.00 g) was added in ether (6 mL) and allowed to reflux for 12 h. The mixture was cooled to 0°C and quenched by the dropwise addition of a 1:1 pyridine:ether solution (4 mL), until no further precipitation occurred. After filtration, the filtrate was concentrated, taken up in pentane (10 mL), and dried with $MgSO_4$ before filtering through Celite. The solvent was then removed and distilled through a Kugelrohr apparatus (90°C/4 Torr) to yield **54** (712 mg, 66%).

Bicyclo[3.2.2]non-6-en-2-one (55)

Ether 54 (612 mg) was dissolved in 3M methanolic NaOH (10 mL) and stirred at ambient temperature for 24 h. The solution was then added to water (25 ml) and extracted with pentane (3x25 mL). The combined organic layers were washed with brine (25 mL) and dried ($MgSO_4$); removal of solvent gave clean 55 (430 mg, 92%).

3,3-Dimethylbicyclo[3.2.2]non-6-en-2-one (49)

This ketone was isolated in 73% yield by fc (5% ethyl acetate in hexanes) and slowly crystallized on standing to a solid that sublimed readily at room temperature; mp 38-39°C. Infrared ($CHCl_3$): 1694 cm^{-1}.

Exact mass calculated for $C_{11}H_{16}O$: 164.1202; found: 164.1200.

^{13}Cmr ($CDCl_3$) δ_C: 23.4 (CH_2), 26.7 (CH_2), 30.5 (CH_3), 32.5 (CH_3), 32.6 (CH), 44.5 (CH_2), 45.9 (C), 50.1 (CH), 127.7, 136.7 (CH=CH), 213.2 (C=O).

^{1}Hmr ($CDCl_3$) δ: 1.14 (s, 3H, *endo*-3-Me), 1.16 (s, 3H, *exo*-3-Me), 1.6-1.95 (m, 6H), 2.64 (m, 1H, H-5), 3.17 (m, 1H, H-1), 6.0 (bdd, 1H, J=8.0, 7.0 Hz), 6.35 (bt, 1H, J=8.0 Hz).

5.2.4 3,3-Dimethylbicyclo[3.2.2]nonan-2-one (56)

3,3-Dimethylbicyclo[3.2.2]nonan-2-one (**56**)

A Parr hydrogenation bottle was charged with palladium on activated carbon catalyst (10% Pd, 70 mg) and then **49** (254 mg) in ethyl acetate (10 mL) was added. The bottle was filled to 58 psi with hydrogen before shaking for 30 min. at room temperature. The mixture was filtered and the solvent evaporated to furnish **56** quantitatively.

Infrared (liquid film): 1692 cm^{-1}.

Exact mass calculated for $C_{11}H_{18}O$: 166.1358; found: 166.1360.

^{13}Cmr ($CDCl_3$) δ_C: 21.8 (2xCH_2), 24.8 (2xCH_2), 29.4 (CH), 30.8 (2xCH_3), 45.0 (C), 45.1 (CH_2), 46.6 (CH), 220.1 (C=O).

^{1}Hmr ($CDCl_3$) δ: 1.18 (s, 6H), 1.6-1.8 (m, 8H), 2.17 (m, 1H), 2.58 (m, 1H).

5.2.5 3,3,7,7-Tetramethylbicyclo[3.3.1]nonan-2,6-dione

3,3,7,7-Tetramethylbicyclo[3.3.1]nonan-2,6-dione (**59**)

After two methylation cycles, a 40% yield of **59** was isolated upon column chromatography on alumina (1% ethyl acetate/hexanes).

Infrared (liquid film): 1705 cm^{-1}.

Exact mass calculated for $C_{13}H_{20}O_2$: 208.1464; found: 208.1466.

^{13}Cmr ($CDCl_3$) δ_C: 27.4 (CH_2), 28.4 (2xCH_3), 30.0 (2xCH_3), 41.3

(2xCH_2), 42.2 (2xCH), 43.1 (2xC), 218.3 (C=O).
^{1}Hmr ($CDCl_3$) δ: 1.00 (s, 6H, 2 x *endo*-3-Me), 1.15 (s, 6H, 2 x *exo*-3-Me), 1.93 (dd, 2H, J=14.6, 8.4 Hz, *exo*-H-4) 1.99 (dd, 1H, J=14.6, 2.5 Hz, *endo*-H-4), 2.24 (t, 2H, J=3.2 Hz, H-9), 2.73 (m, 2H, H-1).

6-*endo*-Hydroxy-3,3,7,7-tetramethylbicyclo[3.3.1]nonan-2-one

The hydroxyketone from the runs with **59** was isolated by chromatography through silica gel and identified as **60** on the basis of the following data.
Infrared ($CHCl_3$ solution): 3687, 3629, 1708 cm^{-1}.
Exact mass calculated for $C_{13}H_{22}O_2$: 210.1621; found: 210.1619.
^{13}Cmr ($CDCl_3$) δ_C: 22.1 (CH_3), 27.5 (CH_3), 28.9 (CH_2), 31.6 (CH_3), 32.5 (CH_3), 32.7 (CH_2), 33.8 (CH), 35.5 (C), 41.9 (CH), 42.8 (C), 45.5 (CH_2), 79.8 (CHOH), 220.9 (C=O).
^{1}Hmr ($CDCl_3$) δ: 0.66 (s, 3H), 0.92 (s, 3H), 1.09 (s, 3H), 1.19 (s, 3H), 1.49 (dd, 1H, J=13.7, 4.2 Hz), 1.56 (bd, 1H, J=12.6 Hz), 1.72 (dd, 1H, J=15.0, 10.5 Hz), 1.96 (dt, 1H, J=13.7, 2.8 Hz), 1.98 (bd, 1H, J=15.0 Hz), 2.34 (m, 1H), 2.45 (m, 1H), 2.48 (m, 1H), 3.51 (d, 1H, J=4.8 Hz).

3,3,7,7-Tetramethyltricyclo[3.3.1.$0^{2,6}$]nonan-2,6-diol (**62b**)

Sodium amalgam (3.5%) was prepared by the method of Fieser and Fieser (79). Sodium amalgam was added in small pieces to a slurry of diketone **59** (100 mg) in water (10 mL). The mixture was stirred at room temperature for 1h, before the

alkaline solution was decanted, acidified, and extracted with ether (3x10 mL). The organic layers were dried ($MgSO_4$) and solvent was removed to yield 75 mg of a pasty white solid, which was then sublimed (100°C/1 Torr) to yield an analytical sample; mp 124-126°C.

Infrared (KBr disc): 3387-3485 cm^{-1}.

Exact mass calculated for $C_{13}H_{22}O_2$: 210.1621; found: 210.1623.

^{13}Cmr ($CDCl_3$) δ_C: 25.6 (2xCH_3), 26.9 (2xCH_3), 33.3 (CH_2), 37.0 (2xC), 38.7 (2xCH), 45.0 (2xCH_2), 90.2 (2xCOH).

^{1}Hmr ($CDCl_3$) δ: 1.04 (s, 3H), 1.10 (s, 3H), 1.29 (dd, 1H, J=11.7, 0.9 Hz), 1.47 (dt, 1H, J=3.6, 1.8 Hz), 1.60 (bs, 1H, exchanges with D_2O), 1.81 (bdt, 1H, J=3.6 Hz), 1.98 (ddt, 1H, J=11.7, 3.6, 1.8 Hz)

Treatment of **62b** with sulphuric acid

Diol **62b** (30 mg) was placed in a Carius tube with 1.0 mL H_2SO_4, and sealed under vacuum. This tube was heated at 160°C for 1 h, then cooled and opened. The black semisolid residue was flushed out with brine (20 mL) and chloroform (20 mL), and neutralized with 3N NAoH. The layers were separated and the aqueous layer extracted with $CHCl_3$ (2x20mL). After drying ($MgSO_4$) and removal of solvent, 2 mg of a sweet smelling oil was recovered.

Exact mass calculated for $C_{13}H_{20}O$: 192.1515; found: 192.1517.

^{13}Cmr ($CDCl_3$) δ_C: See table 2-7.

5.3 EXPERIMENTAL FOR CHAPTER 3

5.3.1 3,3-Dimethylbenzobicyclo[3.2.1]octen-2-one (65)

Benzonorbornadiene (68)

Benzenediazonium 2-carboxylate was prepared from anthranilic acid (34.5 g), isoamyl nitrite and trichloroacetic acid (250 mg) following the procedure of Logullo, Seitz and Friedman (80) using the glassware described by Crews and Beard (43). The solvent was replaced with dichloromethane (150 mL) and freshly distilled cyclopentadiene (50 mL) was added before the mixture was heated under reflux for 5 h. After removal of solvent, the residue was taken up in pentane and the insoluble material removed by filtration through Celite. After the pentane was removed, the residue was distilled to furnish benzonorbornadiene (22.0 g) in 65 % yield, bp 84-86°C/12 Torr (lit.(81) 82.5-83.0°C/12 Torr). ^{13}Cmr ($CDCl_3$) δ_C: 50.8 (2xCH), 70.7 (CH_2), 122.2, 124.8 (4x aryl CH), 143.7 (2xCH), 152.5 (2xC).

Benzonorbornenol (69)

Benzonorbornadiene (22.0 g), was dissolved in dry hexane (75 mL) in a flame-dried flask under N_2 and cooled to 0°C before dropwise addition of 10 M $BH_3.Me_2S$ (9.5 mL) with stirring. The ice-bath was removed and stirring was continued for 3 h before cooling again to 0°C. The temperature was

maintained at <40°C during the sequential dropwise addition of absolute ethanol (100 mL), 3M NaOH (40 mL), and 30% H_2O_2 (40 mL). The reaction mixture was refluxed for 1 h, cooled to room temperature, and the product was recovered by pentane extraction (4 x 100 mL). These extracts were washed with H_2O (50 mL) and brine (50 mL) and the washings were back-extracted with pentane (25 mL). The combined extracts were dried over anhydrous $MgSO_4$ before the solvent was removed to furnish white, crystalline benzonorbornenol (22.3 g, 90% yield), mp 67-70°C (lit.(82) 74.1-75.4°C) which was used without further purification.

^{13}Cmr ($CDCl_3$) δ_C: 39.9 (CH_2), 43.2 (CH), 46.3 (CH_2), 52.6 (CH), 73.8 (CH), 121.2, 122.6, 126.1, 126.7 (aryl CH), 145.4, 150.1 (aryl C).

Benzonorbornenone (70)

A solution of dimethyl sulphoxide (0.7 mL) in dry dichloromethane (5 mL) was cooled to -78°C under N_2. This solution was rapidly stirred during the addition of a solution of trifluoroacetic anhydride (1.0 mL) in dichloromethane (3 mL) and stirring continued for 10 min. Then a solution of benzonorbornenol (800 mg) in dichloromethane (5 mL) was slowly added and the solution stirred for 10 min before the cold bath was removed. After this mixture had warmed to room temperature, triethylamine (2 mL) was added and stirring continued for 45 min before addition of brine (10 mL). The

organic layer was separated and the aqueous layer extracted with dichloromethane (10 mL). The combined organic extracts were dried over anhydrous magnesium sulphate before removal of the solvent. Distillation of the residue through a short-path column gave benzonorbornenone (760 mg) in 95% yield; bp 98-102°C/2 Torr (lit.(83) 65-75°C/0.02 Torr).

^{13}Cmr ($CDCl_3$) δ_C: 40.3 (CH_2), 41.8 (CH), 50.8 (CH_2), 58.1 (CH_2). 121.6, 123.8, 127.0, 127.7 (aryl CH), 140.1, 149.0 (aryl C), 213.8 (C=O).

Pyridinium chlorochromate oxidation of benzonorbornenol

Benzonorbornenol (1.34 g, 8.38 mmol) was added to a rapidly stirred slurry of freshly prepared pyridinium chlorochromate (84) (PCC) (2.7 g, 12.6 mmol), sodium acetate (0.2 g) and Celite (2.7 g) in dry dichloromethane (25 mL). The mixture was refluxed with efficient stirring for 2h, at which point it was cooled to room temperature and filtered through a Buchner funnel, rinsed well with dichloromethane and washed with 1N HCl (10 mL), 10% NaOH (10 mL), water (3x10 mL) and brine (10 mL) before drying over Na_2SO_4 and removal of solvent afforded 1.48 g of a light green oil. This oil was separated by flash chromatography through silica gel (ethyl acetate in hexanes 0%-12%). The first fraction isolated (607 mg) was benzonorbornenone, and the second fraction (464 mg) was identified as the keto-aldehyde 74 on the basis of the spectral data below.

Infrared ($CHCl_3$): 2923, 2900, 1727, 1674 cm^{-1}.

Exact mass calculated for $C_{11}H_{10}O_2$: 174.0681; found: 174.0679.

^{13}Cmr ($CDCl_3$) δ_C: 31.8 (CH), 43.1 (CH_2), 49.8 (CH_2), 123.6, 125.5, 128.0, 135.1 (aryl CH), 136.7, 156.9 (aryl C), 200.5 (CHO), 205.4 (C=O).

^1Hmr ($CDCl_3$) δ: 2.32 (dd, 1H, J=19.3, 3.5 Hz), 2.78 (ddd, 1H, J=13.3, 8.9, 1.0 Hz), 3.03 (dd, 1H, J=19.3, 7.7 Hz), 3.11 (ddd, 1H, J=18.3, 4.8, 1.0 Hz), 3.85 (m, 1H), 7.35-7.76 (m, 5H), 9.88 (t, 1H, J=1.0 Hz).

Trimethylsilyl enol ether (71)

A solution of lithium diisopropylamide (LDA) was prepared in a flame-dried flask under N_2 at -78°C by dropwise addition of diisopropylamine (5.8 mL, 41.5 mmol) to *n*-butyllithium (14.5 mL, 2.5 M in hexane, 36.3 mmol) in dry THF (25 mL). After stirring for 15 min., a solution of benzonorbornenone (4.1 g, 25.9 mmol) in THF (5 mL) was added and stirring continued for 1 h at -78 °C. A quenching solution of trimethylsilyl chloride (6.6 mL) and triethylamine (2 mL) in dry THF (5 mL) was prepared in a flame-dried, nitrogen-purged centrifuge tube. The precipitate was removed by centrifugation and the clear supernatant liquid rapidly injected into the reaction mixture at -78°C which was then allowed to warm to room temperature before the addition of cold, saturated aqueous Na_2CO_3 solution (100 mL). The product was extracted with pentane (3 x 100 mL) and the extracts

washed with brine (50 mL) before drying over anhydrous $MgSO_4$. After removal of solvent, Kugelrohr distillation afforded **71** (5.6 g , 94% yield) bp 115°C/2 Torr.

Exact mass calculated for $C_{14}H_{18}OSi$: 230.1127; found: 230.1133.

^{13}Cmr ($CDCl_3$) δ_C: -0.1 ($SiMe_3$), 48.3 (CH), 53.8 (CH), 67.4 (CH_2), 110.5 (CH), 120.4, 121.6, 123.8, 124.5 (aryl CH), 150.5, 153.3 (aryl C), 171.0 (C).

^{1}Hmr ($CDCl_3$) δ: 0.17 (s, 9H, $SiMe_3$), 2.30 (ddt, 1H, J=6.9, 0.5, 1.7 Hz, *anti*-H-7), 2.51 (dt, 1H, J=6.9,1.6, *syn*-H-7), 3.47 (m, 1H, H-1), 3.75 (dt, 1H, J=3.3, 1.7 Hz, H-4), 5.35 (bd, 1H, J=3.3 Hz, H-3), 6.9-7.3 (m, 4H, aryl H)

Cyclopropylsilyl ether (**72**)

To a flask fitted with a reflux condenser, N_2 purge and magnetic stirrer was added zinc-silver couple (3.82 g, 58.4 mmol). The apparatus was flame-dried and then cooled to room temperature before the addition of methylene iodide (2.6 mL, 32.9 mmol) in dry ether (10 mL). The mixture was warmed with stirring until refluxing occurred without external heating. Upon cessation of reflux, a solution of **71** (4.5g, 19.6 mmol) in ether (30 mL) was added and the mixture refluxed for 17 h before cooling to room temperature. While the mixture was stirred, pyridine-ether (1:1, 14 mL) was added slowly until precipitation ceased. Then the precicpitate was removed by filtration and thoroughly washed with ether. After evaporation of the ether, the residue was taken up in pentane

and passed through Celite to remove the last traces of precipitate before drying over anhydrous $MgSO_4$. Bulb-to-bulb distillation of the material remaining after the removal of solvent gave the cyclopropanated ether **72** (2.9 g) in 61 % yield; bp 125-128°C/? Torr.

Exact mass calculated for $C_{15}H_{20}OSi$: 244.1284; found: 244.1283.

^{13}Cmr ($CDCl_3$) δ_C: 0.8 ($SiMe_3$), 21.2 (CH_2), 26.1 (CH), 42.0 (CH_2), 43.0 (CH), 49.2 (CH), 67.5 (C), 120.8, 122.9, 124.7, 125.1 (aryl CH). 149.0, 150.6 (aryl C).

Benzobicyclo[3.2.1]octan-2-one (**73**)

To a methanolic NaOH solution (3M, 20 mL) was added ether **72** (2.84 g). The reaction mixture was stirred at room temperature for 24 h before the addition of brine (50 mL) and extraction with pentane (3 x 50 mL). The combined organic layers were washed with brine (50 mL) before drying over anhydrous $MgSO_4$. The solvent was removed to furnish ketone **73** (1.98 g, 98% yield).

Infrared (liq. film): 1719 cm^{-1}.

Exact mass calculated for $C_{12}H_{12}O$: 172.0889; found: 172.0885.

^{13}Cmr ($CDCl_3$) δ_C: 29.4 (CH_2), 34.3 (CH_2), 40.1 (CH), 43.2 (CH_2), 57.3 (CH), 123.1$_6$, 123.2$_2$, 126.8, 127.9 (aryl CH), 142.2, 146.0 (aryl C), 209.4 (C=O).

3,3-Dimethylbenzobicyclo[3.2.1]octan-2-one (**65**)

In the standard method, $NaNH_2$ (1.14g, 29.2 mmol) and ketone **73** (837 mg, 4.87 mmol) were refluxed in 10 mL ether with the addition of methyl iodide (1.8 mL, 29 mmol; 0.6 mL, 9.8 mmol) after 2 h and 16 h. After workup and extraction, removal of the solvent gave essentially pure **65** (912 mg, 93% yield) from which trace impurities were readily removed by chromatography on neutral alumina.

Infrared (liq. film): 1705 cm^{-1}.

Exact mass calculated for $C_{14}H_{16}O$: 200.1202; found: 200.1206.

^{13}Cmr ($CDCl_3$) δ_C: 29.8 (CH_3), 32.0 (CH_3), 41.0 (CH), 42.0 (CH_2), 43.6 (C), 44.3 (CH_2), 57.2 (CH), 123.2, 123.5, 126.9, 127.9 (aryl CH), 142.0, 147.0 (aryl C), 214.3 (C=O).

^{1}Hmr ($CDCl_3$) δ: 0.38 (s, 3H, *endo*-3-Me), 1.14 (s, 3H, *exo*-3-Me), 1.85 (dt, 1H, J=13.5, 2.8 Hz, *endo*-H-4), 2.04 (dd, 1H, J=13.5, 3.9 Hz, *exo*-H-4), 2.21 (d, 1H, J=11.4, *syn*-H-8), 2.71 (ddt, 1H, J=11.4, 2.8, 4.8 Hz, *anti*-H-8), 3.41 (m, 1H, H-5), 3.69 (d, 1H, J=4.8 Hz, H-1), 7.1-7.4 (m, 4H, aryl H).

3,3-Dimethyl-6,7-benzobicyclo[3.3.0]octen-2-one (**75**)

The new ketone was separated from **65** by preparative tlc on Silica Gel 60 F-254 plates (0.5 mm) with 9:1 petroleum ether:ether as eluent, and assigned structure **75** based on the spectral data.

Infrared (liquid film): 1738 cm^{-1}.

Exact mass calculated for $C_{14}H_{16}O$: 200.1202; found: 200.1196.
^{13}Cmr ($CDCl_3$) δ_C: 25.2 (CH_3), 25.9 (CH_3), 35.4 (CH_2), 43.4 (CH_2), 43.8 (CH), 46.3 (C), 50.6 (CH), 124.0, 124.9, 127.0 (2) (aryl CH), 142.1, 146.2 (aryl C), 226.0 (C=O).
^{1}Hmr ($CDCl_3$) δ: 0.68 (s, 3H), 1.14 (s, 3H), 2.06 (dd, 1H, J=13.4, 4.0 Hz), 2.34 (dd, 1H, J=13.4, 8.3 Hz), 3.1-3.3 (m, 2H), 3.20 (m, 1H), 3.90 (ddd, 1H, J=8.3, 8.0, 4.0 Hz), 7.14-7.30 (m, 4H).

3-(1'-indanyl)-2,2-dimethylpropionic acid (**76**)

The acidic product isolated from runs with **65** was recrystallized from aqueous ethanol to give beige, powdery crystals, mp 105-107°C and identified as **76**.
Infrared (KBr disc): 2400-3400, 1696 cm^{-1}.
Exact mass calculated for $C_{14}H_{18}O_2$: 218.1307; found: 218.1305.
^{13}Cmr ($CDCl_3$) δ_C: 25.4 (CH_3), 26.2 (CH_3), 31.8 (CH_2), 34.0 (CH_2), 41.9 (CH), 42.4 (C), 46.4 (CH_2), 123.4, 124.3, 126.2, 126.4 (aryl CH), 143.6, 147.5 (aryl C), 184.9 (COOH).
^{1}Hmr ($CDCl_3$) δ: 1.39 (s, 6H), 1.65-1.90 (m, 2H), 2.25-2.50 (m, 2H), 2.75-3.05 (m, 2H), 3.18 (m, 1H), 7.18-7.32 (m, 4H).

Birch reduction of β-tetralone

A 50 mL two-necked round bottomed flask, equipped with a teflon coated magnetic stir bar, dry ice condenser and nitrogen purge was charged with lithium metal (150 mg) and

cooled to -78°C by means of a dry ice/isopropanol bath. Into a separate one-necked flask containing a small piece of sodium metal and $FeCl_3$ (~50 mg), ammonia was condensed from a cylinder of commercial ammonia (Matheson). This ammonia was then redistilled into the reaction flask until ~10 mL had collected, and the deep solution was stirred at -78°C. After 10 mins, a solution of β-tetralone (60 mg) in dry ethanol (10 mL) was added, the solution was stirred vigorously, the dry ice was removed and the mixture was allowed to reflux for 3 h. The deep blue solution had taken on a bronze colour at the interface. The dry ice condenser was removed and the ammonia was allowed to evaporate, at which point the reaction was cautiously worked up with saturated aqueous NH_4Cl (10 mL). The mixture was diluted with water (40 mL) and extracted with 3x50 mL ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent removed to yield 60 mg (100%) of alcohol **80a** as an oil.

Infrared ($CDCl_3$) : 2890, 2915, 3022, 3130-3470 cm^{-1}.

^{13}Cmr ($CDCl_3$) δ_C: 27.9, (CH_2), 31.1 (CH_2), 31.2 (CH_2), 31.6 (CH_2), 38.8 (CH_2), 67.4 (CH), 122.9 (C), 124.2 (CH), 124.4 (CH), 125.3 (C)

^{1}Hmr ($CDCl_3$) δ: 1.5-2.3 (m, 8H), 2.54 (d, 2H, J~1.0 Hz), 4.00 (m, 1H), 7.26 (t, 2H, J=1.3 Hz).

TPAP Oxidation of **80a**

This compound (10 mg) was oxidized using N-methyl-morpholino-N-oxide (NMO, 20 mg) with tetra-n-propyl ammonium per-ruthenate (TPAP, 1 mg) as catalyst. After 30 min reaction at room temperature, the reaction was worked up by the general method given previously. Yield : 10 mg (100 %).
^{13}Cmr ($CDCl_3$) δ_C: 20.5 (CH_2), 26.8 (CH_2), 50.7 (CH_2), 61.7 (CH_2), 72.4 (CH_2), 127.0 (C), 128.2 (CH), 128.4 (C), 128.8 (CH), 210.3 (C=O).

Birch reduction of **65**

The method shown above for β-tetralone was employed in the Birch reduction of **65** (140 mg), using NH_3 (10 mL), Li (400 mg) and EtOH (10 mL). After 3 h reaction and workup, a yield of 124 mg (94 %) of alcohol **81** was obtained.
^{13}Cmr ($CDCl_3$) δ_C: 24.3 (CH_3), 26.3 (CH_2), 28.4 (CH_2), 34.0 (CH_3), 36.0 (C), 38.8 (CH_2), 42.4 (CH), 43.3 (CH_2), 49.3 (CH), 78.1 (CH), 124.4 (CH), 125.1 (CH), 133.4 (C), 136.6 (C).

TPAP oxidation of **81**

Under standard conditions, **81** (124 mg) was oxidized with NMO (150 mg) in the presence of TPAP (2 mg). The crude product was seen to be a 1:2 ratio of **65:78**, the latter of which was identified on the basis of the ^{13}Cmr data below.
^{13}Cmr ($CDCl_3$) δ_C: 25.6, 25.8, 30.5, 30.9, 33.0, 38.9, 39.3, 41.9, 58.3, 124.0, 124.5, 132.7, 140.9, 206.9.

After chromatography through alumina, 115 mg of an oil was isolated which was shown to be comprised of entirely **65**.

5.3.2 3,3-Dimethylbenzobicyclo[2.2.2]octen-2-one (66)

Benzobicyclo[2.2.2]octene (77)

Benzenediazonium-2-carboxylate was prepared according to Logullo *et al.* (84) from anthranilic acid (33.2 g, 242 mmol), isoamyl nitrite (53.4 mL), and trifluoroacetic acid (0.2 mL) in tetrahydrofuran (150 mL) in the glassware described by Crews and Beard (43). After draining the solvent and washing with THF, the solvent was replaced with dichloromethane (150 mL). Freshly prepared cyclohexadiene (33 mL, 347 mmol) was added rapidly via syringe and the reaction was refluxed for 4h. The solvent was removed in vacuo, the black oil taken up in pentane and filtered to remove the black sediment. The solid was washed with pentane until the washings were colourless, the solvent was removed by rotary evaporation, and the product was distilled through a vaccuum distillation apparatus, bp 102-106°C/15 Torr, yield 27.3g (72 %). The desired product (*ca.* 50 %) was accompanied by three minor products; two resulting from ene addition and one from [2+2] addition. Since these hydrocarbons were inseparable by chromatography, they were carried through the synthesis and separated in the final step.

Benzobicyclo[2.2.2]octanol (80)

A 2L 3-necked round-bottomed flask, equipped with a thermometer, addition funnel, condenser and nitrogen purge, was charged with the olefin mixture (87.5 g, 561 mmol) in hexane (250 mL). The solution was cooled to 0°C and 10M borane-methyl sulphide (45 mL, 450 mmol) was added dropwise. The solution was stirred for 3h at room temperature and refluxed for a further 1h. The solution was cooled to 0°C before the sequential, dropwise addition of ethanol (150 mL), 3M NaOH (100 mL), and 30 % H_2O_2 (100 mL). The solution was refluxed for 1.5h, cooled and added to 100 mL brine. The layers were separated, and the aqueous layer was extracted with 5 x 200 mL hexanes. The combined organic layers were washed with 150 mL brine and dried over $MgSO_4$. The solvent was removed to yield a waxy white solid (67.8 g) consisting of a 4:2:1 mixture of three alcohols according to its ^{13}Cmr spectrum.

Benzobicyclo[2.2.2]octanone (81)

The oxidation was carried out by the method of Swern (44). Dichloromethane (50 mL) and dimethyl sulphoxide (3.9 mL, 64 mmol) were combined in a 500 mL 3-necked round-bottomed flask equipped with an addition funnel, thermometer and nitrogen purge. The reaction was cooled to -78°C and trifluoroacetic anhydride (6.0 mL, 48 mmol) was added dropwise. The reaction was allowed to stir for 15 min, and a

mixture containing the alcohol **80** (5.5 g, 32 mmol) in CH_2Cl_2 (50 mL) was added dropwise. The solution stirred at -78°C for 15 min and was then allowed to warm to room temperature. Tr ethylamine (12 mL) was added dropwise and stirring continued for a further 45 min. The reaction mixture was poured into H_2O (50 mL) in a separatory funnel, the layers were separated, the aqueous layer extracted with CH_2Cl_2 (50 mL), and the combined organic layers were dried over $MgSO_4$. Removal of solvent yielded 5.24 g (96%) of a yellow oil containing *ca.* 80 % of benzobicyclo[2.2.2]octenone to judge from the ^{13}Cmr spectrum, representing a 50% yield from the mixture of olefins.

3,3-Dimethylbicyclo[2.2.2]octen-2-one (**66**)

In the standard method, ketone **81** (2.0 g, 11.6 mmol) was methylated using $NaNH_2$ (2.87 g, 73.5 mmol), CH_3I (4.4 mL, 1.4 mL) and ether (20 mL). After workup and removal of solvent, 2.13 g (92%) of a yellow oil was isolated. An analytical sample was provided by sublimation (100°C/1 Torr); mp 37.0-37.5°C.

Infrared ($CHCl_3$): 1725 cm^{-1}

Exact mass calculated for $C_{14}H_{16}O$: 200.1202; found: 200.1201.

^{13}Cmr ($CDCl_3$) δ_C: 21.4 (CH_2), 23.1 (CH_2), 23.8 (CH_3), 26.0 (CH_3), 44.3 (C), 48.1 (CH), 52.6 (CH), 124.8, 125.3, 126.8, 127.1 (aryl CH), 135.2, 143.6 (aryl C), 216.7 (C=O).

^{1}Hmr ($CDCl_3$) δ: 0.73 (s, 3H, *endo*-3-Me), 1.23 (s, 3H, *exo*-3-

Me), 1.47 (dddd, 1H, J=12.6, 11.8, 5.2, 2.6 Hz, *syn*-H-8), 1.71 (ddt, 1H, J=12.8, 11.8, 3.2 Hz, *syn*-H-7), 1.99 (dddd, 1H, J=12.8, 10.2, 5.2, 2.0 Hz, *anti*-H-7), 2.20 (dddd, 1H, J=12.6, 10.2, 3.2, 3.0 Hz, *anti*-H-8), 2.93 (dd, 1H, J=3.0, 2.6 Hz, H-4), 3.55 (dd, 1H, J=3.2, 2.0 Hz, H-1), 7.13-7.24 (m, 4H, aryl H)

7,7-Dimethyl-2,3-benzobicyclo[3.2.1]octen-6-one (**82**)

The new ketone was separated from **66** by column chromatography on silica, and was assigned structure **82** on the basis of the spectral data below.

Infrared (liquid film): 1742 cm^{-1}.

Exact mass calculated for $C_{14}C_{16}O$: 200.1202; found: 200.1197.

^{13}Cmr ($CDCl_3$) δ_C: 21.7 (CH_3), 24.7 (CH_3), 30.3 (CH_2), 34.6 (CH_2), 45.4 (CH), 49.6 (CH), 52.9 (C), 125.7, 126.9, 128.8, 129.2 (aryl CH), 132.5, 141.5 (aryl C), 225.6 (C=O).

^{1}Hmr ($CDCl_3$) δ: 0.72 (s, 3H), 1.25 (s, 3H), 2.06 (dd, 1H, J=11.9, 1.0 Hz), 2.56 (dddd, 1H, J=11.9, 5.5, 4.1, 1.3 Hz), 2.85 (dddd, 1H, J=5.9, 5.5, 2.1, 2.0 Hz), 2.94 (bd, 1H, J=17.2 Hz), 2.95 (bd, 1H, J=4.1 Hz), 3.16 (dd, 1H, J=17.2, 5.9 Hz), 7.0-7.25 (m, 4H, aryl H).

2-Methyl-2-(1',2',3',4'-tetrahydro-1'-napthyl)-propionicacid

The acid obtained from **66** was purified by sublimation (120°C/1 Torr), mp 99-101°C and identified as **83**.

Infrared (KBr disc): 2400-3400, 1709 cm^{-1}.

Exact mass calculated for $C_{14}H_{18}O_2$: 218.1307; found: 218.1305.

^{13}Cmr ($CDCl_3$) δ_C: 22.6 (CH_3), 22.7 (CH_3), 22.7 (CH_2), 25.5 (CH_2), 30.4 (CH_2), 43.6 (CH), 47.6 (C), 125.4, 125.9, 128.9, 129.4 (aryl CH), 136.8, 140.2 (aryl C), 185.3 (COOH).

^{1}Hmr ($CDCl_3$) δ: 1.11 (s, 3H), 1.13 (s, 3H), 1.5-1.7 (m, 2H), 1.9-2.2 (m, 2H), 2.67 (m, 2H), 3.46 (m, 1H), 7.05-7.2 (m, 4H).

5.3.3 3,3-Dimethylbenzobicyclo[3.2.2]nonen-2-one (67)

Trimethylsilyl enol ether (**84**)

The three step ring expansion sequence was carried out in the standard fashion. A three-necked round-bottomed flask with a thermometer and two septa was set up under a flow of N_2. LDA was prepared at -78°C from diisopropylamine (4.0 mL, 28.8 mmol) and 2.5M n-BuLi (10 mL) in THF (10 mL). The ketone **81** (3.1g, 18 mmol) was added in THF (5 mL), and allowed to stir at -78°C for 45 min. In the meantime, a flame-dried and nitrogen purged centrifuge tube was charged with Me_3SiCl (4.5 mL, 36 mmol), Et_3N (1.5 mL) and THF (2 mL). The precipitate was removed by centifugation, and the supernatant liquid was injected rapidly into the reaction mixture. The solution was

allowed to warm to room temperature, then cooled to 0°C and added to a saturated aqueous solution of sodium carbonate in a separatory funnel. The layers were separated and the aqueous was extracted with ether (3x75 mL). The combined organic layers were washed with brine and dried over $MgSO_4$; removal of solvent left 5.15 g of yellow oil which was purified by bulb-to-bulb distillation at 120°C/1.5 Torr. Yield : 3.57g (81 %).

Cyclopropyl silyl ether (**85**)

A 2-necked round-bottomed flask equipped with a condenser, N_2 purge and septum was charged with Zn/Ag couple (2.5g, 37.7 mmol) and the entire apparatus flame-dried under a stream of N_2. After cooling, methylene iodide (2.0 mL, 25.2 mmol) and ether (5 mL) were added and the mixture heated until it began to reflux on its own. At the end of the reflux, the grey solution was sonicated for 15 min, and the silyl enol ether **84** (3.0 g, 12.6 mmol) was added. The reaction mixture was refluxed for 40 h, then cooled to 0°C and a 1:1 pyridine:ether solution was added until no more white precipitate was formed (5 mL). The precipitate was removed by suction filtration, the solid was washed with 3 x 30 mL ether and the liquor was dried with $MgSO_4$. Filtration and removal of solvent yielded 2.91 g yellow oil and bulb-to-bulb distillation, (120°C/1.5 Torr), yielded **85** (2.39 g, 71%). Exact mass calculated for $C_{16}H_{22}OSi$: 258.1441; found: 258.1443.

^{13}Cmr ($CDCl_3$) : 141.4, 139.7 (aryl C) 126.3, 125.8, 124.0, 123.8 (aryl CH), 57.7 (C), 42.6, 35.5 (CH), 25.4, 21.7 (CH_2), 19.1 (CH), 11.1 (CH_2), 1.1 ($SiMe_3$)

Benzobicyclo[3.2.2]nonan-2-one (**86**)

The cyclopropyl silyl ether **85** (2.38 g) and 3M NaOH in MeOH (25 mL) were stirred at room temperature for 18h. The mixture was poured into 100 mL of a 10 % NaCl solution and the product was extracted with 3 x 75 mL pentane. The organic layers was washed with brine and dried over $MgSO_4$. The solvent was removed to yield **86** (1.70 g, 99%).

Infrared (thin film): 1705 cm^{-1}.

Exact mass calculated for $C_{13}H_{14}O$: 186.1045; found: 186.1046.

^{13}Cmr ($CDCl_3$) δ_C : 24.5 (CH_2), 26.3 (CH_2), 31.1 (CH_2), 37.1 (CH), 38.3 (CH_2), 55.0 (CH), 127.7, 127.1_7, 126.9_6, 126.7_4 (aryl CH), 136.9, 141.9 (aryl C), 211.6 (C=O)

^{1}Hmr ($CDCl_3$) δ :1.84-2.05 (m, 5H), 2.20 (m, 2H), 2.44 (m, 1H), 3.30 (m, 1H), 3.6 (m, 1H), 7.13-7.29 (m, 4H).

3,3-Dimethylbenzobicyclo[3.2.2]nonan-2-one (**67**)

In the usual fashion, **86** (1.70 g, 9.13 mmol) was methylated using $NaNH_2$ (2.14 g, 54.8 mmol) and CH_3I (3.4 mL, 1.7 mL). After workup, 1.73 g (89%) of an oil was obtained. The oil was chromatographed through silica gel with hexanes/ethyl acetate as eluent, and the product was then sublimed (100 °C/1 Torr) to yield long white needlelike crystals, mp 97.5 - 98.5°C.

Infrared (thin film): 1692 cm^{-1}.

Exact mass calculated for $C_{15}H_{18}O$: 214.1358; found: 214.1362.

^{13}Cmr ($CDCl_3$) δ_C: 24.3 (CH_2), 28.1 (CH_2), 29.4 (CH_3), 30.1 (CH_3), 37.9 (CH), 45.3 (C), 45.9 (CH_2), 55.2 (CH), 126.4, 126.8, 127.1, 127.6 (aryl CH), 137.0, 141.9 (aryl C), 211.7 (C=O)

^{1}Hmr ($CDCl_3$) δ: 0.42 (s, 3H), 1.07 (s, 3H), 1.7-2.1 (m, 6H), 3.26 (m, 1H), 3.76 (m, 1H), 7.0-7.3 (m, 4H)

3,3-Dimethyl-6,7-benzobicyclo[3.3.1]nonen-2-one (**87**)

The ketone obtained from **67** was purified by preparative tlc as above for **75** and recrystallized from aqueous ethanol, mp 112-115°C.

Infrared (liquid film): 1698 cm^{-1}.

Exact mass calculated for $C_{15}H_{18}O$: 214.1358; found: 214.1352.

^{13}Cmr ($CDCl_3$) δ_C: 28.9 (CH_3), 29.7 (CH_3). 30.2 (CH_2), 33.7 (CH), 34.6 (CH_2), 43.0 (C), 43.6 (CH), 48.0 (CH_2), 126.4, 126.6, 128.6, 128.8 (aryl CH), 134.8, 140.7 (aryl C), 220.5 (C=O).

^{1}Hmr ($CDCl_3$) δ: 0.49 (s, 3H), 1.09 (s, 3H), 1.95 (dt, 1H, J=13.6, 2.7 Hz), 2.05 (dd, 1H, J=13.6, 4.7 Hz), 2.07-2.25 (m, 2H), 2.85 (bd, 1H, J=17.1 Hz), 2.92 (m, 1H), 3.15 (m, 1H0, 3.16 (dd, 1H, J=17.1, 7.0 Hz), 7.01 (d, 1H, J = 3 Hz), 7.12-7.17 (m, 3H).

2,2-Dimethyl-3-(1',2',3',4'-tetrahydro-1'-napthyl)propionic acid (**88**)

The single acid isolated from the runs with **67** was purified by recrystallization from ethanol to yield white needles, mp 87-88°C.

Infrared ($CHCl_3$): 2400-3400, 1698 cm^{-1}.

Exact mass calculated for $C_{15}H_{20}O_2$: 232.1464; found: 232.1462.

^{13}Cmr ($CDCl_3$) δ_C: 19.3 (CH_2), 24.6 (CH_3), 27.2 (CH_3), 28.1 (CH_2), 29.5 (CH_2), 34.7 (CH), 42.1 (C), 47.2 (CH_2), 125.6, 125.7, 128.9, 129.1 (aryl CH), 140.2, 141.7 (aryl C), 184.8 (COOH).

^{1}Hmr ($CDCl_3$) δ: 1.33 (s, 3H), 1.34 (s, 3H), 1.70 (m, 2H), 1.84 (m, 2H), 1.87 (dd,1H, J=14.5, 2.9 Hz), 2.09 (dd, 1H, J=14.5, 10.0 Hz), 2.73 (m, 2H), 2.94 (m, 1H), 7.03-7.18 (m, 4H).

5.3.4 EXPERIMENTAL FOR **CHAPTER 4**

Fenchone, hexamethyldisilazine and 2,2,6,6-tetramethylpiperidine were commercially available from Aldrich, and while the amines were stored on 4Å molecular, these compounds were use without further purification. Ketones **99** (4), **106** (4) and **119a** (5) were available from previous studies.

3-Ethyl-3-pentanol

In a dry one-necked round-bottomed flask equipped with an addition funnel, bromoethane (50 mL) in dry ether (200 mL) was added to magnesium (17.0 g) in ether (200 mL) at such a rate to maintain a gentle reflux while the solution was vigorously stirred. After complete addition, the solution was stirred for a further 1 h, whereupon 3-pentanone (52.9 mL, 0.5 mol) in ether (200 mL) was added over a 1 h period, and the mixture finally refluxed for 4 h. After cooling to 0°C, the mixture was cautiously added to 400 mL ice in a separtory funnel and 6 N HCl was added until all solids dissolved. The layers were separated and the aqueous layer was extracted with 2 x 250 mL ether. The combined organics were washed with brine (250 mL), dried over $MgSO_4$ and concentrated to 150 mL by rotary evaporation. The residue was distilled from CaH_2 and 3-ethyl-3-pentanol (**94**) was collected over molecular sieves, bp 142-143°C, yield 55.3 g (95%).

N-benzyl-9-azabicyclo[3.3.1]nonan-3-one (**107**)

The following solutions were added to a 2 L Erlenmeyer flask equipped with a magnetic stirrer : glutaric dialdehyde (95 mL, 25 wt% in water, Aldrich) in 100 mL H_2O, benzylamine (40 mL) in 400 mL H_2O containing 12 N HCl (35 mL), 1,3-acetonedicarboxylic acid (40 g) in 400 mL H_2O and potassium phosphate monobasic (23.8 g) in 100 mL water with NaOH (3.6 g). The solution was stirred at room temperature for 18 h, 12 N HCl (15 mL) was then added and the mixture heated for 1 h. The mixture was cooled to 0°C and neutralized with NaOH (37.5 g) then extracted with 6 x 250 mL CH_2Cl_2. The organics were dried over Na_2SO_4 and the solvent was removed to yield 39.4 g (70 %) of a brown syrup. While this mixture could be purified and crystallized by the method of Dupeyre and Rassat (51), it was found to be sufficiently pure by its ^{13}Cmr spectrum to use in the next step without further purification.

^{13}Cmr ($CDCl_3$) δ_C: 16.6 (CH_2), 29.3 (2xCH_2), 42.9 (2xCH_2), 53.5 (2xCH), 57.1 (CH_2), 127.1, 128.3$_1$(2), 128.3$_8$(2) (aryl CH), 139.2 (aryl C), 211.5 (C=O)

N-benzyl-9-azabicyclo[3.3.1]nonane (**108**)

A portion of the product from the previous step (25.8 g) was combined with 99 % hydrazine hydrate (23 mL, BDH) and diethylene glycol (150 mL) in a 500 mL one-necked round-bottomed flask equipped with a Dean-Stark trap and condenser. This mixture was heated to ~140°C until water collection ceased (3 h), then was cooled to room temperature and a

solution of KOH (20 g) in water (10 mL) was added. The reaction was then heated to 220°C and stirred for 3 h until nitrogen gas evolution ceased, before cooling to 0°C and careful quenching with ice (500 mL). The mixture was transferred to a separatory funnel and extracted with 3 x 500 mL CH_2Cl_2. The combined organic layer were dried (Na_2SO_4) and concentrated and the dark brown oil was distilled under vacuum. N-benzyl-9-azabicylo[3.3.1]nonane **108**, bp 115-119°C/0.2 Torr, was collected, yield 6.2 g (26 %).
^{13}Cmr ($CDCl_3$) δ_C: 20.9 (2xCH_2), 27.1 (4xCH_2), 50.5 (2xCH), 56.8 (CH_2), 126.4, 128.0(2), 128.2(2) (aryl CH), 140.7 (aryl C)

9-Azabicyclo[3.3.1]nonane (**96**)

The product from the previous step (6.2 g) was combined with palladium (500 mg, 5% on charcoal, Aldrich), acetic acid (60 mL) and perchloric acid (0.5 mL) in a Parr shaker bottle. This bottle was connected to an atmospheric pressure hydrogenator and stirred vigorously at 50°C under an atmosphere of H_2 until hydrogen uptake ceased (~700 mL, 48 h). The bottle was cooled and diluted with water and then gradually neutralized with NaOH pellets. The solution was extracted with CH_2Cl_2 (3x100 mL), and the combined organic layers were dried over $MgSO_4$. Upon removal of solvent, a solid was isolated which on a dry day had the following ^{13}Cmr resonances, δ_C: 20.6 (2xCH_2), 30.6 (4xCH_2), 46.3 (2xCH), and then could be readily purified by sublimation (75°C/0.5 Torr). However, the presence of water shifted the ^{13}Cmr signal for

the β-methylene carbon by -3.1 ppm and the following resonances were observed, δ_C: 19.0 (2xCH_2), 27.5 (4xCH_2), 46.6 (2xCH). It was found that a compound that displayed the presence of water by this nmr shift could not be purified by sublimation or extraction and the base hydrochloride was then prepared by bubbling HCl gas (prepared from H_2SO_4 and KCl) into an ethereal solution of the wet 9-ABN. The hydrochloride salt precipitated from solution and was isolated by filtration and dried on a vacuum pump.

2,2,6-Trimethylcyclohexanone (**109**)

The methylation of 2-methylcyclohexanone (1.0 g) was carried out by two cycles of the typical LDA procedure, using diisopropylamine (1.75 mL) and n-buLi (4.2 mL, 2.55 M) in THF (20 mL) and quenching with methyl iodide (1.1 mL). After workup and extraction, 2,2,6-trimethylcyclohexanone **109** was isolated (1.04 g, 83% yield), and was then purified by chromatography through alumina.

^{13}Cmr ($CDCl_3$) δ_C: 14.8, 21.4, 25.1, 25.5, 36.6, 40.6, 41.7, 45.0, 216.9.

Silyl enol ether **110**

The preparation of the silyl enol ether from **109** (177 mg) followed the standard procedure. After chromatography on silica gel, **110** was isolated in 75 % yield.

^{13}Cmr ($CDCl_3$) δ_C: 1.0 ($SiMe_3$), 17.7 (CH_3), 19.5 (CH_2), 27.5 (2xCH_3), 31.6 (CH_2), 35.1 (C), 40.0 (CH_2), 110.3, 149.9.

Cyclopropyl silyl ether **97c**

The entire product from the foregoing step was cyclopropanated in the standard fashion. The desired compound **97c** (14 mg) was isolated by preparative glc (10'x1/4" 5% SE-30 on Chromosorb W 80-100).

^{13}Cmr ($CDCl_3$) δ_C: 2.0 ($SiMe_3$), 17.7 (CH_3), 22.1, 23.6, 24.9, 28.5, 32.1, 33.9 (C), 37.2, 68.9.

Cyclopropanol **97b**

Hydrolysis of the cyclopropyl silyl ether **97c** (10 mg) was effected by stirring at room temperature overnight in THF (10 mL) containing 1 N HCl (1 mL) by the literature procedure (33). After workup and extraction a compound with the same spectral data as previously reported (48) was isolated.

^{13}Cmr ($CDCl_3$) δ_C: 17.7, 21.4, 23.5 (C), 23.8, 24.2, 27.2, 31.9, 33.1 (C), 37.2, 66.5 (C).

GENERAL PROCEDURES FOR AMIDE REACTIONS

A flame-dried two-necked round-bottomed flask equipped with a condenser and nitrogen inlet, was charged with the amine (3 equivalents), either as the solid (for 9-ABN) or as a heptane solution (TMP/HMDS). In the case of KABN reactions, potassium *t*-butoxide powder (3 equivalents, Aldrich) was added to the flask at the same time as the 9-ABN. After addition of dry heptane (15 mL), the solution was stirred at room temperature and n-buLi (3 equivalents) was slowly introduced

via syringe. The base solution was allowed to stir for 30 min, whereupon a solution of the ketone in heptane (5 mL) was introduced. This reaction was then refluxed for a period of time and aliquots were taken regularly, worked up with 1 N HCl and assayed by glc. At the point at which the reaction was judged complete, the solution was cooled and added to 1 N HCl (25 mL) and ether (25 mL) in a separatory funnel, the layers were separated and the aqueous extracted with 2x25 mL ether. The organic layers were washed with 1 N HCl (25 mL) and brine (25 mL) before drying over $MgSO_4$ and removal of solvent.

Preparation of the methyl alcohols **111** and **112**

Addition of methyllithium (0.5 mL, 1.0 M in hexanes) to the ketone (3 drops) in ether (1 mL) in a vial and subsequent quenching with water and drying over $MgSO_4$ provided the alcohols observed in the corresponding reactions with LTMP.

For **111** :

^{13}Cmr ($CDCl_3$) δ_C: 16.9, 22.1, 23.0, 25.6, 27.2, 27.2, 29.4, 40.9, 48.9, 43.0 (C), 51.9 (C), 79.7 (C).

For **112** :

^{13}Cmr ($CDCl_3$) δ_C: 14.3 (2xCH_3), 21.4 (CH_3), 24.0 (2xCH_2), 24.6$_8$ (2xCH_3), 24.7$_3$ (2xCH_3), 27.2 (2xCH_2), 39.2 (2xCH_2), 44.1 (2xC), 81.0 (C)

LAH reduction of ketones **2** and **106b**

The ketones (3-4 drops) were dissolved in dry ether (2 mL) in a small vial and LAH (~50 mg) was added with a spatula. The mixture stirred for 10 min and was quenched by the cautious addition of an aqueous solution of Na_2SO_4. After dilution with ether (5 mL), drying over $MgSO_4$, and filtration, the solvent was removed to yield the desired alcohols.

exo-/*endo*-fenchol - see ref (10).

5,5,7,7-tetramethylundecan-6-ol

^{13}Cmr ($CDCl_3$) δ_C: 14.2 (CH_3), 23.7 (CH_3), 25.5 (CH_3), 25.9 (CH_3), 26.3 (CH_2), 39.8 (C), 42.1 (CH_2), 81.9 (CHOH).

2,4-Dimethyl-2,4-diphenylpentanone and LTMP/LABN

The products from these reactions were separated by preparative glc (10'x1/4" 5% SE-30 on Chromosorb W 80-100) and characterised on the basis of the spectral data listed below.

For 113 :

^{13}Cmr ($CDCl_3$) δ_C: 25.8 (2xCH_3), 27.6 (2xCH_3), 44.1 (2xC), 85.4 (CHOH), 126.0, 126.7, 128.1 (aryl CH), 148.8 (aryl C).

For 114 :

^{13}Cmr ($CDCl_3$) δ_C: 25.1 (2xCH_3), 27.1 (CH_3), 52.5 (C), 126.0 (2), 126.8, 128.8 (2) (aryl CH), 144.1 (aryl C), 211.3 (C=O).

For 116 :

^{13}Cmr ($CDCl_3$) δ_C: 22.5, 27.3, 25.3 (3xCH_3), 43.7 (C), 77.2 (CH), 116.2 (CH_2), 126.3_0, 126.3_2, 127.2_7, 127.3_1 (2), 127.8, 127.9, 128.1 (2) (9xaryl CH), 137.6, 144.1, 145.5, 146.6 (sp^2 C)

^{1}Hmr ($CDCl_3$) δ: 1.20 (s, 3H), 1.26 (s, 3H), 1.97 (t, 3H, J~1.0 Hz), 4.80 (d, 1H, J ~ 1.0 Hz), 5.09 (s, 1H), 5.19 (d, 1H, J~1.0 Hz), 7.0-7.3 (m, 9H)

3,3-Dimethylbenzobicyclo[3.2.1]octen-2-one (**65**) and LABN

The sole product from the runs with LABN and **65** was isolated by preparative glc (5'x1/4" 15 % OV-101 on Chromosorb G 100-120); its spectral data are recorded below:

Exact mass calculated for $C_{14}H_{16}O$: 200.1202; found: 200.1204.

^{13}Cmr ($CDCl_3$) δ_C: 24.3 (CH_3), 26.5 (CH_3), 32.4 (CH_2), 34.9 (CH_2), 37.5 (CH), 44.9 (CH_2), 42.9 (C), 123.7, 127.3, 128.9 (aryl CH), 128.5, 143.7, 151.8 (aryl C), 202.9 (C=O)

^{1}Hmr ($CDCl_3$) δ: 1.23 (s, 3H), 1.24 (s, 3H), 1.63 (q, 1H, J=11.5 Hz), 1.73 (q, 1H, J=12.5 Hz), 2.08 (dd, 1H, J=12.5, 5.0 Hz), 2.40 (dtd, J=11.5, 6.5, 1.1 Hz), 2.8-3.1 (m, 2H), 3.32 (m, 1H), 7.24 (t, 1H, J=7.6 Hz), 7.39 (dd, 1H, J=7.6, 0.9 Hz), 7.70 (d, 1H, J=7.6 Hz).

2,5,5-Trimethyl-2-phenylcyclopentanone (**119a**) and LABN

The product mixture obtained from the reaction of **119b** with LABN was separated by preparative glc (12'x1/4" 6% FFAP on Chrmosorb W 60-80) and the spectral data for products isolated are listed below. Alcohols **123** were identified after comparison of the ^{13}Cmr spectra to that of the 95:5 mixture of diasteromers produced in the LAH reduction of **119a**. Benzocyclobutenol **122a** was characterized by its spectral data.

For 123a :

^{13}Cmr ($CDCl_3$) δ_C: 24.2, 29.5, 31.3, 34.0, 38.1, 41.5 (C), 51.1 (C), 88.4 (CH), 126.2, 127.5, 128.5, 145.2.

For 123b :

^{13}Cmr ($CDCl_3$) δ_C: 23.0, 24.4, 30.8, 35.0, 37.7, 40.8 (C), 49.9 (C), 88.0, 125.7, 127.3, 128.2, 151.0.

For 122a:

Exact mass calculated for $C_{14}H_{18}O$: 202.1358; found: 202.1364.

^{13}Cmr ($CDCl_3$) δ_C: 20.1 (CH_3), 21.4 (CH_3), 23.9 (CH_3), 33.9 (CH_2), 38.0 (CH_2), 41.3 (C), 59.1 (C), 92.5 (C), 121.1 122.6, 127.5, 129.5 (4xaryl CH), 145.8, 149.9 (aryl C).

^{1}Hmr ($CDCl_3$) δ: 1.02 (s, 3H), 1.11 (s, 3H), 1.38 (s, 3H), 1.0-1.9 (m, 4H), 7.0-7.35 (m, 4H)

Ethyl pyruvate diethyl ketal (124)

Ethyl pyruvate (Sigma, 4.0 mL) was added to trimethylsilyl chloride (4.0 mL) and dry ethanol (50 mL) in a 50 mL one-necked round-bottomed flask, and the mixture stirred for 12 h at room temperature. The solution was added to water (200 mL) in a separatory funnel and extracted with ether (3x150 mL). The combined organic layers were washed with 5% NaOH and brine before drying over $MgSO_4$. The solvent was removed to yield 6.29 g (94%) of pure ketal **124**.

^{13}Cmr ($CDCl_3$) δ_C: 13.7 (CH_3), 14.7 (2xCH_3), 21.6 (CH_3), 57.4 (2xCH_2), 60.8 (CH_2), 99.1 (C), 169.5 (C=O).

2,2-Diethoxypentan-2-one (**125a**)

A flame-dried 50 mL two-necked round-bottomed flask equipped with an addition funnel and a nitrogen purge was charged with freshly milled magnesium (123 mg) from a block of triply sublimed magnesium. To this flask was added benzene (10 mL), THF (1 mL), and ethyl iodide (0.45 mL), and the mixture stirred until the magnesium had entirely dissolved. The mixture was then cooled to 5°C and triethylamine (1 mL) was added to the mixture followed by ester **124** (240 mg) in benzene (2 mL). This concoction was allowed to stir for 6 h at 5-10°C before quenching with 4N HCl (3 mL). The reaction was added 30 mL each of water and ether in a separatory funnel and the layers were separated. The aqueous layer was extracted with ether (2x30 mL), and the ether extracts were washed with saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. Removal of solvent yielded pure **125a** in 55% yield.
^{13}Cmr ($CDCl_3$) δ_C: 7.1 (CH_3), 15.1 (2xCH_3), 20.6 (CH_3), 30.9 (CH_2), 57.3 (2xCH_2), 102.1 (C), 210.0 (C=O).

2,2-Diethoxy-4,4-dimethylpentan-3-one (**125b**)

After dimethylation of **125a** (450 mg) in the standard method, **125b** was isolated and chromatographed on alumina with 20% ether in petrol as eluent, yield 468 mg (89%).
Infrared (liquid film): 1713, 1057, 1134, 1165 cm^{-1}.
Exact mass calculated for $C_9H_{17}O_2$ (M-OEt): 157.1230; found: 157.1232.

^{13}Cmr ($CDCl_3$) δ_C: 15.0 (2xCH_3), 22.3 (CH_3), 26.7 (3xCH_3), 44.3 (C), 57.1 (2xCH_2), 104.5 (C), 212.9 (C=O).

^{1}Hmr ($CDCl_3$) δ: 1.10 (s, 6H), 1.13 (s, 9H), 1.27 (s, 3H), 3.26-3.43 (m, 4H).

Preparation of α-methoxycyclohexanone (128)

Cyclohexene (4.1 g) was epoxidized with *meta*-chloroperbenzoic acid (MCPBA, 9.5 g) in CH_2Cl_2 (75 mL) in the standard fashion (80%). After workup and extraction, a 68 % yield of cyclohexene oxide was obtained.

^{13}Cmr ($CDCl_3$) δ_C: 18.9, 23.1, 51.1.

Cyclohexene oxide (3.3 g), methanol (100 mL) and *para*-toluenesulphonic acid were refluxed for 1 h in a 250 mL one-necked round-bottomed flask, and the MeOH was subsequently removed by rotary evaporation. The residue was partitioned between water (100 mL) and ether (100 mL), the layers were separated and the aqueous layer was extracted with ether (2x100 mL) before the ethereal extracts were dried ($MgSO_4$) and concentrated to afford α-methoxycyclohexanol (3.27g, 75 %).

^{13}Cmr ($CDCl_3$) δ_C: 23.4, 23.5, 28.0, 31.9 (4xCH_2), 55.8 (CH_3), 72.8, 84.4 (2xC).

This alcohol was oxidized with PCC in the standard fashion to yield **128** in 96 % yield.

^{13}Cmr ($CDCl_3$) δ_C: 22.7, 27.2, 33.7, 40.1, 57.1, 83.7, 209.5.

2-Methoxy-2,6,6-trimethylcyclohexanone (**127a**)-

Dimethylation of **128** proceeded by the standard method, and ketone **127a** was isolated in 75 % yield after chromatography on alumina.

Infrared (liquid film): 1703 cm^{-1}. lit (85) (1705 cm^{-1}).

Exact mass calculated for $C_{10}H_{18}O_2$: 170.1307; found: 170.1303.

^{13}Cmr ($CDCl_3$) δ_C: 17.2, 19.9, 25.4, 27.2, 40.5, 41.2, 45.0, 51.4, 79.7, 214.0.

cis-2-Methoxy-2,6,6-trimethylcyclohexanol (**129a**)

Addition of triethylborohydride (0.5 mL, 1.0 M in hexane, Aldrich) to a ethereal solution of **127a**, followed by quenching with water, drying over $MgSO_4$, and removal of solvent yielded **129a** whose spectral data are given below.

^{13}Cmr ($CDCl_3$) δ_C: 18.0, 20.8, 22.5, 31.3, 32.7, 36.2 (C), 39.7, 48.0 (C), 76.8, 82.1.

This product was the major isomer in the homoenolization runs with **127a** and the minor isomer in a LAH reduction for which the spectral data of the major isomer are given below.

For **129b** :

^{13}Cmr ($CDCl_3$) δ_C: 17.0 (CH_3), 19.3 (2xCH_3), 30.8, 33.7, 35.5 (C), 38.2, 48.2 (C), 78.0, 81.2.

2,6,6-Trimethyl-2-methylthiocyclohexanone (**127b**)

Dimethylation of α-thiomethylcyclohexanone (60) was performed as usual, and ketone **127b** was isolated in 60 % yield

after flash chromatography over silica gel.

Infrared (liquid film): 1686 cm^{-1}.

Exact mass calculated for $C_{10}H_{18}OS$: 186.1079; found: 186.1073.

^{13}Cmr ($CDCl_3$) δ_C: 12.0 (CH_3), 17.9 (CH_2), 24.5 (CH_3), 28.0 (CH_3), 29.5 (CH_3), 39.6 (CH_2), 40.0 (CH_2), 43.8 (C), 51.1 (C), 210.7 (C=O).

^{1}Hmr ($CDCl_3$) δ: 1.06, 1.31, 1.40, 1.85 (4xMe), 1.45-2.15 (3xCH_2).

Reaction of **127b** with *t*-BuOK

The neutral product from the homoenolization runs with **127b** was taken up in pentane and extracted with two portions of 3 N NaOH, the aqueous layers were acidified, then extracted with ether. After drying ($MgSO_4$) and removal of solvent, disulphide **131** was isolated and characterized on the basis of the spectral data below.

Infrared (liquid film): 1696 cm^{-1}.

Exact mass calculated for $C_{20}H_{34}O_2S_2$: 370.2000; found: 370.1994.

^{13}Cmr ($CDCl_3$) δ_C: 17.6 (2xCH_2), 25.6, 25.7 (2xCH_3), 27.3, 27.4 (2xCH_3), 27.6 (2xCH_3), 35.9_5, 36.0 (2xCH_2), 39.4_1, 39.4_4 (2xCH_2), 44.4_3, 44.4_6 (2xC), 49.2, 49.4 (2xC), 51.2, 51.4 (2xCH_2), 218.6_0, 218.6_5 (2xC=O).

^{1}Hmr ($CDCl_3$) δ: 1.082, 1.098 (2xs, 6H), 1.124 (s, 6H), 1.188, 1.192 (2xs, 6H), 1.2-2.0 (m, 12 H), 2.753 (d, 1H, J=12.84 Hz), 2.737 (d, 1H, J=12.87Hz), 3.227 (d, 1H, J=12.84 Hz), 3.291 (d, 1H, J=12.87).

The components of the neutral mixture were then separated by flash chromatography through silica with hexanes as eluent. Compounds **132** and **109** were identified on the basis of their ^{13}Cmr spectra; proof for **109** came from independent synthesis (5.4.2), while **132** was characterized by its spectral data.

For **132**:

Infrared (liquid film) 1696 cm^{-1}.

Exact mass calculated for $C_{10}H_{18}OS$: 186.1078; found 186.1084.

^{13}Cmr ($CDCl_3$) δ_C: 17.7 (CH_2), 26.0 (CH_3), 27.0 (CH_3), 27.7 (CH_3), 34.4 (CH_2), 35.2 (CH_2), 39.3 (CH_2), 44.5 (C), 49.7 (C), 219.4 (C=O).

^{1}Hmr ($CDCl_3$) δ: 1.09 (s, 3H), 1.14 (s, 3H), 1.18 (s, 3H), 1.6-2.1 (m, 6H), 2.25 (dd, 1H, J= 13.6, 9.9 Hz), 3.03 (dd, 1H, J=13.6, 8.0 Hz)

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