THE SYNTHESIS AND LITHIUM-AMMONIA REDUCTION OF TRANS-1,7-DIMETHYLTRICYCLO(4.4.0.$0^{2,6}$)DECAN-3-ONE

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THE SYNTHESIS AND LITHIUM-AMMONIA REDUCTION OF

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Finally, the author owes a great deal to his wife, who patiently provided moral support and understanding during the time devoted to this research.

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GLOSSARY OF ABBREVIATIONS

Anal.	C, H analysis
b.p.	boiling point
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
cps	cycles per second
ir	infrared
J	coupling constant (nmr spectrum)
nmr	nuclear magnetic resonance
ppm	parts per million (nmr spectrum)
TMS	tetramethylsilane, nmr standard
glc	gas-liquid chromatography
vpc	vapor phase chromatography

SUMMARY

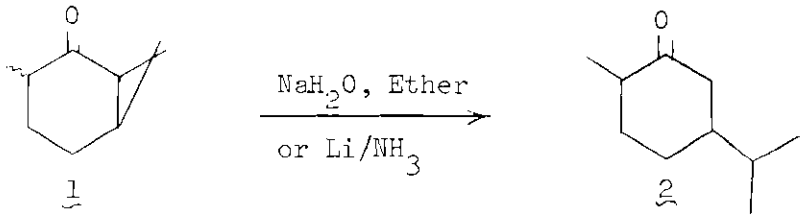
It was the purpose of this research to synthesize trans-1,7-dimethyltricyclo(4.4.0.$0^{2,6}$)decan-3-one and to investigate its behavior when treated with lithium in liquid ammonia. The key steps in the synthesis required the discovery of experimental conditions that would permit the less stable of two possible isomers to be synthesized through two reaction steps. The synthesis used standard synthetic techniques adapted to a previously reported synthetic route to form the desired tricyclic ketone.

It had previously been found that when cis-1,7-dimethyltricyclo(4.4.0.$0^{2,6}$)decan-3-one was treated with lithium in liquid ammonia a high percentage of inversion took place at the βcarbon. When trans-1,7-dimethyltricyclo(4.4.0.$0^{2,6}$)decan-3-one was treated with lithium in liquid ammonia under similar conditions, the same results were evident. This behavior is in contrast with results that would be expected if the reductive cleavage proceeded through a radical-anion intermediate and could possibly be attributed to a concerted mechanism.

CHAPTER I

INTRODUCTION

In recent years interest has intensified in the field of alkali metal-liquid ammonia reductive cleavage of conjugated cyclopropyl rings. In fact, as Staley notes in his review of the reductive cleavage of cyclopropane rings (1), most of the research in this area has been conducted in the past five or six years. This is not to say however that this is a completely new field because as early as 1895, Bayer reported the "suspended metal" reduction of carone, 1, to carvomenthol, 2, by sodium in moist ether, although the structure of 1 and 2 were not known at the time.

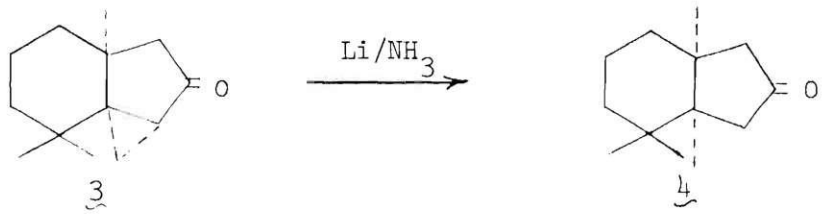


1 2

This particular transformation was later confirmed by Dauben and Deviny (3) and Volkenburgh and co-workers (4). Many other examples of the reductive cleavage of cyclopropyl rings have been reported in recent years and a comprehensive summary is given by Staley in his review article (1). Most of the reported work in the area of reductive cleavage has been directed to the determination of which bond within the cyclopropyl ring will be opened, i. e., the regioselectivity of

the reaction.

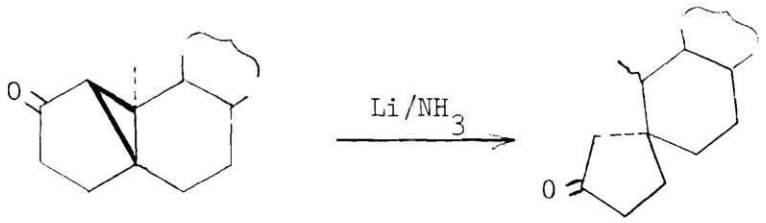
The research related to determining the regioselectivity of reductive cyclopropyl ring opening has led to an important observation, reported initially by Norin (5). In 1963, Norin found in his studies with thujopsene that an almost quantitative yield of 4 resulted from the reduction of cyclopropyl ketone 3 (6).



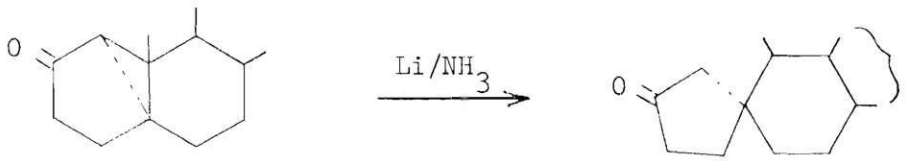
3 4

He subsequently recognized the generality of the regiospecific opening of three-membered rings of conjugated cyclopropyl ketones with lithium in liquid ammonia and made the important observation that "the cyclopropyl bond which is cleaved is the one possessing maximum overlap with the π orbital of the carbonyl groups" (5).

Dauben and Deviny (3) supported this generality in their work (equation (1)), as did Laing and Sykes (7) (equation (2))



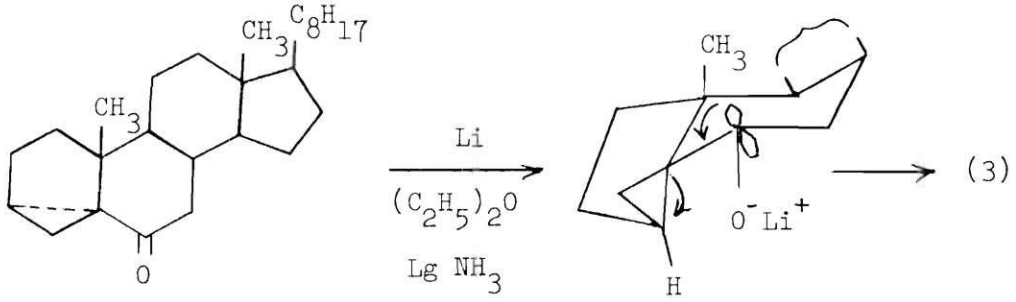
(1)



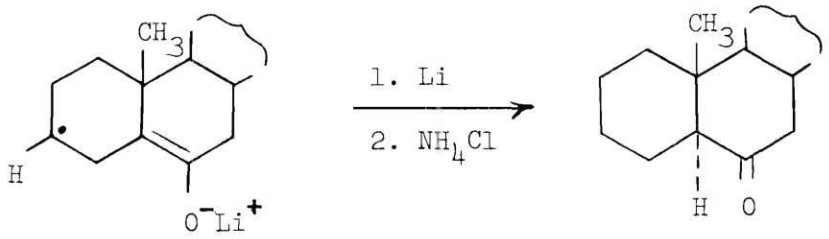
(2)

Many additional examples of this general characteristic have been reported, but Staley feels that many other factors could also be considered to be important (1). This concept will not be addressed in this paper.

The mechanism of the reductive cleavage of cyclopropyl rings is a question that has not yet been fully answered. Some workers feel that the mechanism proceeds through a dianion intermediate during the ring opening step, but most workers have assumed an anion-radical mechanism (1). An example of the anion-radical mechanism is given by House (8,3).

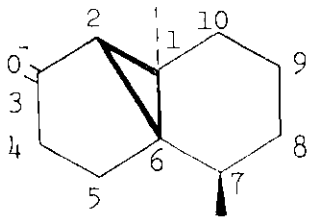


(3)



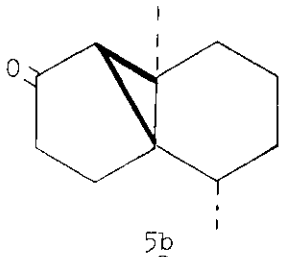
Further work by Staley (9) has lent additional support to the anion radical mechanism, but the evidence is not absolutely conclusive. Staley's work was not conducted with cyclopropyl ketones and he states that since the cyclopropyl ketones possess a highly electronegative oxygen atom, a dianion cleavage mechanism is somewhat more likely (1). Needless to say, more work needs to be done in this area and it is hoped that the work reported here will shed more light in the area of reductive cyclopropyl ketone ring cleavage.

In order to study the stereochemical outcome at the β-position in reductive cleavages of cyclopropyl ketones and also to obtain additional information concerning the mechanisms of the reductive ring opening, a relatively simple pair of compounds were chosen for experimentation.



5a

and



5b

It should be noted that the compounds selected are quite similar to the steroidal derivatives used by Dauben and Deviny (3) and by Laing and Sykes (7). However, in the steroidal cases, the stereochemistry of the products had not been established.

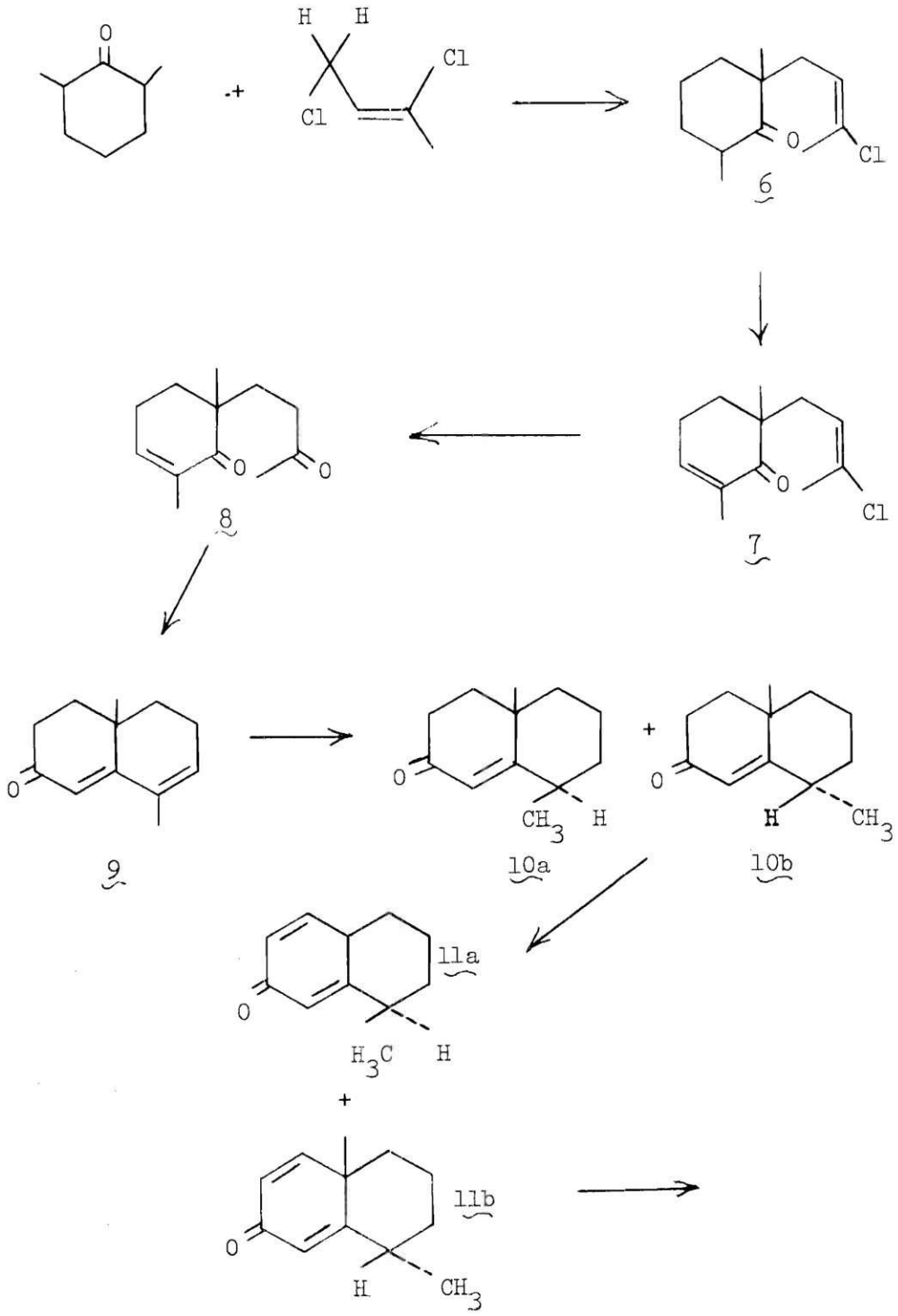
The primary reasons for the selection of these particular compounds was that previous work had been conducted on the cyclopropyl

ketone 5b by Piers and Worster (10). These workers found that when the cyclopropyl ketone 5b was treated with lithium in liquid ammonia, the ketone derived from inversion at the β-carbon was the major product obtained. Using low temperature conditions, the ratio of the inversion to the retention products obtained was greater than 9:1. This was in contrast to the photoreduction of 5b in 2-propanol which afforded an approximate 2:3 ratio of inversion to retention products. The results of Piers and Worster were further substantiated by Chao (11) who found approximately the same ratios of inversion to retention products when he treated the cyclopropyl ketone 5b with lithium in liquid ammonia at -78°C.

It was felt that by synthesizing the cyclopropyl ketone 5a and treating it with lithium in liquid ammonia under the same conditions as those used by Piers and Worster, a direct comparison could be made with the results of Piers and Worster. It was felt that this comparison would yield more information concerning the mechanism of the reaction; specifically, it was hoped that the results would shed some light on the possibility that the reductive ring opening might proceed by a concerted or near-concerted mechanism.

The synthesis of the cycloporpyl ketone 5a employed no new or novel techniques, but did require extensive experimentation in order to find proper conditions for the production of the desired compound. The final approach employed for the synthesis of 5a involved a combination of various techniques previously reported and is depicted in Scheme I.

Scheme I


O
H H
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6
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7
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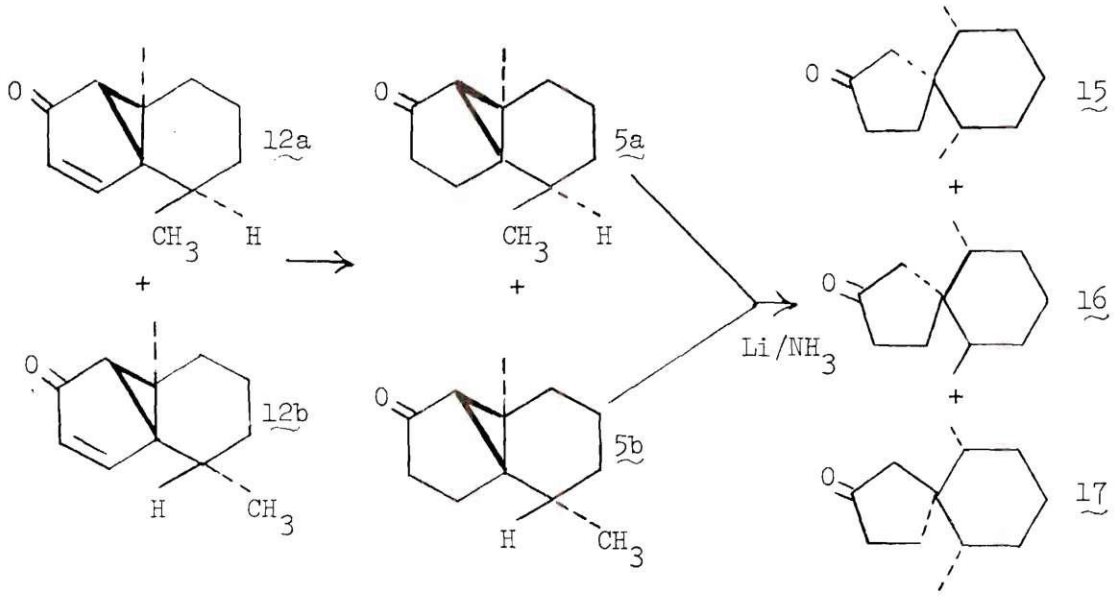


A detailed discussion of the experimentation used to arrive at this scheme is given in Chapter IV of this dissertation. Also, all other experimental routes explored will be discussed in Chapter IV.

CHAPTER II

INSTRUMENTATION AND EQUIPMENT

Infrared spectra were obtained on a Perkin Elmer 457 Spectrophotometer using a liquid film or NaCl 0.1 mm cells with carbon tetrachloride used as the solvent. Proton magnetic resonance spectra were recorded on a Varian A-60D Spectrometer using carbon tetrachloride as the solvent. Positions of nmr absorptions are reported in parts per million (ppm) downfield from tetramethysilane (TMS). The abbreviations s, d, and q, refer respectively to singlet, doublet, and quartet. Solvents were removed with a commercial rotating evaporator unless otherwise stated. All inorganic chemicals used were reagent grade. A Hanau HK 6/20 low pressure mercury lamp or a Hanovia, 450-watt high pressure mercury vapor lamp with Pyrex filter was used for all irradiation experiments. Vapor phase chromatographic studies were conducted on a Perkin Elmer 881 Gas Chromatograph equipped with either a 6' x 1/8" Carbowax K-20M on Chromosorb W HMDS or a 6' x 1/8" Apiezon L on Chromosorb W HMDS column. Preparative vapor phase chromatography was conducted on a Areograph A-90P3 Gas Chromatograph using a 6' x 1/4" Carbowax K20M on Chromosorb W HMDS column. All analyses were conducted by the Atlantic Microlab, Atlanta, Georgia.

CHAPTER III

EXPERIMENTAL

2,6-Dimethyl-2-(γ-chlorocrotyl)cyclohexanone(6)

This compound was prepared by the method of Marshall and Schaeffer (12). Liquid ammonia (300 ml) was collected in a 1-l three-necked round-bottom flask equipped with a mechanical stirrer and reflux condenser. Eighteen grams of sodium and 0.5 g of anhydrous $FeCl_3$ was added and the mixture was allowed to react for one hour. After the ammonia was allowed to evaporate, 300 ml of benzene was added to the sodium amide residue. To this mixture 96.6 g (0.767 mole) of 2,6-dimethyl-cyclohexanone was added dropwise by means of a dropping funnel. The solution was then heated to reflux temperature and allowed to reflux for three hours. The mixture was then allowed to cool overnight. By means of a dropping funnel, 84.0 g (0.672 mole) of 1,3-dichlorobutene were added dropwise to the solution over a period of 45 minutes. The mixture was then heated and allowed to reflux for two hours and then allowed to cool to room temperature. Two hundred ml of 5% HCl were then added dropwise and the solution stirred for 20 minutes. The product was isolated by extraction with ether. After removal of the solvent *in vacuo*, distillation of the residue gave 6, 97.4 g (62.3 percent); bp 80-92°/0.3 mm. (lit[12] bp 92-94°/0.2 mm).

2,6-Dimethyl-2-(γ-chlorocrotyl)-5-cyclohexenone(7)

This compound was prepared by the method of Marshall and Schaeffer (12). A solution of 80.0 g (0.391 mole) of the chlorocrotyl ketone 6 in 400 ml of acetic acid was placed in a 3-l three-necked round-bottom flask equipped with a mechanical stirrer and dropping funnel. The reaction mixture was stirred continuously as 228 ml of 2M bromine in acetic acid was added dropwise over a period of 1.5 hours. The mixture was stirred for an additional 0.5 hr and then 2 l. of water were added. The reaction mixture was extracted with ether and the combined extracts were washed with water, aqueous sodium bicarbonate (caution!), and saturated brine, and dried over anhydrous magnesium sulfate.

The crude bromo ketone was dehydrobrominated by treatment with calcium carbonate. A solution of the crude bromo ketone and 1200 ml of N,N-dimethylacetamide was placed in a 2-l single-necked round-bottom flask and treated with 67.5 g of calcium carbonate. A reflux condenser was fitted to the flask and the solution heated and allowed to reflux for 30 minutes. After cooling to room temperature, most of the solvent was removed at reduced pressure and the residue was thoroughly triturated with hot hexane. The combined hexane portions were washed with water, and saturated brine and dried over anhydrous magnesium sulfate. The product was then distilled under reduced pressure to give 62.0 g (74.9 percent) of 7, bp. 92-103°/0.5 mm (lit[12] bp. 82-90°/0.3 mm).

2,6-Dimethyl-2-(3-oxybutyl)-5-cyclohexene-1-one(8)

This compound was prepared by the method of Marshall and Schaeffer (12). Sulfuric acid (180 ml) was placed in a 500 ml three-necked round-bottom flask and the flask cooled to 0° by means of an ice bath. Nitrogen was bubbled through the sulfuric acid by means of a sintered glass dispersion tube. The chlorocrotyl enone 7 (60.0 g/0.283 mole) was added dropwise over 15 minutes to the cooled sulfuric acid by means of a dropping funnel and the solution was allowed to stir at 0° for one hour. The reaction mixture was poured into one liter of a rapidly stirred ice-water slurry. The product was extracted with ether and the combined ether extracts were washed with water, aqueous sodium bicarbonate, and saturated brine, and then dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo and distillation of the residue gave 8 (45.1 g, 82.0 percent); bp. 92-94°/0.2 mm (lit[12]; bp 97-108°/0.5 mm).

8,10-Dimethyl-1(9),7-hexal-2-one(9)

This compound was prepared by the method of Marshall and Schaeffer (12). In a 2-l three-necked round-bottom flask equipped with a reflux condenser, a mechanical stirrer, and a Dean-Stark trap was placed 950 ml of freshly distilled toluene, 54.0 g (0.232 mole) of the diketone 8, and 13.4 g of p-toluenesulfonic acid hydrate. The mixture was heated to reflux temperature and was allowed to reflux for three hours with azeotropic distillation of water. The mixture was cooled to room temperature and the product was isolated by pouring the mixture into 500 ml of saturated aqueous sodium bicarbonate and

then extracting the product with ether. The combined ether extracts were washed with water and saturated brine, and then dried with anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the residue was distilled to give 37.3 g (91.8 percent) of the dienone 9, bp. 86-93°/0.2 mm (lit[12]; bp. 70-101°/0.1 mm).

cis and *trans*-8,10-Dimethyl-1(9)-octal-2-one(10a and 10b)

Following a procedure derived from that reported by Burn, Kirk, and Petrow (13), a mixture of the *cis* and *trans*-8,10-dimethyl-1(9)-octal-2-one, 10a and 10b, was prepared. To a 500 ml three-necked round-bottom flask equipped with a magnetic stirrer and a reflux condenser was added 250 ml of 95 percent ethyl alcohol, 5.40 g (30.7 mole) of the dienone 9, 50 ml of cyclohexene, and 2.50 g of 10 percent palladium on carbon. The mixture was refluxed for two hours under a nitrogen atmosphere. The reaction mixture was allowed to cool to room temperature and then the catalyst removed by filtration through a scintered glass funnel. Removal of the solvent *in vacuo* and distillation of the residue gave 4.96 g (90.5 percent) of a mixture of *cis* and *trans*-dimethyl octalones, 10a and 10b bp. 75-80°/0.1 mm. No attempt was made at this time to separate the two isomers and the mixture was used immediately in the next step of the reaction scheme.

In addition to the expected absorptions of the *trans* enone 10b as reported by Marshall and Schaeffer (12), nmr spectrum of the

mixture of enones exhibited the following absorptions assigned to the cis isomer, 10a: nmr $\delta^{CCl_4}_{TMS}$ 5.60 (H-1, s), 1.32 (angular CH_3, s), and 1.23 (C-8 CH_3, d, J=7.5 cps). From the nmr data, the ratio of the cis to the trans isomer was shown to be approximately 4:1.

cis and trans-8,10-Dimethyl-1(9),3-hexal-2-one(11a and 11b)

Four and ninety-six hundreths grams (27.9 mmole) of the mixture of enones 10a and 10b and 6.30 g of 2,3-dichloro-5,6-dicyanobenzoquinone was dissolved in 250 ml of benzene in a 500 ml three-necked round-bottom flask fitted with a reflux condenser and magnetic stirrer. The mixture was heated and allowed to reflux for 20 hours under a nitrogen atmosphere. After cooling to room temperature, the solution was filtered through a scintered glass funnel to remove the precipitate, 2,3-dichloro-5,6-dicyanohydroquinone, formed during the reaction. The solution was then washed with freshly prepared 2 percent sodium hydroxide, water, saturated aqueous sodium bicarbonate and saturated brine, and dried over anhydrous magnesium sulfate. The excess solvent was removed in vacuo and distillation of the residue gave 3.46 g (70.8 percent) of a mixture of the cis and trans cross-conjugated dienones 11a and 11b, bp 80-84°/0.1 mm. No attempt was made to separate isomers and the mixture was used immediately in the next step of the reaction scheme.

In addition to the expected absorptions of the trans dienone 11b as determined by Chao (11), the nmr spectrum of the distilled mixture

exhibited the following absorptions assigned to the cis isomer 11a: nmr $\delta^{CCl_4}_{TMS}$ 1.33 (angular CH_3, s), and 1.30 (C-8 CH_3, d, J=7.8 cps). From the nmr data it was also noted that other side products were formed in the reaction. The ratio of 11a:11b was determined to be approximately 2:1.

trans and cis 1,7-Dimethyl-tricyclo(4.4.0.$0^{2,6}$)dec-4-en-3-one(12a and 12b)

The mixture containing the cis and trans cross-conjugated dienones 11a and 11b (3.46 g) was dissolved in 300 ml of dioxane (freshly dried by distillation from sodium) and irradiated with a Hanau HK 6/20 low pressure mercury lamp for 4.5 hours. The mixture was stirred by passing a rapid stream of nitrogen through the solution. After the irradiation was completed, the solvent was removed in vacuo and the oil obtained was placed on a column of 80.0 g of silica gel and eluted with benzene-hexane mixtures. Elution with 50 percent benzene-hexane gave 0.742 g of a mixture of the trans and cis lumi-ketones 12a and 12b. Vapor phase chromatographic analysis using a 6' x 1/8" Apiezon L column showed the mixture to be a 2:1 ratio of 12a:12b. The retention times of 12a and 12b were found to be 4.2 and 5.4 minutes at 160°C with a flow rate of 60 ml/minute. Analytical samples of the two lumi-ketones were collected by preparative vapor phase chromatography using a 6' x 1/4" Carbowax K-20M column at a constant temperature of 155°C and a flow rate of 30 ml/minute. Retention times exhibited were 15.7 and 19.0 minutes respectively for

12a and 12b.

The properties of 12b were found to match those reported by Kropp and Erman (14). The lumi-ketone 12a exhibited the following properties: $\lambda_{max}^{CCl_4}$ 3.37, 3.41, 3.48, 5.90 (C=0), 6.90, 7.28, 7.50, and 8.48μ; nmr $\delta_{TMS}^{CCl_4}$ 7.18 (H-1, q) and 5.78 (H-1, q) (J_{AB}=5.5, J_{AX}=1.0, J_{BX}=1.0 cps), 1.18 (angular CH_3, s), and 0.95 ppm (C-7 CH_3, d, J=6.7 cps).

Anal. $C_{10}H_{16}O$ Found: C, 81.84, H, 9.21

Calc: C, 81.76, H, 9.17

trans-1,7-Dimethyltricyclo(4.4.0.$0^{2,6}$)decan-3-one(5a)

Six hundred sixty milligrams of the mixture of lumi-ketones 12a and 12b were added to 200 ml of 95 percent ethyl alcohol and 150 mg of 10 percent palladium on carbon and the solution shaken on a Parr hydrogenation apparatus under 22.5 psi of hydrogen for three hours. Hydrogen uptake was not measured for this reaction. The solution was filtered through a scintered glass funnel and the solvent removed in vacuo to give 580 mg of a yellow oil. The oil was then placed on 18.0 g of silica gel and eluted with benzene-hexane mixtures. Elution with 5 percent benzene-hexane yielded 70 mg of pure 5a. Further elution with 50 percent benzene-hexane yielded 240 mg of a mixture of isomers shown by vapor phase chromatographic analysis on a 6' x 1/8" Apiezon L column to be greater than 75 percent trans isomer. The residue was shown by VPC to be extremely rich in the cis isomer and was not further utilized.

Further separation of the mixture with the high trans:cis ratio was conducted utilizing preparative vapor phase chromatography on a 6' x 1/4" Carbowax K-20M column at a constant temperature of 155°C and constant flow rate of 120 ml/minute. Retention times for 5a and 5b were found to be 10.6 and 13.2 minutes respectively. An additional 59 mg of the pure ketone 5a were collected.

The trans-ketone 5a exhibited the following properties which are in agreement with those reported by McCurry (15,16): ir $\lambda_{max}^{CCl_4}$ 3.42, 3.48, 5.82 (C=0), 6.85, 8.08, 8.42, and 11.10μ; nmr $\delta_{TMS}^{CCl_4}$ 1.17 (angular CH_3, s), 0.96 (C-7 CH_3, d, J=6.5 cps).

Anal. $C_{10}H_{18}O$ Found: C, 80.85, H, 10.26

Calc: C, 80.83, H, 10.20.

A Representative Example of the Treatment of trans,1,7-Dimethyltricyclo(4.4.0.$0^{2,6}$)decan-3-one with Lithium in Ammonia

The ketone 5a (25 mg) was dissolved in ca 10 ml of anhydrous tetrahydrofuran and was added dropwise over a period of 30 minutes to ca 25 ml of dry ammonia, which contained 12.5 mg of lithium metal, in a 100 ml three-necked round-bottom flask equipped with a magnetic stirrer, acetone-Dry Ice condenser, and dropping funnel. The mixture was stirred for two hours and excess ammonium chloride was added and the resulting reaction mixture was stirred for an additional 15 minutes. The ammonia was then evaporated from the reaction mixture by allowing it to stand at room temperature for ca 1.5 hours. To the residue was added a 50:50 water:ether mixture. The water layer was extracted

several times with ether and the combined ether layers were washed with 5 percent HCl, aqueous soidum bicarbonate, saturated brine and dried over anhydrous magnesium sulfate. The solvents were removed *in vacuo* leaving a dark oil. The oil was dissolved in approximately 5 ml of acetone and oxidized by dropwise addition of Jone's Reagent. Excess Jone's Reagent was neutralized by addition of isopropyl alcohol until a consistent green colored solution was obtained. The solution was then filtered and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the resulting oil was analyzed by nmr and gas chromatography on a 6'x 1/8" Carbowax K-20M column. The retention times of 15, 16, and 17 at 160°C and a flow rate of 60 ml/minute were found to be 7.2, 8.6, and 7.5 minutes respectively. In previous work using acetophenone as a standard, Chao (11) determined that the vpc response factors of 16 and 17 are almost equal. Time did not permit the determination of the response factor of 15, but due to the similarity of structure of 15, 16, and 17, the response factor of 15 was assumed to be nearly equal to that of 16 and 17. Consequently, the ratios of the areas of the peaks as determined by vpc are reported and are tabulated in Chapter IV.

Attempted Catalytic Hydrogenations of 8,10-Dimethyl-1(9), 7-hexal-2-one(9)

a. Hydrogenation on Parr Apparatus using a Palladium Catalyst

To a 500 ml hydrogenation flask was added 1.00 g of the dienone 9, 100 ml of 95 percent ethyl alcohol, and 0.20 g of 10 percent palladium on carbon. The flask was placed on a Parr low pressure

hydrogenation apparatus under a pressure of 25 psi of hydrogen and was shaken for 20 minutes. The solution was filtered through a scintered glass funnel and the solvent removed *in vacuo* to give 0.773 g of a yellow oil. A nmr analysis of the oil revealed that the dienone 9 had been reduced completely to the corresponding saturated ketone.

b. Hydrogenation on Parr Apparatus Using a Homogeneous Catalyst

To a 500 ml hydrogenation flask was added 0.50 g of the dienone 9, 100 ml of 95 percent ethyl alcohol, and 0.10 g of the homogeneous catalyst tris-(triphenylphosphine)rodium chloride. Different times of hydrogenation and different hydrogen pressures were tested using the same quantities of reactant, catalyst, and solvent. In each case, the hydrogenation flask was placed on the Parr apparatus and shaken for 10 minutes (23 psi), 1 hour (25 psi), 21 hours (37 psi) and 24.5 hours (30 psi). After each reaction, the solution was filtered through a scintered glass funnel and the solvent removed *in vacuo* yielding a dark oil. A nmr analysis of each oil indicated that no reaction had taken place.

c. Hydrogenation at Atmospheric Pressure Using a Palladium Catalyst

Five milligrams of 10 percent palladium on carbon and 100 ml of 95 percent ethyl alcohol were placed in a 250 ml single-necked round-bottom flask equipped with a magnetic stirrer and the flask attached to the atmospheric hydrogenation apparatus. After the apparatus had been flushed with hydrogen, the magnetic stirrer was started and the catalyst was hydrogenated. Five-tenths grams of the dienone 9 were added and hydrogenation was begun with the uptake of hydrogen being monitored.

After 50 minutes, the theoretical uptake of hydrogen was completed and the flask removed from the apparatus. The solution was filtered through a scintered glass funnel and the solvent removed *in vacuo*. A nmr analysis of the crude oil indicated that a mixture of the *cis* and *trans* enones 10a and 10b was produced in an approximate 4:1 ratio.

8,10-Dimethyl-1(9),3,7-tetral-2-one(14)

Five and zero-tenths grams (28.4 mmole) of dienone 9, 5 ml of dry acetic acid, and 9.0 g of 2,3-dichloro-5,6-dicyanobenzoquinone were dissolved in 300 ml of benzene in a 500 ml three-necked round-bottom flask fitted with a reflux condenser and a magnetic stirrer. The mixture was heated and allowed to reflux for 48 hours. After cooling to room temperature, the solution was filtered through a funnel packed with 25 g of neutral alumina. The excess solvent was removed *in vacuo* and distillation of the residue gave 2.08 g (42.1 percent) of the trienone 14, bp. 104-112°/2.3 mm (lit[11] bp. 85-86°C/ 0.1 mm).

Attempted Preparation of *cis* and *trans*-8,10-Dimethyl-1(9),3-hexal-2-one(11a and 11b) from the Trienone 14

Four hundred milligrams of 10 percent palladium on carbon and 100 ml of 95 percent ethyl alcohol were placed in a 250 ml single-necked round-bottom flask equipped with a magnetic stirrer and the flask attached to the atmospheric hydrogenation apparatus. After the apparatus had been flushed with hydrogen, the magnetic stirrer was started and the catalyst hydrogenated. Then 0.400 g of the trienone 14

were added and hydrogenation was begun with the uptake of hydrogen being monitored. After three hours, the theoretical uptake of hydrogen had been completed and the flask was removed from the apparatus. The solution was filtered through a scintered glass funnel and the solvent removed *in vacuo*. A nmr analysis showed that both the linearly conjugated and cross-conjugated double bonds were being reduced with no selectivity being evident.

CHAPTER IV

DISCUSSION OF RESULTS

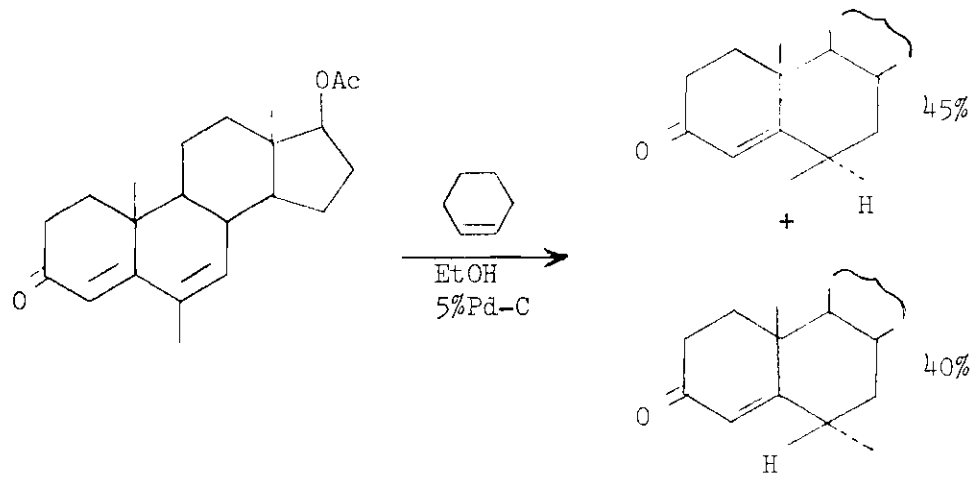
A. The Synthesis of trans-1,7-Dimethyltricyclo(4.4.0.0^{2,6})decan-3-one

Although the main purpose of this research was to study the reductive ring opening of trans-1,7-dimethyltricyclo(4.4.0.0^{2,6})decan-3-one, a secondary objective was to establish a relatively simple pathway to the desired tricyclic ketone 5a. It was decided that a synthetic scheme parallel to that used by Kropp (14) to synthesize the ketone 5b would afford the best opportunity for obtaining 5a.

The first major problem in reaction Scheme I was the synthesis of the enone 10a, the least stable of the two possible isomers. The linearly conjugated dienone 9, appeared to be a logical precurser of 10a as well as 10b, and several attempts were made to carry out selective hydrogenation of the 7,8-bond of the dienone 9. An initial attempt was made using a Parr low pressure hydrogenation apparatus, but it was found that both double bonds were reduced. Several attempts were then made using the homogeneous catalyst tris-(triphenylphosphine) rodium chloride in ethyl alcohol in a Parr apparatus under varied pressures and times of hydrogenation, but no reaction was noted. The hydrogenation was then attempted using a small percentage, by weight, of 10 percent palladium on carbon catalyst and an atmospheric hydrogenation

apparatus. The reaction was monitored closely and when the theoretical amount of hydrogen had been absorbed, the reaction was stopped. After extraction of the solvent *in vacuo*, the resulting yellow oil was analyzed by nmr and the spectrum showed that an approximate 4:1 ratio of the *cis*:*trans* isomers was evident. However, when the reaction was repeated at a later date, only the *trans* dimethyl enone 10b was produced which indicated that the reaction was very sensitive to the reaction conditions.

It was noted that Burn, Kirk, and Petrow (13) had successfully used a hydrogen transfer reaction to reduce a steriodal 6-methyl-4,6-dien-3-one to 6β and 6α-methyl-4-en-3-ones. As can be seen in equation (4), the similarity between the steroid used by Burn *et al* and the dienone used in Scheme I is obvious.

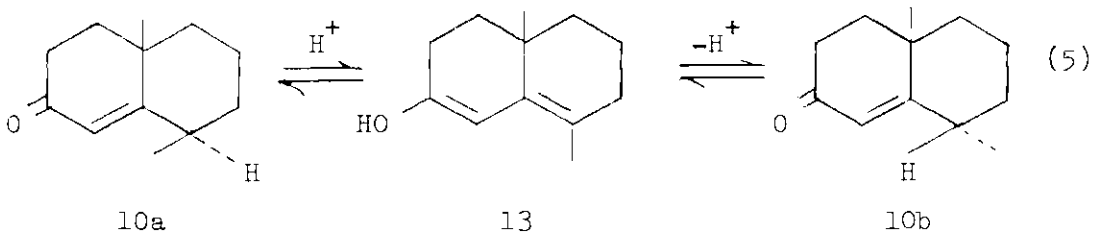


(4)

It was expected that because of steric factors, the transfer of hydrogen would take place from the less hindered or α side of the dienone 9 as was evident in the reduction of the steroid in equation (4). When the reaction was attempted using the dienone 9 as the starting

compound and duplicating the conditions of Burn et al as closely as possible, it was found that the desired enone 10a was formed in high yield. Nmr analysis of the reduction mixture showed that the ratio of 10a to 10b was approximately 4:1 and at times 5:1. Subsequent reactions under the same conditions yielded the same general results so it was decided to use this method in all attempts to synthesize 10a.

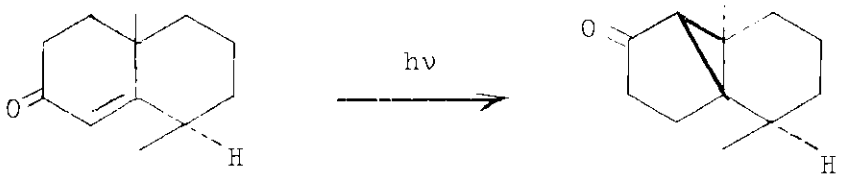
The ease of isomerization of 10a to 10b was discovered when a sample of the mixture was dried overnight over anhydrous magnesium sulfate. It was found that the ratio of 10a to 10b changed from approximately 4:1 to approximately 1:2. This characteristic was studied further by storing one sample of the mixture of 10a and 10b in a closed container in a refrigerator and storing a duplicate sample in a closed container at room temperature. It was found that after a period of three days, the sample stored at reduced temperature did not isomerize to any extent, but the sample stored at room temperature isomerized from an approximate 5:1 ratio to an approximate 1:1 ratio of the cis to the trans isomers. This can be explained by the presence of any trace amounts of acid or base. Because of the 1,3-diaxial methyl-methyl interaction present in 10a, the corresponding trans isomer 10b is much more thermodynamically stable. In the presence of a trace of acid, epimerization at C-8 can take place via the conjugated enol 13 as shown in equation (5). Base catalyzed epimerization at C-8 would involve the conjugate enolate corresponding to 13.



10a 13 10b (5)

This study of the ease of isomerization of 10a is relatively superficial, but it indicated that great care had to be taken when handling the enone 10a.

Kropp (17) has discussed the conversion of enones of the type 10a into bicyclohexanone derivatives by irradiation in t-butyl alcohol. If successful, this reaction would lead directly to the desired cyclopropyl ketone 5a (equation (6)).



10a 5a (6)

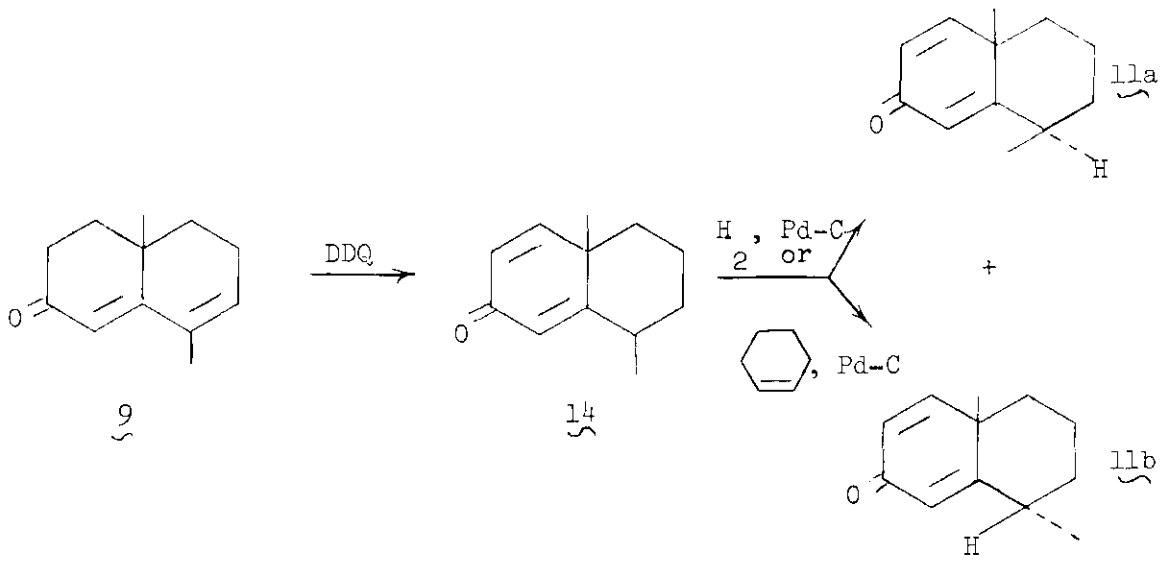
Thus, the mixture of 10a and 10b was irradiated in t-butyl alcohol for extended periods using a Hanovia 450-watt high pressure mercury vapor lamp fitted with a Pyrex filter. After a total irradiation period of 120 hours, nmr and glc analysis of the mixture showed that no skeletal rearrangement had occurred and that the cis isomer

had undergone complete isomerization to the trans isomer. With these negative results, this pathway to 5a was abandoned.

Since the enone mixture could not be converted directly to 5a and 5b, the reaction sequence as depicted in Scheme I was continued. Initial attempts to synthesize the cross-conjugated dienone 11a proved to be unsuccessful. Standard techniques as used by Chao (11) in reacting the mixture of enones 10a and 10b with DDQ yielded almost exclusively the trans dienone 11b, with only a small amount of 11a being detected. The reaction was repeated using different times of reaction, but with the same result; the desired cis isomer was not produced in sufficient quantity.

It was decided to attempt to reverse the order of oxidation and reduction as depicted in Scheme I and Scheme II shows the proposed method of obtaining a mixture of 11a and 11b.

Scheme II



9 14

It was not expected that there would be a great deal of difference in the selectivity of the proposed reduction of the linearity conjugated and cross-conjugated bonds of trienone 14, and this was shown to be true under the reaction conditions used.

The dienone 9 was treated with DDQ in the same manner as the treatment of the mixture of enones 10a and 10b. This yielded the known trienone 14 (11). The trienone was then hydrogenated in an atmospheric pressure hydrogenation apparatus. After workup, the nmr spectrum of the product indicated that both the 3,4 and the 7,8-bonds were being reduced simultaneously with no apparent selectivity of reduction. The trienone 14 was also reduced using the hydrogen transfer technique and the results also showed that both double bonds were again being reduced simultaneously. In view of these results, Scheme II was no longer pursued.

After the failure of Scheme II to produce the desired results, Scheme I was re-examined and some changes were made in the workup of the reaction mixture after the completion of the DDQ oxidation of the mixture of enones 10a and 10b. Instead of filtering the reaction mixture through neutral alumina, the solution was filtered through a scintered glass funnel to remove the precipitate, and then the solution was washed with freshly prepared 2 percent sodium hydroxide solution to remove the residual quinol. The aqueous layer was extracted with ether and the combined organic layers were washed with saturated brine and saturated sodium bicarbonate, and then dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the resulting

yellow-brown oil was distilled. Nmr analysis showed that the cross-conjugated dienones 11a and 11b were formed in an approximate 2:1 ratio. The nmr spectrum also showed the presence of some impurities, one of which was the trienone 14.

An attempt was made at this point to separate the cis isomer from the mixture by utilizing preparative vapor phase chromatography on a 6' x 1/4" Carbowax K-20M column, but the only samples recovered were the trans dienone 11b and the trienone 14. The cis isomer evidently isomerized completely to the trans during gas chromatography. Epimerizations of this type commonly occur during gas chromatography because of the high temperatures of the injector ports and columns. No further attempt was made at this point to separate the mixture and it was decided to continue with the reaction scheme.

The distilled mixture of dienones 11a and 11b was irradiated in dry dioxane with a Hanau NK/20 mercury vapor lamp which emits most of its radiation at 2537 Å. The irradiation proceeded quite smoothly and a mixture of the cyclopropyl enones 12a and 12b was recovered. The impurities were separated from the mixture by liquid chromatography on a silica gel column in the manner used by Kropp when he synthesized 12b. A light yellow oil was recovered and nmr and glc analysis indicated the presence of a 2:1 mixture of 12a and 12b.

The mixture of isomers was then reduced by use of a Parr low pressure hydrogenation apparatus yielding a 2:1 ratio of cyclopropyl ketones 5a:5b. The cyclopropyl ketones were partially separated by repetitious column chromatography on silica gel using benzene-hexane

mixtures as the eluent. For each separation, only a small amount of pure 5a and 5b was recovered. Final separation of the mixture was completed by preparative vapor phase chromatography on a 6' x 1/4" Carbowax K-20M column. The separation procedures required were the greatest cause of low yields, but no effort was made to optimize yields during this reaction.

The cyclopropyl enone 12a exhibited a strong ir absorption at 5.90μ which is assigned to C=O. The following nmr assignments have been made in the case of compound 12a.

Position of Absorption(δ)	Number of Protons	Assignment
7.18 and 5.78 (q, J_{AB}=5.5, J_{AX} and J_{BX} = 1.0 cps)	2H	Proton at C4 and C5
2.32 (m)	1H	Proton at C2
1.18 (s)	3H	CH_3 at C1
0.95 (d, J=6.7 cps)	3H	CH_3 at C7
1.20-1.85	7H	remaining protons

The cyclopropyl ketone 5a exhibited a strong ir absorption at 5.82μ which is assigned to C=O.The following nmr assignments have been made in the case of compound 5a.

Position of Absorption(δ)	Number of Protons	Assignment
1.17 (s)	3H	CH_3 at C1
0.96 (d, J=6.5 cps)	3H	CH_3 at C7
1.23 - 2.10	12H	remaining protons

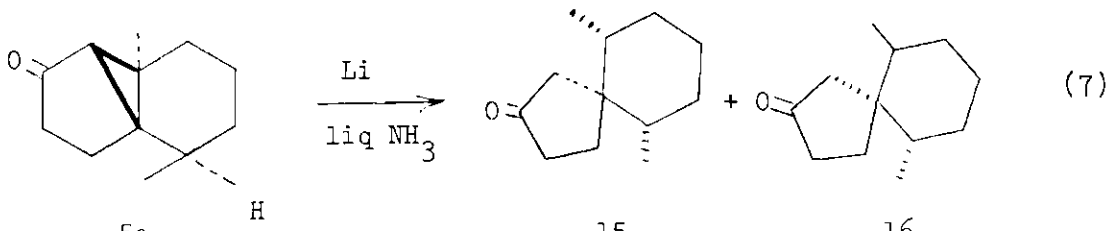
B. Dissolving Metal Reduction of *trans* and *cis*-1,7-Dimethyltricyclo(4.4.0.$C^{2,6}$)decan-3-one(5a and 5b)

The regioselectivity of the reductive cleavage of the cyclopropyl ring in 5b has been previously established (10) and from this and other previous work (3,4), there was little doubt as to the regioselectivity of the reductive cleavage of the cyclopropyl ring in 5a. However, the stereochemical outcome at C-1 and the actual mechanism of the ring opening were not certain.

Since the reaction scheme also yielded the ketone 5b it was decided to run dissolving metal reductions under the same conditions for both 5a and 5b so that direct comparisons could be made. The reaction conditions selected for the various reductions were temperatures of -33°, -78°, and -33° with the presence of *t*-butyl alcohol. The ketone 5b was not reacted with t-butyl alcohol during this study and data for the cyclopropyl ketone 5a was compared with that reported by Piers (10). The solvent selected for each run was tetrahydrofuran which was distilled from lithium aluminum hydride immediately before use. The quantity of lithium metal used was either a *ca* 120 molar excess or a *ca* 12 molar excess. The compound to be reduced was introduced into the lithium-ammonia solution either by a syringe over a period of five minutes or by dropping funnel over a period of 30 minutes. A representative example of the method used in the reduction reactions is found in Chapter III. Each reaction was repeated when possible and the resulting percentages were averaged. The analysis was conducted by vapor phase chromatography on a 6' x 1/8" Apiezon L

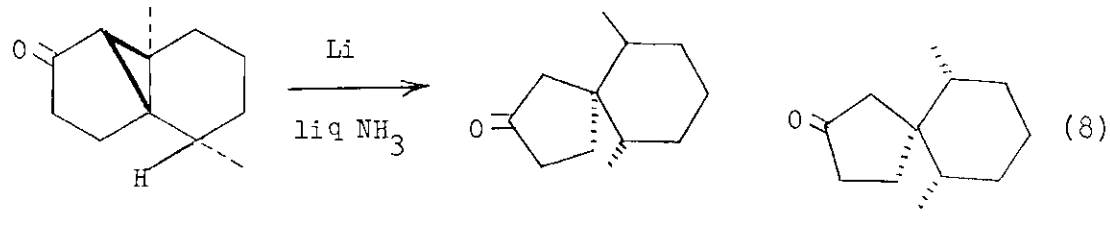
column. The results of the reductive cleavage reactions are listed in Tables 1 and 2.

The products of the dissolving metal reductions have been previously reported by Piers (10) for the ketone 5b and Marshall (18) has characterized the compounds produced by the cleavage of 5a and 5b. The spiroketone products produced in the experiments conducted are shown in equations (7) and (8) and the structures were verified by nmr and vapor phase chromatographic analysis using an internal standard.



(7)

5a 15 16



(8)

5b 16 17

As Piers (10) reported, the reductive ring opening occurs with a high percentage of inversion at the C-1 carbon, and the reactions conducted with the cyclopropyl ketones 5a and 5b verify this fact.

Table 1. The Reduction of trans-1,7-Dimethyltricyclo(4.4.0.$0^{2,6}$) decan-3-one(5a).

Run	Ratio(15:16)	Wt of Li(mg)	Li Equiv. Excess	Wt of Ketone (mg)	Temp °C	Time of Addition
1	64:36	250	120	50	-33°	5 minutes
2	71:29	250	120	50	-78°	5 minutes
3*	70:30	12.5	12	25	-33°	30 minutes
4*	80:20	12.5	12	25	-78°	30 minutes
5*+	67:33	12.5	12	25	-33°	30 minutes

* Experiment not duplicated

\+ 185 mg of t-BuOH added to reaction mixture

Note: Variation between duplicate runs in Runs 1 and 2 was less than 1 percent.

Table 2. The Reduction of cis-1,7-Dimethyltricyclo(4.4.0.$0^{2,6}$) decan-3-one (5b)

Run	Ratio(16:17)	Wt of Li(mg)	Li Equiv. Excess	Wt of Ketone (mg)	Temp °C	Time of Addition
1	64:36	250	120	50	-33°	5 minutes
2	75:24	250	120	50	-78°	5 minutes
3*	84:16	250	120	50	-78°	30 minutes
4*	80:20	25	12	50	-78°	30 minutes
5*+	93:7	15	3	125	-78°	30 minutes

* Experiment not duplicated

\+ Dry ether used as solvent

Note: Variation between duplicate runs in Runs 1 and 2 was less than 1 percent.

It should be noted that the results of Piers in the reduction of 5b could not be duplicated exactly except in Run 5 which duplicated the conditions used by Chao (11). This difference could possibly be explained by a difference in the physical mechanics of the reaction. Piers did not indicate the time of addition of the cyclopropyl ketone and it is evident from Runs 1 and 3 and Runs 2 and 4 when using 5a that time of addition is important. The quantity of lithium used could be important also, but changing from a 120 to a 12 molar excess did not seem to have a great effect as evidenced by Runs 3 and 4 when using 5b.

Even though the results of Piers could not be duplicated, the results support the general trends that were observed. The significant aspect of the various reductions run on ketones 5a and 5b is that the same degree of inversion at the β carbon occurred regardless of the stereochemistry of the methyl group on the C-7 carbon. The reduction results are not consistent with an anion-radical mechanism for the reductive ring opening that actually occurred. This can be seen by examination of the possible conformations and configurations that could exist in an anion-radical intermediate. Assuming that the intermediate anion-radical has time to assume all configurations and conformations, Charts I and II would depict the probable intermediates of the reductive ring cleavage. Chart I shows the possible intermediates of the reduction of 5a and Chart II shows the possible intermediates of the reduction of 5b.

It can be seen from Charts I and II that if the size of the

CHART I

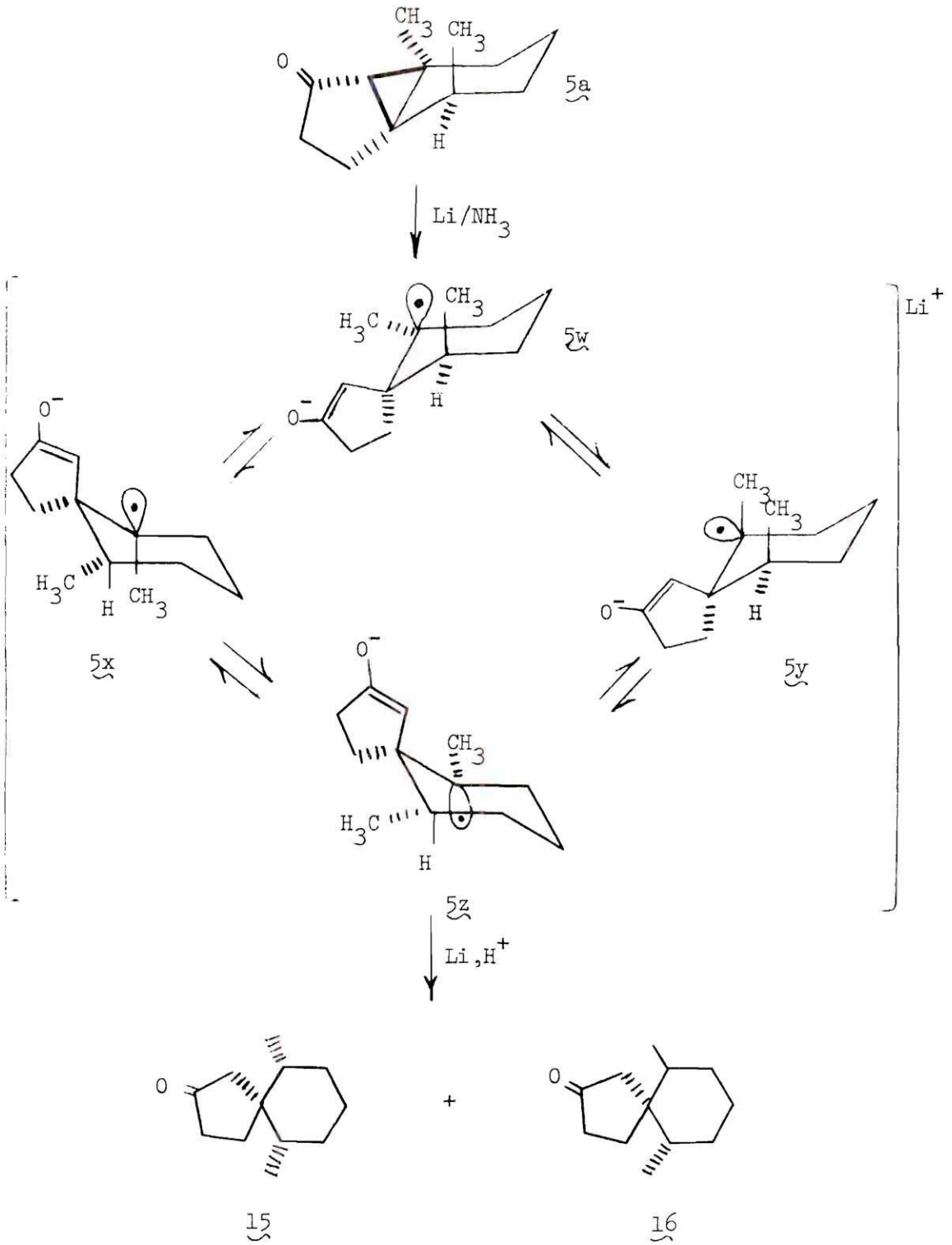
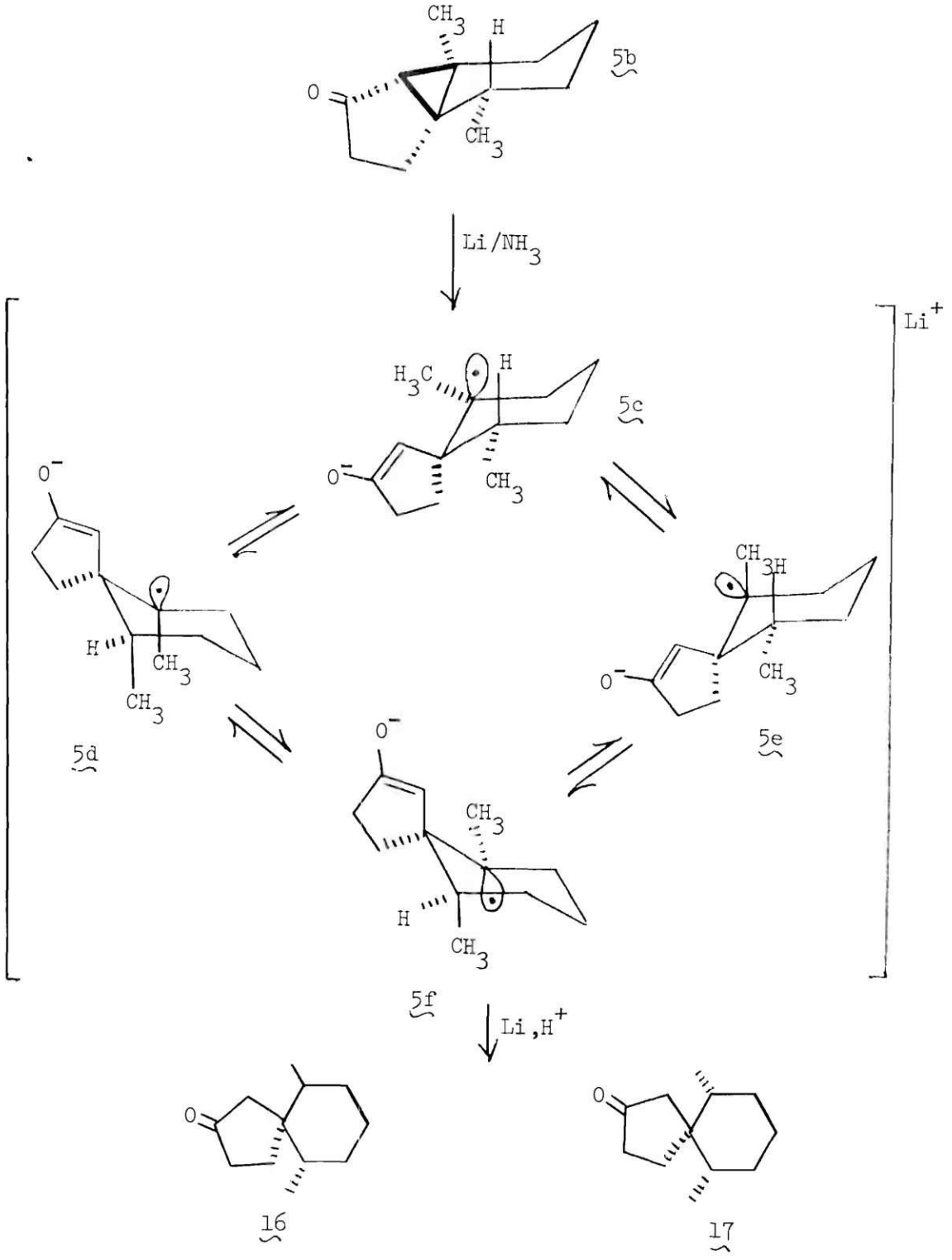

CH3
CH3
O
H
5a
Li/NH3
CH3
H3C
5w
O-
H
Li+
O-
H3C
H
CH3
5x
CH3
CH3
O-
H
5y
O-
CH3
H3C
H
5z
Li,H+
O
+
O
15
16

CHART II


CH3
H
O
CH3
5b
Li/NH3
H3C
H
O
CH3
5c
Li+
O
H
CH3
CH3
5d
CH3
H
O
CH3
5e
O
CH3
H
CH3
5f
Li,H+
O
16
O
17

methyl group at C1 was greater than that of the orbital containing the electron, intermediates 5z and 5c would be the more stable species involved in the reductive reaction and the spiroketones 15 and 17 would be the primary products expected from 5a and 5b respectively. Since the primary product from the reduction of 5b is the spiroketone 16 and not 17, it seems likely that the thermodynamic stability of the intermediates is not the most important factor.

A second assumption is that the radical orbital occupies more space than the methyl group. If this were true, this orbital would try to assume an equatorial position with respect to the cyclohexane ring. Intermediate structures 5x and 5y demonstrate this situation for the reduction of cyclopropyl ketone 5a. However, structure 5y has a very unfavorable 1,3-diaxial methyl-methyl interaction so that structure 5x should be more important. However, electron addition and protonation of 5x with retention of configuration leads directly to 16 which is not the major product of the reduction.

A possible criticism of this treatment might be if a complete dianion mechanism were in effect. If this were the case, the most stable intermediates of the reduction of 5a and 5b might be 5z and 5f, respectively; in these configurations, the anion orbitals would be the greatest distance possible from the enone π system and the polar repulsion would be minimized. It should be noted that these configurations lead to the major products actually reported in the reductive reactions. However, a closer inspection of 5f shows a highly unfavorable diaxial interaction between the C-7 methyl group and the anion orbital.

One would think therefore that the structure 5z would be considerably more favorable because the two methyl groups are in equatorial positions and the anion orbital is at the greatest distance from the π system of the enolate group. Consequently, the percentage of 15 formed from 5a should be significantly higher than the percentage of 16 formed from 5b. This was shown not to be true in that the percentages of 15 and 16 formed from 5a and 5b, respectively, were relatively close.

The conclusion drawn from this analysis is that the dissolving metal reductions of the tested cyclopropyl ketones 5a and 5b proceeds to a significant degree by a concerted mechanism with backside protonation at C-1 taking place as the cyclopropyl ring bond is being broken. On the basis of the results from only two compounds, a statement that the concerted mechanism extends to all reductive cleavages of cyclopropyl rings cannot be made at this time. Much more experimentation would have to be conducted before any generalily could be stated.

CHAPTER V

CONCLUSIONS

trans-1,7-Dimethyltricyclo(4.4.0.$0^{2,6}$)decan-3-one was synthesized and then treated with lithium metal in liquid ammonia under various conditions in order to study the results of reductive ring opening. It was found that the reductive ring opening occurs with an equally high percentage of inversion at the C-1 carbon regardless of the stereochemistry of the methyl group on the C-7 carbon. This result can be explained by the possibility that the reductive cleavage takes place by a concerted or near-concerted mechanism.

CHAPTER VI

RECOMMENDATIONS

Further study on the synthesis of the cyclopropyl enone 12a should be conducted with emphasis on optimization of yields. The enone 12a should then be studied as a possible, readily available, precursor to the natural product β-vetivone.

The study of the dissolving metal reduction of the cyclopropyl ketone 5a should be conducted in other solvent media and under varied other conditions. Also, other related cyclopropyl ketones should be studied to verify the results obtained in this research. With additional data of this type, the possibility of a concerted mechanism could be verified and applied to synthesis involving the reductive ring openings of various cyclopropyl rings.

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