Study on the molecular rearrangements and synthesis of natural products
by Youseung Kim

A thesis submitted in partial fulfillment of the requirements for the degree of DOCTOR OF PHILOSOPHY in Chemistry
Montana State University
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Abstract:
Alkyl substituent effects and a throughspace heteroatom influence on pinacol coupling are noted. Alkyl groups and a heteroatom are shown to direct specifically the course of pinacol rearrangement. The study on the lanthanide shift reagent experiment with a spiranone is described, A few natural products which can possibly be synthesized by the pinacol rearrangement are listed.

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"Though it rain gold and silver in a foreign land and daggers and spears at home, yet it is better to be at home."

Malay Proverb

To my parents

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by

Youseung Kim

A thesis submitted in partial fulfillment
of the requirements for the degree

of

DOCTOR OF PHILOSOPHY

in

Chemistry

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# ABSTRACT

Alkyl substituent effects and a throughspace heteroatom influence on pinacol coupling are noted. Alkyl groups and a heteroatom are shown to direct specifically the course of pinacol rearrangement. The study on the lanthanide shift reagent experiment with a spiranone is described. A few natural products which can possibly be synthesized by the pinacol rearrangement are listed.

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# INTRODUCTION

This thesis is comprised of three parts. Although these three parts are separate projects and have no direct relation to one another, the ultimate goal of these studies is the same, the synthesis of natural products. The first part is a report of the study on the pinacol coupling reaction and the pinacol rearrangement. The second part of this thesis is the study on a new methodology to synthesize natural products using the Mundy N-acyllactam rearrangement. The last part is the report of the synthesis of a constituent from a Civet cat.

# PART I

## Study on the Pinacol Rearrangement

## INTRODUCTION

Since the first observation by Fittig[1] in 1860 that tetramethylethylene glycol, (1), commonly called pinacol, rearranged to form methyl t-butyl ketone, (2), pinacolone, in concentrated sulfuric acid, the pinacol rearrangement has been extensively studied (Figure 1).

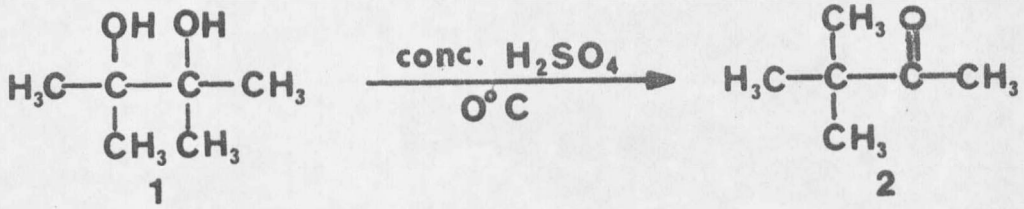



Figure 1. The Pinacol Rearrangement

There are two problems to be concerned with, (1) the pinacol formation and (2) the pinacol rearrangement. Here the two parts are separately introduced and discussed.

## PINACOL COUPLING REACTION

The reductive coupling reaction of carbonyl compounds to form pinacols is a powerful method of carbon-carbon bond formation. Various coupling reaction conditions have been studied by several groups.[2-7] Most frequently used procedures are the [Al-Hg][2-3] and [Mg-Hg]/$TiCl_4$ methods.[6] Recently, Imamoto and coworkers treated aldehydes and ketones with a low-valent cerium reagent to produce the corresponding glycols in high yield.[8]

The accepted mechanism for the reductive coupling reaction involves an anion-radical intermediate, (3) (Figure 2).[9] Mundy proposed a dianion intermediate, (4) for the coupling reaction by the classical [Al-Hg] method.[10] Both Corey[5] and McMurry[4] have agreed that a reduced state of titanium is intimately involved in the

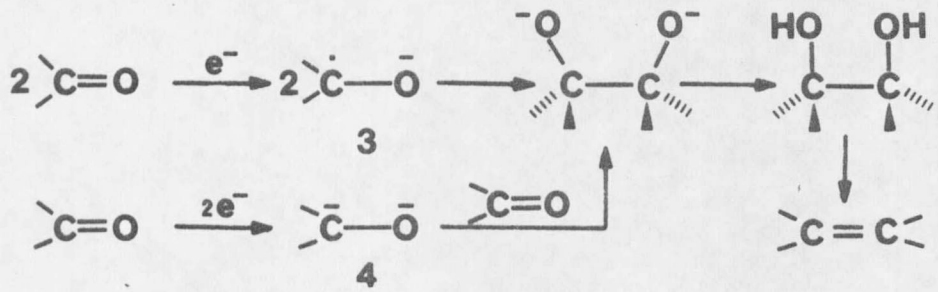



Figure 2. General Mechanisms for the Reductive Coupling

coupling reaction, though there is some question as to the exact oxidation state. There seems to be a tacit assumption that the titanium intermediates enhance the degree of coupling without affecting product composition. McMurry also proposed that pinacols were the precursors to the alkenes.

There have been few studies on the product composition under different reaction conditions. Ourisson[11] has demonstrated that different ratios of meso and dl products can be found under different reaction conditions, and Corey[5] has also presented evidence for cis and trans pinacols during intramolecular coupling reactions, assuming the anion-radical intermediate. We have demonstrated that the stereochemistry of the pinacol derived from R(+) 3-methylcyclohexanone, (5) depends on the method of preparation (Figure 3).[10] Reductive coupling of 5 using the Corey procedure[5]

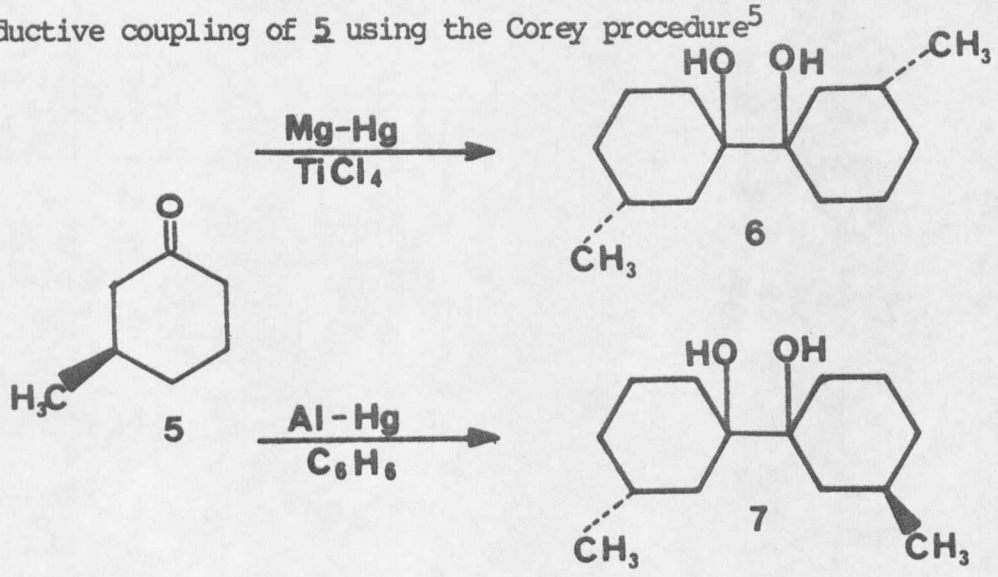



Figure 3. Different Pinacol Products by Different Methods

gave a product formulated as 6 whose NMR spectrum showed only one methyl doublet (J = 6.1 Hz) at 0.88 ppm, consistent with an equatorial methyl group. The [Al-Hg] reductive coupling[3] of 5 resulted in 7, whose NMR spectrum gave two cleanly-resolved methyl doublets (J = 6 Hz) centered at 0.85 ppm and 1.10 ppm, consistent with an equatorial and axial orientation, respectively. This structure assignment was obtained from optical rotation, spectral data, and sulfite ester derivatives.[12] The formation of 6 was easily rationalized by the traditional anion-radical, or ketyl, intermediate (Figure 4). We have proposed a dianion intermediate to form 7 by the fact that reactions with aluminum are well-known to be two-electron transfer reactions coupled with McMurry's evidence for an intermediate dianion in an aromatic system.[4] Thus, the dianion from 5 attacks another molecule of 5 and the resulting intermediate

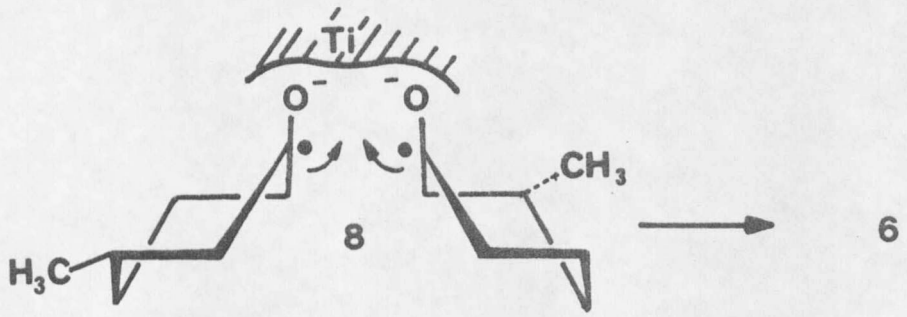



Figure 4. Anion-Radical Coupling of 3-Methylcyclohexanone

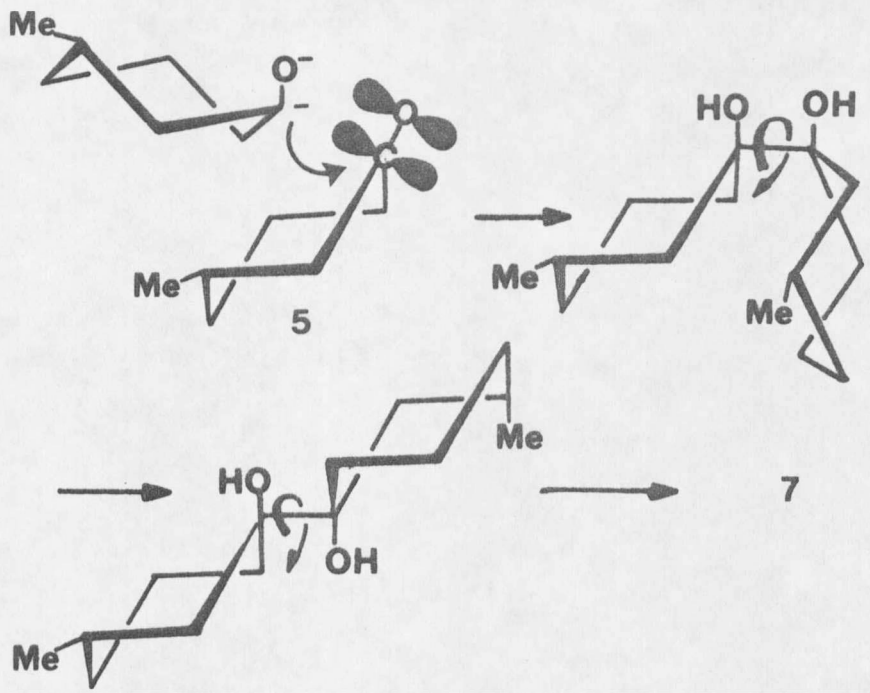



Figure 5. Pinacol Formation by Dianion Intermediate

undergoes immediate conformational reorganization, relieving a large 1,3-axial interaction, to form 7 (Figure 5).

Previous works[2-5,13] have shown that there is a statistical distribution of products from the mixed reductive coupling of ketones. We have studied ring size effects in pinacol coupling for the general reaction shown in Figure 6.[10] Srinivasa[10] utilized equal-molar ratios of the two reacting ketones for the Corey method. The ratios of pinacols and alkenes from these reactions are presented in Table 1. From these data it was suggested that pinacol formation followed no statistical distribution, in contrast to the previous

work, even though there was a predominance of the mixed product in each case. Taking into consideration the fact that alkene formation requires a pinacol precursor by McMurry,[4] the data show some deviation from the statistical distribution.

Table 1. Distribution of Coupling Products

| Experiment | Cycloalkanones | Alkenes | | | Pinacols | | |
|---|---|---|---|---|---|---|---|
| 1 | $C_5 + C_6$ | $C_5$–$C_5$ | $C_5$–$C_6$ | $C_6$–$C_6$ | $C_5$–$C_5$ | $C_5$–$C_6$ | $C_6$–$C_6$ |
| | | 10.2 ± 0.4 | 14.1 1.6 | 4.1 0.6 | 11.4 0.3 | 42.0 2.4 | 18.2 3.8 |
| 2 | $C_5 + C_7$ | $C_5$–$C_5$ | $C_5$–$C_7$ | $C_7$–$C_7$ | $C_5$–$C_5$ | $C_5$–$C_7$ | $C_7$–$C_7$ |
| | | 8.0 ± 3.7 | 4.2 2.9 | 16.7 4.7 | 27.8 4.3 | 33.9 1.6 | 10.8 3.7 |
| 3 | $C_6 + C_7$ | $C_6$–$C_6$ | $C_6$–$C_7$ | $C_7$–$C_7$ | $C_6$–$C_6$ | $C_6$–$C_7$ | $C_7$–$C_7$ |
| | | 1.8 ± 1.0 | 7.2 5.5 | 4.8 5.9 | 28.7 6.5 | 48.8 3.6 | 8.7 6.4 |

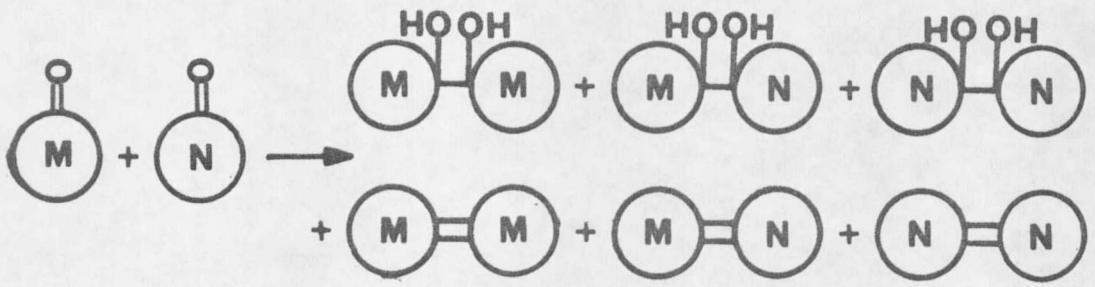



Figure 6. General Scheme of Mixed Pinacol Condensation

The deviation from the statistical distribution was also observed by Dr. R. J. Warnet of our group,[10] who examined the mixed coupling of cyclohexanone, (8), with 2-, (9), 3-, (10), and 4-methylcyclohexanone, (11). In this study, the ring size was held constant while steric congestion about the carbonyl was altered. The results are summarized in Table 2 and Figure 7. It was found that 2-methylcyclohexanone, (9) showed the tendency to avoid self-coupling and a poor disposition towards participation in mixed coupling by the substantial steric effect about the carbonyl. It was also observed that 4-methylcyclohexanone, (11), resisted self-coupling, although there was no good explanation for this observation. It was

Table 2. Product Distribution in the Methylcyclohexanone Studies

| Experiment | Olefin[a] AA | Olefin[a] AB | Olefin[a] BB | Pinacol[a] AA | Pinacol[a] AB | Pinacol[a] BB |
|---|---|---|---|---|---|---|
| 1. 2-Me-B[c] + A[b] | 8.82 | 0.83 | 11.82 | 59.13 | 20.39 | 8.01 |
| | ± 0.16 | 0.16 | 0.29 | 4.36 | 1.27 | 2.15 |
| 2. 3-Me-B + A | 2.05 | 4.74 | 1.75 | 26.21 | 49.61 | 15.62 |
| | ± 0.90 | 1.18 | 0.76 | 2.33 | 2.12 | 5.54 |
| 3. 4-Me-B + A | | | | 39.10 | 51.97 | 8.93 |
| | | | | ± 7.51 | 11.88 | 5.85 |

[a] In percent
[b] A = Cyclohexanone
[c] B = Methylcyclohexanone

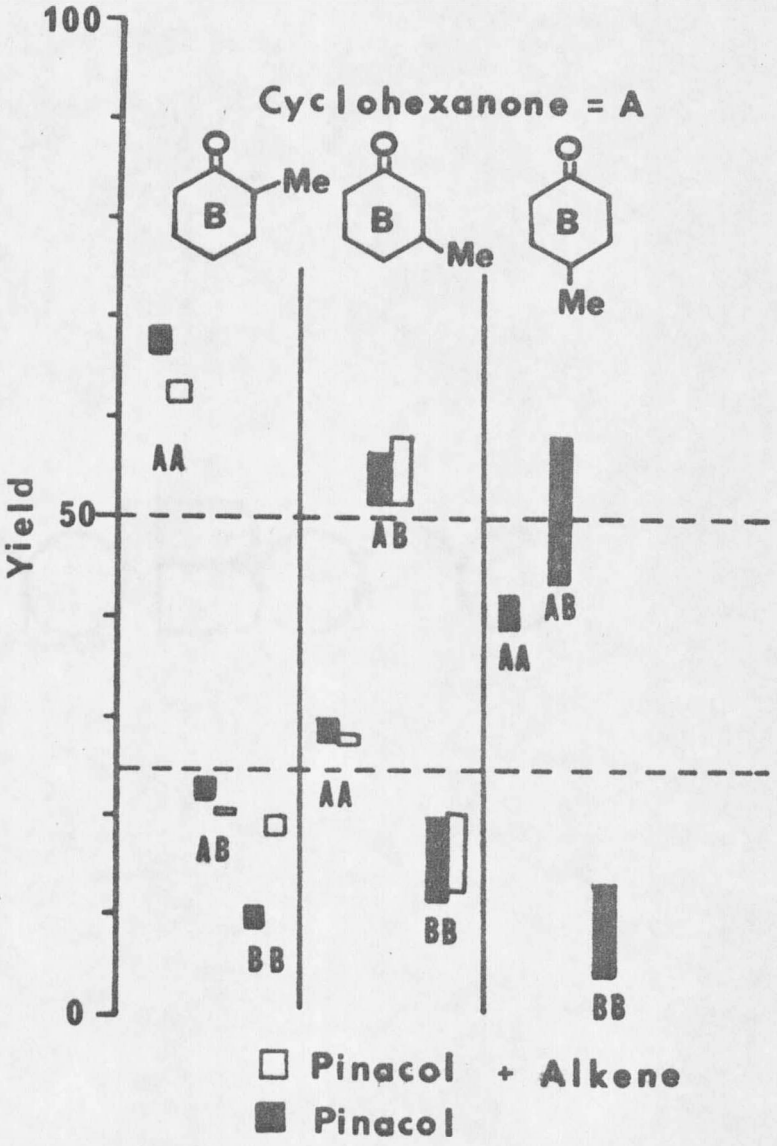



Figure 7. Competitive Coupling of the Methylcyclohexanones

demonstrated from these data that steric effects could change the statistical product distribution.

Temperature effects on the coupling reaction have also been studied by Mundy and coworkers.[10] They observed a decrease in pinacol product with increasing temperature and the corresponding alkene product increasing at the same time (Figure 8). This result supported McMurry's proposal that the pinacols served as precursors to alkenes. They could not observe the temperature effect on the ring size distribution, suggesting that the coupling process was kinetically controlled, and for mixed coupling reactions the product distributions were determined by several factors, such as ring strains and steric effects.

To continue our previous work and to study the steric effect of methyl groups on the self-coupling reaction and the heteroatom effect on the product distribution, we embarked on the preparation of pinacols by the Corey method, because of the ease of reaction and the relatively good yields.

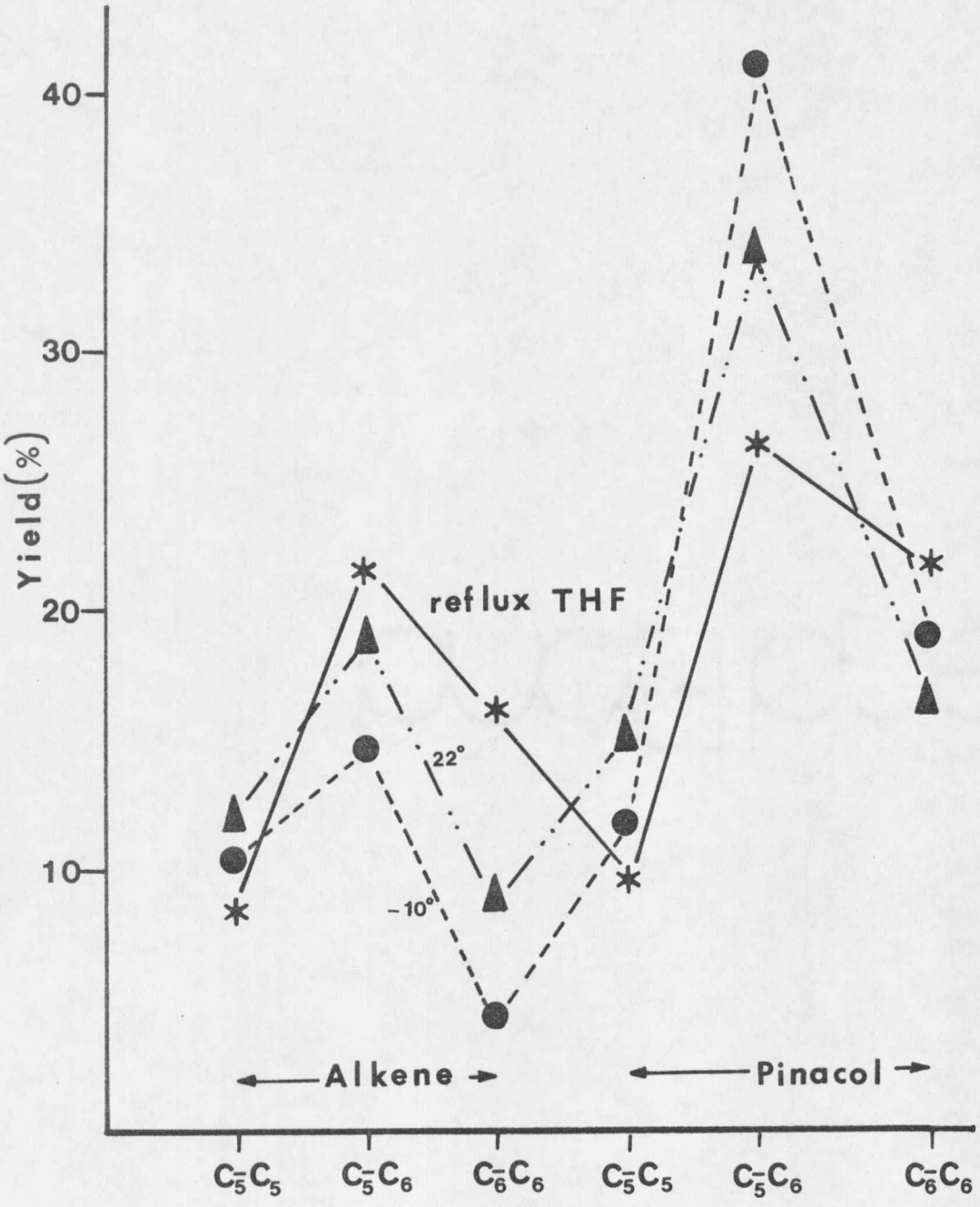



Figure 8. Temperature Effects on Coupling Reaction

## RESULTS AND DISCUSSION

### Self-Coupling Reaction of Methyl Substituted Cyclohexanones

The dimethyl substituted 1,1'-bicyclohexyl diols were prepared by the reductive coupling reaction of the corresponding ketones in the presence of titanium tetrachloride and magnesium amalgam using dry THF as solvent. The reaction was carried out at -10°C under a nitrogen atmosphere. The product mixtures were analyzed by GLC (10-20% SE-30 on Anakrom 60/80 mesh). The results of the reactions are presented in Figure 9 and Table 3.[10]

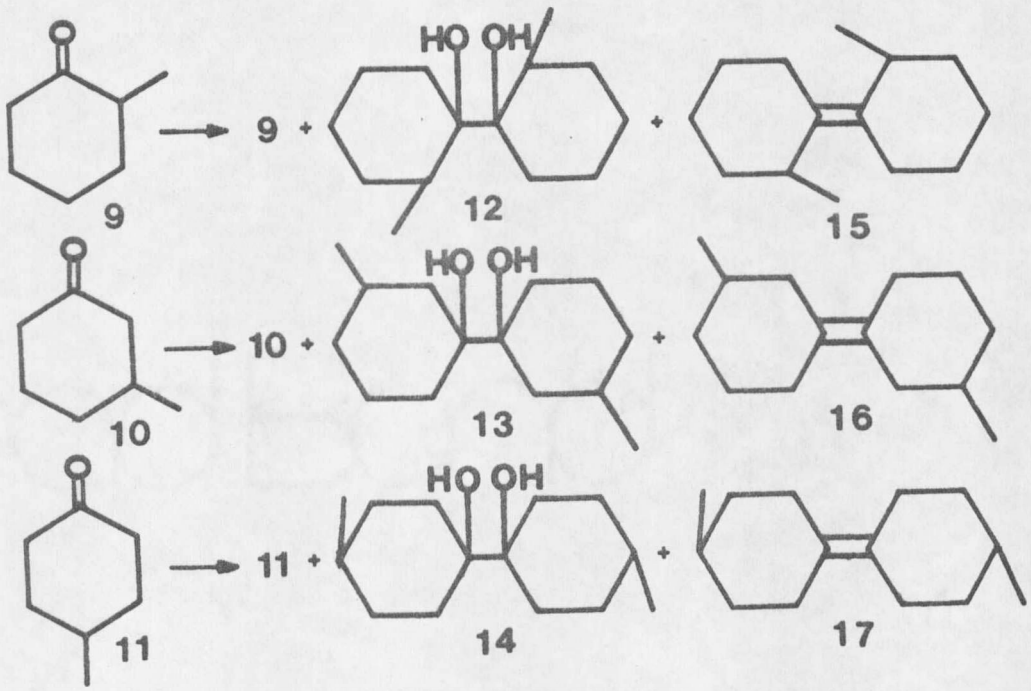



Figure 9. Products from the Reductive Coupling of Methylcyclohexanones

Table 3. Self-Coupling of Methylcyclohexanones

| Methylcyclohexanone | Starting Material | Alkene | Diol |
|---|---|---|---|
| 2- | 88 | 1.8 | 8.6 |
| 3- | 11.3 | 12.9 | 75.8 |
| 4- | 33.7 | 1.7 | 64.6 |

From these results it is seen that 2-methylcyclohexanone, (9) experiences a substantial steric effect about the carbonyl to result in a poor self-coupling. In the case of the coupling reaction of 4-methylcyclohexanone, (11), it is apparent that 11 resists self-coupling, even though the methyl group is sufficiently remote from the carbonyl to preclude any steric effect. These trends match the result of the previous work by Mundy and Warnet.[10] There still is no good explanation for this observation. We also observed that the yield of the alkenes increased with increasing temperature. The pinacols were separated by column chromatography on silica gel using the mixture (1:1) of petroleum ether and ethyl ether as an eluant.

Sulfite Esters of 13 and 14

It is generally recognized that depending on the phase diagram, the physical properties of an enantiomer can differ markedly from those of its racemer. In many instances, the physical properties of the two forms are sufficiently different that even resolution can be

achieved without the need of a chemical resolving agent.[14-15] Such a physical difference was observed during preparation of pinacols. The pinacol, (13) prepared from 3-methylcyclohexanone has a melting point of 83.5-84.5°C. The optically active glycol, (6) ($[\alpha]_D$ = 4.3°) from R(+) 3-methylcyclohexanone, (5), has a melting point at 78.5-79°C. To confirm the stereochemistry of 13, we prepared the sulfite esters[12] of the pinacols. Treatment of 13 and 14 with thionyl chloride in excess dry pyridine yielded the corresponding sulfite esters, (18) and (19) (Figure 10). The same reaction with 12 only produced the dehydration products, presumably because of the steric effect of methyl groups. This method is particularly good because

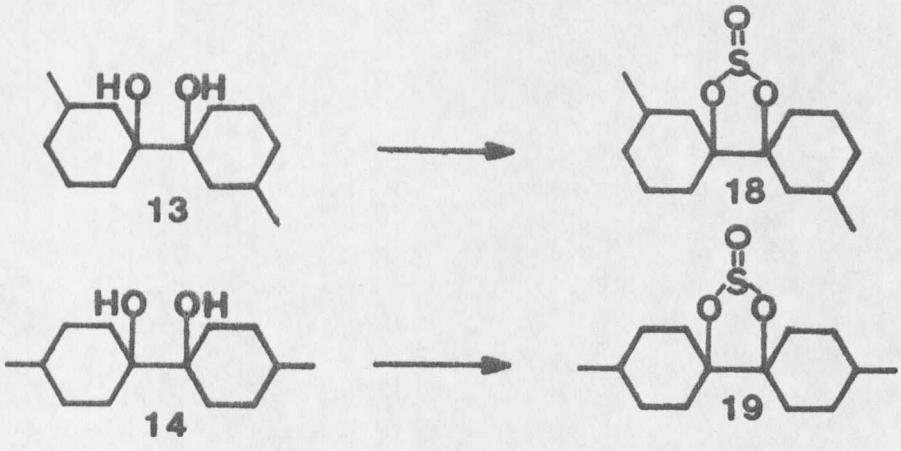



Figure 10. Sulfite Esters of Bicyclopinacols

the tetrahedral sulfur causes the meso pinacol to give two sulfite esters and dl isomer only one. The sulfite esters were analyzed by GLC to show only one compound, and also confirmed from their NMR spectra which gave only one methyl doublet at 0.92-0.94 ppm (6H, d, J = 6.6 Hz) for 18 and at 0.95-0.97 ppm (6H, d) for 19.

Mixed-Coupling Reaction Containing a Heteroatom

The bicyclohexyl pinacols containing heteroatoms were prepared to study a heteroatom influence on the coupling reaction and pinacol rearrangement. We coupled tetrahydropyran-4-one, (20) with a four-fold excess of cyclohexanone, (21), to maximize the mixed coupling by following the accepted procedure.[4,5] After the general work-up procedure, the products were analyzed by GLC (20% SE-30 on Chromosorb 60/80 mesh). The result of the analysis is presented in Figure 11. If we ignore the contribution of an oxygen atom on the coupling reaction, we can expect the statistical distribution ((24 + 27):(23 + 26):(22 + 25) = 1:8:16) because ring size effects are minimized[16] and there are no obvious steric effects. We could observe from this reaction, however, yields of 22 (48.8%); 23 (18.8%); 24 (0%); 25 (26.6%); 26 (2.5%);[17] 27 (2%);[17] and about 1.5% of unidentified material. It is obvious that the amount of 23 and 26 formed from this reaction does not come close to that required if statistically

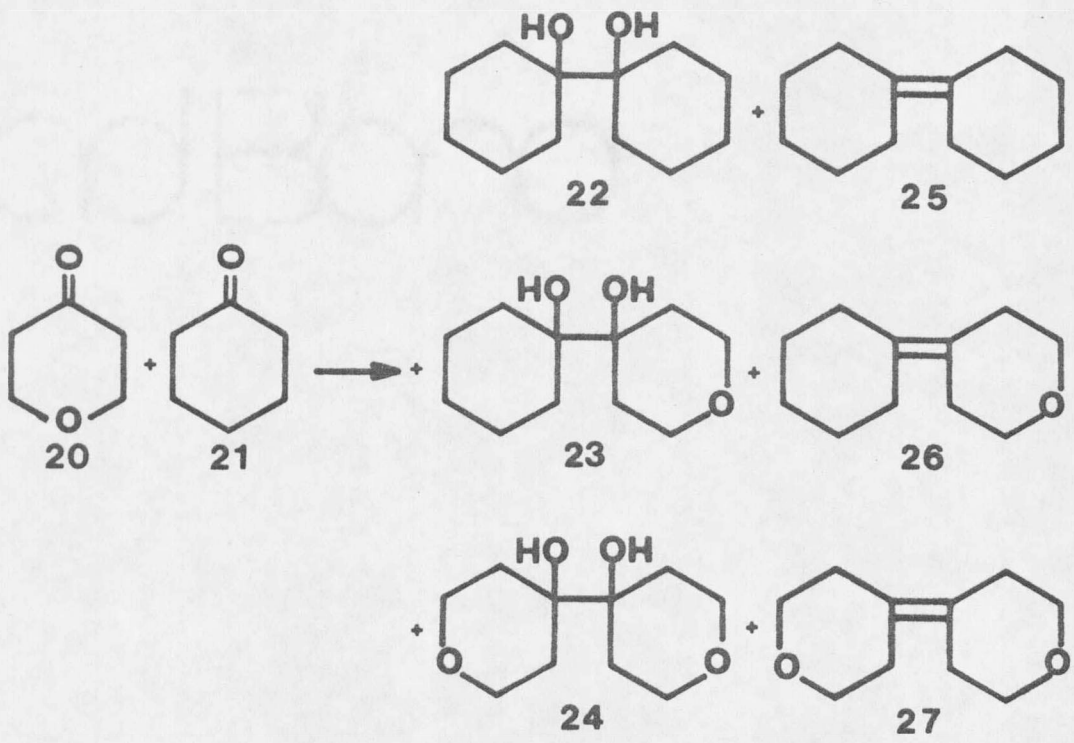



Figure 11. Preparation of 1'-Hydroxycyclohexyl-4-Hydroxytetrahydropyran

driven. The coupling-rate retardation trend of the oxygen atom was also detected from the self-coupling reaction of 20 (Figure 12).

Tetrahydropyran-4-one, (20) was self-coupled by the Corey method to yield 8.9% of the pinacol, (24). The starting material, (20) was mostly recovered and none of the olefin compound, (27) was detected. Tetrahydropyran-4-one was also subjected to the reductive coupling reaction by the classical [Al-Hg] method. None of the coupled products was observed. We could rationalize these results by

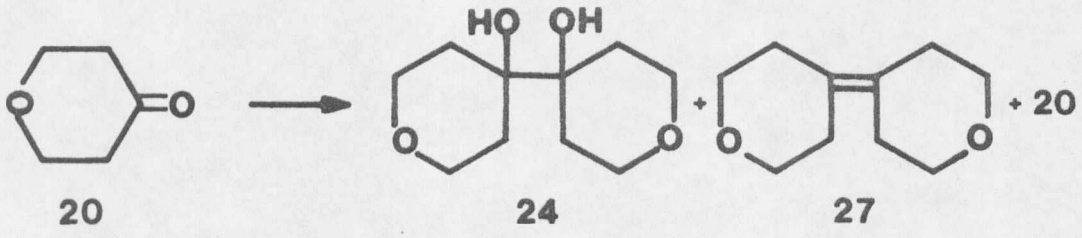



Figure 12. Self-Coupling of Tetrahydropyran-4-One

bringing the concept of an anion-radical mechanism or a dianion mechanism. If we compare the reactivity of intermediates **28**, **29**, assuming the operation of a dipolar effect,[18] and **30** (Figure 13), the anion-radical of cyclohexanone, (**28**), is more reactive than the

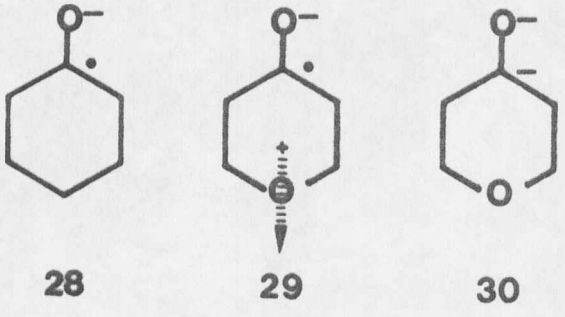



Figure 13. Comparison of Intermediates Reactivity

anion-radical of tetrahydropyran, (**29**) or the dianion intermediate, (**30**). Reducing the reactivity of **29** or **30** can be attributed to a

transannular dipolar effect[18] exerted by the heterocyclic oxygen atom.

Such a heteroatom effect could also be recognized in the mixed coupling reaction containing a sulfur atom. Tetrahydrothiopyran-4-one, (31) was coupled with a four-fold excess of cyclohexanone and analyzed by the same procedure. The result is shown in Figure 14.

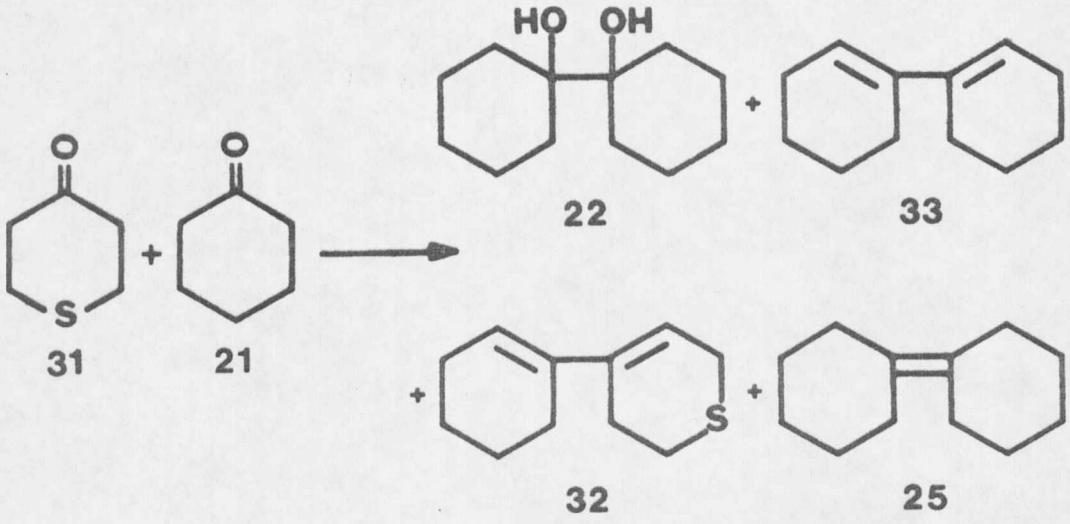



Figure 14. Mixed Coupling of Tetrahydrothiopyran-4-One with Cyclohexanone

We could assume that the olefin compounds, (32) and (33) were the condensation products from the analogous pinacols losing two water molecules by the sulfur containing compound acting like an acid. We could not detect any of the self-coupling products of 31. Only 7% of the mixed-coupling product, (32)[17] was observed, and most of the

products (92%) were the self-coupling products of cyclohexanone, (22, 25, and 33). It is apparent that the amount of the sulfur containing compound formed from this reaction is far from what we expected, and there is no statistical distribution of products. Since the sulfur atom influence on the coupling reaction was greater than that of the oxygen atom, the transannular dipolar effect by heteroatoms might not be the only reason for this result because the oxygen dipolar effect is greater than that of the sulfur. Though we did not try to make a pinacol containing a nitrogen atom,[19] we can conclude that steric effects or heteroatom effects can reduce the reactivity of ketones to change the statistical product distribution.

Future Work

Although the present work has attempted to unravel the alkyl and heteroatom effects on the pinacol coupling reaction, this work is not enough to fully understand those effects. If we examine the product distribution after the mixed coupling of 2-, 3-, and 4-methylcyclohexanone with each other, we can expect more closely some trends of alkyl effect on the coupling reaction. Also, preparation of pinacols with mixed heteroatoms will help to interpret the heteroatom effect. Detailed study has to be done to examine the pinacol reaction.

## PINACOL REARRANGEMENT REACTION

The generally accepted mechanism for the pinacol rearrangement is an acid-catalyzed first order reaction[20] with the rate determining step being the loss of water from **35** to form the carbonium ion, (**36**).[21] The rearrangement can be regarded as a special case of a Wagner-Meerwein rearrangement[21] involving a 1,2-shift from **36** to **38** (Figure 15). Although there was evidence of an epoxide intermediate,

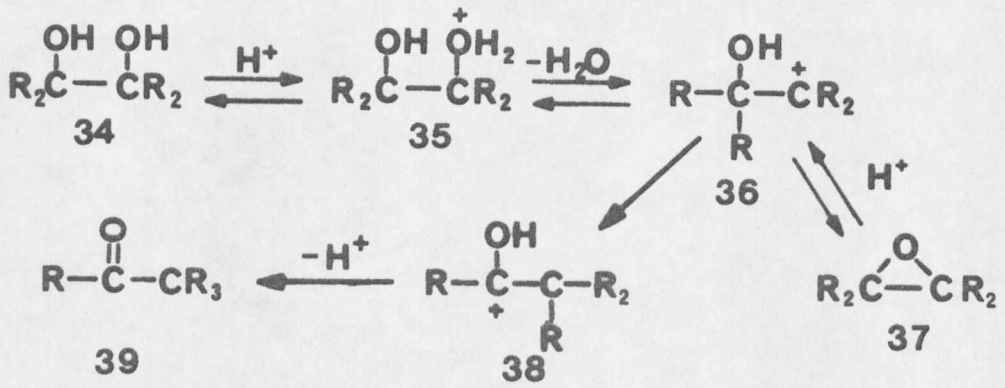



Figure 15. The Mechanism of the Pinacol Rearrangement

(**37**) involved in the rearrangement,[22] such an intermediate does not seem to be possible for hindered glycols, especially the 1,1'-bicycloalkylpinacols. R can be alkyl, aryl, and hydrogen, or any combination of these. Besides sulfuric acid conditions, rearrangements have been carried out in aqueous phosphoric acid, oxalic acid, nitric acid, hydrochloric acid, and perchloric acid. In

some cases,[23] certain Lewis acids such as $Al_2O_3$, $BF_3 \cdot Et_2O$, and $POCl_3$ have been used.

The pinacol rearrangement has been looked upon from several points of view. These include (1) the direction of rearrangement as determined by which of the two hydroxyl groups is initially removed; (2) the migratory aptitudes of the substitutent groups; (3) the effect of the glycol stereochemistry; (4) the stability of the products under reaction conditions; (5) the effect of reaction media; and (6) ring expansion/contraction trends in cyclic systems.

Considerable attempts have been made by several groups[24-26] to study the effect of glycol stereochemistry on the pinacol rearrangement. Bunton and Carr[25] studied the rearrangement of the cis- and trans-1,2-dimethylcyclohexane-1,2-diols using aqueous perchloric acid at various temperatures and found that both the diols produced equal amounts of the ring contraction product. They further noted that the trans diol formed the carbonium ion approximately twice as fast as the cis diol, while the rates of the reverse reactions were almost the same. The interpretation was that in the aqueous solution the cis form was thermodynamically more stable. They also showed that the migrating group could be trans to the leaving group by simply protonating the equatorial hydroxyl group for the ring contraction of the cis glycol, (40) (Figure 16). It was

also observed that the major rearrrangement product of the cis- and trans-1,2-dimethylcyclopentane-1,2-diols, (43) and (44), in aqueous perchloric acid was 2,2-dimethylcyclopentanone, (46), in both cases (Figure 17). This result indicated isomerization of the trans- to

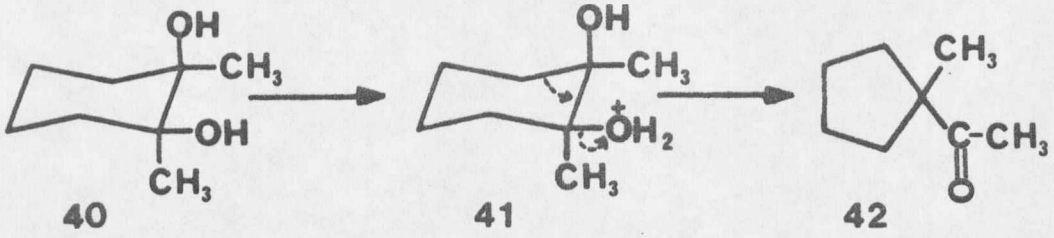



Figure 16. The Ring Contraction of cis-1,2-Dimethylcyclohexane-1,2-Diol

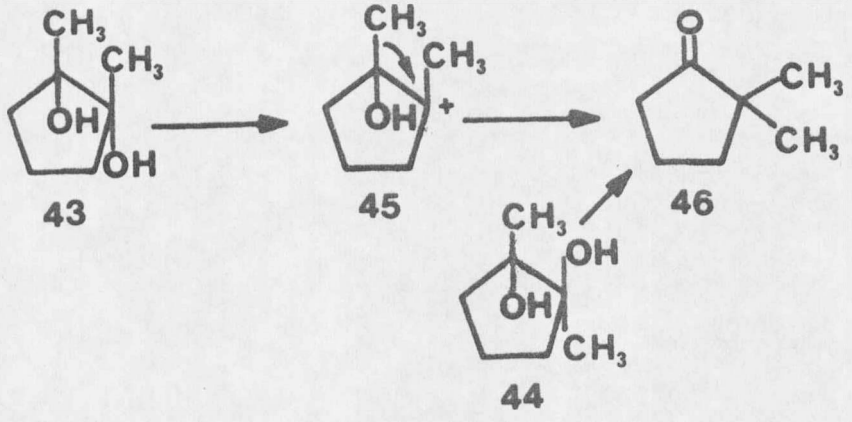



Figure 17. Isomerization of the trans-Diol to the cis-Diol

the cis-diol. Barili and coworkers[26] studied the 1-phenyl-4-t-butylcyclohexane-1,2-diol system and concluded that the carbonium ion formed lost its memory of the previous diol's stereochemistry. With these earlier investigations, it appears that the stereochemistry of 1,2-glycols may not be the key factor in directing the rearrangement.

Several earlier workers[27-28] have attempted to evaluate the effects of ring size on the pinacol rearrangement. Meerwein[27] found that the cyclopentyl glycols, (47), gave more ring expansion than the corresponding cyclohexyl glycols, (48) (Figure 18).

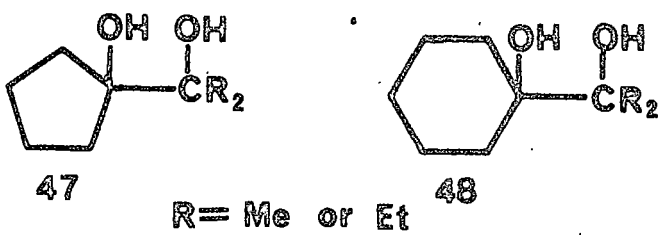



Figure 18. Cyclopentyl and Cyclohexyl Glycols

Sands and Botteron[29] observed that for the rearrangement of cyclopentylcyclohexane-1,1'-diol, (49) in 25% sulfuric acid at reflux, more of spiro[5,5]undecan-7-one, (54) than of spiro[4,6]undecan-6-one, (52) was formed, where the major product was 50 (Figure 19). The results were explained using I-strain arguments.[30] They concluded that the ring expansion products did not reflect ease of carbonium ion formation. Sands[2] also studied the

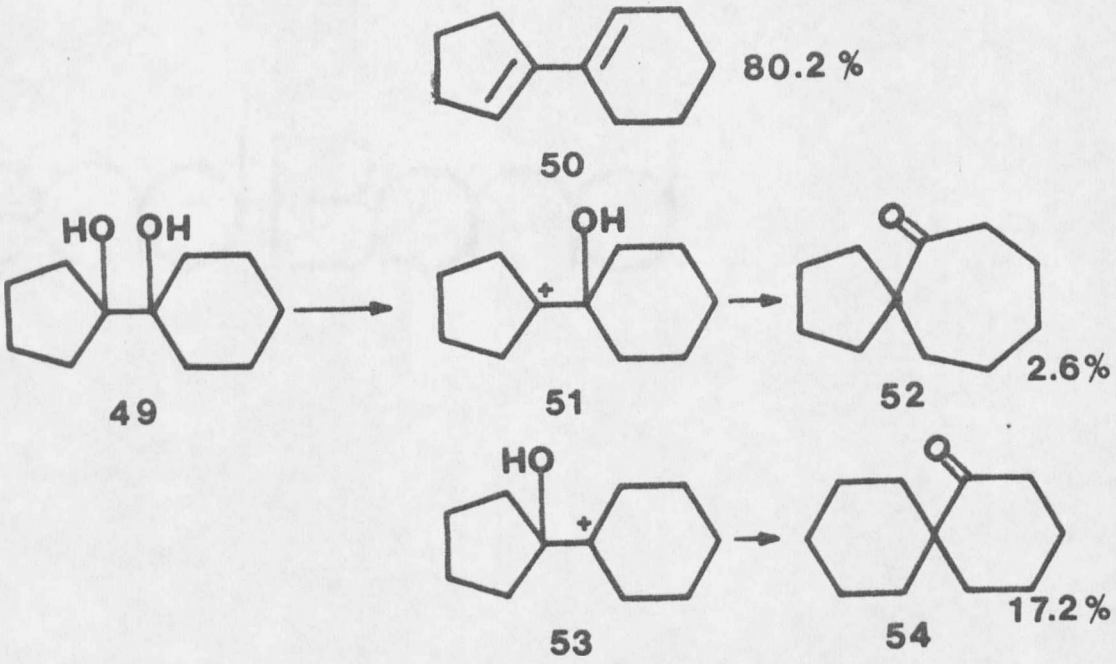



Figure 19. Ring Size Effects: $C_5$ versus $C_6$

rearrangement of cyclopentylcycloheptane-1,1'-diol, (55), in 25% sulfuric acid at reflux (Figure 20). He rationalized this result that the product distribution depended on ring expansion trends as shown in relative strains of 57 and 59.[31]

Botteron and Wood[26] attempted to approach the problem using the ring strain standpoint (Figure 21). The glycols were rearranged in concentrated sulfuric acid at 0°C. This result contradicted the previous argument using I-strain, since there was more reaction on

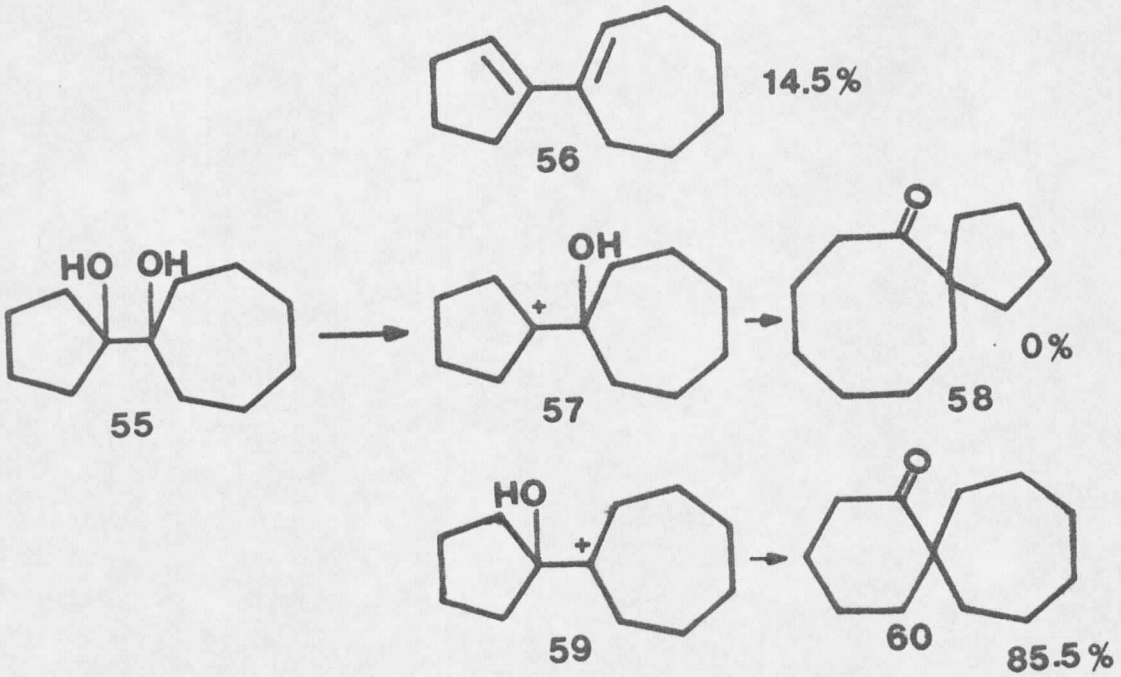



Figure 20. Ring Size Effects: $C_5$ versus $C_7$

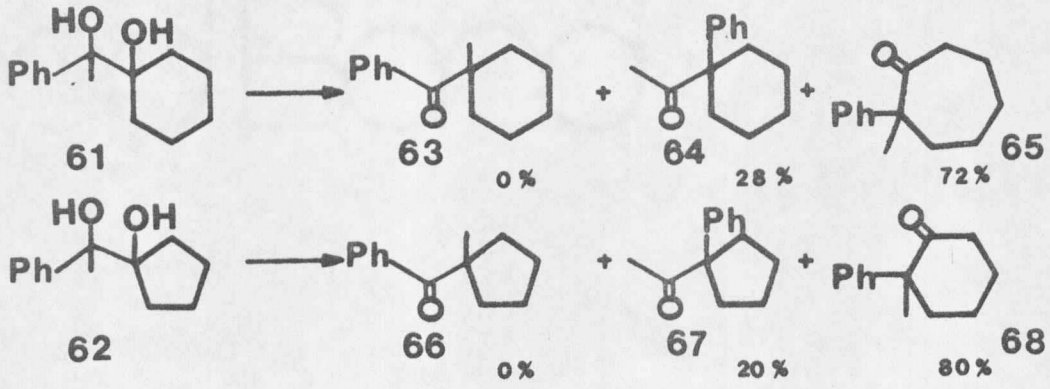


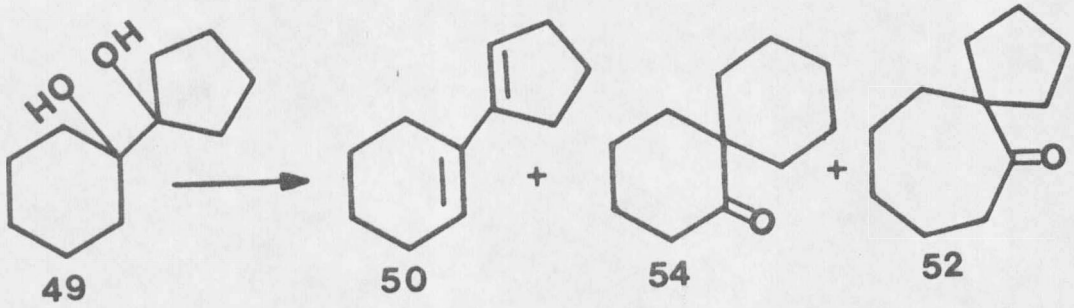

Figure 21. Ring Strain Effects

the 6-membered ring giving 64 than on the 5- to give 67. Their interpretation was that the $C_5$-ring expansion resulted in a release in strain of about 10 Kcal in the transition state[32] and this caused an acceleration in the rate of the reaction, whereas there was a retardation in the rate for the $C_6$-ring expansion because it involved a strained 7-membered ring transition state. They overlooked, however, the fact that the carbonium ion next to a phenyl group was more stable, and this phenomenon affected the rearrangement.

Changes in the reaction conditions have been demonstrated to influence profoundly the products resulting from the reaction.[33] This is best exemplified by the data in Table 4.

For analyzing the ring size effects on the rearrangement of cyclic 1,2-diols, Mundy and Otzenberger[25] examined the cis- and trans-8,9-dihydroxytetrahydroindan, (69), for which the direction of the rearrangement, relative stabilities of the carbonium ions, and the migratory aptitudes were not important (Figure 22). Treatment of the cis- and the trans-glycols with concentrated sulfuric acid at 0°C resulted in complete conversion to the spiro[4,4]nonan-6-one, (71), and the epoxide, (72) was not identified as a reaction product.[34] They also observed that 70 underwent rapid rearrangement to 71 (Figure 23). They concluded that the product stability was probably the determining factor in the rearrangement.

Table 4. Products from a Pinacol Rearrangement as Related to Conditions




| | | | |
|---|---|---|---|
| $POCl_3$/Pyridine | 100 | | |
| 20% $H_2SO_4$ | 76 | 20.1 | 3.9 |
| 50%$H_2SO_4$, 25°C | 76.3 | 15.1 | 8.6 |
| conc. $H_2SO_4$, 0°C | | 43.4 | 56.6 |
| $BF_3$/Ether, HOAc, 25°C | 60 | 19.5 | 20.5 |
| $BF_3$/Ether, 25°C | | 21.7 | 78.3 |

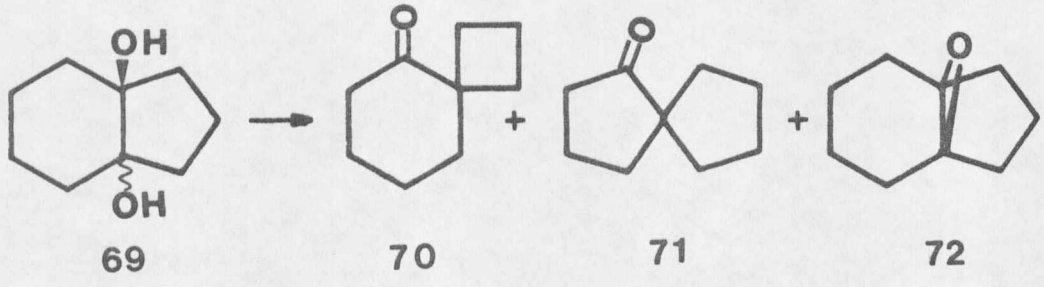



Figure 22. Ring Size Effect on the Rearrangement

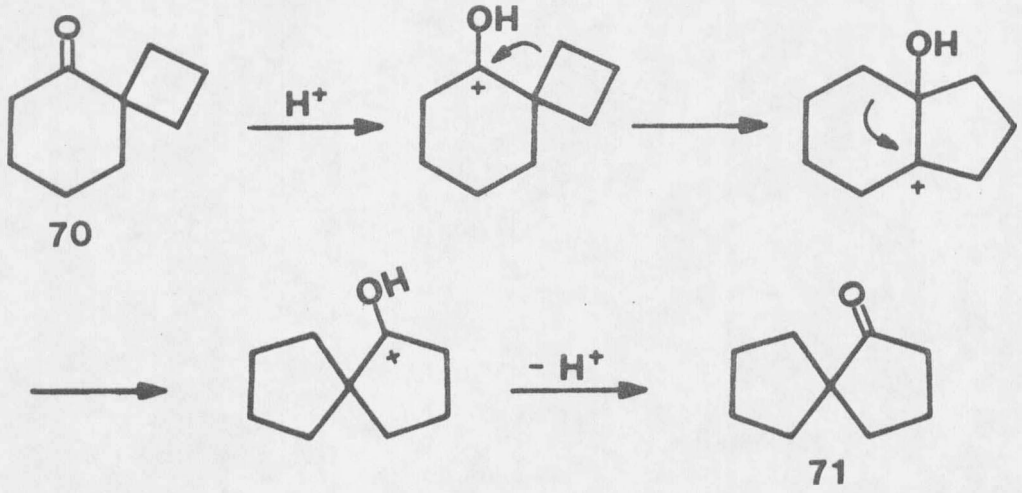



Figure 23. Rearrangement Between Two Spiranones

For another approach to evalate the effect of ring size on the course of the rearrangement, Mundy and Srinivasa[16] selected the system of 1,1'-bicycloalkyl glycols. With the observation that the reaction conditions of concentrated sulfuric acid at 0°C gives excellent conversion to spiranones with minimal alkene formation,[35] they carried out the reactions of which results are presented in Figure 24. From the data the following trends are noted:

$$C_6 \rightarrow C_7 > C_5 \rightarrow C_6 > C_7 \rightarrow C_8$$

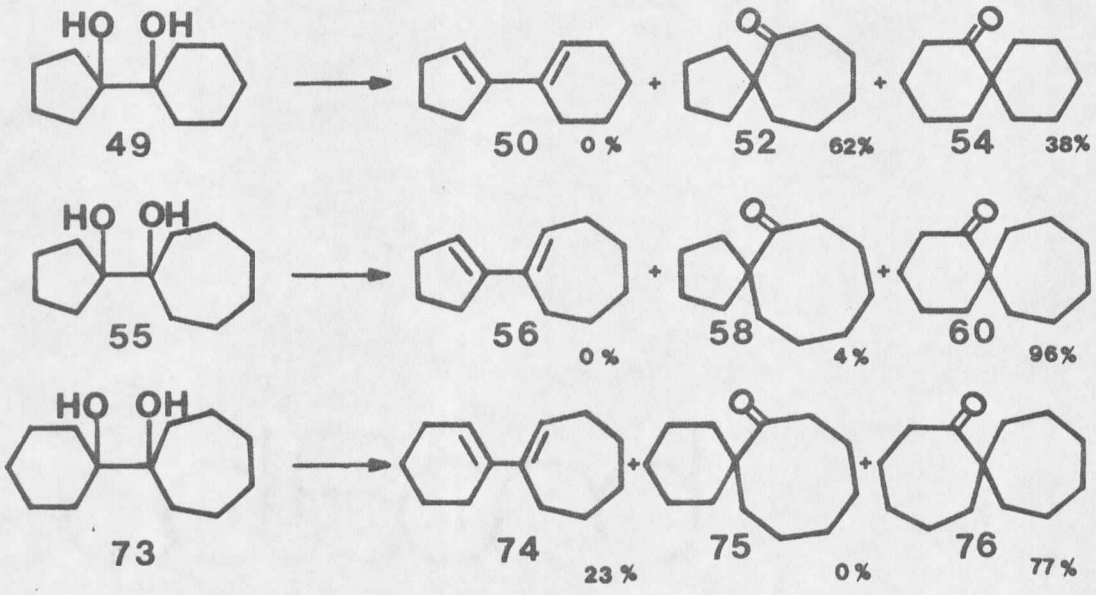



Figure 24. Ring Size Effects on the Pinacol Rearrangement

They rationalized these results by ideas of Stretwieser[31] and Brown[36] that relative reactivities of cycloalkanones to sodium borohydride demonstrated the tendency to maintain $SP^2$ hybridization to be $C_7 > C_5 > C_6$. Thus, 5-membered ring carbonium in **49** should be favored to result in **52** as the major product. For **55**, 7-membered ring carbonium ion should be favored to give **60** as the major product. For **73**, 7-membered ring carbonium ion should be favored to form **76** as the major product. They concluded that the formation of the initial carbonium ion in the pinacol rearrangement would be the major factor

in determining product composition when the reaction was carried out at 0°C with concentrated sulfuric acid.

As can be seen from the literature cited, the glycol stereochemistry, carbonium ion stability, product stability, and the reaction conditions contributed to the course of the rearrangement, though the interpretation of the results in some cases is questionable. In order to examine the factors controlling the pinacol rearrangement, particularly with the view of utilizing this reaction as a synthetically useful and predictable entry into substituted carbocyclic and heterocyclic spiranes, it is necessary to consider remote alkyl and heteroatom influences on the course of rearrangement. An attempt is made in the following section in order to unravel these problems from a broader perspective. For this purpose, only 6-membered rings were chosen, since our analysis required that ring size effects should not be involved. The course of the rearrangement was studied under a standard reaction condition.

## RESULTS AND DISCUSSION

### Alkyl Effects on the Pinacol Rearrangement

The glycols from coupling 2-, 3-, and 4-methylcyclohexanone were placed in concentrated sulfuric acid at 0°C and stirred for two hr, since these conditions were known to give the highest yield of spiranones with minimal alkene formation. After the work-up, the products were analyzed by GLC (20% SE-30 on Anakrom, 70/80 mesh) which indicated only one spiranone product from each pinacol. Possible spiranone products are shown in Figure 25. For rearrangement of 14, there will be only one possible spiranone, (84). However, for rearrangement of 12 and 13 there are two possible spiranones in each case, depending on the migratory aptitude of the bonds.

The rearrangement of 12 gave 51% of a spiranone product, as well as 22% of a non-characterized alkene fraction, about 3% of an unclassified minor product, and 24% of 2-methylcyclohexanone. This latter observation is unique to this pinacol, and there is no mechanistic rationalization for this.

Identification of 78 as the only rearranged product was readily confirmed by a decoupling experiment. Irradiation of the multiplet (1H at 2.82-2.91 ppm) collapsed the methyl doublet (3H at 1.01-1.03 ppm) and the reverse irradiation changed the multiplet of the tertiary α-proton to a doublet of doublets.

Rearrangement of **13** gave 54% of a non-characterized alkene fraction, 44% of a single spiranone and 2% of an unclassified

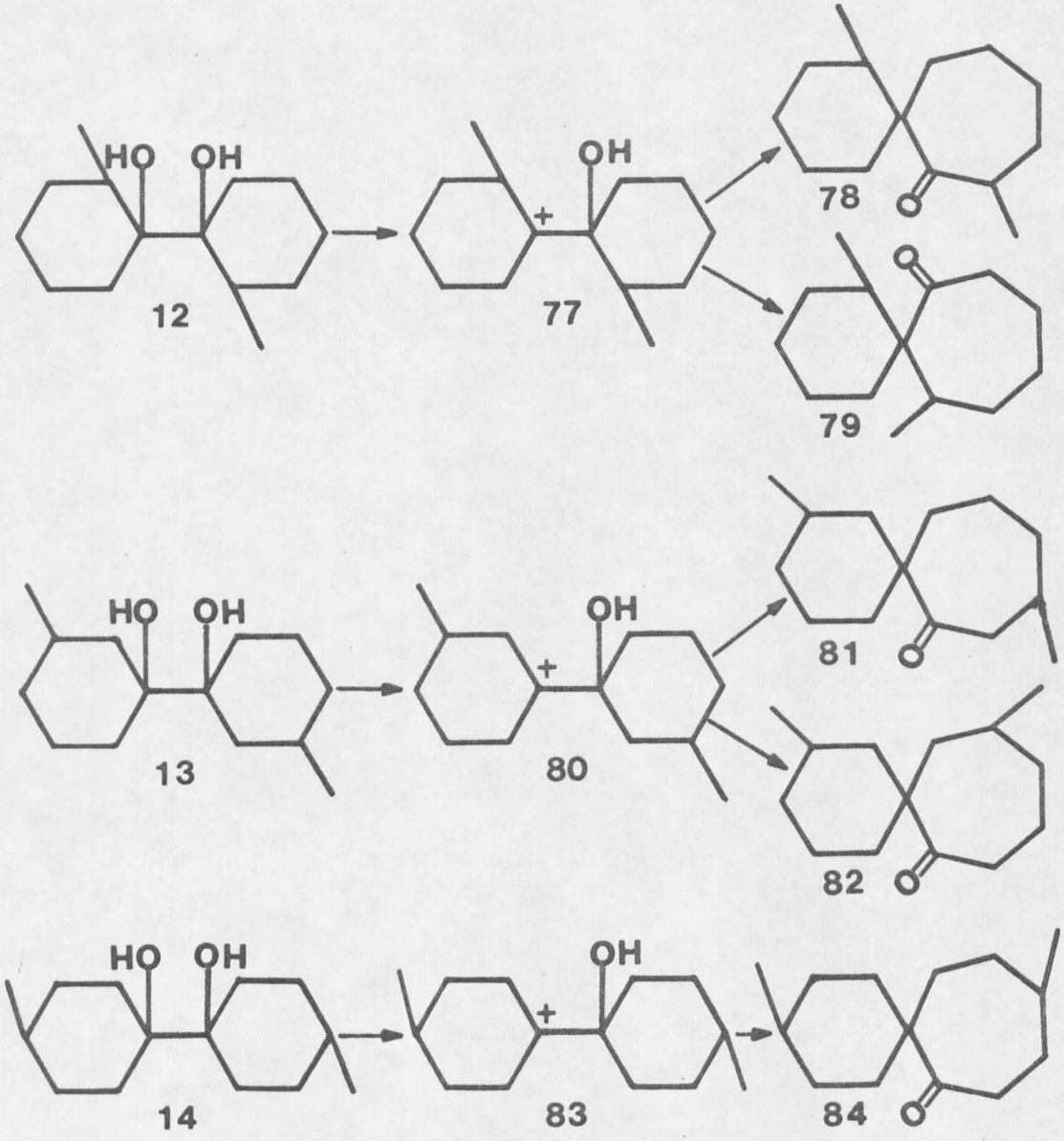



Figure 25. Possible Spiranone Products from the Pinacol Rearrangement

material. The identification of 81 as the rearrangement product was based on the following proton decoupling method. We expanded mechanically the $^1H$ NMR spectrum of the rearranged product by a Brucker 250 MHz spectrophotometer. Irradiation of the methylene envelope at 1.72 ppm resulted in the collapse of the triplet (1H at 2.60-2.69 ppm) to a broad doublet as well as the change of the methyl doublet (3H at 1.01-1.03 ppm) to a singlet. Irradiation of α-proton and methyl protons on the 7-membered ring resulted in the change of the peak at 1.72 ppm. This requires that the proton β- to the carbonyl must be attached to a carbon bearing a methyl group. In order to confirm the structure of 81, we expanded the $^1H$ NMR spectrum mechanically and chemically with the lanthanide shift reagent, $Eu(fod)_3$. To 81 was added ca. 0.05 equivalent amount of $Eu(fod)_3$ to expand the spectrum without line broadening effects. Irradiation of the methylene envelope at 2.00 ppm resulted in the collapse of the triplet (1H at 2.88-2.96 ppm) and at the same time the change of the methyl doublet (3H at 1.03-1.05 ppm) to a broad singlet. It was also observed that one of the α-hydrogen to the carbonyl was shifted ca. 2.61 ppm and two hydrogens were coupled together.

Rearrangement of 14 gave 33% alkene and the one possible spiranone, (84), in 64% yield.

From the results of these rearrangements, it appears that a

highly selective and preferential migration of the lesser substituted bond occurs. A steric effect might be rationalized for 12; however, in 13 the methyl groups are sufficiently remote from the reaction site to preclude this as the source of such high selectivity. It has been suggested by Profesor A. I. Meyers that the migratory aptitude may be a reflection of breaking a weaker bond to give a specific spiranone, since the more substituted bond becomes the more electron-rich bond by the electron donation effect of a methyl group. At this point we have shown that alkyl substituents can selectively direct the course of rearrangement. Additional work has to be done to determine the origins of these effects.

The Lanthanide Shift Reagent Experiment with a Spiranone

In the previous section, product identification was accomplished by simple decoupling experiments. However, in the situation of more complex possibilities, other techniques will be required. It appeared possible that use of the lanthanide shift reagent (LSR) technique with a high resolution NMR instrument might provide definition of the methylene envelope of spiranones and a valuable extension of the method. To test this, we examined the unsubstituted spiranone, (85).

The use of lanthanide shift reagents to determine the structure of organic molecules has been widespread since their discovery in

1969 by Hinckley.[37] Considerable effort has been expended in attempts to understand and utilize these lanthanide-induced shifts.[38-42] The commonly used lanthanide metals in shift reagents are Eu(III) and Yb(III) which induce downfield shifts and Pr(III) which causes upfield shifts. The shift reagent which is most commonly used is $Eu(fod)_3$.[43]

When a shift reagent (L) is added to a substrate (S) in solution, the shift reagent, acting as a Lewis acid, complexes with an electron donor on the substrate forming an L-S complex. This induces a change in the resonance frequencies in the NMR spectrum of the substrate. The lanthanide induced shift is thought to be predominantly of a pseudocontact nature, rather than a contact shift usually expressed by the McConnell and Robertson equation[44-46] (Figure 26). The induced shift ($\Delta\nu$) is the difference between resonance frequencies of the L-S complex and the uncomplexed substrate. The line segment connecting the lanthanide nucleus and the proton under consideration is r, and $\theta$ is the angle between this line and the bond between the lanthanide ion and the donor atom of the substrate. K is an adjustable scaling factor.

In order for the shift data to be of value in structure determination, it is necessary to compare the observed induced shifts with a set of shifts calculated using the McConnell-Robertson equation for each conformation. This operation can be performed by a

$$\Delta\nu = k(3\cos^2\theta - 1)/r^3$$

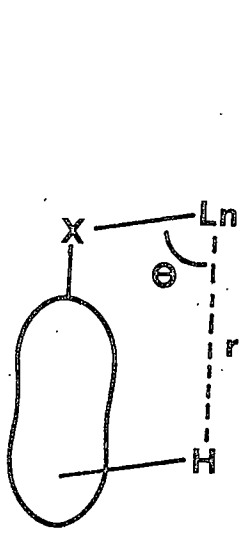



Figure 26. McConnell and Robertson Equation and Idealized Geometric Features of a Lanthanide-Substrate Complex

number of methods.[47-50] PDIGM, a computer program developed by Willcott and Davis,[48] calculates an induced chemical shift for each proton measured using the McConnell-Robertson equation and compares the calculated to the observed value. PDIGM searches, for each incremental distance the lanthanide is moved from the coordinating atom, a sphere around the coordinating atom. The position, reported in polar coordinates, at which the calculated induced shift most closely agrees with the experimental value is printed as output, along with the agreement factor (R), which measures how closely the calculated and experimental induced chemical shifts match. Two commonly held notions about use of these data are (1) that meaningful agreement factors must be < 0.10, and (2) that the distance of the lanthanide from the coordinating site should not be over 3.5 Å.

This LSR experiment has some limitations: (1) the compounds involving more than one functional group can cause problems; (2) line broadening at ratios of [LSR]/[substrate] approaching unity can give rise to the loss of fine structure; (3) there is a possibility that the lanthanide-substrate complex can cause the change of the configuration of the compound. The purpose of the LSR experiment with the spiranone in this study is to relate the methylene protons with the shifted values besides determining the structure.

Initially the shift experiment was performed by incrementally adding a solution of $Eu(fod)_3$ in deuterochloroform to a solution of 85 in the same solvent. It has become common, however, to utilize the incremental dilution method[45] in which a solution containing both the shift reagent and the substrate is diluted with the same concentrated solution of the substrate. Thus the concentration of the substrate remains constant while the concentration of the shift reagent decreases with each dilution.

When the ratio of $[Eu(fod)_3]/[85]$ was reached at ca. 0.2, ten distinguishable peaks of the proton NMR spectrum were observed. The integration was obtained and the decoupling experiment was performed with each dilution. The induced shift of ten peaks was plotted against the ratio of the concentration of $Eu(fod)_3$ to the spiranone, (85) (Figure 27), and the slopes were determined by a linear least

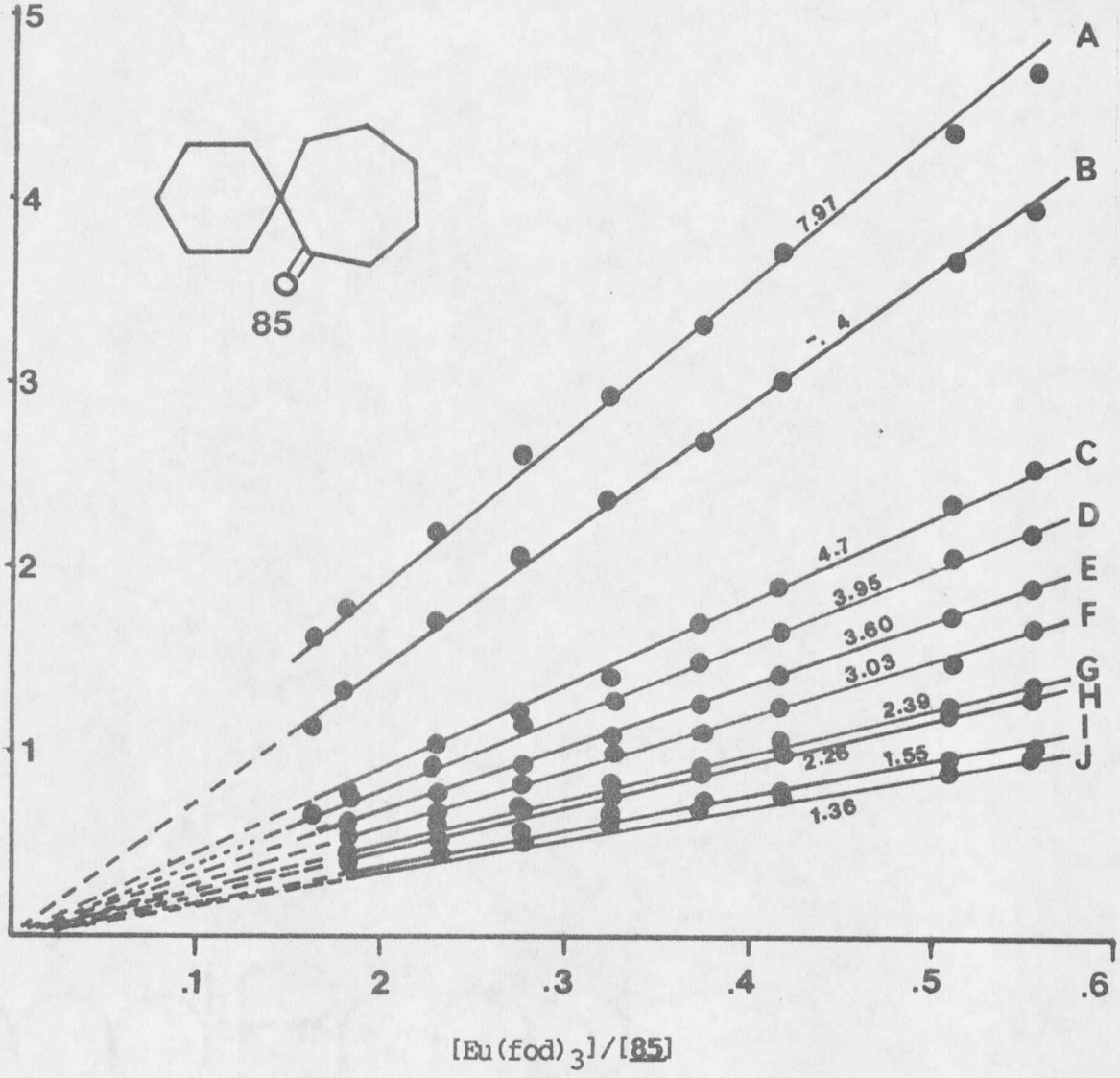



Figure 27. Plot of Change in Shift vs. [Eu(fod)$_3$]/[85]

squares method (Table 5). The result of decoupling experiment is shown in Table 5.

Table 5. Slopes from the Plot of vs. [Eu(fod)$_3$]/[85]

| Peak | Integration | Slope | Correlation Coefficient | Coupled With |
|---|---|---|---|---|
| A | 2H | 7.97 | 0.999 | F |
| B | 2H | 7.24 | 0.999 | H |
| C | 2H | 4.79 | 1.000 | H, J |
| D | 4H | 3.95 | 0.999 | E, G |
| E | 2H | 3.60 | 0.998 | D, G |
| F | 2H | 3.03 | 0.999 | A, H |
| G | 2H | 2.39 | 0.999 | D, E |
| H | 2H | 2.26 | 0.999 | B, C, F, I |
| I | 1H | 1.55 | 0.999 | H, J |
| J | 1H | 1.36 | 0.999 | C, H, I |

The coordinates corresponding to 85 were generated from Dreiding models. The slopes were then assigned to the various protons in each configuration with the base on the result of the decoupling experiment and comparing the relative induced shift amount of each proton by calculation using the McConnell-Robertson equation from Dreiding models. A thorough analysis of each structure with a

variety of slope proton assignments was made. This resulted in the generation of a set of R-values which produced a minimum when plotted against the Eu-O distances (Figure 28). The values of R and the distance at the minimum were 5.97% and 2.32 Å, respectively. The slope proton assignment is shown in Figure 28.

Analysis of other structures and slope-proton assignments did not produce minima, and the lowest agreement factor calculated, with a Eu-O distance span of 2.0-3.5 Å was 12.3%. A Eu-O distance of 2.32 Å is quite reasonable in view of the distances determined for other oxygen containing compounds.[45-46] With this result we can demonstrate that it is possible to distinguish the complex methylene envelope of the proton NMR using a lanthanide shift reagent.

A Heteroatom Effect on the Pinacol Rearrangement

We embarked on the study of a remote heteroatom influence on the course of the pinacol rearrangement. We chose 23, easily prepared by the mixed coupling of cyclohexanone and tetrahydropyran-4-one, as a model system. This model was rationally chosen based on the following considerations: (1) the tetrahydropyran ring is structurally very similar to cyclohexane,[51] thus eliminating ring strain effects, and (2) solvolysis studies have demonstrated that 86

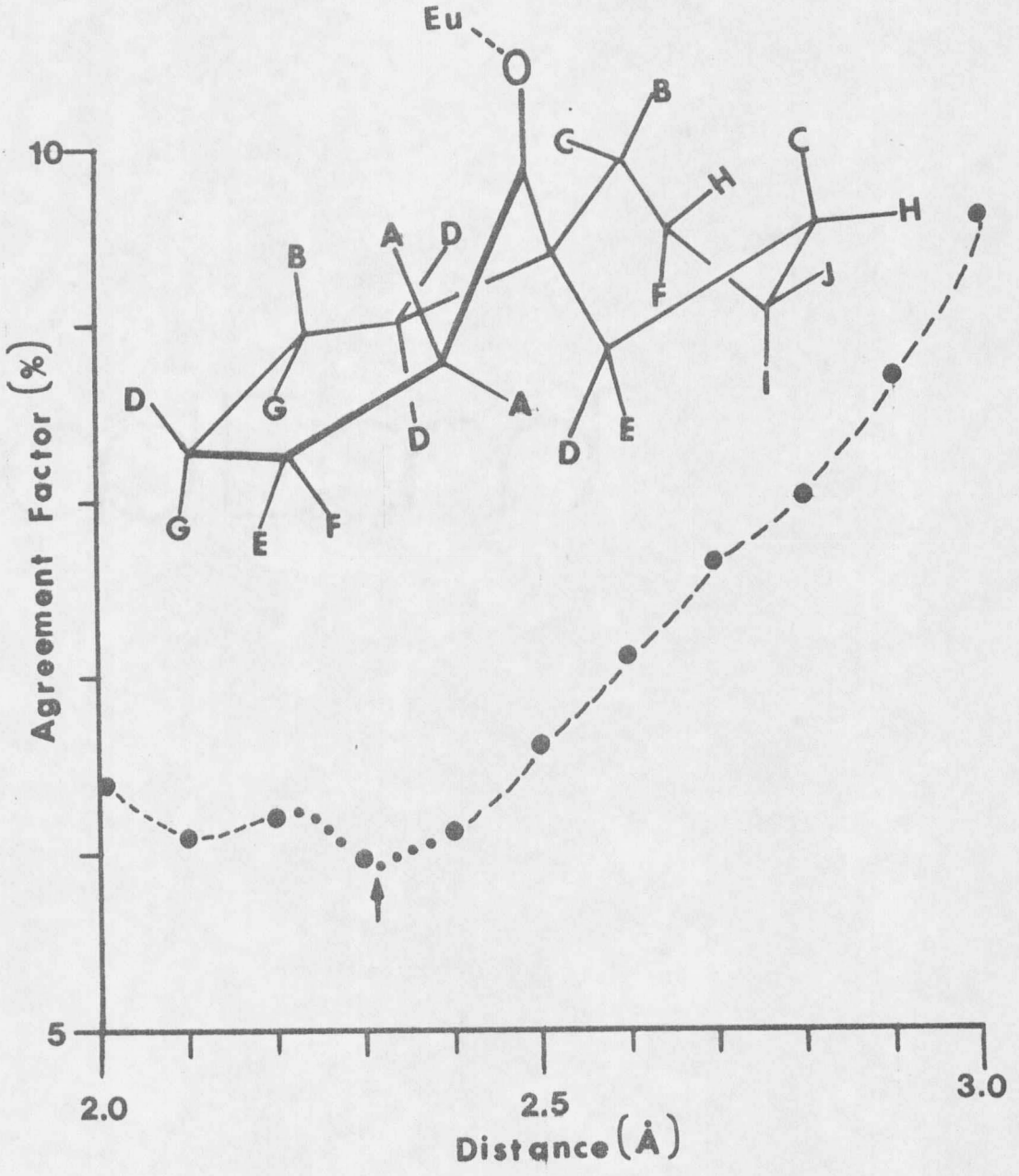
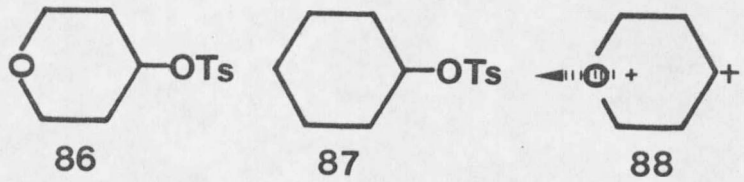



Figure 28. Plot of R-Value vs. Eu-O Distance

is less reactive than **87**, presumably a consequence of transannular dipolar effects[18] (Figure 29).




86 87 88

rel. rate 1 : 37

Figure 29. Transannular Dipolar Effect on First Order Solvolysis

We can expect that there are two possible rearranged products by path A or path B, as shown in Figure 30, and would predict **92** as a major product since carbonium ion formation would be preferred on the cyclohexyl ring moiety by path A, thus eliminating the unfavorable dipole effects. After the general procedure, the viscous product was analyzed by GLC to show 91% of only one spiranone product and 9% of

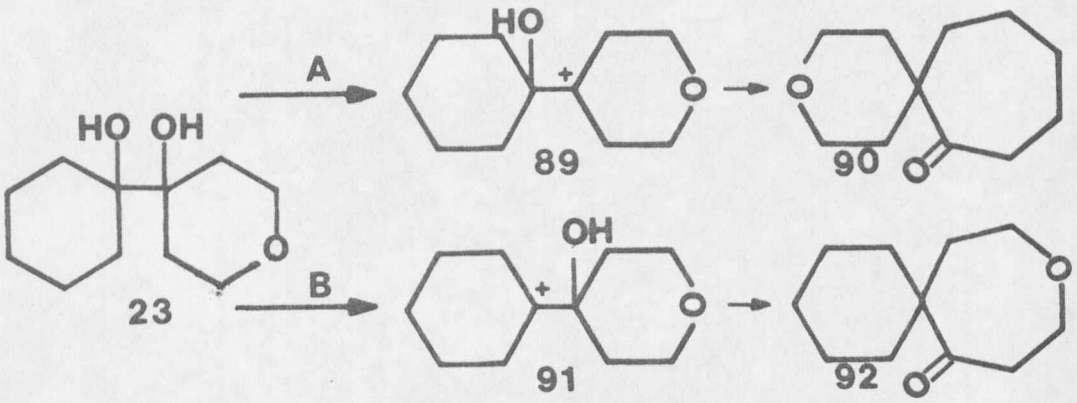



Figure 30. Two Possible Compounds by the Rearrangement

(2H at 1.91-2.00 ppm) is consistent with $H_b$ and a large, complex proton envelope (10H at 1.39-1.76 ppm) is assigned to $H_e$ and $H_c$ (Figure 31). It was also observed that two β-hydrogens ($H_c$) to the oxygen atom were shielded to ca. 1.49 ppm probably by the anisotropic effect of the carbonyl bond. The signals at 3.67-3.72 ppm are most logically assigned to the α-protons to the heteroatom, and integration fits both structures. In a decoupling experiment, irradiation of these protons causes a collapse of the 1.91-2.00 ppm multiplet to distinct doublets centered at 1.99 and 1.93 ppm and simplify the spectrum at 1.44-1.49 ppm. When the protons at 1.91-2.00 ppm were irradiated, simplification of peaks at 3.67-3.72 ppm and 1.44-1.49 ppm was detected. Irradiation of α-protons (at 2.49-

2.54 ppm) to the carbonyl only causes a change in the region of 1.55-1.76 ppm.

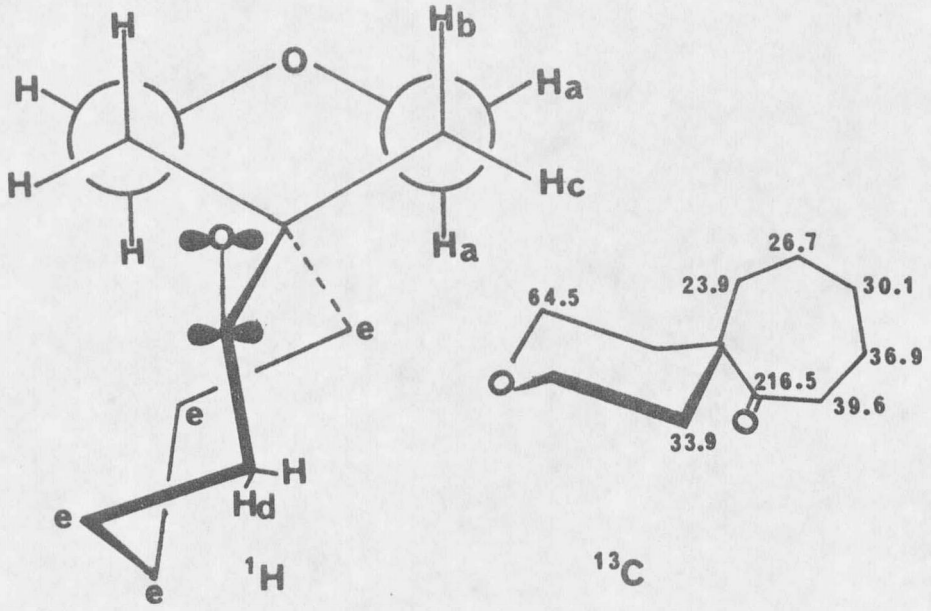



Figure 31. NMR Assignment for **90**

A combination of the broad band and the off-resonance $^{13}C$ NMR spectra resulted in the following signals (ppm relative to TMS): 23.88 (t, 1C); 26.73 (t, 1C); 30.31 (t, 1C); 33.88 (t, 1C); 36.99 (t, 1C); 39.63 (t, 1C); 64.50 (t, 2C); 216.5 (s, 1C). The quaternary carbon was not observed. This combined data, summarized in Figure 31, fix the structure as **90**.

It is apparent that this result contradicts Mundy and Srinivasa's proposal that initial ease of carbonium ion formation controls the course of rearrangement, unless an immediate and total secondary rearrangement occurs (Figure 32).

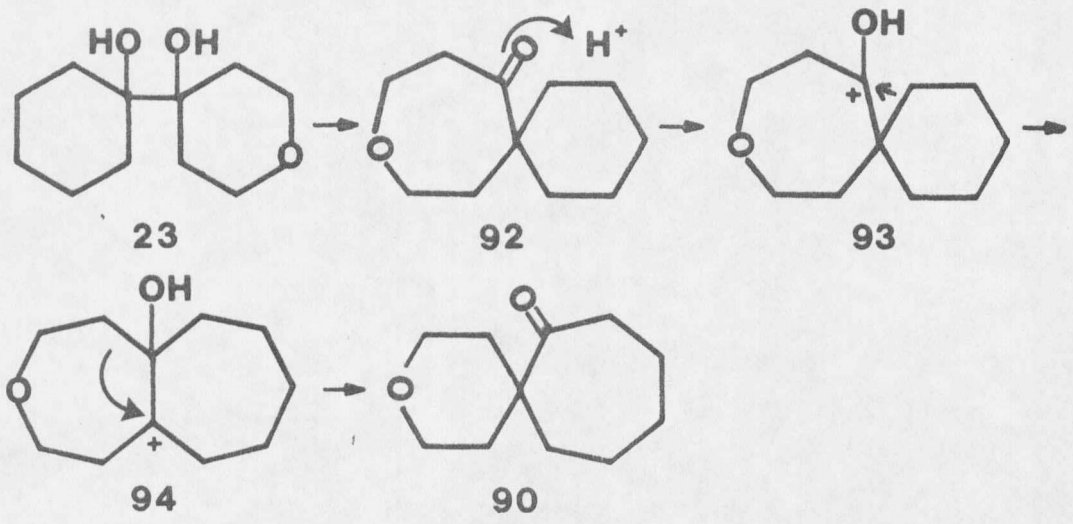
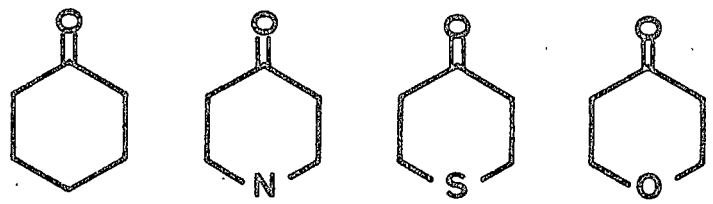



Figure 32. Proposed Secondary Rearrangement of **92** to **90**

We might rationalize the driving force for this secondary rearrangement with the supposed instability of **92** as a result of a proper disposition of the ring oxygen to the carbonyl for a destabilizing dipole effect. A similar effect has been rationalized for the increased rate of sodium borohydride reduction of **95** and **96** relative to cyclohexanone (Figure 33).[52] Interestingly, in this study the obvious molecule to examine was **20**, but their report omits

it. We found that 20 in competition with cyclohexanone is so unreactive that no reduction is observed.




| | 21 | | 95 | | 96 | 20 |
|---|---|---|---|---|---|---|
| rel. rate | 1 | : | 6 | : | 11 | |

Figure 33. Borohydride Reduction Study by the Geneste Group

However, our assumption on the secondary rearrangement has some doubts considering the facts that (1) it appears that a positively charged, $sp^2$-hybridized carbon opposite the oxygen is not so unfavorable by our observation; (2) the dipole effect seems not enough to induce the secondary rearrangement to formulate totally one spiranone in concentrated sulfuric acid at 0°C since an oxygen atom in this condition can be protonated to reduce the dipole effect of a heteroatom; (3) there is no significant ring size effect involved to cause the rearrangement; (4) the secondary rearrangement to produce the thermodynamic product under this condition has rarely been observed, except the high ring strained case;[25] (5) Mundy and

Srinivasa[35,53] proposed that under this condition, a large percentage of the product would reflect kinetic control and that under more dilute sulfuric acid and high temperature, the product would be thermodynamically controlled to experience the secondary rearrangement. Figure 34 shows some of their results. It was also observed that only **52** underwent 100% conversion to **54** when the two

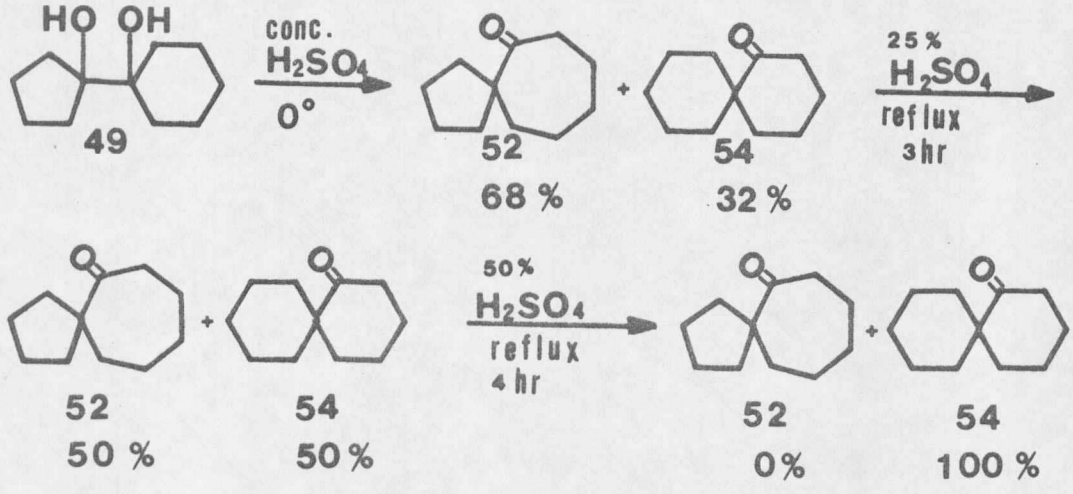



Figure 34. Secondary Rearrangement of the Spiranone Product by Mundy and Srinivasa

spiranones, (**52** and **54**) were separately refluxed with 25% sulfuric acid for two hr. When the spiranone, (**52**), was treated with 96% sulfuric acid at 0°C, no secondary rearrangement occurred. When **23** was treated with 50% sulfuric acid at reflux, one of the major

products was the dehydration compound ($M^+$ = 164) and 3% of **90** was observed by GLC. The other products were unidentifiable.

In order to examine further our doubts on the secondary rearrangement with concentrated sulfuric acid at 0°C, we chose spiro[5,6]dodecan-7-one, (**85**), as a model system, since **85** had the same ring system as **92**, ignoring the contribution of an oxygen atom on the secondary rearrangement. We prepared spiro [5,6]-8-methyldodecan-7-one, (**97**) to distinguish the rearrangement (Figure 35). We

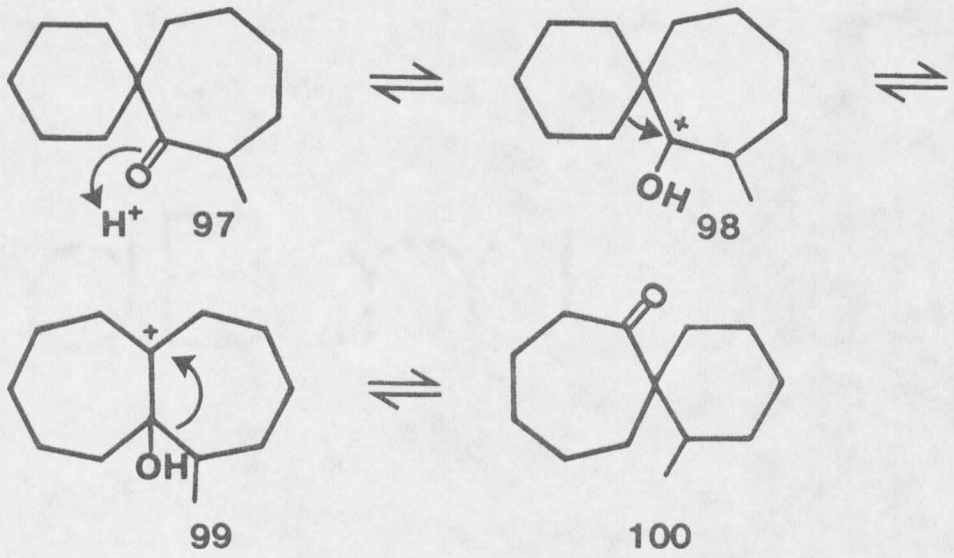
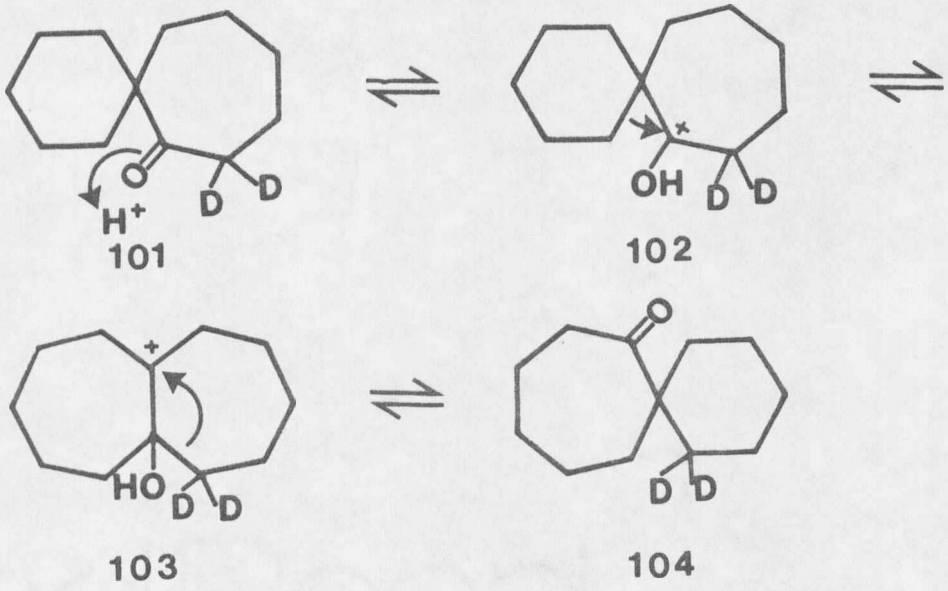



Figure 35. Attempted Rearrangement of **97** to **100**

could expect that there was no driving force since there was not much difference between the stabilities of **97** and **100**. After **97** was treated under the general condition, no rearrangement was observed.

There might be a possibility that methyl group could contribute to resistance towards rearrangement. To avoid any influence from the substitutents and distinguish a product from a starting compound, spiro[5,6]-8,8-dideuterododecan-7-one, (**101**), prepared from **85** with sodium and deuterium oxide, was examined under the general condition (Figure 36). Without any surprise, no rearrangement was observed.




101 102 103 104

Figure 36. Attempted Rearrangement from **101** to **104**

From this observation we feel that the rationalization of dipole effects to cause the rearrangement seems to be unreasonable and that simply preferential formation of **89** produces **90**, though we can not ascribe the source of heteroatom specificity. At this point we can

conclude that there is a highly specific heteroatom effect on the rearrangement under the general condition. Further work has to be done to generalize the heteroatom influence.

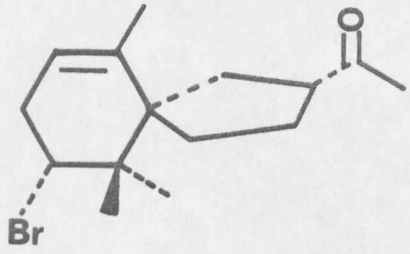
Future Work

Although we have observed that alkyl substituents can selectively direct the course of rearrangement and that specific heteroatom influences are possible, this work is not enough to predict the migratory aptitude, steric requirement, mixed substituent effects, olefin group influence, etc., in the more complicated systems which are useful for synthesis of natural products. Thus, the study on the rearrangement of a variety of mixed coupling glycols should be continued to fully understand alkyl substituent effects and heteroatom influences on the rearrangement.

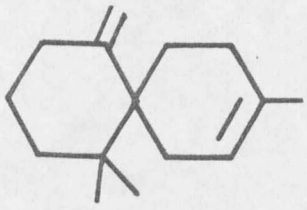
Our ultimate goal in studying the pinacol rearrangement is to offer a simple, elegant way to synthesize many naturally occurring spirocompounds. It may be possible to obtain the desired spiranones by modifying the glycols and the reaction conditions suitably for the rearrangement step. There have been a few reviews[54-56] on the methodologies, including the pinacolic rearrangement of 1,2-glycols, for the synthesis of spirocompounds. Many naturally occurring spirocompounds have been isolated and synthetic strategies have been explored. Table 6 lists a few natural products which might possibly

be synthesized by the pinacol rearrangement.

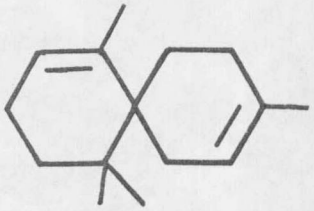
Table 6. Typical Natural Spirocompounds



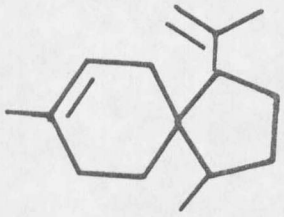

Spirolaurenone[57]



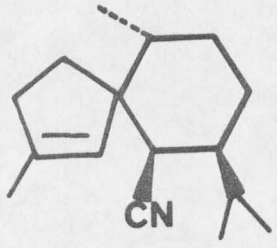
Chamigrene[58]



α-Chamigrene[58]

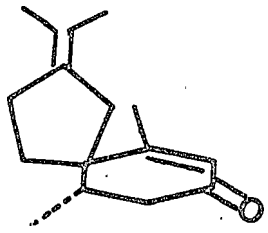


Acoradiene[59]

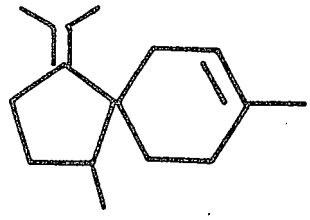



Axisonitile-3[60]

Table 6 (continued)



β-Vetivone[61]



Alaskene[62]

## EXPERIMENTAL

General. $^{1}H$-NMR and $^{13}C$-NMR spectra were run on a Brucker 250 MHz spectrophotometer using deuterochloroform as a solvent and TMS as an internal standard. GLC analyses were recorded by a Varian Aerograph Model 2700 using 10%, 15%, and 20% SE-30 on Anakrom, 70/80 mesh, or 15% SE-30 on Chromosorb W, 60/80 mesh, connecting with 15% Carbowax 20 M on Chromosorb W, 60/80 mesh, as columns. The column temperature was maintained at 200°C and the pressure of the gas flow was kept at 30 psi. Mass spectra were obtained with a Varian Model CH5 mass spectrometer. IR spectra were obtained on a Beckmann IR-5 or a Beckmann IR-20 spectrophotometer using sodium chloride discs. All melting points are uncorrected. Dry THF was prepared by distillation from $LiAlH_4$. Magnesium metal powder (Baker & Adamson) was used, and the purity of titanium tetrachloride (Alfa) was 99.9%. Unless otherwise specified, commonly needed reagents were used as received.

### General Preparation of Pinacols

To a solution of mercuric chloride (0.88 g, 3.2 mMol) in 60 mL of dry THF was added magnesium metal powder (70-80 mesh, 2.88 g, 0.12 Mol) and the resulting mixture was stirred at room temperature for half an hour under nitrogen. The turbid supernatant liquid was withdrawn by syringe and the remaining amalgam was washed in three 20-mL portions of dry THF. To the resulting dull gray amalgam was

added 100 mL of dry THF and the mixture was cooled to -10°C. Titanium tetrachloride (6.6 mL, 60 mMol) was added dropwise to the solution to give a yellow-green slurry. A solution of methylcyclohexanone (4.48 g, 40 mMol) in 100 mL THF was added while allowing the temperature to rise gradually to 0°C. The solution was stirred for 2 hr after the solution turned a dark purple color at 0°C. The reaction products were quenched with 10 mL of saturated potassium carbonate solution followed by stirring for half an hour. The resulting dark purple mixture was diluted with ethyl ether and filtered through hyflo-super cel and ashless filter paper (Whatman No. 41). The filtrate was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and evaporated in vacuo to afford a semi-solid crude mixture. The crude mixture was separated by column chromatography on silica gel using a combination of petroleum ether (35-60°C) and ethyl ether as an eluant. Further purification of pinacols (white crystals) was performed by recrystallization from hexane.

Preparation of 2-Methylcyclohexyl-2-Methylcyclohexane-1,1'-diol, (12)

The reaction for preparing 12 was carried out as described in the general procedure. Quantities of reagents used were the following: 2-methylcyclohexanone (8.96 g, 80 mMol); magnesium (5.76 g, 0.24 Mol); mercuric chloride (1.76 g, 6.4 mMol); titanium chloride

(13.2 mL, 120 mMol). After the work-up, 8.4 g of crude products was obtained. GLC analysis showed that there were 8.6% of 12, 1.8% of the alkene product, (15), and 88% of the starting material, (9).

NMR: 2.14 (2H, s); 1.23-1.83 (18H, m); 0.94-0.97 (6H, d, J = 6.6 Hz).

MS: 226 ($M^+$), 113, 112, 96, 95, 69, 55, 43, 41, 32.

M.P.: 91.5°C.

Calculated for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58

Found: C, 74.56; H, 11.29

Preparation of 3-Methylcyclohexyl-3-Methylcyclohexane-1,1'-Diol, (13)

The pinacol, (13), was prepared by the general procedure using the reagents as follows: 3-methylcyclohexanone (4.48 g, 40 mMol); magnesium (2.88 g, 0.12 Mol); mercuric chloride (0.88 g, 3.2 mMol); titanium chloride (6.6 mL, 60 mMol). After the work-up, 4.2 g of crude products was acquired. GLC analysis showed that there were 75.8% of 13, 12.9% of the alkene product, (16), and 11.3% of the starting material, (10).

NMR: 2.56 (2H, s); 1.10-1.95 (18H, m); 0.88-0.90 (6H, d, J = 6.0 Hz).

MS: 226 ($M^+$), 113, 112, 95, 69, 55, 43, 41.

M.P.: 83.5-84.5°C.

IR: 3450 (s), 2900 (s), 1350 (br s), 1125 (s), 990 (s), 950 (s) $cm^{-1}$.

Calculated for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58

Found: C, 74.49; H, 11.65

Preparation of 4-Methylcyclohexyl-4-Methylcyclohexane-1,1'-Diol, (14)

By the general preparation of pinacols, 14 was prepared using the following reagents: 4-methylcyclohexanone (8.96 g, 80 mMol); magnesium (5.76 g, 0.24 Mol); mercuric chloride (1.76 g, 6.4 mMol); titanium chloride (13.2 mL, 120 mMol). After the work-up, 8.80 g of crude products was obtained. GLC analysis showed that there were 64.6% of 14, 1.7% of the alkene product, (17), and 33.7% of the starting ketone, (11).

NMR: 1.87 (2H, s); 1.13-1.68 (18H, m); 0.89-0.92 (6H, d, J = 5.3 Hz).

MS: 226 ($M^+$), 113, 112, 95, 55, 43, 41.

M.P.: 117.5-118.5°C.

IR: 3400 (s), 2950 (s), 1440 (br m), 1150 (m), 995 (s), 925 (s) $cm^{-1}$.

Calculated for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58

Found: C, 74.39; H, 11.55

Preparation of (+) 3-Methylcyclohexyl-3-Methylcyclohexane-1,1'-Diol, (6)

Compound 6 was prepared by the same method used for preparation of 13.

NMR: 2.67 (2H, s); 1.10-1.95 (18H, m); 0.87-0.89 (6H, d, J = 6.1 Hz).

MS: 226 ($M^+$), 113, 112, 95, 69, 55, 43, 41.

M.P.: 78.5-79°C.

Calculated for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58

Found: C, 74.10; H, 11.58

Preparation of Sulfite Ester of 13, (18)

To 3-methylcyclohexyl-3-methylcyclohexane-1,1'-diol (0.5 g, 2.2 mMol) in 2.5 mL of dry pyridine and 3 mL of ethyl ether, was added dropwise thionyl chloride (0.85 mL, 11.6 mMol) with stirring at 15°C. After the addition, the reaction mixture was stirred for an hour at room temperature and then poured into ice. The organic compound was extracted three times with ether. The combined ether extract was washed with water, saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. 0.42 g (70%) of a liquid product, (18) was obtained after evaporating the solvent. GLC analysis (10% SE-30 on Anakrom, 70/80 mesh or 15% Carbowax-Chromosorb, 60/80 mesh) showed only one compound.

NMR: 1.01-2.24 (18H, m); 0.92-0.94 (6H, d, J = 6.6 Hz).

MS: 208 ($M^+ - 64$), 160, 113, 112, 95, 81, 69, 67, 55, 41, 39.

IR: 2850 (s), 1420 (m), 1360 (w), 1210 (s), 1140 (w), 915 (m), 850 (s), 815 (m), 735 (m) $cm^{-1}$.

Calculated for $C_{14}H_{24}O_3S$: C, 61.73; H, 8.88

Found: C, 61.73; H, 8.88

Preparation of Sulfite Ester of 14, (19)

4-Methylcyclohexyl-4-methylcyclohexane-1,1'-diol (0.4 g, 1.7 mMol) was treated the same as the previous reaction. After the work-up, 0.36 g (75%) of 19, a yellow liquid, was obtained. GLC analysis showed only one compound.

NMR: 1.18-2.27 (18H, m); 0.95-0.97 (6H, d).

IR: 2900 (s), 1450 (m), 1370 (w), 1210 (s), 970 (m), 890 (s), 820 (m), 735 (m).

Calculated for $C_{14}H_{24}O_3S$: C, 61.73; H, 8.88

Found: C, 64.68; H, 9.47

Preparation of 4-Tetrahydropyranylcyclohexane-1,1'-Diol, (23)

The mixed pinacol, (23) was prepared by the general procedure using a four-fold excess of cyclohexanone and tetrahydropyran-4-one. Quantities of reagents used are: cyclohexanone (7.84 g, 80 mMol); tetrahydropyran-4-one (2.0 g, 20 mMol); magnesium (5.76 g, 0.24

Mol); mercuric chloride (1.76 g, 6.4 mMol); titanium chloride (133.2 mL, 120 mMol). After the work-up, the crude product (9.2 g) was analyzed by GLC to show that there were 48.8% of 22, 18.8% of 23, 26.6% of 25, 2.5% of 26, 2% of 27, and 1.5% of an unidentified material. Hexane was poured into the crude products and diols were collected by filtration. Separation of 22 and 23 was carried out by column chromatography on silica gel using methanol and hexane solution (1.5:1 mixture) as an eluant. White crystals, (23) were acquired.

NMR: 3.73-3.88 (4H, m); 2.02 (2H, s); 1.13-1.86 (14H, m).

MS: 200 ($M^+$), 113, 101, 100, 99, 98, 84, 81, 71, 55, 43, 41.

M.P.: 148-148.5°C.

Calculated for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07

Found: C, 65.70; H, 9.84

Preparation of 4-Tetrahydropyranyl-4-Tetrahydropyran-1,1'-Diol, (24)

The pinacol, (24) was prepared by the general procedure using the following reagents: tetrahydropyran-4-one (0.50 g, 5 mMol); magnesium (0.32 g, 13 mMol); mercuric chloride (0.1 g, 0.36 mMol); titanium chloride (0.8 mL, 7.3 mMol). After the work-up, the crude residue was poured into hexane, and the crystals were washed with a small amount of ethyl ether to give 45 mg (8.9%) of white crystals, (24).

MS: 202 ($M^+$), 102, 101, 100, 84, 83, 71, 57, 56, 55, 53, 44, 43, 42, 41, 39, 31, 29.

IR: 3400 (s), 2950 (m), 2850 (m), 1470 (m), 1360 (m), 1310 (m), 1250 (m), 1140 (s), 1100 (s), 1040 (s), 1010 (m), 960 (m), 860 (s), 820 (m) $cm^{-1}$.

Calculated for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97

Found: C, 59.14; H, 9.09

Attempted Mixed Coupling Reaction of Tetrahydrothiopyran-4-One with Cyclohexanone

Using a four-fold excess of cyclohexanone (3.37 g, 34.4 mMol) and tetrahydrothiopyran-4-one (1.0 g, 8.6 mMol), the coupling products were prepared by the general method. After the work-up, the crude and semi-solid product (3.8 g) was analyzed by GLC to show that there were 48% of 22, 41% of 33, 7% of 32, 3% of 25, and 1% of starting materials. The structures of 22 and 25 were confirmed by comparison with the previously prepared authentic samples. The components, (32) and (33) were characterized by the relative GLC retention time and mass spectra.

MS of 32: 180 ($M^+$), 162, 125, 109, 94, 91, 81, 79, 67, 55, 41, 39, 29.

NMR of 33: 5.77-5.78 (2H, d); 2.12-2.20 (6H, m); 1.55-1.72 (10H, m).

MS of 33: 162 ($M^+$), 133, 119, 105, 94, 91, 81, 80, 79, 77, 41.

General Preparation of Spiroketones

To 100 mL of concentrated sulfuric acid (Baker, 96.3%) was slowly added 1 g of a pinacol at 0°C. The mixture was stirred for 2 hr at this temperature and poured onto ice. The organic layer was extracted three times with ethyl ether and washed with saturated sodium bicarbonate solution, water, and saturated sodium chloride solution. The ether solution was dried over anhydrous magnesium sulfate and, after evaporation of solvent, a liquid product was obtained. The compound was further analyzed by GLC (20% SE-30 on Anakrom, 70/80 mesh) and collected for spectral data.

Preparation of Spiro[5,6]-1,8-Dimethyldodecan-7-One, (78)

The rearrangement of 12 (200 mg, 0.88 mMol) was carried out by the general procedure to result in the crude liquid product (137 mg). The product was analyzed by GLC to show 50.7% of 78, 22.4% of olefin mixtures, and 24.3% of 2-methylcyclohexanone.

NMR: 2.82-2.91 (1H, m); 1.40-1.92 (17H, m); 1.01-1.03 (3H, d, J = 6.6 Hz); 0.80-0.83 (3H, d, J = 7.2 Hz).

MS: 208 ($M^+$), 123, 110, 109, 96, 95, 82, 81, 67, 55, 41, 29.

IR: 2870 (s), 2820 (s), 1690 (m), 1450 (m), 1370 (w) $cm^{-1}$.

Calculated for $C_{14}H_{24}O$: C, 80.71; H, 11.61

Found: C, 80.89; H, 11.58

Preparation of Spiro[5,6]-2,9-Dimethyldodecan-7-One, (81)

By the general procedure, 13 (200 mg, 0.88 mMol) was rearranged to yield the crude product (140 mg). GLC analysis showed it contained 44.2% of 81, 53.6% of olefin mixtures, and 2.2% of unidentified compounds.

NMR: 2.60-2.69 (1H, tr); 2.00-2.23 (2H, m); 1.08-1.78 (15H, m); 0.99-1.01 (3H, d, J = 6.6 Hz); 0.84-0.86 (3H, d, J = 5.9 Hz).

MS: 208 ($M^+$), 139, 108, 95, 82, 81, 69, 67, 55, 43, 41, 29.

IR: 2870 (s), 2820 (s), 1690 (m), 1450 (m), 1370 (w) $cm^{-1}$.

Calculated for $C_{14}H_{24}O$: C, 80.71; H, 11.61

Found: C, 80.92; H, 11.60

Preparation of Spiro[5,6]-3,10-Dimethyldodecan-7-One, (84)

The rearrangement of 14 (200 mg, 0.88 mMol) was carried out by the general procedure to yield 137 mg of the crude product. GLC analysis showed that it contained 64.3% of 84, 33.4% of an olefin mixture, and 0.3% of unidentified compounds.

NMR: 2.71-2.77 (1H, tr d); 1.89-2.30 (2H, m); 1.04-1.85 (15H, m); 0.90-0.92 (3H, d); 0.88-0.89 (3H, d).

MS: 208 ($M^+$), 139, 123, 95, 94, 93, 81, 69, 68, 67, 55, 41, 39, 29.

IR: 2870 (s), 2820 (s), 1690 (m), 1450 (m), 1370 (w), $cm^{-1}$.

Calculated for $C_{14}H_{24}O$: C, 80.71; H, 11.61

Found: C, 80.52; H, 11.77

Preparation of Spiro[5,6]-3-Oxoundecan-7-One, (90)

The glycol, (23) (180 mg, 0.9 mMol) was rearranged by the general procedure to yield 91% of 90 and 9% of an unidentified compound ($M^+$ = 180). The identification of 90 was achieved by the decoupling experiment and $^{13}C$ NMR.

$^1H$ NMR: 3.67-3.72 (4H, dt); 2.49-2.54 (2H, d); 1.91-2.00 (2H, m); 1.39-1.76 (10H, m).

$^{13}C$ NMR: 216.5 (1C, s); 64.50 (2C, t); 39.63 (1C, t); 36.99 (1C, t); 33.88 (2C, t); 30.31 (1C, t); 26.73 (1C, t); 23.88 (1C, t).

MS: 182 ($M^+$), 138, 110, 109, 84, 83, 81, 67, 55, 41.

IR: 2880 (s), 2800 (s), 1700 (s), 1450 (w), 1250 (m), 1120 (m) $cm^{-1}$.

Calculated for $C_{11}H_{18}O_2$: C, 72.47; H, 9.95

Found: C, 72.38; H, 10.00

Preparation of Spiro[5,6]-8-Methyldodecan-7-One, (97)

The spiro[5,6]dodecan-7-one, (85) was prepared from the rearrangement of 22. An oil dispersion of sodium hydride (0.60 g, 12.2 mMol) was washed with three portions 10-mL of dry THF under nitrogen. The spiranone, (85) (1.1 g, 6.1 mMol) in 20 mL of THF was

added to sodium hydride in 20 mL of THF and the mixture was stirred for an hour at room temperature, followed by the addition of methyl iodide (2.6 g, 18.3 mMol) in 10 mL of THF. The solution was refluxed for 7 hr. After evaporation of THF, 10 mL of water was added to the semi-solid product in an ice bath. The organic layer was extracted three times with methylene chloride. The combined layer was washed with water, saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Methylene chloride was evaporated in vacuo to give 0.91 g of liquid products. GLC analysis (10% Apiezon on Chromosorb W, 60/80 mesh) showed only 20% of methylation was accomplished. Without separation, 85 and 97 were subjected to concentrated sulfuric acid at various temperatures (0-50°C). No rearrangement product was observed. The NMR spectrum and the decoupling experiment showed that the methyl group (at 1.01-1.04 ppm, d, J = 6.6 Hz) remained at the position α- to the carbonyl.

MS: 194 ($M^+$), 109, 96, 82, 81, 67, 55, 41, 39, 29.

Preparation of Spiro[5,6]-8,8-Dideuterododecan-7-One, (101)

Sodium (51 mg, 2.2 mMol) and 85 (0.2 g, 1.1 mMol) were added to 0.5 mL of deuterium oxide. The mixture was allowed to stand at room temperature for three days. The organic layer was extracted with ethyl ether and analyzed by its NMR spectrum, which showed no

α-proton peaks. After **101** was treated with concentrated sulfuric acid at 0°C by the general method, the product was analyzed by spectral methods. No rearrangement was detected.

LSR Study with Spiro[5,6]Dodecan-7-One, (**85**)

The solution was prepared in an NMR tube by dissolving **85** (9.42 mg, 0.052 mMol) in 0.5 mL of $CDCl_3$ with 1% TMS. $Eu(fod)_3$ was added in portions which permitted the LSR-to-**85** ratio to increase in increments of ca. 0.05. Thus, 20 μL of $Eu(fod)_3$ solution ($9.54 \times 10^{-2}$ Mol/1 μL of $CDCl_3$) was introduced to the sample with each addition. The integrated NMR spectrum and the decoupling experiment of the sample was obtained after each addition of $Eu(fod)_3$. After obtaining spectra at each $[Eu(fod)_3]/[\mathbf{85}]$ ratio, the chemical shifts were recorded and the changes in chemical shifts of all distinguishable signals were calculated. Linear least squares slopes and correlation coefficients of $\Delta\delta$ vs. $[Eu(fod)_3]/[\mathbf{85}]$ plots were obtained using a calculator. The data obtained from the shift study was applied to the computer program PDIGM.

Coordinate files for the conformation of **85** were constructed from Dreiding models. The reasonableness of the coordinate files was determined by calculating the bond distances (within 2 Å) and angles (180°) involving all the atoms of each configuration. This was accomplished through use of the program BOSCAN. Agreement factors (R

values) and Eu-O distances were determined from PDIGM calculations based on the correlation of chemical shift slope assignments to specific protons in a particular geometry and the decoupling experiment result. The values of R and the distance at the minimum were 5.97% and 2.32 Å, respectively. Table 7 contains the Cartesian coordinates of 85 on which the shift study was performed. The entries are in the order of identification, atomic number, x, y, and z coordinates.

Table 7. The Cartesian Coordinates of 85

| | I.D. # | Atomic # | X | Y | Z |
|---|---|---|---|---|---|
| proton | 1 | 1 | 2.9688 | 2.7884 | -1.5877 |
| | 2 | 1 | 3.9065 | 1.2872 | -1.0390 |
| | 3 | 1 | 1.0936 | .9380 | -2.4758 |
| | 4 | 1 | 2.5939 | 1.3277 | -3.4445 |
| | 5 | 1 | 1.7680 | -1.3441 | -2.5208 |
| | 6 | 1 | 3.3420 | -.8614 | -3.2197 |
| | 7 | 1 | 4.2523 | -.3081 | -.8290 |
| | 8 | 1 | 3.8205 | -2.1006 | -1.1871 |
| | 9 | 1 | 1.7561 | -2.0319 | .2369 |
| | 10 | 1 | 2.8809 | -.9057 | 1.1663 |
| | 11 | 1 | 3.7953 | 2.3871 | 1.0143 |
| | 12 | 1 | 3.2534 | .7843 | 1.7331 |
| | 13 | 1 | 1.0418 | 2.1020 | 2.5597 |
| | 14 | 1 | 2.6908 | 2.4355 | 3.3866 |
| | 15 | 1 | 2.8758 | 4.6204 | 2.2256 |
| | 16 | 1 | 1.0652 | 4.5480 | 2.6006 |
| | 17 | 1 | 2.5294 | 4.2427 | -.1195 |
| | 18 | 1 | .8794 | 4.9741 | .2059 |
| | 19 | 1 | .4674 | 2.8377 | -1.0387 |
| | 20 | 1 | .0776 | 2.4589 | .6886 |
| carbon | 1 | 12 | 2.8651 | 1.6985 | -1.3071 |
| | 2 | 12 | 2.2341 | .8497 | -2.4629 |
| | 3 | 12 | 2.6904 | -.6609 | -2.4394 |
| | 4 | 12 | 3.3101 | -.8217 | -.9413 |
| | 5 | 12 | 2.3889 | -1.0043 | .1331 |
| | 6 | 12 | 1.3926 | .0000 | .0000 |
| | 7 | 12 | 2.0897 | 1.6276 | .0000 |
| | 8 | 12 | 2.9069 | 1.8728 | 1.3370 |
| | 9 | 12 | 2.1152 | 2.5646 | 2.5201 |
| | 10 | 12 | 2.0013 | 4.0155 | 2.0123 |
| | 11 | 12 | 1.5949 | 4.1072 | .4890 |
| | 12 | 12 | .9138 | 2.8376 | -.0391 |
| oxygen | 1 | 16 | .0000 | .0000 | .0000 |

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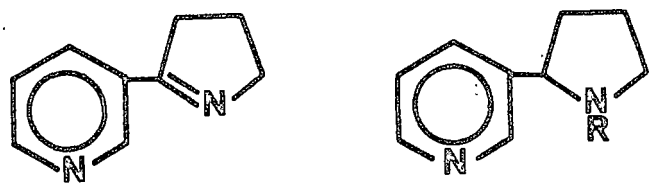
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# PART II

## A New Approach to Natural Products Using the Mundy N-Acyllactam Rearrangement

## INTRODUCTION

Since the identification of a class of alkaloids isolated from the tobacco plant (genus Nicotiana) in 1893,[1] the syntheses of nicotine and related alkaloids such as myosmine, (1), nornicotine, (2), and nicotine, (3) (Figure 37) have been completed by several groups.[2]

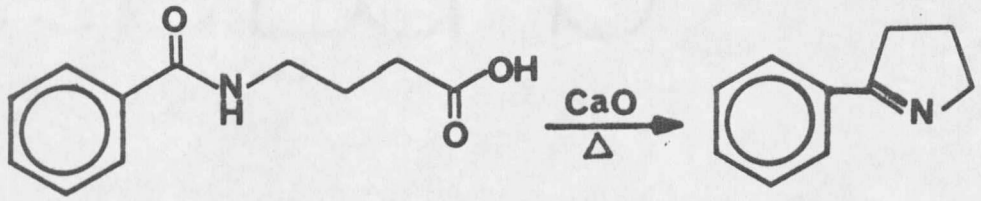


1

2 R= H
3 R= $CH_3$

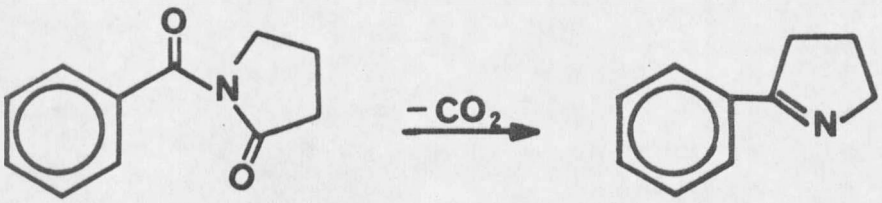
Figure 37. Three Alkaloids from Nicotiana

Mundy and McKenzie embarked on a synthesis of these alkaloids based on the procedure of the calcium oxide pyrolysis of N-benzoyl-4-aminobutyric acid, (4) previously reported by Murakoshi (Figure 38).[3] Mundy realized the reaction of 2-phenylpyrroline might be achieved through the intermediate acyllactam, (5),[4] which then decomposed, liberating $CO_2$ and yielding the desired product (Figure 39). To test this assumption, Mundy and McKenzie subjected N-benzoyl-2-pyrrolidinone, (6) and an equal weight of calcium oxide




4 5

Figure 38. The Murakoshi Synthesis of Phenylpyrroline




6 5

Figure 39. Proposed Intermediate of the Murakoshi Synthesis

to flame-free pyrolysis. The product recovered was 2-phenylpyrroline, (5) (Figure 40).

This pyrolytic rearrangement of an N-acyllactam to a 2-substituted cyclic imine then resulted in a potentially simple entry into pyrroline and piperidine alkaloids. Generally it was observed that coupling of an acid halide (where R = alkyl, aryl, strained cyclic or heterocyclic) with a 5-, 6-, or 7-membered lactam, (7), formed the corresponding N-acyllactam, (8). Pyrolysis of this product over calcium oxide resulted in a presumed loss of $CO_2$

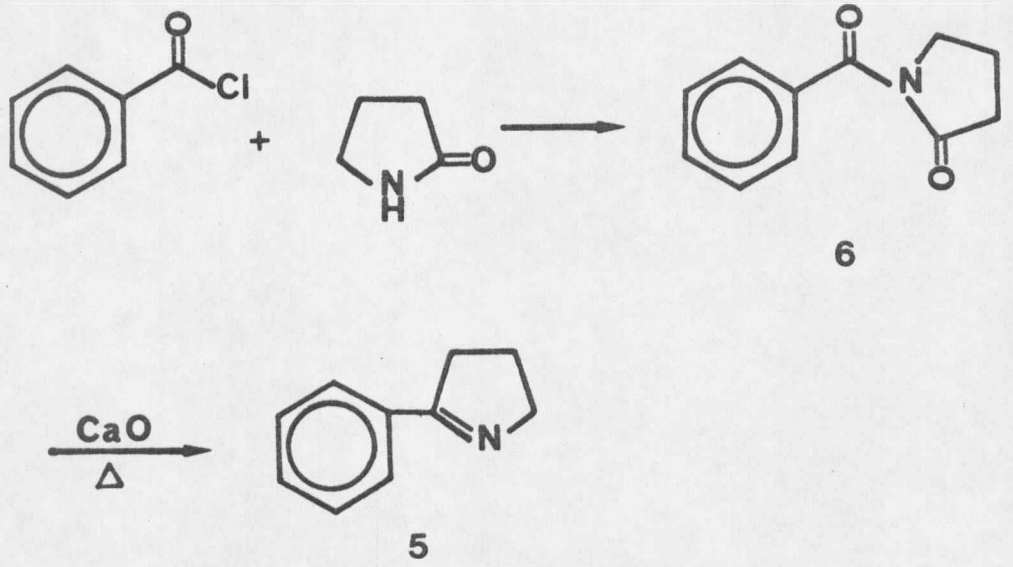



Figure 40. The Mundy and McKenzie Synthesis of Phenyl Pyrroline

accompanied by rearrangement to cyclic imine, (9), as shown in Figure 41.

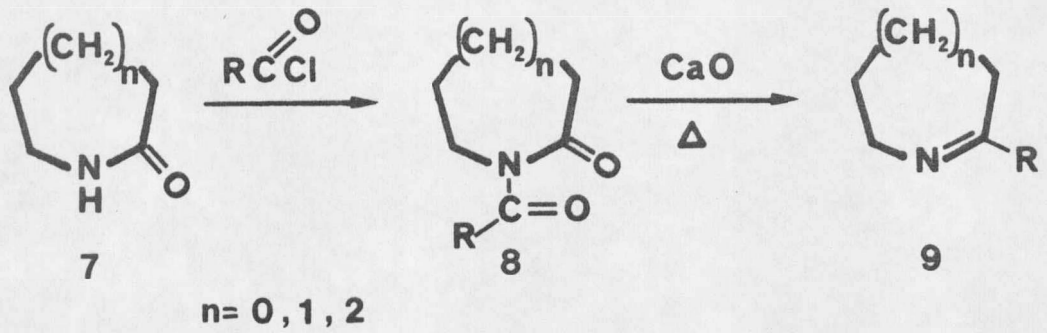



Figure 41. General Synthesis of Cyclic Imines

It was realized by Mundy and Lipkowitz that two possible reaction paths were available for this rearrangement. One was the rearrangement to corresponding products with moderate heat, and the other was thermal cleavage at high temperature and shorter contact time which resulted in 2-pyrrolidinone, (10) (Figure 42). They also investigated the mechanism of the rearrangement and proposed a

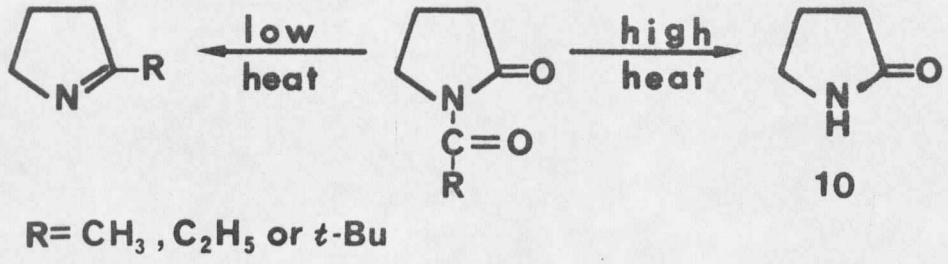



Figure 42. The Dual Thermal Pathway for N-Acyllactam Pyrolysis

partial mechanism.[5] The use of radioisotopes ($^{14}C$), as shown in Figure 43, indicated that the pyrrolidone carbnoyl was lost and the

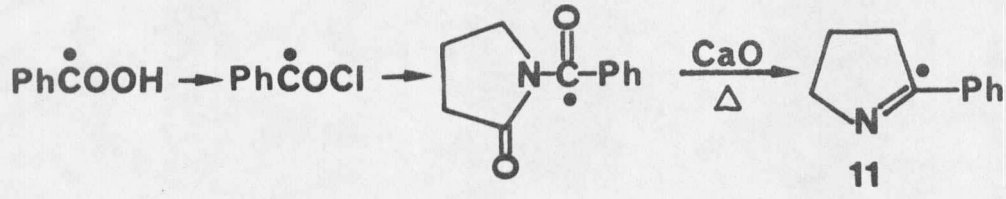



Figure 43. Retention of $^{14}C$ During Pyrolysis

carbonyl carbon of the N-acyl group was maintained in the product, (11). Figure 44 displays the partial mechanism proposed by Lipkowitz. With these results, they concluded that the migrating group was not active but plays a passive role during the rearrangement.

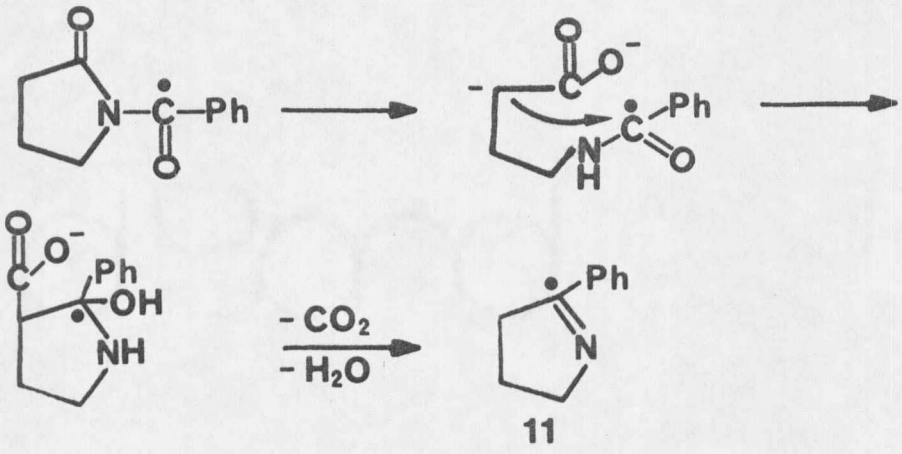



Figure 44. Proposed Mechanism for N-Acyllactam Rearrangement

The N-acyllactam rearrangement is a new approach to the synthetic problem and leads to a relatively simple, high yielding, widely applicable synthesis of pyrrolidine and piperidine alkaloids. The synthesis of otherwise difficult to prepare molecules can be accomplished in this fashion.[6] After Mundy and his coworkers initially investigated this rearrangement, they utilized it for the synthesis of natural products and alkaloids such as myosmine, (1),

anabasene, (12), and γ-coniciene, (13). Figure 45 shows some results of their work.[7-8]

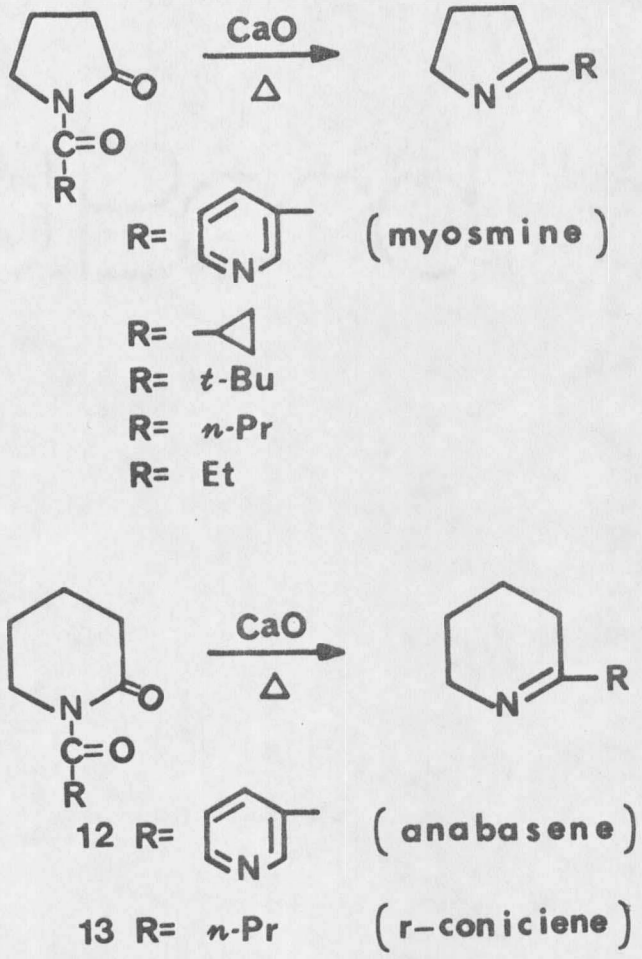



Figure 45. Synthesis of 2-Substituted Pyrrolines and Piperidine

Application of the rearrangement to 6-methyl-2-piperidone has led to a synthesis of optically active dihydropinidine, (15a),

confirming the absolute configuration of the pine alkaloid, pinidine, and to a new synthesis of the fire ant toxin solenopsin A, (**15b**), shown in Figure 46. Table 8 lists molecules which potentially can be synthesized by the Mundy N-acyllactam rearrangement.[9]

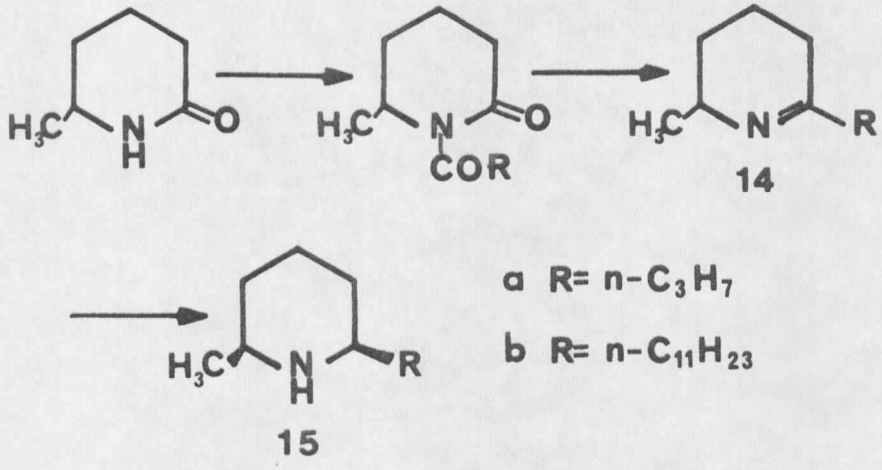
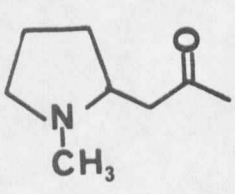


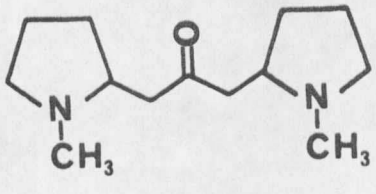

Figure 46. Synthesis of Dihydropinidine and Solenopsin A

Table 8. Molecules Potentially Available by the Mundy N-Acyllactam Rearrangement

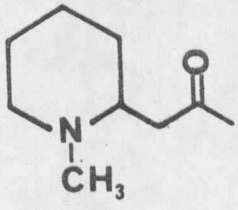
Simple alkaloids of the type characterized by Hygrin[23]




Hygrin

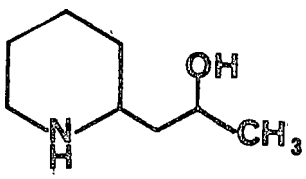



Cuscohygrin

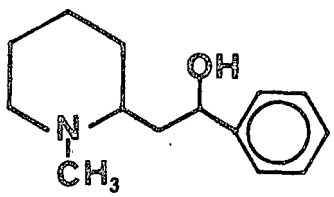



N-Methylpelletierine

Table 8 (continued)

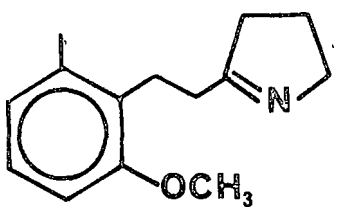



Sedridine

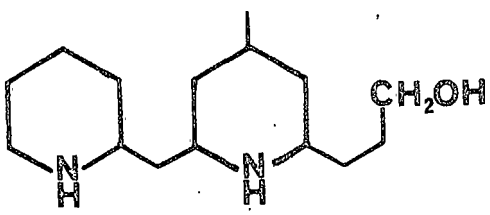



Sedamine

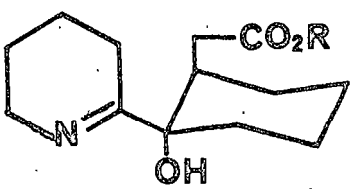
General Intermediates Useful for Alkaloid Synthesis




An intermediate in the synthesis of elaeocarpine and isoelaeocarpine[10]



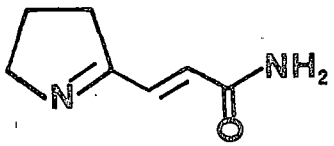

An intermediate necessary for the synthesis of dihydrodeoxyprallocerniune[11]



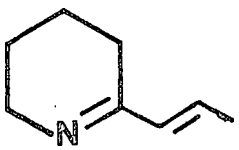

An intermediate for a securinine type alkaloid[12]

Table 8 (continued)

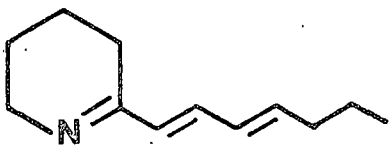
Alkaloids and Antibiotics



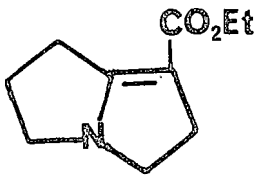

Pyracrimycin[13]




An unstable constituent of immature pomegranate leaves[14]




Nigrifactin[15]




An intermediate for (±)-isoretronecanol and (±)trachelanthamidine[16]

## RESULTS AND DISCUSSION

### Attempted Synthesis of Shihunine, (16)

Shihunine, (16) is the major phthalide-pyrrolidine alkaloid found in several species of Dendrobium lohonense.[17] It is a component of Shi-Hu, a popular Chinese drug sold on the Hong Kong market.[17] A previous synthesis afforded quite low yields of shihunine.[18] Leete has recently reported a one-step synthesis using a dilithio anion prepared from o-bromobenzoic acid and N-methyl-2-pyrrolidinone (Figure 47).[19]

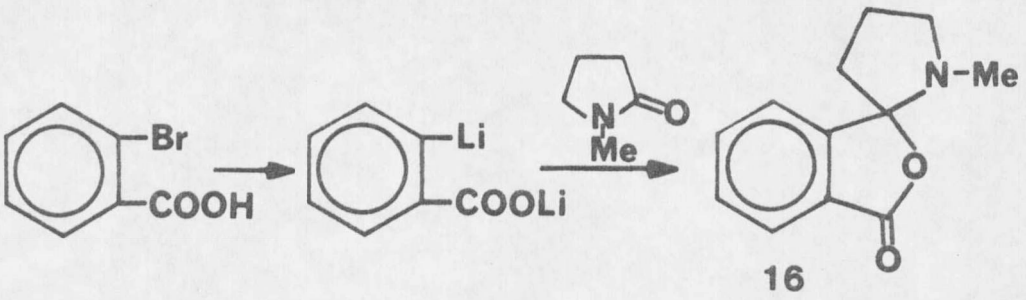



Figure 47. Leete Synthesis of Shihunine

We embarked on the synthesis of this alkaloid utilizing the N-acyllactam rearrangement. This was the first attempt to pyrolyze an ortho substituted N-benzoyllactam. Figure 48 shows the proposed synthesis of shihunine. Mono-methylation of phthalic anhydride with one equimolar amount of potassium hydroxide in methanol gave the mono ester of phthalic acid, (17) in a good yield.[20] Treatment of

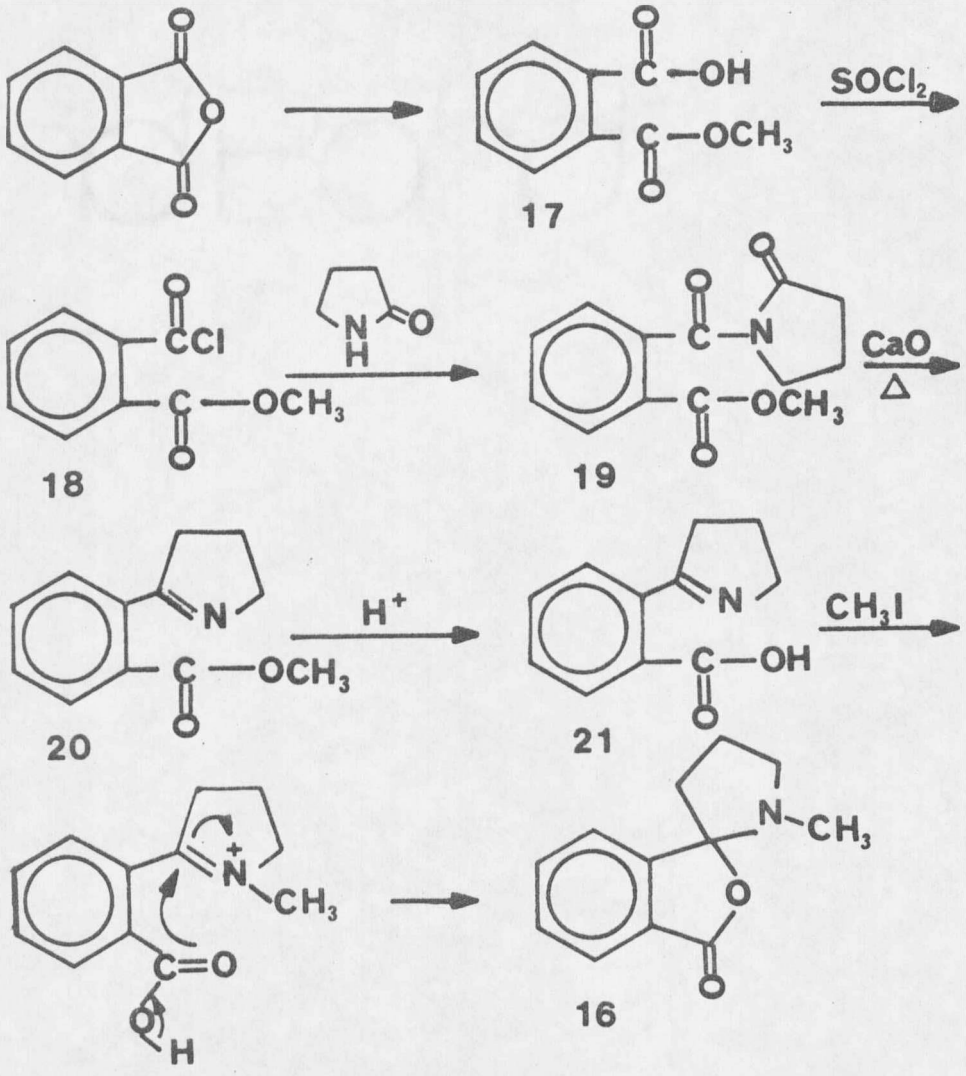



Figure 48. The Proposed Synthesis of Shihunine

17 with excess thionyl chloride in methylene chloride yielded the acyl chloride, (18). Without purification, 18 was reacted with 2-pyrrolidinone in the presence of dry pyridine to produce the N-

acyllactam, (19). The attempted pyrolysis of 19 with equal weight of calcium oxide did not provide any of the rearranged compound, (20). Changing the temperature of the flame and the ratio of calcium oxide and 20 did not facilitate the rearrangement. Recovered materials from the pyrolysis contained a large amount of fragmentations of 20 and a small portion of dimethyl phthalate.

Instead of the previous pathway, an alternative route for synthesis of the intermediate, (21) is shown in Figure 49. A

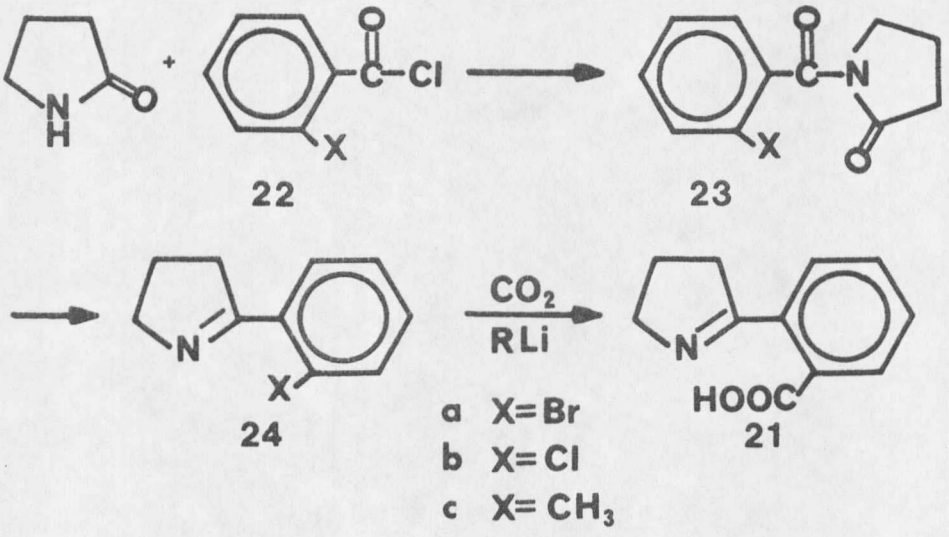


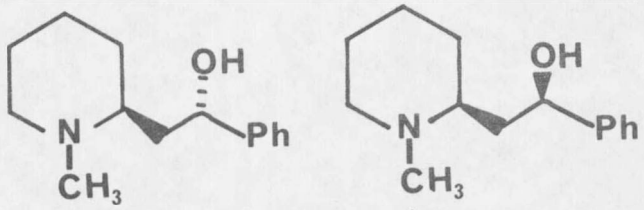

Figure 49. Alternate Route for Synthesis of Shihunine

suitably positioned halogen on the aromatic ring of the imine, (24) can be elaborated to a carboxylic acid by Grignard reaction or an

organic lithium reaction with $CO_2$.[19,21] Acyllactams, (23a) and (23b) were formed from the reaction of 2-pyrrolidinone with o-bromobenzoyl chloride, (22a), and o-chlorobenzoyl chloride, (22b). Attempted pyrolysis of 23a resulted in the thermal cleavages and ca. 13% of rearranged imine, (5) without bromine! There was no trace of rearrangement of 23a. It was assumed that first bromine was eliminated from 23a by heat and then the resulting N-benzoyl-2-pyrrolidinone, (6) was rearranged to leave 5. Pyrolysis of 23b gave only fragmentations of the molecule and a large amount of 2-o-pyrrolidinone.

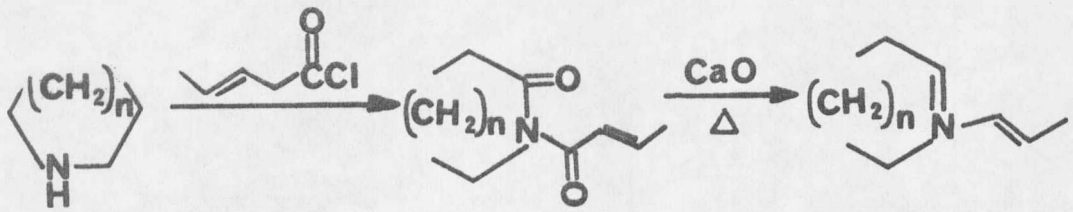
Although Lipkowitz[22] proposed two possible reaction paths, depending on the difference of heat and that the migrating group plays no active role during pyrolysis, it seems likely that his assumption does not fit for the case in the pyrolysis of the ortho-substituted N-benzoyl acyllactam. We prepared N-(o-methylbenzoyl)-2-pyrrolidinone, (23c) to study the role of substitution groups on the rearrangement and also as a different approach for the synthesis of 21. The pyrolysis of 23c was carried out and no rearrangement was observed. These results indicated that steric effect dominates on the rearrangement regardless of the size of a substituent or the nature of electronegativity of a substituent. This steric effect of a substituent was observed by other groups.[16]

Products from the pyrolysis of the conjugated N-acyllactams are potential precursors to the synthesis of natural products and alkaloids such as sedamine, (25), allosedamine, (26), sedridine,



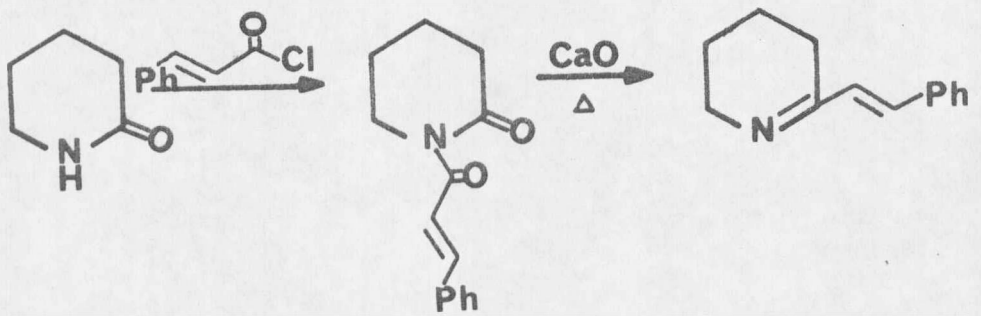

25 26

pelletierine, and ψ-pelletierine.[23] Lipkowitz tried to pyrolyze N-crotonyl-2-pyrrolidinone, (27), and N-crotonyl-2-piperidone, (28), as a model case to synthesize pomegranate alkaloids, though pyrolysis of these N-acyllactams resulted mainly in thermal cleavage products, 2-piperidone and 2-pyrrolidinone (Figure 50). As a part of our study to utilize the N-acyllactam rearrangement to synthesize natural products, we aimed at the synthesis of 25 and 26 isolated from the biting stone crop (Sedum acre L.) (Figure 51). Before we tried the rearrangement on the piperidone system, we used 2-pyrrolidinone as a model case for the pyrolysis of conjugated N-acyllactams since the ring size effect is of minor importance to




27 n= 1
28 n= 2

Figure 50. Attempted Synthesis of a Pomegranate Alkaloid by Lipkowitz




25 + 26

Figure 51. Possible Natural Products from Pyrolysis of the Conjugated N-Acyllactam

this rearrangement. The synthesis of this model is presented in Figure 52. N-Cinnamoyl-2-pyrrolidone, (30), prepared from the condensation of 2-pyrrolidinone and cinnamoyl chloride, (29), was

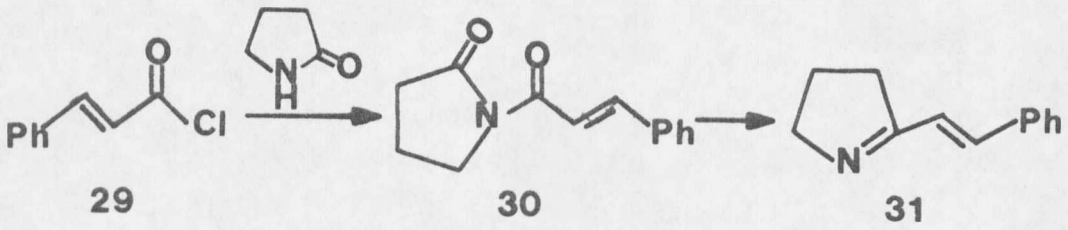



Figure 52. Attempted Pyrolysis of N-Cinnamoyl-2-Pyrrolidinone

pyrolyzed at the various temperatures and conditions. As we expected, but did not wish to find, pyrolysis of the conjugated N-acyllactam did not work. When we mixed 30 with an equal weight of calcium oxide and broken soft glass, the products contained ca. 4.8% of 31 after pyrolysis. This result indicated to us that modifications of the pyrolysis step, like initiating a photo-radical reaction or introducing N-acyllactams into heated CaO with a carrier gas, could be a resolution for this rearrangement. Further work must be carried out.

Attempted Synthesis of Apoferrorosamine, (34)

Apoferrorosamine, (34) is an Fe-free ferrorosamine which is a pigment of Bacillus roseus fluorescens.[24] Due to the similarity in

structure of **34** and myosmine, (**1**), it was decided to attempt the synthesis of **34** by a procedure analogous to the synthesis of myosmine developed in this laboratory. Apoferrorosamine has been synthesized by two groups.[25] The proposed synthesis of Apoferrorosamine is shown in Figure 53, but this synthesis path has some difficulty for making N-picolinyl-2-pyrrolidinone, (**33**). The condensation reaction between 2-pyrrolidone and picolinyl chloride, (**32**), prepared from the reaction of picolinic acid and thionyl chloride,[26-27] did not work in spite of multiple trials. Only decarboxylation of picolinic acid was observed.

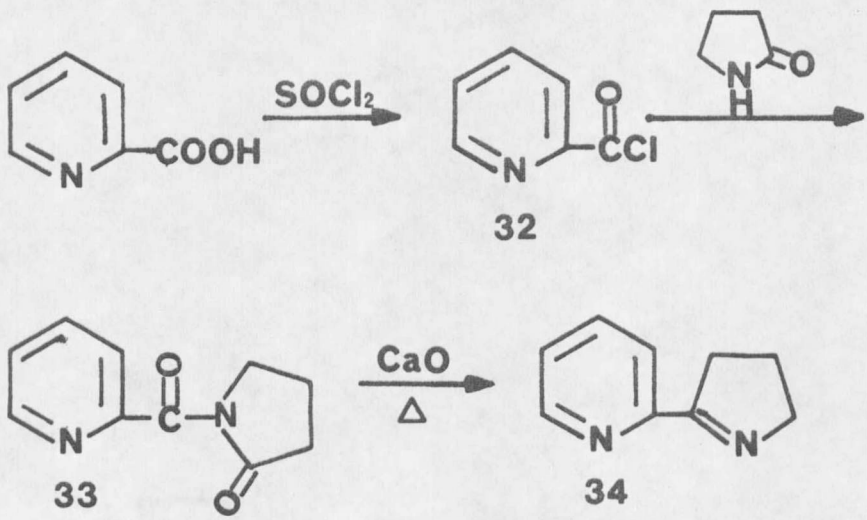



Figure 53. Proposed Synthesis of Apoferrorosamine

A New Approach to Synthesis of 2-Substituted Oxazolines

As part of our continuing study of the scope of the N-acyllactam rearrangement, and with the view towards developing a simple route to mycobactic acid, we embarked on the study of synthesis of 2-substituted oxazolines. The oxazoline ring system, first prepared in 1884, has been shown to possess considerable utility in the synthesis of a variety of functionalized organic compounds and the industrial importance of monomeric and polymeric 2-oxazolines. Various manipulations of the oxazoline ring lead to aldehydes, ketones, lactones, amino acids, thiiranes, and olefins.[28,30] Due to the inertness of the oxazoline ring system to various reagents ($RMgX$, $LiAlH_4$, $CrO_3$, mild acid or alkali), it may be utilized as a protecting group for carboxylic acids during the transformations involving these reagents.[29,30] There are a few good reviews on oxazoline chemistry.[30-32]

The classical method for preparing 2-substituted oxazolines is to utilize α-amino alcohols and carboxylic acids.[33] These oxazolines are also prepared from amides,[34] haloamides,[35] aziridines,[36] epoxides,[37] or hydroxyamides.[38] More recent preparations involve the condensation of α-amino alcohols with isocyanides,[39] nitrile,[40] cyanoallenes,[41] and propargyl-phosphonium salts.[42] Some examples of preparing 2-substituted oxazolines are presented in Figure 54. These 2-alkyl or aryl substituted

oxazolines are important in the polymer industry. They are used in making protective coatings, surface active agents, gasoline and lube oil additives, corrosion inhibitors, antifoam agents, textile

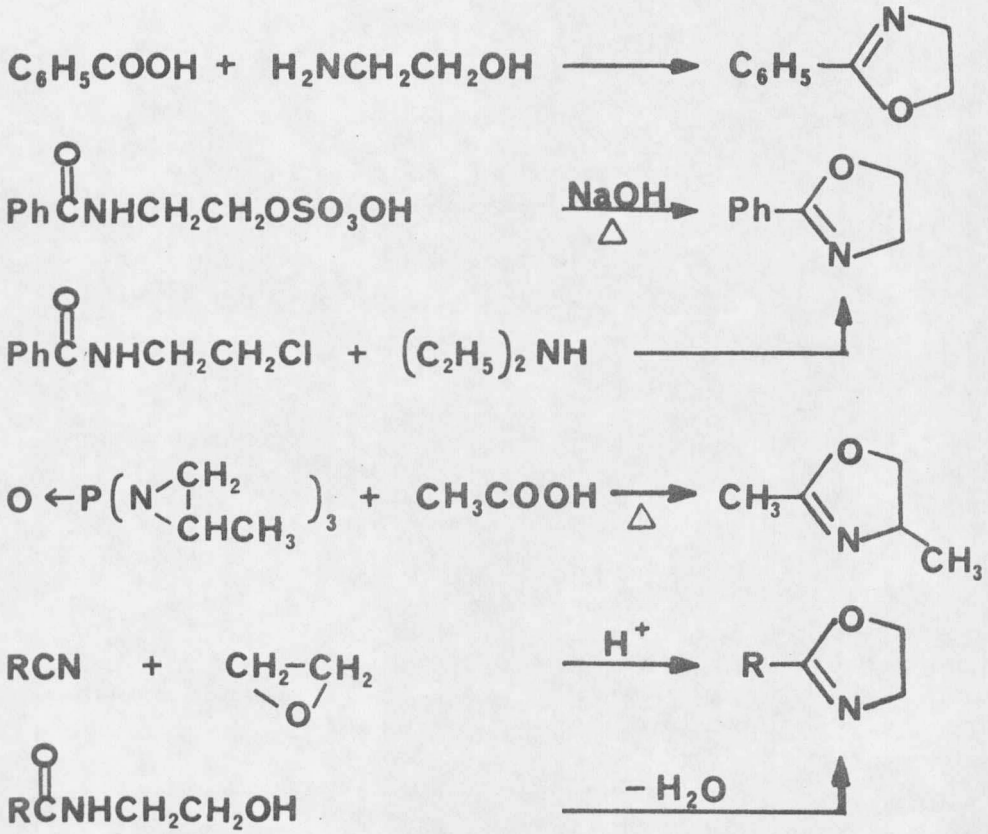


Figure 54. Some Examples of Synthesis of 2-Substituted Oxazolines

chemicals, pharmaceuticals, adhesives and binders, stabilizers for chlorinated hydrocarbons, stabilizers for aqueous formaldehyde solutions, protective films in polish formulations, foam

stabilizers, photography, agriculture, and plasticizers.[31] Due to a variety of utilities, the development of oxazoline chemistry has been popular and widely studied. Here we describe a new methodology to prepare 2-substituted oxazolines.

As representatives for 2-alkyl and aryl substituted oxazoline system, 2-methyl-2-oxazoline, (37a) and 2-phenyl-2-oxazoline, (37b) were selected and synthesized by N-acyllactam rearangement. The 2-methyl-2-oxazoline, (37a) is an effective antimicrobial, used in solution or spray form, which is especially effective against Straphylococcus aureus.[43] This oxazoline, (37a) is useful as solvents and plasticizers for resins and, when polymerized, is useful in forming fibers, films, and molded objects.[44-45] By the addition of a small amount of 37a, chlorinated hydrocarbons can be stabilized against metal induced decomposition.[46] 37a also acts as a competitive inhibitor of acetylcholinesterase,[47] and polymerization of 37a with 2-chloromethyl-2-oxazoline using an oxazolinium perchlorate catalyst is useful in the preparation of coatings and injection-molded articles.[48] The NMR spectrum of 37a provides a good example of long-range spin-spin coupling between the 2-methyl protons and the 4-methylene protons. In this ring system the geometrical restrictions require co-planarity of the atoms involved and the coupling effect is transmitted through the

π-electron system. It is most likely that similar long-range coupling will be detected in other heterocyclic systems with this common structural feature.[49] Besides the usefulness in polymer industry, 2-phenyl-2-oxazoline, (37b) has some reactivities with other functional groups. Some examples are represented in Figure 55.[50-54]

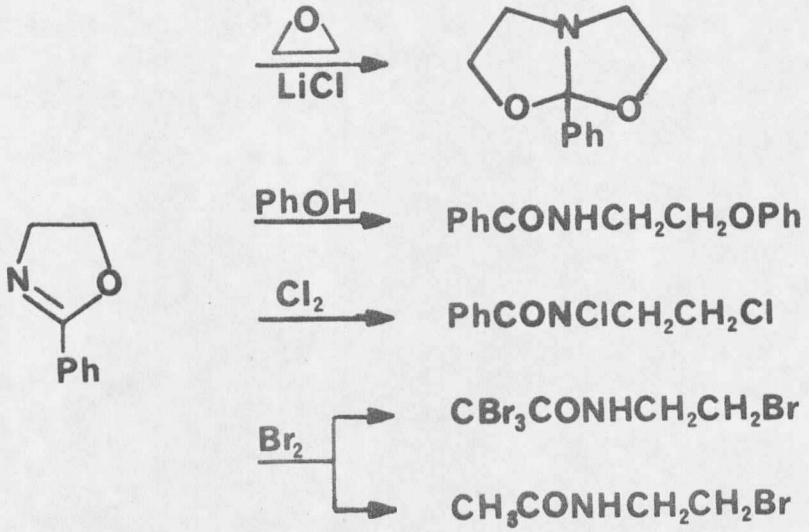



Figure 55. Reactions of 2-Phenyl-2-Oxazoline

The pathway for synthesis of 37a and 37b in analogy to the N-acyllactam rearrangement is shown in Figure 56.

In the first system studied, benzoyl chloride was reacted with 2-oxazolidone, (35) to give 50% of N-benzoyl-2-oxazolidone, (36b). Heating an equal weight of 36b and calcium oxide with an open flame gave 65% of a crude distillate, (37b) which by GLC (¼" X 7'6" 10% Apiezon on Chromosorb W, 60/80 mesh) was shown to be 97% pure.

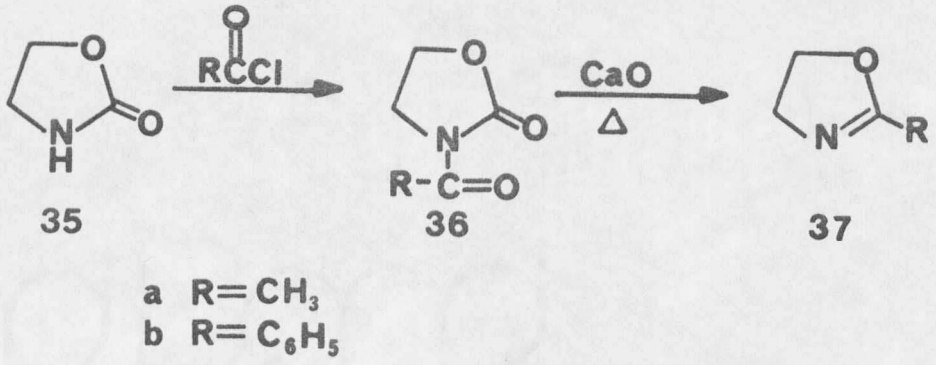



Figure 56. New Methodology to Synthesize 2-Substituted Oxazolines

Using thesame procedure, acetyl chloride was converted to **36a** in 74%. Rearrangement of **36a** occurred very inefficiently, with a large number of uncharacterized fragmentation products accompanying the product, (**37a**). These model systems demonstrated that rearrangement to 2-substituted oxazolines was possible.

After accomplishing the rearrangement of an N-acyllactam containing an oxygen atom, we undertook the study on the N-acyllactam rearrangement containing other heteroatoms to examine the effect of heteroatoms on the rearrangement and to resolve the mechanism of this reaction. N-Benzoyl-2,4-thiazolidinedione, (**39**), N-benzoyl-2-imidazolidone, (**41**), and N,N-dibenzoyl-2-imidazolidone, (**42**) were prepared from 2,4-thiazolidinedione, (**38**) and 2-imidazolidone, (**40**), which are readily available by purchase from Aldrich, with benzoyl chloride (Figure 57). We submitted these

three compounds into an open flame. In the case of **39**, a small amount of benzamide including a large amount of thermal cleavage product was recognized and none of the rearrangement products was detected. In both cases of **41** and **42**, only thermal cleavage

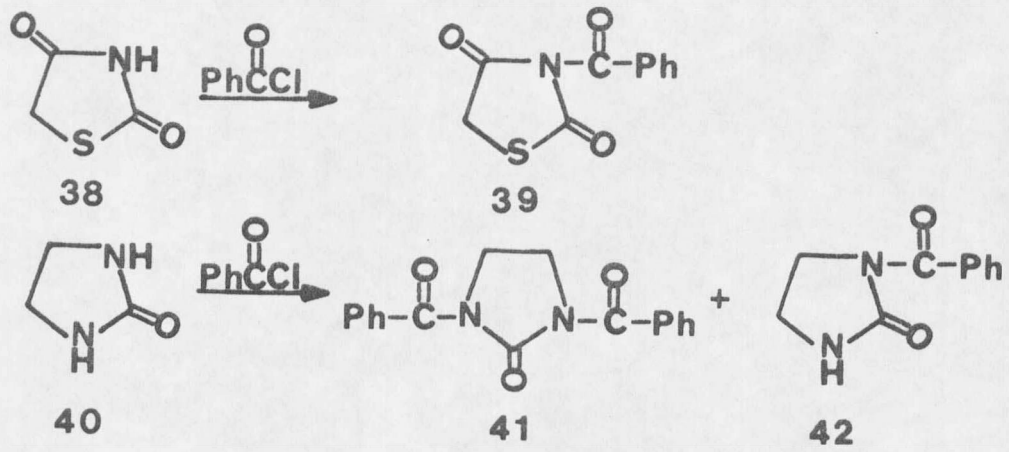
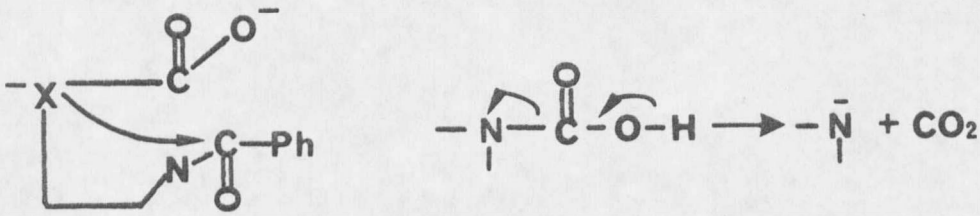



Figure 57. The Synthesis of N-Acyllactams Containing Heteroatoms

products were recognized and none of the rearrangement products was obtained.

In the partial mechanism of the rearrangement proposed by Lipkowitz (Figure 44) there is a dianion intermediate. If we assume this intermediate, then an intermediate containing a heteroatom, (**43**) will be more stable than a carbanion intermediate, since the heteroatom is more electronegative than a carbon atom. Also, if we include the idea that the decarboxylation of a carbamic acid, (**44**) occurs very fast, **43** will be more reactive than a carbanion

occurs very fast, **43** will be more reactive than a carbanion intermediate (Figure 58). This assumption implies that rearrangement of N-acyllactam containing a heteroatom will proceed easily. Although we could not obtain the rearranged product containing a sulfur or nitrogens, we observed that rearrangement of



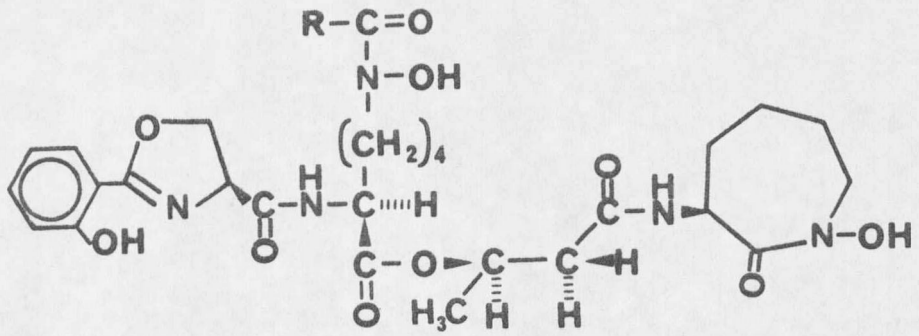
**43** **44**

Figure 58. Stability of an Intermediate Containing a Heteroatom

2-oxazolidones proceeded in relatively high yield. More work has to be done to understand N-acyllactam rearrangement.

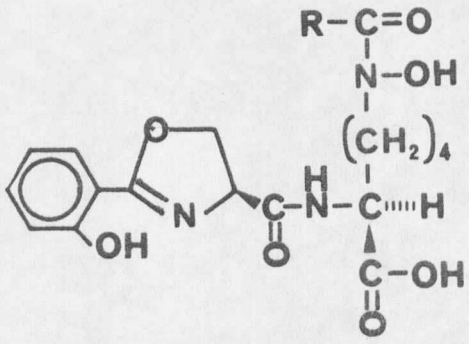
Attempted Synthesis of the Partial Structure of Mycobactic Acid T, (**45**)

Mycobactin T, (**45**) is one of the simplest members of the family of mycobactins discovered and characterized by Snow (Figure 59).[55-56] These compounds are naturally occurring growth factors of Mycobacteria and exceptionally potent chelators of ferric ion. This property, coupled with a high lipophilicity, suggests that the mycobactins are ferric ionophores firmly imbedded in the lipid

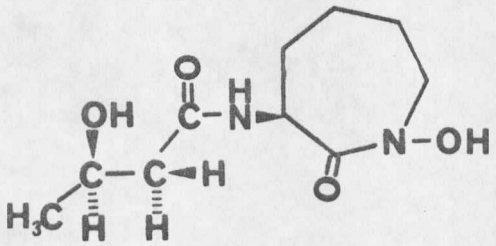


45

R are acyl groups having the total number of C atoms from 18 to 21.



46



47

Figure 59. Structure of Mycobactin T

sheath of Mycobacteria. All of the known mycobactins can be saponified to yield two products, mycobactin acid and cobactin. Cobactin T, (47) was synthesized from E-hydroxynorleucine by

Miller.[57] Our interest was in the other half molecule, mycobactic acid T, (**46**) which contains the 2-hydroxyphenyl-2-oxazoline system. Figure 60 shows our proposed synthesis of mycobactic acid T, (**46**).

Salicyloyl chloride, (**49a**) was prepared from the reaction of salicylic acid, (**48a**) and thionyl chloride.[58] Condensation

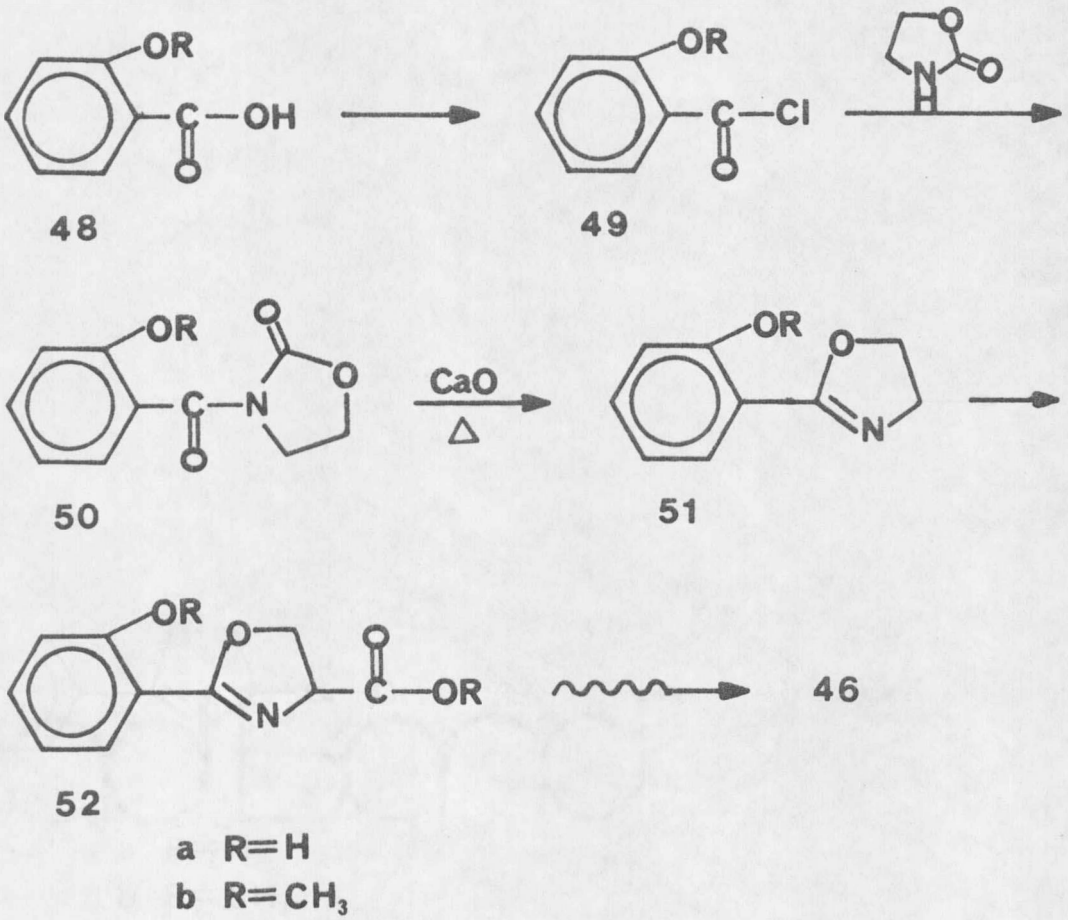
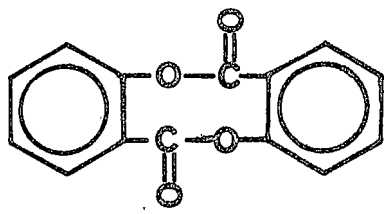



Figure 60. Proposed Synthesis of a Precursor for Mycobactic Acid T

reaction between 49a and 2-pyrrolidine resulted in diester, (53),



53

and N-salicyl-2-oxazolidone, (50a) was not detected.[59] To solve this problem, we picked o-anisic acid as a starting material since a methoxy group can be easily converted to an alcohol group.[60] o-Anisoyl chloride, (49b), prepared by the reported method,[61] was condensed with 2-oxazolidone, (35) to remain N-anisoyl-2-oxazolidinone, (50b) in 75% yield. Pyrolysis of 50b produced o-anisoyl-2-oxazoline, (51b) which was collected by GLC and analyzed by spectral methods. This 2-substituted oxazoline synthesis is a potential route for a precursor to other mycobactins like mycobactin P, mycobactin S, and mycobactin H.[56]

## EXPERIMENTAL

$^1$H NMR spectra were run on a Varian A-60 or Bruker 250 MHz spectrophotometer using deuterochloroform as a solvent and TMS as an internal standard. GLC data were obtained from a Varian Aerograph Model 2700 instrument using 10% silicon SE-30 on Chromosorb W, 60/80 mesh, (¼" X 8') and 10% Apiezon on Chromosorb W, 60/80 mesh (¼" X 7'6") as columns. The column temperature was maintained at 200°C and the pressure of the gas flow was kept at 30 psi. Mass spectra were obtained from a Varian Model CH5 mass spectrometer. All melting points and boiling points are uncorrected. Dry pyridine was prepared by drying over potassium hydroxide pellets for several days, followed by distillation from barium oxide. Unless otherwise specified, commonly needed reagents were used as received.

### General Preparation of the Acylated Lactams

The similarity of the N-acyllactam systems lent themselves to a consistent preparation procedure. Unless otherwise noted, reaction times, conditions, and work-up procedures remained static for generation of all the systems pyrolized. To a stirred solution of acid chloride and the desired lactam was added dry pyridine slowly at 0°C. After the addition was complete, the reaction mixture was stirred at room temperature or gently refluxed at 65°C for 2-10 hr. After cooling, methyl chloride was added to the product, and the

resulting solution was sequentially washed with 5% hydrochloric acid solution, saturated sodium bicarbonate solution, water and saturated sodium chloride solution. The methylene chloride layer was dried over anhydrous magnesium sulfate, and after the filtration, the solvent was evaporated at reduced pressure to leave a product. The remaining product was purified by a variety of procedures.

General Rearrangement Procedure of the N-Acyllactams

The N-acyllactam was mixed thoroughly with an equal weight of calcium oxide and placed in a round-bottomed flask with a side arm. The mixture was gently heated with the flame of a micro burner. When a melting was observed, the heat was continued until the crude product distilled. This product was then collected by preparative GLC or purified by column chromatography. Identification was accomplished by spectral means and combustion analysis.

Preparation of Monomethyl Phthalate, (17)

To a solution of phthalic anhydride (14.8 g, 0.10 Mol) in dry acetone (80 mL) at 25°C was added a solution of potassium hydroxide (5.6 g, 0.10 Mol) in 500 mL of anhydrous methanol until neutrality was reached. The solution was stirred for an hour and evaporated to a small bulk and acidified with 10% hydrochloric acid solution. The precipitated oily material was extracted three times with methylene chloride and the combined organic layers were washed with water,

saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The viscous liquid was obtained after the methylene chloride solution was removed by a rota-evaporator. The viscous liquid crystallized on standing to give white crystals. For further purification the mono ester was recrystallized from cyclohexane and 14.9 g (83%) of 17 was obtained.

NMR: 9.79 (1H, s); 7.86-7.90 (1H, dd); 7.61-7.69 (1H, m); 7.50-7.60 (2H, m); 3.90 (3H, s).

M.P.: 82-83°C; lit. 83-84°C[20].

Preparation of Methyl Ester of N-Phthalyl-2-Pyrrolidinone (19)

Monomethyl phthalate, (17) (10.8 g, 60 mMol) was added to thionyl chloride (20.0 g, 168 mMol) and the mixture was refluxed for 3 hr. The solution was cooled and the excess thionyl chloride was removed at aspirator pressure. To the crude monomethyl ester of phthalyl chloride, (18) in 300 mL of methylene chloride was added 2-pyrrolidinone (7.65 g, 90 mMol) and then dry pyridine (4.74 g, 60 mMol) was added slowly in an ice bath. The solution was stirred for a day at room temperature. After the general work-up procedure, 13.3 g of white crystals was acquired, a yield of 90% from 17.

NMR: 8.01-8.04 (1H, dd, J = 7.9 Hz); 7.44-7.62 (2H, m); 7.25-7.27 (1H, dd); 4.01-4.07 (2H, tr); 3.84 (3H, s); 2.48-2.55 (2H,

tr); 2.06-2.18 (2H, m).

M.P.: 73-77°C.

MS: 247 ($M^+$), 216, 189, 188, 164, 163, 105, 104, 92, 77, 76, 50, 41, 39.

Preparation of N-(o-bromobenzoyl)-2-pyrrolidinone, (23a)

o-Bromobenzoyl chloride, (22a) (5.0 g, 22.8 mMol) was added dropwise to 2-pyrrolidinone (1.96 g, 23.0 mMol) and dry pyridine (1.8 g, 22.8 mMol) cooled by an external cold bath. The combined mixtures were heated gently at 65°C for 8 hr. The work-up procedure was the same as the general procedure. After evaporation of solvent, 5.80 g (95%) of a viscous yellow liquid was collected. The purity by GLC was over 99%.

NMR: 7.54-7.57 (1H, dd, J = 7.9 Hz); 7.24-7.31 (3H, m); 3.97-4.03 (2H, tr, J = 7.3 Hz); 2.55-2.61 (2H, tr, J = 7.9 Hz); 2.08-2.21 (2H, m).

MS: 188 ($M^+$ - Br), 185, 183, 157, 155, 121, 76, 75, 50.

IR: 1745 (s), 1665 (s), 1320 (s), 1240 (m), 1185 (m), 1025 (m), 900 (m), 830 (m) , 770 (s), 750 (s), 735 (m) $cm^{-1}$.

Calculated for $C_{11}H_{10}BrNO_2$: C, 49.28; H, 3.76

Found: C, 49.47; H, 3.96

Preparation of N-(o-chlorobenzoyl)-2-pyrrolidinone, (23b)

o-Chlorobenzoyl chloride, (22b) (17.5 g, 0.10 Mol) was added to 2-pyrrolidinone (10.2 g, 0.12 Mol) and dry pyridine (7.9 g, 0.10 Mol) was added dropwise in a cold bath. The combined mixtures were heated gently for 8 hr. After the general procedure, 20.6 g (92%) of a viscous yellow liquid was collected. The purity by GLC was over 99%.

NMR: 7.29-7.39 (4H, m); 3.97-4.03 (2H, tr, J = 7.3 Hz); 2.55-2.62 (2H, tr); 2.11-2.18 (2H, m).

MS: 188 ($M^+$ - Cl), 141, 139, 121, 113, 111, 75, 50.

IR: 1730 (s), 1670 (s), 1330 (br s), 1235 (s), 1190 (s), 1045 (m), 905 (m), 830 (m), 770 (s), 755 (s), 740 (s).

Calculated for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51

Found: C, 58.98; H, 4.57

Preparation of N-(o-Methylbenzoyl)-2-Pyrrolidinone, (23c)

Dry pyridine (2.3 g, 29 mMol) was added to the mixture of o-toluoyl chloride (4.5 g, 29 mMol) and 2-pyrrolidinone (3.0 g, 35 mMol). Using the general procedure of acylation, a crude liquid was obtained. The colorless liquid was collected at 158-159°C/0.5 mm Hg to give 4.45 g (76%) of product.

NMR: 7.20-7.23 (4H, m); 3.95-4.01 (2H, tr); 2.54-2.60 (2H, tr, J = 7.9 Hz); 2.30 (3H, s); 2.10-2.29 (3H, m).

MS: 203 ($M^+$), 120, 119, 118, 92, 91, 90, 89, 65, 63, 41, 39.

IR: 1740 (s), 1670 (s), 1460 (m), 1380 (s), 1355 (s), 1315 (s), 1230 (m), 1190 (m), 1165 (m), 745 (m) $cm^{-1}$.

Calculated for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45

Found: C, 70.68; H, 6.44

Preparation of N-Cinnamoyl-2-Pyrrolidinone, (30)

Cinnamoyl chloride, (29) (3.0 g, 18 mMol) was added to 2-pyrrolidinone (1.54 g, 18 mMol) at room temperature and the mixture was stirred for 10 minutes. Dry pyridine (1.42 g, 18 mMol) was added dropwise to the mixture in an ice bath and the combined mixture was stirred for half an hour at room temperature and then refluxed gently for 7 hr. The work-up procedure was the same as the general procedure. The crude solid product (3.4 g) was collected after the evaporation of the solvent. The crude solid product was recrystallized with carbon tetrachloride solution or just washed with anhydrous ether which gave 2.7 g of white crystals (69.8%).

NMR: 7.82-7.92 (2H, d); 7.22-7.70 (5H, m); 3.75-4.05 (2H, tr); 2.47-2.82 (2H, tr); 1.86-2.32 (2H, m).

MS: 215 ($M^+$), 132, 131, 103, 77, 51.

M.P.: 99.5-100°C.

IR: 2900 (w), 1730 (s), 1670 (s), 1600 (m), 1335 (s), 1215 (s), 1040 (w), 1065 (m), 990 (s), 940 (w), 875 (w), 830 (w), 770 (s), 710 (m), 685 (m) $cm^{-1}$.

Calculated for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09

Found: C, 72.54; H, 6.09

Preparation of 2-Pyrrolinylstyrene, (31)

Using the general procedure for rearrangement of N-acyllactams N-cinnamoyl-2-pyrrolidinone, (30) (3 g, 14.0 mMol), calcium oxide (3 g) and broken soft glass (3 g) were gently heated providing 10.8 g of crude mixtures. GLC analysis (10% SE-30 on Chromosorb W 60/80) showed that this crude product contained a large amount of thermal cleavage components, 4.1% of an unidentified compound (MS: $M^+$ = 182) and 4.8% of 31.

NMR: 7.30-7.59 (5H, m); 6.99-7.22 (2H, m); 3.96-4.02 (2H, tr); 2.70-2.83 (2H, tr); 1.92-2.01 (2H, m).

MS: 171 ($M^+$), 116.

Preparation of N-Benzoyl-2-Oxazolidone, (36b)

2-Oxazolidone, (35) (1.0 g, 11.5 mMol) was added to benzoyl chloride (4.84 g, 34.5 mMol) and dry pyridine (0.91 g, 11.5 mMol) was slowly added to the mixture in an ice bath. The resulting solution was gently refluxed for 10 hr. After the general work-up,

the crude solid product was obtained after the evaporation of solvent. The crude solids were washed with anhydrous ethyl ether to give 1.1 g (50%) of white crystalline product.

NMR: 7.65-7.67 (2H, dd); 7.51-7.58 (1H, tr); 7.42-7.43 (2H, d, J = 2.0 Hz); 4.45-4.51 (2H, tr, J = 7.9 Hz); 4.13-4.19 (2H, tr, J = 7.9 Hz).

MS: 191 ($M^+$), 105, 77, 51, 50.

M.P.: 167-167.5°C.

Calculated for $C_{10}H_9NO_3$: C, 62.82; H, 5.26

Found: C, 62.87; H, 4.91

Preparation of 2-Phenyl-2-Oxazoline, (37b)

To 0.78 g of 36b was added an equal weight of calcium oxide. The solids were thoroughly mixed and placed in a flask with a side arm. The mixture was gently heated with a micro Bunsen burner until the solid had melted, at which time it was vigorously heated to distill 0.39 g (65%) of a liquid product. GLC (10% Apiezon on Chromosorb W, 60/80) indicated the material to be 97% pure.

NMR: 7.91-7.93 (2H, d); 7.41-7.48 (3H, m); 4.40-4.48 (2H, t, J = 9.2 Hz); 4.03-4.11 (2H, t, J = 9.2 Hz).

MS: 147 ($M^+$), 117, 105, 77, 51.

IR: 3400 (m), 2950 (s), 1640 (s), 1600 (w), 1580 (w), 1500 (w), 1480 (w), 1450 (m), 1365 (s), 1340 (s), 1260 (s), 1085 (s), 1065 (s), 1030 (m), 980 (m), 945 (s), 900 (m), 780 (s), 695 (s), 670 (s) $cm^{-1}$.

Calculated for $C_9H_9NO$: C, 73.45; H, 6.16

Found: C, 73.45; H, 6.16

Preparation of N-Acetyl-2-Oxazolidone, (36a)

In a procedure the same as used for 36b, acetylchloride (2.17 g, 34.5 mMol), pyridine (0.91 g, 11.5 mMol) and 2-oxazolidone (1.0 g, 11.5 mMol) were reacted to yield 1.1 g (74%) of a crystalline product.

NMR: 4.25-4.50 (2H, m); 4.00-4.17 (2H, m); 2.50 (3H, s).

MS: 129 ($M^+$), 101, 88, 44, 43, 42, 29.

M.P.: 63-64°C.

Calculated for $C_5H_7O_3N$: C, 46.51; H, 5.46

Found: C, 46.54; H, 5.56

Preparation of 2-Methyl-2-Oxazoline, (37a)

In a procedure as described for the general procedure, 1 g of 36a and 1 g of calcium oxide were heated to give 0.43 g of liquid product. GLC (10% SE-30 on Anakrom, 60/80) showed about 25% rearrangement product and the remainder as fragmentation products.

The coupling constant between the methylene protons and the methyl protons in the reported NMR spectrum is J = 1.4 Hz and the coupling constant for the adjacent methylene protons is J = 9.5 Hz.[29]

NMR: 4.43-4.46 (1H, tr, J = 7.9 Hz); 4.14-4.18 (1H, tr); 3.48-3.68 (2H, m); 2.00-2.09 (3H, dd).

MS: 85 ($M^+$), 73, 72, 60, 55, 44, 43, 42, 41, 30.

IR: 3220 (s), 2900 (m), 1710 (m), 1630 (m), 1525 (m), 1370 (m), 1230 (s), 1050 (s) $cm^{-1}$.

Preparation of N-Benzoyl-2,4-Thiazolidinedione, (39)

2,4-Thiazolidinedione, (38) (2.34 g, 0.02 Mol) and benzoyl chloride (5.6 g, 0.04 Mol) in methylene chloride (80 mL) were stirred at room temerature for half an hour. Dry pyridine (1.58 g, 0.02 Mol) was added slowly and the resulting mixture was gently refluxed for 9 hr and was cooled to room temperature. After the general work-up procedure, crude crystalline product was obtained. The crude product was washed with ethyl ether to give 3.0 g (68%) of yellow crystals.

NMR: 7.87-7.91 (2H, d); 7.66-7.72 (1H, tr); 7.49-7.55 (2H, tr); 4.15 (2H, s).

M.P.: 107-108°C.

MS: 221 ($M^+$), 106, 105, 78, 77, 51, 50, 46.

Calculated for $C_{10}H_7NO_3S$: C, 54.29; H, 3.19

Found: C, 54.15; H, 3.26

Preparation of N,N-Dibenzoyl-2-Imidazolidone, (41) and N-Benzoyl-2-Imidazolidone, (42)

2-Imidazolidone, (40) (3.3 g, 40 mMol) was added to benzoyl chloride (5.6 g, 40 mMol) at room temperature. Dry pyridine (3.17 g, 40 mMol) was added slowly to the mixture. The solution was stirred for half an hour and then refluxed mildly for 8 hr. After the work-up the crude solid product (5.4 g) was collected. The crude product was washed with hot methanol, giving 2.45 g of white crystalline product, (41). The filtrate methanol solution was evaporated to leave 1.9 g of white crude crystalline compound, (42).

NMR of 41: 7.58-7.62 (4H, d); 7.38-7.54 (2H, t); 7.25-7.43 (4H, tr); 4.08 (4H, s).

MS of 41: 294 ($M^+$), 189, 105, 77, 51.

M.P. of 41: 247-248°C.

Calculated for $C_{17}H_{14}N_2O_3$, 41: C, 69.38; H, 4.79

Found: C, 69,32; H, 4.86

NMR of 42: 7.60-7.64 (2H, m); 7.37-7.54 (3H, m); 5.55 (1H, s); 4.07-4.13 (2H, tr, J = 7.9 Hz); 3.51-3.57 (2H, tr).

M.P. of 42: 154-161°C.

Preparation of o-Hydroxybenzoyl Chloride, (49a)

To salicylic acid (27.6 g, 0.20 Mol) in 100 mL of petroleum ether (bp 35-60°C) was added thionyl chloride (47.6 g, 0.40 Mol) slowly. Aluminum chloride (0.10 g, 0.75 mMol) was added to the solution under nitrogen. The mixture was gently refluxed for 5 hr and the remaining solid was filtered, followed by evaporation of the filtrate, giving 33.2 g of 49a.

B.P.: 126-130°C/12 mm Hg; lit. 58-63°C/0.5 mm Hg.[58]

Preparation of o-Methoxybenzoyl Chloride, (49b)

To a stirred solution of thionyl chloride (35.7 g, 0.30 Mol) was added o-anisic acid (30.4 g, 0.20 Mol). After the addition was completed the reaction mixture was stirred at 60°C for 3.5 hr. The excess thionyl chloride was evaporated and 31.5 g of colorless liquid (92%) was distilled at 170-171°C/30 mm Hg (lit. $b_{10}$ 125-126°C[61]).

Preparation of o-Anisoyl-2-Oxazolidone, (50b)

To a stirred solution of 49b (2.35 g, 13.8 mMol) and dry pyridine (0.91 g, 11.5 mMol) was added slowly 2-oxazolidone, (35) (1.0 g, 11.5 mMol) at 0°C under nitrogen. After the addition was completed, the reaction was gently refluxed for 3 hr. After the general work-up procedure, the crude solid product was washed with

ethyl ether to yield 1.9 g (75%) of white crystals.

NMR: 7.35-7.44 (1H, m); 7.26-7.32 (1H, dd); 6.98-7.04 (1H, dd, J = 8.6 Hz, J = 6.6 Hz); 6.91-6.94 (1H, d, J = 8.6 Hz); 4.42-4.48 (2H, tr, J = 7.3 Hz); 4.15-4.20 (2H, tr, J = 7.3 Hz); 3.82 (3H, s).

MS: 221 ($M^+$), 136, 135, 134, 92, 77.

M.P.: 87-88°C.

Calculated for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01

Found: C, 59.56; H, 5.11

Preparation of o-Anisoyl-2-Oxazoline, (51b)

To 1 g of 50b was added the equal weight of calcium oxide and the mixture of solids was pyrolyzed by the general method. A viscous liquid (0.55 g) was collected, that by GLC (10% SE-30 on Anachrom, 60/80) was shown to be 81% pure (56% yield).

NMR: 7.78-7.82 (1H, dd, J = 2.0 Hz, J = 7.9 Hz); 7.40-7.43 (1H, m); 6.95-7.01 (2H, m); 4.34-4.41 (2H, d, tr, J = 9.2 Hz, J = 2.0 Hz); 4.08-4.15 (2H, tr, J = 9.2 Hz); 3.93 (3H, s).

MS: 177 ($M^+$), 176, 148, 135, 133, 132, 117, 105, 91, 77.

IR: 3380 (s), 2900 (s), 1675 (s), 1460 (m), 1360 (m), 1280 (s), 1040 (s), 1025 (s), 945 (s), 750 (s) $cm^{-1}$.

Calculated for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26

Found: C, 67.71; H, 6.42

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# PART III

## A Total Synthesis of a Constituent from Civet Cat

## INTRODUCTION

The isolation and synthesis of (cis-6-methyltetrahydropyran-2-yl)acetic acid, (1a), a novel compound from Civet, has been reported by two groups.[1-4] Civet is the glandular secretion from the Civet cat (Viverra civetta, living in Asia and Africa), which supplies a fixative for flower perfumes. The Civet musk has the consistency of butter or honey, a clear yellowish or brownish complex of fats and essential oils. Each animal yields less than 1/8 oz per week.[5,6]

Maurer and coworkers, in Geneva, isolated crude volatile acids (0.96%) from 1 kg of commercial natural Civet in the form of their methyl esters containing methyl octanoate and methyl phenylacetate as main components, and methyl nonanoate, methyl decanoate and a methyl heterocyclic ester (ca. 2 mg) as minor components. This new heterocyclic compound was identified as (6-methyltetrahydropyran-2-yl)acetic acid, (1a). In order to confirm the structure and to assign the relative configuration of the natural product, Maurer and coworkers synthesized the two racemic diastereoisomers, (1a) and (1b) by the following route (Figure 61).

Catalytic reduction of the Diels-Alder adduct, (3) of methyl vinyl ketone and ethyl vinyl ether using Raney nickel and hydrogen at 300 atm proceeded stereoselectively to give a 63% yield of the kinetically-controlled cis compound, (4). Hydrolysis of 4 with 0.2 N aqueous HCl gave a 55.7% yield of the anomeric mixture, (5).

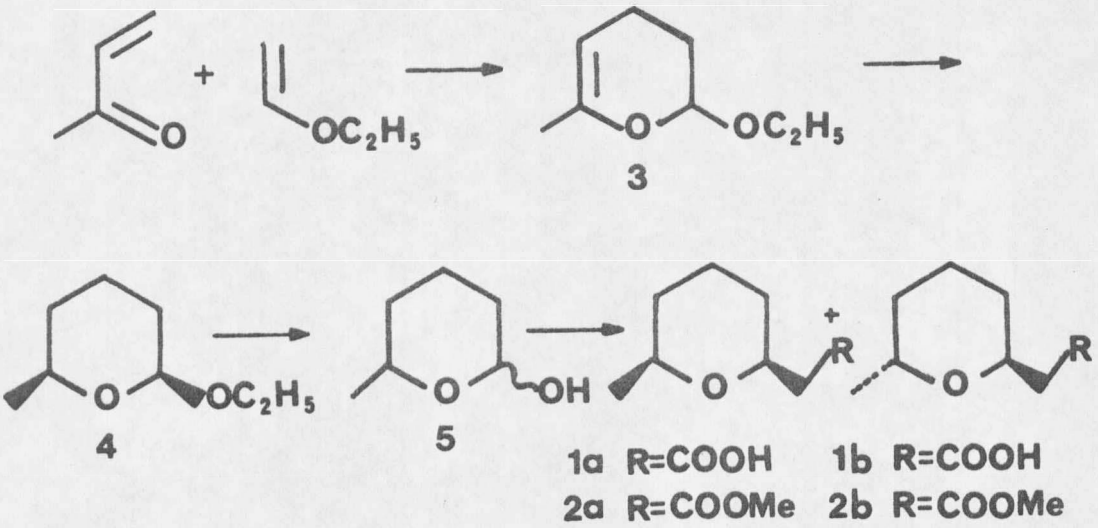



Figure 61. Maurer Synthesis of (6-Methyltetrahydropyran-2-yl)Acetic Acid

Treatment of 5 with methyl dimethylphosphonoacetate in the presence of sodium methoxide yielded an equilibrium mixture (86%) of the cis and trans esters in the ratio of ca. 7:1 (Horner olefination). The more abundant isomer proved to be identical with the methyl ester of the natural product.

Seebach, in Zurich, was also interested in this compound.[2,4] The unsaturated hydroxyacid, (6), is a common precursor to the macrolide, (7), a potential intermediate for the synthesis of pyrenophorine, (8). Pyrenophorine shows antibiotic activity.[7] The tetrahydropyran ring of 1 was opened through the dianion of the THP-acetic acid (1.95 equiv. of LDA, THF, -78° to 0°, 4h; 85% yield) to give the desired (S)-hydroxy acid, (6) (Figure 62). The synthesis

of (+)-(S,S)-(cis-6-methyltetrahydropyran-2-yl)acetic acid is shown in Figure 63. Reaction of the alkali derivative, (10)[8] with

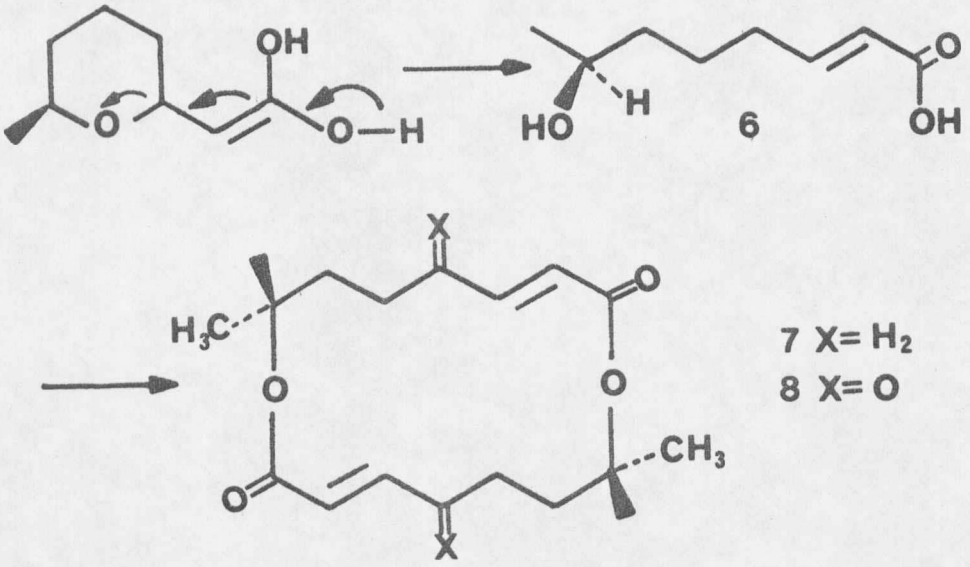



Figure 62. Synthesis of Pyrenophorine from (6-Methyltetrahydropyran-2-yl)Acetic Acid

(-)-(S)-propylene epoxide, (9) furnished the E-hydroxyketone, (11) as the sole product in 50% yield. Treatment of 11 with sodium methoxide caused cyclization to a (3:2)-mixture of cis- and trans-12, while after several days the thermodynamically-controlled product, cis-(12) was quantitatively isolated. The oxime, (13) of this ketone underwent Beckmann type-II cleavage to nitrile (14) which was hydrolyzed to yield (+)-(S,S)-1 (55% from 11). By NMR spectroscopy in the presence of a chiral shift reagent, $Eu(HFC)_3$,

Maurer assigned the S,S-configuration to the natural product, (1a) from Civet.[3]

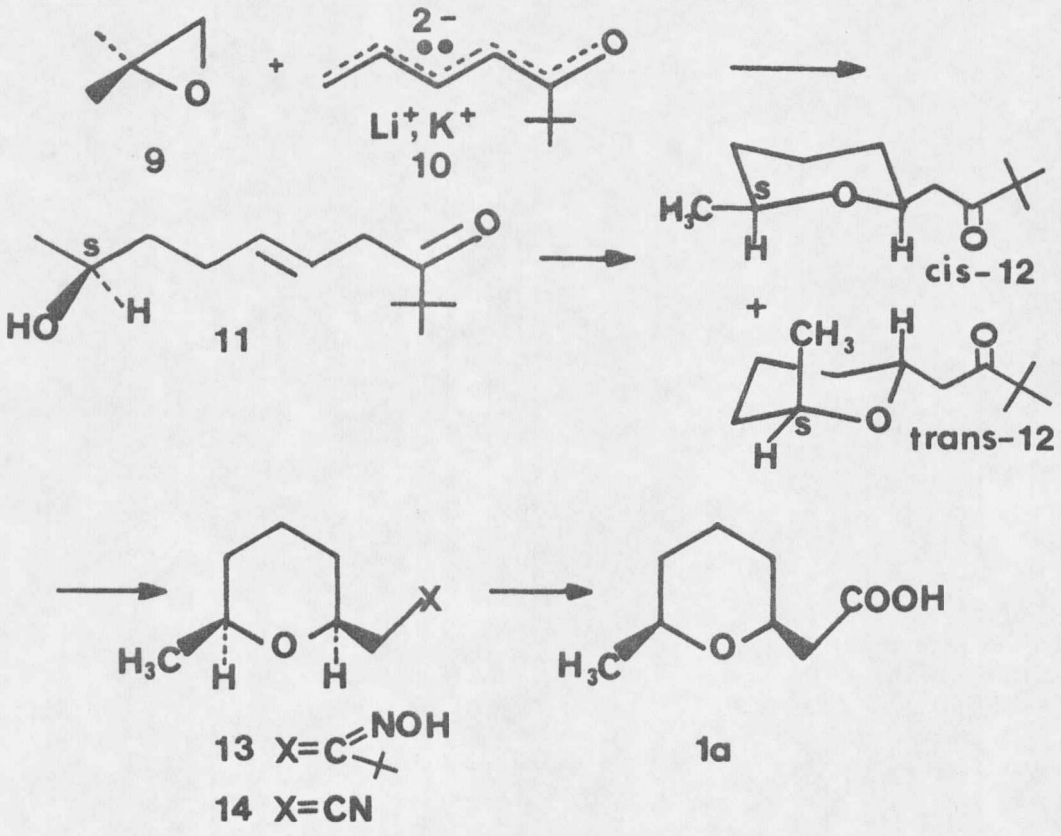



Figure 63. Seebach Synthesis of (6-Methyltetrahydropyran-2-yl)Acetic Acid

Utilizing the observations that (a) the 6,8-dioxabicyclo[3.2.1]octane ring system can be reductively opened to a pyran system,[9] (b) that the cis-2,6-disubstituted pyran derivatives are thermodynamically more stable than the trans isomers,[2] and (c) that

our previous work in the chemistry of insect pheromones resulted in a ready supply of the necessary precursor to our approach,[10] we were prompted to develop the synthesis outlined in Figure 64.

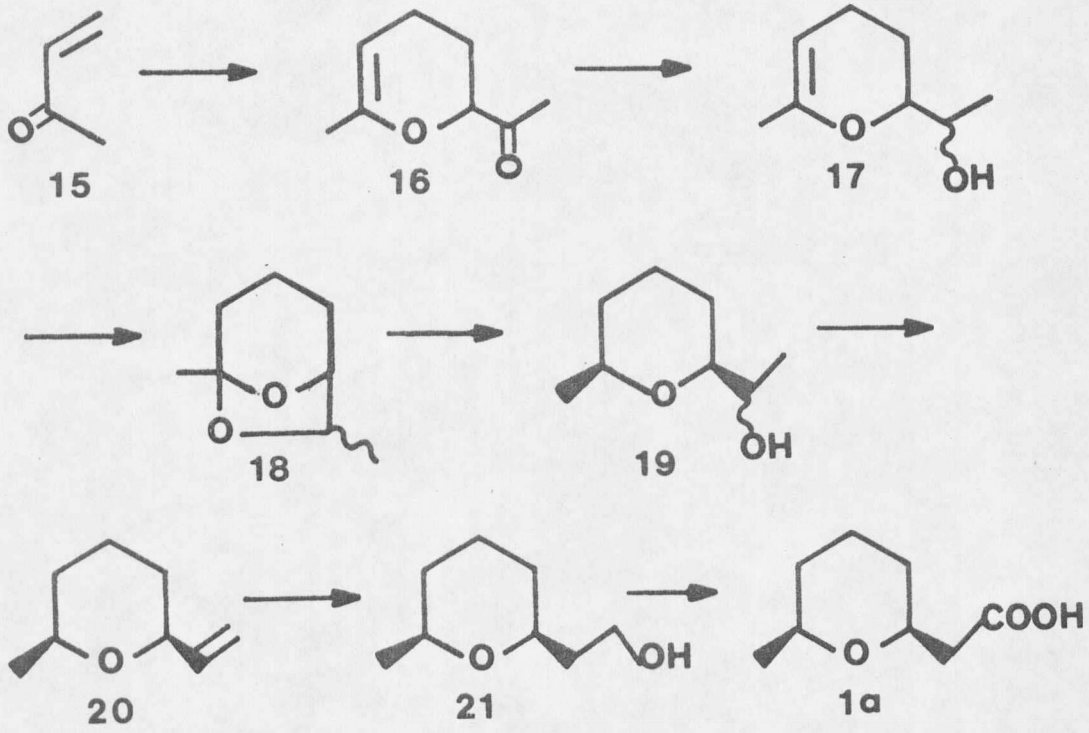



Figure 64. Proposed Synthesis of (6-Methyltetrahydropyran-2-yl)Acetic Acid

## RESULTS AND DISCUSSION

The route starting with the Diels-Alder dimer of methyl vinyl ketone, (**16**), was preferred due to the relative convenience of sodium borohydride reduction. Sodium borohydride reduction of **16** in isopropyl alcohol gave a mixture of threo and erythro isomers, (**17a**) and (**17b**) in a 50:50 ratio (Figure 65). Though we do not fully

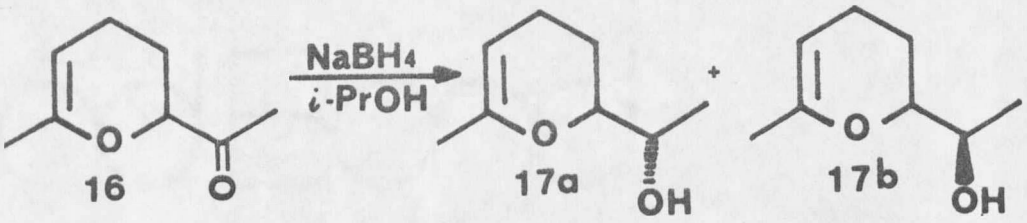



Figure 65. Threo and Erythro of 2-(1-Hydroxyethyl)-6-Methyl-2,4-Dihydropyran

understand the factors controlling the steric course of attack at the carbonyl, the stereochemistry is not important since both products cyclize in the presence of an electrophile, giving the exo and endo mixture (60:40) of **18** in which only the orientation of the methyl group is different (Figure 66).[11]

Catalytic reduction of both bicyclo ketal isomers, (**18a**) and (**18b**) resulted in pyran derivatives. It is interesting to note that of the carbon-oxygen bonds which can be cleaved, only the $C_5$-$O_8$ ketal bond[12] is ruptured specifically giving pyranyl derivatives rather than oxepins. Generally the rate of hydrogenolysis is

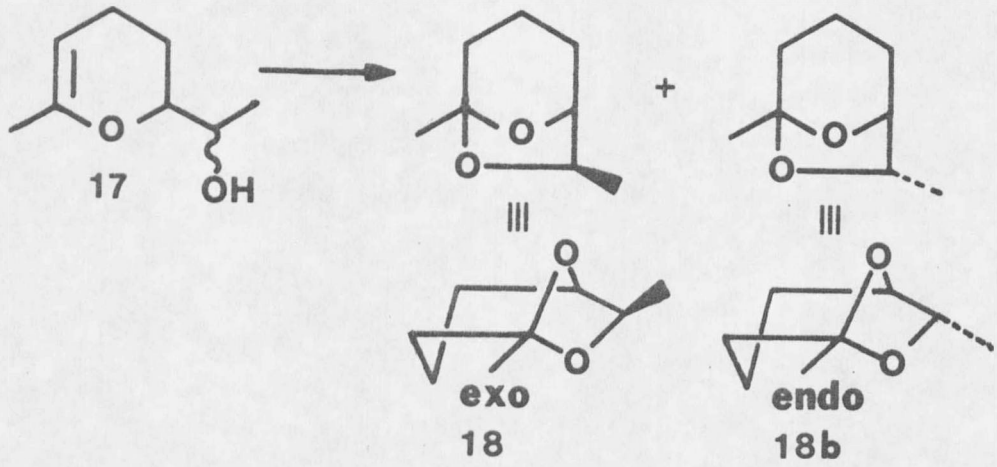



Figure 66. Exo and Endo-5,7-Dimethyl-6,8-Dioxabicyclo[3.2.1]Octane

increased as the bond being cleaved is a better leaving group, supporting the preference of $C_5$-$O_8$ bond cleavage to form pyran.[13] However, the previous work by our group[14] showed that the exo isomer, (**18a**) was much less reactive in the hydrogenation reaction and even after thirty hours reaction time was still detected. This was rationalized as a steric effect of the exo methyl group on the catalyst surface. Due to the low yield of the hydrogenation product, we tried the reaction of **18** with $AlH_3$[15] and $AlH_2Cl$[9] and found that the reductive cleavage reaction of **18** with $AlH_3$ produced exclusively cis-oriented stereoisomers, (**19a**) and (**19b**), in a ratio of 60:40 by regioselective attack of the hydride. $AlH_3$ was prepared by mixing an equimolar amount of lithium aluminum hydride and

aluminum chloride in anhydrous ether solution. The selective pyran ring opening reaction of **18** with $AlH_3$ into the cis isomers, (**19a**) and (**19b**), is rationalized in Figure 67.

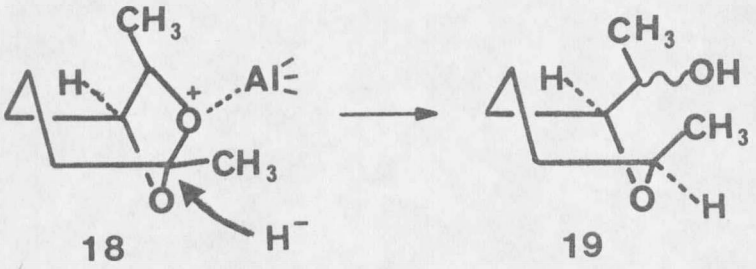



Figure 67. The Selective Ring Opening by $AlH_3$

Brown's work on the hydrogenolysis of acetals and ketals by mixtures of lithium aluminum hydride and aluminum chloride in ether[15] has indicated that, as is the case for the hydrolysis of dioxabicyclooctanes, the rate controlling step of the hydrogenolysis reaction is the cleavage of the $C_5$–$O_8$ bond, weakened by the association of its oxygen atom with the Lewis acid. The association of $O_8$ with aluminum results in the hydride attacking $C_5$ from the opposite side of the complex rather than the hindered side.

We also discovered that the exo bicycloketal, (**18a**) gives the threo alcohol, (**19a**) and the endo bicycloketal, (**18b**) provides the erythro alcohol, (**19b**) which are separated by GLC (15% Carbowax on

Chromosorb W, 60-80 mesh). Figure 68 shows the stereospecific opening of the bicyclic ketals. This phenomenon is supported by the

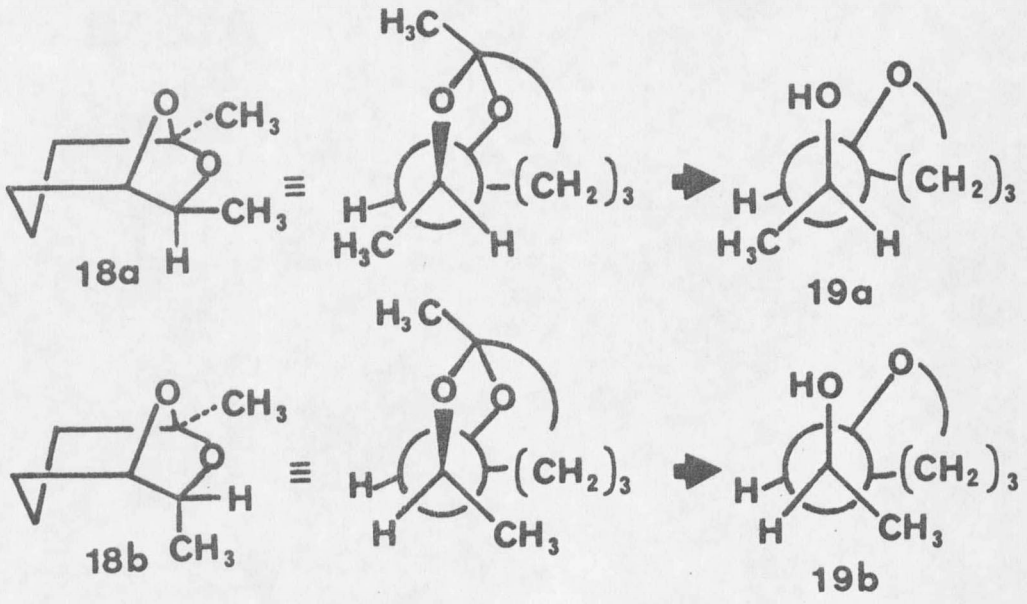



Figure 68. Formation of the Threo and Erythro 1-(cis-6-Methyltetrahydropyran-2-yl)Ethanol

hydrogenation experiment. When the mixture of exo- and endo-acetals, (**18a**) and (**18b**) was hydrogenated for 8 hr, the ratio of unreacted **18a** and **18b** was 80:20 and the ratio of the threo and erythro-**19** produced was 30:70. After all exo- and endo-**18** were hydrogenated with $AlH_3$, the ratio of **19a** and **19b** was 60:40, which is the same as the ratio of **18a** and **18b** as starting materials.

In contrast to the result of the reduction reaction of **18** with $AlH_3$ or $H_2/Pd$, the reaction of **18** with $AlH_2Cl$ produced two other

compounds besides 19a and 19b. These two compounds turned out to be the threo- and erythro-1-(trans-6-methyltetrahydropyran-2-yl)ethanol, (19c) and (19d). The configurational assignments of 19c and 19d are based on the following: (1) IR spectra and MS fragmentation patterns, a peak at m/e 99 which is typical α-cleavage for 2-substituted tetrahydropyrans, of 19c and 19d were almost identical with those of 19a and 19b. (2) The trans isomers, (19c) and (19d) should exist at room temperature as two rapidly equilibrating chair conformations, the two protons at $C_1$ and $C_5$ giving rise to an axial/equatorial time averaged signal in the proton NMR spectrum. Accordingly, the two axial methine protons of the cis isomers, (19a) and (19b) resonate at higher field (δ3.37-3.84 ppm) than the corresponding protons of the trans isomers (δ4.01-4.12 ppm).[1] (3) By the GLC retention time and the NMR peaks of alcohol protons, 19c was assigned to the threo isomer (a proton peak of the alcohol at 2.8 ppm) and 19d to the erythro isomer (at δ2.1 ppm), corresponding to the difference between 19a and 19b. Figure 69 shows the various products distribution in reductive cleavage reaction of 18.

The required cis stereochemistry was established and we had only to refunctionalize the molecule. The several approaches to the required dehydration compound, (20) are shown in Figure 70. To get the Hoffmann elimination-product, (20),[16] the tosylate, (24),

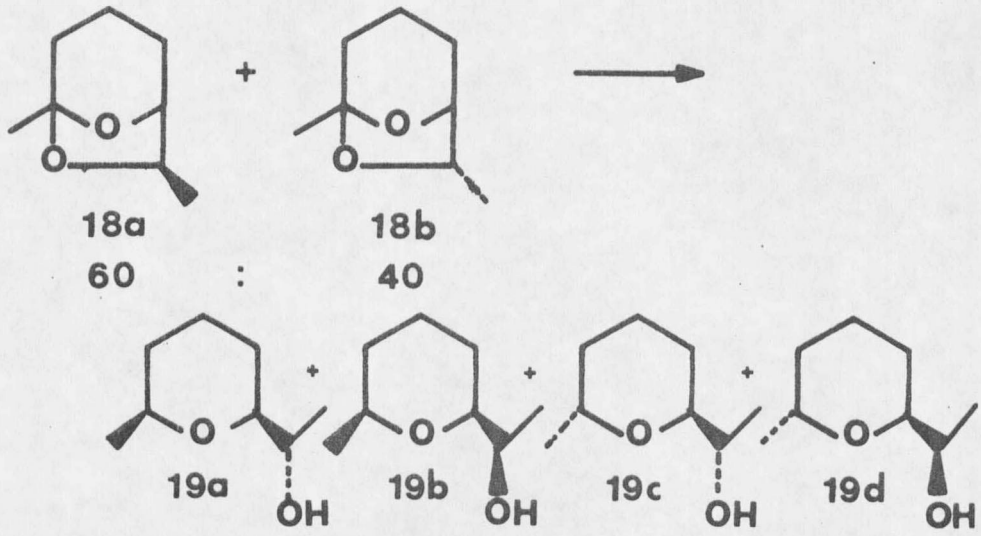
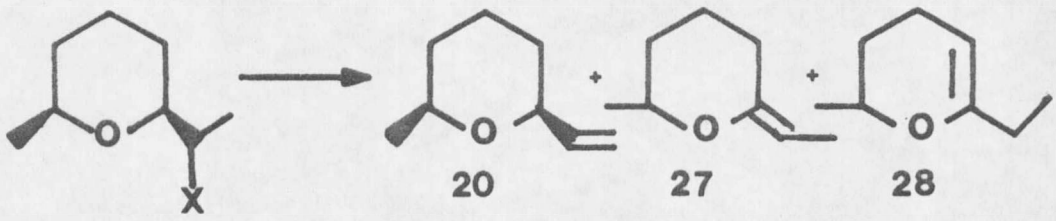



Figure 69. Reductive Cleavage Reactions of 5,7-Dimethyl-6,8-Dioxabicyclo[3.2.1]Octane

produced from toluensulfonyl chloride and pyridine with **19**, was refluxed for 6 hr in DMSO.[17] The product from solvolysis of the tosylate, (**24**) was the undesired compound, (**28**) whose structure was proved by the NMR spectrum and a decoupling experiment, though we could not separate these three isomers, (**20**), (**27**), and (**28**) by GLC. In a decoupling experiment, irradiation of the vinyl proton at 4.44-4.46 ppm simplified the methylene peaks at 1.74-1.82 ppm giving a

good indication that the methyl group at 0.99-1.05 ppm was not




| | | | | |
|---|---|---|---|---|
| 23 X=OAc | : | 100 | 0 | 0 |
| 24 X=OTs | : | 0 | 0 | 100 |
| 25 X=$OCS_2Me$ | : | — | — | — |
| 26 X= =NNHOTs | : | 50 | 0 | 50 |

Figure 70. Attempted Elimination Reactions of 1-(cis-6-Methyltetrahydropyran-2-yl)Ethanol

attached to the vinyl system. Irradiation of the methyl protons at 0.99-1.05 ppm caused a decrease of the 1.97-2.08 ppm multiplet to a broad singlet and had no effect on the vinyl proton. It seems likely that the elimination occurred by the Saytzeff rule to form **27** and the exo-enol ether, (**27**) was transformed into the thermodynamically more stable endo-enol ether, (**28**). To confirm the structure of **28**, a hydroboration reaction was carried out with **28** to give only the threo alcohol, (**19a**). There is no good explanation

for this stereospecific orientation of the hydroboration reaction (Figure 71). The p-toluenesulfonyl hydrazone, (26), prepared by

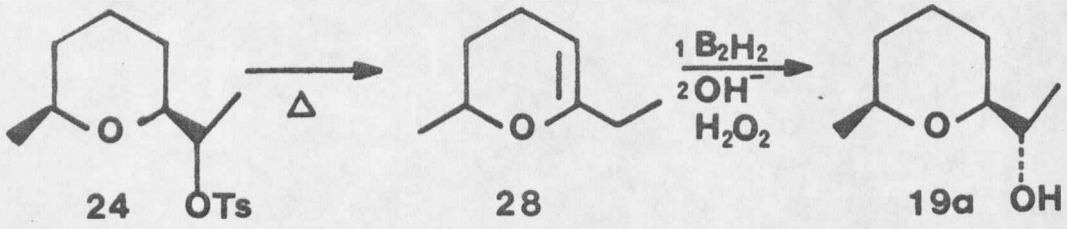


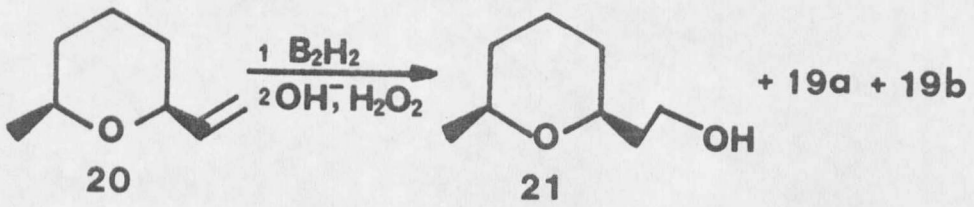

Figure 71. Synthesis of the Threo-1-(cis-6-Methyltetrahydropyran-2-yl)Ethanol

treatment of 6-methyltetrahydropyranyl methyl ketone, with p-toluenesulfonylhydrazine, was heated to 170°C in 1 N sodium ethyleneglycolate until the nitrogen evolution ceased.[18] The NMR spectrum showed that the product was the mixture of 20 and 28 in the ratio of ca. 50:50. The olefinic products formed by the base-promoted decomposition of the p-toluenesulfonylhydrazones are predicted by the operation of the Saytzeff rule. The product distribution of our elimination reaction was almost the same for the Hoffmann and Saytzeff products. Here we also observed that there was no 27; and 27, if formed, was probably equilibrated with 28 and we only detected the thermodynamically stable 28. Also, the Chugaev reaction with 25[19] was attempted, but the yield was poor and there

were by-products which were not easily separated by GLC or distillation. We found that the best way to make the Hoffmann elimination product was by pyrolysis of the acetate, (23).[20] The pyrolysis can be carried out in either the liquid or the vapor phase and the results are usually equally good, although the vapor-phase method has the advantage that the products are maintained at a high temperature for only a short period of time. This ester pyrolysis is extremely simple in experimental procedure, the yields are good, and the absence of solvents and other reactants makes the reaction mixtures easy to work up. The pyrolysis of 23 was carried out in the vapor phase. The pure ester, (23) was added dropwise to the top of a vertically mounted quartz tube packed with broken quartz and heated with a nichrome wire. The product was swept from the reaction chamber by a slow stream of nitrogen and collected in a cold trap. The by-product, acetic acid, was easily separated from olefin, (20) by neutralizing with sodium bicarbonate.

Hydroboration[21] of 20 gave the expected primary alcohol, (21) and also the secondary alcohol, (19) in the ratio of 85:15 (Figure 72). Diborane, generated by the addition of sodium borohydride to boron-trifluoride etherate in diglyme, was swept into a reaction flask containing 20 by applying a slight flow of dry nitrogen. The

mixture of alcohols was separated by distillation under a low pressure.




20 21

Figure 72. Hydroboration Reaction of 2-Vinyl-6-Methyltetrahydropyran

The primary alcohol, (**21**) was oxidized to **1a** by pyridinium chlorochromate (PCC),[22] $C_5H_5NH^+ClCrO_3^-$, pyridinium dichromate (PDC)[23], $(C_5H_5NH^+)_2Cr_2O_7$, and Jones Reagent[24] (Figure 73). Treatment of **21** with PCC in $CH_2Cl_2$ produced **29**, which followed by further oxidation with PDC in dry DMF resulted in **1a**. Direct oxidation of **21** with PDC in DMF or Jones Reagent in acetone created **1a** in a good yield. The DMF and **1a** were separated by column chromatography using silica gel with anhydrous ether as an eluant. After evaporation of solvent, **1a** was successfully crystallized.

The synthesis presented here has the potential of becoming a more efficient source of a synthetic Civet constituent than the other current syntheses for the following reasons: (a) Methyl vinyl

ketone is an economical starting material and is easily acquired; (b) Each reaction step is fairly mild with a good yield; (c) The chemistry of each reaction is commonly known and understood. The overall yield of Civet constituent by this synthesis was 15.5% from methyl vinyl ketone and 24% from its dimer, though we did not attempt to maximize the yields in the multistep synthesis.

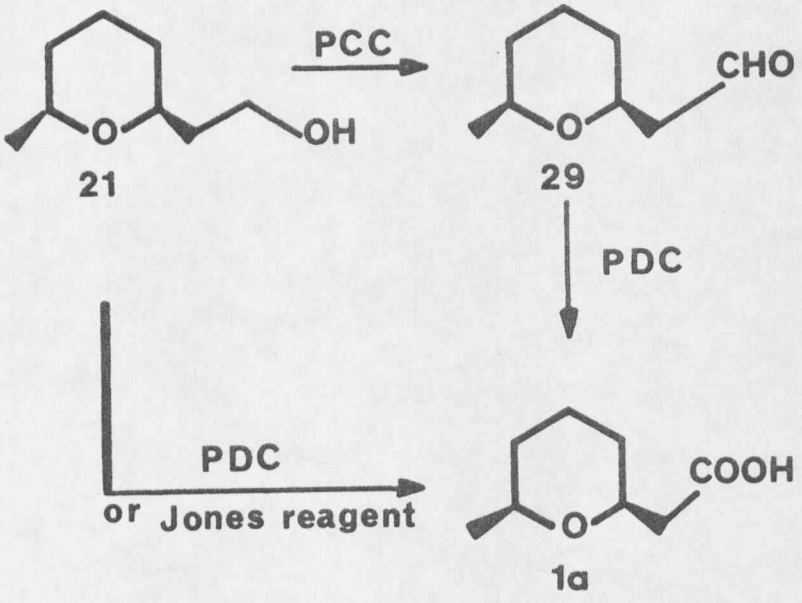



Figure 73. Oxidation Reaction of 2-(cis-6-Methyltetrahydropyran-2-yl)Ethanol

## EXPERIMENTAL

### General Method

$^{1}H$-NMR and $^{13}C$-NMR spectra were recorded on a Bruker 250 MHz spectrophotometer using deuterochloroform as solvent. Chemical shifts are expressed in ppm ($\delta$scale) downfield from tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a Varian Model CH5 mass spectrometer, using inlet temperature of ca. 180°C and electrons of ca. 70 eV energy. IR spectra were recorded on a Beckmann IR-5 spectrophotometer; absorption maxima are given in $cm^{-1}$. Abbreviations are: s = strong, m = medium, w = weak, br = broad. Gas liquid chromatography (GLC) was carried out on a Varian Aerograph series 2700 instrument, using 15% Carbowax 20M on Chromosorb W, 60-80 mesh (1/4" X 8') and 10% SE-30 on Chromosorb W, 60-80 mesh (1/4" X 8'). All boiling points and melting points are uncorrected. Pressures are reported in mm of mercury. Unless otherwise specified, commonly needed reagents were used as received.

### Preparation of 2-Acetyl-6-Methyl-3,4-Dihydro-2H-Pyran, (16)

Methyl vinyl ketone (100 g, 1.43 Mol) was placed in a steel pressure vessel and dimerized at 185°C for 2 hr. After cooling, the contents were distilled at 72-75°C/12 mm Hg to give a colorless

liquid, 58.8 g. The spectral data were identical with the previous work.[25]

Preparation of 2-(1-Hydroxyethyl)-6-Methyl-2,4-Dihydropyran, (17)

To methyl vinyl ketone dimer, (16) (100 g, 0.714 Mol) in 300 mL of dry isopropyl alcohol was added sodium borohydride (7.53 g, 0.199 Mol) in an ice bath and the mixture was stirred for an hour. Water was added and the product was extracted with methylene chloride and dried over anhydrous magnesium sulfate. The alcohol was distilled at 45-50°C/0.5 mm Hg. The spectral data were identical with the previous work.[26]

Preparation of exo- and endo-5,7-Dimethyl-6,8-Dioxabicyclo[3.2.1]Octane, (18)

The freshly distilled alcohol, (17) (81.1 g, 0.571 Mol) was added to 200 mL of dry benzene and a catalytic amount of toluenesulfonic acid. The mixture was stirred at room temperature for 30 min, resulting in an exothermic reaction. Distillation at 58-66°C/12 mm Hg gave 65.14 g of 18. The yield was 64.2% from 16. The spectral data were identical with the previous work.[27] The ratio of exo- and endo-18 was about 60:40, and these compounds were separated by GLC and distillation.

Preparation of 1-(cis-6-Methyltetrahydropyran-2-yl)Ethanol, (19a) and (19b)

$AlH_3$ Method

To a gray suspension of aluminum chloride (107.8 g, 0.808 Mol) in 250 mL of anhydrous ethyl ether was added dropwise lithium aluminum hydride (7.7 g, 0.202 Mol) in 100 mL of anhydrous ethyl ether in an ice bath under nitrogen. Swirling with ether was repeated several times until all the hydride was added and the gray slurry was stirred for an hour. A solution of 18 (57.4 g, 0.404 Mol) in 100 mL of ethyl ether was added at a rate sufficient for gentle refluxing. The mixture was refluxed for 3 hr. Excess hydride was destroyed by the dropwise addition of ca. 10 mL of water and 2 N sulfuric acid was added carefully until no more reaction occurred in an ice bath. The ether layer was separated and the aqueous layer was extracted with ether three times. The combined ether solution was washed with water, saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Distillation at 85-90°C/12 mm Hg gave 49.4 g (84.9%) of 19, a colorless liquid. The ratio of threo- and erythro-19 was 60:40, respectively.

$AlH_2Cl$ Method

To a stirred solution of lithium aluminum hydride (0.427 g, 11.3 mMol) in 10 mL of dry ethyl ether kept at 5°C by an ice bath, was added dropwise 10 mL of ether solution of aluminum chloride

(1.49 g, 11.3 mMol). After the addition, the solution was stirred at room temperature for 15 min. To this stirred mixture was then slowly added a solution of 18 (2.1 g, 15 mMol) in 10 mL of dry ether. The mixture was stirred at room temperature for 2 hr whereupon a 15% aqueous solution of potassium hydroxide was slowly added until no further reaction occurred. The alkaline aqueous layer was extracted with ether and the combined ether solutions were washed with water, saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The residue was analyzed by GLC (15% Carbowax on Chromosorb W, 60/80 mesh) to show that the ratio of 19a, 19b, 19c, and 19d was 29.6:6.3:31.8:32.3.

$H_2$/Pd/C Method

The exo and endo mixture of 18 (20.8 g, 0.146 Mol) in 200 mL absolute ethanol with 0.7 g of 5% Pd/C was hydrogenated under 55 psi for 20 hr. After the solvent was evaporated, 11.9 g of 19 was collected after distillation at 82-87°C/12 mm Hg. The ratio of threo and erythro compound was 28.6:71.4 and also 35.2% of 18a was detected, while there was no trace of 18b by GLC.

NMR of 19a: 3.39-3.59 (2H, m); 3.03-3.11 (1H, m); 2.92 (1H, br s); 1.41-1.86 (6H, m); 1.16-1.18 (3H, d, J = 6.6 Hz); 1.11-1.14 (3H, d, J = 6.6 Hz).

NMR of 19b: 3.37-3.84 (1H, m); 3.46-3.52 (1H, tet); 3.24-3.31 (1H, dd); 2.23 (1H, br s); 1.28-1.89 (6H, m); 1.15-1.18 (3H, d, J = 5.9 Hz); 1.12-1.15 (3H, d, J = 6.9 Hz).

NMR of 19c: 4.01-4.00 (1H, q); 3.73-3.81 (1H, m); 3.34-3.42 (1H, dt, J = 3.0 Hz, J = 8.0 Hz); 2.81 (1H, br s); 1.28-1.74 (6H, m); 1.20-1.23 (3H, d, J = 6.6 Hz); 1.11-1.13 (3H, d, J = 6.4 Hz).

NMR of 19d: 4.08-4.12 (1H, m); 3.79-3.85 (1H, m); 3.48-3.55 (1H, m); 2.07 (1H, s); 1.35-1.75 (6H, m); 1.22-1.24 (3H, d, J = 6.7 Hz); 1.14-1.16 (3H, d, J = 6.6 Hz).

MS of 19a and 19b: 99 ($M^+$ - 45), 81, 71, 57, 55, 45, 43, 41, 39, 29.

MS of 19c and 19d: 99 ($M^+$ - 45), 81, 57, 55, 45, 43, 29.

IR of 19: 3330 (s), 2860 (s), 2800 (s), 1435 (m), 1360 (m), 1075 (s), 1045 (m), 970 (m), 890 (m) $cm^{-1}$.

Calculated for $C_8H_{16}O_2$, (19c): C, 66.63; H, 11.18

Found: C, 66.42; H, 11.24

Calculated for $C_8H_{16}O_2$, (19d): C, 66.63; H, 11.18

Found: C, 65.68; H, 10.56

Preparation of cis-2-Vinyl-6-Methyltetrahydropyran, (20)

Preparation of 1-(cis-6-Methyltetranydropyran-2-yl)Ethyl Acetate. (23)

Acetyl chloride (10.9 g, 0.139 Mol) was added slowly to 19 (20.0 g, 0.139 Mol) and dry pyridine (11.0 g, 0.139 Mol) in an ice bath. The mixture was allowed to stand overnight, then 100 mL of ice water was poured into the flask. The organic layer was separated and the aqueous layer was extracted three times with ether. The combined ether solution was washed with water and saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Distillation at 103-106°C/12 mm Hg gave 23.01 g (89.1%) of a colorless liquid, (23). The ratio of threo- and erythro- 23 was 40:60.

NMR of 23a: 4.76-4.83 (1H, m); 3.39-3.47 (1H, m); 3.29-3.36 (1H, m); 2.05 (3H, s); 1.27-1.87 (6H, m); 1.22-1.25 (3H, d, J = 6.6 Hz); 1.15-1.18 (3H, d, J = 6.6 Hz).

NMR of 23b: 4.86-4.96 (1H, m); 3.29-3.47 (2H, m); 2.07 (3H, s); 1.25-1.89 (6H, m); 1.21-1.23 (3H, d, J = 6.6 Hz); 1.16-1.18 (3H, d, J = 5.9 Hz).

MS: 126 ($M^+$ - 60), 99, 81, 57, 55, 43.

IR: 2930 (s), 2850 (s), 1730 (s), 1440 (s), 1370 (s), 1240 (s), and 1060 (s) $cm^{-1}$.

| | | |
|---|---|---|
| Calculated for $C_{10}H_{18}O_3$: | C, 64.49; | H, 9.74 |
| Found for 23a: | C, 64.40; | H, 9.93 |
| 23b: | C, 64.53; | H, 9.86 |

Pyrolysis of 1-(cis-6-Methyltetrahydropyran-2-yl)Ethyl Acetate, (23)

The pyrolysis of 23 was carried out in the vapor phase at 450°C. The acetate, (23) (15.2 g, 0.082 Mol) in a 25-mL syringe was added at the speed of 10 mL/hr to the top of a vertically mounted quartz tube (i.d. 0.7 cm X 30 cm) packed with broken quartz heated with a nichrome wire as shown in Figure 74. The products were swept from the reaction column by a slow stream of nitrogen and collected in a cold trap using isopropyl alcohol and dry ice. The temperature (450°C) was monitored by inserting a thermocouple between the wall of the column and the nichrome wire. After pyrolysis, the products were neutralized carefully with sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with ether. The commbined ether solution was washed with water, saturated sodium chloride solution and dried over anhydrous magnesium sulfate. After distillation at 45-47°C/12 mm Hg, 8.20 g (79.6%) of a colorless liquid, (20), was collected.

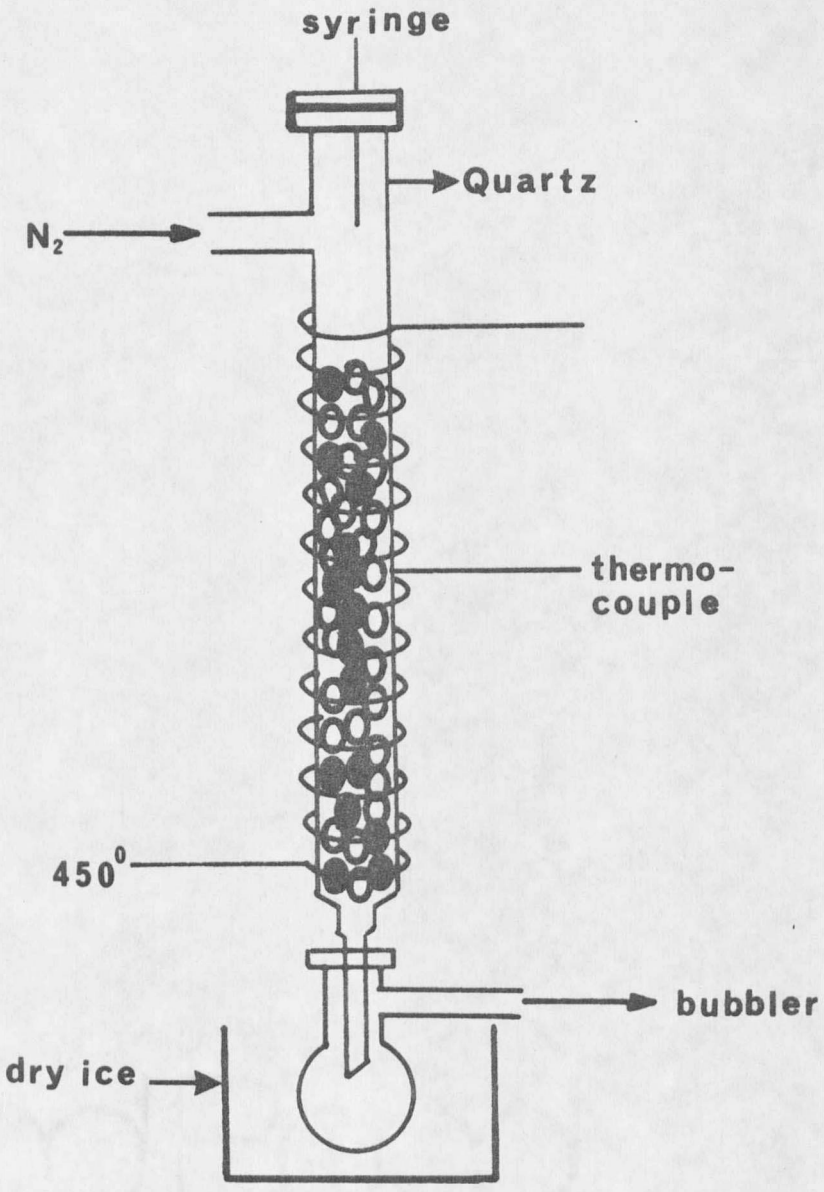



Figure 74. A Typical Apparatus for Vapor-Phase Pyrolysis

NMR: 5.81-5.94 (1H, m); 5.19-5.28 (1H, dt, J = 17 Hz); 5.06-5.11 (1H, dt, J = 10.6 Hz); 3.79-3.86 (1H, m); 3.46-3.54 (1H, m); 1.21-1.85 (6H, m); 1.19-1.21 (3H, d, J = 5.9 Hz).

MS: 126 ($M^+$), 125, 99, 85, 69, 57, 55, 43, 41.

IR: 2925 (s), 2850 (s), 1680 (w), 1650 (w), 1450 (m), 1380 (m), 1315 (m), 1240 (w), 1215 (w), 1165 (w), 1155 (w), 1090 (s), 1080 (s), 1050 (s), 1025 (m), 995 (m), 925 (w), 980 (w), 810 (w), and 755 (w) $cm^{-1}$.

Calculated for $C_8H_{14}O$: C, 76.14; H, 11.18

Found: C, 76.14; H, 11.32

Preparation of 1-(cis-6-Methyltetrahydropyran-2-yl)Ethyl Tosylate, (24)

A solution of 19 (10.0 g, 69.9 mMol) in 25 mL of pyridine was added dropwise to a cooled solution (0°C) of p-toluenesulfonyl chloride (20.0 g, 105 mMol) in 50 mL of pyridine. After completion of the addition, the mixture was then poured into 100 mL of cold water, and within a few minutes the white crystalline tosylate, (24) was formed. After filtration, the tosylate, (24) was washed with petroleum ether (35-60°C) and dried in a vacuum oven, yielding 18.6 g (89.9%) of product.

NMR: 7.78-7.82 (2H, d, J = 7.9 Hz); 7.30-7.33 (2H, d, J = 7.9 Hz); 4.43-4.48 (1H, m); 3.24-3.37 (2H, m); 2.44 (3H, s); 1.32-1.81 (6H, m); 1.26-1.28 (3H, d, J = 5.9 Hz); 1.03-1.06 (3H, d, J = 5.9 Hz).

MS: 283 ($M^+$ - 15), 207, 44.

M.P.: 69-70°C.

Calculation for $C_{15}H_{22}O_4S$: C, 60.38; H, 7.43

Found: C, 60.51; H, 7.70

Preparation of cis-2-Ethyl-6-Methyl-5,6-Dihydropyran, (28)

A solution of 24 (10 g, 33.6 mMol) in 50 mL of dimethyl sulfoxide was heated at 90-95°C under reflux for 5 hr. The solution was allowed to cool to room temperature and poured into an equal volume of a mixture of ice and water. The mixture was extracted three times with petroleum ether (35-60°C). The combined ether solution was washed with water and saturated sodium chloride solution and dried over anhydrous magnesium sulfate. After the distillation at 45-50°C/12 mm Hg, 1.67 g (34.6%) of a colorless liquid was collected.

NMR: 4.44-4.46 (1H, tr); 3.89-3.95 (1H, m); 1.97-2.08 (2H, m); 1.75-1.82 (2H, m); 1.44-1.56 (2H, m); 1.26-1.29 (3H, d, J = 6.6 Hz); 0.99-1.05 (3H, tr).

IR: 2900 (s), 1680 (s), 1450 (m), 1360 (m), 1320 (m), 1240 (s),

1110 (m), 1075 (s), 1000 (m), 955 (w), 890 (s), 755 (s) $cm^{-1}$.

Calculated for $C_8H_{14}O$: C, 76.14; H, 11.18

Found: C, 75.95; H, 11.27

Preparation of 1-(cis-6-Methyltetrahydropyran-2-yl)Ethyl Xanthate, (25)

To a solution of 12 (2.5 g, 17.4 mMol) in 30 mL of dry toluene was added 0.4 g of sodium metal. The mixture was then cooled in an ice bath, the unreacted sodium was removed with a spatula, and 50 mL of anhydrous ethyl ether was added along with an equivalent amount of carbon disulfide (1.32 g, 17.4 mMol). During this addition, the temperature was kept below 40°C. The mixture was stirred overnight and an equivalent amount of methyl iodide (2.47 g, 17.4 mMol) was added dropwise, after which the entire mixture was stirred for another 24 hr. It was then filtered and the ether was removed in vacuo. After the distillation at 143-147°C/12 mm Hg, 3.0 g of a yellow liquid was collected. IR spectra indicated no alcohol group: 2910 (s), 1370 (w), 1210 (br, s), 1040 (br, s) and 885 (w) $cm^{-1}$.

Pyrolysis of 25

The xanthate ester, (25) was pyrolyzed at 160°C for 3 hr. GLC analysis showed that there was only 24% elimination.

Preparation of 6-Methyltetrahydropyranyl Methyl Ketone Tosylhydrazone, (26)

The p-toluenesulfonylhydrazine (1.31 g, 7.31 mMol) was dissolved in 15 mL of 1% ethanolic hydrochloric acid and an equimolar amount of 6-methyltetrahydropyranyl methyl ketone (1.04 g, 7.31 mMol) was added. The solution was heated at reflux for half an hour. An equal volume of water was added after cooling the solution and the solution was cooled to -10°C. The white crystals were collected by filtration, washed with ethanol-water (1:1) mixture, and dried in a vacuum oven. The yield was 1.60 g (73.4%).

NMR: 7.81-7.85 (2H, d, J = 8.6 Hz); 7.28-7.32 (2H, d, J = 7.9 Hz); 3.86-3.92 (1H, dd, J = 2.0 Hz, J = 2.6 Hz); 3.42-3.50 (1H, m); 2.42 (3H, s); 2.40 (1H, s); 1.80 (3H, s); 1.17-1.88 (6H, m); 1.11-1.14 (3H, d, J = 6.6 Hz).

MS: 292 ($M^+$ - 18), 218, 217, 83, 54, 38.

M.P.: 145-147°C.

Calculation for $C_{15}H_{22}N_2O_3S$: C, 58.04; H, 7.14

Found: C, 57.23; H, 7.09

Elimination Reaction of the Hydrazone, (26)

The hydrazone, (26) (4 g, 12.9 mMol) was dissolved in 50 mL of ethylene glycol containing 20 mL of 1N sodium ethyleneglycolate. The mixture was heated to 170°C until the nitrogen evolution ceased.

The product was distilled under aspirator pressure, which gave 0.5 g (31%) of a colorless liquid. The product was analyzed by spectral means and combustion analysis. (Calculated for $C_8H_{14}O$: C, 76.14; H, 11.18, and Found: C, 75.91; H, 11.28). IR spectra closely matched the spectra of 20 and 24. The NMR spectrum was the combined spectra of 20 and 24. By comparing the relative integration of peaks, the ratio of 20 and 24 was ca. 50:50.

Preparation of 6-Methyltetrahydropyranyl Methyl Ketone

Methyl vinyl ketone dimer, (16) (10 g, 71.4 mMol) was poured into 100 mL absolute ethyl alcohol with 5% Pd on charcoal (1 g) in a 500-mL hydrogen bottle. The solution was shaken for 12 hr under 55 psi hydrogen. After the solution was filtered through Celite, and the filtrate was evaporated, 7.9 g (78%) of a colorless liquid was left which distilled at 78-81°C/12 mm Hg.

NMR: 3.76-3.81 (1H, dd, J = 11.9 Hz, J = 2.6 Hz); 3.45-3.48 (1H, m); 2.18 (3H, s); 1.28-1.85 (6H, m); 1.19-1.22 (3H, d, J = 5.9 Hz).

MS: 142 ($M^+$), 99, 81, 57, 55, 43, 42, 41, 39.

IR: 2900 (s), 2810 (s), 1710 (s), 1357 (m), 1085 (s), 1050 (s) $cm^{-1}$.

Calculated for $C_8H_{14}O_2$: C, 67.57; H, 9.92

Found: C, 67.44; H, 10.09

Preparation of 2-(cis-6-Methyltetrahydropyran-2-yl)Ethanol, (21)

A solution of 20 (2.50 g, 19.8 mMol) in 10 mL of dry THF was placed in a 50-mL three-necked flask equipped with a thermometer, a reflux condenser connected to a bubbler, and a dispersion tube connected with Tygon tubing to a 50-mL three-necked flask serving as the diborane generator equipped with a nitrogen inlet and a mercury pressure equalizer. In the generator was placed 3 mL of boron-trifluoride etherate in 3 mL of diglyme. Diborane was generated by the dropwise addition of 9 mL of 1 M solution of sodium borohydride in diglyme using a syringe to the stirred borontrifluoride etherate in diglyme solution. The diborane was passed into the olefin solution (maintained at 20°C) by applying a slight flow of dry nitrogen through the generator. After addition of sodium borohydride, the generator was heated for half an hour at 70°C and disconnected from the hydroboration flask after cooling to room temperature. The excess hydride was decomposed by the addition of 1.5 mL of water. To the organoborane solution was added 3 mL of 3 N sodium hydroxide and 3 mL of 30% hydrogen peroxide dropwise at 30-50°C. The reaction mixture was stirred for an additional hour, then 30 mL of ethyl ether was added. The organic phase was separated and the aqueous phase was saturated with sodium chloride and then extracted twice with 15 mL portions of ethyl ether. The combined

extracts were washed twice with 15 mL portions of saturated sodium chloride solution and dried over anhydrous magnesium sulfate. After the evaporation of ether solvent, 2.30 g of a colorless liquid (80%) was distilled at 112-115°C/12 mm Hg.

NMR: 3.77-3.79 (2H, m); 3.44-3.60 (2H, m); 3.17 (1H, br s); 1.20-1.84 (8H, m); 1.15-1.17 (3H, d, J = 5.9 Hz).

MS: 144 ($M^+$), 99, 81, 75, 55, 45, 43, 42.

IR: 3400 (s), 2900 (s), 1450 (m), 1375 (m), 1325 (m), 1210 (m), 1155 (m), 1085 (s), 1050 (s), 1020 (m) $cm^{-1}$.

Calculated for $C_8H_{16}O_2$: C, 66.63; H, 11.18

Found: C, 66.38; H, 11.02

Preparation of (cis-6-Methyltetrahydropyran-2-yl)Acetyl Aldehyde, (29)

Pyridinium chlorochromate (0.647 g, 3.0 mMol) and sodium acetate (0.049 g, 0.6 mMol) were suspended in 5 mL of anhydrous methylene chloride and the primary alcohol, (21) (0.282 g, 2.0 mMol) in 5 mL of methylene chloride was added in one portion to the magnetically stirred solution. After 2 hr, 50 mL of dry ethyl ether was added and the supernatant decanted from the black gum. The insoluble residue was washed three times with 5 mL portions of anhydrous ethyl ether whereupon it became a black granular solid. The combined organic solution was passed through a short pad of

Florisil and the solvent was removed by distillation. The product (81%) was analyzed by GLC.

NMR: 9.79-9.81 ((1H, tr, J = 2.6 Hz); 3.81-3.90 (1H, m); 3.45-3.52 (1H, m); 2.41-2.66 (2H, m); 1.19-1.87 (6H, m); 1.14-1.17 (3H, d, J = 6.6 Hz).

MS: 142 ($M^+$), 114, 102, 99, 81, 71, 55, 54, 45, 43, 42, 41, 39.

IR: 2910 (s), 2840 (s), 2720 (w), 1730 (s), 1450 (w), 1395 (w), 1375 (w), 1100 (m), and 1085 (s) $cm^{-1}$.

Calculated for $C_8H_{14}O_2$: C, 67.57; H, 9.92

Found: C, 67.35; H, 9.73

## Preparation of (cis-6-Methyltetrahydropyran-2-yl)Acetic Acid, (1a)

### Jones Reagent Method

Jones Reagent was prepared by dissolving chromium trioxide (6.7 g) in 12.5 mL of distilled water. To this solution was added 5.8 mL of concentrated sulfuric acid and the salts which precipitated were dissolved by addition of a minimum quantity of distilled water (the total volume of a solution did not exceed 22.5 mL). To a solution of 21 (0.50 g, 3.47 mMol) in 10 mL of acetone was added Jones Reagent at 20°C until the characteristic orange color of the reagent persisted for 20 min. The solution mixture was stirred for an hour and the green salts were filtered and rinsed

with acetone several times. Isopropyl alcohol was added to the acetone solution until the excess chromic acid was destroyed. The solution was neutralized with sodium bicarbonate and the suspension was filtered. After evaporation of acetone, 10 mL of saturated sodium chloride solution was added and the mixture was extracted three times with ether. The combined ether solution was washed with water, saturated sodium chloride solution and dried over anhydrous magnesium sulfate. After evaporation of ether solution, 0.424 g of white crystals (77%) was collected.

PDC Method

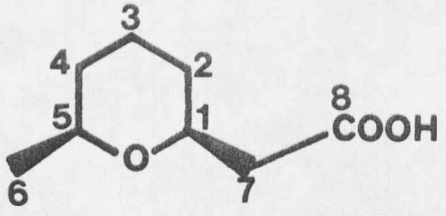
Pyridinium dichromate (4.73 g, 12.5 mMol) was added to 21 (0.513 g, 3.56 mMol) in 9.5 mL of dry DMF, prepared by shaking with potassium hydroxide pellets and distillation from calcium oxide. The solution was stirred for 9 hr at room temperature. Water (80 mL) was poured into the DMF solution and the solution was extracted with ethyl ether three times. The combined ether solution was washed with water, saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. After the evaporation of solvent, the DMF and 1a were separated by column chromatography using anhydrous ethyl ether as an eluant on silica gel. The acid, (1a) was collected first and crystallized by evaporation of ether solution, which gave 0.375 g (67%) of white crystals, (1a).

Oxidation of **29** with PDC

The aldehyde, (**29**) was treated with pyridinium dichromate following the preceeding procedure. The acid, (**1a**) was collected by GLC and its NMR spectrum was identical to that previously prepared.

NMR: 3.73-3.80 (1H, m); 3.51-3.59 (1H, m); 2.52-2.56 (2H, q); 1.24-1.87 (6H, m); 1.19-1.21 (3H, d, J = 5.9 Hz).

$^{13}C$ NMR (TMS in $CDCl_3$): 173.91 (8C), 74.80 (1C), 74.13 (5C), 41.31 (7C), 32.86 (4C), 30.86 (2C), 23.20 (3C), 22.02 (6C).




MS: 158 ($M^+$), 126, 116, 115, 102, 99, 98, 89, 81, 71, 55, 45, 43, 42, 41.

M.P.: 48-51°C; lit. 50-52°C[2], lit. 52-53°C[1].

IR: 2400-3780 (br s), 1740 (s), 1720 (s), 1440 (m), 1380 (m), 1300 (m), 1210 (m), 1185 (m), and 1075 (s) $cm^{-1}$.

Calculated for $C_8H_{14}O_3$: C, 60.74; H, 8.92

Found: C, 61.04; H, 8.95

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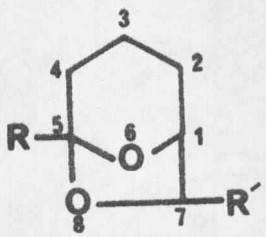
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