



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

ii

To my parents

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

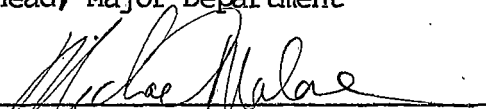
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TABLE OF CONTENTS

	<u>Page</u>
LIST OF TABLESvii
LIST OF FIGURES.	ix
ABSTRACTxiv
INTRODUCTION	1
PART I. Study on the Pinacol Rearrangement.	2
Introduction.	3
Pinacol Coupling Reaction	4
Results and Discussion.	13
Pinacol Rearrangement Reaction.	21
Results and Discussion.	32
Experimental.	54
Literature and Notes.	69
PART II. A New Approach to Natural Products Using the Mundy N-Acylactam Rearrangement.	74
Introduction.	75
Results and Discussion.	84
Experimental.102
Literature and Notes.116

TABLE OF CONTENTS (continued)

PART III. A Total Synthesis of a Constituent from Civet Cat.121
Introduction.122
Results and Discussion.127
Experimental.138
Literature and Notes.156

LIST OF TABLES

	<u>Page</u>
Table 1. Distribution of Coupling Products.	8
Table 2. Product Distribution in the Methylcyclohexanone Studies Experiment	9
Table 3. Self-Coupling of Methylcyclohexanones.	14
Table 4. Products from a Pinacol Rearrangement as Related to Conditions	28
Table 5. Slopes from the Plot of $\Delta\delta$ vs. [Eu(fod) ₃]/[<u>85</u>].	40
Table 6. Typical Natural Spirocompounds	52
Table 7. The Cartesian Coordinates of <u>85</u>	68
Table 8. Simple Alkaloids of the Type Characterized by Hygrin.	81

LIST OF FIGURES

	<u>Page</u>
Figure 1. The Pinacol Rearrangement	3
Figure 2. General Mechanisms for the Reductive Coupling.	4
Figure 3. Different Pinacol Products by Different Methods	5
Figure 4. Anion-Radical Coupling of 3-Methylcyclohexanone	6
Figure 5. Pinacol Formation by Dianion Intermediate	7
Figure 6. General Scheme of Mixed Pinacol Condensation.	8
Figure 7. Competitive Coupling of the Methylcyclohexanones.	10
Figure 8. Temperature Effects on Coupling Reaction.	12
Figure 9. Products from the Reductive Coupling of Methylcyclohexanones	13
Figure 10. Sulfite Esters of Bicyclopinacols	15
Figure 11. Preparation of 1'-Hydroxycyclohexyl- 4-Hydroxytetrahydropyran.	17
Figure 12. Self-Coupling of Tetrahydropyran-4-One.	18
Figure 13. Comparison of Intermediates Reactivity.	18
Figure 14. Mixed Coupling of Tetrahydrothiopyran- 4-One with Cyclohexanone.	19
Figure 15. The Mechanism of the Pinacol Rearrangement.	21

LIST OF FIGURES (continued)

	<u>Page</u>
Figure 16. The Ring Contraction of <u>cis</u> -1,2-Dimethylcyclohexane-1,2-Diol	23
Figure 17. Isomerization of the <u>trans</u> -Diol to the <u>cis</u> -Diol.	23
Figure 18. Cyclopentyl and Cyclohexyl Glycols	24
Figure 19. Ring Size Effects: C ₅ versus C ₆	25
Figure 20. Ring Size Effects: C ₅ versus C ₇	26
Figure 21. Ring Strain Effects.	26
Figure 22. Ring Size Effect on the Rearrangement.	28
Figure 23. Rearrangement Between Two Spiranones	29
Figure 24. Ring Size Effects on the Pinacol Rearrangement.	30
Figure 25. Possible Spiranone Products from the Pinacol Rearrangement.	33
Figure 26. McConnell and Robertson Equation and Idealized Geometric Features of a Lanthanide-Substrate Complex	37
Figure 27. Plot of Change in Shift vs. [Eu(fod) ₃]/[85]	39
Figure 28. Plot of R-Value vs. Eu-O Distance.	42
Figure 29. Transannular Dipolar Effect on First Order Solvolysis	43
Figure 30. Two Possible Compounds by the Rearrangement.	44
Figure 31. NMR Assignment for <u>90</u>	45

LIST OF FIGURES (continued)

	<u>Page</u>
Figure 32. Proposed Secondary Rearrangement of <u>92</u> to <u>90</u>	46
Figure 33. Borohydride Reduction Study by the Geneste Group.	47
Figure 34. Secondary Rearrangement of the Spiranone Product by Mundy and Srinivasa	48
Figure 35. Attempted Rearrangement of <u>97</u> to <u>100</u>	49
Figure 36. Attempted Rearrangement from <u>101</u> to <u>104</u>	50
Figure 37. Three Alkaloids from <u>Nicotiana</u>	75
Figure 38. The Murakoshi Synthesis of Phenylpyrroline	76
Figure 39. Proposed Intermediate of the Murakoshi Synthesis.	76
Figure 40. The Mundy and McKenzie Synthesis of Phenyl Pyrroline.	77
Figure 41. General Synthesis of Cyclic Imines	77
Figure 42. The Dual Thermal Pathway for N-Acylactam Pyrolysis	78
Figure 43. Retention of ^{14}C During Pyrolysis.	78
Figure 44. Proposed Mechanism for N-Acylactam Rearrangement.	79
Figure 45. Synthesis of 2-Substituted Pyrrolines and Piperidine	80
Figure 46. Synthesis of Dihydropinidine and Solenopsin A	81

LIST OF FIGURES (continued)

	<u>Page</u>
Figure 47. Leete Synthesis of Shihunine	84
Figure 48. The Proposed Synthesis of Shihunine.	85
Figure 49. Alternate Route for Synthesis of Shihunine	86
Figure 50. Attempted Synthesis of a Pomegranate Alkaloid by Lipkowitz.	89
Figure 51. Possible Natural Products from Pyrolysis of the Conjugated N-Acylactam	89
Figure 52. Attempted Pyrolysis of N-Cinnamoyl- 2-Pyrrolidinone.	90
Figure 53. Proposed Synthesis of Apoferrerosamine	91
Figure 54. Some Examples of Synthesis of 2-Substituted Oxazolines	93
Figure 55. Reactions of 2-Phenyl-2-Oxazoline.	95
Figure 56. New Methodology to Synthesize 2-Substituted Oxazolines	96
Figure 57. The Synthesis of N-Acylactams Containing Heteroatoms	97
Figure 58. Stability of an Intermediate Containing a Heteroatom.	98
Figure 59. Structure of Mycobactin T.	99
Figure 60. Proposed Synthesis of a Precursor for Mycobactin Acid T.100
Figure 61. Maurer Synthesis of (6-Methyltetra- hydropyran-2-yl)Acetic Acid.123

LIST OF FIGURES (continued)

	<u>Page</u>
Figure 62. Synthesis of Pyrenophorine from (6-Methyltetrahydropyran-2-yl)Acetic Acid124
Figure 63. Seebachs Synthesis of (6-Methyltetrahydropyran-2-yl)Acetic Acid.125
Figure 64. Proposed Synthesis of (6-Methyltetrahydropyran-2-yl)Acetic Acid.126
Figure 65. <u>Threo</u> and <u>Erythro</u> of 2-(1-Hydroxyethyl)-6-Methyl-2,4-Dihydropyran.127
Figure 66. <u>Exo</u> - and <u>Endo</u> -5,7-Dimethyl-6,8-Dioxabicyclo[3.2.1]Octane.128
Figure 67. The Selective Ring Opening by AlH_3129
Figure 68. Formation of the <u>Threo</u> and <u>Erythro</u> 1-(<u>cis</u> -6-Methyltetrahydropyran-2-yl)Ethanol130
Figure 69. Reductive Cleavage Reactions of 5,7-Dimethyl-6,8-Dioxabicyclo[3.2.1]Octane132
Figure 70. Attempted Elimination Reactions of 1-(<u>cis</u> -6-Methyltetrahydropyran-2-yl)Ethanol133
Figure 71. Synthesis of the <u>Threo</u> 1-(<u>cis</u> -6-Methyltetrahydropyran-2-yl)Ethanol134
Figure 72. Hydroboration Reaction of 2-Vinyl-6-Methyltetrahydropyran.135
Figure 73. Oxidation Reaction of 2-(<u>cis</u> -6-Methyltetrahydropyran-2-yl)Ethanol137
Figure 74. A Typical Apparatus for Vapor-Phase Pyrolysis.145

ABSTRACT

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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 Fittig¹ 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).

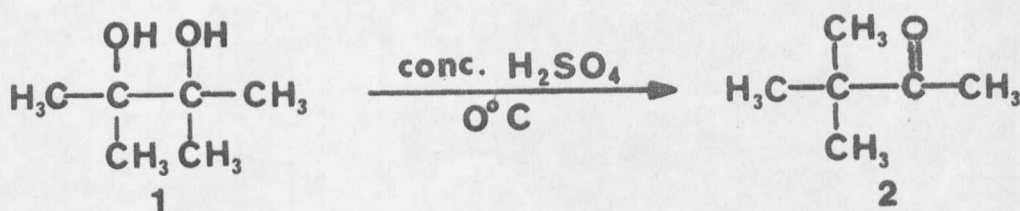


Figure 1. The Pinacol Rearrangement

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]/TiCl₄ 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 Corey⁵ and McMurry⁴ have agreed that a reduced state of titanium is intimately involved in the

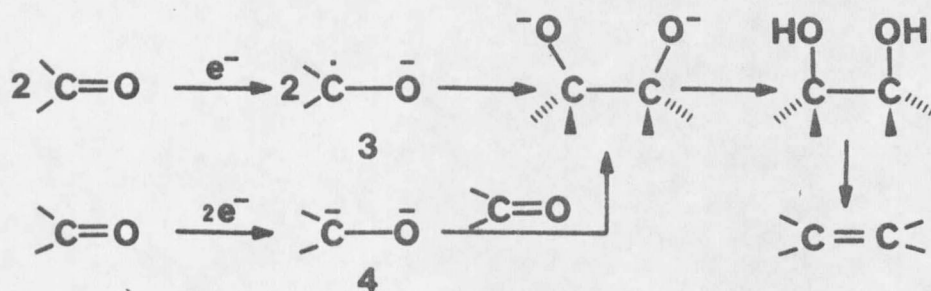


Figure 2. General Mechanisms for the Reductive Coupling

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. Ourisson¹¹ has demonstrated that different ratios of *meso* and *dl* products can be found under different reaction conditions, and Corey⁵ 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 procedure⁵

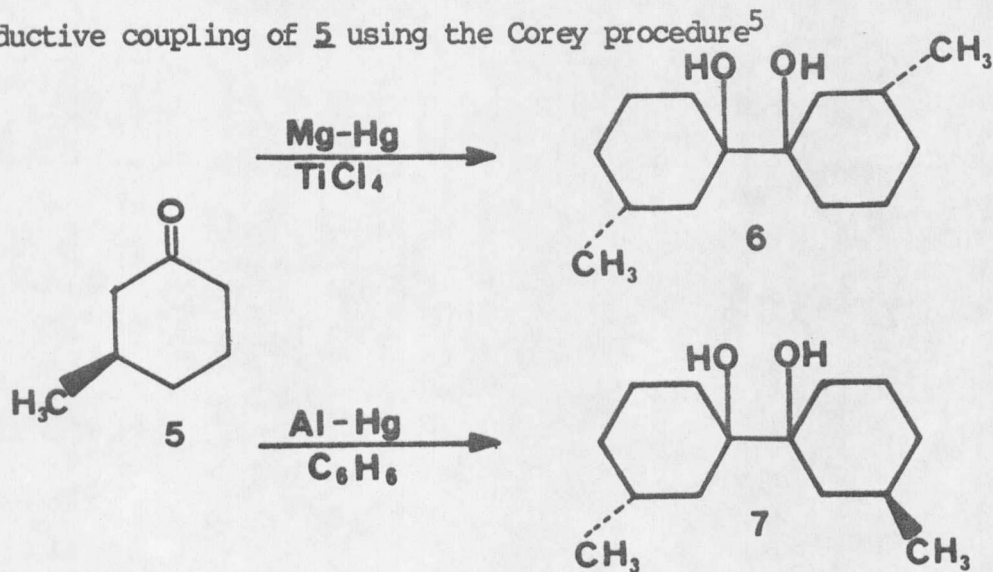


Figure 3. Different Pinacol Products by Different Methods

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 coupling³ 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

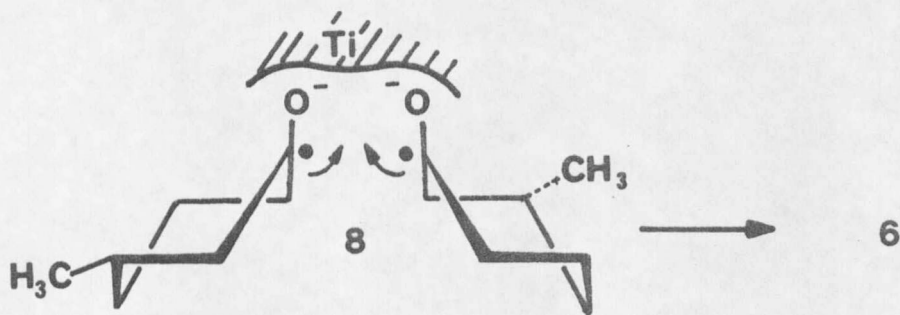


Figure 4. Anion-Radical Coupling of 3-Methylcyclohexanone

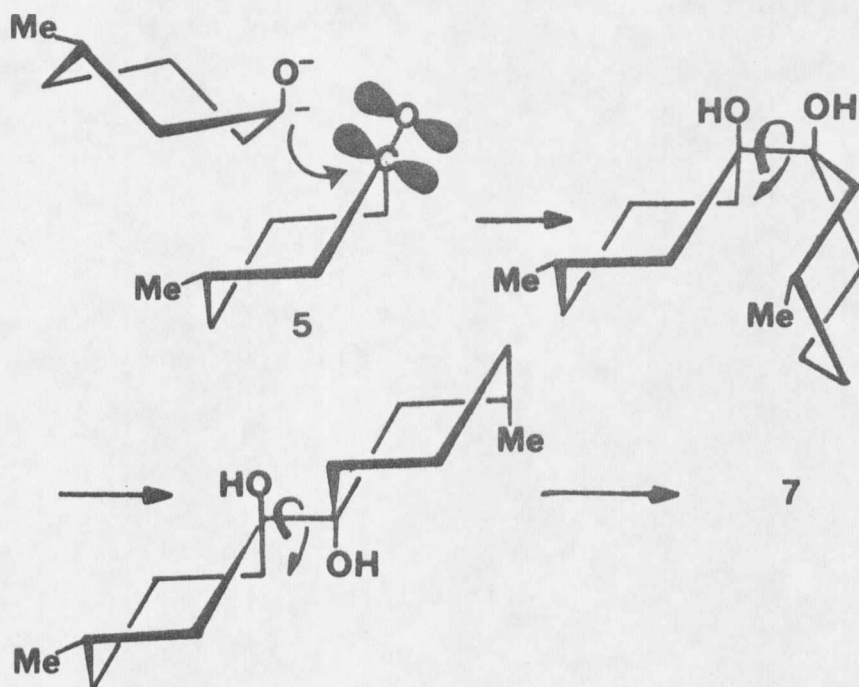


Figure 5. Pinacol Formation by Dianion Intermediate

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 Srinivasa¹⁰ 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

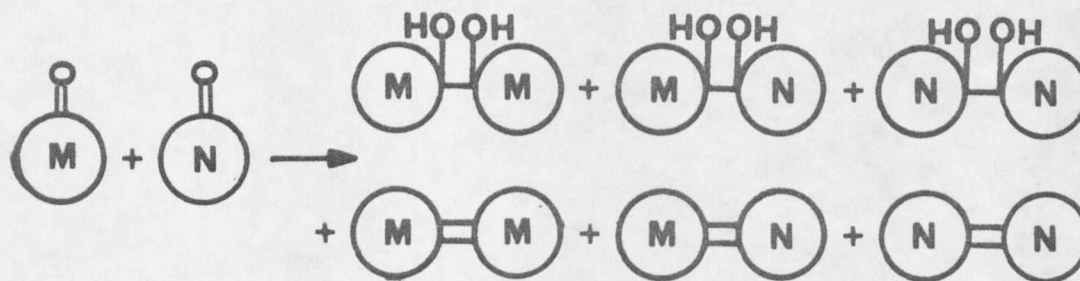


Figure 6. General Scheme of Mixed Pinacol Condensation

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			Pinacol ^a		
	AA	AB	BB	AA	AB	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

^aIn percent

^bA = Cyclohexanone

^cB = Methylcyclohexanone

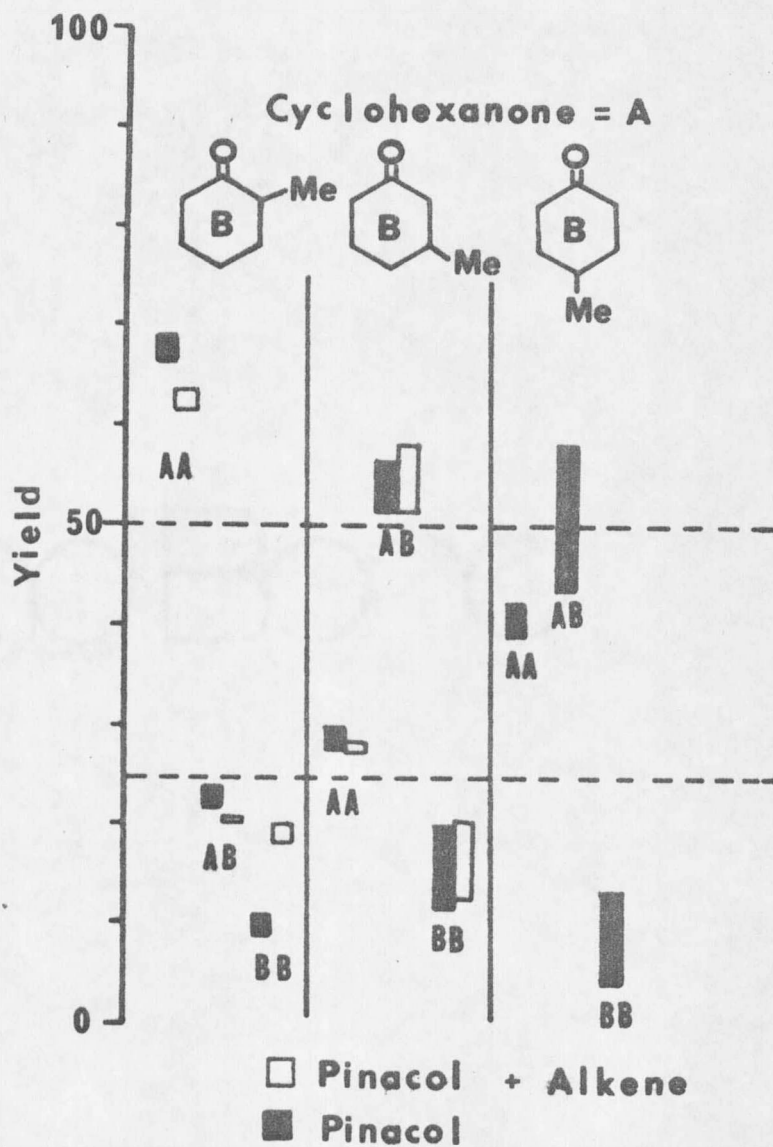


Figure 7. Competitive Coupling of the Methylcyclohexanones

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.

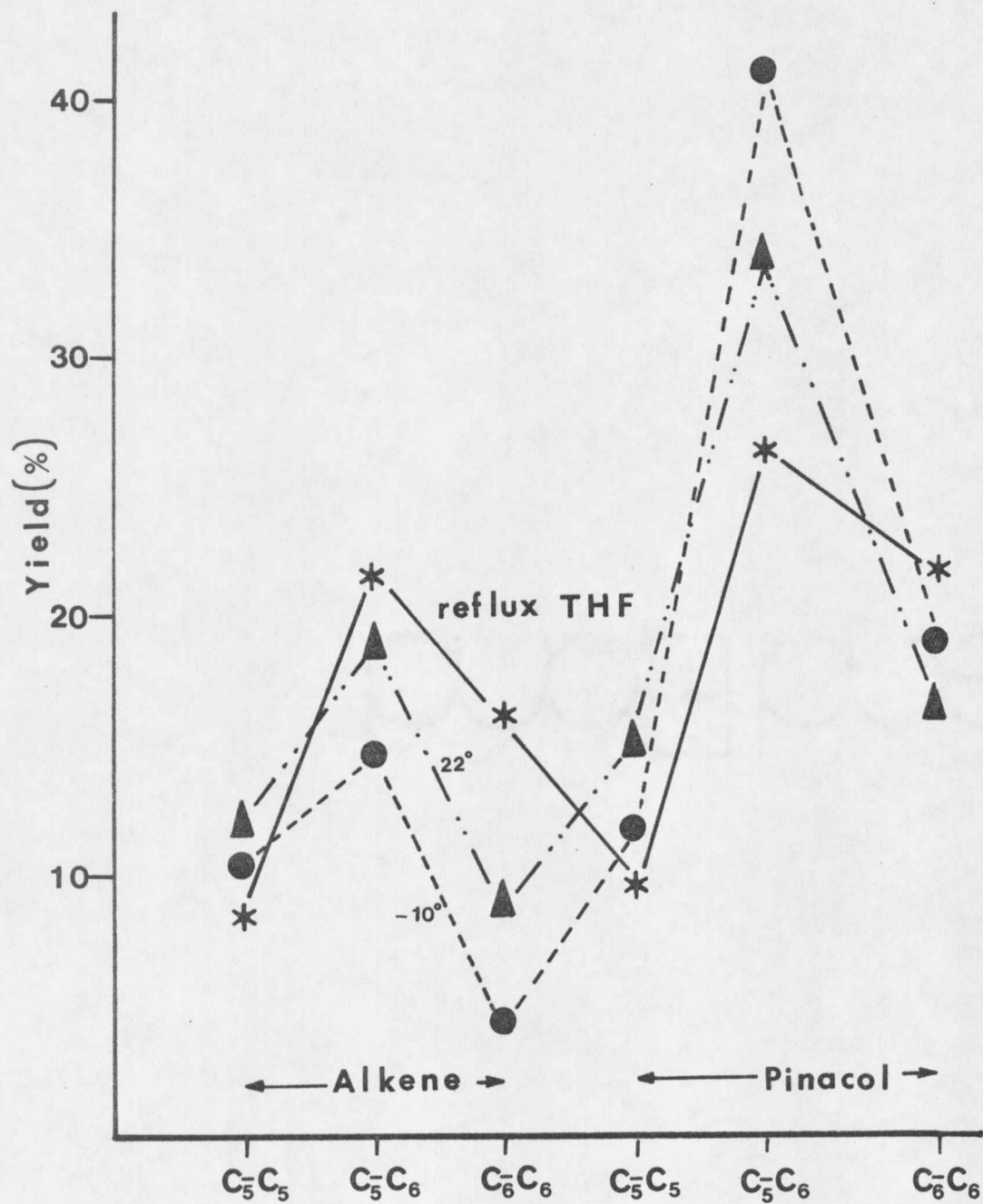


Figure 8. Temperature Effects on Coupling Reaction

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

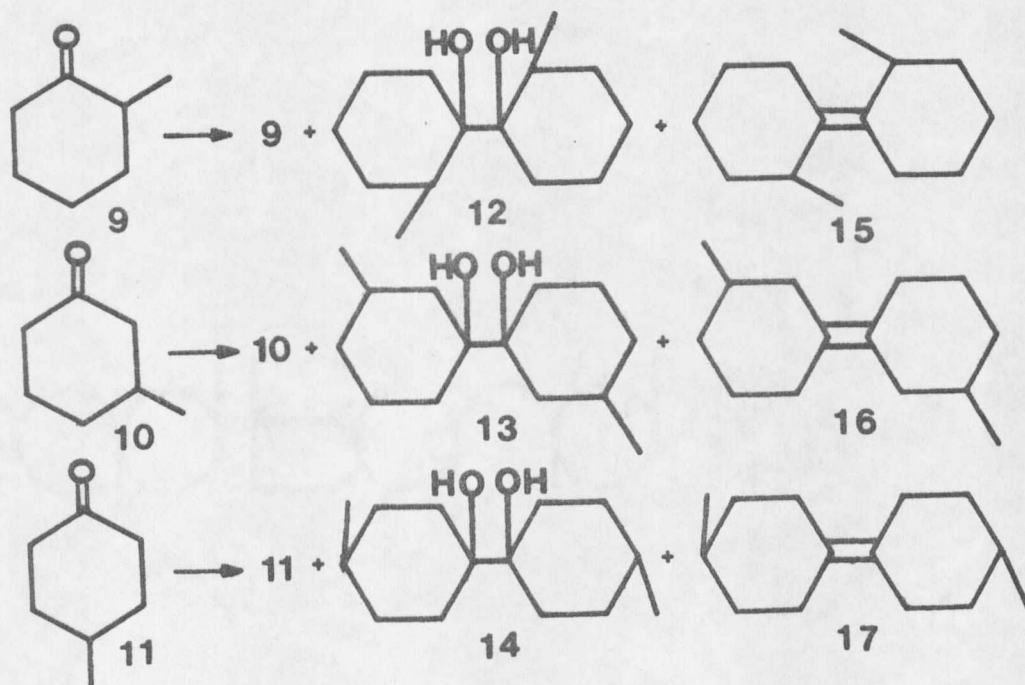


Figure 9. Products from the Reductive Coupling of Methylcyclohexanones

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)** ($[\alpha]_D = 4.3^\circ$) from R(+) 3-methylcyclohexanone, **(5)**, has a melting point at 78.5–79°C. To confirm the stereochemistry of **13**, we prepared the sulfite esters¹² 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

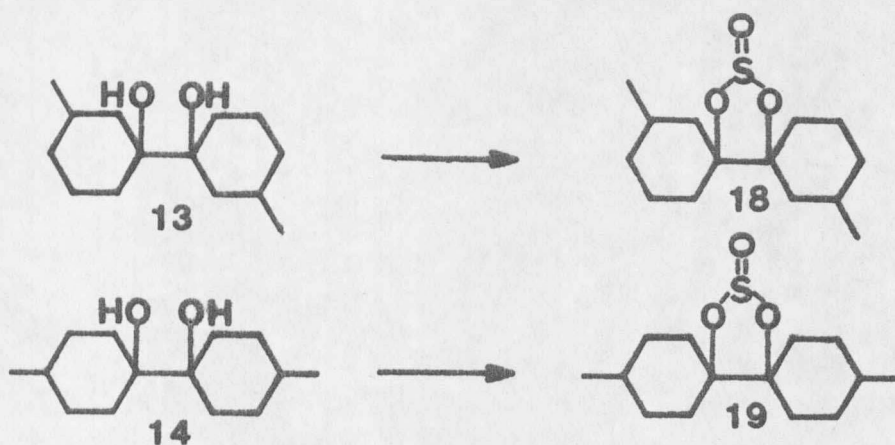


Figure 10. Sulfite Esters of Bicyclopinalcols

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 minimized¹⁶ 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

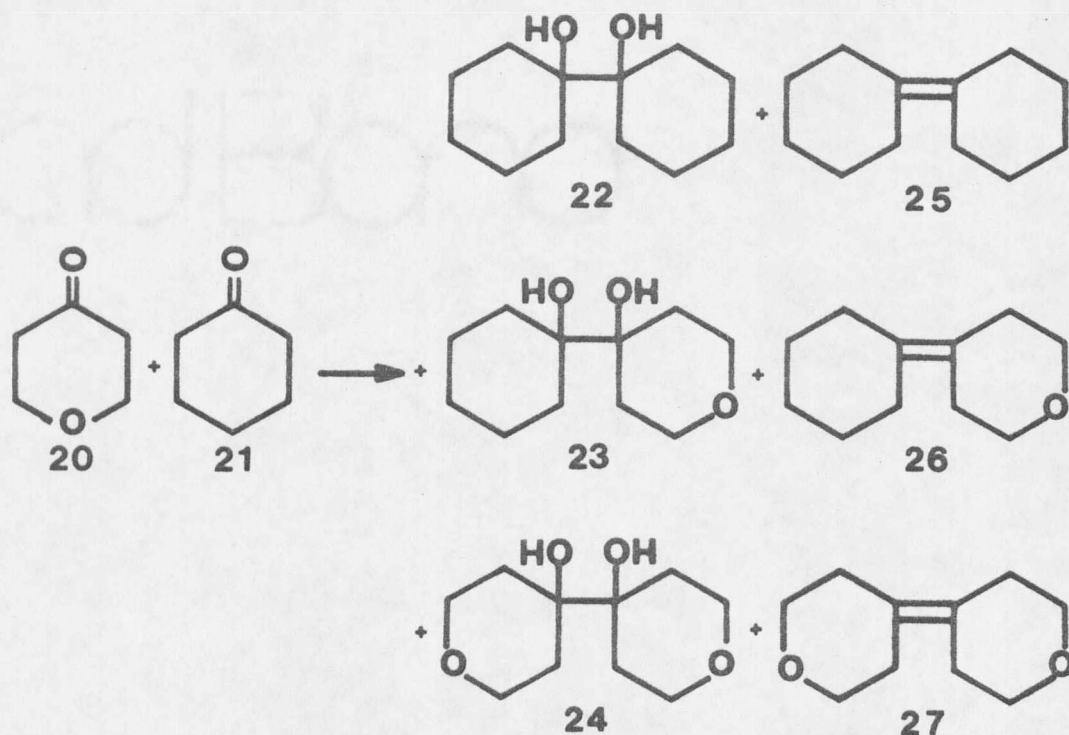


Figure 11. Preparation of 1'-Hydroxycyclohexyl-4-Hydroxytetrahydropyran

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

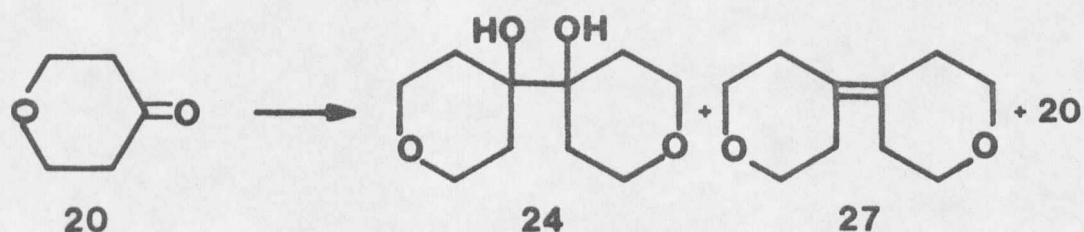


Figure 12. Self-Coupling of Tetrahydropyran-4-One

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

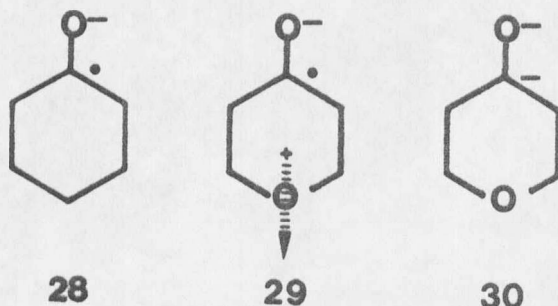


Figure 13. Comparison of Intermediates Reactivity

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

