I. SYNTHESIS OF 4-ALKYL-1,4-DIHYDROPYRIDINES AND RELATED COMPOUNDS.
II. SYNTHESIS AND THERMOLYSIS OF β-CYCLOPROPYL-α,β-UNSATURATED KETONES AND RELATED COMPOUNDS.

by

CHEUK KUN LAU
B.Sc., McMaster University, 1974

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Department of Chemistry

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2075 Wesbrook Place
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ABSTRACT

This thesis is composed of three separate parts. Part I describes the synthesis of a series of 1-carbomethoxy-4-alkyl(aryl)-1,4-dihydropyridines by the reaction of pyridine with lithium phenylthio(alkyl or aryl)cuprate reagents in the presence of methyl chloroformate. In general, the yields of the reactions were reasonably good and the reactions were very regioselective. The efficiency of lithium phenylthio(alkyl or aryl)-cuprate reagents in the preparation of 4-alkyl-1,4-dihydropyridine derivatives was compared with that of lithium dialkyl(aryl)cuprates. It was found that, in most cases, the former reagents offered no advantages over the latter reagents. The use of electrophiles other than methyl chloroformate was also investigated. Acetyl bromide gave reasonable yields of the corresponding 4-alkyl-1,4-dihydropyridine derivatives but when chlorotrimethylsilane and diethylphosphorochloridate were employed, the yields of the corresponding 4-alkyl-1,4-dihydropyridine derivatives were fairly poor. Finally, the 1-carbomethoxy-4-alkyl-1,4-dihydropyridines prepared as outlined above were transformed in good yields into the corresponding 4-alkylpyridines by treatment of the former with methyllithium, followed by oxidation of the resulting 1-lithio-1,4-dihydropyridine derivatives with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. The synthesis of 1-carbomethoxy-4-alkyl(aryl)-1,4-dihydropyridines and their subsequent conversion into the corresponding 4-alkylpyridines introduces a new and fairly efficient way of synthesizing these compounds.

Part II describes the synthesis and thermal rearrangement of a number of β-cyclopropyl-α,β-unsaturated ketones and in certain cases, their trimethyl-

silyl enol ether derivatives. The β-cyclopropyl-α,β-unsaturated ketones were prepared in good yields from the corresponding β-iodo enones by treating the latter with lithium phenylthio(cyclopropyl)-cuprate. The β-iodo enones were obtained in good yields by the reaction of the corresponding β-diketones and α-hydroxymethylenecycloalkanones with triphenylphosphine diiodide. When the cyclic β-cyclopropyl-α,β-unsaturated ketones were thermolyzed, they underwent the expected vinylcyclopropane-cyclopentene rearrangement, giving the corresponding annelated cyclopentenes in reasonable yields. In the case of α-cyclopropylmethylenecycloalkanones, pyrolysis of the corresponding trimethylsilyl enol ethers gave better yields of the corresponding spiroannelated cyclopentenes than did pyrolysis of the parent enones. This new spiro cyclopentene annelation reaction was applied to the preparation of the spiro ketone 198, a key intermediate for the synthesis of a number of spirovetivane sesquiterpenes. The key steps in the synthesis of the spiro ketone 198 involved the preparation and thermolysis of the trimethylsilyl enol ether 200. Copper catalysed conjugate addition of methyl magnesium iodide to 2-cyclohexen-1-one, followed by trapping of the resulting enolate anion with cyclopropanecarboxaldehyde gave the β-hydroxyketone 203 in ∿98% yield. Overall dehydration of 203, *via* base-promoted elimination of acetic acid from the corresponding acetate 211 gave a 78% yield of a mixture of the β-cyclopropyl enones 155 and 156, in a ratio of 13:1, respectively. Treatment of the latter mixture with lithium diisopropylamide, followed by trapping the resulting enolates with chlorotrimethylsilane gave the enol silyl ethers 200 in ∿95% yield. Pyrolysis of 200, followed by hydrolysis of the crude product, gave a 57% yield of a

mixture of the spiro enone 212 and 213, in the ratio of 2.5:1, respectively. The desired isomer 212 was isolated from the mixture and was subsequently transformed into the spiro ketone 198 via a straightforward, four-step sequence of reactions.

Part III describes the synthesis and thermal rearrangement of the tricyclic enones 39 and related compounds. Reaction of lithium phenylthio(syn-7-norcar-2-enyl)cuprate (38) with 3-iodo-2-cyclohexen-1-one and 3-iodo-2-cyclopenten-1-one gave the tricyclic enones 55 and 56, respectively. It was thus clear that the initially formed enones 39 underwent facile Cope rearrangement to give the tricyclic enones 55 or 56 during work-up and/or purification. Reaction of a 1:1 mixture of syn and anti lithium phenylthio(7-norcar-2-enyl)cuprates with 3-iodo-2-cyclohexen-1-one gave a 1:1 mixture of the tricyclic enones 55 and 57. Similarly, reaction of the same cuprate reagent mixture with 3-iodo-2-cyclopenten-1-one gave a 1:1 mixture of the enones 56 and 58. When o-dichlorobenzene solutions of the enones 57 and 58 were refluxed, these compounds readily rearranged to the tricyclic enones 55 and 56, respectively.

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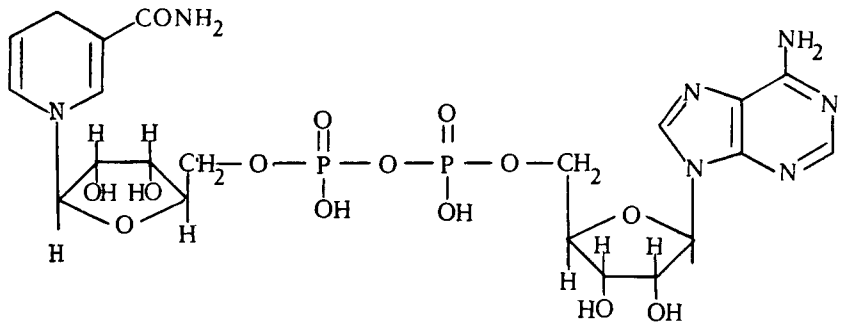
PART I

Synthesis of 4-Alkyl-1,4-dihydropyridines and Related Compounds

INTRODUCTION

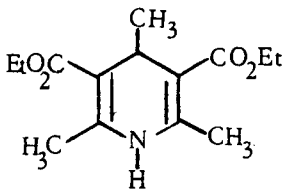
I. General

Dihydropyridines have been known since 1882 when Hantzsch published the synthesis of the first representatives of this class of compounds.[1] Dihydropyridines are of considerable interest because of their physiological properties and because of the role they play in biological systems. The 1,4-dihydronicotinamide moiety appears in the reduced forms of nicotinamide adenine dinucleotide (NADH) 1 and nicotinamide adenine dinucleotide phosphate (NADPH), which are very important hydrogen transfer reagents in biological systems.[2]



1

Dihydropyridines exhibit a wide variety of physiological activities. For example, several analogs of 3,5-diethoxycarbonyl-1,4-dihydro-2,4,6-trimethylpyridine 2 were found to have porphyria inducing activity.[3] Other physiological properties of dihydropyridines include antitumor activity,[4,5] coronary dilating properties,[6] hypertensive activity,[7,8] analgesic, spasmolytic and local anesthetic activity.[9] Some dihydropyridines have found use as herbicides and defoliants.[10]



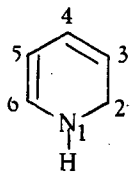
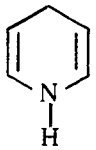
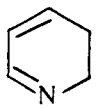
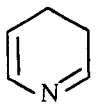
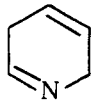
2

Dihydropyridines are important intermediates in certain reactions of pyridines, for example, nucleophilic substitutions,[11] reductions,[12] and acylations in the presence of pyridine.[13] Dihydropyridines which are readily convertible to pyridines also serve as important precursors of the latter.[14]

Studies directed towards understanding the nature of the hydrogen transfer mechanism of the coenzyme NADH (or NADPH) have stimulated the synthesis of a wide variety of model dihydropyridines, especially, 1,4-dihydropyridines. A large number of highly substituted dihydropyridines have been synthesized by the Hantzsch and related ring closure methods and by the reduction of the pyridine ring by complex hydrides.[15] Grignard reagents and organolithium reagents react with simple pyridines to give dihydropyridines in which the 1,2 isomer is always the major product.[15] Until recently, it has been quite difficult to synthesize simply substituted 1,4-dihydropyridines.

II. Structure

Theoretically, dihydropyridines can exist in five isomeric forms, (3-7), but almost all known dihydropyridines have either the 1,2- or the 1,4-dihydro structure (3 and 4, respectively).[15] This can be explained by the participation of the unshared pair of electrons on nitrogen in the π electron system of these two isomers. The isomers 3 and 4 have the highest number of sp^2-hybridized centers.

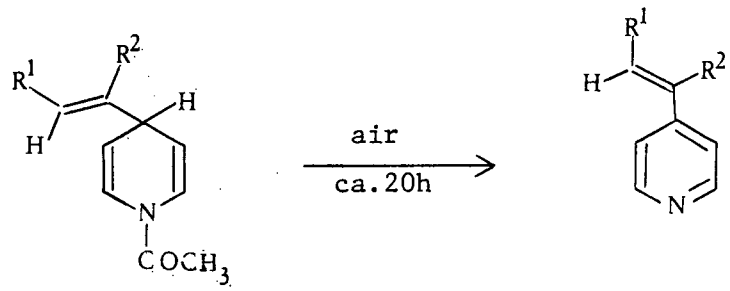
3 4 5 6 7

The structure of dihydropyridines has been the subject of much research and controversy. The incorrect structural assignment of the 1,4-dihydropyridine derivative 2 obtained from the reaction of ethyl acetoacetate, acetaldehyde, and ammonia as a 2,3-dihydropyridine derivative by Hantzsch[1] resulted in a lot of confusion in subsequent studies concerning the structure of dihydropyridines, particularly with regard to the distinction between 1,2 and 1,4 isomers. This was particularly serious in the case of the coenzyme NADH, 1, which was erroneously identified as a 1,2-dihydropyridine[16] until its structure was unambiguously established by deuterium labelling.[17,18] Now, modern spectroscopic methods can readily distinguish between the two types of isomers and unambiguous assignment of structure is relatively straightforward.

The relative stabilities of 1,2- and 1,4-dihydropyridines appears still to be somewhat open to question. HMO calculations on the π systems of the dihydropyridine ring systems indicate that the 1,2 isomer is more stable.[19] However, studies on hydrogen-transfer reactions[20] and equilibration[19,21] indicate that the 1,4-dihydropyridines are thermodynamically more stable than the corresponding 1,2 isomers.

Dihydropyridines are, in general, very reactive compounds. They are very susceptible to oxidation by air[22,23] and most of them decompose readily when left in contact with air.[24] For example, the dihydropyridine derivative 8 was air-oxidized to the substituted pyridine 9 in ca. 20h

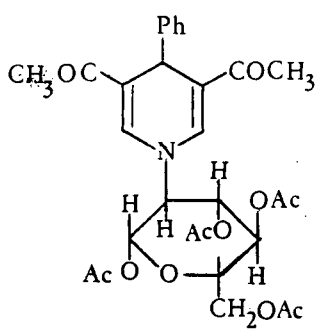
(eq.1).[23] When electron-withdrawing substituents capable of resonance



(1)

8 9

interaction (COR, CO_2R, CN, NO_2) are present on the 3 and 5 positions, the dihydropyridine system is considerably more stable than the unsubstituted case. On the other hand, electron-donating substituents at these positions destabilize these compounds.[25] Alkyl substitution on nitrogen has a mild stabilizing effect, while a glycosyl substituent on nitrogen appears to have a remarkable stabilizing effect. For example, dihydropyridine 10 can be recrystallized from acetic acid-water in the form of pale yellow needles.[26] Highly substituted dihydropyridines seem to be less reactive than those that are unsubstituted; this may be due, at least in part, to steric reasons.



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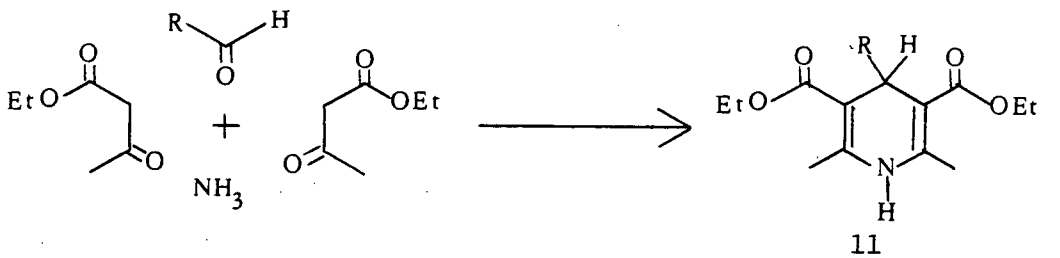
III. Synthesis of Dihydropyridines

There are two basic methodologies for preparing dihydropyridines; one involving the addition of various reagents to a pyridine ring and

the other involving direct formation from aliphatic reagents, as in the Hantzsch and related syntheses.

A. Hantzsch Synthesis and Related Condensations

The original Hantzsch synthesis of dihydropyridines involved the condensation of ethyl acetoacetate with an aldehyde in the presence of ammonia. The product of this reaction was the highly substituted 1,4-dihydropyridine 11, as shown in eq.2.[1] This method has been widely used for the preparation of the dihydropyridines 11, where R is an aliphatic,[27-29] aromatic[30-32] or heterocyclic residue.[30,31,33]



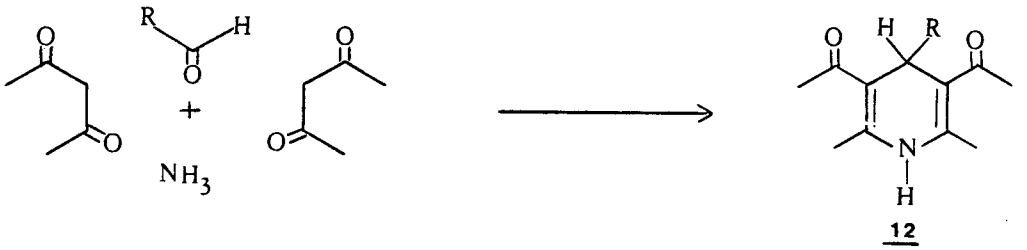
(2)

11

(a) R=CH_3; (b) R=$C_6H_4NO_2$; (c) R=H; (d) R=C_6H_5; (e) R=CH_2CN

The Hantzsch synthesis, as originally devised, has been modified in a great variety of ways. The aldehyde component has been replaced by ketones,[34,35] glyoxylic acid[36,37] and propiolic acid.[38] Ammonium acetate,[25] formamide,[39] hexamethylenetetramine,[40,41] primary amines[42,43] and hydrazine[44,45] have been used as substitutes for ammonia as the source of nitrogen. Finally, the active methylene component has been modified most extensively. The originally employed ethyl acetoacetate has been substituted by 1,3-diketones[46,47] and ω-cyanoacetophenone[25] to give 3,5-diacyl-1,4-dihydropyridines 12 and 2,6-diphenyl-3,5-dicyano-1,4-dihydropyridines 13, respectively, as shown in eq.3 and 4. Similarly, the phenylthioether 14 reacts with benzaldehyde and ammonium acetate to give

dihydropyridine 15 (eq.5).[25]



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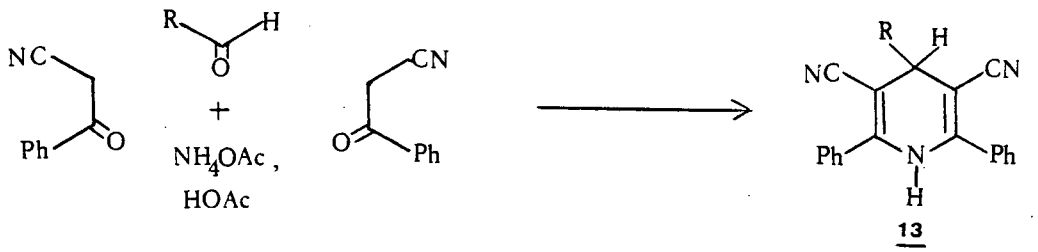

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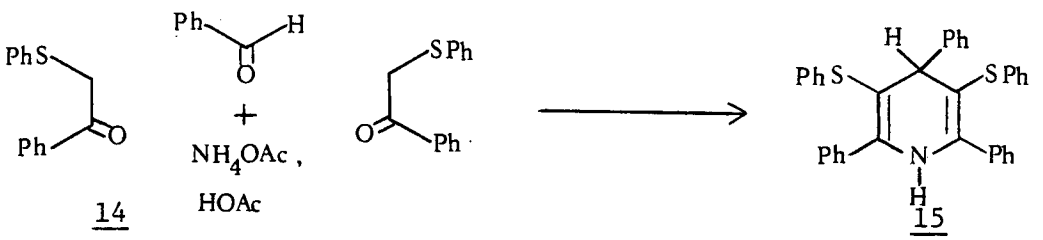
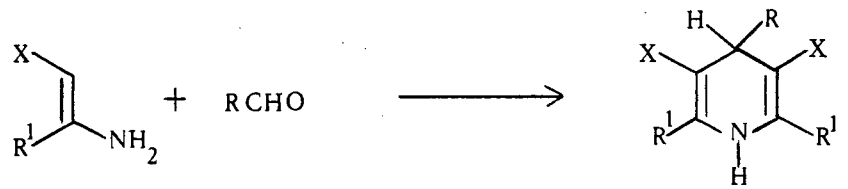


(5)

Enamines can also be used to replace ethyl acetoacetate. For example, enamines of general structure 16 react with aldehydes to give the dihydropyridines 17 (eq.6).[9,31,48] 1,5-Diketones preformed from the reaction of an aldehyde with an active methylene compound provide another variation on the Hantzsch synthesis. For example, diketone 18, derived from condensation of ethyl acetoacetate and formaldehyde, reacts with ammonia to give the dihydropyridine 11c.[49] In a similar fashion, the bis-enamine 19 formed from the reaction of 3-aminocrotononitrile with an aromatic aldehyde was cyclized to the dihydropyridine 20 (eq.8).[50] Aldehydes can also condense with active methylene compounds to give α,β-unsaturated ketones such as 21. These latter compounds can react with an

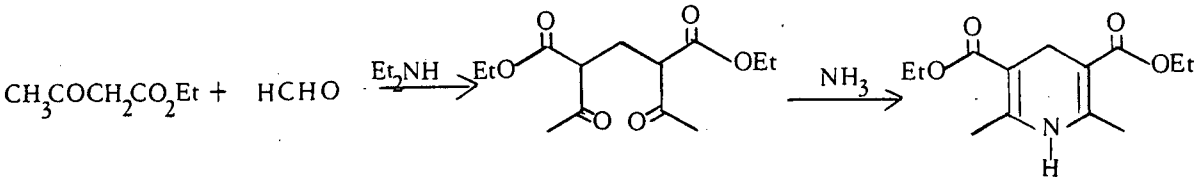
enamine or with a ketone and ammonia, to give the unsymmetrical 1,4-dihydropyridines 22 (eq.9).[51]



(6)

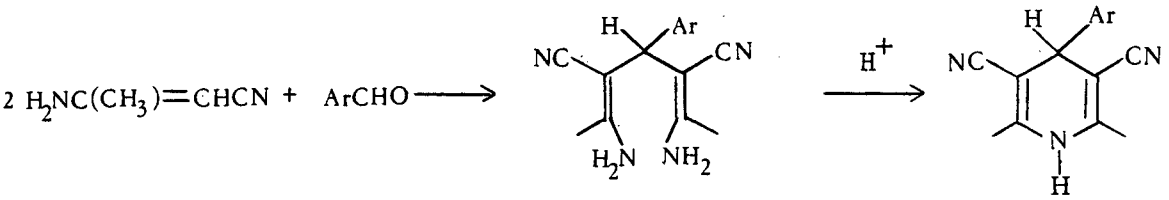
16 17

17(a) R=aryl, R^1=alkyl, X=CO_2Et; (b) R^1=CH_3, X=CN; (c) R^1=Ar, X=CN.



(7)

18 11c



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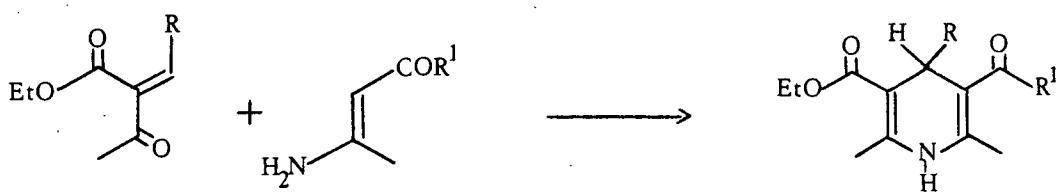
19 20



(9)

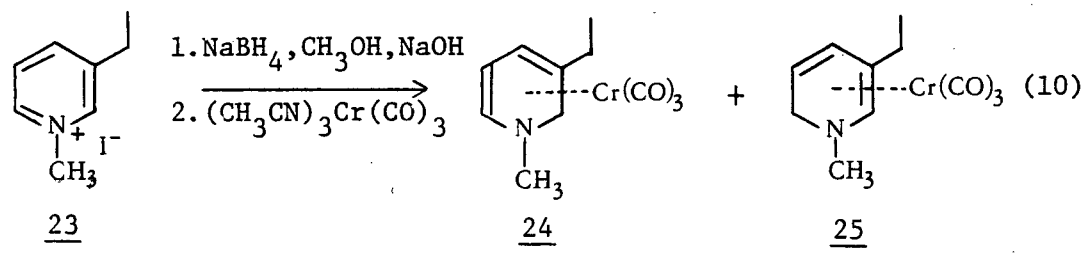
21 22

B. Preparation from Pyridine Derivatives

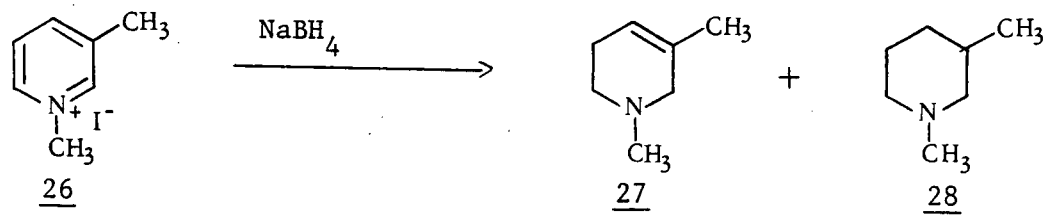
1. Reduction with Complex Hydrides

A number of dihydropyridine derivatives have been prepared by reduction of the corresponding pyridines or pyridinium salts with complex metal hydrides.

Sodium borohydride reduces pyridine and pyridinium salts, usually to an isomeric mixture of 1,2-, 1,4- and/or 1,6-dihydropyridines.[12,52] Depending on the conditions of the reactions and on the type of substituents present on the pyridine ring, the dihydropyridines formed by the initial attack of the hydride ion may undergo further reduction to tetrahydropyridines or may be isolated without further reduction. For example, the pyridinium salt 23 was reduced by sodium borohydride in methanolic sodium hydroxide to the corresponding mixture of 1,2- and 1,6-dihydropyridines, which were isolated as stable tricarbonyl chromium complexes 24 and 25, respectively (eq.10).[53] In a more recent study, it was reported that the pyridinium salt 23 could be reduced by sodium borohydride in a two phase system (ethyl ether, aqueous methanol containing sodium hydroxide) to the corresponding 1,2-dihydropyridine only, and in good yield.[54] In contrast, reduction of the pyridinium salt 26 by sodium borohydride gave a mixture of the corresponding tetrahydropyridine 27 and the piperidine 28 (eq.11).[55]

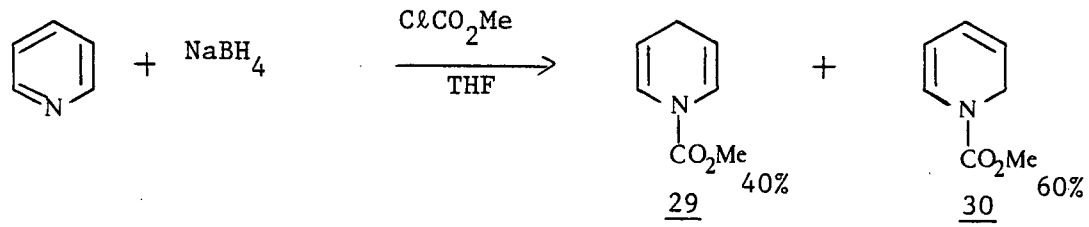


23 24 25



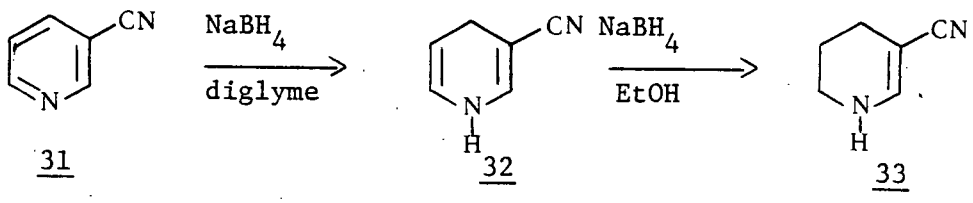
(11)

Pyridine itself can also be reduced by sodium borohydride in the presence of an electrophile to give N-substituted dihydropyridines.[56,57] Thus, reduction of pyridine by sodium borohydride in the presence of methyl chloroformate afforded a mixture of the 1.4- and 1,2-dihydropyridines 29 and 30 (eq.12).[56]



(12)

3-Cyanopyridine 31, when reduced by sodium borohydride in an aprotic solvent (for example, diglyme), produced the corresponding 1,4-dihydropyridine 32.[58] In protic solvents (for example, ethanol) further reduction to the tetrahydropyridine 33 occurred.[58] Similarly, the 3-cyanopyridinium salt 34a was reduced by sodium borohydride in methanol to a mixture of the corresponding di- and tetrahydropyridines 36a and 37a, respectively.[59,61] In alkaline sodium borohydride, the corresponding 1,2- and 1,6-dihydropyridines 35a and 36a, respectively, were formed instead.[59,61] In contrast, the pyridinium salt 34b was reduced by sodium borohydride in methanol to the corresponding dihydropyridines 35b and 36b without being further reduced to tetrahydropyridines.[61] Reduction of the nicotinamide derivatives 34c and 34d by sodium borohydride afforded mainly the corresponding 1,6-dihydropyridines 36c and 36d, respectively.[61,63-65]



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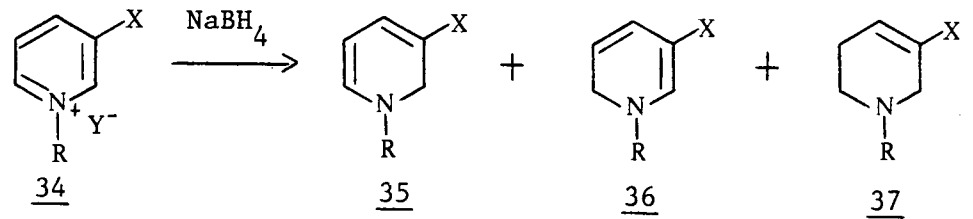
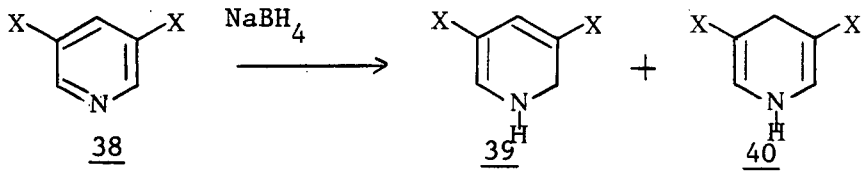


(14)

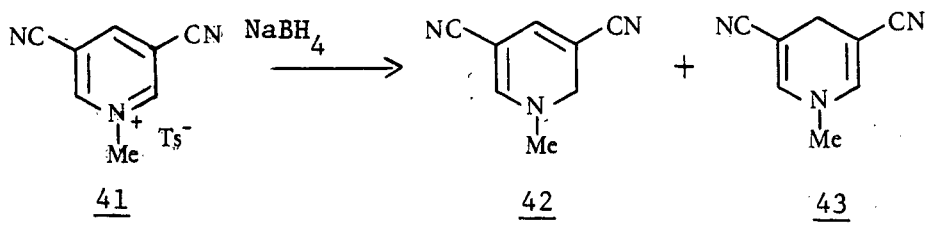
34 (a) R=CH_3, Y=I, X=CN; (b) R=2,6-$Cl_2C_6H_3CH_2$, Y=Br, X=CN; (c) R=CH_3, Y=$MeOSO_3$ X=$CONH_2$; (d) R=n-Pr, Y=I, X=$CONH_2$

Pyridines and pyridinium salts having electron-withdrawing substituents on both the 3 and 5 positions, can be reduced readily by sodium borohydride to the corresponding dihydropyridines. These latter compounds are less susceptible to further reduction than their monosubstituted or unsubstituted counterparts. Thus, the disubstituted pyridines 38a, 38b, 38c[52,66-68] and the pyridinium salt 41[69] were reduced by sodium borohydride to the corresponding mixtures of dihydropyridines as shown in eq. 15 and 16.



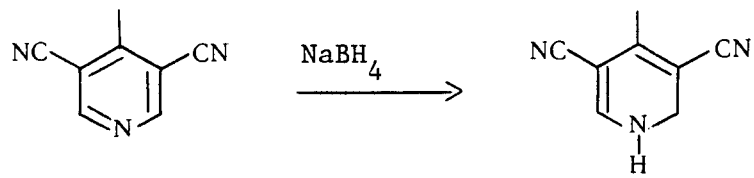
(15)

38(a) X=CN; (b) X=CO_2Me; (c) X=CO_2Et, (d) X=$COCH_3$

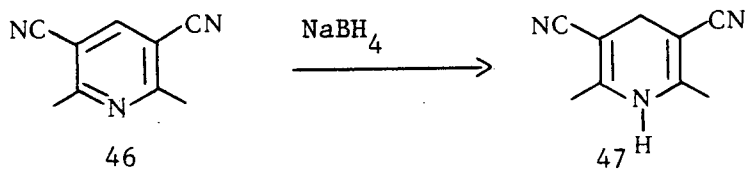


(16)

The ratio of 1,4 to 1,2 isomers formed in the reduction reactions was found to be highly solvent dependent, ranging from 87:13 in pyridine to 37:63 in acetonitrile for the diester 38c.[52] In contrast, sodium cyanoborohydride reduced 38b, 38c and 38d to the corresponding pure 1,4-dihydropyridines.[52] The regioselectivity of the reduction also depends on the position of alkyl substituents on the ring. Thus, sodium borohydride reduction of 3,5-dicyano-4-methylpyridine 44 and 3,5-dicyano-2, 6-dimethylpyridine 46 afforded only the dihydropyridines 45 and 47 respectively.[67,70]

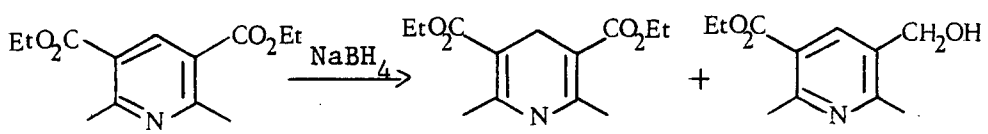


44 45 (17)

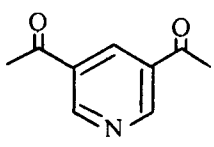


46 47 (18)

Occasionally, reduction of functional groups present on the substituents by sodium borohydride may become a serious problem. For example, the diester 48 was reduced mainly to the monoester 49[70] and the diketone 50 was reduced mainly to the diol 51. In each case only small amounts of the corresponding dihydropyridine was formed.



48 11c 12% 49 37% (19)



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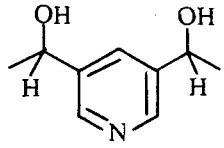
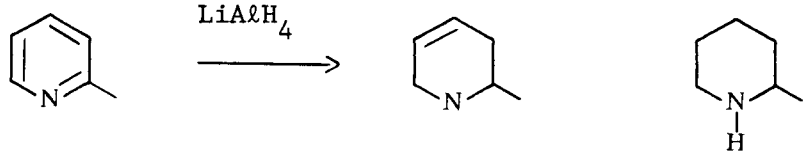


51

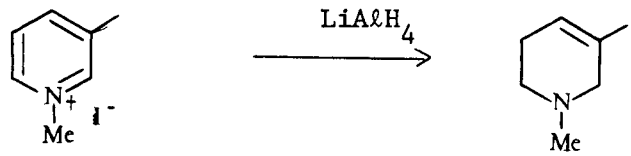
(19)

Lithium aluminum hydride, a very strong reducing agent, reduces pyridine or its alkyl derivatives less selectively than the milder reducing agent, sodium borohydride. For example, α-picoline 52 was reduced by lithium aluminum hydride to a mixture of the tetrahydropyridine 53 and the piperidine 54.[71] Similarly, 1,3-dimethylpyridinium iodide 26 was reduced exclusively to the tetrahydropyridine 27.[72]



52 53 54

(20)

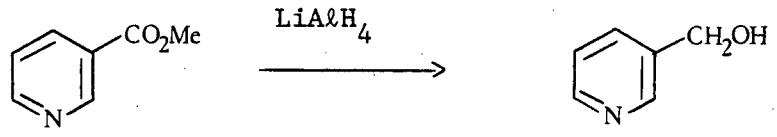


26 27

(21)

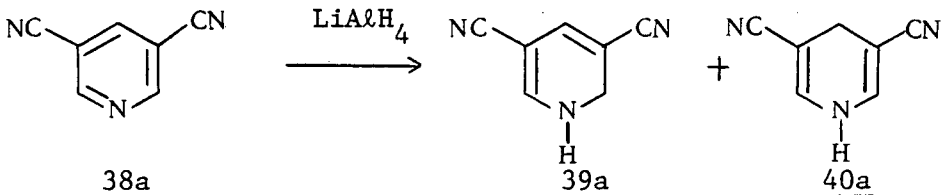
Very often, when lithium aluminum hydride is employed, functional groups present on the substituents are reduced more readily than the aromatic ring.[12] For example, methyl nicotinate underwent reaction with lithium aluminum hydride with exclusive reduction of the ester function (eq.22).[73] The only preparatively useful reaction is that of 3,5-dicyanopyridine in which the ring is reduced more readily than the nitrile

groups (eq.23).[67]



(22)

55 56



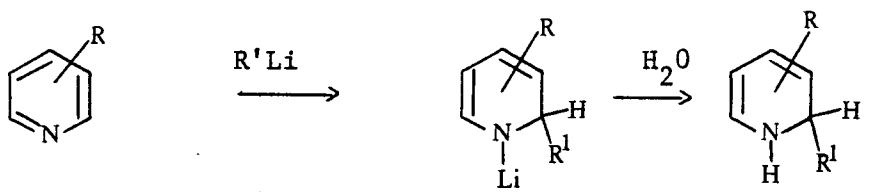
(23)

38a 39a 40a

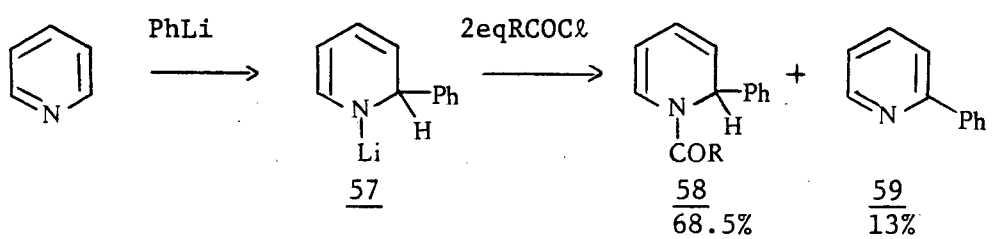
2. Addition of Organometallic Reagents

Certain organometallic compounds react with pyridine, pyridinium salts and pyridine oxides to form dihydropyridines.

Alkyllithium or aryllithium reagents react with pyridine and alkyl pyridines to give 2-substituted 1-lithio-1,2-dihydropyridines which can be hydrolysed to the corresponding 1,2-dihydropyridines (eq.24)[74-79] or react with an electrophile to give N-substituted 1,2-dihydropyridines (eq.25).[78]



(24)

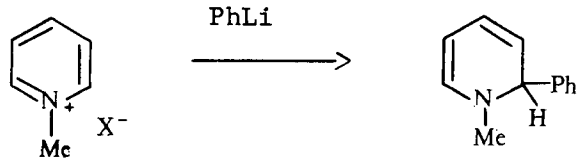


(25)

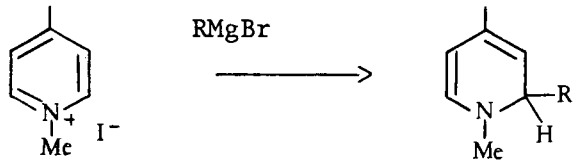
57 58 59

68.5% 13%

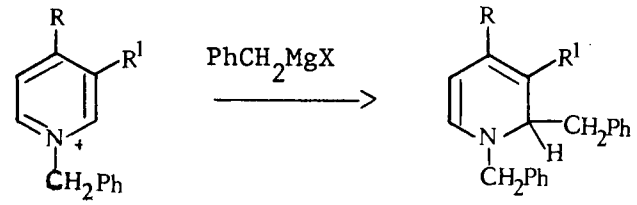
Pyridinium salts and their alkyl derivatives react with alkyl- or aryllithium reagents and with Grignard reagents to give mainly the corresponding 1,2-dihydropyridines For example, the pyridinium salt 60 reacts with phenyllithium to give the dihydropyridine 61[80] and pyridinium salts 62,[81] 64[82-84] and 66[85,86] react with Grignard reagents to give the 2-substituted 1,2-dihydropyridines 63, 65 and 67, respectively.



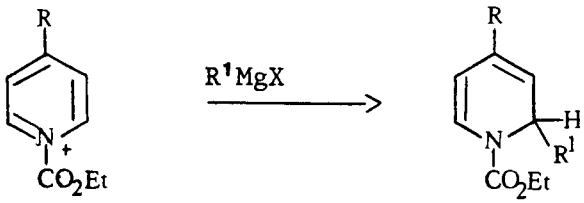
60 61 (26)



62 R=Et, Ph 63 (27)



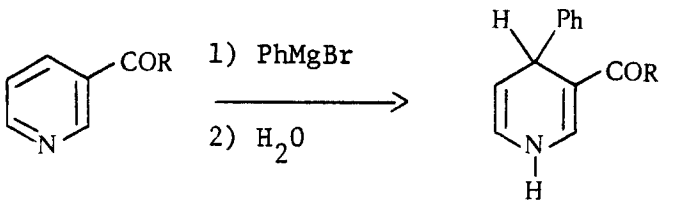
64 65 (28)



66 67 (29)

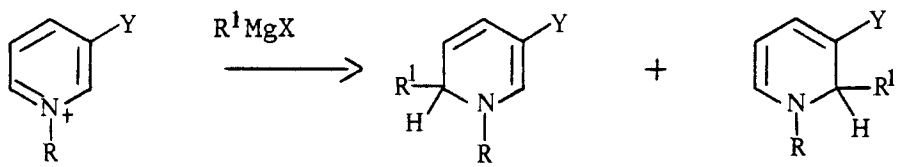
Reaction of pyridyl ketones 68 with Grignard reagents affords the

corresponding 1,4-dihydropyridines 69.[87,88] However, quaternary salts of nicotinic esters or nitriles 70 react with Grignard reagents to give mainly the corresponding 1,6-dihydropyridines 71, accompanied by minor amounts of the 1,2-dihydro isomers 72.[89,90]



(30)

68 69

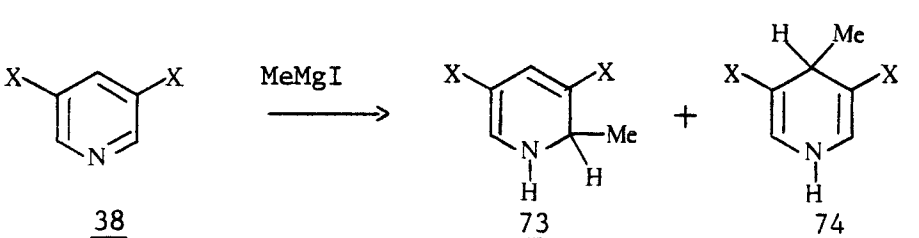


(31)

70 71 72

70 (a) $Y=COOR^2$; (b) Y=CN

Normally, Grignard reagents react with pyridine molecules containing electron-withdrawing groups at the 3 and 5 positions to give a mixture of 1,2- and 1,4-dihydropyridines. For example the disubstituted pyridines 38a, 38b and 38c react with methyl magnesium iodide to afford a mixture of the corresponding dihydropyridines 73 and 74, respectively (eq.32)[27,37,68,91-93]

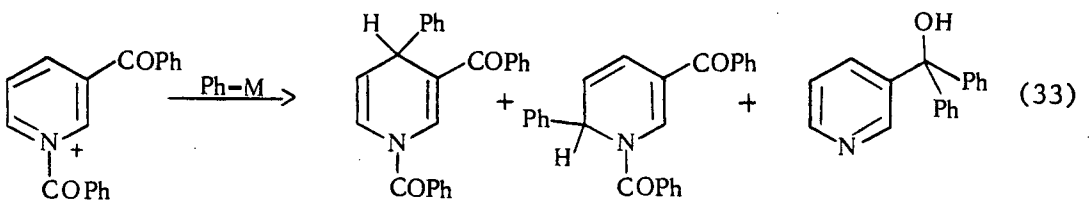


(32)

38 73 74

38(a) X=CN; (b) $X=CO_2Me$; (c) $X=CO_2Et$; (d) $X=COCH_3$

In some cases, the Grignard reagent attacks the substituents rather than the ring moiety. In the case of 38d, for example, the major product of the reaction is the diol formed by attack of the Grignard reagent on the carbonyl group. Recently, it was found that organocadmium reagents, formed from the reaction of cadmium chloride with Grignard reagents, give good yields of ring addition without concommitant addition to the carbonyl substituents on the pyridine ring.[86] For example, the pyridinium salt 75 reacts with phenyl magnesium bromide to give the corresponding dihydropyridines 76 and 77 together with a fair amount of the diphenyl-3-pyridylcarbinol 78. With the phenyl cadmium reagent, none of the pyridylcarbinol was isolated (eq.33).[86]



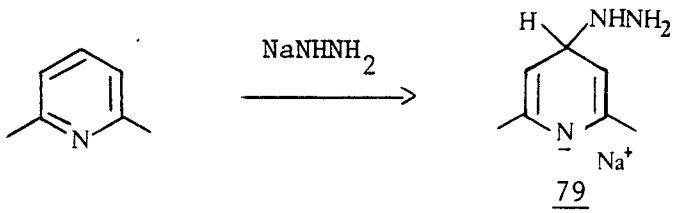
(33)

75		76	77	78
	M = MgBr	13%	49%	15%
	M = Cd	19%	61%	0%

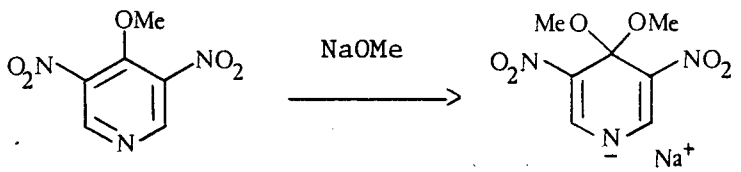
3. Addition of Other Nucleophiles

Pyridine and pyridinium salts also react with a wide variety of other nucleophiles to give dihydropyridine derivatives. For example, sodium hydrazide reacts with 2,6-lutidine[94] to give the adduct 79 and sodium methoxide reacts with 4-methoxy-3,5-dinitropyridine to give the compound 80.[95] Similarly, pyridinium salts react with a wide range of nucleophiles such as carbanions derived from ketones, diethyl malonate,

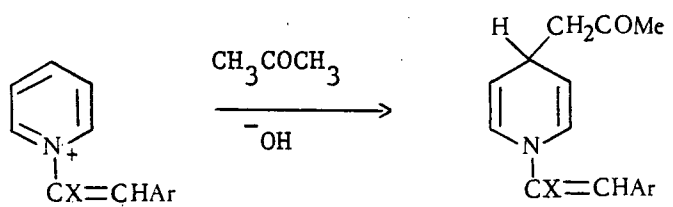
malononitrile, cyanoacetic esters and nitromethane to give 1,4-dihydropyridine derivatives.[96-99] For example, the pyridinium salt 81 reacts with acetone in the presence of strong base to give the 1,4-dihydropyridine 82 (eq.36) and pyridinium salt 83 reacts with the enolate anion derived from diethyl malonate to give the dihydropyridine 84, which was then cyclized to the dihydropyridine 85 (eq.37).[99]



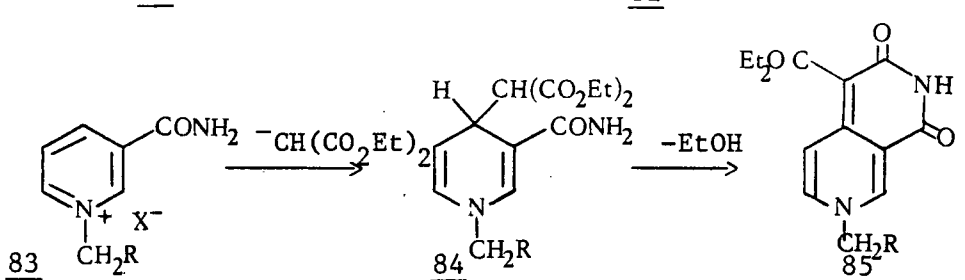
79 (34)



80 (35)



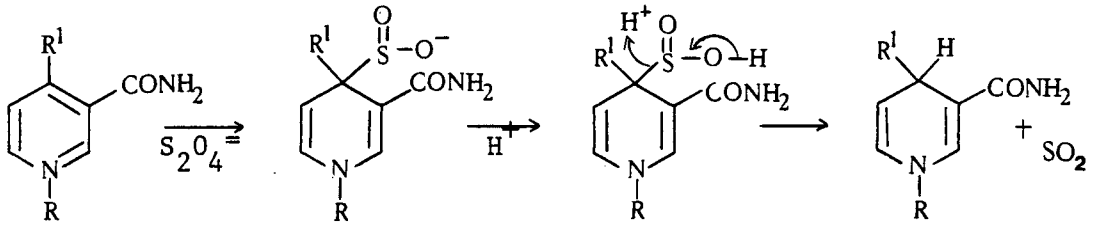
81 82 (36)



83 84 85 (37)

Dithionite reduction of pyridinium salts to dihydropyridines also proceeds by nucleophilic attack to form the intermediate sodium sulfinate derivative (for example 87) which then decomposes in acid to the corresponding dihydropyridine (eq.38).[100,101] A number of 3-substituted and

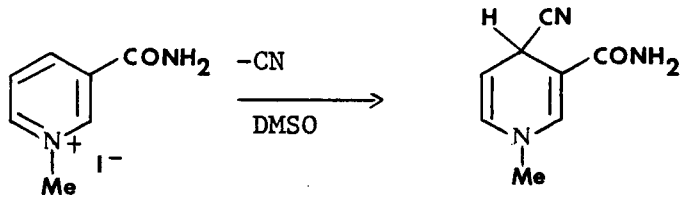
3,5-disubstituted dihydropyridines have been prepared this way.[24,89,102-105]



(38)

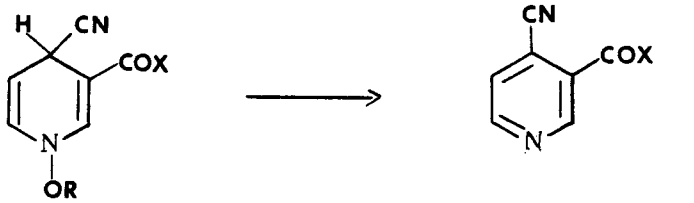
86 87 88 89

Cyanide ion, which has a lower nucleophilicity than the reagents discussed above, reacts only with the more electron-deficient pyridinium salts, preferably those that have electron-withdrawing substituents on the 3 and 5 positions, to give the corresponding 1,4-dihydropyridines.[21,75,106-109] For example, pyridinium salt 90 reacts with cyanide ion in dimethyl sulfoxide to give the adduct 91, which was isolated.[75] However, the formation of the 1,4-dihydro nitrile adduct is usually reversible[110] and the adducts are usually very unstable. For example, the cyanide adducts 92, which have been detected spectroscopically, were not isolated but were readily transformed to cyanopyridines 93 (eq.40).[111]



(39)

90 91

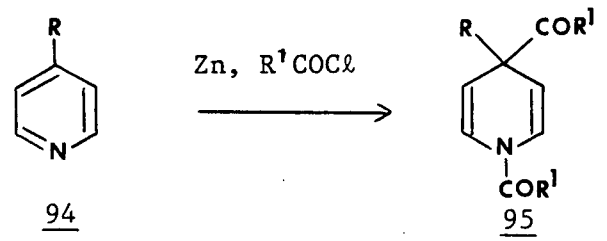


(40)

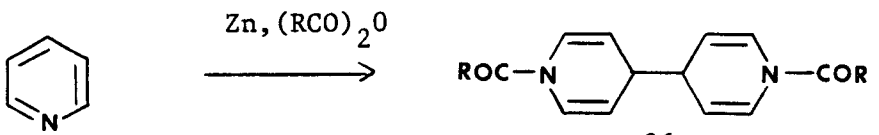
92 93

4. Other Methods

Dihydropyridines can also be prepared by reduction of pyridines or pyridinium salts with metals. Thus, reduction of 4-alkylpyridines 94 by zinc in either acetic anhydride or an acid chloride gave the corresponding 1,4-dihydropyridines 95.[112] With unsubstituted pyridine, the dimer 96 was formed instead.[113-115]

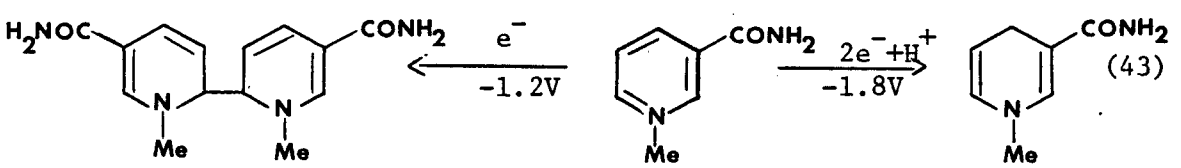


94 95 (41)



96 (42)

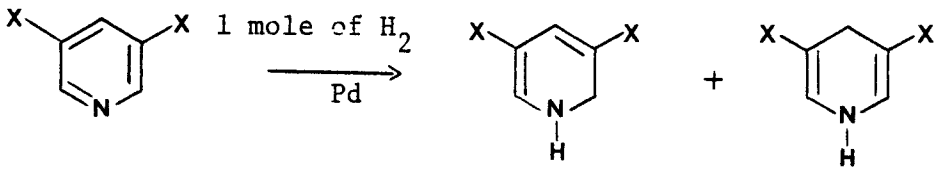
Electrolytic reduction of the pyridinium salt 90 at controlled potentials allowed the isolation of either the dihydropyridine 97 or the dimer 98.[116,117]



98 90 97 (43)

Catalytic hydrogenation can also be used to prepare dihydropyridines. For example, hydrogenation of the disubstituted pyridines 38a, 38b, 38c

and 38d yielded in each case a mixture of the corresponding 1,2- and 1,4-dihydropyridines, with the 1,2 isomer predominating.[118,119]

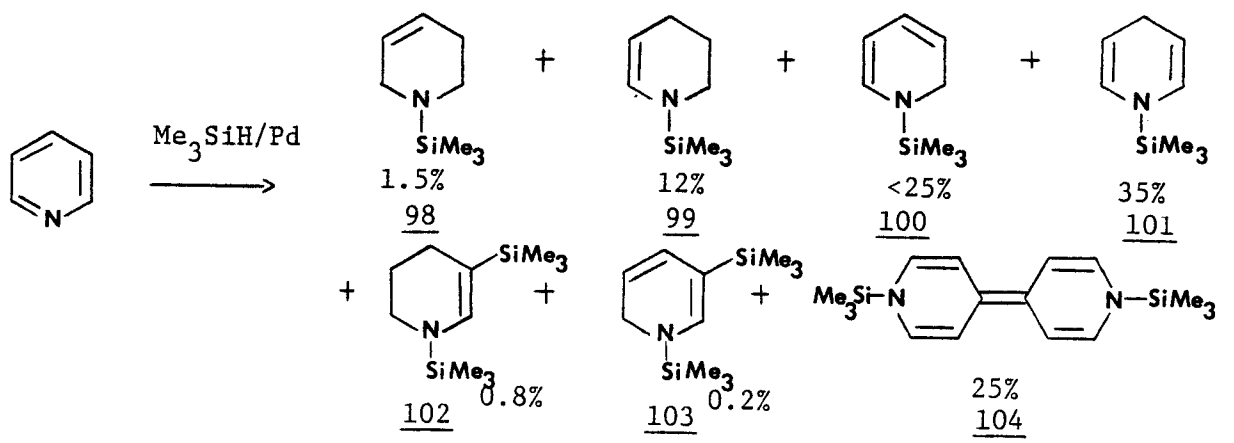


(44)

38 39 40

X = CN, CO_2Me, CO_2Et, $COCH_3$

Catalytic silylation of pyridine by trimethylsilane gave a complex mixture from which the dihydropyridines 100 and 101 were isolated.[22,120] Methanolysis of 101 liberated the parent, 1,4-dihydropyridines 105 (eq.46).



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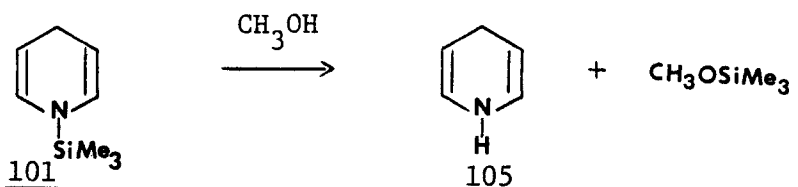
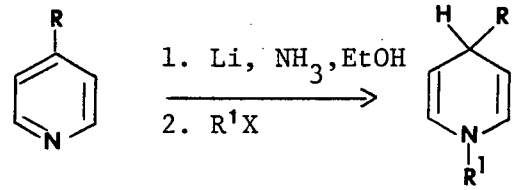


(46)

Alkylpyridines have been reduced by lithium in ammonia.[121] In the presence of an electrophile (for example, an alkyl halide), the N-substituted 1,4-dihydropyridine 107 was isolated (eq.47).

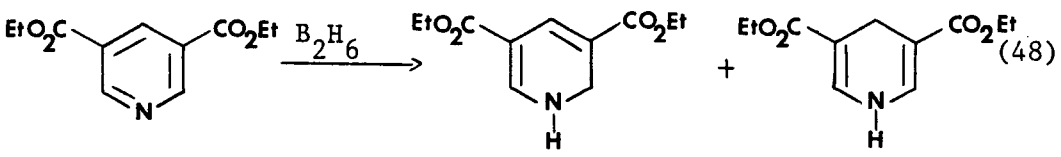


(47)

106 107

R = H, CH_3 R^1 = CH_3, Et, n-Pr

Diborane reduces the diester 38c to the corresponding mixture of 1,4-and 1,2-dihydropyridines (eq.48).[52] The reduction is solvent dependent. In pyridine, the 1,4 isomer is the major product while in tetrahydrofuran, the 1,2 isomer predominates.

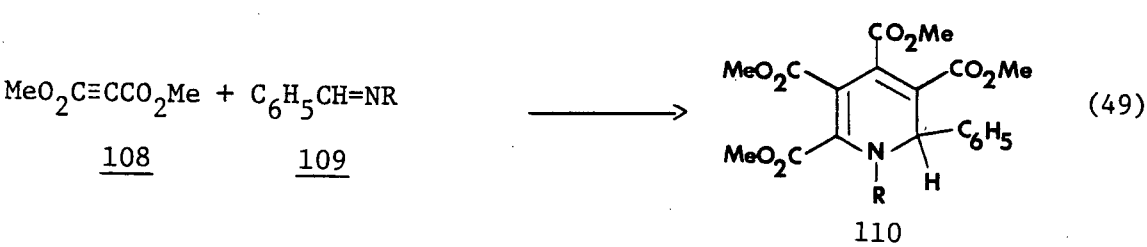


(48)

38c 39c 40e

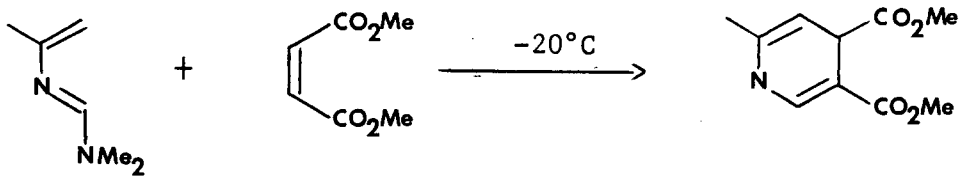
	39c	40e
Solvent = pyridine	9%	91%
= THF	79%	21%

Cycloaddition reactions have also been applied to the preparation of dihydropyridines. Thus, dimethyl acetylenedicarboxylate 108 reacts with the Schiff base 109 to give the 1,2-dihydropyridine 110 (eq.49).[122] Similarly, 1-dimethylamino-3-methyl-2-azabutadiene 111 reacts with the diester 112 to give the 1,4-dihydropyridine 113.[123]



(49)

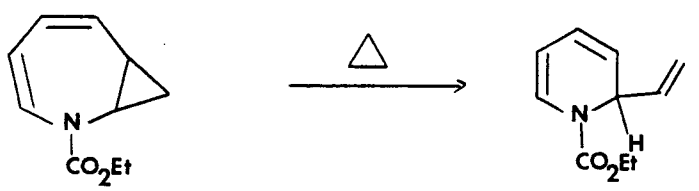
108 109 110



(50)

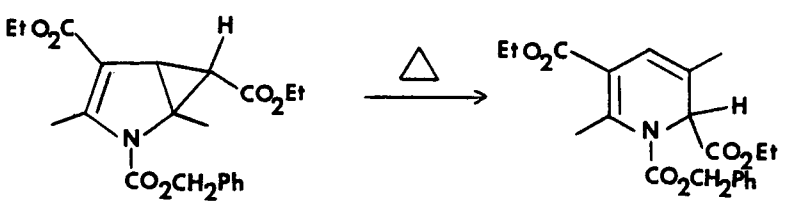
111 112 113

Dihydropyridines have also been prepared from other heterocyclic compounds. For example, pyrolysis of the homoazepine 114 afforded 1-ethoxycarbonyl-2-vinyl-1,2-dihydropyridine 115 (eq.51).[124] Pyrolysis of diethyl 2-azo-2-benzyloxycarbonyl-1,3-dimethylbicyclo [3.1.0]-hex-3-ene-4,6-dicarboxylate 116 gave the 1,2-dihydropyridine 117.[125] Hydrogen halides react with the 4H-azepine 118 to give the dihydropyridine 119 (eq.53).[126] Oxidation of the tricyclic compound 120, followed by spontaneous nitrogen extrusion from the intermediate 121, afforded the N-substituted 1,4-dihydropyridine 122 (eq.54).[127]



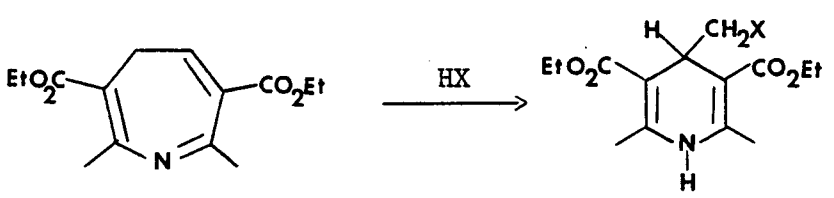
(51)

114 115



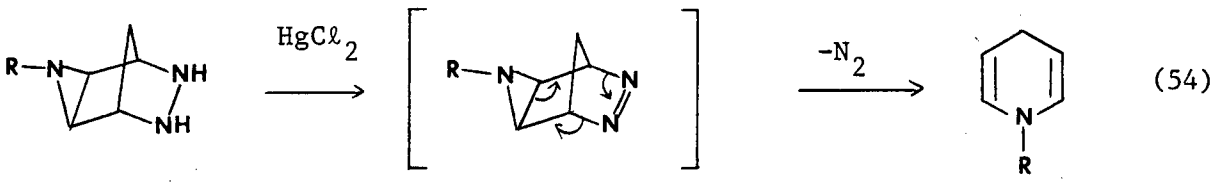
(52)

116 117



(53)

118 119



(54)

120 121 122

R = $C_6H_5SO_2$; C_6H_5 ; Me ; $C_6H_5CH_2CH_2$

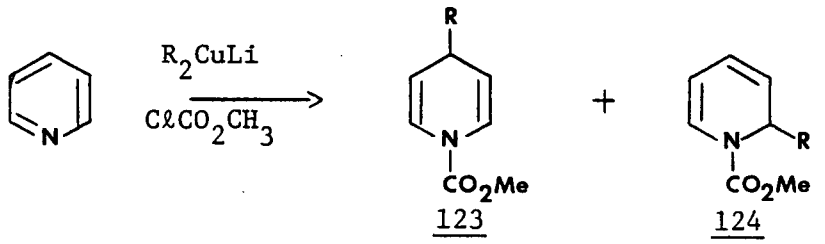
C. Regioselective Synthesis of Simply Substituted 1,4-Dihydropyridines. Objectives of the Work Described in this Thesis.

Of the variety of methods which can be employed in the synthesis of dihydropyridines, the Hantzsch type synthesis has been the most productive. Indeed, hundreds of substituted dihydropyridines have been prepared via this method. However, relatively few simple dihydropyridines have been prepared, since the Hantzsch synthesis works best for the preparation of dihydropyridines that have electron-withdrawing substituents on both the 3 and 5 positions. Furthermore, reduction of pyridinium salts by sodium borohydride is successful only if strongly electron-withdrawing groups are present on the pyridine ring. Almost no success has been achieved with the reduction of the free base. The major difficulties lie in the ease with which the partially reduced pyridines are further reduced to tetrahydropyridines and piperidines, and the readiness with which the dihydropyridines isomerize, oxidize and polymerize. Addition of organometallic reagents to pyridines gives mainly 1,2-dihydropyridines which are not very useful as model compounds for probing the mode of action of enzymes that bear a 1,4-dihydropyridine structure. Addition of other nucleophiles to pyridine also leads to highly substituted dihydropyridines.

In view of these facts, it appeared that there was still a need for better methods of making simply substituted 1,4-dihydropyridines. Catalytic

silylation of pyridine or alkyl pyridines does give simple 1,4-dihydropyridines, but a complex mixture of side products always accompanies the desired product.

In 1974, our research group had developed a new, regioselective method for synthesizing 4-substituted 1,4-dihydropyridines by reacting pyridine with lithium dialkylcuprates in the presence of chloroformate.[128] Thus, addition of methyl chloroformate to a solution of pyridine and the dialkyl (or aryl) cuprate reagent in ether, afforded in good yield a mixture of the corresponding 1,4- and 1,2-dihydropyridines, in which the 1,4 isomer predominated ($\geq$ 89% of the product)(eq.55). The present section of this thesis is concerned with results obtained from a continuation



(55)

R= (a) CH_3; (b) CH_3CH_2; (c) n-Bu; (d) s-Bu; (e) i-Pr; (f) C_6H_5; (g) vinyl

of that work.

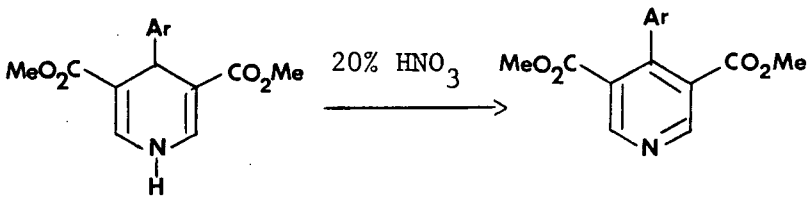
In the earlier work,[128] it was found that lithium dialkylcuprate reagents are quite efficient in transferring a primary alkyl group to the 4-position of the pyridine ring. However, the reaction was not very effective in the case of cuprate reagents containing secondary and tertiary alkyl groups. In work described in this thesis, mixed cuprates [lithium phenylthio(alkyl or aryl)cuprates] were investigated and compared with lithium dialkylcuprates in the aforementioned type of reaction.

Electrophiles other than chloroformate were also investigated. Finally, the 4-substituted 1,4-dihydropyridines synthesized were converted to the corresponding 4-substituted pyridines. Thus, this work provided a new synthesis of simple 4-alkyl and 4-aryl pyridines.

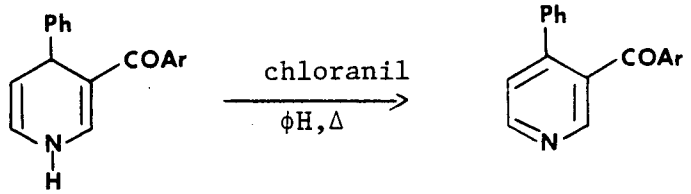
IV. Oxidation of Dihydropyridines

According to one author, "the most important reaction of dihydropyridines is their oxidation to the corresponding pyridines."[14] This is understandable in view of the important role of NADH in hydrogen transfer processes in biological systems and the role dihydropyridines play as intermediates in the reactions of pyridines.

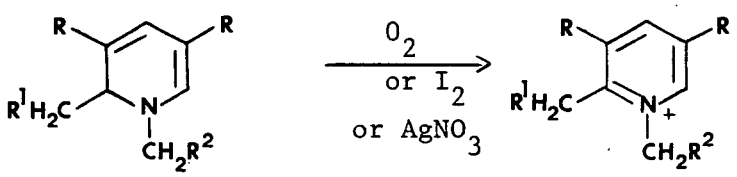
Dihydropyridines can be oxidized by a wide variety of reagents. The oldest and still most commonly used reagents are nitrous or dilute nitric acids,[1,44,48] and chromic acid.[129,130] For example, the dihydropyridine 125 was oxidized to the corresponding pyridine 126 by 20% nitric acid (eq.56).[48] High potential quinones such as chloranil[87] or dichlorodicyanoquinone[131] are also quite commonly used. For example, dihydropyridine 127 was oxidized by chloranil in refluxing benzene to give the corresponding pyridine derivative 128 (eq.57).[87] Silver nitrate[81,132] and iodine[132] have also been employed (for example, eq.58). Sulfur is often used because it is least likely to give side reactions.[28,29] Catalytic dehydrogenation by platinum[133] and palladium[134,135] have also been employed. Other reagents include p-nitrosodimethylaniline,[96] hydrogen peroxide,[136] diisoamyl disulfide,[137] mercuric acetate,[138] and iron or nickel carbonyls.[107] Oxygen or air have been employed in a number of instances (example, eq.1,58)[23,132,139]



125 126 (56)



127 128 (57)



129 130 (58)

DISCUSSION

I. General

In studying the reactions of lithium dialkylcuprates with pyridine in the presence of methyl chloroformate, it was found that when the lithium di-s-butylcuprate reagent was employed, the reaction was not always reproducible. This lack of reproducibility might be attributed to the low thermal stability of sec-alkylcuprates in general,[140] a characteristic which was recognized by Posner et al.[141] In an attempt to circumvent this limitation, Posner et al. synthesized a series of hetero(alkyl)cuprate reagents [Het(R)CuLi (Het=t-BuO,PhO,t-BuS,PhS,Et_2N)] and compared them with other organocopper reagents for their selectivity and efficiency in transferring an alkyl group to several diverse types of organic substrates.[141] It was found that lithium phenylthio(alkyl)cuprates PhS(R)CuLi were superior to other hetero(alkyl)cuprate reagents and lithium dialkylcuprates in transferring secondary alkyl groups in substitution and conjugate addition reactions. For example, n-octyl iodide undergoes replacement of iodide by a s-butyl group when treated with two equivalents of lithium phenylthio(s-butyl)cuprate to give a 67% yield of the corresponding alkane 131. With lithium t-butoxy(s-butyl)cuprate, the yield of the coupling product 131 was 52%. However, only 7% of 131 was isolated when five equivalents of lithium di-s-butylcuprate were employed (eq.59).[141]

$$\underline{n}\text{-}C_8H_{17}I \xrightarrow[\text{solvent}]{R(\underline{s}\text{-}Bu)CuLi} \underline{n}\text{-}C_8H_{17}\text{-}\underline{s}\text{-}Bu \quad (59)$$

131

R	Yield
(a) PhS	67%
(b) t-BuO	52%
(c) s-Bu	7%

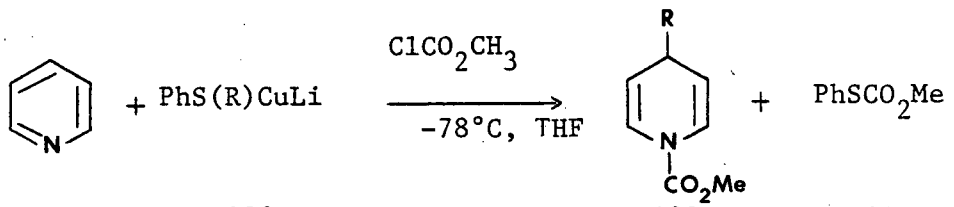
These observations triggered our investigation of the reaction of lithium phenylthio(alkyl or aryl)cuprates with pyridine in the presence of methyl chloroformate.

II. Reaction of Lithium Phenylthio(alkyl or aryl)cuprates with Pyridine in the Presence of Methyl Chloroformate.

Our initial studies were carried out with lithium phenylthio-(n-butyl)cuprate 132c. Following the procedure of Piers and Soucy,[128] a four fold excess of methyl chloroformate was added to a solution of pyridine (one equivalent) and the cuprate reagent (1.4 equivalents) in tetrahydrofuran at -78°C. After the reaction mixture had been stirred for 3h at -78°C, a small amount of methanol was added. The distilled product obtained after work-up was analysed by gas-liquid chromatography (glc) and proton magnetic resonance (^{1}Hnmr) spectroscopy. It was found that the major product of the reaction was methyl phenylthioformate 133, along with some of the expected 1-carbomethoxy-4-n-butyl-1,4-dihydropyridine 123c[128] (eq.60). An analytical sample of each of the two products was obtained by preparative glc. The ^{1}Hnmr spectrum of 133 was identical with that of an authentic sample of the same material obtained by the reaction of thiophenol and methyl chloroformate in the presence of aqueous sodium hydroxide.

However, when the amount of methyl chloroformate used in the above reaction was reduced from four equivalents to one equivalent, the desired product, 1-carbomethoxy-4-n-butyl-1,4-dihydropyridine 123c was obtained in ∿65% yield. Under these conditions, the amount of side product, methyl phenylthioformate 133,was reduced to ∿14% of the product mixture. No trace

of the corresponding 1,2-dihydropyridine derivative was found.



132 123 133

132(a) R=CH_3; (b) R=Et; (c) R=n-Bu; (d) R=s-Bu; (e) R=t-Bu; (f) R=Ph

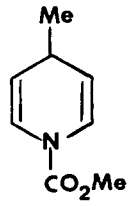
Compound 123c exhibited the characteristic 1,4-dihydropyridine ^{1}Hnmr pattern. The protons at C-2 and C-6 resonated as a two-proton doublet centred at τ3.20, with coupling constant J=8 Hz. The protons at C-3 and C-5 gave rise to a two-proton doublet of doublets centred at τ5.13 (J=8 Hz, J′=2 Hz). Finally, the proton at C-4 produced a one-proton multiplet centred at τ7.05 and the protons of the carbomethoxy group appeared as a three-proton singlet at τ6.20.

The ir spectrum of 123c showed a strong carbonyl absorption at 1730 cm^{-1}, and two other absorption peaks at 1633 and 1690 cm^{-1}.

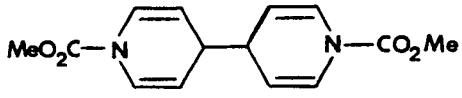
In a similar fashion, the aforementioned procedure was extended to include the use of other lithium phenylthio(alkyl or aryl)cuprate reagents. Some of the results obtained are summarized in Table 1. All of the dihydropyridine derivatives listed in Table 1 exhibited 'Hnmr and ir spectra which were similar to that of compound 123c and all gave satisfactory molecular weight determination (high resolution mass spectrometry).

It was found that when lithium phenylthio(methyl)cuprate was employed, the yield of the desired product, 1-carbomethoxy-4-methyl-1,4-dihydropyridine

123a, was merely 52% (entry 1, Table 1). Attempts to improve the yield by raising the temperature of the reaction mixture from -78°C to 0°C led to the formation of methyl phenylthioformate 133 as the major product. Even at -50°C a considerable amount of 133 was formed as a side product. It was also found that, regardless of the temperature of the reaction mixture, a considerable amount of high boiling residue remained after distillation of the initially isolated crude product. Spectral evidence (^{1}Hnmr) indicated that the major component of this residual material might be the dimer 134. However, attempts to isolate a pure sample of this material failed, since it decomposed extensively



123a

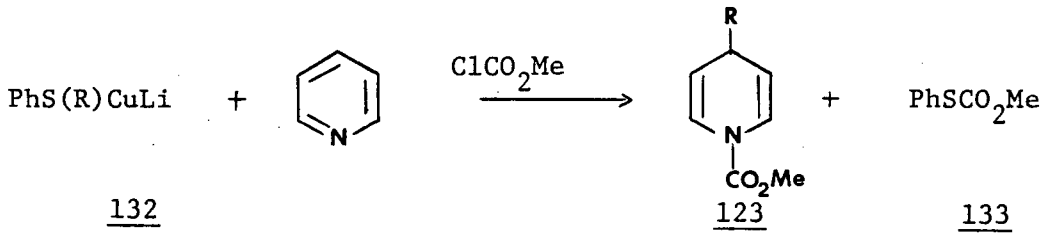


134

when the distillation residue was subjected to column chromatography on silica gel.

It is important to note that compound 123a was quite unstable in air. In fact, a freshly distilled colorless sample of 123a turned green nearly immediately upon contact with air. Indeed, all of the 1-carbomethoxy-4-alkyl(or aryl)-1,4-dihydropyridines which were synthesized during the course of our work were found to be unstable in air, although they were stable for a few weeks if carefully kept under an atmosphere of argon in the freezer. An analytical sample of each of the dihydropyridine derivatives was obtained from each of the reaction product mixtures by means of preparative

Table 1. Reaction of lithium phenylthio(alkyl or aryl)cuprates with pyridine in the presence of methyl chloroformate.



132 123 133

Entry	Cuprate(R)	Yield[a](%) of 123	Ratio of 123:133
1	CH_3-	52	>99:1
2	C_2H_5-	70	88:11
3	$CH_3(CH_2)_3$-	65	86:14
4	$CH_3CH_2\dot{C}HCH_3$	80	89:11
5	$(CH_3)_3C$-	26	50:50[b]
6	C_6H_5	24[c]	>99:1

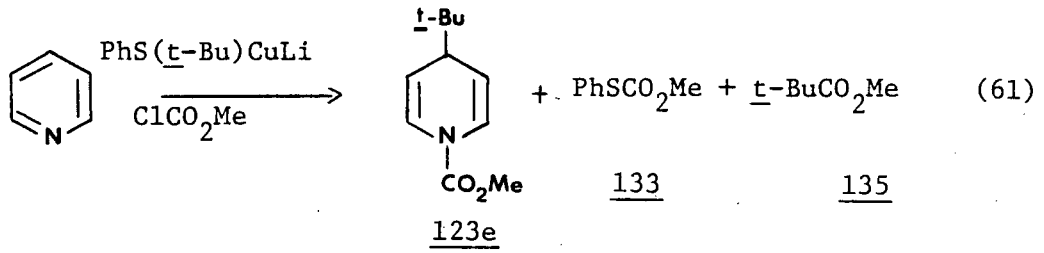
(a) The yield is based on the total material recovered multiplied by the percentage purity as determined by glc.

(b) The ratio here is actually 50% 123 to 50% of side product which was a mixture of 133 plus methyl 2,2-dimethylpropanoate (135).

(c) The major product was biphenyl.

glc. They were characterized by ir, ^{1}Hnmr, and mass spectral analysis as soon as they were isolated.

When the procedure described above was carried out employing lithium phenylthio(ethyl)cuprate and the corresponding s-butyl reagent, the reactions proceeded smoothly and the products were quite clean. Thus, the corresponding products, 1-carbomethoxy-4-ethyl-1,4-dihydropyridine 123b and 1-carbomethoxy-4-s-butyl-1,4-dihydropyridine 123d, were formed in yields of 70% and 80%, respectively (see Table 1, entries 2 and 4). However, when lithium phenylthio(t-butyl)cuprate was used under a variety of reaction conditions, the major products formed appeared to be a mixture of methyl phenylthioformate 133 and methyl 2,2-dimethylpropanoate 135 (eq.61). These two compounds were not separable by preparative glc but the ^{1}Hnmr spectrum of the mixture was almost identical with an authentic 1:1 mixture of the same two materials. The best reaction conditions found gave a yield of approximately 26% (glc yield) of the desired product,

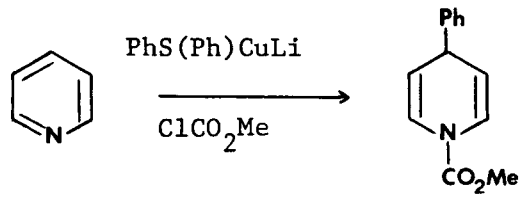


(61)

1-carbomethoxy-4-t-butyl-1,4-dihydropyridine 123e. Approximately equal amounts of the side products 133 and 135 were also formed in the reaction (entry 5, Table 1).

In the case of lithium phenylthio(phenyl)cuprate (entry 6, Table 1), the major product formed appeared to be biphenyl 136. The latter, along

with some other minor impurities, were separated from the desired product 123f by fractional distillation. Comparison of the ^{1}Hnmr spectrum of the former material with that of an authentic sample of biphenyl showed that this material was mainly biphenyl. The presence of biphenyl in the reaction product was further confirmed by a glc coinjection analysis involving an authentic sample of biphenyl and this mixture. The desired product 1-carbomethoxy-4-phenyl-1,4-dihydropyridine 123f was formed in only 24% yield (eq.62).



(62)

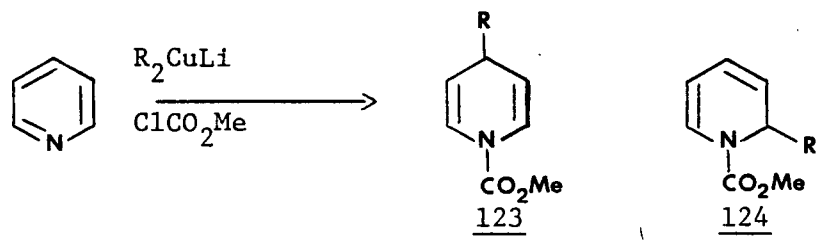
123f

Finally, when lithium phenylthio(vinyl)cuprate was employed, no trace of the expected product 1-carbomethoxy-4-vinyl-1,4-dihydropyridine 123g was found. A small amount of methyl phenylthioformate 133 was isolated together with a considerable amount of a high boiling, unidentified residue.

III. Comparison of Lithium Dialkyl(or diaryl)cuprates with Lithium Phenylthio(alkyl or aryl)cuprates in the Synthesis of 1-Carbomethoxy-4-alkyl(or aryl)-1,4-dihydropyridines.

Since one of the objectives of the work described in this part of the thesis was to investigate the efficiency of lithium phenylthio(alkyl or aryl) cuprates in transferring an alkyl(or aryl) group to pyridine in the formation of 1,4-dihydropyridines, it is appropriate to make a comparison

of the results obtained by using lithium dialkyl(or diaryl)cuprates with those obtained by employing lithium phenylthio(alkyl or aryl)cuprates. A summary of both sets of results is tabulated in Table 2. A perusal of the results summarized in Table 2 clearly shows that lithium phenylthio(s-butyl)cuprate 132d was superior to lithium di-s-butylcuprate in yielding 1-carbomethoxy-4-s-butyl-1,4-dihydropyridine (entry 4, Table 2). The lithium di-s-butylcuprate reagent reacted with pyridine in the presence of methyl chloroformate to yield 56% of a mixture of 1-carbomethoxy-4-s-butyl-1,4-dihydropyridine 123d and 1-carbomethoxy-2-s-butyl-1,2-dihydropyridine 124d in a ratio of 89:11 respectively (eq.63). When lithium phenylthio(s-butyl)cuprate was employed, a mixture of the 1,4-dihydro-



(63)

(a) R=CH_3; (b) R=Et; (c) R=n-Bu; (d) R=s-Bu; (e) R=t-Bu; (f) R=Ph

pyridine 123d and methyl phenylthioformate 133 (in a ratio of 89:11, respectively) was obtained, in which the yield of dihydropyridine 123d was approximately 80%.

When the alkyl group in the cuprate reagent was methyl or primary alkyl, lithium phenylthio(alkyl)cuprates were no better than the corresponding dialkylcuprates. For example, the reaction of lithium dimethylcuprate with pyridine in the presence of methyl chloroformate gave in 81% yield a mixture of the corresponding dihydropyridine

Table 2. Comparison of the use of lithium dialkyl(diaryl)cuprates with the use of lithium phenylthio(alkyl or aryl)cuprates in the synthesis of 1-carbomethoxy-4-alkyl(or aryl)-1,4-dihydropyridines

Entry	R=	R_2CuLi		$PhSCu(R)Li$
		Product Yield[a](%)	Ratio 123:124	Yield[b] of 123(%)
1	CH_3-	81[c]	98:2	52
2	CH_3CH_2	67[c]	96:4	70
3	$CH_3(CH_2)_3$-	86[c]	98:2	65
4	$CH_3CH_2\overset{\prime}{C}HCH_3$	56[c]	98:11	80
5	$(CH_3)_3C$-			26
6	C_6H_5	70[c,d]	90:10	24
		88[e]	84:16	
7	CH_2=CH-	67[f]	51:46	<1
		60[c,g]	72:28	

a) The yield here is based on total material recovered.
b) Same as footnote a), Table 1.
c) Data obtained from E.Piers et al.[128]
d) CuI was used to prepare the cuprate reagent.
e) CuBr was used to prepare the cuprate reagent.
f) Dimethylsulfide complex of CuBr was used to make the cuprate reagent.
g) Tri-n-butylphosphine complex of CuI was used to prepare the cuprate reagent.

derivatives, in which the ratio of the 1,4-isomer 123a to the 1,2-isomer 124a was 98:2 respectively (entry 1, Table 2). When lithium phenylthio(methyl)cuprate was employed, the yield of 1-carbomethoxy-4-methyl-1,4-dihydropyridine 123a was only 50%.

When the incoming group was phenyl, it is clear that lithium phenylthio(phenyl)cuprate was definitely inferior to the diphenylcuprate (entry 7, Table 2). Lithium phenylthio(phenyl)cuprate reacted with pyridine in the presence of methyl chloroformate to give only a 24% yield of the desired product, 1-carbomethoxy-4-phenyl-1,4-dihydropyridine 123f. When lithium diphenylcuprate (prepared from the reaction of phenyllithium and cuprous iodide) was employed, the yield of the corresponding mixture of dihydropyridine derivatives was 70% and the ratio of the 1,4- to 1,2-isomer (123f and 124f, respectively) was 90:10. However, it was found that the reaction of lithium diphenylcuprate with pyridine in the presence of methyl chloroformate was not always reproducible. G.M. Whiteside et al[140] reported that they had difficulties in preparing stable solutions of lithium diphenylcuprates from the reaction of phenyllithium with cuprous iodide. However, they also reported that the problem was solved by substituting cuprous bromide for cuprous iodide.[140] When this method for preparing lithium diphenylcuprate was followed and the resultant reagent was allowed to react with pyridine in the presence of methyl chloroformate in the usual manner, there was obtained an 88% yield of a mixture of 1-carbomethoxy-4-phenyl-1,4-dihydropyridine 123f and 1-carbomethoxy-2-phenyl-1,2-dihydropyridine 124f in a ratio of 84:16.

Although lithium phenylthio(alkyl or aryl)cuprates produced no 1,2-dihydropyridine derivatives reactions with these reagents were not

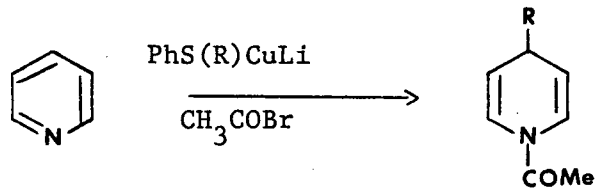
problem free. In most cases, a side product, methyl phenylthioformate 133, was formed in approximately 10% yield and, in the case where the alkyl group was t-butyl, this side product was formed in >25% yield. Thus, the use of lithium phenylthiol(alkyl)cuprates in the reaction with pyridine and methyl chloroformate is complementary to the use of lithium dialkyl(or diaryl)cuprates but cannot take its place in the synthesis of 1-carbomethoxy-4-alkyl(or aryl)-1,4-dihydropyridines.

IV. Reaction of Lithium Dialkylcuprates with Pyridine in the Presence of Acetyl Bromide

The work described above clearly showed that methyl chloroformate served quite well as an electrophile in promoting the reaction of pyridine with various cuprate reagents. Furthermore, the products (N-carbomethoxy dihydropyridines) were sufficiently stable to allow for isolation and characterization. Nevertheless, it was of interest to study the possibility of using alternate electrophiles, not only to determine whether or not the reaction would be efficient, but also in order to prepare simple dihydropyridine compounds containing a substituent on nitrogen other than a carbomethoxy group.

The first alternate we tried was acetyl bromide. The procedure used was essentially the same as with methyl chloroformate. For example, a four fold excess of acetyl bromide in ether was added to a solution of pyridine (1 equivalent) and lithium di-n-butylcuprate (1.2 equivalents) at -78°C. The resulting mixture was stirred at -78°C for 30 min, warmed to 0°C and stirred for an additional 30 min. After work-up, the distilled product (~73% yield) was analysed by glc and it was found to be pure

1-acetyl-4-n-butyl-1,4-dihydropyridine 137c (eq.64). Although the ^{1}Hnmr of this material was slightly different from its N-carbomethoxy counterpart, the 1,4-dihydropyridine structure was clearly present. The protons at C-2 and C-6 of 137c appeared as a pair of doublets (J=9 Hz in each case) centered at τ2.83 and 3.46. The protons at C-3 and C-5, on the other hand, resonated as a two-proton multiplet centered at τ5.05. Finally, the proton at C-4 appeared as a multiplet centred at τ7.05 and the methyl group on the acyl group resonated as a singlet at τ7.83. The ir spectrum of this material showed a strong carbonyl absorption at 1675 cm^{-1} and another fairly strong absorption at 1623 cm^{-1}.



(64)

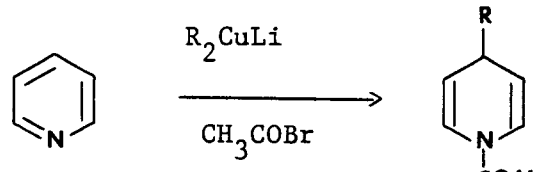
137

137(a) R=CH_3; (b) R=Et; (c) R=n-Bu; (d) R=Ph

Similar results were obtained when lithium dimethylcuprate and lithium diethylcuprate were employed,and the spectral data (^{1}Hnmr, ir) of the corresponding products, 1-acetyl-4-methyl-1,4-dihydropyridine 137a, and 1-acetyl-4-ethyl-1,4-dihydropyridine 137b respectively,were quite similar to those of 1-acetyl-4-n-butyl-1,4-dihydropyridine 137c described above. The results are summarized in Table 3. In general, the yields of 1,4-dihydropyridine derivatives were not bad and, somewhat surprisingly, no trace of the corresponding 1,2-dihydropyridine derivatives were found.

Again, lithium diphenylcuprate posed the same problem as had been encountered earlier. Using cuprous iodide to make the diphenylcuprate,

Table 3. Reaction of lithium dialkylcuprates with pyridine in the presence of acetyl bromide



137

Entry	Cuprates(R)	Product yield(%)
1	CH_3-	59
2	CH_3CH_2-	50
3	$CH_3(CH_2)_3$-	73

the reaction gave a complex mixture of products. When cuprous bromide was employed to make the cuprate reagent , the reaction was cleaner, and the spectral data (^{1}Hnmr) of the crude product indicated that the desired product, 1-acetyl-4-phenyl-1,4-dihydropyridine 137d, was present in the product mixture, along with a considerable amount of unknown impurities. The reaction was not investigated further. When the use of lithium di-s-butylcuprate was investigated, again, a synthetically useless complex mixture of products resulted. Clearly, the above results showed that acetyl bromide did not give results superior to those obtained from methyl chloroformate. Therefore the reaction with acetyl bromide acting as an electrophile for the synthesis of 1,4-dihydropyridine derivatives was not investigated further.

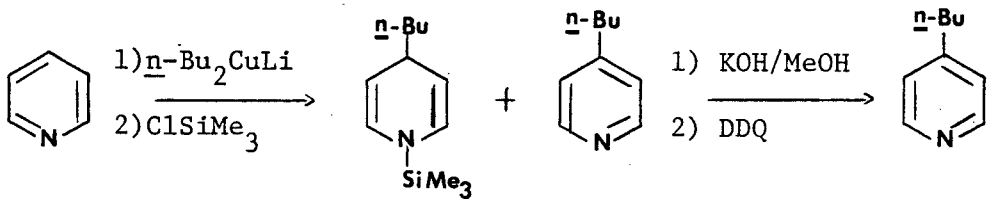
V. Comparison of Different Electrophiles in the Synthesis of 4-Alkyl-1,4-dihydropyridine Derivatives from the Reaction of Lithium Dialkylcuprates with Pyridine in the Presence of the Electrophiles.

Methyl chloroformate and acetyl bromide are both fairly strong electrophiles. They both readily react with pyridine to form pyridinium salts. The latter, probably mainly due to the positive charge on the nitrogen atom and to the electron-withdrawing group (COOMe or COMe) attached to the nitrogen, are apparently quite susceptible to reaction with electron transfer reagents such as cuprates. It was of interest to investigate if weaker electrophilic reagents could serve the same purpose.

In this connection, the reaction of pyridine with lithium di-n-butylcuprate in the presence of chlorotrimethylsilane was investigated first. Under reaction conditions very similar to those used in the case

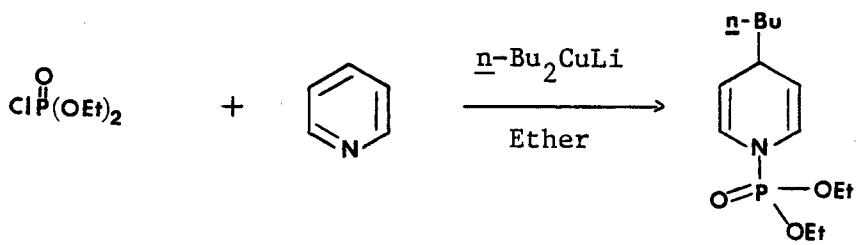
of methyl chloroformate, the expected 1-trimethylsilyl-4-n-butyl-1,4-dihydropyridine 138 was obtained. However, it seemed that this compound was very unstable. Indeed, the ^{1}Hnmr spectrum of the crude product showed that it contained a considerable amount of 4-n-butylpyridine. The presence of 4-n-butylpyridine was confirmed by comparing the ^{1}Hnmr spectra of the crude product mixture with that of a pure sample of 4-n-butylpyridine. The ^{1}Hnmr spectrum of the crude product was interpreted as follows. A pair of doublets (J=5 Hz, J′=2 Hz) centered at τ1.52, was assigned to the protons at C-2 and C-6 of 4-n-butylpyridine, while the pair of doublets (J=5 Hz, J′=2 Hz) at τ2.89, was due to the C-3 and C-5 protons of 4-n-butylpyridine. A triplet (J=7 Hz) centered at τ3.40, was assigned to the two methylene protons on the n-butyl group adjacent to C-4 of the ring of 4-n-butylpyridine. A doublet, (J=8 Hz), which appeared at τ4.07 was assigned to the protons at C-2 and C-6 of the dihydropyridines 138. Another pair of doublets (J=8 Hz, J′=3.5 Hz) centered at τ5.57, was assigned to the C-3 and C-5 protons of the dihydropyridine 138. Finally, a multiplet centered at τ3.00 was assigned to the proton at C-4 of the dihydropyridine 138.

Since the 1-trimethylsily-4-n-butyl-1,4-dihydropyridine 138 was quite unstable, it was not isolated in pure form for characterization. Instead, the crude product mixture obtained from the reaction described above was treated first with methanolic potassium hydroxide (in order to cleave the N-trimethylsilyl group) and then with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (in order to oxidize the resultant 1,4-dihydropyridine). This procedure afforded a 33% isolated yield of 4-n-butylpyridine (eq.65).



138 (65)

Next, the use of diethylphosphorochloridate as an electrophile was investigated. When the reaction was attempted under the usual reaction conditions (addition of diethylphosphorochloridate to a solution of pyridine and lithium di-n-butylcuprate), none of the expected product, 1,4-dihydropyridine derivative 139 was isolated. However, addition of a solution of diethylphosphorochloridate in excess pyridine to a solution of lithium di-n-butylcuprate in ether at -78°C did give the expected product, although the yield was very low (∿17%) (eq.66). The distilled product of the reaction was analysed by tlc and was shown to be the pure dihydropyridine 139. The ^{1}Hnmr of this material showed the characteristic 1,4-dihydropyridine structure. A two proton multiplet between τ3.56 and 3.93 was assigned to the protons at C-2 and C-6 while the protons at C-3 and C-5 were found to resonate at τ5.10-5.46 as a two-proton multiplet. The C-4 proton resonated as a one-proton multiplet at τ6.90-7.23. This material also showed strong absorption at 1680, 1620, 1290 and 1270 cm^{-1} in the ir spectrum.



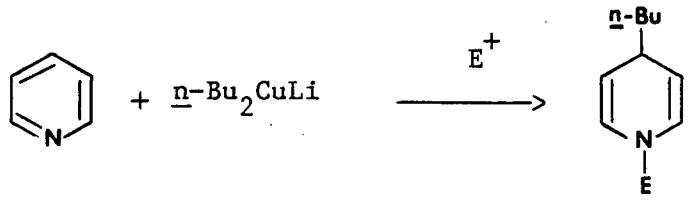
139 (66)

Although the last two electrophiles tried did give the corresponding

dihydropyridine derivatives, methyl chloroformate and acetyl bromide were definitely better choices in terms of giving better yields and cleaner crude products. Table 4 summarizes and compares the results of the four electrophiles in the reaction of lithium di-n-butylcuprate with pyridine. In the presence of methyl chloroformate, pyridine reacts with lithium di-n-butylcuprate reagent to give an 86% yield of a mixture of the corresponding 1,4 and 1,2-dihydropyridine, 123c and 124c, in a ratio of 98:2 respectively (entry 2, Table 4). With acetyl bromide, the yield of the corresponding 1,4-dihydropyridine 137c was 73% and no trace of the corresponding 1,2-dihydropyridine was detected (entry 1, Table 4). When diethylphosphorochloridate was employed, the yield of the corresponding 4-n-butyl-1,4-dihydropyridine derivative 139 was a mere 17% (entry 3, Table 4). With chlorotrimethylsilane, the crude product was a mixture of the expected 1-trimethylsilyl-4-n-butyl-1,4-dihydropyridine 138 and the corresponding oxidized product, 4-n-butylpyridine (entry 4, Table 4).

Although the study just described was very brief, it appeared that the use of chlorotrimethylsilane and diethylphosphorochloridate as electrophiles was of limited synthetic value in the reaction of pyridine with lithium dialkylcuprates. Therefore the use of these reagents was not investigated further.

Table 4. Comparison of different electrophiles in the synthesis of 4-alkyl-1,4-dihydropyridine derivatives from the reaction of pyridine with lithium di-n-butylcuprate.



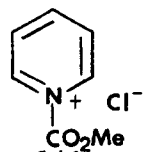
Entry	Electrophile	Product yield(%)
1	CH_3COBr	73
2	$C\ell CO_2CH_3$	86[a]
3	$C\ell PO(OC_2H_5)_2$	17
4	$C\ell Si(CH_3)_3$	>33[b]

(a) The product was a mixture of 1-carbomethoxy-4-n-butyl-1,4-dihydropyridine and 1-carbomethoxy-2-n-butyl-1,4-dihydropyridine in the ratio of 98:2.

(b) The product was a mixture of 1-trimethylsilyl-4-n-butyl-1,4-dihydropyridine and 4-n-butylpyridine.

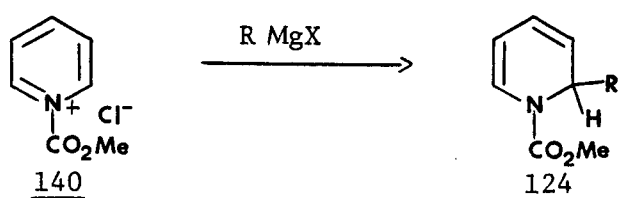
VI. Mechanistic Considerations

Although we have not done any mechanistic studies on the reactions of organocuprate reagents with pyridine in the presence of methyl chloroformate, separate control experiments showed that the cuprate reagents did not react with pyridine directly.[128] For example, when a solution of pyridine and lithium dimethylcuprate in ether was stirred at 0°C for 1h and was then worked up without addition of methyl chloroformate, pyridine could be recovered in greater than 80% yield.[128] These results indicated that the products were probably formed by reaction of the cuprate reagent with the initially formed pyridinium salt 140.



140

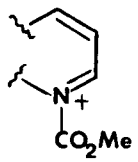
As was already mentioned earlier, pyridine and alkylpyridines undergo nucleophilic attack by alkyllithium or aryllithium reagents to give 2-substituted-1-lithio-1,2-dihydropyridines.[74-79] 1-Carbomethoxypyridinium chloride reacts with Grignard reagents to afford mainly 1-carbomethoxy-2-alkyl-1,2-dihydropyridine (eq.29).[85,86] The high regioselectivity involved in the conjugate addition of cuprate reagents to pyridine in the presence



140 124

of methyl chloroformate indicated that this reaction probably goes via a

mechanism different from that involved in the reactions employing Grignard or alkyllithium reagent. Conjugate addition of cuprate reagents to α,β-unsaturated enones are well documented.[142-145] The N-carbomethoxypyridinium salt system 140 can be considered as an analogue equivalent of an α,β-unsaturated ketone in which the nitrogen atom replaces the oxygen atom in the enone system, as shown below. The carbon-



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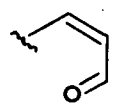
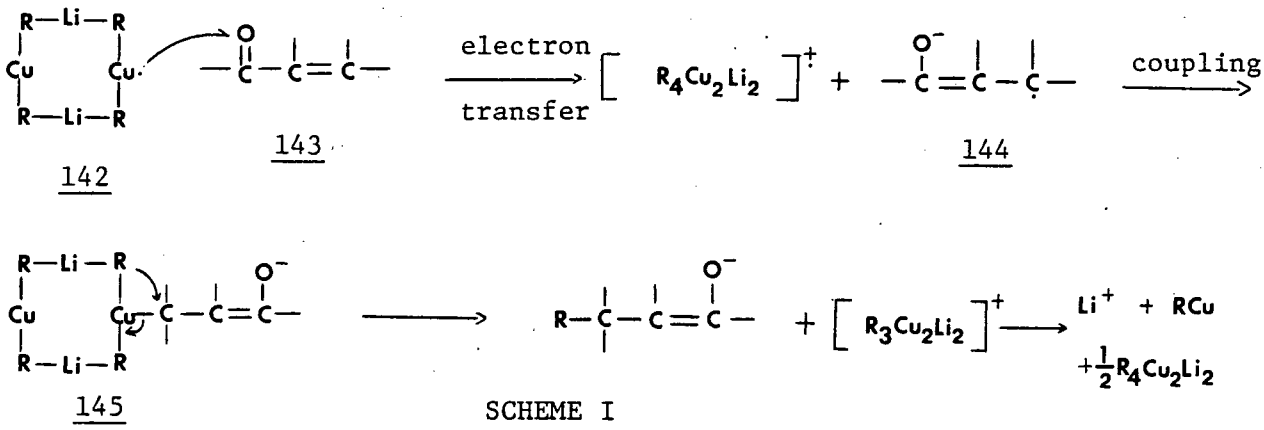


141

nitrogen double bond C=N+ is similar to the carbonyl functionality (>C=O) and the other double bond on the pyridinium ring is analogous to the double bond conjugated to the carbonyl function in the enone system.

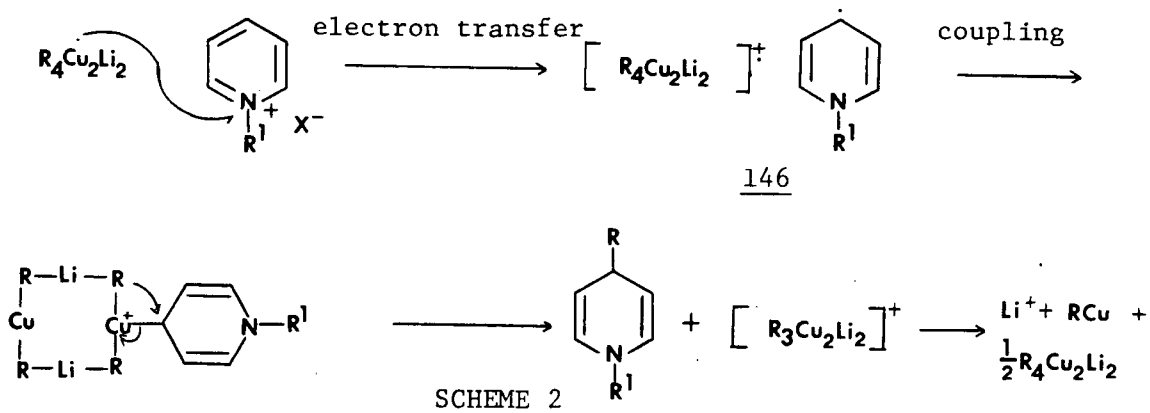
Although the mechanism of conjugate addition of organocuprate reagents to α,β-unsaturated enones is still open to question, the electron transfer hypothesis proposed by H. O. House et al. is currently the most well accepted.[144,145] The limited structural information presently available[145,146] suggests that the lithium dialkylcuprate reagents probably exist as dimers ($R_4Cu_2Li_2$) in ether solution with a cyclic structure having approximately D_{2h} symmetry - structure 142. The charge transfer mechanism suggests an initial transfer of an electron from the cuprate reagent to the unsaturated substrate 143 to form radical anion 144 (Scheme 1). Subsequent transfer of an organic radical from a transient species like 145 would complete the addition sequence.



SCHEME I

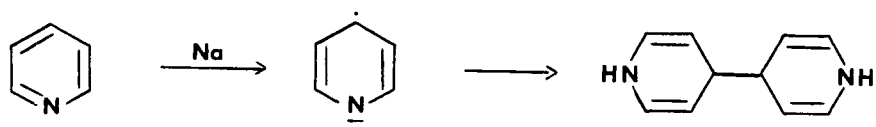
Observations indicating that there is a relationship between the reduction potentials of various unsaturated carbonyl compounds and their ability to react with cuprate reagents has lent support to the mechanism proposed.[144] Such a correlation also allows a fairly reliable prediction to be made as to whether or not an unsaturated substrate will undergo conjugate addition. Various other studies directed towards the elucidation of the mechanism of conjugate addition of cuprate reagents to unsaturated carbonyl compounds have shown that in most cases, an anion-radical is indeed an intermediate in these reactions.[144]

Analogously, a similar mechanism can be postulated for the formation of 4-alkyl-1,4-dihydropyridine derivatives from the reaction of pyridine with cuprate reagents in the presence of an electrophile. Thus it can be proposed that the cuprate reagent transfers an electron to the pyridinium ring to form an electron-transfer complex 146 which then couples with the cuprate reagent to form a transient intermediate 147. Subsequent transfer of an alkyl group from the copper atom of the intermediate to the dihydropyridine ring would give the corresponding product (Scheme 2).



SCHEME 2

Reactions involving electron transfer to pyridine are not new. Certain metals (for example, sodium) transfer one electron to pyridine to form the radical anion 148 which dimerizes readily to tetrahydrobipyridyl 149 (eq.67).[147]



148 149 (67)

Charge-transfer complexes of pyridinium salts were known as early as 1955. E.M. Kosower et al investigated the spectra of substituted 1-methylpyridinium iodides in aqueous solution and obtained evidence for the presence of a charge-transfer complex, the principal contributing forms of which may be depicted as 150 and 151.[148] Kosower also found that

150 151

nucleophiles which form charge-transfer complexes easily, or which might be expected to do so, add to the pyridinium salt at the 4-position, while

those nucleophiles which probably do not form complexes or do so only to a very limited extent, add at the 2-position.[149] These latter findings are in perfect accord with our mechanistic proposal.

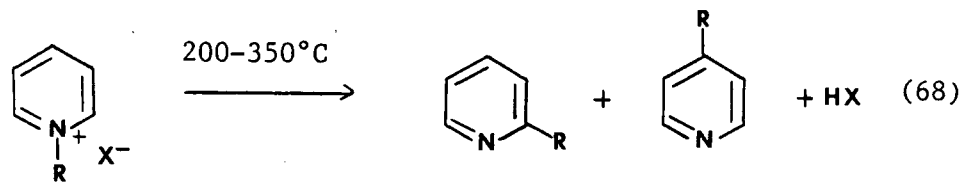
The mechanism suggested above is very tentative and based only on analogy. We have no experimental basis to substantiate our postulation. Therefore, more work should be done in this area if the nature of the reaction is to be understood more fully.

VII. Conversion of 1-Carbomethoxy-4-alkyl-1,4-dihydropyridines to the Corresponding 4-Alkylpyridines.

As has been mentioned previously, one of the most important reactions of dihydropyridine derivatives is their oxidation to the corresponding pyridine compounds. By oxidizing the 1-carbomethoxy-4-alkyl-1,4-dihydropyridines synthesized *via* the reaction of pyridine with organocuprate reagents in the presence of methyl chloroformate, we have provided a new route to the synthesis of simple 4-alkylpyridines.

Synthesis of 4-alkylpyridines from pyridine itself has been a fairly difficult task. Most available methods yield a mixture of 4-alkylpyridines and 2-alkylpyridines. For example, the thermal rearrangement of the pyridinium salts 152 in the Ladenburg rearrangement reaction gave in each case a mixture of the corresponding 2- and 4-alkyl (or aryl)pyridines (eq.68).[150,151] Catalytic alkylation of pyridine by the reaction of the latter with an aliphatic acid in the presence of the corresponding lead salt and a catalyst also affords a mixture of 2- and 4-alkylpyridines, together with dialkylated product (eq.69).[152] When pyridine is heated with a diacyl peroxide in the presence of the corresponding aliphatic carboxylic acid, a mixture of the corresponding 2- and 4-alkylpyridine is

produced (eq.70).[153]



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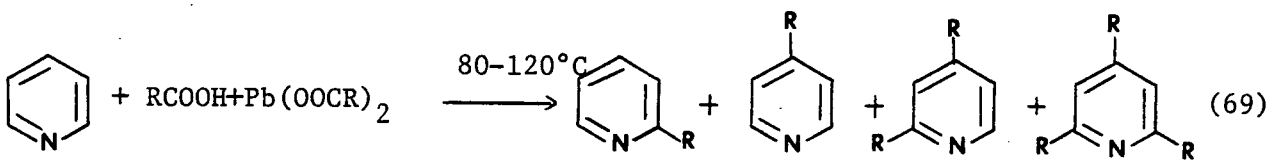
152 R=alkyl, Ph



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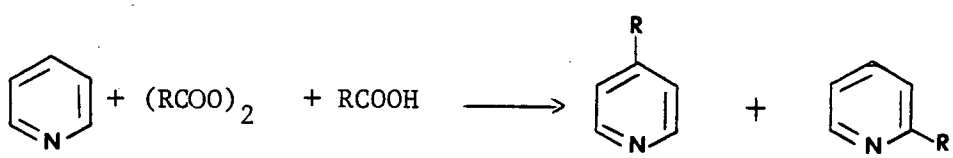
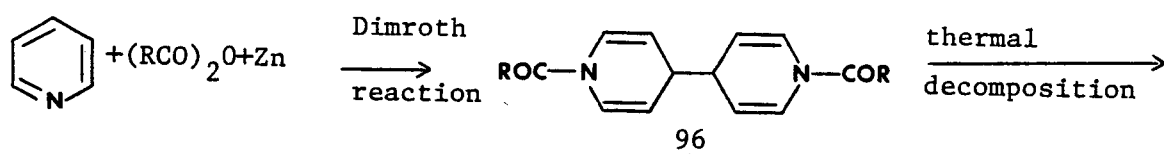


(70)

4-Alkylpyridines can be synthesized directly from pyridine by the Wibaut-Arens alkylation. The overall synthesis involves the reaction of pyridine with an acid anhydride in the presence of zinc (Dimroth reaction), thermal rearrangement of the resultant dimeric product 96 to a 1,4-diacyl-1,4-dihydropyridine 153 and finally, reduction of the latter to a 4-alkylpyridine (eq.71).[154,155]



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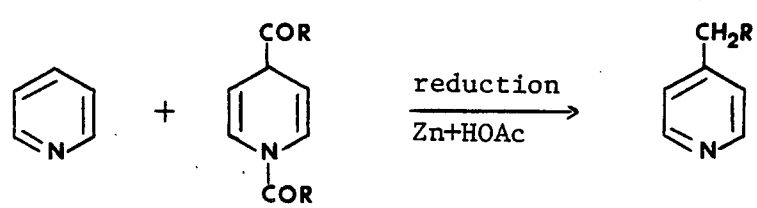
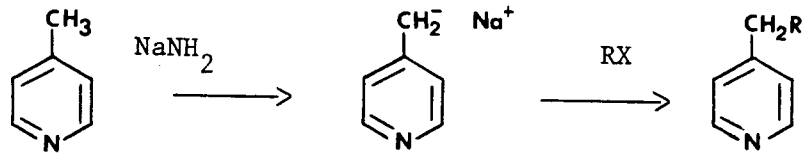


153

(71)

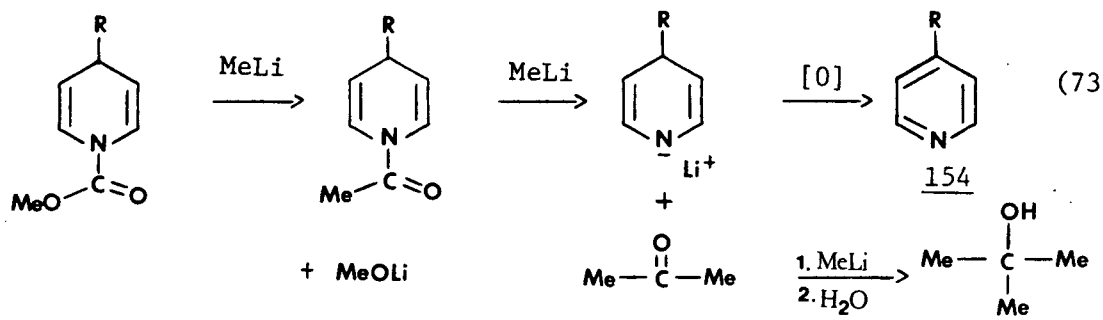
A more efficient synthesis of 4-alkylpyridines uses 4-picoline as starting material. 4-Picoline is first treated with sodium or potassium amide and the resultant anion is allowed to react with various alkyl halides to give the corresponding 4-alkylpyridines (eq.72).[156]



(72)

As had been mentioned previously, dihydropyridines serve as important intermediates in several reactions of pyridine. In fact, a large number of pyridine derivatives may be obtained by oxidizing the corresponding dihydropyridine derivatives synthesized by the Hantzsch and related syntheses. By oxidizing the 1-carbomethoxy-4-alkyl-1,4-dihydropyridines synthesized from the reaction of pyridine with cuprate reagents in the presence of methyl chloroformate, we have developed a fairly efficient method for synthesizing simple 4-alkyl pyridines.

Our initial studies were carried out with 1-carbomethoxy-4-n-butyl-1,4-dihydropyridine. In general, the dihydropyridine derivative was first treated with three equivalents of methyllithium in order to remove the N-carbomethoxy group, and the resulting lithium piperidide derivative was then oxidized in situ by addition of an appropriate oxidizing agent (eq.73). p-Benzoquinone was the first reagent tried in



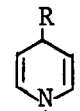
(73)

the oxidation step, but a disappointingly low yield (48%) of 4-n-butylpyridine was obtained. When tetrachloro-1,4-benzoquinone was employed, the yield of 4-n-butylpyridine improved to 65%. Finally, it was found that 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave the most satisfactory yield (73%) of 4-n-butylpyridine. This type of procedure was extended to include other 1,4-dihydropyridine derivatives and the results are summarized in Table 5. In general, 4-alkylpyridines obtained from the oxidation were essentially pure after distillation from the crude products. In each case, the product was analyzed by glc and characterized by ir and ^{1}Hnmr spectroscopy. The spectral data (ir, ^{1}Hnmr) of each product was compared with those of an authentic sample available commercially or with those reported in the literature.

As can be seen from the results summarized in Table 5, the yields of 4-alkyl(aryl)pyridines were fairly good. For example, the yield of 4-ethylpyridine was 89% and the yield of 4-s-butylpyridine was 79% (entry 2 and 4 respectively, Table 5). The only exception was 1-carbomethoxy-4-methyl-1,4-dihydropyridine which gave only a 58% yield of 4-picoline (entry 1, Table 5). The low yield of the latter product may be attributed to mechanical loss owing to its volatility.

Compared with most other methods for synthesizing simple 4-alkylpyridines, the combined synthesis of 1-carbomethoxy-4-alkyl(aryl)-1,4-dihydropyridines and their subsequent conversion to the corresponding 4-alkylpyridines opens a new, clean and fairly efficient way of synthesizing these compounds.

Table 5. Conversion of 1-carbomethoxy-4-alkyl(aryl)-1,4-dihydropyridines to the corresponding 4-alkyl(aryl)pyridines

Entry		Yield(%) of 4-alkyl(or aryl)pyridines		
		p-benzoquinone	tetrachloro-1,4-benzoquinone	DDQ
1	R = CH_3-	55		58
2	CH_3CH_2-			89
3	$CH_3(CH_2)_3$-	48	65	73
4	$CH_3CH_2\overset{\cdot}{C}HCH_3$			79
5	C_6H_5			73

EXPERIMENTAL

General Information

Melting points, determined with a Fisher-Johns melting point apparatus, and boiling points are uncorrected. Ultraviolet (uv) spectra were obtained with a Cary 15 spectrophotometer in methanol solution. Infrared (ir) spectra were obtained with a Perkin-Elmer 710 infrared spectrophotometer, as liquid films or in chloroform solution. Nuclear magnetic resonance (^{1}Hnmr) spectra were obtained with Varian T-60, HA-100 and/or XL-100 spectrometers, in deuterochloroform solution, with tetramethylsilane as internal standard. Low resolution mass spectra were recorded with a Varian/MAT CH4B mass spectrometer. High resolution mass spectra were recorded with a Kratos/AEI MS50 mass spectrometer. Microanalyses were performed by M.P. Borda, Microanalytical Laboratory, University of British Columbia, Vancouver. Analytical gas liquid chromatography (glc) was performed on a Hewlett Packard HP5830A Gas Chromatography unit connected to a HP18850A GC terminal. The following columns were used: (A) 6 ft x 0.125 in., 5% OV-210 on HP chromosorb w (80-100 mesh); (B) 6 ft x 0.125 in., 5% OV-17 on HP chromosorb w (80-100 mesh). Preparative gas liquid chromatography was performed on a Varian Aerograph Model 90-P gas chromatograph, using the following columns: (C) 10 ft x 0.25 in., 10% OV-210 on chromosorb w (60-80 mesh); (D) 10 ft x 0.25 in., 10% OV-17 on chromosorb w (60-80 mesh); (E) 10 ft x 0.25 in., 15% Versamide 900 on chromosorb w (60-80 mesh).

All reactions involving organocopper reagents were performed in

three-necked round-bottomed flasks equipped with a serum stopper, an argon inlet tube, and a glass-covered magnetic stirring bar. Prior to the introduction of solvent or any reagent, the apparatus was dried with a bunsen flame while being evacuated and was then filled with argon. A slight positive pressure of argon was maintained throughout the reaction.

Starting Materials and Reagents

Solutions of methyllithium in ether, ethyllithium in benzene, n-butyllithium in hexane, s-butyllithium in cyclohexane, t-butyllithium in pentane and phenyllithium in benzene were obtained from Alfa Inorganics Inc., and were standardized by the procedure of Gilman et al.[157] Vinyllithium, which is no longer commercially available, was prepared as follow.[158] To a stirred solution of tetravinyltin[159] (6.8 g, 30 mmol) in pentane (150 ml) in a flame-dried 500 ml three-necked flask equipped with a mechanical stirrer and an argon inlet tube was added via a syringe a solution of n-butyllithium in hexane (2.1M, 28.6 ml, 60 mmol) over a period of 10 min. The solution was concentrated by blowing a rapid stream of argon across the surface of the solution for 40 min. The precipitated vinyllithium was filtered under argon, washed twice with pentane and dissolved in 80 ml of anhydrous ether. The solution was then standardized by the procedure of Gilman et al.[157]

Commercial samples of cuprous iodide and cuprous bromide were purified by dissolving them in a saturated aqueous solution of the appropriate halide (potassium iodide or potassium bromide, respectively) followed by treatment of the solution with charcoal, filtration and dilution with water to reprecipitate the copper(I)halide.[160] Phenylthiocopper was prepared by refluxing a mixture of cuprous oxide (9g, 60 mmol) and thiophenol (16g, 136 mmol) in

absolute ethanol (500ml) for seven days.[161] The bright yellow solid phenylthiocopper obtained by filtration of the resultant mixture was washed thoroughly with ethanol and then dried under vacuum. The yield was essentially quantitative.

Anhydrous ether, obtained from Mallinckodt Ltd., was used from freshly opened 1 lb cans without further treatment. Tetrahydrofuran was distilled from lithium aluminum hydride immediately prior to use. Pyridine and triethylamine were distilled from potassium hydroxide and stored over potassium hydroxide. Acetonitrile was distilled from phosphorous pentoxide.

General Procedure for the Preparation of Lithium Dialkylcuprates[162]

To a slurry of cuprous iodide (572 mg, 3 mmol) in cold (temperature varies with different cuprates) dry ether (25 ml) was added a solution of the appropriate commercial alkyllithium reagent (6 mmol). The resulting mixture was stirred at the appropriate temperature for 30 to 60 min (temperature and time vary with different cuprates, see ref. 162 for details). A solution containing 3 mmol of the appropriate lithium dialkylcuprate resulted.

General Procedure for the Preparation of Lithium Phenylthio(alkyl or aryl)cuprates[161]

To a suspension of phenylthiocopper (726 mg, 4.2 mmol) in cold (-20°C) tetrahydrofuran (25 ml) was added a solution of the appropriate alkyl- or aryllithium reagent (4.2 mmol). The mixture was stirred at -20°C (0°C when methyllithium was used) for 30 min. A solution containing 4.2 mmol of the appropriate lithium phenylthio(alkyl or aryl)cuprate resulted.

General Procedure for the Reaction of Lithium Phenylthiolalkyl(or aryl)cuprates with Pyridine in the Presence of Methyl Chloroformate.

To a cold (-78°C) stirred solution of the appropriate lithium phenylthio(alkyl or aryl)cuprate (4.2 mmol) in about 30 ml of tetrahydrofuran (under argon) was added 3 mmol (237 mg) of pyridine. A solution of methyl chloroformate (3 mmol) in tetrahydrofuran (25 ml) was added dropwise over a period of 15 min. The resulting mixture was stirred at -78°C for the appropriate time, warmed to an appropriate temperature and stirred for an additional length of time. Methanol (3 ml) and ether (15 ml) was added to the reaction mixture, the latter was stirred for a few seconds, and then filtered through a short column (4 cm diameter) of florisil (35 g, 60-80 mesh). The column was eluted with an additional 350 ml of ether. Evaporation of the ether, followed by distillation of the residual oil (air bath) gave the final products.

Reaction of Lithium Phenylthio(methyl)cuprate with Pyridine in the Presence of Methyl Chloroformate.

Following the general procedure outlined above, 4.2 mmol of lithium phenylthio(methyl)cuprate was allowed to react with 3 mmol of pyridine and 3 mmol of methyl chloroformate at -78°C for 1h, and at 0°C for an additional 2h. Normal work-up followed by distillation (air-bath temperature ∿50°C, 0.1 Torr) of the crude product afforded 241 mg (52%) of 1-carbomethoxy-4-methyl-1,4-dihydropyridine 123a. This material was pure by glc analysis (column A, 90°C) and exhibited ir (film) ν_{max} 1730, 1690, 1630 cm^{-1}; ^{1}Hnmr, τ3.25 (d, 2H, =C<u>H</u>-N-C<u>H</u>=, J=8Hz), 5.17 (d of d, 2H, =C<u>H</u>-CH(CH_3)-C<u>H</u>=, J=8Hz, J'=3.5 Hz), 6.20 (s, 3H, $-CO_2\underline{CH_3}$), 7.00 (m, 1H, -C<u>H</u>(CH_3)), 8.93 (d, 3H, -CH($\underline{CH_3}$), J=7 Hz). Mol. Wt. Calcd. for

$C_8H_{11}NO_2$: 153.0789. Found (high resolution mass spectrometry): 153.0760. A fair amount of high boiling oil remained after all the 1-carbomethoxy-4-methyl-1,4-dihydropyridine had been distilled. The ^{1}Hnmr of this material indicated that a major component of this material could be the dimer 134,[163] but this material was not investigated further.

Reaction of Lithium Phenylthio(ethyl)cuprate with Pyridine in the Presence of Methyl Chloroformate.

Following the general procedure outlined above, 4.2 mmol of lithium phenylthio(ethyl)cuprate was allowed to react with pyridine (3 mmol) and methyl chloroformate (3 mmol) at -78°C for 3h. The reaction was then quenched with methanol. Normal work-up followed by distillation (air-bath temperature ∿50°C, 0.2 Torr) of the crude oil afforded 400 mg of a colorless oil. A glc analysis of this material (column A, 90°C) showed the presence of one major component (88%) and a minor one (11%). The major component was shown to be 1-carbomethoxy-4-ethyl-1,4-dihydropyridine 123b (70% yield). An analytical sample of the latter, obtained by preparative glc (column C, 110°C), exhibited ir (film) ν_{max} 1727, 1690, 1636 cm^{-1}; ^{1}Hnmr, τ3.20 (d, 2H, =C<u>H</u>-N-C<u>H</u>=, J=8 Hz), 5.17 (d of d, 2H, =C<u>H</u>-CH(CH_3)-C<u>H</u>)=, J=8 Hz, J'=3.5 Hz), 6.20 (s, 3H, $-CO_2\underline{CH_3}$), 7.13 (m, 1H, $-\underline{CH}(CH_2CH_3)$), 8.75 (m, 2H, $-\underline{CH_2}CH_3$), 9.14 (t, 3H, J=7.0 Hz). Mol. Wt. Calcd. for $C_9H_{13}NO_2$: 167.0946. Found (high resolution mass spectrometry) :167.0909.

An analytical sample of the minor component was also obtained by preparative glc (column C, 110°C) and was shown to be methyl phenylthioformate 133. An authentic sample of this compound was prepared by the

reaction of thiophenol and methyl chloroformate in the presence of aqueous sodium hydroxide.[164] Comparison of the ^{1}Hnmr spectra of the authentic material with that of the same material isolated from the reaction mixture and a glc coinjection analysis of the authentic material with the same material isolated from the reaction mixture confirmed the identity of the minor component.

Reaction of Lithium Phenylthio(n-butyl)cuprate with Pyridine in the Presence of Methyl Chloroformate.

Following the general procedure outlined above, 4.2 mmol of lithium phenylthio(n-butyl)cuprate was allowed to react with pyridine (3 mmol) and methyl chloroformate (3 mmol) at -78°C for 3h. Normal work-up followed by distillation (air-bath temperature ∿80°C, 0.2 Torr) of the crude oil afforded 444 mg of colorless oil. A glc analysis of this material (column A, 110°C) indicated that it was a mixture of 1-carbomethoxy-4-n-butyl-1,4-dihydropyridine 123c (86%) and methyl phenylthioformate (14%). An analytical sample of the former, obtained by preparative glc (column C, 110°C), exhibited ir (film) ν_{max} 1730, 1693, 1633 cm^{-1}; ^{1}Hnmr, τ3.20 (d, 2H, =CH-N-CH=, J=8 Hz), 5.13 (dof d, 2H, =CH-CH(n-Bu)-CH=, J=8 Hz, J'=3.5 Hz), 6.20 (s, 3H, $-CO_2CH_3$), 7.05 (m, 1H, -CH(n-Bu), 8.68 (unresolved m, 6H, $-CH-CH_2CH_2CH_2-$), 9.12 (unresolved m, 3H, $-CH_2-CH_3$); yield, 65%. Mol. Wt. Calcd. for $C_{11}H_{17}NO_2$: 195.1253. Found (high resolution mass spectrometry): 195.1259.

Reaction of Lithium Phenylthio(s-butyl)cuprate with Pyridine in the Presence of Methyl Chloroformate.

Following the general procedure outlined above, lithium phenylthio(s-butyl)cuprate (4.2 mmol) was allowed to react with pyridine (3 mmol) and

methyl chloroformate (3 mmol) at -78°C for 1h, and at 0°C for an additional 2h. Normal work-up followed by distillation (air-bath temperature ∿75°C, 0.1 Torr) of the crude oil afforded 519 mg of a colorless oil. A glc analysis (column C, 155°C) of this material indicated that it was a mixture of 1-carbomethoxy-4-s-butyl-1,4-dihydropyridine 123d (89%) and methyl phenylthioformate (11%). An analytical sample of the former, obtained by preparative glc (column C, 155°C), exhibited ir (film) ν_{max} 1730, 1690, 1632 cm^{-1}; ^{1}Hnmr, τ3.15 (d, 2H, =CH-N-CH=, J=8 Hz), 5.22 (d of d, 2H, =CH-CH(s-Bu)-CH=, J=8 Hz, J'=3.5 Hz), 6.20(s, 3H, $-CO_2CH_3$), 7.02 (m, 1H, -CH(s-Bu)). The yield of 123d was 80%. Mol. Wt. Calcd. for $C_{11}H_{17}NO_2$: 195.1255. Found (high resolution mass spectrometry): 195.1250.

Reaction of Lithium Phenylthio(t-butyl)cuprate with Pyridine in the Presence of Methyl Chloroformate

Following the general procedure outlined above, lithium phenylthio(t-butyl)cuprate (4.2 mmol) was allowed to react with pyridine (3 mmol) and methyl chloroformate (3 mmol) at -78°C for 1h, warmed to -20°C and stirred for an additional 1h. Normal work-up followed by distillation (air-bath temperature ∿80°C, 0.2 Torr) of the crude oil afforded 273 mg of colorless oil. A glc analysis (column A, 110°C) of this material showed the presence of two components in the ratio of approximately 1:1. An analytical sample of each component was obtained by preparative glc (column C, 150°C). One of the components was shown to be 1-carbomethoxy-4-t-butyl-1,4-dihydropyridine 123e (∿26% yield) and it exhibited ir (film) ν_{max} 1730, 1690, 1635 cm^{-1}; ^{1}Hnmr, τ3.22 (d, 2H, =CH-N-CH=, J=8 Hz), 5.12 (d of d, 2H, =CH-CH-CH=,

J=8 Hz, J'-4 Hz), 6.26 (s, 3H, $-CO_2\underline{CH_3}$), 7.40 (m, 1H, $-\underline{CH}$(t-Bu)), 9.18 (s, 9H, $-C(\underline{CH_3})_3$).

The ^{1}Hnmr data obtained from the other component indicated that it could be a mixture of methyl phenylthioformate 133 and methyl 2,2-dimethylpropionate 135, but this material was not investigated further.

Reaction of Lithium Phenylthio(phenyl)cuprate with Pyridine in the Presence of Methyl Chloroformate.

Following the general procedure outlined above, lithium phenylthio-(phenyl)cuprate (4.2 mmol) was allowed to react with pyridine (3 mmol) and methyl chloroformate (3 mmol) at -20°C for 30 min, and at room temperature for an additional 20h. Normal work-up, followed by fractional distillation of the crude oil gave two fractions. Fraction one (air-bath temperature up to 95°C, 0.1 Torr) contained a complex mixture of hydrocarbons (250 mg). There was no carbonyl nor C-N absorption in the ir spectrum of this material. Comparison of the ^{1}Hnmr spectra of this material with that of an authentic sample of biphenyl showed that the major constituent of this material could be biphenyl. This was confirmed by a glc coinjection analysis involving a pure sample of biphenyl and the above mixture. This material was not investigated further. Fraction two (air bath temperature ~120°C, 0.1 Torr) was pure 1-carbomethoxy-4-phenyl-1,4-dihydropyridine 123f (152 mg, 24% yield). This material exhibited ir (film) ν_{max} 1725, 1690, 1632 cm^{-1}; ^{1}Hnmr, τ2.79 (m, 5H, phenyl), 3.12 (d, 2H, $=\underline{CH}-\underline{N}-\underline{CH}=$, J=8 Hz), 5.07 (d of d, 2H, $=\underline{CH}-CH(\text{phenyl})\underline{CH}=$, J=8 Hz, J'=3.5 Hz), 5.90 (m, 1H, $-\underline{CH}$-phenyl), 6.22 (s, 3H, $-CO_2\underline{CH_3}$). Mol. Wt. Calcd. for $C_{13}H_{13}NO_2$: 215.0943. Found (high resolution mass spectrometry): 215.0931.

Preparation of Lithium Divinylcuprate-Dimethyl Sufide Complex ($(\rightleftharpoons)_2CuLi\cdot Me_2S$)[165] and its Reaction with Pyridine in the Presence of Methyl Chloroformate.

To a cold (-50°C) solution of $Me_2S\cdot CuBr$ (615 mg, 3 mmol) in ether (5 ml) and dimethyl sulfide (4 ml) was added a solution of vinyllithium in ether (10 ml, 0.6 M, 6 mmol). The resulting solution was stirred at -50°C for 15 min. To this solution was added 2.5 mmol (198 mg) of pyridine followed by the dropwise addition of a solution of methyl chloroformate (15 mmol) in ether (10 ml) over a period of 15 min. The resulting black solution was stirred at -50°C for 2h, warmed to 0°C and stirred for an additional 30 min. This solution was then filtered through a short column of florisil (35 g, 60-80 mesh). The column was eluted with an additional 300 ml of ether. Evaporation of solvent and distillation (air-bath temperature ∿50°C, 0.1 Torr) of the residual oil afforded 253 mg (61%) of a colorless oil. A glc analysis (column A, 100°C) of this material indicated that it was a mixture of 1-carbomethoxy-4-vinyl-1,4-dihydropyridine 123g and 1-carbomethoxy-2-vinyl-1,2-dihydropyridine 124g in the ratio of ca. 1:1. An analytical sample of each compound was obtained by preparative glc (column C, 130°C). The former exhibited ir (film) ν_{max} 1730, 1690, 1635 cm^{-1}; ^{1}Hnmr, τ3.19 (d, 2H, =CH-N-CH=, J=8 Hz) 3.9-4.40 (m, 1H, $\begin{matrix}H\\H\end{matrix}\!\!>\!\!=\!\!<\!\!H$), 4.84-5.26 (diffuse, 4H, =CH-CH(vinyl)CH= and $\begin{matrix}H\\H\end{matrix}\!\!>\!\!=\!\!<\!\!H$), 6.20 (s, 3H, $-CO_2CH_3$), 6.42 (m, 1H, =CH-CH-CH=). Mol. Wt. Calcd. for $C_9H_{11}NO_2$:165.0790. Found (high resolution mass spectrometry): 165.0790.

The latter exhibited ir (film) ν_{max} 1720, 1645, 1585 cm^{-1}; ^{1}Hnmr τ3.27 (d, 1H, =CH-N-, J=7 Hz), 3.91-4.99 (diffuse, 7H), 6.21 (s, 3H, $-CO_2CH_3$); Mol. Wt. Calcd. for $C_9H_{11}NO_2$: 165.0790. Found (high resolution mass spectrometry): 165.0790.

Reaction of Lithium Diphenylcuprate with Pyridine in the Presence of Methyl Chloroformate.

To a solution of lithium diphenylcuprate (6 mmol prepared from cuprous bromide and phenyllithium[140]) in anhydrous ether (25 ml) at -78°C under an atmosphere of argon was added 5 mmol of pyridine. A solution of methyl chloroformate (20 mmol) in ether (25 ml) was added dropwise over a period of 15 min. The resulting mixture was stirred at -78°C for 1h, warmed to 0°C and then stirred for an additional 1.25h. Florisil (3 g) was added to the reaction mixture, the latter was stirred for a few seconds, and then filtered through a short column of florisil (35 g). The column was eluted with an additional 350 ml of ether. Evaporation of the ether, followed by fractional distillation (air-bath) of the residual oil gave two fractions. The first fraction (air-bath temperature up to 110°C, 0.2 Torr) was a complex mixture. ^{1}Hnmr of this material showed that the major component in this mixture was probably biphenyl, but this was not investigated further. The second fraction (air-bath temperature ∿125°C, 0.2 Torr; 897 mg, 89% yield) was shown by glc analysis (column C, 170°C), to be a mixture of 1-carbomethoxy-4-phenyl-1,4-dihydropyridine 123f and 1-carbomethoxy-2-phenyl-1,2-dihydropyridine 124f in the ratio of 84:16. Analytical samples of each compound was obtained by preparative glc (column C, 180°C). Spectral data (^{1}Hnmr, ir) of the former was identical with that of authentic material prepared earlier by M. Soucy.[128] The very small amount of the latter obtained exhibited ir (film) ν_{max} 1720, 1645, 1590 cm^{-1}; ^{1}Hnmr, τ2.30-3.00 (5H, m, phenyl), 3.0-3.37 (m, 1H,), 4.0-4.94 (m, 4H), 6.28 (s, 3H, $-CO_2\underline{CH_3}$).

Reaction of Lithium Dialkylcuprates with Pyridine in the Presence of Acetyl Bromide.

General Procedure

To a solution of the appropriate lithium dialkylcuprate (6 mmol) in dry ether (25 ml) at -78°C under an atmosphere of argon was added 5 mmol of pyridine. A solution of acetyl bromide (20 mmol) in dry ether (25 ml) was added dropwise over a period of 15 min. The resulting mixture was stirred at -78°C for 30 min, warmed to 0°C and then stirred for an additional 30 min. Florisil (3 g) was added to the reaction mixture. The latter was stirred for a few seconds, and then filtered through a short column of florisil (35 g). The column was eluted with an additional 350 ml of ether. Evaporation of the ether, followed by distillation of the residual oil gave the corresponding 1-acetyl-4-alkyl-1,4-dihydropyridine.

Reaction of Lithium Dimethylcuprate with Pyridine in the Presence of Acetyl Bromide.

Following the general procedure outlined above, 6 mmol of lithium dimethylcuprate was allowed to react with 5 mmol of pyridine and 20 mmol of acetyl bromide. Normal work-up followed by distillation (air bath temperature ~65°C, 0.1 Torr) of the crude oil afforded 404 mg (59%) of a colorless oil. A glc analysis (column C, 140°C) of this material showed that it was pure 1-acetyl-4-methyl-1,4-dihydropyridine 137a and it exhibited ir (film) ν_{max} 1680, 1637 cm^{-1}; ^{1}Hnmr, τ2.90 (d, 1H, =CH-N-, J=9 Hz), 3.52 (d, 1H, =CH-N-, J=9 Hz), 5.10 (m, 2H, =CH-CH-CH=), 7.00 (m, 1H, -CH(CH_3)), 7.85 (s, 3H, -$COCH_3$), 8.90 (d, 3H, -CH-CH_3, J=7 Hz). Mol. Wt. Calcd. for $C_8H_{11}NO$: 137.0840. Found (high resolution mass

spectrometry): 137.0836. None of the corresponding 1,2-dihydropyridine derivative was detected.

Reaction of Lithium Diethylcuprate with Pyridine in the Presence of Acetyl Bromide.

Following the general procedure outlined before, 6 mmol of lithium diethylcuprate was allowed to react with 5 mmol of pyridine in the presence of 20 mmol of acetyl bromide. Normal work-up, followed by distillation (air-bath temperature ∿85°C, 0.2 Torr) of the crude oil gave 386 mg (51%) of a colorless liquid. A glc analysis (column C, 145°C) of this material showed that it was pure 1-acetyl-4-ethyl-1,4-dihydropyridine and it exhibited ir (film) ν_{max} 1670, 1625 cm^{-1}; ^{1}Hnmr, τ2.87 (d, 1H, =C<u>H</u>-N-, J=9 Hz), 3.48 (d, 1H, =C<u>H</u>-N-, J=9 Hz), 5.13 (m, 2H, =C<u>H</u>-CH-C<u>H</u>=), 7.13 (m, 1H, -C<u>H</u>(CH_2CH_3)), 7.99 (s, 3H, -CO<u>CH_3</u>), 8.37-8.77 (m, 2H, -CH(<u>CH_2</u>CH_3)), 9.16 (t, 3H, -CH(CH_2<u>CH_3</u>)). <u>Mol. Wt.</u>Calcd. for $C_9H_{13}NO$: 151.0997. Found (high resolution mass spectrometry): 151.0993. None of the corresponding 1,2-dihydropyridine derivative was detected.

Reaction of Lithium Di-n-butylcuprate with Pyridine in the Presence of Acetyl Bromide.

Following the general procedure outlined above, 6 mmol of lithium di-<u>n</u>-butylcuprate was allowed to react with 5 mmol of pyridine in the presence of 20 mmol of acetyl bromide. Normal work-up, followed by distillation (air-bath temperature ∿110°C, 0.1 Torr) of the crude oil gave 653 mg (73%) of a colorless liquid. A glc analysis (column C, 140°C) of this material showed that it was pure 1-acetyl-4-<u>n</u>-butyl-1,4-dihydropyridine and it exhibited ir (film) ν_{max} 1675, 1632 cm^{-1}; ^{1}Hnmr, τ2.83 (d, 1H, =C<u>H</u>-N-, J=9 Hz), 3.46 (d, 1H, -N-CH=, J=9 Hz), 5.05 (m, 2H, =C<u>H</u>-CH-C<u>H</u>=),

7.05 (m, 1H, -C<u>H</u>(<u>n</u>-Bu)), 7.83 (s, 3H, -CO<u>CH$_3$</u>), 8.45-8.90 (diffuse, 6H, -CH(<u>CH$_2$CH$_2$CH$_2$CH$_3$</u>)), 9.10 (t, 3H, -(CH$_2$)$_3$<u>CH$_3$</u>, J=7 Hz). <u>Mol. Wt.</u> Calcd. for $C_{11}H_{17}NO$: 179.1309. Found (high resolution mass spectrometry): 179.1307. None of the corresponding 1,2-dihydropyridine derivative was detected.

<u>Synthesis of 1-Trimethylsilyl-4-n-butyl-1,4-dihydropyridine and its Conversion into 4-n-Butylpyridine</u>

To a cold solution of lithium di-<u>n</u>-butylcuprate (6 mmol) in dry ether (25 ml) at -78°C under an atmosphere of argon was added 5 mmol of pyridine. A solution of chlorotrimethylsilane (702 mg, 6.5 mmol) in ether (25 ml) was added dropwise over a period of 15 min. The resulting mixture was stirred at -78°C for 2h, warmed to 0°C and then stirred for an additional 30 min. Florisil (3 g) was added to the reaction mixture, the latter was stirred for a few seconds, and then filtered through a short column of florisil (35 g). The column was eluted with an additional 350 ml of ether. Evaporation of the ether afforded 520 mg of crude product. A glc analysis (column A, 110°C) of this material indicated the presence of two components in the ratio of ca. 1:1 ^{1}Hnmr indicated that this material was a mixture of 1-trimethylsily-4-<u>n</u>-butyl-1,4-dihydropyridine <u>138</u> and 4-<u>n</u>-butyl-pyridine. The presence of 4-<u>n</u>-butylpyridine in the mixture was confirmed by comparing the ^{1}Hnmr spectrum of the mixture with the ^{1}Hnmr of an authentic sample of 4-<u>n</u>-butylpyridine. The ^{1}Hnmr spectrum of the product mixture was interpreted as follows: τ1.52 (d of d, J=5 Hz, J'=2 Hz, protons at C-2 and C-6 of 4-<u>n</u>-butylpyridine), 2.89 (d of d, J=5 Hz, J'=2 Hz, protons at C-3 and C-5 of 4-<u>n</u>-butylpyridine), 7.40 (t, J=7 Hz, <u>CH$_2$</u>(CH$_2$)CH$_3$,

4-n-butylpyridine), 4.07 (d, J=8 Hz, protons at C-2 and C-6 of the dihydropyridine 138), 5.57 (d of d, J=8 Hz, J'=3.5 Hz, protons at C-3, C-5 of the dihydropyridine 138), 3.00 (m, proton at C-4 of the dihydropyridine 138).

Because of the instability of the dihydropyridine 138, this material was not isolated for characterization. Instead, the crude product mixture obtained above was subjected to oxidation. The crude mixture was dissolved in 20 ml of dry ether. This solution was cooled to -78°C under an atmosphere of argon. A solution of 0.1% potassium hydroxide in methanol (1.5 ml) was added. The mixture was stirred for 10 min, and a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.25 g, 5.5 mmol) in tetrahydrofuran (25 ml) was added dropwise over a period of 10 min. The resulting mixture was warmed to 0°C, stirred for 2h at that temperature, warmed to room temperature and then stirred for an additional 1h. The product mixture was poured into an aqueous solution of sodium hydroxide (10%, 60 ml). The aqueous layer was extracted thoroughly with ether. The combined ether extracts were dried over anhydrous magnesium sulfate. Removal of solvent followed by distillation (air-bath temperature ∿95°C, 16 Torr) of the residual oil afforded 233 mg (33%) of pure 4-n-butylpyridine, [lit. bp. 84°C, 8 Torr].[154,155,166] This material exhibited ir (film) ν_{max} 1602 cm^{-1}; ^{1}Hnmr, τ1.52 (d of d, 2H, =CH-N=CH, J=5 Hz, J'=2 Hz), 2.89 (d of d,2H, =CH-C=CH, J=5 Hz, J'=2 Hz), 7.40 (t, 2H, =C-$CH_2(CH_2)_2CH_3$, J=7 Hz), 8.00-9.30 (diffuse, 7H).

Conversion of 1-Carbomethoxy-4-alkyl(or aryl)-1,4-dihydropyridines to the Corresponding 4-Alkyl(or aryl)pyridines.

A. Using p-Benzoquinone as Oxidant

Conversion of 1-Carbomethoxy-4-methyl-1,4-dihydropyridine to 4-Methylpyridine

To a cold (-5°C) solution of 1-carbomethoxy-4-methyl-1,4-dihydropyridine (306 mg, 2 mmol) in dry ether (10 ml) under an atmosphere of argon was added dropwise a solution of methyllithium (6 mmol) in ether over a period of 10 min. The resulting mixture was stirred for 15 min, and a solution of p-benzoquinone (216 mg, 2 mmol) in ether (10 ml) was added dropwise over a period of 10 min. The resulting mixture was stirred at 0°C for 1h and then poured into an ice-cold 50% aqueous solution of ammonium hydroxide (50 ml). The aqueous solution was extracted thoroughly with ether and the combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the ether, followed by distillation of the residual oil (air-bath temperature ∿65°C, 16 Torr) afforded 102 mg (55%) of pure 4-methylpyridine. A glc analysis (column E, 110°C) of this material, by coinjection with an authentic sample obtained commercially, and comparison of spectral data with that of the authentic sample confirmed the identity of this material.

Conversion of 1-Carbomethoxy-4-n-butyl-1,4-dihydropyridine to 4-n-Butylpyridine.

Following a procedure identical with that described above for 1-carbomethoxy-4-methyl-1,4-dihydropyridine, a solution of 390 mg (2 mmol) of 1-carbomethoxy-4-n-butyl-1,4-dihydropyridine in 10 ml of dry benzene was treated first with methyllithium (6 mmol) and then with p-benzoquinone (2 mmol). Normal work-up, followed by distillation (air bath temperature ∿90°C, 16 Torr) of the crude product afforded 126 mg (48%) of 4-n-butylpyridine. A glc analysis (column E, 130°C) of this material show that it was 95% pure. Spectral data (ir, ^{1}Hnmr) of this material was identical with the authentic material prepared earlier.

B. Using Tetrachloro-1,4-benzoquinone as Oxidant

Conversion of 1-Carbomethoxy-4-n-butyl-1,4-dihydropyridine to 4-n-Butylpyridine

To a cold (-5°C) solution of 1-carbomethoxy-4-n-butyl-1,4-dihydropyridine (195 mg, 1 mmol) in dry benzene (10 ml) was added a solution of methyllithium (3 mmol) in ether. The resulting mixture was stirred for 15 min. A solution of tetrachloro-1,4-benzoquinone (246 mg, 1 mmol) in benzene (20 ml) was added dropwise over a period of 15 min. The resulting mixture was refluxed for 3.5h, cooled to room temperature and then poured into an ice-cold 50% aqueous solution of ammonium hydroxide (80 ml). The aqueous solution was extracted thoroughly with benzene and the combined benzene extracts were dried over anhydrous magnesium sulfate. Evaporation of the benzene, followed by distillation (air-bath temperature ∿90°C, 16 Torr) of the residual oil afforded 87.7 mg (65%) of pure 4-n-butylpyridine.

C. Using 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as Oxidant. General Procedure

To a cold (-78°C) solution of the appropriate 1-carbomethoxy-4-alkyl(or aryl)-1,4-dihydropyridine (2 mmol) in tetrahydrofuran (10 ml) under an atmosphere of argon was added dropwise a solution of methyllithium (6 mmol) in ether over a period of 10 min. The resulting mixture was allowed to stir at -78°C for 45 min. A solution of DDQ (500 mg, 2.2 mmol) in tetrahydrofuran (10 ml) was added dropwise over a period of 10 min. The resulting mixture was stirred at -78°C for 2h, warmed to room temperature and then stirred for an additional 1h. The reaction mixture was poured into an ice

cold 10% aqueous solution of sodium hydroxide (60 ml). The aqueous solution was extracted thoroughly with ether. The combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent followed by distillation (air-bath, 16 Torr) of the residual oil gave the corresponding 4-alkyl(or aryl)pyridine.

Conversion of 1-Carbomethoxy-4-methyl-1,4-dihydropyridine to 4-Methylpyridine

Following the general procedure outlined above, 306 mg (2 mmol) of 1-carbomethoxy-4-methyl-1,4-dihydropyridine was allowed to react first with 6 mmol of methyllithium and then with 2.2 mmol of DDQ. Normal work-up, followed by distillation (air-bath temperature ∿65°C, 16 Torr) of the crude oil gave 108 mg (58%) of pure 4-methylpyridine.

Conversion of 1-Carbomethoxy-4-ethyl-1,4-dihydropyridine to 4-Ethylpyridine

Following the general procedure outlined above, 334 mg (2 mmol) of 1-carbomethoxy-4-ethyl-1,4-dihydropyridine was allowed to react first with 6 mmol of methyllithium and then with 2.2 mmol of DDQ. Normal work-up, followed by distillation (air-bath temperature ∿65°C, 16 Torr) of the residual oil afforded 190 mg (89%) of 4-ethylpyridine. Comparison of the spectral data obtained from the product with that of the commercially available authentic sample and a coinjection experiment involving glc (column E, 100°C) confirmed the identity.

Conversion of 1-Carbomethoxy-4-n-butyl-1,4-dihydropyridine to 4-n-Butylpyridine

Following the general procedure outlined above,390 mg (2 mmol) of 1-carbomethoxy-4-n-butyl-1,4-dihydropyridine was allowed to react first with 6 mmol of methyllithium and then with 2.2 mmol of DDQ. Normal work-up, followed by distillation (air-bath temperature ∿90°C, 16 mm) of the residual

oil afforded 197 mg (73%) of pure 4-n-butylpyridine.

Conversion of 1-Carbomethoxy-4-s-butyl-1,4-dihydropyridine to 4-s-Butylpyridine

Following the general procedure outlined above, 390 mg (2 mmol) of 1-carbomethoxy-4-s-butyl-1,4-dihydropyridine was allowed to react first with 6 mmol of methyllithium and then with 2.2 mmol of DDQ. Normal work-up, followed by distillation (air-bath temperature ∿70°C, 36 Torr) afforded 214 mg (79%) of 4-s-butylpyridine [lit. bp 197°C, 765 Torr].[166] This material exhibited ir (film) ν_{max} 1601 cm^{-1}; ^{1}Hnmr τ1.50 (d of d, 2H, =CH-N=CH-, J=5 Hz, J'=2 Hz), 2.92 (d of d, 2H, =CH-C=CH-, J=5 Hz, J'=2 Hz), 7.10-7.77 (m, 1H, =C-CH(CH_3)(C_2H_5)), 7.83-9.00 (m, 2H, -CHCH$_2$CH$_3$), 8.77 (d, 3H, CH$_3$-CH-, J=7 Hz), 9.18 (t, 3H, -CH_2-CH$_3$, J=7 Hz).

Conversion of 1-Carbomethoxy-4-phenyl-1,4-dihydropyridine to 4-Phenylpyridine

Following the general procedure outlined above, 430 mg (2 mmol) of 1-carbomethoxy-4-phenyl-1,4-dihydropyridine was allowed to react first with 6 mmol of methyllithium and then with 2.2 mmol of DDQ. Normal work-up followed by distillation of the residual oil (air bath temperature ∿130°C, 0.5 Torr) afforded 220 mg (71%) of pure 4-phenylpyridine, mp 70-72°C [lit. mp. 69-73°C]. The spectral data (ir, ^{1}H nmr) of this material were identical with those obtained from a commercially available authentic sample.

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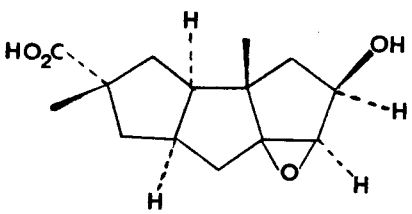
PART II

Synthesis and Thermal Rearrangement of β-Cyclopropyl-α,β-unsaturated Ketones and Related Compounds

INTRODUCTION

I. General

The occurrence of five-membered rings in an increasing number of natural products of biological importance has recently stimulated the development of a wide variety of new synthetic methods for the preparation of cyclopentane rings. For example, the antibiotic sesquiterpenes hirsutic acid 1[1] and coriolin 2[2], the lipophilic antibiotic pentalenolactone 3[3], the sesterterpene retigeranic acid 4[4], the tricyclic sesquiterpenes capnellane 5[5] and zizaene 6[6], all contain two or more fused cyclopentane rings.



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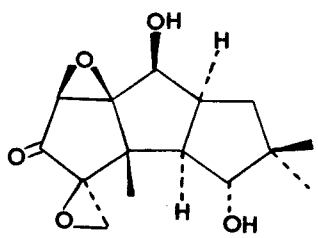

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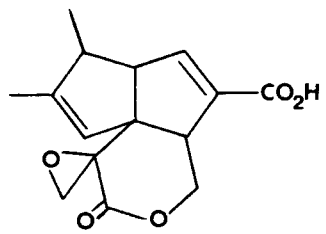

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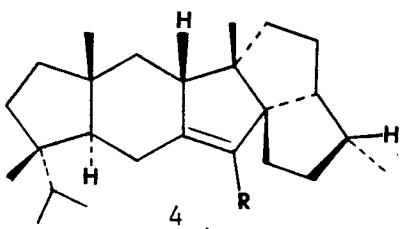

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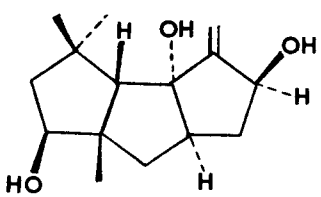

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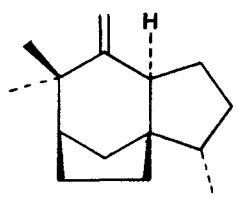


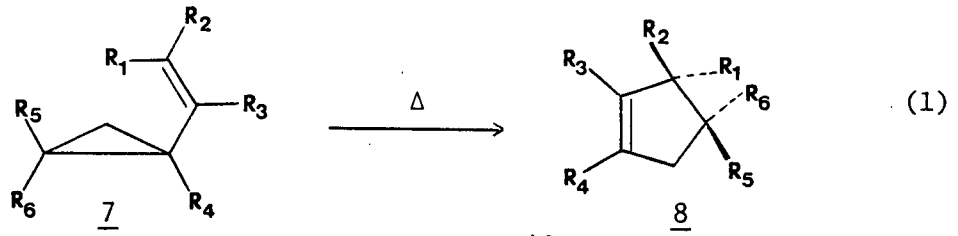
6

Most of the more recently developed methods for constructing cyclopentane rings are based on intramolecular ring closure of acyclic precursors.[7-15] A few novel methods that involve ring contraction[16-18] and ring expansion[19-20] of cyclic compounds have been reported. Cycloaddition reactions have also been employed.[21-26] It was not until quite recently that the well established vinylcyclopropane-cyclopentene rearrangement[27-30] has received considerable attention as a viable and synthetically

valuable method for cyclopentane ring synthesis.

II. Vinylcyclopropane-cyclopentene Rearrangement

The thermal rearrangement of vinylcyclopropane to cyclopentene was first reported by Overberger and Borchert in 1960 (eq.1).[31] Since then, this process has received considerable attention. A wide variety of substituted vinylcyclopropanes having the general structure 7 have been thermally rearranged to cyclopentenes of tne general structure 8 (eq. 1).[32-48]



(1)

7 8

a)[32,33] all R=H

b)[34] R_1=R_2=Me

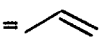
c)[35] R_2=Et

d)[36,37] R_3= X-C$_6$H$_4$-

e)[36] R_3=C≡C-C_3H_5

f)[37-39] R_1=CH_3, R_3=X-C$_6$H$_4$-

g)[38,39] R_2=CH_3, R_3=X-C$_6$H$_4$-

h)[40] R_2 =  , R_3=C≡C-C_3H_5

i)[41] R_4=CH_3

j)[42] R_4=CH_3, R_5, R_6=Cℓ

k)[42] R_5, R_6=Cℓ

l)[43] R_5=CHO

m)[44] R_5=R_6=CO_2Et

n)[45] R_2=CO_2Me, R_5 or R_6=CO_2Me

o)[46] R_3=R_4=CH_3; R_5, R_6= 

p)[47] R_5 or R_6=$N(CH_3)_2$

q)[48] R_5 or R_6=OCH_3

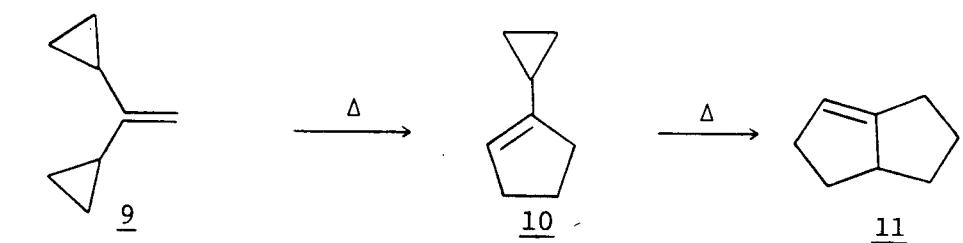
r)[48] R_4=OCH_3

s)[48] R_5 or R_6=Ph

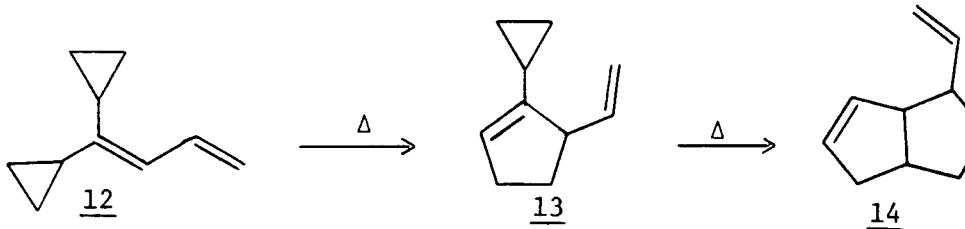
In general, the yields of isolable cyclopentene products in these reactions are fairly high, except when the cyclopropyl group is cis to a

methyl group across the double bond. For example, the rate of thermolysis of compound 7f was comparable to that of the other members of 7, but only a small amount of cyclopentene product 8f was obtained along with a large amount of polymer. It was also found that substitution in the vinylcyclopropane system, both on the ring and around the double bond, exerts considerable influence on the rate of the reaction and plays a role in determining the course of the thermal rearrangement into a cyclopentene.[27,30] These substitution effects will be discussed in more detail later on when the mechanism of the rearrangement is considered.

Stepwise vinylcyclopropane rearrangements occur in compounds 9 and 12 which give, in addition to the monocyclized products 10 and 13, the dicyclized products 11 and 14, respectively (eq. 2 and 3).[36,40] In these examples, the incorporation of a portion of the vinylcyclopropyl moiety into a cyclic structure does not interfere with the reaction. In fact, these transformations represent the first examples of cyclopentene annelation via vinylcyclopropane rearrangement.



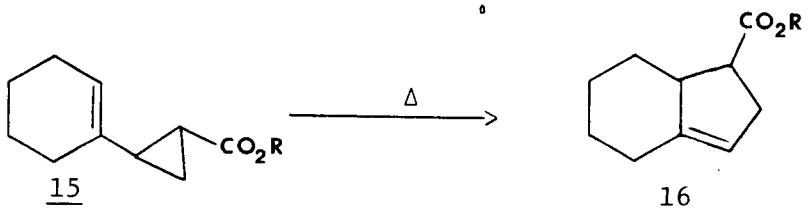
(2)



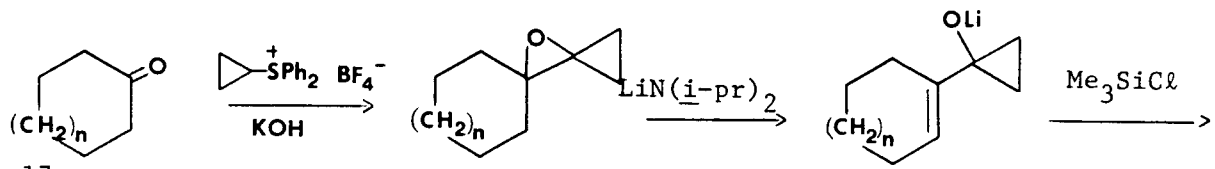
(3)

The idea of using the rearrangement of vinylcyclopropanes as a method for five membered ring annelation has been expanded recently by Stork[49],

Trost[50,51], Corey[52] and Monti[53]. By incorporating appropriate substituents on the cyclopropane ring or on the vinylic double bond, the newly constructed ring may contain a fairly wide variety of functional groups. For example, compound 15 rearranges smoothly at 360°C to the annelated cyclopentene 16 (eq.4).[49] The siloxyvinylcyclopropanes 20, which were prepared from the cycloalkanones 17 via the oxaspiropentanes 18, undergo thermal rearrangement to give the enol silyl ethers 21 in over 90% yield.[50] Hydrolysis of the enol silyl ethers 21 unmasked the carbonyl groups to give the corresponding cyclopentanones 22 (Scheme 1). The enol silyl ethers 21 may also be transformed into a specific enolate , which may then be alkylated to introduce further alkyl groups. For example, treatment of 21b with methyllithium followed by methyl iodide gave the perhydroazulene derivative 23 (eq.5).[50]

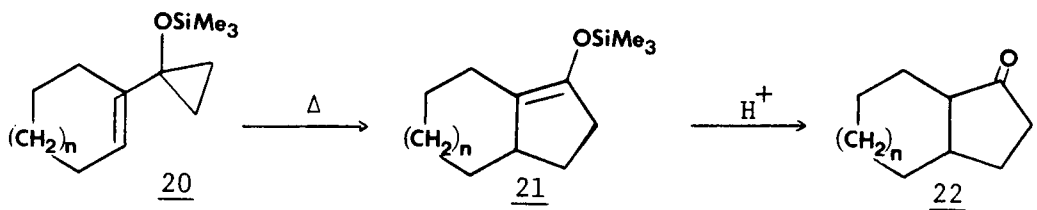


15 16 (4)



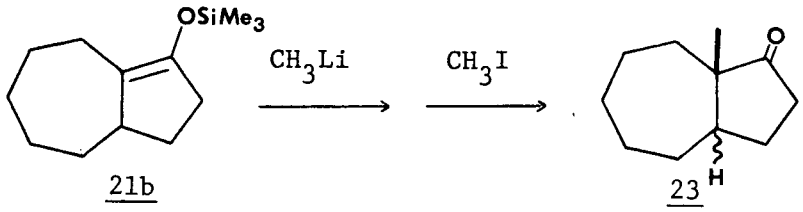
17
a) n=0
b) n=2
c) n=1

18 19



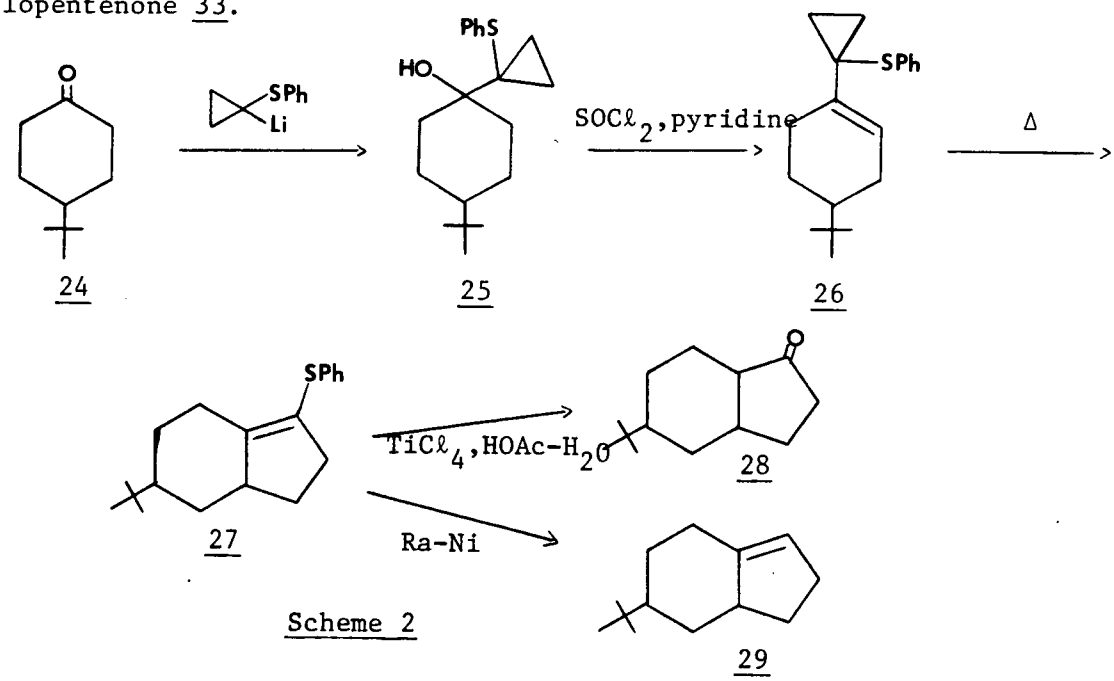
20 21 22

Scheme 1



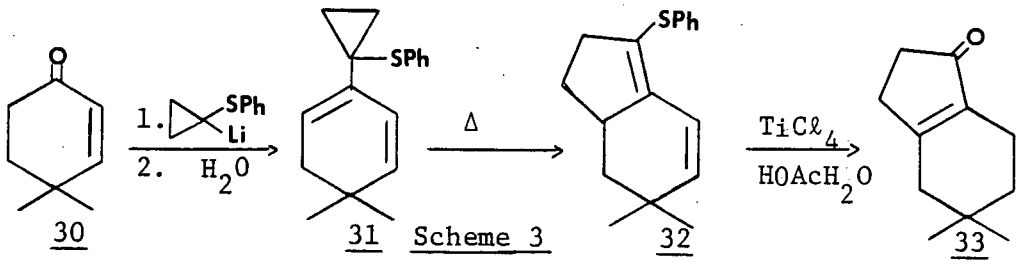
21b 23 (5)

Although this procedure was found to work quite well with saturated cycloalkanones, it failed with α,β-unsaturated cycloalkenones. Furthermore, with cyclohexanone, the yield of the siloxyvinylcyclopropane from the corresponding oxaspiropentane was fairly poor. However, these limitations could be overcome by substituting the siloxy group with a phenythio group.[51] The vinylcyclopropylphenyl sulfide 26 could be prepared by the addition of 1-lithiocyclopropylphenyl sulfide to 4-t-butylcyclohexanone 24, followed by dehydration of the resulting alcohol 25. Pyrolysis of the vinylcyclopropylphenyl sulfide 26 gave the enol thioether 27 which could be hydrolysed to the corresponding cyclopentanone 28 or desulfurized to give the cyclopentene 29 (Scheme 2).[51] Similarly, addition of 1-lithiocyclopropylphenyl sulfide to the α,β-unsaturated ketone 30, followed by dehydration of the latter gave the cyclopropylphenyl sulfide 31. Pyrolysis of this compound, followed by hydrolysis of the resulting enol thio ether 32 afforded the cyclopentenone 33.[51]



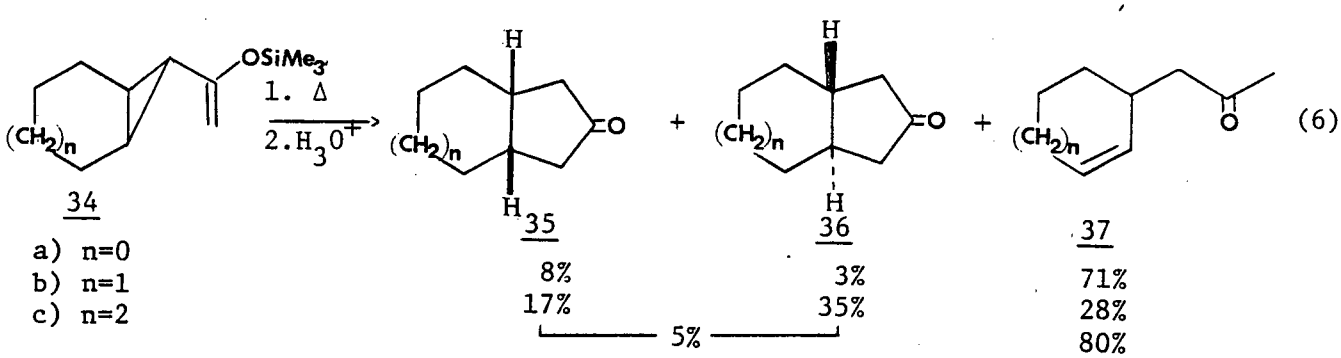
24 25 26 27 28 29

Scheme 2



30 31 Scheme 3 32 33

The last few examples mentioned above demonstrated that the thermal rearrangement of vinylcyclopropane systems which incorporate the carbon-carbon double bond in a ring afford synthetically useful yields of the corresponding cyclopentane derivatives (annelation products). Similar results have been obtained when the cyclopropane ring is fused to another cyclic structure. For example, pyrolysis of the enol silyl ethers 34, followed by hydrolysis of the rearranged products, gave the cyclopentenones 35 and 36, along with considerable amounts of 37 (eq.6).[53] However, pyrolysis of the enol silyl ethers 38, followed by hydrolysis of the resulting products, afforded in good yields the annelated cyclopentanones 39 as the only isolated products (eq.7).[53] In a similar fashion, compound 40 rearranged upon heating to afford the

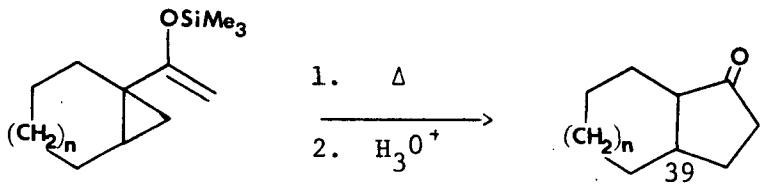


34
a) n=0
b) n=1
c) n=2

35 36 37

8% 3% 71%
17% 35% 28%
5% 80%

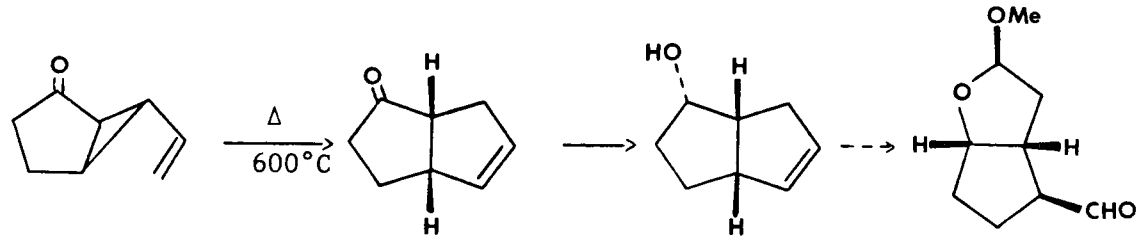
(6)



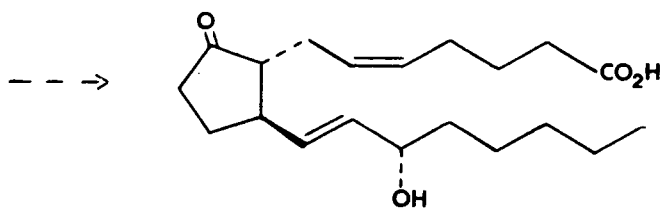
38 → 39 (7)

	Yield
a) n=0	21%
b) n=1	99%
c) n=2	85%

ketone 41. The latter was transformed into the aldehyde 43, which served as an intermediate in the synthesis of 11-deoxyprostaglandin E_2 44 (Scheme 4).[52] It is interesting to note that compound 45, the deoxo derivative of compound 40, undergoes a facile intramolecular "ene" reaction rather than the normal vinylcyclopropane rearrangement. Thus pyrolysis of compound 45 afforded the olefin 48 as the major product along with a small amount of the annelated cyclopentene 47 (eq.8).[52a] Presumably, isomerization of 45 to 46 occurred, prior to the rearrangement to 48.

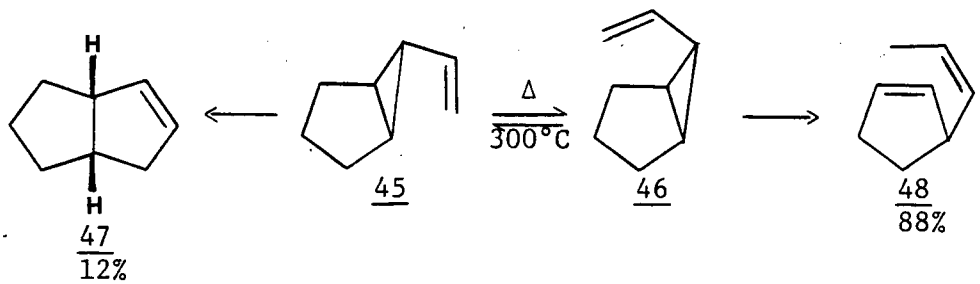


40 41 42 43



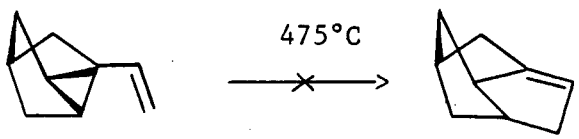
44

Scheme 4



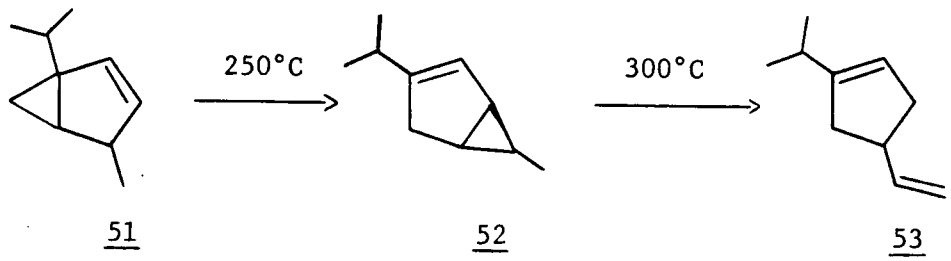
47 12% 45 46 48 88% (8)

The thermal rearrangement of vinylcyclopropane systems is unsuccessful if the product that would be produced is extraordinarily strained. For example, it was found that 1-vinylnortricyclene 49 was recovered unchanged upon heating at 475°C for 25 min.[54] If a normal vinylcyclopropane rearrangement had occurred, the resulting product (50) would have been in violation of Bredt's rule.[55]

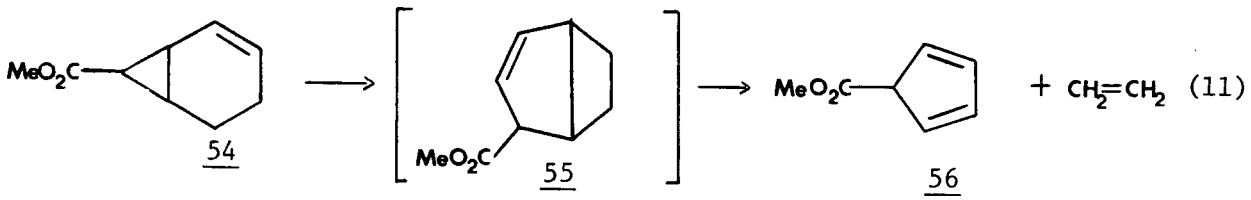


49 50 (9)

Normal vinylcyclopropane rearrangement can take place even if the entire vinylcyclopropane moiety is incorporated into a cyclic framework, provided that there is no excessive ring strain present in the rearranged product and that there is no competitive reaction taking place. For example, at 250°C, β-thujene 51 rearranged to afford a mixture of 52 and 53 while at 300°C, 53 was the only observed product (eq.10).[56] The success of this rearrangement might suggest that higher homologs would rearrange in a similar way. However, pyrolysis of 7-carbomethoxynorcar-2-ene 54 gave a complex mixture in which ethylene and carbomethoxycyclopentadiene 56 were present. Presumably, the latter were formed via the intermediate 55 (eq.11).[57]

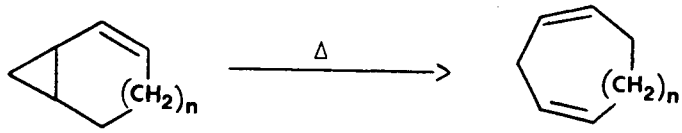


51 52 53 (10)



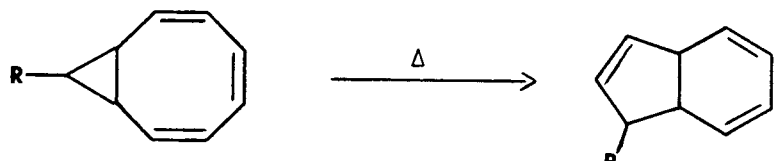
54 55 56 (11)

Pyrolysis of bicyclo[3.1.0]hex-2-ene 57a, bicyclo[5.1.0]oct-2-ene 57b and bicyclo[6.1.0]non-2-ene 57c resulted in transannular hydrogen migration to give the dienes 58a, 58b and 58c respectively, rather than undergoing the vinylcyclopropane-type rearrangement (eq.12).[58,59] The ease of transannular hydrogen migration in the bicyclo[6.1.0]nonene system could be diminished by incorporating additional unsaturation into the system. When this was done, the vinylcyclopropane-type rearrangement took place. For example, pyrolysis of the bicyclo[6.1.0]nonatrienes 59 gave the corresponding dihydroindenes 60 (eq.13).[60-64] Similarly, pyrolysis of the bicyclic unsaturated ketone 61 gave the cyclopentanone 62 as the major product (eq.14).[65]



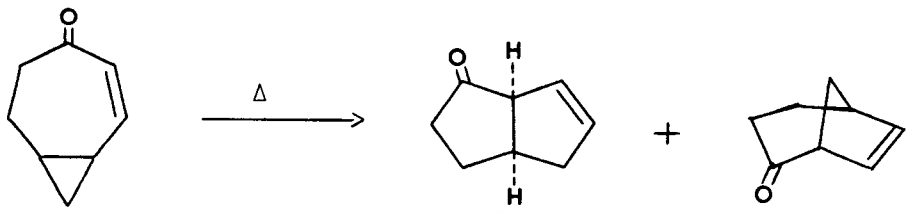
57 58 (12)

(a) n=0; (b) n=2; (c) n=3



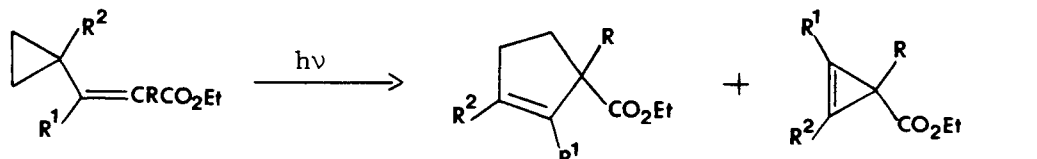
59 60 (13)

(a) R=H; (b) R=Cℓ; (c) R=CO_2Et; (d) R=CH_2OH



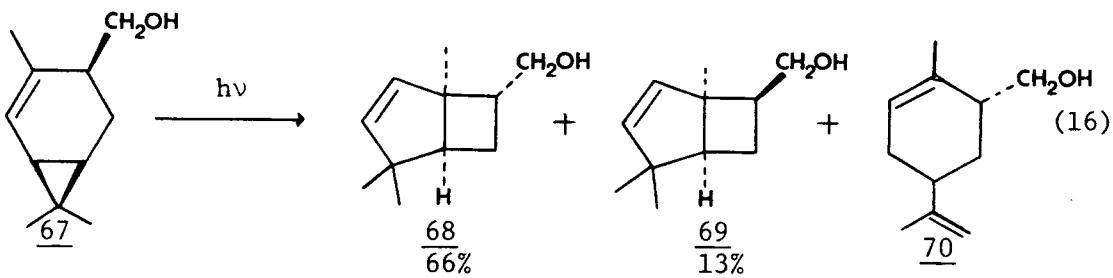
61 → 62 (51%) + 63 (24%) (14)

Vinylcyclopropane-cyclopentene rearrangements may also be effected by means other than heat. Photolysis of the vinylcyclopropane derivative 64 gave the cyclopentene 65 as the major product (eq.15).[66] Irradiation of the bicycloheptene 67 in the presence of a sensitizer gave 66% of the bicyclo[3.2.0]heptene 68 and 13% of its isomer 69 (eq.16).[67] Similarly, irradiation of the bicyclic compound 71 and 73 gave the corresponding bicyclo[3.3.0]octenes 72 and 74 respectively (eq.17 and 18).[68]

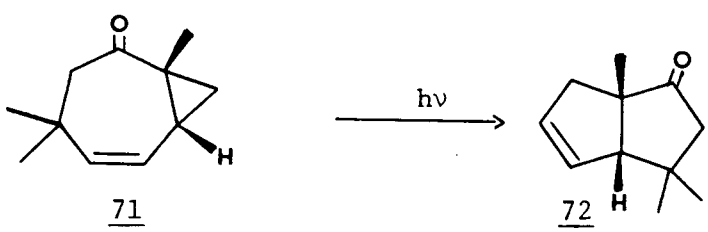


(15)

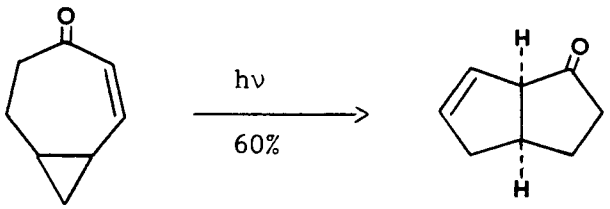
	64	65	66	Yield
a)	R=H, $R^1=R^2=CH_3$	60%	40%	60%
b)	$R=R^2=H$, $R^1=c\text{-}C_3H_5$	88%	trace	67%



67 → 68 (66%) + 69 (13%) + 70 (16)



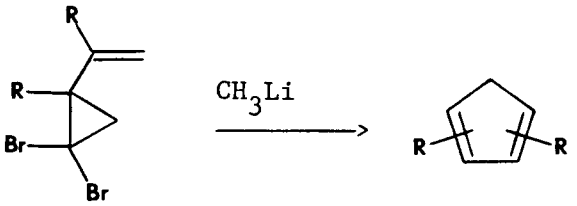
71 → 72 (17)



(18)

73 74

Treatment of 1,1-dibromo-2-vinylcyclopropane 75a with methyllithium gave 86% of the cyclopentadiene 76a and 14% of the penta-1,2,4-triene, while 1,1-dibromo-2-methyl-2-isopropenylcyclopropane 75b gave 95% of a mixture of the dimethylcyclopentadienes 76b (eq.19).[69]

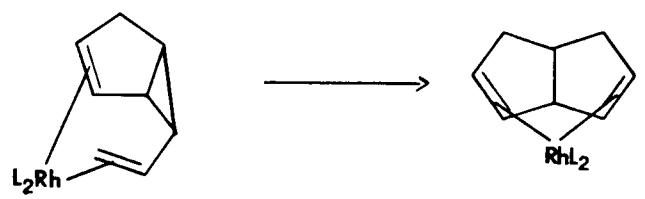


(19)

75 76

(a) R=H; (b) R=CH_3

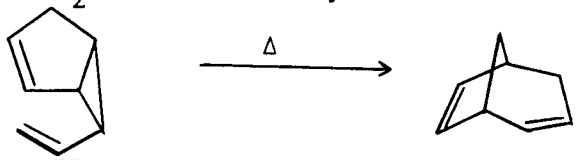
Transition metals have also been used to catalyse the vinylcyclopropane-cyclopentene rearrangement. Thus, a stoichiometric rhodium(I) complex of the vinylcyclopropane 77 rearranges readily to the rhodium(I) complex of bicyclo[3.3.0]octa-2,6-diene (eq.20).[70,71] However, in the absence of the catalyst, the same vinylcyclopropane 77 gave the bicyclo-[3.2.1]octa-2,6-diene 79 via a [3,3] sigmatropic rearrangement (eq.21).[72]



(20)

77 78

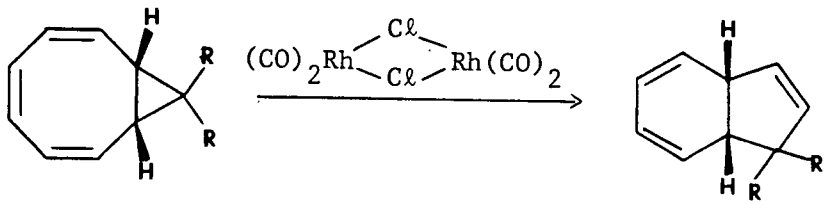
L_2=hexafluoroacetylacetonate



(21)

77 79

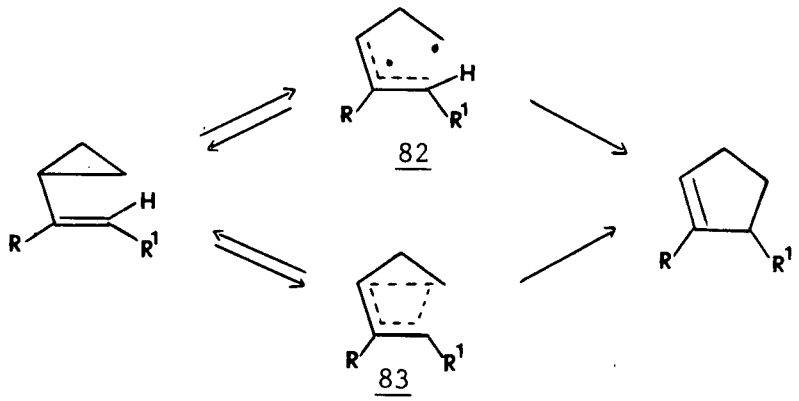
Similarly the bicyclo[6.1.0]nona-2,4,6-triene 80 rearranged readily and quantitatively in the presence of dicarbonylrhodium(I) chloride dimer into the corresponding bicyclo[4.3.0]nonatriene 81 (eq.22).[73]



80 81 (22)

III. Mechanistic Considerations in the Thermal Vinylcyclopropane-Cyclopentene Rearrangement.

The mechanism of the thermal vinylcyclopropane-cyclopentene rearrangement has long been a subject of controversy.[27,28,30] Most of the arguments have focused on the degree to which the process is concerted or stepwise. The vinylcyclopropane rearrangement can be thought to occur via a mechanism in which the rate-determining step is the opening of the cyclopropyl ring to form the diradical 82,[74,75] followed by ring closure as a result of intramolecular coupling of the diradical. On the other hand, it can also be envisaged to proceed via a concerted mechanism involving a Cope-type transition state such as 83 (Scheme 5).[28,41,76]



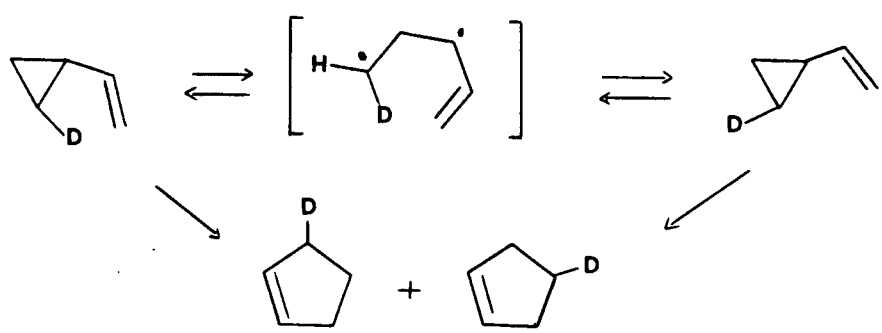
82

83

Scheme 5

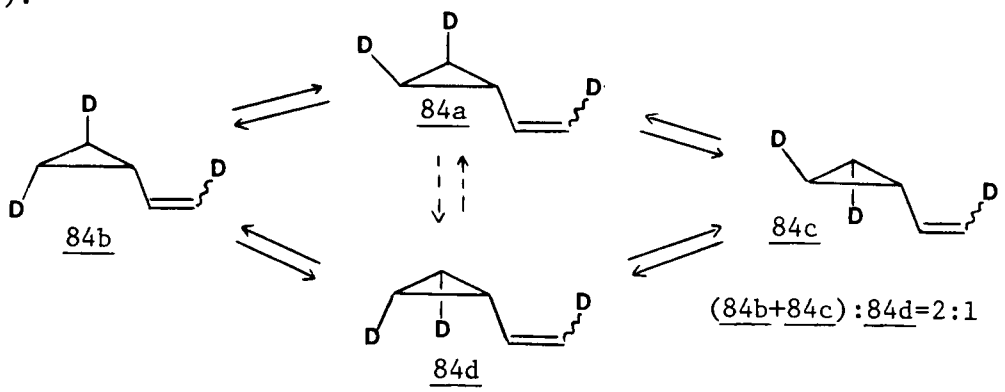
Kinetic data has indicated that the rearrangement is a unimolecular process with an activation energy of ca. 50 kcal/mol.[33,76] The activation energy is about 14 kcal/mol lower than that of ordinary cyclopropane ring cleavage. The difference corresponds quite well to the allylic resonance energy and has been interpreted in terms of a resonance stabilized biradical intermediate.[79]

Current sentiment seems to favor the intermediacy of a diradical rather than a concerted process. Theoretical molecular orbital calculations, based on the MINDO/3 (Modified Intermediate Neglect of Differential Overlap) semiempirical SCF-MO (Self-Consistent Field Molecular Orbital theory) method, predicted that the rearrangement is a "forbidden" biradicaloid process.[80] Wilcott and Cargle were able to conclude, from nmr investigations, that in the thermolysis of monodeuteriovinylcyclopropane, the loss of stereospecificity at the deuterium-labeled site in the cyclopropyl ring is at least five times as fast as the conversion to cyclopentene, thus substantiating the diradical mechanism (Scheme 6).[81] More recently, the same authors have



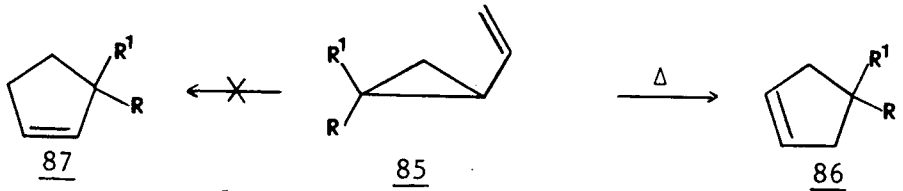
Scheme 6

studied the degenerate rearrangement of 1-(2-deuteriovinyl)-trans,trans-2,3-dideuteriocyclopropane 84a by nmr and have obtained additional evidence supporting the intermediacy of a diradical (Scheme 7).[82]



Scheme 7

Comparative kinetic studies have shown that substitutions on C-2 of vinylcyclopropane with chloro[42], methoxyl[48], phenyl[48], or a dimethylamino[47] group (85a, 85b, 85c, 85d respectively) considerably enhances the rate of rearrangement to the corresponding cyclopentene. Also, the products formed are exclusively the 4-substituted cyclopentenes 86 rather than the 3-substituted isomers 87 (eq.23). The facility with which these reactions take place and the stereoselectivity of the process have been explained by invoking a diradical intermediate.

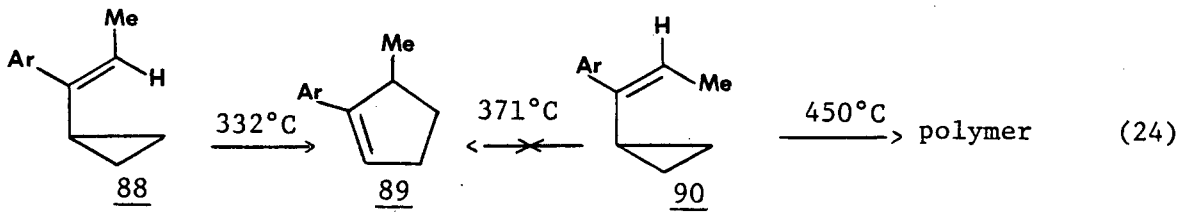


(23)

(a) $R=R^1=C\ell$; (b) R or $R^1=OCH_3$; (c) R or $R^1=Ph$; (e) R or $R^1=NMe_2$

It is of interest to note that when an alkyl group is located cis to the cyclopropyl ring in these vinylcylopropane systems (for example,

as in compounds 90, 91 and 93), the rate of thermal rearrangement is strikingly reduced and the products formed are usually polymers or structurally rearranged olefins (eq.24-26).[37,49,83] In contrast, when the alkyl group is situated trans to the cyclopropyl ring, it has no diminishing effect on the rates of rearrangement.[37,83] This observation has been explained in terms of steric interactions. The cis alkyl groups prevent the rigid allylic radical from remaining planar in the transition state, thereby lowering its allylic resonance energy, raising the energy barrier to ring closure and hence making the reaction pathway towards isomerization to olefins an energetically more favourable process.



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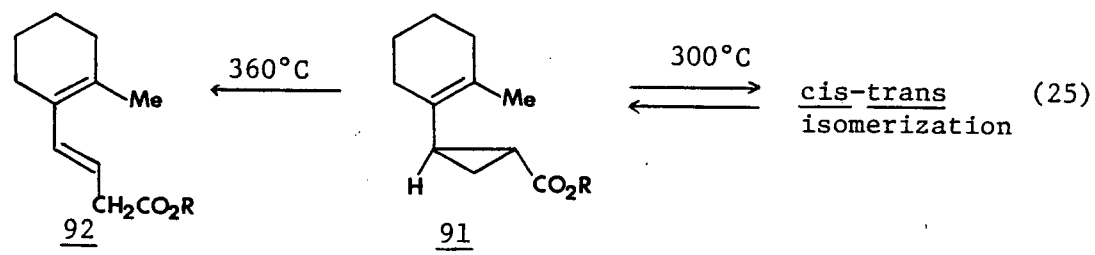

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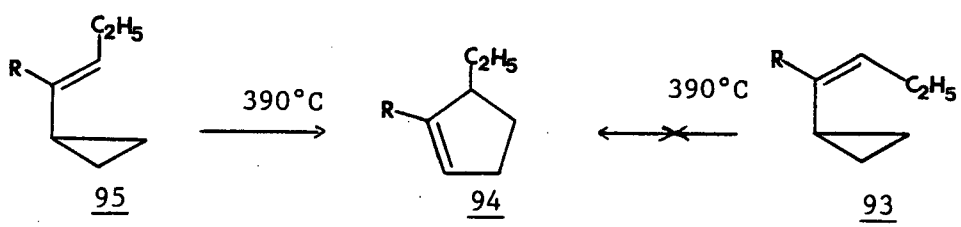
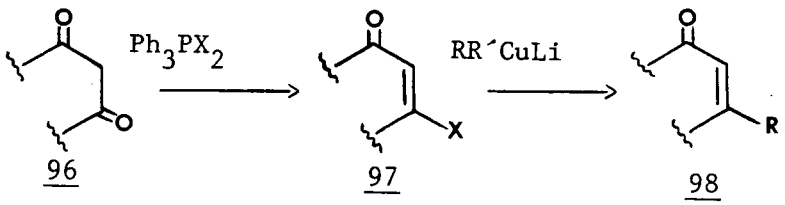


(26)

IV. The Problem

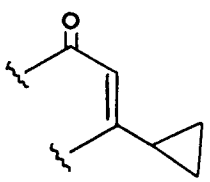
Recently, our laboratory has developed an efficient method for the preparation of cyclic β-halo-α,β-unsaturated ketones from the reaction of

cyclic β-diketones 96 with triphenylphosphine dihalides.[84] These β-halo enones have been converted into a variety of β-alkyl-α,β-unsaturated ketones in good yield by treating the former with various cuprate reagents.[85] Thus, overall, previous work in our laboratory had established an efficient synthetic route for transforming a cyclic β-diketone of the general structure 96 to the corresponding cyclic β-alkyl-α,β-unsaturated ketones of the general structure 98, as shown in the scheme below.



96 97 98

The first objective of the work described in this section of this thesis was to investigate the possibility of extending this methodology to include the synthesis of cyclic β-cyclopropyl-α,β-unsaturated ketones of the general structure 99. It can readily be seen that the latter



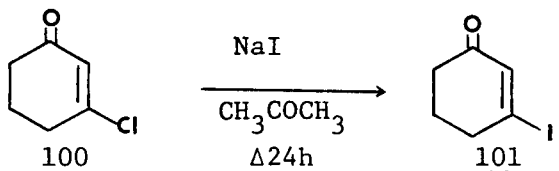
99

compounds incorporate into their structures the vinylcyclopropane moiety, with the vinyl portion of this functionality being part of the α,β-unsaturated ketone moiety. Thus, the second objective of this work was to investigate the thermolysis of these compounds, to determine whether or not they could serve as precursors for an efficient cyclopentane annelation method. Finally, the possibility of applying this methodology to the total synthesis of natural products was also considered worthy of investigation.

DISCUSSION

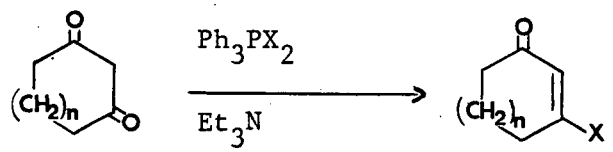
I. Synthesis of Cyclic β-Iodo-α,β-Unsaturated Ketones

The conversion of β-diketones into the corresponding β-chloro-α,β-unsaturated ketones has been achieved by treating the former with a wide variety of reagents: phosphorous trichloride, phosphorus oxychloride, phosgene, acetyl chloride and oxalyl chloride.[86] However, prior to recent work done in our laboratory, the transformation of β-diketones into the corresponding β-iodo-α,β-unsaturated ketones by use of analogous reagents had not been accomplished. In fact, reports concerning the preparation of this class of compounds had been very scarce. 3-Iodo-2-cyclohexen-1-one 101 had been prepared by refluxing 3-chloro-2-cyclohexen-1-one 100 with sodium iodide in acetone for 24h (eq.27).[87] However, the product of this reaction was a mixture of β-iodo and β-chloro enones, and the β-iodo compound obtained was not fully characterized.



100 101 (27)

Recently, Piers and Nagakura[84] reported an efficient conversion of cyclic β-diketones into the corresponding β-halo-α,β-unsaturated ketones by treating the former with triphenylphosphine dihalides in the presence of triethylamine. It was found that the halide could be chloride, bromide, or iodide (eq.28). This represented the first direct conversion of β-diketones into the corresponding β-iodo-α,β-unsaturated ketones, and, in fact, represented the first general synthesis of the latter type of compound.

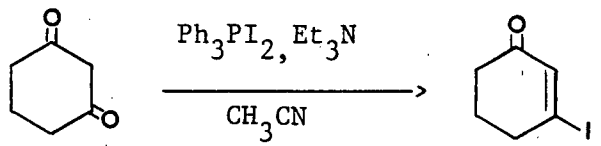


102 103 (28)

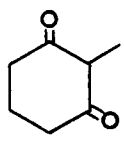
In studying the reaction of these β-halo enones with various cuprate reagents, it was found that the β-iodo enones were superior to the corresponding bromo or chloro derivatives in yielding the corresponding β-alkyl-α,β-unsaturated ketones.[85] Therefore, the β-iodo enones were chosen to be the starting materials to investigate the synthesis of the corresponding β-cyclopropyl-α,β-unsaturated ketones.

The original procedure reported for the conversion of β-diketones into the corresponding β-iodo enones was rather tedious. For example, when 1,3-cyclohexanedione 104 was treated with triphenylphosphine diiodide in acetonitrile in the presence of triethylamine at room temperature, it took four days for complete conversion of the dione into 3-iodo-2-cyclohexen-1-one 101 (eq.29).[84] During the course of the work described in this thesis, the procedure has been simplified and the yields of the reaction products have been improved considerably. Thus, the dione 104 was converted into the corresponding β-iodo enone 101 in 87% yield by refluxing the former with 1.1 equivalents of triphenylphosphine diiodide in acetonitrile in the presence of 1.1 equivalents of triethylamine for 9h. The β-iodo enone 101 was found to be a low melting solid: mp 15-16°C. It exhibited a strong absorption in the uv spectrum at 258 nm, with ε=9000($\pi \rightarrow \pi^*$ transition of α,β-unsaturated ketone). Two strong absorption bands at 1675 and 1595 cm^{-1} in the ir spectrum of this compound also indicated the presence of an α,β-unsaturated carbonyl functionality. The olefinic proton of this compound gave rise to a one-proton triplet at τ3.20 (J=2Hz) in the ^{1}Hnmr spectrum.

The structure of the enone 101 was further confirmed by a satisfactory elemental analysis.



104 101 (29)



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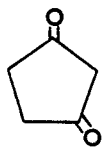

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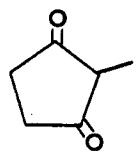
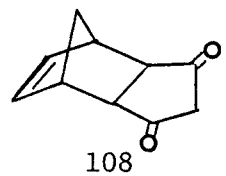


107



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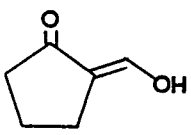

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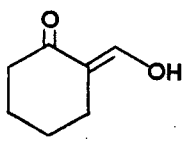

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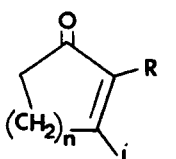
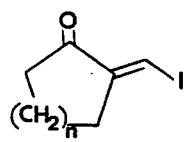
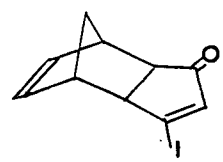


111 n=2, R=CH_3
112 n=1, R=H
113 n=1, R=CH_3

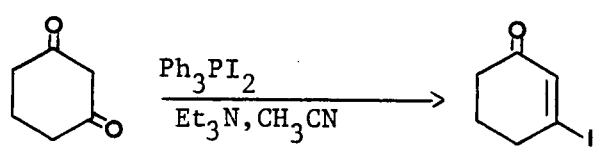


115 n=1
116 n=2



114

Similar transformations were carried using the β-diketones 105-108, inclusive, and the hydroxymethylenecycloalkanones 109 and 110 as starting materials. The results are summarized in Table 1. In each case, the product exhibited spectral data (ir, ^{1}Hnmr) in full accord with the assigned



104 101 (29)

structure, and gave a satisfactory elemental analysis and/or a molecular

weight determination (high resolution mass spectrometry).

Although the data summarized in Table 1 are relatively straightforward, it is appropriate to make a few comments. It was found that the conversion of cyclopentanediones 106 and 107 into the corresponding β-iodo enones 112 and 113, respectively, required a shorter reaction time (3h) than did their six-membered ring counterparts 104 and 105 (entries 3 and 4 vs entries 1 and 2, Table 1).

It is of interest to note that attempted conversion of the dione 108 (prepared from a Diels-Alder reaction between 1,3-cyclopentadiene and 1,3-cyclopentenedione) into the corresponding β-iodo enone 114 under reaction conditions identical with those used for other cyclopentanediones gave only a 30% yield of the desired product 114. Attempts to improve the yield of the reaction by extending the reaction time to 72h gave the same result. Addition of hexamethylphosphoramide as cosolvent, in the hope that a more polar solvent might improve the reaction, showed no effect.

Previous studies in our laboratory by Dr. I. Nagakura had shown that the conversion of 2-hydroxymethylenecyclohexanone 110 into the corresponding β-iodo enone 116 under conditions identical with those employed for the cyclic β-diketones (reflux in acetonitrile) gave a very low yield of the desired product. It was suspected that the β-iodo enone which was formed in this reaction might not be stable enough to survive the high temperature of the reaction mixture. Previous studies had also shown that the conversions of β-diketones into the corresponding β-iodo enones were more efficient when the reactions were carried out in acetonitrile rather than in benzene, a less polar solvent.[84] Thus it was hoped that by the addition of hexamethylphosphoramide, a very polar solvent, to acetonitrile as cosolvent, might improve the efficiency of the conversions of the

Table 1. Conversion of cyclic β-diketones and α-hydroxymethylenecycloalkanones to the corresponding β-iodo-α,β-unsaturated ketones

Entry	Starting material (1,3-dicarbonyl compounds)	Reaction[a] Condition	β-Iodo enone product	(yield)[b]
1.	104	B	101	(87%)
2.	105	B	111	(73%)
3.	106	A	112	(85%)
4.	107	A	113	(92%)
5.	108	A	114	(31%)
6.	109	C	115	(73%)
7.	110	C	116	(94%)

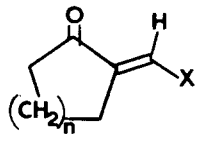
[a] Reaction condition A: 1.1 equiv. of Ph_3PI_2 was used with acetonitrile as solvent. Time of reflux was 3h; B: acetonitrile was the solvent; time of reflux was 9h; C: acetonitrile/HMPA in the ratio of 6:1 was the solvent, reaction was carried out at r.t. for 15h.

[b] The yield was based on distilled pure products.

α-hydroxymethylenecycloalkanones into the corresponding β-iodo enones. This was indeed found to be the case.

The conversions of the α-hydroxymethylenecycloalkanones 109 and 110 into the corresponding β-iodo enones 115 and 116, respectively, were carried out in a manner similar to that used for the β-diketones, except that a 6:1 mixture of acetonitrile and hexamethylphosphoramide was used as solvent, and the reactions were carried out at room temperature for 15h (entries 6 and 7, Table 1). Both of the reactions were highly regioselective and stereoselective, since, in each case, only a single β-iodo enone was formed. On the basis of ^{1}Hnmr spectral data (see below), it appeared that in both of the products the iodine atom was trans to the carbonyl group.

The general principle used in assigning the stereochemistry of the α-halomethylenecycloalkanones 117 and 118 was based on the empirical observations that, in the ^{1}Hnmr spectrum, the β-olefinic protons cis to the carbonyl group in enones of this type resonate downfield from their trans counterparts.[88,89] For example, the β-olefinic proton of compound 119 gives rise to a signal at τ3.55, whereas the corresponding proton in the isomer 120 resonates at τ2.65.[89] However, since our reactions were completely stereoselective, we had only one of the two possible isomers available, and therefore, a direct comparison could not be made.



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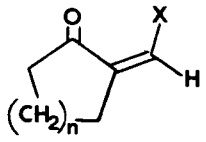

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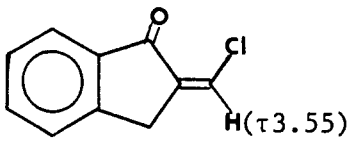

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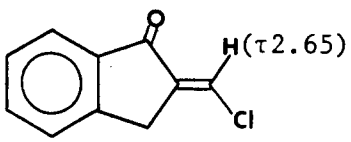

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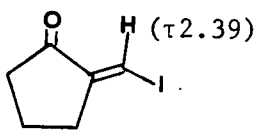

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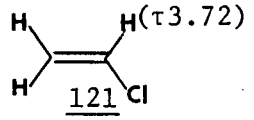

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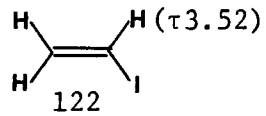

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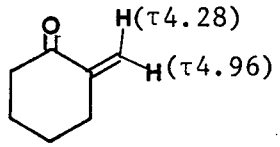

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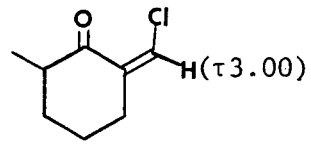
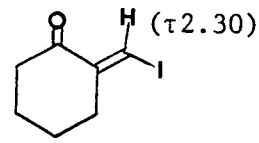


124



116

Our assignments are based on the following arguments. The protons α to the heteroatom in vinyl chloride 121[88] and vinyl iodide 122[90] resonate at τ3.72 and τ3.52, respectively. The difference in chemical shifts of the two protons caused by changing the α-substituent on the ethylene derivatives from chloro to iodo (Δτ) was 0.2. Comparison of the Δτ value of the β-olefinic protons of compounds 120 and 115 (Δτ=0.26) with that of 119 and 115 (Δτ=1.16) indicates that compound 115 should have the same stereochemistry as compound 120, since the Δτ value of their β-olefinic protons (Δτ=0.26) is closer to that between vinyl chloride and vinyl iodide (Δτ=0.2) than the Δτ value between compound 119 and 115. Furthermore, both compounds 115 and 120 have similar molecular structures, and the chemical shifts of their β-olefinic protons are quite similar. More evidence comes from the observation that the cis and trans β-olefinic protons in 2-methylenecyclohexanone 123 resonate at τ4.28 and τ4.96 respectively.[89] The difference in chemical shifts between the cis and trans β-olefinic proton (Δτ) in 123 was 0.68. Thus, taking into account the Δτ value caused by the change of α-substituent on the methylene group from chloro to iodo (0.2τ units), the difference in chemical shift of the β-olefinic protons of 119 and 115 would be expected to be close to 0.9τ units. The observed difference was 1.16, thus providing excellent evidence for the stereochemistry of 115 as assigned.

The same type of argumentation can be applied to the β-iodo enone 116.

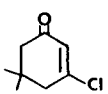
Heathcock et al. reported that the ^{1}Hnmr spectrum of the β-chloro enone 124 showed a β-olefinic proton resonance at τ3.0[88] which differs from that of the β-iodo enone 116 by 0.7τ unit. The difference would appear to be too large for the two compounds to have the same stereochemistry. Furthermore, the chemical shift of the β-olefinic proton of enone 116 (τ2.30) is quite close to those of compounds 115 (τ2.39) and 120 (τ2.65). By analogy, it is clear that compound 116 should possess the stereochemistry as shown.

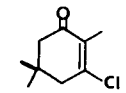
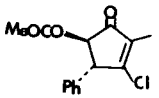
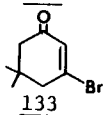
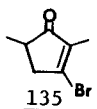
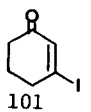
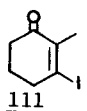
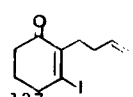
It has been well established that the conjugation of a double bond with a carbonyl group leads to intense absorption in the ultraviolet spectrum ($\pi\rightarrow\pi^*$ transition).[91] It is also well known that there is a regular and significant variation in the wavelength at which the absorption maximum (λ_{max}) occurs, depending upon the substitution pattern on the chromophore. The magnitude of these shifts can be predicted by a set of rules first formulated by Woodward[92] and later modified by Fieser[93] and by Scott.[91] For example, according to the Woodward rules, an α-alkyl substituent causes a bathochromic shift (a shift of the absorption maximum towards higher wavelength) of ∿10 nm. Similarly, a β-chloro substituent causes an increment of ∿12 nm and a β-bromo substituent is supposed to cause an increment of ∿30 nm.[91] However, since no cyclic β-iodo-α,β-unsaturated ketones had been fully characterized prior to our investigation, nothing was known about the effect of a β-iodo substituent on the position of the $\pi\rightarrow\pi^*$ absorption maximum of an α,β-unsaturated ketone. Based on the uv data of the limited number of 3-iodo-2-cycloalken-1-ones and α-iodomethylenecycloalkanones prepared in this laboratory, it was hoped that the extent of the bathochromic shift caused by a β-iodo substituent could be established.

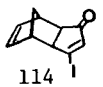
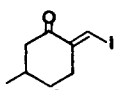
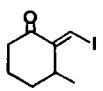
Table 2 lists the $\pi \rightarrow \pi^*$ absorption maxima of a number of parent 2-cycloalken-1-ones and 2-methylenecycloalkanones, along with those of some of the corresponding β-halo compounds. The differences between the absorption maxima of the β-halo enones and that of their parent unsubstituted enones are also listed in Table 2. Clearly, the data summarized in the table showed that the uv absorption maxima of the β-chloro-α,β-unsaturated ketones 130-132 follow the Woodward rules fairly closely (entries 7-9, Table 2). For example, 3-chloro-5,5-dimethyl-2-cyclohexen-1-one 130 showed an absorption maxima at 238 nm[99] which was 12 nm higher than that of the parent 2-cyclohexen-1-one 125 (entries 1 and 7, Table 2). The magnitude of this increment was as expected, since the Woodward rules predicted a ∿12 nm bathochromic shift caused by a β-chloro substituent.[91] Similarly, 3-chloro-2,5,5-trimethyl-2-cyclohexen-1-one 131 had an absorption maximum at 244 nm[100] which was 10 nm higher than that of 2-methyl-2-cyclohexen-1-one (entries 2 and 8, Table 2). The difference in λ_{max} between the β-chloro enones 131 and 130 was 6 nm, which was close to that predicted by the Woodward rules for the effect of an α-alkyl substituent.

It was quite unexpected to find that the positions of the uv absorption maxima of the three β-bromo enones 133-135 shown in Table 2 did not agree with those predicted by the Woodward rules (entries 10-12). All three compounds showed absorption maxima much lower than those calculated by the Woodward rules. Compared with the corresponding α,β-unsaturated ketones, all of them showed a bathochromic shift. However, the magnitude of the shift fell quite short of the 30 nm expected for a β-bromo substituent. For example, 3-bromo-2-methyl-2-cyclohexen-1-one 134

Table 2. The uv absorption maxima (λ_{max}) of some β-halo enones and their parent β-unsubstituted enones

Entry	α,β-Unsaturated Ketones	Observed λ_{max}^{EtoH}(nm)(ε)	Calculated λ_{max}^{EtOH}(nm)[a]	Difference in λ_{max} between β-halo enones and their parent β-unsubstituted enones	Reference
1	 125	226 (10400)			94
2	 126	234			95
3	 127	218 (9500)			96
4	 128	226 (8550)			97
5	 123	231 (7550)			98
6	 129	230 (7400)			98
7	 130	238 (113500)	238	12	99

8	 131	244 (1300)	246	10	100
9	 132	241 (16000)	238	15	101
10	 133	246 (13400)	256	20	99,102
11	 134	246 (13060)	264	12	103
12	 135	243 (12302)	256	17	104
13	 101	258 (9000)		32	105
14	 111	258 (9504)		24	105
15	 136	256 (8377)		32	103
16	 137	260		26	106

17	 112	249 (11353)	31	105
18	 113	248 (11520)	22	105
19	 114	253 (9900)	35	105
20	 116	265 (7198)	34	105
21	 138	261 (7110)	30	105
22	 139	257 (6681)	26	105
23	 115	276 (9170) 263 (shoulder)	45 33	105

[a] The λ_{max}(calc.) was calculated using the Woodward rules: for an α-alkyl substituent, add 10 nm to the parent unsubstituted enone, for a β-chloro substituent add 12 nm and for a β-bromo substituent add 30 nm to the parent enone. For example, the λ_{max} (calc.) for β-bromo enone 133 would be 226 nm (parent enone 125) + 30 nm (β-bromo substituent)=256 nm, whereas the λ_{max} (calc.) of β-bromo enone 134 would be 234 nm (parent enone 126) + 30 nm (β-bromo substituent) = 264 nm.

had a λ_{max} at 246 nm. On the basis of Woodward's rules, the λ_{max} for this compound should be around 264 nm.

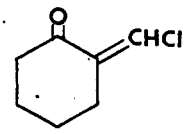
Another significant deviation from the Woodward rules was the observation that the absorption maxima of both 3-bromo-5,5-dimethyl-2-cyclohexen-1-one 133 and 3-bromo-2-methyl-2-cyclohexen-1-one 134 were identical (entries 10 and 11, Table 2). They were predicted to have a difference in absorption maximum by ∿10 nm due to the presence of an extra α-alkyl substituent on enone 134. This anomaly was also found in the β-iodo analogs. For example, 3-iodo-2-cyclohexen-1-one 101 and 3-iodo-2-methyl-2-cyclohexen-1-one 111 were shown to have the same absorption maximum at 258 nm (entries 13 and 14, Table 2). Also, the absorption maxima of 3-iodo-2-cyclopenten-1-one 112 and 3-iodo-2-methyl-2-cyclopenten-1-one 113 occurred at nearly the same wavelength (entries 17 and 18, Table 2).

It is unfortunate that very little uv data regarding cyclic β-bromo-α,β-unsaturated ketones have been reported in the literature. Because of this lack of data, it is not certain whether or not there is a general trend for the abnormal behaviour described above. In any case, it is clear that one has to be careful when applying the Woodward rules in predicting the absorption maxima of β-bromo-α,β-unsaturated ketones.

Concerning the bathochromic effect of a β-iodo substituent, a perusal of the uv data obtained from the β-iodo enones listed in Table 2 showed that there was no regular pattern in the bathochromic shifts. Owing to these irregularities and to the limited data available, it is not possible at this moment to establish a discrete value for the bathochromic shift caused by a β-iodo substituent.

In general, the preparation of cyclic β-iodo-α,β-unsaturated ketones

from the corresponding 1,3-dicarbonyl compounds could be carried out in a simple manner. Furthermore, the products obtained were clean and the yields of products were good. The β-iodo enones were found to be stable and easy to handle. The α-iodomethylenecycloalkanones, though not as stable as the endocyclic analogs, could be stored under an atmosphere of argon in a freezer for a few months without substantial decomposition. However, if exposed to air at room temperature, these compounds darken in color and decompose fairly rapidly (in a day or two). It is also interesting to note that the α-iodomethylenecycloalkanones are apparently considerably more stable than their chloro counterparts. For example, 2-chloromethylenecyclohexanone 140 has been reported to undergo decomposition even at -20°C under nitrogen.[107]



140

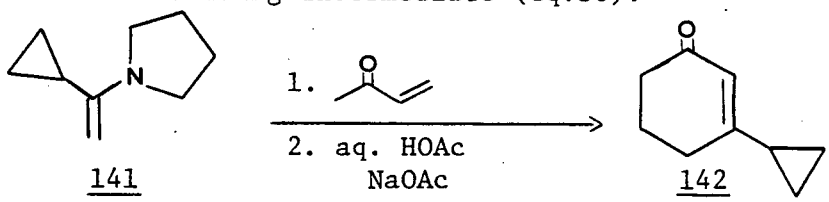
The β-iodo enones, in general, are easier to prepare than their chloro and bromo counterparts. This is mainly because, in the preparation of the triphenylphosphine dihalide reagents, iodine crystals are much easier to handle than noxious chlorine gas or the liquid bromine. The β-iodo enones are also easier to handle (higher molecular weight, less volatile) and are more reactive in certain reactions (for example, reaction with cuprate reagents[85]) than the corresponding chloro or bromo compounds.

β-chloro-α,β-unsaturated carbonyl compounds have in the past become increasingly useful as intermediates in organic synthesis.[86] Since it now appears that the corresponding β-iodo enones can be readily prepared and

since these iodo enones are easier to handle and are more reactive in certain reactions, it is clear that this new class of compounds might also find increasing use as intermediates in organic synthesis.

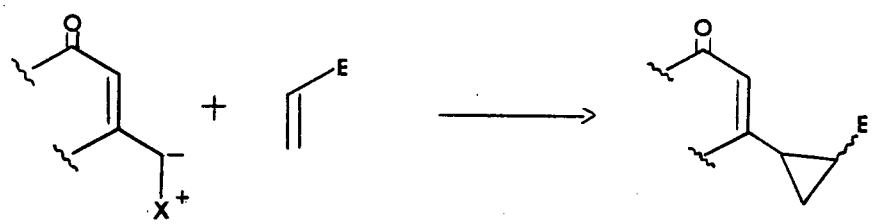
II. Conversion of β-Iodo-α,β-Unsaturated Ketones into the Corresponding β-Cyclopropyl-α,β-Unsaturated Ketones.

Although a wide variety of functionalized vinylcyclopropanes have been synthesized, β-cyclopropyl-α,β-unsaturated ketones have rarely been prepared. 3-Cyclopropyl-2-cyclohexen-1-one 142 has been prepared by the Michael addition of the enamine 141 to methyl vinyl ketone, followed by intramolecular cyclization of the resulting intermediate (eq.30).[108]



141 142 (30)

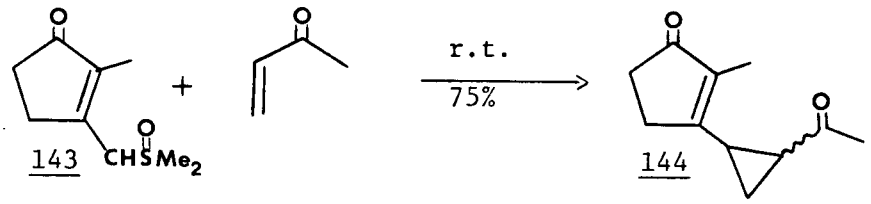
Recently, the addition of allyl-ylides of α,β-unsaturated ketones to Michael acceptors has provided an efficient route to β-cyclopropyl-α,β-unsaturated ketones (eq.31).[109-112]



(31)

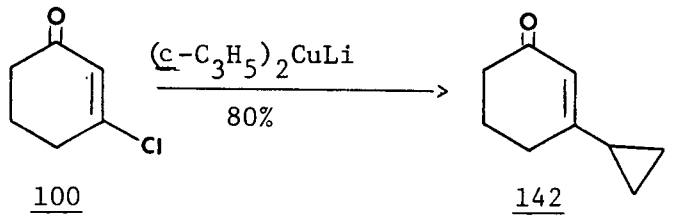
$X=SMe_2$, $\overset{O}{\overset{\|}{S}}Me_2$, $\overset{O}{\overset{\|}{S}}Me(NMe_2)$; E=CN, COR, CHO, CO_2R, NO_2

For example, the ylide 143 reacted cleanly with methyl vinyl ketone to give the vinylcyclopropane 144 in 75% yield (eq.32).[110]



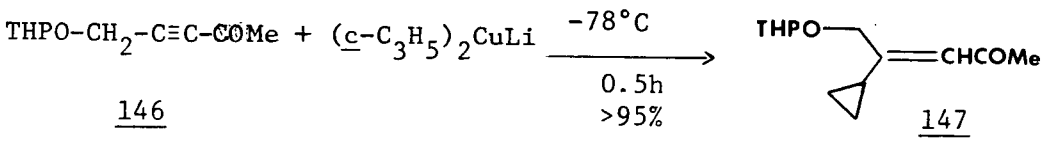
(32)

More recently, Marino et al.[113] utilized the conjugate addition reactions of lithium dicyclopropylcuprate to β-halo, β-alkoxy and β-acetoxy enones in preparing β-cyclopropyl-α,β-unsaturated ketones. For example, the β-chloro enone 100 reacted with lithium dicyclopropylcuprate to give the corresponding β-cyclopropyl enone 142 in 80% yield (eq.32a).[113]



(32a)

The conjugate addition of lithium dicyclopropylcuprate to acetylenic carbonyl compounds to give β-cyclopropyl-α,β-unsaturated ketones also has been reported.[113] For example, treatment of the acetylenic ketone 146 with lithium dicyclopropylcuprate gave the corresponding β-cyclopropyl enone 147, in >95% yield (eq.33a).[113]

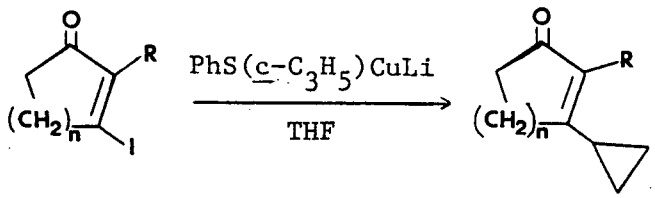


(33a)

THP=Tetrahydropyran

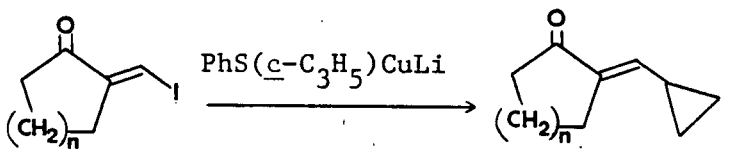
In earlier work in our laboratory, it had been found that cyclic β-halo-α,β-unsaturated ketones reacted with various cuprate reagents to produce the corresponding β-alkyl-α,β-unsaturated ketones in high yield.[85]

The β-halo enones can be prepared easily from the reaction of the corresponding cyclic β-diketones with triphenylphosphine dihalides[84] (described earlier in this thesis). It was therefore of interest to investigate whether or not this procedure could be applied to the preparation of cyclic β-cyclopropyl-α,β-unsaturated ketones. As a result, a series of cyclic β-cyclopropyl-α,β-unsaturated ketones were prepared by the reaction of β-iodo-α,β-unsaturated ketones with lithium phenylthio(cyclopropyl)cuprate (eq.33 and 34). Some of the results are summarized in Table 3.



(33)

101	n=2, R=H	142	n=2, R=H
111	n=2, R=CH_3	146	n=2, R=CH_3
112	n=1, R=H	147	n=1, R=H
113	n=1, R=CH_3	148	n=1, R=CH_3



(34)

115	n=1	149	n=1
116	n=2	150	n=2

A typical procedure for the conversion of β-iodo-α,β-unsaturated ketones into the corresponding β-cyclopropyl enones follows. To a solution of lithium phenylthio(cyclopropyl)cuprate (4.5 mmol) in tetrahydrofuran at -78°C was added a solution of 3-iodo-2-cyclohexen-1-one 101 (3 mmol) in tetrahydrofuran. The resulting mixture was stirred at -78°C for 2.5h. Methanol was added to quench the reaction and the reaction

mixture was filtered through a short column of florisil. Evaporation of the solvent, followed by distillation of the residual oil gave 335 mg (82%) of pure 3-cyclopropyl-2-cyclohexen-1-one 142. The spectral data of this material were identical with those reported in the literature.[90] Similarly, the β-iodo enones 111-116 were transformed into the corresponding β-cyclopropyl enones 146-150, respectively. The results are summarized in Table 3. All of the products listed in Table 3 exhibited spectral data in full accord with the assigned structures. Each of the new compounds also gave a satisfactory elemental analysis and/or molecular weight determination (high resolution mass spectrometry).

Although the data summarized in the table are largely self-explanatory, there are a few minor points that need to be discussed in more detail. For simpler β-iodo enones, like 3-iodo-2-cyclohexen-1-one 101 and 3-iodo-2-cyclopenten-1-one 112, complete conversion into the corresponding β-iodo enones needed only 1.5 equivalents of cuprate reagent, and the reaction was carried out at -78°C for 2.5h (entries 1 and 3, Table 3). However, for β-iodo enones 111 and 113, which contained a methyl group at the α-position, a higher reaction temperature (0°) and more cuprate reagent (2 equivalents) were required to effect complete conversion of the starting material in a reasonable time (entries 2 and 4, Table 3). Apparently, the α-methyl group caused a certain amount of steric congestion, thus impeding the conjugate addition of the cuprate reagent to the β-position.

Similarly, for 2-iodomethylenecycloalkanones 115 and 116, higher temperatures (-20°C and 0°C respectively) than those needed for enones 101 and 112 were required for complete conversion of the starting material

Table 3. Conversion of β-iodo-α,β-unsaturated ketones into β-cyclopropyl-α,β-unsaturated ketones.

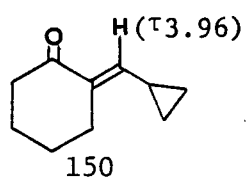
Entry	β-iodo enones	Reaction Condition[a]	β-cyclopropyl enones	(Yield %)
1.	101	A	142	(82%)
2.	111	C	146	(88%)
3.	112	A	147	(97%)
4.	113	C	148	(84%)
5.[b]	115	D	149	(65%)
6.	116	B	150	(82%)

[a] Reaction condition A: 1.5 eq. of PhS(c-C_3H_5)CuLi was used at -78°C for 2.5h; B: 1.5 eq. of PhS(c-C_3H_5)CuLi was used at 0°C for 2.5h; C: 2 eq. of PhS(c-C_3H_5)CuLi was used at 0°C for 2.5h; D: 1.5 eq. of PhS(c-C_3H_5)CuLi was used at -78°C for 1h, at -20°C for 2h.

[b] Reaction was performed by Dr. I. Nagakura.

in a reasonable time (entries 5 and 6, Table 3). A careful analysis of the reaction products obtained from these reactions showed that, in each case, transformation of the 2-iodomethylenecycloalkanone into the corresponding β-cyclopropyl enone was highly stereoselective. Essentially, only one product was obtained from each reaction. The stereochemistry of the products 149 and 150 could readily be assigned as shown on the basis of the ^{1}Hnmr spectra.

The argument employed here was similar to that used in determining the stereochemistry of 2-iodomethylenecyclohexanone (described earlier) and was based on the empirical observation that in the ^{1}Hnmr spectra, the β-olefinic protons cis to the carbonyl group of certain α-alkylmethylenecyclohexanones resonate downfield from their trans counterparts.[89] For example, for 2-methylenecyclohexanone 123,



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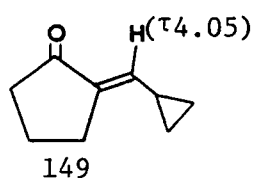
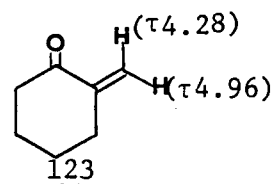
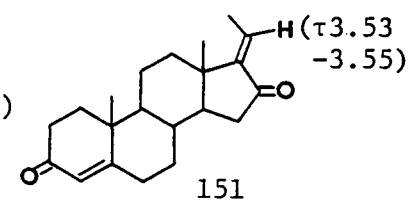


149



123



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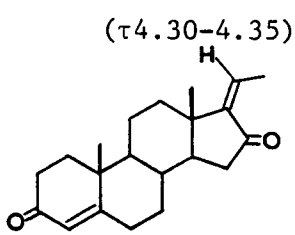

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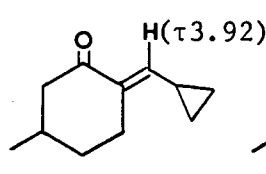
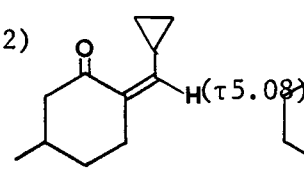


153



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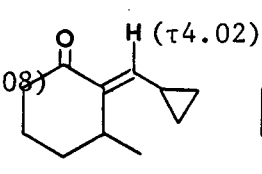

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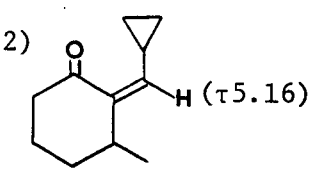


156

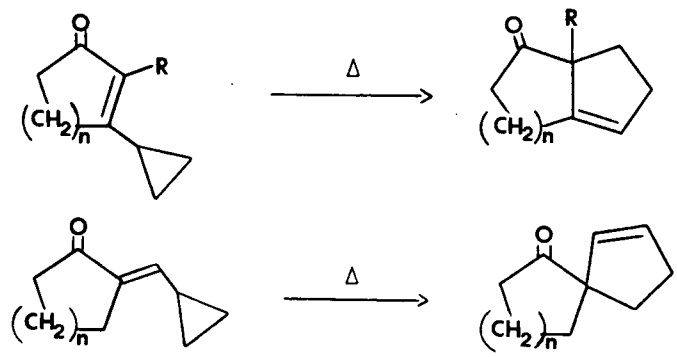
the proton cis to the carbonyl group resonated at τ4.28 while the proton trans to the carbonyl group gave rise to a signal at τ4.96.[89] Also, the β-olefinic proton of compound 151 resonated at τ3.53-3.55 whereas the analogous proton of its isomer 152 gave rise to a signal at τ4.30-4.35.[89]

In a related study described in a subsequent part of this thesis we were able to isolate the two pairs of isomers 153 + 154 and 155 + 156. The β-olefinic protons of compounds 153 and 155 resonated at τ3.92 and 4.02, respectively. On the other hand, the analogous protons of the isomeric pair of compounds (154, 156) gave rise to signals at τ5.08 and 5.16. Since compounds 153 and 155 had the β-olefinic proton resonances downfield from their isomeric counterparts (154, 156), they should have the structure as assigned. As for compounds 149 and 150, we had only one of the two possible isomers available, and therefore, a direct comparison with their isomeric counterparts could not be made. However, a comparison of the chemical shifts of the β-olefinic proton resonances of these two compounds with those of compounds 153 and 155, clearly indicates that 149 and 150, possess the stereochemistry shown.

In general, the transformation of β-iodo enones into the corresponding β-cyclopropyl enones is a very clean process and the yields are high. Furthermore, in no case were we able to detect a product resulting from conjugate addition of a second cyclopropyl group. Finally, all the products obtained by the aforementioned procedure were stable and could be stored indefinitely if they were kept under argon in a freezer.

III. Thermolysis of β-Cyclopropyl-α,β-Unsaturated Ketones

As already mentioned, cyclic 3-cyclopropyl-2-cycloalken-1-ones and 2-cyclopropylmethylenecycloalkanones are basically vinylcyclopropane derivatives. It was therefore of interest to determine whether or not thermolysis of these compounds would result in a cyclopentene-type annelation processes, as depicted by the following schemes.



Two general procedures (A and B) were employed in the investigation of the thermal rearrangement of the aforementioned type of compounds. A detailed description of the general procedure A follows. A pyrex tube, 1.2 (i.d.)x32 cm, filled with glass helices (i.d. 4.76 nm) was washed successively with water, acetone and n-hexane. The column was conditioned by placing it in a furnace and heating it at ∿450°C for 3h. During this period of time, the column was thoroughly purged with a stream of nitrogen. A n-hexane solution of the appropriate β-cyclopropyl enone (200 mg in 20 ml of n-hexane) was added dropwise over a period of 1.5h to the top of the vertically held, heated tube (∿450°C). During this period of time, the stream of nitrogen was discontinued. The pyrolysate from the bottom of the column was cooled by having it pass through a water condenser connected to the bottom of the pyrolysis tube, and was collected in a two-necked flask, equipped with a drying tube and immersed in a cold (-78°C) bath (see diagram 1). After addition of the solution was complete, the hot column was washed with a further 30 ml of n-hexane. Removal of the hexane from the pyrolysate, followed by distillation (air-bath) of the residual oil, gave the thermolysis product.

Thermolysis of 3-cyclopropyl-2-cyclopenten-1-one 147 under the conditions described above (procedure A), gave an 80% yield of a colorless oil. A glc analysis of this material showed the presence of four major components

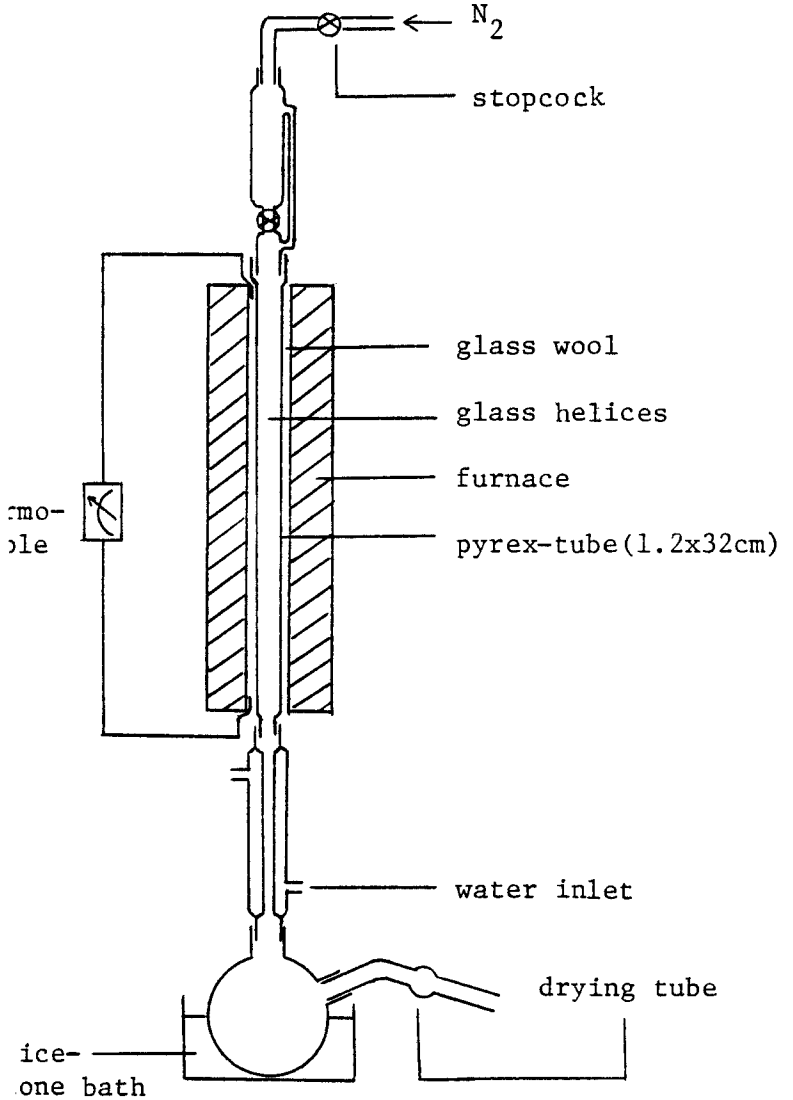


Diagram 1

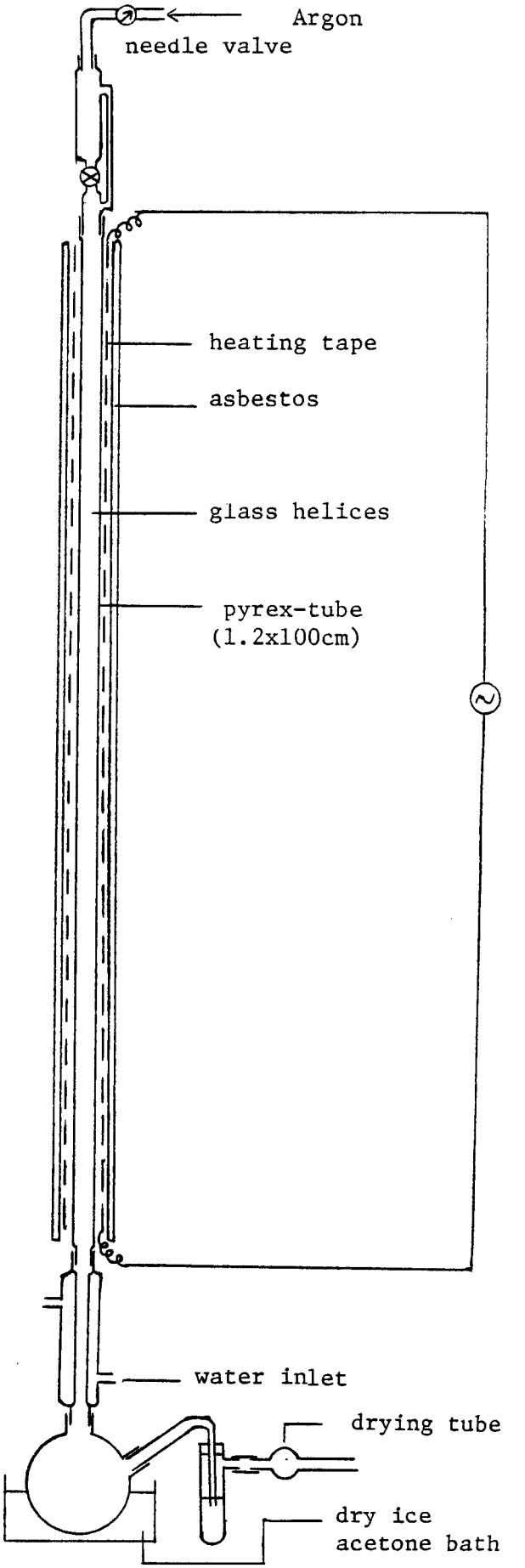
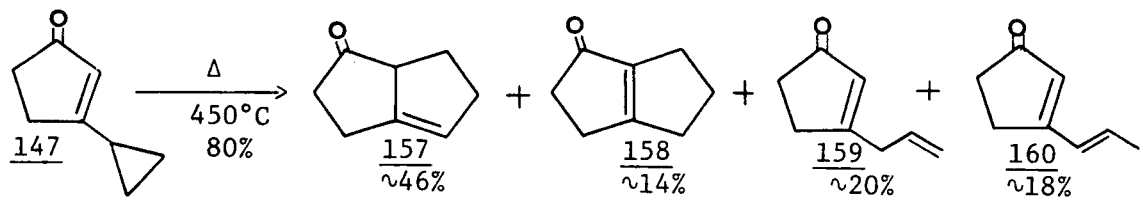


Diagram 2

together with small amounts of minor impurities (∿2%) which were not identified. The major components were shown to be the ketone 157 (∿46%), the enone 158 (∿14%), the dienone 159 (∿20%) and the dienone 160 (∿18%)(eq.34).



(34)

An analytical sample of each major component was obtained by preparative glc. The structures assigned to the thermolysis products 157-160 were supported by spectroscopic data. The uv spectrum of enone 158 (λ_{max} 237 nm, ε=11,370) agreed well with that expected (Woodward's rules) for a compound possessing this structure. The ir spectrum also indicated the presence of a conjugated ketone system (ν_{max} 1690, 1630 cm^{-1}) Finally, the ^{1}Hnmr spectrum of 158 showed only a complex multiplet at τ7.10-7.80, thus clearly indicating the absence of olefinic protons.

The ir spectrum of ketone 157 indicated that the compound was a saturated five-membered ring ketone (ν_{max} 1740 cm^{-1}). The only olefinic proton present appeared as a one-proton multiplet at τ4.58 in the ^{1}Hnmr spectrum. The latter also showed a one-proton multiplet between τ6.57 and 6.88, which could readily be attributed to the tertiary bridgehead proton adjacent to the carbonyl group. When compound 157 was passed through a short column of basic alumina, it isomerized quantitatively to the enone 158.

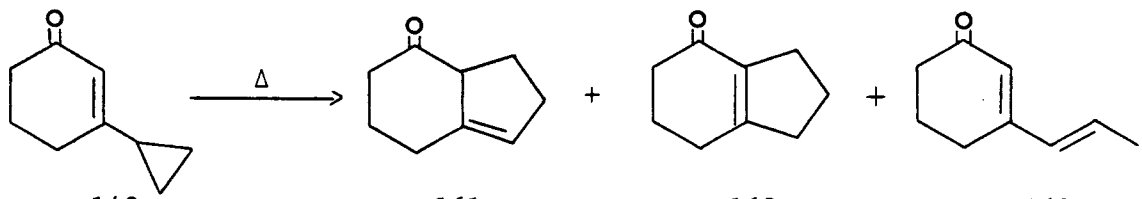
The observed absorption maximum (268 nm, ε=18,630) in the uv spectrum

of the conjugated dienone 160 agreed well with that expected for a compound possessing this structure. The ir spectrum exhibited the expected absorptions at 1640 and 1570 cm^{-1}. In the ^{1}Hnmr spectrum of compound 160, the olefinic proton α to the carbonyl group produced a signal at τ4.09 as a broad, one-proton singlet. One of the two olefinic protons on the propenyl side chain appeared as a one-proton doublet (J=16 Hz) at τ3.44, whereas the other (α to the terminal methyl group) appeared as a one-proton doublet of quartets (J=16 Hz, J'=6 Hz) at τ3.70. The large coupling constant between the two olefinic protons clearly indicated that they are trans to each other. The terminal methyl group of the side chain gave rise to a three-proton doublet (J=6 Hz) at τ8.10.

Both the uv absorption maximum (226 nm, ε=14,090) of the dienone 159 and the infrared spectrum (ν_{max} 1705, 1610 cm^{-1}) of this compound indicated the presence of a conjugated cyclopentenone system. The ^{1}Hnmr spectrum of 159 exhibited a two-proton multiplet between τ4.70 and 5.10, readily attributable to the terminal olefinic protons of the vinyl group, and a two-proton multiplet between τ3.92 and 4.40, which could be assigned to the other two olefinic protons in the molecule. The methylene group of the allyl side chain appeared as a two-proton doublet (J=6.5 Hz) at τ6.88. Isomerization of the dienone 159 to the isomeric compound 160 was effected by passing the former through a short column of basic alumina. The spectral data obtained from the isomerized product were identical with that of the dienone 160 obtained earlier.

Thermolysis of 3-cyclopropyl-2-cyclohexen-1-one 142 under conditions very similar to those described above (procedure A), afforded a 78% yield of a colorless oil. A glc analysis of this material indicated that it was

a mixture of the ketone 161 (∿3%), the enone 162 (∿84%) and the dienone 163 (∿11%), along with a number of minor, unidentified impurities (∿2%). An analytical sample of each of the three thermolysis products was obtained by preparative glc, and each compound was characterized by ir and ^{1}Hnmr spectroscopy. Enone 162 exhibited the characteristic six-membered ring



142 161 162 163 (35)

α,β-unsaturated carbonyl absorptions in the ir spectrum (ν_{max} 1660, 1630 cm^{-1}). The ^{1}Hnmr spectrum of this compound exhibited only a complex multiplet between τ7.2 and 8.3. The melting point [252°C (dec)] of the 2,4-dinitrophenylhydrazone derivative of this material agreed very well with that reported in the literature (251.5°C).[114]

The ir spectrum of ketone 161 indicated that the compound was a saturated six-membered ring ketone (ν_{max} 1718 cm^{-1}). The only olefinic proton present appeared as a broad one-proton singlet at τ4.57. This material also showed a one-proton multiplet centered at τ6.63, which could readily be attributed to the tertiary bridgehead proton adjacent to the carbonyl group. When compound 161 was passed through a short column of basic alumina, it isomerized to the enone 162.

The ir spectrum of the dienone 163 also indicated the presence of an α,β-unsaturated carbonyl functionality (ν_{max} 1670, 1642, 1590 cm^{-1}). The single olefinic proton α to the carbonyl group gave rise to a singlet at τ4.16 in the ^{1}Hnmr spectrum, while the two olefinic protons on the side chain appeared as a multiplet at τ3.82. The terminal methyl group gave rise to a three-proton doublet (J=5 Hz) at τ8.14. These spectral data were identical with those previously reported for this compound.[115]

Although the thermolysis of 3-cyclopropyl-2-cyclohexen-1-one 142 at ∿450°C gave a satisfactory yield of the annelated products 161 and 162, pyrolysis of 3-cyclopropyl-2-cyclopenten-1-one 147 gave significant amounts of the dienones 159 and 160. Since it was desirable to minimize the formation of these undesired side products, it was decided to investigate different thermolysis conditions. It was hoped that by lowering the thermolysis temperature and increasing the contact time (by increasing the length of the thermolysis tube), the thermolysis reaction might be improved and the formation of open-chain dienones might be reduced.

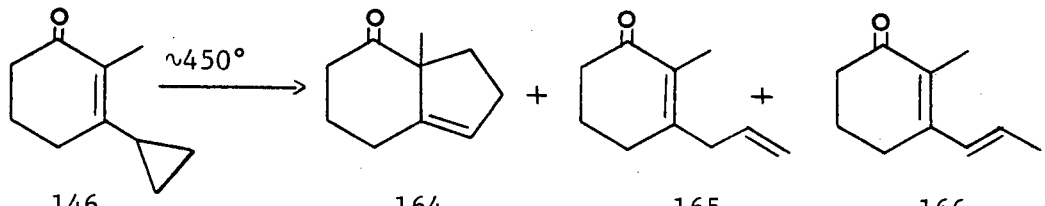
A new pyrolysis apparatus with a longer pyrolysis tube was constructed (as shown in diagram 2). A general experimental procedure (procedure B) employing this set-up follows. A pyrex tube (1.2x100 cm) filled with glass helices (i.d. 4.76 mm) was washed successively with saturated aqueous sodium bicarbonate solution, water, acetone and n-hexane. By means of a heating tape which had been wrapped around it, the column was heated to the desired thermolysis temperature and was kept at this temperature for at least 3h. During this time, the column was thoroughly purged with a rapid flow of argon. A n-hexane solution of the appropriate β-cyclopropyl enone (200 mg in 20 ml n-hexane) was added dropwise, over a period of 1.5h, to the top of the vertically held column. During this period, a very slow flow of argon (∿5 ml/min) was passed through the column. The pyrolysate from the bottom of the column was cooled by allowing it to pass through a water condenser attached to the bottom of the pyrolysis tube, and was collected in a two-necked flask which was equipped with a drying tube and was immersed in a cold (-78°C) bath. After the addition of the solution was complete, the hot column was washed with a further 30 ml of n-hexane. The combined hexane solution was concentrated and the residual oil was distilled to give the pyrolysis product.

3-Cyclopropyl-2-cyclohexen-1-one 142 was chosen as the substrate to study the new thermolysis conditions in some detail. Pyrolysis of this material at ∿425°C (procedure B) gave a 98% yield of a colorless oil. A glc analysis of this material showed that it was a mixture of the ketone 161 (∿31%) and the enone 162 (∿67%), along with very small amounts of unidentified impurities (∿2%). This material was passed through a short column of basic alumina. The column was eluted with ether. Removal of the ether and analysis of the residual oil by glc and ir showed that the ketone 161 had isomerized completely to enone 162.

The above procedure was repeated at 322°C, 400°C and 450°C. The results are summarized in Table 4 (entries 2b-e). At 322°C, no reaction had taken place. At 400°C, some rearrangement occurred, although a considerable amount of starting material was recovered (∿37%). At 450°C, the annelated cyclopentenes constituted ∿96% of the product and no starting material was recovered. However, the yield was considerably lower than that obtained from thermolysis at 425°C and it thus appeared that the latter pyrolysis temperature was the preferred one. In no case was there any of the dienone 163 detected.

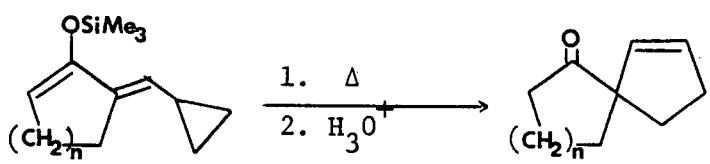
In comparison with the old procedure (procedure A), this new procedure (B) showed a dramatic improvement in terms of giving better yields and less undesired side-products. The use of this new procedure was extended to include the thermolysis of other β-cyclopropyl-α,β-unsaturated ketones. Some of these results are summarized in Table 4 and will be discussed in more detail later. All of the products listed in Table 4 exhibited spectral data in full accord with the assigned structures, and all new compounds gave satisfactory elemental analysis and/or molecular weight determinations (high resolution mass spectrometry).

A preliminary study, performed by Dr. I. Nagakura of our laboratory, showed that thermolysis of 2-methyl-3-cyclopropyl-2-cyclohexen-1-one 146 (procedure A) gave the dienones 165 and 166 as the major products. Only a very small amount of the desired annelated cyclopentene 164 was formed (eq.36).



146 → 164 ~10% + 165 ~18.4% + 166 ~50% (36)

These results were not totally unexpected. We had mentioned earlier in the introduction, that when an alkyl group is placed cis to the cyclopropyl ring across the double bond on a vinylcyclopropane system (as in compound 146), the rate of thermal rearrangement is usually much lower than the rate of rearrangement of unsubstituted cases, and the products formed are usually polymers or structurally rearranged olefins.[37,49,83] In a related study described in a subsequent part of this thesis, it was found that the thermal rearrangement of the trimethysilyl enol ether derivatives of 2-cyclopropylmethylenecycloalkanones gave better yields of the corresponding spiroannelated products than did the corresponding parent enones (eq.37). It was hoped that pyrolysis of the trimethysilyl enol ether derivative of



(37)

enone 146 might also give a better yield of the annelated product 164. Thus,

Table 4. Thermal rearrangement of β-cyclopropyl-α,β-unsaturated ketones and related compounds

Entry	Substrate	Reaction Condition[a]	Products and Products Ratio(%)[b]						Yield[c]
1.	147	∿450°C(A)	157 ∿46%	158 ∿14%	159 ∿20%	160 ∿18%		Unidentified impurities ∿2%	80%
2.	142		161	162	163	142			
a.		∿450°C(A)	∿3%	∿84%	∿11%			∿2%	78%
b.		∿322°C(B)				∿100%			100%
c.		∿400°C(B)	∿37%	∿15%		∿37%		∿11%	100%
d.		∿425°C(B)	∿31%	∿67%				∿2%	98%
e.		∿450°C(B)	∿5%	∿91%				∿5%	71%
3.	171	∿425°C(C)		∿76%				∿24%	67%
4.	167	∿425°C(B)	170(∿75%)					∿25%	50%
5.	172	∿450°C(A)	173(∿75%)		174(∿16%)			∿9%	30%
6.	150	∿450°(A)	175 ∿44%	176 ∿9%	177 ∿38%				74%
7.	184		185	186					
a.		∿450°(A)	∿74%	∿14%				∿12%	74%
b.		∿425°(B)	∿84%					∿16%	85%
8.[d]	149		187	188	189	190	149		
a.		∿450°(A)	∿39%	∿31%	∿9%	∿15%		∿6%	90%
b.		∿425°(B)	∿33%	∿50%			∿9%	∿8%	85%
9.	191	∿425°(C)	∿94%					∿6%	56%

[a](A) Pyrolysis was carried out in a vertical pyrex tube (1.2x32 cm) using procedure A (see text).

(B) Pyrolysis was carried out in a vertical pyrex tube (1.2 cm x 1 m) under a very slow flow of argon (procedure B) (see text).

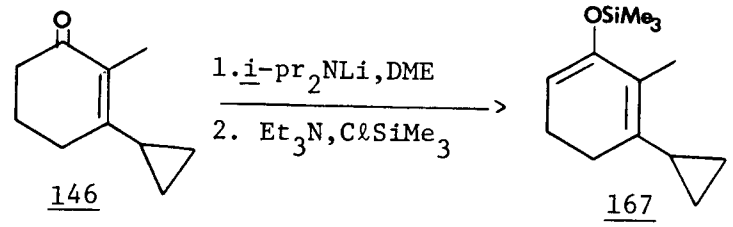
(C) Pyrolysis was carried out in the same way as (B), the crude pyrolysis product was hydrolysed by 1:1 methanol and 1 N aq. HCl.

[b]Product ratio was based on glc analysis of distilled pyrolysate.

[c]Yield is based on the total weight of distilled pyrolysate recovered.

[d]This data was obtained from Dr. I. Nagakura of our laboratory.

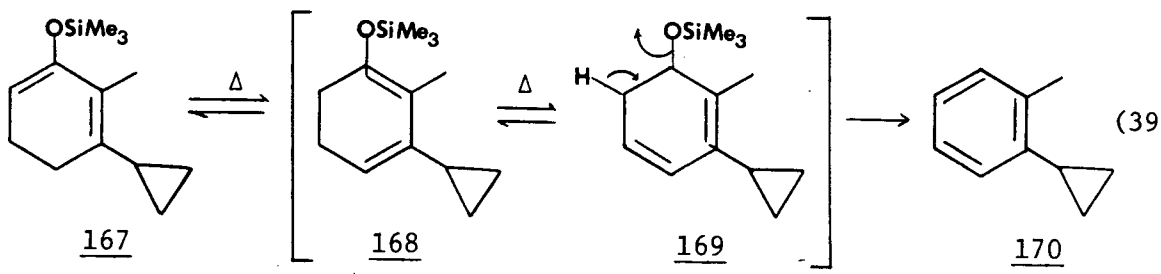
the trimethylsilyl enol ether 167 was prepared, by treatment of the enone 146 with lithium diisopropylamide in 1,2-dimethoxyethane, followed by trapping of the resultant enolate anion with chlorotrimethylsilane in the presence of triethylamine (eq.38). The structure of the silyl enol ether 167 was supported by the ^{1}Hnmr spectrum of the compound



146 167 (38)

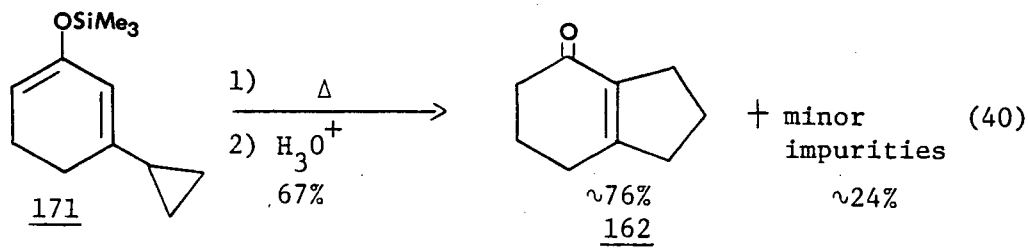
which showed a trimethysilyl group at τ9.91 as a nine-proton singlet. The olefinic proton gave rise to a signal at τ5.20 in the form of a triplet, while the vinyl methyl group appeared as a broad singlet at τ8.20. The ir spectrum of this material showed two weak bands at 1650 and 1600 cm^{-1}.

When the silyl ether 167 was pyrolysed (procedure B), the major product formed was o-cyclopropyltoluene 170 (entry 4, Table 4). Presumably, the silyl enol ether 167 had undergone two successive [1,5] sigmatropic hydrogen migrations to give the intermediate 169. Elimination of $(CH_3)_3SiOH$ from 169 could then give O-cyclopropyltoluene 170 (eq.39).



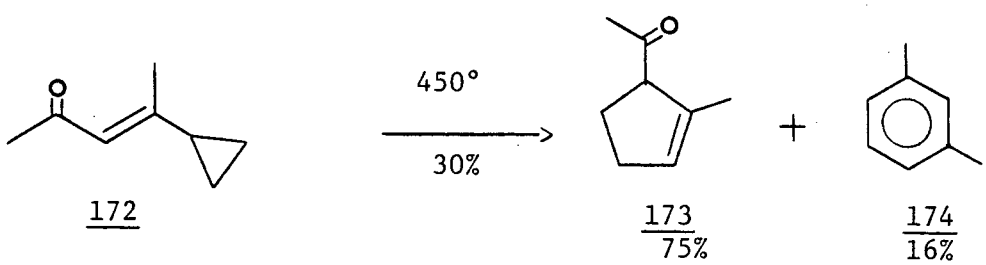
167 168 169 170 (39)

In contrast, pyrolysis (procedure B) of the trimethylsilyl enol ether of 3-cyclopropyl-2-cyclohexen-1-one 171, followed by hydrolysis and work-up, gave a 67% yield of a mixture of the annelated cyclopentene 162 (∿76%) and a number of unidentified impurities (∿24%)(entry 3, Table 4)



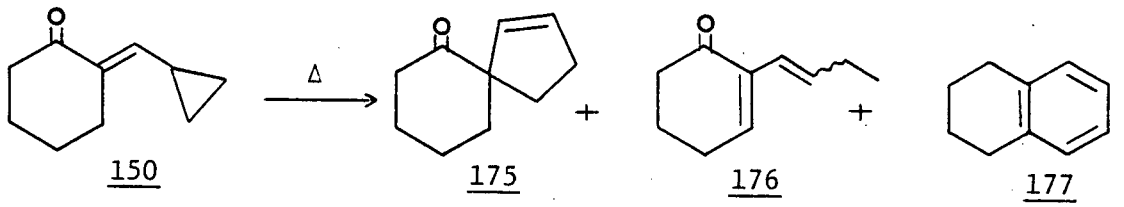
(40)

The only acyclic β-cyclopropyl-α,β-unsaturated ketone investigated during the course of the work described in this thesis was compound 172. Thermolysis of this compound at ∿450°C (procedure A) gave a mixture of the ketone 173 (∿75%) and m-xylene 174 (∿16%) in a total yield of ∿30% (eq.41, entry 5, Table 4).



(41)

The initial studies involving thermal rearrangement of 2-cyclopropylmethylenecycloalkanones were performed on the short thermolysis column, using the old procedure (procedure A). Thermolysis of 2-cyclopropylmethylenecyclohexanone 150 at ∿450°C gave a 74% yield of a mixture of the spiroketone 175 (∿44%), the dienone 176 (∿9%) and tetralin 177 (∿38%), along with a small amount (∿9%) of minor impurities which were not identified (entry 6, Table 4).

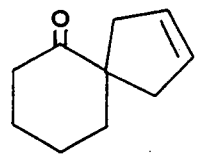


150 175 176 177 (42)

The spiroketone 175 exhibited an interesting ^{1}Hnmr spectrum. From a structural point of view, the two olefinic protons were clearly non-equivalent and were expected to have different chemical shifts. It was therefore surprising to find that these two protons appeared as a sharp two-proton singlet at τ4.24. The rest of the protons showed up as a five-proton multiplet at τ7.40-7.82 and a seven-proton multiplet at τ7.97-8.60. In order to determine whether or not it was possible to distinguish between the two olefinic protons by ^{1}Hnmr, the spectrum of 175 was reinvestigated in the presence of a shift reagent: $Eu(FOD)_3d_{27}$. Under these conditions, the olefinic protons appeared as two sets of doublets of triplets at τ3.58 and 3.94. Each set had coupling constants, J=6 Hz and J'=2 Hz. Furthermore, the original five-proton multiplet at τ7.40-7.80 was transformed into a three-proton multiplet at τ6.44-6.84 and a two-proton multiplet at τ7.14-7.50. The original seven-proton multiplet was shifted to τ7.62-8.12. In a decoupling experiment (in the presence of the shift reagent), irradiation at τ7.29 (the signal due to the two protons α to the double bond) caused the two doublets of triplets at τ3.58 and 3.94 to collapse to an AB pair of doublets (J=5.6 Hz), as would be expected.

To further confirm the position of the double bond in the spiro compound 175, the ^{1}Hnmr spectrum of the isomeric spiroketone 178 (kindly supplied by Dr. R. D. Sands of Alfred University, Alfred, New York[116]) was compared with that of compound 175. As expected, the two olefinic

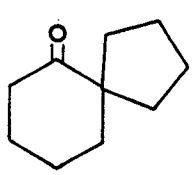
protons of compound 178, which were structurally equivalent, appeared as a singlet. However, the chemical shift of these protons (τ4.50) was slightly different from that of the olefinic protons in compound 175.



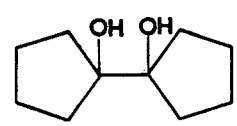
178

Further evidence for the structure of the spiro enone 175 was supplied by the ^{13}Cnmr spectrum (proton decoupled) of this compound. The spectrum showed the presence of two nonequivalent olefinic carbon atoms at δ(ppm) 132.46 and 133.35, a carbonyl carbon atom at 211.48 and a quaternary carbon atom at 64.06. The rest of the carbon centers appeared at δ(ppm) 22.96, 27.67, 31.28, 32.29, and 39.89 (2 carbons).

Finally, in order to confirm the spiro carbon skeleton of ketone 175, this material was hydrogenated (10% Pd/C in methanol) to the saturated spiroketone 179. The spectral data (ir, ^{1}Hnmr) of the latter were identical with those of an authentic sample of 179 prepared from the pinacol rearrangement of the diol 180.[117] The diol 180 was prepared from the dimerization of cyclopentanone using aluminum and mercuric chloride.[101]



179

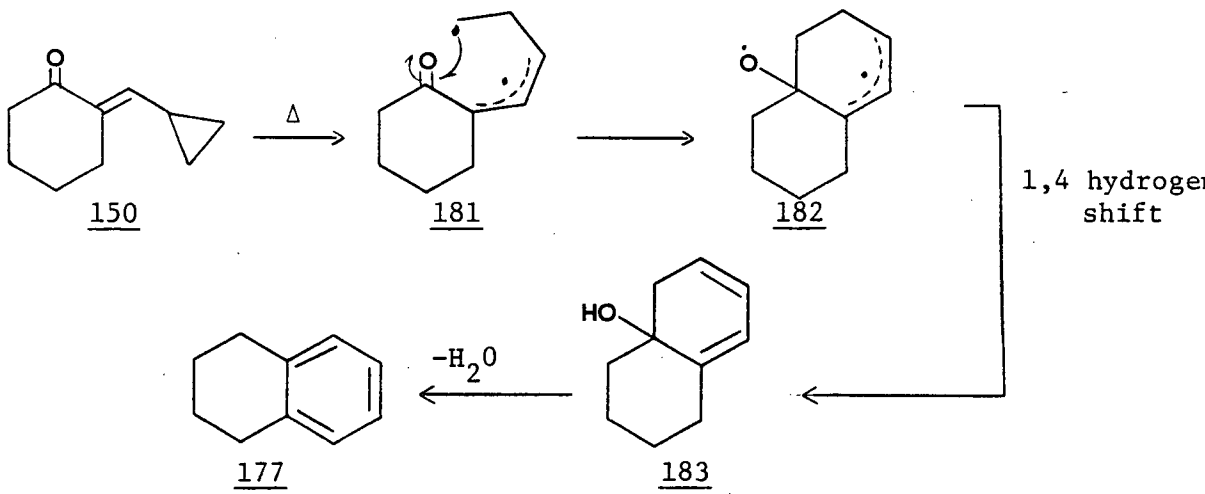


180

The ^{1}Hnmr spectrum of the dienone 176 indicated that it was a mixture of cis and trans isomers. The terminal methyl groups of the isomers resonated at τ8.99 and 9.02. Exhausive hydrogenation of the

mixture gave a single product, 2-n-butylcyclohexanone. Spectral data (ir, ^{1}Hnmr) of the latter were identical to those reported in the Sadtler Index.

The formation of tetralin 177 may be rationalized as follows. Homolysis of the cyclopropane ring would give the diradical 181. Ring closure to give the bicyclic diradical intermediate 182, followed by hydrogen migration would afford the dienol 183. Dehydration of the latter would then give tetralin 177 (Scheme 8).

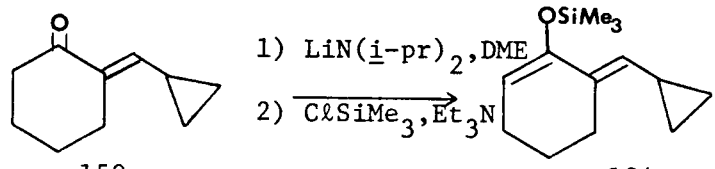


150 181 182 183 177

Scheme 8

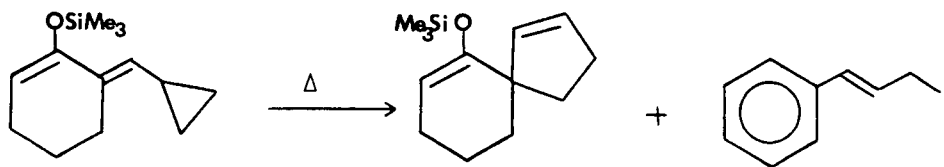
Although the thermolysis of 2-cyclopropylmethylenecylohexanone 150 did give the expected spiro ketone 175, a considerable amount of the undesired tetralin 177 was also formed. Since, as postulated above, the formation of tetralin probably involved the carbonyl functionality, it seemed reasonable to postulate that masking the carbonyl group would eliminate the formation of tetralin. Thus, the trimethylsilyl enol ether of enone 150 was prepared. The trimethylsilyl enol ether 184 was obtained by first treating the enone 150 with lithium diisopropylamide in 1,2-dimethoxyethane, followed by the addition of chlorotrimethylsilane

in the presence of triethylamine (eq.43). The structure of the enol ether 184 was supported by spectral data. In the ^{1}Hnmr spectrum, the olefinic proton on the exocyclic cyclopropylmethylene group resonated as a doublet at τ4.92, with coupling constant = 9.5 Hz. The other olefinic proton on the six-membered ring gave rise to a triplet at τ5.04 with J=4.5 Hz. A nine-proton singlet due to the trimethylsilyl group appeared at τ9.87. The ir spectrum showed two weak absorption bands at 1680 and 1660 cm^{-1}.



150 184 (43)

Thermolysis of the trimethylsilyl enol ether 184 (procedure A) gave a 74% yield of a mixture of the spiro enol ether 185 (∿74%),



184 185 186 (44)

trans-1-phenyl-1-butene 186 (∿14%), and small amounts of unidentified minor impurities (∿12%). No tetralin was detected (eq.44, entry 7a, Table 4). An analytical sample of each of the two major components was obtained by preparative glc and their structures were confirmed by the spectral data. The ^{1}Hnmr spectrum of compound 185 exhibited a one-proton triplet (J=4 Hz) at τ5.28, readily attributable to the olefinic proton of the enol silyl ether group. A one-proton multiplet between τ4.24 and 4.37 and another one-proton multiplet between τ4.45 and 4.60

could be assigned to the other two olefinic protons in the molecule. The trimethylsilyl group gave rise to a nine-proton singlet at τ9.93. The ir spectrum of this material showed a strong absorption at 1655 cm^{-1}.

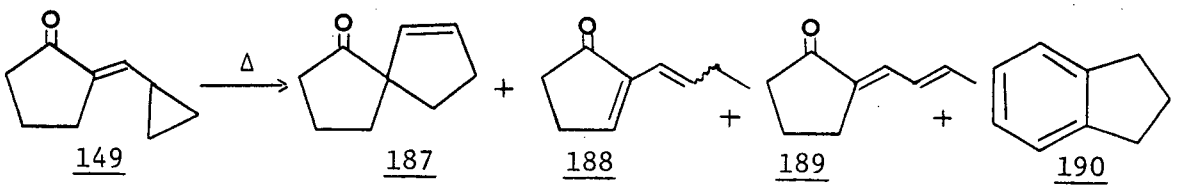
In the ^{1}Hnmr spectrum of compound 186, a five-proton multiplet at τ2.60-3.00 indicated the presence of a monosubstituted benzene ring. The two olefinic protons gave rise to a multiplet between τ3.55 and 4.00. The two allylic methylene protons appeared as a multiplet at τ7.64-8.00, whereas the terminal methyl group showed up as a three-proton triplet at τ8.95 with J=7 Hz. These data were essentially the same as those reported in the literature.[118]

It was thus quite clear that in terms of the yield of spiroannelation product, the thermolysis of the trimethylsilyl enol ether 184 showed considerable improvement over the thermal rearrangement of the parent enone 150. The thermolysis (procedure A) of the enol ether 184 was repeated on a larger scale (1.0g). The crude thermolysis product was hydrolyzed in a 1:1 mixture of methanol and 1N aqueous hydrochloric acid and the hydrolyzed product was subjected to column chromatography. A 50% overall yield of the pure spiro ketone 175 was isolated.

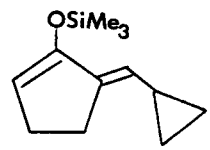
The thermolysis of the trimethylsilyl enol ether 184 was later improved further by employing the new procedure (procedure B) using the long pyrolysis column. Thus pyrolysis of the enol ether 184 at ∿425°C gave an 85% yield of one major product, the spiro enol ether 185 (∿84%), along with a small amount of minor impurities (∿16%) which were not identified (entry 7b, Table 4). No trans-1-phenyl-1-butene was detected.

A preliminary study by Dr. I. Nagakura of our laboratory showed that thermolysis of 2-cyclopropylmethylenecyclopentanone 149 at ∿450°C

(procedure A) gave a fairly low yield of the desired product, the spiro ketone 187. A considerable amount of the undesired dienones 188, 189 and indane 190 was also formed (eq.45, entry 8a, Table 4). In an attempt to improve this reaction, the cyclopropyl enone 149 was pyrolysed at ∿425°C under the new procedure (procedure B)(entry 8b, Table 4). Although the reaction product was somewhat cleaner, the yield of the spiro ketone 187 had not been improved.



149 187 188 189 190 (45)



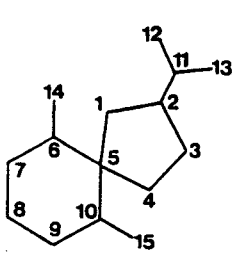
191

Finally, the trimethylsilyl enol ether 191 was prepared via a procedure identical with that employed for the enol ether 184. Thermolysis of the enol ether 191 at ∿425°C (procedure B) followed by hydrolysis of the crude pyrolysis product gave a 56% yield of a colorless oil. A glc analysis of this material showed the presence of essentially one product (∿94%), the spiro ketone 187 (entry 9, Table 4). However, the ir spectrum of this material showed the presence of both saturated and α,β-unsaturated carbonyl compounds. Therefore, this material was subjected to column chromatography. Eventually, a 38% overall yield of the spiro ketone 187 was isolated. The low yield of the latter may be attributed partly to its volatility and to mechanical losses. The structure of spiro ketone was confirmed by spectral analysis. The ir spectrum showed the presence of a five-membered ring ketone (ν_{max} 1742 cm^{-1}). In the ^{1}Hnmr spectrum, the two olefinic protons gave rise to two sets of multiplets at τ4.10 and 4.55.

In general, the thermolysis of the cyclic β-cyclopropyl-α,β-unsaturated ketones described so far gave reasonable yields of the expected annelated cyclopentenes. Since the reactions were simple to perform and the desired products were fairly easy to isolate, this procedure should find more applications in the future as a synthetic method for cyclopentene annelation. Of particular interest is the spiroannelation reaction involving the thermolysis of 2-cyclopropylmethylenecycloalkanones or the corresponding enol silyl ethers. For example, the thermolysis of 2-cyclopropylmethylenecyclohexanone 150 or its trimethylsilylenol ether derivative afforded a spiro[4.5]decane system and it is thus clear that this reaction could serve as a key step in the synthesis of a wide variety of naturally occuring spiro[4.5]decane sesquiterpenes, for example, the spirovetivanes. The possibility of applying this spiroannelation method to the synthesis of spirovetivanes was investigated and constitutes the next portion of this thesis.

IV. Application of Thermal Vinylcyclopropane-Cyclopentene Rearrangement to Spirovetivane Synthesis

The rapidly increasing number of known spirovetivane-type sesquiterpenoids have in common the structurally interesting carbon skeleton 192. Representatives of the spirovetivanes include β-vetivone 193, α-vetispirene 194, β-vetispirene 195, hinesol 196, and anhydro-β-rotunol 197.[119]



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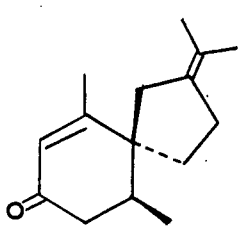

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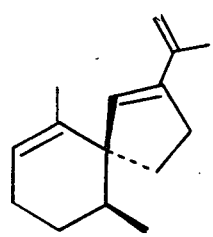

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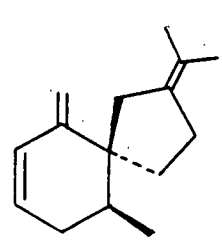

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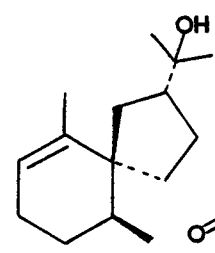

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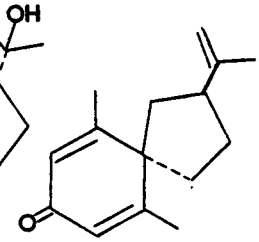
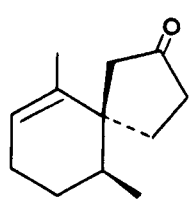


197

The interest in the spirovetivane class of sesquiterpenoids as constituents of essential oils, as stress metabolites, and as proposed intermediates in terpene biogenesis has stimulated considerable synthetic efforts directed towards the preparation of these compounds.[121-132] The first efforts in this area were reported by Marshall and coworkers[120], who had earlier shown that β-vetivone is a member of this group rather than a hydroazulene derivative as originally reported. Due in part to the widely variant oxidation state at carbons 1,2,6,7,8,11,12 and 14 throughout the series, earlier synthetic efforts had concentrated on the construction of specific spirovetivanes.[121-128] Recently, the emphasis has shifted toward the construction of one or more intermediates which could serve as a synthetic precursor of a number of natural products belonging to this class of sesquiterpenes.[129-132] Among the few syntheses that employed this approach[129-132], it is of interest to note that those reported by Caine[129] and Buchi[132] have involved the use of the spiro olefinic ketone 198 as a key intermediate. So far, the latter has been converted into (±)-α-vetispirene 194[129], (±)-β-vetivone 193[132], and (±)-hinesol acetate 199.[132] Here we report a convenient alternative preparation of the synthetic intermediate 198 based on the new thermal spiroannelation method developed earlier, as described in the previous section of this thesis.



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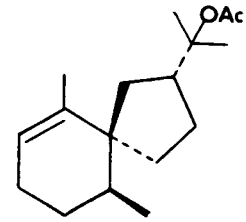
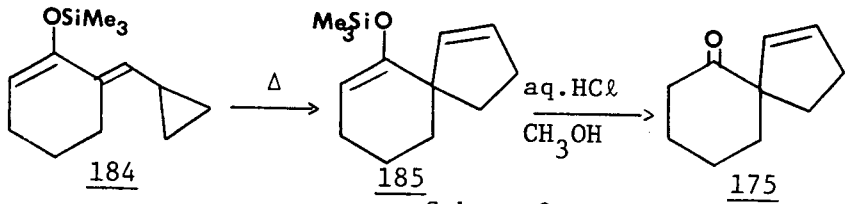


199

As described previously, the spiro enone 175 could be prepared in good yield by the thermal rearrangement of the enol silyl ether 184, followed by the hydrolysis of the initially formed product 185 (Scheme 9).

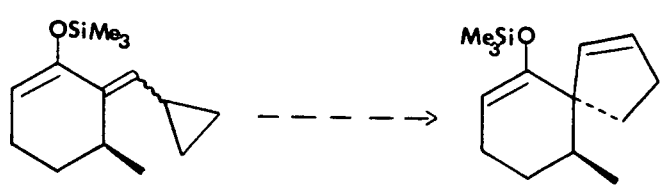
The success of these earlier efforts encouraged us to investigate the possibility of applying this methodology to the synthesis of spirovetivanes.



184 185 175

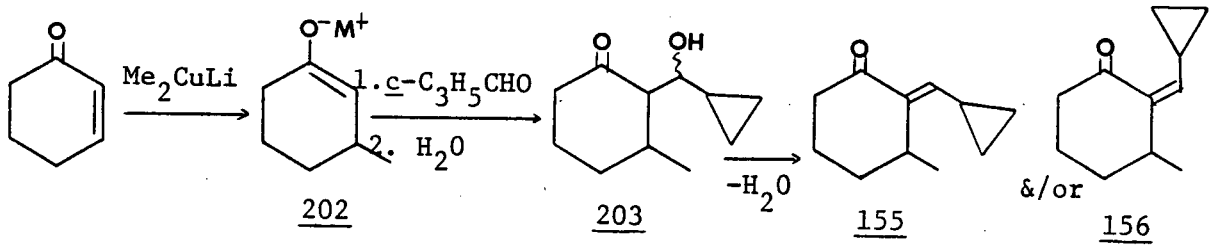
Scheme 9

Since the synthetic intermediate 198 employed by Caine[129] and Buchi[132] had the potential of serving as a synthetic precursor of a fairly large number of spirovetivanes, it was decided to make this compound our synthetic goal. The key step to compound 198 would then be to synthesize a spiro[4.5]decane system that contained both a methyl group at carbon 10 and a suitable functionality on the five membered ring which subsequently could be readily converted to a carbonyl group at carbon 2. One possible candidate was the spiro enol silyl ether 201, which on the basis of the previous work, should be obtainable by thermal rearrangement of the enol silyl ether 200 (eq.46). Hopefully, mainly for steric reasons, the methyl group on the six-membered ring of 200 would, during the thermolytic rearrangement, direct bond formation in the required manner so that the spiro compound 201 would be produced stereoselectively. Thus, the initial synthetic objective was to prepare the enol silyl ether 200 and to carry out the thermal rearrangement of this compound.



200 201 (46)

The conjugate addition of lithium diorganocuprate reagents to α,β-unsaturated carbonyl compounds produces, prior to hydrolysis, an intermediate with the properties of a metal enolate.[133] This reaction intermediate reacts with a variety of electrophilic reagents, such as carbonyl compounds, to give aldol products[134], Michael addition acceptors to form Michael adducts[135], and reactive alkyl halides to form alkylated ketones.[136] Thus, it was expected that the addition of lithium dimethylcuprate to 2-cyclohexen-1-one, followed by trapping the resulting enolate with cyclopropanecarboxaldehyde, would give the ketol 203 regioselectively. Dehydration of the ketol 203 would then give the desired β-cyclopropyl enone 155 and/or 156 (scheme 10).

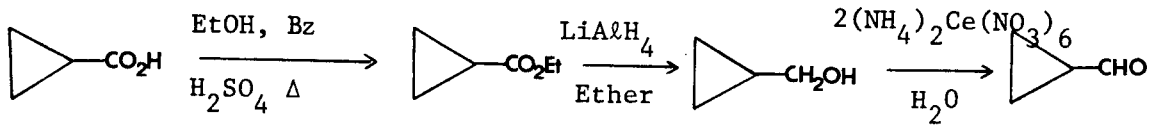


202 203 155 156

Scheme 10

Cyclopropanecarboxaldehyde, which is not commerically available, can be prepared by a wide variety of methods, including reduction of N,N-dimethylcyclopropylcarboxamide with diethoxyaluminohydride[137] and oxidation of cyclopropylcarbinol by pyridinium chlorochromate[138], chromium trioxide and sulfuric acid in dimethylformamide[139], N-chlorosuccinimide and dimethylsulfide[140], or manganese dioxide in pentane.[141] All of these methods were tried, but none of them gave satisfactory isolated yields of the pure aldehyde. Finally, it was found that the method which gave the most satisfactory results (71% isolated yield of pure cyclopropanecarboxaldehyde) involved ceric ammonium nitrate oxidation of cyclopropylcarbinol.[142] The latter, though commercially available, was prepared from cyclopropanecarboxylic acid. Esterification of the acid with

ethanol in refluxing benzene containing a catalytic amount of sulfuric acid[143], followed by lithium aluminum hydride reduction of the resulting ester, gave a 55% overall yield of the cyclopropylcarbinol[144] (Scheme 11). It was found that direct reduction of cyclopropanecarboxylic acid by diborane in tetrahydrofuran failed to give an acceptable yield of cyclopropylcarbinol.[145]

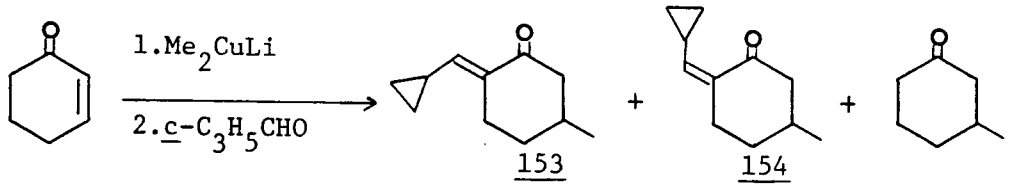


Scheme 11

Addition of 2-cyclohexen-1-one to a cold (0°C) ether solution of lithium dimethylcuprate, followed by trapping of the resulting enolate anion with one equivalent of cyclopropanecarboxaldehyde gave a 60% yield of a colorless oil. A glc analysis of this material showed the presence of a major component (∿70%) and two minor compounds (∿14% and 7% respectively). An analytical sample of each component was obtained by preparative glc. The major component was identified as the enone 153, the regioisomer of the expected product 155. The structural assignment of enone 153 was based on spectral analysis. The β-olefinic proton of enone 153 exhibited a doublet of triplets (J=11 Hz, J'=2 Hz) at τ3.92 in the ^{1}Hnmr spectrum rather than a doublet of doublets as would be expected from the desired regioisomer 155.

One of the minor components (∿7%) was identified as the geometrical isomer 154 of the enone 153. The ^{1}Hnmr spectrum of the enone 154 also exhibited a doublet of triplets (J=11 Hz, J'=2 Hz) for the β-olefinic proton, the chemical shift of which was at τ5.08. The assignment of stereochemistry to the two isomers, 153 and 154 had been discussed earlier in this

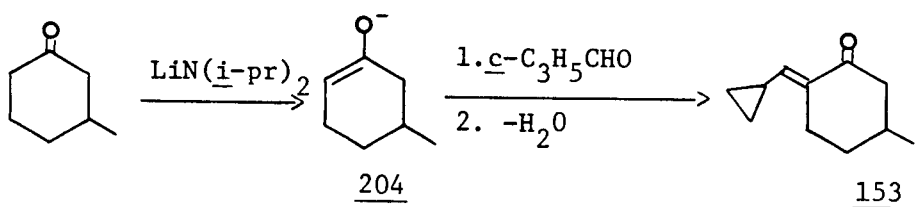
thesis and will not be repeated here.



(47)

Finally, the other minor isomer (∿14%) was found to be 3-methylcyclohexanone by comparing the ^{1}Hnmr spectrum of this material with that of an authentic sample obtained commercially.

In order to show conclusively that the major component obtained from the cuprate reaction was indeed compound 153 and not 155, a specific synthesis of compound 153 was carried out. Thus, addition of 3-methylcyclohexanone to an ethereal solution of lithium diisopropylamide, kinetically generated enolate anion 204.[146] Trapping this enolate anion with cyclopropanecarboxaldehyde, followed by dehydration of the intermediate ketol, gave a 23% yield of 2-cyclopropylmethylene-5-methylcyclohexanone 153 (eq.48). The spectral data obtained from this material were identical with those of the major component obtained from the cuprate reaction described above.

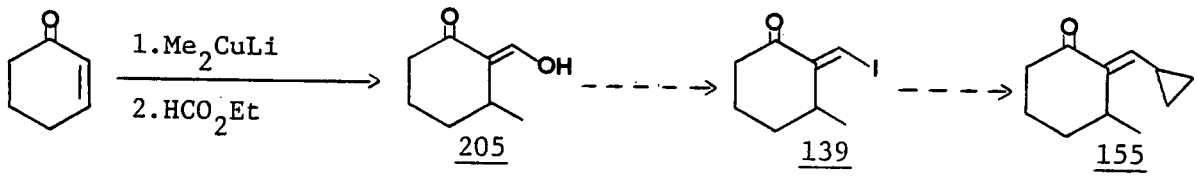


(48)

It was apparent that, in the cuprate addition reaction to 2-cyclohexen-1-one, equilibration and isomerization of the intermediate enolate anion must have occurred prior to the condensation with the aldehyde giving enones 153 and 154 as the resulting products.

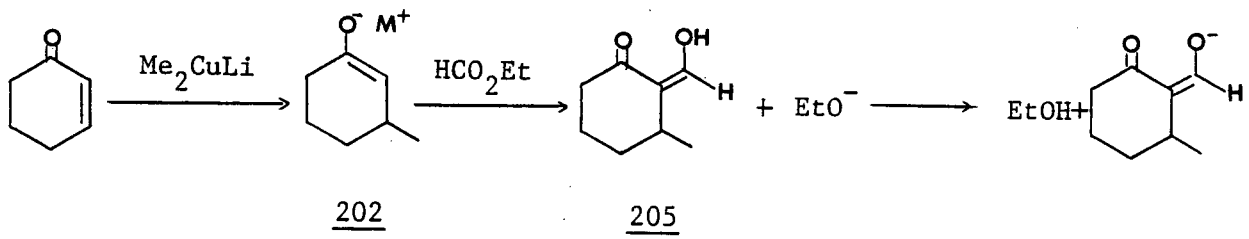
The condensation of the specific enolate 202 with ethyl formate was also investigated. Ethyl formate was chosen because the resulting 2-hydroxy-

methylene-3-methylcyclohexanone 205, if formed, could be readily transformed into 2-cyclopropylmethylene-3-methylcyclohexanone 155 via the corresponding β-iodo enone 139 as described earlier in this thesis for 2-hydroxymethylenecyclohexanone 110 (Scheme 12).



Scheme 12

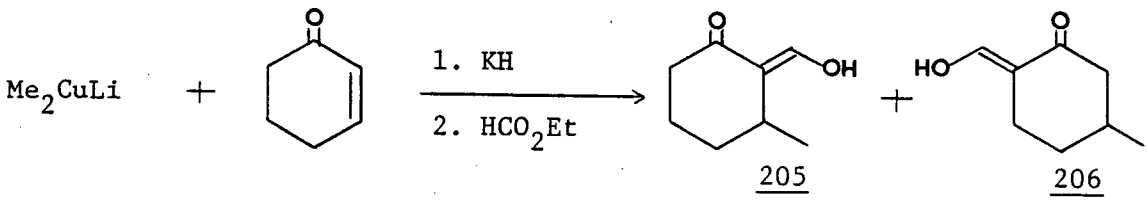
The condensation reaction of ethyl formate with the specific enolate generated by the cuprate addition to 2-cyclohexen-1-one would also give rise to an ethoxide anion (Scheme 13). The latter could abstract a proton from the initially formed product 205 to form ethanol. The ethanol could then serve as a source of protons to allow the kinetically generated enolate 202 to equilibrate.



Scheme 13

It was therefore proposed to add potassium hydride to the reaction mixture so that a significant concentration of ethanol could be avoided. In this way, it was hoped that, in absence of significant amounts of a proton source, equilibration of the intermediate enolate anion would be negligible and hence the reaction might be regioselective. This idea was tried out as follows. To a cold solution (0°C) of lithium dimethylcuprate

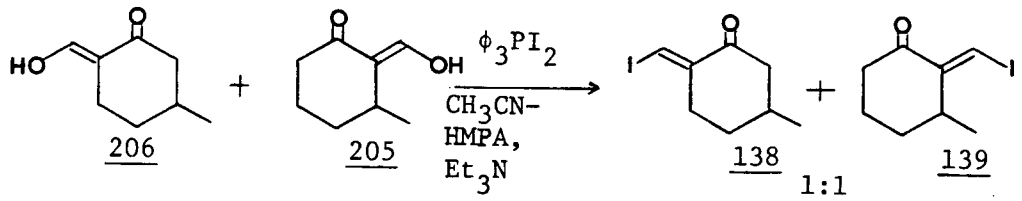
(1.5 eq.) in ether was added one equivalent of 2-cyclohexen-1-one. Then two equivalents of potassium hydride were added, followed by the addition of two equivalents of ethyl formate. The resulting solution was stirred at 0°C for 1h. After work-up, a 41% yield of a 1:1 mixture of 2-hydroxymethylene-3-methylcyclohexanone 205 and 2-hydroxymethylene-5-methylcyclohexanone 206 was obtained (eq.49). The ^{1}Hnmr of this mixture showed the



(49)

presence of two olefinic protons at τ1.30 and 1.36 in the ratio of ∿1:1, corresponding to the two β-olefinic protons on the α-hydroxymethylene groups of the two compounds 205 and 206.

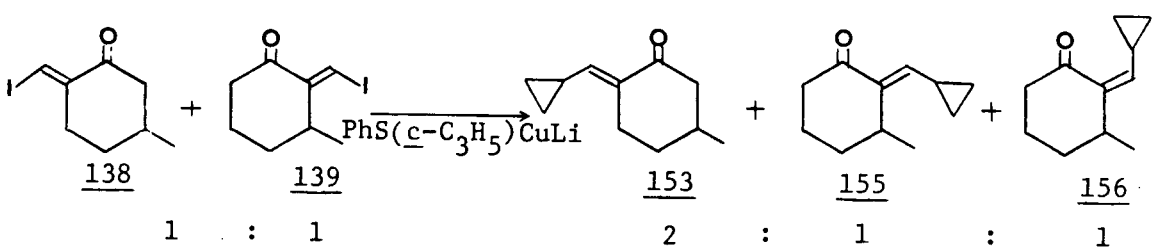
Although it was clear that the above reaction was not regioselective, as had been hoped, it was nevertheless decided to transform the two compounds, 205 and 206 into the corresponding β-cyclopropyl enones, so that the latter could be compared with the β-cyclopropyl enones obtained earlier by condensation of 202 with cyclopropanecarboxaldehyde. Thus, treatment of the mixture of 205 and 206 with triphenylphosphine diiodide in acetonitrile-hexamethylphosphoramide in the presence of triethylamine gave an 82% yield of a 1:1 mixture of the corresponding β-iodo enones 139 and 138, respectively (eq.50). An analytical sample of each of the products 138 and 139 was obtained by preparative glc.



(50)

In each case, the assigned structure was supported by spectral data. The ir of iodo enone 138 showed the presence of an α,β-unsaturated ketone (ν_{max} 1690, 1570 cm^{-1}). The ^{1}Hnmr spectrum showed the presence of only one olefinic proton which resonated at τ2.30 as a triplet (J=2 Hz). The methyl group gave rise to a signal at τ8.97 in the form of a doublet (J=5.5 Hz). Compound 139 exhibited similar spectral data. The ir spectrum of compound 139 showed two strong bands at 1685 and 1565 cm^{-1}. The single olefinic proton showed up as a singlet at τ2.51 in the ^{1}Hnmr spectrum. The methyl group gave rise to a doublet at τ8.94 with J=7 Hz. The allylic proton at C-3 showed up as a multiplet at τ6.64-7.02.

The mixture of iodo enones 138 and 139 was converted into a mixture of the corresponding β-cyclopropyl enones by treating the former with lithium phenylthio(cyclopropyl)cuprate. A 75% yield of a mixture of the β-cyclopropyl enones 153, 155 and 156 in a ratio of 2:1:1, respectively, was obtained (eq.51). An analytical sample of each compound was obtained by preparative glc. The spectral data obtained from compound 153 was identical with those



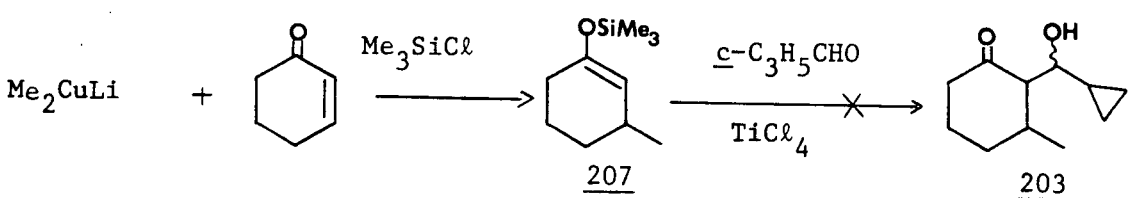
(51)

of the same compound obtained as described earlier. In the ^{1}Hnmr spectrum of the enone 155, the β-olefinic proton appeared as a doublet of doublets (J=11 Hz, J'=1 Hz) at τ4.02. The analogous proton of the isomeric compound

156 gave rise to a doublet of doublets (J=10.5 Hz, J'=2 Hz) at τ5.16. The assignment of stereochemistry to the two isomers, 155 and 156 had been discussed earlier.

On the basis of results obtained from the experiments described above, it was clear that addition of lithium dimethylcuprate to 2-cyclohexen-1-one, followed by trapping of the resulting enolate anion with cyclopropanecarboxaldehyde, did not give the desired product 155. Furthermore, although the alternative procedure involving ethyl formate as trapping agent, did eventually produce some of the desired material, this methodology also failed to give the desired isomer 205 regioselectively. Therefore, other methods were investigated.

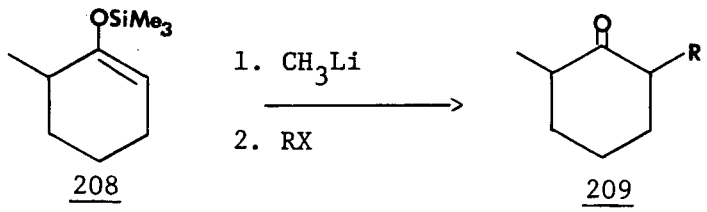
Mukaiyama et al.[147] had reported that silyl enol ethers, prepared from various carbonyl compounds, reacted with aldehydes and ketones in the presence of titanium tetrachloride under mild conditions to give cross-aldol condensation products in good yields. The enol silyl ether 207 was obtained from the 1,4-addition of lithium dimethylcuprate to 2-cyclohexen-1-one, followed by trapping the resulting enolate anion with chlorotrimethylsilane[148] (eq.52). When the Mukaiyama procedure was applied to the trimethylsilyl enol ether 207 and cyclopropanecarboxaldehyde, however, no condensation product was obtained. Only 3-methylcyclohexanone was recovered.



(52)

It is well known that specific enolates generated by the reaction of methyllithium with silyl enol ethers of various carbonyl compounds may be

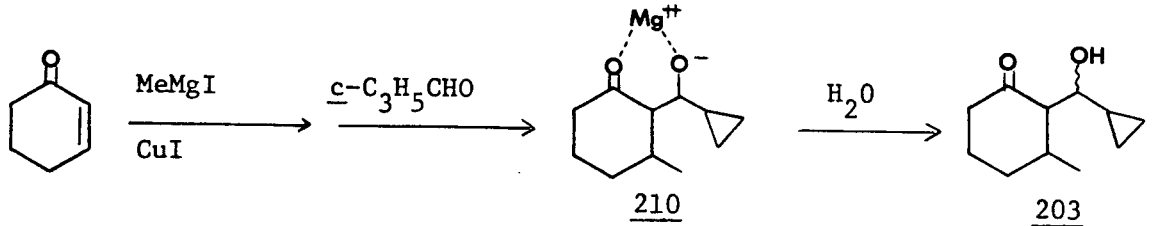
alkylated regioselectively, for example, eq. 53.[149] It was therefore decided



208 209 (53)

to attempt a similar reaction using cyclopropanecarboxaldehyde as the electrophilic trapping reagent. If this reaction had been successful, it should have produced the ketol 203. Unfortunately, when the enol ether 207 was treated with methyllithium, followed by the addition of cyclopropanecarboxaldehyde, only the enone 153 was obtained after work-up. Presumably, equilibration of the intermediate lithium enolate anion had occurred faster than condensation. In view of earlier results obtained from attempts to trap the specific enolate generated directly by cuprate addition to 2-cyclohexen-1-one, this result was perhaps not surprising.

Finally it was found that the specific enolate anion generated by copper catalysed conjugate addition of methyl magnesium iodide to 2-cyclohexen-1-one could be trapped by cyclopropanecarboxaldehyde regioselectively to give the ketol 203 as a mixture of diastereomers in ∿97% yield (Scheme 14). It is important to note that when cyclopropanecarboxaldehyde was added to the ether solution of the specific enolate anion, a thick greyish white precipitate formed immediately and remained undissolved throughout the reaction. The regioselectivity of the reaction may thus be attributed to the insolubility of this intermediate alkoxide anion 210.



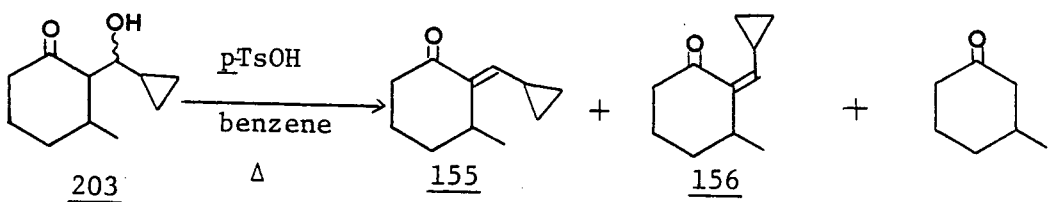
210 203

Scheme 14

The structure of the ketol 203 was supported by its ir spectrum which showed the presence of a saturated six-membered ring ketone (ν_{max} 1700 cm^{-1}) and an alcohol functionality (ν_{max} 3470 cm^{-1}). A tlc analysis of this material showed the presence of two components in approximately equal amounts (spots of equal intensity). This material underwent partial dehydration and retroaldol reaction upon distillation. Because of its instability, it was not purified further but was used directly in the next step.

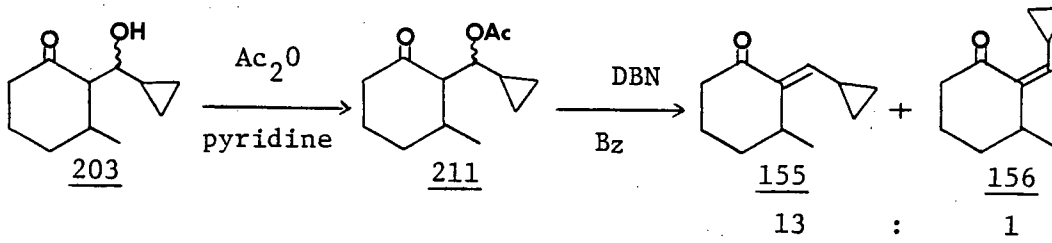
Dehydration of ketol 203 by treatment of this material with p-toluenesulfonic acid in refluxing benzene gave a 6:1 mixture of the enones 155 and 156, respectively, in ∿50% overall yield from 2-cyclohexen-1-one (eq.54). A considerable amount of 3-methylcyclohexanone was also isolated. Apparently, extensive retroaldol reaction occurred under these reaction conditions.

The yield of the mixture of enones 155 and 156 was improved considerably



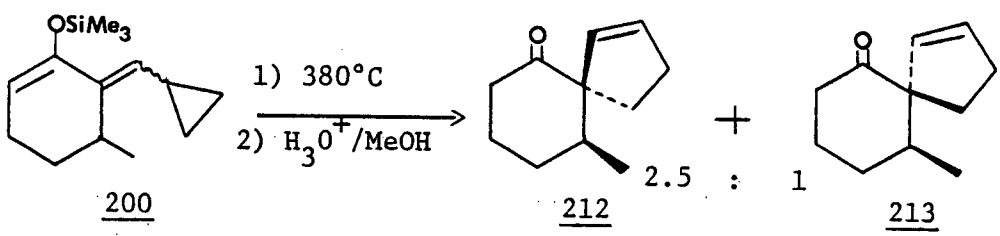
(54)

by first converting the ketol 203 into the corresponding acetate 211 (acetic anhydride, pyridine). The ^{1}Hnmr spectrum of the latter showed that it was a mixture of diastereomers. Elimination of acetic acid from the acetate 211, accomplished by treatment of the latter with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in refluxing benzene, gave an overall 78% yield of a 13:1 mixture of enones 155 and 156, respectively, from the ketol 203 (eq.55).



203 → 211 → 155 + 156 (13 : 1) (55)

Conversion of the mixture of enones 155 and 156 into the corresponding trimethysilyl enol ethers 200 was carried out by the standard procedure (lithium diisopropylamide, glyme, 0°C; chlorotrimethylsilane, triethylamine) as described previously for other enones of similar structure. The formation of enol silyl ether 200 was confirmed by the ^{1}Hnmr spectrum of this material, which showed the presence of the olefinic proton at C-6 as a one-proton triplet (J=3 Hz) at τ5.11. The ir spectrum of this material also showed that the carbonyl functionality was absent. Thermolysis of the enol silyl ether 200 at ∿380°C under argon (procedure B), followed by hydrolysis (1:1 mixture of 1N aqueous hydrochloric acid and methanol) of the resulting crude product afforded a mixture (∿57% yield from 155 and 156) of the spiro enones 212 and 213 in a ratio of about 2.5:1 respectively (eq. 56). The two products were separated by column chromatography of the mixture on silica gel. The assignment of structure and



200 → 212 + 213 (2.5 : 1) (56)

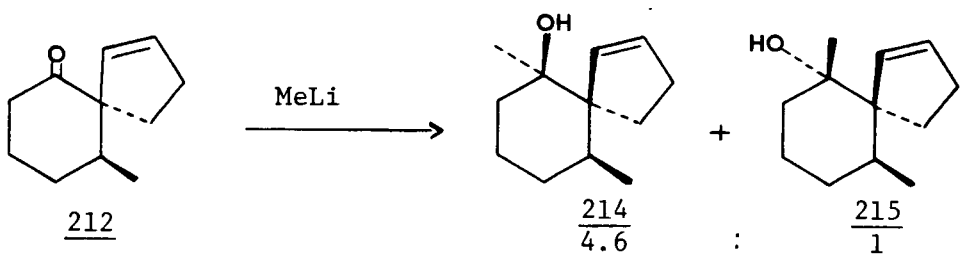
stereochemistry to compounds 212 and 213 were supported by spectral data and by subsequent transformation of 212 into compounds of known structure and stereochemistry.

The spiro enone 212 was a crystalline solid (m.p. 35-38°C). The ir spectrum showed the presence of a saturated six-membered ring ketone (ν_{max} 1705 cm^{-1}). The two olefinic protons gave rise to a multiplet at τ4.02-4.38 in the ^{1}Hnmr spectrum. The methyl group gave rise to a doublet (J=6 Hz) at τ9.10. The rest of the protons produced a multiplet at τ7.16-8.60.

The enone 213 also showed a saturated carbonyl absorption at 1705 cm^{-1} in the ir spectrum. The ^{1}Hnmr of this material showed a two-proton multiplet at τ4.02-4.40 (olefinic protons), a three-proton doublet (J=6 Hz) at τ9.14 (secondary methyl group), a four-proton multiplet between τ7.42 and 7.80 and a seven proton multiplet between τ7.80-8.60.

There was no apparent relationship between the stereochemistry of the reactant 200 and that of the products (212 and 213) in the thermolysis reaction. The same ratio of products was obtained when different samples of 200 containing varying amounts of the two geometric isomers were pyrolysed. Although the stereoselectivity associated with this step was not as high as had been hoped, the minor isomer 213, which had the "wrong" stereochemistry, is not necessarily useless from a synthetic point of view, since it is also a potential intermediate for spirovetivane synthesis.

Treatment of the enone 212 with methyllithium in ether at 0°C afforded a 78% yield of a mixture of the alcohols 214 and 215, in a ratio of ∿4.6:1 (eq. 57). The two isomers were separated by column chromatography on silica gel.

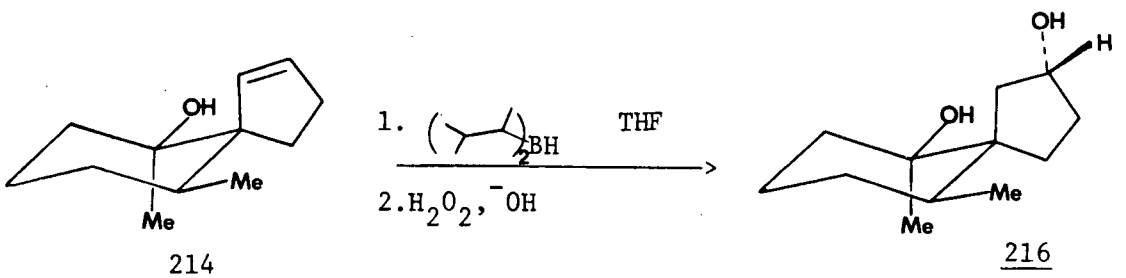


212 → 214 / 4.6 : 215 / 1 (57)

Compound 214 showed the presence of an alcohol functionality in the ir spectrum (ν_{max} 3500 cm^{-1}) and, in the ^{1}Hnmr spectrum, an "extra" methyl group (singlet at τ8.78). This material was identical with an authentic sample of the same material previously prepared and kindly supplied by Buchi and coworkers.[132]

The minor isomer 215 exhibited spectral data very similar to those of compound 214. A strong absorption band at 3490 cm^{-1} in the ir spectrum indicated the presence of an alcohol functionality. In the ^{1}Hnmr spectrum, a three-proton singlet at τ8.96 was assigned to the methyl group α to the alcohol functionality. The other methyl group remained as a three proton doublet (J=6.5 Hz) at τ9.25. Each of the two olefinic protons gave rise to a doublet of triplets (τ4.19 and 4.48). Each signal had the same coupling constants (J=6 Hz, J'=2 Hz).

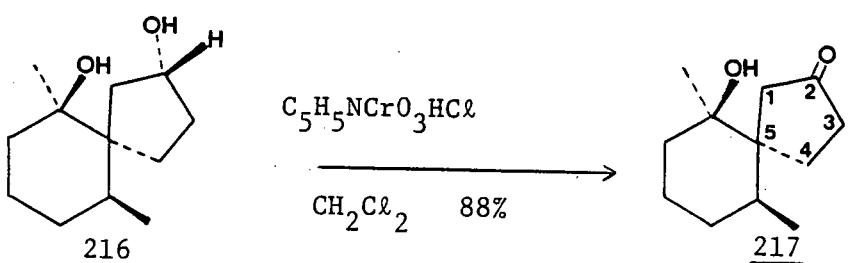
Hydroboration of the olefinic alcohol 214 with disiamylborane in tetrahydrofuran (r.t., 21h), followed by oxidation of the resulting trialkylborane with alkaline hydrogen peroxide gave a single diol 216 in 77% yield (eq.58). Diol 216 was a crystalline solid (m.p. 153-155°C). The ir spectrum showed two alcohol bands at 3480 and 3640 cm^{-1}. No olefinic protons were observed in the ^{1}Hnmr spectrum of this material. A one-proton multiplet at τ 5.55-5.95 was assigned to the proton next to the newly acquired alcohol functionality.



214 216 (58)

The stereochemical assignment of compound 216 was based on steric arguments. In the more stable conformation of compound 214, one of the methyl groups and the hydroxyl group should be equatorial. Since the methyl group is bulkier than the flexible hydroxy group, and since the large hydroborating agent should preferentially attack from the less hindered side of the carbon-carbon double bond, one would expect the diol 216 to be the only (or at least the predominant) product.

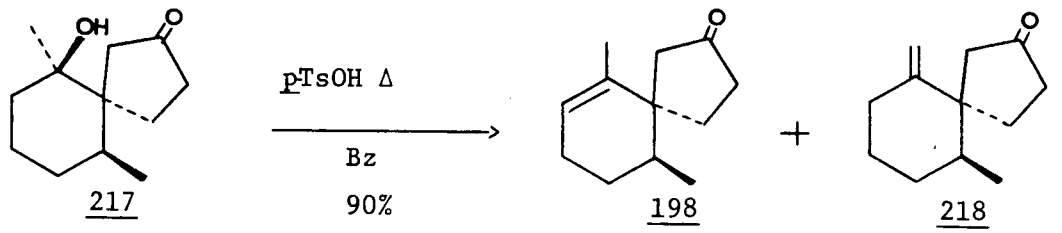
Oxidation of the diol 216 with pyridinium chlorochromate in methylene chloride (r.t. 1h) afforded the ketol 217 in 88% yield (eq. 59). The structure of this material (mp. 51-52°C) was supported by spectral data. The ir spectrum showed the presence of both an alcohol and a saturated carbonyl functionality (ν_{max} 3500, 3660, 1730 cm^{-1}). The ^1H nmr spectrum showed the presence of an AB pair of doublets at τ7.36 and 7.84 (J_{AB}=19 Hz), which integrated for two protons. These were assigned to the two protons at C-1, α to the carbonyl functionality.



216 217 (59)

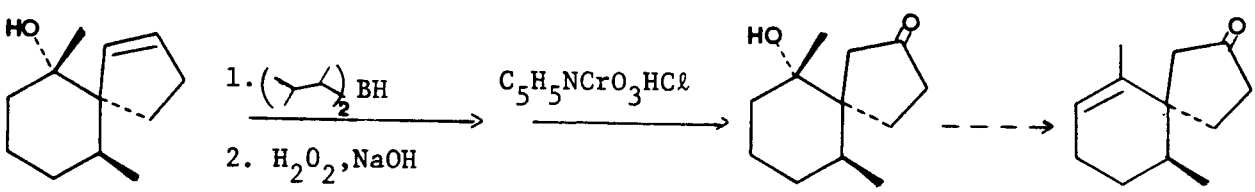
Dehydration of 217 in refluxing benzene containing a catalytic amount of p-toluenesulfonic acid, followed by equilibration of the initially formed dehydration products under the same conditions, afforded a 90% yield of the spiro enones 198 and 218 in a ratio of 9:1 respectively (eq.60). The enone 198 was isolated from the isomeric mixture by preparative tlc. The ir spectrum of this material showed the presence of a five-membered ring saturated carbonyl group at 1740 cm^{-1}. The olefinic proton gave rise to a

multiplet between τ4.49 and 4.66 in the ^{1}Hnmr spectrum. The methyl group on the double bond showed up as a three proton singlet at τ7.76. This material was identical with a sample of the same material previously prepared by Buchi[132] and Caine.[129] We are grateful for their assistance in supplying spectral data and an authentic sample of this material.



217 198 218 (60)

Following a sequence similar to that outlined above, hydroboration of the alcohol 215 with disiamylborane in tetrahydrofuran, followed by oxidation of the resulting diol (not purified) by pyridinium chlorochromate in methylene chloride, afforded (38% overall yield from 215) the ketol 219 (Scheme 15). The ir spectrum of this material showed the presence of both an alcohol and a carbonyl functionality (ν_{max} 3500, 1730 cm^{-1}, respectively). The tertiary methyl group at C-6 gave rise to a three-proton singlet at τ8.84 in the ^{1}Hnmr spectrum. The secondary methyl group at C-10 appeared as a doublet (J=6.5 Hz) at τ9.16. This material was identical with a sample of the same material previously prepared by Caine.[129] We are grateful to Professor Caine for his assistance in supplying spectral data of this material. Ketol 219 had previously been converted into the spiro enone 198.[129]



215 Scheme 15 219 198

EXPERIMENTAL

For general information, see the experimental part of Part I of this thesis.

Reagents and Starting Materials. Cyclohexane-1,3-dione, cyclopentane-1,3-dione, and 2-methylcyclopentane-1,3-dione were obtained from Aldrich Chemical Company Inc. and were used without further purification. 2-Methylcyclohexane-1,3-dione was prepared from cyclohexane-1,3-dione by alkylating the latter with methyl iodide in aqueous dioxane containing sodium hydroxide.[150] The preparation of the tricyclic β-diketone 108, involving a Diels-Alder reaction between cyclopentadiene and cyclopentane-1,3-dione, was carried out in our laboratory by Dr. I. Nagakura. 2-Hydroxymethylenecyclohexanone and 2-hydroxymethylenecyclopentanone were prepared by the formylation of cyclohexanone and cyclopentanone, respectively.[151]

Cyclopropyllithium was prepared by the method of D. Seyferth.[152] To a stirred suspension of 1.5 g (214 mmol) of lithium wire (or ribbon, washed with dry benzene) in 80 ml of cold (0°C) anhydrous ether under an atmosphere of argon was added, dropwise, a solution of cyclopropyl bromide (12.1 g, 100 mmol). The mixture was stirred at 0°C for 1.5h. The resulting solution of cyclopropyllithium containing one equivalent of lithium bromide was standardized by Gilman's procedure[153] and used as such.

Tri-n-butyltin Hydride was prepared by reduction of tri-n-butyltin chloride with lithium aluminum hydride in ether.

I. Synthesis of β-Iodo-α,β-Unsaturated Ketones

General Procedure A. - To a solution of triphenylphosphine (2.88 g, 11 mmol) in dried acetonitrile (50 ml) was added 2.79 g (11 mmol) of iodine crystals. The mixture was stirred at room temperature for 20 min. To the resulting yellow suspension of triphenylphosphine diiodide was added successively

triethylamine (1.1 g, 11 mmol) and the appropriate cyclic β-diketone (10 mmol). The resulting solution was refluxed for 3h. Acetonitrile was removed under reduced pressure. The residual oil was extracted by stirring and decantation with five 30 ml portions of ether. The combined ether extracts were concentrated to about 25 ml and the resulting solution was filtered through a short column of florisil (25 g, 80-100 mesh). The column was eluted with a further 75 ml of ether. Removal of solvent from the combined eluants and distillation of the residual oil gave the corresponding β-iodo-α,β-unsaturated ketone.

General Procedure B. - The general procedure B was essentially the same as procedure A except that the reaction mixture was refluxed for 9h instead of for 3h.

General Procedure C. - To a solution of triphenylphosphine (2.88 g, 11 mmol) in a mixture of dried acetonitrile (50 ml) and hexamethylphosphoramide (8 ml, freshly distilled from lithium aluminum hydride) was added 2.79 g (11 mmol) of iodine crystals. The mixture was stirred at room temperature for 20 min. To the resulting yellow suspension of triphenylphosphine diiodide was added successively triethylamine (1.1 g, 11 mmol) and the appropriate cyclic β-diketone (10 mmol) or α-hydroxymethylenecycloalkanone (10 mmol). The resulting red solution was stirred at room temperature for 15h. Acetonitrile was removed under reduced pressure. The remaining hexamethylphosphoramide solution was extracted by stirring and decantation with five 50 ml portions of pentane. The combined pentane extracts were washed with three 30 ml portions of water and dried over anhydrous magnesium sulfate. Removal of solvent and distillation of the residual oil gave the corresponding β-iodo-α,β-unsaturated ketone.

Synthesis of 3-Iodo-2-Cyclohexen-1-one 101. - Following the general procedure B outlined above, a mixture of cyclohexane-1,3-dione (1.12 g, 10 mmol), triethylamine (1.1 g, 11 mmol) and triphenylphosphine diiodide (11 mmol) in acetonitrile (50 ml) was refluxed for 9h. Normal work-up, followed by distillation (air-bath temperature 75-85°C, 1 Torr) of the crude oil, afforded 1.92 g (87%) of pure 3-iodo-2-cyclohexen-1-one 101 as a colorless oil. This material crystallized in a refrigerator and exhibited mp ∿15-16°C; uv λ_{max} 258nm(ε=9000);ir (film) ν_{max} 1675 cm^{-1} (C=O), 1595 cm^{-1} (C=C); ^{1}Hnmr, τ3.20 (t, 1H, -C=C-H, J=2 Hz), 6.90-7.23 (m, 2H, CH_2-C(I)=), 7.40-8.27 (m, 4H).

Anal. Calcd for C_6H_7IO: C, 32.45; H, 3.17. Found: C, 32.66; H, 3.25.

Synthesis of 2-Methyl-3-iodo-2-cyclohexen-1-one 111. - Following the general procedure B outlined above, a mixture of 2-methylcyclohexane-1,3-dione (1.26 g, 10 mmol), triethylamine (1.1 g, 11 mmol) and triphenylphosphine diiodide (11 mmol) in acetonitrile (50 ml) was refluxed for 9h. Normal work-up, followed by distillation (air-bath temperature 112-118°C, 11 Torr) of the crude oil, afforded 1.72 g (73%) of pure crystalline 2-methyl-3-iodo-2-cyclohexen-1-one 111. This material exhibited mp 57-59°C; uv λ_{max} 258 nm (ε=9500); ir ($CHCl_3$) ν_{max} 1670, 1605 cm^{-1}; ^{1}Hnmr, τ6.80-7.20 (m, 2H, -CH_2-C(I)=), 7.36-7.70 (m, 2H, -COCH_2-), 7.80-8.33 (m, 2H, -CH_2-CH_2-CH_2-), 7.97(t, 3H, =C-CH_3, J=2 Hz).

Anal. Calcd for C_7H_9IO: C, 36.04; H, 3.87. Found: C, 36.23; H, 4.00.

Synthesis of 3-Iodo-2-cyclopenten-1-one 112 - Following the generalprocedure A outline above, cyclopentane-1,3-dione (981 mg, 10 mmol) was allowed to react with triphenylphosphine diiodide (11 mmol) and triethylamine (1.1 g, 11 mmol) in acetonitrile (50 ml). Normal work-up, followed by distillation (air-bath

temperature ∿80°C, 0.2 Torr) of the crude oil, afforded 1.77 g (85%) of pure crystalline 3-iodo-2-cyclopenten-1-one 112. This material exhibited mp 67-68°C; uv λ_{max} 249 nm (ε=11350); ir($CHCl_3$)ν_{max} 1710, 1570 cm^{-1}; ^{1}Hnmr, τ3.36 (t, 1H, -C=C-H, J=1.8 Hz), 6.84-7.10 (m, 2H), 7.44-7.66 (m, 2H).

Anal. Calcd for C_5H_5IO: C, 28.88; H, 2.42. Found: C, 28.98; H, 2.40.

Synthesis of 2-Methyl-3-iodo-2-cyclopenten-1-one 113. - Following the general procedure A, a mixture of 2-methylcyclopentane-1,3-dione (1.12 g, 10 mmol), triethylamine (1.1 g, 11 mmol) and triphenylphosphine diiodide (11 mmol) in acetonitrile (50 ml) was refluxed for 3h. Normal work-up, followed by distillation (air-bath temperature ∿50°C, 0.2 Torr) of the crude oil, afforded 2.03 g (92%) of pure, crystalline 2-methyl-3-iodo-2-cyclopenten-1-one 113. This material exhibited mp 52-53°C; uv λ_{max} 248 nm (ε=11520), shoulder at 210 nm (ε=4655); ir($CHCl_3$) ν_{max} 1701, 1620 cm^{-1}; ^{1}Hnmr, τ6.84-7.20 (m, 2H, $-CH_2-C(I)=$), 7.32-7.60 (m, 2H, $-COCH_2-$), 8.17 (t, 3H, $-C=C-CH_3$, J=2 Hz).

Anal. Calcd for C_6H_7IO: C, 32.43; H, 3.15. Found C, 32.36; H, 3.30.

Synthesis of the β-Iodo Enone 114. - Following the general procedure A, a mixture of the cyclic β-diketone 108 (1.62 g, 10 mmol), triethylamine (1.1 g, 11 mmol) and triphenylphosphine diiodide (11 mmol) in acetonitrile (50 ml) was refluxed for 3h. Normal work-up, followed by distillation (air-bath temperature ∿120°C, 0.2 Torr) of the crude oil, afforded 0.83 g (∿31%) of the pure, crystalline iodo enone 114. This material exhibited mp 78-80°C; uv λ_{max} 253 nm (ε=9900); ir ($CHCl_3$)ν_{max} 1698, 1561 cm^{-1}; ^{1}Hnmr, τ3.61 (s, 1H, -CH=C(I)-), 3.88-4.20 (m, 2H, H-C=C-H), 6.27-6.45 (m, 1H), 6.60-6.80 (m, 1H), 6.85-7.20 (m, 2H), 8.10-8.50 (m, 2H).

Anal. Calcd. for $C_{10}H_9IO$: C, 44.145; H, 3.333. Found: C, 44.15; H, 3.48.

Synthesis of 2-Iodomethylenecyclopentanone 115.[103] Following the general procedure C, 2-hydroxymethylenecyclopentanone (1.02 g, 10 mmol) was allowed to react with triphenylphosphine diiodide (11 mmol) and triethylamine (1.1 g, 11 mmol) in a mixture of acetonitrile (50 ml) and hexamethylphosphoramide (8 ml) at room temperature for 3 days. Normal work-up, followed by distillation of the crude oil, afforded 1.62 g (73%) of a pale yellow crystalline material. This material was recrystallized from ether and was shown to be 2-iodomethylenecyclopentanone 115. A recrystallized sample of 115 exhibited mp 31.5°C; uv λ_{max} 276 nm (ε=9170), 263 nm (shoulder); ir ($CHCl_3$)ν_{max} 1720, 1608 cm^{-1}; ^{1}Hnmr, τ2.39 (t, 1H, -C=C(I)-H, J=1.8 Hz), 7.0-8.3 (m, 6H). Mol.Wt. Calcd. for C_6H_7IO:221.9543. Found (high resolution mass spectrometry): 221.9544.

Synthesis of 2-Iodomethylenecyclohexanone 116. - Following the general procedure C,2-hydroxymethylenecyclohexanone (1.26 g, 10 mmol) was allowed to react with triphenylphosphine diiodide (11 mmol) and triethylamine (1.1 g, 11 mmol) in a mixture of acetonitrile (50 ml) and hexamethylphosphoramide (8 ml) at room temperature for 15h. Normal work-up, followed by distillation (air-bath temperature ∿65°C, 0.4 Torr) of the crude oil afforded 2.22 g (94%) of pure 2-iodomethylenecyclohexanone 116 as a colorless oil. This material crystallized in a refrigerator and exhibited mp ∿15°C; uv λ_{max} 265 nm (ε=7200); ir(film)ν_{max} 1695, 1570 cm^{-1}; ^{1}Hnmr, τ2.30 (t, 1H, -C=C(I)H, J=2 Hz) τ7.32-7.70 (m, 4H), τ7.96-8.42 (m, 4H).

Anal. Calcd. for C_7H_9IO: C, 35.62; H 3.84. Found: C, 35.65; H, 3.76.

Preparation of a 1:1 Mixture of 2-Hydroxymethylene-3-methylcyclohexanone 205 and 2-Hydroxymethylene-5-methylcyclohexanone 206 and the Conversion of the Mixture to the Corresponding β-Iodo Enones 139 and 138, Respectively. - To a cold (0°C) solution of lithium dimethylcuprate (16.5 mmol, prepared from cuprous iodide and methyllithium) in ether (75 ml) was added 1.44 g (15 mmol) of 2-cyclohexen-1-one under an atmosphere of argon. This was followed immediately by the addition of potassium hydride (1.2 g, 30 mmol) and ethyl formate (2.20 g, 30 mmol). The resulting mixture was stirred at 0°C for 1h. Water and ice were added, and the resulting mixture was filtered. The ether layer of the filtrate was extracted with a further 100 ml of 3% aqueous sodium hydroxide. The combined aqueous extracts were acidified and extracted with ether. The combined ether extracts were washed with brine and water and dried over anhydrous sodium sulfate. Removal of the solvent, followed by distillation (air-bath temperature 95-110°C, 10 Torr) of the residual oil, afforded 863 mg (41%) of a 1:1 mixture of the hydroxymethylenecyclohexanones 205 and 206. The mixture exhibited ^{1}Hnmr, τ1.30 (s, α-hydroxymethylene proton), 1.36 (s, α-hydroxymethylene proton), τ8.90 (d, methyl group), 8.93 (d, methyl group).

The above mixture of the hydroxymethylene derivatives 205 and 206 was converted into the corresponding β-iodo enones as follow. Following the general procedure C, the mixture of 205 and 206 (700 mg, 5 mmol) was allowed to react with triphenylphosphine diiodide (5.5 mmol) and triethylamine (0.55 g, 5.5 mmol) in a mixture of acetonitrile (25 ml) and hexamethylphosphoramide (4 ml) at room temperature for 15h. Normal work-up, followed by distillation (air-bath temperature ∿50°C, 0.1 Torr) of the crude oil, afforded 2.05 g (82%) of a colorless oil. A glc analysis

(column A, 120°C) of this material showed that it consisted of a mixture of 2-iodomethylene-3-methylcyclohexanone 139 and 2-iodomethylene-5-methylcyclohexanone 138 in the ratio of approximately 1:1. An analytical sample of each of the products 138 and 139 was obtained by preparative glc (column C, 150°C). The pure iodo enone 139 exhibited uv λ_{max} 257 nm (ε=6681); ir(film)ν_{max} 1685, 1565 cm^{-1}; ^{1}Hnmr, τ2.51(s,1H,-C$\underline{H}$=C(I)-), 6.64-7.02 (m, 1H, -C$\underline{H}$(CH$_3$)-), 7.50-7.78 (m, 2H,-C$\underline{H}_2$-CO-), 7.80-8.50 (m, 4H), 8.94 (d, 3H, -CH(C$\underline{H}_3$), J=7 Hz). Mol.Wt. Calcd. for $C_8H_{11}IO$: 249.9856. Found (high resolution mass spectrometry): 249.9852.

The pure iodo enone 138 exhibited uv λ_{max} 261 nm (ε=7110); ir(film)ν_{max} 1690, 1570 cm^{-1}; ^{1}Hnmr, τ2.30 (t, 1H, -C$\underline{H}$=C(I)-, J=2 Hz), 7.04-8.90 (unresolved m, 7H), 8.97 (d, 3H, -CH(C$\underline{H}_3$), J=5.5 Hz). Mol.Wt. Calcd. for $C_8H_{11}IO$: 249.9856. Found (high resolution mass spectrometry):249.9857.

II. Synthesis of β-Cyclopropyl-α,β-Unsaturated Ketones from β-Iodo-α,β-Unsaturated Ketones.

General Procedure A. - To a cold (-78°C) slurry of phenylthiocopper (779 mg, 4.5 mmol) in dry tetrahydrofuran (30 ml) under an atmosphere of argon was added a solution of freshly prepared cyclopropyllithium (containing lithium bromide; 4.5 mmol) in ether. The resulting mixture was warmed to -20°C and stirred for 20 min. A clear, light brown solution of lithium phenylthio(cyclopropyl)cuprate (4.5 mmol) resulted. The solution was cooled to -78°C. To this solution was added a solution of the appropriate β-iodo-α,β-unsaturated ketone (3 mmol) in dry tetrahydrofuran (6 ml). The resulting mixture was stirred at -78°C for 2.5h. Methanol (2 ml) and ether

(20 ml) were added and the resulting mixture was warmed to room temperature and then filtered through a short column of florisil (30 g, 80-100 mesh). The column was eluted with a further 300 ml of ether. Removal of solvent from the combined eluants and distillation of the residual oil gave the corresponding β-cyclopropyl-α,β-unsaturated ketone.

General Procedure B. - Procedure B was essentially the same as procedure A except that the reaction of the β-iodo enone with the cuprate reagent was carried out at 0°C instead of at -78°C.

General Procedure C. - Procedure C was essentially the same as procedure B except that 2 equivalents (6 mmol) of cuprate reagent was used instead of 1.5 equivalents.

Synthesis of 3-Cyclopropyl-2-Cyclohexen-1-one 142. - Following the general procedure A outlined above, 3-iodo-2-cyclohexen-1-one 101 (666 mg, 3 mmol) was allowed to react with lithium phenylthio(cyclopropyl)cuprate (4.5 mmol) in tetrahydrofuran at -78°C for 2.5h. Normal work-up, followed by distillation (air-bath temperature 62-75°C, 0.3 Torr) of the crude oil afforded 335 mg (82%) of pure 3-cyclopropyl-2-cyclohexen-1-one 142 as a colorless oil. This material exhibited uv λ_{max} 254 nm (ε=17100); ir(film) ν_{max} 1660, 1625, 1610 cm^{-1}; ^{1}Hnmr, τ4.19 (s, 1H, COC=C-H), 7.50-9.34 (m, 11H). These spectral data were identical with those reported in literature.[144,108]

Synthesis of 2-Methyl-3-cyclopropyl-2-cyclohexen-1-one 146. - Following the general procedure C, 2-methyl-3-iodo-2-cyclohexen-1-one 111 (708 mg, 3 mmol) was allowed to react with lithium phenylthio(cyclopropyl)cuprate (6 mmol) in tetrahydrofuran at 0°C for 2.5h. Normal work-up, followed by distillation of the residual oil (air-bath temperature 65-85°C, 0.35 Torr), afforded 396 mg (88%) of pure 2-methyl-3-cyclopropyl-2-cyclohexen-1-one 146 as a colorless

oil. This material crystallized in a refrigerator and could be recrystallized from an ether-hexane mixture. A recrystallized sample of 146 exhibited mp 36-37°C; uv λ_{max} 262 nm (ε=14950); ir(film) ν_{max} 1660, 1600 cm^{-1}; ^{1}Hnmr, τ8.10 (s, 3H, -COC($\underline{CH_3}$)=CH-), 7.40-8.30 (m, 6H), 9.0-9.30 (m, 5H). Mol.Wt. Calcd. for $C_{10}H_{14}O$: 150.1044. Found (high resolution mass spectrometry): 150.1032.

Synthesis of 3-Cyclopropyl-2-cyclopenten-1-one 147. - Following the general procedure A, 3-iodo-2-cyclopenten-1-one 112 (624 mg, 3 mmol) was allowed to react with lithium phenylthio(cyclopropyl)cuprate (4.5 mmol) in tetrahydrofuran at -78°C for 2.5h. Normal work-up, followed by distillation (air-bath temperature ∿65°C, 0.2 Torr) of the crude oil, afforded 355 mg (97%) of crystalline 3-cyclopropyl-2-cyclopenten-1-one 147. This material exhibited mp 31-33°C; uv λ_{max} 244 nm (ε=16270); ir($CHCl_3$)ν_{max} 1700, 1670, 1600 cm^{-1}; ^{1}Hnmr, τ4.12 (t, 1H, -COC=$\underline{C}$-H, J=1.8 Hz), 7.40-7.74 (m, 4H), 8.00-8.32 (m, 1H), 8.78-9.26 (m, 4H). Mol.Wt. Calcd. for $C_8H_{10}O$: 122.0731. Found (high resolution mass spectrometry): 122.0733.

Synthesis of 2-Methyl-3-cyclopropyl-2-cyclopenten-1-one 148. - Following the general procedure C, 2-methyl-3-iodo-2-cyclopenten-1-one 113 (666 mg, 3 mmol) was allowed to react with lithium phenylthio(cyclopropyl)cuprate (6 mmol) in tetrahydrofuran at 0°C for 2.5h. Normal work-up, followed by distillation (air-bath temperature ∿50°C, 0.1 Torr) of the crude oil, afforded 343 mg (84%) of pure 2-methyl-3-cyclopropyl-2-cyclopenten-1-one 148 as a colorless oil. This material exhibited uv λ_{max} 254 nm (ε=18580); ir(film)ν_{max} 1698, 1637 cm^{-1}; ^{1}Hnmr, τ7.6-8.1 (unresolved m, 4H), 8.23 (t, 3H, C=$\underline{C}$-$\underline{CH_3}$, J=1.2 Hz), 8.85-9.20 (m, 5H). Mol.Wt. Calcd. for $C_9H_{12}O$: 136.0887. Found (high resolution mass spectrometry): 136.0888.

Synthesis of 2-Cyclopropylmethylenecyclohexanone 150. - Following the general procedure B outlined above, 2-iodomethylenecyclohexanone 116 (708 mg, 3 mmol) was allowed to react with lithium phenylthio(cyclopropyl) cuprate (4.5 mmol) at 0°C for 2.5h. Normal work-up, followed by distillation (air-bath temperature ∿80°C, 0.2 Torr) of the crude oil, afforded 369 mg (82%) of a colorless oil. A glc analysis (column B, 120°C) of this material showed that it was approximately 96% pure. An analytical sample of compound 150, obtained by preparative glc (column D, 150°C), exhibited mp ∿15°C; uv λ_{max} 265 nm (ε=11750); ir(film)ν_{max} 1680, 1600 cm^{-1}; ^{1}Hnmr, τ3.96 (d of t, 1H, -C=C<u>H</u>(<u>c</u>-C_3H_5), J=11 Hz, J'=2 Hz), 7.24-7.74 (m, 4H), 7.97-8.82 (m, 5H), 8.90-9.51 (m, 4H).

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.69; H, 9.35.

Synthesis of 2-Cyclopropylmethylenecyclopentanone 149.[103] - Following the general procedure A outlined above, 2-iodomethylenecyclopentanone 115 (666 mg, 3 mmol) was allowed to react with lithium phenylthio(cyclopropyl)cuprate (4.5 mmol) in tetrahydrofuran at -78°C for 1h, and at -20°C for another 2.5h. Normal work-up, followed by distillation (air-bath temperature ∿95°C, 0.35 Torr) of the crude oil, afforded 265 mg (65%) of a colorless liquid. A glc analysis (column A, 120°C) of this material showed that it was approximately 94% pure. An analytical sample of 149 was obtained by preparative glc (column C, 150°C) and it exhibited mp ∿18°C; uv λ_{max} 267 nm (ε=14820); ir(film)ν_{max} 1706, 1640 cm^{-1}; ^{1}Hnmr, τ4.05 (d of t, 1H, -C=C-<u>H</u>, J=11 Hz, J'=2.8 Hz), 7.15-9.50 (unresolved m, 1H). Mol.Wt. Calcd. for $C_9H_{12}O$: 136.0887. Found (high resolution mass spectrometry): 136.0902.

Reaction of Lithium Phenylthio(cyclopropyl)cuprate with a 1:1 Mixture of the Iodo Enones 138 and 139. - Following the general procedure B, a 1:1 mixture

of the iodo enones 138 and 139 (750 mg, 3 mmol) was allowed to react with lithium phenylthio(cyclopropyl)cuprate (4.5 mmol) in tetrahydrofuran at 0°C for 2.5h. Normal work-up, followed by distillation (air-bath temperature ∿73°C, 0.2 Torr) of the crude oil, afforded 369 mg (75%) of a slightly yellow liquid. A glc analysis (column A, 120°C) of this material showed that it was composed of a mixture of the β-cyclopropyl enones 156, 155 and 153 in the ratio of approx. 1:1:2, together with some minor impurities (<5%). An analytical sample of each of the compounds 156, 155 and 153 was obtained by preparative glc (column C, 145°C). The pure enone 156 exhibited uv λ_{max} 263 nm (ε=11720); ir(film) ν_{max} 1685, 1610 cm^{-1}; ^{1}Hnmr, τ5.16 (d of d, 1H, -C=C-H, J=10.5 Hz, J'=2 Hz), 8.96 (d, 3H, -CH(CH_3), J=7 Hz), 7.30-9.80 (unresolved m, 12H). Mol.Wt. Calcd. for $C_{11}H_{16}O$: 164.1201. Found (high resolution mass spectrometry): 164.1206.

The pure β-cyclopropyl enone 155 exhibited uv λ_{max} 265 nm (ε=11420); ir(film)ν_{max} 1680, 1600 cm^{-1}; ^{1}Hnmr, τ4.02 (d of d, 1H, -C=C-H, J=11 Hz, J'=1 Hz), 6.58-6.98 (m, 1H), 7.48-9.50 (m, 11H), 8.96 (d, 3H, -CH(CH_3), J=7 Hz). Mol. Wt. Calcd. for $C_{11}H_{16}O$: 164.1201. Found (high resolution mass spectrometry): 164.1205.

The pure enone 153 exhibited mp 54-56°C; uv λ_{max} 265 nm (ε=9810); ir(film)ν_{max} 1680, 1602 cm^{-1}; ^{1}Hnmr, τ3.92 (d of t, 1H, -C=C-H, J=11 Hz, J'=2 Hz), 6.90-9.50 (unresolved m, 12H), 8.98 (d, 3H, -CH(CH_3), J=6 Hz). Anal. Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.06; H9.77.

III. Regioselective Synthesis of 2-Cyclopropylmethylene-5-methylcyclohexanone 153 and 2-Cyclopropylmethylene-3-methylcyclohexanones (155 + 156).

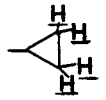
A. Preparation of Cyclopropanecarboxaldehyde

1. Esterification of Cyclopropanecarboxylic Acid. - To 10 g (0.116 mol) of

cyclopropanecarboxylic acid was added 10 g of ethanol, 15 ml of benzene, and 0.1 ml of conc. sulfuric acid. The resulting mixture was refluxed for 4.5h. The ethanol-benzene-water azeotrope was then distilled off. The residual oil was diluted with ether, and washed with dilute sodium bicarbonate solution. The ether solution was dried over anhydrous magnesium sulfate. After removal of the ether, the residual oil was fractionally distilled to give 10 g (73%) of ethyl cyclopropanecarboxylate (bp 130-132°C; lit. reported bp 133-133.5°C[143]). This material exhibited ir(film)ν_{max} 1723 cm^{-1}; ^{1}Hnmr, τ5.91 (q, 2H, $-C\underline{H}_2CH_3$, J=7 Hz), 8.73 (t, 3H, $-CH_2C\underline{H}_3$, J=7 Hz), 8.2-9.6 (m, 5H).

2. Lithium Aluminum Hydride Reduction of Ethyl Cyclopropanecarboxylate.[144] - To a cold (0°C) slurry of lithium aluminum hydride (6.81 g, 0.18 mol) in 300 ml of anhydrous ether, in a dried three-neck flask equipped with a water condenser, a dropping funnel and a nitrogen gas inlet, was added dropwise a solution of ethyl cyclopropanecarboxylate (18.55 g, 0.163 mol) in ether (50 ml), through the dropping funnel. The resulting mixture was warmed to room temperature, and was then refluxed for 17h. Normal work-up, followed by fractional distillation, afforded 8.85 g (75%) of cyclopropylcarbinol (bp 120-122°C, lit. reported bp 123-124°C[144]). This material exhibited ir(film)ν_{max} 3350 cm^{-1}; ^{1}Hnmr, τ6.60 (d, 2H, $-C\underline{H}_2OH$, J=7 Hz), 7.13 (br s 1H, $-CH_2O\underline{H}$), 8.60-9.90 (m, 5H).

3. Oxidation of Cyclopropylcarbinol with Ceric Ammonium Nitrate. - To a solution of ceric ammonium nitrate (114.3 g, 0.21 mol) in water (200 ml) was added 7.15 g (0.1 mol) of cyclopropylcarbinol. The resulting red solution was heated on a steam bath, with constant swirling, until the red color discharged completely. Ice-cold saturated sodium chloride solution

(200 ml) was added to the resulting colorless solution. The resulting mixture was extracted with five 80 ml portions of methylene chloride. The combined methylene chloride extracts were dried over anhydrous magnesium sulfate and sodium bicarbonate. The methylene chloride was removed by fractional distillation and the residual oil was fractionally distilled to give 5.07 g (71%) of cyclopropanecarboxaldehyde (b.p. 98°-100°C, lit. reported bp 97-99°C[142]). This material exhibited ir(film)ν_{max} 1710 cm^{-1}; ^{1}Hnmr, τ1.09 (d, 1H, -C<u>H</u>O, J=6 Hz), 8.95 (d, 4H,  , J=6 Hz), τ8.0-8.34 (m, 1H, -C<u>H</u>-CHO).

B. <u>Synthesis of 2-Cyclopropylmethylene-5-methylcyclohexanone 153</u>. - To a cold (0°C) solution of lithium dimethylcuprate (3.3 mmol) in anhydrous ether (18 ml) under an atmosphere of argon was added a solution of 2-cyclohexen-1-one (288 mg, 3 mmol) in ether (1 ml). The resulting mixture was stirred for 10 min at 0°C. Cyclopropanecarboxaldehyde (210 mg, 3 mmol) was added. The resulting yellow suspension was stirred at 0°C for 1h. Saturated ammonium chloride solution (15 ml) was added and the resulting mixture was stirred vigorously for a few min. The two layers were separated and the aqueous phase was further extracted with three 50 ml portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate. Removal of solvent, followed by distillation of the residual oil (air-bath temperature 115-150°C, 15 Torr), afforded 293 mg (60%) of a colorless liquid. A glc analysis of this material showed the presence of one major component A (∿70%) and two minor components B and C (∿14% and ∿7% respectively), together with small amounts of minor impurities (∿9%). An analytical sample of the major component A was obtained by preparative glc (column D, 160°C) and was shown to be 2-cyclopropylmethylene-5-methylcyclohexanone <u>153</u>. The

spectral data (^{1}Hnmr, ir) of this material were identical with those of the same material prepared earlier by the reaction of lithium phenylthio-(cyclopropyl)cuprate with the corresponding iodomethylenecyclohexanone.

Small amounts of components B and C were also obtained by preparative glc (column D, 160°C). Spectral data (^{1}Hnmr) showed that component B was 3-methylcyclohexanone, while component C was probably compound 154, the geometric isomer of the cyclopropyl enone 153. Component C exhibited ^{1}Hnmr, τ5.08 (d of t, 1H, olefinic, J=11 Hz, J'=2 Hz), 8.98 (d, 3H, $-\dot{C}H(C\underline{H}_3)$, J=6 Hz).

C. Synthesis of 2-Cyclopropylmethylene-3-methylcyclohexanone 155.

1. Synthesis of 2-(1-Cyclopropyl-1-hydroxymethyl)-3-methylcyclohexanone 203. - A 100 ml three-neck flask equipped with an overhead mechanical stirrer and an argon inlet tube, and containing 437 mg (18 mmol) of magnesium turnings, was flame-dried under a steady flow of argon. The flask was cooled to 0°C and dry ether (25 ml) was added. To the resulting stirred suspension of magnesium in ether was added, dropwise, 2.56 g (18 mmol) of methyl iodide. The resulting mixture was stirred at 0°C for 10 min. Cuprous iodide (60 mg, 0.3 mmol) was added to this solution of methyl magnesium iodide and stirring was continued for 5 min at 0°C. After addition of 2-cyclohexen-1-one (1.44 g, 15 mmol), the reaction mixture was stirred at 0°C for 30 min and was then cooled to -78°C. Cyclopropane-carboxaldehyde (1.05 g, 15 mmol) was added dropwise with vigorous stirring. A gummy precipitate formed immediately. The resulting mixture was warmed to 0°C, stirred for 30 min, warmed to room temperature and finally stirred for an additional 30 min. Saturated aqueous ammonium chloride (30 ml) was added and the resulting mixture was stirred for 5 min. The aqueous layer

was separated and thoroughly extracted with four 30 ml portions of ether. The combined ether extracts were washed twice with brine and dried over anhydrous magnesium sulfate. Removal of solvent, gave 2.65 g (97%) of the β-hydroxyketone 203. This material exhibited ir (film)ν_{max} 3470, 3110, 1700 cm^{-1}. A tlc analysis (elution with 1:1 ether-hexane of this material showed the presence of two spots (Rf = 0.3, 0.35) of approximately equal intensity. This material underwent partial dehydration and retroaldol reaction upon distillation as shown by tlc analysis (5 spots) and by the ir spectrum of the distilled product, which showed absorptions due to the presence of both saturated and α,β-unsaturated carbonyl groups, as well as absorption due to a hydroxy group (ir(film)ν_{max} 3480, 1700, 1680, 1602 cm^{-1}). Because of the fact that the ketol 203 was quite unstable, it was not purified further but was used directly in the next step.

2. Dehydration of 2-(1-Cyclopropyl-1-hydroxymethyl)-3-methylcyclohexanone 203. -

a. By Refluxing in Benzene in the Presence of a Catalytic Amount of p-Toluenesulfonic Acid. - The crude β-hydroxyketone 203 (2.65 g, 14.6 mmol), obtained as described above, was dissolved in benzene (60 ml) containing a catalytic amount of p-toluenesulfonic acid (33 mg), and the resulting solution was refluxed. A Dean Stark apparatus was used to trap the water. The progress of the dehydration reaction was followed by tlc analysis of aliquots taken from the reaction mixture. It was found that, one of the two compounds (Rf=0.35) present in the starting β-hydroxyketone mixture dehydrated completely within 3h to give two new compounds, while the other (Rf = 0.3) dehydrated much more slowly and was completely transformed to the

products only after 18h. The benzene solution was washed with saturated aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate. Removal of solvent, and fractional distillation of the residual oil, gave two fractions. The first fraction (air-bath temperature up to ∿50°C, 0.3 Torr) was a light colorless oil (426 mg) and was shown (ir, glc retention time on column A, 120°C) to be 3-methylcyclohexanone (25% yield). A glc analysis (column A, 120°C) of the second fraction (air-bath temperature ∿80°C, 0.4 Torr; 1.40 g, 57% yield) showed the presence of two components in a ratio of 1:6. An analytical sample of each was obtained by preparative glc (column C, 150°C). The major component was shown to be β-cyclopropyl enone 155 and the minor component was shown to be the enone 156, the geometric isomer of the enone 155 (see page 163).

b. Via Base-Promoted Elimination of Acetic Acid from the Corresponding Acetate. (211). - To a solution of the β-hydroxyketone 203 (1.1 g, 6 mmol) in pyridine (20 ml) was added 6 ml of acetic anhydride. The resulting mixture was stirred at room temperature for 17h under an atmosphere of argon. Ether (200 ml) and water (30 ml) were added. The resulting mixture was stirred for 5 min. The ethereal layer was separated and washed successively with three 20 ml portions of 1N hydrochloric acid, 20 ml of brine, two 30 ml portions of saturated sodium bicarbonate and finally 20 ml of brine. After drying over anhydrous sodium sulfate, the solvent was removed and the crude acetate 211 was dried under reduced pressure (vacuum pump) for 2h. The yield of the crude acetate 211 was 1.3 g (98%). This material exhibited ir(film)ν_{max} 1730 cm^{-1}. The ^{1}Hnmr indicated the presence of at least two isomers (acetate methyl groups at τ7.96 and 7.98) although tlc analysis (elution with 1:1 ether-hexane) showed only one spot.

To a solution of the crude acetate 211 (1.12 g, 5.0 mmol) in benzene (80 ml) was added 930 mg (0.75 mmol) of 1,5-diazabicyclo[4.3.0] non-5-ene (DBN). The resulting mixture was refluxed for 17h. Ether (250 ml) was added and the resulting solution was washed with ice-cold dilute hydrochloric acid (1N, 30 ml) and then dried over anhydrous magnesium sulfate. Removal of solvent, followed by distillation of the residual oil, afforded 640 mg (78%) of a colorless oil. A glc analysis (column A, 120°C) of this material showed that it was composed of enones 155 and 156 in a ratio of 13:1, respectively, together with small amounts (<6%) of minor impurities.

IV. Preparation of Trimethylsilyl Enol Ethers of β-Cyclopropyl-α,β-Unsaturated Ketones.

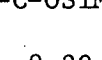
General Procedure.[146a] - An ethereal solution containing 4.0 mmol of methyllithium was concentrated under reduced pressure and the residual organolithium reagent was dissolved in 4 ml of dry 1,2-dimethoxyethane. The resulting solution was cooled to 0°C and was treated with 404 mg (4 mmol) of diisopropylamine. To the resultant, stirred solution of lithium diisopropylamide was added, dropwise, 3 mmol of the appropriate β-cyclopropyl-α,β-unsaturated ketone. Meanwhile a quenching solution, prepared from 2 ml of 1,2-dimethoxyethane, 0.2 ml (∿2 mmol) of triethylamine and 0.6 ml (5.1 mmol) of chlorotrimethylsilane (freshly distilled from N,N-dimethylaniline) was centrifuged to remove any of the insoluble triethylamine hydrochloride. By use of a syringe, this chlorotrimethylsilane solution was added rapidly with stirring to the cold (0°C) solution of the lithium enolate. After addition was complete, a white solid began to separate. The resulting mixture was stirred at 0°C for 15 min. Saturated

aqueous sodium bicarbonate (10 ml) and pentane (30 ml) were added. The aqueous solution was separated and extracted further with three 30 ml portions of pentane. The combined pentane extracts were dried over anhydrous magnesium sulfate. Removal of the pentane, followed by distillation of the residual oil gave the corresponding trimethylsilyl enol ether.

Preparation of the Trimethylsilyl Enol Ether of 3-Cyclopropyl-2-Cyclohexen-1-one. - Following the general procedure outlined above, 3-cyclopropyl-2-cyclohexen-1-one 142 (408 mg, 3 mmol) was first treated with lithium diisopropylamide (4 mmol) and the resultant enolate anion was quenched with chlorotrimethylsilane (5 mmol). Normal work-up, followed by distillation (air-bath temperature ∿80°C, 0.1 Torr) of the crude product, afforded 550 mg of the corresponding trimethylsilyl enol ether 171. A glc analysis (column A, 120°C) of this material showed that it was 91% pure, indicating that the yield of compound 171 was approximately 80%. This material exhibited ir(film)ν_{max} 1650, 1610 cm^{-1}; ^{1}Hnmr, τ4.54 (broad s, 1H, $-\overset{|}{C}=C\underline{H}-\overset{|}{C}(OSiMe_3)=C-$), 5.26 (m, 1H, $CH_2-\underline{CH}=C-OSi(CH_3)_3$)9.86 (broad s, 9H, $Si-(\underline{CH}_3)_3$. Due to the intrinsic instability of this material, it was pyrolysed without further purification or characterization.

Preparation of the Trimethylsilyl Enol Ether of 2-Methyl-3-cyclopropyl-2-cyclohexen-1-one. - Following the general procedure outlined above, 2-methyl-3-cyclopropyl-2-cyclohexen-1-one 146 (450 mg, 3 mmol) was first treated with lithium diisopropylamide (4 mmol) and the resultant enolate anion was quenched with chlorotrimethylsilane (5 mmol). Normal work-up, followed by distillation (air-bath temperature ∿60°C, 0.05 Torr) of the crude product, afforded 612 mg (88%) of the corresponding trimethylsilyl enol

ether 167 as a colorless oil. A glc analysis (column A, 150°C) of this material showed that it was ∿96% pure. This material exhibited ir(film) ν_{max} 1650, 1600 cm^{-1}; ^{1}Hnmr, τ5.20 (t, 1H, -C=CH, J=5 Hz), 8.20 (broad s, 3H, -C=C-CH_3), 9.91 (broad s, 9H, $Si(CH_3)_3$). Due to the intrinsic instability of this material, it was pyrolysed without further purification or characterization.

Preparation of the Trimethylsilyl Enol Ether of 2-Cyclopropylmethylenecyclohexanone. - Following the general procedure outlined above, 2-cyclopropylmethylene-cyclohexanone 150 (450 mg, 3 mmol) was first treated with lithium diisopropylamide (4 mmol) and the resultant enolate anion was quenched with chlorotrimethylsilane (5 mmol). Normal work-up, followed by distillation (air-bath temperature ∿125°C, 16 Torr) of the crude oil, afforded 666 mg of the corresponding trimethylsilyl enol ether 184. A glc analysis (column B, 120°C) of this material showed that it was 91% pure, indicating that the yield of the enol ether 184 was about 91%. This material exhibited ir(film)ν_{max} 1680 (w), 1660 cm^{-1} (w); ^{1}Hnmr, τ4.92 (d, 1H, -C=CH(c-C_3H_5), J=9.5 Hz), 5.04 (t, 1H, CH_2-CH=C-$OSiMe_3$, J=4.5 Hz), 7.40-7.64 (m, 1H, ), 7.72-7.96 (m, 2H, -C=CH-CH_2-), 8.20-8.64 (m, 4H), 8.95-9.44 (m, 2H), 9.52-9.74 (m, 2H), 9.87 (broad s, 9H, $Si(CH_3)_3$). Mol.Wt. Calcd. for $C_{13}H_{22}OSi$: 222.1439 . Found (high resolution mass spectrometry: 222.1438 .

Preparation of the Trimethylsily Enol Ether of 2-Cyclopropylmethylene-3-methyl-cyclohexanone. - Following the general procedure outlined above, a 1:6 isomeric mixture of the β-cyclopropyl enones 156 and 155, respectively, (492 mg, 3 mmol) was first treated with lithium diisopropylamide (4 mmol) and the resultant enolate anions were quenched with chlorotrimethylsilane (5 mmol). Normal work-up, followed by distillation of the crude oil,

afforded 710 mg of the corresponding trimethylsilyl enol ethers. A glc analysis (column B, 120°C) of this material showed that it was 94% pure. On this basis, the yield of the enol ether 200 was about 95%. This material exhibited ir(film)ν_{max} 1650 (w), 1625 (w) cm^{-1}; ^{1}Hnmr, τ4.98 (d, 1H, $-\overset{|}{C}=C\underline{H}(\underline{c}\text{-}C_3H_5)$, J=10 Hz), 5.11 (t, 1H, $CH_2-C\underline{H}=\overset{|}{C}-OSi(CH_3)_3$, J=3 Hz), 8.97 (d, 3H, $-\overset{|}{C}H(C\underline{H}_3)$, J=7 Hz), 6.76-7.12 (m, 1H). Due to the instability of this material, it was pyrolysed without further purification or characterization.

Preparation of the Trimethylsilyl Enol Ether of 2-Cyclopropylmethylenecyclopentanone. - Following the general procedure outlined above, 2-cyclopropylmethylenecyclopentanone 149 (408 mg, 3 mmol) was treated with lithium diisopropylamide (4 mmol) and the resultant enolate anion was quenched with chlorotrimethylsilane (5 mmol). Normal work-up, followed by distillation of the residual oil, afforded 562 mg (90%) of the corresponding trimethylsilyl enol ether 191. A glc analysis (column B, 120°C) showed that this material was pure. It exhibited ir(film)ν_{max} 1615 cm^{-1}(s). ^{1}Hnmr τ4.90-5.32 (m, 2H, olefinic), 9.86 (broad s, 9H, $Si(CH_3)_3$). Due to the instability of this material, it was pyrolysed without further purification or characterization.

V. Thermal Rearrangement Reactions of β-Cyclopropyl-α,β-Unsaturated Ketones and their Trimethylsilyl Enol Ether Derivatives

General Procedure A. - A pyrex tube 1.2(i.d.)x32 cm, filled with glass helices (i.d. 4.76 mm) was washed successively with water, acetone and n-hexane. The column was conditioned by placing it in a furnace and heating it at ∿450°C for 3h. During this period of time, the column was thoroughly purged with a stream of nitrogen. A n-hexane solution of the appropriate β-cyclopropyl-α,β-unsaturated ketone (or the corresponding trimethylsilyl enol ether) (200 mg in 20 ml of n-hexane) to be pyrolysed was added dropwise over a

period of 1.5h to the top of the vertically held heated column (∿450°C). During this period of time, the stream of nitrogen was discontinued. The effluent from the bottom of the column was cooled by having it pass through a water condenser connected to the bottom of the pyrolysis tube, and was collected in a two-necked flask, equipped with a drying tube and immersed in a cold (-78°C) bath (see diagram 1). After addition of the solution was complete, the hot column was washed with a further 30 ml of n-hexane. Removal of the hexane, followed by distillation of the residual oil, gave the rearranged products.

General Procedure B. - A pyrex tube (1.2 x 100 cm) filled with glass helices (i.d. 4.76 mm) was washed successively with saturated aqueous sodium bicarbonate solution, water, acetone and n-hexane. By means of a heating tape which had been wrapped around it, the column was heated to the desired thermolysis temperature and was kept at this temperature for at least 3h. During this time, the column was thoroughly purged with a rapid flow of argon. A n-hexane solution of the β-cyclopropyl enone (or the corresponding trimethylsilyl enol ether)(200 mg in 20 ml n-hexane) to be pyrolysed was added dropwise, over a period of 1.5h, to the top of the vertically held column. During this period of time, a very slow flow of argon (∿5 ml/min) was passed through the column. The effluent from the bottom of the column was cooled by allowing it to pass through a water condenser attached to the bottom of the pyrolysis tube, and was collected in a two-neck flask which was equipped with a drying tube and was immersed in a cold (-78°C) bath (see diagram 2). After addition of the solution was complete, the hot column was washed with a further 30 ml of n-hexane. Removal of hexane, followed by distillation of the residual oil gave the

rearranged products.

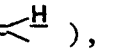
General Procedure C. - Procedure C was essentially the same as procedure B except that the crude mixture of pyrolysis products was not distilled but was subjected directly to hydrolysis. Thus, after the hexane had been removed from the pyrolysate, the residual oil was taken up in a 1:1 mixture (5 ml) of methanol and dilute hydrochloric acid (1N) and the resulting solution was stirred for 30 min at room temperature. The solution was thoroughly extracted with pentane and the combined pentane extracts were dried over anhydrous magnesium sulfate. Removal of solvent and distillation of the residual oil gave the final product(s).

Pyrolysis of 3-Cyclopropyl-2-cyclohexen-1-one 142.

A. At ∿450°C, Procedure A. - Following the general procedure A outlined above, a solution of 3-cyclopropyl-2-cyclohexen-1-one 142 (200 mg) in n-hexane (20 ml) was pyrolysed at ∿450°C. Normal work-up, followed by distillation (air bath temperature ∿110°C, 16 Torr) of the crude oil, afforded 156 mg (78%) of a colorless oil. A glc analysis (column B, 130°C) of this material indicated that it was a mixture of the ketone 161 (∿3%), the enone 162 (∿84%) and the dienone 163 (∿11%), along with a number of minor unidentified impurities (∿2%). An analytical sample of each of the three major components was obtained by preparative glc (column D, 130°C). The pure enone 162 exhibited ir(film)ν_{max} 1660, 1630 cm^{-1}; ^{1}Hnmr, τ7.2-8.3(m). The 2,4-dinitrophenylhydrazone derivative exhibited mp 252°C (dec)(lit.mp 251.5°C).[114]

Anal. (2,4-DNP derivative) Calcd. for $C_{15}H_{16}N_4O_4$: C, 56.96; H, 5.10; N, 17.71. Found: C, 57.09; H, 5.07; N, 17.58.

The pure ketone 161 exhibited ir(film)ν_{max} 1718, 1665 cm^{-1}; ^{1}Hnmr, τ4.57 (broad s, 1H, -C=C-H), 6.63(m, 1H, -CO-CH-). This material was passed through a short column of basic alumina and the column was eluted with ether. Evaporation of the ether from the eluant, followed by analysis of the residual oil by ir, ^{1}Hnmr and glc showed that the ketone 161 had isomerized completely to the α,β-unsaturated enone 162.

The pure dienone 163 exhibited ir(film)ν_{max} 1670, 1642, 1590 cm^{-1}; ^{1}Hnmr, τ3.82 (m, 2H, ), 4.16(s, 1H, -COCH=C-), 7.4-8.2 (m, 6H), 8.14 (d, 3H, -C=C-CH_3, J=5 Hz). These spectral data were identical with those previously reported[115] for this compound.

B. At 322°C, Procedure B. - Following the general procedure B outlined above, a solution of 3-cyclopropyl-2-cyclohexen-1-one 142 (200 mg) in n-hexane (20 ml) was pyrolysed at 322°C. Normal work-up, followed by distillation (air-bath temperature ∿110°C, 16 Torr) of the crude oil afforded 200 mg (100%) of a colorless oil. The infrared spectrum and a glc analysis (column B, 130°C) of this material showed that it was pure starting material, the cyclopropyl enone 142.

C At 400°C, Procedure B. - Following the general procedure B outlined above, a solution of 3-cyclopropyl-2-cyclohexen-1-one 142 (200 mg) in n-hexane (20 ml) was pyrolysed at 400°C. Normal work-up, followed by distillation of the crude oil, afforded 200 mg (100%) of a colorless oil. A glc analysis (column B, 130°C) of this material showed that it was composed of the ketone 161 (∿37%), the enone 162 (∿15%) and the starting cyclopropyl enone 142 (∿37%), along with a number of minor unidentified impurities (∿11%). An analytical sample of each of the three major components

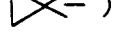
was obtained by preparative glc (column D, 130°C). In each case, the identity of the compound was confirmed by spectral data (ir, ^{1}Hnmr).

D. At 425°C, Procedure B. - Following the general procedure B outlined above, a solution of 3-cyclopropyl-2-cyclohexen-1-one 142 (200 mg) in n-hexane (20 ml) was pyrolysed at 425°C. Normal work-up, followed by distillation of the crude oil, afforded 196 mg (98%) of a colorless oil. A glc analysis (column B, 120°C) of this material showed that it was a mixture of the ketone 161 (∿31%) and the enone 162 (∿67%), along with very small amounts of unidentified impurities (∿2%). This material was passed through a short column of basic alumina. The column was eluted with ether. Removal of the ether and analysis of the residual oil by glc (column B, 130°C) and ir showed that the ketone 161 had isomerized completely to the enone 162.

E. At 450°C, Procedure B. - Following the general procedure B, a solution of 3-cyclopropyl-2-cyclohexen-1-one 142 (200 mg) in n-hexane (20 ml) was pyrolysed at 450°C. Normal work-up, followed by distillation of the crude oil, afforded 142 mg (71%) of a colorless oil. A glc analysis (column B, 130°C) of this material showed that it was composed of the ketone 161 (∿5%) and the enone 162 (∿91%), along with very small amounts of unidentified impurities (∿4%). The identities of the major products 161 and 162 were confirmed by a coinjection experiment involving glc.

Pyrolysis of the Trimethylsilyl Enol Ether of 3-Cyclopropyl-2-cyclohexen-1-one 171. - Following the general procedure C outlined above, a solution of the enol ether 171 (200 mg, 91% pure) in n-hexane (20 ml) was pyrolysed

at 425°C. Normal work-up, followed by distillation (air-bath temperature ∿110°C, 16 Torr) of the crude hydrolysed product, afforded 88 mg of a colorless oil. A glc analysis of this material (column A, 110°C) showed the presence of only one major product (76%) together with a number of minor impurities (24%). An analytical sample of the major product was obtained by preparative glc (column C, 110°C) and was shown (ir, ^{1}Hnmr) to be the enone 162. The number of minor components present in the product mixture were not identified.

Pyrolysis of the Trimethylsilyl Enol Ether of 2-Methyl-3-cyclopropyl-2-cyclohexen-1-one 167. - Following the general procedure C outlined above, a solution of the enol ether 167 (200 mg, 96% pure) in n-hexane (20 ml) was pyrolysed at 425°C. Normal work-up, followed by distillation (air-bath temperature 80-115°C, 16 Torr) of the hydrolysed product afforded 67 mg of a colorless oil. A glc analysis (column B, 110°C) of this material showed the presence of one major component (75%) and a number of minor impurities which were not identified. An analytical sample of the major component was obtained by preparative glc (column D, 115°C) and was shown to be o-cyclopropyltoluene.[155] This material exhibited ^{1}Hnmr τ3.01 (broad s, 4H, aromatic), 7.60 (s, 3H, $-CH_3$), 7.93-8.40 (m, 1H, ), 8.95-9.50 (m, 4H, cyclopropyl).

Pyrolysis of 3-Cyclopropyl-2-cyclopenten-1-one. 147 - Following the general procedure A outlined above, a solution of 3-cyclopropyl-2-cyclopenten-1-one 147 (200 mg) in n-hexane (20 ml) was pyrolysed at ∿450°C. Normal work-up, followed by distillation (air-bath temperature 100-120°C, 16 Torr) of the crude oil afforded 160 mg (80%) of a colorless oil. A glc analysis (column

A, 100°C) of this material showed the presence of four major components together with small amounts of minor impurities (∿2%) which were not identified. The major components were shown to be the ketone 157 (∿46%), the enone 158 (∿14%), the dienone 159 (∿20%) and the dienone 160 (∿18%). An analytical sample of each major component was obtained by preparative glc (column B, 120°C). The pure enone 158 exhibited uv ν_{max} 237 nm (ε=11370); ir(film)ν_{max} 1690, 1630 cm^{-1}; ^{1}Hnmr, τ7.10-7.80 (m). Mol.Wt. Calcd. for $C_8H_{10}O$: 122.0731. Found (high resolution mass spectrometry): 122.0734.

The ketone 157 exhibited ir(film)ν_{max} 1740, 1660 cm^{-1}; ^{1}Hnmr, τ4.40-4.58 (m, 1H, olefinic H), 6.57-6.88 (m, 1H, -COC$\underline{H}$-), 7.16-8.43 (m, 8H). The ketone 157 was isomerized to the enone 158 by passing the former through a short column of basic alumina.

The dienone 160 exhibited uv λ_{max} 268 nm (ε=18630); ir(film) ν_{max} 1640, 1570 cm^{-1}; ^{1}Hnmr, τ3.44 (d, 1H, -C=C-C$\underline{H}$=C- , J=16 Hz), 3.70 (d of q, 1H,-C=C($\underline{H}$)CH_3 J=16 Hz, J'=6 Hz), τ4.09 (broad s, 1H, COC$\underline{H}$=C), 7.12-7.90 (m, 4H), 8.10 (d, 3H,-C=C-C$\underline{H}_3$, J=6 Hz). Mol.Wt. Calcd. for $C_8H_{10}O$: 122.0731. Found (high resolution mass spectrometry): 122.0732.

The dienone 159 exhibited uv ν_{max} 226 nm (ε=14090); ir(film)ν_{max} 1705, 1610 cm^{-1}; ^{1}Hnmr, τ3.92-4.40 (m, 2H, olefinic H), 4.70-5.10 (m, 2H, olefinic H), 6.88 (d, 2H =C-C$\underline{H}_2$-C=, J=6.5 Hz), 7.20-7.95 (m, 4H). The dienone 159 was subjected to isomerization by passing it through a short column of basic alumina. The spectral data obtained from the isomerized product were identical with those of the dienone 160.

Pyrolysis of the β-Cyclopropyl Enone 172. - Following the general procedure A outlined above, a solution of the β-cyclopropyl enone 172[103] (200 mg) in

n-hexane (20 ml) was pyrolysed at ∿450°C. Normal work-up, followed by distillation (air-bath temperature ∿75°C, 25 Torr) of the crude oil, afforded 60 mg (∿30%) of a colorless oil. A glc analysis (column B, 80°C) of this material showed that it was composed of the ketone 173 (∿90%), m-xylene 174 (∿8%) and small amounts of unidentified minor impurities. The identity of m-xylene 174 was confirmed by a coninjection experiment with an authentic sample involving glc and by ^{1}Hnmr of the mixture. An analytical sample of the ketone 173, obtained by preparative glc (column D, 90°C), exhibited ir(film)ν_{max} 3070, 1705, 1655 cm^{-1}; ^{1}Hnmr, τ4.41 (m, 1H, olefinic H), 6.60 (m, 1H, $CH_3CO\underline{CH}$-), 7.91 (s, 3H, -CO$\underline{CH_3}$), 8.30 (broad s, 3H, -$\underline{C}$=$\underline{C}$-$\underline{CH_3}$). These data were identical with those of the same material reported in literature.[157]

Pyrolysis of the Trimethylsilyl Enol Ether of 2-Cyclopropylmethylenecyclopentanone 191. - Following the general procedure C outlined above, a solution of the trimethylsilyl enol ether 191 (200 mg) in n-hexane (20 ml) was pyrolysed at 425°C. Normal work-up, followed by distillation of the crude hydrolysed product, afforded two fractions. Fraction one (air-bath temperature up to ∿90°C, 16 Torr) weighed 87 mg (56%). A glc analysis of this material showed the presence of only one major compound (94%), along with a number of unidentified minor impurities (∿6%). The second fraction (air-bath temperature up to ∿110°C, 16 Torr) weighed 49 mg (18%). A glc analysis of this material showed the presence of the same compound as in fraction one, along with a large amount of higher boiling impurities. Both fractions showed the presence of saturated and α,β-unsaturated carbonyl compounds in the ir spectra. The two fractions were combined and subjected to column chromatography on silica gel (10 g). The column was eluted with 10% ether

in hexane. The major component was isolated (52 mg, 38%) and was shown to be the spiroketone 187. The latter exhibited ir(film)ν_{max} 3050, 1742 cm^{-1}; ^{1}Hnmr, τ4.10 (m, 1H, olefinic H), 4.55 (m, 1H, olefinic H), 7.30-8.70 (m, 10H). Mol.Wt. Calcd. for $C_9H_{12}O$: 136.0887. Found (high resolution mass spectrometry): 136.0925.

Pyrolysis of 2-Cyclopropylmethylenecyclohexanone 150. - Following the general procedure A outlined above, a solution of 2-cyclopropylmethylene-cyclohexanone 150 (200 mg) in n-hexane (20 ml) was pyrolysed at ∿450°C. Normal work-up, followed by distillation (air-bath temperature ∿110°C, 16 Torr) of the crude oil afforded 148 mg (∿74%) of a colorless oil. A glc analysis (column A, 100°C) of this material showed the presence of three major components along with small amounts (∿9%) of minor impurities which were not identified. Analytical samples of each of the three major components were obtained by preparative glc (column C, 100°C). These compounds were shown to be tetralin 177 (∿38%), the dienone 176 (∿9%) and the spiroketone 175 (∿44%).

An analytical sample of tetralin 177 exhibited ^{1}Hnmr τ2.98 (S, 4H, aromatic), 7.20-7.50 (m, 4H), 8.10-8.40 (m, 4H). The ir and ^{1}Hnmr spectra of 177 were identical with those of commercially available tetralin.

The dienone 176 exhibited uv λ_{max} 209 nm (ε=10800), λ_{max} 263 nm (ε=3450); ir(film)ν_{max} 3040, 1678, 1610 cm^{-1}. The ^{1}Hnmr showed the presence of two terminal methyl groups at τ8.99 (t,-$CH_2\underline{CH_3}$, J=7 Hz), and 9.02 (t, -$CH_2\underline{CH_3}$, J=7 Hz) of approximately equal intensity, indicating the presence of a mixture of cis and trans isomers. This material was subjected to hydrogenation (10% paladium on carbon as catalyst, methanol as solvent) and the hydrogenated product was identified (ir, ^{1}Hnmr) as 2-n-butylcyclohexanone.

An analytical sample of the spiroketone 175 exhibited ir(film)ν_{max} 3080, 1710 cm^{-1}; ^{1}Hnmr τ4.24 (narrow m, $w_{\frac{1}{2}}$=2 Hz, 2H, olefinic H), 7.40-7.82 (m, 5H), 7.97-8.60 (m, 7H); ^{1}Hnmr (after addition of 20 mg of the shift reagent $Eu(FOD)_3d_{27}$) τ3.58 (d of t, 1H, olefinic H, J=6 Hz, J'=2 Hz), 3.94 (d of t, 1H, olefinic H, J=6 Hz, J'=2 Hz), 6.44-6.84 (m, 3H), 7.14-7.50 (m, 2H), 7.62-8.12 (m, 7H). In a decoupling experiment, irradiation at τ7.29 caused the two doublet of triplets at τ3.58 and 3.94 to collapse to an AB pair of doublets with J=5.6 Hz; ^{13}Cnmr (protons decoupled) δ(ppm) 22.96, 27.67, 31.28, 32.29, 39.89 (2 carbons), 64.06 (quaternary carbon), 132.46 (olefinic carbon), 133.35 (olefinic carbon), 211.48 (carbonyl carbon).

Mol.Wt. Calcd for $C_{10}H_{14}O$: 150.1044. Found (high resolution mass spectrometry): 150.1027.

The spiroketone 175 was hydrogenated (10% Pd/C in methanol) to the corresponding saturated spiroketone 179, which exhibited ir (film)ν_{max}1700 cm^{-1}; ^{1}Hnmr, τ7.50-7.76 (m, 2H), 7.76-8.78 (m, 14H). These spectral data were identical with those of an authetic sample of 179 prepared from the pinacol rearrangement of the diol 180.[117] The diol 180 was prepared from the reductive dimerization of cyclopentanone by aluminum and mercuric chloride.[117]

Pyrolysis of the Trimethylsily Enol Ether of 2-Cyclopropylmethylenecyclohexanone 184.

A. At ~450°C, Procedure A. - Following the general procedure A outlined above, a solution of the trimethylsilyl enol ether 184 (200 mg, 91% pure) in n-hexane (20 ml) was pyrolysed at ~450°C. Normal work-up, followed by distillation (air-bath temperature ~105°C, 56 Torr) of the crude oil, afforded 148 mg of a colorless oil. A glc analysis of this material

(column B, 120°C) showed the presence of two major components and a number of minor impurities (∿12%) which were not identified. The two major components were isolated by preparative glc (column D, 125°C) and were shown to be the spiro enol ether 185 (∿74%) and trans-1-phenyl-1-butene 186 (∿14%).

An analytical sample of the spiro enol ether 185 exhibited ir(film) ν_{max} 3060, 1655 cm^{-1}; ^{1}Hnmr, τ4.24-4.37 (m, 1H, olefinic H), 4.45-4.60 (m, 1H, olefinic H), 5.28 (t, 1H, -CH=C-OSiMe$_3$, J=4 Hz), 7.58-7.90 (m, 2H), 7.90-8.17 (m, 2H), 8.34-8.62 (m, 6H), 9.93 (s, 9H, -Si(CH$_3$)$_3$). Mol.Wt. Calcd. for $C_{13}H_{22}OSi$: 222.1440. Found (high resolution mass spectrometry): 222.1443.

The spiro enol ether 185 was subjected to hydrolysis by stirring it in 1:1 methanol - dilute hydrochloric acid (1N) for 15 min. After work-up, the pure spiroketone 175 was obtained, the spectral properties (ir, ^{1}Hnmr) of which were identical with those of the same material prepared as described previously.

An analytical sample of trans-1-phenyl-1-butene 186 exhibited ir(film) ν_{max} 3050, 1595, 955, 730, 680 cm^{-1}, ^{1}Hnmr, τ2.60-3.00 (m, 5H, aromatic H), 3.55-4.00 (m, 2H, olefinic H), 7.64-8.00 (m, 2H), 8.95 (t, 3H, -CH$_3$, J=7 Hz). The spectral data listed above were essentially the same as those reported in the literature.[118]

B. At ∿450°C Procedure C (Preparative Scale) - Following the general procedure C outlined above, a solution of the trimethylsilyl enol ether 184 (1.0 g, ∿90% pure) in n-hexane (100 ml) was pyrolysed at ∿450°C. After work-up, the crude hydrolysed product was subjected to column chromatography on silica gel (50 g, 70-270 mesh). The column was eluted

with pentane and 303 mg (∿50%) of pure distilled spiro ketone 175 was isolated. Its identity was confirmed by ir and ^{1}Hnmr data.

C. At 425°C, Procedure B. - Following the general procedure B outlined above, a solution of the trimethylsilyl enol ether 184 (200 mg, ∿90% pure) in n-hexane (20 ml) was pyrolysed at ∿425°C. Normal work-up, followed by distillation (air-bath temperature ∿105°C, 56 Torr) of the crude oil afforded 170 mg (∿85%) of a colorless oil. A glc analysis (column B, 120°C) of this material showed that it was composed of the spiro silyl enol ether 185 (∿84%) and a number of unidentified minor impurities (∿16%). The identity of enol ether 185 was confirmed by the ir and ^{1}Hnmr spectra of this material.

Pyrolysis of the Trimethysilyl Enol Ether of 2-Cyclopropylmethylene-3-methylcyclohexanone 200. A. At ∿380°C, Small Scale. - Following the general procedure C outlined above, a solution of the trimethylsily enol ether 200 (200 mg, ∿90% pure) in n-hexane (20 ml) was pyrolysed at ∿380°C. Normal work-up, followed by distillation (air-bath temperature ∿70°C, 0.4 Torr) of the hydrolysed crude product afforded 119 mg of a colorless oil. A glc analysis of this material showed that it was composed of the spiroketone 212 (∿60%), the spiroketone 213 (∿25%) and a number of unidentified minor impurities (∿15%). An analytical sample of each of the major products was obtained by preparative glc (column C, 110°C). The spiroketone 212 exhibited mp 35-38°C; uv λ_{max} 295 nm (ε=237); ir ($CHCl_3$) ν_{max} 3080, 1705 cm^{-1}; ^{1}Hnmr, τ4.02-4.38 (m, 2H, olefinic H), 7.16-8.60 (m, 11H), 9.10 (d, 3H, $-C\underline{H}_3$, J=6 Hz). Mol.Wt. Calcd. for $C_{11}H_{16}O$: 164.1201. Found: (high resolution mass spectrometry): 164.1212.

An analytical sample of the spiroketone 213 exhibited uv λ_{max} 287 (ε=400); ir(film)ν_{max} 3090, 1705 cm^{-1}; ^{1}Hnmr τ4.02-4.40 (m, 2H, olefinic H), 7.42-7.80 (m, 4H), 7.80-8.60 (m, 7H), 9.14 (d, 3H, $-C\underline{H}_3$, J=6 Hz). Mol.Wt. Calcd. for $C_{11}H_{16}O$: 164.1201. Found (high resolution mass spectrometry): 164.1195.

B. At ∿380°C, Preparative Scale. Following the general procedure C outlined above, a solution of the trimethylsilyl enol ether 200 (8.44 g, 0.036 mol, ∿90% pure) in n-hexane (200 ml) was pyrolysed at ∿380°C. After work-up, the crude hydrolysed product was subjected to column chromatography on silica gel (350 g) and the column was eluted with 10% ether in hexane. A total of 3.35 g (0.021 mol, 57%) of the spiroketones 212 and 213 were isolated after distillation (air-bath temperature ∿50°C, 0.2 Torr). Partial separation of the two isomeric spiroketones 212 and 213 was obtained. Of the total 3.35 g isolated products, 2.03 g was pure spiroketone 212, 0.85 g was pure ketone 213 and the rest (0.47 g) was a mixture of 212 and 213

VI. Synthesis of the Spiroketone 198 - A Key Synthetic Intermediate for the Synthesis of a Variety of Spirovetivane-type Sesquiterpenoids.

Reaction of the Spiroketone 212 with Methyllithium. - To a cold (0°C) solution of the spiroketone 212 (492 mg, 3 mmol) in dry ether (25 ml) was added dropwise a solution of methyllithium (4.5 mmol) in ether. The resulting mixture was stirred at 0°C for 1h, warmed to room temperature and stirred for an additional 1h. Saturated brine (20 ml) was added. The ether solution was separated from the aqueous layer and the latter was extracted with three 30 ml portions of ether. The combined ether extracts were dried

over anhydrous magnesium sulfate. Removal of the ether, followed by distillation (air-bath temperature ∿75°C, 0.4 Torr) of the residual oil afforded 513 mg (95%) of a colorless oil. A glc analysis of this material showed the presence of two components in the ratio of 78:22. This material was subjected to column chromatography on silica gel (50 g). The column was eluted with 15% ether in hexane. The major component (286.2 mg, 53%) was shown to be the spiroalcohol 214 and it exhibited ir(film)ν_{max} 3060, 3500 cm^{-1}; ^{1}Hnmr τ3.93 (d of t, 1H, olefinic H, J=6 Hz, J'=2 Hz), 4.28 (d of t, 1H, olefinic H, J=6 Hz, J'=2 Hz), 7.52-8.02 (m, 3H), 8.10-9.90 (m, 9H), 8.78 (s, 3H, $-\dot{C}(OH)C\underline{H}_3$), 9.42 (d, 3H, $-\dot{C}HC\underline{H}_3$, J=6 Hz). Mol.Wt. Calcd. for $C_{12}H_{20}O$: 180.1515. Found (high resolution mass spectrometry): 180.1556. The spectral data of alcohol 214 listed above were identical with those of the authentic material kindly supplied by Dr. G. Buchi of the Massachusetts Institute of Technology.[132]

The minor component (62.1 mg, 11.5% yield) was shown to be the spiroalcohol 215[129] and it exhibited ir(film)ν_{max} 3070, 3490 cm^{-1}; ^{1}Hnmr τ4.19 (d of t, 1H, olefinic H, J=6 Hz, J'=2 Hz), 4.48 (d of t, 1H, olefinic H, J=6 Hz, J'=2 Hz), 7.54-8.66 (m, 12H), 8.96 (s, 3H, $-\dot{C}(OH)C\underline{H}_3$), 9.25 (d, 3H, $-\dot{C}HC\underline{H}_3$, J=6.5 Hz). Mol.Wt. Calcd. for $C_{12}H_{20}O$: 180.1515. Found (high resolution mass spectrometry): 180.1515.

Another 78.3 mg (∿14.5%) of a mixture of 214 and 215 was also isolated from the column chromatography.

Hydroboration of the Olefinic alcohol 214 with Disiamylborane.[118] To a cold (0°C) solution of borane-tetrahydrofuran (10 mmol, 1M solution in tetrahydrofuran) under an atmosphere of argon was added dropwise 1.4 g (20 mmol) of 2-methyl-2-butene. The solution was stirred at 0°C for 2h. To this solution of disiamylborane was added the olefinic alcohol 214 (180 mg, 1 mmol). The

resulting mixture was stirred at 0°C for 1h, warmed to room temperature and stirred for 21h. It was then cooled to 0°C. Ethanol (1 ml), aqueous sodium hydroxide (3N, 7ml) and 30% aqueous hydrogen peroxide solution (4 ml) were added and the resulting mixture was refluxed for 2h. Brine (5 ml) was added and the resulting mixture was extracted with ether. The combined ether extracts were washed with brine and dried over anhydrous magnesium sulfate. Removal of the ether gave the diol 216 as a yellow solid. The crude diol was recrystallized to give 153 mg (77%) of pure white crystals which exhibited mp 153-155°C; ir ($CHCl_3$)ν_{max} 3480, 3640 cm^{-1}; ^{1}Hnmr, τ8.82 (s, 3H, $-\overset{|}{C}(OH)\underline{CH_3}$) 9.07 (d, 3H, $-\overset{|}{C}H\underline{CH_3}$, J=6 Hz), 5.55-5.95 (m, 1H, $-\overset{|}{\underline{C}}HOH$).

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.54; H, 11.10.

Oxidation of the Diol 216 to the Keto Alcohol 217. - To a slurry of pyridinium chlorochromate (324 mg, 1.5 mmol) in methylene chloride (3 ml) was added a solution of the diol 216 (198 mg, 1 mmol) in methylene chloride (10 ml). The resulting red solution was stirred at room temperature for 1h. Ether (20 ml) was added. The mixture was filtered through a short column of florisil (10 g, 80-100 mesh). The column was eluted with a further 50 ml of ether. Removal of the solvent, followed by distillation (air-bath temperature ∿120°C, 0.2 Torr) of the residual oil, afforded 176 mg (88%) of the keto alcohol 217 as a colorless oil. A glc analysis of this material (column A, 150°C) indicated the presence of only one component. This material could be recrystallized from hexane-ether to give white crystals, mp 51-52°C; ir($CHCl_3$)ν_{max} 3660, 3500, 1730 cm^{-1}; ^{1}Hnmr, τ7.36, 7.84 (AB system, 2H, $-\overset{|}{\underset{|}{C}}-\underline{CH_2}-CO-$, J_{AB}= 19 Hz), 8.72 (s, 3H, $-\overset{|}{C}(OH)CH_3$), 9.18 (d, 3H, $-\overset{|}{C}H\underline{CH_3}$, J=6.5 Hz).

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.53; H, 10.17.

Conversion of the Olefinic Alcohol 215 into the Keto Alcohol 219 - The olefinic alcohol 215 (72 mg) was hydroborated under conditions identical with those used for the olefinic alcohol 214 as described above. Normal work-up, followed by distillation (air-bath temperature up to 135°C, 0.4 Torr) afforded 92 mg of a colorless oil. A glc analysis (column A, 150°C) of this material showed that it was composed of starting material 215 (∿32%), hydroborated product (∿58%), along with a number of unidentified minor impurities (10%). Fractional distillation separated the starting material 214 together with some minor impurities from the hydroborated product. The latter was oxidized by treatment with pyridinium chlorochromate under conditions identical with those used for the oxidation of the diol 216 as described above. Normal work-up, followed by distillation (air-bath temperature ∿120°C, 1 Torr) of the crude product, afforded 30 mg of a colorless oil. A glc analysis of this material (column A, 150°C) showed the presence of only one major component (∿93%) and a number of minor impurities which were not identified. The major component, the keto alcohol 219, exhibited ir(film)ν_{max} 3500, 1730 cm^{-1}; ^{1}Hnmr, τ8.84 (s, 3H, $-\overset{|}{C}(OH)\underline{CH_3}$), 9.16 (d, 3H, $-\overset{|}{C}H\underline{CH_3}$, J=6.5 Hz). The spectral data listed above were identical with those of an authentic sample of the same material provided by Dr. D. Caine of the Georgia Institute of Technology.[129] The overall yield of 219 from 215 was 38%.

Dehydration of the Keto Alcohol 217. - To a solution of the keto alcohol 217 (118 mg, 0.6 mmol) in benzene (20 ml) was added 15 mg of p-toluenesulfonic acid. The resulting solution was refluxed for 87h. The solution was cooled,

successively washed with 5 ml of saturated sodium bicarbonate solution and 5 ml of brine and dried over anhydrous magnesium sulfate. Removal of the solvent and distillation (air-bath temperature 60-65°C, 0.2 Torr) of the residual oil gave 96 mg (90%) of a colorless oil. A glc analysis (column A, 120°C) of this material showed the presence of only one peak (99%). However the ^{1}Hnmr of this material indicated that it was a 9:1 mixture of the isomeric keto olefins 198 and 218 respectively. An analytical sample of the keto olefin 198, obtained by preparative tlc (elution with 1:5 ether-hexane), exhibited ir(film)ν_{max} 2980, 1740 cm^{-1}; ^{1}H nmr τ4.49-4.66 (m, 1H, olefinic H), 7.76 (s, 3H, $-\dot{C}=\dot{C}-CH_3$), 9.12 (d, 3H, $-\dot{C}HCH_3$, J=6.5 Hz). Mol.Wt. Calcd. for $C_{12}H_{18}O$: 178.1358. Found (high resolution mass spectrometry): 178.1360. The ir, ^{1}Hnmr data of the keto olefin 198 listed above were identical with those of authentic samples of the same material kindly supplied by Dr. G. Buchi of the Massachusetts Institute of Technology[132] and by Dr. D. Caine of the Georgia Institute of Technology.[129]

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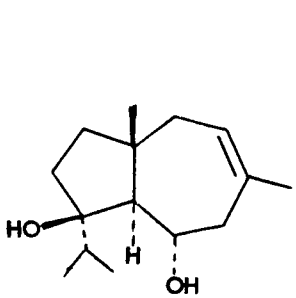
PART III

Reaction of Lithium Phenylthio(7-norcar-2-enyl) cuprate with Cyclic β-Iodo-α,β-unsaturated Ketones

INTRODUCTION

I. General

The facile thermal Cope rearrangement of 1,2-divinylcyclopropane systems to the corresponding cycloheptadienes has been the subject of extensive study.[1,2] However, most of these studies have been primarily concerned with a delineation of the mechanism of the reaction. Little effort has been spent on the investigation of the applicability of this transformation to synthesis. The increasing number of structurally interesting and biologically active natural products bearing a seven-membered ring (for example, the sesquiterpenes jaeschkeanadiol 1, β-himachalene 2, carolenin 3, cordilin 4 and cyclocolorenone 5)[3,4], has prompted recent investigations regarding the possibility of applying this type of transformation to the synthesis of these natural products.



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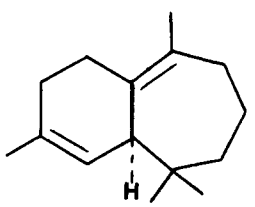

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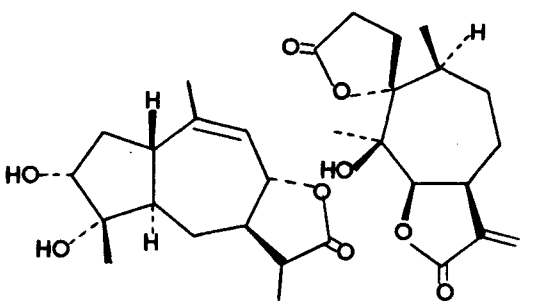
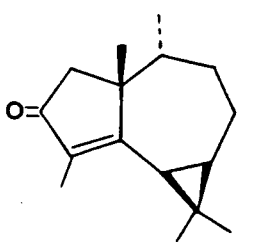


3 4

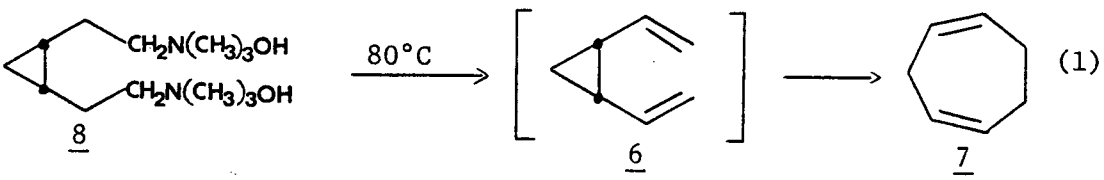


5

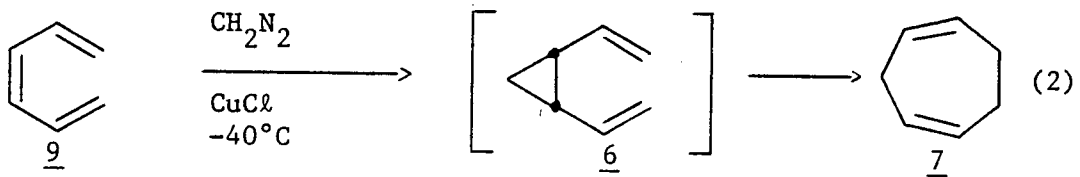
II. 1,2-Divinylcyclopropane Rearrangements

The thermal rearrangement of cis-1,2-divinylcyclopropane compounds to the corresponding cycloheptadiene systems is a very facile process, presumably largely due to the attendant relief of ring strain. In fact, cis-1,2-divinylcyclopropane itself (6) has been isolated only very recently; stable at -20°C, it rearranges to 1,4-cycloheptadiene 7 with a half life of 90 sec at 35°C.[5] In reactions where cis-1,2-divinylcyclopropane would be the expected product, the compound actually isolated has always been 1,4-

cycloheptadiene. For example, pyrolysis of the diquaternary hydroxide 8, yields only the diene 7 (eq.1).[6] Even the reaction of diazomethane with cis-hexatriene in the presence of cuprous chloride at -40°C yielded the diene 7 rather than the cyclopropane 6 (eq.2).[7]

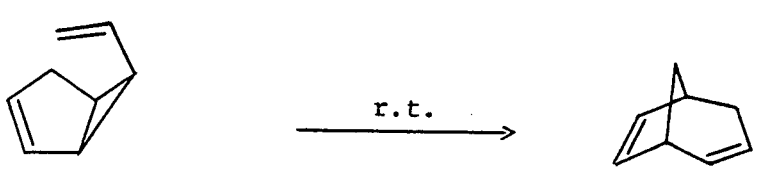


8 6 7 (1)

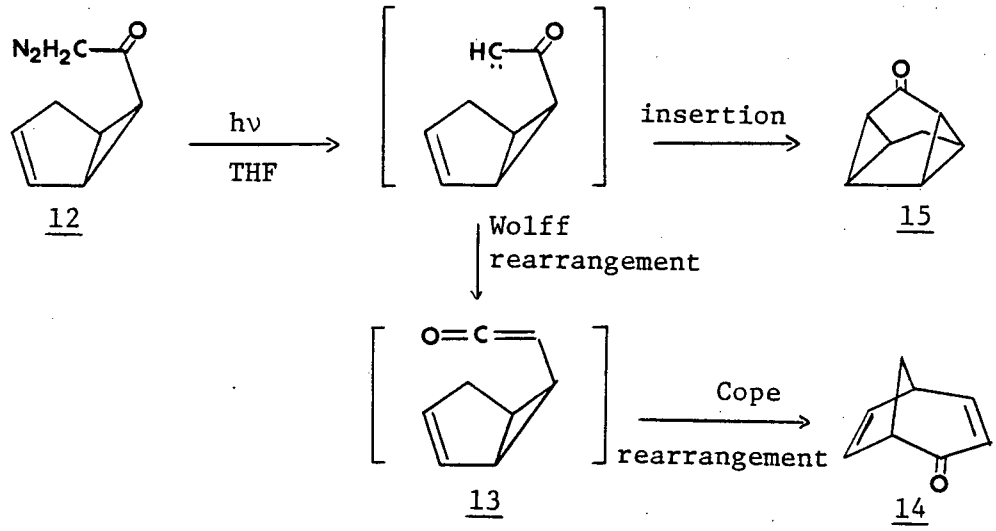


9 6 7 (2)

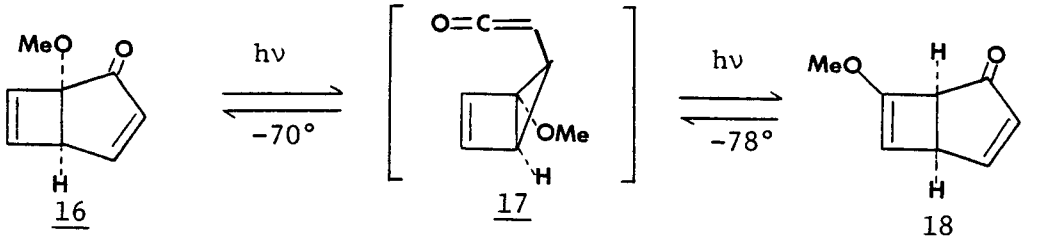
Some derivatives of cis-1,2-divinylcyclopropane are stable enough to be isolated under ordinary conditions of work-up while others have been detected only as transient intermediates. For example, the bicyclic derivative 10 has been isolated, but it rearranges readily at room temperature to the bicyclic compound 11.[8] The ketene 13 was presumed to be the intermediate to account for the photolytic decomposition of the diazoketone 12 to the bicyclic ketone 14 (eq. 4).[9] The labile ketene 17 has been detected in the low temperature (-190°C) irradiation of the methoxyketones 16 or 18 (eq. 5).[10] On warming to -70°C, the ketene spontaneously isomerizes in a Cope process to give an equilibrium mixture of methoxyketones in which the more stable isomer 18 predominates.[10]



10 11 (3)

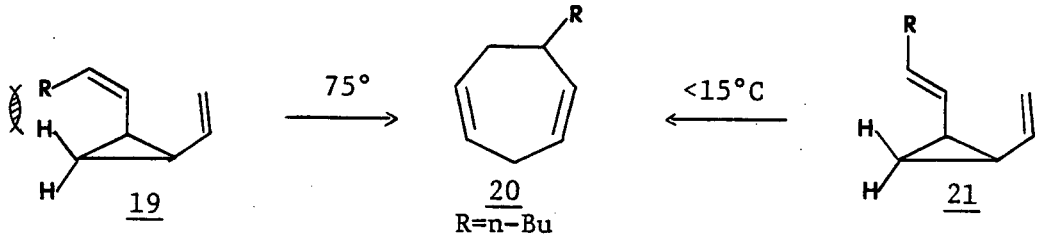


(4)



(5)

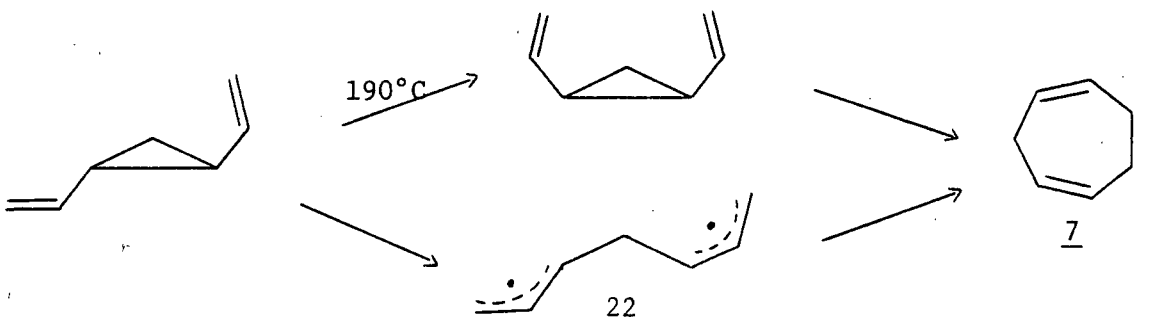
The cis,cis-divinylcyclopropane derivative 19 has been isolated and it rearranges readily to the corresponding cycloheptadiene 20 at 75°C; the more labile cis,trans isomer 21 rearranges in the process of preparation and work-up (eq.6).[11] The stability of the cis,cis-isomer, in contrast to that of the cis,trans-isomer or of cis-divinylcyclopropane itself, has been explained by the steric interaction of the n-butyl group with the cis-methylene hydrogen of the ring, which raises the energy requirement of the boatlike orientation necessary for a concerted rearrangement.



(6)

Trans-1,2-divinylcyclopropane has been prepared and isolated.[12] As expected, it is much more stable than the corresponding cis compound.

However, thermolysis of this compound also gives 1,4-cycloheptadiene as the major product (eq.7).[12] Presumably, the cyclopropane ring undergoes homolysis and recombination to give the cis compound which then rearranges to 1,4-cycloheptadiene 7.[13] A biradical intermediate like 22 has also been suggested.[14]



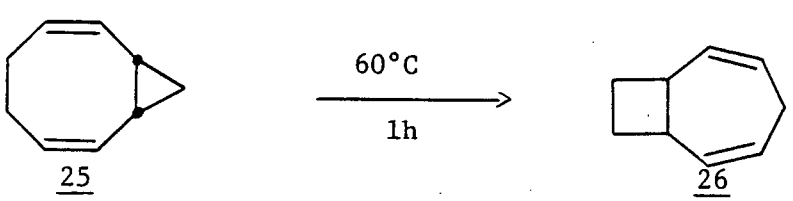
(7)

Similarly, the trans-divinylcyclopropane derivatives 23a and 23b have been isolated and thermally rearranged to the corresponding cycloheptadienes 24a and 24b respectively (eq.8).[11,15]

(a) R=n-Bu; (b) R= C_2H_5

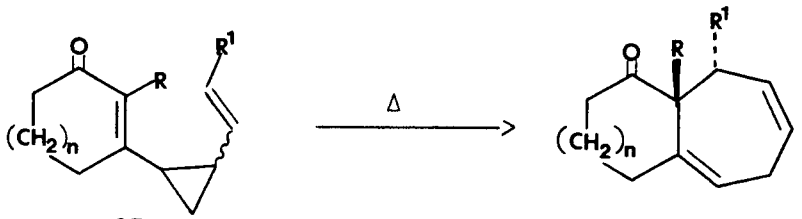
(8)

Incorporating a portion of the divinylcyclopropane moiety into another cyclic structure does not negate the possibility of rearrangement. For example, the bicyclic compound 25 rearranges to the bicyclic compound 26 at 60°C within 1h (eq.9).[16]



(9)

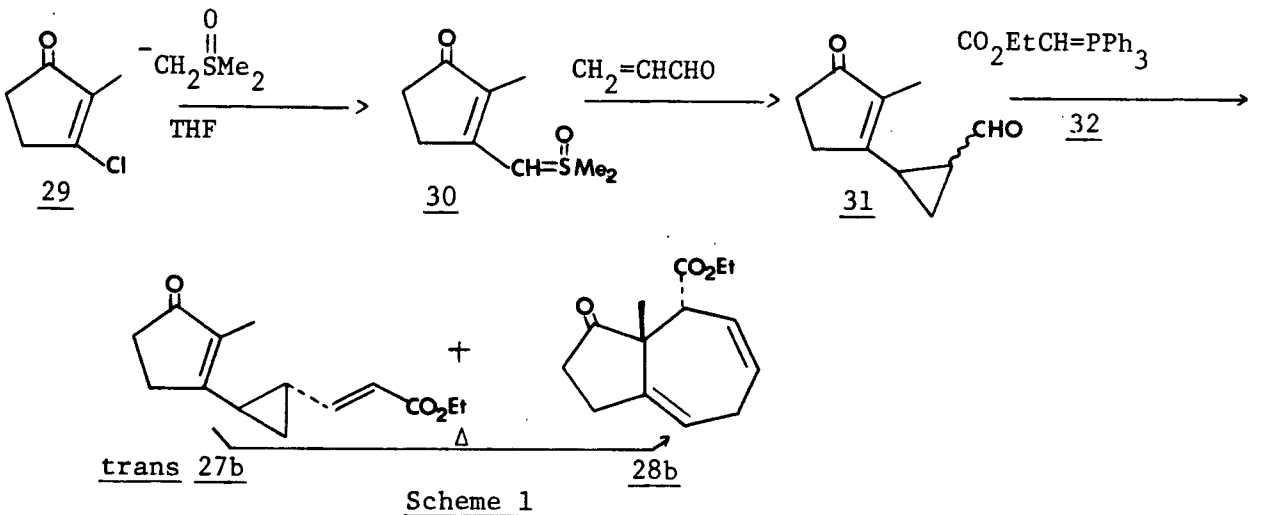
Although the conversion of the 1,2-divinylcyclopropane systems to cycloheptadienes has long been established, the transformation has rarely been applied to synthesis. Recently, Marino and Kaneko reported the use of thermal rearrangement of substituted 3-(2-vinylcyclopropyl)-2-cyclohexen-1-one 27a and 2-methyl-3-(2-vinylcyclopropyl)-2-cyclopenten-1-one 27b for the preparation of the ring fused cycloheptadiene derivatives 28a and 28b respectively (eq. 10).[17,18]



27 28 (10)

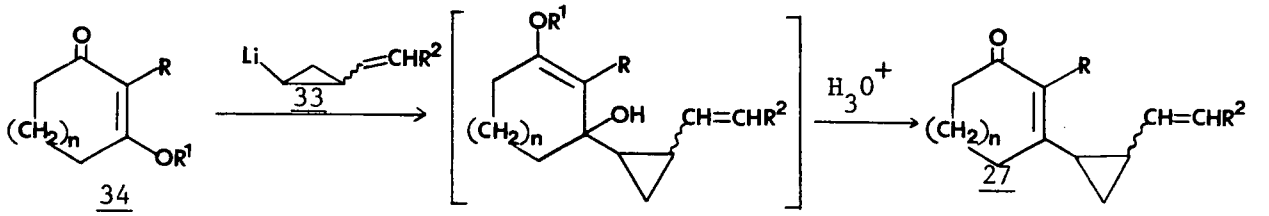
(a) n=1, R=H, R^1=CO_2Et; (b) n=o, R=CH_3, R^1=CO_2Et

However, the synthesis of the compounds 27 involved rather tedious procedures. For example, compound 27b was prepared from 3-chloro-2-methyl-2-cyclopentenone 29. Treatment of the latter with dimethylsulfoxonium methylide gave the sulfoxonium ylide 30. Reaction of the allyl ylide 30 with acrolein gave the vinyl cyclopropane 31. Treatment of compound 31 with the Wittig reagent 32 gave a mixture of the trans-divinylcyclopropane 27b and the rearranged product 28b (scheme 1).[17]



Scheme 1

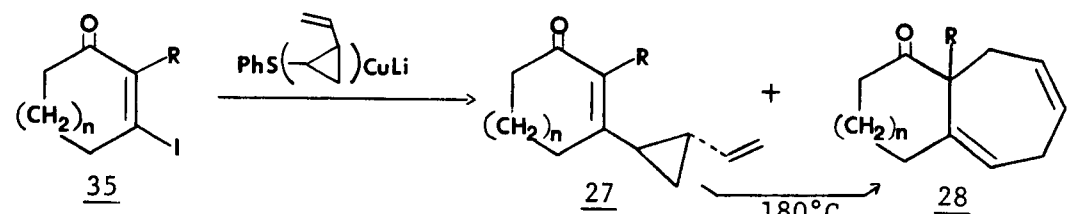
More recently, Marino[19] and Wender[20] independently reported an improved synthesis of 27, by the 1,2-addition of the 2-vinylcyclopropyl-lithium derivatives 33 to 3-alkoxy-2-cycloalken-1-ones 34 (eq. 11).



(11)

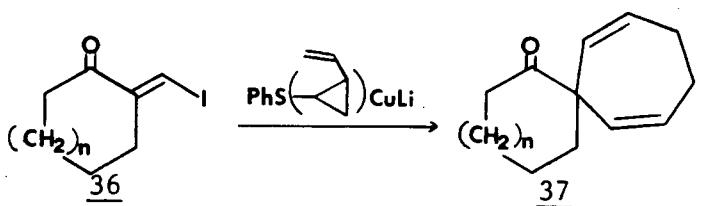
34(a) n=o, R=Me, R^1=Me, (b) n=o, R=Me, R^1=Et, (c) n=1, R=Me, R^1=Et, 33(a) R^2=H, (b) R^2=SPh

At about the same time, a complementary method involving the synthesis and rearrangement of the bicyclic systems like 27 was reported by Piers and Nagakura.[21] Reaction of β-iodo-α,β-unsaturated ketones of general structure 35 and 36 with lithium phenylthio(2-vinylcyclopropyl)cuprate, followed by thermal rearrangement of the resulting β-(2-vinylcyclopropyl)-α,β-unsaturated ketones gave the corresponding cycloheptadienes 28 and 37 respectively, in good yield (eq. 12 and 13).[21]



(12)

(a) n=1, R=H; (b) n=o, R=H (c) n=1, R=CH_3

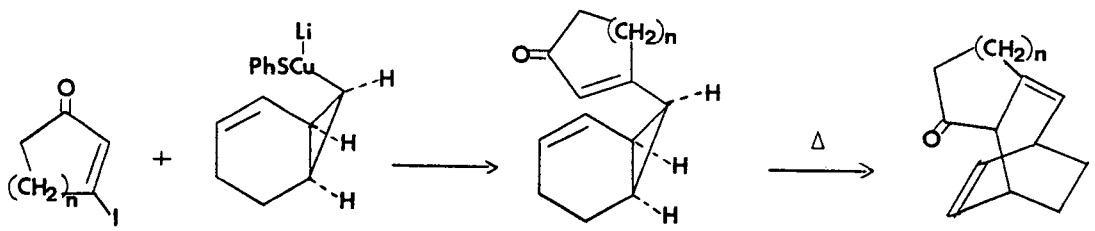


(13)

(a) n=1; (b) n=o

III. The Objective

The aforementioned efficient cycloheptadiene annelation reaction developed in our laboratory stimulated our investigations of the reaction of β-iodo-α,β-unsaturated ketones with lithium phenylthio(endo-7-norcar-2-enyl)cuprate 38. It was of special interest to investigate if thermolysis of the resulting β-alkyl-α,β-unsaturated ketones 39 would give the structurally interesting tricyclic enones 40 as represented in the following scheme:



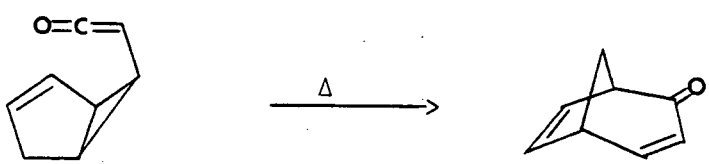
35 38 39 40

DISCUSSION

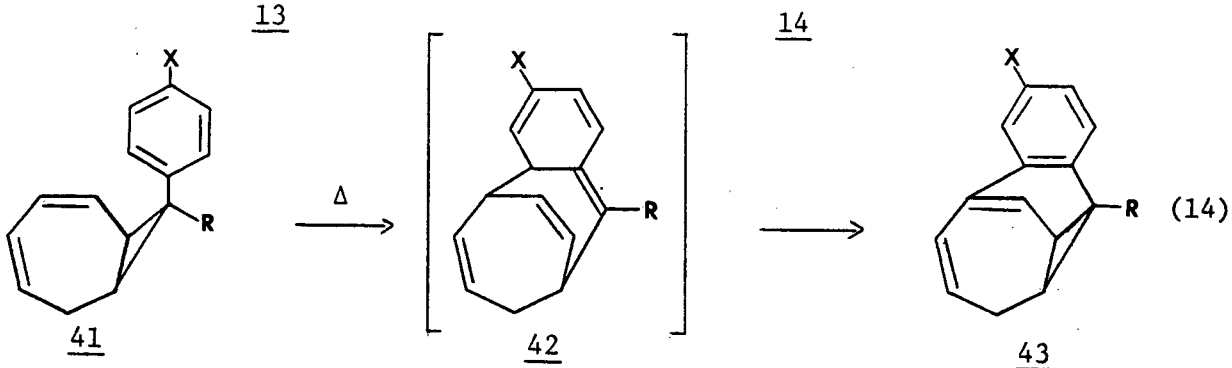
I. General

Divinylcyclopropane derivatives, with part of the divinylcyclopropane moiety incorporated into another cyclic structure or structures, have been shown to be capable of undergoing ordinary Cope type rearrangements. For example, compounds 10 and 13 rearranged readily to the bicyclic compounds 11 and 14 respectively (eq. 3 and 4).[8,9] The thermal rearrangement of compound 41 to compound 43 was interpreted as a Cope rearrangement of 41 to 42, which was subsequently stabilized in a thermally allowed 1,5-homodienyl hydrogen shift with regeneration of the aromatic system to give 43 (eq.14).[21]

10 11 (3)



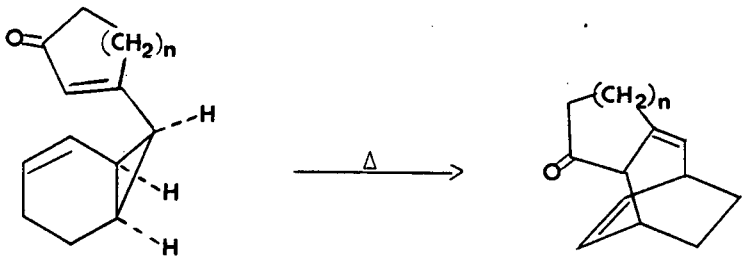
13 14 (4)



41 42 43 (14)

The objective of the work described in this part of the thesis was to synthesize the divinylcyclopropane derivatives of the general structure 39 and to investigate whether or not these compounds would undergo normal Cope

type rearrangement to the corresponding tricyclic compounds of general structure 40 (eq.15).

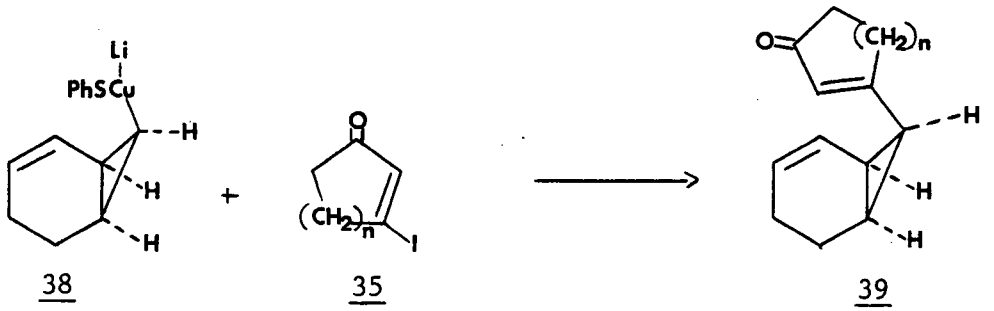


39 40 (15)

(a) n=1 ; (b) n=2

II. Reaction of Cyclic β-Iodo-α,β-Unsaturated Ketones with Lithium Phenylthio(7-norcar-2-enyl)cuprate Reagent.

To synthesize the divinylcyclopropane derivative 39, the previously described methodology involving the transformation of β-iodo-α,β-unsaturated ketones to the corresponding β-cyclopropyl enones was employed. It was expected that if the lithium phenylthio(7-norcar-2-enyl)cuprate reagent 38 could be prepared, it would react with cyclic β-iodo enones in a manner analogous to lithium phenylthio(cyclopropyl)cuprate, and thus produce the desired bicyclic system 39 (eq.16). Thus, the first objective was to prepare the cuprate reagent 38.

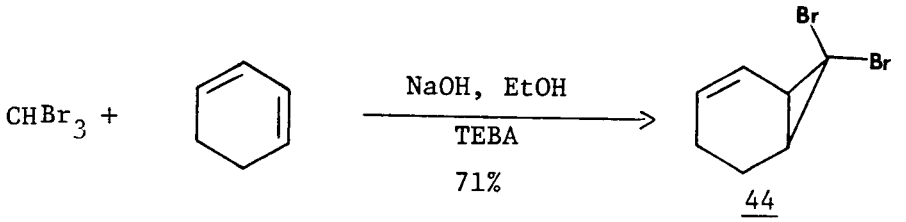


38 35 39 (16)

(a) n=1 ; (b) n=2

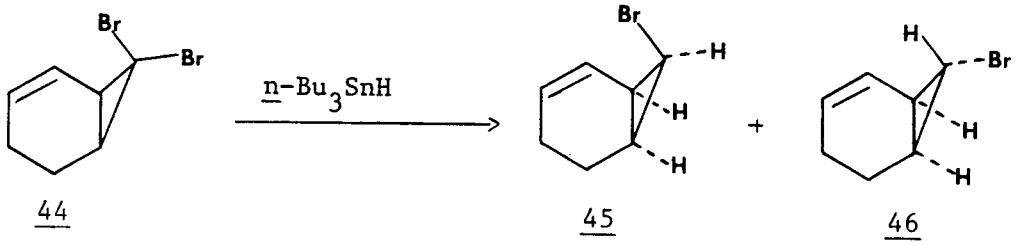
7,7-Dibromonorcar-2-ene 44 was obtained in 71% yield from 1,3-cyclohexadiene by stirring the latter with bromoform in 50% aqueous sodium

hydroxide in the presence of a phase transfer catalyst, triethylbenzylammonium chloride (TEBA)[22] (eq.17). This material exhibited bp 82-85°C (15 Torr)[lit bp 68-70°C (8 Torr)][22], and its spectral data were identical with those reported in the literature.[22]



44 (17)

Preliminary studies by Dr. I. Nagakura of our laboratory had shown that 7,7-dibromonorcar-2-ene 44 could be reduced by tri-n-butyltinhydride to a 1:1 mixture of syn and anti-7-bromonorcar-2-ene 45 and 46, respectively (eq.18). However, only the syn compound 45 was useful in preparing the

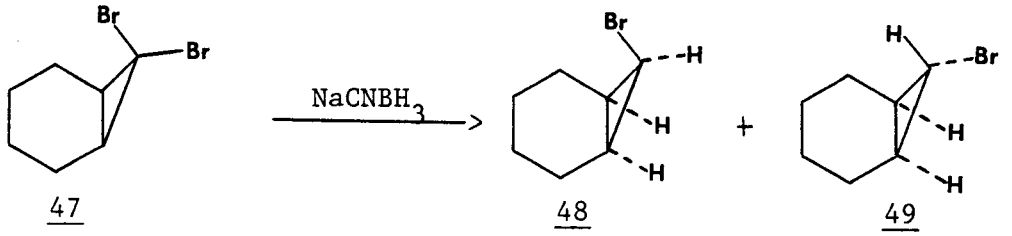


44 45 46 (18)

1 : 1

cuprate reagent 38. Therefore, methods for preparing syn-7-bromonorcar-2-ene 45 stereoselectively were investigated. It had been reported that sodium cyanoborohydride reduction of 7,7-dibromonorcarane 47 gave a mixture of syn- and anti-7-bromonorcarane 48 and 49, in a ratio of 77:21 respectively

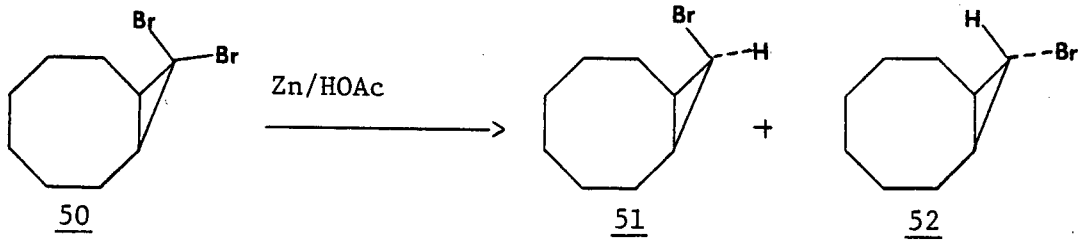
(eq.19).[23] However, when this procedure was employed in an attempted reduction of 7,7-dibromonorcar-2-ene 44, no monobromonorcar-2-ene was obtained.



47 48 49 (19)

77 : 21

Osborn et al had reported that 9,9-dibromobicyclo[6.1.0]nonane 50 could be reduced by zinc in acetic acid to give a mixture of syn- and anti-9-bromobicyclo[6.1.0]nonane, 51 and 52, in a ratio of 9:1 respectively (eq.20).[24] When this method was employed in the reduction of 7,7-dibromonorcar-2-ene 44, a mixture of syn and anti-



50 51 52 (20)

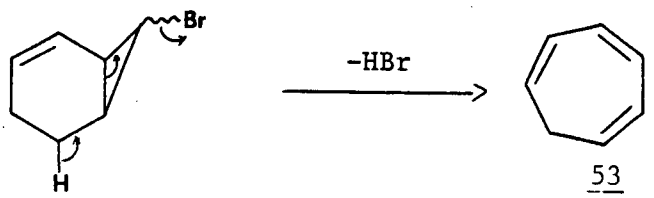
9 : 1

7-bromonorcar-2-ene 45 and 46, in a ratio of ∿9:1, respectively was obtained in 61% yield.

The assignment of stereochemistry to compound 45 and 46 was based on

the ^{1}Hnmr spectral data. The proton at C-7 of the syn-monobromo compound 45 gave rise to a triplet at τ6.63 with J=7 Hz while that of the anti compound 46 produced a triplet at τ7.13 with J=3 Hz. It has been well established that, in cyclopropane systems, the vicinal coupling constants J_{trans}, in general, are lower than J_{cis}.[25] It was thus clear that the three protons on the cyclopropane ring of compound 45 were in a cis relationship, whereas in compound 46, the proton adjacent to the bromine atom was trans to the other two cyclopropyl protons.

Compounds 45 and 46 were quite unstable in air. At room temperature, the mixture turned dark brown within a couple of days. 1,3,5-Cycloheptatriene 53 was found in the "decomposed" material. Presumably, dehydrobromination occurred with ring opening (eq.21). Attempts to separate 45

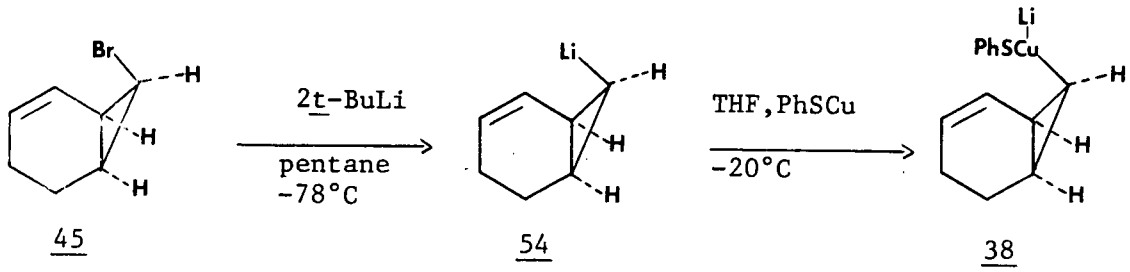


53 (21)

and 46 by subjecting a mixture of the two isomers to column chromatography on silica gel (eluted with hexane) resulted in extensive decomposition to the triene 53, with very poor separation of the surviving desired compounds. Eventually, it was found that pure syn-7-bromonorcar-2-ene 45 could be isolated from the mixture of isomers by carefully subjecting the mixture to column chromatography on 150 times its weight of florisil (120 mesh, elution with hexane).

The pure isomer 45 was employed in preparing the cuprate reagent 38. Treatment of the monobromo compound 45 with two equivalents of t-butyllithium

in pentane at -78°C for 2h generated the syn-lithium intermediate 54 stereospecifically. Addition of tetrahydrofuran and phenylthiocopper to the solution of the lithium intermediate 54 at -20°C gave a clear brown solution of the cuprate reagent 38 (scheme 2).



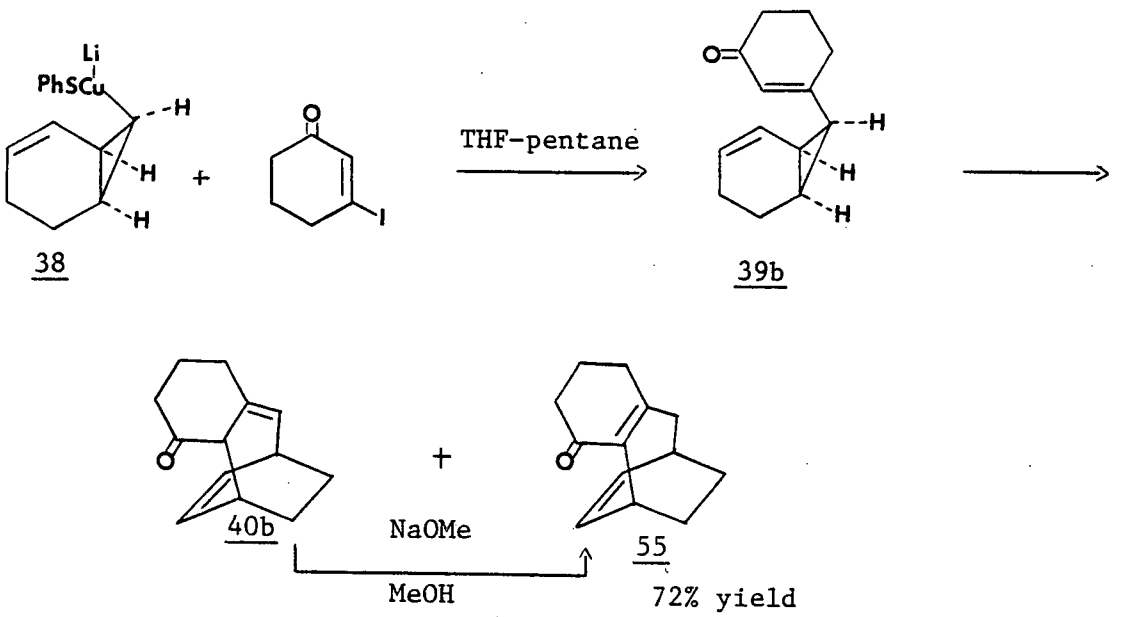
45 54 38

Scheme 2

The cuprate reagent 38 thus prepared was allowed to react with 3-iodo-2-cyclohexen-1-one 35b (2h at -20°C, 2h at 0°C). Examination of the crude product by ir spectroscopy showed that it was composed of a mixture of saturated and α,β-unsaturated carbonyl compounds. A glc analysis of this material showed that it was composed of two major components (∿50% and∿25% respectively) and a number of minor impurities (∿25%). Treatment of this material with sodium methoxide in methanol caused the disappearance of the saturated carbonyl absorption in the ir spectrum , and a single major component (∿80%) resulted (as shown by glc analysis). The latter material was subjected to column chromatography and the major component was isolated and identified as the tricyclic enone 55 (72% yield starting from the β-iodo enone 35b). The enone 55 was a white crystalline solid (mp 59-60°C). Its structure was supported by spectral evidence. A strong absorption band at 251 nm (ε=7556) in the uv spectrum and two strong bands at 1620 and 1660 cm^{-1} in the ir spectrum indicated the presence of an α,β-unsaturated ketone. The ^{1}Hnmr spectrum showed the presence of two olefinic protons, as a symmetrical multiplet at τ3.54-3.98. The doubly allylic proton at one of the bridgehead

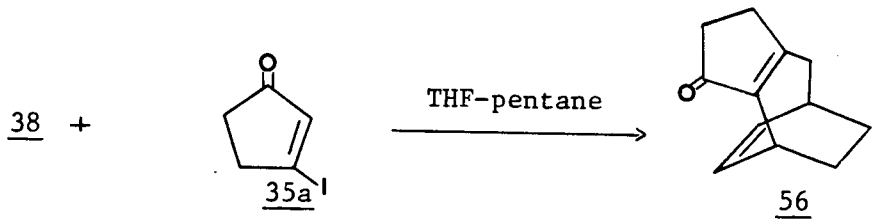
positions gave rise to a multiplet at τ6.19. The rest of the protons appeared as a thirteen-proton multiplet spreading from τ7.32 to 8.40.

It was quite clear from these results that lithium phenylthio(7-norcar-2-enyl)cuprate 38 had indeed reacted with 3-iodo-2-cyclohexen-1-one 35b, to give the expected product 39b, which underwent facile Cope rearrangement to give the tricyclic ketone 40b. The latter isomerized partially under the reaction conditions (or during work-up) to the enone 55. Treatment of the mixture with sodium methoxide in methanol completed the isomerization of 40b to compound 55 (Scheme 3).



Scheme 3

In similar fashion, reaction of 3-iodo-2-cyclopenten-1-one 35a with the lithium phenylthio(7-norcar-2-enyl)cuprate reagent 38 gave the tricyclic enone 56 in 52% yield (eq.22). The spectral data of this material agreed well with the structure assigned. The ir showed the presence of an α,β-

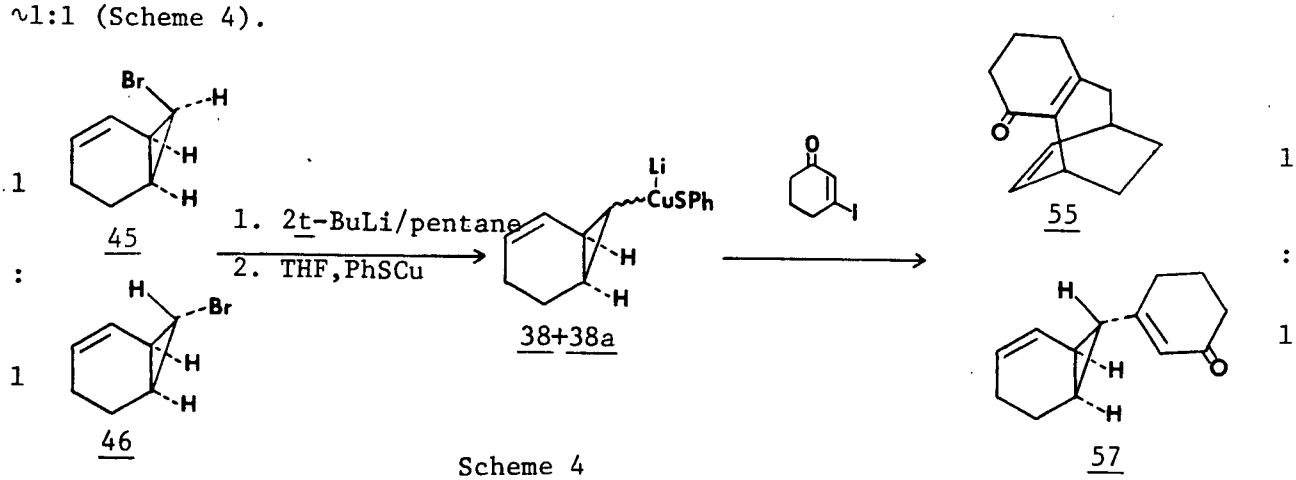


(22)

unsaturated ketone (ν_{max} 1635, 1685 cm^{-1}). A strong absorption band at 243 nm (ε=8005) in the uv spectrum was in agreement with that expected for a compound of this structure. The ^{1}Hnmr showed the presence of two vicinal olefinic protons, each of which gave rise to a doublet of doublets (τ3.67 and 3.98). Each set of signals exhibited the same coupling constants, J=9 Hz, J'=7 Hz. A broad one-proton doublet at τ6.77 with J=7 Hz was assigned to the doubly allylic proton at one of the bridgehead positions.

It was found later that the anti-7-bromonorcar-2-ene 46 was also useful in preparing the tricyclic enones 55 and 56.

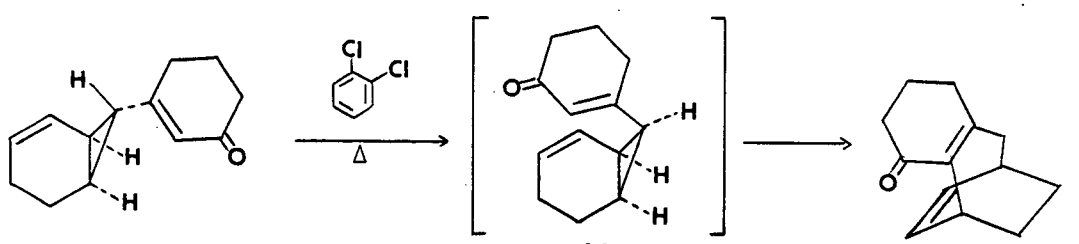
A 1:1 mixture of syn- and anti-7-bromonorcar-2-ene (obtained from the tri-n-butyltinhydride reduction of the dibromo compound 44) was used to prepare a mixture of the cuprate reagents 38 and 38a in a procedure similar to that used in the case of the pure monobromo compound 55. (Scheme 4). Reaction of this mixture of cuprate reagents with 3-iodo-2-cyclohexen-1-one, followed by treatment of the crude product with sodium methoxide in methanol, gave a mixture of the tricyclic enones 55 and 57 in a ratio of ~1:1 (Scheme 4).



Scheme 4

The two compounds were separated by means of column chromatography of the mixture on silica gel. The isolated yield of each component was ∿45%. The enone 57 was a white crystalline solid with mp 53-54°C. Its structure was confirmed by spectral data. The uv spectrum of this material showed a very strong absorption at 260 nm (ε=19159). The ir spectrum showed the presence of an α,β-unsaturated ketone (ν_{max} 1655, 1600 cm^{-1}). Two one-proton multiplets at τ3.94 and 4.43 in the ^{1}Hnmr spectrum were assigned to the two olefinic protons on the isolated double bond. A one-proton broad singlet was assigned to the α-proton of the α,β-unsaturated ketone functionality. The rest of the protons appeared as a thirteen-proton multiplet at τ7.52-8.52.

When a solution of the enone 57 in o-dichlorobenzene was refluxed for 40h, compound 57 rearranged smoothly to the enone 55, in nearly quantitative yield (Scheme 5). Presumably, an exo → endo isomerization had occurred giving the endocyclic intermediate 39b which then rearranged to the tricyclic enone 55 (Scheme 5).

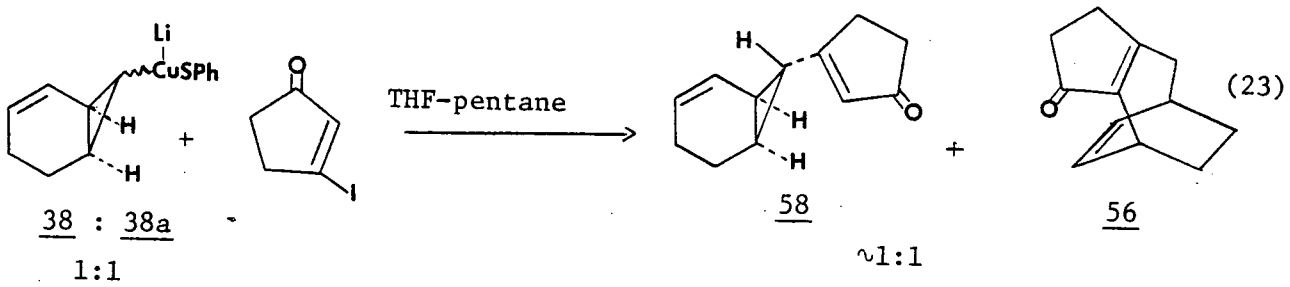


57 39b 55

Scheme 5

In a similar fashion, reaction of 3-iodo-2-cyclopenten-1-one with a mixture of the lithium phenylthio(7-norcar-2-enyl)cuprate reagents (derived from a 1:1 mixture of syn- and anti-7-bromonorcar-2-ene), gave a mixture of the tricyclic enone 56 (28% isolated yield) and the enone 58 (∿30% isolated

yield)(eq.23).



38 : 38a
1:1

58
∿1:1

56

The two compounds were separated by means of column chromatography of the mixture on silica gel. The enone 58 was a white solid, mp 78-79°C. It showed a very strong uv absorption at 269 nm (ε=17176). The two bands at 1695, 1595 cm^{-1} in the ir spectrum indicated the presence of an α,β-unsaturated carbonyl functionality. Two one-proton multiplets at τ3.83 and 4.39 in the ^{1}Hnmr spectrum were assigned to the two olefinic protons on the isolated double bond. A one-proton broad singlet at τ4.13 was assigned to the α-proton of the α,β-unsaturated ketone moiety.

When an o-dichlorobenzene solution of the enone 58 was refluxed for 24h, compound 58 rearranged to the tricyclic enone 56. The latter could be isolated in 96% yield.

On the basis of the results obtained from the experiments just described, it was clear that the conversion of the 3-iodo-2-cyclohexen-1-one and 3-iodo-2-cyclopenten-1-one into the tricyclic enones 55 and 56, respectively, did not require the use of isomerically pure cuprate reagent 38. Thus, the rather tedious purification of endo-7-bromonorcar-2-ene described earlier was unnecessary. In practice, the overall conversions could be carried out most efficiently by the following sequence of reactions: (a) reduction of 7,7-dibromonorcar-2-ene with tri-n-butyltinhydride to give a mixture of the

endo and exo monobromo derivatives; (b) conversion of the latter mixture into a mixture of the corresponding cuprate reagents (38 + 38a); (c) reaction of 38 + 38a with the iodo enones; (d) thermal rearrangement of resultant mixtures of products into the tricyclic enones 55 and 56.

EXPERIMENTAL

For general information, see the beginning of the experimental part of Part I in this thesis.

Synthesis of 7,7-Dibromonorcar-2-ene 44.[22] - To a stirred mixture of bromoform (12.6 g, 50 mmol), 1,3-cyclohexadiene (4.0 g, 50 mmol),triethylbenzylammonium chloride (0.1 g) and ethanol (0.2 ml) was added, dropwise, 25 ml of 50% aqueous sodium hydroxide solution. The resulting mixture was stirred at room temperature for 2.5h. Water (50 ml) and pentane (50 ml) were added and the two phases were separated. The aqueous solution was extracted with three 30 ml portions of pentane. The combined pentane extracts were washed twice with 15 ml of water and dried over anhydrous magnesium sulfate. Removal of the solvent and distillation of the residual oil gave 9.02 g (71%) of 7,7-dibromonorcar-2-ene 44. This material exhibited bp 82-85°C (15 Torr)[lit. bp 68-70°C (8 Torr)][26]; ^{1}Hnmr, τ4.08 (broad s, 2H, olefinic H), 7.70-8.35 (m, 6H).[26]

Reduction of 7,7-Dibromonorcar-2-ene by Zinc in Acetic Acid.[24] - To a solution of 7,7-dibromonorcar-2-ene 44 (12 g, 47.6 mmol) in glacial acetic acid (80 ml) was added, with stirring, 18.56 g (280 mmol) of zinc dust in small portions over a period of two hours at room temperature. After the last portion of zinc dust had been added, the reaction mixture was stirred for another 30 min. Then 50 ml of brine was added and the solid residue in the reaction mixture was removed by filtration. The aqueous filtrate was extracted six times with 75 ml portions of pentane. The combined pentane extracts were washed thrice with 15 ml portions of 10% aqueous sodium hydroxide solution, once with brine and dried over anhydrous magnesium sulfate. Removal of the solvent and distillation of the residual oil gave 5g (61%) of a colorless liquid: bp

80-83°C (50 Torr). A glc analysis of this material (column B, 100°C) showed that it was composed of a mixture of syn- and anti-7-bromonorcar-2-ene (∿91%), 45 and 46 in ratio of 9:1, respectively, along with some minor impurities (∿8%). A pure sample of each of compounds 45 and 46 was obtained by column chromatography of 2g of the mixture on 300 g of 120 mesh florisil (elution with hexane). An analytical sample of 45 exhibited ir(film)ν_{max} 1640 cm^{-1}; ^{1}Hnmr, τ4.20 (m, 2H, olefinic H), 6.63 (t, 1H, -CHBr, J=7 Hz), 7.40-8.65 (m, 6H). Pure compound 46 exhibited ir(film)ν_{max} 1640 cm^{-1}; ^{1}Hnmr, τ3.90 (m, 1H, olefinic H), 4.44 (m, 1H, olefinic H), 7.13 (t, 1H, -CHBr, J=3 Hz), 7.50-8.90 (m, 6H). Compounds 45 and 46 were quite unstable, no elemental analysis was obtained for these compounds.

Reduction of 7,7-Dibromonorcar-2-ene by Tri-n-butyltinhydride.[27] - To 3.53 g (14 mmol) of 7,7-dibromonorcar-2-ene 44 was added, dropwise, 4.06 g (14 mmol) of tri-n-butyltinhydride over a period of 1h. The resulting solution was stirred at room temperature for 3h and then distilled (air-bath temperature 60-80°, 10 Torr) to give 1.26 g (52%) of a colorless oil. Analysis of this material by glc (column B, 100°C) showed that it was composed of a mixture of syn- and anti-7-bromonorcar-2-ene (∿91%) 45 and 46, in a ratio of ∿1:1, along with minor, unidentified impurities (∿9%).

General Procedure for the Preparation of Lithium Phenylthio(7-norcar-2-enyl) cuprates. - A flame dried 50-ml three-necked flask, equipped with a bent side-arm tube containing 258 mg (1.5 mmol) of phenylthiocopper, was evacuated (vacuum pump) and filled with argon. A solution of syn- or anti-7-bromonorcar-2-ene (or a mixture of the two compounds)(259 mg, 1.5 mmol) in 2 ml of anhydrous ether was transferred to the flask. The solution was cooled to -78°C

and a solution of t-butyllithium in pentane (2M, 1.5 ml, 3 mmol) was added dropwise. The resulting solution was stirred for 2h at -78°C. Tetrahydrofuran (10 ml, freshly distilled from lithium aluminum hydride) was added. The phenylthiocopper in the side arm was transferred to the reaction vessel by rotating the bent tube. The mixture was warmed to -20°C and stirred at that temperature for 30 min. A clear brown solution containing 1.5 mmol of the appropriate lithium phenylthio(7-norcar-2-enyl)cuprate resulted and was ready for use.

General Procedure for Reaction of Lithium Phenylthio(7-norcar-2-enyl)-cuprates with β-Iodo-α,β-Unsaturated Ketones. - To a cold (-78°C) solution of the appropriate lithium phenylthio(7-norcar-2-enyl)cuprate (1.5 mmol) in 14 ml of ether-tetrahydrofuran-pentane (under argon) was added a solution of the appropriate β-iodo enone (1.0 mmol) in 2 ml of dry tetrahydrofuran. The dark red solution which formed was warmed to -20°C and stirred at that temperature for 2h and then at 0°C for another 2h. Methanol (2 ml) was added to quench the reaction. The reaction mixture was allowed to warm to room temperature and 15 ml of ether was added. The resulting mixture was filtered through a short column of florisil (15 g, 80-100 mesh). The column was eluted with another 150 ml of ether. Crude products were isolated by evaporation of solvent under reduced pressure.

Reaction of 3-Iodo-2-Cyclohexen-1-one with the Cuprate Reagent Derived from syn-7-Bromonorcar-2-ene. - Following the general procedure outlined above, 1.5 mmol of lithium phenylthio(7-norcar-2-enyl)cuprate (derived from pure syn-7-bromonorcar-2-ene) was allowed to react with 222 mg (1 mmol) of 3-iodo-2-cyclohexen-1-one. Normal work-up gave 173 mg of crude product. The

ir spectrum of this material indicated the presence of a mixture of saturated and α,β-unsaturated carbonyl compounds. A glc analysis of this material showed that it was composed of two major components (∿50% and 25% respectively) and a number minor impurities (∿25%). The crude mixture was dissolved in 15 ml of methanol and a catalytic amount of sodium methoxide was added. The resulting solution was stirred at room temperature for 1h and the methanol was then removed under reduced pressure. To the residue was added 30 ml of brine and the resulting mixture was extracted with three 50 ml portions of ether. The combined ether extracts were dried over magnesium sulfate and evaporated under reduced pressure. The yellow oil which remained showed no trace of saturated carbonyl absorption in the ir spectrum. A glc analysis of this material showed that it was composed of a single major component (∿80%), together with a number of minor unidentified impurities. This material was subjected to column chromatography (25 g silica gel, elution with 25% ether in hexane), and 134 mg (72%) of the major component was isolated and identified as the tricyclic enone 55. The latter material was recrystallized from hexane to give white needles which exhibited mp 59-60°C; uv λ_{max} 251 nm (ε=7556); ir($CHCl_3$)ν_{max} 1620, 1660 cm^{-1}; ^{1}Hnmr, τ3.54-3.98 (m, 2H, olefinic H), 6.19 (m, 1H, -C=C-CH-C=C-), 7.32-8.40 (m, 13H).

Anal. Calcd. for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.94; H, 8.46.

Reaction of 3-Iodo-2-cyclohexen-1-one with the Cuprate Reagents Derived from a 1:1 Mixture of syn and anti-7-Bromonorcar-2-ene. - Following the general procedure, 1.5 mmol of lithium phenylthio(7-norcar-2-enyl)cuprate (derived from a 1:1 mixture of syn- and anti-7-bromonorcar-2-ene) was allowed to react with 222 mg (1 mmol) of 3-iodo-2-cyclohexen-1-one. Normal work-up

followed by sodium methoxide treatment and column chromatography of the crude product on 25 g of silica gel (elution with 25% ether in hexane) afforded 86 mg (45%) of the pure tricyclic enone 55 and 85 mg (45%) of the pure enone 57. The enone 57 was initially obtained as a colorless viscous oil. However, this material could be recrystallized (from hexane) to give a white crystalline solid. The latter exhibited mp 53-54°C; uv λ_{max} 260 nm (ε=19159); ir(film)ν_{max} 1655, 1600 cm^{-1}; ^{1}Hnmr τ3.94 (m, 1H, olefinic H), 4.21 (broad s, 1H, -COCH=C-), 4.43 (m, 1H, olefinic H), 7.52-8.52 (m, 13H).

Anal. Calcd. for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.76; H, 8.65.

Reaction of 3-Iodo-2-cyclopenten-1-one with the Cuprate Reagent Derived from syn-7-Bromonorcar-2-ene. - Following the general procedure outlined above, 1.5 mmol of lithium phenylthio(7-norcar-2-enyl)cuprate (derived from pure syn-7-bromonorcar-2-ene) was allowed to react with 208 mg (1 mmol) of 3-iodo-2-cyclopenten-1-one. A different work-up procedure was used in this reaction. After the reaction was complete, methanol (1 ml), ether (20 ml) and water (10 ml) was added to the reaction mixture. The solid material that formed was removed by filtration and the filtrate was extracted thoroughly with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give a yellow oil. This material was subjected to column chromatography on 25 g of silica gel. Elution of the column with 25% ether in hexane afforded 90 mg (52%) of the pure tricyclic enone 56. The latter was recrystallized from hexane, yielding white flake-like crystals which exhibited mp 70-72°C; uv λ_{max} 243 nm (ε=8005); ir($CHCl_3$)ν_{max} 1685, 1635 cm^{-1}; ^{1}Hnmr, τ3.67 (d of d, 1H, olefinic H, J=9 Hz, J'=7 Hz), 3.98 (d of d, 1H, olefinic H, J=9 Hz, J'=7 Hz), 6.77 (broad d, 1H, J=7 Hz, -C=C-CH-C=C-), 7.40 (m, 1H), 7.50 (m, 2H),

7.72 (broad s, 4H), 8.05-9.40 (m, 4H).

Anal. Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.93; H, 8.12.

Reaction of 3-Iodo-2-cyclopenten-1-one with the Cuprate Reagents Derived from a 1:1 Mixture of syn- and anti-7-Bromonorcar-2-ene. - Following the general procedure outlined above, 1.5 mmol of lithium phenylthio(7-norcar-2-enyl)cuprate (derived from a 1:1 mixture of syn- and anti-7-bromonorcar-2-ene) was allowed to react with 208 mg (1 mmol) of 3-iodo-2-cyclopenten-1-one. Normal work-up, followed by column chromatography of the crude product on 25 g of silica gel (elution with 25% ether in hexane) afforded 49 mg (28%) of the pure tricyclic enone 56 and 53 mg (31%) of the pure enone 58. The enone 58, which was initially obtained as a colorless viscous oil, could be recrystallized from hexane to give white needles. The latter exhibited mp 78-79°C; uv λ_{max} 269 nm (ε=17176); ir(film)ν_{max} 1695, 1595 cm^{-1}; ^{1}Hnmr, τ3.83 (m, 1H, olefinic H), 4.39 (m, 1H, olefinic H), 4.13 (broad s, 1H, -C=CH-C=O), 7.10-8.60 (m, 11H).

Anal. Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.74; H, 8.00.

Thermal Rearrangement of the Enone 57. - A solution of the enone 57 (72 mg) in o-dichlorobenzene (3 ml) was refluxed for 40h. Removal of solvent under reduced pressure (vacuum pump) and distillation (air-bath temperature ∿105°C, 0.4 Torr) of the residual oil gave 68 mg (94%) of a colorless oil. Analysis of this material by glc (column B, 200°C) showed that it was composed of the enone 55 (∿92%) and small amount of minor impurities (∿8%). This material was subejcted to recrystallization (hexane), and pure enone 55 was isolated as white crystals. The spectral data of the latter were identical with those of the same material obtained earlier.

Thermal Rearrangement of the Enone 58. - A solution of the enone 58 (40 mg) in o-dichlorobenzene (1.5 ml) was refluxed for 24h. Removal of solvent and distillation (air-bath temperature ∿105°C, 0.2 Torr) of the residual oil gave 38 mg (96%) of the pure crystalline tricyclic enone 56. A glc analysis (column B, 200°C) of this material showed that it was pure.

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