THE ACID-CATALYZED SELF-CONDENSATION REACTION OF β-DIKETONES IN THE PRESENCE OF 2,2,2-TRIFLUORODIAZOETHANE

by

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(ABSTRACT)

A novel acid-catalyzed self-condensation reaction of β-diketones in the presence of 2,2,2-trifluorodiazoethane (TFD) has been discovered. This reaction is of interest because not many methods are available for the preparation of cyclized products (e.g., aromatic natural products) from β-dicarbonyl units. Acid-catalyzed reactions of 1-phenyl-1,3-butanedione and several substituted derivatives of 1-phenyl-1,3-butanedione with TFD afforded two groups of substituted biphenyl compounds. One of these groups could be an important synthon for the preparation of larger polycyclic aromatic compounds. Several cyclized products have also been obtained from the reaction of 2,4-pentanedione with TFD. Two potential mechanisms have been suggested to describe this cyclization process. Mechanistic studies utilizing dienophiles suggest that the previously described cyclized products have originated from Michael addition

reactions. Several NMR techniques have been utilized to characterize the reaction products which were obtained in this study. These techniques include ^{13}C labeling, the ^{13}C NMR INADEQUATE pulse experiment, and applications of lanthanide shift reagents. The results that were obtained from the lanthanide shift reagent studies illustrate that certain oxygen atoms can be converted to 2,2,2-trifluoroethyl ethers to prevent complexation with lanthanide shift reagents. This methodology was successfully utilized to simplify the interpretation of lanthanide shift reagent results that were obtained from polyfunctional molecules. The reactions of several additional β-diketones have also been studied to better understand the cyclization process.

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INTRODUCTION

The work in this disertation started as an analytical NMR project. Specifically, it was known from previous studies[1] that trifluoroethyl ethers do not complex with lanthanide shift reagents (weak Lewis acids). It was hoped that in polyfunctional molecules, certain functional groups could be deactivated (e.g., hydroxyl groups), thereby simplifying the observed lanthanide induced shifts. Attempts to prepare the cis and trans-trifluoroethyl enol ethers of 2,4-pentanedione as models for this study led to a complex mixture of products. The identities of the compounds in this mixture were unraveled using LC-^{1}H NMR. This LC-^{1}H NMR study indicated that a novel cyclization reaction had occurred. This novel acid-catalyzed self-condensation reaction became the focal point of this dissertation because of the potential synthetic utility of the reaction in aromatic nat ral products preparations. The reactivity of several β-diketones was explored, and the results indicated that this cyclization reaction was potentially attractive as a new preparation for biphenyl compounds.

Chapter I

HISTORICAL

Reactions of Fluorinated and Non-fluorinated Diazo Compounds

Diazo compounds are known to undergo several different types of reactions. For example, O-alkylation, cycloaddition, and homologation reactions have been reported for these compounds.[2] Therefore, one of the major disadvantages in utilizing these compounds is predicting which reaction product will be formed under the experimental conditions that are employed.

Dyatkin and Mochalina[3] have investigated several different reactions of 2,2,2-trifluorodiazoethane (TFD) and have found that this diazo compound undergoes reaction with dichloroacetic acid and benzenethiol (eq 1 and 2).

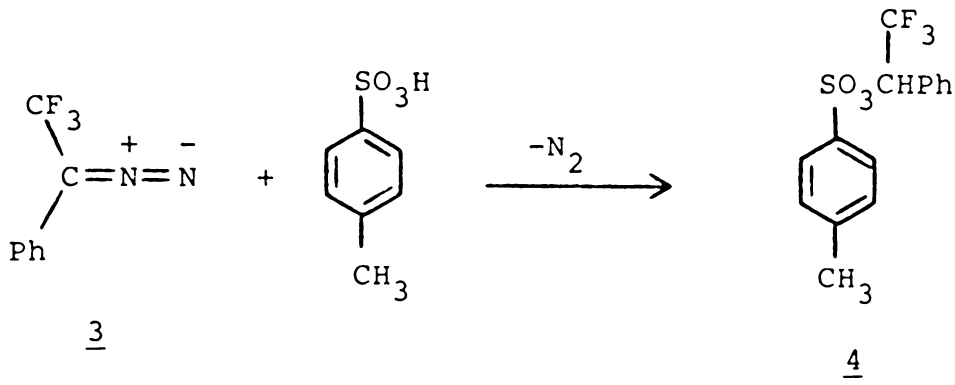
$$CF_3CHN_2 + CHCl_2COOH \xrightarrow{-N_2} \underset{\underline{1}}{CHCl_2COOCH_2CF_3} \qquad (1)$$

$$CF_3CHN_2 + C_6H_5SH \xrightarrow{-N_2} C_6H_5SCH_2CF_3 \quad (2)$$

2

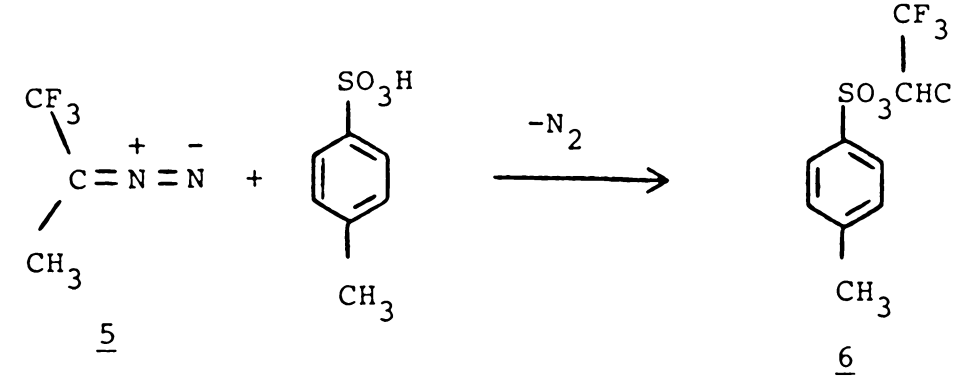
Trifluoroethyl dichloroacetate (1) and phenyl 2,2,2-trifluoroethyl sulfide (2) were the respective reaction products. Koller and Dorn[1] have reported similar reactions of TFD with carboxylic acids, alcohols, and phenols in an investigation of the diazo compound as a potential ^{19}F NMR tagging reagent. The results of this study indicated that a number of trifluoroethyl esters and trifluoroethyl ethers could be prepared. Dorn and Koller have also reported that benzenethiol and hexanethiol react with TFD in the presence of aqueous tetrafluoroboric acid to give the respective trifluoroethyl derivatives. However, amines did not undergo reaction with this diazo compound since amines neutralize the acid catalyst.

Shepard and Wentworth[4] have reported that 1-phenyl-TFD (3) reacts with p-toluenesulfonic acid to give the corresponding p-toluenesulfonate (4) (eq 3).



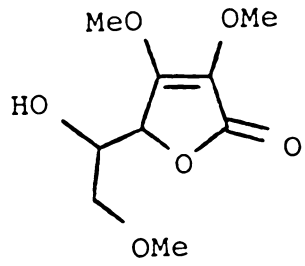
3 4 (3)

However, this diazo compound did not react with benzoic acid. This is in contrast to the reactions of 1,1,1-trifluoro-2-diazopropane and diphenyldiazomethane which provided the respective O-alkylated derivatives of benzoic acid. Thus, the stabilizing effect of the phenyl and the trifluoromethyl groups are clearly illustrated. Shepard and Sciaraffi[5] have reported that 1,1,1-trifluoro-2-diazopropane (5) undergoes reaction with p-toluenesulfonic acid to yield 1-methyl-2,2,2-trifluoroethyl p-toluenesulfonate (6) (eq 4).



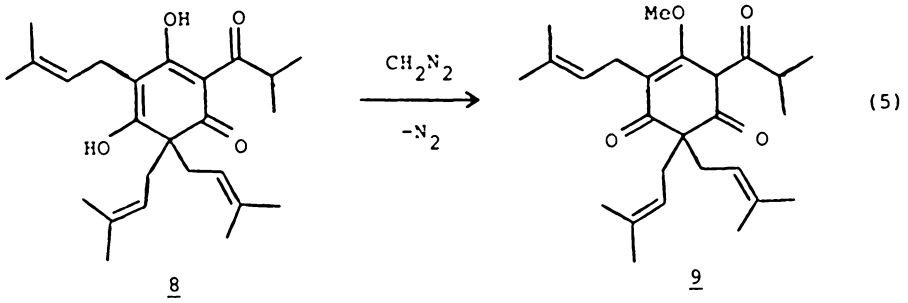
5 6 (4)

Similar O-alkylation reactions have been reported for diazomethane. Roberts et al.[6] have reported that alcoholic hydroxyl groups were methylated by diazomethane in the presence of catalytic amounts of fluoboric acid. Unlike the results which are obtained with normal protonic acids (i.e., nucleophilic attack by the conjugate base on the diazo compound), the conjugate base of fluoboric does not readily react with diazomethane which allows fluoboric acid to serve as a useful methylation catalyst. Several different methyl ethers were prepared including the methyl ethers of desoxycorticosterone and testosterone. The technique was also utilized to convert ascorbic acid selectively to the corresponding trimethyl ether 7.



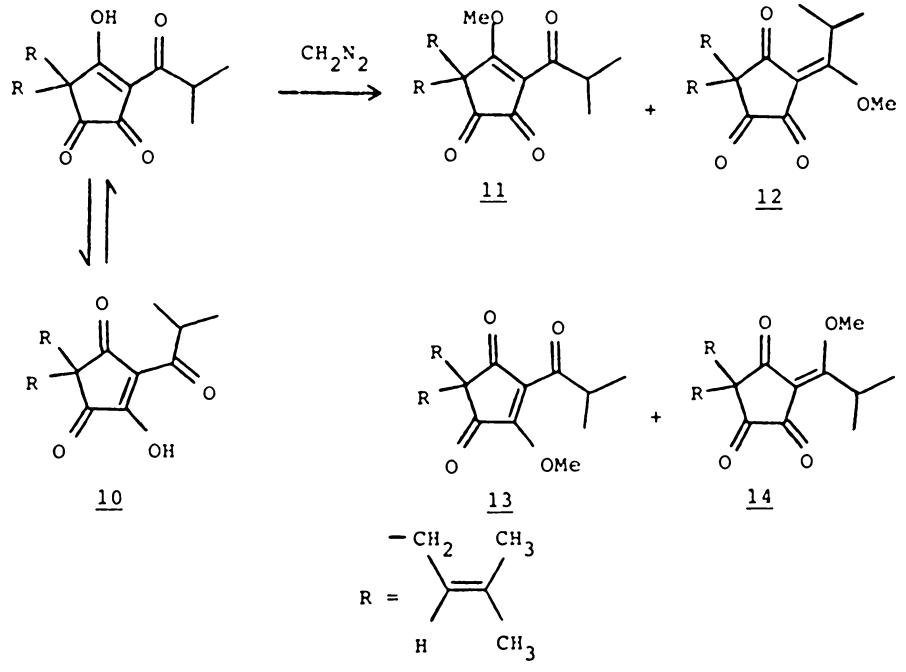
7

Similar reactions of diazomethane were also reported by Connett et al.[7] in the methylation of the hop resins colpulone and cohulupone. Colupulone (8) afforded methyl ether 9 as the major reaction product when treated with diazomethane (eq 5).



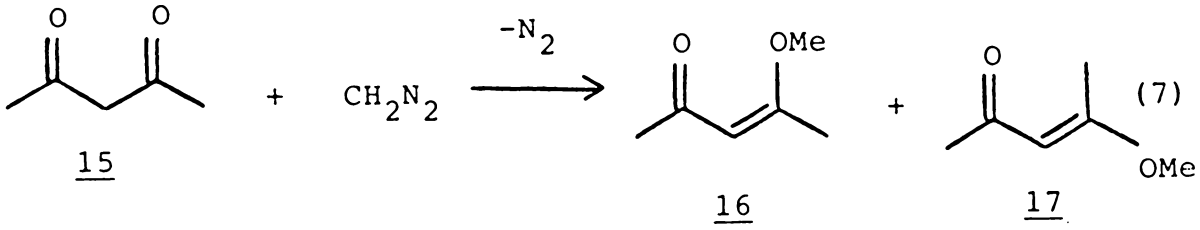
8 9 (5)

Four different mono O-methylation derivatives (10-13) were obtained when cohulupone (14) was treated with diazomethane (eq 6).

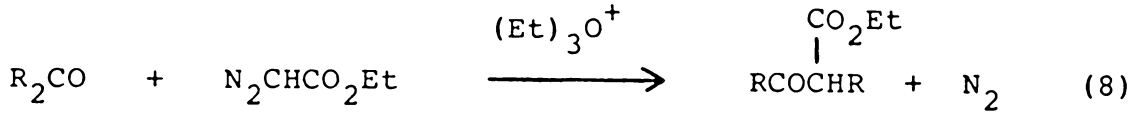


10 11 12 13 14 (6)

Eistert et al.[7] reported that 2,4-pentanedione (15) reacts with diazomethane to yield cis- and trans-methyl enol ethers (16 and 17) as illustrated below. Identification of these isomers[9] and mechanism studies for this reaction[10] have also been reported.



In contrast to the reactions of diazo compounds with hydroxyl groups, ketones and aldehydes undergo homologation reactions in the presence of diazo compounds. Mock and Hartman[11] have reported that ketones undergo homologation reactions in the presence of ethyl diazoacetate and triethyloxonium fluoroborate to yield β-keto esters (eq 8).



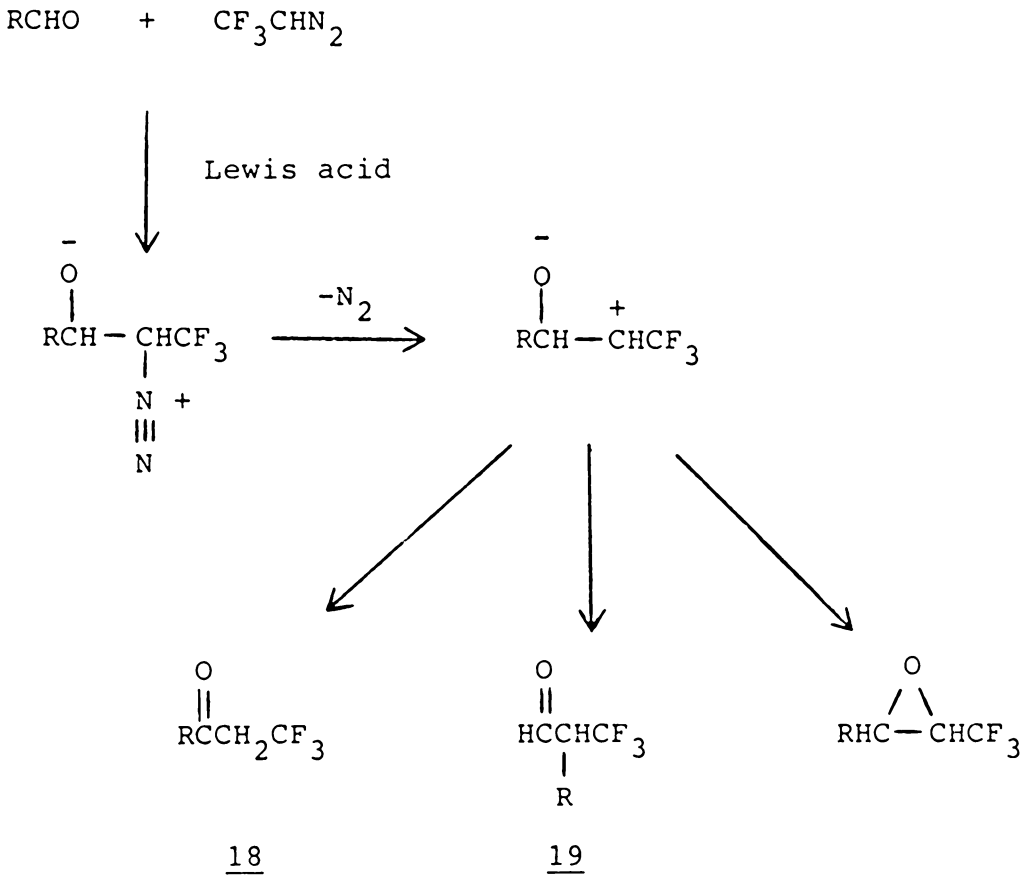
Similar homologation reactions were observed with diazoacetonitrile, TFD, dimethyl diazomethylphosphate, and tert-butyl diazoacetate. These homologation reactions were also observed when antimony pentachloride was used as the acid catalyst.

Mock and Hartman[11] also found that insertions of the methylene synthon favored substitution on the side of the carbonyl bond with the least steric hindrance. This ring expansion reaction was synthetically attractive since hydrolysis and decarboxylation were easily accomplished. In addition, relatively few by-products were obtained. Furthermore, the trifluoromethyl group resulting from the insertion of TFD can be easily removed by mild basic hydrolysis.

Tordeux and Wakselman[12] have reported similar reactions for aldehydes in the presence of TFD and an acid catalyst. With pentanal, cyclohexancarboxaldehyde, and benzaldehyde, this reaction yields mainly homologated ketones (18) and aldehydes (19) substituted by an α-trifluoromethyl group (Scheme 1.1). A 52% yield of ketone 19a is reported for the reaction of pentanal in the presence of $SbCl_5$. A 50-50 mixture of aldehyde 19b and ketone 18b were obtained from cyclohexancarboxaldehyde in the presence of BF_3-etherate. In the presence of BF_3-etherate, benzaldehyde yields aldehyde 19c in 70%. However, in the presence of $SbCl_5$, the above reaction product undergoes further reaction to yield epoxide

Scheme 1.1[12]

Products Obtained from the Reaction of Aldehydes with TFD



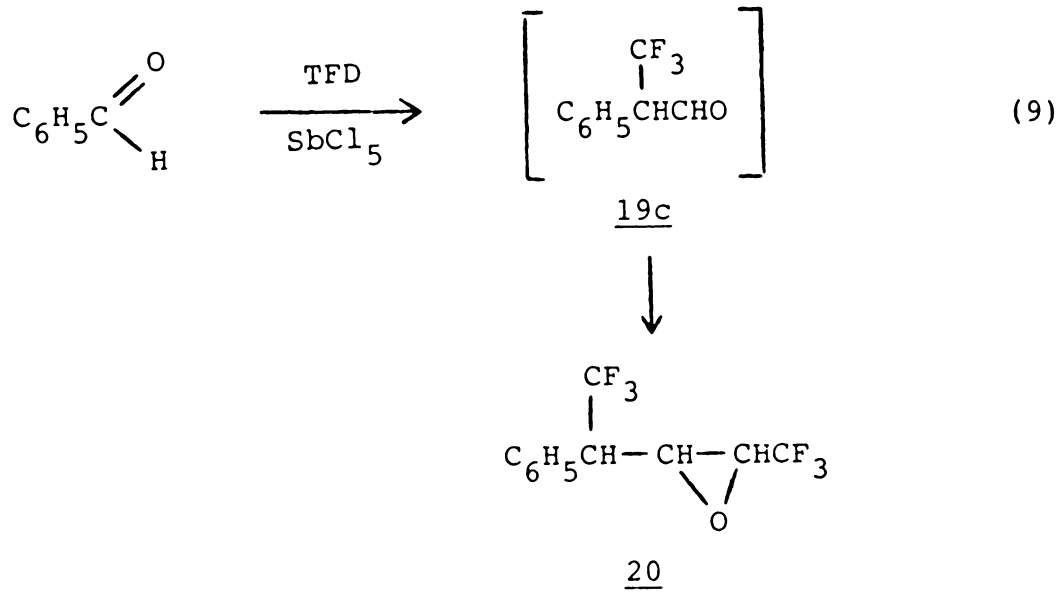
18 19

(a) R = n-butyl

(b) R = cyclohexyl

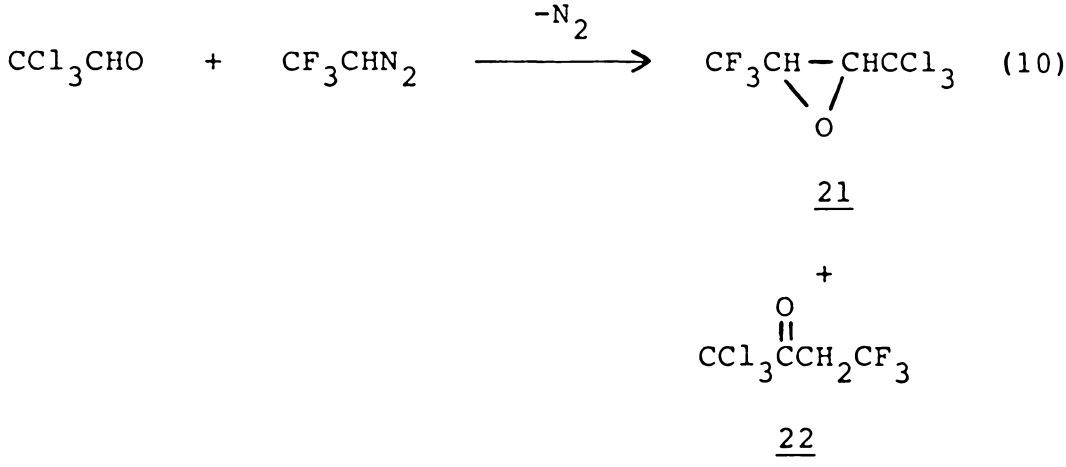
(c) R = phenyl

20 in 41% (eq 9).



(9)

In similar fashion, Dyatkin and Mochalina[3] have reported that chloral affords 1,1,1-trichloro-2,3-epoxy-4,4,4-trifluorobutane (21) and 1,1,1-trichloro-4,4,4-trifluoro-2-butanone (22), in yields of 54 and 32%, respectively, when treated with neat TFD (eq 10).



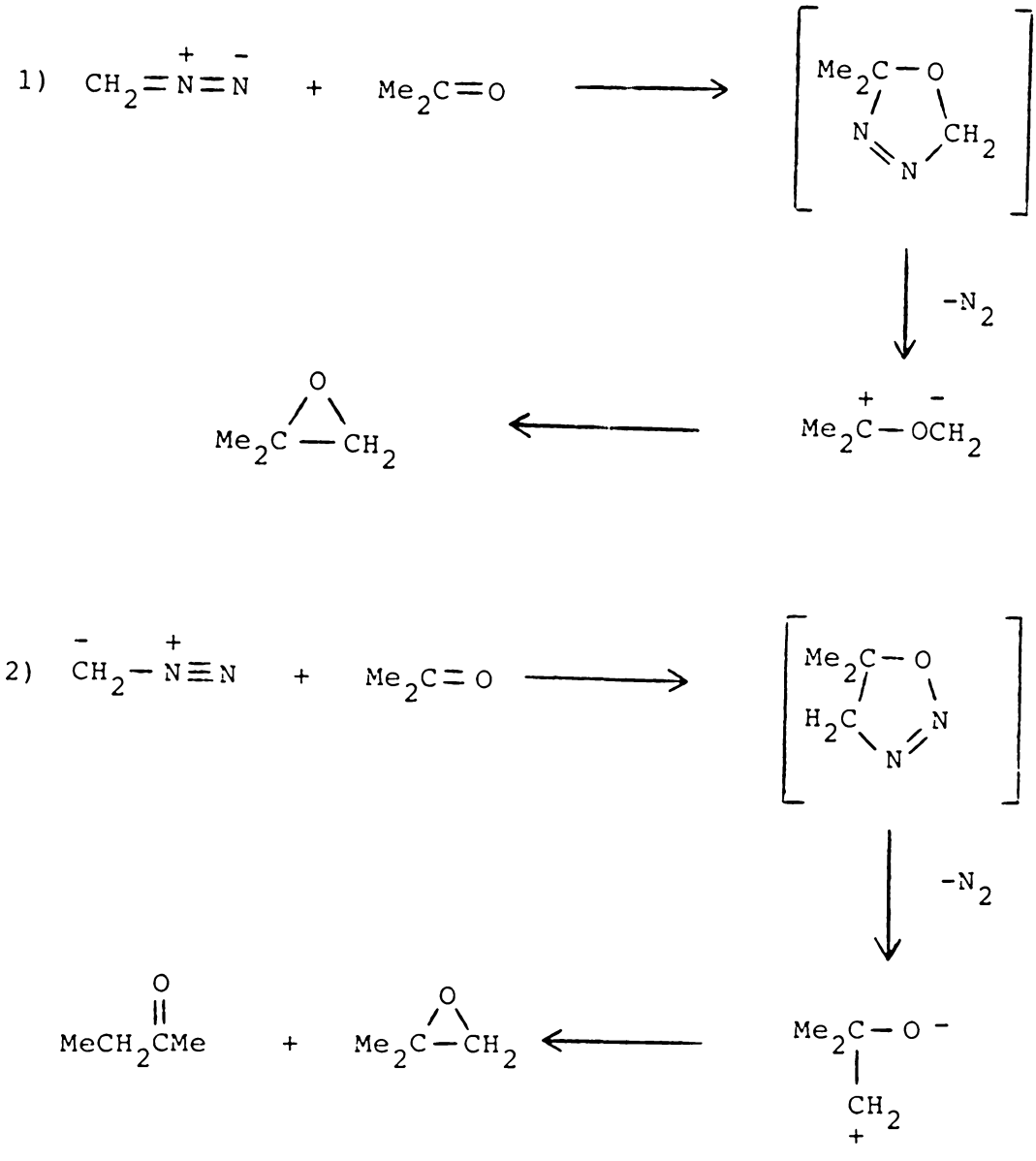
(10)

For years it has generally been accepted that epoxide formation and the homologation reactions which were previously described occur through a mechanism analogous to the one suggested by Tordeux and Wakselman[12] (Scheme 1.1). More recently, this mechanism has been questioned based on the results that were obtained by Bradley and coworkers.[13] Bradley et al.[13] have concluded that the above products are formed via two competing processes which are illustrated in Scheme 1.2. Gutsche and Bowers[14] make similar mechanistic claims based on the product distributions that were obtained when substituent effects were examined for the reaction of diazocarbonyl compounds (Scheme 1.3). Gutsche and Bowers found that bicyclic ketone 24a was the major product obtained from 23a, whereas, epoxide 25b was almost exclusively obtained from 23b.

A number of cycloaddition reactions have been reported for diazo compounds with unsaturated molecules. Atherton and Fields[15] have investigated the cycloaddition reaction of several olefins with TFD in the absence of light. This cycloaddition reaction is illustrated for propene which affords cis- and trans-3-methyl-5-trifluoromethyl-1-pyrazolines (26 and 27) in 83% yield (eq 11).

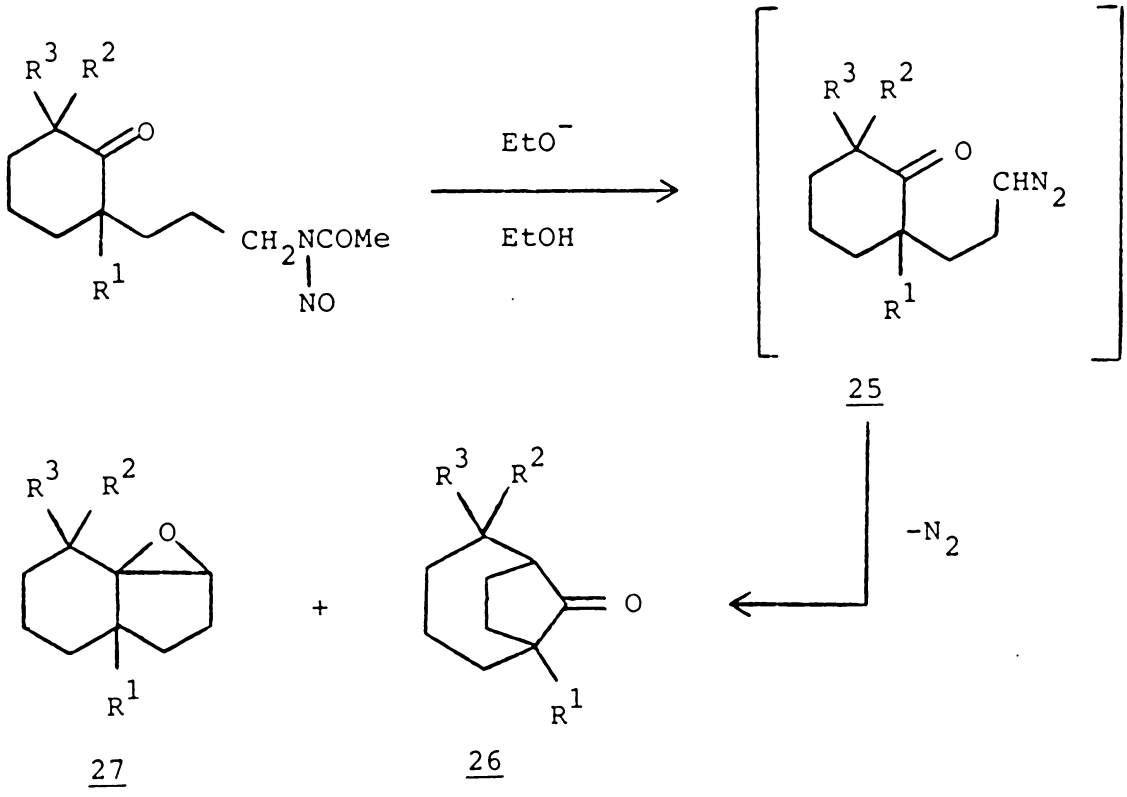
Scheme 1.2[13]

Mechanisms for the Two Competing Reactions of Acetone with Diazomethane



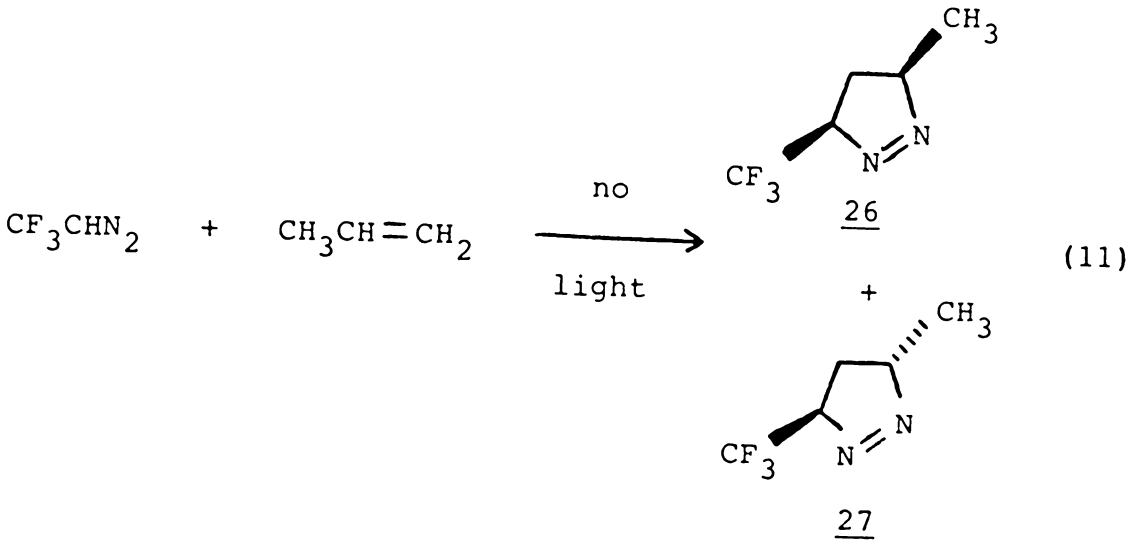
Scheme 1.3[14]

Substituent Effects on the Reaction
of Diazocarbonyl Derivatives



(a) $R^1 = R^2 = R^3 = H$

(b) $R^1 = R^2 = R^3 = Me$



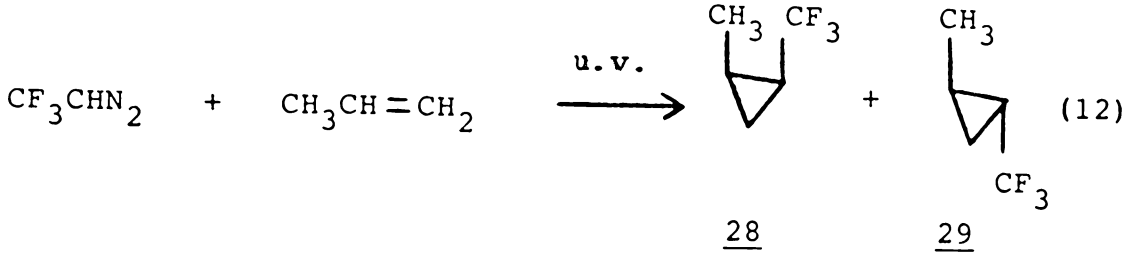
(11)

In the above study, Atherton and Fields found that olefins containing trifluoromethyl groups accelerated the cycloaddition reaction. The results obtained in this study were consistent with a 1,3-dipolar addition of the diazo compound to the olefin.

In an earlier report by Fields and Haszeldine,[16] the photolysis of TFD gave a mixture of products that included a fluorinated polymer. Under these reaction conditions, this polymer was cleaved to yield cis- and trans-1,1,1,4,4,4-hexafluorobut-2-ene which further reacted with TFD to yield the corresponding pyrazoline products. The pyrazoline and polymer formation occurred only when the initial concentration of the diazo compound was high. Additional examples illustrating this 1,3-dipolar addition have recently been reported by Fields and Tomlinson.[17]

Atherton and Fields[15] have also irradiated several ole-

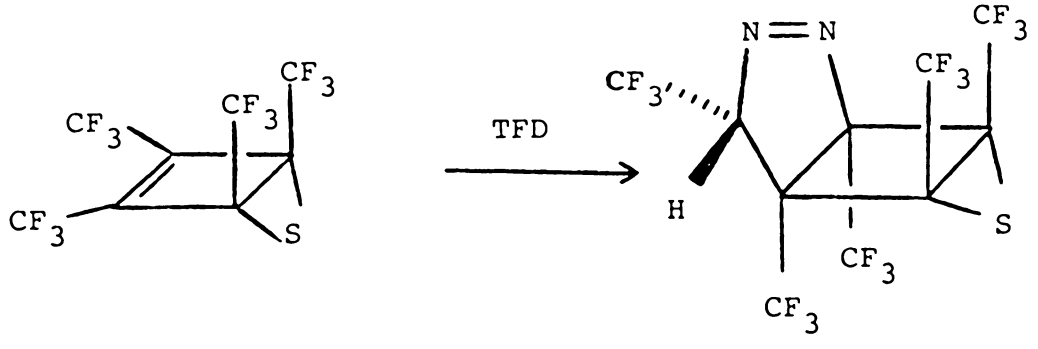
fins in the presence of TFD to obtain cyclopropane derivatives. Under these conditions propene gave a mixture of cis- and trans-1-methyl-2-(trifluoromethyl)cyclopropanes (28 and 29) in 68% yield (54:46 ratio of the respective isomers) (eq 12).



28 29 (12)

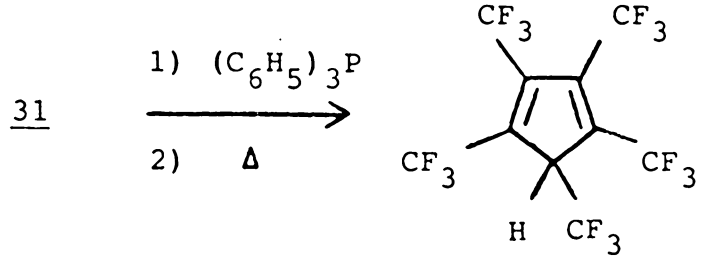
Competing with this reaction was the 1,3-dipolar additon reaction which was previously described.

Leganis and Lemal[18] have reported a similar cycloaddition reaction of TFD with perfluorotetramethyl Dewar thiophene (30) to afford a 75% yield of pyrazolinethiirane 31 (eq 13).



30 31 (13)

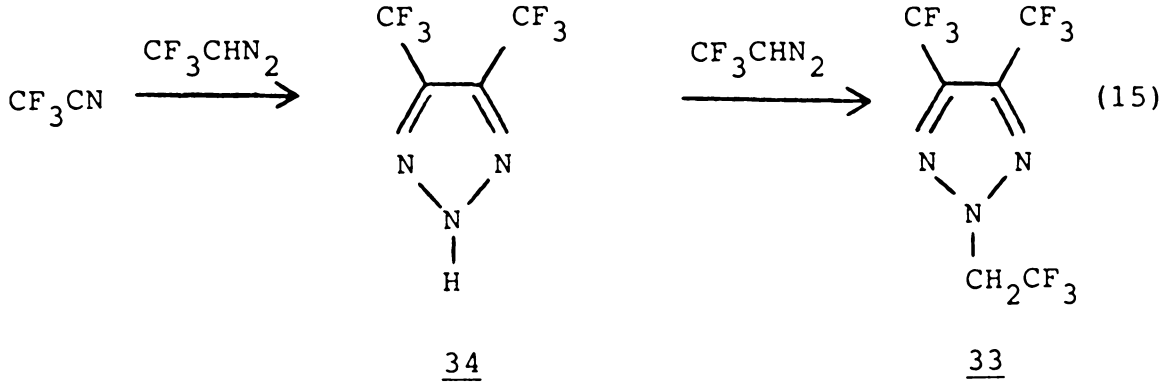
Spectroscopic data indicated that only one stereoisomer was found in the preceding reaction. Pyrazolinethiirane 31 underwent further reaction eventually yielding 5H-perfluoropentamethylcyclopentadiene (32), an extraordinary carbon acid which has a pK_a of ~ -2 (eq 14).



(14)

32

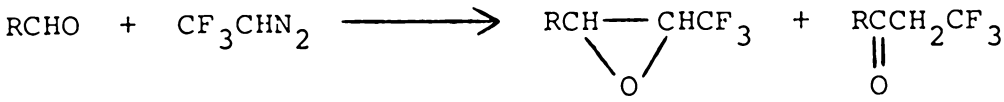
Cycloaddition reactions have also been reported for diazo compounds with molecules containing carbon-heteroatom multiple bonds (e.g., C≡N). Fields and Tomlinson[17] have reported that TFD reacts with nitriles to afford the corresponding five-membered ring products. This reaction is illustrated for trifluoroacetonitrile which afforded 2-trifluoroethyl-1,2,3-triazole 33 in 84% yield presumably via 34 (eq 15).



(15)

34 33

Hexafluoroisopropylideneimine (35) reacted under similar reaction conditions to provide a 19% yield of the triazoline 36 which was formed via a 1,3-dipolar addition to 37 (Scheme 1.4). Fields and Tomlinson also treated chloral and trifluoroacetaldehyde under the above reaction conditions to examine whether or not cycloaddition reactions would occur. Instead, homologation reactions were observed. These reactions provided the corresponding ketones and the cis- and trans-oxiranes which are illustrated below (see eq 10 for similar reactions).



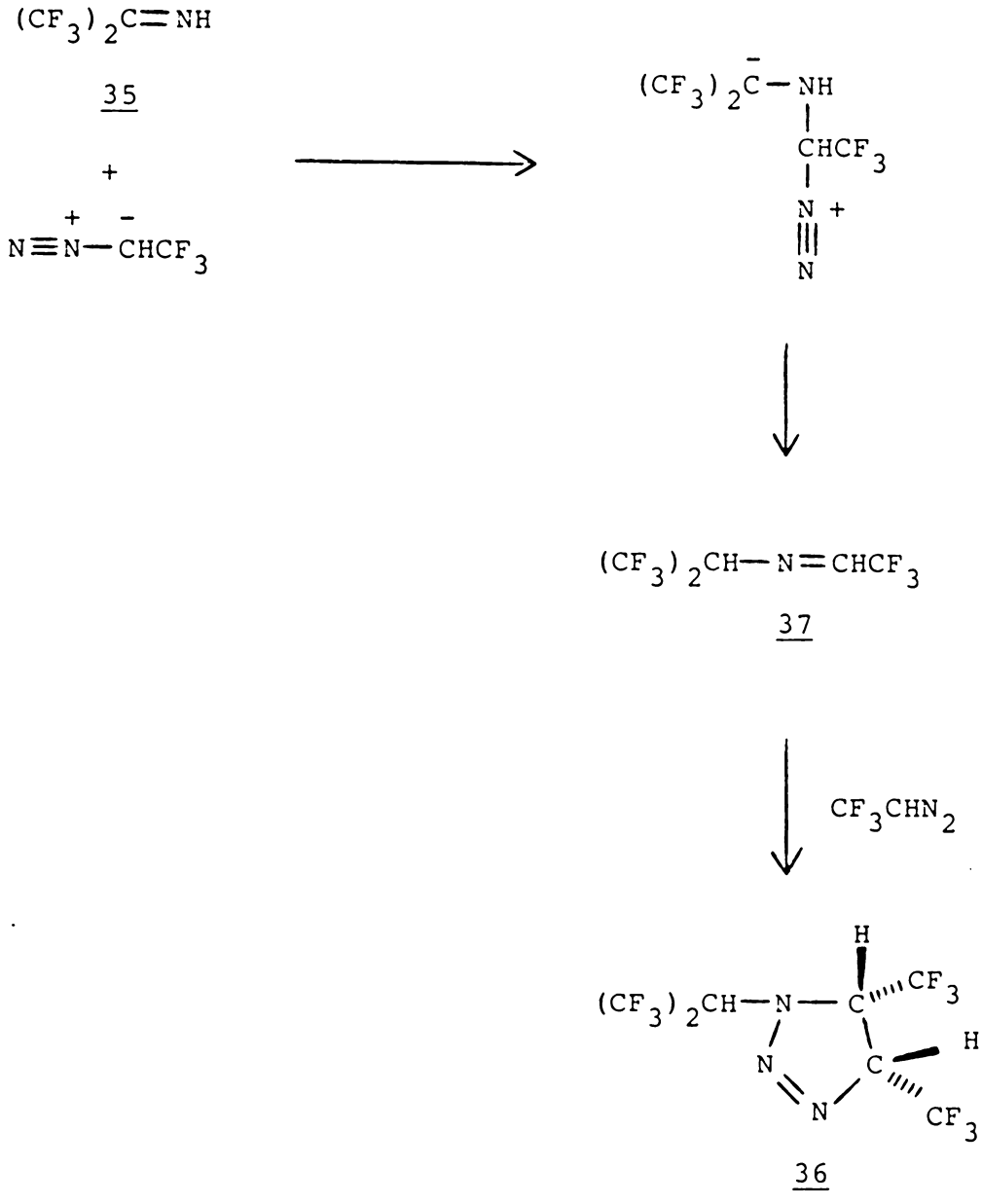
(16)

R = CCl_3, CF_3

This illustrates that cycloaddition products were not

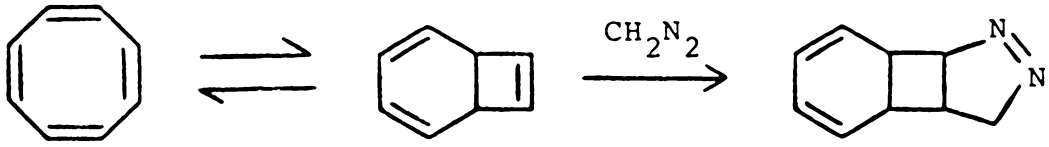
Scheme 1.4[17]

The Reaction of
Hexafluorisopropylideneimine (35)
with TFD



obtained from the reaction of these aldehydes with the diazo compound under the above conditions.

Analogous 1,3-dipolar cycloaddition reactions have been reported for diazomethane. Pyrazoline, pyrazole, triazoline, and triazole are the cycloaddition products that were obtained from olefins, acetylenes, imines, and nitriles, respectively.[20] The reaction of cyclooctatetraene, via its valence tautomer, with diazomethane is one example of this general reaction.[21] This reaction afforded tricyclic pyrazoline 38 as the reaction product (eq 17).



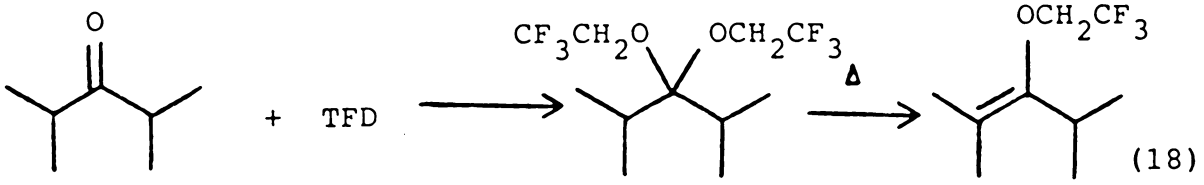
(17)

38

In addition, thiadiazoles can be prepared from the reaction of diazomethane with isothiocyanates using similar methodology.[22]

Analogous to the reactions of TFD with alcohols, phenols, carboxylic acids, etc., TFD will react with any water present in the reaction mixture. Thus, TFD is an excellent water

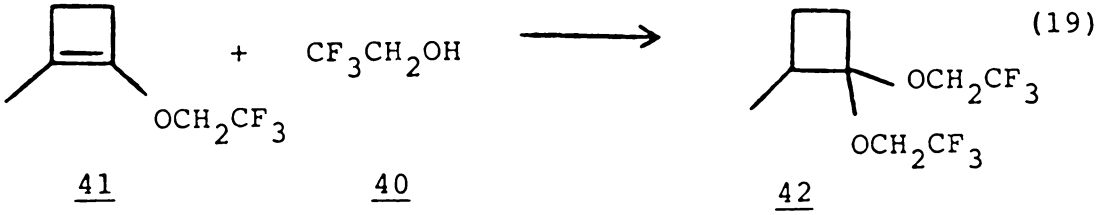
scavenger.[1] In the presence of water, TFD readily reacts with ketones to yield trifluoroethyl ketals.[23] In some cases these trifluoroethyl ketals can readily eliminate 2,2,2-trifluoroethanol to yield trifluoroethyl enol ethers as illustrated below for the diisopropyl ketone derivative (39).



(18)

39

Hanack et al.[24] have also found that 2,2,2-trifluoroethanol (40) will react with 2-methylcyclobutenyl trifluoroethyl ether (41) to yield ketal 42 (eq 19).



(19)

41 40 42

It is also well known that 2,2,2-trifluoroethanol is a poor nucleophile in many displacement reactions.[25] Thus, trifluoroethoxy eliminations reactions are generally not reversible.

In conclusion, O-alkylation, homologation, and cycloaddition reactions could be potential competing reaction path-

ways when treating a ß-diketone with TFD. In addition, ketal reaction formation could also be observed if any water is initially present. Many other reactions of diazo compounds do exist. One such reaction is their utilization in the Arndt-Eistert synthesis. Due to the wide scope of these other reactions, the interested reader is referred to specialized reviews on this topic.[2,26]

The Preparation of Polyketide-type Aromatic Natural Products

It is well known that many aromatic natural products arise from poly-ß-carbonyl intermediates.[27] These naturally occurring pathways have intrigued chemists for years because the mechanism for the biosynthesis of the polyketide aromatic natural compounds is poorly understood. In addition, not many synthetic methods have been utilized to prepare these compounds. Therefore, it is very desirable to develop additional synthetic routes to this group of compounds. These compounds could be used directly as precursors for antibotics and/or other economically important compounds.

Pioneering studies in understanding the biosynthesis of the polyketide natural products were performed by Collie near the turn of the century.[28] However, his work had little impact until there was revival of interest in the biosynthesis of these compounds in the late 1940's. In the early

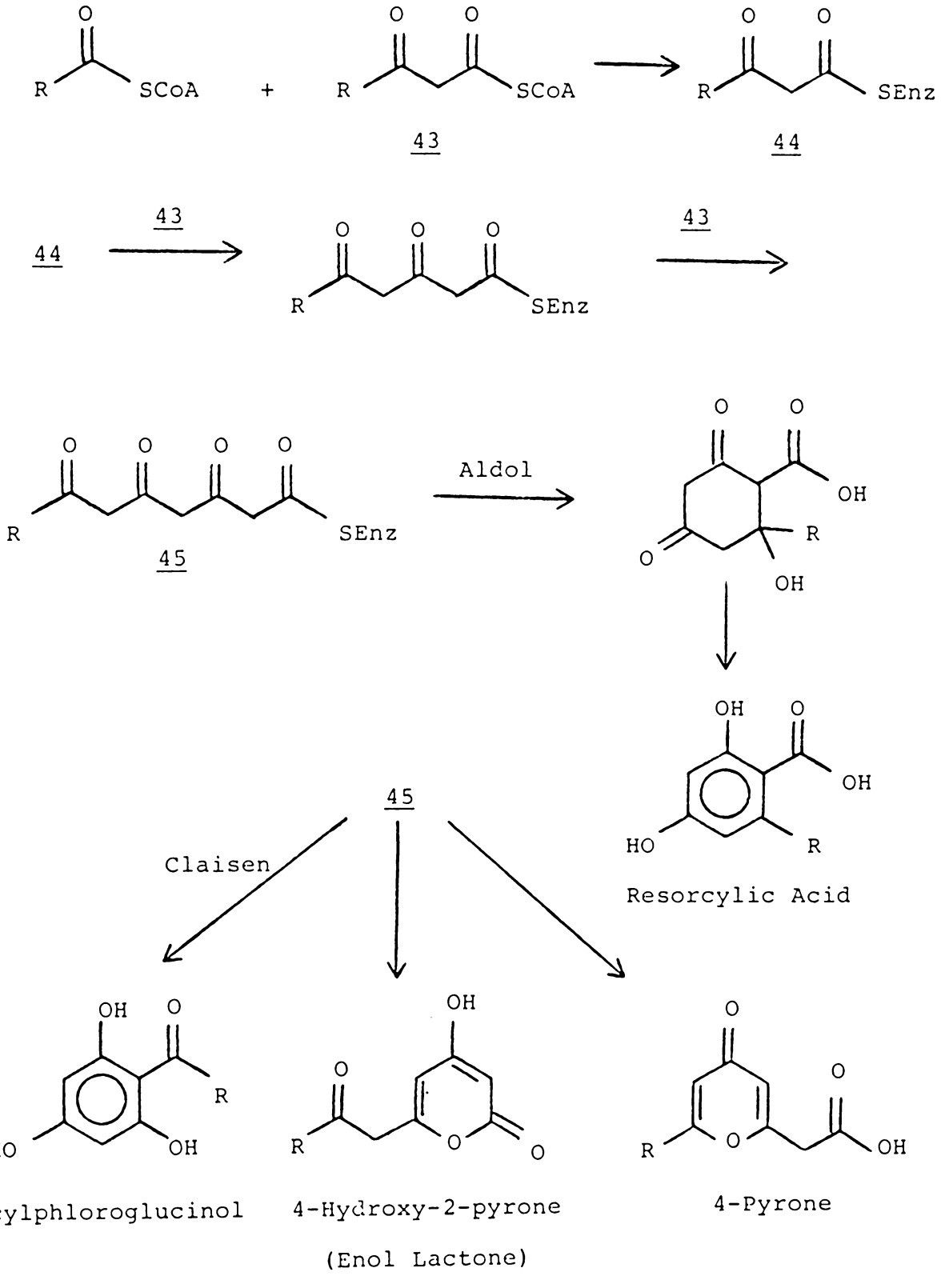
1950's Birch[29] postulated the general method describing how these polyketide compounds could be formed. This process is illustrated in Scheme 1.5 and involves the condensation of coenzyme A esters of acetic acid or other carboxylic acids with malonyl coenzyme A (43). Thiol esters of ß-keto acids (44) are afforded from these condensation reactions. The resulting products can undergo further condensation reactions with malonyl coenzyme A to yield larger homologs in this series which eventually yield the polyketide natural products.

Collie's early studies[28] which led to the development of the polyketide theory were based on the reactions of 2,4,6-heptanetrione (46). Collie found that by utilizing acidic or strongly basic conditions, a cyclization reaction occurred to yield orcinol (47) (Scheme 1.6). Collie also determined that naphthalenediol 48 was formed when 2,4,6-heptanetrione was treated under mild basic conditions. More recently, Collie's work has been reinvestigated by Bethell and Maitland[30] and by Birch[31] to provide additional confirmation of the above reaction products.

The examples presented in Schemes 1.5 and 1.6 illustrate that several different substituents, especially multiple hydroxyl groups, can be incorporated into the corresponding aromatic products. The synthetic preparation of aromatic compounds containing several hydroxyl groups on the aromatic ring using conventional routes is usually difficult. There-

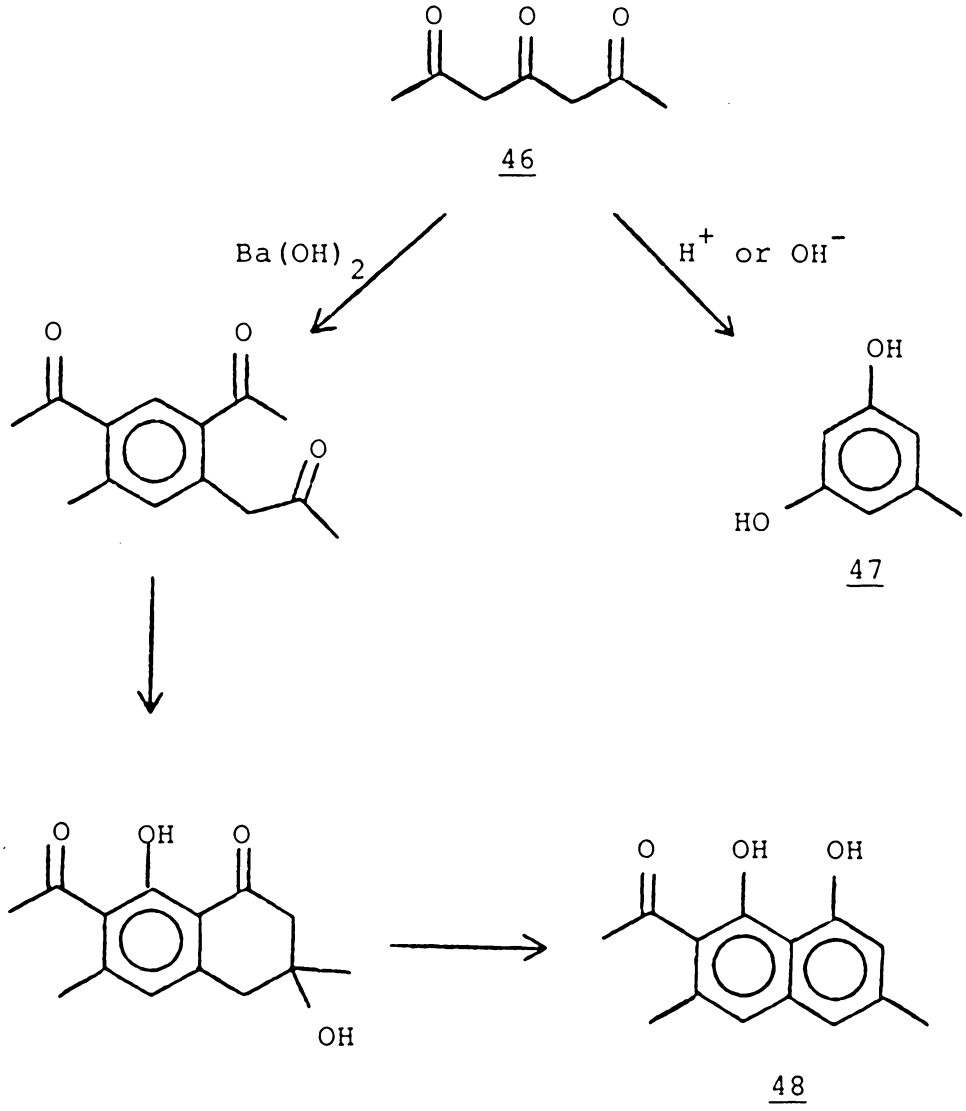
Scheme 1.5[29]

Mechanism for the Biosynthesis of
Polyketide Aromatic Natural Products



Scheme 1.6[28]

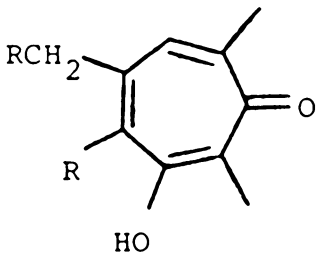
Cyclization Reactions of 2,4,6-Heptanetrione



fore, the synthesis of these compounds from β-dicarbonyl compounds is quite attractive. The polyketide synthesis also provides a method for the introduction of hydroxyl groups that are meta to each other on an aromatic ring. Few synthetic methods are available which yield this same result. Since there are relatively few methods for the preparation of polyketide aromatic natural products, any synthetic route which appears to parallel biosynthetic pathways involving the condensation of β-dicarbonyl units receives considerable attention from organic chemists.

Synthetic Methods Utilized for the Preparation of Cyclic Compounds.

Recent work by Clark and Miller[32] has illustrated that cyclization products could be obtained from a base-catalyzed self-condensation of β-diketones. Clark and Miller have studied the reactions of 2,4-pentanedione and 1-phenyl-2,4-pentanedione with potassium fluoride in refluxing dimethylformamide. Clark and Miller[32] initially reported that 3-hydroxytropone derivatives (49) were formed from these reactions.



(a) R = H

(b) R = Ph

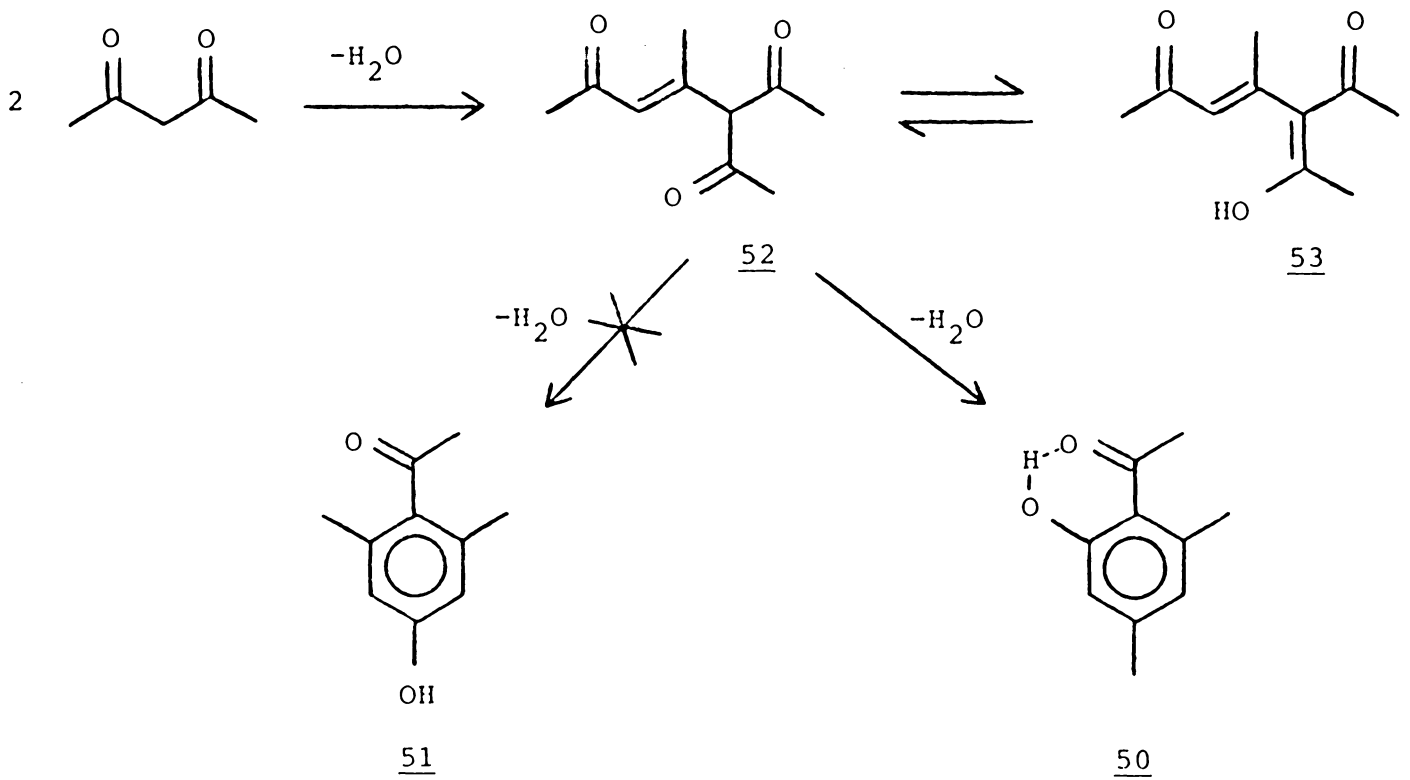
49

Shortly afterward, several workers[33-37] including Clark and Miller[33] reported that the above reaction products were incorrectly assigned and that acetophenone derivatives were actually obtained.

In a revised paper, Clark and Miller[33] reported quantitative cyclization of 2,4-pentanedione to 2-hydroxy-4,6-dimethylacetophenone (50) (Scheme 1.7). Clark and Miller gave three explanations why acetophenone 50 would be favored over 4-hydroxy-2,6-dimethyl acetophenone (51), the symmetric isomer of 50. First, intermediate 52 has three different types of acidic hydrogens, two of which can be abstracted during cyclization to afford acetophenone 50. Second, compound 53 (the enol tautomer of intermediate 52) should stabilize the developing anion since the negative charge can be delocalized on two different carbonyl oxygens. Finally, Clark and Miller have proposed that acetophenone 50 is thermodynamically more stable than its symmetric isomer. Therefore, the reaction yields the more thermodynamically favored product. This additional stabilization is due to hydrogen-bonding between the hydroxyl group and the carbonyl

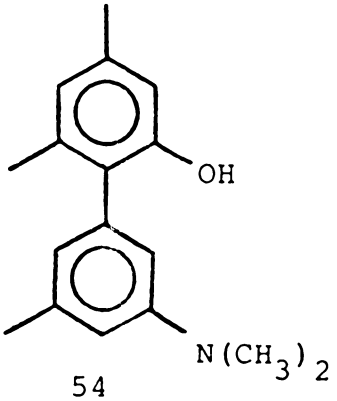
Scheme 1.7[33]

The Condensation Reaction of 2,4-Pentanedione in Potassium Fluoride



group in acetophenone 50.

Utilizing similar conditions, Hase[34] obtained acetophenone 50 (no yield reported) and three additional products (54-56). Compounds 54-56 were isolated in yields of 5.2, 3.2, and 4.6%, respectively.



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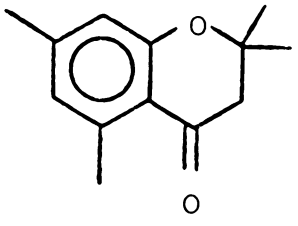

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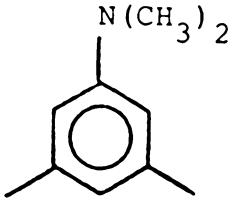


56

Hase determined that treating acetophenone 50 with acetone or 2,4-pentanedione utilizing the same reaction conditions did not yield compound 55.

Mingin and Huisgen[35] have also investigated the above reaction and have obtained a 64% yield of acetophenone 50. These authors reject Clark and Miller's explanation that cyclization was observed under the above conditions due to the considerable solubility of KF in THF. Clark and Miller[33] have proposed that cyclization does not occur under other reaction conditions due to the poor solubility of inorganic bases in organic solvents. Mingin and Huisgen have also rejected that a hydrogen bonded species from the fluoride anion and the enol is the reaction intermediate. Instead,

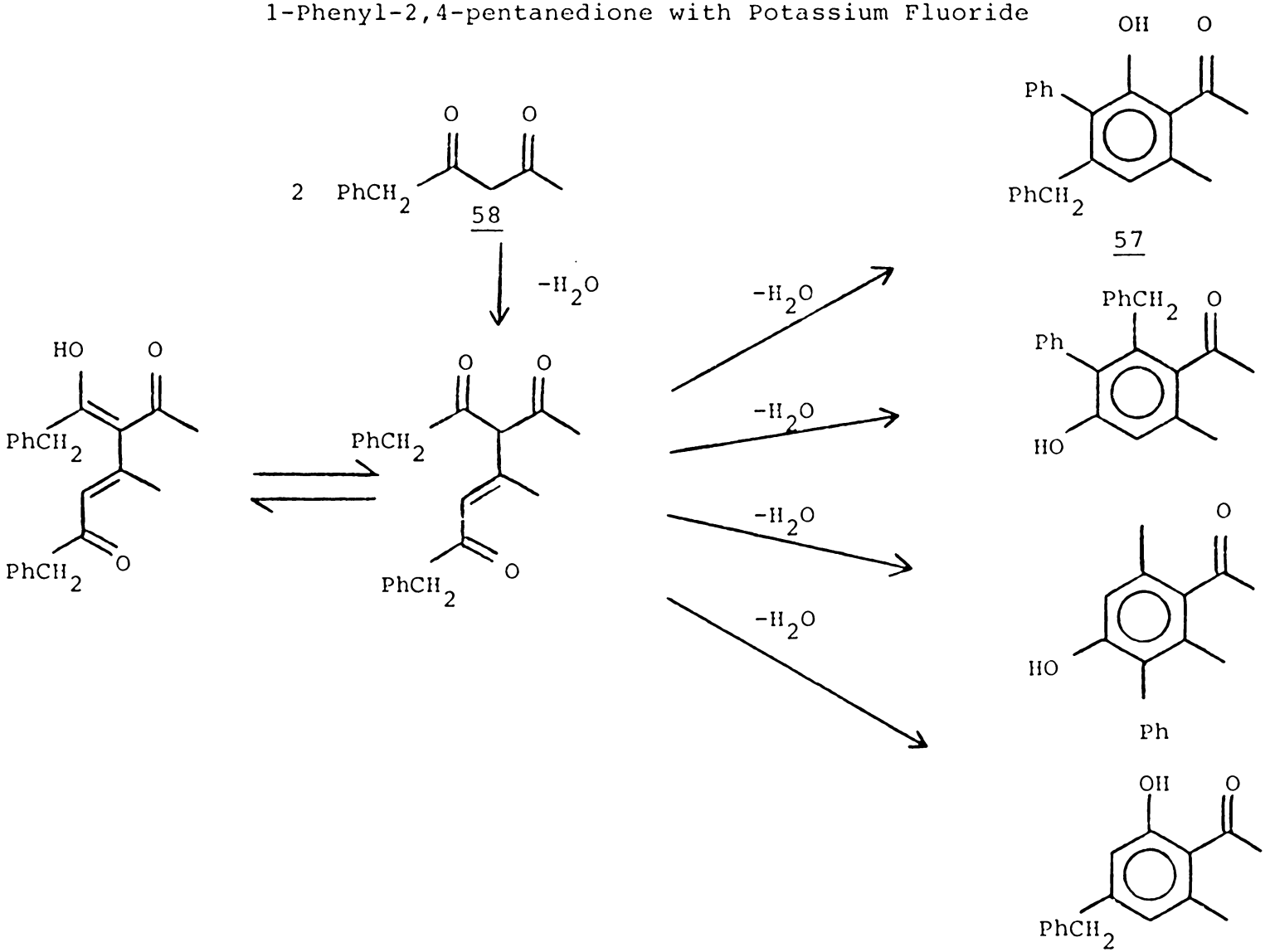
Mingin and Huisgen have proposed potassium acetylacetonate as a reaction intermediate since refluxing 2,4-pentanedione and its potassium acetylacetonate salt in DMF afforded a 51% yield of acetophenone 50.

Clark and Miller[33] have also reported a 52% yield of 4-benzyl-2-hydroxy-6-methyl-3-phenylacetophenone (57) from 1-phenyl-2,4-pentanedione (58). Using the same reaction conditions, Hase[34] has reported that acetophenone 57 was formed in 48% yield. In addition, Hase has also isolated two other products (compounds 59 and 60) in yields of 9.3 and 4.1%, respectively. Scheme 1.8 also illustrates other potential products that could be formed from the self-condensation reaction of 1-phenyl-2,4-pentanedione. By arguments similar to those proposed for the formation of acetophenone 50, Clark and Miller had predicted that cyclization should yield acetophenones 57 and 59. (Note that acetophenone 59 was only experimentally observed by Hase).

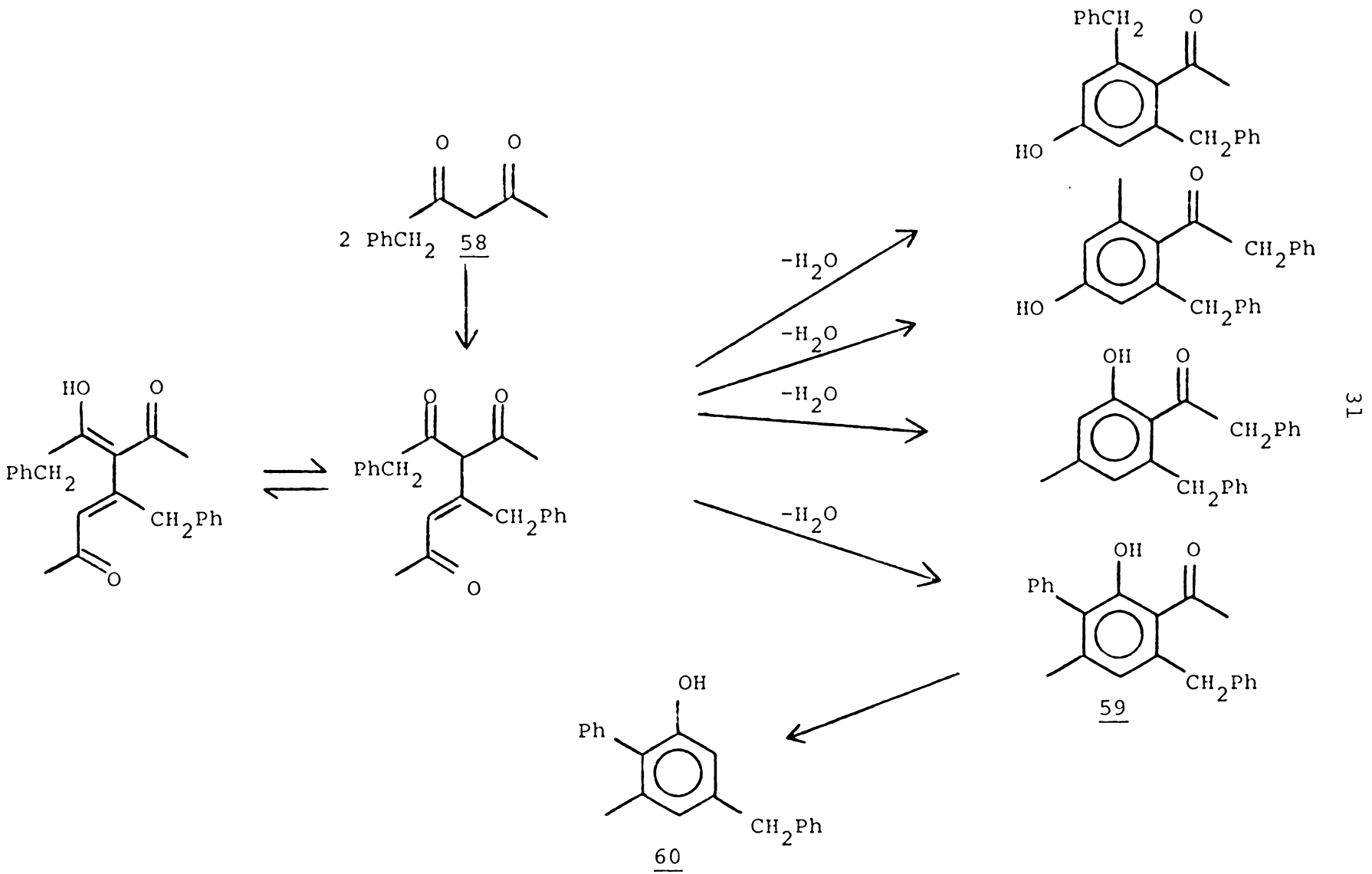
Other dicarbonyl compounds examined by Clark and Miller[33] include 2,3-butanedione and 1,3-cyclohexanedione. These compounds afforded 2,5-dimethyl-1,4-benzoquinone (61) (eq 20) and polycyclic trione isomers (e.g., compound 62) (eq 21), respectively.

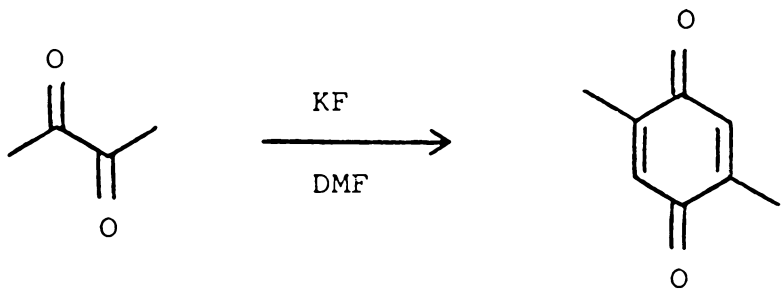
Scheme 1.8[33]

Potential Products for the Reaction of
1-Phenyl-2,4-pentanedione with Potassium Fluoride



Scheme 1.8 (cont.)





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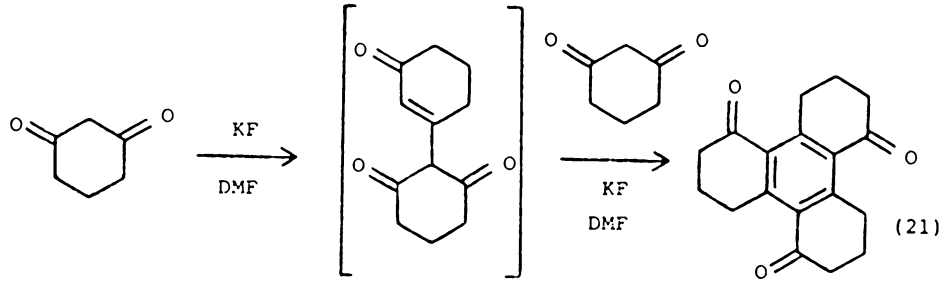

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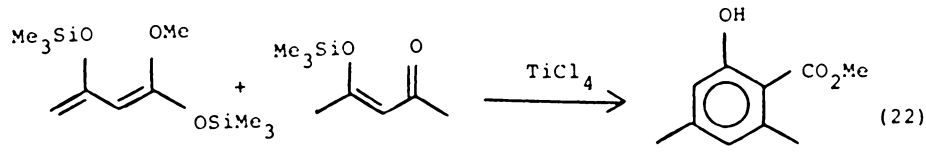
63 62

The formation of 63 is easily understood since an intermediate analogous to those described for 2,4-pentanedione and 1-phenyl-2,4-pentanedione would be obtained. However, this intermediate (63) cannot undergo a intramolecular condensation since the two cyclohexane rings of the reaction intermediate are rigidly locked to prevent formation of a tricyclic compound. Thus an intermolecular condensation between intermediate 63 and 1,3-cyclohexanedione would be favored to yield polycyclic trione 62.

Aromatic compounds can also be prepared from acid-catalyzed condensations of β-dicarbonyl equivalents. Chan and Brownbridge[38] have utilized 1,3-bis(trimethylsiloxy)-1-methoxybuta-1,3-diene (64) as an equivalent for the methyl acetoacetate dianion. This compound when treated with 4-

trimethylsiloxy-3-penten-2-one (65) in the presence of titanium tetrachloride at -78°C yields methyl 4,6-dimethylsalicylate (66).



(22)

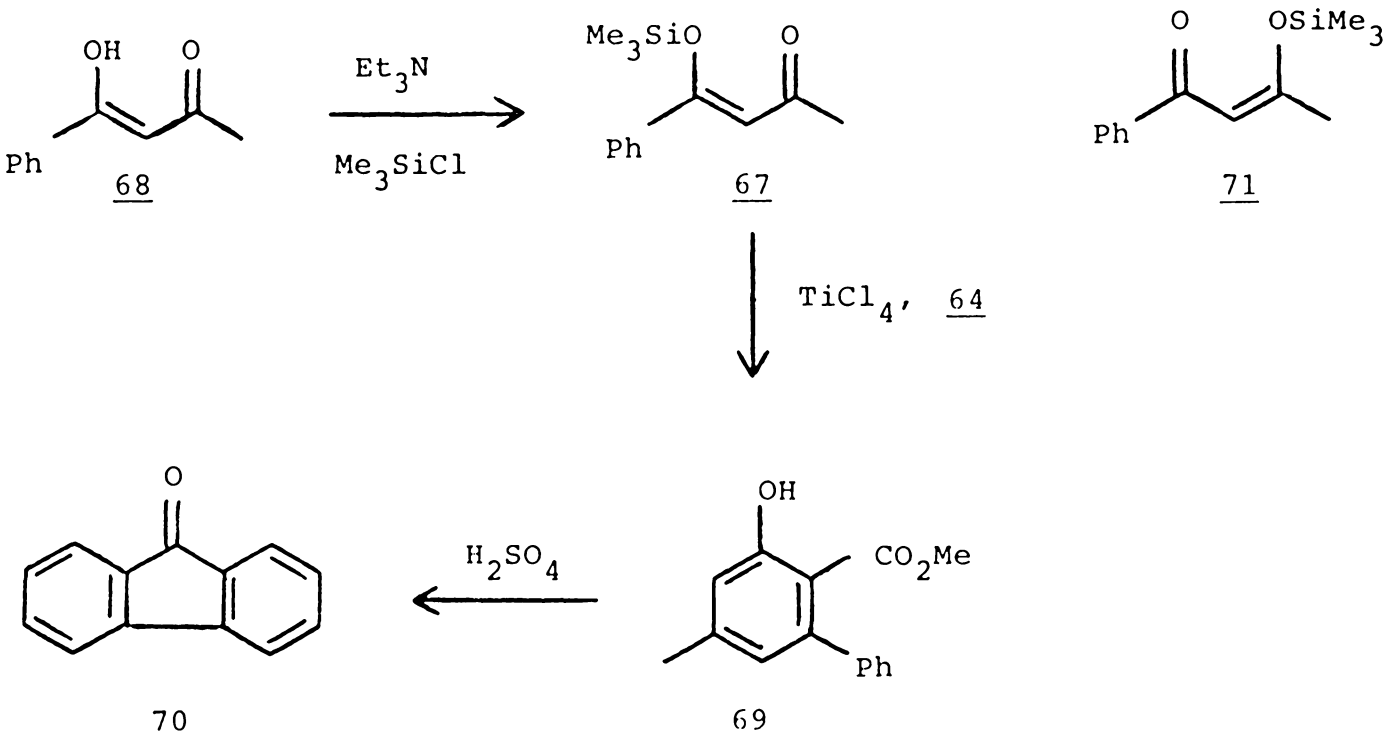
64 65 66

For another reaction in this series, Chan and Brownbridge prepared the β-siloxy enone 67 from the enol form of 1-phenyl-1,3-butanedione (68) (Scheme 1.9). This preparation gave a mixture of geometric isomers but only a single regioisomer. Condensation of 64 and 67 afforded a single aromatic compound (69) which was further converted to fluorenone 70. The conversion to 70 helped establish the structure of compound 69. Chan and Brownbridge postulated that in the above reaction enone 67 undergoes isomerization to 71 because C-4 is more reactive than C-2 in diene 64. It is also believed the initial attack of 64 occurs at the β-carbon of the enone system, consistent with the above results.

Chan and Brownbridge[38] have also studied the reaction of diene 64 with 4-methoxybut-3-en-2-one (72) and 4-methoxy-4-phenylthiobutan-2-one (73) (Scheme 1.10). Two different regioisomers (74 and 75) were obtained from the above reaction. However, problems were experienced when the hemi-

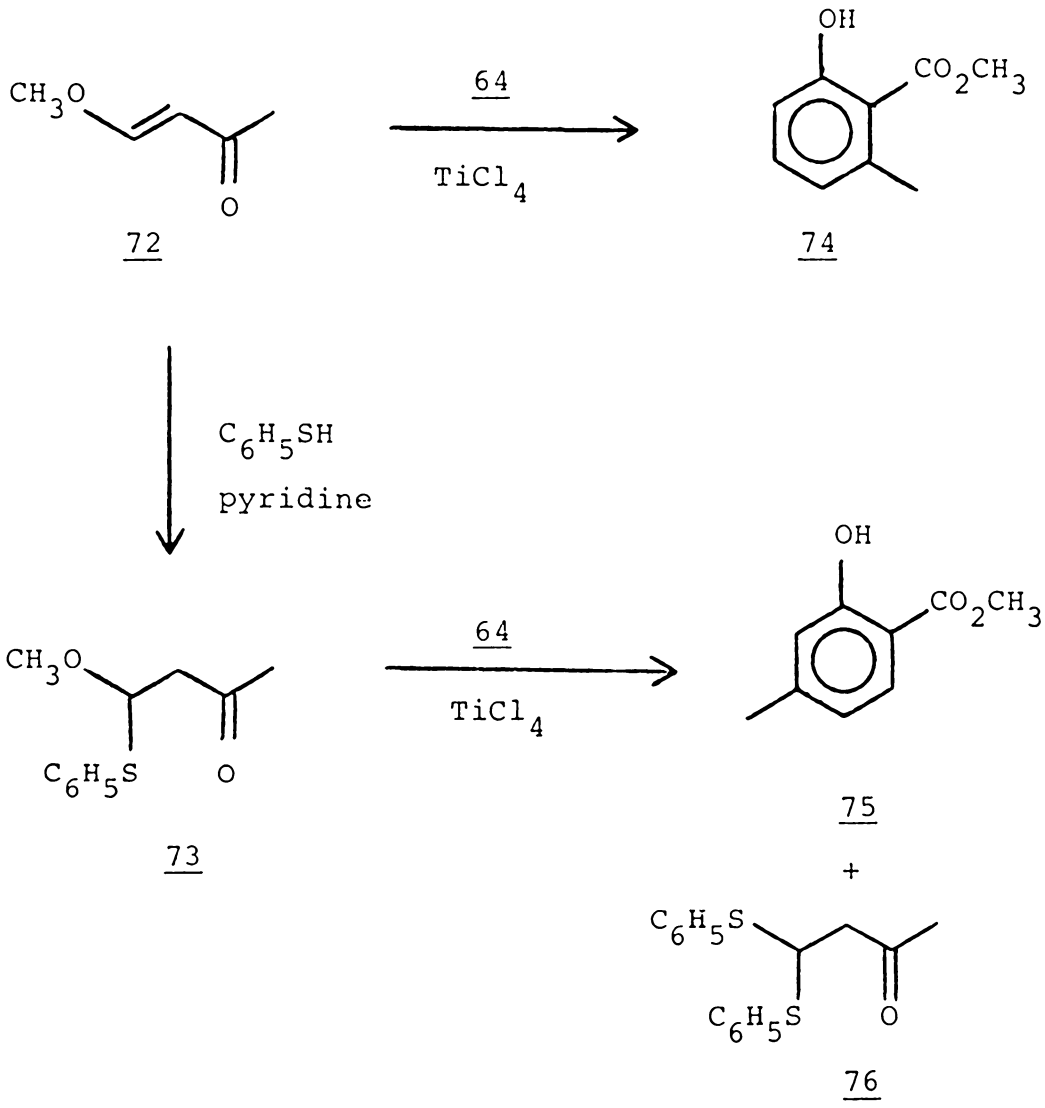
Scheme 1.9[38]

The Preparation of Aromatic Compounds from 1-Phenyl-1,3-butanedione



Scheme 1.10[38]

The Preparation of Different Regioisomers from Electrophiles with Different Reactivities



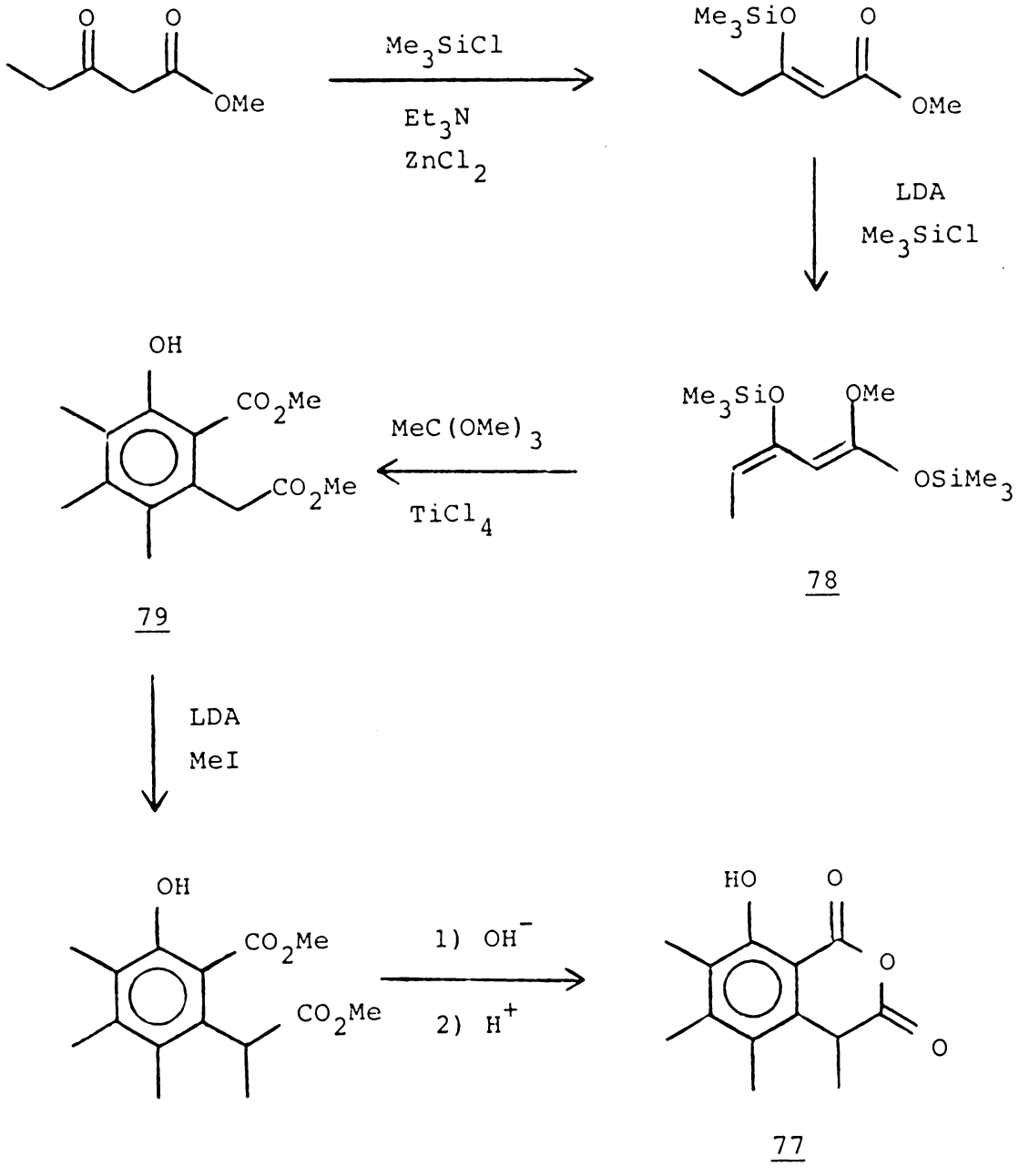
thioacetal 73 was utilized as a carbonyl equivalent. Namely, the benzenethiol generated under the above reaction conditions further attacked unreacted hemithioacetal 73 to yield dithioacetal 76. This problem was avoided when β-ketoacetals were utilized. Yields of 50 and 57% were obtained for compounds 74 and 75, respectively.

The preparation of several other aromatic compounds have also been described by Chan and Brownbridge.[38] From the above studies the authors have established the order of reactivity of the different electrophilic sites. Chan and Brownbridge found that the reactivity of the β-carbon of the enone > ketone > monothioacetal, acetal in the cyclization process (i.e., β-carbon of the enone is more reactive toward nucleophilic attack than the carbonyl carbon of a ketone, etc.)

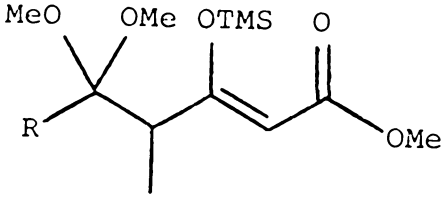
Chan and Brownbridge[39] have prepared an aromatic precursor, which was later converted to sclerin (77), by utilizing a β-carbonyl equivalent analogous to diene 65 (Scheme 1.11). Sclerin, a metabolite isolated from Sclerotina fungi, functions as a plant growth hormone and is believed to originate from the condensation of a naturally occurring penta-β-carbonyl precursor.[40] Chan and Brownbridge have approached the synthesis of this precursor through the condensation of a dicarbonyl equivalent with a tricarbonyl synthon. The key step in this preparation was the treatment of 1,3-bis(trimethylsiloxy)-1-methoxypenta-1,3-diene (78) with methyl orthoacetate and titanium tetrachloride (2:1:2 mole equiv.,

Scheme 1.11[39]

The Preparation of Sclerin (77)
Utilizing a 1,3-Dicarbonyl Equivalent



respectively) which afforded aromatic compound 79 in 53% yield. Compound 79 was further converted to sclerin in two additional steps. In additional examples, yields of 65-68% have been obtained in the preparation of other 3-hydroxyhomophthalates. These 3-hydroxyhomophthalates appear to be formed via the intermediate illustrated below.

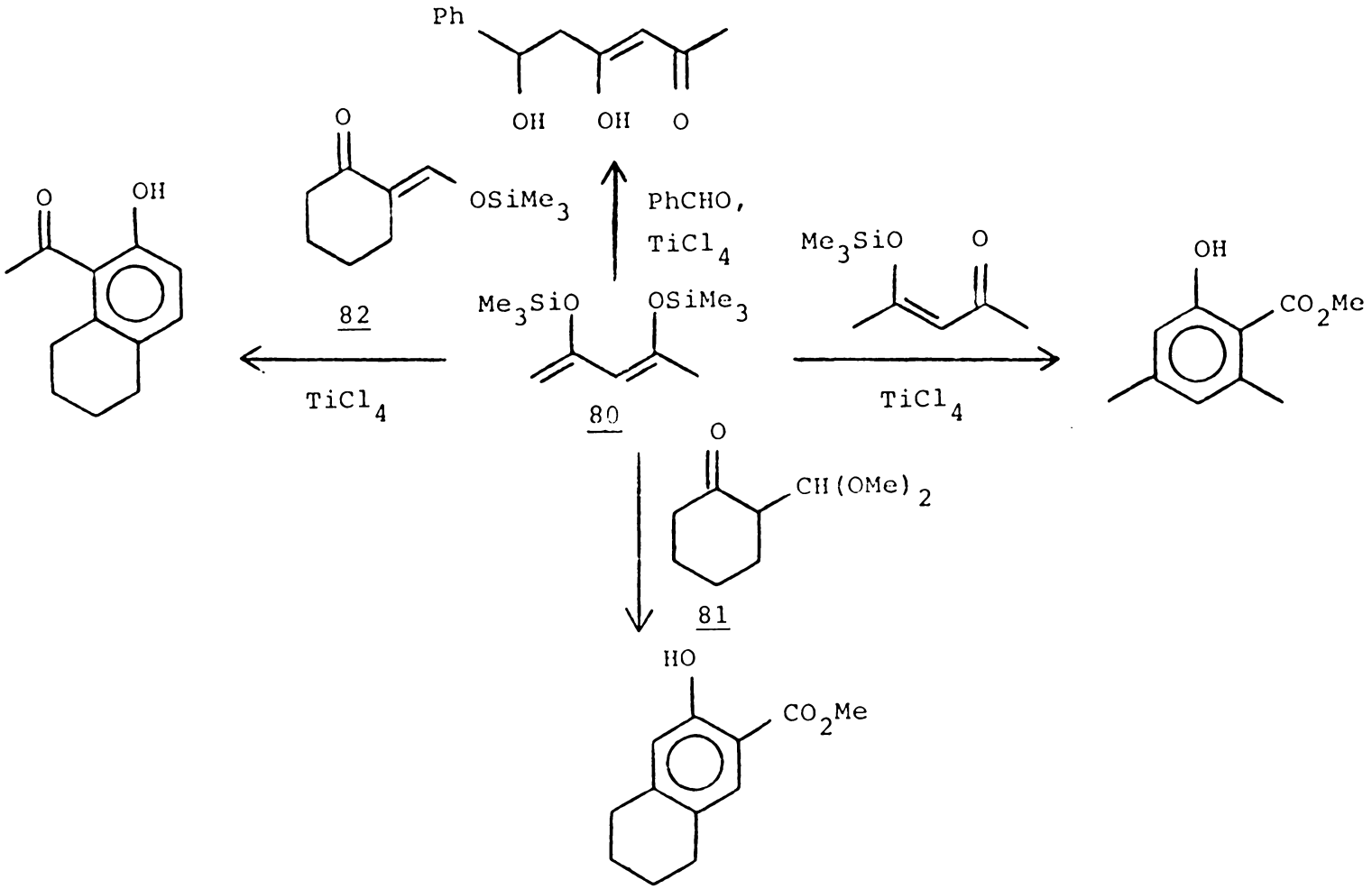


In a third paper, Chan and Brownbridge[41] have illustrated that various substituted phenols can be prepared utilizing similar methology. o-Acetylphenols have been prepared from 2,4-bis(trimethylsiloxy)penta-1,3-diene (80) using several different pathways (Scheme 1.12). Yields of 40-68% were obtained for the various o-acetylphenol products. The authors were even able to prepare o,o'-disubstituted phenols from pentadiene 83 (Scheme 1.13). The condensation reaction of diene 83 with compounds 81 and 82 provided compounds 84 and 85, respectively, with each product being obtained in 40% yield.

The cyclization reactions that have been presented to this point have involved condensation of two three-carbon

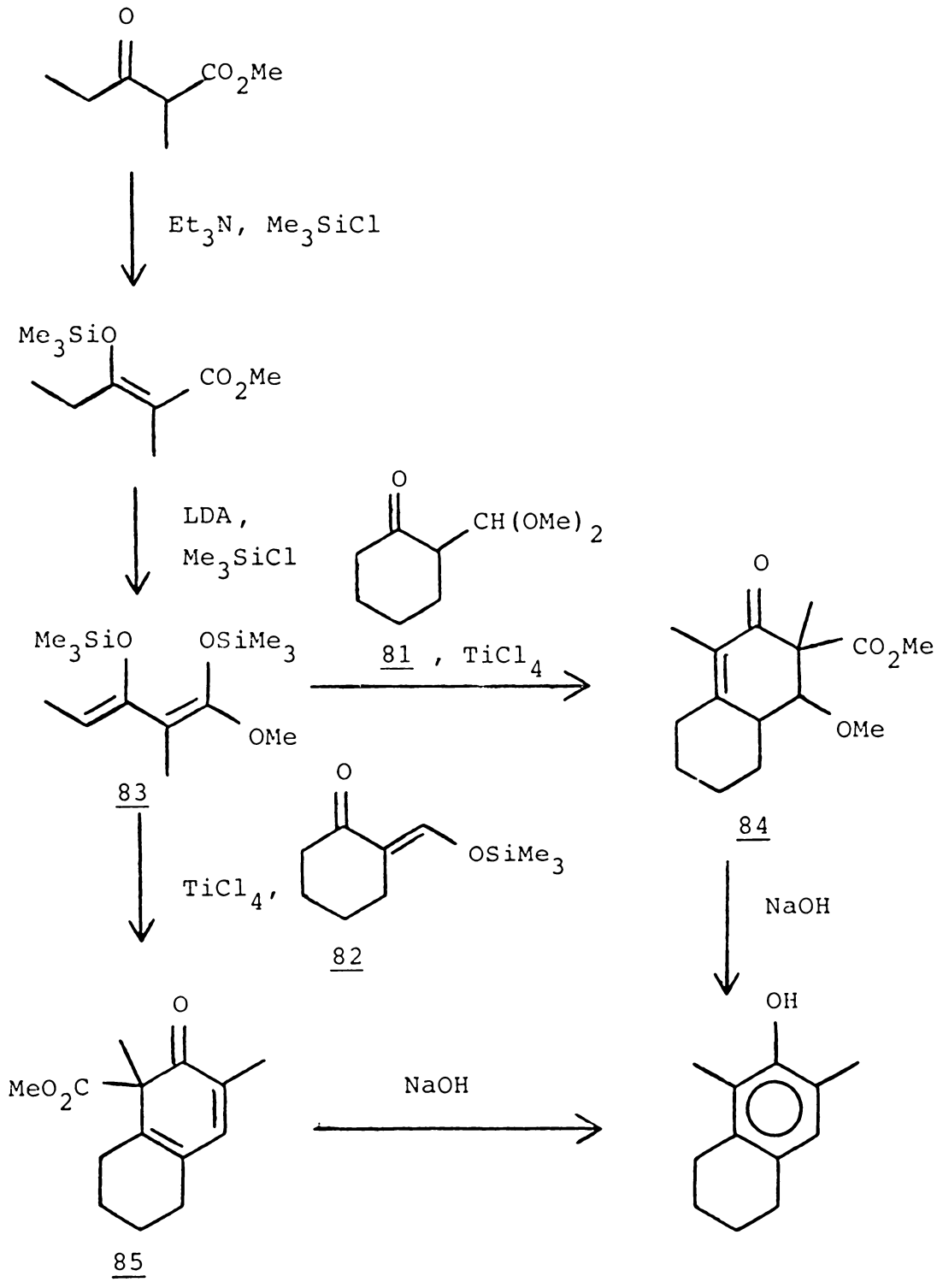
Scheme 1.12[41]

New Methodology for the Preparation of o-Acetylphenols

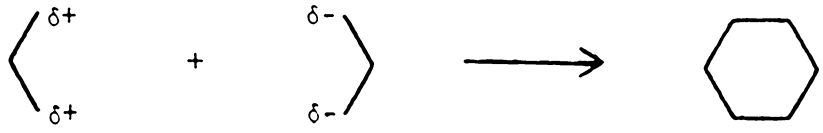


Scheme 1.13[41]

New Methodology for the Preparation of o,o'-Disubstituted Phenols

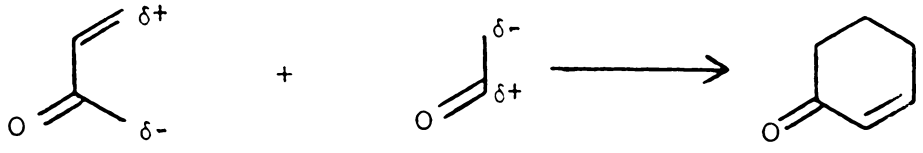


units. One of these units contains only electrophilic sites and the other unit contains two nucleophilic sites (eq 23).



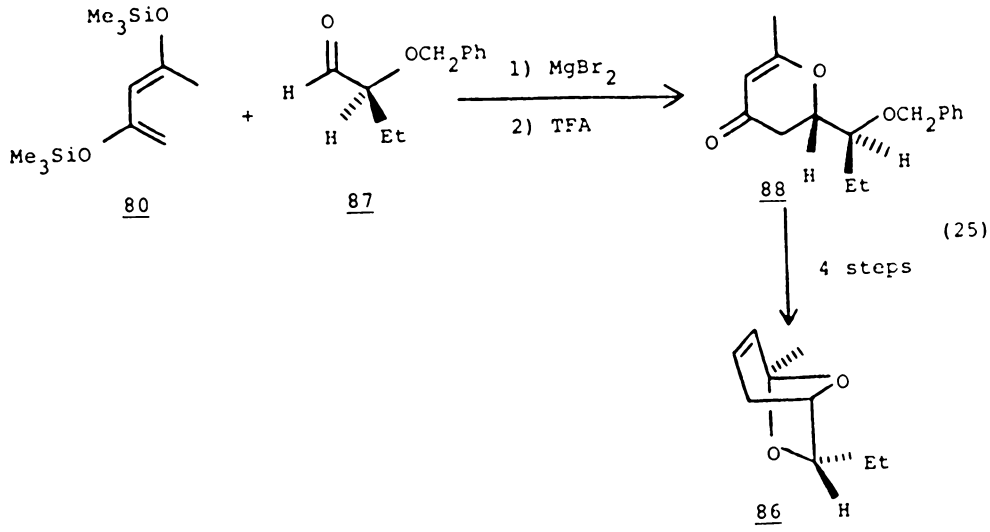
(23)

These reactions are in contrast to the results obtained from Diels-Alder reactions and Robinson annelations which involve cyclizations of a two-carbon fragment with a four-carbon fragment (eq 24).



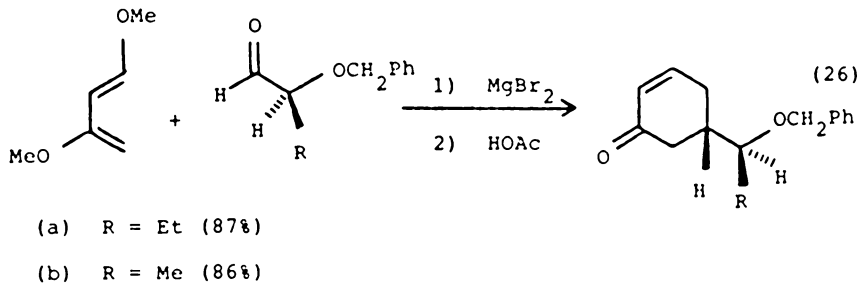
(24)

Danishefsky et al.[42] have reported condensation reactions of diene 80, which was previously described in this chapter, with several different aldehydes in the presence of magnesium bromide. This condensation reaction resembles a Diels-Alder reaction since a four-carbon unit was combined with the carbon and oxygen atoms of the aldehyde. This cyclization was extremely valuable in the preparation of Mus musculus pheromone 86, which helps control the biological instincts of the common house mouse (eq 25).



(25)

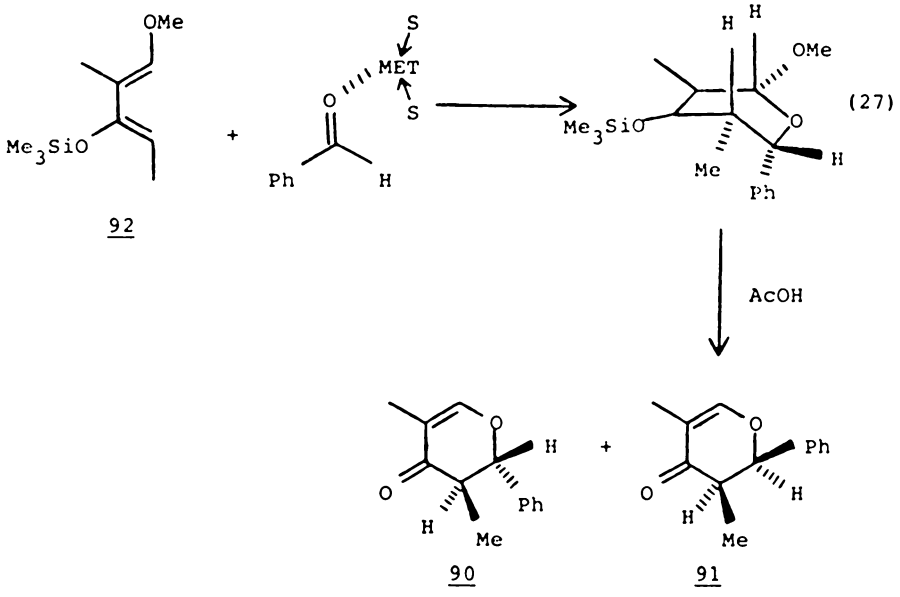
Cyclization of diene 80 with aldehyde 87 followed by treatment with trifluoroacetic acid afforded pheromone precursor 88 in 80% yield. Danishefsky found that magnesium bromide was a very selective catalyst for promoting diastereofacial control in the cyclization reaction of α-oxygenated aldehydes with activated dienes. Other catalysts [e.g., ($BF_3 \cdot OEt_2$, $ZnCl_2$, and $Yb(fod)_3$] were found to yield mixtures of facial isomers and were found to be less effective than $MgBr_2$. This diastereofacial control was also observed for several additional examples as illustrated in eq 26.



(a) R = Et (87%)

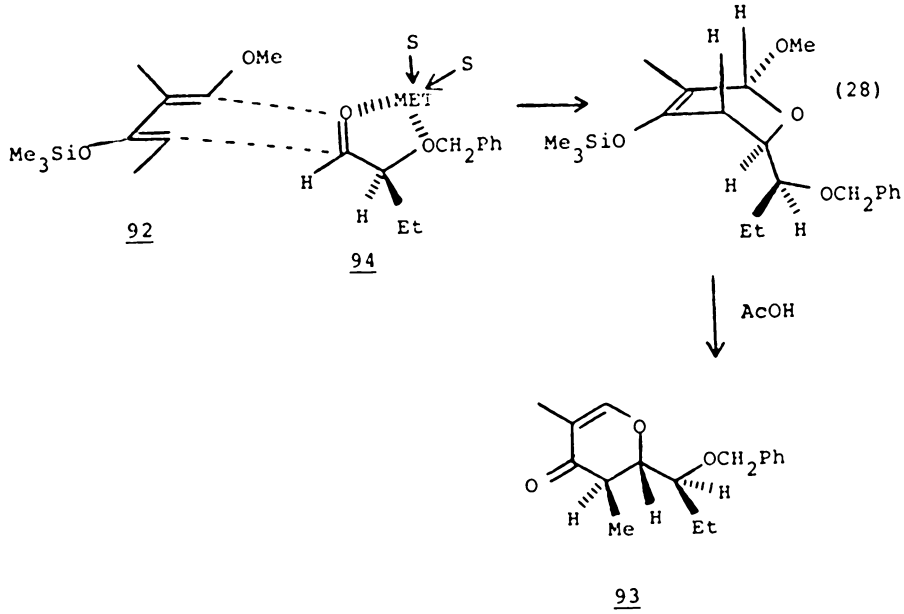
(b) R = Me (86%)

Danishefsky et al.[43] have devoted a second paper to topological and diastereofacial control of condensation reactions involving aldehydes with activated dienes in the presence of Lewis acids. This study suggested that aldehydes such as benzaldehyde could bind with the acid catalyst ($MgBr_2$) resulting in an anti relationship between the phenyl group and the metal of the catalyst (eq 27).



This reaction afforded a 50% overall yield of 90 and 91 in a 38:1 ratio. Therefore, the exo directivity of the catalyst-solvent ensemble appears to be responsible for the endo topology of the above condensation reaction.

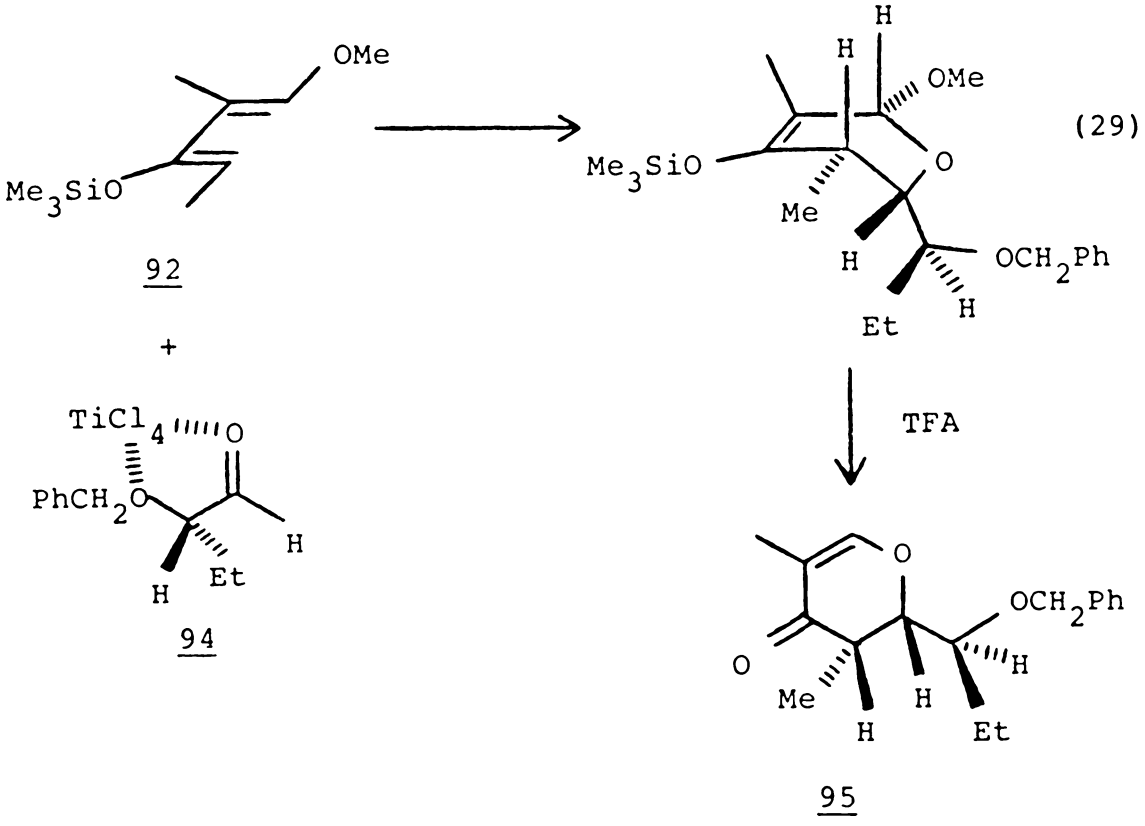
Danishefsky et al.[43] have observed the exo topology in the condensation reactions of diene 92 with α- and β-alkoxy-aldehydes. These aldehydes are believed to undergo chelation with the acid catalyst ($MgBr_2$) which results in a syn relationship between the R group and metal of the acid catalyst (eq 28).



In this reaction both the R group of the aldehyde and the met-

al are oriented exo to the diene. This relationship governs the pathway leading to the exo topology of product 93 which was obtained in 68% overall yield.

Danishefsky et al.[43] have also examined titanium tetrachloride as a reaction catalyst since this compound was reported to provide chelation control in the aldol condensation of β-alkoxyaldehydes with simple silyl enol ethers.[44] In contrast to the reactions which were catalyzed by $MgBr_2$, the $TiCl_4$ promoted cyclization of diene 92 and β-alkoxyaldehyde 94 to afford endo product 95.



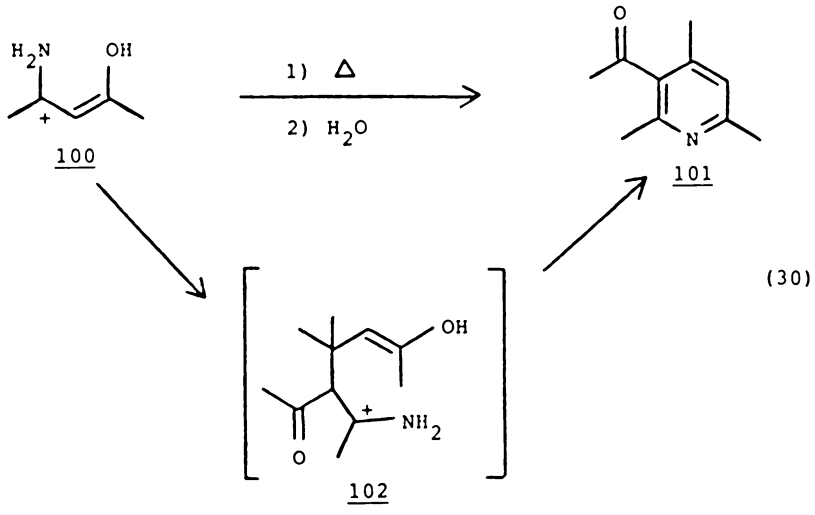
(29)

The nonchelatable benzaldehyde was also examined under these

conditions and was found to yield trans- and cis-pyrones (91 and 90, respectively) in an 8:1 ratio (88% overall yield). As expected, topology favored the exo pericyclic mode in this latter example.

Another example of a hetero Diels-Alder reaction in the presence of a Lewis acid was reported by Danishefsky in the total synthesis of vineomycin B aglycon (96)[45] (Scheme 1.14). Reaction of diene 97 and aldehyde 98 afforded a 92% yield of endo addition product 99. Two additional Diels-Alder reactions of siloxy dienes containing a methoxy group were also reported by Danishefsky and co-workers in preparation of aldehyde 98.

Several related studies have demonstrated cyclizations affording six-membered rings containing hetero atoms. Auricchio et al.[46] have found that heating chlorohydrate 100 followed by treatment with water affords 2,4,6-trimethyl-3-acetylpyridine 101 in 90% yield (eq 30).



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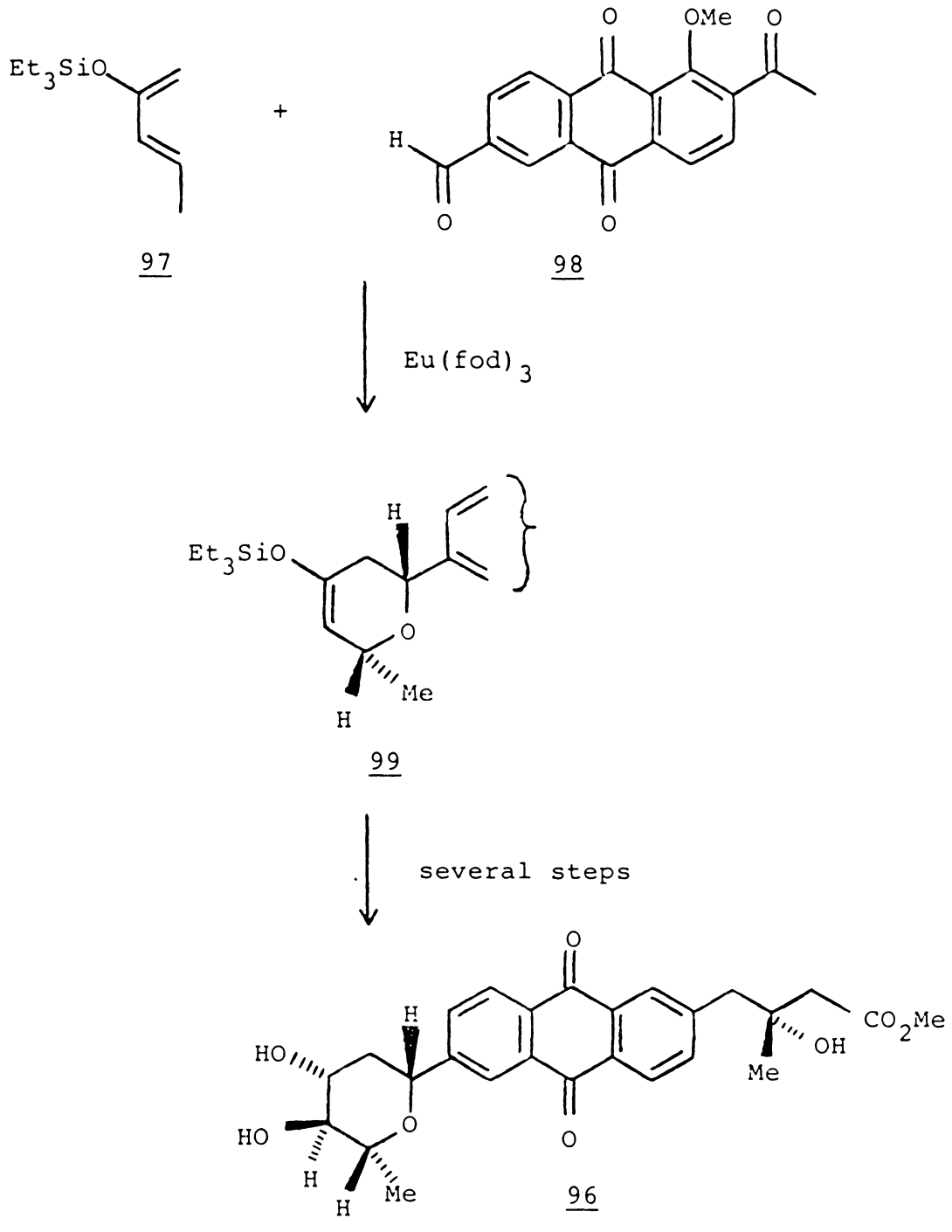
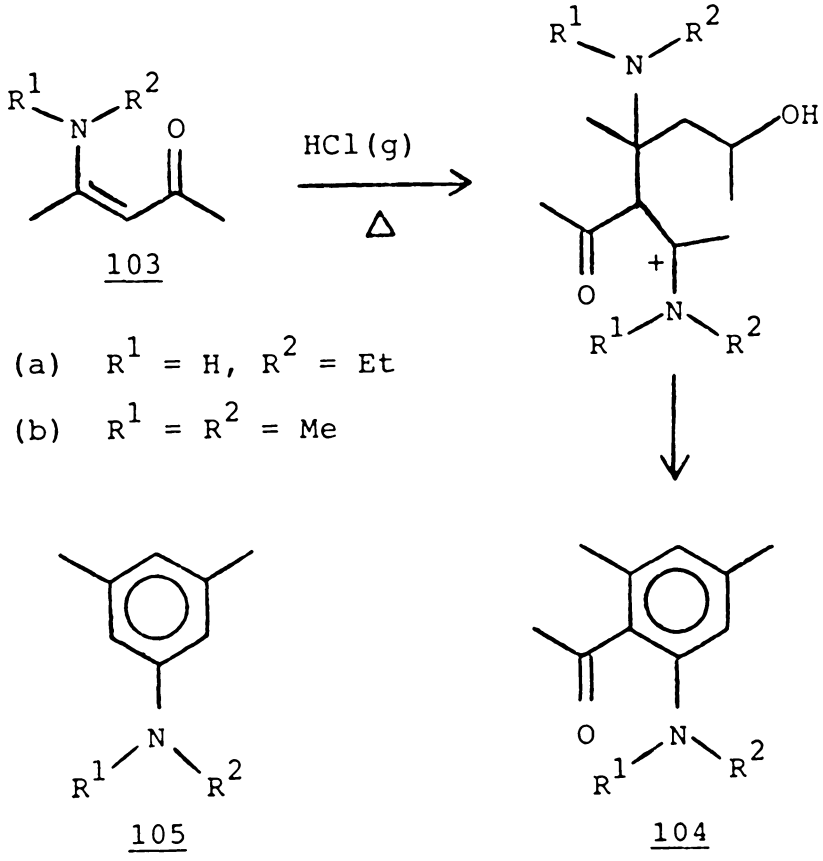
Scheme 1.14[45]

Preparation of Vineomycin B Aglycon (96)
Utilizing a Hetero Diels-Alder Reaction



The authors have suggested that the reaction occurs through intermediate 102. In replacing the hydrogens on the enamine nitrogen with alkyl substituents, a different cyclization pathway was observed (eq 31).



103

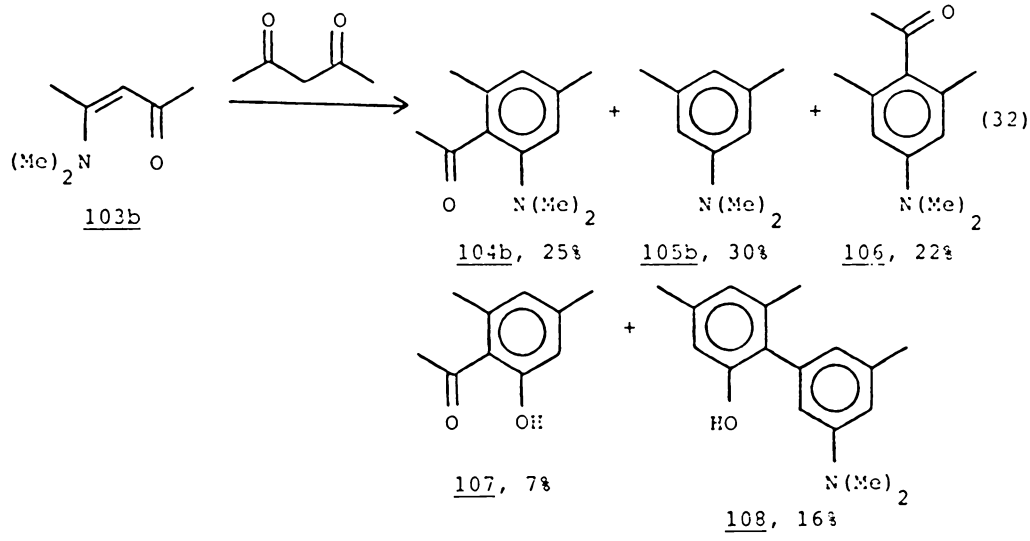
(a) R^1 = H, R^2 = Et

(b) R^1 = R^2 = Me

(31)

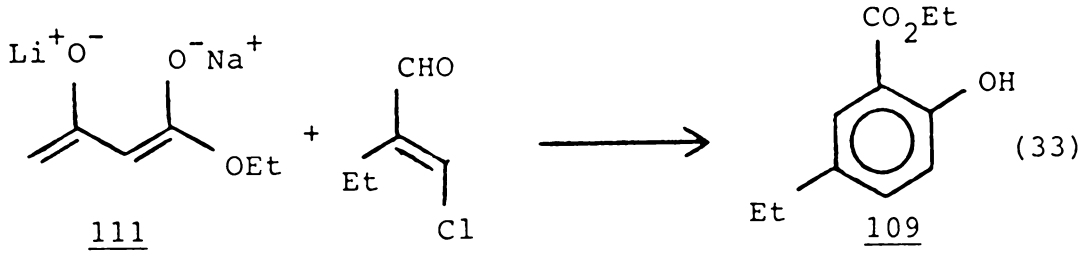
105 104

In these reactions enamino derivatives 103a and 103b afforded the substituted anilines 104a and 104b, respectively. Deacetylated compound 105b accompanied the substituted aniline 104b in the latter example. A final use of this cyclization technique is illustrated in eq 32 where the enamino ketone 103b was treated with 2,4-pentanedione to afford a mixture of products in 60% yield.



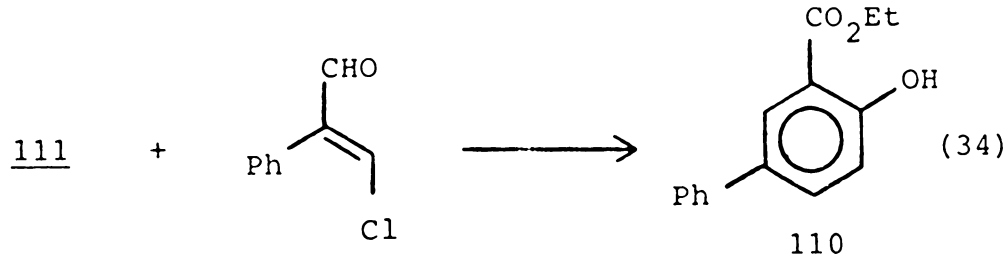
This result also suggests that biphenyl 108 must originate from acetophenone 107 and a molecule of enamino ketone 103b.

Barton et al.[47] have found that enamino aldehydes will undergo condensation reactions with the dianions of β-ketoesters affording 5-substituted 2-hydroxybenzoates. This condensation reaction affords ethyl 5-ethyl-2-hydroxybenzoate (109) and ethyl 5-phenyl-2-hydroxybenzoate (110) in 37 and 64-77% yields, respectively (eq 33 and 34).



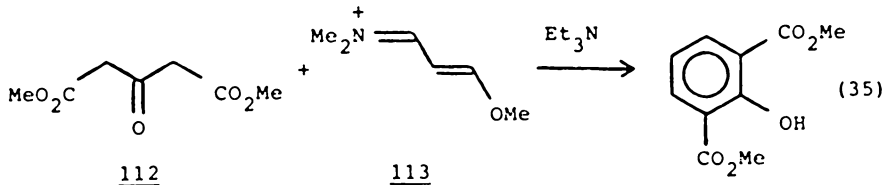
111

109



110

Dimethyl 3-oxopentanedioate 112 (used as an alternative to dianion 111) underwent condensation with compound 113 in the presence of triethylamine to afford dimethyl 2-hydroxybenzene-1,3-dicarboxylate 114 in 14% yield (eq 35).

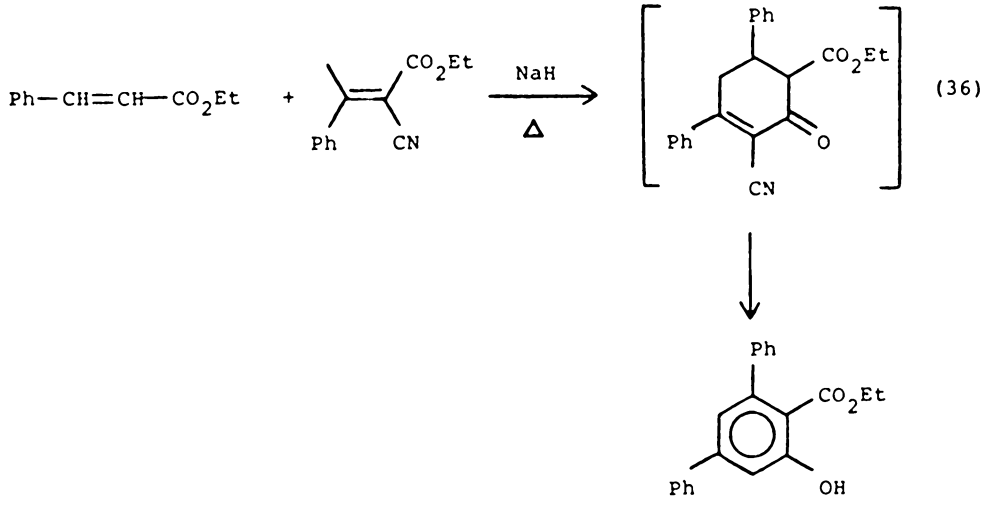


112

113

114

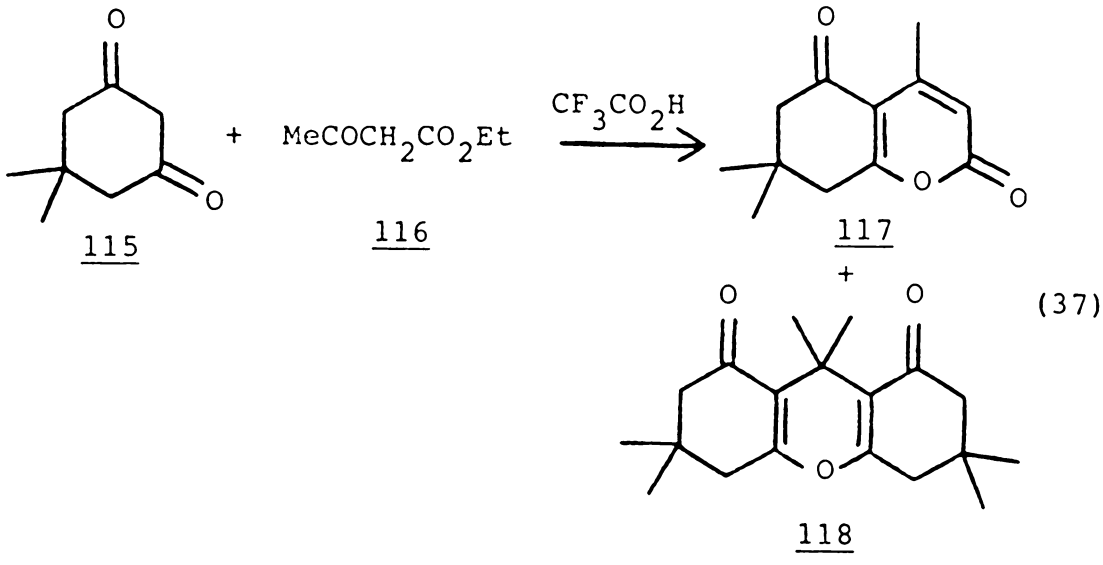
Ivanov and Tcholakova[48] have also prepared a series of ethyl 3-cyano-4,6-diaryl-2-hydroxybenzoates through the base-catalyzed condensation of unsaturated esters. The general procedure is illustrated in eq 36.



(36)

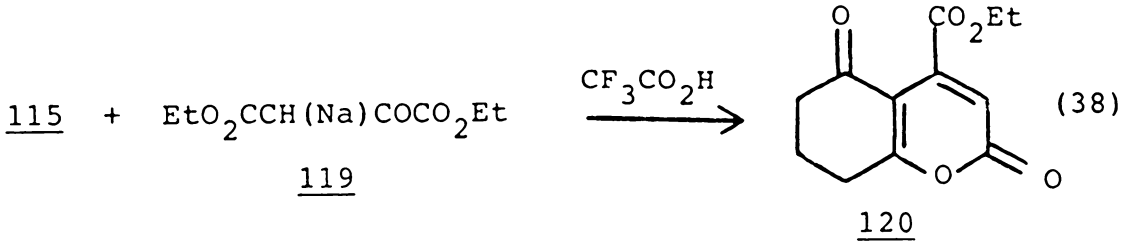
Yields of 33-52% were obtained from the series of unsaturated esters that were used in this study.

In a correction to the literature, Sellstedt[49] has reported that 5,5-dimethyl-1,3-cyclohexanedione (115) undergoes a condensation with ethyl acetoacetate (116) to yield 2-pyrone 117 and xanthene-1,8-dione 118 (eq 37).



115 116 117 118 (37)

A similar condensation of dione 115 with sodium diethyl oxalacetate (119) afforded 2-pyrone 120 in 28% (eq 38)

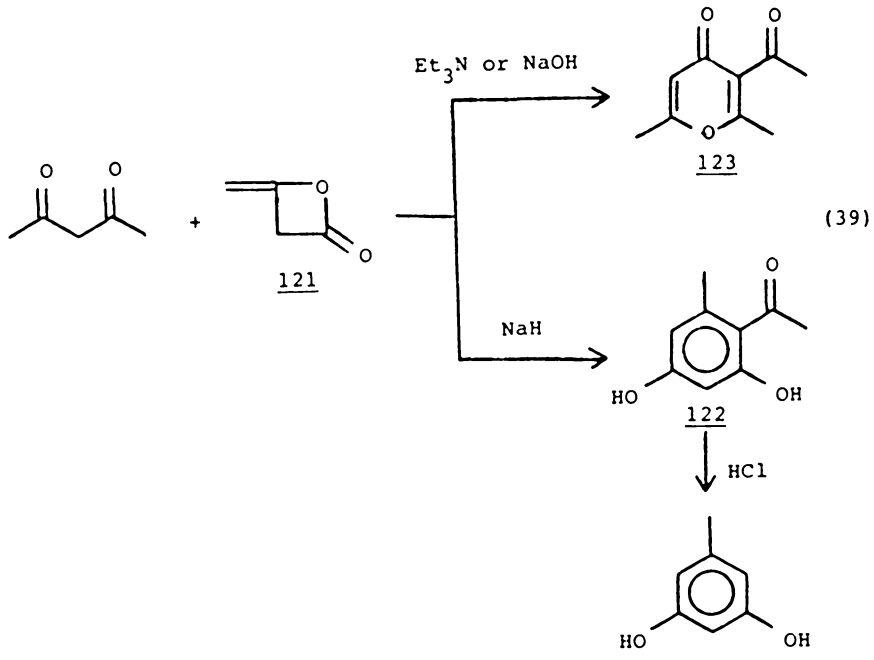


119 120

Despite low yields for these cyclization reactions, Sellstedt has illustrated that 2-pyrones can be prepared by treating 1,3-diketones and β-ketoesters with trifluoroacetic

acid.

Similarly, Kato et al.[50] have determined that diketene reacts with β-diketones to yield substituted aromatic compounds and heterocyclic compounds depending on the reaction conditions. For example, when 2,4-pentanedione was treated with diketene (121) in tetrahydrofuran in the presence of sodium hydride, acetophenone 122 was formed (eq 39).

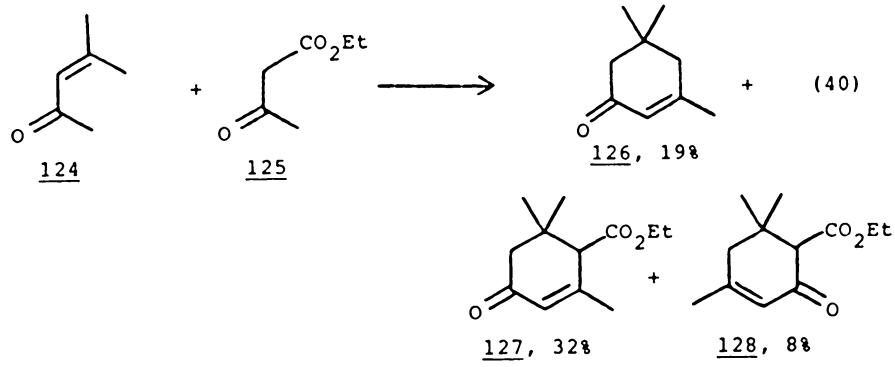


121 123 122 (39)

Acetophenone 122 could be deacetylated on treatment with hydrochloride acid. A second reaction product (4-pyrone 123) was obtained when either triethylamine or sodium

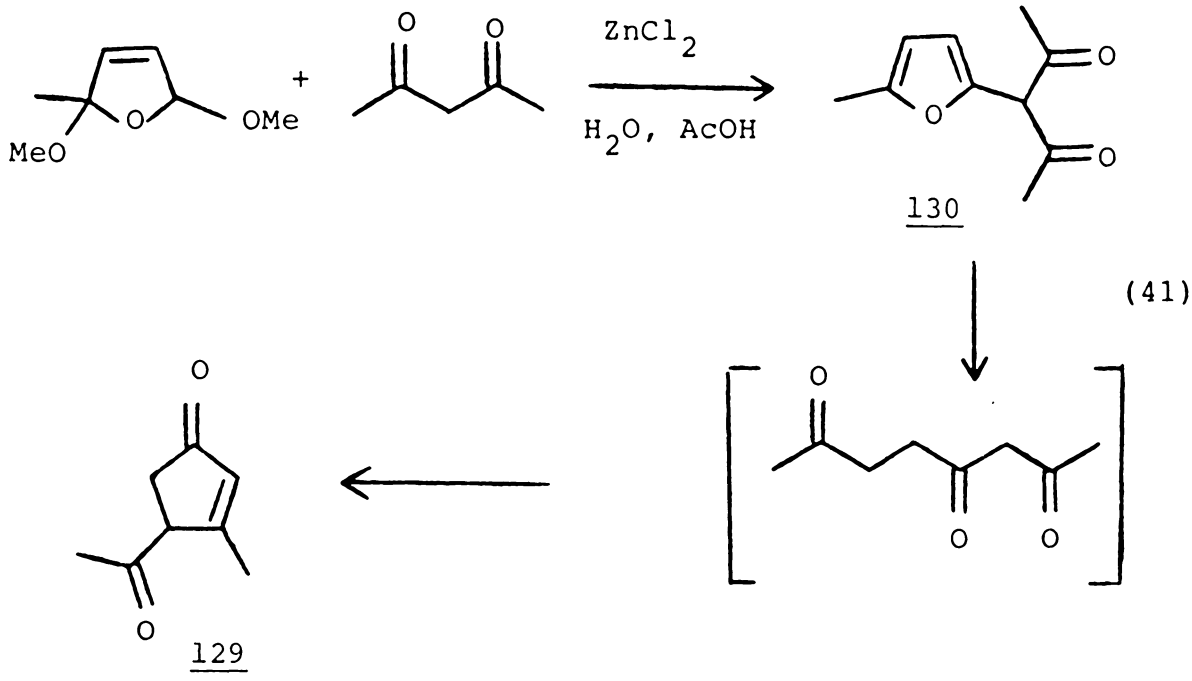
hydroxide was utilized as the reaction catalyst. Acetophenone 122 and 4-pyrone 123 were obtained in yields of 20 and 23.2%, respectively. Several other β-diketones gave similar results when investigated under the above reaction conditions.

Several examples of acid or metal catalyzed Michael reactions involving β-dicarbonyl compounds have appeared in the chemical literature. These examples suggest that a cyclization reaction of β-dicarbonyl equivalents could potentially occur through similar reaction pathways. Surmatis et al.[51] have reported the condensation reaction of mesityl oxide 124 with ethyl acetoacetate 125 in the presence of zinc chloride. A mixture of three cyclization products (126-128) were obtained from this reaction (eq 40).



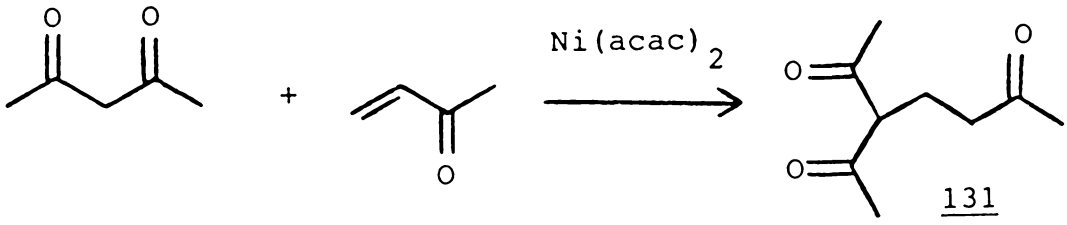
(40)

D'Ascoli et al.[52] have reported that cyclopent-2-enones can be prepared from furan derivatives in the presence of zinc chloride and sulfuric acid. This process afforded cyclopentenone 129 in 70% yield from furan 130 (eq 41).



(41)

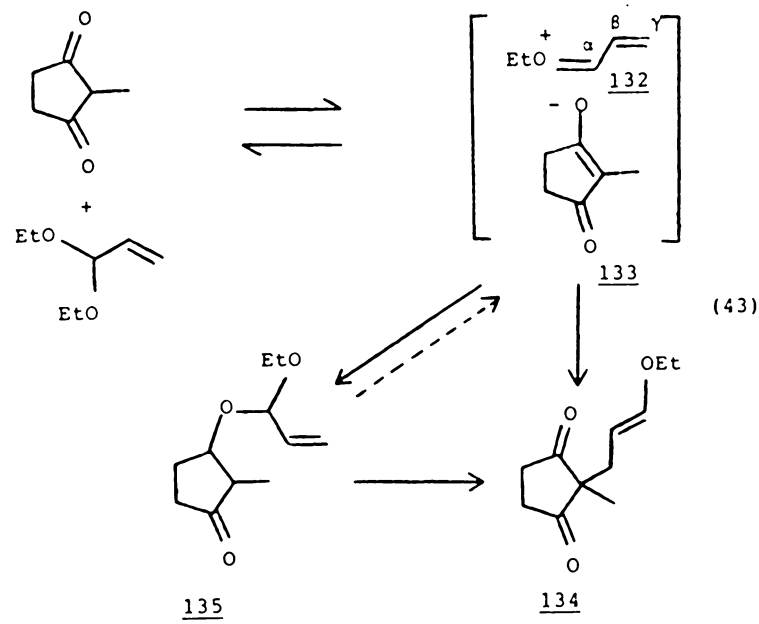
Nelson et al.[53] have reported nickel-catalyzed Michael additions of β-diketones to enone systems. One example is the addition of 2,4-pentanedione to methyl vinyl ketone as illustrated in eq 42.



(42)

A 90% yield of triketone 131 was obtained from this reaction.

Coates and Hobbs[54] have reported a novel variant of the Michael reaction. β-Diketones were found to undergo α-alkoxyalkylation upon reaction with acetals of α,β-enals (eq 43).



(43)

Two mechanisms have been proposed for this process from intermediates 132 and 133. The first occurs through O-alkylation at the α-position followed by a Claisen rearrangement to yield β-diketone 134. The second mechanism involves direct C-alkylation at the α-position to yield β-diketone 134. It has also been proposed that O-alkylation could occur first and that a reversible reaction could rapidly occur reforming intermediates 132 and 133. In this process, β-diketone 134 would ultimately be formed by C-alkylation as described above.

The several different methods which have been described in this section offer new synthetic methodology for the preparation of polyketide aromatic natural products. Further applications of the above methods as well as the discovery of new synthetic preparations will be the focus of chemists in the near future. Mechanistic studies of these new pathways will also attract considerable interest since these studies will provide a better understanding of the cyclization processes which afford the polyketide natural products.

Recent Advances in NMR Methodology for the Characterization of Organic Molecules

Recent advances in the area of NMR spectroscopy have provided new methodology for the characterization of organic molecules. These new developments have been successfully

employed in the separation and the identification of organic compounds. These new techniques include LC-^{1}H NMR, FT NMR pulse sequences, and lanthanide shift reagents.

The LC-^{1}H NMR technique[55] has been utilized for rapid analysis of organic mixtures. To date, this technique has been utilized in the analysis of fuel samples and samples of biological interest.[56] As the name implies, results are obtained by coupling an HPLC system to a ^{1}H NMR detector. This idea originated during the 1970s when a flow NMR technique was utilized in various kinetic studies.[57] In most of this early work, continuous wave NMR experiments were performed. NMR instruments began to receive greater attention as HPLC detectors when Fourier transform NMR spectrometers became available. FT NMR instruments provide rapid data collection and rapid data storage. A continuous-flow HPLC detector must satisfy these two requirements.

Both stopped-flow and continuous-flow techniques[55] have been utilized in LC-^{1}H NMR experiments. Increased S/N can be obtained using the stopped-flow method since longer acquisition times can be employed. However, the continuous-flow experiment offers an advantage over the stopped-flow technique since a more rapid analysis can be obtained.

The main advantage of the on-line ^{1}H NMR detector is that structural information can be obtained during the chromatographic separation. The ^{1}H NMR detector is similar to the mass spectrometry detector since both analytical techniques

offer a large amount of information about the compounds which are separated by HPLC. For example, a wealth of information can be obtained from the chemical shifts, the coupling constants, and the integrations that are observed in the ^{1}H NMR region. In comparison, very little structural information is provided by a refractive index detector.

Another advantage of the LC-^{1}H NMR technique is the nondestructive nature of the ^{1}H NMR detector. For example, samples can be further analyzed after LC-^{1}H NMR separations by coupling the NMR system to a second detector or by collecting the eluting fractions for independent analysis. However, LC-^{1}H NMR is currently limited by its detection limits. Table 1.1[55] illustrates this problem by comparing the detection limits of several other HPLC detectors with those of the ^{1}H NMR apparatus. Improvements in the sensitivity of the ^{1}H NMR detector are currently under investigation and should make the LC-^{1}H NMR apparatus even more attractive for the analysis of organic reaction products.

NMR Pulse Sequences

Several NMR pulse sequences have been utilized for structural assignments. A modification of the INEPT pulse sequence has been routinely utilized to aid in structural assignments of ^{13}C NMR spectra, and the INADEQUATE pulse sequence has been developed to provide $^{1}J_{CC}$ coupling con-

TABLE 1.1[55]

Approximate Detection Limits for
Various spectroscopic Approaches

Spectroscopic Sensitivity	Detection Limit
Mass spectrometry	10^{-10}-10^{-12} g
Fluorescence spectrometry	~10^{-12} g
Infrared spectrometry	10^{-6}-10^{-9} g
Inductively coupled plasma-atomic emission spectrometry	10^{-6}-10^{-9} g
Refractive index	~10^{-6} g
NMR	10^{-4}-10^{-6} g

stants.[58]

The INEPT pulse sequence[58] (insensitive nuclei enhanced by polarization transfer) was introduced by Morris and Freeman[59] in 1979 for the enhancement of nuclei in low natural abundance (e.g., as ^{13}C and ^{15}N). Shortly afterward, Doddrell and Pegg[60] illustrated that this technique could be modified to provide spectral editing (e.g., methyl, methylene, methine, and quaternary ^{13}C assignments).

This modification of the INEPT experiment is now routinely used to distinguish carbon types in the ^{13}C NMR spectrum. This is achieved through a series of three experiments. The first experiment eliminates quaternary carbon signals in ^{13}C NMR spectrum. The second experiment provides only methine carbon signals with all other carbons eliminated from the spectrum. In the last spectrum, quarternary carbons are again absent, and methylene carbon signals are inverted when compared to the signals of methyl and methine carbons. These three spectra can easily be obtained by adjusting a single delay period (Δ) in the pulse sequence. The delay period can be determined for a molecule by approximating the coupling constants present in the sample (Δ = 1/(4J), 1/(2J), and 3/(4J) in the modified INEPT experiment). Generally, all carbons of a particular molecule can be assigned through a single series of experiments since small differences are observed for $^{1}J_{CH}$ coupling constants (J = 120-150 Hz).

The modified INEPT pulse sequence offers several advan-

tages over methods previously utilized to obtain the same information. The modified INEPT sequence provides a rapid method of distinquishing carbon types when compared with the previously used off-resonance technique. In the INEPT modification all carbons appear as single peaks thereby providing a greater signal-to-noise (S/N) ratio. In the off-resonance experiment coupling constants lower S/N by splitting a single carbon resonance into several less intense signals (e.g., the methyl resonance appears as a 1:3:3:1 quartet, etc.). S/N is also increased in the INEPT modifications due to the polarization transfer portion of the pulse sequence. This polarization transfer sequence can result in a maximum enhancement of ~ 4 times the normal ^{13}C NMR signal. In comparison, a normal ^{13}C NMR signal can have a maximum enhancement of about three due to nuclear Overhauser effects (NOE). This comparison is somewhat misleading since shorter relaxation times are observed for the INEPT experiments. The proton spin-lattice relaxation-times of the INEPT pulse sequence are much shorter than the cross-relaxation rates of the normal ^{13}C NMR experiment. Spin-lattice relaxation-times account for relaxation in the INEPT experiment due to the polarization transfer step in the INEPT sequence. Therefore, the aquisition time that is required for the INEPT pulse sequence is much shorter than the acquisition time which is necessary for the a normal ^{13}C NMR experiment. A final advantage of the INEPT modification over the off-reso-

nance experiment is that fewer signals are obtained in the ^{13}C NMR INEPT spectrum which results in easier spectral assignments.

The INEPT pulse sequence which was described above provides spectral editing of the carbon types observed in the ^{13}C NMR spectrum. Similarly, $^{1}J_{CC}$ coupling constants can provide information regarding carbon "connectivity" in organic compounds. Thus, the basic carbon skeleton can be established from this information. $^{1}J_{CC}$ coupling constants are difficult to obtain since the natural abundance of the ^{13}C nucleus is only 1.1%. Therefore, $^{1}J_{CC}$ coupling constants are only present in a few molecules of a sample. These coupling constants appear as weak satellites centered around a very intense ^{13}C NMR signal for the majority of the ^{13}C nuclei which are not coupled to other ^{13}C nuclei. The presence of spin-side bands in the ^{13}C NMR spectrum also makes the detection of these coupling constants difficult.

Freeman et al.[61] have developed a pulse sequence which overcomes the above problems and which has been illustrated for the pyridine molecule. By utilizing a double-quantum experiment, an eight-step pulse sequence is repeated four times to eliminate the central ^{13}C NMR signals which distort the observation of $^{1}J_{CC}$ coupling constants. At the same time, signals from spinning side bands and trace impurities are also eliminated to afford a spectrum containing only $^{1}J_{CC}$ coupling constants.

One problem associated with the INADEQUATE experiment is that long acquisition times are necessary for the pulse sequence in comparison with other ^{13}C NMR experiments. Long acquisition times are required because the signals of the coupling constant are not enhanced by the INADEQUATE technique. Therefore, relatively poor sensitivity is observed in the INADEQUATE experiment. New developments in this area could lead to a higher S/N ratio and could make the INADEQUATE pulse sequence an even more valuable tool in the near future.

In addition to the INEPT and INADEQUATE pulse sequences, several other pulse sequences and NMR methods have been developed for similar applications (e.g., DEPT and two-dimensional NMR studies). The interested reader is referred to more specialized reviews on these topics.[58]

NMR Studies Utilizing Lanthanide Shift Reagents

One final application in the area of NMR spectroscopy for structure elucidation is lanthanide shift reagent studies.[62] Lanthanide shift reagents were introduced by Hinckley[63] in 1969 and have greatly simplified the analysis of complex NMR spectra. These studies involve the addition of a lanthanide metal complex to a sample which contains a functional group acting as a Lewis base (e.g., hydroxyl and carbonyl groups). As a result of metal complexation, NMR signals that were ori-

ginally overlapping are separated over a larger chemical shift region even yielding first-order spectra in some instances. Several different complexes can be employed, however, europium and praseodymium metal complexes are generally used to reduce line broadening. These complexes generally yield downfield and upfield chemical shift changes, respectively. Chemical shift changes are dependent on two primary factors: (1) the distance between the metal atom and observed nucleus, and (2) the angle between the axis along the observed nucleus and the metal atom, and the axis which is made by the metal atom complexing to the atom acting as the Lewis base.

In general, lanthanide shift reagent experiments provide unambiguous results when only one functional group in the molecule complexes with the lanthanide shift reagent. The chemical shift changes which are observed for these compounds are dependent on the previously described factors. When polyfunctional molecules are examined, the results which are obtained from lanthanide shift reagent studies may not be as straightforward. In these polyfunctional molecules, several functional groups can complex with the lanthanide shift reagent. The results that are obtained in these studies are dependent on two major factors. These factors are the functional group basicity and steric effects around this function group.[62a]

Morrill et al.[64] have proposed that the complexation of

the lanthanide shift reagent with various functional groups is adequately described by the hard-soft acid-base (HSAB) principle. Lanthanide shift reagents are hard acids and prefer to complex with hard bases. Based on this principle funcitonal groups containing oxygen atoms would be expected to complex more effectively with lanthanide shift reagents than analogous functional groups which contain sulfur or selenium atoms.[62c] In polyfunctional molecules, a functional group acting as hard base would be expected to complex most effectively with the lanthanide shift reagent. This selective complexation would result in greater chemical shift changes for the nuclei near this functional group provided that substantial steric factors are not observed at the complexation site.

Further problems are also experienced in the analysis of these polyfunctional molecules with lanthanide shift reagents.[62c] When lanthanide shift reagents are initially added to polyfunctional molecules, the functional group acting as the harder base will complex with the shift reagent as previously described. At higher concentrations of the lanthanide shift reagent, complexation at the more basic site can become saturated. As a result, complexation can begin to occur at the less basic site of the polyfunctional molecule. This would create additional chemical shift changes for the nuclei near the second site of complexation. Therefore, the effects of complexation at each site would not be easily

determined.

Several modifications of these polyfunctional molecules can be initiated to provide either an enhancement or a reduction of the complexing ability of a functional group. The complexing ability of a functional group can be enhanced by a conversion to a harder base. Reduction of esters to alcohols and oxidation of a thioethers to sulfoxides[62c] are examples of conversions that can be utilized for this purpose. Similarly, hydroxyl groups can be derivatized to provide weak sites for complexation. This deactivation can be achieved through trifluoroacetate formation,[65] tosylation,[66] or silylation.[66] In addition, Koller and Dorn have reported that derivatization with 2,2,2-trifluorodiazoethane also appears to be an attractive method for deactivation of alcohols and phenols.[1] In the above study, trifluoroethyl derivatives of p-cresol, n-butyl alcohol, and hexanoic acid were examined in the presence of $Eu(fod)_3$. Koller and Dorn[1] found that only the carbonyl oxygen of the hexanoic ester derivative effectively complexed with $Eu(fod)_3$.

In conclusion, several new NMR methods have recently been employed for the structural analysis of organic molecules. These methods include LC-^{1}H NMR, new pulse sequences, and lanthanide shift reagents.

Chapter II

THE ACID-CATALYZED SELF-CONDENSATION REACTIONS OF 2,4-PENTANEDIONE AND 1-PHENYL-1,3-BUTANEDIONE

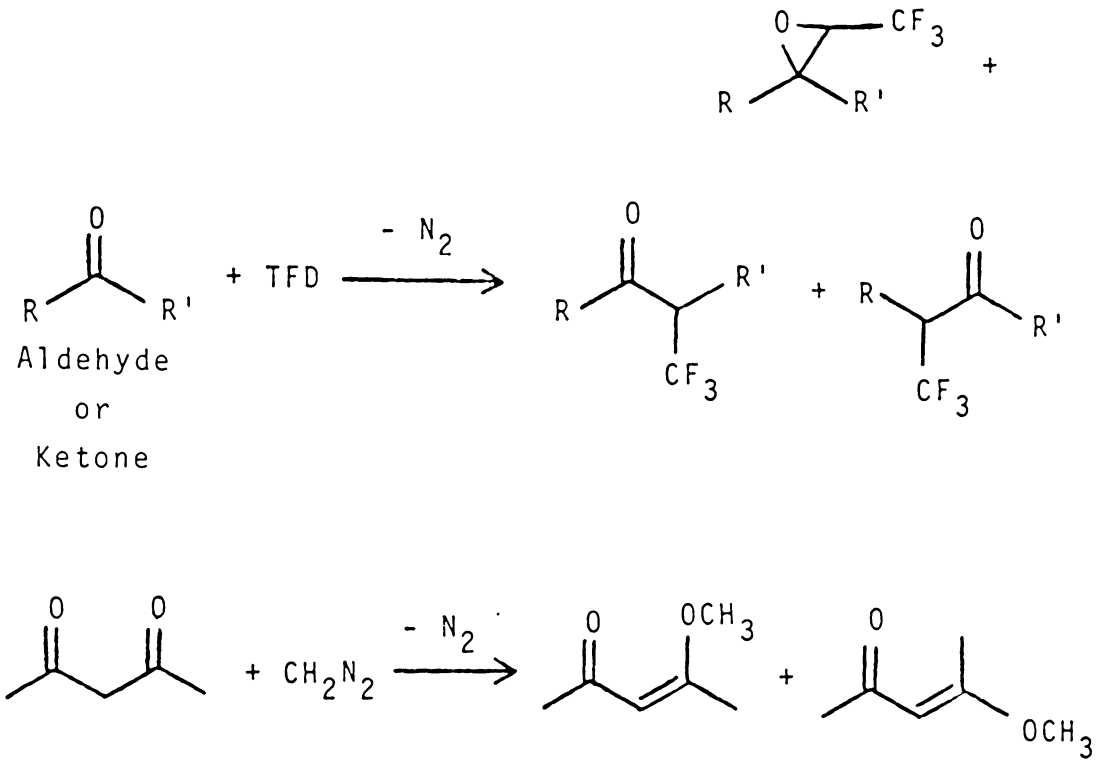
Introduction

Koller[1] reported that several unassigned products were formed on treatment of 2,4-pentanedione with TFD in the presence of an acid catalyst. It was originally assumed that a mixture of trifluoroethyl enol ethers and trifluoroethyl dienol ethers had been obtained. In characterizing the above products, a novel acid-catalyzed self-condensation reaction was discovered. This result was in sharp contrast to the known reactions of diazoalkanes with ketones.[2] For example, the reaction of 2,4-pentanedione with diazomethane[8,10] and the homologation reaction of ketones and aldehydes[11,12] have been previously reported. These results are more fully described in Chapter I and are summarized in Scheme 2.1.

This novel self-condensation reaction was pursued because of the potential synthetic utility of the reaction in aromatic natural product preparations. Although biosynthetic cyclizations of poly-β-carboxyl compounds have been known since the late 1800's,[2,7] similar laboratory synthetic methods have only been recently utilized for the preparation of aromatic natural products.

Scheme 2.1

A Summary of Products Obtained from the Reactions of Diazo Compounds with Aldehydes, Ketones, and β-Diketones

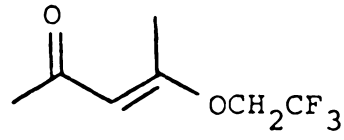


The acid-catalyzed self-condensation reactions that are described in this dissertation offer potential methodology for the preparation of aromatic natural products that have previously been unavailable from condensation reactions of β-dicarbonyl compounds. This chapter will discuss this novel acid-catalyzed self-condensation reaction. In addition, this chapter will also compare this cyclization process to other acid- and base-catalyzed cyclization reactions.

Cyclization Reaction of 2,4-Pentanedione

When a methylene chloride solution of 2,4-pentanedione (136) was treated with TFD in the presence of tetrafluoroboric acid-diethyl ether complex ($HBF_4 \cdot OEt_2$), a mixture of products was obtained. To simplify analysis, the reaction products were refluxed 4 h with methanol, water, and aqueous tetrafluoroboric acid (5:2:1 volumetric ratio). These conditions hydrolyzed most ketals and trifluoroethyl enol ethers that were present in the initial mixture. Upon chromatography, symmetric acetophenone 137 was isolated as the major cyclization product along with several minor cyclization products (138-140), an insertion product (141), and 2,4-pentanedione (see Scheme 2.2 and Table 2.1).[67] Control experiments confirm that TFD and the acid catalyst ($HBF_4 \cdot OEt_2$) must be present for the above cyclization to occur.

The LC-^{1}H NMR[55] technique was utilized to readily assign the products obtained from the reaction of β-diketones with TFD. A portion of the LC-NMR profile for the unhydrolyzed reaction mixture that was obtained from 2,4-pentanedione is shown in Figure 2.1. Several key resonances can be readily assigned for the reaction products in this LC-^{1}H NMR profile. The ^{1}H NMR spectrum of File 1b showed one aromatic singlet at δ 6.61 ppm, and two methyl groups at δ 2.47 and 2.26 ppm, respectively. This spectrum was readily assigned to the major cyclization product (137). (E)-4-(2,2,2-Trifluoroethoxy)-4-penten-2-one (142), the enol ether of 2,4-pentanedione was easily identified in File 1c.

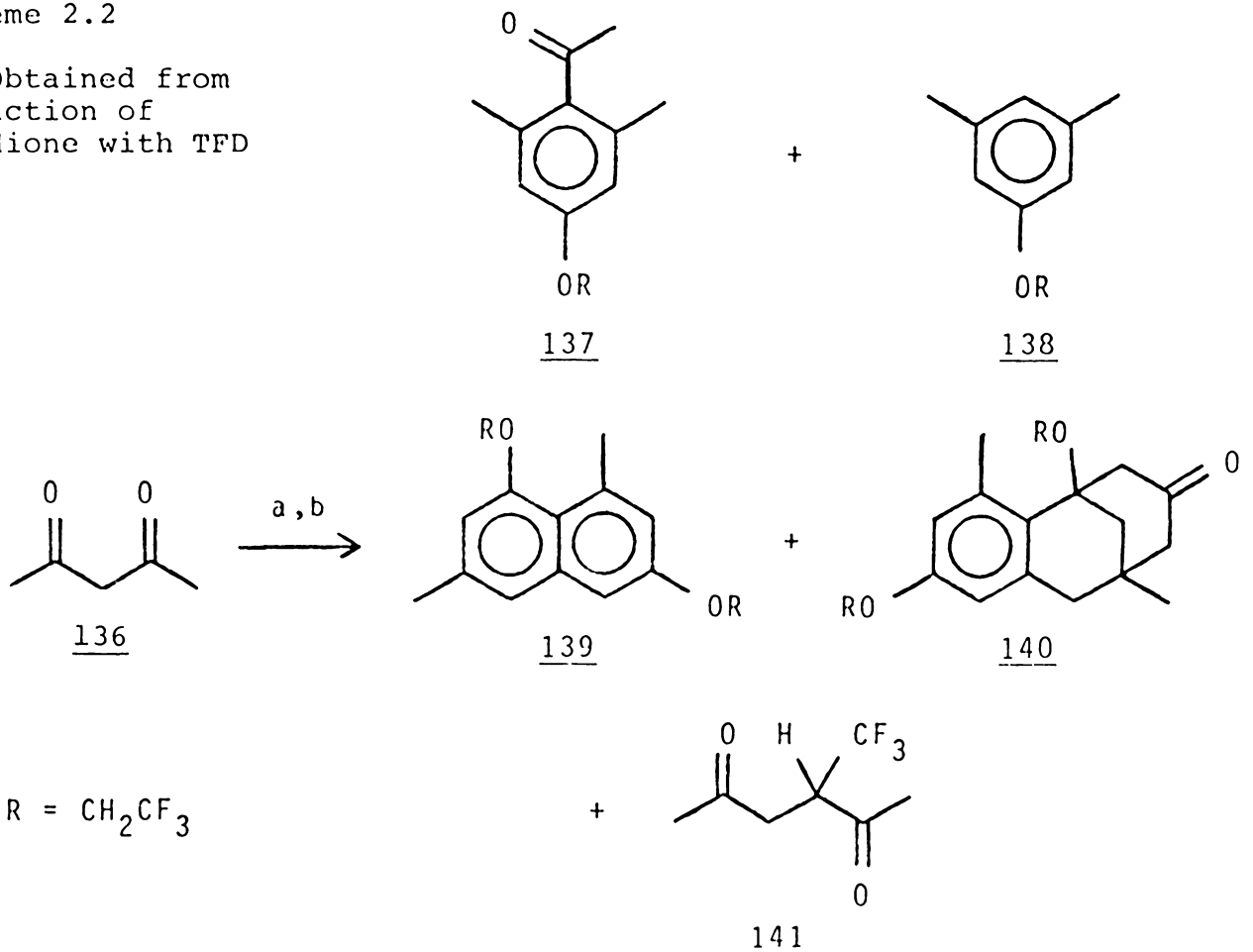


142

The ^{1}H NMR spectrum of File 1a indicated that a mixture of cyclization products were present. In the aromatic region between δ 6.0 and 7.0 ppm, three aromatic singlets were observed. The upfield and downfield aromatic singlets were assigned to compound 138, and the central aromatic singlet was assigned to the 2,2,2-trifluoroethyl enol ether of 137 (enol ether 143). To confirm compounds 138 and 143, the

Scheme 2.2

Products Obtained from the Reaction of 2,4-Pentanedione with TFD



(a) $HBF_4 \cdot OEt_2$, TFD; (b) Refluxing MeOH, H_2O, HBF_4 (5:2:1 volumetric ratio).

TABLE 2.1

Yield Data For β-Diketone Reaction Products

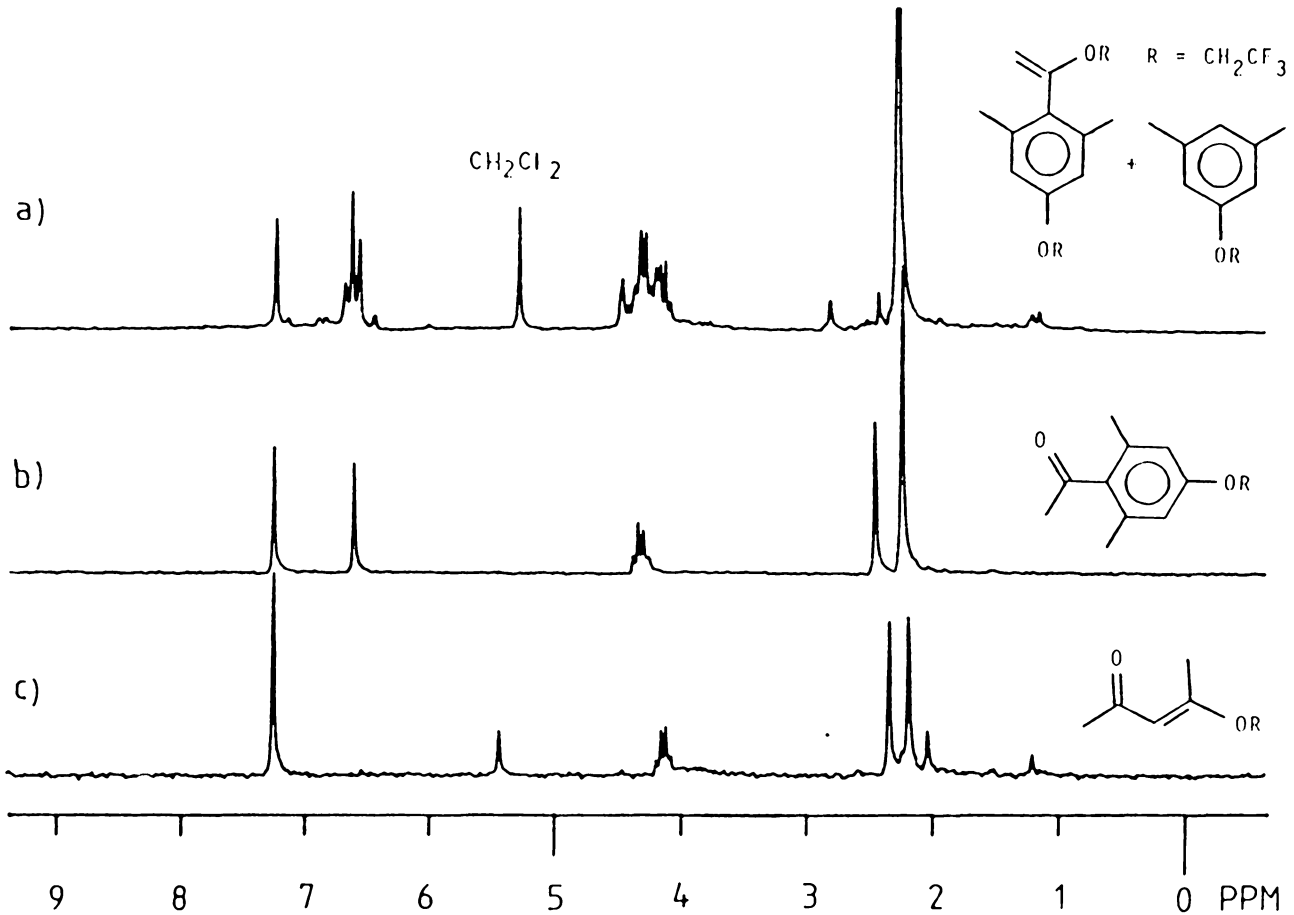
product type	starting β-diketone: 2,4-pentanedione product	yield, %[a]	1-phenyl-1,3-butanedione product	yield, %[a]
cyclization	137	26.6	155	11.6
	138	2.4	157	29.3
	139	4.2		
	140	3.2		
insertion	141	2.7	156	15.3
recovered β-diketones	136	46.9[b]	154	30.6[b]

[a]Values are isolated yields except where noted.

[b]Yield values were obtained from independent NMR experiments.

Figure 2.1

Selective LC-^{1}H NMR files for the 2,4-pentanedione reaction products. These files correspond to spectra of eluting compounds near maximum concentrations. (a) File 3 (elution time of 11 minutes) is the spectrum for a mixture of compounds 138 and 143. (b) File 7 (15 minutes) is the spectrum of acetophenone 137. (c) File 15 (23 minutes) is the spectrum of for enol ether 142. This separation was obtained using a Partisil M9 10/25 PAC column and 99.6% $CDCl_3$ as the solvent.


a)
b)
c)
CH_2Cl_2
OR
R = CH_2CF_3
OR
OR
O
OR
O
OR
9
8
7
6
5
4
3
2
1
0
PPM

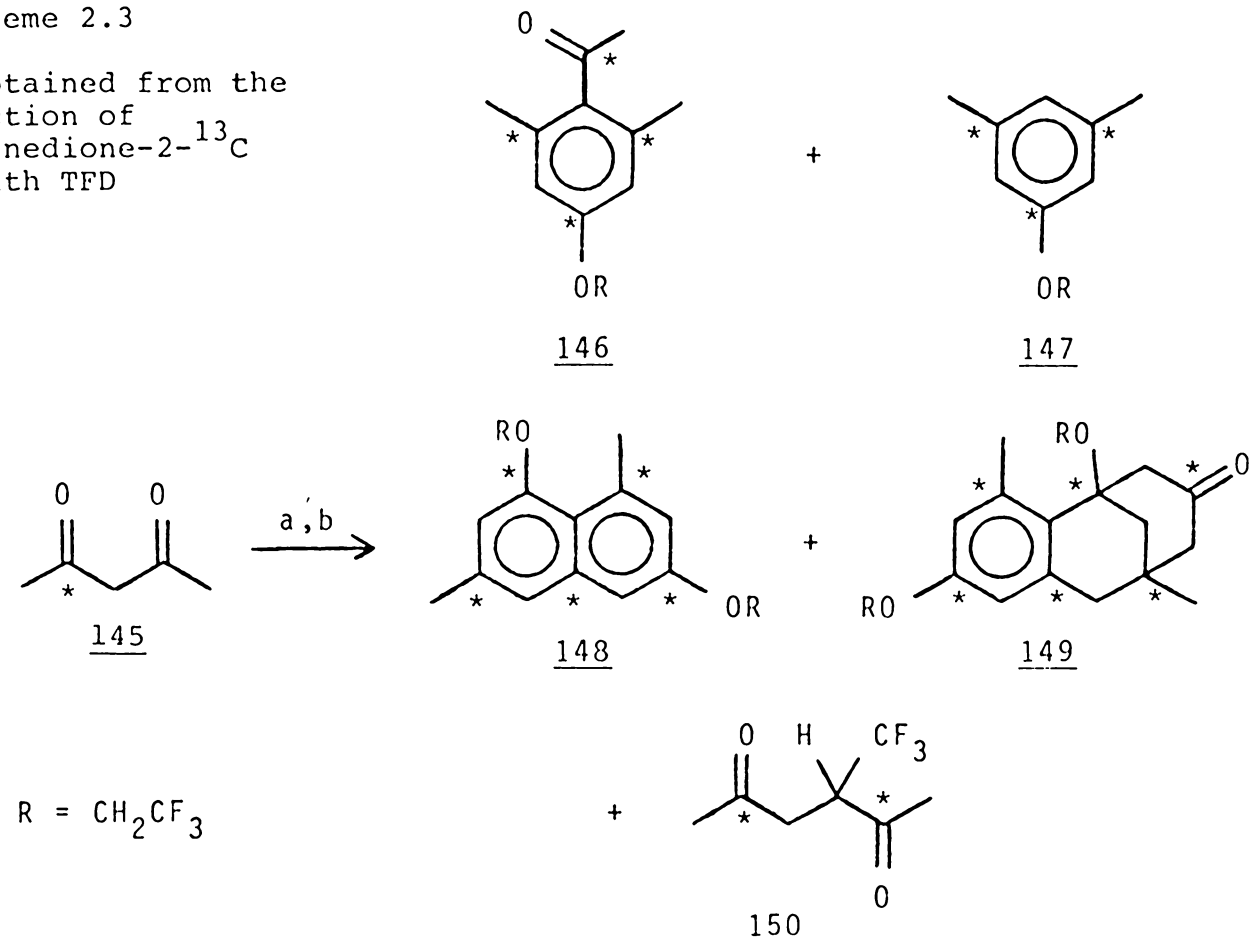
2,4-pentanedione reaction mixture was preparatively separated using conventional HPLC. All signals in the ^{13}C NMR spectrum of the preparative fraction containing compounds 138 and 143 were in total agreement with the above compounds. Further spectroscopic data (e.g., GC/MS) for all fractions which were isolated by HPLC separations were in total agreement with the previously assigned structures. Compounds 137 and 138 were prepared by independent synthesis to further confirm the above assignments.[68]

To confirm the structural assignments of the cyclization products and the regioselectivity of the cyclization reaction, 2,4-pentanedione-2-^{13}C (145) was prepared[69] and treated with TFD using the normal reaction conditions. The products that were detected in the ^{13}C labeling study were consistent with the structures assigned for compounds 137, 138, and 141 (Scheme 2.3). Futhermore, this study also helped deduce structural assignments for the larger molecular weight compounds that have originated from cyclization reactions (compounds 139 and 140).

Several techniques were employed to assign the structure of compound 139 (see Experimental section for complete spectroscopic results). The correct isomer was assigned through the previously described ^{13}C labeling study. Utilizing ^{13}C labeled naphthalene 148, the four aromatic and the two methyl signals were individually irradiated in ^{1}H NMR region while nuclear Overhauser effects (NOE) were observed in the ^{13}C NMR

Scheme 2.3

Products Obtained from the Reaction of 2,4-Pentanedione-2-^{13}C with TFD



(a) $HBF_4 \cdot OEt_2$, TFD; (b) Refluxing MeOH, H_2O, HBF_4 (5:2:1 volumetric ratio).

spectrum by examining the five aromatic quaternary carbons which were ^{13}C enriched (Table 2.2). The NOE enhancements were easily observed since direct $^{1}J_{CC}$ coupling constants were not observed between any of the ^{13}C labeled carbons (i.e., enhancements would have been more difficult to monitor if the five carbon signals had not appeared as singlets). From the NOE experiment, complete carbon "connectivity" was established which eliminated all but one geometric isomer. Similar NOE studies as well as lanthanide shift reagents studies were utilized in the assignment of compound 140.[70]

In order to better understand the mechanistic details of the above cyclization process, the reaction of 2,4-pentanedione with TFD in the presence of $HBF_4 \cdot OEt_2$ was repeated at lower temperatures using limited amounts of TFD. By this procedure, a mixture of enol ether 142 and the corresponding Z-isomer was isolated. After purification, the mixture of E- and Z-isomers was further treated with TFD and $HBF_4 \cdot OEt_2$ under normal reaction conditions to yield a mixture of the previously described cyclization products.

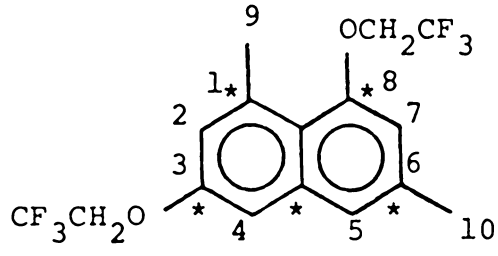
Based on the above findings, intermediates leading to acetophenone 146 most likely originate from the condensations of two 2,4-pentanedione equivalents through a Diels-Alder reaction or a Michael addition. In both mechanisms diene 151 and enol ether 152[71] react to yield intermediates which would eliminate trifluoroethoxy groups to afford enol ether 143 (Scheme 2.4). Enol ether 143 can easi-

TABLE 2.2

NOE Results Obtained from $^{13}C-\{^{1}H\}$ Spectra of Compound 148

resonance irradiated		resonance(s) enhanced[a]
7.14	(H-4)	136.15, 137.56 (C-3, C-4a)
6.89	(H-7)	137.92, 155.30 (C-8, C-6)
6.83	(H-5)	137.56, 155.30 (C-4a, C-6)
6.43	(H-2)	136.15, 155.30 (C-3, C-1)
2.81	(H-9)	136.15 (C-3)
2.42	(H-10)	137.92 (C-8)

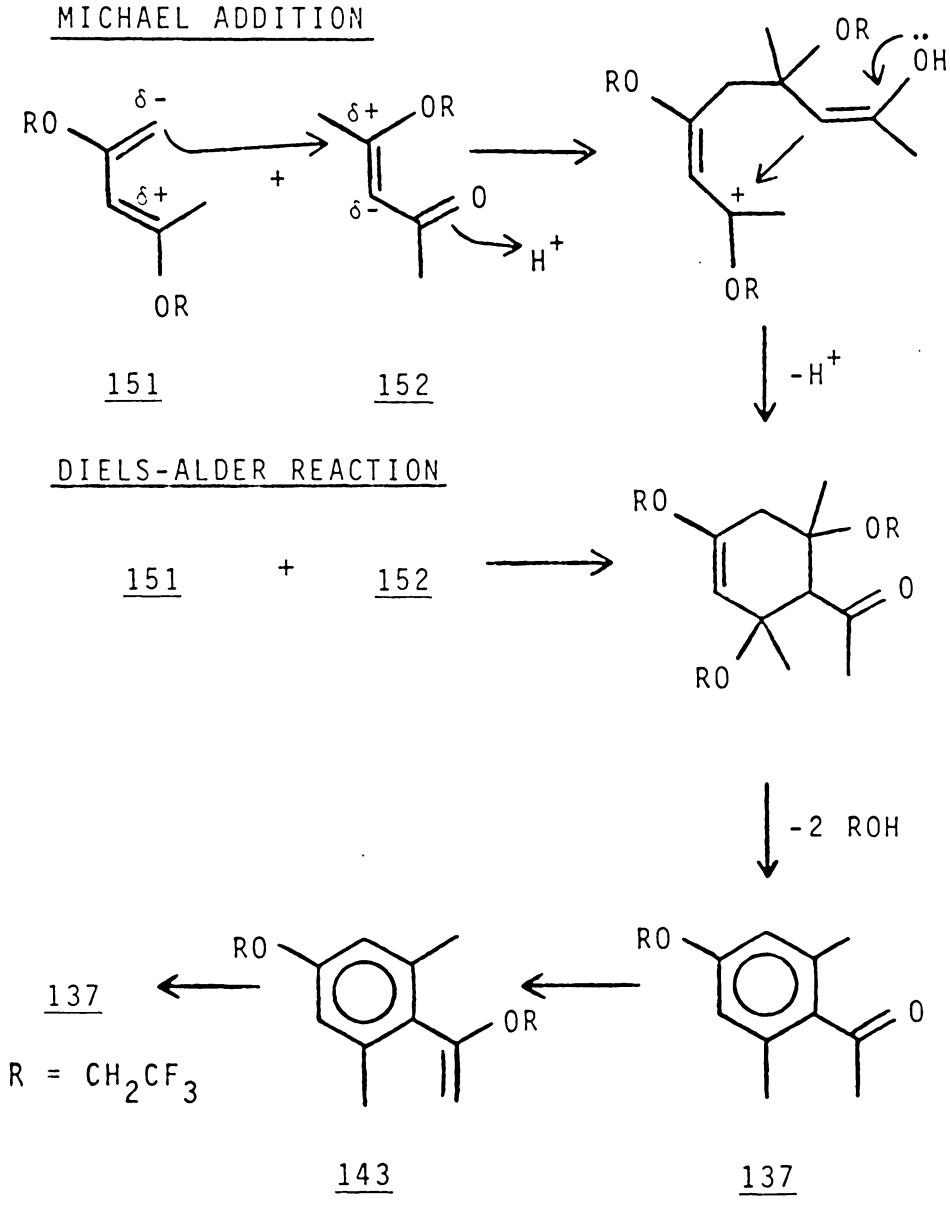
[a]Enhancements from 20-100% were observed



148

Scheme 2.4

Two Possible Mechanisms for the
Cyclization Reaction of 2,4-Pentanedione

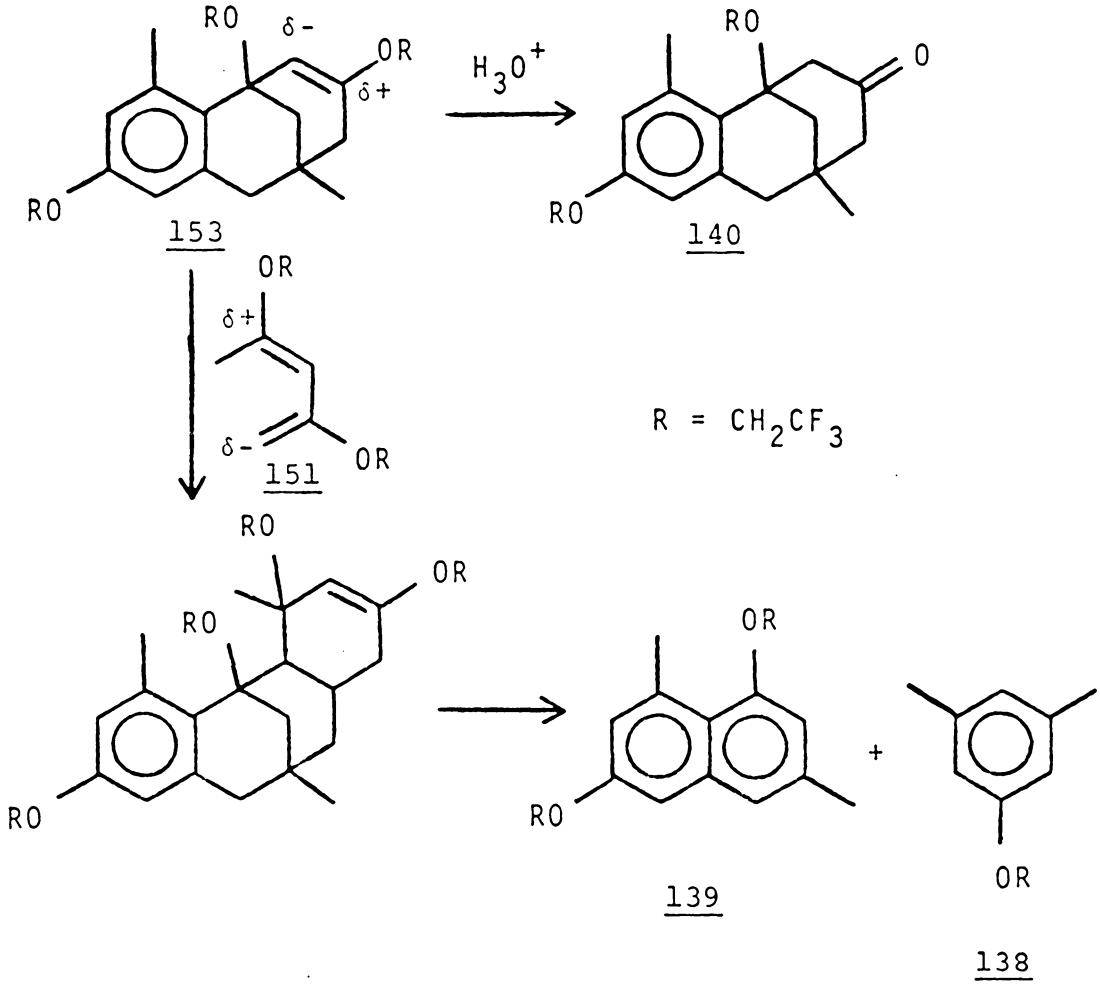


ly be hydrolyzed to acetophenone 137 under the acidic conditions employed.

Unclear at the present time is the origin of naphthalene 139 and aromatic compound 138. One would have expected that some multiple of five would be obtained for the total number of carbons present in these compounds (excluding carbons of trifluoroethoxy groups which originate from TFD). However, compound 138 has eight carbons that must originate from 2,4-pentanedione, and similarly, naphthalene 139 has twelve carbons that must originate from the 5-carbon β-diketone. One could argue that naphthalene 139 arises from ketone 140 or some precursor which leads to ketone 140. However, it seems more probable that ketone 140 is formed from the acid hydrolysis of the corresponding enol ether derivative (153). Before hydrolysis, enol ether 153 could undergo further reaction with a 2,4-pentanedione equivalent to yield a 20-carbon species (excluding carbons of the trifluoroethoxy group) which would decompose to naphthalene 139 (12 carbons) and aromatic compound 138 (8-carbons) through a series of elimination reactions (Scheme 2.5). The formation of this 20-carbon species can be rationalized through the previously described mechanisms. This reaction pathway would also be consistent with the observed ^{13}C labeled pattern in compounds 147 and 148 (the ^{13}C enriched anologous of compounds 138 and 139). Both mechanisms in Scheme 2.4 and 2.5 involve the cyclization of carbon units which contain both an elec-

Scheme 2.5

The Role of Enol Ether 153 in the 2,4-Pentanedione Cyclization Reaction



trophilic site and a nucleophilic site. Such a reaction pathway would result in a ^{13}C labeling pattern on alternating carbons which is consistent with the above results. In support of this mechanistic view, direct $^{1}J_{CC}$ coupling constants between the labeled carbons were not observed in any of the cyclization products. Additional mechanistic studies of these cyclization reactions would provide additional support for the above process.

Cyclization Reaction of 1-Phenyl-1,3-butanedione

When 1-phenyl-1,3-butanedione (154) was employed as the starting β-diketone, several products (155-157) were obtained after hydrolysis (Scheme 2.6). As with the 2,4-pentanedione, the LC-^{1}H NMR technique was utilized to assist in the identification of reaction products (see Figure 2.2). The first compound detected by the LC-^{1}H NMR was biphenyl 155 in File 2a. The three singlets upfield from 7.0 ppm indicated that this compound must be a 1,3,5-trisubstituted aromatic compound. Another phenyl ring, one trifluoroethoxy group, and one methyl group were observed as substituents on the compound contained in this file. The precursor which leads to biphenyl 155 is formed from the cyclization of two 1-phenyl-1,3-butanedione equivalents. The reaction intermediate then eliminates the remaining benzoyl group to yield this biphenyl compound.

Scheme 2.6 Caption:

(a) $HBF_4 \cdot OEt_2$, $0^{\circ}C$; (b) refluxing MeOH, H_2O, HBF_4 (5:2:1 volumetric ratio); (c) $HBF_4 \cdot OEt_2$, $0^{\circ}C$; (d) p-toluenesulfonic acid monohydrate, refluxing benzene.

Scheme 2.6

Products Obtained from the Reaction of
1-Phenyl-1,3-butanedione with TFD

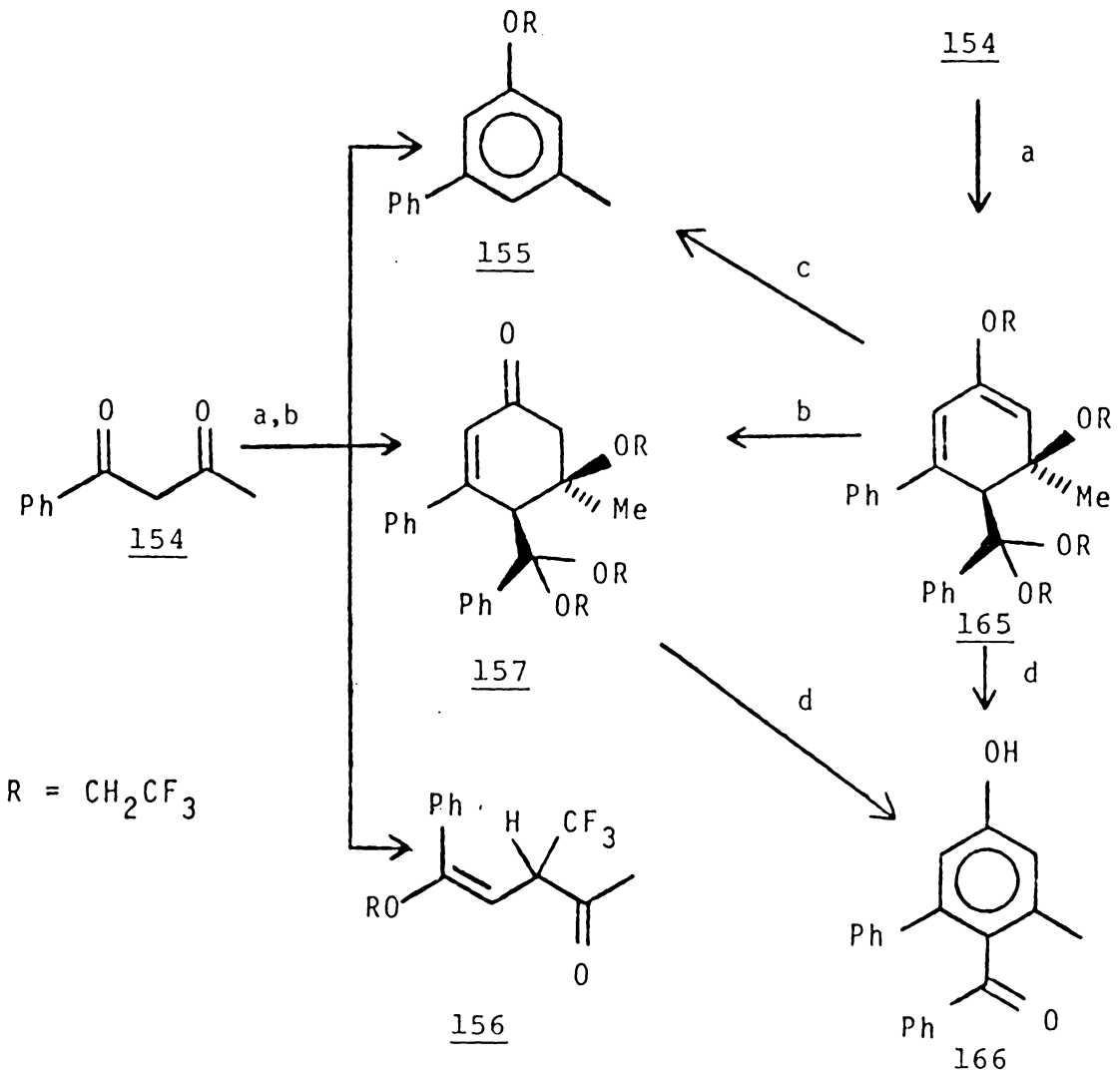
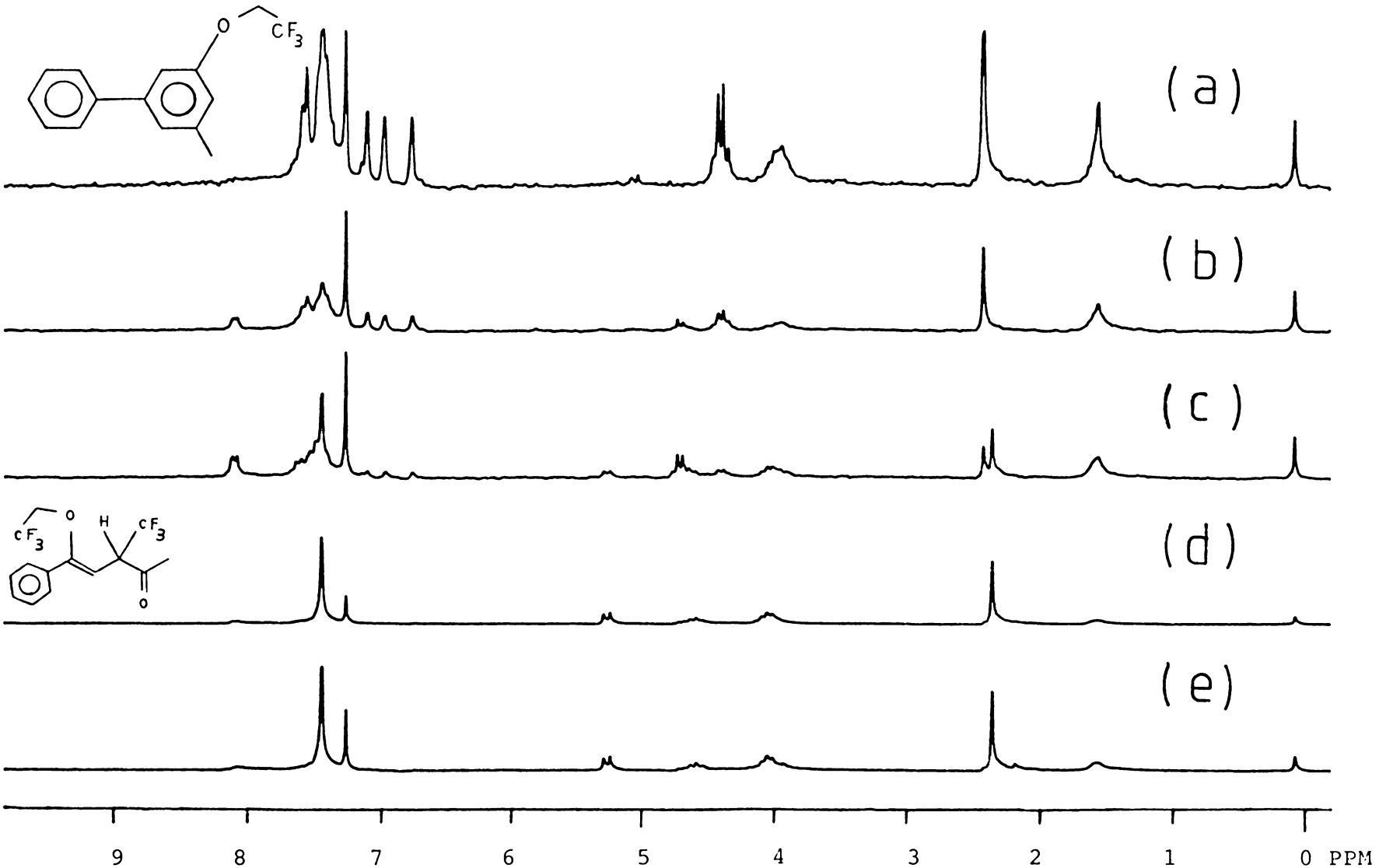
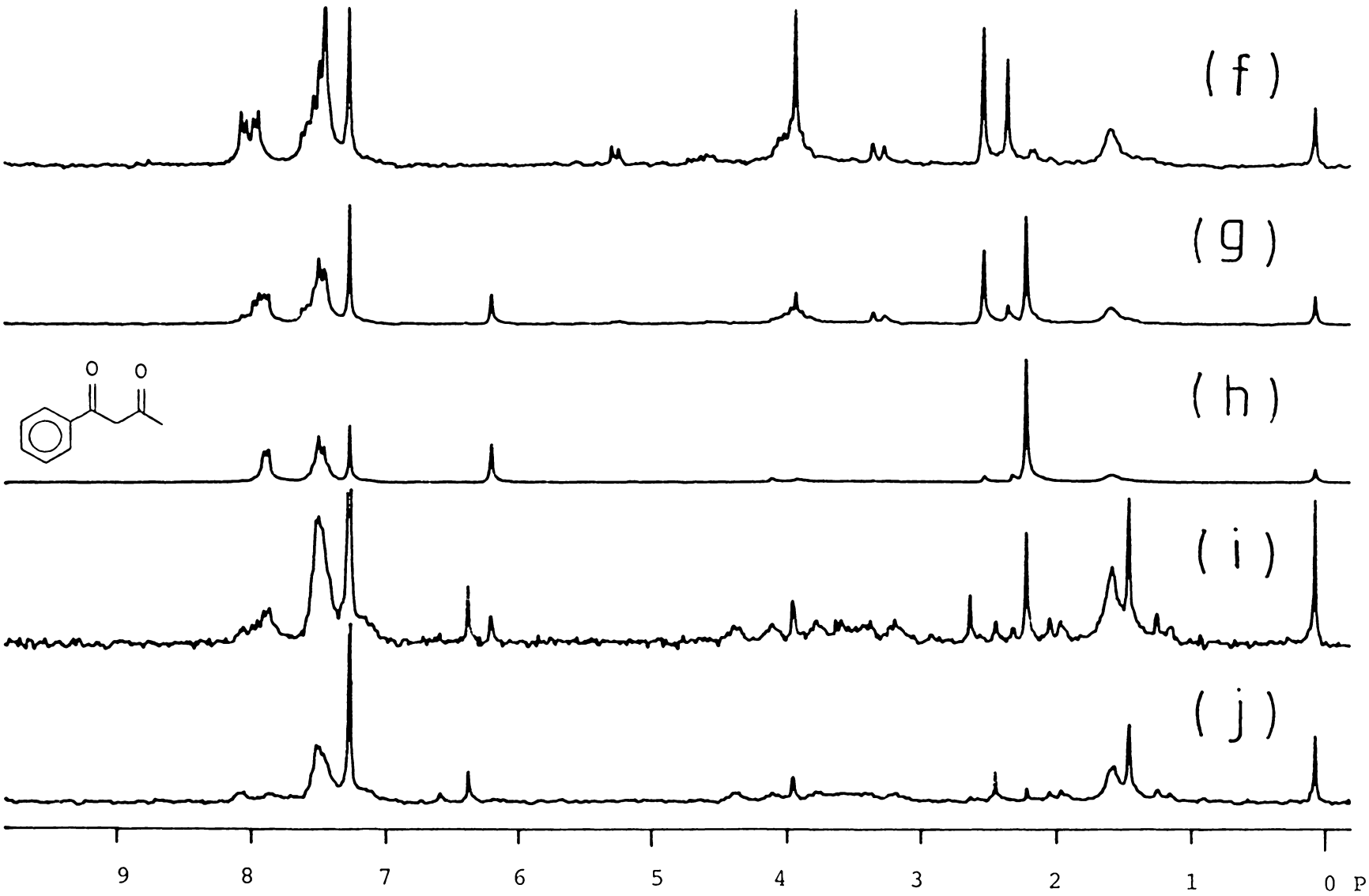


Figure 2.2

Selective LC-^{1}H NMR files of the 1-phenyl-1,3-butanedione reaction products. (a) File 7 (25 minutes) is the spectrum of biphenyl 155. (b) File 8 (26 minutes) is the spectrum of a mixture of biphenyl 155 and trace amounts of 2,2,2-trifluoroethyl benzoate (158). (c) File 9 (27 minutes) shows additional traces of 158. (d) File 10 (28 minutes) and (e) File 11 (29 minutes) are spectra of insertion product 156. (f) File 12 (30 minutes) is the spectrum of a mixture containing insertion product 156, methyl benzoate (159), and 1-phenyl-3-trifluoromethyl-1,4-pentanedione (160). (g) File 13 (31 minutes) is the spectrum containing 160 and 1-phenyl-1,3-butanedione (154). (h) File 14 (31 minutes) is the spectrum of 154. (i) File 19 (36 minutes) is the spectrum of a mixture of 154 and cyclohexenone 157. (j) File 21 (38 minutes) is the spectrum of cyclohexenone 157.


O
CF3
(a)
(b)
(c)
CF3
O
H
CF3
O
(d)
(e)
9
8
7
6
5
4
3
2
1
0 PPM


(f)
(g)
(h)
(i)
(j)
O
O
9
8
7
6
5
4
3
2
1
0 PPM

2,2,2-Trifluoroethyl benzoate (158) was detected by the LC-^{1}H NMR apparatus as a trival product in the reaction mixture (Files 2b-c). This compound was characterized by the trifluoroethoxy group at δ 4.6 ppm. Compound 156 which originates from a homologation reaction was easily identified in File 2d by the olefinic proton at δ 5.3 ppm. This compound also contained a single proton at δ 4.6 which was coupled to both a trifluoromethyl group and the olefinic hydrogen. Methyl benzoate (159) appeared in File 2f along with 1-phenyl-3-trifluoromethyl-1,4-pentanedione (160) which has resulted from hydrolysis of compound 156. The methyl benzoate and trifluoroethyl benzoate that were observed above originate during the elimination process which forms biphenyl 155. The enol form of 1-phenyl-1,3-butanedione eluted in File 2h and exhibited a characteristic olefinic proton downfield at δ 6 ppm. Compounds 154, 158, 159, and 160 contained aromatic protons that were ortho to a carbonyl group. As a result, these compounds exhibited resonances near δ 8 ppm.

The last compound to elute from the LC-^{1}H NMR apparatus was cyclohexenone 157 in Files 2i-j. Poor signal-to-noise was observed due to the long elution of this compound under the employed chromatographic conditions. To obtain additional spectroscopic data for cyclohexenone 157 and the other reaction products, another mixture was prepared from 1-phenyl-1,3-butanedione and was separated using flash chromatography. The stereochemistry for the purified cyclo-

hexenone 157 which was isolated from flash chromatography was established by paramagnetic shift reagent [$Eu(fod)_3$] studies. ^{13}C labeling studies (vide infra)[70] also provided support for this structure. Cyclohexanone 157 could be formed from the cyclization of two 1-phenyl-1,3-butanedione equivalents through one of the mechanisms described for 2,4-pentanedione. Unlike biphenyl 155, a benzoyl group has not been eliminated from cyclohexenone 157. However, the benzoyl group has undergone further reaction to provide the corresponding trifluoroethyl ketal derivative.

To confirm the regioselectivity of the cyclization reaction and to further verify the identity of the cyclized products, 1-phenyl-1,3-butanedione-1-^{13}C was prepared and treated with TFD using the normal reaction conditions[72] (Scheme 2.7). The ^{13}C NMR spectra of the labeled products indicated that the ketal and the olefinic quaternary carbons were labeled in cyclohexenone 164 and that only one labeled quaternary carbon was present in biphenyl 162. Carbon "connectivity" data was obtained for labeled cyclohexenone 164 from INADEQUATE ^{13}C NMR[61] studies. The results of this study are presented in Table 2.3. For cyclohexenone 164, the INADEQUATE experiment indicated that both labeled carbons were directly coupled to the methine carbon ($^1J_{CC}$ coupling constants of 39.1 and 43.5 Hz). The results of the INADEQUATE experiment are consistent with cyclohexenone 164 and have provided carbon "connectivity" in the portion of the mole-

Scheme 2.7

Products Obtained from the Reaction
of 1-Phenyl-1,3-butanedione with TFD

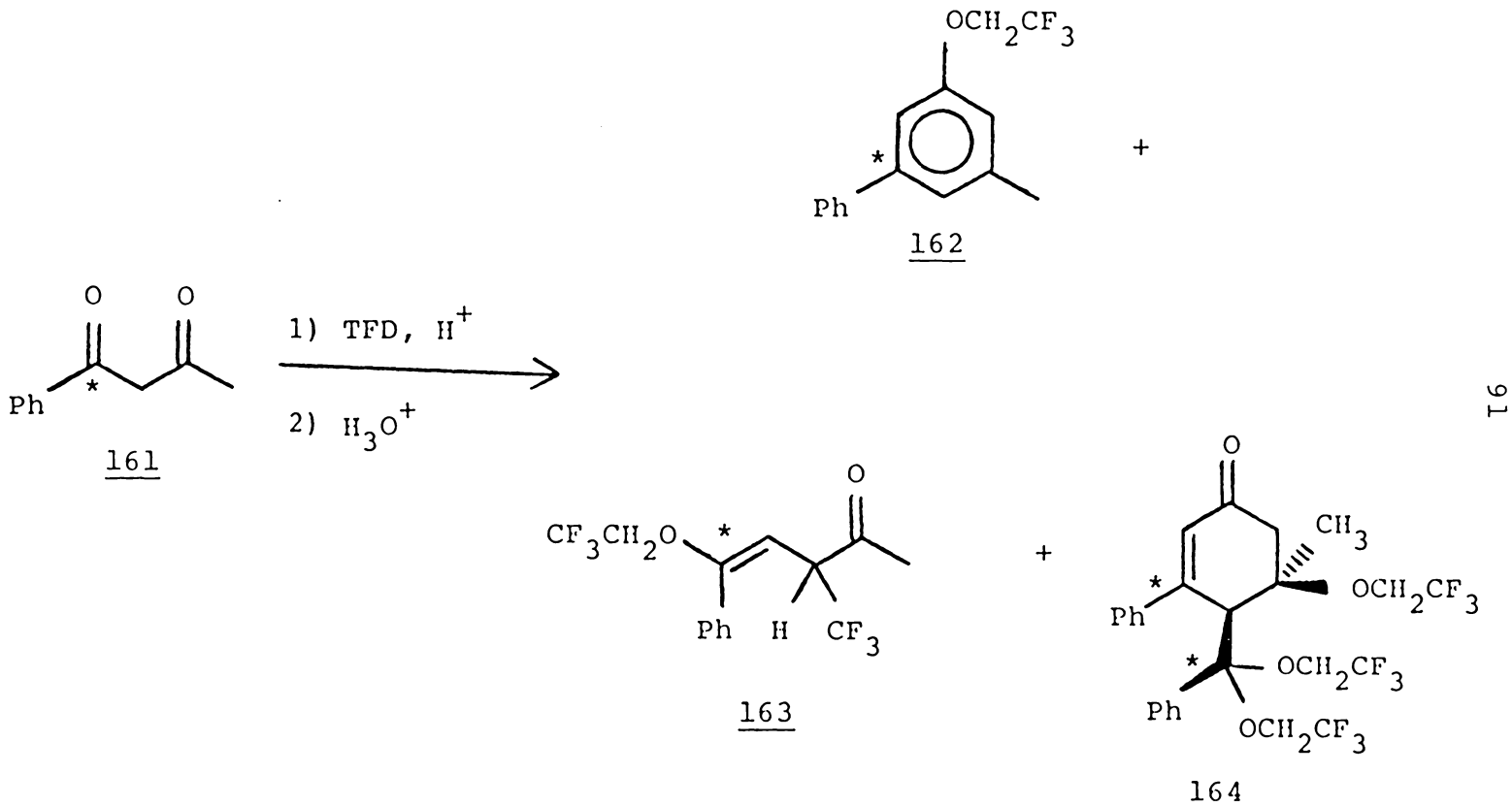
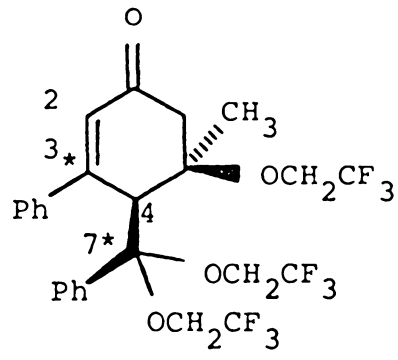


TABLE 2.3

$^{1}J_{CC}$ Coupling Constants for Compound 164
Obtained from INADEQUATE NMR Studies

C_i	C_j	J_{ij}[Hz]
2	3	66.9 ± 1
3	4	39.1 ± 1
3	Ph(C-3)	54.9 ± 1
4	7	43.5 ± 1
7	Ph(C-3)	57.1 ± 1



164

cule opposite the carbonyl group.

The cyclized products 155 and 157 were isolated in 11.6 and 29.3% yields, respectively, after chromatographic separation (Table 2.1). In contrast to the results which were obtained with 2,4-pentanedione, aromatization of cyclohexenone 157 was incomplete. Nevertheless, the combined yield of cyclized products from 1-phenyl-1,3-butanedione was significantly higher than the yield that was obtained from 2,4-pentanedione.

Dienol ether 165 (isolated from mixture prior to hydrolysis, see Scheme 2.6) was easily converted to cyclohexenone 157 under the methanol-water-HBF_4 hydrolytic conditions. Data suggest that the deketalization of cyclohexenone 157 did not occur with methanol-water-HBF_4 due to steric constraints to nucleophilic attack at the ketal carbon. ^1H and ^{13}C NMR data for cyclohexenone 157 provide support for the steric constraints at ketal carbon.[70] These data indicate that phenyl group attached to the ketal carbon has restricted rotation at ambient temperatures (~30°C). Also, dienol ether 165 provided biphenyl 155 when subjected to the original acidic conditions **without** TFD (i.e. a methylene chloride solution of $HBF_4 \cdot OEt_2$ at 0°C). However, cyclohexenone 157 was stable to these same reaction conditions. These observations suggest that dienol ether 165 is a key immediate in the formation of 155 and 157. Furthermore, both cyclohexenone 157 and dienol ether 165 can be quantitatively converted to

biphenyl 166 using p-toluenesulfonic acid monohydrate in refluxing benzene (Scheme 2.6).

The conversion of dienol ether 165 to cyclohexenone 157 is consistent with the stereochemistry indicated. Models of dienol ether 165 support that the cyclohexadiene structure should be planar forcing both the ketal carbon and the adjacent trifluoroethoxy group into the same plane. Proper orbital overlap would be obtained allowing elimination to biphenyl 155 under normal reaction conditions. In cyclohexenone 157, lack of coplanarity for the ketal carbon and the trifluoroethoxy group results in poor orbital overlap for eliminations from this compound under normal hydrolytic conditions. Therefore, cyclohexenone 22 would be expected to be stable to the normal hydrolytic conditions and would not undergo further elimination reactions to form an aromatic product.

Cyclization of Substituted Derivatives of 1-Phenyl-1,3-butanedione

Several substituted derivatives of 1-phenyl-1,3-butanedione were prepared in order to illustrate the potential synthetic utility of the cyclization reactions previously discussed. p-Fluoro, p-methyl, p-methoxy, and o-methyl derivatives of 1-phenyl-1,3-butanedione were prepared[72,73] and treated with TFD in the presence of $HBF_4 \cdot OEt_2$. Yield

data for the resulting reaction products are provided in Table 2.4. From the yield data, it is apparent that the degree of hydrolysis varied from one reaction system to another. For example, when the p-fluoro substitutent was examined, the dienol ether of the cyclohexenone was even isolated after hydrolysis. This illustrates incomplete hydrolysis for this reaction mixture. Nevertheless, the above results can be easily summarized in Table 2.5 which compares the total yields of cyclized products and insertion products with recovered β-diketones. Yield data for 1-phenyl-1,3-butanedione are also included in Table 2.5 for further comparison.

In comparing yields of cyclization and insertion products for the substituted derivatives of 1-phenyl-1,3-butanedione, a preponderance of insertion products were formed from the o-methyl derivative of 1-phenyl-1,3-butanedione. This higher yield of insertion products would be expected since the o-methyl group can sterically hinder cyclization. A slightly different cyclization product (167) was also obtained for the sterically hindered o-methyl β-diketone system. In addition to the normal spectroscopic techniques a lanthanide shift reagent study was utilized to establish the structure of this new cyclization product.[70]

TABLE 2.4

Yield Data for the Substituted
Derivatives of 1-Phenyl-1,3-butanedione

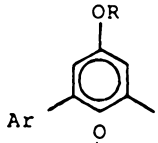
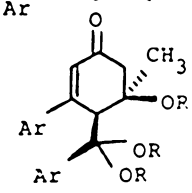
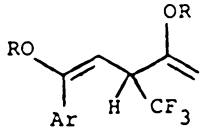
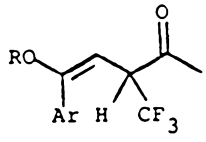
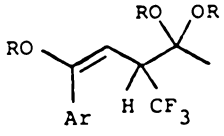
product	substituted derivative of 1-phenyl-1,3-butanedione			
	p-fluoro	p-methyl	o-methyl	o-methoxy
	11.3%	11.1%	0%	14.8%
	12.5	22.4	0	0
	7.1	3.3	3.1	0
	3.1	7.1	21.6	4.5
	4.9	3.9	5.4	1.2

TABLE 2.4 (cont.)

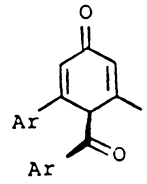
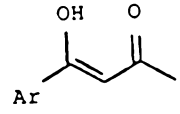
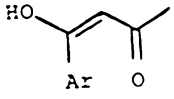
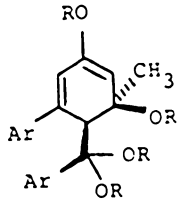
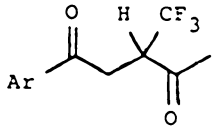
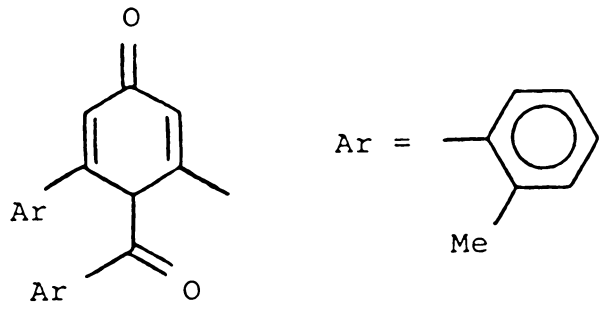
product	substituted derivative of 1-phenyl-1,3-butanedione			
	p-fluoro	p-methyl	o-methyl	p-methoxy
	0%	0%	7.2%	0%
	22.1	20.6	32.2	45.1
	1.3	9.8	0	7.6
	3.9	0	0	0
	0	0	3.0	13.7

TABLE 2.5

Yield Data for the Substituted Derivatives of 1-Phenyl-1,3-butanedione Comparing Types of Recovered Products

	substituted derivatives of 1-phenyl-1,3-butanedione				
product type	p-fluoro	p-methyl	o-methyl	p-methoxy	unsubstituted
cyclic	27.8%	33.5%	7.2%	14.8%	40.9%
insertion	15.1	14.2	33.1	19.4	15.3
recovered β-diketones	23.4	30.4	32.2	52.7	30.6



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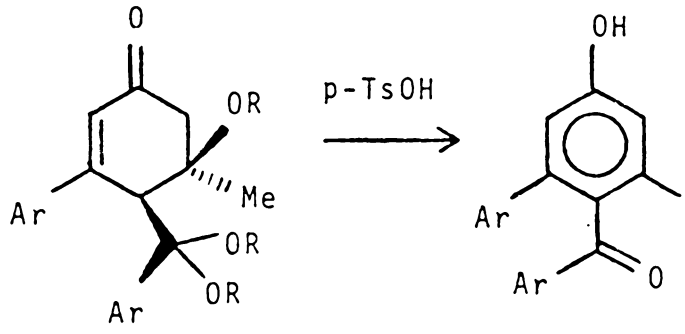
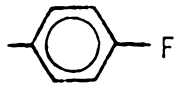
It should also be noted that only a trace amount of the cyclohexenone derivative was obtained from the p-methoxy β-diketone system. The corresponding cyclohexenone derivative could have undergone further reaction during the cyclization process (e.g., polymer formation).

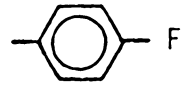
To further explore the potential synthetic utility of these β-diketone self-condensation reactions, the substituted diene 168 and the cyclohexenones 169 and 170 were converted to the corresponding biphenyl derivatives in quantitative yields with p-toluenesulfonic acid monohydrate in refluxing benzene (Scheme 2.8). This conversion demonstrates a new biphenyl preparation from β-diketones. In addition, biphenyl compounds 166, 171, and 172 could ultimately be important synthons in the preparation of larger polycyclic aromatic compounds (i.e., through the Elbs reaction).[74]

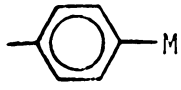
Scheme 2.8

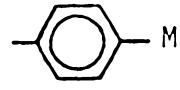
New Methodology for the Preparation of Biphenyl Compounds from Products Obtained from the Reactions of β-Diketones with TFD

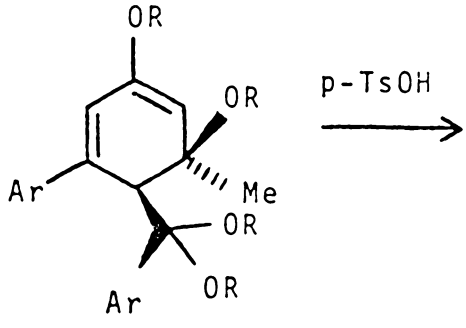


<u>169</u>, Ar =  F

<u>171</u>, Ar =  F

<u>170</u>, Ar =  Me

<u>172</u>, Ar =  Me



<u>168</u>, Ar =  F

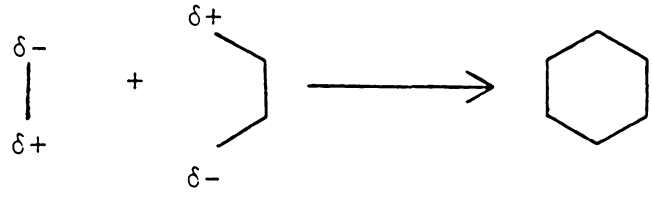
R = CH_2CF_3

Comparison of Cyclization Processes

The cyclization of β-diketones in the presence of TFD and $HBF_4 \cdot OEt_2$ is in sharp contrast to the cyclization reactions of β-diketones and β-dicarbonyl equivalents that were previously described in Chapter I. The base-catalyzed cyclization reactions of β-diketone that were reported by Clark and Miller [33] and others[34-37] involved a condensation between two 3-carbon units, one containing nucleophilic sites and the other containing electrophilic sites (eq 23 in Chapter I). In the previously described base-catalyst study, regioselectivity was observed for the cyclization reaction of 1-phenyl-2,4-pentanedione to predominately compound 57. Similar results have been reported by Chan and Brownbridge[38,39,41] in cyclization reactions utilizing titanium tetrachloride. Both β-dicarbonyl equivalents 65 and 80 act as the 3-carbon fragment with the two nucleophilic sites that will undergo cyclization with several different 3-carbon units containing electrophilic sites.

In the presence of TFD and $HBF_4 \cdot OEt_2$, 2,4-pentanedione and various substituted derivatives of 1-phenyl-1,3-butanedione undergo cyclization reactions to yield products that originate from a condensation between a 4-carbon fragment and a 2-carbon fragment. Conceptually, this condensation is quite similar to the Diels-Alder reaction or the Robinson

annelation. In the condensation, both the 2-carbon unit and the 4-carbon unit contain a nucleophilic site and an electrophilic site (eq 44).



(44)

Although this cyclization process is regioselectively, a single cyclized product is not generally obtained from substituted derivatives of 1-phenyl-1,3-butanedione. That is, the initial reaction products formed during the cyclization process appear to undergo further elimination reactions under the previously described conditions. Therefore, good yields of a single cyclized product cannot be currently obtained from cyclization process. As previously described, the products that are obtained from the acid-catalyzed reaction of β-diketones are uniquely different from the products obtained from similar base-catalyzed reactions (e.g., different reaction products are obtained from 2,4-pentanedione). Therefore, the potential synthetic utility of both cyclization processes is clearly illustrated.

Conclusion

The novel acid-catalyzed condensation reaction of β-diketones in the presence of TFD offers potential synthetic methodology for the preparation of cyclized compounds which were previously unobtainable from the base-catalyzed condensation reactions of β-dicarbonyl units. Two general types of substituted biphenyl compounds have been prepared utilizing this methodology. Substituted derivatives of 166 should be important synthons in the preparation of larger condensed aromatic ring systems. The precise role of 2,2,2-trifluorodiazoethane and mechanistic details of this reaction are not fully understood at the present time.

Experimental

Equipment. NMR data was obtained from either a JEOL FX-200 Spectrometer (^{1}H NMR 199.50 MHz/^{13}C NMR 50.10 MHz/^{19}F NMR 187.70 MHz) or a Bruker WP-200 Spectrometer (^{1}H NMR 200.13 MHz/^{13}C NMR 50.33 MHz). Samples were dissolved in $CDCl_3$, and chemical shifts were referenced to TMS. The notation which is used in reporting carbon types which were confirmed by ^{13}C NMR INEPT results is as follows: s = quaternary, d = methine, t = methylene, q = methyl. Mass spectral data was obtained from a Varian MAT 112 Spectrometer operating at 70eV. The mass spectral probe temperature was 250°C. GC/MS results were obtained by coupling the above system to a 25 meter OV-101 glass capillary column. Samples were eluted over a 150-250°C temperature range. IR data were recorded from a Perkin-Elmer Model 710B Infrared Spectrophometer. UV-VIS results were obtained from a Hitachi 100-60 Spectrometer, and constant wavelength studies in this region were performed using a Bausch and Lomb Spectronic 20. Elemental analysis results for compounds described in this chapter appear in Table 2.6.

2,2,2-Trifluorodiazoethane (TFD). TFD was prepared by modifying the procedure of Fields and Haszeldine.[16] Sodium nitrite (14.9 g, 216 mmoles) was slowly added in three equal portions to an ice-cold solution of 2,2,2-trifluoroethylamine hydrochloride (25.0 g, 184 mmoles) in water (225 mL)

TABLE 2.6

Elemental Analysis Results for Various Reaction Products

compound	theoretical % C	theoretical % H	results[a,b] % C	results[a,b] % H
138	58.82	5.43	59.52	5.80
140	55.61	4.91	55.99	5.24
144	58.54	5.32	59.45	5.55
155	67.66	4.92	66.51	4.97
156	51.54	3.71	51.23	3.83
165	51.54	3.71	51.63	3.81
168	48.85	3.22	48.88	3.34
169	51.50	3.49	51.65	3.62
170	56.19	4.55	55.82	4.55
174	63.38	4.26	62.62	4.73
175	45.09	2.84	46.20	3.04
176	42.62	2.93	43.41	3.10
177	48.85	3.22	49.92	3.54
179	48.35	3.58	49.02	3.74
180	43.69	3.47	43.61	3.51
181	52.95	4.15	53.18	4.27
183	42.39	3.37	42.80	3.55
184	50.57	3.96	51.32	4.13
188	48.35	3.58	48.39	3.73
189	43.69	3.47	44.05	3.56
190	52.95	4.15	53.11	4.26
191	52.95	4.15	53.38	4.17
200[c]	47.07	3.21	46.49	3.31
201[c]	54.05	5.90	54.34	5.94
211[c]	60.46	5.07	60.59	5.05
212[c]	52.95	4.15	52.90	4.20
240[d]	63.15	5.30	62.46	5.27

TABLE 2.6 (cont.)

[a]For comparison, J. Am. Chem. Soc. considers routine analyses which agree with calculated values within ±0.4% as acceptable.

[b]Average value of two analyses.

[c]See Chapter III for a description of this compound.

[d]See Chapter IV for a description of this compound.

and CH_2Cl_2 (225 mL). The mixture was vigorously stirred during the $NaNO_2$ addition which required 15 min. The solution was transferred to a separatory funnel, and the organic layer was collected. The aqueous layer was extracted with 4-75 mL and 1-50 mL portions of CH_2Cl_2. All CH_2Cl_2 extracts were combined, washed twice with cold 10% Na_2CO_3, and stored over $CaSO_4$ at temperatures below 0°C. Yields of 60-65% were obtained using this method. Yield results were determined by ^{19}F NMR spectroscopy (i.e., TFD was compared to a known amount of 1,2-difluorotetrachloroethane). Yields have also been determined spectrophotometrically at 403 nm (ε = 7.9 M^{-1} cm^{-1}).

Cyclization Reactions Utilizing TFD. A 500 mL 4-necked round bottom flask was equipped with a condenser attached to an ice-trap, a rubber septum, an addition funnel, and a nitrogen inlet. The ice-trap which attached to the condenser was connected to a nitrogen bubbler to serve as a nitrogen exit. The flask was also equipped with a stirring bar and was cooled to 0°C. A solution of 2,4-pentanedione (1.5 g, 15 mmoles) in 10 mL of CH_2Cl_2 was added to the reaction flask under nitrogen. A 0.28 M TFD solution (0.17 L, 46 mmoles) was added dropwise to the β-diketone over 1 3/4 h. $HBF_4 \cdot OEt_2$ (0.90 mL, 7.9 mmoles) was added to the reaction flask in several small portions throughout the reaction period. Following the addition of TFD, the reaction continued to stir at 0°C for another 1 3/4 h. The reaction mixture was neutralized with 1

mL of triethylamine. Then, the reaction mixture was washed twice with 5% $NaHCO_3$ and once with water. The organic layer was dried over anhydrous $MgSO_4$ followed by removal of CH_2Cl_2. The mixture was hydrolyzed using 25 mL of methanol, 10 mL of water, and 5 mL of aqueous tetrafluoroboric acid. The above mixture was refluxed with stirring for 4 h. After the hydrolysis period, water and CH_2Cl_2 were added to the mixture to separate the two layers. The organic layer was collected, washed twice with 5% $NaHCO_3$, and washed once with water. The organic layer was dried followed by removal of CH_2Cl_2. (Other reactions described in this chapter have utilized similar reaction conditions **without** triethylamine neutralization prior to treatment with 5% $NaHCO_3$).

The resulting mixture was separated utilizing flash chromatography[75] to provide yield data for the β-diketone. A gradient elution with pentane, methylene chloride, and diethyl ether provided an adequate separation of the 2,4-pentanedione reaction mixture. Compounds 138 and 139 had similar retention times and were further separated by recrystallization from pentane. Compound 139 precipitated from the solution while compound 138 remained soluble in the mother liquor. Compound 140 was further purified by extracting acidic impurities into base with three portions of 5% NaOH. The organic layer that was used in the above extraction was washed once with water, dried over anhydrous $MgSO_4$, filtered, and evaporated under a slow stream of nitro-

gen gas.

The following compounds were obtained from this procedure: acetophenone 137 (0.49 g, 26.6%), aromatic compound 138 (0.036 g, 2.4%), naphthalene 139 (0.074 g, 4.2%), cyclic ketone 140 (0.056 g, 3.2%), and insertion γ-diketone 141 (0.037 g, 2.7%). This procedure also afforded a 46.7% recovery of starting material based on a ^{1}H NMR integration of an independent reaction mixture prior to chromatographic separation.

The 2,4-pentanedione mixture utilized in the LC-^{1}H NMR study was prepared with 2.8 g (28 mmoles) of the starting β-diketone using the previously described procedure. The organic mixture was neutralized with 10% NaOH instead of the previously described triethylamine procedure. This mixture was directly separated using the LC-^{1}H NMR apparatus without the previously described hydrolytic treatment.

LC-^{1}H NMR Conditions. Reaction mixtures originating from 2,4-pentanedione and 1-phenyl-1,3-butanedione were separated using a Partisil M9 10/25 PAC column. $CDCl_3$ (99.6%) was used as the chromatographic solvent in these separations. A flow rate of 1 mL/min was utilized in all separations. The ^{1}H NMR profiles were recorded at 199.50 MHz on a JOEL FX-200 Spectrometer, and chemical shifts were referenced to residual $CHCl_3$ (δ 7.24) appearing in the chromatographic solvent. 24 scans were recorded per file, and total data collection took ~20 minutes. For the 2,4-pentanedione

reaction mixture, fractions were collected as the various compounds eluted from the LC-^{1}H NMR apparatus, and GC/MS data were obtained for the individual fractions. See reference 55 for a more detail description of the LC-^{1}H NMR instrumentation. Additional HPLC separations of the 2,4-pentanedione mixture utilized similar chromatographic conditions with $CHCl_3$ instead of $CDCl_3$ being utilized as the chromatographic solvent.

Control Experiments for 2,4-Pentanedione Cyclization. (a) A mixture of 1.0 g of 2,4-pentanedione and 50 mL of a 0.25 M TFD solution were added to a flask under nitrogen at 0°C. The mixture stirred overnight and was analyzed for reaction products by removal of CH_2Cl_2. ^{1}H and ^{13}C NMR showed unreacted 2,4-pentanedione. (b) A mixture of 2.0 g of 2,4-pentanedione, 10 mL of CH_2Cl_2, and 0.25 mL of $HBF_4 \cdot OEt_2$ was prepared under nitrogen. After 2 h, the organic mixture was neutralized with 10% NaOH (2,4-pentanedione was also extracted into base using these conditions) and washed with water. ^{1}H and ^{13}C NMR results showed only trace amounts of 2,4-pentanedione remaining in the organic layer as no reaction products were formed.

Preparation of 2,4-Pentanedione-2-^{13}C (145). For ^{13}C NMR labeling studies, 2,4-Pentanedione-2-^{13}C (145) was prepared using several known techniques.[69] First, acetic acid-1-^{13}C was prepared from the Grignard reaction of 65 mL of a 3.2 M methyl magnesium bromide solution (208 mmoles) with ^{13}C

labeled carbon dioxide that had been generated from 20.3 g (102 mmoles) of ^{13}C labeled barium carbonate. The acetic acid-1-^{13}C reaction product was titrated with 2M NaOH to generate 5.2 g of sodium acetate-1-^{13}C (61% yield). Bis(acetic-1-^{13}C) anhydride was prepared from 23.4 g (282 mmoles) of sodium acetate-1-^{13}C and 100 g (525 mmoles) of p-toluenesulfonyl chloride using Mandel's procedure.[69] This procedure afforded 7.37 g of bis(acetic-1-^{13}C) anhydride (25.1% yield).

2,4-Pentanedione-2-^{13}C was obtained by treating a mixture of bis(acetic-1-^{13}C) anhydride (7.37 g, 708 mmoles) and acetic anhydride (5.06 g, 49.6 mmoles)[76] with acetone (2.79 g, 48.1 mmoles) and gaseous boron trifluoride. The above mixture was steam distilled, and the distillation fractions were treated with cupric acetate to precipitate the copper salt of the β-diketone. The β-diketone that was recovered after acidification was distilled to yield 3.07 g (63.4% yield) of 2,4-pentanedione-2-^{13}C (145) with 50% label incorporation.

The 3.07 g of the 2,4-pentanedione generated above (30.5 mmoles) were treated with 0.36 L of a 0.25 M TFD solution (91 mmoles) and 2.4 mL of $HBF_4 \cdot OEt_2$ (21 mmoles) using the previously described procedure. This procedure afforded 0.869 g of acetophenone 146 (23.1%), 0.096 g of aromatic compound 147 (3.1%), 0.137 g of naphthalene 148 (3.8%), 0.077 g of cyclic ketone 149 (1.8%), and 0.217 g insertion diketone 150 (3.9%).

Products Obtained from Treatment of 2,4-Pentanedione with TFD (137-143). Products 137-141 were prepared as previously described and were isolated by flash chromatography after the MeOH-H_2O-HBF_4 hydrolysis. Spectroscopic data for each compound are reported below.

For 1-[2,6-dimethyl-4-(2,2,2-trifluoroethoxy)phenyl]-ethanone (137): ^{1}H NMR δ 6.61 (s, 2H), 4.33 (q, 2H, J = 8 Hz), 2.47 (s, 3H), 2.26 (s, 6H); ^{13}C NMR δ 207.62, 157.16 (s), 137.25 (s), 134.85 (s, 2C), 123.32 (CF_3, J = 275 Hz), 114.18(d, 2C), 65.74 ($\underline{C}H_2CF_3$, J = 35 Hz), 32.31 (q), 19.52 (q); ^{13}C NMR of labeled compound 146 δ 207.62, 157.16, 134.85 enhanced; EI/MS, ^{m}/e 246 (M^+, 92%), 203 (M^+ - C_2H_3O, 100).

For 3,5-dimethyl-1-(2,2,2-trifluoroethoxy)benzene (138): ^{1}H NMR δ 6.70 (s, 1H), 6.58 (s, 2H), 4.32 (q, 2H, J = 8 Hz), 2.31 (s, 6H); ^{13}C NMR δ 157.51 (s), 139.64 (s, 2C), 124.23 (d), 123.47 (CF_3, J = 275 Hz), 112.66 (d, 2C), 65.83 ($\underline{C}H_2CF_3$, J = 35 Hz), 21.39 (q); ^{13}C NMR of labeled compound 147 δ 157.51, 139.64 enhanced; EI/MS, ^{m}/e 204 (M^+, 100%), 189 (M^+ - CH_3, 21), 121 (M^+ - CH_2CF_3, 32).

For 1,6-bis(2,2,2-trifluoroethoxy)-3,8-dimethylnaphthalene (139): ^{1}H NMR δ 7.13 (s, 1H), 6.89 (d, 1H, $^4J_{HCCCH}$ = 2 Hz), 6.82 (d, 1H, $^4J_{HCCCH}$ = 2 Hz), 6.43 (s, 1H), 4.40 (q, 2H, J = 8 Hz), 4.39 (q, 2H, J = 8 Hz), 2.80 (s, 3H), 2.42 (s, 3H); ^{13}C NMR δ 155.30 (s), 123.48 ($2CF_3$, J = 278 Hz), 119.75 (d), 119.38 (s), 107.10 (d), 105.46 (d), 65.85 ($\underline{C}H_2CF_3$, J = 36 Hz), 65.61 ($\underline{C}H_2CF_3$, J = 36 Hz), 24.63 (q), 21.63 (q); ^{13}C NMR

of labeled compound 148 δ 155.30 (2C), 137.92, 137.56, 136.15 enhanced; EI/MS, $^{m}/e$ 352 (M^+, 64%), 260 ($M^+ - CH_2CF_3$, 32) UV/vis (hexane), λ_{max} (log ε), 322 nm (3.19), 280 nm (3.72), 231 nm (5.84).

For 2,5-bis(2,2,2-trifluoroethyl)-4,9-dimethyl-5,9-methano-6,8,10-trihydrobenzo-7-cyclooctaneone (140): ^1H NMR δ 6.61 (d, 1H, $^4J_{HCCCH}$ = 2 Hz), 6.43 (d, 1H, $^4J_{HCCCH}$ = 2 Hz), 4.28 (q, 2H, J = 8 Hz), 3.93-3.52 (m, CH_2CF_3, 2H), 2.99-1.98 (8d, 8H), 2.48 (s, 3H), 1.27 (s, 3H); ^{13}C NMR δ 206.47, 156.57 (s), 139.01 (s), 137.83 (s), 127.89 (d), 124.03 (CF_3, J = 278 Hz), 123.27 (CF_3, J = 278 Hz), 117.84 (d), 112.78 (d), 80.27 (s), 65.58 ($\underline{C}H_2CF_3$, J = 36 Hz), 60.82 ($\underline{C}H_2CF_3$, J = 36 Hz), 53.14 (t), 52.87 (t), 52.87 (+), 45.20 (t), 43.43 (t), 33.35 (s), 31.25 (q), 20.57 (q); ^{13}C NMR of labeled compound 149 δ 206.47, 156.57, 139.01, 137.83, 80.27, 33.35 enhanced; EI/MS, $^{m}/e$ 410 ($M^+ - C_3H_6O$, 100).

For 3-trifluoromethyl-2,5-hexanedione (141): ^1H NMR δ 3.7-3.9 (m, $CHCF_3$, 1H), 3.7-3.9 (dd, 1H, $^3J_{HCCH}$ = 10, $^2J_{HCH}$ = -20 Hz), 2.76 (dd, 1H, $^3J_{HCCH}$ = 3, $^2J_{HCH}$ = -20 Hz), 2.43 (s, 3H), 2.21 (s, 3H); ^{13}C NMR δ 204.37, 200.51, 124.48 (CF_3, J = 281 Hz), 50.40 ($\underline{C}HCF_3$, J = 26 Hz), 39.69 (t), 31.33 (q), 29.41 (q); ^{13}C NMR of labeled compound 150 δ 204.37, 200.51 enhanced; EI/MS, $^{m}/e$ 182 (M^+, 100%), 167 ($M^+ - CH_3$, 29), 139 ($M^+ - C_2H_3O$, 23).

In some instances, a second insertion product was observed due to incomplete hydrolysis of the reaction mix-

ture. This product was assigned as 5,5-bis(2,2,2-trifluoroethoxy)-4-trifluoromethyl-2-hexanone. ^{1}H NMR δ 3.91 (q, 4H, $2CH_2CF_3$, J = 8 Hz), 3.80 (dq, 1H, $^{3}J_{HCCH}$ = 9 Hz, $^{3}J_{HCCF}$ = 9 Hz), 3.53 (dd, 1H, $^{3}J_{HCCH}$ = 9 Hz, $^{2}J_{HCH}$ = -5 Hz), 2.68 (d, 1H, $^{2}J_{HCH}$ = -5 Hz), 2.21 (s, 3H), 1.47 (s, 3H); ^{13}C NMR 202.99, 125.69 ($2CF_3$, J = 280 Hz), 123.52 (CF_3, J = 277 Hz), 102.12 (s), 59.94 ($\underline{C}H_2CF_3$, J = 36 Hz), 59.18 ($\underline{C}H_2CF_3$, J = 36 Hz), 43.35 ($CHCF_3$, J = 26 Hz), 38.71 (t), 29.80 (q), 19.32 (q).

Compounds 142 and 143 were isolated prior to the MeOH-H_2O-HBF_4 hydrolysis of the 2,4-pentanedione reaction mixture. These compounds were only observed in the LC-^{1}H NMR and the HPLC separations and have the following spectroscopic data.

For (E)-4-(2,2,2-trifluoroethoxy)-3-pentene-2-one (142): ^{1}H NMR δ 5.46 (s, 1H), 4.16 (q, 2H, J = 8 Hz), 2.33 (s, 3H), 2.18 (s, 3H); ^{13}C NMR 196.25, 169.68 (s), 122.70 (CF_3, J = 275 Hz), 100.91 (d), 64.88 (CH_2CF_3, J = 35 Hz), 32.12 (q), 18.99 (q); EI/MS, ^{m}/e 182 (M^+, 28%), 167 ($M^+ - CH_3$, 100), 83 ($CH_2CF_3^+$, 85).

For 1,3-dimethyl-5-(2,2,2-trifluoroethoxy)-2-[1-(2,2,2-trifluoroethoxy)ethenyl]benzene (143): ^{1}H NMR δ 6.61 (s, 2H), 4.47 (d, 1H, J = 3 Hz), 4.30 (q, 2H, J = 8 Hz), 4.20 (d, 1H, J = 3 Hz), 4.14 (q, 2H, J = 8 Hz), 2.26 (s, 6H); ^{13}C NMR δ 157.54 (s), 156.89 (s), 138.79 (s, 2C), 130.26 (s), 123.23 (CF_3, J = 278 Hz), 113.44 (d, 2C), 88.56 (t), 65.56 ($\underline{C}H_2CF_3$, J = Hz), 64.62 ($\underline{C}H_2CF_3$, J = 35 Hz), 19.83 (q, 2C);

EI/MS, $^{m}/e$ 328 (M^+, 61%), 313 ($M^+ - CH_3$, 21), 121 ($M^+ - CH_2CF_3$, 32).

Preparation of 3,5-Dimethyl-1-(2,2,2-trifluoroethoxy)benzene (138) and 1-[2,6-Dimethyl-4-(2,2,2-trifluoroethoxy)phenyl]ethanone (137). 3,5-Dimethyl-1-(2,2,2-trifluoroethoxy)benzene (138) was prepared by treating 7.7 g (63 mmoles) of 3,5-dimethylphenol with 0.28 L of a 0.25 M TFD solution (70 mmoles) and a catalytic amount of $HBF_4 \cdot OEt_2$ (0.90 mL, 7.9 mmoles). TFD was added to the phenol under nitrogen at 0°C with continuous stirring. The reaction mixture was gradually warmed to room temperature. After 16 h, another 55 mL of the TFD solution (14 mmoles) and 0.25 mL of $HBF_4 \cdot OEt_2$ (2.2 moles) were added to the reaction mixture at 0°C to insure total reaction. After several minutes, the reaction mixture was washed twice with 5% $NaHCO_3$ and once with water. The organic layer was dried over anhydrous $MgSO_4$ followed by removal of CH_2Cl_2. The remaining oil was vacuum distilled yielding 9.2 g of 3,5-dimethyl-1-(2,2,2-trifluoroethoxy)benzene (138) (72% yield, bp 83-89°C at 0.05 mm Hg). ^1H and ^{13}C NMR spetra were identical with those that were obtained for compound 138 in the 2,4-pentanedione cyclization.

Compound 137 was prepared[77] by dissolving 1.6 g (12 mmoles) of aluminum chloride in 20 mL of nitrobenzene. Compound 138 (2.4 g, 12 mmoles) and acetyl chloride (1.0 g, 0.013 mmoles) were respectively added to the reaction mixture at 0°C. The reaction mixture was stirred under nitrogen

for 2 h. The reaction mixture was hydrolyzed by pouring the contents of the reaction flask into ice-water and adding 5 mL of concentrated HCl to the resulting mixture. The aqueous mixture was extracted twice with ether. The ether extracts were washed twice with 5% $NaHCO_3$ and once with water. The organic layer was dried over anhydrous $MgSO_4$ and then evaporated *in vacuo*. The liquid that remained was vacuum distilled yielding 1.1 g (37% yield) of a 40/60 mixture of the symmetric and nonsymmetric acetophenone isomers. These isomers distilled at 73-76^{0}C under 0.025 mm Hg and were further separated using column chromatography on silica gel. Compound 137 was isolated utilizing a gradient elution with pentane and CH_2Cl_2. This process afforded 0.36 g of 1-[2,6-dimethyl-4-(2,2,2-trifluoroethoxy)phenyl]ethanone (137). Eluting prior to the symmetric acetophenone was 1-[4,6-dimethyl-2-(2,2,2-trifluoroethoxy)phenyl]ethanone (144). Compound 137 had ^{1}H and ^{13}C NMR spectra that were identical to those obtained for compound 137 in the 2,4-pentanedione cyclization.

For 1-[4,6-dimethyl-2-(2,2,2-trifluoroethoxy)phenyl]-ethanone (144): ^{1}H NMR δ 6.75 (s, 1H), 6.53 (s, 1H), 4.37 (q, 2H, J = 8 Hz), 2.50 (s, 3H), 2.33 (s, 3H), 2.24 (s, 3H); ^{13}C NMR δ 204.73, 154.07 (s), 140.58 (s), 136.61 (s), 125.74 (d), 123.21 (CF_3, J = 278 Hz), 111.55 (s), 110.33 (d), 66.06 ($\underline{C}H_2CF_3$, J = 35 Hz), 32.19 (q), 21.50 (q), 19.23 (q).

Preparation of 142 and (Z)-4-(2,2,2-trifluoroethoxy)-3-penten-2-

one (152). A mixture of the E- and Z-trifluoroethyl enol ethers 142 and 152 were prepared by adding 0.40 L of 0.32 M TFD solution (0.13 mole) to the reaction apparatus that was described above. The reaction flask was cooled to -89°C with an iso-propyl alcohol-liquid nitrogen bath. A solution of 16.0 g of 2,4-pentanedione (0.16 mole) and 2.0 ml of $HBF_4 \cdot OEt_2$ (18 mmoles) was slowly added to the TFD solution. After 1.5 h of stirring at this temperature, the temperature bath was removed and the reaction mixture was immediately washed with 5% $NaHCO_3$. The mixture was washed with a second portion of 5% $NaHCO_3$ and with a single portion of H_2O. The organic layer was dried with anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. The resulting liquid was vacuum distilled at 33-36°C (0.30 mm Hg). The product was dissolved in CH_2Cl_2 and was washed with two portions of 5% NaOH and one portion of H_2O to remove remaining traces of 2,4-pentanedione. The organic layer was dried and evaporated *in vacuo* as described above. This afforded 5.31 g of enol ethers 142 and 152 in 18% yield (2:1 ratio, respectively). For (Z)-4-(2,2,2-trifluoroethoxy)-3-penten-2-one (152): ^1H NMR δ 5.29 (s, 1H), 4.42 (q, 2H, J = 8 Hz), 2.33 (s, 3H), 2.08 (s, 3H); ^{13}C NMR δ 197.01, 162.79 (s), 122.67 (CF_3, J = 275 Hz), 110.93 (d), 65.90 ($\underline{C}H_2CF_3$, J = 35 Hz), 31.22 (q), 19.36 (q).

The enol ether mixture prepared above (0.64 g, 3.5 mmoles) was treated with 40 mL of a 0.30 M TFD solution (12 mmoles) and 0.15 mL of $HBF_4 \cdot OEt_2$ (1.3 mmoles) at 0°C. The TFD

solution was added to the reaction flask over 1 h, and the reaction mixture was stirred for another 0.5 h before neutralization. The reaction mixture was neutralized by washing the organic layer with 2 portions of 5% $NaHCO_3$ and with a single portion of water. The organic layer was dried with anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. The resulting oil contained a mixture of products analogous to those obtained directly from 2,4-pentanedione as monitored by ^1H NMR spectroscopy.

Products Obtained from Treatment of 1-Phenyl-1,3-butanedione with TFD (155-157). Products 155-157 were prepared by treating 4.49 g (28 mmoles) of 1-phenyl-1,3-butanedione with 0.31 L of a 0.23 M TFD solution (69 mmoles) and 0.75 mL of $HBF_4 \cdot OEt_2$ (6.6 mmoles) using the general procedure that was previously described. The hydrolyzed reaction mixture was neutralized with 5% NaOH instead of 5% $NaHCO_3$.

This procedure afforded 2.31 g of cyclohexenone 157 (29.3% yield), 1.32 g of insertion ketone 156 (15.3%), and 0.428 g of biphenyl 155 (11.6%). It was determined from an independent study that 30.6% of the starting 1-phenyl-1,3-butanedione was recovered from similar reaction mixtures. This independent study was initiated since 5% NaOH had extracted the starting β-diketone from the previously described procedure. Spectroscopic data for each compound is reported below.

For 5-methyl-3-(2,2,2-trifluoroethoxy)biphenyl (155):

^{1}H NMR δ 7.58-7.63 (m, 2H), 7.36-7.52 (m, 3H), 7.14 (s, 1H), 7.01 (s, 1H), 6.80 (s, 1H), 4.43 (q, 2H, J = 8 Hz), 2.44 (s, 3H); ^{13}C NMR δ 157.84 (s), 142.98 (s), 140.70 (s), 140.20 (s), 128.75 (d, 2C), 127.61 (d), 127.16 (d, 2C), 123.43 (CF_3, J = 278 Hz), 122.36 (d), 114.51 (d), 110.97 (d), 65.99 ($\underline{C}H_2CF_3$, J = 38 Hz), 21.59 (q); ^{13}C NMR of labeled compound 162 δ 142.98 enhanced; EI/MS, ^{m}/e 266 (M^+, 100%).

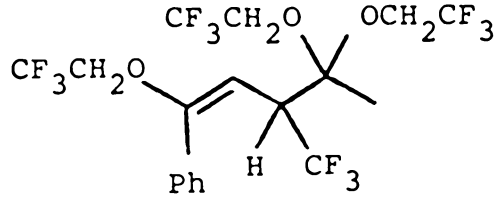
For (E)-5-phenyl-5-(2,2,2-trifluoroethoxy)-3-trifluoromethyl-4-penten-2-one (156): ^{1}H NMR δ 7.44 (broad, 5H), 5.28 (d, 1H, J = 10 Hz), 4.62 (m, $CHCF_3$, 1H, J = 10 Hz, $^3J_{HCCF}$ = 9 Hz), 3.9-4.2 (m, CH_2CF_3, 2H), 2.35 (s, 3H); ^{13}C NMR δ 199.23, 158.23 (q), 132.36 (s), 130.08 (d), 129.03 (d, 2C), 127.22 (d, 2C), 102.75 (d), 66.55 ($\underline{C}H_2CF_3$, J = 26 Hz), 53.15 ($CHCF_3$, J = 26 Hz), 29.81 (q); ^{13}C NMR of labeled compound 163 δ 158.23 enhanced; EI/MS, ^{m}/e, 326 (M^+, 9%), 283 ($M^+ - C_2H_3O$, 100), 77 ($C_6H_5^+$, 38).

For 4-[bis-(2,2,2-trifluoroethoxy)phenylmethyl]-5-methyl-3-phenyl-5-(2,2,2-trifluoroethoxy)-1-cyclohexenone (157): ^{1}H NMR δ 8.0-6.9 (broad, 10H), 6.39 (s, 1H), 4.6-2.9 ($3CH_2CF_2$, 6H), 3.97 (s, 1H), 2.01 (d, 1H, J = 18 Hz), 1.47 (s, 3H), 1.13 (d, 1H, J = 18 Hz); ^{13}C NMR δ 195.59, 157.28 (s), 141.34 (s), 134.39 (s), 130.01 (d), 129.48 (d,2C),[78] 128.78 (d, 2C), 125.39 (d, 2C), 123.79 ($2CF_3$, J = 278 Hz), 123.09 (CF_3, J = 278 Hz), 104.55 (s), 78.15 (s), 60.10 ($\underline{C}H_2CF_3$, J = 35 Hz), 59.81 ($\underline{C}H_2CF_3$, J = 35 Hz), 58.76 ($\underline{C}H_2CF_3$, J = 35 Hz), 52.80 (d), 42.18 (t), 25.71 (q); ^{13}C NMR of labeled compound

164 δ 157.28, 104.55 enhanced; IR (KBr) 1685 cm^{-1}; EI/MS, m/e 287 ($C_{11}H_9F_6^+$, 100%); mp 160-161° (uncorrected); Anal. Calcd for $C_{26}H_{23}O_3F_9$: C, 54.75; H, 4.06. Found C, 54.89; H, 4.39.

In some instances, two other insertion products have also been isolated after hydrolysis. 1-Phenyl-3-trifluoromethyl-1,4-pentanedione (160) was isolated and afforded the following spectroscopic data: ^1H NMR δ 7.96 (d, 2H, J = 7 Hz), 7.3-7.7 (m, 3H), 3.8-4.1 (m, 1H + $CHCF_3$, 2H), 3.32 (d, 1H, $^2J_{HCH}$ = -16 Hz), 2.53 (s, 3H); 244 (M^+, 1%), 105 ($C_7H_7O^+$, 100).

1-Phenyl-3-trifluoromethyl-1,4,4-tris(2,2,2-trifluoroethoxy)-1-pentene (173) was also isolated and had the following spectroscopic data: ^1H NMR δ 7.3-7.5 (broad 5H), 5.06 (d, 1H, J = 11 Hz), 3.8-4.1 ($3CH_2CF_3$ + $CHCF_3$, 7H), 1.56 (s, 3H); ^{13}C NMR δ 158.23 (s), 143.63 (s), 130.03 (d), 129.03 (d, 2C), 127.34 (d, 2C), 124.80 (CF_3, J = 278 Hz), 123.75 (CF_3, J = 278 Hz), 123.63 (CF_3, J = 278 Hz), 123.22 (CF_3, J = 278 Hz), 103.34 (d), 101.88 (s), 66.72 ($\underline{C}H_2CF_3$, J = 35 Hz), 59.71 ($\underline{C}H_2CF_3$, J = 35 Hz), 59.19 ($\underline{C}H_2CF_3$, J = 35 Hz), 46.31 ($\underline{C}HCF_3$, J = 26 Hz), 19.36 (q); EI/MS, m/e 409 (M^+ - OCH_2CF_3, 4%), 225 ($C_6H_7F_6O_2^+$, 100).



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The 1-phenyl-1,3-butanedione mixture that was separated with the LC-^{1}H NMR apparatus was prepared by treating 1.6 g (9.7 mmoles) of phenyl-1,3-butanedione with 0.11 L of a 0.25 M TFD solution (28 mmoles) and 0.35 mL of $HBF_4 \cdot OEt_2$ (3.1 mmoles) as described for 2,4-pentanedione. The organic mixture was neutralized before hydrolysis with 5% NaOH instead of 5% $NaHCO_3$ which was used for the 2,4-pentanedione reaction mixture.

Other compounds isolated by the above technique appeared in trace amounts. Chemical shifts in the LC-^{1}H NMR profile that were assigned to methyl benzoate were identical to the chemical shifts of the pure compound (Fisher).

Preparation of 1-Phenyl-1,3-butanedione-1-^{13}C (161). Several known procedures were adapted to prepare the target molecule.[72] Benzoic-^{13}C acid (mp 114-115°C, uncorrected) was prepared from the Grignard reaction of PhMgBr (generated from bromobenzene and Mg metal) with labeled carbon dioxide that was generated from 90% ^{13}C enriched barium carbonate (21.8 g, 110 mmoles). The PhMgBr utilized in this experiment was generated from 3.4 g (140 mmoles) of magnesium metal and 20.3 g (129 mmoles) of bromobenzene. This procedure afforded 6.40 g of benzoic-^{13}C acid (47.3% yield).

When 5.74 g (46.5 mmoles) of benzoic-^{13}C acid was treated with 23.8 g (200 mmoles) of thionyl chloride and 0.234 g (0.922 mmoles) of iodine, 4.43 g of benzoyl-^{13}C chloride was formed (67.3% yield). Benzoyl-^{13}C chloride (4.43 g, 31.3

mmoles) was added to 4.03 g of methanol (126 mmoles) and 4.50 g of 1,4-diazabicyclo[2.2.2]octane (DABCO, 40.1 mmoles) to generated 4.25 g of methyl benzoate-^{13}C (100% yield). Methyl benzoate-^{13}C (2.57 g, 20.1 mmoles) was treated with 2.06 g (42.9 mmoles) of sodium hydride (50% solution in dispersion oil) and 2.36 g (40.6 mmoles) of acetone in dry ether to generate 0.523 g of 1-phenyl-1,3-butanedione-1-^{13}C (161, isolated in 16.1% yield).

Diethyl ether that was used in the Grignard reaction and in the condensation reaction of acetone with methyl benzoate-^{13}C was dried and distilled from $LiAlH_4$. Acetone was distilled from phosphorus pentoxide and stored over $CaSO_4$ prior to use. Both benzoyl-^{13}C chloride (bp 69°C using a water aspirator) and methyl benzoate-^{13}C (bp 26-30°C at 0.20 mm Hg) were vacuum distilled prior to their usage in the above experiments. 1-Phenyl-1,3-butanedione-1-^{13}C was vacuum distilled at 95°C under 1.2 mm Hg. The 1-phenyl-1,3-butanedione-1-^{13}C was also recrystallized from ethanol-water and dried prior to treatment with TFD.

Spectroscopic data for the above ^{13}C labeled compounds are reported below. For benzoyl-^{13}C chloride: ^{1}H NMR δ 8.14 (dd, 2H, $^3J_{HCCH}$ = 8 Hz, $^2J_{CCH}$ = 8 Hz), 7.70 (t, 1H, J = 8 Hz), 7.53 (dd, 2H, $^3J_{HCCH}$ = 8 Hz, $^3J_{HCCH}$ = 8 Hz); ^{13}C NMR δ 168.39 enhanced.

For methyl benzoate-^{13}C: ^{1}H NMR δ 8.0-8.2 (m, 2H), 7.3-7.6 (m, 3H), 3.93 (d, 3H, $^3J_{COCH}$ = 4 Hz).

For 1-phenyl-1,3-butanedione (161): ^{1}H NMR δ 7.8-8.0 (m, 2H), 7.3-7.6 (m, 3H), 6.19 (d, 1H, $^{2}J_{CCH}$ = 4 Hz), 2.22 (3H, s); ^{13}C NMR δ 183.29 enhanced.

1-Phenyl-1,3-butanedione-1-^{13}C [161, 0.523 g (3.23 mmoles)] was diluted to 3.02 g with unlabeled 1-phenyl-1,3-butanedione.[79] The combined β-diketones (18.6 mmoles) were dissolved in 15 mL of CH_2Cl_2 and were treated with 0.18 L of a 0.26 M TFD solution (47 mmoles) and 0.45 mL of $HBF_4 \cdot OEt_2$ (3.9 mmoles) as described for the preparation of compounds 155-157. The mixture of reaction products was hydrolyzed utilizing the previously described hydrolysis conditions. The resulting mixture was neutralized with the 5% $NaHCO_3$ washing procedure. This procedure afforded 1.60 g of cyclohexenone 164 (30.1% yield), 0.987 g of insertion ketone 163 (17.0%), and 0.409 g of biphenyl 162 (16.5%). Starting material (0.813 g, 26.9%) was also recovered from the reaction mixture.

Preparation of 3,5-bis(2,2,2-trifluoroethoxy)-6-[bis(2,2,2-trifluoroethoxy)phenylmethyl]-5-methyl-1-phenyl-1,3-cyclohexadiene (165): Dienol ether 165 was prepared by the following procedure. First, 1.5 g of 1-phenyl-1,3-butanedione (9.3 mmoles) was treated with 0.10 L of a 0.28 M TFD solution (28 mmoles) and 0.45 mL of $HBF_4 \cdot OEt_2$ (3.9 mmoles) as previously described. To enhance the amount of dienol ether 165 in the mixture, the TFD solution was added over 19 min and the resulting mixture was stirred for another 5 min. Next, 1.8

mL of triethylamine was added to the mixture. The mixture was then washed twice with 5% $NaHCO_3$ and once with water. The organic layer was dried and evaporated to an oil.

The resulting oil was not hydrolyzed with the methanol-water-HBF_4 mixture, but was directly separated by chromatography on neutral alumina. A gradient elution with petroleum ether and methylene chloride was used in the separation of dienol ether 165 from the other reaction products. Dienol ether 165 eluted in the early nonpolar fractions and was recrystallized from pentane and CH_2Cl_2. Dienol 165 (0.256 g) was isolated in 8.5% yield.

For 3,5-bis(2,2,2-trifluoroethoxy)-6-[bis(2,2,2-trifluoroethoxy)phenylmethyl]-5-methyl-1-phenyl-1,3-cyclohexadiene (165): ^1H NMR δ 7.1-7.6 (broad, 10H), 6.10 (s, 1H), 2.8-4.5 (m, $4CH_2CF_3$, 8H), 3.83 (s, 1H), 3.57 (s, 1H), 1.45 (s, 3H); ^{13}C NMR δ 151.31 (s), 141.24 (s), 140.68 (s), 136.13 (s), 128.52 (d, 5C),[80] 127.92 (d), 127.32 (d, 2C), 125.62 (d, 2C), 124.11 (CF_3, J = 281 Hz), 123.79 (CF_3, J = 277 Hz), 123.49 (CF_3, J = 277 Hz), 123.01 (CF_3, J = 277 Hz), 122.78 (d), 104.20 (d), 96.73 (d), 80.22 (s), 64.22 ($\underline{C}H_2CF_3$, J = 36 Hz), 60.78 ($\underline{C}H_2CF_3$, J = 35 Hz), 59.95 ($\underline{C}H_2CF_3$), 59.39 ($\underline{C}H_2CF_3$), 52.28 (d), 24.19 (q); EI/MS, $^m/e$ 652 (M^+, 1%), ($C_{11}H_9F_6O_2^+$, 100%), mp 164-165°C (uncorrected).

Preparation of 5-Methyl-3-(2,2,2-trifluoroethoxy)biphenyl (155). Dienol ether 165 (0.0665 g, 0.10 mmoles) was treated with 0.40 mL of $HBF_4 \cdot OEt_2$ (3.5 mmoles) and 30 mL of CH_2Cl_2 under

nitrogen at 0°C. The mixture stirred for 2.5 h and was quenched with 0.40 mL of triethylamine. The solution was washed twice with 5% $NaHCO_3$ and once with water. After drying and evaporating the organic layer, ^1H and ^{13}C NMR data showed that 5-methyl-3-(2,2,2-trifluoroethoxy)biphenyl (155) was formed as well as several unidentified products.

Preparation of (5-Hydroxy-3-methyl[1,1'-biphenyl]-2-yl)phenylmethanone (166). (5-Hydroxy-3-methyl[1,1'-biphenyl]-2-yl)-phenylmethanone (166) was prepared by treating 0.056 g of dienol ether 165 with 0.053 g of p-toluenesulfonic acid monohydrate (0.28 mmole) and 30 mL of benzene. The mixture was refluxed 2.5 h and gave a brown solution at the end of the refluxing period. Triethylamine (0.30 mL) was added to the reaction mixture resulting in a red solution. The organic mixture was washed twice with 5% $NaHCO_3$ and twice with water. After drying and reducing the organic layer, ^1H and ^{13}C NMR data indicated that biphenyl (166) was the reaction product.

Biphenyl 166 can also be prepared from cyclohexenone 157. Cyclohexenone 157 (0.068 g, 0.12 mmole) was treated with p-toluenesulfonic acid monohydrate (0.043 g, 0.23 mmole). The mixture was stirred and refluxed for 3.5 h under nitrogen. A dark brown mixture resulted which was washed twice with 5% NaHCO and once with water. The organic layer became peach-colored when neutralized. After drying and evaporation of the organic layer, ^1H and ^{13}C NMR results indicated that biphenyl 166 was the only reaction product. For biphe-

nyl 166: ^{1}H NMR δ 7.65-7.69 (m, 2H), 7.10-7.52 (m, 8H), 6.83-6.85 (m, 2H), 5.55 (broad, 1H), 2.31 (s, 3H); ^{13}C NMR δ 199.99, 155.84 (s), 142.23 (s), 140.07 (s), 138.08 (s), 137.79 (s), 132.83 (s), 129.32 (d, 2C), 128.97 (d, 2C), 128.27 (d), 128.16 (d, 2C), 127.98 (d, 2C), 127.28 (d), 116.19 (d), 114.14 (d), 19.98 (q); EI/MS, $^{m}/e$ 288 (M^{+}, 87), 287 (M^{+} - H, 100), 211 (M^{+} - C_6H_5, 50), 105 ($C_7H_5O^{+}$, 10).

Preparation of Cyclohexanone 157. Dienol ether 165 (0.089 g) was treated with 10 mL of methanol, 3 mL of water, and 2 mL of HBF_4. The mixture was refluxed with stirring for 6.5 h followed by treatment with water and methylene chloride. The organic layer was washed twice with 5% $NaHCO_3$ and once with water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. The ^{1}H and ^{13}C NMR spectra of the resulting product showed complete hydrolysis to cyclohexenone 157.

Preparation of Substituted Derivatives of 1-Phenyl-1,3-butanedione. The p-fluoro, p-methyl, p-methoxy, and o-methyl derivative of 1-phenyl-1,3-butanedione were prepared by utilizing known procedures.[72,73] The p-fluoro and p-methyl derivatives were prepared by the condensation reaction of acetone and the appropriate aromatic esters in the presence of NaH. The o-methyl and p-methoxy derivatives was prepared by the condensation reaction of ethyl acetate with the appropriate acetophenones in the presence of NaH. The o-methyl derivative was purified by two vacuum distillations of the β-dike-

tone. The pure β-diketone distilled at 90-93°C under 0.7 mm Hg. The p-methoxy derivative was recrystallized from pentane and methylene chloride. This β-diketone was dried in a vacuum dessicator overnight to remove residual water. Both the p-methyl and the p-fluoro derivatives were precipitated as copper complexes by treatment with cupric acetate. Each β-diketone was regenerated using 20% H_2SO_4 and was extracted into ether. After removal of the ether, the two β-diketones were vacuum distilled. The p-methyl derivative distilled at 93-96°C under 0.40 mm of Hg pressure. The product crystallized at room temperature after distillation. The p-fluoro derivative distilled at 80-95°C under 0.60 mm Hg.

All aromatic precursors were available from Aldrich except methyl p-fluorobenzoate. Methyl p-fluorobenzoate was prepared by slowly adding 8.3 g of p-fluorobenzoyl chloride (52 mmoles) to 5.9 g of DABCO (53 mmoles) and 5.0 g of methanol (0.16 mole) under nitrogen. The acid chloride was added over 1 h, and the reaction mixture was stirred for an additional 1/2 h after the acid chloride was added. Water and CH_2Cl_2 were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted again with CH_2Cl_2, and the organic layers were combined. The organic layer was washed once with 5% $NaHCO_3$, washed once with water, dried over anhydrous $MgSO_4$, and evaporated <u>in vacuo</u>. Methyl p-fluorobenzoate distilled at 44-45°C under 0.85 mm Hg yielding 7.19 g of product (47 mmoles, 90%).

The substituted β-diketones were treated with TFD and $HBF_4 \cdot OEt_4$ using the 2,4-pentanedione reaction procedure. 1-(4-Fluorophenyl)-1,3-butanedione (2.58 g, 14.3 mmoles) was treated with 170 mL of a 0.253 M TFD solution (43.0 mmoles) and 1.45 mL of $HBF_4 \cdot OEt_2$ (12.7 mmoles) to prepare the p-fluoro substituted reaction products. The p-methyl reaction products were obtained by treatment of 2.50 g (14.2 mmoles) of 1-(4-methylphenyl)-1,3-butanedione with 170 mL of a 0.266 M TFD solution (45.2 mmoles) and 0.95 mL of $HBF_4 \cdot OEt_2$ (8.32 mmoles). The p-methoxy substituted reaction products were prepared by treating 3.84 g (20.0 mmoles) of 1-(4-methoxyphenyl)-1,3-butanedione with 295 mL of a 0.215 M TFD solution (63.4 mole) and 1.60 mL of $HBF_4 \cdot OEt_2$ (14.0 mmoles). The steric effects of the cyclization reaction were examined by treating 3.57 g (20.3 mmoles) of 1-(2-methylphenyl)-1,3-butanedione with 420 mL of a 0.190 M TFD solution (79.8 mmoles) and 1.25 mL of $HBF_4 \cdot OEt_2$ (11.0 mmoles).

All spectroscopic data which was obtained for the substituted reaction mixtures after chromatographic separation showed little variation from the data presented for the 1-phenyl-1,3-butanedione reaction products. The o-methyl substituted β-diketone did yield compound 167 which did not correspond with any previously assigned structure. The compound was isolated as a dark red oil which would not crystallize after further chromatographic attempts. Treatment of the compound with 2,4-dinitrophenylhydrazine did not yield a

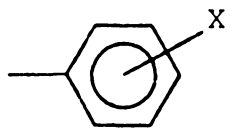
crystalline solid. Spectroscopic data for 167: ^{1}H NMR δ 8.11 (broad, 1H), 7.1-7.6 (aromatics + CH, 9H), 6.07 (s, 1H), 5.94 (s, 1H), 2.49 (s, 3H), 2.44 (s, 3H), 2.21 (s, 3H); ^{13}C NMR δ 192.99, 166.58 (s), 158.73 (s), 147.64 (s), 143.28 (s), 136.65 (s), 135.78 (s), 132.35 (s), 131.27 (d), 130.93 (d), 130.18 (d), 129.06 (d), 128.87 (d), 127.19 (d), 126.12 (d), 125.38 (d), 115.85 (d), 109.79 (d), 97.14 (d), 21.81 (q), 20.69 (q), 20.22 (q); EI/MS, ^{m}/e 316 (M^{+}, 56%), 119 ($C_8H_7O^{+}$, 100), 91 ($C_7H_7^{+}$, 79). See Figure 2.3 for structures of other compounds isolated in this study. See Table 2.4 for yield data obtained in this study.

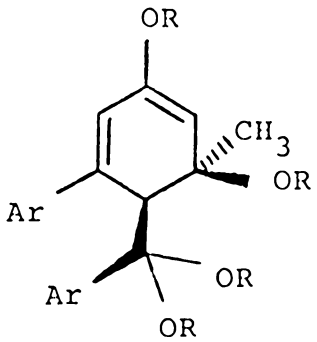
Reaction Products Obtained from 1-(4-Fluorophenyl)-1,3-butanedione. Spectroscopic data for the reaction products that were obtained from 1-(4-fluorophenyl)-1,3-butanedione are reported below.

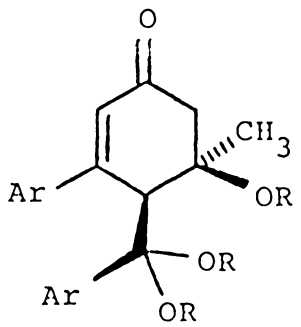
For 3,5-bis(2,2,2-trifluoroethoxy)-6-[bis(2,2,2-trifluoroethoxy)(4-fluorophenyl)methyl]-5-methyl-1,3-cyclohexadiene (168): ^{1}H NMR δ 7.44 (dd, 2H, J = 9 Hz, $^{4}J_{HCCF}$ = 5 Hz), 6.92-7.15 (broad, 6H), 6.07 (s, 1H), 3.1-4.4 ($4CH_2CF_3$, 8H), 3.90 (s, 1H), 3.50 (s, 1H), 1.45 (s, 3H); ^{13}C NMR δ 163.18 (s, J = 248 Hz), 162.73 (s, J = 248 Hz), 151.15 (s), 139.59 (s), 137.21 (s), 131.61 (s), 130.41 (d, 2C, broad), 127.17 (d, 2C, J = 8 Hz), 123.87 ($2CF_3$, J = 278 Hz), 123.34 (CF_3, J = 277 Hz), 122.80 (CF_3, J = 278 Hz), 122.63 (d), 115.47 (d, 2C, J = 22 Hz), 114.23 (d, 2C, J = 21 Hz), 103.80 (s), 96.09 (d), 80.06 (s), 64.19 ($\underline{C}H_2CF_3$, J = 36 Hz), 60.67 ($\underline{C}H_2CF_3$, J = 36 Hz),

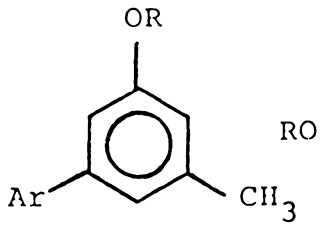
Figure 2.3

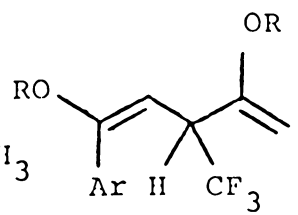
Products obtained from reactions of substituted derivatives of 1-phenyl-1,3-butanedione with TFD.

Ar = 



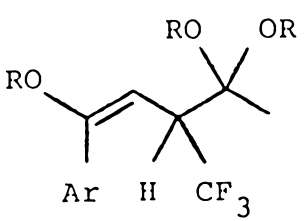


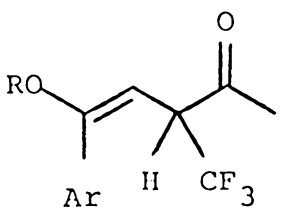


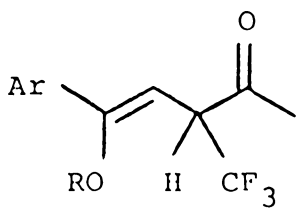


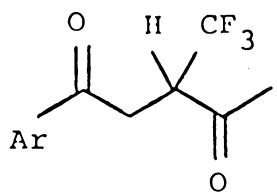
x				
p-fluoro	168	169	174	175
p-methyl	x	170	178	179
p-methoxy	x	x	182	x
o-methyl	x	x	x	188

R = CH_2CF_3









p-fluoro	176	177	x	x
p-methyl	180	181	x	x
p-methoxy	183	184	x	185
o-methyl	189	190	191	192

59.95 ($\underline{C}H_2CF_3$, J = 37 Hz), 58.58 ($\underline{C}H_2CF_3$, J = 34 Hz), 52.29 (d), 24.15 (q).

For 4-[bis(2,2,2-trifluoroethoxy)(4-fluorophenyl)-methyl]-3-(4-fluorophenyl)-5-methyl-5-(2,2,2-trifluoroethoxy)-2-cyclohexen-1-one (169): ^{1}H NMR δ 7.7-8.0 (broad, 2H), 7.50 (dd, 2H, J = 8 Hz, $^4J_{HCCCF}$ = 8 Hz), 7.17 (dd, 2H, J = 8 Hz, $^3J_{HCCF}$ = 8 Hz), 6.9-7.3 (broad, 2H), 6.34 (s, 1H), 3.1-4.5 (6H, $3CH_2CF_3$), 3.88 (s, 1H), 2.09 (d, 1H, J = 18 Hz), 1.45 (s, 3H), 1.25 (d, 1H, J = 18 Hz); ^{13}C NMR[81] δ 194.99, 163.70 (s, 2C, J = 251 Hz), 155.98 (s), 137.36 (s), 131.00-131.98 (broad, d, 2C), 130.42 (s), 129.44 (d), 127.33 (d, 2C, J = 8 Hz), 123.72 (2 CF_3, J = 277 Hz), 123.12 (CF_3, J = 277 Hz), 116.01 (d, 2C, J = 22 Hz), 104.45 (s), 78.21 (s), 60.23 ($\underline{C}H_2CF_3$, J = 35 Hz), 59.97 ($\underline{C}H_2CF_3$, J = 36 Hz), 58.83 ($\underline{C}H_2CF_3$, J = 36 Hz), 53.12 (d), 42.31 (t), 25.76 (q).

For 4'-fluoro-5-methyl-3-(2,2,2-trifluoroethoxy)biphenyl (174): ^{1}H NMR δ 7.51 (dd, 2H, J = 8 Hz, $^4J_{HCCCF}$ = 6 Hz), 7.10 (dd, 2H, J = 8 Hz, J_{HCCF} = 8 Hz), 7.04 (s, 1H), 6.91 (s, 1H), 6.74 (s, 1H), 4.38 (q, 2H, J = 8 Hz), 2.39 (s, 3H); ^{13}C NMR δ 162.69 (s, J = 246 Hz), 157.96 (s), 142.01 (s), 140.32 (s), 136.85 (s), 128.73 (d, 2C, J = 8 Hz), 123.27 (CF_3, J = 277 Hz), 122.29 (d), 115.63 (d, 2C, J = 22 Hz), 114.49 (d), 111.14 (d), 66.12 ($\underline{C}H_2CF_3$, J = 36 Hz), 21.54 (q).

For (Z)-1,4-bis(2,2,2-trifluoroethoxy)-1-(4-fluorophenyl)-3-trifluoromethyl-1,4-pentadiene (175): ^{1}H NMR δ 7.43 (dd, 2H, J = 8 Hz, $^4J_{HCCCF}$ = 4 Hz), 7.12 (dd, 2H, J = 8

Hz, $^{3}J_{HCCF}$ = 8 Hz), 5.36 (d, 1H, J = 10 Hz), 4.43 (d, 1H, J = 4 Hz), 4.22 (d, 1H, J = 4 Hz), 3.9-4.4 ($2CH_2CF_3$ + $1CHCF_3$, 5 H); ^{13}C NMR[82] δ 163.62 (s, J = 250 Hz), 155.85 (s), 155.44 (s), 129.12 (d, 2C, J = 8 Hz), 124.91 (CF_3, J = 281 Hz), 123.25 (CF_3, J = 279 Hz), 123.04 (CF_3, J = 277 Hz), 116.09 (d, 2C, J = 22 Hz), 105.36 (d), 88.14 (t), 66.67 ($\underline{C}H_2CF_3$, J = 36 Hz), 65.23 ($\underline{C}H_2CF_3$, J = 37 Hz), 46.06 ($\underline{C}H_2CF_3$, J = 30 Hz); EI/MS, $^{m}/e$ 426 (M^+, 99%) 357 (M^+ - CF_3, 90), 327 (M^+ - OCH_2CF_3, 36).

For (E)-1-(4-fluorophenyl)-3-trifluoromethyl-1,4,4-tris(2,2,2-trifluoroethoxy)-3-trifluoroethoxy)-1-pentene (176): ^{1}H NMR δ 7.41 (dd, 2H, J = 8 Hz, $^{4}J_{HCCCF}$ = 6 Hz), 7.13 (dd, 2H, J = 8 Hz, $^{3}J_{HCCF}$ = 8 Hz), 5.03 (d, 1H, J = 10 Hz), 3.8-4.1 ($3CH_2CF_3$ + 1 $CHCF_3$, 7H), 1.56 (s, 3H); ^{13}C NMR δ 163.75 (s, J = 250 Hz), 157.24 (s), 129.30 (d, 2C, J = 8 Hz), 129.03 (s), 124.72 (CF_3, J = 280 Hz), 123.71 (CF_3, J = 277 Hz), 123.58 (CF_3, J = 278 Hz), 123.14 (CF_3, J = 278 Hz), 116.22 (d, 2C, J = 22 Hz), 103.56 (d), 101.83 (s), 66.69 ($\underline{C}H_2CF_3$, J = 36 Hz), 59.73 ($\underline{C}H_2CF_3$, J = 36 Hz), 59.22 ($\underline{C}H_2CF_3$, J = 35 Hz), 46.31 ($\underline{C}HCF_3$, J = 27 Hz), 19.39 (q); EI/MS, $^{m}/e$ 427 (M^+ - OCH_2CF_3, 8%), 327 (M^+ - $C_4H_5F_6O_2$, 100).

For (E)-5-(4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)-3-trifluoroethyl-4-penten-2-one (177): ^{1}H NMR δ 7.41 (dd, 2H, J = 8 Hz, $^{4}J_{HCCCF}$ = 4 Hz), 7.13 (dd, 2H, J = 8 Hz, $^{4}J_{HCCF}$ = 8 Hz), 5.28 (d, 1H, J = 10 Hz), 4.58 (m, 1H, J = 10 Hz, $^{3}J_{HCCF}$ = 9 Hz), 3.9-4.2 (m, CH_2CF_3, 2H), 2.34 (s, 3H); ^{13}C NMR δ 199.23, 163.75 (s, J = 249 Hz), 157.18 (s), 129.27 (d, 2C, J =

6 Hz), 128.57 (s), 123.95 (CF_3, J = 281 Hz), 123.22 (CF_3, J = 278 Hz), 116 (d, 2C, J = 23 Hz), 103.05 (d), 66.55 ($\underline{C}H_2CF_3$, J = 35 Hz), 52.74 ($\underline{C}HCF_3$, J = 27 Hz), 30.05 (q); EI/MS, ^{m}/e 344 (M^+, 9%), 301 ($M^+ - C_2H_3O$, 68%).

Reaction Products Obtained from 1-(4-Methylphenyl)-1,3-butanedione. Spectroscopic data for the reaction products that were obtained from 1-(4-methylphenyl)-1,3-butanedione are reported below.

For 4-[bis(2,2,2-trifluoroethoxy)(4-methylphenyl)-methyl]-5-methyl-3-(4-methylphenyl)-5-(2,2,2-trifluoroethoxy)-2-cyclohexen-1-one (170): ^{1}H NMR δ 7.6-7.8 (broad, 2H), 7.42 (d, 2H, J = 8 Hz), 7.27 (d, 2H, J = 8 Hz), 6.9-7.3 (broad, 2H), 6.35 (s, 1H), 3.1-4.5 ($3CH_2CF_3$, 6H), 3.91 (s, 1H), 2.41 (s, 3H), 2.35 (s, 3H), 1.99 (d, 1H, J = 18 Hz), 1.42 (s, 3H), 1.37 (d, 1H, J = 18 Hz); ^{13}C NMR[83] 195.78, 157.47 (s), 140.01 (s), 139.78 (s), 138.49 (s), 131.54 (s), 129.38 (d, 2C), 128.68 (d), 125.41 (d, 2C), 123.86 ($2CF_3$, J = 278 Hz), 123.22 (CF_3, J = 278 Hz), 104.62 (s), 78.23 (s), 60.09 ($\underline{C}H_2CF_3$, J = 32 Hz), 59.74 ($\underline{C}H_2CF_3$, J = 38 Hz), 58.66 ($\underline{C}H_2CH_3$, J = 35 Hz), 52.71 (d), 42.25 (t), 25.67 (q), 21.17 (q, 2C); EI/MS, ^{m}/e 301 ($M^+ - C_{12}H_{11}O_2F_6$, 100%).

For 4',5-dimethyl-3-(2,2,2-trifluoroethoxy)biphenyl (178): ^{1}H NMR δ 7.45 (d, 2H, J = 8 Hz), 7.23 (d, 2H, J = 8 Hz), 7.08 (s, 1H), 6.94 (s, 1H), 6.73 (s, 1H), 4.38 (q, 2H, J = 8 Hz), 2.39 (s, $2CH_3$, 6H); ^{13}C NMR δ 157.82 (s), 142.87 (s), 140.13 (s), 137.79 (s), 137.38 (s), 129.44 (d, 2C), 126.93

(d, 2C), 123.40 (CF_3, J = 278 Hz), 122.14 (d), 114.20 (d), 110.75 (d), 65.96 ($\underline{C}H_2CF_3$, J = 35 Hz), 21.58 (q), 21.06 (q); EI/MS, ^{m}/e 280 (M^+, 100%), 265 ($M^+ - CH_3$, 4).

For (E)-1,4-bis(2,2,2-trifluoroethoxy)-1-(4-methylphenyl)-3-trifluoromethyl-1,4-pentadiene (179): ^{1}H NMR δ 7.31 (d, 2H, J = 18 Hz), 7.21 (d, 2H, J = 18 Hz), 5.33 (d, 1H, J = 10 Hz), 4.41 (d, 1H, J = 4 Hz), 4.30 (m, $CHCF_3$, 1H J = 10 Hz, $^3J_{HCCF}$ = 10 Hz), 4.19 (d, 1H, J = 4 Hz), 4.08 (q, 2H, J = 8 Hz), 3.99 (q, 2H, J = 8 Hz), 2.38 (s, 3H); ^{13}C NMR δ 156.83 (s), 155.55 (s), 139.90 (s), 130.03 (s), 129.56 (d, 2C), 127.05 (d, 2C), 124.94 (CF_3, J = 278 Hz), 122.99 (CF_3, J = 278 Hz), 104.33 (d), 87.92 (t), 66.55 ($\underline{C}H_2CF_3$, J = 35 Hz), 65.15 ($\underline{C}H_2CF_3$, J = 35 Hz), 45.93 ($\underline{C}HCF_3$, J = 29 Hz), 21.23 (q); EI/MS, ^{m}/e 422 (M^+, 100%), 407 ($M^+ - CH_3$, 84), 353 ($M^+ - CF_3$, 98%), 323 ($M^+ - OCF_3$, 24).

For (E)-1-(4-methylphenyl)-3-trifluoromethyl-1,4,4-tris(2,2,2-trifluoroethoxy)-1-pentene (180): ^{1}H NMR δ 7.29 (d, 2H, J = 8 Hz), 7.23 (d, 2H, J = 8 Hz), 5.00 (d, 1H, J = 11 Hz), 3.7-4.1 (3 CF_2CF_3 + $CHCF_3$, 7H), 2.39 (s, 2H), 1.55 (s, 3H); ^{13}C NMR δ 158.29 (s), 140.30 (s), 129.91 (s), 129.73 (d, 2C), 127.22 (d, 2C), 124.80 (CF_3, J = 278 Hz), 123.75 (CF_3, J = 275 Hz), 123.70 (CF_3, J = 284 Hz), 123.25 (CF_3, J = 275 Hz), 102.52 (s), 101.82 (d), 66.61 ($\underline{C}H_2CF_3$, J = 35 Hz), 59.69 ($\underline{C}H_2CF_3$, J = 38 Hz), 59.13 ($\underline{C}H_2CF_3$, J = 35 Hz), 46.23 ($CHCF_3$, J = 26 Hz), 21.29 (q), 19.42 (q); EI/MS, ^{m}/e 423 ($M^+ - OCH_2CF_3$, 8%), 323 ($M^+ - C_4H_5F_6O_2$, 30), 225 ($C_6H_7F_6O_2^+$, 100).

For (E)-5-(4-methylphenyl)-5-(2,2,2-trifluoroethoxy)-oxy)-3-trifluoromethyl-4-penten-2-one (181): ^{1}H NMR δ 7.31 (d, 2H, J = 8 Hz), 7.23 (d, 2H, J = 8 Hz), 5.20 (d, 1H, J = 10 Hz), 4.57 (m, $CHCF_3$, 1H, J = 10 Hz), 4.06 (q, 2H, J = 8 Hz), 4.02 (q, 2H, J = 8 Hz), 2.39 (s, 3H), 2.33 (s, 3H), ^{13}C NMR δ 199.46, 158.35 (s), 140.36 (s), 129.68 (d, 2C), 129.50 (s), 127.16 (d, 2C), 123.98 (CF_3, J = 278 Hz), 123.28 (CF_3, J = 278 Hz), 101.94 (d), 66.49 ($\underline{C}H_2CF_3$, J = 35 Hz), 53.16 ($\underline{C}HCF_3$, J = 26 Hz), 29.87 (q), 21.79 (q); EI/MS, ^{m}/e 340 (M^+, 8%), 297 (M^+ - C_2H_3O, 100).

Reaction Products Obtained from 1-(4-Methoxyphenyl)-1,3-butanedione. Spectroscopic data for the reaction products that were obtained from 1-(4-methoxyphenyl)-1,3-butanedione are reported below.

For 4-methoxy-5-methyl-3-(2,2,2-trifluoroethoxy)biphenyl (182): ^{1}H NMR δ 7.49 (d, 2H, J = 9 Hz), 7.05 (s, 1H), 6.96 (d, 2H, J = 9 Hz), 6.92 (s, 1H), 6.70 (s, 1H), 4.38 (q, 2H, J = 8 Hz), 3.84 (s, 3H), 2.39 (s, 3H); ^{13}C NMR δ 159.41 (s), 157.85 (s), 142.53 (s), 140.10 (s), 133.17 (s), 128.15 (d, 2C), 123.42 (CF_3, J = 278 Hz), 121.94 (d), 114.20 (d, 2C), 113.85 (d), 110.62 (d), 65.97 ($\underline{C}H_2CF_3$, J = 36 Hz), 55.32 (q), 21.56 (q); EI/MS, ^{m}/e 296 (M^+, 100%), 281 (M^+ - CH_3, 28).

For (E)-1-(4-methoxyphenyl)-3-trifluoromethyl-1,4,4-tris(2,2,2-trifluoroethoxy)-1-pentene (183): ^{1}H NMR δ 7.33 (d, 2H, J = 9 Hz), 6.94 (d, 2H, J = 9 Hz), 4.95 (d, 1H, J = 10 Hz), 3.8-4.1 ($3CH_2CF_3$ + $CHCF_3$, 7H), 3.84 (s, 3H), 1.56 (s,

3H); ^{13}C NMR δ 161.00 (s), 157.99 (s), 128.76 (d, 2C), 124.82 (CF_3, J = 281 Hz), 123.72 (CF_3, J = 277 Hz), 123.59 (CF_3 J = 277 Hz), 123.25 (CF_3, J = 278 Hz), 101.86 (d), 101.86 (s), 66.59 ($\underline{C}H_2CF_3$, J = 35 Hz), 59.68 ($\underline{C}H_2CF_3$, J = 36 Hz), 59.13 ($\underline{C}H_2CF_3$, J = 35 Hz), 55.40 (q), 46.27 ($\underline{C}H_2CF_3$, J = 27 Hz), 19.38 (q); EI/MS, ^{m}/e 339 (M^+ - $C_4H_5F_6O_2$, 9%), 225 ($C_6H_7F_6O_2^+$, 100).

For (E)-5-(4-methoxyphenyl)-5-(2,2,2-trifluoroethoxy)-3-trifluoromethyl-4-pentene-2-one (184): ^{1}H NMR δ 7.35 (d, 2H, J = 9 Hz), 6.94 (d, 2H, J = 9 Hz), 5.15 (d, 1H, J = 10 Hz), 4.56 (m, $CHCF_3$, J = 10 Hz), $^3J_{HCCF}$ = 9 Hz), 3.9-4.2 (m, CH_2CF_3, 2H), 3.84 (s, 3H), 2.33 (s, 3H); ^{13}C NMR δ 199.53, 161.08 (s), 158.12 (s), 128.76 (d, 2C), 124.67 (s), 124.06 (CF_3, J = 281 Hz), 123.33 (CF_3, J = 278 Hz), 114.45 (d, 2C), 101.31 (d), 66.47 ($\underline{C}H_2CF_3$, J = 35 Hz), 55.41 (q), 53.18 ($\underline{C}HCF_3$, J = 27 Hz), 29.85 (q); EI/MS, ^{m}/e 356 (M^+ - C_2H_3, 95).

For 1-(4-methoxyphenyl)-3-trifluoromethyl-1,4-pentanedione (185): ^{1}H NMR δ 7.92 (d, 2H, J = 9 Hz), 6.93 (d, 2H, J = 9 Hz), 3.7-4.1 ($CHCF_3$ + one methylene H, 2H), 3.86 (s, 3H), 3.26 (dd, 1H, $^3J_{HCCH}$ = 2 Hz, $^2J_{HCH}$ = -17 Hz), 2.49 (s, 3H); ^{13}C NMR δ 200.78, 194.32, 164.11 (s), 130.46 (d, 2C), 128.70 (s), 124.91 (CF_3, J = 281 Hz), 114.40 (d, 2C), 55.47 (q), 50.55 ($\underline{C}HCF_3$, J = 26 Hz), 35.36 (t), 31.49 (q); EI/MS, ^{m}/e 274 (M^+, 10%), 135 ($C_8H_7O_2^+$, 100).

For 2,2,2-trifluoroethyl p-methoxybenzoate (186): NMR δ 8.03 (d, 2H, J = 9 Hz), 6.95 (d, 2H, J = 9 Hz), 4.67 (q, 2H, J =

9 Hz), 3.88 (s, 3H); ^{13}C NMR δ 164.64 (s), 164.13 (s), 132.17 (d, 2C), 120.75 (s), 113.91 (d, 2C), 60.59 ($\underline{C}H_2CF_3$, J = 36 Hz), 55.50 (q).

For methyl p-methoxybenzoate (187): ^{1}H NMR δ 7.99 (d, 2H, J = 9 Hz), 6.92 (d, 2H, J = 9 Hz), 3.89 (s, 3H), 3.86 (s, 3H).

Reaction Products Obtained from 1-(2-Methylphenyl)-1,3-butanedione. Spectroscopic data for the remaining reaction products that were obtained from 1-(2-methylphenyl)-1,3-butanedione are reported below.

For (E)-1,4-bis(2,2,2-trifluoroethoxy)-1-(2-methylphenyl)-3-trifluoromethyl-1,4-pentadiene (188): ^{1}H NMR δ 7.2-7.4 (broad, 4H), 5.05 (d, 1H, J = 10 Hz), 4.42 (d, 1H, J = 4 Hz), 4.34 (m, $CHCF_3$, J = 10 Hz, $^3J_{HCCF}$ = 9 Hz), 4.20 (d, 1H, J = 4 Hz), 4.13 (q, 2H, J = 8 Hz), 3.81 (q, 2H, J = 8 Hz), 2.31 (s, 3H); ^{13}C NMR δ 156.24 (s), 155.82 (s), 137.21 (s), 132.40 (s), 131.35 (d), 130.67 (d), 129.83 (d), 126.15 (d), 125.08 (CF_3, J = 281 Hz), 123.35 (CF_3, J = 277 Hz), 123.07 (CF_3, J = 277 Hz), 104.67 (d), 87.78 (t), 65.16 ($2\underline{C}H_2CF_3$, J = 36 Hz), 45.66 ($\underline{C}HCF_3$, J = 30 Hz), 19.27 (q); EI/MS, ^{m}/e 422 (M^+, 13%), 407 ($M^+ - CH_3$, 31), 323 ($M^+ - OCH_2CF_3$ 100).

For (E)-1-(2-methylphenyl)-3-trifluoromethyl-1,4,4-tris(2,2,2-trifluoroethoxy)-1-pentene (189): ^{1}H NMR δ 7.15-7.35 (broad, 4H), 4.75 (d, 1H, J = 10 Hz), 3.80-4.20 ($2CH_2CF_3$ + $CHCF_3$, 5H), 3.82 (q, 2H, J = 8 Hz), 2.31 (s, 3H), 1.52 (s, 3H); ^{13}C NMR δ 157.69 (s), 137.14 (s), 132.22 (s), 130.70 (d), 130.26 (d), 130.12 (d), 126.31 (d), 124.91 (CF_3,

J = 280 Hz), 123.87 (CF_3, J = 279 Hz), 123.68 (CF_3, J = 279 Hz), 123.23 (CF_3, J = 279 Hz), 102.47 (d), 101.82 (s), 64.97 ($\underline{C}H_2CF_3$, J = 35 Hz), 59.70 ($\underline{C}H_2CF_3$, J = 33 Hz), 59.03 ($\underline{C}H_2CF_3$, J = 34 Hz), 45.86 ($\underline{C}HCF_3$, J = 27 Hz), 19.29 (q), 19.05 (q); EI/MS, ^{m}/e 423 (M^+ - OCH_2CF_3, 6%), 323 (M^+ - $C_4H_5F_6O_2$, 24), 225 ($C_6H_7F_6O_2^+$, 100).

For (E)-5-(2-methylphenyl)-5-(2,2,2-trifluoroethoxy)-3-trifluoromethyl-4-penten-2-one (190): ^{1}H NMR δ 7.2-7.5 (broad, 4H), 4.93 (d, 1H, J = 10 Hz), 4.61 (m, $CHCF_3$, J = 10 Hz, $^3J_{HCCF}$ = 10 Hz), 3.87 (q, 2H, J = 8 Hz), 2.35 (s, 3H), 2.32 (s, 3H); ^{13}C NMR δ 199.38, 157.87 (s), 137.05 (s), 131.75 (s), 130.74 (d), 130.31 (d), 130.17 (d), 126.30 (d), 124.11 (CF_3, J = 280 Hz), 123.30 (CF_3, J = 280 Hz), 102.06 (d), 65.09 ($\underline{C}H_2CF_3$, J = 35 Hz), 52.92 ($\underline{C}HCF_3$, J = 27 Hz), 29.63 (q), 19.29 (q); EI/MS, ^{m}/e 340 (M^+, 13%), 297 (M^+ - C_2H_3O, 100), 91 ($C_7H_7^+$, 32).

For (Z)-5-(2-methylphenyl)-5-(2,2,2-trifluoroethoxy)-3-trifluoromethyl-4-penten-2-one (191): ^{1}H NMR δ 7.1-7.5 (broad, 4H), 4.98 (d, 1H, J = 11 Hz), 4.18 (q, 2H, J = 8 Hz), 3.62 (m, $CHCF_3$, J = 11 Hz, $^3J_{HCCF}$ = 9 Hz), 2.26 (s, 3H), 2.17 (s, 3H); ^{13}C NMR δ 199.66, 160.38 (s), 137.50 (s), 131.79 (s), 130.86 (d), 130.13 (d), 129.61 (d), 126.01 (d), 124.12 (CF_3, J = 281 Hz), 123.03 (CF_3, J = 278 Hz), 93.45 (d), 65.03 ($\underline{C}H_2CF_3$, J = 36 Hz), 55.30 ($\underline{C}HCF_3$, J = 27 Hz), 29.71 (q), 18.83 (q).

For 1-(2-methylphenyl)-3-trifluoromethyl-1,4-pentane-

dione (192): ^{1}H NMR δ 7.75 (d, 1H, J = 8 Hz), 7.2-7.5 (broad, 3H), 3.9-4.2 (m, $CHCF_3$, 1H), 3.82 (dd, 1H, $^{3}J_{HCCH}$ = 11 Hz, $^{2}J_{HCH}$ = -18 Hz), 3.22 (dd, 1H, $^{2}J_{HCH}$ = -18 Hz, $^{3}J_{HCCH}$ = 2 Hz), 2.51 (s, 3H), 2.47 (s, 3H); ^{13}C NMR 200.70, 199.27, 138.85 (s), 135.99 (s), 132.18 (d, 2C), 128.95 (d), 125.89 (d), 124.88 (CF_3, J = 280 Hz), 50.91 ($\underline{C}HCF_3$, J = 26 Hz), 38.00 (t), 31.43 (q), 21.39 (q).

Preparation of Substituted (5-Hydroxy-3-methyl[1,1'-biphenyl]-2-yl)phenylmethanone Derivatives. (3,4-Dimethyl-5-hydroxy-[1,1'-biphenyl]-2-yl) (4-methylphenyl) methanone (172) was prepared by treating 1.1 g (0.18 mmole) of 170 with 0.060 g (0.32 mmole) of p-toluenesulfonic acid monohydrate in 30 mL of benzene. The mixture was refluxed 4.5 h and was then cooled to room temperature. The reaction mixture was diluted with diethyl ether and water. The organic layer was collected and was washed with two portions of 5% $NaHCO_3$. Then, the organic layer was washed with water, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to a solid. Compound 172 was formed quantitatively (0.057 g, 100%) and was analyzed by ^{1}H and ^{13}C NMR. ^{1}H NMR δ 7.52 (d, 2H, J = 8 Hz), 7.10 (d, 2H, J = 8 Hz), 7.08 (s, 1H), 7.06 (d, 2H, J = 8 Hz), 6.94 (d, 2H, J = 8 Hz), 6.69 (s, 1H), 5.65 (broad OH, 1H), 2.31 (s, 3H), 2.21 (s, 3H), 2.14 (s, 3H); ^{13}C NMR δ 199.86, 155.80 (s), 143.81 (s), 142.01 (s), 137.36 (s, 2C), 136.91 (s), 135.67 (s), 131.84 (s), 129.65 (d, 2C), 129.00 (d, 2C), 128.79 (d, 4C), 115.93 (d), 114.22 (d), 21.63 (q), 21.02 (q), 19.86 (q); EI/MS, ^{m}/e

316 (M^+, 70%), 315 (M^+ - H, 52), 301 (M^+ - CH_3, 100), 225 (M^+ - C_7H_7, 58), 119 ($C_8H_7O^+$, 40), 91 ($C_7H_7^+$, 47).

The same reaction conditions were used to form (4'-fluoro-5-hydroxy-3-methyl[1,1'-biphenyl]-2-yl)(4-fluorophenyl)methanone (171) from 0.132 g (0.22 mole) of cyclohexenone 169 and 0.082 g (0.43 mmole) of p-toluenesulfonic acid monohydrate. This procedure afforded 0.071 g of biphenyl 171 in 100% yield. Compound 171 was also prepared from dienol ether 168 (0.074 g, 0.11 mmole) on treatment with p-toluenesulfonic acid monohydrate (0.045 g, 0.24 mmole). This later procedure afforded 0.035 g of biphenyl 171 in 100% yield. For 171: ^{1}H NMR δ 7.57 (dd, 2H, J = 9 Hz, $^4J_{HCCCF}$ = 5 Hz), 7.14 (dd, 2H, J = 9 Hz, $^4J_{HCCCF}$ = 5 Hz), 6.91 (dd, 2H, J = 9 Hz, $^3J_{HCCF}$ = 9 Hz), 6.83 (dd, 2H, J = 9 Hz, $^3J_{HCCF}$ = 9 Hz), 6.74 (s, 1H), 6.67 (s, 1H), 5.68 (broad OH, 1H), 2.20 (s, 3H); ^{13}C NMR δ 198.45, 165.66 (s, J = 256 Hz), 162.20 (s, J = 247 Hz), 156.11 (s), 141.04 (s), 137.86 (s), 136.03 (s), 134.43 (s), 131.97 (d, 2C, J = 9 Hz), 131.28 (s), 130.57 (d, 2C, J = 8 Hz), 116.05 (d, 2C, J = 37 Hz), 115.28 (d, 2C), 114.51 (d, 2C, J = 36 Hz), 19.82 (q); EI/MS, ^{m}/e 324 (M^+, 82%), 323 (M^+ - H, 100), 229 (M^+ - C_6H_4F, 46), 123 ($C_7H_4FO^+$, 43), 95 ($C_6H_4F^+$, 39).

Chapter III

ADDITIONAL ASPECTS OF THE REACTION OF β-DIKETONES AND RELATED SYSTEMS WITH TFD

Introduction

In Chapter II the acid-catalyzed self-condensation reactions of 2,4-pentanedione and 1-phenyl-1,3-butanedione were described. The potential synthetic utility of these reactions for the preparation of aromatic natural products was emphasized. Chapter II also illustrated that substituted derivatives of 1-phenyl-1,3-butanedione could be used in the preparation of substituted biphenyl compounds. Several of these biphenyl compounds could be attractive synthons for the preparation of even larger polycyclic aromatic compounds (e.g., through the Elbs reactions[1]). However, the total synthetic scope of these cyclization reactions was not discussed in Chapter II. Extensive mechanistic studies were also neglected in the previous chapter. These two topics will be further developed in this chapter.

Several mechanistic studies have been initiated for the cyclization reactions of 1-phenyl-1,3-butanedione and 2,4-pentanedione. In these studies, several attempts were made to isolate reaction intermediates. In addition, various reaction conditions have been investigated to improve the

yield of cyclization products and to further understand the factors which are related to the cyclization process. The reaction parameters which have been examined include solvents, catalysts,[84] temperature effects, time variables, and the TFD:β-diketone molar ratio.

Several different systems have been treated with TFD and $HBF_4 \cdot OEt_2$ to examine the synthetic scope of the cyclization process. β-Diketones exhibiting a number of steric and electronic effects have been examined in this study. The cyclization process has also been tested for a γ-diketone, a β-ketoester, and a vinyl ketone. Preliminary studies have also examined the synthetic utility of mixed condensation reactions between two different β-diketones.

The results that were obtained from the above studies have led to a better understanding of the acid-catalyzed self-condensation reaction of β-diketones. However, during these studies, a number of unanswered questions have also been encountered.

Mechanistic Studies

Several mechanistic studies have been undertaken to help understand the details of the acid-catalyzed self-condensation reaction of β-diketones in the presence of TFD. The knowledge gained from these studies should ultimately provide methodology to improve the yield of cyclized products.

Initial studies in this area have involved examining the effect of TFD on the overall cyclization process. In this study, the amount of TFD utilized per equivalent of β-diketone was examined. In other studies, different rates of addition of the TFD solution to the β-diketone have been studied. Both 1-phenyl-1,3-butanedione and a mixture of the trifluoroethyl enol ethers of 2,4-pentanedione (i.e., compounds 142 and 152) have been utilized in the above studies. Experiments involving the trifluoroethyl enol ethers of 2,4-pentanedione will be described first since this work provides the basis for the later work with 1-phenyl-1,3-butanedione.

Several control experiments have been utilized to provide a better understanding of the cyclization reactions of β-diketones. Some control experiments were described in Chapter II. Additional studies have indicated that trifluoroethyl enol ethers of 2,4-pentanedione (i.e., compounds 142 and 152) did not undergo cyclization reactions in the presence of $HBF_4 \cdot OEt_2$ without TFD. Similarly, a mixture of 2,4-pentanedione and enol ethers 142 and 152 did not undergo cyclization reactions utilizing the above reaction conditions. These experiments clearly illustrate that cyclization products are only obtained in the presence of TFD. The latter experiment also suggests that 2,4-pentanedione does not attack either enol ether 142 or 152 to afford cyclization products. A second experiment was also in agreement with the

previous observation. A mixture of 2,4-pentanedione and enol ethers 142 and 152 was treated with $HBF_4 \cdot OEt_2$ and TFD. The presence of 2,4-pentanedione in the above mixture did not help promote cyclization of trifluoroethyl enol ethers 142 and 152. This suggests that 2,4-pentanedione is not directly involved in the formation of cyclization products (i.e., cyclization products originate from the reaction of trifluoroethyl enol ethers 142 and 152 with some derivative which has resulted from further reaction of the above compounds).

Based on the above observation, trifluoroethyl enol ethers 142 and 152 were treated under a variety of experimental conditions in the hope of maximizing the yield of the cyclization products (Table 3.1). From entries 1 and 2 in Table 3.1, it is apparent that the cyclization reaction of trifluoroethyl enol ethers 142 and 152 did not occur with less than 1 equivalent of TFD. Therefore, the above reaction was repeated using an excess of TFD (entries 3,4, and 5 in Table 3.1). Under these conditions, a greater conversion of the trifluoroethyl enol ethers to aromatic cyclization products was observed. Equal yields of cyclized products were obtained with 2 equivalents (entry 4) and 3 equivalents (entry 5) of TFD, respectively. However, when 3 equivalents of TFD were added to trifluoroethyl enol ethers 142 and 152, a greater preponderance of other products accompanied the aromatic products (e.g., insertion product 141, etc.). Note

TABLE 3.1

Cyclization Reactions of Trifluoroethyl Enol Ethers 142 and 152 with TFD

entry	mmoles of 142 + 152	mmoles of TFD	mmoles of $HBF_4 \cdot OEt_2$	time required for TFD addition	results[f]
1	3.36[a]	3.60	1.31	1 min	Some cyclization; some unreacted 142 and 152 recovered.
2	1.81[b,c]	1.26	0.876	25 min	50:50 mixture of 2,4-pentanedione and enol ether 142 was recovered from the reaction.
3	3.50[a]	12.0	1.31	60 min	More cyclization occurred than for entry 1.
4	3.39[c,d]	6.90	1.75	25 min	14% yield of acetophenone 137 was recovered after hydrolysis.[g]
5	2.72[d]	8.19	1.75	13 min	15% yield of acetophenone 137 with several additional by-products was recovered.[g]
6	4.48	11.48	2.19	5 min[e]	Recovered many ketals from the reaction. Only trace amounts of aromatic compounds were detected.
7	1.63	1.64	0.876	5 min[e]	Enol ethers 142 and 152 were recovered from this procedure.

TABLE 3.1 (continued)

a 3:1 ratio of enol ether 142 to enol ether 152.

b 1:1 ratio of enol ether 142 to enol ether 152.

c Enol ethers 142 and 152 were dissolved in CH_2Cl_2 before treatment with TFD.

d 2:1 ratio of enol ether 142 to enol ether 152.

e Trifluoroethyl enol ethers 142 and 152 and $HBF_4 \cdot OEt_2$ were added to the TFD solution. This inverse addition was utilized in an attempt to prepare intermediate dienes which were believed to be present during the cyclization process.

f The reaction mixture was hydrolyzed with 7.5 mL of methanol, 2.5 mL of water, and 1 mL of HBF_4 (refluxed for 30 min).

g After neutralization with 2 portions of 5% $NaHCO_3$ and a single portion of water, reaction products were monitored by ^1H and ^{13}C NMR spectroscopy.

that insertion product 141 was detected by ^{1}H and ^{13}C NMR after hydrolysis of the reaction mixture utilizing a refluxing methanol-water-HBF_4 solution. From the above experiments, a very rapid addition of TFD to the trifluoroethyl enol ether solution (entry 1 in Table 3.1) was observed to afford a dark-colored reaction mixture. This mixture was darker than the mixtures which were obtained from slower additions of TFD. This dark red-brown color appears to correspond with polymer formation which competes with the cyclization process. To reduce this polymer formation, longer addition times have been employed for the addition of TFD to the β-diketones and the corresponding enol ether solutions.

Other methods have been attempted to increased the yields of cyclization products (Table 3.2). For entries 1 and 2 in Table 3.2, 2,4-pentanedione and $HBF_4 \cdot OEt_2$ have been added to the TFD solution. Recall that in previous experiments, TFD was added to the 2,4-pentanedione solution. The results that were obtained from this inverse addition indicate that various ketals were formed from the procedure. However, the aromatic products were not observed in the ^{1}H and ^{13}C NMR spectra of the above reaction mixtures even when 6 equivalents of TFD were utilized per equivalent of 2,4-pentanedione (entry 2 in Table 3.2). Similar results were obtained when a mixture of 2,4-pentanedione and TFD was treated with $HBF_4 \cdot OEt_2$ to initiate reaction of TFD (entry 3 in Table 3.2).

TABLE 3.2

Cyclization Reactions of 2,4-Pentanedione with TFD

entry	mmoles of 2,4-pentanedione	mmoles of TFD	mmoles of $HBF_4 \cdot OEt_2$	time required for TFD addition	results[i]
1	12.52[a]	26.2	4.38	20 min[g]	Recovered 2,4-pentanedione and several ketals.
2	5.40	32.9	0.175	5 min[g]	Ketals were the major reaction products; no aromatic products were detected.
3	10	32.9	0.876	2 min[h]	Ketals were the major reaction products; aromatic products were detected in trace amounts.
4	20	20.2	3.50[f]	20 min	A mixture of 2,4-pentanedione and enol ether 142 was recovered.
5	10[b,c]	50.6	4.82	60 min	Both insertion product 141 and acetophenone 137 were recovered from this procedure.
6	10[d,e]	16.5	1.31	25 min	Considerable amounts of aromatic compounds were obtained from this procedure.

TABLE 3.2 (continued)

a 2,4-Pentanedione and $HBF_4 \cdot OEt_2$ were dissolved in 9 mL of CH_2Cl_2 prior to reaction.

b This experiment was conducted in the absence of light in an attempt to prevent carbene formation (i.e., to reduce homologation reactions).

c The reaction mixture was hydrolyzed with 20 mL of 2,2,2-trifluoroethanol, 20 mL of water, and 3 mL of $HBF_4 \cdot OEt_2$ (refluxed for 20 h).

d 2,2,2-Trifluoroethanol (10 mmoles) was added to 2,4-pentanedione prior to treatment with TFD.

e 10% Na_2CO_3 was used to neutralize this reaction mixture.

f $HBF_4 \cdot OEt_2$ was added in two portions; one portion was added before the TFD addition, and the second was added after this addition to insure total TFD reaction.

g 2,4-Pentanedione and $HBF_4 \cdot OEt_2$ were added to the TFD solution.

h $HBF_4 \cdot OEt_2$ was added dropwise to a solution containing 2,4-pentanedione and TFD.

i The reaction mixture was neutralized with 2 portions of 5% $NaHCO_3$ and 1 portion of water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated <u>in vacuo</u> to an oil which was examined by ^1H and ^{13}C NMR spectroscopy.

Due to the lack of cyclization that was observed in the above instances, 2,4-pentanedione appears to be immediately reacting with the large excess of TFD which has been employed in these experiments. The intermediates that would be necessary in the cyclization to aromatic compounds (e.g., trifluoroethyl enol ethers) appear to have undergone further reaction in the presence of the higher TFD concentration. Therefore, cyclization with another 2,4-pentanedione equivalent would be less likely to occur.

Reaction conditions have also been varied for the reaction of 1-phenyl-1,3-butanedione with TFD in the presence of $HBF_4 \cdot OEt_2$. Based on the yield data that were obtained for the 2,4-pentanedione reaction system, a 3- to 5-fold excess of TFD to 1-phenyl-1,3-butanedione was employed in these studies. As well as exploring the optimum TFD concentrations, the rate of TFD addition was more extensively studied in these experiments with 1-phenyl-1,3-butanedione. When the TFD to 1-phenyl-1,3-butanedione ratio was increased from 3 to 5, no dramatic changes were observed in the yield distribution of recovered products (Table 3.3). Based on the above experiments, yield data appear relatively unaffected when the TFD to 1-phenyl-1,3-butanedione ratio is increased above three. This is consistent with the results that were obtained from the trifluoroethyl enol ethers of 2,4-pentanedione. That is, the maximum yield of aromatic products was relatively unchanged when the TFD to enol ether

TABLE 3.3

Yield Data for Various Reactions of 1-Phenyl-1,3-butanedione with TFD[a]

product	5 equiv (I)[b,c]	5 equiv (II)[b,e]	3 equiv 1 min[b,e]	3 equiv 11 min[b,e]	3 equiv 130 min[b,e]
biphenyl 155	11.6%	17.4%	1.3%	5.2%	11.6%
cyclohexenone 157	20.3	23.7	3.7	10.9	29.3
total insertion products	--[d]	12.6	11.8	10.2	15.3
1-phenyl-1,3-butanedione	--[d]	31.6	53.8	45.8	30.6

a Yield data were obtained after methanol-water-HBF_4 hydrolysis and chromatographic separation.

b Refers to the number of equivalents of TFD that were utilized per 1 equivalent of 1-phenyl-1,3-butanedione.

c Chromatographic separation with pentane and ethyl acetate.

d The insertion products were not completely resolved from 1-phenyl-1,3-butanedione under these chromatographic conditions.

e Chromatographic separation with pentane, methylene chloride, and diethyl ether.

ratio was increased above two. (A third equivalent of TFD is necessary to prepare the corresponding enol ether from 1-phenyl-1,3-butanedione).

The yields that were obtained from the reaction of 1-phenyl-1,3-butanedione with TFD were altered by varying the time utilized for the TFD addition (Table 3.3). The product distribution was examined after adding three equivalents of TFD to the ß-diketone using three different addition times (1, 11, and 130 minutes, respectively, as reported in Table 3.4). The results of these experiments indicated that the amount of cyclized products (i.e., biphenyl 155 and cyclohexenone 157) increased with the longer reaction times.

In sharp contrast to the increasing yields of cyclized products with longer addition times, the amount of recovered insertion products remained relatively constant (~11%). This suggests that 1-phenyl-1,3-butanedione reacts immediately with TFD to yield homologated reaction products. However, after the initial homologation reaction, 1-phenyl-1,3-butanedione and the corresponding trifluoroethyl derivatives appear to favor other reaction pathways over the homologation reaction. These preliminary results contradict the results that were reported by Mock and Hartman[11] for the homologation reaction of ethyl diazoacetate with ketones in the presence of an acid catalyst. Mock and Hartman found that slightly higher yields of insertion products were obtained if the diazoacetate was slowly added to the ketone

TABLE 3.4

Cyclization Reactions of 1-Phenyl-1,3-butanedione with TFD

entry	mmoles of β-diketone	mmoles of TFD	mmoles of acid-catalyst	time required for TFD addition	results [g,h]
1	11.77[a]	58.6	13.58[d]	6 h	See Table 3.3.[i]
2	11.16[a]	55.6	15.33[d]	3.75 h	See Table 3.3.[i]
3	4.65[a]	13.9	2.19[d]	11 min	See Table 3.3.[i]
4	3.57[a]	10.8	2.19[d]	1 min	See Table 3.3.[i]
5	3.59[b]	10.8	1.75[d]	1 min	1-Phenyl-1,3-butanedione and insertion ketone 156 were recovered from the procedure.[i]
6	3.57[c]	10.8	1.75[d]	1 min	1-Phenyl-1,3-butanedione and insertion ketone 156 were recovered from the procedure.[i]
7	4.88[a]	21.4	3.94[e]	1.83 h	Yellow precipitate formed on addition of $SbCl_5$ to the β-diketone. This precipitate dissolved with the addition of TFD. After hydrolysis, a large amount of 1-phenyl-1,3-butanedione was recovered along with traces of the insertion ketone 156.[j,k]
8	4.64[a]	14.1	1.50[f]	1.58 h	After hydrolysis, the following compounds were detected by conventional methods and by LC-^{1}H NMR: biphenyl 155, cyclohexenone 157, insertion ketone 156, 1-phenyl-1,3-butanedione, and methyl benzoate.

TABLE 3.4 (continued)

a Reaction flask was at 0°C.

b Reaction flask was at 32°C.

c Reaction flask was at -35°C.

d $HBF_4 \cdot OEt_2$ was employed as the acid-catalyst.

e Antimony pentachloride was employed as the acid-catalyst.

f Triethyloxonium tetrafluoroborate was employed as the acid-catalyst.

g Reaction mixture was neutralized with 2 portions of 5% $NaHCO_3$ and 1 portion of water.

h Triethylamine was added to the reaction mixture prior to treatment with 5% $NaHCO_3$.

i Reaction mixture was hydrolyzed with methanol-water-HBF_4 (5:2:1 volumetric ratio, 4 h reflux).

j Reaction mixture was neutralized before hydrolysis with the procedure that was described in reference 7.

k 1-Phenyl-1,3-butanedione and insertion ketone 156 were identified by conventional ^1H and ^{13}C NMR spectroscopy. These compounds were also detected in the LC-^1H NMR profile of this reaction mixture.

as opposed to rapidly adding the diazoacetate in a single portion.

An additional experiment was performed in order to further understand the competition that exist between acid-catalyzed cyclization and homologation reactions. Homologation reactions appear to reduce the yield of cyclized products. Therefore, the yield of cyclized products should be increased by reducing the amount of β-diketone which undergoes homologation reactions. One possible mechanism for the formation of the homologation reaction products involves carbene formation.[16] Therefore, 2,4-pentanedione was treated with TFD and $HBF_4 \cdot OEt_2$ in the absence of light to reduce the possibility of carbene formation. This reaction did not show any decrease in the yield of the homologation reaction products. Thus, another homologation reaction mechanism[12] (other than carbene formation) must account for the formation of insertion product 141.

The largest yield of cyclized products has been obtained when the β-diketone was treated with an excess of TFD. Due to the formation of highly colored reaction products (i.e., polymer formation), the disappearance of the yellow TFD solution cannot be monitored when 1-phenyl-1,3-butanedione or 2,4-pentanedione is treated with TFD. Therefore, the nitrogen that was evolved from the reaction of 2,4-pentanedione with TFD was monitored to determine if complete reaction of the excess TFD had occurred. The amount of nitrogen gas that

was recovered in this experiment was equal to the molar amount of TFD that was initially added to 2,4-pentanedione. This indicated that the complete excess of TFD was utilized in some fashion during the above reaction with 2,4-pentanedione.

Temperature Effects on the Cyclization Process

Temperature effects were also examined for the reaction of 1-phenyl-1,3-butanedione with TFD. This reaction was examined at -35°C, 0°C, and 32°C by treating the β-diketone with a 3-fold excess of TFD over 1 minute (Table 3.4). These reaction mixtures were immediately neutralized with triethylamine. The ^{1}H and ^{13}C NMR spectra for the three unhydrolyzed mixtures were nearly identical indicating that the product distribution was relatively unaffected over a temperature range from -35°C to 32°C. In an independent reaction of 1-phenyl-1,3-butanedione with 2 equivalents of TFD at -78°C (entry 5 in Table 3.5, see the following section), very little reaction of the β-diketone occurred.

Temperature effects have been studied for the reaction of 2,4-pentanedione with TFD at -72°C. In this study a 3-fold excess of TFD was added to 2,4-pentanedione. Nitrogen gas was evolved during the addition of the first equivalent of TFD. However, further addition of TFD did not promote nitrogen evolution. Therefore, trifluoroethyl enol ethers 142

and 152 appear to be the only reaction products formed at -72°C.

Isolation of Reaction Intermediates

To help establish the mechanistic pathway of the acid-catalyzed self-condensation reaction of β-diketones, the isolation of several key reaction intermediates would be of considerable value. In Chapter II, the isolation of the E- and Z-trifluoroethyl enol ethers of 2,4-pentanedione was described. In this chapter several reactions involving these enol ethers have been reported. These reactions have demonstrated the mechanistic importance of the trifluoroethyl enol ethers of 2,4-pentanedione. Attempts were made to isolate the analogous trifluoroethyl enol ethers of 1-phenyl-1,3-butanedione which should have similar mechanistic importance. In similar fashion, isolation of the corresponding trifluoroethoxy dienes of 2,4-pentanedione and 1-phenyl-1,3-butanedione should also be of mechanistic value. Isolation of these dienes would establish their presence in the reaction mixture and would allow further mechanistic studies on the isolated dienes with other potential reaction intermediates (e.g., enol ethers, etc.).

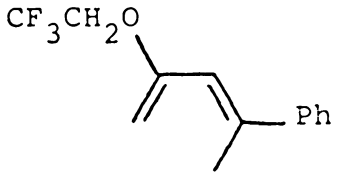
In an attempt to prepare the trifluoroethyl enol ethers of 1-phenyl-1,3-butanedione, the reaction procedure that was previously employed to prepare the enol ethers of 2,4-pen-

tanedione was utilized. However, treatment of 1-phenyl-1,3-butanedione with TFD at -78°C (entry 1 in Table 3.5) yielded only minor amounts of products. In similar fashion, little reaction was observed at -25°C (entry 2 in Table 3.5). The difficulty which was encountered in preparing these trifluoroethyl enol ethers of 1-phenyl-1,3-butanedione suggests that competing reactions could be occurring (e.g., reactions with water). These competing reactions could deplete the TFD concentration in the reaction mixture. As a result, only small amounts of TFD would be available to provide the trifluoroethyl enol ethers of 1-phenyl-1,3-butanedione. These results suggest that additional TFD is needed to form the corresponding trifluoroethyl enol ethers of 1-phenyl-1,3-butanedione.

Problems were also experienced in the preparation of the corresponding trifluoroethoxy dienes of 2,4-pentanedione and 1-phenyl-1,3-butanedione. Two attempts were made to prepare the intermediate diene 151 that would be expected in the 2,4-pentanedione self-condensation reaction. These attempts utilized the addition of the corresponding trifluoroethyl enol ethers of 2,4-pentanedione (i.e., compounds 142 and 152) and $HBF_4 \cdot OEt_2$ to a TFD solution. This procedure should favor formation of potential reaction intermediates over cyclization to aromatic compounds. When a 2.5-fold excess of TFD to enol ethers was employed (entry 6 in Table 3.1), a complex reaction mixture was obtained which con-

tained several different trifluoroethyl derivatives. Due to the number of different compounds that were present in this mixture, separation and isolation of potential intermediates was not further pursued. To reduce the number of trifluoroethyl derivatives for separation, the above reaction was repeated using equal molar amounts of TFD and trifluoroethyl enol ethers 142 and 152 (entry 7 in Table 3.1). However, unreacted enol ethers were also recovered from this procedure.

Difficulties were also experienced when attempting to prepare the corresponding diene of 1-phenyl-1,3-butanedione (compound 193).



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In one experiment, 1-phenyl-1,3-butanedione was treated with 2 equivalents of TFD at -78°C (entry 5 in Table 3.5 that was previously discussed). This procedure afforded very little reaction of the starting β-diketone. In a second attempt to prepare diene 193, a mixture of 1-phenyl-1,3-butanedione and $HBF_4 \cdot OEt_2$ was added to 2 equivalents of TFD at 0°C. A large amount of unreacted 1-phenyl-1,3-butanedione was recovered from this procedure along with a small amount of insertion ketal 194.[85]

TABLE 3.5

Reactions of 1-Phenyl-1,3-butanedione with TFD

entry	mmoles of β-diketone	mmoles of TFD	mmoles of $HBF_4 \cdot OEt_2$	time required for TFD addition	results[g]
1	5.41[a]	5.38	2.19	10 min[h]	1-Phenyl-1,3-butanedione was recovered.[i]
2	5.91[b]	5.85	2.19	10 min[h]	1-Phenyl-1,3-butanedione was recovered.[i]
3	3.62[c,d]	10.8	3.94	20 min	Little reaction of TFD occurred as 1-phenyl-1,3-butanedione was recovered.[i]
4	4.75[c,e]	13.9	2.63	15 min	1-Phenyl-1,3-butanedione, insertion products, and enol ethers were recovered from the reaction mixture.
5	5.62[a]	11.1	2.63	6 min	Little reaction of TFD occurred as 1-phenyl-1,3-butanedione was recovered.
6	5.49[c]	11.1	2.63	20 min[h]	Large amount of 1-phenyl-1,3-butanedione was recovered along with insertion products.

TABLE 3.5 (continued)

a Reaction flask was at 78°C.

b Reaction flask was at -25°C.

c Reaction flask was at 0°C.

d 2,2,2-Trifluoroethanol (3.58 mmoles) was added to 1-phenyl-1,3-butanedione prior to treatment with TFD.

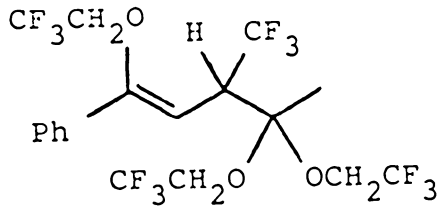
e 2,2,2-Trifluoroethanol (4.63 mmoles) was added to 1-phenyl-1,3-butanedione prior to treatment with TFD.

f 1-Phenyl-1,3-butanedione and $HBF_4 \cdot OEt_2$ were added to a TFD solution over this time period.

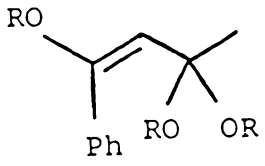
g Reaction mixtures were neutralized with 2 portions of 5% $NaHCO_3$ and 1 portion of water.

h Reaction mixtures were treated with triethylamine prior to additional neutralization with the 5% $NaHCO_3$ procedure.

i The reaction mixture was hydrolyzed with 15 mL of methanol, 5 mL of water, and 2 mL of HBF_4 (refluxed 4 h).



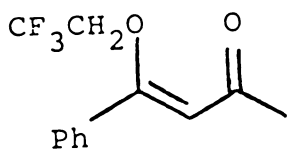
194



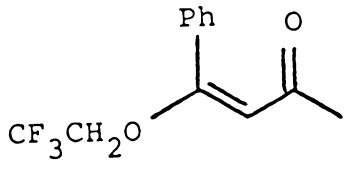
R = CH_2CF_3

195

One final attempt to prepare diene 193 was made by treating equal molar amounts of 1-phenyl-1,3-butanedione and 2,2,2-trifluoroethanol with an excess of TFD (entry 4 in Table 3.5). 2,2,2-Trifluoroethanol was added to this mixture in an attempt to induce formation of ketal 195 which later could eliminate 2,2,2-trifluoroethanol to afford diene 193. However, unreacted 1-phenyl-1,3-butanedione and the corresponding enol ethers were the major compounds isolated from this reaction. Note that this procedure does offer methodology for the preparation of trifluoroethyl enol ethers 196 and 197 that were originally desired for mechanistic studies.



196



197

Additional Mechanistic Studies with 2,2,2-Trifluoroethanol

In an attempt to further confirm that 2,2,2-trifluoroethanol is a weak nucleophile during the reaction of 1-phenyl-1,3-butanedione with TFD, another reaction mixture was prepared using the previously described reaction conditions (entry 3 in Table 3.5). Conceivably, 2,2,2-trifluoroethanol could function as a weak nucleophile during the above process. Cyclization would then be favored which would increase the yields of biphenyl 155 and cyclohexenone 157. After this reaction mixture was hydrolyzed, 1-phenyl-1,3-butanedione was the major compound recovered. This result was consistent with the previously described reaction which was used in an attempt to form diene 193. In both of the above reactions, the addition of 2,2,2-trifluoroethanol to the reaction mixture reduced the amount of cyclization products obtained.

In contrast to the above examples, when a mixture of 2,4-pentanedione and 2,2,2-trifluoroethanol was treated with TFD in the presence of $HBF_4 \cdot OEt_2$, 2,2,2-trifluoroethanol had little effect on the cyclization pathway (entry 6 in Table 3.2). Additional support for this observation was obtained by treating 2,4-pentanedione with TFD under identical conditions in the presence and in the absence of 2,2,2-trifluoroethanol. After hydrolysis, both reaction mixtures contained

13% of acetophenone 137.

To help exclude the possibility of ketal formation in the above reaction, the E- and Z-trifluoroethyl enol ethers of 2,4-pentanedione were treated with $HBF_4 \cdot OEt_2$ and 2,2,2-trifluoroethanol. Utilizing these reaction conditions, ketal formation was not observed. Both this experiment and the observation that 2,2,2-trifluoroethanol did not induce any increase of cyclization products suggest that 2,2,2-trifluoroethanol does not function as a weak nucleophile during the 2,4-pentanedione cyclization. Such a nucleophilic attack would have provided ketals which could have eliminated 2,2,2-trifluoroethanol to form diene 151.

In the above experiments TFD reacted more rapidly with 2,4-pentanedione and the corresponding trifluoroethyl derivatives than it did with 2,2,2-trifluoroethanol. However, due to the low yield of cyclized products that were obtained from 1-phenyl-1,3-butanedione in the presence of 2,2,2-trifluoroethanol, TFD appears to have reacted more rapidly with 2,2,2-trifluoroethanol than it did with 1-phenyl-1,3-butanedione. Therefore, TFD appears to react more readily with 2,4-pentanedione than it does with 1-phenyl-1,3-butanedione. As a result, 2,4-pentanedione could rapidly react with TFD to yield a high concentration of by-products that would not undergo cyclization to aromatic compounds. In contrast, the slower reaction of TFD with 1-phenyl-1,3-butanedione may provide the corresponding

reaction immediates a better opportunity to undergo cyclization reactions. Therefore, the combined yield of cyclization products from 1-phenyl-1,3-butanedione would be slightly higher than the yield which would be obtained from 2,4-pentanedione. This is consistent with the experimental yield distributions discussed in Chapter II. Note that these yield distributions could also be related to the abilities of the methyl and phenyl groups to stabilize reaction intermediates.

The Effect of Different Acid Catalysts on the Cyclization Process

Various acid catalysts have been employed by Koller[84] for the reaction of TFD with alcohols, carboxylic acids, and phenols. This study indicated that $HBF_4 \cdot OEt_2$ afforded the optimum reactions conditions (i.e., maximum yields and no side reaction of TFD with acid catalyst). Several reports[11,12] have indicated that antimony pentachloride ($SbCl_5$) and triethyloxonium fluoroborate can be employed as acid catalysts in the homologation reactions of diazo compounds. The above acid catalysts were not studied by Koller. The acid catalyzed self-condensation reaction of β-diketones and TFD was examined in the presence of these catalysts to determine if these catalysts would improve the yield of cyclization products.

When $SbCl_5$ was added to 1-phenyl-1,3-butanedione (entry 7 in Table 3.4), a precipitate immediately formed due to complexation of the acid catalyst with the β-diketone. This precipitate slowly disappeared when TFD was added to the reaction mixture. Once the reaction mixture was neutralized, 1-phenyl-1,3-butanedione and traces of several compounds containing trifluoroethoxy groups were observed in the ^1H and ^{13}C NMR spectra of the mixture. This mixture was further hydrolyzed with a methanol-water-HBF_4 solution to afford 1-phenyl-1,3-butanedione and traces of insertion ketone 156. A separation which utilized LC-^1H NMR also confirmed that insertion ketone 156 was present in this reaction mixture. Biphenyl 155 and cyclohexenone 157 were not detected in this hydrolyzed reaction mixture. Therefore, $SbCl_5$ was a less attractive acid catalyst than $HBF_4 \cdot OEt_2$ in studying the cyclization reactions.

In similar fashion, triethyloxonium tetrafluoroborate was examined as the reaction catalyst (entry 7 in Table 3.4). After hydrolysis, the biphenyl 155, insertion ketone 156, cyclohexenone 157, and 1-phenyl-1,3-butanedione were detected in the reaction mixture by ^1H and ^{13}C NMR spectroscopy. The LC-^1H NMR technique was also used to confirm the presence of the above compounds in this reaction mixture. From the above results, no apparent advantage or disadvantage was observed for triethyloxonium tetrafluoroborate over the commonly used $HBF_4 \cdot OEt_2$.

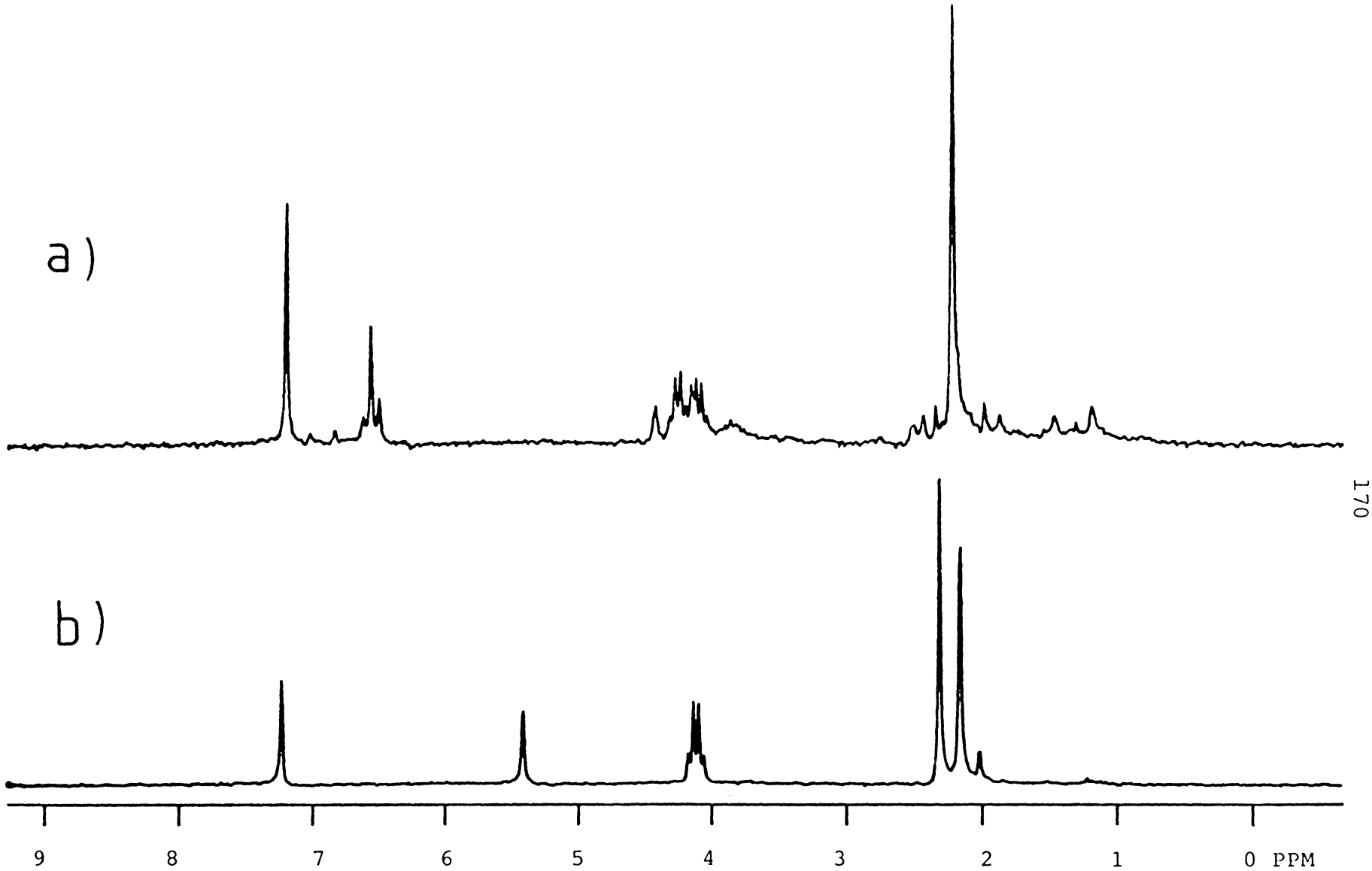
Solvent Effects on the Cyclization Process

Several different solvents have been examined for the reaction of 2,4-pentanedione with TFD. When 2,4-pentanedione was treated with a chloroform solution of TFD, cyclization to aromatic compound 143 was observed. Compound 143 was detected in this unhydrolyzed mixture with the LC-^{1}H NMR apparatus (Figure 3.1). Trifluoroethyl enol ether 142 was also observed in this same reaction mixture. The reaction of 2,4-pentanedione with TFD[86] in methylene chloride was compared to the above reaction in chloroform. This comparison indicated that similar yields of aromatic products were obtained from the two solvent systems. Note that acetophenone 137 was the main cyclization product that was recovered from the reaction of 2,4-pentanedione with a methylene chloride solution of TFD. For some unknown reason, aromatic compound 143 was hydrolyzed to acetophenone 137 in the reaction mixture which had been obtained from the methylene chloride solution of TFD. Similar reaction products were expected from the two solvent systems since both reaction mixtures were handled using identical techniques.

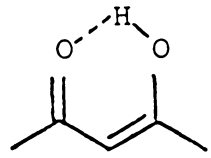
The reaction of 2,4-pentanedione in a nonpolar solvent should provide mechanistic information on the cyclization process. A nonpolar solvent should change the distribution of the two enol forms of 2,4-pentanedione since an increase

Figure 3.1

Selective LC-^{1}H NMR files for the 2,4-pentanedione reaction products that were obtained utilizing a chloroform solution of TFD. (a) File 3 (elution time of 11 minutes) is the spectrum corresponding to a mixture of compounds 137 and 143. (b) File 8 (16 minutes) is the spectrum of trifluoroethyl enol ether 142.


a)
b)
170
9
8
7
6
5
4
3
2
1
0 PPM

of hydrogen-bonding should occur to favor enol 198 in a non-polar solvent.



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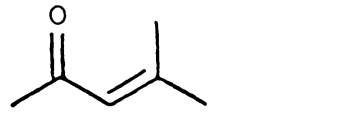
As a result, the amount of the Z-trifluoroethyl enol ether (compound 152) in the reaction mixture could be increased which could provide an increase in the yield of cyclized products.

To test the above hypothesis, a pentane solution of TFD was required. Using the TFD preparation that was previously described in Chapter II, the aqueous layer was extracted with pentane instead of methylene chloride. Problems were encountered since TFD was not very soluble in pentane. Therefore, the pentane solution of TFD was more dilute than the solutions which had been prepared in methylene chloride and chloroform. When a 3.5-fold molar excess of the pentane solution of TFD was added to 2,4-pentanedione, equal amounts of unreacted 2,4-pentanedione and trifluoroethyl enol ether 142 were the major compounds that were isolated after neutralization. The poor reactivity of 2,4-pentanedione utilizing the previous conditions could be due to the increasing importance of competing side reactions (e.g., reactions with water, etc.). These competing reactions could be more favor-

able under these reaction conditions since enol 198 could have additional stability by hydrogen-bonding as previously described. This could reduce the reactivity of enol 198 under the above reaction conditions.

The reaction of 2,4-pentanedione with TFD was initially examined using diethyl ether as the reaction solvent. Using the TFD preparation that was described in Chapter II, the aqueous layer was extracted with diethyl ether instead of methylene chloride. Without further treatment, the diethyl ether solution of TFD was added to a mixture of 2,4-pentanedione and $HBF_4 \cdot OET_2$. Enamine 199 was recovered from this procedure.



199

Further analysis of the original diethyl ether solution of TFD indicated that unreacted 2,2,2-trifluoroethylamine had also been extracted into the organic mixture from the TFD preparation. This amine has attacked 2,4-pentanedione during the reaction procedure to afford enamine 199.

Several attempts were made to remove 2,2,2-trifluoroethylamine from the TFD solution by extracting the solution very rapidly with various acid solutions. Solutions of hydrochloric acid, nitric acid, phosphoric acid, and acetic

acid were individually examined in the extraction procedure. The organic solution was immediately neutralized after the above extractions with 5% sodium carbonate. The amine was most effectively removed (i.e., without additional reactions of TFD) with solutions of hydrochloric acid and acetic acid. Further investigation of the TFD solutions which were extracted with acetic acid showed that TFD did not react with 2,4-pentanedione in the presence of $HBF_4 \cdot OEt_2$. Instead, TFD was found to react with the conjugate base of acetic acid which had remained in the organic layer after the neutralization process. Due to the problems associated with the diethyl ether solutions of TFD, other solvents were explored (e.g., methylene chloride and chloroform).

Investigation of Hydrolytic Procedures

To this point, several mixtures have been obtained from the reaction of β-diketones with TFD. To simplify the analyses of these mixtures, an acid-hydrolysis procedure has been employed. For reaction mixtures which were obtained from 2,4-pentanedione, optimum hydrolytic conditions were achieved with a methanol-water-HBF_4 solution. The selection of this hydrolysis system was based on the testing of several known hydrolytic procedures. Conditions which have been commonly employed for the hydrolysis of vinyl ethers include aqueous sulfuric acid in THF,[87a] aqueous acetic acid in

diglyme,[87b] aqueous hydrochloride acid in diglyme,[87b] and aqueous acetic acid in 1,2-dimethoxyethane.[87c] The results of this hydrolysis study are presented in Table 3.6. The poor results which were obtained with aqueous sulfuric acid in THF are probably due to inhomogenous mixing of the organic and aqueous layers. Poor results were also obtained from perchloric acid due to the low acid concentrations that were employed. In addition, this system was not refluxed because of safety considerations. Aqueous acetic acid in diglyme provided hydrolysis of the vinyl ethers, but the diglyme solvent complicated the analysis of the reaction mixture. No advantage was observed for the methanol-water-HBF_4 conditions over the 2,2,2-trifluoroethanol-water-HBF_4 system except that the former system was slightly more economical. Both alcoholic systems provided superior results over the other hydrolytic conditions.

When the 1-phenyl-1,3-butanedione reaction products were obtained after hydrolysis, several ketals and enol ethers (e.g., cyclohexenone 157 and insertion ketal 173) were isolated due to incomplete hydrolysis of the reaction mixture. The reason(s) for incomplete hydrolysis of cyclohexenone 157 were described in Chapter II. Further hydrolysis of cyclohexenone 157 with the methanol-water-HBF_4 was not observed. In addition, further hydrolysis of cyclohexenone 157 was not achieved with aqueous sulfuric acid in THF or aqueous acetic acid in diglyme. These additional hydrolysis attempts also

TABLE 3.6

Conditions Tested for the Hydrolysis of Vinyl Ethers

amount of 2,4-pentanedione used in preparing vinyl ethers	conditions[c]	results
0.5 g [a]	10 mL 10% H_2SO_4-10 mL THF stirred 4 h [d]	Vinyl ethers were not hydrolyzed.
0.5 g [a]	10 mL 20% H_2SO_4-10 mL THF refluxed 11 h [d]	Vinyl ethers were not hydrolyzed.
0.5 g [a]	15 mL 7% $HClO_4$-15 mL THF stirred 18 h [e]	Vinyl ethers were not hydrolyzed.
0.5 g [a]	20 mL 20% H_2SO_4-20 mL THF refluxed 60 h [d]	Trace amounts of vinyl ethers remained.
0.5 g [a]	20 mL 7% $HClO_4$-20 mL THF stirred 4 days	Vinyl ethers were not hydrolyzed.
1.0 g [b]	15 mL methanol-4 mL water-2 mL HBF_4 refluxed 20 h [f]	Vinyl ethers were hydrolyzed.
1.0 g [b]	15 mL 2,2,2-trifluoroethanol-4 mL water-2 mL HBF_4 refluxed 20 h [f]	Vinyl ethers were hydrolyzed.
1.0 g [b]	15 mL diglyme-4 mL water-2 mL HBF_4 refluxed 20 h [f]	Vinyl ethers were hydrolyzed. Further separation was required to remove diglyme from the hydrolyzed products.

TABLE 3.6 (continued)

a Prepared by treating 2,4-pentanedione with $HBF_4 \cdot OEt_2$ and an excess of TFD. The reaction mixture was neutralized with 2 portions of 5% $NaHCO_3$ and 1 portion of water prior to hydrolysis.

b Prepared by treating 2,4-pentanedione with $HBF_4 \cdot OEt_2$ and an excess of TFD. These reaction mixtures were not neutralized prior to hydrolysis.

c All organic mixtures were neutralized with 2 portions of 5% $NaHCO_3$ and 1 portion of water after hydrolysis.

d These conditions afforded little mixing of the organic and aqueous layers.

e Hydrolyzed mixture was treated with diethyl ether and water to assist the separation of organic and aqueous layers.

f Hydrolyzed mixture was treated with methylene chloride and water to assist the separation of organic and aqueous layers.

confirm the unusual stability of the ketal functionality in cyclohexenone 157 to hydrolytic conditions.

Isolation of 1-Phenyl-1,3-butanedione Reaction Products Prior to Hydrolysis

Most of the experimental results that have been described for the acid-catalyzed reaction of 1-phenyl-1,3-butanedione with TFD have been obtained after hydrolysis with the previously described conditions. This hydrolysis procedure was employed to simplify the analysis of the resulting reaction mixture. In Chapter II, the isolation of cyclohexadiene 165 from an unhydrolyzed reaction mixture was reported. This cyclohexadiene appears to be a key intermediate in the formation of biphenyl 155 and cyclohexenone 156. A second compound which appears to afford several insertion products after hydrolysis was also isolated from this same reaction mixture. This precursor was tentatively assigned as insertion ketal 194 which was previously reported in this chapter. Complete structural assignments for this insertion product have not been pursued even though several interesting spectral features were noted in the ^{1}H and ^{13}C NMR spectra for this compound (Figures 3.2 and 3.3). First, the ^{13}C NMR spectrum of this compound contained two methyl signals of equal intensities and a very broad signal at δ 103.28 ppm (the ketal carbon and the olefinic methine carbon appear to

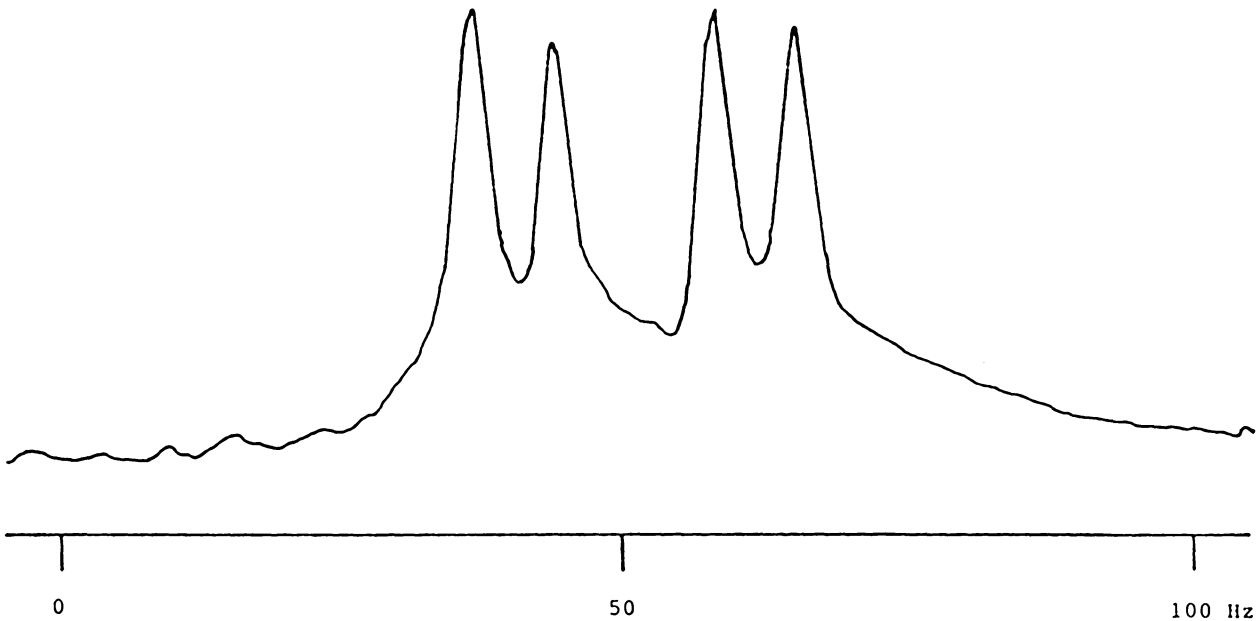


Figure 3.2

A portion of the ^{1}H NMR spectrum of insertion ketal 194. This expansion illustrates the two pairs of doublets appearing in the methyl region of the ^{1}H NMR spectrum (from 1.35 to 1.89 ppm).

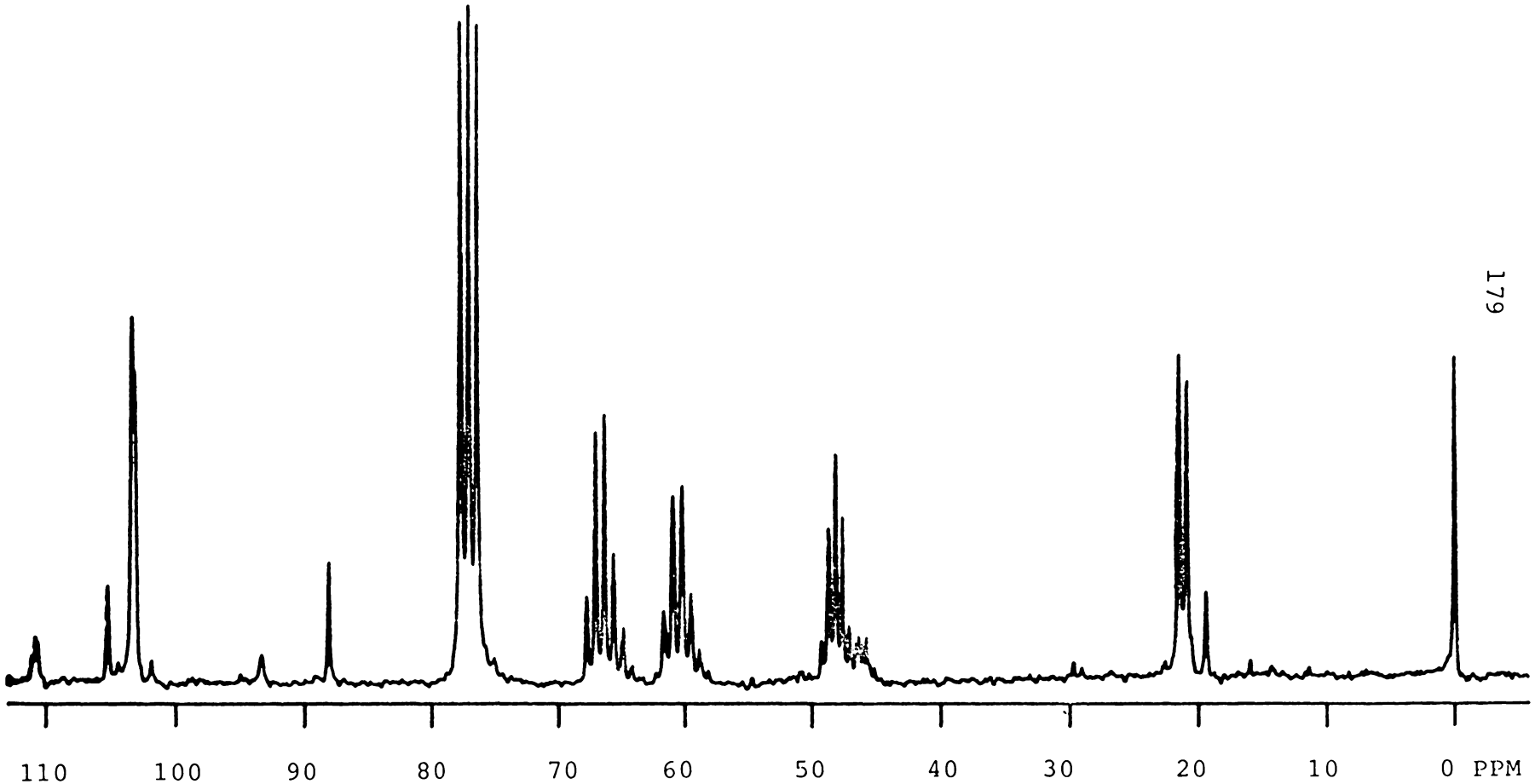
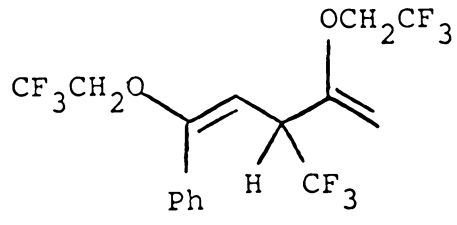


Figure 3.3

A portion of the ^{13}C NMR spectrum of insertion ketal 194.

overlap in this spectrum). Second, two pairs of doublets appear in the methyl region of the ^{1}H NMR spectrum. In addition, two doublets which have almost identical chemical shifts appear in the olefinic region of the ^{1}H NMR spectrum. The above observations suggest that the insertion compound 194 could have restricted rotation due to steric hindrance. This would lead to two conformations of insertation ketal 194 which would be detected in the ^{1}H and ^{13}C NMR spectra (Figure 3.4). The coupling constants that are observed for the two methyl signals could be due to a four-bond coupling of the hydrogens on each methyl group to the corresponding hydrogen on the aliphatic methine carbon. This coupling would be observed since the methyl group and the hydrogen on the methine carbon have an anti-periplanar relationship (Figure 3.5). All other spectroscopic data including an integration of the ^{1}H NMR spectrum are in agreement with insertion ketal 194.

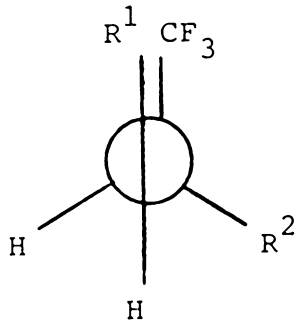
Several other observations are also consistent with insertion ketal 194. When this compound was treated with silica gel, insertion diene 200 was formed.



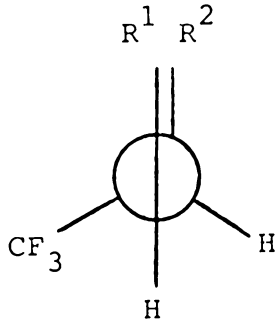
200

Figure 3.4

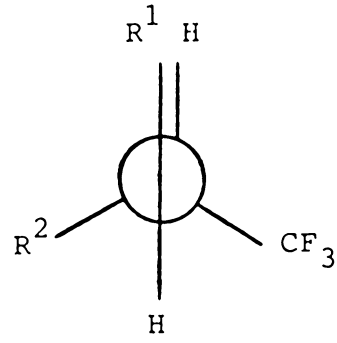
Newman projections for the six conformations of insertion ketal 194. Based on models of the compound, conformations A and B appear to be favored. These models also indicate that R^1 can be positioned at greater distances from the groups on the vicinal carbon than the geminal hydrogen to R^1. For example, the distance from R^1 to the CF_3 group in conformation A is greater than the distance from the previously described geminal hydrogen to the CF_3 group in conformation D. Based on steric arguments alone for these Newman projections, one would have expected that conformation D should be more favorable than conformation A.


R1 CF3
H
R2
H

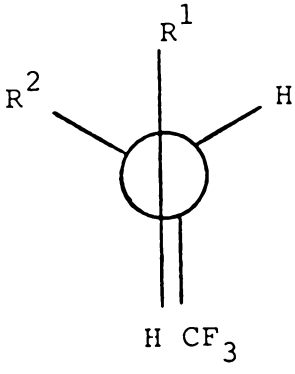
(A)


R1 R2
CF3
H
H

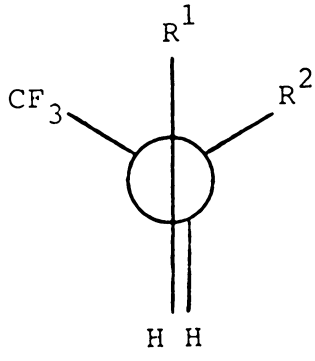
(B)


R1 H
R2
CF3
H

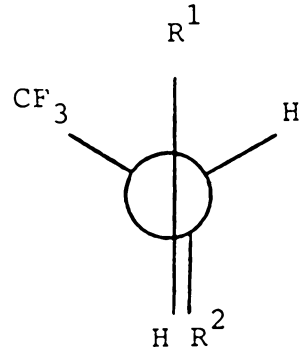
(C)


R1
R2
H
H CF3

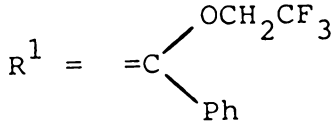
(D)

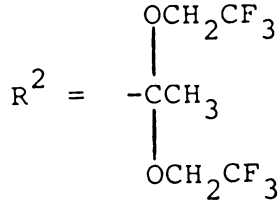

R1
CF3
R2
H H

(E)


R1
CF3
H
H R2

(F)


R1 =
=C
OCH2CF3
Ph


R2 =
-CCH3
OCH2CF3
OCH2CF3

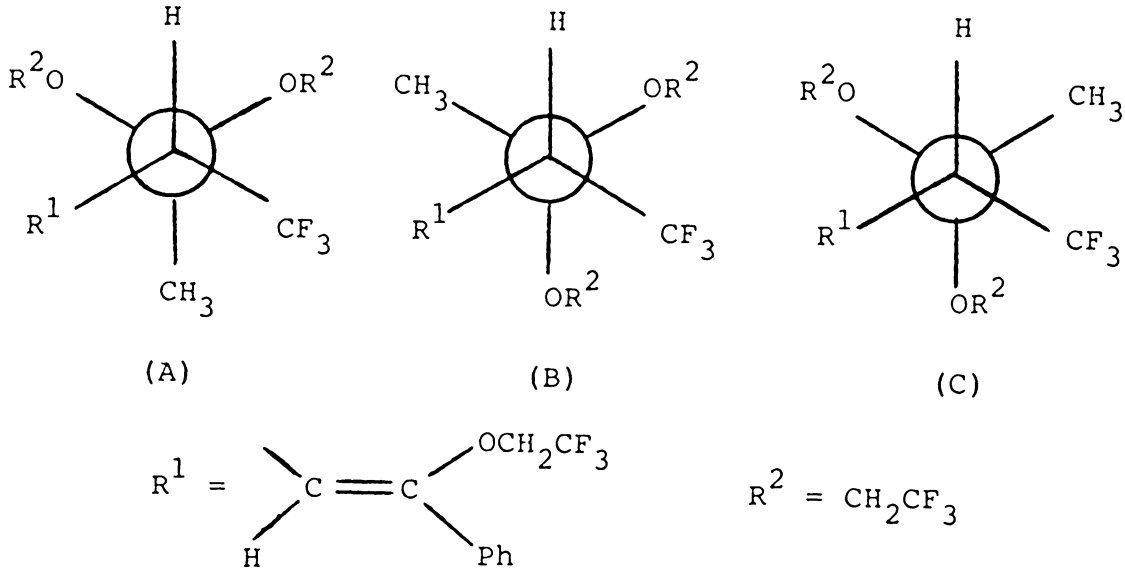


Figure 3.5

Newman projections for insertion ketal 194 illustrating the favored anti-periplanar relationship between the methyl group and the hydrogen on the methine carbon. As a result of fewer steric interactions in conformation A, this conformation is preferred.

Insertion ketal 194 could easily eliminate 2,2,2-trifluoroethanol to afford insertion diene 200. In addition, insertion ketal 194 is slowly converted to insertion ketone 156 over long periods of time. This conversion could occur because of traces of acid and water in the sample. A further driving force for the above conversion would be the thermodynamic instability of insertion ketal 194. Models of insertion ketal 194 suggest that the compound has steric crowding near the carbon-carbon double bond. Both the bulky aliphatic group and the bulky trifluoroethoxy group have a cis-relationship about the double bond. As a result of the steric interactions of these groups, insertion ketal 194 may possess thermodynamic instabilities that would be relieved through the above conversion.

The Treatment of Other β-Diketones with TFD in the Presence of $HBF_4 \cdot OEt_2$

In addition to 1-phenyl-1,3-butanedione and 2,4-pentanedione, a number of other β-diketones have also been treated with TFD and $HBF_4 \cdot OEt_2$. These other β-diketone reactions have provided additional information on the cyclization mechanism and the synthetic scope of the cyclization reaction. The results that were obtained for the reaction of 5,5-dimethyl-1,3-cyclohexanedione with TFD indicated that cyclization had not occurred (entries 1 and 2 in Table 3.7).

TABLE 3.7

Results Obtained from Reactions of β-Diketones and Related Compounds with TFD[a]

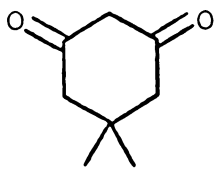
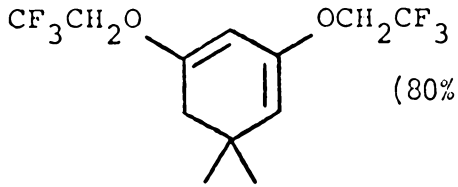
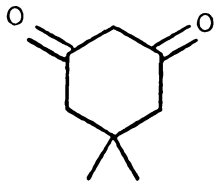
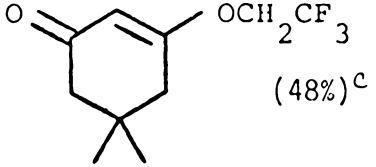
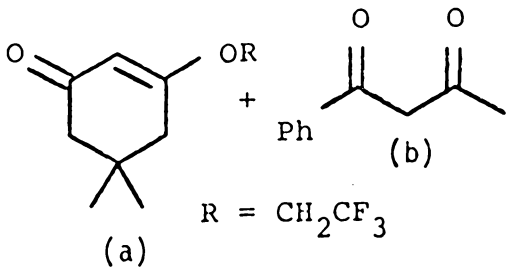
entry	compounds treated with TFD	results before hydrolysis	results after hydrolysis
1		 (80%)[b] 202	
2		 (48%)[c] 201	
3	 (a) R = CH_2CF_3	(b)	Diene 202 (dominating), trifluoroethyl enol ethers of 1-phenyl-1,3-butanedione, and insertion ketal 194 were observed.[d]	Recovered starting materials.[d]

TABLE 3.7 (continued)

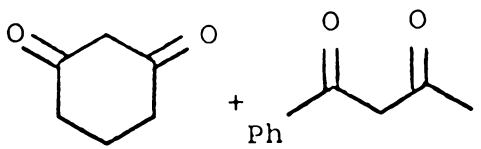
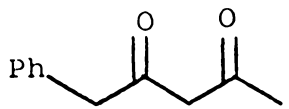
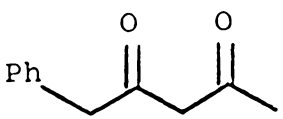
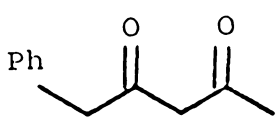
entry	compounds treated with TFD	results before hydrolysis	results after hydrolysis
4	 (a) (b)	Enol ether 201 was dominating.[d]	Starting materials and insertion ketone 156 were recovered.[e]
5		Observed three isomeric forms of starting material and two trifluoroethyl enol ethers of 1-phenyl-2,4-pentanedione.[e]	
6		Observed two trifluoroethyl enol ethers in this reaction. The amount of other trifluoroethoxy groups appeared larger in this reaction mixture than the amounts observed in entries 5 and 7.	Starting materials, insertion diketone 209, and insertion ketone 210 were recovered.
7		Observed two trifluoroethyl enol ethers and several other derivatives.	

TABLE 3.7 (continued)

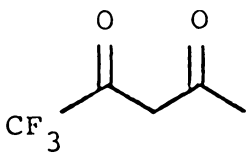
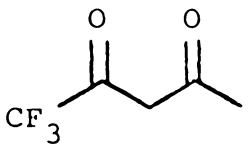
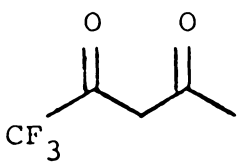
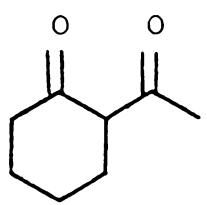
entry	compounds treated with TFD	results before hydrolysis	results after hydrolysis
8		Complex mixture was observed.	Insertion products (220 and 221) and other unidentified products were observed.
9		Complex mixture was observed.	Insertion products 220 and 221 were the major compounds that were recovered. 4 other insertion products were present with signals at δ 5.58, 5.66, 5.83, and 5.91 ppm; several other compounds were present.
10		Complex mixture was observed, however, this reaction mixture appeared to contain fewer products than entry 9.	Insertion ketone 221 was more dominating in this reaction mixture.
11		Looked promising with several olefinic signals observed between δ 115-155 ppm.	Large amounts of starting material were recovered; many minor components were still present in the olefinic region.

TABLE 3.7 (continued)

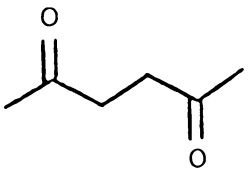
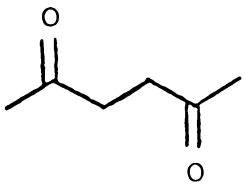
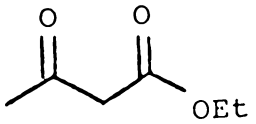
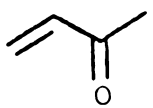
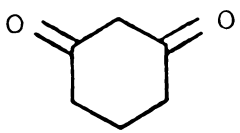
entry	compounds treated with TFD	results before hydrolysis	results after hydrolysis
12		Complex mixture was observed.	Several signals of interest from δ 5.7 to 7.0 ppm in ^{1}H NMR spectrum and from δ 115 to 150 ppm in the ^{13}C NMR spectrum; sample polymerized with time.
13		Complex mixture was observed.	This reaction did not look as promising as entry 12. This reaction afforded a larger amount of starting material than was observed for entry 12.
14		Reaction afforded a large amount of starting material and several trifluoroethyl enol ethers; no aromatic compounds were detected.	

TABLE 3.7 (continued)

entry	compounds treated with TFD	results before hydrolysis	results after hydrolysis
15		Broad methyl and vinyl regions were observed suggesting polymerization.	Less vinylic signals were observed; signals remained broad suggesting polymerization.
16			4 compounds were detected by LC-^{1}H NMR. All 4 compounds had signals in trifluoroethoxy region. Preliminary results suggest that trifluoroethyl enol ether 228 and insertion compound 230 were two of the compounds present.

a See Table 3.8 for experimental conditions.

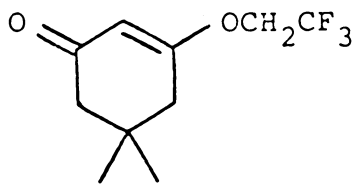
b Observed as the major component in the reaction mixture by ^{1}H and ^{13}C NMR spectroscopy.

c Obtained from chromatographic separation on neutral alumina.

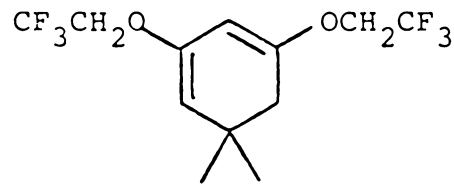
d Observed by ^{1}H and ^{13}C NMR spectroscopy.

e Obtained from chromatographic separation on silica gel.

Both trifluoroethyl enol ether 201 and trifluoroethoxy diene 202 could be obtained from this reaction by varying the reaction conditions.



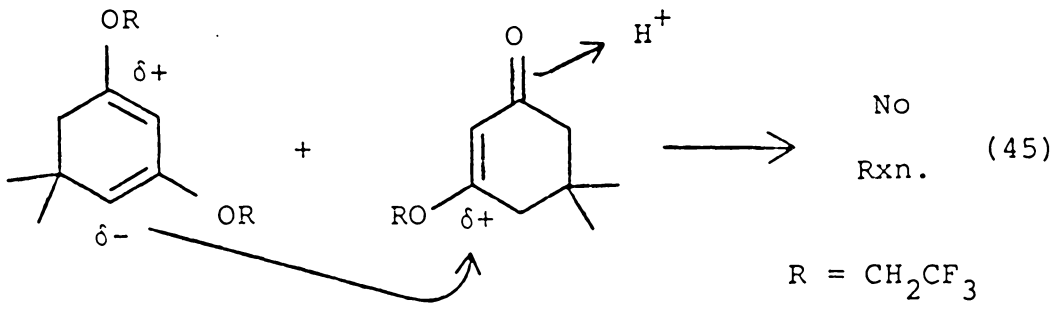
201



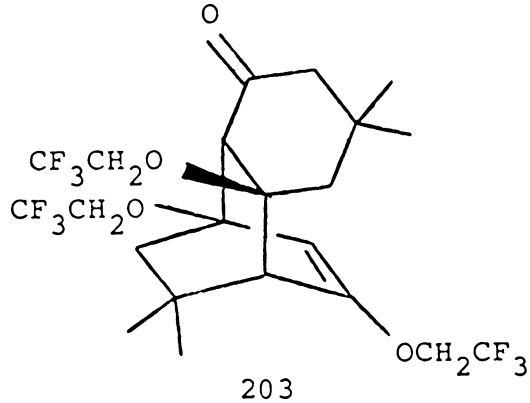
202

Trifluoroethyl enol ether 201 was isolated when the reaction mixture was neutralized with 5% $NaHCO_3$. When the reaction mixture was treated with triethylamine prior to neutralization with 5% $NaHCO_3$, diene 202 was obtained. This suggests that diene 202 was hydrolyzed during the previous neutralization process. Isolation of diene 202 helps establish that the corresponding dienes of 1-phenyl-1,3-butanedione and 2,4-pentanedione could have formed when the respective β-diketones were treated with TFD and $HBF_4 \cdot OEt_2$. These dienes may have been hydrolyzed during the neutralization process. This would have prevented isolation of either diene.

Cyclization reactions were not observed for 5,5-dimethyl-1,3-cyclohexanedione presumably due to a combination of two factors. First, a Michael addition of diene 202 to enone 201 would not be very favorable due to steric hindrance between the combining units in the initial step (eq 45).



Second, if cyclization did occur to intermediate 203, additional thermodynamic stabilization could not be achieved by eliminating 2,2,2-trifluoroethanol to afford a more stable aromatic compound.



203

The above eliminations are not favored due to the structural strain which would result in any hypothetical reaction product. Based on these two factors, cyclization would not be expected for 5,5-dimethyl-1,3-cyclohexanedione.

The above cyclohexanedione was attractive for the study of potential mixed condensations between two β-diketones. The use of 5,5-dimethyl-1,3-cyclohexanedione in this study

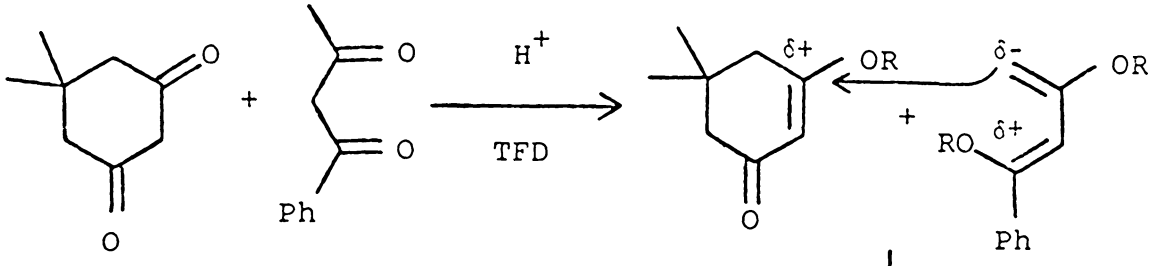
should help favor cyclization of the two β-diketone equivalents since a self-condensation reaction does not occur for this cyclohexanedione under the present reaction conditions. Therefore, a less sterically hindered β-diketone could undergo a mixed-condensation reaction with 5,5-dimethyl-1,3-cyclohexanedione without a competing self-condensation reaction of the cyclohexanedione. The second β-diketone that was employed in this mixed-condensation reaction was 1-phenyl-1,3-butanedione. 1-Phenyl-1,3-butanedione was chosen because it has afforded the highest yield of cyclization products to date.

Some of the potential reaction products that would be expected from the mixed-condensation reaction of 5,5-dimethyl-1,3-cyclohexanedione are illustrated in Scheme 3.1. When the above β-diketones were treated with TFD in the presence of $HBF_4 \cdot OEt_2$ (entry 4 in Table 3.7), these reaction products (e.g., compounds 204 and 205) were not obtained. A mixture of the corresponding trifluoroethyl enol ethers of the two β-diketones and the insertion product 194 was afforded from the above reaction before hydrolysis. On hydrolysis of the above reaction mixture, insertion ketone 156 and the respective β-diketones were isolated after chromatographic separation.

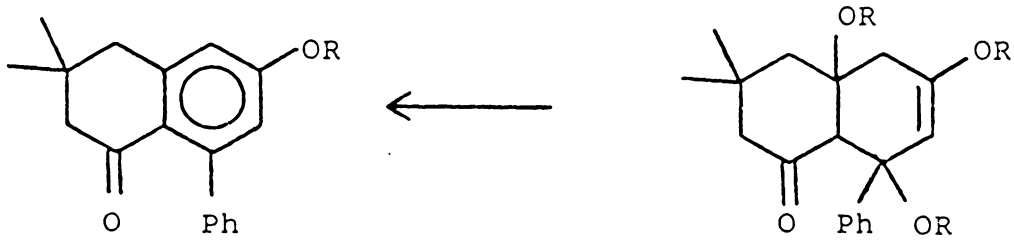
Similar results were obtained when trifluoroethyl enol ether 201 and 1-phenyl-1,3-butanedione were treated with TFD (entry 3 in Table 3.7). Diene 202 was detected in the result-

Scheme 3.1

Potential Products for the
Mixed-Condensation Reaction of
1-Phenyl-1,3-butanedione and
5,5-Dimethyl-1,3-cyclohexanedione
with TFD



R = CH_2CF_3

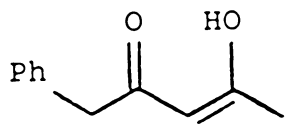


205 204

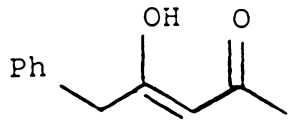
ing mixture since this reaction was neutralized with triethylamine. Note that trifluoroethyl enol ether 201 was isolated from the experiment corresponding to entry 4 in Table 3.7 since this reaction mixture was neutralized with 5% $NaHCO_3$.

Several workers[33,34] have reported a base-catalyzed self-condensation reaction for 1-phenyl-2,4-pentandione. The above β-diketone was treated with TFD in the presence of $HBF_4 \cdot OEt_2$ to examine whether or not an acid-catalyzed self-condensation reaction would occur for this same compound. A dark purple solution was obtained when 1-phenyl-2,4-pentanedione was treated with TFD. This initial observation suggested that a conjugated product was formed. After chromatographic separation of both hydrolyzed and unhydrolyzed reaction mixtures, no evidence of cyclization products was found. However, cyclized products could be present in relatively small amounts (1-5%) which were not detected.

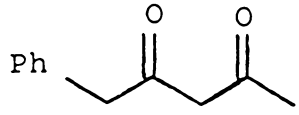
After chromatographic separation of the unhydrolyzed reaction mixture, three isomeric forms of 1-phenyl-1,3-butanedione (i.e., compounds 206-208) and two trifluoroethyl enol ethers (209 and 210) were detected.



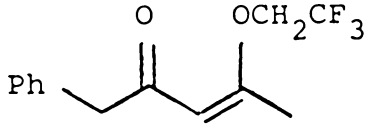
206



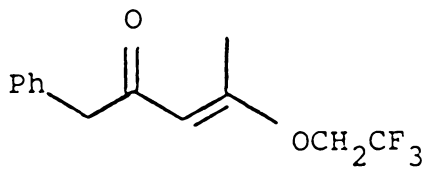
207



208



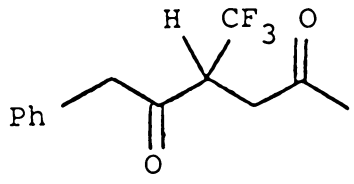
209



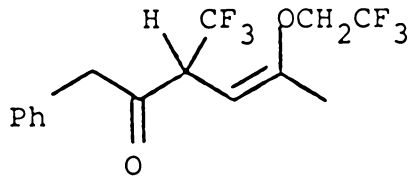
210

Significant hydrolysis of the reaction mixture could have occurred to afford the these products. Some dienes could have formed during the reaction process. However, these dienes would have been hydrolyzed during the 5% $NaHCO_3$ neutralization procedure. Partial hydrolysis of the resulting enol ethers could have also occurred on the silica gel column which was utilized for chromatographic separation. A second possibility to account for the above products would be limited reaction of 1-phenyl-2,4-pentanedione with TFD.

Further analysis of the hydrolyzed reaction mixture that was obtained from 1-phenyl-2,4-pentanedione indicated that several compounds were present in the reaction mixture. After chromatographic separation, a large amount of 1-phenyl-2,4-pentanedione was recovered (64%). Insertion products (i.e., compounds 211 and 212) and some unidentified polymers were also isolated from this reaction mixture.



211



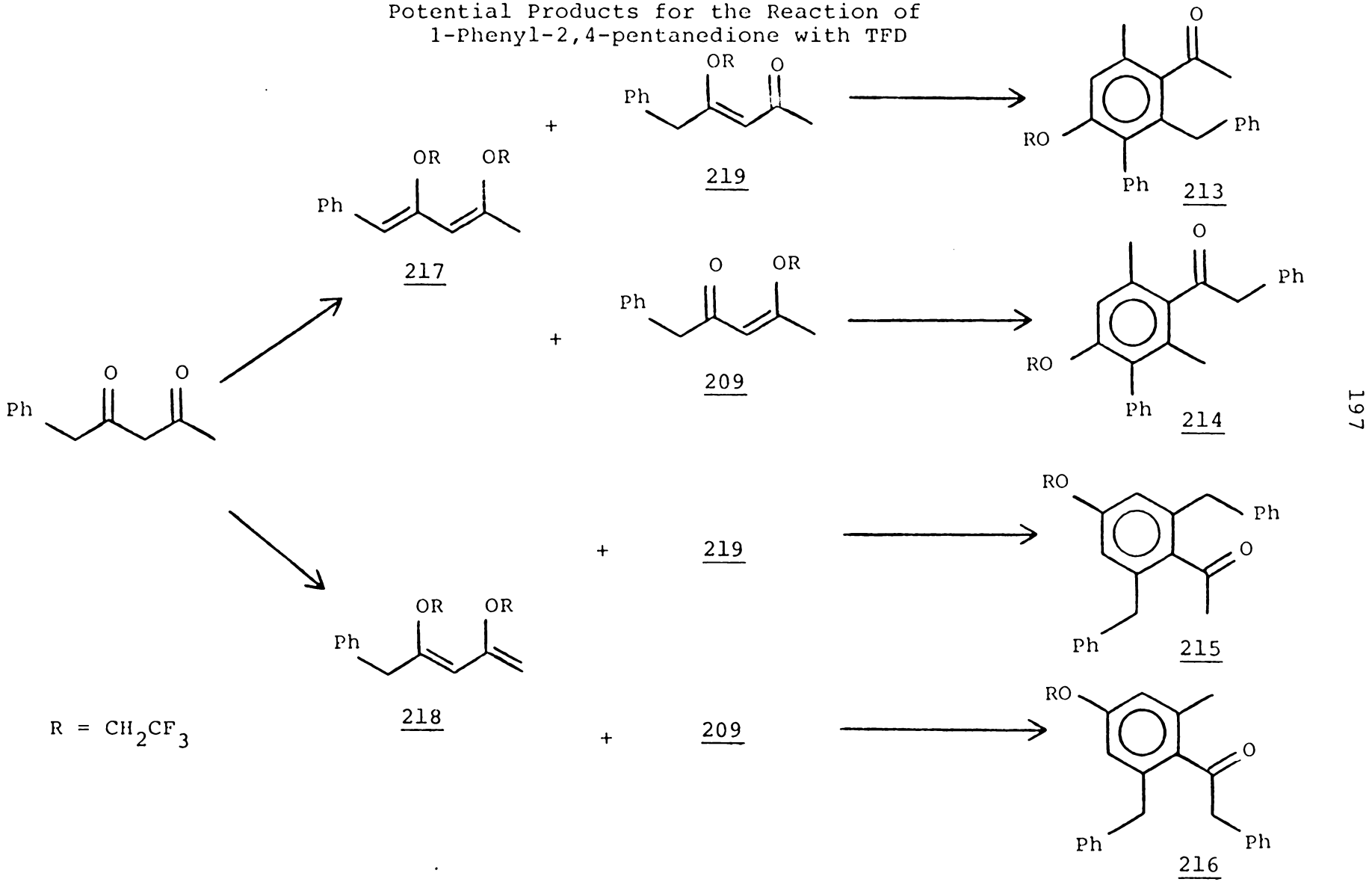
212

The reason why 1-phenyl-2,4-pentanedione did not undergo an acid-catalyzed self-condensation reaction in the presence of TFD is not fully understood.

The 1-phenyl-2,4-pentanedione system was initially very interesting because several different cyclization products (e.g., compounds 213-216) could have formed under the above reaction conditions (Scheme 3.2). It was hoped that a distribution of the above products would have provided mechanistic insight for the cyclization process. These compounds would have originated from the cyclization of dienes 217 and 218 with trifluoroethyl enol ethers 209 and 219. A mixture of the above reaction products would have been expected since small thermodynamic differences should be observed for intermediates 209, 217, 218, and 219. Diene 217 appears slightly more stable than diene 218 due to the conjugation of the two olefinic bonds with the phenyl ring in the former compound. In contrast, less cyclization would be expected from this thermodynamically more stable diene based on the steric hindrance that would be encountered during the initial Michael addition. Steric hindrance in the Michael addi-

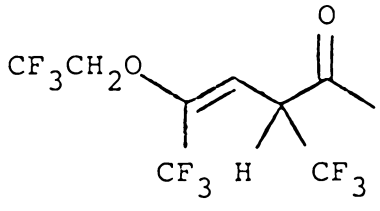
Scheme 3.2

Potential Products for the Reaction of
1-Phenyl-2,4-pentanedione with TFD

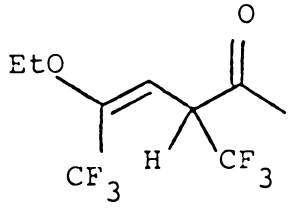


tion of diene 217 presently appears to be the best explanation why an acid-catalyzed self-condensation reaction was not observed for 1-phenyl-2,4-pentanedione.

The reaction of 1,1,1-trifluoro-2,4-pentanedione with TFD in the presence of $HBF_4 \cdot OEt_2$ (entries 8-10 in Table 3.7) provided several unusual products. The predominant reaction products that were obtained after hydrolysis were insertion products 220 and 221.



220



221

Compounds analogous to compound 220 have been previously identified in the reaction mixtures that were obtained from 1-phenyl-1,3-butanedione and 1-phenyl-2,4-pentanedione. Isolation of ethyl enol ether 221 was unusual since an ethyl group had been incorporated into the reaction product. This was surprising because ethyl enol ethers have not been previously isolated from reaction mixtures originating from β-diketones. The ethyl group that has been incorporated into compound 221 appears to originate from cleavage of $HBF_4 \cdot OEt_2$ that was utilized as the acid catalyst. In the above reactions, an increase in the ratio of ethyl enol ether 221 to trifluoroethyl enol ether 220 was observed when the ratio

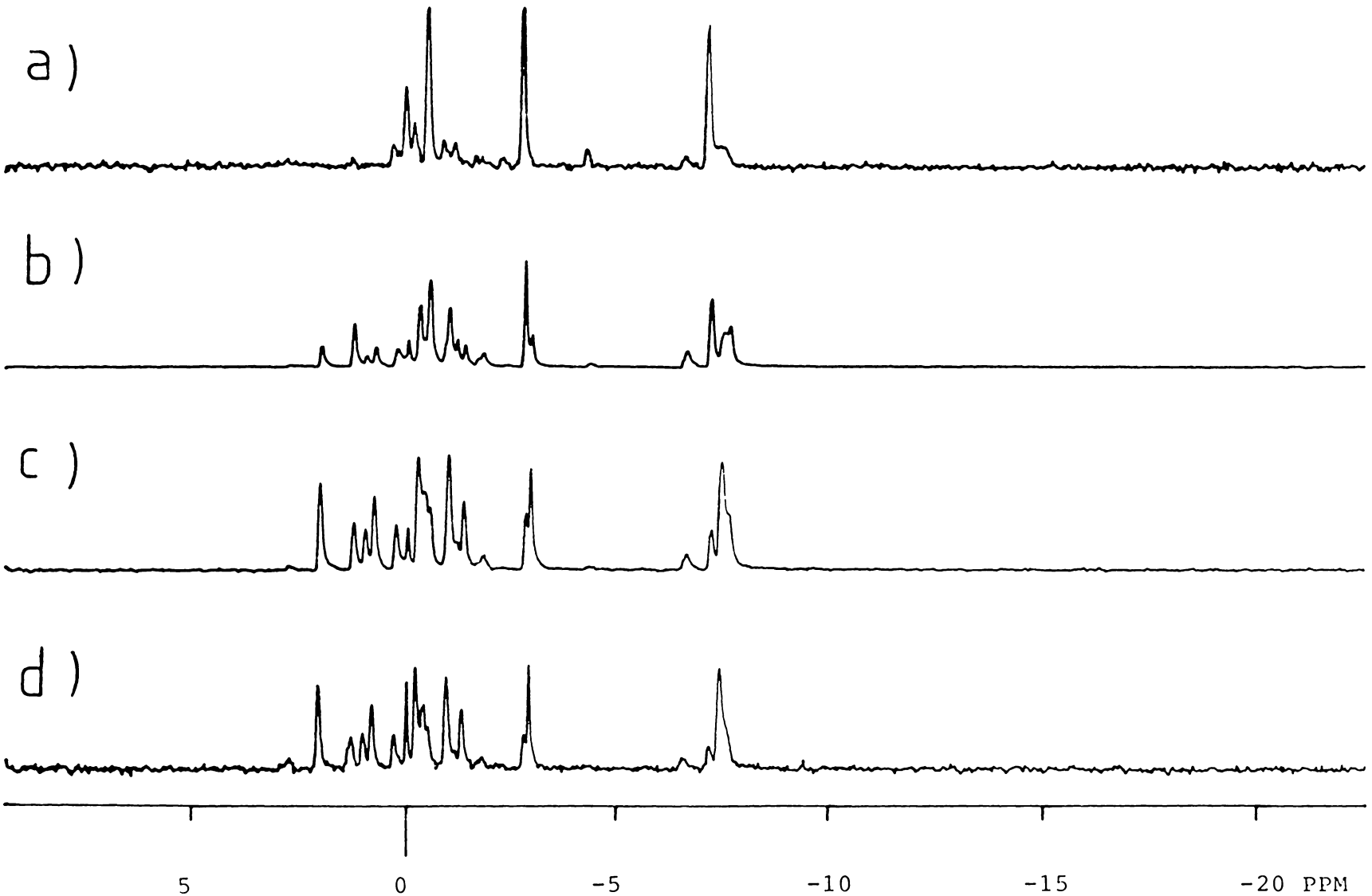
of acid catalyst to starting β-diketone was increased.

Although several reaction products have not been identified in the above mixture, a novel application of the LC-NMR technique[55] was used for the analysis of this mixture. Due to the numerous fluorine containing compounds present in these mixtures (e.g., fluorine compounds originating from both the starting β-diketone and TFD), the LC-^{19}F NMR results (Figure 3.6) were obtained to supplement the more commonly utilized LC-^{1}H NMR technique (Figure 3.7). Applications of the LC-^{19}F NMR have not previously appeared in the chemical literature.[55] The results that were obtained from LC-^{1}H NMR and LC-^{19}F NMR separations clearly illustrate that enol ethers 220 and 221 were present in the above reaction mixture.

As previously mentioned, the reaction of 1,1,1-trifluoro-2,4-pentanedione with TFD did afford some products which have not been identified. After chromatographic separation, one of the above reaction mixtures (entry 8 in Table 3.7) afforded four additional insertion products (e.g., olefinic doublets of the insertion products appeared at δ 5.58, 5.66. 5.83, and 5.91 ppm). The ^{1}H NMR spectra of the two insertion products with doublets at δ 5.58 and 5.66 ppm contained a corresponding ethyl group for each compound. In another ^{1}H NMR spectrum, the doublets at δ 5.83 and 5.91 ppm were only associated with trifluoroethoxy groups. No additional methyl signals were observed in the ^{1}H NMR region for the latter insertion products. The above insertion products

Figure 3.6

Selective LC-^{19}F NMR files of the 1,1,1-trifluoro-2,4-pentanedione reaction products. (a-d) Files 2-5 (16-19 minutes elution times) are spectra of several unidentified compounds. (e and f) Files 6 and 7 (20 and 21 minutes) are spectra corresponding to insertion ketone 220. (g) File 8 (22 minutes) is the spectrum of insertion ketone 221. (h) File 27 (41 minutes) is the spectrum of a late eluting compound which has not been assigned.


a)
b)
c)
d)
5
0
-5
-10
-15
-20 PPM

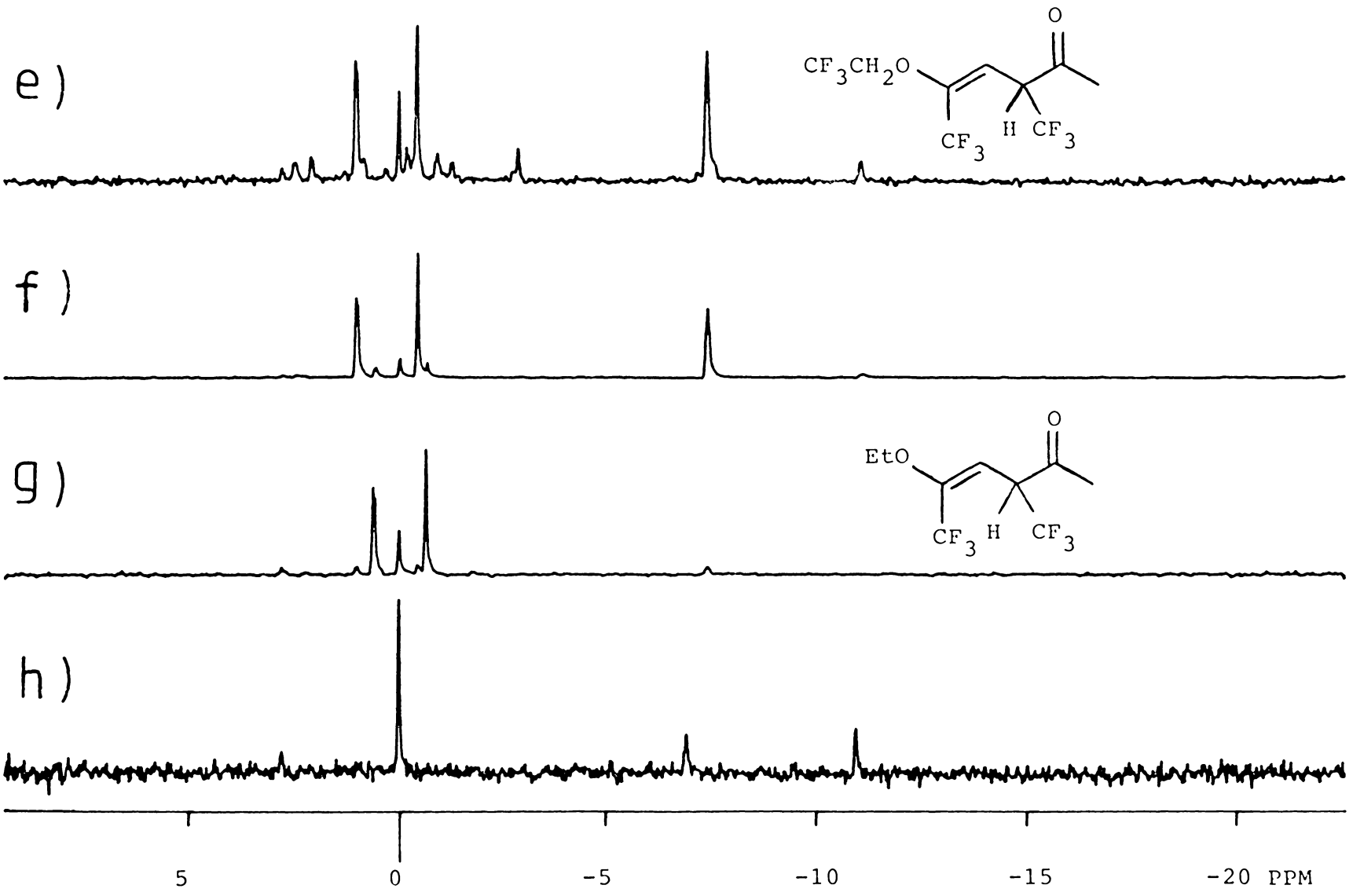
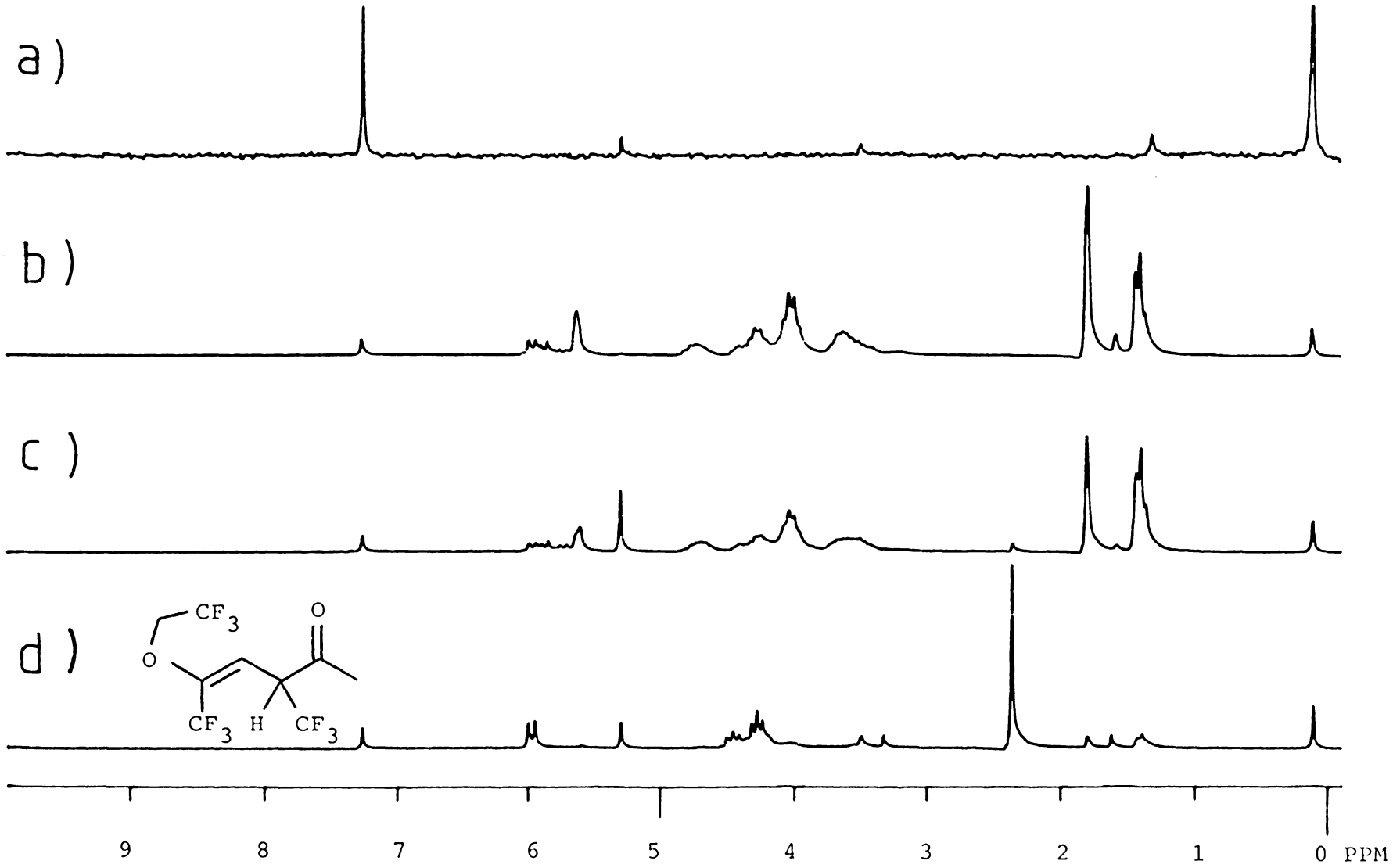
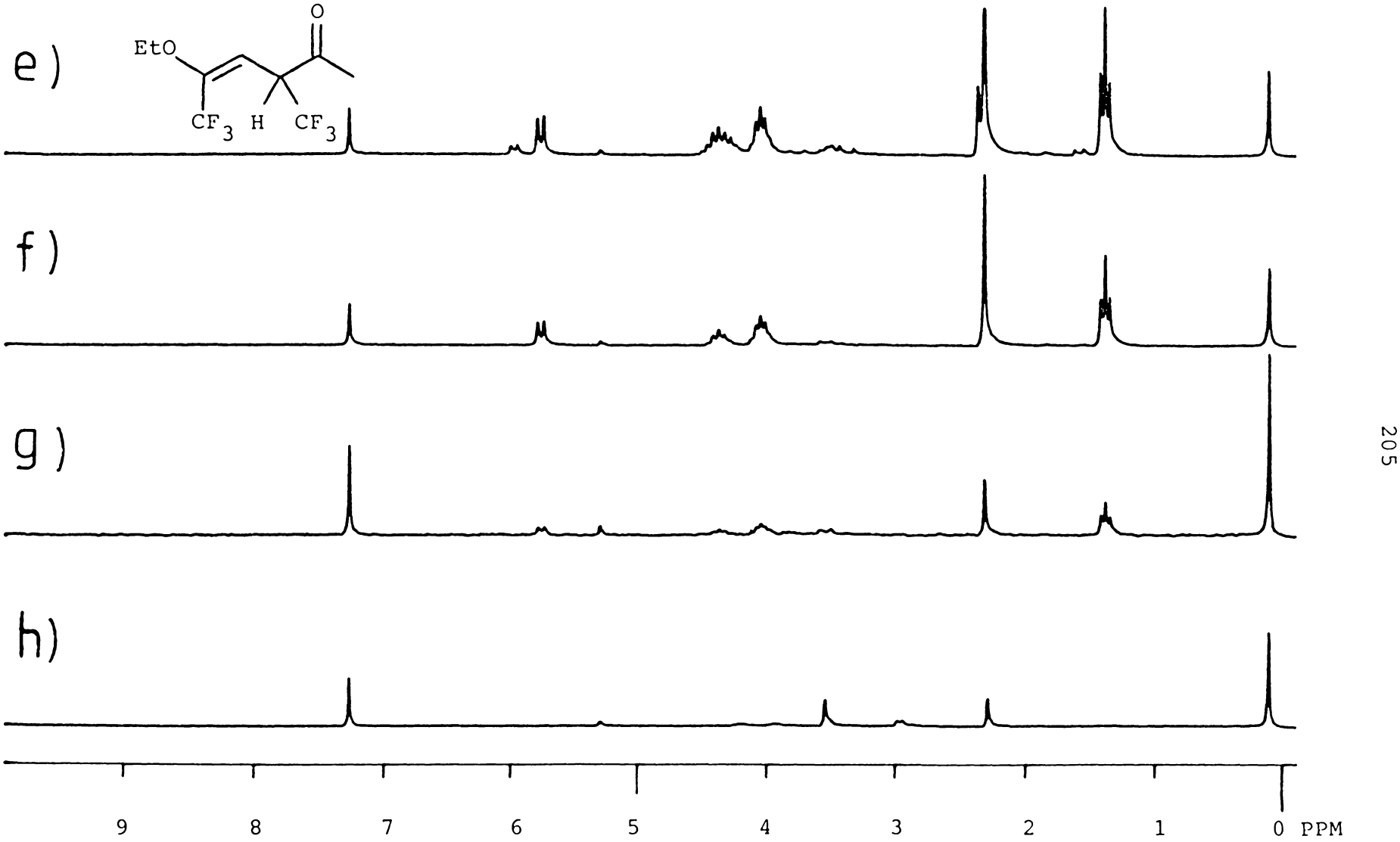

e)
f)
g)
h)
O
CF_3CH_2O
CF_3
H
CF_3
O
EtO
CF_3
H
CF_3
5
0
-5
-10
-15
-20 PPM

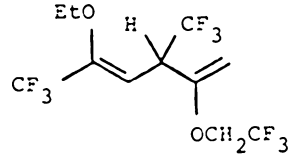
Figure 3.7

Selective LC-^{1}H NMR files of the 1,1,1-trifluoro-2,4-pentanedione reaction products. (a-c) Files 1-3 (elution times of 14-16 minutes) are spectra of several unidentified compounds. (d) File 4 (17 minutes) is the spectrum of insertion ketone 220. (e) File 5 (18 minutes) is the spectrum containing a mixture of insertion ketones 220 and 221. (f and g) Files 6 and 7 (19 and 20 minutes) are spectra of insertion ketone 221. (h) File 18 (32 minutes) is the spectrum of an unassigned structure.

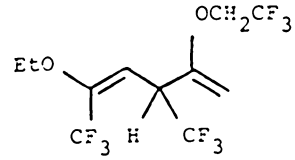

a)
b)
c)
d)
CF3
O
O
CF3
H
CF3
9
8
7
6
5
4
3
2
1
0 PPM


e)
EtO
O
CF3 H CF3
f)
g)
h)
9
8
7
6
5
4
3
2
1
0 PPM

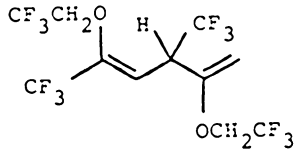
appear to correspond to dienes 222-225.



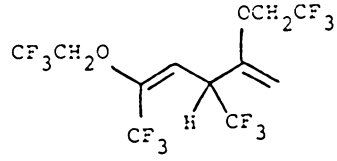
222



223



224

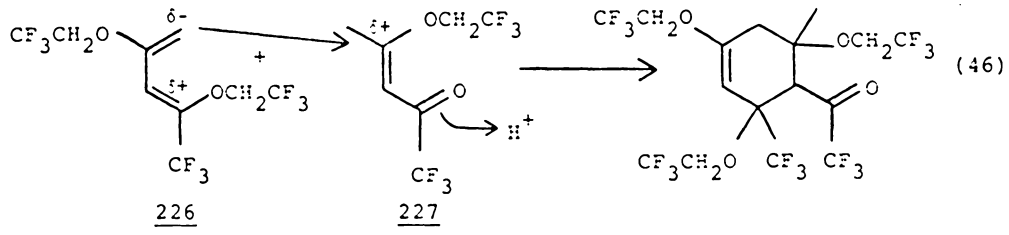


225

Other unidentified compounds have also been isolated from these mixtures. These compounds possess unique structural features that have not been encountered in other reaction mixtures originating from β-diketones. Furthermore, structures for these compounds have not been completely assigned. One compound had a ^{1}H NMR spectrum which possessed aromatic hydrogens (δ 7.5-7.8 ppm) and a complex aliphatic region. This suggests that a small amount of cyclization occurred during the reaction of 1,1,1-trifluoro-2,4-pentanedione with TFD.

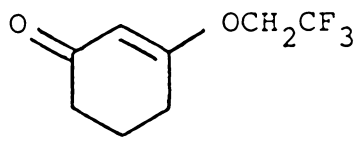
The above results suggest that the intermediates that would be obtained from the reaction of 1,1,1-trifluoro-2,4-pentanedione do not favor cyclization. These intermediates do not exhibit the necessary electronic requirements to

undergo cyclization reactions. For cyclization to occur, diene 226 must undergo nucleophilic attack on enol ether 227.

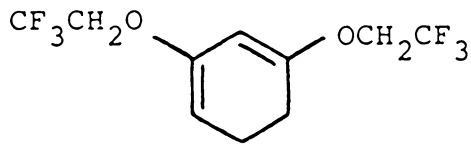


During this attack, a partial positive charge would develop on the carbon adjacent to the trifluoromethyl and the trifluoroethoxy groups. The two electron-withdrawing substituents should destablize the positive charge of this developing carbonium ion. Therefore, electronic factors do not favor a large amount of cyclization for this β-diketone.

The reaction of 1,3-cyclohexanedione with TFD in the presence of $HBF_4 \cdot OEt_2$ was also examined (entry 16 in Table 3.7). Based on the previous study of 5,5-dimethyl-1,3-cyclohexanedione, the reaction of 1,3-cyclohexanedione would be expected to afford similar products (i.e., enol ether 228 and dienol ether 229).

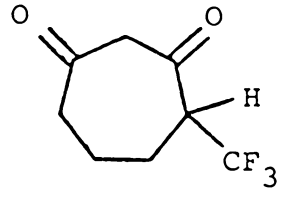


228

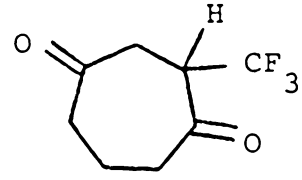


229

Upon hydrolysis, compound 228 and 229 should be converted to 1,3-cyclohexanedione, the starting material. The above reaction mixture was analyzed by LC-^{1}H NMR after hydrolysis. The LC-^{1}H NMR separation indicated that four compounds were present in the above mixture. This preliminary data suggests that this mixture contained trifluoroethyl enol ether 228 and insertion product 230.



230



231

The above insertion product was assigned as compound 230 since the hydrogen originating from TFD did not exhibit a $^{3}J_{HCCH}$ coupling with the α-hydrogen of the β-diketone functionality. A $^{3}J_{HCCH}$ coupling constant would have been observed if structural isomer 231 had been isolated. The two other compounds present in this mixture could not be identified from LC-^{1}H NMR information alone. At this time com-

pounds 228 and 230 are only tentatively assigned because of incomplete spectroscopic data.

2-Acetylcyclohexenone (entry 11 in Table 3.7) was examined since there was a substituent on the α-carbon of the β-diketone systems. All other β-diketones that have been studied in this dissertation were unsubstituted at this α-carbon. The reaction mixture that was obtained by treating this β-diketone with TFD was analyzed both before and after normal hydrolytic treatment. The ^{1}H and ^{13}C NMR spectra of the unhydrolyzed reaction mixture contained a large number of olefinic signals which made the above reaction appear promising. On hydrolysis of this mixture, a large number of the olefins that were initially present in the above reaction mixture were converted to 2-acetylcyclohexenone starting material. Traces of several other compounds were also observed in the ^{1}H and ^{13}C NMR spectra of hydrolyzed reaction mixture. Several resonances appeared in the δ 115-155 ppm region of the ^{13}C NMR spectrum which suggests that some cyclization may have occurred.

Reaction of TFD with Compounds Other than β-Diketones

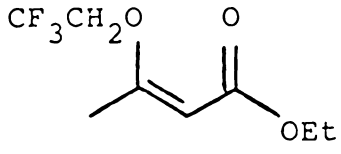
Several related systems were examined utilizing similar reaction conditions. With a better understanding these additional systems, the wider scope of this novel acid-catalyzed self-condensation reaction can be determined. Prelim-

inary results for these systems are reported in Table 3.7. Under the present cyclization conditions, methyl vinyl ketone (entry 15 in Table 3.7) underwent polymerization. Polymerization was observed before and after treatment of the reaction mixture with the hydrolytic conditions. The conclusion that methyl vinyl ketone underwent polymerization was based on the broad signals which were observed in the ^{1}H and ^{13}C NMR spectra. Methyl vinyl ketone appears to be one of the least promising compounds studied in terms of cyclization reactions utilizing normal TFD reaction conditions.

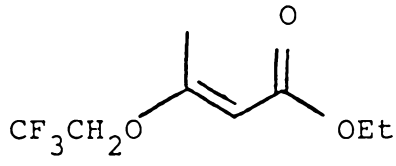
2,5-Hexanedione has been studied to determine whether or not a γ-diketone would undergo an acid-catalyzed self-condensation reaction in the presence of TFD. The reaction of 2,5-hexanedione with TFD in the presence of $HBF_4 \cdot OEt_2$ afforded several products. In the ^{1}H and ^{13}C NMR spectra of the unhydrolyzed reaction mixture, several methyl and methylene carbons were observed. Several signals were also observed in the δ 5.7-7.0 ppm region of the ^{1}H NMR spectrum and in the δ 100-150 ppm region of the ^{13}C NMR spectrum. These signals suggest that some intermolecular condensation reactions have occurred yielding several olefinic compounds. It was not apparent whether or not cyclization reactions occurred during this process. Few signals appeared in the trifluoroethoxy region suggesting that these groups were eliminated during the intermolecular condensation reactions. Normal hydrolytic conditions had little effect

on the reaction mixture as several products were detected after hydrolysis. After chromatographic separation, identification of the above reaction products was extremely difficult since these reaction products rapidly polymerized. The polymerization of the above reaction products suggests that cyclization reactions did not occur. Polymerization of cyclized products would be less likely since further intermolecular condensations between cyclized derivatives would not be expected.

Ethyl acetoacetate was examined to determine whether or not a β-ketoester would undergo an acid-catalyzed self-condensation reaction in the presence of TFD. Initial results on this system suggest that cyclization did not occur for ethyl acetoacetate utilizing the above reaction conditions. Aromatic compounds were not detected in either the ^{1}H or ^{13}C NMR spectrum of the reaction mixture. These spectra indicated a large amount of ethyl acetoacetate was recovered in the reaction mixture. Several trifluoroethyl derivatives of ethyl acetoacetate were also detected. Trifluoroethyl enol ethers 232 and 233 are consistent with the derivatives that were obtained from this reaction.

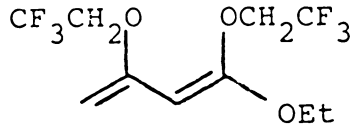


232



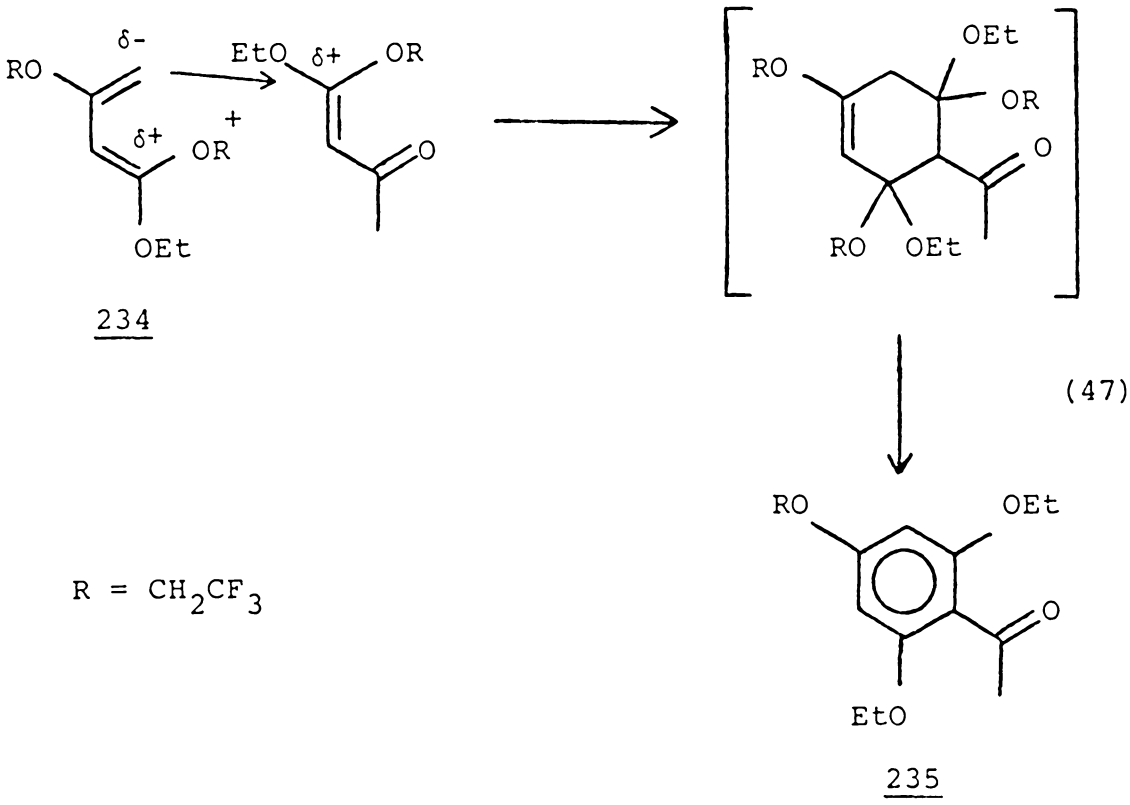
233

Diene 234 was not observed in the previously described mixture since vinyl carbons did not appear in the ^{13}C NMR spectrum (based on characterization by the ^{13}C NMR INEPT experiment).



234

However, diene 234 could have hydrolyzed during the neutralization process. Diene 234 would be a key intermediate for the cyclization of ethyl acetoacetate to aromatic compound 235.



234

(47)

R = CH_2CF_3

235

Conclusion

From the many reactions that have been described in this chapter, it is apparent that the mechanism for the cyclization process is not fully understood. The intermediate dienes that would be obtained from 1-phenyl-1,3-butanedione and 2,4-pentanedione appear to have hydrolyzed during the neutralization process. From investigations of the reaction of 5,5-dimethyl-1,3-cyclohexanedione with TFD, it appears that the above diene intermediates could have been directly isolated from the reaction mixture by employing a neutralization procedure with triethylamine. In addition, optimum

conditions to date have employed slow addition of a methylene chloride or a chloroform solution of TFD to the β-diketone in the presence of $HBF_4 \cdot OEt_2$. Several β-diketones were not observed to undergo acid-catalyzed self-condensation reactions in the presence of TFD. Cyclization reactions of these β-diketones appear to be unfavorable due to electronic and steric effects. All cyclized reaction products that are reported in this chapter are consistent with either a Diels-Alder reaction or a Michael addition.

Experimental

Treatment of (E)- and (Z)-4-(2,2,2-Trifluoroethoxy)-3-penten-2-one with $HBF_4 \cdot OEt_2$. A 0.785 g (4.31 mmoles) mixture of (E)- and (Z)-4-(2,2,2-trifluoroethoxy)-3-penten-2-one (compounds 142 and 152, 3:1 ratio) was treated with 0.15 mL (1.31 mmoles) of $HBF_4 \cdot OEt_2$. Methylene chloride (5 mL) was added to the mixture after 45 min, and the CH_2Cl_2 solution continued to stir for another 2.5 h. The organic layer was washed with 2 portions of 5% $NaHCO_3$ and a single portion of water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. ^1H and ^{13}C NMR results indicated that aromatic products were not obtained with the above conditions and that only the E-trifluoroethyl enol ether and 2,4-pentanedione were recovered.

Control Experiments for (E)- and (Z)-4-(2,2,2-Trifluoroethoxy)-3-pentene-2-one. A mixture of (E)- and (Z)-4-(2,2,2-trifluoroethoxy)-3-penten-2-one (0.310 g, 1.70 mmoles, 2:1 ratio) was treated with 0.173 g (1.73 mmoles) of 2,4-pentanedione, 0.15 mL (1.31 mmoles) of $HBF_4 \cdot OEt_2$, and 5 mL of CH_2Cl_2 at 0^oC. The resulting mixture was stirred 3.5 h and was neutralized with 5% $NaHCO_3$ as previously described. No aromatic products were obtained using the above reaction conditions.

A mixture containing 0.574 g (3.15 mmoles) of (E)- and (Z)-4-(2,2,2-trifluoroethoxy)-3-penten-2-one, 0.315 g (3.15

mmoles) of 2,4-pentanedione, 5 mL of CH_2Cl_2, and 0.25 mL (2.19 mmoles) of $HBF_4 \cdot OEt_2$ was treated with 21.0 mL of a 0.30 M (6.3 mmoles) TFD solution over 40 min. The resulting mixture was stirred for another 1.5 h and was neutralized with 5% $NaHCO_3$ as previously described. ^1H and ^{13}C NMR spectra indicated that starting materials were mainly recovered with cyclized products appearing in trace amounts.

Treatment of 4-(2,2,2-Trifluoroethoxy)-3-penten-2-one with TFD and $HBF_4 \cdot OEt_2$. Several different conditions were employed when treating 4-(2,2,2-trifluoroethoxy)-3-penten-2-one with $HBF_4 \cdot OEt_2$ and TFD to find the optimum conditions for the cyclization reaction. These reaction conditions are described in Table 3.1.

Monitoring the Reaction of 2,4-Pentanedione and TFD by Nitrogen Gas Collection. In this experiment, 2,4-pentanedione (1.0 g, 10 mmoles) was treated with 2 mL (17.5 mmoles) of $HBF_4 \cdot OEt_2$ and 127 mL of a 0.542 M TFD solution (68.9 mmoles). The 2,4-pentanedione solution was under nitrogen gas until the TFD addition began. At this point the nitrogen gas flow was stopped, and nitrogen that was generated from the reaction mixture was collected by water displacement in an inverted graduated cylinder. The total amount of nitrogen gas that was collected was 1.50 L (66.7 mmoles). The TFD solution was added over 1 h, and the reaction mixture stirred for an additional 23 h. The reaction solvent was evaporated in vacuo, and the resulting oil was hydrolyzed with 15 mL of 2,2,2-tri-

fluoroethanol, 5 mL of water, and 2 mL of HBF_4. This mixture was refluxed for 24 h and was treated with CH_2Cl_2 and water to separate the organic and aqueous layers. The organic layer was neutralized with 5% $NaHCO_3$ as previously described. This procedure afforded large amounts of 2,4-pentanedione and small amounts of cyclization products as monitored by ^1H NMR spectroscopy.

Low Temperature Studies on the Reaction of 2,4-Pentanedione with TFD. A mixture of 2,4-pentanedione (1.0 g, 10 mmoles), $HBF_4 \cdot OEt_2$ (0.5 mL 4.38 mmoles), and 5 mL of CH_2Cl_2 was cooled to -72°C under nitrogen. A 0.329 M TFD solution (95 mL, 31.3 mmoles) was added to the 2,4-pentanedione solution in three equal portions at 0.5 h intervals. The first portion of TFD that was added to the mixture resulted in a steady evolution of nitrogen gas. Very little nitrogen gas was evolved from the second and third additions of the TFD solution. The reaction flask was warmed to 0°C which caused additional nitrogen evolution for about 1 h. The organic mixture was evaporated to an oil *in vacuo* and was hydrolyzed with a 2,2,2-trifluoroethanol-water-HBF_4 mixture as previously described. A mixture of insertion product **141** and 2,4-pentanedione were recovered after hydrolysis as monitored by ^1H NMR spectroscopy.

Treatment of (E)-4-(2,2,2-Trifluoroethoxy)-3-penten-2-one with 2,2,2-Trifluoroethanol in the Presence of Acid Catalyst. (E)-4-(2,2,2-trifluoroethoxy)-3-penten-2-one (0.274 g, 1.51

mmoles) in 10 mL of CH_2Cl_2 was treated with 0.156 g (15.6 mmoles) of 2,2,2-trifluoroethanol and 0.100 mL (0.876 mmole) of $HBF_4 \cdot OEt_2$. The reaction mixture stirred at 0^0C for 1 h and was neutralized with 5% $NaHCO_3$ as previously described. The ^1H NMR spectrum of the reaction product showed unreacted enol ether and no conversion to the corresponding ketal.

Cyclization of (E)-4-(2,2,2-Trifluoroethoxy)-3-penten-2-one in the Presence of 2,2,2-Trifluoroethanol and TFD. A mixture of (E)-4-(2,2,2-trifluoroethoxy)-3-penten-2-one (0.320 g, 1.76 mmoles) and 5 mL of CH_2Cl_2 was treated with 1.76 g (1.76 mmoles) of 2,2,2-trifluoroethanol, 0.10 mL (0.88 mmoles) of $HBF_4 \cdot OEt_2$, and 17 mL of a 0.266 M TFD solution (4.5 mmoles). The TFD solution was added over 15 min, and the reaction mixture stirred another 3 h before neutralization. The reaction mixture was neutralized with 5% $NaHCO_3$ utilizing the previously described procedure. A control experiment without 2,2,2-trifluoroethanol was prepared utilizing the above conditions. Both of the above experiments provided a 13% yield of acetophenone 137 (based on ^1H NMR integration) after hydrolysis with a methanol-water-HBF_4 solution (refluxed 4.75 h).

Reaction of 2,4-Pentanedione with a Pentane Solution of TFD. A pentane solution of TFD was prepared to examined solvent effects for the acid-catalyzed self-condensation reaction of 2,4-pentanedione. The pentane solution of TFD was prepared using the procedure described in Chapter II. In this proce-

dure, pentane was substituted for methylene chloride in the extraction procedure. During the pentane extraction, problems were encountered because TFD was more soluble in water than in pentane. As a result, a less concentrated TFD solution was obtained in pentane (0.15 M solution, 41% yield) than in methlene chloride.

A solution of 2,4-pentanedione (0.50 g, 5.0 mmoles) in 5 mL of pentane was treated with 0.25 mL of $HBF_4 \cdot OEt_2$ (2.2 mmoles). The resulting mixture was cooled at 0^oC and was treated with 0.115 L of the 0.15 M TFD solution (17 mmoles) which was prepared above. The TFD solution was added to the reaction flask over 55 min. After addition of TFD, another 0.050 mL (0.44 mmole) of $HBF_4 \cdot OEt_2$ was added to the reaction mixture. The reaction mixture was stirred for another 1.5 h and was neutralized with 2 portions of 5% $NaHCO_3$ and 1 portion of water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The ^1H NMR spectrum of the reaction mixture showed that 2,4-pentanedione and the corresponding E-trifluoroethyl enol ether (1:1 ratio) were the major compounds present.

Reaction of 2,4-Pentanedione with a Diethyl Ether Solution of TFD. The diethyl ether solution of TFD was prepared using the procedure that was previously described. Diethyl ether was used to extract TFD from the aqueous layer.

2,4-Pentanedione (2.80 g, 28.0 mmoles) was treated with 2.00 mL of $HBF_4 \cdot OEt_2$ (1.75 mmoles) and 254 mL of a 0.131 M TFD

solution in diethyl ether (33.3 mmoles) over several hours. The reaction flask was maintained at 0°C over this time period. The reaction mixture was stirred for another 16 h and gradually warmed to room temperature. Another 0.040 L of the 0.131 M TFD solution (5.2 mmoles) was added to the reaction flask without additional nitrogen being evolved. The reaction mixture was neutralized with 2 portions of 10% NaOH and 2 portions of water (note that unreacted 2,4-pentanedione is extracted into the NaOH layer). The ether solution was dried over anhydrous $MgSO_4$, filtered, and evaporated _in vacuo_. 4-(2,2,2-Trifluoroethylamino)-3-penten-2-one (_199_) was isolated from this reaction procedure. After recrystallization from pentane, enamine _199_ (0.183 g, 3.6% yield) afforded the following spectroscopic data. ^{1}H NMR δ 5.15 (s, 1H), 3.78 (q, 1H, J = 9 Hz), 3.82 (q, 1H, J = 9 Hz), 2.06 (s, 3H), 1.98 (s, 3H); ^{13}C NMR δ 197.05 (s), 161.31 (s), 121.41 (CF_3, J = 280 Hz), 98.12 (d), 44.51 ($\underline{C}H_2CF_3$, J = 35 Hz), 29.15 (q), 18.47 (q); ^{19}F NMR δ -5.37 (t, J = 9 Hz); EI.MS, ^{m}/e 181 (M^+, 52%), 166 ($M^+ - CH_3$, 100); CI/MS, ^{m}/e 182 (MH^+, 100); Anal. Calcd for $C_7H_{10}NO$: C, 46.41; H, 5.56. Found C, 46.36; H, 5.15.

Enamine _199_ was also prepared directly from treating 2,4-pentanedione with trifluoroethylamine. In this procedure trifluoroethylamine was generated by adding 13.9 g (0.103 mole) of trifluoroethylamine hydrochloride to a mixture of 8 M NaOH and diethyl ether (50 mL of each reagent).

The ether layer was collected and the aqueous layer was extracted with another 50 mL portion of diethyl ether. The ether layers were combined and dried over anhydrous $MgSO_4$. The ether layer filtered and transferred to a round bottom flask. A mixture containing 2,4-pentanedione (2.5 g, 25.0 mmoles) and of $HBF_4 \cdot OEt_2$ (1.5 mL, 13.1 mmoles) was added to the amine solution. The resulting mixture was stirred for two hours. The ^1H NMR spectrum of the reaction mixture indicated that enamine 199 had formed.

To further investigate the reaction of 2,4-pentanedione with a diethyl ether solution of TFD, 2,2,2-trifluoroethylamine had to be removed from the TFD solution. Small portions of the above TFD solution in diethyl ether were separately washed with four different acids. The acids utilized in this study were 6 M hydrochloric acid, 6 M nitric acid, 6 M phosphoric acid, and 6 M acetic acid. The organic layer was immediately neutralized with 5% $NaHCO_3$ to prevent further acid-catalyzed reactions of TFD from occurring. Acetic acid and hydrochloric acid worked equally well in removing trifluoroethylamine as monitored by ^{19}F NMR spectroscopy. However, TFD solutions that were washed with acetic acid would not undergo an acid-catalyzed reaction with 2,4-pentanedione. Instead, this TFD solution afforded 2,2,2-trifluoroethyl acetate under the above conditions (2,2,2-trifluoroethyl acetate was detected in the ^{19}F NMR spectrum of the initial reaction mixture). This compound had identical spectral

properties with the 2,2,2-trifluoroethyl acetate which had been synthesized by Koller and Dorn.[1] This derivative appears to have originated from the conjugate base of acetic acid which had remained in the TFD soluiton after neutralization with 5% $NaHCO_3$. 2,2,2-Trifluoroethylamine was not detected in any appreciable amounts in the chloroform, methylene chloride, and pentane solutions of TFD.

Preparation of (Z)-1-Phenyl-3-trifluoromethyl-1,4,4-tris-(2,2,2-trifluoroethoxy)-1-pentene (194). (Z)-1-Phenyl-3-trifluoromethyl-1,4,4-tris(2,2,2-trifluoroethoxy)-1-pentene (194) was prepared and isolated by utilizing the procedure described for the preparation of dienol ether 165 in Chapter II. Insertion ketal 194 eluted immediately before dienol ether 165 when the above mixture was separated on neutral alumina. Insertion ketal 194 which was isolated above was layered on a flash chromatography silica gel column for further purification. The above separation afforded additional compounds which have originated from reactions of insertion ketal 194 on silica gel. After further separation on neutral alumina, the insertion ketal 194 mainly afforded diene 200.

(E)-1,4-Bis(2,2,2-trifluoroethoxy)-1-phenyl-3-trifluoromethyl-1,4-pentandiene (200) had the following spectroscopic data: ^1H NMR δ 7.41 (broad, 5H), 5.38 (d, 1H, J = 10 Hz), 4.42 (d, 1H, J = 4 Hz), 4.31 (dq, 1H, $^3J_{HCCH}$ = 10 Hz, $^3J_{HCCF}$ = 9 Hz), 4.20 (d, 1H, J = 4 Hz), 4.09 (q, 2H, J = 8 Hz), 3.95 (q, 2H, J = 8 Hz); ^{13}C NMR δ 156.92 (s), 155.83 (s),

133.16 (s), 129.78 (d), 128.97 (d, 2c), 127.25 (d, 2c), 124.94 (CF_3, J = 281 Hz), 123.34 (CF_3, J = 279 Hz), 123.05 (CF_3, J = 278 Hz), 105.30 (d), 88.07 (d), 66.79 ($\underline{C}H_2CF_3$, J = 35 Hz), 65.36 ($\underline{C}H_2CF_3$, J = 37 Hz), 46.15 ($\underline{C}HCF_3$, J = 30 Hz); EI/MS, $^m/e$ 408 (M^+, 63%), 339 ($M^+ - CF_3$, 51), 309 ($M^+ - OCH_2CF_3$, 24), 77 ($C_6H_5^+$, 100).

Additional (Z)-1-phenyl-3-trifluoromethyl-1,4,4-tris-(2,2,2-trifluoroethoxy)-1-pentene (194) was prepared by modifying the above procedure. The modification used 1.17 g (7.22 mmoles) of 1-phenyl-1,3-butanedione, 0.30 mL of $HBF_4 \cdot OEt_2$ (2.6 mmoles), and 100 mL of a 0.215 M TFD solution (21.5 mmoles) to prepare insertion ketal 194. The TFD solution was added to the mixture containing the β-diketone over 1 min. The reaction mixture was immediately neutralized with 1.5 mL of triethylamine after the TFD addition. After preliminary separation of the reaction products, the chromatographic fraction which contained insertion ketal 194 (0.815 g, 22% yield) was further purified by a second separation on neutral alumina. This second chromatographic separation was utilized to confirm that a single compound had been isolated in the initial separation. Spectroscopic properties of this insertion ketal 194 are described below: ^1H NMR δ 7.43 (broad, 5H), 5.19 (d, 1 H, J = 10 Hz), 3.9-4.2 ($3CH_2CF_3$, 6H), 1.69 (d, J = 6 Hz), 1.60 (d, J = 6 Hz). Integration of the signals at δ 1.69 and 1.60 ppm resulted in a total of 3H for the two conformational methyl groups. All other signals for

the two conformational forms overlapped making assignments for the two conformational forms impossible. ^{13}C NMR δ 158.47 (s), 132.89 (s), 129.97 (d), 129.03 (d, 2C), 127.28 (d, 2C), 124.51 (CF_3, J = 278 Hz), 123.28 ($3CF_3$, J = 278 Hz), 103.28 (d + s, 2C), 66.72 ($2\underline{C}H_2CF_3$, J = 35 Hz), 60.56 ($\underline{C}H_2CF_3$, J = 38 Hz), 48.44 ($\underline{C}HCF_3$, J = 26 Hz), 47.89 ($\underline{C}HCF_3$, J = 26 Hz), 21.52 (q), 20.88 (q). The methyl carbons and the $\underline{C}HCF_3$ carbons were the only resonances which could clearly be identified for the two conformational forms. All other carbon resonances for the two conformations could not be distinguished due to accidental equivalence of these resonances. The two conformational forms were also observed in the ^{19}F NMR spectrum. ^{19}F NMR δ 2.38 (d, J = 9 Hz), 2.28 (d, J = 9 Hz), -6.89 (t, J = 6 Hz), -6.94 (t, J = 8 Hz), -7.11 (t, J = 8 Hz), -7.12 (t, J = 8 Hz). ^{19}F NMR signals at δ -6.89 and -6.94 ppm were assigned to the fluorines of the two trifluoroethoxy ketal groups. These signals were broader than the other fluorine signals and did not show separate resonances for the two conformational forms. Insertion ketal 194 hydrolyzed to insertion ketone 156 over a one year period.

From this second reaction mixture, several trifluoroethyl enol ethers of 1-phenyl-1,3-butanedione were isolated and were tentatively assigned as follows.

For (Z)-4-phenyl-4-(2,2,2-trifluoroethoxy)-3-buten-2-one (196): ^{1}H NMR δ 7.4-7.6 (m, 5H), 5.86 (s, 1H), 4.34 (q, CH_2CF_3, J = 8 Hz), 2.41 (s, 3H).

For (E)-phenyl-4-(2,2,2-trifluoroethoxy)-3-buten-2-one (197): ^{1}H NMR δ 7.46 (broad, 5H), 5.60 (s, 1H), 4.27 (q, CH_2CF_3, J = 8 Hz), 1.97 (s, 3H).

For (Z)-1-phenyl-3-(2,2,2-trifluoroethoxy)-2-buten-1-one (236): ^{1}H NMR δ 7.89 (d, 2H, J = 8 Hz), 7.3-7.6 (m, 3H), 5.83 (s, 1H), 3.87 (m, CH_2CF_3, 2H), 2.10 (s, 3H).

Enol ethers 196, 197, and 236 (0.117 g) were obtained in a yield of 6.6%.

Hydrolysis of 2,4-Pentanedione Reaction Mixtures. Several attempts were made to find the optimum conditions for hydrolysis of vinyl ethers present in the 2,4-pentanedione reaction mixtures. These conditions are reported in Table 3.6.

Treatment of Cyclohexenone 157 with Various Acids and Water. Cyclohexenone 157 (0.345 g, 0.605 mmoles) was treated with 25 mL of methanol, 10 mL of H_2O, and 5 mL of HBF_4. The resulting mixture was refluxed for 20 h. Methylene chloride and H_2O were then added to the above mixture to separate the organic and aqueous layers. The organic layer was separated and neutralized with two portions of 5% $NaHCO_3$ and one portion of H_2O. The organic layer was dried with anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. ^{1}H and ^{13}C NMR spectra of the recoverd oil indicated that cyclohexenone 157 had not been hydrolyzed using the above conditions.

Cyclohexenone 157 (0.345 g, 0.605 mmole) was treated with 11 mL of THF, 4 mL of water, and 1 mL of concentrated H_2SO_4.

The resulting mixture was refluxed for 15 h. After hydrolysis, the mixture was treated with additional water and ether to separate the organic and aqueous layers. The organic layer was neutralized and reduced as previously described. The major compound isolated from this procedure was cyclohexenone 157 as detected by ^{1}H and ^{13}C NMR spectroscopy. Similar results were obtained by treating 0.345 g (0.605 mmole) of cyclohexenone 157 with 7.5 mL of diglyme, 2 mL of acetic acid, and 2 mL of water. The resulting mixture was refluxed for 16 h. The mixture was treated with CH_2Cl_2 and water to separate the organic and aqueous layers. The organic layer was neutralized and reduced as previously described to afford the cyclohexenone 157.

Preparation of 5,5-Dimethyl-3-(2,2,2-trifluoroethoxy)-2-cyclohexenone (201). 5,5-Dimethyl-3-(2,2,2-trifluoroethoxy)-2-cyclohexenone (201) was prepared by the conditions that are reported in Table 3.8. Cyclohexenone 201 (0.942 g, 48%) had the following spectroscopic data: ^{1}H NMR δ 5.32 (s, 1H), 4.18 (q, 2H, J = 8 Hz), 2.38 (s, 2H), 2.24 (s, 2H), 1.09 (s, 6H); ^{13}C NMR δ 198.38 (s), 173.79 (s), 122.68 (CF_3, J = 278 Hz), 102.61 (d), 65.01 ($\underline{C}H_2CF_3$, J = 37 Hz), 50.79 (t), 42.33 (t), 32.46 (s), 28.17 (q, 2C); ^{19}F NMR δ -6.23 (t, 3F, J = 8 Hz). EI/MS, $^{m}/e$ 222 (M^+, 13%), 207 ($M^+ - CH_3$, 4), 166 (47), 97 (43), 68 (100).

Preparation of 1,3-Bis(2,2,2-trifluoroethoxy-5,5-dimethyl-1,3-cyclohexadiene (202). 1,3-Bis(2,2,2-trifluoroethoxy)-5,5-di-

TABLE 3.8

Experimental Conditions for Reactions of β-Diketones and Related Compounds with TFD

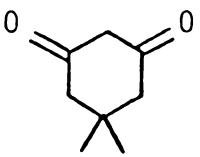
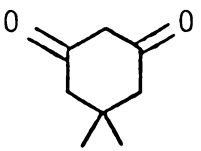
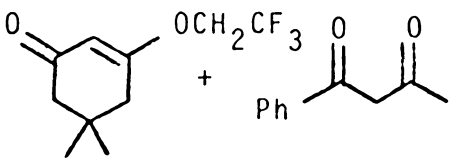
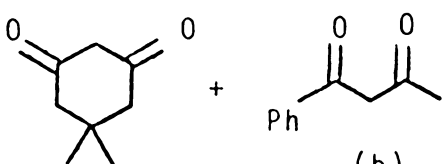
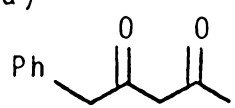
entry	compound(s)	mmoles of compound(s)	mmoles of TFD	mmoles of $HBF_4 \cdot OEt_2$	time required for TFD addition[a]
1		14.28	27.8	10.51	50 min[b]
2		8.79	21.5	8.76	45 min
3	 (a) (b)	2.20 (a) 2.23 (b)	14.3	7.01	50 min[b,c]
4	 (a) (b)	2.79 (a) 2.78 (b)	16.7	4.38	20 min[c]
5		3.22	9.73	2.63	15 min

TABLE 3.8 (continued)

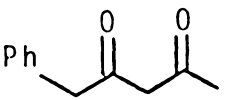
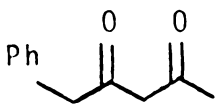
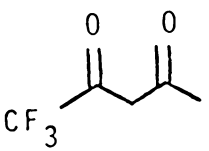
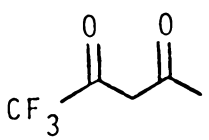
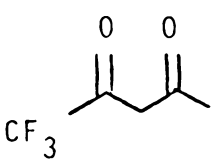
entry	compound(s)	mmoles of compound(s)	mmoles of TFD	mmoles of $HBF_4 \cdot OEt_2$	time required for TFD addition
6		14.28	44.5	7.01	30 min[c]
7		4.31	12.9	5.69	10 min[c]
8		13.2	39.9	5.69	2.0 h[c]
9		19.5	59.6	5.26	2.25 h[c]
10		9.87	29.0	7.01	1.5 h[b,c]

TABLE 3.8 (continued)

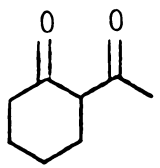
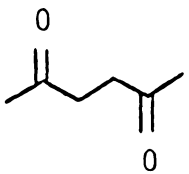
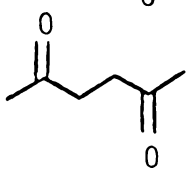
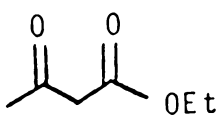
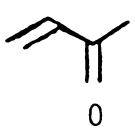
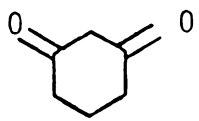
entry	compound(s)	mmoles of compound(s)	mmoles of TFD	mmoles of $HBF_4 \cdot OEt_2$	time required for TFD addition
11		9.49	29.0	5.87	1.5 h [b, c]
12		17.2	49.8	7.88	4.25 h [b, c]
13		8.85	26.6	6.13	2.13 h [b, c]
14		8.45	24.9	7.45	1.75 h [c]
15		10.2	30.6	7.01	1.67 h [c]

TABLE 3.8 (continued)

entry	compound(s)	mmoles of compound(s)	mmoles of TFD	mmoles of $HBF_4 \cdot OEt_2$	time required for TFD addition
16		13.4	39.9	3.94	1.66 h [c]

a Reaction mixture was neutralized with 2 portions of 5% $NaHCO_3$ and 1 portion of water.

b Reaction mixture was treated with triethylamine prior to the 5% $NaHCO_3$ neutralization procedure.

c Reaction mixture was hydrolyzed with methanol-water-HBF_4 (5:2:1 volumetric ratio, 4 h reflux).

methyl-1,3-cyclohexadiene (202) was prepared by the conditions that are reported in Table 3.8. Cyclohexadiene 202 (3.46 g, 80%) had the following spectroscopic data: ^{1}H NMR δ 4.90 (s, 1H), 4.24 (s, 1H), 4.11 (q, 2H, J = 8 Hz), 4.03 (q, 2H, J = 8 Hz), 2.22 (s, 2H), 1.07 (s, 3H); ^{13}C NMR δ 158.19 (s), 150.66 (s), 123.46 (CF_3, J = 277 Hz), 123.12 (CF_3, J = 277 Hz), 100.13 (d), 92.73 (t), 64.52 ($\underline{C}H_2CF_3$, J = 36 Hz), 64.33 ($\underline{C}H_2CF_3$, J = 36 Hz), 41.39 (t), 32.21 (s), 28.44 (q, 2C).

Treatment of 1-Phenyl-2,4-pentanedione with TFD. 1-Phenyl-2,4-pentanedione was treated with TFD in the presence of $HBF_4 \cdot OEt_2$ utilizing the conditions that were described in Table 3.8 (entries 5-7). The reaction mixture was examined before and after the normal HBF_4-MeOH-H_2O hydrolysis. After chromatographic separation (silica gel) of the unhydrolyzed reaction mixture, three isomeric forms of the starting material and two enol ether derivatives of the β-diketone were identified. Spectroscopic data for these compounds are reported below.

For (Z)-4-hydroxy-1-phenyl-3-penten-2-one (206): ^{1}H NMR δ 7.1-7.5 (m, 5H), 5.41 (s, 1H), 3.57 (s, 2H), 2.00 (S, 3H).

For (Z)-4-hydroxy-5-phenyl-3-penten-2-one (207): ^{1}H NMR δ 7.2-7.5 (m, 5H), 5.80 (s, 1H), 3.82 (s, 2H), 2.27 (s, 3H).

For 1-phenyl-2,4-pentanedione (208): ^{1}H NMR δ 7.2-7.4 (m, 5H), 4.14 (s, 2H), 3.66 (s, 2H), 2.24 (s, 3H).

For (Z)-1-phenyl-4-(2,2,2-trifluoroethoxy)-3-penten-2-

one (209): ^{1}H NMR 7.2-7.7 (m, 5H), 5.43 (s, 1H), 4.07 (q, 2H, J = 8 Hz), 3.72 (s, 2H), 2.36 (s, 3H).

For (Z)-5-phenyl-4-(2,2,2-trifluoroethoxy)-3-penten-2-one (209): ^{1}H NMR δ 7.3-7.5 (m, 5H), 5.50 (s, 1H), 4.20 (s, 2H), 4.19 (q, 2H, J = 8 Hz), 2.29 (s, 3H).

A 32.1% recovery (0.180 g) of the three isomeric forms of the starting material (206, 207, and 208) was obtained. Enol ethers 209 and 210 (0.261 g) were isolated in 31.7% yield.

After chromatographic separation of the hydrolyzed reaction mixture starting 1-phenyl-2,4-pentanedione (enol form 206, 1.60 g, 63.6% recovery) and two insertion products (i.e., compounds 211 and 212) were isolated. These insertion compounds had the following spectroscopic data. For 1-phenyl-3-trifluoromethyl-2,5-hexanedione (211): ^{1}H NMR δ 7.1-7.4 (m, 5H), 3.7-4.0 (m, $CHCF_3$, 1H), 3.72 (s, 2H), 3.30 (dd, 1H, $^{3}J_{HCCH}$ = 10 Hz, $^{2}J_{HCH}$ = -20 Hz), 2.74 (dd, $^{3}J_{HCCH}$ = 10 Hz, $^{2}J_{HCH}$ = -20 Hz), 2.39 (s, 3H); ^{13}C NMR δ 204.43, 200.40, 133.18 (s), 129.38 (d, 2C), 128.86 (d, 2C), 127.40 (d), 50.52 ($\underline{C}HCF_3$, J = 26 Hz), 49.44 (t), 38.34 (t), 31.28 (q). Insertion diketone 211 (0.280 g) was isolated in 7.6% yield.

For (E)-1-phenyl-3-trifluoromethyl-5-(2,2,2-trifluoroethoxy)-4-hexen-2-one (212): ^{1}H NMR δ 7.1-7.4 (m, 5H), 4.57 (d, 1H, J = 10 Hz), 4.11 (q, 2H, J = 8 Hz), 3.92 (dq, $^{3}J_{HCCH}$ = 10 Hz, $^{3}J_{HCCF}$ = 8 Hz), 3.59 (s, 2H), 2.05 (s, 3H); ^{13}C NMR δ 199.46, 160.39 (s), 136.39 (s), 128.80 (d, 2C), 128.27 (d,

2C), 126.99 (d), 124.16 (CF_3, J = 281 Hz), 122.99 (CF_3, J = 278 Hz), 90.02 (d), 64.94 ($\underline{C}H_2CF_3$, J = 38 Hz), 54.69 ($\underline{C}HCF_3$, J = 29 Hz), 36.82 (t), 29.29 (q). Insertion ketone 212 (0.258 g) was isolated in 5.3% yield.

Reaction of 1,1,1-Trifluoro-2,4-pentanedione with TFD. 1,1,1-Trifluoro-2,4-pentanedione was treated with TFD utilizing the conditions reported in Table 3.8. After chromatographic separation, (220) and (221) were isolated.

Spectroscopic data for (E)-6,6,6-trifluoro-5-(2,2,2-trifluoroethoxy)-3-trifluoromethyl-4-hexen-2-one (220): ^1H NMR δ 5.91 (d, 1H, J = 10 Hz), 4.2-4.5 (m, CH_2CF_3 + $CHCF_3$, 3H), 2.36 (s, 3H); ^{19}F NMR δ 1.08 (d, 3F, J = 9 Hz), -0.31 (s, 3F), -7.28 (t, 3F, J = 8 Hz). On irradiating the ^1H NMR spectrum at δ 5.91 ppm, a recognizable quartet originated in the δ 4.2-4.5 ppm region. Insertion ketone 220 was isolated in 3.7% yield (0.228 g) utilizing the conditions described for entry 11 in Table 3.8.

Spectroscopic data for (E)-5-ethoxy-6,6,6-trifluoro-3-trifluoromethyl-4-hexen-2-one (221): ^1H NMR δ 5.72 (d, 1H, J = 10 Hz), 4.33 (dq, 1H, $^3J_{HCCH}$ = 10 Hz, $^3J_{HCCF}$ = 8 Hz), 4.03 (m, CH_2, 2H) 2.31 (s, 3H), 1.35 (t, 3H, J = 7 Hz); ^{13}C NMR[88] δ 197.65, 106.78 (d), 69.06 (t), 52.85 ($\underline{C}HCF_3$, J = 36 Hz), 29.70 (q), 15.10 (q); ^{19}F NMR δ 0.67 (d, 3F, J = 8 Hz), -0.58 (s, 3F). Irradiation of the ^1H NMR resonance at δ 1.35 simplified the multiplet centered at δ 4.03 to a pair of doublets for the two nonequivalent methylene hydrogens.

Insertion ketone 221 was isolated in 6.0% yield (0.311 g) utilizing the conditions described for entry 11 in Table 3.8. Several additional insertion products were also isolated in considerable yields (0.900 g) from this procedure. However, structures for these compounds have not been assigned due to insufficient separation.

LC-NMR Studies. The LC-NMR conditions that were utilized to separate the 2,4-pentanedione and the 1,1,1-trifluoro-2,4-pentanedione reaction products were identical to the conditions described in Chapter II with the following exceptions. LC-^{1}H NMR results for the 1,1,1-trifluoro-2,4-pentanedione system were obtained with a 50:50 mixture of $CDCl_3$ and freon-113. LC-^{19}F NMR results for the same system were obtained with a 50:50 mixture of CCl_4 and $CDCl_3$.

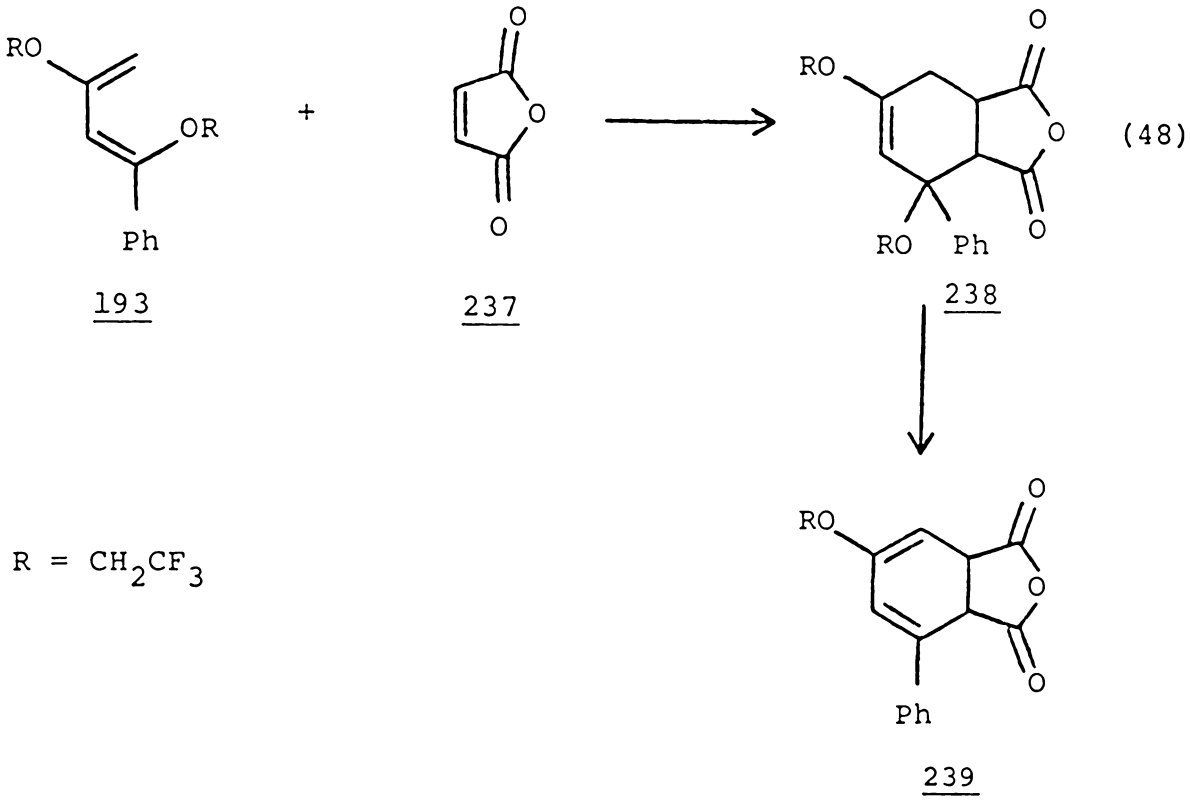
Chapter IV

REACTIONS OF β-DIKETONES WITH DIENOPHILES

Introduction

In Chapters II and III the acid-catalyzed self-condensation reactions of β-diketones with 2,2,2-trifluorodiazoethane (TFD) were discussed. Two possible mechanisms were suggested to account for the observed products. One of the mechanisms was an acid-catalyzed Diels-Alder reaction which appears to be similar to one of the reactions described by Danishefsky.[42,43,45] To better understand the mechanism in the present study, several attempts were made to isolate intermediate dienes from the reaction of 2,4-pentanedione and 1-phenyl-1,3-butanedione with TFD.[89] Since the attempts to isolate these intermediate dienes were unsuccessful, it was believed that the dienes were too reactive for direct isolation. As a result, methods which would trap these intermediates were investigated. Mixtures containing a dienophile and 1-phenyl-1,3-butanedione were treated with TFD and $HBF_4 \cdot OEt_2$ utilizing the previously described reaction conditions. If the β-diketone did undergo an acid-catalyzed Diels-Alder reaction, then the dienophiles added to the reaction mixture would be expected to compete with the dienophile formed from the β-diketone (e.g., 1-phenyl-1,3-

butanedione). These reactions would yield one or more new cyclization products along with the normal reaction products that would be obtained from 1-phenyl-1,3-butanedione. This general pathway is illustrated below for the cyclization of butadiene 193 with maleic anhydride (237).

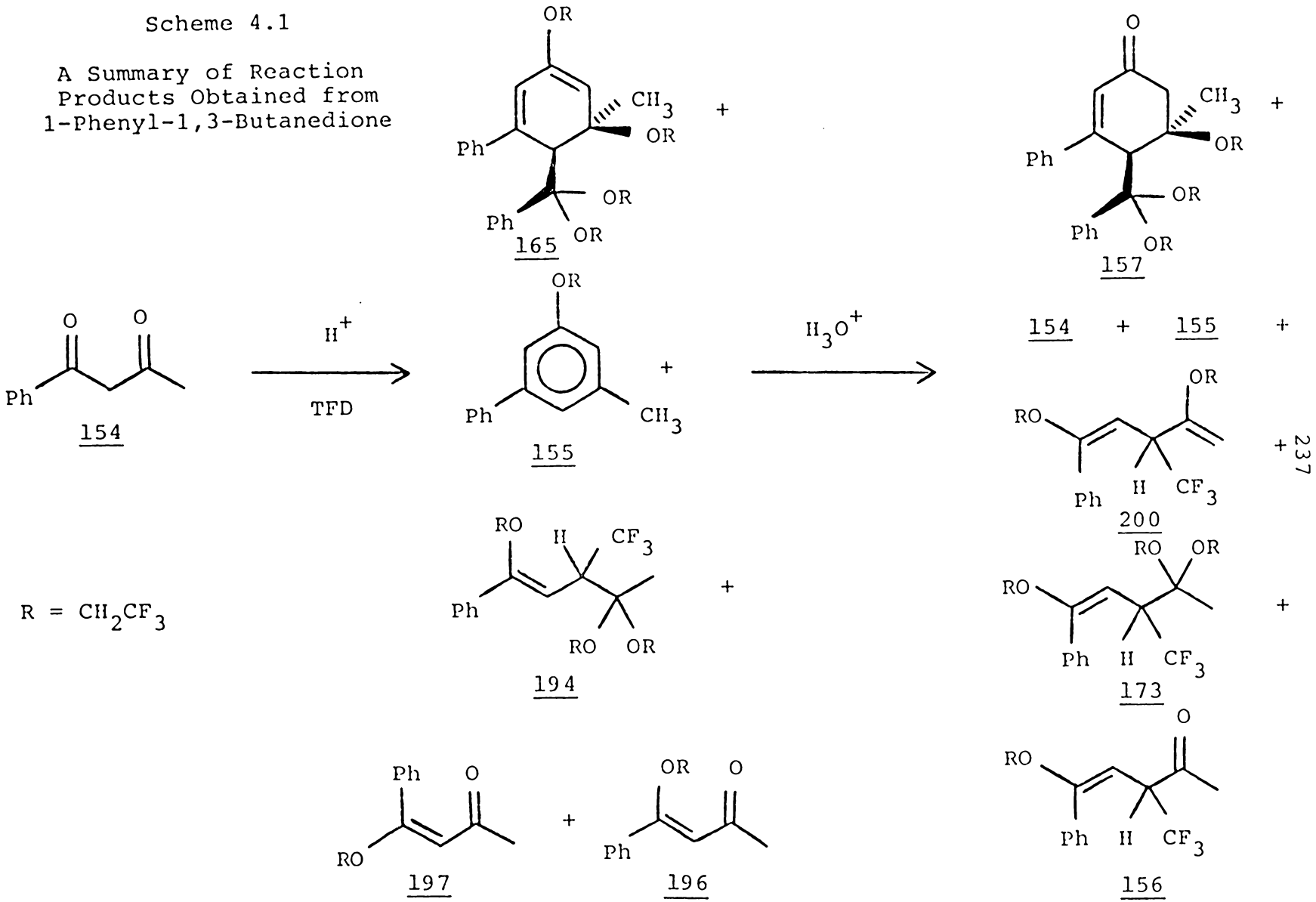


This pathway also illustrates that the initial reaction product (238) could undergo further elimination reactions to yield product 239.

Scheme 4.1 summarizes the reaction products that were obtained from 1-phenyl-1,3-butanedione before and after MeOH-H_2O-HBF_4 hydrolysis.[90] The reaction mixtures that were

Scheme 4.1

A Summary of Reaction Products Obtained from 1-Phenyl-1,3-Butanedione



obtained in this mechanistic study have been analyzed both before and after hydrolysis. In this mechanistic study, 1-phenyl-1,3-butanedione was utilized instead of 2,4-pentanedione since the former β-diketone afforded a higher yield of cyclized products.

Results and Discussion

Two dienophiles (maleic anhydride and dimethyl acetylenedicarboxylate) were separately added to a methylene chloride solution of 1-phenyl-1,3-butanedione. Each mixture was treated with TFD in the presence of $HBF_4 \cdot OEt_2$ to observe the effects of the dienophile on the cyclization process. The reaction mixture containing maleic anhydride and 1-phenyl-1,3-butanedione produced a complex mixture of products. Unreacted starting materials and several reaction products that have originated from 1-phenyl-1,3-butanedione were isolated from this mixture. No cyclization products originating from maleic anhydride were detected by ^{13}C NMR spectroscopy. Since a basic wash procedure was inadvertantly used, it was originally believed that products originating from the maleic anhydride would not have been observed in this experiment. That is, hydrolyzed maleic anhydride products would have remained in the basic aqueous layer as sodium salts accounting for the lack of these products.

The previously described experiment was repeated using

similar conditions except that the reaction mixture was reduced to an oil and then hydrolyzed with aqueous HCl. Any anhydrides would be hydrolyzed to the corresponding carboxylic acids by this procedure. These carboxylic acids would be separated from the 1-phenyl-1,3-butanedione reaction products (which would not contain any carboxylic acid groups) by extraction with base. After extracting the aqueous mixture with ether, compounds 154, 155, 156, 157, 173, and 200 were isolated as expected. The basic layer was then acidified and extracted with ether. Analysis of the second organic extract indicated that maleic acid, fumaric acid, and the enol form of 1-phenyl-1,3-butanedione had been recovered. No additional products resulting from a cyclization reaction of 1-phenyl-1,3-butanedione with maleic anhydride were observed in either of the ether extracts. Therefore, it appears that additional cyclization products were not formed from reactions involving maleic anhydride.

A more reactive dienophile was examined under similar conditions to confirm that a Diels-Alder reaction does not occur with a 1-phenyl-1,3-butanedione in the presence of a dienophile. When a mixture of dimethyl acetylenedicarboxylate and 1-phenyl-1,3-butanedione was treated with TFD in the presence of an acid catalyst, a complex mixture of reaction products was obtained. In addition to the normal reaction products that were expected from 1-phenyl-1,3-butanedione, a new reaction product was observed in the ^{1}H and

^{13}C NMR spectra of the reaction mixture. In both the ^{1}H and ^{13}C NMR spectra, there was a very intense line for the methyl group of the unreacted dimethyl acetylenedicarboxylate and a weak signal appearing upfield from this methyl group. To identify this new compound, the reaction mixture was separated by flash chromatography utilizing silica gel that had been washed with 5% $KHCO_3$ in methanol.[91]

The above chromatographic conditions were employed in an attempt to prevent hydrolysis of the reaction mixture products. Utilizing a gradient elution, three fractions were collected. The first fraction contained a mixture of compounds 155, 165, 173, and 200. Compound 157 was also observed eluting near the end of this first fraction. Insertion products 173 and 200 originated from the hydrolysis of compound 194 during the chromatographic separation. The second fraction corresponded to unreacted dimethyl acetylenedicarboxylate. The final fraction contained a product originating from a cyclization reaction of 1-phenyl-1,3-butanedione with dimethyl acetylenedicarboxylate. This was apparent from the 16 carbon signals which appeared in the ^{13}C NMR spectrum (10 carbons from 1-phenyl-1,3-butanedione and 6 carbons from dimethyl acetylenedicarboxylate.) One unusual feature of the ^{13}C NMR spectrum was that five pairs of equivalent carbons were observed (two aromatic pairs and three pairs originating from dimethyl acetylenedicarboxylate). It was determined from ^{13}C NMR INEPT results that the two equiv-

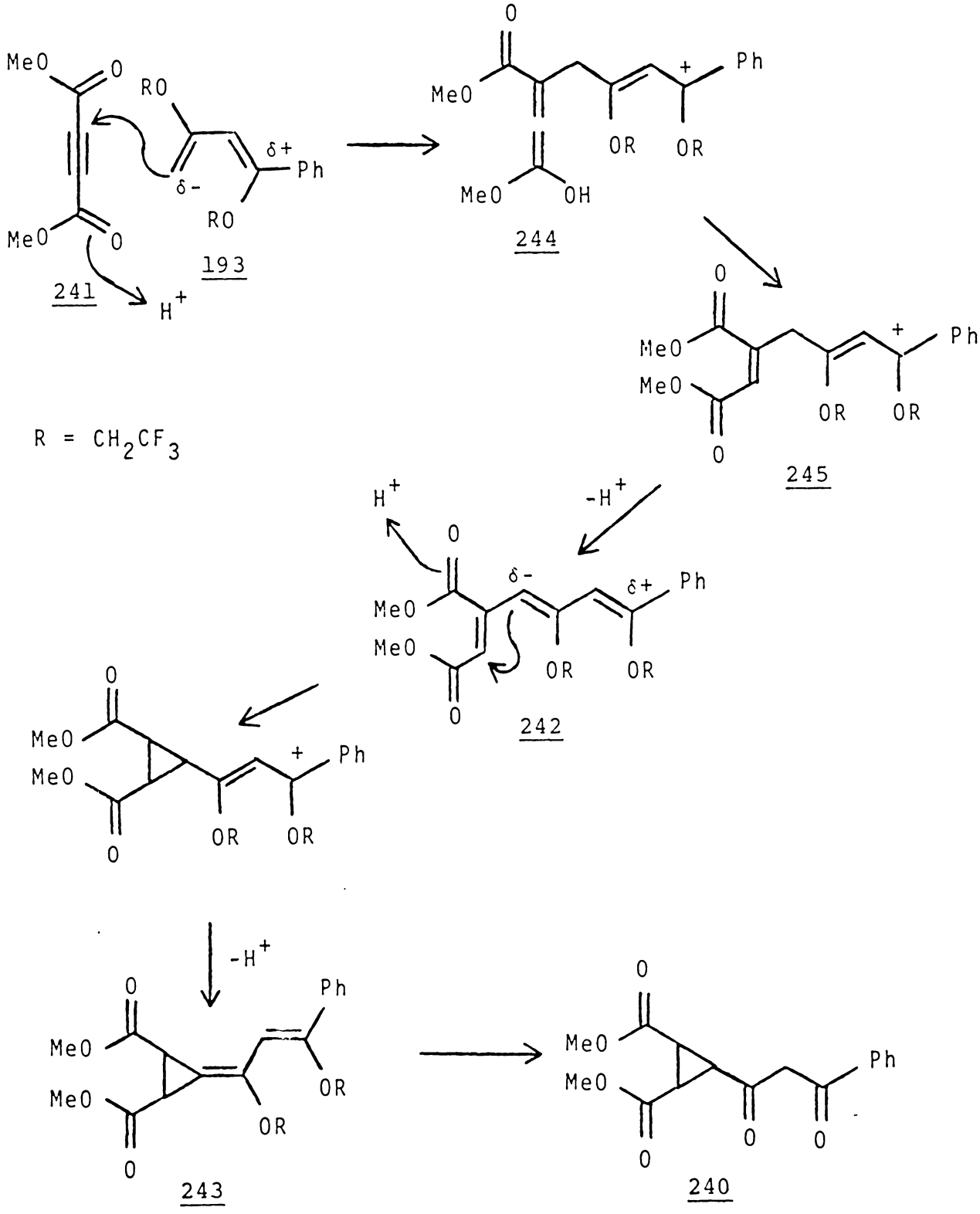
alent acetylene carbons were converted to an equivalent pair of methine carbons. The methyl group originating from 1-phenyl-1,3-butanedione was also converted to a methine carbon during the reaction process. The above results are consistent with cyclopropane 240 (Scheme 4.2).

The stereochemistry of cyclopropane 240 was assigned by ^{13}C-{^{1}H} NMR NOE experiments. When the ^{1}H NMR resonance for the doublet at δ 2.72 ppm was irradiated, NOE enhancements were observed at both δ 168.40 and 192.69 ppm in the ^{13}C spectrum. Similarly, when the triplet at δ 2.95 was irradiated, the same two ^{13}C NMR carbonyl carbons were enhanced. This suggests that the two ester groups must be trans to the substituent containing the 1,3-dicarbonyl group. If all of the above groups were positioned on the same side of the cyclopropane ring, then irradiation of the triplet in the ^{1}H NMR spectrum would only lead to enhancement of the carbonyl carbon of the 1,3-dicarbonyl substituent in the ^{13}C NMR spectrum. Likewise, irradiation of the doublet at δ 2.22 ppm in the ^{1}H NMR spectrum, would lead to enhancement of the ester carbonyl carbons.

In a series of ^{1}H-{^{1}H} NOE experiments, the doublet and the triplet previously described were individually irradiated. The irradiation of one signal never afforded an enhancement of the other resonance in either experiment. It was concluded that the protons at δ 2.72 and 2.95 ppm were trans to each other. If a cis relationship was present, then irra-

Scheme 4.2

A Potential Mechanism for the Formation of Cyclopropane 240



diation of one proton would normally result in enhancement of the other.

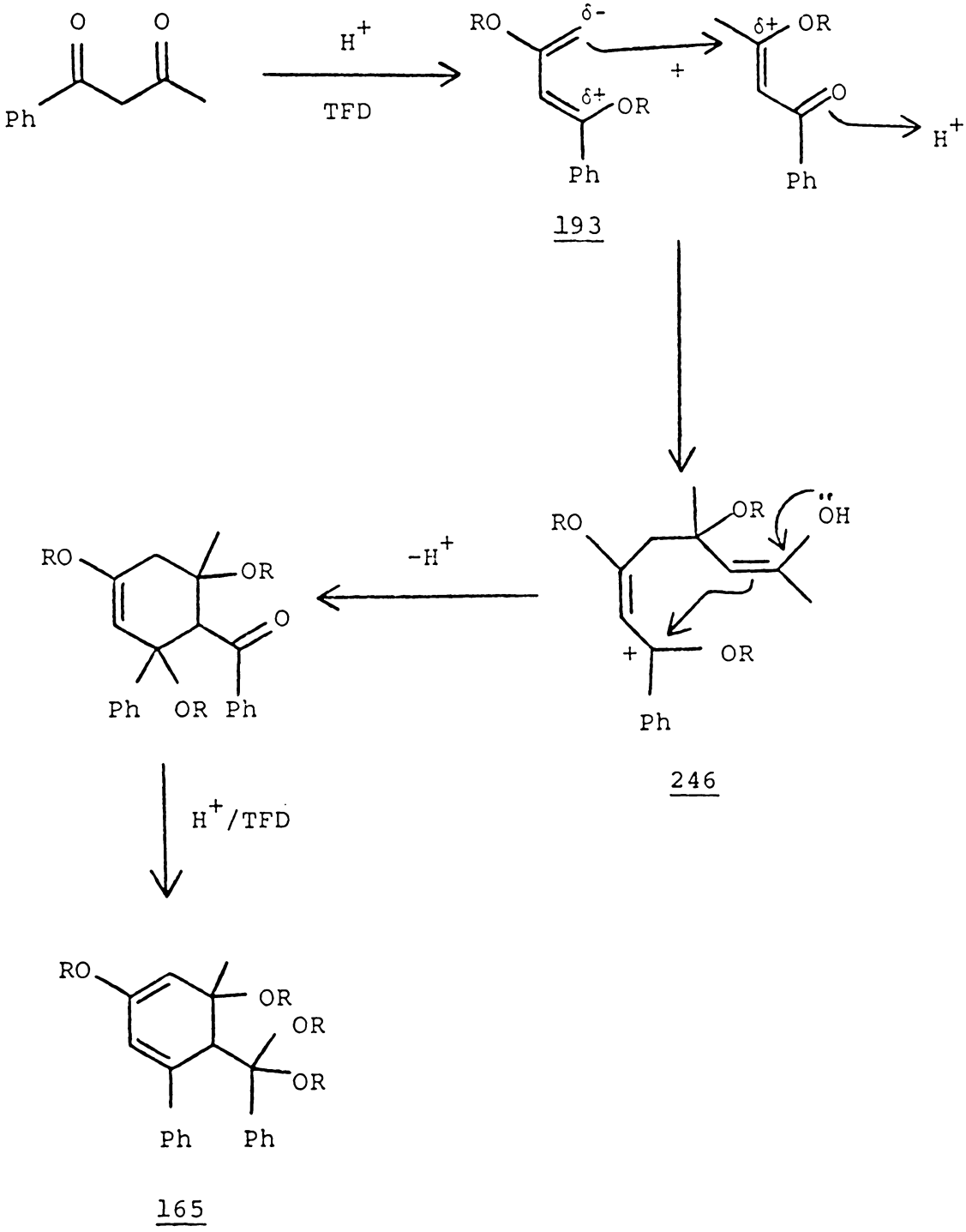
The absence of cyclohexene ring products originating from dimethyl acetylenedicarboxylate and a 1-phenyl-1,3-butanedione equivalent appears to rule out a Diels-Alder mechanism. The formation of cyclopropane 240 can be accounted for by a series of Michael additions to dimethyl acetylenedicarboxylate (Scheme 4.2). Through similar arguments, the formation of cyclized products 155 and 165 can occur through an analogous pathway (Scheme 4.3).

It appears that the first step in the formation of cyclopropane 240 is the Michael addition of diene 193 to acetylene 241. This would yield unsaturated compound 242 which has three conjugated carbon-carbon double bonds. Unsaturated compound 242 would undergo an intramolecular Michael addition to afford diene 243. This diene is believed to undergo rapid hydrolysis on the silica gel column even though the packing material was treated with 5% $KHCO_3$. The ^1H and ^{13}C NMR spectra of the reaction mixture **before** chromatography support this hypothesis since chemical shifts corresponding to cyclopropane 240 were not observed in these spectra. However, some precursor of cyclopropane 240 and several unidentified enol ethers were observed in the spectra of this reaction mixture. The proposed diene 243 is consistent with these observations.

Several factors should favor the cyclopropane ring forma-

Scheme 4.3

The Michael Addition Pathway for the Formation of Dienol Ether 165



tion over cyclization to a cyclohexene ring system. The initial intermediate that is formed from the first Michael addition is allene 244. Allene 244 should be quickly converted to the more stable enone 245 which would lose a proton to afford unsaturated compound 242. Compound 242 favors cyclopropane formation, while in theory, the less stable allene 244 could lead to a cyclohexene derivative. In addition, the cyclization of compound 244 to a cyclohexene derivative cannot occur because the allene system is not flexible enough to position the positive charge near the α-carbon of the enol system for intramolecular cyclization.

In contrast, cyclohexene skeletons are formed in the acid-catalyzed reaction of 1-phenyl-1,3-butanedione with TFD because of the stability of intermediate 246. This intermediate would not be in equilibrium with a second enol form, and would have greater flexibility than allene 244 (Scheme 4.3). This greater flexibility would allow the positive charge to be positioned near the enol system for an intramolecular cyclization. Thus, cyclization to a cyclohexene skeleton is more favorable for the 1-phenyl-1,3-butanedione system.

Conclusion

The acid-catalyzed self-condensation reaction of 1-phenyl-1,3-butanedione with TFD has been investigated in the

presence of two dienophiles. When maleic anhydride and dimethyl acetylenedicarboxylate were separately added to the β-diketone reaction mixture, products originating from a Diels-Alder reaction were not detected. However, dimethyl acetylenedicarboxylate and 1-phenyl-1,3-butanedione did undergo cyclization to form a cyclopropane derivative under these reaction conditions. The cyclopropane derivative was apparently formed through two Michael additions. By analogy, 1-phenyl-1,3-butanedione equivalents could undergo a similar Michael addition to yield a cyclohexene skeleton which could undergo further reaction to afford the previously described cyclization products.

Experimental

Reactions of 1-Phenyl-1,3-butanedione with TFD in the Presence of Maleic Anhydride. Under nitrogen, 20 mL of CH_2Cl_2 was added to a mixture containing 0.771 g (4.76 mmoles) of 1-phenyl-1,3-butanedione, 0.912 g (9.31 mmoles) of maleic anhydride, and 0.20 mL of $HBF_4 \cdot OEt_2$ (1.8 mmoles). The resulting mixture was cooled to 0^oC and was treated with 55 mL of a 0.28 M TFD solution (15.3 mmoles) over a 20 minute period. The mixture was stirred for another 25 min after the TFD addition was complete. At this point, another 0.10 mL of $HBF_4 \cdot OEt_2$ (0.88 mmole) was added to the reaction pot. No additional nitrogen gas was evolved after this addition, indicating that total

reaction of TFD had occurred. The organic mixture was reduced to an oil which was treated with 40 mL of 3 M HCl. The resulting mixture was refluxed for 10 min and then neutralized with 175 mL of 5% NaOH. The resulting aqueous mixture was extracted with 3-40 mL portions of diethyl ether. The basic aqueous layer was acidified with 6 M HCl and then extracted with 3-40 mL portions of diethyl ether. The organic extracts of the neutral and acidic aqueous layers were individually dried with anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. The ^1H and ^{13}C NMR spectra of the organic extract containing the acidic compounds indicated that maleic acid, fumaric acid, and 1-phenyl-1,3-butanedione were present. The ^1H and ^{13}C NMR spectra of the neutral components indicated that a complex mixture was present. The chemical shifts that were observed in these spectra corresponded to 1-phenyl-1,3-butanedione and the β-diketone reaction products previously identified (insertion products 173 and 200, biphenyl 155, and cyclohexenone 157). The acidic components that were obtained from the above extract were not soluble in d-chloroform and had to be dissolved in d_6-DMSO for NMR analysis.

The above procedure was adopted after initially preparing a similar mixture utilizing the procedure described below. Immediately after the second addition of $HBF_4 \cdot OEt_2$, the reactions of TFD appeared complete, and the organic mixture was washed with two portions of 5% $NaHCO_3$ and one portion of

water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. The ^1H and ^{13}C NMR results indicated that a mixture of products was formed. Specifically, compounds 155, 165, 194, 196, and 197 as well as the starting materials were identified in this mixture.

Treatment of 1-Phenyl-1,3-butanedione with TFD in the Presence of Dimethyl Acetylenedicarboxylate. Under nitrogen, 10 mL of CH_2Cl_2 was added to a mixture containing 1.03 g (6.36 mmoles) of 1-phenyl-1,3-butanedione and 2.87 g (20.2 mmoles) of dimethyl acetylenedicarboxylate. Subsequently, 0.40 mL of $HBF_4 \cdot OEt_2$ (3.5 mmoles) was added to the organic mixture at 0^oC. Next, 100 mL of a 0.276 M TFD solution (27.6 mmoles) was added to the reaction flask over 2 h at this same temperature. The reaction was allowed to stir for another 1 h. During this time, another 0.30 mL of $HBF_4 \cdot OEt_2$ was added to insure complete reaction. The reaction mixture was neutralized with 1 mL of triethylamine and was washed with two portions of 5% $NaHCO_3$ and a single portion of water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo* to an oil. The ^1H and ^{13}C NMR spectra indicated the presence of two different methyl esters in this complex mixture. The resulting mixture was separated by flash chromatography on silica gel that had been treated with 5% $KHCO_3$ in MeOH.[91] A gradient elution was utilized in the above separation. Four products originating from the reaction of 1-phenyl-1,3-butanedione with TFD eluted with a 40:60 mixture

of CH_2Cl_2 and pentane. These products corresponded to biphenyl 155, cyclohexadiene 165, insertion ketal 173, and insertion diene 200. Compound 157 was observed eluting at the end of this first fraction. Eluting immediately after the above products was unreacted dimethyl acetylenedicarboxylate. Eluting with 20:80 mixture of diethyl ether and CH_2Cl_2 was dimethyl 3-(1,3-dioxo-3-phenylpropyl)-1,2-cyclopropanedicarboxylate (240) (0.43 g, 22% yield). Spectroscopic data for compound 240: ^{1}H NMR δ 7.89 (d, 2H, J = 7 Hz), 7.4-7.6 (m, 3H), 6.44 (s, 1H), 3.74 (s, 3H), 2.95 (t, 1H, J = 5 Hz), 2.72 (d, 2H, J = 5 Hz); ^{13}C NMR δ 192.69, 180.38, 168.40 (2C), 133.67 (s), 132.57 (d), 128.69 (d, 2c), 126.98 (d, 2C), 97.06 (d), 52.38 (q, 2C), 31.09 (d), 29.10 (d, 2C); EI/MS, m/e 304 (M^+, 11%), 273 ($M^+ - OCH_3$, 9), 272 ($M^+ - CH_3OH$, 15), 245 ($M^+ - CO_2CH_3$, 3), 244 ($M^+ - C_2H_6O_2$, 9), 105 ($C_6H_5CO^+$, 100).

Chapter V

CHARACTERIZATION OF POLYFUNCTIONAL MOLECULES USING LANTHANIDE SHIFT REAGENTS

Introduction

As described in the introduction, the work in this dissertation began as an analytical NMR project. The intent of this original study was to investigate polyfunctional molecules with lanthanide shift reagents.[1] Normally, polyfunctional molecules afford results which are difficult to interpret due to complexation of the lanthanide shift reagent at several different sites.[62] Initial results by Koller and Dorn[1] have suggested that these studies could be simplified by treating polyfunctional molecules with TFD. Koller and Dorn[1] have found that hydroxyl groups can be easily converted to trifluoroethyl ethers. These trifluoroethyl ethers contain oxygen atoms that will not complex with lanthanide shift reagents. Therefore, the number of functional groups that would complex with a lanthanide shift reagent would be reduced by converting hydroxyl groups in a polyfunctional molecule to the corresponding trifluoroethyl ethers.

When β-diketones were investigated in the above study, a novel acid-catalyzed self-condensation reaction was

observed. This novel reaction became the focal point of this dissertation due to the synthetic potential of this reaction for the preparation of aromatic natural products. The reaction of β-diketones with TFD afforded several products which required characterization using lanthanide shift reagents. Lanthanide shift reagent studies were also utilized to assign the stereochemistry of several reaction products. In addition, these studies clearly show that the oxygen atoms of trifluoroethyl ethers will not complex with lanthanide shift reagents. As a result, these studies also support the initial premise that polyfunctional molecules can be easily studied by converting hydroxyl groups to trifluoroethyl ethers. Lanthanide shift reagent studies of several polyfunctional molecules will be described in this chapter.

Results and Discussion

The acid-catalyzed self-condensation reaction of β-diketones in the presence of TFD and $HBF_4 \cdot OEt_2$ was described in Chapter II. In this synthetic study, several compounds were obtained which were further characterized using lanthanide shift reagents. A case in point is dienol ether 165[92] which was prepared by treating 1-phenyl-1,3-butanedione with TFD in the presence of $HBF_4 \cdot OEt_2$. Dienol ether 165 was examined in the presence of various $Eu(fod)_3$ concentrations to illustrate that this molecule does not contain any sites for com-

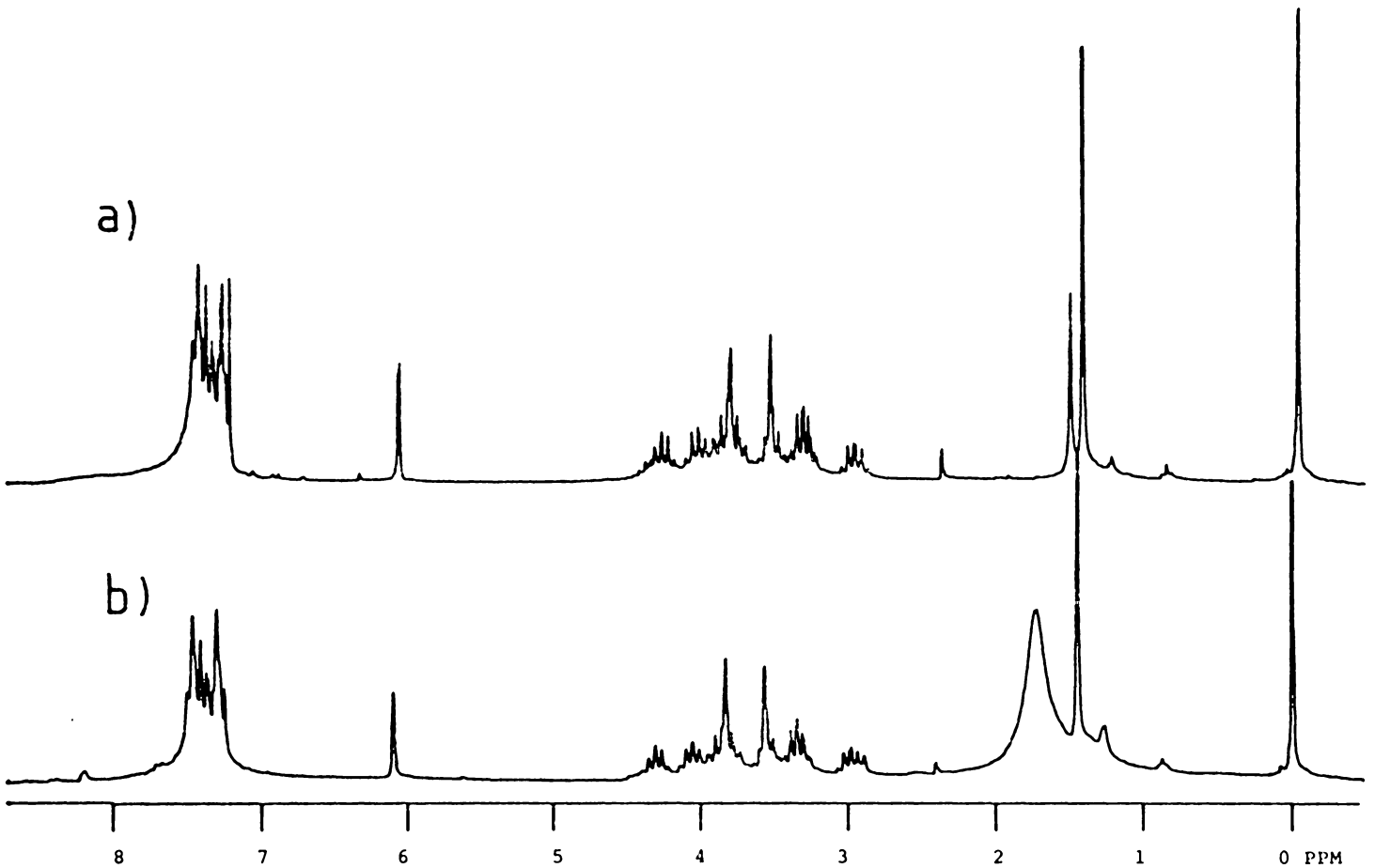
plexation with $Eu(fod)_3$. Dienol ether 165 has four oxygen atoms which have been deactivated as trifluoroethyl ethers. Therefore, the ^1H and ^{13}C NMR signals of dienol enol 165 would not be expected to undergo large chemical shift changes on addition of $Eu(fod)_3$.

The experimental results that were obtained during this study were totally consistent with the above expectations. Figure 5.1 illustrates that significant chemical shift changes were not observed when comparing the ^1H NMR spectrum of dienol ether 165 in the absence of $Eu(fod)_3$ to the ^1H NMR spectrum which was obtained in the presence of lanthanide shift reagent [i.e., 0.46 equivalent of $Eu(fod)_3$]. Similar results were observed in the corresponding ^{13}C NMR spectra. A maximum chemical shift change of only 0.05 ppm was observed in comparing the previously described spectra. Therefore, no significant chemical shift changes were observed for dienol ether 165 on addition of $Eu(fod)_3$. This $Eu(fod)_3$ experiment further illustrates that trifluoroethyl derivatives can be utilized to prevent complexation of oxygen atoms with lanthanide shift reagents.

Based on the above results, lanthanide shift reagents were utilized to characterize other polyfunctional molecules containing trifluoroethyl ethers. Valuable structural information was obtained from $Eu(fod)_3$ studies on cyclic ketone 140 and cyclohexenone 157.

Figure 5.1

The ^{1}H NMR spectrum of dienol ether 165 (a) in the absence of $Eu(fod)_3$ and (b) in the presence of 0.46 equiv of $Eu(fod)_3$.


a)
b)
8
7
6
5
4
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2
1
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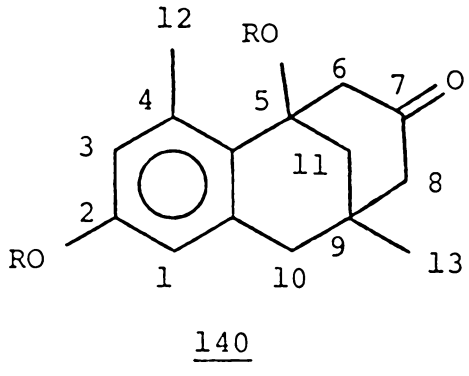
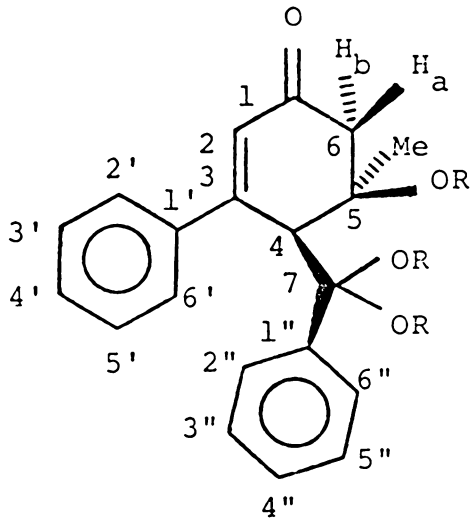


140



$R = CH_2CF_3$ 157

The results that were obtained from these polyfunctional molecules afforded simple interpretations since only one carbonyl oxygen atom was available to complex with the lanthanide shift reagent. Complexation of $Eu(fod)_3$ with the trifluoroethoxy oxygen atoms was not observed in either of these compounds.

Cyclic ketone 140 was one of several compounds that was isolated after treating 2,4-pentanedione with TFD in the presence of $HBF_4 \cdot OEt_2$. Initial spectroscopic results[93] were consistent with cyclic ketone 140. To gain additional structural information for cyclic ketone 140, eight increments of $Eu(fod)_3$ were added to the compound. The chemical shifts of four methylene protons changed dramatically (protons on C-6 and C-8) while the other four methylene protons remained relatively unaffected (protons on C-10 and C-11) (Figure 5.2).

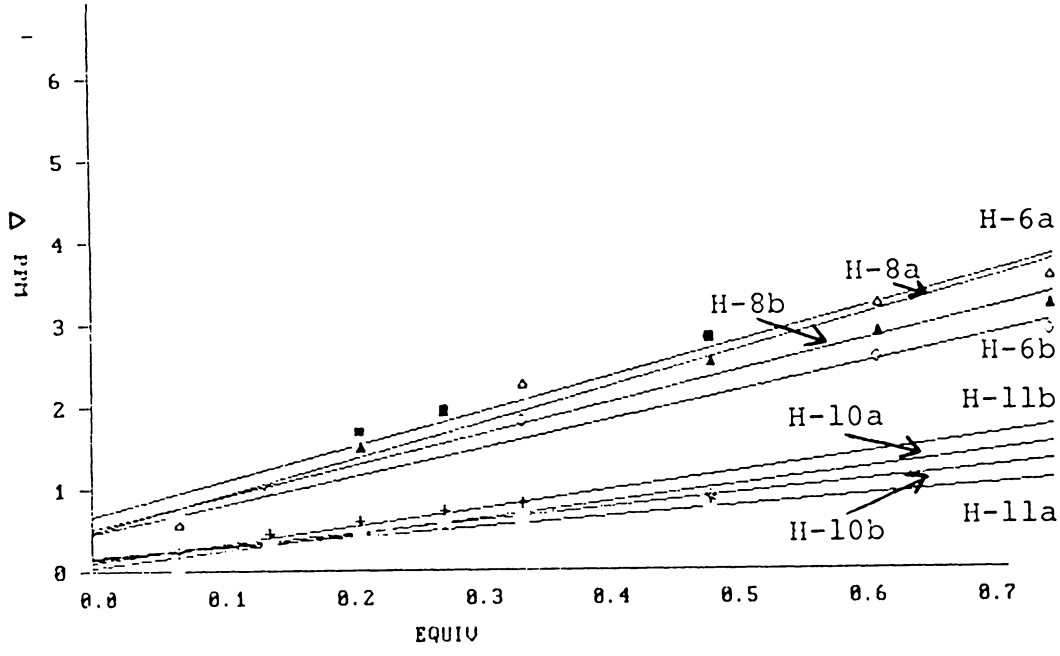
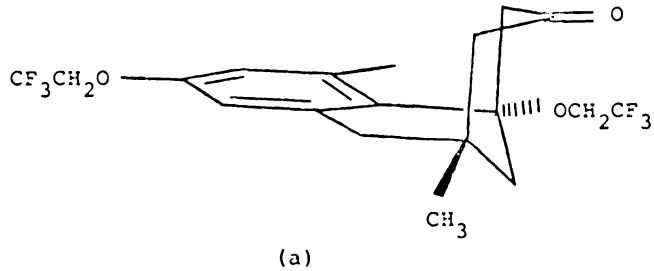


Figure 5.2

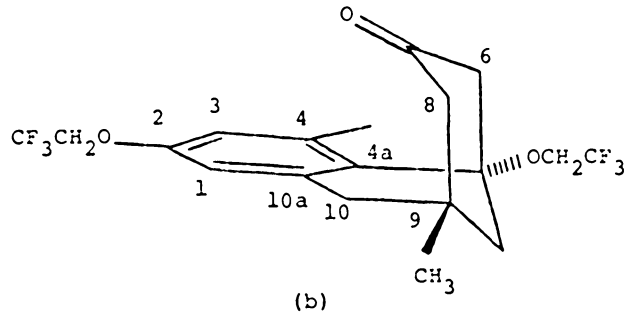
Chemical shift changes for the different methylene protons of cyclic ketone 140. The following notation is used to represent chemical shift changes (original chemical shift in the absence of $Eu(fod)_3$ is reported in parenthesis): (■) H-6a (δ 2.96 ppm); (o) H-6b (δ 2.76 ppm); (▲) H-8b (δ 2.28 ppm); (Δ) H-8a (δ 2.28 ppm); (▼) H-10b (δ 2.82 ppm); (*) H-10a (δ 2.56 ppm); (ϕ) H-11a (δ 2.32 ppm); (+) H-11b (δ 2.01 ppm).

In this study, one methylene carbon (C-6) exhibited very large chemical shift changes in the ^{13}C spectrum (Figure 5.3). A second methylene carbon (C-8) was shifted slightly more than the other two methylene carbons.

The above observations are consistent with models of cyclic ketone 140. Models suggest two potential conformations for the structure which are illustrated below.



(a)



(b)

One conformation of cyclic ketone 140 has the cyclohexanone ring in a "boat" conformation (conformation a). This conformation appears less stable than the corresponding "chair" conformation due to steric interactions. The "chair" conformation (conformation b) of the cyclohexanone ring posi-

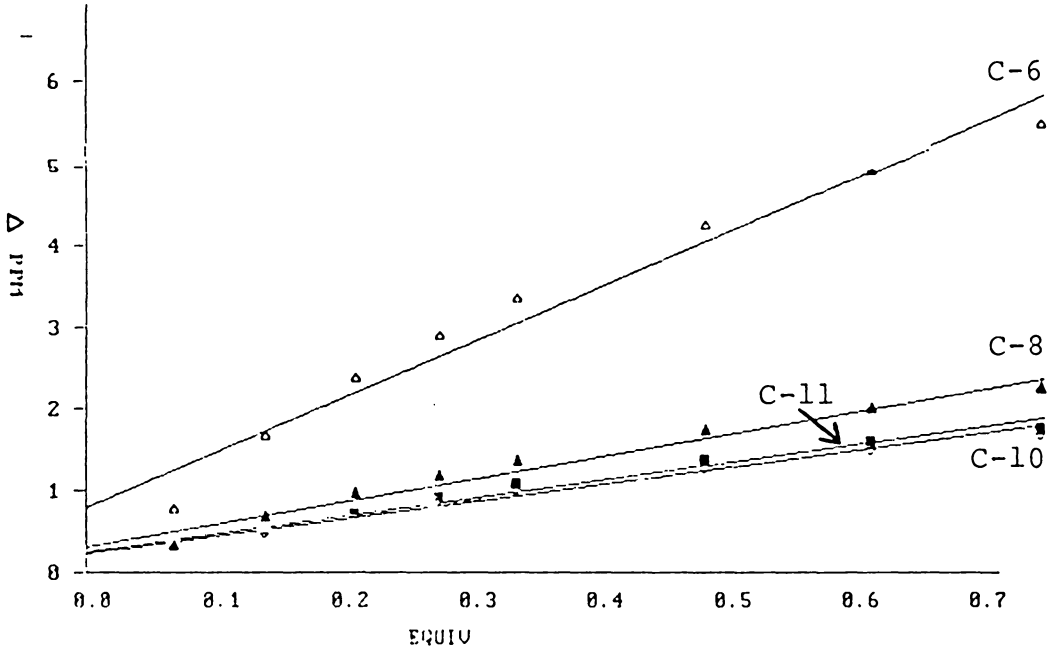


Figure 5.3

Chemical shift changes for the four methylene carbons of cyclic ketone 140 with increasing concentration of $Eu(fod)_3$. (■) C-11 (δ 43.43 ppm); (o) C-10 (δ 45.20 ppm); (▲) C-8 (δ 52.87 ppm); (Δ) C-6 (δ 53.14 ppm).

tions the oxygen atom of the carbonyl group closer to one of the adjacent methylene groups (C-6) than it does to the other. Therefore, C-6 should experience an induced chemical shift change which is considerably larger the chemical shift changes observed at the other three methylene carbons. In addition, the larger chemical shift change that was observed for C-6 cannot be induced from a complexation between the carbonyl oxygen and the oxygen of the trifluoroethoxy group on C-5. This complexation cannot occur since these two oxygen atoms are positioned on opposite sides of the previously described "chair" conformation. In this same study, large chemical shift changes were also induced at the two aliphatic quarternary carbons (C-5 and C-9) (Figure 5.4). Therefore, these two carbons must also be near the point of complexation. The results of the lanthanide shift reagent experiment suggest that two methylene carbons (C-6 and C-8) are adjacent to the carbonyl carbon and that each methylene carbon is further attached to an aliphatic quarternary carbon.

Further observations are also consistent with the above "chair" conformation of cyclic ketone 140. This conformation would position the carbonyl oxygen over C-4a of the aromatic ring. This quaternary carbon exhibited the greatest induced chemical shift change of the six aromatic carbons (Table 5.1). The two quarternary carbons (C-10a and C-4) that are adjacent to C-4a also exhibited chemical shift

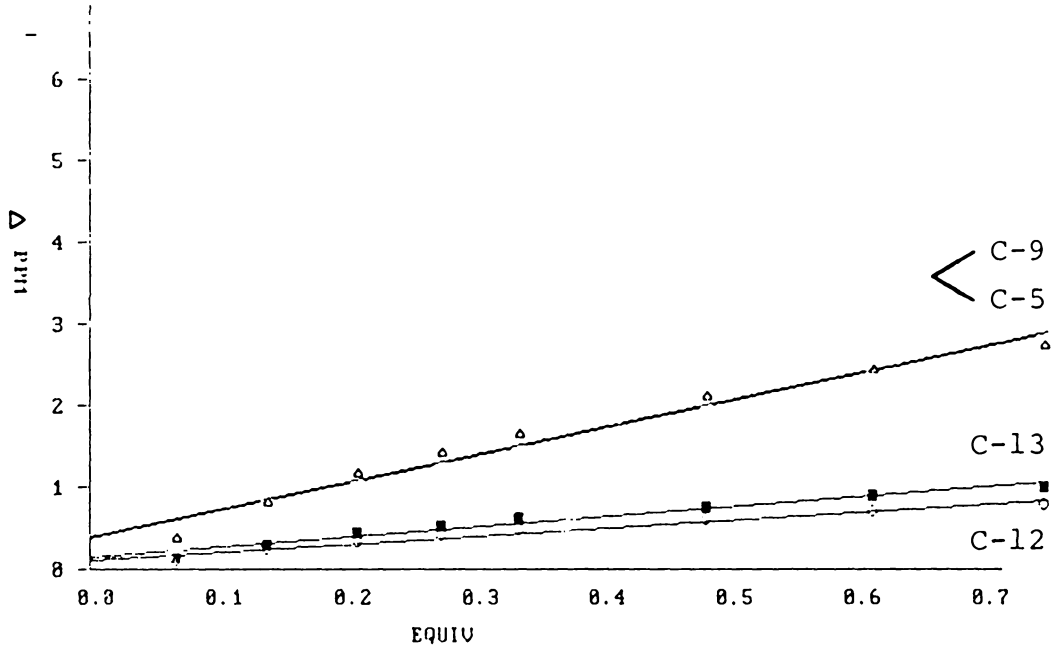


Figure 5.4

Chemical shift changes for the two aliphatic quaternary and the two methyl carbons of cyclic ketone 140. (■) Methyl C-13 (δ 20.57 ppm); (o) methyl C-12 (δ 31.25 ppm); (▲) quarternary C-9 (δ 33.35 ppm); (Δ) quarternary C-5 (δ 80.27 ppm). Note that the plots for C- 5 and C-9 overlap.

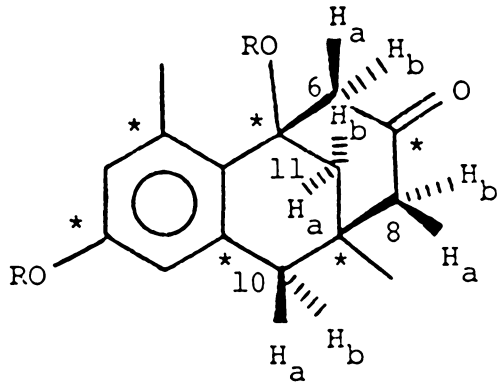
TABLE 5.1

^{13}C NMR Chemical Shift Changes of Aromatic Carbons in Cyclic Ketone 140 on Addition of 0.74 Equiv of $Eu(fod)_3$

Carbon	Chemical Shift Change (ppm)
1	0.99
2	0.79
3	1.05
4	1.89
4a	2.15
10a	1.54

changes which were larger than those observed for the other three aromatic carbons. Therefore, all results that were obtained from the $Eu(fod)_3$ study of cyclic ketone 140 are consistent with the indicated structure. As expected, the oxygen atoms of the trifluoroethoxy group did not complex with the lanthanide shift reagent in this study.

$Eu(fod)_3$ experiments were also utilized in the structural assignment of ^{13}C labeled ketone 149.[94]



149

In the presence of $Eu(fod)_3$, carbon "connectivity" for labeled ketone 149 was established by the examination of nuclear Overhauser effects (NOE) in the ^{13}C NMR spectrum when selective resonances in the ^1H NMR spectrum were irradiated. The lanthanide shift reagent was required since it was difficult to selectively irradiate individual protons in the ^1H NMR spectrum of labeled ketone 149 due to the several overlapping methylene resonances. On addition of $Eu(fod)_3$, the ^1H NMR resonances were resolved so that unambiguous results

could be obtained. NOE results were easily obtained during this experiment by examining the six labeled carbons which appeared as singlets in the ^{13}C NMR spectrum. The results of this study appear in Table 5.2. These results are consistent for the structures of compounds 140 and 149.

Cyclohexenone 157 is a second example of a polyfunctional molecule that has only one site for complexation with lanthanide shift reagents. This molecule was isolated from the reaction of 1-phenyl-1,3-butanedione with TFD in the presence of $HBF_4 \cdot OEt_2$. Studies using lanthanide shift reagents were required to provide additional structural confirmation for cyclohexenone 157. As expected, all induced chemical shift changes were consistent with complexation at the carbonyl oxygen. Analogous chemical shift changes due to complexation of the $Eu(fod)_3$ with the oxygen of the trifluoroethyl ether group were not observed.

The results of ^{1}H NMR lanthanide shift reagent study indicated that the chemical shifts of the olefinic (H-2) and the two methylene protons (H-6a and H-6b) were the only proton chemical shifts to change dramatically (Figure 5.5). Similar results were observed in the ^{13}C NMR spectrum with the exception of a large chemical shift change for C-3 (Figures 5.6 and 5.7). However, this large chemical shift change could be explained since C-3 is in conjugation with the carbonyl carbon through the enone system. The large chemical shift change at C-3 does not appear to originate from direct

TABLE 5.2

NOE Results for ^{13}C-{^{1}H} NMR Studies of Labeled Ketone 149

signal irradiated, δ ppm	signal enhanced, δ ppm	observed in Eu(fod) addition
6.61 (H-4')	139.01, 156.57 (C-3, C-5)	None
6.43 (H-6')	137.83, 156.57 (C-1, C-5)	None
2.56 (H-8a)	33.35, 137.83 (C-7, C-1)	2, 3, 5, 6
2.82 (H-8b)	33.35, 137.83 (C-7, C-1)	5, 6
2.28 (H-6a)	33.35, 206.47 (C-7, C-5)	None, 2, 3
2.28 (H-6b)	33.35, 206.47 (C-7, C-5)	None, 2, 5
2.96 (H-4a)	80.27, 206.47 (C-3, C-5)	2, 6
2.76 (H-4b)	80.27, 206.47 (C-3, C-5)	3
2.01 (H-9b)	33.35, 80.27 (C-7, C-3)	1, 5
2.48 (H-7')	139.01 (C-3')	5
1.27 (H-10)	33.35 (C-7)	None

[a]In general NOE enhancements of 20-100% were observed. Also, the enhanced signal(s) were more easily observed utilizing higher concentrations of the lanthanide shift reagent. This observation was due to proton NMR signals becoming better resolved for irradiation studies.

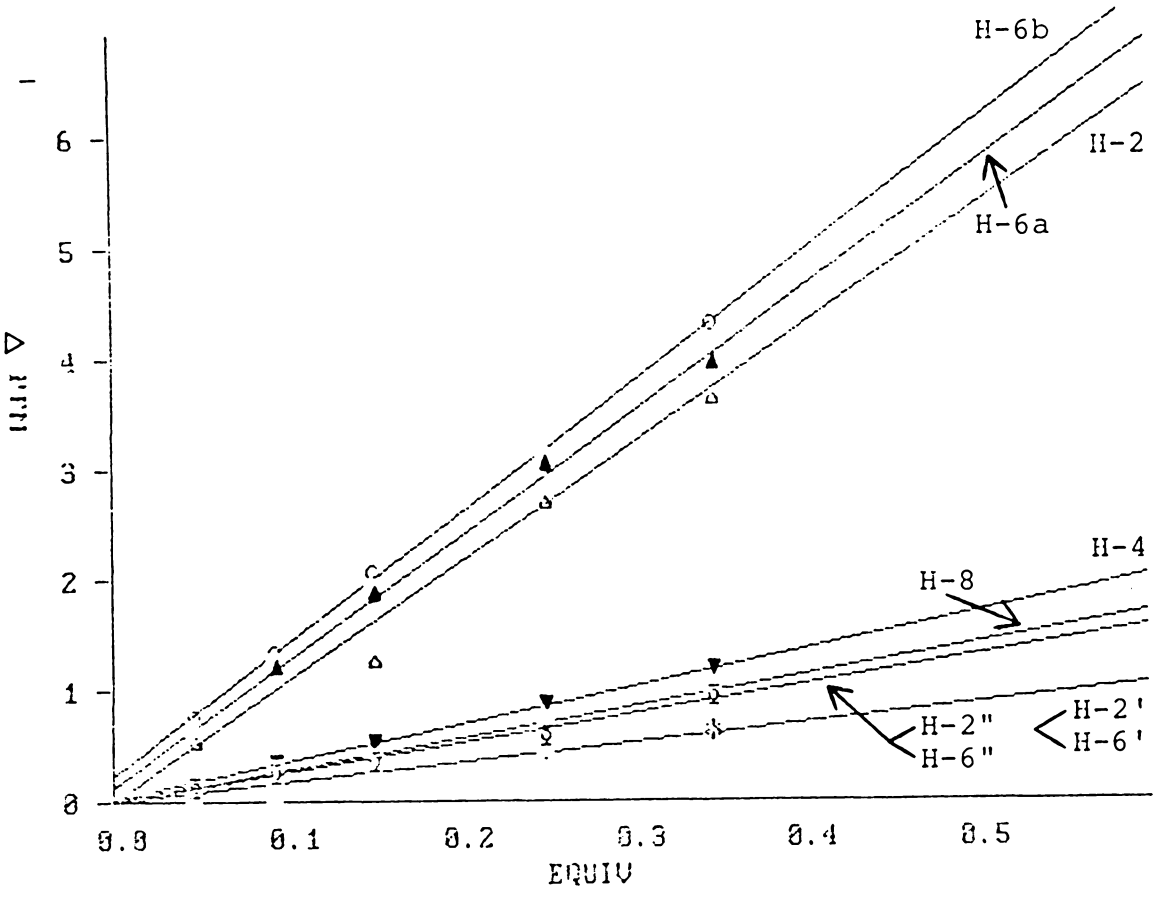


Figure 5.5

Chemical shift changes for different protons of cyclohexenone 157 with increasing concentration of $Eu(fod)_3$. (■) Methyl H-8 (δ 1.47 ppm); (o) methylene H-6a (δ 1.13 ppm); (▲) methylene H-6b (δ 2.00 ppm); (Δ) olefinic H-2 (δ 6.40 ppm); (▼) methine H-4 (δ 3.97 ppm); (*) equivalent aromatics H-2' and H-6' (δ 7.53 ppm); (⧫) equivalent aromatics H-2" and H-6" (δ 7.98 ppm).

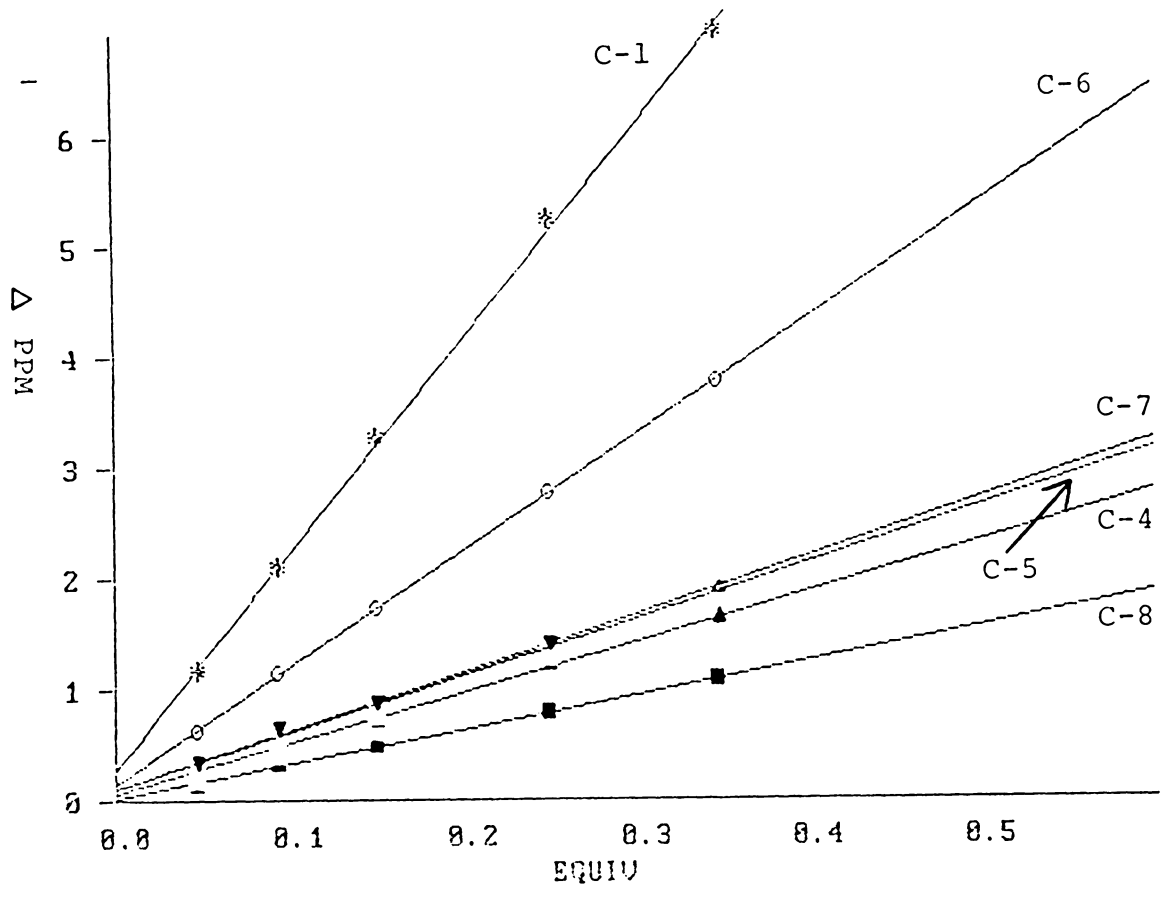


Figure 5.6

Chemical shift changes for the carbonyl and the five aliphatic carbons of cyclohexene 157 with increasing concentration of $Eu(fod)_3$. (■) Methyl C-8 (δ 25.71 ppm); (o) methylene C-6 (δ 42.18 ppm); (▲) methine C-4 (δ 52.80 ppm); (Δ) quarternary C-5 (δ 78.15 ppm); (▼) quarternary C-7 (δ 104.55 ppm); (*) carbonyl C-1 (δ 195.59 ppm).

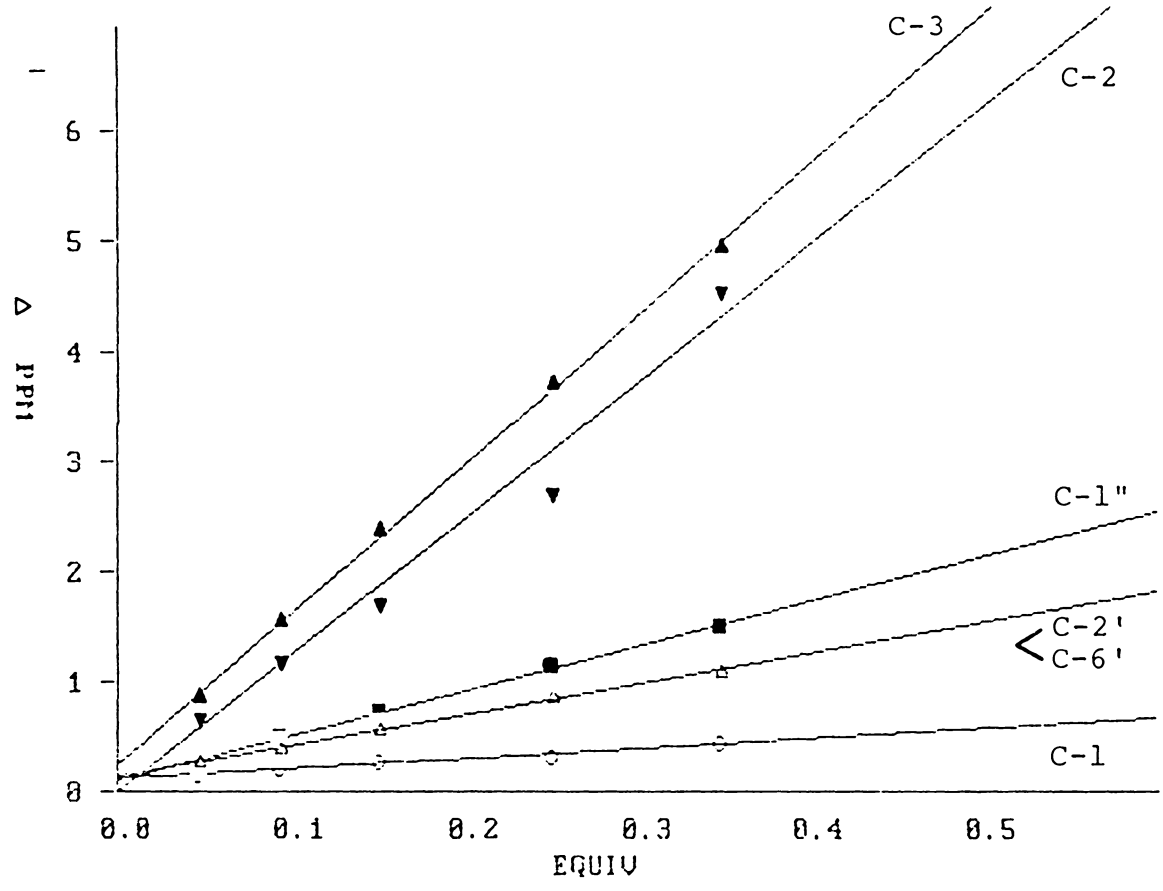


Figure 5.7

Chemical shift changes for aromatic and olefinic carbons of cyclohexenone 157 with increasing concentration of $Eu(fod)_3$. (■) Aromatic quarternary C-1" (δ 134.39 ppm); (o) aromatic quaternary C-1 (δ 141.34 ppm); (▲) olefinic quarternary C-3 (δ 157.28 ppm); (Δ) equivalent aromatic methines C-2' and C-6' (δ 125.39 ppm); (▼) olefinic methine C-2 (δ 129.48 ppm).

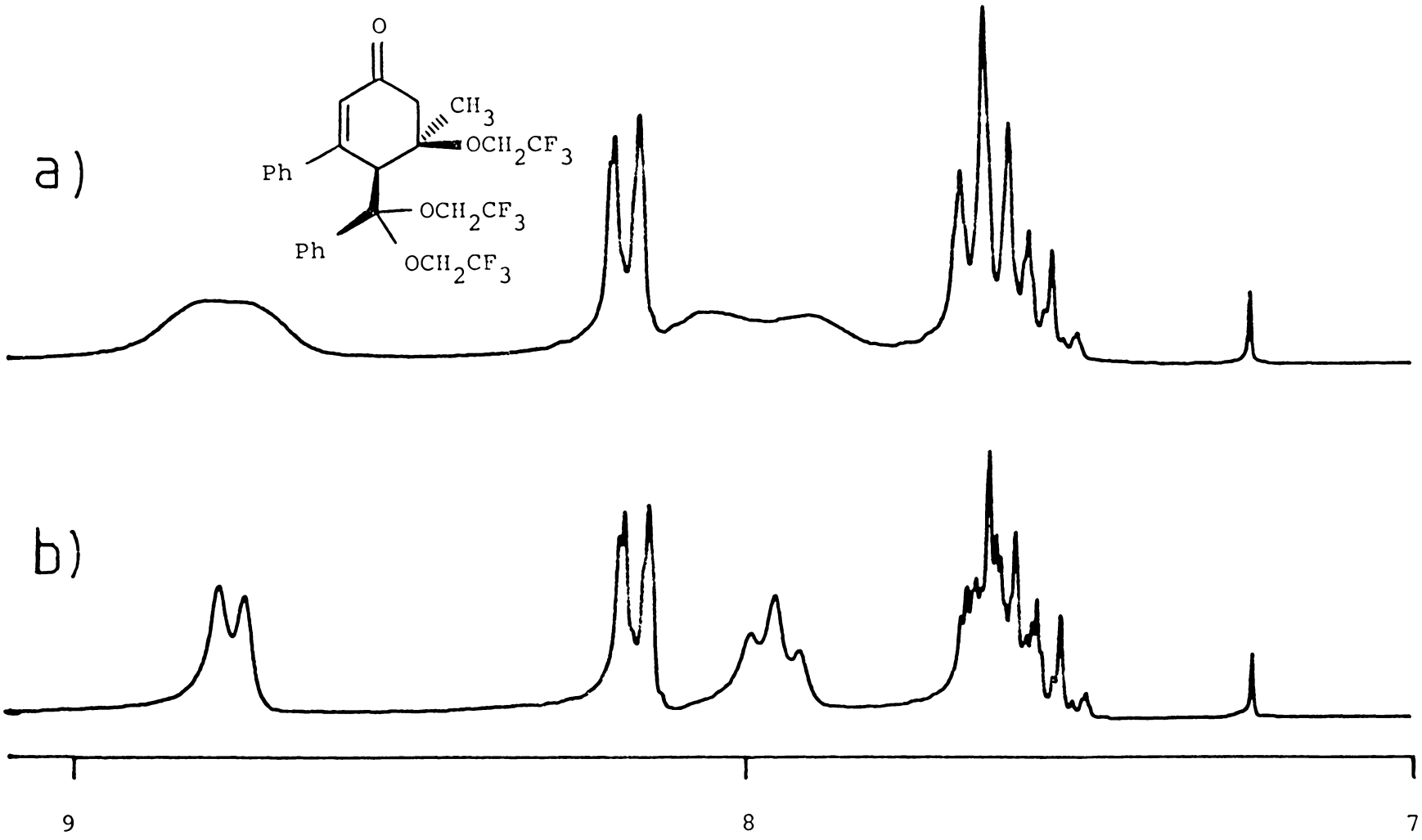
complexation of $Eu(fod)_3$ with the enone system. Steric hindrance due to the phenyl group on C-3 would prevent complexation occurring at C-3. Thus, the results of lanthanide shift reagent study are consistent with cyclohexenone 157.

Additional structural information for cyclohexenone 157 was also obtained from the above $Eu(fod)_3$ study. In Chapters II and III, the unusual stability of cyclohexenone 157 to hydrolysis was described. Under the conditions that were employed, deketalization of cyclohexenone 157 was not observed due to steric contraints which prevented nucleophilic attack at the ketal carbon. The above lanthanide shift also illustrates that the phenyl ring on C-7 has restricted rotation as a result of these steric constraints. Further details of this lanthanide shift reagent study are described below.

In the absence of $Eu(fod)_3$, little information could be obtained from the aromatic ^1H NMR region of cyclohexenone 157. On addition of 0.35 equivalent of $Eu(fod)_3$ to the above sample, the aromatic region of the ^1H NMR spectrum was more clearly resolved. From the $Eu(fod)_3$ experiment, ^1H NMR signals could be observed for both phenyl groups. At ~30^oC, one of the two phenyl groups afforded broad signals in the ^1H NMR spectrum (Figure 5.8). This suggests that the phenyl group on C-7 has restricted rotation. On heating the above sample [i.e., cyclohexenone 157 in the presence of 0.35 equivalent of $Eu(fod)_3$], the broad proton signals became much sharper

Figure 5.8

The aromatic ^{1}H NMR region of cyclohexenone 157 at (a) ambient temperatures (~30°C) and (b) 55°C. These spectra illustrate that one phenyl ring of cyclohexenone 157 has restricted rotation at ambient temperatures. $Eu(fod)_3$ (0.35 equiv) was added to this sample to resolve the aromatic ^{1}H NMR signals.


a)
b)
O
CH3
OCH2CF3
Ph
OCH2CF3
Ph
OCH2CF3
9
8
7 PPM

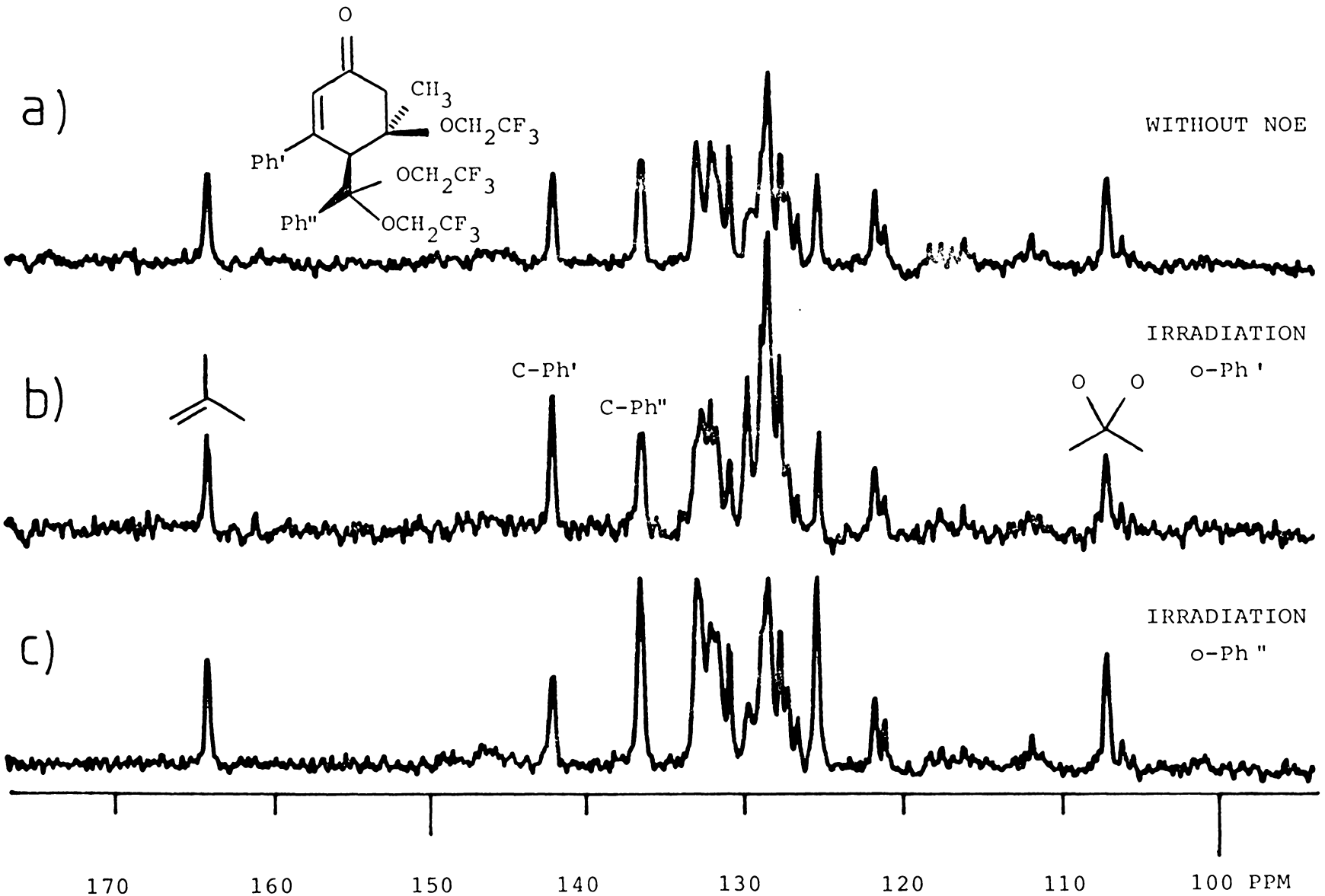
since sufficient energy had been added to overcome the barrier to rotation (Figure 5.8b).

The phenyl group with restricted rotation in cyclohexenone 157 was further assigned by a NOE study in the presence of 0.35 equivalent of $Eu(fod)_3$. Both the sharp ortho aromatic protons (δ 7.53 ppm[95] for the equivalent protons H-2' and H-6') and the broad ortho aromatic protons (δ 7.87 ppm for the equivalent protons H-2" and H-6") were individually irradiated while NOE enhancements were observed in the ^{13}C NMR spectrum (Figure 5.9). When the broad ortho protons were irradiated, the signals for the ketal carbon (δ 104.55 ppm) and C-1" (δ 134.39 ppm) were enhanced. Similarly, when the sharp ortho aromatic protons were irradiated, the signals for C-3 (δ 157.28 ppm) and C-1' (δ 141.34 ppm) showed enhancement. Note that the signals at δ 134.39 and 141.34 ppm were previously assigned by ^{13}C NMR INADEQUATE experiments.[93] The NOE results and the ^{13}C NMR INADEQUATE study clearly illustrate that the phenyl ring attached to the ketal carbon has restricted rotation.

The stereochemistry of cyclohexenone 157 was also assigned from the results of the $Eu(fod)_3$ experiment. Based on models of the system, the methyl group on C-5 can be in either an axial or an equatorical position. Under the conditions employed for the lanthanide shift reagent study, the maximum chemical shift change for the methyl carbon was only 1.09 ppm. The maximum chemical shift changes for the ketal

Figure 5.9

Nuclear Overhauser effects in the ^{13}C NMR spectrum of cyclohexenone 157 on selective irradiation in the ^{1}H NMR spectrum. (a) This shows the ^{13}C NMR spectrum of cyclohexenone 157 without irradiation in the ^{1}H NMR region (without NOE). (b) This spectrum was obtained by irradiating the sharp ortho aromatic protons that had shifted from δ 7.53. The signals at δ 141.79 and 162.23 were enhanced in the ^{13}C NMR spectrum. (c) This spectrum was obtained by irradiating the broad ortho aromatic protons that had shifted from δ 7.87. In the ^{13}C NMR spectrum, the signals at δ 135.89 and 106.34 were enhanced. The protons in the aromatic region were resolved for irradiation by the addition of 0.35 equiv to $Eu(fod)_3$ of cyclohexenone 157.

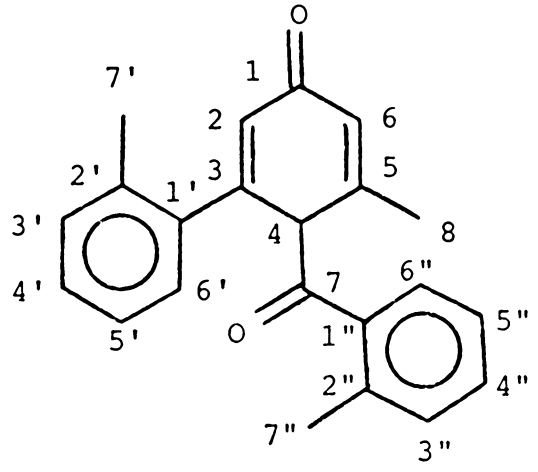

a)
WITHOUT NOE
b)
IRRADIATION
o-Ph'
C-Ph'
C-Ph"
c)
IRRADIATION
o-Ph"
170
160
150
140
130
120
110
100 PPM

carbon and C-1' were 1.79 and 1.50 ppm, respectively. From models of the system, a methyl group in the axial position (i.e., cis to the ketal carbon) should have a much larger chemical shift change than 1.09 ppm. An axial methyl group should exhibit a chemical shift change at least equal to the chemical shift change of the axial ketal carbon. To account for a chemical shift change of only 1.09 ppm, the methyl group must be in a position further from the site of complexation (i.e., the carbonyl oxygen) which would be consistent with its equatorial assignment (i.e., trans to the ketal carbon). The results of the lanthanide shift reagent study are in agreement with the stereochemistry indicated for cyclohexenone 157.

The lanthanide shift reagent results that were obtained from cyclic ketone 140 and cyclohexenone 157 were easily interpreted. For these molecules, complexation of the lanthanide shift reagent only occurred at the carbonyl oxygen. Therefore, the nuclei near this site of complexation are the only nuclei to exhibit large chemical shift changes. The above results illustrate that polyfunctional molecules are easily analyzed when only one active site complexes with the lanthanide shift reagent. These results further illustrate that trifluoroethoxy derivatives have the potential to deactivate hydroxyl groups of polyfunctional molecules.

One final example illustrates the difficulties encountered in studying polyfunctional molecules with more than one

complexation site (e.g., two carbonyl groups, etc.). Cyclohexadienone 167 was prepared by treating 1-(2-methylphenyl)-1,3-butanedione with TFD in the presence of $HBF_4 \cdot OEt_2$. Preliminary spectroscopic data indicated that this product had two carbonyl groups.[93] Therefore, cyclohexadienone 167 was further studied utilizing the $Eu(fod)_3$ shift reagent.



167

The aromatic proton that was originally at δ 8.11 ppm shifted dramatically downfield on the addition of $Eu(fod)_3$ (Figure 5.10). This proton was assigned as the ortho aromatic hydrogen on C-6" (H-6"). This assignment was based on the original downfield chemical shift of the proton and the large chemical shift change of the proton on addition of $Eu(fod)_3$. Only one of the three methyl signals showed a large chemical shift change. This signal was assigned to the protons on

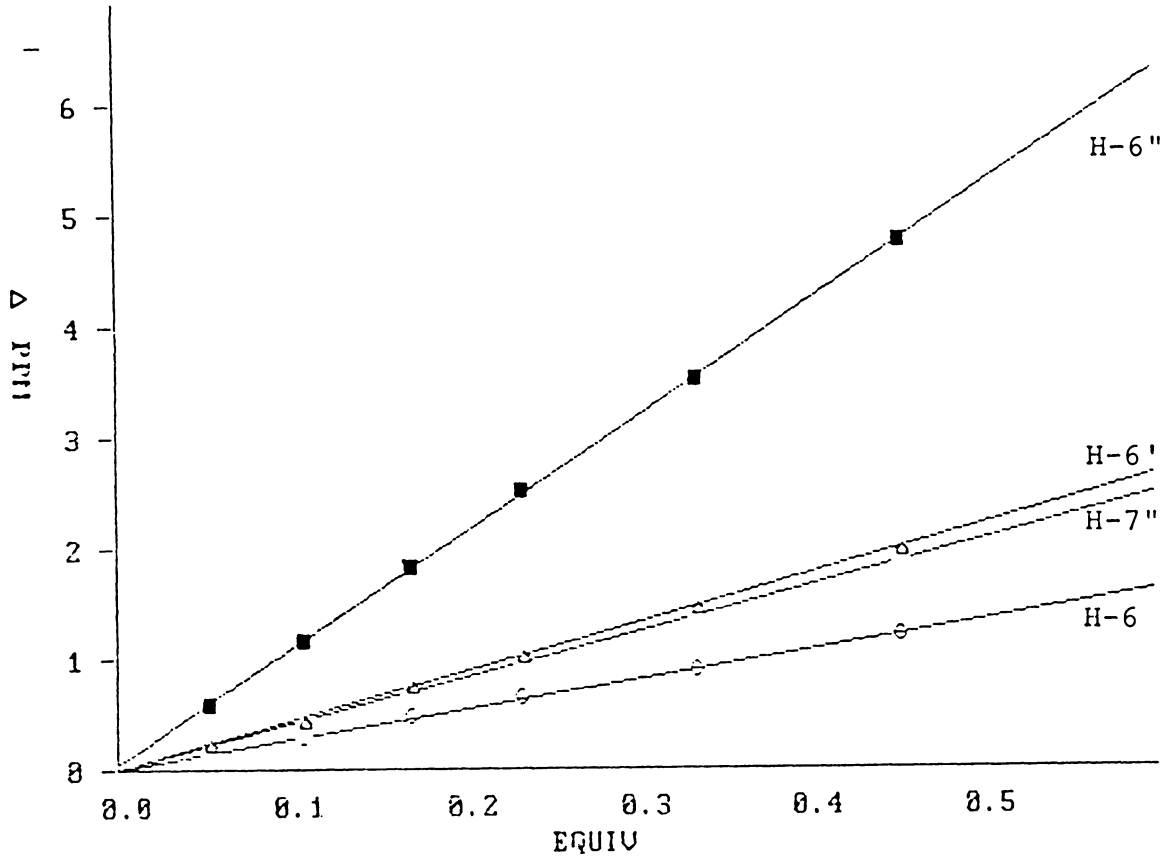
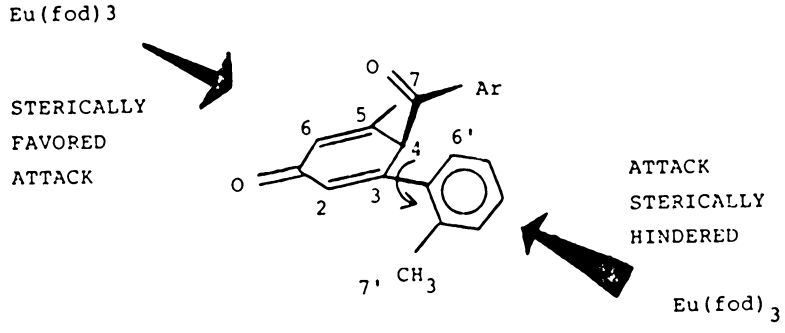


Figure 5.10

Chemical shift changes for different protons of cyclohexadienone 167 with increasing concentration of $Eu(fod)_3$. (■) Aromatic H-6" (δ 8.11 ppm); (o) olefinic H-6 (δ 5.94 ppm); (▲) methyl H-7" (δ 2.49 ppm); (Δ) aromatic H-6' (δ 7.50 ppm).

C-7". This methyl group was also the only methyl group to exhibit a large chemical shift change in the ^{13}C NMR region (Figure 5.11).

In this lanthanide shift reagent study, one of the two olefinic protons had a chemical shift change approximately four times larger than the other. This is understandable since the phenyl ring on C-3 could sterically hinder the approach of $Eu(fod)_3$ to the carbonyl groups from this side of the molecule.



Based on models of the system, the most sterically favored conformation of the phenyl ring has C-7' below the cyclohexadienone ring plane (i.e., trans to the substituent on C-4). However, if any rotation of the phenyl group occurs, then C-7' would provide additional steric hindrance to the approaching lanthanide shift reagent. Thus, the olefinic hydrogen on C-2 would also be affected by the steric hindrance created by the above phenyl ring. That is, the metal atom complexing to the two carbonyl groups would be further

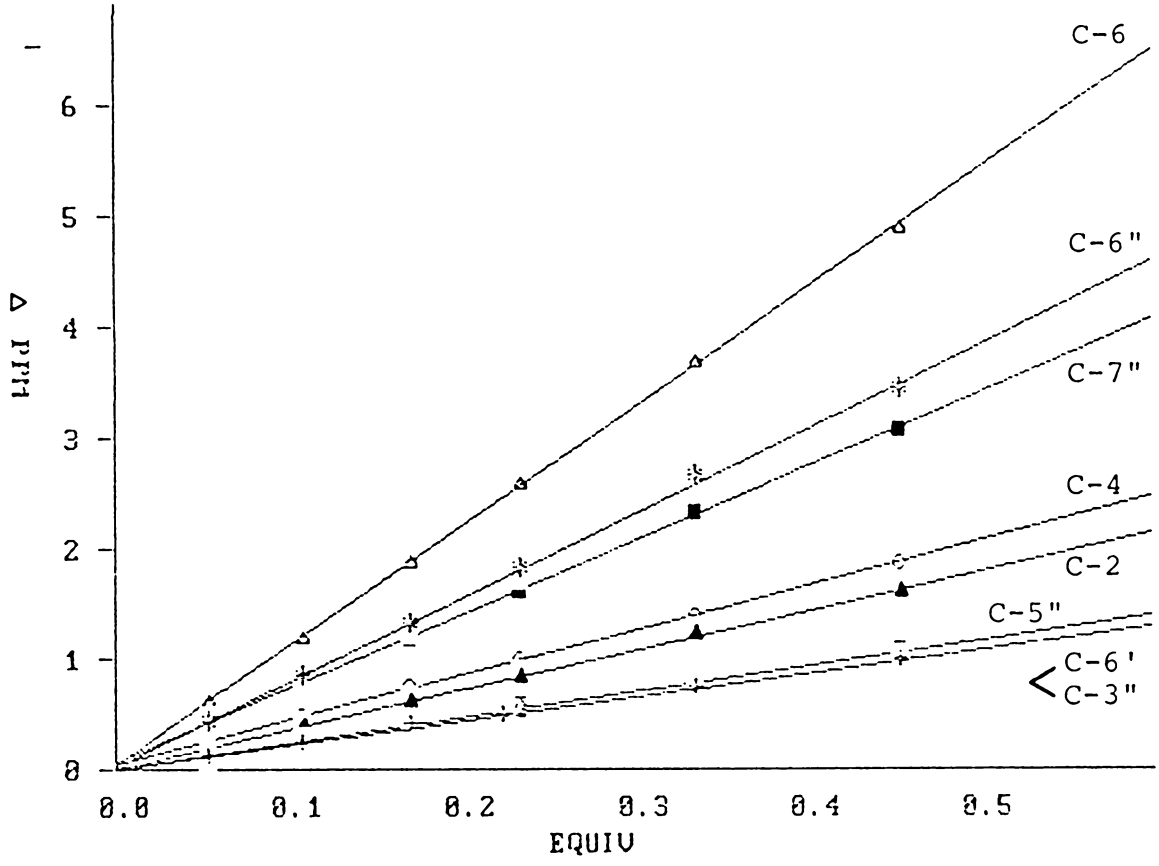
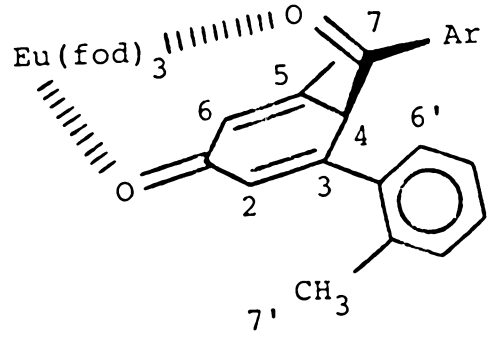


Figure 5.11

Chemical shift changes for different carbons of cyclohexadienone 167 with increasing concentration of $Eu(fod)_3$. (■) Methyl C-7" (δ 20.22 ppm); (o) methine C-4 (δ 97.14 ppm); (▲) olefinic methine C-2 (δ 109.79 ppm); (Δ) olefinic methine C-6 (δ 115.85 ppm); aromatic methines (▼) C-6' (δ 125.38 ppm); (*) C-6" (δ 127.19 ppm); (Φ) C-5" (δ 129.06 ppm); (+) C-3" (δ 130.93 ppm). The absolute value of the chemical shift change for C-4 was plotted since this carbon shifted upfield in the presence of $Eu(fod)_3$.

from H-2 than it would be from H-6 due to this steric hindrance. As a result, H-2 would exhibit a smaller chemical shift change than the proton on the less sterically hindered olefinic bond (H-6).

The only other proton exhibiting a large chemical shift change was an aromatic proton originally at δ 7.50 ppm with $^{3}J_{HCCH}$ = 6 Hz. This signal was assigned as the hydrogen on C-6'. This suggests that complexation could occur between both carbonyl groups with the metal atom in a position close to H-6'. This complexation would cause the downfield chemical shift change that was observed for H-6'.



Addition information could also be obtained for cyclohexadienone 167 by observing chemical shift changes in the ^{13}C NMR spectrum (Figure 5.11 and 5.12). Excluding the large chemical shift changes for the two carbonyl carbons, three aromatic quarternary carbons exhibited large chemical shift changes. Two of these carbons were assigned to C-1" and C-2". The third carbon was assigned as C-5. As was observed

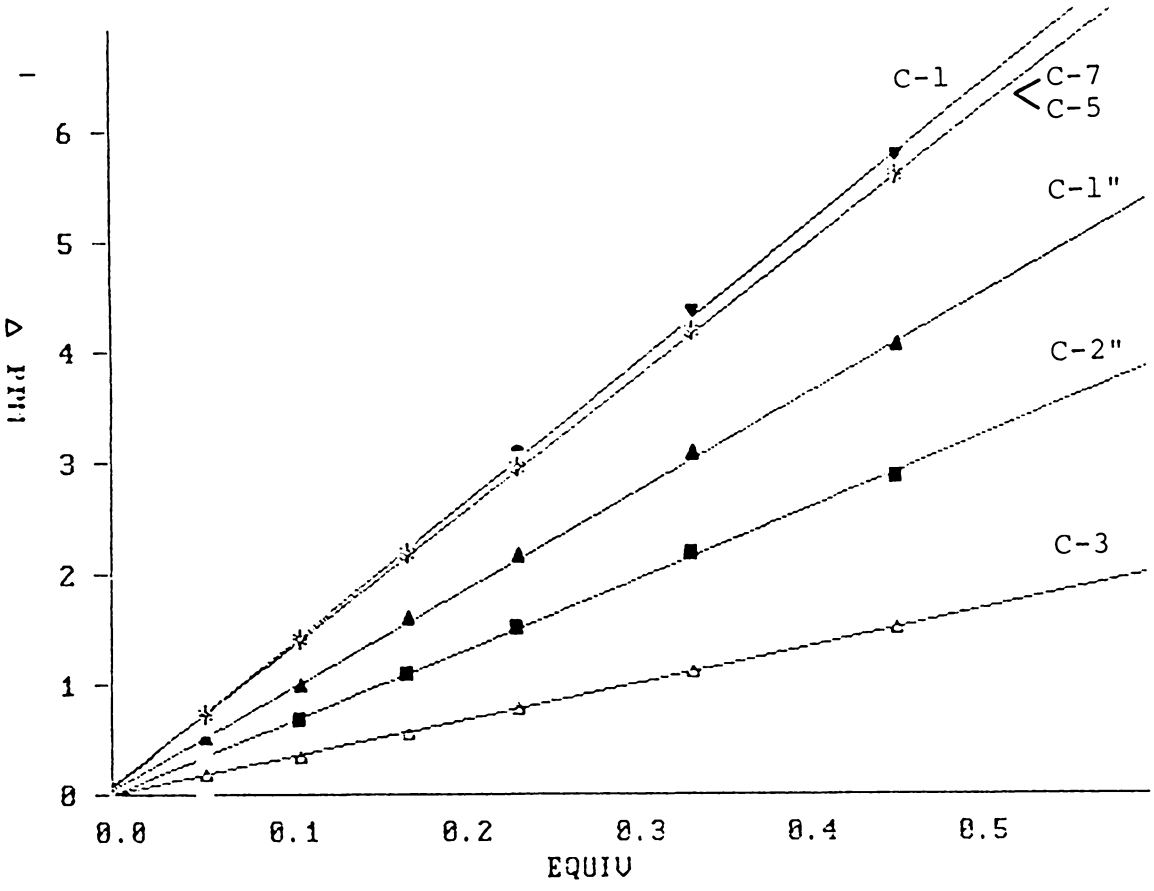


Figure 5.12

Chemical shift changes for different carbons of cyclohexadienone 167 with increasing concentration of $Eu(fod)_3$. (■) Aromatic quarternary C-2" (δ 135.78 ppm); (o) olefinic quarternary C-5 (δ 143.28 ppm); (▲) aromatic quarternary C-1" (δ 147.64 ppm); (Δ) olefinic quarternary C-3 (δ 158.73 ppm); (▼) carbonyl C-1 (δ 166.58 ppm); (*) carbonyl C-7 (δ 192.99 ppm). The absolute value of the chemical shift change for C-7 was plotted since this carbon shifted upfield in the presence of $Eu(fod)_3$. Note that the plots for C-5 and C-7 overlap in this figure.

in the ^{1}H NMR spectrum, C-5 is positioned on the side of the cyclohexadienone ring that exhibits the least steric hindrance to the attack of the metal atom on the carbonyl groups. Therefore, C-5 exhibits a larger chemical shift change than C-3.

Two carbons at δ 115.85 and 127.19 ppm had large chemical shift changes in the downfield methine region. The former carbon was assigned as one of the olefinic methine carbons (C-6). The latter methine carbon was assigned as C-6". Two other methine carbons at δ 97.14 and 109.79 ppm had moderate chemical shift changes. The methine carbon at δ 97.14 ppm as well as the adjacent carbonyl carbon at δ 192.99 ppm exhibited upfield chemical shifts changes. Therefore, the chemical shift at δ 97.14 ppm was assigned as the aliphatic methine carbon (C-4). This carbon appears to exhibit an upfield chemical change shift due to the unusual complexation that is occurring at the adjacent carbonyl group (C-7). This effect is apparently due to the complexation of the metal atom between the two carbonyl oxygen atoms (see previous illustration). The moderate chemical shift at δ 109.79 ppm was assigned to the second olefinic methine carbon (C-2). Again, one olefinic methine carbon had a much greater chemical shift change than the other. This also supports that the phenyl group on C-3 hinders the approach of the lanthanide shift reagent to the carbonyl groups from this side of the cyclohexadienone ring. Thus, all experimental data is in agree-

ment with compound 167.

From the previously described lanthanide shift reagent experiment, compound 167 was characterized as having two carbonyl groups. In this study both carbonyl oxygen atoms complexed with the lanthanide shift reagent. As a result, several different signals in the ^{1}H and ^{13}C NMR spectra exhibited substantial chemical shift changes on addition of $Eu(fod)_3$. Although a large amount of structural information was obtained from the above $Eu(fod)_3$ study, contributions from each site of complexation had to be established. Therefore, ambiguities remain because $Eu(fod)_3$ complexed at more than one site.

Conclusion

Four polyfunctional compounds have been examined in the presence of $Eu(fod)_3$. A polyfunctional molecule was examined which contained only trifluoroethoxy groups. This compound did not significantly complex with $Eu(fod)_3$. Two other compounds that each contained a single carbonyl group and several trifluoroethyl ethers were also examined. In these molecules only the carbonyl oxygen complexed effectively with $Eu(fod)_3$. Finally, one compound was examined that contained two carbonyl groups. In this study, both carbonyl groups complexed effectively with the $Eu(fod)_3$ shift reagent. Therefore, the above results illustrate that tri-

fluoroethyl derivatives of hydroxyl groups can deactivate the above oxygen atoms to simplify lanthanide shift reagent studies of polyfunctional molecules. As illustrated by cyclohexadienone 167, polyfunctional molecules have previously been difficult to analyze because several different nuclei are affected by the complexation of the lanthanide shift reagent at more than one site. As a result of several complexation sites, complicated interpretations of the lanthanide shift reagent results have generally been encountered. The above lanthanide shift reagent studies have also provided structural information on several products which were obtained from cyclization reactions of β-diketones.

Experimental

Equipment. NMR data was obtained from either a JEOL FX-200 spectrometer (^{1}H NMR 199.50 MHz/^{13}C NMR 50.10 MHz) or a Bruker WP-200 spectrometer (^{1}H NMR 200.13 MHz/^{13}C NMR 50.33 MHz). Samples were dissolved in $CDCl_3$, and chemical shifts were referenced to TMS. NOE experiments were performed using the computer software which was supplied with the NMR spectrometers. Variable temperature studies on cyclohexenone 157 were performed on the JEOL FX-200 NMR spectrometer which was equipped with a variable temperature unit.

Sample Preparations. The compounds which were studied in the presence of $Eu(fod)_3$ were prepared from previously described methods.[96] Detailed spectroscopic data for these compounds are reported in Chapter II.

$Eu(fod)_3$ Studies of Dienol Ether 165. $Eu(fod)_3$ was added to 114 mg of dienol ether 165 in the following increments: 19.45, 20.75, 24.62, and 18.35 mg, respectively. The chemical shifts of dienol ether 165 under these conditions are reported in Tables 5.3 and 5.4.

$Eu(fod)_3$ Studies of Cyclic Ketone 140. $Eu(fod)_3$ was added to 46 mg of cyclic ketone 140 in the following increments: 7.80, 8.25, 8.25, 7.64, 7.02, 17.20, 15.20, and 15.60 mg, respectively. The chemical shifts of cyclic ketone 140 under these conditions are reported in Tables 5.5-5.7.

$Eu(fod)_3$ Studies of ^{13}C Enriched Ketone 149. $Eu(fod)_3$ was

TABLE 5.3

^{1}H NMR Chemical Shift Changes
for Dienol Ether 165 on Addition of Eu(fod)$_3$

equiv of LSR	olefinic CH	aliphatic CH	olefinic CH	CH_3
0.000	6.10	3.83	3.57	1.45
0.107	6.11	3.84	3.57	1.45
0.221	6.10	3.83	3.57	1.45
0.357	6.10	3.83	3.57	1.45
0.458	6.10	3.83	3.56	1.45

[a]No addition chemical shift changes were observed in the trifluoroethoxy region.

TABLE 5.4

^{13}C NMR Chemical Shift Changes for Dienol Ether 165 on Addition of $Eu(fod)_3$

	equiv of LSR				
carbon	0.000	0.107	0.221	0.357	0.458
CH_3	24.13	24.14	24.13	24.14	24.13
CH	52.10	52.13	52.13	52.13	52.13
C	80.06	80.09	80.09	80.09	80.09
CH	96.40	96.44	96.44	96.45	96.45
CH	104.03	104.06	104.06	104.07	104.07
CH	122.67	122.68	122.68	122.69	122.69
CH[a]	125.58	125.59	125.59	125.59	125.59
CH[a]	127.30	127.31	127.31	127.31	127.31
CH	127.88	127.89	127.89	127.89	127.89
CH[b]	128.49	128.51	128.50	128.51	128.51
C	135.96	135.99	135.98	136.00	136.00
C	140.50	140.53	140.53	140.54	140.54
C	141.15	141.17	141.17	141.18	141.18
C	151.15	151.17	151.17	151.18	151.17

[a]Represents two equivalent carbons.

[b]Two pairs of aromatic carbons and a single aromatic carbon overlap at δ 128.49 ppm.

TABLE 5.5

^1H NMR Chemical Shift Changes for
Cyclic Ketone 140 on Addition of $Eu(fod)_3$

equiv of LSR	hydrogen type			
	CH_3	CH_3	aromatic	aromatic
0.000	1.27	2.48	6.43	6.61
0.067	1.37	2.61	6.51	6.67
0.14	1.47	2.75	6.61	6.76
0.21	1.53	2.83	6.66	6.80
0.27	1.58	2.90	6.71	6.84
0.33	1.62	2.96	6.75	6.88
0.48	1.71	3.08	6.83	6.94
0.61	1.77	3.16	6.89	6.99
0.75	1.85	3.23	6.94	7.03

TABLE 5.6

^{1}H NMR Chemical Shift Changes for the Eight Methylene Hydrogens of Cyclic Ketone 140 on Addition of $Eu(fod)_3$

equiv of LSR	methylene hydrogen							
	H-6a	H-10b	H-6b	H-10a	H-11a	H-8a	H-8b	H-11b
0.000	2.96	2.82	2.76	2.56	2.32	2.28	2.28	2.01
0.067	3.55	3.03	3.25	2.75	2.49	2.85	2.85	2.23
0.14	-	3.18	3.77	2.95	2.68	-	-	2.46
0.21	4.63	3.28	-	3.07	2.80	-	3.77	2.61
0.27	4.91	3.35	-	3.17	2.90	-	-	2.71
0.33	5.23	3.42	4.59	3.25	-	4.53	-	2.81
0.28	5.78	3.55	-	3.43	-	-	4.79	-
0.61	6.19	-	5.34	-	-	5.50	5.15	-
0.75	6.51	-	5.65	-	-	5.81	5.45	-

TABLE 5.7

^{13}C NMR Chemical Shift Changes for Cyclic Ketone 140 on Addition of $Eu(fod)_3$

equiv of LSR	carbon type						
	CH_3	CH_3	C	CH_2	CH_2	CH_2	CH_2
0.000	20.57	31.25	33.35	43.43	45.20	52.87	53.14
0.067	20.72	31.37	33.73	43.67	45.43	53.19	53.92
0.14	20.88	31.50	34.16	43.98	45.72	53.55	54.81
0.21	21.01	31.60	34.51	44.20	45.93	53.84	55.52
0.27	21.10	31.67	34.77	44.38	46.10	54.05	56.04
0.33	21.18	31.74	34.99	44.53	46.24	54.24	56.50
0.48	21.34	31.86	35.43	44.81	46.51	54.61	57.41
0.61	21.47	31.97	35.78	45.04	46.73	54.89	58.09
0.75	21.57	32.05	36.05	45.22	46.91	55.12	58.65

TABLE 5.7 (cont.)

equiv of LSR	carbon type							
	C	CH	CH	C	C	C	C	C = O
0.000	80.27	112.78	117.84	127.89	137.83	139.01	156.57	206.47
0.067	80.65	112.90	117.96	128.19	138.09	139.22	156.66	208.41
0.14	81.10	113.09	118.14	128.55	138.40	139.48	156.81	210.59
0.21	81.45	113.22	118.26	128.82	138.64	139.67	156.90	212.35
0.27	81.70	113.33	118.36	129.02	138.82	139.82	156.98	213.63
0.33	81.93	113.42	118.44	129.20	138.98	139.95	157.05	214.76
0.48	82.38	113.58	118.59	129.55	139.29	140.19	157.16	217.05
0.61	82.72	113.72	118.72	129.82	139.53	140.39	157.28	218.71
0.75	83.00	113.83	118.83	130.04	139.72	140.55	157.36	220.15

added to 40 mg of ^{13}C enriched ketone 149 in the following increments: 7.27, 6.23, 8.00, 10.80, 11.97, 22.90, and 19.62 mg, respectively. This separated the methylene hydrogens sufficiently that signals ^{1}H NMR in this region could be irradiated to observed NOE enhancements in the ^{13}C NMR spectrum.

Eu(fod)$_3$ Studies of Cyclohexenone 157. Eu(fod)$_3$ was added to 400 mg of cyclohexenone 157 in the following increments: 34.49, 34.27, 40.75, 72.48, and 70.83 mg, respectively. The chemical shifts of cyclohexenone 157 under these conditions are reported in Tables 5.8 and 5.9.

Eu(fod)$_3$ Studies of Cyclohexadienone 167. Eu(fod)$_3$ was added to 125 mg of cyclohexenone 167 in the following increments: 22.69, 21.58, 25.84, 25.58, 41.68, and 48.65 mg, respectively. The chemical shifts of cyclohexadienone 167 under these conditions are reported in Tables 5.10 and 5.11.

TABLE 5.8

^{1}H NMR Chemical Shift Changes for Cyclohexenone 157 on Addition of Eu(fod)$_3$

hydrogen type	equiv of LSR 0.000	0.047	0.094	0.15	0.25	0.35
CH_2	1.13	1.90	2.47	3.20	----	5.45
CH_3	1.47	1.60	1.74	1.91	2.19	2.45
CH_2	2.00	2.60	3.20	3.87	5.05	5.95
aliphatic CH	3.97	4.15	4.32	4.51	4.85	5.15
olefinic CH	6.40	6.93	----	7.65	9.10	10.03
sharp ortho aromatic	7.53	7.62	7.70	7.81	7.98	8.14
broad ortho aromatic	7.87	7.98	8.09	8.22	8.45	8.78

TABLE 5.9

^{13} NMR Chemical Shift Changes for Cyclohexenone 157 on Addition of $Eu(fod)_3$

carbon type	equiv of LSR 0.000	0.047	0.094	0.15	0.25	0.35
CH_3	25.71	25.87	26.05	26.22	26.51	26.80
CH_2	42.18	42.81	43.33	43.92	44.97	45.96
CH	52.80	53.08	53.32	53.55	54.02	54.43
C	78.15	78.49	78.78	79.07	79.59	80.06
C	104.55	104.88	105.18	105.41	105.93	106.34
CH	125.39	125.67	125.79	125.97	126.26	126.49
CH	128.78	128.89	128.94	128.94	129.00	129.06
CH	129.48	129.59	129.70	129.82	129.99	130.17
CH	129.48	130.11	130.64	131.16	132.16	133.03
CH	130.01	130.23	130.35	130.52	130.75	130.98
C	134.39	134.67	134.90	135.13	135.54	135.89
C	141.34	141.50	141.56	141.62	141.67	141.79
C	157.28	158.14	158.84	158.84	161.00	162.23
CO	195.59	196.74	197.68	197.68	200.83	202.53

TABLE 5.10

^{1}H NMR Chemical Shift Changes for Cyclohexadienone 167 on Addition of Eu(fod)$_3$

hydrogen type	equiv of LSR 0.000	0.053	0.11	0.17	0.23	0.33	0.45
CH_3	2.21	2.21	2.22	2.23	2.25	2.27	2.29
CH_3	2.44	2.47	2.51	2.55	2.59	2.66	2.73
CH_3	2.49	2.72	2.95	3.22	3.22	3.48	4.37
olefinic	5.94	6.10	6.24	6.42	6.59	6.85	7.16
olefinic	6.07	6.12	6.15	6.21	6.26	6.34	6.43
aromatic	7.50	7.71	7.93	8.23	8.52	8.95	9.49
aromatic	8.11	8.71	9.28	9.96	10.64	11.65	12.89

TABLE 5.11

^{13}C NMR Chemical Shift Changes for Cyclohexadienone 167 on Addition of $Eu(fod)_3$

Carbon type	equiv of LSR 0.000	0.053	0.11	0.17	0.23	0.33	0.45
CH	20.22	20.68	20.97	21.42	21.85	22.57	23.31
CH	20.69	20.68	20.71	20.74	20.77	20.82	20.85
CH	21.81	21.79	21.79	21.81	21.85	21.87	21.87
CH	97.14	96.88	96.66	96.39	96.14	95.73	95.26
CH	109.79	109.98	110.17	110.41	110.64	111.02	111.41
CH	115.85	116.46	117.05	117.74	118.44	119.55	120.76
CH	125.38	125.48	125.59	125.73	125.86	126.09	126.34
CH	126.12	126.14	126.16	126.20	126.24	126.31	126.34
CH	127.19	127.62	128.03	128.52	129.02	129.84	130.63
CH	128.87	128.88	128.92	128.97	129.02	129.10	129.17
CH	129.06	129.18	129.30	129.46	129.61	129.84	130.12
CH	130.18	130.21	130.27	130.33	130.40	130.51	130.63
CH	130.93	131.04	131.16	131.33	131.42	131.67	131.91
CH	131.27	131.28	131.30	131.33	131.42	131.47	131.52
C	132.35	132.31	132.30	132.28	132.27	132.27	132.25
C	135.78	136.13	136.48	136.89	137.31	137.97	138.67
C	136.65	136.67	136.70	136.76	136.81	136.89	136.98
C	143.28	144.00	144.67	145.45	146.24	147.48	148.84
C	147.64	148.16	148.62	149.23	149.80	150.71	151.69
C	158.73	158.90	159.08	159.29	159.51	159.85	160.23
CO	166.58	167.31	168.00	168.82	169.63	170.92	172.34
CO	192.99	192.27	191.59	190.81	190.04	188.81	187.40

Chapter VI

INVESTIGATIONS OF p-FLUOROBENZENESULFONYL CHLORIDE AND 2,2,2-TRIFLUORODIAZOETHANE AS ^{19}F NMR TAGGING REAGENTS

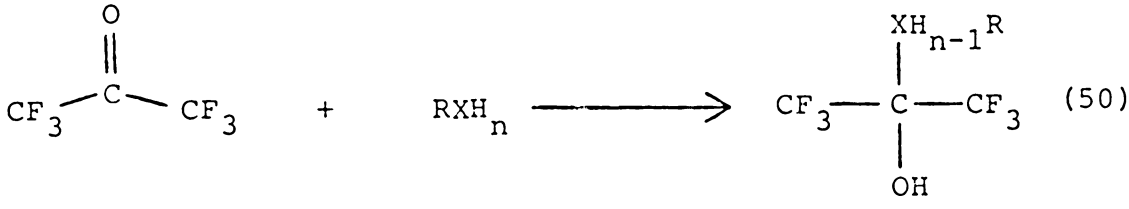
Introduction

As stated in the introduction, this dissertation project began as an analytical NMR study. In addition to the lanthanide shift reagent study that was previously described, ^{19}F NMR tagging reagents were also examined in another analytical study. Two ^{19}F NMR tagging reagents, 2,2,2-trifluorodiazoethane[1] (TFD) and p-fluorobenzenesulfonyl chloride have been examined in the present study. In general, ^{19}F NMR tagging reagents are of interest for the characterization of functional groups that are present in complex organic mixtures (e.g., coals, fuels, biological samples, etc.).[2-6] This methodology is attractive since background signals from fluorine nuclei are usually not present in the organic mixture. Therefore, functional group analysis should be easily accomplished by examination of the ^{19}F NMR spectrum after the organic mixture has been derivatized by the tagging reagent.

Manatt[97] introduced the first ^{19}F NMR tagging reagent in 1966. Utilizing trifluoroacetyl anhydride, Manatt prepared the corresponding trifluoroacetate derivatives of thirty different alcohols (eq 49).

$$(CF_3CO)_2O + ROH \longrightarrow CF_3CO_2R + CF_3CO_2H \qquad (49)$$

Additional studies utilizing other ^{19}F NMR tagging reagents have also appeared in the chemical literature.[98-101] Several of these studies employed hexafluoroacetone as a ^{19}F NMR tagging reagent (eq 50).[99]



(X = O, N, or S)

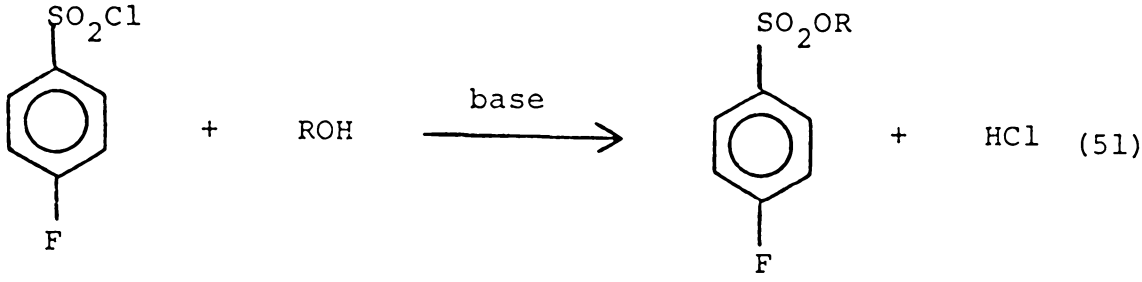
Two problems have been encountered with trifluoroacetic anhydride[97,98] and hexafluoroacetone[99] as ^{19}F NMR tagging reagents. First, the corresponding derivatives of the above compounds often undergo further reactions (e.g., hydrolysis). Second, poor yields have been obtained in some instances for the above derivatives. Therefore, other ^{19}F NMR tagging reagents are under investigation to alleviate the problems cited above. Additional requirements for the "ideal" ^{19}F NMR reagent should include a simple derivative preparation and little or no by-product formation. In addi-

tion, one usually desires reactivity of a tagging reagent with a large number of functional groups.

In an application of Koller and Dorn's previous work,[1] five steroids were treated with TFD. TFD was used to investigate these biological samples because good yields of trifluoroethyl ethers and esters have been obtained by treating alcohols and carboxylic acids, respectively, with TFD.[1] In addition, the stability of trifluoroethyl derivatives to hydrolysis suggested that these derivatives could be further analyzed by other methods (e.g., LC-^{19}F NMR studies). Preliminary studies with p-fluorobenzenesulfonyl chloride as a potential ^{19}F NMR tagging reagent will also be discussed.

Reaction of p-Fluorobenzenesulfonyl Chloride with Alcohols

The reaction of p-fluorobenzenesulfonyl chloride with various alcohols afforded the corresponding p-fluorobenzenesulfonic esters as illustrated below.



(51)

Table 6.1 lists the various alcohols that were employed in this study. The ^{19}F NMR chemical shifts and yield data are

TABLE 6.1

^{19}F NMR Chemical Shift and
Yield Data for p-Fluorobenzenesulfonic
Ester Derivatives of Alcohols

compound	δ ^{19}F (ppm)[a]	yield,[c] %
cholesterol	-36.28	90
2-octanol	-36.37	67
n-propanol	-35.98	12
cyclohexanol	-36.40	100
n-butanol	-35.97	12
iso-butanol	-36.01	85
2,3-butanediol	-35.31/-35.45[d]	23/77[d]
2-methyl-1-butanol	-36.00	51
1-adamantanol	-37.35	41
phenethyl alcohol	-35.98	39
3-phenyl-1-propanol	-35.88	15
cyclopropyl carbinol	-35.96	8
ethylene glycol	-35.11/-35.22[d]	19/15[d]
benzyl alcohol	NR[b]	
benzyhydrol	NR	
triphenyl methanol	NR	
1-methylcyclohexanol	NR	
1-ethylcyclopentanol	NR	
4-methyl-4-nonanol	NR	
3-ethyl-3-heptanol	NR	

a ^{19}F NMR chemical shift are relative to 1,2-difluorotetrachloroethane which was used as an internal standard.

b Notation represents that no reaction was observed in the above study.

c Yields were obtained by integrating the signals of the p-fluorobenzenesulfonic ester derivative and the internal quantitative standard (α,α,α-trifluoroacetophenone).

d Chemical shifts and yields are for the monosubstituted and disubstituted p-fluorobenzenesulfonyl chloride derivatives, respectively.

also reported in Table 6.1 for the corresponding p-fluorobenzenesulfonic esters of these alcohols. In general, low yields of p-fluorobenzenesulfonic esters were obtained. In some instances, especially when sterically hindered alcohols were employed, p-fluorobenzenesulfonic esters were not observed. Yields for some derivatives appear to contradict the results that would be expected from this study (i.e., low yields were also obtained from less sterically hindered alcohols). In addition, large amounts of p-fluorobenzenesulfonic acid (δ -43.95 ppm) were found for most alcohol derivatives. Therefore, some of the p-fluorobenzenesulfonic ester derivatives could have hydrolyzed after ester formation. This would explain the low yields which were obtained for n-propanol and n-butanol.

Several trends were also observed in the ^{19}F NMR chemical shifts of the above p-fluorobenzenesulfonic ester derivatives. Derivatives of primary alcohols exhibited chemical shifts approximately 0.40 ppm downfield from the derivatives of secondary alcohols. Therefore, considerable upfield chemical shifts were observed with addition of an alkyl substituent on the α-carbon of a primary alcohol. Further trends in this series (i.e., tertiary alcohols) could not be established due to the poor reactivity of these sterically hindered molecules. Only minor substituent effects were observed when alkyl groups were substituted at the β-carbon of a primary alcohol. This effect is illustrated for the

derivatives of n-butanol (δ -35.97 ppm) and 2-methyl-1-butanol (δ -36.00 ppm). Furthermore, large chemical shift differences were observed for the derivatives of 1-adamantanol and α-dihydroxy compounds (ethylene glycol and 2,3-butanediol). Derivatives of the above α-dihydroxy compounds illustrate substantial deshielding with oxygenated substituents at the β-carbon. The above trends are consistent with similar trends that have been observed in studies utilizing p-fluorobenzoyl chloride.[100,102]

Reactions of p-Fluorobenzenesulfonyl Chloride with Phenols

Phenols have also been observed to undergo reaction with p-fluorobenzenesulfonyl chloride to afford the corresponding p-fluorobenzenesulfonic esters. Yield data and ^{19}F NMR chemical shifts for several p-fluorobenzenesulfonic ester derivatives are presented in Table 6.2. Good yields were obtained for most compounds. The low yields that were obtained in a few instances (e.g., phenol, p-methoxyphenol, etc.) could be due to further hydrolysis of the sulfonic ester derivatives. The low yields which were obtained from o-cresol and o-iodophenol suggest that the o-subtituents sterically hinder the reaction of the hydroxy group with p-fluorobenzenesulfonyl chloride.

Several trends were observed in the ^{19}F NMR chemical shifts of the above phenolic derivatives. As expected, the

TABLE 6.2

^{19}F NMR Chemical Shift and
Yield Data for p-Fluorobenzenesulfonic
Ester Derivatives of Phenols

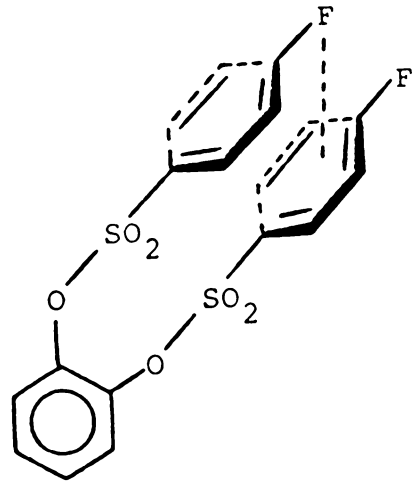
compound	δ ^{19}F (ppm)[a]	yield,[b] %
phenol	-34.55	50
m-phenylphenol	-34.62	100
p-phenylphenol	-34.50	100
pyrocatechol	-33.94/-35.53[c]	47/38[c]
p-methoxyphenol	-33.69	60
m-methoxyphenol	-33.63	100
2-naphthol	-34.47	100
4-ethylphenol	-34.73	68
3-ethylphenol	-34.80	100
4-t-butylphenol	-34.82	100
3-t-butylphenol	-34.90	100
p-bromophenol	-34.11	95
o-bromophenol	-34.06	100
m-bromophenol	-33.94	100
p-iodophenol	-34.10	71
o-iodophenol	-34.13	42
3-nitrophenol	-33.39	100
4-n-propylphenol	-34.84	100
m-chlorophenol	-33.99	100
o-chlorophenol	-34.10	100
o-cresol	-34.68	12
p-cresol	-34.71	50
m-cresol	-34.72	90

a ^{19}F NMR chemical shifts are relative to 1,2-difluorotetrachloroethane which was used as an internal standard.

b Yield were obtained by integrating the signals of the p-fluorobenzenesulfonic ester and the internal quantitative standard (α,α,α-trifluoroacetophenone).

c Chemical shifts and yields are for the monosubstituted and disubstituted p-fluorobenzenesulfonyl chloride derivatives, respectively.

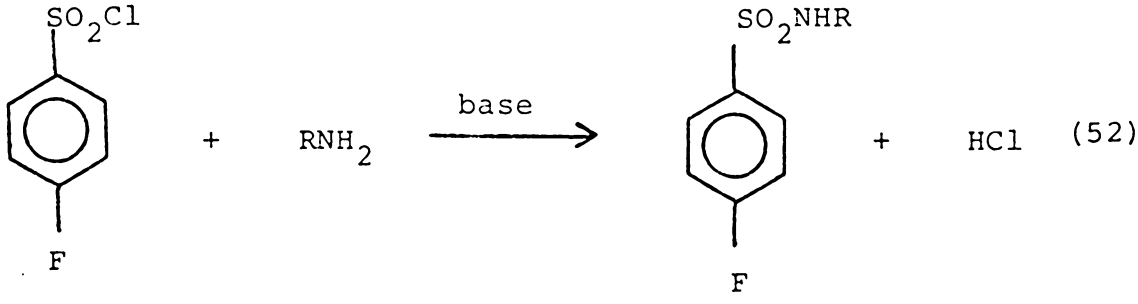
various m- and p-substituted phenols exhibited substantial deshielding effects when eletron-donating groups were replaced by electron-withdrawing groups. This is illustrated by the following series of m-derivatives: 3-t-butylphenol (δ -34.90 ppm), m-cresol (δ -34.72 ppm), phenol (δ -34.55 ppm), m-bromophenol (δ -33.94 ppm), and 3-nitrophenol (δ -33.39 ppm). A similar trend was observed when a series of p-derivatives was examined. The above results were consistent with similar results obtained with p-fluorobenzoyl chloride.[100,102] The monosubstituted derivative of pyrocatechol (δ -33.94 ppm) was consistent with the trends observed for the o-substituted derivatives. However, the disubstituted derivative (δ -35.53 ppm) had a chemical shift which was unusually shielded. This could be partially due to the steric interactions between the two p-fluorobenzenesulfonyl groups. A second explanation is that each fluorine nucleus is shielded by the aromatic ring currents of the second p-fluorobenzenesulfonyl group as illustrated below.



Thus aromatic ring currents could induce the shielding effects which are observed at each fluorine nucleus.

Reaction of p-Fluorobenzenesulfonyl Chloride with Amines

Amines have been observed to undergo reaction with p-fluorobenzenesulfonyl chloride to afford the corresponding p-fluorobenzenesulfonamide derivatives as illustrated below.



(52)

Yield data and ^{19}F NMR chemical shifts for various p-fluorobenzenesulfonamide derivatives are reported in Table 6.3. Good yields were obtained for all amines except t-butylamine. It seems unlikely that steric hindrance alone would account for the low yields since good yields were obtained from several secondary amines.

Small shielding effects were observed for increased alkyl substitution at the α- and β-carbons. As expected, greater shielding effects were observed for substitution at the α-carbon than for similar substitution at the β-carbon. Alkyl substituent effects on the α-carbon are illustrated

TABLE 6.3

^{19}F NMR Chemical Shift and Yield Data for p-Fluorobenzenesulfonamide Derivatives of Amines

compound	δ ^{19}F (ppm)[a]	yield,[b] %
N-methylaniline	-37.61	87
n-butylamine	-39.42	100
t-butylamine	-40.12	32
sec-butylamine	-39.63	100
iso-butylamine	-39.52	100
diethylamine	-38.81	100
di-n-butylamine	-38.80	100
benzylamine	-39.28	100
N-ethyl-n-butylamine	-38.80	100
diethylenetriamine	-37.74/-38.93[c]	17/83[c]

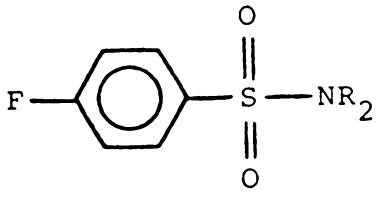
a ^{19}F NMR chemical shifts are relative to 1,2-difluorotetrachloroethane which was used as an internal standard.

b Yields were obtained by integrating the signals of the p-fluorobenzenesulfonamide and the internal quantitative standard (1,1,1-trichlorotrifluoroethane).

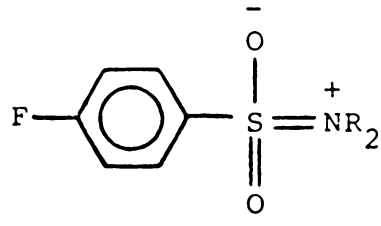
c Chemical shifts and yields are for the monosubstituted and disubstituted p-fluorobenzenesulfonyl chloride derivatives, respectively.

with the following series of amines: n-butylamine (δ -39.42 ppm), sec-butylamine (δ -39.63 ppm), and t-butylamine (δ -40.12 ppm). A small alkyl substituent effect was observed at the β-carbon of the amine. This effect is illustrated by the derivatives of n-butylamine (δ -39.42 ppm) and iso-butylamine (δ -39.52 ppm). The above shielding effects are consistent with similar results which were obtained from p-fluorobenzoyl chloride derivatives.[100]

In contrast to the p-fluorobenzoyl chloride study, p-fluorobenzenesulfonamide derivatives of secondary amines were less shielded than the above primary amine derivative.[100] This effect is illustrated with the p-fluorobenzenesulfonamide derivatives of diethylamine (δ -38.80 ppm) and N-ethyl-n-butylamine (δ -38.80 ppm). Therefore, the results which were obtained for these p-fluorobenzenesulfonamides suggest a substantial contribution of resonance from (b) to the stabilization of this group of compounds.



(a)



(b)

The positive charge on the nitrogen atom of resonance form

(b) helps explain the ^{19}F deshielding that was observed for the amide derivative. Similar results were obtained from 2,2,2-trifluoroacetyl chloride derivatives of primary and secondary amines.[101] However, the p-fluorobenzoyl chloride derivatives of primary amine appeared downfield from the secondary amine derivatives.[100] Thus, an increase in shielding was observed with an increase in alkyl substitution. This effect is illustrated for the corresponding p-fluorobenzamide derivatives of n-butylamine (δ -41.50 ppm) and di-n-butylamine (δ -44.22).[100]

Comparison of p-Fluorobenzenesulfonyl Chloride with Other ^{19}F NMR Tagging Reagents

Several advantages and disadvantages were apparent after preliminary studies of p-fluorobenzenesulfonyl chloride as a ^{19}F NMR tagging reagent. First, the ^{19}F NMR chemical shifts of the p-fluorobenzenesulfonyl derivatives were quite sensitive to subtle structural changes (Figure 6.1). This ^{19}F NMR tagging reagent exhibited a large range of chemical shifts for the various alcohol and phenol derivatives. As was previously reported for p-fluorobenzoyl chloride,[100,102] the sensitivity of the p-fluorobenzenesulfonyl derivatives is due to the ability of the aromatic ring to transmit substituent effects to the para position of the aromatic ring. For comparison, substituent effects are transmitted less effec-

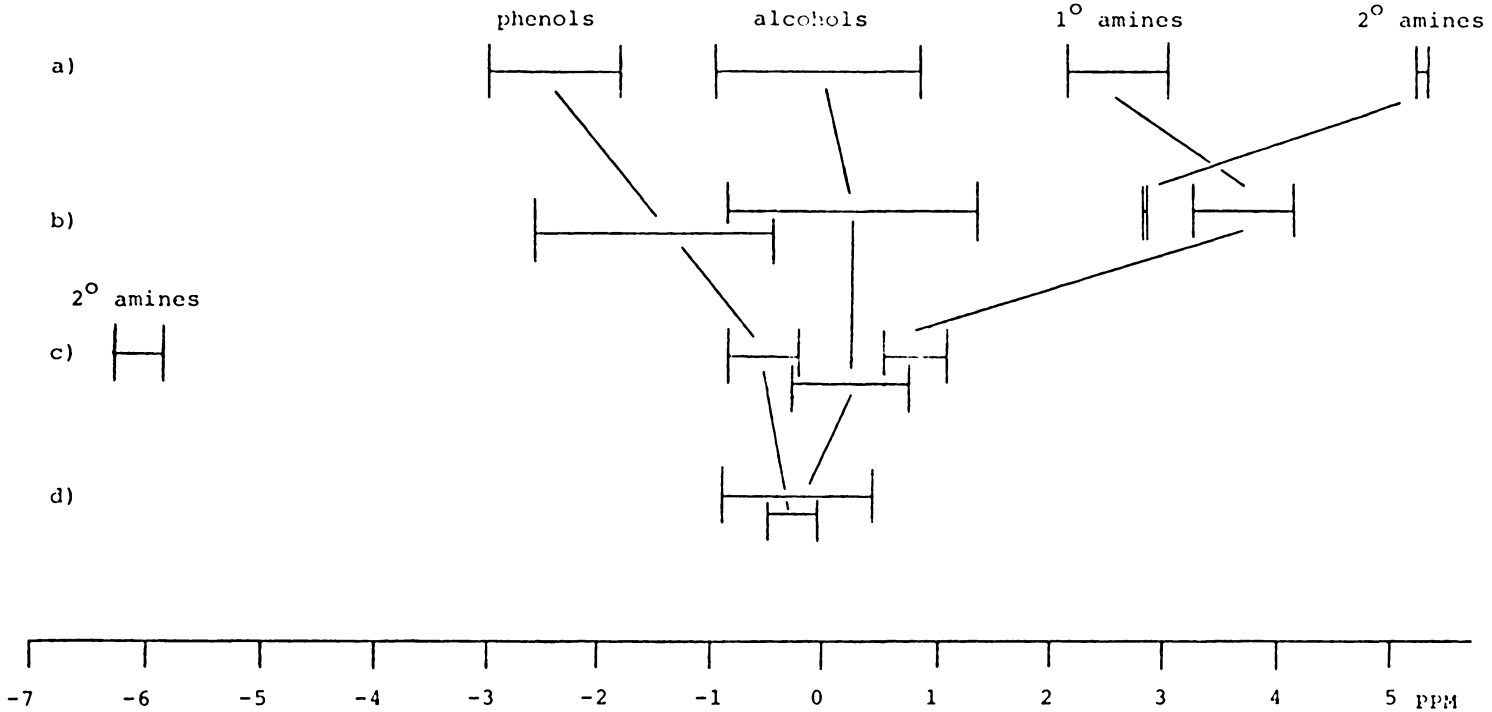


Figure 6.1

Range of ^{19}F NMR substituent effects for derivatives of (a) p-fluorobenzoyl chloride; (b) p-fluorobenzenesulfonyl chloride; (c) trifluoroacetyl chloride; and (d) 2,2,2-trifluorodiazoethane. All derivatives are relative to the corresponding n-butanol derivatives (δ 0.00 ppm).

tively to the fluorine nuclide in 2,2,2-trifluorodiazoethane[1] and trifluoroacetyl chloride[101] derivatives.

However, several disadvantages were observed for the p-fluorobenzenesulfonyl derivatives. Like the trifluoroacetyl derivative,[97,98] two serious disadvantages were encountered. That is, in some instances the sulfonic esters appear to undergo hydrolysis and poor yields were obtained for several alcohols (Table 6.1). As a result of the above disadvantages, many alcohols cannot be quantitatively analyzed. Another disadvantage encountered for the p-fluorobenzenesulfonyl chloride tagging reagent is the narrow chemical shift range observed for secondary amines. In addition, some ^{19}F NMR chemical shifts overlapped for various aromatic and aliphatic sulfonic ester derivatives. These latter disadvantages would cause difficulties in both qualitative and quantitative analysis of various compounds.

The Reaction of Various Steroids with TFD

In an application of TFD as a ^{19}F NMR tagging reagent,[1] five different steroids were treated with TFD. These steroid derivatives were utilized in an attempt to develop LC-^{19}F NMR separations for biological samples which had been treated with ^{19}F NMR tagging reagents. Although, the LC-^{19}F NMR separations were not succesfully obtained at this stage,[103] conventional ^{19}F NMR spectra were recorded for the steroid

derivatives (Table 6.4).

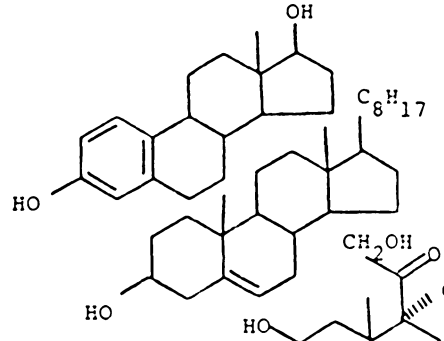
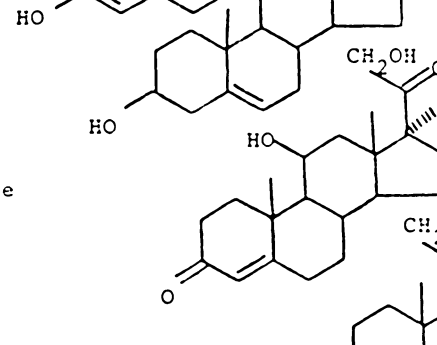
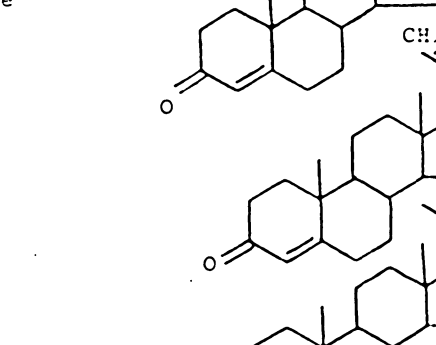
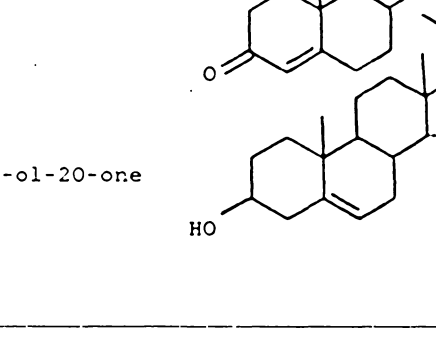
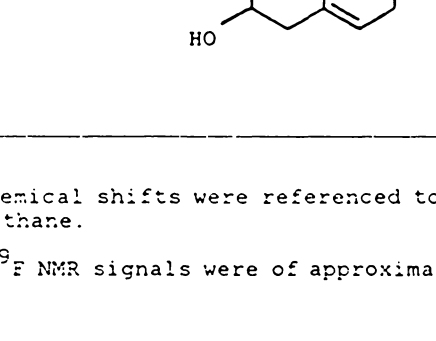
The above reactions did illustrate that TFD could be used to derivatize steroid samples. Some problems with this procedure were immediately obvious due to the poor sensitivity of the trifluoroethoxy derivatives to structural changes. For example, cholesterol and Δ^5-pregnen-3β-ol-20-one have only minor structural differences. As a result, the trifluoroethoxy derivatives of these two steriods had identical ^{19}F NMR chemical shifts at δ -7.20 ppm. Although the ^{19}F NMR chemical shifts of β-estradiol and Reichstein's substance S did not overlap, there was only a 0.16 ppm difference between the chemical shifts of aliphatic and aromatic trifluoroethoxy ethers. Therefore, distinction between phenolic and alcoholic hydroxy groups would most likely be a problem if a more extensive study of steroids were undertaken.

In the above study, hydrocortisone alcohol afforded five signals in the ^{19}F NMR spectrum. Two of these signals are believed to correspond to primary and secondary hydroxyl derivatives. The additional signals that were observed for hydrocortisone alcohol as compared to a single derivative for Reichstein's substance S could not be explained. These three additional signals are believed to be due to impurities in the above sample and/or unexplained ketal formation.

In conclusion, TFD appeared to have limited utility for the characterization of steroid molecules due to the limited ^{19}F NMR chemical shift range of steroid derivatives. In

TABLE 6.4

^{19}F NMR Chemical Shift
Data for 2,2,2-Trifluoroethyl
Derivatives of Various Steroids

compound	structure	δ ^{19}F (ppm)[a]
β-estradiol		-6.73
cholesterol		-7.20
hydrocortisone alcohol		-6.67, -6.83, -6.93, -7.07, -7.73[b]
Reichstein's substance S		-6.87
Δ^5-pregnen-3β-ol-20-one		-7.20

a ^{19}F NMR chemical shifts were referenced to 1,2-difluorotetrachloroethane.

b The five ^{19}F NMR signals were of approximately equal intensities.

addition, by-product formation could become a problem in characterizing certain steroid derivatives.

Conclusion

Although both p-fluorobenzenesulfonyl chloride and TFD undergo reactions with various functional groups, several limitations have been encountered in this limited study. For example, poor yields of sulfonic esters were obtained by treating alcohols with p-fluorobenzenesulfonyl chloride. Some of the alkyl and aromatic sulfonic ester derivatives apparently hydrolyzed during the derivative preparation process. Neither of the above ^{19}F NMR tagging reagents afforded completely resolved chemical shift regions for the various derivatives of alcohols and phenols. Furthermore, TFD derivatives exhibited only minor chemical shift changes to subtle structural changes. Therefore, neither p-fluorobenzenesulfonyl chloride or TFD would appear to be advantageous when compared with p-fluorobenzoyl chloride[100] as a ^{19}F NMR tagging reagent.

Experimental

Varian EM-390 and JOEL FX-60Q nuclear magnetic resonance spectrometers were used to record ^{19}F NMR spectra at 84.7 MHz and 56.20 MHz, respectively. The ^{19}F NMR chemical shifts

were referenced to 1,2-difluorotetrachloroethane (δ 0.00 ppm). Both α,α,α-Trifluoroacetophenone and 1,1,1-trichlorofluoroethane were used as integration references for reporting quantitative yield data. The steroid derivatives examined by ^{19}F NMR were dissolved in $CDCl_3$. Derivatives of p-fluorobenzenesulfonyl chloride were examined by ^{19}F NMR in $CDCl_3$ and pyridine solution (1:1 volumetric ratio). This solvent was also used as the solvent during derivative preparation. The ^{19}F NMR spectra were obtained using a FX-60Q NMR spectrometer with ^{1}H decoupling, whereas, the Varian EM-390 NMR spectrometer did not have the ^{1}H decoupling capability.

Reaction of p-Fluorobenenesulfonyl Chloride with Alcohols, Phenols, and Amines. p-Fluorobenzenesulfonyl chloride was very hygroscopic and required preparation in a dry box. Derivatives that were originally prepared outside the dry box resulted in large yields of p-fluorobenzenesulfonic acid. Pyridine was stored over 4 Å molecular sieves prior to use in the following preparation. A special 5-mm NMR tube was used to prevent sample losses when NMR tubes were transferred to the dry box. These NMR tubes contained a ground-glass joint with a matching top which was secured with a rubber band.

The general procedure that was utilized to prepare derivatives from p-fluorobenzenesulfonyl chloride is described below. The appropriate alcohol, phenol, or amine (0.1-0.3 mmole) was treated in the dry box with a 2- to 3-fold excess of p-fluorobenzenesulfonyl chloride. A mixture of pyridine

(0.5 mL) and $CDCl_3$ (0.5 mL) was added to the NMR tube containing the sample to be derivatized. An immediate reaction was observed when pyridine was added to the reaction mixture. The samples were removed from the dry box. α,α,α-Trifluoroacetophenone or 1,1,1-trichlorotrifluoroethane (0.02 mmole) was added to the sample as the quantitative reference. In addition, 0.02 mmole of 1,2-difluorotetrachloroethane was also added to the samples as the chemical shift reference. 1,2-Difluorotetrachloroethane contained an impurity at δ 2.86 ppm which made it less attractive as a quantitative reference.

Reactions of Steroids with TFD. Steroid derivatives were prepared by treating 1.0 mmole of the steroid with a 0.20 M TFD solution. The amount of TFD that was added to each steroid was dependent on the number of hydroxyl groups present in each steroid. In this study, 15 mL of the TFD solution was utilized for each hydroxyl group that was contained by the steroid. An extra 20 mL of the TFD solution was added to β-estradiol to ensure total reaction. $HBF_4 \cdot OEt_2$ (0.2-0.4 mL) was added to the steroid in 3 mL of chloroform prior to treatment with TFD. All reactions were performed under a nitrogen atmosphere. The reaction mixtures were neutralized with two portions of 10% NaOH and a single portion of water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The ^{19}F NMR spectra were recorded for the isolated steroid derivatives.

CONCLUSION

A novel acid-catalyzed self-condensation reaction of β-diketones in the presence of 2,2,2-trifluorodiazoethane has been discovered. Cyclized products have been obtained from 2,4-pentanedione, 1-phenyl-1,3-butanedione, and substituted derivatives of 1-phenyl-1,3-butanedione. This cyclization reaction is attractive since limited methods are available to prepare cyclized products (e.g., aromatic natural products) from β-dicarbonyl units. Specifically, this cyclization reaction offers potential methodology for the preparation of two general types of biphenyl compounds. In addition, one of these biphenyl types should be an important synthon in the preparation of larger condensed aromatic ring systems.

A preliminary mechanistic study utilizing a dienophile suggests that cyclized products are formed through a Michael addition. However, an acid-catalyzed Diels-Alder reaction has not been totally excluded as a possible reaction mechanism. All cyclized products that were obtained in this study are consistent with both reaction mechanisms. In addition, several β-diketones did not undergo an acid-catalyzed reaction in the presence of TFD. Typically, these β-diketones had steric and/or electronic factors that would destabilize the reaction intermediates in the cyclization process.

Several of the cyclized products that were obtained from the reaction of β-diketones with TFD were characterized utilizing lanthanide shift reagents. In these studies, several oxygen atoms were deactivated by TFD derivatization. As a result, these atoms did not complex with the lanthanide shift reagent. These results illustrate new methodology for the analysis of polyfunctional molecules utilizing lanthanide shift reagents.

Low yields were obtained from the acid-catalyzed cyclization reaction of β-diketones in the presence of TFD. Despite these low yields, the potential synthetic utility of the cyclization process cannot be overlooked. Further investigation of this reaction should lead to a better mechanistic understanding of the cyclization process. A better mechanistic understanding of this reaction is essential if the yield of cyclized products is to be increased. Such improvements are necessary for this reaction to become widely utilized as a synthetic tool.

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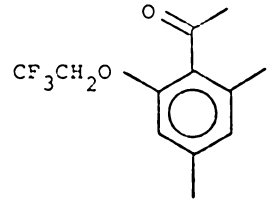
(67) In some instances, a second insertion product was observed due to incomplete hydrolysis of the reaction mixture. This product was assigned as 2,2-bis(2,2,2-trifluoroethoxy)-3-trifluoromethyl-5-hexanone.

(68) Compound 137 and 138 were easily confirmed by independent syntheses. Treatment of 3,5-dimethylphenol with TFD in the presence of tetrafluoroboric acid-diethyl ether complex afforded trifluoroethoxy derivative 138. Friedel-Crafts acylation of compound 138 afforded a 40/60 mixture of 137 and 1-[2,4-dimethyl-6-(2,2,2-trifluoroethoxy)phenyl]ethanone (144), the nonsymmetric geometric isomer of 137. All spectroscopic data for the independently synthesized compounds were identical with the spectra that were obtained from the products isolated in the 2,4-pentanedione cyclization reaction. In addition, the nonsymmetric acetophenone 144 has never been detected in any mixture obtained from 2,4-pentanedione.



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(78) Both an olefinic carbon and an aromatic carbon have the same chemical shifts at δ 129.48 ppm. Two additional pair of equivalent carbons appear as broad signals in the δ 125-130 ppm region due to sterically hindered rotation.

(79) 1-Phenyl-1,3-butanedione-1-^{13}C was diluted in this experiment to achieve approximately the same weight of β-diketone that was used in prior experiments.

(80) Two pairs of aromatic carbons and a single aromatic carbon overlap at δ 128.52 ppm.

(81) A second pair of carbons that were very broad due to hindered rotation of one aromatic ring appeared underneath the signal at δ 166.01 ppm.

(82) One aromatic quarternary carbon overlaps with the signal centered at δ 129.12 ppm.

(83) Two pair of aromatic methine carbons appear as broad carbons in the δ 128-130 ppm region due to hindered rotation of one aromatic ring.

(84) Several acid catalysts have been examined for the reaction of TFD with alcohols, phenols, and carboxylic acids. For details, see Koller, K. L. M. S. Thesis, Virginia Polytechnic Institute and State University, 1979.

(85) A more detailed description of insertion product 194 appears later in this chapter.

(86) For details of the reaction of 2,4-pentanedione with a methylene chloride solution of TFD, see Chapter II.

(87) (a)Earnshaw, C.; Wallis, C.J.; Warren, S. J. Chem. Soc., Perkin Trans. I 1979, 3099. (b) Malhotra, S. K.; Ringold, H. J. J. Am. Chem. Soc. 1965, 87, 3228. (c) House, H. O.; Tefertiller, B. A.; Olmstead, H. D. J. Org. Chem. 1968, 33, 937. (d) Normant, J. F.; Commercon, A.; Bourgain, M.; Villieras, J. Tetrahedron Lett. 1975, 3833.

(88) Chemical shifts for the two trifluoromethyl groups were not observed in the δ 120-126 ppm region of the this spectrum due to poor signal-to-noise. A limited amount of the compound had been isolated from chromatographic separations.

(89) The methods that were used in an attempt to isolate these dienes are described in Chapter III.

(90) See Chapters II and III for a more detailed description of the reaction products obtained from 1-phenyl-1,3-butanedione.

(91) Stork, G.; Nakamura, E. J. Am. Chem. Soc. 1983, 105, 5510.

(92) Dienol ether 165 was isolated from the reaction of 1-phenyl-1,3-butanedione with TFD. This compound is also the precursor which leads to cyclohexenone 157. For a more detailed description of dienol ether 165, see Chapter II.

(93) See Chapter II for a more detailed description of spectroscopic results for compounds 140, 149, 157, 165, and 167.

(94) Since 2,4-pentanedione is a symmetric molecule, two labelled carbons were incorporated into labelled ketone 149 for every unit of labelled 2,4-pentanedione

undergoing cyclization. In examining labelled ketone 149, six labelled carbons were observed in the carbon-13 NMR spectrum. Direct coupling constants were not observed between any of the six labelled carbons. This indicated that an alternating labelling pattern must be present in the labelled ketone 149.

(95) Chemical shift assignments are reported for the original proton chemical shift in the absence of lanthanide shift reagent.

(96) See Chapter II for a detailed description of the procedure used to prepare compounds 140, 149, 157, 165, and 167.

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(103) The LC-^{19}F NMR apparatus was ultimately improved for the analysis of complex organic mixtures. See Chapter IV for further separations utilizing this apparatus (i.e., separations of the reaction mixture which was obtained by treating 1,1,1-trifluoro-2,4-pentanedione with TFD).

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