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The Synthesis of Hindered Aliphatic Ketones for the Future Production of Spiro [4.5] Decane Sesquiterpenes

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THE SYNTHESIS OF HINDERED ALIPHATIC KETONES FOR THE FUTURE PRODUCTION OF SPIRO[4.5]DECANE SESQUITERPENES

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THE SYNTHESIS OF HINDERED ALIPHATIC KETONES

ABSTRACT

A feasible route to spiro[4.5]decanes is the Diels-Alder cycloaddition of 2-alkylidene-1,3-cyclopentanedione and trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene). This thesis reports investigations directed toward establishing the scope of this route. More specifically, efforts were made to prepare stable 2-alkylidene-1,3-cyclopentanedione substrates. This latter goal made it necessary to examine methods of synthesizing hindered aliphatic ketones, the pivotal precursors to such alkylidenes.

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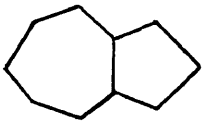
THE SYNTHESIS OF HINDERED ALIPHATIC KETONES FOR THE FUTURE PRODUCTION OF SPIRO[4.5] DECANE SESQUITERPENES

INTRODUCTION

The structure of spiro[4.5]decane(1) stirred curiosity in the middle 1900's. It was first perceived as a perhydro azulene structure; however, it was corrected in 1956 to the spiro structure.[1,2] Spiro[4.5]decane was first isolated from Oil of Sweet Flag through the work of Sorm and was later found in numerous sources.[3] This spirodecane structural feature gained prominence when it was associated with a group of natural products known as sesquiterpenes.

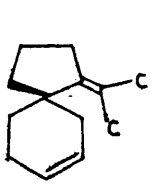


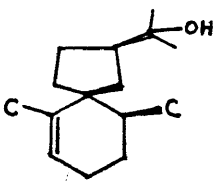
perhydro azulene

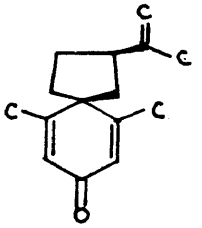
(1)

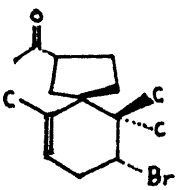
spiro[4.5]decane

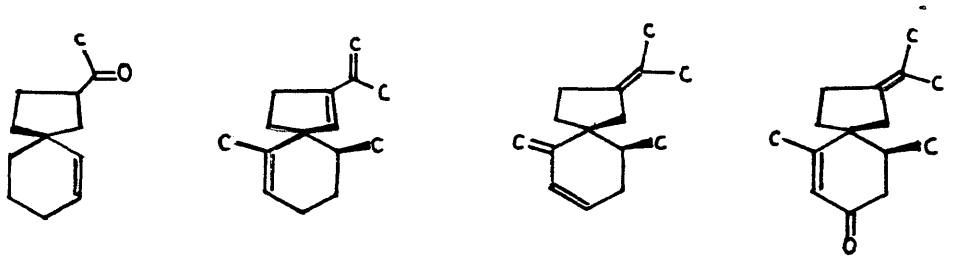
A sesquiterpene, by definition, consists of three isoprene units (2-methyl-1,3-butadiene) arranged in a "head-to-tail" fashion. Not all sesquiterpenes contain the spiro-structure; however, many spiro-sesquiterpenes have been identified and synthesized such as α-alaskene, hinesol, anhydro-β-rotunol, spiroaurenone, spirolaurenone, α- and β-vetispirene and β-vetivone. All of these are spiro[4.5]-







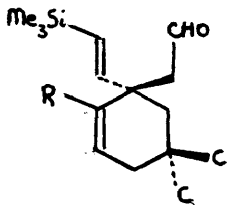


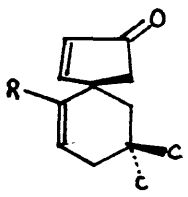


decane derivative.[3,4] Many synthetic pathways to the spiro-carbon have been developed, some of which are discussed below.

A facile synthesis of (±)-quadrone was developed through a vinyl silane-mediated spiroannulation.[5] Using dimedone derivatives and <u>trans</u>-β-(trimethylsilyl)vinyllithium the quarternary carbon center was constructed to make a spiro[4.5]decadienone in three steps as follows:

1. Jones oxidation
2. oxalyl Cl, PhH
3. $TiCl_4$, CH_2Cl_2
   $-30^{\circ}C \rightarrow 25^{\circ}C$

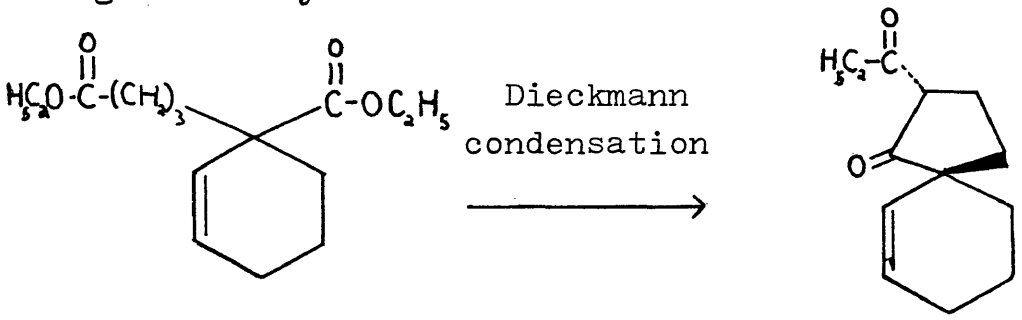




Compound (2) was prepared for the spiroannulation through raising the carbonyl oxidation state and activating the molecule through forming the acid chloride at the end of step 2. Step 3 was an intramolecular Friedel-Crafts acylation.[6]

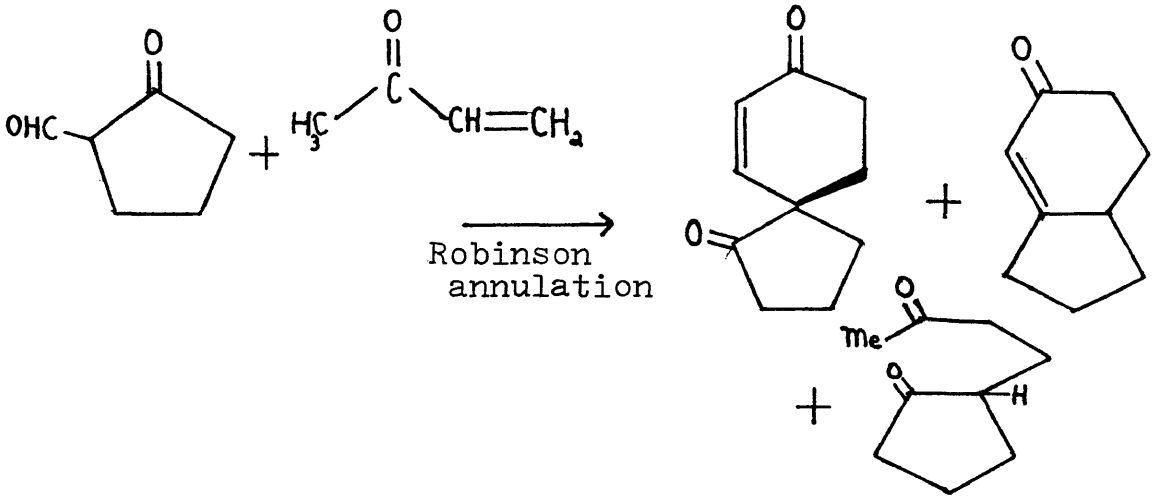
In the initial synthesis of (±)-perhydrohistrionicotoxin the spiro center was constructed from another gem-disub-

stituted cyclohexene. In this case the gem-groups were esters and spiroannulation followed a Dieckmann condensation using sodium hydroxide as the base. The Dieckmann condensa-



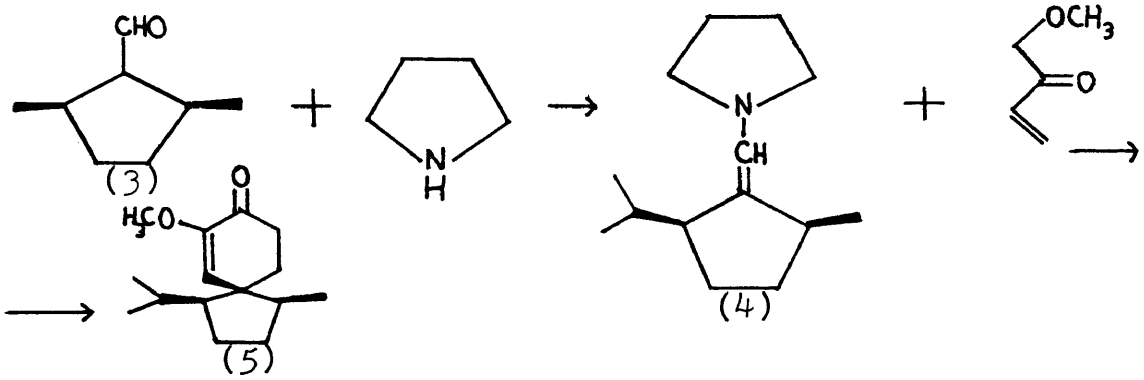
tion produced a cyclic keto ester; therefore, the spirodecene was modified by a hydrolysis-decarboxylation step in order to produce spiro[4.5]dec-6-en-1-one.[7] The following approach of Robinson differs from the previous two because the quarternary carbon and the annulation were generated in the same reaction.

The Robinson annulation reaction, generally used to prepare fused-ring molecules, was adapted to create the spiro-cyclic structure through the Michael addition-aldol condensation sequence. A typical reaction is shown below.



The product, in this instance, is spiro[4.5]dec-6-en-1,8-dione formed by the slow distillation of the adduct of 2-formyl-cyclopentane and methyl vinyl ketone from potassium hydroxide.[8] In this reaction the formyl group is considered to be a methylene group located α to the prominent carbonyl group; therefore, the key to the spirocenter formation is the formyl group.[8] The pitfalls of this approach are the difficulties in obtaining 2-formylcyclopentanone efficiently and the by products of the annulation.[9]

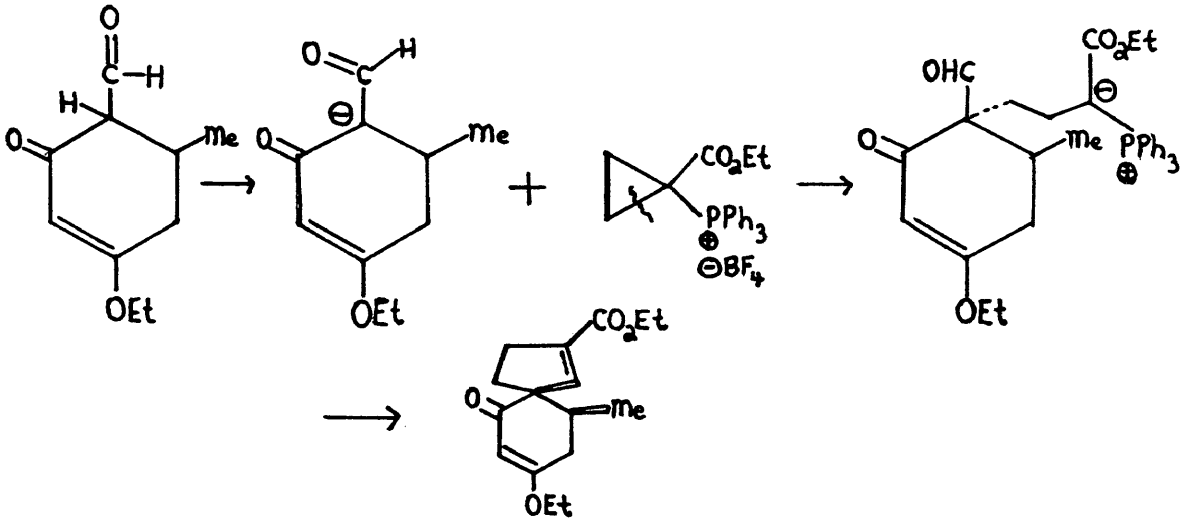
In the synthesis of (-)-acorenone, the actual spirosesquiterpene found by Sorm in the Sweet Flag Oil, a successful approach to the spiro-carbon was realized through an enamine-enone-acetic acid system. The sequence of steps are outlined how compound (3) was introduced to pyrrolidine forming the enamine (4) in a 4:1 mixture of the double bond isomer. This was followed by (4) being stirred in the ab-



sence of solvent at room temperature with excess 1-methoxy-3-buten-2one and one equivalent of acetic acid to give (5). This was the exact product that should have been produced

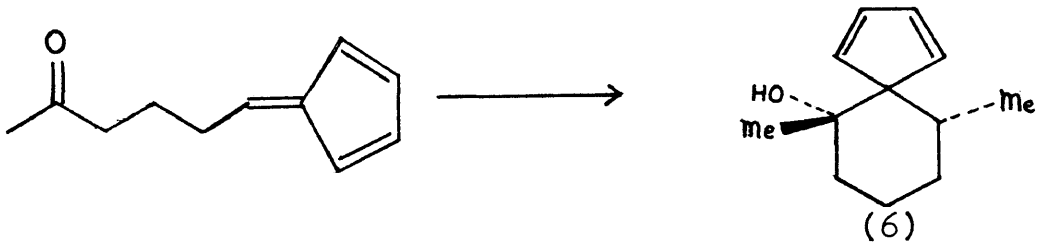
from the Michael addition of 1-methoxy-3-buten-2-one with the less hindered α-face of the enamine followed by the cycloaldolization. Acetic acid was used because it appeared to maintain the balance between not protonating the enamine but catalyzing the cycloaldolization.[10] Accordingly, this mechanism was similar to the one involved in the synthesis of spiro[4.5]dec-6-en-1,8-dione.

A very useful approach was derived to synthesize an assortment of spiroterpenes: β-vetivone, hinesol, α-vetispirene, anhydro-β-rotunol and β-vetispirene. This route relies on the formation of an ylide from carboethoxycyclopropyltriphenylphosphonium tetrafluoroborate and 1-ethoxy-4-formyl-cyclohexene-3-one followed by ring closure through a Wittig mechanism as illustrated.[4] The ring closure was seen



as the carbanion acting as the nucleophile toward the carbonyl carbon of the formyl group. The final structure had nonadjacent opposite charges which collapsed to form the double bond.[11]

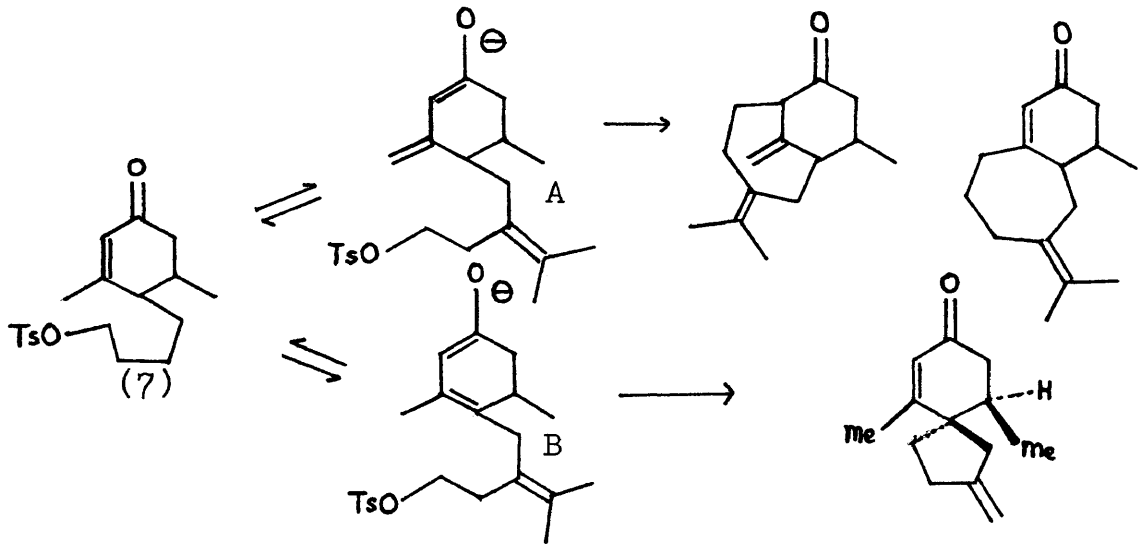
Another approach to β-vetivone had utilized a fulvene intermediate to form the quarternary carbon within 6-hydroxy-6,10-dimethyl spiro[4.5]dec-1,3-diene(6). It was considered that lithium dimethylcuprate would add to 6-(2-oxopentyl)fulvene to form the lithium cyclopentadienide which would induce C(5) to act as a nucleophile toward the carbo-



(6)

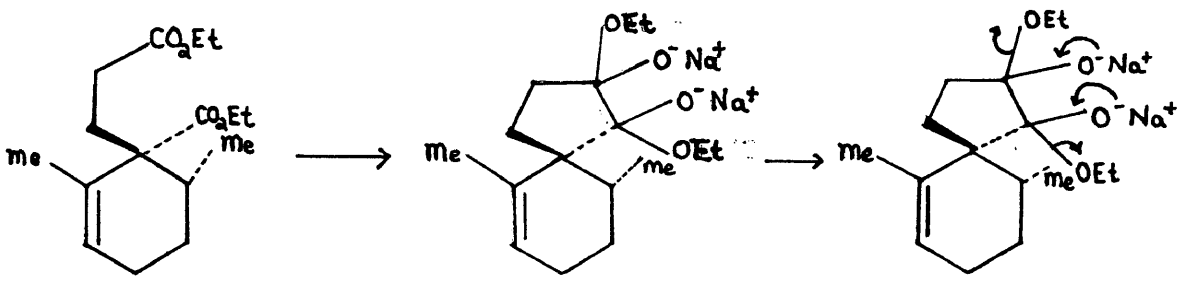
nyl carbon of the side chain forming (6). In this procedure (6) was formed in approximately 85% yield and was the only carbinol formed; however, there was another more direct method.[12]

One procedure illustrated that in the last step the spiro-center and the product β-vetivone were formed simultaneously. This step was the result of an intermolecular γ-alkylation of the α,β-unsaturated precursor induced by the base. The precursor (7), in the presence of a base, exists

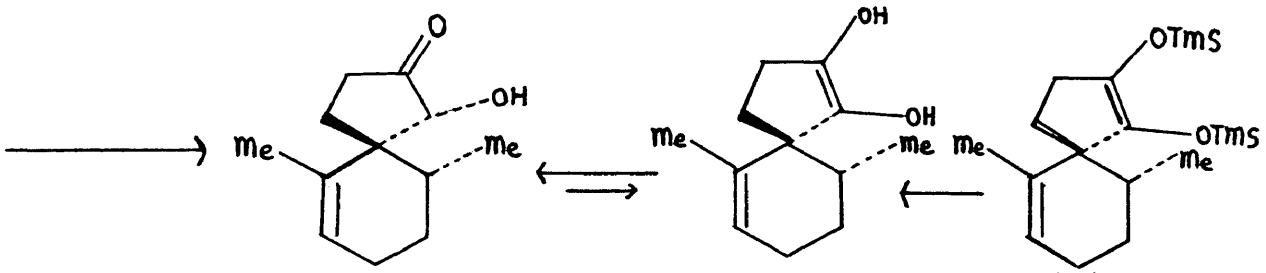


in two forms in equilibrium. It was these two forms that determined whether the reaction would go to α-alkylation or γ-alkylation as illustrated. It was found that in the proportion of H_2O from 0% to 25% increased the amount of the γ-alkylation product or β-vetivone. Dimethyl sulphoxide was chosen as the solvent because it facilitated proton transfer, and the H_2O helps increase the rate of protonation to maintain the equilibrium between A and B. Without the presence of H_2O only the α-alkylation product was formed due to the absence of a proton source to convert A to the precursor (7).[13] Another consideration was that the transition state for the γ-alkylation forming a 5-membered ring was much lower than for the α-alkylation; therefore, the γ-alkylation would predominate.[13]

A wealth of spirovetivanes containing the spiro[4.5]-decane structure has been derived through a spiroacyloin synthon, 6,10-dimethyl-1-hydroxy-spiro[4.5]dec-6-en-2-one. The list includes (±)hinesol, (±)agarospirol, (±)β-vetivone and (±)α-vetispirene. The initial formation of the quarternary carbon occured by an acyloin condensation of a diester (8). In this case the condensation was carried out at



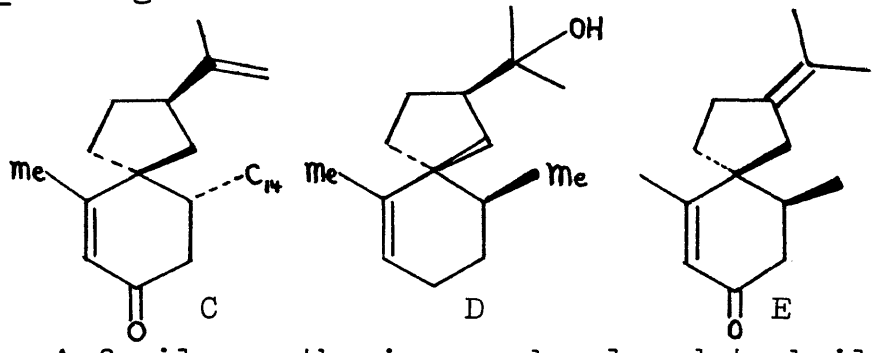
(8)



(9)

reflux in toluene using metallic sodium and trimethylchlorosilane to produce the spirocycle in almost 80% yield.[14] The mechanism appeared as above where (9) was used to make the previously mentioned products.

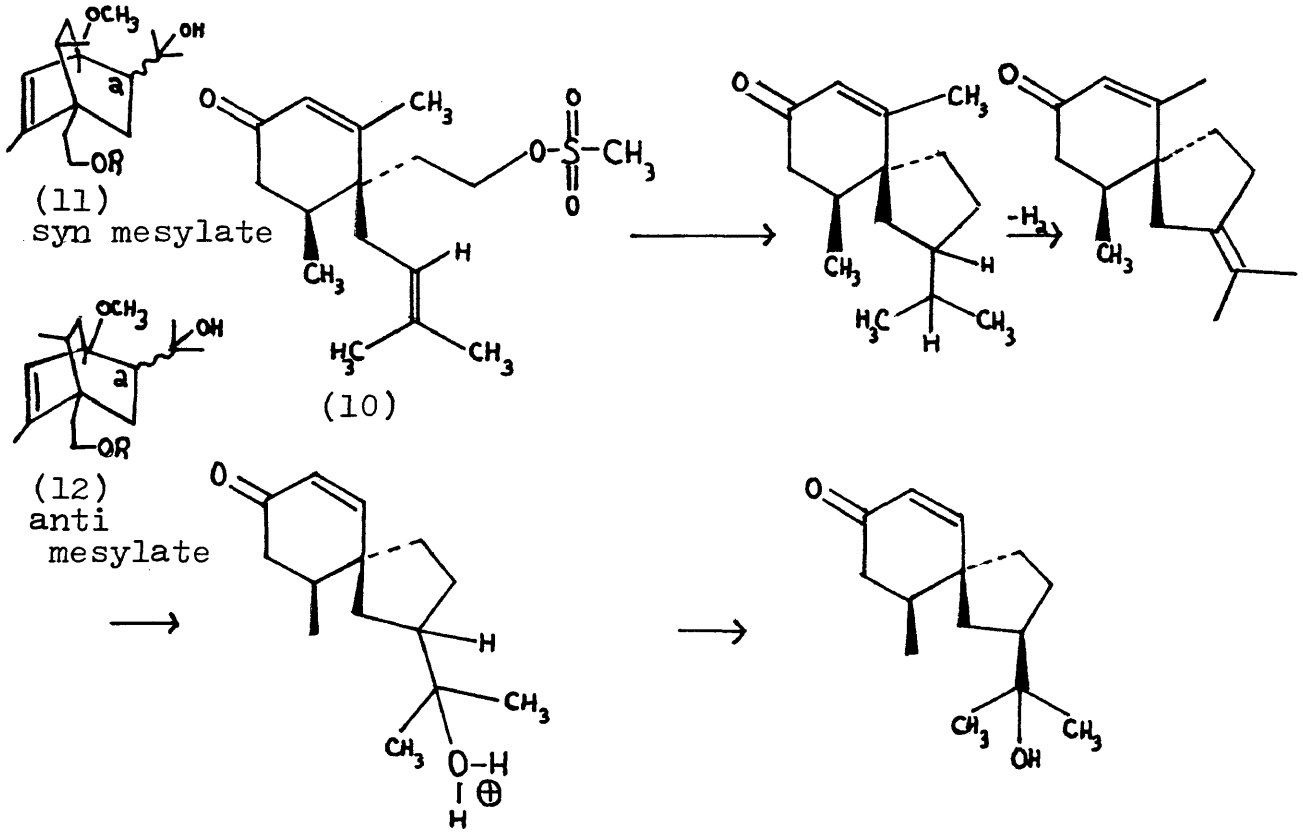
Naturally occuring spirovetivanes were found to be divided into two groups distinguished by their relative configuration about C(4)-C(14) and C(5)-C(6). Solavetivone was known to have the <u>trans</u> configuration while others such as hinesol and β-vetivone, isolated from vetiver oil, had the <u>cis</u> configuration.[15]



C solavetivone
D hinesol
E β-vetivone

A facile synthesis was developed to build the spirovetivanes of the opposing configurations. The major step, the formation of the spiro-center, was achieved through a cationic π-cyclization. The starting material was a prenyl-cyclohexenone. Compound (10) originated from (11), and the prenyl-cyclohexenone with the <u>cis</u>-configuration

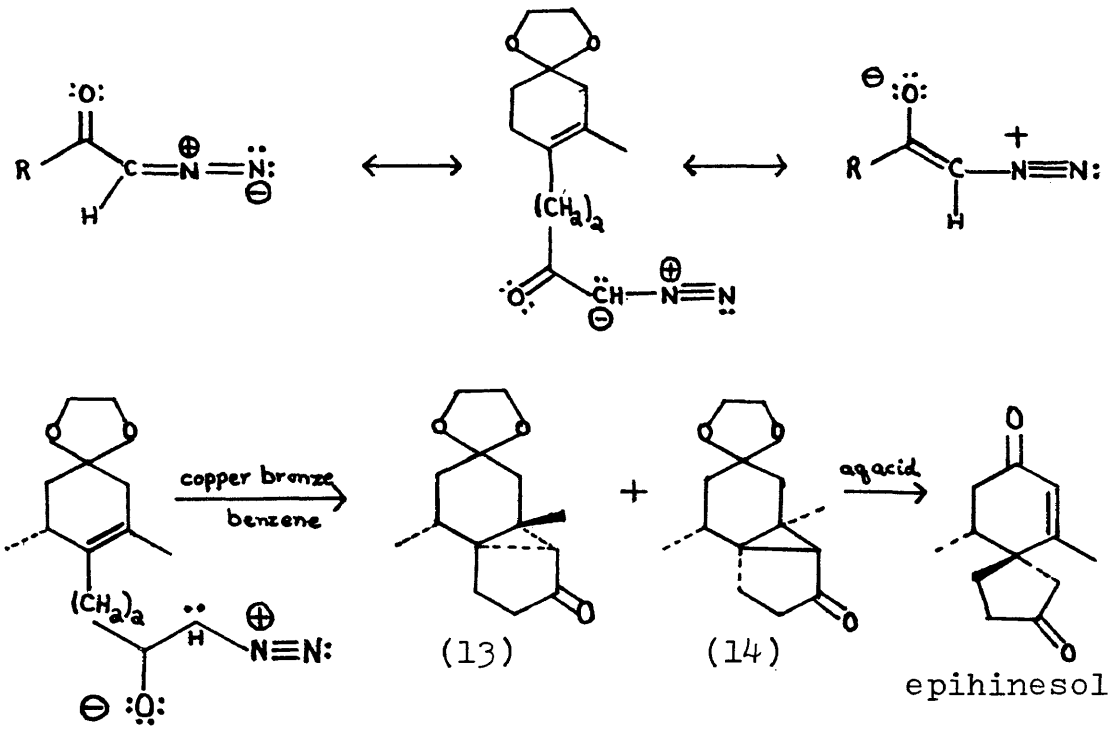
originated from (12). The prenyl-cyclohexenones were formed



by the cleaving action of formic acid on the C(1)-C(2) bond on compounds (11) and (12). It was determined that the cationic π-cyclization must have taken place by an attack of the prenyl double-bond towards the carbocation formed by the removal of the mesyloxyl group ($R = \bar{O}_3SCH_3$).[15] This reaction was a rare example of a stereoselective ring closure forming a spirovetivane explained by the steric repulsion of the ring methyl and the prenyl methyl groups during the approach of the prenyl group and the cation.[15]

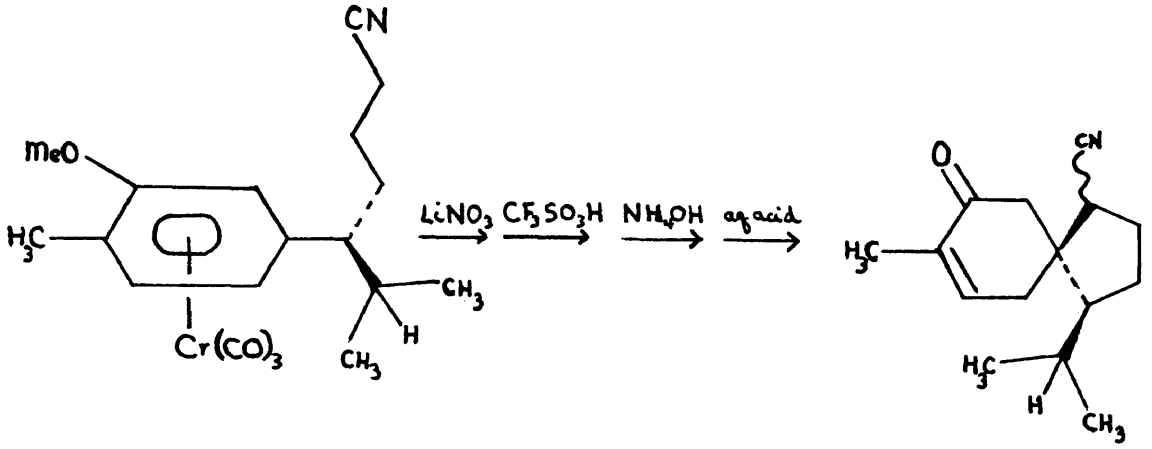
Carbenoids were known to add to double bonds in a 2+1 cycloaddition to form a cyclopropyl structure. This ten-

dency was utilized to produce a ring closure in the synthesis of racemic epihinesol. The carbenoid was a diazoketone



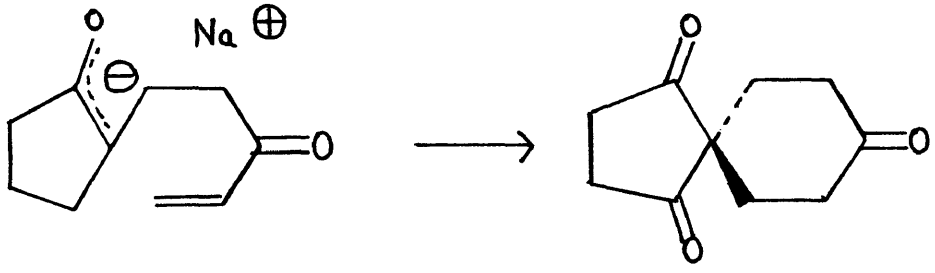
in the presence of copper bronze where a carbene was actually a resonance form of the diazoketone. This ring closure proved to be stereoselective because the carbene could not easily approach the double-bond at the face sterically blocked by the methyl group of this chosen diazoketone.[16] An aqueous acid treatment of (13) and (14) produced a spiro ketone through the bond cleaving that had the greatest overlap with the π-orbital system of the carbonyl group.[17]

Formation of the quarternary carbon in the synthesis of acorenone and acorenone B was performed through an arene-metal complex consisting of a chromium tricarbonyl group and an anisole derivative. The spiro-center formation



relied on the activation and meta-directing effects of the chromium tricarbonyl group on the aromatic ring of the anisole derivative. Furthermore, the formation followed stereospecific control of the spiro-center maintaining a specific exo addition to the coordinated arenes.[18]

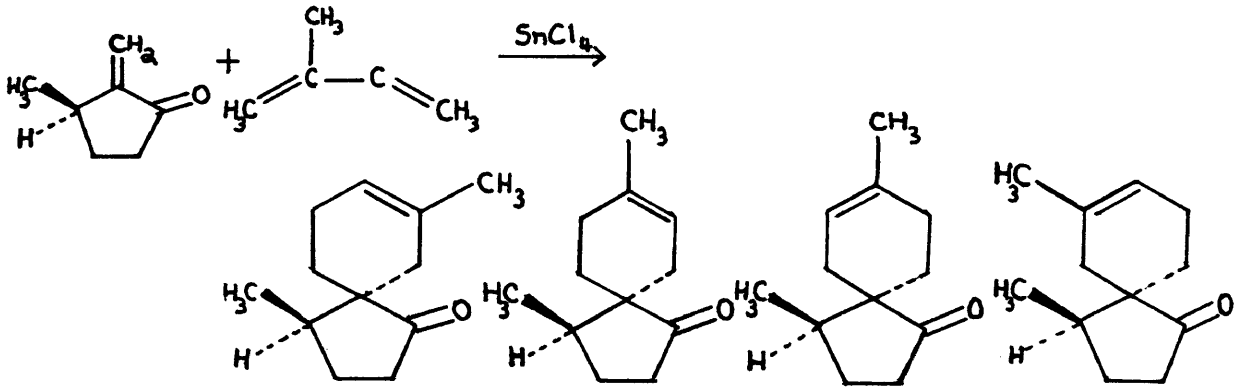
Prostaglaglandin synthesis is a major area of synthetic chemistry. One approach to a PGF_{2a} containing a spiro[4.5]decane skeleton was through the sodium salt of 1,3-cyclopentanedione and 1,4-pentadien-3-one. The intermediate ion formed from the reaction of these reagents at -40°C was subjected to a cyclization <u>in situ</u> through the



introduction of acetic acid at -20°C. The final product was a spiro[4.5]decanetrione.[19] This reaction appeared to proceed by a double Michael addition where the acetic acid

allowed the cyclization to proceed through a second Michael addition. In this case base catalyst was not deemed necessary.

A Diels-Alder cycloaddition has been utilized to provide a final example of the formation of the quarternary carbon. The Diels-Alder mechanism is a $[4\pi+2\pi]$ thermal cycloaddition and can be stereospecific. This stereocontrol has been exibited in the reaction of α-methylenecyclopentanones with an isoprene unit in the presence of a Lewis acid, such as Tin(IV) chloride. The Lewis acid was known

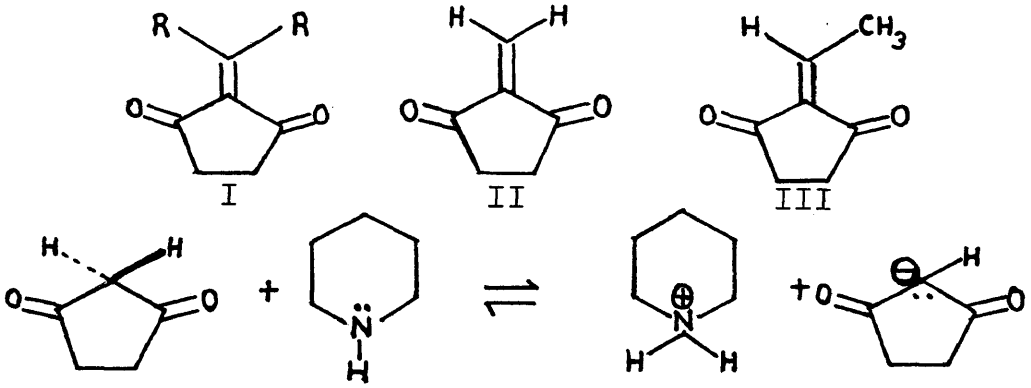


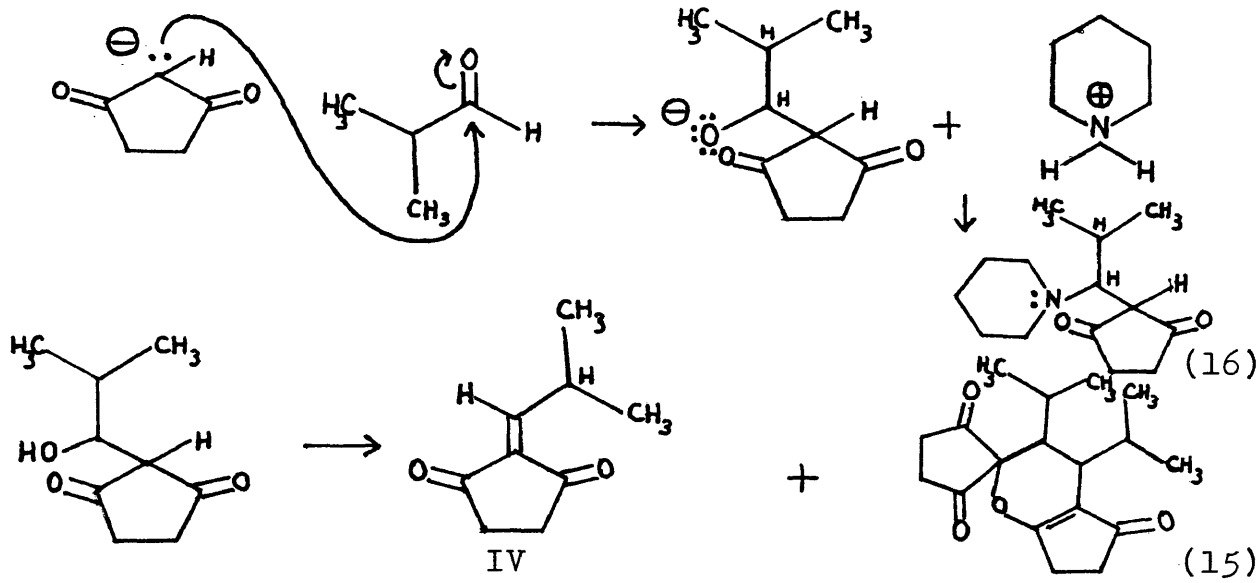
to form a complex with the polar substituent of the dieneophile and accelerate the ring formation. The α-methylenecyclopentanone was very unstable and, therefore, generated *in situ* from a selection of either Mannich bases, α-chloromethylcycloalkanones, α-acetoxymethylcycloalkanones or α-hydroxymethylcycloalkanones.[3]

From the variety of routes previously described it was apparent that each pathway only introduced certain function-

alities to the spirodecane skeleton. Accordingly, it was necessary to develope a more diversified synthon for the production of spirosesquiterpenes. The previous example utilizing the α-methylenecyclopentanones with the isoprene "eneophile" appeared to be the approach. Not only was there the potential for stereocontrol at the spiro carbon, but there was the opportunity to functionalize the 1,3-butadiene and the α-methylenecyclopentanone to create specific site-reactivity in the final spirodecane. Work toward the most advantageous cyclopentane structure to date, generally known as 2-alkylidene-1,3-cyclopentanedione, has been performed.

There has been little recorded information on 2-alkylidene-1,3-cyclopentanediones(I). Even information on its simplest analogs 2-methylene(II) and 2-ethylidene (III) is sparse. During work to synthesize analogues of certain G-regulators from 1,3-diketones and aldehydes a pathway to 2-isobutylidene-1,3-cyclopentanedione(IV) was derived.[20] The route was the Knoevenagel condensation and adopted an acid catalyst, avoiding the bis-adduct(15) of (IV).

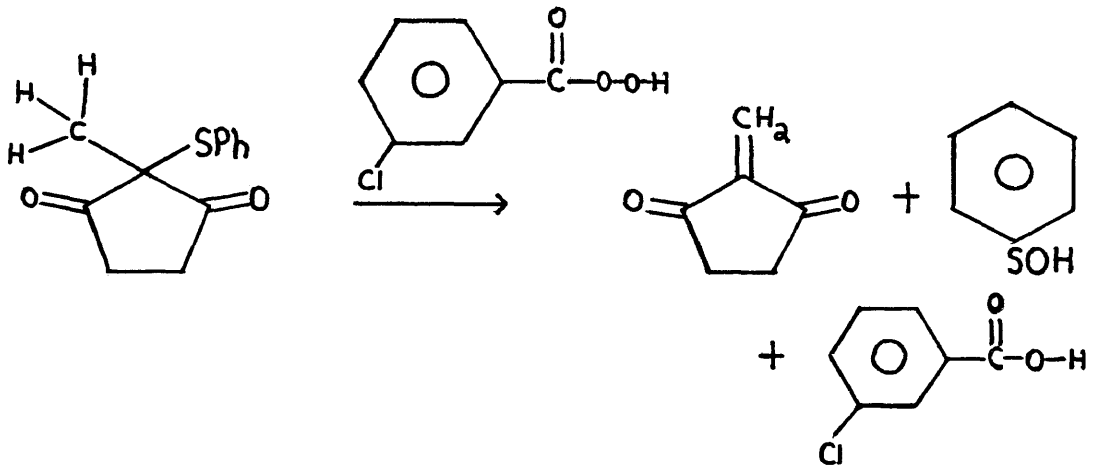




IV (16) (15)

Compound (IV) was characteristically subject to Michael attack. Compound (IV) in the presence of piperidine became the Mannich base (16). Compound (16) in an acidic media exhibited the elimination of the piperidine because the hydrogen bonding between the nitrogen of the piperidine and the oxygen of the enol was alleviated allowing the C-N bond to rotate and the piperidine group to become periplanar with the p-orbital of C-2.[20] This allowed the elimination to form (IV). To date the Knoevenagel condensation is only successful for (IV). Another approach utilized a phenylthio leaving group and carried greater potential for exploitation.

During work to build a dodecahedrane structure a general approach to (I) was derived. The oxidation of a 2-phenylthio-2-alkyl-1,3-cyclopentanedione by the action of m-chloroperoxybenzoic acid brought about (I). The 2-phenylthio was easily derived from the corresponding 2-alkyl-1,3-

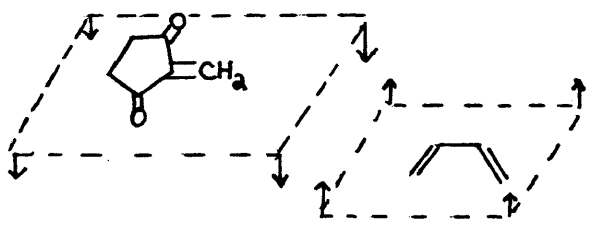


cyclopentanedione by N-phenylthio succinimide, in a specific case the 2-methylderivative was used. Compound (II) was previously determined to be the most reactive of the series of (I) and was trapped in the presence of isoprene for identification.[21] Such proof of its existence gave hope that other members of the series could be constructed. The entrapment of (I) by isoprene introduced the desired route to spiro[4.5]decane, the Diels-Alder reaction of (I) with an appropriate eneophile. Futhermore, this route had more potential than the Knoevenagel condensation since other 2-alkyl-1,3-cyclopentanediones were already known and apparently no obstacles existed toward developing a series of dieneophiles.

The Diels-Alder reaction was an ideal approach to building the spiro structure because it exhibited stereospecificity through a <u>syn</u> addition of an olefin to a conjugated double-bond to form a six-membered ring, possibly a concerted reaction. This cycloaddition was known as a

[4+2] reaction because it involved 4 π-electrons of the conjugated diene and 2 π-electrons of the olefin. To date, no other synthetic approach to spiro[4.5]decane sesquiterpenes offers stereocontrol about the tetrasubstituted carbon. It was assumed that the cycloaddition was suprafacial for both components.[22] This approach also allowed the six-membered cyclohexene ring to be functionalized in a variety of forms.

It was understood that the Diels-Alder reaction took place through interaction of appropriate frontier orbitals. Furthermore, for most known combinations of reactants the working orbitals were the highest occupied molecular orbitals were the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital of the olefin (LUMO). Since all reactions of this type occur by the transfer of electrons from the diene to the olefin, or more generally, from the HOMO to the LUMO, the reactants were subject to the electron releasing or withdrawing effect of the functional groups present. In fact, electron withdrawing groups on the olefin and electron releasing groups on the diene increase both reactivities.[22] Accordingly, there was great opportunity for functionalization of reagents and, therefore, the final product. Concerning (I)



the exocyclic double bond was between two corbonyl groups, exhibiting formidable electron withdrawing capabilities. Thus, this double bond was considered an excellent dienophile.

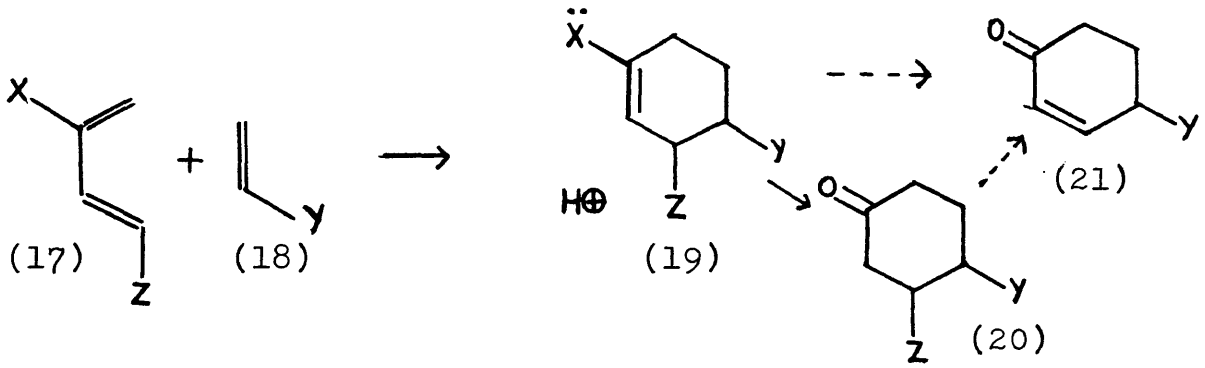
Extensive research has been performed on the reactivity of dienes toward [4+2] cycloadditions. This work revealed that bulky, electron withdrawing, groups in the 2-position of the acyclic dienes, such as butadiene, can accelerate the Diels-Alder reaction because they force the conjugated diene into a quasi cis- conformation necessary for the reaction. Furthermore, a methoxy substituent on the diene, even though it is an electron releasing group, does not induce the increased rate compared to the similar alkyl substituted diene because of the "impared coplanarity."[23] To illustrate, an order of reactivity for substituted butadienes follows:[23]

1-methoxy- > 2-phenyl- > 2,3-dimethyl- > trans-1-methyl- > >2-methyl- > butadiene > trans-1-phenyl- > 2-chloro- > >trans,trans-1,4-diphenyl-

Work independent to this ordering of dienes uncovered an ideal diene that sufficiently functionalized the cyclohexene ring product of the Diels-Alder reaction. This work is discussed below.

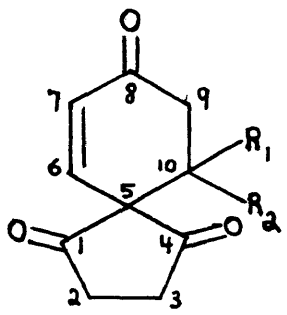
Work by Danishefsky characterized the diene necessary to work with an olefin as reactive as 2-alkylidene-1,3-

cyclopentanedione. The objective was to increase reactivity while forcing the diene into the S-cis conformation, necessary for the Diels-Alder reaction. Accordingly, while Y was an electron withdrawing group, X should allow the conversion of the XC=C enol derivative in (19) to the ketone in (20). Furthermore Z should facilitate a β-elimination in (20)



forming the α,β-unsaturated ketone (21). However, Z has the potential to be retained for later formation of (21), and can thus protect the enone, or maintain its own functionality. An answer to these demands is trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene.[24] (Since this work, reported in 1975 by Danishefsky, the area of silyloxy-substituted 1,3-dienes for the Diels-Alder reaction has blossomed into numerous examples.[25])

Unknown at this time the Diels-Alder reaction of 2-methylene-1,3-cyclopentanedione(II) and trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene should yield primarily spiro[4.5]deca-10,10-dialkyl-1,4,8-trione(V), producing synthetic flexibility at every carbon except C-5. The neces-



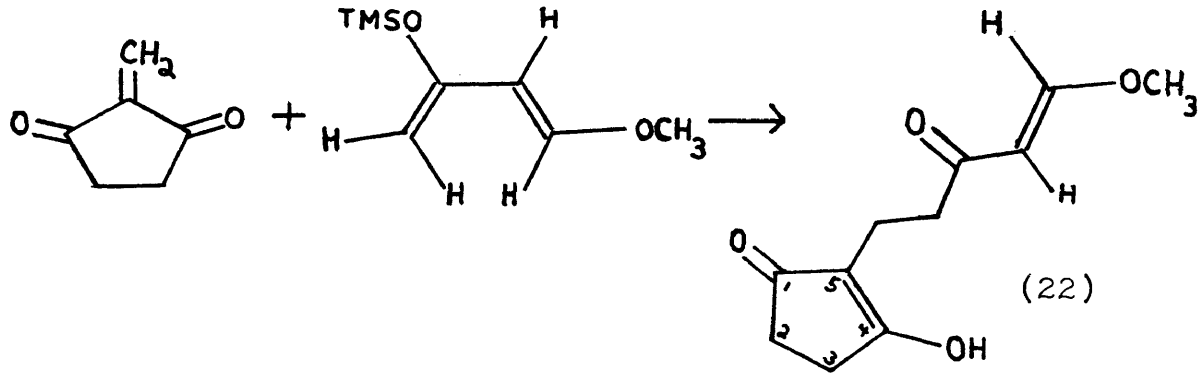
sary diene has been isolated and identified. On the other hand, the exocyclic olefin has never been isolated but only ensnared by aggressive dienes such as isoprene. The best approach, to date, to (I) is in an acidic medium and the diene would be highly sensitive to such an environment. Thus, the problem presents itself.

The most advantageous route towards the spiro[4.5]decane structure appears to be through the production of (I), via a 2-phenylthio-2-alkyl- precursor, and annulation with a specific silyloxybutadiene. The cycloaddition would follow by a Diels-Alder mechanism. Therefore, the need exists for stable 2-alkylidene-1,3-cyclopentanediones to be synthesized and isolated from acidic media in order to react with the desired silyloxybutadiene. As will become apparent, the synthesis of a hindered aliphatic ketone is also necessary and must be accomplished first in order to synthesize the stable exocyclic olefin.

DISCUSSION

The reaction of importance to this project was the Diels-Alder cycloaddition of a 2-alkylidene-1,3-cyclopentanedione(I) and an appropriate conjugated diene to form basically a spiro[4.5]dec-7-ene-1,4-dione. The dienophile would be generated from the 2-alkyl-2phenylthio- precursor and the diene would be the previously described Danishefsky's diene, trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene(MTB).

All attempts at the cycloaddition reaction were unsuccessful. Compound (II) was generated in situ by meta-chloroperoxybenzoic acid(MCPBA) in the presence of MTB, and the reaction was arrested apparently by the destruction of MTB due to its sensitivity to meta-chlorobenzoic acid(MCBA). The presence of MCBA was only avoidable by forming (II) in another vessel where the MCBA would precipitate out and (II) could be "blown-over" into a vessel containing MTB. This adjustment led to the Michael addition product(22) of the diene and olefin as interpreted by NMR analysis(NMR 1 Appen-



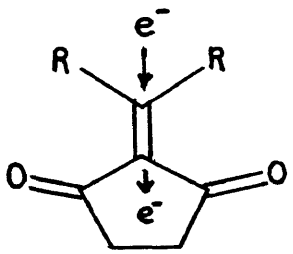
(22)

dix). This being the case, the action of a base, such as pyridine, on (22) should induce a ring closure by creating an electrophile at C-5. As predicted this occured and thus determined the exocyclic olefin did exist(NMR-2 Appendix).

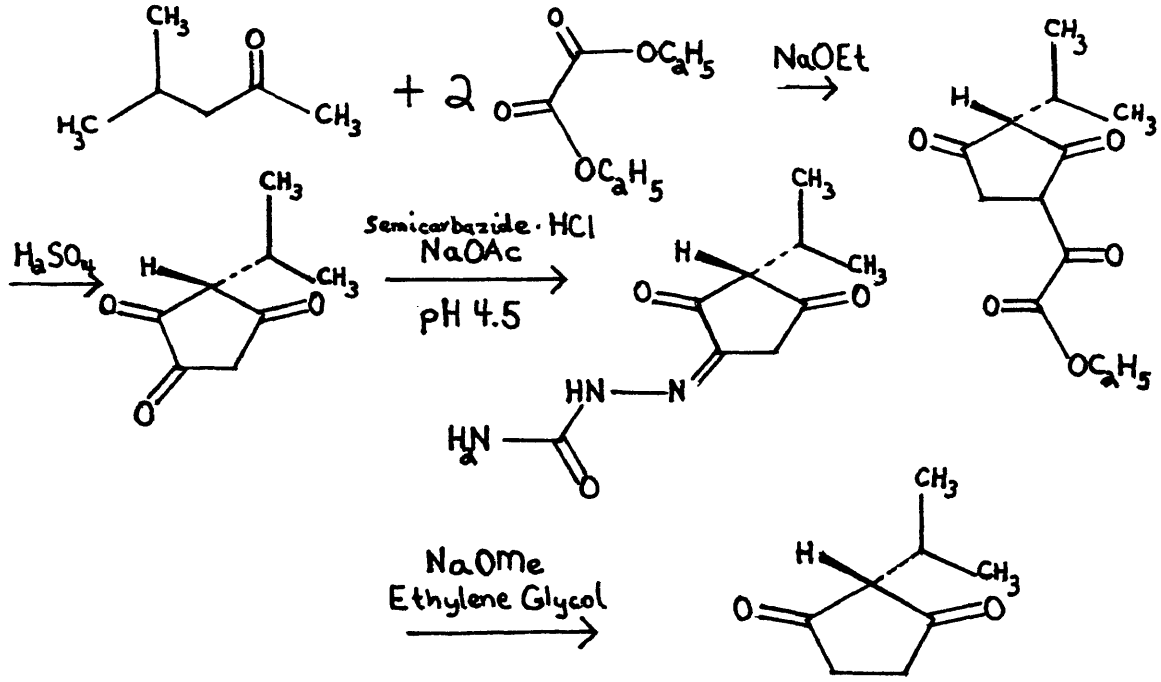
Overlooking the apparent non-concerted ring closure, this initial work outlined the need for a stable (I) that could be made in one reaction vessel from the phenylthio precursor retaining the MCBA in the flask and allowing (I) to be delivered to a vessel containing the MTB alone. Such manipulation of the cyclopentanedione would alleviate the need for another diene that would not be sensitive to MCBA. Another point was that a similarly aggressive diene may be needed that would not be as sensitive to the MCBA such as tert-butyldimethylsilyloxybutadiene. In this project no successful attempt was made to improve the diene;[26] therefore, all work was directed toward forming a stable (I).

The key to a stable (I) was to protect the double bond

by bulky alkyl groups as in the example (IV). The alkyl groups not only block the approach to the double bond they also act as electron releasing groups and slightly hinder the Diels-Alder reaction by slowing the flow of electrons from the diene to the olefin. This effect is of little concern when considering the aggressiveness of MTB.

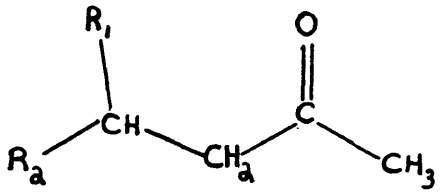


The method used to make the 2-alkyl-1,3-cyclopentanedione was similar to the procedure reported by Hiraga.[27]

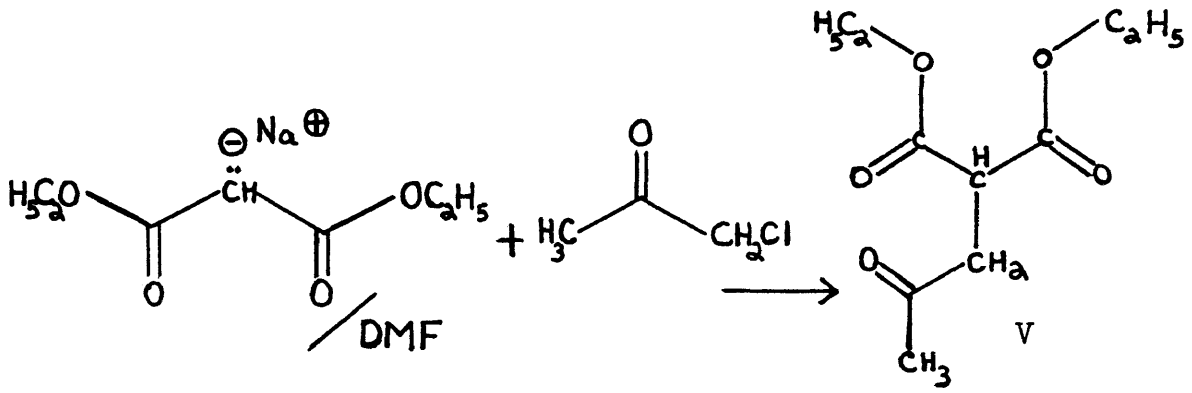


The ketone in step 1 is the only parameter that needs to be changed to synthesize an array of substituted 2-alkyl CPD's. Initially 2-ethyl- and 2-isopropyl- were made in low yields

(10%) following this method, from 2-pentanone and methyl isobutyl ketone, respectively. These results were unexplainable; however, yields were finally improved to 36.5% and 8.9%, respectively. (The only change was that n-decanol was replaced with ethylene glycol.[28]) Reagents 2-pentanone and methyl isobutyl ketone were readily available. The obstacle was the mere fact that highly substituted methyl alkyl ketones were scarce. Therefore, to make a shelf-stable (I) the first priority was to make the corresponding ketone. Accordingly, the course of this project took a new and final turn. To clarify, the purpose of this project finally became to synthesize a highly substituted ketone that when subjected to diethyloxalate under the conditions outlined previously would produce 4-alkyl-2,3,5-trioxocyclopentyl glyoxylate(See Figure 2). The ketones of interest maintained the skeleton shown below.

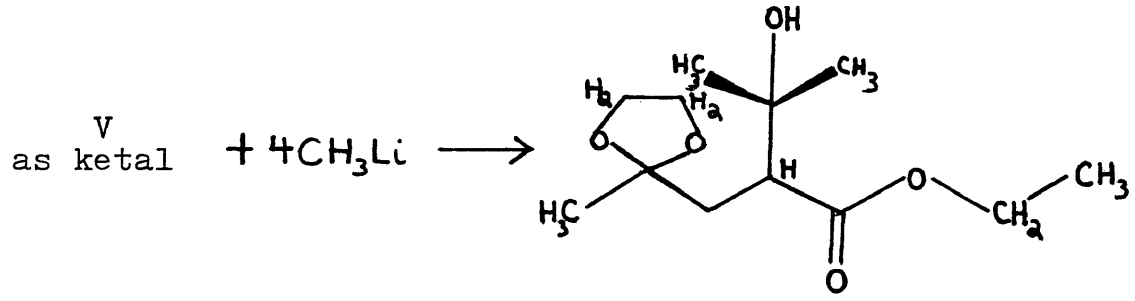


The first work in synthesizing a highly substituted ketone was based on work reported by Mercier and Deslongchamps.[29] The target product was 2,2-dimethyl-1-t-butylpropylidene-1,3-CPD. In this approach sodiomalonate in dimethylformamide was condensed with α-chloro-acetone giving a ketone ester which could be easily converted to the ketal.



V

All of these steps proved easy to perform. At this point both carbonyl carbons were to be methylated through methyllithium. The drawback was that this treatment would only yield a half ester observed by NMR(NMR-3 Appendix). A six fold increase of methyllithium produced the same results.



Therefore, a problem arose during the methylation possibly based on the changing reaction site.

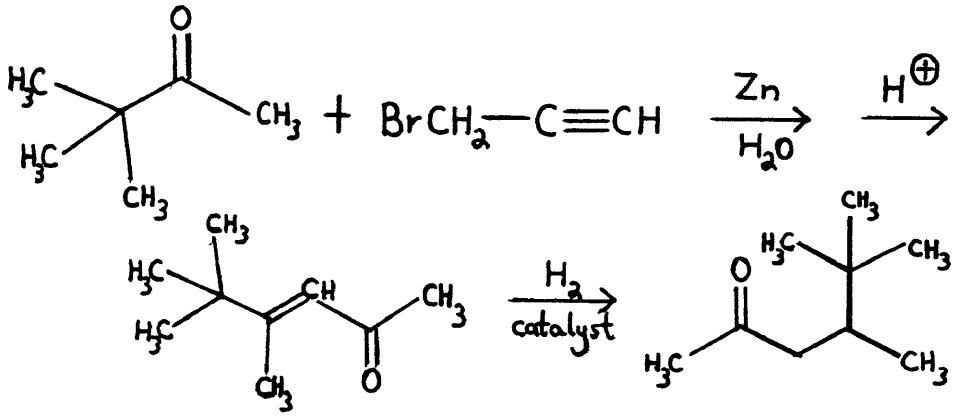
The pathway appeared blocked to the di-t-butyl substituted (I); however, there were some routes via organometallic reactions that could lead to a t-butyl and methyl substituted (I). The object was to use lithium metal and 1-bromopropene, forming the organometallic complex propenyllithium which would add across the carbonyl bond of 3,3-dimethyl-2-buta-

none(pinacolone) alkylating the carbon. All such trials left the pinacolone unreacted. Further trials were performed with magnesium metal forming propenyl magnesium bromide with similar results. In the event the reaction did work, it was planned to proceed with a quenching with benzene sulfenyl chloride, sulfenylation and hydrolysis to bring about a 1,3-carbonyl transposition.[30] However, the opportunity did not occur.

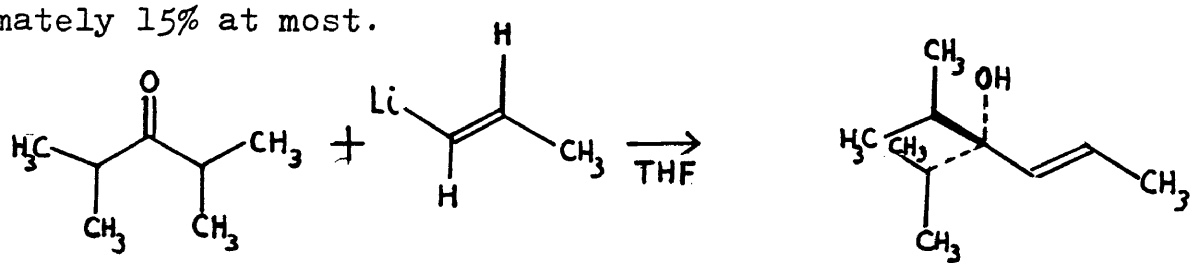
Another Grignard synthesis of a ketone did allow access to the t-butyl substituted 2-methyl-1,3-CPD. Simply generating t-butylmagnesium chloride and allowing it to react with methyl vinyl ketone producing methyl-(3,3-dimethyl-)-butyl ketone after aqueous quenching. This was isolated and identified by NMR(NMR-4 Appendix). To add credence to this project this ketone was subjected to the reaction forming the CPD. Successfully, 2-neopentyl-1,3-CPD was made followed by the phenylthio moiety (See NMR-5,6 Appendix).

Knowing that 2-neopentyl-1,3-CPD could be made an alternative route was attempted to make the precursor 5,5,4-trimethyl-2-hexanone. This route consisted of the Reformatsky condensation of propargyl bromide with 3,3-dimethyl-2-butanone(pinacolone) followed by an acid catalyzed rearrangement to 5,5,4-trimethyl-3-hexen-2-one.[31] This would be followed by a hydrogenation. The rearrangement was related to the Rupe rearrangement. All attempts at this reaction left the

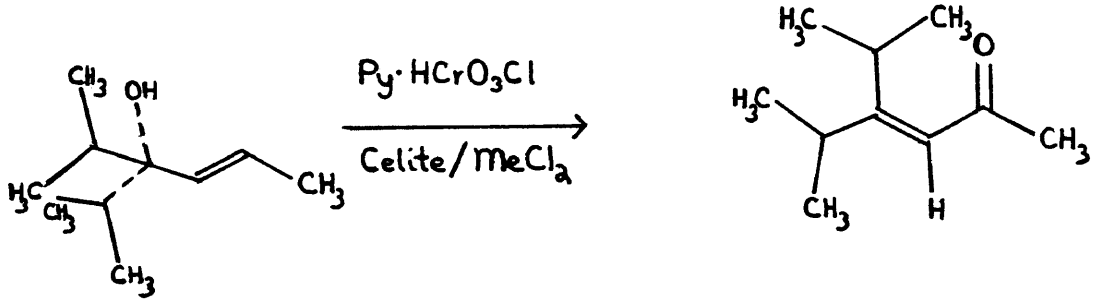
pinacolone unreacted and was eventually aborted.



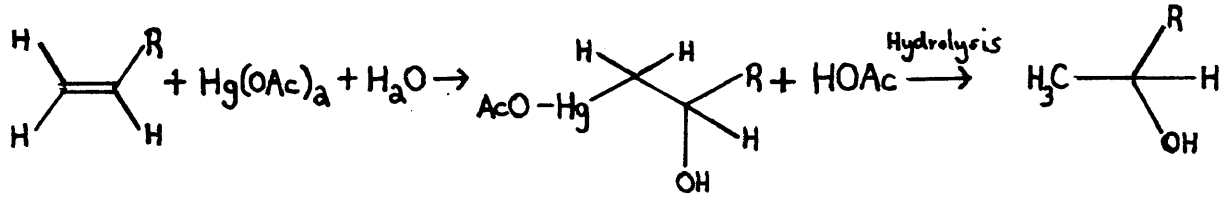
Using di-isopropyl ketone in the presence of propenyl lithium in THF brought about 4-hydroxy-5-methyl-4-isopropyl-2-hexene in the approach. As described before the lithium compound added across the carbonyl. The difference in this approach to the previous unsuccessful approaches was that all reagents were placed in the reaction vessel simultaneously followed by the reaction being followed by GC to watch the starting ketone diminish. Once there was no apparent change in the amount of di-isopropyl ketone the reaction was quenched with MeOH and the product was isolated by vacuum distillation and observed by NMR(NMR-7 Appendix). The product appeared to have been made. The same procedure was used to make 4-t-butyl-5,5-dimethyl-4-hydroxy-2-hexene. The drawback here was that the yields were abominably low, approximately 15% at most.



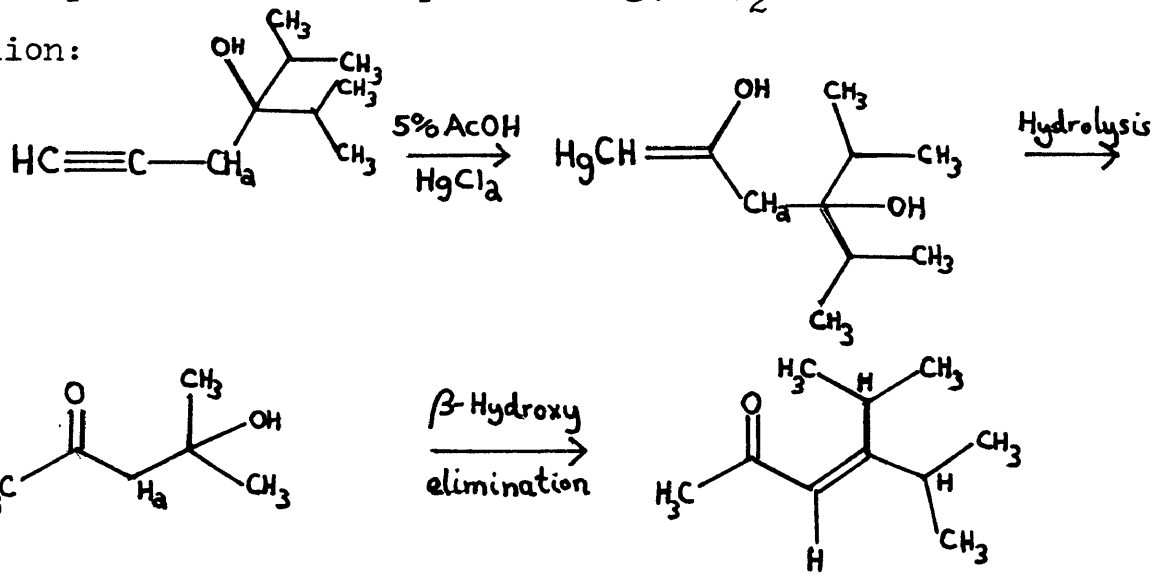
Despite the low yields using vinyllithium attempts were made to induce a 1,3-carbonyl transposition by oxidation of the tertiary alcohol by pyridinium chlorochromate[32,33] and by Jones reagent. The reactions were followed by GC and studied by NMR. No positive results were found and due to the low yields of the enol this approach was dropped.



In the presence of a double bond $Hg(OAc)_2$ was known to add in this fashion:

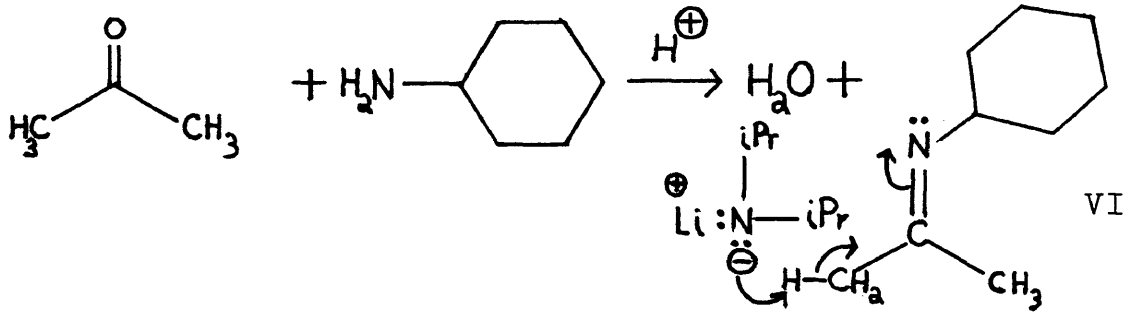


In the presence of a triple bond $Hg(OAc)_2$ should add in this fashion:

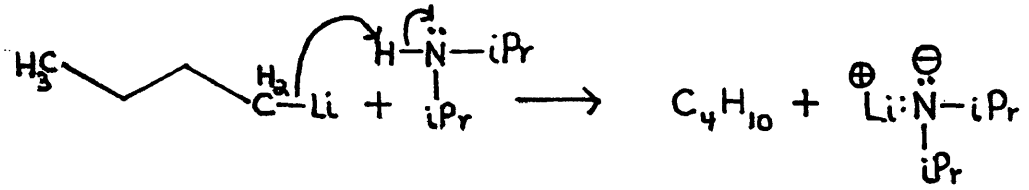


The starting product 4-hydroxy-5-methyl-4-isopropyl-hexyne was easily made through the Grignard's reaction of propargyl magnesium bromide with di-isopropyl ketone. The oxidative-mercuration never occured. Some oxidation did occur but the by-products were unidentifiable.

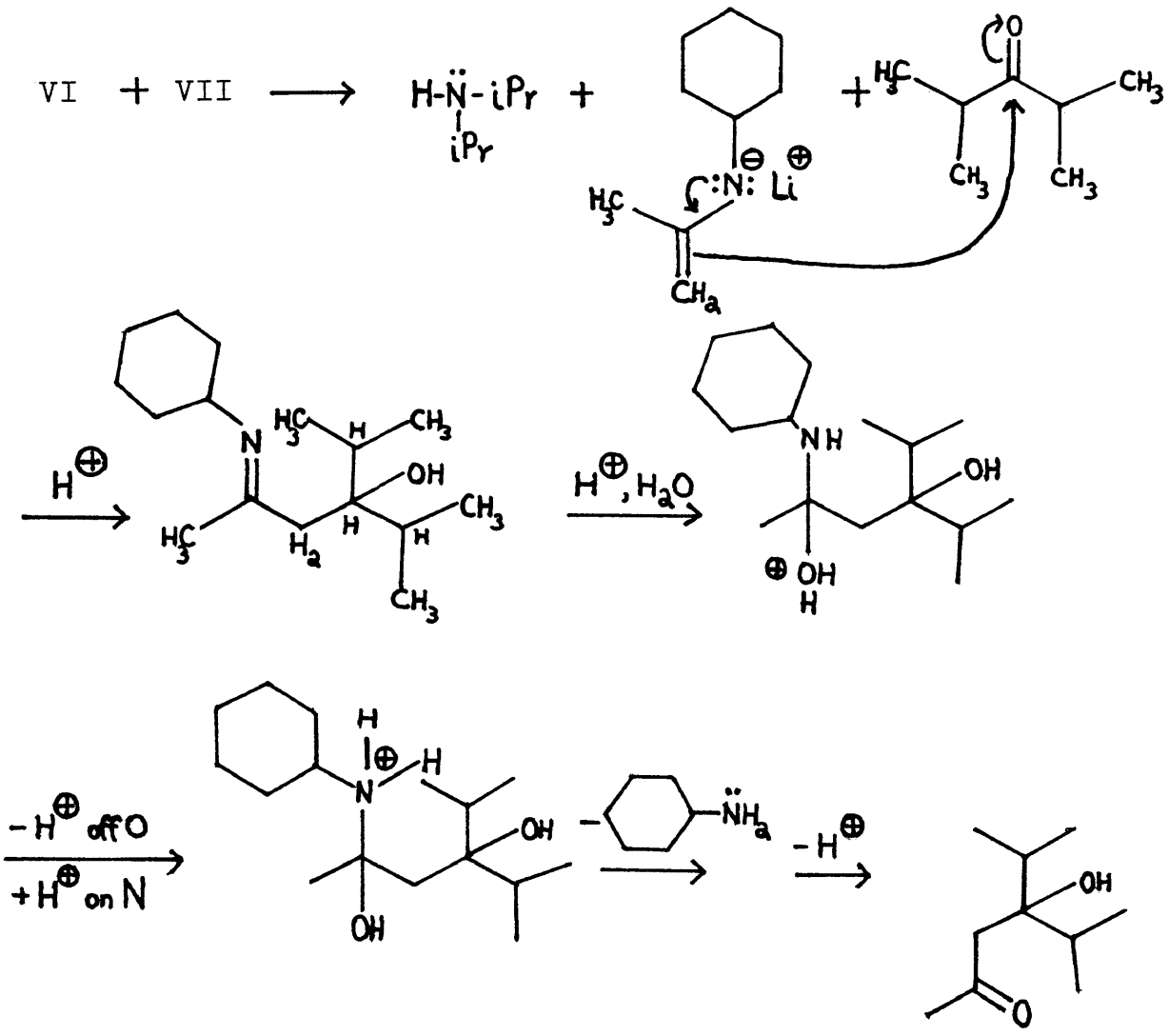
A final attempt to make 5-methyl-4-isopropyl-3-hexene-2-one was through a directed aldol condensation between acetone enolate and diisopropyl ketone. A cyclohexylimine was prepared from acetone and cyclohexylamine. This was introduced to lithium and diisopropyl amine. Lithium diisopropylamide, being a strong base, allowed the formation of an enamide which was then treated with diisopropyl ketone giving β-hydroxyimine. This compound was subjected to heat and aqueous oxalic acid giving the desired enone. This enone was then hydrogenated over Pd/C to yield 5-methyl-4-isopropyl-2-hexanone. This was collected at 23% yield from the initial diisopropyl ketone. Accordingly, this reaction opened the door for other hindered ketones.



VI



VII


VI + VII
H-N-iPr
iPr
Li
CH3
OH
NH
H2O
-H⊕ off O
+H⊕ on N
NH2
-H⊕

EXPERIMENTAL

Spiro[4.5]dec-6-ene-1,4,8-trione(V). Into a minimal amount of $MeCl_2$ was dissolved 1 mmole meta-chloro peroxy benzoic acid. In another vessel 1 mmole of 2-methyl-2-phenylthio-1,3-cyclopentanedione was dissolved in a minimal amount of $MeCl_2$. This solution of 2-methyl-2-phenylthio-1,3-CPD was transferred to another dry flask set-up under N_2. The solution of meta-chloro peroxy benzoic acid was added to the flask of 2-methyl-2-phenylthio-1,3-CPD dropwise by syringe while stirring. After addition of the acid the mixture was ready for transfer.

The mixture was "blown-over" with N_2 through a dry needle into a dry flask containing 5 mmoles of Danishefsky's diene in toluene under N_2. Care was taken to leave the white solid(MCBA) behind. Following the addition the mixture was refluxed for approximately 30 minutes under a water chilled condenser. After allowing the vessel to cool to room temperature the solvent was removed under vacuum while maintaining ambient temperature. The product was ready to be isolated

Into the residue was introduced 2 ml of dry THF and

3 drops of 1 M HCl which changed the solution from yellow to rust color. Next the mixture was diluted with $MeCl_2$ where a black precipitate appeared. Base, $NaHCO_3$, was added to neutralize the remaining acid. The organic layer was decanted and stripped under vacuum where phenyl disulfide precipitated. The minimal amount of liquid was transfered to a vessel where 3 ml of toluene and 3 drops of pyridine were added and then the mixture was refluxed for 3.5 hours. After the reflux the liquid was stripped under vacuum at 40°C and identified by NMR.

2-Isopropyl-1,3-cyclopentanedione. To a vessel affixed with a mechanical stirring bar and N_2 inlet and outlet, all of which had been dried and kept under N_2, was added 250 ml of anhydrous EtOH. This was followed by the slow addition of Na metal to the EtOH under a water cooled condenser. After the addition to facilitate the formation of NaOEt the vessel was lightly refluxed. The vessel was allowed to cool to room temperature and then chilled to 0°C while 1 mole of diethyl oxalate and 0.5 mole of methyl iso-butyl ketone was added dropwise. At this time the solution appeared yellow. Next the mixture was refluxed for 1.5 hours after which all solids were gone and the liquid appeared dark brown. The vessel was cooled over ice.

Into the cool solution was added 324 ml H_2O and 64.9 ml of 96% H_2SO_4, swiftly. A light colored precipitate formed

which dissolved after the mixture was refluxed for 1.5 hours. Addition of 125 ml 50% NaOH w/w induced the formation of more precipitate which was filtered off and washed carefully with MeOH.

The filtrate was brought to a pH 4.5 with the addition of 210 ml glacial acetic acid. This was followed by the dropwise addition over 40 minutes of 112 g semicarbazide HCl and 98.44 g NaOAc in 430 ml H_2O forming a precipitate. The solid was filtered off and washed with MeOH and H_2O. Usually 3 crops of solid were taken for a yield of approximately 23 g semicarbazone.

To the dried semicarbazone was added 234 ml ethylene glycol containing 23.4 g NaOH. This was refluxed for 5.5 hours. Next the solvent was stripped off over a heating mantle followed by cooling over an ice bath. Approximately 150 ml HCl was added to the cooled mixture. The solids were filtered off and dissolved in the minimal amount of H_2O for recrystallization. The crystals collected were determined to be the product by NMR.

2-Isopropyl-2-phenylthio-1,3-cycolpentanedione. Into an appropriate vessel were added 4 mmoles of 2-isopropyl-1,3-cyclopentanedione and 4 mmoles N-phenylthio-succinimide. This was followed by the addition of 20 ml benzene. Next was added 9 mmoles of triethylamine dropwise by syringe over

6 minutes. The solution turned clear from cloudy. This mixture was refluxed for 2 hours and then placed under refrigeration for 12 hours. The solvent was stripped off under vacuum and the residue was triturated with 20 ml hot hexanes four times collecting each hexanes wash. The hexanes were then stripped off and the product collected at 99% yield.

Methyl 3,3-dimethyl ketone. To a 1 liter 3 neck flask under N_2 was added 1.25 moles of Mg turnings followed by 550 ml anhydrous ether. Next 1.35 moles of t-butyl chloride were added slowly and allowed to stir for 4.5 hours. The t-butyl magnesium chloride formed was "blown-over" into a reaction vessel followed by the addition of 0.5 mole of methyl vinyl ketone in 200 ml anhydrous ether dropwise over 5 hours. The solution was stirred for 2 hours and then left overnight.

The reaction was stopped with the addition of 1 kg of ice and 250 g of NH_4Cl and then allowing the ice to melt. The organic layer was separated and washed the remaining aqueous layer with 100 ml ether twice. All the washings were combined with the organic layer and then dried with $MgSO_4$. The solid was suction filtered and the filtrate was stripped of solvent under vacuum. The product was collected by distillation at 46 mm Hg between 55°C and 63°C for 28% yield.

4-Hydroxy-4-isopropyl-5-methyl-2-hexene. Into a dry reaction vessel were weighed 42.4 mmoles of lithium dispersion. The dispersion was prepared by washing with freshly distilled THF, 20 ml at a time, for three times, withdrawing as much THF as possible each time. This was followed by the addition of 10.6 mmoles 1-bromo-1-propene and 8.8 mmoles of diisopropyl ketone with the addition of THF to a total volume of 10 ml, all via an addition funnel. Furthermore, the addition funnel was washed with 5 ml THF. Next the reaction vessel was placed over an ultrasonic bath filled with ice for 2 hours.

The excess lithium remaining after 2 hours was quenched with the slow and careful addition of MeOH turning the reaction mixture grey and viscous. This mixture was washed three times with 10% Na_2CO_3 generating a white precipitate in the aqueous layer. The aqueous layer was separated and washed with 25 ml lab grade ether. All washings were combined and dried with $MgSO_4$. The ether was stripped off and the product was collected at 0.25 to 0.5 torr at 38°C for a 17% yield.

5-Methyl-4-isopropyl-3-hexene-2-one. Into a 2 liter flask was added 239 mmoles of diisopropyl amine in 220 ml dry ethyl ether. Into a 250 ml addition funnel was added 239 mmoles of cyclohexyl amine-N,1-methylethylidene in 100 ml anhydrous ether. Next approximately 240 mmoles of n-butyl

lithium in hexanes (1.65 M) was "blown-over" into an addition funnel. The reaction vessel was cooled over an acetate slush bath while the n-butyl lithium was introduced dropwise over 1.0 hour followed by stirring for 10 minutes. The cyclohexyl amine was added dropwise over 15 minutes at -60°C and the mixture was allowed to warm overnight. The reaction was quenched with H_2O.

The reaction mixture was washed with lab grade ether and the washings were combined and washed with saturated brine solution. The organic layer was dried with $MgSO_4$ and filtered. The ether was stripped off and 50 g of oxalic acid was added to the crude residue in the distillation flask. This mixture was then steam distilled and the organic layer was separated. The product was distilled at 91 mm Hg between 107°C and 117°C.

5-Methyl-4-isopropyl-2-hexanone. The enone formed previously was used. Taking 9.947 g of the enone and 0.500 g of Pd/C catalyst these were mixed in 100 ml ethanol in a thick walled flask used for hydrogenations. The flask was pressurized with H_2 to 37 psi. With aggitation the pressure in the flask dropped 4.3 psi over 1 hour. After one hour the solution was checked by GC to observe the loss of the enone. Next the catalyst was filtered off. The EtOH was distilled away over a steam bath through a water cooled column. The residue was diluted with pentane. This was followed by a

washing with saturated brine solution and then drying the organic layer with $MgSO_4$. The pentane was stripped off leaving the product at a 23% yield.

CONCLUSION

The cornerstone to this project was the Diels-Alder reaction. The hurdle to overcome was the sensitivity of the chosen diene towards an acidic medium. It was thought that if a stable 2-alkylidene-1,3-CPD could be made that could be isolated from the MCBA and added to the Danishefsky's diene on demand the spiro-annulation would work flawlessly. That opportunity never occured since the requisite stable 2-alkylidene-1,3-CPD was never isolated.

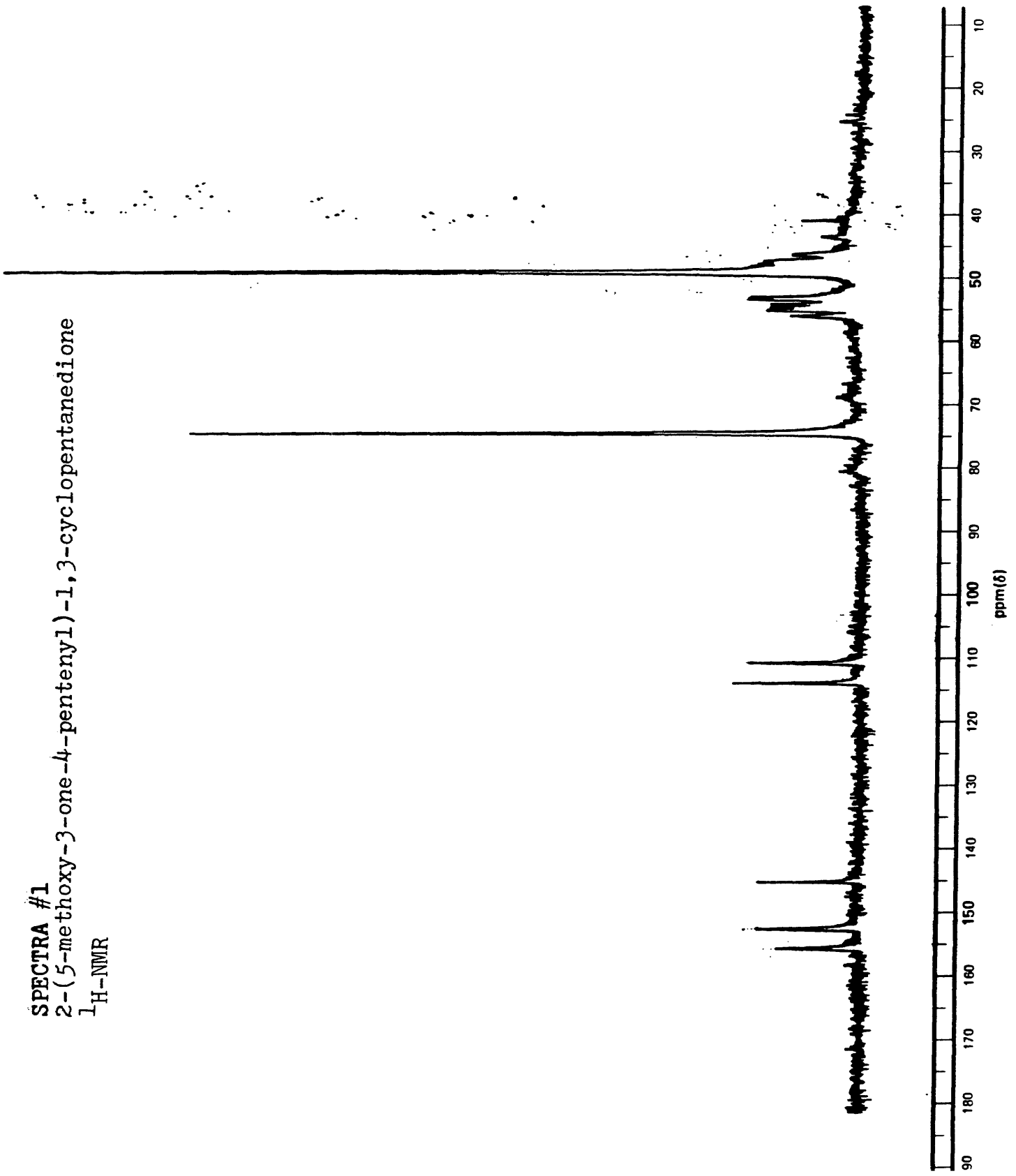
The major portion of this project was directed towards forming a hindered 2-alkyl-1,3-CPD. Attention settled on the cyclization described by Hiraga. Eventually, all efforts were directed toward the ketone precursor with hope that this cyclization would continue to work as the ketones became more exotic. When 2-neopentyl-1,3-CPD was generated it seemed to reinforce all efforts.

The weight of this project seemed to rest on the directed aldol condensation between acetone enolate and diisopropyl ketone. Indeed, this was the only route to a hindered ketone that showed promise. Time permitting, this route should have been exploited. Accordingly, any further

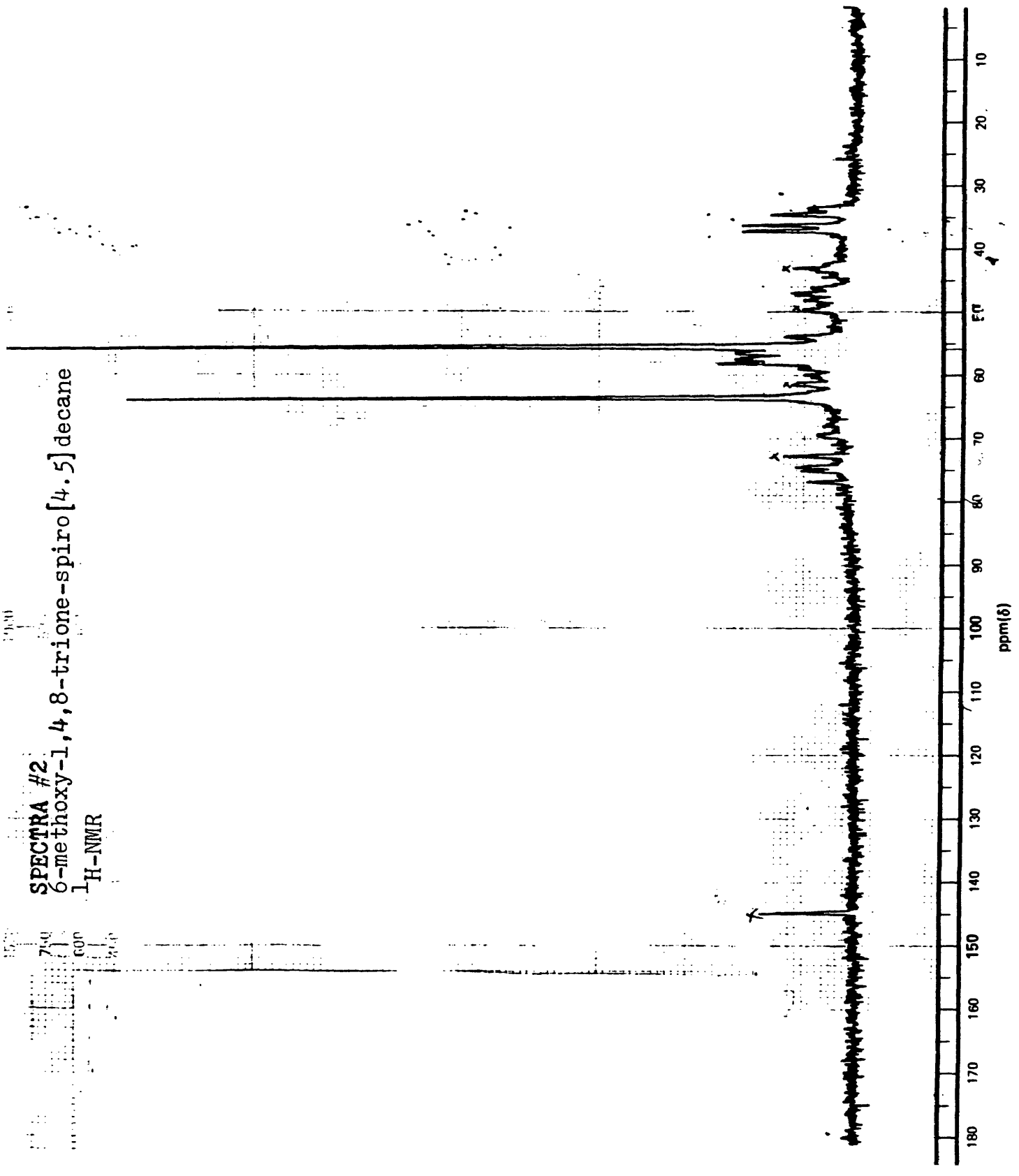
work on this project should exhaust the opportunities with the directed aldol condensation before returning to the Diels-Alder spiro-annulation.

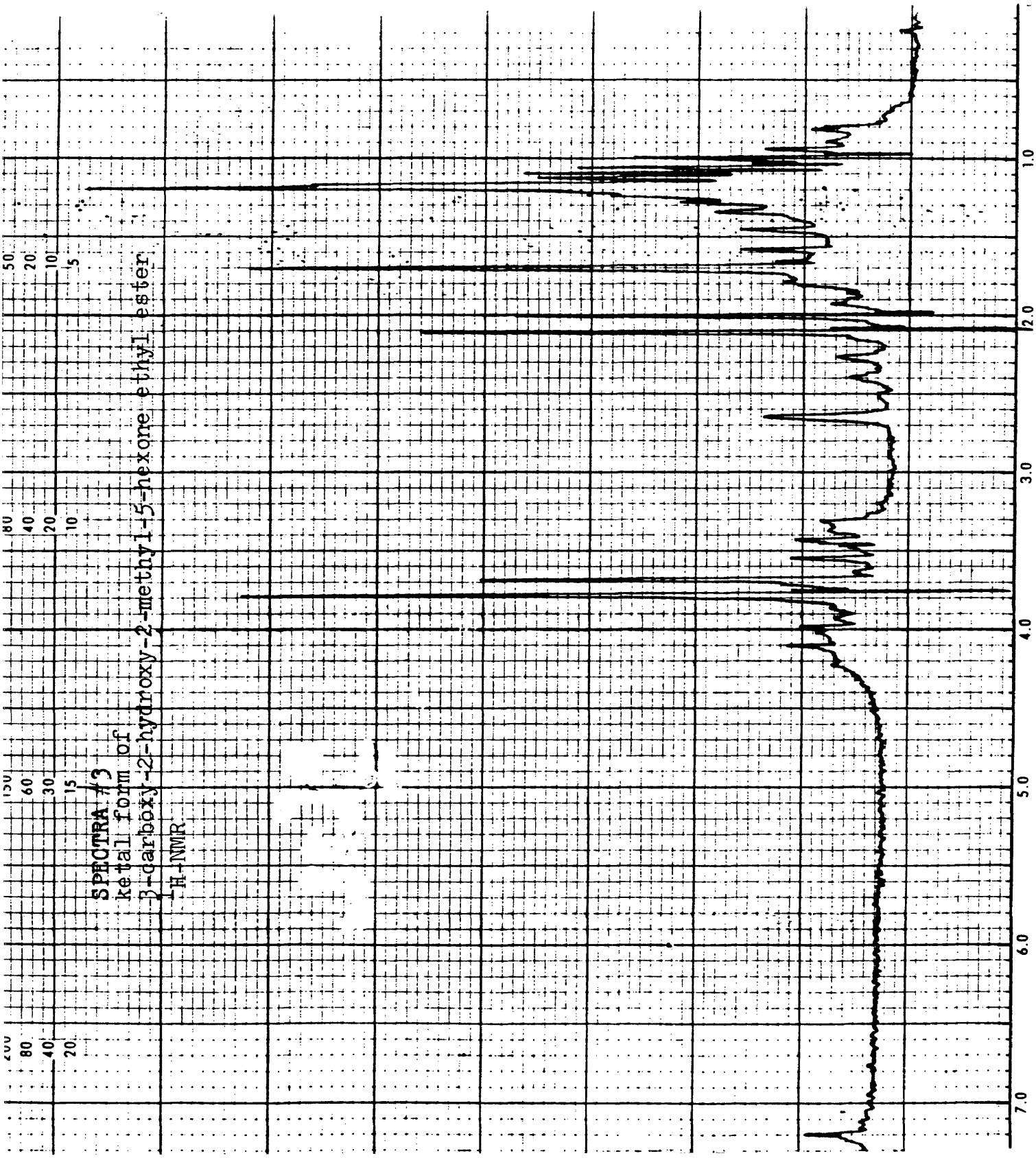
APPENDIX

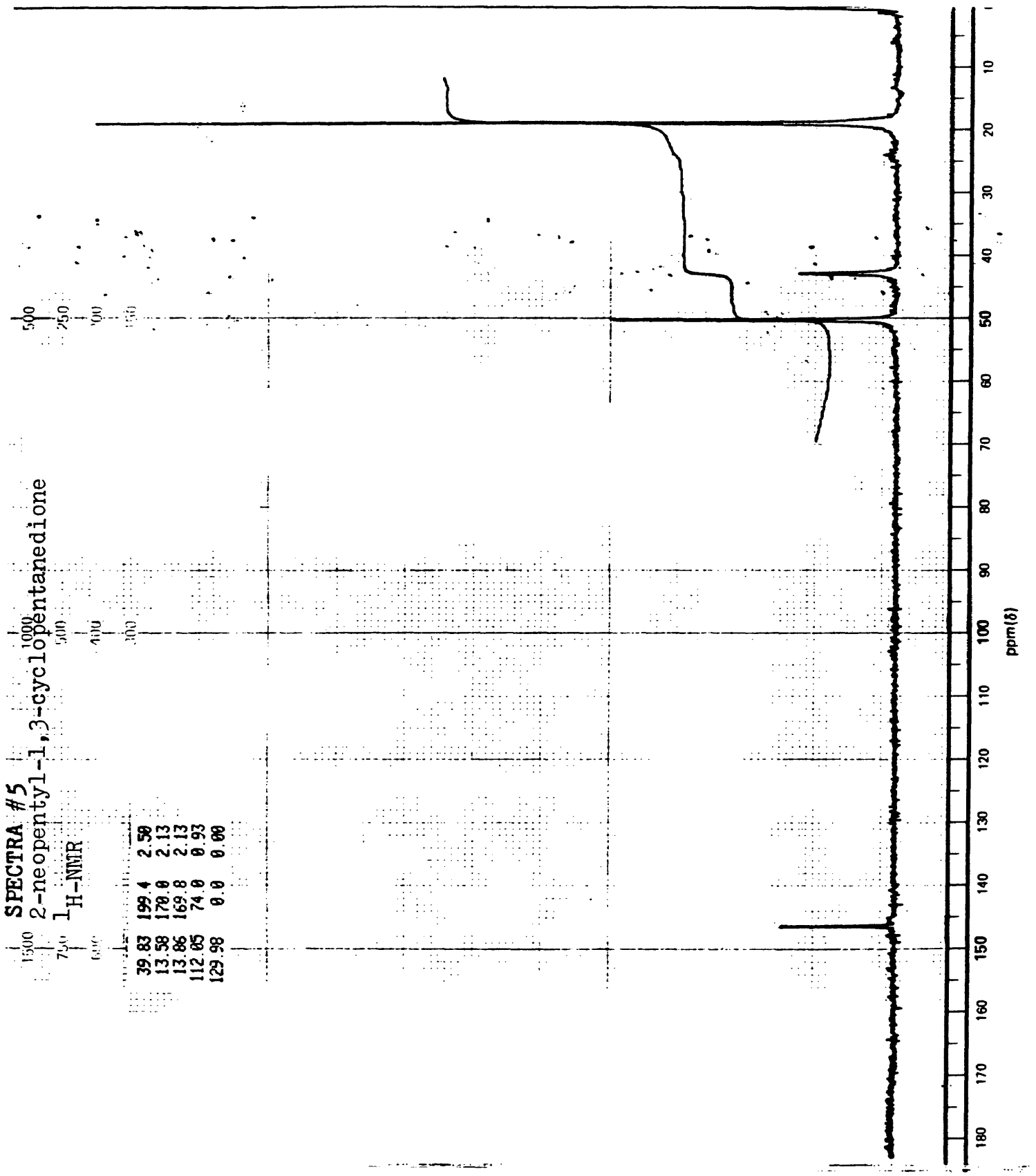
SPECTRA #1
2-(5-methoxy-3-one-4-pentenyl)-1,3-cyclopentanedione
^{1}H-NMR

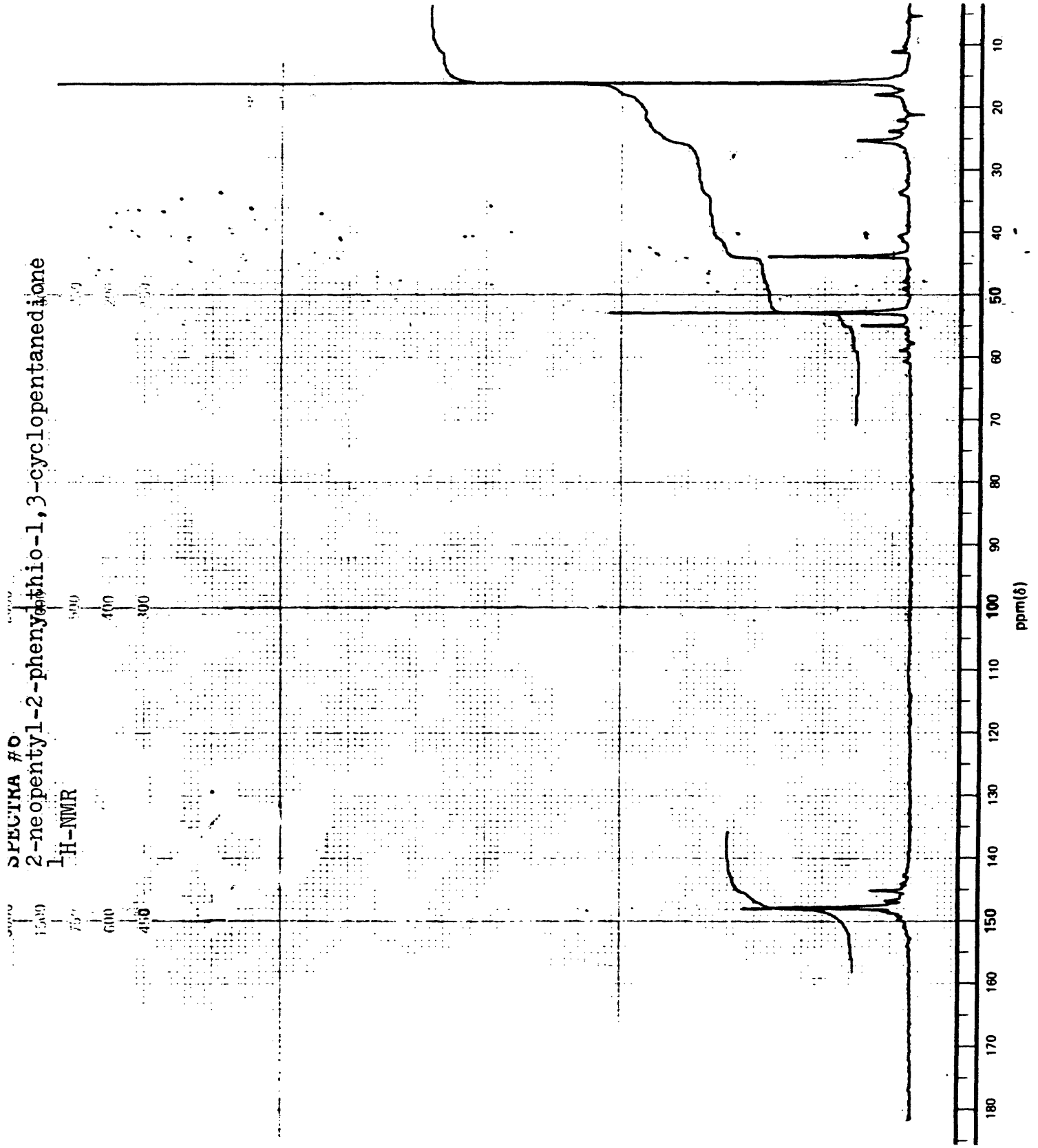


SPECTRA #2
6-methoxy-1,4,8-trione-spiro[4.5]decane
^{1}H-NMR

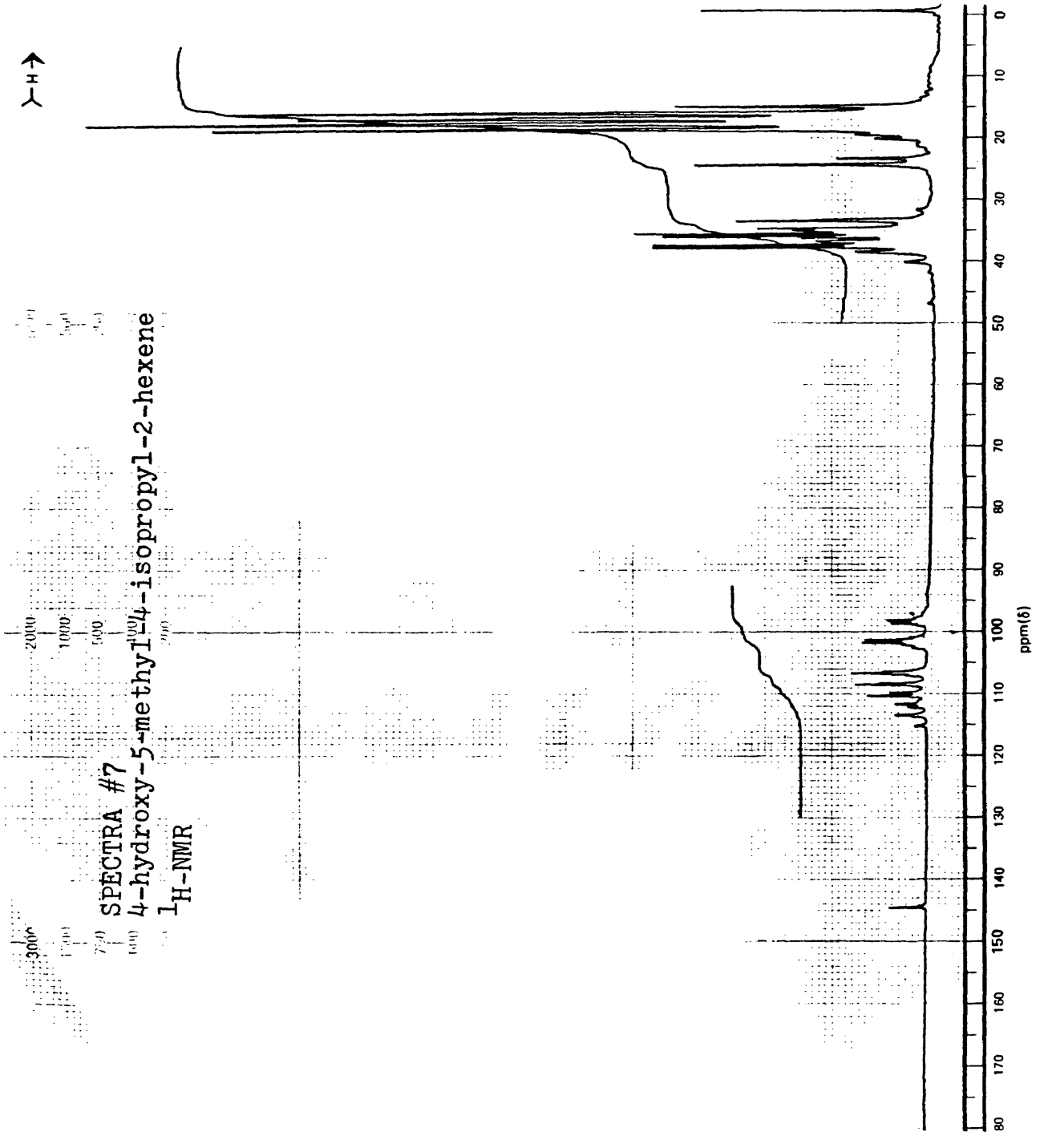



SPECTRA #3
ketal form of
3-carboxy-2-hydroxy-2-methyl-5-hexone ethyl ester
1H-NMR
1.0
2.0
3.0
4.0
5.0
6.0
7.0


SPECTRA #5
2-neopentyl-1,3-cyclopentanedione
1H-NMR
39.83 199.4 2.50
13.58 170.0 2.13
13.86 169.8 2.13
112.05 74.0 0.93
129.98 0.0 0.00
ppm(δ)


SPECTRA #0
2-neopentyl-2-phenylthio-1,3-cyclopentanedione
1H-NMR
ppm(δ)

SPECTRA #7
4-hydroxy-5-methyl-4-isopropyl-2-hexene
^{1}H-NMR



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