1,2-BIS(TRIMETHYLSILYLOXY)CYCLOBUTENE: A STUDY OF ACYLATION METHODOLOGY AND SYNTHETIC APPLICATION

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1,2-BIS(TRIMETHYLSILYLOXY)CYCLOBUTENE: A STUDY OF ACYLATION METHODOLOGY AND SYNTHETIC APPLICATION

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Abstract

Kuwajima and co-workers have reported that the reaction of a ketal and 1,2-bis(trimethylsilyloxy)cyclobutene (**1**) in the presence of a Lewis acid catalyst with subsequent rearrangement of the cyclobutanone intermediate with trifluoroacetic acid affords 2,2-disubstituted 1,3-cyclopentanediones in reasonable yields. We have found that substituents, such as methyl groups, in the α-position to the spiro center significantly reduce the yield of product. In addition, substitution of the 1,2-ethanediol moiety of the ketal with groups such as methyl and phenyl also reduces product yields.

Synthesis of the precursors of the juvenile hormone 6-ethyl-10-methyldodeca-5,9-dien-2-one of the moth *Cecropia* in our first approach involved the addition of an ethyl group to 2-ethyl-2-methylcyclopentane-1,3-dione (**71**) and reduction with sodium borohydride to afford **80** as a precursor for a Grob-type fragmentation. Analysis of **80** using nmr and X-ray crystallography indicated the structure shown in **Figure 5**. The alternative approach to the precursors or the juvenile hormone involved the reduction of **71** with sodium borohydride with subsequent introduction of the ethyl moiety to generate **89**. However, introduction of the ethyl group proved to be irreproducible. Both of our

strategies focused on the construction of the correct relative stereochemistry to enable a Grob-type fragmentation to produce the correct double bond isomer of **69**.

Model studies toward the synthesis of fredericamycin A focused on [2+2] photochemical additions of **1** with various enones, in particular with spiro[3-cyclopentene-1,1'-indan]-2,5-dione (**99**). However, while tests carried out between a simple enone and **1** provided limited results, the reaction between **99** and **1** afforded only starting material.

Acknowledgements

There are a great many individuals and groups to whom I owe an eternal debt of gratitude for helping in the completion of this document. I would like to thank my supervisor, Dr. Jean Burnell, for the opportunity to work in his labs and to engage in research on several challenging projects.

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Glossary of Abbreviations

APT	Attached proton test
Et	Ethyl
GCMS	Gas chromatography-mass spectrometry
hv	Ultraviolet irradiation
ir	Infrared spectroscopy
mp	Melting point
$MgSO_4$	Magnesium sulfate
ms	Mass spectrometry, mass spectrum
$NaHCO_3$	Sodium hydrogen carbonate
nmr	Nuclear magnetic resonance spectroscopy
$SOCl_2$	Thionyl chloride
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography
TMS	Trimethylsilyl
nar	Narrow

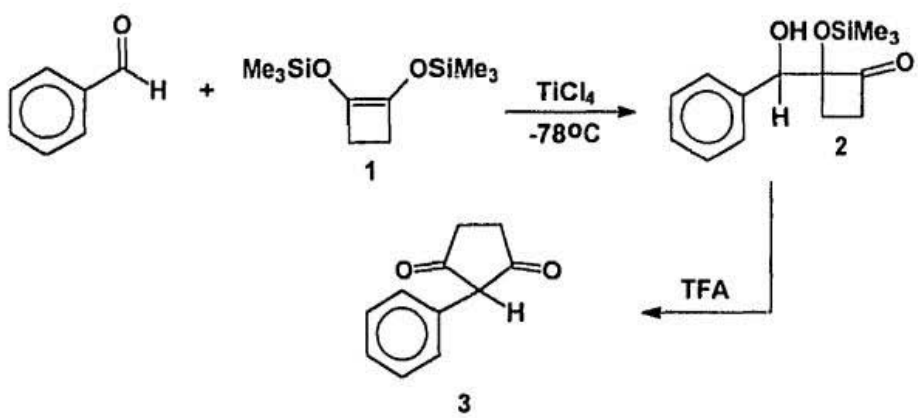
In loving memory of Gram...

Chapter 1

Bis-acylation of Ketals

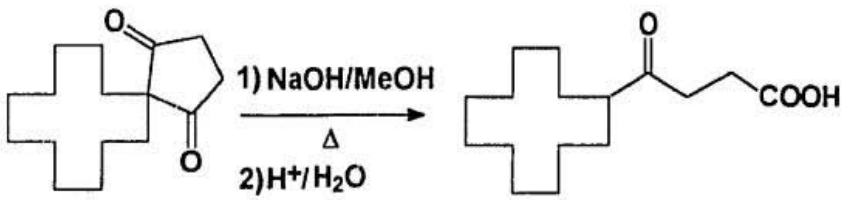
I. INTRODUCTION

In 1977 Kuwajima and co-workers[1] published a geminal acylation procedure for the conversion of acetals and aldehydes into 1,3-cyclopentanedione derivatives through an intermediate pinacol. The value of this method is in the rapid generation of a five-membered ring that possesses two ketone functions. In this process, there is the formation of a quaternary center from a ketone, and the formation of a spiro center from a cyclic ketone. An example of the reaction is shown in **Scheme 1** with benzaldehyde as the substrate. 1,2-Bis(trimethylsilyloxy)cyclobutene[2] (**1**) in the presence of the Lewis acid $TiCl_4$ reacts with benzaldehyde to afford the cyclobutanone **2**. This compound then rearranges to **3** upon treatment with trifluoroacetic acid (TFA) in a yield of 76% over both steps.[1]



Scheme 1

Kuwajima[1] noted that a variety of Lewis acids, e.g. $TiCl_4$, $BF_3.Et_2O$, and tetrabutylammonium fluoride, could accomplish the first step. In addition, Kuwajima[1] showed that the resultant 1,3-cyclopentanedione could be subjected to hydroxide-induced cleavage to afford a γ-ketoacid, as shown in the example in **Scheme 2**.

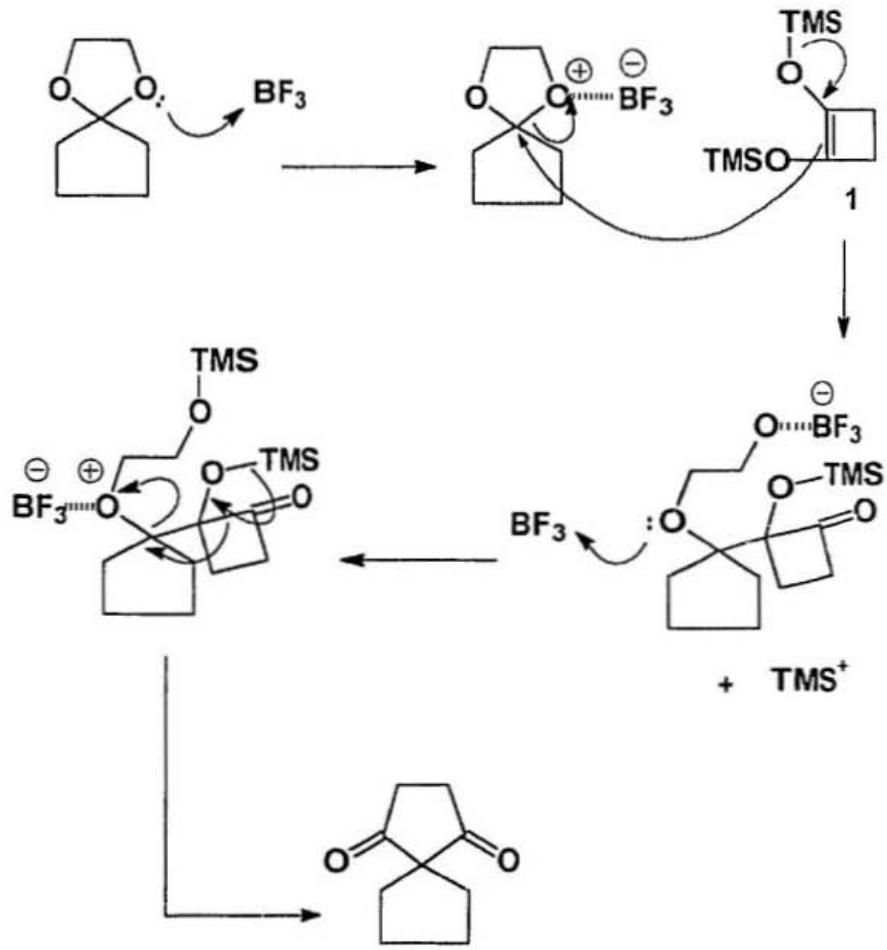


Scheme 2

In 1984, Kuwajima *et al.*[3] updated their earlier procedure, and they assessed more carefully a number of different parameters involved in this geminal acylation. The nature of the Lewis acid proved to be important in the formation of the cyclobutanone. It was found that $TiCl_4$ was the most effective Lewis acid that they tested for reactions of **1** with aldehydes and aliphatic acetals, whereas $BF_3.Et_2O$ was more effective with reactive acetals and ketals. An important parameter in the choice of the acid for the rearrangment of the intermediate pinacol was the ease of removal of excess acid upon work-up. Trifluoroacetic acid was favoured for this reason. Even though acidic media such as *p*-toluenesulfonic acid (*p*TsOH) in hot benzene, $BF_3.Et_2O$, and trimethylsilyl triflate (TMSOTf) in dichloromethane were highly effective, they

were not as easily removed during work-up.

The overall process with a ketal substrate is believed to occur via the mechanism shown in **Scheme 3**. The first step is complexation of a ketal



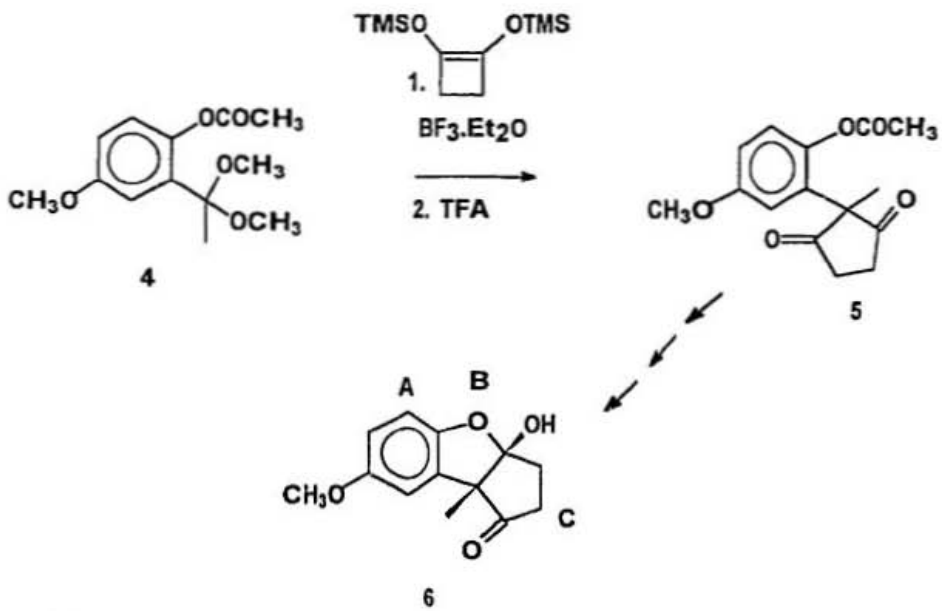
Scheme 3

oxygen with the Lewis acid. Next, there is a condensation between 1 and the ketal complex to give a cyclobutanone intermediate. Complexation of the other ketal oxygen then allows for the rearrangement of the cyclobutanone

intermediate to the 1,3-cyclopentanedione. A point worth noting is that Kuwajima stated that the reaction of **1** and ketones does not occur in either basic or acidic media.

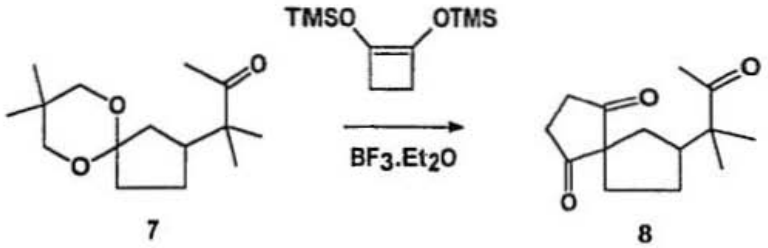
Wu and Burnell[4] were the first, to be later followed by Ayyangar *et al*.,[5] to report a modification to the Kuwajima procedure whereby a large excess of a Lewis acid led directly from a ketal to a 1,3-cyclopentanedione without the necessity of isolation of the cyclobutanone.

A number of groups have capitalized upon the geminal acylation methodology. Some examples follow. Anderson and Lee[6] incorporated the method to generate the C-ring in a functionalized aromatic system **5** in 39% yield from **4** in a route toward analogs of trichothecane **6**, as shown in **Scheme 4**.



Scheme 4

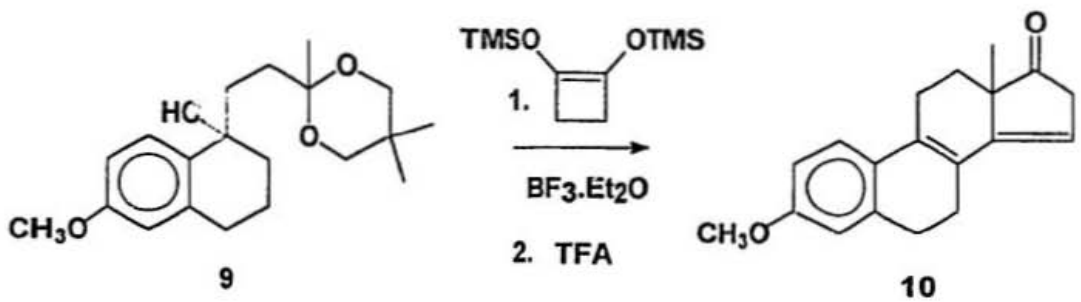
Wu and Burnell[4] used the spiro-annulation of **7** to **8** (**Scheme 5**) to introduce one of the five-membered rings of the fragrant sesquiterpene isokusimone in 85% yield.



7 **8**

Scheme 5

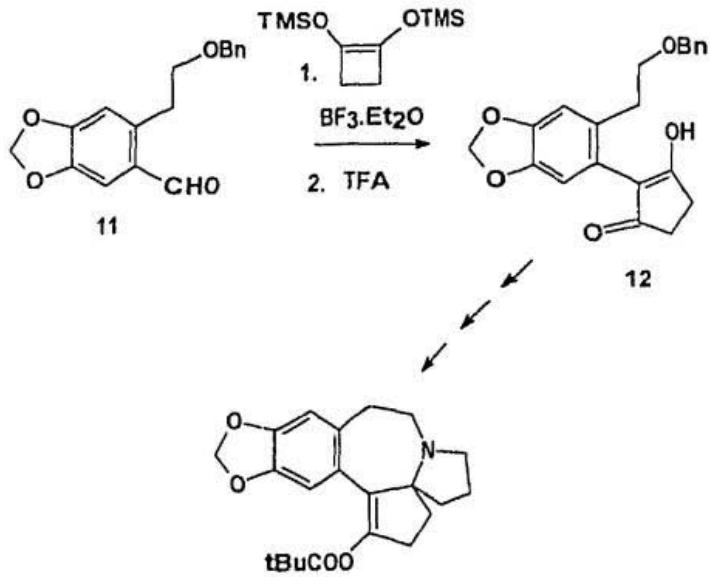
Burnell and Wu[7] also used this method to generate the D-ring of 3-methoxyestra-1,3,5,8,14-pentaen-17-one, an estrone analog. Reaction of **9** with **1** gave a 1,3-cyclopentanedione, which was immediately cyclized again to provide the C-ring in an overall yield of 91% yield, as shown in **Scheme 6**.



9 **10**

Scheme 6

Finally, Kavash and Mariano[8] employed the strategy to generate the intermediate **12** in 73% yield from the aldehyde **11** in the construction of the harringtonine ring system, as depicted in **Scheme 7**.



Scheme 7

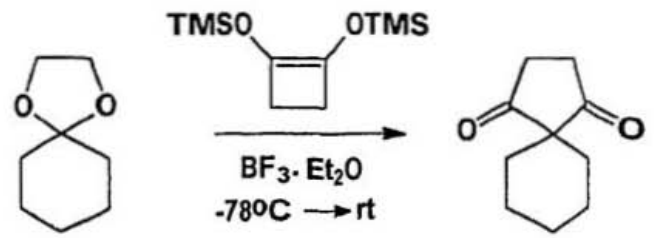
II. RESULTS AND DISCUSSION

Despite the reaction parameters that were considered by Kuwajima and co-workers[1,3] and the examples of the incorporation of this method into synthesis, there remained a need to define more clearly other parameters involved in the reaction. For instance, what influence would the nature of the ketal have upon the outcome of the reaction? Thus, a thorough study was initiated in our laboratory. One point should be mentioned here before details of these studies are presented. Difficulties were encountered in locating some of the 1,3-cyclopentanedione products on thin-layer chromatography (tlc) plates. The diketone products were almost invisible with the usual visualization

techniques, i.e., uv light, I_2, and acid sprays. In order to get around this problem, it was sometimes necessary to allow the column fractions to concentrate by evaporation. In other cases, gas chromatography-mass spectrometry (GCMS) was used to analyze each column fraction.

II. a. Steric Bulk of the Ketal's Alcohol Moiety

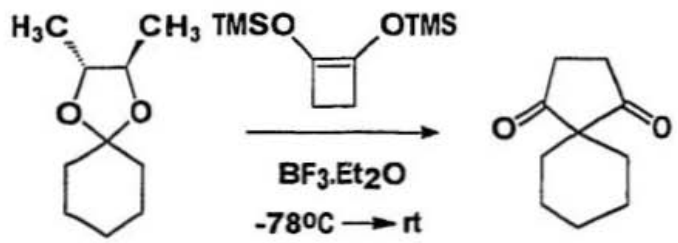
Kuwajima used methyl or ethyl ketals in his series of examples. Kuwajima did not employ ketals derived from 1,2-ethanediol, which is the most commonly seen example of a ketal in synthesis. Thus, it was important for us to demonstrate the formation of the 1,3-diketone **14** from the ketal **13** derived from cyclohexanone. Ketal **13** was treated with 2.5 equivalents of **1** and 15 equivalents of boron trifluoride etherate at -78 °C. The solution was then warmed to room temperature overnight, and aqueous work-up afforded the 1,3-cyclopentanedione **14** in 96% yield, as depicted in **Scheme 8**.



13 **14**

Scheme 8

It was found that the use of a bulkier alcohol moiety for the ketal dramatically reduced the yield of the 1,3-cyclopentanedione. It is unlikely that there is any electronic effect at work here for two reasons. First, methyl groups are not significant electron donors via induction. Secondly, the methyl groups are separated from the reacting center by two bonds. In the case shown in **Scheme 9**, the conversion of the ketal **15** into the dione **16** proceeded in only 48% yield. Burnell and co-workers[9] also found that increasing the steric bulk by replacing the methyls in **15** with phenyl groups precluded conversion of this ketal

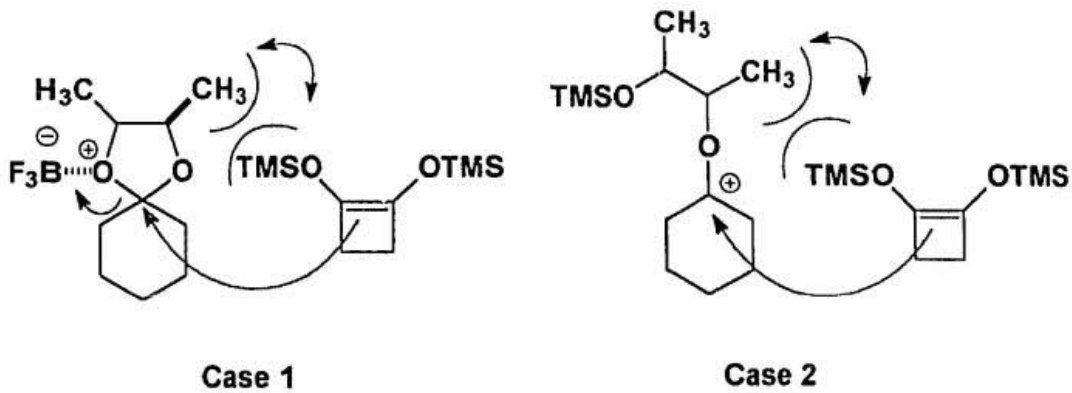


15 **16**

Scheme 9

to **16**. Thus, a bulky ketal can serve as a protecting group for the ketone in these geminal acylation reactions. This is important because work by Jenkins[10] demonstrated that 1,3-cyclopentanediones can indeed be formed directly from ketones. In the case of **15**, steric congestion affects the addition of the 1,2-(bistrimethylsilyloxy)cyclobutene to the ketal, according to **Case 1** and/or **Case 2** as depicted in **Figure 1**. In either situation, some part of the ketal **15** is in very

close proximity to the 1,2-(bistrimethylsilyloxy)cyclobutene and must sterically hinder reaction.

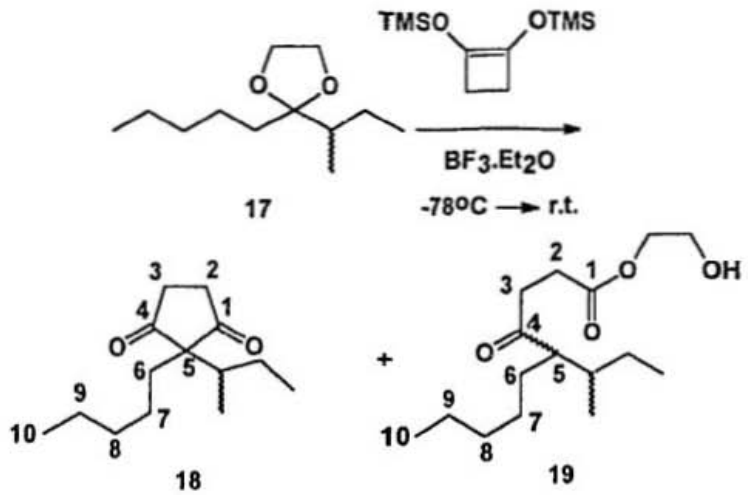


Case 1 **Case 2**

Figure 1: Steric Hindrance in Attack of 1

II. b. α-Substituents

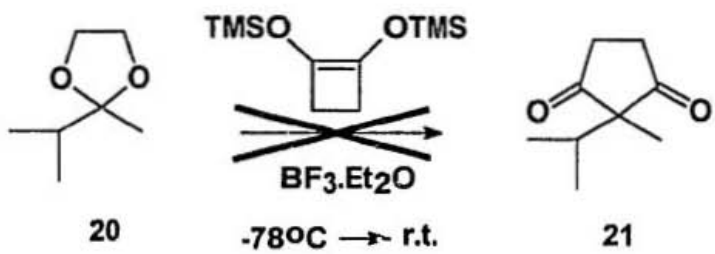
The use of a ketal that is substituted on the 1,2-ethanediol moiety is not a common synthetic situation, but α–substitution is often desirable. Thus, we decided to test the effect of increasing the steric bulk of the substrate by the introduction of α-substituents. The first of these was the reaction of the ketal **17**, derived from racemic 3-methylnonan-4-one and 1,2-ethanediol. Ketal **17** was converted to **18** as shown in **Scheme 10** in only a 28% yield. This was a substantially lower yield than was obtained in the reaction of ketal **13**. However, another column fraction of the reaction of **17** afforded a second product **19** as a mixture of diastereomers in 15% yield. The ^{1}H nmr spectrum of this compound



Scheme 10

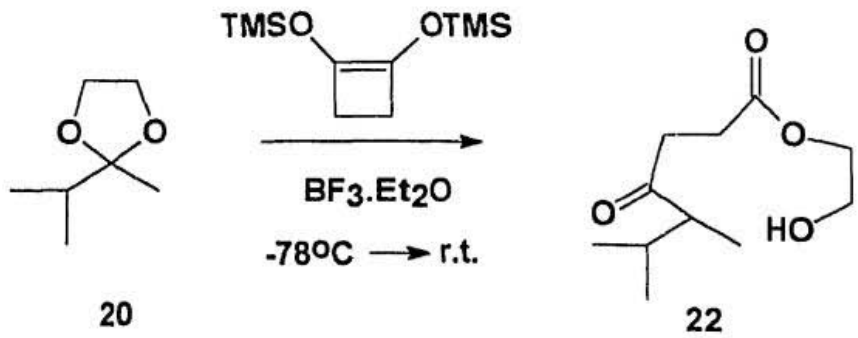
included signals at δ 4.26 and 3.85, which were consistent with the presence of an 2-hydroxyethyl group derived from 1,2-ethanediol. The free 1,2-ethanediol from the reaction must have attacked the 1,3-cyclopentanedione moiety of **18** to force open the ring and generate the ester.

Another example was the ketal **20**, which was exposed to the same conditions as in **Scheme 11**. None of the expected 1,3-cyclopentanedione **21**



Scheme 11

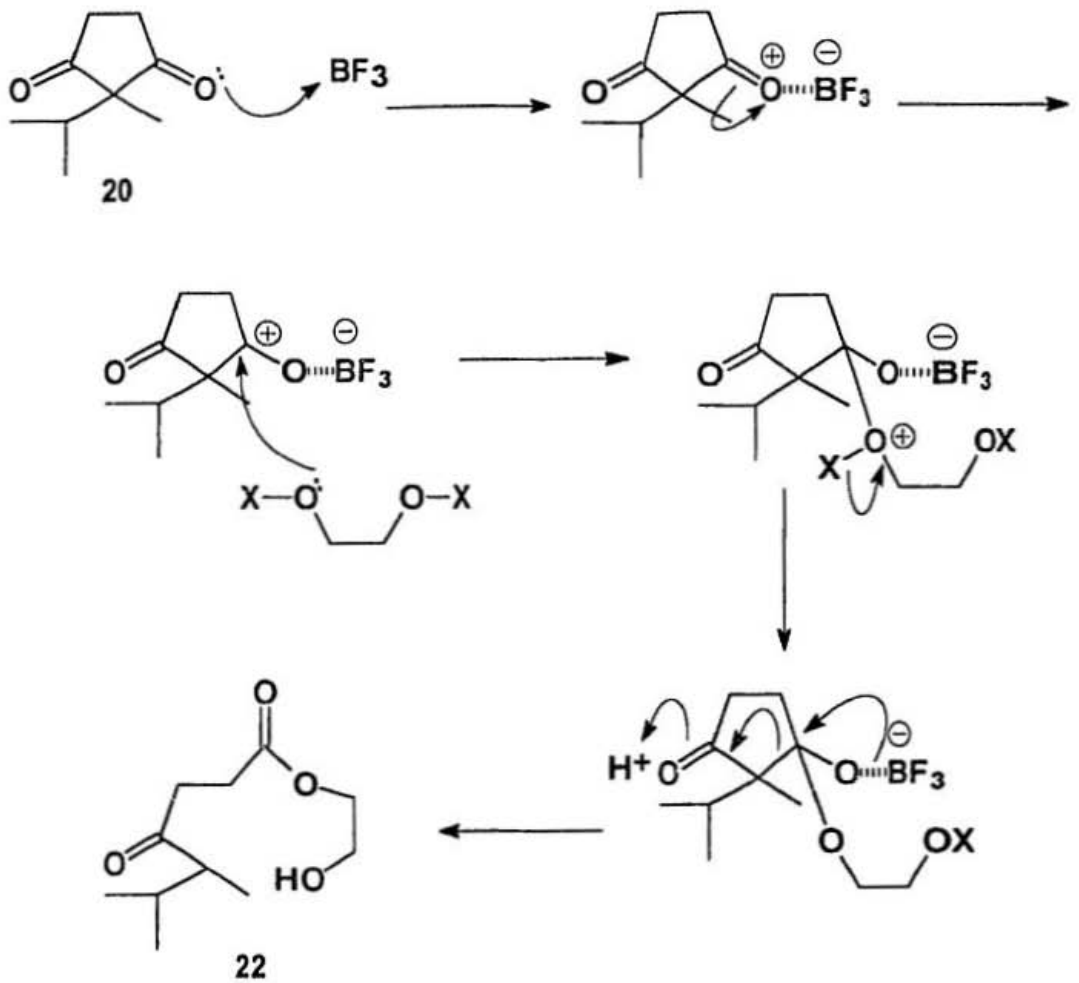
was isolated after chromatography. Instead, the ester **22** was obtained in 19% yield as the only identified material, as indicated in **Scheme 12**. This had to



20 22

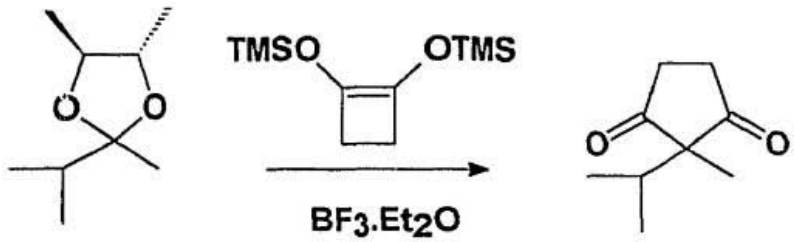
Scheme 12

have been formed from **21**, also by the attack of the 1,2-ethanediol. Clearly, the 1,3-cyclopentanedione was fairly reactive even though it was sterically hindered. Given the results of **Scheme 10** and **Scheme 12**, it was clear that these molecules were undergoing a phenomenon similar to what Kuwajima[1] noted in the original publication which described the formation of γ-ketoacids through base-induced cleavage. In our case, we were victims of a variation of this phenomenon whereby the 1,2-ethanediol released from the ketal acted as a nucleophile and forced an acid-induced cleavage, the postulated mechanism of which is shown in **Scheme 13**. Significantly, for the transformation to the ester to occur, the desired 1,3-cyclopentanedione must have been generated first; the retro-aldol occurred subsequently. Although this appears to be a problem, it is one that is easily solved by making use of the increased steric bulk of the 2,3-butanediol. Therefore, we returned to the dimethyl diol ketals with the idea that the presence of the two methyl groups would decrease the nucleophilicity of the diol and would then prevent the destruction of the 1,3-cyclopentanedione. When



Scheme 13

the dimethyl-substituted ketal **23** was exposed to the same conditions as in **Scheme 14** there was a 56% conversion to **21** as determined by nmr. However, attempts to purify the sample by column chromatography failed, largely due to decomposition of the diketone on the silica. Indeed, we found that 1,3-diketone products derived from more substituted ketals were all prone to decomposition. Given that we also had difficulties in 'visualizing' the 1,3-diketones by tlc,

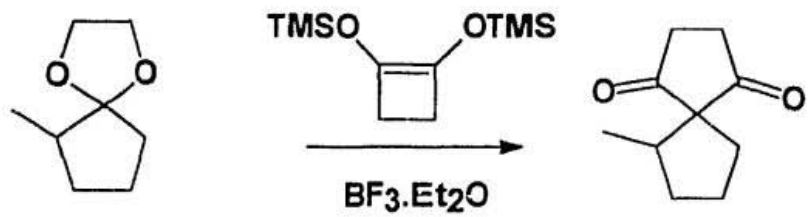


23 21

Scheme 14

chromatography of these materials was rather tricky and could thereby explain lower yields. We believe that recoveries could be enhanced if one were to carry on with the next synthetic step without rigorous purification at the 1,3-diketone stage.

An α-substituted cyclic ketal **24** was subjected to the standard reaction conditions (as defined in the Experimental Section), which afforded the dione **25**, but in only 36% yield (**Scheme 15**). There was none of the opened dione



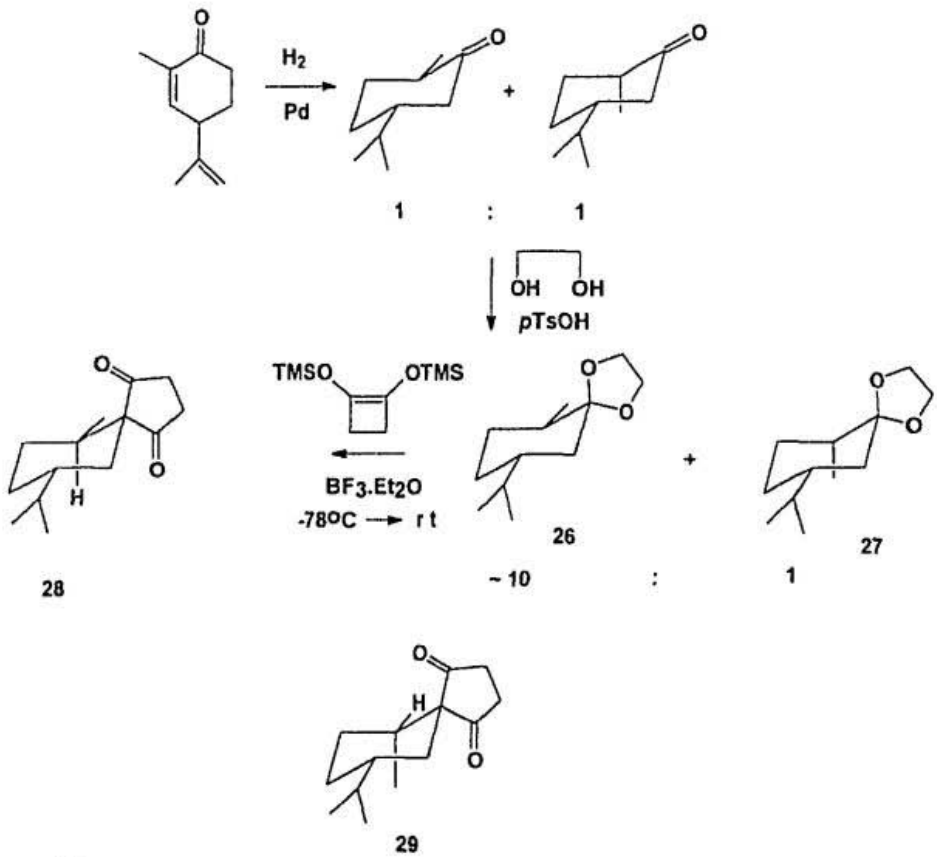
24 25

Scheme 15

material. However, the yield was still far below that of the unsubstituted case.

The reason behind this was that the methyl group was located on one side of the ring. In order for the 1,2-bis(trimethylsilyloxy)cyclobutene to approach, it must have attacked in the position anti to the methyl group. However, there was still a great deal of steric hindrance to the approach of the cyclobutene. If the cyclobutene were to approach syn to the methyl group, the steric hindrance would have been considerably worse. Thus, the net result was that the approach was blocked and the reaction rate dropped significantly.

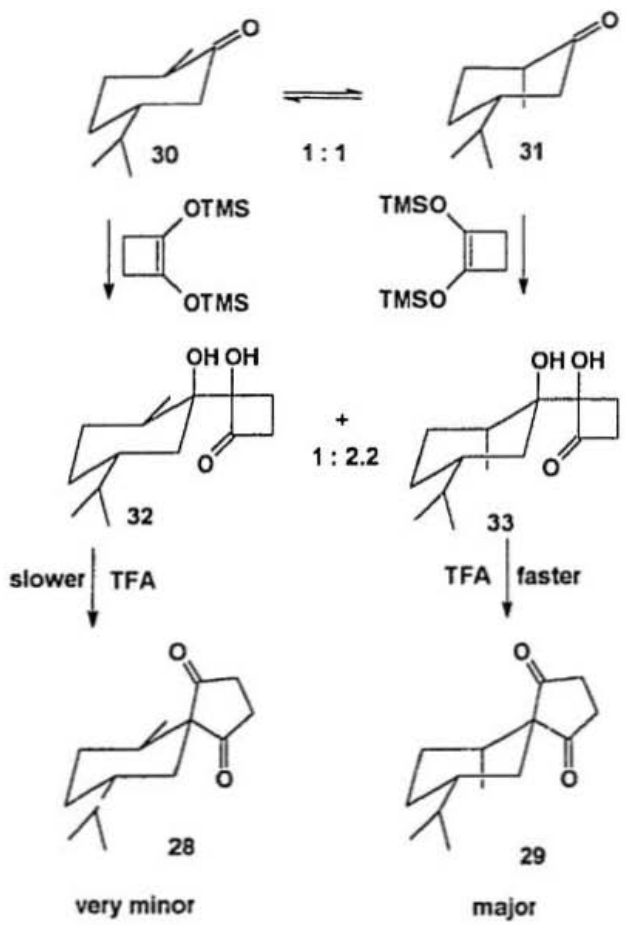
We decided to look at a more complex cyclic example that also had an α-



Scheme 16

α-methyl group. Hydrogenation of (*R*)-carvone gave tetrahydrocarvone as a 1:1 mixture of epimers (**Scheme 16**). Ketalization of this mixture with 1,2-ethanediol and *p*TsOH proceeded smoothly with concomitant epimerization of the α-center to yield an approximately 10:1 mixture of epimeric ketals **26** and **27**, with the major product being the thermodynamically preferred isomer with both the methyl and the isopropyl groups equatorial. Reaction of this mixture with **1** took place more slowly than with ketal **13**, but the desired diketone product **28** was isolated in modest yield after chromatography. It is synthetically important to note that the relative stereochemistry about the cyclohexanone ring was maintained in this reaction, and if any epimeric dione **29** was produced, it was in a quantity that was undetectable. This was consistent with equatorial addition onto the ketal center and subsequent rearrangement without elimination to an intermediate vinyl ether. The relative stereochemistry of the reaction of **26** is in contrast with the reaction of tetrahydrocarvone mixture directly with **1** under the ketone conditions. (The nmr data that shows how the relative stereochemistry was determined is presented below.) This process gave the isomer **29** very predominately, but this result has not yet been rationalized in terms of a mechanism.[10] Jenkins reacted **1** with the 1:1 mixture of ketones under acidic conditions in which the ketones should have been interconvertible by epimerization of the α stereogenic center. A 2.2:1 mixture of diols was isolated,

and then rearrangement of this mixture with trifluoroacetic acid provided very



Scheme 17

predominately dione **29**. Thus, the reaction proceeded under the kinetic regime summarized in **Scheme 17** . If the ketone reaction was also by equatorial attack,[10] then **1** must approach the reacting carbonyl syn to the axial methyl, an event that appears to invite steric hindrance. We can offer two explanations, both of which have important synthetic ramifications for the (room temperature)

ketone versus the (-78 °C) ketal technology. Firstly, the ketone epimer must in fact have a significant population of both isomers **30** and **31** at room temperature. Whereas the isomer **30** should be thermodynamically preferred, **31** is less than 0.2 kcal/mol higher in energy, but it is completely unencumbered for equatorial attack by **1**. Thus, by this route, the major intermediate should be **32**, not **33** as originally claimed.[10] Compound **32** is the same as the result of axial attack by **1** on isomer **30**. Secondly, whereas isomer **30** should indeed be sterically hindering towards incoming **1**, the initial complexation with Lewis acid may be greatly facilitated by the fact that the axial methyl can provide hyperconjugative stabilization of the intermediate carbocation, as shown in **Figure 2**. In the case where the intermediate has an axial methyl, the

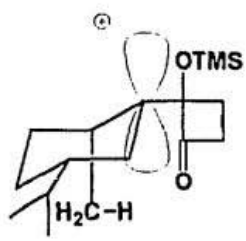


Figure 2: Stabilization of Carbocation

rearrangement of the intermediate to the 1,3-diketone proceeds at a significantly higher rate. The reason for this is that in this intermediate there is a large steric interaction between the cyclobutanone moiety and the α-methyl. This congestion will force the rearrangement to proceed at a higher rate than for

the equatorial intermediate in order to alleviate the strain.

The assignment of the relative stereochemistry of **28** and **29** was done by comparing the ^{13}C nmr spectra of **28** with the diketone **29**, generated directly from the ketone through the procedure of Jenkins and Burnell.[10] These differences are consistent with a γ_{gauche} interaction from an axial substituent (methyl) in **29**.[11] **Table 1** assigns the ^{13}C nmr signals for both

Table 1: ^{13}C nmr Shifts of Diones 28 and 29

	Diketone ^{13}C nmr Shifts	
Assignment	**28**	**29**
C-1 or C-4	217.8	214.6
C-1 or C-4	216.7	214.1
C-2 or C-3	35.7	34.3
C-2 or C-3	35.4	34.7
C-5	60.5	60.8
C-6	36.0	32.7
C-7	28.5	27.6
C-8	29.3	22.1
C-9	36.5	36.6
C-10	35.4	25.2
C-11	17.7	14.6
C-12	32.2	31.7
C-13 or C-14	19.6	19.7
C-13 or C-14	19.2	19.4

compounds. The signals for carbons C8 and C-10 and for the methyl group at C-6 for **29** should be compared with the same ^{13}C nmr signals for **28**.

When the structures shown in **Figure 3** are considered, one can see that in the case of **29**, there are γ_{gauche} interactions whereas in **28**, there are no such interactions.

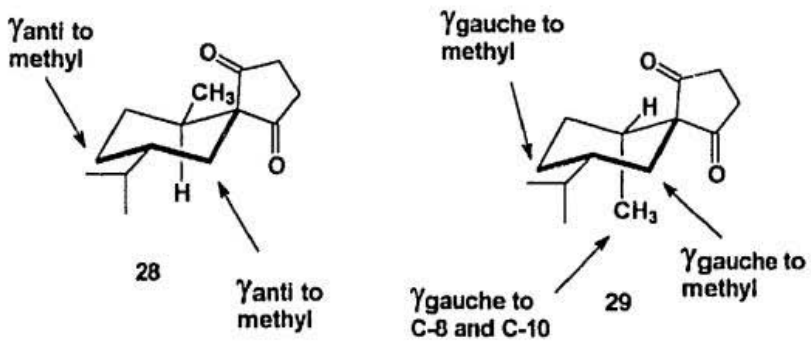
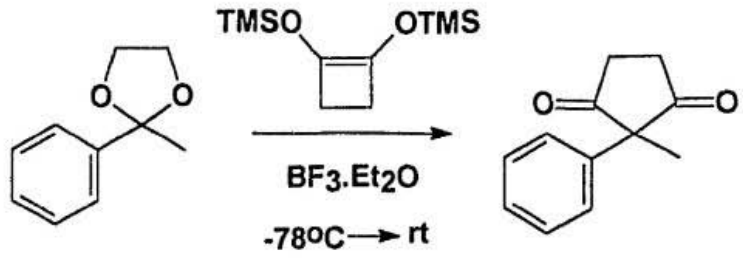


Figure 3: Comparison of γ_{anti} / γ_{gauche} Interactions Between 28 and 29

II. c. Aromatic Substrates

Evidence from other examples studied in our group showed that the presence of an α-double bond reduced yields of 1,3-cyclopentanediones very drastically relative to the saturated compounds.[9] This led to our examination of the aromatic ketal **34** as shown in **Scheme 18**. Ketal **34** was smoothly converted to the 1,3-cyclopentanedione **35** in a synthetically creditable yield of 77%.

It is likely in the cases of α,β-unsaturated compounds that polymerization is



34 35

Scheme 18

responsible for poor yields. Obviously, this is not the case with acetophenone as it is not likely to polymerize, thus eliminating an alternate reaction pathway.

III. CONCLUSIONS

From these results, it is possible to draw a few generalizations. The first of these is that increasing the steric bulk of the glycol moiety of the ketal retards conversion of the ketal to the dione. The implication of this is clear: in cases in which a molecule contains two or more ketone functions one may selectively ketalize one site with a very bulky glycol. That particular reaction center will not be converted as readily to a 1,3-cyclopentanedione, and it can then be deprotected for other synthetic transformations. Another conclusion that we can draw is that the presence of an α-substituent will reduce the yield of product, and, in the case of some acyclic substrates, none of the diketone can be isolated. In the same cases where we have α-substituents on acyclic molecules, the incorporation of a bulky glycol significantly impedes the degradation of the

1,3-cyclopentanedione products by subsequent attack by the liberated glycol to give the keto-ester. Thus, we can conclude that the choice of the glycol can offer choices in terms of product distributions. The very feature of steric bulk that lowers product yields in "unsubstituted" ketals can actually serve to bolster isolable yields of 1,3-cyclopentanedione products when used in cases of α-substituted acyclic ketals. This perhaps leads to the broad lesson of this study: this reaction is very sensitive to the steric environment. Thus, any synthesis employing this methodology will have to take this factor into account as it can provide substantial barriers to synthetic utility. However, this information also permits one to incorporate a high degree of selectivity in a synthesis, which can manifest itself both in terms of shorter synthetic schemes and in the degree of elegance of the design. Finally, we can conclude that the failure of the conjugated ketones/ketals to give acceptable yields is not due to the unsaturation itself, i.e. possible stabilization of carbocations, because acetophenone behaves normally. One might predict that in substrates that may be unsaturated but not enolizable that the reaction will proceed normally, also.

IV. EXPERIMENTAL SECTION

General Procedures

Ketals were obtained by the acid-catalyzed action of a large excess of 1,2-ethanediol in benzene with azeotropic removal of water. Reagent **1** was prepared by the procedure of Bloomfield and Nelke.[2]

All bis-acylation reactions were carried out under an inert atmosphere of nitrogen using dichloromethane distilled from calcium hydride as the solvent. Flash column chromatography ("chromatography") employed 230-400 mesh silica gel with hexane and an increasing proportion of ethyl acetate as eluent. The ratios of ethyl acetate/hexane are reported below. Nuclear magnetic resonance (nmr) spectra were recorded on a General Electric GE 300-NB (300 MHz for ^1H) spectrometer. The ^1H nmr spectra were acquired in solutions of deuteriochloroform ($CDCl_3$). Coupling constants (*J*) are reported in Hz. The ^{13}C nmr spectra (75 MHz) were also acquired in $CDCl_3$, and chemical shifts are relative to the solvent (δ 77.0). ^{13}C nmr shifts are sometimes followed in parentheses by the number of attached protons on that carbon, which were derived from an attached proton test (APT) and/or heteronuclear correlation (HET-CORR) spectra. Assignments quoted for the ^1H and ^{13}C nmr spectra is given when these are reasonably reliable and consistent with the correlation spectra. Whenever possible, assignments have been corroborated by the use of

ChemWindows C-13 NMR Module version 1.2 (Softshell) and *g*NMR for Windows version 3.6 (Cherwell Scientific). Assignment of ^{1}H and ^{13}C spectra are according to an arbitrary numerical scheme chosen for ease of identification and are indicated on the compound structure in the Appendix of nmr spectra. Low and high resolution mass spectral (MS) data were obtained from a V.G. Micromass 7070HS instrument using electron ionization at 70 eV. Infrared (ir) spectra were acquired as thin films using a Mattson Polaris FT-IR instrument, and intensities are noted as (s), (m), (w), (br) for strong, medium, weak, and broad, respectively. A Hewlett-Packard model 5890 gas chromatograph, equipped with a 12.5 m fused-silica capillary column with crosslinked dimethylsilicone as the liquid phase, coupled to a model 5970 mass selective detector was used for gas chromatography-mass spectrometric (GCMS) analyses. Melting points (mp) were obtained on a Fisher-Johns instrument and are uncorrected.

General Reaction Procedure. To a cooled solution (-78 °C) of a ketal and $BF_3.Et_2O$ (15 equiv.) in dichloromethane (20 mL) was added dropwise a solution of **1** (3 equiv.) in dichloromethane (10 mL). The reaction mixture was stirred overnight during which time the temperature was allowed to rise to room temperature (rt). The reaction mixture was poured into ice-water, and the organic layer was washed successively with water (x2), with a saturated

aqueous solution of $NaHCO_3$, and then with a saturated NaCl solution (x2). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. This is hereafter referred to as 'standard work-up'. Flash chromatography afforded the 1,3-cyclopentanediones. Standard visualization methods of tlc plates proved difficult or ineffective in locating the 1,3-cyclopentanediones. In some cases, the 1,3-cyclopentanediones were found using GCMS analysis.

Spiro[4.5]decane-1,4-dione (16)

To a stirred solution of ketal **15** (0.26 g, 2.0 mmol) and $BF_3.Et_2O$ (3.7 mL, 30 mmol) in CH_2Cl_2 (20 mL) at -78 °C was added a solution of **1** (2.0 mL, 6.0 mmol) in CH_2Cl_2 (8.0 mL). The reaction mixture was allowed to warm to rt overnight and standard work-up led, after chromatography (10/90), to spiro[4.5]decane-1,4-dione **16** (183 mg, 72%) as a solid: mp 60-61 °C (lit.[12] mp 61-62 °C); ir ν_{max}: 1755 (w) and 1720 cm^{-1}; ^1H nmr δ: 1.4-1.7 (10H, br m, C-6 H_2, C-7 H_2, C-8 H_2, C-9 H_2, C-10 H_2), 2.68 (4H, s, C-2 H_2, C-3 H_2); ^{13}C nmr δ: 215.8 (C-1, C-4), 55.9 (C-5), 34.3 (C-2, C-3), 29.2 (C-8), 24.9 (C-6, C-10), 20.4 (C-7, C-9); MS: 166 (100, M^+), 137 (25), 124 (32), 112 (61), 111 (46), 85 (46), 81 (37), 67 (74), 56 (44). Exact mass calculated for $C_{10}H_{14}O_2$: 166.0993; found: 166.0985.

2-(1-Methylpropyl)-2-pentylcyclopentane-1,3-dione (18) and 2-Hydroxyethyl 6-methyl-4-oxo-5-pentyloctanoate (19)

To a stirred solution of ketal **17** (0.22 mg, 1.1 mmol) and $BF_3.Et_2O$ (2.0 mL, 16 mmol) in CH_2Cl_2 (20 mL) at -78 °C was added a solution of **1** (0.88 mL, 3.3 mmol) in CH_2Cl_2 (8.0 mL). The reaction mixture was allowed to warm to rt overnight and standard work-up led, after chromatography (15/85), to 2-(1-methylpropyl)-2-pentylcyclopentane-1,3-dione **18** (0.07 g, 28%) as a very pale yellow liquid, and, in a later fraction collected by passing pure ethyl acetate through the column, 2-hydroxyethyl 6-methyl-4-oxo-5-pentyloctanoate **19** (46 mg, 15%) as an oil. For **18**: ir ν_{max}: 1719 cm^{-1}; ^1H nmr δ: 2.66 (4H, nar m, C-4 H_2, C-5 H_2), 1.80-1.61 (3H, m), 1.45 (1H, m, C-6 H_1), 1.31-0.95 (7H, m), 0.92 (3H, d, J = 6.9 Hz, C-14 H_3), 0.85 (3H, t, J = 7.2 Hz, C-13 H_3 or 3H, t, J = 7.0 Hz, C-6 H_3), 0.83 (3H, t, J = 7.0 Hz, C-6 H_3 or 3H, t, J = 7.2 Hz, C-13 H_3); ^{13}C nmr δ: 218.5 (C-1 or C-3), 218.1 (C-1 or C-3), 64.1 (C-2), 41.0 (C-11), 36.9 (C-7 or C-8), 36.8 (C-7 or C-8), 32.9 (C-10 or C-12), 32.2 (C-10 or C-12), 24.4 (C-4, C-5), 22.2 (C-9), 13.9 (C-14), 13.2 (C-13), 12.3 (C-6); MS: no M^+, 195 (34), 169 (53), 168 (25), 154 (33), 139 (54), 126 (28), 125 (56), 112 (100), 69 (27), 55 (65), 41 (80). Exact mass calculated for $C_{12}H_{19}O_2$ (M^+-C_2H_5): 195.1384; found: 195.1380.

For **19**: ir ν_{max}: 3457 (br), 1736 (s), 1709 (s) cm^{-1}; ^1H nmr δ: 4.26 (2H, m, C-15 H_2), 3.85 (2H, nar m, C-16 H_2), 2.96-2.38 (6H, m), 1.76-1.05 (11H, m), 0.96-0.84 (9H, nar m).

2-Hydroxyethyl 5,6-dimethyl-4-oxoheptanoate (22)

To a stirred solution of ketal **20** (0.26 g, 2.0 mmol) and $BF_3.Et_2O$ (3.7 mL, 30 mmol) in CH_2Cl_2 (20 mL) at -78 °C was added a solution of **1** (1.6 mL, 6.0 mmol) in CH_2Cl_2 (8.0 mL). The reaction mixture was allowed to warm to rt overnight. Standard work-up led, after chromatography (5/95), to 2-hydroxyethyl 5,6-dimethyl-4-oxoheptanoate **22** (59 mg, 14%) as a pale yellow liquid: ir ν_{max}: 3459 (br), 1737, 1711 cm^{-1}; ^1H nmr δ: 4.23 (2H, nar m, C-10 H_2), 3.82 (2H, nar m, C-11 H_2), , 2.80 (2H, t, J = 6.7 Hz, C-2 H_2), 2.6 (1H, very br, OH), 2.60 (2H, t, J = 6.7 Hz, C-3 H_2), 2.36 (1H, quintet, J = 7.0 Hz, C-5 H_1), 1.97 (1H, octet, J = 6.8 Hz, C-6 H_1), 1.04 (3H, d, J = 7.0 Hz, C-9 H_3), 0.91 (3H, d, J = 6.7 Hz, C-7 or C-8 H_3), 0.87 (3H, d, J = 6.8 Hz, C-7 or C-8 H_3); ^{13}C nmr δ: 213.3 (C-4), 173.1 (C-1), 66.1 (C-10), 60.9 (C-11), 52.7 (C-5), 36.4 (C-3), 30.2 (C-2), 27.8 (C-6), 21.2 (C-7 or C-8), 18.7 (C-7 or C-8), 12.8 (C-9); MS: no M^+, 199 (2), 186 (2), 174 (7), 155 (22), 145 (24), 112 (21), 101 (100), 85 (24), 71 (73), 45 (29), 43 (70). Exact mass calculated for $C_8H_{14}O_4$ (M^+-C_3H_6 via McLafferty): 174.0892; found: 174.0890.

2-Methyl-2-(methylethyl)cyclopentane-1,3-dione (21)

To a stirred solution of ketal **23** (390 mg, 7.46 mmol) and $BF_3.Et_2O$ (4.5 mL, 37 mmol) in CH_2Cl_2 (20 mL) at -78 °C was added a solution of **1** (2.0 mL, 7.4 mmol) and CH_2Cl_2 (8.0 mL). The reaction mixture was stirred for 27 h during which time the mixture warmed to rt. Standard work-up gave a mixture of the spirodiketone and starting material. Therefore, $BF_3.Et_2O$ (4.5 mL, 37 mmol) and **1** (2.0 mL, 7.4 mmol) were added again to a CH_2Cl_2 (20 mL) solution of the mixture. After stirring for 19 h, standard work-up was executed on the reaction mixture, afforded 213 mg (56%) of a product that ^1H nmr revealed was very predominantly **21**. Attempts to purify this mixture by chromatography led largely to its destruction; however, a small amount (50 mg) of homogenous **21** was recovered: ir ν_{max}: 1759 (m), 1721 (s) cm^{-1}; ^1H nmr δ: 2.74 (4H, symmetrical m, C-4 H_2, C-5 H_2), 2.01 (1H, septet, J = 6.9 Hz, C-7 H_1), 1.06 (3H, s, C-6 H_3), 0.93 (6H, d, J = 6.9 Hz, C-8 H_3, C-9 H_3); ^{13}C nmr δ: 216.8 (C-1, C-3), 59.5 (C-2), 35.6 (C-4, C-5), 33.8 (C-6),17.3 (C-7, C-8), 15.3 (C-9); MS: 154 (28, M$^+$), 139 (100), 112 (24), 111 (32), 83 (25), 56 (18), 55 (27), 43 (12), 41 (20). Exact mass calculated for $C_9H_{14}O_2$: 154.0993; found: 154.0989.

6-Methylspiro[4.4]nonane-1,4-dione (25)

To a stirred solution of ketal **24** (0.35 g, 2.5 mmol) and $BF_3.Et_2O$ (4.5 mL,

37 mmol) in CH_2Cl_2 (20 mL) at -78 °C was a added a solution of **1** (2.0 mL, 7.4 mmol) in CH_2Cl_2 (8.0 mL). The reaction mixture was allowed to warm to rt overnight and standard work-up led, after chromatography (15/85), to 6-methylspiro[4.4]nonane-1,4-dione **25** (146 mg, 36%) as a colourless liquid: ir ν_{max}: 1718 cm^{-1}; ^1H nmr δ: 2.81-2.57 (4H, br m, C-2 H_2, C-3 H_2), 2.25 (1H, br m, C-6 H_1), 1.85 (5H, br m), 1.54 (1H, br m), 0.95 (3H, d, J = 7.2 Hz, C-10 H_3); ^{13}C nmr δ: 217.3 (C-1 or C-4), 216.6 (C-1 or C-4), 66.7 (C-5), 46.9 (C-7), 36.2 (C-6), 35.8 (C-2 or C-3), 34.5 (C-2 or C-3), 33.5 (C-9), 24.6 (C-8), 15.2 (C-10); MS: 166 (64, M^+), 151 (100), 125 (15), 109 (52), 95 (41), 81 (20), 67 (41), 55 (31), 41 (30). Exact mass calculated for $C_{10}H_{14}O_2$: 166.0993; found: 166.0997.

(6*R*,9*S*)-6-Methyl-9-(methylethyl)spiro[4.5]decane-1,4-dione (28)

To a stirred solution of ketal **26** (500 mg, 2.52 mmol) and $BF_3.Et_2O$ (4.6 mL, 38 mmol) in CH_2Cl_2 (20 mL) at -78 °C was added a solution of **1** (1.6 mL, 6.3 mmol) in CH_2Cl_2 (8.0 mL). The reaction mixture was allowed to warm to rt overnight. Standard work-up led, after chromatography (7/93), to 6-methyl-9-(methylethyl)spiro[4.5]decane-1,4-dione **28** as a yellow oil (204 mg, 36%): ir ν_{max}: 1717 cm^{-1}; ^1H nmr δ: 2.92-2.49 (4H, complex m, C-2 H_2, C-3 H_2), 1.81 (3H, m), 1.57 (3H, m), 1.39 (1H, m, C-6 H_1), 1.28-1.00 (2H, m, C-9 H_1, C-12 H_1), 0.83 (3H, d, J = 6.7 Hz, C-13 H_3 or C-14 H_3), 0.82 (3H, d, J = 6.7 Hz, C-13 H_3 or C-14

H_3), 0.75 (3H, d, J = 6.0 Hz, C-11 H_3); ^{13}C nmr δ: 217.8 (C-1 or C-4), 216.7 (C-1 or C-4), 60.5 (C-5), 36.5 (C-9), 36.0 (C-12), 35.7 (C-8), 35.4 (C-2, C-3), 32.2 (C-6), 29.3 (C-7), 28.5 (C-10), 19.6 (C-13 or C-14), 19.2 (C-13 or C-14), 17.7 (C-11); MS: 222 (3, M^+), 179 (1), 138 (10), 125 (15), 106 (48), 105 (23), 91 (100), 86 (25), 84 (40), 43 (31). Exact mass calculated for $C_{14}H_{22}O_2$: 222.1619, found: 222.1614.

For the ketal **(6*R*,9*S*)-6-Methyl-9-(methylethyl)-1,4-dioxaspiro[4.5]decane (26)**: ^1H nmr δ: 3.98-3.91 (4H, complex m, C-11 H_2, C-12 H_2), 1.79-1.73 (1H, m), 1.70-1.58 (3H, complex m), 1.50-1.30 (3H, complex m), 1.14-0.96 (2H, complex m), 0.92-0.84 (9H, complex m, C-8 H_3, C-9 H_3, C-10 H_3); ^{13}C nmr δ: 111.3 (C-1), 65.3 (C-11 or C-12), 64.8 (C-11 or C-12), 41.6 (C-2), 39.9 (C-6), 39.0 (C-4), 32.3 (C-7), 32.0 (C-5), 28.5 (C-3), 19.7 (C-8 or C-9), 19.5 (C-8 or C-9), 13.9 (C-10).

2-Methyl-2-phenyl-1,3-cyclopentanedione (35)

To a stirred solution of ketal **34** (232 mg, 1.43 mmol) and $BF_3.Et_2O$ (2.6 mL, 21 mmol) in CH_2Cl_2 (30 mL) at -78 °C was added a solution of **1** (1.1 mL, 4.3 mmol) in CH_2Cl_2 (6.0 mL). The reaction mixture warmed to rt overnight and then it was poured into water. The organic layer was washed with water (x2) and saturated NaCl solution, and the organic layer was dried over anhydrous

magnesium sulfate, filtered, and the solvent was removed *in vacuo*. Chromatography (15/85) provided 2-methyl-2-phenyl-1,3-cyclopentanedione **35** as a yellow oil (206 mg, 77%): ir ν_{max}: 1765 (m), 1724 cm^{-1}; ^1H nmr δ: 7.38-7.25 (3H, m, C-8 H_1, C-9 H_1, C-10 H_1,), 7.22-7.19 (2H, nar m, C-7 H_1, C-11 H_1), 2.82 (4H, broad symmetrical m, C-4 H_2, C-5 H_2), 1.43 (3H, s, C-12 H_3); ^{13}C nmr δ: 213.0 (C-1, C-3), 136.8 (C-6), 129.3 (C-8, C-10), 127.9 (C-7, C-11), 126.3 (C-9), 61.9 (C-2), 35.2 (C-4, C-5), 19.7 (C-12); MS: 188 (100, M^+), 145 (36), 132 (32), 105 (26), 104 (74), 103 (30), 78 (24), 77 (26), 51 (21). Exact mass calculated for $C_{12}H_{12}O_2$: 188.0837; found: 188.0835.

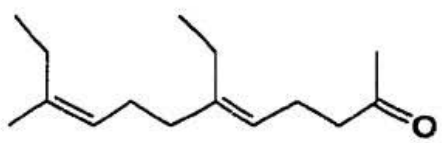
Chapter 2

Synthetic Applications

I. SECTION A: SYNTHETIC APPROACHES TO THE PRECURSORS OF THE JUVENILE HORMONES OF *CECROPIA*

i. INTRODUCTION

From the examples of synthetic applications described in Chapter 1, it is clear that the bis-acylation reaction is potentially useful in the construction of various natural products. We set out to synthesize the precursors of one such natural product, namely the juvenile hormone **36** of the moth *Cecropia*, as a further example of the synthetic utility of this type of reaction and to explore a

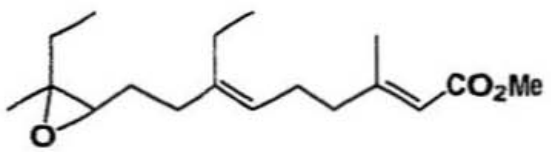


36

novel route to build this system. Our approach entailed the construction of particularly substituted 1,3-cyclopentanediones that could undergo controlled Grob-type fragmentations to afford carbon-carbon double bonds in the correct positions and in the correct geometrical isomers. This would be a significant challenge given earlier work in our group that indicated that these types of 1,3-cyclopentanedione systems are extremely labile. In addition, we had to ensure

that the construction of the 1,3-cyclopentanediones was selective enough so as to prevent too much diastereomeric contamination in the products, thereby ensuring that our approach would have significant advantages over an approach incorporating Wittig chemistry.

A number of groups have worked toward these types of natural products. Mori and co-workers[13] in 1968 employed a linear sequence of attachments to obtain methyl 10-epoxy-7-ethyl-3,11-dimethyl-2,6-tridecadienoate (**37**) in a 15%



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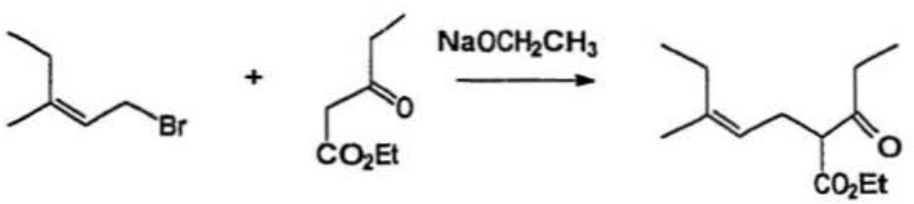
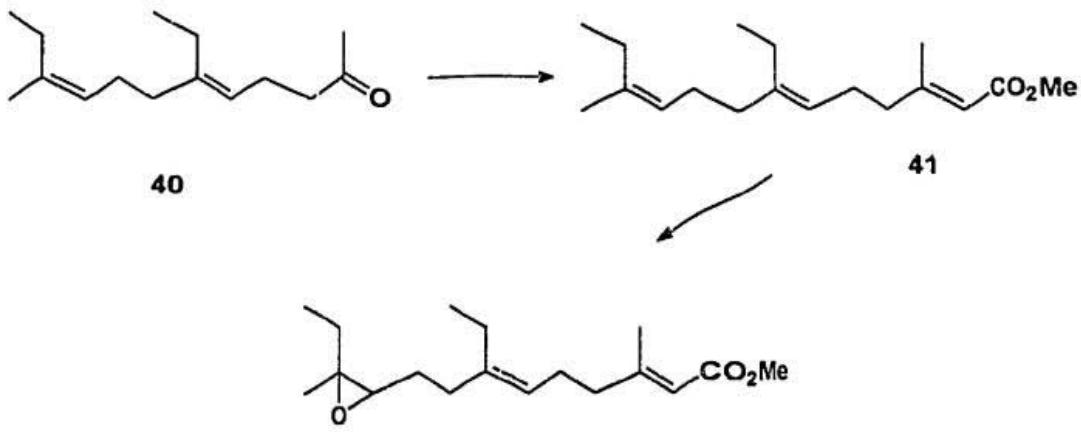
overall yield. Their synthesis started with the addition of the keto-ester **39** to the bromo-alkene **38** in the presence of base (**Scheme 19**). Further transformations



38 **39**

Scheme 19

afforded an intermediate molecule **40**, which underwent a Wittig reaction to give **41** (**Scheme 20**). This material was then epoxidized with peroxybenzoic acid to

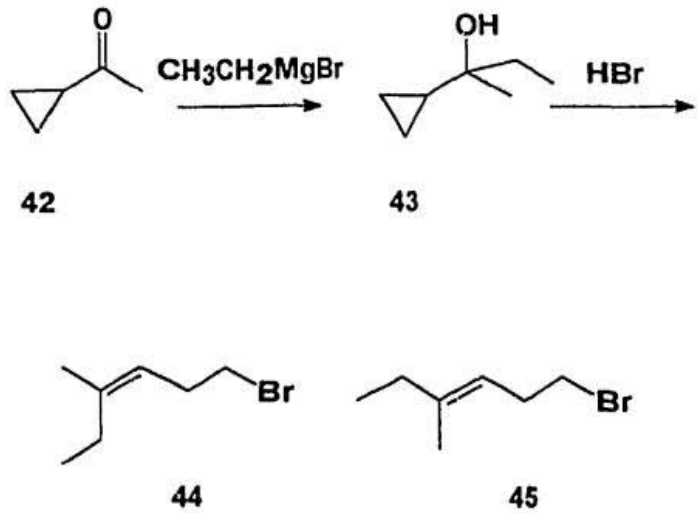


40 41 37

Scheme 20

give a mixture of epoxidized material that included **37**. A significant problem with this synthesis was the lack of control of the geometry of the double bonds. Separation of the geometrical isomers was difficult, which reduced the overall effectiveness of the synthesis.

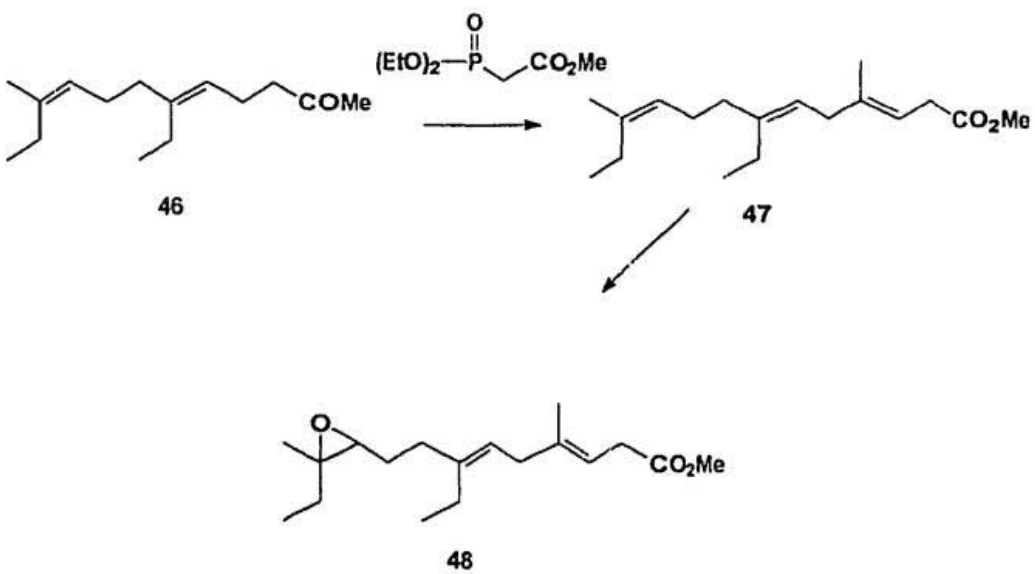
Hanson and Cochrane[14] in 1971 reported two alternative approaches to the synthesis of these hormones. One approach incorporated flexibility with respect to chain length whereas the other provided a higher degree of stereochemical control. The first route made use of the Grignard addition of ethylmagnesium bromide to the ketone **42**. The tertiary alcohol **43** that resulted underwent rearrangement with aqueous HBr to yield a mixture of alkenes **44** and **45** in a 1:3 ratio, as seen in **Scheme 21**. After conversion of **44** and **45** into Grignard reagents and addition to another equivalent of **42** with ring-opening



42 43 44 45

Scheme 21

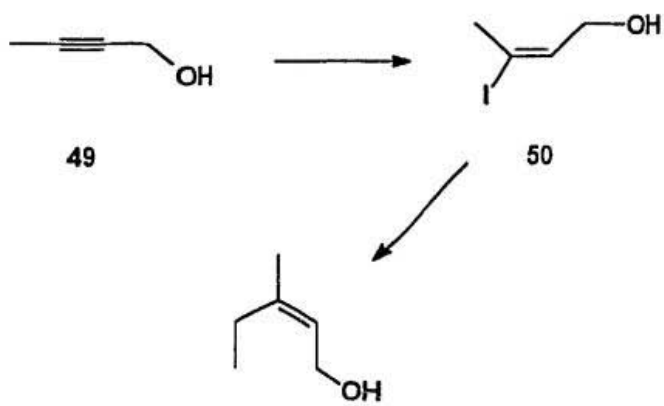
under acid catalysis, the stage was set for a Wittig reaction between diethyl(methoxycabonylmethyl)phosphonate and the ketone **46** to afford **47**. This material was then epoxidized to give the hormone **48**, as seen in **Scheme 22**. In the second approach, care was taken to control the geometry of the first



46 47 48

Scheme 22

double bond. But-2-yn-1-ol **49** was converted to 3-iodobut-2-en-1-ol **50** by treatment with lithium aluminum hydride, sodium methoxide, and iodine. Alkylation of **50** with diethyl cuprate afforded (*Z*)-3-methylpent-2-en-1-ol **51**, but in only 15% yield from **49** (**Scheme 23**). Although this was a stereospecific

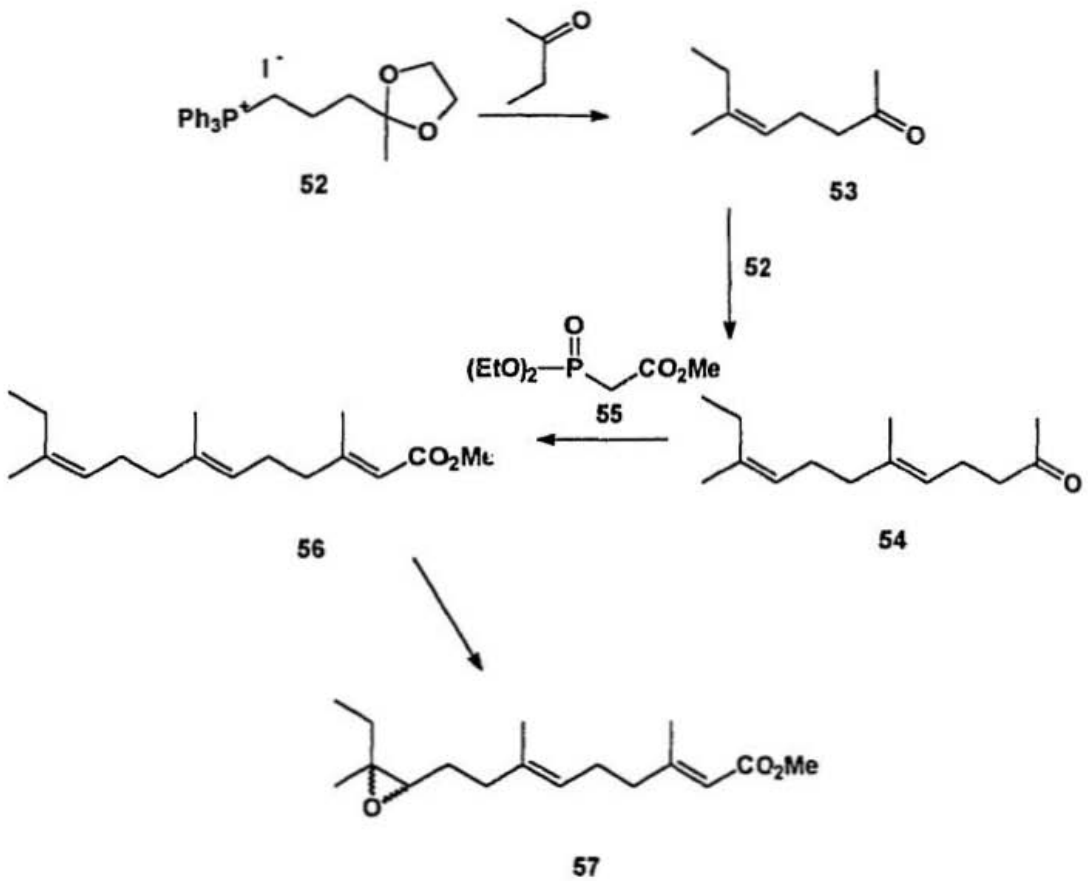


49 **50** **51**

Scheme 23

synthesis, the yield of the alcohol was too low to carry through the remainder of the hormone synthesis. Consequently, a mixture of alcohols was carried through a series of steps which, like the first route, also involved a Wittig coupling.

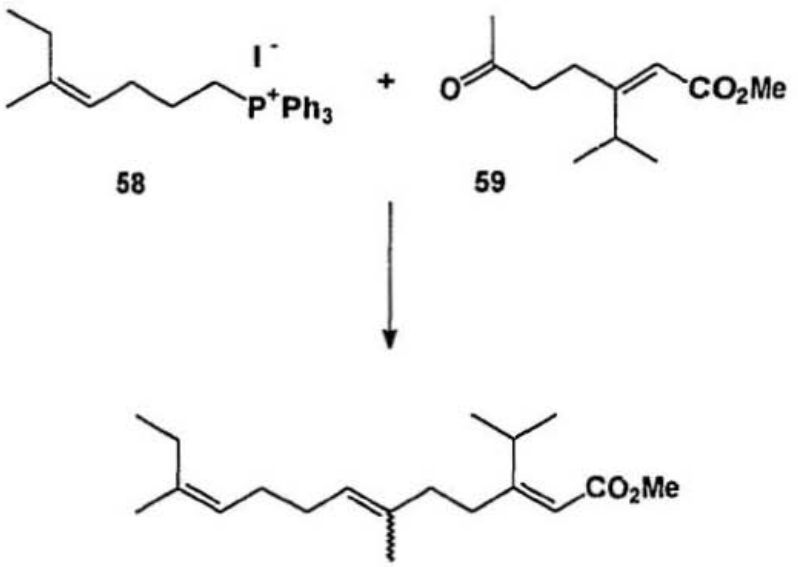
In 1970 Findlay and co-workers[15] reported a linear sequence that also utilized Wittig additions in the extension of the chain. In this case, a triple Wittig coupling sequence was used, as shown in **Scheme 24**. First, addition of the phosphoketal **52** to 2-butanone gave a mixture of isomers that included **53**. This, in turn, was coupled with another equivalent of **52** to give **54** after



Scheme 24

deprotection. Addition of sodium diethyl(methoxycarbonylmethyl)phosphonate **55** to ketone **54** yielded the ester **56** which, after epoxidation, produced the hormone **57** as a racemic mixture, in 14% overall yield.

Kutney *et al.*[16] employed a similar Wittig coupling between **58** and **59** to afford **60** (**Scheme 25**) in 72% yield. Unfortunately, the yield for the entire synthesis was only 0.07%.

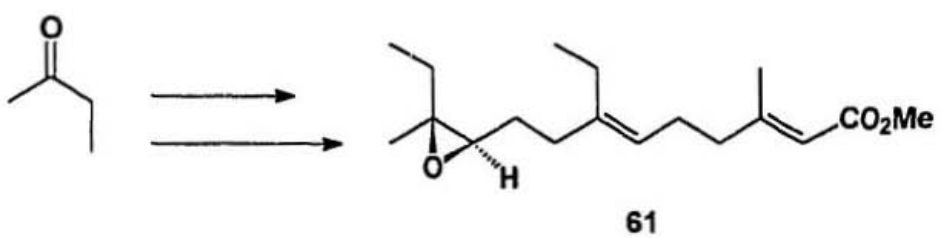


58 **59**

60

Scheme 25

In 1967, Trost and co-workers[17] reported another linear sequence involving multiple Wittig reactions to produce **61** starting with 2-butanone in a

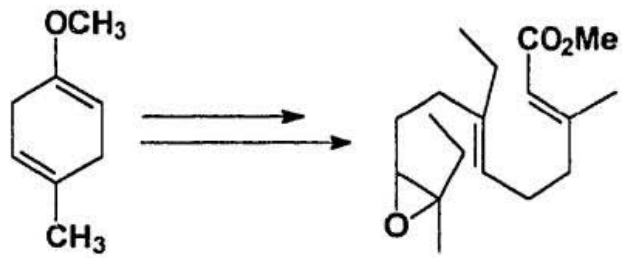


61

Scheme 26

racemic synthesis, which is very similar in strategy to that of Findlay (**Scheme 26**).

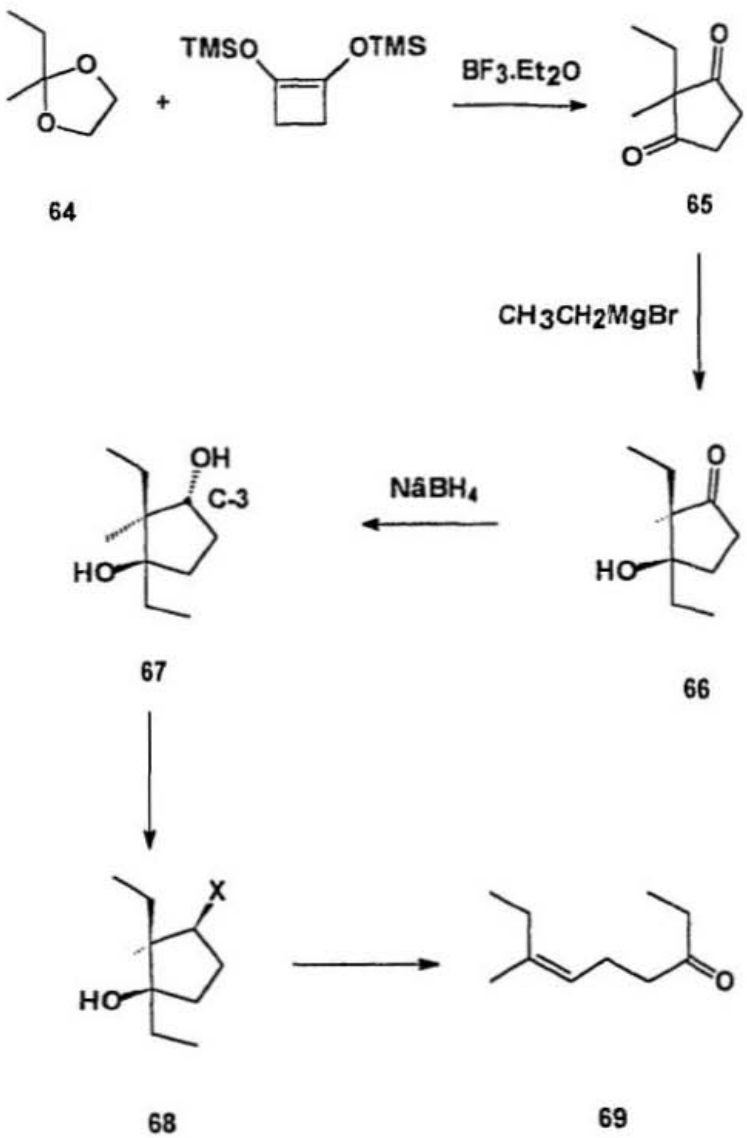
Finally, Corey *et al.*[18] took a departure from the use of Wittig coupling when they synthesized **63** from **62**. The synthesis consisted of a series of functional group transformations and alkylations to afford **63** in 8% overall yield (**Scheme 27**).



62 **63**

Scheme 27

We chose to pursue a linear approach to **37**. However, we would attempt to control the geometry of the carbon-carbon double bonds by setting up the relative stereochemistry in the precursors in such a way as to force elimination to one geometrical isomer. In accord with our experience in the formation of 1,3-cyclopentanediones,[9] our route for the construction of the precursors to **37** (**Scheme 28**) would begin with the formation of the 1,3-cyclopentanedione **65** from the ketal **64**. Grignard addition to **65** should afford **66**, and this could be



Scheme 28

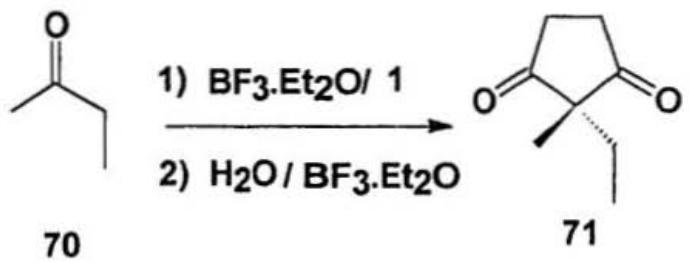
followed by reduction of the remaining ketone to yield the trans-diol **67**. Then, conversion of the secondary alcohol to a leaving group, with stereochemical inversion, would afford **68**. This precursor could then open via a Grob-type[19] fragmentation to generate **69** selectively. Repetition of these steps would allow

for the construction of the remaining links in the carbon chain of **37**. One important change to this proposal came out of work also carried out in our labs by Dr. Tracy Jenkins[10] who developed conditions that permitted the generation of 1,3-cyclopentanediones *directly* from ketones. Note that the direct conversion of ketones to 1,3-cyclopentanediones reduces the number of steps in this synthetic approach.

ii. RESULTS AND DISCUSSION

Approach 1

Direct conversion of 2-butanone **70** to the 1,3-cyclopentanedione **71** proceeded smoothly, as seen in **Scheme 29**, with a very high degree of reproducibility of yields, typically 75-80% on a variety of scales.



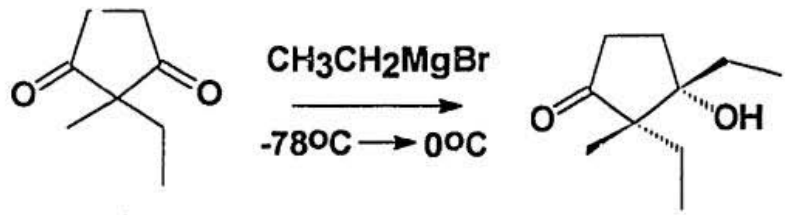
70 **71**

Scheme 29

Column chromatography was not necessary to obtain **71** in a homogeneous form. Instead, simple filtration of the black crude product through

a plug of activated charcoal and Florisil afforded a pale yellow oil that was sufficiently pure to use in the subsequent step.

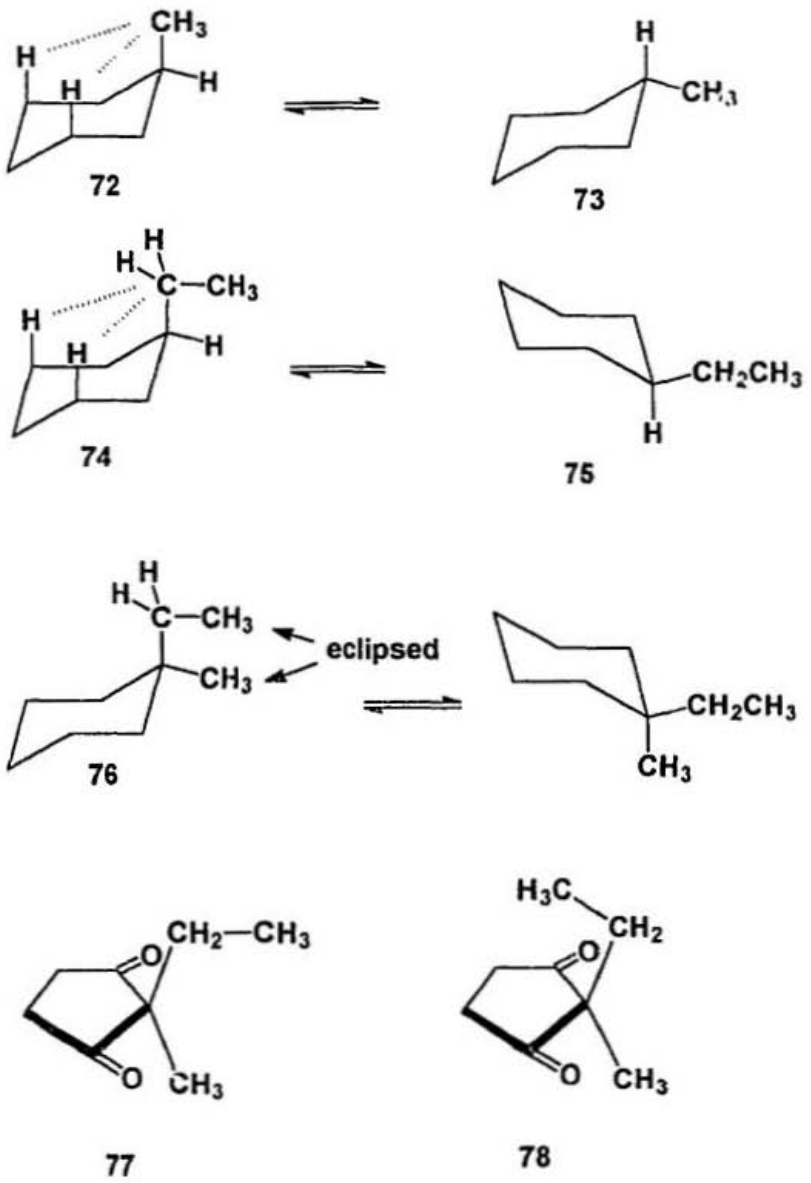
The next step was to introduce the ethyl group (**Scheme 30**). In order to



71 **79**

Scheme 30

achieve maximum facial selectivity with complete reaction in the Grignard addition of ethylmagnesium bromide, the reaction was carried out at low temperature over an extended period. Although two Grignard additions were possible because of the two ketone functions in the substrate, we felt that reaction of one ketone would reduce the solubility of this initial, desired product, i.e., the product of initial addition would be much less available for a second addition. This was indeed the case, and there was a remarkable degree of facial selectivity found in the addition. The ^{13}C nmr spectrum of the crude product mixture indicated that there was a significant factor favouring addition to one face of the ketone, which later proved to be syn to the methyl group. This was interesting in that conventional measures of "size", such as equatorial/axial ratios on cyclohexane, suggest that there is little difference. In **Scheme 31**, one can see that in **72**, there are significant 1,3-diaxial interactions whereas in



Scheme 31

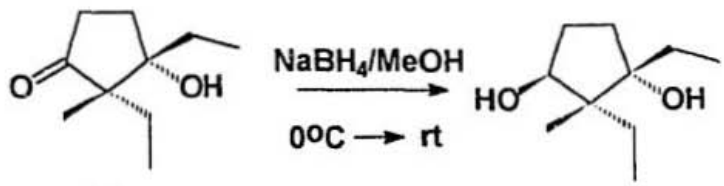
conformer **73** the methyl is in the equatorial position and thereby eliminates repulsive interactions. The same argument is made with respect to **74** and **75** where the ethyl group replaces the methyl group. Once again, in this case, the

A-values for methyl and ethyl groups are nearly identical.[20] Thus, one would not expect to observe any degree of selectivity where these two groups are involved. If we look at **76**, one can see serious steric interactions no matter which conformer the molecule is in. Making the extension to **77** and **78**, one might think that there are steric interactions that will make an arrangement similar to **76** the norm. In the case of the two conformers **77** and **78** there is an eclipsing interaction between the methyl of the ethyl group and the geminal methyl group. There is a dramatic difference in that this molecule has steric interactions only in the case of **77**, and that a simple rotation of a bond allows the methyl group of the ethyl group to sit over the face of the cyclopentane ring in the case of **78**. This would eliminate the eclipsing steric interactions which are encountered in conformer **77**. Since the case of **78** is now a viable situation, one can see how this methyl group now blocks addition to the face of the ring *syn* to the ethyl group and thereby favours addition to the face of the ring *syn* to the methyl and therefore *anti* to the ethyl groups, respectively.

A problem encountered at this stage was one that would plague this approach all the way through, namely the purification of the material by chromatography. Crude yields and spectra appeared good. However, substantial amounts of material were lost during chromatography. The polarity of an alcohol function may have permitted significant amounts of material to

adhere irreversibly to the column, or the material was simply destroyed on silica gel. Thus, **79** was obtained from **71** in only 48% yield after chromatography.

The next stage of the synthesis required the reduction of the second ketone (**Scheme 32**). This was accomplished with sodium borohydride at low



79 **80**

Scheme 32

temperature, again to attain a maximum level of facial selectivity. On the surface when one considers steric hindrance, the two faces of the ring are likely to be very similar. However, the borohydride was expected first to coordinate with the alcohol located at C-3, and then syn-addition of the hydride would produce the product with the two alcohols in a *trans* arrangement, **Figure 4**. Thus the

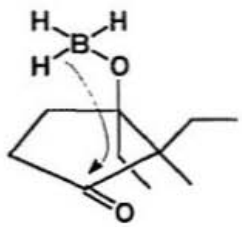


Figure 4: Coordinated Borohydride Addition to the Ketone

reduction of the ketone, **79** afforded the diol, **80** in only 15% yield after column chromatography, but as before, it was the purification that led to very major losses of material. Both ^{1}H and ^{13}C nmr of the crude compounds indicated virtually quantitative conversion to **80**. No water was added to quench this

reaction as the methanol that was used as eluent usually contained sufficient water to destroy any excess borohydride reagent as well as the complexed product. The reasoning behind this was very simple: we felt that we would lose significant amounts of material if extraction from aqueous solution was required. In addition, given that we were losing large amounts of materials during chromatography, we were unwilling to lose any more material by adding an aqueous extraction step to the purification.

An X-ray crystal structure of compound **80** confirmed the *trans* relationship of the alcohols (**Figure 5**).

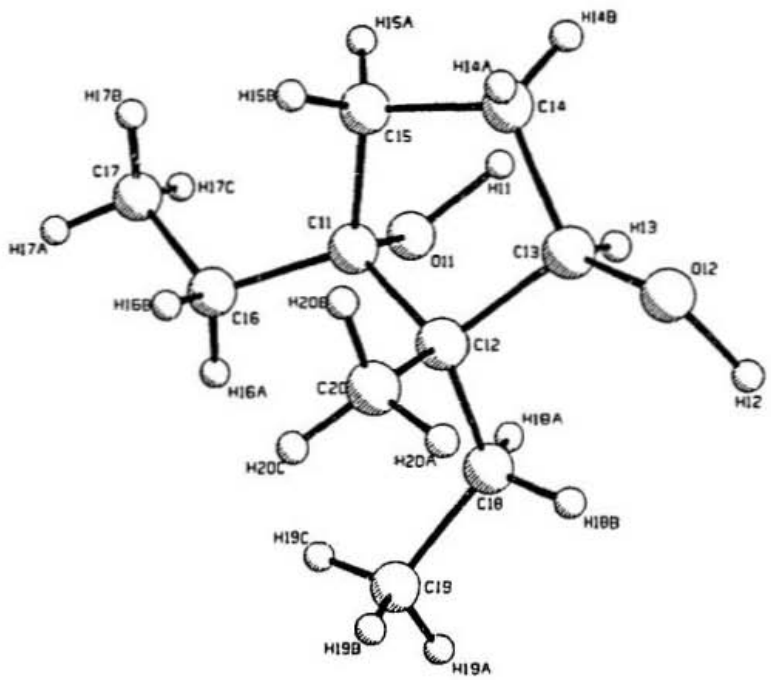
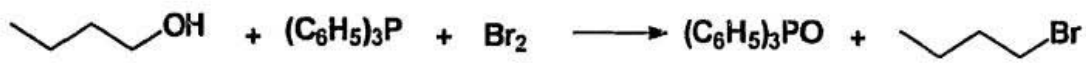


Figure 5: X-ray Crystal Structure of 80

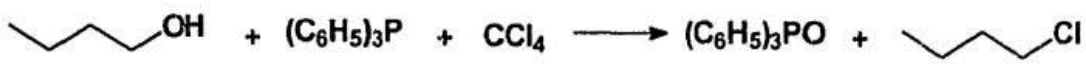
In compound **80**, the two alcohol moieties are *trans* to each other, but for the Grob fragmentation, the leaving group must be cis to the hydroxyl which will become the ketone. Thus, the secondary alcohol must be converted to a good leaving group and the stereogenic center must be inverted. In an effort to evaluate methods for accomplishing the task of converting the secondary alcohol of **80** to a halide, a number of the most promising mild techniques were tried, but none met with any acceptable degree of success. These included the conversion of the 1-butanol **81** to the 1-bromobutane **82** into the presence of triphenylphosphine and bromine by Wiley and co-workers[21] as shown in **Scheme 33**. Downie and co-workers[22] also made use of mild conversion



81 **82**

Scheme 33

conditions to convert **81** to 1-chlorobutane **83** with triphenylphosphine and carbon tetrachloride as seen in **Scheme 34**. Olah and group[23] published a



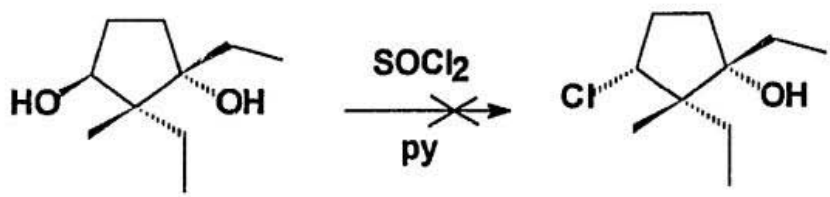
81 **83**

Scheme 34

84 85

Scheme 35

method of converting alcohols to alkylbromides with trimethylsilyl chloride and lithium bromide, **Scheme 35**. Thus, it was decided to employ more vigorous conditions, as outlined in **Scheme 36**. However, an intractable black



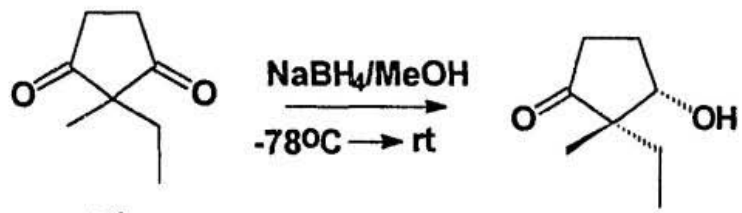
80 86

Scheme 36

product, composed of a very large number of compounds by tlc, was obtained from this method. These preliminary attempts underscore the fact that these acyclic 1,3-cyclopentanedione systems are very labile. Despite early successes with facial selectivity and yields of materials, it was decided to approach the Grob fragmentation precursor from another direction. This decision sprang from two realities. First, the sodium borohydride reduction of the second ketone was very slow, in the order of days to complete. The second reason was the inability to convert the secondary alcohol to a halogen effectively.

Approach 2

Like Approach 1, Approach 2 also set up a precursor for a Grob fragmentation. The preliminary synthetic transformations were carried out in the following manner. First, diketone **71** was reduced with sodium borohydride to **87** in 55% yield after chromatography (**Scheme 37**). Here again the problem of

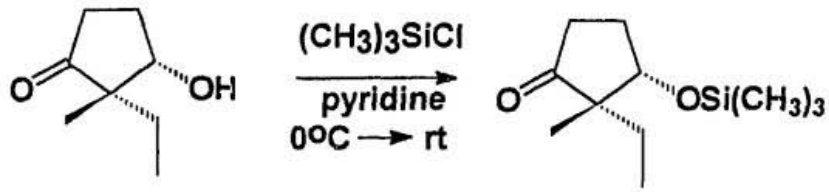


71 **87**

Scheme 37

purifying compounds that contain alcoholic sites came back to trouble us: a crude yield of 98% versus an isolated yield of 55%. As was the case in our first approach, we had to try to demonstrate a very high level of facial selectivity in a situation in which A-values suggested that facial selectivity would be very poor.[20] Again, the ^{13}C nmr spectrum of the crude product indicated that attack from one face was significantly favoured, on the order of 93:7. The same arguments that applied for selective addition of the Grignard reagent to **71** apply here as well, that is to say, that the methyl of the ethyl group will rest above the face of the ring and thereby block addition to that face of the ring. The next stage was the protection the hydroxyl group in **87** with chlorotrimethylsilane to give **88** in 51% yield (**Scheme 38**).

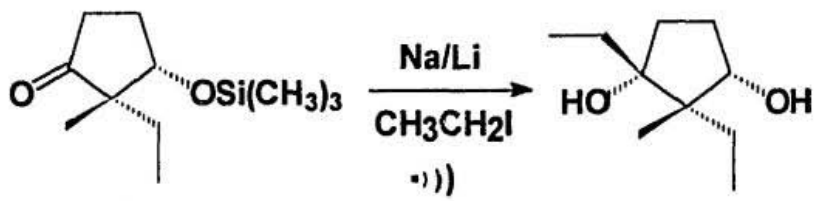
With the protected material in hand, the way was paved for an alkylation



87 88

Scheme 38

by a modified Barbier reaction on the remaining ketone. This was achieved using ultrasonic irradiation of **88** in the presence of a 90:10 lithium/sodium alloy and iodoethane, to provide **89** in an isolated yield of 37% (**Scheme 39**). This



88 89

Scheme 39

reaction generated an ethyllithium reagent. Adjusting the shape of the flask did not impact on the reproducibility of the reaction nor did changing the solvent to diethyl ether from tetrahydrofuran. In addition, an attempt at alkylation with ethylmagnesium bromide afforded only trace amounts of product. In **89** the two hydroxyls were cis as required, thus inversion of the secondary alcohol was not required. We could make this assignment of relative stereochemistry by

considering the ^{13}C nmr shifts of **79**, **80**, and **89** as in **Table 2** where γ_{gauche} interactions force the ^{13}C nmr signal further upfield as compared to shifts without these interactions. In addition, the nuclear Overhauser effect difference spectrum (NOED) of this molecule shown in **Figure 6** shows that saturation of the C-2 methyl signal afforded an enhancement of 4% in the C-3 hydrogen

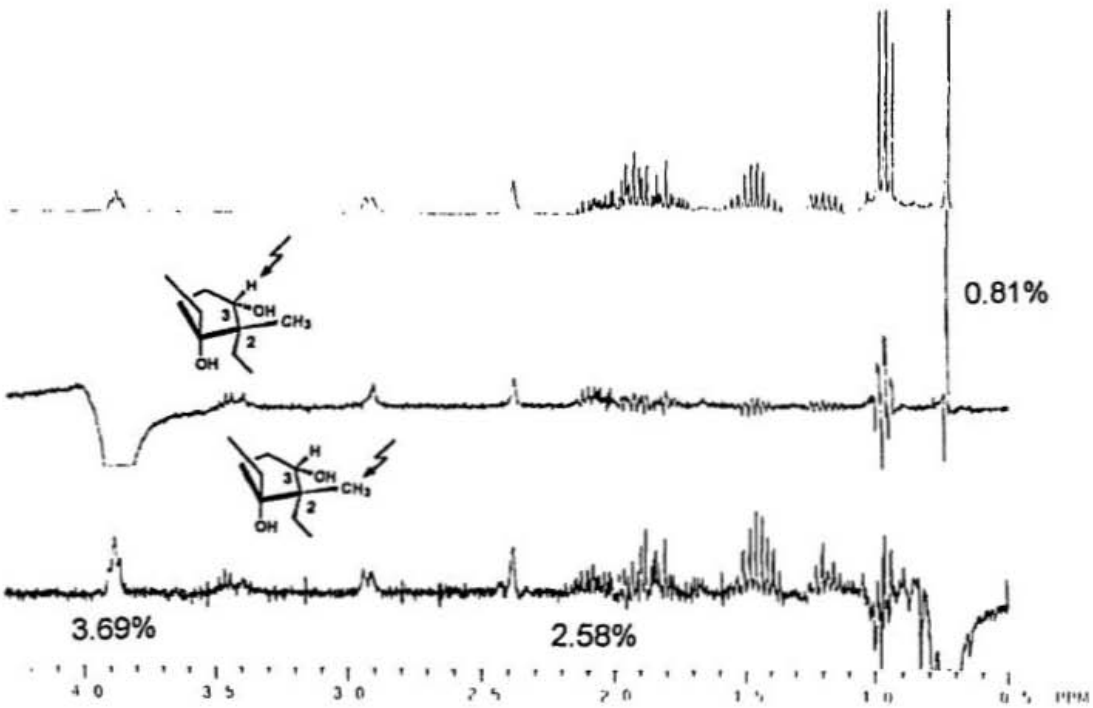


Figure 6: NOED Spectrum of 89

signal. This demonstrates that the methyl and the C-3 hydrogen are syn to one another. The NOED spectrum also shows enhancement of a proton signal at δ

2.09 that is assigned as the proton at C-5 is syn. However, a suitable leaving group would have to be attached to the secondary alcohol to facilitate the Grob fragmentation. The removal of the trimethylsilyl group during the course of the sequence or during work-up came as a bonus. Unfortunately, the alkylation step could not be carried out reproducibly under the modified Barbier conditions.

Table 2: Comparison of ^{13}C nmr Shifts of Compounds 79, 80, and 89

	Compound ^{13}C nmr Shifts		
Assignment	**79**	**80**	**89**
C-1	222.5	79.7	80.9
C-3	82.6	85.1	86.5
C-2	55.4	49.8	51.7
C-5	33.8	29.5	30.8
C-4	30.1	33.1	35.5
C-9	28.4	28.7	27.7
C-6	23.4	26.3	21.4
C-8	16.8	13.6	19.6
C-7 or C-10	8.9	9.4	9.0
C-7 or C-10	7.3	7.5	8.1

The lack of success with either approach to the fragmentation precursors precluded an evaluation of this approach to the control of geometry of the double bond. When the results of Chapter 1, particularly the difficulty associated with working with substrates that have α-alkyl substituents, are considered it is highly

probable that similar influences constrain both approaches. In Approach 1, the sodium borohydride reduction of the ketone to **80** required an inordinate amount of time. Plausibly, the need for a long reduction time arose from the steric congestion near the reaction site. Despite the relatively small size of the molecule, the key features were all contiguous. These features included one quaternary and one tertiary center, as well as the ketone/alcohol of **79** and **80**. Given that lithium aluminum hydride is a more reactive reducing agent compared to sodium borohydride, it is likely that would be less selective given the terms of the Reactivity-Selectivity Principle.[24] Thus, the reduction would likely proceed more quickly but would not have the degree of selectivity that is desired in this particular case. In addition, the difficulties found in converting secondary alcohols to halogens in the substrates that exhibited similar steric environments lent credence to this idea. Finally, the unreliability of the sono-alkylation was also likely a consequence of steric encumbrance. In this case, not only was the substrate itself sterically congested, owing to the presence of the trimethylsilyloxy group, but the alkylating agent was fairly bulky. In any case, if the problems of conversion/inversion with a halogen or adding the alkylating agent could be overcome, then the viability and value of this strategy will again become clear. Yet, despite the obvious problems with the synthetic approaches, there were valuable results gained from this exercise. First, the bis-acylation procedure worked well by producing a 1,3-cyclopentanedione product in very

reasonable yields. Experience from our labs indicated problems with low molecular weight molecules such as **71** in terms of product yields. Due to the high volatility of such small molecules, procedures to remove solvent often lead to loss of the desired product. Another significant discovery was the very high degree of facial selectivity of both Grignard additions and sodium borohydride reductions. In both approaches, there was a very high degree of selectivity for reaction onto the less sterically hindered face of the molecule. Finally, it is fairly certain that severe congestion encountered within a series of contiguously substituted centers, such as the case in these molecules, will offer potential problems to further synthetic transformations. Of course, depending upon the synthetic strategy employed, this could prove to be either a benefit or, in this case, a detriment.

iii. CONCLUSIONS

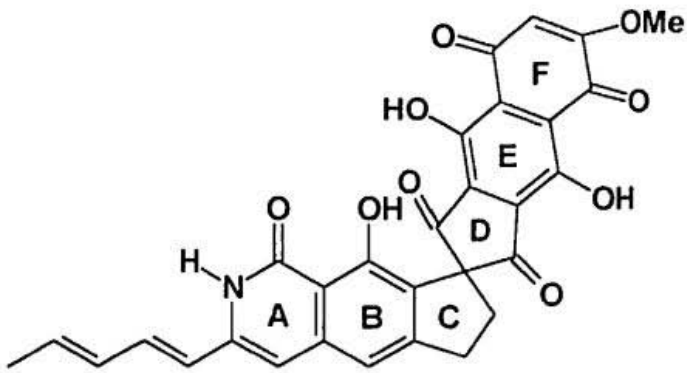
From the results of these two attempts at the synthesis of the precursors of the juvenile hormones of *Cecropia*, it is possible to draw some conclusions. First, it has been demonstrated that conformational factors can render the usual measure of steric size, i.e. A values, as far as methyl and ethyl groups are concerned, inadequate. We have exploited this effect very successfully to reduce diketones with a high degree of facial selectivity. The second conclusion we may draw is that the Grob fragmentation strategy appears to fail because of

the drastic conditions required for the generation of a suitable leaving group even more rapidly destroys the substrate.

II. SECTION B: MODEL STUDIES TOWARDS THE SYNTHESIS OF FREDERICAMYCIN A

i. INTRODUCTION

Fredericamycin A **92** is a chiral metabolite isolated[25] from *Streptomyces griseus* that exhibits significant antitumor, antifungal, and cytotoxic activity.[26] It has been the target of both total syntheses and of model studies. This

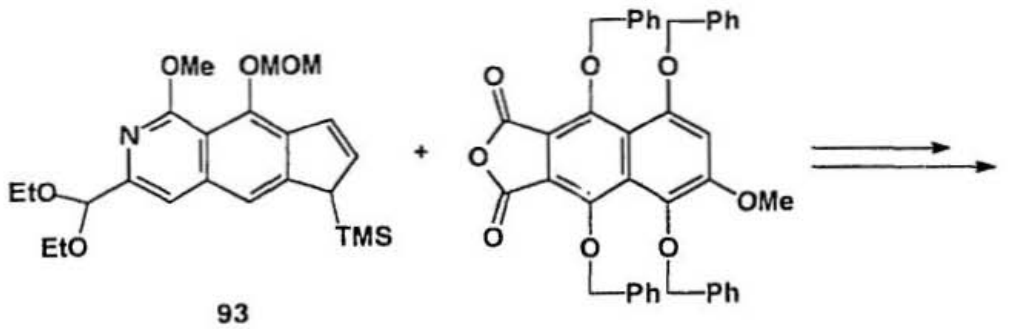


Fredericamycin A

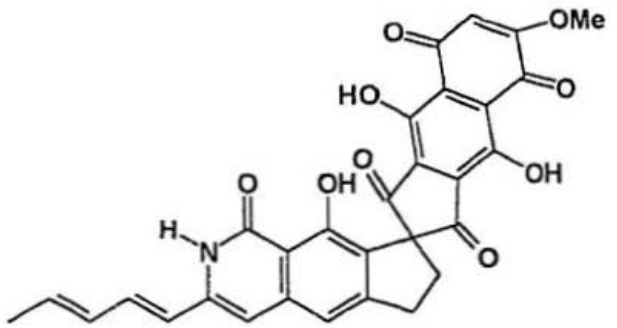
92

compound has six rings and includes a spiro-center and heavy functionalization in terms of oxygen moieties. Kelly and co-workers[27] were the first to synthesize (±)-fredericamycin A in 1986 in an overall yield of 2%. They assembled the ring

system of **92** from the precursors **93** and **94** (**Scheme 40**).



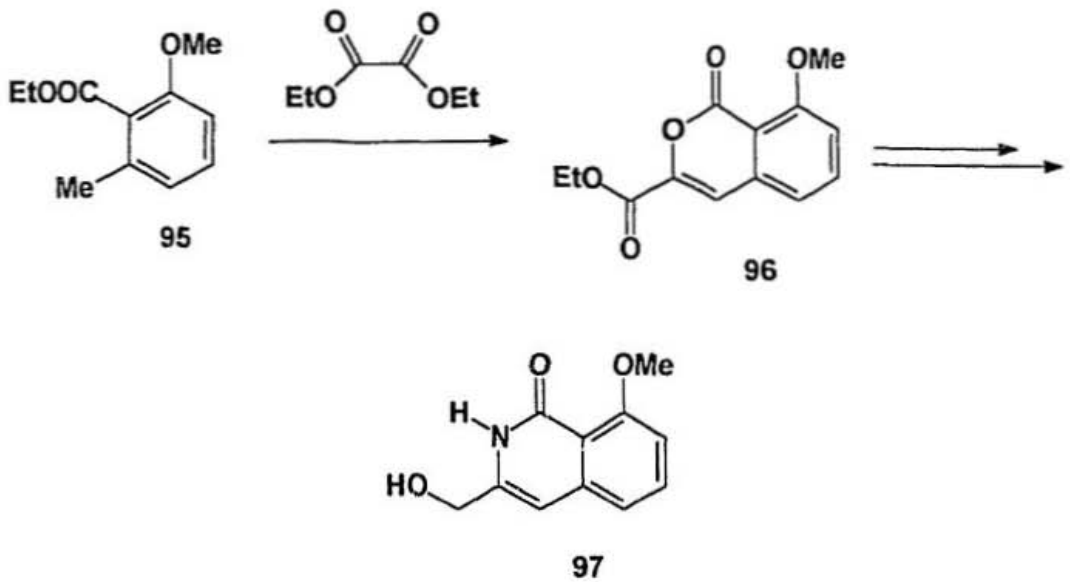
93 **94**



92

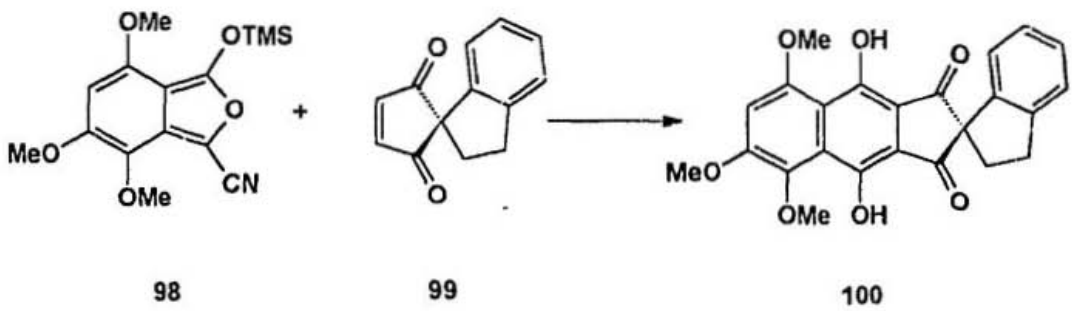
Scheme 40

In 1989 Julia and co-workers[28] reported the details of a study of the construction of the A-B ring system of fredericamycin A (**Scheme 41**). In this work, the aromatic ester **95** was treated with diethyl oxalate, which afforded **96** in 55% yield. Compound **96** was then transformed in a series of steps to **97**.



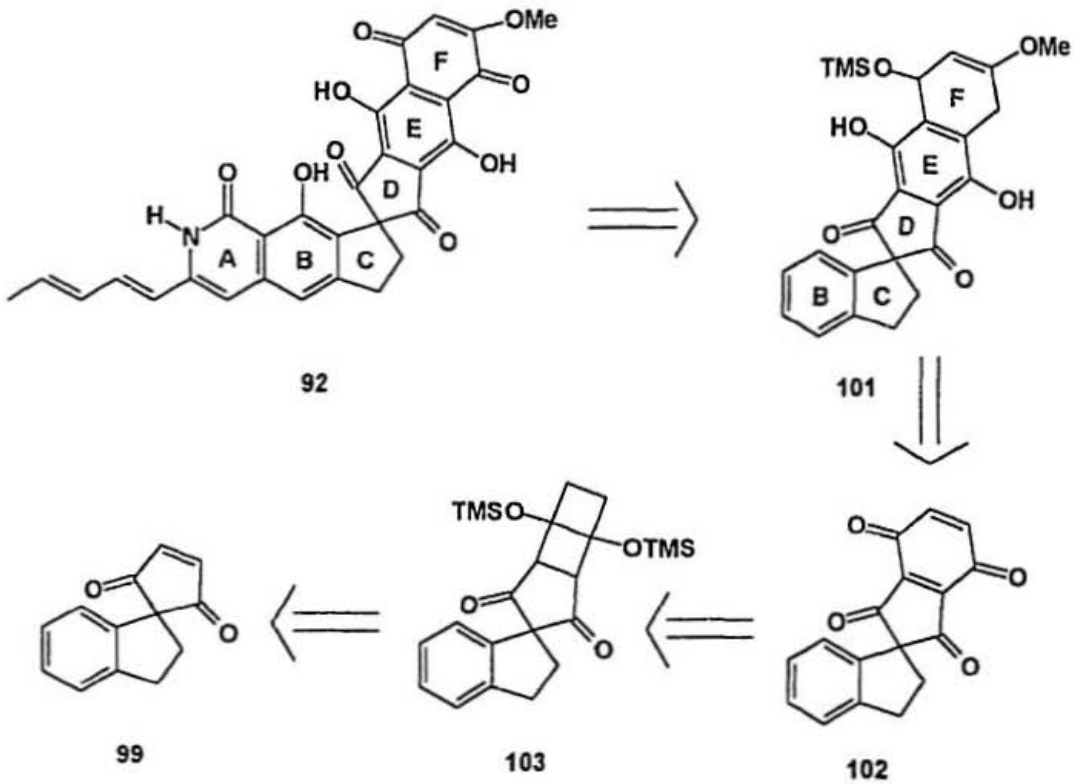
Scheme 41

In 1988, Bach *et al.*[29] reported a series of Diels-Alder model studies of approaches to compounds similar to fredericamycin A. For example, **98** was added to **99** to afford **100** in 62% yield (**Scheme 42**).



Scheme 42

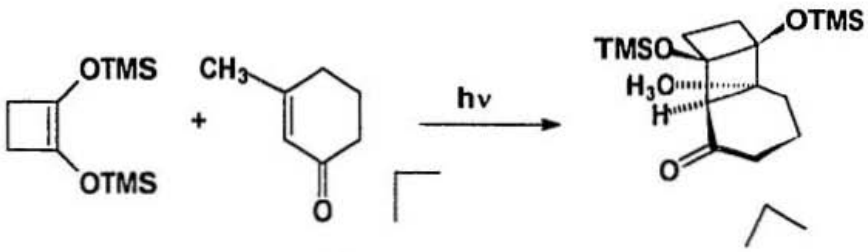
A key step in our strategy towards fredericamycin A was to assemble the A-B-C-D-E-F ring system through a photochemical addition between **99** and **1**. The retrosynthetic analysis presented in **Scheme 43** shows how this would be a key step. In our scenario, **92** is constructed from **101**, which contains the B-C-D-E-F ring system(For the construction of fredericamycin A, it would be necessary



Scheme 43

to use a more complex analog of **99**). Compound **101** is itself derived from **102** using a Diels-Alder reaction with Danishefsky's diene. The tetracyclic compound **102** is the result of cyclobutane bond cleavage of **103**, which in turn is the direct

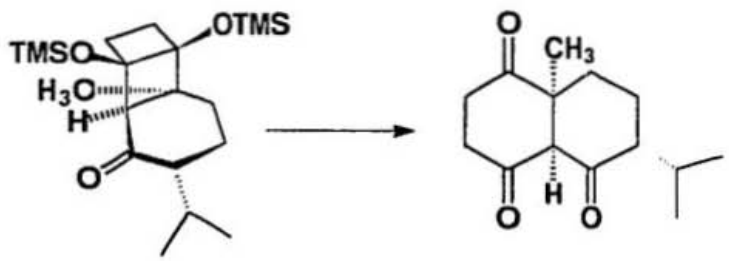
result of the photochemical addition of 1 to the tricyclic enedione **99**. A simple example of this type of addition is provided by the work of Williams and co-workers,[30] in which they carried out an addition of **1** and the enone **104** in hexane to afford the adduct **105** in 73% yield after irradiation at 0 °C with a Corex-filtered medium-pressure mercury lamp for a period of 24 hours (**Scheme 44**). Compound **105** was then desilylated with tetrabutylammonium fluoride and



1 **104** **105**

Scheme 44

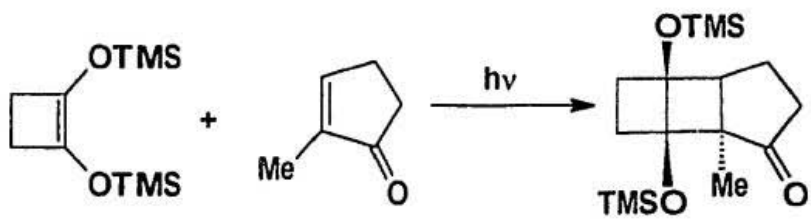
oxidatively cleaved with sodium periodate to afford the 1,4-dione **106** in 71% yield (**Scheme 45**).



105 **106**

Scheme 45

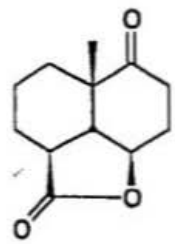
Van Audenhove and co-workers[31] also used this technique for their work toward cis-hydrindanes and cis-decalins. The photochemical additions were carried out between **1** and enones such as **107** at room temperature in pentane or benzene with irradiation at 350 nm to afford an adduct, e.g. **108** in 75% yield (**Scheme 46**). It is worth noting that the ratio of **1** to **107** was 4:1, whereas in the work of Williams (*vide supra*), the ratio of **1** to **104** was 1:1.2. Thus, a variety of conditions are possible for this type of reaction.



1 **107** **108**

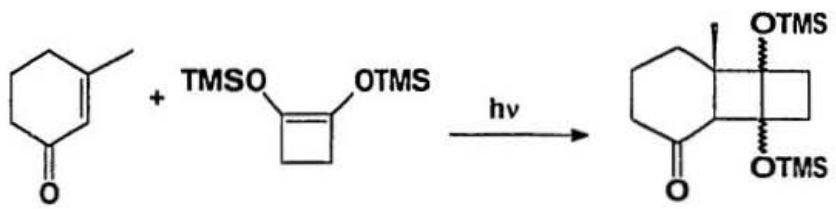
Scheme 46

There are a few examples in which this type of photochemical addition has been incorporated into a synthesis. A couple of examples follow. In 1984, Vandewalle and co-workers[32] developed a route to (±)-3,4,5,5a,7,8,8aα,8bα-octahydro-2aα, 5aβ-dimethyl-2*H*-naphtho[1,8-*bc*]furan-2,6(2a*H*)-dione **109** via the key intermediate **111**, which was generated from a photochemical addition of **1** and **110** in a ratio of 1.2:1 in 80% yield (**Scheme 47**) following photolysis at 350 nm.



109

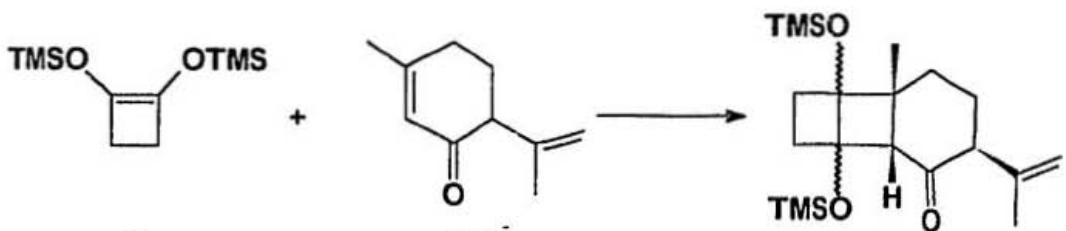
In another example, Anglea and Pinder[33] formed the adduct **113** from **1**



110 **1** **111**

Scheme 47

and **112** in 24% yield during efforts toward the synthesis of (+)-balanitol (**Scheme 48**). Irradiation was carried out at room temperature with an immersion lamp in a solution of **1** and **112** (5:1, respectively) in pentane.



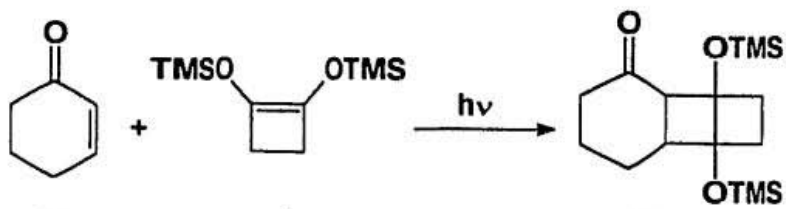
1 **112** **113**

Scheme 48

ii. Results and Discussion

The applicability of photochemical [2+2] cyclizations with **1** under a wide variety of conditions was encouraging. We embarked on the task of exploring the viability of a photochemical key step in a synthesis of (±)-fredericamycin A.

Our first attempts were carried out using simple test molecules. The first reaction was monitored using ^{1}H nmr in order to detect the loss of starting material and the formation of product. This would give us some idea of the amount of time needed under exposure to UV light. This experiment was attempted using 2-cyclohexenone **114** and **1** (**Scheme 49**). A preliminary

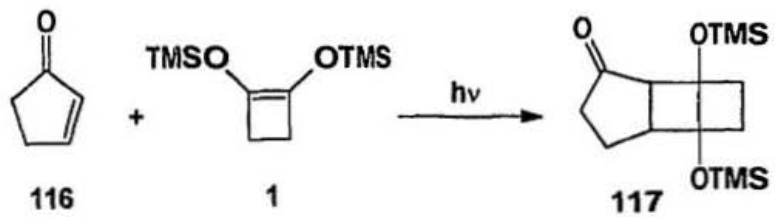


114 **1** **115**

Scheme 49

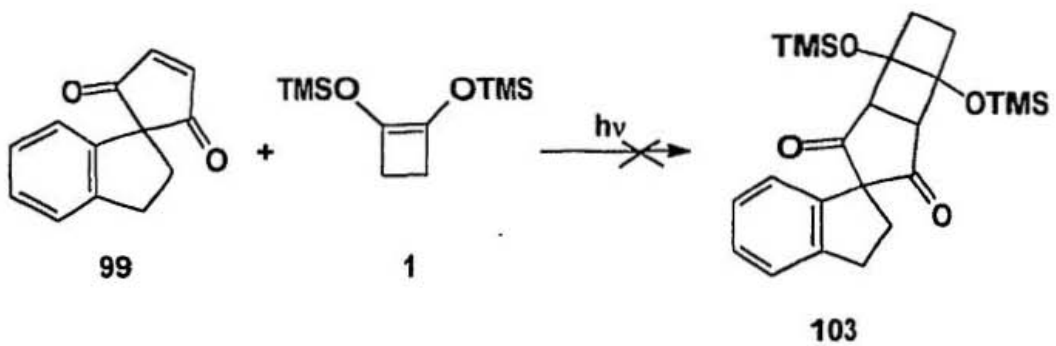
spectrum was taken with the two materials in solution at time t = 0 h. Scans were taken at times t = 67 min, t = 226 min, and t = 346 min. Unfortunately, the only changes observed in the ^{1}H nmr spectra were the loss of the 2-cyclohexenone signals. There were no new signals to accompany the loss of the starting material. The answer seemed to rest with the temperature inside the reactor chamber, which was at an operating temperature in excess of 50 °C.

Under a constant stream of N_2 gas at this temperature, it appeared that the 2-cyclohexenone was being lost due to evaporation. It was clear that the temperature of the reactants was going to have to be kept cool. We developed a water-cooled reaction chamber that could be placed in the reactor chamber as easily as a normal reaction vessel. When 2-cyclopentenone **116** and **1** were irradiated for 24 h at 350 nm in a water-cooled reaction chamber, a small amount of product **117** was recovered after chromatography (**Scheme 50**). Despite the



Scheme 50

very low yield, this result was encouraging. Given this fact, we decided to proceed immediately with a photochemical addition to the synthetic substrate **99**. This substrate **99** was produced by the spiroannulation of 1-indanone[10] and oxidation by Dr. Tracy Jenkins in our laboratory. The material **99** was added to



Scheme 51

1 and irradiated at 350 nm for 42 h, and the reaction was followed by tlc. Chromatography of the resulting crude material afforded only starting materials (**Scheme 51**). The UV absorption spectrum of **99** showed two major absorptions at 230 nm and 330 nm. The Pyrex glass in the water-cooled reaction vessel absorbed UV light in the region of 220-295 nm . Thus, only the longer wavelength absorption was significant, and the irradiation times were very long.

iii. CONCLUSIONS

Although the above results are very preliminary as part of a probing experiment, it is possible to make conclusions that can direct future work. It is clear that the amount of light getting through to the sample was limited and that temperature control was proving to be very difficult, especially in terms of volatile substrates. However, in the case of **99**, volatility was not a problem. In this case, it is possible that the lack of light transmission was not the only problem leading to very modest yields. It is also possible that the excited state of this enedione is too stable or unreactive to undergo addition. It may also be possible that energy is passed from the enedione moiety to the aromatic section of the molecule. In order to counter these problems, there are a couple of possible strategies. First, one could reduce one of the ketone functions and thereby change the wavelength of the absorption. Another possibility is that one could add a substituent to the molecule and again, shift the absorption wavelength(s).

However, though these are sound and logical measures, they involve a long process which is outside the scope of this exploratory project.

III. EXPERIMENTAL SECTION:

i. SECTION A

General Procedures

Reagent **1** was prepared by the procedure developed by Bloomfield and Nelke.[2] Flash chromatography employed 230-400 mesh silica gel with hexane and an increasing proportion of ethyl acetate as eluent. The ratios of ethyl acetate/hexane are reported below. Nuclear magnetic resonance (nmr) spectra were recorded on a General Electric GE 300-NB (300 MHz for ^1H) spectrometer. The ^1H nmr spectra were acquired in solutions of deuteriochloroform ($CDCl_3$), and, unless otherwise stated, shifts are relative to internal tetramethylsilane. Coupling constants (*J*) are reported in Hz. The ^{13}C nmr spectra (75 MHz) were acquired in $CDCl_3$, and chemical shifts are relative to the solvent (δ 77.0). ^{13}C nmr shifts are sometimes followed in parentheses by the number of attached protons on that carbon, which were derived from an attached proton test (APT) and/or heteronuclear correlation (HET-CORR) spectra. Assignments quoted for

the ^{1}H and ^{13}C nmr spectra are given when these are reasonably reliable and consistent with the correlation spectra. Whenever possible, assignments have been corroborated by the use of ChemWindows C-13 NMR Module version 1.2 (Softshell) and *g*NMR for Windows version 3.6 (Cherwell Scientific). Assignment of ^{1}H and ^{13}C spectra are according to an arbitrary numerical scheme chosen for ease of identification and are indicated on the compound structure in the Appendix of nmr spectra. Low and high resolution mass spectra (MS) data were obtained from a V.G. Micromass 7070HS instrument using electron ionization at 70 eV. Infrared spectra (ir) were acquired as casts using a Mattson Polaris FT-IR instrument or a Bomem Michelson Series FT-IR spectrometer and intensities are noted as (s), (m), (w), (br) for strong, medium, weak, and broad, respectively. A Hewlett-Packard model 5890 gas chromatograph, equipped with a 12.5 m fused-silica capillary column with cross-linked dimethylsilicone as the liquid phase, coupled to a model 5970 mass selective detector was used for gas chromatography-mass spectrometric (GCMS) analyses. Melting points were obtained on a Mel-Temp II melting point apparatus are uncorrected.

2-Ethyl-2-methyl-1,3-cyclopentanedione (71)

To a stirred solution of compound **70** (2.92 g, 40.5 mmol) in 100 mL of CH_2Cl_2 was added $BF_3.Et_2O$ (4.98 mL, 40.5 mmol) and **1** (16.2 mL, 60.8 mmol).

This was stirred for one hour, whereupon water (5.1 mL) was added, and the mixture was stirred for 2 min. Heat was evolved during the addition of $BF_3.Et_2O$ (74.7 mL, 608 mmol), and then the mixture was stirred for a further two hours. The reaction mixture was poured into ice-water. The organic layer was removed and washed with water (x2). The combined aqueous layers were re-extracted with CH_2Cl_2 (x2). The combined organic layers were washed with a saturated solution of $NaHCO_3$ then brine. The solution was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed *in vacuo* to afford a black oil. Diethyl ether (20 mL) was added, and the solution was filtered through a column of Florisil and charcoal. A further 300 mL of ether was passed through the column. The combined ether solutions were concentrated *in vacuo* to afford 4.24 g (75%) of 2-ethyl-2-methyl-1,3-cyclopentanedione as a pale yellow oil: ir ν_{max}: 1727 cm^{-1}; ^1H nmr δ: 2.78 (4H, s, C-4 H_2 and C-5 H_2), 1.68 (2H, quartet, J = 7.5 Hz, C-6 H_2), 1.12 (3H, s, C-8 H_3), 0.82 (3H, t, J = 7.5Hz, C-7 H_3); ^{13}C nmr δ: 216.7 (C-1 and C-3), 57.1 (C-2), 35.2 (C-4 and C-5), 28.8 (C-6), 18.1 (C-8), 8.8 (C-7); ms: 140 (38, M^+), 125 (57), 101 (48), 69 (55), 43 (100). Exact mass calculated for $C_8H_{12}O_2$:140.0837; found: 140.0837.

(2*R,3*R**)-2,3-Diethyl-3-hydroxy-2-methylcyclopentan-1-one (79)**

To a stirred solution of compound **71** (1.05 g, 7.48 mmol) and anhydrous diethyl ether (50 mL) at -78 °C was added slowly ethylmagnesium bromide (7.5

mL, 3M in diethyl ether; Aldrich). The reaction was maintained at -78 °C for one hour before being allowed to warm to 0 °C where it was maintained for four hours. The reaction was quenched carefully with ice-water, the organic layer was separated, and it was washed with 6N HCl (x2) and H_2O (x2). The combined aqueous layers were re-extracted with diethyl ether (x4). The combined ether extracts were dried over anhydrous $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Flash chromatography (5/95) afforded (2*R**,3*R**)-2,3-diethyl-3-hydroxy-2-methylcyclopentan-1-one (0.61 g, 48%) as a pale yellow oil: ir ν_{max}: 3462 (br), 1730 (s) cm^{-1}; ^1H nmr δ: 2.38 (2H, complex m, C-5 H_2), 1.96 (2H, complex m, C-9 H_2), 1.56 (4H, complex m, C-4 H_2 and C-6 H_2), 1.00 (3H, t, *J* = 7.5 Hz, C-7 H_3 or C-10 H_3), 0.99 (3H, t, *J* = 7.6 Hz, C-7 H_3 or C-10 H_3), 0.93 (3H, s, C-8 H_3); ^{13}C nmr δ: 222.5 (C-1), 82.6 (C-3), 55.4 (C-2), 33.8 (C-5), 30.1 (C-9), 28.4 (C-6 or C-4), 23.4 (C-6 or C-4), 16.8 (C-7 or C-10), 8.9 (C-7 or C-10), 7.3 (C-8); ms: 170 (1, M^+), 98 (16), 83 (24), 57 (100). Exact mass calculated for $C_{10}H_{18}O_2$: 170.1306; found: 170.1308.

(1*R,2*S**,3*R**)-1,2-Diethyl-2-methylcyclopentane-1,3-diol (80)**

To a stirred solution of compound **79** (6.59 g, 38.7 mmol) and methanol (100 mL) at 0 °C was added sodium borohydride (1.76 g, 46.4 mmol) over a period of fifteen minutes. The reaction mixture warmed to room temperature overnight, and the solvent was removed *in vacuo*. The solid residue was

dissolved in diethyl ether and filtered through a column containing silica gel and Celite using methanol as eluent. Solvents were removed under reduced pressure. Flash chromatography (15/85) afforded (1*R**,2*S**,3*R**)-1,2-diethyl-2-methylcyclopentane-1,3-diol (0.98 g, 15%) as a crystalline solid: mp: 52-55 °C; ir ν_{max}: 3425 (m) cm^{-1} ; ^1H nmr δ: 4.27 (1H, t, *J* = 8.3 Hz, C-3 H_1), 2.19 (1H, complex m,), 1.83 (1H, complex m), 1.53 (7H, complex m), 0.99 (3H, t, *J* = 7.7 Hz), 0.92 (3H, t, *J* = 7.5 Hz, C-7 H_2 or C-10 H_2), 0.80 (3H, s, C-8 H_3); ^{13}C nmr δ: 85.1 (C-1), 79.7 (C-3), 49.8 (C-2), 33.1 (C-9), 29.5 (C-5), 28.7 (C-4), 26.3 (C-6), 13.6 (C-7), 9.4 (C-8), 7.5 (C-10); ms: 155 (10, M^+-OH), 125 (31), 82 (82), 57 (100), 55 (70), 43 (73). Exact mass calculated for $C_{10}H_{18}O$ ($C_{10}H_{20}O_2$ - OH): 155.1436; found: 155.1439.

Attempted synthesis of (1*R, 2*S**, 3*S**)-3-Chloro-1,2-diethyl-2-methylcyclopentan-1-ol (86)**

To a stirred solution of **80** (1.50 g, 8.71 mmol) in CH_2Cl_2 (50 mL) was added pyridine (2.11 mL) and $SOCl_2$ (1.52 mL). This was stirred overnight at room temperature to afford a black material, for which GCMS analysis did not show any component consistent with the structure **86**.

(2*R, 3*R**)-2-Ethyl-3-hydroxy-2-methylcyclopentan-1-one (87)**

To a stirred solution of **71** (1.23 g, 8.77 mmol) and methanol (100 mL) at -78 °C was added sodium borohydride (0.098g, 0.26 mmol) over a period of five hours. Diethyl ether (100 mL) and brine (50 mL) were added to the crude mixture at -78 °C, and the mixture was separated. The aqueous layer was re-extracted with ethyl acetate (x3), and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and filtered, and the solvent removed under reduced pressure. Flash chromatography (25/75) afforded (2*R**, 3*R**)-2-ethyl-3-hydroxy-2-methylcyclopentan-1-one (0.69 g, 55%): ir ν_{max}: 3452 (s), 1727 (s) cm^{-1}; ^1H nmr δ: 4.13 (1H, br, C-3 H_1), 2.45 (1H, m, C-5 H_1), 2.35-2.13 (2H, complex m, C-5 H_1, C-4 H_1), 1.96 (2H, complex m, C-4 H_1, C-3 OH), 1.57 (2H, symmetrical m, C-6 H_2), 0.98 (3H, s, C-8 H_3), 0.93 (3H, t, J = 7.5 Hz, C-7 H_3); ^{13}C nmr δ: 221.1 (C1), 77.2 (C3), 53.4 (C2), 34.1 (C5), 27.7 (C6), 22.6 (C4), 18.6 (C8), 8.2 (C7); ms: 142 (30, M^+), 124 (11), 82 (100), 71 (58), 55 (66), 41 (51), 29 (41), 27 (30). Exact mass calculated for $C_8H_{14}O_2$: 142.0994; found: 142.0990.

(2*R,3*R**)-2-Ethyl-2-methyl-3-trimethylsilyloxycyclopentan-1-one (88)**

To a stirred solution of **87** (0.41 g, 2.9 mmol) and pyridine (3.0 mL) at 0 °C was added chlorotrimethylsilane (1.09 mL, 8.6 mmol), and this was stirred for ten

minutes at 0 °C before being permitted to warm to room temperature while stirring was continued overnight. Water and diethyl ether (3 x 100 mL) were added to the reaction mixture and separated. The combined ether extracts were washed with 3M HCl (x2). The organic layer was then washed with a saturated solution of $NaHCO_3$. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed *in vacuo*. Flash chromatography (10/90) afforded (2*R**,3*R**)-2-ethyl-2-methyl-3-trimethylsilyloxycyclopentan-1-one (0.31 g, 51%) as a yellow oil: ^{1}H nmr δ: 4.02 (1H, t, *J* = 5.0 Hz, C-3 H_1), 2.40 (1H, m, C-5 H_1), 2.26-2.01 (2H, complex m, C-4 H_1, C-5 H_1), 1.88 (1H, complex m, C-4), 1.56 (2H, complex m, C-6), 0.94 (3H, s, C-8 H_3), 0.84 (3H, t, *J* = 7.6 Hz, C-7 H_3), 0.13 (9H, s, $Si(CH_3)_3$); ^{13}C nmr δ: 221.0 (C-1), 77.9 (C-3), 53.3 (C-2), 34.3 (C-5), 28.2 (C-6), 22.8 (C-4), 18.5 (C-8), 8.1 (C-7), 0.1 ($Si(CH_3)_3$); ms from GCMS: 214 (100, M^+), 199 (75),143 (21), 129 (69), 73 (98).

(1*R, 2*S**, 3*S**)-1,2-Diethyl-2-methylcyclopentane-1,3-diol (89)**

To a flask was added sodium metal (0.014 g) and lithium metal (0.092 g). The flask was evacuated and the two metals were heated to form an alloy. The alloy was allowed to cool to room temperature under vacuum. To this material was added anhydrous tetrahydrofuran (40 mL), a solution of **88** (0.053 g, 0.25 mmol) in anhydrous tetrahydrofuran (10 mL) and ethyl iodide (0.16 mL, 2.0

mmol). This mixture was subjected to low energy ultrasonic irradiation overnight. Ice-water was carefully added to the reaction mixture and then layers were separated. The organic layer was washed with H_2O (x2), and the combined aqueous layers were re-extracted with diethyl ether (x2). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed *in vacuo*. Flash chromatography (20/80) afforded (1*R**, 2*S**, 3*S**)-1,2-diethyl-2-methylcyclopentane-1,3-diol (0.016 g, 37%) as a yellow solid: mp: 64-67 °C; ir ν_{max}: 3410 (w), 1216 (s) cm^{-1}; ^1H nmr δ: 3.89 (1H, m, C-3 H_1), 2.96 (1H, br d, J = 7.8 Hz, C-3 OH), 2.38 (1H, br s, C-3 OH), 2.17-1.72 (5H, complex m, C-4 H_2, C-5 H_2, C-6 H_1), 1.49 (2H, m, C-9 H_2), 1.20 (1H, d q, J = 12.6 Hz, 7.5 Hz, C-6 H_1), 0.97 (6H, t, J = 7.5 Hz, C-7 H_3, C-10 H_3), 0.74 (3H, s, C-8 H_3); ^{13}C nmr δ: 86.5 (C-3), 80.9 (C-1), 51.7 (C-2), 35.5 (C-4), 30.8 (C-5), 27.7 (C-9), 21.4 (C-6), 19.6 (C-8), 9.0 (C-7 or C-10), 8.1 (C-7 or C-10); ms: 154 (10, M^+-H_2O), 125 (44), 107 (24), 82 (100), 57 (97), 55 (84), 43 (69), 41 (51). Exact mass calculated for $C_{10}H_{18}O$ (M^+-H_2O): 154.1358; found: 154.1351.

ii. SECTION B

General Procedures

Reagent **1** was prepared by the procedure developed by Bloomfield and Nelke.[2] All reagents were degassed prior to irradiation by bubbling nitrogen gas through reaction solutions for a period of at least 5 minutes. All photochemical reactions were carried out under an atmosphere of nitrogen. Procedures and details regarding chromatography, spectroscopic assignments, etc. are consistent with those described in Section A. All photochemical reactions were carried out using an air-cooled Rayonet Microcore RPR-100 photochemical apparatus equipped with sixteen 350 nm lamps, each producing 24 watts. The water-cooled reactor consisted of a modified condenser that was sealed at the bottom end.

Attempted Synthesis of 1,8-bis(trimethylsilyloxy)tricyclo[6.2.0.$0^{2,7}$]decan-3-one 115

To an nmr tube was added **114** (0.032 g, 0.33 mmol), and **1** (0.31 g, 1.4 mmol) in C_6D_6 (0.21 mL). An initial ^1H nmr scan was carried out at time t=0. Under an atmosphere of N_2, irradiation of the sample was carried out at 350 nm.

^{1}H nmr scans were carried out at t=1 h 7 m, t=3 h 46 m, and t=5 h 46 m, and these showed a progressive loss of **114** without the formation of new signals due to **115**.

1,7-Bis(trimethylsilyloxy)tricyclo[5.2.0.0^{2,6}]nonan-3-one 117

To a water-cooled reaction chamber was added **116** (0.74 g, 9.0 mmol), and **1** (1.7 g, 7.5 mmol), in 2.0 mL of cyclohexane. The solution was irradiated for 24 h at 350 nm. The solvent was removed *in vacuo*. Column chromatography (5/95) afforded 1,7-bis(trimethylsilyloxy)tricyclo[5.2.0.0^{2,6}]nonan-3-one **117** (0.08g, 3.5%) as a yellow oil: ^{1}H nmr δ: 3.11 (1H, m, C-3 H_1), 2.96 (1H, d, J = 11.4 Hz, C-2 H_1), 2.43 (2H, m, C-4 H_2), 2.07 (6H, complex m, C-5 H_2, C-8 H_2, C-9 H_2), 0.18 (9H, s, $Si(CH_3)_3$), 0.17(9H, s, $Si(CH_3)_3$); ^{13}C nmr δ: 218.9 (C-3), 84.4 (C-7), 82.7 (C-1), 54.4 (C-2), 45.4 (C-6), 40.9 (C-4), 30.2 (C-8), 27.3 (C-9), 21.2 (C-5), 1.7 ($Si(CH_3)_3$), 1.4 ($Si(CH_3)_3$).

Attempted synthesis of 1,7-bis(trimethylsilyloxy)spiro(indane-1,4'-tricyclo[5.2.0.0^{2,6}]nonane)-3',5'-dione 103

To a water-cooled reaction chamber was added **99** (0.029 g, 0.15 mmol), and **1** (0.34 g, 1.5 mmol), in 1.0 mL of cyclohexane. The solution was irradiated for 42 h at 350 nm in the water-cooled Pyrex reaction chamber. The solvent was

removed *in vacuo*. Column chromatography (5/95) afforded starting material (0.0017g, 5.8%).

REFERENCES

1. Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 961.

2. Bloomfield, J. J.; Nelke,J. M. *Org. Syn.* **1977**, *Vol. 57*, 1.

3. Shimada, J.-I.; Hashimoto, K.; Kim, B. H.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1759.

4. Wu, Y.-J.; Burnell, D. J. *Tetrahedron Lett.* **1988**, *29*, 4369.

5. Pandey, B.; Khire, U. R.; Ayyangar, N. R. *Synth. Commun.* **1989**, *19*, 2741.

6. Anderson, W. K.; Lee, G. E. *J. Org. Chem.* **1980**, *45*, 501.

7. Burnell, D. J.; Wu, Y.-J. *Can. J. Chem.* **1989**, *67*, 816.

8. Kavash, R. W.; Mariano, P. S. *Tetrahedron Lett.* **1989**, *30*, 4185.

9. Wu, Y.-J.; Strickland, D. W.; Jenkins, T. J.; Liu, P.-Y.; Burnell, D. J. *Can. J. Chem.* **1993**, *71*, 1311.

10. Burnell, D. J.; Jenkins, T. J. *J. Org. Chem.* **1994**, *59*, 1485.

11. Wehril, F. W.; Wirthlin, T. *Interpretation of Carbon-13 Spectra*, Heyden & Son: London, **1976**, 37-38.

12. Burnell, D. J.; Wu, Y.-J. *Can. J. Chem.* **1990**, *68*, 804.

13. Mori, K.; Stalla-Bourdillon, B.; Ohki, M.; Matsui, M.; Bowers, W. S. *Tetrahedron* **1969**, 25,1667.

14. Cochrane, J. S.; Hanson, J. R. *J. Chem. Soc. Perkin I* **1972**, 361.

15. Findlay, J. A.; MacKay, W. D.; Bowers, W. S. *J. Chem. Soc.* **1970**, 2631.

16. Kutney, J. P.; Balsevich, J.; Carruthers, R.; Markus, A.; McGrath, M. J.; Young, R. N.; Worth, B. R. *Bioorganic Chem.* **1978**, *7*, 289.

17. Dahm, K.; Trost, B.; Röller, H. *J. Am. Chem. Soc.* **1967**, *89*, 5292.

18. Corey, E. J.; Katzenellenbogen, J. A.; Gilman, N. W.; Roman, S. A.; Erickson, B. W. *J. Am. Chem. Soc.* **1968**, *90*, 5618.

19. Grob, C. A.; Schiess, P. W. *Angew. Chem.* **1967**, *6*, 1.

20. March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, Fourth Edition, John Wiley & Sons: New York, **1992**, 145.

21. Wiley, G. A.; Hershkowitz, R. L.; Rein, B. M.; Chung, B. C. *J. Am. Chem. Soc.* **1964**, *86*, 964.

22. Downie, I. M.; Holmes, J. B.; Lee, J. B. *Chem. and Ind.* **1966**, 901.

23. Olah, G. A.; Balaram Gupta, B. G.; Malhotra, R.; Narang, S. C. *J. Org. Chem.* **1980**, *45*, 1638.

24. Buncel, E.; Wilson, H. *J. Chem. Ed.* **1987**, 64, 475.

25. Pandey, R. C.; Toussaint, M. W.; Stroshane, R. M.; Kalita, C. C.; Aszalos, A. A.; Garretson, A. L.; Wei, T. T.; Byrne, K. M.; Geoghegan, R. F.; White, R. J. *J. Antibiot.* **1981**, *34*, 1389.

26. Warnick-Pickle, D. J.; Byrne, K. M.; Pandey, R. C.; White, R. J. *J. Antibiot.* **1981**, *23*, 1402.

27. Kelly, T. R.; Ohashi, N.; Armstrong-Chong, R. J.; Bell, S. H. *J. Am. Chem. Soc.* **1986**, *108*, 7100.

28. Julia, M.; Rolando, C.; Vincent, E.; Xu, J.-Z. *Heterocycles* **1989**, *28*, 71.

29. Evans, J. C.; Klix, R. C.; Bach, R. D. *J. Org. Chem.* **1988**, *53*, 5519.

30. Williams, J. R.; Gaggiano, T. J. *Synthesis* **1980**, 1024.

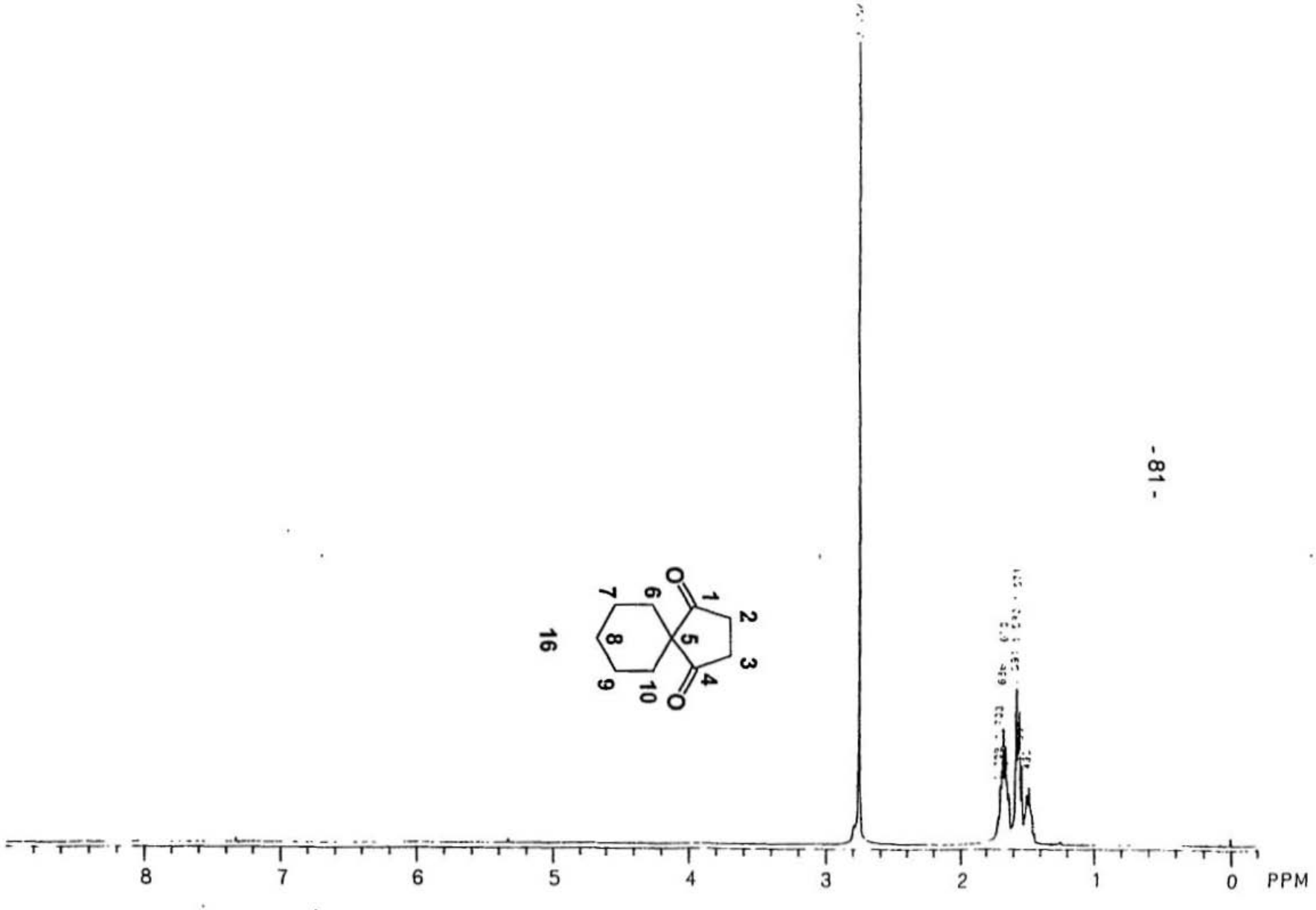
31. Van Audenhove, M.; De Keukeleire, D.; Vandewalle, M. *Tetrahedron Lett.* **1980**, *21*, 1979.

32. Van Hijfte, L.; Vandewalle, M. *Synth. Commun.* **1984**, *14*, 1149.

33. Anglea, T. A.; Pinder, A. R. *Tetrahedron* **1987**, *43*, 5537.

Appendix

Nuclear Magnetic Resonance Spectra


O
O
1
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16
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3
2
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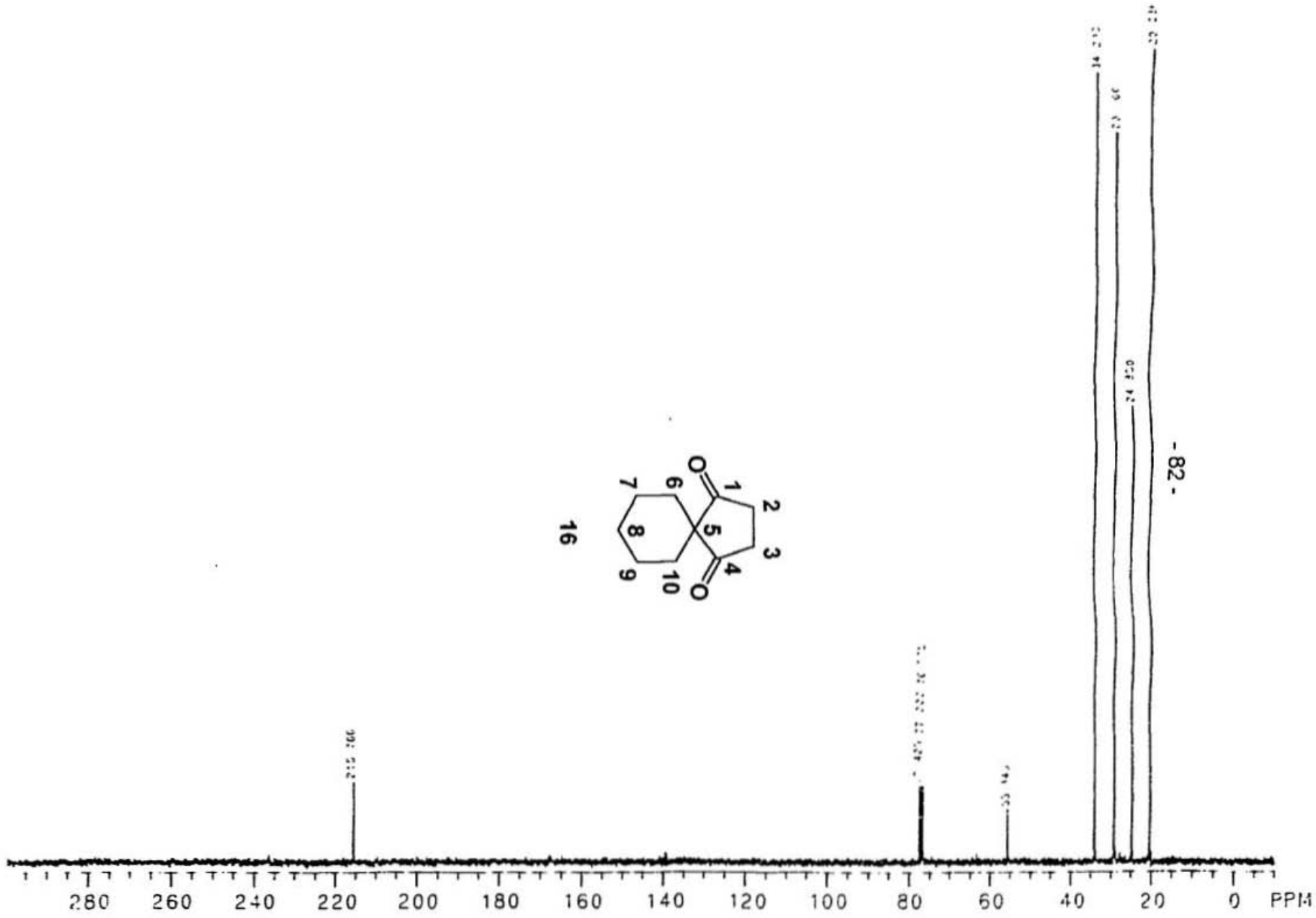
PPM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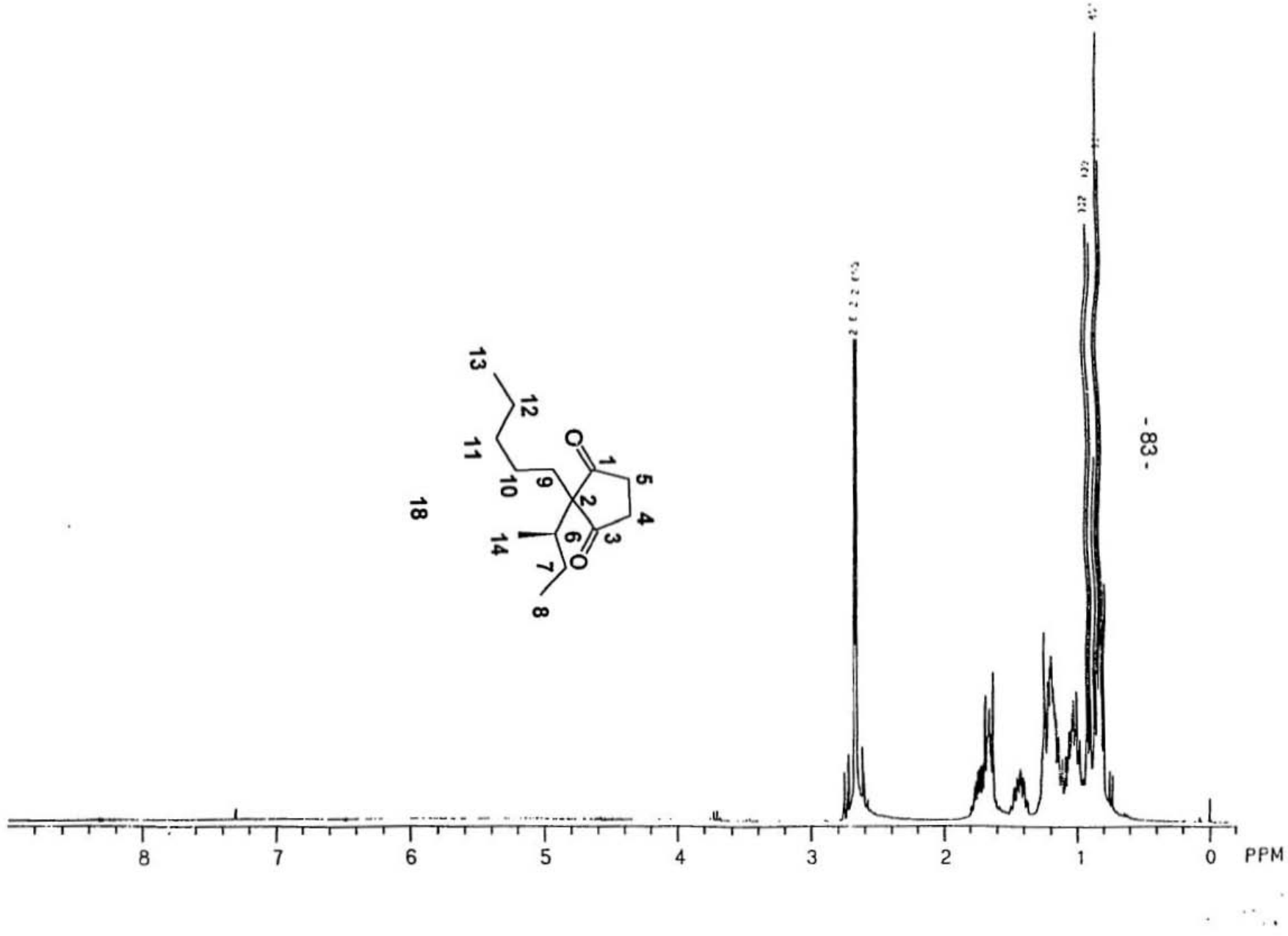
PPM
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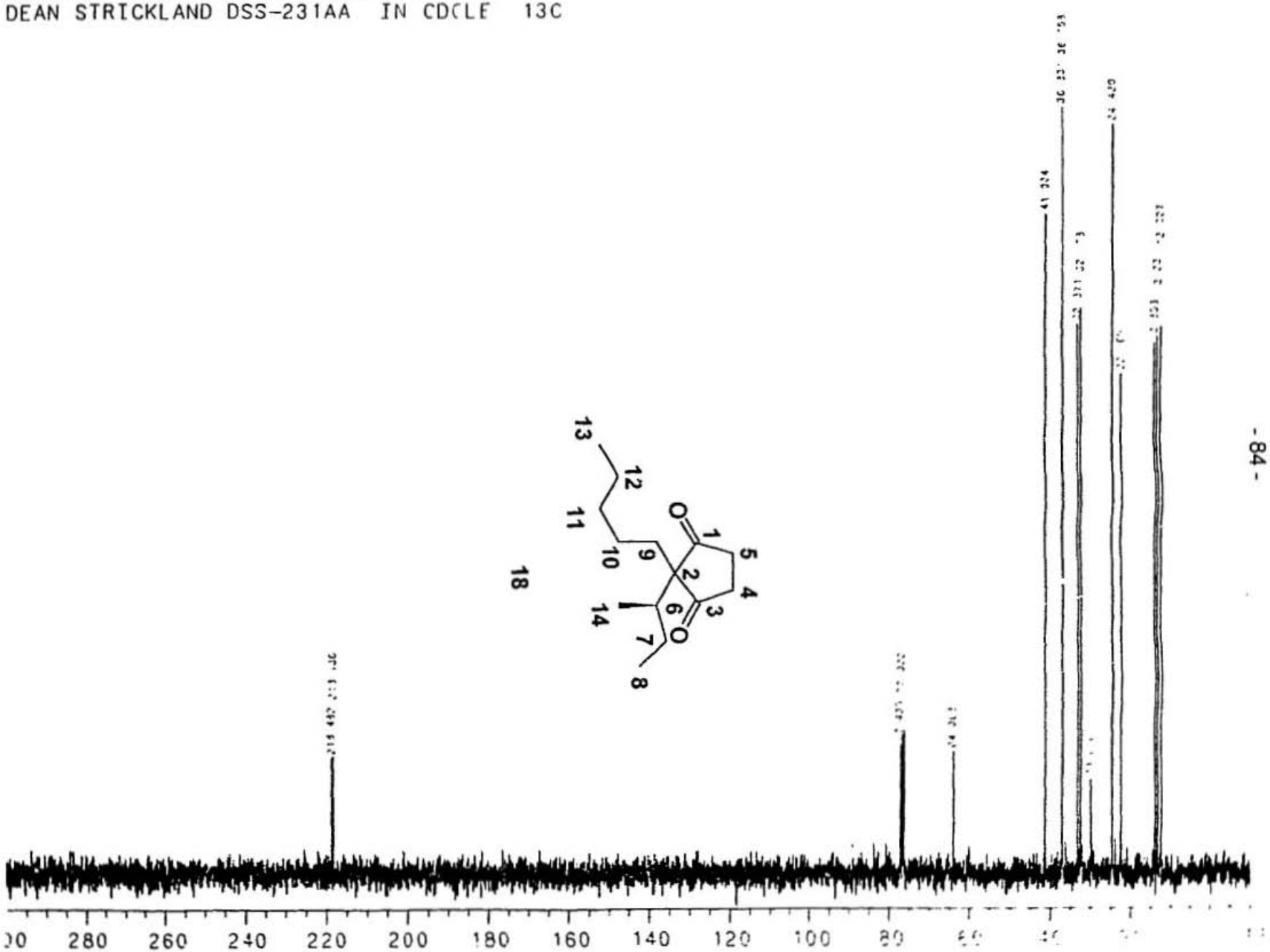
DS1015. 005 CRJ 15OCT92
DEAN STRICKLAND DSS-231AA IN CDCLE 13C



PPM
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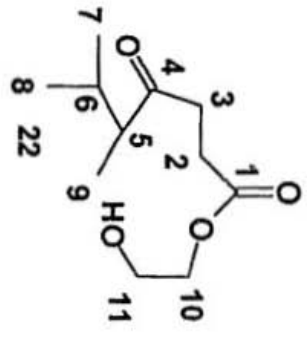
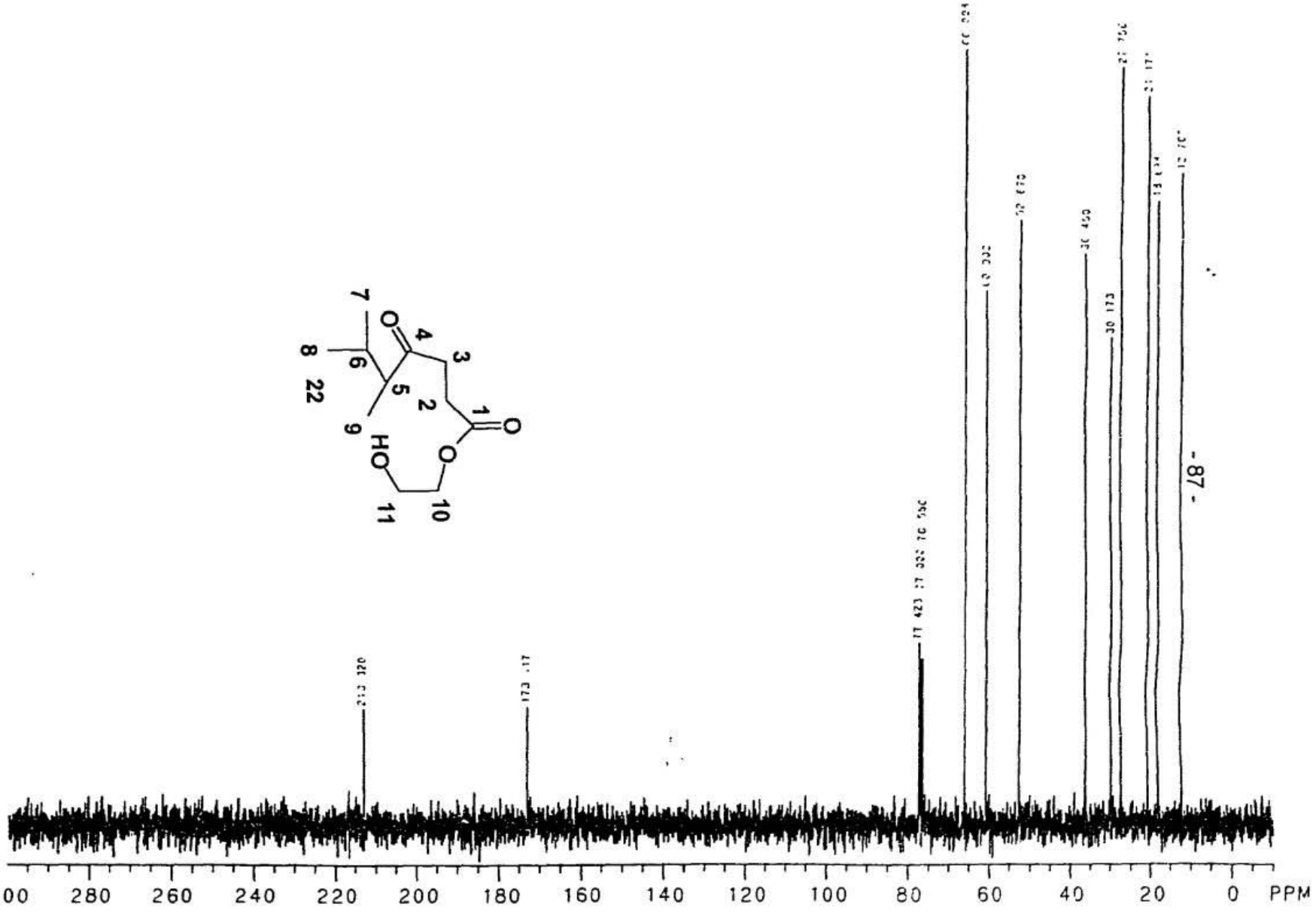
DS1015. 002 CRJ 150CT92
DEAN STRICKLAND DSS-222DAB IN CDCL3 1H

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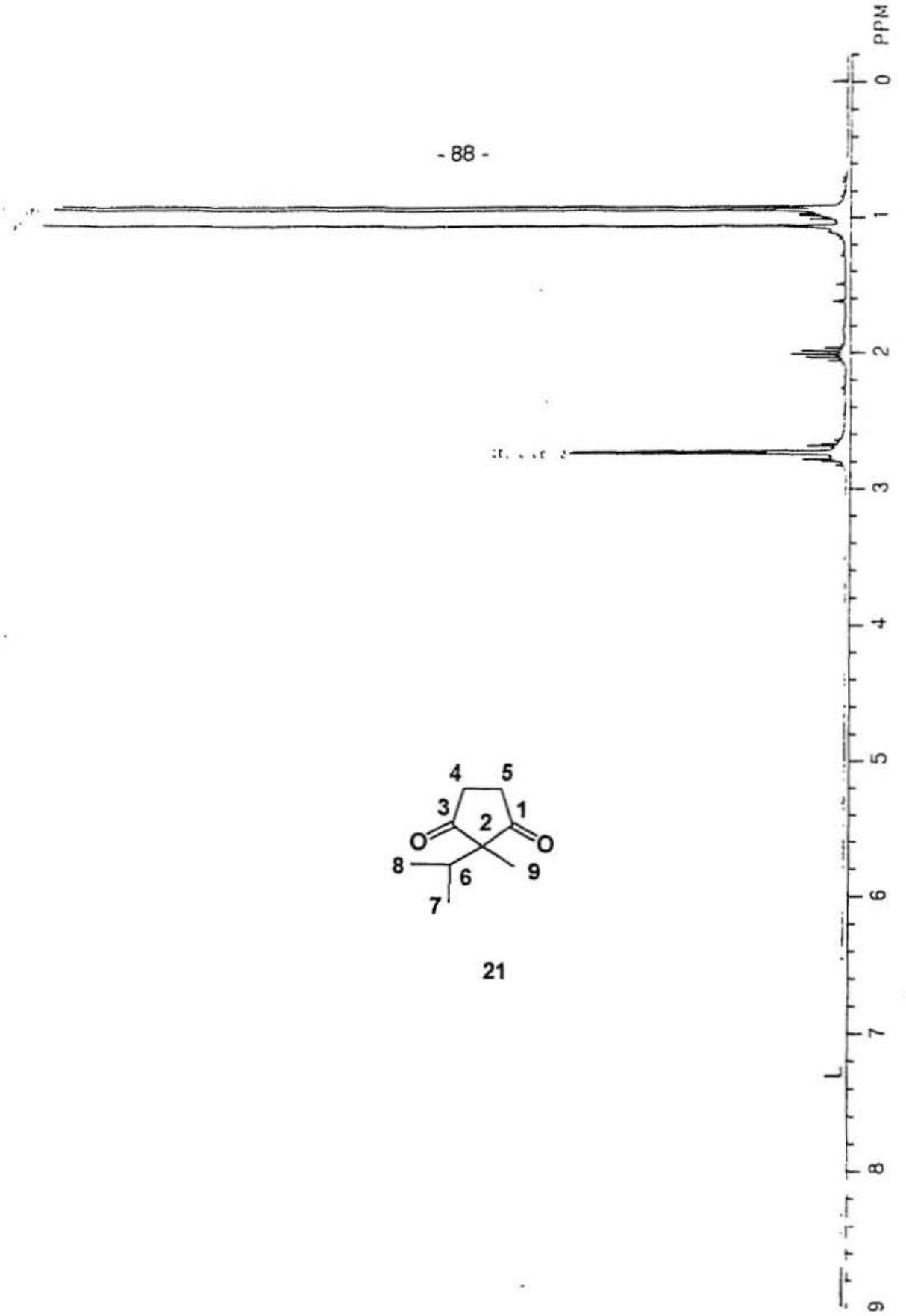
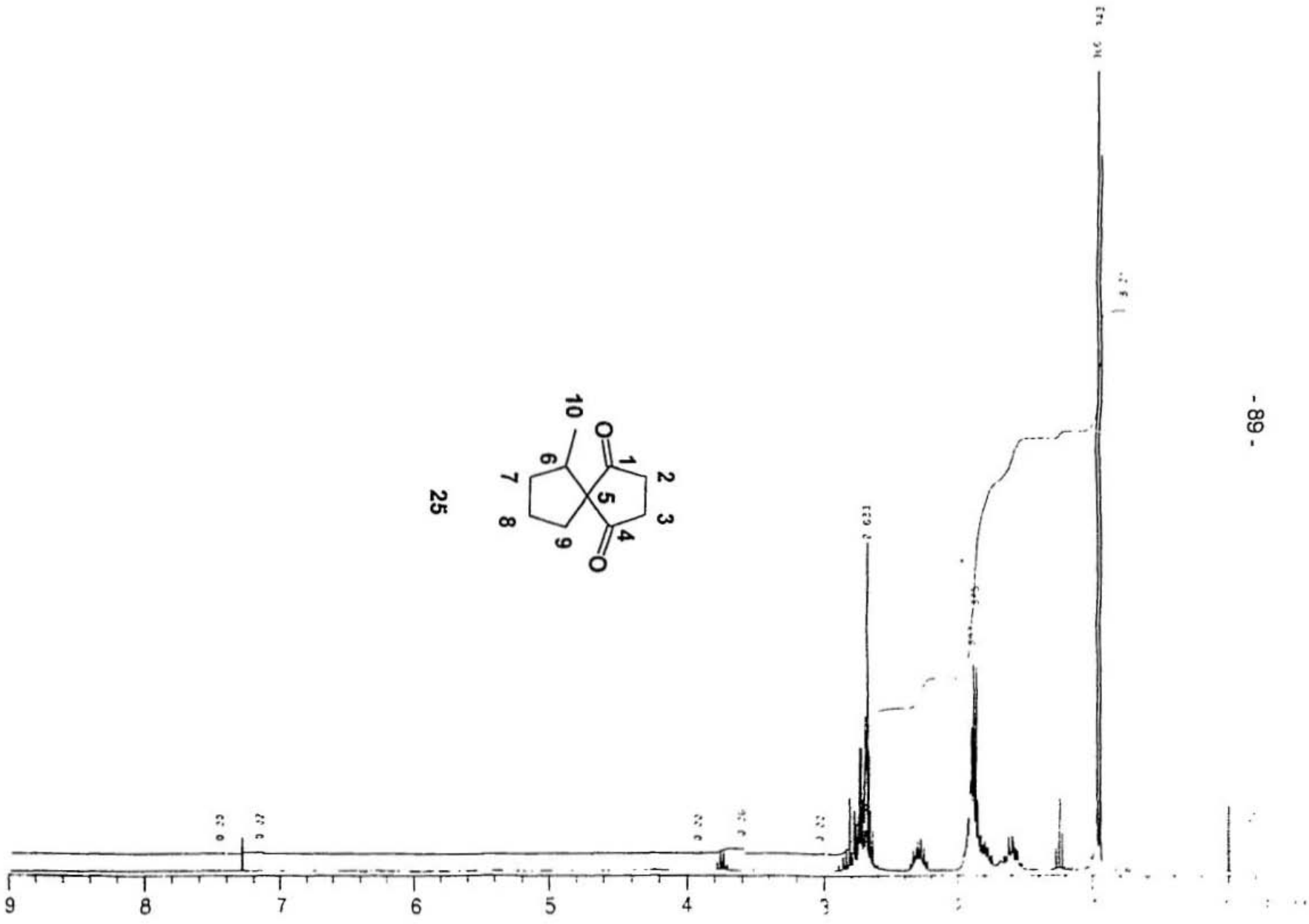
PPM



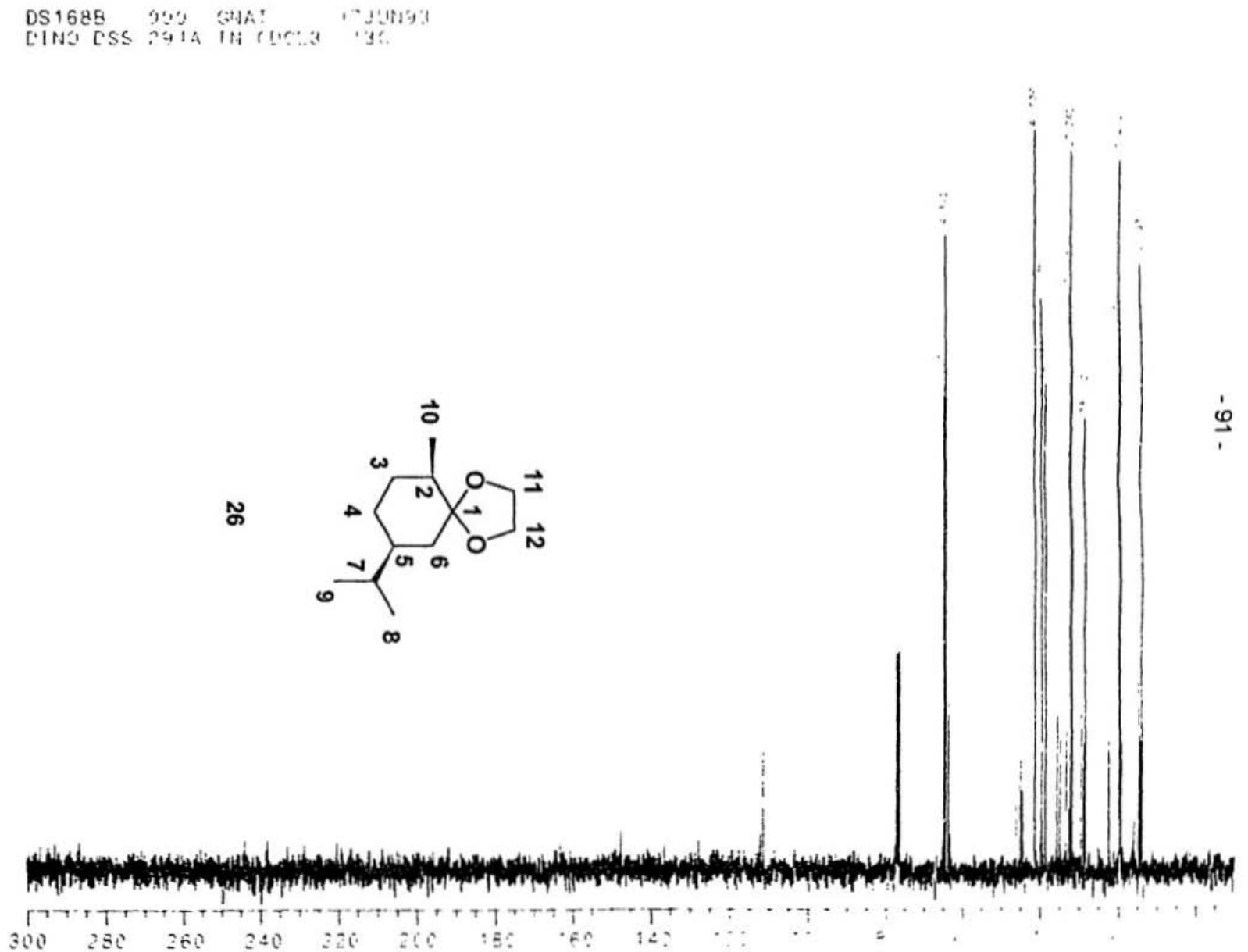
21

DS1029. 001 GNAT 29OCT92
DINOSAUR DSS-240A IN CDCL3 1H



25

26


DS168B 999 GNAT 17JUN93
DINO DSS 291A IN CDCL3 30
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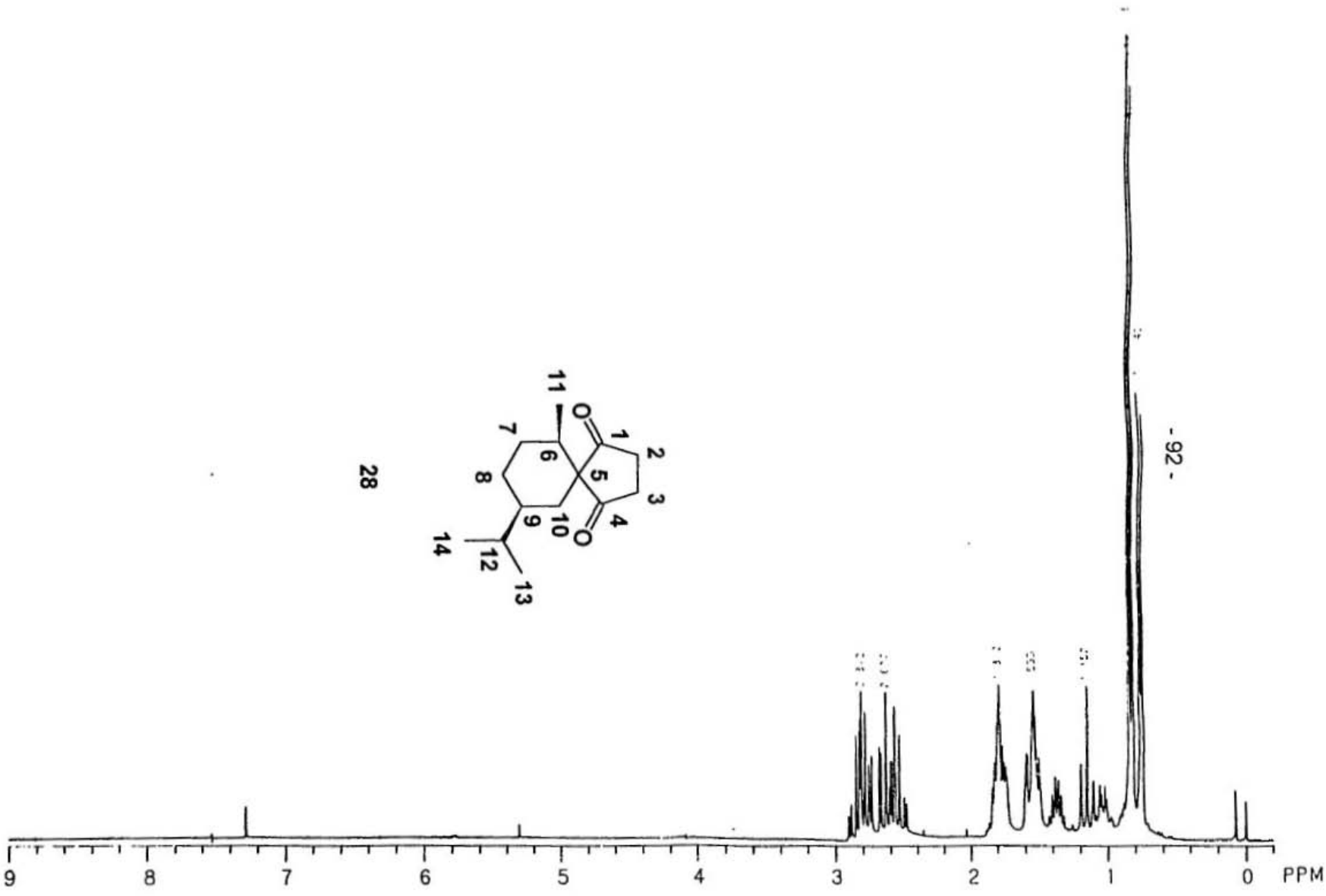
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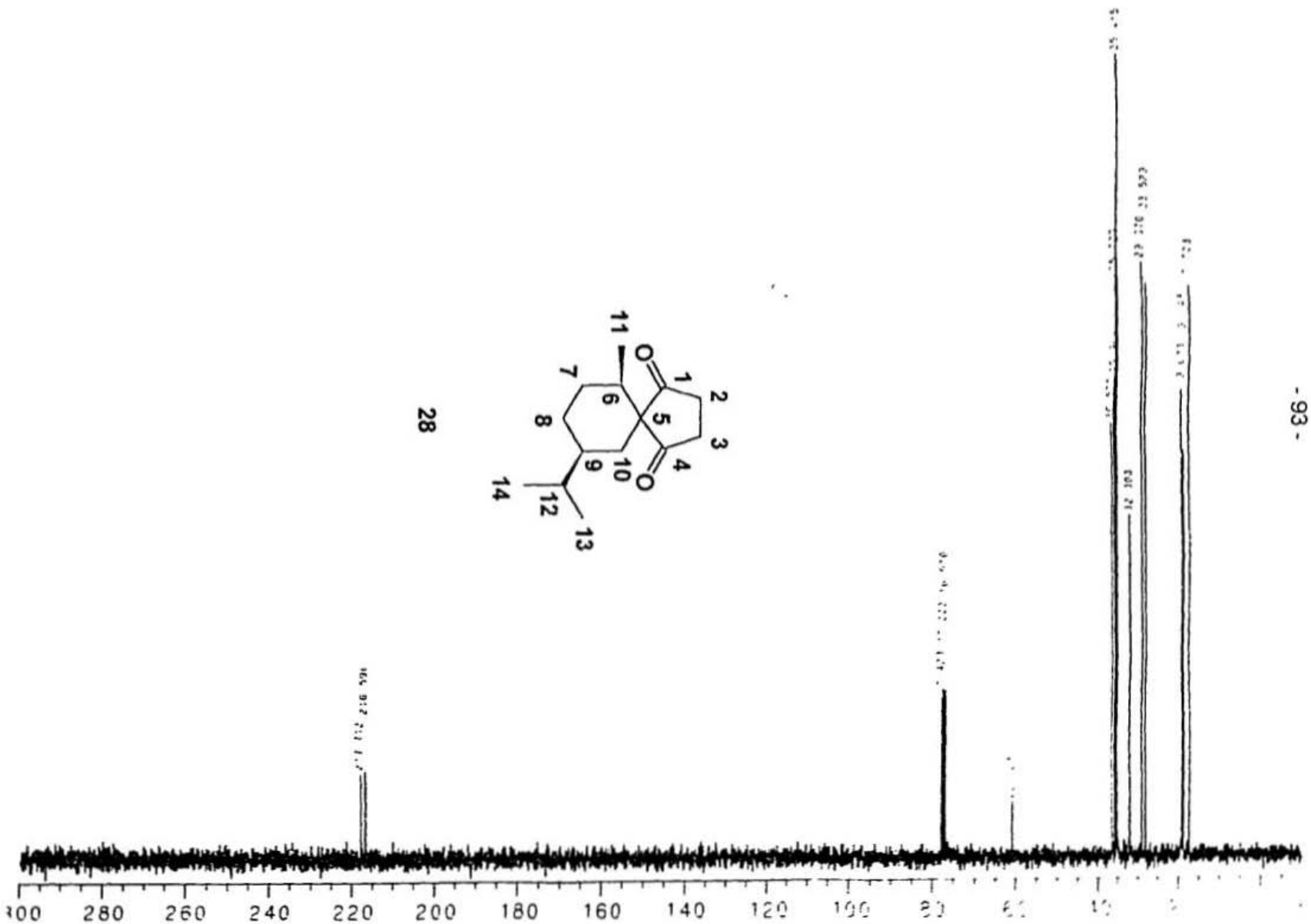
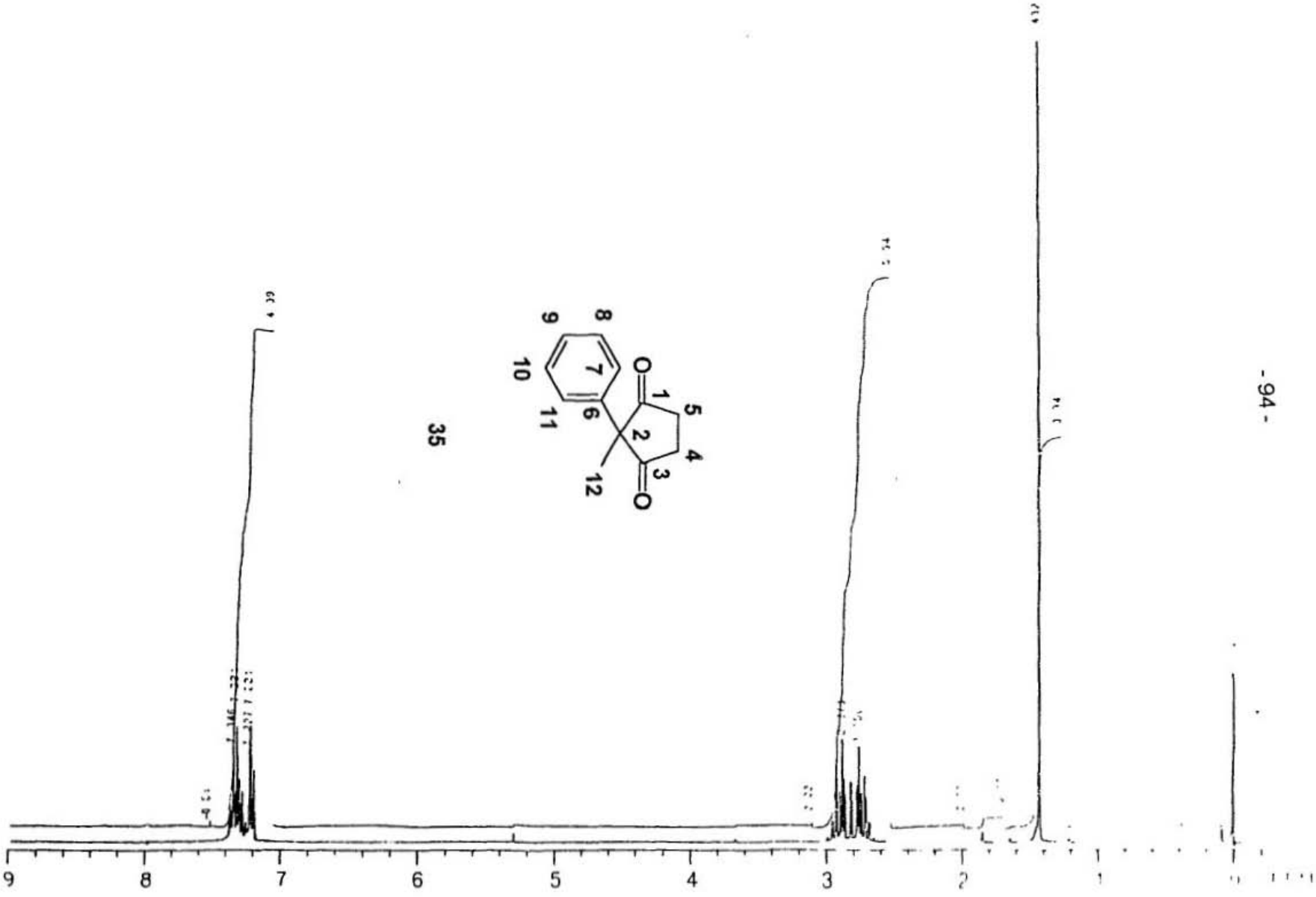
PPM

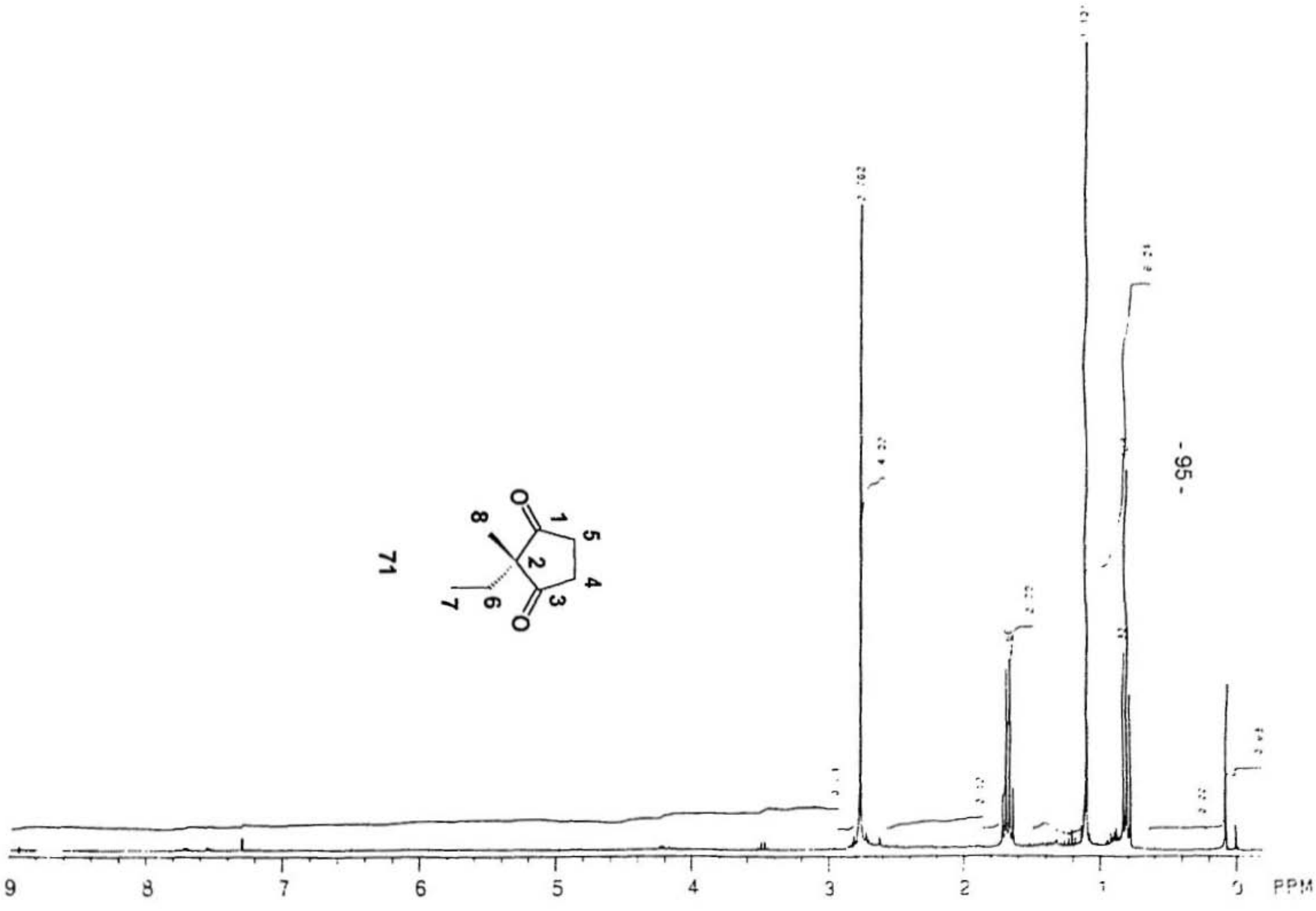
DS195D. 000 GNAT 14JUL93
DINO-THE-ADDLED DSS--302(16-21) IN CDCL3 1H



DS0724. 002 GNAT 24JUL92
DEAN STRICKLAND DSS-224B IN CDCL3 1H



35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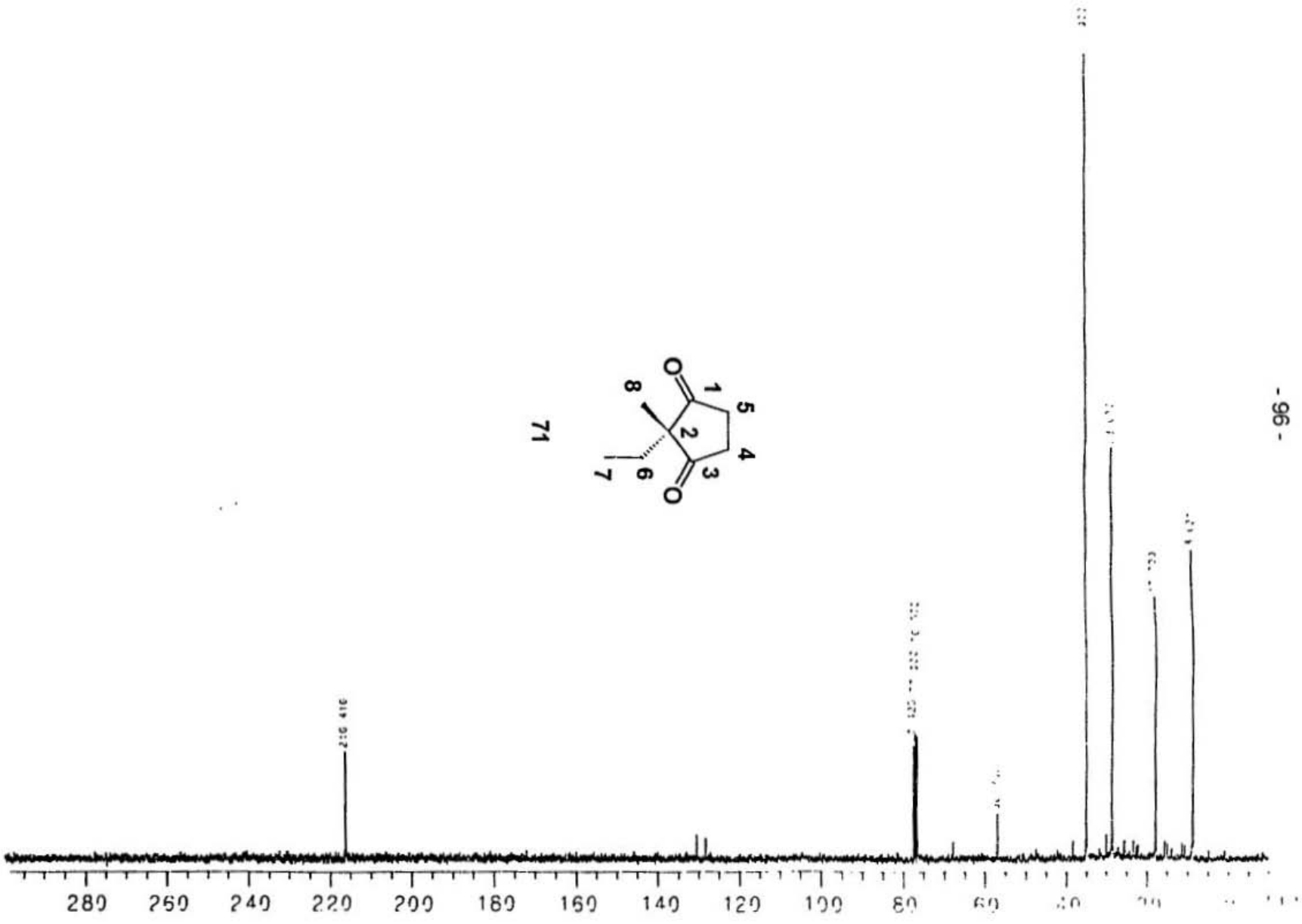
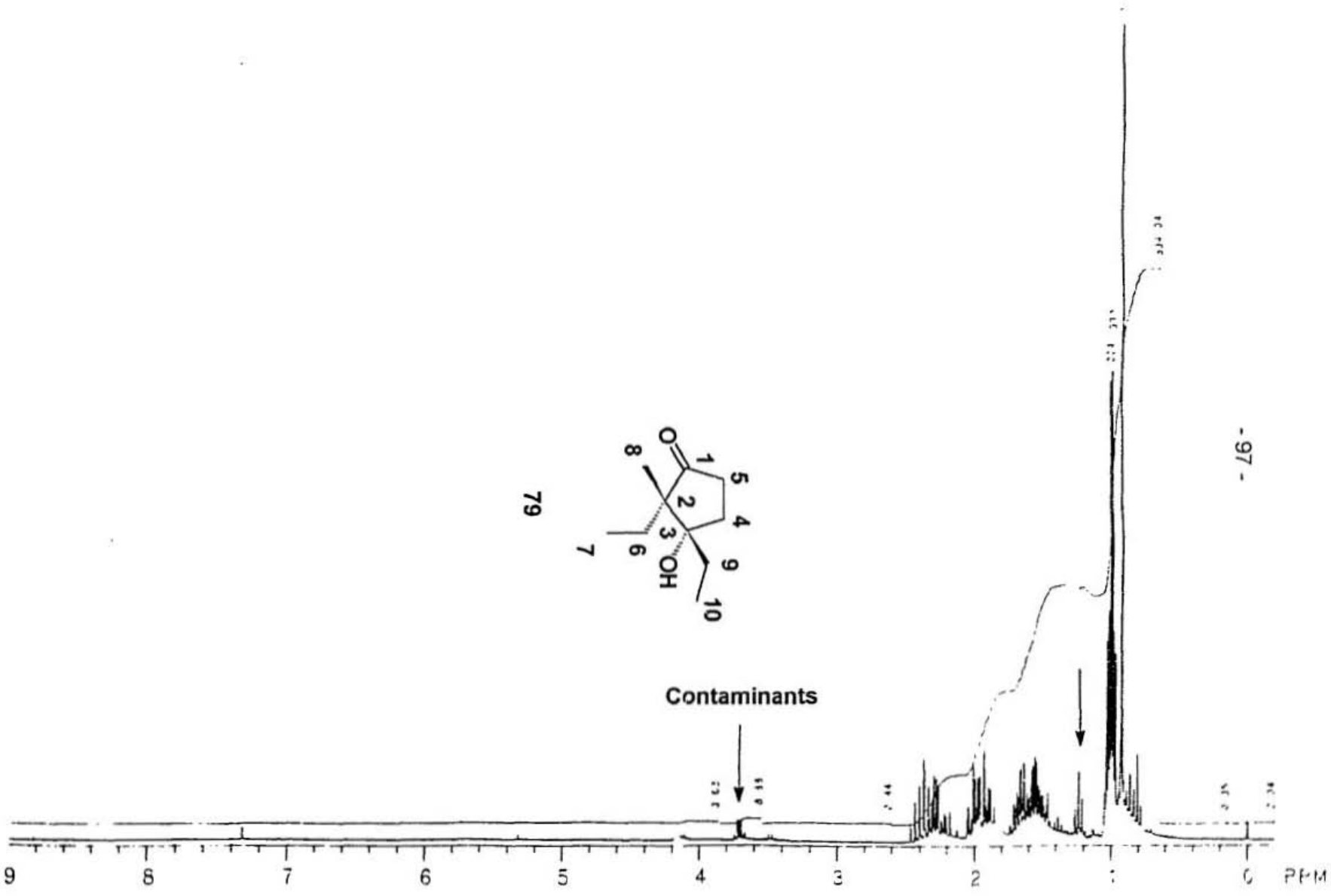
DS1120. 001 GNAT 20NOV91
DEAN STRICKLAND DSS-130A IN CDCL3 13C




Contaminants
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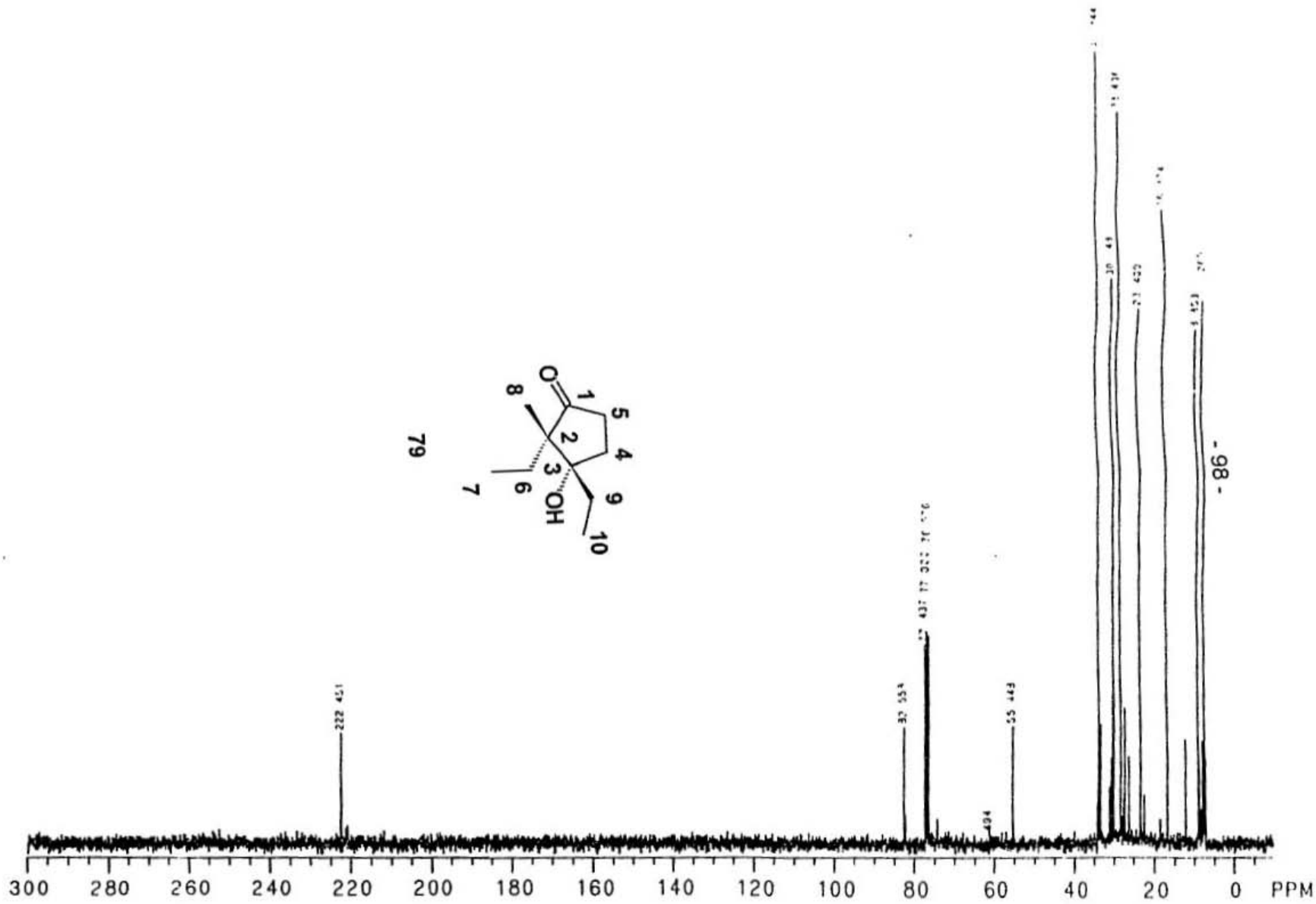
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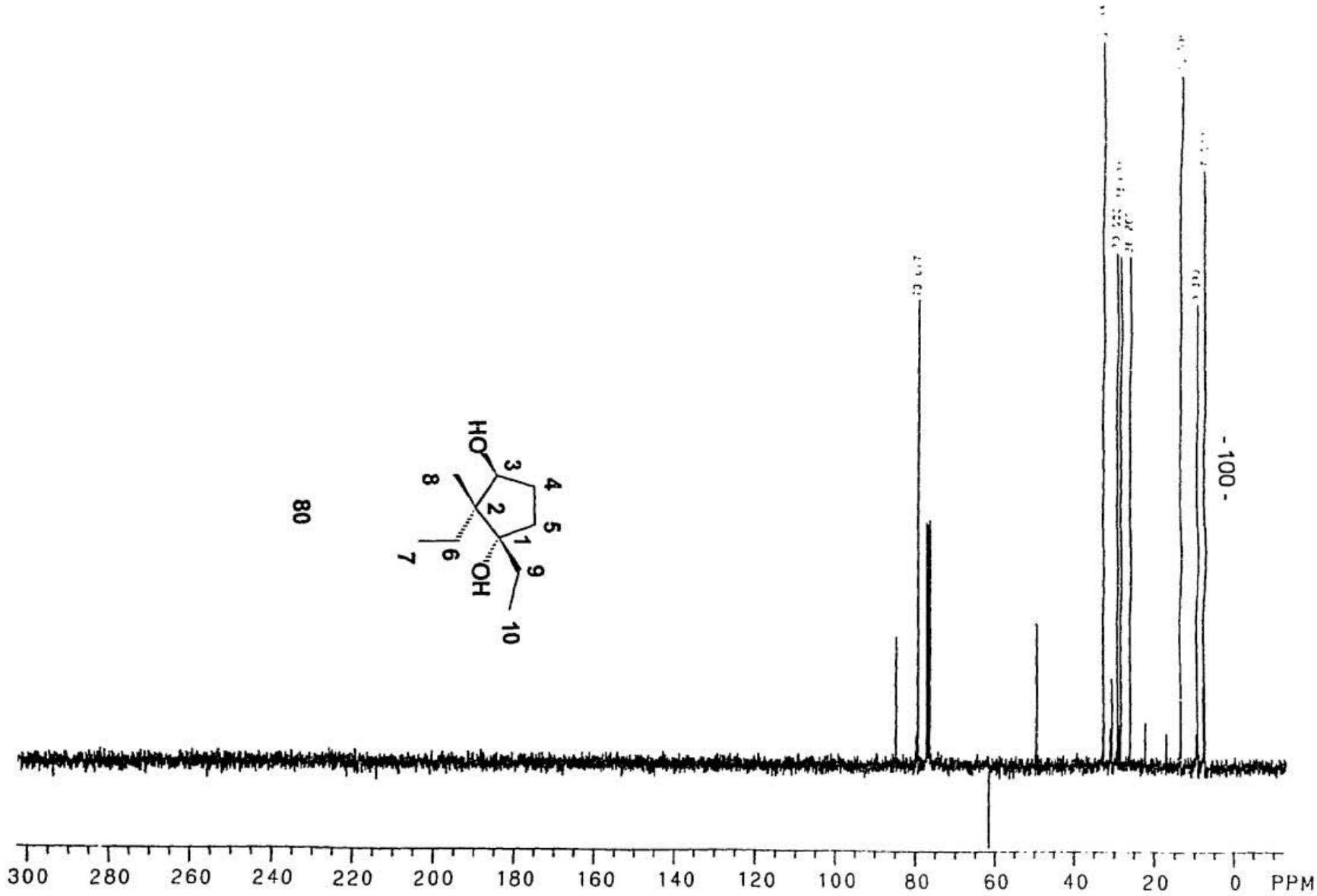
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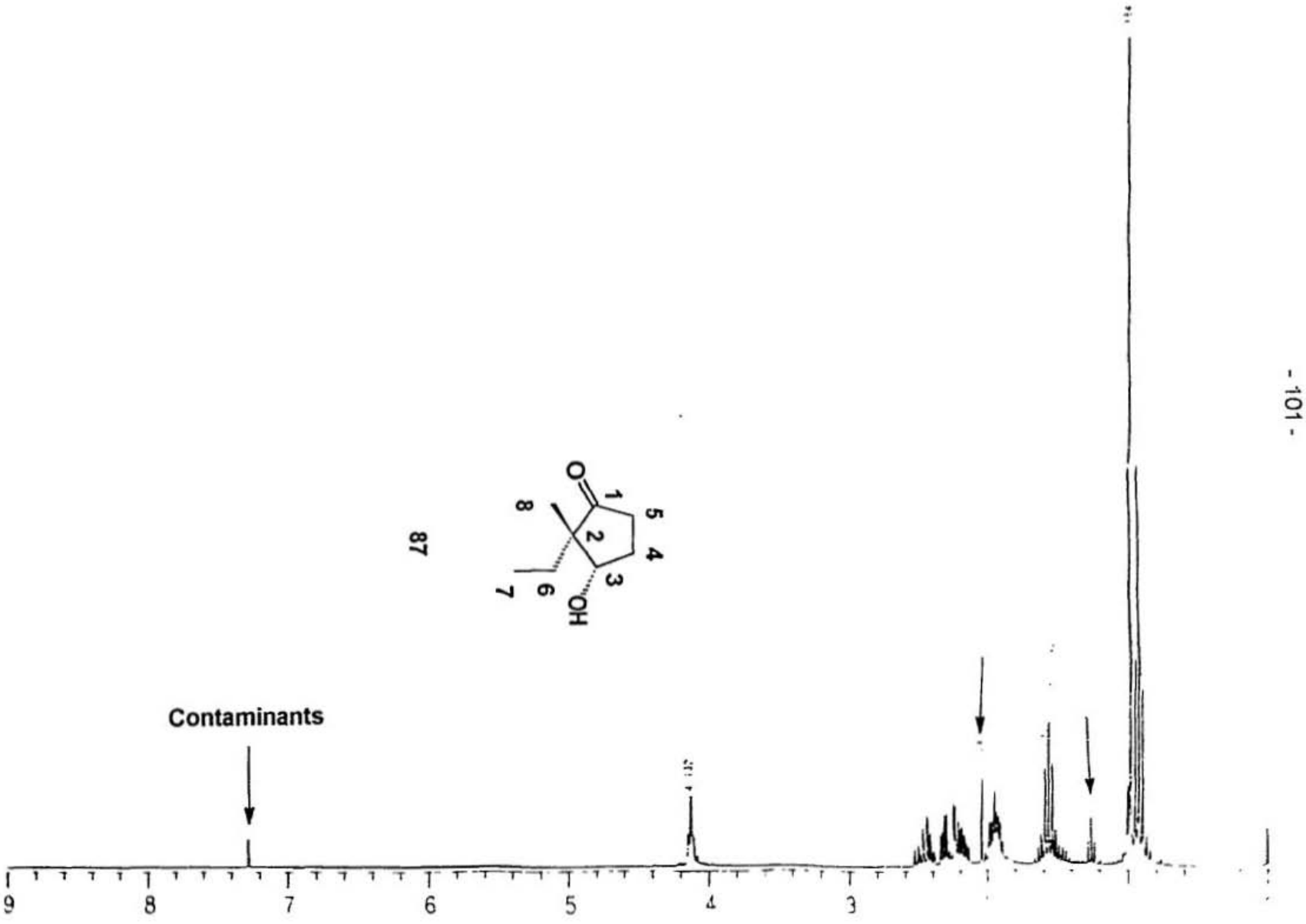
PPM

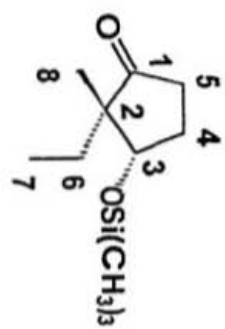
DS102A. 000 GNAT 12APR92
DINOSAUR DSS-267A IN CDCL3 1H



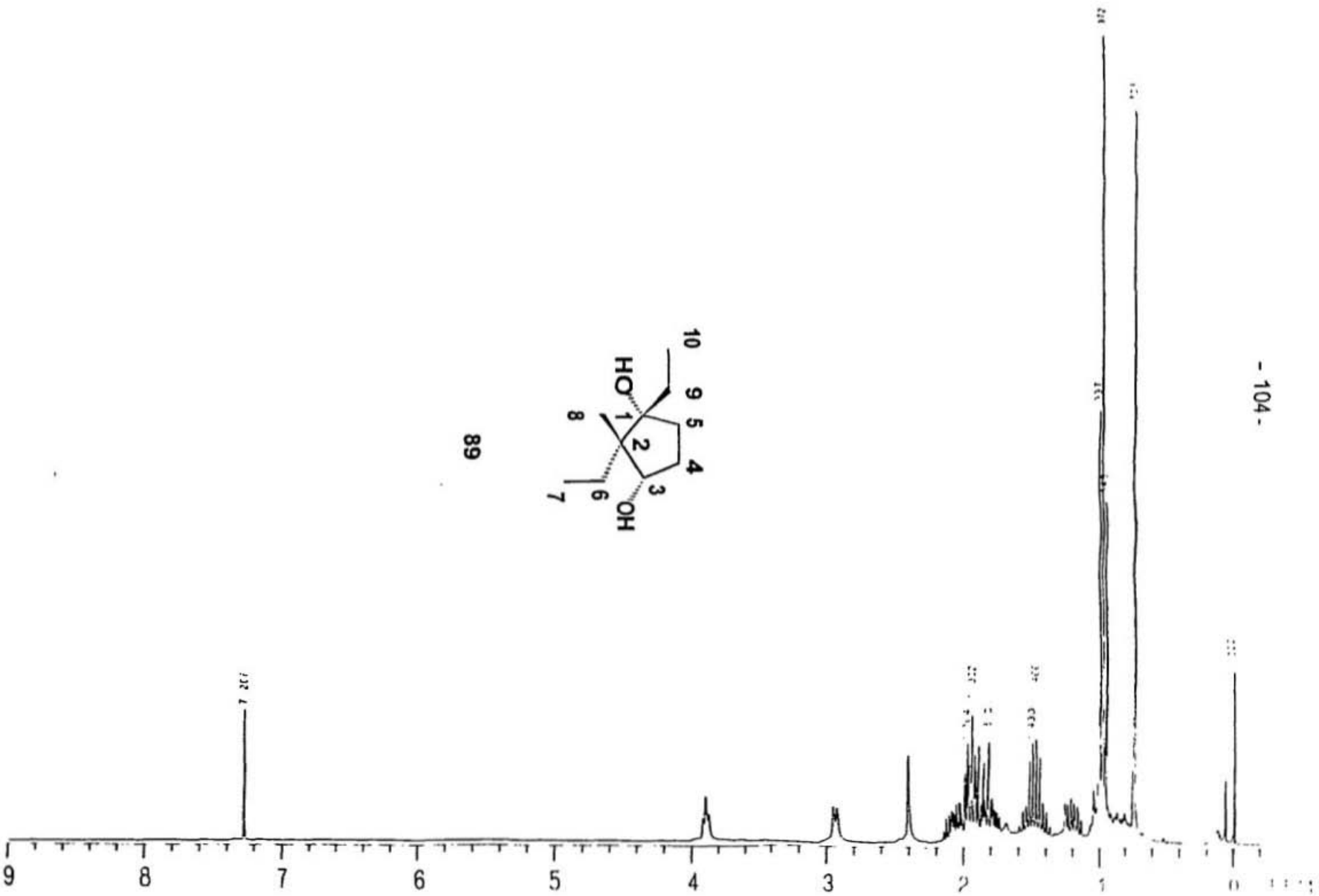
87

88A. 000 GNAT 29MAR92
DINOSAUR DSS-266A IN CDCL3 1H

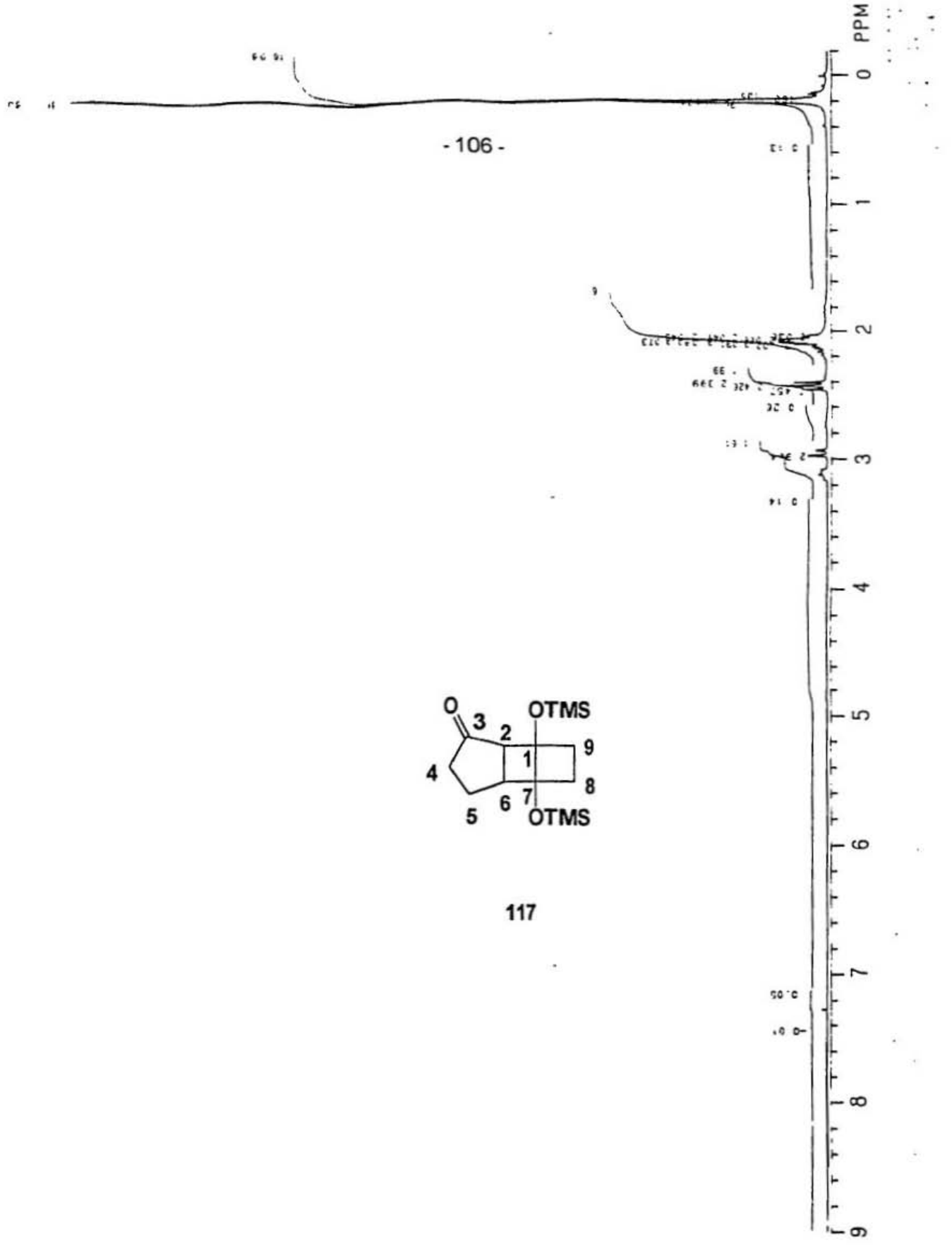
88



DS096A. 000 GNAT 06APR92
DINO DSS-274A IN CDCL3 1H

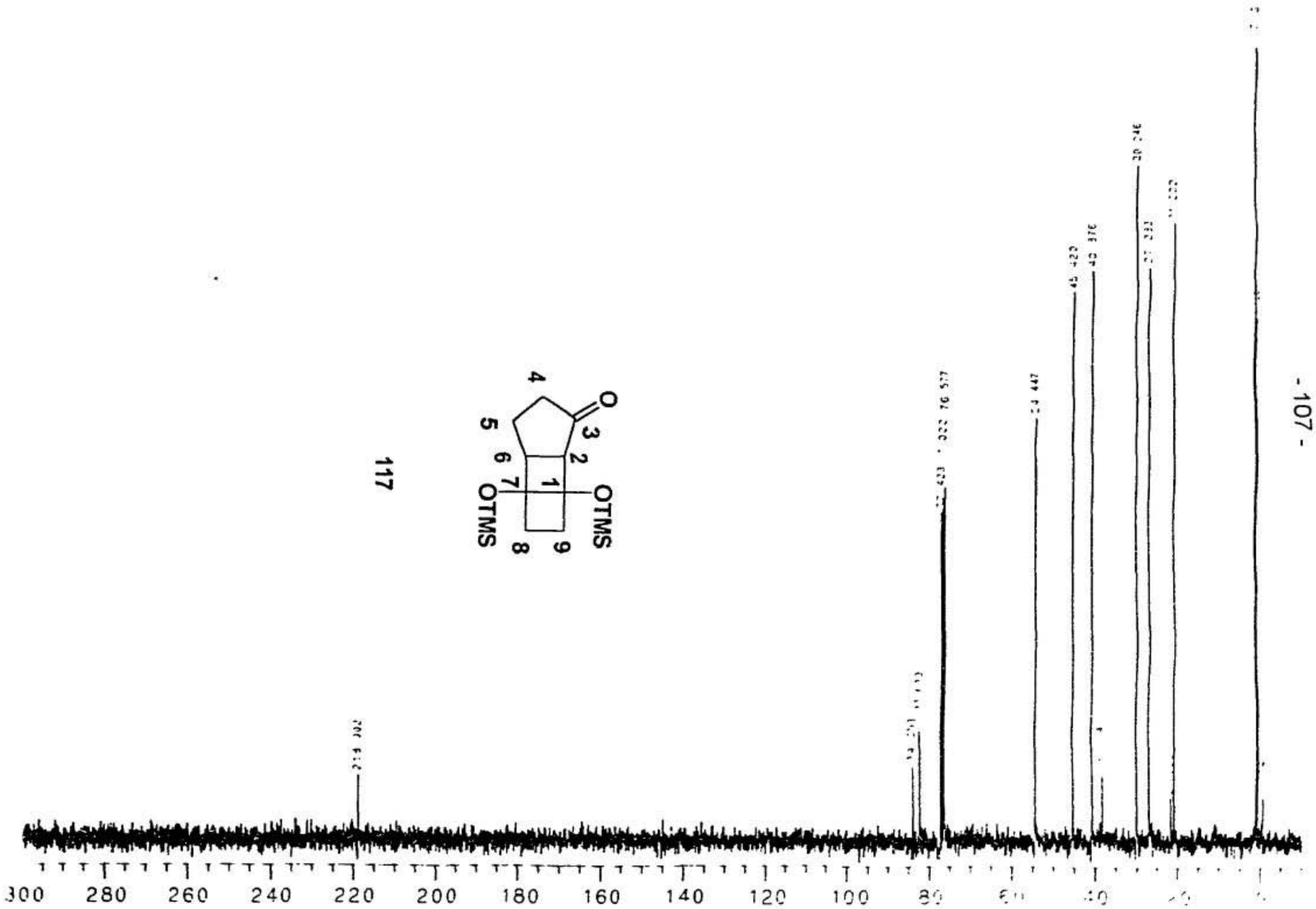


89



117

DS428B. 000 GNAT 04MAR94
DINO DSS-367A IN CDCL3 13



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