GEMINAL ACYLATION OF KETONES, METHODOLOGY, AND APPLICATIONS TO NATURAL PRODUCT SYNTHESES

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TRACY J. JENKINS

GEMINAL ACYLATION OF KETONES, METHODOLOGY, AND APPLICATIONS TO NATURAL PRODUCT SYNTHESES

by

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Abstract

Kuwajima *et al.* reported that the Lewis acid-catalysed reaction of a ketal with 1,2-bis(trimethylsilyloxy)cyclobutene (**1**) followed by rearrangement of the resulting cyclobutanone derivative with trifluoroacetic acid can provide a 2,2-disubstituted 1,3-cyclopentanedione in a reasonable yield. While this transformation has been improved by several groups, we now report, contrary to the literature, the analogous reaction between ketones and **1** occurs. For many substrates addition of a small amount of water to the reaction medium after completion of the first step assisted the subsequent rearrangement to the product, such that reversion of the intermediate to the starting ketone became an insignificant process. Yields were best with cyclohexanones (>90%), but steric hindrance and the presence of conjugated double bonds reduced yields considerably. This new spiro-annulation procedure has been applied to model studies towards the syntheses of fredericamycin A and a [4.3.3]-propellane.

Model studies towards fredericamycin A began with 1-indanone. Geminal acylation with **1** followed by dehydrogenation provided the key enedione, spiro[3-cyclopentene-1,1'-indan]-2,5-dione (**83**), which had established the key spiro center required for fredericamycin A. Our efforts concentrated on the condensation of **83** with 5,7-dimethoxy-1(*3H*)-isobenzofuranone (**143**). In an alternative approach, a Diels-Alder

cyclization between the xylylene precursor, 3,4-bis(dibromomethyl)-1-methoxybenzene (**114**) and **83** was developed.

Our studies towards the synthesis of propellanes was based on a novel intramolecular geminal acylation of a bis(trimethylsilyloxy)-cyclononene moiety (**175**). We had hoped that **175** could be prepared from diethyl 5-(1',3'-dioxocyclopentane)-4-methyl-1,9-nonanedioate (**174**), however geminal acylation of diethyl 4-methyl-5-(1,3-dioxolan-2-yl)nonanedioate (**173**) with **1** provided **174** in only trace amounts. As reported from our studies on the geminal acylation of ketals and ketones with **1** we attributed this lack of reactivity to the methyl substituent. Our second approach concentrated on a symmetrical bis(trimethylsilyloxy)-nonene compound. Double Grignard addition of the organomagnesium compound derived from 5-bromo-1-pentene to an ester gave 1,10-undecadien-6-ol (**177**), which established the carbon skeleton required for the nonene structure. Oxidation to 1,10-undecadien-6-one (**179**), followed by geminal acylation with **1** afforded 2,2-bis(4'-pentenyl)cyclopentane-1,3-dione (**181**). Conversion of the terminal double bonds of **181** into esters gave the nonene precursor, dimethyl 5-(1',3'-dioxocyclopentane)nonane-1,9-dioate (**185**). Unfortunately, our attempts to effect the acyloin condensation (diester **185** to nonene species) and the subsequent intramolecular geminal acylation were not successful.

Acknowledgements

I wish to thank my supervisor, Professor Jean Burnell, for believing in me and giving me the opportunity to study under his supervision. His encouragement and helpful guidance, not to mention the excellent synthetic projects are greatly appreciated.

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Glossary of Abbreviations

APT	Attached proton test
bp	Boiling point
Bu	Butyl
BuLi	*n*-Butyllithium
DIBAL	Diisobutylaluminum hydride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMF	*N,N*-Dimethylformamide
Et	Ethyl
GCMS	Gas chromatography-mass spectrometry
hν	Ultraviolet irradiation
IR	Infrared spectroscopy
LDA	Lithium diisopropylamide
Me	Methyl
mp	Melting point
$MgSO_4$	Magnesium sulfate
MS	Mass spectrometry, mass spectrum
NMR	Nuclear magnetic resonance spectroscopy
NOE	Nuclear Overhauser Effect
PCC	Pyridinium chlorochromate
Ph	Phenyl
TBAF	Tetrabutylammonium fluoride

TsOH	*para*-Toluenesulfonic acid
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TMSOTf	Trimethylsilyl triflate

To those who believed Thank-you

to those who didn't .....

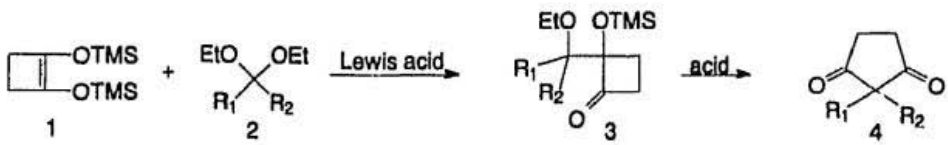
Chapter 1

GEMINAL ACYLATION OF KETONES

I. INTRODUCTION

Kuwajima and coworkers[1] demonstrated that 1,2-bis(trimethylsilyloxy)cyclobutene (**1**) reacted with aldehydes, acetals and ketals, e.g. **2**, under Lewis acid catalysis to afford a cyclobutanone derivative **3** (Scheme 1). For cyclic substrates the cyclobutanone derivative was determined by x-ray analysis to be the result of equatorial nucleophilic addition onto the carbonyl of the substrate.

Scheme 1

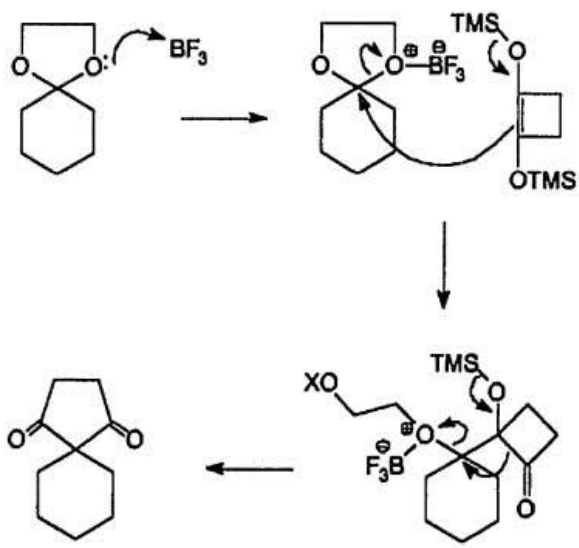


Titanium tetrachloride gave the best results as the Lewis acid catalyst for the reaction with aldehydes and aliphatic acetals, but it was inferior to boron trifluoride etherate with the more reactive acetals and ketals.[1]

Subsequent acid-catalyzed rearrangement of the cyclobutanone

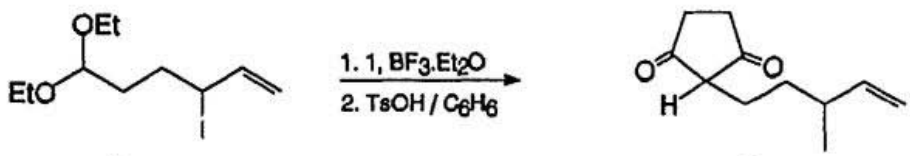
derivative **3**, either as it was or after alkylidenation or reduction of the carbonyl, was reported (Scheme 1).[1] In particular, rearrangement of **3** using excess trifluoroacetic acid (TFA) afforded the 2,2-disubstituted 1,3-cyclopentanedione **4**. Kuwajima[1] noted that *p*-toluenesulfonic acid (TsOH) in hot benzene, $BF_3.Et_2O$, and trimethylsilyl triflate (TMSOTf) in dichloromethane were also effective, but the authors claimed these did not offer the same ease of removal during work-up as did TFA. Both Wu and Burnell[2] and Ayyangar and coworkers[3] reported a more efficient approach using **1** and a large excess of $BF_3.Et_2O$, which afforded the 2,2-disubstituted 1,3-cyclopentanedione directly from a ketal in good yield. The modifications to Kuwajima's initial procedure[1] by both groups

Scheme 2



did not require isolation of the cyclobutanone derivative **3** and afforded the geminally acylated products in a one-pot two-step process in higher overall yield than those reported by Kuwajima. Both Burnell[2] and Ayyangar[3] reported virtually identical experimental procedures, but better yields are reported by the former. The mechanism of the overall transformation is expected to follow the route illustrated in Scheme 2.

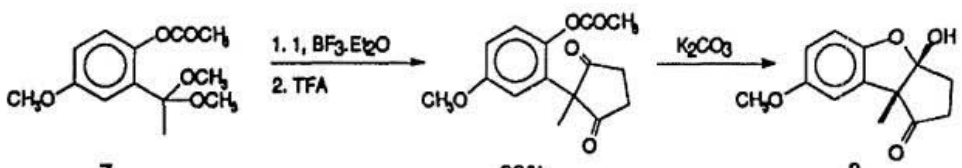
Scheme 3



5 6

The reaction of a ketal with **1** leading to the formation of a 1,3-cyclopentanedione moiety **4** has been thoroughly tested and its synthetic applications clearly demonstrated in the following examples. Compound **6**, a precursor in the synthesis of β-bulnesene, was obtained by Oppolzer's group[4] in two steps from **5** in 41% yield (Scheme 3).

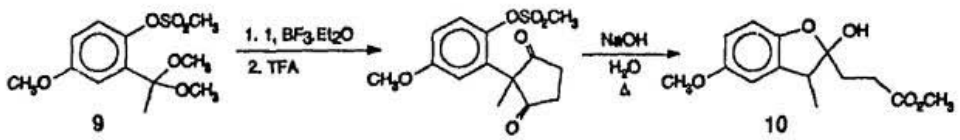
Scheme 4



7 39% 8

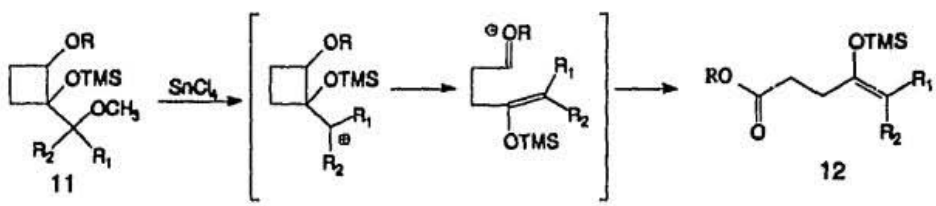
The approach of Lee and Anderson[5] towards the synthesis of trichothecane derivatives concentrated on the key intermediate **8** which they obtained from **7** in 35% (Scheme 4).

Scheme 5



Lee and Anderson[6] also incorporated the reaction in the synthesis of γ-ketocarboxylic acids, notably 2,3-dihydrobenzeno[*b*]furans. The starting ketal **9** was transformed into 2-hydroxy-2-(β-carbomethoxyethyl)-methyl-2,3-hydrobenzo[*b*]furan (**10**) in three steps in an overall yield of 50% (Scheme 5).

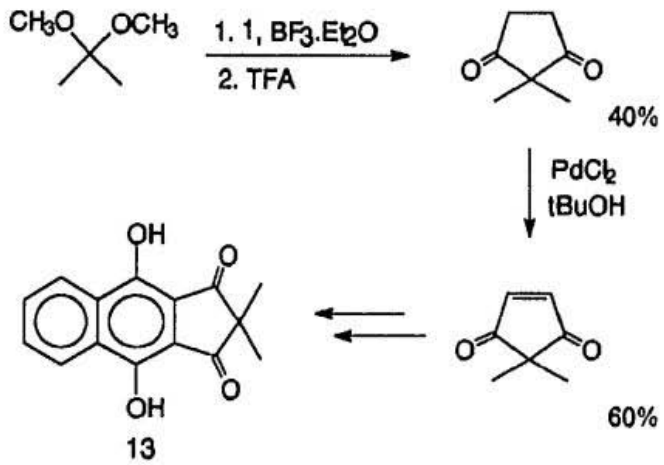
Scheme 6



It should be noted that Kuwajima's group[7] reported a more

efficient method for producing silyl enol ethers of γ-keto esters such as compound **12** using tin tetrachloride as the Lewis acid catalyst (Scheme 6). (Compound **11** was obtained from **1** and the appropriate ketal.) Yields ranged from 70 to 94%.

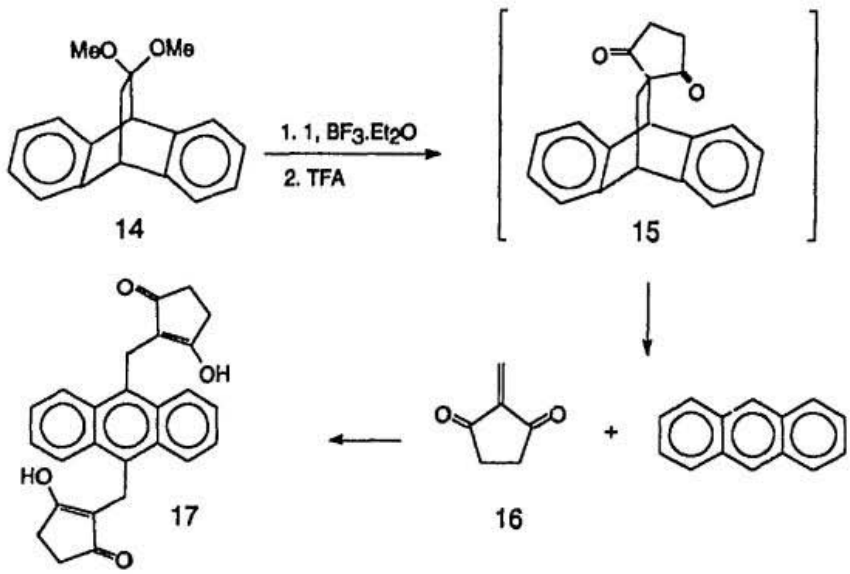
Scheme 7



In an approach to fredericamycin A, Parker *et al.*[8] synthesized 4,9-dihydroxy-2,2-dimethyl-1*H*-benzen(*f*)indene-1,3(2*H*)-dione (**13**) using Kuwajima's procedure to obtain the key 2,2-disubstituted 1,3-cyclopentanedione portion in a 40% yield (Scheme 7).

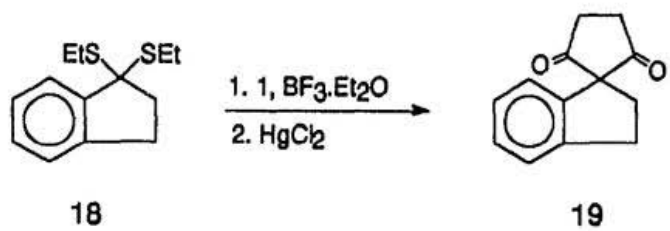
Buni . 'e and Shangraw[9] reported the *in situ* generation of the reactive 2-methylene-1,3-cyclopentanedione **16** from the acid catalyzed *retro*-Diels Alder of **15** (prepared from **1** and ketal **14**). Under the reaction conditions (TFA) only **17** was isolated (Scheme 8).

Scheme 8



Bach and coworkers' Diels-Alder approach to fredericamycin A concentrated on the spiro diketone **19** obtained from thioketal **18** in a 54% overall yield (Scheme 9).[10]

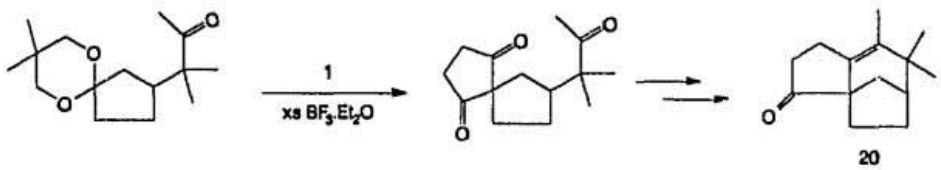
Scheme 9



Wu and Burnell's synthesis of isokhusimone (**20**) exploited the reaction of **1** with a cyclic ketal in the presence of an unprotected methyl

ketone to obtain the triketone directly in 89% yield (Scheme 10).[2b]

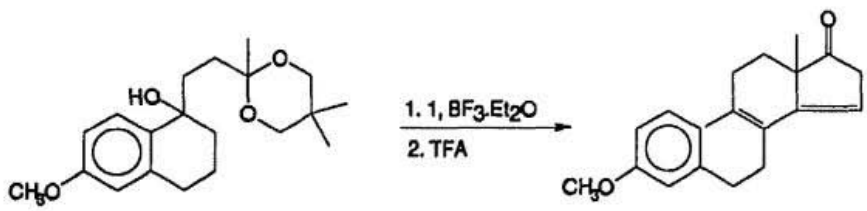
Scheme 10



20

In the synthesis of 3-methoxyestra-1,3,5,8,14-pentaen-17-one (**21**) by the same authors, the key step was the introduction of a D-ring moiety using the reaction between a cyclic ketal and **1**. The intermediate cyclopentanedione was treated with TFA to close the C-ring. The overall yield was 76% (Scheme 11).[11]

Scheme 11



21

While the synthetic utility of the reaction of **1** with ketals and acetals has been clearly demonstrated, we now report that contrary to reports in the literature[1,12,13] the analogous reaction between **1** and

ketones to provide 2,2-disubstituted 1,3-cyclopentanediones does occur. Furthermore, in some instances, notably aryl substrates, the overall yields of the diketone products are superior to those via the corresponding ketals.

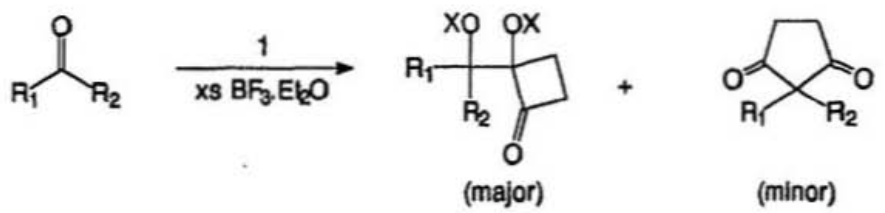
II. DEVELOPMENT OF THE METHODOLOGY

Although one might expect a reaction between **1** and a ketone to occur, Kuwajima and coworkers[1b] reported that this reaction was not observed under a variety of acidic and basic conditions. This apparent unreactivity of silyl enol ethers towards ketones was also reported for other systems.[13] Mukaiyama[14] showed that while titanium tetrachloride-catalysed reactions of silyl enol ethers did proceed with ketones, they were extremely sluggish. Thus, it appeared that if geminal acylation of ketones using **1** were to be successful, it would be necessary to overcome a lack of reactivity.

However, our initial attempts at this reaction indicated that the problem was not one of formation of the cyclobutanone derivative (from the condensation of a silyl enol ether with the ketone substrate) but rather the subsequent rearrangement of that derivative. This conclusion was based on the following evidence. Treatment of some ketones with **1**,

using the conditions that had been proven successful in the preparation of 1,3-cyclopentanediones from ketals, gave crude products that contained little of the starting ketones. Analysis of the crude products by gas chromatography-mass spectrometry (GCMS) indicated that while the starting ketones were largely consumed, large amounts of the cyclobutanone derivatives remained, unlike the reactions involving the ketals (Scheme 12). During column chromatography on silica gel, the cyclobutanone derivatives were almost completely destroyed to give back the starting ketones and only a small amount of the diketone was obtained.

Scheme 12

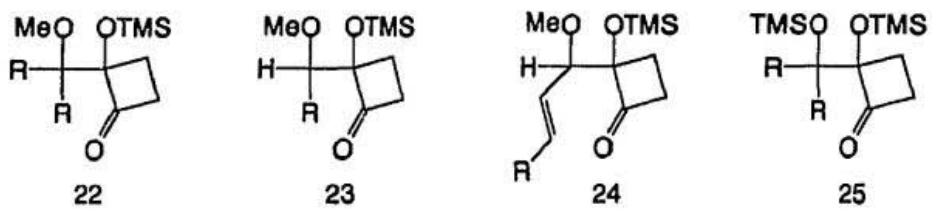


X = H or TMS

Kuwajima[1] reported that the rate of rearrangement of the cyclobutanone intermediates was highly dependent on the nature of the substrate. The product of a ketal (**22**) rearranged the most rapidly. The product from an aliphatic acetal (**23**) exhibited slow conversion, but the rearrangement of the adduct of an unsaturated acetal (**24**) (Figure 1)

afforded complex results. Our research indicated that the cyclobutanone compound derived from a ketone (**25**) was generally much more reluctant to rearrange than those derived from ketals, as the rearrangement of **25** provided a large amount of the starting ketone in addition to the diketone product.

Figure 1. Cyclobutanone Intermediates.



R = Carbon

The one-pot two-step process reported by both Burnell and Wu[2] and Ayyangar and coworkers[3] utilized a large excess of Lewis acid (10 - 15 equivalents) with two to three equivalents of **1**, which were added to a dichloromethane solution of the ketal at -78°C. The solution was stirred overnight during which time it attained room temperature. Aqueous work-up followed by purification gave geminally acylated products in good to excellent yields. This procedure will be referred to as "ketal conditions" hereafter.

Subjecting ketone substrates to these conditions gave only modest yields of cyclopentanedione products. As shown in Table 1, only two

Table 1: Reactions of Ketones and **1** under "Ketal Conditions"

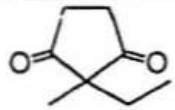
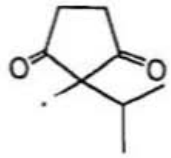
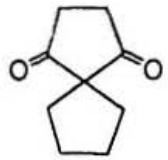
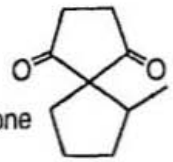
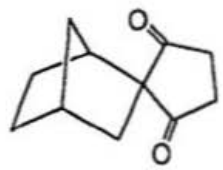
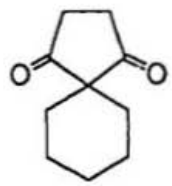
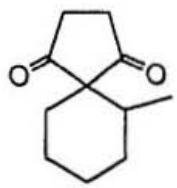
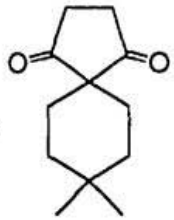
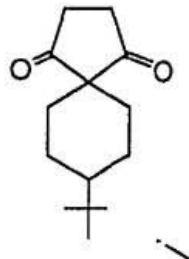
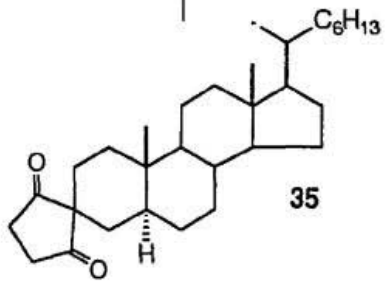
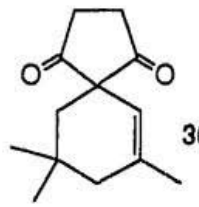
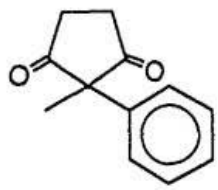
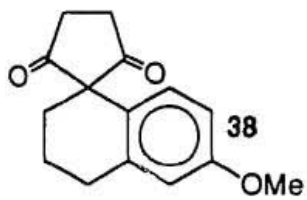
entry	substrate	product		yield (%)
1	butanone		**26**	27
2	3-methylbutanone		**27**	34
3	cyclopentanone		**28**	44
4	2-methylcyclopentanone		**29**	51
5	norcamphor		**30**	42
6	cyclohexanone		**31**	31
7	2-methylcyclohexanone		**32**	18

Table 1: Reactions of Ketones and **1** under "Ketal Conditions" (cont.)

entry	substrate	product		yield (%)
8	4,4-dimethylcyclohexanone		**33**	54
9	4-tertbutylcyclohexanone		**34**	72
10	5α-cholestan-3-one		**35**	87
11	isophorone		**36**	32
12	acetophenone		**37**	34
13	6-methoxy-1-tetralone		**38**	41

substrates, namely 4-*tert*-butylcyclohexanone (entry 9) and 5α-cholestanone (entry 10), gave synthetically acceptable yields. The majority of the substrates provided diketone products in yields less than 45% as the major product was recovered starting ketone.

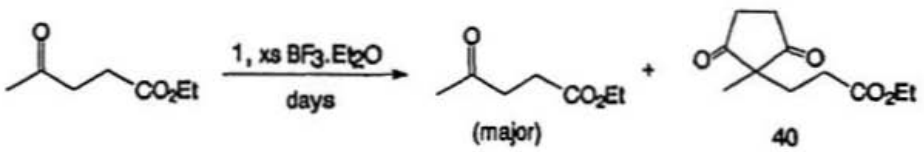
"Ketal conditions" with cyclohexanone provided a dark oil. The volatile component of this material was found to be a single compound by GCMS, the desired 1,3-cyclopentanedione, yet column chromatography on silica gel afforded the geminally acylated product **31** in only 31% yield. This yield was surprisingly low as the ^{1}H nmr spectra of the crude product and GCMS both indicated a high proportion of **31**. The low recovery of product might have been because less concentrated fractions were often invisible under standard thin-layer chromatography (TLC) visualization methods involving acid sprays (ceric ammonium nitrate/H_2SO_4, phosphomolybdic acid, or *p*-anisaldehyde in H_2SO_4) and I_2. This was observed for many 2,2-disubstituted 1,2-cyclopentanediones and in extreme cases the diketones were invisible under TLC visualization even when concentrated solutions were applied. Many samples were purified by concentrating fractions and using GCMS for detection. When the norcamphor diketone **30** was reintroduced to "ketal conditions" only 79% of the material was recovered. Similarly, when cyclohexanone was subjected to "ketal conditions", in the presence of 4-*tert*-butyl-diketone **34** the overall yield of diketone **31** was 35%, but, more

importantly, only 82% of the 4-*tert*-butyl-diketone **34** was recovered. The recovery of **31** and **34** in these experiments suggests that the losses are the result of chromatography or the reaction itself. Noting that diketones **31** and **34** did not participate in additional geminal acylation reactions, which foreshadows the limited reactivity of sterically crowded carbonyls, visualization difficulties on TLC could account for a decrease in yields of diketones by 15 to 20%. This assumption was supported experimentally when 13% of the diketone **26** was not accounted for when the sample was re-chromatographed. These experiments however, did not explain why the crude yield of geminally acylated products are so low under "ketal conditions".

The two experiments using tin tetrachloride as the Lewis acid gave more complex results than did boron trifluoride etherate. The products from both the 2-methylcyclohexanone and cyclohexanone experiments gave messy gas chromatograms containing respectively four and three, major components that exhibited similar mass spectral fragmentations to those of the desired diketone products. In the light of these results the less vigorous $BF_3.Et_2O$ was still the reagent of choice.

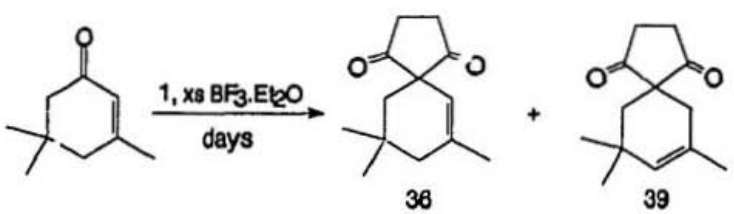
Next we varied the reaction time. However, the yield of 6-methoxy-1-tetralone diketone **38** was unchanged when the reaction time was increased from overnight to three days. Similarly, the ratio of ketone to diketone **40** in the product from the reaction of ethyl levulinate with **1**

Scheme 13



was also unaffected when the reaction time was increased to four days (Scheme 13). Substrates with an alpha double bond were more interesting. As with the other substrates, longer reaction times did not increase the yield, but double bond isomerisation did become a significant process. For example, when the reaction time for the sequence involving isophorone was increased from three days to five, the product was a mixture of diketone **36** (92%) and diketone **39**[2] (8%) in which the double bond had migrated (Scheme 14). Simarily, the crude

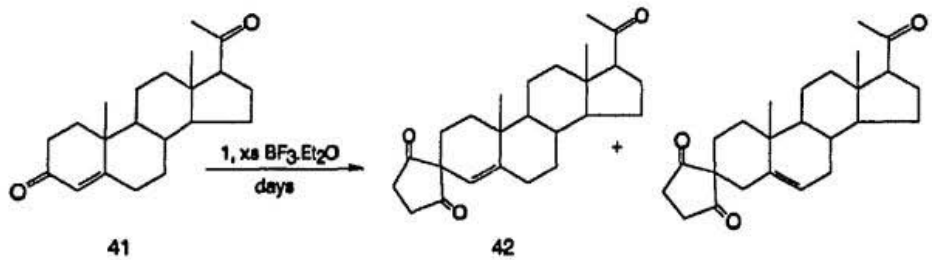
Scheme 14



product obtained from the sequence involving progesterone after 28 days had the same ratio of starting ketone **41** to diketone **42** as the sequence

with a reaction time of only 3 days. However, after 28 days both the starting ketone and the product were mixtures of double bond isomers (Scheme 15). In both the isophorone and progesterone reactions double

Scheme 15



41 42

\+ 41 and its double bond isomer

bond isomerism was detected only in the products from the longer reaction time sequences. In the case of 5α-cholestan-3-one increasing the reaction time did translate into a marginal improvement in yield. While "ketal conditions" gave a mixture of starting ketone (19%) and triketone (82%) (as determined from GCMS), increasing the reaction time from overnight to two days gave a crude material for which the gas chromatogram indicated a single volatile compound, the triketone. Flash chromatography provided the triketone in 87% yield.

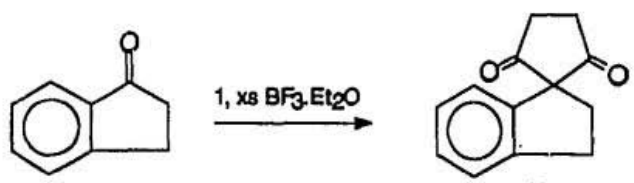
If the cyclobutanone intermediate reverted to the starting ketone, then the effect of the addition of many equivalents of **1** might have been to allow the ketone to be recycled *in situ*. Experimentally, however, the overall yield for the norcamphor diketone **30** decreased from 42% to 12%

when the number of equivalents of **1** was increased from three to eight, whereas with isophorone there was no change in the yield when the number of equivalents of **1** was increased from three to five. If the amount of starting ketone were a consequence of the destruction of the cyclobutanone intermediate, these results indicated that the reversion must have occurred during aqueous work-up. Indeed, the yields of the cyclohexanone diketone **31** and the acetophenone diketone **37** rose to 65% and 62% respectively, when the reaction times were increased to several days and the reaction solution was concentrated directly onto the chromatographic silica, i.e., without aqueous work-up. Under identical conditions, however, norcamphor provided the diketone **30** in only 4% yield. Addition of eight equivalents of **1**, in portions over many hours, to a heated solution of acetophenone and $BF_3.Et_2O$, did raise the yield to 91%. The conditions were wasteful of **1** and were found not to be beneficial for other substrates. In fact, when other substrates were subjected to these conditions the yield was lower than that obtained by using "ketal conditions". For example, 3-methylbutanone provided a crude material which by GCMS analysis contained only 11% of product **27**. Similarly, 6-methoxy-1-tetralone provided the diketone product **38** in only a trace amount under these conditions. In both cases the major component of the crude product was the starting ketone.

GCMS analyses of reaction solutions often indicated only trace

amounts of the starting material with the major signal being that of the diketone product. In addition, there were varying amounts of cyclobutanone intermediates. However, after work-up the proportion of starting ketone was often much higher at the expense of the diketone. It seemed possible that the cyclobutanone intermediate might rearrange to the diketone in the injector port of the gas chromatograph (280°C). The cyclobutanone intermediate might liberate the starting ketone only under the aqueous conditions of work-up. Then subjecting the reaction to heat by heating the reaction solutions at reflux and/or purifying them after work-up by Kugelrohr distillation at high temperatures might improve the overall yields.

Scheme 16



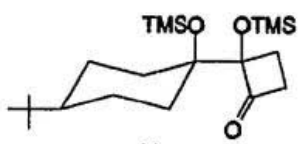
43

Experimentally, only the yield of the 1-indanone diketone **43** (70 - 75%) was improved when the reaction solution was refluxed for several hours prior to work-up and purification by Kugelrohr distillation (Scheme 16). Under the same conditions, isophorone and 6-methoxy-1-tetralone provided only the starting ketones. While cyclohexanone diketone **31**

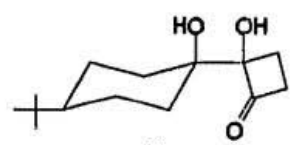
could be prepared, the yield was highly variable (best 55%). As a precautionary measure to ensure that the diketone itself was not consumed at higher temperatures, the acetophenone diketone **37** was heated with **1** and $BF_3.Et_2O$ under the same conditions, and 91% of **37** was recovered after chromatography. Kugelrohr distillation of diketone **37** was not very destructive, 86% of **37** was recovered.

Overall, there were few satisfactory results that arose from time and temperature variations on the "ketal conditions". The problem seemed to be the rearrangement of the cyclobutanone intermediate. Therefore we focused on that step. We found that the initial aldol step producing the cyclobutanone intermediate could be carried out following

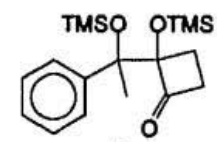
Figure 2. Isolated Cyclobutanone Intermediates.



44



45



46

Kuwajima's ketal procedure, namely using three equivalents of $BF_3.Et_2O$ at -78°C.[1b] It was possible to isolate some intermediates in which the ketone oxygens had become trimethylsilyloxy groups and/or hydroxyls, e.g. **44** and **45** from 4-*tert*-butylcyclohexanone and **46** from

acetophenone (Figure 2), but during work-up and/or isolation there was significant reversion to the starting ketones. Only 10 - 15% (by GCMS) of the product mixtures were the rearranged diketones. Thus, rearrangement studies were performed on crude mixtures which in addition to cyclobutanone derivatives also contained some diketone. The cyclobutanone intermediates typically had retention times 2-4 minutes longer than those of the diketones, but these often exhibited mass spectral fragmentation patterns very similar to that of the diketone, and their highest mass fragment was often the same as that for the molecular ion of the diketone.

The acetophenone derived cyclobutanone **46**, which was obtained as a diastereomeric mixture in a 3.5:1 ratio (by ^{1}H nmr), was treated with a variety of acids. Treatment with TFA, which was successfully employed by Kuwajima in the rearrangement of cyclobutanone derivatives obtained from acetals,[1b] led to very little reaction even when the solution was heated under reflux conditions for many hours.

Crude samples of **46** were also treated with: TsOH, camphorsulfonic acid, Amberlyst 15, and silica gel. Silica gel was studied to determine whether any of the cyclobutanone intermediate in crude products rearranged during chromatography to yield diketone. The silica used was not especially dry for these experiments. After stirring overnight at room temperature the solutions were worked-up in the same way, and the crude products were analyzed by

GCMS. The material from treatment with TsOH indicated a mixture of starting ketone (35%) and diketone **37** (54%); the product from the camphorsulfonic acid sequence showed starting ketone (24%) and diketone **37** (68%); the crude product obtained from treatment with Amberlyst 15 was determined to be starting ketone (8%) and diketone **37** (76%); and the crude product from the silica gel reaction gave a messy chromatogram, but it indicated the starting ketone (6%) and the diketone **37** (67%). From these results it appeared that Amberlyst 15 did catalyze the rearrangement to an high degree (at least for the acetophenone substrate). In preparative experiments, however, Kugelrohr distillation of the crude products led to large amounts of starting acetophenone, despite the fact that GCMS analysis prior to distillation indicated only small amounts of the starting material. This phenomenon was also observed with sequences involving the other acids. For example, Kugelrohr distillation of the crude product from refluxing **46** with TsOH was determined by GCMS to be a mixture of acetophenone (88%) and diketone **37** (2%). The small amount of **37** was most likely generated during cyclobutanone formation and not from acid catalyzed rearrangement of the intermediate. Similarly, GCMS analysis of the solution of **46** and Amberlyst 15 showed only 1% of the ketone with the dominant signal being assigned to diketone **37** (86%), but after aqueous work-up and Kugelrohr distillation GCMS analysis indicated a mixture of the starting ketone (70%) and diketone **37** (30%). Concentrating the

solution of **46** which was stirred with silica gel to dryness (without aqueous work-up) and then placing this silica gel directly on top of a chromatography column (silica), provided the diketone in only 30% yield. This low yield demonstrated that silica was not an effective catalyst for this rearrangement, furthermore, it suggested that it was unlikely that cyclobutanone intermediates rearranged during column chromatography.

Experimentation with strong acids also failed to increase the efficiency of the rearrangement to the diketone. Treatment of **46** with concentrated sulphuric acid in glacial acetic acid afforded, after Kugelrohr distillation, highly colored material, which by GCMS analysis showed one major volatile component, acetophenone. No diketone was detected. Limited success was achieved when H_2SO_4 and silica gel were added to **46**. Chromatography provided the diketone **37** in 50% yield. When the sequence was repeated in the presence of only silica gel (no H_2SO_4) the isolated yield was reduced to 31%, which was similar to the yield under "ketal conditions": 34%. Addition of H_2SO_4 and silica gel to a solution of cyclohexanone, $BF_3.Et_2O$, and **1**, did afford a synthetically acceptable yield of diketone **31**, 75% yield. The conditions, however, were not general because norcamphor under the same conditions furnished the corresponding diketone **30** in only 11% yield. Furthermore, the yield of diketone **30** was found to be independent of the amount of H_2SO_4. This led us to speculate that the key to the process was the moisture

contained in the acid and not the actual acid. Addition of water alone to solutions of a ketone, $BF_3.Et_2O$, and **1**, failed to increase the yield of the desired diketone. The products obtained under these conditions were found by GCMS and ^1H nmr analysis to contain a high proportion of the cyclobutanone intermediate. After much experimentation we found that addition of excess $BF_3.Et_2O$ after the addition of water resulted in an initial exothermic reaction, and, after several hours the diketones were isolated in reasonable yields after work-up.

Our attention now returned to the first step in the process in order to fine-tune the overall yield. The amount of Lewis acid was varied. It was determined that the starting ketone was consumed when as few as 0.5 equivalents of the Lewis acid were present. In some cases, small amounts of both the geminally acylated product and the starting material were also isolated when only 0.5 equivalents of $BF_3.Et_2O$ were used to generate the cyclobutanone derivative. Increasing the amount of $BF_3.Et_2O$ to one molar equivalent, provided the cyclobutanone intermediates (in addition to a small amount of diketone) with only a minimal amount of residual ketone. Also, after considerable experimentation, we found that 2.5 to 3 equivalents of **1** were not necessary. The transformation to the cyclobutanone intermediate was equally successful when only 1.5 equivalents of **1** were used.

We found room temperature to be advantageous over -78°C

because the time required for the reaction was greatly decreased. Isolated yields were similar despite the fact that the crude samples from the room temperature sequences were highly colored, commonly black, oils, as opposed to the tan or yellow oils isolated from the analogous reactions at -78°C. In all cases the room temperature procedure provided crude samples for which nmr and GCMS analysis indicated a very high proportion of the diketone. Most of the impurities and color were removed easily by passing an ethereal solution of the crude product through a small-bore column containing charcoal (3 g) and Florisil (5 - 7 g). Only a few diketone products had to be purified further by chromatography on silica gel.

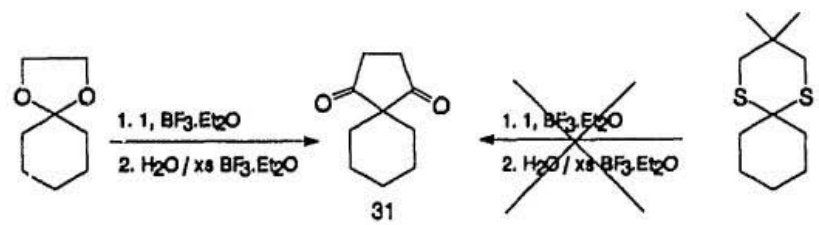
The best general conditions for the intermolecular reaction were addition of 1.0 - 1.2 equivalents of $BF_3.Et_2O$ to a solution of the ketone in dichloromethane at room temperature followed by 1.5 equivalents of **1**. As stated above subsequent rearrangement of the cyclobutanone intermediates was accomplished in the same pot by the addition of water (a volume approximately equal to the volume of $BF_3.Et_2O$ subsequently used) followed shortly thereafter by 15 equivalents of $BF_3.Et_2O$. Aqueous work-up consisted of washing the reaction solution with H_2O, re-extraction of the aqueous layer with CH_2Cl_2, followed by drying the combined organic solutions by washing with brine and then adding $MgSO_4$. Purification was usually by passage through a charcoal/Florisil

plug. For the first attempt with a new substrate, a good starting procedure would involve a reaction time of 1 - 2 h for each step.

When the intermolecular reaction of 1-indanone with **1**, for example, was only allowed five minutes, rearrangement (overnight) followed by isolation gave a 1:1 mixture of ketone and diketone **43**. Increasing the reaction time of the intermolecular step to one hour under similar conditions gave diketone **43** in an overall yield of 71%. Allowing each step to proceed over 19 h gave only a marginal improvement in the yield (75%).

This general procedure was used as a starting point for the optimization of reactions involving a variety of ketones. For some substrates longer reaction times for either the intermolecular reaction or the intramolecular rearrangement, or both, led to higher overall yields. For very unreactive substrates allowing a day for each step gave the best overall yields, but in most cases two hours for each step was sufficient.

Scheme 17



31

These conditions proved equally effective for the 1,3-dioxolane ketal of cyclohexanone (Scheme 17). As a consequence we feel that the reaction of **1** and a ketal can be accomplished under these conditions offering the advantages of decreasing both the required equivalents of **1** and the reaction time in addition to offering a simplified isolation procedure. The 1,3-dithiane ketal of cyclohexanone was unreactive under our conditions (Scheme 17), so this may be used as a protecting group that might allow selective reaction of di- or triketones.

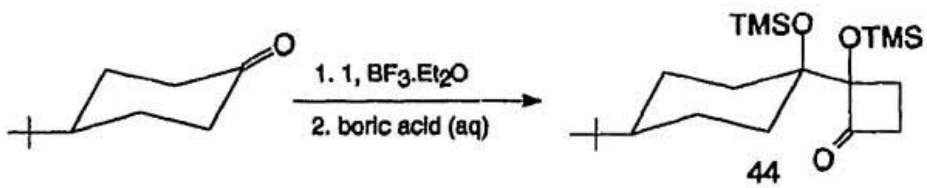
III. MECHANISTIC ANALYSIS

As previously stated, a cyclobutanone intermediate in which the ketone oxygen had become a trimethylsilyloxy group and/or an hydroxyl could be isolated, but, because there was significant reversion to the starting ketone during work-up and chromatography, these intermediates were seldom isolated.

The cyclobutanone derivatives were prepared from a few ketones by quenching a solution of the ketone substrate, one equivalent of $BF_3.Et_2O$ and 1.5 equivalents of **1**, after the intermolecular reaction had taken place (typically 1 - 2 h). For 4-*tert*-butylcyclohexanone, appreciable amounts of the diketone were formed when the reaction time was increased, despite the fact that only one equivalent of $BF_3.Et_2O$ had been

added. Experimentally, stirring a solution of 4-*tert*-butylcyclohexanone under these conditions overnight gave a crude product (78% yield) for which the ^{1}H nmr spectrum showed the diketone **34** to be the major component. Cyclobutanone intermediates which had either trimethylsilyloxy groups or tertiary hydroxyls could be obtained depending upon the conditions used to quench the intermolecular reaction. Addition of a saturated aqueous boric acid solution to a solution of 4-*tert*-butylcyclohexanone, one equivalent of $BF_3.Et_2O$ and 1.5 equivalents of **1** provided after 2 hours a crude product, which was shown by GCMS analysis to be a mixture containing 63% of **44** (Scheme 18).

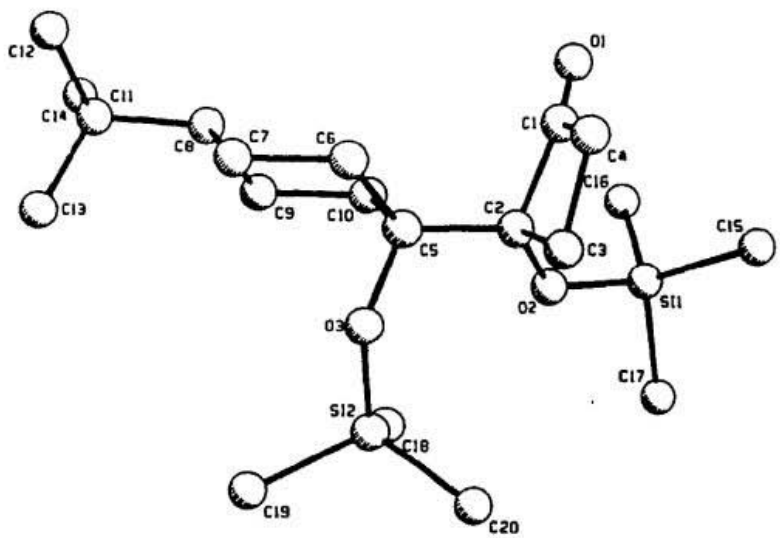
Scheme 18



Chromatography provided the starting ketone (56% recovery) and the cyclobutanone derivative **44** (32% yield). Distinctive spectral features of **44** included the carbonyl stretch at 1784 cm^{-1} in the IR spectrum and ^{1}H nmr resonances for the trimethylsilyl groups as singlets at δ 0.15 and 0.11 ppm. The ^{13}C nmr spectrum included the carbonyl resonance at δ

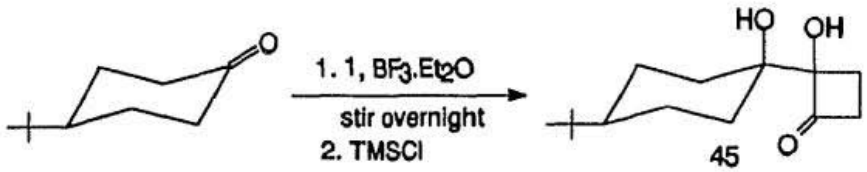
212.7 ppm, and the other quaternary cyclobutanone carbon had a resonance at δ 98.7 ppm. The two carbons bearing the trimethylsilyloxy or hydroxy substituents had characteristic resonances in the ^{13}C nmr with shifts of δ 96 - 98 and 73 - 77 ppm for all cyclobutanone intermediates independent of the starting ketone. The x-ray structure of **44** (Figure 3) revealed it to be the product of an equatorial attack onto the carbonyl. This was the same direction of addition as Kuwajima had observed with the corresponding ketal.[1b]

Figure 3. X-ray Crystal Structure of 44.



Under conditions that we suspected would favor **44**, namely quenching with a large excess of chlorotrimethylsilane (TMSCl), surprisingly the cyclobutanone derivative **45**, in which two oxygens were in the form of tertiary alcohols, was isolated in 35% yield along with 18%

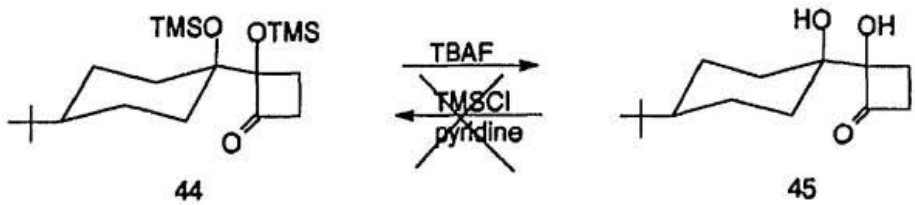
Scheme 19



of the diketone **34** (Scheme 19). Evidence supporting the structure of **45** included quaternary carbon resonances at δ 96.0 and 72.8 ppm in the ^{13}C nmr spectrum.

Whereas the conversion of the doubly silylated cyclobutanone **44** to the diol cyclobutanone derivative **45** proceeded smoothly with tetrabutylammonium fluoride (TBAF), the reverse reaction, conversion of the diol **45** to **44**, was not successful with TMSCl in pyridine; diol **45** was simply recovered (Scheme 20). Neither sequence resulted in

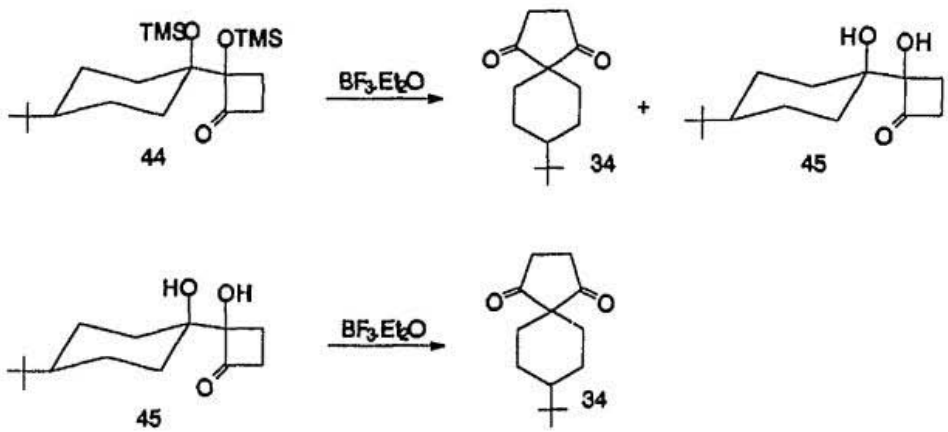
Scheme 20



rearrangement to diketone **34**, which was in agreement with preparative experiments in which synthetically useful yields of diketone were only

obtained after treatment with excess Lewis acid. Addition of H_2O or TBAF without the excess $BF_3.Et_2O$ resulted in the isolation of the diketone in yields typically less than 20%, and 50 - 60% of the starting ketone was recovered.

Scheme 21

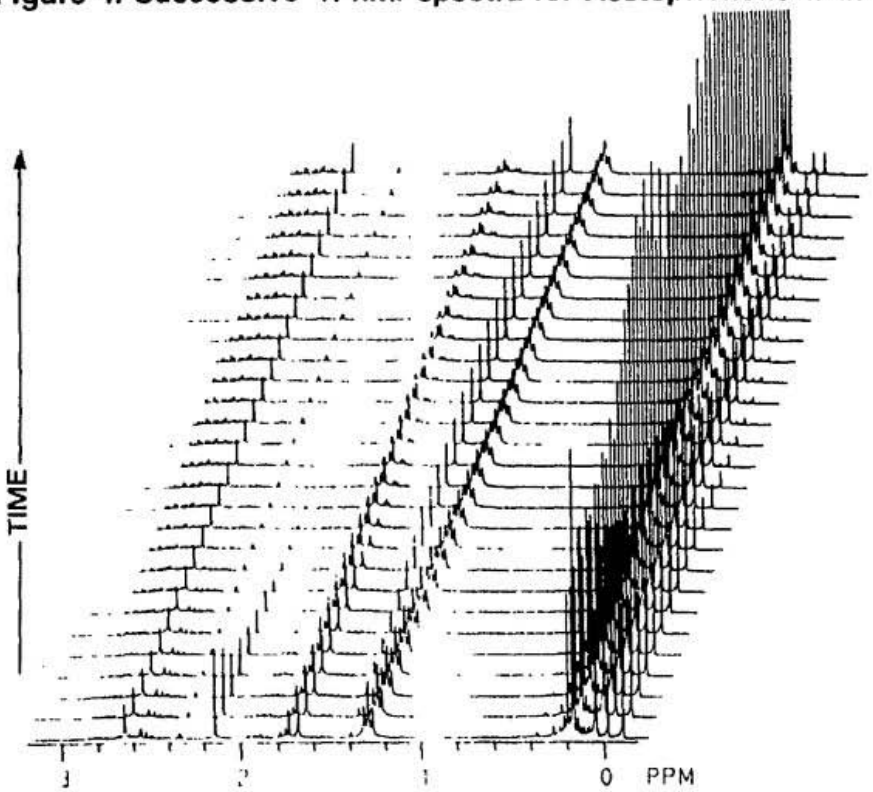


While both cyclobutanone derivatives **45** and **44** rearranged to diketone **34** upon treatment with excess $BF_3.Et_2O$ (no H_2O), the reaction rates for the transformation were different (Scheme 21). Stirring a solution of **45** overnight in the presence of fifteen equivalents of $BF_3.Et_2O$ provided diketone **34** as the only product, whereas under the same conditions **44** provided a mixture of diketone **34** and the diol **45** (7:1, respectively, by ^1H nmr). Decreasing the reaction time from overnight to thirty minutes gave the same result. One explanation may be the

difference in bond strength between the oxygen-silicon (**44**) versus the oxygen-hydrogen bond (**45**). In order for rearrangement to begin, an oxygen-silicon in **44** must be broken, in contrast with an oxygen-hydrogen in **45**. That is rearrangement of **44**, compared to **45**, will be a higher energy process. The fact that under the above conditions ($BF_3.Et_2O$) **44** afforded a mixture of diketone **34** and **45**, is most likely the result of hydrolysis of **44** during aqueous work-up to give **45**. One can speculate that under the experimental conditions we developed that the addition of water and excess $BF_3.Et_2O$ must have facilitated the rearrangement by hydrolysis of one or both of the trimethylsilyloxy groups. We expected TBAF would cleave the trimethylsilyl moieties more effectively than did water but TBAF in the place of H_2O gave a mixture containing diketone **31** (69%) and the diol cyclobutanone derivative (23%) from cyclohexanone. In contrast, with H_2O the yield was 94%. Replacing H_2O with TBAF did improve the yield of 1-indanone diketone **43** to 71%, the best conditions involving reflux afforded **43** in 74%.

The large amount of starting ketone recovered from reactions of a ketone with **1** under the optimized conditions suggested that for these substrates the intermolecular aldol step may not have proceeded with high efficiency or that there was still another intermediate (which we have never been able to isolate) that reverted back to starting ketone instead of rearranging under Lewis acid catalysis. Evidence for the

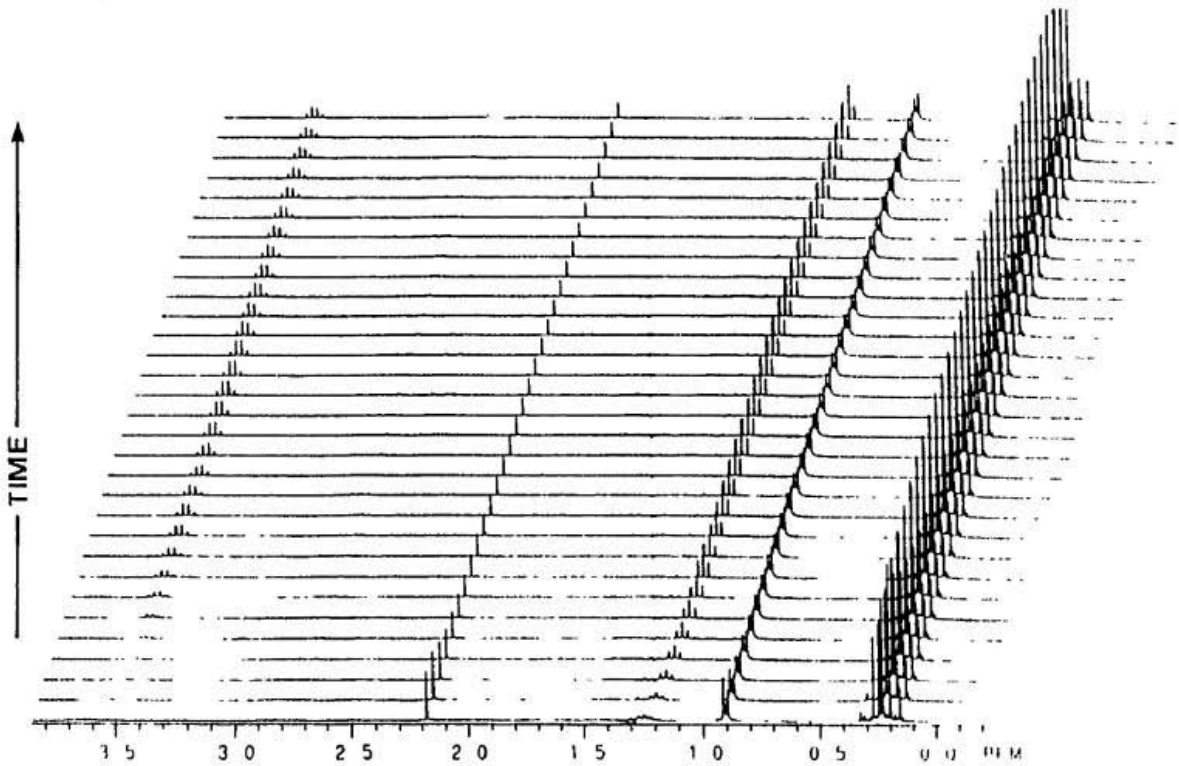
Figure 4. Successive ^{1}H nmr spectra for Acetophenone with 1.



existence of another intermediate was found when the reaction of acetophenone with **1** was followed by ^{1}H nmr (Figure 4). While the major signals were assigned to the diastereomeric doubly silylated cyclobutanones **46**, other signals whose intensity did not decrease with time were also detected. Furthermore, while chromatography of the product from the reaction of 4-*tert*-butylcyclohexanone and **1** provided pure **45** and **44** cyclobutanone intermediates, there were some fractions containing mixtures of the starting ketone and/or the **44** and **45** in addition to a minor component with a similar retention time and fragmentation pattern to **44** and **45** in the GCMS analysis. If this minor

signal were a third cyclobutanone it might have been destroyed on silica to give the starting ketone.

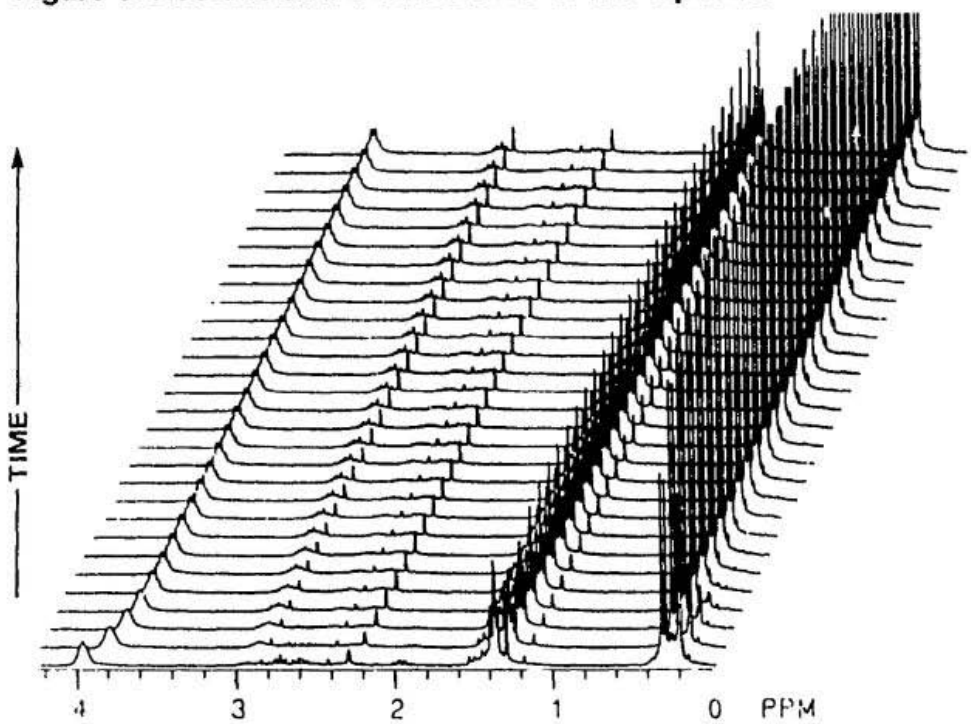
Figure 5. 4-*tert*-Butylcyclohexanone and 1 Successive ^{1}H nmr Spectra.



The reaction of 4-*tert*-butylcyclohexanone with **1** was followed by ^{1}H nmr spectroscopy but unfortunately there was no change in the successive spectra (Figure 5) after ten minutes. The doubly silylated compound **44** was generated quickly, but no diketone signals emerged with time nor did the proportion of the intermediates change with time. When the reaction of acetone with **1** was monitored by ^{1}H nmr

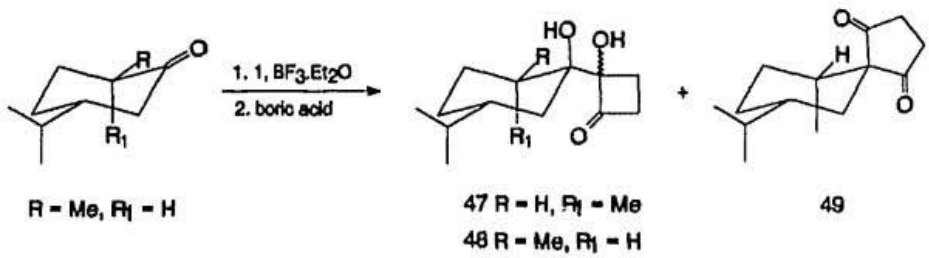
spectroscopy, signals for the doubly silylated cyclobutanone intermediate (analogous to **44**) appeared quickly. In fact, the first acquisition (elapsed reaction time of 5 min) already showed these signals. Successive spectra (Figure 6) did show a decrease in the intensity of these signals, but, unlike acetophenone, no diketone signals emerged. What appeared to be signals for another cyclobutanone intermediate, quite possibly the dihydroxy intermediate arose.

Figure 6. Acetone and 1 Successive ^{1}H nmr Spectra.



Cyclobutanone intermediates were obtained from tetrahydrocarvone (a 1:1 epimeric mixture), a substrate which bore an alpha substituent. Quenching its reaction with a saturated boric acid solution, as in the preparation of compound **44**, provided a mixture that

Scheme 22



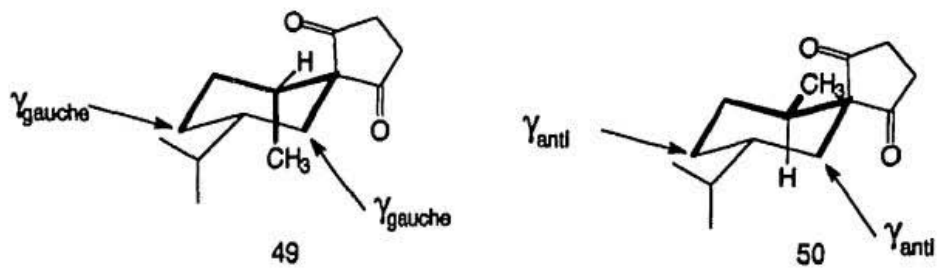
R = Me, R_1 = H

47 R = H, R_1 = Me
48 R = Me, R_1 = H

49

consisted of diol intermediates **47** and **48** (Scheme 22). Chromatography provided the intermediates **47** (12%) and **48** (24%), each as an epimeric mixture with every resonance in their ^{1}H and ^{13}C nmr spectra doubled. In addition, a small amount (11%) of diketone **49** was obtained. It was remarkable that this product consisted very largely of the isomer with the methyl substituent in the axial position. This was in marked contrast with the major isomer obtained when the same tetrahydrocarvone was ketalized and then reacted with **1** under "ketal conditions". Under these conditions the product (**50**) had the methyl substituent in the equatorial position (Figure 7).[16] Hence, depending on the parameters chosen, different isomers of the tetrahydrocarvone diketone could be prepared selectively. The ^{13}C nmr resonances for the methylenes C-7, C-8, C-10 for **50** were δ 35.4, 29.4 and 28.5 ppm. In **49** the influence of the gauche relationship of the axial methyl (at C-6) was obvious from the significantly upfield shifts for the analogous methylenes at δ 27.6, 25.2 and 22.1 ppm.

Figure 7. Diketone Isomers of Tetrahydrocarvone.



The diol **47** had been obtained as a 1:1 mixture, epimeric at C-2 of the cyclobutanone moiety. Successive crystallizations resolved only one of the isomers. Key spectral features of this pure isomer included the carbonyl stretch in the IR spectrum at 1767 cm^{-1}, and the tertiary alcohol resonances in the ^{13}C nmr spectrum at δ 97.9 and 76.1 ppm. From the material that could not be purified, the analogous remaining signals attributed to the other isomer included the resonances at δ 95.8 and 77.0 ppm. These data did not allow us to assign the relative stereochemistry of the pure isomer and unfortunately the crystals were not suitable for x-ray crystallography.

The diol cyclobutanone intermediate **48** with the equatorial methyl was also an epimeric mixture in a ratio of 2.2:1. Unfortunately, crystallization of **48** failed to separate these isomers. The key tertiary alcohol resonances in the ^{13}C nmr spectrum were found at δ 97.1 and 76.0 ppm for the major isomer and at δ 98.7 and 75.3 ppm for the minor

isomer.

In an attempt to isolate and characterize the bis(trimethylsilyloxy) intermediates from tetrahydrocarvone, the intermolecular reaction (tetrahydrocarvone, 1.5 equivalents of **1** and 1.1 equivalents of $BF_3.Et_2O$) was stirred overnight. Work-up, however, provided crude material that was again mainly a mixture of the diols **47** and **48**. Surprisingly, there was no evidence for the bis(trimethylsilyloxy) intermediates. In preparative experiments only the diol cyclobutanone intermediates **47** and **48** (never the silylated derivative) were isolated along with diketones **49** and **50**.

These results allowed us to speculate that the low yields for geminally acylated products with substrates bearing an alpha substituent are the consequence of both the reluctance of the intermolecular reaction to occur due to steric hindrance and a decrease in the efficiency of the rearrangement of the cyclobutanone intermediates.

IV. DISCUSSION OF YIELDS

The methodology was applied to a wide variety of ketone substrates, and, after considerable experimentation, optimal yields were reached for most cases. The optimized yield with each substrate is listed

in Table 2[1]. The results confirmed that the reaction is very sensitive to the steric environment of the ketone as illustrated by a comparison of entry 1 (acetone), which furnished diketone **51** in 84% yield, with entry 6 (3-methylbutanone), in which diketone **27** was isolated in only 52% yield. Substrates having a quaternary center alpha to the ketone failed to react. For example, reintroducing diketone **28** (generated from **1** and cyclopentanone) into the reaction conditions resulted in no additional geminal acylation of the cyclopentanedione ketones. The result ensured that a 2,2-disubstituted 1,3-cyclopentanedione product does not continue to react under these conditions. High yields could only be obtained with unencumbered ketones. Substrates in which the adjacent carbons on both sides of the ketone bore substituents, e.g., 2,4-dimethyl-3-pentanone, also failed to react. The effect of an α-methyl substituent on either the cyclopentanone or cyclohexanone was to reduce the yield by approximately 30%. Cyclopentanone (entry 7) gave diketone **28** in 79% yield as opposed to 2-methylcyclopentanone (entry 8) for which the yield of diketone **29** was 55%. Similarly, cyclohexanone (entry 10) versus 2-methylcyclohexanone (entry 11) showed a decrease in yield from 94% to 62%. The effect of an α-methyl substituent is believed to be twofold: the

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[1] For the results of the actual optimization experiments see the data presented in tabular form for cyclohexanone, 2-methylcyclohexanone, norcamphor, isophorone, and 1-indanone in the Appendix.

Table 2: Reactions of 1,2-Bis(trimethylsilyloxy)cyclobutene (**1**) and Ketones

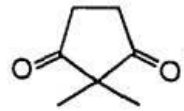
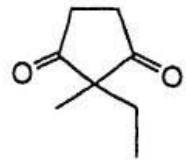
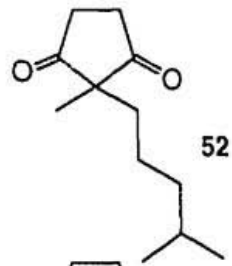
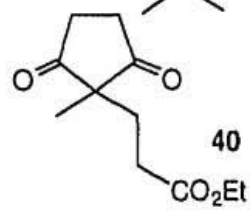
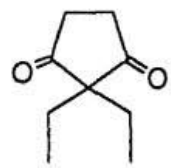
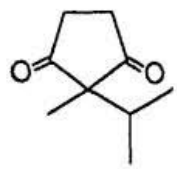
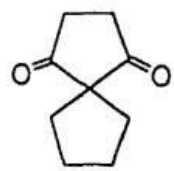
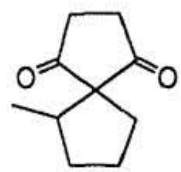
entry	substrate	product	yield (%)
1	acetone	 **51**	84
2	butanone	 **26**	61
3	6-methyl-2-heptanone	 **52**	65
4	ethyl levulinate	 **40**	36
5	3-pentanone	 **53**	47
6	3-methylbutanone	 **27**	52
7	cyclopentanone	 **28**	79
8	2-methylcyclopentanone	 **29**	55

Table 2: Reactions of 1,2-Bis(trimethylsilyloxy)cyclobutene (**1**) and Ketones (cont.)

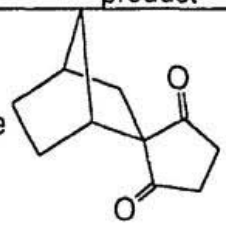
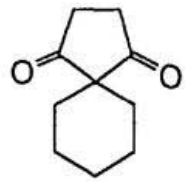
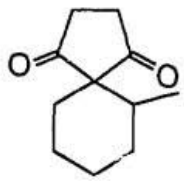
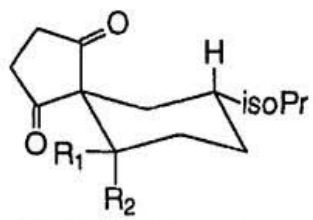
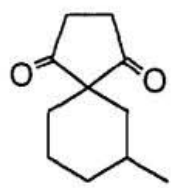
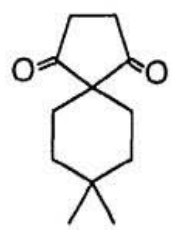
entry	substrate	product		yield (%)
9	bicyclo[2.2.1]heptan-2-one		**30**	75
10	cyclohexanone		**31**	94
11	2-methylcyclohexanone		**32**	62
12	tetrahydrocarvone (1:1 mixture of epimers)			
		49 R_1 = H, R_2 = Me		52
		50 R_1 = Me, R_2 = H		3
13	3-methylcyclohexanone		**54**	93
14	4,4-dimethylcyclohexanone		**33**	90

Table 2: Reactions of 1,2-Bis(trimethylsilyloxy)cyclobutene (**1**) and Ketones (cont.)

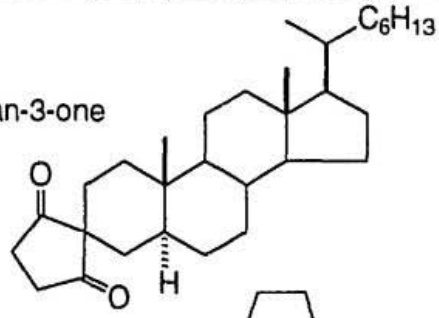
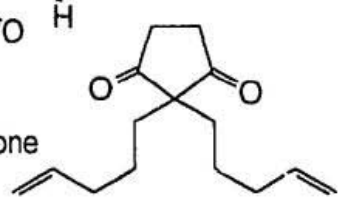
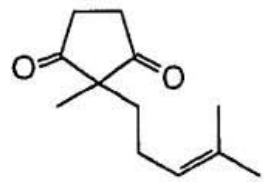
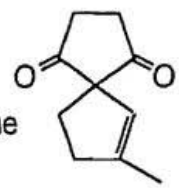
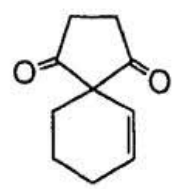
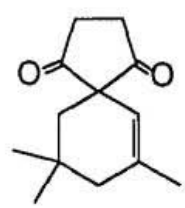
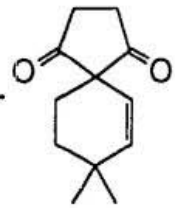
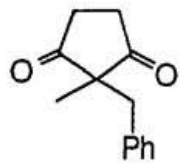
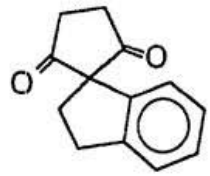
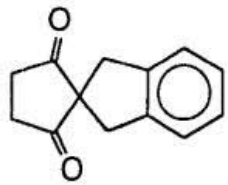
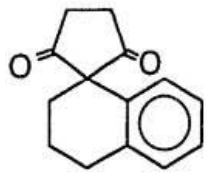
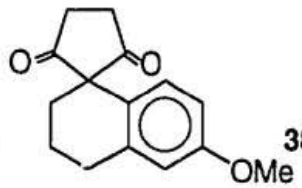
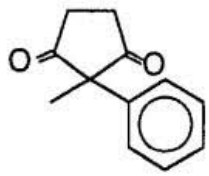
entry	substrate	product	yield (%)
15	5α–cholestan-3-one	 **35**	87
16	1,10-undecadien-6-one	 **55**	78
17	6-methyl-5-hepten-2-one	 **56**	0
18	3-methyl-2-cyclopenten-1-one	 **57**	20[a]
19	2-cyclohexen-1-one	 **58**	2[a]
20	isophorone	 **36**	33

Table 2: Reactions of 1,2-Bis(trimethylsilyloxy)cyclobutene (**1**) and Ketones (cont.)

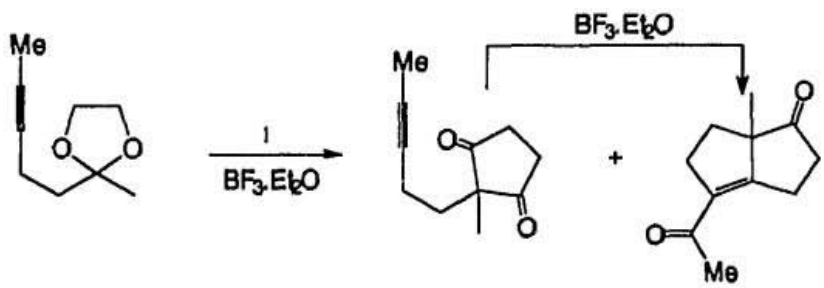
entry	substrate	product		yield (%)
21	4,4-dimethyl-2-cyclohexen-1-one		**59**	71
22	1-phenyl-2-propanone		**60**	51
23	1-indanone		**43**	74
24	2-indanone		**61**	66
25	1-tetralone		**62**	55
26	6-methoxy-1-tetralone		**38**	52
27	acetophenone		**37**	82

[a] From GCMS analysis of the crude product.

initial intermolecular reaction is discouraged because of steric hindrance; and experiments with tetrahydrocarvone indicated that the cyclobutanone intermediate once generated is much more resistant to rearrangement than cyclobutanone species bearing no α-methyl substituent.

The distant δ double bonds in entry 16 appeared not to influence significantly the reaction as the diketone **55** was isolated in good yield (78%). Furthermore, the diketone was predominantly the desired diketone with only a trace of double bond-isomerized material. Unfortunately, when the double bond occupied a γ-position to the ketone, as in entry 17, no diketone product was isolated. In fact, the crude product was found to be a complex mixture from GCMS and nmr

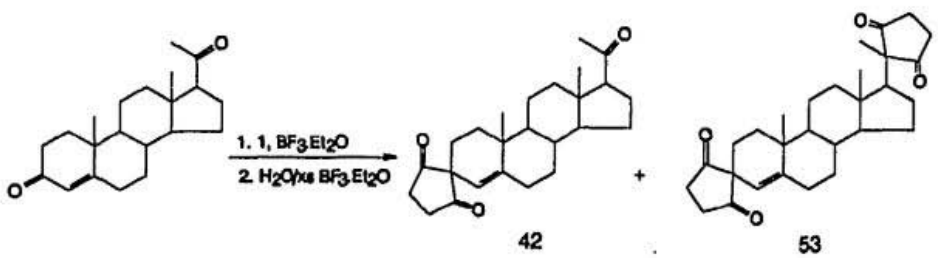
Scheme 23



analysis, but no signals characteristic of a cyclopentanedione moiety could be identified. Recently, Curran showed that substrates of this type undergo further cyclization as illustrated in Scheme 23.[15] However, chromatography of our material failed to provide any cyclization product.

While reactions did proceed when the double bond was in an α-position (entries 18 - 26), the yield was highly dependent upon the substrate. Simple enones (entries 18 - 20) gave poor yields. This was especially true for 2-cyclohexen-1-one (entry 19) in which double bond isomerization during geminal acylation was not deterred. Indeed, nmr analysis of the crude product indicated many olefinic and vinylic resonances, consistent with the TLC plate, which showed many compounds but no major component. In all attempts there was a relatively large amount of intractable material.

Scheme 24

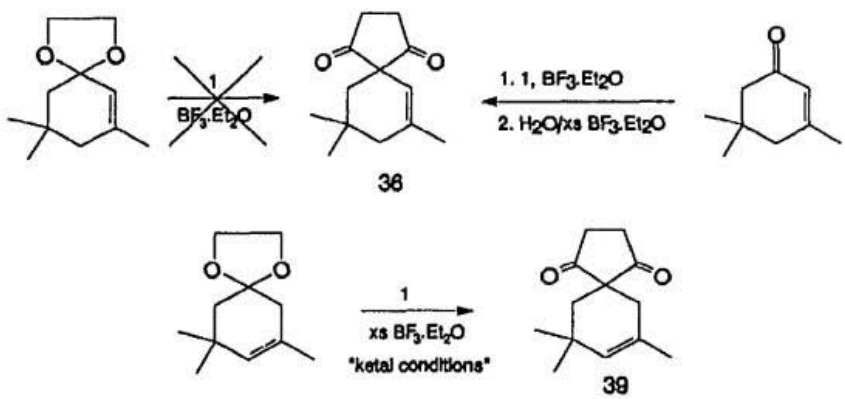


While steric hindrance about the β-carbon inhibited the destruction of the enones (entries 18, 20, and progesterone), and despite the fact that the yields improved dramatically over that reported for entry 19, yields were still synthetically unacceptable except for progesterone and for 4,4-dimethyl-2-cyclohexen-1-one (entry 21). Progesterone gave a respectable yield of spiro-annulated products. The rate of reaction of the

unhindered conjugated ketone at C-3 was faster than that of the α-substituted ketone (C-20) resulting in **42** being isolated in 66% yield whereas only 5% of **53** was obtained (Scheme 24). Increasing the number of equivalents of **1** had little effect on the proportion of **53** that was formed. 4,4-Dimethyl-2-cyclohexen-1-one (entry 21) gave an acceptable yield of diketone **59** probably as a consequence of the fact that isomerization of the enone was prohibited by the disubstitution on the γ-carbon.

While the ketals of conjugated ketones did not furnish any geminally acylated products, when ketalization was accompanied with double bond isomerization these ketals reacted with **1** without further double bond isomerization (Scheme 25).

Scheme 25



α-Keto-aromatic substrates reacted more efficiently than β-keto-

aromatic substrates (entry 23 versus 24 for example), but both types gave yields ranging from 50 to 75%. As seen from Table 2, the best yields were realized for acetophenone (entry 27) and 1-indanone (entry 23), but it is important to note that both of these aromatic substrates were studied much more extensively than the others. 6-Methoxy-2-tetralone decomposed under the reaction conditions, and benzophenone was unreactive.

The methodology that we have developed serves as a convenient process for the geminal acylation of ketones using **1**. It appears that with specific substrates optimization would involve variation of the times of the two steps rather than variation of the amounts of the reagents. This methodology provided many cyclic and acyclic diketones in good yields, but the best yields, all over 90%, were with cyclohexanones. In comparison to the ketal reaction, the new method allows a reaction between **1** and a substrate with an α double bond, albeit it modest yield. Aromatic ketones were superior substrates compared to the corresponding aromatic ketals,[2b] and the amount of **1** required was reduced from typically 2.5 - 3 equivalents to 1.5 as was the total reaction time from overnight to typically 3-4 hours for most substrates. An obvious advantage of this new methodology is that the transformation is shorter by one step, i.e., ketalization, which is not always trivial, is not required. Finally it may be possible for more substituted substrates to favor one

isomer of diketone over another as was discussed for the reactions of **1** with tetrahydrocarvone and with ketalized tetrahydrocarvone.

V. EXPERIMENTAL SECTION

General Procedures.

Compound **1** was prepared by the method of Bloomfield and Nelke.[17] All reactions were performed under nitrogen. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride (CaH_2). Flash chromatography ("chromatography") used 230-400 mesh silica gel, with hexane containing an increasing proportion of ethyl acetate as the eluent. Infrared (IR) spectra were recorded as casts using a Mattson Polaris FT-IR instrument. Nuclear magnetic resonance (nmr) spectra were obtained on a General Electric GE 300-NB (300MHz) instrument. ^1H nmr spectra were obtained at 300 MHz in $CDCl_3$, unless otherwise stated; shifts are relative to internal TMS; coupling constants (*J*) are in Hz. ^{13}C nmr spectra were recorded at 75 MHz, and chemical shifts are relative to solvent (δ 77.0 for $CDCl_3$, 53.8 for CD_2Cl_2); each ^{13}C chemical shift is followed in parentheses by the number of attached protons for each carbon, as determined by attached proton test (APT) and heteronuclear correlation studies. Except where noted, both the low and the high resolution mass spectra (MS) data were obtained on a V.G. Micromass

7070HS instrument. A Hewlett-Packard 12.5 m fused silica capillary column with crosslinked dimethylsilicone as the liquid phase was used for GCMS analysis. Melting points (mp) were determined on a Fisher-Johns apparatus and are uncorrected. Data collection for the x-ray structure was made with a Rigaku AFC6S diffractometer.

Ketal Conditions. To a cooled solution (-78°C) of ketone (2 - 4 mmol) and $BF_3.Et_2O$ (15 equivalents) in CH_2Cl_2 (30 mL) was added dropwise a solution of **1** (2.5 - 3 equivalents) in CH_2Cl_2 (10 mL). The reaction solution was stirred overnight during which time it attained room temperature. The reaction mixture was washed with H_2O (2 x 50 mL). The aqueous layers were re-extracted with CH_2Cl_2 (2 x 50 mL), and the combined organic layers were washed with brine (2 x 60 mL). The organic solution was dried over anhydrous $MgSO_4$, and then the solution was concentrated under vacuum with a rotary evaporator. Purification by chromatography provided the geminally acylated product.

As the spectral data for the material obtained under "ketone conditions" were identical with those of material produced by the ketal route,[16] only the reactions of **1** with ketones will be detailed. All entries in Table 1 were obtained as described above, i.e., "ketal conditions".

Ketone conditions: To a solution of ketone (2 - 4 mmol) in CH_2Cl_2 (10.0 mL) at room temperature was added $BF_3.Et_2O$ (1.2

equivalents) followed by **1** (1.5 equivalents). The reaction was stirred at room temperature for 1 - 2 h, after which time H_2O (equal volume to the $BF_3.Et_2O$ used earlier) was added. This turbid solution was stirred 10 min before $BF_3.Et_2O$ (15 equivalents) was added and the reaction mixture stirred an additional 1 - 2 h. The reaction solution was washed with H_2O (2 x 50 mL). The aqueous layers were re-extracted with CH_2Cl_2 (2 x 50 mL), and the combined organic layers were washed with brine (2 x 60 mL). The organic solution was dried over anhydrous $MgSO_4$, and then the solution was concentrated under vacuum with a rotary evaporator. The crude products were dissolved in ether (100 mL) and filtered through a small bore column containing charcoal/Florisil. The plug was washed with CH_2Cl_2 (70 mL). Concentration of the combined organic solutions under vacuum with a rotary evaporator followed by subsequent high vacuum pumping afforded the diketone products. In some cases the material obtained was not of acceptable purity and was subjected to chromatography.

2-Ethyl-2-methyl-1,3-cyclopentanedione (26). To a stirred solution of butanone (204 mg, 2.84 mmol) in CH_2Cl_2 (9.0 mL) at rt was added $BF_3.Et_2O$ (0.40 mL, 3.4 mmol) followed by **1** (1.15 mL, 4.3 mmol). This solution was stirred for 2 h at rt, after which time H_2O (approx. 0.4 mL) was added followed 10 min later by $BF_3.Et_2O$ (5.2 mL, 43 mmol). The mixture was stirred for 1 h. Work-up and purification

(charcoal/Florisil) provided **26** (243 mg, 61%) as an oil. IR: 1750 (shoulder) and 1720 cm^{-1}. ^1H nmr: δ 2.78 (4H, s), 1.67 (2H, q, J = 7.4), 1.09 (3H, s), 0.81 (3H, t, J = 7.4). ^{13}C nmr: δ 216.4 (2C, 0), 56.9 (0), 35.0 (2C, 2), 28.6 (2), 17.8 (3), 8.7 (3). MS: 140 (51, M^+), 125 (92), 97 (31), 84 (12), 83 (13), 69 (100), 56 (36), 55 (29), 41 (83). Exact mass calcd. for $C_8H_{12}O_2$: 140.0837, found 140.0843.

2-Methyl-2-(methylethyl)-1,3-cyclopentanedione (27). To a solution of 3-methylbutanone (276 mg, 3.21 mmol) and $BF_3.Et_2O$ (0.50 mL, 3.8 mmol) in CH_2Cl_2 (9.0 mL) at rt was added **1** (1.3 mL, 4.8 mmol). The reaction mixture was stirred for 2 h at rt, before H_2O (approx. 0.5 mL) was added followed 20 min later by $BF_3.Et_2O$ (5.9 mL, 48 mmol). The mixture was stirred overnight. Work-up followed by purification (charcoal/Florisil) provided **27** (258 mg, 52%) as a colorless oil. IR: 1725 cm^{-1}. ^1H nmr: δ 2.73 (4H, s), 2,01 (1H, septet, J = 6.9), 1.05 (3H, s), 0.94 (6H, d, J = 6.9). ^{13}C nmr: δ 216.6 (2C, 0), 59.2 (0), 35.4 (2C, 2), 33.6 (1), 17.2 (2C, 3), 15.1 (3). MS: 154 (18, M^+), 139 (100), 111 (31), 83 (51), 69 (8), 56 (24), 55 (60), 43 (30), 27 (51). Exact mass calcd. for $C_9H_{14}O_2$: 154.0993, found 154.09995.

Spiro[4.4]nonane-1,4-dione (28). To a solution of cyclopentanone (211 mg, 2.51 mmol) and $BF_3.Et_2O$ (0.30 mL, 2.5 mmol) in CH_2Cl_2 (9.0 mL) at rt was added **1** (1.0 mL, 3.8 mmol). The reaction mixture was stirred for 1 h at rt prior to the addition of H_2O (approx. 0.35 mL) followed

20 min later by $BF_3.Et_2O$ (4.6 mL, 38 mmol). The mixture was stirred for 1 h. Work-up followed by purification (charcoal/Florisil) provided **28** (300 mg, 79%) as a colorless solid, mp 54 - 57.5°C (lit.[16] 58 - 59.5°C). IR: 1720 cm^{-1}. ^1H nmr: δ 2.48 (4H, br s), 1.61 (8H, br s). ^{13}C nmr: δ 215.8 (2C, 0), 63.0 (0), 34.7 (2C, 2), 34.6 (2C, 2), 26.6 (2C, 2). MS: 152 (100, M^+), 124 (35), 111 (48), 97 (52), 96 (44), 95 (33), 69 (28), 68 (52), 67 (61), 56 (61), 41 (37). Exact mass calcd. for $C_9H_{12}O_2$: 152.0837, found 152.0831.

6-Methylspiro[4.4]nonane-1,4-dione (29). To a solution of 2-methylcyclopentanone (216 mg, 2.20 mmol) and $BF_3.Et_2O$ (0.30 mL, 2.5 mmol) in CH_2Cl_2 (9.0 mL) at rt was added **1** (0.9 mL, 3.4 mmol). The reaction mixture was stirred for 1 h at rt, and H_2O (approx. 0.3 mL) was added followed 10 min later by $BF_3.Et_2O$ (4.5 mL, 37 mmol). The mixture was stirred for 1 h. Work-up followed by purification (charcoal/Florisil) provided **29** (200 mg, 55%) as an oil. IR: 1718 cm^{-1}. ^1H nmr: δ 2.81 - 2.57 (4H, br m), 2.25 (1H, br m), 1.85 (5H, br m), 1.54 (1H, br m), 0.95 (3H, d, J = 7.2). ^{13}C nmr: δ 217.3 (0), 216.6 (0), 66.7 (0), 46.9 (1), 36.2 (2), 35.8 (2), 34.5 (2), 33.5 (2), 24.6 (2), 15.2 (3). MS: 166 (64, M^+), 151 (100), 125 (15), 109 (52), 95 (41), 81 (20), 67 (41), 55 (31), 41 (30). Exact mass calcd. for $C_{10}H_{14}O_2$: 166.0993, found 166.0997.

Spiro(bicyclo[2.2.1]heptane-2,1'-cyclopentane)-2',5'-dione (30). To a solution of bicyclo[2.2.1]heptan-2-one (206 mg, 1.87 mmol) and

$BF_3.Et_2O$ (0.25 mL, 2.0 mmol) in CH_2Cl_2 (9.0 mL) at rt was added **1** (0.75 mL, 2.9 mmol). The reaction mixture was stirred for 1 h at rt, after which time H_2O (approx. 0.3 mL) was added followed 10 min later by $BF_3.Et_2O$ (3.4 mL, 28 mmol). The mixture was stirred for 1 h. Work-up followed by purification (charcoal/Florisil) provided **30** (250 mg, 75%) as colorless crystals, mp 112 - 113°C (lit.[1b] 109.5 - 110.5°C). IR: 1760 (shoulder) and 1715 cm^{-1}. ^1H nmr: δ 3.07 - 2.51 (4H, m), 2.48 (1H, br d), 2.37 (1H, br apparent t), 1.89 - 1.76 (2H, m), 1.57 - 1.18 (6H, m). ^{13}C nmr: δ 213.2 (0), 213.1 (0), 66.4 (0), 48.7 (1), 37.0 (2), 36.9 (1), 35.2 (2), 34.3 (2), 32.7 (2), 27.8 (2), 24.3 (2). MS: 178 (19, M^+), 149 (46), 112 (100), 93 (15), 79 (13), 67 (19), 66 (12), 65 (13). Exact mass calcd. for $C_{11}H_{14}O_2$: 178.0993, found 178.0993.

Spiro[4.5]decane-1,4-dione (31) from Cyclohexanone. A solution of cyclohexanone (212 mg, 2.17 mmol) in CH_2Cl_2 (9.0 mL) was cooled to -78°C, and $BF_3.Et_2O$ (0.30 mL, 2.5 mmol) was added followed by a solution of **1** (0.90 mL, 3.4 mmol) in CH_2Cl_2 (4.0 mL) over 15 min. The reaction mixture was stirred at -78°C for 3 h, then it was allowed to attain rt over the next 2 h. H_2O (approx. 0.4 mL) was added, and the solution was recooled to -78°C before $BF_3.Et_2O$ (4.0 mL, 33 mmol) was added. The mixture was stirred overnight during which time it was allowed to return to rt. Work-up followed by purification (charcoal/Florisil) provided **31** (337 mg, 94%) as large white crystals mp 60 - 61.5°C (lit.[1b]

61 - 62°C). IR: 1755 and 1720 cm^{-1}. ^1H nmr: δ 2.68 (4H, s), 1.7 - 1.4 (10H, m). ^{13}C nmr: δ 215.6 (2C, 0), 55.7 (0), 34.1 (2C, 2), 29.0 (2C, 2), 24.7 (2), 20.3 (2C, 2). MS: 166 (100, M^+), 137 (25), 124 (32), 112 (61), 111 (46), 85 (46), 81 (37), 67 (74), 56 (44). Exact mass calcd. for $C_{10}H_{14}O_2$: 166.0993, found 166.0985.

Spiro[4.5]decane-1,4-dione (31) from the Ketal of Cyclohexanone. To a solution of 1,4-dioxaspiro[4.5]decane (306 mg, 2.16 mmol) and $BF_3.Et_2O$ (0.30 mL, 2.5 mmol) in CH_2Cl_2 (9.0 mL) at rt was added **1** (0.9 mL, 3.2 mmol). The reaction mixture was stirred for 2.5 h at rt, and H_2O (approx. 0.4 mL) was added followed 10 min later by $BF_3.Et_2O$ (4.0 mL, 33 mmol). The mixture was stirred overnight. Work-up followed by purification (charcoal/Florisil) provided **31** (343 mg, 96%).

6-Methylspiro[4.5]decane-1,4-dione (32). To a solution of 2-methylcyclohexanone (228 mg, 2.03 mmol) and $BF_3.Et_2O$ (0.30 mL, 2.5 mmol) in CH_2Cl_2 (9.0 mL) at rt was added **1** (0.8 mL, 3.1 mmol). The reaction mixture was stirred for 1 h at rt, and H_2O (approx. 0.4 mL) was added followed 10 min later by $BF_3.Et_2O$ (3.7 mL, 30 mmol). The mixture was stirred overnight. Work-up followed by purification (charcoal/Florisil) provided **32** (227 mg, 62%) as an oil. IR: 1715 cm^{-1}. ^1H nmr: δ 2.90 - 2.48 (4H, m), 1.95 - 1.17 (9H, m), 0.75 (3H, d, J = 6.3). ^{13}C nmr: δ 217.4 (0), 216.3 (0), 60.0 (0), 35.6 (2), 35.5 (1), 35.3 (2), 32.0 (2), 28.9 (2), 25.2 (2), 20.0 (2), 18.0 (3). MS: 180 (74, M^+), 165 (65), 126 (21), 125

(39), 123 (24), 112 (100), 111 (23), 109 (22), 95 (24), 81 (38), 67 (45), 56 (32), 55 (31), 53 (25), 41 (46). Exact mass calcd. for $C_{11}H_{16}O_2$: 180.1149, found 180.1149.

8,8-Dimethylspiro[4.5]decane-1,4-dione (33). A solution of 4,4-dimethylcyclohexanone (230 mg, 1.83 mmol) in CH_2Cl_2 (9.0 mL) was cooled to -78°C, and $BF_3.Et_2O$ (0.20 mL, 1.6 mmol) was added followed by a solution of **1** (0.80 mL, 3.1 mmol) in CH_2Cl_2 (4.0 mL) over 15 min. The reaction mixture was stirred at -78°C for 3.5 h, then it was allowed to attain rt over the next 1.5 h. H_2O (approx. 0.3 mL) was added, and the solution was recooled to -78°C before $BF_3.Et_2O$ (3.3 mL, 27 mmol) was introduced. The mixture was stirred overnight during which time it was allowed to return to rt. Work-up followed by purification (charcoal/Florisil) provided **33** (320 mg, 90%) as cream-colored crystals: mp 65 - 66.5°C. IR: 1756 (shoulder) and 1715 cm^{-1}. ^1H nmr: δ 2.76 (4H, s), 1.61 (4H, m), 1.47 (4H, m), 0.95 (6H, s). ^{13}C nmr: δ 215.4 (2C, 0), 55.1 (0), 34.0 (2C, 2), 32.9 (2C, 2), 28.7 (0), 27.6 (2C, 3), 25.2 (2C, 2). MS: 194 (52, M^+), 179 (12), 151 (21), 138 (15), 137 (16), 125 (100), 112 (96), 111 (31), 95 (27), 93 (20), 83 (20), 81 (25), 69 (36), 67 (22), 56 (42), 55 (33), 53 (27), 41 (67). Exact mass calcd. for $C_{12}H_{18}O_2$: 194.1306, found 194.1300.

8-*tert*-Butylspiro[4.5]decane-1,4-dione (34) Directly from the Ketone. To a solution of 4-*tert*-butylcyclohexanone (171 mg, 1.11 mmol) and $BF_3.Et_2O$ (0.15 mL, 1.2 mmol) in CH_2Cl_2 (9.0 mL) at -78°C was

added **1** (0.50 mL, 1.9 mmol) in CH_2Cl_2 (4.0 mL) over 20 min. The reaction mixture was stirred for 3 h at -78°C before it was allowed to attain rt. H_2O (approx. 0.2 mL) was added, and the mixture was cooled again to -78°C before $BF_3.Et_2O$ (2.0 mL, 16 mmol) was added. The mixture was allowed to attain rt overnight. Work-up followed by purification yielded **34** (232 mg, 94%) as colorless crystals: mp 82.5 - 84°C. IR: 1753 (shoulder) and 1721 cm^{-1}. ^1H nmr: δ 2.75 (4H, br s), 1.76 - 1.49 (9H), 0.87 (9H, s). ^{13}C nmr: δ 215.7 (0), 215.6 (0), 55.0 (0), 46.7 (1), 34.3 (2), 34.1 (2), 32.2 (0), 29.9 (2C, 2), 27.2 (3C, 3), 21.5 (2C, 2). MS: 222 (10, M^+), 207 (8), 166 (59), 165 (23), 124 (13), 112 (21), 111 (23), 81 (11), 67 (10), 57 (100), 41 (43). Exact mass calcd. for $C_{14}H_{22}O_2$: 222.1619, found 222.1628.

Spiro(5α-cholestane-3,2'-cyclopentane)-1,3-dione (35). To a solution of 5α-cholestan-3-one (304 mg, 0.788 mmol) in CH_2Cl_2 (35 mL) was cooled to -78°C, and $BF_3.Et_2O$ (1.5 mL, 12 mmol) was added followed by a solution of **1** (0.53 mL, 2.0 mmol) in CH_2Cl_2 (5.0 mL) over 12 min. The reaction mixture was allowed to warm to rt, and stirring was maintained for 48 h. Work-up afforded a brown solid, and chromatography of this provided **35** (310 mg, 87%) as colorless crystals: mp 150.5 - 152°C. IR: 1761 (shoulder) and 1721 cm^{-1}. ^1H nmr: δ 2.73 (4H, m), 2.0 - 0.9 (unresolved signals), 0.90 (3H, d, J = 6.4), 0.863 (3H, d, J = 6.6), 0.859 (3H, d, J = 6.6), 0.82 (3H, s), 0.64 (3H, s). ^{13}C nmr: δ

215.5 (2C, 0), 56.4 (0), 56.2 (1), 56.1 (1), 53.5 (1), 42.4 (0), 39.8 (2), 39.4 (1), 39.4 (2), 36.0 (2), 35.7 (1), 35.3 (1), 35.1 (0), 34.4 (2), 34.0 (2), 32.8 (2), 31.8 (2), 31.5 (2), 28.2 (2), 28.1 (2), 27.9 (1), 24.6 (2), 24.0 (2), 23.7 (2), 22.7 (3), 22.5 (3), 20.7 (2), 18.5 (3), 11.9 (3), 11.0 (3). MS: 454 (29, M^+), 439 (30), 330 (18), 329 (13), 301 (26), 300 (47), 299 (100), 231 (41), 191 (32). Exact mass calcd. for $C_{31}H_{50}O_2$: 454.3808, found 454.3819.

7,9,9-Trimethylspiro[4.5]dec-6-ene-1,4-dione (36). A solution of 3,5,5-trimethyl-2-cyclohexen-1-one (220 mg, 1.62 mmol) in CH_2Cl_2 (10 mL) was cooled to -78°C, and $BF_3.Et_2O$ (2.9 mL, 24 mmol) was added followed by a solution of **1** (1.3 mL, 5.0 mmol) in CH_2Cl_2 (6.0 mL) over 16 min. The reaction mixture was allowed to warm to rt, and stirring was maintained for 65 h. Work-up afforded a black, viscous oil, and chromatography of this provided **36** (108 mg, 33%), which solidified on standing: mp 58 - 59.5°C. IR: 1723 cm^{-1}. ^1H nmr: δ 5.05 (1H, br s), 2.84 (4H, m), 1.82 (2H, br s), 1.75 (3H, br s), 1.62 (2H, s), 1.00 (6H, s). ^{13}C nmr: δ 212.6 (2C, 0), 139.7 (0), 112.8 (1), 62.9 (0), 43.3 (2), 38.3 (2), 34.7 (2C, 2), 30.2 (0), 29.2 (2C, 3), 24.5 (3). MS: 206 (100, M^+), 191 (49), 163 (24), 150 (28), 135 (20), 121 (22), 107 (94), 91 (42). Exact mass calcd. for $C_{13}H_{18}O_2$: 206.1306, found 206.1299.

2-Methyl-2-phenyl-1,3-cyclopentanedione (37) by Multiple Additions of 1. A solution of acetophenone (509 mg, 4.24 mmol) in

CH_2Cl_2 (300 mL) was cooled to -78°C before $BF_3.Et_2O$ (7.7 mL, 13 mmol) was added followed, dropwise, by a solution of **1** (3.4 mL, 13 mmol) in in CH_2Cl_2 (10 mL). This was stirred for 15 min before the mixture was allowed to attain rt. The mixture was heated at reflux for 12 h, 16.5 h, and 38 h, at which times aliquots were removed and analysed by GCMS and additional **1** was added (1.0 mL, 1.0 mL and 3.0 mL, respectively). After heating for a total of 44 h, GCMS indicated that no acetophenone remained. The reaction was allowed to cool, and work-up provided a black residue. Vacuum distillation in a Kugelrohr apparatus gave **37** as a pale yellow oil (726 mg, 91%). IR: 1765 (shoulder) and 1724 cm^{-1}. ^1H nmr: δ 7.38 - 7.19 (5H, m), 2.82 (4H, br symmetrical m), 1.42 (3H, s). ^{13}C nmr: δ 212.9 (2C, 0), 136.8 (0), 129.1 (2C, 1), 127.8 (0), 126.2 (2C, 1), 61.7 (0), 35.0 (2C, 2), 19.6 (3). MS: 188 (100, M^+), 159 (7), 145 (28), 132 (28), 105 (27), 104 (78), 103 (27), 78 (24), 77 (24), 51 (26). Exact mass calcd. for $C_{12}H_{12}O_2$: 188.0836, found 188.0828.

2-Methyl-2-phenyl-1,3-cyclopentanedione (37) by Ketone Conditions. To a stirred solution of acetophenone (211 mg, 1.76 mmol) in CH_2Cl_2 (9.0 mL) at rt was added $BF_3.Et_2O$ (0.25 mL, 2.0 mmol) followed by **1** (0.70 mL, 2.7 mmol). After 2 h, GCMS analysis of the mixture indicated the presence of **37** (73%) and **46** (19%) with only 2% acetophenone remaining; 30 min later H_2O (approx. 0.3 mL) followed after 10 min by $BF_3.Et_2O$ (3.3 mL, 27 mmol), and stirring was continued

for 1 h. Work-up followed by purification (charcoal/Florisil) afforded **37** as a pale yellow oil (273 mg, 83%), but GCMS revealed that this was contaminated by approximately 1% acetophenone.

1',2',3',4'-Tetrahydro-6-methoxyspiro[cyclopentane-1,1'-naphthalene]-2,5-dione (38). To a solution of 6-methoxy-1-tetralone (198 mg, 1.13 mmol) and $BF_3.Et_2O$ (0.40 mL, 3.3 mmol) in CH_2Cl_2 (9.0 mL) at rt was added **1** (0.90 mL, 3.4 mmol). The reaction mixture was stirred at rt for 47 h. An additional 0.40 mL (1.5 mmol) of **1** was added, and the mixture was stirred for another 45 h. After addition of H_2O (approx. 0.4 mL) and $BF_3.Et_2O$ (2.1 mL, 17 mmol), the mixture was stirred for 3 days. Work-up followed by purification (charcoal/Florisil) gave 234 mg of yellow, oily crystals that GCMS revealed to contain 1% starting ketone, 86% **38**, and 5% unrearranged intermediates. Chromatography yielded **38** (142 mg, 52%) as colorless crystals: mp 116.5 - 117.5°C. IR: 1716 cm^{-1}. ^1H nmr: δ 6.70 - 6.64 (2H, m), 6.45 (1H, m), 3.75 (3H, s), 2.94 (4H, br symmetric m), 2.83 (2H, m), 1.92 (4H, narrow m). ^{13}C nmr: δ 215.0 (2C, 0), 158.6 (0), 139.9 (0), 129.3 (1), 123.9 (0), 114.0 (1), 112.9 (1), 62.0 (0), 55.1 (3), 35.1 (2C, 2), 31.7 (2), 29.1 (2), 17.9 (2). MS: 244 (100, M^+), 188 (42), 174 (21), 160 (89), 159 (23), 145 (23), 115 (27). Exact mass calcd. for $C_{15}H_{16}O_3$: 244.1099, found 244.1107.

7,9,9-Trimethylspiro[4.5]dec-7-ene-1,4-dione (39). Increasing the

reaction time for the sequence reported above for (**36**) from 3 days to 5 days provided yellow crystals (30% yield), which, by GCMS analysis, revealed a mixture of **36** (92%) and **39** (8%). The gas chromatogram and mass spectrum of **39** were identical with that reported by Wu and Burnell.[2,16]

2-(2-(Carboethoxy)ethyl)-2-methyl-1,3-cyclopentanedione (40). A solution of ethyl levulinate (221 mg, 1.54 mmol) in CH_2Cl_2 (38 mL) was cooled to -78°C, and $BF_3.Et_2O$ (2.7 mL, 22 mmol) was added followed by a solution of **1** (1.2 mL, 4.6 mmol) in CH_2Cl_2 (6.0 mL) over 30 min. The reaction mixture was allowed to warm to rt, and stirring was maintained for 43 h. Work-up provided a dark oil, and chromatography afforded **40** as an oil (118 mg, 36%). IR: 1764 (shoulder) and 1723 cm^{-1}. ^1H nmr: δ 4.08 (2H, q, J = 7.2), 2.86 (4H, s), 2.28 (2H, t, J = 7.5), 1.97 (2H, t, J = 7.5), 1.26 (3H, t, J = 7.2), 1.15 (3H, s). ^{13}C nmr (C_6D_6): δ 214.5 (2C, 0), 172.6 (0), 60.4 (2), 54.9 (0), 34.6 (2C, 2), 29.2 (2), 28.9 (2), 19.6 (3), 14.1 (3). MS: 212 (M^+, 9), 167 (12), 166 (13), 138 (62), 125 (100), 110 (21), 99 (15), 97 (26), 96 (13), 95 (13), 69 (29), 55 (70), 53 (11), 43 (20), 41 (45). Exact mass calcd. for $C_{11}H_{16}O_4$: 212.1048, found 212.1070.

Reaction of Progesterone (41) with 1. To a solution of **41** (259 mg, 0.824 mmol) in CH_2Cl_2 (20 mL) was added $BF_3.Et_2O$ (0.25 mL, 2.0 mmol) followed by (0.70 mL, 2.7 mmol) of **1**. After stirring for 19 h at rt, H_2O (approx. 0.2 mL) followed 10 min later by $BF_3.Et_2O$ (1.5 mL, 12

mmol) were added. After stirring for 2.5 h, the solution was worked-up. Chromatography provided **42** as pale yellow crystals (208 mg, 66%) and in a more polar fraction, **53** (19 mg, 5%) as cream-colored crystals. The nmr spectra revealed that each was contaminated with less than 10% of its 5-ene isomer. For **42**: mp 135.5 - 138°C. IR: 1721 and 1703 cm^{-1}. ^1H nmr: δ 4.86 (1H, br s), 2.83 (2H, m), 2.12 (3H, s), 1.07 (3H, s), 0.63 (3H, s) and other signals unresolved 2.9 - 0.9; NOE enhancement: irradiation at δ 4.86 gave an enhancement of m at 2.83 (0.5%) and a double m at 2.08 (3%); irradiation at δ 2.83 gave an enhancement of br s at δ 4.86 (4.5%) and a small signal for a minor isomer at 5.30 (m). ^{13}C nmr: δ 214.8 (0), 213.2 (0), 209.5 (0), 151.4 (0), 111.9 (1), 63.6 (1), 60.5 (0), 56.0 (1), 53.4 (1), 44.0 (0), 38.7 (2), 36.8 (0), 35.7 (1), 34.8 (2), 34.6 (2), 32.6 (2), 32.5 (2), 32.2 (2), 31.5 (3), 25.0 (2), 24.3 (2), 22.7 (2), 21.4 (2), 19.1 (3), 13.3 (3). MS: 382 (100, M^+), 367 (12), 191 (45), 190 (23), 164 (27), 43 (79). Exact mass calcd. for $C_{25}H_{34}O_3$: 382.2506, found 382.2513. For **53**: mp 267 - 268°C. IR: 1759, 1719 cm^{-1}. ^1H nmr: δ 4.84 (1H, s), 2.91 - 2.62 (8H, m), 2.38 - 0.80 (m), 1.13 (3H, s), 1.03 (3H, s), 0.61 (3H, s), and a small signal for a minor isomer at 5.38 (m). ^{13}C nmr: δ 217.8 (0), 216.8 (0), 214.9 (0), 213.0 (0), 151.4 (0), 119.0 (1), 60.5 (0), 56.9 (1), 55.6 (0), 54.9 (1), 53.3 (1), 42.9 (0), 38.9 (2), 36.7 (0), 35.5 (1), 35.2 (2), 34.2 (2), 34.8 (2), 34.2 (2), 32.5 (2), 32.3 (2), 32.1 (2), 24.9 (2), 22.9 (2), 21.7 (2), 21.0 (2), 20.7 (3), 19.0 (3), 14.9 (3). MS: 450 (100, M^+), 435

(7), 422 (8), 339 (8), 323 (12), 191 (65), 190 (38), 164 (45), 147 (22), 135 (19), 113 (22), 107 (25), 105 (32), 91 (45). Exact mass calcd. for $C_{29}H_{38}O_4$: 450.2768, found 450.2761.

2',3'-Dihydrospiro[cyclopentane-1',1'-[1*H*]indene]-2,5-dione (43). A solution of 1-indanone (210 mg, 1.59 mmol) in CH_2Cl_2 (80 mL) was cooled to -78°C and $BF_3.Et_2O$ (2.9 mL, 24 mmol) was added followed by a solution of **1** (1.7 mL, 6.5 mmol) in CH_2Cl_2 (6.0 mL) over 18 min. The reaction mixture was stirred at -78°C for 20 min before being allowed to warm to rt, and 1.5 h later the solution was heated at reflux for 1.5 h. Work-up gave a red-brown oil that was distilled under vacuum in a Kugelrohr apparatus to give a bright yellow oil (247 mg), which GCMS revealed was 85% **43**. Chromatography of a similarly derived sample yielded **43** as colorless crystals: mp 104 - 105.5°C. IR: 1754 (shoulder) and 1722 cm^{-1}. ^1H nmr: δ 7.33 - 7.10 (3H, m), 6.89 (1H, d, J = 7.5), 3.15 (2H, t, J = 7.4), 2.92 (4H, center of complex m), 2.37 (2H, t, J = 7.4). ^{13}C nmr: δ 213.1 (2C, 0), 144.7 (0), 140.6 (0), 128.2 (1), 126.8 (1), 125.3 (1), 122.4 (1), 69.8 (0), 35.4 (2C, 2), 32.8 (2), 31.6 (2). MS: 200 (94, M+), 144 (56), 130 (15), 129 (15), 116 (82), 115 (100). Exact mass calcd. for $C_{13}H_{12}O_2$ 200.0837, found 200.0838.

(1'α,4'α)-2-(4-*t*-Butyl-1-trimethylsilyloxycyclohexyl)-2-trimethylsilyloxycyclobutanone (44). To a solution of 4-*tert*-butylcyclohexanone (215 mg, 1.40 mmol) and $BF_3.Et_2O$ (0.20 mL, 1.6

mmol) in CH_2Cl_2 (10 mL) at rt was added 1 (0.60 mL, 2.3 mmol). The reaction mixture was stirred at rt for 2.7 h. A saturated aqueous boric acid solution (approx. 0.3 mL) was added, and the mixture was stirred overnight. Work-up afforded a white solid (355 mg) for which GCMS analysis included only 4% starting ketone, 8% diketone **34**, and 63% **44**. Chromatography provided the starting ketone (120 mg, 55% recovery) and **44** (99 mg, 32%) as large colorless crystals: mp 62.5 - 64°C. IR: 1784 cm^{-1}. ^1H nmr: δ 2.82 - 2.59 (2H, m), 2.49 (1H, ddd, J = 6.6, 10.5, 12.3), 1.95 (1H, ddd, J = 3.0, 3.0, 10.2), 1.82 (1H, ddd, J = 8.4, 11.1, 12.3), 1.67 (1H, dddd, J = 3.0, 3.0, 3.0, 12.3), 1.60 - 1.47 (2H, m), 1.36 (1H, dddd, J = 3.3, 12.3, 12.3, 12.3), 1.29 - 1.12 (2H, m), 1.04 (1H, br ddd, J = 3.8, 12.2, 12.2), 0.89 (1H, partially overlapped m), 0.84 (9H, s), 0.15 (9H, s), 0.11(9H, s). ^{13}C nmr: δ 212.7 (0), 98.7 (0), 75.8 (0), 47.3 (1), 41.2 (2), 34.6 (2), 32.3 (0), 30.8 (2), 27.5 (3C, 3), 25.1 (2), 22.1 (2), 21.9 (2), 2.4 (3C, 3), 1.5 (3C, 3). MS: 384 (0.5, M$^+$), 329 (12), 328 (38), 327 (21), 230 (18), 227 (53), 147 (27), 75 (32), 73 (100), 62 (13), 57 (43), 45 (47), 41 (20).

(1'α,4'α)-2-(4-*t*-Butyl-1-hydroxycyclohexyl)-2-hydroxycyclobutanone (45). To a solution of **44** (20 mg, 0.052) in CH_2Cl_2 (2.0 mL) was added approximately 0.1 mL of a 1 M solution of TBAF in THF (Aldrich). The solution was stirred at rt for 6 h. Work-up provided no **34**, just **45** (8.8 mg, 70%) as a colorless solid: mp 147 -

149.5°C. IR: 3376 and 1757 cm^{-1}. ^1H nmr: δ 3.41 (1H, br s), 3.02 - 2.75 (2H, m), 2.33 (1H, ddd, *J* = 6.4, 11.1, 12.6), 2.03 (1H, ddd, *J* = 8.7, 11.2, 12.6), 1.90 - 1.70 (2H, m including apparent br s at 1.81), 1.70 - 1.50 (4H, m), 1.44 - 1.21 (3H, m), 0.97 (1H, m), 0.87 (9H, s). ^{13}C nmr: δ 213.1 (0), 96.0 (0), 72.8 (0), 47.6 (1), 42.3 (2), 32.4 (0), 30.5 (2), 27.5 (3C, 3), 23.4 (2), 21.8 (2), 21.7 (2). MS: no M^+, 222 (1.3, M^+- H_2O), 207 (2), 184 (2), 155 (14), 123 (10), 98 (13), 95 (14), 81 (21), 57 (100), 43 (37), 41(42). Exact mass calcd. for $C_{14}H_{22}O_2$ (M^+- H_2O): 222.1619, found 222.1626.

8-*tert*-Butylspiro[4.5]decane-1,4-dione (34) from 44. To a solution of **44** (13 mg, 0.033 mmol) in CH_2Cl_2 (2.0 mL) was added a drop of H_2O followed by $BF_3.Et_2O$ (0.06 mL, 0.5 mmol). The reaction solution was stirred at rt overnight. Work-up provided 8.3 mg of a cream-colored solid, ^1H nmr analysis revealed was composed of **45** and **34**, in a 1:1.8 ratio, respectively.

8-*tert*-Butylspiro[4.5]decane-1,4-dione (34) from 45. A solution of **45** (18 mg, 0.075 mmol) and $BF_3.Et_2O$ (0.15 mL, 1.2 mmol) in CH_2Cl_2 (2.0 mL) was stirred at rt for 17.5 h. Work-up provided **34** (17 mg, 100%).

2-(1-Phenyl-1-trimethylsilyloxyethyl)-2-trimethylsilyloxy-cyclobutanone (46). A solution of acetophenone (229 mg, 1.91 mmol) in CH_2Cl_2 (75 mL) was cooled to -78°C, and $BF_3.Et_2O$ (0.12 mL, 0.98 mmol)

followed, dropwise, by a solution of **1** (1.5 mL, 5.7 mmol) in CH_2Cl_2 (6.0 mL) over 30 min. The solution was allowed to warm to rt over the next 2 h, and then it was heated at reflux for 1 h. Work-up provided a bright yellow liquid. Chromatography gave **46** (a diastereomeric mixture in a 3.5:1 ratio, by ^1H nmr) as an oil: IR: 1793 cm^{-1}. ^1H nmr for the major isomer: δ 7.51 (2H, br d, J ~ 7.1), 7.41 - 7.27 (3H, m), 2.88 (1H, ddd, J = 8.7, 11.7, 17.6), 2.70 (1H, ddd, J = 5.7, 10.8, 17.6), 2.50 (1H, ddd, J = 5.7, 11.7, 12.2), 1.83 (3H, s), 1.66 (1H, ddd, J = 8.7, 10.8, 12.2), 0.15 (9H, s), 0.08 (9H, s); and some discernable signals for the minor isomer: δ 2.70 - 2.48 (m), 1.94 (1H, m), 1.77 (3H, s). ^{13}C nmr for the major isomer: δ 213.6 (0), 143.6 (0), 127.1 (2C, 1), 127.0 (2C, 1), 126.9 (1), 97.1 (0), 79.3 (0), 41.8 (2), 24.2 (2), 22.9 (3), 2.5 (3C, 3), 2.1 (3C, 3); and some discernable signals for the minor isomer: δ 211.6 (0), 143.5 (0), 126.6 (2C, 1), 98.0 (0), 79.4 (0), 41.3 (2), 25.5 (2), 24.2 (3), 2.5 (3C, 3), 1.7 (3C, 3). MS: 350 (0.3, M^+), 294 (24), 232 (12), 231 (6), 193 (47), 147 (19), 75 (14), 73 (100), 45 (14). Exact mass calcd. for $C_{18}H_{30}O_3Si_2$: 350.1732, found 350.1753.

(1'α,4'α)-2-(2-Methyl-5-methylethyl-1-hydroxycyclohexyl)-2-hydroxycyclobutanone (47) and (48). To a solution of tetrahydrocarvone (9:1 mixture of epimers) (291.8 mg, 1.90 mmol) in CH_2Cl_2 (10.0 mL) was added $BF_3.Et_2O$ (0.3 mL, 2.1 mmol) followed by **1** (0.8 mL, 2.8 mmol). The reaction solution was stirred for 3.5 h after

which time an aqueous saturated boric acid solution (0.3 mL) was added. The reaction mixture was stirred overnight. The solution was washed with H_2O (2 x 30 mL) and the aqueous solutions were re-extracted with CH_2Cl_2 (2 x 30 mL). The organic solutions were washed with brine (50 mL) and dried over $MgSO_4$. Concentration at reduced pressure followed by chromatography (5% EtOAc/hexanes) gave starting ketone (33.4 mg, 11% recovery), mixture of **47** and **48** (169.0 mg, 37% if pure) and diketone **49** (48.0 mg, 11%). Rechromatographing the cyclobutanone mixture on a small bore column provided **47** (105.1 mg, 23%) as opaque crystals (mixture of diastereomers from ^{1}H nmr ratio determined to be 1:1.5) and earlier fractions provided **48** (34.0 mg, 7%) as colorless crystals (mixture of diastereomers from ^{1}H nmr ratio 3:1).

While rechromatographing failed to resolve the mixtures, successive recrystallizations did allow one isomer of **47** to be resolved. For this isomer of **47**: m.p 130 - 131.5°C. IR: 3508, 3341 and 1768 cm^{-1}. ^{1}H nmr: δ 2.93 (2H, overlapping unsymmetrical t), 2.66 (1H, br s), 2.56 (1H, m), 1.91 (3H, unresolved m), 1.62 (2H, br AB d, J = 1.5), 1.56 (3H, br s), 1.37 - 1.49 (6H, unresolved m), 1,00 (3H, d, J = 7.2), 0.88 (6H, br t, J = 5.7). ^{13}C nmr: δ 210.8 (0), 97.9 (0), 76.1 (0), 42.7 (2), 38.3 (1), 34.9 (2), 32.6 (1), 30.4 (2), 29.1 (2), 23.8 (2), 22.3 (1), 20.0 (3), 19.3 (3), 15.6 (3). MS: no M$^+$, 222 (11), 207 (25), 179 (10), 165 (16), 155 (56), 151 (21), 139 (12), 138 (16), 137 (49), 125 (18), 123 (22), 111 (32), 109

(24), 97 (18), 95 (66), 83 (21), 82 (23), 81 (64), 69 (43), 68 (10), 67 925), 55 (63), 45 (46), 43 (100), 41 (69), 29 (37), 28 (21), 27 (24). Resolved signals for the minor isomer of **47**: ^{13}C nmr: δ 214.8 (0), 95.8 (0), 43.9 (2), 38.1 (1), 32.9 (1), 32.0 (1), 28.6 (2), 25.2 (2), 22.7 (2), 19.3 (3), 15.2 (3). For **48** (mixture 3:1 from ^1H nmr): IR: 3456 and 1763 cm^{-1}. ^1H nmr (CD_2Cl_2): δ 2.88 (6H, m), 2.66 (2H, m), 1.65 - 2.03 (10H, unresolved m), 1.24 - 1.55 (16H, unresolved m), 0.82 - 0.94 (30H, overlapping d). ^{13}C nmr: δ 213.3 (213.2), 98.7 (97.1), 76.0 (75.3), 43.5 (43.0), 38.8 (38.6), 37.6 (36.0), 32.9 (32.8), 31.4 (31.3), 28.9 (28.8), 26.0 (23.8), 20.1 (19.5), 17.0 (16.9).

(6*S*,9*R*)-6-Methyl-9-(methylethyl)spiro[4.5]decane-1,4-dione (49) and (6*R*,9*R*)-6-Methyl-9-(methylethyl)spiro[4.5]decane-1,4-dione (50). To a solution of tetrahydrocarvone (1:1 mixture of methyl epimers; 340 mg, 2.20 mmol) and $BF_3.Et_2O$ (0.30 mL, 2.6 mmol) in CH_2Cl_2 (9.0 mL) was added **1** (0.9 mL, 3.3 mmol) at rt, and the reaction mixture was stirred for 22.5 h. H_2O (approx. 0.4 mL) was added, followed 10 min later by $BF_3.Et_2O$ (4.0 mL, 33 mmol). This was stirred for 30 h. Work-up followed by purification (charcoal/Florisil) provided 408 mg of a yellow oil. Chromatography of the oil gave 12 mg of recovered tetrahydrocarvone, **50**[16] (14 mg, 3%) and the more polar isomer **49** (254 mg, 52%) as a yellow oil: IR: 1759 (shoulder) and 1719 cm^{-1}. ^1H nmr: δ 3.01 - 2.74 (2H, m), 2.66 - 2.49 (2H, m), 2.07 - 1.74 (3H, m), 1.70 - 1.00 (6H, m), 0.91

(3H, d, J = 5.0), 0.874 (3H, d, J = 6.7), 0.869 (3H, d, J = 6.8). ^{13}C nmr: δ 214.6 (0), 214.1 (0), 60.8 (0), 36.6 (1), 34.7 (2), 34.3 (2), 32.7 (1), 31.7 (1), 27.6 (2), 25.2 (2), 22.1 (2), 19.7 (3), 19.4 (3), 14.6 (3). MS: 222 (21, M^+), 207 (8), 179 (12), 151 (13), 138 (59), 126 (59), 125 (100), 112 (37), 111 (24), 98 (46), 95 (25), 55 (54), 43 (37), 41 (87). Exact mass calcd. for $C_{14}H_{22}O_2$: 222.1618, found 222.1604.

2,2-Dimethyl-1,3-cyclopentanedione (51). To a solution of acetone (165 mg, 2.84 mmol) and $BF_3.Et_2O$ (0.35 mL, 2.9 mmol) in CH_2Cl_2 (9.0 mL) at rt was added **1** (1.1 mL, 4.2 mmol). The reaction mixture was stirred for 1 h at rt, and H_2O (approx. 0.4 mL) was added followed 10 min later by $BF_3.Et_2O$ (5.1 mL, 42 mmol), which provoked a vigorous exothermic reaction. The mixture was stirred for 1 h, and work-up followed by purification (charcoal/Florisil) which afforded **51** (299 mg, 84%) as a pale yellow solid, mp 36.5 - 38°C. IR: 1725 cm^{-1}. ^1H nmr: δ 2.81 (4H, s), 1.15 (6H, s). ^{13}C nmr: δ 216.3 (2C, 0), 52.6 (0), 34.5 (2C, 2), 20.2 (2C, 3). MS: 126 (54, M^+), 111 (19), 83 (18), 70 (100), 56 (23), 55 (21), 42 (83). Exact mass calcd. for $C_7H_{10}O_2$: 126.0680, found 126.0678.

2-Methyl-2-(3-methylbutyl)-1,3-cyclopentanedione (52). A solution of 6-methylheptanone (303 mg, 2.37 mmol) in CH_2Cl_2 (35 mL) was cooled to -78°C, and $BF_3.Et_2O$ (4.5 mL, 37 mmol) was added followed by a solution of **1** (1.6 mL, 6.1 mmol) in CH_2Cl_2 (6.0 mL) over

25 min. The reaction mixture was allowed to warm to rt, and stirring was maintained for 3 days. Work-up provided a dark, viscous oil, from which chromatography afforded **52** (300 mg, 65%) as an oil: IR: 1764 (shoulder) and 1724 cm^{-1}. ^1H nmr: δ 2.76 (4H, apparent narrow d, J = 0.6), 1.58 (2H, m), 1.49 (1H, m), 1.22 - 1.03 (4H, m), 1.09 (3H, s), 0.82 (6H, d, J = 6.6). ^{13}C nmr: δ 216.3 (2C, 0), 56.4 (0), 38.7 (2), 35.7 (2), 34.9 (2C, 2), 27.2 (1), 22.1 (2C, 3), 22.0 (2), 18.5 (3). MS: 196 (1.4, M^+), 181 (1), 153 (4), 125 (100), 113 (30), 112 (60), 97 (24), 82 (17), 69 (27), 41 (61). Exact mass calcd. for $C_{12}H_{20}O_2$: 196.1462, found 196.1454.

2,2-Diethyl-1,3-cyclopentanedione (53). To a solution of 3-pentanone (243 mg, 2.83 mmol) and $BF_3.Et_2O$ (0.40 mL, 3.4 mmol) in CH_2Cl_2 (9.0 mL) at rt was added **1** (1.1 mL, 4.2 mmol). The reaction mixture was stirred for 3.7 h at rt, and H_2O (approx. 0.4 mL) was added followed 10 min later by BF_3 Et_2O (5.2 mL, 42 mmol). The mixture was stirred overnight. Work-up followed by purification (charcoal/Florisil) yielded **53** (204 mg, 47%) as an oil that crystallized during storage: mp 62 - 63.5°C. IR: 1720 cm^{-1}. ^1H nmr: δ 2.74 (4H, s), 1.68 (4H, q, J = 7.5), 0.77 (6H, t, J = 7.5). ^{13}C nmr: δ 217.4 (2C, 0), 62.0 (0), 36.2 (2C, 2), 27.7 (2C, 3). MS (from GCMS): 154 (82, M^+), 139 (100), 126 (27), 125 (91), 111 (24), 97 (33), 83 (48), 69 (20), 55 (59). Exact mass calcd. for $C_9H_{14}O_2$: 154.0993, found 154.0983.

7-Methylspiro[4.5]decane-1,4-dione (54). To a solution of 3-

methylcyclohexanone (205 mg, 1.83 mmol) and $BF_3.Et_2O$ (0.25 mL, 2.0 mmol) in CH_2Cl_2 (9.0 mL) at rt was added **1** (0.75 mL, 2.9 mmol). The reaction mixture was stirred for 1 h at rt, and H_2O (approx. 0.3 mL) was added followed 10 min later by $BF_3.Et_2O$ (3.3 mL, 27 mmol). The mixture was stirred for 1 h. Work-up followed by purification (charcoal/Florisil) yielded **54** (306 mg, 93%) as a colorless solid: mp 68 - 70.5°C. IR: 1714 cm^{-1}. ^1H nmr: δ 2.76 (4H, m), 1.94 (1H, m), 1.90 - 1.53 (5H, m), 1.41 (1H, ddd, J = 3.9, 12.9, 13.4), 1.13 (1H, dd, J ~ 12.7, 13.1), 0.89 (1H, m), 0.87 (3H, d, J = 6.6). ^{13}C nmr: δ 215.9 (0), 215.5 (0), 56.7 (0), 36.8 (2), 34.3 (2), 34.2 (2), 33.6 (2), 29.0 (2), 26.2 (1), 22.2 (3), 20.6 (2). MS: 180 (55, M^+), 165 (6), 151 (5), 125 (21), 124 (49), 112 (100), 111 (25), 95 (37), 81 (43), 69 (28), 67 (38), 55 (69), 41 (51). Exact mass calcd. for $C_{11}H_{16}O_2$: 180.1149, found 180.1162.

2,2-Bis(4-pentenyl)-1,3-cyclopentanedione (55). To a solution of 1,10-undecadien-6-one (1.75 g, 10.6 mmol) and $BF_3.Et_2O$ (1.3 mL, 11 mmol) in CH_2Cl_2 (90 mL) was added **1** (4.2 mL, 16 mmol) at rt, and the reaction mixture was stirred for 11 h. H_2O (approx. 1.3 mL) was added followed 10 min later by $BF_3.Et_2O$ (20 mL, 165 mmol). This was stirred for 3.5 h. Work-up followed by purification (charcoal/Florisil) provided 2.15 g of a brown oil, which GCMS analysis showed was 90% **55**, some unrearranged material, and less than 5% starting ketone. A colorless sample was obtained by chromatography: IR: 1722 and 1641 cm^{-1}. ^1H

nmr: δ 5.69 (2H, m), 4.95 (4H, m), 2.71 (4H, s), 1.96 (4H, apparent q, *J* = 7.0), 1.62 (4H, m). ^{13}C nmr: δ 217.3 (2C, 0), 137.3 (2C, 1), 115.1 (2C, 2), 60.8 (0), 36.1 (2C, 2), 34.6 (2C, 2), 33.7 (2C, 2), 23.7 (2C, 2). MS: no M^+, 205 (2), 167 (52), 166 (33), 141 (26), 125 (25), 124 (17), 112 (44), 111 (35), 99 (21), 81 (38), 79 (26), 68 (27), 67 (54), 55 (69), 53 (26), 41 (100).

Reaction of 6-methyl-5-hepten-2-one with 1. Attempt to prepare 56. To a solution of 6-methyl-5-hepten-2-one (198.5 mg, 1.58 mmol) in CH_2Cl_2 (9.0 mL) was added $BF_3.Et_2O$ (0.2 mL, 1.6 mmol) and **1** (0.6 mL, 2.4 mmol). The reaction was stirred 1.5 h prior to the addition of H_2O (0.3 mL). After further stirring 10 min, $BF_3.Et_2O$ (2.9 mL, 24.0 mmol) was added and then the reaction solution was stirred overnight. Work-up followed charcoal/Florisil purification provided a brown oil, (71.5 mg, 23% yield if pure). GCMS very complex with the major signals all containing a mass fragment corresponding to **56**. In addition many higher mass fragments were present. A small portion of this material was heated with TFA under reflux to give a black tar upon work-up, but unfortunately, GCMS analysis indicated no new signals. Chromatography (2% EtOAc/hexanes) of the remaining material, gave a small sample, a yellow oil whose nmr did not suggest **56** nor any further cyclized material as reported by Curran.[15]

7-Methylspiro[4.4]non-6-ene-1,4-dione (57). To a solution of 3-

methyl-2-cyclopenten-1-one (222 mg, 2.31 mmol) in CH_2Cl_2 (9.0 mL) was added **1** (0.95 mL, 3.6 mmol) followed by $BF_3.Et_2O$ (0.30 mL, 2.5 mmol), and the reaction mixture was stirred at rt for 1h. H_2O (approx. 0.4 mL) was added followed by $BF_3.Et_2O$ (4.2 mL, 34 mmol), and this was stirred for 1 h. Work-up followed by purification (charcoal/Florisil) gave 210 mg of a viscous oil for which GCMS analysis indicated a mixture of double bond isomers, including the major peak (41%), with this MS: 164 (100, M^+ required for $C_{10}H_{12}O_2$), 149 (14), 136 (29), 121 (20), 108 (83), 80 (82), 79 (94), 77 (34). The ^1H nmr spectrum of the mixture showed olefinic multiplets at δ 5.95, 5.18, and 5.01 in a ratio of 4:1:2.5, respectively.

Spiro[4.5]dec-6-ene-1,4-dione (58). A reaction of 2-cyclohexen-1-one (251 mg, 2.61 mmol) under conditions very similar to those for **36** and subsequent chromatography ultimately provided only 9.3 mg (approx. 2%) of a yellow oil, which GCMS suggested contained a mixture of **58** and its double bond isomer (3:1, respectively). For **58**: MS: 164 (96, M^+), 136 (13), 135 (10), 122 (12), 108 (58), 80 (57), 79 (100), 77 (37).

8,8-Dimethylspiro[4.5]dec-6-ene-1,4-dione (59). To a solution of 4,4-dimethyl-2-cyclohexen-1-one (214 mg, 1.73 mmol) and $BF_3.Et_2O$ (0.20 mL, 1.6 mmol) in CH_2Cl_2 (9.0 mL) at rt was added **1** (0.70 mL, 2.7 mmol). The reaction mixture was stirred for 1 h at rt prior to the addition of H_2O (approx. 0.2 mL) followed 10 min later by $BF_3.Et_2O$ (3.2 mL, 26

mmol). The mixture was stirred for 70 min. Work-up followed by purification (charcoal/Florisil) afforded **59** (237 mg, 72%) as pale yellow crystals: mp 78.5 - 80°C. IR: 1755 (shoulder) and 1716 cm^{-1}. ^1H nmr: δ 5.88 (1H, d, J = 9.9), 5.11 (1H, d, J = 9.9), 2.85 (4H, m), 1.79 (2H, m), 1.60 (2H, m), 1.04 (6H, s). ^{13}C nmr: δ 213.3 (2C, 0), 143.3 (1), 117.2 (1), 60.0 (0), 34.6 (2C, 2), 31.7 (2), 31.1 (0), 28.9 (2C, 3), 25.6 (2). MS: 192 (48, M^+), 177 (100), 149 (18), 131 (20), 121 (43), 107 (17), 93 (34), 91 (30), 77 (29). Exact mass calcd. for $C_{12}H_{16}O_2$: 192.1149, found 192.1141.

2-Benzyl-2-methyl-1,3-cyclopentanedione (60). To a solution of 1-phenyl-2-propanone (260 mg, 1.94 mmol) and $BF_3.Et_2O$ (0.30 mL, 2.5 mmol) in CH_2Cl_2 (9.0 mL) at rt was added **1** (0.80 mL, 2.9 mmol). The reaction mixture was stirred for 2.3 h at rt prior to the addition of H_2O (approx. 0.4 mL) followed 10 min later by $BF_3.Et_2O$ (3.6 mL, 29 mmol). The mixture was stirred overnight. Work-up followed by purification (charcoal/Florisil) afforded 317 mg of a pale brown oil from which chromatography yielded **60** (300 mg, 51%) as waxy yellow crystals: mp 42 - 43°C. IR: 1724 cm^{-1}. ^1H nmr: δ 7.21 (3H, m), 7.03 (2H, m), 2.95 (2H, s), 2.55 (2H, m), 2.05 (2H, m), 1.19 (3H, s). ^{13}C nmr: δ 217.2 (2C, 0), 135.6 (0), 129.4 (2C, 1), 128.4 (2C, 1), 127.0 (1), 58.1 (0), 42.8 (2), 35.6 (2C, 2), 19.8 (3). MS: 202 (33, M^+), 187 (10), 159 (18), 145 (11), 117 (18), 91 (100). Exact mass calcd. for $C_{13}H_{14}O_2$: 202.0993, found 202.0989.

2',3'-Dihydrospiro[cyclopentane-1,2'-[1*H*]indene]-2,5-dione (61). To a solution of 2-indanone (259 mg, 1.96 mmol) and $BF_3.Et_2O$ (0.30 mL, 2.5 mmol) in CH_2Cl_2 (9.0 mL) at rt was added **1** (0.80 mL, 2.9 mmol). The reaction mixture was stirred for 2 h at rt prior to the addition of H_2O (approx. 0.4 mL) followed 10 min later by $BF_3.Et_2O$ (3.6 mL, 29 mmol). The mixture was stirred overnight. Work-up followed by purification (charcoal/Florisil) provided **61** (258 mg, 66%) as a beige solid: mp 112 - 114°C. IR: 1721 cm^{-1}. ^1H nmr: δ 7.17 (4H, br s), 3.22 (4H, s), 2.84 (4H, s). ^{13}C nmr: δ 213.7 (2C, 0), 139.2 (2C, 0), 127.1 (2C, 1), 124.2 (2C, 1), 62.0 (0), 40.0 (2C, 2), 34.7 (2C, 2). MS: 200 (56, M'), 172 (100), 158 (53), 143 (42), 128 (47), 116 (74), 115 (85), 58 (59). Exact mass calcd. for $C_{13}H_{12}O_2$: 200.0837, found 200.0858.

1',2',3',4'-Tetrahydrospiro[cyclopentane-1,1'-naphthalene]-2,5-dione (62). To a solution of 1-tetralone (296 mg, 2.03 mmol) and $BF_3.Et_2O$ (0.30 mL, 2.5 mmol) in CH_2Cl_2 (9.0 mL) at rt was added **1** (0.80 mL, 2.9 mmol). The reaction mixture was stirred for 2.2 h at rt prior to the addition of H_2O (approx. 0.4 mL) followed 10 min later by $BF_3.Et_2O$ (3.7 mL, 31 mmol). The mixture was stirred overnight. Work-up followed by purification (charcoal/Florisil) provided 312 mg of a pale brown solid that GCMS analysis showed was a 1:3.3 mixture of 1-tetralone and **62**. A colorless, analytical sample was obtained by chromatography: mp 102.5 - 104°C. IR: 1719 cm^{-1}. ^1H nmr: δ 7.21 - 7.03 (3H, m), 6.53 (1H, d, J =

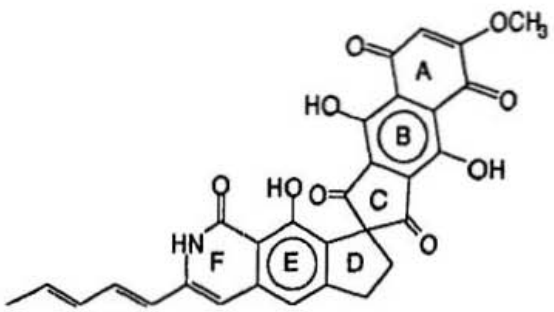
7.6), 2.91 (4H, complex m), 2.82 (2H, narrow m), 1.92 (4H, narrow m). ^{13}C nmr: δ 214.7 (2C, 0), 138.4 (0), 131.7 (0), 129.6 (1), 128.3 (1), 127.4 (1), 126.2 (1), 62.3 (0), 35.1 (2C, 2), 31.4 (2), 28.6 (2), 17.8 (2). MS: 214 (100, M$^+$), 186 (16), 158 (43), 130 (64), 129 (73), 128 (40), 115 (37). Exact mass calcd. for $C_{14}H_{14}O_2$: 214.0993, found 214.0995.

Chapter 2

STUDIES TOWARDS THE SYNTHESIS OF FREDERICAMYCIN A

I. INTRODUCTION

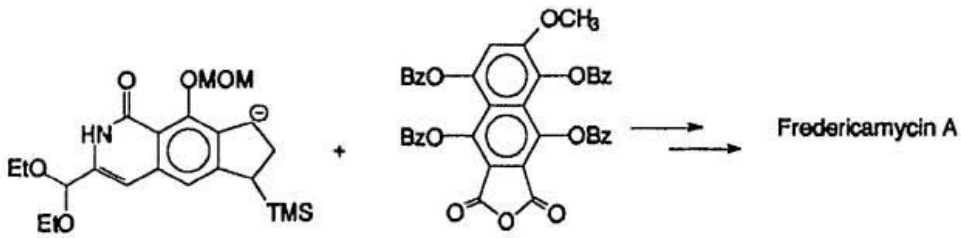
Fredericamycin A, isolated from strains of *Streptomyces grieseus* in 1981,[18] is an antitumor and antibiotic compound which, unlike other



Fredericamycin A

members of this class, has a unique L-shape structure owing to the spiro ring system.[19] As a result of its promising anticancer activity, there have been numerous model studies[20-30] and four successful total syntheses.[31-35] While the first total synthesis of fredericamycin A was reported by Kelly and workers[20,31] in 1986, it was 1992 before the second synthesis was completed.[32] In 1993, two additional total syntheses have been reported.[33,34]

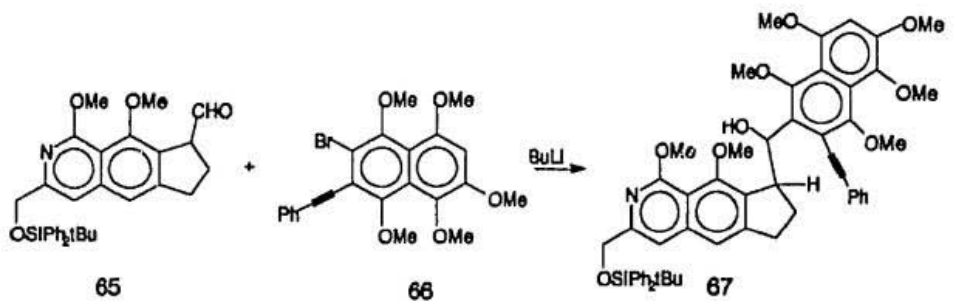
Scheme 26



63 64

A common strategy for the synthesis of fredericamycin A was to establish the spiro center by the condensation of a lower DEF ring synthon with an upper ABC synthon. Indeed, the inital synthesis by Kelly and workers[20, 31] provided (±)- fredericamycin A (in less than 1% overall yield) with the key step being the base induced cyclization of the lower DEF synthon **63** with the upper ABC synthon **64** (Scheme 26).

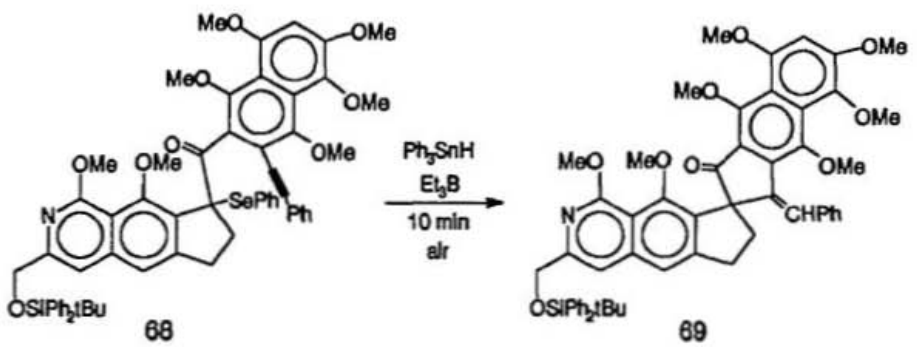
Scheme 27



65 66 67

Both Clive[32] and Rao[33] established the key spiro center using radical cyclization. Clive and coworkers[21, 32] prepared the pentacyclic alcohol **67** (68%) by the condensation of aldehyde **65** with the carbanion derived from bromide **66** (Scheme 27) and subsequent functional group manipulation led to the radical precursor **68**. 5-*exo*-Digonal closure using triphenyltin hydride gave the spirocyclic compound **69** in 50% yield as a single isomer (Scheme 28).

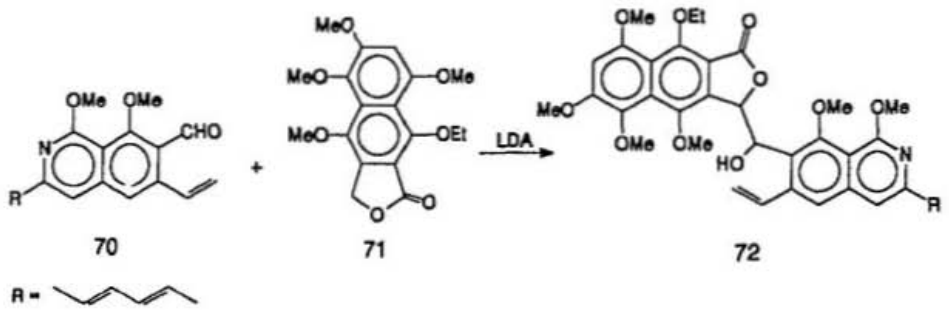
Scheme 28



68 69

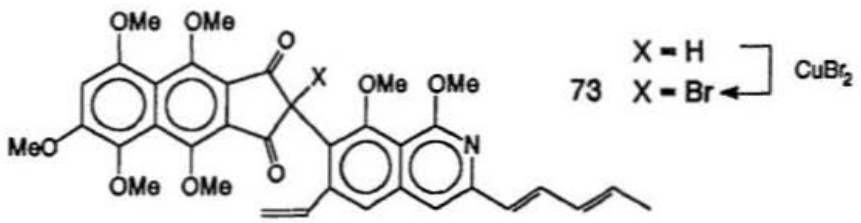
Rao and coworkers[22, 33] gained access to the key spiro center using a 5-*endo*-trigonal radical cyclization. Aldol condensation of aldehyde **70** with the ABC synthon **71** in the presence of lithium diisopropylamide (LDA) furnished adduct **72** (54%) (Scheme 29). Sodium methoxide-mediated rearrangement of **72** (58%) followed by introduction of a halogen using copper(II) bromide and maganese(III) acetate in acetic acid gave the radical precursor **73** (Scheme 30). Radical

Scheme 29



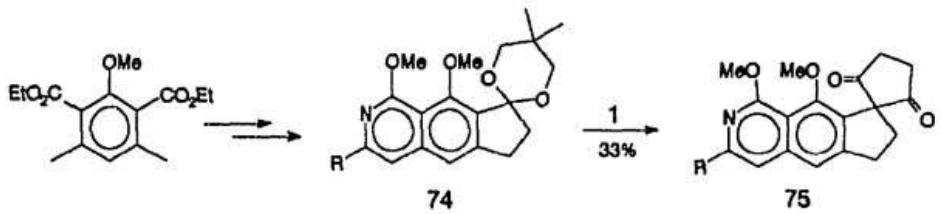
cyclization followed by dehalogenation yielded the hexamethyl ether of fredericamycin A in 55% yield.

Scheme 30



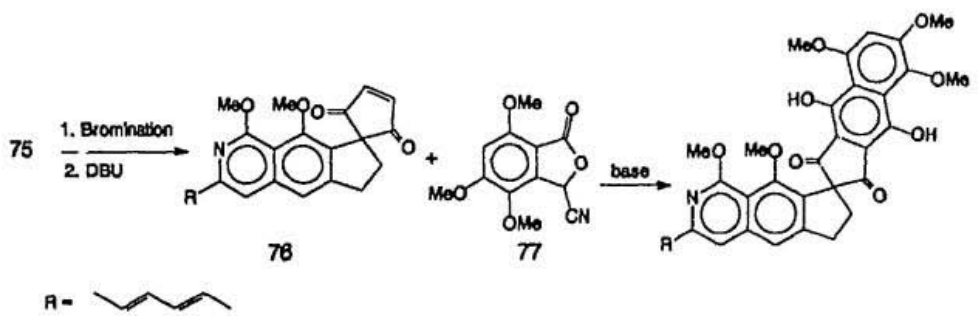
While our work was in progress, Julia and coworkers[23, 34] published the total synthesis of fredericamycin A using a very similar approach to ours. The entire lower portion of fredericamycin A including the spiro center was prepared using the "ketal conditions" developed in our laboratories with 1,2-bis(trimethylsilyloxy)cyclobutene **1**.[16] Spiroannulation of ketal **74** with **1** afforded spiro diketone **75** in 33% yield

Scheme 31



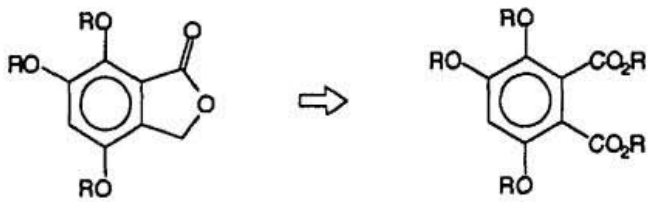
(Scheme 31). Subsequent bromination and dehydrobromination provided the key enone **76**. Condensation of the AB synthon, lactone **77** (see earlier model studies by both Parker[24] and Bach[25] for similar AB ring

Scheme 32



construction), with enedione **76** under basic conditions (LDA then NaH) gave access to the complete carbon skeleton with all the oxygen functionalities of fredericamycin A (Scheme 32).

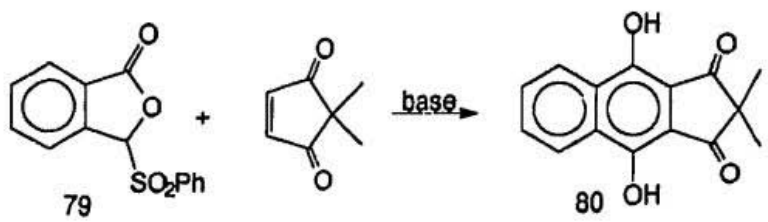
Scheme 33



78

In addition to these total syntheses there have been numerous model studies and partial syntheses. Parker and coworkers[8, 24] concentrated their efforts on the preparation of the trialkoxyphthalic acid derivative **78**, which was to serve as the ABC ring precursor (Scheme 33). Subsequent transformation to the analogous lactone was intended to lead to the ABCDEF rings using an isobenzofuran approach developed

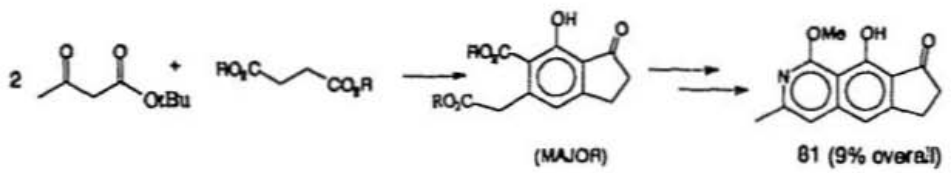
Scheme 34



79 80

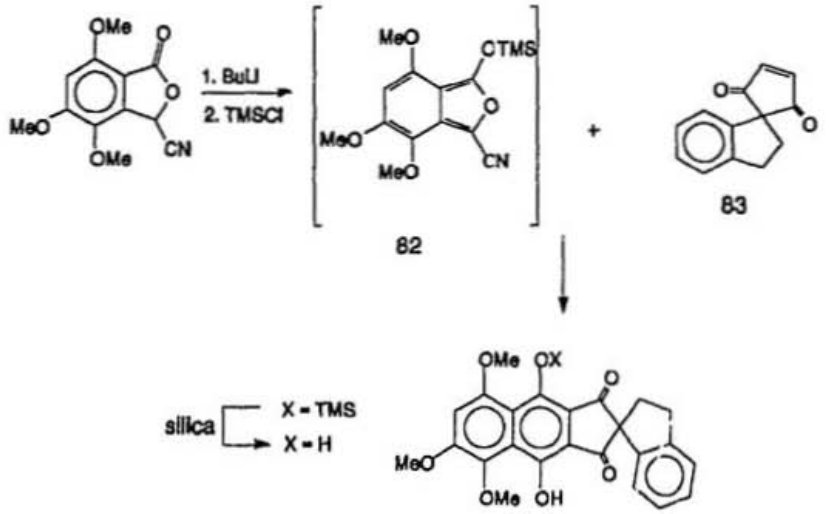
previously (**79** to **80**)[24a] (Scheme 34) in conjugation with the DEF synthon **81** (Scheme 35).[24d]

Scheme 35



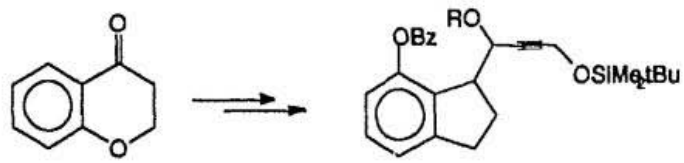
An extension to Parker's isobenzofuran approach was adopted by Bach and coworkers,[25] who reported a Diels-Alder cyclization between the isobenzofuran **82** (generated *in situ*) with enone **83** (Scheme 36).

Scheme 36



Boger and Jacobsen[25] furnished the ABCDE rings using an alkyne-chromium carbene complex benzannulation reaction followed by

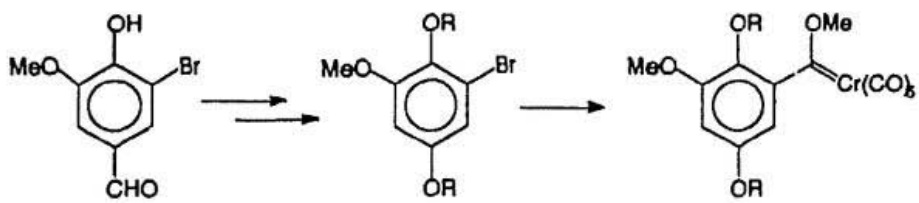
Scheme 37



84

aldol cyclization. Alkyne **84** (Scheme 37), prepared from 4-chromanone in six steps in 36% overall yield, was coupled with the chromium carbene **85** (Scheme 38), generated from vanillin in 43% overall yield (chromium carbene being established by metallation), to afford the key tetracyclic compound **86** in a single step in 48% yield (Scheme 39). Cleavage of the silyl ethers, Swern oxidation of the alcohols, and aldol closure established the ABCDE rings.

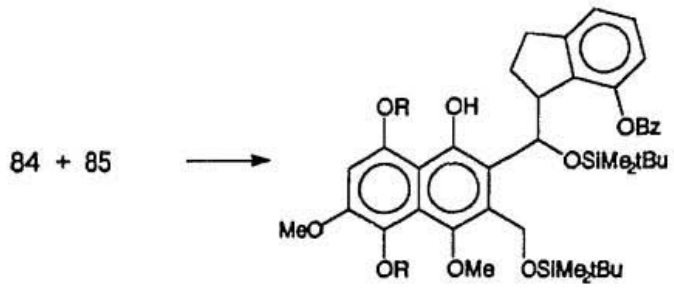
Scheme 38



R = CH_2OMe

85

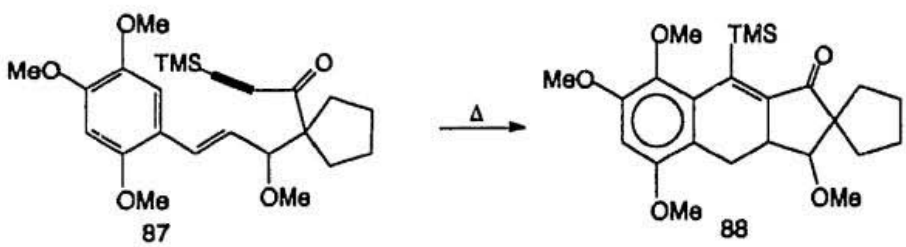
Scheme 39



86

Terashima[27] accessed the ABCD rings using an intramolecular Diels-Alder cyclization. Dieneyne **87** furnished adduct **88** (Scheme 40) in a high yield since the configuration of the carbon-carbon single bond of the diene portion was fixed (only s-cis dienes will partake in the Diels-Alder reaction). The result demonstrated that this method may be used with an optically active dieneyne derivative to enable an optically active synthesis of fredericamycin A.

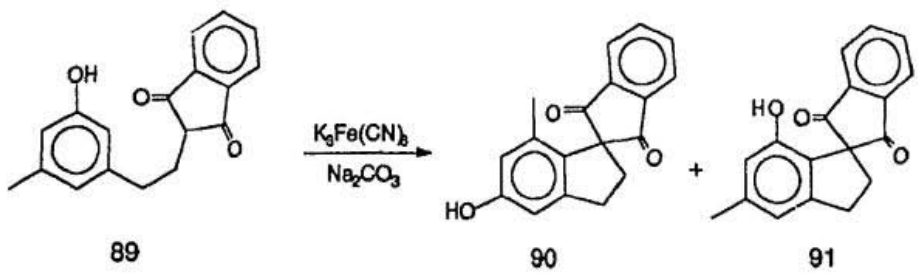
Scheme 40



Kende and Ebetino[20] approached the spiro center by a phenoxy-

enoxy radical cyclization. Treatment of β-diketone **89**, prepared from 3,5-dimethylphenol in 18% overal yield, with ferricyanide provided a mixture of **90** (67%) and the desired tetracyclic compound **91** (8%) (Scheme 40). The authors reported that the yield increased with the introduction of an iodine in the 4-position of the aromatic starting material. The iodine analogue of **91**, however, was recovered in less than 50% yield.

Scheme 41

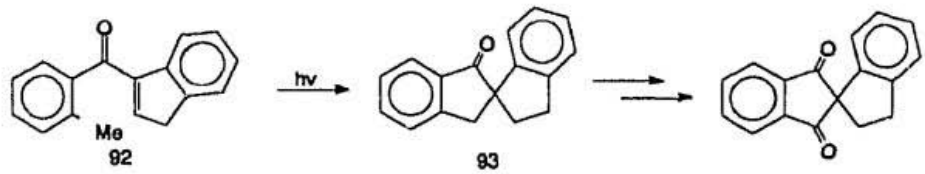


89 90 91

A novel, two-step photochemical approach toward fredericamycin A was reported by Mehta and Subrahmanyam.[29] Enone **92**, prepared by the condensation of an indenyl anion with 2-methylbenzoyl chloride, provided the spirocyclic compound **93** (Scheme 42). The mechanism presumably involved a 1,6-hydrogen abstraction from the methyl substituent followed by spirocyclization. Unfortunately, introduction of the second carbonyl in the C ring was found to be a multistep task.

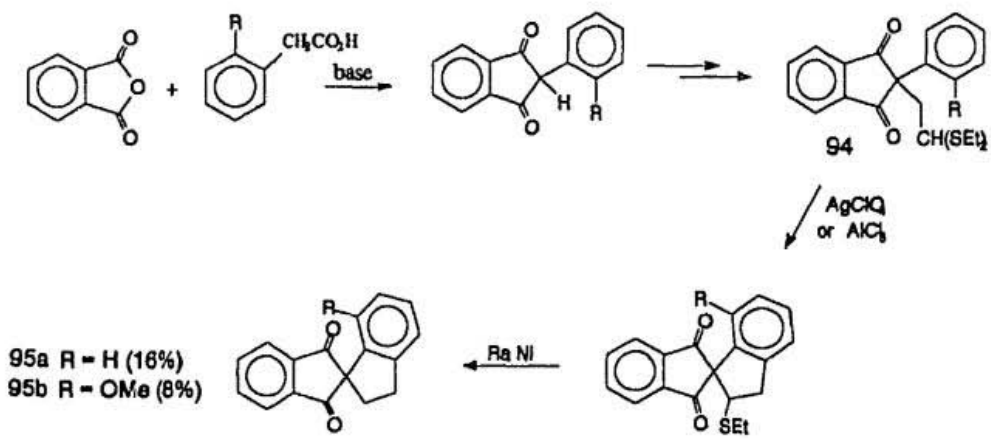
Model studies by Braun and Veith[30] (Scheme 43) concentrated on an intramolecular Friedel-Crafts cyclization. The key thioacetal substrate

Scheme 42



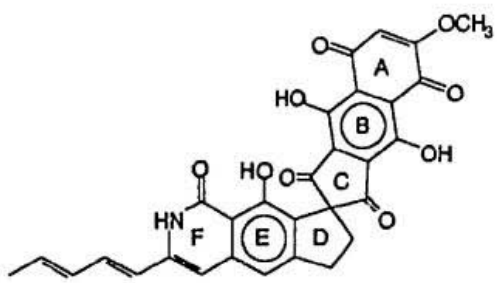
94 was derived from phthalic anhydride in several steps and provided the desired tetracyclic compounds **95a** and **95b** upon treatment with aluminum trichloride or silver perchlorate.

Scheme 43

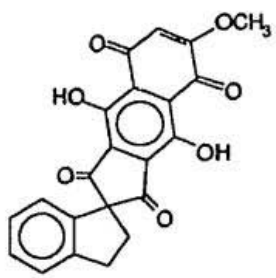


II. RESULTS AND DISCUSSION

Our synthetic studies towards fredericamycin A focused on the preparation of the molecule **96**, which addressed the ABCDE rings. The spiro center, which had proved troublesome in other approaches, would be established by geminal acylation of 1-indanone with 1,2-



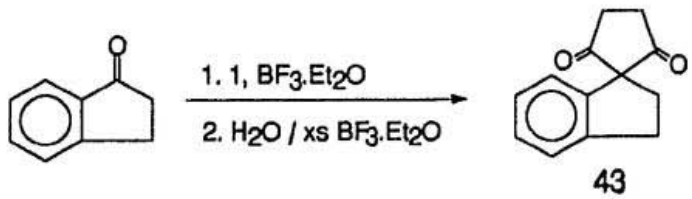
Fredericamycin A



96

bis(trimethylsilyloxy)cyclobutene (**1**). Indeed, the preparation of **43** (Scheme 44) was described in the previous chapter.

Scheme 44

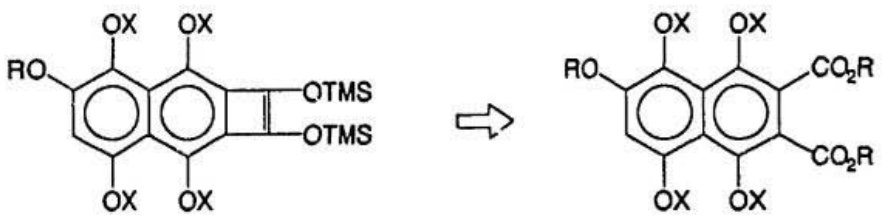


43

Our initial attempts to extend this methodology was to employ a

much more elaborate cyclobutene reagent. Thus, we hoped to not only incorporate the C ring but also the A and B rings during the geminal acylation step. For such a transformation to be successful, a fused tricyclic cyclobutene would be required such that its rings were either aromatic at the onset or had functionality in place to allow aromatization in a later step. Noting the high degree of oxygen substitution on both the A and B rings it seemed beneficial to have an aromatic cyclobutene derivative such as **97** (Scheme 45), in which not only were the rings

Scheme 45

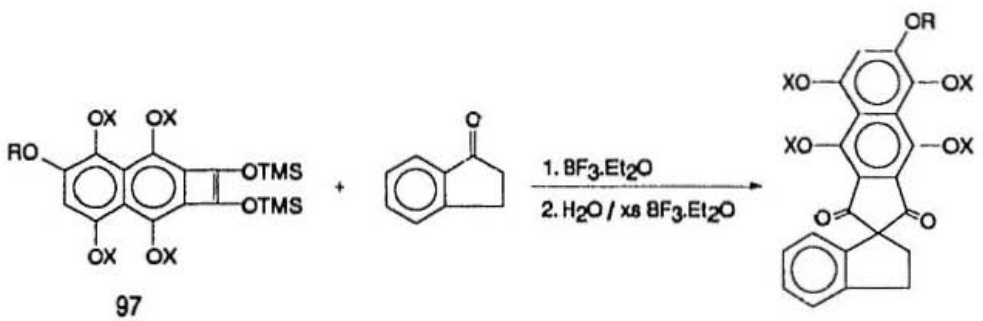


97 **98**

aromatic, but they also possessed the required oxygen substituents. The conjugated aromatic cyclobutene derivative **97** was expected to be of much higher energy than **1**, as all four carbons of the cyclobutene moiety would be sp^2. Furthermore, the diester required to generate such a cyclobutene analogue, **98**, would be more rigid than an aliphatic diester, and this might discourage the acyloin coupling. However, if the cyclobutene **97** could be prepared, even as a short-lived species, and

the subsequent geminal acylation were successful, the entire ABCD ring system with the oxygen substituents, in addition to a nonfunctionalized E ring, could be realized in a single synthetic transformation (Scheme 46).

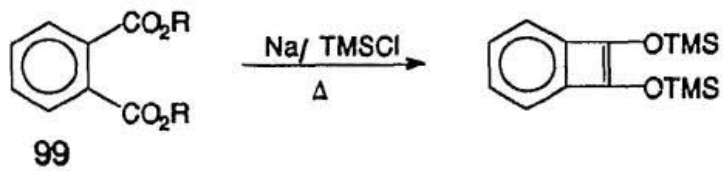
Scheme 46



97

Model studies utilized the nonsubstituted phthalate **99** and it was subjected to conditions used for the preparation of **1** (Scheme 47).[17] All the fractions obtained during vacuum distillation of the product boiled at temperatures greater than 100°C / 2 mm Hg and were highly colored. The ^{13}C nmr spectrum of the fractions all contained resonances for the starting diester **99**, and while some spectra included minor signals assigned to TMS and aromatic resonances, there were also alkane resonances. These resonances suggested that reduction and/or polymerization of the starting material and/or product may have occurred as both the starting material and solvent were aromatic. In an attempt to avoid these processes, the reaction was repeated under milder

Scheme 47

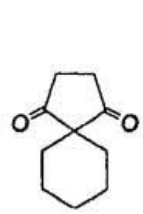


99

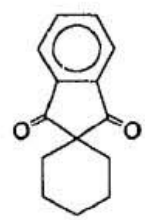
conditions as reported by Ruhlmann[35a] such that the sodium/TMSCl/toluene solution was cooled to room temperature prior to the addition of the diester. As an additional precaution, vacuum distillation of the product was not attempted. Removal of the solvent by simple distillation under a nitrogen atmosphere left a highly colored liquid, which, from nmr analysis, was found to be mainly the starting diester **99**.

It was possible that the cyclobutene species was generated but in such a small quantity that its nmr signals were masked by the residual starting diester, or that the cyclobutene species was of such high reactivity that it was consumed in polymerization and/or decomposition pathways. We reasoned that while chromatography would not directly provide the proposed cyclobutene (stability of cyclobutenes on silica is poor), if the proposed cyclobutene could be reacted with a carbonyl moiety, the subsequent geminally acylated product could be isolated from residual starting diester **99**. Isolation and characterization of such

an acylated product would not only prove the *in situ* generation of the cyclobutene but would also give an indication of the efficiency of the geminal acylation reaction. In practice, ketalized cyclohexanone was added to the filtrate obtained from the acyloin sequence, followed by an excess $BF_3.Et_2O$. Aqueous work-up provided a crude product whose nmr spectrum was dominated by signals for the remaining diester. Chromatography gave a 64% recovery of diester **99**, but, more importantly, there was a series of later fractions (crude yield 30%) that,



31

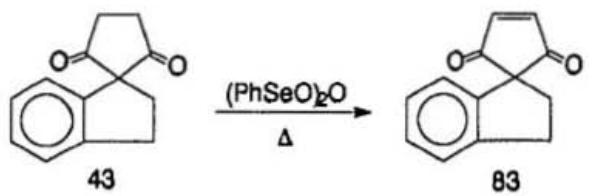


100

while impure, indicated the geminally acylated product **100**. Unfortunately, both the diester **99** and the putative geminally acylated product **100** had similar R_f's making separation difficult. As a result the nmr spectra of the putative product **100** also included resonances for the starting material. The ^1H nmr spectrum included two aromatic resonances at δ 7.5 and 7.8 ppm, two broad, ill-defined alkane resonances between δ 1.0 - 1.3 ppm, in addition to four multiplets from δ 1.7 to 2.0 ppm having approximately equal integration. Included in the

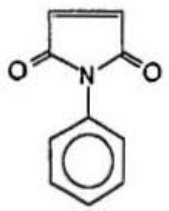
^{13}C nmr spectrum were a number of resonances that were similar to the resonances reported for the analogous carbons of spiro[4.5]nonane-1,4-dione (ppm) **31**:[1] δ **100** (vs **31**) 202.2 (215.0), 52.6 (55.6), 33.9 (39.1), 29.6 (29.0), 24.7 (24.7), 20.3 (20.3) ppm in addition to aromatic and ester type resonances. While this data does support an acylation product, repeating the experiment failed to provide the proposed acylated product **100** free from the starting diester. In all attempts the recovery of the diester was typically 60 - 77%, suggesting that if the acyloin sequence were successful, the subsequent geminal acylation would not afford the desired diketone in a synthetically acceptable yield. Faced with a low chemical conversion and no pure samples to determine actual yields, we turned to a sequential route for the addition of rings A, B, and C. A compound with ring C was dione **43** that was prepared in the methodological study (Chapter 1).

Scheme 48

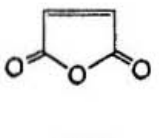


43 **83**

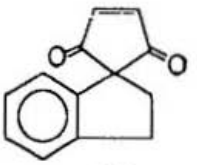
Dehydrogenation of dione **43** with benzeneselenic anhydride provided enedione **83** in 59% yield (Scheme 48). Its ^{1}H nmr spectrum



101



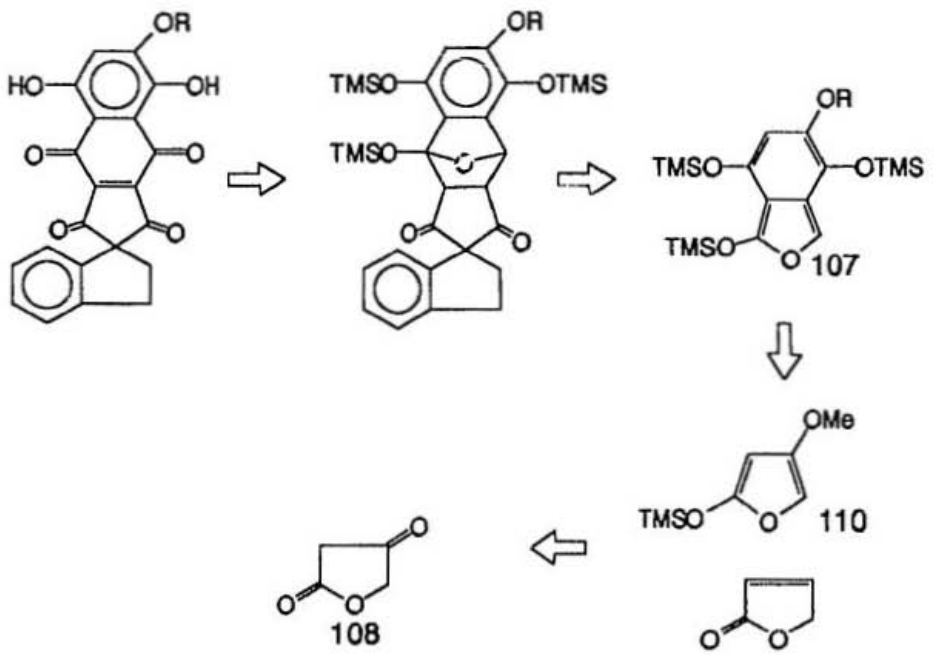
102



83

included vinylic hydrogen resonances at δ 7.45 ppm. The structure of enedione **83** was similar to that of *N*-phenylmaleimide **101** and maleic anhydride **102**, two very effective Diels-Alder dienophiles. It

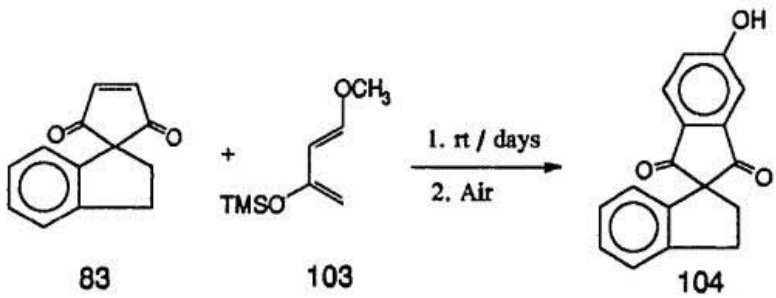
Scheme 49



was this correlation that suggested the possiblity of generating the A and

B rings by successive Diels-Alder cyclizations, as depicted in Scheme 49. However, the limitations of enone **83** as a dienophile with conventional dienes was quickly realized. Indeed, no evidence for any Diels-Alder adduct between **83** and 2-methoxyfuran could be obtained even under catalysis by ethylaluminum chloride. Even the more reactive Danishefsky's diene (*trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene) (**103**) was very reluctant to cyclize. A solution of **83** and **103** (1.5 equivalents) even after being heated at reflux for 8 days, provided only 13% of adduct **104**, which had aromatized by the loss of methanol during chromatography (Scheme 50). Its ^{13}C nmr spectrum included carbonyl resonances at δ 203.0 and 201.4 ppm in addition to alkane resonances

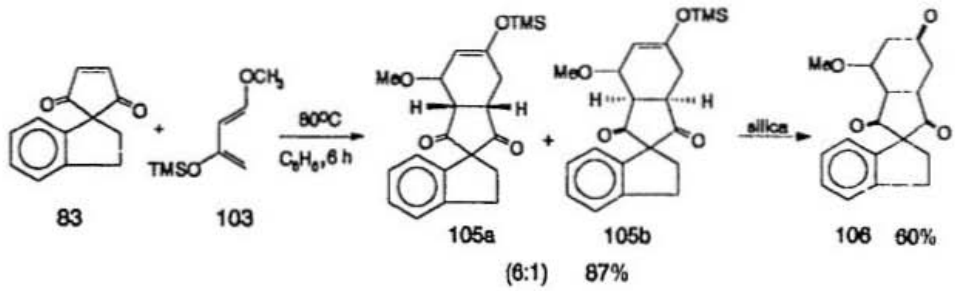
Scheme 50



83 103 104

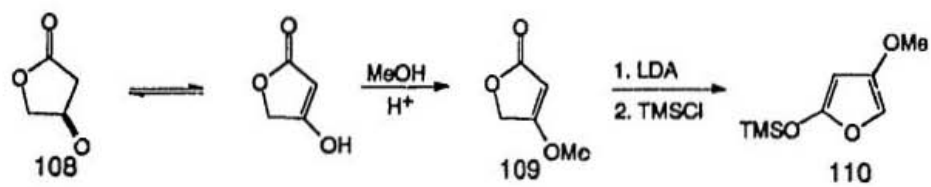
at δ 68.5, 33.4, and 32.9 ppm. The ^{1}H nmr spectrum included two distinctive one-proton aromatic resonances at δ 7.05 and 7.92 ppm. This was in contrast to the same sequence by Bach and coworkers[25c] in which **106** was obtained after chromatography (Scheme 51). These authors

Scheme 51



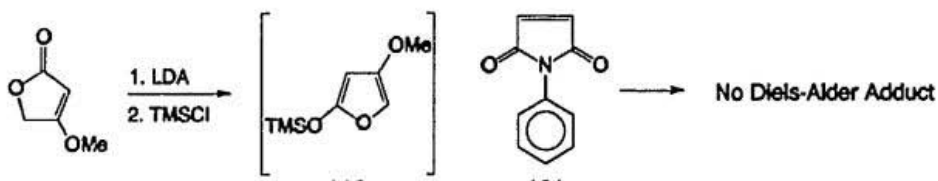
reported that a mixture of diastereomers **105a** and **105b** (87%) was obtained after heating the reaction at reflux for six hours, but the trimethylsilyl group was lost upon chromatographic workup affording **106** (60%). One can speculate that the increase in reaction time from 6 h to 8 days was the major difference. It is important to note however, that we had observed very little consumption of the starting materials by TLC during the first hours of reaction.

Scheme 52



The apparent unreactivity of enone **83** with 2-methoxyfuran was a concern as our retrosynthetic analysis (Scheme 49) hinged upon a cyclization involving a highly substituted furan diene. The substituted furan diene **110**,[35b] derived from tetronic acid **108** (Scheme 52), was studied as it more closely resembled the required bicyclic furan diene **107**. Futhermore, we hoped that the additional electron donating group would induce Diels-Alder reactivity. Before attempting the Diels-Alder cyclization with enone **83**, the analogous sequence with the more reactive *N*-phenylmaleimide **101** was studied. Unfortunately, experimental efforts to trap diene **110**, generated from the treatment of enone **109** with

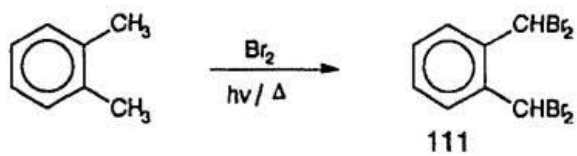
Scheme 53



109 110 101

LDA and TMSCl, with **101** failed (Scheme 53). Despite a low recovery of starting materials, no evidence for a Diels-Alder product could be found. The result suggested that the less reactive dienophile **83** would not undergo a Diels-Alder cyclization under these conditions.

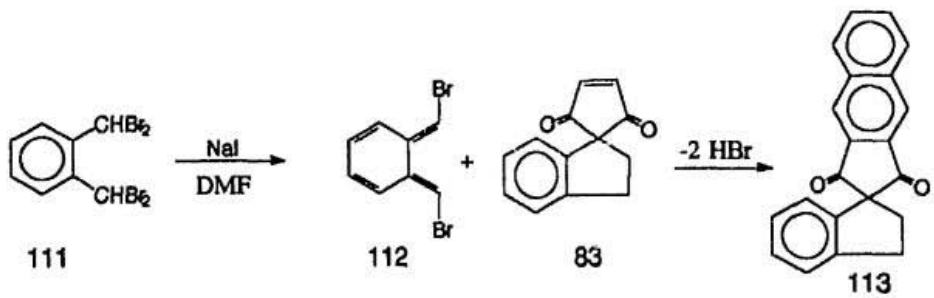
Scheme 54



111

Xylylene derivatives are much more reactive in Diels-Alder reactions owing to concomitant restoration of aromaticity. Such derivatives have been used successfully in the synthesis of a number of polycyclic ring systems.[36] Bromination of *ortho*-xylene[37] allowed access to the nonfunctionalized xylylene precursor, compound **111**, in 60 - 70% yield (Scheme 54). Subsequent treatment of **111** with sodium iodide in a

Scheme 55

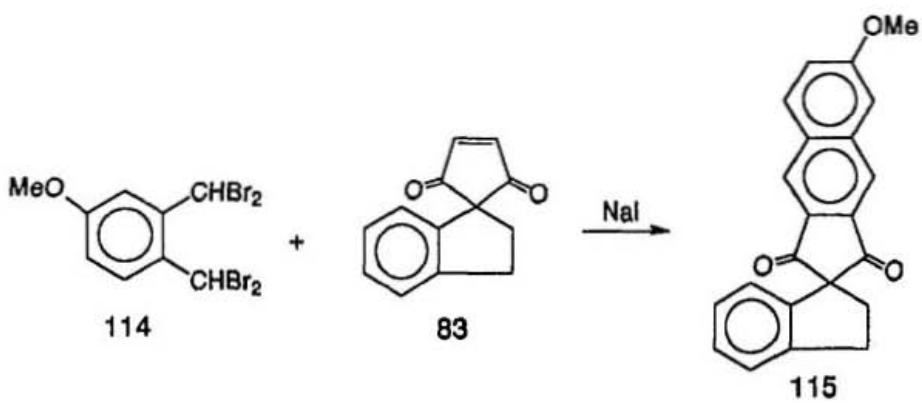


111 112 83 113

refluxing dimethylformamide (DMF) solution[38] allowed the *in situ* generation of diene **112**, which could be trapped in the presence of enedione **83** to give pentacyclic compound **113** (Scheme 55). Neither

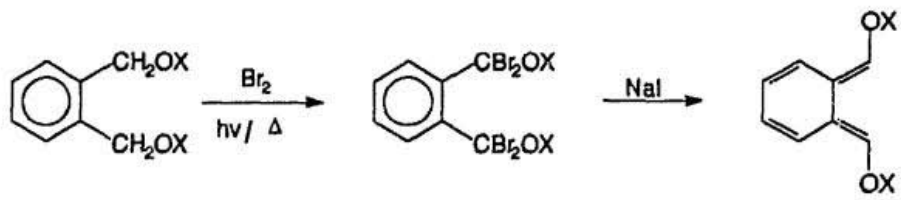
chromatography nor crystallization provided pure **113**, rather a mixture of enone **83** and the desired adduct **113** was obtained. In an attempt to obtain **113** free of **83**, the sequence was repeated using three equivalents of tetrabrominated **111**, which allowed the isolation of adduct **113** in 47% yield. The IR spectrum for **113** included two carbonyl resonances at 1734 and 1705 cm^{-1}. Included in the ^{13}C nmr spectrum was the carbonyl resonance at δ 201.6 ppm and the spiro carbon at δ 68.5 ppm. The ^{1}H nmr spectrum included aromatic resonances with the singlet at δ 8.60 ppm being most distinctive. The transformation was not optimized, but a similar reaction by Bach and workers found activated zinc to be superior to NaI.[25c] It was important first to functionalize the brominated precursor to allow incorporation of some oxygen substituents.

Scheme 56

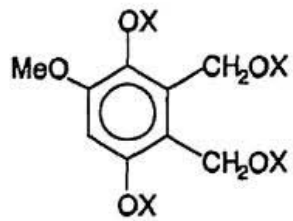


The methoxy was introduced using 3,4-dimethylanisole instead of *ortho*-xylene as the starting material. Tetrabrominated **114**, prepared in the same manner as that reported from *ortho*-xylene, provided adduct **115** (Scheme 56), albeit in a lower yield (14%). Again, the sequence was not optimized. Unlike the unfunctionalized adduct **113**, however, the material obtained by chromatography was only partially soluble in $CDCl_3$. The soluble material contained **115**. The insoluble white powder that remained was readily dissolved in CD_3OD, and it showed no resonances assigned to **115**. The adduct **115** obtained in this way was of reasonable purity, contaminated by only trace amounts of the CD_3OD-soluble material. The ^1H nmr spectrum of **115** included aromatic resonances at δ 8.48, 8.02, and 6.62 in addition to the methoxy resonance at δ 4.00 ppm. The ^{13}C nmr spectrum included carbonyl resonances at δ 201.9 and 201.4 ppm, and the aromatic carbon bearing the methoxy substituent appeared at δ 160.5 ppm. Derivatizing such a methoxy compound would allow incorporation of what would become the quinone oxygens in addition to the methoxy substituent of the A ring. A similar scheme was previously reported,[25c] but it did not address the B ring oxygens. Work by other groups[24, 25, 29] has demonstrated the reluctance of an unfunctionalized B ring to be oxidized. Therefore, it was very important to have oxygen functionality established in what would become both the A ring (OMe and phenolic) and the B ring (quinone).

Scheme 57



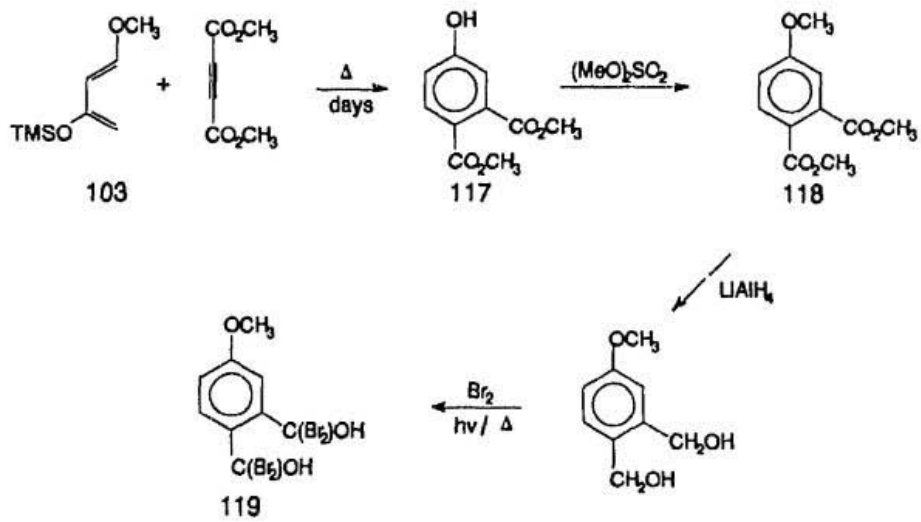
While the required oxygens of the A ring may be derived from a highly substituted anisole derivative, the oxygens of the B ring would require the sites of bromination to be primary alcohol derivatives



116

(Scheme 57). A target such as **116** would be necessary but its sensitivity towards bromination and subsequent xylylene generation is unknown. As shown in Scheme 58, it was hoped that the trisubstituted aromatic **119** could be prepared to serve as a model compound. Diels-Alder reaction of dimethyl acetylenedicarboxylate with Danishefsky's diene **103** provided the aromatic diester **117** in 58% yield. The adduct

Scheme 58

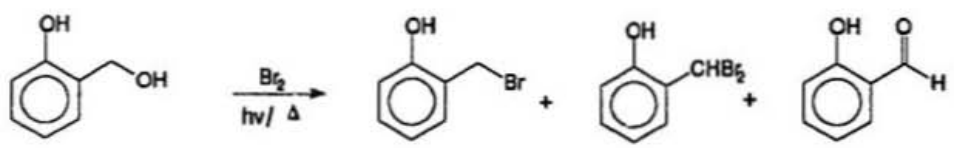


103 117 118 119

had aromatized by the loss of methanol, just as we had found with the sequence involving enedione **83**. The ^{1}H nmr spectrum of the product included the phenolic resonance at δ 8.06 ppm in addition to aromatic resonances at δ 7.73, 7.01 and 6.93 ppm. Protection of **117** using dimethyl sulfate proceeded smoothly to afford **118**, but in a low yield (39%). We suspected that ester hydrolysis may have been a competing reaction to give the polar dicarboxylic acid, which would not have been eluted during chromatography. Unfortunately, ester reduction was not straightforward using $LiAlH_4$ as the material isolated after chromatography had a complex nmr spectrum. Under the assumption

that at least some material was reduced to the alcohol, the product was brominated. The compound itself was to serve only as a model study, so no attempts were made to isolate and characterize the protected benzyl alcohol derivative or the brominated analogue **119**. Subsequent trapping of the xylylene with *N*-phenylmaleimide **101** was not successful.
It was uncertain whether this was because the tetrabrominated species had not been prepared or that the xylylene had not been generated. Later work involving the reduction of another aromatic diester **136** was only accomplished using DIBAL at -78°C. All products recovered from attempts to reduce the diester with $LiAlH_4$ were found to be complex, which suggested that the former reason was correct.

Scheme 59



120 121 122 123

Bromination of 2-(hydroxymethyl)phenol **120** (Scheme 59), under conditions that had proven successful in brominating xylene and the derivative with the methoxy substituent, provided a crude product which from the nmr spectra suggested a mixture of the monobromo product

121 (the nmr spectrum obtained on the crude product included the following resonances: in the ^{1}H nmr spectrum a singlet at δ 4.50 ppm, while the ^{13}C nmr spectrum included a benzyl resonance at δ 27.1 ppm), the further brominated derivatives such as **122** (the ^{13}C nmr spectrum included an additional alkane resonance at δ 32.8 ppm whereas the aromatic region suggested a mixture of at least three different compounds) and the oxidized derivative **123** (the ^{1}H nmr spectrum of the crude product also included an aldehyde resonance at δ 9.80 ppm and a carbonyl resonance at δ 194.9 ppm was observed in the ^{13}C nmr spectrum). One possible explanation for the formation of aldehyde **123** is through the bromo compound **124** as illustrated in Scheme 60. While it is still uncertain as to whether a brominated protected benzyl alcohol can be prepared, we redirected our attention to base-induced cyclizations.

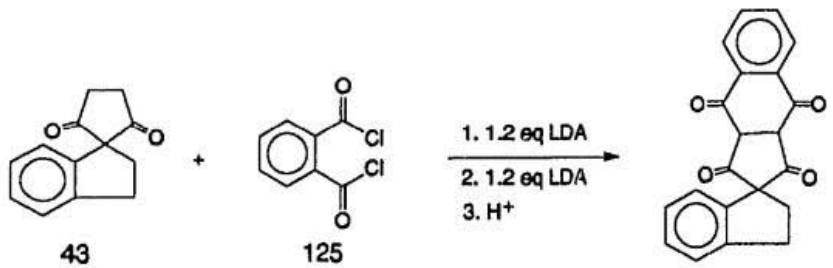
Scheme 60

124 123

To a solution of **43** and LDA was added diacid chloride **125**, obtained from the treatment of phthalic anhydride with phosphorus pentachloride (PCl_5),[39] the product obtained after an additional equivalent

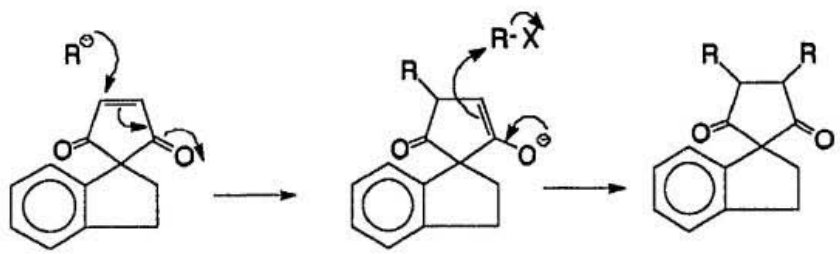
of LDA was added, gave very little indication of any reaction as the starting materials were not consumed (Scheme 61).

Scheme 61



1,4-Nucleophilic additions to enedione **83** were more successful. Subsequent 1,2-addition would give the desired carbocycle as illustrated in Scheme 62. A suitable nucleophile would be the anion obtained by the

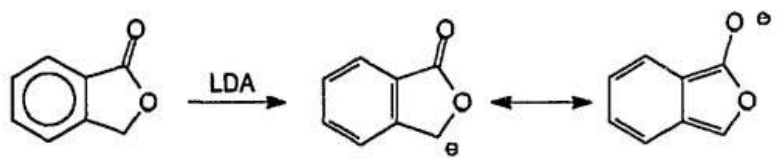
Scheme 62



deprotonation of bicyclic lactone **126**. Deprotonation at the benzylic position would result in two potential reaction modes, via the two resonance structures **127** and **128** (Scheme 63). The former should react as a nucleophile, whereas the latter might react by a Diels-Alder

cyclization. Both would result in the formation of the same product.

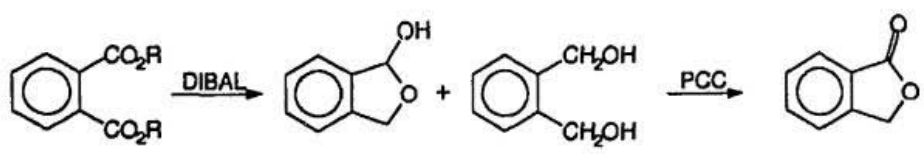
Scheme 63



126 127 128

Lactone **126** was obtained from the pyridinium chlorochromate (PCC) oxidation of the crude DIBAL product (lactol **129** and diol **130**) (Scheme 64), the yield was unexpectedly low, 60% from the starting diester using normal DIBAL conditions.[40] The yield increased to approximately 75% by gently heating the resulting gel after the DIBAL

Scheme 64

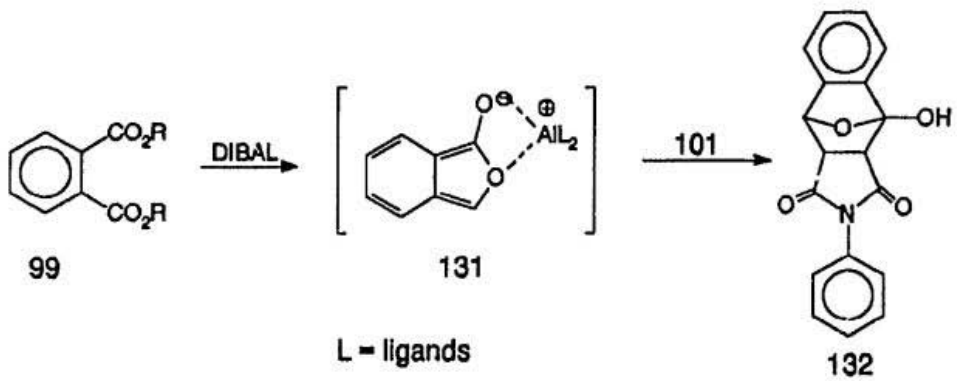


99 129 130 126

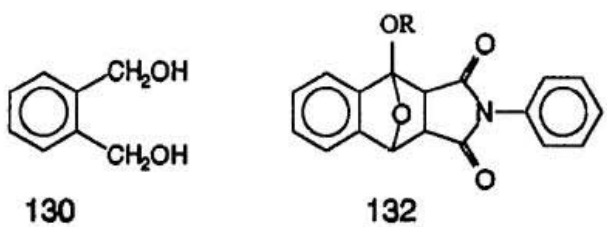
solution was quenched and washing it with a large volume of dichloromethane (300 mL). Spectral characteristics of lactone **126** included the carbonyl resonance in the ^{13}C nmr spectrum at δ 171.1 in

addition to the benzylic carbon at δ 69.6 ppm. The benzylic hydrogen resonance in the ^{1}H nmr spectrum was observed at δ 5.33 ppm.

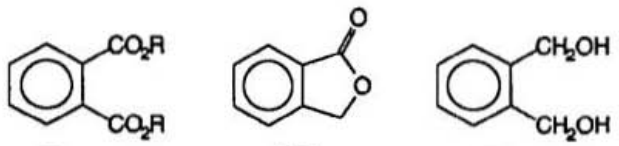
Scheme 65



As discussed above, deprotonation of **126** can provide two canonical forms of the same anion, **127** and **128**. If the latter were dominant, one would expect that during the reduction of diester **99**,which was likely to proceed through an intermediate such as **131**, a Diels-Alder cyclization might occur if a dienophile were added. Some ambiguous evidence for adduct **132** was found upon addition of *N*-phenylmaleimide



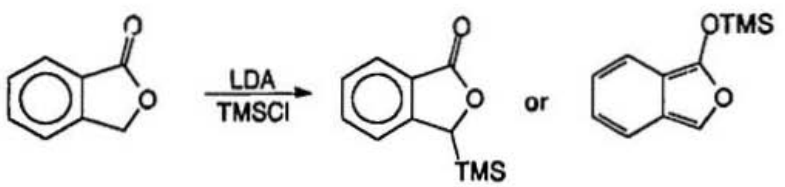
101 to a solution of DIBAL and diester **99** (Scheme 65). Chromatography, not unexpectedly, established the major component to be the diol **130** (the ^{13}C nmr spectrum included a benzyl resonance at δ 63.4 ppm), but in addition it yielded a small amount (4%) of adduct **132**. It's ^{1}H nmr spectrum included a multiplet at δ 4.5 ppm, a double doublet



99 126 130

at δ 3.4 ppm, a double doublet at δ 2.8 ppm, and two distinct aromatic signals at δ 7.5 ppm and 7.3 ppm. However, reproducibility was a problem as subsequent experiments yielded only diester **99**, lactone **126** and diol **130**.

Scheme 66

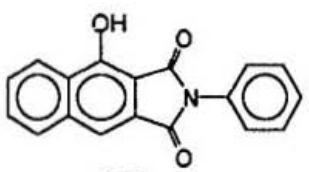


126 133 134

Deprotonation of lactone **126** and trapping with chlorotrimethyl-

silane gave overwhelmingly **133**, not the O-alkylated product **134** (Scheme 66). Included in the ^{13}C nmr spectrum of **133** were resonances at δ 170.9, 77.9, and -4.4 ppm. This result suggested that nucleophilic addition rather than Diels-Alder cyclization was the better reaction path. It is possible that the isobenzofuran **134** was generated *in situ*, but, being extremely reactive, it was destroyed on workup as the ^{13}C nmr spectrum of the product also included resonances for the starting lactone **126**. The intensity of these resonances (lactone **126**) were approximately half compare with those attributed to **133**.

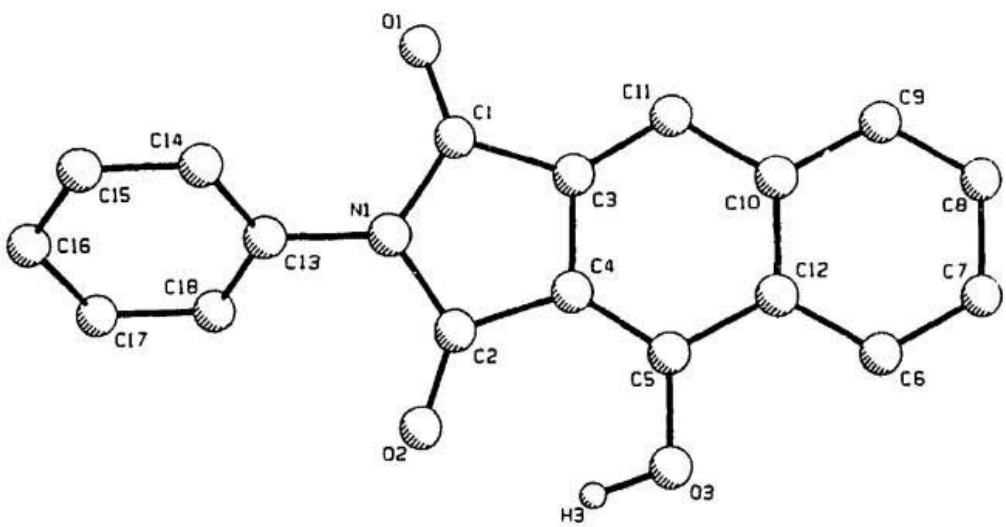
Deprotonation of lactone **126** with LDA followed by the addition of *N*-phenylmaleimide **101** afforded a highly colored solution. Chromatography gave a fraction that contained a crystalline colorless solid (16%), which was insoluble in many deuterated solvents ($CDCl_3$, CD_3OD, C_2D_6O, C_6D_6), but it had a limited solubility in d_6-dimethyl sulfoxide. A second fraction (17%) was less pure, but contained mainly the same compound. The nmr spectra were consistent with an aromatic product. The adduct was assigned structure **135**, in which one of the



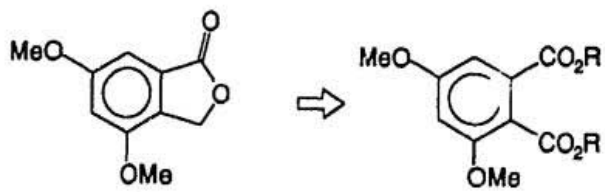
135

oxygens of **126** was lost to generate a second aromatic ring. It's ^{13}C nmr spectrum included a carbonyl resonance at δ 166.3 ppm in addition to a phenolic resonance at δ 152.5 ppm. The ^{1}H nmr spectrum included multiplets at δ 8.42 and 8.15 ppm, both integrating to two protons, in addition to a singlet at δ 8.02 ppm. Recrystallization from dimethyl sulfoxide provided crystals suitable for x-ray analysis, which confirmed structure **135** (Figure 8). Because the reaction was to serve only as a model the reaction was not further studied.

Figure 8. X-ray Crystal Structure for 135.



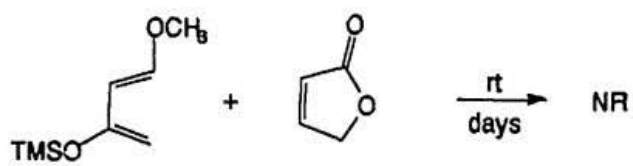
If one oxygen could be incorporated in each of the A and B rings (in addition to the required methoxy substituent), subsequent oxidation to the desired phenolic and quinone systems should be feasible. Therefore, our efforts concentrated on the preparation of lactone **137** despite the



137 136

fact that under the reaction conditions one oxygen of the B ring was lost. Bach[24c] had reported that chromium trioxide in 80% acetic acid solution failed to oxidize the 4- and 9-positions of the B ring in a compound similar to **115**. They attributed the reluctance of the aromatic ring to undergo oxidation to deactivation by adjacent cyclopentane ring carbonyls. Parker and coworkers[23] reported the preparation of a triply oxygenated aromatic diester in a related study.

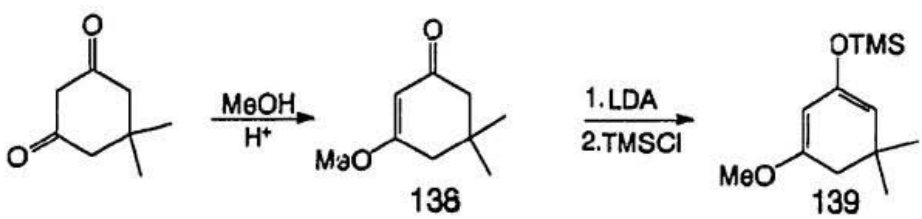
Scheme 67



As determined from model studies with phthalide, a suitable precursor for the lactone appeared to be the substituted aromatic diester **136**. The preparation of **136** by Diels-Alder sequences was studied. It

was hoped that the Diels-Alder adduct from Danishefsky's diene and furanone could be oxidized to **136**. However, no adduct was detected even after 6 days at room temperature (Scheme 67). Furthermore, heating this reaction solution at reflux overnight was also fruitless as only the starting furanone (35%) was recovered. Our earlier investigation showed that cyclization involving Danishefsky's diene and dimethyl acetylenedicarboxylate did afford an aromatic diester in which one oxygen was lost to gain aromaticity. If another substituent could be lost instead of the desired oxygen the idea could be of synthetic use. Protection of the enol of dimedone as the methyl ether was accomplished using Amberlyst 15 and methanol which afforded **138** in excellent yield (Scheme 68). The ^{13}C nmr spectrum included the methoxy resonance at δ 55.1 ppm while the ^{1}H nmr spectrum included the vinylic hydrogen resonances at δ 5.36 ppm in addition to the methoxy singlet at δ 3.71 ppm.

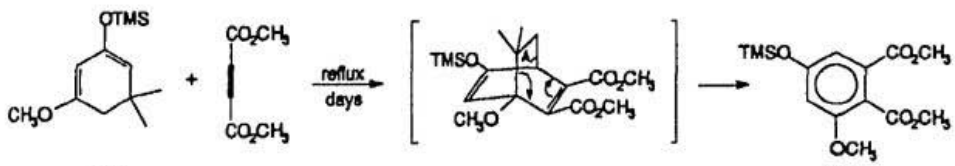
Scheme 68



Deprotonation and subsequent trapping of the enolate with TMSCl,

gave the desired oxygen-alkylated diene **139** (Scheme 68) in greater than 80% yield. The regiochemical purity was easily evident from nmr analysis. The ^{1}H nmr spectrum showed only two vinylic hydrogen resonances at δ 4.72 and 4.37 ppm, and the ^{13}C nmr spectrum contained nine signals including the trimethylsilyloxy resonance at δ 0.15 ppm.

Scheme 69



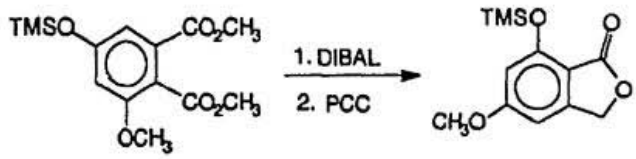
139 140

Diels-Alder cyclization between diene **139** and dimethyl acetylene-dicarboxylate slowly afforded the desired aromatic diester **140** (Scheme 69) that was not purified for fear of cleaving the trimethylsilyloxy group during chromatography.

DIBAL reduction of **140** followed by PCC oxidation gave less than 1% of the desired lactone **141**[1] (Scheme 70). (Its ^{1}H nmr spectrum included aromatic resonances at δ 6.90 and 6.62 ppm in addition to the

[1] The structure of **141** was assigned from comparison with lactones **143** and **144**. Included in the ^{1}H nmr spectra of **141** was a methoxy resonance at δ 3.86 ppm which was very similar for that in **143** which had a shift at δ 3.89 ppm.

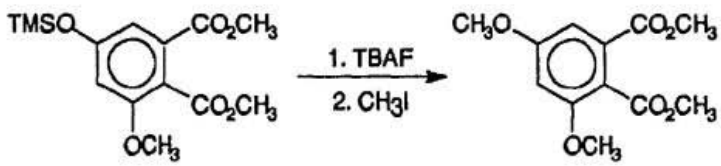
Scheme 70



140 141

trimethylsilyloxy resonance at δ 0.31 ppm.) The major product was the desilylated lactone. Therefore, diester **140** was converted into the

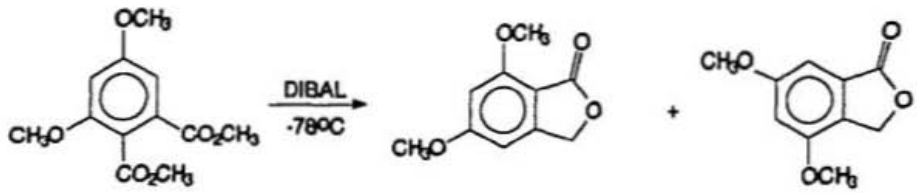
Scheme 71



140 142

dimethoxy derivative **142** by cleaving the silyl ether with TBAF followed by reprotection as the methyl ether using iodomethane (Scheme 71). DIBAL reduction of **142** followed by PCC oxidation gave lactones **143** (60%) and **144** (less than 10%) (Scheme 72). The regiochemistry of **143** and **144** was assigned based upon the NOE (Nuclear Overhauser Effect) enhancement of the H-3 singlet by 4% upon irradiation of H-4 for **143**. Futhermore, lactone **143** showed two distinct methoxy resonances in its ^{1}H nmr spectrum, at δ 3.95 and 3.89 ppm, wheras the ^{1}H nmr spectrum

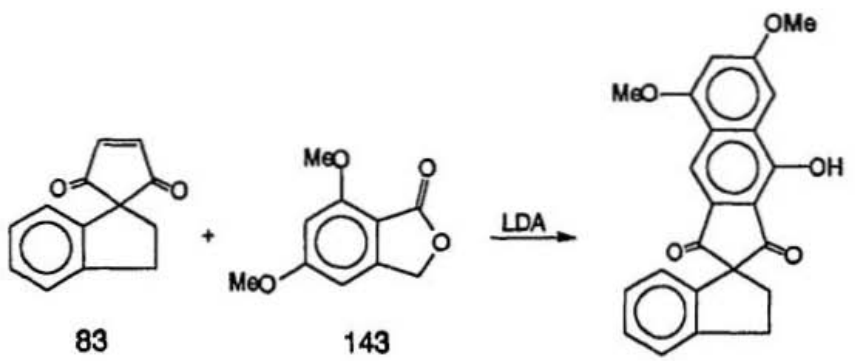
Scheme 72



142 143 (major) 144 (minor)

for the minor lactone **144** gave a single methoxy signal at δ 3.88 ppm. With the functionalized lactone **143** in hand, condensations with enone **83** were attempted in the hope of preparing the tetracyclic compound **145** (Scheme 73).

Scheme 73



83 143 145

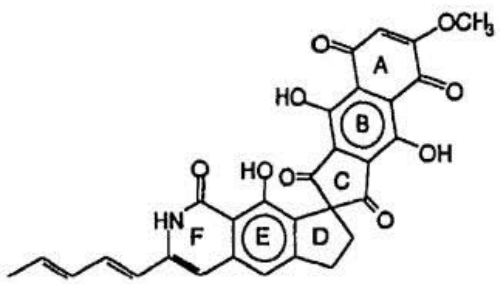
A solution of the lactone anion, generated with LDA, and enedione **83** was stirred overnight, but chromatography led only to the recovery of

the starting materials, **83** (17%) and **143** (79%). (Under the same conditions the analogous silylated lactone **141** was also unsuccessful, as chromatography provided recovered lactone **141** (31%) and **83** (100%), as was the regioisomer, lactone **144**).

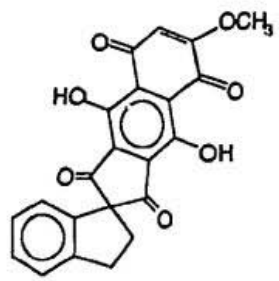
Experiments in which the lactone **143**, not the enedione **83**, was the limiting reagent, and using many equivalents of LDA, resulted in consumption of the starting materials but failed to effect the desired transformation. Repeating the sequence but with only two equivalents of LDA yielded a crude product that from nmr analysis showed new resonances in the aromatic region. Chromatography and crystallization gave a product whose structure we could not assign from the nmr data. The ^{1}H nmr spectrum suggested that it was composed of **83** and lactone **143** in a 2:1 ratio, but, unfortunately, the crystals were not suitable for x-ray analysis. We suspected the product might have been derived from the desired tetracyclic compound by additional deprotonation and incorporation of the second enedione molecule. When the sequence was repeated using 1.2 eq LDA we recovered only starting materials: enedione (48%) and lactone **143** (95%). While to date the conditions required to generate the direct precursor for the synthetic target have not been found, it is believed that with further experimentation, especially varying the concentration of the base or the base itself, the desired cyclized material can be prepared. In related work by both Parker[24] and

Bach[25] one equivalent of *tert*-butyllithium was successful for the reaction utilizing a derivatized lactone. Both of these routes involved isobenzofuran intermediates.

Figure 9. Target Molecule for Fredericaymcin A Synthesis.

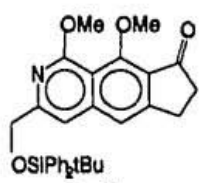


Fredericamycin A



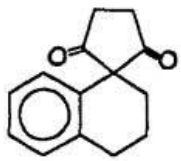
96

One crucial difference between our synthetic target **96** and fredericamycin A (Figure 9) is that the target compound did not contain an oxygen substituent in the E ring. This functionality in addition to the remainder of fredericaymcin A might be attained by starting from ketone **146**, prepared by Clive and coworkers,[32] instead of 1-indanone.

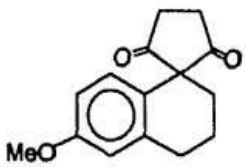


146

During the development of the geminal acylation of ketones with **1** (Chapter 1 of this manuscript), we did not evaluate substrates bearing a β-oxygen substituent. For a δ-substituent there was little effect on the overall yield as both α-tetralone and 6-methoxy-1-tetralone gave nearly



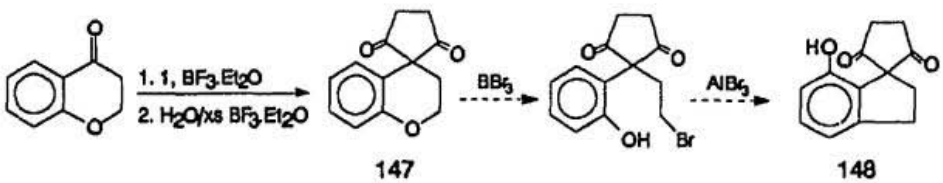
62



38

identical yields of cylopentanedione products **62** and **38**: 55 and 54%, respectively. It was hoped that this would also be true for aromatic substrates with a β-substituent such as ketone **146**.

Scheme 74



147 **148**

If this route fails, the E ring substituent may be realized via 4-chromanone. Geminal acylation of chromone with **1** gave **147** in 35%

yield. It is planned to cleave the ether function using boron tribromide and to recyclize to **148** (Scheme 74). Dehydrogenation of **148** with benzeneselenic anhydride would afford the analogous enone, which could replace the unfunctionalized enedione **83**.

III. Experimental

For general experimental conditions and instrumentation see Chapter 1. Each nmr resonance has been assigned where the numbers after the H (for ^{1}H nmr resonances) or C (for ^{13}C nmr resonances) denote the numbering scheme used for naming. For example, δ 7.45 (2H, s, H-3, H-4) refers to a ^{1}H nmr resonance integrating to two protons which are attached to carbons 3 and 4, respectively.

Spiro[3-cyclopentene-1,1'-indan]-2,5-dione (83). To a solution of diketone **43**[2] (312.9 mg, 1.56 mmol) in chlorobenzene (80 mL) was added benzeneselenic anhydride (0.68 g, 1.9 mmol). The reaction mixture was heated at reflux overnight. Removal of the solvent under vacuum furnished a tan oil. Chromatography (2% EtOAc/hexanes) afforded **83** (182 mg, 59%) as yellow crystals: mp 58.5 - 61°C. IR: 1767 (shoulder) and 1703 cm^{-1}. ^{1}H nmr: δ 7.45 (2H, s, H-3, H-4), 7.30 (1H, symmetrical m, H-5'), 7.11 (1H, symmetrical m, H-4'), 6.78 (1H, m, H-7'),

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[2] See Chapter 1 for preparation and characterization.

3.21 (2H, t, J = 7.5, H-3'), 2.39 (2H, t, J = 7.5, H-2'). ^{13}C nmr: δ 204.2 (C-2, C-5), 150.2 (C-3, C-4), 145.4 (C-7a'), 140.1 (C-3a'), 128.4 (C-5'), 126.8 (C-4'), 125.2 (C-6'), 122.2 (C-7'), 63.1 (C-1), 31.8 (C-2'), 31.7 (C-3'). MS: 198 (M^+, 100), 170 (M^+ - CO, 29), 155 (2), 141 (37), 115 (87), 82 (14), 58 (37). Exact mass calcd. for $C_{13}H_{10}O_2$: 198.0680, found 198.0689.

Spiro[cyclohexane-1,2'-(2*H*)indene]-1',3'-dione (100). Following the procedure of Ruhlmann,[35] sodium metal (1.24 g, 54.0 mmol) was boiled in toluene (250 mL) for 1.5 h. After cooling to rt, TMSCl (7.5 mL, 5.9 mmol) was added to the suspension followed by **99** (5.9 g, 27 mmol). After the additions were complete the reaction mixture was heated at reflux for 3.5 h and the mixture was maintained at approximately 60°C overnight. After refluxing for an additional 7.5 h, the reaction mixture was allowed to cool, after which time it was filtered under a N_2 atmosphere. To the filtrate (under N_2) was added cyclohexanone ketal (461 mg, 3.25 mmol) and $BF_3.Et_2O$ (1.3 mL, 9.7 mmol). The solution was stirred overnight. The solution was washed with H_2O (2 x 50 mL), and the aqueous layers were re-extracted with ether (2 x 50 mL). The combined organic solutions were washed with brine (70 mL), dried over $MgSO_4$, and evaporated at reduced pressure. The crude material was filtered through a charcoal/Florisil plug as descibed in Chapter 1 before chromatography (2% EtOAc/hexanes), which provided **99** (3.82 g, 64% recovery) and, in a later fraction, impure **100** (209 mg, 30% yield,

tentative structure). ^{1}H nmr resonances included aromatic patterns at δ: 7.8 and 7.5 in addition to alkane resonances at δ: 1.6 and 1.3. Resonances in the ^{13}C nmr of interest included δ: 202.2, 133.9, 131.0, 128.8 (2C), 125.6, 122.0, 52.6, 33.94, 29.6, 26.6, 24.7, 23.3, 22.1, 14.0.

5'-Hydroxyspiro[2',1-indane-2*H*-indene]-1',3'-dione (104). To a solution of **83** (212 mg, 1.07 mmol) in benzene (2.0 mL) was added **103** (30 mg, 1.6 mmol). The starting materials were not consumed after stirring at room temperature overnight. The reaction solution was heated under reflux for 7 days. Evaporation of the benzene at reduced pressure followed by chromatography (35% EtOAc/hexanes) yielded **104** (55.0 mg, 13%) as yellow, hair-like crystals: mp 210 - 213.5°C. IR: 3366, 1736, and 1692 cm^{-1}. ^{1}H nmr (CD_3OD): δ 7.92 (1H, d, *J* = 8.4, H-7'), 7.27 - 7.37 (4H, m, H-4, H-4', H-6' and phenolic H), 7.20 (1H, m, H-5), 7.05 (1H, symmetrical m, H-6), 6.59 (1H, d, *J* = 7.8, H-7), 3.22 (2H, t, *J* = 7.5, H-3), 2.47 (2H, two overlapping t, *J* = 7.5, H-2'). ^{13}C nmr (CD_3OD): δ 203.0 (C-1'), 201.4 (C-3'), 166.9 (C-5'), 146.9 (C-3a' or C-7a), 146.7 (C-7a or C-3a'), 143.7 (C-7a'), 135.8 (C-3a), 129.2, 127.8, 127.0, 126.0, 125.5, 123.6 (unassigned signals for C-4, 5, 6, 6', 7'), 109.1 (C-4), 68.5 (C-2'), 33.4 (C-2), 32.9 (C-3). MS: 264 (M^+, 61), 247 (9), 235 (5), 207 (5), 178 (4), 149 (17), 115 (15), 62 (12), 45 (26), 28 (100). Exact mass calcd. for $C_{17}H_{12}O_3$: 264.0786, found 264.0776.

2(5*H*)-4-methoxyfuranone (109). To a solution of tetronic acid

(424 mg, 4.24 mmol) in MeOH (30 mL) were added Amberlyst 15 beads (2.0 g). The solution was stirred at rt for 4 days. Filtration followed by concentration directly on chromatographic silica provided **109** (166.1 mg, 35%) as orange crystals upon flushing the column with MeOH: mp 58.5 - 60°C. ^{1}H nmr: δ 5.12 (1H, t, *J* ~ 1.1, H-3), 4.64 (2H, d, *J* = 1.2, H-5), 3.91 (3H, s, methoxy). ^{13}C nmr: δ 180.3 (C-2), 88.7 (C-4), 67.6 (C-3 and C-5), 59.4 (methoxy). An earlier fraction provided **2(5*H*)-4,4-dimethoxy-furanone** (15.5 mg, 3%) as a pale yellow liquid. IR: 1789 cm^{-1}. ^{1}H nmr δ: 4.26 (2H, s, H-5), 3.28 (6H, s, methoxy), 2.73 (2H, s, H-3). ^{13}C nmr δ: 173.1 (C-2), 104.4 (C-4), 72.2 (C-5), 49.8 (methoxy), 38.0 (C-3). MS: 146 (M$^+$, 6), 115 (28), 104 (10), 89 (5), 88 (86), 73 (11), 71 (26), 59 (14), 58 (28), 45 (21), 43 (100), 42 (31), 41 (34). Exact mass calcd. for $C_6H_{10}O_4$: 146.0578, found 146.0589.

1,2-Bis(dibromomethyl)benzene (111). A solution of *ortho*-xylene (30.0 mL, 250 mmol) in CCl_4 (45 mL) was heated at reflux for 0.5 h. While maintaining reflux the solution was irradiated with a 100W flood light, 2 - 3 cm away from reaction vessel, and a solution of bromine (1.8 mL, 18 mmol) in CCl_4 (10 mL) was added over 3 h. The reaction solution was heated at reflux and irradiated for an additional 5 h before being allowed to cool to rt. The reaction vessel was left open to the atmosphere overnight. The sample was filtered through a charcoal / Florisil pad which was washed with CCl_4 (200 mL). Evaporation at

reduced pressure afforded a rust colored solid. This material was dissolved in hot $CHCl_3$ (400 mL) and filtered through a charcoal plug. The solution crystallized upon storing in the refrigerator to give colorless crystals. Filtration to remove the solvent followed by drying under vacuum gave **111** as colorless crystals (43.12 g, 41%): mp 110.5 - 112.0°C. IR: 1230 and 1135 cm^{-1}. ^1H nmr: δ 7.66 (2H, m, H-2, 4 or H-3,4), 7.32 (2H, m, H-3,4 or H-2,4), 7.12 (2H, s, dibromomethyl H). ^{13}C nmr: δ 130.3 (C-2,3,4,5), 129.3 (C-1,6), 36.4 (dibromomethyl). MS: 343 ($M^+(^{81}Br)$+ 1, 100), 341 (M^+ (^{79}Br), 99), 339 (33), 264 (14), 262 (28), 183 (34), 181 (35), 131 (15), 102 (51), 101 (13), 75 (15), 51 (47), 50 (24). Exact mass calcd. for $C_8H_6Br_2$ (^{81}Br): 342.7971, found 342.7996 and for $C_8H_6Br_2$ (^{79}Br): 340.8000, found 340.7999.

Spiro[2*H*-benz(*f*)indene-2,1'-indan]-1,3-dione (113). To a solution of **83** (255 mg, 1.29 mmol) in DMF (16 mL) was added **111** (1.73 g, 4.10 mmol). The mixture was heated at reflux overnight, and then stirred for one day at rt during which time the mixture gelled. The material was transferred into a stirred solution of $NaHSO_3$ (0.65 g, 6.2 mmol) in H_2O (30 mL). After stirring for 10 min, the contents were transferred to a separatory funnel and extracted with ether (3 x 50 mL). The combined organic solutions were washed with brine (75 mL), dried over $MgSO_4$, and concentrated under vacuum. The resulting black tar was purified by chromatography (3% EtOAc/hexanes) to yield **113** (180

mg, 47%) as beige crystals: mp 211 - 212.5°C. IR: 1734 and 1705 cm^{-1}. ^1H nmr: δ 8.60 (2H, s, H-4 and H-9), 8.13 (2H, symmetrical m, H-5,8), 7.73 (2H, m, H-6,7), 7.34 (1H, d, J = 7.5, H-4'), 7.21 (1H, two overlapping t, J = 7.5, H-6'), 7.02 (1H, symmetrical m, H-5'), 6.61 (1H, d, J = 7.8, H-7'), 3.35 (2H, t, J = 7.5, H-3'), 2.64 (2H, t, J = 7.5, H-2'). ^{13}C nmr: δ 201.6 (C-1, C-3), 145.4, 142.3, 137.1, 136.5, 130.6, 129.7, 128.2, 126.7, 125.2, 124.9, 122.7, 68.5 (C-2), 32.7 (C-2' or 3'), 32.1 (C-3' or 2'). MS: 298 (M^+, 99), 283 (11), 269 (7), 239 (12), 208 (5), 183 (14), 155 (10), 118 (44), 91 (5), 69 (100), 51 (16). Exact mass calcd. for $C_{21}H_{14}O_2$: 298.0993, found 298.0990.

3,4-Bis(dibromomethyl)-1-methoxybenzene (114). The procedure was as for **111** except that 3,4-dimethylanisole (1.16 g, 8.53 mmol) and Br_2 (3.3 mL, 34.0 mmol) were used and the sequence was refluxed 8 h. The solution was filtered through a large bore column containing charcoal (3 g) and Florisil (1.5 g). Concentration of the filtrate under vacuum provided crude **114** (3.85 g, 99% if pure) as a red, viscous oil. Key resonances from the nmr spectrum of the crude product included: ^1H nmr: δ 7.18 (1H, unsymmetrical d, J = 2.4, H-6), 7.12 (2H, s, dibromomethyls), 7.06 (1H, s, H-2), 6.85 (1H, dd, J = 8.7, 2.7, H-5), 3.83 (3H, s, methoxy). ^{13}C nmr: δ 160.5 (C-1), 139.0 (C-3 or C-4), 137.1 (C-3 or C-4), 130.8 (C-2), 115.9 (C-2 and C-6), 55.6 (methoxy), 36.4 (dibromomethyl), 36.2 (dibromomethyl). MS: 372 (M^+ (^{81}Br), 71), 371 (M'

(^{79}Br), 71), 293 (27), 292 (18), 229 (36), 227 (35), 212 (12), 211 (41), 149 (35), 148 (95), 133 (37), 121 (45), 105 (22), 89 (50), 82 (43), 77 (29), 59 (49), 51 (43), 45 (61), 43 (100). Exact mass calcd. for $C_9H_8OBr_2$: (^{81}Br): 372.8085, found 372.8102 and (^{79}Br): 370.8106, found 370.8114.

6-Methoxyspiro[2*H*-benz(*f*)indene-2,1'-indan]-1,3-dione (115). A solution of **83** (230 mg, 1.16 mmol), NaI (1.04 g, 6.93 mmol) and **114** (1.65 g, 3.65 mmol) in DMF (16 mL) was heated under reflux overnight. The solution was allowed to cool and it was stirred at rt for 2 days. The reaction mixture was poured into a H_2O (50 mL) and stirred vigorously. After 10 min, $NaHSO_3$ (0.58 g, 5.5 mmol) was added and stirring was continued for 10 min. The solution was extracted with ether (3 x 50 mL), and the combined organic solutions were washed with brine (75 mL), dried over $MgSO_4$, and concentrated at reduced pressure. Chromatography (5% EtOAc/hexanes) of the black oil gave **115** (53.8 mg, 14%) as a tan powder: mp 235 - 239°C. Upon dissolving in $CDCl_3$ a white powder remained (soluble in CD_3OD). Its nmr spectrum, however, was not compatabile with that of the $CDCl_3$ soluble material (**115**). For **115**: ^{1}H nmr: δ 8.52 (1H, s), 8.45 (1H, s), 8.02 (1H, d, *J* = 9.0), 7.35 - 7.40 (5H, m), 7.20 - 7.29 (2H, m), 7.19 (1H, br t, *J* = 7.5), 6.62 (1H, d, *J* = 7.5), 4.00 (3H, s, methoxy), 3.34 (2H, t, *J* = 7.8, H-2'), 2.62 (2H, t, *J* = 7.8, H-3'). ^{13}C nmr: δ 201.9 (C-1 or C-3), 201.3 (C-1 or C-3), 160.5 (C-6), 145.4, 138.7, 137.8, 135.5, 132.0, 128.2, 126.7, 125.2, 124.8, 123.3,

123.0, 122.8, 107.5, 69.5 (C-2), 55.6 (methoxy), 32.7 (C-2' or C-3'), 32.2 (C-2' or C-3'). Note that two carbons must have the same chemical shift. MS: 328 (M^+, 100), 313 (12), 299 (3), 268 (2), 240 (2), 213 (12), 185 (8), 156 (10), 142 (5), 115 (15). Exact mass calcd. $C_{22}H_{16}O_3$: 328.1099, found 328.1095.

Dimethyl 4-hydroxyphthalate (117). To a solution of **103** (533 mg, 3.10 mmol) in benzene (8 mL) was added dimethyl acetylene-dicarboxylate (0.50 mL, 4.0 mmol). The solution was stirred at rt under a nitrogen atmosphere, and the progress of the reaction was followed by TLC. After 5 days the solution was concentrated directly onto the silica gel used for chromatography. Chromatography (2% EtOAc/hexanes) provided **117** (359 mg, 55%) as a yellow waxy solid: mp 76.5 - 80°C. IR: 3369 and 1721 cm^{-1}. ^1H nmr: δ 8.06 (1H, br s, phenol), 7.73 (1H, d, J = 8.4, H-3), 7.01 (1H, d, J = 2.4, H-5), 6.93 (1H, symmetrical m, H-6), 3.90 (3H, s, methoxy), 3.86 (3H, s, methoxy). ^{13}C nmr: δ 182.8 (2C, carbonyl), 169.6 (C-4), 167.2 (C-2), 159.7 (C-1), 131.8 (C-3), 117.2 (C-5), 115.2 (C-6), 52.9 (methyl ester), 52.4 (methyl ester). MS: 210 (M^+, 30), 179 (M^+-OMe, 100), 149 (4), 120 (3), 85 (62). Exact mass calcd. for $C_{10}H_{10}O_5$: 210.0528, found 210.0518 and for $C_9H_7O_4$ (M^+- OMe): 179.0344, found 179.347.

Dimethyl 4-methoxyphthalate (118). To a two-phase system of 50% NaOH/H_2O (70 mL) and CH_2Cl_2 (100 mL) was added crude **117**

(0.77 g, 3.7 mmol), $(MeO)_2SO_2$ (1.4 g, 11 mmol), and tetrabutylammonium iodide (4.0 g). The mixture was stirred vigorously at rt overnight. The solution was washed with H_2O (100 mL) and the organic layer was re-extracted with saturated $NaHCO_3$ (100 mL) and brine (100 mL). The solution was dried over $MgSO_4$ and concentrated at reduced pressure. Chromatography gave **118** (325 mg, 39%) as a yellow oil. IR: 1725 cm^{-1}. ^1H nmr: δ 7.81 (1H, d, J = 8.7, H-6), 7.06 (1H, d, J = 2.7, H-3), 6.99 (1H, dd, J = 8.4, 2.7, H-5). ^{13}C nmr: δ 168.8 (carbonyl), 166.6 (carbonyl), 162.0 (C-4), 135.6 (C-2), 131.482 (C-3), 122.0 (C-1), 115.6 (C-5 or C-6), 113.3 (C-5 or C-6), 55.6 (methoxy), 52.7 (methyl ester), 52.3 (methyl ester). MS: 224 (M^+, 30), 193 (M^+- OMe, 100), 165 (7), 107 (5), 92 (4), 77 (6), 63 (8), 28 (10). Exact mass calcd. for $C_{11}H_{13}O_5$: 244.0684 found, 224.0676.

Bromination of 2-(hydroxymethyl)phenol (120). A solution of 2-hydroxybenzyl alcohol (1.14 g, 9.17 mmol) in CCl_4 (45 mL) was heated at reflux for 0.5 h. While maintaining reflux the reaction solution was irradiated with a 100W flood light ~2 - 3 cm away from reaction vessel during the addition of bromine (1.8 mL, 18 mmol) in CCl_4 (10 mL) over 3 h. The reaction solution was heated at reflux and irradiated for an additional 5 h before allowed to cool to rt. The reaction vessel was left open to the atmosphere overnight. The sample was filtered through a charcoal/Florisil pad, which was washed with CCl_4 (200 mL).

Concentration at reduced pressure provided a orange oil which crystallized under vacuum: mp 63 - 65°C. Nmr suggested a mixture of 2-bromomethylphenol **121**, 2-dibromomethylphenol **122**, and 2-hydroxybenzaldehyde **123**. For **121**: ^{1}H nmr: δ 4.50 (benzyl H's) in ^{13}C nmr: δ 27.1 (bromomethyl) For **122**: ^{1}H nmr: δ 6.99 (benzyl H) in ^{13}C nmr: δ 32.8 (dibromomethyl), and for **123**: ^{1}H nmr: δ 9.81 (aldehyde) in ^{13}C nmr: δ 194.9 (aldehyde).

1(3*H*)-isoBenzofuranone (126). From 130. To a solution of **130** (71.5 mg, 0.52 mmol) in CH_2Cl_2 (90 mL) was added PCC (0.14 g, 0.62 mmol). The solution was stirred overnight at rt. The reaction mixture was filtered through a large bore column containing silica gel (~ 30 - 40 g). The silica plug was washed with ether (100 mL) and CH_2Cl_2 (90 mL) and the combined organic solutions were concentrated under reduced pressure. Chromatography (5% EtOAc/hexanes) yielded **126** (39.0 mg, 56%) as colorless crystals. **From diester 99:** To a solution of **99** (447 mg, 2.01 mmol) in toluene (15 mL) cooled to -78°C, was added DIBAL (4.0 mL, 6.0 mmol). After stirring for 3.5 h, H_2O (3 mL) was added over 5 min. The gelatinous mixture was allowed to warm to rt over 40 min. The solution was washed with H_2O (2 x 50 mL) and the combined aqueous solutions were re-extracted with ether (2 x 30 mL). The combined organic solutions were washed with brine (50 mL), dried over $MgSO_4$ and concentrated at reduced pressure to give a colorless toluene solution.

PCC (0.88 g, 4.0 mmol) was added and the mixture was stirred overnight. Filtration through a silica pad provided, after chromatography (10% EtOAc/hexanes), **126** (132 mg, 49%) as colorless crystals: mp 64.0 - 65.0°C. IR: 1757 cm^{-1}. ^1H nmr: δ 7.93 (1H, d, *J* = 7.8, H-7), 7.70 (1H, overlapping t, *J* = 7.8, H-5), 7.53 (2H, two overlapping dd, *J* = 7.5, 6.6, H-4, H-6), 5.34 (2H, s, H-3). ^{13}C nmr δ: 171.1 (C-1), 146.5 (C-3a), 133.9 (C-7a), 129.0 (C-5, C-6), 125.7 (C-7), 122.1 (C-4), 69.6 (C-3). MS: 134 (M^+, 44), 105 (100), 77 (44), 50 (12). Exact mass calcd. for $C_8H_6O_2$: 134.0367, found 134.0354.

Attempt to trap intermediate isobenzofuran generated from 99 and DIBAL with 101. To a solution of **99** (669 mg, 3.01 mmol) in toluene (20 mL) at -78°C was added DIBAL (6.0 mL 1.2 M solution, 6.3 mmol). After stirring for 3 h, a solution of **101** (363 mg, 2.10 mmol) in toluene (10 mL) was added. After stirring for 3 h, the solution was allowed to warm to rt (1 h) then ice was added slowly. The resulting gel was filtered through Celite, the Celite pad was washed with H_2O (100 mL) and ether (100 mL). The organic solutions were washed with H_2O (2 x 50 mL), and the aqueous solutions re-extracted with ether (2 x 100 mL). The combined organic solutions were washed with brine (75 mL) and dried over $MgSO_4$. Concentration at reduced pressure provided a yellow oil upon evaporation at reduced pressure. Chromatography (10% EtOAc/hexanes) gave **101** (308 mg, 85%), **4-hydroxy-3a,9a-dihydro-1*H*-**

benz[*f*]isoindole-1,3(2*H*)-dione-4,9-oxide 132 (24.6 mg, 4%) and **1,2-bis(hydroxymethyl)benzene 130** (95.4 mg, 23%). For **130**, beige crystals: mp 46.5 - 48°C. IR: 3275 cm^{-1}. ^1H nmr: δ 7.29 (4H, s, H-3,4,5,6), 4.61 (4H, s, benzyl), 3.85 (2H, br s, hydroxy). ^{13}C nmr: δ 139.3 (C-1, C-2), 129.6 (C-3, C-6), 128.4 (C-4, C-5), 63.9 (benzyl). MS: 120 (M^+, 100), 119 (74), 92 (20), 91 (90), 89 (8), 79 (22), 77 (28), 65 (19), 51 (15). Exact mass calcd. for $C_8H_{10}O_2$: 120.0575, found 120.0575. For **132** (major resonances from impure material): ^1H nmr: δ 7.53 - 7.40 (4H, m, H-5,6,7,8), 7.35 - 7.24 (5H, m, phenyl H), 4.50 (1H, dd, *J* = 18.0, 8.4, H-3a), 3.42 (1H, dd, *J* = 18.0, 5.7, H-9a).

3-Trimethylsilyl-1(3*H*)-isobenzofuranone (133). THF (20 mL) was cooled to 0°C and diisopropylamine (0.4 mL, 2.9 mmol) was added followed by *n*BuLi (1.3 mL of a 2.5 M solution, 3.1 mmol). After stirring for 1 h, the reaction solution was cooled to -84°C (EtOAc/liquid N_2), and **126** (356 mg, 2.66 mmol) in THF (10 mL) was added over 25 min. After stirring for 1 h, TMSCl (0.7 mL, 5 mmol) was added. The solution was stirred overnight while it attained rt. Filtration followed by concentration at reduced pressure gave a pale orange oil which crystallized on standing. Nmr analysis showed **133** to be the major product. IR: 1755 cm^{-1}. ^1H nmr: (integration as it apppeared on the spectrum of the crude material) δ 7.64 (3H, dq, *J* = 7.8, 0.9), 7.43 - 7.51 (4H, m), 7.35 (2H, dd, *J* = 7.8, 0.6), 5.33 (2H, br s), 0.12 (17H, s, trimethylsilyl). ^{13}C nmr (major

resonances): δ 170.9, 150.2, 133.5, 127.2, 125.6, 120.6, 77.9, -4.4.

4-Hydroxy-2-phenyl-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione (135). THF (20 mL) was cooled to 0°C and diisopropylamine (0.5 mL, 3.3 mmol) was added followed by *n*BuLi (1.6 mL of a 2.5 M solution, 3.5 mmol) over 5 min. The solution was stirred at 0°C for 1.5 h, before it was cooled to -78°C . To this solution was added dropwise a solution of **126** (398 mg, 2.97 mmol) in THF (10 mL). The solution was stirred for 2 h before a solution of **101** (455 mg, 2.63 mmol) in THF (10 mL) was added in four portions over 5 min. After an additional 4 h, TMSCl (0.8 mL, 6.0 mmol) was added, and the solution was stirred overnight while it attained rt. Filtration and concentration at reduced pressure gave a brown oil. Chromatography (5% EtOAc/hexanes) provided **135** (121 mg, 16%) as yellow crystals: mp 206 - 209.5°C. TLC visualization for **135** was poor and a second sample (126 mg, 17%) was obtained by blindly collecting later fractions (the purity of this sample was ~90% from ^{13}C nmr). IR: 3340 (weak), 1765, and 1688 cm^{-1}. ^{1}H nmr (CD_3SOCD_3): δ 8.43 (1H, m, H-5), 8.15 (1H, m, H-8), 8.02 (1H, s, H-9), 7.75 (2H, symmetrical m, H-6, H-7), 7.59 - 7.43 (5H, m, phenyl H). (The phenolic H was not identified. We suspect it was buried beneath other signals). ^{13}C nmr (CD_3SOCD_3): δ 166.3 (C-1, C-3), 152.5 (C-4), 136.6 (C-9a), 132.1 (C-3a), 130.0, 129.7, 128.8, 128.5 (C-8a), 128.3, 127.9, 127.4, 124.0, 116.6, 107.1 (C-4a). MS: 289 (M^+, 100), 245 (26), 217 (10), 169 (5), 114 (15), 77 (13). Exact mass

calcd. for $C_{18}H_{11}O_3N$: 289.0738, found 289.0725.

3-Methoxy-5,5-dimethyl-2-cyclohexen-1-one (138). To a solution of 5,5-dimethyl-1,3-cyclohexanedione (1.86 g, 0.13 mmol) in MeOH (50 mL) was added Amberlyst 15 beads (~ 2 g), and this was stirred overnight. Filtration followed by concentration at reduced pressure gave a viscous oil. Chromatography (30% EtOAc/hexanes) yielded **138** (1.69 g, 83%) as a pale yellow oil. IR: 1657 and 1609 cm^{-1}. ^1H nmr: δ 5.36 (1H, s, H-2), 3.71 (3H, s, methoxy), 2.29 (2H, s, H-4), 2.20 (2H, s, H-6), 1.08 (6H, s, methyls). ^{13}C nmr: δ 198.4 (C-1), 176.2 (C-3), 100.4 (C-2), 55.1 (methoxy), 50.2 (C-4), 42.0 (C-6), 27.6 (2C, methyls). MS: 154 (34), 143 (17), 111 (4), 98 (100), 91 (51), 79 (3), 69 (32), 68 (69), 55 (8), 41 (14), 40 (26).

1-Methoxy-5,5-dimethyl-3-trimethylsilyloxy-1,3-cyclohexadiene (139). To a cooled (-78°C) LDA solution (1.2 equivalents, 12.1 mmol) was added a solution of **138** (1.55 g, 10.1 mmol) in THF (10 mL) over 15 min. After stirring for 1.5 h, TMSCl (2.6 mL, 21 mmol) was added, and the solution was allowed to warm to rt overnight. Filtration followed by vacuum distillation afforded **139** (1.69, 72%) as a colorless liquid: bp 62 - 63°C/2 mm Hg. IR: 1656 and 1610 cm^{-1}. ^1H nmr: δ 4.72 (1H, br s, H-2), 4.37 (1H, br s, H-4), 3.58 (3H, s, methoxy), 2.10 (2H, br s, H-6), 1.01 (6H, s, methyls), 0.20 (9H, s, trimethylsilyloxy). ^{13}C nmr: δ 159.8 (C-3), 147.4 (C-1), 107.3 (C-2), 93.5 (C-4), 54.7 (methoxy), 42.1 (C-6), 28.7

(2C, methyls), 0.15 (3C, trimethylsilyloxy). MS: M^+ not found, 212 (38), 211 (100), 195 (37), 154 (36), 144 (42), 98 (63), 75 (38), 73 (63), 69 (38), 68 (48). Exact mass calcd. for $C_{11}H_{21}O_2Si$ (M^+- Me): 211.1153, found 211.1139.

Dimethyl 3-methoxy-5-trimethylsilyloxyphthalate (140). To a solution of **139** (1.49 g, 6.58 mmol) in benzene (10 mL) under an argon atmosphere was added dimethyl acetylenedicarboxylate (1.3 mL, 9.9 mmol). The reaction solution was heated under reflux for 8 days. Concentration under reduced pressure yielded crude **140** (1.8 g, 90%) as an orange waxy solid. The major component was **140** and further purification was not undertaken for fear of cleaving the trimethylsilyloxy group. ^{1}H nmr: δ 7.03 (1H, d, J = 2.0, H-4), 6.62 (1H, d, J = 2.1, H-6), 3.86 (3H, s, methoxy), 3.83 (6H, s, methoxy), 0.27 (9H, s, trimethylsilyloxy). ^{13}C nmr: δ 167.6 (carbonyl), 165.3 (carbonyl), 157.5 (C-3), 156.8 (C-5), 129.4 (C-1), 128.0 (C-6), 112.6 (C-2), 105.5 (C-5), 55.9 (methoxy), 53.2 (ester methyl), 52.3 (ester methyl), -0.1 (trimethylsilyloxy). MS: 240 (M^+- TMS, 23), 209 (100), 181 (7), 151 (13), 136 (8), 92 (9), 69 (13), 57 (13), 41 (13).

5-Methoxy-7-trimethylsilyloxy-1(3H)-isobenzofuranone (141). To a solution of **140** (1.80 g, 5.79 mmol) in toluene (15 mL) cooled to -78°C was added DIBAL (11.6 mL, 17.0 mmol). After stirring at -78°C for 2 h, the solution was allowed to warm to 0°C, and the solution was

poured into a vigorously stirred ice/H_2O (150 mL) mixture. The resulting gelatinous mixture was filtered through a Celite pad, and the aqueous layer extracted with ether (3 x 50 mL). The combined organic solutions were washed with brine (75 mL), dried over $MgSO_4$, and concentrated at reduced pressure. Chromatography (20% EtOAc/hexanes) gave **141** (14.0 mg, 1%) as pale yellow crystals: mp 225 - 229°C. ^{1}H nmr and mass spectroscopy indicated the major product to be the desilylated analogue. ^{1}H nmr: δ 6.90 (1H, d, J = 1.5, H-6), 6.62 (1H, d, J = 1.8, H-4), 5.20 (2H, s, H-3), 3.86 (5H, s, methoxy), 0.31 (11H, s, trimethylsilyloxy)[3]. MS: 252 (M^+, 100), 237 (71), 223 (50), 198 (15), 180 (12), 151 (19), 135 (12), 104 (15), 73 (52). Exact mass calcd. for $C_{12}H_{16}O_4Si$: 252.0817, found 252.0802.

Dimethyl 3,5-dimethoxyphthalate (142). To a solution of **140** (1.73 g, 5.57 mmol) in CH_2Cl_2 (15 mL) was added TBAF (4.8 mL of a 1.0 M solution, 4.8 mmol). After stirring at rt for 3 h, iodomethane (0.5 mL, 7.3 mmol) was added, and the mixture was stirred overnight. Concentration at reduced pressure provided a red colored oil which crystallized upon standing. GCMS analysis showed a mixture of dimethyl acetylenedicarboxylate (remaining from **140** preparation) 22%, and **142** 50%. The sample was not further purified.

5,7-Dimethoxy-1(3H)-isobenzofuranone (143) and 4,6-

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[3] Integration not consistent with structure!

dimethoxy-1(3H)-isobenzofuranone (144). To a cooled (-78°C) solution of impure **142** (108 mg, 0.42 mmol) in CH_2Cl_2 (15 mL) was added DIBAL (0.80 mL of a 1.6 M solution, 1.3 mmol). After stirring for 3 h, the solution was allowed to warm to 0°C and ice/H_2O (5 mL) was added dropwise. The resulting gel was filtered through a Celite pad[4]. The Celite pad was washed with H_2O (50 mL) and CH_2Cl_2 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic solutions were washed with brine (50 mL), dried over $MgSO_4$, and concentrated at reduced pressure. The residue was dissolved in CH_2Cl_2 (15 mL) to which PCC (0.2 g, 0.8 mmol) was added, and this was stirred overnight. Filtration through a silica plug, as for **126**, followed by concentration and chromatography (10% EtOAc/hexanes) gave **144** (2.0 mg, 5%) as pale yellow crystals, and later fractions gave **143** (50 mg, 60%). For **143**: mp 131 - 132.5°C. IR: 1749 cm^{-1}. ^1H nmr: δ 6.49 (1H, br s, H-4), 6.42 (1H, br s, H-6), 5.17 (2H, s, H-3), 3.95 (3H, s, methoxy), 3.89 (3H, s, methoxy). ^{13}C nmr: δ 166.7 (C-1), 159.5 (C-5, C-7), 151.6 (C-7a), 106.3 (C-3a), 98.7 (C-4 or C-6), 97.5 (C-6 or C-4), 68.5 (C-2), 55.9 (2C, methoxy). NOE irradition of H-3 gave a 4% enhancement of H-4. MS: 194 (M^+, 73), 176 (50), 165 (47), 148 (100), 135 (29), 120 (13), 106 (14), 92 (12), 77 (18), 63 (25), 50 (20). Exact mass calcd. for

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[4] Filtration was greatly aided by gently warming the sides of the suction funnel using a heat gun. Under these conditions the yield was dramatically improved from 15% to typically 60%.

$C_{10}H_{10}O_4$: 194.0578, found 194.0585. For **144**: ^{1}H nmr (100 MHz): δ 6.95 (1H, d, *J* = 2.5, H-7), 6.68 (1H, d, *J* = 2.5, H-5), 5.25 (2H, s, H-3), 3.88 (6H, s, methoxy). MS (from GCMS): 194 (70), 193 (13), 165 (100), 137 (23), 122 (17).

Attempted reaction of 143 with 83. To a LDA solution (2.0 mmol) cooled to -78°C, was added a solution of **143** (190, 0.98 mmol) in THF (3 mL) over 25 min. The solution was stirred for 1 h prior to the addition of a solution of **83** (274 mg, 1.38 mmol) in THF (4 mL) over 25 min. The solution was warmed to rt over 0.5 h, after which time TMSCl (0.3 mL, 2.4 mmol) was added. After stirring for 5 - 10 min, the reaction solution was concentrated to half its original volume and filtered through a plug of Florisil (10 g). The plug was washed with CH_2Cl_2 (200 mL), and the combined organic solutions were concentrated at reduced pressure but did not provide any material with nmr signals consistent with the expected product. The Florisil plug was re-extracted with MeOH (300 mL), and concentration of this solution followed by chromatography (20% EtOAc/hexanes) gave tan crystals (31 mg) which GCMS indicated was a mixture of **83** (5%) and an unknown material (70%). Successive recrystallizations afforded white crystals with the following spectroscopic features. ^{1}H nmr: δ 7.34 - 7.26 (m), 7.11 - 7.23 (m), 6.83 (d, *J* = 7.5), 6.45 (dd, *J* = 20.7, 1.8), 5.30 (s), 4.44 (s), 3.954 (s), 3.932 (s), 3.76 (unsymmetrical dd, *J* = 9.9, 1.2), 3.56 (d, *J* = 9.6), 3.35 - 3.15 (m

including t, J = 6.6), 3.15 - 3.0 (m including two s), 2.95 - 2.80 (m), 2.70 - 2.55 (m), 2.55 - 2.41 (m), 1.57 (br s). ^{13}C nmr: δ 214.3, 146.0, 145.4, 128.8, 128.2, 126.8, 126.4, 125.9, 125.0, 124.7, 124.7, 122.0, 99.9, 99.0, 81.6, 78.6, 77.2, 56.5, 56.12, 56.05, 55.2, 54.2, 33.9, 33.5, 33.0, 31.9, 31.2.

Spiro compound from chromanone (147). To a solution of 4-chromanone (523.3 mg, 3.54 mmol) in CH_2Cl_2 (10 mL) was added $BF_3.Et_2O$ (0.5 mL, 3.9 mmol) and then **1** (1.4 mL, 5.3 mmol) neat. Solution stirred at rt 2 h before H_2O (0.5 mL) was added. After further stirring 10 min, $BF_3.Et_2O$ (6.5 mL, 53.0 mmol) was added and the resulting solution stirred overnight. The reaction solution was washed with H_2O (2 x 50 mL) and the combined organic solutions were re-extracted with CH_2Cl_2 (2 x 40 mL), washed with brine (50 mL), dried over $MgSO_4$ and concentrated at reduced pressure. Chromatography (5% EtOAc/Hexanes) gave **147** (269.8 mg, 35%) as cream colored crystals: mp 99.5 - 102°C. IR: 1723 cm^{-1}. ^1H nmr δ: 7.16 (1H, dt, J = 7.8, 1.8, H-5), 6.90 (1H, dd, J = 7.2, 1.2, H-6 or H-7), 6.82 (1H, dt, J = 7.5, 1.2, H-7 or H-6), 6.56 (1H, dd, J = 7.5, 1.5, H-8), 4.27 (2H, t, J = 5.4, H-3), 2.92 (4H, symmetrical m, H-4', H-5'), 2.019 (2H, t, J = 5.4, H-2). ^{13}C nmr δ: 213.6 (C-1', C-3'), 155.2 (C-4a), 129.2 (C-6 or C-7), 128.0 (C-7 or C-6), 120.8 (C-5), 117.7 (C-8), 117.6 (C-8a), 60.8 (C-4' and C-5'), 57.0 (C-1), 35.2 (C-3), 28.9 (C-2). MS: 216 (M^+, 100), 187 (6), 160 (37),

146 (21), 145 (7), 132 (30), 131 (85), 115 (4), 103 (12), 77 (18), 76 (7), 66 (8), 63 (6), 51 (17), 50 (7), 39 (8), 28 (10), 27 (9). Exact mass calcd. for $C_{13}H_{12}O_3$: 216.0786, found 216.0782.

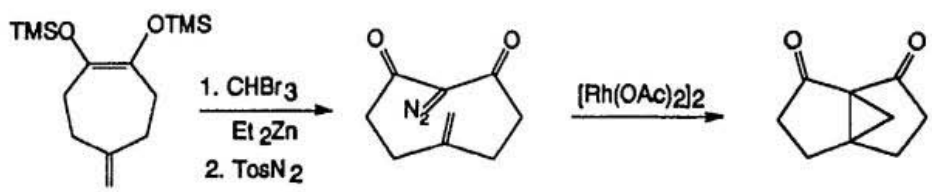
Chapter 3

STUDIES TOWARDS THE SYNTHESIS OF A [4.3.3]-PROPELLANE

I. INTRODUCTION

The name "propellane" was coined by Ginsburg for compounds having three non-zero bridges and one zero bridge between a pair of bridgehead carbons. While propellanes have been the subject of a great deal of research, mostly concerning their spectroscopic and physical organic characteristics and behaviour. Indeed, Ginsburg has published several volumes on propellanes, which cover the literature through part of 1984,[41] and since that time Wiberg has written two reviews.[42] As a result, only a few examples of propellane syntheses will be illustrated in this manuscript. These have been chosen to be representative of the different synthetic strategies that have been pursued.

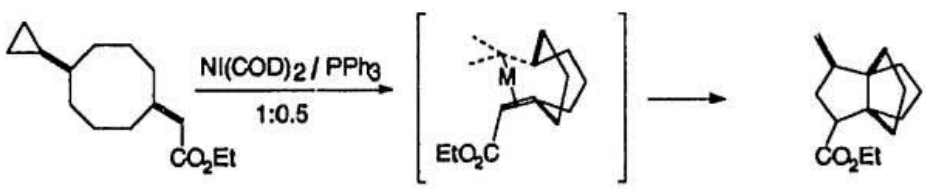
Scheme 75



149 (25%) 150

Transannular ring closure has been used successfully by several groups. Reingold and Drake[43] accessed [3.3.1]-propellane-2,8-dione (**150**), by the transannular addition of a carbene to the exocyclic double bond of **149** (Scheme 75). Rhodium acetate-catalyzed decomposition provided **150** quantitatively. Yamago and Nakamura[44] obtained the [3.3.3]-propellane **152** by a metal-catalysed transannular ring closure of the methylene cyclopropane **151** (Scheme 76). The authors reported that Ni(1,5-cyclooctadiene)$_2$ in the presence of 0.5 equivalents of triphenylphosphine effected cyclization solely in the desired manner in 74% yield.

Scheme 76

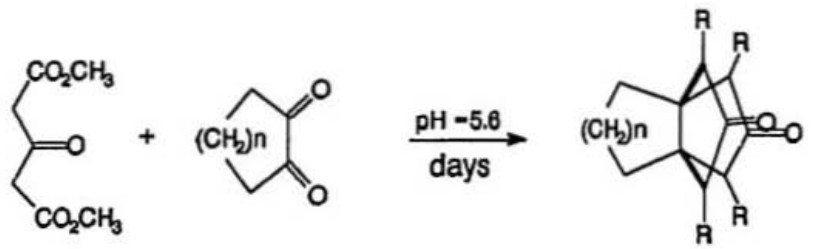


151 **152 (74%)**

More conventional chemistry such as acid- and base-catalysed cyclizations of bicyclic precursors have also been proven successful for propellane formation. Weber and Cook[45] gained entry to the [n.3.3]-propellanes (n = 10, 6, 4, and 3) by acid-catalyzed cyclization of two glutarate molecules and an alicyclic 1,2-dione (Scheme 77). For

example, the authors reported that stirring a solution of dimethyl 3-

Scheme 77

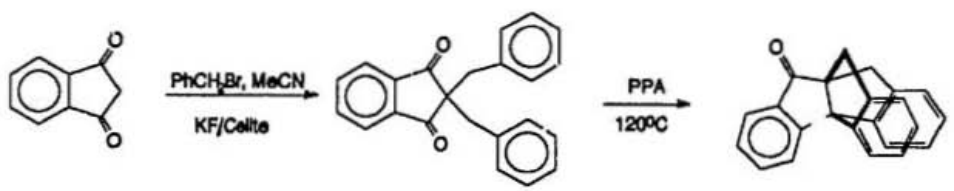


153 70 - 90%

n = 8, 4, 2, 1
R = CO_2Me

ketoglutarate and an alicyclic 1,2-dione in an aqueous buffer (pH = 5.6) afforded good yields of propellanes **153** after several days. Kuck and Paisdor[46] offered a new and efficient route to tribenzo[3.3.3]-propellanes

Scheme 78

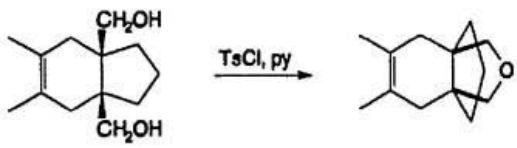


154 (82% overall)

such as **154** from 1,3-indanedione (Scheme 78). Based on earlier work

by Thompson and coworkers,[47] the key step was the cyclodehydration of the 2,2-disubstituted diketone using polyphosphoric acid (PPA). Mundy and Wilkening[48] gained access to simple propellanes by nucleophilic displacement via diol **155**. Treatment of diol **155** with *p*-toluenesulfonyl chloride afforded the propellane **156** albeit in a low yield (36%) (Scheme 79).

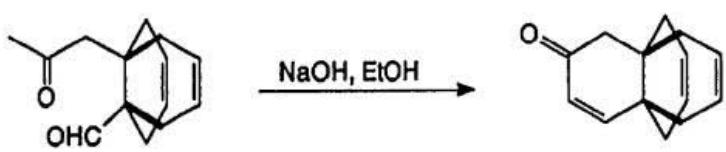
Scheme 79



155 **156**

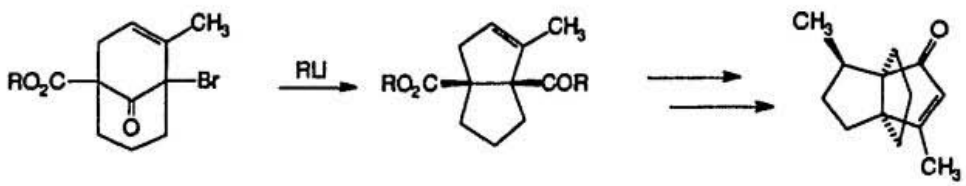
Paquette and coworkers prepared [4.4.4]-propella-3,6,10-trien-2-one **158** by the-base catalysed aldol closure of the bicyclic precursor **157** (Scheme 80).[49]

Scheme 80



157 **158 (54%)**

Scheme 81

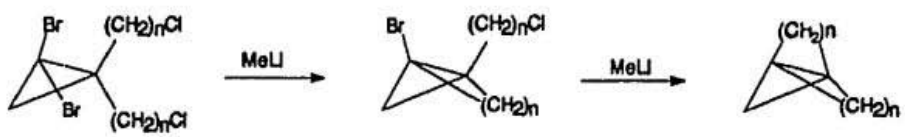


159 160 (70%) 161 (64%)

R = $(MeO)_2POCH_2$

Kraus and Shi[50] synthesized propellanes from bridgehead bromide precursors, e.g. **159**. Upon nucleophilic addition, these precursors underwent Favorskii rearrangement to give a bicyclic precursor, **160**, which was now suited for aldol cyclization (Scheme 81). The authors suggested the mechanism to involve the addition of the nucleophile to the carbonyl group of **159** to give the bicyclic precursor **160**, followed by base-catalysed aldol closure to furnish **161**.

Scheme 82

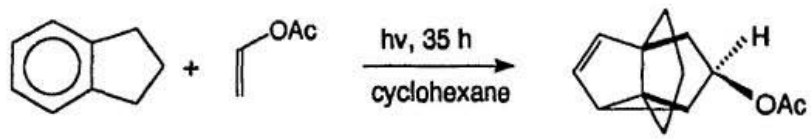


162 163

n = 3 (11%), 4 (34%)

There are numerous examples of syntheses of small-ring propellanes based on the nucleophilic displacement of a leaving group. For example, Fuchs and Szeimies[51] reported the synthesis of [n.n.1]-propellane **163** from a dihalogenated cyclopropane **162** (Scheme 82).

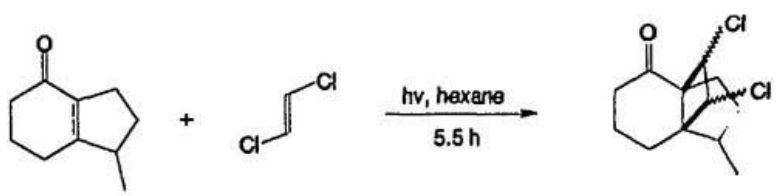
Scheme 83



164

Photochemical pathways have also been studied, especially by Wender and Dreyer[52] in their work towards modephene. The [3.3.3]-propellane skeleton of modephene was quickly established by the

Scheme 84

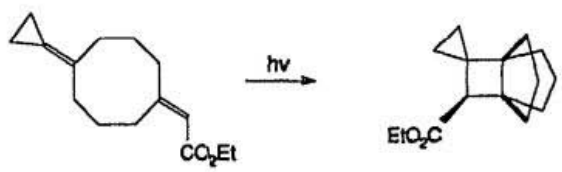


165 166

photochemical addition of an olefin to an aromatic substrate (Scheme 83). *meta*-Addition of vinyl acetate to indan provided the propellane **164**

(21% based on consumed starting indan). Smith and Jerris[53] reported a [2 + 2] photochemical addition as the key step in their synthesis of modephene. Irradiation of a solution of enone **165** and 1,2-dichloroethene provided the propellane **166** in 67% yield (Scheme 84). Yamago and Nakamura[44] accomplished a transannular [2 + 2] photoaddition of **151** to generate **167** in 90% yield (Scheme 85).

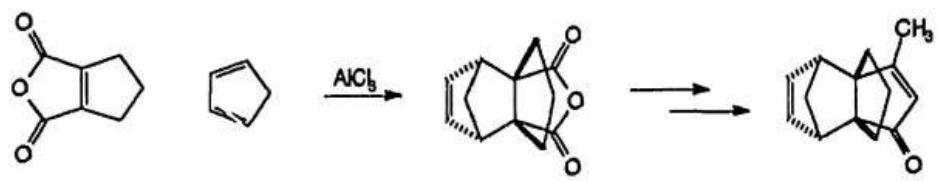
Scheme 85



151 167 (90%)

Diels-Alder cyclization was employed by Ghosh and coworkers[54] in their short and convient strategy for the synthesis of [3.3.3]-propellanes. Hydrolysis of the adduct **168**, followed later by an aldol closure provided **169** in 62% overall yield from cyclopentadiene (Scheme 86).

Scheme 86

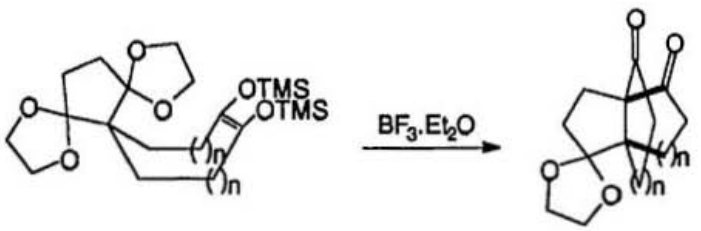


168 (90%) 169

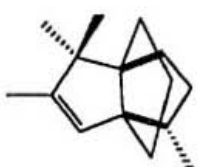
II. RESULTS AND DISCUSSION

Our attempt to gain access to medium-sized-ring propellanes was based on the spiroannulation reaction first reported by Kuwajima and

Scheme 87



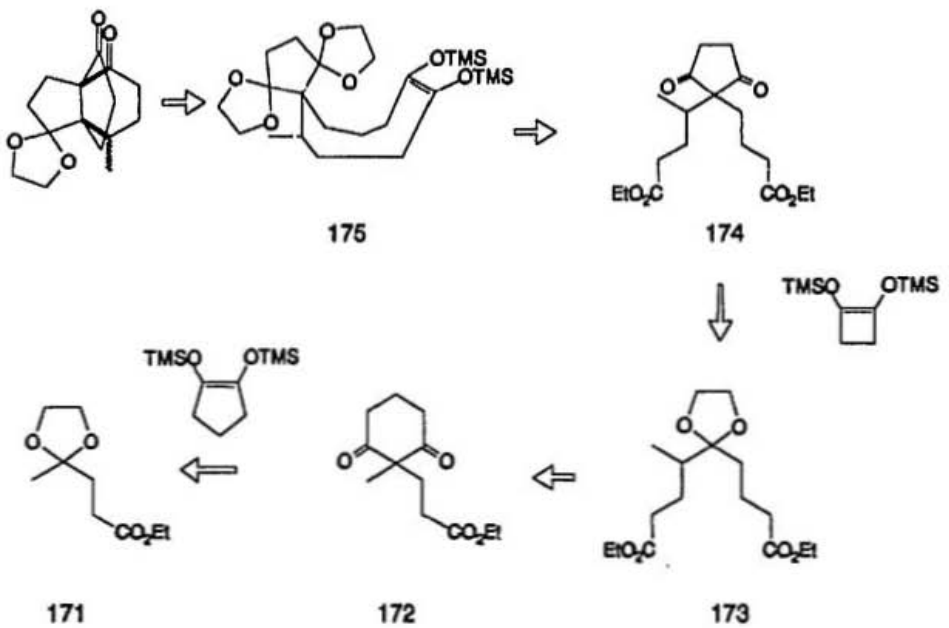
coworkers[1] and extensively studied in our laboratories.[2,16,55] It was hoped that one could perform an intramolecular spiroannulation of the type illustrated in Scheme 87. Thus, by preparing different 1,2-bis(trimethylsilyloxy) ring sizes, a variety of propellanes might be realized, including the natural product modephene **170**. However, while



170

the reactions of **1** and 1,2-bis(trimethylsilyloxy)cyclopentene have been studied[2] and employed in total synthesis,[3-12] the reactivity of such larger bis(trimethylsilyloxy) rings is unknown. If the geminal acylation did proceed, it would be the first intramolecular cyclization of this type.

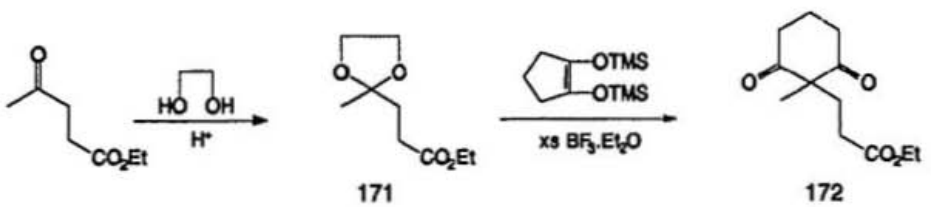
Scheme 88



It was believed that the carbon framework could be assembled by successive geminal acylations, as illustrated in the retrosynthetic analysis in Scheme 88. The first, involving the ketal of ethyl levulinate and 1,2-bis(trimethylsilyloxy)-cyclopentene,[2a] would provide the precursor for the preparation of the key 1,2-bis(trimethylsilyloxy)cyclononene (**172 -> 173**).

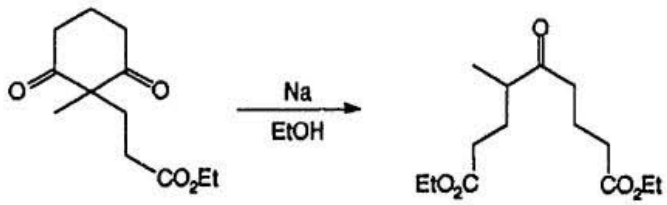
The second geminal acylation, this time involving **1**, would provide the remainder of the carbons for the framework of the propellane (**174**). If the substituted bis(trimethylsilyloxy)cyclononene species **175** were prepared its reactivity might require that the crude material be treated with a Lewis acid and the propellane (rather than the bis(trimethylsilyloxy) derivative) be isolated directly.

Scheme 89



Under the conditions reported by Wu and Burnell,[2a] treatment of the ethylene ketal of ethyl levulinate **171** with 1,2-bis(trimethylsilyloxy)-cyclopentene under boron trifluoride etherate catalysis gave **172** (Scheme 89), for which the ^{13}C nmr spectrum showed a ketone carbonyl at δ 209.7 ppm and an ester carbonyl at δ 172.7 ppm. Chromatography of **172** gave poor recovery, therefore, the crude product was treated with sodium ethoxide to yield directly the keto-diester **176** (Scheme 90). Its ^{13}C nmr spectrum included carbonyl resonances at δ 213.0 ppm and

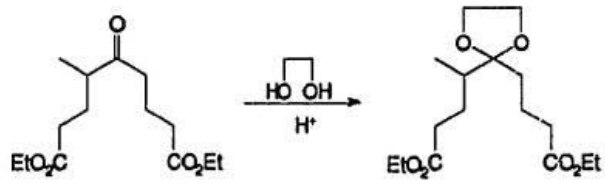
Scheme 90



172 **176**

173.1 ppm, the latter being attributed to both ester functions. The crude yield of keto-diester **176** (based on **171**) was 85%. This implied that the conversion to 1,3-cyclohexanedione **172** must have been high, and the

Scheme 91



176 **173**

yield of **172** after chromatography was poor due to TLC visualization difficulties as previously discussed[1]. Ketalization of **176** was accomplished using standard conditions to provide **173** (Scheme 91). Its

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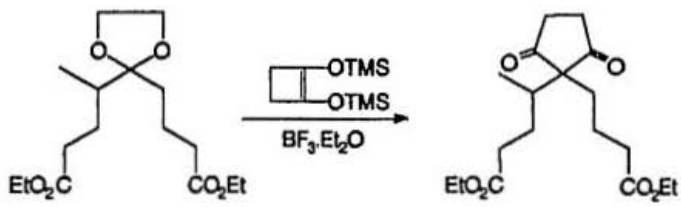
[1]This reaction has been reported by Wu and Burnell[2a] but unlike these authors our attempts failed to provide respectable yields of **172** after chromatography. We attribute this difference to TLC visualization difficulties. For individual reaction parameters considered see Table 8 in the Appendix.

^{13}C nmr spectrum had only carbonyl resonances for the ester functions and it possessed a quaternary resonance at δ 113.0 ppm. It was interesting that whereas the nmr spectra of the product showed the material to be reasonably pure, chromatography led to poor recovery (41%).

Scheme 92



170 174

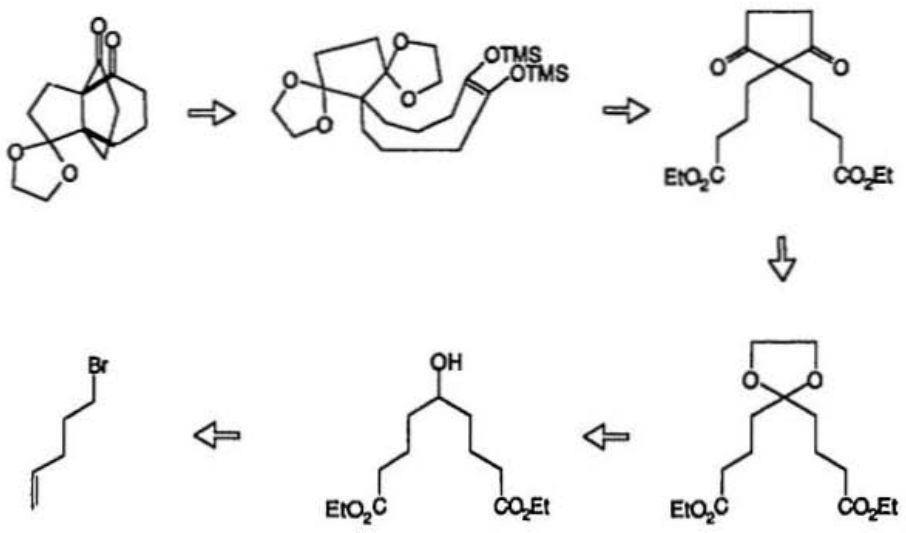
Generation of the diketone **174** (Scheme 92) in more than trace quantities was unfortunately not successful[2]. At best the crude product was determined from GCMS analysis to contain the geminally acylated product, **174** in only 27%. The major component in all attempts was hydrolysed starting material, **176**. From the combination of several crude products a small sample (less than 1% yield) of **174** of approximately 90% purity was obtained after tedious chromatography. Its ^{1}H nmr spectrum included a doublet at δ 0.93 ppm, attributed to the methyl

[2]Table 9 in the Appendix provides a summary of the conditions and parameters that were studied, but compound **174** remained elusive as the reaction was not reproducible.

resonance, in addition to a resonance at δ 2.73 ppm characteristic of the cyclopentandione hydrogens. Included in the ^{13}C nmr spectrum was the quaternary carbon resonance at δ 63.4 ppm.

This work was carried out prior to the extensive studies on geminal acylation of ketals[2,16] and ketones.[55] In retrospect, the result with **173** is not surprising as it is consistent with studies involving other substrates bearing an alpha methyl substituent with **1**. In all cases, there was a sharp decrease in yield compared to substrates having no alpha substituent.

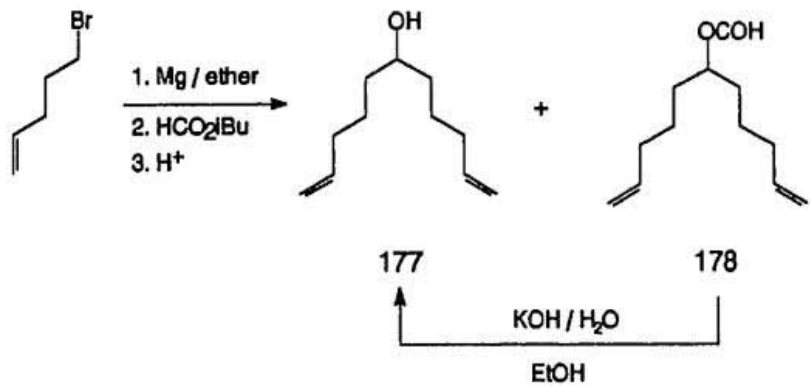
Scheme 93



The initial strategy was modified to avoid the α-methyl substituent, as depicted in our second retrosynthetic analysis (Scheme 93). The

symmetrical framework was to be generated by a double addition of the Grignard reagent derived from 5-bromo-1-pentene to a formyl ester. After oxidation and subsequent geminal acylation with **1**, oxidation of the terminal double bonds to esters, might afford the precursor required for propellane formation.

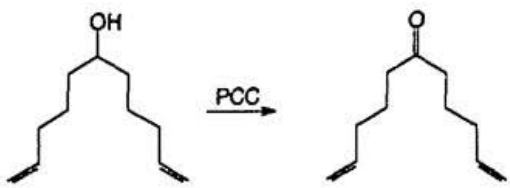
Scheme 94



After considerable experimentation, good yields of the desired alcohol **177** were obtained in a two step process (Scheme 94). Generation of the organomagnesium compound from 5-bromo-1-pentene, followed by the addition of isobutyl formate gave a mixture of the alcohol **177** (with its ^{13}C nmr spectrum showing an alcohol resonance at δ 71.3 ppm and its IR spectrum including an OH stretch at 3400 cm^{-1}) and the ester **178** (for which the ^{13}C nmr spectrum showed a formate resonance at δ 160.7 ppm, and its IR spectrum included a carbonyl stretch at 1722

cm^{-1}). Simple base hydrolysis of the mixture provided acceptable yields of crude **177**. Chromatography proved unnecessary as good yields of ketone **179** could be obtained by direct oxidation of crude **177** with PCC (Scheme 95). Characteristic for **179** was the carbonyl resonance at δ

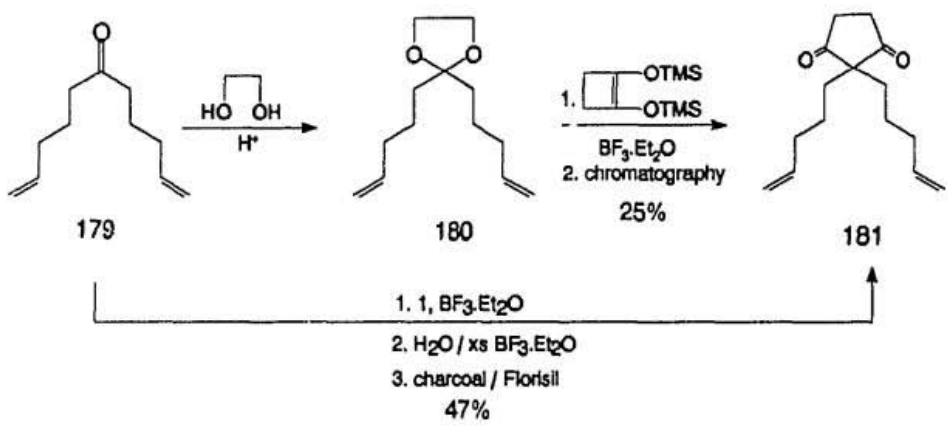
Scheme 95



177 179

210.5 ppm in the ^{13}C spectrum in addition to the carbonyl stretch at 1714 cm^{-1} in its IR spectrum.

Scheme 96

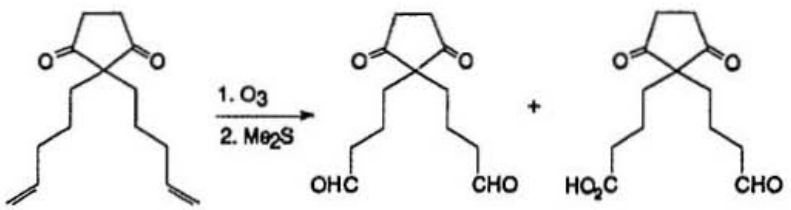


Ketalization of **179** gave **180** (84%) with 1,2-ethanediol under standard conditions. The ^{13}C nmr spectrum for **180** included the quaternary carbon resonance at δ 111.6 ppm and its ^{1}H nmr spectrum revealed a dioxolane resonance at δ 3.92 ppm. Subsequent geminal acylation gave a poor yield of the 2,2-disubstituted-1,3-cyclopentanedione **181** (Scheme 96), despite the fact that the crude reaction product was determined from GCMS analysis to contain a high proportion of **181**. The ^{13}C nmr spectrum of **181** showed a ketone resonance at δ 217.4 ppm, and the distinctive cyclopentanedione hydrogens appeared at δ 2.71 ppm in the ^{1}H nmr spectrum. Suspecting, as before, that the low yield was at least partly a consequence of our inability to detect the diketone using conventional TLC visualization methods during chromatography, we focused on the preparation of **181** from the ketone **179**, because our modified "ketone procedure" obviated the need for chromatography. As discussed in Chapter 1, diketone products of acceptable purity could be obtained by filtration through a Florisil/charcoal plug. Thus, treatment of crude ketone **179** with **1** under the "ketone conditions" gave **181** in 47% yield, approximately twice that obtained when the analogous ketal substrate was employed (25%).

With the cyclopentanedione moiety established, it was now necessary to convert the terminal double bonds into esters. Periodate-permanganate oxidation[56] of the terminal double bonds of **181** failed to

provide any of the desired dicarboxylic acid **184**. The best conditions were found to be ozonolysis with reductive work-up followed by subsequent oxidation rather than ozonolysis with oxidative work-up.

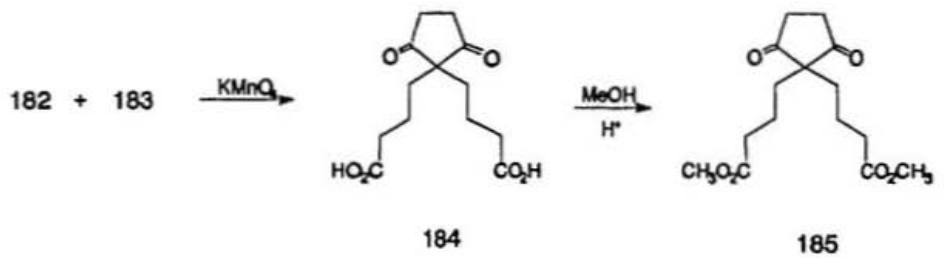
Scheme 97



181 182 183

Bubbling ozone through a solution of **181** followed by addition of dimethyl sulfide gave a mixture of the dialdehyde **182** and some more oxidized material, **183** (Scheme 97). The ^{13}C nmr spectrum of the crude product included two carbonyl resonances, one at δ 201.2 ppm, characteristic of an aldehyde and the other at δ 162.9 ppm, characteristic of a carboxylic acid. This crude material was oxidized to the diacid **184** using a potassium permanganate solution in a phosphate buffer (Scheme 98).[57] The ^{13}C nmr spectrum of **184** included the ketone resonance at δ 216.4 ppm and the carboxylic acid resonance at δ 176.9 ppm. Esterification with Amberlyst 15 in methanol provided the key diester **185** (Scheme 98). The ^{13}C nmr spectrum for **185** showed two carbonyl resonances, one for the ketones at δ 216.2 ppm and the other for the esters at δ

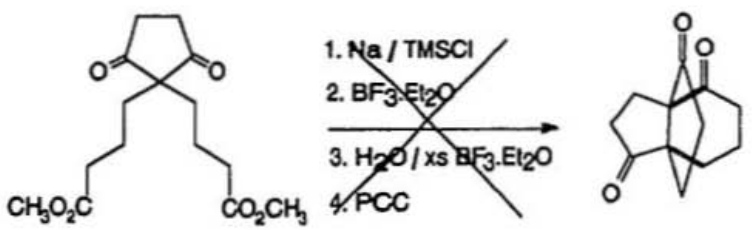
Scheme 98



184 185

173.0 ppm, in addition to the methyl resonance at δ 51.5 ppm. The ketones were not ketalized to any degree. The diester **185** was obtained in 55% overall yield from 5-bromo-1-pentene.

Scheme 99



185 186

What remained was the key process of preparing the 1,2-bis(trimethylsilyloxy)cyclononene compound and its spiroannulation

(Scheme 99)[3]. With the **185** in hand, and in light of the research involving **1** and ketones, direct access to the propellane skeleton was attempted without protection of the ketone functions. Under the same conditions as we had used for the preparation of **1**,[17] the diester **185** was boiled in toluene with 8.5 equivalents sodium metal and 6.7 equivalents of chlorotrimethylsilane to give a golden yellow solution. No attempt was made to isolate an intermediate cyclononene, but rather $BF_3.Et_2O$ was added and the solution was stirred overnight. Water was added followed by excess $BF_3.Et_2O$. This should have afforded the spiroannulated product **186**, but in the event that the ketones had been reduced by the excess sodium in the acyloin step, PCC was added to bring all oxygen functions to at least the ketone oxidation level. Unfortunately there were no ketone resonances in the ^{13}C nmr spectrum of the crude product, and both the ^{13}C and ^{1}H nmr spectra were very complex. No starting material was recovered.

Ultrasonic irradiation affects chemical reactions in solution by the generation of sound waves which induces rapid growth and sudden collapse of bubbles. The overall result is an intense localized pressure and temperature change during collapse of these bubbles. More importantly because these are localized changes it does not elevate the

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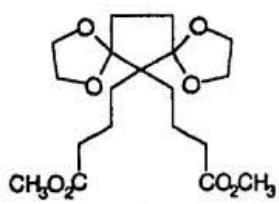
[1]For a detailed account of the parameters considered see Table 10 in the Appendix.

temperature of the total reaction solution. Futhermore, many organic transformations involving metals have been developed or improved from ultrasonic studies.[58] We felt that the use of ultrasonic conditions might favor the desired acyloin reaction, which is a process known to occur on the suriace of the metal. Unfortunately, this also failed to give any acyloin product or geminal acylation product. Unlike the previous conditions, however, the major component could be identified from crude spectra as the starting diester **185.** This result demonstrated that whereas ultrasonic irradiation was mild enough to leave the ketones untouched, it also failed to be of use in facilitating the desired acyloin sequence.

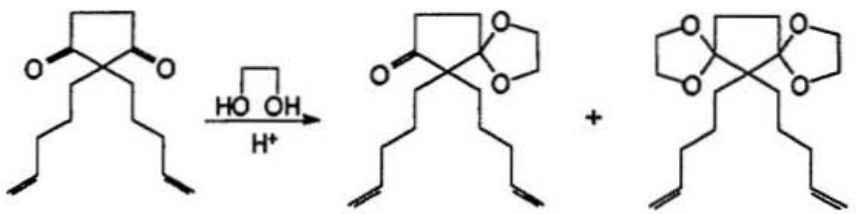


187

The failure of ultrasonic irradiation led us to reconsider the inital conditions using boiling toluene, as it was important to determine whether the acyloin reaction actually took place. The most likely problem with this reaction would be reduction or coupling reactions involving the ketone functions. Therefore, the diester **187**, with the ketones protected as ketals, was considered. To avoid a possible problem with

transesterification, this ketalized derivative was prepared from **181** so that ketalization preceded ester formation.

Scheme 100

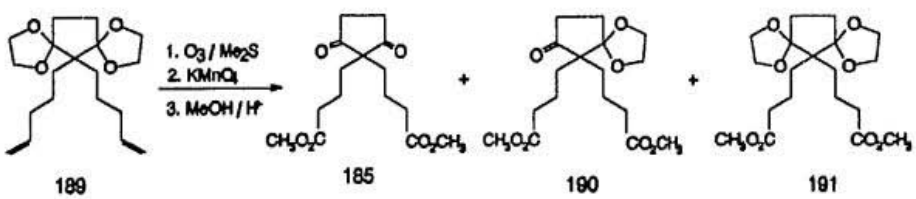


181 **188** **189**

Acid-catalysed ketalization of **181** with 1,2-ethanediol was difficult, presumably because this involves the formation of three adjacent quaternary centers. The major product was the mono-ketal **188** (Scheme 100). The ^{13}C nmr spectrum included a ketone resonance at δ 216.5 ppm and a quaternary carbon at δ 117.0 ppm, and the IR spectrum showed a carbonyl stretch at 1740 cm^{-1}. A very small amount of the diketal **189** was also obtained by chromatography. It had no carbonyl signals in either the IR or the ^{13}C nmr spectra but included in its ^{13}C nmr spectrum was a quaternary carbon resonance at δ 117.9 ppm. Reintroduction of monoketal **188** back into the ketalization conditions did not generate any more of the desired diketal **189**. Attempts to recycle the monoketal resulted in its destruction. Spectral analysis of the crude product showed evidence of double bond isomerization and opening of

the cyclopentanedione ring. Ketalization using 2,2-dimethyl-1,3-propanediol was unsuccessful even when the Dean-Stark water separator was filled with anhydrous copper sulfate or Molecular Sieves to facilitate water removal, as only starting **181** was recovered. Ketalization using 1,2-bis(trimethylsilyloxy)ethane under trimethylsilyl trifluoromethane sulfonate catalysis was also unsuccessful.

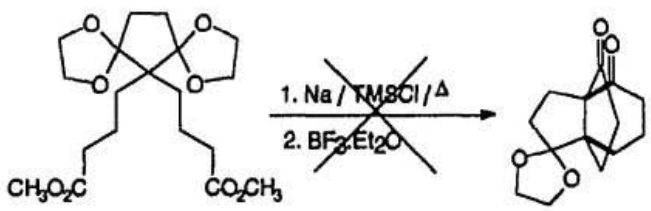
Scheme 101



The ketalization using 1,2-ethanediol was not optimized, due in part to uncertainty regarding the stability of a ketal under the conditions required for ester formation, and also the uncertainty as to whether the desired propellane skeleton can be accessed from such a precursor. As discussed for the diester **185**, the ketalized analogue was prepared from the terminal double bond precursor in the same manner. Ozonolysis with reductive work-up, followed by oxidation with permanganate in a phosphate buffer and esterification with Amberlyst 15 in methanol gave a

mixture of diester **185** (57%), the monoketal **190** (9%), and diketal **191** (32%) (by GCMS analysis) (Scheme 101). The mixture was treated with sodium metal and chlorotrimethylsilane in boiling toluene in the hope of obtaining some evidence for a propellane (Scheme 102). The filtrate obtained from the acyloin step was cooled to -78°C prior to the addition of $BF_3.Et_2O$. Aqueous work-up followed by flash chromatography gave only one identifiable compound, the diester **185**.

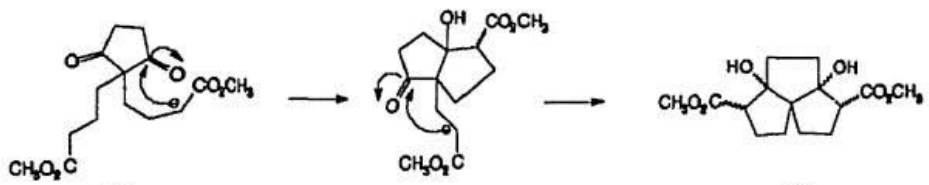
Scheme 102



191

Faced with no satisfactory conditions for generation of the propellane skeleton, the diester **185** was treated with a variety of non-nucleophilic bases in the hope of preparing the angularly fused triquinane, **192** (Scheme 103). Aldol cyclization onto the ketones of the 1,3-cyclopentanedione moiety should allow access to such a system as illustrated in Scheme 103. Initial attempts using a large excess of NaH gave only what appeared to be polymeric material. The ^{13}C nmr spectrum of this product showed no evidence for either ester or olefinic

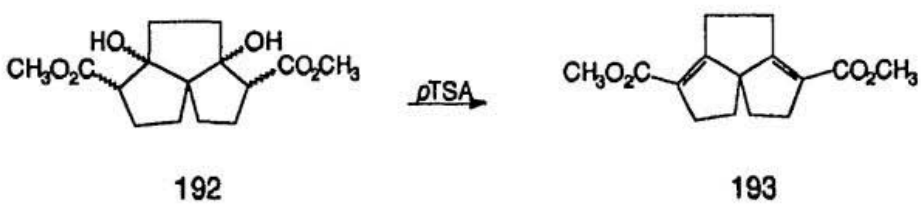
Scheme 103



185 192

functionality, but the alkane region was extremely complex. Addition of sodium metal to a methanol solution of the diester did show some evidence for aldol condensation. Among the volatile components were what appeared to be (by GCMS) a mixture of cyclopentanedione ring opened analogues of starting diester **185** and two isomers having the correct molecular ion for **192** (the chirality of the carbinol centers will give diastereomeric mixtures). Dehydration should force the mixture to a single compound if double bond isomerization does not occur (Scheme 104), so the crude material was heated in the presence of *p*TSA.

Scheme 104



192 193

Chromatography failed to give any pure fractions and while the ^1H nmr spectrum of some fractions did include olefinic resonances (may possibly be double bond isomers of **193**) in addition to methoxy resonances, the amount of material isolated was very small (all combined fractions would account for only 1 - 2% yield). Inverse addition led to a crude product for which the ^{13}C nmr spectrum was very complex in the aliphatic region, but it did show olefinic and ester signals. Flash chromatography gave a very small amount (less than 1%) of a material that showed olefinic signals at δ 125.7, 128.2, 128.3 ppm and an ester resonance at δ 173.7 ppm in its ^{13}C nmr spectrum. The ^1H nmr spectrum showed no olefinic resonances (the dehydrated triquinane would have tetrasubstituted double bonds) and many methoxy singlets in the δ 3.6 to 3.8 ppm range in addition to a very complex aliphatic region likely due to polymeric impurities. The volatile component of this material was analysed by GCMS, and this showed what may have been a mixture of the non-dehydrated triquinane (M^+ 298: (4), M^+- H_2O: 280 (12)) having a 27% peak area and the singly dehydrated triquinane (M^+ 280: (8), M^+- H_2O: not observed) having a 9% peak area. The mixture was stirred in the presence of *p*TSA for 16 days after which GCMS analysis indicated isomers of two singly dehydrated triquinanes in a ratio of 3.5:1. Chromatography failed to give pure fractions and only trace amounts of material were recovered.

Two-pot sequences were also studied in which only one

deprotonation at a time should occur. Both the sequence employing *t*-BuOK and NaH failed to give any evidence for a triquinane derivative as both crude materials were, from nmr analysis, found to be only polymeric material. Unlike the one-pot processes, no olefinic or carbonyl resonances were detected in the ^{13}C nmr spectra.

Further experimentation will be required if such triquinane species are to be accessed from diester **185**. From our studies it is uncertain whether the cyclopentanedione hydrogens are also abstracted, especially when large number of equivalents of base are used, and whether intermolecular/intramolecular coupling of the anion with the ester function is a competing reaction.

III. EXPERIMENTAL

For general remarks and instrumentation see Chapter 1. As discussed in Chapter 2 nmr spectra resonances have been completely assigned with the numbers referring to the numbering scheme.

Ethyl 4-(1,3-dioxolan-2-yl)-pentanoate (171). To a solution of ethyl levulinate (12.7 g, 88.6 mmol) in benzene (75 mL) was added *p*TSA (~0.3 g) and 1,2-ethanediol (10.9 g, 0.18 mol). The mixture was heated under reflux overnight with azeotropic removal of water. After cooling, the solution was washed with saturated $NaHCO_3$ (70 mL) and

then with H_2O (50 mL). The aqueous layers were re-extracted with ether (2 x 50 mL). The combined organic solutions were washed with brine (75 mL), dried over $MgSO_4$ and concentrated at reduced pressure. Vacuum distillation of the yellow residue gave **171** (12.5 g, 75%) as a colorless liquid, b.p. 68 - 69°C / 1 mm Hg: IR: 1740 cm^{-1}. ^1H nmr: δ 4.11 (2H, q, *J* = 7.2, ester CH_2), 3.92 (4H, symmetrical m, dioxolane), 2.35 (2H, t, *J* ~ 7.7, H-2), 1.99 (2H, t, *J* ~ 7.7 H-3), 1.29 (3H, s, H-5), 1.24 (3H, t, *J* = 7.2, ester CH_3). ^{13}C nmr: δ 172.5 (C-1), 108.3 (C-4), 64.0 (2C, dioxolane), 59.4 (ester CH_2), 33.4 (C-2), 28.3 (C-3), 23.2 (ester CH_3), 13.5 (C-5). MS: no M^+, 173 (M^+ - CH_3, 15), 143 (M^+ - ethyl, 20), 129 (9), 99 (56), 87 (cleavage between C-3 and C-4, 100), 43 (88). Exact mass calcd. for $C_8H_{13}O_4$ (M^+ - CH_3): 173.0813, found 173.0809.

Ethyl 3-(1'-methyl-2',6'-dioxocyclohexane)propanoate (172).

The following is a representative procedure[4]: A solution of **171** (306 mg, 1.62 mmol) in CH_2Cl_2 (30 mL) was cooled to -78°C. $BF_3.Et_2O$ (3.0 mL, 24 mmol) was added followed, dropwise, by the addition of a solution of 1,2-bis(trimethylsilyloxy)cyclopentene (4.1 mmol, 1.2 mL) in CH_2Cl_2 (10 mL). The mixture was stirred for 45 h during which time the mixture attained room temperature. The dichloromethane solution was washed with water (2 x 30 mL), and the aqueous layer was re-extracted with CH_2Cl_2 (2 x 40 mL). The combined organic solutions were washed with brine (75 mL),

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[4]For individual experiments see Table 8 in the Appendix.

dried over $MgSO_4$ and concentrated at reduced pressure. The dark residue (GCMS showed one volatile component) was dissolved in ether (150 mL) and purified by filtration through a charcoal / Florisil plug to give **172** (99.0 mg, 27%) as a red viscous oil. Nmr showed one major set of signals that was consistent with those in the literature.[2a] ^1H nmr: δ 4.09 (2H, q, ester CH_2), 2.69 (4H, m, H-4' and H-6'), 2.10 - 2.22 (4H, m, H-1 and H-2), 1.90 - 2.09 (2H, m, H-5'), 1.26 (3H, s, C-1' CH_3), 1.21 - 1.24 (3H, br t, ester CH_3). ^{13}C nmr: δ 209.7 (C-2' and C-6'), 172.7 (C-3), 64.2 (C-1'), 60.5 (ester CH_2), 37.7 (C-3' and C-5'), 30.4 (C-2), 29.4 (C-1), 20.7 (C-5'), 17.5 (C-1' CH_3), 14.1 (ester CH_3).

Diethyl 4-methyl-5-oxononanedioate (176). After bubbling a stream of nitrogen through a solution of crude **172** (3.47 g, 15.4 mmol) in EtOH (60 mL), freshly cut sodium (42 mg, 18 mmol) was added. The reaction mixture was stirred at room temperature under N_2 until the sodium had been consumed. Water (200 mL) was added, and the aqueous layer was re-extracted with CH_2Cl_2 (3 x 50 mL) and EtOAc (2 x 50 mL). The combined organic solutions were washed with brine (75 mL), dried over $MgSO_4$ and concentrated at reduced pressure to give **176** (1.88 g, 85%) as a tan oil. No purification was undertaken. IR: 1700 and 1730 cm^{-1}. ^1H nmr: δ 4.12 (2H, q, J = 7.2, ester CH_2), 4.10 (2H, q, J = 7.2, ester CH_2), 2.62 (1H, m, H-4), 2.50 - 2.59 (2H, m, H-7), 2.25 - 2.39 (4H, m, H-2 and H-8), 1.96 (1H, m, H-6), 1.83 - 1.93 (2H, m, H-3),

1.65 (1H, symmetrical m, H-6), 1.26 (3H, t, J = 7.2, ester CH_3), 1.24 (3H, t, J = 7.2, ester CH_3), 1.09 (3H, d, J = 6.9, methyl). ^{13}C nmr: δ 213.0 (C-5), 173.1 (C-1 and C-9), 60.31(ester CH_2), 60.27 (ester CH_2), 45.5 (C-4), 39.9 (C-6), 33.7 (C-2 or C-8), 31.7 (C-2 or C-8), 27.5 (C-7), 18.7 (C-3), 16.3 (methyl), 14.1 (2C, ester CH_3). MS: 272 (M^+, 0.7), 227 (M^+ - OEt, 7), 181 (50), 143 (α-cleavage between C-5 and C-6, 100), 115 (59), 101 (22), 87 (39), 55 (40), 43 (23). Exact mass calcd. for $C_{12}H_{19}O_4$ (M^+ - OEt): 227.1282, found 227.1292.

Diethyl 4-methyl-5-(1,3-dioxolan-2-yl)nonanedioate (173). To a solution of **176** (4.11 g, 15.1 mmol) in benzene (75 mL) was added 1,2-ethanediol (1.87 g, 30.2 mmol) and *p*TSA (~200 mg). The reaction mixture was heated under reflux overnight with azeotropic removal of water. GCMS analysis of the mixture still indicated unketalized material. Additional 1,2-ethanediol (3.6 g, 60 mmol) and *p*TSA (~500 mg) were added, and the system was heated under reflux for an additional 20 h. After cooling, the solution was washed with H_2O (2 x 50 mL), then the aqueous layers was re-extracted with ether (2 x 50 mL). The combined organic solutions were washed with brine (75 mL), dried over $MgSO_4$ and concentrated at reduced pressure. Chromatography (5% EtOAc/hexanes) of the brown residue afforded **173** as a pale yellow liquid (1.98 g, 41%): IR: 1730 cm^{-1}. ^1H nmr: δ 4.12 (4H, q, J = 7.2, ester CH_2), 3.94 (4H, s, dioxolane), 2.21 - 2.43 (4H, m, H-7 and H-2 or H-8), 1.90 (1H,

symmetrical m, H-6), 1.63 - 1.78 (5H, m, H-4, H-3 and H-2 or H-8), 1.41 (1H, m, H-6), 1.25 (6H, t, J = 7.2, ester CH_3), 0.93 (3H, d, J = 6.9, methyl). ^{13}C nmr: δ 173.6 and 173.3 (C-1 and C-9), 113.0 (C-5), 65.02 and 64.96 (dioxolane), 60.0 (ester CH_2), 38.9 (C-4), 34.2 (C-7), 32.8 (C-2 or C-8), 32.5 (C-2 or C-8), 26.4 (C-6), 18.6 (C-3), 14.1 (ester CH_3), 13.9 (C-4 CH_3). MS: M^+ not found, 271 (M^+ - OEt, 16), 225 (8), 201 (cleavage between C-5 and C-6, 39), 187 (cleavage between C-4 and C-5, 100), 113 (29), 99 (63), 55 (24). Exact mass calcd. for $C_{14}H_{23}O_5$ (M^+ - OEt): 271.1544; found 271.1532.

Diethyl 5-(1',3'-dioxocyclopentane)-4-methyl-1,9-nonanedioate (174). A solution of **173** (186 mg, 0.57 mmol) in dry CH_2Cl_2 (30 mL) was cooled to -78°C under N_2. Tin tetrachloride (8.6 mmol, 1.0 mL) was added at once, followed by the dropwise addition of a solution of **1** (1.43 mmol, 0.40 mL) in dry CH_2Cl_2 (6.0 mL). The mixture was stirred overnight during which time the mixture attained room temperature. The dichloromethane solution was washed with water (2 x 50 mL), and the aqueous layers were re-extracted with CH_2Cl_2 (2 x 30 mL). The combined organic solutions were washed with brine (2 x 50 mL), dried over $MgSO_4$ and concentrated at reduced pressure. During aqueous work-up emulsions were encountered. GCMS analysis of the crude material showed hydrolyzed starting ketal **176** (major) and **174** (approximately 20%). After repeated chromatography (1.5 drops of MeOH per 10 mL of

CH_2Cl_2), a small sample of **174** (35 mg, 8%) as a yellow oil was obtained. IR: 1710 cm^{-1}. ^1H nmr: δ 4.11 (2H, q, J = 7.2, ester CH_2), 4.10 (2H, q, J = 7.2, ester CH_2), 2.71 (4H, narrow m, H-4' and H-5'), 2.20 - 2.41 (4H, m, H-2 and H-8), 1.91 (1H, m, H-4), 1.76 (1H, m, H-6), 1.61 - 1.72 (4H, m, H-3 and H-7), 1.40 (1H, m, H-6), 1.24 (3H, t, J = 7.2, ester CH_3), 1.22 (3H, t, J = 7.2, ester CH_3), 0.91 (3H, d, J = 6.9, methyl). ^{13}C nmr: δ 216.9 (C-1' and C-3'), 172.9 and 172.6 (C-1 and C-9), 63.4 (C-5), 60.4 (ester CH_2), 37.5 (C-4), 36.53 and 36.48 (C-4' and C-5'), 34.3 (C-2 or C-8), 32.1 (C-2 or C-8), 31.2 (C-7), 26.3 (C-6), 19.9 (C-3), 14.1 (ester CH_3), 13.6 (C-4 methyl). MS: 340 (M^+, 39), 294 (40), 267 (47), 239 (cleavage between C-3 and C-4, 70), 193 (239 - OEt, 85), 165 (193 - CO, 85), 137 (61), 81 (59), 55 (100). Exact mass calcd. for $C_{18}H_{28}O_6$: 340.1884; found 340.1871.

1,10-Undecadien-6-ol (177). To a suspension of freshly cut Mg ribbon (129 mg, 5.29 mmol), anhydrous ether (0.4 mL) and a crystal of I_2, was added a solution of 5-bromo-1-pentene (880 mg, 5.91 mmol) in anhydrous ether (0.8 mL) at a rate that maintained a gentle reflux. After the addition was complete, the solution was stirred at room temperature for 10 min, and then it was heated in a water bath for 15 min. After cooling to 0°C, a solution of methyl formate (436 mg, 7.26 mmol) in anhydrous ether (0.4 mL) was added in three portions over approximately 5 min. The solution was stirred an additional 20 min

before quenching (at 0°C) with saturated NH_4Cl (3 mL). The organic layer was washed with H_2O (2 x 10 mL), then the aqueous layers were re-extracted with ether (3 x 10 mL). The combined organic solutions were washed with brine (2 x 10 mL), dried over $MgSO_4$ and concentrated at reduced pressure. The dark yellow oil was shown (by GCMS) to be a mixture of the alcohol **177** (27%) and **(1,10-undecadien-6-yl) formate 178** (62%). The crude sample was heated in a solution of KOH (0.9 g) in EtOH (20 mL) and H_2O (3.0 mL) for 30 min. The solvent was removed under reduced pressure and chromatography (5% EtOAc/hexanes) of the residue gave **177** as a yellow oil (215 mg, 48%). For **177**: IR: 3400 and 1690 cm^{-1}. ^1H nmr: δ 5.80 (2H, symmetrical m, H-2 and H-10), 4.92 - 5.03 (4H, m, H-1 and H-11), 3.57 (1H, narrow m, H-6), 2.27 (1H, br s, OH), 2.03 - 2.09 (4H, m, H-3 and H-9), 1.37 - 1.57 (8H, m, H-4, H-5, H-7, and H-8). ^{13}C nmr: δ 138.6 (C-2 and C-10), 114.4 (C-1 and C-11), 71.3 (C-6), 36.7 (C-3 and C-9), 33.6 (C-5 and C-8), 24.8 (C-4 and C-7). MS: M^+ not found, 135 (2), 121 (3), 81 (M^+ - H_2O and cleavage between C-5 and C-6, 100), 67 (20), 55 (70). For **178**: a light yellow oil (1.24 g, 43%). IR: 1722 and 1641 cm^{-1}. ^1H nmr: δ 8.08 (1H, s, CHO), 5.78 (2H, symmetrical m, H-2 and H-10), 4.93 - 5.00 (4H, m, H-1 and H-11), 5.03 (1H, m, H-6), 2.06 (4H, dq, J = 7.5, 1.5, H-3 and H-9), 1.55 - 1.61 (4H, m, H-5 and H-7), 1.37 - 1.47 (4H, m, H-4 and H-8). ^{13}C nmr: δ 160.8 (CHO), 138.1 (C-2 and C-10), 114.7 (C-1 and C-11), 73.7 (C-6), 33.3 (C-

3, C-9 and C-5, C-7), 24.3 (C-4 and C-8). MS: M^+ not found, 167 (M^+-CO, 2), 149 (9), 109 (11), 95 (20), 81 (76), 41 (100).

1,10-undecadien-6-one (179). To crude **177** (169 mg, 1.01 mmol) in CH_2Cl_2 (10 mL) was added PCC (467 mg, 2.17 mmol) and, to facilitate stirring, a Scoopula-tip of silica gel. The solution was stirred overnight before ether (150 mL) was added, and the solution was filtered through a silica gel plug. Evaporation of the filtrate at reduced pressure gave a yellow oil. Chromatography (5% EtOAc/hexanes) provided **179** (157 mg, 94%). IR: 1715 and 1641 cm^{-1}. ^1H nmr: δ 5.78 (2H, symmetrical m, H-2 and H-10), 4.93 - 5.00 (4H, m, H-1 and H-11), 2.40 (4H, dq, J = 7.5, ~2, H-3 and H-9), 2.05 (4H, br q, H-5 and H-7), 1.62 - 1.72 (4H, m, H-4 and H-8). ^{13}C nmr δ: 210.5 (C-6), 137.8 (C-2 and C-10), 115.0 (C-1 and C-11), 41.8 (C-3 and C-9), 33.0 (C-5 and C-7), 22.6 (C-4 and C-8). MS: 166 (M^+, 0.5), 112 (21), 97 (cleavage between C-5 and C-6, 35), 69 (59), 58 (44), 41 (100). Exact mass calcd. for C_6H_9O (cleavage between C-5 and C-6): 97.0653, found 97.0648.

6-(1',3'-Dioxolan-2'-yl)undeca-1,10-diene (180). To a solution of **179** (114 mg, 0.69 mmol) in benzene (75 mL) was added 1,2-ethanediol (0.20 g, 3.5 mmol) and *p*TSA (~ 0.5 g). The mixture was heated under reflux overnight with azeotropic removal of water. After cooling the solution was washed with H_2O (2 x 50 mL), and then the aqueous layers were re-extracted with ether (2 x 50 mL). The combined organic

solutions were washed with brine (75 mL), dried over $MgSO_4$ and concentrated at reduced pressure. Chromatography (10% EtOAc/hexanes) of the residue afforded **180** as a yellow liquid (122 mg, 84%): IR: 1650 cm^{-1}. ^1H nmr: δ 5.80 (2H, symmetrical m, H-2 and H-10), 4.93 - 5.03 (4H, m, H-1 and H-11), 3.92 (4H, s, dioxolane), 2.05 (4H, br q, J = 7.2, H-3 and H-9), 1.58 - 1.64 (4H, m, H-5 and H-7), 1.40 - 1.50 (4H, m, H-4 and H-8). ^{13}C nmr: δ 138.6 (C-2 and C-10), 114.5 (C-1 and C-11), 111.6 (C-6), 64.9 (dioxolane), 36.5 (C-5 and C-7), 33.8 (C-3 and C-9), 23.0 (C-4 and C-8). MS: no M^+, 141 (cleavage between C-5 and C-6, 100), 99 (57), 69 (13), 55 (18), 41 (43).

2,2-Bis(4'-pentenyl)cyclopentane-1,3-dione (181). From ketal 180: A solution of **180** (104 mg, 0.49 mmol) in CH_2Cl_2 (20 mL) was cooled to -78°C. $BF_3.Et_2O$ (1.05 g, 7.41 mmol) was added at once, followed, dropwise, by the addition of a solution of **1** (350 mg, 1.50 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred overnight during which time the mixture attained room temperature. The reaction solution was washed with water (2 x 30 mL), and the aqueous layers were re-extracted with CH_2Cl_2 (2 x 25 mL). The combined organic solutions were washed with brine (50 mL), dried over $MgSO_4$ and concentrated at reduced pressure. Chromatography (5% EtOAc/hexanes) gave **181** as a yellow oil (36.0 mg, 31%).

From ketone 179: To a solution of **179** (1.96 g, 11.8 mmol) in

CH_2Cl_2 (70 mL) at rt was added $BF_3.Et_2O$ (1.5 mL,12 mmol) followed by **1** (4.7 mL, 18 mmol). Water (0.7 mL) was added after 26 h, followed 10 min later by $BF_3.Et_2O$ (22.0 mL, 1.76 mol). The solution was stirred overnight before being washed with water (2 x 50 mL). The aqueous layers were re-extracted with CH_2Cl_2 (2 x 50 mL). The combined organic solutions were washed with brine (75 mL), dried over $MgSO_4$ and concentrated at reduced pressure. The brown residue was taken up in ether (150 mL) and filtered through a charcoal/Florisil plug (as described in Chapter 1), to give **181** as a red oil (1.89 g, 47%): IR: 1722 and 1641 cm^{-1}. ^1H nmr: δ 5.80 (2H, symmetrical m, H-4' and H-4' of other tether), 4.93 - 5.00 (4H, m, H-5' and H-5' of other tether), 2.71 (4H, s, H-4 and H-5), 1.92 - 1.99 (4H, br q, J = 6.9, H-3' and H-3' of other tether), 1.59 - 1.65 (4H, m, H-1' and H-1' of other tether), 1.14 - 1.25 (4H, m, H-2' and H-2' of other tether). ^{13}C nmr: δ 217.4 (C-1 and C-3), 137.5 (C-4' and C-4' of other tether), 115.2 (C-5' and C-5' of other tether), 60.9 (C-2), 36.2 (C-4 and C-5), 34.7 (C-1' and C-1' of other tether), 33.8 (C-3' and C-3' of other tether), 23.8 (C-2' and C-2' of other tether). MS: no M^+, 205 (2), 167 (52), 141 (26), 125 (25), 112 (44), 99 (21), 81 (34), 67 (54), 55 (69), 41 (100), 39 (42).

5-(1',3'-dioxocyclopentane)nonane-1,9-dial (182). A stream of ozone was bubbled through a solution of **181** (343 mg, 1.47 mmol) in dry CH_2Cl_2 (75 mL) at -78°C until the blue color persisted. Oxygen was

bubbled through the solution until the solution was devoid of color. The solution was placed under a N_2 atmosphere and dimethyl sulfide (3.5 mL) was added. The solution was stirred overnight while it attained room temperature. Concentration at reduced pressure gave a pale yellow oil. Chromatography (20% EtOAc/hexanes) provided a small sample of **182** as a pale yellow oil (70.7 mg, 20%), but the major component was a mixture of **182** and **183**. For **182**: IR: 1720 cm^{-1}. ^1H nmr: δ 9.78 (2H, s, CHO), 2.74 (4H, s, H-4' and H-5'), 1.61 - 1.69 (8H, m, H-2, H-4 and H-6 , H-8), 1.23 - 1.31 (4H, m, H-3 and H-8). ^{13}C nmr δ: 216.6 (C-1' and C-3'), 201.8 (C-1 and C-9), 60.2 (C-2'), 36.1 (C-4' and C-5'), 34.4 (C-2 and C-8), 31.2 (C-4 and C-6), 18.8 (C-3 and C-7). For **183**: the ^{13}C nmr spectrum included resonances at δ 201.2 and 162.9 ppm in addition to those resonances assigned to **182**.

5-(1',3'-Dioxocyclopentane)nonane-1,9-dioic acid (184). The pH of a suspension of **182** (201 mg, 0.84 mmol) in *t*-BuOH (3.2 mL) was adjusted to 5 - 6 by the addition of a 1.2 M phosphate buffer (2.2 mL) before the addition of $KMnO_4$ (3.2 mL of a 1.0 M aqueous solution). The reaction mixture was stirred for 15 min before saturated aqueous Na_2S0_3 (5.0 mL) was added. Adjustment to pH 3 by the addition of ice cold, dilute HCl, was followed by extraction with ether (3 x 35 mL), drying of the combined organic solutions over $MgSO_4$ and concentration at reduced pressure to afford **184** as a yellow oil (117 mg, 51%): IR: 3412

and 1720 cm^{-1}. ^{13}C nmr δ: 216.4 (C-1' and C-3'), 176.9 (C-1 and C-9), 69.6 (C-2 and C-8), 60.5 (C-5), 35.9 (C-4 and C-6), 33.8 (C-4' or C-5'), 33.6 (C-5' or C-4'), 19.5 (C-3 and C-7).

Dimethyl 5-(1',3'-dioxocyclopentane)nonane-1,9-dioate (185). To a solution of crude **184** (5.55 g, 20.6 mmol) in MeOH (100 mL) were added Amberlyst-15 beads (~1 g). This was stirred for 10 h. The beads were removed by filtration, and the solution was concentrated at reduced pressure. The tan residue was purified by dissolving it in ether (100 mL) and filtering the solution through a charcoal/Florisil plug. Concentration at reduced pressure gave **185** (4.57 g, 74%) as a yellow viscous oil: IR: 1735 and 1724 cm^{-1}. ^1H nmr: δ 3.65 (6H, s, ester CH_3), 2.75 (4H, s, H-4' and H-5'), 2.23 (4H, t, J = 7.2, H-4 and H-6), 1.61 - 1.63 (4H, m, H-2 and H-8), 1.45 - 1.48 (4H, m, H-3 and H-7). ^{13}C nmr: δ 216.3 (C-1' and C-3'), 173.0 (C-1 and C-9), 60.4 (C-5), 51.5 (2C, ester CH_3), 35.9 (C-4' and C-5'), 33.72 (C-4 and C-6), 33.66 (C-2 and C-8), 19.7 (C-3 and C-7). MS: 298 (M^+, 3), 266 (5), 234 (19), 221 (8), 179 (14), 151 (32), 137 (17), 115 (31), 97 (29), 79 (28), 55 (100), 41 (71), 39 (10). Exact mass calcd. for $C_{15}H_{22}O_6$: 298.1415; found 298.1419.

6-(1'-(1",3"-Dioxolan-2"-yl)-3'-oxocyclopentane)undeca-1,9-diene (188) and 6-(1',3'-bis(1",3"-dioxolan-2"-yl)cyclopentane)undeca-1,9-diene (189). To a solution of **181** (519 mg, 2.22 mmol) in benzene (75 mL) was added 1,2-ethanediol (2.0 g, 0.30 mol) and *p*TSA (0.5 g). The

reaction mixture was heated under reflux with azeotropic removal of water for approximately 30 h. After cooling, the solution was washed with H_2O (2 x 50 mL), and the aqueous layers were re-extracted with ether (2 x 50 mL). The combined organic solutions were washed with brine (75 mL), dried over $MgSO_4$ and concentrated at reduced pressure. Chromatography (5% EtOAc/hexanes) of the brown residue afforded **188** (297 mg, 48%) as a yellow liquid and **189** (121 mg, 17%) as a dark yellow oil. For **188**: IR: 1740 and 1641 cm^{-1}. ^1H nmr: δ 5.69 (2H, symmetrical m, H-2 and H-10), 4.84 - 4.94 (4H, m, H-1 and H-11), 3.90 (4H, symmetrical narrow m, dioxolane), 2.23 (4H, br t, J = 8.1, H-5 and H-7), 1.89 - 1.99 (4H, m, H-4' and H-5'), 1.53 - 1.64 (2H, m, H-3), 1.35 - 1.46 (2H, m, H-9), 1.21 - 1.31 (4H, m, H-4 and H-8). ^{13}C nmr: δ 216.5 (C-3'), 138.5 (C-2 and C-10), 117.0 (C-1 and C-11), 114.3 (C-1'), 64.5 (dioxolane), 56.0 (C-6), 34.8 (C-5 and C-7), 34.0 (C-4'), 29.6 (C-5'), 27.8 (C-3 and C-9), 22.5 (C-4 and C-8). MS: 278 (M^+, 1), 223 (54), 209 (5), 167 (4), 99 (100), 87 (10), 67 (19), 55 (29), 41 (45). Exact mass calcd. for $C_{17}H_{26}O_3$: 278.1881, found 278.1878. For **189**: IR: 1642 cm^{-1}. ^1H nmr: δ 5.84 (2H, symmetrical m, H-2 and H-10), 4.91 - 5.03 (4H, m, H-1 and H-11), 3.90 (8H, s, dioxolane), 1.99 - 2.05 (4H, q, J = 6.6, H-5 and H-7), 1.88 (4H, s, H-4' and H-5'), 1.54 - 1.61 (4H, m, H-3 and H-9), 1.43 - 1.51 (4H, m, H-4 and H-8). ^{13}C nmr: δ 139.2 (C-1 and C-11), 117.9 (C-1' and C-3'), 114.0 (C-2 and C-10), 64.0 (dioxolane), 52.6 (C-6), 35.0 (C-

3 and C-9), 32.4 (C-4' and C-5'), 27.9 (C-5 and C-7), 23.3 (C-4 and C-8). MS: 322 (M^+, 1), 276 (1), 223 (100), 205 (3), 167 (4), 119 (2), 100 (79), 86 (23), 67 (23), 56 (14), 41 (53), 27 (14). Exact mass calcd. for $C_{19}H_{30}O_4$: 322.2141, found 322.2143.

Attempt to prepare dimethyl 5-(1',3'-bis(1",3"-dioxolan-2"-yl)cyclopentyl)nonane-1,9-dioate (191). Following the procedure previously reported for the transformation of **181** to **185**, noting the following changes: the starting diene being **189** (621.2 mg, 1.93 mmol) and that characterization and purification were omitted. Ozonolysis, oxidation and esterification were performed sequentially on the crude product obtained from the previous sequence. GCMS of the crude product after esterification indicated a mixture of the nonketalized diester **185** (27%): GCMS: no M^+, 234 (23), 189 (21), 164 (17), 151 (29), 123 (26), 105 (25), 67 (35), 55 (100); **dimethyl 5-(1'-(1",3"-dioxolan-2"-yl)-3'-oxocyclopentane)nonane-1,9-dioate 190** (10%): GCMS: no M^+, 255 (13), 241 (10), 179 (12), 151 (13), 137 (13), 99 (100), 86 (18), 55 (62) and **dimethyl 5-(1',3'-bis(1",3"-dioxolan-2"-yl)cyclopentane)nonane-1,9-dioate 191** (42%): GCMS: no M^+, 342 (8), 311 (7), 255 (46), 199 (15), 179 (17), 151 (20), 99 (100), 55 (58). Chromatography (5% to 60% EtOAc/hexanes over 500 fractions) using a small bore column with approximately 10 g of silica was not successful in separating the compounds. None of the fractions collected contained either of the

compounds above despite the increase in polarity to 60%. Stripping the column with EtOAc provided a pale yellow oil (190 mg, 27% if pure) which from GCMS analysis indicated a mixture of **185** (32%), **190** (9%) and **191** (57%). This mixture was not purified but was treated directly with sodium and chlorotrimethylsilane in boiling toluene following the procedure sucessfully used in the preparation of **1**.[17] After boiling in toluene for 9 h, the solution was filtered under a nitrogen atmosphere to give a yellow toluene solution. This filtrate was cooled to -78°C where $BF_3.Et_2O$ (15 equivalents based upon **185**). The solution was stirred overnight where it was allowed to attain rt. The solution was washed with water (2 x 70 mL) and the aqueous solutions were re-extracted with CH_2Cl_2 (2 x 75 mL). The combined organic solutions were washed with brine (70 mL), dried over $MgSO_4$, and concentrated at reduced pressure. Unfortunately, no evidence for the propellane skeleton was found from nmr analysis of the crude product. The major component was identified as **185**.

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17. Bloomfield, J. J.; Nelke, J. M. *Org. Synth.* **1988**, *Coll. Vol. VI*, 167. It was important that **1** be pure, therefore redistillation of **1** under vacuum is strongly recommended if impurities are evident in its ^{1}H nmr.

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Appendix

SUB-APPENDIX 1. DATA TABLES

SUB-APPENDIX 2. ^{1}H NMR SPECTRA

SUB-APPENDIX 1. DATA TABLES

The following abbreviations have been used in the Data Tables.

Column	Column chromatography
Crude	Crude product
days	typically 5 - 8 days
INT	Cyclobutanone intermediate
Kugelrohr	Kugelrohr distillation
LA	Lewis Acid
Neat	Reagent added without dilution
Pdt	2,2-disubstituted 1,3-cyclopentanedione
SM	Starting material
Sub	Substrate
RT	Room temperature
5Ring	1,2-bis(trimethylsilyloxy)-cyclopentene

Table 3: Optimization of Cyclohexanone with 1.

Experiment #	RATIO Ketone 1 BF_3Et_2O	Ketone Conc mol/L	Quantity 1 in CH_2Cl_2	Add^n time min	RXN Sequence	Time	Isolation	Notes
1	1 0 2.5 15	0 03	0 6/6 0	35	-78°C to RT overnight	17 h	Not Isolated Crude 54% GCMS=100%	Diketone not isolated
2	1.0 2 5 15	0.08	2 0/6 0	39	-78°C to RT overnite	27 h	Column yield=31% GCMS=100%	Hard to detect using TLC Crude good, suspect isolation problem
3	1 0 2 5 15 Lewis Acid=$SnCl_4$	0 07	2 0/6 0	35	-78°C to RT overnite	21 h	Not isolated GCMS very messy	4 signals with m/z 166 (intermediate?) Total area still only 30%
4	1 0 2.5 15	0 20	13 5/20 0	50	-78°C to RT overnite	23 h	Kugelrohr 62% GCMS=84%	Corrected yield=52%
5	1 3 3	0 03	1 6/6 0	35	Add^n @ -78°C Stir 2 h warm RT Stir @ RT 1 5 h Silica/conc H_2SO_4 Stir 4 h	6 h	Column yield=75% GCMS=100%	Yield=75% Note GCMS of soln after attaining RT showed only diketone
6	1 3 15	0 03	1 6/6 0	40	-78°C to RT Stir @ RT for days	6 days	Column 65% GCMS=65%	Corrected yield=41% Note no aqueous workup
7	1 0 2 5 15 H_2O/xs BF_3Et_2O	0 03	1 6/6 0	19	Add^n @ -78°C Stir 20 min Warm to RT (1 25 h) prior to refluxing 1 5 h	3 h	Kugelrohr 58% GCMS=91%	Corrected yield=53% Suspect isolation problem as spectra on crude was good
8	1 3 15 H_2O/xs BF_3Et_2O	0 03	1 9/6 0	20	Add^n @ -78°C Stir 20 min Warm to RT (1 25 h) prior to refluxing 1 5 h	3 h	Kugelrohr 75% GCMS 90%	Corrected yield=68%
9	1 3 15	0 03	1 8/6 0	20	Add^n @ -78°C Stir 20 min Warm to RT(1h 15min) prior to refluxing 1 5 h	3 h	Kugelrohr 49% GCMS=68%	Corrected yield=33% Note SM was freshly distilled
10	1 3 15	0 03	1 8/6 0	15	Add^n @ -78°C Stir 20 min Warm to RT(1h 15min) prior to refluxing 1 5 h	3 h	Kugelrohr 55% GCMS 96%	Corrected yield=53%

Table 3: Optimization of Cyclohexanone with **1** (cont.)

Experiment #	RATIO Ketone 1 BF_3Et_2O	Ketone Conc mol/L	Quantity 1 in CH_2Cl_2	Add' time min	RXN Sequence	Time	Isolation	Notes
11	1 3 15	0 03	1 7/6 0	22	Add' @ -78°C Stir 20 min Warm to RT(1', 15min) prior to refluxing 1 5 h Stir @ RT days	41 h	Kugelrohr 50% GCMS 100%	Yield=50%
12	1 0 1 2 1 0	0 24	0 7/4 0	18	Add' @ -78°C Stir 3 h	3 h	Aqueous workup mostly intermediate Sample diluted and treated with xs BF_3Et_2O -78°C to RT overnite	Crude GCMS>95% intermediate Only trace of diketone
13	1 0 1 5 1 0 H_2O/xs BF_3Et_2O	0 24	0 9/4 0	20	Add' @ -78°C Stir 3 h Warm to RT (2 h) H_2O (10 min) Recool to -78°C xs BF_3Et_2O -78°C to RT overnight	24 h	charcoal/Florisil yield=84% Spectra good	Yield=85%
14	1 0 1.5 1 0 H_2O/xs BF_3Et_2O	0 24	0 9/4 0	18	Add' @ RT Stir 1h H_2O (10 min) xs BF_3Et_2O Stir 40 min	2 h	charcoal/Florisil yield=78% NMR good	NMR integration not exact may be some SM??
15	1 0:1.5 1.0 H_2O/xs BF_3Et_2O	0 24	0 9/4 0	19	Add' @ RT Stir 5 min H_2O (10 min) xs BF_3Et_2O Stir 30 min	0 5 h	charcoal/Florisil yield=70%	Some unknown (trace) also detected in NMR
16	1.0:1 5 1.0 H_2O/xs BF_3Et_2O	0 25	0 9	Neat	Add' @ RT Stir 1 h $[CH_3(CH_2)_3]_4NF$ xs BF_3Et_2O Stir 1 h	2 h	NOT ISOLATED Crude GCMS 69% and 23% intermediate	Note TBAF used instead of H_2O
17	1.0:1 5 1 0 H_2O/xs BF_3Et_2O	0 25	1 2	Neat	Add' @ RT Stir 1h H_2O (10 min) xs BF_3Et_2O Stir 1h	2 h	charcoal/Florisil yield=86% All spectra good	Yield=86%

Table 3: Optimization of Cyclohexanone with **1** (cont.)

Experiment #	RATIO Ketone 1 BF_3Et_2O	Ketone Conc. mol/L	Quantity 1 in CH_2Cl_2	Add^n time min	RXN Sequence	Time	Isolation	Notes
18	1.0.1.5 1 0 H_2O/xs BF_3Et_2O	0 22	0 8	Neat	Add^n @ RT Stir 1 h xs BF_3Et_2O Stir 1 h	2 h	charcoal/Florisil yield=61% GCMS=53%	Incomplete reaction GCMS also showed 42% intermediate Note no H_2O added.
19	1.0 1 5 1 0 H_2O/xs BF_3Et_2O	0 23	0 9	Neat	Add^n @ RT Reflux 1 h Cool (15 min) xs BF_3Et_2O Stir 1 h	2 5 h	charcoal/Florisil yield=39% GCMS= 49%	Incomplete Rxn GCMS also showed 12% SM Note no H_2O added
20	1 0 1 5 1 0 H_2O/xs BF_3Et_2O	0 24	0 9/4 0	20	Add^n @ -78°C Stir 3h Warm to RT (1 5h) H_2O (10 min) Recool to -78°C xs BF_3Et_2O Stir overnight	23 h	charcoal/Florisil yield=94% Spectra good	Yield=94%
21	1 3 3 H_2O/xs BF_3Et_2O	0 10	1 6	Neat	Add^n @ RT Stir 22 h H_2O (10 min) xs BF_3Et_2O Stir 3 h	26 h	Column Yield=59% ~2% recovery of diketone used as dope	Note sample doped with another spiro diketone but both had same Rf

Table 4: Optimization of 2-Methylcyclohexanone with **1**.

Experiment #	RATIO Ketone 1 BF_3Et_2O	Ketone Conc mol/L	Quantity 1 in CH_2Cl_2	Add' time min	RXN Sequence	Time	Isolation	Notes
1	1 0 2 5 15	0 03	0 8/4 5	25	-78 C to RT overnight	19 h	Not isolated GCMS=31%	Diketone not isolated Very messy chromatograph
2	1 0 2 5 15 Lewis Acid=$SnCl_4$	0 06	1 4/6 0	35	-78 C to RT overnight	26 h	Not isolated GCMS=6%	$SnCl_4$ catalysis very poor for diketone formation
3	1 0 2 5 15	0 05	1 3/6 0	35	-78 C to RT overnight	27 h	Not isolated GCMS very messy	GCMS showed diketone 41% and opened diketone isomers 17 and 19%
4	1 0 2 5 15	0 07	1 8/6 0	20	-78 C to RT overnight	24 h	Column yield=18% GCMS=98%	Corrected yield=17%
5	1 0 2 5 15	0 07	2 0/6 0	25	-78 C to RT Stir @ RT for days	4 days	Column yield=26% GCMS=100%	Yield=26% Note GCMS of crude showed 58% diketone and 25 and 11% of opened isomers
6	1 8.15	0 02	Added in sequence of 3, 3, 1 and 1 eq	Neat	Add' @ RT Reflux days	2 days	Kugelrohr 56% GCMS=59%	Corrected yield=33% GCMS showed 19% SM
7	1 7.15	0 01	8 additions of 1 eq	Neat	LA added @ RT 1 added @ reflux	2 days	Kugelrohr=62% GCMS=50%	Corrected yield=31% GCMS showed 14% SM Additional 1 did not improve yield
8	1 3.15 then BF_3Et_2O and TFA	0 07	1.6/6 0	32	Add' @ -78 C Stir 7 h 15 eq BF_3Et_2O Stir overnight	24 h	Aqueous workup Retreat crude with BF_3Et_2O Aqueous workup Retreat crude with TFA	GCMS results SM . pdt Int 5 40 42 (normal) 0 .74 .16 (2nd BF_3Et_2O) 28 .69 0 (TFA)
9	1.0.1 5.1 0	0 20	0 8/4 0	21	Add' @ -78 C Stir 3 h Quench @ -78 C	3 h	Crude SM 12%, pdt 2%, and int 70% was treated with TFA	charcoal/Florisil GCMS SM 56% and pdt 42% No int present
10	1 0 1 5 1 0 H_2O/xs BF_3Et_2O	0 21	0 8	Neat	Add' @ RT Stir 1 h H_2O (10 min) xs BF_3Et_2O Stir 1 h	2 h	charcoal/Florisil yield=63% GCMS=91%	Corrected yield=57%

Table 4: Optimization of 2-Methylcyclohexanone with **1** (contd.)

Experiment #	P⁺TiO Ketone 1.BF_3Et_2O	Ketone Conc mol/L	Quantity 1 in CH_2Cl_2	Add⁺ time min	RXN Sequence	Time	Isolation	Notes
11	1 0 1.5 1 0 H_2O/xs BF_3Et_2O	0 20	0 7	Neat	Add⁺ @ RT Stir 2 h H_2O (10 min) xs BF_3Et_2O Stir 1 h	3 h	charcoal/Florisil yield=49% GCMS=40%	GCMS also showed 17% SM and 35% intermediate
12	1 0 1 5 1 0 H_2O/xs BF_3Et_2O	0 23	0 8	Neat	Add⁺ @ RT Stir 1 h H_2O (10 min) xs BF_3Et_2O Stir 18 h	18 h	charcoal/Florisil yield=62% NMR pure	Yield=62% Suggests rearrangement step requires more than 2 h See experiments 10 & 11
13	1 0 1 5 1 0 H_2O/xs BF_3Et_2O	0 23	0 9	Neat	Add⁺ @ RT Stir 1 h H_2O (10 min) xs BF_3Et_2O Stir overnight	1⁺ h	charcoal/Florisil yield=47% NMR good trace of SM GCMS=79%	Yield=47%
14	1 0 1 5 1 0 H_2O/xs BF_3Et_2O	0 22	0 8	Neat	Add⁺ @ RT Stir 1h H_2O (10 min) xs BF_3Et_2O Stir 1 h	2 h	charcoal/Florisil yield=65% GCMS 2% SM 55% pdt and 29% intermediate	¹C NMR complex mixture of intermediate and diketone
15	1 0 1 5 1 0 H_2O/xs BF_3Et_2O	0 23	0 9	Neat	Add⁺ @ RT Stir 1h H_2O (10 min) xs BF_3Et_2O Stir overnight	20 h	charcoal/Florisil yield=~7% GCMS=60%	Some SM detected in NMR-20:1 Yield=~40%
16	1 0 1 5 1 0 H_2O/xs BF_3Et_2O	0 22	0 8	Neat	Add⁺ @ -78°C Stir 2 h Warm to RT (1 5h) H_2O (10 min) Recool to -78°C xs BF_3Et_2O Stir overnight	23 h	charcoal/Florisil yield=65% GCMS only 28%	Note SM 44% suggesting -78 C is not as effective as RT for aldol step See entry 15
17	1 3 3 H_2O/xs BF_3Et_2O	0 19	1 4	Neat	Add⁺ @ RT Stir 4h H_2O (10 min) xs BF_3Et_2O Stir 3 days	3 days	charcoal/Florisil yield=96% GCMS=79%	Corrected yield=75%

Table 5. Optimization of Norcamphor with **1**.

Experiment #	RATIO Ketone 1 BF_3Et_2O	Ketone Conc mol/L	Quantity 1 in CH_2Cl_2	Add^n time min	RXN Sequence	Time	Isolation	Notes
1	1.0 2.5 1.5 0	0.02	0.4/7.0	35	-78°C to RT overnight Recool to -78°C Stir 2 h	20 h	No pdt isolated GCMS=100% SM	73% recovery of SM
2	1.0 2.5 1.5 0	0.07	1.5/6.0	20	-78°C to RT overnight	20 h	Column yield=42% GCMS=100%	Yield=42%
3	1.8 1.5	0.07	4.5/5.0	25	-78°C to RT overnight Stir days	2.5 days	Column yield=12%	Soln had polymerized possibly due to xs 1 hence suspect pdt still trapped in gel
4	1.8 1.5	0.08	5.0/6.0	28	-78°C to RT overnight	19 h	Column unsuccessful No pdt detected Again heavy gel problem on workup-polymer	xs 1 does not improve yield
5	1.0 2.5 1.5 0	0.01	1.0/7.0	23	-78°C to RT overnight	25 h	Column yield=53%	TLC of crude was good Suspect isolation problem
6	1.3 1.5	0.03	7.0/10.0	35	-78°C to RT	28 h	Kugelrohr 79% GCMS=60%	Corrected yield=47% Note GCMS also showed 31% SM
7	1.3 1.5	0.03	1.6/6.0	19	Add^n @ -78°C Stir 20 min Warm to RT (1.25 h) prior to refluxing 1.5 h	3 h	Kugelrohr 58% GCMS=91%	Corrected yield=53% Suspect isolation problem as spectra on crude was good
8	1.3.1.5	0.02	4.0/10.0	30	Add^n @ -78°C Aliquots removed and studied using GCMS	10 h	No pdt even after 1.5 h @ -78°C Pdt only detected at temp 0°C or higher Ratio levelled 1 to 3 in favour of pdt	Note some SM remained even after @ RT for 3 h Final ratio 17% SM and 73% pdt with total rxn time 9 h

Table 5. Optimization of Norcamphor with **1** (contd.).

Experiment #	RATIO Ketone 1.BF_3Et_2O	Ketone Conc. mol/L	Quantity 1 in CH_2Cl_2	Add' time min	RXN Sequence	Time	Isolation	Notes
9	1.3.15	0.02	4.0/10.0	15	Add' @ -78°C Warm to RT(1h) prior to refluxing days	2 days	Aliquots removed and quenched at intervals during reflux. Ratio determined by GCMS	After 7 h reflux pdt 81% and SM 8% As reflux time increases pdt % decreases and int detected After 23 h reflux 7% SM remained 1 eq 1 added next GCMS 1 h later no SM Note pdt maintained 85% and int 12%
10	1.3.15	0.02	4.0	Neat	Add' @ RT Then reflux	23 h	GCMS showed only SM	Suspect immediate reflux does not allow the initial aldol step to proceed
11	1.0.4.5.15.0 Initially 3 eq of 1 ; ien additional 1.5 eq added	0.02	4.0/10.0	12	Add' @ -78°C Warm to RT(1h 15mn) prior to refluxing overnight	26 h	Kugelrohr 94% GCMS=70% also 11% SM	Corrected yield=66% GCMS after 20 h showed 1:1 SM pdt After more 1, SM ~6%
12	1.0.1.5.1.0 H_2O/xs BF_3Et_2O	0.21	0.8	Neat	Add' @ RT Stir 2h H_2O (10 mn) xs BF_3Et_2O Stir 1 h	3 h	charcoal/Florisil yield=76% GCMS=83% and 4% SM NMR very good	Corrected yield=63%
13	1.0.1.5.1.0 H_2O/xs BF_3Et_2O	0.25	0.9	Neat	Add' @ RT Reflux 1 h Cool (15 mn) add H_2O (10 mn) xs BF_3Et_2O Stir 1 h	2 h	charcoal/Florisil yield=54% GCMS=100%	Yield=54%
14	1.0.1.5.1.0 H_2O/xs BF_3Et_2O	0.19	0.7	Neat	Add' @ RT Reflux 1 h Cool (15 mn) add H_2O (10 mn) xs BF_3Et_2O Stir 1 h	2 h	charcoal/Florisil yield=76% GCMS=100%	Yield=76%

Table 5. Optimization of Norcamphor with **1** (contd.).

Experiment #	RATIO Ketone 1 BF_3Et_2O	Ketone Conc mol/L	Quantity 1 CH_2Cl_2	Add' time min	RXN Sequence	Time	Isolation	Notes
15	1.0:1.5:1.0 H_2O/xs BF_3Et_2O	0.21	0.8	Neat	Add' @ RT Stir 1 h H_2O (10 min) xs BF_3Et_2O Stir 1 h	2 h	charcoal/Florisil yield=75% GCMS=100% NMR good	Reflux as above is not required
16	1.0:1.5:1.0 H_2O/xs BF_3Et_2O	0.23	0.8	Neat	Add' @ RT Stir 1 h H_2O (10 min) xs BF_3Et_2O Stir 1 h	2 h	charcoal/Florisil yield=72% GCMS=95% NMR good	Corrected yield=68%
17	1.0:1.5:1.0 H_2O/xs BF_3Et_2O	0.20	0.8	Neat	Add' @ RT Stir 1h H_2O (10 min) xs BF_3Et_2O Stir overnight	18 h	charcoal/Florisil yield=41% NMR showed mixture of SM and pdt	Incomplete Rxn
18	1:3:15	0.03	1.5/6.0	30	Add' @ -78°C Stir 1.5 h Warm to RT Stir 18 h Note silica and H_2SO_4 added after 3 h	21 h	Column yield=11% GCMS=53%	Suggests H_2O and xs BF_3Et_2O are required for useful yields
19	1:3:3	0.03	1.5/6.0	30	Add' @ -78°C Stir 2 h Warm to RT(1.5 h) add silica and H_2SO_4 Stir 1 h	5 h	Column yield=8% GCMS=94%	Poor yield
20	1:2.5:15	0.02	1.4/6.0	35	Add' @ -78°C Allow to attaint RT Stir RT days	6 days	Column yield=4% GCMS=100%	Yield=4%
21	1.0:1.5:1.0 H_2O/xs BF_3Et_2O	0.22	0.8	Neat	Add' @ RT Stir 1 h H_2O (10 min) xs BF_3Et_2O Stir 1 h	2 h	charcoal/Florisil yield=91% GCMS=71%	GCMS indicated 6 % SM and 16% INT
22	1.0:1.5:1.0 H_2O/xs BF_3Et_2O	0.23	0.9/4.0	15 min	Add' @ -78°C Warm to RT(1.5 h) H_2O (10 min) Recool to -78°C xs BF_3Et_2O Stir overnight	24 h	charcoal/Florisil yield=75% GCMS=81%	GCMS also showed 10% int

Table 6: Optimization of Isophorone with **1**.

Expenment #	RATIO Ketone 1 BF_3Et_2O	Ketone Conc. mol/L	Quantity 1 in CH_2Cl_2	Add° time min	RXN Sequence	Time	Isolation	Notes
1	1.0 2.5 1.5 0	0.01	0.4/5.0	33	-78°C to RT overnight Recool to -78°C (4 h)	26 h	Not isolated Only SM identified	No evidence for diketone
2	1 5 15	0 04	2.2/5 0	20	-78°C to RT overnight Stir @ RT	3 days	Column yield=32% GCMS=100%	Suspect low yield due to polmerization(xs 1 used)
3	1.3 3	0 02	1 2/6 0	35	Add° @ -78°C Stir 1h 40 min Warm to RT (1 5 h) Silica / H_2SO_4 Stir 1 h	4 h	Column yield=20% GCMS=91%	Corrected yield=18% 45% based on recovered SM
4	1 3 15	0 02	1 2/6 0	13	Add° @ -78°C Stir 20 min Warm Rt (1h 15min) Reflux 1 5 h	3 h	Kugelrohr GCMS=100% SM	No diketone detected 99% recovery of SM
5	1 3 15	0 02	1 4/6 0	20	Add° @ -78°C Stir 20 min Reflux 3 days	3 days	Kugelrohr yield=69% GCMS=32%	GCMS showed 60% SM Pdt isomers w r t double bond only 7 3 and 25%
6	1 3 15	0 16	1 3/6 0	16	-78°C to RTovernight Stir @ RT days	3 days	Column yield=33% GCMS=100%	Yield=33%
7	1 3 15	0 03	1 2/6 0	20	-78°C to RT overnight Stir @ RT days	5 days	Column yield=33% GCMS=92%	Corrected yield=27% Note GCMS showed 8% of double bond (shifted) pdt
8	1 0 1 5 1 0 H_2O:xs BF_3Et_2O	0 17	0 6	Neat	Add° @ RT Stir 3h H_2O(10 min) xs BF_3Et_2O Stir 40 min	4 h	Not isolated Crude GCMS 77% SM Pdt only 8 and 14%	Incomplete rxn Note pdt ~1 1 ratio of shifted and unshifted double bond isomers
9	1 0 1 5 1 0	0 16	0 6	Neat	Add° @ RT Stir days	3 days	charcoal/Fionsil yield=60% GCMS=25% SM only 51% pdt	Very little pdt Suggests that H_2O and xs BF_3Et_2O are needed
10	1 1 5 1 0 $[CH_3(CH_2)_3]_4NF^-$ xs BF_3Et_2O	0 16	0 6	Neat	Add° @ RT Stir 1h $[CH_3(CH_2)_3]_4NF^-$ (10min) xs BF_3Et_2O Stir 1 h	2 n	Not isolated Crude GCMS showed SM 38% and pdt 54%	Suspect insufficient rxn time

Table 7: Optimization of 1-Indanone with **1**.

Experiment #	RATIO Ketone:1 BF_3Et_2O	Ketone Conc mol/L	Quantity 1 in CH_2Cl_2	Add^n time min	RXN Sequence	Time	Isolation	Notes
1	1:3:15	0.02	1.3/6.0	15	Add^n @ -78°C Stir 20 min Warm to RT (1h10mn) prior to refluxing 1.5 h	3 h	Column yield=5% GCMS=83%	Crude GCMS=97% Stripping of column gave a dark oil GCMS 68% pdt
2	1:3:15	0.02	1.4/6.0	18	Add^n @ -78°C Stir 20 min Warm to RT (1h10mn) prior to refluxing 1.5 h	3 h	Kugelrohr=72% GCMS=93%	Corrected yield=67% Note Kugelrohr appears superior for isolation over column
3	1:4:15	0.02	1.7/6.0	18	Add^n @ -78°C Stir 20 min Warm to RT (1h10mn) prior to refluxing 1.5 h	3 h	Kugelrohr=78% GCMS=95%	Corrected yield=74%
4	1:3:15	0.17	1.3/6.0	20	Add^n @ -78°C Stir 20 min Warm to RT(40mn) Stir 46 h	3 days	Column yield=49% GCMS=98%	Corrected yield=48% Note other fractions collected after pdt and GCMS showed 85% M$^+$=200 but retention time was 4 min longer (intermediate)
5	1.0:1.5:1.0 H_2O/xs BF_3Et_2O	0.18	0.7/4.0	16	Add^n @ RT Stir 5 min H_2O (10 min) xs BF_3Et_2O Stir 30 min	30 min	charcoal/Florisil yield=75% GCMS=51% and SM 49%	Note 1 to 1 mixture of SM to pdt suggests there was insufficient time allowed for initial aldol step
6	1.0:1.5:1.0 H_2O/xs BF_3Et_2O	0.18	0.7/4.0	20	Add^n @ RT Stir 1 h H_2O (10 min) xs BF_3Et_2O Stir 30 min	1.5 h	charcoal/Florisil yield=73% NMR showed diketone with trace of SM and ether	Corrected yield=71% With aldol step rxn time increased from 5 min to 1 h, yield increased by 40%
7	1.0:1.5:1.0 H_2O/xs BF_3Et_2O	0.16	0.6	Neat	Add^n @ RT Stir 1 h H_2O (10 min) xs BF_3Et_2O Stir 1.5 h	3 h	Charcoal plug only Sample colored and contained some charcoal	Note Florisil needed to obtain cleaner samples
8	1.0:1.5:1.0 H_2O added at start xs BF_3Et_2O	0.17	0.6	Neat	H_2O added at start Add^n @ RT Stir 1 h xs BF_3Et_2O Stir 1.5 h	1.5 h	Not isolated Crude GCMS 100% SM	Critical that the aldol step be anhydrous Suggests H_2O needed for rearrangement of intermediate

Table 7: Optimization of 1-Indanone with **1** (contd.).

Experiment #	RATIO Ketone:1 BF_3Et_2O	Ketone Conc. mol/L	Quantity 1 in CH_2Cl_2	Add^n time min	RXN Sequence	Time	Isolation	Notes
9	1.0:1.5:1.0 H_2O/xs BF_3Et_2O	0.17	0.65/4.0	20	Add^n @ -78°C Stir 3 h Warm to RT(1h) H_2O/xs BF_3Et_2O Recool to -78°C Stir overnight	20 h	charcoal/Florisil yield=76% GCMS=89%	GCMS showed 9% SM NMR 1.2 to1.0 pdt:SM
10	1.0:1.5:1.0 H_2O/xs BF_3Et_2O	0.16	0.6	Neat	Add^n @ RT Stir 1 h $[CH_3(CH_2)_3]_4NF$ xs BF_3Et_2O Stir 1 h	2 h	charcoal/Florisil yield=71% GCMS=100%	NMR showed some SM 15 to 1 from integration
11	1.0:1.5:1.0 H_2O/xs BF_3Et_2O	0.17	0.7	Neat	Add^n @ RT Stir 1 h H_2O/xs BF_3Et_2O Stir 1 h	2 h	charcoal/Florisil yield=63% GCMS=67% SM 23%	Incomplete rxn
12	1.0:1.5:1.0 H_2O/xs BF_3Et_2O	0.17	0.7	Neat	Add^n @ RT Reflux 1 h Cool (15 min) H_2O/xs BF_3Et_2O Stir 1 h	2 h	charcoal/Florisil yield=67% GCMS=100%	NMR and GCMS excellent
13	1.0:1.5:1.0 H_2O/xs BF_3Et_2O	0.17	0.6	Neat	Add^n @ RT Reflux 1 h Cool (15 min) xs BF_3Et_2O Stir 1 h	2 h	charcoal/Florisil yield=61% GCMS=81% SM 18%	Note no H_2O added yet incomplete rxn
14	1.0:1.5:1.0 H_2O/xs BF_3Et_2O	0.19	0.7	Neat	Add^n @ RT Reflux 21 h Cool (15 min) xs BF_3Et_2O Stir 1 h	22 h	charcoal/Florisil yield=63% GCMS=100%	Note no H_2O yet complete rxn in this case where the initial aldol step was subject to reflux conditions
15	1:3:3 H_2O/xs BF_3Et_2O	0.18	1.3	Neat	Add^n @ RT Stir 3 h H_2O (10 min) xs BF_3Et_2O Stir days	3 days	charcoal/Florisil yield=76% GCMS=89% NMR good	Corrected yield=67%
16	1:3:3 H_2O/xs BF_3Et_2O	0.17	1.2	Neat	Add^n @ RT Stir 3 h H_2O (10 min) xs BF_3Et_2O Stir days	4 days	charcoal/Florisil yield=76% GCMS=89% NMR good	Same sample repurified by column chromatography yield=38% GCMS=100% NMR excellent

Table 8: Optimization for the Geminal Acylation of **171** with 1,2-bis(trimethylsilyloxy)cyclobutene.

Experiment #	Sub/5Ring/LA	Molar Conc	Conditions	Crude	Notes
1	1.0:1.5:15.0	0.06	Cool to -78°C Stir overnight 5Ring added as soln over 30 min	Mixture of SM and diketone. Flash, impure pdt, SM recovered	Hydrolysed SM and impure diketone
2	1.0:2.5:15.0	0.07	Cool to -78°C Add LA stir 30 min then 5Ring over 30min. Stir 19h	Crude GCMS pdt 62% and INT 36%	Column failed to give any pure diketone
3	1.0:2.5:15.0	0.08	Cool to -78°C Add LA stir 30 min then 5Ring over 17h. Stir 48h	Crude messy pdt only 16% by GCMS	addⁿ of 5ring soln over long period gave poor yield
4	1.0:2.5:15.0	0.06	Cool to -78°C 5Ring added fast (5 min)	Hydrolysed SM no pdt detected	No pdt with fast addⁿ of 5Ring
5	1.0:3.5:15.0	0.07	Cool to -78°C add 2.5 eq 5Ring stir 19h add1eq 5Ring stir 2 h	Messy crude pdt, no diketone detected	Sequence failed to provide pdt
6	1.0:2.5:15.0	0.06	Cool to -78°C Add 5Ring stir @ -78°C 48 h	Pdt only 13% by GCMS	Very little rxn @ -78°C 48 h
7	1.0:2.5:15.0	0.06	Cool to -78°C Add 5Ring 1h Stir overnight	Mostly hydroysed SM	Only trace of pdt in GCMS
8	1.0:2.5:15.0	0.05	Cool to -78°C Add 5Ring Stir overnight Then @ rt 50h total	Crude GCMS 100% pdt No hydrolysed SM detected	Florisil/ charcoal removed most of the color
9	1.0:2.5:15.0	0.06	Cool to -78°C stir for 48h	Crude GCMS 9% pdt, 21% hydrolysed SM	Still SM unlike entry 8 where soln stirred @ rt

Table 8: Optimization for the Geminal Acylation of **171** with 1,2-bis(trimethylsilyloxy)cyclobutene (cont.).

Experiment #	Sub/5Ring/LA	Molar Conc	Conditions	Crude	Notes
10	1.0:2.5:15.0	0.12	Cool to -78°C Warm to rt overnight then stir for 26h	Crude GCMS pdt 85% but TLC very streaky	Florisil x 5 Yield = 27%
11	1.0:2.5:15.0	0.16	Cool to -78°C Warm to rt overnight then stir for 26h	Crude GCMS, pdt major signal but only 50%	Florisil Yield = 58%
12	1.0:2.5:15.0	0.09	Cool to -78°C Warm to rt overnight then stir for 26h	Rxn divided into 3 portions, all pooled after aqueous	Crude not as good for more conc runs but 5Ring was not fresh
13	1.0:2.5:15.0	0.08	Cool to -78°C Warm to rt overnight then stir for 26h	Two identical runs pooled for workup	Crude GCMS 65% pdt, INT 20%
14	1.0:2.5:15.0	0.19	Cool to -78°C Warm to rt overnight then stir for 26h	Crude GCMS pdt 45%	Unknown detected 55%
15	1.0:2.5:15.0	0.27	Cool to -78°C Warm to rt overnight	Crude GCMS only 60% pdt	Unknown (m/z 243) 22% also detected
16	1.0:1.9:15.0	0.10	Cool to -78°C Warm to rt overnight	Crude GCMS pdt only 29% mostly SM	Less than 2.5eq 5Ring not as effective
17	1.0:2.5:15.0	0.07	Cool to -78°C Warm to rt overnight then stir 25h	Crude GCMS pdt 100%	Used without purification in next step

Table 9: Attempt to prepare **174**.

Experiment #	Sub/1/LA	Molar Conc	Conditions	Crude	Notes
1	1.0:2.5:15.0	0.03	Cool to -78°C Stir overnight 1 added as soln over 60 min	No diketone only SM detected in GCMS	Hydrolysed SM and impurity from 1
2	1.0:8.0:15.0	0.02	Cool to -78°C Stir overnight 1 added as soln over 60min	Crude GCMS no pdt, only hydrolysed SM	Additional 1 failed to give pdt.
3	1.0:3.0:15.0	0.02	Cool to -78°C Stir overnight 1 added as soln over 60 min	Crude GCMS no diketone	Hydolysed SM, no pdt
4	1.0:2.5:15.0 LA=$SnCl_4$	0.02	Cool to -78°C Stir overnight 1 added as soln over 60 min	Crude SM 33% and pdt 27%. Change in LA resulted in emulsions	Emulsions v ry severe during work-up
5	1.0:3.0:15.0 LA=$SnCl_4$	0.02	Cool to -78°C Warm to rt overnight, stir 2 days @ rt. 1 added as soln over 60 min	Crude SM 37% and pdt 18%. Similar to experiment 4 despite the increase time	Additional time did not irnprove ratio of SM:pdt. Some pdt detected
6	1.0:2.5:15.0 LA=$SnCl_4$	0.02	Cool to -78°C Remove after add^{n}s.Stir 2 days. 1 added as a soln over 1 h	No pdt detected only SM. Appears temp -78°C beneficial	Removing immediately from -78°C appears to prohibit the rxn
7	1.0:2.5:15.0 LA=$TiCl_4$	0.01	Keep @-78°C overnight quench cold	No pdt detected	$TiCl_4$ as catalyst. NR
8	1.0:2.5:15.0 LA=$SnCl_4$	0.02	Keep @-78°C overnight. Warm to rt	Trace of pdt <1%	Very little rxn. Longer rxn time required
9	1.0:2.5:15.0 LA=$SnCl_4$	0.01	Add^n @ rt stir 22 h	Crude no pdt	Appears add^n @ -78°C best

Table 9: Attempt to prepare **174** (cont.).

Experiment #	Sub/1/LA	Molar Conc	Conditions	Crude	Notes
10	1.0:2.5:15.0 LA=$SnCl_4$	0.01	Cool to -78°C Warm to rt overnight then stir for 26h	Crude GCMS no pdt only hydrolysed SM	Rxn not predictable
11	1.0:2.5:15.0 LA=$SnCl_4$	0.01	Cool to -78°C Warm to rt overnight	No pdt detected	Only hydrolysed SM
12	1.0:2.5:15.0 LA=$SnCl_4$	0.01	Cool to -78°C Warm to rt overnight Recool stir overnight	No pdt detected	Cannot reproduce result for pdt
13	1.0:2.5:2.0 LA=$SnCl_4$	0.01	Cool to -78°C Warm to rt overnight	No pdt detected	Less LA did not destroy all the SM (ketal).
14	1.0:2.5:15.0 LA=$SnCl_4$	0.01	Cool to -78°C Warm to rt overnight then recool for 3.5h Warm to rt	Crude GCMS no pdt	Fresh LA used but still no pdt
15	1.0:2.5:15.0	0.01	Cool to -78°C Warm to rt overnight	Crude GCMS no pdt	BF_3 etherate used no pdt
16	1.0:2.5:15.0	0.01	Cool to -78°C Warm to rt overnight Recool stir 3.5h	Crude GCMS no pdt	Adjusted pH to 7 and re-extracted still no pdt
17	1.0:2.5:15.0 LA=$SnCl_4$	0.02	Cool to -78°C Warm to rt overnight Recool stir 3h	Crude GCMS pdt 8%	Pdt detected but major hydrolysed SM

Table 9: Attempt to prepare **174** (cont.).

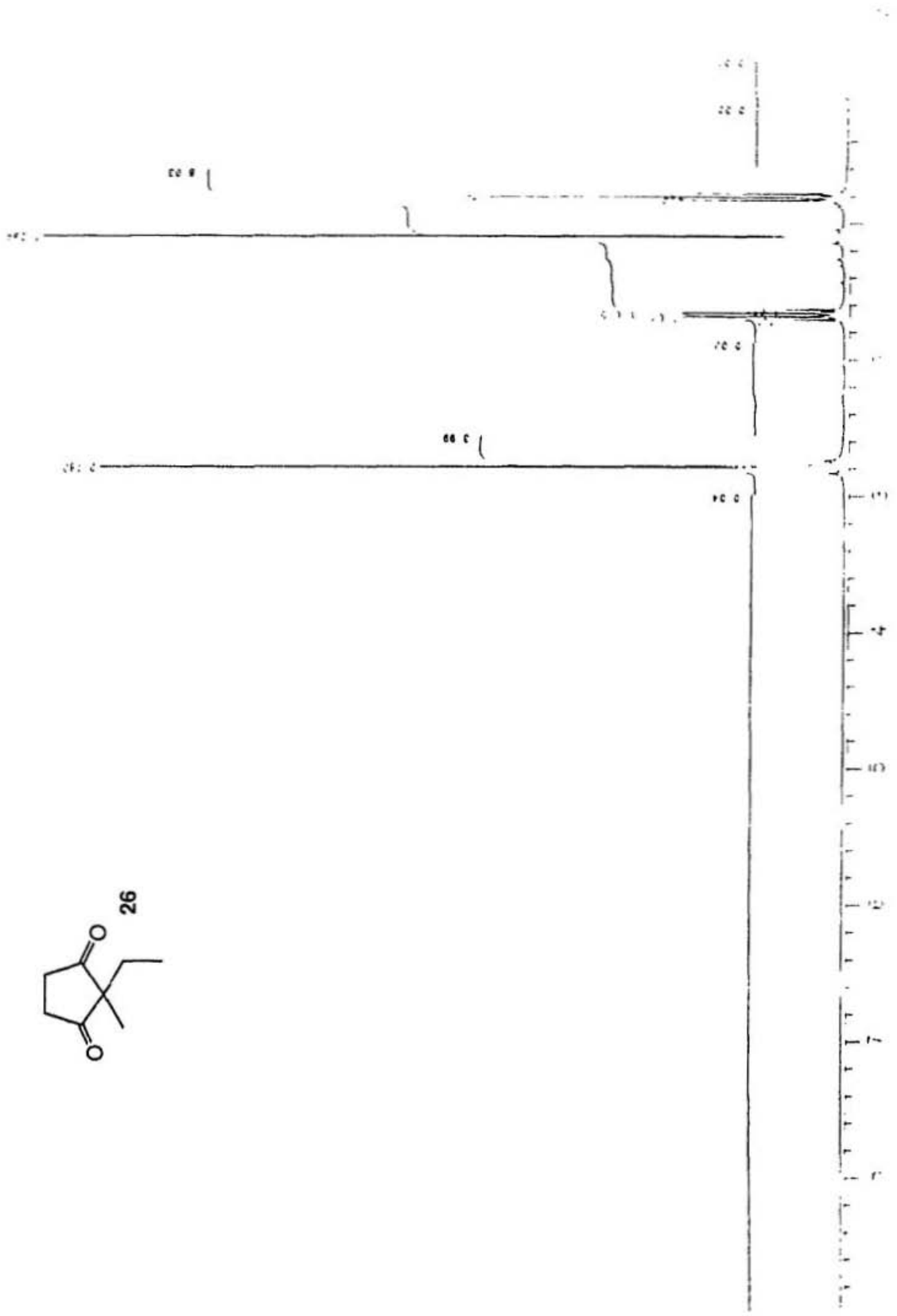
Experiment #	Sub/1/LA	Molar Conc	Conditions	Crude	Notes
18	1.0:2.5:15.0 LA=$SnCl_4$	0.01	Cool to -78°C Warm to rt overnight	GCMS showed pdt with only 18% peak area	filtered thru celite to aid emulsion before extraction
19	1.0:10.0:15.0 LA=$SnCl_4$	0.02	Cool to -78°C Warm to rt overnight Recool stir 3.5h	pdt ~1% hydrolysed SM 21%	GCMS complex suspect due to xs **1**

Table 10: Attempt to Access the Propellane Skeleton from **185**.

Entry	185/Na/TMS	185/toluene	rxn time	Procedure
1	1.0:8.5:6.7	0.024	10.5 h reflux	Reflux add **185**/TMSCl over 2h. Reflux additional 8 h. Cool and filter. $BF_3.Et_2O$ (3eq) added immediately after filtration and soln stirred overnight under N_2. H_2O/xs $BF_3.Et_2O$ added and solution further stirred overnight.. Aqueous work-up was followed by treatment of the crude with PCC. Stir 1h before filtering through silica. No carbonyl signals in ^{13}C nmr spectrum (very complex). Does not appear to indicate propellane, polymeric material formed.
2	1.0:4.0:4.0	0.008	4.5 h)))))	Na/toluene, ultasound for 1 h prior to the add^n of **185**/TMSCl soln over 1 h. The mixture was further irridated for an additional 1 h. Solution filtered under N_2 where xs $BF_3.Et_2O$ was immediately added. Solution stirred overnight. Aqueous work-up followed by spectral analysis showed major signal to be the starting ester, **185**.
3	1.0:6.0:6.0	0.009	2 h)))))	Na/toluene ultasound for 10 min prior to the add^n **185**/TMSCl soln over 10 min. The mixture was further irridated for an additional 2 h. Solution filtered under N_2 where xs $BF_3.Et_2O$ was immediately added. Solution stirred overnight. Aqueous work-up followed by spectral analysis showed major signal to be the starting ester, **185**.

SUB-APPENDIX 2. ^{1}H NMR SPECTRA.

The ^{1}H nmr spectra of the synthetic samples are arranged in the order in which they appear in the text and unless otherwise noted were recorded in $CDCl_3$.



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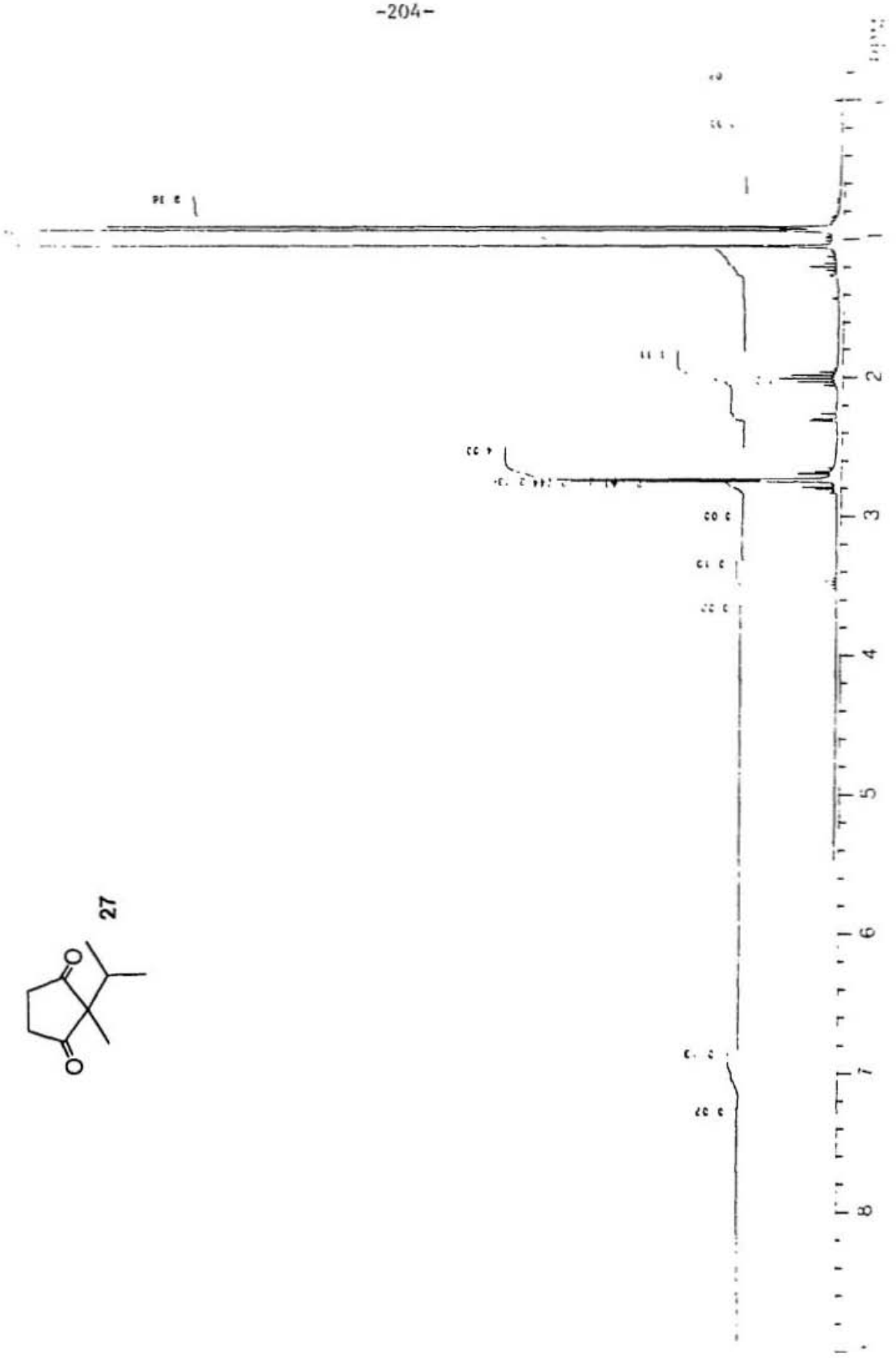

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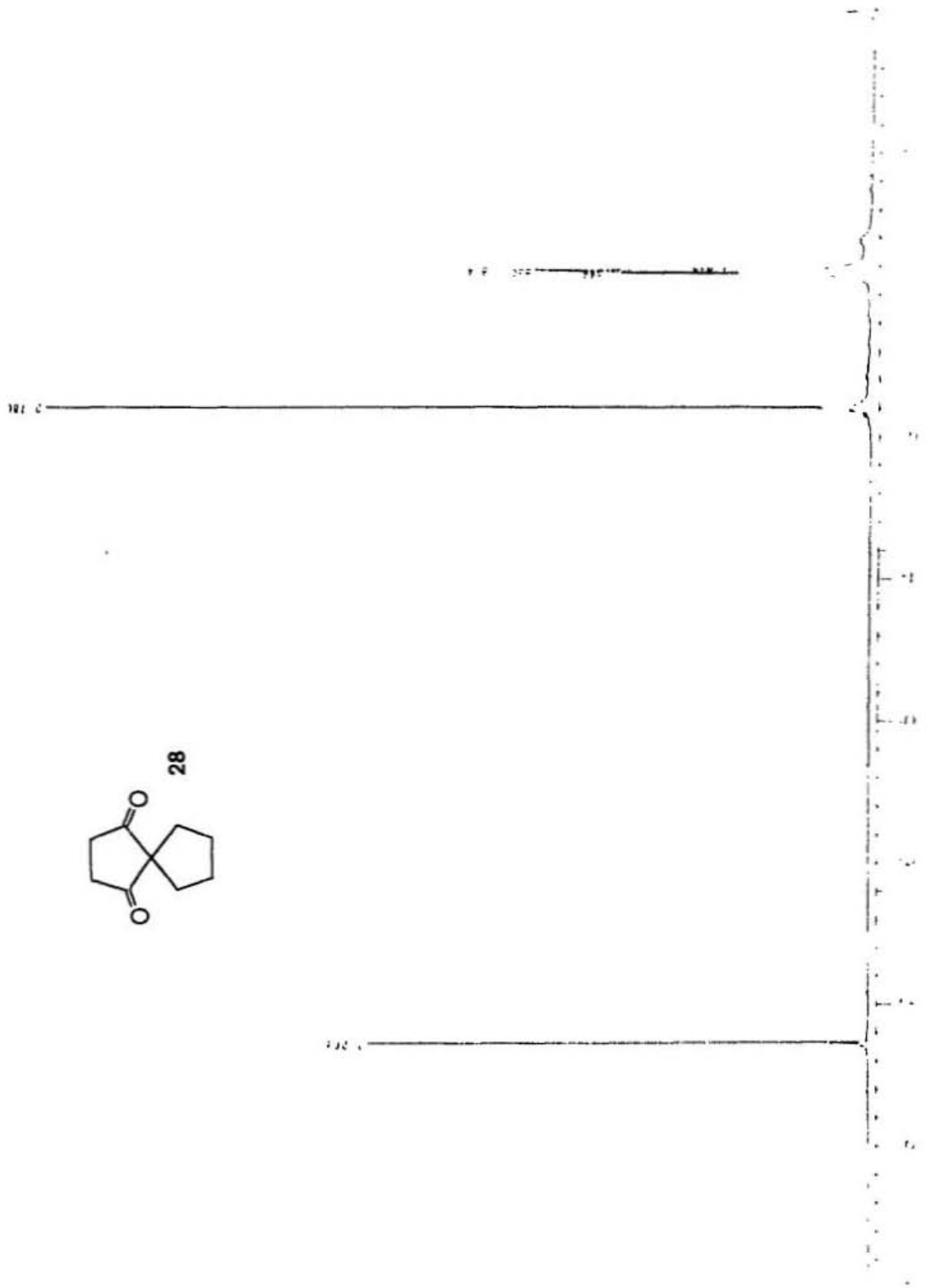

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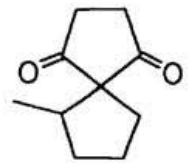

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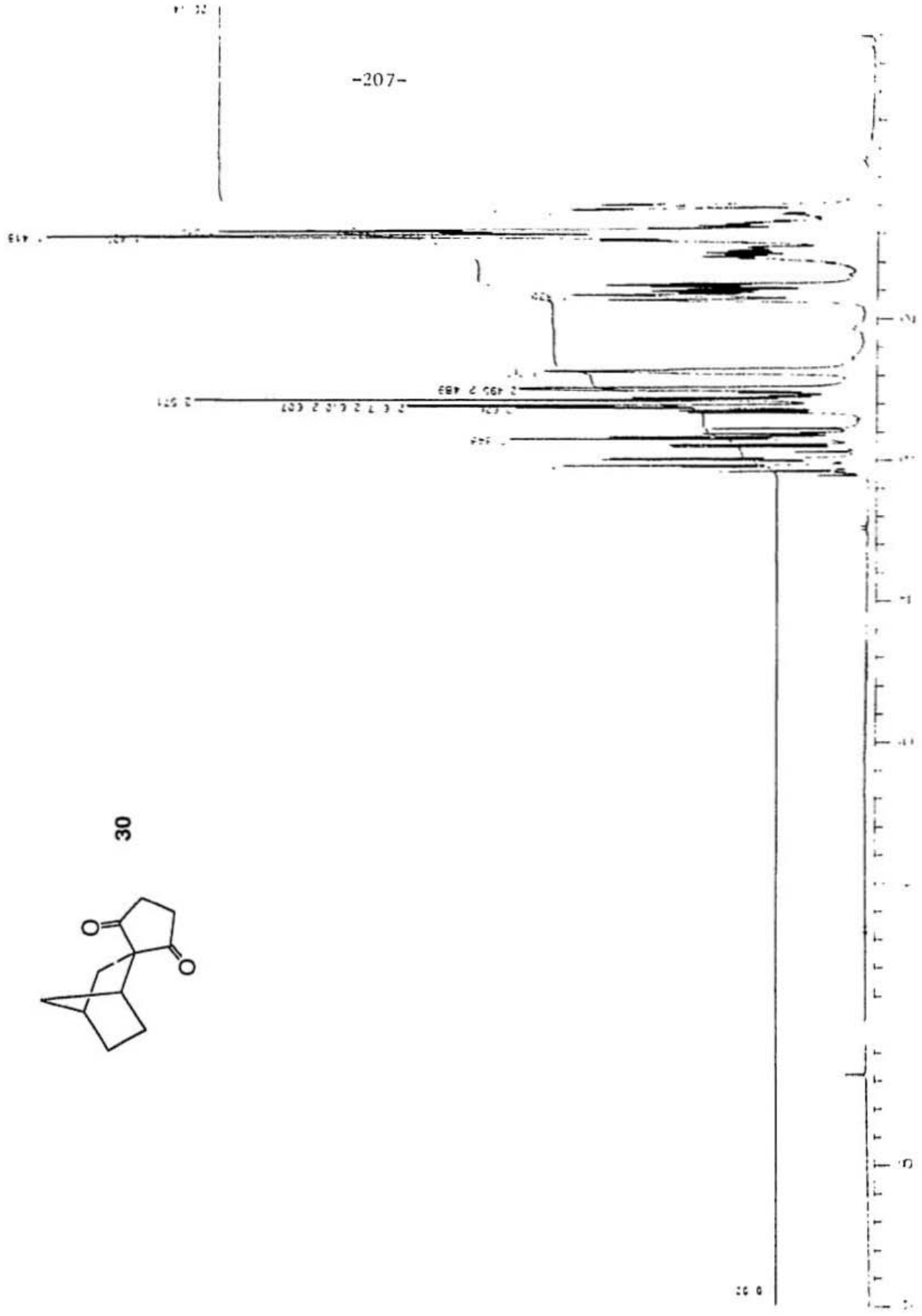

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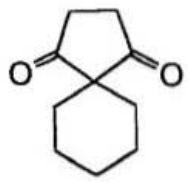

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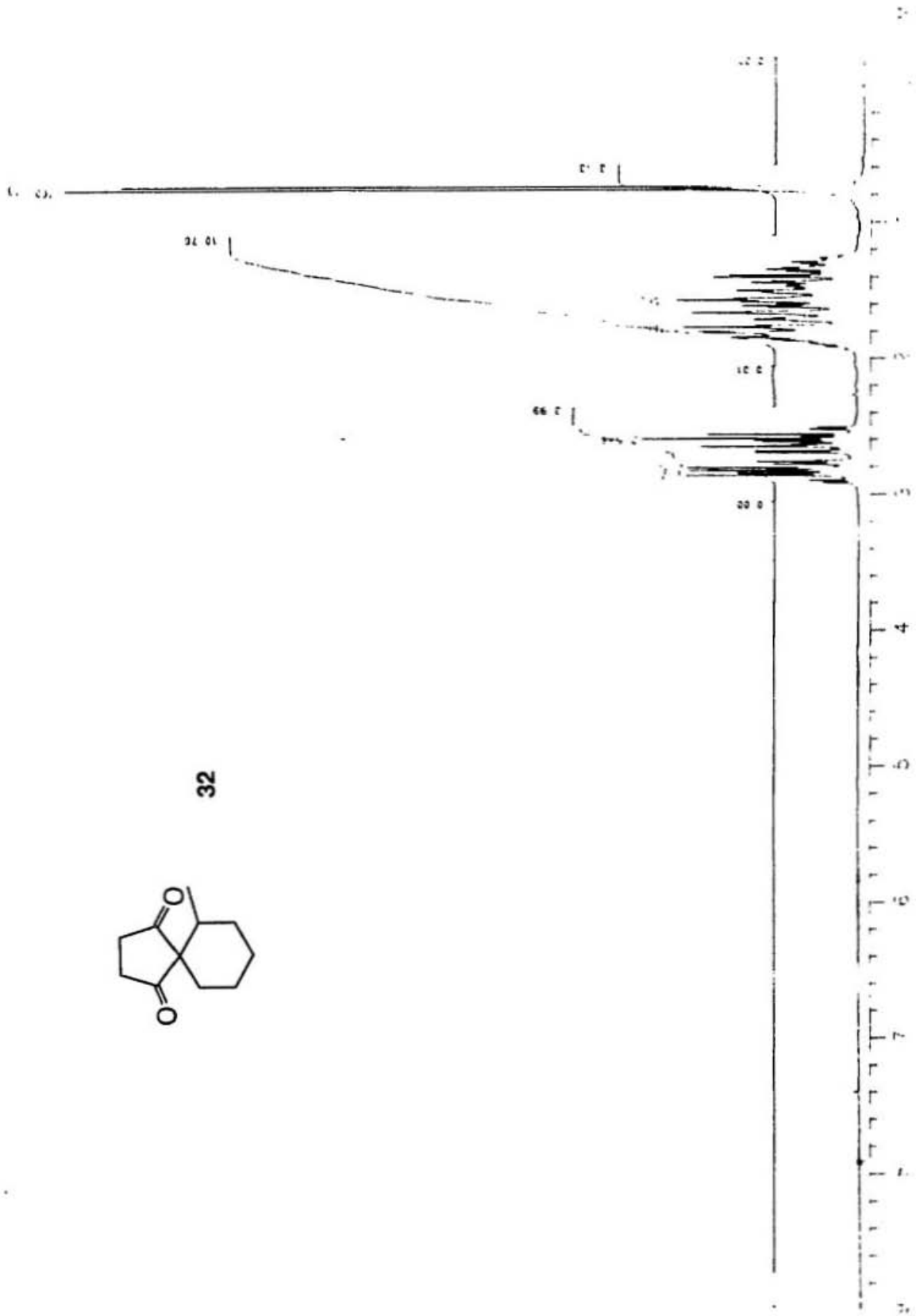

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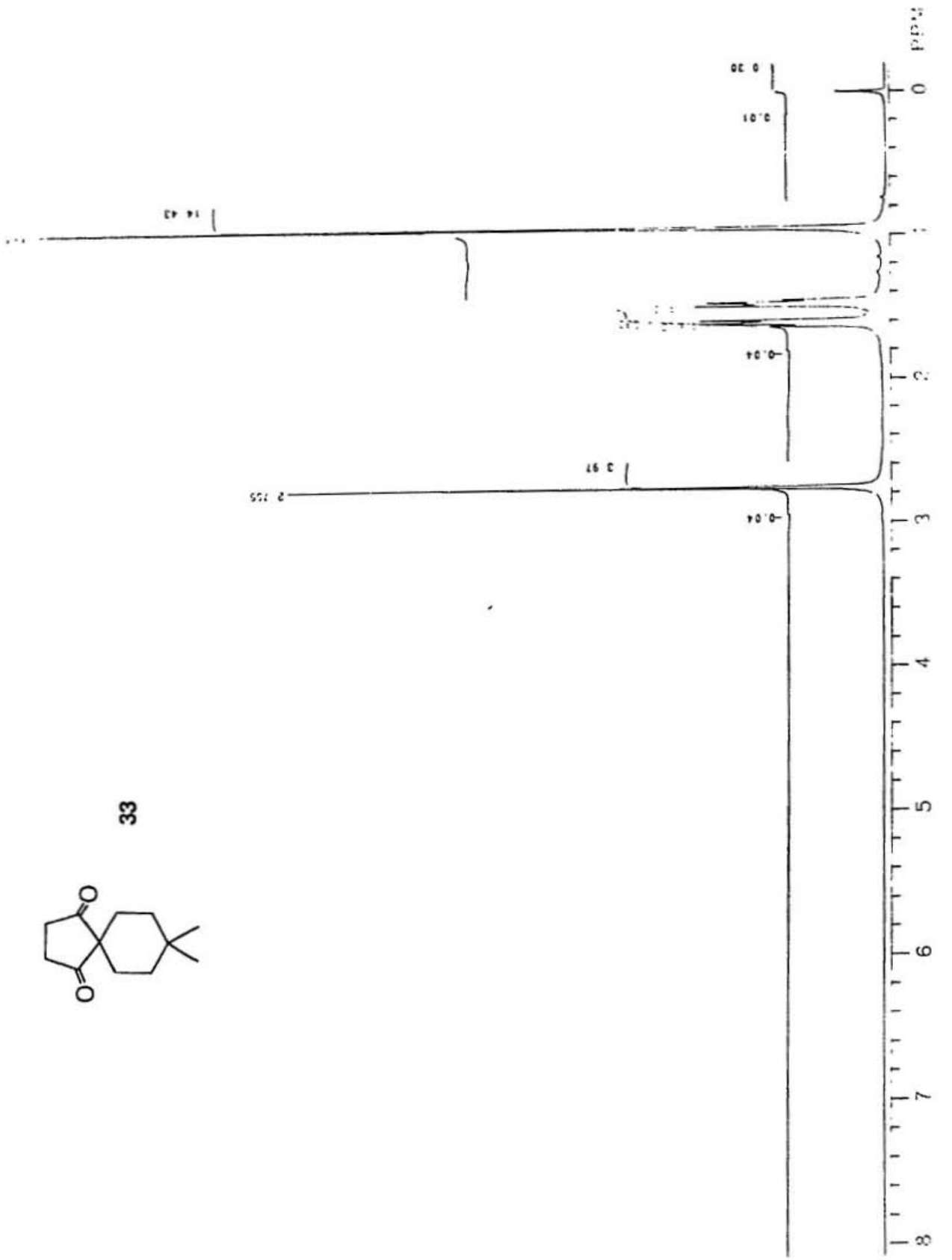

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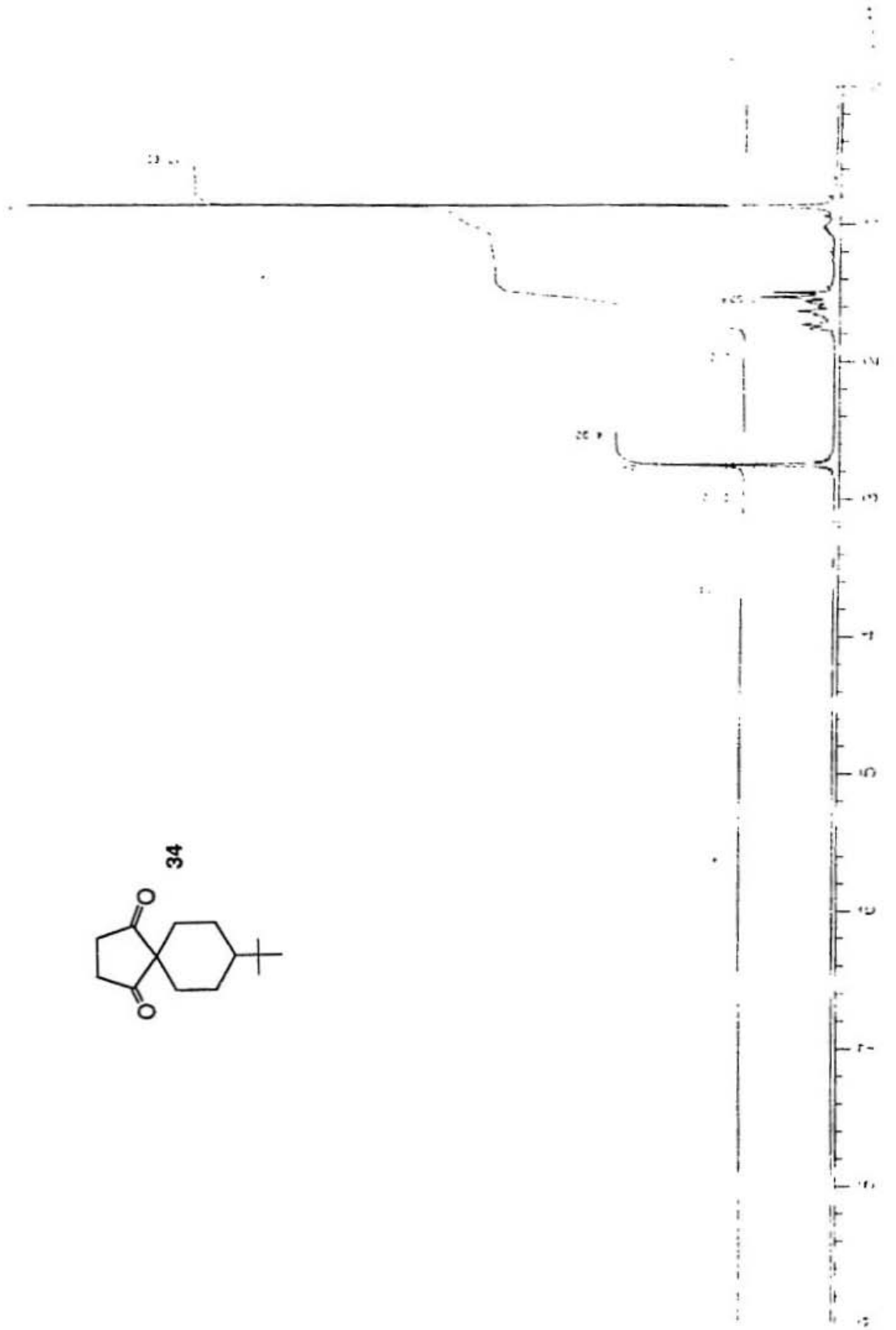

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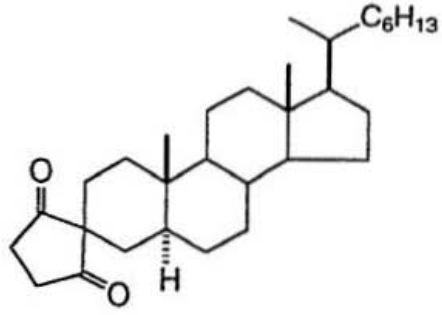

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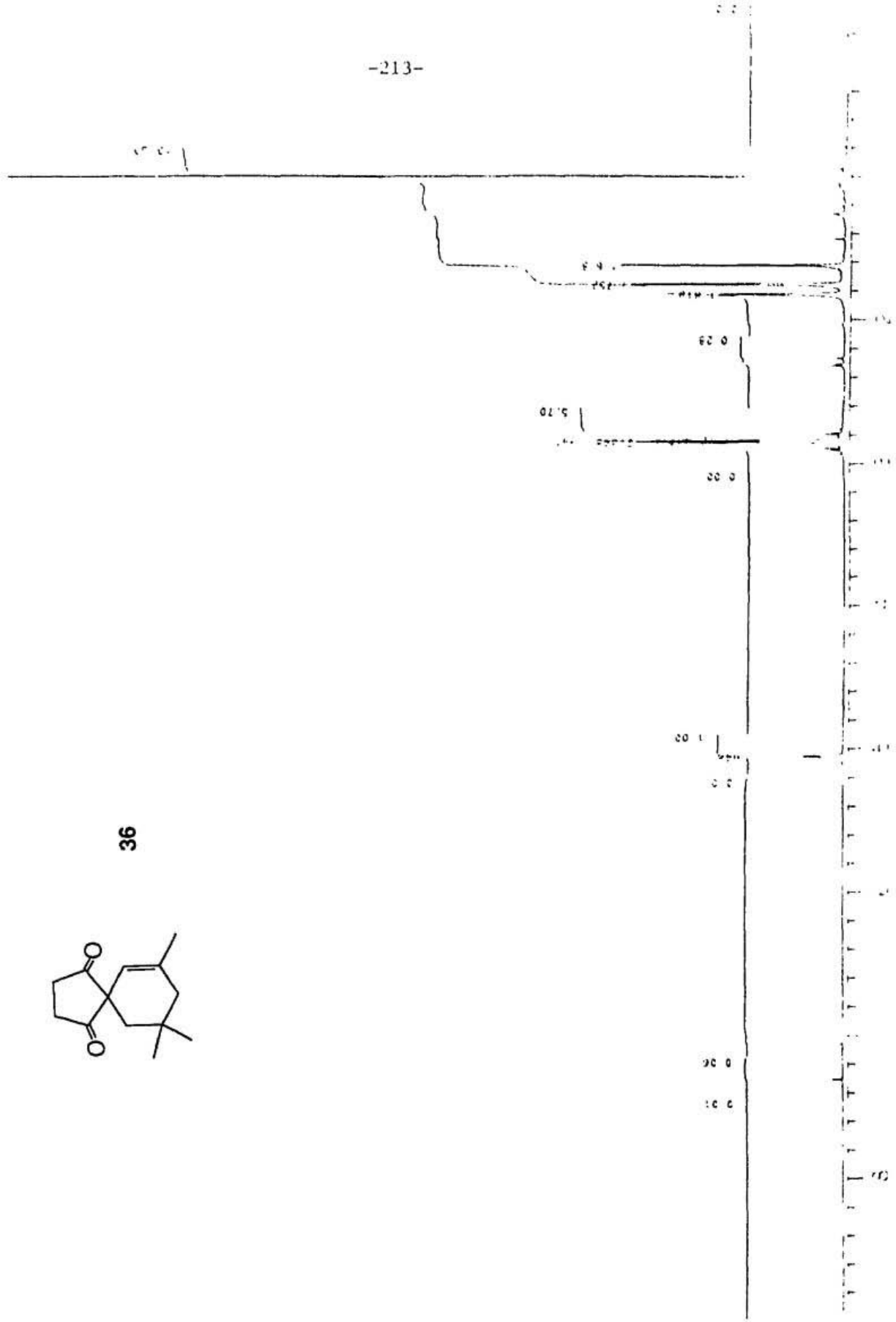

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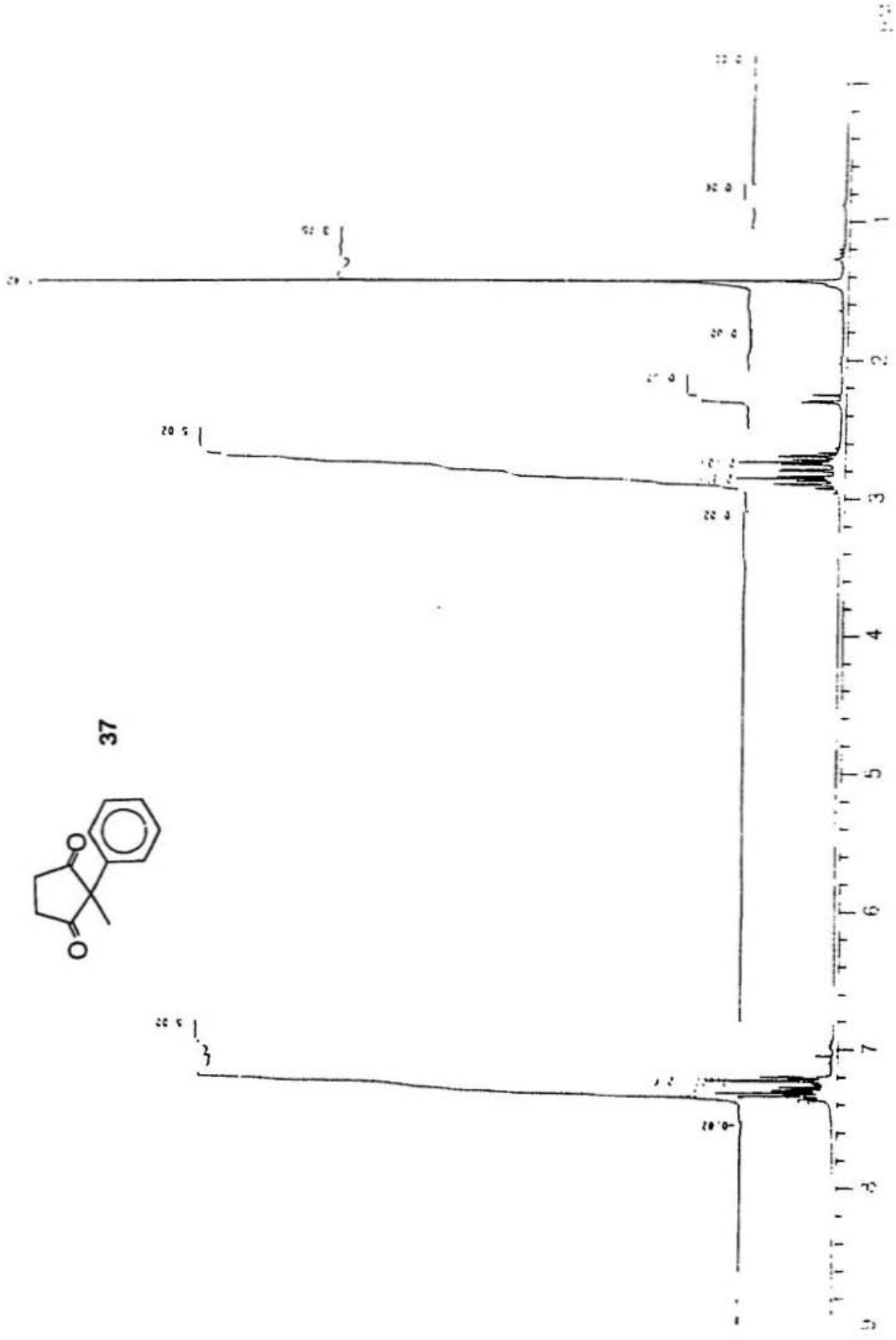
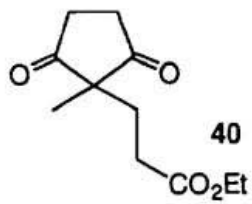


37

38
OMe
O
O



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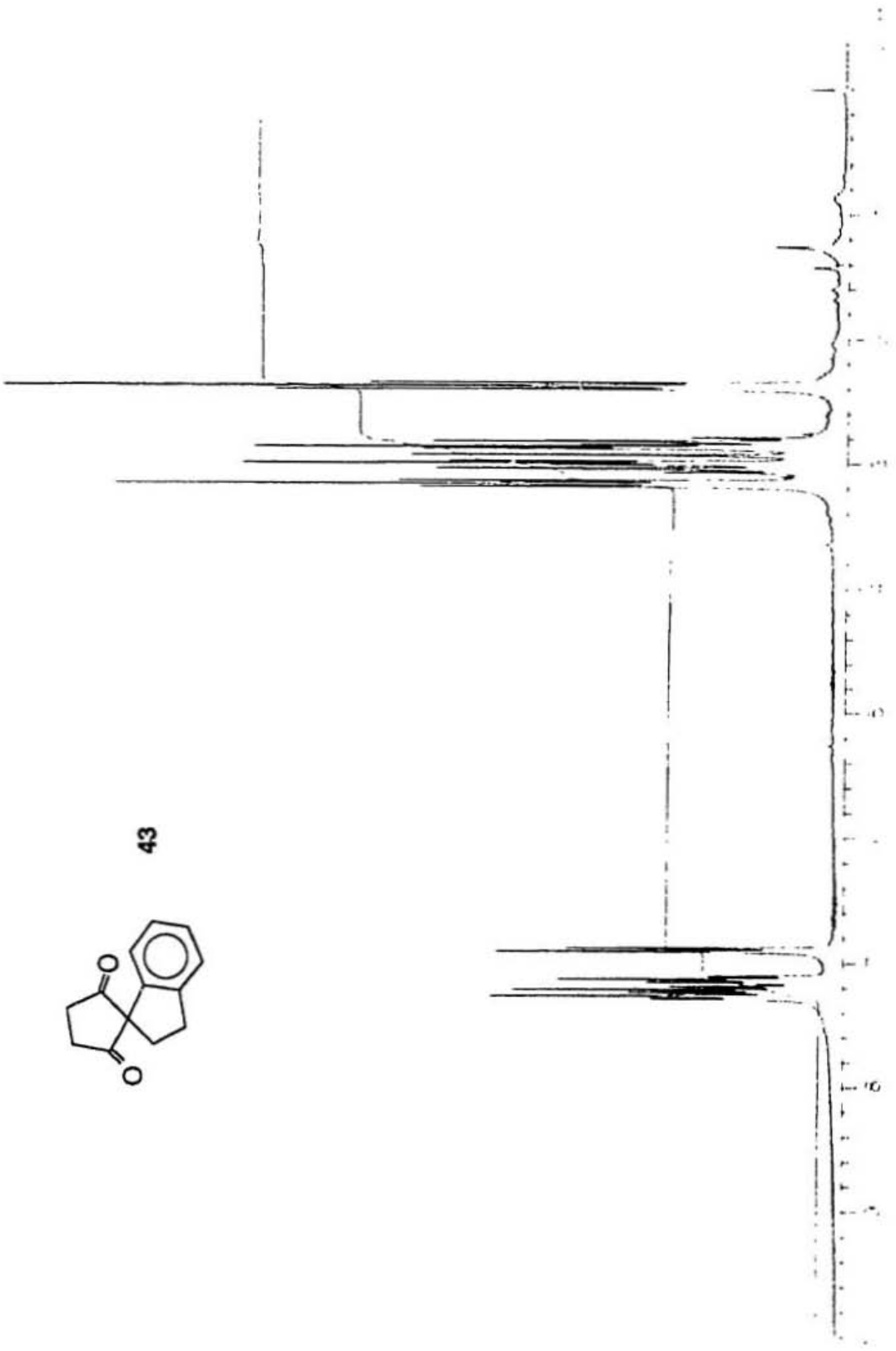
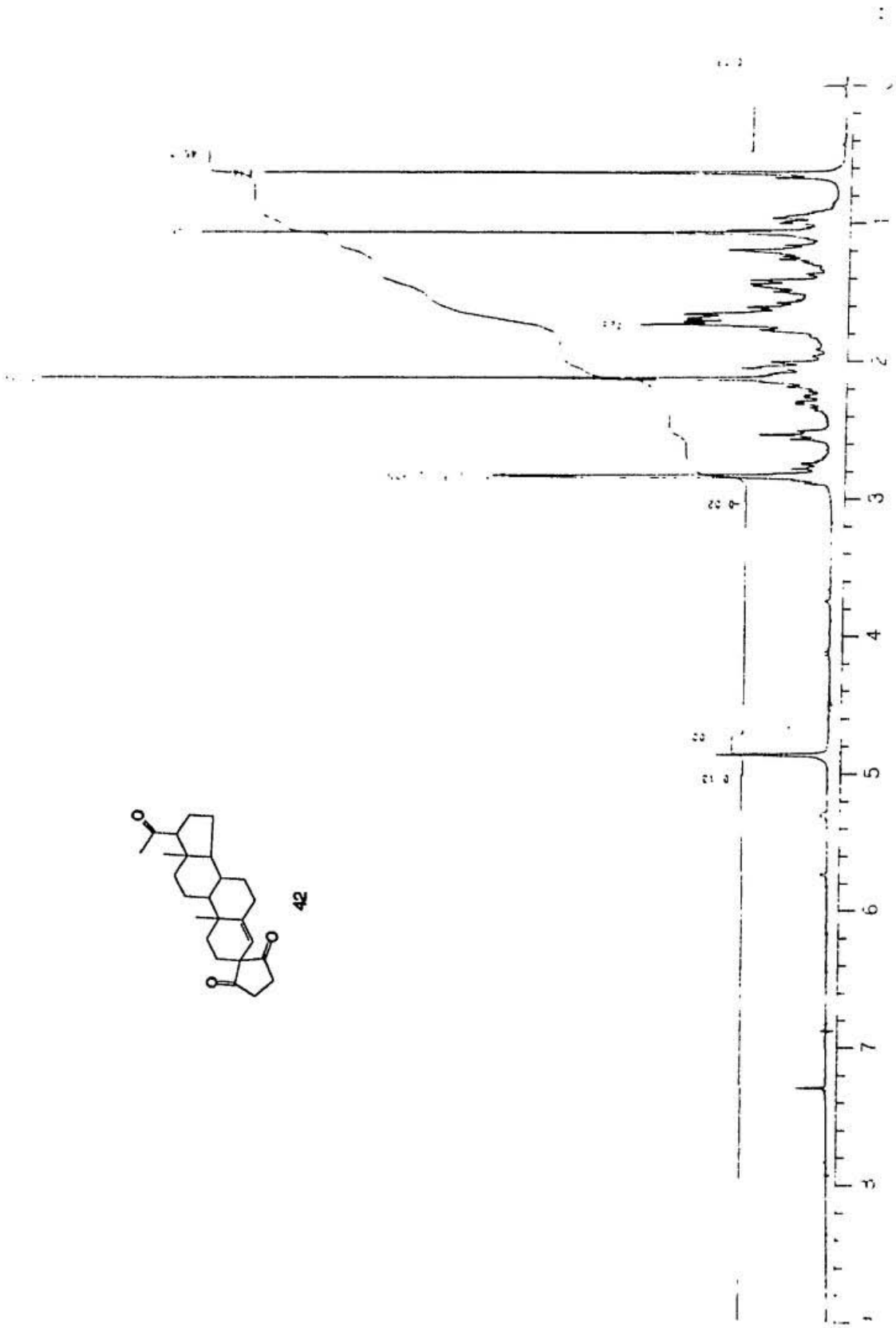

43
O
O
δ
3
2
1



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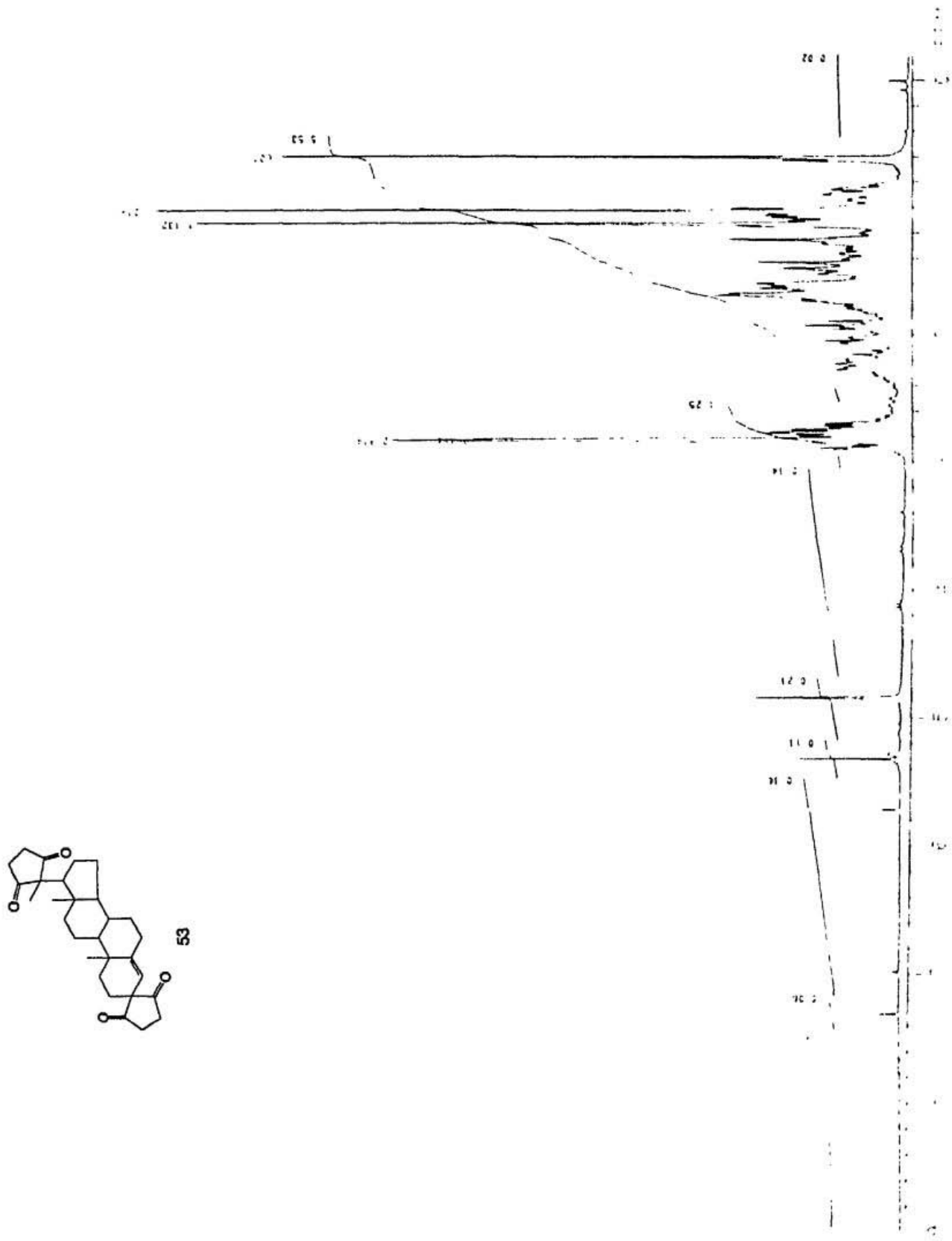

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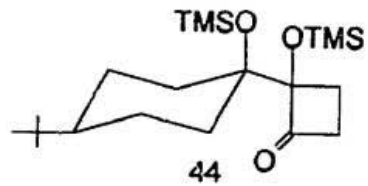

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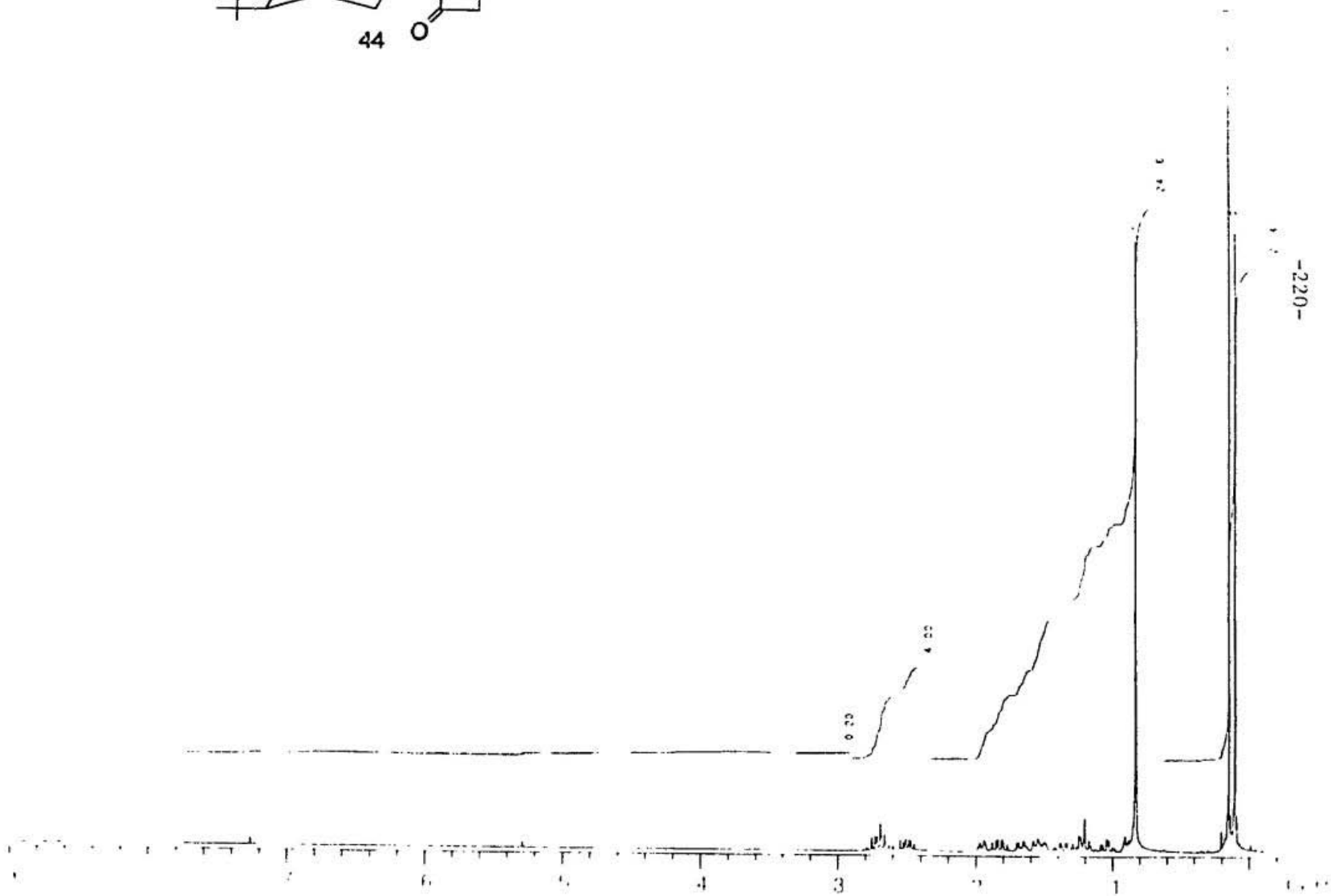

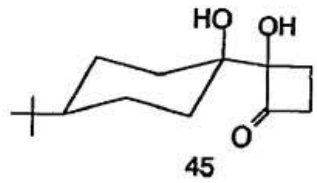

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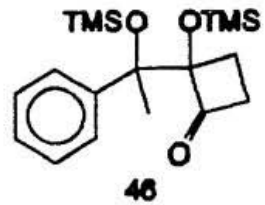

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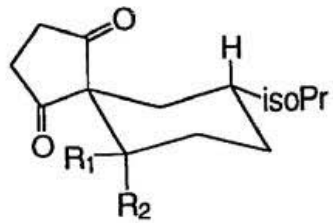
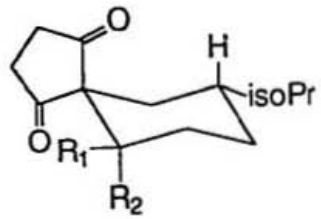
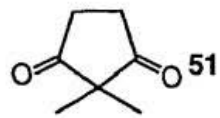


49 $R_1 = H$, $R_2 = Me$



50 R_1 = Me, R_2 = H



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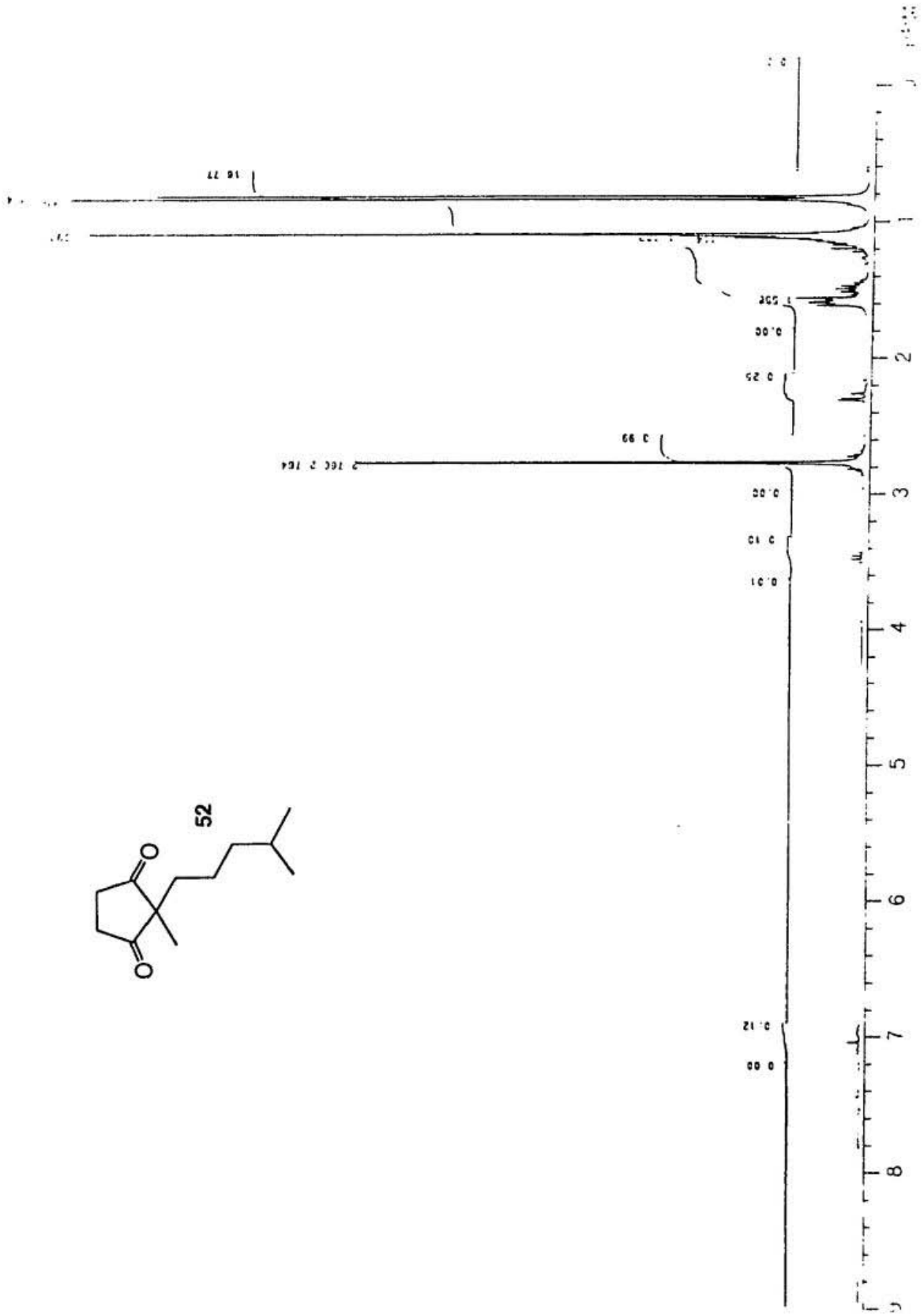

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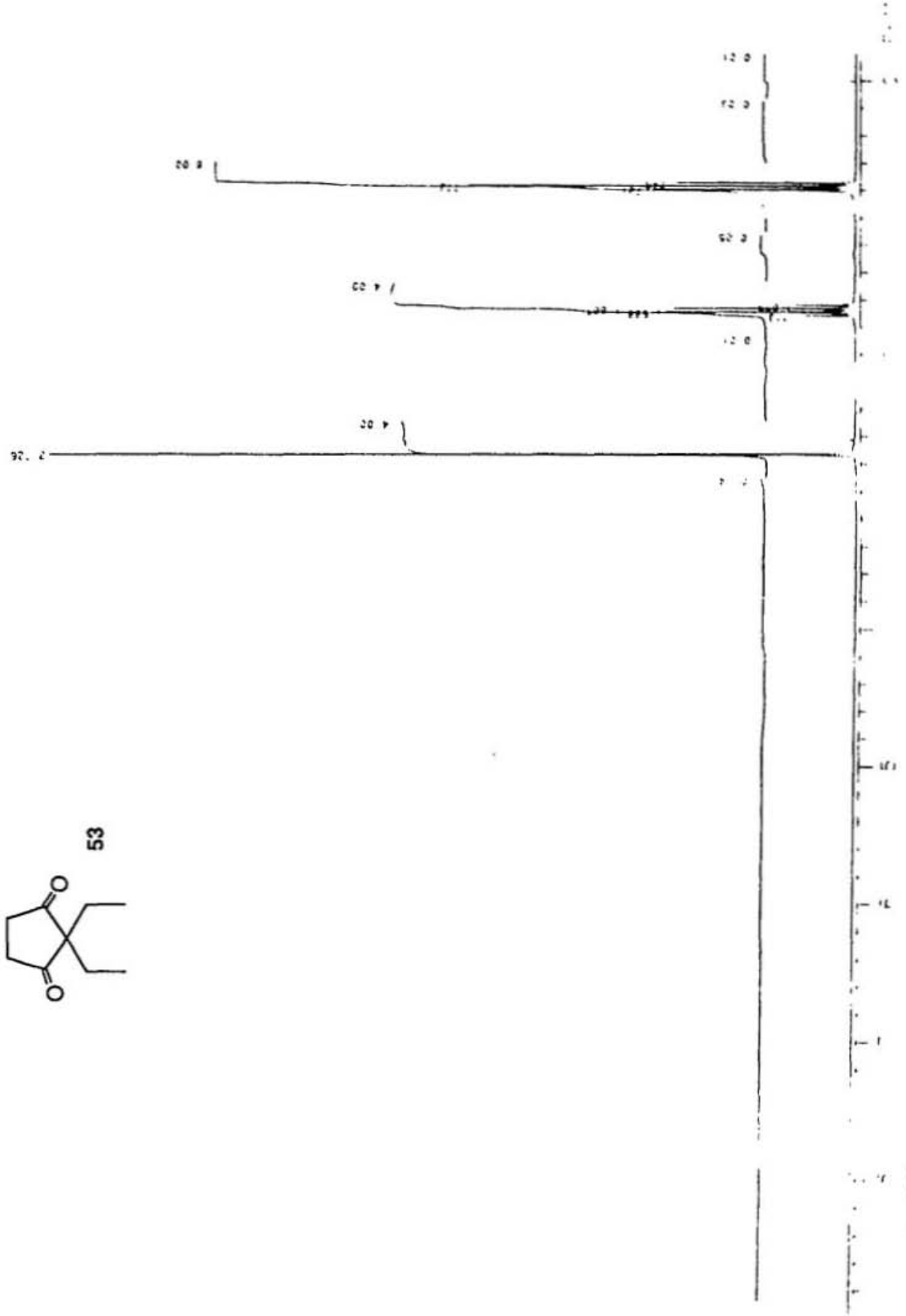

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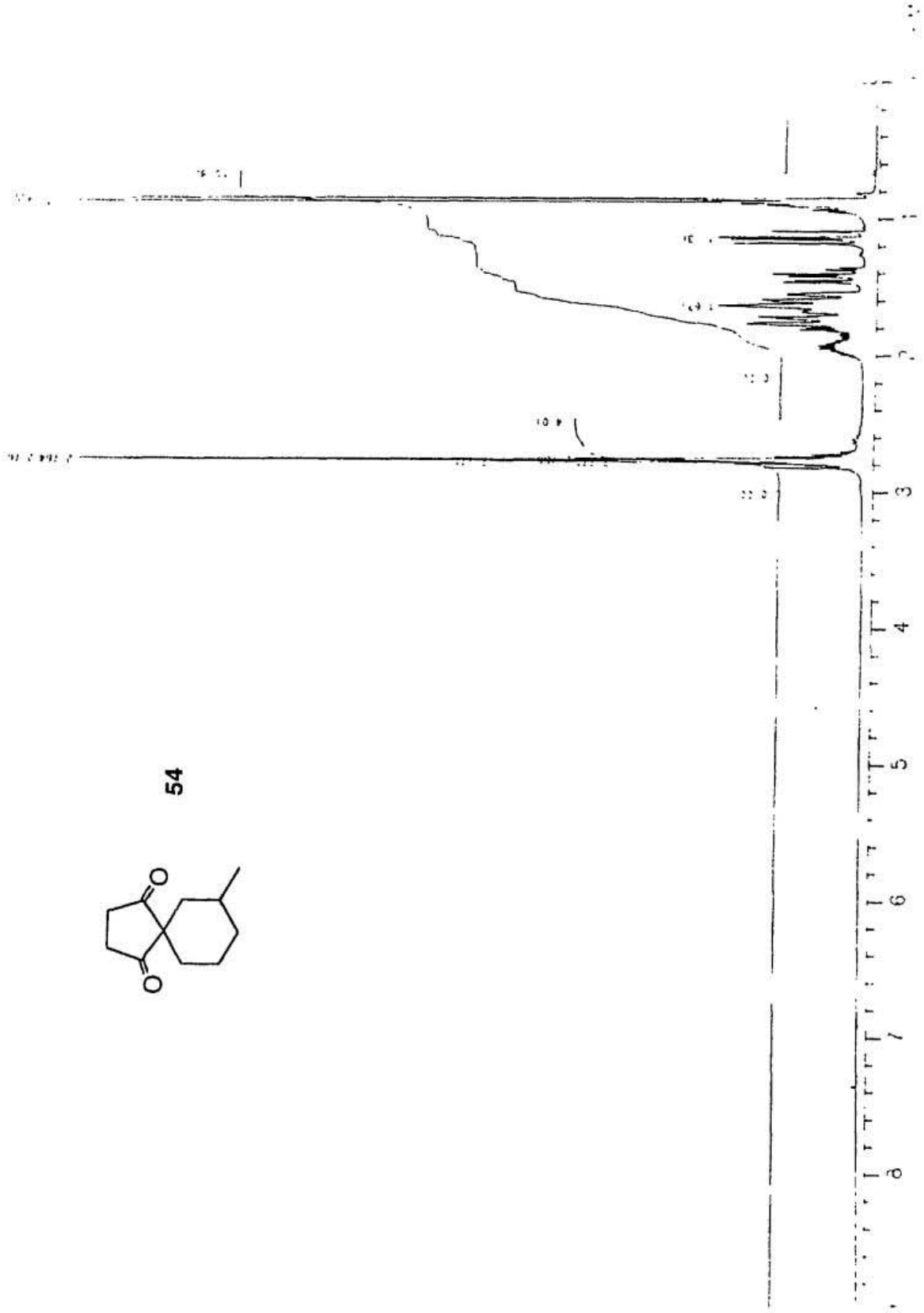

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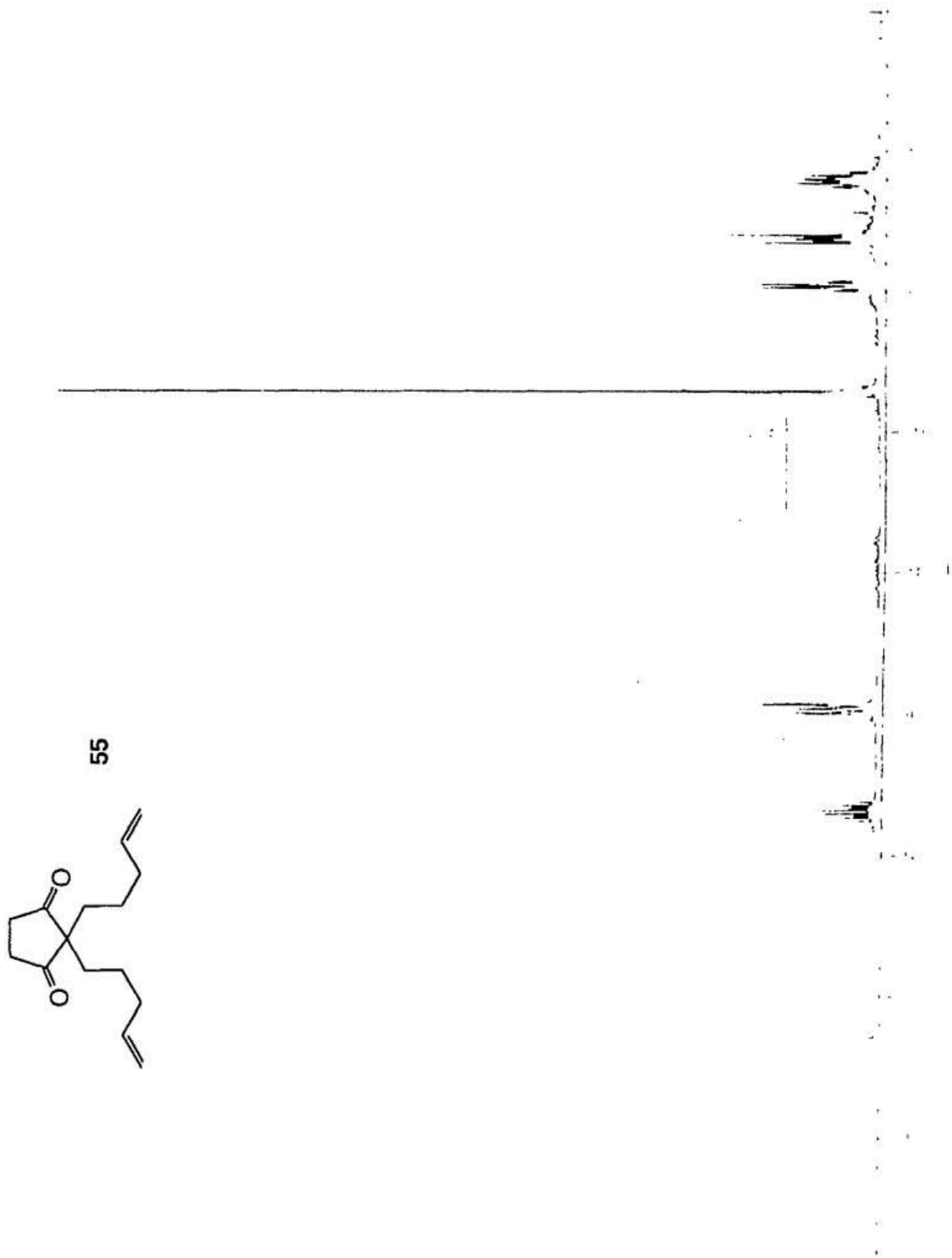

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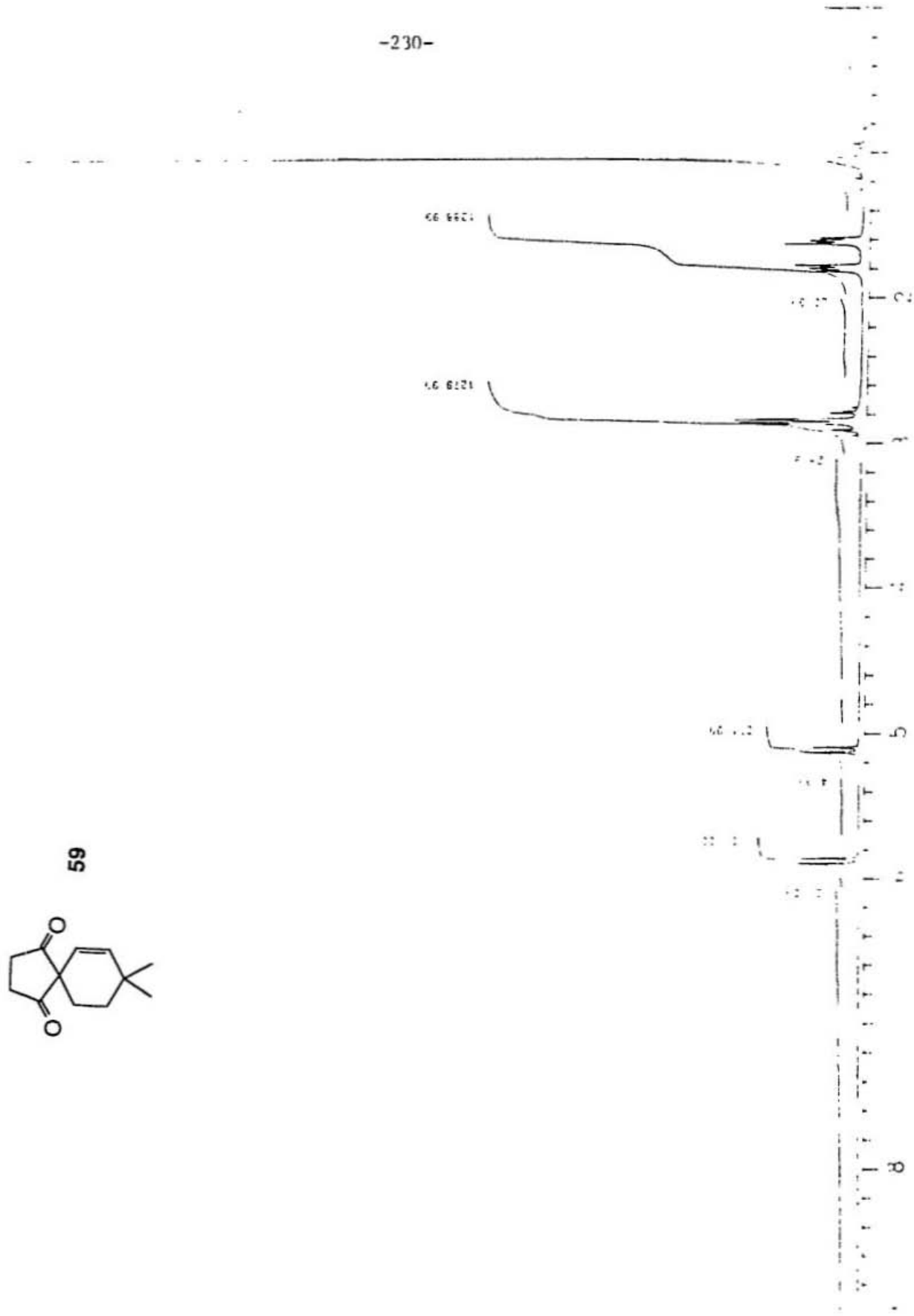

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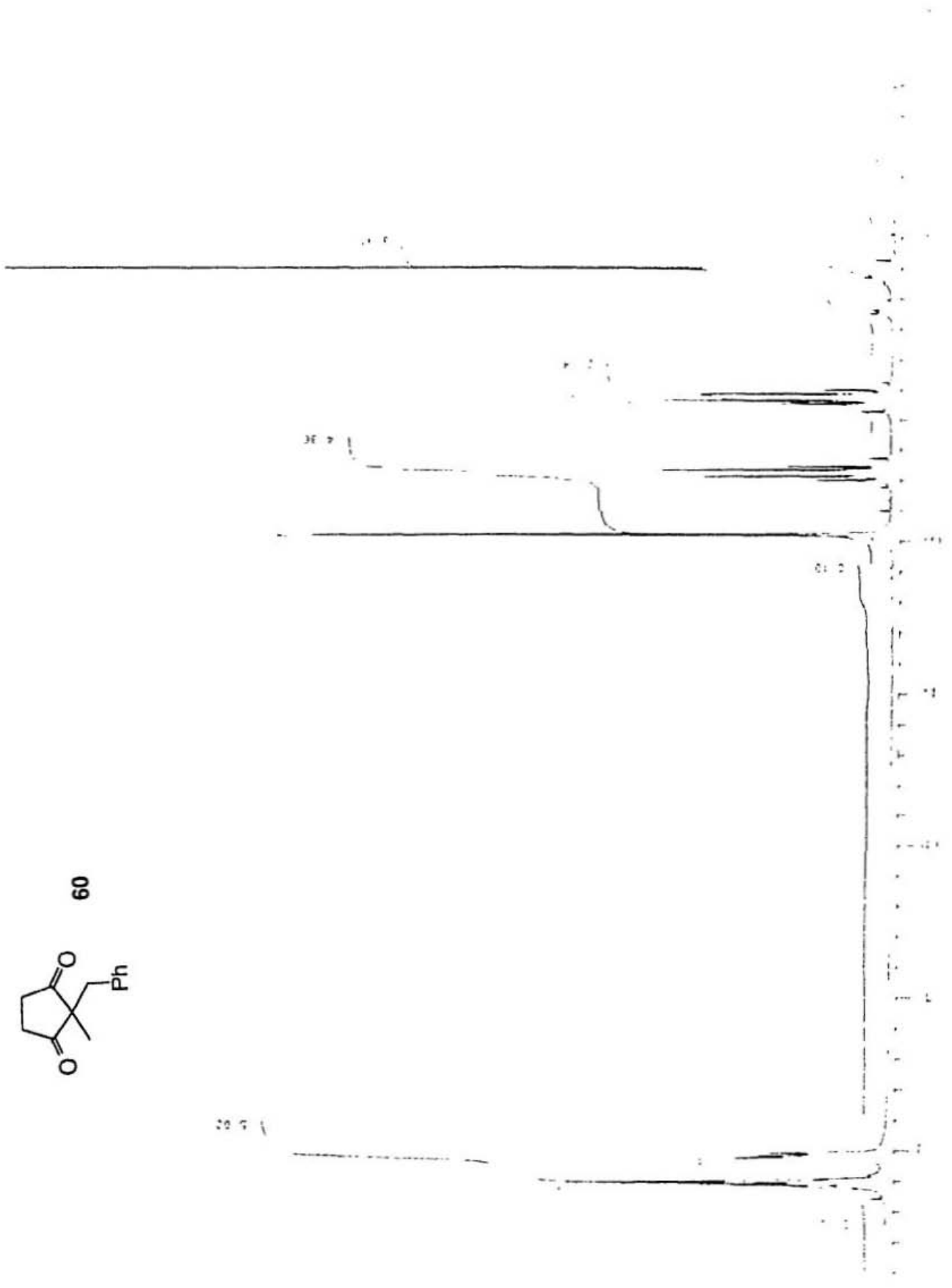

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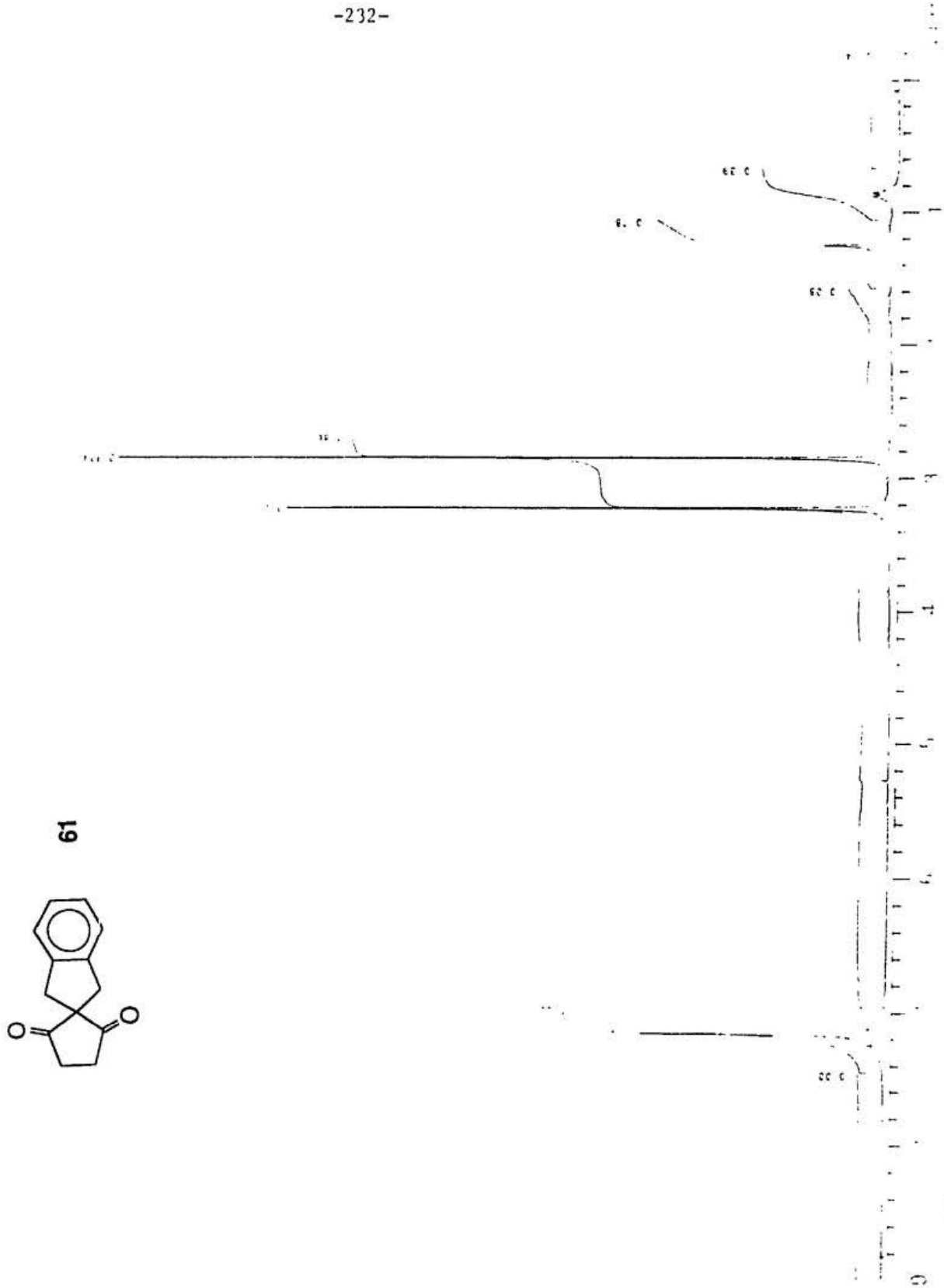

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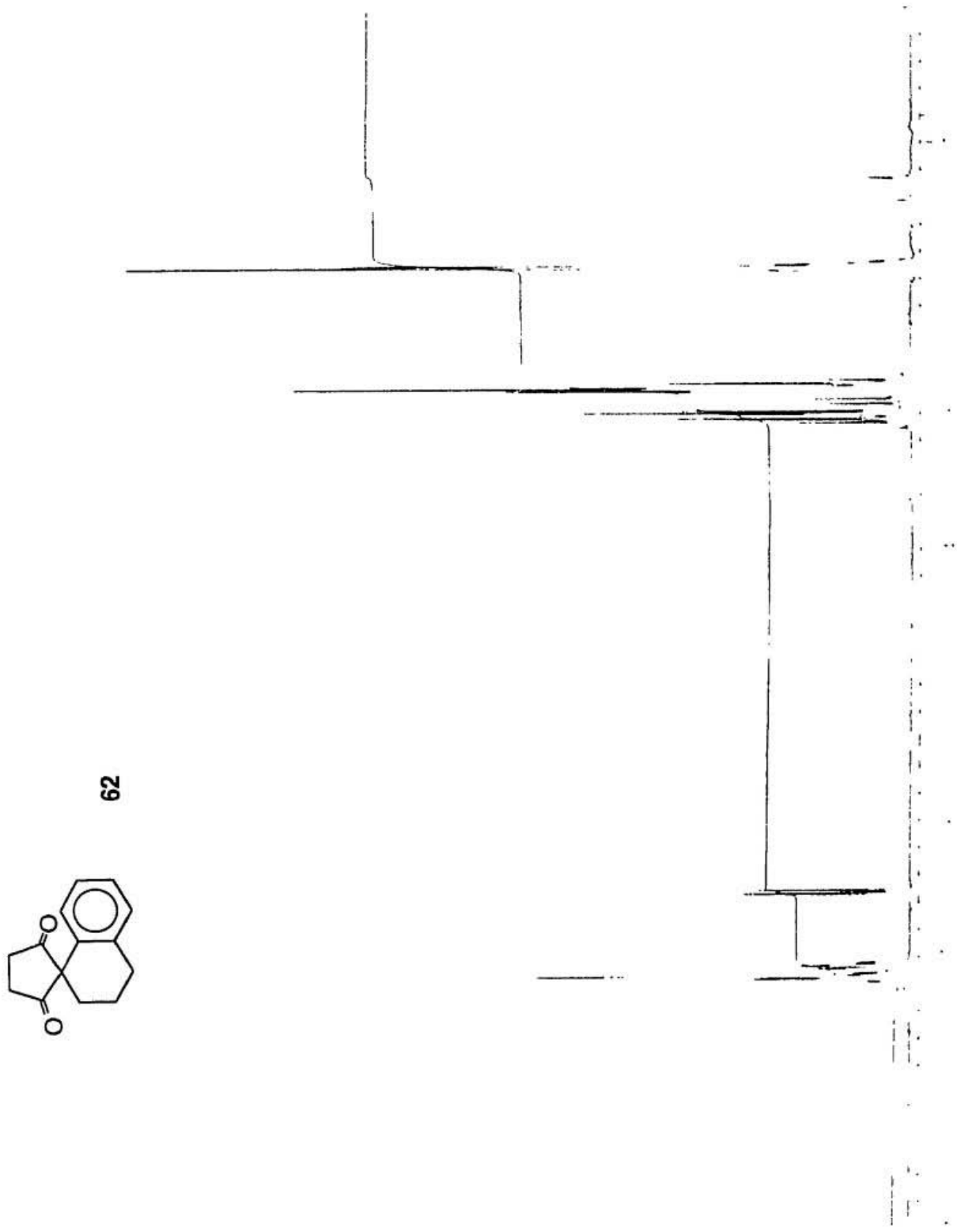

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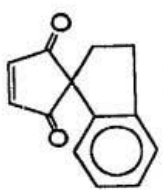

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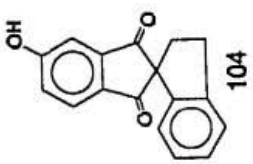

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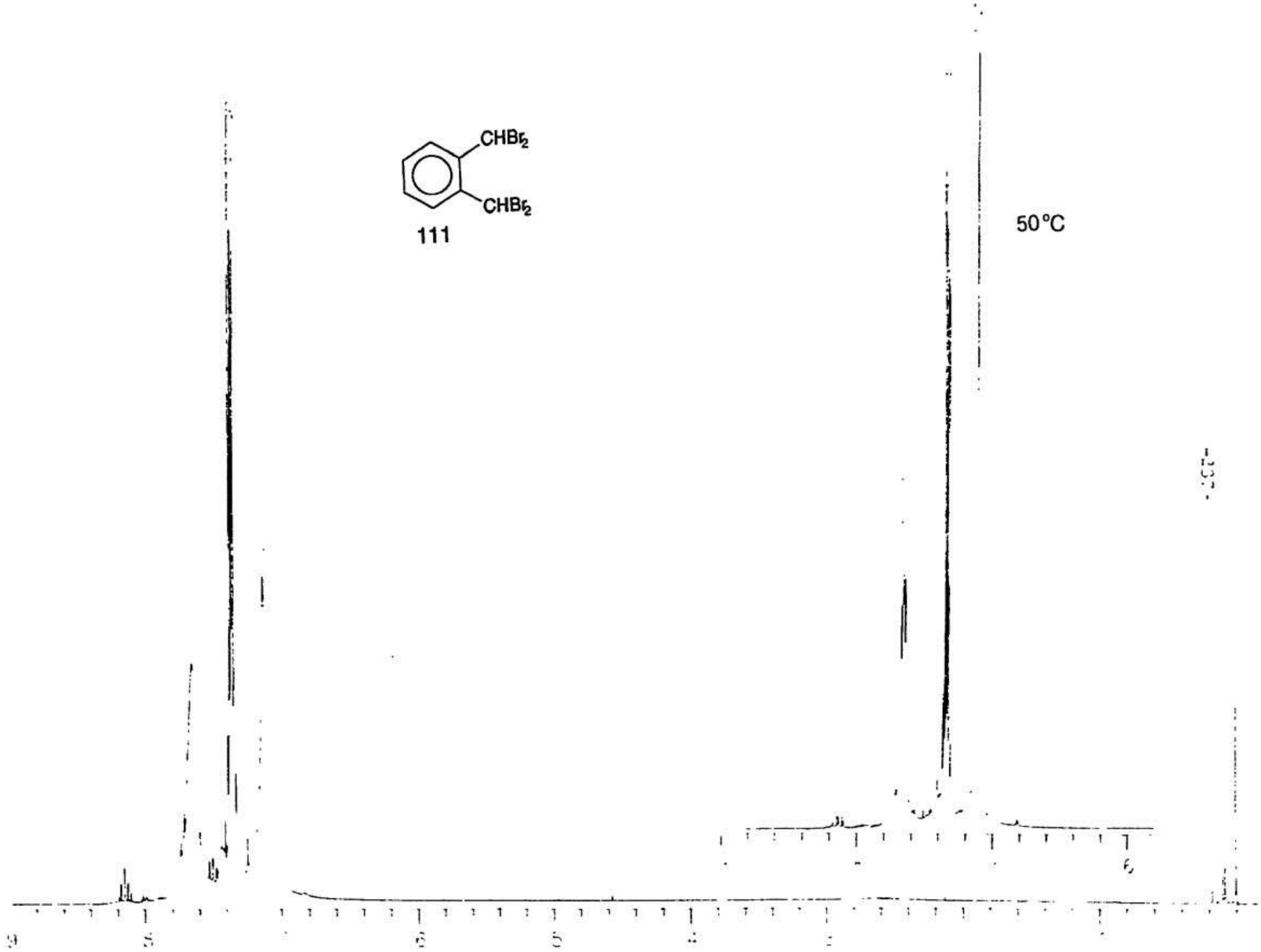
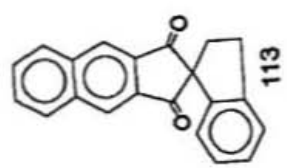

CHBr2
CHBr2
111
50°C



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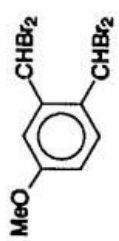

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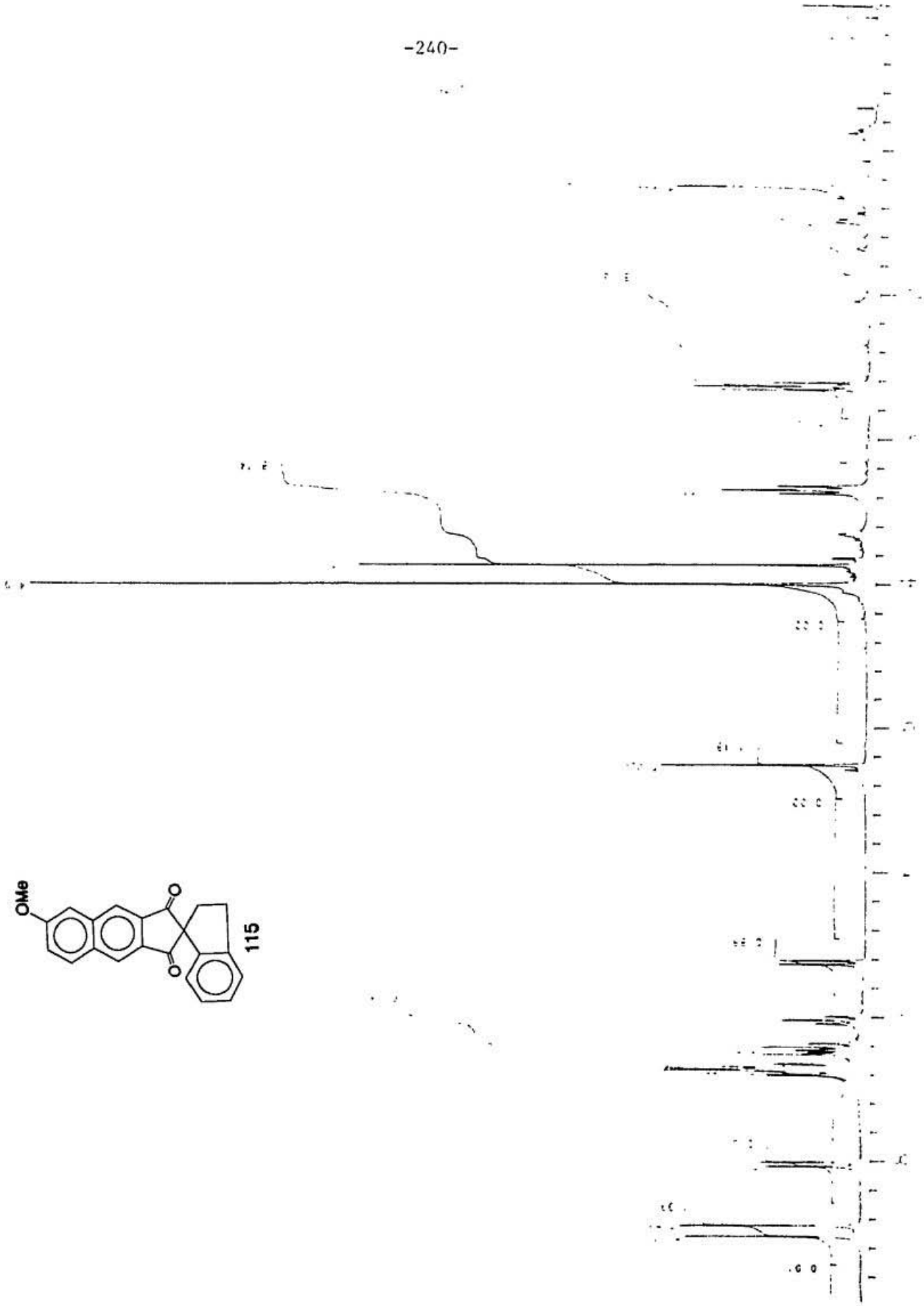
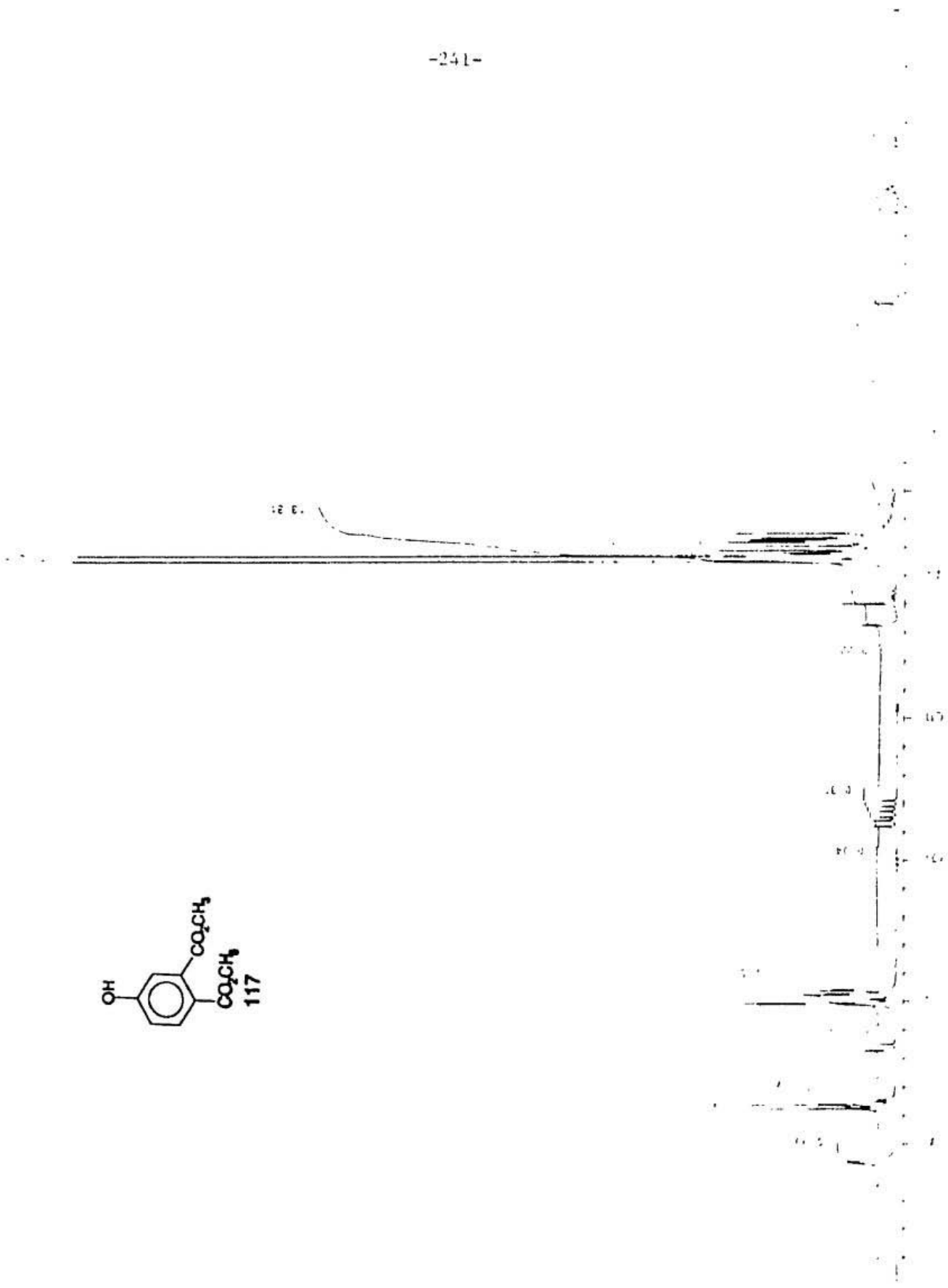

OMe
O
O
115



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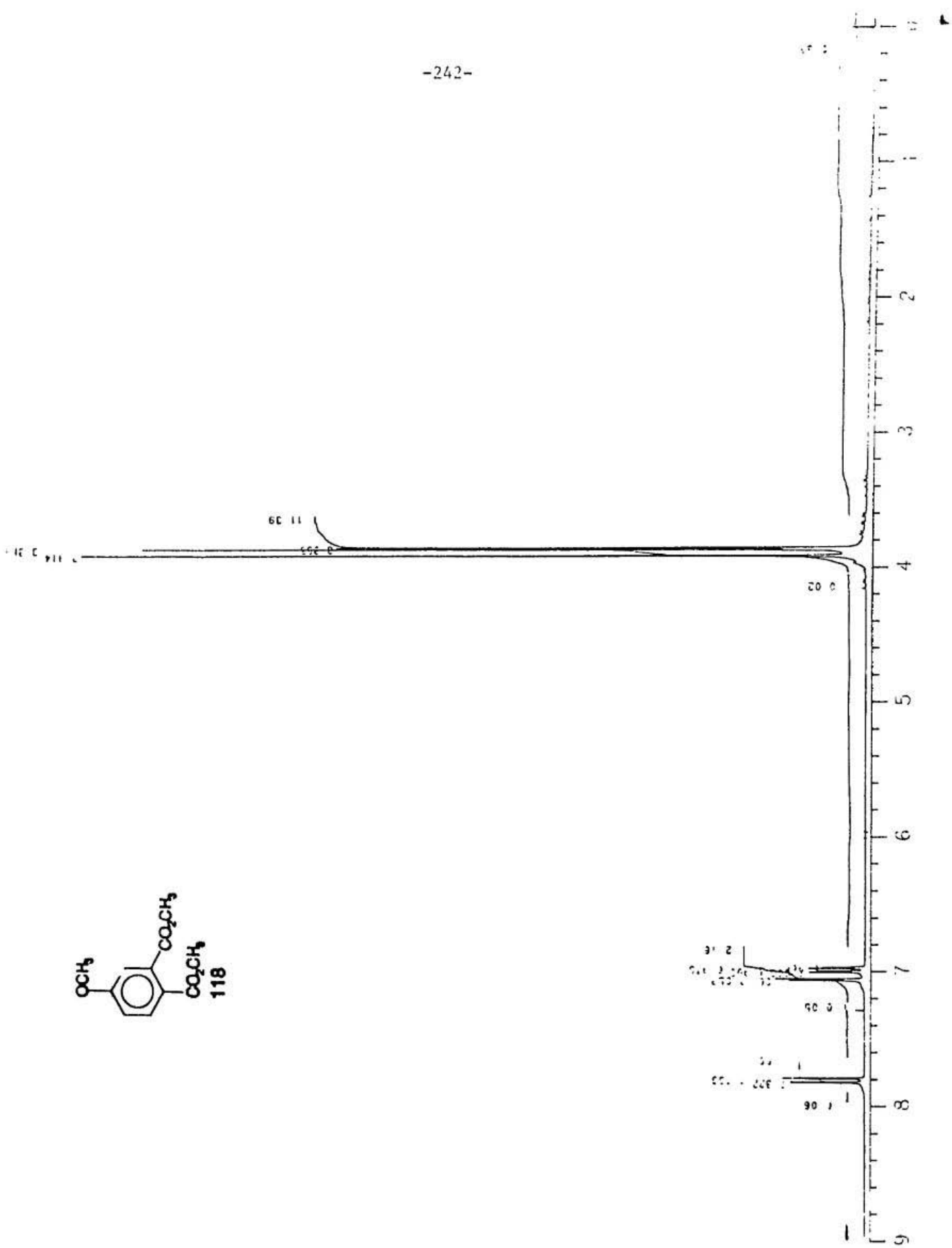

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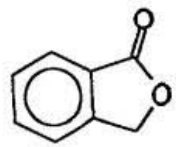

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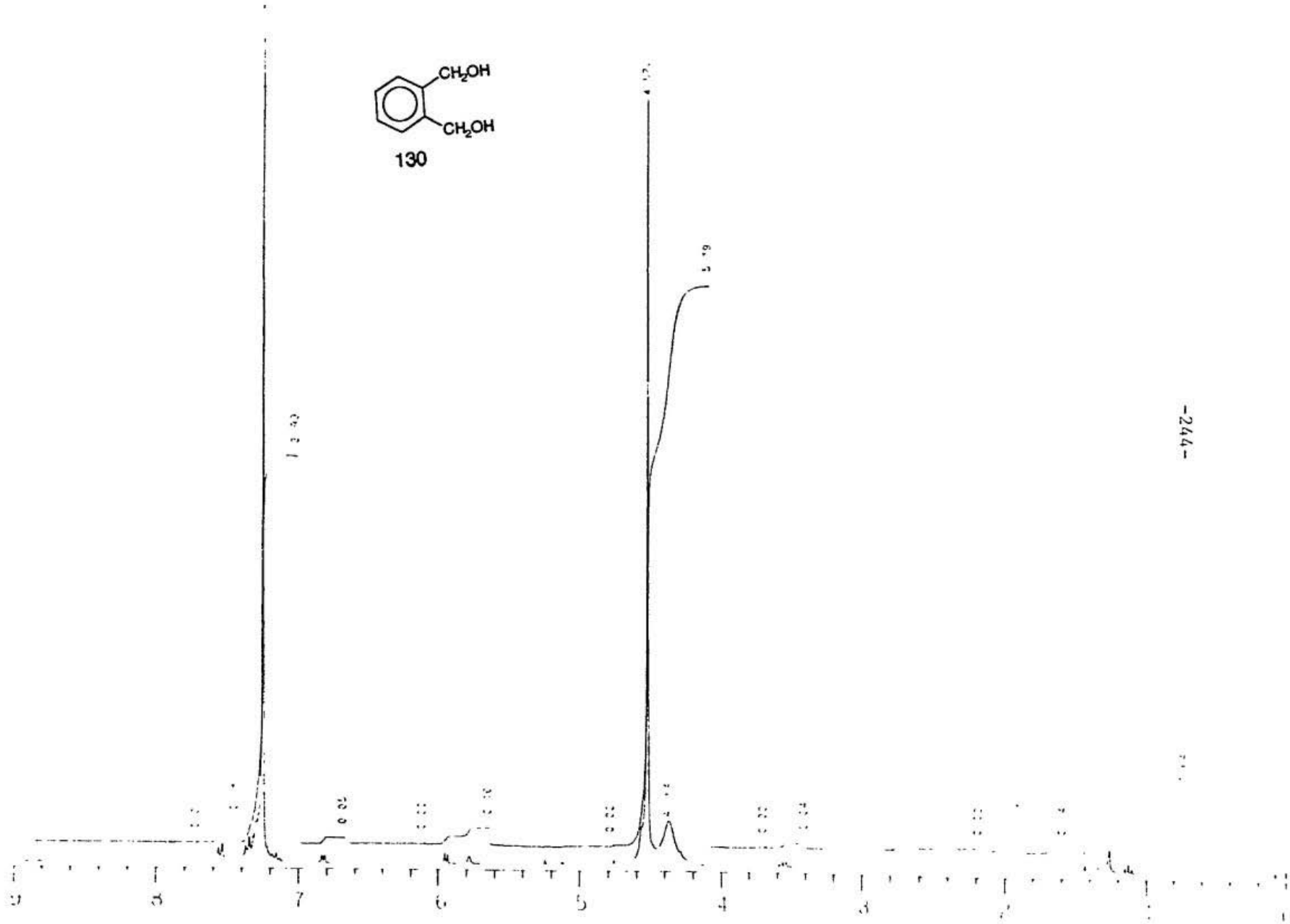

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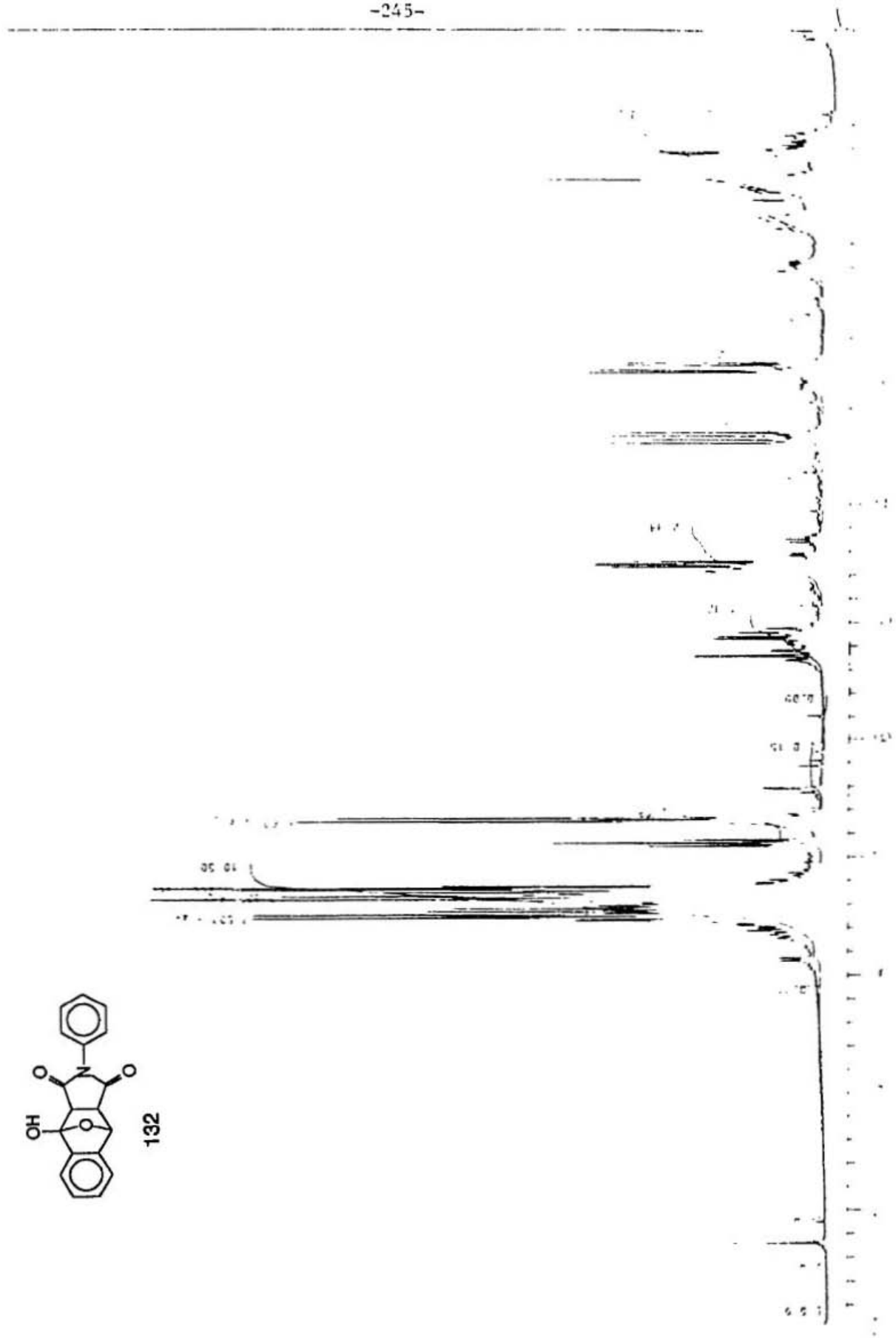

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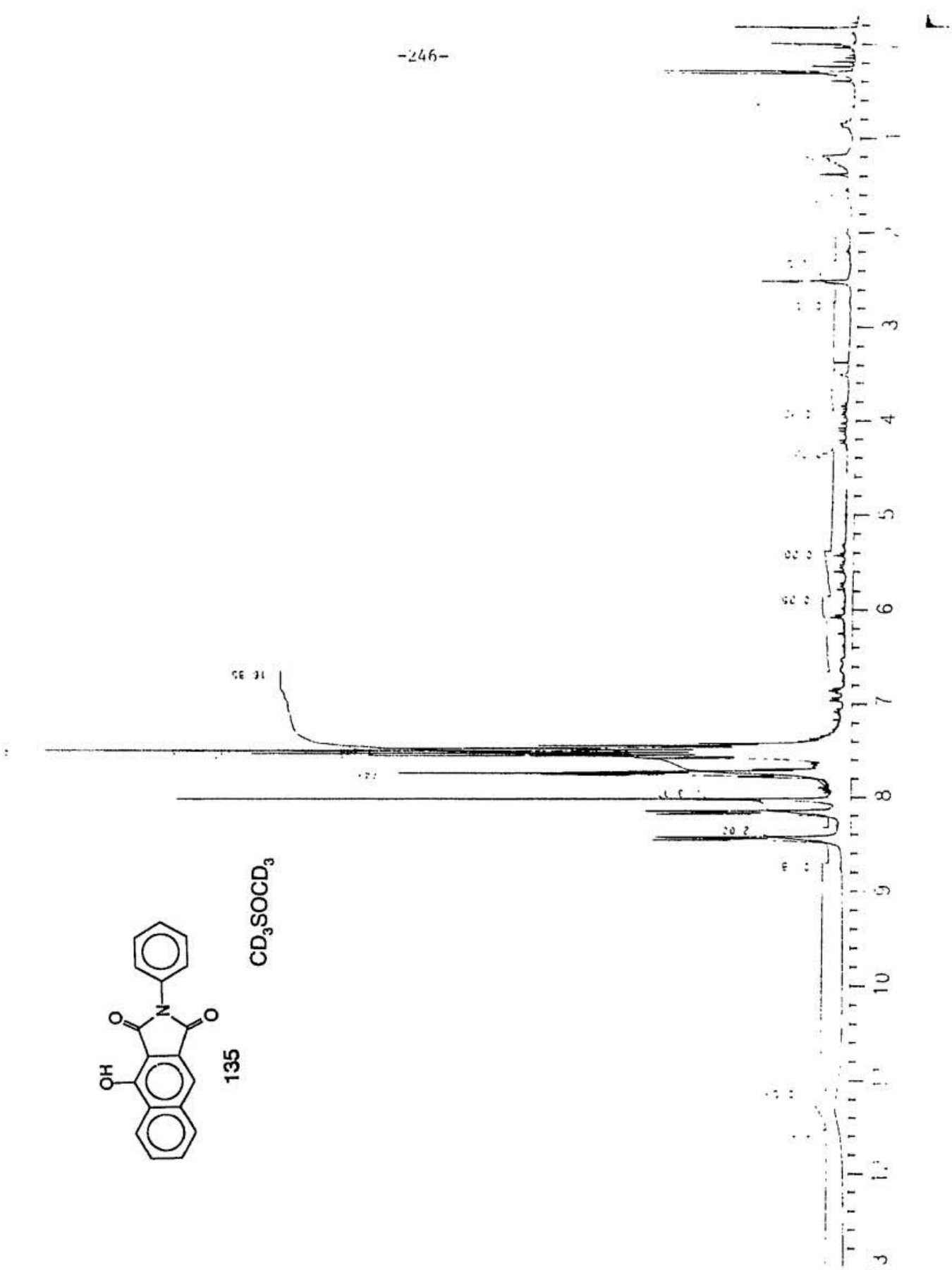
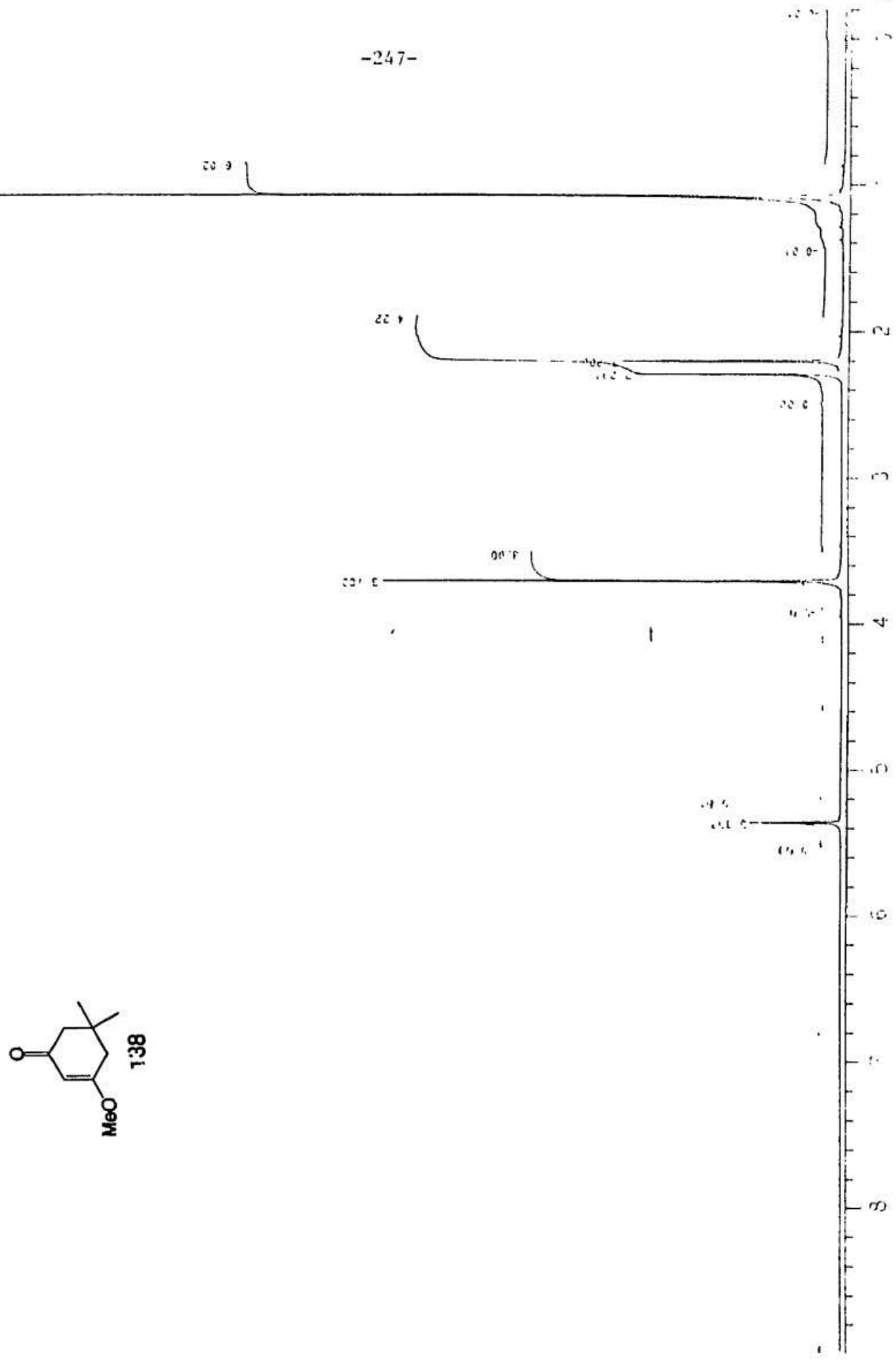

135
CD_3SOCD_3



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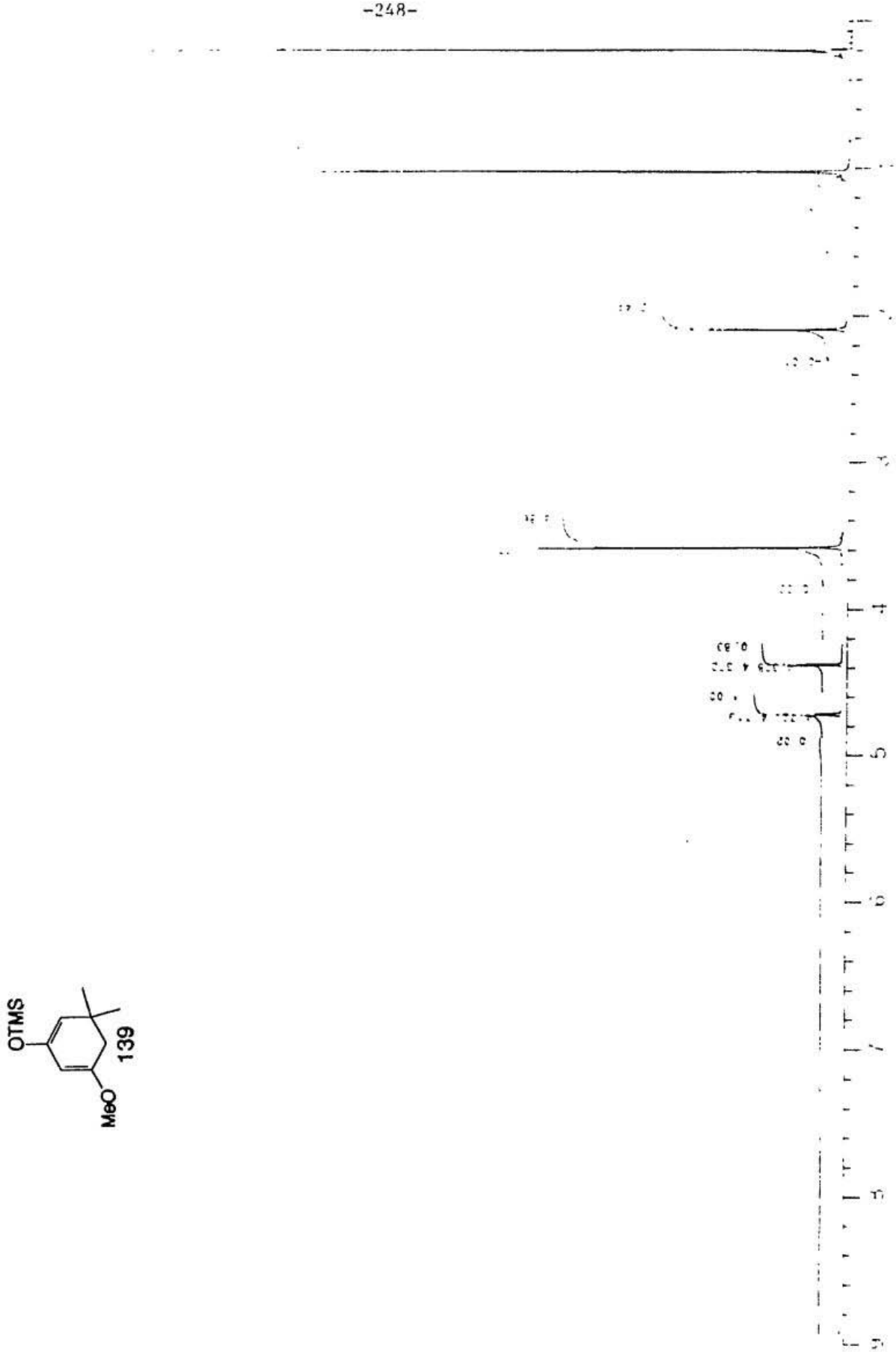
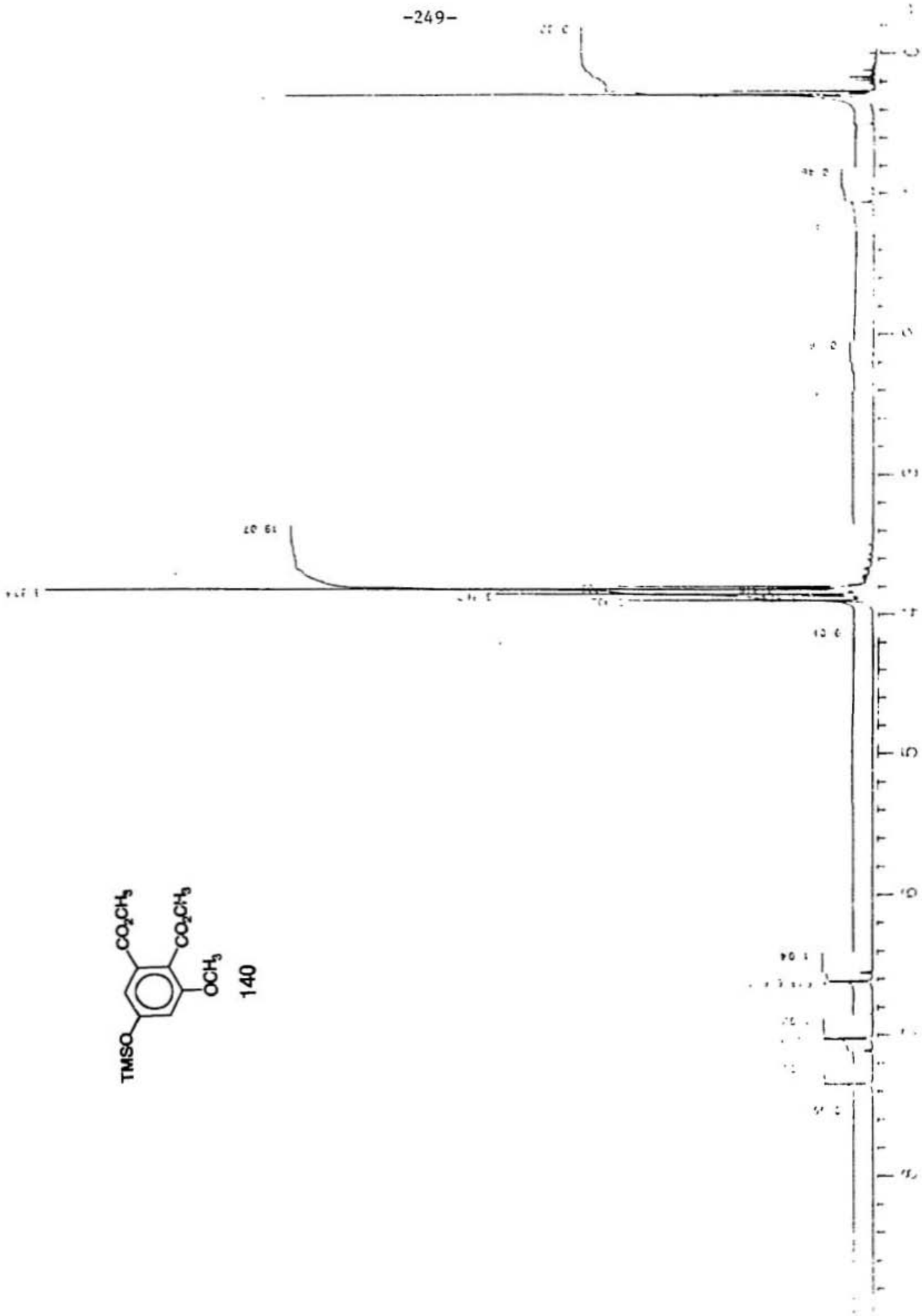

OTMS
MeO
139



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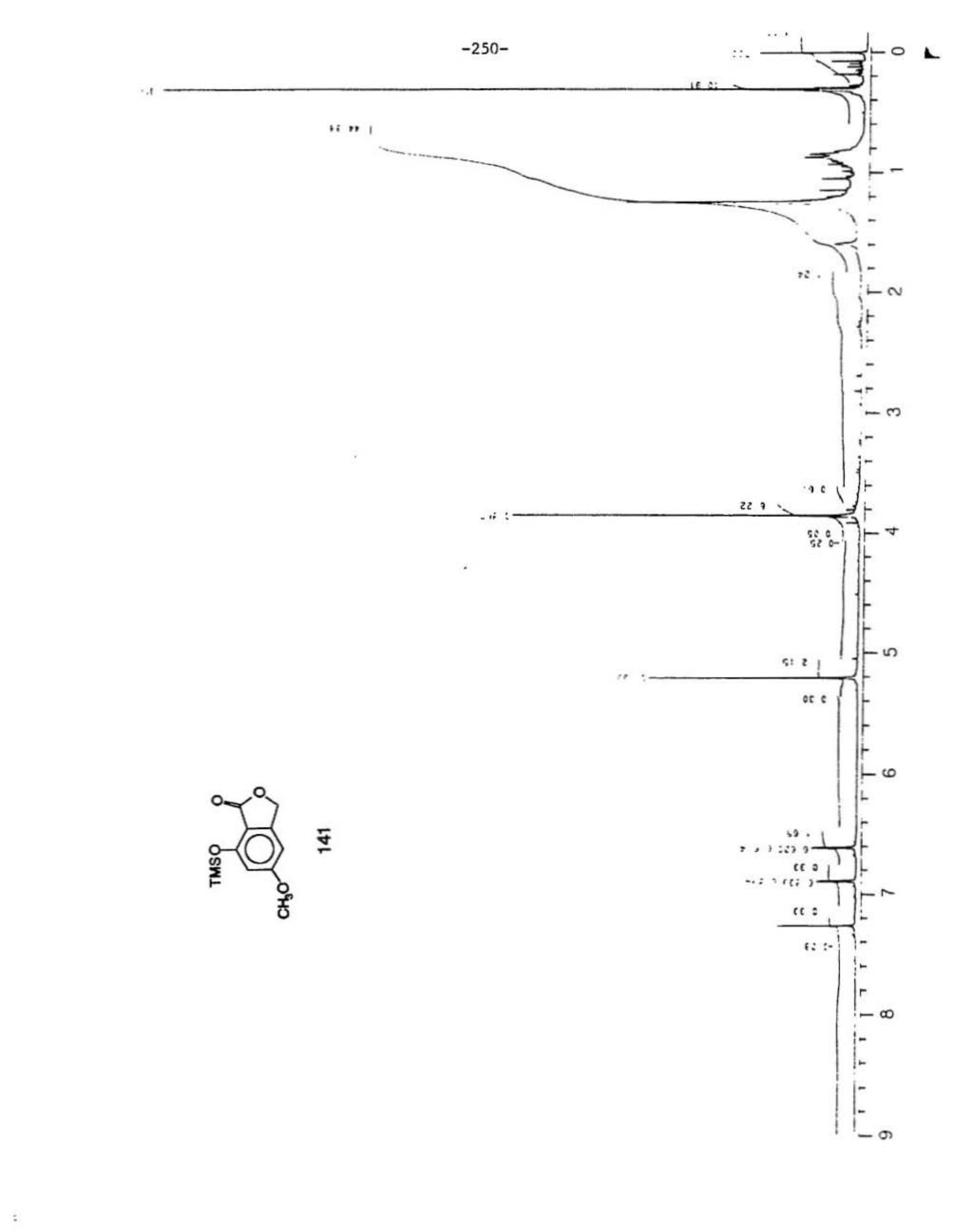

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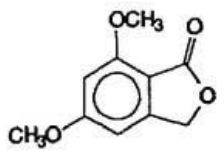

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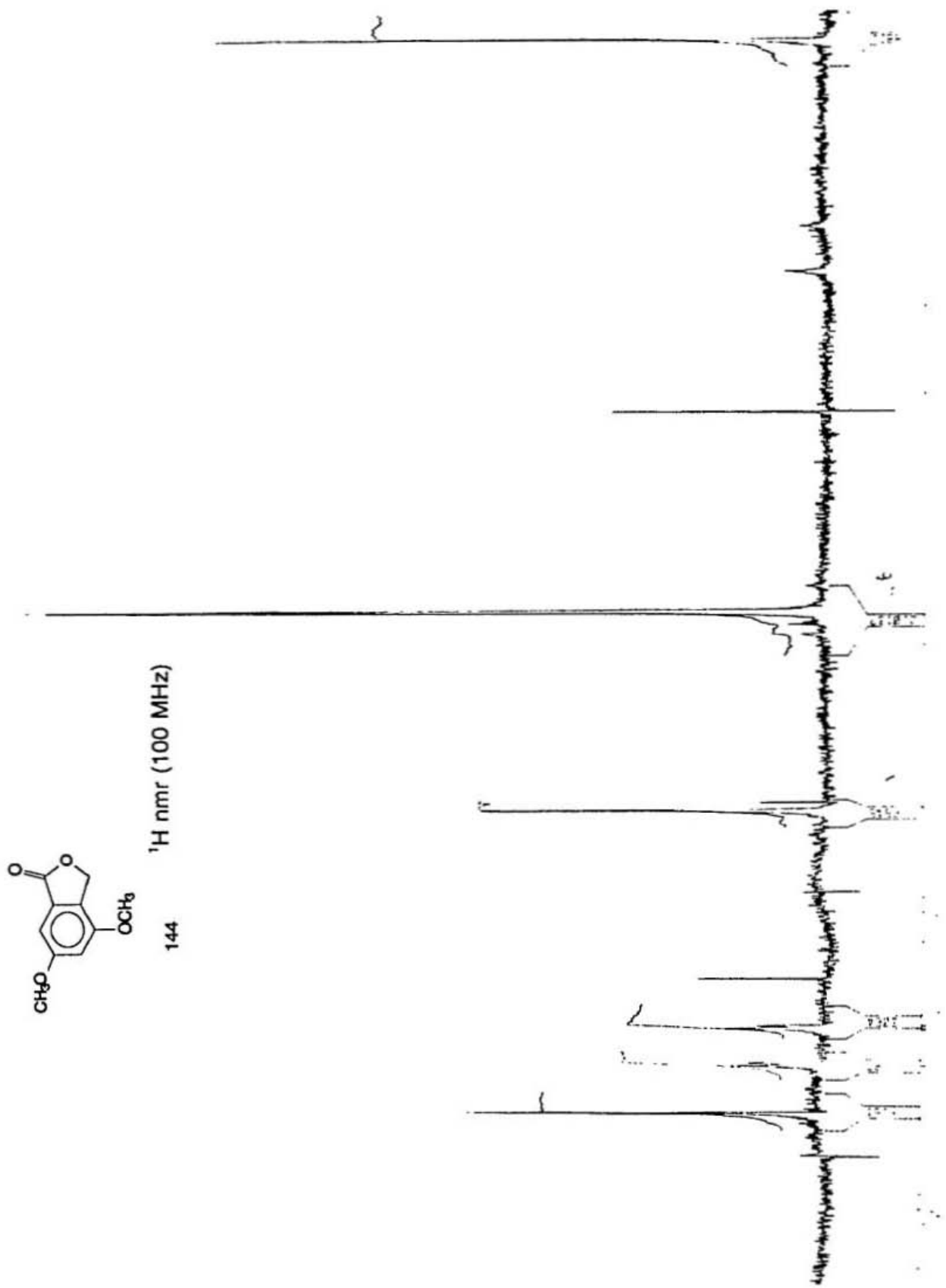
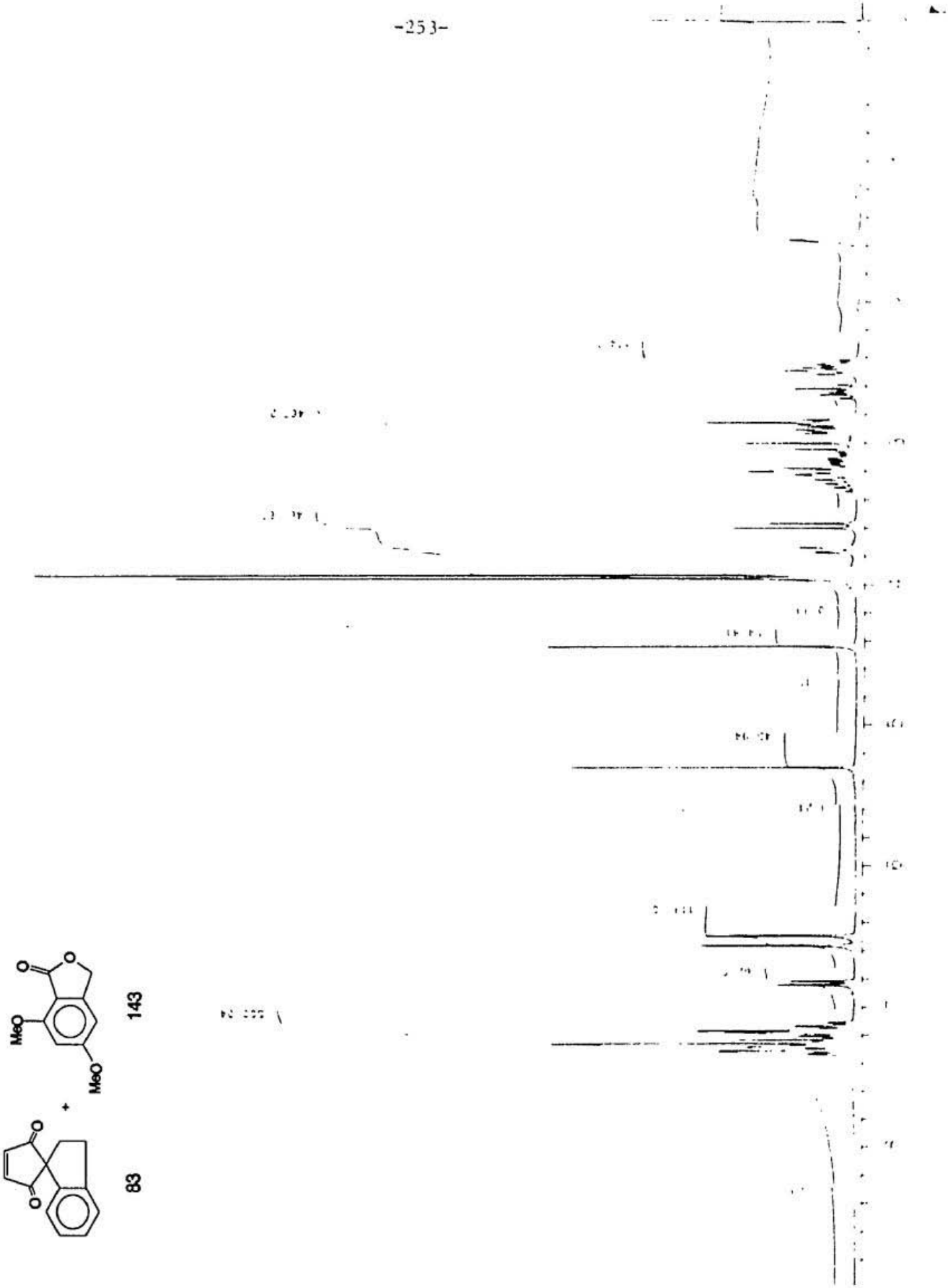
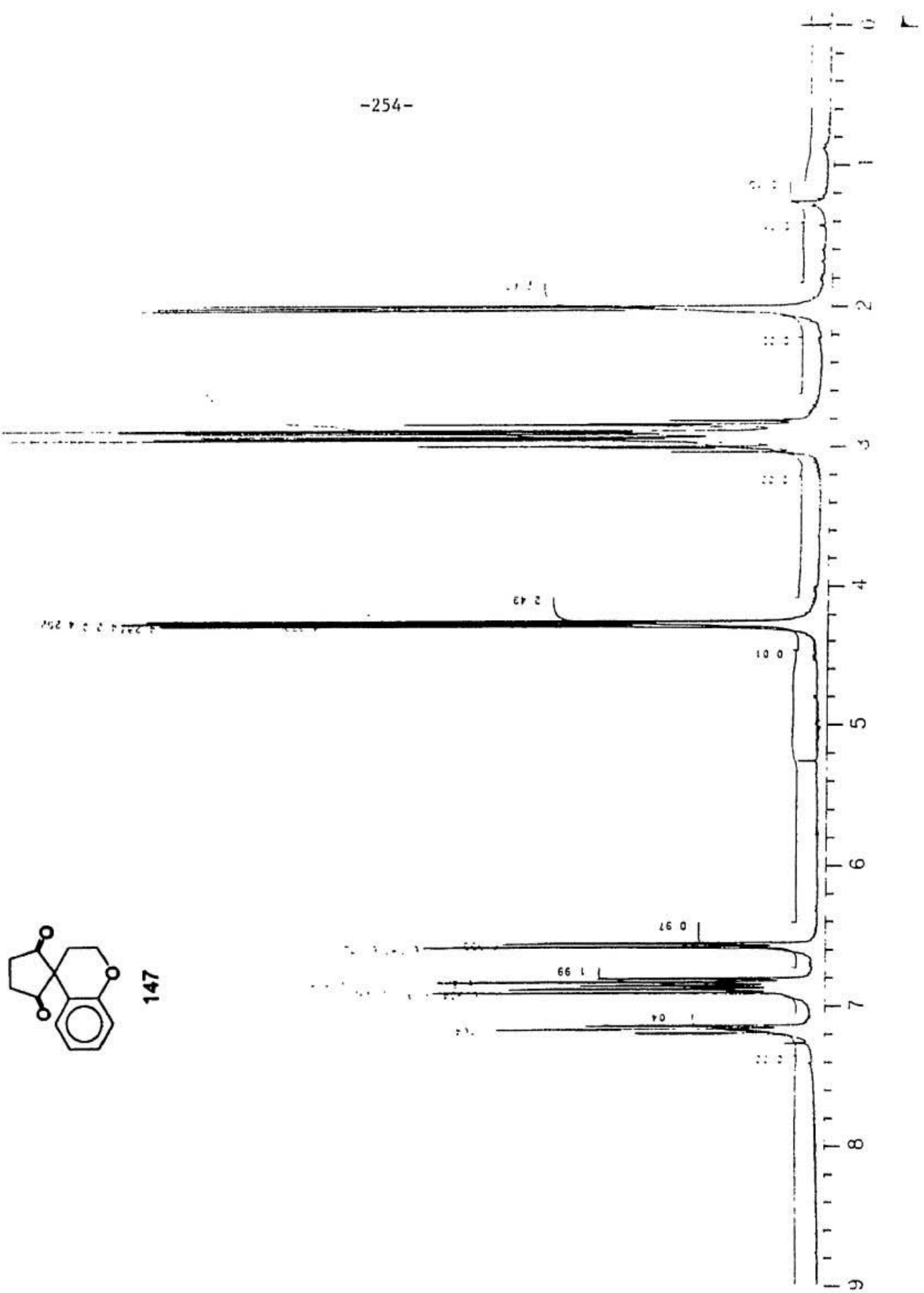

^{1}H nmr (100 MHz)
144
OCH$_3$
CH$_3$O


MeO
MeO
143
+
83



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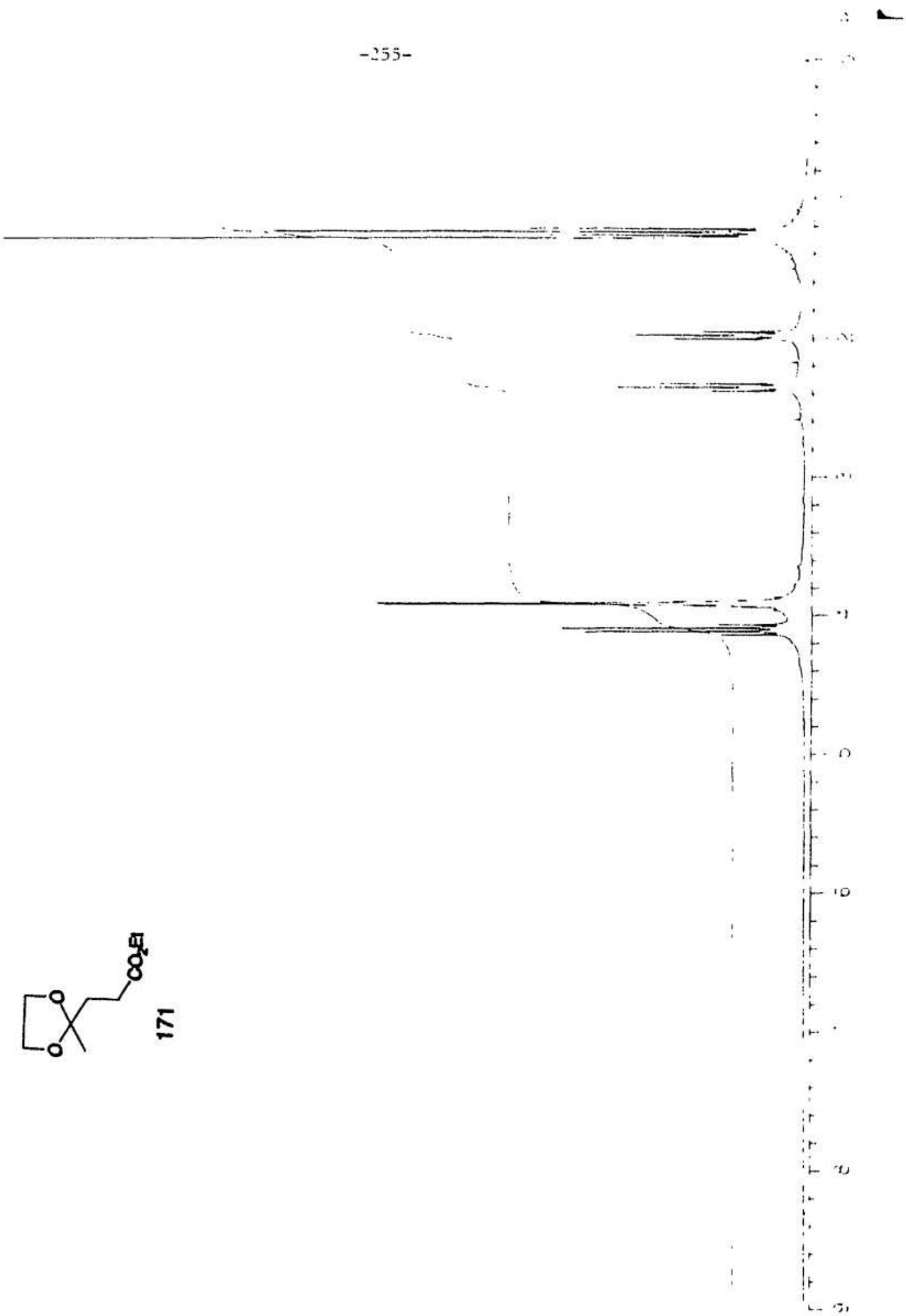

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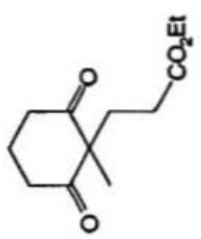

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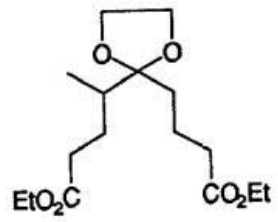

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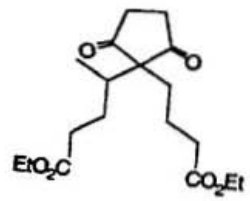

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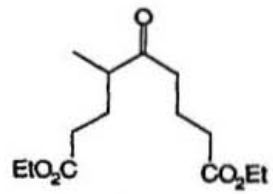

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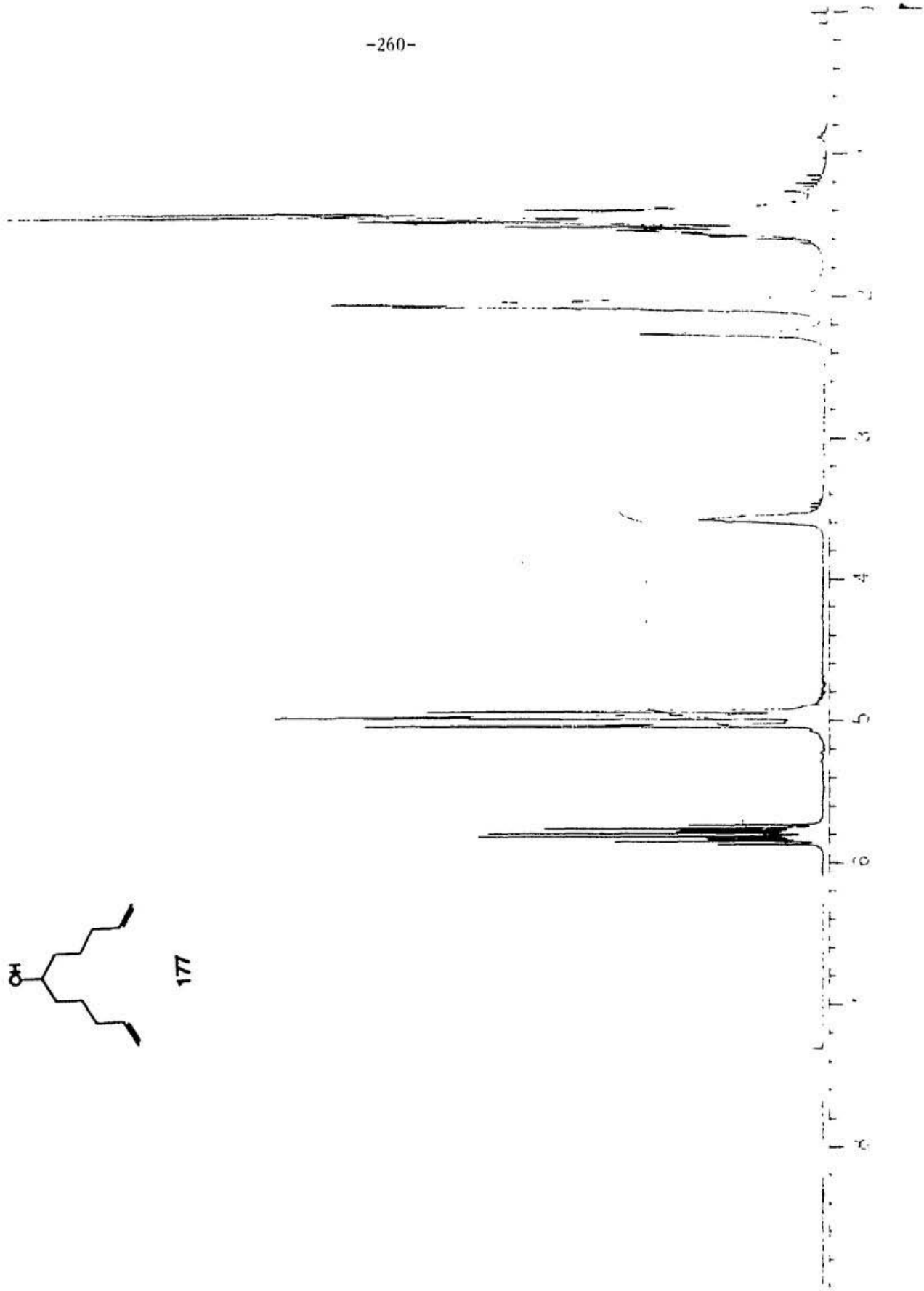
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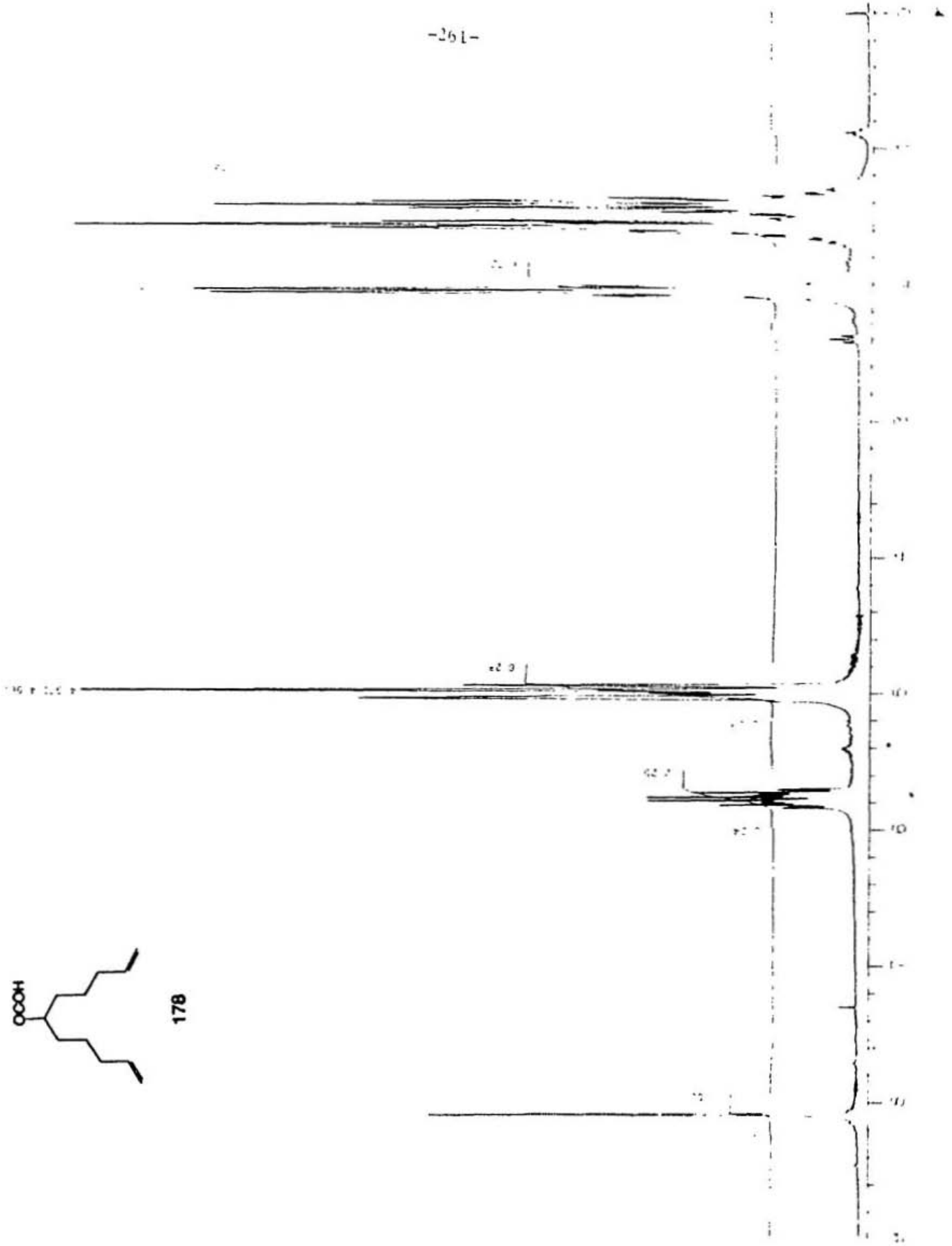

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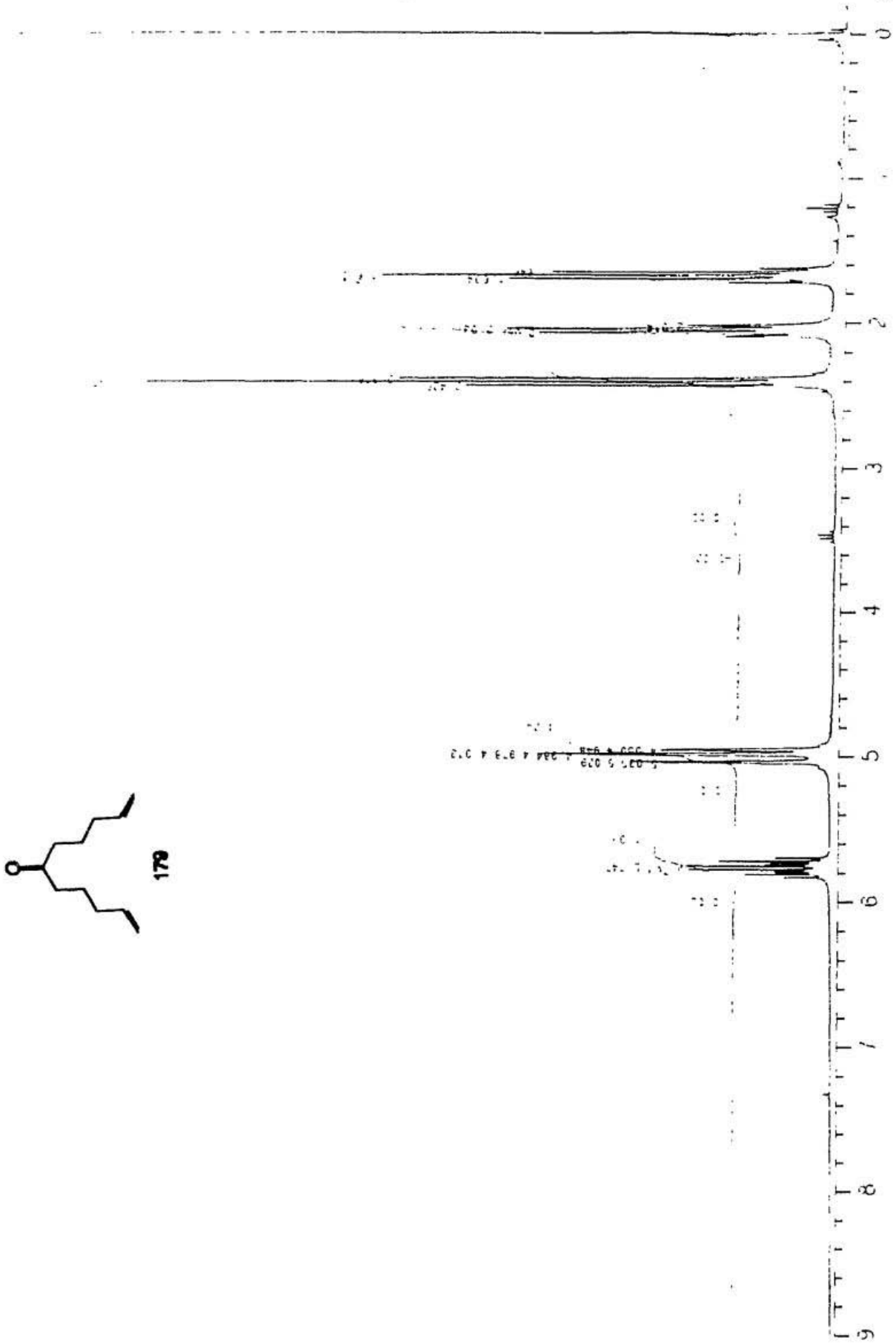

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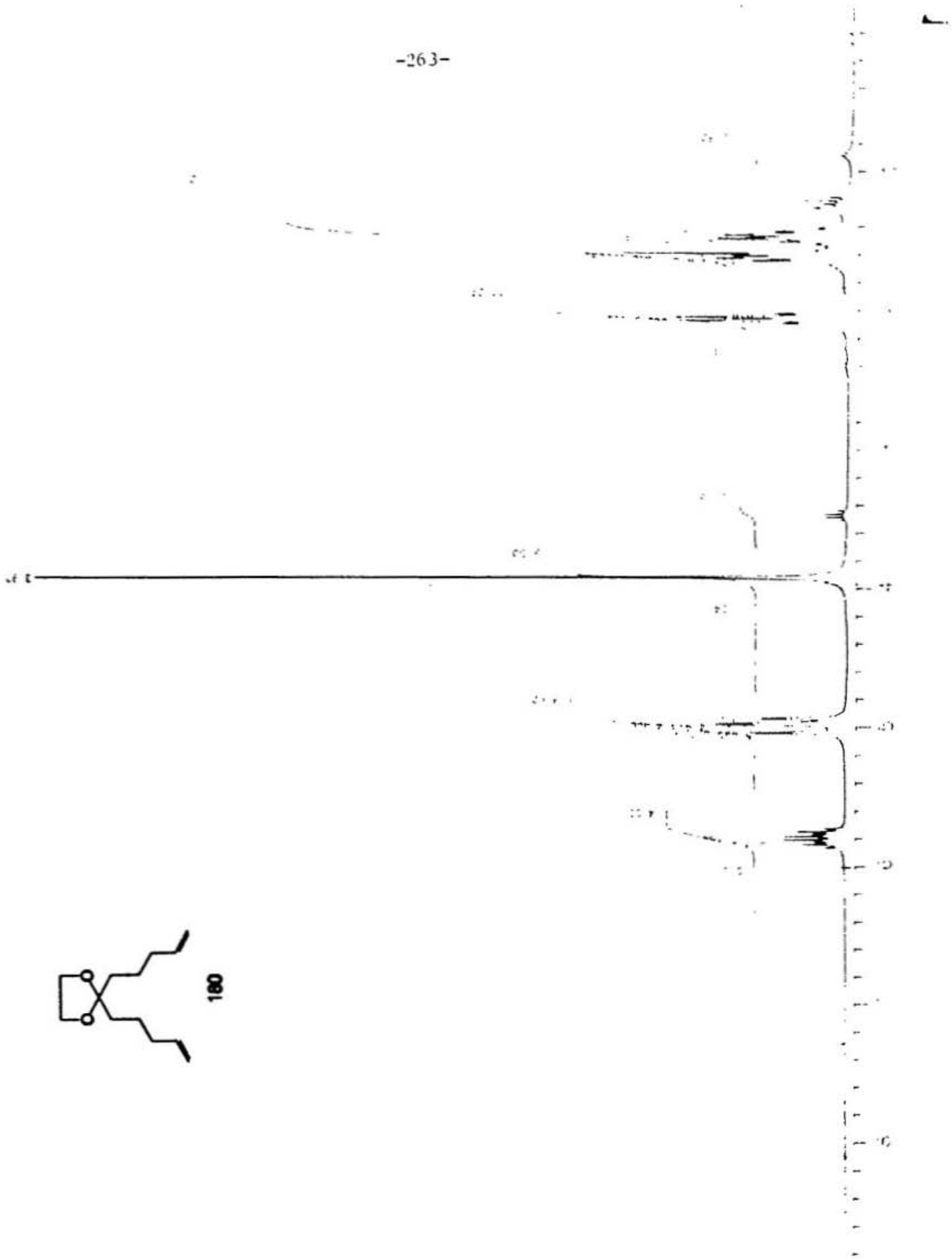

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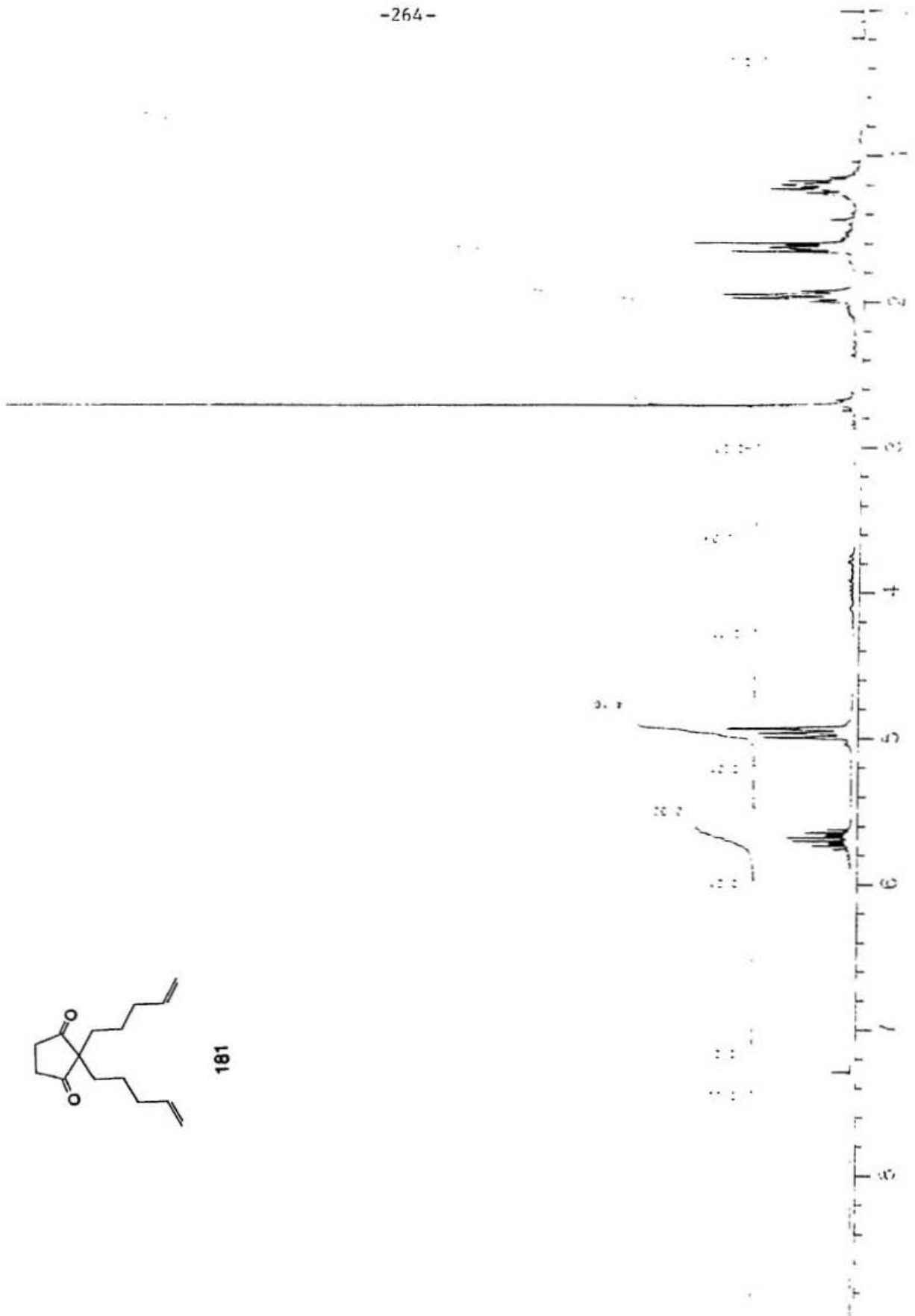

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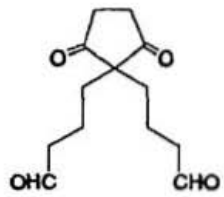

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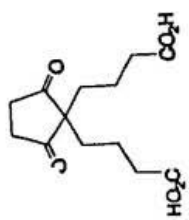

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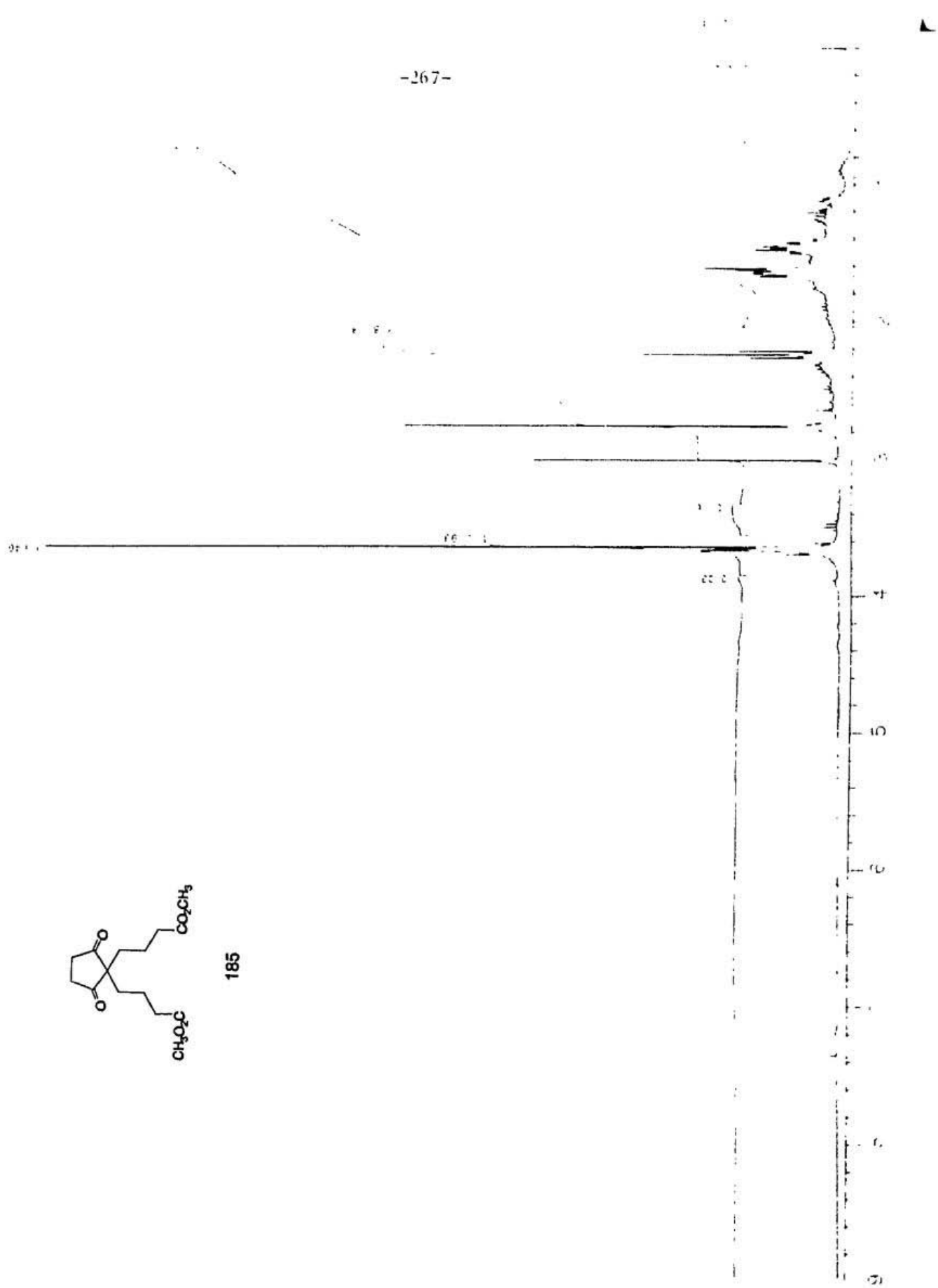

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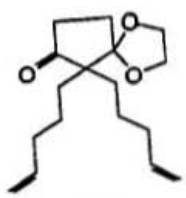

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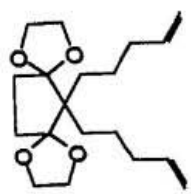

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